Inverse Problems in Soft Tissue Biomechanics & Mechanobiology I
CONVEX PROGRAMMING FORMULATIONS OF THE MATERIAL IDENTIFICATION PROBLEM WITH TOTAL VARIATION REGULARIZATION

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SUMMARY
The material identification problem addressed consists of determining the constitutive parameters distribution of a linear elastic solid using displacement measurements. Given the important applications of the problem and attending the interest in the development of new efficient methods, in this work two new efficient formulations of the problem are presented. A novel approach for the application of the Total Variation regularization term is applied. Numerical examples are solved using synthetic input data with error. The proposed formulations present great advantages in terms of efficiency when compared to other formulations.

Key words: Material Identification, Convex programming, Elasticity, Inverse problems, Full-field measurements

1 INTRODUCTION
The material identification problem (MIP) considered consists of determining the constitutive parameters distribution of a linear elastic solid using complete displacement measurements. The resolution of real life identification problems, such as breast cancer diagnosis [1], involves high computational costs. This is why there is great interest in the development of new efficient methods for the resolution of the MIP.

In the last decades several methods using full-field measurements (FFM) have been developed [2], where the Constitutive Equation Gap Method [4] can be presented as one of the most important. These methods have been applied to the characterization of many different materials from alloy plates to arterial segments [2, 3].

The identification methods developed provide acceptable even when error is present in the data. For that end regularizations techniques are applied, and the Total Variation (TV) functional has proven to be effective for its application in real life problems [1].

In this work two recently developed formulations of the identification problem based on the CEG and the TV are presented [5]. The new extension of the conic formulation for the MIP using several displacement fields is also presented. These formulations allow to solve the problem with high efficiency and precision using convex programming algorithms. Numerical examples are solved using synthetic data with error. The proposed formulations present remarkable advantages in terms of efficiency when compared to other reference formulations such as the CEGM.

2 FORMULATIONS OF THE MIP
The MIP is formulated in the continuum as an optimization problem in the following manner

$$\min_{\mathcal{C} \in \mathcal{C}} \mathcal{J}(u(\mathcal{C}) - u^m) + \mathcal{R}(\mathcal{C}),$$

(1)
where \( C \) is the constitutive tensor field or distribution, \( \mathbb{C} \) is the feasible set of \( C \), \( \mathbf{u}(\mathbb{C}) \) is the solution of the direct problem of elasticity for the field of constitutive parameters \( \mathbb{C} \), \( \mathbf{u}^m \) is the measured displacements, \( J \) is the error term and \( R \) is the regularization term.

### 2.1 Error term formulations

Each formulation is defined by its error term, in this section different formulations are briefly shown considering a Finite Element Method discretized domain. The first two are based in the literature and the last two were recently presented in [5]. In addition in this work an extension of the conic formulation is presented. The material is assumed to be isotropic with known Poisson ratio, therefore the unknown field is the young modulus distribution \( E \) and \( \mathbb{C} = E \mathbb{C}_1 \). A feasible interval for the values of \( E \) is considered \([E_{\text{min}}, E_{\text{max}}]\).

#### 2.1.1 Quadratic error in displacements - NPQED

The first term is the quadratic error in displacements

\[
\text{(NPQED)} \left\{ \begin{array}{l}
\min_{E} \quad \frac{1}{2} \| \mathbf{U}(E) - \mathbf{U}^m \|_{M_u}^2 \\
\text{s.t.} \quad E_{\text{min}} \leq E \leq E_{\text{max}}
\end{array} \right.
\]

where \( M_u \) is a positive definite symmetric matrix, \( \mathbf{U}^m \) is the vector of measured nodal displacements. The optimization problem consists of a general Nonlinear Programming problem.

#### 2.1.2 Constitutive Equation Gap - NPCEG

The same procedure is applied to the CEG functional leading to the following formulation

\[
\text{(NPCEG)} \left\{ \begin{array}{l}
\min_{E} \quad \frac{1}{2} \| \mathbf{U}(E) - \mathbf{U}^m \|_{K(E)}^2 \\
\text{s.t.} \quad E_{\text{min}} \leq E \leq E_{\text{max}}
\end{array} \right.
\]

where \( K(E) \) is the stiffness matrix corresponding to the young modulus distribution \( E \). This problem is also solved as a Nonlinear Programming problem.

#### 2.1.3 Second-order conic programming formulation - CPCEG

Operating with the formulation NPCEG the following equivalent second-order Conic Programming formulation is obtained

\[
\text{(CPCEG)} \left\{ \begin{array}{l}
\min_{E, \tau_U, \tau_F, e, \tilde{\sigma}} \quad \frac{1}{2} \tau_U + \frac{1}{2} \tau_F \\
\text{s.t.} \quad (\mathbf{U}^m)^T \mathbf{K}(E) \mathbf{U}^m \leq \tau_U \\
\quad \sum_{i=1}^{n_E} e_i \leq \tau_F \\
\quad \sum_{i=1}^{n_E} \mathbf{B}_i^T \tilde{\sigma}_i = \mathbf{F} \\
\quad \| \tilde{\sigma}_i \|^2 \leq E_i e_i, \quad i = 1, \ldots, n_E \\
\quad E_{\text{min}} \leq E \leq E_{\text{max}}
\end{array} \right.
\]

where \( e_i \) and \( \tilde{\sigma}_i \) are auxiliary variables, and \( \mathbf{F} \) is the vector of nodal external loads. This formulation is valid for one displacement field, however as it is presented in this work an extension for several displacement fields can be easily obtained.
2.1.4 Quadratic programming formulation - QPCEG

Considering the formulation NPCEG with a minor modification in the functional, the following quadratic programming formulation is obtained

\[
\min_{E, S} \frac{1}{2} \mathbf{S}^T \mathbf{M}^{(k)} \mathbf{S}
\]

s.t.

\[
\mathbf{K}(E) \mathbf{U}^m + \mathbf{B}^T \mathbf{S} = \mathbf{F}
\]

\[
E_{\text{min}} \leq E \leq E_{\text{max}}
\]

\[
E \in \mathbb{R}^{n_E}, \quad \mathbf{S} \in \mathbb{R}^{3n_E}
\]

where \( \mathbf{B} \) is the assembled matrix of the derivatives of the interpolation functions and \( \mathbf{S} \) is a vector of auxiliary variables.

2.2 Regularization term

The Total Variation (TV) regularization functional is considered, which is given by:

\[
\mathcal{R}(E) = \| \nabla E \|_{L_1(\Omega)}^2 = \int_{\Omega} |\nabla E| \, d\Omega.
\]

This functional penalizes distributions presenting high gradients in \( \Omega \), such as highly oscillating distributions, however it does not penalizes excessively high gradients concentrated in sets of zero measure, such as surfaces or curves.

One important disadvantage of the TV is that it is a non-differentiable function of \( E \). This feature may impede the use of gradient-based optimization algorithms. In this work the following equivalent differentiable form of the regularization term as an linear programming problem (with differentiable functions) is used:

\[
\mathcal{R}(E) = \| \mathbf{P} E \|_1 = \min_{\mathbf{Z}} \frac{1}{n_{\text{seg}}} \mathbf{Z}
\]

s.t.

\[
\mathbf{P} E - \mathbf{Z} \leq 0
\]

\[
-\mathbf{P} E - \mathbf{Z} \leq 0
\]

\[
\mathbf{Z} \in \mathbb{R}^{n_{\text{seg}}}
\]

where \( \mathbf{P} \) is a \( n_{\text{seg}} \times n_E \) matrix, \( n_{\text{seg}} \) is the number of segments or interfaces between elements of the mesh and \( \mathbf{Z} \) is a vector of auxiliary variables.

3 RESULTS AND CONCLUSIONS

3.1 Numerical results

In order to compare the performance of the described formulations, four numerical examples are solved. The problems are similar to the most used in the material identification literature. In all the numerical examples solved, errors are introduced in the data in order to avoid committing an inverse crime.

One of the examples solved is frequently considered in the literature. It consists of a square domain under a plane strain state with a square stiffer inclusion submitted to a uniaxial tension load obtaining the reference displacements shown in Figure 1(a). Interpolation errors are added to the reference displacements, obtaining the measured displacements \( \mathbf{U}^m \).

To solve the optimization problems of the formulations NPQED and NPCEG the MATLAB \textit{fmincon} function is used. The CPCEG formulation is solved using Sedumi v1.30 in MATLAB and the formulation QPCEG is solved using the MATLAB function \textit{quadprog}.

In Table 1 the results obtained are presented, where \( \delta_E L_1 \) and \( \delta_E \infty \) represent \( L_1 \) and \( L_\infty \) measures of the function of the relative error of \( E \), respectively.

The relative errors distribution obtained for the CPCEG formulation is shown in Figure 1(b).
Other examples are solved, showing that the proposed methods are able to obtain appropriate results for different kinds of problems, even when mesh interpolation error is considered or when the displacements correspond to a nonlinear elastic material.

### 3.2 Conclusions

Two new formulations of the material identification problem using full-field displacement measurements were presented. The first one, called CPCEG, defines a second order cone optimization problem, while the second one, called QPCEG, defines a convex quadratic programming problem. Both formulations can be applied using efficient interior-point algorithms. It was shown that the use of these approaches leads to a considerable reduction in the time of resolution when compared against other currently used formulations, providing accurate results even when the measurements have random and interpolation error. In addition, it was shown how the TV regularization technique can be applied without losing the key features of the proposed formulations.

**REFERENCES**


A VARIATIONAL FRAMEWORK TO IDENTIFY RESIDUAL DEFORMATIONS USING A MULTI-CONFIGURATION SETTING

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SUMMARY

In this work we present a variational framework for the characterization of residual deformations in arterial tissue. The approach makes use of a classical mechanical setting in the finite strain regime. Knowledge of more than one equilibrium configuration of the arterial vessel allows to set up a proper cost functional to measure the mechanical imbalance resulting from incorrect residual deformations. This naturally leads to a minimization problem in which the target variables are these residual deformations such that the equilibrium is achieved for all known configurations. An example is presented to show illustrate the proposed approach.

Key words: residual deformation, residual stress, arterial tissue

1 INTRODUCTION

When modeling arterial tissues it is necessary to take into account the interaction of the constitutive components, such as elastin, collagen fibers and smooth muscle cells. The literature addressing constitutive modeling is vast (see for example [2, 4]). Also, an increasing interest in the scientific community led to the development of different methods for estimation of material parameters, both using ex-vivo and in-vivo experimental data (see for example [1, 5]). At the same time, it has been acknowledged that arterial vessels have residual stresses in their unloaded configurations [6]. This fact motivated numerous research efforts addressing the effects of residual stresses (RSs) in arterial wall mechanics [7, 8].

Remarkably, the role played by RSs has changed in the last years, from being only a consequence of growth and remodeling to playing a fundamental functional role in the setting of proper mechanobiological conditions in vascular vessels [3]. Most approaches to deal with RSs rely on the association of RSs and the so-called recoverable residual deformations (RRDs), in the sense that the energy stored in the structure can be recovered when, for instance, performing excision in the tissue.

This lack of knowledge with respect to RSs and RRDs can definitely benefit from the integration of computational modelling, data assimilation, imaging techniques (such as IVUS) and motion tracking strategies (such as optical-flow). Data assimilation techniques have nowadays become a standard approach also in bioengineering practice, particularly in cardiovascular modelling, however, there has not been contributions directed towards the estimation of RSs.

The goal of this work is to present a mechanical formulation in a variational setting which allows the estimation of RSs from data similar to that encountered in in-vivo and in-vitro scenarios. Fundamentally, the mechanical formulation that describes the equilibrium in the arterial tissue is considered in the finite strain regime, and it is assumed that more than one equilibrium configuration is known. Then, a cost functional is proposed to measure the mechanical imbalance due to incorrect RRDs at the
given equilibrium configurations. Hence, the characterization of RSs turns into an optimization problem where the target variables are the RRDs. An example with manufactured solution is presented to illustrate the concepts behind this approach.

2 METHODOLOGY

Figure 1 presents a two-configuration mechanical setting used in the present work for different mechanical loads (e.g. pressures \(p_a\) and \(p_b\)). Configuration \(\Omega_v\) is a state of unloaded and separated material constituents of the arterial wall (with zero stress state and free of RRDs), which is the reference configuration for the constitutive equations. Material domain \(\Omega_m\) is free of loads, but has RRDs \((F^r)\), which cause a residual stress state \((\sigma^r)\). Configuration \(\Omega_a\) and the \(\Omega_b\) represent two configurations with mechanical equilibrium with their corresponding external loads \((p_a\) and \(p_b\)). Tensors \(F^v\) and \(F^u\) denote the corresponding deformation gradient tensors, and \(F^v = F^vF^r\), \(F^u = F^uF^r\) are the material expressions for the total deformation tensor with respect to \(\Omega_v\), which is never used, while \(\Omega_m\) is an unknown in the problem. In turn, \(\Omega_a\) and \(\Omega_b\) are known data, as well as displacement fields \(w\) between these configurations.

We assume the tissue to be hyperelastic whose strain energy function is \(\Psi\). Then, the second Piola-Kirchhoff and Cauchy stress tensors are

\[
S^r = \frac{\partial \Psi}{\partial C^r}, \quad \sigma^r = \frac{1}{\det F^r} F^r S^r (F^r)^T, \quad \tag{1}
\]

where \(F^r\) is described in configuration \(\Omega_m\), and \(C^r = (F^r)^T F^r\). The following relations hold between the coordinates of \(\Omega_m\), \(\Omega_a\) and \(\Omega_b\), \(x_a = x_m + v_m, x_b = x_m + u_m\) and \(x_b = x_a + w_a\). Then, we have the following definitions \(F^u = I + \nabla_m u_m, F^v = I + \nabla_m v_m, F^w = I + \nabla_a w_a\).

The mechanical problem in \(\Omega_m\) (written in \(\Omega_a\)) reads

\[
\int_{\Omega_a} \sigma^r_a \cdot ((F^v_a)^T \nabla_a \hat{\nu})^a d\Omega_a = 0 \quad \forall \hat{\nu} \in \mathcal{V}_a, \quad \tag{2}
\]

where \(\mathcal{V}_a = \{ v \in H^1(\Omega_a) ; v_{|\Gamma_D} = 0 \}\), and \(\sigma^r_a\) is related to \(\sigma^r\) and \(S^r\) through the following expression \(\sigma^r_a = \frac{1}{\det F^v_a} F^v_a (\sigma^r)_a (F^v_a)^T = \frac{1}{\det F^u_a} F^u_a (\sigma^r)_a (F^u_a)^T\).

Figure 1: Problem setting for the characterization of residual deformations (RRDs).
In $\Omega_a$ and $\Omega_b$ the mechanical problems (both written in configuration $\Omega_a$) read

$$
\int_{\Omega_a} \sigma^{vr} \cdot \nabla^a \tilde{\mathbf{v}} \, d\Omega_a = \int_{\Gamma_a} \rho_a \mathbf{n}_a \cdot \tilde{\mathbf{v}} \, d\Gamma_a \quad \forall \tilde{\mathbf{v}} \in \mathcal{V}_a, \quad (3)
$$

$$
\int_{\Omega_a} \sigma^{(v+w)r}_a \cdot ((\mathbf{F}^w)^T \nabla^a \tilde{\mathbf{v}})^s \, d\Omega_a = \int_{\Gamma_a} (p_b)_{a} (\mathbf{F}^w)^{-T} \mathbf{n}_a \cdot \tilde{\mathbf{v}} \, det \mathbf{F}^w \, d\Gamma_a \quad \forall \tilde{\mathbf{v}} \in \mathcal{V}_a, \quad (4)
$$

where $\sigma^{vr} = \frac{1}{\text{det} \mathbf{F}^r} \mathbf{F}^{vr} (\mathbf{S}^{vr})_a (\mathbf{F}^{vr})^T$ and $\sigma^{(v+w)r}_a = \frac{1}{\text{det} \mathbf{F}^r} \mathbf{F}^{vr} \mathbf{S}^{(v+w)r} (\mathbf{F}^{vr})^T$.

Recall that $\Omega_a$ and $\Omega_b$, in corresponding equilibrium with pressure loads $p_a$ and $p_b$, together with w are given data. Then, the goal is to find $\mathbf{F}^r$ and $\mathbf{v}$ such that (2), (3), (4) are satisfied.

Consider an arbitrary pair $(\tilde{\mathbf{F}}^r, \tilde{\mathbf{v}})$ (described in $\Omega_a$) not mechanically consistent with (solution of) the problem. Then, we define the functional $R_m = R_m(\tilde{\mathbf{F}}^r, \tilde{\mathbf{v}}) \in \mathcal{V}_a$, associated with the mechanical imbalance in $\Omega_m$ (residual of equation (2)); and the functional $R_b = R_b(\tilde{\mathbf{F}}^r, \tilde{\mathbf{v}}) \in \mathcal{V}_a$, associated with the mechanical imbalance in domain $\Omega_b$ (residual of equation (4)).

Let $\mathcal{V}_a = \text{span} \{ \Phi_1, \Phi_2, \ldots \}$, where $\Phi_i$ denotes the $i$-th element of that basis. Then, the above functionals are completely characterized as follows $R_m^i(\tilde{\mathbf{F}}^r, \tilde{\mathbf{v}}) = \langle R_m(\tilde{\mathbf{F}}^r, \tilde{\mathbf{v}}), \Phi_i \rangle$, $i = 1, 2, \ldots$ and $R_b^i(\tilde{\mathbf{F}}^r, \tilde{\mathbf{v}}) = \langle R_b(\tilde{\mathbf{F}}^r, \tilde{\mathbf{v}}), \Phi_i \rangle$, $i = 1, 2, \ldots$. Then, we introduce the cost functional that characterizes the mechanical imbalance as a function of the RRDs

$$
\mathcal{F}(\tilde{\mathbf{F}}^r, \tilde{\mathbf{v}}) = \frac{\eta_m}{2} R_m(\tilde{\mathbf{F}}^r, \tilde{\mathbf{v}}) \cdot R_m(\tilde{\mathbf{F}}^r, \tilde{\mathbf{v}}) + \frac{\eta_b}{2} R_b(\tilde{\mathbf{F}}^r, \tilde{\mathbf{v}}) \cdot R_b(\tilde{\mathbf{F}}^r, \tilde{\mathbf{v}}),
$$

where $R_m$ and $R_b$ are vectors containing components $R_m^i$ and $R_b^i$, respectively, and $\eta_m$ and $\eta_b$ are weighting factors.

Then, the identification of RRDs can be stated in variational form: given $\Omega_a$, $\Omega_b$, $\mathbf{w}$, $p_a$, $p_b$ and the constitutive parameters, find $(\tilde{\mathbf{F}}^r, \tilde{\mathbf{v}})$ such that

$$
(\mathbf{F}^r, \mathbf{v}) := \text{argmin}_{D \times \mathcal{U}_a} \mathcal{F}(\mathbf{F}^r, \mathbf{v}),
$$

subjected to

$$
\int_{\Omega_a} \sigma^{vr} \cdot \nabla^a \tilde{\mathbf{v}} \, d\Omega_a - \int_{\Gamma_a} \rho_a \mathbf{n}_a \cdot \tilde{\mathbf{v}} \, d\Gamma_a = 0 \quad \forall \tilde{\mathbf{v}} \in \mathcal{V}_a, \quad (6)
$$

where $D$ is the space of tensor fields with positive determinant and $\mathcal{U}_a$ is the set of kinematically admissible solutions.

### 3 RESULTS AND CONCLUSIONS

The identification of RRDs is performed in a thick-walled cylinder subjected to internal pressure. Considering a known material configuration with RRDs (and associated RSs), given the inner pressure levels $p_a$, $p_b^1$ and $p_b^2$, the equilibrium configurations $\Omega_a$, $\Omega_b^1$ and $\Omega_b^2$ are calculated obtaining a complete manufactured solution. Then, we assume $\Omega_a$, $\Omega_b^1$, $\Omega_b^2$, $\mathbf{w}^1$, and $\mathbf{w}^2$ to be input data.

For the spatial discretization linear 1D finite elements for the radial displacement field are considered, and piecewise constant RRDs. Three different spatial discretizations are explored (2, 4 and 8 finite elements). Spatial integration is performed using 4 Gauss-points.

The material configuration is defined by the inner and external radii $r_i = 5.6$ mm and $r_e = 7$ mm. And a compressible Neo-Hookean material is considered, being $\Psi = C_1 (\tilde{T}_1 - 3) + k_{vol} (J - 1)^2$, with where $\tilde{T}_1 = J^{-2/3} \text{tr} (C)$, $J = \text{det} \mathbf{F}$, with $C_1 = 15 \text{kPa}$ and $k_{vol} = 365 \text{kPa}$, (yielding $\nu = 0.46$). Also, it is $p_a = 1 \text{kPa}$, $p_b^1 = 2 \text{kPa}$ and $p_b^2 = 3 \text{kPa}$.

For this example, the target RSs and RRDs are based on a continuous RS field of the following form $\sigma^r(\rho_m) = \text{diag}\{\sigma^r_{m,\rho}(\rho_m), \sigma^r_{m,\theta}(\rho_m), \sigma^r_{m,z}(\rho_m)\}$. A linear form for $\sigma^r_{m,\theta}$ is assumed and $\sigma^r_{m,\rho}$ is obtained from the equilibrium ($\sigma^r_{m,z}$ exerts no power).

An interior-point algorithm available in MATLAB Optimization Toolbox is employed. The initial condition is $\mathbf{F}^r = I$ for the 2-element problem, then this solution is used for the 4-element case.
and so forth. First we take $\eta_1, \eta_2 = 100$ and $\eta_m = 0.1$, next, they are switched to $\eta_1, \eta_2 = 1$ and $\eta_m = 0.1$, and finally to $\eta_1, \eta_2 = \eta_m = 1$.

Figure 2 presents the identified RRDs for each discretization and the comparison with the target solution. For the obtained RRD and RSs fields, the errors are shown in Table 1.

![Figure 2: Principal stretches characterizing the RRDs. Comparison between results (dashed) and the discrete target solution (solid).](image)

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Table 1: Relative errors in the RRD, RSs and displacement fields.

It can be seen that the proposed method allows the identification of the RRD field, which improves as the number of finite elements is increased, achieving a relative error (measured in the $L^2$ norm) of $3.29 \cdot 10^{-2}$ for the 8-element case.

REFERENCES

IDENTIFYING THE ELASTIC PROPERTY DISTRIBUTION OF SOFT SOLIDS QUANTITATIVELY FROM LIMITED KNOWN DISPLACEMENTS ON BOUNDARIES: A THEORETICAL STUDY

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SUMMARY

This paper presents a novel inverse approach to determine the heterogeneous material property distribution quantitatively from limited known displacements on specimen’s boundaries. The approach requires multiple boundary displacement datasets measured by applying multiple indentations sequentially at different locations. The feasibility of the proposed method is tested successfully by two numerical examples that have clinical relevance. We observe that the novel inversion technique performs well in recovering a quantitatively interior elastic property distribution. This method has the potential for clinical application and the experiments will be conducted in the future to further show the proof the concept.

Key words: inverse problem in elasticity, boundary displacements, non-homogenous shear modulus distributions

1 INTRODUCTION

Characterizing heterogeneous elastic property distribution has great potential in clinical application, e.g., detecting breast or skin tumors non-invasively, understanding the subtle neurodegenerative processes, etc. This requires displacement data in the domain of interest and the displacements can be measured by ultrasound, magnetic resonance imaging (MRI), etc. These imaging modalities are usually capable of measuring the displacement fields throughout the entire domain. With the full field displacement data, the non-homogenous material property can be acquired by strain images as the reciprocal relationship between the strain and the elastic property. However, this approach assumes that the stress is constant everywhere in the problem domain, which is not true for a non-homogenous elastic property distribution. Furthermore, strain images are highly noisy that limits its clinical application. Another approach to obtaining the material property distribution is to solve the inverse problem. In previous works[1,2], the inverse problem is posed as a constraint minimization problem where the equilibrium equations should be satisfied. This regularized inversion technique has been applied to map the non-homogenous linear elastic[1,2] and hyperelastic properties[3] using the displacement field of the entire domain. Recently, a novel inverse method using only boundary displacement data to map the interior material property distribution has been proposed[4]. The significant advantage of this method is that the boundary displacements are easy to measure with high accuracy. One approach to measure displacement data is to employ digital image correlation systems (DIC) which have fairly high resolutions. Additionally, DIC systems are also cheaper than other imaging modalities. However, this methodology cannot easily ensure a unique solution of the inverse problem, thus multiple boundary displacements datasets should be measured and utilized to solve the inverse problem.

In this paper, we will map the interior material properties quantitatively solely utilizing boundary displacement data. An introduction of the proposed inverse strategy will be presented in Section 2.

In Section 3, two numerical experiments are exhibited to show the feasibility of the novel inverse
approach. We will also briefly discuss the numerical results in Section 3 and end with conclusions in Section 4.

2 METHODOLOGY

In this paper, the inverse problem is posed as constrained minimization problem where the equilibrium equations should be satisfied. The objective function to be minimized is written as:

\[
\pi = \sum_{i=1}^{n} \int_{\Gamma_i} (\mathbf{u}^i - \mathbf{u}_{\text{meas}}^i)^2 d\Gamma + \alpha \text{Reg}(\mu)
\]

The first term on the left hand side is referred to as the displacement correlation term where the misfit between the computed \( \mathbf{u}^i \) and measured \( \mathbf{u}_{\text{meas}}^i \) displacement fields on the specimen’s partial boundaries \( \Gamma_i \) are minimized. The computed displacements are obtained by solving the forward problem in elasticity at current estimated shear modulus distribution by finite element methods. \( i \) represents the displacement dataset number. Since the displacement information on the boundary is very limited, we have to measure and utilize multiple displacement datasets to ensure the uniqueness of the solution to the inverse problem. The second term is the TVD regularization term which penalizes the inverse problem and the relevant mathematical formula is

\[
\text{Reg}(\mu) = \sqrt{\nabla \mu^2 + c^2}
\]

where \( c \) is a small constant. \( \alpha \) is the regularization parameter selected based on the smoothness criteria[1-3].

The inverse problem will be solved by a gradient based technique named limited-LBFG method where the objective function value and its gradient with respect to material properties. To evaluate the gradient efficiently, the adjoint method will be introduced and it results in only solving two linear problems in every inverse minimization call[5, 6]. The inversion technique presented herein has been widely applied to map the heterogeneous elastic and hyperelastic property distributions using the full field displacement data. In this work, we will attempt to obtain the non-homogenous elastic property distribution quantitatively using the boundary displacement datasets. The proof of concept will be shown by numerical experiments. That is, the proposed inverse approach will be tested by the simulated displacement datasets obtained solving forward problems for a target elastic property distribution. In this work, we will apply the indentation on the simulated samples and collect multiple boundary displacement datasets by changing the location of the indentation. As such, the unique solution of the inverse problem is likely to be guaranteed.

3 RESULTS AND DISCUSSIONS

In this first numerical example, there is a stiff inclusion with a radius of 0.1cm embedded in a 1cm*1cm background as shown in Fig.1. The target shear modulus values of the soft background and the stiff inclusions are 10kPa and 50kPa, respectively. The bottom edge is fixed in both direction and the indentation is applied on the lateral or top side as shown in Fig.1(a) and (b), respectively. Additionally, each indentation induces a force of 0.05N. For the case that the indentation is applied laterally(see Fig.1(a)), the forces are applied in pairwise on left and right sides simultaneously and aligned horizontally with the same magnitude but in opposite directions. The problem domain is discretized by 7200 linear triangular elements and the forward problem is solved by finite element methods. The displacement data is assumed to be measured on the traction free boundary and the specifically measured edge is marked by red color as displayed in Fig.1. Fig.2(b) and (c) are the recovered shear modulus distributions with 7 and 13 boundary displacement datasets, respectively. The first seven indentations are applied on the lateral sides, the last six are applied on the top edge. In this case, we will not introduce any noise into the datasets. Fig.1(d) is the shear modulus plot over the horizontal line across the center the inclusion. We observed that the location of the inclusion can be characterized and the shape of the inclusion is well preserved. However, the inclusion seems to become larger than the target and the reconstructed shear modulus value of the inclusion is significantly underestimated. It seems that the bigger size of inclusion compromises the sharp loss of the shear modulus value in inclusion. Compared to Fig. 2(b) and 2(c), it is clear to see that with an increasing number of boundary displacement datasets utilized, the inclusion is mapped better as the shape of the inclusion become more circular and the reconstructed shear modulus value increases slightly. As we utilize the incomplete boundary displacements to solve the inverse problem, it is extremely difficult to obtain
a unique solution. To this end, we have to collect and utilize more datasets for solving the inverse problem to ensure a unique solution.

![Fig.1: The problem domain with a stiff inclusion surrounded by a soft background. The arrows indicate the indentation locations, and the red line represents the side we minimize. (a) The indentations are sequentially applied pair-wise at both lateral sides (net force is zero), and we utilize boundary displacements on the top edge as measured data; (b) The indentation is applied on the top edge, and we utilize boundary displacements on the left edge as measured data; (c) The indentation is applied on the top edge, and we utilize boundary displacements on the right edge as measured data. (Unit in the scale bar: 10kPa)](image1)

![Fig.2: (a) Target shear modulus distribution for comparison; (b) the reconstructed shear modulus distribution when 7 displacement fields are used; (c) the reconstructed shear modulus distribution when 13 displacement fields are used; (d) shear modulus plot over the horizontal line through the center of the inclusion for the target and reconstructed shear modulus distribution. (Unit in the scale bar: 10KPa)](image2)

The second example shown in Fig.3 is a semi-circle represents an idealized breast with an idealized tumor. In this model, the shear modulus values of the background and the inclusion are 5kPa and 25kPa, respectively. In this case, we fix the bottom edge and apply the indentations on the curved top edge. Additionally, we add 0.1% random noise into the boundary displacement datasets to mimic the actual displacement data measured from DIC system. The boundary displacements are assumed to be measured on the curved top edge. Fig.3(b) is the recovered shear modulus distribution with 5 boundary displacement datasets. The results reveal that the shear modulus is recovered well in both the shape and shear modulus value of the inclusion even with 5 boundary displacement datasets. Since the displacements on the curved boundary are used as the measured data to solve the inverse problem and the bottom edge is the fixed and used as the Dirichlet boundary condition, we actually utilized the complete boundary displacement information to solve the inverse problem in the second numerical example. As a result, the inclusion is mapped better in the second numerical case than that of the first.

![Fig.3: (a) Target shear modulus distribution for comparison; (b) the reconstructed shear modulus distribution when 5 displacement fields are used (Unit in the scale bar: 1kPa)](image3)
4 Conclusions

The paper presents a novel inversion technique to reconstruct the heterogeneous shear modulus distribution quantitatively utilizing displacement data on specimen’s boundary. Two numerical example has been exhibited and we observe that this methodology is capable of mapping the stiff inclusion well. This inverse approach has potential in detecting breast tumors non-destructively.

REFERENCES

ESTIMATING TRANSVERSELY ISOTROPIC MATERIAL PARAMETERS FROM MR ELASTOGRAPHY USING OPTIMISED VIRTUAL FIELDS

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SUMMARY
Magnetic resonance elastography (MRE) is a non-invasive technique to estimate stiffness of biological tissue. However, in order to understand pathological changes in tissues such as muscle, it is important to estimate anisotropic properties. This work investigates the use of the optimised virtual fields method to estimate transversely isotropic (TI) material parameters from simulated MRE displacements in a finite element beam model. Two material parameter formulations were implemented to estimate a) all five independent parameters in the elasticity matrix and b) three parameters which describe a nearly incompressible TI material. Identification of parameters in the first formulation with added Gaussian noise was affected by the lack of identifiability of Poisson’s ratios, and hence, the fibre Young’s modulus. The identification of parameters in the second formulation was less affected by the addition of noise to the displacement data. However, the third parameter, representing the anisotropic tensile ratio, was consistently underestimated.

Key words: magnetic resonance elastography, transverse isotropy, optimised virtual fields

1 INTRODUCTION
Magnetic resonance elastography (MRE) has developed over the past two decades as a non-invasive method of estimating stiffness of biological tissue. Numerous inversion algorithms exist (e.g. manual, direct inversion of the Helmholtz wave equation, local frequency estimation, etc.) which, for the most part, assume that the tissue is isotropic.

Many biological tissues such as muscle and tendons are arranged in fibres and are better described by a transversely isotropic (TI) material law which has a greater stiffness along the axis of symmetry. In the case of TI, a linearly elastic material can be fully described by five independent parameters. However, all five parameters are difficult to estimate from elastography displacements since three parameters in the elasticity matrix depend on accurate estimation of the longitudinal (dilatational) wave speed (i.e. compressibility), which is on the order of 300 times greater than the shear (distortional) wave speed. Therefore, other studies have reduced the number of estimated parameters to either two (e.g. [1]) or three parameters (e.g. [2]), avoiding estimation of compressibility. Only one paper (to the author’s knowledge) has estimated all five independent parameters from MRE displacements [3].

It is necessary to induce both fast (i.e. fibre stretching) and slow (i.e. cross-fibre stretching) shear waves in order to estimate three or more parameters to characterise TI materials [2, 4]. Of the studies estimating three parameters, only two used simulated data with known material properties [4, 5]. However, neither study accurately estimated all three parameters, even in the noise-less case. It is not clear whether this was due to a lack of identifiability from the available displacement information,
a fault in the inversion method used, or an incorrect assumption made in the material parameter formulation.

The virtual fields method (VFM), based on the variational formulation of the equilibrium equations, is an inverse method which has previously been applied to MRE displacement data to estimate isotropic shear moduli (e.g. [6, 7]). An optimised VFM has also been implemented, which minimises the impact of Gaussian noise on the estimated shear modulus [8]. In this study, the optimised method was adapted for the estimation of TI material properties from simulated MRE data with and without Gaussian noise, in both five- and three-parameter formulations.

2 METHODOLOGY

The VFM utilises the principle of virtual work in order to solve for the material properties from a set of full-field displacements (or strains).

\[-\int_V \sigma : \epsilon^* dV + \int_S T : u^* dS + \int_V b \cdot u^* dV = \int_V \rho \omega^2 \cdot u^* dV \quad (1)\]

The test function \((u^*)\), in this case a complex valued harmonic displacement field, was set to zero on the boundaries, eliminating the boundary traction term \((\int_S T : u^* dS)\). Body forces \((b)\) were assumed to be negligible and the forcing frequency was assumed to be the same as the resulting displacement frequency. Thus, Equation (1) was simplified to:

\[-\int_V \sigma : \epsilon^* dV = \int_V \rho \omega^2 \cdot u^* dV \quad (2)\]

where \(\sigma\) is the internal stress, \(\epsilon^*\) is the virtual strain field, \(\rho\) is the material density, \(\omega\) is the loading frequency and \(u^*\) is the virtual displacement field.

In the first formulation, all five independent parameters of the elasticity matrix, \(C_{11}, C_{33}, C_{44}, C_{66}\) and \(C_{13}\), were estimated. The internal stress was written as a function of these five unknown parameters multiplied by the measured strains. Since five parameters were estimated, applying five independent virtual displacements fields \((u^*)\) led to a set of five linear equations and five unknowns. One point of difference from [8] is that, in this study, complex measured and virtual displacements were used to represent harmonic displacements rather than time discretized displacement fields. Then, an optimised VFM [9] was implemented which modelled the noise as Gaussian. By assuming an analytic model of noise which is based solely on the applied numeric virtual field, the method obtained the optimal virtual field which minimised the variance in the estimated material properties due to the Gaussian noise in measured displacements. Then, the engineering constants: \(E_1, E_3, G_{12}, G_{13}\) and \(\nu_{13}\), were directly calculated from the inverse of the elasticity matrix.

In the second formulation, the transversely isotropic model was rewritten in terms of four parameters: \(\kappa, G_{12}, G_{13}\) and \(\tau\) [10].

\[
\begin{align*}
C_{11} &= \kappa + \frac{8}{9} G_{12} + \frac{4}{9} \tau \\
C_{33} &= \kappa - \frac{4}{9} G_{12} + \frac{16}{9} \tau \\
C_{44} &= G_{12} \\
C_{13} &= \kappa + \frac{2}{9} G_{12} - \frac{8}{9} \tau \\
C_{12} &= \kappa - \frac{10}{9} G_{12} + \frac{4}{9} \tau \\
C_{66} &= G_{13}
\end{align*}
\quad (3)
\]

Where \(\tau = G_{12} \cdot E_3/E_1\). This formulation lent itself to separating the longitudinal wave motion (dominated by \(\kappa\)) from the shear wave motion. Specialisation conditions were applied to the numeric virtual fields to ensure that the term multiplied by \(\kappa\) was zero, thus, only three parameters were estimated: \(G_{12}, G_{13}\) and \(\tau\).

MRE displacements were simulated in a finite element beam model using a direct steady-state harmonic analysis in Abaqus 6.13 (Dassault Systèmes Simulia Corp., Providence, USA). Fibres were
aligned with the z-axis of the beam and two loads were applied to induce fast and slow shear waves. The reference parameters in the nearly incompressible, TI beam model were: $E_1 = 12.00$ kPa, $E_3 = 36.00$ kPa, $G_{12} = 3.27$ kPa, $G_{13} = 12.00$ kPa and $\nu_{13} = 0.167$.

Figure 1: Beam with two displacement boundary conditions applied to the side ($dy = 1$ mm) and top ($dx = dz = 1$ mm) surface nodes.

### 3 RESULTS AND CONCLUSIONS

The estimated parameters are listed in Tables 1 and 2 below for the beam simulation without noise. The resulting mean and standard deviation of estimated parameters are also reported for cases with 15% added Gaussian noise (30 Monte-Carlo simulations).

<table>
<thead>
<tr>
<th></th>
<th>$E_1$</th>
<th>$E_3$</th>
<th>$G_{12}$</th>
<th>$G_{13}$</th>
<th>$\nu_{13}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beam</td>
<td>12.065 kPa</td>
<td>35.938 kPa</td>
<td>3.292 kPa</td>
<td>12.014 kPa</td>
<td>0.168</td>
</tr>
<tr>
<td>Beam + 15% Gaussian Noise</td>
<td>13.342 ± 0.261 kPa</td>
<td>18.635 ± 82.271 kPa</td>
<td>3.270 ± 0.004 kPa</td>
<td>12.141 ± 0.023 kPa</td>
<td>0.595 ± 0.069</td>
</tr>
</tbody>
</table>

Table 1: Results from five-parameter optimised VFM estimation.

<table>
<thead>
<tr>
<th></th>
<th>$G_{12}$</th>
<th>$G_{13}$</th>
<th>$\tau$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beam</td>
<td>3.278 kPa</td>
<td>12.062 kPa</td>
<td>8.790 kPa</td>
</tr>
<tr>
<td>Beam + 15% Gaussian Noise</td>
<td>3.261 ± 0.002 kPa</td>
<td>12.055 ± 0.026 kPa</td>
<td>8.230 ± 0.276 kPa</td>
</tr>
</tbody>
</table>

Table 2: Results from three-parameter optimised VFM estimation.

For the five parameter estimation method without noise, all parameters were estimated accurately (less than 1% error from true parameters). In the Monte-Carlo simulation with added Gaussian noise, both shear moduli were estimated accurately. The transverse Young’s modulus ($E_1$) was overestimated slightly but still showed little variance. The fibre Young’s modulus and Poisson’s ratio, however, were not estimated accurately, and varied widely between noise samples.

When identifying three parameters from the MRE displacement field, the two shear parameters were identified accurately, whereas the $\tau$ parameter, representing the anisotropic tensile ratio, was underestimated ($\tau_{true} = 9.81$ kPa). With added Gaussian noise, the two shear moduli were still estimated accurately. The estimated $\tau$ parameter from data with Gaussian noise varied little but was always underestimated.
Since the beam material is nearly incompressible ($\nu_{31} = 0.49999$), $C_{11}$, $C_{33}$ and $C_{13}$ go towards infinity. Therefore, the linear problem to solve in the five parameter estimation method was poorly conditioned. The three parameter estimation has the advantage that the parameters being estimated are not dependent on the Poisson’s ratios and are on similar scales, making the problem well-conditioned. Despite this fact, the anisotropic tensile ratio parameter ($\tau$) was consistently under-estimated, even in the case without noise.

These results are consistent with [4], in which the tensile anisotropic ratio was not well-estimated. Further research is required to determine the reasons for this behavior. The optimised VFM, however, has been shown to be capable of estimating transversely isotropic material parameters from MR elastography displacement fields.

**REFERENCES**


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VALIDATION OF FULL FIELD MEASUREMENT OF AORTIC WALL MOTION BY 4D-ULTRASOUND

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SUMMARY

Time-resolved three-dimensional ultrasound combined with speckle tracking algorithms (4D ultrasound) is a non-invasive medical imaging technique that provides full field displacement data of aortic and aneurysmal wall motion in vivo. Combined with inverse techniques to identify the parameters of an orthotropic and nonlinear elastic constitutive equation, this data type has the potential to overcome known limitations in the identification of the individual constitutive behavior of the human aortic and aneurysmal wall in a clinical setting. In this study results of the validation of 4D ultrasound displacement measurement are presented. Spearman’s Rank correlation between measurements of the cyclic diameter change of a pressurized specimen of porcine aorta by 4D-ultrasound and by two CMOS cameras is highly significant. The relative error for measurements of displacements of about 1 mm as are observed in vivo in young volunteers as well as in atherosclerotic and aneurysm patients is 10% and below, only. Analysis of human in vivo data shows that 3D-displacements of this size are observed in the majority of volunteers and patients, regardless of age, atherosclerosis, or existence of an aortic aneurysm. The validation study shows that 4D ultrasound is a reliable non-invasive imaging method for the acquisition of full field displacement data in vivo in the physiologically relevant order of magnitude.

Key words: 4D ultrasound, full field measurement, aorta, validation

1 INTRODUCTION

The knowledge of the individual anisotropic and nonlinear-elastic properties of the human aortic and aneurysmal wall is a requirement for reliable patient-specific wall stress analyses. The observation of the change of these properties over time may provide insight in the growth, remodeling and aging effects in biological tissues.

Often, only two load cases can be observed in a clinical setting since the possibilities of non-invasive blood pressure measurement are limited. Mostly, only diastolic and systolic values of transmural pressure are available from sphygmomanometry. Parameter identification of an orthotropic and non-linear hyperelastic constitutive equation that is appropriate for modeling the constitutive behavior of the aneurysmal wall tends to be an ill-posed problem in such cases. It has been shown that the use of heterogeneous displacement or strain fields is an appropriate means to improve the reliability of constitutive parameter identification based on the observation of only few load cases [1,2].

4D ultrasound is a non-invasive medical imaging technique that provides fields of trajectories of discrete material points of human soft tissues in a Lagrangian reference frame. Using a modified commercial 3D echocardiography device, the authors have established this technique for imaging
heterogeneous displacement and strain fields of the aortic and aneurysmal wall [3,4] and have proposed a Finite Element Model Updating workflow for the identification of the parameters of an orthotropic and non-linear elastic constitutive equation [5] based on these data [6,7]. Since constitutive parameter identification based on full field data is sensitive to uncertainties or systematic deviations in the data [1], the authors present the results of a validation study of 4D ultrasound displacement measurement in this paper.

2 METHODOLOGY

Using a custom-built inflation-extension testing device, a tubular specimen of porcine aorta with dimensions of 15 mm x 130 mm (luminal diameter x length) was loaded physiologically by axial prestretch that was held constant, and a cyclic pressure amplitude that was applied with a frequency of 1 Hz. In 11 experiments, constant axial prestretches of 1.31, 1.42, and 1.61 and pressure amplitudes ranging from 12 mbar to 120 mbar were applied resulting in diameter changes from 0.19 mm to 3.66 mm. All experiments were performed in physiological saline solution at 37°C in order to provide acoustic properties of the medium that are close to the in vivo conditions, in particular the sound velocity of 1540 m/s in human soft tissue. The cyclic deformation of the specimen was measured in parallel by 4D ultrasound and optically capturing a field of view of about 30 mm in longitudinal direction of the specimen. Temporal resolution of optical and ultrasound measurements was about 40 images/s. Three-dimensional deformation of the specimen’s luminal surface was measured by use of a commercial customized 4D ultrasound device (Artida, Toshiba Medical Systems, Otawara, Japan) that was equipped with a 3D transthoracic probe (Toshiba, PST-25SX, 3.5 MHz phased array matrix transducer) resulting 3D displacement fields of up to 1080 material points that are distributed regularly over the specimen with distances of about 1 mm between two material points in longitudinal and circumferential direction [3,7]. Simultaneously, the deformation of the specimen was measured optically by two 8-bit CMOS cameras with a resolution of 1280 x 1024 pixels. The specimen was prepared with an irregular optically visible speckle pattern. Diameter change and 2D displacement fields of the the outer wall surface were determined in the two 2D views that were orthogonal to each other. An in-house threshold-based edge detection method and a DIC code proposed by [8] were used for these purposes, respectively. Both were coded using MATLAB (The Mathworks, Inc., Natick, Massachusetts, USA). Diameter change and 2D displacement fields in projection planes corresponding to the optical measurements were extracted from three-dimensional ultrasound data and registered on the optical 2D data. Spearman’s Rank Correlation was calculated for the comparison of diameter change over one pressure cycle. The deviation of the diameter amplitudes and the displacement fields between the minimum and maximum diameter configurations of the specimen were determined.

Fig. 1: Comparison of the 4D-ultrasound and optical reference measurement of cyclic the diameter change of a tubular specimen of porcine aorta load with pressure amplitudes and axial prestrain: (a) \( \Delta p = 120 \) mbar, \( \varepsilon_{\text{ax}} = 47\% \), (b) \( \Delta p = 36 \) mbar, \( \varepsilon_{\text{ax}} = 41\% \), and (c) \( \Delta p = 20 \) mbar, \( \varepsilon_{\text{ax}} = 47\% \).

3 RESULTS AND CONCLUSIONS

The chosen load cases resulted in two distinct groups of experiments: three experiments showed diameter changes of > 2 mm corresponding to displacements > 1 mm (“large deformations”), whereas all other load cases resulted in diameter changes of < 0.8 mm corresponding to displacements < 0.4 mm (“small deformations”).
Spearman’s Rank correlation was highly significant \((p < 0.01)\) for all load cases and all observed sizes of diameter change. Correlation coefficients \(> 0.99\) were obtained for large deformations, whereas correlation coefficients ranged between 0.89 and 0.93 for small deformations. Fig. 1 shows diameter change over time curves for three exemplary load cases.

Fig. 2: Exemplary 2D displacement fields obtained by (a) 4D ultrasound and by (b) optical measurement with speckle tracking. (c) shows the experimental arrangement for the simultaneous 3D displacement measurement by ultrasound and two optical 2D displacement measurements of an aortic specimen in vitro.

Fig. 2 shows the good agreement between 2D displacement fields obtained by optical measurements and by 4D ultrasound for an experiment with large deformations. Average deviation between 4D ultrasound and optical displacement measurement is between 0.05 and 0.1 mm for large displacements and < 0.05 mm for small displacements. This results in relative errors of 10% and below for large displacements. In contrast, relative errors may exceed 30% for small displacements. Fig. 3 shows that 4D ultrasound tends to overestimate large displacements and underestimate small displacements.

Fig. 3: Bland-Altman plot showing the size of the average deviation between displacement measurement by 4D ultrasound and by optical measurement (vertical axis) and the dependency on the size of the measured displacements (horizontal axis). C01 to C11 refer to validation experiments where a porcine aortic sample was exposed to different combinations of axial prestretch \((1.31, 1.42, 1.61)\) and transmural pressure ranging from 12 mbar to 120 mbar.

In order to rate these results, the authors evaluated in vivo 3D displacements and in-plane strains of the infrarenal aortic segments of young volunteers without known cardiovascular diseases \(< 60\) y.o., \(n = 20\), patients with atherosclerosis \((> 60\) y.o., \(n = 20\)), and patients with abdominal aortic aneurysms \((\text{AAA}, > 60\) y.o., \(n = 20\)). The atherosclerotic and the aneurysmal patient groups showed considerable stiffening of the wall tissue indicated by a significant reduction in circumferential strain compared to the group of healthy volunteers [4]. Despite this, the median value of cyclic 3D displacements – which are the primary measured values of 4D ultrasound – are of a similar size in all three groups (young: median \([1^{\text{st}}\text{ quartile}, 3^{\text{rd}}\text{ quartile}] = 0.89 [0.77, 1.06] \text{ mm}, \text{atherosclerotic}: \)
1.00 [0.56, 1.36] mm, AAA: 0.98 [0.77, 1.28] mm). I.e. for the majority of patients and volunteers in all groups large average displacements are observed in vivo. In 86% of the investigated AAA average displacements exceeding 0.7 mm were observed (0.99 mm [0.88 mm, 1.31 mm]). In these data sets 15.5% [5.9%, 36.6%] of the material points showed displacements smaller than 0.7 mm, and 2.9% [0.7%, 11.8%] of the material points showed displacements smaller than 0.5 mm. In future work, the impact of the identified measurement uncertainties on results of the FEMU approach to constitutive parameter identification will be examined. Based on this, criteria for the exclusion of in vivo data sets will be defined.

REFERENCES

INVERSE ANALYSIS AND HYBRID VERTEX/CELL-CENTRED MODEL FOR EMBRYO MORPHOGENESIS

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SUMMARY

We present the application of customised Particle Image Velocimetry (PIV) and mechanical inverse analysis for the computation of the traction field during morphogenesis of the central nervous system in Drosophila fly. From a set of confocal images at different time instants we retrieve a set of displacements on a set of discrete locations. These displacements are in turn used to compute the traction field and the displacements on the whole domain. We also present the forward analysis using a hybrid cell-centred and vertex model for the analysis of wound healing in Drosophila wing disk. Special attention is paid to the remodelling events, which are handled with an equilibrium preserving map that maintains the nodal/vertex tractions between connectivity changes.

Key words: inverse, morphogenesis, central nervous system, vertex, cell-centred, wound healing

1 INTRODUCTION AND METHODOLOGY

1.1 Particle Inverse Analysis (PIV)

We here develop a three-dimensional image correlation technique for the analysis of z-stacks of two dimensional confocal images at different time instants during embryonic development of Drosophila fly. The displacement $u_0$ of glial cells of the central nervous system (see green particles in Figure 1) are tracked.

Figure 1: Experimental confocal images during embryo development of central nervous system (in green).

Figure 2: Left: arrows showing retrieved displacements $u_0$ from three-dimensional images on confocal domain. Centre: deformed domain according to computed displacements $u_1$. Right: computed tractions $t$. 
1.2 Mechanical Inverse analysis

The displacement \( u_1 \) at the remaining nodes of the domain and the tractions \( t \) that best fit mechanical equilibrium are computed by solving the following minimisation problem,

\[
(t, u_1) = \arg\min_{t, u_1} J(t, u_1),
\]

with

\[
J(t, u_1) = ||K_0 u_0 + K_1 u_1 - A t||^2.
\]

Here, matrices \( K_1 \) and \( K_0 \) are standard stiffness finite element matrices, and \( A \) is a loading matrix that converts the nodal tractions into nodal forces. Due to the assumption of incrementally small displacements and linearity of the material, the resulting normal equations are linear, and can be solved in an uncoupled manner for \( u_1 \) and \( t \). Also, it can be proved that as far as \( m \equiv \text{dim}(T) \leq n_0 \equiv \text{dim}(U_0) \), i.e., the number of traction degrees of freedom is not greater than the number of applied displacements, the system of equations is stable and does not require regularisation for the nodally interpolated traction field [3].

1.3 Forward Vertex/Cell-centred analysis

We present also a hybrid cell-centred/vertex model where non-linear elastic potentials \( \Psi_x \) and \( \Psi_v \) are respectively defined between any two neighbouring cell-centres (nodes) \( x_i \) and between two vertices \( y_I \) on a cell-cell boundary (vertices). Vertices are located using standard finite element interpolation \( y_I = N_i(\xi_I) x_i \) (see Figure 3). The nodal positions are found by minimising the total energy \( \Psi = \Psi_x(x) + \Psi_y(y(x)) \), with respect to \( x \) and keeping \( \xi_I \) constant and equal to \( \xi_0 = \{1 1\}/3 \), which corresponds to locate the vertices at the barycentres of the underlying triangulation. This minimisation yields a set of non-linear equations, which are solved with an iterative Newton-Raphson process.

The resting length \( L \) of each cell-centred and vertex element is also allowed to vary according to the evolution law

\[
\dot{L} = \gamma (\varepsilon^e - \varepsilon^c)
\]

with \( \varepsilon^e \) the elastic strain, and \( \varepsilon^c \) the cell contractility. This parameter controls the strain at which no more changes in the resting length occur, and aims to mimic internal remodelling and the cell contractile homeostatic state [2].

In order to handle the cell-cell connectivity changes, we have implemented an equilibrium preserving map which recomputed the resting length of all the elements in order to maintain the same nodal and vertex resultant between remeshing events. The latter consists on a Delaunay triangulation of the nodes (cell-centres) and locating the vertices at \( \xi_0 \) or at the straight line between neigbouring vertices. Further imposition of area constraint and relaxation of the parameter \( \xi \) allows us to simulate the wound healing process in Drosophila fly wing disk (see the Results section).

2 RESULTS

The analysis of the domain in the central nervous system has been carried out from confocal images. The computed (self-equilibrated) tractions on a sequence of time-steps is an indicator of the cell-cell activity, which reveals some oscillations in their mechanical response (see Figure 4). The origin and regulation of this oscillations is currently under investigation.

We have also used the vertex model described in subsection 1.3 on a squared domain with around 100 cells. We have ablated 5 cells, and imposed a contractility around the cells at the leading edge of the wound. The internal ablated cells have been assigned a very low stiffness at their vertex bar neighbouring ablated-ablated cells, and the nodal bars connecting ablated-living and ablated-ablated
cells. By imposing a constant contracility we managed to simulate the wound closure up to a point where lamellipodia is needed (see Figure 5).

In order to better represent the rounded edge of the wound, the values of $\xi$ are allowed to vary, giving rise to a purely vertex model on some regions of the domain.

Figure 5: Numerical results of wound healing simulations with in silico ablated five cells. Contractility is additionally applied on the wound edge.

3 CONCLUSIONS AND FUTURE WORK

We aim to also apply the inverse analysis to the planar and three-dimensional images of wound healing. This task involves the extension of the vertex model to three-dimensions and the inverse methods to non-linear problems, which requires solving the non-linear normal equations iteratively.

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CLASSIFYING STRESS STRAIN CURVES OBTAINED AT RUPTURE AND NON-RUPTURE SITES IN ASCENDING THORACIC ANEURYSM TISSUE USING MACHINE LEARNING

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SUMMARY

In a previous study, the authors and collaborator have collected a large number of tension-strain curves from ascending thoracic aneurysm (ATAA) tissues in vitro. The curves were obtained at different locations in tissue samples, some at rupture sites and most from non-rupture sites. A question arises as to whether the curves at rupture and non-rupture sites are statistically different. In this work, we employ a k-Nearest Neighbors algorithm to classify the curves. A model that can differentiate curves from rapture and non-rupture locations has been established. The accuracy of the classification is evaluated by 10-fold cross validation.

Key words: ATAA, rupture, k-Nearest Neighbors

1 INTRODUCTION

Abnormal widening or ballooning in the root of the ascending aorta is called ascending thoracic aortic aneurysm (ATAA). It affects approximately 10 out of 100,000 persons per year [1] and is ranked the 15th leading cause of death in individuals aged 65 years together with abdominal aneurysm [2]. A typical ATAA grows silently over many years until sudden dissection or rupture causing life-threatening internal bleeding [3]. Study has shown that the mortality rate of the ruptured ATAA is so high that only forty-one percent of the patients were alive on arrival at an emergency hospital, and the overall mortality rate was 97% to 100% [4]. Early diagnosis and surgical treatment to prevent dissection or rupture can lower mortality to only 3-5% [5]. To prevent the ATAA rupture, evaluating the rupture potential is critical. From a biomechanical point of view, rupture happens when the local wall stress causing by blood pressure and other loadings exceeds the strength of the wall tissue. To investigate the local conditions of ATAA tissue, the authors and collaborators [6, 7, 8] have developed a combined experimental and computational approach to obtain the full field tension, strain and material properties. The study revealed that the rupture location is highly correlated to the local elastic properties. The finding confirmed an observation [9] that certain features in the stress-strain curve are suggestive of rupture risk and thus the features may be utilized to evaluate rupture risk. However, these features may not be easily observed. In this study, we leverage a large database of ATAA stress strain curves collected in a previous study, and apply a k-Nearest Neighbors algorithm to classify the curves and search possible patterns.

2 METHODOLOGY

2.1 Rupture Location Identification

Full field tension strain data were identified in a previous study [6, 7, 8]. Tissue sample of 2×2 cm² were meshed into approximately 400 elements each and the tension strain data at each Gauss point in the mesh were identified. A typical tension-strain curve is shown in Fig. [1(a)]. Material parameters were then obtained by performing constitutive regression. The Gasser-Ogden-Holzapfel
(a) Tension-strain curve; $t_{11}, t_{22}, t_{12}$ are three components of in-plane tension; $\lambda_{1,2}$ are the in-plane stretches

(b) $\mu_1$

(c) $\mu_2$

(d) $\gamma$

(e) $\kappa$

(f) Fiber angle

**Figure 1**: Tension-strain curve and material parameters distribution

(GOH) model was used to fit the tension-strain data:

$$w = \frac{\mu_1}{2} (I_1 - \ln (I_2) - 2) + \frac{\mu_2}{4\gamma} \left(e^{\gamma(I_1-1)^2} - 1\right)$$

(1)

Here $I_1 = \text{tr} \ C$ and $I_2 = \det C$ are the principal invariants of the Cauchy-Green deformation tensor and $I_\kappa = C : (\kappa I + (1 - 2\kappa) \ M \otimes M)$ is a compound invariant consisting of isotropic and anisotropic contributions. In the compound invariant $I_\kappa$, the unit vector $M$, parameterized by the angle its makes to the horizontal axis, defines the orientation of the collagen fibers in the reference configuration while $\kappa$ characterizes the angular dispersion of the fibers. There are five material parameters in the model, i.e. $\mu_1, \mu_2, \gamma, \kappa, \theta$. The material parameters were identified by constitutive regression individually at each Gauss point. The parameters were found to be highly heterogeneous; an example of parameter distribution is presented in Figures 1(b) - 1(f). Ten samples were characterized; domain average $R^2$ value is from $0.93 \sim 0.99$, indicating an excellent fitting quality. Hence, each set containing the five parameters can be treated as the characteristic of the corresponding curve. The material set is used as the classifier. Rupture location was identified from the photo image of the second last loading step (the one immediate preceding rupture), or the post rupture image if the one before does not show distinct cracks. The average values of the horizontal and vertical directions of the crack were assumed to be the location of rupture initiation, that is the rupture site. The material parameters inside a small window containing the rupture site are used to defined the mechanical properties at the rupture site.

### 2.2 $k$-Nearest Neighbors Algorithm

The $k$-Nearest Neighbors ($k$-NN) algorithm is a non-parametric approach used for classification and regression [13]. In $k$-NN, an object is classified by taking consideration of the similarity to its neighbors. The object will be assigned to the class which is the most common among its $k$ nearest neighbors ($k$ is a positive integer, typically small). $k$-NN is a instance-based learning, or lazy learning algorithm,
Table 1: Material parameters table

<table>
<thead>
<tr>
<th>Element (Gauss point)</th>
<th>$\mu_1 (\text{N/mm})$</th>
<th>$\mu_2 (\text{N/mm})$</th>
<th>$\gamma$</th>
<th>$\kappa$</th>
<th>$\theta$</th>
<th>Rupture label</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(1)</td>
<td>0.00</td>
<td>1.85</td>
<td>15.05</td>
<td>0.17</td>
<td>1.79</td>
<td>NON-RUPTURE</td>
</tr>
<tr>
<td>1(2)</td>
<td>0.02</td>
<td>1.61</td>
<td>9.67</td>
<td>0.34</td>
<td>1.05</td>
<td>NON-RUPTURE</td>
</tr>
<tr>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>179(1)</td>
<td>0.00</td>
<td>0.87</td>
<td>9.55</td>
<td>0.47</td>
<td>0.57</td>
<td>RUPTURE</td>
</tr>
<tr>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

Table 2: Cross validation with different number of neighboring points

<table>
<thead>
<tr>
<th>Number of Neighbors</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-fold Loss Rate</td>
<td>3.38%</td>
<td>3.04%</td>
<td>3.06%</td>
<td>3.06%</td>
<td>3.02%</td>
<td>2.89%</td>
<td>2.84%</td>
<td>3.06%</td>
<td>2.82%</td>
</tr>
</tbody>
</table>

where all computation is deferred until classification and the function is only approximated locally. In this work, the training parameters are considered as vectors in a multidimensional feature space defined by the material set, each with a class label. Material sets in rupture location are labeled as “RUPTURE” and the ones in non-rupture are labeled as “NON-RUPTURE”, correspondingly. In the training phase, the vectors of the labeled material sets are stored in the material parameters table. Sample table is shown in Table 1. In the classification phase, a query point is classified by assigning the label which is the most frequent among the $k$ training parameters nearest to that query point. Here, $k$ is a user-defined constant. There are many distance metrics in $k$-NN. In the present work, the Euclidean distance is used to estimate the multidimensional distance.

2.3 N-fold cross validation

The classification was validated using 10-fold cross validation. In an $N$-fold cross validation, the original data set was randomly partitioned into $N$ equal sized subsets. A single subset among the subsets was retained as the validation data for testing the model, and the rest $N-1$ subsets were used as training data. The cross validation process was then repeated $N$ times (the folds), with each of the $N$ subsets used exactly once as the validation data. The $N$ results from the folds were averaged to produce a single estimation. The 10-fold cross validation is most commonly used [14] and is adopted in this study.

3 RESULTS AND CONCLUSIONS

4609 material sets from two patients are used to train the model. Among them, there are 162 sets from rupture locations and 4447 sets from non-rupture locations. 10-fold cross validation is employed to evaluate the model. The number of neighbors, $k$, plays an important role in the validation. However, there is no fixed rule on selection of parameter $k$. It usually depends on size of data. To assess the influence of $k$, the validation results from different $k$ were calculated and are presented in the Table 2. The loss rate is defined as percentage ratio of the number of missing prediction by the model and the total number of tested data set. Generally, larger values of $k$ can reduce the loss rate on the classification, but potentially blur the class boundary. As can be seen from the table, the loss rate trend from $k=1$ to $k=9$ is decreasing with some oscillations. The average loss rate is very small (~ 3%). The result indicates that the model trained by the $k$-NN algorithm is decently good. The fact that the data sets came from two different patients indicates that the $k$-NN model may be able to handle intra-subject situation. However, the patient number is too small to be conclusive. With more data from more patients in the future, the model can be improved and can be evaluated against the potential to identify rupture-like responses.

REFERENCES


ESTIMATION OF IN VIVO MECHANICAL PROPERTIES OF THE AORTIC WALL

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SUMMARY

The aortic wall is always loaded in vivo, which makes it challenging to estimate the material constants of its nonlinear, anisotropic constitutive equation from in vivo image data. Previous approaches largely rely on computationally expensive, inverse finite element models. This abstract presents two methods that are accurate and of low computation cost: 1) the stress computation based method and 2) the multi-resolution direct search method. The first method builds the objective function upon stress fields, which can be solved directly from constitutive equations. In the multi-resolution direct search approach, data-driven techniques and direct search strategy are applied to find the optimal parameters. Numerical experiments were performed for validation and comparison of these two methods.

Key words: material parameter estimation, statically determinate, principal component analysis

1 INTRODUCTION

Numerical estimation of the material parameters often employs the inverse techniques. However, from biomechanics prospective, the configuration from in vivo images is always loaded, which makes it challenging to estimate its constitutive parameters from in vivo image data. A well-adopted approach for the characterization of the in vivo properties typically follows the steps of 1) recover or estimate the unpressurized geometry, 2) deform the geometry in finite element (FE) simulations with in vivo loading and boundary conditions with estimated constitutive parameter, and 3) by using certain optimization methods, the estimated constitutive parameters will be adjusted, and optimal parameters will be identified such that some physical measurements (e.g. strain/displacement) are matched between the simulated, deformed configuration and the in vivo loaded configuration. Using such strategies, Wittek et al. [1, 2] developed two methods to determine patient-specific material parameters of the human aorta from in vivo strain measurement. However, since a large number of FE iterations are needed to reach the optimal solution, these methods are very time consuming. For example, in the study reported in [1, 2], it took about 1-2 weeks to find the optimal parameters. In this abstract, we propose two methods for inversely estimating the constitutive parameters of the aortic wall. The stress computation based method utilizes some special conditions (mesh correspondence, statically determinate, see Table 2 for details) to build the objective function upon stress fields which can be solved directly from constitutive equations and make it possible to avoid costly FE simulations. However, if the in vivo data does not provide such information, the finite element framework would still be applicable. To reduce the number of iterations, a multi-resolution direct search method is developed where data-driven techniques are applied to preselect candidate material parameters, and a direct search strategy is used to find the optimal parameters.

2 METHODOLOGY

1.1 Constitutive model
The Holzapfel–Gasser–Ogden (HGO) model from [3] was used to model the constitutive response of aortic wall tissue. The strain energy function is expressed by

$$\Psi = C_{10} (I_1 - 3) + \frac{k_1}{2k_2} \sum_{i=1}^{2} \left[ \exp\{k_2 [\kappa I_1 + (1 - 3\kappa) \bar{I}_4] - 1 \} \right] - 1 + \frac{1}{D} \left[ J^{p-1} - \ln J \right]$$  \hspace{1cm} (1)

A parameter $\theta$ defines the angle between mean local fiber direction and the circumferential axis of the local coordinate system. The five material parameters $(C_{10}, k_1, k_2, \kappa, \theta)$ will be estimated from in vivo imaging data by using the methods proposed in section 1.2 and 1.3.

1.2 The stress computation based method

The parameter estimation process of the first method is shown in Figure 1. This method assumes that the displacement field from diastole to systole is known (i.e. mesh in the diastolic and systolic phase should have the same correspondence). It utilizes the fact that the stress field of the aortic wall is approximately determined by the geometry and blood pressure load, and weakly depends on material properties, which has been theoretically justified by Miller and Lu [4] and numerically verified by Joldes et al [5].

Given the deformed configurations of the aortic wall at 2 cardiac phases, $\mathbf{x}_a$ at the diastole phase and $\mathbf{x}_b$ at the systole phase, the “almost-true” stress of each element $m$ of the aortic wall at the 2 phases, $\sigma^m_a$ and $\sigma^m_b$ respectively, are calculated by using an infinitesimal finite element method with a very stiff material. The relative deformation gradient $F_{ab}^m$ from the diastolic configuration to the systolic configuration is calculated by using the relative displacement field $\mathbf{u}_{ab}$ between the two configurations. Then, using the candidate constitutive parameters $(C_{10}, k_1, k_2, \kappa, \theta)$, the systolic stress can be estimated. The estimated $\sigma^m_{b, est}$ is then compared with the “almost-true” systolic stress $\sigma^m_{b}$, and any discrepancy will indicate that the candidate parameters are different from the optimal parameters and hence need be adjusted by nonlinear optimization algorithms.

$$f = \sum_{m=1}^{N} \sum_{i=1}^{3} \sum_{j=1}^{3} w_{ij} \left[ \sigma^m_{b,i,j} - \sigma^m_{b,est} \right] \left( C_{10}, k_1, k_2, \kappa, \theta \right)^2$$  \hspace{1cm} (2)

where $N$ is the number of elements used in the optimization, $ij$ is the component index of a 3×3 matrix/tensor, $w_{ij}$ is the weighting factor, if $i = j, w_{ij} = 1/6$, if $i \neq j, w_{ij} = 1/12$. By solving this optimization problem, the optimal parameters $(C_{10}, k_1, k_2, \kappa, \theta)$ can be obtained.

1.2 The multi-resolution direct search method

Without the special requirements (i.e., mesh correspondence, statically determinate), we developed another method by using finite element (FE) and multi-resolution direct search, which is illustrated
in Figure 2. Using backward displacement method, the unpressurized geometry is recovered from diastolic geometry. The estimated systolic geometry is obtained by applying systolic pressure to the unpressurized geometry. The goal is to adjust the constitutive parameters to minimize the node-to-surface distance between the “true” systolic geometry and FE-deformed systolic geometry

\[ g = \sum_{n=1}^{M} \sum_{i=1}^{N} |x^n_{b,i} - x^{n,est}_{b,i} | \]

where \( n \) is the index of a node in the aorta meshes and \( M \) is the number of nodes; \( x^n_{b,i} \) is the 3D nodal position at the systolic phase from in vivo imaging. The nearest point to \( x^n_{b,i} \) on the FE-deformed aorta surface is \( x^{n,est}_{b,i} \).

We developed an optimization algorithm using the multi-resolution direct search which can significantly speed up the process. Specifically, the parameters \( \left(C_{10}, k_1, k_2, \kappa, \theta\right) \) are represented in the space derived from the principal component analysis (PCA) on the stretch-stress curves. Then, the space is uniformly sampled with 4 different layers (i.e. resolutions), from coarse to fine. In the top layer, a number of 12 points (i.e. representatives) were sampled from PCA space, which corresponds to 12 sets of constitutive parameters. A total of 117, 1197 and 10529 points were sampled in the second, third and bottom layer respectively. Next, the links between the points at two adjacent resolutions were established by using local neighbor searching method, which produces about 20 links from a point in a layer to the points in the next layer. As a result, every point from the top resolution is linked to points in the bottom resolution. The direct searching starts from the top layer by evaluating the 12 candidate parameters, and the best parameters will be identified by evaluating the objective Eq.(3). The searching starts again from the second layer by only evaluating the points linked to the best point in the first layer. Once the searching process reaches the bottom layer, the best point will be identified, which gives the best constitutive parameters.

3 RESULTS AND CONCLUSIONS

We validated the two methods by numerical experiment using data of an ascending aortic aneurysm patient. The “true” parameters were derived from bi-axial tensile test. The geometry of the aorta at systolic phase was reconstructed from 3D CT images. By using the “true” parameters and the reconstructed geometry, the unpressurized geometry was obtained by using the backward displacement method [6]. The unpressurized geometry was inflated in FE under the diastolic blood pressure to obtain the geometry at the diastolic phase. The reconstructed systolic geometry and the FE-generated diastolic geometry were treated as “true” data to evaluate the methods.

Figure 3 Stretch-stress curves in 3-protocol numerical stretch-controlled tensile experiments. (a) (b) and (c) from stress computation based method, (d) (e) and (f) from multi-resolution direct search method. 1) strip biaxial tension in the circumferential direction (a) and (d); 2) equi-biaxial tension (b) and (e); 3) strip biaxial tension in the longitudinal direction (c) and (f).

To evaluate the result, numerical stretch-controlled 3-protocol biaxial tensile experiments were performed in MATLAB with the estimated parameters and the “true” parameters, and the stress and
stretch at the circumferential direction (subscript “1”) and longitudinal direction (subscript “2”) were recorded. For each patient, we obtained \( \sigma_1 \) and \( \sigma_2 \) using 3 protocols of numerical experiments: 1) in the circumferential strip biaxial tension, we fixed \( \lambda_2 = 0 \) while increasing \( \lambda_1 \); 2) in the equi-biaxial tension, we kept the ratio \( \lambda_1/\lambda_2 = 1 \); 3) in the longitudinal strip biaxial tension, we fixed \( \lambda_1 = 0 \) while increasing \( \lambda_2 \).

<table>
<thead>
<tr>
<th></th>
<th>( C_{10} ) (kPa)</th>
<th>( k_1 ) (kPa)</th>
<th>( k_2 )</th>
<th>( \kappa )</th>
<th>( \theta (\degree) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>“True”</td>
<td>29.91</td>
<td>512.56</td>
<td>0.00</td>
<td>0.3190</td>
<td>90.00</td>
</tr>
<tr>
<td>Stress based</td>
<td>33.52</td>
<td>512.32</td>
<td>0.01</td>
<td>0.3160</td>
<td>86.82</td>
</tr>
<tr>
<td>Multi-resolution</td>
<td>5</td>
<td>300</td>
<td>0.00</td>
<td>0.2000</td>
<td>45.00</td>
</tr>
</tbody>
</table>

Table 1 “True” and estimated parameters from the two methods

The estimated parameters are shown in Table 1, and the corresponding stretch-stress curves from the numerical 3-protocol biaxial experiments are shown in Figure 3. The material parameters and stretch-stress curves have been successfully recovered.

<table>
<thead>
<tr>
<th>Prerequisite and performance</th>
<th>Stress based</th>
<th>Multi-resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>In vivo loaded geometries at 2 phases needed?</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Mesh correspondence of 2 phases needed?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Wall thickness assumptions</td>
<td>Measurement or assumptions at the 2 phases</td>
<td>Assume constant at unloaded configuration</td>
</tr>
<tr>
<td>Statically determinate structures needed?</td>
<td>Yes (e.g. aortic wall)</td>
<td>No (e.g. aortic wall, heart valves)</td>
</tr>
<tr>
<td>FEA needed iteratively?</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Time cost on a desktop (quad-core CPU and 32 GB RAM)</td>
<td>1-2 hours</td>
<td>1-2 days</td>
</tr>
<tr>
<td>Accuracy</td>
<td>Very well</td>
<td>Reasonably well</td>
</tr>
</tbody>
</table>

Table 2 Comparisons between the two methods

Comparisons of the two methods are listed in Table 2. Generally, the stress computation based method is faster and more accurate, but it requires the mesh correspondence condition and is only applicable to statically determinate structures such as the aortic wall. When these conditions are absent, e.g. mesh correspondence is not available or for applications such as heart valves, the multi-resolution direct search method will use the framework of updating FE to estimate the material parameters with acceptable speed and accuracy.

REFERENCES

Intracranial Aneurysms: Connecting Hemodynamics, Biomechanics & Wall Characteristics III
EXPERIMENTAL INVESTIGATION OF TRANSITIONAL FLOW IN CEREBRAL ANEURYSMS

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SUMMARY

The onset of transitional flow in cerebral aneurysms has previously been demonstrated in numerical simulations but it remains to be seen if this phenomenon is present in vivo as the detection of such flow fluctuations is difficult with the resolution of modern imaging. Here, we experimentally investigate the presence of transitional flow in physical models of aneurysms previously studied in numerical simulations. We detect the presence of transition in aneurysms through wall vibrations recordable by a microphone, and correlate it with the flow fluctuations detected in numerical simulations.

Key words: aneurysm, transitional flow

1 INTRODUCTION

Computational fluid dynamics (CFD) has demonstrated its ability to discriminate cerebral aneurysms based on their rupture status by computing flow dependent forces that act in aneurysms [1]. Recent CFD simulations have predicted the presence of a flow regime in aneurysms that, in spite of the low Reynolds number in the parent artery, is not laminar but exhibits high frequency fluctuations which resemble transitional flow [6]. The presence of such a flow regime in aneurysms in vivo, however, can only be ensured by extensive validations. Recent comparisons of CFD and phase contrast magnetic resonance (PC-MR) imaging [4] depict a close resemblance between PC-MR and CFD for aneurysms in which numerical simulations predict laminar flow, while vivid differences are reported for aneurysms with transitional flow. Such studies improve the confidence in the accuracy of CFD and suggest the requirement of high resolutions in simulations for the capture of such a flow.

In the study at hand, we aimed to investigate the presence of transitional flow by conducting experiments on the physical models of the same aneurysms that were previously studied in numerical simulations [6, 2], and to check whether the flow fluctuations were detectable through a microphone (i.e. via pseudo-sound produced by aneurysm wall-vibrations) and X-ray PTV measurement, and if so, whether the intensity of flow fluctuations correspond to previous numerical simulation studies.

2 METHODOLOGY

Two previously studied aneurysms, one with transitional flow shown in figure 1a, and another with laminar flow were developed in multiple sizes and materials. We denote them as Model A and Model B following [2]. All models were rigid but the roughness varied among the models. From a previous direct numerical simulation study, which was conducted using a lattice Boltzmann method [2, 5], it was known that the flow inside the aneurysm transitioned to a weakly turbulent regime at Re=351 in one of the aneurysms while it remained laminar up to at least Re=650 in the second model. These findings were under stationary inflow conditions, and the simulations resolved the smallest scales that can appear in a turbulent flow, namely the Kolmogorov micro-scales [2, 5].

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In the present experiments, the flow was gravity driven and consisted of a 10 litre container elevated roughly 2 metres above the aneurysm model, with a 3 litre container used to catch the water. Although other driving mechanisms e.g. pumps were considered, the gravity driven flow was given precedence for its simplicity, and to avoid spurious noise in the acoustic measurement.

Data acquisition for the acoustic method was performed using a National Instruments myDAQ and an in-house built amplifier previously determined to be linear. The amplifier included an analog second order low pass filter, limiting measured frequencies to less than 4096 Hz, and the sampling frequency was set to 16384 Hz. Welch's periodogram method was used to estimate the Power Spectral Densities (PSDs) and 218 data points were found sufficient.

A block diagram of the stereographic X-ray setup can be seen in figure 1b. The distance from the origin to the detector 1 and 2 was 110mm and 100mm, respectively. The distance from source 1 to detector 1 and source 2 to detector 2 was 636 mm and 552 mm, respectively. Two 400W X-ray sources were used, with a voltage range of 20-100kV and current range of 0.5-10mA, resulting in X-rays emitted in a cone shaped beam from a 0.5mm focal spot. The X-ray generator settings were set to 40kV and 4mA in the FlowCapture software that controlled the X-ray machine.

3 RESULTS

The acoustic signal was found to be independent of the position, model and run. The acoustic measurements were similar to the noise that was present at no flow for aneurysm model A up to Re=300, and up to Re=600 for model B. Figures 1a-1d show the power spectral density with respect to frequency for various Reynolds numbers, for the aneurysm with transitional flow [2]. The signature of the power spectrum of the fluctuations at Re=130 matches the power spectrum of the noise. At Re=300 (figure 1b), there is a tendency of higher magnitudes in the fluctuations (shown in blue) at frequencies of a few hundred Hertz. This tendency is amplified at Re=400 (figure 1c), and here there is a clear separation between the two curves in the frequency range 20-600 Hz.

The wall vibrations are caused by pressure fluctuations in the flow, which for fully developed turbulence should scale as \( f^{-7/3} \), where \( f \) is the frequency. In Figure 1d, the power spectra at various Reynolds numbers are shown overlaid on each other to demonstrate the tendency of increased vibrations more clearly. Even though transitional effects seems to occur already at Re=300, fully developed turbulence seems not to be present before between Re=1500 or Re=3200. A corresponding plot from the previous DNS [2] is shown in figure 1e.

4 CONCLUSIONS

The experimental study on physical models depicts the onset of transitional flow in aneurysms at nearly the same Reynolds numbers as in previous numerical simulation studies [2, 5]. The analysis of the power spectral densities was possible by recording sounds from off-the-shelves microphones. X-ray PTV measurements failed to identify the transition, most likely due to the usage of particles that were too big to follow the flow at sufficiently low Reynolds numbers.
A direct comparison to DNS studies is not possible due to the detailed flow features that were captured by that study. This study validates the presence of transitional like phenomena in aneurysms.

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WHERE DOES CFD IDENTIFY LESION INSTABILITY IN SMALL ANEURYSMS?

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SUMMARY

In our observation, wall enhancement MRI allows for directly identifying areas of disturbed contrast permeability, i.e. inflammation, thrombus or a combination of both, and thus visualizes areas of instability in the aneurysm wall. In presented cases, regions of enhancements were compared with wall shear stress (WSS) distribution obtained from computational fluid dynamics (CFD). In our findings, areas of wall enhancement match well with either low or high WSS, however, other areas of low or high WSS were observed without identification of any wall enhancement.

Key words: CFD, MR, Wall Enhancement, Wall Shear Stress, Aneurysm Instability

1 INTRODUCTION

In current clinical practice, Magnetic Resonance Imaging (MRI) may be used to estimate stability of the increasingly incidentally found, unruptured aneurysms. MR imaging with Gadolinium may allow for direct delineation of structural instability by visualization of shape irregularity, contrast enhancement, growth, or a combination of these morphological indicators of destructive remodeling.

The process of destructive remodeling of the aneurysm wall leads to critical structural impairment and aneurysm instability over time, and where identified, a preemptive strategy with active treatment may be warranted.

A lack of endothelial competence, which likely involves inflammatory reactions, can be visualized by wall enhancement on MR examinations [1,2]. In small aneurysms, the leakage of contrast material is likely associated with either a leaking endothelial layer or presence of thrombus layering the inner surface of an aneurismal cavity, or a combination of both. Both these changes lead to an increased permeability and allow for contrast accumulation, hence, an enhancement, that is nowadays best visualized in "black-blood"-T1-W high-resolution MRI sequences.

With enhancement becoming a key parameter, indicating ongoing lesion instability and likely indicating inflammatory periods of destructive remodeling, understanding the relation between the tissue compartments concerned is of interest. Computational Fluid Dynamics (CFD) allows for calculation of kinetic energy of blood, which is widely accepted as a factor and responsible for the continuous stimulation of vascular wall remodeling at the cellular level [3-5].
2 METHODOLOGY

CFD studies were carried out after segmentation from 3D-RA imaging data sets to achieve best possible morphological quality of vessel lumen reconstruction and detailed aneurysm geometry. Areas of wall enhancement, thought to represent biologically unstable areas of the aneurysm dome, were segmented from Gadolinium enhanced MRI manually. MRI datasets were aligned and matched to reconstructed 3D-RA blood vessel surfaces by post-processing. In one case of visible shape difference of aneurysm lumen and aneurysm outer surface, CFD was done for both the two different shapes, i.e. the lumen shape and the aneurysm wall shape.

2.1 MR examinations

For all patients identified with an incidentally found, unruptured small aneurysm, a standard MRI evaluation protocol is applied for further evaluation of the aneurysm wall stability. This includes Black-Blood-T1-W high-resolution MRI sequences (3T-Skyra, Siemens or 3T-Ingenia, Philips) performed before and after use of (Gadovist®, 1.0 mmol/ml, Bayer Vital, Leverkusen, Germany, dose 0.1ml/kg bw). Four patients were chosen to perform additional CFD analysis (Table 1). Resolutions of MR black-blood slices in these cases were 0.31×0.31×2.2 mm (case A), 0.39×0.39×2.2 mm (case B, D), and 0.50×0.50×2.2 mm (case C). Note that case C exhibited two aneurysms, located next to each other (C1 and C2). Two readers identified areas of aneurysm wall enhancement and areas that were identified by both readers as enhancing, were matched and projected to the vessel lumen surfaces obtained by segmentation and reconstruction of 3DRA data.

2.2 CFD analysis

All aneurysm geometries were reconstructed from 3DRA imaging (Digital subtraction angiography, Allura, Philips). Voxel resolution was 0.07×0.07×0.07 mm (case A), 0.17×0.17×0.17 mm (case B, D), and 0.50×0.50×0.7 mm (case C). CFD was carried out using a commercial package (Fluent 14.0, ANSYS). The inflow boundary was set as a mass flow condition with a physiologically representative waveform. To avoid disturbances three pulses were simulated, but only the third pulse was taken into consideration for analysis. As outlet conditions in bifurcation geometry the outflow mass was divided according to cubic law. Pressure boundary of 0 Pa was applied in side wall aneurysm cases, i.e. with a single outlet. The vessel walls were assumed as rigid and no-slip. The fluid was simplified as incompressible, isothermal, and Newtonian with a density of 1056 kg/m3 and a viscosity of 0.0035 Pa s. WSS and streamlines at systolic peak were visualized in post-process to compare with the existence of wall enhancement.

3 RESULTS AND CONCLUSIONS

3.1 Results

Table 1 summarizes presence and degree of wall enhancement on MR in each aneurysm. In aneurysms with wall enhancement, areas of enhancements match well with areas that are exposed to either high WSS or low WSS. However, areas with exposure to either high WSS or low WSS did not always present with enhancement.

In case A, strong wall enhancement was observed on two sides of the aneurysm; both along lower WSS areas near to the eddy center of the flow vortex. Matching the MRI with the aneurysm lumen obtained from 3DRA indicated the existence of a sizable thrombus apposition. When subtracting the clot volume, the concerned area showed extensive low WSS. This might explain, why clot was forming in this area. Obviously, the development of a sizable clot volume secondarily changes the shear map of an aneurysm lumen, indicating the general problem of interpretation of CFD based on a perspective that is limited to the lumen shape only. In case A, also a high WSS region was observed along the inflow jet, however, without observation of wall enhancement.

Case B aneurysm showed significant wall enhancement in low WSS regions and slight enhancement in high WSS regions.

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Case C presented with two aneurysms close to each other. C1, the more proximal and larger aneurysm exhibited enhancement in areas, both of high WSS and low WSS, whereas the more distal, smaller aneurysm C2 exhibited an area of faint enhancement only in an area of low WSS. Although in both aneurysms similar values of WSS exposures (average of ~2Pa at systolic peak) were observed, only the proximal one exhibited visible signs of wall instability (enhancement).

Case D showed an enhancement in both, high and low WSS areas. In the low WSS area, the aneurysm lumen presented a shape irregularity with outward bulging. There was also presence of increased enhancement in a wall segment of the parent artery adjacent to the aneurysm exposed to low WSS.

3.2 Conclusions

In small aneurysms, wall enhancement can be observed in both, low WSS or high WSS areas. These are thought to represent areas of destructive remodeling, i.e. the hallmark of structural aneurysm wall instability involving inflammatory processes. Enhancement was more pronounced in areas of low WSS.

In our findings, mirroring current disease understanding, areas of wall enhancement match well with either low or high WSS, however, other areas of low or high WSS were observed without identification of wall enhancement.

We conclude, that CFD alone cannot predict, whether there is active destructive remodeling, identified by enhancement (inflammation), or not. One may argue that the energy of blood flow drives development of inflammation in cases that are ready to undergo a destructive remodeling, whereas, blood flow conditions alone seem unlikely to trigger and entertain lesion wall instability in cases that are not ready to undergo a destructive remodeling. This is in accordance with conclusions made in atherosclerosis research [5].

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We present a preliminary case from a recently-funded, three-year prospective study aimed at comparing hemodynamics from patient-specific CFD to focal patterns of aneurysm wall pathology observed by intraoperative microscopy during surgical clipping. For this case, elevated residence times coincided with a region of superthin wall, whereas high temporal gradients of wall shear stress coincided with a region of atherosclerotic wall. High-frequency flow instabilities were present in the sac, but did not show a clear association with wall pathology. Although obviously preliminary, these findings highlight a complex relationship between local hemodynamics and the heterogeneous aneurysm wall.

Key words: intracranial aneurysm, CFD, flow instabilities

1 INTRODUCTION

Associations between hemodynamic parameters and aneurysm rupture are commonly based on rupture status observed retrospectively. Prospective studies are challenged by the relatively low annual rate of rupture, requiring perhaps thousands of cases to be surveilled. On the other hand, direct comparison of hemodynamics to wall pathology is challenged by the difficulty of imaging the aneurysm wall non-invasively [1], or of obtaining and mapping aneurysm tissue at surgery [2]. Instead, following Kadasi et al. [3], here we propose to compare CFD models derived from 3D angiography against images of the aneurysm wall obtained through the intraoperative microscope during surgical clipping. Our hypothesis is that vulnerable regions of the aneurysm wall, whether they are thin or thick, are associated with abnormal wall shear stress (WSS) patterns.

2 METHODOLOGY

The subject of this study was a patient scheduled to undergo surgical clipping of an unruptured middle cerebral artery (MCA) aneurysm. Informed consent was obtained, and the study was approved by hospital ethics review. Rotational 3D angiograms were acquired as part of routine workup prior to surgery.

The lumen was digitally segmented, from the cervical internal carotid artery (ICA) to the distal MCA (M2) branches, using a gradient-based watershed method. Care was taken by the operator to trim small outlet or side branches. An cycle-averaged flow rate of 5.9 mL/s was assumed at the ICA inlet, and used to scale a representative flow rate waveform shape [4], from which fully-developed velocities were prescribed. Traction-free boundary conditions were imposed at all outlets, with outlet pressures adjusted iteratively to achieve a prescribed flow division determined from a reduced-order model, under the assumption of a square law flow split at each bifurcation.
In this case, 40% of the flow (2.4 ml/s) was predicted for the parent (M1) segment. Viscosity was assumed to be a constant 3.5 cPoise, and walls were assumed to be rigid.

The CFD simulation was performed using our well-validated, minimally-dissipative solver [6]. A finite element volume mesh was generated using the Vascular Modelling ToolKit (VMTK), with a resolution of at least 0.3 mm along the parent artery, and 0.18 mm in the sac, resulting in approximately 4 million tetrahedral and boundary layer elements. The cardiac cycle was discretized into 10,000 uniformly-spaced time steps per cardiac cycle, and two cycles were used to wash out initial transients.

Standard hemodynamic wall parameters were computed from the CFD models, including time-averaged wall shear stress (TAWSS), oscillatory shear index (OSI) and relative residence time (RRT). WSS fluctuations were quantified as the root-mean-square value of the temporal wall shear stress gradient (TWSSG) over the cardiac cycle, and the recently-introduced spectral power index (SPI), which is designed to highlight high-frequency (>25Hz) fluctuations [7]. These maps were compared, visually, to a photograph of the aneurysm wall acquired through the intraoperative microscope, taking care to orient the CFD model to the surgical view.

3 RESULTS AND CONCLUSIONS

As shown to the right, in this case the wall was heterogeneous, exhibiting superthin (1), atherosclerotic (2) and normal (3) tissue regions. TAWSS was generally low in the sac, with regions of modest OSI near the superthin and normal wall. RRT was elevated primarily at the superthin region, and lowest at the thickened region. TWSSG was elevated in the thickened region (but also in the parent and daughter arteries), whereas SPI was generally low throughout. These findings are at odds with a recent report of high TAWSS at thinning sites and high RRT at thickening sites in a cohort of four Acom aneurysms [8]; however, this might be due to our small sample, also from a different cerebrovascular site.

We ultimately expect to include more than 100 cases based on the ~40 MCA clippings historically performed at Toronto Western Hospital each year, including both unruptured and ruptured cases. As we move forward, CFD models will be derived from high-resolution 4D CT angiography, allowing us to include cases (e.g., emergency ruptures) that may not be clinically indicated for catheter angiography, and also allowing us to derive patient-specific inflow rates in addition to lumen geometry [9]. To facilitate quantitative comparisons and statistical analysis, a interactive tool has been commissioned to allow the neurosurgeons to paint, onto the segmented lumen surface and blinded to the CFD results, the various wall regions observed from video and multiple still images recorded from the intraoperative microscope.

REFERENCES


FLOW INSTABILITY MAY NOT CLOSELY CORRELATE WITH THE RUPTURE OF CEREBRAL ANEURYSMS AT THE INTERNAL CAROTID ARTERY

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SUMMARY

Recent studies report that flow instability may correlate with the rupture mechanism of cerebral aneurysms. However, how flow instability contributes to aneurysm rupture remains to be elucidated. In this study, computational fluid dynamic (CFD) simulations of 10 ruptured and 25 unruptured cerebral aneurysms located at the internal carotid artery (ICA) were conducted to investigate the potential association between the flow instability and aneurysm rupture. Our results demonstrate that lower pressure losses and flow fluctuations are closely correlated with aneurysm rupture rather than the flow instability, which is associated with high-pressure loss and high-WSS.

Key words: cerebral aneurysm, flow instability, computational fluid dynamic, internal carotid artery

1 INTRODUCTION

It is generally accepted that hemodynamic factors, especially the wall shear stress (WSS), play important roles in the formation, progression and rupture of cerebral aneurysms. However, findings regarding the association of WSS with aneurysm rupture have been diverse, or even controversial [1-2]. For instance, Xiang et al. [1] found, based on CFD studies on 38 ruptured and 81 unruptured aneurysms, that low WSS and high oscillatory shear index (OSI) related significantly to aneurysm rupture. In contrast, Cebral et al. [2] demonstrated a strong correlation between Maximum WSS and aneurysm rupture through a statistical analysis on 210 cerebral aneurysms. In recent years, many studies investigated flow instability in cerebral aneurysms using either experimental or numerical methods, which paved a new way towards a more comprehensive understanding of the biomechanical mechanisms underlying aneurysm rupture [3-5]. Our previous study indicated that the ruptured aneurysms exhibit obviously temporal flow instabilities rather than unruptured aneurysms of the same patient. The flow fields associated with the ruptured aneurysms present highly disturbed flows, which are characterized by pronounced velocity and WSS fluctuations at systole [4]. However, Varble et al. [5] recently investigated the flow instabilities in 56 MCA aneurysms and proposed that the flow instability fails to differentiate ruptured from unruptured aneurysms.

There obviously exist a controversy of high- and low flow associated with the mechanism of aneurysm rupture, which may be caused by the complicated rupture mechanism or different experiment designs [6]. Moreover, the potential connection of flow instability with aneurysm rupture and other proposed indicators is still not completely defined. In the present study, computational fluid dynamic (CFD) simulations of 35 ICA cerebral aneurysms were performed under pulsatile flow simulations. High spatial and temporal resolutions of CFD were employed to capture essential high-frequency flow instability inside cerebral aneurysms. The goal of this study is to explore the possible correlation between flow instability and aneurysm rupture, and determine
whether such flow instability could be associated with high pressure loss and elevated WSS for the aneurysms.

2 METHODOLOGY

2.1 Geometric modeling

The patient data utilized in this study is a subset of the data obtained from the Aneurisk database. All the ICA sidewall aneurysm models from the repository were selected to minimize selection bias. The patient-specific surface models of cerebral aneurysms were reconstructed with the level sets segmentation algorithm implemented in Vascular Modeling Toolkit. We included the primary vessel geometry features including the long cervical segments upstream, middle and anterior cerebral arteries downstream. The inlet boundary condition was specified at the ICA, which is far away from the aneurysm. The outlets were extended by 20 diameters of each outlet to reduce the effects of boundary artifacts. A commercial software (ANSYS ICEM 15.0) was eventually employed to produce the high-resolution mesh composed of tetrahedral and prism elements. Five prism layers were utilized to solve near-wall regions with an average nodal space increasing by 1.2. Tetrahedral elements were generated for the remainder of the lumen with a minimum element size of 0.025 mm and maximum element size of 0.1 mm. Mesh-dependence was studied together with the time increment effect and a mesh system with a minimum element size of 0.025 mm and a time step 0.25 ms was confirmed to be capable to provide sufficiently high resolution of the flow instability in the present cerebral aneurysms models.

2.2 Computational fluid dynamic modeling

At the inlets we imposed fully developed Womersley velocity profiles based on a typical volumetric waveform (Figure 1a). At outlets zero pressures and zero velocity-gradients were imposed. On vessel surfaces a rigid wall with non-slip boundary conditions was implemented in all simulations. The blood was assumed to be an incompressible Newtonian fluid with a constant density of 1025 kg/m$^3$ and a dynamic viscosity of 0.0035 Pa·s. The blood flow in the aneurysm was modeled with the unsteady three-dimensional Navier-Stokes. The simulations took an average of 38 hours on a PC with an Intel Xeon (2.9GHz); parallel processing with a cluster of 32 nodes was conducted with Platform Computing. All the simulations were performed for nine cardiac cycles and the computed results from the third cycle were employed for final analysis.

2.3 Data analysis

We evaluated several hemodynamic factors to seek their potential association with aneurysm rupture. In order to allow comparison among different aneurysms, normalized WSS is defined as time averaged WSS normalized by the average parent vessel WSS in the same model; Normalized mean WSS (NMWSS) is further spatially averaged over the aneurysm sac.

Pressure Loss Coefficient (PLC) quantifies the relative total pressure difference in the aneurysm sac, but normalized to inlet dynamic pressure.

$$PLC = \frac{(0.5pu_{in}^2 + P_{in}) - (0.5pu_{out}^2 + P_{out})}{0.5pu_{in}^2}$$  \hspace{1cm} (1)

The aneurysm hemodynamics could present local highly disturbed flow with notable aperiodic characteristics \cite{4}. To quantify the cycle-to-cycle variations, we made decomposition of the instantaneous velocity $u_i(x, t)$ with a mean $\bar{u}_i(x, t)$ and a fluctuating component $u'_i(x, t)$ ($i = 1, 2, 3$), so that

$$u_i(x, t) = \bar{u}_i(x, t) + u'_i(x, t).$$  \hspace{1cm} (2)

Thus the fluctuating kinetic energy (FKE) can be defined as,

$$FKE(x, t) = \frac{1}{2} < u'_i(x, t) \cdot u'_i(x, t)>.$$  \hspace{1cm} (3)
We define the aneurysms exhibiting substantial flow instabilities as unstable with $\text{FKE} > 10^{-4} \, \text{m}^2/\text{s}^2$, and the others as stable.

Figure 1. CFD modeling: (a) The inlet flow rate waveform over two complete cardiac cycles with an average velocity of 0.31 m/s. (b) Subdivision of the aneurysm (red part) and vessel regions. The pressure losses were calculated through the pressure differences between the inlet and outlet planes. (c) Mesh information: calculation domain and boundary-fitted prism layers.

Figure 2. Volumetric rendering of fluctuating kinetic energy (FKE) for 10 ruptured (top two rows) and 25 unruptured aneurysms (bottom five rows). Unstable aneurysms R1&R5 and U1-U11 (black arrows) manifest apparent energy fluctuations, while the others appearing empty show no fluctuations.

3 RESULTS AND CONCLUSIONS

Figure 2 illustrates the volumetric rendering of energy fluctuations of the aneurysms. Energy fluctuation appears in both the rupture and unruptured groups. 2 ruptured and 11 unruptured aneurysms (black arrows) exhibited pronounced fluctuation energies corresponding with high-
flows, and thus were classified as unstable whereas the other aneurysms were classified as stable. Note that model R5 exhibit profound fluctuation energies compared to unruptured aneurysms. Figure 3 displays the scatter plot of NMWSS versus PLC for ruptured-unruptured aneurysms. Most of the unstable aneurysms (black solid circles) are exposed to relatively higher PLC and elevated NMWSS, whereas the stable aneurysms (black open circles) were more likely to present lower PLC and NMWSS. In particularly, two aneurysms R1&U11 (half black solid) present relatively less unstable state with either higher PLC or NMWSS. Flow instability is very likely to inherently associate with high pressure loss as well as high-flow in cerebral aneurysms.

Our findings demonstrated that the ruptured aneurysms present obviously lower flow fluctuations and pressure losses, although 2 ruptured and 11 unruptured aneurysms obviously experienced higher flow fluctuations compared to other aneurysms. These observed results between ruptured and unruptured aneurysms imply that flow instability is not closely correlated to aneurysm rupture, inherently associated with high pressure loss and high-flow in cerebral aneurysms.

Figure 3. Scatter plot of Normalized Mean WSS (NMWSS) versus pressure loss coefficient (PLC) for ruptured and unruptured ICA aneurysms. The black solid and open circles represent the unstable and stable ruptured aneurysms respectively, whereas the red arrows point to the ruptured aneurysms. Flow instability mostly occurs in aneurysms with high-pressure losses as well as elevated WSSs. In particularly, two aneurysms (half black solid) present relatively less unstable state with either higher PLC or NMWSS.

REFERENCES

EVALUATION OF ANEURYSMAL LOCATIONS IN THREE DIMENSIONAL ARTERIAL BENDING STRUCTURE

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SUMMARY

The purpose of this study is to evaluate an aneurysm location using 3D geometric parameters such as curvature and torsion along arterial centerline to elucidate the relationship between vascular geometry of peri-aneurysmal environment and aneurysmal formation as well as rupture. The paper presents a new penalized spline fitting method to optimize curvature and torsion automatically from the medical images. The present method is applied to patient data with two aneurysms. The locations of two aneurysms coincided with the curvature peak positions, and also reversal of the torsion was observed at the position upstream near their locations.

Key words: spline, curvature, torsion, 3D arterial bending structure

1 INTRODUCTION

Cerebral aneurysmal subarachnoid hemorrhage often leads to a devastating event associated with high mortality and long term disability. Clinical and experimental studies strongly suggest that hemodynamic factors play an important role in cerebral aneurysm formation, growth, and rupture [1]. Evaluation of rupture location using computational hemodynamics with patient-specific arterial geometry has been performed to examine hemodynamic forces such as wall shear stress (WSS) and WSS gradient (WSSG). The three-dimensional (3D) arterial bend can be expressed using curvature and torsion along the centerline of an artery. Lauric et al. [2] investigated the relation between the curvature along the carotid siphon bend and hemodynamic forces such as WSS and WSSG. Since curvature and torsion are derived using higher derivative, it is difficult to obtain smooth and accurate interpolation automatically using a B-spline or a NURBS function. The paper presents an optimized method to derive curvature and torsion from the medical images. In order to obtain a better understanding, both curvature and torsion are used to examine association of the aneurysmal location with the 3D bending structure. The present method is applied to patient data, and aneurysm locations are evaluated using curvature and torsion along arterial centerline of arterial bending structure in the peri-aneurysmal environment.

2. METHODOLOGY

Three dimensional arterial geometric modeling is performed by an image-based modeling system, V-Modeler, which is developed in our laboratory [3]. V-Modeler has several functions such as arterial segmentation, surface reconstruction of arterial lumen, extraction of arterial centerlines, and calculation of geometric parameters such as curvature, torsion, and radius. The arterial centerlines are converted into spline functions optimized using a penalized spline fitting method (SFM) in order to smooth the centerlines with some errors caused by digital image discretization and noisy bend.
In order to derive a B-spline curve and its derivatives, let \( \mathbf{P}(t) = (x, y, z) \) be a position vector along curves as a function of a parameter \( t \) as follows:

\[
\mathbf{P}(t) = \sum_{i=1}^{n} B_{i,k}(t) \mathbf{x}_i ,
\]

where \( B_{i,k}(t) \) is the \( i \)-th normalized B-spline basis function of order \( k \) (degree \( k-1 \)) defined by the Cox-de Boor recursion formulas and \( \mathbf{x}_i = (x_i, y_i, z_i) \) is the positions vector of the \( n \) control polygon vertices. The \( n \)-th derivative of B-spline curve \( \mathbf{P}^{(n)}(t) \), is obtained from the \( n \)-th derivative of basis function, \( B_{i,k}^{(n)}(t) \).

\[
\mathbf{P}^{(n)}(t) = \sum_{i=1}^{n} B_{i,k}^{(n)}(t) \mathbf{x}_i
\]

The geometric parameters such as curvature \( \kappa \) and torsion \( \tau \) on the spline curve are given by:

\[
\kappa = \frac{1}{s''^2} \sqrt{\left(x''\right)^2 + \left(y''\right)^2 + \left(z''\right)^2}
\]

\[
\tau = \frac{1}{\kappa^2 s'^4} \begin{vmatrix}
    x' & y' & z' \\
    x'' & y'' & z'' \\
    x''' & y''' & z'''
\end{vmatrix}
\]

where \( x', x'', ... \) are 1\textsuperscript{st}, 2\textsuperscript{nd}, and 3\textsuperscript{rd} derivative of \( x \) in terms of \( t \), respectively, and \( y', y'', ... \) are as well. The variable \( s' \) is defined as below,

\[
s' = \sqrt{\left(x'\right)^2 + \left(y'\right)^2 + \left(z'\right)^2}
\]

The arterial radius along the centerline is obtained as the average radius of cross section of artery normal to the centerlines resulting from segmentation of the arterial lumen from the medical images.

The SFM is commonly dealt with as penalized spline regression with combination of a 3\textsuperscript{rd} degree basis function and a penalty term of 2\textsuperscript{nd} derivative of the fitted curve [4,5]. We propose to use a 5\textsuperscript{th} degree basis function and penalty of 4\textsuperscript{th} derivative in order to optimize curvature and torsion of the fitted curve. The 3\textsuperscript{rd} derivative of B-spline curve is used to calculate its torsion given by equation (3).

The degree of B-spline basis function requires the 5\textsuperscript{th} degree basis function at minimum in order to assure continuity and smoothness of 3\textsuperscript{rd} derivative along the B-spline curve. In addition, the penalty requires 3\textsuperscript{rd} or 4\textsuperscript{th} derivative at minimum in order to control 3\textsuperscript{rd} derivative of the fitted curve. The coefficients \( \lambda_3 \) and \( \lambda_4 \) for optimization are determined to minimize the objective function \( S \) given by:

\[
S = \sum_{j=1}^{m} \left| \mathbf{y}_j - \mathbf{P}(t_j) \right|^2 + \lambda_3 \int_{t_{\min}}^{t_{\max}} \left( \frac{d^3 \mathbf{P}(t)}{dt^3} \right)^2 dt + \lambda_4 \int_{t_{\min}}^{t_{\max}} \left( \frac{d^4 \mathbf{P}(t)}{dt^4} \right)^2 dt
\]

where \( \mathbf{y}_j \) is the \( j \)-th data point with a total of \( m \) data points. The system of equations for minimization of \( S \) can be written as:

\[
\mathbf{B}' \mathbf{Y} = \left( \mathbf{B}' \mathbf{B} + \lambda_3 \mathbf{B}' \mathbf{B}_3 + \lambda_4 \mathbf{B}' \mathbf{B}_4 \right) \mathbf{Y} ,
\]

where \( \mathbf{B} \) is an \( n \)-by-\( m \) matrix for each element \( \left( \mathbf{B} \right)_{ij} = B_{i,k}(t_j) \), and \( \mathbf{B}_3 \) and \( \mathbf{B}_4 \) are the matrix representation obtained from the penalty terms of 3\textsuperscript{rd} and 4\textsuperscript{th} derivatives, respectively. The matrices...
\(X\) and \(Y\) are \(n\)-by-3 and \(m\)-by-3 matrices with elements \(x_i\) and \(y_j\), respectively. Singular Value Decomposition is applied to solve the system equation resulting in:

\[
X = (B^T B + \lambda_3 B_3^T B_3 + \lambda_4 B_4^T B_4)^{-1} B^T Y
\]  

We use Akaike Information Criterion (AIC) to identify optimal \(\lambda_3\) and \(\lambda_4\) in equation (6). AIC is proposed as the relative quality of statistical models for a given set of data [6]. AIC is given by

\[
AIC = -2 \ln L + 2 \dim
\]

where \(\dim\) is the effective dimension of equation (6). The variable \(L\) is the Gaussian log-likelihood, and is defined as:

\[
L = \prod_{j=1}^{m} \frac{1}{(2\pi)^{\frac{3}{2}} \sigma_0} \exp \left( - \left( y_j - \sum_{i=1}^{n} B_{ij} (t_j) x_i \right)^2 / 2 \sigma_0^2 \right).
\]

AIC can be written as:

\[
AIC = \sum_{j=1}^{m} \left( y_j - \sum_{i=1}^{n} B_{ij} (t_j) x_i \right)^2 / \sigma_0^2 + 2m \cdot \ln \sigma_0^2 + 3m \cdot \ln 2\pi + 3 \cdot 2 \cdot \text{trace}(H),
\]

where \(H\) is defined as

\[
H = B(B^T B + \lambda_3 B_3^T B_3 + \lambda_4 B_4^T B_4)^{-1} B^T.
\]

and \(\text{trace}(H)\) in equation (10) is the effective dimension [5,6].

### 3 PATIENT DATA

Contrast-enhanced Computed Tomography (CT) imaging data of a 42-year-old female patient with two aneurysms in the left internal carotid artery were used. The data were acquired with a CT scanner Aquilion One (Toshiba Medical Systems, Tokyo, Japan). The in-plane resolution was 0.214 mm and the slice thickness was 0.25 mm. The patient provided informed consent, and the ethics committee at our institute approved the use of anonymized image data for this study.

### 4 RESULTS

Figure 1 shows the results of the positions A1 and A2 of two aneurysms and the corresponding curvature peak positions C1-C5 along the internal carotid artery. The longitudinal profiles of curvature-torsion and radius are shown in Fig. 2. By locating the radius peak from the radius profile, we can identify the locations of the aneurysms A1 and A2. The locations of aneurysm A1 and A2 almost coincide with those of curvature peaks C4 and C5, respectively. The torsion T3 at the curvature peak-to-peak from C3 to C4 becomes opposite comparing to the torsions at T1,T2,and T4 of other curvature peaks, indicating that the direction of the local helix have changed at the position just before the aneurysm A1.

In the curvature-torsion profile, the absolute value of the torsion tends to approach zero near the curvature peak and to increase between curvature peaks. If a 3D curve is on a plane, the torsion must be 0 at all positions along the curve. Since the torsion is close to 0 near the curvature peak in the curvature-torsion profile, the local centerline near the curvature peak is on the plane. On the other hand, since the absolute value of the torsion is a large value between curvature peaks, the centerline in this section is not on the plane.
In order to evaluate the relationship between the vascular geometry and the location of aneurysm, a numerical method was developed to derive 3D geometric parameters such as curvature and torsion using the B-spline method from the medical images. The present method was applied to the medical images of the patient with two aneurysms in the carotid artery, and the locations of the two aneurysms were identified on the radius profile along the arterial centerline with respect to the curvature-torsion profile. The locations of two aneurysms in the internal carotid artery almost coincided with the curvature peak position, and also reversal of the torsion was observed at the position upstream of the position of each aneurysm.

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USING SHAPE DESCRIPTORS TO CATEGORIZE INTRACRANIAL ANEURYSMS

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SUMMARY

Medical imaging plays a central role in the risk assessment of intracranial aneurysms, but to date a broadly accepted quantitative measure to assess the information encoded in these images is lacking. To close this gap, we relate established shape descriptors to expert assessments of aneurysm morphology. Firstly, we extract 3D models of aneurysms from 3D angiographies and calculate geometry indices and moment invariants describing size and shape of the aneurysm and its surrounding arteries. In a follow-up step these quantitative shape descriptors are compared to human assessments of qualitative morphological characteristics like irregularity or the presence/absence of blebs. Preliminary results are based on 137 aneurysm models.

Key words: Intracranial aneurysms, morphology, case matching

1 INTRODUCTION

Aneurysm morphology, as seen in medical imaging data, plays an important role in the assessment of the disease, but a quantitative measure to characterize shape is still lacking in clinical practice. For instance, irregularly shaped aneurysms have been associated with higher rupture risk [1], but as of today, quantitative criteria to distinguish between regular and irregular shapes have not been established.

Previous studies quantifying morphological properties of intracranial aneurysms [2–6] used the extracted morphological measures to directly predict the aneurysm’s rupture status (ruptured / unruptured) as a surrogate problem for predicting its stability status (stable / unstable). But the rupture labeling is problematic; an unruptured aneurysm might be unstable (growing), in which case the shape characteristics in common with aneurysms from the ruptured class. Furthermore, a rupture event may change the aneurysm shape in some cases [7, 8].

Here, we work towards a shape query system to find similarly shaped aneurysms in a medical database. In order to understand how the different shape descriptors encode morphological characteristics of the aneurysms, we assess which of these descriptors may be used to discriminate between regularly and irregularly shaped aneurysms, and which ones can be used to describe shape and geometrical characteristics like blebs, lobules or inclination angle.
2 MATERIALS AND METHODS

We processed 3D rotational angiography (3DRA) data by extracting a 3D model of the aneurysm and the surrounding vasculature by means of a standardized vessel lumen segmentation procedure (similar to [6]). After isolation of the aneurysm with planar cuts, its shape is described with morphological indices and generic shape descriptors. Statistical discriminability was tested separately or combined. The processing pipeline is depicted in Figure 1.

Figure 1: Processing pipeline for the morphological characterisation of aneurysms. From a 3D rotational angiography (3DRA) a 3D model of the aneurysm is extracted by means of vessel lumen segmentation and planar cuts. Next, a variety of shape descriptors are calculated and compared to experts’ assessments of shape characteristics. The aim of this study is to select shape descriptors that best reproduce the experts’ assessments. These will be useful in a case retrieval system that an expert can use to search aneurysms from a database with similar morphological characteristics.

Several morphological descriptors were taken into account: A total of 13 size and geometry indices (GI) such as aspect ratio (AR), non-sphericity index (NSI) or ellipticity index (EI) as reviewed by [3] are calculated for the aneurysm dome. We extended this list of morphological descriptors by the writhe-number based indices as introduced by [5] and the Zernike Moment Invariants (ZMI) as discussed in [9] and [6]. ZMI of order 20 and 40 are taken into consideration resulting in 121 or 441 different numerical values respectively. A summary of shape descriptors is given in Table 1.

The quantitative shape features are compared to operator assessments of shape regularity and presence/absence of specific shape characteristics such as blebs/lobules, dilations, parent vessel topology (see Table 1). Two types of tests are performed: 1) Given binarized averages of operator assessments for a single shape characteristic, the shape features are tested for discriminability. 2) The aneurysms are sorted twice based on the operator assessment and geometry indices respectively; on the resulting order a rank distance metric is calculated. ZMI shape descriptors come with an own distance measure that allows calculation of pairwise distances and to query similar cases.

<table>
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<td>Zernike moment invariants</td>
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<td>Location rel. to parent</td>
<td>Scheme</td>
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Table 1: Left: The different shape and size features considered in this study and their numbers. A geometry index is a single shape characterizing number; whereas a shape descriptor consists of an ensemble. Right: the shape characteristics assessed by an operator. For most of the shape characteristics, we used a 9-level Likert scale to account for the fact that in some cases an unambiguous characterization cannot be made. For the location we used a simple scheme to describe the position of the aneurysm neck relative to the bifurcation center and the parent vessel. The aneurysm models have been assessed in randomized order.
3 PRELIMINARY RESULTS AND OUTLOOK

The data used in this preliminary study consists of 137 ruptured and unruptured aneurysms of 111 consecutive patients for which 3DRA datasets are available, acquired at the University Hospital Geneva in the time period from 2006-2010. The average aneurysm size was 6.8 mm (std: 3.4 mm). Two assessments of shape characteristics were available, performed by one operator at two different days. Preliminary results indicate that geometry indices based on convex hull (NSI, EI) and curvature are most adapt to describe complex, irregularly looking shapes. Whereas the retrieval of similar shapes based on ZMI is possible, a similitarity measure based on ZMI is less robust and the resulting distance-based ranking is difficult to interpret.

The dataset is to be expand on additional 350 cases, the work flow will be repeated for multiple shape assessing operators. Furthermore we will investigate the combination of shape features and shape characteristics.

4 ACKNOWLEDGMENTS

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COMPARISON OF INTRACRANIAL ANEURYSM HEMODYNAMICS BETWEEN 7T 3D PC-MRI AND IMAGE-BASED CFD

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SUMMARY

Time-resolved phase-contrast MRI (PC-MRI) and image-based Computational Fluid Dynamics (CFD) are two methods that can visualize detailed 3D blood flow field in intracranial aneurysms (IAs). CFD is traditionally performed by assuming generalized inflow boundary conditions in a parent artery. Herein, we performed CFD simulation on 9 IAs using generalized inlet boundary conditions and compared with high-resolution 7T PC-MRI. Our results show that the flow pattern and wall shear stress (WSS) distribution are quite similar between the two approaches. Besides, the quantification of flow and WSS show a moderate agreement between the two approaches. We conclude that CFD simulation using generalized inlet boundary conditions generates fairly similar results as 7T PC-MRI.

Key words: intracranial aneurysm, 3D PC-MRI, CFD

1 INTRODUCTION

Abnormal hemodynamic forces have been associated with initiation, growth, and rupture of intracranial aneurysms (IAs) [1]. 3D PC-MRI and Computational Fluid Dynamic (CFD) are the most common tools for visualization of detailed blood flow in IAs; however, each approach has its strength but also its own drawbacks. The spatial resolution of 3D PC-MRI is limited. On the other hand, CFD simulations are mostly performed using generalized inlet boundary conditions. Previous comparison between 3D PC-MRI and CFD simulation have shown that the volumetric flow pattern and velocity vectors in the aneurysm sac have good agreement; however, more inconsistency can be seen near the aneurysm wall. This inconsistency is more noticeable for velocity-derived parameters such as wall shear stress (WSS) [2, 3]. Therefore, for calculating velocity-derived parameters, spatial resolution of PC-MRI measurement must be as high as possible [2]. Previous study confirmed that utilization of 7T PC-MRI can provide higher signal to noise (SNR) ratio and consequently improve the flow visualization and quantification [4]. In this study, we compared blood velocity vectors and wall shear stress (WSS) obtained from high-resolution in vivo 7T PC-MRI with those obtained from CFD in 9 IAs. The aim of this study was to investigate whether velocity-derived hemodynamic parameters calculated by CFD using generalized boundary conditions agree with 7T PC-MRI.

2 METHODOLOGY

Eight patients with intracranial aneurysms successfully underwent both CTA and time-resolved 3D PC-MRI imaging. The CTA images were used for 3D reconstruction of the aneurysm geometry, thus CFD, and 3D PC-MRI was used to obtain time-resolved flow data set.
2.1 Computational Fluid Dynamics

The 3D geometry of the aneurysms was reconstructed using computed tomography angiography (CTA) images and open source Vascular Modeling Toolkit (www.vmtk.org). The inlet and outlet surfaces are extended to have fully developed flow at the inlet and avoid backflow at the outlets. We used commercial software StarCCM+ for mesh generation and CFD simulation. The geometries were converted to computational domains using 0.1 mm size polyhedral elements and three refined prism layer on the lumen. The wall was assumed to be rigid and blood was considered as a Newtonian fluid with viscosity of $\mu=0.0035 \text{ Pa}$ and density of $\rho=1056 \text{ kg/m}^3$. A location-based flowrate was set at the inlets for each IA. A pulsatile waveform derived from a healthy person, obtained by transcranial Doppler ultrasound measurements, was applied at the inlets. The percentage distribution of the flowrates at the outlets was defined based on Murray's Law. A cardiac cycle of 0.928 s was prescribed for all the cases. A constant time step size of 0.001 s was used for the entire simulation. The convergence criterion was set as $10^{-5}$ and the simulation was run for three cardiac cycles. The third cardiac cycle was used for comparison with 3D PC-MRI. More details about the CFD methodology can be found in [5].

2.2 3D PC-MR

3D PC-MRI measurements were conducted on a 7T MRI scanner (Philips Healthcare, Best, The Netherlands) with a 32-channel receive head coil and a volume-transit coil (Nova Medical, Wilmington, Massachusetts). The imaging parameters were as follow: Voxel size of $0.5 \times 0.5 \times 0.5 \text{ mm}^3$, field of view of $190 \times 190 \times 20 \text{ mm}^3$; velocity-encoding of 150 cm/s for each velocity-encoding direction, TE/TR/flip angle was 4.1 ms /8.6 ms /20º. Six retrospectively gated cardiac phases were obtained by using a peripheral pulse unit. Acquired temporal resolution ranged between 209 and 286 ms, depending on the heart rate. The average of scan duration was approximately 13 minutes. The 3D PC-MRI data were corrected for background phase offsets and velocity phase wraps. The aneurysm lumen was semi-automatically masked in commercial software (Mimics, Materialise, Leuven, Belgium) using phase contrast magnitude images at the time frame with the highest blood signal. The transition between aneurysm lumen and brain tissue was defined as the aneurysm wall. WSS was calculated as previously described [2]. In short, the WSS vector was estimated at the wall based on the 3D spatial velocity gradient perpendicular to the vessel wall. The wall was assumed to be rigid and blood was considered as a Newtonian fluid with viscosity of $\mu=0.0035 \text{ Pa}$.

2.3 3D PC-MRI vs. CFD post-processing, statistical analysis and visualization

For both CFD and 3D PC-MRI, the time-resolved velocity and WSS vectors were averaged over time. A CFD mask was created using the 3D coordinates of the geometry. The CFD and 3D PC-MRI masks were co-registered using rigid registration. Subsequently, CFD velocity and WSS vectors were interpolated to the 3D PC-MRI mask. Spearman’s correlation coefficients ($\rho$) were determined for every aneurysm to quantify the agreement between velocity and WSS magnitude values. After a Fisher z-transformation, a t-test was used to investigate if the Spearman correlation coefficients were significantly different from zero. P value <0.05 implies that Spearman correlation coefficient is significant. Bland-Altman analysis was performed as well to derive mean differences and limits of agreement. Velocity was visualized with vectors color-coded for velocity magnitude. For easy-to-grasp qualitative visual comparison, the WSS magnitude values were subdivided into three ranges: the lower third was color-coded in blue, the medium third was color-coded in green and the upper third was color-coded in red.

3 RESULTS AND CONCLUSIONS

Eight patients (with nine IAs) underwent both CTA and PC-MRI Imaging. Table 1 shows the aneurysm’s location and dimension, along with the imaging resolution. In figure 2 the velocity vectors and trichotomized WSS patterns are shown for all 9 nine aneurysms. Spearman’s $\rho$ is given as well. Both qualitatively and quantitatively, moderate agreement was found for both velocity and dichotomized WSS. The mean $\rho$ was 0.45 for velocity...
and 0.46 for WSS, both significantly different from zero (P<0.001 for velocity, P=0.001 for WSS). The mean difference between CFD and 3D PC-MRI was 0.02±0.07 m/s and 4.3±2.6 Pa for velocity and WSS, respectively. The limits of agreement were 0.28±0.08 m/s and 8.7±3.4 Pa for velocity and WSS, respectively. For the CFD simulations performed in this study, generalized inlet boundary conditions, obtained from a healthy person, were used. An earlier study [6] showed that differences between generalized and patient-specific inlet boundary conditions can be large in quantification of intra-aneurysmal hemodynamics. We found here that the agreement between CFD and high resolution 7T 3D PC-MRI was moderate but significant for both velocity and WSS. Mean differences for velocity were close to zero. This indicates that CFD simulation with generalized inlet boundary conditions produces fairly similar velocity flow pattern as MRI. WSS was on average 4 Pa lower at 3D PC-MRI compared to CFD. This is probably a result of the limited spatial resolution of 3D PC-MRI. However, subdividing of the WSS results to three ranges showed a good similarity between 3D PC-MRI and CFD, especially the spatial patterns of low and high WSS. The determination of locations of low and high WSS may be clinically relevant, since it has been shown [7] that regional WSS corresponds with regional wall thickness. Wall thickness may be an important predictor for aneurysm rupture. Further study in larger cohorts is warranted to elucidate the relationship between intra-aneurysmal hemodynamics, wall thickness and aneurysm rupture. Oscillatory shear index was available from both CFD and 3D PC-MRI. However, since the temporal resolution of the 3D PC-MRI measurements was low, these results were not used further.

Table 1: summary of aneurysm cases and imaging modality

| Absolute Height*, average (range), mm | 6.24 (2.39-10.43) |
| Age, average (range), years | 58 (45-73) |
| Gender, female: male | 7:1 |
| Location | Number of cases |
| Vertebral Artery | 1 |
| MCA | 8 |
| Total | 9** |
| Imaging Voxel size (mm × mm × mm) | |
| CTA | 0.4 × 0.4 × 0.9 |
| 3D PC-MR | 0.5 × 0.5 × 0.5 |

* Height is defined as the maximum distance between the neck plane and the dome
** One patient had two aneurysms
ACOM = anterior communicating artery
MCA = middle cerebral artery

![Figure 1. First column: 3D velocity vectors as simulated by CFD. Second column: 3D velocity vectors as measured by 3D PC-MRI. Third column: dichotomized WSS values as measured by CFD. Fourth column: dichotomized WSS values as measured by 3D PC-MRI. The numbers indicate the spearman correlation coefficients between CFD and PC 3D-MRI.](image-url)
In conclusion, velocity and WSS derived from CFD simulations showed moderate agreement with 3D PC-MRI. This confirms that for simulating intra-aneurysmal hemodynamics using CFD, generalized inlet boundary conditions can be applied.

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Biomechanics, Mechanobiology & Translation in the Heart III
IMMERSOGEOMETRIC FLUID–STRUCTURE INTERACTION ANALYSIS OF PATIENT-SPECIFIC HEART VALVE DESIGNS

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SUMMARY

In this work, we present a patient-specific heart valve simulation using immersogeometric fluid–structure interaction analysis. The patient-specific aortic root geometry is reconstructed from the medical image data and is represented using trivariate non-uniform rational B-splines. We then parametrically design prosthetic heart valves according to the aortic root, using a Rhino/Grasshopper-based interactive geometric design platform. We simulate the coupling of the deforming, patient-specific aortic root and parametrically designed heart valves, and the surrounding blood flow under physiological conditions through a cardiac cycle. The results demonstrate the effectiveness of the proposed framework in practical computations with greater levels of physical realism.

Key words: Heart valves, immersogeometric analysis, fluid–structure interaction

1 INTRODUCTION

Heart valves are structures that ensure the unidirectional blood flow through the heart by opening and closing in response to hemodynamic forcing. Hundreds of thousands of diseased valves are replaced by prosthetics annually. Bioprosthetic heart valves (BHV) are prosthetics composed of thin flexible leaflets that are fabricated from biological materials and mimic the structure of native heart valves to avoid pathological hemodynamics. The principal drawback of BHV is its durability. Accurate and realistic computational analysis of these devices could provide insights into the mechanical processes that contribute to their deterioration, streamlining the design process of new prosthetics.

In this work, we proposed a framework for analyzing a patient-specific bioprosthetic heart valves using immersogeometric fluid–structure interaction (FSI) [1]. The patient-specific aortic root geometry is reconstructed from the medical image data and is represented using non-uniform rational B-splines (NURBS). However, unlike the aortic root, medical images usually do not provide enough information for leaflet reconstruction. To circumvent this challenge, we use a Rhino/Grasshopper-based interactive geometric design platform [2] to parametrically design prosthetic heart valves according to the aortic root.

Due to the complex motion of the heart valve leaflets, the blood flow domain undergoes large deformations, including changes of topology. The FSI simulations are carried out using our hybrid immersogeometric/arbiterary Lagrangian–Eulerian methodology [3], which allows us to efficiently perform a computation that combines a boundary-fitted, deforming-mesh treatment of the artery with a non-boundary-fitted treatment of the leaflets. We simulate the coupling of the deforming, patient-specific aortic root and parametrically designed heart valves, and the surrounding blood flow under physiological conditions through several cardiac cycles. The results demonstrate the effectiveness of the proposed framework in practical computations with greater levels of physical realism.
2 METHODOLOGY

2.1 Arterial wall modeling

Let X be the coordinates of the reference configuration and let y be the displacement with respect to the reference configuration. The coordinates of the current configuration, x, can be obtained by x = X + y. The deformation gradient tensor F is defined as

\[ F = \frac{\partial x}{\partial X} = I + \frac{\partial y}{\partial X}, \]

where I is the identity tensor.

Let \( S_d \) and \( V_d \) be the trial solution and weighting function spaces for the solid problem. The arterial wall is modeled as a three-dimensional hyperelastic solid and the variational formulation which represents the balance of linear momentum for the solid is stated as follows: find the displacement \( y \in S_d \), such that for all weighting functions \( w_s \in V_d \)

\[
\int_{(\Omega_s)_t} w_s \cdot \rho_s \frac{\partial^2 y}{\partial t^2} \, dx + \int_{(\Omega_s)_0} \nabla_X w : P \, d\Omega - \int_{(\Omega_s)_t} w_s \cdot \rho_s f_s \, d\Omega - \int_{(\Gamma^h)_t} w_s \cdot h_s \, d\Gamma = 0. \tag{2}
\]

In the above, \( (\Omega_s)_0 \) is the solid domain in the reference configuration, \( \nabla_X \) is the gradient operator on \( (\Omega_s)_0 \), \( P = F(S + S_0) \) is the first Piola–Kirchhoff stress tensor, where \( S \) is the second Piola–Kirchhoff stress tensor, \( S_0 \) is the tissue prestress tensor [4], and \( \Gamma^h \) is the subset of the solid domain boundary on which the traction \( h_s \) is applied. \( S \) is given by

\[
S = \mu J^{-2/3} \left( I - \frac{1}{3} \text{tr} C^{-1} \right) + \frac{1}{2} \kappa (J^2 - 1) C^{-1}, \tag{3}
\]

where \( \mu \) and \( \kappa \) are interpreted as the blood vessel shear and bulk moduli, respectively, \( J = \det F \) is the Jacobian determinant, and \( C = F^T F \) is the Cauchy–Green deformation tensor. Equation (3) is a generalized neo-Hookean model with dilational penalty [5].

2.2 Thin shell formulations for the leaflets

The heart valve leaflet is modeled using the hyperelastic version of the isogeometric Kirchhoff–Love thin shell proposed by [6]. The spatial coordinates of the shell mid-surface in the reference and current configurations are given by \( X(\xi_1, \xi_2) \) and \( x(\xi_1, \xi_2) \), respectively, parameterized by \( \xi_1 \) and \( \xi_2 \). \( \xi_3 \in [-h_{th}/2, h_{th}/2] \) is the through-thickness coordinate and \( h_{th} \) is the shell thickness. The weak form of the structure subproblem in the case of a thin shell structure is stated as

\[
\int_{\Gamma_t \cap (\Omega_t)_t} w_s \cdot \rho_s h_{th} \frac{\partial^2 y}{\partial t^2} \, dx + \int_{\Gamma_0 \cap (\Omega_t)_0} \delta E : S \, d\xi_3 \, d\Gamma + \int_{\Gamma_t \cap (\Omega_t)_t} \delta E : S \, d\xi_3 \, d\Gamma = 0, \tag{4}
\]

where \( \delta E \) is the variation of the Green–Lagrange strain, \( \Gamma_0 \) and \( \Gamma_t \) are the shell mid-surface in the reference and deformed configurations, respectively. \((\Omega_t)_t \) and \((\Omega_t)_0 \) are the fluid domain in the reference and deformed configurations, respectively. \( h_{th}^{net} = h_2(\xi_3 = -h_{th}/2) + h_2(\xi_3 = h_{th}/2) \) sums traction contributions from the two sides of the shell. In this work, we use a Fung-type material model in which a neo-Hookean term is added onto the strain energy function, accounting for the low strain response [2].

2.3 Immersogeometric FSI framework

The blood flow in the aorta can be described by the Navier–Stokes equations of incompressible flows on a moving domain. The Arbitrary Lagrangian–Eulerian (ALE) formulation is employed to handle
the deforming artery wall. The spatial discretization of the Navier–Stokes equations makes use of the ALE–VMS formulation. The ALE–VMS formulation may be interpreted both as a stabilized formulation and a turbulence model.

The solid arterial wall is discretized using trivariate NURBS. A conforming fluid–solid interface discretization is considered in this work. The enforcement of kinematic and traction compatibility between the blood flow and the wall is handled using a monolithic FSI formulation described in detail in [5]. The motion of the fluid–solid interface provides the boundary conditions for solving the linear elastostatic problem for the fluid mesh motion.

The BHV leaflets are immersed into a moving blood-flow domain. The imersogeometric FSI problem is formulated using an augmented Lagrangian approach, which was originally proposed in [7] to handle boundary-fitted mesh computations with nonmatching fluid–structure interface discretizations and was extended to non-boundary-fitted (i.e., immersed) FSI problems in [1]. The tangential component of the Lagrange multiplier \( \lambda \) is formally eliminated from the formulation, resulting in weak enforcement of no-slip conditions at the fluid–structure interface. The normal component of the Lagrange multiplier \( \lambda = \lambda \cdot n \) is retained in the formulation in order to achieve better satisfaction of no-penetration boundary conditions at the fluid–structure interface.

### 2.3.1 Penalty coupling of the leaflet–wall motion

To couple the structural motion of the leaflets and the artery wall, we employ a penalty approach to weakly enforce the compatibility of displacement in leaflet–wall connecting area. The valve edges, except the free edges, are deliberately extruded to intersect with the artery wall. On the intersected locations, the following penalty formulation is applied:

\[
\int_{\Gamma_s \cap (\Omega_s)} \beta_{\text{disp}} \left( w^{(\text{shell})}_s - w^{(\text{solid})}_s \right) \cdot \left( y^{(\text{shell})}_s - y^{(\text{solid})}_s \right) \, d\Gamma = 0.
\]

In the above, the superscripts (shell) and (solid) stand for the quantities for the leaflets and the artery wall, respectively. \( \beta_{\text{disp}} \) is the penalty parameter, selected based on the balance of solution stability and matrix conditioning.

![Figure 1: Volume rendering of the velocity field at several points during a cardiac cycle (0.86s).](image)
3 RESULTS AND CONCLUSIONS

Figure [1] shows several snapshots of the details of the fluid solution fields, computed using the proposed method. The geometry of the patient-specific aortic root was obtained using techniques proposed in [8]. The heart valve was designed using our recently proposed IGA-based parametric design and geometry modeling platform [9]. We compute for several cycles from the homogeneous initial condition, until reaching a time-periodic solution. The results show that the designed valve is fully opened during the systole, and properly closed during diastole. As the valve fully opens, we see a transition to turbulent flow. As the valve fully closes, the solution becomes effectively hydrostatic. These results demonstrate the effectiveness of the proposed framework for simulating a patient-specific heart valve design with greater levels of physical realism.

REFERENCES


UNDERSTANDING TURBULENT FLOW ISSUING FROM THE AORTIC VALVE

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SUMMARY
Aortic stenosis is a common valvular heart disease where an obstruction at the aortic valve triggers turbulent blood flow causing excessive viscous pressure loss and unphysiological wall-shear stress patterns. Improved therapy of aortic stenosis requires a better understanding of these complex flow phenomena. We use high-fidelity numerical methods to study the hydrodynamic instability mechanisms leading to turbulent blood flow in the wake of the aortic valve. This includes free-stream instabilities of the core jet as well as instabilities related to fluid-structure interaction between blood flow, valve tissue and the aortic wall.

Key words: aortic valve, turbulent flow, fluid-structure interaction

1 INTRODUCTION
Aortic stenosis is a common heart disease where the aortic valve (AV) fails to fully open such that it obstructs systolic blood flow from the contracting left ventricle toward the ascending aorta. This disease is characterized by excessively high losses in blood pressure as the blood flow passes through the AV. Turbulent flow structures in the wake of the AV are probably a major contributor to these viscous pressure losses. Turbulent flow has also been observed in AV prostheses which are used to replace stenotic AV.

It is suspected that turbulent flow in the wake of the AV is also a factor in the subsequent development of aortic diseases such as aneurysms or dissections in the aortic arch. Furthermore, the flow issuing from the AV is believed to be responsible for the physiological wash-out of the sinus portions. Insufficient wash-out has been related to flow stasis in the sinus portions and subsequent thrombus formation.

A detailed understanding of the dynamics of the flow field in the wake of the AV is therefore important for a better understanding of valvular heart disease. Specifically, a better understanding of the mechanisms leading to turbulent flow may lead the way to improved designs of prosthetic AV. Here, we will present computational results providing more insight on the development of turbulent flow past the AV. This includes hydrodynamic instability mechanisms relevant for aortic valve dynamics. For simplicity, we will focus on the systolic phase with a nearly constant flow rate through the valve. We will neglect the effect of flow pulsatility which is certainly relevant for aortic valve dynamics, but which is beyond the present scope of the study.

2 BLOOD FLOW PAST THE AORTIC VALVE
The AV separates the left ventricle of the heart from the aorta. It consists of three independent membranous cusps. The AV sits in the aortic root which comprises three bulges known as sinus of Valsalva or sinus portions. The AV is fully opened during systole and is closed tightly during diastole.
At least three basic hydrodynamic instability mechanisms may play a role in the development of turbulent flow. First, there is the classical shear layer instability (also known as Kelvin–Helmholtz instability) which can cause vortical flow disturbances along the edge of the central jet issuing from the valve orifice. Second, the flow over the cavities formed of the sinus portions can be interpreted as a driven cavity configuration with its associated instability modes. Third is a flutter instability driven by the interaction of the blood flow with the supple valve cusps which governs the vortex shedding from the tips of the cusps.

These three mechanisms involve different levels of physical complexity: The shear layer instability is a free-stream instability governed by the scales of the central jet flow only. The driven cavity instabilities are governed by flow scales and the morphology of the sinus portions and the valve cusps. And, finally, the flutter instability is additionally governed by the mechanical properties of the cusp tissue.

Understanding these mechanisms in the context of aortic valve hemodynamics can help designing better valve prostheses leading to lower levels of turbulence in the wake (less viscous pressure loss, less blood trauma, more physiological wall-shear stress patterns on the ascending aorta) as well as better wash-out function of the sinus portions (reduced risk for thrombus formation). Physical experiments using transparent phantoms of the aortic root and pulsatile flow loops are an excellent means to study aortic valve hemodynamics in a near-physiological configuration. In such experiments, we have observed simultaneously transitional jet flow in the ascending aorta, complex vortical flow in the cavities of the sinus portions and travelling waves along the cusps. However, the multi-physics aspect of the involved mechanisms render computational models a much better tool for the systematic study of turbulent flow past AV.

3 HIGH-PERFORMANCE COMPUTATIONAL MODELLING OF AV BLOOD FLOW

For the quantitative study of the mechanisms leading to turbulent flow, we use a versatile computational model which allows us to study the different effects separately, systematically and at high numerical fidelity.

The basis of our model is a Navier–Stokes solver using high-order finite differences on a rectilinear grid and a low-storage Runge–Kutta scheme with adaptive time step sizes for time integration [2]. The soft tissue of the heart valve and the aortic root are modelled with a dedicated finite element solver based on a trust region method [1] using anisotropic constitutive laws [3].

The coupling between fluid and structure is done via the immersed boundary method [6] where we transfer fluid velocities to boundary conditions for the structure and reaction forces from the structure (visco-elastic and inertial forces) to the fluid grid. The transfer between the structured fluid grid and the moving unstructured finite-element grid requires an efficient algorithm which computes transfer matrices between the two meshes to perform correct mapping in a weak sense [4].

For the implementation of rigid structures (e.g. solid walls or walls with prescribed kinematics) we use a penalization method via the force density field in the Navier–Stokes equations [5].

All modules of the computational model (flow solver, structural solver, transfer library, penalization method) are integrated in the multi-physics simulation framework MOOSE (mooseframework.org). The code is optimized for modern hybrid high-performance computing platforms such as the Cray XC50 system at the Swiss National Supercomputing Centre CSCS. This optimization includes combined MPI/OpenMP parallelization for multi-core CPUs and GPU optimization with CUDA for dedicated numerical kernels (e.g. divergence and gradient operators, Jacobi smoothers) for which we will demonstrate enhanced computational performance allowing us to study complex configurations in an efficient manner.

4 COMPUTATIONAL RESULTS

We will present results from different numerical experiments to provide new insight on turbulent flow past aortic roots. These experiments include (a) simulations with rigid structures to eliminate the influence of fluid-structure interaction and (b) full fluid-structure interaction simulations to study...
fluttering of the valve cusps. We will further discuss how these results can be combined with 4D phase-contrast magnetic resonance imaging using data assimilation techniques. Finally, we compare these results to theoretical results on hydrodynamic instability and to data from physical experiments for the FSI instabilities observed on the valve cusps. In particular, we will compare results with respect to cavity dimensions, jet diameter and mechanical properties of the leaflet cusp.

5 CONCLUDING REMARKS

Numerical simulations of the flow in the aortic root allow us to study hemodynamic instability mechanisms leading to turbulent flow in the wake of the AV. This shall provide a better understanding of the pathophysiology of AV diseases and improve the design of AV prostheses leading to better cardiac health.

REFERENCES


CHANGES IN 3D BLOOD FLOW DYNAMICS WITH DIFFERENT LEFT ATRIAL APPENDAGE MORPHOLOGIES

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SUMMARY

The left atrial appendage (LAA) is an interesting structure in the left atria that presents a large inter-subject morphological variability. Furthermore, its role in the whole cardiovascular system is not fully known yet, in particular its influence in atrial haemodynamics and in thrombus formation. The main goal of this work is to study changes in blood flow dynamics in the left atria with different LAA morphologies. Computational Fluid Dynamics (CFD) simulations were run on an ideal ellipsoidal left atria with different real LAA geometries coming from imaging data of eleven patients. Boundary conditions were set up to replicate pressure and velocity measurements in the pulmonary veins and the mitral valve from literature. Relevant indices characterizing the simulated flows such as vorticity were related to LAA shape parameters. Our study suggests that left atria normal haemodynamics is independent of LAA morphology. Additionally, high vorticity values are found in regions more susceptible to thrombus generation, such as in LAA geometries with lobes near the ostium. A more thorough investigation involving a more complete LAA geometrical and blood flow characterization is needed to better understand the thrombus formation phenomenon.

Key words: Left Atrial Appendage, haemodynamics, vorticity, thrombus formation, shape.

1 INTRODUCTION

The left atrial appendage (LAA) is a secondary chamber attached to the main body of the left atrium. One of the main characteristics of LAAs is their geometrical variability, which is quite patient-specific. Researchers have proposed to classify them into four types of shapes (chicken wings, windsocks, cactus or cauliflowers [1]), but there is no consensus about them. It is more interesting to better understand its role in cardiovascular haemodynamics and in critical processes such as thrombus formation. It has been hypothesized that the LAA function acts as a decompression chamber during left ventricular systole and in periods of high left atrial pressure [2] but its functioning is not fully known. Moreover, around 90% of thrombi in the left atria are originated in the LAA in patients with non-valvular atrial fibrillation (NVAF), with apparent preference in morphologies different to chicken wing [1] but this is still under debate and the mechanisms causing thrombosis remain unclear. Finally, the long-term haemodynamics consequence of occluding the LAA, which is the recommended therapy to reduce the risk of stroke in NVAF patients with contraindications for anticoagulants, has not been properly studied.

For all these reasons, studies relating blood flow dynamics with LAA morphologies may shed some light on the relevance of this structure in some critical cardiovascular issues. Advanced imaging techniques such as 3D Rotational Angiography (3DRA) allows the 3D reconstruction of LAA geometries but, unfortunately, it is not possible to obtain highly detailed observations to characterize the haemodynamics in the left atria and the LAA. On the other hand, Computational Fluid Dynamics (CFD) simulations can be used for these studies. To the best of our knowledge, there is only one paper [3] generating blood flow simulations in the LAA with CFD, where the authors analyzed two different patient-specific LAA geometries.
In this work, we study the relation of LAA morphology and left atrial haemodynamics. Simple morphological parameters representing LAA geometry (e.g. size, ostium diameters, number of lobes, tortuosity) are jointly analyzed with indices characterizing blood flow patterns obtained from CFD simulations (e.g. pressure, velocities, vorticity, streamlines, Reynolds’ number). The in-silico experiments were based on an ideal ellipsoidal left atria, together with realistic inlet (i.e. pulmonary veins) and outlet (i.e. mitral valve) boundary conditions, where different LAA geometries obtained from patient-specific imaging data were added, generating a set of eleven CFD simulations.

2 MATERIALS AND METHODS

The pipeline for generating the set of CFD simulations started with the segmentation of patient-specific 3DRA images to obtain LAA geometries. The resulting binary masks were then processed to generate volumetric meshes, which were integrated with an ideal ellipsoidal left atria. The following step involved the definition of the physiological boundary conditions for the simulations. Finally, morphological and haemodynamics indices were derived and jointly analyzed.

2.1 Generation of left atrial meshes from imaging data

Data from eleven patients with atrial fibrillation from OLV Hospital in Aalst, Belgium, was studied. The ethical committee approved this study and informed consent was obtained from every participating volunteer. The 3D Rotational Angiography images were acquired with an Innova 3D system (GE Healthcare, Chalfont St Giles, UK) and reconstructed with the scanner workstation, providing isotropic 3D images with 0.23 mm and 0.45 mm volumetric pixel size for 512 and 256 pixels per dimension, respectively. Segmentation of the left atria and LAA was achieved with semi-automatic thresholding and region-growing algorithms available at the scanner console. From the resulting binary masks, surface meshes (with triangular elements) of the LAA were generated with the classical Marching Cubes method. A Taubin filter was applied to smooth the surface mesh while preserving the original volume (using Meshlab\(^1\)).

An ideal left atria was generated in the form of an ellipsoid (see Fig. 1a) with dimensions matching the average volume of the eleven real LAs (55 x 70 x 90 mm; 173 ml). Subsequently we manually added (using MeshMixer\(^2\)) four synthetic pulmonary veins (PV, i.e. tubes in Fig. 1a, 12 mm of diameter) and defined the mitral valve region (diameter of 25 mm), also based on real data. The ideal left atria was completed when adding the real LAA, placing them in the same location and spatial relations with respect to the PVs and mitral valve, resulting in a set of eleven ideal LAs with different LAA geometries. In some cases the real LAA needed a rotation or translation due to its particular geometry and to avoid overlapping with the ideal LA.

![Fig. 1. a) An example of a real left atria (LA) and the ideal one including a realistic left atrial appendage (LAA). b) Blood velocities applied to the pulmonary veins during the ventricular systole and diastole [4].](attachment:fig1.png)

2.2 Left atrial blood flow simulations.

Computational fluid dynamics simulations were used to study the LAA role in atrial hemodynamics. A first order implicit unsteady formulation was used for the solution of the momentum equations in conjunction with a standard partial discretization for the pressure (under-
relaxation factors set by default to 0.3 and 0.7 for the pressure and momentum, respectively). Blood flow in the LA was modeled with the classical incompressible Navier–Stokes and continuity equations. Residuals of mass and momentum conservation equations lower than 0.001 were considered as absolute convergence criteria. Blood was modeled as an incompressible Newtonian fluid with density $\rho=1060 \text{ kg/m}^3$ [5]. The dynamic viscosity of blood in large vessels and the heart at normal physiological conditions is $\mu=0.0035 \text{ Pa-s}$ [5]. Simulations were run using a laminar flow hypothesis under isothermal and non-gravitational effects. All walls were simulated rigid and with no-slip conditions. The differential equations were solved using a time-step $\Delta t=0.01s$.

At the inlets of the left atrial model (i.e. the four PVs) a time-varying pressure function was applied (see Fig. 1b) following clinical observations available in Fernandez-Perez et al. [4]. At the outlet (i.e. the mitral valve, MV) a pressure of 8 mmHg [6] was imposed during the ventricular diastolic phase. In ventricular systole, the MV is closed and was simulated as a wall boundary. The systole phase lasted 0.4s and the diastole phase lasted 0.65s [4].

Fig. 2. Geometric parameters on LAA.

### 2.3 Indices characterizing atrial haemodynamics and LAA morphologies

The following indices characterizing the shape of LAA (see Fig. 2), inspired on measurements used by clinicians to decide LAA occlude device dimensions and intervention planning, were studied: the diameters ($d_1, d_2$) and height of the ostium (equivalent to the landing zone concept); a straight-line length (H) estimating the depth of the LAA; and a geometric factor representing the tortuosity of the LAA ($\tau=(H/2+H_0)/H$, being always larger than 1, where $H_0$ is the distance between the middle point of H and the further point of the LAA; since blood flow pathways in the LAA are not straight lines, higher values of $\tau$ indicate more tortuous pathways). The Paraview software [3] was used for visualization and post-processing of simulations. Initially, the local Reynolds number was estimated from the CFD simulations to determine the blood flow regime. Mean flows and pressure waves were also measured for a whole cardiac cycle at the inlets of the LA (e.g. PVs) and specifically in the LAA. The velocity streamlines of simulated flows were used to verify the fluid dynamics profiles and vorticity ($w$, calculated as the second variant of the velocity gradient tensor) were also computed, indicating the preferences zones for stroke.

### 3 RESULTS AND CONCLUSIONS

Table 1 lists indices representing geometric differences between the studied LAA morphologies. One can easily observe the variability of ostium diameters but they all fit with the available LAA occlude devices. Nevertheless, in two cases (ID=2 and 8) the ostium height was close to zero, predicting a complex LAA occlusion intervention since some depth is needed to deploy the device. As for the haemodynamics indices, Maximum Reynolds numbers of $321 \pm 14$ and $228 \pm 21$ were obtained during diastole and systole, respectively, indicating a laminar flow regime in both phases for all cases. Fig. 3 depicts the mean velocity profile during ventricular diastole in the mitral valve for the eleven different models and one without any real LAA (e.g. equivalent to an occluded LAA). These profiles are in good agreement with equivalent measurements from a clinical case reported in Fernandez-Perez et al. [4]. Analyzing results shown in Fig. 3, we did not find substantial differences among the different models, suggesting that mean velocity profiles are independent of LAA morphology. The ideal model (without LAA) also presents the same behavior in the MV, implying that the occlusion of the LAA does not affect the hemodynamic parameters in the diastolic phase. On the other hand, LAA morphology had more influence in blood flow patterns during the systolic phase (Fig 3). In diastole, the blood follows a laminar and parallel behavior but does not clearly penetrate the LAA due to the opening of the mitral valve. Finally, we observed that LAA morphologies with lobes near the ostium were consistently associated with high vorticity values, and likely being potential candidates for coagulation and risk of thrombus formation. These

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preliminary results jointly analyzing LAA shape and blood flow indices are very promising and pave the way towards a better understanding of the role of LAA shape and its occlusion in thrombus formation and risk of stroke.

Fig 3. Left: mean velocity in the mitral valve during the diastolic phase. Right: Streamline velocities for systolic and diastolic peak (0.2 s and 0.62 s, respectively).

Table 1: LAA morphological indices.

<table>
<thead>
<tr>
<th>ID</th>
<th>LAA Volume (mL)</th>
<th>d1 (mm)</th>
<th>d2 (mm)</th>
<th>H (mm)</th>
<th>Lobes (Yes/No)</th>
<th>H0 (mm)</th>
<th>Ostium Height (mm)</th>
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<tr>
<td>1</td>
<td>9.91</td>
<td>27.8</td>
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<td>32.21</td>
<td>2.11</td>
</tr>
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</table>

Fig 4. Computational Fluid Dynamics simulation results focused on four different LAA morphologies. Top: flow streamlines coloured based on velocity magnitude. Bottom: brown areas indicate higher vorticity values.

4 REFERENCES

PERSONALISED MODELLING TO PREDICT LEFT VENTRICULAR HAEMODYNAMICS AFTER MITRAL VALVE REPLACEMENT

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SUMMARY

Mitral valve replacement with bioprosthetic implants has important consequences on the left ventricular haemodynamics. The rigid frame of the device pushes the native valve leaflets close to the aortic valve: this configuration can generate outflow obstruction, which in turn causes abnormal intraventricular pressure gradients and decreased systolic function with potentially fatal outcomes. Image-based, personalised models of ventricular haemodynamics are deployed to predict the degree of outflow obstruction and the variation in pressure gradients with different sizes of prostheses. These models are proposed as a tool to assist and to personalise interventional decisions for mitral valve replacement.

Key words: computational fluid dynamics, mitral valve replacement, outflow obstruction

1 INTRODUCTION

Transcatheter mitral valve replacement (TMVR) offers a new treatment option for patients who are contraindicated from cardio-thoracic surgery [1]. Due to the structural complexity of the mitral valve (MV) and the difficulty to remove the native anatomical structure, these procedures are extremely challenging: a complete understanding of the native valve interaction with the prosthesis, and the associated risks, is currently lacking. Specifically, Left Ventricular Outflow Obstruction (LVOTO) is a possible complication with severe outcomes [2]. The high resistance against which the heart is pumping, and the subsequent deterioration of cardiac function, trigger adaptation mechanisms leading to pressure-overload and myocardial hypertrophy [3]. Since a common outcome of hypertrophy (especially septal hypertrophy) is LVOTO, this process can create a negative feedback loop with adverse outcome [4]. Detecting the potential onset of LVOTO before surgery is thus of critical importance. However, despite recent advances in this surgical technique, there are currently no guidelines for predicting post-operative haemodynamics and LVOTO. Most candidates to TMVR present distinctive ventricular anatomy and function, which results in high-inter-individual variability in blood flow and wall motion patterns. While it is possible to image both blood flow and wall motion before TMVR, these images only describe the current state of the patient providing no information on how we expect the ventricle to respond once the valve is implanted. With this study, we propose to personalise computer models of left ventricular haemodynamics using imaging data acquired pre-TMVR and use them not only to understand the current pathophysiological state of the patient, but also to predict the blood flow response post-TMVR and the degree of LVOTO caused by the implant.

2 METHODOLOGY

Ventricular haemodynamics was modelled in 5 patients who received a prosthetic mitral valve as part of a valve-in-valve, valve-in-ring, or valve in calcified mitral annulus procedure. The models
were customised to the patient-specific anatomy and wall motion derived from ECG-gated multi-phase Computed Tomography (CT) series. A simplified representation of the implanted valve was used in the models. In this approach the device was represented by a rigid cylinder with diameter $D$ and height $H$ corresponding to the size of the prosthetic valve to be implanted (Fig 1). In each patient, the height of the valve frame was also varied with respect to the commercially available sizes to assess the impact of different valvular aspect ratios on the ventricular haemodynamics. This approach allowed us to treat the valve as a boundary condition on the flow domain, whereby zero flow velocity is prescribed on the skirting of the valve (i.e. the cylinder side wall), and a velocity inflow is applied to the mitral plane (i.e. the top of the cylinder). The bottom surface of the cylinder is an open boundary to allow the blood to fill the ventricular cavity. The blood pool is initially segmented at end-systole from the CT data. A triangular surface grid is morphed to the smoothed segmentation and used to create a tetrahedral volume mesh, which is the starting point of the numerical simulations. The wall motion is tracked from the multi-phase CT series using an algorithm based on temporal sparse free form deformations [5], which has been specifically adapted to this type of datasets. The tracked wall motion is then applied to the mesh at end systole to obtain the endocardial velocity that will then be used to drive the flow simulation. The flow velocity profile at the mitral and aortic valve planes is modelled as a quartic function whose maximum velocity is derived from the Doppler data. The shape of these velocity profiles is tuned to ensure a volume flux in and out of the ventricle that is compatible with the change in volume from the tracked wall motion. The patient-specific models are used to compute the flow field using an Arbitrary Lagrangian Eulerian (ALE) finite-element technique coupled with a penalty method implemented in the CHeart software [6-8]. Computational fluid dynamics simulations of the cardiac cycle are performed before the procedure (without valve) and after the procedure (with the implanted valve). Virtual scenarios with different aspect ratios of the prostheses were also simulated to characterise the impact of different valve types on the blood flow dynamics inside the ventricle. Three cardiac cycles were simulated in each patient and scenario, and the results from pre-TMVR and post-TMVR models were compared. Specifically changes in intraventricular pressure gradients (IVPG), obstruction fraction (OF), and energy dissipation were quantified during the cardiac cycle.

3 RESULTS AND CONCLUSIONS

3.1 Validation study

A patient with severely reduced ejection fraction underwent TMVR with a prosthetic device with $D=26\text{mm}$ and $H=19\text{mm}$. Unlike the standard routine, whereby CT data are only acquired before intervention, CT data were collected both immediately before and after TMVR. Echocardiography data (pulsed and continuous wave, Colour Doppler) were also acquired in the two states. These unique
datasets allowed the creation of two independent models based on the pre- and post-TMVR dataset for predictive and validation model respectively. Both models were validated against velocities derived from the ultrasound data. The results from the post-TMVR model were then compared to the predictions from the pre-TMVR model when a rigid cylinder with the same size and position of the prosthesis was added. Although differences in the wall motion were observed between the pre- and post-TMVR in the apical/mid-cavity region, the motion of the valve planes was consistent in the two states. The changes in OF and in the aorto-mitral angle $\alpha$ from the pre- and post-TMVR models are shown in Fig. 2. The OF from the post-TMVR model reached a maximum of approximately 6% at mid systole, close to that predicted by the pre-TMVR model. Similar agreement was found in the location of the obstructed region projected onto the aortic valve plane.

Throughout the cardiac cycle, the aorto-mitral angle $\alpha$ showed a similar trend in the two models with maximum/minimum discrepancy of 11$^\circ$ and 3$^\circ$. A 15% difference in the peak IVPG in the LVOT was also observed between the two models. In the clinics these values are currently extrapolated from the maximum Doppler velocity using the simplified Bernoulli equation. However, any underestimation of the maximum flow velocity would result in an even greater error in the pressure gradient, since its value is derived from the square of the velocity. Further, the Doppler-derived pressure gradients can only be obtained after valve implantation, and hence are not available for pre-operative assessment. The ability to predict them pre-TMVR is therefore a key addition to the decision-making process.

![Fig 3 A) Hemodynamics visualized through streamlines of blood coloured by velocity magnitude at mid-diastole and mid-systole. B: Pressure iso-contours and IVPG in the outflow tract.](image)

### 3.2 Patient study

Datasets from 5 patients were modelled. A model without prosthesis (baseline) and one with prosthesis with D and H based on commercially available sizes were generated for each patient. The frame height was also increased and decreased in additional models. Cases 1, 3, 4 and 5 have moderate to good ejection fraction, while Case 2 is a heart failure patient with a severely dilated ventricle. In this latter case no obstruction fraction was observed with any of the valve sizes tested. Fig. 3A illustrates the blood flow dynamics at mid-diastole and mid-systole for Case 1 at baseline (Case 1A) and with the largest frame height tested (Case 1D). In Case 1A, three vortices were observed during filling: the main early diastolic vortex below the mitral valve leaflets, a smaller counter-rotating vortex in the apical region and a large vortex in the outflow tract during the second
half of diastole. Changes to these flow features took place when a prosthetic valve was added to the model (Case 1D). The apical vortex disappeared, while the outflow tract vortex was disrupted by the presence of the frame and the blood flow velocity in this region decreased significantly compared to that in Case 1A in the same phase. Finally, the region of maximum flow velocity (originally found just above the apical vortex in Case 1A) was progressively shifted towards the upper part of the cavity and away from the apex. Similar features were also observed in Case 3, 4 and 5. The pressure isocontours and the IVPG in the LVOT were also substantially different (Fig 3B). The sudden drop in the peak systolic IVPG suggests that the obstruction due to the valve frame can cause a pressure recovery as the blood flows through the narrowing, generating a localised decrease in the pressure gradient between this “bottle-neck” and the aortic valve. However, the total IVPG between the apex and the aortic valve increased in all cases with increasing OF due to the higher resistance to the outflow caused by the obstruction, with an almost linear increase of up to 38% in the peak IVPG observed for OF values up to 40%. Finally, in the models with an implanted valve, the percentage increase in power loss due to friction was calculated with respect to the baseline model in each case (with the exception of Case 2, where no obstruction was observed due to the dilated cavity and to the large $a$). An increase in power loss between 30% and 45% was observed in Case 1, 4, and 5 in the models with a commercial size of valve (Fig. 4). This relationship was not observed in Case 3, which showed no significant change in power loss for increasing OF; in this patient the lowest frame height was found to lower the power loss with respect to the baseline case, suggesting an improvement of efficiency.

In conclusion, this modelling approach was initially applied to one case with pre- and post-TMVR imaging datasets for validation of its potential to predict LVOT obstruction and blood flow after TMVR. Models of 5 patients were then created to predict the patient-specific haemodynamic response of the left ventricle to a prosthetic valve implantation. This showed that the presence of the device, when associated with a degree of outflow obstruction, leads to a mitigation of the peak systolic IVPG in the LVOT that can be linked to the pressure recovery caused by the narrowing of the LVOT due to the valve frame. However, the peak systolic IVPG between apex and aortic valve was found to rise proportionally to the percentage of obstruction, with a linear increase of up to 38% for OF values up to 40%. This was also associated with an increase in the power loss due to friction, suggesting that larger prostheses might result in decreased haemdynamic performance during systole. Overall these models provides a way to quantify two key metrics to assist the clinical decision making process in TMVR, i.e. the degree of obstruction caused by different valve sizes, and the associated changes in the systolic pressure gradients before implantation.

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AN EFFICIENT VALVE MODEL BASED ON RESISTIVE IMMERSED SURFACES ENHANCED WITH PHYSIOLOGICAL DATA

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SUMMARY

In order to reduce the complexity of heart hemodynamics simulations, one-way coupling approaches are often considered as an alternative to fluid-structure interaction (FSI) models. A possible shortcoming of these simplified approaches is the difficulty to correctly capture the pressure dynamics during the isovolumetric phases. In this work, we propose an enhanced resistive immersed surface (RIS) model of cardiac valves which overcomes this issue. The benefits of the model are investigated and tested in blood flow simulations of the left heart.

Key words: Heart hemodynamics, Resistive immersed surfaces, One-way coupling.

1 INTRODUCTION

Despite the major progress achieved during the last fifteen years (see, e.g., [1, 2]), the full simulation of heart hemodynamics with FSI remains a very challenging problem in scientific computing. Among the main fundamental difficulties, we can mention the large deflections of interfaces, the topology changes induced by contacting leaflets and the subsequent high pressure-drops. In order to mitigate the complexity of the problem, simplified models have recently been proposed (see [3, 4, 5, 6]). Basically, these approaches combine a simplified modeling of valves dynamics with an one-way kinematic coupling of the heart hemodynamics with the myocardium mechanics. This means that synthetic or measured displacements are imposed on the boundaries of the fluid cavities.

The reduced complexity of replacing a full FSI model in the heart with a one-way coupling approach comes however at a price. Indeed, since the dynamical aspects of the coupling are neglected, pressure within the ventricle is not correctly determined during the isovolumetric phases. In this work, we propose an approach which overcomes this issue. The main idea consists in enhancing a resistive immersed surface (RIS) model for valves dynamics [6, 7] with pressure data coming from measurements or from mechanical simulations. Thus, with this improvement, both kinematic and dynamic aspects of the coupling between fluid and structure are taken into account allowing the correct definition of the pressure when both valves are closed.

2 METHODOLOGY

For the sake of simplicity, we consider only the two fluid cavities – left ventricle and atrium – of the left heart. The corresponding fluid domain is denoted by $\Omega(t)$. We assume that its boundary $\partial\Omega(t)$ is partitioned as $\partial\Omega(t) = \Gamma_{\text{wall}}(t) \cup \Gamma_{\text{ext}}(t)$, where $\Gamma_{\text{wall}}(t)$ corresponds to the part where the motion is prescribed (i.e., the internal walls of the ventricle and the atrium) and $\Gamma_{\text{ext}}(t)$ to the external boundaries (i.e., the aorta and pulmonary veins) where a given pressure $p_{\text{ext}}$ is enforced. We denote by $n$ the outward unit normal to $\partial\Omega(t)$. The closed configurations of the aortic and mitral valve are given in terms of an oriented surface denoted $\Sigma(t)$, immersed in $\Omega(t)$, and with an unit normal $n_{\Sigma}$ (pointing outwards the left ventricle).
The opening and closing dynamics of the aortic and mitral valves are described by a simplified immersed resistive surface model [6, 7] in which the mechanics of the leaflets are neglected. We assume that the pressure within the left ventricle $p_{LV}$ is known (e.g., via measurements or simulations) and that both $p_{ext}$ and $p_{LV}$ are homogeneous in space. We introduce the notation $\delta P = p_{ext} - p_{LV}$. The dynamics of the blood velocity $u$ and pressure $p$ in $\Omega(t)$ are described by the following system involving the Navier-Stokes equations in ALE formalism where $\cdot_A$ is the ALE time derivative and $w$ is the computational mesh velocity:

$$
\rho \left( \frac{\partial u}{\partial t} \right)_A + (u - w) \cdot \nabla u - \nabla \cdot \sigma(u, p) + (R(t)(u - w) + \delta P \sigma_{\Sigma(t)}) \delta \Sigma(t) = 0 \quad \text{in} \quad \Omega(t),
$$

$$\nabla \cdot u = 0 \quad \text{in} \quad \Omega(t),
$$

$$u = w \quad \text{on} \quad \Gamma_{wall}(t),
$$

$$\sigma(u, p)n = -p_{ext}n \quad \text{on} \quad \Gamma_{ext}(t).$$

Here, the symbol $\delta \Sigma(t)$ denotes Dirac’s measure on $\Sigma(t)$ and $R(t)$ is a time-dependent function, with values in $[0, R_{max}]$, which describes the opening and closing dynamics of the valves (see [6, 7]). Note that (1)$_1$ enforces the following interface condition across $\Sigma(t)$:

$$[\sigma(u, p)n_{\Sigma(t)}] + R(u - w) = -\delta P n_{\Sigma(t)} \quad \text{on} \quad \Sigma(t).$$

where the symbol denotes the $[,]$ jump across $\Sigma(t)$. Using the incompressibility condition (1)$_2$, we can show that in the case of both valves are closed (i.e., $R(t) = R_{max}$), the relation (2) yields $R_{max}^{-1} (p - p_{ext}) = -R_{max}^{-1} \delta P$ in the left ventricle, so that $p$ is equal to $p_{LV}$ as wished. The case $\delta P = 0$, i.e., without any interface pressure correction, corresponds to the original immersed resistive surface model [6, 7], which enforces $p = p_{ext}$ during the isovolumetric phases.

3 RESULTS

The motion of the endocardium is prescribed using a displacement field obtained from an electromechanical model of the heart [8]. This displacement is extended to the inside of the ventricle using an appropriate non-linear lifting operator [9]. The aortic valve model comes from a computerized tomography (CT) scan and the mitral valve model has been designed with the software 3-matic from physiological in vivo data [10]. Finally, the physiological ventricular pressure $p_{LV}$ used for the correction in our tests comes from the above mentioned electromechanical simulations [8].

In order to illustrate the difficulties mentioned in the introduction, we first present the results obtained without any correction in the RIS model. In terms of blood velocity and vortices, we computed the velocity field for a typical cardiac cycle lasting 0.8 s. Its typical shape during the filling of the ventricle is depicted in Figure 1 (left). These results are relatively close to the behavior observed in in vivo experiments [4, 11]. Blood flow is oriented towards the anterior side of the ventricle surface inducing a local vortex near the apex before the opening of the aortic valve. These results are representative of other 3D simulations we ran. On the contrary, the pressure shows a non-physiological behavior during isovolumetric phases (i.e., when both valves are closed). In vivo studies [12] show that the ventricular pressure should decrease towards the atrium pressure immediately after the closing of the aortic valve. In the simulations, it remains equal to the aortic pressure for an additional period of around 0.20 s, as depicted in Figure 1 (right).

To highlight the benefits of the proposed correction, a comparison of the computed pressure with and without the new term is carried on with a simplified geometry of the heart. The setting of this toy model is presented in Figure 2 (left). The pressure is set to 100,000 dyn/cm$^2$ at the outlet and to 0 dyn/cm$^2$ at the inlet. An arbitrary periodic displacement has been applied on the ventricle’s boundaries $\Gamma_2$ to simulate the beating of the heart. Finally, the imposed pressure $p_{LV}$ is a periodic function we chose – depicted in Figure 2 (right) – mimicking the global behavior of the ventricular pressure in real physiological cases. Each change of value of $p_{LV}$ corresponds to the closing or opening of a valve. This is simultaneous with the change of value of the resistance of the valves as shown in Figure 2 (right).
The results obtained with the toy model are presented in Figure 3. In Figure 3 (left), no correction is applied. The computed pressure inside the ventricle is then not well-defined when both valves are closed and get an arbitrary intermediate value between atrium’s pressure and aorta’s pressure. In Figure 3 (right), the correction is applied on both closed valves. One can observe that the ventricular pressure is now correctly defined when both valves are closed and equal to $p_{LV}$, the chosen imposed pressure.

Figure 1: Typical computed results in the realistic full heart model. On the left: 2D cut of the velocity field in cm/s during ventricle’s filling. On the right: volume-averaged pressure values in dyn/cm$^2$ with respect to the time in s during a cardiac cycle. The atrium is colored in red, the ventricle in yellow and the aorta in blue.

Figure 2: Definition of the toy model. On the left: definition of volumes ($\Omega_i$), boundaries ($\Gamma_i$) and RIS ($\Sigma_i$). On the right: definition of the pressure imposed on the ventricle $p_{LV}$ in dyn/cm$^2$ and of the resistance of each valve with respect to the time in s.

Figure 3: Comparison of volume-averaged pressure values in dyn/cm$^2$ with respect to the time in s for the toy model. On the left: results computed without corrective term. On the right: results computed with corrective term. The atrium is colored in red, the ventricle in yellow and the aorta in blue.

4 CONCLUSION

A new reduced model for heart valves has been presented to correct the problem of definition of the ventricular pressure during isovolumetric phases. It consists in enhancing the original RIS model with an additional term involving a priori data on the ventricle pressure during the isovolumetric phases. Several tests have been performed to illustrate its benefits: a simulation on a full heart model without any correction to highlight the problem and a comparison of the computed pressure on a simplified geometry with and without the correction.
The proposed approach offers a good compromise between complex fully coupled fluid-structure simulations and physiologically inaccurate one-way coupling simulations. The next step will be the integration of this strategy into the left heart model in order to correctly simulate the opening and closing of the valves as well as the correct ventricular pressure during the whole cardiac cycle.

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REFERENCES


HEMODYNAMICS OF THE AORTIC JET AND IMPLICATIONS FOR DETECTION OF AORTIC STENOSIS MURMURS

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SUMMARY

In this study, a one-way coupled hemodynamic-hemoacoustic method is used to study the murmurs generated in a modeled aorta with different degrees of aortic valve stenosis. The blood flow is solved by a sharp-interface immersed boundary method (IBM). Wall pressure from the flow is used as the source for the acoustic simulation, wherein high-order numerical schemes are employed to solve the linear viscoelastic wave equation. Flow simulations show that the location of the maximum pressure fluctuation is not very sensitive to the degree of stenosis. Acoustic simulations show that the murmur source location can be predicted accurately from epidermal surface signal.

Key words: heart murmurs, hemodynamics, hemoacoustics, multiphase simulation

1 INTRODUCTION

It is widely recognized that early detection and treatment of heart diseases can reduce mortality as well as the cost of therapy dramatically [1]. Cardiac auscultation, a technique based on the fact that different heart conditions produce distinct heart murmurs [2], has been the diagnostic modality of choice for over a hundred years for early detection, since it is non-invasive and inexpensive. However, despite this long history, we still lack a full understanding of the biophysics behind cardiac auscultation. An aortic stenosis is known to generate distinct ejection murmurs [3, 4] and here we use computational modeling to study the biophysics of aortic stenosis murmur generation and propagation.

2 METHODOLOGY

Blood in large vessels is usually treated as Newtonian fluid [5], and it is governed by the following incompressible Navier-Stokes equation,

\[
\frac{\partial U_i}{\partial t} + U_j \frac{\partial U_i}{\partial x_j} + \frac{1}{\rho_f} \frac{\partial P}{\partial x_i} = \frac{1}{Re} \frac{\partial^2 U_i}{\partial x_j \partial x_j}, \quad \frac{\partial U_i}{\partial x_i} = 0, \quad i, j = 1, 2, 3
\]

where \( U_i \) is the flow velocity vector, \( P \) is the pressure, \( \rho_f \) is the fluid density, and \( Re \) is the Reynolds number based on the inlet diameter (\( D \)) and inlet velocity (\( U \)). The computational domain is illustrated on the left side of Fig. 1. \( Re \) is set to 2000 in this study, and this is located in the transitional flow regime. The direct numerical simulation (DNS) is employed for these simulations and a carefully-designed grid refinement study is carried out to ensure that the current 128(width) × 384(length) × 370(height) grid, is capable of capturing flow behaviors accurately. In this study, we assume a steady flow through aortic valve in order to eliminate the complexity of flow pulsatility. Furthermore, the stenosed aortic valve at peak systole is modeled in a simple way by assuming a smooth area constriction.
The time history of the wall pressure on the modeled aorta is stored and used as the boundary condition for the acoustic simulations, as shown on the right side of Fig. 1. The modeled thorax is treated as a homogeneous linear viscoelastic material in which the deformation is governed by the following equation

\[
\frac{\partial \mathbf{v}_i}{\partial t} + \frac{1}{\rho_s} \frac{\partial p_{ij}}{\partial x_j} = \frac{\eta}{\rho_s} \frac{\partial}{\partial x_j} \left( \frac{\partial \mathbf{v}_i}{\partial x_j} + \frac{\partial \mathbf{v}_j}{\partial x_i} \right),
\]

\[
\frac{\partial p_{ij}}{\partial t} + \frac{\lambda}{\rho_s} \frac{\partial u_k}{\partial x_k} \delta_{ij} + \mu \left( \frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i} \right) = 0,
\]

where \(\mathbf{v}_i\) is the structural velocity vector, \(\rho_s\) is the tissue density, \(\eta\) is the viscosity, and \(\lambda, \mu\) are the first and second Lame's constant of the material.

The thoracic domain is discretized by a 190 \times 360 \times 220 uniform Cartesian mesh, and the interface between the modeled aorta and the modeled thorax is treated by a high-order approximating polynomial method [6]. To accurately capture the wave propagation, a sixth-order compact scheme is used for spatial discretization, and a fourth-order Runge-Kutta method is used for time marching.

3 RESULTS

3.1 Hemodynamics

Results from three different degrees of area-stenosis (s), 50%, 75% and 90%, will be presented here. The stenosis is axisymmetric, so the jet velocity (\(u_j\)) and jet diameter (d) can be calculated as follows

\[u_j = U/(1 - s),\quad d = D\sqrt{1 - s} .\]

Fig. 2 shows the distribution of computed vorticity on the frontal plane of the modeled aorta. In all three cases, we can observe a jet forming at the stenosis, and breaking down further downstream. In the 50% and 75% stenosis cases, the jet remains laminar for a noticeable distance after the stenosis, while, in the 90% case, the instability comes into effect immediately, causing an early transition in the jet. According to previous study [7], while arterial murmurs do not correlate well with the turbulent structures in the post-stenotic region, but they do correlate well with wall pressure fluctuation. Here, since the inflow is steady, the pressure fluctuation is simply calculated by \(p' = p - \bar{p}\), where \(\bar{p}\) is the time averaged pressure. Fig. 3 shows the surface distribution of the root-mean-square (RMS) of the wall pressure fluctuation. In the 50% and 75% stenosis cases, low-magnitude pressure fluctuations are observed at the jet impingement point. However, in the 90% case, the jet impingement location shows the strongest fluctuation. This is consistent with Fig. 2, as the jet in the 90% stenosis starts transitioning before it hits the lateral wall, while the impinging jet is still quite laminar in the first two cases. To qualitatively identify the main source of the murmurs, the temporal history of pressure fluctuation at various locations on the anterior surface of the modeled aorta are monitored (see Fig. 4.1). The recorded signal is then used to calculate the spectral energy distribution. The monitor points with the highest intensity are marked with arrows in Fig. 4.1. The colors of the arrows match that of the legend of each case. Fig. 4.1 clearly shows that the main sources of the murmurs are located downstream of the stenosis, and are clustered within 1D of each other. Since
the peak locations are relatively insensitive to the severity of the stenosis, it might serve as a good metric to distinguish aortic stenosis from other heart conditions in clinic.

Figure 2 Vorticity component ($\Omega d/u_0$) distribution on the frontal plane of the modeled aorta. Positive value means pointing outward of the plane.

Figure 3 Root-mean-square (RMS) of the wall pressure fluctuation ($p'/(\rho_f u_0^2)$) distribution.

Figure 4 1) Monitor points (marked by red dots) is evenly distributed on the anterior surface of the aorta. Spectral energy ($p^2/(\rho^2 U^4)$) calculated from the pressure history on the monitor points for 2) 50%, 3) 75% and 4) 90% cases is plotted against y axis; the peak location is indicated in 1) with matching color arrows.

3.2 Hemoacoustics

Similar to the hemodynamic simulations a group of monitor points are placed on the anterior surface of the modeled thorax (colored in red in Fig. 5.1). The wall-normal velocity is recorded and used to calculate the epidermal surface signal intensity. Fig. 5.2-5.4 are the two-dimensional projection of the anterior surface, and the outlines of the aorta are included for clarity. The red regions in these plots indicate the locations with the highest acoustic signal intensity and are related to the source of
the murmur. We can see that they show great agreement with the sources predicted in Fig. 4.1. This indicates that, for this simple configuration, the surface signal can accurately predict the source of the murmurs.

![Image](image.png)

Figure 5 1) Epidermal surface of the modeled thorax. Spatial distribution of the intensity of the surface signal calculated from the wall-normal velocity history on anterior surface for 2) 50%, 3) 75% and 4) 90% case.

4 CONCLUSIONS

The hemodynamics and hemoacoustics of aortic stenosis murmurs are modeled in order to understand the biophysics behind cardiac auscultation. A modeled aorta with three different degrees of stenosis, 50%, 75% and 90%, is employed. The hemodynamic simulations indicate that the main source of the murmur lies in the post-stenotic region. The severity of the stenosis has a limited effect on the source location. The hemoacoustic simulations find that when the thorax is treated as a homogeneous material, the epidermal surface signal accurately predicts the source of the murmur in all three cases. Future study will focus on the effect of flow pulsatility and material heterogeneity on the murmurs.

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UNIFIED CONTINUUM FLUID-STRUCTURE INTERACTION MODELING OF THE LEFT VENTRICLE WITH AORTIC VALVES

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SUMMARY

In this paper we present a finite element model of the blood flow in the left ventricle (LV), including fluid-structure interaction (FSI) simulation of aortic valves. A Unified Continuum (UC) approach is used to discretize the combined (unified) fluid-structure continuum using a finite element method. The computational mesh tracks the structure deformation, and mesh smoothing is used in the fluid part of the domain to maintain mesh quality. Modeling of contact between the leaflets is part of the UC-FSI method, and the model is implemented in the FEniCS-HPC open source software framework that is shown to scale to thousands of cores.

Key words: keyword 1, keyword 2, keyword 3

1 INTRODUCTION

The context of this work is the development of a patient-specific finite element simulation model of the blood flow in the left ventricle (LV), to be used as a complement to medical imaging in a clinical setting. In previous work we have established a patient-specific simulation pathway, for which the LV model is individualised based on echocardiography data \cite{1}.

In this work we focus on the extension of the LV finite element model to include the fluid-structure interaction (FSI) of the aortic valves. Computational modeling of aortic valves poses several challenges, including: (i) the formulation of suitable geometric and constitutive models, and (ii) solving the coupled FSI problem. Here we extend the LV finite element model of the blood flow in the LV to include FSI simulation of valves, where we use a Unified Continuum (UC) approach to discretize the combined (unified) fluid-structure continuum using one monolithic finite element method. We let the computational mesh track the structure deformation, and in the fluid part of the domain we employ mesh smoothing to maintain mesh quality \cite{2}.

2 METHODOLOGY

The LV model is based on a local ALE finite element method, with the deformation of the endocardium provided as data obtained from echocardiography. The valve models are explicitly represented aligned with the mesh, and the moving leaflets result in mesh deformation in the fluid part of the domain, which is mitigated by mesh smoothing algorithms. The coupled equations are solved using a monolithic approach based on the UC model of the ALE-FEM-FSI problem including also contact between the leaflets, which is handled within the UC model by changing constitutive law for fluid elements that are identified as being inside a contact zone.

The models are implemented in Unicorn \cite{3} as part of the FEniCS-HPC open source software \cite{4}. Unicorn run on regular workstations or laptops, but is also optimized for massively parallel hardware architectures opening for large scale simulations using supercomputers.
3 RESULTS AND CONCLUSIONS

Preliminary results for the LV model including aortic valves are illustrated in Figure 1 for a mechanical bileaflet valve, and in Figure 2 for a native biological valve. The mechanical bileaflet valve is attached to the patient-specific LV model, whereas the biological valve is separated from the LV model, connected by boundary conditions only.

The full LV model including valves currently run on the Cray XC40 system Beskow at the PDC Center for High Performance Computing at KTH.

We note from these preliminary results that the computational model is robust, including contact between the leaflets, see Figure 3. Basic flow characteristics reported in the literature are also observed in the simulations.

In this work we extend these results by also connecting the biological valve model to the LV. Validation, robustness and uncertainty quantification of the complete patient-specific pathway is investigated elsewhere [1].

![Figure 1](image1.png)

Figure 1: Simulation of blood flow in the LV model with a mechanical bileaflet valve model attached. The images illustrate the mesh deformation as the leaflets open and close (left), and the connection of the LV and valve models (right).

REFERENCES


Figure 2: Illustration of the finite element model of the aortic root and the biological valve.

Figure 3: The deformation of the biological valve mesh and the corresponding geometric orifice area (GOA) over one heart cycle, illustrating in particular the contact between the leaflets.
FLUID-COMPOSITE STRUCTURE INTERACTION AND BLOOD FLOW

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SUMMARY

This work discusses a class of fluid-structure interaction problems involving composite, multi-layered structures interacting with the flow of an incompressible, viscous fluid. One example is the interaction between blood flow and arterial walls with and without vascular prostheses called stents, where arterial walls are modeled as multilayered structures. We show that the presence of a thin fluid-structure interface with mass corresponding to the intimal layer, smooths out the propagation of the pressure wave in the arterial system. Furthermore, our FSI simulations indicate high intramural strain gradients within the arterial wall with atheroma, treated with vascular stents, which may be a precursor for in-stent restenosis.

Key words: composite structures, arterial walls, fluid-structure interaction

1 INTRODUCTION

Fluid-structure interaction problems with composite structures arise in many applications. One example is the interaction between blood flow and arterial walls. Arterial walls are composed of several layers, each with different mechanical characteristics and thickness. Thus, we focus on a nonlinear fluid-structure interaction (FSI) problem between an incompressible, viscous fluid and a composite elastic structure consisting of two layers: a thin layer (membrane) in direct contact with the fluid, and a thick layer (3D linearly elastic structure) sitting on top of the thin layer. The coupling between the fluid and structure, and the coupling between the two structures is achieved via the kinematic and dynamic coupling conditions modeling no-slip and balance of forces, respectively. The coupling is evaluated at the moving fluid-structure interface with mass, i.e., the thin structure. To solve this nonlinear moving-boundary problem in 3D, both a monolithic and a partitioned scheme were developed. They are combined with an Arbitrary Lagrangian-Eulerian (ALE) approach to deal with the motion of the fluid domain. By using this class of models we show how multi-layered structure of arterial walls influences the pressure wave propagation in arterial walls, and how the presence of atheroma and the presence of a vascular device called a stent, influence intramural strain distribution throughout different layers of the arterial wall. The detailed intramural strain distribution provided by this model can be used in conjunction with ultrasound B-mode scans as a predictive tool for an early detection of atherosclerosis.

2 METHODOLOGY

We developed a loosely-coupled scheme (a kinematically coupled $\beta$-scheme \cite{11}) and a monolithic scheme \cite{3} to solve the following fluid-structure interaction problem.
Fluid. The fluid flow in $\Omega^f(t)$ is governed by the Navier-Stokes equations for an incompressible, viscous fluid:

$$\rho_f (\partial_t u + (u \cdot \nabla)u) - \nabla \cdot \sigma = 0$$
$$\nabla \cdot u = 0$$

for $t \in [0, T]$, where $\rho_f$ is the fluid density, $u$ is the fluid velocity and $\sigma$ the Cauchy stress tensor. For Newtonian fluids $\sigma$ has the following expression $\sigma(u, p) = -pI + 2\mu_f \epsilon(u)$, where $p$ is the pressure, $\mu_f$ is the fluid dynamic viscosity and $\epsilon(u) = (\nabla u + (\nabla u)^T)/2$ is the strain rate tensor. The fluid is driven by the inlet and outlet boundary conditions:

$$\sigma n^f_{in} = -p_{in}(t)n^f_{in}$$
$$\sigma n^f_{out} = -p_{out}(t)n^f_{out}$$

where $n^f_{in}$ and $n^f_{out}$ are the outward normals to the inlet and outlet fluid boundaries, $\Gamma^f_{in}$ and $\Gamma^f_{out}$, respectively.

Structure. The structure equations are defined in Lagrangian coordinates in terms of the displacement field $d$ of the thick structure from its given material reference configuration $\hat{\Omega}^s$, and, for the thin structure, in terms of the displacement $\eta$ from its reference configuration $\hat{\Gamma}$. The equations governing the elastodynamics of the thick structure are given by the equations of 3D linear elasticity:

$$\rho_s \partial_t d - \nabla \cdot \Sigma(d) = 0$$

where $\rho_s$ is the density of the thick structure, and $\Sigma(d)$ is the first Piola-Kirchhoff stress tensor. We assume $\Sigma(d) = 2\mu_s \epsilon(d) + \lambda_s (\nabla \cdot d)I$. Here, $\epsilon(d) = (\nabla d + (\nabla d)^T)/2$ is the strain rate tensor, $\mu_s$ and $\lambda_s$ are the Lamé constants. We assume that the structure is clamped at the inlet and outlet sections $\Gamma^s_{in}$ and $\Gamma^s_{out}$, and that the normal stress at the external structure boundary $\Gamma^s_{ext}$ is equal to zero:

$$d = 0$$
$$\Sigma(d) n^s_{ext} = 0$$

where $n^s_{ext}$ denotes the outward normal to $\Gamma^s_{ext}$.

The thin structure elastodynamics is described by a model for a linearly elastic, isotropic membrane, proposed in [2]. In weak form, the model is given by the following:

$$\rho_m h \int_{\Gamma} \partial_t \eta \cdot \zeta d\Gamma + h \int_{\Gamma} \Pi_\gamma(\eta) : \nabla_\gamma \zeta d\Gamma = \int_{\Gamma} [\Pi_\gamma(\eta) n^s] : \zeta d\Gamma \quad \forall \zeta \in V^m,$$

where $[\cdot]$ on the right hand-side denotes the jump (in the normal stress across $\hat{\Gamma}$), and the test space $V^m$ for the clamped membrane problem is given by: $V^m = \{ \zeta \in (H^1(\hat{\Omega}^s))^3 | \zeta_{|_{\Gamma}} \in (H^1(\Gamma))^3, \zeta = 0 \text{ on } \Gamma^s_{in/out} \}$. Here $\eta = (\eta_x, \eta_y, \eta_z)$ denotes the structure displacement, $\rho_m$ denotes the structure density, $h$ denotes the structure thickness, $n^s$ is the outward normal to the solid domain $\hat{\Omega}^s$, and

$$\Pi_\gamma(\eta) = \frac{E_m}{1 + \nu_m} \epsilon_\gamma(\eta) + \frac{E_m \nu_m}{1 - \nu_m} \nabla_\gamma \cdot \eta,$$

where $\epsilon_\gamma(\eta) = (\nabla_\gamma \eta + (\nabla_\gamma \eta)^T)/2$, $\nabla_\gamma \cdot \eta = \text{Trace}(\epsilon_\gamma(\eta))$ and $\nabla_\gamma(\cdot)$ denotes the surface gradient. Practically, the surface gradient can be computed as $\nabla_\gamma(\eta) = \nabla_\eta(I - n^s \otimes n^s)$, where the symbol $\otimes$ denotes the outer product and $I$ is the identity operator. The coefficients $E_m$ and $\nu_m$ are the membrane Young’s modulus and the Poisson’s ratio, respectively.

Initially, the fluid, the thin structure and the thick structure are assumed to be at rest, with zero displacement from the reference configuration:

$$u = 0, \quad d = 0, \quad \eta = 0, \quad \partial_t d = 0, \quad \partial_t \eta = 0, \quad \text{at} \quad t = 0.$$
The ALE mapping. In order to describe the evolution of the fluid domain, we adopt an *Arbitrary Lagrangian-Eulerian* (ALE) approach. We consider an ALE mapping $\mathcal{A}$ that maps the reference domain to a current domain via the harmonic extension of the boundary data (location of the boundary) onto the entire domain. The domain velocity $\mathbf{w}$ is then defined as

$$\mathbf{w}(t, \cdot) = \frac{d\mathcal{A}}{dt}(t, \mathcal{A}(t, \cdot)^{-1}),$$

where $\mathcal{A}$ is the ALE mapping. Recall that the ALE time derivative of a function $F$ can be written as:

$$\partial_t F\big|_x = D_t F(t, \mathcal{A}(t, x)) = \partial_t F(t, x) + \mathbf{w}(t, x) \cdot \nabla F(t, x), \text{ for } x = \mathcal{A}(t, \mathbf{x}), \mathbf{x} \in \hat{\Omega}^f,$$

where $D_t$ denotes the total derivative with respect to time. With these definitions, we can write the incompressible Navier-Stokes equations in the ALE formulation as follows:

$$\rho_f \partial_t \mathbf{u} + \rho_f (\mathbf{u} - \mathbf{w}) \cdot \nabla \mathbf{u} - \nabla \cdot \mathbf{\sigma} = 0 \quad \text{in } \Omega^f(t), \quad (11)$$

$$\nabla \cdot \mathbf{u} = 0 \quad \text{in } \Omega^f(t), \quad (12)$$

for $t \in [0, T]$. Since the time derivative is now computed on the reference domain, the ALE formulation is well-suited for the time discretization.

**Coupling conditions.** The fluid and the composite structure are coupled via the kinematic and dynamic boundary conditions. The *kinematic coupling conditions* describe continuity of velocity at the fluid-structure interface and continuity of the displacement (glued structures): (no-slip condition)

$$\mathbf{u} \circ \mathcal{A} = \partial_t \eta, \quad \eta = \mathbf{d} \quad \text{on } \tilde{\Gamma} \times (0, T). \quad (13)$$

The *dynamic coupling condition* describes the second Newton’s law of motion of the fluid-structure interface:

$$J \frac{\partial \mathbf{n}^f}{\partial t} \big|_{\Gamma(t)} + \mathbf{\Sigma} n^s + \mathbf{\Pi}_f(\eta) n^s = 0 \quad \text{on } \tilde{\Gamma} \times (0, T), \quad (14)$$

where $J$ denotes the Jacobian of the transformation from Eulerian to Lagrangian coordinates, and $\mathbf{n}^f = \frac{\partial \mathbf{w}}{\partial \mathbf{x}}$ denotes the normal fluid stress at the deformed fluid-structure interface, evaluated with respect to the reference configuration. Vector $\mathbf{n}^f$ is the outward unit normal to the deformed fluid domain. Since equation (14) states that the load acting on the thin structure is equal to the jump in the normal stress across it, the dynamic coupling condition (14) defines the dynamics of the thin fluid-structure interface with mass, and can be written as:

$$\rho_m h \int_\Gamma \partial_t \eta \cdot \mathbf{\zeta} d\Gamma + h \int_\Gamma \mathbf{\Pi}_f(\eta) : \nabla \mathbf{\zeta} d\Gamma = - \int_\Gamma \left( J \frac{\partial \mathbf{n}^f}{\partial t} \big|_{\Gamma(t)} + \mathbf{\Sigma} n^s \right) : \mathbf{\zeta} d\Gamma, \forall \mathbf{\zeta} \in \mathbf{V}^m.$$

### 3 RESULTS AND CONCLUSIONS

![Figure 1: Fluid-structure interface displacement (top) and velocity (bottom) shown at times $t = 1$ ms, $t = 6$ ms, and $t = 12$ ms. Notice dissipative effects by the fluid-structure interface with mass, shown in dashed line.](image)

We compared the solutions of the fluid-multi-layered structure interaction problem with the solutions of the FSI problem containing a single layered structure (a thick structure) of the same combined...
thickness as the thin-thick case. Our results indicated that the presence of the thin fluid-structure interface with mass regularizes the solution of the full FSI problem. The top row in Fig. 1 shows the plots of the fluid-structure interface with mass at three different times ($t = 1$, $t = 6$, $t = 12$ ms), while the bottom row in the same figure shows the plots of the fluid-structure interface velocity at the same times. The red curves correspond to the case when only one thick structure is present, while the dashed curves correspond to the case with the thin-thick structure. We see dissipative behavior in the second case due to the inertia of the fluid-structure interface with mass. This was mathematically justified in [4]. Therefore, we conclude that the presence of a thin fluid-structure interface regularizes the FSI solution. This produces a pressure wave traveling with a smaller amplitude and a slight delay.

Figure 2: Fluid-structure interface displacement (top) and velocity (bottom) shown at times $t = 1$ ms, $t = 6$ ms, and $t = 12$ ms.

We conclude this abstract by showing the FSI simulations for the flow of blood in a stented artery with atheroma, sketched in Fig. 2 left. Fig. 2 middle and right show the displacement magnitude at the systolic peak of the arterial section containing the stent. Fig. 3 right shows the cross-section of the arterial wall reported in Fig. 2 above, indicating high shear strains in the arterial wall depicted by the range in the colors of intramural displacement within the vascular wall. This is compared with a post-mortem pathological image of a stented artery with restenosis, shown in Fig. 3 left.

Figure 3: Cross-section of arterial wall treated with a stent. Left: Post-mortem pathological image of in-stent restenosis. Right: Intramural axial displacement during systole of arterial wall. Location of stent struts is also shown. Observe large difference in axial displacement within the computationally modeled arterial wall through the cross-sectional cut.

REFERENCES


MULTISCALE MODELING OF RED BLOOD CELLS PASSING THROUGH NARROW SLITS

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SUMMARY

We applied a multiscale model to study the dynamics of red blood cells (RBCs) squeezing through submicron slits. This study is motivated by the mechanical filtration of RBCs by inter-endothelial slits in the spleen. The deformation of RBCs is investigated using numerical simulations by coupling finite element method and boundary element method. The simulations results provided guidance for future experiments to explore the dynamics of RBCs under extreme deformation.

Key words: Boundary integral, finite element, Stokes flow

1 INTRODUCTION

The mechanical filtration of red blood cells (RBCs) by the interendothelial slits in the human spleen plays a significant role in recycling of old RBCs in normal circulation, hereditary blood disorders, and infectious diseases such as malaria. Red blood cells (RBCs), with a diameter around 8 µm, frequently squeeze through the IESs in our spleens with a width less than 1 µm [1, 2]. This is the RBC’s regular ‘physical fitness test’, which actually damages diseased RBCs in malaria, hematological disorders, and sickle cell disease influences 1 billion people (killing 1 million per year) [3]. To maintain the homeostatic of blood, old RBCs after 120 days lifetime are recycled, while millions of new RBCs are generated in bone marrow per second. Old RBC’s lose surface area gradually in the circulation and become less deformable. They cannot pass the IES in the spleen, and trapped or slowed down old RBCs are destroyed and the hemoglobin molecules and iron inside RBCs are recycled by the macrophages, a group of large white blood cells, in the spleen. Although other factors such as exposure of inner PS layer and altered adhesion properties between RBCs and endothelial cells might contribute to the recognition of old RBCs, various evidence shows that mechanical filtration of less deformable old RBCs plays a major role.

2 METHODOLOGY

We solve the fluid-structure interaction problem between RBCs and the narrow slit by combining a boundary-element fluid model with a multiscale structural model of the cell membrane. The fluid model we use is based on the low-Reynolds number assumption and mathematically depicted by boundary-integral equations [6]. In this approach the cell membrane is represented by distributions of Stokeslets, which is then solved using the boundary-element method. In the structural side, the cell membrane is represented by a three-level multiscale model that relates the mechanics of the complete cell to its detailed molecular architecture [7]. The details of the models can be found in our previous publications [4-7].

The potential of the RBC membrane including these two different components is written as

\[ U = U_s + U_b + U_{a+y} + U_{int} \]
where $U_s$ is the spectrin's potential energy from the cytoskeleton, $U_b$ is the bending energy from the lipid bilayer, $U_{a++}$ corresponds to the area and volume conservation constraints from the lipid bilayer, and $U_{int}$ is the potential energy of the interaction between the lipid bilayer and the cytoskeleton. The detailed expressions for $U_s, U_b, U_{a++}$ and $U_{int}$ can be found in [6.7]. The vertex in the spectrin cytoskeletal network is projected onto the closest triangle face of the lipid bilayer, and the distance and relative velocity between the cytoskeleton vertex and its projection point on the lipid bilayer are obtained. The corresponding elastic force on the vertex $i$ of the cytoskeleton is given as $\mathbf{f}_i^e = k_{bs}(d_j - d_{j0})\mathbf{n}_j$, where $\mathbf{n}_j$ is the normal direction of the lipid bilayer surface at the projection point of vertex $i$, $k_{bs}$ is the vertical interaction stiffness, and $d_j$ and $d_{j0}$ are current and initial distances. The tangential friction force between the lipid bilayer and the cytoskeleton on the vertex $i$ of the cytoskeleton is given as $\mathbf{f}_i^f = -f_{bs}[\mathbf{v}_j - (\mathbf{v}_j \cdot \mathbf{n}_j)\mathbf{n}_j]$, where $f_{bs}$ is the tangential friction coefficient, and $\mathbf{v}_j$ is the relative velocity between the vertex $i$ and the corresponding projection point $i'$ on the lipid bilayer.

3 RESULTS

Our two-component model has been validated against various experiments, including micropipette aspiration, thermal fluctuations, tank-treading in shear flow, torque rheology, and confined channel [4-7]. Our results show that the deformed cell shapes predicted in the simulations are consistent with the observed shapes in the microfluidic experiments with narrow slits [8], as shown in Fig. 1. We showed that our numerical approach is capable of simulating the extreme deformation of RBCs in the submicron slits.

![Figure 1. Predicted red blood cell shape in a submicron slit](image)

4 CONCLUSIONS

We applied a multiscale model to study the dynamics of red blood cells (RBCs) squeezing through submicron slits. The extreme deformation of RBCs was investigated. We demonstrated that our numerical algorithm is capable of simulating the large deformation of RBCs. The simulations results provided guidance for future experiments to explore the dynamics of RBCs under extreme deformation.

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MODELING CELL-CELL INTERACTIONS IN YEAST MATING

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SUMMARY

Cell-cell communication is important to cell functionality. Successful cell communication requires coordination of intricate intracellular and extracellular pathways. In this work, we build a computational framework that accounts for the molecular dynamics inside and outside the cell, as well as cell morphogenesis. Through computer simulations, we found strategies that budding yeast cells use for efficient and successful mating. The results will be compared with experiments.

Key words: cell-cell communication, budding yeast, cell signaling, cell polarization

1 INTRODUCTION

Cell-to-cell communication is fundamental to biological processes which require cells to coordinate their functions. A simple strategy adopted by many biological systems to achieve this communication is through cell signaling, in which extracellular signaling molecules released by one cell are detected by other cells via specific mechanisms. These signal molecules activate intracellular pathways to induce cellular responses such as cell motility or cell morphological changes. Proper communication thus relies on precise control and coordination of all these actions.

The budding yeast *Saccharomyces cerevisiae*, a unicellular fungi, has been a model system for studying cell-to-cell communication during mating because of its genetic tractability. In this work, we performed for the first time computer simulations of the yeast mating process. Our computational framework encompassed a moving boundary method for modeling cell shape changes, the extracellular diffusion of mating pheromones, a generic reaction-diffusion model of yeast cell polarization, and both external and internal noise. Computer simulations revealed important robustness strategies for mating in the presence of noise. These strategies included the polarized secretion of pheromone, the presence of the alpha-factor protease Bar1, and the regulation of sensing sensitivity; all were consistent with data in the literature. In summary, we constructed a framework for simulating yeast mating and cell-cell interactions more generally, and we used this framework to reproduce yeast mating behaviors qualitatively and to identify strategies for robust mating.

2 METHODOLOGY

2.1. Mathematical Models of Yeast Mating

As described in the Introduction, mating occurs when an a-cell and α-cell are in close proximity. They sense the pheromone gradient generated by the partner and project toward the source. Cells are labeled with a marker for active Cdc42 ($u_2$ in our simulations), and a marker for the polarisome. From a simulation standpoint, this process can be broken down into a series of steps from the secretion and diffusion of pheromones to the resulting growth in the mating projection.
The models are based on previous work simulating polarization of a single cell with either a static [1] or moving [2] boundary, in which a linear gradient served as the input, and a Lagrangian framework was applied to capture the deformation of the cell membrane. Describing the mating process between two cells required solving diffusion equations for the ligands in the extracellular space, which evolved according to the shifting positions of the pheromone sources. These sources in turn depended on the sensing of the ligand input and the resulting morphological response of the cells. Thus, to capture the shape changes, a level set function was evolved together with the molecule dynamics along the membrane for each cell.

2.1.1. Application of level set method
The previous model with single cell consists of surface diffusion-reaction equations, which is solved in Lagrangian coordinate. However, this approach is hard to apply to the model with more than one cell as well as their interaction involved. Therefore we apply the level set method [3], which can track the moving curve front implicitly by solving a HJ equation. It is also straightforward to extend to the case with multiple cells by introducing the level set functions for different cells respectively. The surface diffusion can be extended equivalently to an operator defined on the entire computational domain. With the level set method, it is also convenient to define the intracellular and extracellular space. Coupling with the pheromone diffusion in the extracellular space becomes straightforward.

2.1.2. Deterministic model
Each cell is represented by the following generic mathematical model. The mating pheromone is denoted by \( f \), which is the external cue of cell polarization. Our model contains two membrane-associated species \( u_1 \) and \( u_2 \) which are initially uniformly distributed and undergo polarization upon sensing the pheromone signal. The system forms a two-stage cascade in which the output of the first stage \((u_1)\) is the input to the second stage. The variables \( v_1 \) and \( v_2 \) provide negative feedback (integral feedback control) to regulate \( u_1 \) and \( u_2 \). The cell grows in the direction determined by \( u_2 \).

This generic model is patterned after the two-stage yeast pheromone-induced cell polarity system [4]. Roughly speaking, the variable \( u_1 \) represents the protein G\( \beta_\gamma \), which is the output of the heterotrimeric G-protein system and the input to the Cdc42 system, and \( u_2 \) represents active Cdc42, which is the master regulator of yeast cell polarization. Finally, the center of the \( u_2 \) distribution represents the polarisome which directs new secretion driving mating projection growth.

Initially, we described the cell as a unit circle. Let \( \phi(x,t) \) be the corresponding level set function which satisfies \( S = \{ x : \phi(x,t) = 0 \} \) and represents the cell membrane for \( t \geq 0 \). Consequently, the level set function separates the whole computational domain \( D \) into two parts: the intracellular space \( \Omega \), consisting of all points such that \( \phi(x,t) < 0 \), and the extracellular region, \( \Omega^c = \{ x : \phi(x,t) > 0 \} \). The dynamics of the diffusing pheromone ligand \( f \) which represents either \( \alpha \)-factor or \( \alpha \)-factor) and the two membrane-associated species \((u_1, u_2)\) are described in Eqs. (1) - (5):

\[
\begin{align*}
\frac{\partial f}{\partial t} &= D_a \Delta f + S_a(x,t) - k_{a}f, \quad x \in \Omega^c \quad (1a) \\
\frac{\partial f}{\partial t} &= D_a \Delta f + S_a(x,t) - k_{a}f, \quad x \in \Omega^c \quad (1a) \\
\frac{\partial u_1}{\partial t} &= D_i \Delta u_1 + \frac{k_{i1}}{1 + (\beta_i f)^{-\eta_i}} + \frac{k_{11}}{1 + (\gamma_i u_1 p_1)^{-\eta_i}} - (k_{i2} + k_{i3} v_1) u_1 \quad (2) \\
\frac{\partial v_1}{\partial t} &= k_{14}(\bar{u}_1 - k_{15}) v_1 \quad (3) \\
\frac{\partial u_2}{\partial t} &= D_i \Delta u_2 + \frac{k_{20}}{1 + (\beta_2 u_1)^{-\eta_2}} + \frac{k_{21}}{1 + (\gamma_2 u_2 p_2)^{-\eta_2}} - (k_{22} + k_{23} v_2) u_2 \quad (4)
\end{align*}
\]
\[
\frac{\partial v_2}{\partial t} = k_{24} (\tilde{u}_2 - k_{2\alpha}) v_2
\]  

(5)

Eqs. (2) - (5) are restricted on the domain \( S = \{ x : \phi(x,t) = 0 \} \). In Eq. (2), instead of \( f \), we use the normalized distribution \( \tilde{f} \); in this definition, the constant 0.1 is added to make the parameter consistent with [2].

The level set function is updated by solving a Hamilton-Jacobi function where the velocity field \( V \) is a function of \( u_2 \), and formulated as

\[
V(x,t) = V_{amp} \cdot u_2 \cdot \langle \tilde{n}, \tilde{d}_{max} \rangle.
\]

(7)

\( V_{amp} \) is a constant specified with respect to the time scale, \( \tilde{n} \) is the unit normal vector equal to \( \nabla \phi / |\nabla \phi| \), and \( \tilde{d}_{max} \) is the growth direction which is defined as the unit normal vector at the center of the polarisome. Note that in Eq. (1) we denote the source of \( \alpha \) pheromone by \( S_\alpha(x,t) \) or \( S_\alpha(x,t) \), which is a localized Gaussian distribution with support on the membrane. Given the above definitions for one cell, it is straightforward to simulate a mating process involving multiple cells of different mating types. In the two-cell simulations, cells initially are a circle of radius 1 centered 4 \( \mu \)m from one another.

3 RESULTS AND CONCLUSIONS

3.1. Robustness Strategies for Optimizing Mating Efficiency

In its natural environment, yeast mating is efficient and robust to a variety of perturbations. In this section, we explored how features of the mating process could promote more robust and efficient mating. Using our simplified simulation framework, we compared different mating scenarios by modifying the model parameters.

3.1.1. Polarized pheromone source distribution

One important variable is the spatial distribution of the pheromone source. There are two main possibilities with respect to the pheromone source: isotropic or non-isotropic (polarized) secretion. In the isotropic scenario, pheromone is secreted uniformly from all points on the membrane. In the non-isotropic scenario, the source would be polarized to the front. Intuitively, one may imagine that the polarized source distribution would contribute to accurate mating by helping the projections find each other, and in the simulations described above we used the polarized source as the default. We compared these two alternatives below.

Figure 1 shows two simulations with different source functions. It is obvious that non-isotropic source can improve the mating efficiency by leading cells to grow in the right direction. Even when cells sense the gradient with some error due to the noises and orient to unaligned directions, the dynamic source can modify its pheromone distribution gradually and clarify the direction, which is necessary to a successful mating in a noisy environment.

3.1.2. The presence of the \( \alpha \)-factor protease \( \text{Bar1} \) improves mating efficiency.

The \( \alpha \)-cell can secrete a protease, \( \text{Bar1} \), to degrade \( \alpha \)-factor around it during the mating. Experimentally, cells without \( \text{Bar1} \) can indeed mate efficiently when the number of \( \alpha \)-cells is not too high; mating efficiency decreases with more \( \alpha \)-cells. The idea is that at denser populations of \( \alpha \)-cells the background level of \( \alpha \)-factor increases without the presence of \( \text{Bar1} \). This background
level can saturate the sensing apparatus in a similar fashion to the supersensitive mutants preventing gradient detection.

We simulated the increase in background α-factor with a new uniform source function. This increased the global α-factor levels while the cells generated the local α-factor dynamics. The simulated bar1Δ cells did not mate as efficiently. Thus Bar1 helps at all concentrations but its beneficial effects increase at higher background concentrations of α-factor.

3.2. Estimate of the a-factor diffusion constant
We imaged mating mixes using both Bar1+ and bar1Δ cells as well as a combination of the two. We found that mating was short-range when the a-cells were Bar1+, i.e., both a- and α-cells made short projections. With the bar1Δ a-cells, there was longer-range mating with only the a-cells forming longer projections. We hypothesized that degradation of α-factor by Bar1 resulting in short-range mating in the Bar1+ matings. The projection length in both simulations and experiments was defined by subtracting the initial cell radius from the distance between the center of the cell and the point that is farthest from the center on the cell membrane. The asymmetry in projections lengths in the bar1Δ matings was reminiscent of our simulations in which we varied the a-factor diffusion rate (data not shown). In particular, as the a-factor and plotted this α-cell length for both simulations and experiments in Fig. 2. In the simulations we varied the a-factor diffusion rate from 0.1 to 100. From this comparison we estimate that the a-factor diffusion rate is 1 µm²/s.

Fig. 2. (A) Projection lengths in bar1Δ versus Bar1+ a-cells. The top two panels are fluorescent images of Spa2-GFP (a-cell) and Spa2-mCherry (α-cell) showing the adjacent/overlapping polarisomes indicating a successful mating. The bottom two panels are DIC images that depict the projection morphologies of the mating cells. Scale bars = 5 µm. (B) The relative projection lengths of α-cells versus a-cells in simulations compared to experiments. In the top bar graph, the α-cell projection length is presented as the fraction of the sum of the two projection lengths (n = 25 matings for Exp.); the average and standard deviation (error bars) are shown. The two-cell simulations with noise were performed for varying α-factor diffusion values: Dα = 0.1, 1, 10, and 100 µm²/s. The average and standard deviation of the normalized α-cell projection length from 10 simulations are shown. In the bottom bar graph, the corresponding unnormalized a-cell and α-cell projection lengths (mean ± SD in µm) are shown. The a-cells in both experiments and simulations are bar1Δ.

REFERENCES

NUMERICAL ANALYSIS OF RETROGRADE FLOW IN THE LAMELLIPIDIUM OF CELL

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SUMMARY

Cells rely on a complex interplay of sub-cellular elements for motility and migration. Certain regions of epithelial and keratocytes cells such as lamellipodium are made of a complex mixture of actin monomers and filaments which, under certain conditions, polymerize at the front of the cell and depolymerize at the rear of lamellipodium. Dynamic actin turnover has been proposed as a fundamental process for leading edge protrusion and cell motility in general. Apart from some examples in the biophysical community, a consistent numerical model to account for such complex interactions is still missing. Here, we adopt a theoretical model of the treadmilling process and perform a fully implicit finite element formulation for its analysis. We consider a constitutive model by a set of PDEs where different forms of actin filaments and actin monomers are considered. Moreover, clear structure and implementation of such coupled problem allows for easy extension of our methodology to include other models or future improvements. Our results shows an excellent correlation with experimental results from literature. All together, our results unveil a promising applicability of our approach to establish a in-silico testing platform for actin treadmiling.

Key words: bio-mechanics, cellular physics, tread-milling, finite element method, coupled-PDEs

1 INTRODUCTION

Actin dynamic is unarguably a fundamental part in cell motility, migration and morphology [1, 2]. And, therefore, it is involved in a large number of applications in bio-mechanics. An explicit understanding of the actin cycle at different spatial and temporal levels of the cell have been, and still is, a jigsaw in biology. Actin dynamics controls a wide range of cellular processes and it has been proposed as a key player in protrusion of the leading edge [3], considered as the main exploratory mechanism of the cellular environment. Motor myosin II team up with actin filaments to establish the mechanisms required for cell polarization [4], contractibility and subsequent crawling [5]. During this intriguing and well orchestrate coupling of subcellular components, actin and myosin II have raised as the most determining ones for cell motility [1]. The backward movement of actin in the cell body is commonly known as retrograde flow, defined as a continuous flow of cellular components from the outer margin of the cell, the leading edge, to the rear of the cell. Retrograde flow is dictated by a passive movement of actin when polymerize agains the plasma membrane or an adventive movement of actin due to myosin pushing forces.

In short, the actin dynamic turnover is dictated by a continuous assembly and disassembly of different elements. Actin monomers nucleized promoted by Formin, Profilin and cofilin [6] and polymerize rapidly after a period of slow nucleation [2, 7]. Actin filaments, F-Actin, are defined as polar (all monomers point in the same direction) acquiring a fast-growing end, the +end or barbed end, and a slow dissociating end, - end or pointed end. The dissociation and disassociation rates control the rate of filament formation [7]. Furthermore, F-Actin undergoes a complex reaction while forming and
disassembling. Barbered ends terminates its formation when capping proteins associate in a process referred as capping inhibiting further growth. Pointed end F-Actin dissociates mediated by ADP and coflin producing ADP-actin dissociations, where ATP replace the ADP bound via profilin, providing a pool of new actin monomer ready to bind the barbered ends \([1, 2]\). Arp2/3 \([3, 2]\), via nucleation by different promoting factors, activates and promotes the formation of new branches of actin filament along the barbed end of the actin filament \([9]\). The Arp2/3-dependent formation of actin filaments has been experimentally demonstrated \([3, 9]\).

Apart from tremendous achievements in experimental cell biology in the context of retrograde flow, mathematical and computational model have kept well behind of its experimental counterparts. Mathematical theories and computational models are highly reliable, reproducible and low-cost tools that can help to unravel many of the open questions in cellular biology. In the context of actin treadmilling Pollard and co-workers\([10]\), among others, stablized the basic mathematical foundation to account for actin polymerization and depolymerization in the context of cell motility. Mogilner and coworkers and impulsed the field with complex and accurate mathematical models \([11, 12]\). Still, many aspects remain elusive in the modeling of such important phenomena.

In this work, we develop a fully implicit finite element model to describe in a coupled fashion how all the actors involved in retrograde flow work together. We focus on fast motile cells, such as keratocytes, where both the protrusion and the retrograde flow speed remains steady along cell crawling. Moreover, we focus on a portion of the front of the cell. Therefore, we can choose as our frame of analysis a system of cell frame of reference that moves at constant speed with the cell. We reproduce some of experimental results reported in literature and we move forward in hypothesis eventual responses due to easy manipulation of cellular mechanisms in our numerical approach.

### 2 METHODOLOGY

#### 2.1 Dynamics of actin monomers

we set the transport equations describing the complex interplay between the different actin monomers forms. We account here for four forms of the actin monomer concentration. Following \([11]\), we consider the concentration of ADP-G-actin-ADF/cofilin \(\rho^s\), ADP-G-actin-profilin \(\rho^p\), ATP-G-actin-profilin \(\rho^a\) and ATP-G-actin-thymosin \(\rho^\beta\). These forms account for the sequestering occurs due to three main proteins, ADF/cofilin, profilin and thymosin. \(\rho^s\) and \(\rho^\beta\) represents the dynamics of ADP-G-actin sequestered by coflin and profilin. \(\rho^p\) and \(\rho^a\) represents the dynamics of ATP-G-actin sequestered by thymosin and profilin. This set of equation can be modeled as follow:

\[
\begin{align*}
\frac{\partial \rho^B}{\partial t} + \gamma \rho^B &= s^B = n \\
\frac{\partial \rho^s}{\partial t} + \mathbf{a} \cdot \nabla \rho^s - \nabla \cdot (\nu \nabla \rho^s) + k_1 \rho^s &= s^4(\rho^s) = k_{-1} \rho^p + J_d \\
\frac{\partial \rho^p}{\partial t} + \mathbf{a} \cdot \nabla \rho^p - \nabla \cdot (\nu \nabla \rho^p) + (k_{-1} + k_2) \rho^p &= s^p(\rho^s) = k_1 \rho^s \\
\frac{\partial \rho^a}{\partial t} + \mathbf{a} \cdot \nabla \rho^a - \nabla \cdot (\nu \nabla \rho^a) + k_{-3} \rho^3 &= s^3(\rho^a) = k_{-3} \rho^3 + k_2 \rho^p \\
\frac{\partial \rho^\beta}{\partial t} + \mathbf{a} \cdot \nabla \rho^\beta - \nabla \cdot (\nu \nabla \rho^\beta) + k_{-3} \rho^3 &= s^\beta(\rho^a, \rho^p) = k_{-3} \rho^3 + k_2 \rho^p
\end{align*}
\]

The above equation define the complex association and dissociation kinetics of actin filaments. The \(s(\cdot)\) terms correspond to source terms of each constituent. The \(\mathbf{a}, \nu, \sigma\) are the convection, diffusion and reaction coefficients. Based on the mathematical description in \([11]\), the convection velocity is same as the protrusion velocity in the cell frame of reference. The rest of the material parameters describe the formation rates of the different constituents. The set of transport equation are discretized in time and space, following a classical finite element formulation (see \([13]\) for more details).

#### 2.2 Linearization of the equations

In order to compute the fully implicit and monolithic non-linear coupling problem of the retrograde flow interaction we recast the residual form of each component in the physical problem. We solve
incrementally the system of equations by means of a Newton-Raphson scheme after the linearization of the discrete equations. The linearization of the residual form can be written as

$$\text{LinR} = R + \partial_\rho R \Delta \rho$$ with

$$R = \begin{bmatrix} R^B & R^s & R^p & R^\beta & R^\alpha & R^{mc} & R^m \end{bmatrix}$$ the residuals and

$$\rho = \begin{bmatrix} \rho^B & \rho^s & \rho^p & \rho^\beta & \rho^\alpha & \rho^{mc} & \rho^m \end{bmatrix}$$ the unknowns

To close up the set-up of the non-linear finite element procedure, the updating for the global unknowns increments $\rho$ are $\rho_{n+1} = \rho_n - R_n \partial_\rho R_n^{-1}$. A 2D domain of a sector in the front of the cell was used with a mesh of 2nd order quadrilateral elements and with appropriate Boundary conditions as suggested in [11].

3 RESULTS

The concentrations at steady state obtained using the fully coupled numerical model, are shown in Fig. 1 along the symmetric axis of the domain. The results are in agreement with [11]. The concentrations of barbed ends, ADP-G-actin-ADF/cofilin, ADP-G-actin-profilin are suggested to be almost uniform by [11]. The full numerical model validates these assumptions, as seen in the figure. The 2-D profiles of ATP-G-actin-thymosin $\rho_\beta$ and ATP-G-actin-profilin $\rho_a$ are shown in Fig. 2.

Two primary sources drive the coupled system to a non-zero solution. One is the $J_d(x)$, the source term for ADP-G-actin-ADF/cofilin ($\rho_s$), which represents the depolymerization of actin filaments. Since, the $J_d(x)$ is roughly uniform, it leads to a uniform concentration of ADP-G-actin-ADF/cofilin and ADP-G-actin-profilin. Other source is the consumption of ATP-G-actin-profilin at the leading edge, which is imposed as a boundary condition. This leads to the non-uniform profiles of ATP-G-actin-thymosin and ATP-G-actin-profilin.

![Figure 1](image1.png) On the left, concentrations ($\mu$M) of Barbed ends ($\rho_B$), ADP-G-actin-ADF/cofilin ($\rho_s$) and ADP-G-actin-profilin ($\rho_P$). On the right concentration of ATP-G-actin-thymosin ($\rho_\beta$) and ATP-G-actin-profilin $\rho_a$ are shown along the thickness of the lamellopodium.

![Figure 2](image2.png) Concentration ($\mu$M) of ATP-G-actin-thymosin $\rho_\beta$ and ATP-G-actin-profilin $\rho_a$ on left and right respectively. Top edge represents leading edge of cell while bottom edge is the contour of cell nucleus.
4 CONCLUSION

In conclusion, our approach presents a flexible tool to model the complex actin flow in motile cells. We have presented a fully implicit finite element formulation of a set of coupled transport equations that reproduce the actin treadmilling. Our results have shown good agreement with previous mathematical and experimental results. The home-made code can be extrapolated to include a mechanical problem, e.g. a Stoke flow or cell membrane protrusion, for a full definition of the cell motility. We hope this current effort to be the first step for further consideration in the modeling of cell motility.

REFERENCES


MATHEMATICAL DEEP LEARNING FOR BIOMOLECULAR DATA

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SUMMARY

Machine learning, particularly deep learning, has been very popular in recent years for dealing with large data sets and becomes extremely powerful when integrated with advanced mathematical descriptors, such as those from differential geometry, algebraic topology, graph theory, and partial differential equations. Some of the best results are obtained in the predictions of solvation free energies, partition coefficients, protein-drug binding affinities, and protein mutation impacts.

Key words: geometry, topology, graph theory, deep learning

1 INTRODUCTION

Biology is believed to be the last forefront of natural sciences. The exponential growth of biological data has paved the way for biological sciences to transform from qualitative, phenomenological and descriptive to quantitative, analytical and predictive. Mathematics, including machine learning, has become a driving force behind this historic transformation as it did to quantum physics a century ago. I will discuss how to combine differential geometry, algebraic topology, graph theory and partial differential equation with deep learning to arrive at the cutting edge predictions of a vast variety of experimental data, including solvation free energies, partition coefficients, protein-drug binding affinities, and protein mutation impacts.

2 FEATURE FUNCTIONAL THEORY (FFT)

Goal: To predict microscopic and macroscopic relationships in biomolecular data

Basic assumptions:

- Representability assumption: there exists a microscopic feature vector that can uniquely characterize, and distinguish one molecule from another
  \[ \mathbf{v}_i = (\mathbf{x}_i, \mathbf{o}_i) = (x_{i1}, x_{i2}, \ldots, x_{iN}, o_{i1}, o_{i2}, \ldots, o_{ik}) \]
  where \( \mathbf{x}_i \) and \( \mathbf{o}_i \) are microscopic and macroscopic features, respectively.
- Similarity assumption: molecules with similar microscopic features have similar macroscopic features.
- Feature-function relationship assumption: the macroscopic features, i.e., solvation and binding free energies, of molecule A are functionals of microscopic feature vectors:
  \[ \Delta G_A = f_A(\mathbf{x}_A, \mathbf{v}_1, \mathbf{v}_2, \ldots, \mathbf{v}_N) \]

Microscopic features In the present work, we consider the following microscopic features:

- Geometric: atomic surface areas, volume & curvatures, see Figure 1.
- Topological: Persistent homology, see Figure 2.
- Graph theory: discrete Laplacian, rigidity & flexibility.
- Electrostatic: atomic charges, dipoles, quadrupoles & reaction filed energies generated by using the Poisson-Boltzmann equation.
- van der Waals: Lennard-Jones potentials.
topological invariants from a set of discrete nodes such as atoms in a protein, or a protein in a protein complex. For a given configuration, independent components, rings and cavities are topological invariants and their numbers are called Betti-0, Betti-1 and Betti-2, respectively. To study topological invariants in a discrete data set, simplicial homology utilizes a specific rule such as Vietoris-Rips (VR) complex, Čech complex or alpha complex to identify simplicial complexes. Specifically, a 0-simplex is a vertex, a 1-simplex is an edge, a 2-simplex is a triangle, and a 3-simplex represents a tetrahedron. Algebraic groups built on these simplicial complexes are employed in simplicial homology to systematically compute various Betti numbers. A filtration process introduced to generate a series of Betti barcodes.

**Macroscopic features:** The following macroscopic tasks are considered in the present work.

- Protein-ligand binding affinities
- Protein mutation energy changes (stability changes)
- Drug partition coefficients
- Drug solvation free energies
- Protein-DNA/RNA binding energies
- Protein-protein binding affinities

**Machine learning algorithms:** The following machine learning algorithms are utilized in conjunction with mathematical descriptors to predict biomolecular data sets in the present work.

- Support vector machine
- Decision tree learning
- LambdaMART
- Random forest
- Gradient boosted regression trees (GBRT)
- Convolutional neural network

3 RESULTS AND CONCLUSIONS
Figure 3 illustrates our results for four typical tasks in molecular biophysics. Among them, solvation analysis is crucial for the understanding of solvation process, which is a prerequisite for the understanding of other biological processes. Protein-ligand binding is a fundamental biological process that is vital to many other biological processes, such as signal transduction, metabolic pathways, enzyme construction, cell secretion, gene expression, etc. Accurate prediction of protein-ligand binding affinities is vital to rational drug design, our understanding of protein-ligand binding and binding induced function. Partition coefficients are essential for drug design and discovery. Finally, mutation that changes protein amino acid sequences through non-synonymous single nucleotide substitutions (nsSNPs) plays a fundamental role in selective evolution. It may alter the original balance and leads to the loss or the creation of certain functions. As shown in the figure, the integration of mathematical descriptors and machine learning algorithms is able to generate some of the best results for all of the problems, including solvation predictions, protein ligand bind affinity prediction, partition coefficient prediction, and protein mutation impact prediction.
STOCHASTIC MULTISCALE CARDIOVASCULAR MODELING UNDER COMBINED BOUNDARY CONDITION AND MATERIAL PROPERTY UNCERTAINTY

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SUMMARY

Transition from a deterministic to a fully stochastic framework for the analysis of cardiovascular flow is discussed in this contribution. Specifically, we show how uncertainty on the model boundary conditions can be estimated using Markov chain Monte Carlo on a reduced representation and combined with independent uncertainty on the material constitutive parameters. To do this, we propose a propagation approach characterized by multi-wavelet stochastic expansion, able to cope with arbitrary correlated and distributed random inputs.

Key words: multiscale cardiovascular modeling, uncertainty quantification, boundary condition uncertainty, material parameters uncertainty

1 INTRODUCTION

Recent advances in computational models for cardiovascular flow and the increasing availability of computational resources on large clusters offer new possibilities for systematically quantifying uncertainty in numerical simulations. This is particularly important in applications where deterministic results are insufficient to fully describe a certain phenomenon. Hemodynamics is one such application, affected by a multiplicity of uncertainty sources. Typical examples are the inability to precisely characterize patient-specific physiologies due to errors or inconsistency in the data collected clinically. Additionally, for cases where hemodynamics interacts with vessel wall deformations (i.e., fluid-structure interaction phenomena), the variability in constitutive parameters (e.g., elastic modulus for a linear elastic incompressible material model) and thickness may affect the distribution of internal forces in the vessel and the hemodynamics.

In this talk, we propose an approach to uncertainty quantification in cardiovascular simulation that combines model reduction, parameter estimation and uncertainty propagation. In particular, we focus on the propagation of random inputs that are partially estimated through the solution of an inverse problem (i.e., boundary conditions) and partially determined through a Karhunen-Loève decomposition of a Gaussian random field with assigned covariance (material model). While a variety of uncertainty propagation approaches are discussed in the literature, they typically assume independent random inputs instead of inferring these inputs directly from the data. The novelty of the proposed approach relates to the development of an adaptive framework for uncertainty propagation able to handle arbitrarily correlated and distributed random inputs determined either through the solution of an inverse problem or from a modal decomposition of histologically admissible Gaussian random fields. Also, applications to realistic multi-scale cardiovascular models demonstrate the practical usability of the proposed approach.

In summary, our approach aims at quantifying the confidence in simulated hemodynamics due to heterogeneous uncertainty sources. This will lead to the ability to perform robust comparisons of hemodynamic outputs, for example, among competing surgical options.
2 METHODOLOGY

2.1 Overview: stochastic multi-scale modeling for cardiovascular flow

Consider a complete probability space \((\Omega, \mathcal{F}, P)\) where \(\Omega\) is a set of elementary events, \(\mathcal{F}\) is a Borel \(\sigma\)-algebra of subsets of \(\Omega\) and \(P\) is a probability measures on \(\mathcal{F}\). Also consider a vector \(y = (y_1, y_2, \ldots, y_d) \sim \rho(y)\) of random inputs \(y_i : \Omega \rightarrow \Sigma_{y_i} \subseteq \mathbb{R}, i = 1, \ldots, d\) representing either boundary condition or material model parameters, i.e., \(y = (y_{bc}, y_m)\). A multi-scale model is denoted by \(G : \mathbb{R}^d \rightarrow \mathbb{R}^n\), mapping a single realization of the \(d\)-dimensional input vector to \(n\) outputs of interest, i.e., \(o = G(y_{bc}, y_m)\).

Assume we can construct a condensed, computationally inexpensive representation \(o = G^*(y_{bc})\) or, in other words, perform a model reduction from \(G\) to \(G^*\) that accounts for vessel resistance, compliance, and inertia. This is followed by a second step (data assimilation), where a vector of patient-specific measurements (e.g., pressure, flow, volume, etc.) \(z\) is collected, and the following statistical model assumed

\[
    z = G^*(y_{bc}) + \epsilon^*,
\]

with Gaussian i.i.d. zero-mean error vector \(\epsilon^*\), having variance \(\sigma^2_i, i = 1, \ldots, n\) and modeling both measurement errors and model inadequacy. A posterior \(P(y_{bc} \mid z)\) is obtained by Bayesian conjunction of the likelihood \(P(z \mid y_{bc})\) induced by the statistical model in (1) and a prior on the boundary condition parameters \(P(y_{bc})\), i.e., \(P(y_{bc} \mid z) = P(z \mid y_{bc})P(y_{bc})/P(z)\). The prior \(P(y_{bc})\) may be determined according to experience with manual parameter tuning, should include population variability, and can be refined to improve the identifiability of the parameters \([1]\). In practice, the problem of assimilating data into the reduced lumped parameter model \(G^*\) translates in the ability to efficiently sample from the posterior \(P(y_{bc} \mid z)\). Due to the fact that \(G^*\) is a non-linear map, and only time statistics (e.g., average, minimum or maximum values over one heart cycle) of clinical data are normally represented in \(z\), independent samples from \(\rho(y_{bc}) = P(y_{bc} \mid z)\) are obtained using Markov chain Monte Carlo.

2.2 Multi-resolution uncertainty propagation

To statistically characterize the results of the multi-scale model \(G(y_{bc}, y_m) = G(y)\) that cannot be represented through \(G^*(y_{bc})\), we employ forward uncertainty propagation. An example of such quantities are local flow features (e.g., blood pressure/velocity) that can only be captured by solving the three-dimensional incompressible Navier-Stokes equations. To do so, we assume statistical independence between the boundary conditions parameters \(y_{bc}\) and the material model parameters \(y_m\) and formulate the propagation problem as finding the distribution \(\rho(o)\) of the multi-scale model outputs, from the knowledge of the random input distribution \(\rho(y) = \rho(y_{bc})\rho(y_m)\).

Consider, for simplicity, a single-output model \(G(y) : \mathbb{R}^d \rightarrow \mathbb{R}\), i.e., the solution of the discretized incompressible Navier-Stokes equations at a pre-defined space-time location. In such a case, we are interested in estimating the \(p\)-th order centered moment, i.e.,

\[
    \mu_p = \int_{\Sigma_y} [G(y) - \mu_G]^{\otimes p} \rho(y) dy,
\]

where \(\mu_G = \int_{\Sigma_y} G(y)\rho(y) dy\). A truncated expansion of \(G(y)\) in terms of a family \(\psi_i(y) = \prod_{j=1}^d \psi_{i_j}(y_j), i = (i_1, i_2, \ldots, i_d)\), of multi-wavelets is introduced at this point, such that:

\[
    G(y) \approx \sum_{i \in I} \alpha_i \psi_i(y), \quad \text{and} \quad \int_{\Sigma_{y_i} \times \Sigma_{y_j}} \psi_i(y_i) \psi_j(y_j) \rho_i(y_i) \rho_j(y_j) dy_i dy_j = \delta_{i,j},
\]

where the set of multi-indexes \(I\) is determined from the selected tensor product space and basis order, and \(\delta_{i,j}\) is the Kronecker delta. A detailed construction of multi-wavelet basis in arbitrary dimensions is discussed in \([4]\). In words, the response of interest is expanded into a combination of bases that are orthonormal in a Hilbert space weighted by the product of the marginals. Also, we estimate the
coefficients $\alpha_i$ by performing sparse regression from a set of random input realizations $y^{(k)}$, $k = 1, \ldots, M$ and associated model evaluations $G(y^{(k)})$, $k = 1, \ldots, M$, in an effort to minimize $M$ by exploiting the expected structure of $\alpha_i$, $i \in I$.

For independent random inputs $y$, the properties of $\psi_i(y)$ lead to a simple expression for the first two moments of $G(y)$, i.e., $\mu_1 = \alpha_0$ and $\mu_2 = \sum_{i \in I} \alpha_i^2$. However, random inputs are often not independent in practical applications. Specifically, we consider the case where $N$ samples $y^{(k)}$, $k = 1, \ldots, N$, are generated from the joint distribution $\rho(y)$ of $y$, for example, through a MCMC solution of an inverse problem. In this case, constructing an orthonormal set $\{\psi_i(y), i \in I\}$ from tensor products of univariate basis functions is significantly more difficult. This is dealt with, by a change of measure in the expectations $\bar{\nu}_p$ or $\nu_p$ (see, e.g., [2]). Let’s multiply and divide the integrand of $\bar{\nu}_p$ by the product of the marginals $\prod_{i=1}^d \rho_i(y_i)$ to obtain (see, e.g., [1]):

$$\bar{\nu}_p = \int_\Omega \left[ G(y)^p \frac{\rho_i(y_i)}{\prod_{i=1}^d \rho_i(y_i)} \right] \prod_{i=1}^d \rho_i(y_i) \, dy = \int_\Omega F(y) \prod_{i=1}^d \rho_i(y_i) \, dy,$$  \hspace{1cm} (4)

where the coefficients $\{\alpha_i, i \in I\}$ that determine the stochastic expansion of $F(y)$ according to the basis $\psi_i(y)$, will encode the statistics of $G(y)$. Note also that regression of $F(y)$ from $\{G(y^{(i)}) : i = 1, \ldots, M\}$ requires the computation of $\{\beta(k) = \rho(y^{(k)}) / \prod_{i=1}^d \rho_i(y^{(k)}), k = 1, \ldots, M\}$.

It is easy to see how the coefficients $\beta(k)$, $k = 1, \ldots, M$ do not change for any additional source of uncertainty which is independent from those already considered. Specifically, consider a vector of $d_{bc}$ dependent boundary condition parameters $y_{bc}$ distributed as $\rho(y_{bc})$ and a vector of $d_m$ material model parameters $y_m$ distributed as $\prod_{i=1}^{d_m} \rho(y_{mi})$, which are mutually independent and also independent from $y_{bc}$. Under these assumptions, the moments of $G(y)$ are expressed as

$$\bar{\nu}_p = \int_\Omega G(y)^p \beta(y) \prod_{i=1}^{d_{bc}} \rho_i(y_{i,bc}) \prod_{i=1}^{d_m} \rho_i(y_{i,m}) \, dy = \int_\Omega F(y) \prod_{i=1}^{d_{bc}} \rho_i(y_{i,bc}) \prod_{i=1}^{d_m} \rho_i(y_{i,m}) \, dy.$$  \hspace{1cm} (5)

3 RESULTS AND CONCLUSIONS

We apply the procedure outlined above to a multi-scale model of the coronary circulation following bypass graft surgery. This model is characterized by a discrete 3D representation of the anatomy of interest plus a specific peripheral circulation model providing the boundary conditions. This is designed to give a detailed representation of the coronary circulation in patients, e.g., with specific attention to the shift in time between systolic aortic pressure and peak coronary flow due to the action of the intra-myocardial pressure. Boundary condition parameters were estimated using MCMC from a non-invasive set of clinically acquired targets, after paying particular attention to the identifiability of both the whole circulation model and its compartments [5].

The uncertainty in the mechanical properties of the aortic arch and coronary arteries was included using two spatially varying quantities, i.e., the Young modulus for near incompressible material and wall thickness. Spatial variability of the elastic modulus was modeled through a Gaussian random field of assigned mean and covariance, after independent Gaussian mode amplitudes were obtained through the Karhunen-Loève expansion, and after considering several possible expressions for the covariance consistent with the expected histology. The thickness was instead obtained through the solution of a random elliptic PDE with uncertainty in the boundary conditions (i.e., outlet thickness) and diffusion coefficient, through sparse polynomials chaos expansion [3].

As shown in Figure [1] the proposed multi-wavelet propagation agrees well with the results from Monte Carlo Simulation and both approaches quantify a limited variability of the time-averaged wall shear stresses, i.e., a limited ratio between standard deviation and mean. This is consistent with two observations. Identifiable parameters are typically estimated with a limited variance (otherwise they would not be identifiable), and therefore one can expect the stochastic response to be generally smooth for perturbations in these parameters. The second observation is that variations in vessel’s wall material properties are expected to induce minor changes in the shear stress distribution in the coronaries, due
to their large radial stiffness (small diameter). Due to the small underlying variance, the Monte Carlo Sampling estimate of the response statistics may provide a useful comparison.

In the future, we will work to include geometrical uncertainty in the proposed framework. This is motivated by the operator-dependent segmentation of CT or MRI images that is performed during model construction, and to changes in the post-operative configuration implemented during surgery. In the context of total cavo-pulmonary connection in Fontan completion surgery, geometrical uncertainty in a competing flow configuration may significantly affect the results (e.g. right to left pulmonary flow split), and therefore will be essential to perform robust hemodynamic assessments.

REFERENCES


HIGH ORDER DISCONTINUOUS GALERKIN-MONTE CARLO SIMULATOR FOR TURBULENT TRANSPORT

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SUMMARY

The discontinuous Galerkin-Monte Carlo (DG-MC) methodology has proven to be very effective for large eddy simulation (LES) of turbulent transport. This is demonstrated in this work by conducting LES of a temporally developing mixing layer. Various orders of accuracy are employed for the DG to investigate the effect of $p-$ refinement. The overall predictive capability of the simulator is established via comparisons with previous direct numerical simulation (DNS) data. It is shown that DG-MC has the capability to capture the larger portion of the the resolved energy with very low numerical dissipation. The success of DG-MC simulator warrants its further extension to turbulent dominated flow applications in biomedical engineering e.g. artery and cerebrospinal flows.

Key words: Large eddy simulation, filtered density function, Monte Carlo methods, turbulent flows, discontinuous Galerkin

1 INTRODUCTION

It is now widely recognized that large eddy simulation (LES) provides an optimum means of predicting the unsteady structure of turbulent transport at large Reynolds numbers. In LES, however, the numerics and the physical modeling are intimately coupled. In its explicit implementations, the LES physical variables are passed through a (low-pass) filter and the goal is to predict their transport at the large scales. The success in doing so depends on two factors: (1) how accurately are the “cut off” subgrid scales (SGS) modeled, and (2) how this modeling interacts with the numerics. Because of this coupling, performing grid-independent LES has proven to be a daunting task [1]. Moreover, if the SGS closure is too complicated, the computational requirements become the bottleneck, defeating the purpose of affordable simulations all together.

In this work, we present the results from the hybrid discontinuous Galerkin (DG)-Monte Carlo (MC) simulator [2]. The former allows LES with both $h$ and $p$ refinements [3]. The latter provides robust modeling of the SGS transport via the filtered density function (FDF) methodology [4, 5]. The DG flow solver has the capability to deal with complex geometry and also provides high-order approximation for LES [6]. The FDF model is represented by an ensemble of MC particles, each carrying the physical information about the SGS quantities.

The DG-MC simulator exhibits several attractive features. A significant advantage is that DG allows convergence to the direct numerical simulation (DNS) limit via both $h-$ and $p-$ refinements. The polynomial of degree $p$ in DG method gives the $p+1$ order of accuracy. Based on the close to exponential convergence of the DG, the procedure is much more efficient than the conventional approach of refining the grid (reducing $h$). Another advantage is that the DG variables can readily be evaluated at the MC particle’s locations since these variables are represented by polynomials within each element. Hence, there is no loss of accuracy due to the use of a lower order interpolation method as is typically used in conventional approximations.
2 SIMULATIONS

To demonstrate its capability, the DG-MC methodology is employed for LES of a temporally developing mixing layer. The flow configuration is a classical fluid mechanics problem and has been considered in several previous LES and DNS; e.g. see Refs. [7, 8] and is described in more detail in Ref. [2]. The layer consists of two parallel streams travelling in opposite direction with the same speed. The coordinates $x$, $y$, and $z$ denote the streamwise, the cross-stream, and spanwise directions, respectively. The velocity components along these directions are denoted by $u$, $v$, and $w$ in the $x$, $y$, and $z$ directions, respectively. The flow variables are normalized with respect to the half initial vorticity thickness, $L_r = \frac{\delta_v(t = 0)}{2}$; $\delta_v = \frac{\Delta U}{|\partial \langle \vec{u} \rangle / \partial y|_{max}}$, where $\langle \vec{u} \rangle$ is the Reynolds averaged value of the filtered stream-wise velocity and $\Delta U$ is the velocity difference across the layer. The reference velocity is $U_r = \frac{\Delta U}{2}$. The computational domain is discretized on equally spaced mesh with about 35,937 cells. This allows the simulations with Reynolds number $Re = \rho U_r L_r / \mu = 50$, and Mach number $Ma = U_r / a_r = 0.2$. The variables $\rho$ and $\mu$ denote the density and the molecular viscosity.

![Figure 1: Contour plots of the filtered scalar field for $p = 4$. (a) FDF, (b) DG. Reprinted from Ref. [2] with permission of the authors.](image)

The computational domain is a cube box with $0 \leq x \leq L, -L/2 \leq y \leq L/2$ and $0 \leq z \leq L$. The length $L$ is specified such that $L = 2^{n_p} \lambda_u$, where $n_p$ is the desired number of successive vortex pairings and $\lambda_u$ is the wavelength of the most unstable mode corresponding to the mean streamwise velocity profile imposed at the initial time. A hyperbolic tangent profile is utilized to assign the velocity distribution at the initial time. A hyperbolic tangent profile is utilized to assign the velocity distribution at the initial time. The 3D field is parameterized in a procedure somewhat similar to that in Ref. [8].

For comparison, we consider the Reynolds averaged values. The SGS stress denoted by $\tau(a, b)$ with $\tau(a, b) = \langle ab \rangle_L - \langle a \rangle_L \langle b \rangle_L$; We also considered the resolved and the total components of the Reynolds averaged moments. The former is denoted by $R(a, b)$ with $R(a, b) = \langle a \rangle_L \langle b \rangle_L - \langle a \rangle_L \langle b \rangle_L$ and the latter denoted by $r(a, b)$ with $r(a, b) = \langle ab \rangle - \tau$. Note that for a generic filter, $r(a, b) = R(a, b) + \tau(a, b)$.

Figure [1] provides the instantaneous contour plot of the filtered scalar from both DG and MC. It is shown that the consistency of the FDF simulation as the MC results are in agreement with those via DG. The resolved and total stresses for three various orders of accuracy are presented in Fig. [2]. In all cases, the total energy remains somewhat constant. It is shows that as the value of $p$ increases, the amount of resolved energy increases. This is in accord with the expectation that with increased resolution, the influence of SGS scales becomes less pronounced.

These simulations demonstrate that the DG-MC simulator provides a powerful tool for LES of turbulent transport [2]. The methodology can be useful for applications in biomedical engineering, where accurate modeling of large scale transport is important.
Figure 2: Cross-stream variation of the Reynolds-averaged values of the resolved and total scalar variance. (a and b) $p = 2$, (c and d) $p = 3$, (e and f) $p = 4$. Reprinted from Ref. [2] with permission of the authors.

REFERENCES


Modelling & Simulation of Cerebrospinal Fluid & Intracranial Dynamics
EFFECT OF CEREBROSPINAL FLUID MODELLING ON SPHERICALLY CONVERGENT SHEAR WAVES DURING BLUNT HEAD TRAUMA

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SUMMARY

The MRI-based computational model, previously validated by tagged MRI and HARP imaging analysis technique, is employed to study transient wave dynamics during blunt head trauma. Three different constitutive models are used for the cerebrospinal fluid (CSF): incompressible solid elastic, viscoelastic and fluid-like elastic. Simulations indicate that the blunt impacts give rise not only to a fast pressure wave but also to a slow, shear wave that converges spherically towards the brain center. It is observed that this convergent shear wave is dependent on the constitutive property of the CSF whereas the peak pressure is not as significantly affected.

Key words: Blunt head trauma, Cerebrospinal fluid, Stochastic wave propagation

1 INTRODUCTION

Blunt head trauma (BHT) is a brain injury without damage to skull. It occurs in traumatic events such as transportation accidents, falls, sports-related injuries, and explosions. While several brain injury mechanisms, even including the skull bone flexure, have been proposed, we approach the topic from the standpoint that understanding wave dynamics in a human brain is key to understanding brain damage in BHT. In particular, we employ a powerful MRI-based finite element (FE) head model allowing studies of head impact processes. That model has been compared to, and validated by, the tagged MRI and harmonic phase (HARP) imaging analysis technique on in vivo human brain deformation data \(^{1}\).

The focus of this work is the cerebrospinal fluid (CSF) layer which plays a crucial role during head trauma. It provides cushioning for the brain, damping out shocks that would otherwise cause concussions. Additionally, the brain-skull interface greatly influences the propagation of mechanical waves within the brain. Thus, the modeling of this layer is crucial in studying head trauma to the brain. Numerical models often simplify the CSF as a soft solid material to avoid the complications of a coupled fluid-solid simulation. The constitutive models assumed for the soft solid vary for different models. One approach is to consider a nearly incompressible solid with a bulk modulus much larger than the shear modulus \(^{2,3,4}\). Another approach is to use a linear viscoelastic model with shear relaxation behavior. A Maxwell viscoelastic model with a high bulk modulus and zero long-term shear modulus was used in \(^{5}\). The third approach is to use an elastic solid with fluid-like behavior through an equation of state (EOS) constitutive relation where pressure is related to the bulk modulus. These three constitutive models are compared using our FE model under three load cases: frontal, top and side impacts. We find that the choice of CSF constitutive model plays a significant role in wave propagation during simulation of impacts \(^6\). Additionally, we show that the wave amplification due to spherical geometry is balanced by damping due to tissues viscoelasticity and the heterogeneous brain structure, suggesting a stochastic competition of these two opposite effects.
Our FE head model is based on a T1- and T2-weighted structural magnetic resonance imaging (MRI) dataset of a specific subject \[4\]. Image voxels (1 mm scale) are directly converted to eight-node hexahedral FEs. Individual elements are assigned tissue types based on image segmentation results. The model includes four different tissue types: skull, CSF, grey matter, and white matter - all assumed homogeneous and isotropic. A custom C++ code is used to convert the image voxels one-to-one into eight-node hexahedral elements, so as to obtain the FE mesh, see Fig. 2 in \[4\]. Traction and displacement continuity is assumed at the material interfaces, ensuring that neither tangential sliding nor normal separation is allowed. The scalp and facial structures are excluded, and structures such as membranes and blood vessels are not explicitly modeled, as their dimensions are below the size of a single element (1 mm). Overall, the model has a total of 1,061,799 elements and 1,101,599 nodes. A mesh smoothing technique is also implemented to obtain smooth mesh surface and interfaces between different tissues to improve numerical accuracy. We believe that our model is the first high resolution study of wave propagation in BHT simulations.

The governing equation for wave motion in a linear elastic, isotropic, homogeneous material is:

\[
\rho \frac{\partial^2 u_k}{\partial t^2} = \mu \nabla^2 u_k + (\lambda + \mu) \frac{\partial}{\partial x_k} (\nabla \cdot \mathbf{u})
\]

where \(u_k\) are the displacement components. \(\lambda\) and \(\mu\) are the so-called Lamé constants of elasticity while \(\rho\) is the material density. The constitutive equation relates the Cauchy stress \(\sigma\) to the strain \(\varepsilon\) and can be expressed as:

\[
\sigma = 2\mu \varepsilon + \lambda \text{trace}(\varepsilon) I
\]

where \(\varepsilon = 1/2(\nabla \mathbf{u} + (\nabla \mathbf{u})^T)\) is used to compute the strain under the small strain assumption.

The choice of mechanical material properties is based on data available in the literature and listed in Table 1 in \[6\], with all tissues assumed to be homogeneous and isotropic. The skull is assumed to be linear elastic. The brain tissues are assumed to be linear viscoelastic in shear but elastic in bulk behavior, with continuity of traction and displacement assumed at material interfaces. The CSF is modeled using three different constitutive models as described earlier. The first formulation uses a linear, nearly incompressible, elastic solid with bulk modulus much larger than the shear modulus. The second formulation makes use of a linear viscoelastic material where the shear behavior is characterized by the standard linear solid model. The long-term shear modulus is set to zero while the short-term shear modulus is taken to be much smaller than the bulk modulus. The final formulation uses an elastic solid with fluid-like constitutive behavior. This is done using an equation of state (EOS) constitutive model where the pressure \(p\) is a function of density \(\rho\) and internal energy \(E_m\). In ABAQUS, we use the Mie-Grüneisen EOS constitutive model \[7\]:

\[
p = \frac{\rho_o c_o^2 \eta}{(1 - s\eta)^2} \left(1 - \frac{\Gamma_o \eta}{2}\right) + \Gamma_o \rho_o E_m,
\]

where \(\rho_o\) is the reference density, \(\eta = 1 - \rho/\rho_o\) is the nominal volumetric compressive strain and \(\Gamma_o, c_o, \text{ and } s\) are material constants.

Blunt forces are applied to the head following that done in the frontal cadaveric impact experiment \[8\]. This corresponds to a distributed load lasting 9 ms, with peak pressure of 4.37 MPa. The load is applied to the head in three settings: frontal, top, and side impact.

### 3 RESULTS AND CONCLUSIONS

The constitutive modeling of the CSF plays an important role in the propagation of these shear waves. This can be seen in Figure [1] for a frontal impact at a fixed time during the simulation. In the case of a solid CSF constitutive model (Fig. [1]a), the spherically convergent shear wave is observed quite...
Figure 1: Von Mises stress distribution (sagittal view) for a front impact using different constitutive models for the CSF layer.

(a) Solid  
(b) Viscous  
(c) Fluid-like

Figure 2: Coup pressure time history for the three CSF constitutive models for a frontal impact clearly. Using the viscoelastic model (Fig. 1b), a more diffuse wave is observed which travels inwards towards the center of the brain, eventually dissipating before traveling a large distance towards the center of the brain. Reflections of the wave are obtained in this case. The fluid-like constitutive model (Fig. 1c) shows even weaker shear wave propagation. Overall, attenuations of the shear waves were observed in all three cases and there is no amplification of stress waves. Thus, we conclude that the viscous attenuation of brain tissues and heterogeneities within the brain structure is sufficient to prevent amplification.

In general, we observe that the CSF constitutive model did not have a major effect on the peak pressure, given in Fig. 2. We note that the fluid-like constitutive model permits larger magnitude pressure during impacts. More interestingly, the attenuation of the pressure wave is reduced compared to the solid and viscoelastic constitutive models. This could be attributed to the simplistic modeling of the meninges in our model, which would otherwise provide support to the brain. We have purposefully chosen the CSF material properties to be stiffer to attempt to capture the presence of these protective layers. The results obtained indicate that for the fluid-like constitutive model, this technique fails to provide adequate mechanical support. Instead, more accurate modeling of these layers would be required. The results for the viscoelastic model closely matches those obtained using the solid-like model. However, the attenuation is larger for the viscoelastic model, as seen in the pressure history.

The unique architecture of the human head, consisting of the hard solid skull, the membranes and CSF, and the viscoelastic brain core, leads to partial conversion of the pressure impact into a shear wave converging towards heads center. However, the shear wave does not increase in intensity as they converge inward. This can be explained from the standpoint of a stochastic competition of wave
amplification due to spherically convergent implosion with (i) wave damping due to brain tissue viscoelasticity and (ii) the highly heterogeneous brain structure which introduces extra wave scattering. It appears that for impact loadings, such as studied here, the viscous attenuation and spatial distortion due to structural brain heterogeneities win and there is no significant amplification of stress in the head’s center.

REFERENCES


A ONE-DIMENSIONAL COMPUTATIONAL MODEL OF THE SPINAL CEREBROSPINAL FLUID

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SUMMARY
Global models for the dynamics of coupled fluid compartments of the Central Nervous System (CNS) require simplified representations of the individual components which are both accurate and computationally efficient. This paper presents a one-dimensional model for computing the flow of cerebrospinal fluid (CSF) within the spinal sub-arachnoid space under the simplifying assumption that it consists of two coaxial tubes representing the spinal cord and the spinal sub-arachnoid space. We first perform rigorous analysis of the first-order non-linear system. We find that the system is elliptic-hyperbolic, and hence ill-posed, for some values of parameters, being hyperbolic otherwise. The system cannot be written in conservation-law form and thus an appropriate numerical approach is required, namely the path conservative approach. The designed computational algorithm is shown to be second order accurate in both space and time, and the method of coupling it with unsteady inflow conditions is presented. Such an approach is sufficiently rapid to be integrated into a global, closed loop model for computing the dynamics of coupled fluid compartments of the central nervous system.

Key words: cerebrospinal fluid, finite volume, high order

1 INTRODUCTION

There are multiple disorders where the development of a coupled global model for the dynamics of CNS fluid compartments incorporating an explicit representation of wave motion in the spinal column may be important. One example is Syringomyelia, a disorder in which a cyst of CSF forms within the spinal cord, causing irreversible damage, and has a prevalence of approximately 1:1200 in the USA [5].

The pathogenesis of Syringomyelia is believed to be due to fluid dynamic processes within the spinal column. As the flow of CSF into the spinal sub-arachnoid space is produced primarily by the net difference between incoming arterial flow and outgoing venous flow of blood to the brain (the transcranial flux), then there is a strong motivation to understand firstly the normal characteristics of flow within the spinal column, and secondly to explore the impact of modifications to the overall system on the flux of CSF within the spinal column.

Coupling with a global model requires the development of a numerical approach which is both rapid to compute (so that many cycles can be run to achieve a periodic state), and accurate. It should also preserve, to as great an extend as possible, the transmission of pulsatile waves along the spinal column, and permit coupling to a model of the CNS fluid compartments. This paper presents a one-dimensional, co-axial model of the spinal column following [1]. After analysing the mathematical character of the non-linear system we design a second order non-linear numerical method that can accurately capture large scale (nonlinear) perturbations. Validation of the method is presented for linear and non-linear perturbations, and finally an unsteady computation is presented where an unsteady pulsatile flow is specified as a boundary condition to the computation.
The six unknowns of the system are $A_t$ (left) shows the variation of the cord area for the nearly linear and the non-linear case at

The computations are run until the velocity of the spinal cord, $A_a$ a simple tube law \cite{6}, the governing equations can be written as follows:

$$\begin{align*}
\partial_t A_c + \partial_x (A_c U_c) &= 0 \\
\partial_t (A_d - A_c) + \partial_x [(A_d - A_c) U_a] &= 0 \\
\partial_t (A_d U_c) + \partial_x (A_d U_c^2) + \frac{C_d^2}{A_c} A_c \partial_x A_d + \frac{C_d^2}{A_{c0}} A_c \partial_x A_c &= 0 \\
\partial_t [(A_d - A_c) U_a] + \partial_x [(A_d - A_c) U_a^2] + \frac{C_d^2}{A_{d0}} A_d \partial_x A_d &= 0
\end{align*}$$

(1)

The six unknowns of the system are $A_c, U_c$ and $P_c$ being the cross-sectional area, the pressure and the velocity of the spinal cord, $A_d$ represents the total cross sectional area of dura mater, $U_a$ and $P_a$ are the velocity and the pressure of CSF in spinal subarachnoid space; $\rho$ is the density of CSF and cord material which is assumed to be the same. The system of equations has two unusual properties, it cannot be written in conservation-law form and is of mixed elliptic-hyperbolic type. The system is hyperbolic in all conditions considered within this work, and so may be solved using the recently developed path conservative framework of Parés \cite{2}. To this end we deploy a suitable approximate Riemann solver based on \cite{3} and \cite{4}. Coupled to an ENO reconstruction, the resulting algorithm is second order accurate in space and time, and non-linear (able to accurately capture non-linear elastic jumps). Details of this scheme will be included in the full paper.

\section{RESULTS AND CONCLUSIONS}

Two test cases have been employed. The first utilises the method of manufactured solutions to demonstrate that the numerical scheme achieves the desired second order of accuracy. The second test case compares the performance of the scheme for a linear problem, compared to its analytical solution.

The chosen test case is adopted from Cirovic and Kim \cite{11}, where here $C_c = 1\text{m/s}$, $C_d = 1\text{m/s}$, the domain is $x \in (0, 1)$ and $A_{0d} = 2A_{0c}$ and $r_{0c} = 0.005\text{m}$. The initial velocities $v_{0a} = v_{0c} = 0$ and the initial cross-sectional area of the cord is constant. A narrow Gaussian perturbation is applied to the dura area of initial perturbation amplitude $0.01A_{0d}$ centred on $x = 0.5$, given by

$$A_d^0 = A_{0d} \left[ 1 + 0.01 \exp \left( \frac{-(x - 0.5)^2}{0.05 * 2^2} \right) \right].$$

(2)

The computations are run until $t = 0.2s$ at a CFL=0.8 with grid resolutions of 64 up to 2048. Figure 1 (left) shows the variation of the cord area for the nearly linear and the non-linear case at $t = 0.2s$, showing excellent agreement.

The second test case examines the robustness of the new method for strong shock waves. This test problem includes a strong discontinuity in CSF velocity at $x = 0.5$:

$$(A_c, A_d, U_c, U_a) = \begin{cases} (A_{0c}, A_{0d}, 0, 0), & \text{if } x > 0.5 \\ (A_{0c}, A_{0d}, 0, 1.5\text{m/s}), & \text{otherwise} \end{cases}$$

(3)

Figure 1 (right) shows results on a 64 and 2048 grid for a domain $x \in (0, 1)$ at $t = 0.1s$. This demonstrates that the scheme robustly captures large perturbations.

The full paper will additionally present unsteady results based on a prescribed pulsatile inflow flux of CSF, and cord pressure. This methodology would permit the integration of the spinal model with zero-dimensional brain models \cite{7} and through this connection, a closed global CNS model of the form proposed in Müller and Toro \cite{8}, \cite{9}.
Figure 1: Linearised analytical and computation results for the Cord Area at $t = 0.2s$ for the linear problem (left), strongly non-linear case at $t = 0.1s$ (right).

REFERENCES


MODELLING PULSATILITY IN THE CONTEXT OF NORMAL-PRESSURE HYDROCEPHALUS VIA MULTIPLE-NETWORK POROELASTICITY

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SUMMARY

Idiopathic Normal Pressure Hydrocephalus (iNPH) is a neurological disease characterized by a triad of symptoms and enlarged ventricles. The pulsatility of the intracranial pressure and the compliance of the brain parenchyma may be key factors in understanding the pathology. Although mathematical modelling and computer simulation has shown to be a promising route to address NPH, these key aspects have not been studied in full detail. In this study, we consider the multiple-network poroelastic theory as an overarching model for the poroelastic brain parenchyma. Standard finite element formulations of these equations lead to severe locking. Here, we propose a new formulation that is robust with respect to the incompressible limit and demonstrate the superior accuracy of the method both numerically and theoretically. Further, we propose and evaluate new ways of modelling pulsatility and compliance within the brain parenchyma in view of recent physiological hypotheses.

Key words: poroelasticity, multiple-network, preconditioning, normal-pressure hydrocephalus, pulsatility

1 INTRODUCTION

Idiopathic Normal Pressure Hydrocephalus (iNPH) is a poorly understood disease characterized by a triad of symptoms and enlarged ventricles, and at the same time, a mean intracranial pressure (ICP) within the normal range. Computational modelling and simulations have been used extensively to investigate different hypotheses surrounding the disease, see e.g \([1]\). However, many fundamental questions remain unanswered.

At a macroscopic scale, brain tissue deformation and tissue fluid flow may be modelled as fluid flow in a poroelastic medium, e.g. via multiple-network poroelasticity\([6]\). For the numerical approximation of multiple-network poroelasticity, we observe that non-physical pressure oscillations and poor convergence under critical parameter regimes can easily appear if attention is not paid to the discretization.

The main limitations of previous works consist in considering simplified geometries, non-physical boundary conditions and unrealistic parameters. For example, some authors consider a significant transmantle pressure gradient (1.0 – 5.0 mmHg) between the ventricles and the SAS \([3, 2]\) even though a pressure gradient of such magnitude has not been observed in iNPH patients. Indeed, Eide et al. \([4]\) compared ICP in different areas of the brain and found no evidence of a spatial pressure gradient. On the other hand, it is well known that only a small spatial pressure gradient, not detectable by the sensors used in \([4]\), is necessary to drive observable fluid flow in the aqueduct. ICP measurements have extensively been used by Eide et al. to predict the success of treatment of iNPH patients by shunting: patients with elevated pulsatile ICP amplitude are more likely to be responsive to the intervention \([5]\). This observation underlines the notion that pulsatility and compliance could play a role in the development and treatment of the disease.
The main aim of this work is two-fold: first, we present a new robust numerical discretization of the multiple-network poroelasticity equations and an efficient preconditioner for the iterative solution of the new formulation; and second, we consider new computational models for representing brain pulsatility in a multiple-network poroelasticity context.

2 METHODOLOGY

We base our study on the multiple-network poroelasticity theory (MPET). In this theory, each of (a subset of) the physical fluid networks in the parenchyma is represented by an homogenized network permeating a solid and elastic matrix. The governing equations are based on first principles (conservation of momentum and conservation of mass for each network separately) [6]: Find the displacement \( u \) and network pressures \( p_a \) for \( a = 1, \ldots, A \) such that

\[
\rho \ddot{u} - \nabla \cdot \sigma^* + \sum_{a=1}^{A} \alpha_a \nabla p_a = f, \tag{1}
\]

where \( \rho \) is the tissue matrix density, \( \sigma^* \) is the extra-stress tensor, \( \alpha_a \) is the Biot parameter for network \( a \), and \( f \) represents additional body sources, and such that for each network \( a \):

\[
\nabla \cdot (K_a \rho_a \ddot{u}) - s_a \dot{p}_a - \alpha_a \nabla \cdot \ddot{u} + \nabla \cdot (K_a \nabla p_a) - \sum_{b \neq a} \gamma_{ba} (p_a - p_b) = g_a, \tag{2}
\]

where \( \rho_a \) is the density of network \( a \), \( s_a \) represents the compressibility, and \( K_a \) is the permeability tensor. The transfer is modelled considering that the flux is driven by the difference in pressure between the two networks \( \gamma_{ba} (p_a - p_b) \) where \( \gamma_{ba} \) is the transfer parameter. A source/sink term can be taken into account with \( g_a \). Assuming isotropic linear elasticity for the tissue matrix for illustration purposes, the extra stress reads as

\[
\sigma^* = 2 \mu \varepsilon + \lambda \nabla \cdot u I, \tag{3}
\]

where \( \mu \) and \( \lambda \) are the Lamé constants.

A standard mixed finite element formulation of the system of equations (1)–(2) performs poorly in the incompressible limit, indeed a reduction in convergence rate is easily observed. To robustly discretize (1)–(2), we propose introducing a new variable \( p_0 \) (the total pressure) defined as

\[
p_0 = \lambda \nabla \cdot u - \sum_{a=1}^{A} \alpha_a p_a, \tag{4}
\]

which upon substitution into (1)–(2) leads to a new formulation:

Find \( u \) and \( p_a \) for \( a = 0, \ldots, A \) satisfying

\[
-\nabla \cdot (2 \mu \varepsilon(u) + p_0 I) = 0, \tag{5}
\]

\[
p_0 - \lambda \nabla \cdot u + \sum_{a=0}^{A} \alpha_a p_a = 0, \tag{6}
\]

\[
- s_a \dot{p}_a - \alpha_a \left( \sum_{i=0}^{A} \alpha_i \dot{p}_i \right) + \nabla \cdot (K_a \nabla p_a) - \sum_{b \neq a} \gamma_{ba} (p_a - p_b) = 0, \tag{7}
\]

for all \( a = 1, \ldots, A \) where \( \alpha_0 = 1.0 \) and the acceleration terms, external forces and sources/sinks have been neglected.

3 RESULTS AND CONCLUSIONS

We present results for the two network case \((A = 2)\) here. We used the method of manufactured solution to determine the convergence rate. The convergence plots of Figure 1 demonstrate how convergence deteriorates with the classical formulation but is restored with the total pressure formulation. We used the lowest order Taylor–Hood polynomial spaces.
Figure 1: $H^1$ norm of the error for the displacement vs the element size of the mesh in logarithmic scale for $\lambda = 10^5$. In blue the results obtained with the classical formulation, in green the results obtained with the total pressure formulation.

Table 1: Number of iterations of the Krylov solver varying different parameters.

<table>
<thead>
<tr>
<th>$\lambda$</th>
<th>$K_{1,2}$</th>
<th>$N$</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>8</td>
<td>16</td>
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<tr>
<td>$10^0$</td>
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<tr>
<td>$10^0$</td>
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<td>$10^3$</td>
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<tr>
<td>$10^5$</td>
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</table>

Starting from the work of Lee, Mardal and Winther [7], we also propose a block diagonal preconditioner using the total pressure formulation:

$$\text{diag} \left\{ (-\mu \Delta)^{-1}; I^{-1}; ((s_1 + \delta \gamma + \frac{\alpha^2}{\lambda}) I - \delta K_1 \Delta)^{-1}; ((s_2 + \delta \gamma + \frac{\alpha^2}{\lambda}) I - \delta K_2 \Delta)^{-1}\right\} \quad (8)$$

where $\delta$ is the time step deriving from the time discretization and $I$ is the mass matrix. To examine the performance of the preconditioner, we consider a unit square test case varying the mesh resolution, $\lambda$ and permeability coefficients $K_1$ and $K_2$. The resulting number of iterations of the preconditioned Krylov solver are reported in Table 1. We observe that the number of iterations stays within a bounded range, indicating that the preconditioner is robust with respect to variations in these parameters.

We will also present computational results for the poroelastic displacement, fluid pressures and the fluid velocities induced by a pulsative blood flow pattern. Particular emphasis will be placed on the quantifying effect of pulsatile modelling choices, the sensitivity of the results to key material parameters and network assumptions.
REFERENCES


FLUID-STRUCTURE INTERACTION ANALYSIS OF CEREBRAL SPINAL FLUID WITH A COMPREHENSIVE HEAD MODEL SUBJECT TO A CAR CRASH-RELATED WHIPLASH

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SUMMARY

If you have been involved in a car accident, whiplash injuries need to be taken very seriously. What protects your brain from severe injuries in such scenarios is the cerebrospinal fluid (CSF). The primary function of CSF is to cushion the brain within the skull and serve as a shock absorber for the central nervous system. In this study we observe this function using a comprehensive head model and advanced fluid-structure interaction (FSI) simulations with realistic whiplash boundary and initial conditions.

Key words: whiplash, comprehensive head/brain model, fluid-structure interaction, car accident

1 INTRODUCTION

Many reports focus on high speed motor vehicle collisions due to the large amount of property damage; therefore, injuries resulting from low speed collisions, especially brain injury from whiplash, are often overlooked. The neurological symptoms of whiplash, such as attention and memory issues, vertigo, and confusion, may not develop until weeks after the accident and are more difficult to treat than the physical aspect of pain. A detailed simulation of the brain injury due to whiplash may help identify the brain injury and therefore will aid in the treatment.

While the significance of including CSF in the numerical simulations has been shown [1], the current finite element studies reported in the literature often lack more detailed anatomical structures [2][3].
Moreover, the cerebrum consists of two cerebral hemispheres, equal halves of the brain, and is positioned over and around most other brain structures. Each cerebral hemisphere is divided into four lobes by sulci and gyri. The sulci are the grooves and the gyri are the bumps that can be seen on the surface of the brain. The CSF fills a system of cavities at the centre of the brain, known as ventricles, and the subarachnoid space surrounding the brain and the spinal cord (Fig. 1).

In this study, we present fluid-structure interaction analysis of a realistic head/brain model exposed to realistic conditions typical to car crash accidents. Over half of all reported traumatic brain injuries are the result of an automobile accident. There are other similar types of traumatic brain injuries in which the brain is bruised, e.g. coup [6] and contrecoup [7] injuries, which happen when a moving object impacts the stationary head or when the moving head strikes a stationary object, respectively. The exact mechanism for the brain injuries is a subject of much debate [8]. Complete understanding of the cushioning effect of the CSF is therefore still elusive and a detailed analysis of this function is axiomatic to the treatment and prevention of brain injuries.

Figure 2: The depiction of the entire head model with skull, cerebrum, cerebellum, pituitary gland and brainstem, respectively. The subarachnoid space and other cavities are filled with fluid particles (blue dots surrounding the brain model, in the lower right corner). The entire model with half the skull is also shown (lower left).
2 METHODOLOGY

2.1 Crash conditions

To simulate the crash conditions later prescribed to our comprehensive head model, the HUMOS2 (HUman MOdel for Safety) [9] is used in the car crash sled test with a 3-point seat belt simulated using RADIOSS (Atair Engineering, Michigan, USA). The HUMOS2 is a human numerical model based on real human data. It includes skeleton, muscles, organs, and ligaments. The acceleration/deceleration values of the HUMOS2’s head from the sled test are then used to prescribe the velocity to a more comprehensive head model described below.

2.2 Head model

The velocity extracted from the above sled test simulation using a human numerical model is used to test the interaction of the CSF and brain/skull using a more comprehensive head model. The model of the head, namely skull, cerebrum, cerebellum, brainstem and pituitary gland, is shown in Fig. 2. The model is based on the digital imaging and communications in medicine (DICOM) images; thus, making it patient specific. The only major anatomical features missing in this model are the meninges, i.e. the three membranes that envelop the brain and spinal cord to protect the central nervous system. The arachnoid granulation, depicted in Fig. 1, is neglected, too. The fluid in the very short time period during which the accident scenario occurs can be considered static, therefore its flow does not need to be accounted for. Also, it is reasonable to assume that the flow of the CSF itself does not significantly contribute to the cushioning effect of the CSF. Both of these assumptions make the presence of the granulations negligible.

2.3 Computer Simulations

Fluid motion and boundary interaction were solved with the IMPETUS Afea SPH Solver®, while large deformation in the solid parts was simultaneously solved with the IMPETUS Afea Solver®. Both the solvers use a commodity GPU for parallel processing. All solid elements were fully integrated removing the possibility of hourglass modes and element inversion that plagues the classic under-integrated elements. Both fluid and solid domains and their interaction were solved with an explicit integration scheme. All simulations were solved on a standard workstation. Parallel acceleration was achieved with a Tesla K40 GPU with 12 GB of Graphic DDR memory and 2880 CUDA Cores. To confirm that convergence was reached, h-refinement of the finite element mesh was performed and the solution was found to yield same results. The SPH equations are described in more details in our previous work [10]. We have opted to use the SPH method because using traditional fluid-structure interaction (FSI) techniques can still be computationally expensive and challenging when it comes to their parallelization [11]. In order to use the traditional FSI techniques, the complexity of the geometry used would have to be sacrificed.

3 RESULTS AND CONCLUSIONS

Relative displacement of the fluid particles compared to the brain can be observed. It can be seen that the fluid particles located in the front lobe have been pushed by the motion of the brain and thus allowing the brain in that region to come to contact with the skull, see inside the dashed ellipses in Fig. 3. The impact of the brain against the skull, and the many sharp edges, shelves, and protrusions on its inner surface, is known to be directly related to brain-associated problems after whiplash.

Using this methodology, the contact of the brain with the skull despite the presence of the CSF can be observed up to a certain speed and the probability of brain injury can be subsequently assessed by measuring the stress values on the brain. The overall effect and function of the CSF can be analyzed. No symptom should be taken lightly in the event of a whiplash injury, especially that some of the symptoms may not develop until weeks after the accident. Therefore, our understanding of the mechanism of whiplash injury is axiomatic.
Figure 3: At $T = 0.025$ s, the skull reached the speed of $9 \text{ m/s}^{-1}$ (red color), compared to the initial relative position of the fluid particles to the brain it can be seen that the front of the brain is not protected with the same thickness of CSF and, in fact, is in contact with the skull.

REFERENCES


POROELASTIC MODELLING OF CSF CIRCULATION VIA THE INCORPORATION OF EXPERIMENTALLY DERIVED MICROSCALE WATER TRANSPORT PROPERTIES

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SUMMARY

We outline how multicompartmental poroelasticity is applied to the study of dementia. We utilize a 3D version of our poroelastic code to investigate the effects within parenchymal tissue. This system is coupled with multiple pipelines within the VPH-DARE@IT project which account for patient/subject-specific boundary conditions in the arterial compartment, in addition to both an image segmentation-mesh and integrated cardiovascular system model pipeline respectively. This consolidated template allows for the extraction of boundary conditions to run CFD simulations for the ventricles. Finally, we outline some experimental results that will help inform the MPET system.

Key words: Dementia, Poroelasticity, Cerebrospinal Fluid, Glymphatic system, CFD, FEM

1 INTRODUCTION

Mild cognitive impairment (MCI) is defined as a state between normal ageing and dementia. It is defined as objective cognitive impairment relative to the person’s age, with concern about the cognitive symptoms, in a person with essentially normal functional activities who does not have dementia [1].

The function of the brain depends on the transport of a multitude of fluids, namely blood, cerebrospinal fluid (CSF), interstitial fluid (ISF) and intracellular fluid. The ability to model these intertwined fluid transport processes within brain tissue in an anatomically accurate and patient-specific manner is of ever-increasing significance, especially since integrative systems possess numerous interactions with the external world which, either directly or indirectly, affect brain function and homeostasis.

Aquaporins (AQPs) are defined as a set of integral membrane transport proteins with a primary function of facilitating water movement across cell membranes in response to osmotic gradients. In this work, AQP4 is targeted as it is the most predominant aquaporin in the brain. It is located on the external and internal glial limiting membranes, the basolateral membrane of ependymal cells and astrocytes. In the latter, AQP4 occupies three key locations, namely the perivascular astrocyte end feet, perisynaptic astrocyte processes and in processes that involve K⁺ clearance, such as nonmyelinated axons and the nodes of Ranvier. This tactical distribution suggests that AQP4 controls water fluxes into and out of the brain parenchyma. AQP4 has been deemed to possess the essential role of controlling the water balance in the brain [2].

In the brain, it is understood that waste products and metabolites are transported by convection (incorporating diffusion and advection). Diffusion is the dominant transport mechanism for smaller molecules and shorter distances. However, studies have shown that advection may be the dominant transport mechanism for larger molecules [3] such as amyloid-β [4], both within the perivascular spaces and within the brain’s interstitium.

In a series of work by Nedergaard and colleagues proposed a glymphatic hypothesis [4], i.e., a clearance system based on a hydrostatic pressure difference between the periarterial and perivenous compartments drives advective water flow directed from the periarterial space, through
the astrocytic endfoot layer, extracellularly through the brain parenchyma and through the
perivenous endfoot layer where it returns into the perivenous space. Furthermore, they showed that
cerebral arterial pulsation drives the paravascular fluid exchange between CSF and ISF, and they
have also shown the CSF-ISF exchange to be facilitated by astrocytic AQP4 [4]. This system is
referred to as the **glymphatic system**.

The first goal of this work is to firstly develop Multiple-network Poroelastic Theory
(MPET) based models capable of representing the aforementioned fluid transport processes in the
cerebral environment. For these models to accurately represent the transport mechanisms taking
place, parameters such as diffusion constants and water permeabilities are crucial. Experiments
were therefore performed to address these parameters and variables, and the results incorporated
within the developed poroelastic model. There were two types of experiments that took place: (i)
intracranial pressure (ICP) recordings in response to injections of artificial cerebral spinal fluid and
(ii) microscale imaging of tracer convection (diffusion and advection). This paper will focus on the
prior. Both wild-type mice and mice lacking aquaporin AQP4 water channels in the astrocytes were
used.

The second goal of the work is to portray the novelty of being able to link a Computational
Fluid Dynamics (CFD) focused study with a 3D multi-compartmental poroelasticity solver which
in turn allows for novel observations of cerebral fluid flow in the cerebroventricular system and its
interaction with the surrounding parenchyma (for instance, observing swelling and/or draining in
the periventricular region). In this way, we can investigate current developments in the field of
dementia, such as whether sleep drives metabolic clearance from the brain, which ties together the
glymphatic system, subject/patient-specific cerebroventricular modelling, various solution fields
borne out of the subject/patient-specific MPET solver (for parenchymal tissue) and the
experimental results that aid in outlining a more accurate use of parameters for this type of
modelling platform.

## 2 METHODOLOGY

### 2.1 Multiple-Network Poroelastic Theory (MPET)

Poroelasticity is known to have numerous applications in biomedical engineering as well as soil
mechanics and reservoir engineering. MPET is used to develop a spatio-temporal model of tissue
displacement and fluid regulation in varying scales within the cerebral environment. The field
equations are discretized using the finite-element method, and in all three spatial dimensions.

Specifically, the field equations of the MPET system stem from the fully dynamic, classical
Biot system [5]. For a single compartment, this consists of the Navier equation representing
momentum balance, and the Duhamel equation for the mass balance representing the diffusive
Darcy fluid flow:

\[
\rho \ddot{u} - (\lambda + \mu) \nabla (\nabla \cdot u) - \mu \nabla^2 u - \alpha \nabla p = f \\
\gamma \dot{p} + \alpha \nabla \cdot u - \nabla \cdot \kappa^s (\nabla p - \rho g) = s
\]

In equations 1a and 1b, \( \rho \) represents the density of a porous and permeable matrix, \( \dot{\rho} \)
represents the density of the fluid, \( \lambda \) and \( \mu \) are the Lamé parameters (dilation and shear moduli of elasticity), \( \alpha \)
is the Biot-Willis constant, \( \kappa^s \) is the symmetric permeability tensor divided by the fluid viscosity, \( \gamma \) is
the constrained specific storage coefficient, \( g \) is the gravity vector, \( s \) is a source/sink term and
finally, \( u \) and \( p \) are the solid matrix displacement (mean displacement of particles forming the solid
matrix) and the scalar pore pressure, respectively. In its current form, the MPET model comprises
of four separate fluid compartments, arterial blood, arteriole/capillary blood, venous blood and
CSF/ISF [5]. The resulting system of equations and finite element discretization template are
described for a 2D application in [5]. Boundary conditions are applied through the VPH-
DARE@IT project consolidated poroelastic pipeline and the literature [5].

### 2.2 Intracranial Pressure: Experimental procedures

The experiments were conducted on male adult (12–26 weeks, weighing 21–35 g) constitutive
Aqp4\(^{-/-}\) (n = 6) [3] with C57BL/6J mice as controls (n = 6). The animals were allowed ad libitum
access to food and drinking water. The mice were anesthetized with an intraperitoneal injection of a
Zoletil-Xylazine-Fentanyl cocktail. Body temperature was monitored and kept at 37 °C. Tracheostomy was performed and mice mechanically ventilated with room air at 100 breaths per minute (bpm), volume 0.25-0.35 ml/min. Blood gases, blood pressure and oxygen saturation were monitored with a thigh sensor for mice. Oxygen saturation was at all times above 90%. A 30 GA needle connected to tubing and a 50 µl Hamilton syringe was inserted into the cisterna magna and fixed with tissue adhesive. A small craniotomy was made in the skull and the ICP catheter connected to a pressure transducer inserted 2 mm under the dura towards bregma. When a stable pressure was measured, baseline values were recorded for 1 min, before artificial cerebrospinal fluid (aCSF) was infused at 2 µl/min for 5 min by a pump, as described by Iliff et al., 2012. All experiments were performed in a manner that complies with Norwegian laws, and all protocols were approved by the Animal Care and Use Committee of the Institute of Basic Medical Sciences, University of Oslo, Norway.

2.3 Infusion test

The conventional interpretation of an infusion test (outlined in §2.2) is when the CSF production rate is temporarily altered over a finite period of time in order for CSF pressure to rise to a new plateau value before declining back to the original level once infusion has been halted. This type of test provides clinically useful outputs, such as the resistance to CSF outflow and cerebral compliance, which are both used by the MPET model. These two important parameters are estimated via a compartmental model of the form [6]:

$$\left[ e \left( p(t) - ICP_0 \right)^{-1} \right] \frac{dp(t)}{dt} + \frac{p(t) - ICP_0}{R_{CSF}} = Q_{inf}$$  \hspace{1cm} (2)

In the above, \(p(t)\) is the CSF pressure (mmHg), \(ICP_0\) is the baseline CSF pressure (mmHg), \(R_{CSF}\) is the resistance to outflow (mmHg ml\(^{-1}\) min), \(Q_{inf}\) is the infusion rate (ml min\(^{-1}\)), \(C(p)\) is the compliance of the mouse brain (ml mmHg\(^{-1}\)), \(ICP_0\) is the reference pressure (mmHg) and \(e\) is the cerebral elasticity (ml\(^{-1}\)).

For constant infusion (as in in §2.2), the solution to Equation 2 is utilized, and \(e\) is calculated using a nonlinear least squares method (Levenberg-Marquardt) in MATLAB.

2.4 CFD based cerebroventricular fluid complexity

Flow through the multidimensional ventricles (obtained via T1-weighted acquisition) is solved using the Multiphysics software CFD-ACE+ (ESI Group, Paris, France) which is based on the finite volume approach, along with central spatial differencing, algebraic multigrid scheme and the SIMPLEC pressure–velocity coupling. The coupling between the poroelastic solver and the flow solver is achieved through appropriate CFD-ACE+ user-defined subroutines. Mesh generation for the cerebroventricular volumes was achieved via the use of CFD-VisCART (ESI Group, Paris, France), which is an unstructured adaptive Cartesian grid generation system. Boundary conditions for the inlets and outlets are obtained via the 3D MPET solver.

**Figure 1:** The fluid transfer restrictions placed between the four compartments (a) Flow is prohibited between the CSF/ISF and arterial network, whilst directional transfer exists between the a and c, c and v, c and e and e and v networks respectively [5].
3 RESULTS AND CONCLUSIONS

Figure 2: a) CSF/ISF clearance solution field within parenchymal tissue arising from the 3D MPET solver b) Ventricular geometry of a control subject used for the CFD simulations c) Streamlines merged with the u-component of velocity in the fourth ventricle of a control subject. d) Range of cerebral elasticity for AQP4-null and Wild Type (WT) controls. e) Range of resistance to CSF/ISF outflow for AQP4-null and WT controls. For the latter two plots, the visual arrangement of WT and AQP4-null data are paired according to the order of the respective set of experiments taking place.

In Fig. 2 above, we depict a selection of results from the broader context of this work. Utilizing the MPET solver pipeline within the VPH-DARE@IT project, we are able to use the research platform to acquire subject/patient-specific imaging data (~n = 50 control and ~n = 50 MCI cases) to segment (see Fig. 2b) and mesh) the parenchymal tissue volumes (linear tetrahedral elements) and cerebroventricular system. Permeability tensors that are generated from the principle eigenvector of the diffusion tensors are also included in the datasets. In the process, we also incorporate lifestyle data (such as ECG and blood pressure profiles over 24 hours) from the patients/subjects which create a subject profile that is supported by cardiovascular data. Both of these elements are feed an integrated open-loop cardiovascular model that provides the arterial compartment of the MPET system with the necessary boundary conditions in the cortical surface (applied to left/right cerebrum and cerebellum) and cerebral ventricles. One of the many solution fields of the MPET system is CSF/ISF clearance (see Fig. 2a). Others include parenchymal tissue displacement, CSF/ISF swelling, intracranial pressure, arterial and venous blood pressure and capillary perfusion. Using the 3D MPET solver in this way allows us to extract CSF profiles at the inlet and outlet locations of the cerebroventricular system (lateral ventricles, foramen of Magendie, bilateral foramina of Luschka and central canal) over a window of time corresponding to an event of high or low activity (such as exercise and sleep), and thus running transient CFD simulations (see Fig. 2c) to assess the complexity of CSF flow within the ventricles for both control subjects and MCI patients. Preliminary results indicate abnormal peak aqueductal CSF velocities in a small group (n = 3) of MCI patients (as high/low as ~11/0.8 mm/s, compared to an average of around ~1-2 mm/s) In this coupled setting, we are able to consider accounting for the influence of the glymphatic system within our work. The experimental results obtained in this study (see Fig. 2d, e) are currently being embedded within the MPET system, in order to give us a better theoretical understanding of the effects of AQP4 on the global response of the parenchymal tissue in the ageing brain (such as the link between mislocalization of AQP4 and amyloid-beta plaques [7]).

REFERENCES

COMPUTATIONAL TOOLS TO ASSESS IMPEDANCE, PRESSURE AND STRAIN FOR SUBJECTS WITH CHIARI MALFORMATION

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SUMMARY

Three computational tools were developed to characterize the in vivo brain biomechanical environment of Chiari malformation (CM) patients. The first tool computes CSF flow impedance using phase contrast magnetic resonance imaging (pcMRI)-based numerical models. The second calculates the unsteady pressure field within the spinal canal from pcMRI. The third computes the brain tissue strain using a novel MRI sequence. Impedance in CM patients decreased after decompression surgery, but remained higher than in healthy volunteers. Feasibility of the pressure calculations was demonstrated but validation is still needed. Elevated strain was found in the CM patient as compared to the healthy control.

Key words: Chiari malformation, CFD, DENSE MRI, 4DpcMR, strain analysis

1 INTRODUCTION

Type I Chiari malformation (CM) is classically characterized by cerebellar tonsil herniation (CTH) greater than 5 mm below the foramen magnum. However, it is well-documented that CTH does not necessarily correlate with neurological symptom severity or surgical outcome. Because CTH creates a partial blockage of fluid movement between the cranial and spinal compartments of the subarachnoid space (SAS), it is thought that the resulting changes in the hydrodynamic environment, specifically increased pressure on neural tissues, may contribute to the symptomatology of CM. Thus, using specialized magnetic resonance imaging (MRI) modalities and numerical techniques, our group has developed tools to quantify CSF flow resistance, CSF pressure, and neural tissue strain near the cervicomedullary junction and cervical subarachnoid space (SAS). The preliminary results suggest that these computational tools may provide insights into the differences in biomechanical stress and strains that are present in CM patients compared to healthy controls.

2 METHODOLOGY

We investigated the hydrodynamic environment in the cervical spinal SAS of CM patients pre- and post-surgery (n=19) in terms of SAS geometry (hydraulic radius) and longitudinal impedance (LI) to flow and compared the results to values observed in healthy volunteers (n=15). Subject-specific cervical (SAS) geometries were modeled from high-resolution T2-weighted anatomic MR images. CSF flow waveforms were obtained from pcMR images taken in the transverse plane at the C2, C6, and T2 levels of the spine. Geometries and C2 flow waveforms were combined to create subject-specific computational fluid dynamics models from which LI was calculated.

The calculation of relative pressure, \( p \), from a known measured velocity field, \( \mathbf{u}_F \), was achieved by solving the pressure Poisson equation (PPE). The PPE and its corresponding boundary condition on
a fluid region, $\Omega_F$, can be obtained directly from the Navier-Stokes equation and have the following forms:

$$\nabla^2 p = \nabla \cdot \mathbf{b}_F \text{ on } \Omega_F$$

$$\nabla p \cdot \mathbf{n} = \mathbf{b}_F \cdot \mathbf{n} \text{ on } \partial \Omega_F$$

where, $\partial \Omega_F$ is the surface enclosing the fluid region and $\mathbf{n}$ is the outward normal vector on this surface. In equation (1), $\mathbf{b}_F$ is a known function of velocity filed, body forces, $\mathbf{f}_b$, and kinematic viscosity, $\nu$:

$$\mathbf{b}_F = \nu \nabla^2 \mathbf{u}_F + \mathbf{f}_b - \mathbf{u}_F \cdot \nabla \mathbf{u}_F - \frac{\partial \mathbf{u}_F}{\partial t}$$

The irregular flow domain $\Omega_F$ was embedded in an extended cuboid domain based on the approach proposed by Song et al. [1]. The transformed version of equation (1) in the extended domain was discretized using second order finite difference schemes and solved numerically using a Poisson solver developed based on the Fourier method [2]. The performance of the pressure calculation technique was tested on a mathematical phantom generated based on a patient-specific CFD model of CSF motion in the upper cervical SAS. The reference velocity and pressure solutions were obtained using CFD. In order to mimic the voxel-based structure of pMRI data, CFD velocities were averaged into structured grids with various voxel sizes and were used as the input for the PPE-based pressure calculation algorithm. The resulting relative pressure distribution was used to calculate pressure difference and the LI between the two ends of the model. The accuracy of these pressure-based parameters was assessed by comparing them against the value obtained directly from the CFD.

Cine displacement encoded stimulation echo (DENSE) MRI was carried out, based on the sequence described by Zhong et al. [3], on an adult healthy volunteer and an adult patient diagnosed with CM. In brief, for each subject, mid-sagittal brain and cervical spinal cord MR image were localized using a rapid scout scan on a 1.5T whole body scanner equipped with a four-channel head coil and a single channel neck coil (Avanto, Siemens Medical Solutions, Germany). Two multiphase data sets were acquired, one for displacement encoding in the craniocaudal (head-foot) and one in the dorsal-ventral direction. Phase reference images without displacement encoding were also acquired to correct the background phase error in DENSE measurements due to field inhomogeneity. The images were acquired for approximately 700 ms during each cardiac cycle after the R wave of ECG with a total of 13–16 cardiac phases. Other imaging parameters were: FOV = 225 – 262 x 300 – 350 mm, matrix = 192 x 256, slice thickness = 7 mm, temporal resolution = 34 ms, echo time = 1.9 ms, flip angle = 15°, and displacement encoding frequency = 1.5 cycle/mm. Subjects were imaged in the supine position with the neck in a neutral position.

An internally developed MATLAB-based software was used to post-process and analyze the obtained phase images. The post-processing steps include: noise filtering, automatic spatial and temporal phase unwrapping [4], manual phase unwrapping (if necessary), and region of interest (ROI) selection. Furthermore, sagittal two-dimensional Eulerian displacement map measured by the DENSE sequence were analyzed to quantify the CNS tissue deformation in terms of peak bulk displacement, motion distribution, and were used to calculate principal Lagrangian Green strain [5, 6], for different brain structures.

### 3 RESULTS AND CONCLUSIONS

Using the FM and 25 mm caudal to the FM as common reference planes, mean values of LI in dyn/cm$^5$ were 458 ± 62, 376 ± 56, and 237 ± 11 for the pre-surgery, post-surgery, and healthy volunteer groups, respectively. Mean cerebellar tonsil descent (CTD) was measured to be 9.5±1.2, 6.9±1.0, and -1.7±1.0 mm for the pre-surgery, post-surgery, and healthy volunteer groups respectively. Statistical analysis showed a significant difference in LI between CMI patients pre-surgery and post-surgery (65.1 dyne/cm$^5$ average decrease, $p = 0.016$). Mean LI in pre-surgery CMI patients was significantly higher than in healthy volunteers ($p = 0.002$). Mean values of LI has been demonstrated to follow a similar trend to CTD in CM patients before and after surgery. However, values of LI can differ greatly from that of CTD in specific cases where CSF space was small indicating LI may be a better indicator of CSF flow blockage than CTD.
Figure 1 compares the craniocaudal pressure difference waveforms and the mid-sagittal relative pressure distributions between the PPE-based estimation and the reference CFD solution of the subject-specific numerical phantom. Good agreement was observed between the reference and the estimated pressure distributions and pressure difference waveforms with the maximum of 6.4% difference between the two. The relative pressure estimation shown in Figure 1 was obtained from a structured grid with the voxel size of 0.25 mm. Increasing the voxel size to a more realistically achievable value in 4D PCMRI (1.0 mm) decreased the accuracy of the method to a great degree, as the maximum error between the reference CFD and the estimated pressure difference waveforms was increased to 28.2%.

Figure 1. Comparison of the craniocaudal pressure difference waveforms and the mid-sagittal relative pressure distributions obtained from the reference CFD and estimated using the PPE-based technique in the subject-specific numerical phantom.

Figure 2 compares the distribution of the brain tissue displacement and principal strain on the mid-sagittal slices at the time point corresponding to the peak strains. In both healthy and CM cases, the regions of high principle strain were observed near the boundaries of different brain structures as shown by the yellow arrow. These regions are not a real representation of increased strain, as they demonstrate the separation of different structures and not displacement gradient in one structure. Furthermore, a concentrated region of high strain was observed near the cerebellar tonsils in the CMI patient and not in the healthy subject (shown by the red arrow). The existence of this region was expected from the increased displacement gradient near the tonsils. Additional studies are necessary to see if this increased strain is consistent in a larger CM patient population and if its existence correlates with the symptomatology of CM.

In conclusion, we present preliminary results for three computational tools based on novel MRI protocols to acquire geometry, CSF velocity, and tissue displacement within the brain and cervical spinal canal. These tools were developed to obtain estimates of the in vivo impedance to CSF flow, pressure, and tissue strain in order to better understand the role biomechanics in the pathophysiology of CM. Future studies of resistance, pressure, and tissue strain from these computational tools should be conducted in concert with symptomatology assessments in order determine the precise role of biomechanical forces in the pathophysiology of CM.
Figure 2. Left: Distribution of peak lateral to medial and craniocaudal displacement in the mid-sagittal slices in the healthy subject (top) and the CMI patient (bottom). Right: Distribution of peak principal strain in the mid-sagittal slices in the healthy subject (top) and the CMI patient (bottom).

REFERENCES


COMPUTATIONAL INVESTIGATION OF THE DISTRIBUTION OF CEREBRAL BLOOD FLOW AND CORTICAL OXYGEN PERFUSION

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SUMMARY

A mathematical model of the cerebral microcirculation and cortical oxygen perfusion based on fluid dynamical and reaction kinetic principles is presented. Computations were performed on anatomically accurate 3D replica of the secondary mouse cortex including all neuronal and glial cells as well as the complete angiome of the microcirculatory blood supply. For steady conditions, oxygen exchange between the red blood cells, the blood plasma and the brain tissue as function of hemodynamic parameters can be predicted. Oxygen perfusion in the cortex is modelled over multiple length scales from the large pial blood vessels to down to the level of individual brain cells. Even sub-cellular concentration gradients between cytoplasm and mitochondria are predicted. The dynamics under pulsatile microcirculatory oscillation are described subject to the biomechanics of distensible blood vessels. The model predictions for hemodynamics states, oxygen tension of the tissue and vessels in agreement with all currently available experimental measurements.

Key words: Cerebral Hemodynamics, Cortical Oxygen Supply, Microcirculation

1 INTRODUCTION

A systems approach is adopted for this study that combines computational fluid mechanics, control theory and biological imaging to explore the regulation of relative cerebral blood flow (rCBF). This dynamic model is used to test and validate competing hypothesis about the fundamental principles of decentralized, distributed blood flow control in the human brain. This model reveals the importance of the spatial and temporal distribution of biochemical signals such as vasodilatants, which are essential parameters toward realizing each control strategy. These signaling mechanisms induce a physiological response in the cerebral blood vessels, whose dynamic caliber adjustment assume the role of actuators.

Cerebral autoregulation maintains constant blood supply in spite of wide pressure disturbances caused by posture changes and decreased cardiac output. Functional hyperemia generates dynamic response under closed loop control which we predict according to the proposed distributed decentralized cerebral control mechanism. Significant contributions have been made to the field of computational modeling of blood flow in the brain, proposed mathematical models that rigorously compute the fluid flow in critical arterial circuits[1-3], or three-dimensional models of the microvasculature[4-6] so far have not explained the distributed, decentralized control strategy of cerebral blood flow. To fill this gap in knowledge is the ultimate goal of this research.

2 METHODOLOGY

A morphologically accurate model of the entire cerebral microcirculation has been constructed (Fig. 1). The blood supply consisting of cylindrical blood vessel network is embedded in a Carthesian mesh representing the brain tissue. Blood flow is modeled as a bi-phasic medium composed of plasma and red blood cell (RBC) phase. The non-Newtonian two-phase blood flow is computed using a novel drift flux model[7], which accounts for plasma skimming leading to uneven hematocrit distribution, and faster RBC over plasma speed. The drift-flux model is also computationally much more efficient than prior bi-phasic models, and suitable for large-scale simulations of microcirculatory networks which contain loops and multi-furcations. More details on bi-phasic blood...
flow computations can be found elsewhere[7-9]. The brain tissue also encompasses the two separate domains: (i) the extracellular space as well as (ii) somata of individual cells (neurons and glial cells). The equations to predict oxygen exchange are described briefly next.

**Steady oxygen exchange.** To model blood-tissue oxygen exchange, oxygen species balances for blood and tissue oxygen transport were formulated. The oxygen conservation for blood is given in eq. 1, where $C_b$ is the concentration of oxygen in the blood vessel, $S$ is the surface area, $w$ is the vessel wall thickness, and $K_w$ is the oxygen permeability of epithelial tissue. Oxygen mass exchange is driven by the concentration difference, $\Delta C_{t-b}$, between oxygen in the blood and in the brain tissue. Tissue oxygen tension in the volumetric brain mesh, $C_t$, was balanced with the dynamic diffusion-reaction eq. 2. The transient oxygen conservation balance accounts for tissue oxygen accumulation, $dC_t/dt$, mass exchange due to the difference in oxygen tension between vessels and the brain cells, $\Delta C_{t-b}$, oxygen consumption due to cellular metabolism in terms of the cerebral metabolic rate of oxygen consumption, $CMRO$, and free diffusion in the extravascular space, $\nabla D \nabla C_t$, with diffusion coefficient[10], $D$. The coupled system eq. 1- 2 was solved simultaneously after full discretization of the spatial domains with finite volume techniques, and implicit time discretization.

**Pulsatile blood flow dynamics.** Steady simulations cannot predict blood flow control as it occurs in functional hyperemia after a neuronal firing event. Therefore, an extension of simulations to full dynamics which accounts for oscillatory blood flow in distensible blood vessels is needed. Blood vessel lumen can change due to two mechanisms: (i) passively, in response to altered transmural pressure differences, which occur naturally due to blood pressure pulsations; and (ii) actively, due to deliberate vasodilation/contraction due to muscular or pericyte control of vessel lumen or resistance. The main objective here is not to render accurately blood vessel wall mechanics (passive response), but rather to elucidate the dynamic interaction between oxygen demand after neuronal firing with the induced increased blood flow response (active response). In systems theory, this situation is described as a set-point tracking problem. The simplified equations of mass conservation, momentum conservation, and tube distensibility are given in eq. 4-5, where $\bar{A}$ is the cross sectional area, $\bar{A}$ is the nominal area, $\bar{A}^0$ is the initial cross sectional area, $Q$ is the volumetric flux of blood, $\bar{Q}$ is the nominal flux, $P$ is the blood pressure, $\rho$ is the density of the blood, $E_i$ is the adjusted Young’s modulus, and $\gamma$ is the viscous friction coefficient defined as $\gamma = 8\pi\mu/\rho$. A sinusoidal pressure boundary condition
was implemented according to eq. 6. The governing equations were linearized at conditions corresponding to an average inlet pressure with an average value between systole and diastole, the nominal cross-sectional area, $\bar{A}$, and volumetric flux blood flow, $\bar{Q}$, can be determined for a single blood vessel. Eq (5) is given a linear elastic wall model, but can easily be replaced with more realistic quasilinear wall mechanics (e.g. QLE model by Fung[11]). More interestingly is the situation for active control of vessel lumen by vasodilation or contraction in which vessel lumen does not follow from the transmural pressure difference, but is set by an active control element (e.g. arterial muscle or pericytes). Effective approaches to solving the moving wall problem involves the Riemann[12] spectral[13] methods, or normal mode analysis of the linearized Navier-Stokes equations[14].

3 RESULTS AND CONCLUSIONS

Oxygen tension predictions in the blood vessels were compared to recent in vivo two-photon PO2 microscopy mouse experiments which measured arterial and venous RBC oxygen at different cortical depths. Figure 2(B) reflects the predicted penetrating arteriole RBC oxygen content as fairly uniform between cortical layers. The predicted arterial oxygen tension and measured arterial tension differed by less than 10%. This amount of error is within the level of error due to experimental methods. The predicted venous RBC oxygen tension agree with the venous RBC oxygen tension recently measured by the Charpak[15] lab. Three-dimensional oxygen tension patterns in blood vessels are depicted in Figure 2(B). Figure 2(B) reflects the heightened tissue oxygen tension in the arteriole and venule compared to the capillary bed.

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Figure 2. Simulated states in the murine cortical tissue. Using the proposed method, the distribution is predicted for pressure (A), hematocrit (B), and RBC oxygen saturation (C). The color range is from high (red) to low (blue) pressure, hematocrit and RBC oxygen concentration values, respectively.

The mean tissue oxygen tension was found to be 22.2 +/- 11.2 mmHg, which is 45.1 mmHg lower than the mean arterial tension, 67.3 +/- 3.6 mmHg, and 16.0 mmHg lower than the average venule, 38.2 +/- 9.0 mmHg. Total oxygen consumption in different compartments predicted that tissues near arterioles (within a distance < 10 mm) have higher oxygen metabolism, followed by tissues in the vicinity of venules. The average CMRO in the more distant tissues (distance> 10 mm)
amounted to 1.15 +/- 0.13 mmole/g/min. In Figure 2, tissue oxygen tension is plotted along three rays collinear with the x, y, and z axes penetrating the domain center. Along all directions, the profiles show tissue oxygen tension spikes in the vicinity penetrating arterioles, marked with red dotted lines, and draining venules, marked with dotted blue lines. Between vessels, the tissue oxygen tension is relatively uniform with a mean of 22.2 +/- 11.2 mmHg. This fairly even oxygen tension falls within the physiological range of 18-40 mmHg, which is highlighted as a gray shaded box for clarity. Although the boundary zones follow similar trends, they are omitted in Figure 2 to limit the analysis to the core. Reported profiles were invariant to finer mesh resolutions with edge lengths of 6.6 mm, thus demonstrating mesh independence.

For dynamics, oscillatory changes of hemodynamic states were predicted. We will discuss adaptations of eq (4-6) for predicting blood response to different setpoint tracking scenarios.

REFERENCES

Standard Session IV
PARAMETRIC AND SEGMENTED FEMORAL SURFACES IN FINITE ELEMENT MODELS OF CAM IMPINGEMENT

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SUMMARY

Geometric parameterisation can be used to automatically generate a range of bone geometries, including femurs with cam deformity. This study verified patient-specific parametric finite element models of 20 cam patients under impingement conditions with comparison to their patient-specific segmentation-based equivalents. The parameterisation system was used to generate further cases that demonstrated that clinically used alpha angles should not be relied on for estimating impingement severity, emphasising the importance of reporting the full 3D geometry used in hip joint models.

Key words: femoroacetabular impingement, finite element analysis, geometric parameterisation

1 INTRODUCTION

Abnormal bone morphology in the hip is associated with femoroacetabular impingement, in which repeated contact between the femoral head/neck and acetabular rim can result in pain and soft tissue damage [1]. In order to investigate the effects of bone morphology on tissue strains, it is useful to be able to automatically generate many different geometries representative of the population variation. This can be achieved using a parametric approach to finite element models of the hip [2, 3], but it is important that changes in geometry are well defined. Clinically used radiographic measurements such as the alpha angle, which estimates the asphericity of the femoral head, are highly dependent on 2D radiographic view of the joint and do not capture the full three-dimensional geometry [4]. Furthermore, parametric models should be compared with segmented patient-specific models in order to understand the effects of smoothing out local undulations in subject-specific articular geometries [5].

The first aim of this study was to establish the effect of geometric simplification in finite element models of impingement by comparing models with geometrically parameterised femurs against their segmented femur equivalent, built from 20 patients diagnosed with cam deformity (excess bone on the femoral neck) (Figure 1). The second aim of the study was to demonstrate the capability of the bone parameterisation system in distinguishing the effects of cam size and position, beyond what is possible using an alpha angle measurement.

Figure 1 – Examples of meshed models showing segmented and parameterised femurs, and the acetabulum. Femoral cartilage elements are blue, acetabular labrum elements are red, and acetabular cartilage elements are green. Rigid bone surfaces are in grey.
2 METHODOLOGY

Femurs of 20 patients with clinically diagnosed cam deformity were segmented from CT scans using Simpleware ScanIP 7.0 (Synopsys) and developed into finite element models within Abaqus 6.14 (SIMULIA). A previously developed parameterisation method was used to generate an equivalent parametric model for each segmented model by capturing the femoral head, neck and cam using fitted spheres and ellipses [6], resulting in root mean squared surface fitting errors in the region of 0.6 mm. A simplified spherical acetabulum, including the labrum and acetabular cartilage, was developed and scaled to the head radius of each femur. Bones were modelled as rigid surfaces. Soft tissues were modelled as linearly elastic and meshed with hexahedral elements, and the labrum and acetabular cartilage were assigned transversely isotropic properties defined according to typical collagen fibril alignment. With the acetabular bone fully constrained in all cases, the femurs were constrained in translation at their head centres in a flexion position and then internally rotated to cause impingement against the labrum. The maximum displacements in the labrum and tensile strains at the cartilage-labrum junction were recorded throughout this rotation and compared between the segmented and parametric cases.

Three elements were used across the thickness of the acetabular cartilage and labrum. Displacements seen in the models were converged at this mesh density, but local strain was more sensitive to mesh resolution. Doubling the number of elements across the cartilage thickness (whilst maintaining a good element aspect ratio) in the model with the largest cam resulted in an increase in strain of around 20%, however this was less than the difference between subjects and caused a large increase in required computation time.

In order to demonstrate the capability of the parameterisation system, it was used to generate cases with identical geometry except for the radius and position of the cam. The parameters defining the neck region were adjusted to define two cam radii (low and high radii) and two positions (more anterior or more superior cam), resulting in four different models. Alpha angles of these parametric femurs were measured in an anterior-posterior (AP) view using ImageJ (National Institutes of Health). These models were then run with boundary conditions to simulate flexion up to 90° followed by up to 35° of internal rotation to mimic a clinical impingement test.

3 RESULTS AND DISCUSSION

A typical deformation pattern in the labrum and cartilage-labrum junction is shown in Figure 2. Maximum displacement occurred at the labral tip and this gave one indication in each case of the severity of impingement as the labrum was deformed by the cam. Tensile strain (reported as maximum principal logarithmic strain) occurring at the cartilage-labrum junction area was also of interest because this deformation may be a cause of cartilage surface fibre damage.

![Figure 2](image)

*Figure 2 – Example of a cross section of the deformed (bright colour) and undeformed (shaded) cartilage-labrum junction. Regions of high tensile strain are displayed in red.*

Similar displacements and strains occurring in the segmented and equivalent parametric models (Figure 3) suggests that these outputs were relatively insensitive to the local undulations on the articular surface, which were present in the segmented models but smoothed out in the parametric representation. Displacement of the labrum is a result of the position and peak size of the cam. When a poorer fit between the parametric and segmented surfaces at the cam region was present, impingement contact occurred at appreciably smaller rotation angles in one of the models, depending on whether the parametric surface over- or under-estimated the radius of the segmented cam. Earlier contact in the model with the larger radius resulted in more displacement of the acetabular soft tissue at lower angles of rotation. When higher labral displacement occurred in the segmented or parametric
model, the tensile strain in the cartilage-labrum junction was usually also higher, since the cartilage was both more compressed by the cam and pulled more as a result of the labral displacement. However, discrepancies in the local fit between surfaces at the cam region could be such that the labral tip displacement was higher, whilst the cartilage was compressed less and had lower tensile strain. This emphasises that although a low overall geometrical fitting error can be achieved, this does not guarantee that the parametric geometry is able to precisely capture the shape of all cams, and the fit in localised regions may be poorer than the overall fit, which in the impingement scenario is of particular importance in the cam region.

Figure 3 – Graphs comparing segmented and parametric models for each of the 20 cam patients, showing maximum labral displacement and cartilage-labrum junction strain with increasing internal rotation of the femur. The x-axes show internal rotation in degrees. Displacements (blue, left y-axes) are in mm. Strains (red, right y-axes) are maximum principal logarithmic strains. Results from segmented models are displayed as solid lines, and the equivalent parametric model results in each case are displayed as dashed lines.

The four additionally generated parametric models had the same geometry except that the cam was varied in position and radius (Table 1). In the simulated movement (flexion followed by internal rotation),cams positioned more anteriorly resulted in more severe impingement in the models. However, the alpha angle on both the anterior cam models was lower than those on the superior cam models. This was because the alpha angles were taken in the AP view, meaning the superior cams were more visible. In the anterior cam models, the alpha angle increased only slightly when the cam radius was increased, but the severity in the model (as indicated by tensile strain and labral displacement at given rotations) increased dramatically. For superior cams, increasing the cam radius substantially increased the alpha angle, but the additional severity observed in the model was less than that seen between the anterior cam models. Thus using a single alpha angle, it was not possible to predict the severity of impingement. The differences in severity predicted by the models were a result of both the size and the position of the cams defined in the parametric system.
Table 1 – Overview of parametric models demonstrating the problems inherent in relying on alpha angle measurements to predict severity. Results reported are: converged internal rotation, and at this rotation, the maximum principal logarithmic strain in the cartilage-labrum junction, and maximum labral displacement. The anterior cam models did not converge past a certain level of rotation due to very high deformation of elements at the cartilage labrum junction.

<table>
<thead>
<tr>
<th>Cam geometry</th>
<th>Low radius</th>
<th>High radius</th>
<th>Low radius</th>
<th>High radius</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior location</td>
<td>$\alpha = 63.4^\circ$</td>
<td>$\alpha = 83.1^\circ$</td>
<td>$\alpha = 41.5^\circ$</td>
<td>$\alpha = 44.6^\circ$</td>
</tr>
<tr>
<td>Anterior location</td>
<td>Converged rotation = $35^\circ$</td>
<td>Tensile strain = $0.30$</td>
<td>Displacement = $4.93$ mm</td>
<td>Converged rotation = $35^\circ$</td>
</tr>
</tbody>
</table>

4 CONCLUSION

This study has quantified the effect of taking a smooth parameterised geometric approach when evaluating the effect of femoroacetabular impingement, by comparison with a gold standard segmentation approach. The displacement discrepancy was driven by local fitting error, which can be controlled to be less than 1 mm. Poor local fit in the cam region can also result in differences in tensile strain in the cartilage-labrum junction, but trends between the segmented and parametric models were similar. Overall the results presented here provide an indication that models with parametric femoral geometry can yield similar results to those with segmentation-based geometry, when used to simulate a basic impingement scenario. Furthermore, specific cases have been generated using the parametric approach and used to demonstrate the enhanced capability of a three-dimensional analysis over the current clinical measure of a planar alpha angle. It was shown that potential for tissue damage, as indicated through local strain, was not at all predicted by the alpha angle measure. Future work could further use a parametric approach in order to investigate the effects of additional morphological changes in both the femur and acetabulum, and in this way stratify the patient population.

REFERENCES

A MODELING FRAMEWORK TO ESTIMATE PATELLOFEMORAL JOINT CARTILAGE STRESS USING KNEE JOINT KINEMATICS

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SUMMARY
Subject-specific knee joint computational modeling incorporates geometry that can provide individualized, detailed contact mechanics. Finite-element (FE) models have recently incorporated the use of subject-specific geometry to generate clinically relevant results for surgical planning and improved rehabilitation techniques. However, these FE models are typically limited to analyzing a small sample of joints and positions due to complexities involved with contact modeling and computational convergence. We propose a framework for modeling subject-specific knee joint contact mechanics using rigid body spring-based models driven by highly accurate joint-specific kinematics during the performance of functional tasks.

Key words: knee contact mechanics, discrete element modeling, joint kinematics

1 INTRODUCTION
The knee is one of the most at-risk joints for developing osteoarthritis (OA), a debilitating joint disease that has a 50% lifetime risk at the tibiofemoral joint and afflicts 25% of the population at the patellofemoral joint [1]. The development of OA in the knee joint, particularly the patellofemoral joint, is commonly thought to result from increased joint stress at the articular surfaces due to maltracking of the bones. The use of computational models is a highly attractive solution for studying the effect of joint injuries and diseases, like OA, on joint mechanics. Both finite element analysis (FEA) [2 - 4] and discrete element analysis (DEA) [5] have been used to estimate patellofemoral cartilage contact stresses. These models have been shown to predict cartilage contact stresses consistent with experimental data. However, the use of FEA models can be both time and computationally expensive. DEA (or rigid body spring modeling) is an alternative and computationally efficient method for estimating cartilage stress. [5].

DEA models commonly require estimations of muscle and soft-tissue forces in conjunction with load-based optimization techniques to operate. Displacement control of these models can bypass several of the passive and active force assumptions utilized with current control methods. Theoretically, these displacement-driven models could be incorporated with highly accurate in vivo kinematic data collection techniques, such as biplane fluoroscopy, to estimate knee joint mechanics in patients with knee OA during functional tasks.

The objective of this study was to develop a framework for employing DEA methods driven by patellofemoral joint kinematics for estimating patellofemoral joint contact stresses. We assessed the models ability to predict patellofemoral joint contact stress across multiple knee flexion angles by comparing the model’s results with values reported in the literature employing force-controlled methods.

2 METHODOLOGY
In this study, two fresh-frozen cadaveric knees (mean age: 61 ± 13 years) were utilized to develop the computational models and evaluate the proposed framework. Each knee was prepared by removal of all skin and soft tissue more than 10 cm proximal and distal to the tibiofemoral joint.
line except for the quadriceps tendons and capsular ligaments. The femoral and tibial ends were potted to allow for insertion of the knees into an experimental testing jig. In order to track the motion of the bones, registration blocks were fixed to the medial tibia, medial femur and central patellar bones using cyanoacrylate and baking soda. The modeling framework can be described in three parts: 1) create subject-specific model geometry and computational mesh; 2) obtain subject-specific joint kinematics and position computational models; and 3) perform computational simulations.

2.1 Creating subject-specific model geometry and computational mesh

Several steps were taken to create subject-specific bone and cartilage geometry and generate a discrete element mesh for each knee. First, sagittal plane magnetic resonance (MR) images of each knee were acquired with a 3.0-T General Electric (Milwaukee, WI) MR scanner using an eight-channel knee coil and a fat-suppressed, fast spoiled gradient recalled echo (SPGR) sequence [3]. In order to visualize the registration blocks affixed to each bone, a petroleum jelly mixture was placed over each cube prior to scanning. Once completed, the MR images were imported into a segmentation software suite (Mimics®, Materialise Inc., Ann Arbor, MI). Each knee was manually segmented and 3-dimensional surfaces of the femur, patella, and their respective articular cartilage and registration blocks were created. The surface renderings created from the segmentations were imported into an FE pre-processor (Hypermesh®, Altair Engineering Inc., Troy, MI). Once imported, a mesh refinement process was implemented, generating triangular shell elements for both bones (avg. mesh size = 1.0 mm) and articular cartilage surfaces (avg. mesh size = 0.5 mm).

2.2 Obtaining subject-specific joint kinematics and positioning computational models

After obtaining the MR images, each knee specimen was mounted in a custom designed knee jig. The knee jig was designed to allow for unconstrained six degree of freedom motion throughout knee flexion-extension while allowing simulated muscular forces to be applied to the quadriceps tendons via a clamp and pulley system. For this study, each specimen was positioned at 15° increments from 15° to 60° of tibiofemoral knee flexion. At each position, physiologic tensile forces were applied to each quadriceps tendon to simulate functional activities [5]. Additionally, a compressive force of 350 N was added to simulate tibiofemoral joint loading conditions.

The current study consisted of two global reference frames: a digitizer reference frame (experimental data) and the MR image reference frame (the computational model). Experimental knee joint kinematics were collected using a mechanical digitizer (Faro Arm®, Lake Mary, FL) to digitize points on three predefined faces of each registration block across the loading conditions. After collecting the experimental data, the digitized points were imported into a custom Matlab program (Mathworks, Natick, MA) in order to calculate orthonormal local coordinate systems for the femur, patella, and tibia bones. These coordinate systems were calculated by fitting the data points on each face to a plane equation using a least-squares optimization technique. The optimization routine generated a local coordinate system for each block, with the origin located on the corner of the block and unit normal vectors from these planes being the coordinate axes [6].

In order to relate the experimental positions of the knee joint to the computational model generated from the MR scans, a “co-registration” technique was employed using the local coordinate systems on each registration block [6]. The computational models were imported into a CAD-based program (©2013 Geomagic Studio, 3DSystems, Rock Hill, SC) in order to generate local coordinate systems for each registration block using similar methods as done experimentally. Once both local coordinate systems were defined, an affine transformation matrix was formed to allow for positioning of a vector from the local to global reference frame of each space. The inverse transformation allows points (geometry) in the global reference frame to be transformed to the local coordinate system. These transformation matrices were utilized to relate the position of the femur and patella (along with the articulating cartilage surfaces) from the experimental conditions into the MR image coordinate system, thus positioning the joint in each of the experimental loaded states. This method has been shown to have an accuracy level of ± 0.1 mm for translations and ± 0.1° for rotations [6].
2.3 Perform computational simulations

DEA was utilized for the computational analysis at each position by creating compression-only springs \((E = 4 \text{ MPa}, \nu = 0.42 [7])\) at the centroid of each element of the femoral and patellar cartilage surfaces [5]. Contact stresses were estimated using the following linear elastic equation:

\[
P = \frac{(1 - \nu)E}{(1 + \nu)(1 - 2\nu)}h d,
\]

where \(E\) and \(\nu\) are the Young’s modulus and Poisson ratio, respectively, \(h\) is the undeformed surface to surface cartilage thickness and \(d\) is the spring deformation upon positioning the joint to its final, loaded state. The undeformed surface to surface cartilage thickness was calculated by identifying the nearest neighbor element from the patellar subchondral surface (master surface) to the femoral bone elements under the femoral cartilage. Spring deformation was determined through a penetration analysis, where overlapping femoral and patellar cartilage elements were identified by implementing a nearest neighbor searching routine. In short, a space partitioning tree was developed for each element on the patellar surface to identify regional elements on the femoral cartilage surface that were within a particular radius (5mm). An additional selection criterion to identify elements that were in overlap was implemented as follows: the dot product of each patellar cartilage element’s outward normal vector and the vector connecting closest femoral cartilage elements must be nearly antiparallel (~ -1) to be considered in overlap [5, 7]. The magnitude of the minimum distance of overlapping, paired elements defined the amount of deformation, \(d\). This algorithm was implemented for every element on the patellar cartilage surface. Contact stress was then calculated for each element (equation 1) and divided into medial and lateral patellar facet regions, defined by drawing a line through the inferior apex to the superior-most point on the base of the patella. The DEA algorithm was implemented using MATLAB (2015a, The Mathworks, Natick, MA). Outputs from the model in the current study include average and peak contact stresses across the different flexion angles, which were indirectly compared to results from prior FEA-based models at the same flexion angles.

3 RESULTS AND CONCLUSIONS

This study has demonstrated a framework for employing displacement-driven computational models in estimating patellofemoral joint contact mechanics. A sample result of the contact stresses from the computational model for both knees at 15° can be seen in Figure 1. The fringe plot demonstrates the importance of developing subject-specific models, as the contact stress distribution between the two knees from the current study is strikingly different at the same flexion angle. The use of subject-specific joint geometry and cartilage as input to a model, like in the current study, can reveal joint-specific regions of contact that may be problematic, which would be clinically informative if applied to patients requiring rehabilitative or surgical interventions.

![Figure 1: Patellofemoral contact stress plots at 15° of flexion for two knee joint specimen.](image-url)
The magnitudes of the average and peak contact stresses from the model in the current study are similar to prior studies [2-4], which can be seen in Figure 2. Specifically, Fitzpatrick and co-workers report values for average and peak contact stress ranging from 1.0 – 1.4 MPa and 2.7 – 3.3 MPa, respectively [2], while average and peak stresses from the current study range between 1.1 – 1.3 MPa and 2.3 – 2.8 MPa, respectively, across similar flexion angles. Our model exhibits similar trends for both average and peak contact stress compared to stresses computed by Fitzpatrick et al. across the flexion angles [2]. Specifically, there is a noticeable decrease in both average and peak stresses from 15 degrees to 30 degrees of flexion, which then increases at both 45 and 60 degrees of flexion. Additionally, the results from the current model also fall within values reported by Farrokhi et al. [3] and Besier et al. [4], although both of these studies were limited in the flexion angles analyzed. The similarities in the magnitude and trends of the contact stresses provide confidence that the model from the current study is able to estimate joint contact stress driven solely by accurate kinematics. A number of limitations with the current study should be noted. First, results are indirectly compared with prior studies, which implemented different modeling techniques. However, these prior studies provide a benchmark for results from the current model. Additionally, cartilage is modeled as a linear, elastic material, though this assumption can be suitable under small durations of loading. Future studies will perform direct experimental validation of several knee specimen. We plan on implementing these future validated computational models with accurate, in vivo 3D knee joint kinematics to estimate knee joint contact mechanics in patients with knee OA during dynamic activities. This novel modeling technique could potentially allow for near real-time joint contact predictions and allow clinicians to prescribe patient-specific treatment based on the model’s joint-specific contact results. The current study presents groundwork for the potential use of displacement-driven models in assessing the effect of clinical intervention strategies for patients with patellofemoral joint dysfunction.

REFERENCES

EFFECT OF THE CONSTITUTIVE MODEL OF BRAIN TISSUE ON THE DYNAMIC RESPONSE OF HEAD TO BLAST SHOCKWAVES

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SUMMARY

Constitutive modeling the brain tissue is a challenging task in all finite element (FE) analyses of brain injury. We conducted a computational analysis to understand the role of the tissue’s constitutive model on the brain’s response to blast loads by modeling the brain tissue as linear elastic, hyperelastic, viscoelastic, and hyper-viscoelastic. Based on the kinematic and kinetic injury criteria, the dynamic responses of brain tissue were compared in terms of intracranial pressure (ICP) and shear stress. We observed that while the constitutive model of the brain significantly altered shear responses, it did not have a significant effect on the ICPs.

Key words: Blast-induced Traumatic Brain Injury, Brain tissue constitutive model, TBI injury threshold, Finite Element Analysis

1 INTRODUCTION

Due to the conflict during and after Afghanistan and Iraq wars, there has been an increased research interest in the study of blast induced traumatic brain injury (bTBI). In addition, during past decades, development of efficient FE and computational methods, have facilitated the understanding bTBI [1-6]. A comprehensive study of the bTBI needs several steps such as development of a FE head model which can be constructed from Magnetic Resonance Images (MRI). After that and before applying the boundary conditions, the constitutive material modeling plays an important role in bTBI simulations. Therefore, to better understand the bTBI mechanisms and injury criteria, the effect of the constitutive model of the brain tissue should be examined. The bTBI injury mechanisms starts with the interaction and propagation of high frequency pressure wave inside of skull. Then, the acceleration of the head causes ICP, shear stress and strain in the brain tissue and neural systems. These mechanisms lead to concussion, diffuse axonal injury (DAI), and contusions [7]. Therefore, there is need for bTBI criteria in terms of mechanical parameters such as pressure, strain, shear stress, or even von-Mises stresses of brain tissue.

By utilizing these mechanical parameters as injury criteria for bTBI, the role of brain tissue constitutive model become noteworthy. In this FE study of bTBI, four different currently acceptable brain tissue constitutive models were employed and brain’s dynamic response to an identical blast load were compared to investigate the effect of the constitutive model. Material models used are linear elastic, hyperelastic, linear viscoelastic and hyperviscoelastic.

2 METHODOLOGY

To compare the brain’s responses to identical blast shockwave using different constitutive models, the FE head model was exposed to blast loads from the front. Time histories of brain tissue responses in terms of ICP and shear stress were recorded and compared for all brain material models. The neck was considered free due to the short duration of the blast event [8]. Generation, propagation and interaction of the blast shockwaves with the head were carried out using LS-DYNA software. The details of the computational algorithm can be found in [5, 8, 9].
2.1 FE Head and blast model

The human FE head model includes 11 components: skull, cerebrospinal fluid (CSF), pia mater, falx, tentorium, neck, facial bone, facial skin, scalp, dura mater, and brain, as depicted in Figure 1(a). This head model has been validated against experimental impact tests of Nahum et al. [10] in terms of ICP at coup and countercoup site. The validation test results are shown in Figure 1(b). To model the blast by FE software, the coupling method of multi-material in Eulerian-Lagrangian domain was used. As shown in Figure 1(c), a 50 cm cube is considered as the blast medium with non-reflecting boundary condition. This cube is connected to the ambient layer to model the explosion of 70 gr TNT with the distance about 85 cm from the front of the head [8, 11].

![Figure 1](image)

Figure 1. (a) NDSU FE head model and all components, (b) the FE head model validation against impact tests, and (c) the FE blast model in nonlinear FE code LS-DYNA

2.2 Brain tissue constitutive FE model

Four different constitutive models were considered for brain tissue in this study:
- Linear Elastic
- Hyperelastic
- Linear Viscoelastic
- Hyperviscoelastic

These material models were adopted from the published literatures based on experimental measurements. The mechanical parameters are tabulated in Table 1. The strain energy of hyperelastic and hyperviscoelastic models are given by Mooney-Rivlin energy method with just the first two terms. In addition, the time-dependent characteristic of the brain tissue can be described by convolution integral with the shear relaxation modulus.

<table>
<thead>
<tr>
<th>Material Model</th>
<th>Density (kg/m)</th>
<th>Poisson Ratio</th>
<th>Young Modulus (kPa)</th>
<th>Mechanical Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linear Elastic [12]</td>
<td>1040</td>
<td>0.48</td>
<td>675</td>
<td></td>
</tr>
<tr>
<td>Hyperelastic [13]</td>
<td>1040</td>
<td>0.49999948</td>
<td>C(10) (Pa) 514.62</td>
<td>C(20) (Pa) 566.08</td>
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<tr>
<td>Viscoelastic [12]</td>
<td>1040</td>
<td>2.19</td>
<td>G(0) (kPa) 41</td>
<td>G(\infty) (kPa) 7.8</td>
</tr>
<tr>
<td>Hyperviscoelastic [8]</td>
<td>1040</td>
<td>2.19</td>
<td>C(10) (Pa) 3102.5</td>
<td>C(20) (Pa) 3447.2</td>
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<tr>
<td></td>
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<td></td>
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<td>G(2) (kPa) 23285</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(\beta_1) (1/sec)</td>
<td>(\beta_2) (1/sec)</td>
</tr>
</tbody>
</table>

3 RESULTS AND CONCLUSIONS

By solving the nonlinear and transient fluid-solid interaction FE code, the blast pressure propagation is calculated at different time steps. The pressure contours are depicted in Figure 2.
A common TBI criterion is ICP. The maximum ICP at coup and countercoup site are calculated for different brain materials by averaging the pressure over a region including few elements. The ICP variations with time at these sites are illustrated in Figure 3 (a) and (b). As it can be seen, results predicted by the linear elastic model are inconsistent with ones predicted by other models. In addition, the peak ICP contours for different materials in Figure 3(c) show that the maximum ICPs predicted by linear viscoelastic and hyperelastic models are localized at coup site, but linear viscoelastic and hyperviscoelastic models distribute the pressure on frontal and lateral regions and tend to predict the maximum ICP near parietal-temporal regions.

Another common TBI injury criteria is the maximum shear stress. Shear stresses predicted by these materials are also averaged over some elements and the peak shear stress contours are demonstrated in Figure 4. It can be seen that while the ICP values predicted by these constitutive models slightly vary, the shear stress responses vary significantly among different models. The linear elastic model for the brain tissue results in a higher shear stress while the hyperelastic model predicts lower shears stresses. However, the time-dependent models predict similar results with minor difference in temporal fluctuations.

We believe that the considerable differences between the responses of time-dependent models and the other model pertain to the method that shear stress is calculated. For instance, the linear viscoelastic and hyperviscoelastic models involve the shear relaxation modulus function, which is obtained by experimental measurements. These relaxation measurements are related to the strain rate during the compression and tensile tests. Considering the time-dependent characteristic of biological tissues and their nonlinear behavior under large deformations (blast loading), we can conclude that linear elastic constitutive model fails to accurately predict the brain dynamic response under dynamic loads and hence is a weak assumption. In addition, while considering a nonlinear strain energy model (such as Mooney-Rivlin) for the brain tissue, dose not considerably affect the ICP responses, it underestimates the shear responses as it predicted very low shear stresses. Moreover, the shear relaxation modulus as a time dependent function, plays a great role in shear stress bTBI criteria. Finally, shear stress showed to be a more reliable injury criterion than ICP since it is associated with the deviatoric response of the brain tissue to loading and hence is greatly affected by the brain material.
REFERENCES

TOWARDS UNDERSTANDING BLAST-INDUCED BRAIN INJURY MECHANISMS: A FINITE ELEMENT ANALYSIS

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SUMMARY

Understanding the injury mechanisms is the first step in treatment and prevention of blast-induced traumatic brain injury (bTBI). A computational study using finite element analysis (FEA) was carried out to investigate possible bTBI mechanisms upon interaction of blast waves with the head. A detailed FE head model was exposed to blast shockwaves and intracranial shockwave propagation, brain tissue shearing, and skull deformation were sought as possible bTBI mechanisms. Measuring the intracranial pressure and shear stress at different regions of the brain, it was observed that among other mechanisms, shockwave propagation imposed the highest injury risk on the brain.

Key words: Blast-induced Traumatic Brain Injury, Finite Element Analysis, Injury mechanism, Intracranial pressure, Shear stress

1 INTRODUCTION

Due to its serious long-term consequences, bTBI has become a major concern among military members and hence requires a great attention. Unfortunately, most of the soldiers are diagnosed with bTBI due to the increased use of improvised explosive devices (IED) in the battlefields. The moral issues and complex nature of bTBI makes it almost impossible to perform experimental studies. Hence, numerical methods such as FEA have grown in the past decade to facilitate the study of bTBI. While some researchers have investigated bTBI mechanisms, many researchers have focused on examination and improvement of current protective tools [1-6]. The first step to treating, and more importantly preventing bTBI is to understand the possible injury mechanisms involved with that. Upon impingement of blast waves on the head, shockwaves start to propagate inside the cranium, brain tissue shears in response to the load, and skull starts to deform. These mechanisms can lead to the development of shear stress and strains as well as increased ICP levels at different regions of the brain which can lead to different injuries such as concussion, diffuse axonal injury, and skull fracture. Moss et al. [1] and Panzer et al. [3] introduced skull flexure and cavitation as possible bTBI mechanisms, respectively, by studying the interaction of blast waves with simplified head models. Sarvghad-Moghaddam et al. [2] mainly looked into the concussive injuries imposed due to the intracranial shockwave propagation. They also pointed out the importance of directionality consideration when studying bTBI. Chafi et al. [7] studied the importance of brain tissue’s shear deformations as well as shear strain in the development of diffuse injuries. We conducted a computational study to investigate possible injury mechanisms when head was exposed to injurious blast overpressures. The tissue responses of the brain at different regions in terms of ICP and shear stress as well as the relative displacement of the skull were recorded. The focus of our research was to find out which injury mechanism is prevalent at injurious levels and whether other mechanism play an important role in the development of different injuries.

2 METHODOLOGY

2.1 FE discretization and blast modeling
A detailed 3D finite element head model was used for our study. This head model includes the major components of the head such as skull, pia and dura mater, CSF, brain, and tentorium. Our head model was validated against the experimental results of Nahum et al. [8] for frontal impacts on cadavers. For modeling the blast, a cubic domain with a side length of 50 cm was developed to simulate the generation and propagation of shockwaves through arbitrary a multi-material Lagrangian-Eulerian (ALE) algorithm. Fluid-structure interaction between the shockwaves and the head was implemented using a penalty method in LS-DYNA. An overpressure of 700 kPa was developed around the head by simulating the detonation of 100 grams of TNT at a 70 cm stand-off distance from the head. The details of the head model and the employed blast model, as well as the computational model can be found in [9, 10]. Head model and the blast domain are shown in Figure 1.

![Figure 1. (a) FE head model, (b) Blast domain and loading conditions](image)

**2.2 Material models**

The Eulerian domain was filled with air, which was modeled as an ideal gas at 25 °C and 1 atm using the equation of state (EOS). All the head components were modeled as linear elastic materials except for the brain tissue. Due to the viscoelastic nature of the brain tissue and its nonlinear response under large deformation, a hyperviscoelastic constitutive model was adopted for it. Material properties of the head components and brain tissue are presented in Tables 1 and 2, respectively. More details on the material properties can be found in [9, 10].

<table>
<thead>
<tr>
<th>Head Component</th>
<th>Density (g/cm³)</th>
<th>Elastic Modulus (GPa)</th>
<th>Poisson’s Ratio</th>
<th>Bulk Modulus (GPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scalp/Skin</td>
<td>1.2</td>
<td>0.0167</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td>Skull</td>
<td>1.21</td>
<td>8.0</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td>Dura, falx, tentorium</td>
<td>1.133</td>
<td>0.0315</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>Pia mater</td>
<td>1.133</td>
<td>0.0115</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>Facial bone</td>
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<td>5.54</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td>Cervical Vertebrae</td>
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<td>0.354</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>CSF</td>
<td>1.004</td>
<td></td>
<td>0.499</td>
<td>2.19</td>
</tr>
</tbody>
</table>

**Table 2. Parameters of hyper-viscoelastic brain material**

<table>
<thead>
<tr>
<th>$C_{10}$ (Pa)</th>
<th>$C_{01}$ (Pa)</th>
<th>$G_1$ (kPa)</th>
<th>$G_2$ (kPa)</th>
<th>$\beta_1$ (s⁻¹)</th>
<th>$\beta_2$ (s⁻¹)</th>
<th>$K$ (GPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3102.5</td>
<td>3447.2</td>
<td>40.744</td>
<td>23.285</td>
<td>125</td>
<td>6.6667</td>
<td>2.19</td>
</tr>
</tbody>
</table>
3 RESULTS AND CONCLUSIONS

Tissue responses of the brain in terms of maximum shear stress and ICP were evaluated at different regions of the brain. Propagation of pressure within the brain tissue is shown in Figure 2, with the peak ICP occurring at the coup site. ICP was evaluated at the coup, countercoup, and brainstem. On the other hand, the maximum shear stress was recorded at frontal and parietal lobes, corpus callosum, and brainstem. It was observed that while the ICP variation with time approached zero after about 5 milliseconds after the blast waves hit the head (Figure 3(a)), the shear stress continued to vary afterwards (Figure 3(b)). This could be due to the fact that the pressure response of the brain is mainly dominated by the relative motion of the brain with respect to skull while the shear response is mainly dictated by the deviatoric response of the brain tissue. Our model predicted a peak ICP of 392 kPa [2] which is within the range for severe TBI. The negative pressure at the countercoup site is about -250 kPa which could impose the risk of cavitation [3]. Unlike the coup site, the peak ICP at the brainstem is well below the injury criteria for concussion. Based on the criteria introduced by Zhang et al. [11], (50% risk of mild TBI for shear stresses over 7.8 kPa) the maximum shear stress values in Figure 3(b) do not predict any injury. Hence, we can deduce that intracranial shockwave propagation was the main injury mechanism in our model. One possible conclusion might be that at injurious levels of blast overpressure, brain is more prone to concussive injuries than the DAI injuries due to the brain tissue shearing injury mechanism. Moreover, Figure 3(b) reveals that frontal lobe and brainstem experience highest shear stress and the corpus callosum undergoes lower shearing forces.

Figure 2. Variation of ICP within the brain tissue at (a) 0.8 ms; (b) 1.1 ms; and (c) 1.4ms after the interaction of shockwaves with the head (Units in KPa).

Figure 3. Temporal variation of (a) ICP and (b) maximum shear stress at different brain’s regions

Figure 4 shows the relative displacement of two nodes on the frontal and occipital bones of the skull. Our model predicted a peak relative displacement of 0.9 mm for a blast overpressure of 700 kPa. This would imply that the skull flexure would be the second most possible injury mechanism in our analysis since the deflection of the skull is not negligible and could bring about the concern for skull fracture. Our study highlights the importance of injury mechanism in understanding different aspects of bTBI. The outcomes of such study could be used toward developing preventive strategies and protective tools. Possible future works could involve performing similar studies at higher blast intensities and other blast directions to investigate the contribution of each injury mechanism in different loading conditions.
REFERENCES

FAILURE MODE ANALYSIS OF TIBIAL PLATEAU FRACTURE IN COMPRESSION: COMPARISON OF SCREws ONLY AND SCREW AND PLATE FIXATIONS

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SUMMARY

This study investigates the failure modes of tibial plateau fractures that have been treated with lag screws or with screws and buttress plates. A computational evaluation of the relative strengths of each support method can determine the most effective ways to treat tibial plateau fractures as well as point out the weak points of each mechanism. Finite element (FE) modeling showed that screw fixation was not as strong as the screw and plate, but the failure mode was the same in each. Furthermore, neither method of fixation showed to be sufficient to maintain fracture line’s stability during walking steps.

Key words: Buttress plate, Lag screw, Tibial plateau fracture, Finite element analysis, Failure modes

1 INTRODUCTION

A tibial plateau fracture occurs at the proximal end of the tibia, primarily affecting function of the knee joint. There are two fixation methods used to treat these fractures: lag screw, and screw and buttress plate. Screw supports place a series of screws along the fracture to clamp the pieces of the bones together. Screw and plate supports add a plate to the screws to reduce the force on the individual screws (Figure 1). Previous studies have tested tibias treated with a screw and plate support. Ratcliff et al. analyzed the failure of two forms of screw and plate supports, namely medial buttress plates and lateral locking plates and found that they were able to withstand forces up to 4136 N and 2895 N, respectively [1]. Similarly, Lindeque and Baldini compressed artificial tibias that had Schatzker type V tibial plateau fractures treated with Zimmer, DePuy, and Synthes brand locking plates, and found that they failed at 1724, 2051, and 1724 N, respectively [2]. However, a comparison of these support techniques to screws only fixation has not yet been completed. This study will therefore seek to compare failure strength and failure mechanisms of screw fixation, and screw/buttress plate fixation.

2 METHODOLOGY

2.1 Geometry and material properties

Finite element modelling was used in order to predict the failure modes of the three methods of internal fixation. Three dimensional models of a tibia with plateau fracture fragment, supported by lag screws only (Figure 2(a)) as well as lag screws and a proximal tibia buttress plate (Figure 2(b)) were created.
Tibia and fracture fragment were modelled as a 3mm tibial cortical bone with a wall thickness of 3 mm. The cortical bone was modelled as orthotropic using the material properties from Knets and Malmeisters [3]. Lag screws were modelled as stainless steel cylindrical beams with a diameter of 5mm bonded to the walls of the bone and the buttress plate when present. The tibia buttress plate was also modelled as a 3 mm thick stainless steel component contoured anatomically to the fracture site and 6 bolt holes were considered on it for fixation. All the material properties are presented in Table 1. In the screws only fixation, three lag screws fix the bone fragment in its proper anatomical position, as shown in Figure 2(a). For the screw and plate fixation, three lag screws anchor the buttress plate to the bone along the tibial shaft and three lag screws pass through the top of the buttress plate, fixing the bone fragment in its proper anatomical position, as shown in Figure 2(b).

<table>
<thead>
<tr>
<th>Elastic Material Properties</th>
<th>Density(kg/m²)</th>
<th>Elastic modulus(GPa)</th>
<th>Poisson's ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stainless Steel Screws and Buttress Plate</td>
<td>7750</td>
<td>193</td>
<td>0.31</td>
</tr>
</tbody>
</table>

| Orthotropic Material Properties | \( E_X(GPa) \) | \( E_Y(GPa) \) | \( E_Z(GPa) \) | \( G_{XY}(GPa) \) | \( G_{YZ}(GPa) \) | \( G_{XZ}(GPa) \) | \( \nu_{XY} \) | \( \nu_{YZ} \) | \( \nu_{XZ} \) |
|----------------------------------|---------------|----------------------|----------------|
| Tibia Cortical Bone              | 6.91 | 8.51 | 18.4 | 2.41 | 3.56 | 4.91 | 0.49 | 0.14 | 0.12 |
### 2.2 Loading and boundary conditions

A Static structural analysis was carried using ANSYS 17.2 to simulate a ramped distributed force loading on the tibial plateau while keeping the tibia shaft fixed as shown in Figure 3. The tibial shaft is fixed because we are only concerned with injury to the fracture site. The loading and boundary conditions are identical for both assemblies. Varying the force with time allows the current research to establish the force level required for failure. A 0.5 mm relative motion of any portion of the fracture line is considered a medically significant failure of fixation because it would impede or reverse bone healing. The interface within the fracture line is modelled as having a friction coefficient of 0.1. Tibial bone, fragment and buttress plate were meshed using tetrahedral elements while the screws were modelled using hexahedral mesh elements. The mesh was refined near the screw holes to estimate the stresses and deformations at these sites more accurately.

Figure 3. Loading and boundary conditions for (a) screws only and (b) screws and buttress plates fixations

### 3 RESULTS AND CONCLUSIONS

Our results showed that screws and plate fixation provided greater positional stability than the screws only assembly due to the stiff buttress plate supporting the lag screw ends. However, both fixation methods failed by deformation of the bone surrounding the fracture line, most severely at the weight bearing surfaces near the fracture line. As it can be seen in Figure 4, the maximum deformation occurs at the weight bearing site near the fracture line. While the screws and plate model predicted slightly lower deformations compared to the screws only fixation due to the frictional reaction forces, the orders of magnitude of the deformations were the same and clinically significant. This indicates that a 1000 N peak loading could cause clinically significant relative motion within the fracture line which might impede or even reverse bone healing. The screws only fixation caused movement of the entire bone fragment, giving rise to 0.5 mm shearing relative motion along the entire fracture line, while screws and plate fixation led to such a magnitude of relative motion at the peak stress site in Figure 4 (b).

Figure 4. Deformation contours for (a) screws only; and (b) screws and plate fixations (Units in m)
Maximum stress concentrations and magnitudes for both methods of fixation are shown in Figures 5. It can be observed that the maximum stress in the screws and plate fixation occurred at an isolated point along the inner edge of the fracture line. For the screws only fixation, the maximum stress occurred on the uppermost lag screw’s far end, supporting the bending forces within that lag screw. This indicates that additional deterioration of bone tissue due to stress beyond the bone material limits may occur at the far ends of the lag screws. However, this is not the case with buttress plate fixation because the near ends of the lag screws are supported, which limits the bending moments supported within the screws.

Figure 5. Stress distribution for (a) screws only; and (b) screws and plate fixations (Units in Pa)

This study provides insights into the mechanisms of tibial plateau fracture fixation failure. In buttress plate fixation, excess relative movement occurred only at the weight bearing site near the fracture because the bone fragment was positionally stable. In the screws only fixation, the excess relative movement occurred along the entire fracture line due to the movement of the entire bone fragment. Furthermore, examining the stress concentrations of each method showed that the screws only fixation’s excessive movement can give rise to high stress concentrations in the screw holes at the far end of the lag screw. This could be considered as a significant mechanical weakness of this method of fixation. The current research indicates that while both methods of fixation are inadequate to withstand walking, buttress plate fixation may better preserve fracture healing in cases of accidental weight bearing.

REFERENCES

FINITE ELEMENT MODELING OF A CEMENTLESS ACETABULAR CUP: INFLUENCE OF FRICTION AND OF BONE PROPERTIES

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SUMMARY

Biomechanical phenomena occurring at the bone-implant interface during and after the press-fit insertion of acetabular cup (AC) implants are poorly understood because of i) the complexity of bone tissue, ii) remodeling phenomena and iii) the presence of a rough interface. Two finite element (FE) models are proposed in this study. A 2D axisymmetric FE model which aims at modeling the implant insertion and pull-out process taking into account the effect of friction, bone properties and the geometry of the cavity, is proposed. A 3D FE simulation of an osseointegrated AC implant is developed to investigate the effects of bone anisotropy.

Key words: acetabular cup, finite element analysis, friction, bone anisotropy, interference fit

1 INTRODUCTION

Hip arthroplasty has become a common surgical intervention [1]. However, surgical failures still occur, leading to dramatic consequences. Aseptic loosening is one of the most common causes of failure [2] and it is related to the implant biomechanical behavior. The implant primary stability refers to the quality of the mechanical insertion established at the end of the surgery. More specifically, it gives a measure of the resistance capacity of the implant inserted in the bone cavity to various stresses. A sufficient primary stability is necessary to reduce the relative micromotions at the bone-implant interface, which may lead to the formation of fibrous tissue around the implant [2]. The long-term fixation of the AC implant is obtained by osseointegration phenomena [3], which leads to a bounded bone-implant interface after the bone healing process. Several studies focused on the effect of the AC implant shape, material and surface treatment on its biomechanical properties [4-6]. However, the relation between bone properties and the AC implant macroscopic mechanical behavior remain poorly established. Moreover, the complex biomechanical phenomena occurring at the bone-implant interface involving friction and adhesion is still poorly understood [7]. The present study aims to provide a better understanding of the interfacial phenomena and their implication in the biomechanical behavior of the AC implant. Accordingly, two finite element analyses are proposed. Firstly, a 2D axisymmetric FE model aiming to simulate the implant insertion taking into account the implant press-fit and a pull-out test, is developed. The effects of friction, bone properties and of the cavity geometry on primary stability, are considered. The second model is a 3D FE simulation and considers an osseointegrated AC implant. The effects of trabecular bone anisotropy are investigated.

2 MATERIALS AND METHODS

2.1 Modeling the acetabular cup implant insertion

A 2D axisymmetric finite element model is implemented in order to simulate the implant press-fit insertion into bone tissue, as well as a pull-out test, which allows to determine the AC implant primary stability by quantifying the pull-out force, which cannot be done in the operating room.
Quasi-static conditions are assumed and the geometrical configuration described in Fig. 1a) has been chosen similarly as in previous papers by our group [8-13]. Bone is modeled by a linear elastic and isotropic material and several values of the Young modulus of bone tissue $E$ have been investigated in a range varying between 0.1 and 1 GPa [4]. Moreover, several values of interference-fit comprised between 0.1 mm and 2.5 mm were considered. A classical Coulomb friction law was taken into account at bone-implant interface and different values of the friction coefficient were chosen between 0.1 and 1 [5].

### 2.2 Modeling the biomechanical properties of an osseointegrated acetabular cup implant

Furthermore, a 3D finite element analysis of a fully osseointegrated AC implant has been carried out in order to investigate the influence of the peri-implant anisotropic properties of trabecular bone tissue on the biomechanical behavior of the AC implant at the macroscale [14]. The proposed approach consists in coupling numerical simulation tools with high resolution imaging techniques and multiscale analyses in order to understand the determinants of the biomechanical behavior of the AC implant under physiological conditions. Stress and strain distributions in the homogenized peri-implant bone were computed for different loading conditions of the AC implant. The geometrical configuration is shown in Fig. 1b).

Thirteen bovine trabecular bone samples were imaged using micro-computed tomography ($\mu$CT) with a resolution of 18 µm. The anisotropic biomechanical properties of each sample were determined at the scale of the centimeter based on a dedicated method using asymptotic homogenization. The material properties obtained with this multiscale approach were used as input data in a 3D finite element model to simulate the macroscopic mechanical behavior of the AC implant under different loading conditions.

![Figure 1: synoptic sketch of the two proposed FEM simulations](image)

1a) Geometrical and mechanical configuration of the 2D axisymmetric model. 1b) Geometrical and mechanical configuration of the 3D model.

### 3 RESULTS AND DISCUSSION

#### 3.1 Acetabular cup implant insertion

Concerning the 2D axisymmetric simulation, the main finding is the strong influence of the friction coefficient on the overall biomechanical response of the AC implant. The pull-out force is shown to increase as a function of the friction coefficient $\mu$ for constant values of $E$ and of interference fit. Similarly, the pull-out force increases linearly as a function of $E$ for constant values of $\mu$ and interference fit. Moreover, as shown in Fig. 2, the pull-out force $F$ varies non-linearly as a function of the interference fit for constant values of $E$ and of $\mu$, and reaches a maximum value $F_0$ at a given interference fit $IF_0$, which corresponds to the optimal stability condition. Note that $IF_0$ does not depend on the value of $E$ but increases when $\mu$ increases from 0.1 up to 0.4 and then stay constant and equal to 1.7 mm (for a value of $E=200$ MPa) for values of $\mu$ higher than 0.4. Moreover, the value of $F_0$ is shown to increase as a function of $\mu$ (between 0.1 and 1, which corresponds to the physiological range).
The effective contact area and the polar gap were quantified. When the friction coefficient increases, the contact area moves towards the bone cavity rim. The polar gap also increases as a function of the friction coefficient and of the interference-fit.

![Figure 2: Variation of the pull-out force as a function of the interference-fit for several values of friction coefficient. The value of the Young's modulus of the surrounding bone tissue is taken equal to 200 MPa. Optimal values of interference-fit are indicated by a red dot.](image)

3.2 Biomechanical properties of an osseointegrated acetabular cup implant

As shown in Fig. 3, the largest stress and strain magnitudes were found around the equatorial rim and in the polar area of the AC implant. All macroscopic stiffness quantities were significantly correlated ($R^2>0.85$) with BV/TV (bone volume/total volume). Moreover, the maximum value of the von Mises stress field was significantly correlated with BV/TV ($R^2>0.61$) and was always found at the bone-implant interface. However, the mean value of the microscopic (at the scale of the trabeculae) decrease as a function of BV/TV for vertical and torsional loading and do not depend on BV/TV for horizontal loading. These results highlight the importance of the anisotropic properties of bone tissue.

![Figure 3: Cross-sectional view of the Von Mises stress field in the implant and in the peri-implant bone for a bone sample (BV/TV=18.0%) under a) vertical loading and b) horizontal loading.](image)

ACKNOWLEDGEMENTS

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REFERENCES

AN ITERATIVE APPROACH FOR MODELING ADHESION IN
SURGICAL SIMULATIONS

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SUMMARY
In this work, we aim to improve the accuracy of surgical simulation by modeling adhesion forces between a rigid tool and a soft biological tissue. Adhesive forces are surface forces that cause surfaces under contact to adhere to each other. For this, we chose an appropriate rate-dependent adhesion model which is effective in capturing the physics of bonding and debonding at the contact surfaces. We propose a new iterative algorithm that can incorporate arbitrary adhesion models while solving for normal forces due to contact in real-time. Our algorithm avoids the need for modeling of adhesion through Lagrange multipliers, thereby circumventing the need to solve a large mixed linear complementarity problem (MLCP) system. To demonstrate this approach, we present the results of modeling adhesion between a liver and a rigid surgical tool.

Key words: surgical simulation, adhesive contact

1 INTRODUCTION
During a surgery, at the time of contact between a tool and an organ tissue, various effects come into play, such as friction and adhesion. Adhesion forces act in the direction opposite to normal contact forces causing surfaces under contact to adhere to each other. This effect becomes more prominent in the surgical procedure, where the tool interacts with a soft biological tissue [1]. One of the aims in surgical simulation is to accurately model such interactions.

In addition to the need for a high fidelity in tissue interaction modeling, real-time performance requirement presents a challenge in surgical simulation algorithm design. We need fast algorithms to incorporate the adhesion phenomenon, so as to make it feasible for real-time surgical simulation. Gascón et al. (2) attempted to model adhesion as a constraint-based formulation. However, in our approach we depend on the contact tracking of the scene objects, and exploit our understanding of the physics of the rate dependent laws of adhesion. This helps us in developing a faster and relatively simpler algorithm. This is explained in detail in the next section.

In the present work, we model the adhesion effect, with an aim to increase the accuracy of force-feedback to the haptics device, thereby rendering the medical simulation more realistic. We develop a novel iterative technique to address the challenge of making adhesion modeling feasible for the real-time medical simulation.

2 METHODOLOGY
We model bonding and debonding phase of adhesion based on the model provided in [2]. The rate dependent debonding model is the linearized version of the debonding model given in [3]. Below are the rate laws for bonding and debonding for a given $i^{th}$ point with adhesion effect.
Bonding:

\[ \dot{\beta}_i = r \max (p_i - \beta_i p_0, 0) \]  

Debonding:

\[ \dot{\beta}_i = \frac{1}{\eta} \min (W - C_i g_i^2 \beta_i, 0) \]

Where \( \beta_i \in [0, 1] \) is the adhesion intensity factor, \( C_i \) is the adhesion stiffness, \( g_i \) is the gap function, \( W \) is the maximum adhesion energy, and \( \eta \) is the adhesion viscosity. The bonding model states that for a given bonding state, \( \beta_i \), there is a minimum saturation pressure, \( p_i \), required to start the bonding, and depending on its value, \( \beta_i \) can asymptotically saturate at a value lower than maximum possible value of 1. The debonding model is based on the associated elastic potential energy as a function of the bonding gap and adhesion intensity at the point of contact. Also, the debonding model states that a decrease in the adhesion intensity can be viewed as a thermodynamic phenomenon, where a release of heat energy takes place when the elastic energy breaches the maximum adhesion energy.

We assume that adhesion does not take place when the distance between two surface nodal points, one on the deformable body and the other point the rigid body, is greater than a reference gap, \( g_{\text{ref}} \). Based on this assumption, and based on the model of adhesion described above, one can conclude that any point on the surface of the interacting bodies in a scene, can either be in one of the three states:

1. Not under contact, and no adhesion \((g_i > g_{\text{ref}}, \beta = 0, \dot{\beta} = 0)\)
2. Under contact, and bonding \((g_i = 0, \beta_i > 0)\)
3. Not under contact, and debonding \((0 < g_i \leq g_{\text{ref}}, \dot{\beta}_i < 0)\).

For a given point \( i \) on the deformable body surface, there will be a corresponding point, \( i' \), on the rigid body surface which is at a distance \( g_i \) less than the reference gap \( g_{\text{ref}} \). By identifying such nodal surface points on the interacting objects and tracking them at every time step, we can construct a set of nodal points, \( S \), such that any point in this set is either in the state of bonding or debonding or the points considered for contact \( S_{\text{cfc}} \). For any point in \( S_{\text{debond}} \), we can compute the force of adhesion, \( F_{i}^{\text{adh}} \) as \( C_i g_i^2 \beta_i^2 \).

In [2] the authors have provided a numerical method to solve for the motion under contact and adhesion forces. However, this method has limitations when applied to the case of real-time simulations. In this work, we provide details of a new iterative scheme we have formulated that can model unilateral contact with adhesion in real-time.

The aim of this algorithm is to avoid expensive static condensation of the effective stiffness matrix at every time step in order to facilitate real-time simulation required for medical simulations. We have based this algorithm following the philosophy of iterative technique to solve for friction as described in [4]. Our algorithm first forms the required MLCP for the frictionless contact as that described in [4]. We then use solve this MLCP along with adhesion forces using a modified Iterative Constraint Anticipation (ICA) (refer [2]).

At every time step, the contact points in \( S_{\text{cfc}} \) are discarded and the collision is performed to populate \( S_{\text{cfc}}^{t+\Delta t}(0) \), where \((0)\) represents the initial set before the first iteration of the solver. The MLCP for friction less contact is formed. Then, the modified iteration is performed as shown in Algorithm 1.
At a given iteration $k$ of this modified algorithm, first the states of the points are updated to get $S_{bond}(k), S_{debond}(k)$, and $S_{cfc}(k)$. This is done by always referring to states at previous known solution at time $t$. Second, the bonding gaps of each point in $S(k)$ is updated using the latest known displacement from the iteration at time $t$. This is then used inside the rate dependent bonding model in conjunction with the explicit Euler for the rate term to update the bonding strength for every point. Third, the $F_{adh}(k) = C_i g_i(k) \beta_i(k)^2$ is computed for all points in $S_{debond}(k)$ that depends on the gap. The gap at each contact point in $S_{debond}$ is computed as $g_i(k) = \|p_i(k) - p_i'(k)\|_2$ where $i'$ is the corresponding bonding point of $i$ on the rigid surface computed at the first instance of bonding and $p$ represents the position. $F_{adh}(k)$ is then assembled into global adhesion vector $F_{adh}$ and then added to the effective force inside the ICA algorithm. The iteration is stopped when $\|u(k) - u(k-1)\|_1 \leq \delta_{tol}$ where $\delta_{tol}$ is the tolerance for convergence.

Algorithm 1: Iterative method for modeling adhesion

1: **Initialize nodal states** $S^t \to S^{t+\Delta t}(0)$
2: Discard $S_{cfc}^t$
3: Collision detection to update $S_{cfc}^{t+\Delta t}(0)$
4: **Form MLCP without adhesion forces**
5: **Perform ICA** (with adhesion forces $\forall i \in S^{t+\Delta t}$)
6: **do**
7: Update bonding states $S_{bond}(k), S_{debond}(k), S_{cfc}(k)$
8: Update $g_i \in S_{bond} \cup S_{debond}$
9: Compute $F_{adh}i \forall i \in S_{debond}(k)$
10: Compute Jacobian $G$
11: **Perform one iteration of ICA** with $F_{eff} \leftarrow F_{eff} + G^T F_{adh}$
12: Update $u(k)$
13: **While** $\|u(k) - u(k-1)\|_1 \leq \delta_{tol}$

This algorithm treats the adhesive forces as directed in any direction in the hemispherical dome (see figure 1). Separate Lagrange multipliers for tangential and normal adhesion that would result in a large system of equations are not required in this formulation.

3 RESULTS AND CONCLUSIONS

![Figure 2: Interaction of a rigid tool surface with liver tissue](image)

We tested our algorithm on a liver organ that is modeled using a co-rotational formulation. A user interacts with the liver as shown in figure 2 using a rigid spherical actor in real-time using a haptic device. The adhesive forces have shown time-dependent sticking effects. The liver is composed of
2217 degrees of freedom. With Young’s modulus of $2.0 \times 10^5 \text{ N m}^{-2}$, Poisson’s ratio of 0.3 and the time step size $\Delta t = 0.003 \text{ sec}$, we observed an average frame rate of 126 in the presence of the adhesion contacts.

Figure 3 shows the convergence of our new adhesion solver with the following parameters: $C_i = 10^8 \text{ N m}^{-3}$, $W = 1$, $\eta = 0.2$, $\Delta t = 0.003 \text{ sec}$ and gravity of $9.8 \text{ N m}^{-2}$. The tolerance used for terminating the iteration is $\delta_{\text{tol}} = 10^{-6}$. Figure 3 shows the error to be monotonically decreasing with the number of iterations.

In conclusion, we have demonstrated a novel method for simulating adhesive forces in real-time that is useful for surgical simulation scenarios. The proposed methods brings various advantages including (a) faster therefore suitable for real-time simulations, (b) ability to incorporate arbitrary adhesion models and (c) tunable for accuracy versus speed of simulation (not possible with previously reported direct methods). We plan to employ this algorithm in various surgical simulation scenarios to enhance visual fidelity. Further, haptic fidelity can be improved by using the computed adhesive forces to render force feedback to the user.

4 ACKNOWLEDGEMENT

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DIFFICULTY SCENARIO MODELING FOR VIRTUAL ARTHROSCOPIC ROTATOR CUFF SURGERY WITH GAML

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SUMMARY
This study presents creation of difficulty scenarios for virtual simulation of Arthroscopic Rotator Cuff (ARC) repair surgery using our Generative Anatomy Modeling Language (GAML) framework. ARC surgery is a minimally invasive surgical procedure in the shoulder performed through tiny scalpel incisions. We are developing a virtual simulation of the ARC surgery supporting various difficulty scenarios. GAML framework supports geometry modification commands that were used to perturb the base 3D models of the shoulder anatomy and generate rotator cuff tears with respecting the non-linear geometry constraints of the shoulder anatomy. The modification on the geometry is fulfilled with our nonlinear optimization model.

Key words: rotator cuff, surgery simulation, modeling language

1 INTRODUCTION
The rotator cuff is a group of muscles (Subscapularis, Supraspinatus, Infraspinatus, and Teres Minor) that surround the upper arm and keep it firmly in the shoulder socket. These tendons provide support and rotational motion of the arm. Injuries (e.g. tears in the muscles) in these rotator cuff muscles can cause constrained motion, severe pain, and weakness of the arm. This ailment can be seen among athletes, or people performing physically intense activities. The risk of rotator cuff damage also increases with age [1]. The condition is first treated with non-surgical methods such as physical therapy and/or steroid injections, but if these treatments fail, surgery is another option.

Although there exist challenges in skill requisition for ARC, there is no standard training or assessment platform. Societies in arthroscopy and orthopedics outline minimum experience requirements for surgeon specialty, but there is no established measurement for skill proficiency level. Currently, the most widely used training methods are the use of cadavers, and 1-to-1 apprenticeship based model, the use of animals, which however possess several disadvantages such as costs and low fidelity, risks, ethical concerns respectively [2][3].

Our goal is to develop a virtual reality based arthroscopic rotator cuff tear diagnosis and repair surgery simulator platform. One of our objectives in our simulator is to incorporate various difficulty scenarios. In ARC, the difficulty often arises from the current state of patient’s shoulder depending on the severity of injury. Therefore, scenario creation involves generating 3D virtual models of the injury cases owing to the severity levels. In this study, we present both these difficulty scenarios and the process of creating these with GAML which is geometry processing language that we specifically designed for tasks of this nature.

2 METHODOLOGY
GAML is developed by our Π-SoFMIS framework based on WebGL technology [4,5]. The language in GAML framework allows visualization and processing 3D virtual geometries represented in JavaScript Object Notation (JSON) format. 3D Realistic rendering is provided by the use of built-in GLSL shaders and enabling the use of various texture maps (e.g. normal, glossy, alpha etc.). As Π-SoFMIS works on web browsers, the GAML framework can be used on any hardware (e.g. Tablets, Phones) regardless of the device specifications. GAML also uses a JavaScript Bison library, Jison,
for parsing and syntax checking of given commands with respect to its context-free grammar. The language supports low level commands such as basic affine transformations; translate, rotate, scale for manipulating a geometry or high level commands to create medical scenarios such as scar, tears, etc. Alteration on human anatomy models should satisfy certain constraints for a realistic (anatomically plausible) and acceptable output. To satisfy anatomical constraints, GAML uses a non-linear optimization model [6]. In GAML, any modification of 3D models (e.g. translation, rotation, deformation etc.) is given to the optimization model to ensure that the desired action is valid with the given constraints.

Table 1. Nonlinear optimization model and constraints for transformation of a node.

| Subject to: | \( \text{Min: } \sum_{j=1}^{N} \delta_j |p_j - p_{\text{destination}}| \) |
|-------------|--------------------------------------------------|
| \( \text{Dist}_{ij} - |p_i - p_j| = 0, \) | for \((i,j) \in A\) (1) |
| \( \cos^{-1} \left( \frac{(p_{iu} - p_{iu}) \cdot (p_i - p_j)}{|p_{iu} - p_{iu}| \cdot |p_i - p_j|} \right) - \theta_{ij} < 0, \) | for \((i,j) \in B\) (2) |
| \( |p_{iu} - p_j|_{k-\text{axis}} - |p_i - p_j|_{k-\text{axis}} = 0, \) | for \((i,j,k) \in B'\) (2a) |
| \( \text{Dist}_{ij} - \Delta d_{\text{max}} - |p_i - p_j| < 0, \) | for \((i,j) \in C\) (3) |
| \( |p_i - p_j| - \text{Dist}_{ij} - \Delta d_{\text{max}} < 0, \) | \(\forall (i,j) \in A \) and \( i,j \subseteq M, k_i > 0, A \cap C = \emptyset\) (4) |

In our model, \( p_i \) is the position of the joint \( i \) and also a node of the 3D Mesh \( M \). For every joint \( i \), there can exist a movement within the user defined allowable joint space. There can be up to four constraints (Equations 1-4 in Table 1) for each pair of joints \((i,j)\). \( A \) is the set of joint pairs \((i,j)\) with absolute distance constraints, while \( B \) and \( C \) are sets for angle and flexibility constraints respectively. \( B' \) is a set of \((i,j,k)\) elements, where \( i \) is not permitted to pivot about \( j \) around \( k-\text{axis} \). \( p_{iu} \) is the initial point \( i \), while \( \theta_{ij} \) is the maximum angle that joint \( i(p_i) \) is allowed to pivot about joint \( j(p_j) \). \( \text{Dist}(i,j) \) is the distance between the two joints. Stiffness ratio \( (k_i) \) is used to calculate \( \Delta d_{\text{max}} \) which is the maximum displacement allowed between the two joints.

A virtual 3D scene of the rotator cuff muscles surrounding the humeral head and representations of constraint joints in the muscles are presented (Figure 1). Green circles represent the joints on the object, while red circles represent the joints that are in the threshold. In an attempt to modify the humeral head position to a desired location (Figure 2), our optimization model computes the optimum location (Figure 3) that avoids the creation of aberrant anatomy. The humeral is translated to an optimum location and any constraints (relative distance, angle, flexibility, connectivity) for the muscles connected to the humeral head are satisfied. The joint representation of the scene after the translation is given in (Figure 3). The scene without constraints after transformations is given in (Figure 2).
2.1 ARC Difficulty Scenarios

In ARC, the size, shape, and location of the rotator cuff tear affects the surgical planning and complexity of the repair. In addition, other factors such as physiological condition of the shoulder can adversely impose difficulty. We therefore used six independent assessment factors to create different difficulty scenarios [1, 7]. These assessment factors are size of tear, age, tear-grade, number of compromised tendons, muscle/fat ratio, and presence of any damage on humeral head. Each of these factors are assigned to numerical difficulty points. A difficulty of a scenario is determined with summation of the all difficulty points of the factors used in that scenario. Using these factors, we generated four classes of the difficulty scenarios; Difficulty level 1 (easy) is ranging from 0 to 4 points with none of the assessment factors over 1 point. Difficulty level 2 (moderate) is 5 to 9 points with at most one assessment factor with 2 points. Difficulty level 3 (hard) is 10 to 13 points. Difficulty level 4 (extremely hard) is 13 and more points.

The first assessment factor is the tear size. Tear sizes of less than 1cm is 1 point, 1-3 cm is 2 points, 3-5 is 3 points, and greater than 5 is 4 points difficulty. Patient’s age is correlated with the size of a tear and the amount of debris caused by the tear. Therefore, a case of 65 years and older patient is given as 1 point, while a patient younger than 65 is given as 0-point difficulty. Tear-grade factor refers to the depth of the tear. A tear less than 3mm deep is 1 point, 3 to 6 mm deep is 2, and more than 6mm in depth is 3 points difficulty. Another assessment factor is compromised tendons. Stage 1A is a partial thickness tear (not torn all the way through the tendon), and it is 1 point, while stage 1B is a full thickness tear isolated to supraspinatus, and it is given as 2 points. Stage 2 includes compromised tendons of supraspinatus and portion of the infraspinatus, and it is given as 3 points. Stage 3 includes compromised tendons of entire supraspinatus, infraspinatus, and subscapularis, and is given as 4 points. Stage 4 is a rotator cuff arthroplasty that denotes severe complication. Damaged humeral head is another factor that increases the complexity of a case. As the rotator cuff muscles need to be fixed to the humeral head, tears need to be cleaned, pulled, and anchored on the humeral head. Before anchoring process, the humeral head needs to be cleaned adequately; however, damaged humeral head complicates this process. Therefore, a damaged humeral head is given 1 point and no damage to the humeral head is 0-point difficulty.

In muscle/fat ratio factor stage 1 refers to a condition where there exist some fatty streaks in muscle and it is given as 0 points. In Stage 2 factor has more fatty streaks in muscle, with more muscle than fat and it is 1 point. Stage 3 has equal amount of fat and muscle and it is given as 2 points. In Stage 4, there is fatter than muscle and it is 3 points difficulty. The factor and point-based scoring system (Table 2) for ARC difficulty scenarios can be seen below. Red colored factors are non-zero factors.

### Table 2. Factor based scoring system for ARC.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Size of Tear</th>
<th>Age</th>
<th>Tear Grade</th>
<th>Compromised Tendons</th>
<th>Muscle Fat Ratio</th>
<th>Damage to humeral head</th>
<th>Total Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Easy</td>
<td>&lt;1 cm (1pt)</td>
<td>&lt;65 (0pt)</td>
<td>&lt;3 mm deep(1pt)</td>
<td>Stage 1A(1pt)</td>
<td>Stage 1 (0pt)</td>
<td>No (0pt)</td>
<td>3</td>
</tr>
<tr>
<td>Moderate</td>
<td>&lt;1 cm (1pt)</td>
<td>&gt;65 (1pt)</td>
<td>&lt;3 mm deep(1pt)</td>
<td>Stage 1B(2pt)</td>
<td>Stage 2 (1pt)</td>
<td>Yes (1pt)</td>
<td>7</td>
</tr>
<tr>
<td>Hard</td>
<td>3-5 cm (3pt)</td>
<td>&lt;65 (0pt)</td>
<td>&gt;6 mm deep(3pt)</td>
<td>Stage 1B(2pt)</td>
<td>Stage 3 (2pt)</td>
<td>No (0pt)</td>
<td>10</td>
</tr>
<tr>
<td>Extremely Hard</td>
<td>&gt;5cm (4pt)</td>
<td>&gt;65 (1pt)</td>
<td>&gt;6 mm deep(3pt)</td>
<td>Stage 4(5pt)</td>
<td>Stage 1 (0pt)</td>
<td>Yes (1pt)</td>
<td>14</td>
</tr>
</tbody>
</table>

The base scene where there are no tears on the rotator cuff muscles is shown in (Figure 4). Rotator Cuff muscles are selected using the selection tool and the selection size of the tool has been adjusted.
“Easy” scenario using the tear creation command with GAML is created. The tear as an output of this operation is shown in (Figure 5).

3 RESULTS AND CONCLUSIONS

In this work, we defined the difficulty scenarios for virtual simulation of ARC. We used our GAML framework to generate variations in scenarios by executing geometry modification commands on the 3D base geometry. While focusing on the 3D model generation, our GAML framework handles the validity of the generated scenario with the given constraints. These constraints ensured that output is not irrational and the geometry modifications (e.g. translation, deformation) remain within the desired or acceptable level of accordance with the shoulder anatomy. Our constraints are directly applied in the non-linear optimization model. The geometry commands in our framework finds optimum solution to the non-linear optimization problem and satisfy the anatomical constraints at all times. Our future work is to incorporate these scenarios to our simulator in progress and perform validation studies to assess the validity of the scenarios.

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Inverse Problems in Soft Tissue Biomechanics & Mechanobiology II
REVERSE ENGINEERING: A TISSUE-MIMICKING MOCKUP FOR ABDOMINAL AORTIC ANEURYSM (AAA)

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SUMMARY

Treatments for vascular diseases with minimally invasive approach have been tremendously improved over the past few decades. This is in part due to the advancement in medical imaging processing and the booming medical device industry. However, failures of certain percutaneous treatments, such as the endovascular repair for AAA, reveal our insufficient understanding of the aortic wall biomechanics. In this regard, we are encouraged to develop a tissue-mimicking mockup that exhibits the major mechanical, anatomical and pathological characteristics of AAA, in order to study the interaction between AAA and stent grafts, and to improve our numerical simulations for the virtual planning tool.

Key words: tissue-mimicking mockup, hydrogel, biomechanics, abdominal aortic aneurysm

1 INTRODUCTION

Abdominal aortic aneurysm (AAA) is an asymptomatic pathological condition due to the dilation of abdominal aorta along with progressive wall degeneration (Fig. 1). Endovascular aneurysm repair (EVAR) is a promising percutaneous approach to exclude the AAA sac from systemic pressure through the implantation of a stent graft (SG), restoring a healthy blood flow along the aorta. However, current failures of EVAR treatment reflect our inadequate knowledge of the biomechanical interaction between the aortic wall and SG. In particular, major factors in AAA wall degeneration such as the wall stiffening, the development of intraluminal thrombus (ILT) and the calcification, all contribute to the complex interaction between the aortic wall and SG. Therefore, a virtual planning tool to predict the possible outcomes and complications of EVAR is believed to improve the quality and effectiveness of EVAR treatments.

In this study, a series of tissue-mimicking mockups (TMM) of AAA with wall degeneration characteristics have been developed for EVAR experiments; the experimental results will be ultimately combined with our numerical simulations and clinical records to develop a virtual planning tool for endovascular specialists. While eliminating the cross-species and cross-specimen variability, this TMM provides an essential path to reverse engineer the complex biomechanics of the AAA wall. Being mechanically, anatomically and pathologically realistic, this TMM may also be an academic training/demonstrating platform for future medical specialists.

2 METHODOLOGY

The TMM in this study is mainly made of hydrogel, polyvinyl alcohol cryogel (PVA-C). This hydrogel is suitable for many imaging modalities (ultrasound, CT and MRI) and has excellent biocompatibility. It also has great flexibility in mechanical property adjustment in order to mimic different soft tissues.
To fabricate PVA-C, first we must prepare the PVA solution according to the desired concentration ratio, then carefully inject it into a set of molds to avoid bubble formation. The filled mold is then tight-sealed and placed inside a programmable fridge for specific thermal cycling.

**Mechanically Realistic**

A series of mechanical tests (uniaxial tensile and shear) have been performed with various PVA-C specimens, in order to compare with the relevant data of human tissue from literatures (Fig. 2–3). By varying the parameters of thermal treatment during hydrogel fabrication (especially the number of thermal cycles), we are able to create PVA-C with its mechanical strength very similar to that of the human AAA wall [1], the ILT [2], as well as the abdominal fat [3].

**Anatomically Realistic**

Since the PVA-C phantom must be fabricated in one piece, a subset of cavity molds and dissolvable molds have been designed to take into account the aneurismatic, bifurcating and tortuous characteristics of the AAA. An air-tight system has also been designed to encase the AAA and a radiopaque spine (Fig. 5), which can maintain a pressure of 100 mmHg inside the AAA and of 12 mmHg surrounding the AAA, representing the intraluminal and abdominal pressure respectively.

**Pathologically Realistic**

By adding different portions of CaCO$_3$ or ABS, we can also use PVA-C to mimic various degrees of calcification in human AAA [4]. A multi-layer molding technique along with a specific molding-demolding sequence, have also been applied to embed the ILT and calcifications into the AAA wall (Fig. 4).

**3 RESULTS AND CONCLUSIONS**

A TMM for the AAA with ILT, calcifications and surrounding abdominal fat has been developed in a patient-inspired geometry. An EVAR experiment has been successfully performed using this TMM (Fig. 6). Our experimental results reveal that not only the ILT and calcifications, but also the spine and surrounding fat provide a framework to account for the interactions with the SG and guidewires. This observation provides an insight to fine-tune our existing numerical models for the virtual planning tool.

We are in the process of extending this TMM to a patient-specific geometry, along with further improvements in the mold design and techniques. Besides, fatigue experiments under pulsatile flow condition will also be considered in future.

**REFERENCES**


Figure 1: abdominal aortic aneurysm (left) and endovascular aneurysm repair (right)

Figure 2: uniaxial tensile stress of PVA-C vs. human AAA wall [1] (left); uniaxial tensile stress of PVA-C vs. human ILT [2] (right)

Figure 3: shear stress of PVA-C vs. human abdominal fat [3] (left); uniaxial tensile stress of calcified PVA-C vs. calcified human AAA wall [4] (right)
Figure 4: multi-layer molding technique (up); PVA phantom (low) with ILT (shown in red)

Figure 5: a customized pressurized system to encase the AAA phantom (hidden in fat), some surrounding abdominal fat and a radiopaque spine

Figure 6: an EVAR experiment using this TMM, performed by an interventionalist in the angiography suite
CORRELATION OF THE MACROSCOPIC MECHANICAL BEHAVIOR AND THE MICROSTRUCTURAL EVOLUTION OF MICE SKIN

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SUMMARY

The dermis, main component of the skin, is composed of collagen network that influences its mechanical behavior at different scales. Its behavior prediction requires characterizing the influence of the microstructure on the mechanical properties. Thus, a bi-axial tensile test coupled independently with macroscopic and microscopic measurements was developed. In one hand, the mechanical parameters of a Holzapfel’s constitutive behavior were identified on 5 mice from displacement field measurements and, in other hand, the affine transformation was tested from SHG (Second Harmonic Generation) microstructural measurements. This work finally underlying the limits of the adopted behavior to predict the microstructural evolution.

Key words: Identification, Affine transformation, Microstructure, Hyperelasticity.

1 INTRODUCTION

Skin is a multi-layered composite structure where the most important, from a mechanical point of view, is the dermis \cite{1}. The dermis is a “collagen-rich” tissues where the collagen network bathes in an extra-fibrillar matrix (proteoglycans, elastin, etc.). The behavior of the skin, which have a hierarchical microstructure that influences its mechanical behavior at different scales, is not always well understood, but is an important issue in many applications. For instance, stress distribution could be an ergonomic indicator to design devices such as car seats, wheelchairs or razors.

Many tests, uni-axial \cite{2} or biaxial \cite{3}, have been interested in mechanical characterization (elasticity, hyperelasticity, relaxation, etc.) without taking into account data on the evolution of their microstructure. However, there is a strong link between the microstructure of the connective tissues and their macroscopic mechanical properties \cite{1}. In this framework, an investigation of the correlation between the macroscopic mechanical properties and the microstructural properties was carried out on different tissues by using SHG (Second Harmonic Generation) (skin \cite{2}, liver \cite{3}, amnion \cite{4}). These studies were concentrated on the evolution of the microstructure and mechanical properties without offering a coupled microscopic and macroscopic predictive model.

In this present study, a bi-axial tensile test coupled independently to macroscopic measurement and microscopic measurements was developed. In one hand, the mechanical parameters of a frequently-used Holzapfel’s behavior were identified from a DIC (Digital Image Correlation) displacement field measurements and, in other hand, the affine transformation, induced by the adopted behavior, was tested from microstructural SHG (Second Harmonic Generation) measurements.
2 METHODOLOGY

2.1 Macroscopic behavior

A FEMU (Finite Element Model Updating) approach has been developed in order to identify a mechanical behavior. It aims at minimizing a cost function, chosen as the quadratic difference between the measured and simulated quantities (i.e. displacement fields and reaction forces), by an iterative procedure in order to identify the constitutive parameters. The minimization is performed using a Broyden-Fletcher-Goldfarb-Shanno (BFGS) algorithm under Matlab in which 5 different initializations were done to avoid the convergence toward a local minimum and to check the uniqueness of the solution. Afterwards, only the identification with the lowest cost function will be presented.

The first input are displacement field and reaction force measurements. The biaxial test (fig.1a) was adapted from the uni-axial test from Bancelin et al. [2]. Ex vivo skin samples of 4-week mice, of which the epidermis and the hypodermis were previously removed, are cut in a cross shape (fig.1b). The skin is then covered with graphite powder to create a texture allowing displacement field measurement using DIC (Digital Image Correlation) (fig.1c). These samples are then inserted into holding jaws: the antero-posterior axis is aligned with the X-axis of the traction device. The initial dimensions of the sample is then measured with a digital caliper. The sample is slowly stretched until small forces (above 0.02N) are detected in the two directions. The sample dimensions are then measured using a digital caliper. The loading path is imposed alternatively on each of the two axes (fig.1d) with a loading speed of the order of $10^{-4}\, \text{s}^{-1}$. During the test the skin images are acquired with an 8-bit CCD camera connected to a telecentric lens. The pixel size is then $5.5\, \mu\text{m}$. Constant hydration is obtained by spraying mineral water on the sample every 3 minutes. Displacement fields are finally measured with CMV (CorrelManuV [5]).

![Figure 1](image1.png)

Figure 1: a) Custom-made biaxial traction device. b) Illustration of sample cut. c) Sample covered with graphite powder allowing thus the displacement field measurement by DIC. d) loading path way . e) In-situ custom-made device. f) Sample on which the acquisition zones are located. g) SHG acquisition example.

The second input are simulated displacement fields and reaction forces. Simulation are performed on Abaqus. A 2D FE model of the biaxial experiment was developed, consider the plane stress assumption. The geometry of the mice skin is obtained with the reference image acquired during the DIC process. Then, the region of interest is segmented with Matlab using an automatic routine. A subset that includes all the nodes of the displacement field is created and then a refinement is finally performed (fig.1a,b). Thereafter, the 3-node linear mesh (CPS3) is created with matlab (202775 nodes). The skin tissue is assumed to be homogeneous: the parameters of the energy did not depend on the location [2]. It is assumed that the incorporated tissues contributed to the average, in terms of hyperelastic properties. Due to the presence of the dermal fibers, murine skins are modeled as an anisotropic, hyperelastic material. A Holzapfel’s behavior was chosen to describe the mechanical response of the skin [6]. This behavior is parametrized by 5 components: $C_{10}$ describe the non-collagenous isotropic ground material behavior, $k_1$ and $k_2$ the contributions from collagen fibers, $\kappa$ describes the level of fiber dispersion along the mean fiber direction $\alpha$ with ($0 \leq \kappa \leq 1/3$).
2.2 Microstructural evolution

The microscopic measurement protocol is similar to the macroscopic protocol in a mechanical point of view (i.e. cut and placement in holding jaws and loading path) (fig.1e). Nevertheless, loads are carried out with strain increments of 5% to acquire microstructural images. Moreover, mice skins are marked in 3 zones (one central zone and two zones in the arms) to allow the acquisition of microstructural images in the same place during the SHG (fig.1f). These acquisitions allow a local monitoring of the microscopic strain thanks to the hair follicles (fig.1g). As presented in Bancelin et al. [2], from these images, a morphological filter is applied to obtain the distribution of the collagen network. To obtain quantitative information, the OI (Orientation Index) is represented during strain in each area. The OI is relative to the fiber fraction aligned in a given fiber direction ($\theta_x$) from distribution ($I(\theta)$). In practice, the given fiber direction ($\theta_x$) is imposed on $0^\circ$ (X-axis), such as (eq[1]):

$$OI = \frac{\int_{-90^\circ}^{90^\circ} I(\theta)\cos^2(\theta - \theta_x)\delta\theta}{\int_{-90^\circ}^{90^\circ} I(\theta)\delta\theta} - 1] \times 100$$ (1)

Holzapfel’s behavior, as presented above, induces that the microstructure evolution during traction is affine [7]. The evolution of the distribution of the network of collagen fibers follows exactly the strain and is easily represented knowing the kinematic of the transformation [7].

3 RESULTS AND CONCLUSIONS

3.1 Parameter identification

The identified parameters are presented in Table 1. It was found that for each skin the identified value for each parameter is very similar with the exception of the main orientation angle of the fibers. These results highlight the repeatability of our test and the relatively low inter-individual variation.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>WT1</th>
<th>WT2</th>
<th>WT3</th>
<th>WT4</th>
<th>Mean</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{10}$ (kPa)</td>
<td>170</td>
<td>125.7</td>
<td>47.8</td>
<td>94.2</td>
<td>109.4</td>
<td>51.5</td>
</tr>
<tr>
<td>$k_1$ (kPa)</td>
<td>56.2</td>
<td>31.6</td>
<td>43.3</td>
<td>62.3</td>
<td>48.3</td>
<td>13.7</td>
</tr>
<tr>
<td>$k_2$ ($\times 10^8$)</td>
<td>3.86</td>
<td>0.19</td>
<td>41.1</td>
<td>5</td>
<td>12.5</td>
<td>19.13</td>
</tr>
<tr>
<td>$\kappa$ ($\times 10^6$)</td>
<td>0.295</td>
<td>0.011</td>
<td>16.398</td>
<td>0.049</td>
<td>4.189</td>
<td>8.141</td>
</tr>
<tr>
<td>$\alpha$ ($^\circ$)</td>
<td>32.7</td>
<td>52.6</td>
<td>-7.2</td>
<td>44.5</td>
<td>30.6</td>
<td>26.5</td>
</tr>
</tbody>
</table>

3.2 Microstructure evolution analysis

The initial distribution of the central zone has a quasi-homogeneous distribution while in the arms, the distribution seems to be slightly oriented probably due to the pre-loading carried out during the positioning of the sample. Moreover, in the central part (fig.2g), it can be seen that there is a reorganization along the axis of loading that is confirmed by the shape of the OI (fig.2g). As a reminder, the loading is carried out successively in each direction. The calculated distribution (fig.2a,d) reproduces well the reorganization during loadings. In the horizontal and vertical zones, two distinct behaviors are observed. In fact, (fig.2), the measured IO reproduces the same type of behavior as before. On the contrary, in the vertical zone (fig.2), the reorganization of the measured OI is continuous (no successive reorganization in each direction). This type of behavior was expected because in the arms we expected behavior similar to a one-axial test. It is therefore probable that in the horizontal zone our observation is too close to the center of the specimen which leads to this similar behavior.

In general, when we compare the measured and simulated OI (fig.2g,h,i), predictions are in agreement for low local strain. On the contrary, for large strain, the OI difference seems bigger.
Figure 2: a,b,c) Reorientation of the collagen fibers samples at low strain and d,e,f) at larger strain for murine skin. Initial orientation distribution of fibers (blue), experimentally measured orientation distribution (dashed black), and theoretical distribution calculated from the averaged local strain (dotted dash red) for the same samples. g,h,i) Evolution of the OIs measured (dotted black) and calculated (dashed black), and their difference (measured minus calculated) (red), as a function of the applied stretch, respectively in the central, horizontal and vertical area.

4 CONCLUSION

This work allows us to identify, from a macroscopic measure, a behavior widely used to characterize biological materials. A small dispersion of the identified parameters is observed for each parameters (excepted angle), which validates the results. The affine hypothesis, underlying used behavior, was also tested from local strain measurements. This hypothesis is qualitatively good for small strains but generates more important errors for large strain. Consequently, Holzapfel’s law does not appear to contain sufficient information to describe the macroscopic vs. microscopic interaction present in the skin. Indeed, it is possible that there is a structural effect that is not taken into account in this affine hypothesis. The future work will focus on describing a more complex model in which fibers interact at the microscopic scale.

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ON THE 3D PROPERTIES OF PASSIVE MYOCARDIUM: 
AN INVERSE MODEL-EXPERIMENTAL APPROACH

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SUMMARY

Despite the significant progress made in the two-dimensional experimentation and modeling of myocardial tissues, substantial needs to obtain and model its full 3-D behavior still remain. In this study, using an optimal design of experiments, we obtained an optimal set of loading conditions and collected new experimental data on the 3-D mechanical behavior of cubic samples of infarct left ventricular myocardium. Next, we implemented an inverse histologically-informed finite element model to estimate the material parameters of infarct sample. We showed that the optimal design is necessary to obtain the estimates that are capable to predict the behavior of the samples under general loading conditions.

Key words: Passive myocardium, Three-dimensional properties, Inverse model

1 INTRODUCTION

The early studies for constitutive modeling of myocardium, which were based on transversely isotropic symmetry, used the experimental measurements from two-dimensional (2-D) biaxial tests to estimate material parameters [1]. This is, of course, possible only when the model is a priori assumed to be a special case of a transversely isotropic solid which can be quantified only through 2-D biaxial tests [2]. However, more recent studies on the histology of the myocardium, as well as on its mechanical response [3], have demonstrated that the myocardium is locally orthotropic. Therefore, biaxial tests and transversely isotropic models are not sufficient to fully characterize the myocardium behavior. Along these lines, only a few experimental works have dealt with three-dimensional characterization of the myocardium. Perhaps the most notable one is the work of Dokos et al. [3] which conducts simple shear tests on cubic samples of myocardium from six different orientations using an experimental apparatus designed to apply simple shear. The samples were cut from adjacent regions of the lateral left ventricular (LV) midwall of pig hearts, with sides aligned with the microstructural material axes (f, n, s; fiber, normal, sheet). Later on, several studies have used the experimental data of Dokos et al. to estimate the material constants based on the existing models via inverse analytical/computational models (see [4], for example).

Although the shear experiments of Dokos et al. provide useful insights into the anisotropic character of the myocardium behavior, there still remains a need for more comprehensive sets of experimental data. Acquisition of such datasets is particularly important because myocardial tissues undergo complex combinations of loading conditions including tension, compression, and shear within a cardiac cycle. In this connection, it is plausible that a deformation set consisting of both simple shear and other 3-D loading conditions could be a better choice for characterizing the myocardium response, i.e. it provides more predictive estimates of the involved parameters. To verify this, one needs to accomplish an optimal design of experiments to determine an optimal set of loading conditions for characterizing mechanical behavior of cubic samples of the myocardium.
2 METHODOLOGY

We conducted an optimal design of experiment to find an optimal set of loading conditions needed to characterize the cubic samples of the myocardium. Our optimality analysis was based on an orthotropic constitutive model for the myocardium that incorporates structural features of cardiac architecture within the "fiber-normal-sheet" description of the myocardium. Next, we carried out the deformation tests resulting from the optimal design of experiments by applying controlled displacement on cubic samples of infarcted myocardium. Finally, to estimate the material constants in our constitutive model of the myocardium using the acquired experimental data, we developed an inverse algorithm that integrates the experimental measurements and the corresponding results from a sequence of finite element (FE) simulations into a nonlinear regression method. The overview of our methodology is shown in Fig. 1.

2.1 Kinematics and Constitutive Behavior

Without loss of generality [5], consider a cubic myocardium sample undergoing the deformation gradient $F$ of the following form

$$
F_{ij} = \begin{pmatrix} \lambda_1 & 0 & 0 \\ \kappa_{21} & \lambda_2 & 0 \\ \kappa_{31} & \kappa_{32} & \lambda_3 \end{pmatrix},
$$

in the Cartesian coordinate system $\{e_i\}$ where $\lambda_1$, $\lambda_2$ and $\lambda_3$ are stretches along orthogonal axes $e_1$, $e_2$ and $e_3$, respectively, and $\kappa_{21}$, $\kappa_{31}$, and $\kappa_{32}$ are three transverse shears. Here, we assume that the local mechanical behavior of myocardium is characterized by the orthotropic Fung energy function of the form

$$
W(E) = \frac{1}{2} c_0 [e^{Q(E)} - 1],
$$

where $c_0$ is a positive constant and $Q$ is expressed as

$$
Q = \alpha \{c_0, c_1, c_2, c_3, c_4, c_5, c_6\} = \begin{pmatrix} c_1 E_{11}^2 + c_2 E_{22}^2 + c_3 E_{33}^2 + 4c_4 E_{12}^2 + 4c_5 E_{13}^2 + 4c_6 E_{23}^2, \end{pmatrix}
$$

where $E$ is the Green-Lagrange strain tensor, and $\alpha = \{c_0, c_1, c_2, \ldots, c_6\}$ are unknown constants. The first Piola-Kirchhoff stress tensor $P$ is obtained as

$$
P = F \frac{\partial W}{\partial E} - p F^T,
$$

where $p$ is an unknown hydrostatic pressure. Also, the stress vector on the face of the sample with the normal $n$ is given by

$$
p = P n.
$$

2.2 Optimal Design of Experiment

In the context of three-dimensional tests with displacement boundary conditions, there are varieties of loading conditions which can be applied to the tissue sample. Therefore, it would be important to obtain an optimal set of loading conditions which results in the best "determinability" of the unknown constitutive parameters. Indeed, making use of this optimal set of loading conditions, the parameters can be estimated by only necessary number of loadings, and such estimates are least
sensitive to variations in the loading conditions, as well as to small errors in the experimental data. For practical purposes, we conduct the optimization over ten chosen sets of individual deformation modes (i.e. different subsets of the form (1) denoted by \( \mathbf{d} \)) although our analysis can be extended to optimize over more general and complex kinematical sets.

A general criterion to determine the optimal design of experiments for a given model is to minimize the covariance between the unknown parameters involved in the model. For ordinary least square problems, and upon these assumptions, the covariance matrix is approximately given by \[ \text{cov}(\alpha^*) \approx M^{-1}s^2, \] (6)
where \( \mathbf{M} = \mathbf{J}^T \mathbf{J} \) is usually referred to as the information matrix, \( \alpha^* \) is the optimized value of \( \alpha \), \( s \) is the estimated variance of the observed error, and \( \mathbf{J} \) is the sensitivity matrix given by

\[ \mathbf{J} = \frac{\partial \mathbf{p}}{\partial \alpha}(\alpha^*, \mathbf{d}). \] (7)

Several optimality criteria have been proposed to minimize the confidence region, which are usually given in terms of maximizing certain measures of the information matrix \( \mathbf{M} \). Among them, we chose the following ones in our study three criteria: A-optimality, D-optimality, and E-optimality. D-optimality is the most common one which aims to maximize the determinant of the information matrix \( \mathbf{M} \).

2.3 Triaxial Device and Infarct Myocardium

We developed a triaxial mechanical testing device (herein referred to as the Triax), featuring a novel attachment system that allows us to apply individual or combined deformation modes in different directions and planes on the same cubic sample and measure the resulting force response generated in all three directions (Fig. 2a,b). The Triax was validated by characterizing mechanical behavior of isotropic and anisotropic synthetic gel samples under different deformation protocols.

The optimal deformation set was applied to 4-week ovine infarct samples (Fig. 2c). The ischemic infarction was induced at the posterior of the LV via ligations along the obtuse marginal artery within a cohort of 3 adult Dorset sheep with weights ranging 40–50 kg. The excised infarct sample measured about 10x10x10 mm that spanned the entire transmural thickness of the heart wall.

3 RESULTS AND CONCLUSIONS

3.1 Optimal Design

Based on the D-optimality criterion, the results of ODE indicate that the set of loading conditions consisting of both simple shear modes and pure shear modes (Fig. 3) is the optimal set among the ten sets considered in our study. The results from A-optimality and E-optimality criteria were found to be consistent with this conclusion. Our analysis suggested that this optimal set reflects a considerably better “determinability” for estimating 3-D properties of myocardium than the “simple shear” deformation set which consisted of only simple shear modes. In contrast, the deformation sets which included no simple shear modes were found to lead to

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Five protocols consisting of three pure shear modes and two simple shear modes were sufficient to estimates the 7 unknown parameters $\alpha = \{c_0, c_1, c_2, \ldots, c_6\}$ in the Fung model. A good fit was observed for all protocols with the goodness-of-fit $r^2 = 0.93$ (Fig. 4).

![Figure 4](image) The fit of Fung’s model to the infarcted cube response under optimal set of loading conditions.

### 3.3 Finite Element (FE) Simulations

Our FE model was equipped with actual fiber orientation distribution measured from histology of the same sample. The 9-pin boundary conditions used in the experiment was exactly implemented in the FE model. The relatively homogeneous distribution of stress was observed far from the sample faces (Fig. 5).

![Figure 5](image) A representative example of the FE modeling of the infarct sample under pure shear XY illustrating two cross sections with distribution of values of relevant Cauchy stress components.

To the best of our knowledge, the present work is the first work that carries out a full three-dimensional study including optimal design, experimental tests, and inverse computational modeling to characterize the mechanical properties of passive ventricular myocardium. The application to infarct myocardium confirms the robustness of our approach, and applications to passive normal myocardium will be carried out in future works.

### REFERENCES


NUMERICAL MODEL REDUCTION FOR THE ASSESSMENT OF INTERFACE PRESSURE APPLIED ON THE LOWER LIMB BY MEDICAL COMPRESSION BANDAGES

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SUMMARY

Medical compression bandages consist in a stretched fabric, wrapped around the leg, whose action mechanism is pressure. A better control of interface pressure would lead to a better controlled treatment. The study proposes a numerical model reduction approach to assess the impact of different parameters on interface pressure. First, a numerical simulation was designed. Then the leg geometry was parameterized. Eventually the contribution of 7 parameters (5 related to leg geometry, bandage tension and skin-to-bandage friction) on the variation of interface pressure was assessed and a response surface was derived. This provided a patient-specific reduced model to compute interface pressure.

Key words: Compression bandages, Geometrical parameterization, Model reduction, Finite element simulation

1 INTRODUCTION

Compression bandages are medical textile devices designed for the treatment of venous or lymphatic insufficiency. Interface pressure, which consists in the pressure applied by the bandage onto the limb skin, is the therapeutic dosage of the treatment. This pressure is then transmitted to the vessels though soft tissues. This interface pressure depends on various parameters related to the bandage (mechanical properties of the different bandages components for example), the patients (patient’s leg morphology) and their interaction (friction). Several clinical studies have investigated the interface pressure applied on the lower limb by different bandages [1] [2] [3]. Though these studies helped to understand interface pressure generation, for now, the only way to predict/compute interface pressure is Laplace’s Law:

\[ P = \frac{n \cdot T}{r_C}, \quad T > 0, \ r_C > 0, \]

with \( P \) the interface pressure, \( n \) the number of layers of the bandage, \( T \) the bandage tension (i.e. the force needed to stretch the bandage) and \( r_C \) the local radius of curvature. However, the use of this equation is called into question [4] [5].

The objective was to develop a new method to compute interface pressure applied by compression bandages, though a reduced-order modeling approach. This method was based on the development of a finite-element model of bandage application and the evaluation of its sensitivity to various parameters. Then, patients’ leg morphologies were parameterized and eventually, the impact of 7 parameters (5 morphological parameters, bandage mechanical properties and skin-to-bandage interactions) on interface pressure was assessed, in order the have a predictive model for interface pressure.
2 METHODOLOGY

2.1 Numerical simulation

A complete numerical model of the application of bandage on the leg was designed, using the software Abaqus®. This model was composed of a 3D deformable leg geometry (see below) and a bandage, wrapped on the leg. Leg soft tissue were considered as a single homogeneous hyper elastic material whose behavior was described with a Neo‐hookean constitutive equation:

$$U = c_{10} \left( \bar{I}_1 - 3 \right) + \frac{K}{2} (J^{el} - 1)^2$$

(2)

with $\bar{I}_1$ the first invariant of the isochoric deformation, $J^{el}$ the elastic volume ratio, $c_{10}$ the shear modulus and $K$ the bulk modulus. The bandage was modeled with shell elements, whose mechanical behavior was orthotropic elastic.

The boundary conditions depended on the leg geometry as the bandage was wrapped on the leg with a 1.3 stretch and were computed in Matlab®. The bandage was first stretched (to a 1.3 stretch) and then applied in a two-layer spiral-pattern on the leg (i.e. a 50% overlapping application technique) (Figure 1). Leg-to-bandage contact as well as bandage-to-bandage contact allowed no penetration and their tangential behavior was described with a Coulomb’s Law:

$$|Tangential\ force| = Friction\ coefficient(\mu) \ast |Normal\ force|.$$  (3)

2.2 Leg geometry parameterization

To compute interface pressure with Laplace’s Law, the leg geometry is locally described with its local radius of curvature. In this study, a parametric description of the leg geometry was needed. It should require as few parameters as possible. This objective was reached thanks to the proper orthogonal decomposition (POD) of $N = 35$ leg geometries, acquired with a 3D optical scanner in a previous study [6]. The leg geometries $\{U^i\}_{i=1..N}$ could all be described using the first $K$ vectors of the orthogonal basis $\{\phi_k\}_{k=1..K}$, $K$ being chosen as small as possible, within a reasonable reconstruction error.

First, the geometries were positioned in the same reference frame and normalized to their lengths. Then, in order to reduce the dimension of each leg description, legs were divided into 100 slices, each approximated with Fourier polynomials:

$$R(\theta) = R_0 + \sum_{m=1}^{n} a_m \ast \cos(m\theta) + \sum_{m=1}^{n} b_m \ast \sin(m\theta).$$  (4)

For $n = 5$, each slice was described with 11 Fourier polynomials coefficients and the coordinates of the center $(x_0, y_0)$. Eventually, every leg geometry was given with 1300 coefficients: $U^i \in \mathbb{R}^{1300}$. 

Figure 1: Illustration of the Finite Element model of bandage application: bandage longitudinal strain and interface pressure distribution.
Then the POD basis was built following the same methodology described by Gogu et al. [7]. An approximation of the geometries \( \tilde{U}^i \) was given as a linear combination of the basis vectors:

\[
\tilde{U}^i = \sum_{k=1}^{K} \alpha_{i,k} \phi_k = \sum_{k=1}^{K} < U^i, \phi_k > \phi_k, \quad K < N
\]  

The mean reconstruction error \( \text{mean}(\| U^i - \tilde{U}^i \|) \), as a function of the size of the orthogonal basis \( K \), is presented in Figure 2. Taking only the first 4 POD vectors, the difference between the reduced model and the full leg is less than 2 mm for 95% of all the measuring points of all the legs.

![Figure 2: Median absolute error between the initial geometry and the reconstruction, with regards to the basis dimension](image)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Lowest Value</th>
<th>Highest Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \mu \text{skin} - \text{bandage} )</td>
<td>0.15</td>
<td>0.3</td>
</tr>
<tr>
<td>( T ) [N/mm]</td>
<td>0.29</td>
<td>0.68</td>
</tr>
<tr>
<td>Leg length [mm]</td>
<td>184.86</td>
<td>290.43</td>
</tr>
<tr>
<td>1(^{st}) geometrical parameter</td>
<td>-0.920</td>
<td>-0.503</td>
</tr>
<tr>
<td>2(^{nd}) geometrical parameter</td>
<td>-0.109</td>
<td>0.119</td>
</tr>
<tr>
<td>3(^{rd}) geometrical parameter</td>
<td>-0.092</td>
<td>0.068</td>
</tr>
<tr>
<td>4(^{th}) geometrical parameter</td>
<td>-0.081</td>
<td>0.095</td>
</tr>
</tbody>
</table>

Table 1: Range of the different parameters for the model reduction approach

2.3 Selection of parameters for model reduction

A model reduction approach helps to model a complex phenomenon, impacted by a large number of parameters, with a very few iterations of the complete model. This approach is equivalent to design of experiments [8].

In this study, it was hypothesized that the parameters impacting interface pressure were the bandage tension (\( T \)), the bandage-to-bandage friction coefficient (\( \mu_{\text{bandage} - \text{bandage}} \)), the skin-to-bandage friction coefficient (\( \mu_{\text{skin} - \text{bandage}} \)), the leg soft tissue mechanical properties (\( c_{10} \) - Equation 2) and the leg morphology. The interface pressure considered in the approach was the mean pressure over a disk whose radius was 25 mm (as the pressure sensor used in the experiments [6]) and located on the internal face on the leg at the height of measurement point B1 (where the Achille’s tendon turns into the gastroscnemius muscles [9]) (Figure 3).

A preliminary sensitivity analysis, on a mean leg geometry, showed that skin-to-bandage friction and bandage tension were responsible for over 90% of interface pressure variation. Consequently, the leg soft tissue mechanical properties (\( c_{10} \) - Equation 2) and the bandage-to-bandage friction were removed from the problem definition and set to their mean values, respectively \( \bar{c}_{10} = 5 \text{ kPa} \) and \( \mu_{\text{bandage} - \text{bandage}} = 0.6 \).

The leg morphology was defined with 5 parameters: the leg length and 4 geometrical parameters given by the geometrical parametrization (median reconstruction error = 0.72 mm). It was then possible to build an unsaturated factorial design of experiments [8], with 7 parameters (5 morphological ones, skin-to-bandage friction and bandage tension), whose variation ranges are presented in Table 1.

This approach required to run only 9 numerical simulations to derive the reduced model response.

3 RESULTS AND CONCLUSIONS

This numerical approach provided the reduced model response (interface pressure) as a function of 5 morphological parameters, bandage tension and skin-to-bandage friction (Figure 4). In the range of variation investigated in this study (Table 1), bandage tension was the most influencing parameter, followed by morphological parameters. It can be noticed that all these 7 parameters give a very relevant
description of interface pressure variation ($R^2 = 0.99$). These results also support the description of leg morphology with 5 parameters. Thanks to this approach, the interface pressure could be computed for any patient and any bandage with a linear combination of the 7 parameters in a few minutes, instead of a few days for the numerical simulation. This linear model needs to be confronted to experimental pressure measurements for validation.

Figure 3: Area of interest for the mean leg geometry

Figure 4: Contribution of the different parameters to pressure variation (scaled to mean pressure)

REFERENCES


MECHANICAL CHARACTERIZATION AND CONSTITUTIVE MODELLING OF TEXTILE-BASED IMPLANTS

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SUMMARY

Textile-based implant (mesh) treatment is considered as a standard of care for abdominal wall hernia repair. Computational models contribute to optimizing the mechanical performance of meshes. This paper presents models of two knitted mesh implants based on advanced testing and validated against functional experimental data.

Key words: abdominal wall hernia, knitted textile-based implant, constitutive modeling

1 INTRODUCTION

Abdominal wall hernia (AWH) is an abnormal protrusion of the abdominal cavity contents and/or pre-peritoneal fat through a defect or weakness in the abdominal wall. The fundamental biological mechanisms of AWH may be resumed in fascial pathology resulting in primary AWH and surgical wound failure leading to incisional hernia [1].

Today, AWH repair is one of the most common and frequent surgical operations worldwide and the use of surgical mesh has become standard of care. Despite tremendous progress in the treatment, complications remain with AWH repair and reported recurrence rates are still high [2,3]. It is estimated that about one million mesh implants are used every year in hernia repair worldwide [4] and that 348,000 ventral hernia repairs were performed for 2006 in the Unites States with the total cost of US $3.2 billion [5]. Thus, AWH repair and its complications represent significant socio-economic burden.

Robust and reliable computational model of the implant and, more generally, the repair should enable better understanding of the underlying mechanical phenomena, accurate prediction of acute clinical outcome and optimization of the implantable device from mechanical standpoint. In this study, models of two knitted prosthetic mesh implants (denoted as Mesh A and Mesh B) are proposed based on advanced product testing and validated against functional experimental data [6].

2 METHODOLOGY

2.1 Mechanical characterization

Different mechanical tests were performed for each mesh implant: uniaxial quasi-static cyclic test, biaxial quasi-static cyclic tensile test and uniaxial tensile relaxation test. All tests were carried out in a 37°C water bath with gauge dimensions of 25x25 mm².

Uniaxial quasi-static cyclic test was carried out in an Instron® ElectroPuls E3000 system fitted with a 250N load cell in 3 directions: warp, weft and diagonal. VIC-3D™ (Correlated Solutions) digital image correlation system was used to estimate Poisson's ratio.
A TA Instruments ElectroForce® planar biaxial test device fitted with two 225N load cells was used to assess the mechanical coupling between warp and weft directions in an equibiaxial quasi-static cyclic tensile test. Strain values were determined from the clamp displacements assuming pure biaxial loading.

Finally, the short-time response of the implants was characterized from a uniaxial tensile relaxation test in the previously described Instron® system. This test was also performed in 3 directions: warp, weft and diagonal.

### 2.2 Constitutive modelling and identification

Three different models (linear elastic orthotropic, hyperelastic and hypoelastic) were explored to model the constitutive behavior of shell implant meshes. Each of them has advantages and drawbacks.

A simple linear orthotropic model was first used. The parameters of this model ($E_1$, $E_2$, $v_{12}$ and $G_{12}$) were identified from the first loading curves from uni- and bi-axial tests.

Subsequently, a hyperelastic strain energy function based on [8] and adapted for shells was used:

$$ W = W_{el} + \sum_{i=1}^{8} \omega_i F_i W_c I_{4(i)}, $$

with $W_{el}$ a hyperelastic strain energy function, $W_c$ is the hyperelastic strain energy associated with each direction and which is degraded by $F_i$ depending on the loading history and $I_{4(i)}$ is the 4th invariant of the $i^{th}$ direction [8]. The 8 directions and associated weights $\omega_i$ correspond to the cubature formula for numerical integration over a disk. A Fung orthotropic strain energy function was chosen for $W_{el}$ [9].

Constitutive parameters for $W_{el}$ were identified on the first response based on uni- and bi-axial tests using an optimization algorithm (genetic algorithm followed by fmincon in Matlab®) to minimize the difference between experimental and numerical force values. The same procedure was then subsequently used to identify the parameters for $W_c$ and $F_i$ based on the cyclic uniaxial data. Note that this model does not account for hysteresis.

Finally, a hypoelastic model was used with an incremental formulation of the stress $\sigma$ such as:

$$ \sigma^T = C : D, $$

where $\sigma^T$ is the Green–Naghdi rate of the Cauchy stress tensor, $C$ is the fourth-order stiffness tensor of the material and $D$ is the rate of deformation tensor. This formulation is convenient because $C$ can be dependent on the current loading state but also the loading history. In this case, $C = C(E, E_{max}, \bar{E})$ with $E$ the Green-Lagrange strain tensor, $E_{max}$ the maximum strain previously attained and $\bar{E}$ the strain rate. More specifically, the following tensor was used:

$$ C = \begin{bmatrix} \frac{1}{E_1} & -v_{21} & 0 \\ -v_{12} & \frac{1}{E_2} & 0 \\ 0 & 0 & \frac{1}{2G_{12}} \end{bmatrix}^{-1} $$

with

$$ \begin{cases} E_1 = f_1(\epsilon_{11}, \max(\epsilon_{11}), \text{sign}(\dot{\epsilon}_{11})) \\ E_2 = f_2(\epsilon_{22}, \max(\epsilon_{22}), \text{sign}(\dot{\epsilon}_{22})) \\ G_{12} = g_{12}(\epsilon_{12}, \max(\epsilon_{12}), \text{sign}(\dot{\epsilon}_{12})) \\ \nu_{12} = g_{12}(\epsilon_{11}), \nu_{21} = g_{21}(\epsilon_{22}) \end{cases} $$

where $f_i$ and $g_i$ are interpolating functions directly fitted onto the experimental curves (no optimization needed). This model reproduces the non-linearity, anisotropy, Mullins effect, permanent set and hysteresis of the material.

To account for the short-time viscoelastic effect, a reduced relaxation function $G(t)$ was chosen such as:

$$ G(t) = 1 + \sum_{i=1}^{3} g_i \exp(-t/\tau_i). $$

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The three $g$ and $\tau$ terms from these Prony series were characterized by directly fitting the relaxation function to the relaxation tests, assuming an instantaneous strain step. The viscoelastic effect can then be associated to the elastic response based on the approach described in [7].

![Figure 1: Illustration of force-strain curves under uniaxial and biaxial tension.](image)

### 2.3 Validation

Previously acquired functional experimental data [10] was used to validate the constitutive models. The experimental set-up consisted of a hemispherical plunger loading a circular mesh with point fixations represented by metal rods fitted with markers. Distribution of reaction forces at the mesh fixation points was determined via rod continuum mechanics and positions of markers recorded by marker tracking system. A finite element (FE) model of this experiment was built in Abaqus® as seen in Figure 2 (A) and numerical reaction forces at the fixation points were compared to the experimental data.

![Figure 2: FE model of the validation experiment (A) and comparison of experimental and numerical forces at fixation points for mesh A (B) with the linear orthotropic model.](image)

### 3 RESULTS AND CONCLUSIONS

Both implants exhibited Mullins effect (a strong dependency to the maximum strain previously encountered), a large irreversible permanent set and a strong hysteresis due to the entanglement of fibers under uniaxial quasi-static cyclic test, as seen in Figure 1. Strong coupling between warp and weft directions, characterized by large Poisson’s ratio ($>1$), was observed. Same forces were measured at much lower strain in equibiaxial test compared to uniaxial test (e.g. 40N reached at 2.8% strain compared to 19% strain respectively in warp direction for mesh A) as seen in Figure 1. Relaxation tests highlighted a strong viscoelastic effect with 50% of stress relaxed in tenths of milliseconds. Directional dependency of identified constants was not judged significant.
Linear elastic orthotropic formulation was found satisfactory to model Mesh A. Figure 2 illustrates experimental and numerical forces at the fixation points for Mesh A. While simulations resulted in perfectly symmetric distribution of reaction forces, experiments showed slight deviations from symmetric distribution. It is mainly attributed to the backlash between rods representing fixations and textile pores and can hardly be captured by a model based on continuum hypothesis. However, the average error was only 14%. The model was not suitable for Mesh B due to its high non-linearity which motivated further development of hypoelastic and hyperelastic models.

The hypoelastic model perfectly matched the experimental uniaxial and biaxial stress-strain curves by definition. It has the advantage of interpolating the response between experimental points and, thus, can accurately capture Mullins effect, anisotropic non-linear behavior and hysteresis. However, when the loading conditions differ from testing conditions, the response must be extrapolated, which can lead to non-physical results (e.g. negative stiffness matrix). Extensive testing under different loading conditions ensured the coverage of a large experimental domain.

The hyperelastic model did not match experimental results as closely (partly because the strong hysteresis effect was not reproduced), but provided a satisfactory agreement overall. The advantage of this model is that it remains thermodynamically stable under all loading conditions [8].

Textile-based implants used for AWH repair are complex heterogeneous and anisotropic structures exhibiting elasto-visco-plastic behavior. Despite recent attempts [10], computational modeling of complex knitted textile implants based on their structure remains challenging. This abstract presents advanced continuum models of AWR mesh implants. Although these models remain phenomenological and do not describe mechanistic effects within the structure, they are able to provide accurate mechanical response to complex boundary conditions.

REFERENCES

NON DESTRUCTIVE IDENTIFICATION OF PATIENT SPECIFIC MECHANICAL PROPERTIES – APPLICATION TO PELVIC SYSTEM

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SUMMARY

This work presents a non-destructive method allowing a patient-specific characterization of the mechanical properties with an application on the pelvic organs. The developed protocol is based on an experimental data bank on mechanical properties of soft tissues, geometrical analysis from clinical MRI, displacement field analysis from dynamic MRI and Finite Element model of complete system including ligaments, muscles and fasciae. The output parameters are providing the mechanical properties of each organ. The presented results are based on a generic and a patient-specific geometry providing in both cases the mechanical properties of pelvic organs.

Key words: Inverse Method, large strain, hyperelasticity

1 INTRODUCTION

The mobility of the woman pelvic system is complex and suffers from a lack of understanding in literature. It depends on the geometrical aspects at several levels (organs, suspension structures) and on the mechanical behaviour of the soft tissues \cite{1, 2}. Such multi-parameter problem makes complex the investigation of physio-pathological phenomena, strongly conditioned by inter-individuality dispersion. During the past decade, the advances in mathematical modeling and computer sciences, makes it possible to develop patient-specific models of the pelvic system. The Finite Element (FE) method is commonly used to investigate organ mobility and the mechanisms involved and to provide better understanding of the important patient-specific aspects of the problem \cite{2}. Due to the dispersion of the mechanical properties observed on these biological tissues and difficulties to characterise it with in vivo methods, carrying out patient-specific simulations is a challenging task. The geometrical inter-individuality also presents a scientific barrier but can be more easily removed by advances in imaging techniques \cite{3}.

The purpose of this work is to tackle that issue by using an inverse finite element analysis. Mechanical properties of the tissues are optimized in order to obtain a specific displacement of the cervix on the FE model. By measuring the displacement field of the organs with dynamic MRI analysis, one could determine patient-specific mechanical properties of the pelvic organs. This work presents results obtained in a first step on a generic model of the pelvic system and then a validation step on a specific patient model.

2 METHODOLOGY

2.1 Model definition

Our previous work allowed us to generate a complete FE model of the pelvic system, integrating all the organs and sustainable structures such as muscles and ligaments, significantly impacting the mobility of organs and especially the cervix area \cite{2}. This model results from the analysis and
modelling of the pelvic system through MRI data of several patients. The geometry of this generic model is developed to represent mobility of the pelvic system in agreement with the one observed by image registration from dynamic MRI [3]. The MRI data is performed according to a standard clinical protocol. Data information is collected with a 3 Tesla MRI through 3 sequences of 2D images on the axial, coronal and sagittal incidences (Resolution 512x512, Pixel size: 0.7 mm). Thanks to the help of surgeons, the images are then used to generate a representative 3D model from the segmentation of each anatomical structure (Avizo Standard edition 7® Visualization Sciences Group VSG, SAS). At this step it is then necessary to make this model compatible with the FE simulation. This work is carried out thanks to CAD tools (CATIA, Dassault Systèmes) and consists of creating surface patches to make the geometries compatible with a FE mesh. These geometries are then imported into our FE simulation software (Abaqus/CAE 6.12-2 software, Dassault Systèmes Simulia Corp.). We apply the boundary conditions to assembly of all structures (ligaments, muscles, inter-organ fasciae) as well as pressure loading [2]. The mechanical properties of soft tissues come from others characterization works already published [4, 5].

In order to validate our approach, we applied this FE model protocol on a specific patient. Since we are able to define the patient-specific geometry, an average mapping of the mechanical properties and the analysis of the displacement fields, we may identify the real properties of the patient thanks to the development of an inverse method. The studied patient presents a normal gynaecologic examination without noticeable medical history.

2.2 Inverse method

As the aim is to characterize the mechanical properties of soft tissues, input parameters are defined only on these material aspects on our FE simulation protocol. The optimization is controlled by the C0 coefficient of the Yeoh model [6]. As the C1 value corresponds to the large strain area, we decided to index these value on the C0 parameter, in the range limit that we observed on experimental data. If the C0 is stiffer the C1 value of the same organ may also be stiffening in accordance with their own mechanical properties. These functions were calculated for each parameter of the model, in order to map the intervals between the first and the third quartile (fig.1c). All parameters can be determined once the optimal C0 value of each organ has been computed by the optimization algorithm. The optimization employs a Levenberg-Marquardt algorithm [7]. Our control variable is based on the position of the cervix as this area is the most representative to analyze pelvic mobility [2]. Maximum and minimum admissible C0 values are given by the statistics obtained on mechanical tests related to 2000 tests (fig.1c). The whole algorithm runs automatically. At each step a new C0 is determined for each organ. Then the other C1 coefficients are calculated for the vagina, rectum and bladder. These values are set in a new input file (.inp) for Abaqus. A special python file is generated in order to launch the FE simulation without any user intervention. When the simulation is completed, the magnitude of the displacement of the cervix area is recovered from Abaqus data. If the estimated value is outside the admissible range of values, the iterative optimization process is stopped in order to avoid unnecessary and time-consuming computation.
3 RESULTS

The optimization algorithm was first tested on a symmetrical generic model. The target displacement for the cervix was set at 8mm corresponding to an average value of the measured displacement on MRI and based on the previous work corresponding to the physiological mobility [2]. The model converged after twelve iterations with a displacement about 8mm for a computed C0vag value of 0.16 (fig.5a). The C0 and C1 values for the vagina, rectum and bladder, yielded by this optimization are the following: C0vag=0.16, C1vag=0.45, C0rec=0.1, C1rec=0.09, C0bla=0.06, C1bla=0.03.

In order to validate our approach, the optimization algorithm was tested on the patient-specific geometry. The target displacement value at the cervix was measured at 14.5mm on the dynamic MRI of the patient. The computed value to reach this displacement are C0vag=0.13, C1vag=0.34, C0rec=0.09, C1rec=0.07, C0bla=0.05, C1bla=0.01. We then compared the displacements given by our FE simulation to those computed from medical-imaging data analysis (fig.2). Displacements of a dozen voxels (8mm) are studied in a given region of interest (ROI) of the MRI, and nodal displacements are considered in the same ROI of the FE model for comparison.

As the optimization criterion is only to match the displacement magnitude at the cervix, it is interesting to verify the accuracy of our approach by analyzing the displacement field in other areas of the pelvic system (fig3a). The displacements are also studied for the bladder, vagina and rectum in three ROI: the top, the front and the back of the organs (fig3b).

It is worth mentioning that the FE model used in this study is only representing the lower part of the rectum hence making it difficult to accurately simulate the behavior at the top and back of this organ.
4 DISCUSSIONS AND CONCLUSION

In this study we have shown that we could determine the mechanical hyperelastic properties of the pelvic organs using MRI data and an inverse FE method. The developed algorithm converged for both symmetric and asymmetric geometries of pelvic organs. Using this method, the general kinematics of the pelvic organs can be simulated for a given patient.

Comparing displacements on fig.3a and 3b, the method gives a good approximation of each organs in the range of experimental data bank. The displacement are, in average, accurate for each organs. However, the displacement at the back of the vagina is important in our FE simulation. Multiple factors can explain this gap: properties of the fascia could influence the mobility, mechanical properties could be non-uniform within the organ tissue, contrast gel escaping the vagina during the push is not taken into account. One can notice that the FEM is less accurate for the rectum (larger dispersion at the front and top, lower at the back). The observed mobility on the rectum is complex and difficult to simulate due to its boundary conditions by the lower part of the abdomen or the upper part of the rectum. New boundary conditions to this part of the model should improve the simulated kinematics of the back of pelvis. Mobility in the lower part is also difficult to represent due to the fluid escape during dynamic MRI exam. Despite of that, we can also notice that the image registration techniques used may not be optimized to analyse the bottom displacement field. The MRI techniques and its related precision can also lead to uncertainties on our inverse method.

The structures on the vagina are however correctly identified due to our knowledge of the definition of suspension structures, allowing to validate more precisely the response on the mobility of the cervix.

Finally, in this study we used a value of $10^{-3}$ MPa for the cough effort, as found in the literature [8]. However, this value varies between individuals [9]. Patient-specific simulations should take this parameter into account to guaranty the validation of observed mobility. Further improvement of the method also lies in the development of a more powerful optimization algorithm, not only based on the cervix location.

One of the perspectives of this work is to apply this protocol on a physical model in synthetic polymers, which we start to develop from our generic model. This tool would be compatible with MRI and instrumented to control the loading conditions. This strategy would permit us to know all our inputs, such as the geometry of the system, the boundary and loading conditions and the mechanical properties of the constituent materials.

REFERENCES

Integrative Modelling of Soft-Tissue Mechanobiology II
EXPERIMENTAL METHODS TO DRIVE COMPUTATIONAL GROWTH AND REMODELING FRAMEWORK FOR IN SITU TISSUE ENGINEERED VASCULAR GRAFTS

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SUMMARY

Continuum mechanics based growth and remodeling (G&R) tools represent an emerging advancement for rational design of tissue engineered vascular grafts (TEVGs). In this work, we focus on a novel acellular biodegradable TEVG that has shown to produce a mature neoartery 90 days post-implantation. Particularly, we aim to further refine the predictive capabilities of our G&R model by introducing a methodology for obtaining physical data. This data is required to model graft degradation and ECM deposition; key factors which guide time evolving neoarterial mechanical homeostasis.

Key words: Continuum mechanics, growth and remodeling, small diameter tissue engineered vascular grafts

1 INTRODUCTION

Small diameter TEVGs represent the holy grail of tissue engineered blood vessel conduits. Cell-free, small diameter TEVGs that harness in-host growth and remodeling (G&R) capabilities represent an advancement in the field that have the potential to provide an alternate solution to the problems faced by autografts and cell-seeded TEVGs [1]. Despite the remarkable success of this technology in animal models, much of its development is based on a trial and error investigation which calls for a more rational design of TEVGs for accelerated development. G&R theory based computational frameworks, are tools that are being used for numerical hypothesis testing [2] to guide rational design of bi-layered composite grafts: a porous poly-glycerol sebacate (PGS) core and electrospun polycaprolactone (PCL) outer sheath. These grafts have shown mature elastin and nerve regeneration at 90 day post-implantation in small animals [3].

The main requirement for successful neoartery formation is the effective interplay between PGS degradation and extracellular matrix (ECM) deposition. This interaction needs to be effectively captured in the G&R tool in order to accurately predict long-term remodeling response of these grafts. However, currently there is little experimental data to guide even the qualitative features of such an analysis.

2 METHODOLOGY

2.1 Theoretical Model

We model the evolving G&R response of these neoarteries by using a constrained mixture model wherein the mechanical response is guided by establishing a homeostatic stress response. Briefly, each of the constituents is modeled as hyperelastic such that

\[ W(s) = \sum_{\alpha=1}^{n} W^{\alpha}(s) = \sum_{\alpha=1}^{n} \frac{Q^{\alpha}(\tau)}{m^{\alpha}(s)} q^{\alpha}(s-\tau) W^{\alpha}(C_{\alpha}(\tau)) d\tau \]  (1)
where, $W(s)$ is the total strain energy of the mixture, $\rho^\alpha(0)$ is the density of constituent $\alpha$ at remodeling time $s = 0$, $Q^\alpha(s)$ is the survival function that represents remaining mass and $\bar{W}^\alpha(C_{n(0)}(s))$ represents the evolving strain energy function of the degrading constituent. $m^\alpha(\tau)$ and $\bar{W}^\alpha(C_{n(\tau)}(s))$ represent the rate of deposition of constituents and their associated strain energy function.

Our previous computational parametric studies showed that input parameters like degradation and ECM rate constants highly influence long-term remodeling. Using an experiment based mechanistic approach, we also showed that these TEVGs degrade through surface erosion and that material constants associated with surface erosion and mechanical degradation can be obtained through an in vitro experimental investigation [4]. The loss in mechanical properties was found to be well modeled using a scalar damage theory

$$W^{PGS}(s) = \zeta(s) \left[ \frac{\beta^{PGS}_0}{2} (I_1 - 3) \right]$$

(2)

where, $\beta^{PGS}_0 = 34.43 kPa$ and $\zeta(s)$ represents the damage function such that $0 \leq \zeta(s) \leq 1$.

In this work, we introduce a methodology to longitudinally evaluate graft degradation and ECM deposition in vivo to understand their evolving strain energy function $\bar{W}^\alpha(C_{n(\tau)}(s))$. This data will be used to further develop the G&R framework, enabling an enhanced understanding of the process of neoarterial evolution.

### 2.2 Graft Fabrication and Testing

Grafts were fabricated by the method of solvent cast salt leaching. Briefly, PGS prepolymer was synthesized as before [5], salt porogens of 25-32 $\mu$m were packed and a PGS solution (adjusted as 3:1 mass ratio of salt:PGS) was added to salt templates followed by curing in the vacuum oven. The outer sheath was fabricated by electrospinning PCL (Mn = 80 kDa, Sigma-Aldrich, St. Louis, MO) on the outer surface of the PGS. 10mm long grafts were implanted in male Sprague-Dawley (Charles River Laboratories, Boston, MA) rats using end-to-end interposition without the use of any anticoagulation treatment postoperatively. Remodeling was tracked and neoarteries were explanted at 1 and 3 months post-implantation. In vitro stretch was measured prior to explantation and the explanted neoarteries were evaluated using microCT and by conducting biaxial pressure-inflation testing. Briefly, neoarteries were scanned using a 0.35$\mu$m resolution microCT (Skyscan 1272, Bruker Corporation, Billerica, MA), providing distinct data sets for the PGS core and surrounding tissue. Following microCT studies, the neoarteries underwent biaxial pressure inflation testing using a custom designed mechanical testing device compatible with multiphoton microscopy, figure 1. Mechanical testing consisted of four preconditioning cycles followed by inflating the neoartery from 7-120 mmHg for 3 cycles at 0, 10, 20 and 40% stretch. A multiphoton microscope (MPM)(Olympus FV1000 MPE, Tokyo, Japan) was used to image the collagen fibers in 2D planar images which were then used to generate 3D reconstructions of the fiber architecture. The image stacks were post processed to obtain quantitative information about fiber orientation and tortuosity under loading [6]. In particular, vessels were imaged at each of the axial stretches at 7 and 120 mmHg using an excitation wavelength of 810nm and a water immersion objective. Collagen fiber tortuosity and orientation were measured in the 3D

![Figure 1: (a) Custom designed mechanical testing device for biaxial pressure-inflation testing of neoarteries. Device can be setup under a multiphoton microscope thereby enabling imaging of collagen fibers under various loading conditions. (b) 90 day neoartery mounted on device with strain markers.](image)
reconstructed MPM stacks [6]. This data were incorporated in a fiber recruitment model to obtain a constitutive model for evolving mechanical properties of neoarteries.

3 RESULTS AND CONCLUSIONS

Neoarteries were patent and vascularized by day 30 and continued to maintain patency by 90 days as seen in figure 2.

Figure 2: In vivo image of graft implanted at day 0 and remodeled neoartery at days 30 and 90. Scale represents 1mm.

Evaluation using MicroCT showed that most PGS was degraded by day 14 as seen in figure 3. This behaviour was shown to be dominated by a concentration gradient driven diffusion in our in vitro studies [4]. This is incorporated in the FE G&R tool as a diffusion-based erosion model and the changes in mechanical properties are modeled using a scalar damage theory.

Figure 3: Longitudinal MicroCT evaluation of neoarteries showed that most PGS degraded by day 14.

Figure 4 shows the stress-stretch response of the neoarteries and the microstructural collagen behavior under various loading conditions. Quantification of collagen tortuosity and orientation from the fiber tracing at different time points provide the constants (e.g. deposition stretch $G^a(\tau)$, rate of production $m^a(\tau)$) required for the G&R tool.

In summary, neoarteries were successfully created in vivo after end-to-end interposition of acellular, synthetic bioreabsorbable vascular grafts. An experimental methodology was introduced and illustrated for obtaining mechanical and structural data for the evolving neoartery and eroding scaffold. These data were derived from our custom biaxial inflation system, MPM imaging and micro-CT analysis. Incorporation of the resulting data-driven strain energy functions and degradation models in our finite element G&R model will improve the predictive capabilities of the G&R tool which can further be used for design of TEVGs.
Figure 4: Circumferential Cauchy stress-stretch response of a representative sample of (a) 1 month neoartery and (b) 3 month neoartery under 0, 20 and 40% in vivo axial stretch (AS). Multiphoton images of collagen fibers at 7 and 120 mmHg are shown as projected 2D stacks across the thickness of neoarteries. Scale bar, 100 µm.

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ENDOTHELIAL CELL ELONGATION UNDER SHEAR STRESS - A COMPUTATIONAL MODEL TO CONSOLIDATE OBSERVED CELL SHAPE CHANGES

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SUMMARY

The endothelium, a single layer of cells that lines all blood vessels, is the principal sensor of hemodynamic wall shear stress (WSS). Changes in WSS are associated with diseases as inflammation, atherosclerotic plaque formation or aneurysms. It has long been established that endothelial cells are elongated under physiological blood flow conditions, but become cobblestone in culture under no flow conditions. To quantify this change of cell morphology, we measured the circularity and aspect ratio of porcine aortic endothelial cells cultured in physiological flux (30 dynes/cm²) or static condition. A parsimonious biomechanical cell-vertex model allows us for the first time to explain the observed changes in cell morphology by local changes in the cell boundary tension associated with changes in the architecture of the cytoskeletal network.

Key words: endothelia, cell-vertex-model, wall shear stress

1 INTRODUCTION

Vascular endothelial cells are continuously exposed to flow, deviations from physiological flow conditions are associated with numerous diseases [1,2][3][4][5]. Endothelial cells are the sensors of arterial walls responding to a number of stimulating factors including changes in wall shear stress (WSS); whereas endothelial cells in physiological flow conditions elongate in the direction of blood flow, they loose this directionality in regions of low flow [6][7]. Until now no mechanical model exists to describe this WSS dependent adaptive change of endothelial cell morphology. Here, we propose an in silico model that explains the elongation of porcine aortic endothelial cells under physiological flux conditions by local changes in the tension of the cell boundary. In our model these changes depend both on the strength and directionality of the blood flow.

2 METHODOLOGY

Flow experiments Primary porcine aortic endothelia cells were isolated as previously described [8] and cultured in Dulbecco’s Modified Eagle Medium supplemented with 10% fetal calf serum and 100 µg/mL heparin. Cells were seeded on 1% gelatin coated coverslip for the static condition or on 1% gelatin coated Ibidi chambers for the flow condition. After confluence was reached, endothelial cells cultured in the Ibidi chambers were subjected to a constant flow of 30 dynes/cm² for 48 hours at 37°C and 5% CO₂. In a final step, cells were fixed with methanol for 5 minutes at -20°C. Cells were incubated with antibody against CD31 (endothelial cell membrane receptor, Santa Cruz sc-1506) and gamma-cytoplasmic actin [9] for two hours at room temperature, followed by incubation with DAB-anti-mouse and FITC-anti-goat antibodies. Nuclei were stained with 4’,6-diamidino-2-phenylindole (DAPI) and cells were mounted in Vectashield medium. Pictures have been obtained by confocal laser scanning microscopy (Leica SP5).
Shape measurements  We introduced the circularity measure \( C = 4\pi A_\alpha / L_\alpha^2 \), where \( A_\alpha \) is the area of the cell \( \alpha \) and \( L_\alpha \) its perimeter. Whereas this measure is 1 for a perfectly circular cell, it is smaller than 1 for all other cell shapes. Cell elongation was quantified by the aspect ratio of the cell’s fitted ellipse, i.e. the ratio of major axis to minor axis. Geometry measurements in confocal microscopy of endothelial cells were performed with the imaging processing package Fiji [10], geometry measurements of simulated cells were automated within Matlab (MATLAB 2016b, The MathWorks, Natick, 2016). Tests for statistical significant difference between no flow and physiological flow conditions were performed with the statistical software package R.

Line tension depending on direction of blood flow leads to elongated cells  We model endothelial cells within the framework of a two-dimensional vertex model, where the junctions between cells are defined by straight lines (edges) connecting vertices [11,12,13]. The resulting polygonal cell shapes are obtained by minimizing an energy function describing the visco-elastic properties of the cells. The ‘line tension’ term of the energy function (Fig. 1) mimics the cytoskeletal contractility in the cortical bundles associated with the adherens junctions and the mechanics of cell-cell adhesion [11,12]. In our extension of previous cell-vertex models (reviewed in [14]), the line tension term depends both on the strength and direction of the blood flow: in flux conditions, the line tension factor \( \lambda_{\text{WSS}}(\Theta) \) is greater than one for all cell edges orientated within an angle smaller than a threshold angle \( \Theta_{\text{threshold}} \) from the direction perpendicular to the blood flow and one otherwise. For a given wall shear stress we obtain from the energy function in Fig. 1 the corresponding dimensionless energy function as

\[
\bar{E} = \frac{E}{KA_0^2} = \sum_{<i,j>} \lambda_{<i,j>}(\Theta) l_{ij} \frac{L_{ij}}{A_0} + \frac{1}{2} \sum_{\alpha} \left( \lambda_{\text{area}}(A_\alpha - A_0) + \lambda_{\text{perimeter}}(L_\alpha^2 - L_0^2) \right),
\]

where we introduced the dimensionless parameters \( \bar{\lambda} = \frac{\lambda}{KA_0^2} \) and \( \bar{\Gamma} = \frac{\Gamma}{KA_0} \) and dropped the superscript \( \text{WSS} \) to simplify the notation. An increased line tension factor of an edge \( \lambda_{<i,j>}(\Theta) \) results in its shrinkage in the energy minimizing step of the cell-vertex-model algorithm [11,13] giving rise to less round cells and a directionality of the cell’s orientation. To obtain an agreement with the experimentally observed circularity, aspect ratio and mean cell area in flux and no-flux-conditions, we varied the threshold angle \( \Theta_{\text{threshold}} \) as well as the factors \( \bar{\lambda} \) and \( \bar{\Gamma} \).

3 RESULTS AND CONCLUSIONS

We observed an increase in the aspect ratio and a decrease of the circularity of porcine aortic endothelial cells in physiological flux conditions as compared to the no-flux-conditions (Fig. 2B-D). In the exemplary simulation run shown in Fig. 2F we have chosen a line tension factor of \( \lambda_{<i,j>} = 80 \) for

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**Figure 1:** Mechanical energy function describing cell shapes. In extension of previous models [14], the line tension term includes an additional factor \( \lambda_{<i,j>}(\Theta) \lambda_{\text{WSS}} \), which depends both on the angle \( \Theta \) between a cell edge \( <ij> \) and the applied shear stress \( \lambda_{\text{WSS}} \).

\[
\lambda_{<i,j>}(\Theta) \lambda_{\text{WSS}} = \left\{ \begin{array}{ll}
\lambda_{\text{WSS}} & \text{if } \Theta < \Theta_{\text{threshold}} \\
1 & \text{if } \Theta > \Theta_{\text{threshold}}
\end{array} \right.
\]
Figure 2: Endothelial cells in experiment (A-D) and simulation (E-H). A and B: Porcine aortic endothelial cells. CD31 immunostaining in red denotes the cell-cell borders, gamma-actin filaments are stained in green and nuclei are marked in blue by DAPI. E and F: Simulated endothelial cells. The chosen line tension factors were $\lambda_{ij}^0(\Theta) = 1$ for all cell edges in panel E and $\lambda_{ij}^{WSS}(\Theta) = 80$, if $\Theta < 35^\circ$, 1 otherwise in panel F. C and G: Aspect ratio in experiment (C) and simulation (G). D and H: Circularity in experiment (D) and simulation (H). $N$ denotes the number of cells, statistical significance of differences between no flow and physiological flow conditions were tested with a one-sided Mann-Whitney U test, corresponding p-values given.

all cell edges in a range of $90^\circ \pm \Theta_{\text{threshold}}$ with $\Theta_{\text{threshold}} = 35^\circ$ from the direction of blood flow. For all other edges as well as no-flux simulations (Fig. 2E) the line tension factor is 1. $\bar{X} = 0.12$ and $\bar{r} = 0.04$ were chosen as in 111. Based on our experimental observations (data not shown), we reduced the target area of the cells by a factor 1/2 in flux simulations. With the given parameter set, the simulation reproduces qualitatively the increase of the aspect ratio (Fig. 2G) and decrease of the circularity (Fig. 2H) from no-flow to physiological flow conditions. All measured changes in cell shape in experiment and simulation were statistically significant with p-values smaller than 0.001 tested by a one-sided Mann-Whitney U test.

In our model, an increase in the line tension of a cell’s energy function reflects an increase in the energy stored in its cytoskeletal network. Remarkably, we observed in our experimental data set a rearrangement of the gamma-cytoplasmic actin network from no flux to the flux conditions: whereas in the no flux conditions gamma-cytoplasmic actin was allocated alongside the cell edges (Fig. 2A), it undergoes a redistribution forming highly organized filamentous networks in the direction of blood flow in the flux conditions (Fig. 2B). This rearrangement of gamma-cytoplasmic actin, a component of the cytoskeletal network, might partly cause the observed cell elongation. Future work will further investigate this phenomenon.

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IMPACT OF FLOW ON THE NUCLEAR TRANSLOCATION OF NF-κB

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SUMMARY
We investigate in vitro and in silico the impact of hemodynamics on the temporal activation and nuclear translocation of NF-κB in vascular endothelial cells (ECs). We exposed human umbilical vein endothelial cells (HUVEC) to low and high shear stress for 360 minutes and measured live the nuclear NF-κB concentration. We observed an increase in nuclear NF-κB concentration at low shear stress, while at high shear stress no significant effect was observed. We created a numerical model to simulate the intracellular pathway of nuclear translocation of NF-κB in response to shear stress. The previous findings of low and high shear stress were used to fit the model. The model was applied to a backward facing step, and showed that stagnation and reattachment zones are prone to an increased nuclear NF-κB concentration.

Key words: NF-κB, Hemodynamics, Inflammation

1 INTRODUCTION
NF-κB is a key promoter of inflammatory responses in vascular ECs and plays a pivotal role in cell growth, survival and apoptosis. Mis-regulation of NF-κB is related with inflammation, autoimmune and metabolic diseases and cancer [1]. It has been shown that shear stress has a large effect on temporal and spatial concentration of NF-κB [2-11] in ECs. However, the exact dynamics of the nuclear translocation of NF-κB in response to shear stress remain unknown. A better understanding of how hemodynamics influence the activation and nuclear translocation of NF-κB, which is mainly responsible for inflammatory responses in ECs, would shed more light in the development of vascular diseases (atherosclerosis or aneurysms). We aim to explore the real time nuclear translocation of NF-κB in ECs exposed to shear stress, create a numerical model by coupling hemodynamics and NF-κB dynamics, and also predict the nuclear NF-κB concentration in disturbed flow regions and image-derived vessel geometries.

2 EXPERIMENTAL METHODOLOGY
HUVECS (PromoCell, Heidelberg, Germany) of passage 3 were transfected with a GFP-RelA (a gift from Warner Greene) and H2B-mCherry plasmid (a gift from Robert Benezra) and maintained in endothelial growth medium (PromoCell, Heidelberg, Germany). The cells were grown in a 6-channel Ibidi slide (Ibidi, Planegg/Martinsried, Germany). 5 channels were connected to a perfusion system and exposed to a shear stress equivalent to 2 and 20 dyne/cm². The perfusion liquid was DMEM with 10% FBS and 2% L-Glutamine at 37°C. The perfused cells were imaged with a Zeiss Axio Observer Inverted Widefield microscope (Zeiss Microscopy, Jena, Germany) for 360 minutes. Single cells were tracked with a custom-made tracking software. The nuclear GFP-RelA intensity was calculated for each cell at each time point.
3 NUMERICAL METHODOLOGY

We have developed an intracellular signalling model that predicts the temporal concentration of NF-κB in ECs exposed to low and high shear stress. The schematic of the model is depicted in Figure 1. Brief description of the pathway model: Active IKK is activated by shear stress, A20 and auto-phosphorylation of its C-terminals. Active IKK phosphorylates IkBα, which unbounds NF-κB. Unbound NF-κB travels into the nucleus where it promotes the transcription of IkBα and A20. Newly synthesized IkBα proteins bind again to NF-κB and inhibit its function and mobility [12, 13].

4 EXPERIMENTAL RESULTS

The effects of low and high shear stress on the nuclear translocation of GFP-RelA are shown in Figure 2. It shows that under low shear stress, an increased nuclear GFP-RelA intensity after 180 until 360 minutes was measured. On the other hand, high shear stress caused no significant change in nuclear GFP-RelA intensity when compared to static conditions.

5 NUMERICAL RESULTS

The shear induced NF-κB pathway model was fitted to the previous findings, interpolated and exemplified with a backward facing step channel, as shown in Figure 3A. A step channel is a good example of disturbed flow – a flow condition often found in vascular diseases (stenosis). In Figure 3B the nuclear NF-κB concentration of an endothelial cell population at the bottom wall after the step is shown for 480 minutes. It can be observed that the nuclear NF-κB concentration is high at the stagnation and reattachment zone, while the recirculation zone and developed flow region shows a low nuclear NF-κB concentration. Initially (after 30 minutes) all regions experience a high
nuclear NF-κB concentration, however only the stagnation and reattachment zones never recover and keep a high nuclear NF-κB concentration constant over time. This might indicate that stagnation and flow reattachment zones are prone to inflammatory reactions and might be crucial positions for disease progression and development.

6 CONCLUSIONS

We imaged successfully in real time HUVECs transfected with GFP-RelA under high and low shear stress. We observed that low shear stress promotes nuclear translocation of NF-κB, while high shear stress didn’t show any significant effect. We applied these findings to a computational model and predicted that stagnation and reattachment zones after a backward facing step channel experience a high nuclear NF-κB concentration.

REFERENCES

FINITE ELEMENT SIMULATION OF REFERENCE POINT INDENTATION ON BONE

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SUMMARY

Reference Point Indentation (RPI) is a novel technique aimed to assess bone quality. Measurements are recorded by the BioDent instrument that applies multiple indents to the same location of cortical bone. Ten RPI parameters are obtained from the resulting force-displacement curves. Using the commercial finite element analysis software Abaqus, we assess the significance of the RPI parameters. We create an axisymmetric model and employ an isotropic viscoelastic-plastic constitutive relation with damage to simulate indentations on a human cortical bone. The RPI outputs are computed for different simulated test cases and then compared with experimental results, measured using the BioDent instrument.

Key words: Reference Point Indentation, Finite element method, Cortical bone, Bone strength.

1 INTRODUCTION

The mechanical properties of bone are generally measured using traditional materials testing approaches such as compression, tension, three or four-point bending, and fracture toughness tests. The basic limitations of these methods are that they are ex-vivo and destructive. The RPI technique was invented to allow in-vivo measurements of bone material properties, relevant to the risk of bone fracture (Hansma et al., 2006). The instrument utilizes a cyclic loading to indent cortical bone multiple times at the same location (Fig. 1). The force-vs-displacement response, generated by the RPI technique (Fig. 2), allows the calculation of ten RPI parameters. These RPI parameters are summarized in Table 1 for easy reference. The BioDent 1000™ RPI instrument (Active Life Scientific, Inc., Santa Barbara, CA) is an experimental device used to perform the RPI tests and utilizes a software which computes the RPI parameters.

The RPI technique has received considerable interest in the bone mechanics community. There have been nearly fifty journal papers published from several different perspectives since its invention. Computer simulations can provide additional insight into the RPI technique. To date, there has only been one computational study on the RPI method (Hoffseth et al., 2015), which simulated an indentation of the cortical bone using an Osteoprobe, another RPI device designed with clinical setting in mind.

In this study, we simulate RPI on human cortical bone, mimicking the BioDent tests, using the finite element method (FEM) available in the commercial software Abaqus (V6.14). Our model utilizes the isotropic viscoelastic-plastic constitutive model proposed by (Zhang et al., 2010) for human cortical bone. This constitutive law has eight material constants and we vary four of these constants: (Young’s modulus, yield stress, viscous parameter and damage parameter). Additionally, experimental factors (indentation peak load, number of cycles, and indenter tip radius) are varied in the simulations. The force-versus-displacement response is obtained for each case, post-processed
to calculate the RPI parameters, and compared with experimental results (Granke et al., 2014). The effects of the input variables on the RPI outputs are reported, and the relationship between the RPI parameters and the elastic, viscoelastic and plastic material behavior of bone are investigated to gain a better understanding of the RPI technique.

2 METHODOLOGY

An axisymmetric finite element (FE) model was built to simulate indentations on human cortical bone, as illustrated in Fig. 3. The final FE model, used in this study, contained 52,780 4-node bilinear axisymmetric quadrilateral elements to represent bone tissue (substrate) as a cylinder of radius 2 mm and height 2 mm. The conical indenter had a 45-degree half angle and was modelled using 2,500 4-node bilinear axisymmetric quadrilateral elements. The size of the substrate was chosen to be about 50 times larger than the indentation depths (~40 μm). To preserve simulation accuracy, a biased meshing technique was adopted to ensure that a small enough element size was used near the indentation zone (~2 μm), while the elastic properties of steel were used to simulate the indenter tip. The bottom edge nodes of the substrate representing a human cortical bone were fully restrained while the vertical edge nodes of the sample were kept free. Interactions between the cortical bone and the indenter tip in the FE model were represented using surface-to-surface and finite sliding algorithms.

Due to the large deformations and contact between the indenter and the bone sample, a nonlinear FEA was performed, where geometric and contact nonlinearities were included. The RPI parameters were computed from the force-displacement data generated from the nonlinear RPI simulations.

3 RESULTS AND CONCLUSIONS

The finite element method within Abaqus software V6.14 was used to simulate RPI on human cortical bone and provided new data on how the RPI parameters are related to the material constants used to represent human bone properties (Zhang et al., 2010). Simulation results are in good agreement with the experimental study of (Granke et al., 2014).

The simulation results indicate that RPI parameters are sensitive to the material properties of human cortical bone. The unloading slopes were found to be good indicators of the elastic modulus. ID1 and TID RPI parameters have the same strong relationship to the material constants, where both are inversely proportional to the elastic modulus, compressive yield stress, viscous constant, and indenter tip radius. On the other hand, ID1 and TID are proportional to the damage parameter and the maximum applied load. Also, the IDI is found to have a limited relation to the damage parameter, indenter tip radius, and elastic modulus. However, IDI was found to be strongly inversely proportional to the compressive yield stress, and strongly proportional to the viscosity constant and maximum applied load.

These simulations provide new insights into the RPI technique, which can generate data on bone material properties. Further insights can be obtained by conducting more accurate simulations and doing further experiments using the RPI technique. Such studies are needed before the RPI method becomes more widely accepted and utilized.

REFERENCES


Table 1. Description of RPI outputs.

<table>
<thead>
<tr>
<th>RPI Output</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>ID1</td>
<td>Maximum first cycle indentation depth</td>
</tr>
<tr>
<td>LS1</td>
<td>First loading cycle force vs displacement loading slope</td>
</tr>
<tr>
<td>US1</td>
<td>First loading cycle force vs displacement unloading slope</td>
</tr>
<tr>
<td>CID1</td>
<td>Creep distance for the first loading cycle</td>
</tr>
<tr>
<td>TID</td>
<td>Total test probe penetration depth</td>
</tr>
<tr>
<td>IDI</td>
<td>Indentation distance increase from first cycle to last cycle</td>
</tr>
<tr>
<td>AvCID</td>
<td>Average of creep indentation depth over all cycles</td>
</tr>
<tr>
<td>AvUS</td>
<td>Average force vs displacement unloading slope over all cycles</td>
</tr>
<tr>
<td>AvLS</td>
<td>Average force vs displacement loading slope over all cycles</td>
</tr>
<tr>
<td>AvED</td>
<td>Average of energy dissipated over 3rd to last test cycles</td>
</tr>
</tbody>
</table>

Figures:

**Figure 1.** Reference point indentation cyclic loading. a) Typical 5 cycles of BioDent RPI loading. b) Loading function.
Figure 2. Typical force vs displacement curves for RPI first and last loading cycles with parameters.

Figure 3. Axisymmetric finite element model of reference point indentation.
ON THE CONSTITUTIVE MULTI-SCALE MODELING FOR FIBROUS TISSUES

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SUMMARY

The work presents a multi-scale methodology to model the constitutive behavior of fibrous biological tissues. The present model is based on the Method of Multi-scale Virtual Power (MMVP) which provides a systematic procedure to connect micro- and macro-scales. At the micro-scale, the representative volume element (RVE) is composed by a set of connected fibers, modeled as one-dimensional nonlinear trusses. At the macro-scale, a classical model from continuum mechanics is formulated in the finite strain incompressible regime. Model response will be verified in the conference talk against well-known fitted phenomenological constitutive equations available in the literature.

Key words: fibers networks, representative volume element, arterial tissue, virtual power principle

1 INTRODUCTION

Constitutive modeling of arterial tissue is a core subject to deeply understand the onset and progress of some cardiovascular diseases. This role has been played by phenomenological models that, in the attempt to represent more complex biomechanical phenomena, required to increase the number of constitutive parameters, which are not always easy to identify by empirical experiments (e.g. [3] for a review). To overcome this drawback as well as to reach a deeper understanding of tissue behavior, the construction of models that explicitly take into account the mechanical interactions between basic tissue components is a natural choice. This leads to the so-called constitutive multi-scale models.

Thus, we have developed a novel multi-scale model to address the material response at an observable scale (hereafter macro-scale) of fibrous tissues. In such model, the fine scale (hereafter micro-scale) features a fibrous (collagenous) architecture [4]. The model was constructed in the well-established framework proposed by the Method of Multi-scale Virtual Power (MMVP) [1], which has proven to be suitable in deriving multi-scale models even in the case of material failure [7, 8].

Noteworthy, in the context of biomechanics, up to authors knowledge, very few works have addressed the same problem. We highlight the contributions reported in [5, 6, 9] which also modeled the non-affine behavior of collagen hyperelastic networks in a multi-scale context, but, conceptually, using a different approach.

The aim of this contribution is to present in the conference talk some recent numerical results that demonstrate the predictive capabilities of the model derived in [4].

In Section 2 we overview the main features of the multi-scale model methodoly and the final remarks are outlined in Section 3.
2 METHODOLOGY

As mentioned, the present multi-scale methodology deals with tissues featuring a nonlinear behavior at macro-scale resulting from the interaction of biological fibers, for example collagen, at micro-scale, as illustrated in Figure 1. Since these tissues usually feature an incompressible behavior, we consider that hypothesis in the macro-scale model. To represent the geometry of the network we denote

\[ \mathcal{N}_{\text{net}} = \text{nodes in the network} = \{i, i = 1 \ldots, n\}, \quad (1) \]

\[ \mathcal{F}_{\text{net}} = \text{fibers in the network} = \{\alpha = (i_\alpha, j_\alpha) \in \mathcal{N}_{\text{net}} \times \mathcal{N}_{\text{net}}, i_\alpha \neq j_\alpha, \alpha = 1, \ldots, m\}, \quad (2) \]

Figure 1: Macro-scale continuum and discrete fiber architecture in the micro-scale domain.

To model the non-affinity of the model at the micro-scale we postulate that the displacement field in the micro-scale, node-wise, is given by

\[ \begin{align*}
\mathbf{u}_i^\mu &= \mathbf{G}_{|\mathbf{x}} \mathbf{y}_i^\mu + \mathbf{\tilde{u}}_\mu^i, \\
i &\in \mathcal{N}_{\text{net}},
\end{align*} \quad (3)\]

where \( \mathbf{G}_{|\mathbf{x}} \) is the gradient of displacement arriving from the macro-scale that is uniformly inserted in the RVE, \( \mathbf{y}_i^\mu \) is the coordinate of node \( i \) and \( \mathbf{\tilde{u}}_\mu^i \in \mathcal{W}_\mu \), where the space \( \mathcal{W}_\mu \) is the space of kinematically admissible micro-scale displacements satisfying proper kinematical constraint as a result of the kinematic link between macro-scale and micro-scale (see details in [1]). Then we formulate the Principle of Multi-scale of Virtual Power, which can be seen as a generalized version of the Hill-Mandel principle of macro-homogeneity as follows.

**Principle of Multi-scale of Virtual Power.** Given \( \mathbf{G}_{|\mathbf{x}} \in \mathbb{U} \), the macro-scale stress tensor \( \mathbf{P}_{|\mathbf{x}} \), is in mechanical equilibrium with the network stress state, \( \{\mathbf{S}_\mu^\alpha\}_{\alpha=1}^m \), if the following variational equation is satisfied

\[ \mathbf{P}_{|\mathbf{x}} \cdot \mathbf{G}_{|\mathbf{x}} = \frac{1}{|\Omega_\mu|} \sum_{\alpha \in \mathcal{F}_{\text{net}}} V_\alpha \mathbf{S}_\mu^\alpha \cdot \mathcal{D}_\mu^\alpha(\mathbf{G}_{|\mathbf{x}}, \mathbf{\tilde{u}}_\mu) \quad \forall (\mathbf{G}_{|\mathbf{x}}, \mathbf{\tilde{u}}_\mu) \in \mathbb{V} \times \mathcal{W}_\mu. \quad (4)\]

Where \( \mathcal{D}_\mu^\alpha(\cdot, \cdot) \) is a appropriate deformation measure for a single fiber \( \alpha \), \( V_\alpha \) is the fiber volume, \( |\Omega_\mu| \) is the RVE volume (including empty space), \( \mathbb{U} \subset \mathbb{R}^{n_d \times n_d} \) (\( n_d \): spatial dimensions) is an admissible nonlinear manifold that takes into account the macro-scale incompressibility constraint and \( \mathbb{V} \subset \mathbb{R}^{n_d \times n_d} \) is its tangent space.

One of the consequences of this principle is the following homogenization formula for the macro-scale stress tensor

\[ \mathbf{P}_{|\mathbf{x}} = \frac{1}{|\Omega_\mu|} \sum_{\alpha \in \mathcal{F}_{\text{net}}} V_\alpha \mathbf{S}_\mu^\alpha, \quad (5)\]

where \( \mathbf{S}_\mu^\alpha = s_\mu^\alpha \otimes \mathbf{a}_\alpha \), being \( \mathbf{a}_\alpha \) the direction vector of the fiber and \( s_\mu^\alpha \) is a stress-like vector given constitutively. Another consequence is the problem to be solved at the RVE.
(Micro-scale mechanical equilibrium). Given $G|_x \in U$, find $\hat{u}_\mu \in \widehat{\mathcal{U}}_\mu$ such that the following variational equation holds

$$\sum_{\alpha \in \mathcal{F}_{net}} A_\alpha s^\alpha_\mu \cdot \Delta^\alpha \hat{u}_\mu = 0 \quad \forall \hat{u}_\mu \in \widehat{\mathcal{U}}_\mu,$$

(6)

where $A_\alpha$ is the cross-section area of the fiber, $\Delta^\alpha$ means a difference between nodes values of the fiber and finally, $s^\alpha_\mu$ is related to $D^\alpha_\mu(G|x, \hat{u}_\mu)$ through a micro-scale constitutive functional of the form $s^\alpha_\mu = \tilde{s}^\alpha_\mu(D^\alpha_\mu(G|x, \hat{u}_\mu)).$

We can also prove that the homogenization formula given in (5) is equivalent to

$$P|_x = \frac{1}{|\Omega_\mu|} \sum_{i \in \mathcal{N}_{net}} t^i \otimes y^i.$$

(7)

where $\mathcal{N}_{net}$ is the of nodes along the RVE boundary, $t^i$ is a traction vector function only of the fibers stress states at the node $i$.

(Remark). The relation (7) may be understood as the discrete counterpart of the well known homogenization formula for stress based on boundary data in classical continuum mechanics that reads (see [2])

$$P = \frac{1}{|\Omega_\mu|} \int_{\partial \Omega_\mu} t \otimes y \, d\partial \Omega_\mu,$$

(8)

where $\Omega_\mu$ is the RVE domain, with boundary $\partial \Omega_\mu$, and $t$ is the traction vector over the boundary.

3 FINAL REMARKS

In this short communication we have reviewed the main features of our multi-scale model for fibrous tissues. This is the basic methodology from which the numerical examples will be presented in the conference. We highlight that this is a novel approach where the micro- and macro-scale kinematics linking is clearly stated and the stress homogenization formula is a straightforward consequence from basic principles and the kinematical setting. The both contributions are a depart from previous approaches of the field.

REFERENCES


Preliminary Investigations on Scaling Laws for Lipid Monolayers Instabilities on Lung Surfactants

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SUMMARY

Surfactants at air/water interfaces in lungs are subject to cyclic dynamical straining during breathing. In this work, preliminary studies towards an understanding of the collapse mechanisms exhibited by lipid monolayers on lungs surfaces affected by pathologies such as Adult Respiratory Distress Syndrome-ARDS are presented. Resulting stress relaxation must be characterized to capture the essential features of such collapses. These arise in the form of large buckled regions of the surfactants at the lung interfaces. The current predictions based on Molecular Dynamics do not relate collapse through bending at the observed experimental scales, although they qualitatively are in agreement with them. Henceforth, a predictive strategy that can provide the right scalings is still missing. A platform owing the first insights on the scalings and the length scales involved in such phenomena is envisioned as a thin film mimicking the lipid monolayer on a viscous substrate.

Key words: Lipid monolayers, lungs collapse mechanisms, lung surfactants

1 INTRODUCTION

This preliminary work is part of parallel researches on scaling laws of lipid films experiencing mechanically and thermally induced instabilities. Such structures are encountered in surfactants at air/water interfaces [1]. These systems often undergo mechanical stresses because of the reduction in area of the interfaces that they cover. This is an issue appearing during the breathing cycle, as the surface area on lungs does experience very significant cyclic changes. As the interface is covered by surfactant, such area changes will place mechanical stress on the surfactant layer. Because interfacial stability relies on surfactant stability at the interface, there is substantial interest in understanding how the surfactant layer responds to stress.

The most well characterized forms of stress relaxation in these systems are first or-order phase transitions from lower density to higher density phases. Here we study stress relaxation in lipid monolayers that occurs once chemical phase transitions have taken place. At these highly compressed states, the monolayer undergoes global mechanical relaxations termed collapse. Our experimental studies on different types of monolayers, allowed for determining a correlation between in-plane rigidity of the monolayers and buckling-like collapse modes [2]. Such rigidities can be characterized by analyzing in-plane morphology on numerous length scales.

The phenomenon described above does not happen in functioning lungs. Indeed, optimal conditions entail lungs to keep very large and non-broken surfaces across which gas exchange can occur. Such surfaces are maintained by surfactants stabilizing interfaces that otherwise would have very high energies. Surfactants must cyclically (dynamically) adjust, and so their density, to keep their role of stabilizers even during large and continuous expansions and contractions.
The first order thermodynamic phase transitions entails changes from lower to higher densities whenever area squeezing occurs, while the reversed transition is encountered during area expansions.

Whenever lungs diseases like Adult Respiratory Distress Syndrome-ARDS are present, surfactant collapses are known to occur. Such mechanisms can be seen as a mechanical phase transitions for the system, and they happen when in-plane phase transitions have been exhausted as a means of relaxing compressive stresses and in-plane stresses build-up in the surfactant covered interface. Out-of-plane buckling become favorable mechanisms to reduce those stresses, thereby leading to folding.

Here we will present preliminary results on the scalings of the onset of buckling zones, the precursors of folds. This happens in particular in solid-like behaving interfaces. Indeed, experimental data show the tunability of collapse structures with sub phase composition [2]. For instance this happens by adding glycerol to the sub phase induces a monolayer stiffening, thereby exhibiting a solid-like behavior.

Although successful Molecular Dynamics simulations predict similar instances at very low length scales (10 nm, see [3]), the collapse mechanisms described above arise at much larger ones. A platform based on the work in [4], [5], [6] explaining the reasons why this is the case can be singled out as a semi-solid elastic thin film deposited on a viscous monolayer and subject to imposed squeezing. An argument based on the film inextensibility and on the balance of the power expended on the film and on the viscous substrate delivers preliminary results on the scaling sought.

REFERENCES


Cardiovascular Mathematics:
From the Computer Room to the
Bedside II
VIRTUAL ENDOGRAFT DEPLOYMENT IN THE THORACIC AORTA AS A PREDICTOR OF TEVAR MIGRATION

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SUMMARY

Thoracic endovascular aortic repair (TEVAR) is a consolidated technique to treat aneurysmatic aorta. Endograft migration is one of the most common complications found in follow-up studies. In four patients of our iCardioCloud database which underwent TEVAR, drag force might be an indicator of late endograft migration. We propose a virtual deployment procedure combined with computation of blood flow to predict the haemodynamics of the stented aorta and post-operative drag force. Good agreement is found between the real and predicted haemodynamics. Computational tools can reliably predict the outcomes of TEVAR and special attention has to be paid to drag forces.

Key words: TEVAR, CFD, virtual surgery, drag force

1 INTRODUCTION

Thoracic Endovascular Aortic Repair (TEVAR) is a consolidated procedure to treat thoracic aortic diseases such as aneurysms [1] and dissections [2]. The procedure is performed through a catheter-guided deployment of one or more stent-grafts, which are metallic tubular structures covered by a polymeric skirt.

Complications after TEVAR are related both to the sub-optimal apposition of the device to the aortic wall [3] and to post-operative haemodynamics resulting in endoleaks, migration or collapse of the stent-graft and development of a false aneurysm [4].

Such clinical complications are linked to the mutual interactions between the aortic wall, the stent-graft, and the haemodynamics, which are unfortunately not yet taken into account during the pre-operative planning. Motivated by these considerations, we developed a computational framework which is able to predict the post-TEVAR haemodynamics by combining medical image analysis, structural finite element analysis (FEA) and Computational Fluid Dynamics (CFD). The motivation for this approach is a first finding on a subset of four patients from our iCardioCloud database treated for thoracic saccular disease. When drag force (DF) was calculated in the stented region, only the one with the highest covered area and DF presented stent migration in a 1 year follow up.

In our proposed framework, we tackle the three main steps: realistic simulation of the stent-graft deployment by structural FEA, creation of a CFD-suitable domain based on FEA outcomes based on image distance and CFD analysis to compute post-TEVAR haemodynamics. Although such a framework is designed to be general, allowing to predict the implant of a given prothesis in a given position for a given patient, the present study proposes the analysis of a real clinical case, which allows us to compare the simulation and the post-operative reality to validate our approach.
2 METHODOLOGY

2.1 Patient selection and image segmentation
Four patients with thoracic aortic disease who underwent TEVAR were selected from our iCardioCloud database. Computational Tomography Angiography (CTA) was segmented with the software suite VMTK [5] in order to obtain the 3D reconstruction of the thoracic aorta.
In two of the patients (#1 and #2) only one endograft was placed by the surgeon whereas in the other two (#3 and #4) four of them were used due to the extension of the disease. Figure 1 shows the pre and post-operative geometries of all the patients. Additionally, follow-up imaging one year after the procedure was retrieved from the hospital.

Figure 1: Pre (top) and Post (bottom) operative 3D reconstructions of the thoracic aorta in four patients from the iCardioCloud database.

2.2 Mesh generation and Computational fluid dynamics
The post-operative computational domains were meshed with the software suite VMTK and tetrahedral meshes of 1.5M to 2.5M elements were constructed. The Navier-Stokes equations were solved using the lifeV software [6] and blood flow was simulated for 6 cycles. Blood’s viscosity was 3.5 cP and density 1.06 g/cm$^3$. The boundary conditions were in all cases patient-specific, using each patient’s flow wave retrieved from PC-MRI in the ascending aorta and 3 element Windkessel circuits in the outflow vessels.
The DF and surface area were calculated in the portion of the aorta where the prosthesis/es were deployed based on the pressure and WSS fields retrieved from the CFD.

2.3 Virtual deployment procedure
Following the procedure described in [7] a model of the stent-graft selected by the surgeon was created to define a mesh suitable for structural FEA.
The set-up of the input file for the structural FEA was supported by an in-house developed Python script allowing the user to select a given endograft model from the predefined design library and proximal landing point. The numerical analysis was non-linear involving large deformations and contact; we use Abaqus/Explicit (Simulia, Dassault Systemes, Providence, RI, USA) as finite element solver. As described earlier by our group's work [7], first the endograft was crimped by a catheter and curved from a straight position to the vessel's centerline. In this step, the catheter and the struts of the prosthesis have a frictionless contact interaction. Once the stent is in place, a uniform (or stepwise) enlargement of the catheter surface along its length allows the endograft re-expansion to simulate its deployment; in this step of the analysis a (frictionless) contact pair between the stent struts and the luminal surface of the artery is activated. Figure 2 shows the steps of the deployment. Patient #1 was chosen for the virtual procedure due to its geometrical simplicity as a test case.
2.4 Virtual geometry generation

To combine the aorta with the virtually deployed stent, we constructed two distance images of 0.4 mm x 0.4 mm x 0.4 mm for each of the surfaces in order to have enough spatial resolution to capture the stent's volume. A distance image is an image in which, for each voxel, the value of the distance of that voxel from a reference surface is stored. For the aorta the distance image assumes negative values inside the aorta, positive outside and zero on the aortic surface. For the volume stent, the distance image was computed with positive values inside the 'volume' of the stent and negative outside. The two images are combined using the maximum operator in order to obtain a final image with negative values inside the lumen and positive values both outside the lumen and inside the stent. The resulting image is segmented extracting the negative values with a region growing method with a seed inside the lumen; in this way, only the regions in which the blood can flow are included in the final geometry. Finally, the obtained solid model is turned into a volumetric mesh of linear tetrahedral elements with VMTK software suite, in order for CFD simulations to be carried out.

3 RESULTS AND CONCLUSIONS

Drag forces and surface areas can been seen in table 1. Furthermore, an image showing the stent-graft migration for patient #4 together with the modulus and direction of the drag force are illustrated in figure 3.

<table>
<thead>
<tr>
<th>Surface area [cm²]</th>
<th>Drag force [N]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>Patient 2</td>
</tr>
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<td>104</td>
<td>109</td>
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Table 1: Covered surface area and drag force in the four analyzed patients.

Figure 3: Post-operative (left) and 1 year follow up (right) CTA scans of patient #4 showing distal endograft migration. Modulus and direction of the drag force in the systolic peak (center).
The qualitative comparison between the haemodynamics of patient #1 are shown in figure 4. In particular, drag forces were compared and a difference of 13% is found.

Figure 4: CFD comparison between the real post-operative haemodynamics and the virtually predicted geometry.

From the results shown, we can confirm that drag force needs special attention in order to predict late endograft migration. Naturally, a bigger cohort of patients is needed to confirm this finding. The procedure we proposed shows that an appropriate FEA simulation together with CFD can reliably predict the haemodynamics of TEVAR. Further work needs to be done in order to deploy multiple stents in the same aorta.

REFERENCES


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ASSOCIATION BETWEEN WALL SHEAR STRESS AND CLINICAL CORONARY ARTERY DISEASE PROGRESSION – DO EVALUATION METHODS DRIVE CONCLUSIONS

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SUMMARY

Computational fluid dynamics (CFD) modeling is increasingly moving from a research tool to a methodology for guiding patient management and informing clinical management decisions, particularly in cardiovascular medicine and patients with coronary artery disease (CAD). Indeed, much focus has centered on developing hemodynamic-based prognostic measures to identify high-risk (vulnerable) lesions, which may warrant pre-emptive treatment. Herein, we discuss our recent efforts in developing patient-specific computational models to evaluate the association between wall shear stress (WSS) and CAD progression, with particular focus on evaluating the employed analysis methods and understanding inherent limitations that may lead to data misinterpretation.

Key words: coronary artery disease, hemodynamics, intravascular ultrasound, wall shear stress

1 INTRODUCTION

Acute coronary syndromes are a significant clinical problem, not only because of their frequency (>1.1 million annually in America), but also due to the diagnostic challenge in the early detection of rupture prone atherosclerotic plaques (i.e., vulnerable plaques). Image-based prognostic markers for identification of vulnerable plaques have demonstrated poor predictive value for major adverse cardiovascular events [1]. Furthermore, recent clinical data provide strong evidence that lesions attributed to ACS undergo rapid progression prior to myocardial infarction, suggesting that plaque risk-stratification strategies should focus on identifying the contributing factor(s) for rapid CAD progression to determine the coronary lesions at highest risk for rupture.

Given the known correlation between near-wall flow patterns and the non-uniform distribution of coronary lesions, considerable focus has been directed at developing computational methods to quantify the patient-specific coronary hemodynamic environment and, more recently, evaluating the prognostic utility of hemodynamic metrics in identifying rapidly progressing CAD and plaque vulnerability. Accordingly, prospective clinical trials evaluating the prognostic value of WSS in determining the characteristics of intravascular ultrasound (IVUS) defined CAD progression have been performed [3,4,5]. Although these studies have provided critical insight on the complex relationship between WSS and CAD progression in the clinical setting, the employed analysis methods markedly differ by the degree of spatial averaging of the computed hemodynamic data and localized association between WSS and CAD progression. As spatial accuracy and specificity are required when identifying rupture prone coronary lesions, particularly as pre-emptive treatment are considered, careful understanding of the impact that employed analysis have data evaluation and interpretation must be carefully address.
In this study, we examined differences between previous employed analysis methods that evaluated the association between WSS and CAD progression in the clinical setting. In addition to evaluating the characterized hemodynamic environments when employing these methods, we also examined the association between WSS and CAD progression.

2 IMAGE-BASED MODELING

2.1 Clinical image acquisition

Patients (n = 20) enrolled in a previously described prospective study that evaluated the association between WSS and virtual histology-IVUS (VH-IVUS) defined plaque progression were included in this investigation. The enrollment criteria and clinical data acquisition methods have been previously described in detail [3]. Briefly, patients presenting with an abnormal noninvasive stress test or stable angina and determined to have a non-obstructive lesion requiring physiologic evaluation were enrolled. Patients underwent baseline and 6-month follow-up catheterizations to collect biplane angiography, VH-IVUS images of the proximal left anterior descending coronary artery, and Doppler derived velocity data. The Institutional Review Board at Emory University approved the study, and each patient provided informed consent.

2.2 Geometry reconstruction and CFD modeling

The patient-specific CFD modeling techniques employed have been previously described in significant detail [3, 5]. Briefly, the end-diastolic 3-dimensional (3D) lumen geometry was created by fusing biplane angiographic and segmented VH-IVUS image data. The diameter and spatial orientation of major branching coronary vessels were identified in the image data and included in the reconstruction of the indexed vessel. A volume was created from the resulting lumen point cloud (Geomagic Studio 11), flow extensions were added, and the volume was discretized with tetrahedral and prismatic elements (ICEM CFD, ANSYS, Inc.). The computational mesh was imported into a commercial software package (Fluent, ANSYS, Inc.) to numerically solve the Navier-Stokes and continuity equations. Patient-specific pulsatile velocity data were digitized from the intracoronary velocity acquisitions and applied as a series of spatially uniform profiles at the model inlet. Outlets were assumed traction-free, and a no-slip boundary condition was applied at the rigid wall. Blood was assumed to be an incompressible Newtonian fluid with a density and dynamic viscosity of 1060 kg/m$^3$ and 3.5 cP, respectively. Following solution convergence, nodal WSS vectors were extracted across the cardiac cycle. Data were post-processed to quantify time-averaged WSS (TAWSS) and WSS angle deviation (WSSAD), a measure of temporal vector oscillation, across the cardiac cycle.

2.3 Analysis of hemodynamic data and focal plaque progression

Three previously employed analysis methods were utilized to characterize the baseline hemodynamic environment (Fig. 1). First, hemodynamic data were evaluated in consecutive 3 mm coronary segments, which encompassed 6 VH-IVUS images (0.5 mm between images; herein, segment method [4]). Segments were divided into quarter cylinders, hemodynamic data (TAWSS, WSSAD) were averaged within each quarter cylinder, and the minimum values of TAWSS and WSSAD were assigned to the entire segment. Second, hemodynamic data were extracted at the location of each acquired VH-IVUS image, and data were spatially averaged around the lumen circumference (herein, circumferential method; [3]). Third, extracted cross-sectional hemodynamic data were divided into 8 focal regions, and data were averaged within each region (herein, sector method; [5]). Note that all
hemodynamic data comparisons were performed at the sector level. Thus, while there were 8 values of, for example, TAWSS per cross-section by employing the sector method, the same spatially (circumferentially) averaged hemodynamic value was assigned to all 8 sector per cross-section for the circumferential method. Similarly, hemodynamic values identified utilizing the segment method were assigned to all sectors in the 6 VH-IVUS images within a defined segment.

Baseline and follow-up VH-IVUS images were co-registered in the axial and circumferential directions with the aid of anatomic markers and a developed and validated multivariate cross-correlation algorithm [6]. Changes in VH-IVUS defined total plaque and constituent (fibrous tissue, fibrofatty tissue, necrotic core, dense calcium) areas were quantified in focal regions (sectors) by taking the difference between corresponding sectors in co-registered images. Although hemodynamic parameters are continuous and dynamic variables, data were classified to aid in establishing an association between WSS and CAD progression. Accordingly, TAWSS values were defined as low (<10 dynes/cm²), intermediate (10-25 dynes/cm²), and high (>25 dynes/cm²). Likewise, WSSAD values were classes as low (<45º), intermediate (45-90º), and high (>90º). Finally, sectors where low TAWSS and high WSSAD co-localized (i.e., low and oscillatory WSS) were identified.

3 RESULTS AND CONCLUSIONS

Examination of the computed hemodynamic data with the three analysis methods yielded significant differences in evaluated values. The segment, circumferential, and sector methods yielded TAWSS values of 16.30 ± 11.25 dynes/cm², 26.11 ± 16.82 dynes/cm², and 24.78 ± 20.31 dynes/cm², respectively (p < 0.01). Moreover, the range of reported TAWSS values were greatly affected by employed method, as the segment, circumferential, and sector methods resulted in TAWSS ranges of 65.95 dynes/ cm² (1.84 – 67.79), 115.55 dynes/ cm² (2.15 – 117.70), and 362.60 dynes/ cm² (1.02 – 363.62), respectively. Similar differences between the analysis techniques were also observed when examining the WSSAD values, as the segment, circumferential, and sector methods yielded WSSAD values of 9.35 ± 11.69°, 26.75 ± 26.59°, and 26.23 ± 39.55°, respectively (p < 0.01). Finally, the range of WSSAD values varied considerably between the analysis methods with ranges of 110.81° (0.41 – 111.22), 123.98° (0.61 – 124.59), and 178.20° (0.22 – 178.43), respectively.

Notable differences were also observed across the segment, circumferential, and sector analysis techniques when comparing the association between hemodynamics and CAD. For example, the segment method demonstrated regression of total plaque area (i.e., reduction in area across 6-month follow-up) across all baseline TAWSS environment; however, the circumferential and sector methods resulted in total plaque area progression in areas of low TAWSS, but regression of total plaque area in areas of intermediate and high TAWSS. Distinct differences were also observed in areas characterized by low and oscillatory WSS (Fig. 2). Employing the segment or circumferential methods, we observed regression of total plaque, fibrous, and necrotic core tissues; yet using the sector method, we observed regression of total plaque, fibrous, and fibro-fatty tissue, but progression of necrotic core and dense calcium, which suggests a phenotypic transformation towards a more vulnerable plaque.

In conclusion, our study demonstrates the critical importance that employed analysis methods have when characterizing the coronary hemodynamic environment. Furthermore, it highlights that careful understanding of the impact that spatial averaging has on focal metrics should be considered when interpreting results, particularly when evaluating the association between WSS and CAD. Future clinical investigations that employ advanced analysis methods are warranted and have the potential
to advance the prognostic utility of patient-specific CFD modeling in the early identification of high-risk coronary lesions.

4 ACKNOWLEDGEMENTS AND FUNDING

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REFERENCES

FINITE ELEMENT ANALYSIS OF A NEW TYPE OF POST DILATATION BALLOON CATHETER IN PCI

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SUMMARY

At present, percutaneous coronary intervention (PCI) is the most effective treatment of coronary heart disease (CHD). Unfortunately, the tip of the post-dilatation balloon catheter cannot smoothly pass through curved vessel (with a stent in it). According to a newly proposed catheter, 3D CAE models were constructed. Finite element analysis of the proposed catheter model and the traditional catheter model are implemented when they pass through curved vessel with a stent in it. The contact force and strain distribution were compared and then evaluation will be made of its clinical application.

Keywords: finite element analysis, post dilatation, stent, catheter

1 INTRODUCTION

In recent years, the incidence and mortality of coronary heart disease (CHD) have increased significantly. It is estimated that by 2020, the death rate of coronary heart disease will increase by 50% (approximately 25 million people per year) [1]. Percutaneous coronary intervention (PCI) has the advantages of short course of treatment, less trauma and obvious curative effect, which is the most effective treatment of CHD [2-3]. Post dilatation of balloon refers to dilating the balloon again by using a higher pressure than the implanting pressure in the stent after firstly implanting the stent to ensure the complete attachment between the stent and vascular wall, which reduces the probability of thrombosis in the stent and the rate of restenosis after operation. The tip of the post-dilatation balloon catheter in clinical is the same as predilatation catheter. It is like a cone which is conducive to the catheter passing through the narrow lesion site. But this type of catheter’s tip is always stuck in the stent because of the
existence of the step-like structure (Fig. 1D). It may cause stent deformation, lead to acute myocardial infarction and even induce death of patients. A new type of balloon catheter with a spherical tip was proposed (Fig. 1C) [4]. The aim of this study is to test the performance of the new type of catheter by performing finite element analysis in Abaqus. The stent deformation and contact force between these two catheter tips and stent surface were analyzed. The performances of the new and traditional catheter are compared. In-vitro experiments will be conducted to verify the results of the simulation.

2 METHODOLOGY

The 3D CAE models of stent, catheter, guide wire and vessel are constructed and assembled. The radius of curvature of the stent and vessel is 10 mm. The assembled models are in Figs. 1A-B. The dimensions and structure of the two catheter tips are shown in Figs. 1C-D.

![Figure 1: three-dimensional models](A) New type of balloon catheter model; (B) traditional balloon catheter model; (C) new type of balloon catheter tip; (D) traditional balloon catheter tip.

These geometries were imported into ABAQUS v6.13 [5-6]. The mechanical properties of each component in the model were listed in Table 1. To mimic the situation in clinical application, we assumed two ends of the vessel as fixed in the computational model. The vessel and the stent are tied. Surface to surface contact was set between the outer surface of the catheter and the inner surface of the stent. The friction coefficient of this contact was considered as 0.3 according to the material properties. The other contact pairs are all general contact. The catheter moves along the guide wire and passes through curved vessel with a stent in it.

| Table 1 Parameters of the materials in the proposed model [7] |
|---------------------------------|-----------------|-----------------|
| Stent                           | 24500           | 0.33            | 6.45            |
| Catheter tip                    | 1500            | 0.3             | 1.07            |
| Catheter                        | 3600            | 0.3             | 1.15            |
| Guide wire                      | 180000          | 0.3             | 7.8             |
| Blood vessel                    | 2               | 0.3             | 1               |
3 RESULTS AND CONCLUSIONS

Fig. 2 shows that the new type of catheter passes through stent easily (Figs. 2A-C), while the traditional catheter cannot pass it through under the same conditions (Figs. 2, D-F). The deformation of stent caused by the traditional catheter is much larger than that caused by the new type of catheter, which exactly validates the design idea. The vessels were hidden in Fig. 2 A-B, D-E in order to display the results more clearly.

Figure 2: Visualizations of FEA for the postdilatation.

(A) The stress distribution of new catheter, T=0.8s; (B) The stress distribution of traditional catheter, T=0.8s; (C) The stress distribution of new catheter, T=1.1s; (D) The stress distribution of traditional catheter, T=1.15s; (E) The cutaway view of the new catheter model; (F) The cutaway view of the traditional catheter model.

Shown in Fig.3 is the total force between the tip and stent of the two models. The Maximum value of the force from the traditional model is 2.3N, which is much larger than 0.54N in the new catheter model. It is indicated that this new type of catheter will be easier to pass through curved vessel (with stent in it) than the traditional one. The force of the traditional catheter model decreases after reaching the highest point because the tip of the catheter passes through the stent surface after the large deformation of the stent.
In this study, finite element analyses of a newly proposed balloon catheter model and traditional catheter model are implemented under the condition of passing through the curved vessel (with stent in it). By comparison, we can conclude that the novel catheter outperforms the traditional catheter in this process. The output from this study can provide the important implication for clinical application of the newly developed catheter. In future work, in vitro experiment will be conducted, in which the contact/frictional force will be measured using Fiber Bragg Grating (FBG) sensors to validate the computational model in this study.

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5 REFERENCES

SURFACE AND VOLUMETRIC MESHING OF STENTED LUMENS USING CGAL

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SUMMARY

In this work, we present the use of the geometric capabilities of the Computational Geometry Algorithms Library (CGAL) on processing polyhedral patient-specific representations of bioresorbable stents embedded in their lumen. We focus on the preservation of the sharp features of the geometry (i.e., the stent salient edges) to treat the input surface and its volumetric meshing. Finally, we present computational fluid dynamics results and the importance of sharp geometric features on the flow and wall shear stress.

Key words: Bioresorbable stent, Meshing, Computational Hemodynamics, CGAL

1 INTRODUCTION

Cardiovascular Artery Diseases (CAD) are a leading cause of death (up to 25\% of all death). In particular, CAD may lead to heart attack due to coronary narrowing due to atherosclerosis. Two major treatments are available: 1) Coronary Aortic By-pass Graph (CABG), by rerouting bloodflow distal to the stenotic part of coronaries, and 2) Percutaneous Coronary Intervention (PCI), which consist the revascularization of the stenotic lumen by angioplasty and often a stent is introduced to prevent blockage from happening. After revascularization and if a stent is used, the flow of blood is perturbed by the presence of the stent struts, which appears as small obstacle inside the lumen (see Figure 1b).

The study of the impact of stents on bloodflow is of primary importance in order to evaluate their effect and to design them. Most often in-vivo and in-vitro studies are very expensive and difficult, if not impossible to perform. For these reasons, in-silico approaches, such as Computational Fluid Dynamics (CFD), have become extremely popular in medical research. Many stents design are present on the market today, composed of different materials (e.g., metallic or polymeric) and shapes (such are, circular or squared cross sections).

In particular, stent geometry is of primary importance, and therefore accurate stent reconstruction and meshing is fundamental for computational hemodynamics studies in stented vessels.

In a previous work, the Emory Task Force in Cardiovascular Mathematics has developed a technique to reconstruct, after PCI, patient-specific Bioresorbable Stents (\(^1\)) from several medical imaging techniques. Particular features of these stents are: thick struts (with respect to metallic ones) and box shaped cross sections.

Box shaped cross sections calls for a particular attention from the fluid dynamics point of view since they introduce singularities in the fluid domain. Indeed, it is well known (see, e.g., [2]) that such singularities will lead to more significative flow recirculation, proximal and distal to the stent struts. Such flow patterns are of clinical importance since they may induce thrombus formation [5]. For these reasons, particular attention has to be devoted to the preservation of such features while performing surface and volumetric reconstruction of stented vessel with bioresorbable scaffolds.
The Computational Geometry Algorithms Library (CGAL) [3] offers multiple facilities to deal with polyhedral surfaces, as well as meshing capabilities with a focus on features preservation. In particular, we will show an implementation of an automatic strut detection system, isotropic surface remeshing, Laplacian smoothing, mesh repair, and volumetric meshing of the stented lumen with a focus on automation. We will also show the impact of several meshing strategies on the CFD calculations performed using finite elements with the library LifeV [4]. Furthermore, attention will be on Wall Shear Stress (WSS) calculations, since it is well known now that WSS has a significant impact on plaque progression and necrotic core progression (see, e.g., [6]).

2 METHODOLOGY

Any numerical simulation requires a computational domain. In this work we follow the standard approach that consists in, first, constructing a polyhedral representation of the boundary of the domain and, second, perform the meshing of the interior of that domain.

2.1 Stented Vessel Surface Reconstruction

The stented vessel boundary is composed of two parts: 1) the lumen and 2) the stent. Conceptually, the computational domain is the boolean difference of the lumen and the stent (see Figure 1).

![Figure 1: Stent and Lumen prior to boolean difference.](image)

Boolean operations of polyhedral surfaces are notoriously known for being difficult due to round-off errors. Fortunately, CGAL provides Nef polyhedral mechanism that allows for robust boolean operations. However, ill-shaped triangles are introduced near the intersection of the lumen and the stent. CGAL allows for isotropic remeshing via the Polygon Mesh Processing module. Special care has to be taken in order not to be smoothed by the remeshing (see Figure 2). CGAL’s isotropic remeshing provides two important functions: feature preservation (edge or vertex based) and polyline tangential relaxation (i.e., polyline endpoints remains fixed but intermediate segment vertices are allowed to move tangentially to the polyline). The struts features are automatically detected using the faces dihedral angles. Indeed, the domain is smooth everywhere except at the intersection of the stent and the lumen, as well as the stent salient edges inside the lumen (see Figure 2b).

If required the same approach for the struts features detection can be used to smooth the obtained surface using a Laplace-Beltrami type smoothing for example, while protecting the features. Our experience shows that the isotropic remeshing in CGAL may introduce self-intersection triangles even if the initial surface is manifold. To treat this problem we may use self-intersection removing mechanics. CGAL has such a mechanism implemented, see [7] for a review on polyhedral mesh repairing.

As discussed earlier, the approach of building a closed polyhedral surface and then mesh the enclosed volume. As such, this section can be used by many volumetric mesher. However, CGAL offers and tetrahedral volumetric capabilities, which we present in the next section.
2.2 Stented Vessel Volume Reconstruction

Once we have a correct closed surface, we can now build its volumetric counterpart. Unlike most volumetric mesher, CGAL mesher \[8\] does not maintain exactly the input surface but it only approximate it to a target value defined by the user. Furthermore, CGAL mesher allows for feature preservation, which can either be provided by the user or automatically detected, as performed previously. The feature preservation mechanism is based on the method of protecting balls (see \[9\]). As with the polyline tangential relaxation presented in the previous section, the protection ball method allows for relaxing the constrained features (in our case edges) and thus it reduces the impact of potential noises near the selected edges. The approximation of the constrained creases is controlled by the user who can specify a target edge length. Such a feature is also possible while performing a surface isotropic remeshing. An example of remeshing with Tetgen \[10\] and CGALmesh is presented in Figure 3.

![Remeshing with CGAL and Tetgen](image)

Figure 3: Example of a volumetric meshing. The initial surface is identical to the boundary of the Tetgen mesh.

3 RESULTS AND CONCLUSIONS

We now show some CFD results obtained using the mesh presented in Figure 4. Our use of the geometric capabilities of CGAL allows us to perform very accurate simulation as it can be seen by the presence of flow recirculation around the stent struts (see Figure 4a). We also obtain precise WSS on the struts (see Figure 4b) as described in \[11\] on a straight tube with an overkill mesh.

Additional discussions will concern, inter alia, automation process, a critical point for use in medical research over large pools of patient, boundary layer generation, and user parameters and mesh sizes.

In this work, we followed the standard approach of first generating a polygonal surface and then mesh its enclose volume. However, CGALmesh allows for using different input, such as level-set surfaces from 3D medical images. Such a capability of the mesher opens new possibilities for our research.
Figure 4: CFD results obtained using Emory Task Force in Cardiovascular Mathematics Finite Element incompressible transient Navier-Stokes solver using XSEDE resources.

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SIMVASCULAR: AN OPEN SOURCE PIPELINE FOR PATIENT-SPECIFIC IMAGE-BASED CARDIOVASCULAR SIMULATION

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SUMMARY

We present a fully open source software package, SimVascular, which covers the complete cardiovascular simulation pipeline, including medical image segmentation, anatomic modeling and patient-specific blood flow simulation. This package has contributed to numerous advances in personalized medicine, surgical planning and medical device design. Recently, SimVascular has been revitalized to enhance functionality, extensibility, usability, efficiency and accuracy of image-based modeling. We have replaced all previously required commercial components with open source alternatives, and introduce a new software architecture with an improved graphical user interface (GUI), data manager, and improved easy-of-use. These advances are intended to foster cardiovascular modeling research, clinical collaboration, and support our growing user community.

Key words: cardiovascular, patient-specific CFD, hemodynamics, open-source

1 INTRODUCTION

Cardiovascular disease is the leading cause of death worldwide. Local blood flow disruptions play a critical role in both the causes and consequences of cardiovascular disease. Three-dimensional modeling and simulation of cardiovascular hemodynamics can provide invaluable data to augment clinical imaging and predict outcomes of surgical interventions for individual patients [1]. However, cardiovascular patient-specific simulation requires a complex multi-step process of image segmentation, meshing, flow simulation, and analysis, which is often daunting for the user. To meet these needs, SimVascular (www.simvascular.org) was developed originally in the lab of Charles Taylor at Stanford University and first publicly released in 2007. It has been used to create a publicly available repository of over 100 clinical cases (www.vascularmodel.org) representing different parts of the vasculature.

Several major barriers prevented initial widespread adoption of SimVascular by new users and limited its educational use as well as applicability to large-scale clinical and research studies. Barriers included: 1) the cost and complications associated with three embedded and required commercial components, 2) the overall complexity of image-based blood flow simulation, and 3) a lack of organized maintenance, documentation, and support. To overcome these barriers, the SimVascular revitalization project was launched in 2013 [2]. Here, we present its major features and recent advances, with focus on the recent re-design of the software architecture and graphical user interface.

2 METHODOLOGY

2.1 SimVascular Architecture
The architecture of SimVascular is summarized in Fig. 1. Using CMake, our team has simplified the compilation process for SimVascular to support users across all major platforms: Linux, Windows and Mac OS X. Though we continue to internally support select commercial components (Parasolid and MeshSim), SimVascular is now fully open source by integrating open source alternatives including: OpenCASCADE, MMG, Vascular Modeling Toolkit (VMTK), Tetrahedral Mesh Generator (TetGen), and the SimVascular Linear Solver (svLS). An improved documentation website (simvascular.org) has been launched, including software guides and clinical case study examples.

2.2 SimVascular Application

The SimVascular Application is developed using Medical Imaging Interaction Toolkit (MITK), and provides a friendly and clean GUI (Fig. 2) that loads SimVascular and MITK plugins dynamically. The plugins contain various tools for image visualization/processing, modeling, meshing, simulation and so on. The Data Manager uses a project format to organize all the data for one simulation case and provide the user with easy access to the associated data and tools. An undo/redo feature enables users to restore data to the previous states. The SimVascular Application greatly enhances the interactive environment to let users handle data more efficiently, and simplifies the procedures required for the modeling/simulation pipeline.
2.3 SimVascular Pipeline

SimVascular provides a complete pipeline for the process of cardiovascular modeling and simulation. Fig. 3 shows the typical steps of image-based modeling in SimVascular, although alternative and additional steps may be employed.

![SimVascular pipeline](image)

**Figure 3. SimVascular pipeline. Adapted from Ref. 2.**

**Image Handling:** Image data can be loaded from a variety of sources, including DICOM, VTK, MetaImage and other file formats. The Wokbench offers a number of tools to view and manipulate the data in 2D/3D space in the multi-view Display, in reslices or by volume rendering.

**Path Planning:** A vessel path (centerline) is defined by a set of control points. Users are able to easily locate center points based on vessel cross section using the multi-view Display. Image can also be resliced along a vessel path to enable users to check the quality and modify the path.

**Image Segmentation:** SimVascular enables creating contours of the vessel lumen along the paths via algorithm-based methods (level set, threshold), and interaction-based or manual ways (circle, ellipse, polygon, spline polygon). Fourier smoothing, interactive shifting/scaling are incorporated. Batch segmentation by level set or threshold is implemented for automated segmentation of an entire vessel with minimal user intervention. Integrated direct 3D image segmentation based on level set methods is also available.

**Anatomic Modeling:** SimVascular can loft 3D solid models for vessels based on 2D segmentation and unions the vessels to create a complete 3D model of the vasculature of interest. There are types of models: analytic (OpenCASCADE, Parasolid) and discrete (vtkPolyData). For discrete models, SimVascular provides robust Boolean operations for discrete triangulated surfaces, algorithms to combine 2D and 3D image segmentations in a single model, and global/local surface operations like smoothing, remeshing, decimation, subdivision, trimming, etc. [3] (Fig. 4). For analytic models, typical CAD procedures such as blending, cutting, and Boolean operations are available.

![Discrete model surface operations](image)

**Figure 4.** Example of discrete model surface operations. (1) initial model (2) trimming and hole filling (3) smoothing, decimation, and subdivision. Adapted from Ref. 2.

**Meshing:** SimVascular generates a tetrahedral unstructured mesh for the 3D anatomic model that is suitable for computational hemodynamics, using TetGen. To enhance mesh quality, advanced options are provided, including local refinement near selected surfaces, boundary layer meshing, spherical refinement, and radius-based meshing. Users can check the quality of surface mesh and
inner volume mesh. Mesh adaption tools utilizing \textit{a-posteriori} error estimates are also integrated. SimVascular continues to support meshing with the commercial package MeshSim.

**Boundary Conditions:** The SimVascular pipeline enables users to perform hemodynamic simulations at realistic flow rates and pressures. Time dependent flow rates in a specified profile (plug, parabolic or Womersley) or lumped parameter heart models may be defined for the inlet(s). Impedance boundary conditions, Windkessel-type boundary conditions (resistance, RC circuit, RCR circuit), and more complicated lumped parameter network (LPN) models like coronary boundary conditions and closed loop boundary conditions can be specified at the outlets by fitting available clinical data to the parameter model [4]. No-penetration, no-slip boundary conditions are applied for vessel walls. For a deformable wall, fluid structure interaction (FSI) is incorporated using the coupled momentum method (CMM) [5], with the wall modeled as a linear elastic material with uniform or variable elastic modulus and thickness along the vessel.

**Running Simulation:** SimVascular solves the 3D Navier-Stokes equations using a finite element solver with the streamline-upwind/Petrov-Galerkin (SUPG), pressure-stabilizing/Petrov-Galerkin (PSPG) methods and backflow stabilization [6]. Simulations can be run with a single core or with multiple cores using the Message Passing Interface (MPI) in a desktop computer or cluster. The SimVascular solver has been shown to achieve excellent scalability in prior work. SimVascular can post-process the simulation results and export relevant hemodynamic quantities such as velocity, pressure, wall shear stress (WSS), and oscillatory shear index, in VTK formats to facilitate visualization.

**3 RESULTS AND CONCLUSIONS**

SimVascular has been significantly improved throughout the pipeline with expanded functionality and increased ease of use. In particular, the most recent version provides a new re-engineered modular software architecture and improved graphical user interface with increased image handling capabilities and ease of use. Since the inception of the revitalization project in 2013, SimVascular has attracted more 1,500 unique users worldwide and has been utilized in over 80 abstracts and journal publications. Active research and development continues on new image segmentation techniques based on machine learning and neural networks as well as on algorithms to convert discrete surface triangulations directly to analytic surface models. Work on an optimization module to enable users to automate device design and perform virtual surgical planning is also underway.

**REFERENCES**

**FLUID STRUCTURE INTERACTION SIMULATION OF AN INTRA-ATRIAL FONTAN CONNECTION**

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**SUMMARY**

A rigid wall assumption is commonly used in the numerical evaluation of total cavopulmonary connection (TCPC) hemodynamics. Previous study evaluated the impact of wall compliance on extra-cardiac TCPC but not the presumably more compliant intra-atrial TCPC. In this study, a fluid-structure interaction (FSI) simulation was performed using a patient specific intra-atrial TCPC. The simulated wall deformations were validated by comparing with clinical data. Differences between rigid wall and FSI simulations were found in instantaneous pressure drop and power loss through the TCPC, as well as hepatic flow distribution; but no significant difference was observed in the time-averaged quantities.

**Key words:** Fontan, Fluid-Structure Interaction, Hemodynamics

**1 INTRODUCTION**

The Fontan procedure is a common palliation for patients with single ventricle heart defect. It is usually completed by constructing an intra-atrial (IA) tunnel or using an extra-cardiac (EC) connection from the inferior vena cava (IVC) to the pulmonary arteries (PAs) as the Fontan pathway (FP). Together with the superior anastomosis, this forms the total cavopulmonary connection (TCPC). In all cases, the resulting geometries and constitutive materials can be very different. An IA TCPC is more bulgy and compliant at the IA tunnel where vena caval flows mix and re-circulate prior to entering the PAs, while an EC TCPC is composed of a stiffer cylindrical synthetic graft (e.g. Gore-Tex and Dacron grafts) so flow is more streamlined towards the PAs [1]. Even though the TCPC procedure results in favorable short-term outcomes, the patients remain at risk for long term complications [2]. It has been suggested that some of these complications may be attributed to the unfavorable hemodynamics in the connection [3]. For example, there has been evidence showing the possible link between TCPC energy dissipation and patient exercise tolerance [4, 5]. Also, unbalanced distribution of hepatic blood flow between the two sides of lungs has been associated with the risk of pulmonary arteriovenous malformations (PAVM) [6, 7].

Computational fluid dynamics (CFD) serves as a valuable tool to resolve the complex flows in the TCPC, and to understand the hemodynamics of both types of the connections. Previous studies applied various modeling assumptions to simplify the analysis and reduce computational cost. One such assumption is that the vessel wall is rigid. In the past ten years, few studies emerged and explored the effect of TCPC wall compliance on simulated hemodynamics. Bazilevs et al. [8], demonstrated the difference in resting and exercise hemodynamics between rigid wall and fluid-structure interaction (FSI) analysis for EC anatomies. Orlando et al. [9], carried out a similar analysis using an idealized TCPC model with prescribed material properties and flow rates in the vena cavae, left and right pulmonary arteries (LPA and RPA) and suture lines, after which they

* This is not the current affliction of the author. But the current study was completed when the author was in Georgia Institute of Technology
found that deformable model has 10% higher power loss than the rigid model. The main limitation of the aforementioned studies are their non-patient-specific numerical setups. To bridge this gap, Long et. al. also performed an FSI analysis of two patient specific EC TCPCs with varying wall properties [10]. All these studies established the difference between hemodynamics in rigid and deformable TCPC models, but their clinical relevance is still to be investigated as the prescribed wall properties are yet to be validated against patient-specific data. Additionally, only idealized TCPCs and EC TCPCs were investigated so far. The impact of wall deformation on the presumably more compliant TCPC, the intra-atrial ones, has not been well understood.

Therefore, the objective of this work is to quantify the difference in TCPC hemodynamics between rigid and compliant walls for an intra-atrial TCPC by using the FSI simulation. The wall deformation obtained from the FSI simulations will be compared with the in vivo patient-specific wall deformation. Finally, the qualitative and quantitative difference of TCPC hemodynamics between rigid wall and compliant wall conditions will be compared.

2 METHODOLOGY

2.1 Patient image acquisition and reconstruction

Single ventricle patients with a TCPC anatomy were selected from the Georgia Tech/Children’s Hospital of Philadelphia Fontan database. With informed consent and Institutional Review Board approval, an intra-atrial patient was selected, based on the following criteria: (i) single superior vena cava (SVC) and (ii) no apparent vessel stenosis. Anatomic and phase-contrast magnetic resonance image (PC-MRI) acquisition was performed on the patient. Static steady state free precession imaging was utilized to acquire patient specific anatomic images and 3D anatomies were reconstructed. PC-MRI was utilized to acquire through-plane velocity profiles across the vena cavae over a cardiac cycle under resting breath-held conditions. Patient specific flow conditions were obtained by segmenting PC-MRI images at the inlet’s cross section. The change in vessel cross-sectional area was also obtained from the segmented PC-MRI slices.

2.2 Hemodynamic assessment

The finite element method solver LifeV (www.lifev.org) was utilized in this work. The FSI solver is presented in Passerini et. al. and has been validated with experimental data of the propagation of a pressure wave in a fluid-filled elastic cylindrical tube [11]. The structural model is based on the assumption that the wall is linear elastic. Although this is certainly a simplification of the real constitutive law for the vessel wall, it provides a reasonable starting point, which is however quite indicative for the purposes of this research. The interaction between fluid and structure domains is implemented using the arbitrary Lagrangian-Eulerian (ALE) approach.

Flow extensions of 2 cm were added to each inlet and outlet to enable flow development. The inflow waveform obtained from PC-MRI was applied as inlet flow boundary conditions. P2 finite elements were used for fluid and structure velocity while P1 finite elements were used for fluid pressure. 1.5 mm mesh edge length was used based on a grid-independent study, resulting in 97,800 fluid tetrahedral elements and 82,200 structure tetrahedral elements. The duration of one cardiac cycle was 0.86 s, obtained from the MRI data. A time step of $5 \times 10^{-4}$ s was utilized at least for 3 cycles for both rigid wall and FSI simulations. A Young’s modulus of 0.07 MPa, Poisson ratio of 0.3 and wall thickness of 2.0 mm was prescribed. Homogeneous material properties were assigned at the vessel wall.

To compare wall deformation between the FSI simulation and in vivo data, a deformation index (DI) was computed to quantify the amplitude of cross sectional area change at the FP and the SVC, since they are the more compliant vessels of the TCPC: $DI = \frac{(A_{\text{max}} - A_{\text{min}})}{A_{\text{mean}}} \times 100\%$, where $A_{\text{max}}$, $A_{\text{min}}$, and $A_{\text{mean}}$ are maximum, minimum, and time-averaged cross sectional area.

3 RESULTS AND CONCLUSIONS

3.1 Results
From the FSI simulation results, the vessel cross-sectional areas of FP and SVC were extracted throughout the cardiac cycle. The vessel areas were compared between FSI and PC-MRI data (Table 3). Since the location of the PC-MRI slice of the FP was outside the CFD domain, comparison of absolute values of wall displacement was not feasible; therefore, DI was used for comparisons instead. Simulation results showed that DI from the simulation was in close agreement with the DI of the PC-MRI data at the FP. For the SVC, the maximum and average areas were similar between FSI and PC-MRI, but DI was underestimated in the simulation since the simulated minimum SVC area was higher.

<table>
<thead>
<tr>
<th>Vessel area</th>
<th>FSI simulation</th>
<th>PC-MRI data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FP</td>
<td>SVC</td>
</tr>
<tr>
<td>Average (cm²)</td>
<td>3.74</td>
<td>1.99</td>
</tr>
<tr>
<td>Change (cm²)</td>
<td>0.20</td>
<td>0.07</td>
</tr>
<tr>
<td>DI</td>
<td>5.3%</td>
<td>3.4%</td>
</tr>
</tbody>
</table>

The instantaneous pressure drop (FP – LPA pressure) and power loss across the TCPC in the cardiac cycle are shown in Fig.1, respectively. The pressure drop and power loss waveforms of the rigid wall and FSI simulations shared similar shapes, while the waveforms of the FSI simulation lag behind that of the rigid wall simulation. Comparing the maximum and minimum pressure drops and power losses, the rigid wall simulation has larger fluctuations than that of the FSI simulation. The maximum pressure drop and maximum power loss were lower in the FSI simulation, which is likely to be due to the increase of the TCPC volume in the FSI simulation. When comparing the time-averaged pressure drop and power loss, the differences between the two simulations were small (pressure drop difference = 0.01mmHg, TCPC power loss difference = 0.1mW).

To assess the impact of wall deformation on particle residence times and hepatic flow distribution (HFD), a Lagrangian particle tracking analysis was performed with ParaView software (Kitware Inc., Clifton Park, NY, USA). For each condition, approximately 700 particles were seeded at the FP at intervals of 0.001 s over one cardiac cycle (0.86 s) and were passively advected with the flow for five additional cardiac cycles. HFD was then calculated by counting the percentage of particle seeded at FP existing through LPA.

A significant difference was observed in the particle washout time between the rigid and FSI simulations. It took 1.77s (~2 cardiac cycle) for 95% of the FP particles to leave the TCPC for the FSI simulation, while it took much longer (3.16 s) for 95% of the FP particles to exit the domain for the rigid wall simulation. However, no difference was observed in HFD between the rigid and FSI simulations as the HFD for both cases are 19%.

### 3.2 Discussion and conclusions

In the current study, the simulated wall deformation of the FP and SVC was compared with PC-MRI data. Using a normalized metric, the deformation index, the change in vessel area at the FP and SVC were compared between the numerical simulation and PC-MRI data to validate the FSI simulations.
Pressure drop and power loss were compared between rigid wall and FSI simulations. Instantaneous pressure drop and power loss vary between FSI and rigid wall simulations. Comparing the maximum and minimum pressure drops and power loss, the rigid wall simulation has larger fluctuations than that of the FSI simulation, which is in agreement with previous similar study on carotid artery [12]. Additionally, particle washout time has significant difference between the rigid wall and FSI simulations. However, the differences in time-averaged pressure drops (0.01mmHg) and power losses (0.1mW) between the two simulations were small. Hepatic flow distribution was also quantified; but there was no difference in time-averaged HFD between the two conditions, which agrees with Long et al. [10].

The results in this work suggest that wall deformation has impact on the instantaneous hemodynamic metrics of the TCPC and particle washout time. However, FSI has little impact on time-averaged quantities (pressure drop, power loss, HFD, which are important hemodynamic metrics commonly focused for surgical planning of TCPC patients [13]. Therefore, the results support the notion that a rigid wall assumption is a reasonable assumption for such image-based surgical planning systems.

REFERENCES

CRIMSON Workshop: Simple Prototyping of Material & Boundary Conditions in 1D & 3D Blood Flow Simulations
CRIMSON: AN INTEGRATED SOFTWARE FRAMEWORK FOR IMAGE BASED CARDIOVASCULAR SIMULATION

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SUMMARY

The purpose of this work is to provide an overview of the CRIMSON (CardiovasculaR Integrated Modelling and SimulatiON) software environment. CRIMSON provides a powerful, complete and user-friendly system for performing computational hemodynamics studies, permitting segmentation of vascular structures from medical images, construction of analytic arterial geometric models, finite element mesh generation, designing and applying boundary conditions, running incompressible Navier-Stokes simulations, and post-processing and visualizing the results, including velocity, pressure and wall shear stress fields.

CRIMSON leverages in open-source standards such as MITK, VMTK, OpenCascade, and Verdandi, and provides state-of-the-art 1D and 3D fluid-structure interaction solvers.

CRIMSON aims to provide a cardiovascular simulation environment that is both easily customizable for the research community and user-intuitive for a wider audience, including clinicians and students.

Keywords: Open Source, Hemodynamics Software, Python Prototyping

1 INTRODUCTION

The finite element method (FEM) has developed into a well-understood and reliable engineering tool, routinely applied in fields where the problems are described by partial differential equations. However, in the biomedical engineering field, the methods and software tools for applying FEM are in an early stage of development. In this work we are particularly concerned with problems involving the solution of the incompressible Navier-Stokes equations in complex geometries derived from patient-specific arterial or venous imaging data. The objective is often either an increased understanding of a certain cardiovascular disease; to develop a virtual environment in which to test the performance of various medical devices; and, more recently, to provide surgeons and interventionalists with a tool to perform virtual surgical planning.

Despite some notable success stories, a serious limiting factor in the application of FEM-based cardiovascular simulations has been the arcane nature of existing software packages and workflows. The simulation workflow often requires using multiple pieces of software. Recently, HeartFlow Ltd. developed a commercial cardiovascular simulation solution for estimating the severity of coronary lesions: taking medical imaging data (CT) as an input, it produces a “virtual Fractional Flow Reserve” index, also known as “FFF-CT” [1].

However, there is currently no good robust, user-friendly, and expandable solution to perform FEM-based cardiovascular simulation in a research setting. There is a clear need for a software platform that is user-friendly, provides powerful capabilities, and is expandable, all while presenting an intuitive, modern, well-designed and error-proof GUI.
2 METHODOLOGY

The conceptual ancestor of CRIMSON is the SimVascular GUI [2]. Although SimVascular also consists of a workflow that enables going from image data manipulation all the way to FEM-based simulation, it lacks in a number of key aspects, namely: the ability to specify boundary conditions in a flexible, intuitive and expandible manner; the lack of a method for automatic parameter estimation; routines for dynamic control and cardiovascular auto-regulation; and finally, a modern, python-based GUI that enables easy prototyping of new functionality. For these reasons it was determined that CRIMSON should re-implement and expand upon the power and functionality of SimVascular, and that it should improve on the usability and accessibility, for example by allowing complete and error-preventing boundary condition specification in the GUI, by including undo/redo stacks to protect the user, and by limiting the interaction that users must have with text-based configuration files.

2.1 Libraries and Frameworks

The Medical Imaging Interaction Toolkit (MITK), via ITK and VTK, provides functionality for manipulation, segmentation, and visualization of medical image datasets. It features three orthogonal views, a 3D volumetric rendering of the image data, as well as data storage and undo/redo functionality [3]. MITK, due to its flexibility, degree of adoption and current level of support and development, has been adopted as the foundation of the CRIMSON environment.

The use of analytic geometric models was considered necessary, because these provide a smooth reference geometry from which to generate meshes of differing levels of refinement, and their parametric nature supports data interchange with other software packages, for example CAD tools, in which manipulation of the baseline geometry and Boolean operations are simple tasks. Furthermore, such representations are essential as we move towards modelling and simulation using Iso-Geometric Analysis (IGA) [4]. In CRIMSON, we have used the OpenCascade libraries [5] for analytical definition of a geometric model. These functionalities include lofting and sweeping to create the solid model from the segmented vessel contours, blending the intersecting vessels into a full geometry, filleting and Boolean operations, as well and importing CAD models created in external packages.

Boundary condition specification is a key component of FEM-based cardiovascular modeling. These boundary conditions are often times defined by Lumped-parameter Networks (LPN), consisting on electric circuit analogues such as resistors, compliances, inductors, diodes, etc. It is important that the boundary condition specification workflow of the simulation environment is flexible (i.e., it enables simple definition of complex circuits), easy to use (i.e., intuitive), and modular (i.e., they should be specified without the need for modifying the underlying FEM Navier-Stokes flow solver). To assist with boundary condition design and specification, CRIMSON provides the Netlist Editor Boundary Condition Toolbox (NEBCT). This presents a drag & drop interface for assembling LPN boundary conditions. It additionally allows the tagging of components for Python-specified adjustment during simulation, and will create user-customizable Python object templates for each of these. These objects can implement mathematical models of physiological processes in the vascular region represented by the boundary condition circuit, and are used by the flowsolver’s embedded Python interpreter during simulation. NEBCT is based upon the QSapecNG electrical circuit simulation software [6].

In the simulation workflow, the task that takes the longest part of the total work time is, quite often, parameter estimation. Indeed, determining the numerous parameters of the model (both material properties such as stiffness or LPN parameters defining the boundary conditions), requires running multiple simulations, and manually adjusting the numerical values of these parameters until a reasonable match of the available data is achieved. Most importantly, while other tasks of the simulation workflow are rather deterministic (i.e., the user knows how to proceed in order to achieve a certain goal), this aspect is far less clear when adjusting the parameters of the model. In the CRIMSON environment, we wanted to address these issues by using data assimilation techniques that
can make use of time-resolved data to automatically determine the model parameters that render the closest match between simulation results and data. Specifically, we used a reduced-order unscented Kalman filtering capabilities from the Verdandi library [7, 8].

From the point of view of technical capability, the CRIMSON Flowsolver must scale well in parallel and work on many different platforms and MPI implementations, including x86-64 workstations, SGI-UV, IBM Power8 and Blue Gene. Both the CRIMSON Flowsolver and the CRIMSON GUI must protect users from common input and configuration errors; this is important in increasing the usability of the software to non-experts, and sets it apart from a large portion of existing academic software efforts. In order to support the unpredictable nature of upcoming research requirements, it must also offer high flexibility at low effort to more technically-inclined and advanced users.

### 2.2 Architecture, data structures, and control mechanisms

The major components of the full CRIMSON system are illustrated in Figure 1; many of the smaller components have been omitted due to space limitations.

![Figure 1: The major components and libraries which make up CRIMSON, arranged by conceptual depth from the user. The user only sees the tip of the iceberg; a large quantity of the complexity is hidden, so the clinical or student user need not be exposed to the details of deeper aspects. Items shown in grey are currently under active development.](image)

### 3 RESULTS AND CONCLUSION

In this paper, we will provide a practical demonstration of the software GUI, functionality, and current state of development. Key and novel components of the software will be highlighted. We will also demonstrate specific applications of the software to the areas of cardiovascular disease research and complex surgical planning of cardiovascular procedures.

Finally, we will discuss future directions and strategies for wider adoption and sustained development.
REFERENCES


A VERSATILE LUMPED PARAMETER VALVE MODEL AND CUSTOM ELASTANCE-BASED HEART MODEL AS A CFD INLET BOUNDARY CONDITION IN CRIMSON

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SUMMARY
This study describes a new lumped parameter left heart model for use as an inlet boundary condition in three-dimensional aortic flow simulations. The left ventricle is represented by a time-varying elastance and pressure-dependent source resistance, while the valve model predicts valve dynamics based on haemodynamic interactions for both normal and pathological valves. The left heart model was implemented in CRIMSON, using the drag-and-drop ‘netlist’ circuit editor, and a python script interface that enables runtime control of parameter values. Aortic haemodynamics are compared for normal, stenotic and incompetent valves.

Key words: computational fluid dynamics, aortic valve, stenosis, regurgitation

1 INTRODUCTION
A prescribed flow waveform is commonly used as an inlet boundary condition in aortic computational fluid dynamics (CFD) simulations. However, this approach precludes study of ventriculo-valvular-vascular coupling dynamics. A simple and versatile valve model was previously described for use in reduced order (0D or 1D) models [1], which predicts valve dynamics based on the instantaneous valvular pressure difference and can be used to study the impact of stenosis and/or regurgitation on ventricular and circulatory haemodynamics. However, the benefits of such a versatile valve model have not been realised in CFD studies.

CRIMSON (Cardiovascular Integrated Modelling and Simulation) is a new environment for cardiovascular modelling that incorporates a user-friendly segmentation tool, a state-of-the-art 3D fluid solver that incorporates the coupled momentum method to represent deformable walls, and the ability to set up custom lumped parameter boundary conditions (‘netlist circuits’) [3, 2, 4]. The aim of this study was to incorporate the valve model of Mynard et al [1] into a lumped parameter left heart model for use as a versatile inlet boundary condition for 3D aortic flow simulations using CRIMSON.

2 METHODOLOGY
2.1 Aortic valve model
The valve model has been described previously [1]. Briefly, the transvalvular pressure difference ($\Delta p$) was governed by the Bernoulli equation as follows:

$$\Delta p = B|q| + L \frac{dq}{dt}$$

(1)

The Bernoulli resistance ($B$) is given by

$$B = \rho / 2A_{\text{eff}}^2$$

(2)
and valve inertance \( L \) is given by

\[
L = \rho l_{\text{eff}} / A_{\text{eff}}
\]  

(3)

where \( q \) is valve flow, \( \rho = 0.00106 \text{ g/mm}^3 \) is blood density and \( l_{\text{eff}} \) is the valve effective length. Valve effective area \( (A_{\text{eff}}) \) varied in time according to

\[
A_{\text{eff}} = A_{\text{ann}} \left[ (M_{\text{rg}} - M_{\text{st}}) \zeta(t) + M_{\text{rg}} \right]
\]  

(4)

where \( A_{\text{ann}} \) is the valve annulus area, \( 0 \leq M_{\text{rg}} \leq 1 \) is an index of valve regurgitation \( (M_{\text{rg}} = 0 \) for a competent valve; \( M_{\text{rg}} = 1 \) for 100% insufficiency), \( 0 \leq M_{\text{st}} \leq 1 \) is an index of valve stenosis \( (M_{\text{st}} = 1 \) for a non-stenosed valve; \( M_{\text{rg}} = 1 \) for an atretic valve). The index of valve state \( (0 \leq \zeta \leq 1) \) is governed by the following differential equation,

\[
\frac{d \zeta}{dt} = \alpha K_V (\Delta p - \Delta p_{\text{thresh}})
\]  

(5)

where \( \alpha = 1 - \zeta \) when the valve is opening \( (\Delta p > 0) \), \( \alpha = \zeta \) when the valve is closing \( (\Delta p < 0) \), \( K_V \) is a coefficient that may differ between opening and closing (here assumed to be the same for both), and \( \Delta p_{\text{thresh}} \) (herein set to zero) is a threshold pressure difference that must be reached before opening or closing commences.

### 2.2 Left heart model implementation in CRIMSON

The left heart model was implemented via the CRIMSON ‘netlist’ circuit editor (Figure 1), which allows custom circuits to be built, via a drag-and-drop interface, for use as boundary conditions. The CRIMSONPython library enables circuit element values to be set dynamically at runtime. Left ventricular (LV) chamber elastance \( (E_{\text{LV}}) \) was described with a standard curve, as in [1], with the time-varying \( E_{\text{LV}} \) values prescribed during the simulation via a python script. Similarly, the pressure-dependent source resistance \( (R_{\text{LV}}) \) was defined, via a separate python script, as \( R_{\text{LV}} = K_s p_{\text{LV}} \), where \( K_s \) is a constant and \( p_{\text{LV}} \) is current LV pressure taken from the simulation at runtime.

A constant left atrial pressure \( (p_{\text{LA}}) \) drives ventricular filling via an open-or-closed mitral valve consisting of a diode \( (D_{\text{MV}}) \) and constant inertance \( (L_{\text{MV}}) \). The aortic valve was represented with the more realistic valve model described above, using inertance and resistance elements \( (L_{\text{AV}} \) and \( R_{\text{AV}}) \). The Bernoulli resistor in Eq. (2) was transformed into a time-varying Ohmic resistor (as is available in CRIMSON) as follows:

\[
R_{\text{AV}} = \begin{cases} 
B |q| & , \ |q| > 1 \\
B & , \ |q| \leq 1
\end{cases}
\]  

(6)

where the condition \( |q| < 1 \) ensures that \( R_{\text{AV}} \) cannot fall to zero and provides a \( C^0 \) continuous transition between these two expressions; in addition, since the CRIMSON solver employs flow units of \( \text{mm}^3/\text{s} \), \( |q| < 1 \) is negligibly small compared with peak aortic flow \( (\sim 5 \times 10^5) \). Valve inertance was calculated via Eq. (3). Noting that \( B \) and \( L \) are inversely proportional to \( A_{\text{eff}} \), division by zero (when the valve is closed) was avoided by setting \( R_{AV}^n = R_{AV}^{n-1} \) and \( L_{AV}^n = L_{AV}^{n-1} \) when \( A_{\text{eff}} < 10^{-15} \), where \( n \) is the time step. To avoid large pressure transients generated by the numerical solution when the valve was opening or closing, a small ‘aortic root’ compliance \( (C_{\text{AR}} = 0.01 \text{ mm}^3/\text{Pa}) \) and inertance \( (L_{\text{AR}} = 10^{-5} \text{ g/mm}^4) \) were inserted between the valve and 3D interface.

A 3D true FISP magnetic resonance angiogram, from a patient with repaired aortic coarctation, was segmented using CRIMSON. Parameters for the inlet and outlet boundary conditions (LV minimum and maximum elastance, \( p_{\text{LA}} \) and outlet 3-element windkessel parameters) were iteratively adjusted by trial and error to achieve normal aortic pressures/flows and LV pressures/volumes. These preliminary simulations were performed in purely zero dimensions, that is, with the 3D aortic domain ‘collapsed’ into a lumped parameter compartment, a time-efficient approach that allowed simulation of 5 cardiac cycles in under 30 seconds. Keeping the final parameter values fixed (Table 1), we then performed simulations with 1) the aortic valve described by a simple diode; 2) the dynamic aortic valve described above, representing a normal healthy valve \( (K_V = 0.12 \text{ Pa}^{-1} \text{s}^{-1}) \); 3) aortic valve stenosis \( (K_V = 0.012 \text{ Pa}^{-1} \text{s}^{-1}) \), further details in Section 2.3; 4) aortic valve regurgitation \( (M_{\text{rg}} = 0.15; K_V = 0.12 \text{ Pa}^{-1} \text{s}^{-1}) \).
2.3 Stenosis modelling

Modelling a stenosis with the aforementioned techniques accounts for the reduced inflow and increased pressure drop, but does not account for the narrowing of the inflow boundary and resultant high velocity jet that is a key feature of aortic stenosis. To account for these features, the area of 3D model inlet boundary was reduced by 87% over a very short distance, thus leading to a high velocity jet. In this case, the pressure loss mainly occurs downstream to the valve (i.e. in the 3D model). Thus, for the 0D valve model, we set \( M_{st} = 1 \) so that very little pressure drop occurs over \( R_{AV} \) when the valve was open. The total transvalvular pressure drop \( \Delta p \) used to determine valve state was then estimated as

\[
\Delta p = \Delta p_{0D} - \frac{1}{2} \rho u_{jet}^2
\]

where \( \Delta p_{0D} \) is the pressure drop across the 0D valve \((R_{AV} \text{ and } L_{AV})\), and the jet velocity \( (u_{jet}) \) was given by \( q^{n-1}/A_{ann} \) (with \( A_{ann} \) being the inlet area for the 3D model).

3 RESULTS AND CONCLUSIONS

Figure 2 displays LV and aortic (Ao) haemodynamics, along with time-varying valve effective area. Unlike the simple diode valve, the dynamic valve model results in a realistic LV-Ao pressure drop, transitory reverse Ao flow at end-systole and a dicrotic notch in the pressure waveform. Modelling stenosis results in a large LV-Ao pressure drop, reduced flow and a high velocity jet that impinges...
on the aortic wall (Figure [3]), while the incompetent valve is associated with substantial regurgitation during diastole, causing reverse aortic flow, and a low diastolic pressure (Figures 2 & 3).

In conclusion, the versatile dynamic 0D valve model can be coupled to 3D aortic flow simulations via a python interface in CRIMSON. This allows flexibility in terms of model design as well as dynamic control of element values. Additional work is needed to improve the valve stenosis modelling, such as using patient-specific velocity profiles and orifice geometries, and more accurately representing the localised forces that determine valve opening and closure.

4 ACKNOWLEDGMENTS

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REFERENCES


CRIMSON: INTEGRATION OF A ONE-DIMENSIONAL BLOOD FLOW SOLVER

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SUMMARY

We present the integration of Nektar1D, a one-dimensional (1-D) blood flow solver, in CRIMSON. The solver requires a 1-D model of arterial geometry, extracted from clinical data or from a 3-D solid model, as input. It also requires inflow and outflow boundary conditions determined from in vivo data: (a) cardiac output is imposed as an inflow boundary condition at the aortic root; and (b) terminal outflow boundary conditions are given by 0-D lumped parameter models of peripheral arterial resistance and compliance. A detailed description of the CRIMSON workflow for a model of the aortic circulation, together with a comparison between 3-D and 1-D simulations, will be provided during the presentation.

Key words: patient-specific modelling, 3-D/1-D blood flow modelling, haemodynamics

1 INTRODUCTION

Blood pressure and flow waveforms measured in the arteries of the cardiovascular system contain valuable information for the assessment of cardiovascular function. Several studies have shown that one-dimensional (1-D) modelling offers a good compromise between accuracy and computational cost for simulating the propagation of these waveforms in the systemic circulation [1, 2, 3]. Therefore, there is potential for applying the 1-D formulation to study clinically relevant problems. However, robust tools are required to personalise the 1-D formulation for a given patient. Creating patient-specific models of the larger human arteries, such as the aortic model in [4], is a tedious procedure. Furthermore, due to the limitations of in vivo data acquisition, non-patient-specific modelling assumptions are often necessary. In the aortic model, data inconsistencies in heart rate, vessel geometry and mean aortic flow rates also had to be identified and accounted for.

The integration of Nektar1D, a validated computational framework of 1-D arterial haemodynamics [5], within CRIMSON [6], a software framework for patient-specific 3-D blood flow simulation, allows us to go from the image processing of the in vivo data to the patient-specific simulation and visualisation of pressure, flow and area waveforms. This work uses the in vivo data of the aortic circulation from [4]. The aorta and the supraaortic arteries are represented by 1-D segments, and outflow boundary conditions are represented by 0-D lumped parameter models of the perfusion of more peripheral vessels.

2 METHODOLOGY

The 1-D formulation consists of two main elements: (a) a patient-specific 1-D model of arterial geometry generated from magnetic resonance (MR) images of the upper thoracic aorta and (b) a numerical
framework for the simulation of blood flow, known as Nektar1D, which solves the nonlinear 1-D equations of mass and momentum conservation in compliant vessels. The 1-D equations follow from applying conservation of mass and momentum in a control volume of a 1-D segment,

\[
\begin{align*}
\frac{\partial A}{\partial t} + \frac{\partial Q}{\partial x} &= 0 \\
\frac{\partial Q}{\partial t} + \frac{\partial}{\partial x} \left( \frac{\alpha Q^2}{A} \right) + \frac{A}{\rho} \frac{\partial P}{\partial x} &= \frac{f}{\rho}
\end{align*}
\]

where \( A = A(x, t) \), \( Q = Q(x, t) \), and \( P = P(x, t) \) are the vessel cross-sectional area, flow rate and pressure, respectively. \( f(x, t) \) is the frictional force per unit length and \( \alpha(x, t) = \frac{1}{2\pi} \int_A u^2 \sigma \) is a non-dimensional profile shape factor which accounts for the non-linearity of the sectional integration of the velocity \( u(x, t) \). The velocity profile is then required to close the system, since it affects convective accelerations and \( f \).

A Voigt-type visco-elastic law which neglects the effects of wall inertia and longitudinal pre-stress is used as the constitutive law which relates blood pressure and vessel area [5]

\[
P = P_e(A; x) + \frac{\Gamma(x)}{A_0(x)\sqrt{A}} \frac{\partial A}{\partial t},
\]

with

\[
P_e(A, x) = P_{\text{ext}} + \frac{\beta(x)}{A_0(x)} \left( \sqrt{A} - \sqrt{A_0(x)} \right),
\]

where \( P_e \) is the elastic component of pressure, and \( P_{\text{ext}} \) is a reference pressure value. \( \beta(x) \) and \( \Gamma(x) \) are related to wall elasticity and viscosity, to the wall viscosity through the arterial pulse wave velocity and diameter. Finally, the reference area \( A_0(x) \) is the area when \( P = P_{\text{ext}} \) and \( \frac{\partial A}{\partial t} = 0 \).

1-D MODEL GEOMETRY EXTRACTION PIPELINE

Figure 1: CRIMSON geometry extraction pipeline: (i) original 2-D/3-D medical image; (ii) segmentation pathlines and contours created from the imaging data; (iii) 3-D model generated through vessel lofting; (iv) topology of the centrelines and contours adapted to the geometry required by the 1-D model; and (v) final 1-D model geometry: segments and vessel areas. Modified from [4].
Inflow and outflow boundary conditions are required for the 1-D formulation. The 1-D geometry is obtained as shown in Figure 1. CRIMSON allows us to extract valuable information from in vivo data to create 1-D models of arterial geometry and blood flow. Figure 1 shows the 1-D geometry extraction from the medical image, (i), in this case obtained using magnetic resonance imaging (MRI). For segmentation purposes, pathlines and contours are used in (ii). The 1-D geometry can also be extracted directly from a 3-D solid model, (iii), if it is available. 1-D centrelines and contours are shown in (iv). The generated 1-D segments and contours seen in (v) determine the geometry of the 1-D model. Volume conservation at bifurcations must be ensured.

The only inflow boundary condition, imposed at the aortic root, is the time-dependent blood flow rate through the aortic valve. Every outflow boundary condition is determined by the flow distribution at the outlet of each terminal vessel: they are modelled using three-element Windkessel models (0-D lumped parameter models) which account for peripheral vascular compliance and resistance. To account for fluid-structure interaction, an algebraic relationship between blood pressure and vessel area, known as the tube law, is required. Here we will use a visco-elastic tube law. The ends of every 1-D segment shown in (v) (Figure 1), can be connected to another segment or to a terminal boundary condition. The pulse waves generated by the cardiac pump propagate along the axial direction of each segment, partially reflecting due to vessel tapering, at bifurcations and at boundary conditions.

### 3 RESULTS AND CONCLUSIONS

![Figure 2: Aortic model taken from [4]. 1-D (red line) and 3-D (blue line) simulations compared to in vivo data (black line): flow (Q), area (A) and pressure (P) waveforms at (a) ascending aorta; (b) left common carotid; (c) descending aorta (upper part); and (d) descending aorta (lower part) — in vivo data is shown where available.](image_url)
Figure 2 compares \textit{in vivo} data to the original 3-D and 1-D simulations of blood flow in the aortic model in [3].

Fully integrated in CRIMSON, Nektar1D performs identically to the stand-alone version. However, the construction of patient-specific geometries from medical imaging data and the specification of boundary conditions using CRIMSON is greatly streamlined and less error-prone. Additionally, 3-D and 1-D simulation results for blood pressure, flow and velocity can be visualised and compared with ease within the CRIMSON platform.

4 ACKNOWLEDGMENTS

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REFERENCES


DESIGNING DYNAMIC BOUNDARY CONDITIONS IN CRIMSON:
PATIENT-SPECIFIC ELASTANCE AND DATA BROADCASTS

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SUMMARY
To-date, computational haemodynamics has predominantly involved simulating periodic conditions. This approximation is appropriate in steady cases where there are no changes in internal or external environment, but in reality the haemodynamic state is set by multifarious control systems which interact with one another, driving the system towards the dynamic equilibrium of the periodic simulation case. In the present work, we describe the powerful tools that we have created as part of CRIMSON, including the Dynamic Lumped Parameter Network Framework, which allows users to attach arbitrary mathematical models to the lumped parameter regions of the vasculature in order to implement such control, or similar dynamic adjustments during the simulation. The system’s ability to impose arbitrary run-time parameters will be illustrated for the creation of patient-specific heart models.

Key words: computational haemodynamics, control systems, crimson, elastance

1 INTRODUCTION
An important topic in computational haemodynamics (CH) is to develop the capability for including models of the multifaceted cardiovascular control systems and transitional phenomena which occur within the human body in compensation for changes in internal or external state. In the current state of the art, few such models are available, and those which are available are not necessarily easy to import into a particular workflow; certainly it is not possible to use them in high-performance computing environments without a substantial effort and extensive software development experience.

In the present work, we discuss the CRIMSON (CardiovasculaR Integrated Modelling and Simulation) Netlist Editor Boundary Condition Toolbox, and the associated CRIMSON Dynamic Lumped Parameter Network (LPN) Framework (DLPNF). Our interest is in simulations which are multidomain [2]; those in which different regions of the vasculature are approximated by different types of models, having for example a large vessel region in which blood flow is modelled in three dimensions using the Navier-Stokes equations, together with upstream or downstream regions which are modelled using LPNs and which are used to generate boundary conditions for the Navier-Stokes problem. The models of interest are those which have their influence in the LPN domain, and whose effects can be expressed in terms of changes of resistance, compliance, flow permittance, inductance, or regionally-imposed pressure or flow values. These tools make it easy for researchers using CRIMSON to import existing control or dynamic adjustment models in to their CRIMSON simulations, or to develop new ones with greatly reduced barriers to entry. The latter is due to the fact that whilst CRIMSON is high-performance software written in low-level languages, the Dynamic LPN Framework allows users to express their models using Python. We illustrate in terms of a patient-specific ventricular elastance.

Some examples of work that has been performed in this domain include modelling of the systemic arterial baroreflex, which implements control effectors for the heart rate, peripheral resistance, venous unstressed volume and cardiac contractility, with the central blood pressure as input [3]; or recent work on coronary microvascular resistance control in a model of coronary metabolic autoregulation.
Recent uses of the NEBCT and the DLPNF include examination of models of heart valve closure [4], examination the application of patient-specific time-varying ventricular elastance functions in examination of aortic haemodynamics and cardiac workload changes in TEVAR [5], and the creation of an electrophysiologically-driven heart model [6].

2 CONCEPTS AND METHODOLOGY

CRIMSON supports agile design of both LPN boundary condition models and associated dynamic adjustment models in two ways. The first is that the customisation of LPN models can be performed using a drag-and-drop interface, in which the desired components are arranged into the appropriate network structure (Figure 1). We refer to these circuits as netlist LPNs. Their rigid structure enables the second key concept - the attachment of dynamics scripts, written in Python, to any entity (node or component) within the netlist LPN. During a simulation, dynamics scripts attached to nodes may adjust that node’s pressure, and dynamics scripts attached to components may adjust either that component’s parameter (resistance, inertance, compliance, etc.), or they may prescribe the flow through that component. Dynamics scripts may be autonomous, or they may receive and integrate input data from elsewhere in the simulation. An example of a broadcast is indicated in green in Figure 1; this LV pressure could be received and used by any other LPN. We illustrate in blue a coronary LPN receiving this to model the systolic extravascular compression effect.

2.1 Workflow

We give an overview of the workflow, supported by CRIMSON, that takes place when working with dynamically adjusted netlist LPN models, applied as boundary conditions to a three-dimensional vascular model.

1. The three-dimensional model geometry is segmented from medical imaging data, blended into a single solid model, and then a finite element mesh of it is generated.

2. The flow boundary of interest is identified by the user by clicking on it in the interactive 3D rendering of the geometry; this minimises the chance of an attachment error being made.

3. The Netlist Editor Boundary Condition Toolbox is opened, and the user assembles the desired netlist LPN using the drag-and-drop interface, for example forming the left heart model LPN shown in Figure 1.

4. The user writes a Python script containing a control class inheriting from a CRIMSON base. The class must have a specific method returning a floating point number, dependent on the current time-step and/or haemodynamic state, which will be assigned as the value of the parameter of interest of the associated component or node.

5. Drop-down menus available for each component and node are used to identify those which are to have dynamic adjustment scripts attached to them, and to provide the name of the script which will be used.

6. The user returns to the master CRIMSON GUI, and loads the just-created netlist LPN into the current boundary dialogue. The dynamically-adjusted LPN model is now connected to the geometry, and will be run during the simulation.

2.2 The NEBCT system: illustration creating a patient-specific elastance heart model

Use of the above workflow will be illustrated by first creating a heart model (Figure 1), then by applying patient-specific time-varying elastance function. We demonstrate how this elastance function can be created using a variety of different levels of richness in the available patient data, describing ways to compensate for lower quality data. Using the DLPNF, the resulting elastance function will be applied to the ventricle of a heart model which we draw using the NEBCT, and ultimately used to generate the aortic surface boundary condition.
2.2.1 Creation of the Elastance Function

We give a series of strategies for creating a patient-specific elastance function; these are summarised in Table 1. The flexibility afforded by the NEBCT and DLPNF assists greatly in many of these, and are used in all cases to impose the elastance function on the final simulation.

**Strategy 1.** In the best-case scenario, the available patient data includes the ventricular volume and pressure with a high temporal resolution; i.e. a high-quality recording of the PV loop. In this case, there is almost nothing to do; the elastance function can be created by aligning the pressure and volume curves in time, then dividing the pressure by the volume. The result is saved as a set of time-elastance pairs, in whichever format your Python library of choice can load at run-time. The elastance controller Python class is then written to give the elastance at time $t$ during the simulation.

**Strategy 2.** In the next-best scenario, (2A) time-resolved ventricular pressure data and aortic valve flow data are available. In this case, we can form the partial integral function with respect to time of the aortic valve flow, starting from either a measured or estimated ventricular end-diastolic volume, thus creating a ventricular volume curve which is valid whilst the valve is open. We then align the pressure and volume curves in time, and divide the pressure curve by the volume curve in order to create a patient-specific elastance function whilst the valve is open. The curve can then be completed by fitting extrapolating exponential curves or a single Gaussian, then performing Fourier smoothing and scaling to preserve the maximum elastance. A similar strategy (2B) can be followed when the full-cycle ventricular volume curve is available together with the aortic root pressure. The curves can be aligned temporally, the valve-open elastance created, and then the complete function extrapolated as previously. The final closely-related strategy (2C) is used when the aortic root pressure curve and the aortic valve flow is available. The indefinite integral of the aortic valve flow is formed, aligned in time with the aortic root pressure curve, then the extrapolation step is performed. Note that strategies 2B and 2C are only appropriate if the valve is not stenosed.

**Strategy 3.** If aortic valve flow is available (3A), or if it can be inferred (3B), and only estimated mean and/or pulse aortic root pressure is available, then we can use preliminary simulation to generate an aortic root pressure curve. The preliminary simulation involves imposing a time-varying flow as a Dirichlet boundary condition on the aortic root, and adjusting the boundary conditions such that the aortic root pressure data is matched, together with any other haemodynamic parameters of interest. The aortic root pressure curve is then extracted, and then Strategy 2C can be followed.

**Strategy 4.** If no time-resolved valve flow or ventricular volume data is available, but (4A) time-resolved aortic root pressure or (4B) time-resolved ventricular pressure is, then this pressure can be imposed upon the aortic inflow surface, and the other boundary conditions tuned to achieve physiological flows. The resulting inflow curve can be used with the pressure curve to create the elastance.
function, as before. Note that 4B is only appropriate in the absence of aortic valve stenosis.

**Strategy 5.** In the case where only summary data on pressure and flow are available, then in order to use a heart model, a generic elastance function such as that of Pope et al. [1] should be used. The maximum elastance and timing parameters should be adjusted to match the available data.

All the above strategies can equally well be applied to the right ventricle, and we note that many of the strategies assume a competent atrioventricular valve. Care should be taken when this is not the case. The toolbox gives us the flexibility to experiment with different options here during the creation of the elastance function with a minimum of friction.

<table>
<thead>
<tr>
<th></th>
<th>Full Cycle $P_{LV}(t)$</th>
<th>Aortic Root $P(t)$</th>
<th>No Time-Resolved Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full Cycle $V_{LV}(t)$</td>
<td>1</td>
<td>2B</td>
<td>3B</td>
</tr>
<tr>
<td>Aortic Valve $Q(t)$</td>
<td>2A</td>
<td>2C</td>
<td>3A</td>
</tr>
<tr>
<td>No Time-Resolved Flow</td>
<td>4B</td>
<td>4A</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 1: Identifying which strategy to use when creating a custom elastance function when different levels of data are available. The numbers correspond to the Strategies in the text.

### 3 CONCLUSIONS

Using the example of imposing a patient-specific ventricular elastance function, we have explained that the CRIMSON NEBCT and DLPNF can be used to create custom LPN boundary conditions which change dynamically during simulation, following some user-defined rules expressed as a Python class. The chosen example illustrates the principles; they can be applied more generally to adjust any LPN component type, and the adjustment can be based on a mathematical model rather than an imposed curve if so desired. We have also introduced a set of strategies which can be used to create a suitable elastance function with different levels of quality in the available data.

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### REFERENCES


SPECIFICATION OF PATIENT-SPECIFIC VELOCITY PROFILE CONDITIONS FROM FLOW-MRI WITHIN CRIMSON

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SUMMARY

Variability of blood flow characteristics which occurs in abnormal vessel morphologies are linked to a range of cardiovascular morbidities. The impact of vessel morphology on the blood flow can however be observed using phase contrast MRI, which in its 2D modality provides a time-resolved blood velocity map at a given slice in the image data. In this paper we show how these velocity maps can be used in combination with geometric models obtained from MRA in order to simulate patient-specific blood flow characteristics via computational fluid dynamics.

Key words: computational fluid dynamics, phase-contrast MRI, blood velocity map

1 INTRODUCTION

Image-based Computational fluid dynamics (CFD) simulations are a powerful and non-invasive tool for assessing functional hemodynamic parameters [1]. These parameters help describe the blood flow, including the stress induced on the vessel walls, which in turn may lead to pathological changes in the vessels. Patient-specific CFD is thus becoming a valuable source of information for cardiovascular disease research, decision-making and treatment planning in the clinic.

In order to support easy use of CFD among the clinicians we have previously developed CRIMSON - a software that integrates image processing and numerical modelling algorithms in an intuitive graphical user interface [2]. The software enables great amount of customization in terms of defining material and boundary condition properties with the possibility of incorporating patient-specific data. This software has recently been extended by supporting the use of patient-specific inflow velocity profiles, as opposed to imposing idealised velocity profiles (e.g. parabolic) in the earlier versions of CRIMSON. While such profiles provided good approximations in majority of healthy cases, they could not account for great inflow variability which occurs in abnormal vessel morphologies.

2 METHODOLOGY

2D Phase contrast MRI (PC-MRI) is an imaging technique which yields a 2-dimensional velocity-encoded image. It is usually performed on a plane orthogonal to the vessel of interest at the point of most significance to case at hand. Conversely, magnetic resonance angiography (MRA), which is used to create a patient-specific geometrical model, produces a 3-dimensional image. The two images also usually have different resolutions and orientations relative to the patient, which makes combining the two data for simulation purposes a non-trivial task.

In order to be able to use the velocity profile obtained from PC-MRI as a boundary condition on inlet faces of the 3D model generated from MRA, we have devised a method to map the PC-MRI image directly onto the meshed model. The process starts by loading the PC-MRI image into the CRIMSON software and then visualizing it side-by-side next to the 3D image. The goal is to observe the same cross-section of the vessel in both PC-MRI and 3D MRA image and co-register them. Since
PC-MRI contains only one slice which is already in the cross-section plane, the position of the same plane needs to be found in the 3D MRA image. CRIMSON software enables visualization of the cross-sections along the vessel path, but in order to do this the user needs to first define the vessel centreline in the 3D MRA image by manually placing points. Once the centerline is defined, the user is then given the ability to scroll through the cross-sections of the 3D image to locate the point on the vessel where the PC-MRI image was taken. After the correct cross-section of the 3D image has been located, the user needs to manually segment the vessel contour in both images, either by fitting a circle/ellipse or by placing points. The final input required from the user is the orientation alignment of the two images. In order to do this, the user needs to manually specify the in-plane angle between the 2D image and the slice from the 3D image.

If the user chose to segment the vessel contours by placing points, the full shape is obtained by interpolating the contour to a cyclic B-spline contour with \( N \) nodes. In the next step, the software automatically calculates displacement vectors between the corresponding points on the 3D MRA and PC-MRI contour. Finally, the software determines a dense smooth deformation field by interpolating the vectors between the corresponding points using a smooth 2D B-spline field. The deformation vector, along with the data about rotation needed to initially align the two contours, is used to assign velocity values to the nodes of the finite element mesh belonging to the inlet face. The results of intermediate steps of the mapping algorithm can be observed in Figure 1.

### 3 RESULTS AND CONCLUSIONS

The described process of using patient-specific velocity profile obtained from PC-MRI and mapping it to the 3D model has already been used to assess hemodynamics of thoracic aorta in various aortic valve pathologies \[3\]. The morphology of the aortic valve has a high impact on the flow characteristics (Figure 2), which makes this application a good case to illustrate the importance of utilizing patient-specific inflow velocity profiles. In addition from using PC-MRI-derived velocity profiles, the authors of the study compared the results with those obtained using idealized profile models (parabolic and plug).

In conclusion, the results of the simulations showed that idealized velocity profiles were able to provide a realistic description of the blood flow for normal aortic valve, but not for the abnormal morphologies. Moreover, the study illustrated how CFD can be used to assess and localize blood flow abnormalities, such as increased wall shear stress and asymmetric flow, which in case of the aorta can...
lead to formation of aneurysms. This information is a valuable addition to what is currently a main criteria for determining treatment of aorta - a simple measurement of aorta size. Patient-specific CFD is a powerful and non-invasive method for functional assessment which has the potential to greatly benefit the decision-making process in the clinic. The presented integration of data from PC-MRI images into a user-friendly CFD software will increase the usage of patient-specific models in regular diagnostics and treatment management.

REFERENCES


CRIMSON WORKSHOP: FLUID-STRUCTURE-INTERACTION SIMULATIONS OF HEMODYNAMICS WITH SPATIALLY VARIABLE PROPERTIES OF THE ARTERIAL WALL

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SUMMARY

In this paper we describe the CRIMSON module for the specification of spatially variable tissue properties of the arterial wall. This feature is fundamental to computationally investigate the complex interplay between hemodynamics and mechanical properties of the vessel. This interplay has a fundamental role in the origin and progression of cardiovascular disease. Using the CRIMSON framework, we developed 3D fluid-solid-interaction (FSI) mouse-specific models of induced hypertension having appropriate regional variations in wall properties, based on comprehensive biaxial data. We showed how these types of simulations can be valuable tools to investigate local and global changes in hemodynamics in mouse models of cardiovascular diseases.

Key words: arterial stiffness, mouse hemodynamics, crimson

1 INTRODUCTION

Stiffness of the central arteries is recognized as an indicator of cardiovascular function and an initiator of the disease [1, 2]. It is known that there is a positive feedback loop between local properties of the arterial wall and global hemodynamics, which can progressively aggravate the disease conditions regardless of the underlying cause [3]. For this reason, there is a strong motivation to investigate the complex interplay between arterial stiffening and hemodynamics.

Computational modeling is a powerful tool to understand the origin and progression of cardiovascular disease as well as to study normal and pathologic cardiovascular function. The data-driven computational framework CRIMSON [4] allows to perform fluid-structure simulations of hemodynamics, specifying regionally varying biaxial tissue properties. This feature is fundamental to keep into account the deformability of the vessel and therefore to capture the wave propagation phenomena in the cardiovascular system.

Herein we present the CRIMSON module for the specification of spatially variable tissue properties of the arterial wall and we illustrate an application. We developed 3D fluid-solid-interaction mouse-specific models based on comprehensive biaxial data of a wild type mouse and a fibulin-5 deficient mouse Fbln5−/−. Fibulin-5 is a protein involved in the genesis of elastin fiber, these genetically modified mice show defective elastic fibers in the aortic wall which lead to tortuous vessels and changes in vessel mechanics [5]. Loss of elastic fiber integrity is one of the primary contributors to increased arterial stiffening in normal aging and in pathologic conditions such as hypertension and aortic aneurysms.
2 METHODOLOGY

CRIMSON is a software that provides a number of tools for medical image data analysis, preprocessing, segmentation and blood flow simulation. It combines a 3D geometric model, Windkessel models, a fluid-structure interaction (FSI) model with regionally varying tissue properties, a posteriori gradient-based mesh adaptation method, and an external tissue support formulation. A FSI method is necessary to capture pulse wave propagation within an arterial network, CRIMSON employs a coupled momentum method developed by Figueroa and Taylor [6]. Here, the elastodynamic equations representing the deformation of the wall are incorporated in the stabilized finite element formulation of the Navier-Stokes equations and a traction field describing the wall behavior is applied as boundary condition to the lateral boundary of the fluid domain. The vessel wall is modeled as a linear elastic membrane characterized by a 5x5 stiffness matrix, a Poisson ratio $\nu$ and a thickness $h$. The order of the components of the stiffness matrix corresponds to the directions: $\theta\theta$, $ZZ$, $\theta Z$, $\rho\theta$, and $\rho Z$; where $\theta$ is the circumferential direction, $Z$ the axial direction and $\rho$ the radial direction. This stiffness matrix is first defined in the cylindrical coordinates of the mechanical testing, but then transformed according to the local in vivo coordinate system given by unit normal vectors in circumferential, axial, and radial directions. CRIMSON allows to specify spatially variable tissue properties, namely material...
stiffness (both isotropic and anisotropic) and thickness. For each vessel, the user can specify different tissue properties at discrete points along the vessel path. Between two different locations the values of stiffness and thickness are linearly interpolated by CRIMSON; hence value of stiffness and thickness have continuous distribution along the vessel path. Finally, for each surface triangle element of the mesh belonging to the wall boundary, CRIMSON computes the projection of the surface triangle centroids to the vessel path and it assigns the correspondent tissue properties.

In this work in vivo and in vitro data were collected in wild type and Fbln5<sup>-/-</sup> mice between 20 and 22 weeks of age. Mean blood velocity was acquired with ultrasound at ascending thoracic aorta and cardiac output was measured with trans-thoracic echocardiography. Central aortic pressure was measured using a SPR-1000 pressure catheter. 3D geometric models were obtained by segmenting Micro-CT imaging of the mouse aorta and its main branches. Nine pairs of intercostal arteries were subsequently added to each models. A flow waveform, computed from the experimental measurements of blood velocity and cardiac output, was prescribed as inlet boundary condition. Windkessel models were coupled at each outlet of the geometric model representing the distal vasculature to the level of capillaries. The Windkessel parameters were tuned to match experimentally measured pressure and flow splits. Lastly, we assigned values of linearized stiffness to the vessel wall as explained above. In order to rigorously quantify arterial mechanics, we used consistent methods of biaxial testing and data analysis that focus on near physiologic conditions. A two-dimensional four-fiber family constitutive model was first fitted using pressure-diameter, axial-force and axial stretch data measured in vitro at four different locations down the mouse aorta for both wild type and fibulin-5 deficiency mouse. Regional values of linearized biaxial material stiffness over the physiologic range of diastolic-to-systolic pressures were then computed from the constitutive model, using the theory of small on large [7], at in vivo conditions. Specific experimental and theoretical methods for quantifying biomechanical properties of the vessel wall are described in details in Ferruzzi et al. [8]. Stiffness values were assigned at locations indicated by the black points in Figure 1 within the ascending thoracic aorta, descending thoracic aorta, suprarenal abdominal aorta and infrarenal abdominal aorta and linearly interpolated or extrapolated to obtain a continuous distribution. The 3D aortic geometries are colorimetrically mapped according to the circumferential material stiffness (MPa).

3 RESULTS AND CONCLUSIONS

Figure 2 shows computed local and global hemodynamics based on measured regional biaxial tissue properties in wild-type and Fbln5<sup>-/-</sup> datasets. The Fbln5<sup>-/-</sup> mice exhibit marked increases in aortic tortuosity and biaxial stiffening of the descending and suprarenal aorta. The computed pulse pressure in the ascending thoracic aorta (point A, in red) follows closely the pressure measured experimentally (in black) and it increased by 43% (41 vs. 29 mmHg) in the Fbln5<sup>-/-</sup> model. While this hemodynamics metric can be measured experimentally, once calibrated against appropriate data, the computational model provides further information for regions that are inaccessible in the lab. For example, the pulse pressure increased by 30% at the level of the renal arteries in the Fbln5<sup>-/-</sup> model (25 vs. 19 mmHg), which could not easily be measured directly in the mouse. Pulse Wave Velocity (PWV), a clinical metric to measure central artery stiffness, was also evaluated. It increased, as expected, by 35% (4.6 vs. 3.4 m/s) in the Fbln5<sup>-/-</sup> model.

These types of computations will provide valuable insights into local and global changes in hemodynamics in mice models of cardiovascular diseases. This is a preliminary comparison that shows the potential that can be reached by this approach.

4 ACKNOWLEDGMENTS

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Figure 2: Wild type and fibulin-5 deficiency (Fbln5−/−) mouse models - in vivo and computed hemodynamics

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Reliable Predictions in Biomedical Applications: Uncertainty Quantification, Bayesian Inference & Model Selection II
INFORMATION SENSITIVITY FUNCTIONS FOR STUDYING IDENTIFIABILITY OF PARAMETRIC DYNAMICAL SYSTEMS

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SUMMARY
An extension to sensitivity functions based on the information-theoretic criteria of differential entropy and mutual information is presented. These information sensitivity functions quantify the amount of information gained through the measurements of a parametric dynamical system about the model parameters. This information gain can then be used to compare the parameters based on their relative ease of estimation, study which type of measurements and associated time-intervals are most informative about a given parameter, and study parameter identifiability, i.e. the question that given a set of measurements and associated uncertainty, which parameters can be reliably estimated.

Key words: identifiability, inverse-problems, information-theory, sensitivity functions

1 INTRODUCTION
In parametric dynamical systems, the question of parameter identifiability, i.e. whether the system parameters can be estimated given a certain set of uncertain physical measurements, remains both important and challenging to address. Indeed, such an identifiability study should be performed before the inverse problem of estimating the parameters is attempted and can, at least in principle, guide the type and frequency of measurements that should ideally be taken to obtain relatively better parameter estimates. While sensitivity analysis has been widely used to determine which model outputs (measurements) are most sensitive to which parameters, it does not quantify whether parameter estimation will be successful or not, except in the trivial case where the sensitivity of all the measurements to a given parameter is identically zero. Furthermore, parameter correlations and measurement noise are typically ignored in standard sensitivity analysis. Thomaseth and Cobelli [1] introduced generalized sensitivity functions (GSF) which assess where (in the time course of the measurements) information about individual parameters is most concentrated. While partly motivated by information-theoretic criterion, GSF are particularly hard to interpret in the presence of multiple sets of correlated parameters. This is because correlations need to be assessed by the magnitude of oscillations in GSF and in the presence of many oscillations it can become increasingly hard to determined which pairs of parameters are correlated. Pant and Lombardi [2] formulated a method to assess parameter information gain and its relation to parameter identifiability based on rigorous information-theoretic criteria of differential entropy and mutual information. While this method offers easy interpretation and is quite generic in terms of the structure of noise in the measurements, it is computationally expensive as it relies on a Monte-Carlo type estimation [3] of the associated information-theoretic quantities. In this article, an extension of the method in [2], which offers easy interpretation, is presented so that the required information-theoretic quantities of entropy and mutual information can be computed only by sensitivity functions (i.e. gradient information alone), thereby reducing the heavy cost associated with the Monte-Carlo type alternative. However, this extension limits its applicability to employ a Gaussian structure on both the priors for the parameters and the measurement noise. For most biological systems, these assumptions may be justified and the reduced computational cost in assessing parameter information gain and consequently parameter identifiability may hence prove beneficial.
2 METHODOLOGY

Consider the following dynamical system governed by a set of parameterised ordinary differential equations (ODEs)

\[ \dot{x} = f(x, \theta, t) \quad x(t_0) = x_0(\theta) \]

where \( t \) represents time, \( x \in \mathbb{R}^d \) is the state vector, \( \theta \in \mathbb{R}^p \) is the parameter vector, the function \( f : \mathbb{R}^{d+p} \rightarrow \mathbb{R}^d \) represents the dynamical system, and \( x_0 \) represents the initial condition at time \( t_0 \). Let \( S \in \mathbb{R}^{d \times p} \) denote the matrix of sensitivity functions for the system in equation (1), i.e. \( S = \nabla_{\theta} x \).

It is well known that \( S \) satisfies the following ODE system (obtained by differentiating equation (1) with respect to the parameter vector \( \theta \))

\[
\dot{S} = (\nabla_x f) S + \nabla_{\theta} f \quad S(t_0) = \nabla_{\theta} (x_0(\theta))
\]

Let \( x_n \) and \( S_n \) denote respectively the state vector and the matrix \( S \) at time \( t_n \). Under a Gaussian assumption, the prior uncertainty in \([x_0^T, \theta]^T\) can be written as follows

\[
\text{Mean } \left( \begin{bmatrix} x_0 \\ \theta \end{bmatrix} \right) = \mu_0 = \begin{bmatrix} \mu_{x_0} \\ \mu_{\theta} \end{bmatrix}, \quad \text{Cov } \left( \begin{bmatrix} x_0 \\ \theta \end{bmatrix} \right) = \Sigma_0 = \begin{bmatrix} S_0 S_0^T & S_0 \\ S_0^T & I_p \end{bmatrix},
\]

where \( I_p \) is an identity matrix of size \( p \).

Consider a linearisation of equation (1) around the mean values \((\mu_{x_n}, \mu_{\theta})\) at time \( t_n \) as

\[
x_{n+1} \approx x_n + \nabla_x f \bigg|_{x_n} \Delta t + \nabla_{\theta} f \bigg|_{\theta_n} (x_n - \mu_{x_n}) \Delta t + \nabla_{\theta} f \bigg|_{\theta_n} (\theta_n - \mu_{\theta}) \Delta t \]

and a first order discretisation of equation (2) as

\[
\frac{S_{n+1} - S_n}{\Delta t} = \nabla_x f \bigg|_{x_n} S_n + \nabla_{\theta} f \bigg|_{\theta_n}
\]

Starting from equation (3) one can propagate the means and covariances of the state forward in time using equation (4). Furthermore, by using equation (5) this propagation can be written only in terms of the sensitivity matrices \( S \). The end result is that the covariance of the joint probability distribution of \([x_n^T, x_{n-1}^T, \ldots, x_0^T, \theta]^T\) can be analytically written only in terms of the sensitivity matrices up to time \( t_n \), i.e. the matrices \( S_n, S_{n-1}, \ldots, S_0 \). Consider a linear observation operator where \( y_n \in \mathbb{R}^m \) is measured at time \( t_n \) according to

\[
y_n = H_n x_n + \epsilon_n,
\]

where \( H_n \in \mathbb{R}^{m \times d} \) is the observation operator and \( \epsilon_n \) is the measurement noise. Let \( \epsilon_n \) be independently (across all measurement times) distributed as

\[
\epsilon_n \sim \mathcal{N}(O_m, \Sigma_n),
\]

where \( O_m \) is a zero vector and \( \Sigma_n \) is the covariance structure of the noise. Now using equation (6) and the joint probability distribution of \([x_n^T, x_{n-1}^T, \ldots, x_0^T, \theta]^T\), one may analytically write the covariance of the joint probability distribution of \([y_n^T, y_{n-1}^T, \ldots, y_0^T, \theta]^T\) in terms of the sensitivity matrices, \( S_n, S_{n-1}, \ldots, S_0 \), the observation operators, \( H_0, H_{n-1}, \ldots, H_0 \), and the noise covariance matrices \( \Sigma_n, \Sigma_{n-1}, \ldots, \Sigma_0 \). Note that if the observation operator is non-linear it can be replaced by the tangent operator for the propagation of covariance.

The quantity of interest to assess information gain is the decrease in differential entropy of the parameters when the probability density changes from the prior density \( p(\theta) \) to the posterior density \( p(\theta | y_n^T, y_{n-1}^T, \ldots, y_0^T) \). This decrease in differential entropy, i.e. decrease in uncertainty and hence gain in information, is also the mutual information between the parameter vector \( \theta \) and the measurement vector \([y_n^T, y_{n-1}^T, \ldots, y_0^T]^T\). Since the entire joint covariance of \([y_n^T, y_{n-1}^T, \ldots, y_0^T, \theta]^T\) is available, one may compute mutual information between an individual parameter \( \theta_i \) and the measurements \([y_n^T, y_{n-1}^T, \ldots, y_0^T]^T\); this quantity shows (as a function of increasing \( n \)) how information
is gained about the parameter from the measurements and are called information sensitivity functions (ISF). Similarly, conditional mutual information between two parameters $\theta_i$ and $\theta_j$ given the measurements $[y_n^T, y_{n-1}^T, \ldots, y_0^T]^T$ quantifies the amount of correlation between the parameter estimates (see [2] for details). Finally, the computed quantities of mutual information and conditional mutual information can be used to assess parameter identifiability [2]. With the aforementioned recursion and Gaussian assumption on priors and noise structure, these quantities can be computed by only computing the sensitivity functions $S$.

3 RESULTS AND CONCLUSIONS

To demonstrate information sensitivity functions, a three-element Windkessel model, as shown in Figure 1a with inlet flow-rate as shown in Figure 1b, is considered. This example is also considered in [2] and the reference values of the parameters and measurement noise are adopted in this study. The measurement in this case is the inlet pressure $P_{in}$ and there are three model parameters: the proximal resistance, $R_p$, the compliance, $C$, and the distal resistance, $R_d$. Figure 2 show the normalised (to restrict between 0 and 1) information sensitivity functions and the generalized sensitivity functions of [1]. It is notable that the ISFs do not show oscillations as the underlying mutual information
criterion ensures that information gain is strictly non-decreasing. This is also intuitive as by adding a measurement the information that has already gained about the parameter cannot be decreased. In this particular example, the oscillations exhibited by the GSFs are not particularly large and furthermore since there are only three parameters interpretation of GSFs does not present any problems. Here, the ISFs and the GSFs convey similar information. For example, from both the ISFs and GSFs, it is clear that the information about the parameter $R_p$ lies in a very small time interval, $t \in [0.4, 0.5]$, and that information about the other two parameters $C$ and $R_d$ is available in the entire cardiac cycle. Lastly, even though the ISFs shown in Figure 2 are normalised to be compared with GSFs (which are designed to start at 0 and end at 1), the unnormalised ISFs inherently quantify which parameters are relatively easy or hard to estimate. For example, starting from a prior of unit variance for all the three parameters, the total information gains at the end of all the measurements for the parameters $R_p$, $C$, and $R_d$ is approximately 0.3 nats, 0.6 nats, and 1.0 nats, respectively. These magnitudes imply while the parameter $R_d$ is easiest to be estimated, the parameter $R_p$ is approximately three times as difficult to estimate as its information gain is almost a third of the information gain in $R_d$.

To conclude, novel sensitivity functions based on information theoretic criterion are presented. These are particularly useful when compared to generalized sensitivity functions as they are guaranteed to be strictly non-decreasing and hence unlike GSFs do not exhibit oscillations. This property makes them relatively easier to interpret. Furthermore, the magnitude of information gain can be used to rank the parameters for ease of estimation, and this magnitude can further be extended to study identifiability as presented in [2]. While these functions offer a computational advantage to the functions presented in [2], especially for dynamical systems where gradients can be easily computed (either directly or through an adjoint), they are restricted to employ Gaussian priors and Gaussian measurement errors. These assumptions may be justified for a variety of dynamical systems encountered in physiology, and in many cases simple reparameterisation of the model can be employed to convert, for example, log-Normal errors to Gaussian errors. In future, these sensitivity functions will be tested on other physiological models governed by both ordinary and partial differential equations.

REFERENCES


INFLUENCE OF VALVE POSITION AND INFLOW DIRECTION ON INTRAVENTRICULAR FLOW: UNCERTAINTY QUANTIFICATION OF PATIENT-SPECIFIC CARDIAC FLOW SIMULATIONS

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SUMMARY

In the following, the robustness of an echocardiography-based pathway for patient-specific CFD modelling of the left ventricle (LV) has been evaluated. In particular, the model robustness has been quantified with respect to changes in intraventricular valve parameterization, with analysis performed on two subjects with normal and reduced LV function, respectively. Initial results for changes in valve positioning indicate a flow feature output deviation of below 10\% when shifting valve position within 5\% of the apex-base distance. Additional uncertainty quantification is planned for shifted inflow direction, as well as in the choice of intraventricular flow feature output to use for analysis.

Key words: Patient-specific modelling, uncertainty quantification, left ventricle

1 INTRODUCTION

Realistic computational models and efficient numerical methods in combination with refined medical imaging has enabled patient-specific studies of complex biological phenomena, in particular within the area of biofluid dynamics. For cardiovascular applications, the study of blood flow motion through computer simulation has enabled a better understanding of aneurysmal growth [1] and rupture risk [2], as well as of cardiac remodeling mechanisms and complex 3D flow [3]. For the case of patient-specific cardiac flow simulation, ultrasound-based imaging has been suggested as an alternative to traditional computed tomography (CT) and magnetic resonance imaging (MRI)-based modelling pathways in order to overcome issues with temporal image gating as well as to enable for a more direct connection to daily clinical practice where echocardiography is the primary point-of-care [4]. However, with echocardiography providing less clear anatomical details, the influence of chosen boundary conditions might become crucial to clearly quantify, especially when treating intraventricular valve regions where distinct influences have been reported from e.g. valve opening mode [5], or in the choice of pressure/velocity boundary condition definition [6]. With an echo-based patient-specific model pathway for left ventricular modelling developed in our group [7], the aim of this study is to perform a detailed investigation of valve region influence on simulated flow field output. In particular, an uncertainty quantification study is planned for the relation between the simulated flow field output and valve region positioning and
inflow direction, respectively, all in order to understand the importance of such before potentially continuing into future clinical modelling scenarios.

2 METHODOLOGY

An existing pathway for patient-specific flow modelling of the left ventricle (LV) from transthoracic echocardiography (TTE) [7] was used to simulate the intraventricular flow of two subjects: one with normal LV function (ejection fraction (EF) = 57%, cardiac output (CO) = 4.1 l/min) and one with reduced LV function (ejection fraction (EF) = 23%, cardiac output (CO) = 1.5 l/min). In short, the pathway consisted of:

a) **Image acquisition**: 4D (3D + time) TTE of the entire LV, acquired in this study using a GE Vivid E9 (4VD, 1.7MHz/3.3MHz) at a frame rate of 45 and 34 fps for the subject with normal and reduced LV function, respectively.

b) **Endocardial segmentation**: Semi-automated segmentation of the endocardial border throughout the entire cardiac cycle using the 4D AutoLVQ [8] of the GE EchoPAC system (v. 1.13).

c) **Valve identification**: Delineation of mitral (MV) and aortic valve (AV) regions in the acquired 4D TTE images, subsequently projected onto the segmented surface mesh.

d) **Mesh generation**: Generation of tetrahedral volume mesh from the initial segmented endocardial surface mesh using anisotropic tetrahedral mesh elements with a maximum allowed side length of approximately 0.85 mm (using ANSA 15.3 (BETA CAE Systems S.A., Greece)). The resulting volume mesh consisted of approximately 2 000 000 cells for each subject.

e) **Numerical simulation**: Simulation of intraventricular flow, using an Arbitrary Lagrangian-Eulerian (ALE) formulation of the governing Navier-Stokes equations, with mesh updates performed continuously during all discrete time steps.

Following all outlined steps, velocity and relative pressure field was acquired for the entire LV for all time steps.

With previous studies indicating the influence of valve region definition on the entire LV flow [5,6], focus was put on quantifying output uncertainty in relation to LV valve definitions in the aforementioned simulation pathway. First, the influence of valve positioning was evaluated. For this, repeated models with varying MV and AV position was created for both investigated subjects, with each valve shifted 5% of the entire LV distance between apex and base towards a more anterior, inferior, septal, or lateral position, respectively, from its originally identified position. In total this generated a set of 7 models for each subject.

With repeated models generated, 17 spherical regions (radius = 5 mm, equaling around 850 nodes) were distributed inside each LV, in which differences in regional flow velocities were evaluated as a function of changing MV and AV position, respectively. The chosen regions were positioned to correspond to conventionally used 17-segment models of the LV [9]. Differences were quantified by evaluating the coefficient of variation, CV, at defined time steps in the cardiac cycle, with CV defined as:

\[
CV = \frac{\sigma}{\mu}
\]

with \(\sigma\) and \(\mu\) representing standard deviation and mean value, respectively. In addition to this, potential global changes in intraventricular flow behavior was qualitatively assessed by generating mean flow fields over diastole and systole, respectively.

Evaluations of the impact of perturbations of inflow direction are on-going, with details of such future developments given in the discussion section. Refined quantification of flow features are similarly planned.
3 RESULTS AND DISCUSSION

Table 1 shows the difference in CV for the subject with normal and reduced LV function, respectively, upon changes in MV and AV positioning.

Table 1: CV over the entire cardiac cycle, for normal (1) and reduced (2) LV, respectively. Data is given for the 17 spherical regions projected onto the 17 segment heart model [9], with 1 being the most basal anterior segment, and 17 being the most apical one.

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As seen, average deviations of around 5 – 7% was seen for all segments. No clear trend between basal or apical regions could be derived, even though slightly higher deviations in the more lateral sections for the shifting MV placement, as well as with a slight increase in CV towards more apical sections. In general, perturbations of MV seemed to generate higher CV for both normal and reduced LV patients, with a seemingly consistent difference of around 1% between the two.

With regards to discrete temporal positions, highest deviations were seen during the time points of predicted highest intraventricular velocities. At peak systole CV of up to a maximum of 51% was seen for the normal LV patient (segment 16), and up to 37% for the subject with reduced LV function (segment 14). Similarly, at peak E-wave, maximum CV of 42% was seen for the subject with normal LV function (segment 2) and of 27% for the subject with reduced LV function (segment 4). Interestingly, the highest peak systole deviations were observed at apical segments, whereas highest E-wave deviations were seen at more basal segments.

Figure 2 shows an example of average diastolic and systolic velocity fields for an investigated model perturbation. From a qualitative comparison, no major changes in general flow pattern was visible from any of the evaluated perturbations. However, with the method implemented, refined analysis in the form of e.g. quantitative jet geometry or flow component metrics, as well as a more detailed division of flow in diastole, is planned.

Figure 1: Average diastolic (top row) and systolic (bottom row) for the subject with normal LV function, for three perturbations of MV positioning. Note that each row has its own color axis.

The above findings indicate a rather robust behavior with respect to defined MV and AV positioning, with an average variation of below 10% for both evaluated subjects. With that in mind, singular time point deviations of up to 50% were observed in singular regions, indicating the challenge in evaluating highly regional flows without accurate boundary condition definitions.
Overall, even though initial indications are given by the presented work, an increased study population is needed to infer any statistically significant findings, both with regards to regional error deviations, as well as for potential differences between normal and reduced LVs. Additionally, potential model improvements in the form of additional heart chambers of valve leaflet inclusions could be added. However, added model complexity might come at a cost of boundary condition sensitivity; a matter that might be explored in future uncertainty quantification studies.

In addition to the above, studies are planned to evaluate the influence of inflow direction on regional flows, where in the above an inflow direction perpendicular to the defined MV cells have been imposed. Additionally, quantitative metrics are to be derived from the generated average flow fields in the form of e.g. diastolic jet depth or by quantifying changes in flow components as a function of model perturbation.

4 CONCLUSIONS

The robustness of an echocardiography-based pathway for patient-specific CFD modelling of the left ventricle was evaluated with respect the intraventricular valve positioning. Within evaluated position shifts, an output variation of below 8% was reported for both valves and for both subjects with normal and reduced LV functionality, respectively. With the model pathway in place, a more refined uncertainty quantification is planned to evaluate the effect of valve inflow direction, as well to infer clearly defined metrics for the evaluation of changes in intraventricular flow fields.

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REFERENCES

PATIENT SPECIFIC MODEL VALIDATION: A ROLE FOR UNCERTAINTY QUANTIFICATION AND SENSITIVITY ANALYSIS

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SUMMARY

Patient specific models in the clinic operate under significant uncertainties about model parameters and calibration data. As such it is important to account for these uncertainties when choosing appropriate models and submodels for patient specific simulations. Traditional approaches might consider model validation based on detailed experimental data measuring the system or subsystem across a wide range of conditions and individuals; however, this approach does not account for the lower quality calibration data available for patient specific simulations. We propose a method for applying uncertainty quantification and sensitivity analysis to augment traditional validation when selecting models for patient specific simulations.

Key words: model selection, uncertainty quantification, arterial blood flow

1 INTRODUCTION

Recently many have suggested a new era where personalized simulations based on mathematical models incorporating physiological and physical principles may be used directly in the clinic to inform treatment and diagnosis of diseases. Some examples already in use are tools to evaluate the severity of coronary stenosis \cite{1, 2}, and another tool to plan the creation of vascular access for dialysis \cite{3}. However, the data and models involved in these simulations almost always suffer from uncertainties and biases due to limitations in the accuracy of the data and simplifications of the models, required to make simulations feasible for clinical purposes. As these models may be used to make decisions about treatment, these uncertainties have risks associated with their use, i.e. perhaps the model indicates a false positive and subsequently treatment costs and side effects may incurred unnecessarily. No better is the case where the model mistakenly causes no treatment to be performed and the patient’s status subsequently worsens, at worst causing mortality. These risks must be accounted for minimized to an acceptable level for confidence in routine clinical usage of computational models.

These risks motivate a somewhat different approach to model analysis in comparison to traditional model validation based on detailed experimental data. In the traditional situation, the best model is typically that model which can relate input data to prediction with the least error; however, in laboratory situations the inputs and predicted quantities are often known to quite high accuracy and precision. Clinical applications often have much less precision in the available measurements, and typically it is of interest to predict quantities that cannot be measured, thus no reference values are available for comparison. We suggest an approach to model selection and development that acknowledges the importance of choosing models which not only accurately fit data in the traditional sense, but that are also sufficiently reliable in the clinical context. This approach consists of applying uncertainty quantification and sensitivity analysis prior to model selection to determine which models may perform best in clinical settings.

We demonstrate the application of this approach for determining which arterial wall model may be most suited for patient specific simulations of arterial hemodynamics given noninvasive clinical measurements. Our example suggests that changing the perspective used for model validation and selec-
Figure 1: We present intervals accounting for 95% of the probability distribution (dashed lines) and the expected value (solid lines) of patient specific model of pressure and flow in the splenic artery for the three wall models \textit{quadratic} (red), \textit{logarithmic} (blue) and \textit{arctan} (green) compared with experimental data (black).

2 METHODOLOGY

To demonstrate this new approach of model choice and validation based on a balance of accuracy and risk, we consider the application of 1D blood flow models for patient specific simulations. In particular we developed a model calibration process to perform patient specific simulations based on clinical measurement of arterial lumen area, pulse wave velocity, and blood pressure. Based on these measurements we performed a patient specific arterial blood flow simulation using the framework presented by Eck. et al. \cite{4}. We then evaluated this process using data generated from a 37-vessel synthetic network that has been used widely for validation of 1D blood models \cite{5,6,7,8}. We first compared the model performance given exact measurements for the calibration procedure to quantify the deterministic model error, then we performed uncertainty quantification and sensitivity analysis based on realistic uncertainties in the calibration measurements to quantify the reliability of the model during clinical usage. In particular we employed polynomial chaos to propagate uncertainties and to evaluate sensitivity indices.

We performed the outlined analytical procedure for three widely used relations for arterial pressure and cross sectional area. The most complex of these models is based on experimental data \cite{9} and was developed by Stergioupolous et al. \cite{10} and applied to 1D blood flow modelling by Raymond et al. \cite{11}. We will refer to this as the \textit{arctan} model. Another model was derived from experimental data by Hayashi et al. \cite{12} and applied to 1D blood flow modelling by Eck et al. \cite{4}. We will refer to this as the \textit{logarithmic} model. Finally, perhaps the most widely used model is based on Laplace’s law and linear elasticity for thin walled tubes. This model was used in a recent benchmarking paper on 1D blood flow modeling \cite{8}. We will refer to this as the \textit{quadratic} model.

3 RESULTS AND CONCLUSIONS

The results of our analysis showed that while the most complicated model, \textit{arctan}, was perhaps most accurate in the deterministic sense, more simple models may be more reliable with respect to the calibration procedure we developed for model personalization. Further the results of sensitivity analysis suggest that while the two more complicated models, \textit{arctan} and \textit{logarithmic} may require all three measurements, the \textit{quadratic} model requires only two of three measurements (area and wave speed) and thus may be a more efficient model for routine clinical application of personalized measurements.

In conclusion, we presented a conceptual framework for model choice and validation in the context of model personalization that accounts for the intrinsic uncertainties of the measurements required for model calibration. We demonstrated the application of this framework to the examples of performing personalized model predictions based on 1D blood flow simulations of a synthetic arterial network using three distinct models of the arterial wall. We showed that this framework may change the model that is deemed best if the criterion is to balance lowest uncertainty in model prediction with general accuracy. We encourage further development of model validation and selection strategies that explicitly acknowledge the limitations of clinical measurement procedures in contrast to the more...
detailed measurements that may be available for validation of the underlying physical and mechanistic models used to build patient specific models.

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TOWARDS A MULTI-FIDELITY HEMODYNAMIC MODEL PIPELINE FOR THE ANALYSIS OF CARDIOVASCULAR FLOW UNDER UNCERTAINTY

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SUMMARY

Deterministic hemodynamic models are successfully employed in various branches of cardiovascular disease research. However, their widespread adoption is hindered by their inability to account for uncertainty stemming from multiple sources. A possible approach to performing stochastic analysis on these systems, while maintaining reasonable computational cost, is to leverage multiple varying-fidelity models of the same cardiovascular flow. In this context, we propose an automatic pipeline to convert three-dimensional vascular models into their one-dimensional approximations, and discuss its validation and integration in the SimVascular software suite. Finally, various approaches for non-intrusive uncertainty propagation are demonstrated and compared using one-dimensional parametric models.

Key words: one-dimensional hemodynamics, uncertainty quantification, multi-fidelity uncertainty propagation, finite element cardiovascular modeling

1 INTRODUCTION

Hemodynamic modeling is increasingly being adopted in the diagnosis and treatment of cardiovascular disease and surgical planning. Examples include non-invasive detection of hemodynamically significant stenosis in the coronary and peripheral arteries from clinical image data, or testing surgical designs for total cavopulmonary connections in palliative surgeries for patients with single ventricle physiology. Hemodynamic modeling generally consists of anatomic model construction from medical image data, followed by solution of the incompressible Navier-Stokes equations governing blood flow in elastically deformable vessels. However, various simplifying assumptions can be made to generate models of “intermediate complexity.” For example, it is possible to disregard the surrounding vessel deformability (so-called rigid wall assumption) which avoids the solution of the elastic problem and fluid-structure interaction coupling. Further simplifications may be related to the flow dimensionality and patient specific geometry of the vasculature. The so-called one-dimensional formulation of hemodynamics, for example, integrates the equations across the vessel cross section, thereby reducing the dimensionality to solve for flow and cross sectional area as a function of time and axial distance. This is typically done for Newtonian flow with deformable, impermeable and elastic walls, allowing for a range of material models.

A linearization of the incompressible Navier-Stokes equations around rest conditions leads to a formulation which is analogous to the evolution of voltage and current in an electrical circuit, the so-called zero-dimensional (or lumped parameter) formulation. These are computationally inexpensive and are often employed to provide boundary conditions in multi-scale cardiovascular models, which consist of a coupling between a stabilized finite element solver and a lumped parameter model of the peripheral circulation.

In contrast to many other branches of computational mechanics, computations of biological and biomedical systems are intrinsically affected by multiple sources of uncertainty. Under these conditions, a deterministic description of the hemodynamic response provides limited information of...
the process under study. This motivates the transition to a stochastic framework where all parameters affecting boundary conditions, material constitutive behavior and model geometry are defined in probability with distributions either assumed or assimilated from available patient-specific data.

In this talk, we discuss our efforts to create an automatic pipeline generating a cascade of varying-fidelity cardiovascular models ranging from computationally inexpensive, patient agnostic lumped parameter models to computationally intensive, patient-specific models of blood flow. Due to the computational cost of performing stochastic analysis (parameter estimation and uncertainty propagation) directly on the multi-scale models, this pipeline facilitates the statistical characterization of quantities not significantly affected by the three-dimensionality of the local flow field and whose statistical characterization can be performed at a reduced computational cost.

We also show the integration of the proposed pipeline in the SimVascular open source framework [1] (www.simvascular.org), in which the one-dimensional model is automatically generated based on the vessel centerline paths and segmentations created in SimVascular from the medical images acquired on the patient. We also present a validation study, comparing the pressures and flows obtained from the one-dimensional and three-dimensional models and critically discuss their difference in light of the underlying assumptions.

Finally, we discuss the initial steps towards the development of a framework for uncertainty propagation that takes advantage of a cascade of models with increasing fidelity.

1.1 Mathematical model for one-dimensional hemodynamics

We provide a brief summary of the one-dimensional formulation of hemodynamics adopted in this talk in this section. This formulation, adapted from the Newtonian method developed by Hughes and Lubliner [2], assumes flow in the axial (z) direction, uniform pressure across cross sections, and a non-slip condition at the walls. The constitutive relationship proposed by Olufsen et al. [4] relates pressure and radial wall deformation.

The numerical solution is determined by solving the variational formulation, arising from the incompressible Navier-Stokes equations for conservation of momentum and mass in a cylinder, with a modified Newton-Raphson iterative scheme. Additional details of this stabilized space-time finite element method are explained in [5]. A wide range of boundary conditions are available for the one-dimensional formulation, with details of the implementation presented in [3].

2 METHODOLOGY

2.1 Three-dimensional to one-dimensional model pipeline

Our one-dimensional solver accepts input files divided into several cards. Joints are defined at the intersection of straight vascular segments, specifying the segments entering and exiting the joint. Segments are straight cylindrical tubes connected through joints, representing a blood vessel with axis-symmetric deformation. Input waveforms (flow or pressure) are prescribed at the inlet joint, while boundary conditions can be applied to the model outlets. Both initial and boundary conditions use data tables to specify temporal or frequency dependence. Linear elastic and material models can be described through material cards, for example using the constitutive models introduced by Olufsen and others [4]. Work is underway to extend the code with the ability to couple the inlets/outlets with a zero-dimensional lumped parameter model.

We created a python script pipeline to automatically convert SimVascular segmentation group files into an input file compatible with the one-dimensional solver. The geometry of the model, consisting of path centerlines and cross-sectional segmentations, is extracted and converted into joints and segments by automatically detecting the intersections between different Simvascular segmentation groups. The script handles simple joints (two segments connected linearly), as well as more complex configurations with multiple inlets and outlets, such as a parent vessel bifurcating into two child branches. All intersections are recorded and their cards are written to the input file, along with the specified boundary condition, initial condition and material property cards.
2.2 Validation with patient-specific modeling

The results from the one-dimensional solver were validated by comparing the model outputs generated from a three-dimensional model with those converted to a one-dimensional model through the proposed pipeline for two patient models. The first is a patient-specific model of the aorto-iliac bifurcation. This model was chosen for the length of the vessel, to demonstrate the change in pressure and flow waveforms along the vessel length to confirm these results are replicated in both solvers.

This model is illustrated in Figure 1a. The second is a patient specific model including the thoracic aorta and the coronary arteries. This model was selected to perform model validation under a wide range of vessel diameters, as well as to ensure proper functioning for future uncertainty quantification work using coronary model databases. This model is illustrated in Figure 2a.

For both models, resistance boundary conditions at the outlets and both steady and pulsatile inlet waveforms were utilized. Outlet resistance values were tuned to produce physiological pressure and flow output waveforms, with an average pressure of 80 mmHg and the Womersley flow profile resulting in 5 L/min of blood flow. The three-dimensional simulations were run with a rigid wall assumption, and the one-dimensional model was run with an Olufsen material model, where parameters defining the elastic modulus \( k_1, k_2, \) and \( k_3 \) were given by \( 2 \times 10^7, -22.5267, \) and \( 8.65 \times 10^5 \) respectively.

2.3 Uncertainty quantification

Perturbations in boundary conditions, constitutive model and geometrical parameters can be easily implemented using a one-dimensional formulation, by direct interaction with the input file format. Ease of parameterization together with limited solution cost make a one-dimensional hemodynamics solver ideal to perform comparison between the performance of various non-intrusive methods for uncertainty quantification. Moreover, by systematically exploring the solution associated with various parameter realizations is is possible to further study the robustness of the implemented solver.

In this talk, a preliminary investigation is presented that considers uncertainty in the outlet resistances in a model of the aorto-iliac bifurcation. Several methods were compared, including Monte Carlo and Quasi-Monte Carlo simulation, generalized polynomial chaos (gPC) and a recently proposed generalized multi-resolution expansion for uncertainty propagation.

3 RESULTS

The aorto-iliac bifurcation Figure 1a and coronary models Figure 2a are analyzed under steady state and pulsatile flow conditions. Flow profiles generated with the one-dimensional and three-dimensional solvers, illustrated for the two models in Figure 1b and Figure 2b respectively, agree well both in shape and amplitude. Conversely, the two solvers generate slightly different pressure profiles as shown in Figure 1c and 2c. These differences are, however, justified due to the respective underlying assumptions for the deformability of the vessel walls. We expect these differences to be minimized by including fluid-structure interaction capabilities to the three-dimensional solver.

4 CONCLUSIONS AND FUTURE WORK

The results of our validation study confirm the consistency of three-dimensional and one-dimensional model outputs. The results are also consistent with the formulation of the two underlying solvers where the difference in vessels model deformability justified the observed differences in output pressures and flows. This relates to the wall material model implemented in the one-dimensional solver and the rigid wall formulation considered instead in the three-dimensional case.

Our parametric studies confirmed the robustness of the one-dimensional hemodynamic solver to a variation in the boundary conditions, material and geometrical parameters. In our uncertainty study, convergence to the output statistics confirmed the expectations, with Monte Carlo approaches requiring the larger number of model realizations followed by Quasi-Monte Carlo and gPC. Multi-
resolution uncertainty propagation required the least number of model evaluations taking advantage of built-in adaptivity.

Future work will be devoted to perform additional validation tests using the SimVascular’s fluid structure interaction capability, and on investigating how to take advantage of a cascade of automatically generated multi-fidelity cardiovascular models to speed up the computation of the response statistics.

REFERENCES

ACCELERATED PARTICLE FILTER METHOD FOR STATE ESTIMATION BASED ON A REDUCED MODEL: AN APPLICATION TO THE HYPERThERMIA TREATMENT OF CANCER

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SUMMARY

In this paper, the hyperthermia treatment of cancer induced by near-infrared laser and assisted by plasmonic nanoparticles is formulated as a state estimation problem. The solution of the problem is obtained with the Particle Filter, with an online update version of the Approximation Error Model (AEM), by using simulated temperature measurements assumed available from one single sensor.

Key words: inverse problem, particle filter, approximation error model, hyperthermia

1 INTRODUCTION

With the rapid development of computational resources, Particle Filters have become a very popular class of numerical methods for the solution of state estimation problems within the Bayesian framework[1-3]. In such kind of problems, the available measured data is used together with prior knowledge about the physical phenomena and the measuring devices, in order to sequentially produce estimates of the desired dynamic variables. This is accomplished in a probabilistic framework, so that, the solution of the state estimation problem consists in estimating a posterior probability density [1-3].

Unlike methods from the Kalman filter family, particle filters do not rely on local linearizations or any prior assumptions about the posterior probability density[1-3]. The posterior probability density, target of the solution of the state estimation problem, is then represented by a set of samples with associated weights, referred to as particles [1-3]. These features make the particle filter method a very useful approach for the quantification of uncertainties present in the mathematical formulation of a given physical phenomena, as well as in the measurements which might be eventually available. Although quite powerful, the associated computational cost of particle filter methods is generally high, especially in multiphysics problems. In these situations, one might make use of model reduction techniques and the Approximation Error Model (AEM), which was introduced in [4]. The AEM was successfully applied to the hyperthermia treatment of cancer by the authors [5]. However, in [5] the approximation errors were computed solely based on the prior information available for the parameters. We now extended such an analysis with an online update of the statistics of the modeling errors, as advanced in [6]. The algorithm of Liu and West [3] is applied for the solution of the state estimation problem.

2 STATE ESTIMATION PROBLEM AND TRANSIENT APPROXIMATION ERROR

The formulation of a non-stationary inverse problem in terms of evolution and observation models is referred to as a state estimation problem [1,4]. Let the state vector be $\mathbf{x}_k$, which contains all the state variables that describe the system at a given time instant $t_k$. We further assume known the
state evolution model and the observation model, which are respectively defined by the functions $f_k$ and $g_k$ [2]:

$$ x_k = f_k(x_{k-1}, \theta, w_{k-1}) \quad , \quad k = 1, \ldots, M \tag{1.a} $$

$$ z_k = g_k(x_k, \theta) + v_k \quad , \quad k = 1, \ldots, M \tag{1.b} $$

where $\theta$ is a vector containing all the non-dynamic parameters of these models, while $w_k$ and $v_k$ represent the noises in the state evolution model and in the observation model, respectively. The objective of the state estimation problem is then to obtain information about the state vector $x_k$ based on the evolution and observation models defined by equations (1.a,b) [2,4].

In the filtering problem addressed here, the target density is the joint posterior probability density of the state variables and non-dynamic parameters, $\pi(x_k, \theta | z_{1:k})$. The Liu and West version of the particle filter [3] is used in this work for the estimation of $\pi(x_k, \theta | z_{1:k})$.

The state evolution and observation models, given by equations (1.a,b), are assumed to accurately represent the physics of the problem and of the measurement techniques, respectively. The computational cost for the calculations involved in equations (1.a,b) might be high, especially for multiphysics problems such as the one in this work. The statistical model reduction technique, referred to as the Approximation Error Model (AEM), enables the use of reduced models and accurately takes care of the mismatch between the complete and the reduced models. In the nonstationary version of the Approximation Error Model, the modeling errors are treated as additional noises in the evolution state-observation models and computed with the prior information available for the model parameters.

Following the approach developed in [7], let $f_k'(x_k', \theta', w_k')$ and $g_k'(x_k', \theta')$ be reduced evolution and observation models, respectively. The reduced parameter vector $\theta'$ and the reduced state vector $x_k'$ might be of dimensions smaller than those of $\theta$ and $x_k$, respectively, which appear in the complete models $f_k(x_k, \theta, w_k)$ and $g_k(x_k, \theta)$. For models defined by discrete numerical methods of partial differential equations, a straightforward choice for reduced models is the use of coarse meshes. Hence, we consider the existence of a linear operator, typically an interpolation mapping $P$, between a sufficiently refined mesh and a coarse mesh, so that $x_k' = P(x_k)$ [7]. The reduced evolution and observation models are then given respectively by

$$ x_k' = f_k'(x_k', \theta', w_k') + \omega_k' \tag{2.a} $$

$$ z_k = g_k'(x_k', \theta') + v_k' + v_k \tag{2.b} $$

where $\omega_k'$ and $v_k'$ represent the modeling errors at time $t_k$, which are given by:

$$ \omega_k' = P_k f_k(x_{k-1}, \theta, w_{k-1}) - f_k'(x_k', \theta', w_k') \tag{3.a} $$

$$ v_k' = g_k(x_k, \theta) - g_k'(x_k', \theta') \tag{3.b} $$

In order to obtain samples of the modeling errors, a Monte Carlo simulation is performed by sampling over the prior distribution of the parameters. Then, by assuming the modeling errors as Gaussian, their statistics can be computed. With the objective of obtaining better estimates of the statistics of the modeling errors, an importance sampling error approach, which gathers the information of the measurements, was suggested in [6]. In this approach, the importance weights are computed with the likelihood of the samples of the accurate models. It should be noticed that, during the computation of the modeling errors, samples of the accurate model are available. Thus, if these samples are saved, they can be used in equation (4) to compute the following approximate conditional means and covariances of the modeling errors, as the measurements sequentially become available:

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where $f_\omega$ and $g_\nu$ represent the mean or the covariance of the modeling errors $\omega_k$ and $\nu_k$, respectively, while $w_k$ and $\tilde{w}_k$ represent the corresponding importance weights computed with the likelihood based on the complete model.

3 PHYSICAL PROBLEM AND MATHEMATICAL FORMULATION

The physical problem under analysis in this work involves the heating of a cylindrical phantom with an external collimated Gaussian laser beam under constant illumination. The phantom is assumed to be made of polyvinyl chloride plastisol (PVC-P) [8] and to contain a disk inclusion coaxial with the cylinder. This inclusion simulates the tumor and is supposed to be made of PVC-P loaded with gold nanorods, as illustrated by figure 1. The dimensions of the phantom are also presented in figure 1.

![Fig. 1 Sketch of the phantom containing the tumor](image)

The laser beam is assumed to be co-axial with the cylindrical medium. The laser radiation propagation in the phantom is modelled with the $\delta$-P1 diffusion approximation that is coupled to the transient heat conduction problem. For the sake of brevity the mathematical formulation is not presented here but can be readily found in [5,8]. Both radiation and heat conduction problems were solved with finite volumes and the alternating direction implicit (ADI) scheme [8]. In this work, the state variables are given by the temperatures at the discrete points inside the domain that coincide with the center of finite volume elements used in the discretization of the forward problem.

4 RESULTS AND CONCLUSIONS

Figures 2.a and 2.b present a comparison of the estimated and exact temperature distributions at the end of the heating period. The measurement errors are additive, Gaussian, uncorrelated, with zero mean and a constant standard deviation of 0.5 °C. These figures show that the temperatures in the region were accurately estimated and the model reduction is appropriately taken care of by the Approximation Error Model that was applied in this work. The estimated transient temperature variations at the sensor position and at a position where no measurements were available are shown by Figures 3.a and 3.b, respectively. It can be noticed in these figures that accurate estimates of the temperatures were obtained, demonstrating the robustness of the present approach. Moreover, the speed-up of the solution of the state estimation problem was about 100 times when the reduced model was used instead of the complete model.
Fig. 2 Comparison of the exact (a) and estimated (b) temperatures for \( N=500 \) particles at \( t=150 \) s

Fig. 3 Comparison of the estimated and exact temperatures for \( N=500 \) particles at: (a) the sensor position \((r = 2 \text{ mm, } z = 6 \text{ mm})\); (b) position \( r = 0 \text{ mm, } z = 10.5 \text{ mm} \)

REFERENCES

Mathematical Modelling of Biological Fluid Flows & Transport: Applications to Translational Medicine II
MATHEMATICAL MODELLING OF A FLUID FLOW IN COLLAPSIBLE TUBES

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SUMMARY

The paper presents a mathematical model governing a flow in a tube with collapsible walls. The model describes both stationary and non-stationary (oscillatory) modes. The governing system is obtained under a two-layer flow scheme assumption, used to describe pseudoshocks or regions of continuous transition from supercritical to subcritical flows.

Key words: collapsible tube, Starling resistor, two-layer flow

1 INTRODUCTION

A study of a fluid flow in a channel with a deformable wall is of high interest not only from the point of view of many applications (such as industry, biomechanics and biomedicine), but also in terms of construction and investigation of mathematical models describing the mutual motion of the fluid and the channel wall. A fairly detailed overview of theoretical models and main applications is given in [1].

One of the major problems of the theory describing the joint motion of the fluid and channel with compliant wall is a problem of a pulse wave propagation. To study these wave processes, one-dimensional model is widely use, which is similar in structure to the shallow water equations and one-dimensional gas dynamics. The closure relation ("equation of state") in this case is a relation between the pressure and cross-section area of the channel lumen. In the case of axially symmetric channel of a circular cross section (a tube with an elastic wall) with positive transmural pressure (pressure difference in the fluid and in the environmental medium), one deals with a medium with a convex equation of state, which sufficiently well describes the propagation of the pulsation waves [1,2]. However, in the case of a relatively small discharge when the transmural pressure is negative, the tube starts to shrink non-axisymmetrically that leads to new phenomena, such as for example sudden collapse of the tube and the development of large-amplitude self-excited oscillations. Figure 1 shows a scheme of a Starling resistor, allowing experimental and theoretical investigation of non-stationary phenomena observed in a thin flexible tube with low discharge of a liquid pumped through it. Note that for negative transmural pressures, the equation of state looses its convexity, and in the shallow water theory, formation of the hydraulic jumps corresponding to rarefaction shock waves is possible [3,4,5].

An attempt to describe the flow instability, depicted in figure 1, faces two major challenges: the need for taking into account energy losses due to the development of a turbulent boundary layer and setup of the boundary conditions on the boundaries of flexible and rigid tubes [1].

These problems can be solved within the framework of a two-layer flow scheme described below. An approach developed in [6,7] for description of a pseudoshock or a region of continuous transition from supercritical (supersonic) to subcritical (subsonic) flow in incompressible fluid and barotropic gas through the development of a turbulent boundary layer is used.
2 TWO-LAYER MODEL

Consider an axisymmetric flow of an ideal incompressible fluid in a tube with elastic walls, in which the continuous transition from supercritical to subcritical flow (pseudoshock) occurs. The mechanism of this transition is associated with the development of a turbulent boundary layer, the average flow velocity in which is less than the velocity of the main stream. If we assume that the boundary layer is formed in the vicinity of the elastic wall of the channel and the flow is symmetrical about its axis, then within the limits of this approach, it is sufficient to consider a two-layer flow scheme [6, 7]. Under these assumptions, the equations of motion take the form of:

\[
\begin{align*}
(su)_t + (su)u_x &= -\sigma q, \\
(su) + (\bar{s}u)_x &= \sigma q, \\
(u + uu)_x + \rho^{-1}p_x &= 0, \\
(su^2 + \bar{s}(\bar{u}^2 + q^2))_t + \rho^{-1}(s + \bar{s})p_x &= 0, \\
(su^3 + \bar{s}(\bar{u}^2 + 3q^2))_x + \rho^{-1}(su + \bar{s})p_x &= -\sigma \kappa q^3.
\end{align*}
\]

Here, \(s\) and \(u\) are the area and the velocity in the potential liquid core; turbulent boundary layer is characterized by its cross-section area \(\bar{s}\), average velocity \(\bar{u}\), and shear rate \(q\). Empirical parameters \(\sigma\) and \(\kappa\) are responsible for the mass transfer between the layers and the dissipation of energy. The pressure in the fluid depends on the cross-section area \(S = s + \bar{s}\) and the elastic properties of the wall along the tube. Henceforth, following [5], we choose the constitutive equation ("tube law") in the form:

\[
p = K(x) \bar{p}(S/S_0), \quad \bar{p}(\xi) = \xi^{10} - \xi^{-3/2},
\]

where \(S_0\) is the cross-section area corresponding to the zero transmural pressure.

For analysis of equations (1) it is convenient to obtain differential consequences for the variables \(\bar{u}, q\):

\[
\begin{align*}
\bar{u}_t + \bar{u}u_x + 2qq_x + \bar{s}^{-1}q^2s_x + \rho^{-1}p_x &= \frac{\sigma q}{\bar{s}}(u - \bar{u}), \\
q_t + q\bar{u}_x + \bar{u}q_x &= \frac{(u - \bar{u})^2 - (1 + \kappa)q^2}{2\bar{u}} \sigma.
\end{align*}
\]

Using differential consequences (3), it can be shown that (1) has one contact and at least two "sound" characteristics. In general case, system (1) is not hyperbolic, but the presence of at least three real characteristics allows numerical calculations using standard schemes.

3 NUMERICAL EXPERIMENTS

To illustrate the ability of the model to describe various flow regimes, we performed a number of computer simulations.

Numerical calculations based on equations (1–2) were performed using the 1-order Godunov and the 2-order Nessyahu–Tadmor schemes. Computations were carried out in dimensionless variables with the following parameters: tube length \(L = 30\), \(\sigma = 0.15\), \(\kappa = 6\), for discretisation in space \(N = 600\).
nodes were used. Empirical parameters σ and κ are chosen according to [6, 7]. The elastic properties of the channel wall are set by function

\[ K(x) = 1 + 3/(1 + \alpha (x - \lambda L)^8)^2. \]

Function \( K(x) \) introduces a region about \( x = \lambda L, \lambda \in (0, 1) \), of a local fourfold increase in tube stiffness. The parameter \( \alpha \) governs the width of the region. By varying stiffness function \( K(x) \) one can obtain different flow regimes [6, 7].

On the left border of the channel \( x = 0 \), the incoming supercritical flow is prescribed; at \( x = L \) no conditions are set, since the choice of function \( K = K(x) \) provides a supercritical condition on the right edge of the flow domain.

4 RESULTS AND CONCLUSION

In the first test (figure 2a) unperturbed tube cross-section area \( S_{in} = 1.2 \), the incoming flow velocity \( u_{in} = 25 \), the parameter \( \alpha = 0.01 \). In the second test (figure 2b) \( S_{in} = 0.8, u_{in} = 4 \) and \( \alpha = 0.1 \). The initial area of the turbulent layer at \( x = 0 \) is 0.1 of the channel cross-section area.

The results of the calculations show that if \( S_{in} > 1 \), i.e. in the region of convexity of the equations of state (2), smooth pseudoshock is formed, which can be either stationary or moving upstream depending on the incoming flow parameters and the boundary conditions. In figure 2b even in the absence of flow perturbations and steady-state boundary conditions, the flow becomes substantially non-stationary and exhibits quasi-periodic waves of large amplitude.

The proposed mathematical model is able to describe such flow regimes due to introduction of energy loss in boundary layer, without which no oscillatory solutions exist [1]. The mathematical model can be used to simulate flows in Starling resistor, which is a basic experimental setup for many physiological flows such as cardiovascular system, pulmonary system and others.

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THE EFFECT OF MOUTH-THROAT GEOMETRY ON REGIONAL DEPOSITION IN THE TRACHEOBRONCHIAL TREE

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SUMMARY

In silico methods offer a valuable approach to predict localized deposition in the tracheobronchial tree, important in the topical treatment of respiratory diseases and the systemic administration of drugs with limited lung bioavailability. In this study, we examine the effect of extrathoracic airway variation on regional deposition in order to assess whether standard mouth-throat models can be adopted for more efficient predictions. Despite large qualitative differences in the extrathoracic airways, deposition patterns and efficiencies in the tracheobronchial region remain largely unaffected for particles smaller than 6 microns. The findings suggest that for drug delivery applications, standard mouth-throat models could be adopted to predict deposition in the central airways.

Key words: inhaled drug delivery, regional deposition, conducting airways

1 INTRODUCTION

Pulmonary drug delivery is widely used for the topical treatment of pulmonary infections and respiratory diseases such as asthma, COPD and cystic fibrosis. More recently, the inhaled route has also been adopted for the systemic administration of drugs, due to the favourable absorption characteristics of the lungs. The efficacy of drug delivery depends, in part, on the site of deposition within the airways. Therefore, quantifying regional deposition is important in assessing and optimising topical treatments as well as systemic delivery of drugs with limited lung bioavailability.

In recent years, there have been significant advancements in pulmonary imaging techniques for \textit{in vivo} measurement of aerosol deposition [1]. However, spatial resolution remains insufficient for visualisation of localized deposition. For inhalation product development, the current industry standard is the use of standardised throat models mounted on cascade impactors, which provide estimates of total lung deposition but cannot determine regional deposition.

\textit{In silico} models can complement \textit{in vivo}\textit{ in vitro} testing and provide detailed information on regional deposition. However, high-fidelity simulations in realistic geometries of the respiratory airways are computationally demanding [2]. The aim of this study is to examine the effect of the extrathoracic airways on localized deposition in the tracheobronchial tree, in order to assess whether standard mouth-throat models can be used to predict deposition in the central airways. By adopting precomputed flowfields in these standard models, simulations can then be restricted to the tracheobronchial tree resulting in significant savings in computational cost.

2 METHODOLOGY

Three extrathoracic airways geometries, with different geometric and deposition characteristics, are merged onto the same tracheobronchial tree in order to examine the effect of the mouth-throat on the flow dynamics and deposition patterns in the central airways. The full geometries are shown in figure 1.
Large eddy simulations (LES) with a dynamic Smagorinsky sub-grid scale model are performed at a steady flow rate of 30 L/min [3]. For geometries R1 and S2, the inlet Reynolds number is in the laminar regime, therefore a parabolic velocity profile is prescribed at the inlet. For S1a, turbulent inflow conditions are obtained from a precursor simulation in a pipe. At the outlets, flow rates are prescribed to match in vitro measurements [4]. The ventilation distribution to the left and right lungs is non-uniform, with 71% of the inhaled volume entering the right lung.

To model the aerosol transport and deposition, a Lagrangian particle-tracking scheme is adopted. The equations of motion solved for the particle velocity and position are given by

\[ m_p \frac{du_p}{dt} = F_D + F_G + F_B, \]
\[ \frac{dx_p}{dt} = u_p, \]

where \( m_p, u_p \) and \( x_p \) are the mass, velocity and position of the particle respectively. The forces acting on the particles are the drag, \( F_D \), gravity, \( F_G \), and Brownian forces, \( F_B \). One-way coupling is adopted, and deposition is assumed once a particle comes into contact with the airway wall, due to the presence of sticky mucus gel. At each time step, 10 particles are released at random locations on the inlet plane, and 100,000 particles in total are tracked for each size.

### 3 RESULTS AND CONCLUSIONS

#### 3.1 Flow field

Figure 2 shows contours of mean velocity magnitude in the mouth-throat region and the trachea across the three geometries. Large qualitative differences in the flow characteristics can be observed in the extrathoracic airways. In the trachea however, the flow has time to develop and these differences are significantly diminished at the exit (figure 2b). Mean velocity fields in the main bronchi and smaller airways in generations 3 and 4 are shown in figure 3. Minor differences exist across geometries in the first bifurcation and the left main bronchus (figure 3a). A slightly larger variation is observed in the right bronchus, which can be attributed to the higher ventilation of the right lung. Further down the tracheobronchial tree, we continue to observe a similar trend. Variations in the flow are more prominent in the right lung, as shown in figure 3c. Overall however, despite significant differences in the extrathoracic flow dynamics, the mean velocity in the tracheobronchial tree remains qualitatively similar across the three geometries. Inspection of the secondary flow motion and turbulent kinetic energy reveals similar results.

#### 3.2 Aerosol deposition

The deposition fractions as a function of particle size, in the mouth-throat region and tracheobronchial tree, are shown in figure 4. In the extrathoracic airways, the large effect of geometric variation on
deposition efficiency is evident. In the tracheobronchial tree however, for particles smaller than 6 microns, total deposition is largely unaffected by the mouth-throat geometry. The deposition of 6 micron particles is shown in more detail in figure 5. Beyond the trachea, similar deposition patterns are observed across all three geometries, and deposition fractions show similar values even at a localized level (figure 5b).

For particle sizes typically used in drug delivery applications, i.e. 1-5 microns, localized deposition in the central conducting airways is largely unaffected by the mouth-throat geometry and could therefore be predicted using a standard extrathoracic model. Future work will verify these findings in different tracheobronchial geometries and at higher flowrates, which are relevant to more specific drug delivery applications in the upper tracheobronchial region.
Figure 4: Total deposition: Deposition fraction versus particle size in (a) the extrathoracic airways; and (b) the tracheobronchial tree.

Figure 5: Localized deposition for 6µm particles: (a) segment numbering on tracheobronchial tree [4]; (b) deposition fraction versus segment ID; and (c) deposition patterns.

REFERENCES


COMPUTATIONAL ANALYSIS OF NITRIC OXIDE BIOTRANSPORT IN PERMEABLE CAPILLARY INFLUENCED BY RED BLOOD CELL

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SUMMARY
In this work, we combined the spring network model of red blood cell (RBC) with IB-LBM to simulate the motion of a RBC in permeable capillary firstly. Based on the flow field, Nitric oxide (NO) production rate from endothelium was calculated by wall shear stress (WSS). NO distribution in capillary was obtained using IB-FDM. The results show that the lower NO concentration region is closely related to the RBC position in capillary. Moreover, when the transmembrane resistance of RBC is extremely smaller the plasma NO concentration gradients become flat and the lower NO region is restricted in the RBC core.

Key words: red blood cell, lattice Boltzmann method, immersed boundary method, permeable capillary, nitric oxide

1 INTRODUCTION
As a signal transduction molecule, NO can mediate a variety of physiological process in microcirculation [1]. Most importantly, NO released from endothelium was identified as a key regulation factor of arteriolar tone [2]. In addition, since the abundance of endothelial cells exist in capillary wall, capillary network forms an NO source and it contributes to NO transport to arteriolar wall. Mitchell and Tyml [3] concluded low basal levels of NO affect capillary blood flow by modulating local hemoconcentration and leukocyte adhesion and higher levels of NO may cause a remote vasodilation to increase microvascular blood flow. Thus, NO released from capillaries and its concentration distribution in and around capillaries play an important role in mediating blood velocity and physiological processes.
In order to carry out its physiological effect in microcirculation, NO must diffuse from its synthetic site to the target cells. As a small diatomic molecule, NO can diffuse freely and can be taken away by fluid. Most importantly, NO may be consumed and degraded by numerous reactions in the process of transmission. In particular, when NO diffuses from endothelial cells to capillary lumen, NO can be reacted with abundant hemoglobin in RBCs fast. On the other hand, an increase of vascular permeability to water and change of osmotic pressure in tissue can lead to transformation of flow field in capillary in some pathological conditions. And different motion and deformation of RBC would happen subsequently. Thus, when RBCs move and deform with fluid in permeable capillary, different resistance results from RBC membrane can modulate NO bioavailability. The objective of this study is to investigate the
influence of the movement and deformation of a RBC on NO distribution in a capillary.

2 METHODOLOGY

A 2D spring network including 60 particles was used to express the relation between the displacement and energy of particles. This model includes three energy stored in Stretch/compression spring, bending spring and the spring representing the incompressibility. LBM was used to calculate the collision and migration processes of fluid particles, where a force term was added to account for the influence of body force on the fluid. Employing Immersed boundary method, force term could be calculated through distributing RBC membrane force to the adjacent fluid grid points and the velocity of RBC membrane particles would be updated through interpolating the velocities of the adjacent fluid grid points.

Within the monolayer endothelium cells, WSS-dependent NO production rate is a critical parameter for determining NO concentration. A real-time experimental measurement found that the relationship between NO production rate and WSS is hyperbolic dependent. The specific equation to calculate NO production is as follows:

\[
R_{NO} = R_{\text{basal}} + R_{\text{max}} \frac{|\tau|}{|\tau| + a} \tag{1}
\]

NO transport in capillary is mainly determined by the following transient diffusion-convection equation.

\[
\begin{align*}
\text{intracellular:} & \quad \frac{\partial c_i}{\partial t} - D_i \Delta c_i - \bar{u} \nabla c_i - k_i c_i = F_{i,j} \\
\text{extracellular:} & \quad \frac{\partial c_e}{\partial t} - D_e \Delta c_e - \bar{u} \nabla c_e - k_e c_e = F_{e,j}
\end{align*} \tag{2}
\]

Where \(c_i\) and \(c_e\) are NO concentration in intracellular and extracellular, \(D_i\) and \(D_e\) are the diffusion coefficient of NO in intracellular and extracellular. \(k_i\) and \(k_e\) are first-order reaction rate constants of NO with hemoglobin in intracellular and extracellular, which are set to be \(2.047 \times 10^6 \text{s}^{-1}\) and \(44.5 \text{s}^{-1}\) respectively.

Regarding the permeability of RBC membrane to NO, we employed IBM as well to distribute NO flux \(f_{x_i}\) through RBC membrane to the adjacent fluid grid points \(\bar{x}_f\).

\[
F_{i,j} = \sum_m D(\bar{x}_m - \bar{x}_f)f_{x_i} \tag{3}
\]

\[
f_{x_i} = \frac{1}{dt} p_m (c'_e - c'_i) \tag{4}
\]

In Eq.4, \(p_m\) represents the permeability of RBC membrane to NO. \(c'_e\) and \(c'_i\) represent NO concentration of the two fluid nodes in the normal of the membrane closest to the RBC membrane particle.

Fig.1 shows the computational domain we employed to simulate the motion of RBC and NO concentration distribution. In this straight capillary, the blood can exchange with tissue in the
middle position. The sizes of vessel were labeled in Fig.1. The pressures at inlet and outlet are set to 0.3334 and 0.333 (LBM unit) respectively. In the process of calculating NO concentration, NO fluxes at inlet and outlet are set to be zero.

Fig.1  Schematic diagram of computational domain

3 RESULTS AND CONCLUSIONS

3.1 NO concentration distribution in capillary influenced by different permeability of capillary wall

Fig.2 (a) shows NO concentration distribution in impermeable capillary when the RBC arrives different positions of the capillary (t in Fig.2 represents calculation step). In this case, we assumed NO can diffuse across the membrane freely. Due to high NO consumption rate inside RBC, the concentration of NO in RBC is approximately close to zero. Moreover, the plasma NO concentration around RBC gives a large decrease due to free diffusion across membrane and convective effect. Fig.2(b) shows NO concentration distribution in exosmotic capillary when RBC moves forward along the capillary with free transmembrane diffusion. In this figure, the filtration coefficient of capillary wall and osmotic pressure were set to 0.001 and 0.32 (LBM unit). In exosmotic capillary, due to the decreased NO production rate and blood flow velocity along capillary, NO concentration along axial direction of capillary reduced significantly when the impact of RBC is not considered. When the motion of a RBC in the exosmotic capillary is considered, RBC gradually transformed from umbrella-shape into crescent shape. In addition, because of longer staying time of RBC in the capillary, remarkable lower NO concentration region appeared in the area of exit of capillary. Fig.2(c) gives NO concentration distribution in endosmotic capillary when a RBC is at different position of the capillary with free transmembrane diffusion. In this case, the filtration coefficient of capillary wall was set to 0.001. But the osmotic pressure was set to 0.347 (LBM unit), the tissue fluid can flow into the capillary. Because blood flow velocity increased along endosmotic capillary, NO production rate consequently increased. Contrary to the case in the exosmotic capillary, lower NO concentration region appeared in the entrance of capillary. Compared the three figures, we can find that the lower NO concentration region is the smallest in the impermeable capillary.

3.2 NO concentration distribution in capillary influenced by different permeability of RBC membrane

As can be observed from Fig.3 (a), when the transmembrane permeability is decreased, the region of larger plasma NO concentration gradient influenced by RBC has been decreased. Fig.3 (b) and (c) show the NO profiles along the radial and axial direction of capillary across the RBC area. It can be seen clearly the NO concentration profile at plasma layer become
sharper with the membrane permeability increasing because more NO passes through membrane into RBC core and reacts with hemoglobin. Meanwhile, the NO concentration at the capillary wall is decreased slightly with the membrane permeability increasing.

Fig. 2 NO concentration distribution in (a) impermeable capillary, (b) exosmotic capillary and (c) endosmotic capillary when the RBC arrived in different position with free transmembrane diffusion.

Fig. 3 Effect of different permeability of RBC membrane on (a) NO concentration distribution in impermeable capillary (b) the variation profile of NO concentration in the radial direction when x=78 (c) the variation profile of NO concentration along the axial direction when y=16, where RBC area is from x=73 to 92.

3.3 Conclusions

A model about NO transport in a permeable capillary containing a RBC has been developed, including the computation of blood flow velocity, RBC deformation, NO production rate, and NO concentration distribution. It is found that the lower NO concentration region is appeared in the exit of the exosmotic and the entrance of the endosmotic capillary and it is evidently larger than that in the impermeable capillary. The lower NO concentration region in capillary may be related to the position which easily induces microangiopathy. In addition, the plasma NO concentration gradient influenced by RBC is increased with the permeability of RBC membrane. Different hematocrit should be considered to investigate NO transport influenced by more RBCs.

REFERENCES

EVALUATING LIVER TISSUE MICROARCHITECTURE FUNCTION THROUGH GENERATION OF REPRESENTATIVE UNITS WITH DEFINED BOUNDARY CONDITIONS

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SUMMARY

Mathematical modeling of tissue function is highly sensitive to the choice of spatial representation. Recent advances in imaging techniques permit to obtain high-resolution scans of micro-architecture of vascularized tissue pieces. The direct use of such images makes the choice of boundary conditions extremely challenging. As an alternative, a representative tissue unit for which boundary conditions are known can be generated from statistical sampling of the concrete architecture.

In this work, we will explain the pipeline from generation until evaluation of blood vessel networks taking as an example the liver, including modeling of flow, compound transport and detoxification by the cells in representative liver units. We will also explain how simplifications or abstractions of the tissue geometry can impact the simulation results.

Key words: tissue functional unit, microcirculation, compound transport and metabolism, liver, sensitivity analysis

1 INTRODUCTION

The choice of spatial representation can impact the tissue model output, especially when considering metabolism of a substance in an organ micro-architecture. Therefore, when modeling transport and metabolism of a substance, the chosen spatial representation needs to be detailed enough in order not to modify the functional impact of the tissue on the concentration profile of the substance.

From confocal scans of tissue stacks, it is possible to obtain the micro-architecture of a tissue and analyze and quantify its main components separately (vascular network, cells’ positions and bile canaliculi network in case of the liver). This allows to simulate the transport of a drug or metabolite concentration profile into the tissue as well as exchanges with the surrounding cells and metabolism within cells. Yet, as those stacks are physically cut out of the tissue and represent only part of the network, imposing proper boundary conditions is challenging. To avoid this problem, it is possible to generate a statistically representative piece of tissue for which boundary conditions are more easily defined. Hoehme et al. [1] have generated a liver functional unit (called liver lobule) from a statistical analysis of confocal stacks. Starting from this network, our work improves the generation procedure to obtain a network with geometrical features closer to concrete liver architecture.

This communication presents the approach used as well as the impacts of those improvements on the modeled liver microarchitecture perfusion and function. In this aim, we will (i) introduce the generation of a representative network, focusing on the chosen geometrical indicators; (ii) explain how the representativeness of such a generated tissue can be evaluated, proposing dedicated indicators; (iii) study the effect of the architecture on the hemodynamics patterns and on the dispersion of a transported substance bolus; (iv) analyze the impact of the new architecture on the...
modeled liver function, through a model of ammonia detoxification, defined by Ghallab, Celliere et al. [2,3].

2 METHODOLOGY

Mice healthy liver confocal stacks have been stained and imaged at IfADo, Dortmund, Germany, following the protocol defined by Hammad et al. [4]. Using the image analysis tool TiQuant [5], the obtained confocal scans have been segmented to extract sinusoidal (capillary) and biliary networks as well as the hepatocytes’ (liver cells) positions. A statistical analysis has then been performed to collect, among others, distributions of branches’ lengths, radii, bifurcation angles, as well as cells’ volumes. Contact surface areas between blood vessels and hepatocytes as well as between hepatocytes and bile have also been calculated. Figure 1 shows the workflow from the confocal stacks to the generation of a statistically representative liver lobule.

Figure 1 – Workflow from confocal images to a statistically generated liver lobule.

Among those statistics, some are used to generate the network such as the radii, cells’ volume, bifurcation angles and total number of cells in a lobule. We have proposed indicators of the representativeness of the generated network such as the branches’ lengths distribution, and total length of the sinusoidal network.

Blood flow, transport and ammonia metabolism have then been simulated in the generated network. Blood flow has been modeled as a resistive network, taking into account the effect of red blood cells by Pries’ law [6] for viscosity. Boundary conditions were set in order to reproduce the measured average flow speeds in mouse. This results in a large algebraic system of equations solved by an iterative linear solver. Transport of ammonia in the blood, modeled by a 1D transport PDE, has been coupled with its metabolism in the cells modeled by a system of non-linear first order ODEs, through a passive uptake of ammonia. The metabolism model inside the hepatocytes was previously calibrated on healthy and drug-induced-damaged liver [2,3]. Ammonia levels at the liver outlet were predicted from known input levels. A comparison of the obtained hemodynamics (pressure, flow, wall shear stress) patterns as well as ammonia concentrations profiles in the different geometries has been performed.

3 RESULTS AND CONCLUSIONS

The distributions of branches’ lengths and radii provide significant insight on the representativeness of the generated blood vessel network, as they have the most impact on blood flow and transport. We propose a representative liver lobule that improves the sinusoidal network and hepatocytes’ number and volume, and discuss the limits of this geometry. Moreover, possible improvements will be highlighted along with the associated challenges, mostly concerning the coupling of the vessel network generation and the hepatocytes’ positions and volumes.

We find, for example, that while the effect of an increase or decrease of individual geometric network parameters on the hemodynamics may be predicted a priori, this is not the case for combined geometrical network parameters. This finding suggests, that the network parameters need
to be evaluated based on specific parameter distributions emerging from the experimentally analyzed tissue samples. E.g., having six (as in Fig. 2) instead of three inlets into a lobule homogenizes the flow pattern and hence the concentration distribution in space. This impacts the modeled ammonia detoxification, therefore the modeled liver function. We discuss the impact of boundary conditions, such as (i) imposed pressures, (ii) imposed total inflow in the lobule, (iii) number of blood inlets, on the flow pattern, see Figure 2, as well as on concentration distribution of ammonia. A systematic parameter study will be presented.

**Figure 2** - Example of hemodynamics patterns in a 3D representative lobule, view from the top

Such networks have been generated from mouse livers, but, provided that the same statistics are obtained, this technique can be extended to other animals such as pigs, and to humans.

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MATHEMATICAL MODELING FOR LIVER FUNCTIONS ESTIMATION WITH INDOCYANINE GREEN MEASUREMENTS

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SUMMARY

The indocyanine green (ICG) clearance, presented as plasma disappearance rate is, presently, a reliable method to estimate the hepatic function. However, this technique is not instantaneously available and thus cannot be used intra-operatively (during liver surgery). This article proposes to extract more information from the tissue imaging intensity, i.e. the liver concentration dynamics, by interpreting it through a dedicated pharmacokinetics model. The model output sensitivity to parameter is studied in two different regimes of the dynamical system. Then, parameters for different liver states are estimated, and their link with liver function is investigated.

Key words: Pharmacokinetic model, Sensitivity analysis, Parameter estimation, Indocyanine green fluorescence imaging, Liver functions estimation

1 INTRODUCTION

The indocyanine green is a fluorescent dye exclusively removed from the blood circulation by the liver cells \cite{1,2}. The ICG plasma disappearance rate is one of the most reliable method to estimate the hepatic ‘function’. The liver function can be divided in two steps, the uptake by the liver cells (the removal of ICG from the blood) and the secretion into the bile. A poor pre- or intra-operative evaluation of the liver function in liver surgery is an indicator of post-operative complications. Mathematical modeling of the processing of ICG by the liver may allow a better understanding of the liver functions and improve its assessment during surgery.

Several groups have worked on pharmacokinetic model of ICG concentration in blood. Compartmental pharmacokinetic models have been studied for healthy and cirrhotic patients \cite{3,4} and considering two fractions of ICG with different disappearance rate in pigs \cite{5}. In \cite{6} a minimal physiological model for liver uptake and excretion rate estimation has been developed. Parameter estimation has been based on arterial ICG concentration over time in dogs that are awake and under anesthesia. In \cite{7}, compartment models have been proposed to model the pharmacokinetics of ICG in cancerous tumors. Tissue ICG concentration, after injection of tumor cells under rat skin, has been used to estimate the exchange rate between blood and tissue with the extended Kalman filter. Liver tissue ICG concentration has been measured and the measurements have been fitted with a sum of two exponential functions in \cite{8,9}. Two parameters are estimated from the fitted measurements, interpreted as an uptake parameter and a removal rate from the liver.

Here, we focus on a more precise description of ICG processing by the liver, including three compartments for the liver model (sinusoids, hepatocytes and bile canaliculi). The description of the exchanges between the different liver tissues is a novelty compared with the previous models. Parameters are estimated by an inverse problem from the liver tissue measurements. The impact of different liver conditions on model parameters is studied.

2 METHODOLOGY

After injection, the indocyanine green arrives to the liver through blood vessels. It enters the liver through the sinusoids (smallest liver vessels where the exchanges occur), then an exchange between
Figure 1: Schematic representation of the pharmacokinetics model of ICG processing by the liver.

sinusoids and hepatocytes happens and ICG is secreted by the hepatocytes into the bile canaliculi. Finally the ICG exits the liver through the hepatic veins in blood or it reaches the common bile duct in bile. We build a pharmacokinetics model that represent each of these processes (see figure 1). The evolution of the concentration in each compartment over time is described by a system of ordinary differential equations (see eq. (1)). The ICG amount in the liver is assumed to be the sum of the amount of ICG in each liver compartment; sinusoids, hepatocytes and bile canaliculi.

\[
\begin{align*}
\frac{d}{dt}(V_{\text{blood}}C_{\text{blood}}) &= FC_s - FC_{\text{blood}} \\
\frac{d}{dt}(V_sC_s) &= FC_{\text{blood}} - (K_1 + F)C_s + K_1C_h \\
\frac{d}{dt}(V_hC_h) &= K_1C_s - K_1C_h - K_2(C_h) \\
\frac{d}{dt}(V_{bc}C_{bc}) &= K_2(C_h) - K_3C_{bc}
\end{align*}
\]  

(1)

The volume of each compartment and the liver inflow are estimated from literature. The parameters quantifying the exchanges between the different compartments are estimated by solving an inverse problem, where the ICG amount in the liver over time are the observations. First, a sensitivity analysis is performed to assess the sensitivity of model output to the parameters of interest, as well as parameter correlations. Two sensitivity tools are used: the traditional sensitivity and the generalized sensitivity [10, 11]. These tools are local analyses thus the initially chosen parameters impact the sensitivity functions. Therefore, the sensitivity analysis is performed for two different sets of parameters, representing two regimes of the dynamical system. In the first regime, a fast decrease of liver amount of ICG occurs, while in the second regime the decrease of ICG amount is slower. Then, the inverse problem is solved on synthetic data (for both regimes) to verify the approach. The method to estimate model parameters is the unscented Kalman filter [12, 13]. Three runs of the UKF algorithm are performed with different initial parameters to ensure the convergence.

3 RESULTS

The sensitivity analysis combined with inverse problem resolution on synthetic data (with added noise), enable a good understanding of model parameter dependency. In the two regimes, the sensitivity of model output is different as well as the correlation between the parameters. Because of the correlations between parameters and after solving few inverse problems on synthetic data, it was found that all exchanged parameters cannot be estimated. The sensitivity analysis and the inverse problem on synthetic data have shown that the parameter estimation is improved when parameter $K_3$.
is known for the first regime, and when \( K_1 \) is known in the second regime. Knowing \( K_3 \) in the first regime and \( K_1 \) in the second one, with three runs of UKF, the observation curve are well fitted (Figure 2). Figure 2 shows that the three runs are required to obtain a good fit of the observation curves, specially in the second regime (when the decrease of the liver amount is slow).

With the information on parameter estimation feasibility for synthetic data, the parameters are estimated with measurements on rabbit liver reported in [9] for two liver conditions (with a slow and a fast decrease of the ICG amount in the liver). In [9], typical indocyanine green curves of concentration over time in the rabbit liver are given. The ICG concentration is measured in a control group as well as after a bile ligation [9]. In the bile ligation group (second regime type), the parameter \( K_3 \) is known (set to zero because of the ligation), the other parameters can then be estimated with three runs of UKF. Next, the parameter \( K_1 \) is known (from the first estimation with bile ligation group curve), and the other parameters are estimated with the control group curve.

The estimated parameters are different in the two groups. In comparison with the control group, after bile ligation the secretion coefficient from hepatocytes to bile canaliculi is reduced (divided by around 300). These first results seem to indicate that bile ligation has an impact on liver cells secretion function.

4 CONCLUSIONS AND PERSPECTIVES

The three-compartment model for the liver, is able to reproduce the different types of measurements reported in [9]. Moreover the exchanges between the different liver tissue are represented and can be quantified. To estimate parameters and ensure convergence three runs of UKF are required. Further work will focus on the adaptation of the model to clinical applications, to propose a new method to estimate the liver functions intraoperatively.

REFERENCES


BOUNDARY LAYER CONSIDERATIONS IN A MULTI-LAYER MODEL FOR LDL ACCUMULATION

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SUMMARY

Boundary layer effects for Low-Density Lipoprotein (LDL) concentration problems in a multi-layer artery model are analyzed in this paper. Both a straight artery and aorta-iliac bifurcation are analyzed. Mass, momentum and species governing equations are written by means of the porous media theory and solved with the commercial finite-element based code COMSOL Multiphysics. For the straight artery, it is shown that the intramural pressure affects the concentration boundary layer, i.e. it increases with hypertension. Finally, an expression for the boundary layer of a straight artery that takes into account hypertension effects is also derived.

Key words: LDL deposition, Multi-layer model, Hypertension

1 INTRODUCTION

Predicting Low-Density Lipoprotein (LDL) deposition in an artery is of primary importance, due to the role that it has in the atherosclerotic plaque genesis. Such predictions can be performed by modeling the arterial wall with a wall-free, a single-layer or a multi-layer model [1]. The latter model is the most accurate one, since it enables us to analyze the concentration distributions within each layer of the artery. Both analytical and numerical approaches have been utilized. Analytical solutions were derived for straight arteries [2, 3], curved arteries [4] as well as taking into account hypertension and hyperthermia conditions [5]. When the geometry is more complex, as for stenosed arteries [3, 6, 7] or bifurcations [8], a numerical approach is necessary.

Since the arterial wall is permeable, LDL concentration in the lumen of the artery is affected by the so-called concentration polarization effect that causes deposition of LDL at the lumen/endothelium interface. The endothelium is the selective membrane in direct contact with the free blood flow in the lumen. This effect causes a boundary layer in the lumen, i.e. an increase of the concentration in near the wall. This phenomenon depends on various conditions, such as the geometry. In particular, for stenosed arteries, the region affected by this phenomenon is quite extensive due to high gradients caused by the lumen section reduction [9]. A boundary-layer approach for a curved artery was employed by Wang and Vafai [4]. In their work, an analytical solution was derived by considering that the concentration has a parabolic trend in the boundary-layer region [10].

In the current work, boundary layer effects for an aorta-iliac bifurcation and a straight artery under hypertensive conditions are analyzed. In order to solve the velocity, pressure and concentration field, Navier-Stokes and porous media equations are used in the lumen region and in the artery wall respectively. These equations are solved by a finite element method. An expression for the boundary layer thickness is also derived, in order to describe the region affected by the presence of the arterial wall.
2 METHODOLOGY

A sketch of an arterial wall is depicted in Fig. (1a). Four layers make it up: endothelium, intima, Internal Elastic Lamina (IEL) and media. The tunica adventitia, that is a layer adjacent to the tunica media, is replaced by a boundary condition [1, 2]. The aorta-iliac bifurcation geometry is presented in Fig. (1b). Iliac #1 and #2 diameters and length are 1.28 and 1.24 cm and 6.1 cm and 5.8 cm, respectively [11]. A symmetric configuration of the angulations (40°) is considered here [8]. Geometrical values of the straight artery are the same as that used in Yang and Vafai [2]. In particular, the lumen radius $r_{\text{lumen}}$ is equal to 3.1 mm, while the length $L$ is equal to 124 mm [2]. Governing equations are written assuming a Newtonian fluid [8]. A cylindrical coordinate $(r, z)$ system is employed for computations. Our computational scheme has been validated with experimental results from Meyer et al. [12].

![Figure 1 – a) Straight artery model with arterial wall and b) aorta-iliac bifurcation](image)

3 RESULTS AND CONCLUSIONS

For the aorta-iliac bifurcation, the concentration field in the proximity of the wall is presented in Fig. (2) for the iliac #1. It is shown that a flow recirculation zone exists just downstream of the curvature, that causes the wall shear stresses to become negative. It is known that low or negative wall shear stresses promote the formation of the atherosclerotic plaque. This causes a local enhancement in terms of the concentration; in particular, this zone coincides with the recirculation zone.

Concentration profiles for the straight artery for various axial coordinates are presented in Figs. (3a) and (3b) for transmural pressure $\Delta p$ are 70 mm Hg and 160 mm Hg, respectively. The transmural pressure is a driving force for the solute through the arterial wall, and it increases with the hypertension. It is shown that the closer to the wall, the higher concentration. Further, this effect looks to increase with the axial coordinate.

Boundary layers for different transmural pressures are presented in Fig. (4). A boundary layer criterion of $c/c_0 = 1.001$ has been chosen, i. e. the boundary layer starts when $c/c_0$ is higher than this value. The ratio $c/c_0$ is the dimensionless LDL concentration, with $c_0$ representing the inlet reference value, that is equal to $28.6 \cdot 10^{-3}$ mol/m$^3$. It is shown that the boundary layer increases with the axial coordinate, and a power-law fit of the numerical data is also reported.

Finally, multiple non-linear regression on numerical data has been performed in order to obtain the boundary layer thickness $\delta$ for different axial coordinate and transmural pressure:
\[
\delta \left( \Delta p, \frac{z}{L} \right) = a \Delta p^b \left( \frac{z}{L} \right)^c
\]  

with \( a = 2.73 \cdot 10^{-5}, b = 0.1646 \) and \( c = 0.377 \). With this expression, it is possible to estimate the boundary layer and to understand how the solute remains trapped in the lumen layer.

**Figure 2** – Dimensionless concentration fields and velocity vectors downstream of the iliac #1

**Figure 3** – Dimensionless concentration profiles \( c/c_0 \) in the proximity of the endothelium for different dimensionless axial coordinates \( z/L \) and transmural pressures: a) \( \Delta p = 70 \text{ mmHg} \) and b) \( \Delta p = 160 \text{ mmHg} \)
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INCLUSION OF DETAILED PURKINJE NETWORKS IN COMPUTATIONAL ELECTROPHYSIOLOGY

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SUMMARY

In this talk we consider the coupled problem arising between the electrical propagation in the Purkinje network and in the myocardium. We also discuss a method to generate personalized networks. The numerical results highlight the suitability of our strategies to describe both normal and pathological electrical conditions.

Key words: Purkinje network, activation times, action potential

1 INTRODUCTION

In this talk we aim at describing the electrical propagation in the human ventricle. To this aim, we consider a detailed Purkinje network, which is known to provide the source term for the myocardial activation. However, in some pathological cases, two electrical fronts propagate, one coming from the network as in the normal case, and one coming from the myocardium. Thus, suitable coupling methods between the network and the myocardium should be addressed.

A second important issue related to the inclusion of Purkinje fibers in computational models concerns the difficulty to obtain patient-specific networks due to the impossibility to detect them from standard radiological images.

2 METHODOLOGY

We discuss the coupling between Purkinje network and myocardium where monodomain subproblems are considered. The inclusion of monodomain model is of great interest, in particular in view of the electro-mechanical coupling in presence of Purkinje network. The monodomain model for the network is obtained following [1] and modeling explicitly the gap-junctions. This allows us to easily manage the conditions at the bifurcations. The 3D-1D coupled problem is obtained by writing suitable interface coupling conditions at the Purkinje muscle junctions (PMJ). We discuss the well-posedness of the coupled problem [2].
Concerning the development of personalized Purkinje networks, we start from clinical measures on the activation times acquired at the endocardium to adapt a fractal initial network [3] in order to minimize the discrepancy between measures and results [4,5].

3 RESULTS AND CONCLUSIONS

We compare for an idealized geometry the results obtained with the monodomain models with the ones given by the coupling between Eikonal problems. We also consider the Wolff-Parkinson-White (WPW) syndrome, characterized by an anomalous myocardial source of activation which requires the solution of an implicit coupling.

Our results were able to recover two important features of the electrical activation in the ventricle: first of all the so called push-and-pull effect characterizing the propagation through the Purkinje-Muscle junctions (PMJ) which are the interfaces between network and myocardium. Secondly, we were able to model the PMJ delay, that is the physiological delay which the electrical signal experiences at the PMJ, when passing from the network to the myocardium and viceversa.

Finally, we consider an application to a realistic case of a human ventricle and we address preliminary results about the cardiac resynchronization therapy, by searching for optimal locations of the stimulation points.

Cross-validation tests highlight that the generation of personalized networks greatly improves the accuracy with respect to the initial fractal network [4]. Moreover, the proposed strategy is able to manage pathological cases such as the WPW syndrome and the presence of scar regions [5]. Preliminary results on the effects of the inclusion of the Purkinje network in an electro-mechanical simulation are also reported.

REFERENCES

NUMERICAL MODELING OF THE INTEGRATED ELECTRO-MECHANO-FLUID PROBLEM FOR THE LEFT VENTRICLE

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SUMMARY
We propose different strategies for the numerical approximation of an integrated heart model describing the electromechanics of the myocardium and the fluid dynamics of the blood inside the left ventricle. Regarding the mathematical model, we consider the monodomain equation and the Bueno-Orovio minimal ionic model for the description of the electrophysiology and the Holzapfel-Ogden strain energy function within the active strain framework for the mechanics. The fluid-structure interaction uses the Navier-Stokes equations in ALE formulation. The Finite Element method is used for the space discretization, while Backward Differentiation Formulas are used for the time discretization. Monolithic and staggered schemes are compared with a particular focus on preconditioning strategies based on the FaCSI concept. The different approaches are tested in a high performance computing framework with a patient-specific geometry obtained from medical MRI images through segmentation and compared in terms of accuracy and efficiency.

Key words: electrophysiology, passive and active mechanics, fluid-structure interaction, integration of heart models, preconditioners

1 INTRODUCTION

The mathematical modeling of the heart involves numerous difficulties inherited by the complexity of its functioning. This is due to the intrinsic multiphysics nature of the problem: a satisfactory model should indeed describe a wide range of different phenomena such as the evolution of the action potential in the myocardium and the deformation caused by the muscles contraction [1]. However, while a good knowledge of the modeling of each phenomena is established, further studies are necessary in order to better investigate their interactions. From the numerical point of view, the characteristic time and spatial scales greatly vary among the physics under study posing the challenge of obtaining meaningful results at each considered scale. In this work, we focus on the Electro-Mechano-Fluid interactions of the Left Ventricle (LV).

2 METHODOLOGY

2.1 Electrophysiology

The electrophysiology model describes the complex electrochemical reactions occurring in the myocardium, triggered by an impulse delivered through the Purkinje fibers. This impulse causes a quick depolarization of the cardiomyocytes transmembrane potential, which in turn drives the concentration of different ion species. The ongoing interactions between the ions concentration and the potential cause a cascade effect generating a fast traveling wave known as action potential propagating through the myocardium.
We use the monodomain equation for the description of the evolution of the cellular transmembrane potential $V$ strictly coupled with a ionic model in the form of a system of ODEs:

\[
\begin{align*}
\chi \left( C_m \frac{\partial V}{\partial t} + I_{\text{ion}}(V,w) \right) &= \nabla \cdot (J F^{-1} D_m F^{-T} \nabla V) + I_{\text{app}} & \text{in } \Omega_0^s, \ t \in (0,T), \\
(J F^{-1} D_m F^{-T} \nabla V) \cdot N_s &= 0 & \text{on } \partial \Omega_0^s, \ t \in (0,T), \\
\frac{dw}{dt} &= \alpha(V)(w^\infty(V) - w) + \beta(V)w & \text{in } \Omega_0^s, \ t \in (0,T), \\
V(0) &= V_0, \ w(0) = w_0 & \text{in } \Omega_0,
\end{align*}
\]

where $\chi$ and $C_m$ are physical parameters and $D_m$ is the anisotropic myocardium conductivity tensor which depends on fibers and sheets direction (see Fig. 1). The domain $\Omega_0^s$ represents the (undeformed) myocardium and $N_s$ the outward directed unit normale vector on its boundaries. The coupling between the monodomain equation and the ionic model is represented by the ionic currents $I_{\text{ion}}(V,w)$ and the terms $\alpha(V), \beta(V), w^\infty(V)$, while the diffusive term encodes a feedback of the mechanics through the deformation tensor $F = I + \frac{\partial d_s}{\partial X_s}$ (where $X_s$ and $d_s$ are the reference coordinates and the displacement of the domain, respectively).

We use the Bueno-Orovio minimal ionic model [2] for its known simplicity and efficiency on large scale 3D geometries.

### 2.2 Active and passive mechanics

The mechanics model takes into account a number of different features of the myocardium. The passive properties of the muscle are modeled with the momentum conservation equation where the stress tensor derives from the Holzapfel-Ogden strain energy function $\mathcal{W}(F)$ [3] and, since moderate volume changes are observed during the heartbeat, we enforce an almost incompressibility condition by considering an additional term in the strain energy. The active mechanics, which is driven by the electrophysiology and defines how the muscle contracts without external loads, is encoded in the definition of the strain tensor $F_A(\gamma_f)$ in the active strain framework. The internal state variable $\gamma_f(x,t)$ represents the local shortening of the myocardium in the direction of the fibers and we assume that its evolution can be modeled with the following differential equation:

\[
\begin{align*}
\frac{\partial \gamma_f}{\partial t} &= \varepsilon \Delta \gamma_f + \psi(\gamma_f, w, d_s) & \text{in } \Omega_0^s, \ t \in (0,T), \\
\nabla \gamma_f \cdot N_s &= 0 & \text{on } \partial \Omega_0^s, \ t \in (0,T), \\
\gamma_f(0) &= \gamma_f, 0 & \text{in } \Omega_0^s,
\end{align*}
\]
where $\psi$ is a non linear function and $\epsilon \in \mathbb{R}^+$ is a smoothing parameter. The momentum equation then reads:

$$
\begin{cases}
\rho_s \frac{\partial^2 \mathbf{d}_s}{\partial t^2} - \nabla \cdot \mathbf{P}(\mathbf{d}_s, \gamma_f) = 0 & \text{in } \Omega_f^e, \ t \in (0, T), \\
K_N (\mathbf{d}_s \cdot N_s) N_s + \mathbf{P}(\mathbf{d}_s, \gamma_f) N_s = 0 & \text{on } \Gamma_0^{epi} \cup \Gamma_0^{base}, \ t \in (0, T), \\
\mathbf{P}(\mathbf{d}_s, \gamma_f) N_s + \sigma_f(\mathbf{u}_f, p_f) N_s = 0 & \text{on } \Gamma_0^{endo}, \ t \in (0, T), \\
\mathbf{d}_s(0) = \mathbf{d}_{s,0}, \ \frac{\partial \mathbf{d}_s}{\partial t}(0) = \mathbf{d}_{s,0} & \text{in } \Omega_f^t.
\end{cases}
$$

(1)

where $\mathbf{d}_s$ is the structure displacement, $\rho_s$ is the density and

$$
\mathbf{P}(\mathbf{d}_s, \gamma_f) = \det(F_A) \frac{\partial \mathbf{W}(F_E)}{\partial F_E} F_A^{-T}, \quad F_E = FF_A^{-1}.
$$

The first boundary condition in Eq. (1) can be interpreted as a generalized Robin boundary condition, which allows us to penalize the displacement in the normal direction on the epicardium and on the base, while the second one represents the continuity of the normal component of the mechanics and fluid stresses at the endocardium, $\sigma_f$ being the Cauchy stress tensor of the fluid.

### 2.3 Fluid dynamics and FSI

We use the Navier-Stokes equations to describe the fluid dynamics of the blood in the LV [4]. The Fluid-Structure Interaction (FSI) problem arising from the coupling of the fluid and of the mechanics subproblems is modeled by imposing the geometrical adherence of the deformed fluid and structure domains, and the continuity of the velocities and normal stresses at the interface [5]. In order to impose the geometrical adherence, we consider at each time $t$ the harmonic extension $\mathbf{d}_f$ to the fluid domain $\Omega_f^t$ of the trace of the solid displacement $\mathbf{d}_s$ at the interface:

$$
\begin{cases}
- \Delta \mathbf{d}_f = 0 & \text{in } \Omega_f^t, \\
\mathbf{d}_f = \mathbf{d}_s & \text{on } \Gamma_0^{endo}.
\end{cases}
$$

(2)

The solution of this problem defines the ALE map $A_t(\mathbf{X}_f) = \mathbf{X}_f + \mathbf{d}_f(\mathbf{X}_f, t) \ \forall \mathbf{X}_f \in \Omega_f^t$. The Navier-Stokes equations for an incompressible fluid written in ALE coordinates then read:

$$
\begin{cases}
\rho_f \frac{\partial \mathbf{u}_f}{\partial t} |_{\mathbf{X}_f} + \rho_f((\mathbf{u}_f - \mathbf{v}) \cdot \nabla) \mathbf{u}_f - \nabla \cdot \sigma_f(\mathbf{u}_f) = 0 & \text{in } \Omega_f^t, \ t \in (0, T), \\
\nabla \cdot \mathbf{u}_f = 0 & \text{in } \Omega_f^t, \ t \in (0, T), \\
\mathbf{u}_f \circ A_t = \frac{\partial \mathbf{d}_s}{\partial t} & \text{on } \Gamma_0^{endo}, \ t \in (0, T), \\
\sigma_f \mathbf{n}_f = \mathbf{g} & \text{on } \partial \Omega_f^t \setminus \Gamma_0^{endo}, \ t \in (0, T), \\
\mathbf{e} \mathbf{u}_f(0) = \mathbf{u}_{f,0} & \text{in } \Omega_f^t,
\end{cases}
$$

(3)

where $\Omega_f^t$ is the fluid domain at time $t$, $\mathbf{v} = \frac{\partial \mathbf{d}_s}{\partial t}$ is the fluid domain velocity, $\frac{\partial}{\partial t} |_{\mathbf{X}_f} = \frac{\partial}{\partial t} + \nabla \cdot \mathbf{v}$ is the ALE derivative, and $\mathbf{u}_f$ and $p_f$ are the velocity and pressure of the fluid, respectively. The first boundary condition in Eq. (3) represents the continuity of the velocities on the interface $\Gamma_0^{endo}$.

### 2.4 Numerical approximation and preconditioning

We use the Finite Element Method for the spatial discretization of the Partial Differential Equations and Backward Differentiation Formulas for the discretization of the time derivatives. We consider both fully implicit and semi-implicit schemes, the semi-implicit ones being obtained by linearizing the non-linear terms with an extrapolation of the variables at the current time from a linear combination of the solutions at previous steps.

The fibers and sheets fields are approximated as in [6] through a procedure which takes into account a transmural variation of the fibers direction, as suggested from medical observations. Moreover, the
method described in [7] is used for the computation of the prestress of the myocardium since the reference geometry (obtained from MRI images) does not correspond to a stress free configuration.

We use monolithic and staggered approaches for the solution of the approximated problem. In the monolithic case the linear system arising from the numerical approximation of the fully coupled problem is such that the choice of the scheme leads to different patterns of the non diagonal blocks of the system matrix. In such case the system needs to be properly preconditioned in order to ensure the convergence of the linear solver. We follow the approach described in [8] by considering a block Gauss-Seidel approximation of the system matrix, where the inverses of the diagonal blocks are replaced by the SIMPLE preconditioner in the fluid case, and by Multigrid or Additive Schwarz otherwise. On the other hand, in the staggered case, we use different timesteps for the electrophysiology and the fluid-structure by performing subiterations on the electrophysiology problem.

3 RESULTS AND CONCLUSIONS

![Figure 2: Transmembrane potential and myocardium deformation at four different time instants.](image)

In this work we show preliminary results of coupled simulations on patient-specific large scale geometries. Semi-implicit and implicit time schemes are considered and we show that, even if it requires smaller timesteps, the semi-implicit scheme is overall computationally more efficient. Monolithic and staggered approaches are compared with the monolithic fully implicit one as a benchmark in order to evaluate the accuracy of the method.

REFERENCES

PATIENT-SPECIFIC MODELING OF VENTRICULAR HEMODYNAMICS IN SINGLE VENTRICLE PHYSIOLOGY

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SUMMARY

Single ventricle congenital heart defects, in which babies are born with only one functional ventricle, undergo three palliative surgeries starting as neonates, by the end of which the single ventricle becomes the systemic pumping chamber. However, ∼30% of patients with single right ventricle physiology develop early cardiac failure before reaching adulthood. This is because the native right ventricles are not designed to withstand systemic pressures or demands and undergo maladaptive remodeling resulting in abnormal hemodynamics. We present an efficient and validated computational framework for performing patient-specific modeling of ventricular hemodynamics in patients with single ventricle physiology. The framework uses efficient registration methods for creating ventricular models and employs a stabilized finite element method based flow solver that is coupled with immersed boundary method for modeling heart valves. We will compare hemodynamics in single right and single left ventricle patients and discuss identification of key hemodynamic biomarkers of ventricular remodeling for early risk assessment of failure in this high risk population.

Key words: patient-specific modeling, single ventricle hemodynamics, variational multiscale method, immersed boundary method

1 INTRODUCTION

Among the most severe birth-related defects [4, 5] are those with single ventricle (SV) physiology, in which a baby is born with only one functional ventricle [1]. SV patients typically undergo a series of three open-chest surgeries starting as neonates [1], with survival rates of only 71% at 10 years [2]. An alternative physiology is created at the end of the three-staged surgical course, with only one ventricle that pumps blood to the systemic circulation, and venous return flowing passively into the lungs [1]. Depending on which ventricle performs the systemic function, these patients are classified as either single ‘left’ ventricle (SLV) or single ‘right’ ventricle (SRV).

There are significant differences in the morbidity and mortality between these two groups with higher susceptibility to failure for single right ventricles (SRV). The predominant among these is hypoplastic left heart syndrome (HLHS, SRV physiology, 1 in 4344 births in US [6], 5 year survival 40-70% [1, 2, 3]) which manifests as an underdeveloped left ventricle at birth, and has a higher risk of failure compared to other SV patient groups [1, 2, 3]. When subjected to chronic volume and pressure loads, the SRV undergoes maladaptive remodeling such as dilatation, from a crescent-shaped cross-section to a more circular shape, thereby resulting in abnormal hemodynamics [7, 8]. While some SRV patients maintain good cardiac function, others experience early cardiac failure. There are currently no clinical tools to predict which patients are at elevated risk for early cardiac failure, and the underlying mechanisms behind this failure remain unclear. There is an unmet need for improved management and non-invasive risk assessment that can predict the onset of HF in these patients.

We present an efficient framework for patient-specific computational modeling of ventricular hemodynamics, to quantify the abnormal hemodynamics associated with maladaptive remodeling in SRV...
physiology. The framework uses efficient deformable image registration methods for creating ventricular models and employs a stabilized finite element method based flow solver based on arbitrary Lagrangian-Eulerian (ALE) formulation of Navier-Stokes equations and variational multiscale methods to simulate incompressible blood flow in moving domains. The presence of cardiac valves is simulated using an immersed boundary method that is coupled with the present ALE-based finite element flow solver. In this preliminary study, we apply the present framework to 6 SV patients (3 SLV + 3 SRV), comparing hemodynamic characteristics between the two subgroups. We aim to identify and measure potential hemodynamic markers of maladaptive ventricular remodeling and eventually correlate simulation results with patient outcomes data in a sufficiently large cohort. Early identification of HF in single ventricle patients and improved management could lead to improved outcomes and quality of life for this high-risk patient population.

2 METHODOLOGY

We developed an efficient workflow to perform patient-specific modeling of ventricular hemodynamics in SV patients (Fig. 1). Steps in this workflow include:

- Short-axis slices from the patients MRI data are processed to enhance contrast and filtered for noise reduction.
- Segmentation is performed at one selected cardiac phase to extract the triangulated ventricular surface using Simvascular [9] open-source image-to-blood flow modeling toolkit.
- Registration is then performed on the MRI images using B-spline-based deformable registration methods [10, 11], and the computed displacements are used to morph the previously segmented surface to extract the ventricular motion.
- Boundary conditions are imposed using reduced order models of ventricular preload and afterload [12].
- Ventricular hemodynamics is simulated by solving the Navier-Stokes equations governing incompressible blood flow using our in-house stabilized finite element method based flow solver. To account for the moving domains, the governing equations are written in arbitrary Lagrangian-Eulerian (ALE) formulation [13] and discretized using residue based variational multiscale methods. Time integration is based on generalized-α method that is stable and second order accurate.
- Atrio-ventricular valves pose a significant computational challenge but at the same time are necessary to realize physiological flow patterns in the ventricle [14]. In the present framework, we model the cardiac valves using an immersed boundary method [15] based on extended Nitsche’s method for weakly applied Dirichlet boundary conditions and finite cell integration [16].

Our framework is the first of its kind presenting an efficient, yet powerful, and a comprehensive workflow for simulating patient-specific ventricular hemodynamics together with a realistic representation
of the effects of cardiac valves. The alternate approach is to segment each cardiac phase and then register the segmented ventricular surfaces using template based mapping methods, which adds significant workload [17, 18] and presents a critical bottleneck for studying large patient data sets [17]. The present framework substantially reduces modeling duration by leveraging a novel segmentation/registration pipeline, wherein we segment only one cardiac phase and perform the registration directly on the patient images to extract ventricular motion. Moreover, this semi-automatic approach will significantly minimize manual intervention and associated errors in performing multiple segmentations, and makes the process highly repeatable, which is necessary for performing large clinical studies.

Since the ventricular walls are moving and executing large deformations, while the present ALE-based formulation is on a body-conformal mesh, one has to perform remeshing during the cardiac cycle to avoid distorted finite elements and reduce errors due to numerical approximation. We choose zero Jacobian criterion to perform dynamic remeshing in addition to remeshing at all the phases where the image data is available. Remeshing is followed by solution interpolation to transfer the variables from the old mesh to the new ones. We have employed an efficient parallelized octree-based search algorithm [20] to perform the interpolation and it is to be noted that the total cost of remeshing and data interpolation is less than 5% of the total computational overhead of the ALE-based flow solver. We have also quantitatively validated the flow solver for ventricular flows against in vitro data in a simplified left ventricle [19] and will perform further comparison with available 4D MRI-based flow measurements. All the simulations are performed on Comet high performance cluster (XSEDE, NICS) employing 240 computing cores and it takes about 2 days to simulate ventricular hemodynamics for one cardiac cycle on a 10 million tetrahedral mesh.

3 RESULTS AND CONCLUSIONS

We have performed preliminary computations of intraventricular hemodynamics in a patient with hypoplastic left heart syndrome (SRV physiology) and in another patient with tricuspid atresia (SLV physiology) and the flow field is visualized in Fig. 2 as stream traces colored by the magnitude of velocity. Although in the preliminary computations we haven’t introduced any valve model, one can clearly identify significant differences in the complex flow dynamics of the single right and single left ventricles.

We will perform quantitative comparison of ventricular hemodynamics across SV patient subgroups (3 SLV, 3 SRV patients) with emphasis on the hemodynamic differences between single left and single right ventricle physiologies. Insights developed here will be used for a future study performed on a large cohort of SV patients with a long-term follow up, where the simulation results will be correlated with patient outcome and thereby, assess the risk of heart failure.
REFERENCES


A PREDICTIVE PATIENT SPECIFIC MODEL FOR THE HUMAN ATRIUM

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SUMMARY

We propose and validate a novel method to generate patient-specific models of the left atrium that captures tissue heterogeneities. A personalised model is generated from a set of measured local activation times (LATs) obtained by pacing the left atrium in the proximity of the coronary sinus with an s¹-s² pacing protocol. The model is then validated by evaluating the correlation between a set of measured LATs, obtained by pacing on the high right atrium and a set numerically computed LATs. Validation is performed on 4 clinical cases.

Key words: Patient-specific models, local activation times, parameter fitting

1 INTRODUCTION

Atrial fibrillation (AF) is a common arrhythmia, affecting almost 2.5 million people in the US, [1] and is associated with an increased incidence of cardiovascular disease, stroke and premature death [2]. Biophysical model enabled the study of the mechanisms that underpin arrhythmia’s in the ventricle and the atria, [3]; however, their inability to capture the significant variability in physiology typical of AF patients limits their potential to make quantitative predictions of patient response to treatment and thus to inform clinical procedures. In this work we apply the algorithm developed in [4] to locally constrain the model parameters of the modified Mitchell-Schaeffer (mMS) ionic model [5], when the conduction velocity (CV) restitution and the effective refractory period (ERP) are known for a single s¹ cycle length. Differently from other data assimilation techniques, [6] this approach allows the generation of locally personalised computational models of the human atrium in a clinical time scale when local tissue variability is not negligible. Local parameter values are constrained from a set of LATs obtained by applying an external stimulus in the proximity of the coronary sinus (CS), following an s¹-s² pacing protocol [7], and measuring the local electrograms (EGM) with a multi-polar catheter. The model is then validated by comparing the LATs generated by applying the s¹-s² pacing protocol and stimulating on the high right atrium region (HRA), with those obtained by numerical simulations of the same experiment. The validation process is applied on 4 clinical cases.

2 METHODS

From a set of LATs recording, local CV restitutions are evaluated with the procedure described in section 2.1 and then used to locally constrain the model parameters as described in section 2.2. From the evaluated local parameter values, a computational model is finally obtained as described in section 2.3. The pipeline to generate a computational model from multi-polar catheter measurements is depicted in Figure 1.
2.1 LATs and local CV evaluation

An external stimulus is applied either on CS or on the HRA and following an $s_1$-$s_2$ pacing protocol where 3 stimuli are applied with an inter-pacing interval $s_1 = 470$ ms, followed by a premature pacing $s_2$. The protocol is repeated for 28 values of $s_2$, ranging between 343 and 200 ms. Bipolar EGM were recorded on the surface of the left atrium with a multi-polar catheter and up to 100 locations per case. For each location an EGM was available, LATs were evaluated as the time corresponding to the first peak on the EGM trace, and then linearly interpolated on the region covered by the catheter. For each $s_2$ applied in the pacing protocol, local CV modulus was determined as the inverse of the magnitude of the gradient of LATs and used to build local CV restitution curves.

2.2 Local electrophysiology and parameter fitting

Atria tissue electrophysiology is modelled with the mono-domain approximation of the bidomain model \[9\], when intra- and extra- cellular conductivities are proportional up to a constant. The mMS ionic model described in \[5\] was chosen to characterise the source term; similarly to the original Mitchell-Schaeffer model \[10\], mMS captures the measured CV and ERP restitution properties with the smallest numbers of parameters to constrain, and it is proven to be stable to pacemaker behaviour independently of the choice of its parameter values. Parameters are fitted by applying the algorithm described in \[4\]; this algorithm fits the CV restitution and the ERP value (here approximated by the $s_1$-$s_2$ functional block) to a set of pre-computed CV restitutions and ERP, obtained by solving a computational model with a set of known parameters. In this work, a data set of 16436 restitutions were evaluated with the parameter values summarised in Table 1, and keeping the gate potential value fixed and equal to $v_{gate} = 0.05$.

2.3 Computational model

The parameter values were interpolated on regions where no measurements were available through a harmonic extension operator; a Gaussian filter with covariance $\sigma^2 = 2$ and a median filter were then applied to smooth the parameter values and to remove possible outliers. A computational mesh with an imposed edge length $h = 215 \mu m$ was generated on the 2D surface describing the anatomy and obtained from the NavX electroanatomical mapping system. The computational model was then discretized in space with linear finite elements;
the non-linear term describing the ionic current was treated with a splitting technique. The ionic model was discretized in time with a forward-Euler scheme, while the diffusive parabolic PDE with a Crank-Nicholson scheme; a constant time step $dt = 50 \mu s$ was chosen for both sub-problems. Simulations were performed with the Cardiac Arrhythmias Package (CARP), an electrophysiology solver suitable for hyper-computing.

3 VALIDATION PROCESS

A set of LATs were computed by simulating the atrium electrophysiology following an external stimulus applied on the HRA and with the $s_1, s_2$ pacing protocol, with $s_2 = [280, 292, 298, 304, 310, 322, 329, 336, 343]$. On the computational model, the external stimulus was applied to the circular region with radius $R = 1$ and centred on the measured early depolarisation for a coupling interval $s_2 = 343 \text{ ms}$. For each of the $s_2$ considered in the validation process, the mean difference between the measured and the computed LATs was evaluated and used as an offset on the computed LATs; this to take into account of the time required by the depolarization front to propagate from the right atrium to the left atrium. The correlation between computed and measured LATs was then evaluated through 4 indicators: the linear regression coefficients $(m, q)$ of the regression line $y = mx + q$, where points $(x, y)$ correspond to the measured and computed LATs and over the whole set of coupling interval $s_2$ tested in the validation; the coefficient of determination $r$ between measured and computed LATs; and $s_l$ expresses the ratio between the two principal components of the covariance. The overall validation process is depicted in Figure 2.

4 RESULTS AND CONCLUSIONS

The validation of the proposed method was applied to 4 cases suffering from paroxysmal atrial fibrillation who underwent to pulmonary veins isolation. For each clinical case, the scatter plot of the measured and computed LATs is depicted in Figure 3, while the indicators are summarised in Table 2.

Case 1 to 3 presented small discrepancies between measured and evaluated data, while all the cases presented a coefficient of determination greater than 0.8 and a ratio between the principal components of the covariance not greater than 0.1.

REFERENCES

Figure 3: Scatter plot of the estimated (y-axis) vs measured (x-axis) LATs; each colour corresponds to a different $s_2$ coupling interval. The linear regression line $y = mx + q$, is plotted in red, the line $y = x$ in black. The red ellipse corresponds to the covariance ellipsoid of $x$ and $y$.

<table>
<thead>
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<th>m</th>
<th>q</th>
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<td>0.91</td>
<td>0.05</td>
</tr>
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<td>0.10</td>
</tr>
</tbody>
</table>

Table 2: Correlation indicators for each of the 4 cases


We present a simple linear finite element method for incompressible active elasticity under quasistatic and dynamic conditions. The method is based on a variational multiscale analysis and it is efficient in handling the complex geometries used in cardiac electromechanics. We apply the new method to study atrial electromechanics using an active strain formulation.

**Key words:** atrial electromechanics, finite element method, incompressible elasticity.

1 INTRODUCTION

Personalized patient-specific models are becoming an important tool for diagnosis and therapy planning. In such models, a geometrical representation of the organ of interest is created from medical images capturing complex morphological structures. Here we focus on the left atria, where the morphologies associated with the left ventricular appendage influence the risk of embolic events [1].

From a computational standpoint, the geometrical representation is of fundamental importance. In the finite element method, typically, one employs tetrahedral or hexahedral discretizations. Whenever complex geometries are considered hexahedral discretization are very hard to generate, while tetrahedral meshes can be created in an automated way. On the other hand, tetrahedral elements are known to suffer locking whenever incompressible materials are considered.

The constraint of incompressibility is difficult to treat numerically as it gives rise to saddle-point problems and associated Ladyzhenskaya–Babuška–Brezzi (LBB) conditions (also known as infsup conditions) [6]. Spurious pressure checkerboard modes and volumetric locking are instantiations of the pathologies associated with finite elements that do not satisfy the LBB conditions. An additional element of complexity considered is the simulation of time-dependent problems, which may pose specific challenges to methods initially developed for static computations. Using the variational multiscale method [2,3], we develop a displacement/pressure and velocity/pressure formulations for incompressible anisotropic nonlinear elasticity using linear tetrahedral elements. The new method can be directly applied to active mechanics and it is suitable for studying cardiac electromechanics.

2 METHODOLOGY

The quasistatic equations of Lagrangian mechanics read

\[-\nabla \cdot \text{dev}[\sigma] - \nabla p = \rho b,\]

\[J = 1,\]
Figure 1: Solution of the incompressible electromechanical problem with linear finite elements: left) pressure field; center) squared fiber stretch (4th anisotropic invariant); right) activation $\gamma_f$.

where the first equation represents the static momentum equations and the second one represents the local incompressibility constraint. The scalar $J$ is the determinant of the deformation gradient tensor $F$ mapping a vector in the reference configuration to a vector in the current configuration.

For hyperelastic materials, the stress tensor is defined through the free energy $\psi$, such that

$$\sigma = \frac{\partial \psi}{\partial F} F^T.$$

In particular, for incompressible active materials we can assume that the free energy takes the form

$$\psi = \psi_P(F) + \psi_A(F, F_A) + p(J - 1),$$

where $F_A$ is an internal variable representing active deformations [5]. The total energy is the sum of the energy $\psi_P$, coming from the passive components of the tissue, and the energy $\psi_A$ of the contractile part of the muscle. The active deformation gradient and the total deformation gradient are related to each other through the relation $F = F_E F_A$. We further assume that the active deformations are transversely isotropic, so that the tensor $F_A$ can be represented in the form

$$F_A = (1 + \gamma t) I + (\gamma_f - \gamma t) f_0 \otimes f_0.$$

Considering isochoric active deformations, the equation enforcing incompressibility does not change. Therefore, in order to use equal order polynomials for the displacement and the pressure, we circumvent the LBB condition modifying the weak form of the incompressibility constraint to

$$\left( J, q \right)_{\Omega_0} - \left( u', F^{-T} \nabla q \right)_{\Omega_0} = (1, q)_{\Omega_0}$$

where the fine-scales displacements $u'$ represent an estimate of the error of the momentum balance in each element.

Under dynamic conditions, the incompressibility constraint needs to be written in rate form, using the relation $\dot{J} = \nabla \cdot \mathbf{v} = 0$. Then, the weak dynamic incompressibility constraint is modified introducing the fine-scales velocities $\mathbf{v}'$ such that

$$\left( \nabla \cdot \mathbf{v}, q \right)_{\Omega_0} - \left( \mathbf{v}', \nabla q \right)_{\Omega_0} = 0.$$

3 RESULTS AND CONCLUSIONS

Some preliminary results are shown in Fig. 1, where we show the solution of the electromechanical problem in a thin slab of tissue. The simulation uses only linear finite elements, and the mechanical incompressible problem does not show instabilities in pressure field. We extend the new technology to a patient-specific left atrial model where we used the data in [4, 8] to reconstruct the fiber field, as shown in Fig. 2.

Linear elements can be successfully used for problems in incompressible elasticity with large deformations under quasistatic and dynamic conditions. In addition, the use of tetrahedral discretization allows to easily generated meshes for patient-specific simulations. Therefore, linear finite elements can be a valuable tool for cardiac electromechanics.
Acknowledgments

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MODELING OF TRANSIENT CARDIAC ELASTOGRAPHY

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SUMMARY

Experimental studies show the potential of the application of elastography to cardiac imaging, but also reveal dramatic changes in the measured stiffness properties over the cardiac cycle. Therefore, there is a clear need for associating this varying apparent stiffness with actual constitutive parameters – e.g. passive elastic moduli and active contractilities – that can be used to characterize the state of the myocardium, which requires the consideration of a biomechanical model. We outline a methodological and numerical approach to characterize elastographic shear waves for a very general constitutive behavior and without resorting to the usual “small strain” assumption. In our presentation, we will show some detailed results obtained with a beating heart biomechanical model, and compare the computed wave velocities with published experimental measurements.

Key words: Shear wave elastography, cardiac modeling

1 INTRODUCTION

Elastography techniques have raised a growing interest in clinical applications for soft tissue characterization over the past decades, the tissue stiffness being highly sensitive to structural changes associated with physiological and pathological processes \([1, 2]\). In particular, very recent elastographic techniques, like Acoustic Radiation Force Imaging (ARFI) \([3]\), Shear Wave Elasticity Imaging (SWEI) \([4]\) and Supersonic Shear Imaging (SSI) \([5]\), are based on the propagation of shear waves, the measurement of which is often referred to as “transient elastography”. Experimental studies such as those presented in \([6, 7, 8]\) show the potential of the extension of transient elastography to cardiac imaging. Nevertheless, such studies also reveal dramatic changes in the measured stiffness properties over the cardiac cycle. Therefore, there is a clear need for associating this varying apparent stiffness with actual constitutive parameters – e.g. passive elastic moduli and active contractilities – that can be used to characterize the state of the myocardium. This requires the consideration of a biomechanical model that can accurately reflect the complex behavior of the myocardium and of the organ \([9]\), from which the equations governing the resulting elastographic waves can be derived. Our objective here is to outline this approach from a methodological standpoint, and to compare model simulation results with actual experimental data.

2 MODELING

To fix the ideas, we consider an elastic finite strain dynamic formulation in total Lagrangian form. The corresponding principle of virtual work written in the reference configuration \(\Omega_0\) reads

\[
\forall t \in [0, T], \forall \vec{\psi}^* \in \mathcal{V}, \quad \int_{\Omega_0} \rho_0 \ddot{\vec{y}} \cdot \vec{\psi}^* \, d\Omega_0 + \int_{\Omega_0} \Sigma(e) : d\vec{e} \cdot \vec{\psi}^* \, d\Omega_0 = \int_{\Omega_0} \rho_0 \vec{f} \cdot \vec{\psi}^* \, d\Omega_0 + \int_{\Gamma_0} t_0 \cdot \vec{\psi}^* \, dS,
\]

where \(\vec{y}\) denotes the displacement field – hence \(\ddot{\vec{y}}\) is the acceleration – \(\rho_0\) is the solid mass per unit volume, \(\Sigma\) the second Piola-Kirchhoff stress tensor, \(\vec{e}\) the Green-Lagrange strain tensor – namely, the energy conjugate of \(\Sigma - \vec{f}\) – are volume-distributed forces and \(t_0\) surface-distributed forces applied on
Γ_N ⊂ ∂Ω_0 (if any). The differential quantity
dl_{v} \cdot v^* = \frac{1}{2} ((\nabla_{\xi} v^*)^T \cdot F + F^T \cdot \nabla_{\xi} v^*)
corresponds to the derivative of the Green-Lagrange strain tensor with respect to displacements in
the admissible space of test functions \mathcal{V}, with \(F\) the deformation gradient. Note that \(\xi\) stands for
the position vector in the reference configuration \(Ω_0\).

An elastic wave corresponds to a “small perturbation” of the above dynamics in the form \(y = \bar{y} + \tilde{y}\),
where \(\bar{y}\) is a given reference trajectory, and \(\tilde{y}\) the perturbation. As both \(y\) and \(\bar{y}\) satisfy \((1)\), the
governing equation for the small perturbation \(\tilde{y}\) can be derived by linearizing \((1)\) around \(\bar{y}\), which
classically yields
\[\forall v^* \in \mathcal{V}, \quad \int_{Ω_0} \rho_0 \ddot{\tilde{y}} \cdot v^* \, dΩ_0 + \int_{Ω_0} d_y \cdot \ddot{\tilde{y}} : \frac{\partial \Sigma}{\partial e} \cdot d_y \cdot v^* \, dΩ_0 + \int_{Ω_0} \Sigma : ((\nabla_{\xi} \tilde{y})^T \cdot F \nabla_{\xi} v^*) \, dΩ_0 = 0.\]
(2)
As is well-known in nonlinear mechanics, we obtain a tangent stiffness operator with two distinct
contributions (associated with the last two above integrals), the first being often called material stiff-
ness and the second geometric stiffness – or prestress effect. This total tangent stiffness operator can
be summarized in the form
\[\int_{Ω_0} \nabla_{\xi} \tilde{y} : C^{\text{Lag}} : \nabla_{\xi} v^* \, dΩ_0,\]
where \(C^{\text{Lag}}\) denotes a fourth-order tensor representing the tangent constitutive relation defined in this
Lagrangian framework. From a practical point of view, in a finite element code this tensor is usually
computed as part of the Newton algorithm when solving the nonlinear problem associated with the
solution \(y\) characterized by \((1)\).

Elastographic waves, however, are measured in the actual (deformed) object, and therefore more
directly analyzed in the light of a stiffness operator defined in the form
\[\int_{Ω_t} \nabla_{\xi} \tilde{y} : C^{\text{Eul}} : \nabla_{\xi} v^* \, dΩ_t,\]
where \(Ω_t\) denotes the deformed configuration, \(\xi\) the associated position vector – i.e. the Eulerian po-
tion – and \(C^{\text{Eul}}\) the fourth-order tensor representing the tangent constitutive relation in the Eulerian
frame, from which the so-called Christoffel tensor can be directly deduced to compute shear wave
velocities that are actually measured in transient elastography [6, 7]. Using the chain rule we have
\[\nabla_{\xi} (\cdot) = \nabla_{\xi} (\cdot) \cdot F^{-1},\]
and we directly infer
\[C^{\text{Eul}} = J^{-1} F \cdot C^{\text{Lag}} \cdot F^T,\]
(3)
with \(J = \det F = dΩ_t/dΩ_0\), and where all the quantities in the right-hand side are readily at hand
in the finite element computation. Therefore, we can compute the tensor \(C^{\text{Eul}}\) needed to characterize
the shear wave as a by-product of the dynamical equation solution, once the Newton algorithm has
converged at each time step, and we obtain one such tensor for each quadrature point.

3 RESULTS AND CONCLUSIONS

We have outlined a methodological and numerical approach to characterize elastographic shear waves
in a general mechanical model. This approach extends the classical derivation of the Christoffel ten-
sor, for a very general constitutive behavior and without resorting to the usual “small strain” assump-
tion. In our presentation, we will show some detailed results obtained when applying this approach
with the heart model of [9] – see an example in Fig. 1 – and compare the computed wave velocities
with published experimental measurements.
REFERENCES


TRANSCATHETER PACING SYSTEMS: COUPLED FLUID-ELECTRO-MECHANICAL CARDIAC COMPUTATIONAL MODEL

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SUMMARY

In this work we present the fully coupled triple-field (blood, electrophysiology and tissue mechanical action) cardiac computational model (3F-CCM) as a simulation tool for a transcatheter pacing system (TPS). The final goal is to analyze the stresses suffered by the tissue-pacemaker system as tissue contracts under the action of electrophysiology and blood flows around. The stresses are concentrated in the pacemaker anchoring tines. This work shows preliminary results in two toy configurations assessing robustness and performance of the 3F-CCM, based in BSC’s HPC-based Alya multi-physics simulation code.

Key words: Cardiac Computational Modelling, Pacemaker, HPC

1 INTRODUCTION

Transcatheter pacing systems (TPS) are delivered percutaneously via a minimally invasive approach and deployed using a catheter. The TPS is a tiny device, which is anchored in the endocardium of the right ventricle through the deployment of a number of tines. In this paper we present a simulation strategy to compute forces and dynamical behaviour once the TPS is deployed and working. The simulation scenario is the TPS once deployed in the ventricle, which delivers in the tissue an initial electrical impulse. This impulse propagation induces a continuum and strong muscular contraction, which in turn performs work against blood within the cardiac cavities. The pacemaker is fixed on the moving pericardium suffering forces from both the solid and the fluid. The problem is then decomposed on a Fluid-Structure Interaction scheme. On the solid phase, there are two materials: tissue and pacemaker, while on the fluid phase, we solve two problems: fluid mechanics and mesh deformation. The goal is to study the mechanical forces on the pacemaker and how its presence alters flow dynamics.

2 METHODOLOGY

The simulation tool is Alya, an HPC-based multi-physics code developed at BSC. Alya is specifically designed to run efficiently in supercomputers, retaining its efficiency when solving multi-physics problems. It solves coupled partial differential equations in a modular way using an hybrid MPI / OpenMP strategy. Alya’s application range is wide, including biomedical research, aerospace, environment or oil and gas industry. In biomedical research, Alya is used to perform organ-level biomechanics simulations mostly for cardiac [1], vascular [2] and respiratory systems [3]. The code is especially well-suited for large-scale runs, such as those shown in [4], paper that includes the largest cardiac electromechanical simulation scaled so far, with 3.5 billion tetrahedra of an unstructured mesh for a biventricular cavity in 100,000 cores of NCSA’s Blue Waters supercomputer.

In this paper, the TPS is modelled with an hyperelastic material, two orders of magnitude harder than tissue. Tissue is modelled with an Ogden-Holzapfel material, with active and passive stresses. Active
stress goes only along the fibers, linked to the electrical field through a Hunter, McCulloch, ter Kreus electromechanical coupling model. Electrical activation is here done with a simple FitzHugh-Nagumo model, and it is coupled back to the solid because it propagates in the deformed configuration. Flow is incompressible and solved in an algebraic fractional step method and fluid is Newtonian. FSI is simulated with a partitioned Arbitrary Lagrangian-Eulerian (ALE) scheme, in which two parallel instances of Alya (one for the tissue and the other for the blood) are interacting with each other through an Aitken relaxation coupling algorithm to avoid added-mass effect.

Figure 1: Snapshots’ sequence of the three-field simulation for the ventricle and TPS. They represent a long-axis’ cut with velocity vectors, a short-axis’ cut with the von Mises stress to measure effort concentration and a close-up of the TPS, with velocity vectors and von Mises stress.

In this work, the simulations performed where of two kinds: a fully coupled 3F-CCM of a toy TPS within a filled left ventricle and an electromechanical simulation of the toy TPS with the tines anchored in the tissue. Figure 1 shows four snapshots of the ventricle systole. They represent a long-axis’ cut with velocity vectors, a short-axis’ cut with the von Mises stress to measure effort concentration and a close-up of the TPS, with velocity vectors and von Mises stress. The ventricle’s fibers field is generated with a rule-based Streeter model and the ventricle outflow has a first-order Windkessel pressure model stabilized to avoid oscillations related to inverted flows. The electrical impulse starts right below the TPS.

Figure 2: TPS tines simulation. Set-up and a snapshot of a long axis cut, coloured by the Cauchy stress component $\sigma_{xy}$.

In the second kind of simulations performed, the TPS is anchored through the tines in an active piece of cardiac tissue. Figure 2 shows the set-up and a snapshot of a long axis cut, coloured by
the Cauchy stress component \( \sigma_{xy} \), transversal to the main contraction and to the fiber field which runs along the Z axis. Figure 3 shows a snapshots’ sequence of the contracting tissue and the TPS. Tissue is coloured by the electrical activation propagation. Figure 4 is a snapshots’ sequence of the contraction, showing the dynamics of the anchoring tines. Observe that the right bottom corner of the TPS slightly penetrates the tissue. The reason is that in these preliminary results, no self-contact algorithm is present.

![Snapshots of the contracting tissue and the TPS](image)

Figure 3: Snapshots’ sequence of the contracting tissue and the TPS. Tissue is coloured by the electrical activation propagation.

3 RESULTS AND CONCLUSIONS

In this work we present some preliminary results of a three-field cardiac computational model, where blood, tissue and electrical activation are strongly coupled, applied to a toy geometry of a transcatheter pacing system. We show the results of two different kind of simulations. These results are preliminary: the TPS geometry is extremely simplified, the cardiac geometry is only an sectioned left ventricle, fiber fields are rule-based modelled, etc. The future lines are clear and under development: improving all these simplifications. Although simple, these simulations show the potential of the proposed scheme.

REFERENCES


Figure 4: Snapshots’ sequence of the contraction, showing the dynamics of the anchoring tines.

Modelling Cardiovascular Devices: Design, Testing & Patient-Specific Applications I
NUMERICAL MODEL OF TRANSCATHETER AORTIC VALVE REPLACEMENT: EFFECT OF POSITIONING AND HEART BEATING ON PROCEDURAL OUTCOME

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SUMMARY

Transcatheter aortic valve replacement (TAVR) is an effective therapy for inoperable patients with severe aortic stenosis. However, peri-procedural complications, such as valve migration and paravalvular leakage (PVL) have been reported. Our aim is to develop a computational approach to investigate the effect of valve positioning and heart motion on the risk for migration and PVL. Patient-specific CFD models were capable of quantifying the flow through the paravalvular gaps, showing a direct effect of the initial TAVR positioning on the degree of PVL. The Living Heart Human Model was able to successfully assess TAVR devices performance in a beating heart.

Key words: TAVR, FEA, CFD

1 INTRODUCTION

Calcific aortic stenosis is a degenerative process in which the aortic valve narrows due to the formation and growth of calcium deposits on its leaflets. Transcatheter aortic valve replacement (TAVR) has become the only lifesaving solution for patients that cannot undergo the standard surgical valve replacement [1]. Despite its promising outcomes, adverse events such as prosthesis migration have been reported [2] and peri-procedural complications such as paravalvular leakage (PVL) and cardiac conduction abnormalities may occur as a result of suboptimal placement, leading to poor device performance. Although newer-generation valves appeared to reduce the risk for aortic regurgitation by adding an outer skirt at the base of the stent as in the Sapien 3 TAVR valve[3], PVLs is still affecting TAVR long-term performance and survival rates. Corrective procedures, such as balloon post-dilation, valve-in-valve implantation or transcatheter PVL repair are performed but little is known about the safety, efficacy, and the impact of these measures on the clinical outcome [4]. Furthermore, even though a better anchorage with the native valve is guaranteed with stiffer stents, the interference with the cardiac conduction fibers and the increased compression in the region of the atrio-ventricular (AV) node may dramatically increase the risk of heart blockage. Permanent pacemaker implantation (PPM) rates alarmingly increased up to 17%, regardless of the type of valve being implanted. The prevalence goes up even higher to 27% for the Medtronic CoreValves, being critical for those patients with baseline cardiac conduction abnormalities [5]. The impact of these complications has therefore hindered TAVR expansion to lower-risk patients, even though comparable outcome to surgical treatment was reported in terms of the survival rate and stroke incidence rates [6]. The aim of this study is to evaluate the effect of various TAVR deployment positions on the procedural outcome by assessing the risk and the degree of post-procedural paravalvular regurgitation. The effect of the heart beating was also investigated to assess the anchorage of various valves during the heart beating.

2 METHODOLOGY

We first modeled the balloon-expandable Edwards SAPIEN and self-expandable Medtronic
CoreValve crimping processes. Subsequently, the crimped SAPIEN stent was deployed by balloon-inflation in a patient-specific calcified aortic root, reconstructed from pre-TAVR CT scans of a patient for whom valve migration into the left ventricle (LV) occurred during TAVR procedure at the Stony Brook University Hospital. The deployment location was parametrized in three deployment positions: midway, in which stent centroid is placed on the annulus plane, distal, and proximal, where the stent centroid was shifted by 30% towards the aorta and the LV, respectively. Additional details on the reconstruction of the patient-specific anatomy and the FE analyses of the TAVR stent and balloon are given in our recent study [7]. The resulting deformed configurations were used to generate new models to assess post procedural hemodynamics during diastole. Particularly, the PVLs were investigated and quantified. The walls of the fluid domain of both the vessel and the prosthetic stent, were processed in ANSYS 17 SpaceClaim to obtain smoothed and merged domains while retaining the detailed features. A FE analysis was carried out in order to displace the prosthetic leaflets and cuff from their pre-crimped to the end-recoil configuration, followed by the valve closing by applying diastolic transvalvular pressure difference. The resulting valve geometry was smoothed and assembled with the root to create the fluid domain and was meshed in ANSYS Fluent Meshing 17 with tetrahedral cells. The aortic inlet and the coronary outlets were extruded with a length of 5 hydraulic diameters in order to minimize the effect the boundary conditions (BCs) on the region of interest. The funnel shaped ventricular outflow tract was created by extruding and scaling the aortic annulus edge. The mesh was converted to polyhedra and transient diastolic Computational Fluid Dynamics (CFD) analyses were conducted in ANSYS Fluent 17, assuming homogeneous and Newtonian blood and laminar flow. The aortic, the ventricular pressure and the main coronary arteries flow waveforms were applied as BCs. Additionally, approximately 30,000 particles were injected in the fluid domain above the stent at the beginning of the simulation in order to track their trajectories through the paravalvular gaps for each configuration. The root mean square of the regurgitating flow rate was calculated and the overall area of the paravalvular gaps was estimated through effective orifice area (EOA).

Additionally, in order to assess the effect of the heart beating on the valve performance, the same balloon-expandable valve and other self-expandable TAVR devices were evaluated. Specifically, the commercially available Medtronic Evolut R and a novel polymeric valve developed by our group (Polynova Cardiovascular, Inc., Stony Brook, NY) were crimped and their deployment was simulated in the beating Living Heart Human Model (LHHM) (Simulia). The LHHM is an anatomically and physiologically realistic model of an adult male heart, which includes the four chambers, major vessels, electrophysiology, and fibrous architecture of the myocardium [8]. An electrical analysis was used to compute the spatiotemporal pacing of the heart which was then employed in a subsequent mechanical analysis that allows device-heart interactions to be modeled. Therefore, this model has the potential to capture several phenomena such as the influence of the beating on the dynamics and kinematics of the TAVR stent. Furthermore, in order to mimic the stenotic tissue morphology, the native aortic valve leaflets were adapted to include characteristic calcification patterns necessary for TAVR stent anchoring.

3 RESULTS AND CONCLUSIONS

The proximal deployment resulted in higher risk for valve migration, with a 70% decrease in total contact area at the beginning of the recoil, when the stent migrated into the LV cavity [7]. Given the migration found in the proximal configuration, the PVL was therefore assessed in the midway and distal cases only. Peak velocities were comparable (6.57 vs. 6.29 m/s for the midway and distal
cases, respectively) and occurred in the instant when the aortic-ventricular pressure difference was the highest (100 ms after the onset of diastole). The midway case resulted in larger regurgitation regions in which the blood flowed through the stent struts, suggesting that the location of the stent is too proximal. The distal case had more limited PVL and confined in the region between the stent and the non-coronary leaflet (Figure 2). Particle trajectories and velocity field comparison showed the presence of regurgitation in both configurations, with the midway case experiencing significantly higher flow through the struts. The distal case resulted in six-fold decrease in flow rate (32 vs. 207 ml/s) through the paravalvular gaps and comparable increase in EOAs (0.33 vs. 0.05 cm$^2$). Particles flowed through the gaps more rapidly in the midway configuration than in the distal one, confirming the existence of a more substantial leakage in the regions around the deployed stent.

The post-deployment behavior of an Edwards Sapien and Medtronic CoreValve TAVR valve stent in a calcified beating heart were studied using the LHHM. The self-expandable stent was gradually deployed by pulling a constraining cylindrical sleeve from the ventricular side towards the aorta, whereas the balloon-expandable stent was deployed by inflating a linear-elastic balloon up to 3.5 atm. Each deployment was simulated for one cardiac cycle, consisting of a beating (0.5 s) and a recovery (0.5 s) step. The preliminary results are presented in Fig. 3 (left and mid) at the end of the beating step where the calcification deposits have anchored the stent and prevented its dislocation. In an earlier version of this model of deployment in healthy LHHM, the Core Valve stent started to migrate into the aorta while the ventricle was contracting. The healthy heart model was also employed to test the Polynova stent behavior (Fig. 3, right), which also showed poor anchorage and resulted in migration into the ventricle. These results confirm the assumption that the calcium deposits provide anchoring to the stent. In all the deployment simulations, the initial position of the stent has been shown to play a major role in the distribution and the extent of the contact pressure between the stent and the native valve. The stress contours in the leaflets also demonstrate the higher stresses in the calcific deposit region where the material is stiffer and thus provides higher contact pressures. Efforts are currently directed to better understand the effect of mechanical forces exerted from the deployed TAVR devices in the AV region. This information will be used to alter the electrical conductivity of the myocardium and to ultimately investigate the effect of such condition on the cardiac mechanics. Furthermore, the Polynova valve is being tested through an independent Fluid-Structure Interaction (FSI) simulation to better understand the leaflets’ dynamics and mechanical behaviors under physiological hemodynamic conditions. A future direction is to implement FSI in the LHHM by incorporating CFD to study the TAVR valves’ post-deployment flow dynamics.

In conclusion, the CFD models were capable of investigating the post-deployment hemodynamics, specifically in the flow through the paravalvular gaps, showing a direct effect of the initial TAVR positioning on the degree of post-TAVR PVL. LHHM served as a valid computational tool for assessing TAVR devices performance in the beating heart. This combined approach might be used as a predictive tool for procedural planning in order to ultimately achieve better clinical outcomes.
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IMPACT OF HEART FAILURE SEVERITY ON PREOPERATIVE PLANNING OF VENTRICULAR ASSIST DEVICE CONFIGURATIONS

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SUMMARY

This computational fluid dynamics study investigates the necessity of incorporating heart failure severity in the preoperative planning of Left Ventricular Assist Device (LVAD) configurations. A parametric study was conducted examining a common range of LVAD to Aortic Root-Flow Ratios (LVAD/AR-FR). The results show that LVAD/AR-FR can have a significant and irregular impact on the perfusion and shear stress-related haemodynamic parameters of the subclavian and carotid arteries. Furthermore, it is found that a larger portion of the flow is directed towards the thoracic aorta in the expense of the carotid and subclavian arteries, regardless of LVAD/AR-FR.

Key words: boundary conditions, haemodynamics, LVAD

1 INTRODUCTION

In the literature, there appears to be no emphasis on the haemodynamic effect of the Flow Ratio (FR) between the LVAD cannula outlet and Aortic Root (LVAD/AR-FR). This ratio varies from case to case depending on different parameters such as level of heart failure and amount of physical activity of the patient. The exact contribution of the remnant native cardiac output to the aortic flow is generally unknown at any given time, however, it can vary from patient to patient anywhere between roughly 5 – 30% [1,2].

There is scope for work that defines whether or not it is necessary to incorporate the LVAD/AR-FR into the preoperative planning of an LVAD configuration, in order to accurately improve the effects on the cardiovascular system post implantation. Therefore, the aim of this work is to quantify the cardiovascular effects associated with the common range of LVAD/AR-FRs using computational fluid dynamics.

2 METHODOLOGY

A parametric analysis of different LVAD/AR-FRs are examined and compared against a reference solution. A three-element Windkessel model is used in order to accurately capture the physiological back-pressure response of the outlets. Metrics of the perfusion, as well as shear stress based parameters are assessed and discussed, showing the importance of including LVAD/AR-FR in the LVAD performance studies as well as preoperative LVAD planning.
Seven tests are studied in this work. ‘Test 0’ is used as a representative of normal aortic haemodynamics for comparison purposes, which does not include a cannula. ‘Tests 1-6’ represent a patient with an implanted LVAD suffering from various extents of heart failure. In all tests, a no-slip boundary condition is applied to all walls and a rigid wall model is assumed [3,4].

For all tests, a uniform velocity profile was imposed at the inlets. For ‘Test 0’, the patient-specific PC-MRI waveform by [5] was applied to the AR. ‘Tests 1-6’ scaled this AR waveform by 5 to 30% in increments of 5% (corresponding to LVAD/AR-FRs between 70 to 95%). A constant flow rate from the cannula compensated for the unfulfilled total aortic flow to bring total flow rate for all tests to 3.2 L/min (in accordance with the in vivo flow rate by [5]).

A mesh of 3.2 million elements was used. Simulations were ran using ANSYS CFX 17.1 for 4 cardiac cycles, results were recorded on the final cardiac cycle.

3 RESULTS AND CONCLUSIONS

The general irregular behaviour of the subclavian and carotid arteries to LVAD/AR-FR indicates that the perfusion and wall shear stress-based haemodynamic metrics within these arteries cannot be accurately predicted unless the LVAD/AR-FR is incorporated into the computational preoperative planning of the optimal LVAD configuration. The consistently excessive perfusion to the thoracic aorta suggests that regardless of LVAD/AR-FR, the thoracic aorta will most likely experience adequate perfusion. Incorporating LVAD/AR-FR whenever possible into the preoperative planning process, will aid in more accurately improving the effects on the circulatory system post LVAD implantation.

![Flow ratio (%) between the Time-Averaged Flow Rate (TAFR) through the corresponding artery and the total TA FR through the system. Positive and negative ratios represent inlets and outlets, respectively.](image)

Figure 1 – Ratio (%) between the Time-Averaged Flow Rate (TA FR) through the corresponding artery and the total TA FR through the system. Positive and negative ratios represent inlets and outlets, respectively.
Figure 2 – Time-averaged blood flow velocity streamlines coloured by Time-Averaged Velocity (TAV).

REFERENCES


ENERGY GAIN IN FAILING FONTAN CIRCULATION USING A CA VOPULMONARY-ASSIST DEVICE

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SUMMARY

Treatment options for severe complications in patients with failing Fontan circulations are limited to heart transplantation. A need exists for a medical device to bridge these patients to transplantation and no such device currently exists. In the present study, computational fluid dynamics simulations were conducted for a proposed bridge-to-transplant device to quantify the energy gain in the total cavopulmonary connection under varying flow conditions. These simulations predict a net energy gain at low Reynolds numbers without detrimental effects such as significant recirculation regions.

Key words: Computational Fluid Dynamics, Fontan Circulation, Cavopulmonary-Assist Device

1 INTRODUCTION

It is estimated that the incidence of congenital heart disease is as high as 6 in 1000 live births [1]. Patients born with congenital heart diseases such as tricuspid atresia and hypoplastic left heart syndrome have only one functioning ventricle. To treat these patients, a series of procedures are performed to modify their vasculature, the last of which is the Fontan procedure [2]. For the extracardiac form of the Fontan procedure, the inferior vena cava (IVC) is anastomosed to the pulmonary arteries via a synthetic graft called the extra-cardiac conduit (ECC), resulting in a 4-way junction with the superior vena cava (SVC) called the total cavopulmonary connection (TCPC). In this configuration, early mortality rates are low, but these rates increase in adulthood [3]. Many patients exhibit complications of a failing Fontan circulation such as elevated Fontan pressures and liver congestion with severe cases resulting in death. Current treatment options are limited to heart transplantation. However, with long wait times for donor hearts and a lack of medical devices available for use as a bridge to transplant, there is a high wait list mortality.

Several cavopulmonary-assist devices have been proposed in the literature [4]–[6], but all of these devices are still in the development stage. Disadvantages of previously proposed devices include the requirement for invasive implantation procedures, complexity due to moving parts, and recirculation regions in the flow field. As a result, none have yet been implemented for clinical use. In this study, we propose a customized double-lumen cannula, inserted into the TCPC and coupled to a commercially-available blood pump, as a cavopulmonary-assist device in a bridge-to-transplant capacity for patients with failing Fontan circulation. The proposed device siphons systemic venous blood flow from the IVC and SVC into an external blood pump and redirects it into the pulmonary arteries inside the TCPC of failing Fontan patients. The cannula device is minimally-invasive and does not have moving components. The objective of this study is to test an initial cannula design using computational fluid dynamics (CFD) to determine energy gain in the Fontan circulation and flow stability due to the presence of this device.
2 METHODOLOGY

An idealized pediatric TCPC geometry (Figure 1) was created from average measurements of angiogram data from 8 healthy and 2 failing pediatric patients with mean ages of 4 and 5 years, respectively. Curvature of the ECC was then modified based on recommendations from a cardiac surgeon. An initial cannula prototype design was then inserted into the TCPC geometry. Energy gain in the TCPC geometry was then determined through CFD simulations using the commercial finite-volume solver FLUENT v. 16.2 (ANSYS, Inc., Canonsburg, PA, USA) with varying flow rates.

Simulations were run for cannula flow rates from 0 to 0.75 L/min and cardiac indices from 2.0 to 3.0 L/min/m², which correspond to total flow rates of 1.37 to 2.06 L/min. Simulations for cannula flow rates of up to 0.5 L/min were done using a laminar solver while the 0.65-0.75 L/min cases were conducted using a transition k-kl-omega turbulence model. All cases were steady-state and blood was assumed to be a Newtonian fluid with density and viscosity of 1056 kg/m³ and 0.0035 kg/m/s, respectively. All CFD simulations were run using a relatively coarse mesh with 445,000 elements and run to convergence of 1×10⁻⁴ or 1×10⁻³ for laminar and turbulence simulations, respectively.

Mass flow boundary conditions were applied at the inlets of the IVC and SVC with magnitudes set to 65% and 35% of the total flow rate, respectively. Pulmonary vascular resistance of a failing Fontan circulation was modelled by adding resistance parameters on the left and right pulmonary arteries which update the outlet boundary pressures at each iteration. These resistances were implemented through a user-defined function.

Energy gain across the TCPC was calculated as:

\[ E = \sum_{outlets} Q_{out} P_{tot, out} - \sum_{inlets} Q_{in} P_{tot, in} \] (1)

3 RESULTS AND CONCLUSIONS

Figure 2 shows velocity contours in the right and left pulmonary arteries for a representative simulation at a cardiac index of 2.4 L/min/m² and a cannula flow rate of 0.375 L/min. This simulation predicts no significant areas of recirculation in both pulmonary arteries where flow from the cannula mixes with the systemic venous blood flow from the IVC and SVC. The cannula flow in the left pulmonary artery is pushed upwards due to higher IVC flow compared to that in the right pulmonary artery.
Figure 2: Velocity contours in the pulmonary arteries for a cannula flow rate of 0.375 L/min and a cardiac index of 2.4 L/min/m².

Figure 3: Energy gain for different cannula flow rates ranging from 0 L/min to 0.5 L/min.

Figure 3 shows the energy gain for different cannula flow rates at varying cardiac indices. Net energy gain was observed at 0.375 L/min flow rate and cardiac index of 2.2 L/min/m² and increased at higher cannula flow rates. The Reynolds number of the cannula flow ranged from 0 (no flow) to 1200 (0.75 L/min). For the higher cannula flow rates (greater than 0.5 L/min), simulations were only performed for cardiac indices of greater than 2.6 L/min/m² because of increasing recirculation and convergence issues when cannula flow and systemic flow velocities were substantially different.

In addition to energy gain as a measure of performance in cavopulmonary-assist devices, pressure rise across the TCPC is also an important measure for increasing pulmonary blood flow in the presence of high pulmonary vascular resistance. Several studies have used lumped parameter models for design of cavopulmonary-assist devices. For pediatric Fontan patients, a pressure rise of 6-8 mm Hg is required for cavopulmonary-assist devices to treat failing Fontan circulations [4] and for adult Fontan patients this requirement is approximately 2-5 mmHg [5]. In the present simulations, the maximum rise in total pressure was approximately 1.2 mmHg in the 0.75 L/min cannula flow rate case.

Currently, the cannula flow rate represents up to 42% of total cardiac output. Ongoing work is being conducted to refine the cannula design to reduce areas of recirculation, increase total cannula flow rate up to at least 50% of total cardiac output, and calculate the hemolysis index to determine if hemoglobin damage is a limiting factor of this proposed device. Findings from this preliminary
work will be applied to both pediatric and adult Fontan models (including patient-specific models) and used to improve the cannula design.

The present CFD simulations show that a customized cannula device with an external pump can provide net energy gain inside the TCPC (of up to 4.8 mW). This represents the first step towards the development of a cavopulmonary-assist device for bridge-to-transplantation for patients with failing Fontan circulation.

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**REFERENCES**


IN SILICO MODELING OF HEMODYNAMICS IN INTRACRANIAL ANEURYSM PATIENTS TREATED USING FLOW DIVERTERS AND ITS CORRELATION WITH CLINICAL OUTCOME

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SUMMARY

Treatment of intracranial aneurysms (IAs) using flow diverters (FDs) is the preferred treatment option. Despite high success of FDs, post-treatment complications like partial occlusion and delayed IA rupture have been reported. CFD modeling of FD-treated IA patients provide insights into hemodynamic modifications due to FD-implant, which can potentially predict the treatment outcome. We recapitulated the clinical intervention of FD-treated IAs in 22 patients, followed by CFD to obtain pre- and post-FD hemodynamics in the IAs. Hemodynamic modifications were correlated with clinical outcomes. There was statistically significant difference in the increase in relative residence time between successfully and unsuccessfully treated IAs.

Key words: intracranial aneurysm, flow diverters, computational fluid dynamics, virtual stenting, patient-specific application

1 INTRODUCTION

Flow diverters (FDs) - densely woven stent-meshes with high metal coverage rate and low porosity have emerged as the preferred treatment modality for intracranial aneurysms (IAs), especially for traditionally challenging wide-necked and fusiform IAs. FDs aim at inducing stasis in the IA sac, which promotes pro-thrombotic environment in the aneurysm. The dense-mesh like structure of FDs also facilitate endoluminal reconstruction of the parent artery. Although generally successful, undesirable outcomes like delayed occlusion and post-treatment rupture of the IAs leading to subarachnoid hemorrhage have been reported in the literature.1,2 In principle, implantation of a FD redirects the blood flow away from the aneurysm into the parent artery, inducing blood stasis in the sac leading to thrombosis and eventual obliteration of the aneurysm. However, for patients with failed clinical outcomes, we believe that sufficient flow diversion from the IA could not be achieved, failing to produce pro-thrombotic environments in the aneurysmal sac. In silico image-based computational fluid dynamic (CFD) analysis of IA patients treated using FDs can predict the blood flow dynamics before and after the FD-implant in the IA, which can provide insights on contrasting blood flow modifications in different clinical outcomes in different patients. Furthermore, the understanding of different hemodynamics in successful and failed outcomes can enable the clinicians to investigate different FD-related treatment strategies before the actual intervention.

With that goal in mid, we have previously developed an efficient virtual stenting workflow3, 4 which mimics the clinical implantation of the FD in patients in real-time. In this study, we have shown the clinical potential of VSW and CFD in assisting the clinicians in FD-treatment decision-making. We used VSW to recapitulate the clinical FD intervention on 22 IA patients, 15 of which were successfully treated, and 7 IAs failed to occlude. CFD simulations were performed on the
virtually treated IA models to obtain pre- and post- treatment hemodynamics, which was correlated with the clinical outcome of the patients.

2 METHODOLOGY

Twenty-two patient-specific IA cases were included in this study with the approval from the IRB at University at Buffalo. The IAs were located at the internal carotid artery (ICA) in all of these patients, which were treated using the commercially available FD: the Pipeline Embolization Device (PED, Covidien, Irvine, CA). The following clinical information were collected for each patient:
1. 3D digital subtraction angiographic (DSA) image for IA model segmentation
2. FD device specification and landing zone of the device for device deployment
3. 12-month clinical follow-up information for clinical outcome information

Virtual Stenting Workflow

An in-house virtual stenting workflow\(^3, 4\) was used to recapitulate the clinical FD deployment in each IA model. Briefly, the VSW includes 3 main steps: (1) Parent vessel isolation, where the parent vessel is obtained from the IA model, (2) simplex mesh initialization and expansion, where a generalized simplex mesh structure is placed into the parent vessel and expanded based on the mathematical forces applied on the simplex mesh. (3) Finally the FD pattern is mapped on the simplex mesh to obtained the final deployed FD geometry. The workflow of the virtual stenting method is shown on a patient-specific IA in Figure 1. The whole VSW workflow takes less than a minute to deploy a FD in a patient-specific IA model. We have recently validated the VSW algorithm against the high fidelity finite element method and micro-CT based imaging data.\(^5\)

![Figure 1: Virtual stenting workflow on a patient-specific IA geometry](image)

CFD Analysis and Hemodynamic Parameters Analyzed

After the deployment of the FD, volumetric meshing and CFD simulations were performed on the untreated and virtually treated IA models in STAR-CCM+ v10.02 (CD-adapco, Melville, NY) under physiological flow conditions. A healthy subject’s flow waveform was normalized with constant flow rate, and was prescribed at the inlet for all the IA models. Blood was modeled as Newtonian fluid, with density and viscosity as 1056 kg/m\(^3\) and 0.0035 Pa-s. Traction-free boundary conditions was prescribed at the outlet of the IA models.

To quantify the flow modification in the IA after the placement of the FD, hemodynamic changes in the following parameters were calculated:
1. Inflow rate (IR): flow entering the IA at the neck plane
2. Aneurysmal averaged velocity (AAV): average of the velocity magnitude inside the IA sac
3. Relative residence time (RRT)\(^6\): indicates the time blood spends at the IA wall
4. Shear rate (SR): gradient of velocity in the IA sac
5. Wall shear stress (WSS): Stress caused by the blood on the IA wall.
Wilcoxon rank-sum test (for abnormally distributed data) was performed for each hemodynamic parameter to assess the statistical significance of the observed difference between the successfully and unsuccessfully treated IAs. The statistical analysis was performed using the software SPSS (SPSS Inc., Chicago, IL).

3 RESULTS AND CONCLUSIONS

Figure 2 & 3 show hemodynamics in two representative successful and unsuccessful cases, along with the clinical images before the treatment and at 12-month follow-up. The figures show the 3D rendering of the velocity magnitude in the flow domain, and vortex corelines in black representing the core of the complex vortex structure, with streamlines around them representing strength of the structures.

Figure 2: Pre- and post-treatment velocity magnitude rendering and vortex corelines (black) with associated velocity streamlines for two representative aneurysms with successful outcome. Also shown is the angiographic image of the aneurysms before treatment and at 12-month follow-up showing complete obliteration of the aneurysm at follow-up. The complex vortex structures present in both the aneurysms in the pre-treatment CFD (left) are diminished after implantation of the FD (right).

Figure 3: Pre- and post-treatment velocity magnitude rendering and vortex corelines (black) with associated velocity streamlines for two representative aneurysms with unsuccessful outcome, as seen in the clinical follow up images. For these unsuccessful clinical cases, persisting vortex corelines and the swirling streamlines around them even after the FD placement (right) suggest that the FD was unable to disrupt the complex flow inside the aneurysm.
Quantification of hemodynamic parameters (Figure 4) showed a statistically significant difference in RRT (p-value=0.003) between the partially occluded and completely occluded groups. All other hemodynamic parameters did not show any statistically significant different among these two groups.

Figure 4: Flow change in hemodynamic parameters in aneurysms occluded within 12 months (blue) versus aneurysm with incomplete occlusion after 12-month clinical follow-up (red). Only RRT showed statistically significant different between the two groups.

The implantation of a FD reduces the blood flow in the aneurysm, which is evident from the changes in all the hemodynamic parameters after the deployment of a FD. But only the increase in RRT was statistically different in the two groups. This can be related to the fact that higher RRT gives the blood higher exposure time near the wall of the IA, hence promoting pro-thrombotic conditions in the successful cases. For the unsuccessful cases, relatively lower RRT was not enough to thrombose the IA sac. RRT can be a potentially useful hemodynamic parameter that can help in prediction of the occlusion of FD-treated IAs.

This study presents preliminary results of an ongoing study, where we plan to apply the VSW to a large number of clinical cases, and develop a statistical model for prediction of the outcome of FD-treated IAs. Owing to the high efficiency of VSW, we hope that this workflow can be implemented in the clinical setting, and help clinicians in a priori prediction of outcome of IAs treated using FDs.

REFERENCES
COMPUTATIONAL MODELLING OF THE MECHANICAL PERFORMANCE OF A MAGNESIUM STENT UNDERGOING UNIFORM AND PITTING CORROSION IN A REMODELLING ARTERY

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SUMMARY

A computational modelling framework is developed that combines magnesium alloy degradation and neointimal remodelling, that is capable of simulating both uniform (best case) and localised pitting (realistic) stent corrosion in a remodelling artery. The framework is used to evaluate the effects of the neointima on the mechanics of the stent, when the stent is undergoing uniform or pitting corrosion, and to assess the effects of the neointimal formation rate relative to the overall stent degradation rate (for both uniform and pitting conditions).

Key words: Computational Modelling, Biodegradable Magnesium Stent, Neointimal Remodelling

1 INTRODUCTION

Coronary stents have revolutionised the treatment of coronary artery disease by providing mechanical support to the artery following the angioplasty procedure and overcoming problems such as acute recoil and late negative remodelling [1]. For biodegradable stents, what is lacking in computational modelling literature is the representation of the active response of the arterial tissue in the weeks and months following stent implantation, i.e. neointimal remodelling. The phenomenon of neointimal remodelling is particularly interesting and significant in the case of biodegradable stents, when both stent degradation and neointimal remodelling can occur simultaneously [2], presenting the possibility of a mechanical interaction and transfer of load between the degrading stent and the remodelling artery.

The objective of the present paper is to build on the previous investigations reported in Boland et al. [3], [4] to develop computational modelling framework that accounts for several major physiological stimuli responsible for neointimal remodelling and combine this with a magnesium corrosion model that is capable of simulating both uniform (best case) and localised pitting (realistic) stent corrosion. Using the modelling framework, the second objective is to investigate the effects of the presence of the neointima on the mechanical performance (scaffolding support) of the biodegrading stent.

2 METHODOLOGY

Previous models used by the authors to simulate neointimal development (Boland et al. [3], [4]) are driven by artery stresses due to stent deployment and does not include other factors known to effect neointimal formation such as low endothelial shear stress [5]–[7] which is a limitation. Thus a model which considers both the stress in the artery due to stent deployment and endothelial shear stress due to blood flow as the primary stimuli for neointimal development may provide alternative patterns of arterial remodelling (neointimal growth).

A continuum damage mechanics (CDM) approach is taken for this alternative neointimal remodelling approach. A damage variable due to Von Mises stress in the artery (D_VM) is calculated...
through a stent deployment and recoil simulation. Separately, a computational fluid dynamics (CFD) model for blood flow is used to compute transient arterial wall shear stresses around the deployed stent. The damage variable due to these wall shear stresses ($D_{\text{WSS}}$) is calculated based on the time-averaged wall shear stresses (TAWSS) during a cardiac cycle. These two damage variables ($D_{\text{VM}}$ and $D_{\text{WSS}}$) are subsequently used as the stimuli in a final neointimal remodelling simulation which is described in detail in section 2.3.

### 2.1 Stent Deployment and Recoil Simulation

A three-layer cylindrical artery is modelled using an anisotropic Holzapfel–Gasser–Ogden (HGO) formulation. The HGO materials models were calibrated using the average stress-strain response of uniaxial tensile tests on 13 specimens in Holzapfel et al [8]. The stent is modelled using the properties of magnesium (Mg) AZ31 alloy [9], [10]. The stent geometry is a representation of the Biotronik Magmaris stent. Stent deployment was simulated using contact with a radially expanding rigid cylinder into the artery followed by radial contraction to allow for stent recoil.

The Von Mises (VM) stress in the artery was outputted from the deployment simulation and used to calculate $D_{\text{VM}}$. Lower and upper threshold limits of VM stress were selected based on the average VM stress in the artery and the average plus three times the standard deviation of VM stress in the artery respectively. If the VM stress in an element was below the average stress the element was considered undamaged a value of zero is applied to $D_{\text{VM}}$ for that element. Similarly, if the VM stress in an element was above the upper threshold limit the element was considered to be completely damaged and a value of one was applied to $D_{\text{VM}}$ for that element. A linear interpolation was used to apply $D_{\text{VM}}$ values to elements with VM values between the threshold limits.

### 2.2 CFD Simulation

The geometry for the CFD model was approximated from the deformed meshes of the stent deployment and recoil simulation. Abaqus software was used to create a surface mesh of the internal space around the artery and stent; where blood flow would occur. This surface mesh is extruded on both ends by 35mm to negate entrance and exit flow effects and subsequently is transformed into a volume mesh. This volume mesh is imported into Abaqus cae and forms the final geometry for the CFD analysis. A section of this mesh is illustrated in Fig. 1a.

Abaqus CFD is used for the transient blood flow analysis. A Carreau-Yasuda viscosity model is used for the CFD flow analysis to account for the shear thinning nature of blood [11]. Developed flow was simulated with a transient parabolic velocity profile at the inlet. The amplitude of the average flow velocity applied to the inlet was taken from [11] to simulate basal flow in the LAD coronary artery. Zero pressure boundary condition was applied to the outlet surface. No slip boundary conditions were applied to the entire external surface of the fluid geometry.

Wall shear stresses (WSS) were outputted for the surfaces of interest specifically in the region adjacent to stent struts. The time-averaged wall shear stress (TAWSS) was then calculated for each surface face. These TAWSS values were subsequently used to calculate values for $D_{\text{WSS}}$. Numerous clinical studies have provided evidence that low endothelial shear stress promotes neointimal formation [5], [7]. According to reference [12] WSS < 0.5 Pa is considered low, so based on this 0.5 Pa was selected as the upper threshold limit and element surface faces with values greater than or equal to 0.5 Pa were assigned a $D_{\text{WSS}}$ of zero. Surface faces with a very low wall shear stress (<0 Pa) were assigned maximum DWSS values of 1. A linear interpolation was used to apply $D_{\text{WSS}}$ values to elements with TAWSS values between the threshold limits (0 Pa and 0.5 Pa).

Figure 1: (a) Section of volume mesh used in the CFD model of blood fluid flow around the deployed stent in an artery. (b) Model set up for neointimal remodelling simulation showing half of the 3-layer artery (pink/red/dark red), expanded magnesium stent (black) and neointima/ghost mesh (white/transparent).
2.3 Neointimal Remodelling Simulation

The set up for neointimal remodelling simulation is illustrated in Fig. 1b. A three-layer artery modelled using the anisotropic HGO model as before, is supported by an expanded magnesium stent as shown in Fig. 1b. The stent is modelled using the properties of magnesium (Mg) AZ31 alloy. The stent geometry is a representation of the Biotronik Magmaris stent. The magnesium degradation models used in this study are adapted from the phenomenological uniform and pitting corrosion models of Grogan et al. [9] and are described in detail in Boland et al [3], [4].

The arterial lumen is filled with mesh of deactivated finite elements, namely the “ghost mesh” (see Fig. 1b), with negligible initial mechanical properties. The elements in the ghost mesh become activated according to the CDM neointimal remodelling. The activation of elements in the ghost mesh is representative of the remodelling of the artery through the growth of new neointimal tissue and entails a change in the material properties assigned to those elements. The newly activated elements change from a very soft material (negligible initial mechanical properties) to a stiffer material representative of neointimal tissue.

Both of the damage variables ($D_{VM}$ and $D_{WSS}$) are entered into the final neointimal remodelling simulation as mapped analytical fields which are subsequently used to control the distribution of thermal body heat flux and thermal surface heat flux loads respectively. The thermal loads cause the artery to heat up with non-uniform distribution depending on the damage variables ($D_{VM}$ and $D_{WSS}$). The magnitude of the thermal loads are initially controlled to ensure that the body heat flux associated with $D_{VM}$ and surface heat flux associated with $D_{WSS}$ each provide 50% of the total heat added to the simulation. This results in both stimuli being equally responsible for the location of neointimal development. The transfer of this heat into the ghost mesh causes activation of elements and neointimal remodelling when the local temperature exceeds a certain threshold.

3 RESULTS AND CONCLUSIONS

A contour plot of $D_{VM}$ for the intima material calculated from the stent deployment and recoil simulation is shown in Fig. 2a. The outline of the stent struts can clearly be seen in the contour plot, illustrating that the highest $D_{VM}$ values are located where the intima is in contact with the struts of the magnesium stent. A contour plot of $D_{WSS}$ due to blood flow calculated from the CFD simulation is shown in Fig. 2b. As illustrated in Fig. 2b, large $D_{WSS}$ values are concentrated in regions closest to stent struts and particularly stent connectors due to low flow velocities in these regions.

![Figure 2](image)
REFERENCES


VARIATION OF STRUT PARAMETER EFFECTS WITH WALL DEFORMATION ON STENT DEPLOYMENT VIA SURROGATE MODEL

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SUMMARY

Broad observation on stent design effect to the intravascular environment is necessary to improve the stent treatment efficacy. This study focuses on how stent behaves under variance of its geometrical change under wall deformation due to stent-vessel contact. Kriging based surrogate model is used to estimate the behavior of intravascular environment during stent deployment. Optimal parameters of 0.1 - 0.15 mm strut size and 2.5 - 3.0 mm strut gap is predicted to minimize the presence of low wall shear stress along the deployment area. Besides, flow behavior on different strut geometry configuration is well predicted by this surrogate model.

Key words: stent, surrogate model, kriging, computational simulation

1 INTRODUCTION

In recent years, several optimization methods for stent design improvement have been considered in order to find the best design criteria to achieve best result on the treatment. Study on optimization of stent design via a surrogate model has begun in 2008 by Srinivas et al. which presents some alternative candidates of optimal cardiovascular stent with combination of its gap and cross-sectional design based on Computational Fluid Dynamics (CFD) simulation[1]. Moreover, optimal design for cerebral aneurysm flow diverter and followed by its 3-dimensional optimization is proposed based on its hemodynamic performance via Kriging estimation method [2, 3]. In 2014, some optimization on strut placement design both in idealized and realistic vessel geometry has been conducted to reduce the flow inside aneurysm dome based on simulated annealing with lattice Boltzmann (LBM) method [4, 5]. Zhang et al., also tried to optimize flow diverter through random modification on the strut’s starting phase and LBM based CFD simulation [6]. However, all these researches did not include the factor of wall deformation on their simulations. Some experimental data shows that when a stent deployed the vessel wall, it would push the vessel wall in which resulted in deformation of vessel wall along the deployment area [7]. Furthermore, from our previous study, it appears that simulation with wall deformation causing a significant wall shear stress (WSS) change [8].

Besides its function as a physical model in searching for an optimal design, a surrogate model also comes with extra benefit. From a surrogate model, we are able to do a broad exploration of system behavior that also could be valuable information for further predictions in the design process [9]. In this research, design optimization for a stent with rectangular strut shape, which considers hemodynamics interaction with vessel wall deformation, has been conducted. Computational simulation with interaction between blood flow and stent – vessel surfaces has been conducted by a Finite Element Method (FEM) simulation. The optimization steps have proceeded via a surrogate model constructed by the Kriging estimation method. From the constructed surrogate model, we can
estimate the optimal stent design parameters and also broadly explore the stent performance behavior related to the design parameters. This study aims to observe how strut design parameters (gap and size) affect stent behavior on the percentage of low wall shear stress (WSS) area along deployment area via the Kriging based surrogate model.

2 METHODOLOGY

The ranges of stent size and inter-strut gap are set from 0.05 mm to 0.45 mm and from 1 mm to 3 mm, respectively. Twenty-five combinations of strut gap and size are sampled by the Halton sequence method in order to obtain space filling and uniform samples. Each sample case consists of 9 rectangular struts positioned by specific prescribed inter-strut gap. An idealized stent deployment system in 2-dimensional axisymmetric geometry has been constructed and simulated by COMSOL Multiphysics 5.0 (Comsol Inc., USA).

The simulation process begins with structural deformation with 5.5% [7] displacement prescribed on stent-vessel contact followed by the fluid-structure interaction (FSI) simulation to simulate the interaction between blood flow and vessel wall. Stent material is assumed as NiTi with 80GPa Young modulus and 0.33 Poisson ratio. Blood is assumed as the Newtonian fluid with 1050 kg/m$^3$ density and 0.0035 kg/ms dynamic viscosity. The vessel wall is defined as the linear elastic material with 0.7 MPa Young modulus and 0.45 Poisson ratio. The static pressure of 100 mmHg from the average value of human normal blood pressure and the dynamic pressure induced by blood flow are imposed on the contact surface between blood flow and solid domain of stent and vessel. Each computational simulation spends around 2 minutes per iterations which can be considered as a cheap computational cost. However, as previously explained that the purpose of surrogate model on this study is to do a better analysis of the relationship between WSS and design variables. Such analysis is difficult to be performed by solely performing the optimization algorithm.

The objective function is to minimize the low WSS area percentage since low WSS is recognized as a strong factor which promotes atherosclerosis [10]. Surface data of low WSS area distributions is obtained and analyzed to find the relation between the design factor of gap and size with hemodynamic behavior inside the blood vessel. This process begins with exporting WSS data along the deployment area as the simulation result and analyzing it statistically in each sample case. Each sample data is collected and processed with Kriging estimation using our developed in-house software. From this computational process, the surrogate model of low WSS area (WSS < 1 Pa [10]) depending on strut size and gap configuration is obtained.

3 RESULTS AND CONCLUSIONS

3.1 Simulation results

Deformed geometry is obtained as shown by Fig.1, afterwards flow domain is added and CFD analysis is performed with mechanical loads on the vessel wall from the flow’s dynamic pressure and also 100mmHg static pressure which representing human’s normal average blood pressure. As a result, WSS magnitude is calculated along the blood vessel and statistically analyzed to find the low WSS area (< 1 Pa) from each numerical samples. In addition, as a result of interaction between blood flow and vessel wall, deformation is observed with an infinitesimal order which can be neglected for any further analysis.

![Fig.1 Deformed geometry of stent deployment area](image_url)
3.2 Surrogate model

The surrogate model of low WSS area (in percentage) with respect to size and gap configuration is shown as the contour plane graph shown in Fig.2. The green dots are the sampling points which are used to construct the surrogate model.

![Contour plane graph of surrogate model from low WSS area vs strut size and gap. Color bar representing the low WSS area (in percentage).](image)

From Fig.2, the optimal design can be estimated, as the minimum value of low WSS area percentage is observed in the area of 0.1 – 0.15 mm strut size with gap between 2.5 – 3 mm. Moreover, it can be observed that the percentage of low WSS area increases more dramatically as the strut size increases. And this percentage reaches the highest value under the strut size around 0.35 - 0.4 mm. This value reduces again with the strut size larger than 0.4 mm, although it is considered to exceed the standard size of stent strut. On the other hand, the influence of inter-strut gap is less significant on the percentage of low WSS area. Thus, it is clearly shown that the strut size has more significant effect on the percentage of low WSS area.

3.3 Conclusions

Besides its function to find an optimized parameter criterion, kriging estimation is also useful to observe the behavior of design and how it influences the performance parameters such as WSS. In this research, we can conclude that low WSS area along stent deployment area is more strongly affected by stent strut’s size than its gap. In addition, optimal stent design is estimated with the strut size of 0.1 – 0.15 mm and the inter-strut gap 2.5 – 3 mm. Although some recent development of stent designs is more likely to reduce the strut size and gap, but this study suggests that higher low WSS tendency is found on smaller and denser stent configuration.

Future work with more sample points through further exploitation steps is necessary to improve the surrogate model quality. Further optimization method will be used to obtain more accurate optimal design combinations between strut’s size and gap. Different stent strut shape should also be investigated to find out the effect of the strut shape on intravascular flow conditions.

4 ACKNOWLEDGMENTS

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COMBINING MATHEMATICAL MODELLING WITH IN-VITRO EXPERIMENTS TO PREDICT IN-VIVO DRUG-ELUTING STENT KINETICS

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SUMMARY

In this paper we describe a combined in-vitro experimental and mathematical modelling approach to predict in-vivo drug-eluting stent kinetics. We coated stents with a mixture of sirolimus and a novel acrylic-based polymer in two different ratios. Our results indicate differential release kinetics between low and high drug dose formulations. Furthermore, mathematical model simulations of target receptor saturation suggest potential differences in efficacy.

Key words: Drug-eluting stents, drug delivery, coupled partial differential equations, in-vivo experiments

1 INTRODUCTION

Mathematical and computational modelling is increasingly being used in the design and testing of medical implants. In particular, modelling of drug-eluting stents (DES) for the treatment of Coronary Heart Disease (CHD) has received much attention in the literature [1]. Many aspects of these devices have been modelled, including deployment, structural and fluid mechanics, and drug-delivery. A common theme has been to use modelling to try to infer the optimal design of a DES [2, 3]. Some authors have focussed on a single feature such as the geometry (e.g. strut thickness), materials, or drug loading, whilst others have considered multi-objective optimisation. Regarding the drug delivery aspect, there exist studies which have used modelling retrospectively to demonstrate agreement with in-vivo drug release and tissue uptake data [4, 5]. Usually this involves a fitting procedure, where an algorithm is used to determine the model parameter set which best fits the data. These studies are limited in the fact that they cannot be used in a predictive sense. To the best of our knowledge, there exists no published studies which have attempted to validate and parameterise a model using in-vitro data before using the parameterised model to predict in-vivo kinetics. This is precisely the focus of the current study.

2 METHODOLOGY

2.1 Drug release

We verified experimentally that a novel acrylic-based polymer (acceleratETM AT, Biomer Technology Ltd, UK) could be combined with sirolimus to produce a coating which releases drug at clinically relevant concentrations, initially by coating glass coverslips and then Flash stents (Conic Vascular,
Santiago de Compostella). The stents were coated with low and high doses of sirolimus/polymer (in ratios 25:75 and 75:25, respectively) using a Sono-Tek Ultrasonic Spray system (Milton, NY, USA). Two coats were applied. The stents were assessed for release of sirolimus over a period of 28 days by immersing in 1.5 ml of release medium (phosphate buffered saline:ethanol 90:10), and transferring to fresh release medium at regular sampling points to maintain sink conditions. The amount of sirolimus in release medium was determined by ultraviolet spectroscopy.

Our previous mathematical modelling of drug release from the Cypher stent revealed that in-vitro release was well described by a relatively simple one-dimensional diffusion model [7], whereas in-vivo release was captured by a diffusion-dissolution model, indicating that differences in drug solubility between the in-vitro and in-vivo release medium may be important [5]. We therefore fit the drug release data for each coating formulation to the diffusion model, and separately to the diffusion-dissolution model.

2.2 Coupled drug release and tissue uptake

The parameterised model of drug release from Section 2.1 was then coupled with a model of drug transport in the arterial wall accounting for diffusion, advection and two modes of binding (specific receptor and non-specific extracellular matrix binding), utilising porcine arterial tissue transport parameters from the literature [4, 5, 6]. As well as providing the opportunity to predict the uptake and retention of drug in the arterial wall, this model allowed us to simulate spatial wall drug concentration and receptor saturation, which have been linked with DES efficacy yet are difficult to measure experimentally.

An in-vivo experimental study was subsequently conducted. Briefly, low and high dose stents were deployed in male Landrace pig coronary arteries with drug release and mass of drug in tissue quantified at 1 day, 7 days and 28 days. Animal care and all procedures conformed to the requirements of the U.K. Animals (Scientific Procedures) Act 1986.

3 RESULTS AND CONCLUSIONS

3.1 In-vitro drug release

At the end of the in-vitro experiments, stents were immersed in ethanol to strip any remaining drug. In all cases, we observed that not all of the initial drug mass was released by 28 days, despite the release profiles appearing to asymptote. We therefore assumed that some quantity of drug would never be released (as has been observed with other commercial stents, e.g. TAXUS) and so normalised release data by the cumulative mass of drug released by the final measurement time point. Whilst our low drug dose formulations were very well described by a simple diffusion model, the fit to the high dose formulation data was not so good. In Figure 1 we compare in-vitro drug release from the low and high dose formulations with two applied coats. The best-fitting diffusion coefficient in the high dose case is an order of magnitude less than in the low dose case. This may suggest that drug transport in the high dose case is more complex than diffusion alone, or perhaps that one or more of the model assumptions are not appropriate. Results from fitting to a diffusion-dissolution model essentially reproduced Figure 1, suggesting that the more complex diffusion-dissolution model is no better at capturing the release. Since in the high dose case, the ratio of drug to polymer is 75:25, the validity of the diffusion model (i.e. the dilute species assumption) may be called into question, and multi-species diffusion models may be more appropriate.

3.2 In-vivo drug release

Our preliminary results indicate that for the low dose stents, drug elution is complete by 1 day, in agreement with the in-vitro drug release profile. However, for the high dose stents, whilst the duration of drug release is the same (28 days) for the in vitro and in-vivo cases, the release rate is significantly faster in-vivo: approximately 85% of drug is released within 1 day in-vivo, compared
with approximately 60% in-vitro. In agreement with the in-vitro release, the remainder of drug is released at a slower rate over the following 27 days.

### 3.3 Efficacy

It is generally accepted [4] that the fraction of drug bound to target receptors is an indicator of DES efficacy, yet there is currently no straightforward way to measure this in-vivo. We therefore used our mathematical model of coupled drug release and tissue uptake to predict target receptor binding levels for both low dose and high dose stents, using porcine coronary artery wall model parameters from the literature [4][5][6]. In Figure 2, we observe that the model predicts target receptor saturation within 1 day for both low dose and high dose stents. Despite drug elution for the low dose stent being complete by 1 day, target receptors remain saturated for approximately the first 3 days, with a declining rate of saturation over the remainder of the 28 days. In contrast, the high dose stent results in near 100% target receptor saturation for the majority of the first 2 weeks, followed by a steady decline for the remainder of the study. Simulations of non-specific extracellular matrix (ECM) binding revealed that neither the low dose nor the high dose stent delivered drug at levels capable of reaching saturation. Histological analysis, important for assessing efficacy experimentally, is ongoing. The results from this analysis will be assessed in conjunction with model predictions of receptor saturation.

### 4 CONCLUSIONS

In this study we have successfully developed two novel DES with distinct release profiles. By comparing experimental drug release data with our diffusion-based mathematical model, we have shown that the model captures the release of drug from the low dose stent very well and less well for the high dose stent. In an attempt to assess efficacy, we have used our parameterised model to simulate the level of sirolimus bound to target receptors. Our preliminary results indicate differential levels of receptor saturation between low dose and high dose stents, indicating possible differences in efficacy. Experimental analysis of DES efficacy is ongoing.

### 5 ACKNOWLEDGEMENTS

We would like to acknowledge the support of Biomer Technology Ltd, who provided the polymer used in this study. They also provided access to coating equipment and their technical expertise during production of the coated stents. We would also like to acknowledge the UK Engineering and Physical Sciences Research Council (EPSRC) (Grant numbers EP/J007242/1 and EP/J007579/1) and the EPSRC Impact Acceleration Account at the University of Strathclyde, for helping to fund this work.
Figure 2: Simulated arterial binding kinetics. LEFT: Low dose stent. RIGHT: High dose stent. In both cases the model predicts target receptor saturation within 1 day. The % of drug bound receptors decreases more rapidly for the low dose stent. Neither low dose nor high dose stents result in ECM non-specific binding site saturation.

REFERENCES


Reduced-Order Modelling of the Cardiovascular System - Challenges & Translational Opportunities I
CHALLENGES IN 1D FFR: A COMPUTATIONAL CASE STUDY

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SUMMARY

Fractional Flow Reserve (FFR) is the current gold standard for evaluating the functional severity of coronary stenoses. FFR is performed invasively in the cath lab and represents the fraction of the normal maximal coronary blood flow that is achieved in the presence of a stenotic artery. It is derived from the ratio of the mean hyperemic distal intracoronary pressure to the mean arterial or aortic pressure. In recent years, several non-invasive methods have been proposed for the estimation of coronary circulation in patients with coronary artery disease. The aim is to develop better strategies for risk assessment to increase the diagnostic yield of cardiac catheterization. In this regard, ‘personalisation’ of coronary flow computations vs. model complexity is a great challenge. We aim to investigate the role of certain ‘geometrical’ and ‘physiological’ parameters pertaining to the model and the influence of hemodynamic conditions on FFR by comparing results from 3D computations with an approach based on reduced-order models (0D-1D).

Key words: fractional flow reserve, reduced-order models

1 INTRODUCTION

Various methods (3D, reduced-order or hybrid/multi-scale models, analytical solutions, machine-learning, etc.) have been proposed for the computation of FFR, generally from coronary imaging data [1, 2, 3, 4, 5, 6, 7]. In most methods, a patient-specific geometrical model is created using a semi-automatic approach. Additional information based on form and function relationships is then added to the physiological model which complements the physical model used to solve coronary flow and pressure.

In this work, we propose an approach entirely based on coupled 0D-1D models, but where no assumption is made regarding the stenosis, i.e. no physiological stenosis model. The computational domain is represented by a definition as accurate as possible of the geometry and the FFR is determined solely based on the physical model, supplemented with appropriate boundary conditions (coronary model). The coronary model is based on previously published models (see for instance [8]).

Our aim is to evaluate the accuracy of our approach by comparing results from our model with those obtained from 3D simulations. We have generated a series of cases with different stenosis severity and aspect ratio. We also investigate cases with serial and non-axisymmetric stenoses or stenoses with surface ‘irregularities’.

2 METHODS

2.1 Coronary model

A representation of the computational domain is shown in FIG. To determine the parameters of the coronary model, we assumed a cardiac output of 5 l min−1 at rest. The prescribed total mean coronary flow was 4.0% of the cardiac output and divided to each branch in proportion of its outlet cross-sectional area.
For each coronary outlet, coronary venous resistance was calculated on the basis of the mean flow to that branch and assigned venous pressure (we used a value of 20 mmHg). We then computed coronary arterial resistance and coronary arterial micro-circulation resistance using branch mean flow and a prescribed mean arterial pressure. To account for hyperaemia, we scaled down all resistances thus calculated by a factor of 0.24 (see for instance [11]). The capacitance values were adjusted to give physiologically realistic coronary flow and pressure waveforms.

To represent the intra-myocardial pressure acting on the capacitance C2 (see [1]), we used a prescribed left ventricular pressure waveform, as we did not use a heart model. This pressure waveform corresponds to the inlet flow waveform used as boundary condition at the inlet.

2.2 1D model and material properties

We use a standard DG formulation with a spectral/hp spatial discretisation (see [13]), and incorporate variable material properties. After extracting the centrelines from the 3D domain, we obtained a ‘distribution’ of radii along each branch which is then used to determine the reference area and material properties. Material properties ($\beta$) are determined as in [12]. The pressure-area relationship is given by

$$p - p_{\text{ext}} = p_0 + \frac{\beta}{A_0} \left( \sqrt{A} - \sqrt{A_0} \right)$$

2.3 Preliminary results

Due to the small number of cases, we did not determine the overall indices of diagnostic accuracy, but rather focused on the analysis and correlation on a per-vessel basis. Preliminary results show that our approach based on reduced-order models is comparable to the 3D method. A detailed analysis of each case also reveals where reduced-order models may fail and/or need to be improved. These results also provide an important comparison of technologies with other established non-invasive methods, essential for the advancement of this field of research.
REFERENCES


A FRAMEWORK FOR MINIMIZING THE NUMBER OF UNCERTAIN PARAMETERS IN 1D ARTERIAL BLOOD FLOW MODELS

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SUMMARY
As computational models of the cardiovascular system are applied in modern personalized medicine, maximizing certainty of model input becomes crucial. Increasing the number of arterial segments in a model result in a more realistic description of the system, but also introduce more uncertain parameters. We present a framework that aims at minimizing the number of arteries in distributed one-dimensional models, preserving key features of flow and pressure waveforms. A previously proposed method and a new method for lumping 1D segments is incorporated in the framework. The framework have been tested for different criteria for maximum deviation with the original 55-artery model. The previously proposed method yield better results in lumping peripheral arteries, whereas the new method give better results when more compliant arteries are lumped. Our novel framework make it possible to find the important vessels to include in a 1D model for a given clinical application.

Key words: 1D blood flow, 0D models, model reduction

1 INTRODUCTION

Three-dimensional (3D), One-dimensional (1D), lumped models (0D) and combinations of two or more of these (e.g closed loop models) continue to contribute towards better understanding of the hemodynamic system. However recent advances in numerical methods, computational power and imaging techniques have made it evermore relevant with predictive models either to be used in diagnostics or as tools for clinicians in weighting and planning interventions. As a consequence maximizing certainty of model inputs becomes crucial. Furthermore, balancing model complexity with the number of uncertain parameters becomes an integral part in model development.

Studies have showed that models based on 1D nonlinear equations for blood flow in compliant vessels are able to represent the main aspects of pressure and flow waves in large arteries [1]. The 1D formulation has also compared well with corresponding 3D compliant arterial models [1, 2], and with in vitro experiments [1, 3]. Recent studies show that computational method based on hybrid 1D and 0D models [4] show similar ability in diagnosing hemodynamic significance of coronary artery lesions (FFR), comparing with methods using 3D computational fluid dynamics (CFD) [5].

One of the major benefits of distributed 1D models is their relatively low computational cost. Furthermore they are attractive given their ability to investigate how great parts of the systemic circulation interact, including anywhere from one to more than 4 million arteries [1, 6]. However in a clinical application the number of arteries to include depend on the problem at hand, how accurate one can assign parameters and boundary conditions and how much interactions there are between vessels (e.g the importance of capturing wave reflections due to intricate network topology). Previous work has been done showing that one can reduce the number of arteries by appropriately replacing them with boundary conditions, keeping good agreement between the baseline- and reduced model [7]. Here we present a framework that tries to balance model complexity with the number of uncertain parameters;
for a given problem minimize the number of vessels with constraints of maximum deviation with a corresponding detailed model.

2 METHODOLOGY

The solutions of the 1D equations presented here were solved with the flow-solver STARFiSh [8], represented as the MacCormack or McC scheme in [1]. The baseline models; a 55-artery model (systemic, excluding cerebrals) and a 96-artery (including cerebrals) provides pressure and flow waveforms that contain the main features observed in vivo under normal physiological conditions. Inflow boundary data, parameters for geometry and outflow boundary conditions (three element windkessel (WK3) models) were adapted from [9].

2.1 Reducing the number of arterial segments: a new approach

A method for reducing the number of arterial segments was presented in [7]. Their approach is to

a) Integrate over the 1D domain of terminal vessels to estimate the resistance \(R_v\) and compliance \(C_v\).

b) Lump terminal vessels coupled to WK3 models into two-element windkessel (WK2) models with parameters \(R_{new}\) and \(C_{new}\). The resistances in the WK3 and the resistance of the vessel are added, whereas the compliance is impedance weighted. 

c) Apply electrical analogy for resistance and compliance to reduce WK2 models in parallel (bifurcations where daughter vessels are terminal vessels) into a single WK3 model. 

d) Perform steps a-c in a systematic manner to reduce the network to the size of interest.

\[
R_v = 2 (\xi + 2) \pi \mu K_3, \quad K_3 = \int_0^1 \frac{1}{A_d} dx, \tag{1a}
\]

\[
C_v = \frac{K_1}{\rho}, \quad K_1 = \int_0^1 \frac{A_d}{c_d} dx. \tag{1b}
\]

In Eq. (1a) and (1b), \(\xi\) is a velocity profile parameter, \(\mu\) the blood viscosity, \(\rho\) the density, \(A_d\) and \(c_d\) the area and pulse wave velocity at diastolic pressure.

In cases where the network does not only contain bifurcations, e.g in the cerebrals where there are anastomosis and communicating arteries, the direction of the flow and thus determining if one should treat a junction as a bifurcation or an anastomosis is not trivial. However it is possible to estimate time averaged flow and pressure in the distributed network without solving a transient nonlinear problem. For every vessel we have a drop in pressure from the inlet to the outlet of the domain, and for every junction there should be conservation of mass or flow rate \((Q)\). The drop of pressure along a vessel is related to the resistance \(R_v\), and the pressure at the distal end of terminal vessels relate to the resistance \(R = R_1 + R_2\), where \(R_1\) and \(R_2\) are resistances in the WK3 model. The mean flow into the system can be found by integrating the inflow data. The network is thus reduced to a linear system of resistances in series and parallel and may be solved using linear algebra.

The above method give estimates of mean flow and pressure everywhere in the distributed network and make it possible to reduce more complicated networks where traversing from the periphery towards the root is not obvious from a geometrical point of view. An alternative method for reducing arterial segments in 1D network can be performed by performing the following steps: 

a) Estimate mean values of flow \((\bar{Q})\) and pressure \(\bar{P}\) by solving a linear steady state solution of the electrical analogous 1D network. 

b) Estimate the resistance at the position of interest by evaluating \(R_{new} = (\bar{P} - P_v) / \bar{Q}\), where \(P_v\) is the venous pressure or rather the outflow WK3 pressure. Further estimate compliance \(C_{new}\) by adding all compliance contributions from the periphery. 

c) Replace all arteries peripheral to the point of interest with a WK3 model with total resistance \(R_{tot} = R_{new}\) and compliance \(C = C_{new}\).
Worth noting is that in the first method (method 1) a weighting of the peripheral compliance is performed (total impedance-weighted peripheral compliance), whereas in the new method (method 2) the compliance of peripheral arteries are summed (total peripheral compliance).

2.2 Framework for optimizing the number of arterial segments in 1D networks

Here we present a framework for reducing the number of vessel segments still assuring wanted features of pressure and or flow to be within acceptable agreement with the corresponding full model:

- Define a baseline model
- Locate the area(s) of interest appropriate for your problem (e.g. Aortic/Carotid pressure)
- Define a threshold for pressure and or flow (e.g. norm, pulse or mean error)
- Reduce the baseline model at possible sites and solve the reduced 1D networks
- Find the network with the fewest number of arteries subject to the constraint of the threshold

In the reduced models, WK3 models replaced the removed vessels with parameters \( C = C_{new} \), \( R_1 = Z \) (characteristic impedance) and \( R_2 = R_{new} - R_1 \) at the corresponding sites.

<table>
<thead>
<tr>
<th>RMS-criteria (%)</th>
<th>Ascending Aorta (inlet)</th>
<th>Right Brachial (midpoint)</th>
<th>Left Carotid (outlet)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>vessels (no.)</td>
<td>method</td>
<td>vessels (no.)</td>
</tr>
<tr>
<td>0.25</td>
<td>37</td>
<td>1</td>
<td>39</td>
</tr>
<tr>
<td>0.5</td>
<td>27</td>
<td>1</td>
<td>31</td>
</tr>
<tr>
<td>1.0</td>
<td>19</td>
<td>1</td>
<td>21</td>
</tr>
<tr>
<td>1.5</td>
<td>7</td>
<td>2</td>
<td>19</td>
</tr>
<tr>
<td>2.0</td>
<td>5</td>
<td>2</td>
<td>9</td>
</tr>
</tbody>
</table>

Table 1: Results from optimization framework described in sect. 2.2 for selected arteries, and with varying constraint (RMS-error between pressure of the reduced- and the 55-artery baseline model). The table shows the number of vessel segments and which reduction method produced the optimized network. Method 1 correspond to the previously proposed method and method 2 the new method, both described in sect. 2.1

3 RESULTS AND CONCLUSIONS

The method for estimating mean values of \( Q \) and \( P \) were compared with corresponding time averaged 1D transient solutions in a network of 96 systemic arteries (including cerebals) and showed good agreement in all segments. The method estimated a mean pressure value of 99.6 mmHg at the ascending aorta, deviating 0.1 mmHg from the corresponding time averaged transient value. This in turn indicates that good estimates of the resistance \( R \) can be based on this method, and it also make it possible to trace back from terminal vessels in the direction of the mean flow to estimate values such as \( C \) in networks with complicated topology.

The framework described in sect. 2.2 have been tested for three different areas of interest; pressure at the proximal end of the Ascending Aorta, midpoint of the right Brachial artery and the distal end of the left Carotid artery. Different root mean square errors (RMS-errors) were used as thresholds for maximum deviation between baseline and reduced models. The baseline model was a 55-artery model (excluding cerebals) and all possible combinations (4924) of reducing the network down to a single aortic bifurcation was solved using the 1D flow-solver. Both of the reduction methods described in sect. 2.1 were used to reduce the baseline network and RMS-errors between baseline and reduced models were calculated. Table 1 shows the number of vessel segments in the reduced network resulting from the optimization, and also which of the two methods produced it. Worth noting is that for the cases where mostly peripheral arteries are removed the previously proposed method yields the best result whereas the new method gives better results when more compliant arteries are removed. Figure 1 show the pressure waveform of the reduced 19 network model resulting from

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setting an RMS-criterion of 1 % for the Left Carotid artery. Here method 1 gives an RMS-error of 0.9 % comparing with the baseline pressure, whereas method 2 result in an RMS-error of 1.2 %. In the more extreme case where the network is reduced to a single aortic bifurcation, method 1 and method 2 gives RMS-errors (pressure) at the Aortic root of 4.3 % and 2.1 % respectively.

Our framework make it possible to reduce the number of segments, and thus also the number of uncertain parameters by a substantial amount without significantly altering pressure and flow waveforms.

REFERENCES


EFFECTIVE IMPLEMENTATION OF BOUNDARY CONDITIONS AT VESSEL'S JUNCTIONS IN THE 1D MODELS OF HEMODYNAMICS

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SUMMARY

Three types of boundary conditions at vessel’s junctions are considered including Bernoulli theorem, Hagen-Poiseuille condition and pressure continuity condition. Effective implementation is proposed which is based on the equivalent transformation and reduction in general case of the arbitrary number of the connected vessels.

Key words: 1D hemodynamics, vessel’s junction, boundary conditions

1 INTRODUCTION

In the most 1D models of hemodynamics boundary conditions can be classified as inlet boundary conditions representing the outflow from the heart, the boundary conditions at the vessel’s junctions and outflow boundary conditions at the terminal arteries or arterio-venous gradient condition. The inlet conditions are generally set as predefined time function of heart volumetric output profile or aortic pressure or as a coupling with the heart model. The outflow conditions applied in the models with truncated arterial tree \cite{1,2,3}. The arterio-venous gradient condition is applied in the models of closed circulation \cite{4,5}. It is based on the Hagen-Poiseuille condition, which relates pressure drop and volumetric flow by hydraulic resistance coefficient. The boundary conditions at the vessel’s junctions usually stated as the total pressure continuity (Bernoulli theorem) e.g. \cite{7}, the Hagen-Poiseuille condition e.g. \cite{5} or the pressure continuity condition \cite{4,6}. They also include mass (flow) conservation condition and compatibility conditions of hyperbolic task for the internal part of the vessels in the junction. The arteries and veins junctions include bifurcations, trifurcation, anastomoses, merging or structural one-to-one connections. The junction may have no distinct inlet and/or outlet vessels. The flow direction in the junction may be changed dynamically. Thus, uniform formulation without prescribed assumption on the flow direction is needed to cover the whole cases of possible junctions. In this work three approaches are considered in uniform manner for an arbitrary number of connected vessels. Effective reduction of these formulations is performed and analysed.

2 METHODOLOGY

Typical 1D model of hemodynamics describes the flow of viscous incompressible fluid through the network of elastic tubes. The flow in every tube (vessel) is described by the set of hyperbolic equations of mass and momentum conservation. The 1D model includes

- inlet boundary conditions which represent the outflow from the heart;
- the boundary conditions at the vessel’s junctions;
- outflow boundary conditions at the terminal arteries or arterio-venous gradient condition.
A review of the recent approaches to 1D modelling of hemodynamics can be found in [8]. In this work the model from [5] is used for the blood flow simulation in the vessel. It can be stated as

\[
\frac{\partial \mathbf{V}}{\partial t} + \frac{\partial \mathbf{F}(\mathbf{V})}{\partial x} = \mathbf{G}(\mathbf{V}),
\]

where \( t \) is the time; \( x \) is the spatial coordinate counted off from one of the vessel’s junction points; \( \rho \) is the blood density; \( S(t, x) \) is the vessel’s cross-section area; \( u(t, x) \) is the linear velocity averaged over the cross-section; \( p(S) \) is the pressure; \( f_{fr} \) is the friction force. The \( p(S) \) is specified as

\[
p(S) = p_* + \rho_w c_w^2 f(S),
\]

\[
f(S) = \begin{cases} 
\exp (\xi - 1) - 1, & \xi > 1 \\
\ln \xi, & \xi \leq 1,
\end{cases}
\]

where \( \rho_w \) is vessel wall density, \( p_* \) is pressure in the tissues surrounding the vessel; \( \xi = S/S_0, S_0 \) is the unstressed cross-sectional area. \( c \) is the velocity of the small disturbances propagation in the material of the vessel’s wall.

Boundary conditions at the vessels junctions must include compatibility condition of (1) at the terminal point of the vessel in the junction along outgoing characteristic and mass conservation condition

\[
\mathbf{w}_{ki} \cdot \left( \frac{\partial \mathbf{V}_k}{\partial t} + \lambda_{ki} \frac{\partial \mathbf{V}_k}{\partial x} \right) = 0, k = k_1, k_2, \ldots, k_{M_l}, \quad (4)
\]

\[
\sum_{k=k_1,k_2,\ldots,k_{M_l}} \varepsilon_k S_k (t, \bar{x}_k) u_k (t, \bar{x}_k) = 0. \quad (5)
\]

where \( \mathbf{w}_{ki} \) and \( \lambda_{ki} \) are the left eigen vectors and eigen values of the Jacobi’s matrix \( \frac{\partial \mathbf{F}}{\partial \mathbf{V}} \). The set (4),(5) can be closed by one of the following options

- Bernoulli theorem

\[
\frac{u_k^2(t, \bar{x}_k)}{2} + \frac{p_k(S_k(t, \bar{x}_k))}{\rho} = \bar{F}^l, k = k_1, k_2, \ldots, k_{M_l}, \quad (6)
\]

- Hagen-Poiseuille pressure drop condition

\[
p_k (S_k(t, \bar{x}_k)) - p^l_{\text{node}} = \varepsilon_k R_k^l S_k(t, \bar{x}_k) u_k (t, \bar{x}_k), k = k_1, k_2, \ldots, k_{M_l}, \quad (7)
\]

- Pressure continuity condition

\[
p_k (S_k(t, \bar{x}_k)) = p^l_{\text{node}}, k = k_1, k_2, \ldots, k_{M_l}, \quad (8)
\]

where \( l \) is index of the junction, \( k_1, k_2, \ldots, k_{M_l} \) are indices of the vessels at the junction, \( M_l \) is the total number of the vessels in the junction \( l \); \( p^l_{\text{node}} (t) \) is pressure at junction; \( R_k^l \) is hydraulic resistance coefficient for the vessel \( k \) in the junction \( l \). For the vessels, which coordinates are started at the junction \( \varepsilon_k = 1, \bar{x}_k = L_k \), for the vessels, which coordinates are ended at the junction \( \varepsilon_k = -1, \bar{x}_k = 0 \).

Combinations (4),(5),(6) or (4),(5),(7) or (4),(5),(8) are the mixed sets of algebraic and differential equations with \( 2M_l + 1 \) unknown parameters. Discretization of (4) results in linear relationship between discrete image of \( S_{km} \) and \( u_{km} \) at the terminal points at the upper time layer (grid indices are omitted)

\[
u_{km} = \alpha_{km} S_{km} + \beta_{km} \quad (9)
\]
It allows to reduce one of the above sets to nonlinear set of algebraic equations, which can be transformed to the set of \( M_l \) equations with unknown vector \( S = \{ S_{km} \}_{m=1}^{M_l} \). It can be generalized as

\[
Q(S) = A S^{II} + BS + RP(S) + D = 0, \tag{10}
\]

where

\[
S^{II} = \{ S_{km}^{2} \}_{m=1}^{M_l}, P = \{ p_{km}(S_{km}) \}_{m=1}^{M_l}.
\]

In the case \( 4, 5, 6 \)

\[
A_{mn} = \delta \alpha_{km}, A_{mn} = 0, m \neq n,
B_{mn} = \frac{\beta_{km}}{2 \alpha_{km}} \left( \delta - \frac{\varepsilon_{km}}{2 \alpha_{km}} \right), B_{mn} = -\varepsilon_{km} \beta_{km}, m \neq n,
R_{mn} = 2 \left( \delta - \frac{1}{\alpha_{km}} \right), R_{mn} = -\frac{2}{\alpha_{km}}, m \neq n,
D_m = \beta_{km}^{2} \left( \delta - \frac{\varepsilon_{km}}{\alpha_{km}} \right), \delta = \sum_{m=1}^{M_l} \varepsilon_{km}, m, n = 1, \ldots, M_l.
\tag{11}
\]

In the case \( 4, 5, 7 \)

\[
A_{mn} = \Delta \varepsilon_{km} \alpha_{km}, A_{mn} = 0, m \neq n,
B_{mn} = \Delta \varepsilon_{km} \beta_{km}, B_{mn} = 0, m \neq n,
R_{mn} = -\sum_{n=1}^{M_l} \prod_{p=1}^{M_l} R_{km}^{l}, R_{mn} = \prod_{p=1}^{M_l} R_{km}^{l},
D_m = 0, \Delta = \sum_{i=1}^{M_l} \prod_{j=1}^{M_l} R_{km}^{l}, m, n = 1, \ldots, M_l.
\tag{12}
\]

The set \( 4, 5, 6 \) can be reduced to single equation by the following way. As well as \( 2 \) is monotone function, \( 8 \) can be uniquely resolved as

\[
S_{km} = \tilde{p}_{km} \left( p_{\text{node}}^{l} \right), \tag{13}
\]

where \( \tilde{p} \left( p \right) \) is inverse function to the function, which is given by \( 2 \). Substituting \( 13 \) and \( 9 \) to \( 5 \)

the single nonlinear equation with variable \( p_{\text{node}}^{l} \) can be derived

\[
\sum_{k=k_{1}, k_{2}, \ldots, k_{M_l}} \varepsilon_{k} \left( \alpha_{k} \tilde{p}_{k}^{2} \left( p_{\text{node}}^{l} \right) + \beta_{k} \tilde{p}_{k} \left( p_{\text{node}}^{l} \right) \right) = 0. \tag{14}
\]

\( 10 \) and \( 14 \) can be solved by Newton method. For \( 10 \) it can be written as

\[
S_{r+1} = S_{r} - J(S_{r})^{-1}Q(S_{r}), J = \left\{ \frac{\partial Q_{i}}{\partial S_{j}} \right\}. \tag{15}
\]

Null approximation \( S_{0} \) for the iterations can be taken from the previous time step, which partly validates convergence of Newtons method, since the time step is relatively small.

### 3 RESULTS AND CONCLUSIONS

Several boundary conditions statements at the vessel’s junctions are presented in this work. It was shown that in two cases the set of \( 2M_l + 1 \) equations can be reduced to the \( M_l \) similar nonlinear equations and in one case to the one nonlinear equation. Since the previous time step value is used as null approximation, the Newton method can be applied to these nonlinear sets. It means, that computational cost of the Jacobi matrix inverse transformation in \( 15 \) is reduced from \( O \left( (2M_l + 1)^{3} \right) \) to \( O \left( M_l^{3} \right) \), which is almost by a factor of 10.
REFERENCES


A MULTI-SCALE MODEL OF THE MATERNAL HUMAN CARDIOVASCULAR SYSTEM DURING PREGNANCY

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SUMMARY
In this work a closed loop 1D-0D computational model of the maternal human cardiovascular system is presented. The model includes 417 one-dimensional vessels from the systemic and pulmonary systems. In the systemic system venous valves are included, and external pressure is exerted on the inferior vena cava which decreases venous return to simulate the effects of the gravid uterus in the supine position. Results are compared with data collected from various studies over the course of pregnancy, and velocity waveforms are compared with published Doppler measurements.

Key words: 1d-0d cardiovascular network, pregnancy model, closed loop, implicit scheme

1 INTRODUCTION
Over the course of human pregnancy the maternal physiology undergoes significant changes such as a 50% increase in blood volume, an increase in cardiac output, a decrease in peripheral resistance, and the enlargement of various vessels such as the uterine and ovarian arteries and veins. A large number of health issues can arise which can include high blood pressure (hypertension), low blood pressure (hypotension) and placental insufficiency (under-developed placenta and low blood flow to the placenta) which can severely reduce foetal development.

Recently a closed loop model was proposed by Mynard and Smolich which includes interactions between heart chambers, and specialised vascular beds for the liver and coronary systems. The cardiovascular network used in this work is based on with the addition of 21 vessels and three vascular beds (right and left ovary and womb/placenta). In addition many of these vessels enlarge as pregnancy progresses which increases blood flow to the placenta, ovaries and kidneys.

In this work a pregnancy model is simulated for a human woman in the supine position (no gravity within vessels). An external pressure is applied to the inferior vena cava to simulate the effect of the gravid uterus which is known to reduced venous return. The enhanced trapezoidal rule method (ETM) is used to solve the equations, and has been shown to correctly predict the strength and speed of shocks, which could potentially occur during venous collapse. The results are compared with measured data from a number of studies which investigated various changes in cardiovascular responses in pregnant women, and digitised Doppler (velocity) waveforms in the uterine artery.

2 METHODOLOGY
2.1 Closed loop 1D model
The one-dimensional representation of blood flow in a deformable visco-elastic tube is governed by the conservation of mass, conservation of momentum and a visco-elastic constitutive law

\[
\frac{\partial A}{\partial P} \frac{\partial P}{\partial t} + \frac{\partial Q}{\partial x} = 0,
\]
\[
\frac{\rho}{A} \frac{\partial Q}{\partial t} + \frac{\rho}{A} \frac{\partial}{\partial x} \left( \frac{Q^2}{A} \right) + \frac{\partial P}{\partial x} + \frac{\xi \mu \pi Q}{A^2} = 0, \quad (2)
\]
\[
P - P_{ex} - P_0 = \frac{2 \rho c_0^2}{b} \left[ \left( \frac{A}{A_0} \right)^{b/2 + a_1} - \left( \frac{A}{A_0} \right)^{a_2} \right] + \frac{\Gamma}{A_0 \sqrt{A}} \frac{\partial A}{\partial t}, \quad (3)
\]
where \( t \) is the time, \( x \) is the axial coordinate in the vessel. \( P, P_0 \) and \( P_{ex} \) are the hydrostatic, reference, and external pressures respectively, \( A \) is the area, \( A_0 \) is the area at the reference pressure, \( c_0 \) is the wave speed at the reference pressure, \( Q \) is the volumetric flow rate, \( \rho \) is the density of blood, \( \xi \) is the friction coefficient, \( \mu \) is the viscosity of blood, \( \Gamma \) is the wall viscosity coefficient, \( b \) is calculated as in [2]. The fitting parameters \( a_1 \) and \( a_2 \) are only non-zero in systemic venous vessels and are used to follow constitutive relationship of [2] (where \( a_1 = 0, a_2 = 0 \)) at and above the reference pressure, whilst allowing vessel collapse at low transmural pressures. At vessel junctions conservation of mass and conservation of total pressure are held as constraints.

2.2 Lumped heart model

The heart model was originally developed by [9] and further developed in [2]. The heart model used in this work is identical to [2] which contains three types of interaction. These are 1) an external pressure from the pericardium, 2) interactions between contralateral chambers (left-right interactions), and 3) descent of the atrio-ventricular plane which aids atria filling during ventricular contraction. The pressure in a chamber is modelled using

\[
P = P_{pc} + E_{nat} (V - V_{P=0}) - R_s Q + \frac{E_{nat}}{E_{sept}} P^*, \quad (4)
\]
where \( P \) is the pressure in a chamber, \( P_{pc} \) is the pressure in the pericardium, \( E_{nat} \) and \( E_{sept} \) are the native and septal chamber elastances respectively, \( V \) and \( V_{P=0} \) are the volume and residual volume of the chamber respectively, \( R_s \) is a source resistance, \( Q \) is the chamber volumetric outflow, and \( P^* \) is the pressure in the contralateral chamber.

2.3 Lumped valve models

Heart valves and venous valves are modelled as in [2,9] where

\[
\Delta P = B Q |Q| + L \frac{\partial Q}{\partial t}, \quad (5)
\]
\[
B = \frac{\rho}{2 A_{eff}}, \quad L = \frac{p_{eff}}{A_{eff}},
\]
\[
A_{eff} = (A_{eff,max} - A_{eff,min}) \zeta + A_{eff,min},
\]
\[
\frac{\partial \zeta}{\partial t} = K_{vo} (1 - \zeta) \Delta P, \quad \frac{\partial \zeta}{\partial t} = K_{vc} (\zeta) \Delta P, \quad (8)
\]
where \( \Delta P \) is the pressure difference across the valve, \( B \) is the Bernoulli resistance, \( L \) is the inertance, \( Q \) is the volumetric flow rate through the valve, \( l_{eff} \) is the effective orifice length, \( A_{eff} \) is the effective area, \( \zeta \) is the valve state, \( K_{vo} \) and \( K_{vc} \) are the valve opening and closing rate coefficients.

2.4 Physiological adaptions during pregnancy

During pregnancy the maternal cardiovascular system undergoes significant physiological changes which need to be accounted for in the model. These include 1) up to an additional 50% blood volume, 2) a decrease in systemic vascular resistance, 3) enlarging of vessels near the womb and ovaries, 4) heart chamber remodelling, 5) increased heart rate, stroke volume and cardiac output, 6) additional external pressures from the foetus and/or uterus acting on the inferior vena cava (and potentially the abdominal aorta) in supine position.
In a closed loop cardiovascular model the blood volume in the system is normally defined purely by initial conditions such as the initial pressures. To allow a change of volume in the system during simulations the compliance elements in the vascular beds are adapted to be in the form

\[ C \left( \frac{\partial P}{\partial t} - \frac{\partial P_{ext}}{\partial t} \right) = Q + \Phi, \]  

where \( C \) is the compliance, \( P \) and \( P_{ext} \) are the hydrostatic and external pressures, \( Q \) is the net flow rate, and \( \Phi \) is a sink term (in arterioles) or a source term (in venules). Thus allowing blood volume in the system to be controlled with more accuracy by incrementally adding or removing blood volume per time step.

2.5 Vascular network and numerical implementation

The vascular network is based on the closed loop model by Mynard and Smolich [2]. There is an addition of the utero-ovarian system, which includes the vascular beds of the ovaries and the womb (including the placenta); and vessels such as the uterine and ovarian arteries and veins. Moreover these vessels increase in diameter over the duration of pregnancy, although the majority of this increase occurs by the end of the second trimester as occurs in human physiology. An external pressure (which increases over the duration of pregnancy) is applied to the the inferior vena cava which simulates the effect of the gravid uterus when in the supine position.

The system equations (1D vessels, vascular beds, heart model, valve model) are solved using the globally implicit enhanced trapezoidal rule method (ETM) developed by Carson and Van Loon [3].

3 RESULTS AND CONCLUSIONS

The results are shown at various stages of pregnancy with a woman in the supine position. Figure [1] indicates the model captures the general behaviour of the measured stroke volume and therefore cardiac output (as heart rate is defined) over the range of pregnancy. The total peripheral resistance used by the model (calculated based on expected flow distributions) is generally larger than the measured data, although the general behaviour is captured. Figure [2] shows good agreement of the model predicted uterine artery velocity waveforms, and the digitised waveforms from [8]. The model under predicts the diastolic blood velocity when compared with the measured waveforms for the second and third trimesters.

In the future there are plans to develop the model in order to investigate the cardiovascular response to postural changes during pregnancy. This could not only aid in understanding the individual mech-
Figure 2: Comparison of velocity waveforms from Doppler measurements and the simulated model in the first, second and third trimesters.

anisms behind physiological adaptation during pregnancy, but also be used to investigate health conditions such as venous insufficiency and placenta insufficiency.

REFERENCES


A MULTI-SCALE MODEL OF THE CORONARY CIRCULATION WITH INCORPORATION OF THE FLOW AUTOREGULATION MECHANISM

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SUMMARY

The coronary circulation is featured by complex anatomical architecture, dynamic interaction between blood flows and myocardial contraction and high capability of flow regulation. In this study, a multi-scale modeling method was developed to integrate coronary arteries, intramyocardial vessels and flow autoregulation mechanism into a unique computational platform so as to quantitatively address the characteristics of coronary blood flows under various conditions. Model predictions agreed well with in vivo measurements. In particular, the flow autoregulation phenomenon in the presence of coronary arterial stenosis was reasonably reproduced. Future studies would focus on applying the model to address issues arising from clinical practice.

Key words: coronary circulation, multi-scale model, flow autoregulation

1 INTRODUCTION

Coronary arterial disease is a major cause of death and has long been the subject of numerous studies. Clinical diagnosis of coronary arterial disease relies mainly on medical imaging techniques (e.g., CTA and DSA), although fractional flow reserve (FFR) is occasionally measured to assess the functional status of coronary circulation in the presence of critical coronary arterial stenosis. However, detailed quantification of coronary hemodynamic variables remains difficult to in vivo measurement, and, in particular, the majority of in vivo measurements are limited to large epicardial arteries.

In the context, computational methods have been widely employed to provide insights into hemodynamic phenomena not accessible with traditional in vivo methods. Computational models presented in the literature varied in form from simple open-loop ones that focus on the coupling of coronary hemodynamics and myocardial mechanics [1,2] to sophisticated closed-loop multi-scale ones capable of accounting for the interaction between coronary hemodynamics and systemic hemodynamics [3]. These studies have contributed greatly to the understanding of coronary hemodynamics under various pathophysiological conditions. Nevertheless, several important issues remain to be addressed in more detail. For instance, what is the best way to model the dynamic behaviors of blood flows in intramyocardial vessels? How to account for the flow autoregulation phenomenon upon variations of perfusion pressure?

The main objective of the present study was to develop a computational model for the coronary circulation to simulate intramyocardial blood flows and reproduce the flow autoregulation phenomenon in the presence of stenotic lesions in coronary arteries. To the aim, a geometrical multi-scale modeling method was adopted, in which the coronary circulation was represented by a one-dimensional (1-D) model of epicardial coronary arteries coupled with a multi-layer lumped-parameter (0-D) model of intramyocardial vessels and a 0-1-D model of systemic hemodynamics. A flow autoregulation mechanism was incorporated into the model through a parameter tuning
algorithm which operates to automatically fit model predictions to a perfusion pressure-flow curve reconstructed from experimental data.

2 METHODOLOGY

The model of the coronary circulation was embedded into a 0-1-D model of the cardiovascular system developed in our previous study [4] (see Fig.1). The modeling strategy enabled coronary hemodynamics to be simulated as part of systemic hemodynamics, thereby making it possible to perform numerical simulations under various pathophysiological conditions.

Figure 1 Schematic description of a computational model of the coronary circulation coupled with a closed-loop cardiovascular model. Panel A, a 0-1-D model of the cardiovascular system; Panel B, a 1-D model of epicardial coronary arteries; Panel C, a multi-layer 0-D model of intramyocardial coronary vessels.

2.1 Modeling of the coronary circulation

The coronary arterial tree consisted of 87 large coronary arteries and 53 penetrating arteries. The anatomical structure and geometrical data of the coronary arteries were derived from a previous study [3]. The 1-D governing equations for blood flows in coronary arteries were obtained by integrating the continuity equation and Navier-Stokes equations over arterial cross section [4]:

\[
\frac{\partial A}{\partial t} + \frac{\partial Q}{\partial z} = 0, \quad (1)
\]

\[
\frac{\partial Q}{\partial t} + \frac{\partial}{\partial z} \left( \alpha \frac{\partial^2 Q}{\partial z^2} \right) + \frac{A \partial P}{\rho \partial z} + F_r \frac{Q}{A} = 0, \quad (2)
\]

where \( t \) is the time and \( z \) the axial coordinate; \( A, Q \) and \( P \) represent the cross-sectional area, volume flux and pressure, respectively; \( \alpha \) is the momentum-flux correction coefficient and \( F_r \) the friction force per unit length. The system of Eqs.1 and 2 was completed by a constitutive equation which accounts for the viscoelastic behavior of vessel wall upon varying transmural pressure:

\[
P + \tau_a \frac{\partial P}{\partial t} = \phi(A) + \tau_e \frac{\partial \phi(A)}{\partial t}, \quad \text{with} \quad \phi(A) = \frac{Eh}{\tau_0 (1-\sigma^2)} \left[ \frac{A}{A_0} - 1 \right] + P_0. \quad (3)
\]

Here, \( \tau_a \) and \( \tau_e \) represent the relaxation times for constant stress and constant strain, respectively; \( E \) is the Young’s modulus, \( h \) the wall thickness; \( P_0, A_0 \) and \( \tau_0 \) refer respectively to the pressure,
cross-sectional area and radius of artery at the reference state; and $\sigma$ is the Poisson’s ratio. Flows in different arteries were linked by imposing conservation of mass and continuity of total pressure at the bifurcations [4].

The coronary arterial tree had 71 distal ends, each of which was connected to a lumped parameter model of the corresponding intramyocardial vascular system. Herein, each intramyocardial vascular system was divided into multiple layers according to the penetration depth from the epicardium. It is noted that the number of layer division was not set in prior but determined by numerical experiments. The vessels in each layer were again divided into the arterial, capillary and venous compartments to account for the longitudinal distribution of resistance and compliance. Intramyocardial pressure was estimated from the cavity blood pressure and shortening-induced intramyocyte pressure [3] and distributed in a linear manner among layers depending on their penetration depths. The resistance and compliance in each vascular compartment were set to be functions of local blood volume to account for vascular deformation in response to the time-varying changes of intramyocardial pressure.

2.2 Coronary autoregulation model
Coronary flow autoregulation is an important local mechanism for flow preserve upon variations of perfusion pressure. In the study, a perfusion pressure-flow curve was constructed through fitting discrete experimental data [5] using a polynomial function (Fig.2, Left). In model-based simulations, the curve was used as a reference when adjusting coronary arteriolar resistances to compensate for the reduction in coronary blood flow caused by stenotic lesions present in coronary arteries.

![Figure 2 Left: Relationship between coronary perfusion pressure and flow rate. The continuous line illustrates the fitted polynomial function based on experimental data. Right: Simulated mean flow rates vs perfusion pressures in the LAD. The open circles (labeled '1~5') represent five stenotic conditions characterized by area stenosis rates of 51%, 80%, 91%, 94%, 96%, respectively. The simulated flow waves are plotted for stenosis rates of 51% and 96% (the black solid and broken lines exhibit flow waves simulated with and without the incorporation of flow autoregulation mechanism, respectively).](image)

3 RESULTS AND DISCUSSION
A series of numerical experiments were firstly performed to determine the required number of layer division for intramyocardial vessels. It was found that a 30 layer division was sufficient to limit the simulated changes of total coronary flow rate resulting from increasing the number of layer division to less than 1%. Thereafter, simulations were carried out for both normal physiological and hyperemic conditions. Obtained results are compared against in vivo measurements [6] in Table 1. Model simulations agreed reasonably with in vivo data in terms of both coronary and systemic hemodynamic variables. The left panel of Fig. 3 shows the model-simulated flow waves in three large coronary arteries (i.e., left anterior descending artery (LAD), left circumflex artery (LCx) and right coronary artery (RCA)). The flows in the LAD and LCx were diastole-dominated, with a typical flow impedance phenomenon in systole, whereas, the flow wave in the RCA exhibited a relatively uniform flow distribution between systole and diastole. These characteristics are consistent with general in vivo observations. The right panel of Fig. 3 shows the simulated flow waves at the small arterial level of three myocardial layers distal to a LAD branch. The flow waveforms were featured by enhancing flow impedance in systole and increasing pulsatility over the cardiac cycle toward the endocardium.
Table 1 Comparison of model simulations and in vivo measurements under normal and hyperemic conditions

<table>
<thead>
<tr>
<th></th>
<th>Baseline (In vivo measurement)</th>
<th>Simulation</th>
<th>Hyperemia (In vivo measurement)</th>
<th>Simulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/minute)</td>
<td>65±8</td>
<td>66</td>
<td>96±11</td>
<td>96</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>113±5</td>
<td>114</td>
<td>113±6</td>
<td>116</td>
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<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>74±8</td>
<td>75</td>
<td>70±5</td>
<td>70</td>
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<tr>
<td>Cardiac output (L/minute)</td>
<td>5.19±0.83</td>
<td>5.11</td>
<td>7.60±1.19</td>
<td>7.50</td>
</tr>
<tr>
<td>LAD flow (mL/minute)</td>
<td>76.15±33.41</td>
<td>74.28</td>
<td>256.15±110.84</td>
<td>258.46</td>
</tr>
<tr>
<td>LCx flow (mL/minute)</td>
<td>54.62±24.59</td>
<td>52.99</td>
<td>163.85±67.18</td>
<td>166.67</td>
</tr>
<tr>
<td>RCA flow (mL/minute)</td>
<td>68.46±31.87</td>
<td>67.99</td>
<td>217.69±76.70</td>
<td>219.21</td>
</tr>
</tbody>
</table>

Figure 3 Simulated flow waves in epicardial coronary arteries (Left) and intramyocardial small arteries distal to a LAD branch (Right).

The right panel of Fig.2 illustrates the simulated pressure-flow relationships when stenoses of various degrees were created in the LAD. With the incorporation of flow autoregulation mechanism, the simulated results matched reasonably with the pressure-flow curve derived from experimental data. In contrast, removing flow autoregulation mechanism led to considerable underestimate of flow, especially in the case of severe coronary stenosis.

In summary, the study presented a computational model of the coronary circulation capable of not only simulating coronary flow waves under various physiological conditions but also accounting for the flow autoregulation phenomenon in the presence of coronary arterial stenosis. Future studies would focus on applying the model to solve problems arising from clinical practice, such as patient-specific hemodynamic simulation and image-based prediction of FFR.

ACKNOWLEDGEMENTS
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REFERENCES
ANALYTICAL SOLUTIONS OF WAVEFORMS IN THE ARTERIAL NETWORK AND PRESSURE DECOMPOSITION ANALYSIS

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SUMMARY
We present analytical solutions of a 1-D dynamical theory of blood flow in networks of flexible vessels that is based on a generalized Darcy’s theory. We explore the structure of such analytical solutions for single vessels and simple networks, and identify the role of the different contributions to the pressure wave in such systems. We also show how reducing our 1-D model to a simpler 0-D Windkessel-type model allows us to obtain analytically parameters related to the system compliance and resistance.

Key words: 1-D arterial haemodynamics; 1-D blood flow modelling; Generalized Darcy’s model; Pulse wave propagation; Pressure decomposition.

1 INTRODUCTION
The pulse wave generated by the contraction of the left ventricle propagates in the arterial tree and produces changes in blood pressure and flow in time and space. These changes are determined by physical properties of the cardiovascular system, some of which are altered by disease. The shapes of pressure and flow contours carry valuable information about the functionality of the cardiovascular system. An analytical model of the aorta and large arteries would allow one, in principle, to investigate the role of individual physical properties of the cardiovascular system on pulse waveforms; and to identify properties responsible for pathological conditions that should be targeted for treatment.

We have recently presented a novel linear 1-D dynamical theory of blood flow in networks of flexible vessels [1], that is based on a generalized Darcy’s theory [2][3], and for which a full analytical solution exists in frequency domain (ω-domain). Our model has shown good agreement with existing 1-D and 3-D numerical schemes [4]. Our analytical solution captures the main features of pulse waveforms in large arteries and networks and it enables the understanding of relevant mechanisms.

Our aim in this work is to further explore the structure of such analytical solutions. We present the example of the upper thoracic aorta pressure decomposition, for which our analytical treatment allows us to identify the terms leading to some of the features of the pressure wave, such as the advancement of the dicrotic notch and the pressure decay during diastole.

Our aim is also to show that this type of analytical solutions can be reduced to simpler 0-D models of the Windkessel type, and that this allows one to know how the vessel parameters and the boundary conditions enter the system compliance and resistance.

2 METHODOLOGY
By assuming the vessel wall to be impermeable, blood to be a Newtonian fluid, of density ρ and viscosity η, and no-slip boundary conditions for the axial velocity at the average wall position, R₀, conservation of momentum, in ω-domain, gives an expression for the local axial velocity of the fluid, that is linearly related to the pressure gradient along the flow direction x. Averaging such expression over the cross sectional area at a certain x, leads to a linear relation between the average flow, and
the pressure gradient in \( \omega \)-domain, that is a generalized Darcy’s law, valid locally at any point along the flow direction. By assuming the vessel wall to be a linear elastic tube that follows Hooke’s law, one gets and expression that relates changes in pressure with changes in the luminal cross-sectional area. When these ones are coupled to the axial velocity by conservation of mass, we obtain a second expression that relates pressure and flow in \( \omega \)-domain. These two equations lead to equations for pressure and pressure gradient along a given vessel, whose analytical solution, in \( \omega \)-domain, gives the pressure and pressure gradient at any point along the flow direction in terms of the pressure at the vessel extremes; or in terms of an inflow in one extreme and a pressure in the other one.

We consider flow conservation at each node of the network and equal pressures in the extreme of the vessels merging in a node. Our formulation gives a system of equations for the pressures at the nodes that can be written in matrix form. The solution of the system requires inversion of a matrix of order \( NxN \) where \( N \) is the number of nodes in the network. Such inverted matrix has to be multiplied by the vector of inflows in order to give the vector of pressures at the nodes. Our results have to be further explored for each particular case.

We present the simple example of the upper thoracic aorta pressure decomposition, for which our analytical treatment allows us to identify the terms leading to some of the features of the pressure wave during a cardiac cycle, such as the advancement of the dicrotic notch and the pressure decay during diastole. For this single-vessel model we consider boundary conditions consisting of the inflow, \( Q_{in} \), in one extreme, and a three-element Windkessel (WK) in the other, as shown in Fig. 1.

Figure 1: Representation of a vessel, with an inflow and a three-element WK as boundary conditions.

The WK model considered, relates the pressure, \( \hat{p}_o \), and the flow, \( \hat{Q}_{Wk} \), at the end point of a terminal vessel. It consists of a resistance \( R_1 \) connected in series with a parallel combination of a second resistance \( R_2 \) and a compliance \( C_{Wk} \). The resistance \( R_1 \) is equal to the characteristic impedance of the end point in the terminal vessel in order to minimize wave reflections [5]. The model equation in frequency domain is

\[
\hat{Q}_{Wk} = \frac{\hat{p}_0}{\hat{Z}}; \quad \text{where the impedance, } \hat{Z}, \text{ is given by } \hat{Z} = \frac{R_1 + R_2 - i\omega R_1 R_2 C_{Wk}}{1 - i\omega R_2 C_{Wk}}.
\]

Our formulation leads to the following expression for the pressure along the elastic vessel

\[
\hat{p}(x) = \hat{T}_1(x) + \hat{T}_2(x) + \hat{T}_3(x) \quad \text{with } \hat{T}_1 = \left[ \frac{\sin(k_c x) \cos(k_c x)}{\cos(k_c x) - \hat{Z} M \sin(k_c x)} \right] \hat{Q}_{in} \hat{M}; \quad \hat{T}_2 = \frac{\sin(k_c x)}{M}; \quad \hat{T}_3 = \left[ \frac{\cos(k_c x)}{\cos(k_c x) - \hat{Z} M \sin(k_c x)} \right] \hat{Q}_{in} \hat{Z}.
\]

Here \( k_c^2 = \frac{i\omega C \eta}{A_0 K(\omega)} \) and \( M^2 = \frac{i\omega C A_0 K(\omega)}{\eta} \); \( C \) is the vessel compliance, \( A_0 \) is the average cross-sectional area, and \( K(\omega) \) is the dynamic permeability of a tube of cross-sectional area \( A_0 \).

We plot Eq. (2) in time domain and show it, on the left-hand side (LHS) of Fig. 2, as a function of space and time. The right-hand side (RHS) of Fig. 2 shows the color map of the same function. The white dots indicate the position of the diastolic pressure and the dicrotic notch at different times. We also compute the three different pressure terms along the aorta in time-domain and show two of them in Figs. 3a, 3b. On the LHS, we show the corresponding contribution to the waveform at the midpoint of the vessel. On the RHS we show the space-time color map of two of the terms composing the pressure wave.
The second minimum of $T_2(t)$, determines the advancement of the dicrotic notch, this is indicated with white squares in Fig. 3 and with green squares on the RHS of Fig. 2, while $T_3(t)$, determines the pressure decay during diastole, as can be seen in Fig. 3. These results tell us that the advancement of the dicrotic notch depends only on the vessel properties and the inflow from the heart, and not from boundary conditions; while the pressure decay at diastole has a strong dependence on the boundary condition. Additionally, the first minimum of $T_1(t) + T_2(t)$, determines the position of the diastolic pressure. This one is shown, for different times, on the RHS of figure Fig. 2 with green rectangles. These ones, are very close to the white dots coming from the full pressure signal.

In order to reduce our 1-D model to a 0-D Windkessel theory of the kind introduced by [6], we develop a low frequency approximation for the $x$-average of Eq. (2). In this limit, to first order in $\omega$, the equation for the approximated low frequency pressure, $p_{LF}(t)$, is equal to the one for the Windkessel pressure in [6], except for the value of the parameters. The solution to this equation, is given by

$$p_{LF}(t) = p_d e^{-\frac{t}{\chi RC}} + e^{-\frac{t}{\chi RC}} \frac{R_s}{\chi RC} \int_0^t Q_{in}(t)e^{\frac{t}{\chi RC}} dt$$

(3)

where $p_d$ is the diastolic pressure. $\chi_{RC}$ and $R_s$ are obtained analytically in terms of the properties of the vessel and the boundary condition.
Figure 4: Low frequency limit for the pressure and comparison between the excess pressure and the inflow.

Following [6], we compute the excess pressure as the difference between the pressure at the inlet of the thoracic aorta, given by Eq. (2) in time domain, evaluated at $x = 0$, and the approximated low frequency pressure, $p_{LF}$, given by Eq. (3). That is, $p_{ex} = p_{in} - p_{LF}$. We show $p_{in}$ and $p_{LF}$ in Fig. 4a. In Fig. 4b we show that the shape of the excess pressure is similar to the one of the inflow wave just as in reference [6]. This shows that a reservoir pressure of a Windkessel-type theory [6] is nothing else than the low-frequency approximation of the total pressure.

3 RESULTS AND CONCLUSIONS

Analytical solutions are a useful tool to investigate the role of individual physical properties of the cardiovascular system on pulse waveforms. Our model can be applied to different networks and a detailed analysis of the solution, in each case, might lead to identify the system properties leading to the features of pressure waves that change in pathological conditions. Our decomposition of the upper thoracic aorta gives novel insights of which terms of the pressure wave come from the heart, which come from the aorta’s wall, and which come from the boundary conditions. Furthermore, we reduce our 1-D model to a 0-D Windkessel-type model. This allows us to show that a Windkessel-type pressure is a low frequency approximation of the total pressure.

Our model can partially account for tapering and stenosis by segmenting the vessels in consecutive cylindrical shorter vessels that progressively change radius.

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REFERENCES


Eye Biomechanics
THE INFLUENCE OF CHOROIDAL SWELLING ON DEFORMATIONS AT THE OPTIC NERVE HEAD

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SUMMARY

Computational models have provided vital insight for understanding the impact of intraocular pressure (IOP) and intracranial pressure on optic nerve head (ONH) deformation. Here, we expand on these computational models to investigate the effect of choroidal swelling on human ONH deformation, since swelling may influence ONH strains. We found that choroidal swelling increased the peak strains in the ONH, although not always to the same degree as a doubling of IOP. However, sustained choroidal swelling may alter the loading environment of the ONH and potentially induce the activation of mechanosensitive cells.

Keywords: optic nerve head, choroid, ocular mechanics, finite element modeling

1 INTRODUCTION

Glaucoma is the second leading cause of blindness worldwide, affecting over 70 million people [1]. This disease is characterized by the loss of retinal ganglion cells (RGCs) at the optic nerve head (ONH). The ONH experiences a highly complex biomechanical environment, since it is directly exposed to several pressures: blood pressure, intraocular pressure (IOP), and (posteriorly) retrolaminar tissue pressure and intracranial pressure (ICP). Since elevated IOP is the major risk factor for developing glaucoma, early work used finite element (FE) models to investigate the impact of IOP and ICP on ONH deformation [2,3,4]. Here, we expand on these FE models to investigate the biomechanical effects of an increase in choroidal volume, simulating choroidal swelling which may play an important role in ONH pathology [5]. Our goal was to develop an FE model of the human ONH to simulate the acute effects of choroidal swelling on ONH deformation, and to compare these effects to those of elevated IOP.

2 METHODOLOGY

2.1 Geometry and Finite Element Model
Our model geometry extended established models of the posterior eye in humans [3,4]. In short, the model included a posterior sclera, peripapillary sclera, annular scleral ring, lamina cribrosa, prelaminar neural tissue (PLNT), pia mater, dura mater, and optic nerve. We also incorporated a central retinal vessel to include the effects of blood pressure as represented by a mean arterial pressure (MAP). Finally, we included two additional components: Bruch’s membrane and the choroid (Figure 1).
Figure 1: Our geometric model, focused on the optic nerve head used for finite element simulations. Each tissue component is identified.

The posterior sclera, peripapillary sclera, annular ring, pia mater, and dura mater were modeled as neo-Hookean solid matrices with embedded collagen fibers following von Mises distributions [4,6]. The fiber orientation, alignment, and material properties were based on an earlier published FE model [4]. Bruch’s membrane, neural tissues, and the lamina cribrosa were modeled as linear-elastic, with the respective Young’s modulus and Poisson ratio for each tissue component based on previously reported values [3,7]. The choroid was represented as a mixture material with a linear-elastic solid matrix and a Donnan equilibrium component to allow a prescribed amount of volume change via swelling. The Young’s modulus of the choroidal matrix was based on literature values of passive choroidal material properties [8]. Our geometry and mesh were generated in the open-source program Gmsh (V.2.8.3) [9]. Our FE simulations used FEBio [10]. The geometry of the eye for FE analysis was treated as axisymmetric—represented as a 3° wedge about an axis of symmetry passing through the central retinal vessel due to constraints of the FEBio solver.

2.2 Loading Conditions
To simulate the loading environment at the ONH we specified three pressures: IOP, ICP, and MAP. Our present model simulates an individual in an upright position; thus, ICP was set to 0 mmHg and MAP was set to 57 mmHg [3,4]. For the baseline simulation, we set an IOP = 15 mmHg and specified no choroidal swelling. To investigate the impact of choroidal swelling we utilized the same pressure loads as our baseline condition and imposed a 5 μL increase in choroidal volume. This increase in choroidal volume is estimated to occur during a single cardiac cycle or after steady-state has been reached in head-down tilt experiments [11,12]. For comparison, we also simulated the impact of elevated IOP (IOP = 30 mmHg). The loading conditions are summarized in Table 1.

<table>
<thead>
<tr>
<th>Loading Condition 1</th>
<th>Loading Condition 2</th>
<th>Loading Condition 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>IOP</td>
<td>15 mmHg</td>
<td>15 mmHg</td>
</tr>
<tr>
<td>Choroidal Swelling</td>
<td>0 μL</td>
<td>5 μL</td>
</tr>
</tbody>
</table>

Table 1: The three simulated loading environments at the ONH. We examine the impact of choroidal swelling (Loading Condition 2) compared to elevated IOP (Loading Condition 3). All simulations used ICP = 0 mmHg and MAP = 56 mmHg.

2.3 Outcome Measures
Our outcome measures were the strains within the PLNT, lamina cribrosa, and retrolaminar optic nerve. We focused our analysis to include the PLNT to within 1 mm of the lamina cribrosa and of the retrolaminar optic nerve to within 1 mm posterior to the lamina cribrosa. We specifically compared the peak 1st (95th percentile) and 3rd (5th percentile) principal strains in each tissue region. We chose the peak strains because cells are sensitive to changes in mechanical strain [13].

3 RESULTS AND CONCLUSIONS
Choroidal swelling dramatically altered the distributions of 1st and 3rd principal strains within the ONH (Figure 2). We noted that choroidal swelling had a large impact at the PLNT. Similar to
earlier research, elevating IOP also increased strains in the ONH, with a larger impact on the strain distributions in the lamina cribrosa and retrolaminar optic nerve.

Figure 2: Contour plots of principal strains in the optic nerve head for three loading conditions (Table 1). The top row shows the 1\textsuperscript{st} principal strain (red) while the bottom row shows the 3\textsuperscript{rd} principal strain (blue). We found that 5 uL of choroidal swelling drastically altered the strain distribution within the prelaminar neural tissue.

Compared to the baseline case (IOP = 15 mmHg), choroidal swelling increased the peak 1\textsuperscript{st} and 3\textsuperscript{rd} strains in the PLNT, lamina cribrosa, and retrolaminar optic nerve (Table 2). However, elevating IOP from 15 to 30 mmHg caused a larger increase in the peak 1\textsuperscript{st} and 3\textsuperscript{rd} strains within the lamina cribrosa and retrolaminar optic nerve.

<table>
<thead>
<tr>
<th>Tissue Region</th>
<th>Peak Strain</th>
<th>IOP = 15 mmHg</th>
<th>IOP = 30 mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prelaminar Neural Tissue</td>
<td>1\textsuperscript{st} Principal Strain</td>
<td>1.08%</td>
<td>3.01%</td>
</tr>
<tr>
<td></td>
<td>3\textsuperscript{rd} Principal Strain</td>
<td>-1.91%</td>
<td>-2.83%</td>
</tr>
<tr>
<td>Lamina Cribrosa</td>
<td>1\textsuperscript{st} Principal Strain</td>
<td>0.88%</td>
<td>1.01%</td>
</tr>
<tr>
<td></td>
<td>3\textsuperscript{rd} Principal Strain</td>
<td>-1.09%</td>
<td>-1.35%</td>
</tr>
<tr>
<td>Retrolaminar Optic Nerve</td>
<td>1\textsuperscript{st} Principal Strain</td>
<td>0.76%</td>
<td>0.97%</td>
</tr>
<tr>
<td></td>
<td>3\textsuperscript{rd} Principal Strain</td>
<td>-1.45%</td>
<td>-1.87%</td>
</tr>
</tbody>
</table>

Table 2: Computed peak 1\textsuperscript{st} and 3\textsuperscript{rd} principal strains from each tissue region examined in the optic nerve head. The peak strains all increased after choroidal swelling; however, elevating IOP to 30 mmHg generally had a larger overall effect on increasing strain magnitudes. One exception to this general trend was in the PLNT: in this region, choroidal swelling had a larger impact on the 1\textsuperscript{st} principal strain than did elevating IOP.

These results illustrate that choroidal swelling can alter the strain environment of the ONH. Interestingly, swelling the choroid by only 5 uL caused peak strains in the PLNT larger than or comparable to those resulting from doubling IOP from 15 to 30 mmHg. We suggest that prolonged or large degrees of choroidal swelling may result in ONH strains that initiate a mechanobiological response of the local cell population. These results highlight the potential impact of choroidal swelling on strains in the ONH and motivate further study of this effect in certain ocular pathologies.

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OCULAR CONNECTIVE TISSUE BIOMECHANICS ASSESSMENT BY MEANS OF NON-CONTACT OPTICAL TECHNIQUES

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SUMMARY

We developed a testing platform based on non-contact optical coherence techniques to investigate the relationship between in-vivo optic nerve head (ONH) response to intraocular pressure (IOP) and ex-vivo quantification of the corneoscleral biomechanics. One eye of a brain-dead organ donor (BDD) was imaged by Optical Coherence Tomography (OCT) to acquire the in-vivo IOP-dependent deformations of the ONH. Following organ harvesting the eye was enucleated and dissected in two hemispheres. Electronic Speckle Pattern Interferometry (ESPI) quantified the response to IOP of the posterior and anterior globes. This testing platform will investigate the relationship between corneoscleral and ONH biomechanics.

Key words: optic nerve head biomechanics, sclera biomechanics, cornea biomechanics

1 INTRODUCTION

The biomechanical behavior of the optic nerve head (ONH) microenvironment is thought to drive connective tissue remodeling and the resulting cupping of the lamina cribrosa (LC) in glaucoma that is observed clinically and associated with increasing axonal injury and eventual RGC death.\[3\] Variation of in-vivo morphology of the LC surface has been shown between racial groups and with age as measured with Optical Coherence Tomography (OCT).\[4\]

Computational and experimental studies in animal models have suggested that the LC microenvironment is strongly influenced by the structural stiffness of the peripapillary sclera (ppScl)\[5, 6\] and the morphology and density of the LC.\[7\] In a recent study from our group, following an acute IOP elevation mechanical compliance test, a longer axial length and increased corneal resistance factor and hysteresis corresponded with a greater acute posterior displacement of the LC.\[8\] Furthermore, the stiffness of the ppScl has also been shown to increase with aging and more dramatically in eyes from donors of African compared to those of European descent.\[9, 10\].

As a result of the aforementioned observations, altering the mechanical response of the LC and sclera has been proposed as a new non-IOP lowering treatment approach for glaucoma.\[11-13\] Despite the high interest in understanding the link between the IOP-induced mechanical response of the ONH and vulnerability to glaucomatous injury, prior studies have been unable to resolve this association due to our inability to measure ONH and ppScl mechanical response in-vivo and non-invasively.

Understanding how ONH deformations are modulated by the peripapillary- and corneosclera mechanical compliance will provide important knowledge for the development of sclera rigidity manipulation therapeutic procedures for glaucoma.

As part this effort, this work focuses on the development of a testing platform that leverages on non-contact interferometric techniques to investigate the relationship between ONH and corneoscleral biomechanics.
2 METHODOLOGY

Before organ harvest (in-vivo test), one eye from a brain-dead organ donor (BDD) underwent an ocular examination followed by a mechanical compliance test assessing the in-vivo 2D and 3D IOP-dependent volumetric deformations of the ONH and ppScl. Following organ harvest (ex-vivo test) a mechanical compliance test was performed to quantify by electronic speckle pattern interferometry (ESPI) the 3D IOP-dependent surface deformations of the outer coat of cornea, sclera, and ppScl. The maximum shear and maximum principle component of the strain tensor was used as a metric of the tissue’s structural rigidity.

2.1 Time-dependent in-vivo ONH deformations

For the in-vivo test, the anterior chamber of the eye was cannulated with a 27-gauge butterfly needle and IOP was adjusted by digital manometric control to 10 mmHg. Before increasing the IOP, a cube scan (1024x768x148 pixel) of the entire ONH was performed. This provided the reference morphology used for the computation of the in-vivo 3D strain maps (Fig. 2). Following the 3D raster scan, the IOP was quickly raised from 10 to 30 mmHg. During the IOP elevation ~270 B-scans (video recording) of one vertical sagittal section centered in the ONH were recorded. While maintaining the IOP at 30mmHg, the cube scan of the entire ONH was repeated. The IOP increase was electronically controlled in order to synchronize the video recording with the pressure elevation time. By a template-matching approach, both the 2D and 3D displacement fields for the time-changing (2D test) and static IOP (3D test) were quantified. The displacement and strain fields can then either be reduced or interpolated to form a continuous field.[14] On a common workstation the strain maps of the 2D and 3D quantifications are efficiently computed in less than 1 and 4 minutes respectively. The maximum shear strain was computed by differentiation of the displacement field.

2.2 Scleral inflation testing and full-field 3d displacement and strain measurement

Cornea and sclera displacement measurement underwent mechanical inflation testing as performed in our previous studies.[15] Briefly, following enucleation the eye will be dissected and clamped in a custom pressurization device at the equator. The scleral shell was preconditioned and inflation tested from 10 to 30 mmHg with a steady increase in IOP (1 mmHg/s). Mid-peripheral and peripapillary scleral strain were calculated by analytical differentiation of the ESPI displacement measurement.[16]. The freshly enucleated (non-fixated) shape of the posterior pole was acquired by means of a recently developed custom Multiview 3D shape reconstruction technique that provides the full geometry of the eye at an accuracy lower than 20 micrometers. After the posterior pole was tested, the anterior segment of the eye (including the cornea) was mounted on the same pressurization apparatus and the inflation test was identically repeated for the anterior segment of the eye.
3 RESULTS AND CONCLUSIONS

Figure 2: 3D maximum shear strain map computed by digital volume correlation approach [2] that computes the relative change in position of each material point representing the ONH tissue morphology when this is subject to an acute IOP elevation from 10 to 30 mmHg.

In both the 2D and 3D in-vivo tests, steep strain gradients were often observed in the proximity of neighboring tissue interfaces such as the lamina-prelaminar tissue (Fig. 1, and Fig. 2) or the lamina-ppScl interface (Fig. 2, white arrows at the inferior ONH margin). This sharp variation of the strain was recurrently observed in regions where mechanical rigidity rapidly changed.[17] From a qualitative analysis we assessed that the 2D and the 3D strain values were similarly high in the lamina region and low in the prelaminar and axonal regions. These findings were in agreement with those obtained in a previously performed study based on our 2D strain quantification method on 7 non-human primates.[18] Consistently, the strain in the prelaminar-tissue was markedly lower than in the laminar region. From the ex-vivo inflation test it was possible to notice that a high gradient of strain was resolved in regions with sharp change in the mechanical rigidity or morphology. In the cornea, high values of strain were observed in the limbus region, close to the apex, and around muscle insertions (Fig. 3, right). In the sclera, high gradients of strain were observed around the optic nerve but not in the mid-peripheral region (Fig. 3, left).

We proposed a testing platform for the in-vivo and ex-vivo quantification of the ONH, cornea, and sclera biomechanical response to IOP of an eye.

Strain levels resulted to be particularly high in all the connective tissues (cornea, peripapillary sclera, and lamina) but not in the axonal regions. It is plausible to hypothesize that the ONH anatomy and mechanical structure it is such that the deformations are sustained by the collagenous tissues and mitigated in the axonal regions. While this is just a hypothesis, its testing may be of high importance for the understanding of the implication of ONH biomechanics and glaucoma.

Figure 3. Maximum Principle Strain (tensile) field mapped on the textured 3D model: sclera (left) and cornea (right). The custom ESPI merges displacements and specimen geometry data to finely resolve the local spatial distribution of the IOP-time-dependent deformations.
REFERENCES


A MESH-FREE APPROACH TO INCORPORATE REALISTIC ANISOTROPIC AND HETEROGENEOUS MATERIAL PROPERTIES INTO EYE-SPECIFIC MULTI-SCALE MODELS

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SUMMARY

Commercial finite element modeling packages do not have the tools necessary to effectively incorporate the complex anisotropic and heterogeneous material properties typical of the biological tissues of the eye. We developed a new mesh-free approach to incorporate realistic material properties into patient-specific finite element models of the human eye.

Key words: mesh-free, patient-specific modeling, ocular biomechanics

1 INTRODUCTION

The biomechanics of the human eye tissues play an important role in the functionality of the organ. The development of realistic and patient-specific multi-scale models of the eye can provide new insight into the role of ocular biomechanics in physiological and pathophysiological conditions. It is one challenge to obtain and translate the geometry of the organ’s macro-structure into eye-specific finite element models, but it is another challenge to incorporate realistic material and eye-specific micro-structural properties into such models. The main load bearing constituent of the ocular coats is fibrillar collagen (Type I). The collagen fibrils together with other constituents introduce highly nonlinear, anisotropic, and heterogeneous material properties into the eye tissues. Most commercially available finite element software packages are now equipped with micro-structurally motivated constitutive models for the realistic simulation of collagenous tissues as found in the eye. However, software tools to translate highly heterogeneous and anisotropic properties are typically not provided. Typically a set of analytical coordinate systems (Cartesian, cylindrical, and spherical coordinate systems) are available in commercial finite element packages to define anisotropic material orientations. Finite elements are often grouped into element sets to define heterogeneous material parameters across the model. These strategies seem to provide sufficient options to the user to effectively generate generic models of the eye but are insufficient to incorporate highly heterogeneous material properties into eye-specific multi-scale models, leaving the solution of this task completely to the end user. In this paper, we propose a mesh-free approach to effectively translate heterogeneous and anisotropic material properties into eye-specific finite element models. While we use eye-specific models of the optic nerve head to illustrate the advantages of our new methodology, it can be applied to any tissue, organ, or other mechanical problem with similar challenges.

2 METHODOLOGY

Eye-specific finite element models of five human optic nerve heads (ONHs) were created from 3D reconstructions of the ONH connective tissues acquired using a microtome-based serial sectioning...
and block face imaging device [1,2,3]. The models include the sclera, lamina cribrosa, pre- and retro-
laminar tissues, retina, and pia. Anisotropic material properties were defined at convenient locations
(control points) at which anisotropic material directions could be identified based on the reconstructed
tissue micro- or macro-structure. Otherwise their locations were arbitrary and independent of the
finite element mesh.

We used a mesh-free approach to approximate the anisotropic and heterogeneous material properties
of a finite element model. Let \( m \) be a heterogeneous material parameter that is defined at \( N \) control
points \( c_I \) with \( I = 1, \ldots, N \). The approximated value of the material parameter \( m \) is computed at a
point \( x \) as

\[
\tilde{m}(x) = C_\rho \sum_{I=1}^{N} \phi\left( \frac{||x - c_I||}{d_{ref} \rho} \right) m(c_I),
\]

where \( C_\rho \) is a normalization constant, \( d_{ref} \) is a reference distance, \( \rho \) is a dilation parameter, and \( \phi \) is
the window function. Typically, the approximated material parameters are computed the Gauss points
of each finite element. We use the common cubic spline function to define the window function

\[
\phi(x) = \begin{cases} 
8(|x| - 1)x^2 + 4/3 & |x| \leq 0.5 \\
8(1 - |x|)^2/3 & 0.5 < |x| < 1 \\
0 & 1 \leq |x|.
\end{cases}
\]

The normalization constant is computed as

\[
C_\rho = \left[ \sum_{I=1}^{N} \phi\left( \frac{||x - c_I||}{d_{ref} \rho} \right) \right]^{-1}.
\]

The reference distance \( d_{ref} \) represents a characteristic length such as the thickness of the sclera. The
dilation parameter \( \rho \) controls the degree of smoothing. Note that the dilation parameter must be large
enough to avoid aliasing, while excessively large value for \( \rho \) will lead to excessive smoothing. A
value of \( \rho = 2 \) was used in this contribution. \( d_{ref} \) was set to 800\( \mu \)m, 100\( \mu \)m, and 100\( \mu \)m for the
sclera, pia, and lamina cribrosa, respectively.

To incorporate realistic anisotropic material properties into realistic, patient-specific finite element
models of a human organ is not a trivial task and can be approached in different ways. We will use
our mesh-free method to approximate a local basis used to define the anisotropic material directions.
Let \( e_i \) be an orthonormal basis that represents the anisotropic material directions. We assume that
this basis can be experimentally measured or estimated at the control points \( c_I \) (\( I = 1, \ldots, N \)). We
introduce a second orthonormal basis \( r_i \), which represents a reference coordinate system. The finite
rotation between these two bases can be expressed by the so-called Rodrigues rotation vector

\[
\omega = \omega n,
\]

which can be obtained from the spectral decomposition of the rotation tensor \( R \)

\[
R = e_i \otimes r^i \text{ with } \det R = 1.
\]

Note that \( R \) has one real eigenvalue equal to 1 with the unit eigenvector \( n \) and two complex conjugate
eigenvalues equal to \( \cos(\omega) \pm i \sin(\omega) \), where \( \omega \) represents the rotation angle around the direction \( n \). We use our mesh-free approach [1] to approximate the Rodrigues rotation vector \( \omega \) at a point \( x \) in
the finite element mesh

\[
\tilde{\omega}(x) = \tilde{\omega} n = C_\rho \sum_{I=1}^{N} \phi\left( \frac{||x - c_I||}{d_{ref} \rho} \right) \omega(c_I).
\]

The approximated rotation vector is then used to calculate the rotation tensor

\[
\tilde{R}(x) = I + \sin(\tilde{\omega}) \hat{n} + (1 - \cos(\tilde{\omega})) \hat{n} \hat{n}.
\]
and finally the approximated local material basis as

\[ \tilde{e}_i = \tilde{R}_i r_i. \]  

(8)

In equation (7), \( \hat{n} \) represents an abbreviation for \( \hat{n} = n \times \). The approximated basis \( \tilde{e}_i \) is used to define local anisotropic material properties using our previously published constitutive formulation [4]. An arbitrary coordinate system can be used to define the orthonormal reference basis \( r_i \) in (5) including a Cartesian coordinate system. We use a spherical coordinate system instead of a Cartesian system to define \( r_i \) in this paper as the spherical coordinate system represents a good approximation of the eye’s overall shape and, therefore, leads to smaller variations in the rotation vector. If the variation between control points is small, only a coarse grid of control points is needed to provide a good approximation of the local basis.

3 RESULTS AND CONCLUSIONS

Eye-specific finite element models of human ONHs were generated using quadratic ten-node tetrahedral elements (Figure 1 A). It was convenient to define anisotropic orientations at the anterior and posterior scleral surface based on the eye-specific geometry of each sclera. Control points were seeded on the posterior and anterior scleral surface (Figure 1 B). We used the surface geometry to calculate a normal orientation at each control point. The circumferential orientation was obtained at the ONH by fitting an ellipse to the anterior insertion points of the lamina cribrosa into the sclera. The tangential direction of this ellipse was projected to each control point on the sclera surface and used to define the circumferential orientation. The meridional direction was obtained from the orthonormality condition. The mesh-free approach was effective in approximating these orientations across the scleral thickness and between the control points (Figure 1 C, D). The approximated properties allowed the effective modeling of the anisotropic circumpapillary ring of collagen fibers in the sclera, while following the eye-specific anatomical features of the individual eye (Figure 1 E). Using the same approach as outlined for the sclera, similar eye-specific results were obtained for the pia. For the lamina cribrosa, anisotropic material properties were directly obtained from the 3D reconstructions of its micro-structure and were effectively interpolated across the laminar elements using our mesh-free approach (Figure 1 F).

We have developed a new software tool to effectively incorporate complex anisotropic and heterogeneous material properties that are either estimated at convenient locations or directly obtained from the tissues micro-structure into eye-specific finite element models. The approach should simplify future studies to investigate optic nerve head remodeling in eye-specific models and to elucidate the role of biomechanical factors in glaucoma.

REFERENCES


Figure 1: A: The eye-specific finite element mesh of a human donor ONH. B: Control points seeded onto the anterior surface of the sclera. C, D: Sections through the ONH showing the scleral control points (red points) at which the anisotropic material properties were defined. The black arrows represent the approximated normal (C) and meridional (D) directions using the mesh-free interpolation approach. E: The approximated anisotropic directions from C and D were used to model the anisotropic circumpapillary ring of collagen fibers in the sclera. F: Selected control points in the eye-specific lamina cribrosa along the section through the ONH model and the interpolated predominant anisotropic orientations of the laminar beams; local laminar density was incorporated as well. The anisotropic material properties of the lamina were obtained from eye-specific 3D reconstructions of the connective tissue micro-structure at the control points and then interpolated using the mesh-free approach.
DEPTH-DEPENDENT DEFORMATION OF THE OPTIC NERVE HEAD MEASURED BY HIGH FREQUENCY 3D ULTRASOUND SPECKLE TRACKING

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SUMMARY

Glaucoma is a leading cause of irreversible blindness and is characterized by the loss of neural tissue that is responsible for transmitting visual signals from the retina to the brain. We have used a 3D ultrasound speckle tracking technique and computational modeling to evaluate the deformation within the human optic nerve head (ONH) during intraocular pressure (IOP) increase. Our experimental data showed that IOP elevation led to substantial and depth-dependent deformation in the ONH, which may play an important role in the disease process of glaucoma.

Key words: ultrasound speckle tracking, optic nerve head biomechanics, 3D deformation, glaucoma

1 INTRODUCTION

The primary function of the eye is to convert light into electrical signals to be interpreted by the visual cortex. The eye is consistently subjected to mechanical loading from the intraocular pressure (IOP) and other external forces, and thus its role as a biomechanical structure is critical in maintaining vision. It has been suggested that changes in tissue biomechanical properties may play a role in disease and specifically in glaucoma [1, 2]. The optic nerve head (ONH) is the location where the retinal ganglion cell (RGC) axons turn to exit the eye through the scleral canal and the initial site of axonal damage in glaucoma [3]. The ONH includes the peripapillary sclera, the porous lamina cribrosa (LC) which spans the scleral canal, and the prelaminar neural tissue (PLNT) and retrolaminar neural tissue (RLNT) on either side of the LC. The peripapillary sclera and LC are collagenous load bearing tissues which are known to help preserve the shape of the eye and provide structural support to the RGC axons during changes in mechanical loading. However, the relationship between ONH deformation and glaucoma development remains unclear.

Various techniques have been developed with the goal of characterizing the material properties of ocular tissues and their response to mechanical loads. Such methods include uniaxial and biaxial tensile testing [4, 5] and inflation testing [6, 7]. These measurements are accompanied by a number of limitations including the disruption of natural tissue geometry or measurements being restricted to the tissue’s outer surface or a single cross-section. We have recently built upon our 2D ultrasound speckle tracking technique [8] to allow for 3D measurements of ocular tissue deformation. Using this new method, we have measured volumetric displacements and strains throughout the posterior sclera during changes in IOP [9]. Computational modeling is also a widely used approach to predict ocular tissue deformation [2, 10]. The goal of this study was to combine our 3D ultrasound speckle tracking technique and computational modeling to better understand the mechanical response of the ONH to IOP elevation.

2 METHODOLOGY
2.1 Human ONH Inflation Testing

Eight human donor globes were tested as whole globes without any dissection and within 36 hrs postmortem. The globes were secured in space using two long spinal needles and immersed in 0.9% saline. IOP was controlled by infusing phosphate-buffered saline into the anterior chamber via a 20G needle connected to a reservoir. A second 20G needle was inserted into the anterior chamber and connected to a pressure sensor (P75, Harvard Apparatus). The globes were preconditioned with 20 IOP cycles from 15 to 19 mmHg and equilibrated at 15 mmHg for 30 minutes. Ultrasound scans were performed at IOP levels of 15 (reference), 17, and 19 mmHg. A 55 MHz ultrasound probe (Vevo 660, VisualSonics) was used to acquire 3D scans of the ONH at each IOP level. Each scan covered a 7.68 mm x 7.68 mm area centered at the scleral canal. The scans were performed after equilibration times of 30 seconds, 15 minutes, and 30 minutes at each IOP level in order to evaluate tissue creep. The structures present in each volume included the peripapillary sclera, the lamina cribrosa (LC), and the PLNT and RLNT. Due to low signal intensity, the retina and choroid were excluded from all analyses. A 3D ultrasound speckle tracking method was used to calculate micron-level vertical displacements and compressive strains during changes in IOP [11]. Two sub-volumes were defined to compare the tissue deformation within and outside of the scleral canal (Fig. 1).

![Figure 1. ONH volume (blue) with sub-volumes within and outside of the scleral canal (left) and ultrasound image of ONH cross-section showing location of two sub-volumes (right).](image)

2.2 Computational Modeling Simulation

A 2D axisymmetric model of a human eye was generated for comparison to experimental results (COMSOL Multiphysics 5.2a). The geometry was constructed based on literature values and included the cornea, sclera, LC, retina, pia and dura mater, and PLNT and RLNT. All structures were modeled as isotropic and nearly incompressible. A 2 mmHg load was applied to the interior surface of the globe to simulate an IOP increase of 15 to 17 mmHg. Baseline Young’s modulus values were also taken from the literature, and the values were adjusted to match the experimental measurements made using ultrasound speckle tracking. Vertical displacements and compressive strains were plotted for regions within and outside the scleral canal and peripapillary sclera.

3 RESULTS AND CONCLUSIONS

Elevation of IOP during inflation testing induced a complex pattern of deformations within the ONH. The tissues within the scleral canal (LC and neural tissue) exhibited larger posterior displacements compared to the surrounding peripapillary sclera. Removing the bulk posterior displacements revealed a strong depth-dependent mechanical response to IOP elevation throughout the entire ONH volume within or outside the scleral canal (Fig. 2, top). Outside of the scleral canal, a consistent trend was observed with posterior (positive) displacements for the anterior peripapillary sclera and anterior (negative) displacements for the more posterior sclera. On average, the transition from posterior to anterior displacements occurred at a depth equal to 37 ± 3% of the scleral thickness measured from the anterior surface of the sclera. A similar trend was observed within the scleral canal, although the transition zone occurred slightly more posteriorly at 42 ± 12% depth for the six healthy eyes. The two glaucoma eyes deviated from this trend, with very small...
relative displacements after removal of bulk displacements throughout the entire tissue thickness. In all eyes, the lateral deformation was minimal. Creep was detected by repeated scans at different equilibration time points (Fig. 2, bottom). After removal of the bulk displacements, the anterior ONH showed continued displacement in the posterior direction while the posterior ONH moved in the anterior direction as time increased. These increases in tissue deformation over time were observed for the volumes within and outside of the scleral canal. Although the bulk displacements were larger for the volume within the scleral canal, the relative displacements after bulk displacement removal were smaller compared to the displacements of the peripapillary sclera.

**Figure 2.** Top: Vertical displacements through the thickness of the ONH for all eight globes after removal of bulk displacements; Bottom: creep at 17mmHg for one globe.

To match the spatial distributions of vertical displacements and compressive strains between experimental measurements and computational models, a layer with a much lower modulus was introduced in the anterior sclera (Fig. 3). The Young’s modulus values which produced a similar pattern of deformation as in experimental observations were: posterior sclera, dura mater, pia mater = 9 MPa, PLNT and RLNT = 0.0015 MPa, LC = 3 MPa, cornea = 1.8 MPa, and anterior sclera = 0.0015 MPa; although the displacements and strain magnitudes measured experimentally were both larger than those predicted by the model.

**Figure 3.** 2D cross-sections of vertical displacements (top) and compressive strains (bottom) measured experimentally and predicted by a model. Half of the model cross-section is displayed due to symmetry. Note that the retina and choroid were removed in the experimental analysis.
This study has demonstrated the ability of our 3D ultrasound speckle tracking method to measure deformation of the ONH during increases in IOP. Larger bulk posterior displacements of the LC, PLNT, and RLNT were detected compared to the peripapillary sclera. The peripapillary sclera showed significant thinning/compression in its anterior third, while the larger posterior bulk displacements of the LC and neural tissue may help to limit compression within and posterior to the LC. The large compression of the anterior third of the peripapillary sclera was distinct and future studies are needed to further examine the microstructure of this layer [12]. The depth-dependent displacement within the canal is likely due to the presence of the LC; and the transition point appeared more variable than that outside the scleral canal, likely due to differences in the position of the anterior surface of LC. The two glaucomatous eyes exhibited little relative displacement throughout the thickness of the scleral canal, possibly related to a loss in neural tissue in the regions evaluated in this study. A computational model of the ONH with a compliant anterior sclera and moderately stiff LC showed good agreement with the general pattern shown in the measured compressive strains. However, the isotropic model has limited capacity in predicting the lateral response. Our results showed minimal lateral deformation in the small pressure increase from 15 to 19 mmHg. Future models will incorporate a collagen annulus ring surrounding the scleral canal to better capture the lateral response. In conclusion, the 3D nature of the measurements presented in this study generated a more complete characterization of ONH deformation, which may improve our understanding of the role of biomechanics in glaucoma.

REFERENCES

DECODING THE LOAD-BEARING FUNCTION OF THE OPTIC NERVE HEAD MICROSTRUCTURE THROUGH SPECIMEN-SPECIFIC MODELING

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SUMMARY

It is hypothesized that the microstructure of the lamina cribrosa (LC) provides mechanical support to the axons of the optic nerve as it exits the eye. We created specimen-specific finite element models of the optic nerve head (ONH) from high resolution polarized light microscopy data. These models demonstrate that the stresses in the sclera and lamina due to intraocular pressure (IOP) are highly inhomogeneous, with forces transmitted along individual collagen bundles across the sclera. Understanding the mechanics of the ONH on the collagen fiber level is essential for the study of glaucoma initiation and progression.

Key words: microstructure-based modeling, optic nerve head, lamina cribrosa

1 INTRODUCTION

Glaucoma is the leading cause of irreversible blindness world-wide [1]. It is widely considered that glaucomatous vision loss occurs as the result of mechanical damage to the neural tissues of the ONH (Fig. 1), due to the effects of IOP. The LC is a meshwork of collagenous connective tissue thought to provide mechanical support to the retinal ganglion cell axons as they exit the eye.

Fig. 1. The eye and ONH. (Left) Anatomy of the eye highlighting the ONH. Coronal cross-section of a sheep ONH showing collagen density information from polarized light microscopy. Note the inhomogeneity in both the sclera and lamina cribrosa.
The ONH and LC have been major interests in the field of ocular biomechanics and several computational models have been built to study the effects of IOP on the LC and ONH [2-4]. Recently, microstructure-based models of the ONH have been built using small angle light scattering (SALS) [3] and micro-CT [4]. However, the resolution of these models has been limited and they have not provided much insight into the mechanics of individual scleral collagen fiber bundles or LC beams, which are on the scale of 10-50 μm.

Our goal is to understand how the microarchitecture of the lamina and sclera bears the mechanical load caused by IOP, thus protecting the delicate neural tissues within the LC. To this end, we constructed specimen-specific, inhomogeneous, non-linear, anisotropic, finite element models of the ONH based on high resolution polarized light microscopy data.

2 METHODOLOGY

Two sheep eyes were obtained from a local abattoir and pressure fixed with 10% formalin at 5 mmHg. As described elsewhere [5], the ONHs were excised and 30 μm thick coronal cryosections obtained. Six or more serial sections through the region of the ONH including the LC were imaged using an Olympus SX16 microscope and Olympus DP80 camera with a 0.8x objective and 1x magnification setting resulting in images with a resolution of 4.4 μm per pixel. Polarized filters and custom code were used to determine collagen fiber orientation and energy, an optical measure of collagen density [6]. Serial images were aligned and registered using Avizo Wind v8.0.1 (FEI, Hillsboro, Oregon). Thickness-averaged energy and fiber orientation were calculated using Matlab 2015b (Mathworks, Natick, MA) (Fig. 2).

**Fig. 2.** Collagen density and collagen orientation plotted by element.

All meshing and model construction was done in Matlab, using the GIBBON toolbox (gibboncode.org). Briefly, a circular disk was defined with a tetrahedral mesh consisting of 505,995 quadratic tetrahedral elements. The average element edge length was 30 μm. Energy and orientation data were averaged over all pixels contained within an element using circular statistics for the orientation data. All tissues were modeled as a neo-Hookean ground substance with a 2D distribution of fibers. Fibers were modeled with an exponential power-law. Fiber and ground substance strain energy density were both weighted by the energy data obtained from PLM to account for variations in collagen density as follows.

\[
W_{\text{Elem}} = \frac{E_{\text{Elem}}}{E_{\text{Elem}}} (W_{\text{Fiber}} + W_{\text{Ground}})
\]

(Eqn. 1)

Elements with a mean energy equal to the mean energy of the entire sclera, \(E_{\text{Elem}}\), were assigned material properties fit to literature values for human sclera [7]. Uniform boundary pressure was applied to the edges of the model, representing uniform hoop stress similar to the approach recently used by Zhang et al. [3]. Models were solved using FEBio v2.3.0 (Musculoskeletal Research Lab, Univ. of Utah).

3 RESULTS AND CONCLUSIONS
Our models were capable of predicting stresses in individual fiber bundles and beams (Fig. 3). Stresses were highest in the fibers of the peripapillary sclera surrounding the canal. In both eyes, the stress around the canal was asymmetric, peaking on one side of the canal. The sclera does not appear as a gelatinous continuum; instead loads are transmitted across individual fiber bundles from the boundary of the model all the way to the canal (Fig. 4). Specifically, we note large fiber bundles in the sclera that are oriented tangentially to the canal. Peak strains were found in the pores of the lamina cribrosa near the periphery of the lamina (Fig. 5).

**Fig. 3.** Fiber stresses are shown with both an unsaturated color scale to highlight the stress magnitudes (left column) and a saturated color scale to highlight the load bearing fibers of the sclera (right column). Our models demonstrated that stresses are transmitted through continuous fiber networks. The stresses peaked in the peripapillary sclera adjacent to the scleral canal where collagen density was highest. Small pockets of low stress were also observed in the sclera, suggesting significant microstructural inhomogeneity.

**Fig. 4.** A close up view of the load-bearing fiber network in eye 2. A large fiber bundle oriented tangentially to the scleral canal is highlighted (black arrow). Image shown rotated 90° from Fig. 3.
Fig. 5. Our models predict maximum strains in the pores of the lamina cribrosa. These strains are higher at the periphery of the lamina than in the central lamina.

In conclusion, our models are the first to incorporate detailed, specimen-specific maps of connective tissue density, representing both collagen anisotropy and inhomogeneity. These models allowed us to show how IOP induced stresses are transmitted through the fibrous microstructure of the sclera and lamina. We found that the sclera and lamina are not a continuum material at microscale level, but rather a complex network of interwoven fibers. Understanding how the organization and connectivity of the scleral fibers and laminar beams determines the strains in the neural tissue pores of the lamina cribrosa will provide needed insight into the development and progression of glaucoma.

REFERENCES

INFLUENCE OF NERVE TISSUE ON THE BIOMECHANICAL RESPONSE OF THE HUMAN LAMINA CRIBROSA

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SUMMARY

Primary open angle glaucoma (POAG) is the second leading cause of blindness and the leading cause of irreversible blindness worldwide. Cell death occurring near the lamina cribrosa (LC) is a hallmark of POAG. The mechanical environment of this structure is of critical importance as these cells are responsible for transmitting visual information to the brain. In this work we perform simulations of the pressure response of the LC where the intricate microstructure of the collagenous beams and surrounding nerve tissue are explicitly modeled. A particular focus is given to the contribution of nerve tissue to the LC response.

Key words: lamina cribrosa, finite elements, glaucoma

1 INTRODUCTION

Retinal ganglion cells (RGCs) are neurons located near the inner surface of the retina that are responsible for transmitting visual information from the eye to the brain. The lamina cribrosa (LC) is a cribriform soft tissue composed primarily of fibrillar collagen and elastin whose primary role is to project RGC axons as they exit the optic nerve head (ONH). Current literature has shown that the LC is a critical location where RGC cell death occurs in primary-open-angle-glaucoma (POAG) [1]. A thorough understanding of the mechanical behavior of the soft tissues of the LC is therefore necessary to elucidate mechanisms through which the retinal ganglion cell axons in the optic nerve are damaged as well as to better factors associated with individual variation in POAG susceptibility, as is known to occur in those from various racial/ethnic backgrounds. There have been several studies focused on identifying the mechanical properties of the human sclera, however comparatively fewer reports are provided in the literature where the mechanical response of the human LC are rigorously characterized. This may be due to the complex shape, microstructure, and location of this structure in the ONH.

Towards this end our research team has devoted significant effort into using nonlinear optical microscopy techniques to generate intraocular pressure (IOP) dependent in-vitro strain maps of the human LC from fresh human donor eyes. This imaging approach utilizes the second harmonic signal of collagen as quantified using two photon microscopy. An important limitation of our approach is the lack of signal collected in the pores of the LC that do not contain fibrillar collagenous signal (as produced from SHG imaging).

The purpose of this abstract is to quantify the degree to which computational discretization of nerve tissue within the human LC influences the overall displacement and strain fields within the human LC. This information will be critical to more thorough and extensive computational simulations of the human LC performed in the future, including those utilizing an inverse finite element simulation approach to identify the constitutive properties of the human LC.
2 METHODOLOGY

2.1 Sample Procurement, Imaging and Image Processing

2.1.1 Sample Procurement

All sample procurement methods were approved by the University of Arizona's Institutional Review Board. A single human donor eye was acquired from Midwest Eye Bank from which the LC was isolated and underwent a brief mechanical and chemical digestion. The LC was then mounted into a pressure chamber and subjected to four pressures (5, 15, 30, and 45 mmHg) while being imaged from the anterior aspect using a two photon microscope.

2.1.2 IOP Dependent Nonlinear Optical Microscopy

Two photon imaging was performed using a Ti:Saph (Mira 900, Coherent, Inc) tunable 120 fs pulsed light source. The excitation wavelength of the laser was $\lambda = 780\text{nm}$ and collection was done in the epidirection using a dichroic mirror (405 nm), a 377/50 nm bandpass filter (SHG), and a 460/80 nm bandpass filter. Digital images were acquired using a 4X objective (NA = 0.3) resulting in a pixel size of $2.5\mu m$ in the x- and y-direction and $5\mu m$ in the z-direction.

2.1.3 Image Segmentation

The SHG images were segmented using an in house multiscale wavelet decomposition method with adaptive scale selection implemented in Matlab. This approach can efficiently handle segmentation of highly inhomogeneous LC beams (see Figure 1).

![Figure 1: Segmented LC from two photon imaging](image)

2.2 Computational Simulations

A subdomain of the entire human LC was chosen for this analysis. Our goal was to investigate the influence of the material properties of tissues that do not generate SHG in the LC (e.g., nerve tissue, axons etc., hereafter referred to as nerve tissue) in determining the displacement and strains of the collagenous beams of the LC (SHG positive) in our pressure experiments. Provided below are details regarding these computational simulations.

2.2.1 Geometric Discretization, Boundary Conditions, and Material Properties

The subdomain was located within the body of the LC and was $150 \times 150 \times 50 \mu m$ in size, with the smallest dimension being aligned in the anterior posterior direction. The Gibbon toolset in Matlab was used to discretize both the nerve and collagen tissue using over 700,000 linear tetrahedral elements. The average element length of each collagen and nerve element was 1.1 and 0.6 $\mu m$, respectively. The boundaries of the cuboidal domain whose plane normals are orthogonal to the anterior posterior
direction were fixed in all three translational degrees of freedom and the anterior facing surface was exposed to a pressure of 45 mmHg. Both nerve and collagenous tissues were assumed to be hyperelastic, nearly incompressible and isotropic. Both tissues were assumed to be neoHookean as defined by the values of $C_{10}$ and $D_1$. These values for nerve tissue were varied in a controlled manner and the displacements and principal strains of the collagenous portion of the LC were quantified as a function of nerve tissue properties. The collagen within the LC beams was assumed to have a $C_{10}$ value of 500,000 Pa and a $D_1$ value of 1E-6 (1/Pa) for all simulations.

### 3 RESULTS AND CONCLUSIONS

The maximum change in mean strain across all nerve property simulations run was relatively small (approximately 0.0006). Therefore the strains in the collagen of the LC were not largely influenced across this range of nerve tissue properties. As one can also see from Figure 3, nerve tissue does not further restrict the deformation of the collagenous laminar beams below a $C_{10}$ value of approximately 20,000 Pa. Depending on the literature source, the modulus of brain tissue has been reported to be anywhere from 100Pa to 31,000 Pa [2, 3]. Taken together, for the collagen properties assumed here, these results suggest that nerve tissue in the LC does not govern LC collagen beam deformation.

There are several limitations worth discussing in this abstract. First and foremost, the size of the domain used in this study was only a small portion of the entire human LC. Future work in our laboratory will focus on addressing this limitation by expanding the region simulated to include as much of the LC as is possible. Another main limitation of this work is the assumption of an isotropic material response. This may particularly inaccurate in the case of the collagen present in this tissue. We believe that the approach presented here can easily be expanded to include constitutive models utilizing a fiber based anisotropic material model. Future work in our laboratory will also focus on similarities and differences between modeling the collagenous beams of the LC (as is done in his work) in comparison to utilizing larger more computationally efficient yet microstructurally based constitutive models.
Figure 3: Stress contour plot of the collagen domain within a heterogeneous LC and the mean principal strains in this subdomain for various values of nerve $C_{10}$. Note the asymptotic behavior when the nerve tissue properties reach 20,000 Pa.

REFERENCES


DIFFERENCES IN SIMULATED REFRACTIVE OUTCOMES OF PHOTOREFRACTIVE KERATECTOMY (PRK) AND LASER IN-SITU KERATOMILEUSIS (LASIK) FOR MYOPIA IN SAME-EYE VIRTUAL TRIALS

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SUMMARY
Computational mechanics is increasingly used for assessing the structural and optical consequences of cornea refractive procedures. In practice, surgeons who elect to perform PRK rather than LASIK must reduce the programmed refractive treatment magnitude to avoid overcorrection of myopia. Building on a recent clinical validation study of finite element analysis (FEA)-based predictions of LASIK outcomes, this study compares predicted responses in validated LASIK cases to theoretical PRK treatments for the same refractive error. Simulations in 20 eyes demonstrated that PRK resulted in overcorrections relative to LASIK and that the magnitude of overcorrection increased as a function of attempted correction.

Key words: cornea, refractive surgery, finite element analysis

1 INTRODUCTION
Structural analysis using the FEA method is a useful tool for investigating clinical hypotheses related to the biomechanical impact of surgical interventions in the eye. The fine link between the cornea’s geometry and its refractive performance along with the high precision of corneal refractive surgery interventions provide a privileged clinical system in which to explore the potential of simulation-based engineering science to facilitate outcome prediction and clinical decision-making.

In a recent study [1], we investigated the predictive accuracy of a computational modeling approach to LASIK, the most commonly performed form of keratorefractive surgery worldwide. LASIK involves creation of a partial-thickness corneal flap that is hinged to allow access to the underlying residual stromal bed. The residual corneal stromal bed is then accessed by lifting the flap, and excimer laser ablation is performed with a spatial profile specific to the patient’s refractive error. PRK is similar to LASIK but foregoes the flap in favor of more superficial corneal ablation. In clinical practice, PRK is often preferred in patients with thinner or atypical corneal geometries because it is structurally more conservative while achieving similar refractive outcomes to LASIK. However, surgical planning often requires programming a surgeon-specified treatment offset to account for a clinical trend toward overcorrection of myopia with PRK. The magnitude of this correction is based on historical trends with minimal patient-specific input.

In this study, we perform a same-eye trial comparing simulated corneal shape changes using a prior virtual patient LASIK cohort to simulated outcomes for PRK with the same attempted refractive change.
2 METHODOLOGY

1.1 Subjects

Consecutive charts of 20 eyes of 12 subjects that underwent LASIK for myopia or myopic astigmatism were included in the study. Patients were selected by a retrospective review of corneal tomography under an institutional review board (IRB)-approved research protocol (Cleveland Clinic IRB protocol #13-213). Eyes with at least 10mm of corneal coverage in Scheimpflug-based anterior segment scans (Pentacam HR, Oculus Optikgerate GmbH, Germany) were selected.

1.2 Modeling Method

Patient-specific corneal tomograms were exported and preoperative Cartesian coordinates for the anterior and posterior corneal surfaces were interpolated and meshed with 8-node hexahedral brick elements (Figure 1) with custom software (SpecifEye v0.1, OptoQuest, Cleveland OH). The cornea was represented as a nonlinear, anisotropic, hyperelastic, nearly incompressible material with depth-dependent material properties and crimp behavior as detailed in a prior report [1]. A microstructural fiber-reinforced material model representing collagen fibers was combined with an isotropic Neo-Hookean solid extrafibrillar matrix to produce a composite corneal stroma. Normative corneal material constants were assumed to be invariant across eyes. A generic sclera was implemented (Figure 1A) and a physiological intraocular pressure was applied. LASIK was modeled as illustrated in Figure 1B, and PRK models for the same eye implemented the same ablation profile but directly below the epithelium. A nominal wound layer was included at the flap boundaries to simulate the convalescent postoperative state. Stress-free configurations were determined using an iterative approach described previously [2] and modified by our group [3]. Finite element solutions were obtained using Abaqus v6.11 (Dassault Systemes Simulia Corp., Providence, RI).

Figure 1. Representative mesh of a preoperative whole-eye model (A) and a corneal cross-section illustrating the sublayers specified in LASIK simulations (B). PRK was modeled with an ablated lenticule directly under the epithelium (top layer) and with no flap delineation.

1.3 Corneal curvature analysis

After simulation, anterior corneal surface coordinates from pre- and post-treatment geometries were exported from the solver into SpecifEye where simulated keratometry values (in diopters, D) representing the steep and flat principle axes of the corneal surface were calculated then averaged to estimate the spherical refractive power of the cornea. Pairwise (PRK vs. LASIK) changes in anterior corneal curvature for each procedure were calculated and assessed for differences with a paired Student’s t test (with p<0.05 indicating statistical significance). Additionally, the relationship between the magnitude of the PRK-LASIK difference and the level of attempted myopic correction was assessed by linear regression (Minitab 17, State College, PA).

3 RESULTS AND CONCLUSIONS

The range of simulated corrections was determined by the clinical refractive errors of the sample (-0.75D to -7.75D in spherical equivalent terms with a mean and standard deviation of -3.41 ±
Mean keratometric power decreased by an additional $0.23 \pm 0.16$ D in PRK simulations compared to LASIK ($p<0.001$). The magnitude of relative PRK overcorrection increased as attempted correction increased (Figure 3) and 92.8% of the variance was accounted for by a linear relationship \((-0.05D - (0.08D \times \text{attempted spherical equivalent correction}), p<0.001\).

In conclusion, a finite element model previously validated in a myopic LASIK population demonstrated a tendency toward greater corneal flattening in PRK simulations than in LASIK simulations with equivalent patient-specific geometries and material property assumptions. This is consistent with a clinical need for surgeon adjustments to the treatment algorithm to avoid unintended hyperopic refractive error when PRK is selected instead of LASIK. While differences in ablative efficiency between PRK and LASIK due to intraoperative hydration differences have been proposed as an explanation for this phenomenon, the present study demonstrates differences without appealing to hydration and suggests that differences in residual stromal bed strains result in greater relative corneal steepening in LASIK that undermines myopic correction. These findings offer insight into the biomechanical differences between PRK and LASIK, the refractive consequences of these differences, and the potential utility of patient and case-specific approaches to surgical planning.

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Modeling & Simulation of Cancer
DRUG INDUCED RESISTANCE vs. DRUG TOLERANCE IN CANCER TREATMENT: A SIMPLE MODEL and ANALYSIS

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SUMMARY

Acquired resistance is a resistance that may occur during chemotherapeutic treatment. This type of drug-induced resistance is one of the major obstacles against cancer treatment. In the current work, we have modified our recently reported model in drug resistance to include the elements that can describe acquired resistance and drug tolerance. The modified model is analyzed through a series of numerical simulations, and the behavior of cell populations is examined and discussed.

Key words: Chemotherapy, Drug Resistance, Drug Tolerance, Cancer Modelling

1 INTRODUCTION

Acquired and Intrinsic drug resistance are two major drug resistances that can bar the effectiveness of chemotherapeutic cancer treatments. The resistance may occur due to different reasons such as pharmacologic resistance, when the drug cannot reach the tumor site, or when it is not active in the tumor site. It can additionally result from the genetic mutation of tumor cells [1]. Drug resistance that exists in the system, even prior to the treatment, is known as intrinsic resistance. In contrast, drug resistance can be induced as a result of the interaction of tumor cells with the chemotherapeutic drugs. This type of resistance is known as acquired resistance. Gene mutation is one of the major causes of acquired drug resistance. Currently, no comprehensive knowledge exists about a more effective therapeutic approach in cases that show acquired chemotherapeutic drug resistance. In addition, we have inadequate knowledge of whether such drug resistance can be eliminated or controlled during the treatment.

Recent studies highlight the critical role that the immune system or immune enhancer drugs carry to reverse or delay acquired chemotherapeutic resistance. The current study of Smith et al. indicates that some drugs such as HIV1-protease inhibitor nelfinavir can potentially prolong responses to chemotherapeutic agents and delay the occurrence of chemotherapeutic drug induced resistance [2]. In addition, the results of another recent study conducted by Zhu et al. show that the induction of T-cell immunity can reverse the chemotherapeutic resistance in ovarian cancer [3]. Collectively, this current evidence suggests that the acquired drug resistance can be affected and suppressed as a result of the presence of the enhanced immune system.

Throughout a series of mathematical models and numerical simulations we examined the dynamic of normal and tumor cells in a conjoint core model, where the growth of these two sub-categories of cells can mutually affect one another. The model was analyzed when the system was treated by chemotherapeutic agents [4]. The mathematical model was then expanded to include the terms that can express the role of the immune-system in the growth and control of tumor cells [5]. In addition, we analyzed the drug resistance situations. We first focused on the intrinsic drug resistance. We made a distinction between two groups of tumor cells: the first group considered to be drug sensitive, and the second group that intrinsically show resistance to the drug. The system was then numerically evaluated under different chemotherapeutic strategies [6].

In our recent work, which is currently under revision, the mathematical model that had been developed to express the intrinsic drug resistance was modified to introduce and include the
elements that can express acquired drug resistance. In this work and under a simple approach, we consider that tumor and normal cells grow independently. We then identify three groups of tumor cells: wild tumor cells, mutated tumor cells, and drug resistant tumor cells. We will include the elements of the immune system into our model and evaluate the role of the immune system in enhancing drug tolerance.

2 METHODOLOGY

2.1 Gompertzian Growth Core Model and Acquired Drug Resistance

In the current model, we consider that tumor and normal cells independently grow and follow the Gompertzian growth pattern. We also rely on the evidence that in some types of cancers, acquired drug resistance can result from the interaction of those groups of tumor cells that carry a specific mutated gene [1]. As a result, three groups of tumor cells were considered. The first group includes those that are still responsive to the administered drug, and are known as wild tumor cells, \( T \). The second group is those tumor cells that are still responsive to the drug, but carry a mutated gene that causes drug resistance as they interact with the introduced drug. These tumor cells are placed in the category of mutated tumor cells, \( T_M \). The third group of tumor cells are not responsive to the drug. These tumor cells, \( T_R \), are part of mutated tumor cells that have become resistant to the drug after interacting with the chemotherapeutic agent. The dynamics of the system are expressed below:

\[
\begin{align*}
\frac{dT(t)}{dt} &= r_T T(1 - \frac{T_{\text{total}}}{K_T}) - \frac{aET}{g_E + T_{\text{total}}} - \tau_T(t) - a_T(1 - e^{-MC})T; & T(0) = T_0 & (1a) \\
\frac{dT_R(t)}{dt} &= r_T T_R(1 - \frac{T_{\text{total}}}{K_R}) - \frac{aET_R}{g_E + T_{\text{total}}} + \tau_{M \rightarrow R}(1 - e^{-MC})T_M; & T_R(0) = T_{R0} & (1b) \\
\frac{dT_M(t)}{dt} &= r_M T_M(1 - \frac{T_{\text{total}}}{K_M}) - \frac{aET_M}{g_E + T_{\text{total}}} + \tau_T(t) - \tau_{M \rightarrow R}(1 - e^{-MC})T_M; & T_M(0) = T_{M0} & (1c) \\
\frac{dI(t)}{dt} &= -\mu_I I + \frac{p_I EI}{g_I + T_{\text{total}}}; & I(0) = I_I & (1d) \\
\frac{dN(t)}{dt} &= -r_N N(1 - \frac{N}{K_N}); & N(0) = N_0 & (1f)
\end{align*}
\]

In the above equations, \( T_{\text{total}} = T + T_M + T_R \). \( K_N, K_T, K_R, \) and \( K_M \) are the carrying capacity of normal cells and three types of tumor cells with the unit of cells. The per capita growth rates are expressed by \( r_T, r_R, r_M \) with the unit of time\(^{-1}\). The term \( \tau_T(t) \) in equations 1a and 1b expresses the transition of wild tumor cells to mutated tumor cells. The term \( \tau_{M \rightarrow R}(1 - e^{-MC})T_M \) in equations 1b and 1c represents the transition of the mutated tumor cells to resistant tumor cells. The toxic effect of the administered drug, which leads to the reduction in populations of cells, has been expressed by \( \varphi \) \((1 - e^{-MC})T \), \( \varphi = T \), \( T_M \) on wild tumor cells as mutated tumor cells. The equations 1d and 1e include the elements of the immune system. The mathematical terms were initially introduced by Panetta and Kirschner, and have been used in previous models as well [7]. In these equations, \( E(t) \) are effector cells that include T cells and are cytotoxic to tumor cells. IL-2 is the cytokine responsible for the T cells’ activations and is expressed by \( I(t) \). \( \mu_E \) and \( \mu_I \) represent the natural loss of E cells and IL-2 with the rates of \( \mu_E \) and \( \mu_I \). The activation terms are \( p_E EI / g_E + I \) and \( p_I EI / g_I + T_{\text{total}} \), where \( p_E \) and \( p_I \) are proliferation rate, and \( g_E \) and \( g_I \) are the half saturation for the proliferation term.

2.2 Case Study and Numerical Simulation

The numerical simulations to evaluate the dynamic of tumor cells were conducted based on the following cases: First, we assumed that the treatment with the chemotherapeutic drug starts at \( t=50 \) days. The amount of the drug will not stay constant in the tumor site, and diffuses exponentially, with the decaying constant of \( 10^3 \). Tumor cells’ gene mutation is assumed to begin at the same time.
that the drug is introduced to the system, \( t=50 \) days. The gene mutation rate is considered to be constant. The transition of the mutated tumor cells to drug resistant tumor cells was set to be started at \( t=100 \) days, with a constant rate. Under these simulation conditions the dynamic of tumor cells were simulated numerically. Second, the first case was simulated in the presence of the immune system. Third, we considered that the transition of the mutated tumor cells to the drug resistant tumor cells can be affected by the number of E cells. To implement this condition, we assumed that the transition rate exponentially decays with the number of E cells and at a decay rate of \( 10^{-3}/\text{day} \). Lastly, we evaluated the case by assuming that the immune system decreases the mutation rate of wild tumor cells to mutated tumor cells. The parameters of the simulations are summarized in table 1.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common Parameters of Tumor Growth</td>
<td>( K_T=K_{T^M}=KT_E=10^6 ) (cells) ( r_T=r_{T^M}=r_M=0.2 )</td>
<td>Carrying capacity of tumor cells</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Growth rate for tumor cells</td>
</tr>
<tr>
<td>Common Parameters Related to the Immune System</td>
<td>( C_E=3<em>10^{-4}/\text{day} ) ( \mu_E=0.03/\text{day} ) ( \mu_T=10/\text{day} ) ( a=2/\text{day} ) ( g_T=30\text{cells} ) ( p_T=5/\text{day} ) ( g_I=2</em>10^7\text{cell} ) ( p_I=2/\text{day} )</td>
<td>Antigenicity \nDeath rate of E cells \nHalf-life of effector molecules \nCancer clearance terms \nHalf-saturation proliferation \nProliferation rate effector molecules \nHalf saturation of production \nProliferation rate immune molecules</td>
</tr>
<tr>
<td>Specifications of the Decaying Drug</td>
<td>( C=0.2\exp(-0.001t) ) (mg.m(^{-2})) ( a_T=0.15 ) (day(^{-1}))</td>
<td>( C: ) Initial value of drug \nDrug clearance rate</td>
</tr>
<tr>
<td>Transition Rate to the mutated tumor cells ( \tau_I )</td>
<td>Case I: ( 10^{-2} ) (day(^{-1})) \nCase II: ( 10^{-3} \exp(10^{-3}E(t)) ) (day(^{-1}))</td>
<td>I: Constant transition rate \nII: Decaying transition rate due to the presence of the immune system with the constant of ( 10^{-3} ) (cell(^{-1}))</td>
</tr>
<tr>
<td>Transition Rate from Mutated Cells to Resistant Tumor Cells ( \tau_{M \rightarrow R} )</td>
<td>Case I: ( 10^{-2} ) (day(^{-1})) \nCase II: ( 10^{-3} \exp(10^{-3}E(t)) ) (day(^{-1}))</td>
<td>I: Constant transition rate \nII: Decaying rate due to the presence of the immune system with the constant of ( 10^{-3} ) (cell(^{-1}))</td>
</tr>
</tbody>
</table>

Table 1: Simulation Parameters

### 3 RESULTS AND CONCLUSIONS

In figure 1, the dynamic of three types of tumor cells is numerically simulated. Figure 1A shows this dynamic in the absence of the immune system. Wild tumor cells start to grow. Part of them will be converted to mutated tumor cells. Also, under the influence of the chemotherapeutic agent, their population shrink and die out of the system. Meanwhile, some of the mutated tumor cells transition to drug resistant tumor cells. This group of drug-resistant tumor cells grow quickly, and will be dominant cells in the system. The mutated tumor cells also die out of the system as they are still responsive to the drug. In figure 1B, the elements of the immune system are included in our equations. As can be seen, the population of the three groups of tumor cells decreases as a result of interacting with effector cells. In figure 1C, we assumed that the transition rate from mutated tumor cells to resistant tumor cells decreases exponentially by the number of effector cells. The number of effector cells can be enhanced by immune booster drugs, or even by the presence of a strong immune system.

As can be seen, the growth of the drug resistant tumor cells (dotted line) starts with a delay, as compared with the case in which we considered the mutation to the drug resistant tumor cells to be constant and independent of the number of effector cells (dashed line). These phenomena, also reported by Smith et al. [2], are introduced as drug induced tolerance.
Figure 1: Population dynamic of tumor cells. The orange curve shows the dynamic of wild tumor cells. The purple curve shows the dynamic of mutated tumor cells, and the red curve shows the dynamic of drug resistant tumor cells. “→ ←” in the figures show the delay which is created as a result of the presence of the immune effector cells. All simulation parameters are expressed in Table 1, and the dynamic of each type of tumor cells is analyzed and explained in the text.

In the figure 1D, the mutation of wild tumor cells to mutated tumor cells is considered to be affected by the number of effector cells. However, less delay in the creation of drug resistance can be observed. This model can be comprehensively assessed under different case of parameters, in the presence of different immune boosting drugs, immune deficiencies, and under the conjoint core model where the growth of normal and tumor cells affect one another.

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ON ULTIMATE DYNAMICS OF THE KIRSCHNER-PANETTA CANCER MODEL

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SUMMARY

In this paper we examine ultimate dynamics of the Kirschner- Panetta model describing the tumor immunotherapy. We provide new upper ultimate bounds for variables of this model. Conditions of the nonexistence of compact invariant sets are given. We present sufficient conditions on model parameters and treatment parameters under which all trajectories in the nonnegative orthant tend to the tumor-free equilibrium point. We discuss our results and concern biological implications of our work.

Key words: Kirschner- Panetta tumor model, immunotherapy, ultimate dynamics

1 INTRODUCTION

Modeling immunotherapy of the tumor-immune interactions is one the main researching directions in mathematical oncology, see e.g [1] with bibliography therein. One of the basic models in this area is the well-known Kirschner-Panetta model (KP-model) proposed in [2]. Differential equations describing dynamics of this model are given by

\[
\begin{align*}
\dot{x} &= cy - \mu_2 x + \frac{p_1 x z}{z + g_1} + s_1, \\
\dot{y} &= r_2 y - r_2 b y^2 - \frac{a x y}{y + g_2}, \\
\dot{z} &= -\mu_3 z + \frac{p_2 x y}{y + g_3} + s_2.
\end{align*}
\]

Here \(y(t)\) describes the number of tumour cells at the moment \(t\); \(x(t)\) refers to the number of immune cells at the moment \(t\); \(z(t)\) describes the concentration of effector molecules at the moment \(t\); in the single tumor-site compartment.

The parameter \(c\) is known as the "antigenicity" which characterizes the strength of the tumor to generate effector immune cells; \(\mu_2\) is the death rate of immune cells; \(p_1\) is the proliferation rate of immune cells; \(g_1\) is the half saturation for proliferation term; \(r_2\) is the cancer growth rate; \(b\) is the logistic growth of cancer capacity; \(a\) is the cancer clearance term; \(g_2\) is the half saturation for cancer clearance; \(p_2\) is the production rate of immune molecule; \(g_3\) is the half saturation of production; \(\mu_3\) is the half-life of effector molecule. Further, \(s_1\) represent a treatment term where by a physician administers effector cells that have been taken from a patient, stimulated to a large degree, and then subsequently infused back into the patient. The term \(s_2\) is a treatment term that represents administration of the cytokine interleukin-2 (manufactured) by a physician to a patient, to stimulate again effector cell growth and proliferation; \(s_1, s_2 > 0\).

In this work we continue studies of global dynamics of the KP-model initiated in the paper [3]. Our main assumption is that \(p_1 > \mu_2\), i.e. the proliferation rate of immune cells is larger than their death rate. We derive new ultimate bounds for immune cells population and for the concentration of effector molecules. Further, we establish the nonexistence conditions of compact invariant sets and present new global tumor eradication conditions. The complete journal version is under preparation.
2 METHODOLOGY

Our approach is based on the localization method of compact invariant sets, see [4]. This method has been recently applied successfully to studies of various cancer models, [3, 5, 6, 7, 8, 9, 10, 11, 12], and may be described briefly as follows. We consider a nonlinear system

\[ \dot{x} = F(x), \]

where \( x \in \mathbb{R}^n \), \( F(x) = (F_1(x), \ldots, F_n(x))^T \) is a differentiable vector field. Let \( h(x) \in C^\infty(\mathbb{R}^n) \) be a function such that \( h \) is not the first integral of the system (2). The function \( h \) is used in the solution of the localization problem of compact invariant sets and is called a localizing function. By \( h|_U \) we denote the restriction of \( h \) on a set \( U \subset \mathbb{R}^n \). By \( S(h) \) we denote the set \( \{ x \in \mathbb{R}^n \mid L_F h(x) = 0 \} \), where \( L_F h(x) \) is a Lie derivative with respect to \( F \). Suppose that we are interested in the localization of all compact invariant sets located in the set \( U \). Further, we define

\[
\begin{align*}
    h_{\inf}(U) & := \inf \{ h(x) \mid x \in U \cap S(h) \}; \\
    h_{\sup}(U) & := \sup \{ h(x) \mid x \in U \cap S(h) \}.
\end{align*}
\]

**Proposition 1.** 1. For any \( h(x) \in C^\infty(\mathbb{R}^n) \) all compact invariant sets of the system (2) located in \( U \) are contained in the set \( K(U; h) \) defined by the formula \( \{ x \in U \mid h_{\inf}(U) \leq h(x) \leq h_{\sup}(U) \} \) as well. 2. If \( S(h) \cap U = \emptyset \) then the system (2) has no compact invariant sets in \( U \).

Below by \( \mathbb{R}^3_{+,0} \) we denote the nonegative orthant in \( \mathbb{R}^3_+ \). Since the biologically feasible domain is \( \mathbb{R}^3_{+,0} \) all our objects (trajectories, sets etc.) appeared below are considered only in \( \mathbb{R}^3_{+,0} \).

3 RESULTS AND CONCLUSIONS

Let us remind some known ultimate bounds: \( y_{\max} := b^{-1} \) for \( y \)-variable; \( x_{\min} := s_1 \mu_2^{-1} \) for \( x \)-variable; \( z_{\min} := s_2 \mu_3^{-1} \) for \( z \)-variable. Firstly, we present new upper bounds \( x_{\max} \) and \( z_{\max} \) for variables \( x \) and \( z \) respectively.

**Theorem 1.** 1) All compact invariant sets in \( \mathbb{R}^3_{+,0} \) are located in

\[
K_{32} = \left\{ z \leq z_{\max} := \frac{s_2}{\mu_3} + \frac{\gamma(\mu_3 + r)^2}{4\gamma^2\mu_3} \right\} \cap \mathbb{R}^3_{+,0},
\]

with

\[ \gamma = \max(1; g_2 g_3^{-1}) p_2 a^{-1}. \]

2) Suppose that \( s_2 > p_1 - \mu_2 \). Then all compact invariant sets in \( \mathbb{R}^3_{+,0} \) are located in the polytope \( K \) as

\[
K = \{ x_{\min} \leq x \leq x_{\max}; y_{\min} \leq y \leq y_{\max}; z_{\min} \leq z \leq z_{\max} \},
\]

\[
x_{\max} : = \begin{cases} \frac{c+s_1 b}{b(z_{\min}+g_1)^{\xi-1}}, & \text{with } \xi > 1, \\ \frac{c+s_1 b}{b(z_{\max}+g_1)^{\xi-1}}, & \text{with } 0 < \xi < 1. \end{cases}
\]

As a consequence, we get that the attracting set of the system (1) is located in the polytope \( K \). Let

\[
B = \frac{p_1 s_2}{g_1 \mu_3 + s_2}.
\]

Then we establish

**Theorem 2.** Suppose that

1) \[ \mu_2 + r > B; \]

2) \[ 4ac > (\mu_2 + r - B)^2; \]

2) Besides, the following condition on treatment parameter \( s_1 \) is fulfilled:

\[
c g_2 > s_1 > \max\{c; \frac{4ar}{4ac - (\mu_2 + r - B)^2}\} \]

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Then the system has no compact invariant sets located in $\mathbb{R}^3_+ \cap \{ y > 0 \}$.

In what follows, we examine the case $p_1 > \mu_2 > B$. Then the tumor-free equilibrium point is given by the formula

$$O_1 = (O_{11}, O_{12}, O_{13}) = \left( \frac{s_1(g_1\mu_3 + s_2)}{\mu_2(g_1\mu_3 + s_2) - p_1s_2}, 0, \frac{s_2}{\mu_3} \right), \text{ with } s_2 < \frac{\mu_2\mu_3g_1}{p_1 - \mu_2}.$$

The point $O_1$ is locally asymptotically stable if, in addition, we claim that

$$s_1 > \frac{rg_2}{a}(\mu_2 - B). \quad (4)$$

Our main result is

**Theorem 3.** Suppose that

$$s_1 > \frac{r(bg_2 + 1)^2}{4ab}(\mu_2 - B). \quad (5)$$

Then the system in $\mathbb{R}^3_+$ is globally asymptotically stable respecting $O_1$.

Finally, we compare our tumor clearance bounds with other bounds from [2] and [3] and concern biological implications.

**Conflict of interest.** The author has declared that no conflict of interest exists.

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IMPACT OF TUMOR OXYGENATION ON DRUG RESISTANCE EVOLUTION UNDER HYPOXIA-ACTIVATED PRODRUG THERAPY

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SUMMARY
Hypoxia-activated prodrugs (HAPs) have been designed to target low-oxygen regions within tumors, where drug-resistant clones may thrive. We demonstrated in previous mathematical modeling work that, when combined with standard tyrosine kinase inhibitor therapy, they may have the potential to significantly improve treatment outcomes for patients with EGFR-mutant non-small cell lung cancer (NSCLC). Here, we extend this work to investigate how varying tumor oxygenation may be used to alter response to the combination therapy. Our framework can be used to develop optimal therapeutic regimens that may further reduce tumor burden and probability of resistance in patients with NSCLC.

Key words: drug resistance, tumor hypoxia, cancer evolution

1 INTRODUCTION
The heterogeneity of the tumor microenvironment (TME) has been shown to play a crucial role in the emergence and evolution of drug resistance [1]. Specifically, solid tumor vasculature is notoriously disorganized [2], leading to spatial variation in the concentrations of drug, nutrients, and oxygen. This can lead to sustained cell proliferation in low-drug regions, which then promotes the production of drug-resistant mutants. These regions of low drug concentration often coincide with hypoxic (low oxygen) conditions since both drugs and oxygen diffuse into tumors via the blood vessels. Hypoxia-activated prodrugs (HAPs) such as evofosfamide have been designed to specifically target these oxygen-deprived portions of the TME [3]. Under normoxic (normal oxygen) conditions, evofosfamide penetrates effectively through tumor tissue; it only metabolizes into an active drug upon entry into a hypoxic region [4]. This novel action allows evofosfamide to target cells in a region of the TME often unreachable by standard therapies, whose range is usually confined to more well-vascularized regions.

Although HAPs have failed to show a survival benefit in several recent clinical trials, our previous work has demonstrated the importance of determining the correct dosing sequence and timing in order to maximize therapeutic benefit [5]. One standard therapy currently used to treat EGFR-mutant NSCLC is erlotinib, a tyrosine kinase inhibitor that binds to EGFR. Although most patients are initially responsive to erlotinib, patients eventually develop resistance within 12-18 months on average [6]. Therefore, novel strategies designed to prevent or delay the onset of resistance to erlotinib are of great clinical importance.

In [7], we developed a stochastic mathematical model, informed by experimental and clinical data, to predict the evolutionary dynamics of a population of cancer cells within a heterogeneous TME during treatment with erlotinib and evofosfamide. We optimized over the space of tolerated combination dosing schedules to find maximally effective strategies. Our model predicts that the dosing schedules with the greatest potential to minimize tumor burden and probability of resistance are those that sequentially alternate between erlotinib and evofosfamide doses while minimizing the treatment break after a dose of evofosfamide and before the next dose of erlotinib.

Here, we extend our model from this previous work to study the effect of changing the TME on response to treatment with erlotinib and evofosfamide. Since erlotinib response is microenvironment-dependent and evofosfamide is hypoxia-activated, it may be possible to improve predicted treatment
outcomes even further by manipulating the state of the TME. We compare predicted treatment outcomes using a standard TME with those using TMEs where the overall oxygen concentration throughout the tumor has been either increased or decreased. This comparison provides insight into how alterations to the TME could be leveraged to maximize the therapeutic benefit of these drugs. The addition of this work contributes to a more complete understanding of the interactions between cancer cells and their microenvironments as well as provides a potentially improved strategy for optimal tumor control in NSCLC patients.

2 METHODOLOGY

To capture the effect of microenvironmental heterogeneity on the cancer cell population dynamics, we use a pseudo-spatial compartment-based model of the TME in which cells are distributed amongst a weighted series of environmental habitats with varying concentrations of oxygen and drug [1]. Each environmental compartment has some inherent oxygen concentration so that the total collection of compartments is representative of the range of oxygen concentrations observed in solid tumor physiology. Oxygen decays spatially away from the nearest blood vessel, and we parameterize this decay rate using estimates of the half-length away from the vessel. This decay rate, together with the oxygen concentration in each compartment, allows us to define (for each compartment) a distance away from the nearest blood vessel at which that volume of cells is located. The relative contribution of each of these compartments to the TME as a whole is determined based on experimental data capturing the relative frequencies of oxygen partial pressures throughout solid tumors [8]. A schematic of this model is shown in Figure 1.

Within each compartment, we model the population of cancer cells during treatment using a two-type continuous-time birth-death process. For simplicity, we assume the evolutionary dynamics within each compartment are independent. In compartment $i$, let $X_i(t)$ represent the number of erlotinib-sensitive cancer cells at time $t$, and let $Y_i(t)$ denote the number of erlotinib-resistant cells at time $t$. The sensitive cells in compartment $i$ proliferate and die with rates $\lambda_{X,i}(t)$ and $\mu_{X,i}(t)$, respectively, and the resistant cells proliferate and die with rates $\lambda_{Y,i}(t)$ and $\mu_{Y,i}(t)$. These time-dependent birth and death rates reflect the effect of treatment on the population of cancer cells in compartment $i$ and therefore depend on the concentrations of both oxygen and drug found in that compartment. Each time a sensitive cell divides, a mutation may arise with probability $u = 10^{-7}$, giving rise to a new resistant cell. We start with an initial population of $M_i = 1.6 \cdot 10^6$ sensitive cells and no resistant cells. The number of sensitive cells $M_i$ initially in compartment $i$ is calculated using the relative compartment weights.

The evolutionary dynamics of this population of cancer cells can be described using analytic approximations for the probability of resistance and means of the sensitive and resistant cells. Specifically, the mean of the sensitive cells in compartment $i$ is $\mathbb{E}[X_i(t)] = M_i \exp \left[ \int_0^t (\lambda_{X,i}(\tau) - \mu_{X,i}(\tau)) \, d\tau \right]$.

The mean of the resistant cells is $\mathbb{E}[Y_i(t)] = \int_0^t b_i(\tau) \exp \left[ \int_0^\tau (\lambda_{Y,i}(\eta) - \mu_{Y,i}(\eta)) \, d\eta \right] d\tau$, where $b_i(t) = M_i \exp \left[ \int_0^t (\lambda_{X,i}(\tau) - \mu_{X,i}(\tau)) \, d\tau \right] \lambda_{X,i}(t)u$. Lastly, the probability of resistance
in compartment $i$ is $\mathbb{P}[Y_i(t) > 0] = 1 - \exp \left[ \int_0^t \left( 1 - P^\text{ext}_i(T, t) \right) dT \right]$, where $P^\text{ext}_i(T, t) = \frac{\int_{0}^{t} \mu_{Y,i}(\tau + T) \omega_i(\tau, T) d\tau}{1 + \int_{0}^{t} \mu_{Y,i}(\tau + T) \omega_i(\tau, T) d\tau}$ and $\omega_i(\tau, T) = \exp \left[ \int_0^\tau \left( \lambda_{Y,i}(\eta + T) - \lambda_{Y,i}(\eta + T) \right) d\eta \right]$. Detailed derivations of these equations are outlined in [9].

As previously stated, the birth and death rates of sensitive and resistant cells in compartment $i$ depend on both the oxygen concentration in compartment $i$ and the concentrations of erlotinib and evofosfamide, which vary over time, depending on dosing schedule. To estimate the temporal effects of these drugs on the growth kinetics in each compartment, we use (i) experimentally derived birth and death rates under a spectrum of environmental perturbations of oxygen and erlotinib concentration, (ii) experimental results on cell viability in response to evofosfamide therapy, and (iii) pharmacokinetic data mapping erlotinib and evofosfamide dose to plasma concentration. For a detailed description of how this model is parameterized, see [7].

3 RESULTS AND CONCLUSIONS

In [7], we used the model to examine the evolutionary dynamics of a tumor undergoing a wide variety of therapies with erlotinib and evofosfamide, and found that the dosing schedules with the highest potential to minimize probability of resistance and tumor burden are those that alternate sequentially between erlotinib and evofosfamide. Here we investigate the possibility of further improving treatment outcomes during combination therapy with these drugs by altering tumor oxygenation levels.

We predict the evolutionary dynamics of three different tumors (one well-oxygenated, one poorly-oxygenated, and one whose oxygen profile mirrors standard tumor physiologic data) undergoing therapy with two separate combination dosing regimens. For each of these tumors and each of the two therapies, the predicted mean tumor size and probability of resistance up to recurrence time (the time at which the cancer cell population reaches its initial size once again) are plotted in Figure 2. The blue curves show the evolutionary dynamics of a tumor with a 13.16% oxygen concentration at the blood vessels, which matches tumor physiologic data [8]. The red curves show the dynamics of a more well-oxygenated tumor (26.32% at the blood vessels) and the yellow curves show the dynamics of a more poorly-oxygenated tumor (6.58% at the blood vessels). Predictions for a dosing schedule in which the patient is given 150 mg erlotinib daily on the first 5 days of each week and 575 mg/m$^2$ evofosfamide on the last day of each week are shown in Figures 2A and B. Predictions for a dosing schedule in which the patient receives one dose of 150 mg erlotinib and one dose of 248 mg/m$^2$ evofosfamide in every 36-hour period (the optimal dosing schedule identified in [7]) are shown in Figures 2C and D.

These results suggest that treatment with a combination of erlotinib and evofosfamide may be more effective on poorly-oxygenated tumors and less effective on well-oxygenated tumors. Although we observe a benefit to poorly-oxygenated tumors during therapy with each drug since cellular growth rates are reduced as oxygen levels are lowered, changes in tumor oxygenation play a larger role in response to evofosfamide than to erlotinib. This is because evofosfamide is hypoxia-activated, and hence more effective at lower oxygen concentrations. Thus tumor oxygenation differences lead to a more dramatic difference in response during the dosing schedule used in Figure 2C vs. the dosing schedule used in Figure 2A. In light of these observations, we conclude that the optimal treatment strategies proposed in [7] may be improved further by decreasing the oxygen throughout the tumor and maximizing the number of evofosfamide doses.

The addition of this work suggests another approach with the potential to further improve treatment outcomes for patients with NSCLC. In [7], our model predicted that, while the emergence of resistance is inevitable during monotherapy with erlotinib, the addition of evofosfamide may result in tumor eradication for a significant fraction of patients. Here we have shown that this combination strategy may be improved upon even further with the addition of therapy aimed at decreasing tumor oxygenation. Given the correct timing and dosing sequence of erlotinib and evofosfamide, the combination of these two drugs, together with additional therapy to decrease oxygen concentration throughout tumors, may have the potential to significantly improve treatment outcomes for NSCLC patients.
Figure 2: **Comparison of evolutionary dynamics over time for tumors with varying oxygen profiles.** Mean tumor size (A) and probability of resistance (B) are calculated up to recurrence time for a dosing schedule consisting of 150 mg erlotinib daily for days 1–5 and 575 mg/m$^2$ evofosfamide given on day 7 of every week. Mean tumor size (C) and probability of resistance (D) are plotted for a dosing schedule consisting of one dose of 150 mg erlotinib and one dose of 248 mg/m$^2$ evofosfamide given every 36 hours. Results are shown for a tumor with a concentration of 13.16% oxygen at the blood vessels in blue, 26.32% oxygen in red, and 6.58% oxygen in yellow.

**REFERENCES**


A MORAN MODEL FOR COMPETITION AMONG MUTANTS

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SUMMARY

Studying dynamics of mutants is very important because of their crucial role in cancer initiation and progression. In this work, we design a Moran model to investigate the competition among mutants with various fitnsses and resistances in a renewing tissue. We calculate the probability and time that mutants take over the entire tissue or being washed out from the tissue. We observe that some mutants vanish from the tissue before a new mutation occurs. Furthermore, a sub-colon can be removed from the tissue before the appearance of another sub-colon.

Key words: cancer, cell dynamics, stochastic processes, fixation probability of mutants

1 INTRODUCTION

Studying cell dynamics such as cell division and death rates can assist us to determine the origins of several diseases like cancer. Understanding the division patterns of cells in healthy and malignant tissues can also suggest ways of altering the structure of the tissue to minimize the number of mutants and control cells growth rates.

Mathematical models have been developed to investigate cell dynamics in both normal and malignant tissues [1-7]. Many of these models focus on dynamics of mutants, because of their importance in the initiation and progressions of tumors, see e.g. [8-14]. Since cell dynamics are stochastic, some of these studies are using stochastic models such as Moran processes to model cell dynamics [15-20]. In this work, we also develop a Moran model to study the competition among mutants in taking over the entire tissue. We obtain the fixation probability and the time to fixation of each types of mutants with fitness \( r \) and resistance \( d \).

Recently, the probability \( P_R \) of a mutant intestinal stem cell replacing its neighbor for various mutants was empirically obtained [21]. If we assume the fitness of wild-type (w.t.) cells is one, then based on this mouse experiment, the fitness of mutant \( APC^{+/−} \) is \( r = 1.6 \), and the fitness of mutant \( APC^{−/−} \) is \( r = 3.8 \). Surprisingly, the fitness of \( P53^{R172H} \) mutants is \( r = 0.9 \) in the normal colon, while the fitness of the \( P53^{R172H} \) mutant is \( r = 1.4 \) in the inflammatory environment. In other words, when there are \( j \) number of mutants and \( i \) number of w.t. cells competing to divide and fill out the available empty space, with probability \( \frac{r_j}{r_j + 1} \), a mutant cell will divide and fill out the empty space. Here, we consider a range of fitness values for \( r \) such that the mutants can be disadvantageous (\( r < 1 \)), neutral (\( r = 1 \)), or advantageous (\( r > 1 \)) compared to w.t. cells.

2 METHODOLOGY

We develop a stochastic model for a renewing tissue, which consists of various types of mutants. We assume that wild-type cells have relative resistance 1, and mutants have relative resistance \( d \). At each updating time step, one cell is randomly chosen to die based on its relative resistance, and one cell is randomly chosen to divide based on its fitness.

Here, we assume there are two types of mutants \( M_1 \) (with fitness \( r_1 \) and resistance \( d_1 \)) and \( M_2 \) (with fitness \( r_2 \) and resistance \( d_2 \)). The algorithm is: at each updating time step, a cell is randomly chosen to die, and then a cell is randomly chosen to divide. When a death occurs, with probability \( \frac{r_j}{r_j + 1} \), a w.t.
cell dies, or with probability \( \frac{m_1}{d_1D} \), an \( M_1 \) mutant dies, or with probability \( \frac{m_2}{d_2D} \), an \( M_2 \) mutant dies. When a division happens, it is either the division of a w.t. cell with probability \( \frac{w}{R} \), or an \( M_1 \) mutant with probability \( \frac{w}{R} \), or an \( M_2 \) mutant with probability \( \frac{w}{R} \). Where, \( m_1 \) and \( m_2 \) are respectively the number of \( M_1 \) and \( M_2 \) mutants, and \( D = m_1/d_1 + m_2/d_2 + w \) and \( R = w + r_1m_1 + r_2m_2 \).

Then, the transition probabilities are

\[
\begin{align*}
P(m_1, m_2) \rightarrow (m_1 + 1, m_2) &= \frac{w r_1 m_1}{D}, \\
P(m_1, m_2) \rightarrow (m_1, m_2 + 1) &= \frac{w r_2 m_2}{D}, \\
P(m_1, m_2) \rightarrow (m_1 - 1, m_2) &= \frac{m_1}{d_1 D}, \\
P(m_1, m_2) \rightarrow (m_1, m_2 - 1) &= \frac{m_2}{d_2 D}.
\end{align*}
\]

Therefore, the probability \( \phi(m_1, m_2, t) \) of being at the state \((m_1, m_2)\) at time \( t \) satisfies the following equation:

\[
RD \frac{\partial \phi(m_1, m_2, t)}{\partial t} = \frac{m_1 + 1}{d_1} \phi(m_1 + 1, m_2, t) + \frac{m_2 + 1}{d_2} \phi(m_1, m_2 + 1, t) + r_2 (m_2 - 1) \frac{m_1 + 1}{d_1} \phi(m_1 + 1, m_2 - 1, t) + r_1 (m_1 - 1) m_2 + 1) \frac{m_2}{d_2} \phi(m_1 - 1, m_2 + 1, t) - \frac{w [r_1 m_1 + r_2 m_2 + m_1 + m_2]}{d_1} - \frac{m_2}{d_2} \phi(m_1, m_2, t).
\]

Hence, the generating function \( G = \sum_{m_1, m_2} \phi(m_1, m_2, t) x_1^{m_1} x_2^{m_2} \) satisfies the following equation:

\[
\begin{align*}
DR \frac{\partial G}{\partial t} &= \frac{r_1 x_1}{d_1} \frac{\partial G}{\partial x_1} + \frac{r_2 x_2}{d_2} \frac{\partial G}{\partial x_2} \\
&\quad - \frac{(r_1 + \frac{1}{d_1}) x_1 \frac{\partial G}{\partial x_1} + (r_2 + \frac{1}{d_2}) x_2 \frac{\partial G}{\partial x_2}}{} \\
&\quad + \frac{w [r_1 x_1^2 + r_2 x_2^2]}{d_1} + \frac{r_1 x_1^2}{d_2} - \frac{r_2 x_2^2}{d_2} \frac{\partial G}{\partial x_1} \frac{\partial G}{\partial x_2}.
\end{align*}
\]

The fixed points of \( G \) are \((x_1^*, x_2^*) = (1, 1), (x_1^*, x_2^*) = (\frac{1}{r_2}, \frac{1}{r_1})\). Since the system has three steady states (the progeny of either w.t. cells, or \( M_1 \) mutants, or \( M_2 \) mutants taking over the entire tissue), we have

\[
G(x_1, x_2, t \rightarrow \infty) = \phi(0, 0, t \rightarrow \infty) + \phi(N, 0, t \rightarrow \infty) x_1^N + \phi(0, N, t \rightarrow \infty) x_2^N.
\]

Moreover, since \( G(x_1, x_2, 0) = x_1^{m_1^0} x_2^{m_2^0} \) and \((x_1^*, x_2^*)\) are fixed point of \( G \), where \( m_1^0 \) and \( m_2^0 \) are the initial number of \( m_1 \) and \( m_2 \) mutants, we get

\[
x_1^{m_1^0} x_2^{m_2^0} = \phi(0, 0, t \rightarrow \infty) + \phi(N, 0, t \rightarrow \infty) x_1^N + \phi(0, N, t \rightarrow \infty) x_2^N.
\]

Also, \( G(1, 1, t) = 1 \) implies that \( \phi(0, 0, t \rightarrow \infty) + \phi(N, 0, t \rightarrow \infty) + \phi(0, N, t \rightarrow \infty) = 1 \). If the initial number of \( M_1 \) mutants is zero, then the probability that its progeny will take over the tissue is zero. Thus,

\[
x_2^{m_0^0} = \phi(0, 0, t \rightarrow \infty) + \phi(N, 0, t \rightarrow \infty) x_2^N \\
x_1^{m_0^0} = \phi(0, 0, t \rightarrow \infty) + \phi(N, 0, t \rightarrow \infty) x_1^N.
\]

We denote the probability of the progeny of \( M_1 \) mutants taking over the entire tissue when there are \( m_1 \) and \( m_2 \) number of \( M_1 \) and \( M_2 \) mutants at the initial time by \( \pi_{(m_1, m_2)}^{M_1} \). Equations (6) imply that \( \pi_{(m_1^0, 0)}^{M_1} = \frac{1 - \frac{1}{(r_1 x_1^*)^N}}{1 - \left(\frac{1}{(r_1 x_1^*)^N}\right)} \) and \( \pi_{(0, m_2^0)}^{M_2} = \frac{1 - \frac{1}{(r_2 x_2^*)^N}}{1 - \left(\frac{1}{(r_2 x_2^*)^N}\right)} \).
Furthermore, if $m_1^0 + m_2^0 = N$, then $\phi(0, 0, t \to \infty) = 0$, and

$$x_1^* m_1^0 x_2^* N^{-m_1^0} = \phi(N, 0, t \to \infty)x_1^* N + \phi(0, N, t \to \infty)x_2^* N$$

(7)

Hence, $\pi^{M_1}_{(N-m_1^0)} = \frac{1-(r_2 d_2 r_1 d_1)}{1-(r_1 d_1 r_2 d_2)} m_1^0$ and $\pi^{M_2}_{(N-m_2^0)} = \frac{1-(r_1 d_1 r_2 d_2)}{1-(r_2 d_2 r_1 d_1)} m_2^0$.

### 3 RESULTS AND CONCLUSIONS

The derived formulas for fixation probabilities of mutants explain the reason behind observing disappearance of some sub-clones and appearance of new ones over time. If with a very small probability a mutation occurs, then a sub-colon can disappear before a new mutation occurs. These results would also give some insights about the order of mutations in a colon.

For example, assume a tissue includes 50 $APC^{-/-}$ mutants, which have fitness 3.8, and 50 P53 mutants with fitness 0.9. Assume all mutants have the relative resistance 2.

The probability that the progeny of $APC^{-/-}$ mutants will take over the entire tissue is $1 - (0.38 \cdot 50) = 1$. The probability of the progeny of P53 mutants taking over the entire tissue is $1 - (0.09 \cdot 10) = 5.28 e^{-32}$. These results are in perfect agreement with the results of numerical simulations (Fig. 3).

This results indicate that in competition between $APC^{-/-}$ and P53 mutants, $APC^{-/-}$ mutants will win and take over the entire tissue, unless a new advantageous mutation occurs on P53 mutants before they are removed from the tissue.

---

**Figure 1:** Number of mutants over time. This figure shows the number of $APC^{-/-}$ ($M_1$) and P53 ($M_2$) mutants over time. At the initial time of this stochastic numerical simulation, there are 50 $APC^{-/-}$ mutants, which have fitness 3.8, and 50 P53 mutants with fitness 0.9.

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Mathematical Models of Asymmetric Damage Segregation in Stem Cell Aging

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SUMMARY

In this research, we propose a novel model to integrate stem cell proliferation and differentiation with physiological changes in aging process. Two-compartmental structured PDEs are used to model stem cells and terminally differentiated cells (TD cells). It is assumed that cell cycle progression is continuous while division is discrete, and asymmetric damage segregation takes place at division. Feedbacks from stem cell niche or TD cells are studied. Aging effect is added through the influence of damage accumulation on stem cell proliferation, differentiation and death. Analysis and numerical simulations are conducted to study steady state populations and benefits of asymmetric division.

Key words: stem cells, feedback regulation, asymmetric damage segregation, aging process, structured population model.

1 INTRODUCTION

Stem cells are characterized by their ability to both self-renew and generate differentiated cells. Available data suggest that most stem cells are able to switch between symmetric and asymmetric divisions, and tissue homeostasis depends on the relative importance of symmetric and asymmetric cell division, cell differentiation, and death \cite{1}. Research suggests that the decline in adult tissue maintenance and the increase in cancer formation might be a consequence of stem cell aging \cite{2}. A level of commonality in stem cell aging across tissues and organisms is implied by decline in regenerative capacity due to depletion or dysfunction of stem cells \cite{3}. Despite chronological aging, “replicative aging”, due to accumulation of cellular damage during cell divisions, is also important for stem cells (Fig. 1A), especially those in tissues with high turnover \cite{4}. Molecular damages such as protein aggregates, dysfunction organelle, and DNA damages are commonly recognized as drivers of age-related stem cell decline. Recent evidence suggests that to slow the accumulation of such damage, daughter cells destined to become a new stem cell asymmetrically inherit less damaged cellular components (Fig. 1B). Yet the detailed mechanisms remain unclear.

Driven by the gap between molecular details and observable phenomena at the tissue level, mathematical models are employed to address key questions and provide quantitative insights into stem cell renewal, differentiation and decline of cellular function in aging process. The current mathematical models focus on two different aspects. In one aspect, multi-compartmental models, in which the cell population is divided into hierarchical subpopulations, are used to describe stem cell renewal and differentiation. Systems of ODEs or PDEs can describe the dynamics of cell population at discrete or continuous maturation stages and transitions coordinated by cell division \cite{5, 6}, for which feedback regulations and conditions for steady state population are studied. In another aspect, a few recent papers consider various mechanisms associated with aging through agent-based computational models. For example, \cite{7} shows that asymmetric segregation shortens the averaged population doubling time and population mean damage levels, and optimize population-level growth and fitness.
In this research, we propose a novel model to integrate stem cell proliferation and differentiation with physiological changes in stem cell aging process. A system of hyperbolic PDEs is used to model two compartments in cell lineage: dividing cells and post-mitotic cells. It is assumed that cell cycle progression of stem cell is a continuous process and stem cell division is a discrete. Stem cell renewal and differentiation are modeled through boundary conditions. Asymmetric damage segregation takes place at division. Cell death is modeled as an outcome of damage accumulation. Feedback regulations from stem cell niche or TD cells on stem cell proliferation, differentiation and damage accumulation are studied. Aging effect can be added to the model through the influence of damage accumulation on stem cell proliferation and differentiation. Replicative aging is modeled by adding discrete age classes. The original model is expanded into a large system consisting of different age classes. Analysis and numerical simulations are carried out to study the steady state population and benefit of asymmetric division.

2 METHODOLOGY

We consider a structured population model and assume that there are two stages in cell lineage: stem cells and TD cells. The population density functions of stem cells and TD cells at time $t$ with state variables cell cycle stage $p$ and damage level $d$ are denoted by $S(t, p, d)$ and $T(t, p, d)$, respectively. The evolution of density functions are described by a system of hyperbolic PDEs and corresponding boundary conditions.

2.1 Model assumptions

- Cell death is controlled by damage accumulation. When damage level $d$ reaches lethal threshold, a cell is removed by an apoptosis-like process. For stem cells, damage accumulation speed $V_d$ may be affected by damage level and may be regulated by short-range signaling secreted by stem cell niche or long-range signaling secreted by TD cells. For TD cells, similar damage accumulation is also considered but its accumulation speed and lethal threshold may be different.

- For stem cells, cell cycle progression $p \in [0, p^\ast]$ is described as a continuous process with speed $V_p$. A stem cell becomes two daughters at the end of a cell cycle when $p$ reaches $p^\ast$. After each cycle, the cell cycle stage is reset to $p = 0$. The speed of cell cycle progression $V_p$ may be regulated by short-range or long-range signaling. For TD cells, $p \in [0, \infty)$, since they do not divide.

- Renewal and differentiation process takes place at cell division. We can describe the regenerative process through boundary conditions at $p = 0$. We assume a stem cell can undergo three types of division: symmetric renewal (SR), symmetric differentiation (SD), and asymmetric division.
renewal and differentiation (ASR) with probability $\delta_1, \delta_2, \delta_3$ and $\delta_1 + \delta_2 + \delta_3 = 1$. Cell fate decision $\delta_i$ may be affected by damage level $d$ and may be regulated by certain signaling.

- When a stem cell with damage level $d$ divides, damages are partitioned between two daughters with three cases: (SR) two stem cells with damage levels $\alpha_1 d$ and $\alpha_2 d$ ($\alpha_1 + \alpha_2 = 1$); (SD) two TD cells with damage levels $\beta_1 d$ and $\beta_2 d$ ($\beta_1 + \beta_2 = 1$); (ASR) one stem cell and one TD cell with damage levels $\gamma_1 d$ and $\gamma_2 d$ ($\gamma_1 + \gamma_2 = 1$).

### 2.2 Main equations and boundary conditions

Based on the above assumptions, the governance equations and boundary conditions are as follows:

\[
\frac{\partial S}{\partial t} + \frac{\partial V_p S}{\partial p} + \frac{\partial V_d S}{\partial d} = 0
\]

(1)

\[
\frac{\partial T}{\partial t} + \frac{\partial U_p T}{\partial p} + \frac{\partial U_d T}{\partial d} = 0
\]

(2)

where $V_p, U_p \geq 0$ are cell cycle progression speeds, and $V_d, U_d \geq 0$ are damage accumulation speeds.

Stem cell renewal and differentiation are described by boundary conditions at $p = 0$:

\[
V_p S(t, 0, d) = \frac{\delta_1}{\alpha_1} V_p S(t, p^*, \frac{d}{\alpha_1}) + \frac{\delta_1}{\alpha_2} V_p S(t, p^*, \frac{d}{\alpha_2}) + \frac{\delta_3}{\gamma_1} V_p S(t, p^*, \frac{d}{\gamma_1})
\]

(3)

\[
U_p T(t, 0, d) = \frac{\delta_2}{\beta_1} V_p S(t, p^*, \frac{d}{\beta_1}) + \frac{\delta_2}{\beta_2} V_p S(t, p^*, \frac{d}{\beta_2}) + \frac{\delta_3}{\gamma_2} V_p S(t, p^*, \frac{d}{\gamma_2})
\]

(4)

At the boundary $d = 0$, we impose no-flux conditions:

\[
S(t, p, 0) = 0, \quad \text{for } t > 0, \quad p \in [0, p^*]
\]

(5)

\[
T(t, p, 0) = 0, \quad \text{for } t > 0, \quad p \in [0, \infty).
\]

(6)

### 2.3 Numerical scheme

For the simulation we use the third-order WENO scheme and the third-order TVD Runge-Kutta time integrator.

## 3 RESULTS AND CONCLUSIONS

- Starting with the simple model with constant $V_p, V_d, U_p, U_d$ and $\delta_i$, we are able to show that (i) when the self-renewal fraction $f_r = \frac{2\delta_1 + \delta_3}{2} < \frac{1}{2}$, stem cell population will extinct; (ii) when $f_r > \frac{1}{2}$, the relative speed of proliferation and damage accumulation, and damage partition
scheme $\alpha_i, \beta_i, \gamma_i$ play an important role in stem cell population evolution. Parameters have to satisfy certain conditions in order to make cell population bounded. The numerical simulations are consistent with analytical analysis.

- Starting with $f_r > \frac{1}{2}$, we consider three kinds of feedbacks on stem cell proliferation $V_p$, cell fate decision $\delta_i$ and damage accumulation process $V_d$ (a few regulations are demonstrated in Fig. 2). Our simulation shows that (i) negative feedback on self-renewal leads to steady populations with $f_r$ converging to $\frac{1}{2}$ (Fig. 2A); (ii) negative feedback on proliferation rate $V_p$ leads to steady populations with $V_p$ converging to 0 (Fig. 2B); (iii) negative feedback on damage accumulation leads to steady population with death balancing with regeneration (Fig. 2C). Combinations of these three feedbacks with carefully chosen parameters are able to produce steady population quickly without oscillation.

- Chronological aging is modeled through negative feedback of damage level on stem cell proliferation and differentiation. Replicative aging is introduced into the model through dividing the population of stem cell into discrete age classes. The benefits of asymmetric damage segregation are studied by measuring population mean damage level and the recovery time to steady state after large loss of TD cells.

REFERENCES

NUMERICAL SIMULATION OF THERMOSENSITIVE LIPOSOME-MEDIATED DELIVERY OF DOXORUBICIN TO SOLID TUMOUR UNDER HIGH INTENSITY FOCUSED ULTRASOUND HEATING

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SUMMARY

Thermo-sensitive liposome (TSL) coupled with high intensity focused ultrasound (HIFU) heating has emerged as a potential solution to overcome the barriers in chemotherapy. In this study, a numerical platform incorporating key drug transport processes has been developed and applied to a 2-D prostate tumour reconstructed from MRI. Results show that HIFU heating with a feedback control mode is able to elevate the tumour temperature rapidly to a level required to trigger drug release, thereby achieving highly localised treatment through increased drug concentration in tumour regions while minimising drug accumulation in normal tissues.

Key words: Drug delivery, High intensity focused ultrasound, Thermo-sensitive liposome, Solid tumour

1 INTRODUCTION

Chemotherapeutic agents are routinely delivered to solid tumour by intravenous administration in clinic. However, the treatment efficacy is strongly limited by the barriers of insufficient drug concentration in tumour interior and serious side effects caused by systemic cytotoxicity. TSL-mediated drug delivery coupled with HIFU heating has demonstrated the potential advantage of this novel drug delivery system for localised treatment while minimising drug concentration in the surrounding normal tissue.

By encapsulating chemotherapeutic drugs in TSL, drug release is triggered upon heating. A series of studies have been carried out to improve TSL stability at body temperature while maximising the release rate at mild hyperthermia [1,2]. Fast temperature elevation can be obtained by laser, microwaves, radiofrequency electric current and HIFU [3]. Ultrasound has been used clinically to apply thermal therapy non-invasively at targets that are unavailable to other heating methods [4], and localised drug release with HIFU heating has been tested in in vivo experiments on rabbits [5, 6]. Given the complex physiological and biochemical processes of heat transfer and drug transport which depend on interactions between drugs and intratumoural environment, mathematical modelling provides an effective method to investigate TSL-mediated drug delivery [3,7].

In the present study, an improved mathematical model coupling bioheat transfer under controlled HIFU heating and drug transport are applied to a 2-D prostate tumour and its surrounding normal tissue reconstructed from MRI to investigate the TSL-mediated drug delivery process. Heat-induced variations in physical and transport properties of drugs, tumour and normal tissue are considered as temporally and spatially dependent. Anticancer efficacy is evaluated in terms of the percentage of survival tumour cells by employing a suitable pharmacodynamics model based on the predicted intracellular drug concentration.
2 METHODOLOGY

2.1 Interstitial fluid flow

The biophysical environment for drug delivery inside a tumour consists of interstitial transport and fluid exchange with blood stream and lymphatic system. Given the dimension of drug transport (i.e. the size of a tumour) is typically several orders of magnitude larger than the inter-capillary distance, tumour and its surrounding normal tissue can be treated as porous media and therefore Darcy’s law can be used to describe the interstitial fluid flow.

2.2 Drug transport

After systemic administration, chemotherapeutic agents experience a number of processes, including convection in the blood stream, permeation through the blood vessel wall into tumour extracellular space, convection and diffusion within the interstitium and cell uptake. Bioavailable drugs may also bind with proteins and be cleaned up by the lymphatic system. These processes can be described by convection-diffusion-reaction equations with respect to drug concentration in different tumour compartments.

2.3 HIFU heating

The temperature of tumour can be raised by the application of HIFU. However, the temperature difference between tumour tissue and blood may result in heat exchange. Blood flows in and out of the ultrasound focus region can further cool down the tumour. Therefore, a heat transfer model is required in order to predict tumour temperature variations during TSL-HIFU treatment.

2.4 Pharmacodynamics

Bioavailable doxorubicin inside tumour cells may interrupt the DNA duplication and thereby kill the cells. An experiment-based pharmacodynamics model is utilised to predict the real-time cell density accounting for drug cytotoxicity, cell proliferation and physical degradation.

3 RESULTS AND CONCLUSIONS

The maximum temperature in the modelled tumour can be raised rapidly to the target value of 42°C, which can be maintained by the feedback control system. This is followed by a graduate fall after the end of heating until the temperature returns to 37°C in 20 minutes. Continuous blood perfusion keeps removing heat from the HIFU-focal regions and results in lower temperature in blood.

Fig 1. Maximum temperature as a function of time under HIFU heating.
The spatial distributions of both TSL-encapsulated and free doxorubicin are highly heterogeneous, with enhanced drug accumulation and cell killing in the HIFU focus region to achieve localised treatment.

![Image](image.png)

Fig 2. Spatial distributions of doxorubicin concentration (left) and cell survival fraction (right) in tumour.

Simulation results demonstrate the advantage of TSL-mediated drug delivery in achieving localised treatment against tumour. The mathematical model established in this study can be used to assist the design and optimisation of treatment regimens.

REFERENCES

A CANCER CELL MOBILE FORAGING STRATEGY IN THE “CANCER SWAMP” PROMOTES THE LETHAL METASTATIC PHENOTYPE

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SUMMARY

Prostate cancer is the second leading cause of cancer-related death in men and is responsible for approximately 28,000 deaths annually in the United States. Despite decades of research, the process by which cancer cells leave the primary tumor to form a distant lethal metastasis remains unknown. Novel paradigms to understand this process are necessary to understand the biology of metastasis and to develop new treatment strategies. We describe a novel ecological framework to study lethal metastatic disease: an autoeutrophic “cancer swamp” that gives rises to metastatic clones whose behavior can be studied through the application of optimal foraging theory.

Key words: metastasis, foraging, prostate cancer, ecology

1 INTRODUCTION

Prostate cancer is the most commonly diagnosed cancer in men with approximately 220,000 new cases diagnosed in the United States each year. Advances in the treatment of localized disease have improved five-year survival to near 100%, but metastatic disease remains incurable [1].

Clinical metastasis is the ultimate result of a cancer cell that escapes the primary tumor, travels through the vasculature, and eventually invades a secondary site as a disseminated tumor cell. While the processes that define the steps of the metastatic cascade have been the focus of the cancer research community for decades, the functional phenotype and environmental pressures that generate these rare lethal cells of the primary tumor that initially seed a metastasis remain unknown.

The majority of modern metastasis research is based on Stephen Paget’s 1889 “seed and soil” hypothesis, which states that metastatic cancer cell “seeds” must fall on congenial target organ “soil” [2]. Most work continues to elucidate the compatibility between a metastatic cancer cell and the metastatic site, but the implications of the primary tumor “soil” on the pre-metastatic “seed” have been largely neglected.

Over the last decade, it has been suggested that metastatic disease is best understood by combining the ecological concepts of individual adaptation (cancer cell) in response to the selective pressures of the environment (primary tumor microenvironment). Applying principles of evolutionary ecology, including ecosystem destruction and optimal foraging theory, provide a greater understanding of the functional phenotype of the lethal metastatic cells.

2 METHODOLOGY
2.1 Application of ecological theory to cancer biology
As described in the INTRODUCTION, metastasis biology has striking parallels to ecology. We identified aspects of cancer biology and cell biology that could be placed within an ecological framework, including ecosystem disruption, movement ecology, and optimal foraging theory. Specifically, we defined cancer terms within a set ecological vocabulary (Table 1).

This denoted application of ecology to our cancer biology questions gave rise to specific cancer ecology models: autoeutropication of the cancer swamp [3], the movement ecology of lethal metastatic cells [4], and optimal foraging of cancer cells [5]. Finally, we applied restoration ecology principles to reclassify current and propose novel therapeutic strategies for the treatment of metastatic disease [3].

2.2 Prostate cancer cell culture

2.2.1 Induction of epithelial-to-mesenchymal transition
As previously described [6], human prostate cancer cell line PC3 cells were cultured in the presence of pro-tumor M2-macrophage conditioned media for 3 days. The co-culture resulted in highly-motile mesenchymal-like cells.

2.2.2 FACS analysis
Using standard protocols, PC3 cells were stained with a fluorescently tagged IFNg-receptor antibody. Number of positively-stained cells were measured by FACS (S3e Cell Sorter, BioRad) and analyzed by FloJo.

2.2.2. Measurement of cell migration in response to presence of cytotoxic T-cells
Human prostate cancer cell line PC3 cells were stimulated with conditioned media from human CD8+ cytotoxic T-cells. Using time-lapse photography (photograph every 2 minutes for 6 hours, Evos microscope) and subsequent cell-tracking (ImageJ), total PC3 cell movement was assessed.

3 RESULTS AND CONCLUSIONS

3.1 Establishment of an ecological framework to metastasis biology

Table 1. Terms of cancer ecology

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Species</td>
<td>a group of individuals with a shared lineage and similar functional traits</td>
<td>Cancer cells, T-cells, macrophages, fibroblasts</td>
</tr>
<tr>
<td>Predator</td>
<td>an individual that attacks and kills another individual</td>
<td>Cytotoxic T-cell, M1 macrophage</td>
</tr>
<tr>
<td>Ecosystem</td>
<td>All the species and abiotic environment that form a self-regulating unit</td>
<td>Tumor, organ system</td>
</tr>
<tr>
<td>Resource</td>
<td>Depletable factor essential for survival, movement, or proliferation</td>
<td>Sugar, oxygen, lipids</td>
</tr>
<tr>
<td>Foraging</td>
<td>The search for and consumption of resources in a habitat</td>
<td>Cancer cell &gt; oxygen</td>
</tr>
<tr>
<td>Biosphere</td>
<td>All of the ecosystems of a system (e.g. earth)</td>
<td>Patient</td>
</tr>
</tbody>
</table>

In order to apply an ecological paradigm to cancer biology and cell biology, we first established a set vocabulary to describe cell biologic and tumor biologic terms in an ecological context. Many established aspects of cancer biology have striking parallels to ecology (Table 1).

3.2 Optimal foraging of metastatic cancer cells

In order to survive, any living individual must acquire resources to fulfill the basic metabolic needs of life. In order to find these resources, organisms forage using various strategies (e.g. stationary or mobile) that are dependent on a balance among an individual’s phenotypic abilities, reward of resource gain, and risk from predation (Figure 1). Optimal foraging theory (OFT) describes the foraging strategy for an individual that provides maximal resources at minimal cost.

A mobile foraging strategy wherein foraging is optimized by moving among resource patches, abandoning a patch as it becomes resource-poor and going in search of a resource-abundant patch. It is likely that cancer cells that adopt a mobile foraging strategy are more likely to be successful...
metastatic clones as they will have adapted to gain other pro-
metastatic characteristics: ability to move, to invade through
local tissue, to evade predation, and survive in the circulation.
Applying OFT to cells in the primary “cancer swamp” will
allow us to identify, predict, and, eventually, modulate, the
environmental pressures that give rise to the rare lethal
metastatic cells [5].

3.2.1 Autoeutrophication of the “cancer swamp” results in altered resource availability
Long before clinical detection, a 1mm³ tumor has already overwhelmed the host vasculature,
resulting in local nutrient exhaustion and accumulation of cellular and metabolic waste. Rapid cell
proliferation leads to exhaustion of the local energy sources, including oxygen, glucose, and other
essential nutrients, and overwhelms the local host feedback systems, resulting in a hypoxic, acidic,
and nutrient-poor “cancer swamp” [3].

This process of ecosystem-overloading is a common phenomenon in ecology, evident in the
eutrophic ecosystems of watersheds that result in algal blooms and red tides. An important
distinction in our cancer model is that the “cancer swamp” of a tumor is autoeutrophic: it is self-
initiating and self-maintaining by the cancer cells themselves [3]. As the growing tumor changes
the ordered native ecosystem into a disordered malignant microenvironment, it simultaneously
creates a habitat that exerts selective pressure leading to profound phenotype transformations in
future generations of cancer cells born into the environment. Natural selection ensues and selected
cancer cells survive to continue the process locally or through a diaspora to a secondary site.

3.2.2 Functional phenotypic ability for movement
Cancer cells use a variety of foraging strategies in the primary tumor “cancer swamp.” The
movement ability of an individual is a determinant of its foraging strategy. Carcinomas arise from
highly proliferative epithelial cells that have low movement capacity, defining them as obligate
stationary foragers. In contrast, the rare subset of cells that have undergone an epithelial-to-
mesenchymal transition acquire the option for a mobile foraging strategy, including the ability for
rapid locomotion and ability to evade predation. These characteristics likely increase the metastatic
potential of these rare cells.

As is common in all rapidly disordered ecosystems, the “cancer
swamp” is subject to secondary invasion by non-native species,
including invaded by pro-tumorigenic and pro-metastatic host cells,
including tumor-promoting M2-macrophages. The secretome of M2-
macrophages has the capacity to induce an epithelial-to-mesenchymal
transition (EMT). Notably, many other modes of induction of EMT
have been described, including acidic pH and hypoxia, both present in
the “cancer swamp.” Cells that undergo an M2-macrophage-mediated EMT gain a critical
functional phenotype for a movement-based foraging strategy: movement.

3.2.3 Predation risk alters foraging strategy
In order to optimize foraging, an organism must reduce predation risk, either through camouflage
or evasion. From a cancer cell perspective, predators include anti-tumor CD8+ cytotoxic T-cells.
OFT predicts that a cell that may have otherwise adopted a stationary foraging strategy due to high
resource availability may alter strategies to evade the risk, and potentially
dead, from the predator. Evading predation risk through movement has two
requirements: 1) ability to detect the predator and 2) ability to move in
response to the stimulus.

CD8+ cytotoxic T-cells secrete high levels of IFNg. First, using standard
FACS analysis we found that the human PC3 prostate cancer cell line
expressed IFNg receptor, thus they had the capacity to detect the presence
of the predator cells. Next, to determine if cells would alter their foraging
strategy in the presence of “predation risk stimulus,” we stimulated PC3
cells with human donor CD8+ cytotoxic T-cell conditioned media. We

![Figure 2. M2-induced EMT](image)

![Figure 3. PC3 cell movement in response to CD8+ cond. media](image)
found that the stimulated PC3 cells exhibited significantly increased movement compared to control. This data suggests that, consistent with what is observed in an ecological setting, that cancer cells alter their foraging strategy based on predation risk.

REFERENCES


Standard Session V
THE TRANSLOCATION OF NICOTINE FROM HUMAN LUNG TO SYSTEMIC REGIONS DUE TO E-CIGARETTE AEROSOL INHALATION: A NUMERICAL STUDY

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SUMMARY

In this study, an experimentally validated Physiologically Based Pharmacokinetic (PBPK) model is developed to predict the translocation of nicotine in the whole human body after the deposition in the respiratory system due to the consumption of electronic cigarette (EC). Parametric analyses are performed to evaluate the health risks of direct EC aerosol inhalation with different puffing behaviors, and the use of different EC products and conventional cigarettes. Our numerical results indicate that the model can predict the profile of nicotine concentrations at multiple organs. This PBPK model paves the way to a multiscale model which will be a noninvasive tool for the chronic health risk assessment of human exposure to EC aerosols.

Keywords: Nicotine; Electronic Cigarette; PBPK; Parametric Analyses

1 INTRODUCTION

In the past decade, electronic cigarette (EC) products have been invented and claimed to be the “healthier” substitutes to conventional cigarettes. Instead of combustion, EC use heating coils to vaporize the liquid solution (i.e., e-liquids), which contains nicotine, propylene glycol (PG), glycerol, flavor additives, and impurities such as cotinine [1]. Due to the high number of e-liquid formulations and different puffing behaviors of EC users, it is necessary to systematically study the relationship between intake and uptake of nicotine and other EC aerosol components, which pave the way for a generalized health risk assessment tool.

There is a huge body of experimental research to evaluate the health risks of different EC toxicants. Although Physiologically based pharmacokinetic (PBPK) models have been employed on different numerical studies, researches are few to focus on the systemic translocation of EC components. Furthermore, a multiscale Computational Fluid-Particle Dynamics (CFPD)-PBPK model will lead to a non-invasive model, which has the capability of predicting the chronic effect of using ECs. Thus, in this study, we developed a whole-body PBPK model with the assumption of flow-limited compartments.

2 METHODOLOGY

The PBPK models developed for inhaled carcinogens has been carried out by taking the toxicant’s distribution through blood flow with the biological structure of tissues which are considered as homogeneously rate-limited diffusion [2]. Also, liver and kidney are both considered as metabolize sites.

2.1 Governing Equations

The physicochemical properties of toxicants must be determined before the final decision can be made about the dominant diffusion sites in each compartment. Specifically, the diffusion can be blood-limited or tissue-limited. Because of the lipophilic (hydrophilic) characteristics of nicotine, flow-limited diffusions are dominant through all the compartments [3]. Furthermore, the division of compartments depends on the focus and goal of different studies. Since the PBPK model is designed to be combined with the CFPD model, the inputs of the nicotine will be obtained from the lung deposition data. The biological sketch of the compartments being considered in the present PBPK model is shown in Figure 1. In the following equations, subscription T and i represent “tissue” and
“hepatic/renal” respectively. General time-dependent differential equations have been developed for the perfusion-limited tissue model.

\[ V_T \frac{d}{dt} C_T = Q_T \left( C_{T, \text{inlet}} - \frac{C_T}{K_T} \right) - IC_i \frac{C_T}{K_T} \]  

Figure 1. The schematic view of compartments configuration.

For elimination mechanisms, the intrinsic hepatic clearance (IC\textsubscript{H}) and intrinsic renal clearance (IC\textsubscript{R}) are considered for liver and kidney respectively. Apparently, the elimination term is equal to zero for the non-eliminating organs.

For tissues other than the venous pool, arterial pool, and lung, the inlet concentration \( C_{\text{inlet}} \) is equal to arterial pool concentration. Moreover, as the inlet concentration for the venous pool, the average amalgamation of interconnected organs to the venous pool can be calculated as:

\[ C_{\text{inlet}} = \frac{1}{Q_{\text{venous}}} \sum T \left( C_T / K_T \right) \]  

where \( Q_{\text{venous}} \) is the cardiac output which represents total blood circulation flow rate, which is identical for venous, arterial, and lung. For the liver, the same procedure as venous inlet can used by combining gastrointestinal tract and arterial pool.

In this study, The only inputs of nicotine is by EC aerosol inhalation and the induced deposition in human respiratory systems. Other irregular routes of action have been neglected, e.g., skin contact. Assuming the equilibrium always holds between inhaled air and pulmonary blood concentrations at the alveolar site, the blood-air partition coefficient can be introduced as [4]:

\[ \beta = \frac{C_{\text{inhaler}}}{C_{\text{alveolar}}} \]  

The mass balance around the combining sections of alveolar and lung will be:

\[ \dot{Q}_{\text{alveolar}} (C_{\text{inhaler}} - C_{\text{alveolar}}) = \dot{Q}_{\text{venous}} (C_{\text{arterial}} - C_{\text{venous}}) \]  

Based on Eqs. (3) & (4), \( C_{\text{arterial}} \) can be expressed as:

\[ C_{\text{arterial}} = \frac{\dot{Q}_{\text{alveolar}} C_{\text{inhaler}} + \dot{Q}_{\text{venous}} C_{\text{venous}}}{\dot{Q}_{\text{venous}} \beta} \]  

where \( C_{\text{inhaler}} \) is the deposition concentration of nicotine due to the consumption of EC.

### 2.2 Boundary Conditions

In this study, the experimental data presented for tobacco cigarette by [5, 6] was used for model validation. Two set of boundary conditions of nicotine infusion have been employed, i.e., 40 µg/min for 30 minutes and 95 µg/min for 2 minutes. For EC consumption presented by [7], simulations were also performed and compared. Specifically, EC liquid with 3.87 ng/ml nicotine has been used by ten heavy smokers for 90 minutes, who was abstained from smoking 6 hours before the clinical test.

Advanced puffing behaviors can be modeled using respiratory system CF-PD model which can be coupled with the PBPK model to simulate EC aerosol transport and deposition in subject-specific human respiratory systems to obtain more accurate deposition data.

### 2.3 Parameter Values

The accuracy of a PBPK model relies on the selection of parameters for compartments including tissue volume, flow rate, blood-tissue partition coefficient, renal and hepatic intrinsic
clearance, blood-air partition coefficient, and alveolar flow rate at rest. Parameter values used in this study are listed in Table 1 [3,4].

Table 1. Physiochemical parameters of nicotine and tissues

<table>
<thead>
<tr>
<th>Compartment Name</th>
<th>Volume (L)</th>
<th>Blood Flow (L/min)</th>
<th>Blood-Tissue PC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial Pool</td>
<td>1.4</td>
<td>6.1</td>
<td>1</td>
</tr>
<tr>
<td>Venous Pool</td>
<td>4</td>
<td>6.1</td>
<td>1</td>
</tr>
<tr>
<td>Muscle Group</td>
<td>34.4</td>
<td>1.65</td>
<td>2.5</td>
</tr>
<tr>
<td>Fat Group</td>
<td>10</td>
<td>0.3</td>
<td>1</td>
</tr>
<tr>
<td>Vessel-reach Group</td>
<td>1.55</td>
<td>1.35</td>
<td>3</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>2.4</td>
<td>1.25</td>
<td>2</td>
</tr>
<tr>
<td>Liver</td>
<td>1.5</td>
<td>0.3</td>
<td>9</td>
</tr>
<tr>
<td>Kidney</td>
<td>0.3</td>
<td>1.25</td>
<td>15</td>
</tr>
<tr>
<td>Liver Hepatic Clearance</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney Renal Clearance</td>
<td>0.17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>0.6</td>
<td>6.1</td>
<td>2</td>
</tr>
<tr>
<td>Blood-Air PC</td>
<td></td>
<td></td>
<td>52</td>
</tr>
</tbody>
</table>

3 NUMERICAL SETUP

The set of ODEs in the model has been solved using 4th order Runge–Kutta method. The time step size is 0.01 second. The initial value was considered zero for all compartments before the period of smoking and after that, the C\textsubscript{inhaled} was set to zero and the new initial value settings calculated from the end of smoke intake period has been modeled.

4 MODEL VALIDATIONS

The results of the PBPK model for plasma concentration versus total volume are compared and presented in Figure 2. Figures 2 (a) and (b) show the comparisons that have been carried out by defining the experimental result and the model developed by [3] at two initial conditions for a conventional cigarette. As mentioned, the optimization of two clearance values around possible ranges was the pre-setup of Robinson et al. model and the cotinine concentration has also been considered. Besides, in their model a venous infusion compartment (VIC) was added to the system to control the chemical administration and reduce the overestimation of venous concentration resulted from the unsaturated distribution of nicotine. It worths mentioning that CFPD model and mass balance over the arterial-alveolar joint is beneficial because it can predict more reliable results of the system without adding an extra compartment to the system.

Figure 2 (c) shows the comparison between our numerical simulation results using PBPK model and the data of an EC consumption study [7]. The experimental data are average nicotine concentrations of the ten smokers. Good agreement can be observed between the two studies.

![Figure 2. (a) Tobacco cigarette profile for 2 min infusion of 95 µg/min nicotine, (b) for 30 min infusion of 140 µg/min nicotine, (c)) EC profile for 90 min infusion of 3.87 ng/ml nicotine](image)

RESULTS AND DISCUSSION

Cigarette puffing behaviors cause different toxicants intake profile, which leads to different tissue concentration distribution. The initial nicotine concentration in cigarettes also has impacts on the uptakes in the human body. It was reported that increasing cigarette nicotine yields can lower puffing volume and duration with a slightly lower flow rate [8]. On the other hand, switching to ECs bears a time for smokers to find their behavior in a way that conventional cigarette users tend to increase the puff duration and decrease the puff flow rate after switch to use EC [9].

Puffing behavior differences was discussed and initiated in developed model. Individual experience of smoking can also force a new condition into the system. Besides, individual body type and specification put its influence by having changes in renal and hepatic clearances, organs volume,
and partition coefficient. This can be seen at different sex, gender, age, and condition of the body. As a result, by these changes various errors can occur.

Based on the model, different smoked nicotine brings different concentration profile and removing period of that carcinogen from the human body. Longer puffing period and higher level nicotine intake bear a longer process for the system to be able to remove that chemical completely. It was discussed previously, that smoker’s body nature tend to change in a way to become more effective in removing the carcinogens from the body. It was explained by finding higher renal clearance level at regular smokers [10].

Parametric analyses using different nicotine intake levels based on different puffing behaviors will be performed and added to the current study.

SUMMARY

The PBPK model shows the capability to accurately predict nicotine translocations at different physiological arranged compartments of the human body. The urinary nicotine levels with different nicotine infusion conditions have been studied and validated with existing experimental data. Our preliminary results indicated that the removing section of the concentration profile is with higher change at an instant time after finishing administration period. This can be induced from complete equilibrium of arterial-alveolar joint and adding CF-PD model can be used to correct this error for the future work. To generalize the model for predicting other chemicals, it needs the specific renal and hepatic clearance data for parameter value determinations.

REFERENCES

NANOPARTICLE DEPOSITION IN NASAL CAVITY AIRWAYS AND
THE IMPORTANCE OF A GOOD IMPLEMENTATION OF
BROWNIAN DIFFUSIVITY

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SUMMARY
Nanoparticle deposition in human nasal cavity has great medicine interests, e.g. drug delivery, surgery or polluted air respiration. The complex geometry of nasal cavity and large amount of nanoparticles involved require the use of High Performance Computing (HPC) simulations. When nanometer particles scales are involved, Brownian diffusion becomes essential but its implementation in a distributed memory computational environment is not always straightforward. In this paper we will compare different solutions proposed in the literature and apply our simulations to a real patient benchmark.

Key words: human airways, deposition, Brownian diffusion, random generators.

1 INTRODUCTION
Nanoparticle deposition in human nose cavity can be split in two main challenges: fluid simulation and particle tracking. Flow will be solved using Large Eddy Simulation (LES) which gives the capability to simulate transient regime considering a constant flow rate \( Q = 20L/min \). Particles considered can vary between diameters \( 1nm < d_p < 150nm \). This range of sizes is crucial in the study of aerosol’s drug delivery, and in this scope the Brownian diffusion becomes one of the most important factors when simulating its motion. Two main solutions can be found in the literature when simulating Brownian diffusivity: adding random noise over displacement or consider it as a randomized force. Both solutions need the implementation of a random generator, in order to properly simulate the Brownian motion in a parallel simulation code. In the literature, three main solutions have been proposed[1]: the leapfrog method, sequence splitting or independent sequences.

Pros and cons of different Brownian implementations and parallelization of random generator will be argued and once chosen the most suitable configuration, results will be compared with a real patient benchmark [2].

2 METHODOLOGY
On the one hand, the incompressible Navier-Stokes equations are considered when solving the fluid, based on a stabilized finite element method. The stabilization is based on the Variational MultiScale (VMS) method which is considered as an implicit Large Eddy Simulation method. On the other hand, particle transport is solved by a Lagrangian method [7]. To track particles, the Newton’s 2nd law is solved for each particle, obtaining its acceleration. Next, position and velocity are integrated in time with a semi-implicit Newmark-\( \beta \) integration scheme. As the Newmark-\( \beta \) is a semi-implicit scheme, an inner Newton-Raphson iterator is also applied. Finally, to ensure the convergence, an adaptive time step strategy is applied.

The forces over the particles considered are the drag and Brownian. Lift force is neglected, according to [5], it becomes significant for microparticles but remains small for nanoparticles. Drag is the force the particle experiments because of the fluid. Herein, Ganser’s formula [3] is used. Brownian
diffusivity is the random motion of particles resulting from their collisions with the molecules of the fluid. This diffusivity can be applied as a force, e.g. [4], or a random walk by modifying the position of each particle, e.g. [5]. Both implementations will be compared.

Parallelizing Brownian diffusion means the experiment must ensure uncorrelated and non-overlapped series of random numbers and if possible, producing the same results independently on the number of processors involved. Literature proposes three different solutions: the leapfrog method, sequence splitting and independent sequences.

The leapfrog method ideally generates the same sequence of random numbers for different number of processors. Let $X_i$ be the $i$-th value of a random numbers sequence. For processor $P$ of an $N$ processor machine, generate the sub-sequence $X_P, X_{P+N}, X_{P+2N}, ...$. The potential problems with this method is guaranteeing uncorrelated elements in the sequence, which is more usual when the number of physical processors is power of 2.

Sequence splitting splits the sequence into non-overlapping contiguous sections, each generated by a different processor. The length of the sections $L$ depends on the user, then processor $P$ would generate the sequence $X_{PL}, X_{PL+1}, X_{PL+2}, ...$. This method can find out the same correlation problems than the method before, and it does not produce the same sequence for different numbers of processors.

Finally, independent sequences consists in running the same sequential generator on each processor but with different initial seeds. The initialization of the seed on each processor is critical. Any correlation within the seeds could have dire consequences. Many default random generators use the CPU time as the seed, which is not suitable in parallel codes. If different processors call the seed at the same time, they will generate the same sequence. Even if initial seed is correctly randomized, there exist no guarantee that sequences will not overlap.

As far as any of the aforesaid methods has its own limitations, anyone can be equally used. The two first methods in a unbalanced environment with a variable number of particles in different processors can make this generators more expensive than necessary. So in our case, for its simplicity, independent sequences method with a seed combining the time and CPU rank will be the chosen option.

Two experiments will be carried out. The first one will compare the results obtained by applying Brownian diffusion applied to the displacement or to the force. In the second one, a healthy patient, 53-year-old, non-smoking male geometry from magnetic resonance imaging (MRI) scans is studied. This set of MRI results were also used in several previous studies as a benchmark [2].

For the second experiment, an unstructured mesh was employed, due to the complex shape of the computational domain. In addition a five prism boundary-layer was generated near the wall surface, as shown in Figure 1.

![Figure 1: Unstructured mesh of the human nasal cavity: a) View of 3D mesh, b) view of mesh resolution in selected slice and c) detail of the zoom with prism layers.](image)

### 3 RESULTS AND CONCLUSIONS

In order to ensure a good behavior of the parallelized Brownian diffusion, a mathematical experiment is considered. Assuming that $N$ particles start from the origin at the initial time $t = 0$, the diffusion equation has the solution given by equation 1, where $x$, $t$ and $D$ mean the position of the particle, time and diffusivity coefficient.

$$
\rho(x, t) = 1 - e^{-\frac{x^2}{4Dt}}
$$

(1)
Different time steps $\delta t$ are chosen in the interval $10^{-6} \leq \delta t \leq 5 \cdot 10^{-4}$. Each experiment with same time interval is repeated 10 times to minimize the random factor and the mean relative error $\langle e_r \rangle$ is calculated comparing the experiment result with the theoretical one. Results are shown in Figure 2. Applying Brownian motion as a force or as a displacement gives similar results for small time steps $\delta t < 5 \cdot 10^{-5}$. In this case, applying the diffusion over the displacement obtains even more accurate results, but simultaneously, this method also starts to diverge sooner, whereas applying it over force keeps working fine when $\delta t < 3 \cdot 10^{-4}$. It must be noticed that the error using the force could not be calculated with $\delta t = 5 \cdot 10^{-3}$, because the Newmark-$\beta$ was not able to converge. It means, Brownian force can affect the stability of the integration scheme. According to this, the next experiment will be done using a $\delta t = 10^{-5} s$ applying the diffusion over the displacement.

Figure 2: Comparison of the error in Brownian dissipation with different time steps between force and displacement.

The real patient simulation considers a transient and unsteady airflow. A time window of $0.02 s$ is chosen to compute the mean flow and the turbulence measures. This time window was taken as sufficiently long due to the fine temporal resolution available and short-scale transients.

Figure 3: Pressure distribution in the human nasal cavity wall when inhalation flow rate is $20 L/min$.

Figure 4: Velocity fields in human nasal cavity at a constant inlet flow rate of $20 L/min$. Mean velocity contours in five selected slices, see Figure 3.

Physiologically, the airflow through the respiratory system is driven by the pressure drop. Figure 3 presents the static pressure drop with Pressure distribution in the human nasal cavity wall when...
inhalation flow rate is $20\text{L/min}$.

![Deposition Efficiency vs Particle Size](image)

Figure 5: (a) Model validation of nanoparticle transport and deposition in a human nasal cavity. (b) Nanoparticle deposition in a human nasal cavity.

When the airflow is considered transient and unsteady, the mean velocity provides an overview of the dominant persistent flow features. Figure 4 shows the mean velocity in five different cross sections of the airway, see the location in figure 3.

Nanoparticle deposition on the ideal wall condition, i.e. perfectly absorbing wall, are presented. Particles with in effective diameter range $1\text{nm} < d_p < 150\text{nm}$ are compared to the experimental data reported by [6] and numerical result produced [2]. The result is plotted in Figure 5 (a). We can observe good agreement with the results from the literature.

In addition, accurate particle tracking and deposition of nanoparticles give information of the precise location of deposition through the nasal cavity, Figure 5 (b).

4 CONCLUSION

Brownian diffusion in distributed memory computation requires a parallel random generator. We presented three options and chose the independent sequences method for its simplicity (CPU time must not be the seed). Next, we tested if diffusion had to be applied over force or over displacement. We showed applying it over displacement using about $\delta t \sim 10^{-5}$ can be the optimum configuration. Finally, we simulated a real patient benchmark obtaining very similar results to the experimental ones and better than previous numerical simulations.

REFERENCES


PREDICTION OF INTER-SUBJECT VARIABILITY OF AIRFLOW DISTRIBUTION IN THE CONDUCTING HUMAN AIRWAYS

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SUMMARY

Little is known about the variability in conducting airway airflow characteristics in healthy subjects. To shed light on the influence of airway morphometric variability on air distribution, we performed physiologically-based computational simulations in three geometries created from CT images of healthy female adults. Computational simulations are performed by coupling the image-based airway geometry to distal airway mechanics, where airflow is driven by a pressure differential.

Key words: respiratory, inhalation and exhalation, airway resistance

1 INTRODUCTION

Recent advances in computational frameworks, which enable creation of image-based airway geometries and simulation of physiologically-based flows provide detailed insight into patient-specific ventilation distribution. While significant focus has been geared towards understanding the influence of geometry and respiration parameters on the flow field characteristics in either idealized or subject-specific geometry, little attention has been directed towards understanding differences between subjects. Therefore, in an attempt to shed light on the correlation of airway morphometric variability on airflow characteristics, we performed physiologically-based computational simulations in three geometries created from CT images of adults.

Unsteady airflow simulations are performed in three subject-specific pulmonary airway geometries to predict variability in ventilation and airway resistance across subjects of similar age. Creation of the airway geometries and performance of airflow simulations are completed with our previously-developed frameworks [5, 6]. Conducting airway geometric models of the three subjects are constructed from clinically-obtained thoracic CT images. Spanning from the trachea to the most distal conducting airways distinguishable on the images, 3D conducting airway geometries of each subject are created manually with the open source software, SimVascular [7]. All three subjects are female and their ages, at the time of the CT scan, are 25.8, 35.7, and 37.2 for subjects 1, 2, and 3 respectively.

2 METHODOLOGY

Unsteady airflow simulations: airflow throughout the respiration cycle is calculated by solving the Navier-Stokes equations with physiologically realistic boundary conditions, assuming that the air is
incompressible (fluid density: $\rho_f = 1.2E - 6g - mm^{-3}$), Newtonian (viscosity: $\mu = 1.81E - 5g - (mm - s)^{-1}$), and that the walls are rigid:

$$\frac{\partial \mathbf{u}}{\partial t} + [\mathbf{u} \cdot \nabla] \mathbf{u} = -\frac{1}{\rho_f} \nabla p + \frac{\mu}{\rho_f} \nabla^2 \mathbf{u}$$  \hspace{1cm} (1)

$$\nabla \cdot \mathbf{u} = 0, \hspace{1cm} (2)$$

where $\mathbf{u}$ and $p$ are the fluid velocity and pressure, respectively. Airflow is driven by a pressure differential between the terminal airways ($\Gamma_{i,j}$) and the trachea ($\Gamma_{trachea}$). Assuming negligible pressure drop between the mouth and trachea, we set the pressure equal to atmospheric ($P_{atm} = 0 \text{ cm } H_2O$) at the trachea face. At the airway walls ($\Gamma_{wall}$) a no slip boundary condition is prescribed.

**Peripheral boundary conditions:** Boundary condition descriptions at the distal faces ($\Gamma_{i,j}$) is not straightforward, as the spatial description of the time-dependent flow or pressure cannot be experimentally measured. Thus, it necessary to choose distal boundary conditions carefully, in order to best represent physiological conditions. To mimic the negative, relative to atmosphere, pressure that derives air in and out of the lungs, we choose to represent the lung periphery by a resistor and capacitor connected in series, driven by the time-dependent driving pressure ($P_D$, Figure 1), described by:

$$P_D(t) = R_{global} Q(t) + \frac{V(t)}{C_{global}} - P_{atm}$$  \hspace{1cm} (3)

where $Q(t) = \frac{dV(t)}{dt}$, and $R_{global}$ and $C_{global}$ are the respiratory resistance and compliance, respectively and are estimated based on data collected in anesthetized and paralyzed adults [1]. Assuming a sinusoidal respiration waveform, $V(t)$ is defined as: $V(t) = -\frac{1}{2} TV \cos \left( \frac{2\pi t}{T_B} \right) + TV$, where $T_B$ is the total time for one breath, $\frac{1}{RR}$, and $TV$ is the tidal volume; values were chosen to represent an average healthy adult. The coupling between the 3D and 0D models is completed by passing flow rate ($Q_{\Gamma_{i,j}}$) to the $LPN$ [3].

Pressure at each of the distal faces ($P_{\Gamma_{i,j}}$) are calculated by $P_{\Gamma_{i,j}} = R_{i,j} \frac{V_{\Gamma_{i,j}}}{dt} + C_{i,j} V_{\Gamma_{i,j}} + P_D$, where $V_{\Gamma_{i,j}} = \int_0^t \int_{\Gamma_{i,j}} \mathbf{u} \cdot \mathbf{n} \ ds \ dt'$; $\mathbf{u}$ is the air velocity, calculated by solving the Navier-Stokes equations, and $\mathbf{n}$ is the unit vector normal to the boundary. For each subject, $R_{i,j}$ and $C_{i,j}$ are estimated, assuming proportionality to the subtending lobe volume and terminal airway’s cross-sectional area. Here, we assume that the lobar fractions are 0.25, 0.20, 0.25, 0.09, and 0.21 for the left inferior, left superior, right inferior, right middle, and right superior lobes, respectively [4].

**Numerical Calculation of Airflow:** The incompressible Navier-Stokes equations are solved with a stabilized Galerkin finite element method with a custom linear solver that incorporates a combination
of GMRES and conjugate gradient methods. The second order generalized α-method is employed for the time integration. To avoid flow divergence at Γ_{trachea} and Γ_{i,j}, which may occur when the relationship between pressure and flow is applied as a boundary condition, and thus a velocity profile is not described, we apply a backflow stabilization framework with β = 0.1 [2].

3 RESULTS AND DISCUSSION

Airway geometries, with the five lobes outlined, are shown in Figure 1. Tracheal diameter is smallest in subject 1 and largest in subject 2. The trachea and main bronchi are more elliptical in subjects 2 and 3 than in subject 1, with the greatest ellipticity seen in subject 3. Subject 2’s left main bronchi’s cross-sectional area reduces at a greater rate between the main carina and the bifurcation leading to the left inferior and superior lobes, compared to the other two models.

The global resistance and compliance are estimated as 
\[ R_{\text{global}} = 0.007 \frac{\text{cmH}_2\text{O}}{\text{s} \cdot \text{ml}} \] and 
\[ C_{\text{global}} = 59 \frac{\text{ml}}{\text{cmH}_2\text{O}} \] and the tidal volume is set to 500 ml and the respiratory rate to 0.25 [1] s. Distal pressure, calculated from Eqn. 3 and applied as the boundary condition, is shown in Figure 2A. As the same lobar fractions are applied for each subject, the time dependent lobar flow rate and volume is the same between subjects and thus a representative simulation result is shown in Figure 2B and C. The absolute average pressure at \( \Gamma_{i,j} \) (calculated over all airways within a given lobe) is higher during inspiration, than expiration, for all subjects. For subjects 1 and 2, the greatest pressure drop was seen for the two bottom lobes (left and right inferior, Figure 2D and E).

Airflow velocity magnitudes, plotted on slices through the center of each model, are shown in Figure 3. In general, flow velocities are largest near the inner bifurcations for each of the three models during inspiration. Relative to the trachea diameter, the diameter of the left main bronchi is smaller in subjects 1 and 2 than in subject 3, resulting in higher flow speeds in the left bronchi than found in the right bronchi. Peak velocity magnitudes are found at the reduced cross-sectional area directly before the bifurcation leading to the two left lobes of subject 2 (Figure 3C).

As the air travels in the opposite direction during exhalation (from the distal airways to the trachea), flow patterns are characteristically different between expiration and inspiration (Figure 3). Air originating from two daughter branches, merges together in the parent branch, causing regions of high near wall shear stress just proximal to the bifurcation zones (data not shown).

Surface pressure for the three subjects at time of maximum flow rates at inhalation and exhalation is shown in Figure 4. In these conducting airways, pressure drops are relatively small, and it is expected that the majority of the pressure drop is located in the compliant regions of the lung. The maximum resistance in the 3D geometry is 0.09, 0.10, and 0.11 \( \frac{\text{cmH}_2\text{O}}{\text{ml} \cdot \text{s}} \) and the average is 0.07, 0.04, and 0.05 \( \frac{\text{cmH}_2\text{O}}{\text{ml} \cdot \text{s}} \) for subjects 1, 2, and 3, respectively.

4 CONCLUSION
By coupling distal respiratory mechanics to 3D image-based conducting airways of healthy adults, we are able to predict variations in airflow and pressure distribution and airway resistance across three female subjects of similar age. Geometric differences, including the level of airway ellipticity and cross-sectional area, dictate differences between subjects on the location of maximum flow velocity magnitudes. However, airway resistances did not vary significantly between subjects. Future studies shall focus on coupling experimentally derived ventilation, for example those collected with MRI, to incorporate subject-specific distal ventilation. In addition, investigating the relationship between the airflows and particle deposition hotspots is of interest for future work.

Acknowledgments: We would like to thank Dr. Jeff Feinstein for providing us with the thoracic CT images and the Information Technology Services, Research Computing at Northeastern University for providing high performance computing and storage.

REFERENCES


SOLVING THE CHEMICAL MASTER EQUATION WITH THE FINITE STATE PROJECTION AND INEXACT UNIFORMIZATION IN QUANTIZED TENSOR TRAIN FORMAT

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SUMMARY
The chemical master equation (CME) arises in biochemical modeling. Solving it directly is difficult due to the curse of dimensionality. We tackle that challenge by a numerical scheme based on the quantized tensor train (QTT) format, which allows us to represent the solution in a compressed form that scales linearly with the number of species/dimensions. We allow the finite state projection to expand adaptively based on proven error criteria, and evaluate the QTT-formatted exponential operator through a combination of the uniformization technique with the alternating minimal energy (AMEn) algorithm.

Key words: chemical master equation, finite state projection, tensor train decomposition, inexact uniformization

1 INTRODUCTION
Stochasticity plays a significant role in biochemical networks. Consider a system of $N$ molecular species that interact through $M$ reaction channels $R_1, \ldots, R_M$. The dynamical state of the system is a time-dependent vector $x = (x_1, \ldots, x_N)^T$ of nonnegative molecular populations. If the system is in state $x$ and reaction $R_k$ occurs, the system transitions to state $x + \nu_k$, where the state change vector $\nu_k$ is called the stoichiometric vector corresponding to $R_k$. From the current state $x$, the relative chance of each reaction occurring in the next infinitesimal time interval is determined by a set of $M$ propensities $\alpha_1(x), \ldots, \alpha_M(x)$. The formulation of the underlying Markov jump model gives rise to the chemical master equation (CME)

$$\frac{\partial}{\partial t} P(x, t) = \sum_{k=1}^{M} \alpha_k(x - \nu_k)P(x - \nu_k, t) - \alpha_k(x)P(x, t), \quad (1)$$

where $P(x, t)$ is the probability for the system to be in state $x$ at time $t$. Thus, the CME gives us the probability distribution of all possible states at all time, making it possible to build predictive models of cell regulatory networks. Unfortunately, the CME suffers from the curse of dimensionality that makes an efficient solution elusive.

Here, we report on a new time-stepping method for solving the CME that is motivated by recent developments in tensor train decomposition. We reduce the dimensionality of the CME using a combination of the finite state projection and the quantized tensor train (QTT) format. While the QTT has been applied to the CME before, our method is original in two aspects. First, we change the FSP and the QTT components adaptively across the integration steps in order to capture regions of the state space with high probability mass. Second, we employ an exponential time integration scheme that evaluates the QTT-formatted exponential operator at each time step using a novel formulation of the inexact uniformization technique that leverages the AMEn iterative method. We give more mathematical details in the Methodology section and present two numerical examples in the Results section to illustrate the efficiency of our approach.
2 METHODOLOGY

By using the finite state projection\cite{5} approach, we approximate the Markovian dynamics of the CME by a Markov process with a finite state space of the form $H := \times_{s=1}^{N} \mathcal{I}_s$, in which all states on the boundary are absorbing states. This leads to a linear dynamical system of the form

$$\frac{d}{dt} p(t) = A p(t),$$

where $p$ is a vector of size $\prod_{s=1}^{N} \mathcal{I}_s$ indexed by the states in $H$ and $A$ the transition rate matrix of the reduced Markov process. Assuming that $\mathcal{I}_s = 2^{L_s}$, $s = 1, \ldots, N$, representing $p$ in the QTT format consists of treating it as a $2 \times 2 \times \ldots \times 2$ tensor, where the number of dimensions is $L := \sum_{s=1}^{N} L_s$, and applying the tensor train decomposition\cite{3} to get

$$p(i_1, \ldots, i_N) = G_1(q_1^{(1)}) \ldots G_{L_1}(q_1^{(1)}) \ldots G_{L_2}(q_1^{(N)}) \ldots G_{L_N}(q_1^{(N)}),$$

where $\{q_j^{(s)}\}_{j=1}^{L_s} \subset \{1, 2\}$ are intuitively the binary bits that represent $i_s$, and $G_j^{(s)}(q)$ are matrices of appropriate dimensions. The three-dimensional tensors $G_j^{(s)}(:, :, :) := G_j^{(s)}(q)$ are called the QTT cores. Storing the QTT cores requires much less entries than the explicit formulation of $p$ as we will see in the Results section. A distinct feature of our method is that we do not fix the sizes $\mathcal{I}_s$ from the onset, but allow them to stretch adaptively to accommodate the spread of the probability distribution so that $H$ will always contain states with high probabilities. This ensures that the FSP approximation remains close to the true solution of the CME. The state space expansion is done directly in the QTT representation by inserting new matrices into the right-hand-side of $(3)$.

With the FSP and the QTT format determined, advancing the solution from $t_k$ to $t_k + \tau$ amounts to evaluating

$$p(t_k + \tau) := \exp(\tau A) p(t_k),$$

where we tacitly view the matrices and vectors involved as QTT tensors. Popular matrix exponential methods such as the Krylov algorithm requires matrix-vector products that lead to the excessive storage complexity, even in the QTT format and we instead employ a tensor formulation of the inexact uniformization method\cite{8}. Let $P := \frac{1}{\alpha}A + I$ where $\alpha$ is an appropriate scale parameter to make the computation stable. Let $f_j := P^j p(t_k)$, $j = 0, \ldots, m$, then the Taylor approximation leads to

$$p(t_k + \tau) \approx \sum_{j=0}^{m} \frac{e^{-\alpha \tau} (\alpha \tau)^j}{j!} f_j,$$

The necessary QTT-formatted vectors $f_j$ are evaluated by applying the AMEn algorithm\cite{9} on the linear system

$$\begin{pmatrix} I \\ -P & I \\ -P & I \\ \vdots & \ddots & \ddots \\ -P & I \end{pmatrix} \begin{pmatrix} f_0 \\ f_1 \\ f_2 \\ \vdots \\ f_m \end{pmatrix} = \begin{pmatrix} f_0 \\ 0 \\ 0 \\ \vdots \\ 0 \end{pmatrix}. \tag{6}$$

While the analysis of AMEn\cite{9} was only done for symmetric positive definite systems, the solver works well for non-symmetric problems in practice. In addition to the inexactness of the FSP, another inexactness comes from the residual of the iterative method, and the stricter the AMEn tolerance the less inexact the Taylor evaluation. We found that this AMEn formulation leads to a significant speed-up over a more straightforward approach that evaluates the matrix-vector products sequentially.

3 RESULTS AND CONCLUSIONS

We implement our algorithm in MATLAB 2015a, with the tensor train routines from the TT-toolbox version 2.2, which is publicly available at https://github.com/oseledets/TT-Toolbox. We specifically use the MEX-Fortran implementation of AMEn in the file fort_amen_solve.f for fast executions of the tensor linear system solves. Our testing platform is an ASUS UX51VZA laptop running Ubuntu Linux with 8 GB of RAM and 2.1 GHz Intel core i7 CPU.
3.1 A stochastic model of genetic toggle switch

We revisit the example solved by Kazeev et al. [6]. There are two species $U$ and $V$ that inhibit the production of each other. We set the initial rectangle to the size of $2^5 \times 2^5$ and integrate to $t_f := 100$. Our method detects equilibrium at $t \approx 11.065$, which leads to an early return. We ended up using only about 592 seconds of CPU time. The equilibrium distribution displays biomodality, which is a well-known characteristic of this system (Fig. 1).

3.2 Regulation of p53

The p53 gene is famously known as an important barrier against the development of cancerous cells. Here, we revisit a model of p53 regulation from [10]. We set the integration time $t_f := 1000$ and, to make the problem challenging, an initial state of high protein populations $x = ([RNA_{nuc}], [RNA_{cyt}], [MDM2_{cyt}], [MDM2_{nuc}], [ARF], [p53]) = (0, 0, 0, 1000, 1000, 1000)$.

Our method was able to solve the problem in 864 seconds. Fig. 2 illustrates the performance and adaptivity of our algorithm. We stress how the number of cores in the QTT format increase as the algorithm extends the FSP to explore the likely states. The maximum number of cores is 43, meaning that the FSP has to keep over $2^{43}$ states. Yet, the QTT format was able to compress the information on this enormous set of states into a compact representation that costs no more than 122,030 entries. The marginal distributions from the QTT format fit tightly with those generated by $10^6$ trajectories using Gillespie’s algorithm [12], as seen in Fig. 3.

3.3 Conclusions

The similarity with what is obtained by Gillespie’s algorithm gives us confidence in our early results, which clearly demonstrate the potential of the tensor based approach in treating the dimensionality problem of the CME.

REFERENCES


Figure 2: p53 example. **Left plot:** The accumulated CPU time and storage requirement of the QTT solution across integration steps. **Right plot:** Number of cores and the maximal TT-rank in the QTT representation of the solution.

Figure 3: p53 example. Marginal distributions of cytoplasmic MDM2 (left) and p53 (right), generated from the QTT solution (line) and one million SSA trajectories (bar).


A STUDY ON FLUID CHARACTERISTICS OF FIBONACCI SPIRAL MICROCHANNELS
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SUMMARY

A study on fluid characteristics of a Fibonacci spiral microchannel was carried out in the present work to predict fluid flow, velocity distribution on the cross section of the model. The Computational Fluid Dynamics software (ANSYS Fluent 14) and Taguchi method were used to simulate and optimize the parameters of the Fibonacci spiral microchannel. In addition, the Minitab 17 software was also used to analyze the simulated data. The result shows that the most significant factor in velocity was achieved for the design of the Fibonacci spiral microchannel.

Keywords: Spiral channel, Microchannel, Taguchi method, Fibonacci sequence and Golden ratio.

1 INTRODUCTION

Tuckerman and Pease [1] were the first to research micro-channel applications. Their work was designed to evaluate the performance of force liquid flows in Microchannel Heat Sinks (MCHS) and the results revealed that the minimum thermal resistance per unit area $R_T(0.1K/Wm^2)$ was obtained. After the first investigation of MCHS by Tuckerman and Pease, more than a thousand papers have been reported about the investigations of various configurations of MCHS by using many different theoretical and experimental methods. With the development of technologies, MCHS not only used in the industry of electronic and electrical engineering but also used in other fields, such as Chemical and Biological applications. In biological industry, many microchannel devices have been studied extensively for different applications, and the spiral microchannel device is the most interested one. Martel and Toner [2] conducted research on the spiral micro-channel device. They focused on the dynamics and the characteristics of the particle motions in the low aspect ratio channel. The results showed that, the primary and secondary streak was observed in the lowest aspect ratio channels at high average downstream velocities. Jimenez et al. [3] investigated the efficient separation of micro particles in a spiral channel by using a high flow-rate inlet. Bhagat et al. [4] studied spiral micro-channels by using dean flows and differential migration. The results showed the strong effect of dean flows on the microfluidic devices. Santana et al. [5] studied numerically mixing reactions of Jatropha curcas oil and ethanol for producing biodiesel by using a spiral-micro-mixer. The results showed that the highest conversion of vegetable oil in biodiesel was obtained with the T-micro-mixer and the spiral-micro-mixer. Wang et al. [6] used a micro-chip with double spiral micro-channels to study a new micro-flow injection chemiluminescence system. The results proved that the new system had the advantages of high sensitivity and precision. MacInnes et al. [7] demonstrated experimentally by using a rotating spiral micro-channel to produce multistage distillations. The prototype design of this device obtained the results can demonstrate the practical feasibility of a rotating spiral contacting and providing initial quantitative data used to evaluate the performance achieved of the device. Hasabnis [8] initially focus on applying a spiral channel in bio-cells, and the results obtained showed the relationships among critical geometrical parameters, i.e. width, cross-section, curvature, etc. Amin [9] investigated a differential format spiral micro-channel with variable channel width. Guan et al. [10] studied three-dimensional spiral channels, and focused on the particle streams along the depth and the width of the cross-section of the channel. Their results showed that the particles concentrated near the top and bottom of the
channel. Based on the results, we can understand more about the balance of the force in spiral channels.

Although, the spiral microchannel phenomena have been studied in a variation of designs in the fields of biology, biochemistry, separation bacteria, blood, and bio-energy, but still fewer studies on the fluid characteristics of Fibonacci spiral channels.

The purpose of the present study is to employ the Fibonacci sequence in the design of microchannel parameters and investigate fluid characteristics on a spiral microchannel. This investigation will find the most significant parameters design factors on the Fibonacci spiral microchannel. Therefore, the optimal dimensions of the spiral microchannel are utilized to predict the velocity distribution of the channel, as well as the working conditions of the channel on biomedical fluid and nanofluid.

2 METHODOLOGY

2.1 Fibonacci sequence and Fibonacci spiral.

The sequence $F_n$ of Fibonacci number was defined by the recurrence in relation to mathematical terms:

$$F_n = F_{n-1} + F_{n-2} \quad (1)$$

With the seed values:

$F_1 = 1, F_2 = 1 \text{ or } F_0 = 0, F_1 = 1$

By drawing circular arcs and connect the opposite corners of the squares in the Fibonacci sequence use, referred to Equation 1, we can create the Fibonacci spiral which approximates with the golden ratio and is shown in Figure 1 with values $1,1,2,3,5,8,13,21,... (mm)$.

2.2 The model design, conceptual framework and computational setup.

The Taguchi method is employed to identify the effects of different parameters of the present Fibonacci spiral microchannel on the outlet velocity to establish the initial factors. The levels and dimensions of each factor are selected and listed in Table 1.

<table>
<thead>
<tr>
<th>Parameters and values levels</th>
<th>Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: The channel width (mm) $W_c$</td>
<td>0.3</td>
</tr>
<tr>
<td>B: The channel height (mm) $H_c$</td>
<td>0.2</td>
</tr>
<tr>
<td>C: Environment temperature</td>
<td>23</td>
</tr>
<tr>
<td>D: Inlet flow rate $U$ (ml/min)</td>
<td>1</td>
</tr>
</tbody>
</table>

For this model, $L_9$ is suitable for the study was chosen for investigation and five repetitions are run for response variables (outlet velocity). There are 44 degrees of freedom and four design parameter factors. In the present study, the optimal level of the process parameters is the level with the smaller mean values is better. In addition to the factor analysis, the correlation and the regression analysis relative to the model framework tests are performed to analyze data.

Based on the reviewed literature, the descriptive research model was investigated in this study and the conceptual framework of the study was proposed.

$E\{YY_i\} = \beta_0 + \beta_1 A_i + \beta_2 B_i + \beta_3 C_i + \beta_4 D_i + \epsilon_i$

Hypothesis this model: $H_c$ (the variables: $x$) is significant and positively related to outlet velocity ($V_{out}$).

Where $E\{YY_i\}$ are the values of the response variables in the $i^{th}$ trial for Model I. $\beta_0, \beta_1, \beta_2, \beta_3, \beta_4$ are parameters for this model. The variables $x = (A_i, B_i, C_i, D_i)$ are known to be constants, namely,
the value of the predictor variables in the $i^{th}$ trial for this model. The random error terms $e_i$ are with the means of $E\{e_i\} = 0$ and variances $\sigma^2\{e_i\} = \sigma^2, i = 1,2,3,...,9$.

The three-dimension computational of the fluid flow was set as pressure-based as type, velocity formulation is absolute, steady laminar flow with wall motion is a stationary wall, a shear condition with no slip. Meshing statistics with the number of elements are 4.8 million, meshing metric with skewness number is 0.89 max. The results were obtained from the simulation by using Ansys FLUENT 14.0 software package. Minitab 17 software is used for factor analysis, correlation analysis, and regression analysis.

3 RESULTS AND CONCLUSIONS

3.1. Correlation Matrix Analysis

Based on the results from Minitab output, the correlations between predictor variables and response variables for this model have been obtained. Table 2 shows the correlation between predictor variables and response variables for this model, factors $A$ have the strongest positive correlation with a outlet velocity ($r = 0.645$), which indicating that if factors $A$ increase, that will lead to an increase in outlet velocity. Factor $B$ have the strongest negative correlation with outlet velocity ($r = -0.617$), which indicating that if factors $B$ increase, that will lead to a decrease in outlet velocity.

3.2 The interaction effect of predictor variables

Following the analysis mentioned before, a multiple regression analysis was performed to find the factors that affect response variables, as well as the interaction between predictor variables. The $t^*$ test values were performed to present the interaction effects at a level significant (T-Value) ($\alpha = 0.5$):

$H_0: \beta_i = 0$, there is no interaction between predictor variables.

$H_a: \beta_i \neq 0$, there are interactions between predictor variables.

From the Minitab outputs, the results of the absolute of $t^*$ values for each combination of any two factors for outlet velocity are given in Table 3. For the level of significance, ($\alpha = 0.5$) we require:

$$t\left(\frac{1 - \alpha}{2}; d_f \text{ of error}\right) = 2.776$$

Since:

$|t^*| \leq 2.776$, we may conclude $H_0, \beta_i = 0$.

$|t^*| \geq 2.776$, we may conclude $H_a, \beta_i \neq 0$.

Table 2 The correlation analysis

<table>
<thead>
<tr>
<th>Model</th>
<th>EYV</th>
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<tr>
<td>A</td>
<td>-0.245</td>
</tr>
<tr>
<td>B</td>
<td>-0.617</td>
</tr>
<tr>
<td>C</td>
<td>-0.17</td>
</tr>
<tr>
<td>D</td>
<td>0.645</td>
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</table>

Table 3 T-test values for Model ($E(YV)$)

<table>
<thead>
<tr>
<th>Factors</th>
<th>Model</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>1.5</td>
<td>0.46</td>
<td>3.78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>0.06</td>
<td>2.27</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>0.66</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
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</tbody>
</table>

For this model: There is an interaction between factor A’D

3.3 Regression Analysis

Table 4 show the F-Value and P-Value, which can be used to analyze the affection between predictor variables and response variables, and a value of 0.05 is chosen to indicate a significant affection for each model. Based on F-Value and P-Value of each predictor variable (factor), we can conclude:

Table 4 Analysis of variance for ($E(YV)$)

<table>
<thead>
<tr>
<th>Source</th>
<th>DF</th>
<th>Adj SS</th>
<th>Adj MS</th>
<th>F-Value</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regression</td>
<td>4</td>
<td>0.079660</td>
<td>0.019915</td>
<td>6.00</td>
<td>0.035</td>
</tr>
<tr>
<td>A</td>
<td>1</td>
<td>0.005577</td>
<td>0.000557</td>
<td>1.68</td>
<td>0.265</td>
</tr>
<tr>
<td>B</td>
<td>1</td>
<td>0.035423</td>
<td>0.035423</td>
<td>10.67</td>
<td>0.031</td>
</tr>
<tr>
<td>C</td>
<td>1</td>
<td>0.000028</td>
<td>0.000028</td>
<td>0.01</td>
<td>0.931</td>
</tr>
<tr>
<td>D</td>
<td>1</td>
<td>0.038632</td>
<td>0.038632</td>
<td>11.64</td>
<td>0.027</td>
</tr>
<tr>
<td>Error</td>
<td>4</td>
<td>0.013276</td>
<td>0.0003319</td>
<td>1.60</td>
<td>0.148</td>
</tr>
<tr>
<td>Total</td>
<td>8</td>
<td>0.092936</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For this model: Factor B and D have a significant effect on outlet velocity ($P = Value = 0.031, 0.027 \leq 0.05$), respectively. Factors A and C have no significant influence on outlet velocity ($P = Value = 0.365 and 0.931 \geq 0.05$, respectively). In other words, we conclude $H_B$ and $H_D$ and reject $H_A$ and $H_C$. 

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In addition, the average performance effects of each factor of the outlet velocity plot are also obtained for a visual inspection and the results contour result at the outlet cut view as given in **Figure 2 and Figure 3**, respectively.

**Figure 2** The main effects plot of data mean for model ($E(YV)$)

**Figure 3** The contour plot for model ($E(YV)$) at the outlet cut view

For this Model: The optimal combination factor of the outlet velocity is $A_3B_3C_3D_1 (W_C = 0.5 \text{ (mm)}(A_3) H_C = 0.5 \text{ (mm)}(B_3) C_3$ and $U = 1 \text{ml/min}(D_1)$.

### 3.4 Conclusions

The computational Fluid Dynamics software (CFD) (ANSYS 14) and Taguchi method were conducted to predict outlet velocity of the design of a Fibonacci spiral microchannel, and the results indicated the most valuable combination factors. The optimal combination of outlet velocity is $A_3B_3C_3D_1$. There is an interaction between factor $A'$D and factor $B$ and $D$ has the most significant effect on outlet velocity.

### REFERENCES


TOWARDS THE INTEGRATION OF CALCIUM DYNAMICS INTO ARTERIAL WALL MECHANICS

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SUMMARY

The target of this work is the investigation of the role of smooth muscle (SM) cells in the large artery wall dynamics. The study focuses on an arterial ring under isometric conditions and subjected to different calcium dynamics scenarios. For coupling the media intercellular calcium concentration with the wall stress state a multiscale approach has been adopted. The intercellular calcium concentration is computed along a network representing the smooth muscle layer. This information is passed in real time to the arterial wall structural model, which has been modeled as a multi layer composite hyperelastic material. Results shows the dependence between the cellular configuration and active stress generated.

Key words: calcium dynamics, hemodynamics, arterial wall

1 INTRODUCTION

Physiological regulation of blood flow can be subdivided into three primary control domains: (i) rheological conditions imposed by the mechanics of blood flow through variable vascular geometries, (ii) arterial wall contractile apparatus, located within the vascular smooth muscle (SM), and (iii) the endothelium, a monolayer of cells lining the inner surface of blood vessels, which operates as an active interface, that translates and amplifies the electrochemical signalling between domains (i) and (ii). The ability of a blood vessel to adapt to variable rheological requirements, by responding to electrochemical signalling generated by the endothelium, is a fundamental measure of vascular health. The smooth muscle contractile machinery is driven by a complex intracellular calcium dynamics \cite{2,3}.

In the present work we propose a strategy for evaluating the stress response in the arterial wall induced by subministration of drugs able activate the SM contractile machinery. The contractile state of SM constitutes one side of the non linear relationship between stress and deformation of the vascular structure. In the absence of fluid flow it becomes the only force-generator mechanism. Under these assumptions, we propose to simulate the mechanical behaviour of an arterial ring isolated in a physiological solution and subjected to a drug intervention. For doing this, we have integrated a realistic calcium cell network within an arterial structural dynamics model. For describing the complex calcium dynamics associated with the SM layer, we have used our recently developed methodology \cite{4}. To perform the structural analysis of the arterial wall, a finite element technology based on hybrid elements has been used. The arterial wall is subdivided into media and adventia layers, and for both layers the theory of fibre reinforced material is assumed. Calcium signal from cell network is transferred to finite elements discretization of the media layer by using an interpolation technique based on Radial Basis Function. The methodology proposed in \cite{5} has been adopted for converting the element calcium concentration into active stress. We remark that in this way the inlet calcium signal differs element by element and depends on the resulting cellular coupling.
2 METHODOLOGY

The arterial wall is constituted by the adventia and media layers. The adventia is just described as an fiber reinforced hyperelastic material. For the media instead, a multiscale modelling is adopted. This is cause such a layer presents an active component able to generate stress related to the intercellular calcium dynamics of SM. We consider a cellular level, where the calcium dynamics occurs, and a finite element mesh level, where the structural solution is calculated. The cluster of cells is arranged by following the cellular morphology of the tissue described. We remark that the calcium dynamics equations do not present any intrinsic spatial dependence. The cellular calcium concentration is passed to the finite element framework by using RBF interpolating techniques. The nodal values of calcium concentration are then used for computing the cross-bridges states along the time. By knowing the state’ fractions it has been possible evaluate the active component of Piola stress tensor and therefore the structural calculations.

2.1 Intercellular calcium

The variables necessary to compute the calcium dynamics at cellular level are the intracellular calcium concentration $\chi$, the intercellular calcium concentration $\zeta$ and the membrane potential $\eta$. The temporal evolution of these variables is described through the following non linear system of equations:

$$\frac{d\chi}{dt} = A - E_{Ca} \frac{\eta - z_{Ca1}}{1 + e^{-(\eta - z_{Ca1})/R_{Ca}}} + E_{Na/Ca} \frac{\chi}{\chi + x_{Na/Ca}} (\eta - z_{Na/Ca})$$

$$- B \frac{\chi^a}{\chi^a + x_{b}^a} + C_r \frac{\chi^{pr}}{\chi^{pr} + x_{r}^{pr}} \zeta^{mr} + y_{mr} - D \chi^b (1 + \frac{\eta - z_{d}}{R_{d}}) + L \zeta$$

$$\frac{d\zeta}{dt} = B \frac{\chi^a}{\chi^a + x_{b}^a} - C_r \frac{\chi^{pr}}{\chi^{pr} + x_{r}^{pr}} \zeta^{mr} + y_{mr}$$

$$\frac{d\eta}{dt} = -\gamma [E_{Cl} \frac{\chi}{\chi + x_{Cl}} + 2E_{Ca} \frac{\eta - z_{Ca1}}{1 + e^{-(\eta - z_{Ca1})/R_{Ca}}}$$

$$+ E_{Na/Ca} \frac{\chi}{\chi + x_{Na/Ca}} (\eta - z_{Na/Ca}) + E_{K} (\eta - z_{Na/Ca}) \frac{\chi}{\chi + \beta e^{-(\eta - z_{Ca3})/R_{K}}}]$$

An accurate description of each term and all coefficients can be found in [3].

2.2 Cross-bridges kinetics

The dynamics associated to the cross-bridge activation is carried out by using a modified version of the model proposed by Hai and Murphy, which describes the myosin through four different states, whose fractions are $n_M$, $n_{M^p}$, $n_{AM^p}$, $n_{AM}$. The temporal evolution of these states’ fractions is described through a linear system. For more details, see [5].

2.3 Arterial wall mechanics

From the structural point of view the wall has been modeled as a multilayered hyperelastic material. For both adventia and media the free energy function can be split into an isochoric and volumetric components:

$$\Psi^{med} = \Psi^{med}_{vol} + \Psi^{med}_{adv}$$

$$\Psi^{adv} = \Psi^{adv}_{vol} + \Psi^{adv}_{adv}$$

For both materials we follow the strategy proposed in [1].
2.3.1 Media Layer

The isochoric component of media layer consists of an active and passive components:

\[ \Psi_{\text{med}}^{\text{med}} = \Psi_{\text{med}}^{\text{act}} + \Psi_{\text{med}}^{\text{pas}} \]  

Both components depend on the stretching of the contractile unit (\( \lambda \)), that is related to the fourth invariant and thus

\[ \lambda = \sqrt{I_4^{\text{med}}} = a_{\text{med}}^0 \cdot \text{Ca}_{\text{med}}^{\text{med}} \]  

where \( \text{C} \) is the Right Cauchy deformation tensor and \( a_{\text{med}}^0 \) is the direction of the media unstressed fiber.

The active component is also depending on the kinetic states’ fractions \( n_{\text{AMp}} \) and \( n_{\text{AM}} \):

\[ \Psi_{\text{med}}^{\text{act}} = \frac{\mu_{\text{act}}}{2} (n_{\text{AMp}} + n_{\text{AM}}) (\lambda - \bar{u}_{fs} - 1)^2 \]  

The passive one is instead modeled as a classical anistropic material with one fiber aligned with the smooth muscle cells:

\[ \Psi_{\text{med}}^{\text{pas}} = \frac{\mu_{\text{p}}}{2} (I_4^{\text{med}} - 3) + \frac{C_{\text{med}}^{\text{med}}}{2C_2^{\text{med}}} \{ \exp[C_2^{\text{med}} (I_4 - 1)^2] - 1 \} \]  

where \( \mu_{\text{p}}^{\text{med}}, C_1^{\text{med}} \) and \( C_2^{\text{med}} \) are material constants.

2.3.2 Adventia Layer

This layer, that is passive, is modeled as a neo hookean material reinforced by two family of fibers:

\[ \Psi_{\text{adv}} = \sum_{i=4,6} \frac{\mu_{p}^{\text{adv}}}{2} (I_4^{\text{adv}} - 3) + \sum_{i=4,6} \frac{C_1^{\text{adv}}}{2C_2^{\text{adv}}} \{ \exp[C_2^{\text{adv}} (I_i - 1)^2] - 1 \} \]  

where \( \mu_{p}^{\text{adv}}, C_1^{\text{adv}} \) and \( C_2^{\text{adv}} \). The invariants are computed as

\[ I_i^{\text{adv}} = a_i^{\text{adv}} \cdot \text{Ca}_i^{\text{adv}} \]  

with \( a_i^{\text{adv}} \) as fiber direction vector.

2.3.3 Numerical methods

As the cellular calcium dynamics is independent from the arterial dynamics, it has been before all structural calculations. For the solving such a ODE system, an adaptive Runge-Kutta method has been employed. The calcium dynamics has been compute by explicit Euler. The structural solver is based on hybrid finite element technology.

3 RESULTS AND CONCLUSIONS

This methodology has been applied to ring made of arterial material. This element is fixed at the outer surface and is loaded from the inner surface. At first we test the model by considering as input a spatially homogenous intercellular calcium concentration signal. This involves, with respect to the control case (without active stress components), a slight increment in displacement, limiting the compression of the material.

We note that further studies with a more realistic calcium dynamics need to be carried out in order to provide enough elements for an appropriate discussion.
Figure 1: Arterial ring with inner pressure load along the internal surface

REFERENCES

Biomechanics, Mechanobiology & Translation in the Heart V
A RULE-BASED METHOD TO MODEL MYOCARDIAL FIBER ORIENTATION IN CARDIAC BIVENTRICULAR GEOMETRIES INCLUDING THE OUTFLOW TRACTS

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SUMMARY
Rule-Based Methods (RBM) are often used for assigning fiber orientation in cardiac models, which is necessary for realistic electrophysiological simulations. However, RBM have been developed to assimilate data mostly from the Left Ventricle (LV). In consequence, fiber information from RBM is not available or does not match with histological data in other areas of the heart, having a negative impact in cardiac simulations beyond the LV. We present in this work a RBM where fiber orientation is explicitly modeled in the Right Ventricle (RV) and both Outflow Tracts (OTs) following observations from histology. This allows performing electrophysiological simulations involving these anatomical structures such as in the case of Outflow Tract Ventricular Arrhythmias (OTVAs).

Key words: fiber orientation, rule-based method, arrhythmia, electrophysiological simulations

1 INTRODUCTION
Outflow tract ventricular arrhythmias (OTVAs) are a type of arrhythmia where the Site of Origin (SOO) of the ectopic beat is placed in one of the two outflow tracts. In order to treat this disease, clinicians need to localize this site and ablate it by Radio Frequency Ablation (RFA). Usually they localize the ectopic focus by careful inspection of the ECG by experienced observers and confirm it during the intervention with electro-anatomical mapping data. Unfortunately, there are cases where the origin cannot be properly defined with the ECG since both OTs are very close physically. Personalized electrophysiological simulations have shown promising results to support clinical decisions in cardiology \[1\]. Therefore, they could be used to help clinicians to determine the SOO in OTVAs. However, most simulation studies in the literature have focused in the left ventricle due to the complexity of obtaining accurate data of the right ventricle, especially on fiber orientation (e.g. with Diffusion Tensor Magnetic Resonance Imaging). Even the ones including biventricular geometries do not consider the outflow tracts, using anatomical meshes with a basal plane substantially below the valves. In consequence, the Rule-Based Methods usually employed to generate myocardial fiber orientation for the simulations do not include specific information about the RV or the outflow tracts, preventing the use of cardiac simulations in OTVA data.

We present here an adaptation of an existing RBM \[2\] that includes specific fiber orientation in relevant cardiac regions in OTVA, mainly the RV and OTs, following observations from histological data. According to this data, fiber orientation has a longitudinal direction from the apex towards the two valves (pulmonary and tricuspid valves) in the RV sub-endocardium. Fiber orientation in the sub-endocardium and sub-epicardium of the OT have a longitudinal and circumferential direction,
Figure 1: Histological data of the heart. Left: Fiber configuration in the RV sub-endocardium, showing longitudinal directions (dashed blue lines) to the pulmonary and tricuspid valves. Right: Slice of the RVOT showing longitudinal direction in the sub-endocardium wall. RA=right atrium, CS=coronary sinus respectively. The developed RBM can provide fiber estimations in personalized and detailed heart geometries, independently processing both ventricles, which gives flexibility to generate different fiber configurations. Fiber configurations obtained with the new method are compared with DT-MRI data and state-of-the-art RBMs in a simple heart geometry without OTs for verification purposes. Then, several electrophysiological simulations are performed in patient-specific OTVAs geometries to replicate clinical observations in these patients.

2 METHODOLOGY

The developed method is based on Bayer et al.’s work [2] but with several improvements in order to:

- Generate fiber orientations in heart geometries including both outflow tracts.
- Include the bi-directional longitudinal fibers from the apex to the valves in the RV endocardium (see Figure 1) instead of the ones usually employed, defined for the left ventricle from Streeter’s observations [2].

In order to assign fiber orientation we first generate a local orthonormal reference system at each node of a given personalized geometry. The geometries are patient-specific tetrahedral meshes that have been extracted from CT imaging. The coordinate system axes are the longitudinal $\hat{e}_l$, transmural $\hat{e}_t$ and circumferential $\hat{e}_c$ directions. Transmural and longitudinal directions are defined by solving the Laplace equation using different surfaces of the geometry (RV and LV endocardium, epicardium, apex and the four valves) as Dirichlet boundary conditions. Once we have both directions, we obtain the circumferential direction calculating the cross product and finally the fiber direction rotating the obtained vector an angle $\alpha$.

Transmural direction ($\nabla \Phi$) is defined solving the Laplace equation between the endocardium and epicardium of each ventricle independently, and subsequently computing the gradient of the Laplace solution. The Laplace equation is simultaneously computed for both ventricles, assigning a negative value to the LV endocardium and positive to the RV one, allowing independent fiber configurations for both ventricles and possible discontinuities such as in the septal wall. Longitudinal direction ($\nabla \Psi$) is defined separately in each ventricle. This direction is the result of a weighted sum of the apex-basal gradient ($\nabla \Psi_{basal}$) plus an apex-valve ($\nabla \Psi_{valve}$) gradient. These two main directions were already described by Greenbaum et al. [4] and can be visualized in Figure 1 (dashed blue lines). The previous sum is weighted by a function $f$, which is obtained by solving another Laplace equation for each ventricle between the pulmonary-tricuspid valve and also between aortic-mitral valve. In this way, we obtain a distribution of values that allow us to define the fiber change near the OT in different geometries. As a result, for each ventricle we get as longitudinal direction:

$$\nabla \Psi = \nabla \Psi_{basal} \cdot f + \nabla \Psi_{valve} \cdot (1 - f)$$

(1)
Using the previously calculated gradients, we set up a local coordinate system for each vertex. The vectors of this system are the following:

\[
\hat{e}_l = \frac{\nabla \Psi}{\| \nabla \Psi \|} \quad \hat{e}_t = \frac{\nabla \Phi - (\hat{e}_l \cdot \nabla \Phi) \cdot \hat{e}_l}{\| \nabla \Phi - (\hat{e}_l \cdot \nabla \Phi) \cdot \hat{e}_l \|} \quad \hat{e}_c = \hat{e}_l \times \hat{e}_t
\]  

(2)

Finally, we assign the fiber orientation rotating counterclockwise the vector \( \hat{e}_c \) an angle \( \alpha \) which is defined in each ventricle as:

\[
\alpha = \alpha_{\text{endo}}(f) \cdot (1 - d) + \alpha_{\text{epi}}(f) \cdot d
\]  

(3)

where \( d \) is the transmural depth normalized from 0 to 1. The different values of \( \alpha_{\text{endo}} \) and \( \alpha_{\text{epi}} \) are chosen in order to replicate the results of different histological studies as the ones made by Streeter, Damian Sanchez-Quintana [3] or Greenbaum [4].

3 RESULTS

The results of applying the developed method to different geometries can be seen in Figure 2. One interesting analysis can be done by measuring the angle difference between fiber configurations provided by the proposed method and the existing RBM ones or possible measurements in the same heart. Magnetic Resonance Imaging data from an ex-vivo human heart available from the John’s Hopkins database (http://cvrgrid.org/data/ex-vivo), which also includes fiber information from DT-MRI, was used for this experiment, as shown in Figure 3. The main differences are found in the RV endocardium, where longitudinal directions from the apex towards the pulmonary and tricuspid valves have been forced, while in the other methods fibers are more circumferential, when comparing to histological data (see Figure 1). Unfortunately, data was only available in this dataset below a certain basal plane, substantially below the outflow tracts and the valves, preventing the evaluation of the proposed RBM with ground-truth data.
For verification purposes, we have also run electrophysiological simulations using the developed RBM on geometries of OTVA patients and qualitatively compared our results with literature. In particular, the morphology of the 10 ms isochrone measure in the RV endocardium after an ectopic focus seems to give hints on the SOO: if the long axis is more longitudinal the SOO should be in the RVOT (following the fibers in the OT); while LVOT origins create more isotropic isochrones or with a larger perpendicular axis [5].

The simulations were performed with SOFA software (an Open Source medical simulation software available at http://www.sofa-framework.org) using the Mitchell-Schaeffer model in 5 different geometries from OTVA patients placing the SOO in different parts of the OTs. Some results can be seen in Figure 4 and Table 1. These results show a statistically significant difference between the ratios of the RVOT isochrones and RCC isochrones, with a p-value of $p < 0.001$.

![Figure 4: 10 ms isochrones from simulations in two patients with different sites of origin: the RVOT ventricular outflow tract (a. and c.) and the Right Coronary Cusp (RCC) of the LVOT (b. and d.)](image)

<table>
<thead>
<tr>
<th>Patient</th>
<th>RVOT origin 10 ms isochrone Long/Perp ratio</th>
<th>RCC origin 10 ms isochrone Long/Perp ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 1</td>
<td>2.13 ± 0.18</td>
<td>1.22 ± 0.08</td>
</tr>
<tr>
<td>Patient 2</td>
<td>2.4 ± 0.2</td>
<td>1.11 ± 0.06</td>
</tr>
<tr>
<td>Patient 3</td>
<td>1.8 ± 0.2</td>
<td>0.95 ± 0.04</td>
</tr>
<tr>
<td>Patient 4</td>
<td>2.11 ± 0.2</td>
<td>0.99 ± 0.04</td>
</tr>
<tr>
<td>Patient 5</td>
<td>1.9 ± 0.2</td>
<td>1.20 ± 0.06</td>
</tr>
<tr>
<td>All</td>
<td>2.1 ± 0.2</td>
<td>1.09 ± 0.06</td>
</tr>
</tbody>
</table>

4 CONCLUSIONS

The proposed RBM, including fiber information specific to the RV and in both OTs of the ventricles, guided by histological data, allows running electrophysiological simulations where these regions are important such as in OTVA patients. It can also be used for assigning more detailed fiber orientation to other parts of the heart (e.g. the septum) where fiber orientation is still a debate. In addition, the proposed RBM may also have an impact in mechanical simulations of the heart involving the RV since contraction is highly dependent on myocardial fiber distribution.

REFERENCES


MODELLING CARDIAC STRUCTURAL HETEROGENEITY VIA SPACE-FRACTIONAL DIFFERENTIAL EQUATIONS

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SUMMARY

We discuss here the use of non-local models in space and fractional order operators in the characterisation of structural complexity and the modeling of propagation in heterogeneous biological tissues. In the specific, we consider the application of space-fractional operators in the context of cardiac electrophysiology, where the lack of clear separation of scales of the highly heterogeneous myocardium triggers peculiar features such as the dispersion of action potential duration, that have been observed experimentally, but cannot be described by the standard monodomain or bidomain models. We describe the methodology and compare the results of a standard monodomain model with results of a model with a non-local component in space.

Key words: Cardiac electrophysiology, Monodomain model, fractional Laplacian

1 INTRODUCTION

The mechanical activity of cardiac chambers is governed by the excitation patterns produced by the electrophysiology of the heart itself. Accuracy in the description of such an activity is thus of paramount importance when attempting to capture the overall cardiac dynamics.

Mathematical models of electrical propagation in excitable media are typically developed via the homogenisation principle, namely, under the assumption that microscopic inhomogeneities in the medium have a negligible effect on the transport phenomena observed at the macroscopic scale. In highly heterogeneous structures, such as cardiac or neural tissue, where there is no clear separation of scales, this hypothesis is questionable. In fact, experimental data point at peculiar features of the electrophysiological dynamics, such as wide action potential foot [1] and a marked dispersion of action potential duration (APD) [2], that cannot be captured by standard models. Alternative modeling strategies are thus needed to provide additional insight into the effect produced by structural heterogeneity on electrical pulse propagation.

In the last few decades, mathematical models involving differential operators of non-integer order have been considered in a variety of disciplines (such as physics, engineering, chemistry, rheology, economics) with the aim of reproducing transport phenomena whose characteristics significantly deviate from the classical Markovian and Gaussian features, typical of standard diffusion models. Although the interest in fractional operators linked to practical applications is increasingly growing, the successful implementations of fractional models to model real life phenomena are still scarce.

To the best of our knowledge, the work by Bueno-Orovio et al. [3] is the first example of using a space-fractional mathematical model in cardiac electrophysiology. The biophysical justification behind the use of such a fractional operator for this particular application is based on potential electric field theory. The inhomogeneities present on a variety of length scales in biological tissue give rise to secondary sources that add up to the primary source field corresponding to the assumption of a uniform and infinite volume conductor. These secondary sources can be seen as a dipole modulation of the electrical potential associated with a point source in a homogeneous tissue (monopole). By
using Riesz potential theory, the authors in [3] showed that a fractional model can be interpreted as a smooth transition between monopole and dipole behaviour, with increasing degree of heterogeneity as the order of the fractional operator decreases. Although capturing peculiar features of action potential propagation in heterogeneous media, and showing good agreement with experimental data, their numerical simulations are restricted to one dimensional intervals.

The numerical methodology introduced in [3] is based on the approximation of eigenpairs of the nonlocal operator. If its extension to two and three dimensional cartesian domains is pretty straightforward, its application to real geometries is not practical, as eigenvalues and eigenfunctions are not known analytically in these cases.

Motivated by the promising results provided by the use of space-fractional differential operators, and by the lack of treatment of non cartesian geometries, we developed in [5] a method to approximate fractional operators on general bounded domains with a variety of boundary conditions. This method allows us to devise a nonlocal model of electrical wave propagation that is consistent with the physical intuition and interpretation of the problem, and is flexible enough to be considered on realistic cardiac geometries.

2 METHODOLOGY

Mathematical models of electrical signal propagation in cardiac electrophysiology consist of suitable spatially distributed formulations of specified cell models reproducing the response of a single excitable cell to an applied electrical stimulus. Cell models describe the temporal evolution of the transmembrane potential $u$ and the changes in $u$ caused by the opening and closing of the various ion channels present in the cell membrane, driving the movement of ions into and out of the cell. A classical approach adopted in order to account for pulse propagation is to introduce spatial dependence in the model via the monodomain formulation. The latter consists of a coupled ODE-PDE system whose PDE component is a nonlinear parabolic equation (see, e.g. [4]).

The space-fractional formulation of the monodomain model can obtained by replacing the diffusion term in the parabolic part with a nonlocal operator. Here we consider the fractional Laplacian of order $s \in (0, 1)$, $(-\Delta)^s$, and the resulting system reads:

$$\chi \left( C_m \frac{\partial u}{\partial t} + I_{ion}(u, z) \right) = -D(-\Delta)^s u + I_{stim}$$

$$\frac{dz}{dt} = f(u, z),$$

(1)

where $\chi$ is the cell surface-to-volume ratio, $C_m$ is the membrane capacitance per unit area, $z$ is a suitable vector of secondary variables used in the description of the dynamics of the ion channels in the cell membrane, $I_{ion}$ is the sum of all transmembrane ionic currents, $D$ is a constant conductivity, $I_{stim}$ is the electrical stimulus, and $f$ is a vector-valued function describing the temporal evolution of $z$. System (1) is completed by suitable initial conditions and homogeneous Neumann boundary conditions to model an insulated domain.

The crucial issue with fractional order differential operators is that they are naturally defined on the entire space $\mathbb{R}^n$, $n \geq 1$. However, in the majority of practical cases one needs to mathematically model quantities that are defined on a bounded domain $\Omega \subset \mathbb{R}^n$ only. The main challenge is how to suitably restrict, adapt, or interpret the definition of a fractional operator so that it preserves its nonlocal character, all while providing a well-posed problem on $\Omega$.

Based on the spectral definition of the fractional Laplacian and via the heat semi-group formalism, we propose in [5] a novel numerical approach for the discretisation of fractional powers of the Laplacian on bounded and possibly irregular domains, coupled with homogeneous Dirichlet, Neumann, or Robin boundary conditions. Combining finite elements and a suitable quadrature rule, the method is well suited for treating complex domains like the cardiac chambers. The main focus in [5] is the discretisation of $(-\Delta)^s u$ for a given function $u : \Omega \to \mathbb{R}$, but our approach provides a natural framework for the numerical treatment of fractional parabolic problems on bounded domains such as [1].
3 PRELIMINARY RESULTS

Promising results have been obtained in one spatial dimension in [6], where the authors investigate the effect of changing the order of the fractional Laplacian on action potential shape and spatial propagation. We present here some preliminary results on a two dimensional slice of cardiac tissue reconstructed from CT scan. The ionic model we implemented is the Rogers-McCulloch variant of the FitzHugh-Nagumo one [7], featuring a resting potential of 0 mV, a peak potential of 100 mV, and an APD of around 100 msec. In this first set of tests we consider a constant conductivity in the whole domain. In Figure 1, we plot the spatial domain Ω (left), and the time course of the action potential computed with the fractional monodomain (with $s = 0.75$) at five different points labeled from A to E (right): APD dispersal and wide foot of the depolarization phase are visible.

In Figure 2, we compare, in terms of APD, the results of a standard monodomain and a spatial fractional monodomain. In particular, we compute $APD_{90}$, namely the APD computed at 90% repolarization. The use of fractional monodomain allows us to capture a pronounced dispersion of $APD_{90}$, a feature expected in highly heterogeneous structures [1] that the standard formulation of the monodomain fails to exhibit.

4 CONCLUSIONS

The fractional monodomain, being nonlocal, shows great potential in modeling the effect of cardiac microstructure on the electrical propagation in the myocardium. The theoretical approach followed in [5] and the numerical method developed therein, allow us to set up the problem on general bounded
domains and to treat numerically system (1) in this general setting. We show how this strategy can be implemented on bounded geometries of practical interest, coupled with physically meaningful boundary conditions.

REFERENCES


SIMULATION OF A HUMAN LEFT VENTRICULAR HEMODYNAMICS USING EMBEDDED BOUNDARY MESH METHODS

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SUMMARY

The main objective of this work is to numerically simulate a Left Ventricular (LV) human heart response in normal conditions using nonconforming meshes to discretize the problem domain.

To attain this goal, we use an approach recently developed by the authors to deal with fluid and solid interaction. The main challenge here is to apply it to a complex geometry, typical of biomedical problems. The approach starts with a parallel preprocess that approximates nonconforming meshes to the problem domain by removing a number of elements. Then, an Embedded Boundary (EB) mesh implementation imposes the velocity of the boundary problem inside such meshes using a high order kriging interpolation.

The physics of fluid is described by the incompressible Navier-Stokes equations. They are solved using a parallel implementation of a variational multiscale Finite Element (FE) method.

Results will be compared with a simulation using a conforming mesh.

Key words: embedded boundary mesh method, finite element method, parallel implementation, left ventricular hemodynamics

1 INTRODUCTION

Computer simulations are able to determine the response of a human anatomy system in different possible scenarios with the great advantage of not being restricted to any ethical implication. They have then a great potential to become a very important tool for a better understanding of human diseases and their corresponding treatments.

Simulations have to provide accurate results in order to become a reliable tool for decision making in medical treatment or diagnosis. Nevertheless, anatomical human systems commonly involve the interaction of different physics and very complex geometries. Accurate results on the solution of biomechanical problems require then a number of algorithms that process efficiently a big quantity of data in order to solve the complex human anatomical system. Thus, arriving at a powerful code entails the integration of different algorithmic solutions written to efficiently run in thousands of processors.

In particular, our work is focused on the numerical simulation of a LV human heart hemodynamics in normal conditions using nonconforming meshes. To attain this goal, we use an approach recently developed by the authors to deal with fluid and solid interaction. Eliminating thus the creation of conforming meshes for such complex geometries.

The approach start with a parallel preprocess that approximates nonconforming meshes to the problem domain by removing a number of elements. For that, elements are first labeled into two categories: inside and outside elements using an skd-tree structure to geometrically represented the boundary problem in order to optimize the identification. Inside elements are those whose volumes of intersection with the embedded problem domain are big enough. The rest of the elements are removed from
the assembly process, the outside elements. To illustrate this first step consider the surface mesh representation of the LV human heart shown in Figure 2. Consider also that it is completely embedded inside the mesh of hexahedral elements shown in Figure 1a. Resulting inside and outside elements are shown in Figure 1b represented by red and white squares respectively.

Velocity is then finally imposed on the nodes located at the interface between these two kinds of elements by interpolating the problem boundary velocity using a new Embedded Boundary method. In our implementation, a high order kriging interpolation is implemented [2] in order to preserve the quadratic convergence in a FE implementation for the case of linear Lagrange elements with piecewise linear polynomial degree [3].

The physics of the fluid is described by the incompressible Navier-Stokes equations. They are then stabilized using a Variational Multiscale FEM and solved using a fractional step like scheme at the algebraic level. Parallelization is carried out using a master-worker strategy and implemented inside the Alya System [4].

2 METHODOLOGY

Mesh of a LV human heart was generated from a high-resolution magnetic resonance image of ex-vivo human heart. Boundary conditions have then to be imposed in order to define the inlet at the mitral and outlet at the aortic tubes respectively. The velocities at the rest of the boundaries are defined with no-slip, rigid wall boundary conditions.

In particular, a constant blood flow velocity of 90cm/s [5] is used as inlet boundary, red triangles in Figure 2. At the elements near to the outlet, blue triangles in Figure 2, a higher viscosity is imposed in order to reduce wave reflection caused by impedance mismatch between the inside and outside of the outlet tube.

In this scenario, a set of simulations is then proposed using an Embedded Boundary (EB) mesh framework. Beginning with a nonconforming mesh of 64000 hexahedral elements, see Figure 1a, two successive levels of refinement generate hexahedral meshes of 512000, and 4000000 elements respectively. In Figure 3a, 3b, and 3c we can see all these nonconforming meshes once the outside elements was removed.

In order then to determine the correctness of the coding, results of previous simulations will be compared with the results obtained using a conforming mesh of tetrahedral elements, see Figure 2. The focus will be put on the pressure drop between the inlet at the mitral and outlet at the aortic tubes respectively.
Figure 2: Inlet, triangle red elements, and outlet, triangle blue elements, conditions at the boundary problem domain

(a) Inside elements of nonconforming mesh of 64000 hexahedral elements
(b) Inside elements of nonconforming mesh of 512000 hexahedral elements
(c) Inside elements of nonconforming mesh of 4 millions hexahedral elements

Figure 3: Inside elements of nonconforming meshes
Table 1: Pressure drop between the inlet at the mitral and outlet at the aortic tubes respectively is shown for the conforming and nonconforming meshes

<table>
<thead>
<tr>
<th>Mesh Type</th>
<th>Conforming Mesh</th>
<th>64000 hexahedral mesh</th>
<th>512000 hexahedral mesh</th>
<th>4 millions hexahedral mesh</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressure drop (kPa)</td>
<td>14.97</td>
<td>15.53</td>
<td>18.78</td>
<td>37.64</td>
</tr>
</tbody>
</table>

3 RESULTS AND CONCLUSIONS

In Table 1 the pressure drop between the inlet at the mitral and outlet at the aortic tubes respectively is shown for the conforming and nonconforming meshes. As we would expect, the difference of the results between these two kinds of meshes is smaller for a higher level of refinement. Results can consider to be good enough from the nonconforming mesh of 512000 hexahedral elements.

Embedded mesh boundary methods will prove to be a valide alternative to solve solid and fluid interaction problems for laminar and transient flows. Such methods use nonconforming meshes, eliminating thus the creation of conforming meshes for complex geometries. Embedded mesh boundary methods can be also used for large movement of solids inside a fluid [2]. They avoid large deformations for meshes that cannot be handle for ALE strategies.

REFERENCES


VARIATIONAL MODEL FOR CARDIAC ELECTROPHYSIOLOGY: TOWARD EFFICIENT SIMULATIONS OF ELECTRICAL PROPAGATION

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SUMMARY

In this work we present a new phenomenological electrophysiology model for cardiac tissue. This model is based on a Gradient-Flow reformulation of the electrophysiology equations. Using this formulation, we derive bounds on the time-step size that guarantee convergence of gradient-descent methods. We show that the model describes adequately the shape of the action potential and the restitution properties of cardiac tissue. In order to demonstrate this, a problem of re-entrant arrhythmia for a two dimensional cardiac tissue is solved.

Key words: Cardiac Electrophysiology, Gradient-Flow formulation, Variational principles, Electrophysiology model

1 INTRODUCTION

Cardiovascular disease is the leading global cause of death, claiming more lives than all forms of cancer combined [4]. Despite the big efforts towards the development of new drug therapies and devices, broader applications in this area rely on patient specific data [1]. In this context, numerical methods for the simulation of cardiac electrophysiology represent a powerful tool that can help in the improvement of therapies and devices [7]. However, the acceptance of these methods in the medical community depends of the reliability and robustness of the electrophysiology models used to simulate the cardiac response.

The numerical solution of the cardiac electrophysiology equations has been mainly solved using finite-difference, finite-volume and finite-element approximations for the spatial discretization, whereas the time integration has been predominantly addressed by finite-difference schemes [5, 6]. In cardiac electrophysiology, the most traditional time-integration schemes used are explicit and semi-implicit Euler methods, which are suitable for large-scale simulations where solving a large linear system of equations for every time-step is generally avoided. However, it is well known that stringent time-step constraints arise from stability considerations for such methods as the mesh size decreases, thus reducing their computational efficiency. An alternative approach is the use of implicit Euler methods, which offer larger time-steps at the price of solving a set of non-linear equations at every time-step.

In [3], we have shown that the implicit Euler integration scheme is equivalent to solving an incremental saddle point problem, which allows for a mathematical analysis of the constraints on the time-step size. Based on the results of variational analysis, we derive bounds on the time-step size that guarantee the convergence of gradient-descent methods for the FitzHugh-Nagumo equations. However, the FitzHugh-Nagumo model is not very suitable for modelling many important problems in cardiac tissue, such as the problem of re-entrant cardiac arrhythmias. Therefore, a variational model for cardiomyocytes for which analytical estimates can be derived remains as an outstanding problem.
2 METHODOLOGY

Let $B \subseteq \mathbb{R}^N$ be the physical domain of interest, where $N$ is any positive integer. We define $\phi : B \times \mathbb{R}^+ \to \mathbb{R}$ as the transmembrane potential, and $r = (r_1, r_2, r_3, ..., r_M) : B \times \mathbb{R}^+ \to \mathbb{R}^M$ as the gating variables, or internal variable that control the cell recovery. Then, the electrophysiology equations can be described as

\begin{align*}
C_\phi \frac{\partial \phi}{\partial t} - \text{div}(D \nabla \phi) &= f_\phi(\phi, r) \quad (1) \\
C_r \dot{r} &= f_r(\phi, r) \quad (2)
\end{align*}

where $C_\phi \in \mathbb{R}^+$ and $C_r \in \mathbb{R}^{M \times M}$ are symmetric and positive definite tensor. The term $D \nabla \phi$ characterizes the natural propagation of the excitation waves. Here $D \in \mathbb{R}^{N \times N}$ is a symmetric conductivity tensor and positive definite. The governing equations are complemented with Newmman and Dirichlet boundary conditions

\begin{align*}
\phi(x) &= \bar{\phi} \quad x \in \partial B_\phi \\
q \cdot n &= \bar{q} \quad x \in \partial B_q
\end{align*}

Initial conditions are also considered as $\phi|_{t=0} = \phi_0(x)$ and $q|_{t=0} = q_0(x)$. The choice of the recovery variables and the source terms establish the particular electrophysiology model, there are many formulations reported in the literature

Inspired on the mathematical structure of the FitzHugh-Nagumo model, here we propose an ionic model whose expressions take the form

\begin{align*}
f_\phi(\phi, r) &= c_1(\phi - \alpha)(1 - \phi) - c_2 \phi r \quad (5) \\
f_r(\phi, r) &= \frac{c_2}{2} (\phi^2 - \frac{r^2}{d} - \frac{\kappa}{d} r^3) \quad (6)
\end{align*}

where the parameter $\alpha$ represents an activation threshold for the transmembranal potential. In particular, it follows that equations (5),(6) derive from a generalized electrochemical potential, thus conforming to the variational framework presented in [3], namely

\begin{equation}
\mathcal{E}[\phi, r] := \int_{\Omega} \left\{ \frac{1}{2} \nabla \phi \cdot D \nabla \phi + F(\phi, r) \right\} dx + \int_{\partial \Omega_q} \phi \bar{q} dS \quad (7)
\end{equation}

where $F : \mathbb{R} \times \mathbb{R} \to \mathbb{R}$ is an electrochemical density associated to the transmembrane ionic currents, such that

\begin{align*}
f_\phi(\phi, r) &= \frac{\partial F}{\partial \phi}, \\
f_r(\phi, r) &= \frac{\partial F}{\partial r}
\end{align*}

Further, we define the rate potential as

\begin{equation}
\Psi := \int_{\Omega} \psi(\dot{\psi}, \dot{r}) dx = \int_{\Omega} \left\{ \frac{1}{2} \dot{\psi}^2 - \frac{1}{4} \frac{c_2}{d^2} \dot{r}^2 \right\} dx \quad (10)
\end{equation}

It follows that the monodomain equations (1) and (2) are recovered from the gradient-flow problem

\begin{equation}
0 \in \delta \Psi + D \mathcal{E} \quad (11)
\end{equation}

where $D$ represents the Fréchet derivative and $\delta$ is the sub-differential operator.

To perform temporal integration of the monodomain problem, we partition the time domain into a sequence of finite intervals $[t_{n+1}, t_n]$ with $\Delta t = t_{n+1} - t_n$, and define the incremental potential is defined as

\begin{equation}
G_n[\phi, r] := \int_\Omega \Delta t \psi \left( \frac{\phi - \phi_n}{\Delta t}, \frac{r - r_n}{\Delta t} \right) + F(\phi, r) + \frac{1}{2} \nabla \phi \cdot D \nabla \phi. - \int_{\partial \Omega_q} \phi \bar{q} dS. \quad (12)
\end{equation}
Once the incremental potential is defined we can use the result given in [3]. Within this it was demonstrated that the incremental update from \((\phi_n, r_n)\) to \((\phi_{n+1}, r_{n+1})\) corresponds to the optimization problem

\[
\min_{\phi \in S} \max_{r \in V} G_n(\phi, r)
\]

Moreover, it can be prove that this problem has a unique solution if

\[
\frac{1}{\Delta t_{\text{convex}}} > \max \left\{ \frac{c_1}{3} \left( \alpha^2 - \alpha + 1 \right), \frac{d}{3\kappa} \right\}.
\]

Therefore, we found a time-step bound that guarantees strict convexity in \(\phi\) of the objective function defined in [13] for the proposed electrophysiological model. This ensures convergence of gradient-descent methods, such as Newton-Raphson methods. This time-step bound depends on the model parameters selected, which are setted by adjusting the restitution curve, Action Potential Duration (APD) and initial upstroke of the action potential using experimental data [2]. It was verified that the model is not sensitive to variations of the parameters \(\kappa\) and \(d\). On the contrary, is was established that the parameters \(c_1\) and \(c_2\) have a significant influence over the initial upstroke and APD, respectively. In this sense the selection of \(c_1\) is critical, due to the fact that \(c_1\) is proportional to the initial upstroke and inversely proportional to the time-step bound.

3 RESULTS

In order to see that the condition (14) is guaranteed, an action potential propagation over a single cell was simulated using different values for the time-step. From these simulations, we have obtained the error in each iteration from the evaluation of the residual norm. Figure 3 shows the residual error versus the number of iterations for a given time-step. In this case \(\Delta t_{\text{convex}} = 0.78\ ms\) and we see that for \(\Delta t < \Delta t_{\text{convex}}\) quadratic convergence is achieved.

![Figure 1: Residual error versus number of iterations for the proposed model](image)

On the other hand, in order to see the performance of the model in problems of cardiac arrhythmias, a simulation over a tissue were implemented. A two dimensional rectangular tissue model were used, using a finite element discretization of 50 \(\times\) 50 quadrilateral linear elements. The simulation were performed during 6000 \(\text{ms}\) and using \(\Delta t = 0.01\ ms\). In order to generate an spiral wave an stimulation were performed over an small area of the tissue at \(t = 1300\ ms\).

The numerical simulation of the re-entrant spiral was achieved using a Newton-Raphson scheme to solve the resulting nonlinear system of equations. Figure 3 shows that spiral formation was reached at 1800 \(\text{ms}\), demonstrating that the proposed model is capable of simulate pathologies at tissue level. Then, in contrast with the FitzHugh-Nagumo model, that is also a variational model, this model is suitable to simulate action potential propagation in cardiac tissue.
In this work we have developed a new electrophysiological model for the human myocardium which is based on a gradient-flow reformulation of the electrophysiological equations and its temporal discretization. As a consequence of this, a time-step bound that guarantees the strict convexity of the incremental problem can be derived. Therefore, convergence of gradient-descent methods is ensured. This advantage is not encountered, or may difficult to find for cardiac electrophysiological models reported to date. Finally, this time-step bound depends only on the model parameters, which can be set in order to fit the restitution properties of the human myocardium.

REFERENCES


Modelling Cardiovascular Devices: Design, Testing & Patient-Specific Applications II
DEVELOPMENT OF A VISCO-HYPERELASTIC SOLID MECHANICS SOLVER FOR THE PENN STATE PVAD MEMBRANE

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SUMMARY

A finite-volume solid mechanics solver was developed and validated for the hyper-viscoelastic segmented poly(ether urethane) urea (SPEUU) membrane of the Penn State PVAD. The hyper-viscoelastic material properties of SPEUU were first determined using uniaxial tensile testing. The solid mechanics solver was validated with the same simple uniaxial testing and also with both steady and pulsatile experiments of the SPEUU membrane in a modified PVAD acrylic model and a two camera tracking system.

Key words: pediatric, ventricular assist device, visco-hyperelastic, computational

1 INTRODUCTION

Children with congenital heart disease face the highest wait-list mortality rate in all of transplantation medicine with 23% dying within 6 months of being added [1]. Despite this, only recently has a pediatric ventricular assist device (PVAD), the Berlin Heart EXCOR, been approved for use in the United States [2]. As part of developing a reliable PVAD, it is necessary to accurately predict the hemodynamics within the device due to higher hemolysis and thrombosis rates in PVADs compared to adult VADs [3]. Very little work has been done on the modeling of blood pumps due primarily to the moving components within the pump and the strong fluid-solid interactions that occur. For pulsatile devices, this includes the interactions of both air and blood with a moving membrane. To accurately model the pump, it is necessary to use a strongly-coupled fluid-structure interaction (FSI) computational model. As a first step towards a full FSI model, an accurate solid mechanics solver for modeling of the PVAD’s membrane needs to be developed.

The Penn State PVAD uses a segmented poly(ether urethane) urea (SPEUU) membrane with a variable structural makeup that allows for the toughness, flexibility, durability and biocompatibility needed in a medical device. However, the SPEUU material exhibits unique mechanical properties including hyperelasticity, cyclic softening and hysteresis [4] that complicate its modeling. Therefore, to improve the design of future pulsatile PVADs, a finite-volume solid mechanics solver will be developed to accurately model the hyper-viscoelastic SPEUU PVAD membrane and ultimately, incorporated into a tightly-coupled FSI solver.

2 METHODOLOGY

2.1 Material Characterization

To determine the hyperelastic and viscoelastic parameters of the PVAD SPEUU membrane, uniaxial tests were performed on dog-bone samples cut from manufactured PVAD membranes according to ASTM D638 Standard Test Method for Tensile Properties of Plastics (Fig. 1-A) with a scale factor of 55/115 (Fig. 1-B). All tests were performed on a Lloyd Tensile Testing Machine (AMETEK, Inc.) with a 5N load cell. Each SPEUU sample was first cyclically loaded to a strain of 20% at a strain rate of 20 s⁻¹ to collect data for hyperelastic characterization and then again loaded and held fixed at a strain of 20% for 30 seconds to collect stress relaxation data for viscoelastic
characterization. Five dog-bone SPEUU samples (measured thickness = 0.305 ± 0.04 mm and density = 1195.9 ± 8.7 kg/m³) were tested and averaged for complete material characterization.

2.2 Dog‐bone Computational Simulations
A new hyper‐viscoelastic finite‐volume solid mechanics solver was developed using OpenFOAM (OpenCFD, Ltd.) software based on previous solvers developed by Tukovic and Jasak [5] and the displacement‐pressure based finite‐volume formulation by Bijeljona et al [6]. To validate the solver, the same experimental uniaxial data were used to compare to computational simulations. A dog‐bone model was created using Pointwise (Pointwise, Inc.) with the same ASTM dimensions. The 20 s⁻¹ strain rate was applied on the top of the dog‐bone while the bottom was fixed and the sides were traction free. Both the Cauchy and first Piola‐Kirchhoff (PK1) stresses were compared in the dog‐bone gauge section. To validate the numerical solutions, both a systematic grid study and a time‐step independence study were performed on the dog‐bone model.

2.3 Membrane Experimental Simulations
An acrylic model was created to mimic the general geometry of the PVAD but with enlarged chambers and straight walls along with a two‐camera tracking system (Fig. 2). The acrylic model was split into air (Fig. 2‐A) and blood‐analog (Fig. 2‐C) chambers separated by a modified SPEUU membrane (Fig. 2‐B) to replicate the operation of the actual Penn State PVAD. A pneumatic driver was used to alternatively pump and vacuum air from the acrylic model air chamber and facilitate membrane motion. A set of 129 markers were drawn onto the blood contacting surface of the SPEUU membrane in a bike wheel‐spoke pattern (see Fig. 5). Using an in‐house Matlab code to locate the markers and a discrete linear transform (DLT) Matlab code made available by Reinschmidt and van Den Bogert [7], the 3D location of each marker were determined (Fig. 2‐D). Both steady and pulsatile pressures were applied to the PVAD membrane by the pneumatic driver. Four steady pressures were chosen (251, 336, 934 and 3730 Pa) such that the membrane was displaced to four distinct positions and both simplified sinusoidal (60 bpm and 500 ms systole) and physiological (75 bpm and 340 ms systole) waveforms were applied.

2.4 Membrane Computational Simulations
Both 2D and 3D membrane models were created using Pointwise and the experimental pressure waveforms from the pneumatic driver were used as boundary conditions on the air surface, while the edge of the membrane was fixed and the blood surface was traction free. The steady experiments were compared directly to the steady simulations while the pulsatile experiments were compared to the pulsatile simulations at discrete points during a full membrane cycle. The respective displacements of the 129 markers were compared using a residual norm analysis.

3 RESULTS AND CONCLUSIONS
3.1 Material Characterization
The five SPEUU samples’ loading curves were averaged (Fig. 3-A) and fit to five common hyperelastic constitutive models (Fig. 3-B) using an in-house Matlab code. The Mooney-Rivlin model (Eq. 1) was shown to have the best fit with coefficients $C_1=0.333$ MPa and $C_2=1.334$ MPa:

$$\Sigma_{MR} = 2(C_1 + \frac{C_2}{\lambda} - \frac{C_2}{\lambda^2} - \frac{C_2}{\lambda^3})$$  \hspace{1cm} (1)

For non-linear visco-hyperelastic materials, the stress depends on both the time and strain (Eq. 2):

$$\Sigma(\lambda, t) = S_{HE}(\gamma) \ast g(t)$$  \hspace{1cm} (2)

where $S_{HE}(\gamma)$ is the strain-dependent hyperelastic stress and $g(t)$ is a Prony series (Eq. 3) [8]:

$$g(t) = g_\infty + \sum_{i=1}^{n} \frac{\gamma_i}{t^i}$$  \hspace{1cm} (3)

The five SPEUU samples’ stress relaxation curves were averaged (Fig. 3-C) and fit to a 3-term Prony series (Fig. 3-D). The resulting Prony-series coefficients were $g_\infty = 0.906$, $g_1 = 0.0508$, $g_2 = 0.0399$, $Z_1 = 0.8943$, and $Z_2 = 10.6829$.

Figure 3: A) PK1 Stress (MPa) vs. stretch loading data (all five samples and average). B) PK1 Stress (MPa) vs. stretch curve fit of hyperelastic models. C) Normalized stress vs. time (s) relaxation data (all 5 samples and average). D) 3-term Prony Series fit to average relaxation data.

3.2 Dog-bone Computational Simulations
The average percent difference over the entire loading/unloading cycle between the experimental and computational results was less than 3% for both the Cauchy (Fig. 4-A) and PK1 (Fig. 4-B) stresses. Ignoring the viscoelastic behavior of the SPEUU material, an analytical solution exists for the hyperelastic stress of a Mooney-Rivlin material (see Eq. 1) under uniaxial tension. The difference between the predicted analytical results and the computational results was less than 2% for both Cauchy (Fig. 4-A) and PK1 (Fig. 4-B) stresses.

Figure 4: Comparison of experimental, computational and analytical results for both the A) Cauchy stress (MPa) and B) PK1 stress (MPa).
3.3 Membrane Experimental Simulations
Both the steady and pulsatile experimental camera images were reconstructed using the DLT Matlab code (Fig. 5-A). The displacement of the 129 membrane surface markers was calculated for the steady state simulations and tracked throughout the cycle for the pulsatile simulations. For comparison, the initial un-displaced marker coordinates were mapped to the membrane mesh to find their corresponding computational cells. The respective 129 different computational cells were similarly tracked throughout the simulations and their displacements determined.

3.4 Membrane Computational Simulations
Steady and pulsatile simulations with both 2D and 3D membrane models were performed using the visco-hyperelastic solver in OpenFOAM. Grid refinement and time-step studies were performed on the 60 bpm pulsatile 2D simulation and it was determined that 4-cells through the thickness of the membrane (nearly isotropic cells) and a time step of 1e-6 were necessary such that the membrane displacements were independent of the computational parameters. Ultimately, the 3D computational simulations were used to compare the motion of the 129 experimental markers to their respective 129 computational cells.

3.5 Conclusions
The Penn State PV AD SPEUU membrane is a visco-hyperelastic material that can be accurately described using a Mooney-Rivlin hyperelastic model and a 3-term Prony series model. A finite-volume solid mechanics solver was developed in OpenFOAM and validated using a simplified uniaxial dog-bone model and then with both steady and pulsatile 2D and 3D computational membrane models. This solver will be incorporated into a future FSI solver to simulate the complex interactions of air, membrane and blood in the Penn State pulsatile pneumatic PVAD.

REFERENCES
VISCOELASTIC MODEL FOR DESCRIBING THE RESPONSE OF TRANSCATHETER AORTIC VALVES
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SUMMARY
Transcatheter aortic valves (TAV) have revolutionized the treatment of aortic valve disease. In this study, a novel fractal structural model is proposed to model viscoelastic response of these bioprosthetic valves. The dynamic of the valve in response to fluid dynamic loads is examined using a coupled fluid–structure interaction (FSI) methodology based on immersed boundary technique. By using a fractional viscoelastic solid model for the embedded collagen fibers of the valve and use hyperelastic model for elastin, we study the viscoelastic and stress relaxation in TAV. Novel numerical solutions for the calculation of the convolution integral from the fractal model is proposed through realization of the Laplace transformation of the model and show the computational benefits of the new procedure.

Key words: bio-prosthetic valves, hemodynamics, fluid structure interaction, fractal viscoelastic model

1 INTRODUCTION
Transcatheter aortic valve replacement (TAVR) has emerged as an alternative to surgical aortic valve replacement (SAVR) in patients with severe aortic stenosis who are otherwise considered inoperable or at high operative risk. The most common design of a TAV is bio-prosthetic leaflets, constructed out of porcine or bovine pericardium, that are sutured to a metal scaffolding. In addition to the relative ease of implantation, a significant advantage of bio-prosthetic transcatheter valves over mechanical valves is the much lower incidence of valve thrombosis or clot formation [1]. However, it has long been speculated that these studies, being mostly based on voluntary registries, might significantly underestimate thrombosis risk [2]. One of the potential factors is related to the biomimetic design of these valves and the arrangement of its embedded fibers. In particular, the tissue properties of valve leaflets affect their local dynamics and modify the local hemodynamic status. Thus, in order to better understand the causal mechanisms of thrombosis formation on TAV, a better structural model of the bio-prosthetic aortic valves is required. Most biological fibers, including aortic valve fibers, display creep and stress relaxation behaviors well described using fractal derivatives. In fact, it can be argued that since collagen fibers are a hierarchy of constituents that self-assemble at different length scales from tropocollagen molecules to fascicles and fibers, they are fractal structures and fractal calculus is right procedure to model their structural response [3,4,5].

Here, using fractal derivative to model time dependent nature of collagen fiber forces we investigate the dynamic of TAV with a coupled FSI simulation, and the main consequence of fractal modeling is discussed.

2 METHODOLOGY
A coupled fluid–structure interaction (FSI) methodology based on immersed boundary technique is developed for modeling the coupled flow-structure interaction in TAVs. The blood flow is model with the incompressible Navier-Stokes equation,
\[
\frac{\partial u_i}{\partial x_i} = 0; \quad \frac{\partial u_i}{\partial t} + u_j \frac{\partial u_i}{\partial x_j} = -\frac{1}{\rho} \frac{\partial p}{\partial x_i} + \frac{\partial \tau_{ij}}{\partial x_i}
\]  
(Eq. 1)

where \(u_i\) is the flow velocity, \(p\) the pressure, and \(\tau_{ij}\) is the fluid stress. The equations of motion is written as, \(M \ddot{X} + aM \dot{X} + \frac{\partial \Psi^a(X(t))}{\partial X} = F_{\text{ext}}\), where \(M\) is mass matrix, \(a\) is the mass-proportional damping coefficient and \(\Psi^a(X(t))\) is the fractal strain energy. The high-order adaptively refined subdivision shell finite-element technique is employed to accurately solve for the dynamics of the leaflets [6,7]. A penalty-based sliding contact approach is employed to model the contact between adjacent leaflets during the closure of the valve and the use of the high-order description of leaflets allows accurate penalization of the penetration of the leaflets [8]. A fully coupled fluid–structure interaction (FSI) methodology based on immersed boundary technique is used for modeling the coupled flow-structure interaction in valve simulations.

We will model the response of collagen fibers with a 1D Standard Linear Solid (SLS) model and define the fiber viscoelastic second-Piola Kirchhoff stress, \(S(t)\), to be

\[
S(t) + \tau_0^{\text{rel}} \frac{\partial S(t)}{\partial t} + \tau_0^{\text{rel}} \frac{\partial S(t)}{\partial t} = S_0(t) + \tau_0^{\text{rel}} \frac{\partial S_0(t)}{\partial t} + \tau_0^{\text{rel}} \frac{\partial S_0(t)}{\partial t},
\]

where \(\tau_0\) is the fractional order, \(\tau_0^{\text{rel}}, \tau_0^{\text{rel}}\) are the relaxation parameters and \(S_0(t) = \frac{\partial \Psi^a}{\partial E}\) is the hyperelastic stress tensor [4,9]. To efficiently calculate the required fractional derivatives [10], a fast realization technique [11] is employed through fitting a space-state model to the kernel function that relates \(S(t)\) to \(S_0(t)\).

3 RESULTS

Significant challenges are encountered in conducting these simulations including the modeling of contact for complex (asymmetric) leaflet motion and the acceleration of the coupled simulations so as to conduct the large number of cardiac cycles required to gain required sufficient statistics. The initial simulations were promising and show the efficiency of fractal derivative representation. It provides a sequence of the valve deformation and a detailed view of the effect of leaflet motion on the turbulence of the aortic.

4 CONCLUSION

The development of computational models that can capture the coupled physics associated with hemodynamics, leaflet motion and leaflet viscoelastic response is highly challenging. The initial simulations show that the computational model developed here is capable of providing useful details regarding the coupling between flow and the leaflets and further efforts will focus on model improvement and validation.

REFERENCES

MODELING EXOGENOUSLY CROSSLINKED TISSUES UNDER CYCLIC LOADING

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SUMMARY

One of the most crucial effects involved in the mechanical failure of bioprosthetic heart valves is the permanent set effect; especially in the early stage (2-3 years). Permanent set will permanently alter the shape of the bioprosthetic heart valves, resulting in extraneous stress on the valve leaflets. While this process does not actually damage the tissue, it will accelerate the mechanical failure. Thus, we developed permanent set constitutive model for exogenously crosslinking tissue, using the underlying mechanism of the scission-healing behavior of the glutaraldehyde crosslinker and the microstructure of the tissue to predict the mechanical response after cycling.

Key words: soft tissue mechanical, constitutive model, bioprosthetic heart valve

1 INTRODUCTION

Despite the overall advancements in the treatment of cardiovascular diseases, heart valve surgeries have seen little real improvements in life expectancy since 1985, where the survival rate after 10 years is still 29.7% [1]. This is despite over 100,000 heart valve surgeries done per year in the U.S. alone, costing over $20 billion in surgical cost alone. Bioprosthetic heart valves (BHV) derived from Exogenously crosslinked (EXL) tissue, such as bovine pericardium (BP), are by far the most popular surgical replacements. The field has also been heading in the direction of percutaneous devices to minimize surgical risk. However, this technology is still in its early stages, with a 2-year mortality rate of 43.3% [1]. Percutaneous BHVs significant increase the complexity of BHV designs, requiring much thinner leaflets than traditional BHVs for folding and compression. This significantly increases the demand on durability of these devices as the leaflets will be under significantly higher stresses.

BHV failure results from leaflet structural deterioration mediated by mechanical fatigue and/or tissue mineralization. In general, while mineralization is associated with serious structural deterioration, significant structural damage is known to occur independently from calcification [2]. Most research for BHV devices focus on calcification, but it is also crucial to maintain the optimal mechanical response of the BHV leaflets, which will in turn help maintain the structural integrity of the BHV leaflets and thus improve the durability of BHVs. The most important effect during the early stages (2-3 years) of cyclic loading is the permanent set (PS) effect. PS permanently changes the shape of the BHV and how it deforms (Fig. 1A&B), without induce any actual damage or fatigue. However, this will result in regions of high stress concentrations in the leaflets, which will accelerate the failure of the device. Understanding and being able to model and predict EXL tissue under PS is thus especially important. In the present work, we developed a structurally-based PS constitutive model to help to better understand and predict the change in mechanical property that occurs due to cyclic loading, and aid in the design of new BHVs.
2 METHODOLOGY

2.1 General considerations

We assume that the mechanism responsible for PS is the scission-healing reaction of glutaraldehyde polymer. This allows that EXL matrix of the leaflet to change in reference state, but not necessarily disrupt the collagen fiber architecture. Thus, the key mechanism of our model is to use the PS of the matrix to convect the collagen fiber architecture, which can then be used to predict the change in mechanical response of the whole leaflet.

2.2 Constitutive model for EXL tissues

We developed a EXL model with EXL BP, taking into account the three main contributor to the mechanical response: collagen, EXL matrix, and fiber-fiber interactions [3]. The model shows a significant stiffening of the non-fibrous matrix after EXLing and that an interaction term was necessary to match the mechanical response. We further extended the model using a full structural derivation of the interaction term. By having all the mechanism being structurally-based, we can determine the new mechanical response of the EXL tissue based on the change in the fiber micro-structure.

2.3 Permanent set model

PS is initially used to describe elastomer [4]. To model PS in EXL tissue, we separate the matrix into parts of a time evolving mixture, each with a different reference state that evolves depending on the strain history of the BHV leaflet (Fig. 1C). The form for the matrix is shown below, where \( \hat{F} \) is the strain history, \( \mu \) is the matrix modulus, and \( r, \alpha, \) and \( \beta \) are constant controlling the shape of the response.

\[
\tilde{S}_{m} (C, \hat{F} (\hat{s})) = \mu \left( (I_1 (\hat{F}) - 3)^{\alpha-1} + r (I_1 (\hat{F}) - 3)^{\beta-1} \right) \left( \tilde{B}^{-1} (s) - \tilde{B}_{33}^{-1} (s) C_{33} C^{-1} \right)
\]

The entire process is governed by one rate constant following first order kinetics. The resulting PS that occurs, which is a shape change described by a deformation gradient from the 0-cycle state to the current stress-free state, depends on the mixture of the matrix in equilibrium as below

\[
S_{\text{total}} (C, s) = e^{-k_{PS}} \tilde{S} (C, \hat{F} (0) = \mathbf{I}) + \int_{0}^{s} k_{PS} e^{-k_{PS} (s-\hat{s})} \tilde{S} (C, \hat{F} (\hat{s})) d\hat{s}
\]

Similarly, where \( \hat{F} \) is the strain history, \( \tilde{S} \) is the EXL model including the matrix term in equation 1. The PS deformation is then used to convect the collagen fiber microstructure and predict the new mechanical response using the EXL tissue model in section 2.2.

To establish the form and validate the model, we used extant data from two type of experiments: strain controlled and stress controlled. The strain controlled PS data was presented by Sun et al. [5].
EXL BP was cycled up to 65 million cycles at 16% peak strain. We used this primarily to establish the form of the model. Here, we fit the PS deformation and mechanical response at 0 and 30 million cycles, then used that to predict the PS and mechanical response at 65 million cycles. Since the strain history was controlled directly, we simplified the model into two states corresponding to the origin and loading state as a way to establish the model form and its predictive capabilities.

To implement and validate the full model in a dynamic simulation, we used the stress controlled data presented by Sellaro et al. [6]. Here, EXL BP was cycled up to 50 million cycles at 500kPa. The specimens were also tested parallel to the preferred collagen fiber direction (PD) as well as the orthogonally (XD). Because this is stress controlled, the strain history will change as PS occurs. Here, we first use the 0 cycle mechanical response for the XD specimens to predict the strain history and fit the PS deformation. The results were then validated by predicting the mechanical response at 20 and 50 million cycles. The model was the further validated by using the rate constant from the XD specimens to predict the experimental data from the PD specimens.

Next, we developed a finite element (FE) model with the real BHV geometry, utilizing the methods of Aggarwal and Sacks [7] to map the collagen fiber microstructure directly to the finite element mesh. PS is solved using finite difference in time and using the total Lagrangian for the strain history (Fig. 2A&B). The model was validated by simulating the experimental studies, and used to study how initial BHV geometry and material properties affect PS (Fig. 2C).

![Figure 2](image-url)  
**Figure 2:** A-B) Finite model showing the valve geometry with mapped fiber architecture. C) Parametric study of the fiber direction of in the leaflet on the stress distribution of the leaflet under loading.

### 3 RESULTS AND CONCLUSIONS

The most important finding is that microstructure change alone can predict the change mechanical response ($p > 0.07$). In addition, the PS model appears to under predicts the experimental data, which suggests that there is no detectable structural damage at this stage, else experimental data would be lower. Additionally, we further found that our model was able to fit the PS deformation under both strain (Fig.3A) and stress control. The model predicts the PS and mechanical response at 65 million cycled under strain control very well (Fig.3B&C), as well as being able to predict the mechanical response of the stress controlled XD oriented specimen well just by fitting the PS deformation. Furthermore, the rate constant from the XD specimens ($2.2 \times 10^{-6}s^{-1}$) was able to predict the PS and mechanical response of the PD specimens, which agrees very well both in terms of the PS deformation (Fig.3A) and mechanical response (Fig.3C&D). In addition, the rate constant was comparable between the two studies with the strain controlled specimens ($2.3 \times 10^{-6}s^{-1}$). This suggests that the strain-level dependence was small at this range of deformations.

#### 3.1 Conclusions

In this work, we developed the first PS model for EXL tissues based on the underlying scission/healing of the crosslinker. The results show that PS has significant impact on the early stages of BHV cycling, and our PS model is able to capture and more importantly predict how the shape and mechanical response of the EXL BHV leaflet change during this stage. We used the PS model to perform computational simulations on the effect BHV geometry as well as material properties and crosslinking chemistry on the leaflet stresses. Thus, proper design of BHVs needs to properly account for the PS effect to best improve their performance and durability.
Figure 3: A) The best fit PS deformation for the strain controlled specimens, where the solid line shows the model, the dashed line shows the model with double the rate constant and dotted line shows the model with half the rate constant. The boxed data points are not fitted but are predicted from the model. B) The best fit mechanical response at 0M cycle. C) The predicted mechanical response at 65 million cycle from the 0 cycle data and PS deformation.

Figure 4: A) The predicted PS deformation for the strain controlled PD specimens using the rate constant (2.2x10^-6 s^-1) from the XD fit, where the solid line shows the model, the dashed line shows the model with double the rate constant and dotted line shows the model with half the rate constant. B) The best fit mechanical response at 0M cycle. C) The predicted mechanical response at 20 million cycle and D) the predicted mechanical response at 50 million cycle.

ACKNOWLEDGEMENTS

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REFERENCES


HIGH ORDER FINITE ELEMENT SIMULATIONS FOR FLUID DYNAMICS VALIDATED BY EXPERIMENTAL DATA FROM THE FDA BENCHMARK NOZZLE MODEL

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SUMMARY

The objective of the present work is to construct a sound mathematical, numerical and computational framework relevant to blood flow simulations and to assess it through a careful validation against experimental data. We perform simulations of a benchmark proposed by the FDA for fluid flow in an idealized medical device, under different flow regimes. The results are evaluated using metrics proposed in the literature and the findings are in very good agreement with the validation experiment.

Key words: CFD, validation, medical device, open source finite element software

1 INTRODUCTION

A challenging benchmark was proposed by the US Food and Drug Administration (FDA) in [1] in order to assess the stability, accuracy and robustness of computational methods in different physiological regimes. The findings of 28 blinded investigations were reported in [2] and, as critically analyzed in [3], practically all CFD solvers failed to predict results that agreed in a satisfactory manner with the experimental data. Several subsequent papers tackled this question, by employing different numerical approaches: for instance a finite-element based direct numerical simulation method in [4] or a large-eddy simulation method in [5].

We aim at contributing to the effort of improving the reliability and reproducibility of computational studies by performing a thorough validation of the fluid solver developed in the open source finite element library Feel++ [6]. In the current investigation, we present results corresponding to three Reynolds numbers 500, 2000 and 3500 obtained by using a direct numerical simulation method for the Navier-Stokes equations. In particular we implement and compare low order as well as high order approximations including for the geometry and we discuss some issues not previously reported in the literature.

2 METHODOLOGY

Benchmark description. The FDA benchmark nozzle model provides a comprehensive dataset of experimental measures using a well-defined geometry corresponding to an idealized medical device (see Figure 1 for a schematic sketch of the domain and [1, Sec. 2.1] for the precise dimensions of

<table>
<thead>
<tr>
<th>$Re_i$</th>
<th>$Re_t$</th>
<th>FLOW RATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>167</td>
<td>500</td>
<td>$5.21 \cdot 10^{-6}$</td>
</tr>
<tr>
<td>667</td>
<td>2,000</td>
<td>$2.08 \cdot 10^{-5}$</td>
</tr>
<tr>
<td>1,167</td>
<td>3,500</td>
<td>$3.64 \cdot 10^{-5}$</td>
</tr>
</tbody>
</table>

Figure 1: Computational domain (top) and flow regime specifications (bottom); $Re_i$ and $Re_t$: Reynolds number in the inlet section and throat section, respectively.
computational domain, we used \( \mathbf{G} \) language, seamless interpolation, mesh adaption and seamless parallelization. Regarding the com-

The comparison with experimental data is made in terms of (i) wall pressure difference (normalized to the mean throat velocity) versus axial distance; and (ii) axial component of the velocity (normalized to the mean inlet velocity) along the centerline:

\[
\Delta p^\text{norm} = \frac{p_z - p_{z=0}}{\frac{1}{2} \rho f \overline{u}_i^4} \quad \text{and} \quad \overline{u}_z^\text{norm} = \frac{u_z}{\overline{u}_i} \quad \text{where} \quad \overline{u}_i = \frac{4Q}{\pi D_t^2}, \quad \overline{u}_t = \frac{4Q}{2D_t^2},
\]

and \( Q \) is the volumetric flow rate retrieved from \( Re_t \) (see Figure 1). Furthermore, we present results on two validation metrics reported in [2], also assessed in [4]: a conservation of mass error metric \( E_Q \) (on a percentage basis) and a general validation metric \( E_z \) comparing average experimental velocity data with computed axial velocities.

**Fluid equations and numerical approach.** We now turn to the mathematical and the numerical setting. We consider the homogeneous, incompressible, unsteady Navier-Stokes equations, which read in conservative form: find \( (\mathbf{u}, p) \) such that \( \rho \left( \frac{\partial \mathbf{u}}{\partial t} + (\mathbf{u} \cdot \nabla) \mathbf{u} \right) - \mu \Delta \mathbf{u} + \nabla p = 0, \quad \text{div} (\mathbf{u}) = 0, \) in \( \Omega \times I \). The set \( \Omega \subset \mathbb{R}^3 \) represents the spatial domain described in Figure 1. \( I = (0, T) \) is the time interval, \( \mathbf{u} \) and \( p \) are the velocity and pressure of the fluid and \( \rho \) and \( \mu \) are the density and the dynamic viscosity of the fluid, respectively. We supplement the equations with initial and boundary conditions. At \( t = 0 \), the fluid is considered to be at rest, \( \mathbf{u}(x, t) = 0 \). A Poiseuille velocity profile is imposed on \( \Gamma_{\text{inlet}} \), homogeneous Dirichlet condition on \( \Gamma_{\text{wall}} \) and a free outflow on \( \Gamma_{\text{outlet}} \).

We refer to [8, Sec. 2] regarding the variational formulation, the finite element discretization including low to high order geometry as well as the time discretization. We choose the generalized Taylor-Hood finite element for the velocity-pressure discretization; the notation \( \mathcal{P}_N \text{G}_{k_{geo}} \) is used to specify exactly the discretization spaces for the velocity, pressure and geometry, respectively.

The benchmark hereafter is developed in the framework of the Finite Element Embedded Library in C++, Feel++[6], that allows to use a very wide range of Galerkin methods and advanced numerical techniques such as domain decomposition. The ingredients include a very expressive embedded language, seamless interpolation, mesh adaption and seamless parallelization. Regarding the computational domain, we used Gmsh. The construction used the following steps: (i) start with a 2D geometry embedding the benchmark metric locations and customizing characteristic mesh size depending on the region and (ii) extrude by rotation to obtain the device geometry. Finally we use the PETSc interface developed in Feel++ and in particular the FieldSplit preconditioning framework to implement block preconditioning strategies such as PCD [7]. Note that PCD requires specific tuning with respect to boundary conditions.

### 3 RESULTS AND CONCLUSIONS

We perform simulations for three Reynolds numbers evaluated in the throat \( Re_t = 500, 2000, 3500 \), with several mesh refinements and polynomial order approximations. The fluid’s prescribed density is \( \rho = 1056 \text{kg/m}^3 \) and viscosity \( \mu = 0.0035 \text{Pa.s} \). The mesh characteristics are described in Table 1. At \( Re_t = 500 \), the simulation is carried out until \( t = 3s \), time reasonably close to the steady state, and we choose the time step equal to \( \Delta t = 10^{-3} \). At \( Re_t = 2000 \) (resp \( Re_t = 3500 \)), the numerical experiments were carried out until \( t = 0.45s \) (resp \( t = 0.4s \)), time when the turbulent regime was fully developed and we set \( \Delta t = 10^{-4} \).

<table>
<thead>
<tr>
<th>( h_{\text{min}} )</th>
<th>( h_{\text{max}} )</th>
<th>( h_{\text{average}} )</th>
<th>( N_{\text{elt}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>1.9 \times 10^{-4}</td>
<td>2.9 \times 10^{-3}</td>
<td>1.3 \times 10^{-3}</td>
</tr>
<tr>
<td>M1</td>
<td>1.6 \times 10^{-4}</td>
<td>1.8 \times 10^{-3}</td>
<td>7.6 \times 10^{-4}</td>
</tr>
<tr>
<td>M2</td>
<td>1.4 \times 10^{-4}</td>
<td>1.96 \times 10^{-3}</td>
<td>6.0 \times 10^{-4}</td>
</tr>
<tr>
<td>M3</td>
<td>8.5 \times 10^{-5}</td>
<td>1.7 \times 10^{-3}</td>
<td>3.5 \times 10^{-4}</td>
</tr>
<tr>
<td>M4</td>
<td>6.3 \times 10^{-5}</td>
<td>2.0 \times 10^{-3}</td>
<td>5.8 \times 10^{-4}</td>
</tr>
<tr>
<td>M5</td>
<td>1.4 \times 10^{-4}</td>
<td>2.6 \times 10^{-3}</td>
<td>4.1 \times 10^{-4}</td>
</tr>
</tbody>
</table>

Table 1: Characteristic lengths of the different meshes: \( h_{\text{min}}, h_{\text{max}}, h_{\text{average}} \) are respectively the minimum, maximum and average edge length in the meshes and \( N_{\text{elt}} \) is the number of tetrahedra.
Figure 2 shows the results in the three flow regimes for the normalized axial velocity and the normalized pressure difference along the z axis, respectively. In each case, we can see satisfactory agreement with the experimental data. However, for $Re_t = 2000$, we observe that the numerical jet breakdown point is captured further downstream than the experimentally observed breakdown point. As recently highlighted in [5], the prediction of the axial location of the jet breakdown is extremely sensitive to numerical parameters, therefore a possible explanation of this mismatch may be the accuracy of the numerical integration. Finally, we illustrate in Figure 3 the computation of metrics $E_z$ and $E_Q$ for several mesh refinements at $Re_t = 500$. The metric $E_z$ takes small values in each numerical experiment, identifying a good agreement between computed and experimental data, and displays only small variations with respect to mesh refinement. On the other hand, the metric $E_Q$ is more sensitive to this factor: error doesn’t exceed the $\sim 2\%$ except for the coarse mesh $M0$ where, in two locations, the error increases up to $\sim 10\%$. Furthermore, we note that the $P_3P_2G_1$ approximation doesn’t improve the results for the coarse mesh, but that a satisfactory error below $2\%$ is retrieved when using a $P_3P_1G_2$ approximation. Additional tests to complement the study of the impact of high order approximation are ongoing.

Conclusions and perspectives We validated our computation fluid dynamic framework against this FDA benchmark for three different regimes and different discretization and solution strategies. Perspectives include a full report on our findings including in terms of iteration and timing performances as well extending our results to the turbulent range.

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Figure 2: Comparison between experimental data and numerical results for the normalized axial velocity along $z$ (left) and the normalized pressure difference along $z$ (right), for $Re_t = 500$ (top) $Re_t = 2000$ (middle) and $Re_t = 3500$ (bottom).

Figure 3: Validation metrics $E_z$ (left) and $E_Q$ (right) for $Re_t = 500$. 

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Reduced-Order Modelling of the Cardiovascular System - Challenges & Translational Opportunities II
FORMATION MECHANISM OF BLOOD PRESSURE PROFILES

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SUMMARY

In traditional Chinese and Greek medicine, blood pressure profiles are believed to be important indicators of the state of human body. Strong correlations between diseases and the types of blood pressure profiles, such as between hypertension and wiry pulse profile, have been discovered in medical measurements. In this work, one-dimensional model of the interaction between blood flow and blood vessel walls is used to describe the propagation of blood pulse waves in arterial trees. The formation mechanisms of important characteristics of blood pulse profiles, such as the dicrotic wave and the predicrotic wave, are explained in detail by the propagation of blood pulse waves. Consistent with medical observations, our numerical studies show that vessel thickening as a result of hypertension lead to the formation of wiry pulse. These results suggest that the change of the arterial tree structure in patients can lead to significant change in blood pulse phase, thus providing useful information in medical diagnosis.

Key words: blood pulse wave, pressure profile, one-dimensional model

1 INTRODUCTION

Studying pulse of blood pressure, such as the amplitude and the rhythm, is a useful way in diagnosis of different cardiovascular diseases, such as hypertension, atherosclerosis, and stenosis. A lot of methods has been applied to measure physiological and mechanic properties of blood flow in arteries, including different types of experiments and mathematical models. In the aspect of mathematical modeling, one-dimensional models for blood flow and blood pressure in the large arteries are shown to be able to capture the profile and propagation property of pulse waves.

In Traditional Chinese Medicine, the pressure profile at the radial artery is used for diagnosis. Though there have been many studies on the correlation between pressure profiles and diseases, the formation mechanism of typical characteristics of pressure waveform, such as the dicrotic wave, the dicrotic notch, and predicrotic wave, are not well understood.

2 METHODOLOGY

- A fast numerical simulation algorithm is developed for the simulation of one-dimensional models of blood pulse waves;
- Simulation in the arterial system of large arteries is used to study the propagation of blood pulse waves;
- The boundary conditions at vessel junctions are reformulated to describe the wave reflection and wave transmission.
3 RESULTS AND CONCLUSIONS

- A reformulation of boundary conditions is used to understand the wave reflection and transmission at vessel junctions. This is helpful for understanding the formation mechanism of the characteristics of pressure profiles at the radial artery:

The original boundary condition can be write as

\[ q_p = q_l + q_r \quad \text{and} \quad p_p = p_l = p_r, \]

where \( p \) and \( q \) are the blood pressure and blood flow rate at the vessel bifurcation point, and the subscript indices \( p, l, \) and \( r \) are used to represent the parent-, the left daughter, and the right daughter vessels. The reformulated boundary condition is

\[
\begin{bmatrix}
\mathcal{R}^-_p \\
\mathcal{R}^-_l \\
\mathcal{R}^-_r
\end{bmatrix} =
\begin{bmatrix}
2\alpha_p - 1 & 2\alpha_l & 2\alpha_r \\
2\alpha_l & 2\alpha_l - 1 & 2\alpha_r \\
2\alpha_r & 2\alpha_l & 2\alpha_r - 1
\end{bmatrix}
\begin{bmatrix}
\mathcal{R}^+_p \\
\mathcal{R}^+_l \\
\mathcal{R}^+_r
\end{bmatrix},
\]

where \( \mathcal{R}^+ \) and \( \mathcal{R}^- \) are the Riemann variables for forward and backward blood pulse waves at the vessel junction, \( \alpha_i = \frac{C_{1i}}{C_{1p} + C_{1l} + C_{1r}} \) and \( C_{1i} = \frac{1}{R_{1i}} \) is the reciprocal of the characteristic resistance, \( R_{1i} \), of vessel \( i \), \( (i = p, l, \text{ or } r) \). In particular, when \( 2\alpha_p - 1 > 0 \), there is a positive reflection for the forward wave in the parent vessel.

- A potential explanation is provided for the emergence of wiry pulse profile and smooth pulse profile in hypertension patients and pregnant patients, respectively (as shown in Figure 1). In particular, wiry pulse profiles are related to arteriosclerosis in which the wave speed are significantly increased and smooth pulse profiles are related to local changes in blood flow in arteries in kidney and placenta for pregnant patients.

![Figure 1: Blood pressure profiles at right radial artery.](image)

The left panel: blood pressure profiles for different Young’s modulus \( E \): \( E_0 \) (blue), \( 1.5E_0 \) (red), \( 2E_0 \) (green), and \( 4E_0 \) (black). The wave speed is proportional to \( \sqrt{E} \). The middle panel: the blood pressure profiles for \( \xi = 2.5 \) (black), \( \xi = 2.6 \) (red), and \( \xi = 2.7 \) (blue), where \( \xi \) is the power used in structured tree model. \( \xi \) is used to describe micro-vessel rarefaction. A small \( \xi \) means loss of a lot of small vessels. The right panel: pregnancy leads to the formation of smooth pulse profile: before pregnancy (red), 21-week gestation (blue), and 36-week gestation (green).

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UNDERSTANDING CENTRAL BLOOD PRESSURE DETERMINANTS USING 1-D MODELLING

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SUMMARY

The three-element Windkessel is used to assess central blood pressure and derive physiological implications about its determinants. The study was performed on three different populations: 1) a numerical cohort (n=3,044) of virtual healthy subjects; 2) 13 normotensive volunteers (10 males, mean±SD, 47±10 years) who were administered a mix of 4 drugs (dobutamine, norepinephrine, phentolamine and nitroglycerin); and 3) 158 hypertensive patients (81 males, mean±SD, 46±17 years). For each Windkessel component and derived parameters, the populations were divided into quartiles (normotensive and hypertensive cohort) or quintiles (numerical cohort) of increasing components values and ANOVA analyses were performed to investigate the impact of each parameter on pulse pressure. Pulse wave velocity and volume of blood entering the artery at time of peak pressure were found to be the main driver of pulse pressure increase.

Key words: Central Blood Pressure, Windkessel, Pulse Wave Velocity

1 INTRODUCTION

Central Blood pressure (cBP) is considered to be the best predictor of cardiovascular events and several devices have been designed to assess it. Recent studies have shown that few parameters were required to estimate the entire cBP waveform \cite{1} or that only a small number of arteries was needed to derive information that account for the whole arterial system \cite{2}. Similarly to those approaches, Windkessel models were first defined to describe the hemodynamics of the arterial system in term of common electrical elements with physiological implications \cite{3}. However, if pressure waveforms are frequently derived from various inputs components, the reverse process is seldom performed (i.e., definition of components representing physiological parameters from pressure and flow waveforms). In this study, we first estimate cBP waveforms through three-element Windkessel models in various type of cohorts, and then, we investigate if Windkessel inputs and other derived parameters can physiologically explain cBP variations.

2 METHODOLOGY

This study used three cohorts of various natures: 1) a numerical population of virtual healthy subjects (n=3,044) as described in \cite{4}; 2) 13 normotensive volunteers (10 males, mean±SD, 47±10 years) who were administered a mix of 4 drugs (dobutamine, norepinephrine, phentolamine and nitroglycerin); and 3) 158 hypertensive patients (81 males, mean±SD, 46±17 years). For each population, cBP waveforms were first reconstructed through three-element Windkessel models and the accuracy of systolic blood pressure (SBP) estimates was investigated; secondly, the populations were divided into quartiles (normotensive and hypertensive patients) or quintiles (numerical cohort) of increasing values of the Windkessel components and ANOVA analyses were conducted on corresponding pulse pressures (PP) to determine determinants of PP variations.
Table 1: Accuracy of SBP estimates across cohorts.

<table>
<thead>
<tr>
<th>Cohort</th>
<th>n</th>
<th>SBP error (mean±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numerical</td>
<td>3,044</td>
<td>-0.24±2.72 mmHg</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>10</td>
<td>-0.01±3.40 mmHg</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>10</td>
<td>-0.02±6.00 mmHg</td>
</tr>
<tr>
<td>Phentolamine</td>
<td>12</td>
<td>-0.05±4.26 mmHg</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>7</td>
<td>-0.04±4.71 mmHg</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>158</td>
<td>-1.42±4.33 mmHg</td>
</tr>
</tbody>
</table>

Figure 1: Examples of waveforms obtained when reconstructing the original pressure (blue) through the Windkessel model (red). The left panel shows samples extracted from the numerical cohort and the right panel depicts cases drawn from the clinical cohorts. For each population, a normotensive and a hypertensive case are highlighted, respectively in the top and lower panels.

3 RESULTS AND CONCLUSION

On average, SBP estimates were very accurate with errors <2 mmHg in hypertensive patients and <1 mmHg otherwise (Table 1, Figure 1). ANOVA analyses show that PP across divisions of Windkessel components were significantly different (p<0.05) for pulse wave velocity (PWV), compliance (C), blood volume entering the artery until SBP (V), peak flow and cross sectional area (A) in all three types of population. Overall, high PWV, V as well as low C and A led to high PP. A sensitivity analysis was performed on a baseline model (Figure 2) and showed that the main factor in PP increases is flow rate, followed by PWV. This finding could have potential implications on hypertension treatments as drugs usually target tissue stiffness (C) while flow rate regulation might lead to better outcomes.
Percent of evolution of baseline parameter (%)

Figure 2: Sensitivity analysis performed on the analytical solution of the three-element Windkessel model. From a baseline value, each Windkessel parameter is made varying -50% to 100%. Baseline parameters: \(PWV = 3.1\) m/s; diastolic cross sectional area \(A = 5.0 \times 10^{-4}\) m\(^2\); peak flow velocity = 0.7 m/s; \(R_{\text{distal}} = 1.2 \times 10^8\) \(\Omega\); \(C_{\text{distal}} = 4.5 \times 10^{-9}\) m\(^3\)/Pa.

REFERENCES


ARTERIOLAR PRESSURE IN THE BRAIN. IMPLICATIONS IN HYPERTENSION

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SUMMARY

We present a computational model to study arteriolar pressure in the cerebral circulation and its relation to systemic pressure. Emphasis is given to the simulation of hypertensive conditions. Blood flow circulation is modeled using the ADAN model, while the peripheral circulation in two selected vascular territories, up to the level of arterioles, is simulated using a 1D model in automatically constructed networks of vessels. The model predicts, even in hypertension, significant differences in arteriolar pressure between the base of the brain and over cortical territories. This can help to understand the different mechanisms behind stroke occurring at these places.

Key words: blood flow, hypertension, brain perfusion, stroke

1 INTRODUCTION

There is confusion in the literature with regard to the role of hypertension in different forms of cerebral small vessel disease. Small white matter intensities on magnetic resonance imaging tend to be lumped together, as if they were all the same, perhaps because of widespread use of magnetic resonance imaging. From the anatomical point of view, there is a clear contrast between the peripheral territories at the base of the brain (the region called vascular centrencephalon) and the territories over the cerebral cortex. In fact, the vascular centrencephalon is perfused by short straight arteries, while the small arterioles of the cortex are supplied by long arteries with many branches. This raises question whether the direct connection of small vessels to large arteries in the centrencephalon prejudicially transmits high pressure to arterioles or not, by contrast to the inescapable pressure drop occurring in large arteries that supply the arterioles over the convexity. Failure in understanding regional pressure drop in the brain may have led to confusion about the pathogenesis of small vessel disease. In such context, small subcortical white matter intensities often attributed to “small vessel disease”, and lobar hemorrhages, should not be attributed to hypertensive small vessel disease; and other pathophysiological mechanisms should be explored.

Although it may be intuitively obvious that the blood pressure must be lower over the convexity than in the so-called vascular centrencephalon, the pressure gradient from the base of the brain to the small arterioles of the convexity has not been previously quantified. Our goal is to study the relation between arterial blood pressure at the radial artery and arterial blood pressure at the base of the brain and over the convexity.

2 METHODOLOGY

Blood flow is modeled using 1D equations for mass and momentum conservation. A non-linear viscoelastic model is considered to describe the behavior of the arterial wall. Equations are solved using

The ADAN model supplies blood to 28 specific organs and to 116 vascular territories. We selected two specific territories for the construction of CCO-networks: at the base of the brain, supplied by a lenticulostriate artery (diameter 582 μm, inflow 0.0548 ml/s, territory with 4000 vessels); and in the parietal lobe over the cortex, supplied by the posterior parietal branch of the middle cerebral artery (diameter 1039 μm, inflow 0.123 ml/s, territory with 20000 vessels).

In small vessels, blood rheology is modeled as suggested in [7] to account for viscosity variation as function of the vessel diameter. At terminal locations of arteriolar networks, microcirculation is modeled by resistive elements, which are computed to ensure that average flow rate is the same for all the outlets of the network. The same mathematical 1D model adopted for large arteries is used for the vessels in the arteriolar networks.

A normotensive scenario is set up using the calibration criteria proposed in [2]. Structural changes taking place in the hypertensive condition are considered through the following model parameters: arterial wall thickness, lumen radius, total resistance of the network and total compliance of the network. In the hypertensive scenario wall thickness was increased 50%, vessel radii were reduced 10%, terminal resistance was increased 60% (mean arterial pressure is then incremented 50% in central arteries) and terminal compliance was reduced 23% in accordance with the stiffening observed in arterial vessels. These alterations are in agreement with reported data [1, 3, 6, 8].

### 3 RESULTS

Table 1 reports mean, systolic and diastolic pressures at selected vessels in both centrencephalic and cortical areas for both scenarios normotensive and hypertensive. Figure 1 displays arterial pressure in the arteriolar networks of the lenticulostriate artery and of the posterior parietal branch of the middle cerebral artery. A first group of vessels corresponds to vessels with diameter $D \in [210 \mu m, 230 \mu m]$, and a second group corresponds to diameter $D \in [50 \mu m, 70 \mu m]$. The mean and standard deviation of the pressure waveform are also displayed.

<table>
<thead>
<tr>
<th>Artery</th>
<th>$D$</th>
<th>MAP</th>
<th>SBP</th>
<th>DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radial a.</td>
<td>2.389</td>
<td>93 N/147 H</td>
<td>117 N/186 H</td>
<td>71 N/108 H</td>
</tr>
<tr>
<td>Internal Carotid a.</td>
<td>4.839</td>
<td>100 N/155 H</td>
<td>117 N/190 H</td>
<td>77 N/115 H</td>
</tr>
<tr>
<td>Distal Medial Striate a.</td>
<td>0.545</td>
<td>92 N/145 H</td>
<td>110 N/178 H</td>
<td>70 N/106 H</td>
</tr>
<tr>
<td>Prefrontal a.</td>
<td>0.962</td>
<td>80 N/130 H</td>
<td>94 N/159 H</td>
<td>61 N/95 H</td>
</tr>
<tr>
<td>Temporal branch of Middle Cerebral a.</td>
<td>0.923</td>
<td>82 N/131 H</td>
<td>97 N/161 H</td>
<td>62 N/96 H</td>
</tr>
<tr>
<td>Lenticulostriate a.</td>
<td>0.582</td>
<td>95 N/149 H</td>
<td>113 N/182 H</td>
<td>73 N/109 H</td>
</tr>
<tr>
<td>$[210 \mu m, 230 \mu m]$ arterioles of Lentic. a.</td>
<td>0.210/0.230</td>
<td>83 N/135 H</td>
<td>99 N/166 H</td>
<td>63 N/98 H</td>
</tr>
<tr>
<td>$[50 \mu m, 70 \mu m]$ arterioles of Lentic. a.</td>
<td>0.050/0.070</td>
<td>72 N/121 H</td>
<td>85 N/150 H</td>
<td>54 N/87 H</td>
</tr>
<tr>
<td>Posterior Parietal branch of Middle Cerebral a.</td>
<td>1.039</td>
<td>71 N/117 H</td>
<td>84 N/144 H</td>
<td>53 N/85 H</td>
</tr>
<tr>
<td>$[210 \mu m, 230 \mu m]$ arterioles of Post. Pariet. a.</td>
<td>0.210/0.230</td>
<td>55 N/101 H</td>
<td>64 N/124 H</td>
<td>41 N/73 H</td>
</tr>
<tr>
<td>$[50 \mu m, 70 \mu m]$ arterioles of Post. Pariet. a.</td>
<td>0.050/0.070</td>
<td>47 N/93 H</td>
<td>55 N/114 H</td>
<td>35 N/66 H</td>
</tr>
</tbody>
</table>

Table 1: Diameter (in μm) and systolic, mean and diastolic arterial pressure (SBP, MAP and DBP in mmHg, respectively) at several arterial locations with focus in cerebral arteries for the normotensive (N) and hypertensive (H) cases.

### 4 DISCUSSION

Model predictions confirm a marked drop in blood pressure from the large arteries at the base of the brain to the small vessels over the convexity. In the normotensive case, with a blood pressure of 117/71 in the radial artery, the blood pressure in a lenticulostriate artery is 113/73, dropping to 84/53 in the posterior parietal branch of the middle cerebral artery, and to 55/35 in small arterioles of the parietal bed. In the hypertensive case, with a blood pressure of 186/108 in the radial artery, the pressure in the lenticulostriate artery is 182/109, dropping to 144/85 in the posterior parietal branch and to 114/66 in small arterioles over the convexity.

Thus it is hypothesized that small WMI over the convexity, and lobar hemorrhages, cannot be attributable to hypertension, but are more likely due to other arteriolar pathologies, for example amyloid...
Figure 1: Arterial pressure predicted by the ADAN model at different sites in the intracranial vasculature for normotensive (N, blue) and hypertensive (H, red) cases. The mean arterial pressure is reported in brackets.
REFERENCES


MODEL-BASED EVALUATION OF THE CARDIOVASCULAR FUNCTION IN HUMAN THERMOREGULATION: AN INTEGRATED COMPUTATIONAL STUDY

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SUMMARY

Convective heat exchange via the cardiovascular system (CVS) is considered to be the most important heat exchange pathway inside the body, however, the effects of cardiovascular characteristics on human thermoregulation during passive heat stress are poorly understood. We propose an integrated multi-segment human thermoregulation model coupled with a closed-loop multi-scale cardiovascular model to predict cardiovascular functions in human thermoregulation. The coupled thermoregulation model is validated capable of predict cardiovascular hemodynamics and thermal responses during varying environmental temperatures.

Key words: Bioheat transfer, thermoregulation, cardiovascular system

1 INTRODUCTION

The cardiovascular system (CVS) plays a crucial role in human thermoregulation. José [1] pointed out that vascular convective heat transfer is the most important heat-exchange pathway inside the body, and over 50% of the heat flow in body tissues is transferred via the flowing blood [2]. Cold stress or heat stress (caused by external thermal environment or exercise) would also result in cardiovascular strains, such as heat stress may result in significant cardiovascular adjustments that are necessary to maintain adequate cardiac output (CO) and skin blood flow through adjusting heart rate, cardiac contractility, and peripheral vascular resistance to maintain internal temperature within a narrow range under different heat-stressed conditions [3].

Over the past several decades, a large number of human thermoregulation models have been developed for different purposes [4-9]. To the best of our knowledge, however, there are no studies have taken into account a complete closed-loop CVS except the one developed by zhang et al. [10], in which the CVS is represented via an integrated closed-loop lumped-parameter cardiovascular model. The objective of this study is to evaluate the cardiovascular function in human thermoregulation. We incorporate a closed-loop multiscale cardiovascular model into a multi-segment integrated thermoregulation model to compute the convective heat exchange between the CVS and surrounding core tissues, and the blood perfusion within core tissues for the first time.

2 METHODOLOGY

The presented thermoregulation model consists of two parts: the controlled system and controlling system. The controlled system includes a multi-segment integrated thermal model of the human body and a closed-loop multi-scale thermo-fluid model of the CVS. The controlling system is the so-called physiological thermoregulatory system, which can regulate body temperature through sweating, shivering, peripheral vasomotion, and CVS adjustments.

2.1 Multi segment integrated bio heat model of the human body

A total of six cylindrical elements is used to represent the thermal characteristics of the whole human body, which include head, trunk, right/left upper extremity, and right/left lower extremity, as shown in figure 1a. And each element is subdivided into two layers (core and skin) with uniform thermal characteristic and temperature, the details of a two-layered model for one element and its
interaction with surrounding environment are shown in figure 1b. The heat exchange between two adjacent two elements is via the flowing blood, and the conductive heat exchange is ignored.

The energy balance equation for core tissue is expressed as

$$C_{cr} \frac{dT_{cr}}{dt} = M - W - \alpha Q_{res} - Q_{cr-sk} + \dot{m}_{perfusion} \cdot c_b \cdot (T_{art} - T_{cr}) - \dot{m}_{sk} \cdot c_b \cdot (T_{cr} - T_{sk})$$

$$+ \sum_{arteries} \left[ h_{res} \cdot A_{artery} \right] \left[ T_{art} - T_{cr} \right] + \sum_{veins} \left[ h_{res} \cdot A_{vein} \right] \left[ T_{vein} - T_{cr} \right]$$

where $C_{cr}$ is the thermal capacity of the core tissue, $T_{cr}$ is core temperature, $M$ is core metabolic heat production, $W$ is external work, $Q_{res}$ is respiratory heat loss, $Q_{cr-sk}$ is conductive heat exchange between the core and skin, $\dot{m}_{perfusion}$ is the total perfusion rate of blood entering core tissue, $c_b$ is blood specific heat, $\dot{m}_{sk}$ is skin blood flow, $T_{sk}$ is skin temperature, $h_{res}$ is the pulsating heat convection coefficient of the blood flow, $A_{artery}/A_{vein}$ is surface area of artery/vein vessel, $T_{art}/T_{vein}$ is temperature of artery/vein blood.

Skin is the primary mode by which exchange heat with the environment via convection, evaporation and radiation. Therefore, the energy balance equation for skin can be expressed as

$$C_{sk} \frac{dT_{sk}}{dt} = Q_{cr-sk} - Q_{e} - Q_{cr} + \dot{m}_{sk} \cdot c_b \cdot (T_{cr} - T_{sk})$$

where $C_{sk}$ is thermal capacity of skin, $Q_e$ is the convective/radiative heat exchange between skin and environment, and $Q_{cr}$ is the evaporative heat loss from skin.

### 2.2 Closed-loop multi-scale cardiovascular model

The cardiovascular model used in this study is composed of detailed 0D lumped-parameter descriptions of the four heart chambers and peripheral vascular beds, and 1D descriptions of the major systemic and pulmonary circulation, as shown in figure 2. The detailed geometrical data of 1D cardiovascular network and connections between terminal arteries and veins are given in Mynard and Smolich [11].

The 1D governing equations for blood flow in larger arteries and veins can be represented as follows [11]

$$\frac{\partial A}{\partial t} + \frac{\partial A u}{\partial x} = 0$$
\[ \frac{\partial u}{\partial t} + u \frac{\partial u}{\partial x} + \frac{1}{\rho} \frac{\partial p}{\partial x} = -\frac{22\pi \mu}{\rho} \frac{u}{A} \]  

(4)

where \( A \) is the cross-sectional area of the vessel, \( t \) is the time, \( x \) is the axial coordinate along the vessel, \( u \) is the average axial velocity, \( p \) the average internal pressure over the cross section, \( \mu \) is the blood viscosity (0.035 poise), \( \rho \) is the density of blood (1050 Kg/m³).

The constitutive equation used to describe pressure-area relation of the arteries and veins is

\[ p - p_{\text{ext}} = \frac{2 \rho \chi^2}{b} \left[ \left( \frac{A}{A_0} \right)^{\frac{b}{2}} - 1 \right] + P_0 \]  

(5)

where \( p_{\text{ext}} \) is the external pressure, \( c_0 \) is the reference pulse wave velocity, \( b \) is a constant used to determine the shape of the pressure-area relationship, \( A_0 \) is the reference cross-sectional area at the reference pressure \( P_0 \). The detailed methods used to determine \( c_0 \) and \( b \) can be found in [5].

Here we assume that the entire CVS are all distributed within the core tissues, therefore the energy balance equation for 1D blood flow is expressed as

\[ \frac{\partial T_b}{\partial t} + \frac{q}{A} \frac{\partial T_b}{\partial x} = -\frac{h_{\text{ves}} \cdot A_s}{c_b \cdot \rho \cdot A} (T_b - T_{cr}) \]  

(6)

where \( T_b \) is the blood temperature, \( q \) is the blood flow rate, \( h_{\text{ves}} \) is the heat transfer coefficient of the blood vessel, \( A_s \) is surface area of the blood vessel per unit.

Figure 2. Schematic representation of the closed-loop multiscale cardiovascular model, which consists of 1D representations of (a) systemic arteries, (b) systemic veins, (c) cerebral arteries, (d) cerebral veins, (e) pulmonary arteries, (f) pulmonary veins, and 0D lumped-parameter representations of (g) peripheral vascular bed, (h) right heart, (i) left heart.

### 2.3 Physiological thermoregulatory system

The basic processes of thermoregulation can be summarized as follows: when body temperatures increase above the threshold settings (37°C), the temperature signals will initiate vasodilation and sweating to liberate heat from the body; When body temperatures fall below the threshold settings, the temperature difference will initiate vasoconstriction and shivering to constrain heat within body. The detailed description of the thermoregulatory mechanisms used in our model, such as shivering, sweating, vasomotion, heart rate, is given in zhang et al. [10].

### 3 RESULTS AND CONCLUSIONS
Figure 3 shows comparison of the mean body (core and skin) temperatures between model predictions and *in vivo* measurements. The results suggest that the predicted results agree well with the *in vivo* measured results from Munir et al. [12]. The simulation results show that the developed thermoregulation model is validated to be capable of predicting human transient thermal responses and cardiovascular function during varying thermal environments.

**REFERENCES**

Computationaly-Guided Design of Cell Culture Bioreactors
3D MODELING OF TRANSPORT THROUGH POROUS SCAFFOLDS
SUBJECT TO DYNAMIC PRESSURE

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SUMMARY
In cardiac tissue engineering, the use of bioreactors is fundamental for applying controlled mechanical stimuli on the cells and recreate a physiological environment for cardiomyocytes cultures. This work analyses the behavior of fluid-dynamic quantities and oxygen distribution through 3D porous scaffolds dynamically perfused in culture by an innovative Sensorized Squeeze PRESSure (S²PR) bioreactor, able to apply a periodic contactless hydrodynamic pressure. Computational results confirm experimental evidences of cell vitality inside the scaffold and their analysis represents a useful feedback to optimize bioreactor design and scaffold fabrication.

Key words: CFD models, bioreactor design, cardiac tissue engineering

1 INTRODUCTION
Current tissue engineering strategies are aimed at reproducing in vitro the mechanical and biochemical context of the physiological environment, in term of both tissue architecture and physical stimuli [1]. In this context, the use of bioreactors in combination to 3D constructs is fundamental for recreating the physiological milieu with exchange of nutrients and metabolites [2, 3]. Focusing on cardiac tissue engineering, several studies have demonstrated the role of mechanical forces and fluid motion on the organization and function of cardiomyocytes, improving the nutrient transport and inducing cytoskeletal re-organization [4]. When bioreactors are used in combination with porous scaffolds, the entity and the distribution of fluid-induced forces inside the structure are very complex, as they not only depend on the working conditions of the system but also on 3D microstructural parameters of the scaffold, like pore diameter, porosity, and pore interconnectivity [5]. Computational methods are powerful tools able to estimate local fluid-induced shear, pressure and velocity fields in bioreactor environments. Previous studies have shown that a fluid-dynamic environment can be represented using time-invariant CFD models, in order to quantify the fluid-structure interactions applied to the cells or the transport of nutrients promoted by fluid motions [5-8]. However, very few studies have attempted to combine fluid perfusion through the interconnected pores and cell consumption of oxygen considering the effective micro-architecture of the scaffold [5, 6], instead of its global characteristics (i.e. porosity, permeability) [9-11].

In this work, we present a new approach for implementing time-dependent CFD models, consisting of a 2D macro-scaled model and 3D micro-scaled models of a gelatin porous cryogel, able to predict the levels of shear stress and hydrodynamic pressure acting on cells within the construct and quantify oxygen transport and consumption inside the scaffold subject to the hydrodynamic stimulus generated by the Sensorized Squeeze Pressure bioreactor (S²PR).
2 METHODOLOGY

The $S^2$PR is an innovative stimulation chamber, provided with a force and position sensor, which imposes a cyclic and contactless overpressure on cell cultures, using a vertical piston movement [12]. It assures high precision and control of the piston movement with an accuracy of 5 µm. The force sensor (Flexiforce A201, Tekscan, Inc. MA, USA) is placed under the sample brace in order to detect any contact between the piston and the scaffold (Figure 1). The bioreactor was used in the cell culture experiments to stimulate cardiac cells seeded onto porous scaffolds consisting in gelatin cryogels fabricated using the freeze-dry method from gelatin 5% w/v in deionized water, chemically cross-linked with glutaraldheyde 100 mM. Gelatin cryogels have been characterized in an aqueous environment, pointing out average values of porosity (90%), permeability ($13 \times 10^{-12} \text{m}^2$) and elastic modulus (12 kPa). MicroCT images of the material have been used to estimate the average fiber thickness (50 µm) and the average pore diameter (150 µm). Cell cultures show high viability of cells after 24 h in the $S^2$PR, with results comparable to static control.

The computational models developed to predict the fluid-dynamic and oxygen environment inside the dynamically cultured porous cryogels were implemented using Comsol Multiphysics (COMSOL Inc., Burlington, MA, USA). Fluid-dynamics of the entire system is evaluated using the same conditions as in [9]. Time-dependent 2D models of the transverse section of the bioreactor chamber were first realized to evaluate pressure and velocity profiles around the construct due to the piston motion. In order to reproduce the fluid-dynamic conditions of the $S^2$PR stimulus, three different physics modes were implemented: i) Navier-Stokes equations for an incompressible fluid to describe the laminar fluid flow in the bioreactor chamber, ii) Brinkman equations to characterize the flow in the porous scaffold, iii) the Arbitrary Lagrangian-Eulerian (ALE) method to model the piston motion. The scaffold domain was defined using the porosity and permeability previously reported for gelatin cryogels. To couple the 3 modes, the velocity field evaluated in the laminar flow regime was applied as a boundary condition of the Brinkman module. The moving mesh was used to consider changes in the geometry of the meatus due to the cyclic piston motion which generates the squeeze stimulus. The fluid-dynamic results from the 2D models were applied to an idealized 3D geometry of the porous scaffold [7] to evaluate the oxygen consumption and transport within the construct and the shear-stress inside the porous structure during the stimulation. For the Oxygen Consumption (OC) analysis we only considered a 10° sector of the fluid domain in the cylindrical scaffold. Oxygen diffusion and convection as well as consumption were considered, comparing both the static (OC-S) and dynamic (OC-D) conditions during the squeeze pressure stimulation.

In the OC-D approach we applied pressure profiles, exported from the 2D model (Figure 2), as inlet boundary conditions respectively at the top and the sides of the construct. In both the OC models, a constant oxygen concentration of 0.21 mol/m$^3$ was imposed in the scaffold domain at $t = 0$ and as a boundary condition at the top and sides of the scaffold. Oxygen consumption was implemented as a mass outflux $R(c)$ (in moles/m$^2$/s) from the total internal surface area of the scaffold, using the Michaelis Menten kinetics. The mesh of the OC-S and OC-D models were built defining parameters such as...
maximum and minimum element size, maximum element growth rate, curvature factor and resolution of narrow regions. These values allowed a mesh with just over $10^6$ tetrahedral elements to be obtained without any problem of convergence, reducing the computational costs. The model was solved using the MUMPS solver. To better describe the interaction between the media and the porous cryogel during cyclic stimulation in the bioreactor we also implemented a fluid-structure interaction model. Due to the high complexity in implementing a computational fluid-structure interaction model, we considered a 1 mm side cube at the center of the scaffold instead of the triangular slice with the same structure and mechanical properties used for the transport models. Given the symmetry of the system we focused on a quarter of the cube corresponding to a parallelepiped. Symmetry conditions were imposed at the two internal surfaces of the parallelepiped, while a single pressure profile $p_R(t)$ was applied to the top and the two lateral faces. To determine the importance of the fluid-structure interaction on the evaluation of the effective shear-stress inside the porous structure, the FSI model was compared to a simple Laminar Flow (LF) model with the same scaffold geometry and fluid properties. The mesh consisted in 217173 free tetrahedral elements, and the model was solved using the PARDISO solver.

3 RESULTS AND CONCLUSIONS

The results of the 2D models quantify pressure and flow velocity at specific time-points. Specifically, the changes in fluid motion were analyzed at discrete time points in terms of pressure and velocity during the generation of the squeeze pressure by the S²PR piston, focusing on the instant when the piston is at its lowest and highest position.

The results of the 2D axial symmetric models highlighted the importance of characterizing fluid-dynamics and time-dependent movement of the piston in the presence of porous cryogel, even considering just the macro-properties of the scaffold, underlining that the fluid changes its direction and velocity according to the piston motion.

Space averaged pressure profiles $p_R(t)$ and $p_A(t)$ from the 2D models were used as inlet boundary conditions for the OC-D model to evaluate the effect of the hydrodynamic stimulus applied by the bioreactor on transport and oxygen consumption. A transport model in static conditions without the pressure-driven convective contribution (OC-S) was developed in parallel to determine how the dynamic stimulus changes the oxygen content within the porous scaffold. The pressure generated flow clearly improves the penetration of the oxygen through the scaffold (Figure 3A). The oxygen concentration increases in the dynamic case but only where the porous structure is adequately perfused by the culture medium.

![Figure 3](image.png)

*Figure 3. A) Oxygen concentration in the scaffold after 200 seconds in the OC-S and the OC-D models. B) Shear stress values exported from FSI model.*

The scaffold strain computed by the FSI model is maximum in the axial direction, but never greater than 1%, indicating that the non-contact squeeze pressure causes negligible pore deformation and
the scaffold remains within the linear elastic region. Average shear stress values are significantly (10³-fold) lower than the values computed by the LF model (Figure 3B), demonstrating the need to implement a FSI model when a fluid-induced stimulus is applied to a complex porous scaffold. In fact, the simple Laminar-Flow conditions applied to both the 2D and 3D models gave average shear stress values in the range of those known to compromise cell vitality. Considering the positive results from the cell culture experiments, we can affirm that the implementation of a 3D fluid-structure interaction model is mandatory for accurately mimicking the fluid dynamics inside the bioreactor. Computational models can be used as further feedback to improve S²PR bioreactor functioning.

REFERENCES


IN-SILICO CHARACTERISATION OF THE KIRKSTALL QV900 IN-VITRO SYSTEM FOR ADVANCED CELL CULTURE

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SUMMARY
We have developed an in-silico model of the Kirkstall Quasi-Vivo QV900 cell culture system. The QV900 consists of a series of connected sealed chambers, within which cells can be cultured in a low shear stress flow environment. By modelling fluid flow and oxygen transport within the chambers, we have been able to simulate flow patterns and shear stress/oxygen levels experienced by the cells, and we have demonstrated that physiologically relevant oxygen concentration gradients can be achieved by configuring connected chambers in a particular way.

Key words: Cell culture systems, bioreactors, fluid dynamics, drug toxicity testing

1 INTRODUCTION
Understanding the behaviour of cells, especially when subjected to stimuli, is one of the key goals in toxicology research. Current experimental investigations focus on either in-vivo experiments, which involve animals, or in-vitro experiments, where cells are grown outside of the body in conditions that poorly mimic reality. Recent developments in 3D bioreactor technology have provided a way of better representing the in-vivo situation [1]. Kirkstall Ltd have developed a family of cell culture systems called Quasi Vivo which consist of interconnected cell culture chambers, each used to culture cells or tissues under dynamic nutrient flow, providing more physiologically accurate conditions [2]. This technology provides a functional median between traditional whole-organism animal and human studies and the microfluidic human-on-a-chip systems still under development.

The QV900 (Fig.1) system consists of an optical tray suitable for holding six chambers which can be connected together in any combination, providing a high degree of flexibility and the potential to culture cells over a more defined set of conditions. Additionally, three dimensional structures of cells can be incorporated within this system: cells can be placed in the chamber as multi-layer structures, such as scaffolds or spheroids, leading to an environment which more closely mimicks in-vivo conditions.

The primary aim of this work was to simulate flow patterns and shear stress/oxygen levels experienced by the cells and to establish whether or not physiologically relevant oxygen gradients could be obtained using this system.

2 METHODOLOGY
In this study, we focus on HepG2 liver cells. These cells typically suffer from a lack of expression of (phase 1 and 2) metabolising enzymes in-vitro, despite being highly expressed in-vivo. It is believed that a flow environment may improve the expression of these metabolising enzymes. An additional complication is that HepG2 liver cells are very sensitive to shear stress, with high levels resulting in decreased cell viability, so we must ensure that low levels of shear stress are maintained at the cell surface.
2.1 Fluid dynamics

We firstly constructed, in COMSOL Multiphysics, a 3D representation of a single QV900 chamber with cells placed at the base of the chamber. The fluid flow velocity and pressure were solved for using the Navier-Stokes equations, assuming that the fluid is incompressible and is adequately represented as a Newtonian fluid:

\[
\nabla \cdot \mathbf{u} = 0, \quad (1)
\]
\[
\rho \frac{\partial \mathbf{u}}{\partial t} + \rho (\mathbf{u} \cdot \nabla) \mathbf{u} = -\nabla p + \mu \nabla^2 \mathbf{u}, \quad (2)
\]

where \( \mathbf{u} \) is the velocity field, \( \rho \) is the fluid density, \( p \) is the pressure and \( \mu \) is the dynamic viscosity.

2.2 Oxygen transport

The transport of oxygen through the fluid was modelled using a convection-diffusion equation:

\[
\frac{\partial c}{\partial t} + (\mathbf{u} \cdot \nabla) c = D \nabla^2 c, \quad (3)
\]

where \( c \) is the concentration of oxygen and \( D \) is the diffusion coefficient of oxygen in the fluid. For the purposes of this study, we choose the values of \( \rho, \mu \) and \( D \) assuming the fluid is water. We model the cells as a thin layer of thickness \( h_c \) at the bottom of the chamber. Within the cells, oxygen diffuses with diffusion coefficient \( D_c \) and is consumed according to Michaelis-Menten kinetics:

\[
\frac{\partial c}{\partial t} = D_c \nabla^2 c - \frac{V_{\text{max}} c}{K_m + c}, \quad (4)
\]

where \( V_{\text{max}} \) is the maximum consumption rate and \( K_m \) is the Michaelis-Menten constant. It is assumed that there is no appreciable flow within the cells.

2.3 Initial and boundary conditions

Initially, the fluid velocity is zero in the chamber and the oxygen concentration is zero within the chamber and cell layer. At the inlet to the chamber, a parabolic velocity profile is assumed with the magnitude being derived from the volumetric flow rate \( Q \), which can be controlled in experiments. No-slip conditions are imposed on all the walls of the chamber and at the outlet, we impose pressure with no viscous stress.

Regarding oxygen transport, we assume that the walls of the chamber and connecting tubes are impermeable. At the inlet we assume a constant supply of oxygen at concentration \( c = c_i \) and at the outlet we impose a convective flux only. Continuity of concentration is assumed at the fluid/cell interface.
2.4 Connecting chambers

Our model was subsequently extended to include connected chambers. Chambers were connected in a simple way by joining the outlet of one chamber with the inlet of another via a short length of tubing. This allowed us to assess the effect of multiple connected chambers on the flow patterns and oxygen concentration/shear stress experienced by the cells.

3 RESULTS AND CONCLUSIONS

Using our COMSOL model we simulated the fluid dynamics and oxygen transport for a range of flow rates, using experimentally measured parameter values relevant to HepG2 cells. In Figure 2 we display some steady state results for the single chamber case with $Q = 180 \mu L/min$. As expected, the oxygen concentration in the chamber decreases with depth. Along the cell surface a gradient in oxygen concentration is established, with higher values closer to the inlet tube. Two flow recirculation zones are observed at the bottom of the chamber. The peak shear stress experienced at the cell surface is found to coincide with the centre of the chamber. Results from the other flow rates considered will be presented at conference.

![Figure 2: COMSOL results for $Q = 180 \mu L/min$. Upper left: Oxygen concentration profile. Upper right: Flow profile. Lower left: Bird’s-eye view of oxygen concentration at the cell surface. Lower right: Bird’s-eye view of shear stress at the cell surface.](image)

We sought to determine whether or not cell surface oxygen concentration gradients close to those observed along a hepatic sinusoid could be achieved using this system. Our results (not shown) indicate that such gradients cannot be obtained within a single chamber. However, by connecting chambers in a particular way, we can obtain gradients which are more physiologically relevant. Our findings, which are currently being validated experimentally, may have important implications in terms of devising appropriate cell culture systems for in vitro liver drug toxicity testing.
REFERENCES


DISTRIBUTED AND LUMPED PARAMETER MODELS FOR THE CHARACTERIZATION OF HIGH THROUGHPUT BIOREACTORS

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SUMMARY

We focus on a specific model of bioreactor, with multiple input/outputs, aimed at generating osteochondral constructs, i.e., a biphasic construct in which one side is cartilaginous in nature, while the other is osseous. We next develop a general computational approach to model the microfluidics of a multi-chamber, interconnected system that may be applied to human-on-chip devices. This objective requires overcoming several challenges at the level of computational modeling. The main one consists of addressing the multi-physics nature of the problem that combines free flow in channels with hindered flow in porous media.

Key words: Computational fluid dynamics and mass transport; Coupled fluid-porous interaction; Distributed and lumped parameter models; High throughput bioreactors; Osteochondral tissue

1 INTRODUCTION

A number of in vitro approaches have been used over time for high throughput drug screening or toxicology testing. However, most currently available systems are only partial approximations of human biology and their predictive capacity is consequently limited. In fact, such systems are either based on human cell cultures, not capturing the complexity of cell behavior in a three dimensional (3D) environment, or they are based on animal tissues fragments, 3D in nature but only partially biosimilar to human tissues and unable to account for interactions with other organs. To overcome these limitations, next generation bioreactors are being developed to generate multiple human cell-based tissue analogs within the same fluidic system to better recapitulate the complexity and interconnection of human physiology. These efforts aim at creating multi-tissue organ systems (cardiovascular, gastro-intestinal, musculoskeletal, etc.) that ultimately can be joined in an interconnected human-on-chip device capable of providing a veritable representation of the body complex response to diseases and potential drug treatments [1-3].

The effective development of these devices requires a solid understanding of their interconnected fluidics, to predict the transport of nutrients and waste through the constructs and improve the design accordingly. In this work, we have focused on a specific bioreactor with multiple input/output aimed at generating osteochondral constructs, i.e., a biphasic constructs in which one side is cartilaginous in nature, while the other is osseous. This bioreactor [4-6] represented in Figure 1 has been chosen since it comprises both a dual chamber system to host a single biphasic tissue construct with distinct fluidics (Fig.1, top), and a set of interconnected chambers with common fluidics (Fig. 1, bottom). Starting from this specific bioreactor, we have developed a general approach to model the microfluidics of a multi-chamber, interconnected system that may be applied to human-on-chip devices.
2 METHODOLOGY

The microphysiological osteochondral bioreactor analyzed in this work is aimed at the study of osteoarthritis (OA), a major pathology of articular joints, affecting over 33% of the population over the age of 65 [7]. The hallmark of this disease that affects all tissues in the joint, is the progressive degeneration of cartilage which begins well before clinical symptoms manifest, ultimately requiring joint replacement surgery [8]. The high incidence of this painful and disabling pathology begs for the understanding of the causes and mechanisms of its development, in order to identify reparative drug therapies to arrest or even regenerate the damaged tissues and ultimately avoid surgery. A novel strategy in this respect adopts a tissue engineering approach and the use of bioreactors [4, 6] to generate a high number of identical in vitro constructs that can replicate the pathogenesis of joint diseases for the identification of therapeutic targets and for drug screening [4, 9-11]. Critical in this respect is the development of a representative model of the interactions between cartilage and other joint tissues and, in particular, with the subchondral bone. In fact, there is growing evidence of the exchange of nutrients, cytokines, and hormones in vivo between bone and cartilage. The osteochondral (OC) unit is then conceived as the main target of OA, to reflect the dynamic cartilage/bone interplay in both health and disease [4, 12-17]. The medium to high throughput system studied in this work, which we call high-throughput bioreactor (HTB) hereon, is the first of its kind. It hosts in a single chamber a biphasic construct, with separate fluidics for its cartilaginous and osseous components, effectively creating a dual-chamber setup (Figure 1) [5, 6]. In this way, cartilage and bone will be in contact and able to signal to each other, while each is exposed to its ideal culture medium. Furthermore, the HTB allows the generation and culture of a high number of identical OC constructs similar in dimensions to native tissue biopsies [4-6]. It must be noted that the physiological functions of the examined tissue are primarily load bearing and force transduction, which imply a key role for the extracellular matrix (ECM), also an essential player in the regulation of cell differentiation, physiology and response to insults [4, 18, 19]. Consequently, a bioreactor that accommodates a significant ECM tissue component to recapitulate at least some of the physiological aspects of the osteochondral complex requires a relatively larger volume, in the order of millimeters rather than the hundreds of micrometers more common in microfluidic systems. To generate a construct that mimics tissue physiology, the bioreactor chamber is filled with a cell-laden porous polymeric scaffold. Hence, the larger size and the presence of porous scaffold within the insert makes nutrient perfusion within the device a potential challenge, since to avoid cellular hypoxia and to obtain adequate tissue development, nutrients must travel a longer path to reach the inner regions within the bioreactor. In this context, we use computational fluid dynamics to assess the hydrodynamic properties of the system. Previous works [2, 20-22] evaluated the fluid mixing and transport of nutrients between chambers in the same unit of a forced perfusion setup, but to our knowledge there are no similar studies about the interaction of fluid and porous constructs in a design with more effective fluidics as the one in Figure 1. Furthermore, to achieve a high-throughput drug screening system, single bioreactor dual-chambers (bioreactor unit) have been connected and combined in a multi-unit system, organized in sequential and parallel rows (Figure 1). In the 96 wells design presented in Figure 1, individual units are connected only in series, 8 at a time as this design is best suited for drug or toxicological screening; to assess for instance a dose response, each array of 8 units can be subjected to a different concentration of the compound under examination.

The specific objective of this work is to develop a methodology to characterize the flow and transport in a HTB by means of a computational modeling approach, combining distributed and lumped parameter models. In particular, we have assessed the degree of perfusion and mixing of nutrients in each region of the device, evaluating the effect of different scaffold types. The computational model was then used to compare two different engineered constructs, a hydrogel (methacrylated gelatin, GelMA [5, 23]) and a porous polymeric scaffold (poly-L-lactate, PLLA)[24]. The first one features very small pore size and is solute permeable, the second one shows larger pore size and is impenetrable to fluid and nutrients. Performing such simulations requires overcoming several challenges at the level of computational modeling. The main one consists of addressing the multi-physics nature of the problem that combines free flow in channels with hindered flow in porous media. Fluid dynamics is then coupled with advection-diffusion-reaction equations that model the transport of biomolecules throughout the system and their interaction with living tissue. Besides these modeling challenges, the complex configuration of the bioreactor poses significant difficulties in building the CAD
model and discretizing its parts with a computational mesh suitable for the application of a numerical scheme. We have adopted here a commercial platform, ANSYS (ANSYS Inc., Canonsburg, PA), which features advanced multi-physics simulation capabilities. Another challenging aspect of this work is then to stretch the limits of the ANSYS platform to address the complex problem at hand. Ultimately, our aim is to provide a predictive approach useful for the general organ-on-chip community. To this end, we have developed a lumped parameter approach that allows us to analyze the behavior of multi-unit bioreactor systems with a modest computational effort, provided that the behavior of a single unit could be fully characterized. If the linearity conditions are satisfied, this computational methodology is independent from the specific osteochondral nature of the biological system being studied. Our approach simply describes a network of interconnected multi-chamber units. Consequently, we believe that our approach can be directly applied to predict the flow and transport of a generic human-on-chip setup, even those comprising multiple physiological systems (e.g., a liver model connected to a kidney model, connected to a bone model, etc.) with single or multi-chamber units.

Figure 1: Different bioreactor configurations. 1 cell (top left), 1-unit in cross section (top right), 4-units (bottom left) and 96-units. (bottom right).

3 RESULTS AND CONCLUSIONS

From the methodological standpoint, we have overcome the challenge of developing a complex multi-physics model of the bioreactor. We have also succeeded in implementing the model into a commercial computational platform, showing the significant potential of computational tools on biomedical research, including analytical cases integrating quantitative biology and translational medicine. Future developments of this study consist of experimental validation of the models and their application to explore different bioreactor configurations. Such findings will allow optimization of the model by incorporating the multi-faceted factors that affect its behavior and functionality.

REFERENCES

MODELING THE ROLE OF DYNAMIC MECHANICAL STIMULI ON DENSE CONNECTIVE TISSUE FORMATION AND PROPERTIES IN CARDIOVASCULAR TISSUE ENGINEERING

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SUMMARY

A myriad of external stimuli is available in current bioreactors and it has become axiomatic that mechanical conditioning promotes engineered tissue (ET) formation. We have observed that upon mechanical conditioning, vascular smooth muscle cells are stimulated to produce not only more extracellular matrix (ECM), but also of better quality. The ability to quantify and predict cell growth, matrix production, and matrix stiffness (outputs) in response to a multitude of controllable stimuli (inputs) results in a useful design tool supported by careful designed experiments and is of critical importance for successful clinical development of all tissue engineering (TE) applications.

**Key words:** mechanical conditioning, extracellular matrix, growth and remodeling

1 INTRODUCTION

Living engineered tissues (ETs) may circumvent ongoing problems in pediatric valve replacement [1] and may present potential alternatives to autografts and synthetic grafts in coronary artery bypass grafting surgery [2] by offering the possibility of natural integration with native tissue, restoration of physiological function, optimum hemodynamic performance, and the potential for growth, remodeling, and self-repair. Although a myriad of external stimuli are available in current bioreactors (e.g. oscillatory flows, mechanical conditioning, large deformation stimuli, etc.), there remain significant bioengineering challenges in determining and quantifying parameters that lead to optimal ECM development and structure for the long term goal of obtaining ETs exhibiting tissue architecture and functionality equivalent to native tissue. It has become axiomatic that mechanical conditioning promotes ET formation (Figure 1), either in vitro in organ-level bioreactors or in tissue-level bioreactors with idealized-geometry TE constructs, or in vivo. However, the underlying mechanisms remain largely unknown. Efforts to date have been largely empirical, and a two-pronged approach involving novel theoretical developments and close-looped designed experiments is necessary to reach a better mechanistic understanding of the cause-effect interplay between cellular proliferation and differentiation, newly synthetized ECM, and tissue formation, in response to the controllable conditions such as scaffold design, oxygen tension, nutrient availability, and mechanical environment during incubation.

2 METHODOLOGY

We evaluate the influence of dynamic mechanical conditioning and exterior flow oscillatory shear stress on the proliferative and synthetic behavior of ETs by employing a novel theoretical framework for TE [3]. We employ mixture theory to describe the evolution of the biochemical constituents of the TE construct and their intertwined biochemical reactions, evolving poroelastic models to evaluate the enhancement of nutrient transport occurring with dynamic mechanical deformations, and computational fluid dynamics (CFD) to assess the exterior flow boundary conditions developed in needled-nonwoven scaffolds in the flex-stretch-flow (FSF) bioreactor (Figure 2) [4-6]. Subsequently, we investigate the effects of large deformation on ECM synthesis.
and stiffness under strip biaxial strain with elastomeric scaffolds (Figure 3). We have developed an analysis methodology to de-couple the response of the scaffold from de novo ECM, and to quantify the mechanical properties and anisotropy of de novo ECM with biaxial testing [7].

2.1 Modeling engineered tissue growth under static conditions

We model the TE construct as an evolving tri-phasic mixture – three phases simultaneous coexist: oxygen $\rho_o$, cells $\rho_c$, and ECM $\rho_m$. Dissolved oxygen diffuses accordingly to Fick’s 1st law with and ECM dependent diffusivity $D_o(\rho_m)$, is transported with solvent velocity $\nabla$, and is consumed by cells with reaction rate $q_o(\rho_c, \rho_o)$. The governing equation for dissolved oxygen is

$$\dot{\rho}_o - \nabla \cdot (D_o \nabla \rho_o) + \nabla \cdot \nabla \rho_o = q_o.$$ 

Oxygen diffusivity decreases as matrix is produced, from the oxygen’s diffusivity in water towards the diffusivity in tissue. Oxygen metabolic consumption $q_o$ follows Michaelis-Menten kinetics [9]. Cells move by chemotaxis with oxygen being the chemotactic sensitivity and maximum bound for cell phase $\rho_c^{\text{max}}$ was chosen [10]. The cell phase is governed by

$$\dot{\rho}_c - \nabla \cdot [-D_c \nabla \rho_c + \chi(1 - \rho_c/\rho_c^{\text{max}}) \nabla \rho_o] = g_c,$$

where $D_c$ is the diffusivity of the cell phase, $\chi$ is the chemotactic sensitivity, and $g_c(\rho_c, \rho_o)$ is the cell proliferation rate. Cells experience growth inhibition, and even toxicity, at very high oxygen concentrations, and anoxia at very low oxygen concentration – due to the importance of oxygen supply and concentration, oxygen is the growth-limiting phase and 1st-order inhibition kinetics is assumed [11]. Oxygen-fed cells synthesize collagen and incorporate it into the ECM; in engineered constructs, ECM deposition begins at the construct periphery, where an oxygen-optimal environment promotes a higher cell density and more synthesis. Over time of cultivation, a limiting steady-state $\rho_m^{\text{max}}$ is approached at which there is a balance of production, degradation and incorporation of collagen [9]. The dependence upon oxygen is 1st-order, and the governing equation for the ECM is

$$\dot{\rho}_m = k_m \rho_c \rho_o (1 - \rho_m/\rho_m^{\text{max}})$$

where $k_m = k_m^o + k_m^f(\mathbf{F})$ is the matrix production rate, considered to be deformation-dependent (where $\mathbf{F}$ is the deformation gradient) and with a basal rate when strains are zero. Highly oscillatory flow fields develop around flexed configurations of rectangular scaffolds in FSF bioreactors [6]. CFD simulations were conducted to assess wall shear stress profiles around the undeformed and flexed specimens. Oxygen transport is enhanced due to oscillatory exterior flow and Neumann boundary conditions on the oxygen phase with an oscillatory shear index (OSI)-dependent oxygen transfer coefficient are employed. The TE construct boundary is impervious to the cell phase (no flux boundary condition) and the ECM phase does not require boundary conditions. For initial conditions, matrix is initially absent, cells are homogeneously distributed with initial cell seeding $\rho_c^{\text{ini}}$, and oxygen is homogeneously present at the exterior tension $\rho_o^{\text{ext}}$.

2.2 Modeling engineered tissue growth under dynamic conditions

Tissue engineered constructs are evolving porous materials with porosity as a function of ECM, i.e. $\varphi(\rho_m)$. The coupling between mechanical deformation and enhanced oxygen transport is described
with poroelastic models composed of a porous solid saturated with fluid. We consider the fluid inviscid and the solid hyperelastic with stored energy function \( W(\rho_m, \mathbf{C}) \), thus the Cauchy stress is \( \mathbf{T}^s = -p(\varphi - 1) \mathbf{I} + 2F(\partial W/\partial \mathbf{C})(\mathbf{F}^T) \) with \( p \) the pore pressure and \( \mathbf{C} = \mathbf{F}^T \mathbf{F} \). Mass and linear momentum balance of the entire poroelastic mixture are given by [12]

\[
\nabla \cdot \mathbf{v}^s + \nabla \cdot \varphi / \varphi = 0
\]
\[
\nabla \cdot \mathbf{T}^s - \nabla p = 0
\]

where \( \mathbf{v}^s \) is the solid velocity. Darcy’s law governs \( p \) and \( \mathbf{v} \), i.e. \( \mathbf{v} = -K \nabla p / \varphi \) and \( K(\rho_m) \) is the ECM-dependent permeability.

2.3 Modeling the mechanical behavior of engineered tissue grown under large strains

Poly(ester urethane)urea (PEUU) scaffolds micro-integrated with vascular smooth muscle cells (VSMCs) were manufactured by electrospraying and electrospinning [13]. The biosynthetic response of micro-integrated VSMC ring constructs was investigated at 1 Hz cycles for three culture durations of 7, 14 and 21 days and 3 strain levels: low (15%), intermediate (30%) and high (50%) [14] (Figure 3). Square specimens from ET constructs mechanically conditioned for 21 days at 30% strain (regime which resulted in the highest ECM production) were prepared for planar biaxial mechanical testing (methodology described in detail in [15]). Subsequently, the polymer phase of ET constructs was isolated by degrading the de novo ECM with 0.25% Trypsin EDTA for 50% [14] (Figure 3). Square specimens from ET constructs mechanically conditioned for 21 days were coalesced into an average response of the de novo ECM (n=4), and compared with experimental results of untreated bovine pericardium (BP) [18].

3 RESULTS AND CONCLUSIONS

Engelmayr et al. [4] seeded ovine vascular smooth muscle cells in non-woven scaffolds and subjected them to cyclic flexure, a major mode of heart valve deformation, at physiologic amplitude and frequency. After 3 weeks of incubation, flexed constructs exhibited higher collagen frequency. After 3 weeks of incubation, deformation, at physiologic amplitude and flexure, a major mode of heart valve scaffolds and subjected them to cyclic

![Figure 3](image)

**Figure 3.** 3D visualization of the transmural cross-section of a FSF specimen and simulated ECM profiles.
concentration, more homogeneous transmural cell and ECM distributions (Figure 4), and significant trends of increased stiffness. CFD simulations were conducted to assess wall shear stress profiles around the undeformed and flexed specimens (Figure 5). Simulation results compare favorably to existing experimental data, and most importantly, the theoretical framework for mechanically conditioned ET growth permits the in silico exploration and optimization of conditioning protocols (e.g. changing flexure amplitude or frequency) in a rational and cost-effective manner.

Under large deformations, augmented collagen synthesis at 30% cyclic strip biaxial strain was observed, whereas constructs subjected to 15 or 50% strain showed minimal increases over static specimens. Biochemical assay results were corroborated by histological assessment: cell and ECM rich regions formed lamellae and improved mechanical integrity of the construct. Systematic evaluation of constructs before and after ECM degradation showed consistent compliance increases and allowed the determination of the mechanical contribution of the de novo ECM (Figure 6). Subsequent modeling indicates that the ECM phase exhibits a highly nonlinear response, however it is mildly anisotropic. Fits to a structural model resulted in collagen fiber stiffness of 15.36 ± 5.23 MPa, about half of 30.99 MPa of BP but much higher than ever obtained with infinitesimal deformations in the FSF bioreactor. Comparable fiber orientations were observed; however, fiber recruitment occurred at minimal or at zero strains (≈ 8% in BP). Lack of undulation and mild anisotropy indicates inferior microstructural organization and the insufficient collagen maturation of highly specific dense connective tissues.

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Engineering in Female Pelvic Health
TOWARDS A MICROSTRUCTURALLY-MOTIVATED MODEL OF THE MURINE VAGINAL WALL

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SUMMARY

The etiology of pelvic organ prolapse remains unclear; however, altered extracellular matrix turnover in the vaginal wall and its surrounding support structures has been implicated. Towards this end, we present a mathematical model capable of describing the mechanical response of the nonpregnant murine vaginal wall with microstructural implications. We submit that this preliminary framework can be extended to a growth and remodeling model amenable to hypothesis-driven studies to determine potential mechanobiological mechanisms of prolapse as well as to design targeted intervention strategies.

Key words: vaginal wall, constitutive model, women’s health

1 INTRODUCTION

Pelvic Organ Prolapse (POP) is a global health concern characterized by a loss of pelvic support leading to the descent of the female pelvic organs into the pelvic cavity. POP may result in the protrusion of these organs through the vagina and lead to issues that often reduce quality of life. With a lifetime risk of 11% and a 30% re-operation rate [1], there is a pressing need for alternative POP treatments. However, despite the high incidence of POP, its underlying etiologies and mechanisms are still poorly understood. This is due, in part, to its many confounding risk factors (pregnancy, vaginal childbirth, advancing age, menopause, obesity, genetic factors) and a limited understanding of the basic microstructural composition and biomechanics of the vaginal wall and its surrounding support structures. For example, increased elastic fiber degradation end-products and fragmented elastic fibers have been observed in patients with prolapse compared to nonsymptomatic controls [2]. Further, it has been hypothesized that elastic fiber fragmentation will correlate to decreased structural integrity and increased risk of prolapse [2], however the mechanical and biological mechanisms by which elastic fiber damage may contribute to prolapse are poorly understood. Towards this end, microstructurally-motivated growth and remodeling (G&R) models have demonstrated the ability to predict (patho)physiologic processes and evolving tissue structure by considering the production and removal of each load-bearing constituent [3]. Such models afford time- and cost-efficient frameworks to test hypotheses regarding pathological mechanisms, clinical interventions, as well as timing of intervention strategies. Before G&R models can be developed, however, a constitutive relation with microstructural implications must be identified. Therefore, the objective of this study is to establish a microstructurally-motivated constitutive model capable of describing the biaxial extension-inflation response of the nonpregnant murine vaginal wall. Due to its similarity in geometry and composition to arteries, we hypothesize that the murine vaginal wall will be best described by a four-fiber family function paired with a cubic term.

2 METHODOLOGY

2.1 Mechanical testing

Vaginal tissue was explanted from 12 nonpregnant female C57/BL6 mice (IACUC approved),
euthanized at 4-6 months of age while in estrus. The in vivo axial stretch was estimated by measuring the in situ to ex vivo change in distance between stain lines placed during dissection [4]. Samples underwent pressure-diameter (P = 0 to 25 mmHg at three different axial extensions around the estimated in vivo axial stretch) and force-length preconditioning and mechanical testing within a pressure myograph wherein the reference configuration was defined as the point at which the vagina began to buckle at 4 mmHg. Following testing, a ring (~0.5 mm thick) was cut transversely at the location at which the tissue diameter was tracked during the mechanical testing in order to quantify unloaded thickness.

2.2 Stress calculation

Mean circumferential and axial Cauchy stresses and stretches were calculated from the processed biaxial data as follows [5],

\[
\langle t_{\theta\theta} \rangle = \frac{p r_l}{r_o - r_l}, \quad \langle t_{zz} \rangle = \frac{p r o^2 + L}{\pi (r_o^2 - r_l^2)}, \quad \lambda_{\theta\theta} = \frac{r}{R}, \quad \lambda_{zz} = \frac{l}{L}, \quad \lambda_{rr} = \frac{l}{\lambda_{\theta\theta} \lambda_{zz}}
\]

where \( \langle t_{\theta\theta} \rangle \) and \( \langle t_{zz} \rangle \) are the mean circumferential and axial Cauchy stresses, respectively. \( P \) is the pressure measured by the pressure transducer, \( r_l \) is the deformed inner radius, and \( r_o \) is the deformed outer radius, calculated from on-line measurements of the outer diameter. \( L \) is the unloaded length, \( r \) and \( R \) are the deformed and undeformed “middle” (average) radii, respectively, \( \lambda_{zz} \), \( \lambda_{\theta\theta} \), and \( \lambda_{rr} \) are the axial, circumferential, and radial stretches, respectively, and \( l \) is the deformed length. Radial stretch and the deformed inner diameter were inferred from the incompressibility assumption. For example,

\[
V = \pi \left( R_o^2 - R_i^2 \right) L, \quad r_l = \sqrt{r_o^2 - \frac{V}{\pi l}}
\]

where \( R_o \) is the undeformed outer radius, \( R_i \) is the undeformed inner radius, calculated from the unloaded wall thickness determined during opening angle experiments, and \( V \) is the mean volume.

2.3 Constitutive modeling

In order to quantify the mechanical behavior of the murine vaginal wall, vaginal tissue was modeled as an incompressible, homogeneous, hyperelastic material undergoing finite quasistatic isothermal deformations. The Cauchy stress tensor was calculated by the following,

\[
t = pI + \frac{2}{\det F} F \frac{\partial W(C)}{\partial C} F^T
\]

where Lagrange multiplier \( p \) is used to enforce incompressibility and \( \det F = 1 \). Several forms of the strain energy function \( W \) were chosen, motivated by experimental results and will be discussed in Sec. 3 below. For each selected form of \( W \), material parameters were simultaneously fit to experimental measures of stress and strain from the in vivo and 4% above in vivo pressure-diameter loading protocols using the built in non-linear least squares solver in Matlab and were averaged over three trials [6]. Vaginal tissue was assumed to be transversely isotropic \( W = W(\mathbf{I}_1, \mathbf{I}_4) \) [7]. The strain energy function was additively decomposed into an isotropic term representing the response of the elastic fiber-dominated ground matrix, dependent on the first strain invariant \( \mathbf{I}_1 = tr(C) \), and an anisotropic term representing the response of the collagen fibers and passive smooth muscle, dependent on the fourth strain invariant \( \mathbf{I}_4 = \mathbf{N} \cdot C \cdot \mathbf{N} \) giving \( W(\mathbf{I}_1, \mathbf{I}_4) = W_{iso}(\mathbf{I}_1) + W_{aniso}(\mathbf{I}_4) \) [8]. Response functions were plotted in order to determine suitable functional forms of the isotropic term [9]. Each identified functional form was evaluated for goodness of fit by calculating \( R^2 \) values for each sample. Additionally, correlation coefficients were calculated for each selected \( W \) and \( \det R_{ij} \) was used to determine if the model was over-parameterized (\( \det R < 10^{-4} \)) as described previously [10]. For example,

\[
Z = \left[ \frac{\partial t}{\partial x_1} \frac{\partial t}{\partial x_2} \frac{\partial t}{\partial x_3} \ldots \frac{\partial t}{\partial x_n} \right]
\]

where \( t \) is the Cauchy stress, and \( x_i (i=1,2,\ldots,n) \) are the n material parameters for the selected strain energy function (SEF). The correlation matrix \( R \) of \( Z \) was calculated using the built in corcoeff function in Matlab.
3 RESULTS AND CONCLUSIONS

Motivated by studies in vasculature (c.f., [11]) and the experimental results of the mechanical tests performed herein (Fig. 1), several microstructural models were selected as candidates to describe murine vaginal wall mechanics. Prior studies in arteries have utilized models considering isotropic and anisotropic strain energy components with a neo-Hookean term and a four-fiber family function, respectively, which based on tissue microstructure takes into account families of collagen fibers oriented in the longitudinal and circumferential directions, as well as two symmetrical families oriented diagonally [12]. While it is known that the vaginal wall contains smooth muscle oriented in the circumferential and longitudinal directions [13], the collagen fiber organization remains unknown. Response function plots of the experimental measurements suggest that either a cubic or quadratic function would be appropriate to capture the isotropic behavior of the ground matrix; however, pilot studies revealed that the quadratic term was frequently over-parameterized. Thus, the cubic functional form was selected and paired with four-, three-, and two-fiber family functions considering varying fiber orientations. To begin with, we implemented a SEF considering a four-fiber family and anisotropic function and a cubic isotropic term.

\begin{equation}
W = c(I_1 - 3)^3 + \sum_{k=1}^{4} \frac{c_k}{4c_0} \left\{ e^{c_k((\lambda_k)^2-1)^2} - 1 \right\}
\end{equation}

with

\begin{align}
I_1 &= \lambda_r^2 + \lambda_\theta^2 + \lambda_\phi^2, & \lambda_k^2 &= \sqrt{\lambda_r^2 \sin^2(\alpha_k^r) + \lambda_\theta^2 \cos^2(\alpha_k^\theta)}
\end{align}

where superscript \( k \) represents the fiber family, \( \alpha_k^r \) is the angle of the \( k \)th fiber family with \( \alpha_1^r = 0 \) (axial direction), \( \alpha_2^r = \pi/2 \) (circumferential direction), \( \alpha_3^r = -\alpha_1^r = \alpha \) (diagonal directions), and \( c, c_1^r \) (stress-like), and \( c_2^r \) (non-dimensional) are material parameters. This SEF fit the experimental biaxial data reasonably well with an average \( R^2 \) value of 0.94. However, the correlation matrix revealed that the model was over-parameterized (\( detR = 4.94 e^{-08} \)) and indicated that the axial parameters were redundant. Hence, the cubic term from Eq. (1) was also coupled to a three-fiber family function,

\begin{equation}
W = c(I_1 - 3)^3 + \sum_{k=1}^{3} \frac{c_k}{3c_0} \left\{ e^{c_k((\lambda_k)^2-1)^2} - 1 \right\}
\end{equation}

where \( k = 1 \) represents the circumferential fibers and \( k = 2, 3 \) are the diagonal fiber families. This SEF resulted in an average \( R^2 \) value of 0.92, however the model was still over-parameterized for 11 of the 12 samples. The cubic term was also paired with two additional two-fiber family SEFs,

\begin{equation}
W = c(I_1 - 3)^3 + \sum_{k=1}^{2} \frac{c_k}{2c_0} \left\{ e^{c_k((\lambda_k)^2-1)^2} - 1 \right\}
\end{equation}

where in one model, \( k = 1 \) and \( k = 2 \) represent the fibers oriented in the symmetrical diagonal directions, and in the other, they represent the fibers in the axial and circumferential directions, respectively. The model considering two diagonal fiber families resulted in an average \( R^2 \) value of 0.90 (Table 1) and was not over-parameterized (\( detR = 4.95 e^{-03} \)). The model considering circumferential and longitudinal fiber families was, however, over-parameterized and resulted in an average \( R^2 \) value of 0.66. Lastly, to evaluate the ability of a phenomenological model to fit the experimental data, a Fung-type SEF was implemented [12] of the form:

\begin{equation}
W(Q) = \frac{1}{2} \frac{k}{4} (e^Q - 1), \quad Q = c_{\theta\theta} E_{\theta\theta}^2 + c_{zz} E_{zz}^2 + c_{\theta z} E_{\theta} E_{z}
\end{equation}

where \( k \) is a stress-like scaling factor, \( c_{\theta\theta}, c_{zz}, \) and \( c_{\theta z} \) are non-dimensional model parameters representing the stiffness in the circumferential and axial directions and the interaction between them, respectively. This SEF resulted in an average \( R^2 \) value of 0.87 and was over-parameterized for 7 of the samples.

In summary, all forms of \( W \) except the diagonal two-fiber family were found to be over-parameterized, thus the two-fiber family with two symmetrical diagonal families of collagen was selected as the best candidate to model the biaxial properties of the murine vaginal wall. Future work, however, is needed to further refine this model and validate the microstructural implications of each parameter. While it is known that vaginal smooth muscle is oriented in the circumferential and longitudinal directions, little is known about the orientation of collagen and elastic fibers within the vaginal wall. Comparison of the two-fiber family models (i.e. diagonal fibers vs circumferential and
longitudinal fibers) presented herein suggests that collagen is primarily aligned diagonally with a slight preference towards the circumferential direction (Table 1, α parameter). Future work will utilize the model to quantify the change in the elastic fiber-dominated matrix term before and after enzymatic digestion of elastin with elastase.

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Table 1: Material parameters and $R^2$ values from the two-fiber family diagonal SEF for twelve samples.

REFERENCES

THE EFFECTS OF MATERNAL ANATOMY ON THE MECHANICAL LOADING OF THE SOFT TISSUE THAT SUPPORT THE FETUS

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SUMMARY

Soft tissue mechanics may play a role in maintaining a healthy pregnancy and triggering the onset of labor. Currently, the level of mechanical loading on the uterus, cervix, and fetal membranes during pregnancy is unknown, and it is hypothesized that the over-stretch of these tissues contribute to the premature onset of contractility, tissue remodeling, and membrane rupture, respectively, which lead to preterm birth. This work uncovers the maternal anatomy parameters that influence tissue loading. Finite element models of pregnant anatomy at different gestation time points will be presented to calculate the mechanical loads of the soft tissues that protect the fetus.

Key words: pregnancy, reproductive biomechanics, finite element analysis

1 INTRODUCTION

During pregnancy, the uterus and fetal membranes (i.e. amniotic sac) must grow and stretch to accommodate the fetus. Simultaneously, the cervix must remodel and be a mechanical barrier to keep the fetus within the uterus. All three tissues must withstand mechanical forces to protect, support, and maintain an optimal growth environment for the developing baby. Then, in a reversal of roles, ideally nearing term, the uterus begins to contract and the cervix deforms (shortens and dilates) to allow for a safe delivery of the fetus. The magnitude of stress and stretch of these soft tissues supporting the fetus are thought to control physiologic processes that regulate tissue growth, remodeling, contractility, and membrane rupture, and it is generally hypothesized that these mechanical signals are clinical cues for normal labor and preterm birth\cite{1}.

Clinically, uterine over-distention has been associated with spontaneous preterm birth because twin pregnancies\cite{3, 4} and patients with excess amniotic fluid tend to deliver early\cite{5}. Additionally, the mechanical failure of the uterine cervix caused by the premature remodeling, shortening and dilation of the cervix is thought to be the final common pathway for many etiologies of spontaneous preterm birth\cite{6, 7}. Yet, the mechanical stress and stretch of these tissues during pregnancy have not been determined, preventing an understanding of normal labor processes and an evaluation of the risk of preterm birth.

The goals of this work are to take advantage of existing temporal x-ray data of the pregnant human anatomy\cite{8} to construct finite element (FE) models of the pregnant abdomen (Fig.1) and to calculate the magnitude of tissue stress and stretch at various gestation time points. X-ray data show that the gravid uterus goes from a spherical shape before 20 weeks to an elliptical shape after 20 weeks when the fetal growth rate begins to accelerate. During this elliptical
growth its walls thin and its longitudinal diameter grows more quickly than the anterior-posterior and left-right diameters, with maximum elongation rate occurring between 20 and 32 weeks \cite{8, 9}. This particular study focuses on the effect of uterine shape throughout gestation on tissue stretch in the uterus and in the cervix, particularly at the internal cervical os, which is the hypothesized site of premature cervical remodeling \cite{10}.

2 METHODOLOGY

FE models (FEBio 2.3.1) of the pregnant abdomen were built using a customized computer script (Trelis Pro 15.1.3, csimsoft LLC) based on uterine diameters and wall thickness measurements taken via x-ray from pregnant patients at four gestational timepoints: 20, 25, 30, and 35 weeks \cite{8}. Cervical, fetal membrane, and abdominal parameters were kept constant to investigate the influence of uterine dimensions only. Cervical dimensions used in each model were obtained from ultrasound of one nulliparous 35 year-old patient at 25 weeks gestation \cite{2}. The method to generate the parametric geometry is published elsewhere \cite{2}. Briefly, geometry of the uterus, cervix, fetal membrane, and abdomen were generated by Boolean addition and subtraction operations on geometric primitives. The uterus was built by transforming two spherical surfaces into ellipsoids representing the outer and inner uterine walls. The shells were scaled, translated, and rotated to accurately portray uterine wall thickness. The cervix was built as a thick-walled cylinder. Its edges were rounded at either end to create anatomical corners and to match the clinical presentation of the uterocervical connection. The vaginal canal was built by fitting a spline to three points on the outside edge of the cervix at the external os and one point on the approximate location of the vaginal introitus. The fetal membrane was generated with unit thickness in an ellipsoid method similar to the creation of the uterus.

For FE analysis, the uterus and cervix were modeled as collagenous composite materials meshed using linear tetrahedral elements, based on material fits to passive length-tension curves of pregnant tissue \cite{11, 12}, while the FM was modeled as Ogden nonlinear material meshed with hexahedral elements \cite{13}. The fetal membrane was prescribed a tied contact to the inner uterine wall and a sliding contact to the cervical internal os. To compare how uterus shape and structure alone influence loading patterns, intrauterine pressure (IUP) was applied at contraction magnitude (8.67 kPa) \cite{14} and the magnitude of the principal tissue stretch was calculated. The extent of cervical stretch was evaluated as a percentage of cervical internal os region (yellow in Fig.1) volume above a 1.05 stretch threshold.
3 RESULTS AND CONCLUSIONS

There are visible differences in the magnitude and pattern of tissue stretch at the various gestational timepoints (Fig. 2). According to the x-ray data, uterine diameters increase and uterine wall thickness decrease as gestational age increases [8, 9]. As a result, uterine and cervical stress and stretch increase overall with gestation. The most drastic change in the loading pattern and magnitude in the uterus and cervix is between 20 and 25 weeks. The volume ratio of the internal cervical os stretch above a 1.05 threshold jumped from 8.93% to 51.1%. This drastic increase is most likely due to the shape change of the uterus from a spherical structure to an elliptical structure and also the increase in diameter. After the 25 weeks of gestation, as the uterus elongates the stretch pattern remains the same and the volume percent of the cervical os loaded above 1.05 stretch slightly increases from 51.1% to 61.3%.

The uterine shape change from a spherical structure to an elliptical structure had the largest influence on the change in loading pattern within the uterus and cervix. As the uterus becomes more elliptical, the overall amount of cervical stretch increases at the internal os. This uterine shape change interestingly happens within the gestational timeframe that the cervix softens, according to longitudinal in vivo aspiration data [15]. As shown in Figure 3, uterine stretch is greater at the internal surface of the uterine wall, where the intrauterine pressure is applied in the model. The inset shows higher tissue stretch in the lower uterine segment on the inner surface of the uterus, and gradually decreases toward the external uterine surface.

This study represents a first attempt to model the pregnant abdomen during the course of gestation. Understandably, obtaining longitudinal data on pregnant humans is difficult. Hence, we utilize an existing time-course dataset to inform our FE models of pregnancy at gestational ages of 20 to 35 weeks. As we discovered in our previous work [2] various material, anatomical, and contact factors influence the loading of the soft tissues that surround the fetus. Hence, the methods and results here have a set of limitations. First, as gestation progresses the IUP increases with the growth of the baby and the volume of the amniotic fluid. How this increase in IUP coupled with geometric changes influence the mechanical environment remains to be determined. Second, the material properties of the tissues evolve during pregnancy. The characteristics of this remodeling behavior is the topic of our current research and is currently being implemented into our modeling studies. Lastly, the maternal anatomy is idealized as simple geometric shapes, where the bends and folds in the uterine wall are neglected. The influence of these realistic anatomic features are also currently being investigated.

REFERENCES


CREEP BEHAVIOR OF SWINE CARDINAL LIGAMENTS

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SUMMARY

The cardinal ligament (CL) is one of the major pelvic ligaments providing structural support to the vagina/cervix/uterus complex. This ligament has been studied mainly with regards to its important function in reconstructive surgeries for pelvic organ prolapse. The creep properties of the CL have not been fully determined, despite the important in vivo mechanical role of this ligament within the pelvic floor. To advance our limited knowledge about the viscoelastic properties of the CL, we conducted planar equi-biaxial tests on CL specimens isolated from swine and measured the resulting in-plane strain using the digital image correlation (DIC) method.

Key words: cardinal ligament, planar biaxial testing, digital image correlation, viscoelasticity, creep

1 INTRODUCTION

Pelvic floor disorders (PFDs), such as urinary incontinence, fecal incontinence, and pelvic organ prolapse (POP) are a growing component of women’s health issues in the United States. It has been estimated that in 2010 over 28 million women had at least one PFD and this number is expected to increase to 44 million by 2050 [1]. Traditionally, native tissue repairs have been adopted to treat POP but mesh augmented repairs have become more common over the past years. Many women experienced adverse side effects to mesh augmented procedures, such as pain, mesh erosion, dyspareunia, and recurrence of POP [2]. These complications were, most likely, triggered by the mismatch in properties between the native tissue and the synthetic mesh.

Damage to pelvic supportive ligaments, such as the cardinal ligament (CL), contributes significantly to the development of PFDs. The CL is a visceral ligament that connects the upper vagina/cervix to the pelvic sidewall and provides support to the vagina, cervix, and uterus. The CL is parallel to the body axis and is vertically oriented when a woman is in an upright position. Through a more recent structural characterization of the CL, the CL has been found to be a suitable attachment point for a synthetic mesh in surgical repair of POP [3].

Investigating the effect of constant loading on the time-dependent mechanical behavior of the CL and other supportive ligaments is essential since these ligaments are constantly under tension and experience large changes in length and curvature in vivo [4]. The CL undergoes changes in tension as a woman sits and stands upright but, over time, these changes are exacerbated with fluctuations in weight and during pregnancy, when the growing fetus exerts additional tension on the pelvic organs. These loads are likely to cause an increase in the tissue’s length over time, compromising the support function of the CL and contributing to the development of POP.

In this study, we investigate the effects of equi-biaxial loads on the mechanical properties of swine CLs. The swine is selected as animal model due to histological similarities that exist between the CL in swine and the CL in humans [5, 6]. More specifically, the creep properties are evaluated after three 1200 s long equi-biaxial loads are applied along the main in vivo loading direction of the CL and the direction perpendicular to this one. While the CL specimens are loaded, accurate strain maps are obtained using the Digital Image Correlation (DIC) method. This study extends our limited knowledge about the time-dependent mechanical behavior of the CL, providing insight into the effect of constant loading on the supportive function of CL within the pelvic floor.
2 METHODOLOGY

This study was conducted with the approval of the Institutional Animal Care and Use Committee (IACUC) at Virginia Tech. Four adult (3 to 4 year-old, approximately 450 lbs) domestic swine were obtained from a slaughterhouse (Gunnoe Sausage Co, Goode, VA). The CLs were harvested from the swine using techniques detailed in our previous study \[5\]. They were hydrated with phosphate-buffered saline solution (PBS, pH 7.4, Fisher Scientific, USA) and then frozen at -20°C. They were thawed at room temperature and cut into approximately 3 × 3 cm\(^2\) specimens. A total of 24 specimens were used for mechanical testing. Before mechanical testing, the thickness of each specimen was measured in 4 different locations using a digital caliper (accuracy ± 0.05 mm, Series 573, Mitutoyo, Japan) under a 50 g compressive load. The average thickness of each specimen was then computed and used for stress measurements. Each specimen was immersed in a solution of PBS and methylene blue, 1% aqueous solution (Fisher Science Education, USA) and a speckle pattern was created on each specimen using an aerosol fast dry gloss white paint (McMaster-Carr, USA). Two CCD cameras (Prosilica GX 1660, Allied Vision Technologies, Exton, Pennsylvania, USA) equipped with macro lenses (AT-X 100mm F2.8 AT-X M100 Pro D Macro Lens, Tokina, Tokyo, Japan) were employed to capture high resolution (1600×1200 pixel) images of each specimen during testing. The 3D digital image correlation (DIC) system (VIC-3D, Correlated Solutions, Columbia, South Carolina, USA) was used to perform the non-contact strain measurement. Each specimen was gripped with 4 safety pins on each of the four sides and mounted into a planar biaxial testing system equipped with four 20 N load cells (accuracy ± 0.02 N, Instron, UK). The two axial loading directions were selected to be the main in vivo loading direction of the CL and the direction perpendicular to this one. For each specimen, the distances between the two closest safety pins on opposite sides of the specimen were used to compute the two side lengths of the specimens using ImageJ (NIH, Bethesda, MD). Each of those lengths were then multiplied by the specimen’s average thickness to determine the specimen’s undeformed cross-sectional area along the main in vivo and perpendicular loading directions. The specimen was then placed in a bath made of acrylic glass (Perspex, UK) which was filled with PBS at room temperature (21°C). The bath was then enclosed with a cover also made of acrylic glass.

Specimens (\(n = 22\)) were split into three groups, group 1, group 2, and group 3, based on their thicknesses and, consequently, magnitude of the equi-biaxial load applied during creep testing. Thinner specimens were subjected to lower equi-biaxial loads to avoid their premature damage and failure during testing. Specimens in group 1 (\(n = 7\)) were preloaded to 0.1 N and preconditioned by loading/unloading them from 0.1 N to 1 N ten times at 0.05 N/s loading rate. Following preconditioning, the specimens were unloaded and allowed to recover for 600 s (=10 min). They were then stretched at a 0.05 N/s loading rate until an equi-biaxial load of 1 N was reached. The equi-biaxial load of 1 N was held constant for 1200 s (=20 min). Specimens in group 2 (\(n = 8\)) and group 3 (\(n = 7\)) followed the same protocol but the maximum equi-biaxial loads achieved during preconditioning and held over the 1200 s long time interval were 2 N and 3 N, respectively.

Using the DIC method, the local Lagrangian strain in both axial loading directions over a square region in the center of the specimen was recorded every second for the entire duration of the test. These local axial Lagrangian strains were then averaged, resulting, at every second, in a single average Lagrangian strain along the main in vivo loading direction and a single average Lagrangian strain along the perpendicular direction. The average axial Lagrangian strain calculated for one specimen in each of the axial directions will be further referred simply as “strain” along such direction. In each specimen group, the strains along both loading directions were also averaged resulting in a mean strain in the main in vivo loading direction and a mean strain in the perpendicular loading direction. A Tukey’s HSD test using \(\alpha = 0.1\) for statistical significance was performed to compare the peak strains (strains at the end of the creep test, that is at \(t = 1200\) s) between the two loading directions at each equi-biaxial load (1 N, 2 N, or 3 N equi-biaxial load). All data were analyzed using Minitab statistical software (Minitab 17, Minitab Inc.).
3 RESULTS AND CONCLUSIONS

The mean stresses for specimens in group 1 \((n = 7)\) subjected to creep tests at 1 N equi-biaxial load were found to be 0.0686 MPa and 0.0648 MPa in the main *in vivo* and perpendicular loading directions, respectively. The mean pre-creep strain (i.e. the mean strain at the beginning of the creep test) in the main *in vivo* loading direction was lower than the mean pre-creep strain in the perpendicular loading direction. The mean strain over time remained lower in the main *in vivo* loading direction compared to the perpendicular loading direction (Figure [1](a)). As shown in Figure [1](a), when comparing the mean peak strains (i.e. the mean strains at the end of the creep test) between the two loading directions, the mean peak strain in the perpendicular loading direction was found to be higher than the mean peak strain in the main *in vivo* loading direction.

For specimens in group 2 \((n = 8)\) subjected to 2 N equi-biaxial loads, the mean stresses in the main *in vivo* and perpendicular loading directions during creep were found to be 0.0924 MPa and 0.0898 MPa, respectively. Unlike specimens in group 1, the mean pre-creep strain in the main *in vivo* loading direction was higher, but not significantly higher, than the mean pre-creep strain in the perpendicular loading direction. The mean strain over time continued to be higher in the main *in vivo* loading direction compared to the perpendicular loading direction (Figure [1](b)). This was in contrast with the findings for specimens in group 1. Specifically, when comparing the mean peak strains between the two loading directions, the mean peak strain in the main *in vivo* loading direction was found to be higher than the mean peak strain in the perpendicular loading direction (Figure [1](b)).

For specimens in group 3 \((n = 7)\) subjected to 3 N equi-biaxial loads, the mean stresses were determined to be 0.112 MPa and 0.107 MPa in the main *in vivo* and perpendicular loading directions, respectively. As seen for specimens in group 1, the mean pre-creep strain along the main *in vivo* loading direction was also lower than the mean pre-creep strain in the perpendicular loading direction. Similarly, over the duration of the creep tests, the mean strain along the main *in vivo* loading direction remained lower than the mean strain along the perpendicular loading direction (Figure [1](c)). As shown in Figure [1](c), the mean peak strain in the perpendicular loading direction was found to be significantly higher than the mean peak strain in the main *in vivo* loading direction.

In summary, the peak strains were different in the two loading directions for specimens in groups 1, 2, and 3. For specimens in groups 1 and 3, the mean peak strain was higher in the perpendicular direction but, for specimens in group 2, the mean peak strain was lower in such direction (Figure [1](b)). This anisotropy was most likely determined by the micro-structural organization of the ligament. SEM and histological analyses indicated that the collagen fibers in the CL were loosely organized, although they seemed to be primarily oriented in the main *in vivo* loading direction [5]. The presence of more fibers in one loading direction could have caused the specimen to be stiffer and creep less in that direction. It must be also noted that, among the three groups, specimens in group 2 exhibited the largest amount of variability with regards to specimen thickness. This variability may have accounted for the different results among specimens in groups 1, 2, and 3 along the two axial loading directions. Together with the knowledge about the anatomy, histology, and micro-structure of the CL, a better understanding of the time dependent properties of the CL can provide valuable insights into the development of effective surgical techniques to treat pelvic floor diseases such as POP.

REFERENCES


Figure 1: Mean strain vs. time curves and box plots of peak strains for (a) specimens in group 1 subjected to 1 N equi-biaxial loads during creep tests (mean values computed over $n = 7$ specimens), (b) specimens in group 2 subjected to 2 N equi-biaxial loads during creep tests (mean values computed over $n = 8$ specimens), and (c) specimens in group 3 subjected to 3 N equi-biaxial loads during creep tests (mean values computed over $n = 7$ specimens). The data along the main in vivo loading direction and along the perpendicular loading direction are reported in orange and green, respectively. Specimens experienced lower strains in the main in vivo loading direction at 1 N and 3 N equi-biaxial loads, but higher strains in such direction at 2 N equi-biaxial loads.


AN EXPERIMENTAL AND COMPUTATIONAL STUDY OF POROSITY IN A PROLAPSE REPAIR DEVICE

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SUMMARY

Pelvic organ prolapse is a gynecologic condition that negatively impacts a woman’s quality of life and is observed in elderly and parous women (women who have given birth). As of 2011, vaginal meshes made of polypropylene were being used in 1/3 of all cases to repair prolapse. However, as use escalated so did the incidence of mesh related complications, prompting the FDA to issue two public health warnings. This paper investigates the impact of multiaxial loads on mesh porosity, a design feature in mesh related to complications, using an experimental and computational approach.

Key words: pelvic organ prolapse, polypropylene mesh, pore size

1 INTRODUCTION

Pelvic organ prolapse (prolapse) results when support to the female pelvic organs, including the vagina, bladder, urethra, rectum, and uterus, is lost [1]. Skeletal muscles (levator ani) and a series of connective tissues lift and anchor the vagina within the pelvis, forming a central load-bearing complex that, in turn, supports the remaining pelvic organs. When this complex can no longer resist intraabominal pressures, gravity, and/or inertial forces stemming from activities of daily living, either the bladder, urethra, rectum and/or uterus bulge into the vagina. This is recognized as prolapse. Nearly 50% of all parous women (women who have given birth) have some degree of vaginal laxity consistent with prolapse, which is congruent with vaginal childbirth being the number one risk factor for the development of prolapse [2]. Yet, the majority of these cases are asymptomatic and are of little clinical significance. For approximately 11% of women [3], however, the prolapse becomes symptomatic as the vagina is pushed towards or beyond the vaginal opening (i.e. introitus). In the most severe cases, the vagina completely everts outside of the body with the pelvic organs filling it from behind. Symptomatic prolapse negatively impacts quality of life and is generally associated with depression, social isolation, poor self-image, reduced intimacy, pain, and urinary and rectal dysfunction.

Surgical approaches to restore support to the vagina initially focused on repairs using a patient’s native tissues. These procedures aim to repair tissue defects, decrease the width and/or length of the vagina, and anchor the vagina via new connective tissue attachments to the pelvis or pelvic ligaments. Unfortunately, these procedures fail in 40% of cases [4], resulting in multiple operations. This is likely due to already weak native tissues and/or that the new load bearing structure is barely capable of supporting the loads that were previously resisted by a collection of connective tissue and skeletal muscle. As an alternative, some surgeons turned to synthetic devices to form a more permanent load bearing structure. The most successful of these devices, after much trial and error, was a knitted mesh made of polypropylene filaments that was adopted from abdominal hernia repair procedures. The knitted mesh design allowed these devices to be more compliant and created large pores (<1mm) to allow for tissue ingrowth. Based on early successes
and strong industry backing along with the high probability of failure for native tissue repairs, variations of these polypropylene devices were being used in 1/3 of all cases to repair prolapse by 2011.

However, increasing patient reports of complications including pain, mesh exposure into the vagina, mesh erosion into other organs, and mesh contraction following implantation caused the FDA to investigate the safety of synthetic mesh for pelvic organ prolapse repair. In 2008 and again in 2011, the FDA issued public health warnings about serious complications associated with mesh usage for specific gynecological repair procedures and this has generated a tremendous amount of litigation worldwide with major mesh manufactures pulling their products from the market. Currently, mesh use for prolapse repair and urinary incontinence procedures is undergoing a dramatic decline leaving patients with few successful surgical options.

Research into mesh use for abdominal hernia repair has revealed some of the factors associated with a lack of mesh-host tissue integration. One of the most critical appears to be a pore size greater than 1mm [5]. It is hypothesized that a phenomenon known as “bridging fibrosis” could be an underlying mechanism linking pore size to complications, i.e. the fibrotic tissue generated by the innate immune response to single filament is close enough to that around a neighboring filament to “bridge” together, preventing adequate mesh-host tissue integration. These data have lead our group to investigate whether pore size could also be contributing to complications in the gynecological arena, and whether the mechanical environment influences pore geometry following implantation. The objective of this study was to experimentally characterize changes in porosity in response to tension and use those results to develop a finite element simulation of a Restorelle™ DirectFix A device to predict changes in porosity in response to multiaxial loads.

2 METHODOLOGY

To demonstrate the impact of pore geometry of synthetic mesh on its porosity in response to the application of a uniaxial tensile load, a currently available mesh, Restorelle™ (Coloplast, Minneapolis, MN), was tested. Samples were trimmed to a typical implantation size for an abdominal sacral colpopexy procedure (75mm clamp to clamp distance, aspect ratio of 5) and with pore orientations of 0° (square shaped pore) and 45° (diamond shaped pore) with respect to the orientation recommended for implantation (Figure 1). Using image analysis, mesh porosity was compared between orientations in response to uniaxial tensile forces of 0.1, 5, and 10 N (all deemed to be within the physiologic range).

To translate these experimental results to the transvaginal Restorelle™ DirectFix A device and eventually for in-vivo simulations, a 3D finite element model of the mesh was developed. The geometry of the synthetic mesh was created in SOLIDWORKS™ (Dassault Systèmes SOLIDWORKS Corp., Waltham, Massachusetts) and discretized with linear hexahedral elements (Figure 1, right). The material was assumed to be Neo-Hookean with the knots of the simulated mesh device assigned a different Young’s modulus and Poisson’s ratio than the rest. Material parameters were determined based on an inverse finite element analysis using FEBio (FEBio.org, University of Utah) with experimental load versus displacement data from 0° and 45° orientations serving as inputs.

A custom testing rig was then created to experimentally load a Restorelle™ DirectFix A device multi-axially. DirectFix A is made of the same knitted mesh that was tested uniaxially, but is cut for transvaginal implantation. The mesh geometry consists of four arms extending from a central region. In surgery, the arms are used for fixation of the mesh in the pelvis and the central region is fixed to the vagina. As shown in Figure 2, each arm was loaded using a weight of 250g with the arms placed at a prescribed angle (condition 1: upper arms at 40° and lower arms at -20° from horizontal, condition 2: upper arms at 15° and lower arms at -45° from horizontal). Two posts were used in the central region to stabilize the mesh from translating within the testing rig. A computational simulation of the DirectFix A device was developed as described above applying
boundary conditions consistent with the experimental setup using the custom rig. Deformations in the experimental setup were limited to be planar, although it was possible for mesh fibers to move overtop of one another. The simulation was constrained to only allow 2D deformations. A parameter called “mesh burden”, conceptually defined as the regional amount of mesh per unit area, was calculated by determining the amount of mesh (based on either pixels or nodes) contained within a circle with a radius of 2mm. This is a more clinically relevant parameter that negatively correlates with porosity, i.e. a high mesh burden indicates a low porosity. Thus, a color map could be generated for visualization of regional mesh burden. A convergence analysis was performed to ensure that the change in mesh burden for the simulation was minimal as the number of elements was increased geometrically.

Finally, the simulation was utilized to examine the impact of loading variables on mesh burden. A traction vector of either 0.5 N, 1 N, or 2.5 N was applied to each mesh arm simultaneously and the 2D components of the vector were varied to alter the orientation of the applied load. A total of 27 finite element simulations were performed where the impact of the orientation of the vector applied to the upper arms, orientation of the vector applied to the lower arms, and the magnitude of those vectors on mesh burden could be determined. For this simulation, five discrete points around the central body of the mesh were fixed to simulate suture fixation to the vagina.

3 RESULTS AND CONCLUSIONS

Data obtained from the uniaxial tests of Restorelle™ mesh revealed that orientation of the mesh pores with respect to the loading axis has a significant impact on mesh porosity with increases in tension (Figure 3). When the mesh was oriented at 0° (square pore) there was negligible change in porosity even with loads up to 10 N. However, when the mesh was rotated by 45° (diamond pore), a load of 5 N dramatically decreased porosity. In this configuration, no pores had a diameter greater than 1mm. Thus, the orientation of the pore geometry with respect to the direction of the applied load can result in significant changes in porosity.

Multiaxial loading of the Restorelle™ DirectFix A device that is cut from the Restorelle™ mesh showed that mesh burden increases (porosity decreases) most significantly along the lower mesh arms and between the upper mesh arms (Figure 4; note: data normalized to peak mesh burden so that comparisons could be made between that calculated based on imaging versus finite element node data). The latter becomes more pronounced as the orientation of the upper arms becomes more acute. The mesh burden predicted by the computational simulation corresponded well with the regional increases observed experimentally, but tended to predict an overall greater amount of mesh burden throughout the mesh for condition 1 and a slight underestimate in the upper mesh arms for condition 2.

The parametric study demonstrated that the location of increased mesh burden for this device was consistently located in the lower mesh arms and between the upper mesh arms for all 27 simulations (Figure 5). The degree of mesh burden was positively correlated with the applied tension and was more sensitive to it than the orientation of the mesh arms for this study. This
corresponds with clinical findings described by Feiner et al. 2010 [6] that identified the most common places for complications in transvaginal mesh. These included the area between the upper mesh arms and in the lower mesh arms. In addition, complications are more readily expected by clinicians with over-tensioning of these devices in-vivo. While tensioning can be controlled surgically at the time of implantation, the amount of tension that the device experiences once the patient stands and becomes active is not as predictable, especially for obese patients.

Collectively, the results of this study suggests that mesh burden may be a helpful predictor of complications in-vivo, and that there are mesh design, surgeon specific, and patient specific factors that likely play a role in the changes of porosity of mesh for prolapse repair. Future studies will be aimed at better understanding mesh burden in simulations of the in-vivo loading environment that include mesh-vagina interaction, and to identify alternative designs for these devices that minimize regional increases in mesh burden following implantation.

ACKNOWLEDGEMENTS
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Standard Session VI
CHARACTERIZATION OF PULMONARY ARTERIES IN A SUGEN-HYPOXIA PULMONARY ARTERIAL HYPERTENSION ANIMAL MODEL

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SUMMARY

The mechanisms underlying pulmonary arterial hypertension remain understudied. By modeling the vessel distention in normo- and hypertensive groups, we intend to quantify the changes in the mechanical properties of the pulmonary arteries. Our modeling efforts showed that the vascular remodeling is non-uniform. These results were corroborated through the quantification of the structural change in the vessel fibers by means of multiphoton microscopy.

Key words: Pulmonary arterial hypertension, cardiovascular biomechanics, multiphoton microscopy, sugen hypoxia

1 INTRODUCTION

Pulmonary arterial hypertension (PAH) is a disease of the heart and lungs characterized by elevated blood pressure. As the disease progresses, pulmonary vessels remodel. Although remodeling allows the vessels to withstand elevated pressures, it also compromises their ability to store and deliver the entire stroke volume of the right ventricle (RV), leading to heart failure as the end stage of the disease [1]. Currently, there are medications to lessen the symptoms and improve the quality of life of the patients, however, the only curative option remains lung transplantation [2]. Here, we aim to characterize the mechanical properties of the left and right pulmonary arteries and determine how fiber structural organization supports the mechanical changes in PAH.

2 MATERIALS AND METHODOLOGY

The experimental protocol used for this study was approved by the University of Illinois at Chicago Animal Care and Use Committees. Pulmonary arterial segments were harvested from eleven 12-week-old male Sprague-Dawley rats weighing 350 grams. At 8 weeks of age, six animals were injected with a placebo solution, while the rest of the animals were treated with 20 mg/kg subcutaneous injection of Sugen 5416 (Sigma-Aldrich) to induce PAH. After injection, the animals were exposed to 3 weeks of chronic hypoxia, followed by 3 weeks of normoxia. Six weeks after injections, post-invasive hemodynamic measurements confirmed the normotensive state of the placebo and hypertensive state of the sugen-hypoxia (SuHx) animals before the left (LPA) and right (RPA) pulmonary arteries were harvested.

The harvested segments were cut in half and cannulated with blunt needles that closely matched the diameter of the vessel. The distal portion of the RPA and the proximal segment of the LPA underwent tubular biaxial testing. They were fixed to the cannula on both ends with glue (Permabond 240 High Viscosity) to prevent slipping of the vessel and a suture line (FST Braided Silk Suture 5-0) was added as a reference for measuring axial length. After preparation, the vessels were subjected to two biaxial protocols: circumferential and axial. In the circumferential protocol, vessels were cyclically stretched between 40% and 45% of their ex-vivo length while pressure and flow were prescribed to match the mean pressure measured in vivo. For the axial protocol, vessels were subjected to pulsatile flow of 0.5 Hz and pressure matching the in-vivo conditions. The axial protocol, vessels were cyclically stretched between 40% and 45% of their ex-vivo length while pressure and flow were prescribed to match the mean pressure measured in vivo.
Vessel diameter, pressure, axial length and force were measurements used to create a stress-strain relation for an elastic orthotropic material. The constitutive relation was framed within the quasilinear viscoelasticity theory (Equations 1-2).

\[ \epsilon_j(t) = K(0) S_j^{(e)}[F_j(t)] + \int_{t_0}^t S_j^{(e)}[F_j(y)] \frac{dk(t-y)}{dy} \, dy \, , \, j = \theta, z \] (1)

Where \( K(t) = 1 - \sum_{i=1}^{n} C_i e^{-t/h_i} \) is the creep function with \( C_i \) representing the amplitude associated with relaxation time \( (h_i) \). Here \( \theta \) refers to the circumferential direction and \( z \) the axial. The elastic response relating to pressure and axial forces were defined as in Equation 2 and strain related to area and length as in Equation 3.

\[ S_\theta^{(e)}[p(t)] = \frac{r_0(1 - \nu_{\theta\theta} \nu_{zz})}{E_{\theta\theta}} \cdot \nu_{\theta\theta}, \quad S_z^{(e)}[f(t)] = \frac{1 - \nu_{zz} \nu_{zz}}{E_z} \cdot \sigma_z \] (2)

\[ A(t) = \frac{A_0}{(1 - \varepsilon(t))^2} \, , \, L(t) = L_0(\varepsilon_z(t) + 1) \] (3)

\( r_0 \) and \( A_0 \) are the radius and cross-sectional area at zero pressure at \textit{ex-vivo} length, \( h \) wall thickness, \( L_0 \) \textit{ex-vivo} length, \( \nu \) Poisson’s ration, and \( E \) is Young’s elastic modulus.

The proximal portion of the RPA and the distal segment of the LPA were also cannulated and imaged under a multiphoton microscope. Using the scanned images, the collagen fiber distributions were traced and quantified with the directionality function in the software Fiji [3]. By scanning the vessels at the same depth location of the wall thickness, the images from different treatment groups were compared. Angle measurements range from -\( \lambda_0^\circ \) to \( \lambda_0^\circ \). Here the \( 0^\circ \) corresponded to axial while \( \pm \lambda_0^\circ \) corresponded to circumferential alignment.

### 3 RESULTS AND DISCUSSION

The average \textit{in vivo} RV systolic pressure measured in the PL group was 31.2±2.1 mmHg, while in the SuHx group was 76.6±9.8 mmHg confirming PAH. Using the stress-strain relation from Equation 1, the pressure-area and vessel length-load relations were predicted (Figure 1). In the axial direction the SuHx vessels became more compliant, there was no statistical difference with the PL group. The circumferential stiffness (Young’s modulus) significantly increased from the placebo group to the SuHx group in the LPA \((1.9±1.6 \times 10^3 \text{ to } 9.0±5.8 \times 10^3 \text{ mmHg} \, [p<0.0262])\), and only a slight decrease in stiffness of the RPA \(3.4±1.3 \times 10^3 \text{ to } 2.9±2.7 \times 10^3 \text{ mmHg} \). The difference between Young’s modulus of the LPA and RPA indicates that the two vessels are not remodeling uniformly. This is reinforced by the changes in fiber orientation: the average fiber orientation of the LPA significantly increased from the placebo to SuHx group \((2.6±0.8^\circ \text{ to } 7.2±3.3^\circ)\) (Figures 2-3). The realignment of the fibers in the LPA to a higher degree (closer to the circumferential direction) could be responsible for the increase in the circumferential vascular stiffness. Mechanical change in the circumferential direction was also manifested in the pressure-area relation by becoming linear in form for the hypertensive state. This was especially apparent in the LPA and can be attributed to the increase in stiffness (or decrease in the elastic properties) of the vascular wall.

The increase in the circumferential Young’s modulus of the LPA reflects the rise in the stiffness in the lumen distention due to the high pressure present at the severe stage of PAH. Similar to our findings, Drexler et al. also reported an increase in the stiffness of the LPA, but no significant difference was found in the RPA in their PAH hypoxic-animal model when using a bubble test [4]. In a previous study using tubular biaxial tests, Pursell et al. showed that in a monocrotaline induced PAH model the RPA becomes significantly stiffer in the circumferential direction at the advanced disease stage (Young’s modulus increase from \(3.4±3.1 \times 10^3 \text{ to } 22.9±12.7 \times 10^3 \text{ mmHg} \) [5]. Since SuHx induced PAH has been shown to produce obliteration in the distal pulmonary vasculature, which are similar to the “plexiform” injuries found in human idiopathic PAH [6], the disagreement in findings can be attributed to the monocrotaline and hypoxia PAH inducing a different remodeling process. Furthermore, our findings that the collagen fibers of the LPA tend towards the
circumferential direction are consistent with a study by Tian et al. where the dominant collagen fiber orientation was found to be in the circumferential direction [7].

**Figure 1.** Representative pressure-area plots of model fitted to data from the LPA of A) placebo animal and B) SuHx animal and load-length plots of model fitted to data from the LPA of C) placebo animal and D) SuHx animal. The differences in length, pressure, and cross-sectional area are based on in vivo measurements.

**Figure 2.** Representative multiphoton images of collagen fibers from a LPA of A) placebo animal and B) SuHx animal. Note that both vessels were imaged at the atmospheric pressure.
Figure 3. Histogram of collagen fiber orientation (in angles) of the pulmonary vessels of normotensive and hypertensive groups. A) Placebo-LPA and B) SuHx-LPA. The angles range from -90 to 90 degrees where 0 degrees corresponds to axial while ± 90 degrees correspond to circumferential alignment. Here, the peak in fiber orientation shifted towards the circumferential direction.

In conclusion, our study reveals an asymmetrical adaptation of the LPA and RPA in PAH with an increase of Young’s Modulus in the LPA. Although the dominant fiber orientation shifts towards the circumferential direction, more studies are needed to determine if more drastic changes occur at later stages of the disease. Future studies will also include delineating with fiducial marker to match the strain field during mechanical testing and imaging field.

REFERENCES

PREDICTING RIGHT HEART FAILURE IN PATIENTS WITH PULMONARY HYPERTENSION

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SUMMARY

Standard of care in precapillary (group I) pulmonary hypertension (PH) includes serial right ventricular (RV) catheterizations in order to monitor RV performance and pulmonary bed pressures, unfortunately with associated costs and side effects related to invasive procedures. Our aim was two-fold: 1) to develop a biventricular finite-element model coupled to a lumped-parameter circulatory system of PH; 2) to assess accuracy of proposed computational model in predicting hemodynamic impairment due to PH and abnormal motion of interventricular septum

Key words: pulmonary hypertension, right ventricular failure, lumped-parameter model; finite element

1. INTRODUCTION

Pulmonary hypertension (PH) is a pathological condition in which the mean pulmonary artery pressure is higher than the normal condition [1]. Specifically, PH is defined when right ventricular (RV) pressure exceeds 25 mmHg at rest [2]. This condition may ultimately lead to right ventricular failure (RVF). Conceptualized hemodynamically, RVF occurs at the point at which cardiac output (CO) and blood pressure drop despite an increased RV end-diastolic pressure (Ref). Although PH can be seen at echocardiography [3], pressure measurements by Swan-Ganz catheterization of right side represent the gold standard for the diagnosis of PH and to assess disease severity [4, 5]. Our aim was two-fold: 1) to develop a biventricular finite-element model coupled to a lumped-parameter circulatory system of PH; 2) to assess accuracy of proposed computational model in predicting hemodynamic impairment due to PH and abnormal motion of interventricular septum.

2. MATERIALS AND METHODS

2.1 Patient Study Group

We retrospectively identified 10 patients with Group I PH underwent right-sided cardiac catheterization to monitor the progress of pulmonary disease. Standard echocardiography and delayed enhanced (DE) CMR were performed within 2 weeks from RV catheterization in order to collect hemodynamic and morphological data. Specifically, left ventricular (LV), ejection fraction, cardiac output (CO), cardiac index (CI) and pulmonary capillary wedge pressure (PCWP) were collected from standard 2D or Doppler echocardiography. While, RV end-diastolic and end-systolic volume, RV stroke volume, RV cardiac output, RV ejection fraction were measured from DE-CMR.

2.2 Lumped-Parameter Modelling of PH
To simulate the hemodynamic impairment due to PH, we used the CircAdapt open-source cardiovascular tool (www.circadapt.org/) as a lumped-parameter model of heart and circulation (see Figure 1). The CircAdapt is configured as a network composed of several module types representing myocardial walls, cardiac valves, large blood vessels, and peripheral vasculature to enable real-time simulation of hemodynamic under normal and pathological conditions. Both RV and LV end-diastolic and end-systolic volumes as collected by DE-CMR were used as input parameters in the lumped-parameter model. We interactively adjusted the pulmonary vascular resistance (PVR) and myocardial contractility parameters (i.e. passive stiffness and active contraction) to match both LV and RV ventricular volumes. For each patient, the model output consisted in the RV and LV pressure-volume loops, which were used as boundary conditions in the biventricular finite-element model. Additionally, standard hemodynamic parameters such as the CO were computed with CircAdapt and then compared to those derived by RV catheterization.

2.3 Finite Element analysis
Numerical simulations were performed according to our previously described biventricular model [6, 7]. The substantial difference with this model was the use of the Holzapfel’s constitutive formulation and a thermal-mechanical analog approach to describe active myocardial contraction [8]. This allowed us to avoid numerical issues that are often observed with the Fung’s law. LV and RV geometries were obtained via parameterized geometric surfaces initialized by morphological measurements collected by DE-CMR. The biventricular model represented the end-systolic ventricular-chamber configuration and then meshed with brick elements in ABAQUS FE code (Simulia, Inc., Providence, RI). Cardiac myofiber angles at epicardium and endocardium were 60° with respect to the circumferential direction of LV wall. We fully constrained the displacement of the ventricular basal line because the mitral valve annulus and aortic valve annulus are much stiffer than the myocardium. For each patient, RV and LV pressure loading profiles computed with the lumped-parameter simulation of PH were applied to the endocardium using the hydrostatic fluid cavity modeling capabilities of ABAQUS/Standard. Thus, the passive heart behavior was calibrated by iteratively adjusting the material parameters C of Holzapfel’s law in order to match the measured values of RV and LV end-diastolic volumes. Similarly, the active heart behavior was tuned by scaling the fictitious temperature field. Septal motion was compared to that observed in 4 healthy patients investigated previously by our group [6, 7].

3. RESULTS AND DISCUSSION
At linear regression analysis, primary dependent (i.e. predicted) variables were CI and PCWP (see Table 2). The lumped model was able to predict CI and CO with high accuracy (R=0.82 and p<0.001 for CI and R=0.74 and p<0.001) and moderately high the SV of right chamber (R=0.68 and p=0.012). However, predictions of PCWP was just moderate only for predicted mPAP (R=0.52, p=0.041). Moreover, a positive good correlation was found between the predicted SM and RV time delay (R=0.69 and p=0.036) and between predicted SM and PVR (R=0.70 ans p=0.048) as demonstrated by Pearson’s coefficients. It is worthy of consideration that CI is considered as a prognostic indicator to assess the severity of PH [1]. Although a large cohort is needed, the lumped-parameter modeling appears promising to distinguish the less from the most “malignant” PH. Additionally, this tools is based on non-invasive measures as compared to that achieved by catheterization.
<table>
<thead>
<tr>
<th>Variables</th>
<th>Lumped Model</th>
<th>Outcome: CI (Cath)</th>
<th>Outcome: PCWP (Cath)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke Volume (mL)</td>
<td>54.2±15.2</td>
<td>0.68 (0.01)</td>
<td>0.03 (0.7)</td>
</tr>
<tr>
<td>Cardiac Output (L/min)</td>
<td>4.1±1.1</td>
<td>0.74 (&lt;0.001)</td>
<td>0.02 (0.72)</td>
</tr>
<tr>
<td>Cardiac Index (L/min/m²)</td>
<td>2.4±0.6</td>
<td>0.82 (&lt;0.001)</td>
<td>0.02 (0.72)</td>
</tr>
<tr>
<td>RV Systolic Pressure (mmHg)</td>
<td>64.2±12.9</td>
<td>0.01 (0.97)</td>
<td>0.14 (0.36)</td>
</tr>
<tr>
<td>Systolic Pulmonary Artery Press. (mmHg)</td>
<td>62.5±12.8</td>
<td>0.01 (0.79)</td>
<td>0.03 (0.71)</td>
</tr>
<tr>
<td>Diastolic Pulmonary Artery Pressure (mmHg)</td>
<td>37.1±10.1</td>
<td>0.12 (0.37)</td>
<td>0.52 (0.04)</td>
</tr>
</tbody>
</table>

When compared to controls, myocardial fiber stresses calculated at several anatomic locations of ventricular chambers were found higher in patients with PH than controls, with greater magnitudes for the simulated exertional scenario (Figure 2 and 4). A significant difference was noted for ES myocardial stress in both LV and RV free wall of controls (29.0±2.8kPa for LW and 4.5±0.7kPa for RV) with respect to that of PH at rest (47.6±18.5kPa for LW, p=0.005, and 30.1±12.1kPa for RV, p=0.005) and exercise (59.7±16.1kPa for LW, p=0.011, and 69.6±24.8kPa for RV, p<0.001, Figure 2). A similar statistically significant difference was found for ED stress at LV and RV free wall as well as the posterior LV wall. In a different way, stress at mid-septum was higher in PH than controls, although not significantly different. Using a similar biventricular finite-element model, Wenk and collaborators [9] found that RV end-systolic myocardial stress in patients with dilated cardiomyopathy was 58.5 kPa, although RV volume was reported as morphologically normal. Similarly, end-diastolic RV myocardial stress in PH was found higher than that showed by healthy patients (150 kPa for PH compared to 13 kPa for normal hearts). Most importantly the interventricular septum exhibited an abnormal motion throughout cardiac beating. As PH became more severe, the pattern of septal motion was characterized by a normal left-ward shift towards RV during diastolic filling followed by an abnormal right-ward shift towards LV during ejection and isovolumic relaxation phases. This was likely caused by the time courses of simulated ventricular pressures. In simulation of PH, RV pressure exceeded LV pressure during systole, with pressure decay delayed with respect to that of LV. This time course was not observed for healthy patients where interventricular septum did not move over LV. A similar mechanism of abnormal motion for the interventricular septum can be seen clinically in PH [2] and corroborated by Lumens and collaborators [10].

Figure 1: End-systolic myocardial wall stress showing abnormal motion of interventricular septum (left); pressure-time and pressure-volume loop obtained by the lumped-parameter model (right)
Figure 2: Maximum values of average myocardial fiber stress at (A) end-systole and (B) end-diastole for healthy controls and patients with PH at rest and exercise; *significantly different from healthy controls (p<0.05); #significantly different from patients with PH at rest (p<0.05); AW: anterior wall; LW: lateral wall; PW: posterior wall; S: interventricular septum; RV: right ventricular free wall

4. Conclusions
In this study, a computational method including both lumped-parameter and biventricular FE modeling was used to improve our understanding on the mechanics underlying RV failure in patients with PH. When compared to gold-standard measurements from right-cardiac catheterization, linear regression analysis demonstrated that lumped-parameter modeling predicts RV functional performance in terms of CI and CO with high accuracy - hemodynamic parameters commonly associated to the severity of the pulmonary artery disease [1]. We also found that the increased RV pressure load due to PH disease leads to altered myocardial fiber stresses around ventricular chambers and to paradoxical motion of interventricular septum towards LV free wall. Exercise-associated RV myocardial stresses were higher than resting stresses, thereby portending adverse cardiac remodeling. Interestingly, the correlation between the predicted SM and PVR was significant and this may be important for the potential clinical implication of our approach. If confirmed, the proposed computational technique may enable less invasive clinical procedure and realistic computational predictions of ventricular mechanics and interactions for an improved management and characterization of right heart failure in patients with PH

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REFERENCES
SEX DIFFERENCES IN RIGHT VENTRICULAR-PULMONARY VASCULAR INTERACTIONS IN PULMONARY HYPERTENSION

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SUMMARY

Pulmonary arterial hypertension (PAH) is a progressive disease that affects the pulmonary vasculature, the right ventricle (RV), and the efficiency of their interactions. Sex differences in the incidence and progression of PAH are well known. Given the evidence that healthy women have more compliant pulmonary arteries than healthy men [1], that pulmonary arterial compliance reduces RV workload with exercise [2], and that a poor cardiopulmonary response to exercise is associated with poorer survival [3], we hypothesize that a progressive loss in pulmonary artery compliance in PAH, which is attenuated by female sex, impairs the cardiopulmonary response to exercise and leads to RV decompensation.

Key words: ventricular-vascular efficiency, estrogen, stiffness

1. INTRODUCTION

PAH is a fatal disease characterized by a progressive increase in pulmonary vascular resistance (PVR) and ultimately leads to RV failure [4-7]. Loss of pulmonary arterial compliance is a powerful predictor of mortality in PAH [5, 8] as is the efficiency of right ventricular-pulmonary arterial (RV-PA) coupling [9, 10]. Despite availability of 14 FDA-approved medications, the prognosis of PAH remains quite poor with a five-year survival rate of only 55% [11]. PAH affects four times more women than men [12] and women with PAH have better survival rates than men with PAH [13-15]. Even though female sex is a major determinant of survival in PAH, no sex steroid-directed therapies exist [13-15]. Animal studies have shed some light on the role of estrogen [16-18], but still the mechanisms remain incompletely understood. Moreover, only one recent study has investigated how loss of estrogen (via menopause) affects response to treatment [19]. Since RV function is a major determinant of functional capacity and prognosis in PAH, any therapy must ultimately impact the RV to maintain and improve function. However, the mechanisms by which PAH leads to RV dysfunction, and their sex- and estrogen-dependence, are unclear, which has slowed the development of effective therapies for both men and women.

Increased PVR and mPAP are associated with RV hypertrophy, but improving or reversing increases in mPAP does not prolong survival unless accompanied by improvement in RV function [20]. In contrast, loss of compliance of the proximal, conduit pulmonary arteries (PAs) is a strong predictor of mortality in PAH [5, 8]. Also, compliance of the distal PAs enables the pulmonary vasculature to accommodate increases in cardiac output during exercise [2]. There are multiple mechanisms by which PAH leads to loss of PA compliance, including increased stretch [21], wall thickening and wall collagen accumulation [22, 23]. In addition, female sex [17, 24] and estrogen [17, 18] are contributors to PA compliance. However, how sex and estrogen modulate the known mechanisms of loss of PA compliance and its impact on RV dysfunction remain unknown.

A potentially untapped resource in prognoses for PAH is the response to exercise stress [25]. Indeed, the definition normal and abnormal responses to exercise stress are still being debated [26, 27]. We recently demonstrated that PA compliance decreases with exercise in healthy subjects [28] and patients with systemic sclerosis-associated PAH [29] while the total PVR does not change [30]. Thus, we hypothesize that a progressive loss in pulmonary artery compliance in PAH, which is attenuated by female sex, impairs the cardiopulmonary response to exercise and leads to RV...
decompensation. Here we lay out the evidence for this hypothesis, a methodology to test it, and invite feedback.

2. METHODOLOGY

In order to quantify the relationship between PA stiffening and RV function at rest and during exercise in PAH patients, and to determine sex differences in those relationships, we will perform exercise during invasive right heart catheterization (exercise+RHC) as well as during magnetic resonance imaging (exercise+MRI) with techniques established by our group [28, 30]. From exercise+RHC, we quantify heart rate, cardiac output, pulmonary artery pressures, pulmonary vascular compliance, RV-PA coupling efficiency estimated from the single beat method, and, if ultrasound images of the main pulmonary artery (MPA) can be obtained simultaneously, MPA stiffness index $\beta$ [31], at rest and with increasing levels of exercise. From exercise+MRI, we measure heart rate, MPA diameter, and MPA flow rest and with increasing levels of exercise. To date, we have performed exercise+RHC 22 PH patients (12 ♀) and exercise+MRI in 6 PH (5 ♀) patients and 7 age-matched control subjects (6 ♀).

3. PRELIMINARY RESULTS AND CONCLUSIONS

The exercise+RHC studies demonstrated that total PVR, which is the steady RV afterload, did not change whereas pulmonary vascular compliance decreased (i.e., the unsteady RV afterload increased) with exercise; as a consequence, the RC time constant of the pulmonary circulation decreased (Fig. 1) [30]. MRI at rest was performed in 18 (9 ♀) of the 22 patients who underwent exercise+RHC testing. With offline synchronization of measured RV pressures (RHC at rest) and volumes (MRI at rest) we used the single beat method to derive end systolic elastance ($E_{es}$), effective arterial elastance ($E_a$), and their ratio, the efficiency of ventricular-vascular coupling ($\eta=E_{es}/E_a$). We observed that the efficiency of RV-PA coupling at rest was associated with the ability to achieve a high exercise workload (Fig. 2). While these studies did not confirm our hypothesis that women have an impaired pulmonary arterial biomechanical response to exercise, there are several potential reasons that merit further discussion and investigation. Enrollment was insufficient to test for sex differences, especially considering the heterogeneity of the population in terms of type of PAH, duration of PAH, medication regimen, and age. Second, the intensity of exercise was low; most subjects did not reach VO$_2$ max during exercise+RHC testing. Third, other factors that affect exercise capacity were not tested in this study, including gas exchange during rest and incremental exercise.

Figure 1. PA compliance $C_{PA}$ and RC time constant decreased with exercise in patients with PAH; PVR did not change (not shown). *$p < 0.05$ vs. 0 W; †$p < 0.05$ vs. 15 W [from ref. 29].

Figure 2. Maximum workload $W_{max}$ achieved by high-$\eta$ and low-$\eta$ subjects; $n=18$ (9 ♀). *$p<0.05$
The exercise+MRI studies, performed in both healthy and PH subjects, demonstrated that heart rate and cardiac output were significantly increased with exercise in both groups. MPA RAC decreased from 0.27±0.05 at rest to 0.22±0.06 with exercise for control subjects and in PH subjects, RAC decreased from 0.15±0.02 to 0.11±0.01 (Figure 3) and β both increased from 3.9±0.54 m/s and 1.98±0.27 at rest to 5.75±0.70 m/s and 3.25±0.26 with exercise. Given the mostly female PH population in this study group, we recruited a mostly female healthy control group. However, this prevented us from investigating sex differences.

While exercise+RHC enables collection of comprehensive datasets on RV afterload and RV pressure changes with exercise, RV volume can only be inferred from cardiac output and heart rate. Building on our recent success in measuring PA stiffness changes with exercise+MRI, we recently measured RV volume changes also (Fig. 4).

In the future, with offline synchronization of measured RV pressures (exercise+RHC) and volumes (exercise+MRI), we will use the 2nd derivative single beat method developed by Bellofiore A et al. to compute $E_s/E_a$. This novel technique may be more suitable to measuring RV function with clinically practical methods and reduced variability [32].

To date, our results confirm that 1) MPA stiffness increases with acute exercise in both healthy and diseased groups, 2) in patients with PAH, exercise-induced stiffening of pulmonary arteries aggravates RV afterload, and 3) it is feasible to monitor PH progression through assessment of the ventricular-vascular coupling. Preliminary analyses did not find sex differences, but sex differences in both incidence and progression of PAH are known to exist. Investigation into the mechanisms of sex differences in PAH incidence and progression may lead to novel therapies for both men and women.

**REFERENCES**


Poster Abstracts
A COMPUTATIONAL MODEL FOR OPTIMIZATION DESIGN OF CONSTRUCTION HELMET

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SUMMARY
Construction helmets are essential personal protective equipment for reducing exposure to traumatic brain injury at work sites. We proposed a finite element modeling approach that would be suitable for engineers to optimize construction helmet design. The model includes essential anatomical structures of a human head (i.e., skin, scalp, skull, cerebrospinal fluid, brain, medulla, spinal cord, cervical vertebrae and discs) and major engineering components of a construction helmet (i.e., shell and suspension system). We demonstrated the evaluation of the performance of a construction helmet using the proposed computational method.

Key words: finite element analysis, brain injury, helmet design

1 INTRODUCTION
Traumatic brain injuries (TBIs) are among the most common severely disabling injuries in the United States; during 2002-2006, approximately 1.7 million cases occurred in civilians annually [1]. Work-related TBIs occur frequently in such industries as construction. A total of 7294 work-related TBI fatalities were identified during 2003-2008, which accounted for 22% of all occupational injury fatalities [2]. Among the leading causes of work-related TBI death, falls and contact with objects/equipment represented 47% [2]. The work-related TBI fatalities due to contact with objects may be reduced by using properly designed and manufactured helmets.

Finite element (FE) models have not only been used in the investigation of injury mechanisms [3], but also in the design of head protective systems [9]. For example, Afshari and Rajaari [5] developed FE models to study the protective effectiveness of the helmet during the head-ground impact of a motorcyclist. Teng et al. [6] developed FE models of a bicycle helmet with foam liners and validated their model with impact tests. Although these models included detailed helmet geometries and material properties, they did not include realistic anatomical structures of the human head. Yang and Dai [7] developed FE models to study the ballistic helmet impact; their models included realistic geometries and material properties of the helmet and human head. These models have been further developed by Long et al. [8] to assess the performance of construction helmets.

Most of the previous head-brain models are used for frontal impacts and do not include the neck. It is widely believed that the effects of the neck and body mass on the brain responses during short impact intervals (duration less than 7 milliseconds) are negligible [4]; however, the effects of the neck and body mass have not been quantified. Our goal is to develop a practical FE model that would include essential anatomical details of the human head-brain; at same time, it would be small enough to be suitable for engineers to optimize construction helmet design.
2 METHODOLOGY

2.1 Finite element model

The helmet model consisted of a shell and a suspension system (Fig. 1A-B). The shell geometry was obtained by scanning a representative, commercially available construction helmet (Model V-Gard, MSA Safety Inc., Pittsburgh, PA, USA). The geometry of the suspension system was constructed using commercially available software Solidworks (Autodesk, Inc., San Rafael, CA, USA). The 3D geometries of the shell and suspension were then imported into ABAQUS (Abaqus US/Feasol, Boston, MA) to generate FE meshes. The model of the helmet shell was constructed using shell elements, whereas that of the suspension system was generated using 3D continuous elements. The suspension system was constrained to the helmet shell at four plug locations.

Figure 1: FE model of the head-helmet. A: Helmet shell. B: Helmet suspension system. C: Cross-sectional view of the head-helmet complex. D: Simulation of a top impact.

The FE meshes of the head-brain-neck complex were developed by using a commercially available database (Materialise, Leuven, Belgium). The dimensions of these head surface meshes represent approximately the 50th percentile of Caucasian males. The head-brain-neck complex consisted of scalp, skin tissues, skull, cervical vertebrae (C1, C2, and C3), discs, brain, medulla, cerebrospinal fluid (CSF), and spinal cord (Fig. 1C). The brain tissues included the cerebrum, cerebellum, and a part of the brain stem (midbrain and pons) (Fig. 1C). The spinal cord included the surrounding pia mater. The CSF was considered to cover the entire external surface of the brain, medulla, and the spinal cord. The discs contained both annulus fibrosus and nucleus pulposus. Within each of
these components (i.e., brain, medulla, CSF, spinal cord, and discs), the material was considered homogeneous. The connections between the tissues were assumed perfect bond, without relative sliding during deformation. The CSF (thickness 1.3 mm) was constructed using membrane elements, whereas all other components were constructed using three-dimensional continuous elements. The falling object was cylindrical (diameter 28.5 mm, length 100 mm) and was modeled using 3D continuous elements (Fig. 1D). A point mass of 10 kg was connected to the vertebral bone at the neck, simulating the inertial effects of the rest of the body during impact.

2.2 Material properties

The helmet shell was considered to be made of typical ABS plastic. The suspension top belt side ring was considered to be of high strength polymers. The front cushion of the suspension system was of soft foam material. The falling cylinder was considered to be made of steel and had a mass of 2 kg. All materials of the helmet components were considered to be linearly elastic. The scalp, skull bone, cervical discs, and vertebral bone were considered to be linearly elastic. The CSF was considered as a weak, elastic and nearly incompressible medium. The skin, brain, medulla, and spinal cord were considered to be hyperelastic and viscoelastic. The finite deformation formulation was used in describing the constitutive models due to large tissue deformations.

2.3 Simulations

Using the proposed model, we simulated the impact force and brain acceleration during an impact of an object on top of the helmet. Initially, the cylinder was at a height of 3.27 m above the helmet top and it fell due to gravity; it reached a speed of 8 m/s just before impacting on the helmet (Fig. 1D).

3 RESULTS AND CONCLUSIONS

The impact force between the cylinder and helmet shell as well as that between the head and suspension system as a function of the time are shown in Fig. 2A. The simulations indicate that the cylinder bounced and separated from the helmet shell (impact force became zero) after the initial impact; and that the impact force between the head and suspension system did not reach the peak at the same time as that between the cylinder and helmet shell. The ratio of the initial peak of $F_b$ (contact force of head-helmet suspension) to that of $F_a$ (contact force of object-helmet) is ap-
proximately 60%, which represents one of the aspects of the helmet performance. The calculated distributions of the acceleration in the brain (Fig. 2B) show that the maximal values were at the occipital region. It is interesting to see that the maximal acceleration was observed around 3 ms, a delay about 0.3 ms from the peak of $F_b$. The delay of the acceleration peak is likely caused by the viscous effects of the soft tissue materials.

Typical falling objects in construction site are small and have a mass around 2 kg, such as hand tools, bricks, bolts, etc. The mass and dimension of the falling object simulated in our study is representative for real situations. In the simulations, we selected an impact velocity of 8 m/s for the object, which is approximately correspondent to an object falling height of 5 m, assuming a worker has a height of 1.8 m. This height is typical at construction sites of residential buildings in the United States. The purpose of this study is to develop a model; once the model is validated, it can be applied to analyze or to numerically reconstruct accidents at construction sites.

4 FUNDING, CONFLICT OF INTEREST, AND DISCLAIMERS

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The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health. Mention of company names or products does not imply endorsement by the National Institute for Occupational Safety and Health.

REFERENCES


PREDICTING THE EFFECTS OF STRAIGHT AND TAPERED STENTS ON BLOOD FLOW PROPERTIES IN THE AORTA

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SUMMARY
Coarctation of the Aorta is a congenital heart disease with a severe prognosis. Several treatments are available, but all treatments have side effects. Furthermore, since some treatments have only been commonly used in the past two decades, clinical data that could be used to compare the long-term outcomes of the treatments are unavailable.

We simulate blood flow through one-dimensional models of treated aortas to assess the impact of treatments on blood flow properties. In this study, stent treatments are modelled and we find that straight stents, as opposed to stents that taper with the aorta, exhibit preferable blood flow properties.

Key words: coarctation, aorta, stent, model

1 INTRODUCTION
A serious congenital heart disease, Coarctation of the Aorta (CoA) is characterised by a narrowing of the aorta, decreased blood flow downstream of the narrowing, and increased blood flow upstream [1]. Treatments that increase the lifespan of patients are available, but treated patients experience a decreased lifespan and an increased incidence of other diseases, such as hypertension and aneurysms [2]. Stent placements have emerged as a viable alternative to surgical techniques [3]; however, since they have been commonly used only since the 1990s, long-term clinical data are unavailable. A stent treatment involves inserting a compressed metal mesh inside the coarctation on a catheter, then expanding the metal mesh until it dilates the coarctation and is embedded in the artery wall.

Computational fluid dynamics has been used extensively to simulate blood flow in various vessels, in both one-dimensional (1D) and three-dimensional (3D) models. Compared to in vivo measurements, in vitro experiments and 3D models, 1D models have successfully reproduced many features of the fluid dynamics of blood flow in large human arteries like the aorta, including pressure, flow and area waveforms [4].

In this paper we use 1D models of treated aortas. We represent the stent treatments in the aorta by increasing the artery wall stiffness in the region that the stent covers, to determine if the increased stiffness from stents can explain complications, such as hypertension, seen in treated patients. We also model a stent that tapers with the natural tapering of the aorta, as well as a straight stent, to see the effect of the stent shape.

2 METHODOLOGY
The aorta is a thick-walled, elastic vessel that carries blood from the heart. The contraction of the heart produces blood flow velocity and pressure waves that interact with the artery walls [5]. When the heart contracts, there is a sudden increase in blood volume in the aorta. The aorta exhibits compliance; it distends when blood is pumped into it, then contracts, producing a subsequent pulse wave.

The assumptions made in this 1D formulation are: the aorta is compliant; the blood flow is laminar [6], as blood in large arteries has a low Reynolds number [7]; the pulse wave has forward and
\( R = 12 \text{ mm} \)
\( \bar{Q} = 6.17 \text{ L min}^{-1} \)
\( h = 1.2 \text{ mm} \)
\( \rho = 1060 \text{ kg m}^{-3} \)
\( \mu = 0.004 \text{ Pa s} \)

Figure 1: Schematics of the artery used to model a tapered aorta, where \( x \) is the position along the longitudinal axis of the aorta, \( h \) is the wall thickness, \( \bar{Q} \) is the volumetric blood flow rate, \( R \) is the radius of the luminal cross-section, \( E \) is the Young’s modulus of the artery wall, \( \Psi \) is the artery wall viscosity, \( \rho \) is the density of blood, and \( \mu \) is the viscosity of blood.

backward components that result in the artery pulsing in synchrony (long wavelength approximation) \[8\]; the central axis of the artery is fixed; artery wall deformations only occur radially; blood pressure is constant over luminal cross-sections of the aorta \[9\]; the artery wall is impermeable; blood is homogeneous, incompressible and Newtonian \[10, 11\]; and gravity is negligible in larger arteries \[8\].

The governing equations are derived from the principles of: conservation of mass,

\[
\frac{\partial}{\partial t} A(x,t) + \frac{\partial}{\partial x} A(x,t)u(x,t) = 0,
\]

where \( x \) is the position along the longitudinal axis of the aorta, \( t \) is time, \( A(x,t) \) is the cross-sectional area of the aorta, and \( u(x,t) \) is blood flow velocity; and conservation of momentum,

\[
\frac{\partial}{\partial t} A(x,t)u(x,t) + \frac{\partial}{\partial x} \alpha(r, x, t)A(x,t)u(x,t)^2 = -\frac{A(x,t)}{\rho} \frac{\partial P(x,t)}{\partial x} + \frac{f(x,t)}{\rho},
\]

where \( r \) is the position along the radial axis of the aorta, \( \alpha(r, x, t) \) is the momentum flux correction factor that accounts for Poiseuille type flow patterns \( (\alpha = 1.1 \text{ is used in this study to fit experimental data [9]}) \), \( P(x,t) \) is blood pressure, \( f(x,t) \) is the frictional force per unit length, and \( \rho \) is blood density \[12\].

Fluid-structure interaction in the model is accounted for by a relationship between blood pressure and cross-sectional area. The assumptions made are: the artery walls are thin, isotropic, homogeneous, incompressible and impermeable; the walls deform axi-symmetrically across their circular cross-sections; and longitudinal pre-stress can be ignored \[12, 8\]. This leads to the following Voigt-type visco-elastic laws:

\[
P = P_e(A, x) + \frac{\Gamma(x)A_0(x)}{\sqrt{A}} \frac{\partial A}{\partial t},
\]

with \( P_e(A, x) = P_{ext} + \frac{\beta(x)}{A_0(x)} (\sqrt{A} - \sqrt{A_0(x)}) \), \( \beta(x) = \frac{4}{3} \sqrt{\pi} E(x) h(x) \), and \( \Gamma(x) = \frac{2}{3} \sqrt{\pi}\psi(x) h(x) \), where \( P_{ext} \) is extramural pressure, \( A_0 \) is the cross-sectional area when \( P = P_{ext} \) and \( \frac{\partial A}{\partial t} = 0 \), \( P_e \) is the elastic component of pressure, \( h(x) \) is the aorta wall thickness, \( E(x) \) is the Young’s modulus of the aorta wall and \( \psi(x) \) is the wall viscosity.

The radius of the aorta decreases along its length \[13\], and this is approximated in our model by linearly decreasing the radius of the cylindrical aorta (Figure 1). The input boundary condition is a high degree polynomial, interpolated from recordings of human heart beats \[14, 8, 4\]. The boundary condition at the outlet is a three-element Windkessel model \[8, 12\].

Stent treatments for CoA remove the narrowing in the aorta, resulting in increased stiffness within the stent, which we model by altering the Young’s modulus of the aorta wall. Simulations, using the same parameters as previously \[15\] and as indicated in Figure 1, were run with the 1D blood flow package Nektar 1D (http://haemod.uk/nektar) \[12\]. Mesh independence was confirmed by increasing the number of elements from the usual 188 to 251.
In order to compare the treatments, we have plotted (Figure 2) pressure, velocity, change in radius, and wall shear stress (a) along the length of the aorta at $t = 12.54s$ (which was chosen because it is within the systolic period of the heartbeat, when the parameters might be assumed to have their greatest biological effect) and (b) over the period of a heartbeat at $x = 20.0893cm$ (which was selected to show the parameters in a region that was outside the treated region, and also to examine the effects of the treatments on downstream blood flow). Absolute change in aorta wall radius was calculated by subtracting the initial radius from the simulated radius.

Change in aorta wall radius is decreased in the region of increased wall stiffness in aortas treated with stents, compared to normal (healthy) aortas. The aorta with the straight stent, compared to the tapered stent, had decreased change in aorta radius upstream of the stent, and similar change in radius elsewhere.

Blood flow velocity is increased in the regions of the stent treatments, compared to other regions. The straight stent has decreased blood flow velocity in the region of the aorta that is downstream of the stent, compared to the tapered stent and the normal aorta, except at the end, and lower velocity than the tapered stent within the stent. Over the period of a heart beat cycle, the highest peak blood flow velocity is seen in the tapered stent treatment, then the straight stent, followed by the normal aorta. The results for wall shear stress mirror the results for blood flow velocity.

Blood pressure is closer to the normal aorta in the straight stent, compared to the tapered stent, in the region upstream of the stent. The stent treatments have similar blood pressure values in the region downstream of the stent. Over the period of a heart beat cycle, the stent treatments have similar peak
blood pressure values, which are higher than the peak value seen in the normal aorta.

Our results suggest that straight stents are preferable to tapered stents, assuming that blood flow properties closer to the normal aorta are preferable. The blood pressure and change in aorta wall radius results upstream of the stent are slightly superior for the straight stent, which may respectively translate to decreased hypertension and incidence of aneurysms in treated patients. The straight stent also exhibited lower wall shear stress in the region of the aorta downstream of the stent, compared to the normal aorta and tapered stent, which may be preferable due to the relationship between high wall shear stress and aneurysm formation and rupture \[16\].

REFERENCES


A MATHEMATICAL MODEL TO PREDICT THE PRESENCE OF AN INTRACRANIAL ANEURYSM

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SUMMARY

This work concerns the problem of detecting an intracranial aneurysm when detection using MR or CT scanning is not possible or is ineffective. The method used is based on 0D mathematical model of cerebral haemodynamics, constructed using clinical data, and provides good reliability.

Key words: intracranial aneurysm, mathematical model, aneurysm presence criteria

1 INTRODUCTION

Human cerebral circulation is a complex haemodynamical system. It consists of elastic vessels surrounded by elastic brain tissue and vessels containing blood, which is a liquid with complex rheology [1]. Cerebrovascular pathologies are not as common as heart or aorta pathologies [2], however their occurrence presents high risks of mortality and disability. There are currently two different approaches to the treatment of cerebrovascular pathologies: microsurgery [3] and noninvasive methods, an example of which is presented in [4]. Intracranial aneurysms (IA) are reasonably common in almost all ethnicities, with incidences of ruptured aneurysms occurring in approximately 2 per 10 000 people, and unruptured aneurysms occurring in approximately 1 per 50 people. In particular, the rupture of an IA in pregnant woman presents a high rate of mortality [5]. This paper presents a method of detecting cerebral aneurysms in humans. In this work we model human cerebral circulation as a single tuned circuit, consisting of blood flow, elastic vessels and elastic brain gel tissue. We use the non-linear Van der Pol – Duffing equation as a mathematical model of cerebrovascular circulation. This research consists of three stages: clinical measurements, data processing and analytical research, with this paper dealing with the analysis of processed data. Clinical data was obtained at Meshalkin Institute of Circulation Pathology, Novosibirsk, Russian Federation. The data was obtained using real-time cerebrovascular measurements during neurosurgery treatments. The pressure and velocity were measured using ComboWire sensor and ComboMap station (Volcano Corp.) [6]. The data for 7 patients (a total of 99 measurements) was collected and processed. All measurements were made in the arteries of the brain. Due to ethical considerations, we will identify the patients using only the first letters of their surnames: G1, K1, P1, P2, T1, R1, S1. The data set for the clinical measurements of each patient consists of pressure and velocity values obtained from 5 second to 2 minute intervals of time. The position of the ComboWire sensor in the blood vessel was varied during these measurements, with a minimum of 5 secs in each position. The data obtained was processed as described in [7].
1.1 Additional information

The mathematical model being used is based on experimental data and is described by Van der Pol–Duffing nonlinear ordinary differential equation:

\[ \varepsilon q'' + (a_1 + a_2 q + a_3 q^2)q' + (b_1 q + b_2 q^2 + b_3 q^3) = ku, \quad (1) \]

where \(q\)–pressure and \(u\)–velocity are both dimensionless quantities in some position in the blood vessel, and both are functions of time. The mathematical model constructed in [9] allows us to expand the region of haemodynamical parameters that can be investigated and to try different models of external force (right hand side of this equation). Comparison of the numerical solution of Eq. 1 with the clinical data shows that this equation provides a good approximation of the clinical data (pressure and velocity values).

2 METHODOLOGY

Let us assume that upload force is given by \(u = \sin(2\pi \omega t)\). After several substitutions, as in [8], or using the more modern approach [11], Eq. 1 gives us the following dynamical system:

\[
\begin{align*}
p' &= -(b_1 q + b_2 q^2 + b_3 q^3) + k \sin 2\pi \theta, \\
\varepsilon q' &= a_3^2 p - a_1 a_3 q - a_2 a_3 q^2 / 2 - a_3^2 q^3 / 3, \\
\theta' &= \omega.
\end{align*}
\]

(2)

The prime in the above equation denotes differentiation with respect to \(t\), and

\[ p = \varepsilon q' / a_3^2 + a_1 q / a_3 + a_2 q^2 / a_3^2 + q^3 / 3. \]

When \(\varepsilon\) is small, the system (2) is slow-fast. Basic properties of such systems are described in [8, 9].

The right-hand side of the second equation of this system defines a slow surface. For system (2), a slow surface \(S\) is defined by formula:

\[ f(p, q, \theta) \equiv a_3^2 p - a_4 a_3 q - \frac{a_2 a_3 q^2}{2} - a_3^2 \frac{q^3}{3} = 0. \]

(3)

The study of solutions to the slow subsystem of system 2 is important. This is because it is known [10] that the solution of Eq. 1 is in the vicinity \(\delta(\varepsilon)\) of a slow surface \(S\) and therefore consists of a combination of the solutions of slow and fast subsystems for almost all \(t\), except some small time interval \(T\). The points of \(S\) satisfy Eq. (3). After several transformations, system 2 over the surface \(S\) takes the form:

\[
\begin{align*}
q' &= -(b_1 q + b_2 q^2 + b_3 q^3) + k \sin 2\pi \theta, \\
\theta' &= (q^2 + q a_2 / a_3 + a_1 / a_3) \omega.
\end{align*}
\]

(4)

It is necessary to find the singularities and stationary points of system (4), to investigate the properties of the solution of this system. The Jacobian matrix of this system is the following:

\[ J = \begin{pmatrix} -\langle b_1 + 2b_2 q + 3b_3 q^2 \rangle & -2\pi k \cos 2\pi \theta \\
2q + a_2 / a_3 & 0 \end{pmatrix}. \]

It is reasonable to consider only hyperbolic singularities for living systems, such as the one under consideration here. This assumption is required because, for living systems, some variability of the parameters is inevitable. This variability allows such systems to stay stable under small perturbations of the parameters. More detailed analysis is explained in [11].

Note. Using numerical investigation, only hyperbolic singularities of system (4) were found as \(\omega\) was varied.

3 RESULTS AND CONCLUSIONS

All hyperbolic singularities of system (4) were classified.

Definition: We say that a measurement has index \(n\) if system (4) has \(n\) distinct hyperbolic singularities.

We now present the how the measurement index for patient G1 varies (a) before treatment (b) during the operation and (c) after the operation, for different positions in the blood vessel close to the abnormality. An angiogram and a schematic diagram of the measurements are presented below (Fig. 1).
The number in the square/pentagon/circle denotes the ordinal number of the measurement. A square represents the measurement index equaling zero, a pentagon represents the index equaling 2, and a circle the index equaling 4.

**Note.** Fig. 1 shows that, before the operation, the index of the measurement close to the intracranial aneurysm is equal to 2 or 4.

Comparison of the analytical results with the clinical results allows us to investigate the reliability of the test.

<table>
<thead>
<tr>
<th>Patient id</th>
<th>Gender, age</th>
<th>Aneurysm size</th>
<th>Aneurysm location</th>
<th>Test</th>
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<tbody>
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<td>M, 42</td>
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<td>ICA</td>
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<tr>
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<td>F, 65</td>
<td>Giant</td>
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<tr>
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<td>F, 55</td>
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<td>ICA</td>
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<tr>
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<tr>
<td>T1</td>
<td>F, 67</td>
<td>Giant</td>
<td>ICA</td>
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**Table 1:** Results of statistical test

**Analysis of Test.** The presence of an intracranial aneurysm can be confirmed by index value. In terms of the Van der Pol – Duffing mathematical model this translates to the presence of singularities. The statistics obtained are shown here (view Table 2) and justify what is shown in Table 1. In the column "Test", sign "+" signals that the clinical results support the test hypothesis, sign "−" signals that the test hypothesis is refuted by the results and "±" signals that results obtained do not contradict the test hypothesis. As seen in Table 2, the test hypothesis is supported by 71.5% of investigations, and refuted by 14.3% of the cases considered. These statistics show the test has a rather high reliability. For patient R1 the test hypothesis could not be supported or refuted by any measurements, because there were no measurements taken close to the aneurysm, but otherwise R1 did not contradict the hypothesis. For the location we most frequently considered for the aneurysm (ICA), the test had a reliability of 75%. Concerning to the size of the aneurysm, the test hypothesis was supported by the results for 100% of the normal aneurysms, but had a reliability of only 50% for giant aneurysms. We also successfully applied the test to silicon ICA bifurcation (with aneurysm as shown in Fig 2). The indexes of the measurements are shown in Fig. 2. Here arrows show the direction of the flow, and a rectangle represents an aneurysm. This diagram shows that the vessel with the abnormality has a complex regime far from the bifurcation. This contrasts with the second vessel, which has 0-index far from the bifurcation.
From a physiological point of view, this test is reasonable. A living system cannot live normally under complicated conditions. The existence of such systems depends completely on their ability to save energy and to transform energy optimally. The presence of abnormalities (such as aneurysms or AVMs) makes such systems less effective, as a blood vessel with an aneurysm cannot optimally transport blood from the aneurysm to distal parts of the brain tissue. We have that the test is supported by the measurements obtained before the operation. The influence of treatment on the differential properties of Van der Pol – Duffing model could not be discussed from the data considered and requires further research. The test can be applied to detect very small aneurysms or intranidal aneurysms (aneurysms located close to an AVM or inside an AVM).

The medical and engineering communities should be made aware of the proposed test. 0-d models of cerebral haemodynamics combined with modern measurement techniques allow for modelling in a reasonable timescale. This allows the further development of personalised treatment protocols in vascular neurosurgery.

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REFERENCES

ESTIMATING IMPORTANT PARAMETERS OF A BIOCHEMOMECHANICAL MODEL IN VASCULAR ADAPTATION

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SUMMARY

A complex system of mechanical and biochemical processes during physiological perturbations are studied to analyze cardiovascular tissue growth and remodeling. A prior constrained mixture model of stress-mediated arterial adaptation coupled with biochemical kinetics processes is used to predict the adaptation of arteries for sustained changes of blood pressure. A large number of parameters are utilized in this study, including stress-stretch, muscle tone and mass turnover parameters. The importance of the parameters (via sensitivity and correlation analysis) are prioritized, and those that best fit experimentally verifiable results are estimated. Finally, temporal changes in arterial geometry and wall stress during early adaptation (a week to months) are predicted.

Key words: Sensitivity analysis, constrained mixture model, arterial adaptation

1 INTRODUCTION

Vascular walls are made up of different constitutes such as collagen, smooth muscle cells, and elastin that could be modeled by mixture theory\cite{1}. The model components can include the rates at which the multiple collagen fibers are generated and removed; the cell proliferation rates; flow-induced vasoactive muscle tone; and chemical synthesis/removal reactions, which can be mediated by in vivo loads (e.g., hoop and wall shear stresses). By making a proper choice of the number of the constituents and the type and the number of the processes to include in the model, most previous computational Growth and Remodeling (G&R) aimed to predict the behavior of the different constituents under chemical and mechanical stimuli.\cite{1,2} Those studies have investigated ranges of the constituent’s turnover rates and several possible functions of degradation coupled to the states of mechanical stresses through the corresponding changes in the general geometry of the vessel. Recently, we extended the vascular adaptation computational model that replaces the stress-mediated collagen turnover rates by a more realistic collagen synthesis/removal model that includes the subcellular synthesis of procollagen as well as its transition from an intermediate state to mature cross-linked fibers with mechano-regulated removal. In the extended biochemomechanical model, additional unknown parameters from the chemical kinetics of collagen synthesis/removal should be related to physiological loads and mechanical stresses (e.g., circumferential wall stress and wall shear stress). When we develop the extended model, it is imperative to ensure that the model is capable of being predictable in the mechano-regulated kinetic process. The aim of this study is, therefore, to prioritize the important parameters (via sensitivity and correlation analysis) and to estimate those that best fit experimentally verifiable results. By analyzing the sensitivity of the measurable variables, like radius and thickness, of the artery to changes in these parameters, we can identify parameters that could be easily computed with better certainty. The sensitivity analysis also enables us to identify correlated parameters, which may not be separately estimated.
2 METHODOLOGY

2.1. Biochemomechanical model

The biochemomechanical model is sketched in Figure 1. Time, blood pressure, and flow rate are independent variables. The outputs are thickness and internal radius.

There are thirty-one parameters to model arterial G&R. Twenty-seven parameters, which are related to the kinetics and muscle tone, are determined by conducting stress and stretch tests. The input data to compute these parameters are obtained from experiments on animal models.[3] The passive and active mechanical behavior are estimated using in vitro inflation-extension tests from mouse carotid arterial sections. Collagen is assumed to be concentrated in adventia in four orientation; and similarly, artery media is composed of muscle cells and elastin. We set the mean age of collagen to be at 100 days, and we used energy per mass combined with distribution function.[2] The stress-mediated collagen synthesis/removal kinetic model is a set of first-order differential equations as shown below

\[
\frac{dC_i}{dt} = k \left( K_g (\sigma - 1) - K_{sh} (\tau - 1) + 1 \right) - (k_2 + \mu_2) C_i,
\]

\[
\frac{dC_F}{dt} = k_2 C_i - \mu_F C_F,
\]

where \( C_i \) and \( C_F \) are intermediate and mature (crosslinked) collagen; \( k, K_g, K_{sh}, k_2 \) and \( \mu_2 \) are constants; \( \sigma \) and \( \tau \) are normal stress and shear stress (normalized with respect to hemostatic stresses) respectively. Since the relations are nonlinear, therefore, we used Newton-Raphson iteration to determine the final changes in radius of the artery. We used commercial software (Matlab and C++) for the simulation.

2.2. Selecting important parameters

Two approaches, ordinary least square (OLS) and the sequential method, are employed to optimally determine the mass turnover parameters.[4] Simulated data and data from published literature [5] are used to optimally evaluate \( K_g \) and \( K_{sh} \).

These are the main steps to estimate the parameters[6]:

a) Compute the sensitivity (normalized)

\[
X'_{ij} = \frac{\partial x_i}{\partial \theta_j} \approx \frac{\eta_i (\beta_i - \beta_j + \delta \beta_j - \delta \beta_i) - \eta_i (\beta_i - \beta_j - \delta \beta_j + \delta \beta_i)}{\delta}, \quad \delta = 0.001
\]

b) Compute the correlation between two parameters:

\[
\rho_{m} = \frac{\sigma_{mJ}}{\sigma_m \sigma_j}, \quad \sigma_{mJ} \text{ covariance of parameters } m, j.
\]

The correlation between the parameters could be indirectly identified by observing the linear dependency of the parameters corresponding sensitivity vectors.

c) Compute Predictably:

\[
P = \frac{\max(x'_{ij}) - \min(x'_{ij})}{\max(\eta_{ij}) - \min(\eta_{ij})} \text{ or } P = \frac{\max|x'_{ij}|}{\max|\eta_{ij}|}.
\]

If the parameter of interest is not correlated with other parameters and if \( P > 0.1 \), then it may be easily computed.
d) Inversely estimate the parameters by using either OLS or sequential method.
e) Analyze the statistical significance of the computed parameters like standard errors and confidence intervals.

3 RESULTS AND CONCLUSIONS

As shown in Figure 2, we plotted the sensitivity curves, checked the leaner dependency of the sensitivity vectors, and checked the predictability of the parameters. The arterial wall thickness is affected little by $k_2$ and $\mu_2$ compared to $K_g$ and $K_{sh}$. The latter two parameters are also uncorrelated. This indicates that $K_g$ and $K_{sh}$ are more important and easily predictable compared to $k_2$ and $\mu_2$.

![Figure 2: a) Scaled sensitivity curves ($\beta_1 = k_2, \beta_2 = \mu_2, \beta_3 = K_g, \beta_4 = K_{sh}$); b) Linear dependency between $K_g$ and $K_{sh}$. From the graph we can see that the ratio of sensitivity curves between $K_g$ and $K_{sh}$ is not constant, which indicates that the two curves are not linearly dependent (and uncorrelated).](image)

Therefore, $k_2$ and $\mu_2$ are kept constant at 0.2 and 0.1, respectively, and the other two parameters are estimated. After the nonlinear estimation, the predicted arterial wall thickness compared with the observed thickness. [5] As plotted in Figure 3, the corresponding 95% confidence intervals and prediction bands are also computed.
Figure 3. Simulation results for arterial wall thickness and the estimation confidence intervals over 56 days (\(h_{\text{observed}}\): the measured thickness, \(h_{\text{predicted}}\): predicted thickness, Confidence Band: 95% confidence limits of the estimation, Prediction Band: prediction limits of the estimation)

We further computed parameter confidence intervals, root mean square, covariance matrix, and correlation matrix. We also analyzed the residuals and crosschecked the standard statistical assumptions. \(K_g = -16 \pm 2\) and \(K_{sh} = 124 \pm 9\). The detail of our result will be presented during the conference.

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REFERENCES


A COMPUTATIONAL STUDY OF INFLUENCE OF CHANGES IN BLOOD PRESSURE ON GROWTH OF ABDOMINAL AORTIC ANEURYSM

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SUMMARY

Hypertension is regularly considered a risk factor for higher expansion rate of abdominal aortic aneurysm (AAA) and its rupture, while hypotension is mostly ignored. The only investigation between hypotension and AAA is related to investigation of relation between preoperative hypotension due to rupture and high mortality rate. In this work, using finite element model with implemented growth and remodeling model, we are studying influence of blood pressure changes on abdominal aortic aneurysm growth. Finite element method allows us to analyze 3D axially symmetric and asymmetric aneurysm.

Key words: abdominal aortic aneurysm, hypotension, growth and remodeling

1 INTRODUCTION

Abdominal aortic aneurysms (AAAs) often remain asymptomatic until rupture, an event with high mortality rate. Current clinical capabilities for predicting rupture, a reliable computational tool for predicting patient-specific AAA outcome, and thus an understanding of a disease continue to remain wanting. Therefore, clinical interventions will continue to be based primarily on the maximum AAA diameter or expansion rate of the lesion, and certain rupture risk factors, including smoking, female gender, and hypertension.

Hypertension is commonly considered a risk factor for higher expansion rates of AAA and, thus, rupture [1], [2]. Interestingly, a computational study using finite elements on two patients-specific geometries with the same maximum AAA diameter predicted 13% lower stress on hypertensive patient compared to normotensive one, despite a present clinical thinking that hypertension increases wall stress [3]. Conversely, there are no studies investigating relationship between hypotension and AAA growth. This might be due to our perception that higher blood pressure means wall stresses are higher, and thus rupture risk as well. However, this might not be the case, since arteries adapt to new pressure in order to retain wall stresses on homeostatic value. It is also worth noting that unlike hypertension, hypotension is rarely treated. The only exception where hypotension is linked to AAA is related to hypotension after rupture. Several large group studies from the 80s [4], [5] investigated preoperative (advanced age, female gender, hypotension, or cardiac arrest), intraoperative and postoperative factors causing complications and high mortality rate of surgical repair of ruptured abdominal aortic aneurysms, showed that approximately 67% of patients undergoing operation had persistent preoperative hypotension due to rupture and hemorrhage (systolic blood pressure <90 mmHg). Still, hypertension is considered one of the main risk factors, while hypotension is ignored.

In our previous work, we have conducted a computational case study on idealized cylindrical thrombus-laden aneurysms showing that development of hypertension during AAA evolution indeed results in higher expansion rates and likelihood of rupture. However, persistent hypertension before aneurysm development resulted either in stabilization or rupture at the smaller AAA sizes (3.5-4 cm), depending on other mechanical and biochemical properties of aorta. This could be
explained by changes hypertension introduces to healthy aorta. If healthy blood vessel adapted to the new, higher blood pressure, its thickness increased in order to lower stresses back to homeostatic value. Hypertension leads to progressive changes in vascular structure, function, and material properties that often manifest grossly as increased wall thickness, radial dilatation, and axial lengthening [6]. Similarly, hypotension would lead to aortic thinning, which is potentially dangerous during AAA growth. It is also important to note that due to decreased load, production of structurally important constituents (i.e. collagen) might be decreased. Therefore, in this contribution we study the importance of blood pressure during AAA growth. Hypotension stage and time of hypotension development is considered.

2 METHODOLOGY

To model G&R of AAA, we used computational model described in Karšaj et al. [7]. The model is based on continuum mechanics and models artery as constrained mixture of elastin, smooth muscle cells and several collagen fiber families. Constituents are bound to move together, but each of them can have different stress state. Smooth muscle and collagen fibers have continuous turnover while elastin can only be degraded. Current mass of each constituent $k$ can be computed as:

$$M^k(s) = M^k(0)Q^k(s) + \int_0^s \dot{m}^k(\tau)q^k(s-\tau)\ d\tau,$$

where $q^k(s-\tau)$ is survival function that defines a fraction of constituent produced at past time $\tau$ that remained at current time $s$, with a special case $Q^k(s) = q^k(s-0)$. $M^k(0)$ is an initial mass of constituent and $\dot{m}^k(\tau)$ is constituent production rate.

Anisotropic, Cauchy stress in the aortic wall is calculated as:

$$\sigma = \frac{2}{\det(\mathbf{F})} \mathbf{F}^T \mathbf{W} \mathbf{F} + \sigma^{active} \mathbf{m}^{SMC} \otimes \mathbf{m}^{SMC},$$

where $\mathbf{F}$ is overall deformation gradient, with associated right Cauchy-Green tensor $\mathbf{C} = \mathbf{F}^T \mathbf{F}$ . $\sigma^{active}$ is active stress contribution from smooth muscle contractility oriented in the direction of the cells ($\mathbf{m}^{SMC}$). Finally $W$ is overall stored energy function defined as $W = \sum_k W^k$. Stored energy function of each constituent at current time $s$ is defined as:

$$W^k(s) = \sum_k M^k(0) \hat{W}^k \left( C^{k(0)}(s) \right) Q^k(s) + \int_0^s \sum_k \hat{W}^k \left( C^{k(\tau)}(s) \right) \dot{m}^k(\tau) q^k(s-\tau) \ d\tau$$

with $\hat{W}^k$ being specific stored energy function of constituent $k$, and $C^{k(\tau)}(s)$ being right Cauchy-Green tensor of constituent $k$ with respect to its natural configuration.

Through user defined subroutines, we implemented the model in finite element analysis software FEAP. Unlike previous implementations of growth and remodeling model in finite elements, we did not use deviatoric split, but mixed formulation. This proved to be more stable and eliminated some of the numerical problems. Incompressibility was enforced using Augmented Lagrange method.

3 RESULTS AND CONCLUSIONS

Using FEAP with implemented G&R model we analyzed healthy aorta for case of 20% decrease in blood pressure. Fig. 1 shows that after abrupt decrease in blood pressure, aortic diameter first decreases as a result of mechanical response, however, due to G&R it starts to increase and stabilize on its homeostatic value. At the same time aortic wall is thinning (Fig. 2). Simulated results for wall thickness are in agreement with membrane theory for hemodynamic perturbation.

According to this theory if new blood pressure $P$ is $P = \gamma P_h$, with $P_h$ being homeostatic pressure, then new wall thickness $h$ is equal $h = \gamma h_h$, where $h_h$ is homeostatic thickness. For case of 20%
blood pressure decrease, and with no change in blood flow, wall thickness will decrease on 80% of its original value, which in this case is decrease from 1.2 mm to 0.96 mm. Observed aortic wall thinning can potentially be dangerous during AAA development and growth. We plan to test this hypothesis, simulating different blood pressure changes before and during AAA growth. Special emphasis will be placed on hypotension and results will be compared with hypertension. Unlike our previous study, this will be performed using 3D finite elements on more realistic geometry (e.g. fusiform and saccular aneurysm).

Fig. 1. Evolution of luminal diameter of healthy aorta in case of abrupt 20 % decrease in blood pressure

Fig. 2. Evolution of wall thickness of healthy aorta in case of abrupt 20 % decrease in blood pressure

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REFERENCES


COMPUTATIONAL PREDICTION OF THE EFFECT OF LVAD FUNCTION ON MECHANICAL UNLOADING AND ELECTROMECHANICAL DELAY

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SUMMARY

The goal of this computational study was to predict the effect of LVAD on mechanical responses and electromechanical delay (EMD) for four HF cases ranging from mild to severe HF. We constructed an integrated model of an LVAD-implanted cardiovascular system. We altered Ca\textsuperscript{2+} transient magnitude, scaling it from 1 to 0.7 to mimic increasing severity of HF characterized by systolic dysfunction. The findings indicated that HF-induced Ca\textsuperscript{2+} transient remodeling prolonged mechanical activation time (MAT) and decreased pumping efficacy. LVAD shortened MAT and improved the pumping efficacy. The computational study demonstrated that LVAD shortens EMD by mechanical unloading of the ventricle.

Key words: ventricular electromechanical model, calcium transient, left ventricular assist device

1 INTRODUCTION

Heart failure (HF) is a chronic and progressive condition, with the heart muscle being unable to pump the appropriate amount of blood to fulfill the needs of the human body. A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee concluded that HF is a major cause of morbidity and mortality, and that it contributes significantly to health expenses around the world [1].

A subset of HF includes dyssynchrony between cardiac depolarization and myofiber shortening, which in turn further increases the severity of HF. The time interval between the local myocyte depolarization (electrical activation) and onset of myofiber shortening (mechanical activation) is termed electromechanical delay (EMD) [2]. Normal EMD is typically about 10 ms, and long EMD implies lack of synchrony in cardiac electromechanical activation and a decrease in ventricular pumping efficacy [2].

Constantino et al. [3] identified four major aspects that contribute to prolonged EMD under dyssynchronous HF conditions: remodeled cardiac structure (both heart shape and fiber structure), altered electrical conduction, deranged Ca\textsuperscript{2+} handling, and increased stiffness of the tissue. The timely application of electrical stimulation (termed as cardiac resynchronization therapy (CRT)) can alter the electrical conduction pattern in the ventricles, provide synchrony, and improve the pumping of the heart. The study by Constantino et al demonstrated that CRT reduced cardiac EMD by reducing the overall electrical activation time [4]. Furthermore, it also found that deranged Ca\textsuperscript{2+} handling resulting in a diminished magnitude of the Ca\textsuperscript{2+} transient, was the primary factor responsible for prolonged EMD. The other three factors had a much smaller contribution to EMD.
An experimental study conducted by Russell et al. in canine and human hearts showed that a mechanical load prolonged the EMD [5]. Although the findings of these studies suggested that EMD decreases if the mechanical load of the ventricles decreases, no research to date has validated this suggestion. A left ventricular assist device (LVAD), used to support cardiac function and improve cardiac output, also reduces the mechanical load of the ventricles by enabling an improved pump function. In a previous study of ours, we developed a computational model of the ventricles with LVAD support and showed that the LVAD decreased ventricular afterload and improved coronary perfusion [6].

The goal of the present study was to examine, using similar computational modeling, the effect of LVAD on the three-dimensional (3D) distribution of EMD in the failing heart, and to test the hypothesis that LVAD overall shortens EMD by reducing mechanical afterload. The use of computational modeling overcomes the inability of experimental methodologies to measure and quantify the EMD distribution in the heart.

2 METHODOLOGY

In this study, the 3D image-based electromechanical model of failing ventricles [7] was combined with a lumped model of the circulatory system and LVAD function [6] to construct an integrated model of an LVAD-implanted cardiovascular system.

The electromechanical model of the failing ventricles used in this study had two dynamic components, namely electrical components and mechanical components, as described in a previous study [7]. The electrical component of the model simulated the propagation of a transmembrane potential wave by solving the monodomain equations based on Ten Tusscher et al. [8] on a finite element tetrahedral mesh comprising of 241,725 nodes and 1,298,751 elements. The mechanical component of the model simulated ventricular contraction. Ventricular contraction is a result of the active tension generated by the myofilaments of ventricular cells based on Rice et al. [9]. Ventricular deformation is represented by equations of passive cardiac mechanics, given that the myocardium is an orthotropic (due to fiber and laminar sheet organization), hyperelastic, and nearly incompressible material with passive mechanical properties defined by an exponential strain energy function. The model comprised of 356 nodes and 172 Hermite elements.

The 3D ventricular modeling involved the generation of two groups of models, namely, a control group with no mechanical support and a LVAD group. In a manner similar to the single myocardial cell simulations, four different Ca\textsuperscript{2+} transient magnitudes were used (HF1 to HF4). A continuous LVAD with a pumping flow rate of 3 L/min was assumed. Thus, 3D ventricular simulations were executed for eight different conditions, and model responses including spatial distribution of myocardial tension and contractile ATP consumption, strain distribution, and hemodynamic responses (blood pressure, volume, and flow rate) were compared.

As in Gurev et al. [2], the EMD was defined as the time interval between the local electrical activation time (EAT) and the local onset of myofiber shortening (mechanical activation time [MAT]). The local electrical activation time was defined as the transmembrane voltage exceeding 0 mV, and the onset of myofiber shortening was defined as the time instant at which the myofiber was shortened to 10% of its maximal value. The EMD was obtained by subtracting EAT from MAT at every point in the ventricles. Finally, the 3D distributions of EAT, MAT, and EMD were compared between the control group and the LVAD for the 4 different levels of HF severity.

3 RESULTS AND CONCLUSIONS

The results indicated that tension and ATP consumption rate were decreased in the LVAD and control groups following the decrease in Ca\textsuperscript{2+} transient magnitude. For the same HF severity condition, LVAD decreased tension and ATP consumption. Specifically, LVAD therapy reduced contractile ATP consumption by 10% in HF1, 8% in HF2, 17% in HF3, and 35% in HF4. These results demonstrated that LVAD reduced the LV mechanical load and contractile energy consumption, especially under severe HF. However, strain increased when Ca\textsuperscript{2+} transient was decreased. The LVAD treatment reduced ventricular strain for severe HF.
LVAD fully assisted the LV in pumping blood in the HF3 and HF4 conditions, while the same in the HF1 and HF2 conditions it provided only partial assistance. The reason why the LVAD did not fully assist in the distribution of blood under conditions HF1 and HF2 was because the LV pressures in these cases exceeded the aortic pressures during the systolic phase. Under HF3 and HF4 conditions, the blood volume from the LV was fully unloaded by the LVAD and transported directly toward the aorta by passing it through the aortic valve. The aortic pressure under HF4 was the same as under HF3 (113 mmHg). The LVAD function not only reduced the LV pressure by mechanical unloading, but also maintained sufficient aortic pressure in the coronary arteries.

In a manner similar to the data for the overall ATP consumption rate, the more severely failing ventricle performed less stroke work to pump blood. Additionally, the LVAD group performed less stroke work as compared to the control group. This was because LVAD assisted the LV to pump blood into the aorta. The LVAD therapy reduced LV stroke work by 60% in HF1, 50% in HF2, 42% in HF3, and 77% in HF4.

Fig. 1 shows the transmural distribution of electrical activation time (Fig. 1A), and MAT and EMD (Fig. 1B). It also shows the average time of MAT and EMD throughout the entire ventricles for different HF severity in LVAD and control groups (Fig. 1C). Overall, MATs were prolonged for increasing severity of HF while all the EATs were constant. Therefore, more severe HF resulted in longer EMDs (Fig. 1B). The spatial average of MATs was 159 ms in HF1, 160 ms in HF2, 162 ms in HF3, and 163 ms in HF4. Therefore, the spatial average of EMDs was 79 ms, 81 ms, 82 ms, and 83 ms, respectively. LVAD therapy reduced MAT at each severity level and thereby also reduced EMD. The LVAD therapy reduced the average MAT by 1% in HF1, 2% in HF2, 3% in HF3, and 6% in HF4. Therefore, average EMDs were reduced by 1%, 2%, 4%, and 18%, respectively. Results indicated that both MAT and EMD were reduced by the mechanical unloading even under mild HF conditions (HF1) in the control group. Thus, LVAD reduced MAT and EMD in all cases.

The results indicated that the differences in the cardiac responses between LVAD and control groups were not significant under mild HF conditions. In practical, the use of LVAD is not necessary for the heart under mild HF conditions. In contrast, under the most severe HF, LV and aorta pressures, energy consumption, stroke work, tension, strain activation, MAT, and the EMD showed significant improvement under LVAD treatment.

In conclusion, LVAD shortens EMD by mechanical unloading in mild HF, and its performance in-
creases with the severity of the HF. This computational study validated the hypothesis that the LVAD can shorten EMD by mechanical unloading in the ventricle.

REFERENCES


IMAGE-BASED COMPUTATIONAL MODELING OF AEROSOL LEAKAGE THROUGH N95 RESPIRATORS

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SUMMARY

This research presents a computational fluid dynamics (CFD) approach to quantify the aerosol leakage through respirators for different face-respirator combinations. Center for Disease Control’s anthropomorphic face geometries were CT scanned after donning different respirators and converted to CFD meshed using reconstruction and meshing software. Subsequently, a numerical methodology was developed to simulate air flow around the face-respirator geometry. The amount of airflow leakage through the gaps due to poor face-mask fitting was quantified as a function of flow rate. The results showed that the percentage of flow leakage is related to the gap area in a near-logarithmic fashion. The gap area ranged from 0.2% to 2.7% of the total mask surface area (150 cm²), while the corresponding flow leakage ranged from 21.2% to 91.6% respectively.

Key words: Computational fluid dynamics, image based modeling, respirator

1 INTRODUCTION

In the event of airborne pandemic or bio-terror attack, personal protective equipment (PPE) such as N95 respirators will form the first line of defense against hazardous bio-aerosols. The effectiveness of PPEs is strongly dependent upon their ability to prevent aerosol leakage through gaps between the human face and PPE, in addition to the intrinsic penetration through the respirator’s porous layers [1, 2]. The leakage through gaps can be significantly reduced by performing fit testing and selecting appropriately sized respirator. However, during a public health emergency, fit-testing of respirators may not be possible and leakage of aerosol through the gaps could compromise the effectiveness of the PPE. It is important to quantify how the performance of the PPE degrades as a function of gap area.

This research presents a computational fluid dynamics (CFD) approach for quantifying the aerosol leakage through respirators for multiple human face-respirator combinations under realistic flow conditions. The gap surface area for different face-respirator combinations has been recently quantified by our group [3]. This study utilizes the CFD model further and establishes a relationship between the amount of flow leakage and the gap surface area for each of the face-respirator combinations. The leakage results from this study will eventually be combined with our recently published lung deposition [4] and comprehensive risk assessment models [5] to quantify the infection risk to pediatric and adult populations when exposed to various types of bio-aerosols such as Bacillus anthracis or Influenza virus.
2 METHODOLOGY

2.1 Headforms and respirators

Four adult headforms and two brands of respirators, shown in Fig. 1, were selected for evaluating the gaps between the face and respirator. The geometric data of the headforms were obtained from an anthropomorphic survey of 3,997 US workers, conducted at the National Personal Protective Technology Laboratory at the Center for Disease Control [6], and categorized based on shape and size as: small, medium, large, and short/wide. Subsequently, mannequins resembling realistic solid models of each of the headforms were obtained using 3D printing (Materialise, Inc.). The two respirator brands, labeled as Model A and Model B, belonged to the class of N95 surgical respirators, which are certified by the National Institute for Occupational Safety and Health (NIOSH) and regulated by the US Food and Drug Administration (FDA). Therefore, eight unique headform-respirator combinations were obtained by donning each of the two respirators on all four headforms.

Figure 1: An image of headforms and N95 respirators

2.2 Obtaining the Computer Aided Design (CAD) geometry

Computed Tomography (CT) was used to resolve the gap between the face and the mask for different mask-face combinations. Before the CT scans, the inside layer of the mask was coated with a thin layer of gold to enhance the contrast of the mask layer relative to the face. The CT slices were reconstructed using Mimics and 3-matics software and converted to 3D CAD geometry. A computational domain of size 150x150x200 mm³ which includes the face, respirator and the surrounding enclosure are shown in Fig 2. An inlet tube of diameter, 6 mm, was attached to the front side of the enclosure (opposite the face and respirator), while the outlet was modeled as a circular region (diameter = 6 mm) on the mouth (Fig. 2). The domain was then meshed into finite volumes consisting of tetrahedral elements (3-matic, Materialise Inc.). The mesh around the face and respirator region was refined to accurately solve the leakage flow through the gaps. Subsequently, the meshed computational domain was exported for processing in a CFD solver, CFX (Ansys, Inc.).
2.3 Numerical Methodology

A 3-step numerical methodology, developed in-house, will be adopted for simulating the airflow and aerosol transport around and through the face-respirator geometry. In the first step, the porous media properties (porosity and linear resistance coefficient) of the masks were obtained by performing a no-leakage CFD simulation of the masks attached to the flat plate. For this simulation, all the aerosol penetration was assumed to happen through the porous layers of the mask. The pressure drop required across the mask to attain the necessary flow was measured experimentally for both masks. Subsequently, the mask porosity and the linear resistance coefficient were adjusted in the CFD simulations until the pressure drop matched with the experimental data. After completion of the first stage, for mask Model A, the simulation resulted in porosity value of 0.5 and linear resistance coefficient value of 93700 kg m$^{-3}$s$^{-1}$, while for mask Model B, the simulation resulted in porosity value of 0.5 and linear resistance coefficient value of 89800 kg m$^{-3}$s$^{-1}$.

In the second step, fluid flow calculation through the face-respirator geometry was performed using the mask properties obtained from the first stage. An inlet boundary condition of zero static pressure was specified at the inlet and mass flow rate was specified at the mouth outlet. This combination of boundary conditions simulates a suction flow through the inlet. Subsequently, the amount of fluid flow through the leakage sites and through the porous layers of the mask was determined. Converged solution could not be obtained for two of the eight face-respirator combinations (not included in this paper). These combinations need to undergo mesh refinement in the fine gap areas in order to accurately solve the fluid flow and obtain a converged solution.

In the third step, which is currently underway and will be described in a future publication, a particle tracking algorithm is used to track the leakage of aerosols through the leakage sites between face and the respirators. The flow split between the leakage sites and the mask (obtained from the second step) was provided as the input for this stage. The input parameters for aerosol transport including the density (2250 kg/m$^3$) and aerosol size (100 nm) were obtained from the experimental studies. Finally, the amount of aerosol leakage is obtained as a function of flow rate to evaluate the relationship between the gap surface area and the leakage percentage for different face-respirator combinations.

3 RESULTS AND CONCLUSIONS

The variation of flow leakage as a function of gap surface area for two different intake flow rates of 10 LPM and 70 LPM is shown in Fig. 4. The gap surface area for the eight human face-respirator combinations were obtained from image based modeling and ranged from 0.2% to 2.7% of the total mask surface area (150 cm$^2$) [5], while the flow leakage varied from 21.2% to 91.6% respectively. The rate of increase of flow leakage is observed to be high up to a gap surface area of 200 mm$^2$. 
beyond that rate of increase is much more gradual. A logarithmic fit is obtained for the computed data points. As expected, flow leakage is observed to increase with gap surface area.

![Graph showing variation of CFD simulations based flow leakage with gap surface area for intake flow rates of 10LPM and 70LPM](image)

**Figure 4. Variation of CFD simulations based flow leakage with gap surface area for intake flow rates of 10LPM and 70LPM**

**Assumptions and limitations:** While simulating the flow and aerosol transport, the face was treated as a rigid boundary and the compliance of the skin was not modeled. Consequently, the gap surface area at the leakage sites could be different from the values reported in this study. Future study will evaluate how incorporation of a distensible boundary can impact the accuracy of the leakage rates predicted by the CFD simulations.

**Future work:** Future studies will provide the co-relation between gap surface area and aerosol leakage (instead of the flow leakage reported here). The aerosol leakage % obtained from the CFD will also be validated with the experimental results. Subsequently, the leakage results will be input to our comprehensive risk assessment model [5] to quantify the infection risk to pediatric and adult populations when exposed to various types of bio-aerosols.

**REFERENCES**

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AN APPROACH TO NONINVASIVE FRACTIONAL FLOW RESERVE CALULATION WITH A PATIENT-SPECIFIC PRESSURE-FLOW BOUNDARY CONDITION

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SUMMARY

This study presents a steady-state computational fluid dynamics method with a patient-specific pressure-flow boundary condition in order to reduce the computational time and to improve the accuracy of FFR\textsubscript{CT}.

Key words: fractional flow reserve, boundary conditions, coronary blood flow, steady-state computational fluid dynamic

1 INTRODUCTION

Coronary computed tomography angiography-derived fractional flow reserve (FFR\textsubscript{CT})\textsuperscript{1,2}, which is a noninvasive functional parameter for the diagnosis of coronary artery disease, can solve the clinical problems of invasive fractional flow reserve (FFR) effectively\textsuperscript{3}. However, the accuracy and the computational time consuming are two main problems of FFR\textsubscript{CT}. This study presents a steady-state computational fluid dynamics method with a patient-specific pressure-flow boundary condition in order to solve the above-mentioned problems.

2 METHODOLOGY

Firstly, a mathematical model of coronary blood flow at hyperemia was presented. Some independent physiological parameters of coronary blood flow were selected, including the myocardial mass, diastolic blood pressure and heart rate\textsuperscript{4-5}. Choy et al\textsuperscript{4} verified the scaling law between coronary blood flow and myocardial mass with an exponent 0.75 by in vitro measurement experiment of animal heart. Left ventricular myocardial mass accounted for about 85% of the whole myocardial mass\textsuperscript{6}. So the relationship between coronary blood flow (Q\textsubscript{cor}) and left ventricular myocardial mass (M\textsubscript{L}) can be expressed as \( Q_{cor} \propto (M_{L}/0.85)^{0.75} \). Besides the myocardial mass, perfusion pressure and perfusion time are the two main factors influencing the coronary blood flow, namely the aorta diastolic blood pressure (P\textsubscript{d}) and heart rate (HR) which were normalized as the average of 85 mmHg and 75 bpm respectively for human being. So we can get the mathematical model expressed as \( Q_{cor} = k \frac{P_{d}}{85} \frac{75}{HR} \frac{M_{L}}{0.85}^{0.75} \). Referring to human myocardial blood flow\textsuperscript{7}, we can get the constant \( k=12 \).

Then, based on the “form-function” relationships\textsuperscript{8} and the vessel length-based method\textsuperscript{9}, we
presents a vessel volume-based method to calculate flow division fraction over the left anterior descending (LAD) artery, the left circumflex (LCX) artery, and the right coronary artery (RCA).

Finally, integrated the shear stress formula of the Hagen-Poiseuille flow, the uniform shear hypothesis and Murray’s law, the flow rate of coronary outlet \( Q \) can be calculated by \( Q \propto a^3 \), the parameter \( a \) is the vessel diameter.

Sixteen cases of patients with coronary stenosis were employed for finite element analyses.

3 RESULTS AND CONCLUSIONS

3.1 Results

The coronary blood flow of patients at hyperemia is 573±153 mL/min calculated by the present method, and the myocardial blood flow at hyperemia is 3.47±0.61 mL/min/g. These results were in clinical physiological range.

Tables 1 and 2 represent the results of the coronary flow division (in percentage) over LAD, LCX, and RCA for the 16 patients using the vessel volume-based method and the vessel length-based one, respectively. Among the 16 patients, 14 cases (88%) were right coronary dominant. The flow division fraction of RCA has significant difference. Comparison of the flow division over LAD, LCX and RCA with clinical statistical data\(^{10}\) is shown in table 3. Averaged fractions of the flow division over LAD, LCX, and RCA by the vessel volume- and length-based methods were almost identical to those by the clinical measurement.

Table 4 represent the comparison of coronary FFR\(_{CT}\) and invasive FFR. Among the 16 patients (20 stenosed vessels), the results of ischemia diagnosis of 18 vessels (90%) are consistent with invasive FFR at a threshold of \( \leq 0.80 \).

### Tab.1 Flow division fraction(%) over LAD, LCX, and RCA for the 16 patients using the vessel volume-based method

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<th>LCX(%)</th>
<th>RCA(%)</th>
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<th>LCX(%)</th>
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### Tab.2 Flow division fraction(%) over LAD, LCX, and RCA for the 16 patients using the vessel length-based method

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Tab. 3 Comparison of average fraction of coronary flow division over LAD, LCX, and RCA.

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Note: Here, the vessel volume-based method and the vessel length-based one tested 16 patients whereas the clinical data did 496 patients.

Tab. 4 Comparison of coronary FFR<sub>CT</sub> and invasive FFR for the 16 patients

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<th>Patient NO.</th>
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3.2 Conclusions
There are some limitations in this study. 1. The number of calculation cases is only a few. 2. In this study, we ignored the coronary microcirculation disorder and myocardial injury, so in theory, FFR<sub>CT</sub> will be smaller than the invasive FFR. 3. This study is a pure fluid simulation, without considering patient-specific material properties of blood vessels and plaques. 4. This study is for steady-state calculation, so it will lose some information varied periodically.

The coronary FFR<sub>CT</sub> has good consistency with invasive FFR under the patient-specific pressure-flow boundary conditions. At the same time, the steady-state calculation greatly reduces the computational time. This study offers a new way for improving FFR<sub>CT</sub> method, as well as promotes the clinical application of FFR<sub>CT</sub>.

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REFERENCES


COMPUTATIONAL PREDICTION OF THE CARDIAC ELECTROMECHANICAL RESPONSES DUE TO G229D KCNQ1 MUTATION

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SUMMARY
Several studies have identified mutation in KCNQ1 has strong correlation with atrial fibrillation. However, the mechanism by which mutation induces the occurrence of ventricular fibrillation and reduction of cardiac mechanics remains poorly understood. Here, we predicted the ventricular electromechanical responses due to G229D KCNQ1 mutation using computational model of the heart. Our study demonstrated that mutation induced not only ventricular electrical but also mechanical responses by shortening action potential duration (APD), accelerating repolarization phase during normal sinus rhythm, shortening wavelengths of electrical propagation during reentry, and decreasing ventricular pumping functions.

Key words: Mutation, G229D KCNQ1, fibrillation, computational model

1 INTRODUCTION
Over the last decade, we have looked on the mutation, primarily in the ion channel gene, underlying a number of the arrhythmias [1]. Several studies have reported that gain-of-function mutations in KCNQ1 are linked to familial atrial fibrillation (AF) [2-6]. KCNQ1, a gene encoding of K+ channel, assembles with the KCNE1, forming a slow delayed rectifier current (I_{KS}), which is crucially responsible for proper repolarization of cardiac action potential (AP) [7]. The alteration of I_{KS} may lead to serious arrhythmias, ventricular fibrillation, and cardiac arrest [7].

The recent study of Hasegawa et al. [5] and Zulfa et al. have revealed that G229D, mutation caused by an amino acid change from glycine to aspartic acid at position 229 in transmembrane segment 4 of KCNQ1, resulting in gain-of-function of I_{KS}. According to their study, the enhancement of I_{KS} significantly shortened the APD in the atrial, but only slightly in the ventricle. Here, we hypothesized that although with small APD shortening, G229D KCNQ1 mutation also has a possibility to generate the fibrillation in the ventricle.

Moreover, although several computational studies have been carried out regarding to KCNQ1 mutation, none of them take into account the mechanism by which the mutation promotes the alteration in the mechanical behavior of the heart. As the main role of the heart to pump blood for body’s metabolism, knowing how far the mutation induces the cardiac mechanical behavior is very important. In this study, we predicted using magnetic resonance imaging (MRI)-based electromechanical model of the heart [8, 9] that G229D KCNQ1 mutation can induce not only electrical but also mechanical behavior of the heart.

2 METHODOLOGY
2.1 Computational model
To achieve the goals of this study, we used the finite element electromechanical model of the heart combined with a lumped-parameter model of the circulatory system, developed by previous studies [8, 9]. The finite element electromechanical model consists of 241,725 nodes and 1,298,751
elements of linear tetrahedral mesh for the electrical properties, and 356 nodes and 172 elements of non-linear hexahedral mesh for the mechanical properties. The ventricular geometry, fiber, and sheet structure of the model were built from high-resolution MRI and diffusion tensor (DT) MRI scans of canine ventricle in the heart failure condition. The ventricular wall consists of three different compartments including endo, M, and epi cells.

The electrical and mechanical properties of the model were coupled via intracellular calcium (Ca2+) transient, which connects detailed models of local membrane kinetics and local cardiac myofilament dynamics throughout the ventricles. The electrical properties was represented by the human ventricular AP model of ten Tusscher et al. [10] based on bidomain equation, which describes the flow of currents from cell to cell due to active ion exchange across myocyte membranes [11]. To explore the role of G229D KCNQ1 mutation, the \( I_{Ks} \) equation in ten Tusscher model was modified with the formulation from Hasegawa et al. [5], to simulate the mutant (G229D) and wild-type (WT) condition. The mechanical properties illustrate the active contraction and deformation of ventricles. The ventricular contraction was resulted from the development of active tension, represented by myofilament dynamics model of Rice et al. [12]. The ventricular deformation was described by the stress equilibrium equations of passive cardiac mechanics, with the myocardium assumed an orthotropic, incompressible, and hyperelastic material with passive properties defined by an exponential strain energy function [13].

To simulate the interaction between the blood and the ventricles (i.e., hemodynamic responses), the electromechanical model was coupled with a circulatory model, following the coupling method of Gurev et al. [9]. The intraventricular pressures were added to the endocardial surfaces, and the ventricular volumes were expressed as functions of the degrees of freedom of the endocardial surface nodes using the divergence theorem. The initial conditions of the circulatory model were determined from the elastic model of ventricular contraction.

### 2.2 Simulation protocol

The single cell simulations were carried out using a standard S1-S2 protocol [14]. Briefly, a single S2 extra stimulus was delivered after 30 S1 stimuli applied at a basic cycle length (BCL) of 1 s. The S1-S2 interval was progressively shortened from 1 s to 300 ms in steps of 20 ms and from 300 ms to the refractory period in steps of 2 ms. The APD restitution curves were generated by plotting the \( \text{APD}_{90} \) (i.e., APD at 90 % repolarized from the peak potential) against BCL and diastolic interval (DI). DI, equals to the S1-S2 interval minus \( \text{APD}_{90} \) of the response to the last S1 stimulus.

In 3D tissue, the electrical propagation waves were observed by applying two pace activation scenarios (i.e., during normal sinus rhythm, and reentry). During sinus pacing, the electrical impulse was initiated at purkinje fibers, which was integrated at the endocardial surface of the ventricle, with 200 cm/s of conduction velocity (CV). During reentry, a S1-S2 protocol was used, by applying 2 S1 stimuli in the apex of the ventricle with the same BCL of 600 ms. This stimulus will produce waves that propagate in all directions. When the refractory tail of this wave reached the middle of the medium, S2 stimulus was applied, parallel with the S1 stimulus but only three-quarters of the length of medium. This will produce a second wave front with a curly tip, generating reentry.

The results from electrical simulation were then coupled with intracellular Ca\(^2+\) transient, which served as the inputs for mechanical simulation. The mechanical simulation was carried out up to 12 s for sinus pacing, and 10 s for reentry, to obtain the steady-state responses. For both cases, we use the BCL of 600 ms. From this simulation, we computed the ventricular hemodynamic responses, such as pressure, volume, and contractile ATP consumption rate.

### 3 RESULTS AND CONCLUSIONS

Our simulation in single cell showed that compared to the WT condition, G229D mutation increased the \( I_{Ks} \) density (Fig. 1A-C), which led to shorten ventricular \( \text{APD}_{90} \) (Fig. 1D-F). The measured \( \text{APD}_{90} \) under WT condition were 289ms, 364ms, and 290ms for the endo, M, and epi cells, respectively. Under mutation, the \( \text{APD}_{90} \) were slightly shortened about 6%, 0.3%, and 8% for
endo, M, and epi-cells, respectively. This result was consistent with the study from Hasegawa et al.[5], that the ventricular APD$_{90}$ was not markedly affected by the G229D mutation. Based on APD$_{90}$ restitution curves (Fig. 1G-L), mutation maintained shorter APD$_{90}$ than that of under WT condition, for all BCL and DI ranges. Under the WT condition, the alternans occurred at BCL of 250 ms and DI of 100 ms. However, alternans could not be observed under the G229D mutation condition. This is because the slope of APD$_{90}$ restitution curves under mutation is less steep than that of under WT condition, resulting in more stable activation.

**Fig. 1** Single cell simulation responses on different type of myocardial model (endo, M, epi) for WT and G229D mutation conditions. Profiles of $I_{Ks}$ (A-C); shape of ventricular action potential (D-F); APD$_{90}$ restitution curves vs. BCL (G-I); APD$_{90}$ restitution curves vs. DI (J-L).

In 3D ventricular tissue, the repolarization phase was faster with G229D mutation than WT condition during sinus pacing (Fig. 2A). During reentry, mutation generated shorter wavelengths of membrane potential propagation (Fig. 2B), resulting in higher reentrant rate. The higher reentrant rate led to higher beat rate in the ventricle (see the mechanical response figures), indicating the occurrence of ventricular fibrillation. The simulated pressure waveforms showed that mutation decreased the LV and aortic pressure, both during sinus pacing (Fig. 2C) and reentry (Fig. 2D). This indicates that ventricle has less force to pump blood out of the ventricle. Based on the PV loop curves, mutation generated smaller loop, both during sinus (Fig. 2E) and reentry (Fig. 2F), indicating smaller stroke work (i.e., amount of work performed by the ventricle in one cycle ventricular contraction) under mutation. Mutation also decreased the ATP consumption rate by approximately 29.4% during sinus pacing (Fig. 2G), and 20.8% during reentry (Fig. 2H).
In conclusion, our simulation study revealed that G229D KCNQ1 mutation can induce ventricular fibrillation by altering electrical and mechanical behavior of the heart. In cellular level, the enhancement of $I_{Ks}$ in G229D mutation shortened ventricular APD$_{90}$ about 6%, 0.3%, 8%, in endo, M, and epi-cells, respectively. In 3D tissue, mutation accelerated repolarization phase during normal sinus rhythm and shortened wavelengths of electrical propagation during reentry. Furthermore, mutation decreased the ventricular pumping functions by reducing the pressure, stroke work, and contractile ATP consumption rate, both during normal sinus rhythm and reentry.

ACKNOWLEDGEMENT

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PREDICTING SUPRASPINATUS TEAR PROPAGATION BASED ON TENDON TISSUE DEGENERATION

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SUMMARY

Degenerative rotator cuff tears remain a clinical significant problem that is difficult to treat. Subject-specific finite element modeling provides an opportunity to assess the effects of important factors such as tendon tissue degeneration. This study develops computational models of the rotator cuff to investigate the effects of tissue degeneration on the propagation of supraspinatus tendon tears and finds that tendons that are more severely degenerative are at greater risk for tear propagation at loads as low as 100N. Overall, this study identifies effects of tendon degeneration on supraspinatus tear propagation, supporting the early detection and treatment of rotator cuff tears.

Key words: rotator cuff tears, finite element model, subject-specific model

1 INTRODUCTION

Degenerative rotator cuff tears are a significant clinical problem due to their high incidence rate and no clear consensus on treatment [1,2]. Poor tendon quality due to severe degeneration has been cited as a potential factor related to poor patient outcomes after repair [3,4]. Previous studies have found that chronic tears are associated with greater tissue degeneration and that tendon mechanical properties decrease with increased degeneration [5,6]. Therefore, there is an important relationship between the amount of degeneration and the mechanical behavior of tendons with degenerative tears. Computational models could be developed to assess the effects of different pathologies on the behavior of the rotator cuff, but previous models are limited by their simplifying assumptions of material properties and inability to predict tear propagation. The objective of this study was to investigate the effects of tissue degeneration on propagation of rotator cuff tears by using an experimentally validated, subject-specific finite element model of supraspinatus tendon. It was hypothesized that tears in tendons with higher amounts of degeneration (decreased modulus and failure properties) would propagate at lower loads.

2 METHODOLOGY

An experimentally validated finite element model of the rotator cuff was developed using subject-specific geometry and anisotropic material properties taken from an intact cadaveric shoulder specimen. Material properties for the anterior, middle, and posterior thirds of the supraspinatus tendon were experimentally measured and determined using a single family fiber-reinforced Neo-Hookean material model [7]. The finite element model was validated by applying the experimental boundary conditions to the intact model and predicting a similar strain distribution (within 3% strain). Tears were introduced to the model geometry and tear propagation was modeled by inserting novel cohesive elements along potential propagation paths. The failure behavior of the cohesive elements was defined based on a cohesive traction-separation law [8] that includes strength and fracture toughness of the tendon material through the parameters $\sigma_{\text{max}}$ (ultimate stress) and $\delta_{\text{max}}$ (maximum separation before complete failure):

$$\sigma = k_c \delta$$
The stiffness of the cohesive elements, $k_c$, is defined by the failure properties of the material:

$$k_c = \frac{S \sigma_{\text{max}} - 1}{1 - S \sigma_{\text{init}} \delta_{\text{max}}}.$$ 

The fracture toughness of supraspinatus tendon at the macroscopic scale was estimated from the change in mechanical energy required to increase tear area [9] using previously collected experimental cyclic loading data [10]. Tears were 1 cm wide and located in the center of the tendon anterior-posterior width, at the posterior edge of the tendon, or at the anterior edge. The material properties obtained from mechanical testing were varied across the tendon width for each tear location to investigate the effect of tissue degeneration on tear propagation (Table 1). A tendon with minimal degeneration was assigned an ultimate stress of approximately 6 MPa, while severe degeneration was assigned an ultimate stress of 2 MPa [6]. The medial edge of the tendon was displaced 5 mm at an angle representing 70° of glenohumeral abduction to induce propagation. Model outputs included critical load required to propagate the tear, and principal stress and strain at the tear tips.

### 3 RESULTS AND CONCLUSIONS

Tendons with the most degeneration required the lowest stress to propagate tears (Fig. 1). The critical load for tear propagation was highest in the posterior third, with loads ranging from 207-488 N. Both anterior and middle tears showed similar loads required to propagate the tear, ranging from 120-280 N. Stress and strain at the tear tips decreased with increased degeneration, with values generally higher at the anterior tip than at the posterior tip (Table 1). Although tendon stress and strain decreased, tendon tissue at the tear edges reached the ultimate stress at lower loads in tendons with more severe degeneration, compared to less degenerative tendon tissue. Therefore, for the same amount of displacement, the tear with severe degeneration was much larger than for minimal or moderate degeneration.

**Fig. 1:** Simulations for a 1 cm-wide tear for minimal, moderate, and severe degeneration. For the same amount of displacement, the tear for severe degeneration was twice as large as the tear for minimal degeneration. Much lower stresses were required to propagate the tear for severe degeneration.
The primary finding for the geometry and material properties of the model was that tendons at more severe stages of degeneration are at higher risk for tear propagation, confirming the hypothesis under study. This confirms the importance of diagnosing and treating rotator cuff tears early, before the tendon can degenerate further and tears can propagate. For tendons with moderate and severe amounts of degeneration, the load required to propagate the tear ranged from 100-200 N. This is within the range of supraspinatus activity experienced during activities of daily living, indicating that propagation may be more likely in patients with severe tendon degeneration. A limitation of this study was that the material properties used to estimate tissue degeneration were from a study that measured degeneration at the tendon insertion, and not from the tendon mid-substance. Future simulations of tear propagation due to tendon degeneration should take into account changes in mechanical properties and fiber orientation throughout the whole tendon due to degeneration.

**REFERENCES**


| Table 1: Critical Failure Values at Tear Propagation by Amount of Degeneration |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                | Ultimate Stress (MPa) | Fiber Modulus (MPa) | Load (N) | Tear Tip Stress (MPa) | Tear Tip Strain (% Strain) |
|                                | Anterior | Posterior | Anterior | Posterior | Anterior | Posterior |
| Ant                             | Min      | 5.8       | 9.9      | 284      | 4.0      | 8.5      | 22.7     | 24.1     |
|                                | Mod      | 4.0       | 6.6      | 211      | 3.3      | 6.1      | 18.3     | 19.3     |
|                                | Severe   | 2.0       | 3.3      | 122      | 2.3      | 3.1      | 14.8     | 12.1     |
| Mid                             | Min      | 5.8       | 14.4     | 280      | 6.7      | 5.2      | 32.6     | 22.1     |
|                                | Mod      | 4.0       | 9.6      | 215      | 5.3      | 4.2      | 24.8     | 18.7     |
|                                | Severe   | 2.0       | 4.8      | 132      | 2.9      | 2.4      | 15.6     | 12.9     |
| Post                            | Min      | 4.3       | 7.9      | 488      | 7.7      | 2.2      | 18.9     | 12.1     |
|                                | Mod      | 2.9       | 5.3      | 357      | 5.4      | 1.7      | 17.2     | 10.2     |
|                                | Severe   | 1.5       | 2.6      | 207      | 2.6      | 1.0      | 10.4     | 7.0      |
IMAGE SEGMENTATION TECHNIQUES FOR CARDIOVASCULAR BIOMEDICAL APPLICATIONS

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SUMMARY

The work addresses several image segmentation techniques for generation of individualized computational domains for various cardiovascular biomedical applications. We present a new technique for image segmentation and mesh generation of heart ventricles from dynamic contrast enhanced Computed Tomography images.

Key words: image segmentation, mesh generation

1 INTRODUCTION

In this paper we develop and present methods and algorithms for construction of patient-specific discrete geometric models for cardiovascular biomedical applications. Each application imposes specific restrictions on both the input medical images and the output patient-specific discrete model, and, therefore, requires a specific class of 3D reconstruction methods.

Personalized modeling of cardiac hemodynamics received a great deal of attention, and a vast number of models have been described in the literature. Local hemodynamics modeling requires the patient-specific local reconstruction of coronary and cerebral arteries \cite{1, 2}. Given an imaging dataset, one performs image segmentation, volume reconstruction, and numerical discretization.

Modeling of cardiac electrophysiology may be formalized as the full-scale study of the heart electrical activity from inner-cellular level to the cardiac tissues level \cite{3}. The reconstruction of personalized anatomical model of the pathological heart is one of the crucial steps in electrophysiology modeling. The bidomain model requires an accurate anatomical model of patient heart and myocardium anisotropy structure. Patient-specific segmentation should be focused on the heart tissues as well as surrounding organs in the thorax region.

The cornerstone of medical image processing is the segmentation process that assigns labels to the voxels. Various medical image segmentation techniques have been developed \cite{4, 5, 6}. The most promising fully automatic segmentation methods belong to atlas-based techniques. The patient-specific segmentation is obtained from the atlas of presegmented images. This atlas should contain enough different cases for accurate mapping of the new patient data. Thus atlas-based approach requires huge amount of segmentation expert work for preparation of atlases and the development of algorithms dealing with big data. Semi-automatic segmentation technologies require interaction with the operator. They are used primarily for precise local segmentation, where only one organ or tissue is processed. In our previous work we used several techniques for adaptation of the once segmented reference human model to different individuals. This technique relies on anthropometric scaling, control points mapping and supervised segmentation \cite{7, 8}.

In this work we introduce our previous patient-specific segmentation techniques and present in detail methods for segmentation and mesh generation of heart ventricles using dynamic contrast enhanced Computed Tomography (ceCT) images.
2 METHODOLOGY

Vascular segmentation techniques were addressed in details in our previous works [9, 10]. We will briefly highlight the main steps of our pipeline. Input data are DICOM datasets obtained with contrast enhanced Computed Tomography Angiography (ceCTA). Essential steps of this method consist of aorta segmentation, computation of vesselness values, searching branches of aorta arch or ostia points, and removing segmentation errors near aorta boundary. We use fast variant of the isoperimetric distance trees algorithm [11] for aorta identification. The coronary arteries network is reconstructed by the use of Frangi vesselness filter [12], which is based on Hessian 3D analysis of the ceCTA image and is applicable to all tubular structures in the vascular dataset.

We examined several techniques for automatic segmentation of soft tissues, and developed methods for detailed segmentation of the heart [13], and automatic segmentation of surrounding tissues in the thorax [10]. In this work we will focus on segmentation and mesh generation for dynamic datasets.

2.1 Dynamic cardiac images segmentation

We developed the technology for generation of a dynamic mesh for heart ventricles. In this work we focus on the left ventricle. We tested the proposed pipeline on the anonymized dynamic chest ceCT dataset of 100 images with $512 \times 512 \times 480$ voxels and $0.625 \times 0.625 \times 0.25$ mm resolution.

At the first stage we applied 3D non-local means smoothing [14], cropped, and resampled the input images. Resulting smoothed images have $96 \times 96 \times 96$ voxels and $1.25 \times 1.25 \times 1$ mm resolution. We selected several images for manual segmentation at different stages of cardiac cycle: the beginning of systole (image #0), the end of systole (image #30), and the middle of rapid inflow during diastole (image #50). We used levelset method from ITK-SNAP package [15] for user-guided segmentation, and segmented four materials: left ventricle, left atrium, aorta, and right ventricle and atrium combined (Fig. 1a).

![Figure 1: Segmentation of ceCT images: (a) manual segmentation of image #50, (b) automatic segmentation of image #80. Segmentation colors: left ventricle (red), left atrium (blue), aorta (green), right ventricle and atrium (yellow).](image)

At the next stage we applied machine learning techniques to segment all images. We constructed the random forest classifier, trained on the manually segmented images. The result of classification is post-processed using a combination of mathematical operations: dilation, erosion, and construction of connected regions (Fig. 1b).

At the final stage we reconstruct the position of valve planes by the principal component analysis of the interfaces between left ventricle and left atrium, and between left ventricle and aorta. We compute the mean position of the valve planes across all images. We assume these planes will be fixed during the cardiac cycle for simplicity of mesh generation and numerical modeling.

We construct the unstructured tetrahedral mesh for the first image #0 using Delauney triangulation from CGAL Mesh library [16]. The left ventricle domain is defined implicitly by segmented image,
the valve planes are defined explicitly. We also split each tetrahedron with all four nodes lying on the boundary, enforcing at least one internal node in each tetrahedron. We deform the mesh by node movements for each subsequent image. At the first stage we move only boundary nodes simultaneously propagating and smoothing the surface mesh. We shift each boundary node in the direction of weighted sum of two vectors: vector along the surface normal towards the new position of the boundary surface (weight 0.2), and vector towards the center of surrounding nodes (weight 0.4). We repeat this procedure until the maximum movement distance drops below $\varepsilon = 0.001$ mm, or until the maximum number of 2000 iterations is exceeded. We pay special attention to the nodes on the valve planes: they should always stay on the planes (Fig. 2).

At the second stage we apply simultaneous untangling and smoothing algorithm [17, 18]; the boundary nodes are fixed, and only the internal nodes are shifted. As mentioned above, we enforced all tetrahedra to have at least one internal node, thus we greatly improved the robustness of untangling stage.

As the final result we constructed the series of topologically invariant dynamic meshes for the left ventricle based on the dynamic ceCT images (Fig. 3) containing 14033 mesh nodes and 69257 tetrahedra.

3 RESULTS AND CONCLUSIONS

We introduced several segmentation techniques for cardiovascular biomedical applications developed in our group. The detailed algorithms and corresponding results are presented in our previous papers [9, 10, 13]. A new technique for segmentation and mesh generation using dynamic ceCT images was proposed, and results are presented in Figs. [15]. The segmented images and constructed meshes are used in hemodynamics and electrophysiology modeling [7, 8, 9].

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FLOW FIELD SIMULATION IN THE AORTIC VALVE WITH VARIOUS ANGLE BETWEEN THE AORTIC VALVE ORIFICE AND THE ASCENDING AORTIC AXES

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SUMMARY

Two patient cases analysis: We measured the angles between the aortic valve orifice and the ascending aortic axes from CTA images of a normal case and two patient cases with neo-aortic valve insufficiency after arterial switch operation. The angles are 0, 16.5 and 39 degree respectively. We propose hypothesis: the angles cause the difference of pressure distribution on the both sides of two leaflet surfaces. It increase the risk of aortic valve insufficiency because of leaflets mismatch.

Methods: The three 2-dimensional geometries of aortic valve were created, and applied blood pressure of 100 and 92mmHg respectively on the left ventricular outflow tract and aortic side, and then simulated the flow pattern and difference of pressure drop across the left and right leaflets through solving the steady flow. Results: In the normal case, mainstream direction maintain straight. For patient 1, main stream direction turn along axis of the aortic valve orifice and the ascending aortic in the left ventricular segment. Patient 2, mainstream direction turn along axis in the aorta. Compared with the normal case, the difference of pressure drop across the left and right leaflets were 94Pa and 413Pa respectively. Conclusions: compared with normal case, aortic valve orifice direction increase the difference of pressure drop across the left and right leaflets. Further research will evaluate the axial displacement, contact force and coaptation of leaflets with the fluid structure coupled method.

Key words: Arterial Switch Operation, Aortic Valve, Orifice Direction, Closure Performance

1 INTRODUCTION

The arterial switch operation (ASO) is now preferred surgical approach to treat complete transposition of the great arteries (TGA) presenting in the neonatal period. Although this surgery is thought to be an improvement compared with the earlier procedures, late cardiac complications have been reported in children. Neo-aortic valve insufficiencies are approximate 15% after a 75 month follow-up. At least moderate neo-aortic regurgitation is present in 3.4%.^1^ We measured the angles between the aortic valve orifice and the ascending aortic axes from CTA images of a normal case and two patient cases with neo-aortic valve insufficiency after arterial switch operation. The angle are 16.5 degree and 39 degree respectively measured from CTA images of the two patients (Figure 1 middle and right). The angle is close to 0 degree measured from CTA images of the normal case (Figure 1 left). Based on the medical background, we propose hypothesis: the angle between the aortic valve orifice and the ascending aortic axes cause the difference of pressure distribution on the both sides of two leaflet surfaces. It increase the risk of aortic valve
insufficiency because of leaflets mismatch.

In order to investigate the effect of angle between the aortic valve orifice and the ascending aortic axes on closure performance of neo-aortic valve, we create 2-dimensional fluid models of aortic root in the opened state and accomplish the computational fluid dynamic simulation. From the simulation results, we investigated the flow field of the two patient cases and the normal case in terms of the flow pattern and the difference of pressure drop across the left and right leaflets.

![Figure 1: CTA image (left) a normal case, (middle) patient 1, (right) patient 2](image)

### 2 METHODOLOGY

The three 2-dimensional geometries of aortic valve were created using the geometric constraints and modeling dimensions suggested by Marom [2], namely normal, patient 1, patient 2. The parametric dimensions (sinotubular junction diameter, DSTJ=9.7mm, sinus diameter, SD=12.3mm, sinus height, h_s=6.51 mm, valve height, h_L=42 mm) are scaled with respect to the aortic annulus diameter (DAA =9.7 mm). Initial geometry of leaflet is an opened state with an angle of 60 degrees on the aortic annulus. A thickness of the valvular leaflets is considered 0.3 mm. The lengths of D1, D2=20mm were added upstream and downstream representing the initial tract and ascending aorta. (Figure 2)

![Figure 2: Geometries of aortic valve (left) a normal case, (middle) patient 1, (right) patient 2](image)

The 2-dimensional geometries of the fluid were created in SolidWorks 2013 (SolidWorks, Concord, MA). For all meshes, ANSYS ICEM CFD was employed as the mesh generator. The number of nodes and elements are 1629 and 1521 respectively for the model A. all models were applied blood pressure of 100 and 92mmHg respectively on the left ventricular outflow tract and aortic side. The method of computational fluid dynamics was applied to accomplish steady state calculation with double precision format. All models of aortic valve were solved and post-processed by commercial finite element software Fluent on Xeon 8 3.60 GHz workstation with 16.0 GB RAM.

### 3 RESULTS AND CONCLUSIONS

#### 3.1 Results
Figure 3 show the flow pattern through the aortic valve of the two patient cases and the normal case. In the normal case, mainstream direction maintain straight (Figure 3 a). For patient 1, (Figure 3 b c) main stream direction turn along axis of the aortic valve orifice and the ascending aortic in the left ventricular segment. Patient 2, mainstream direction turn along axis in the aorta.

![Flow pattern through the aortic valve](image)

Figure 3 flow pattern through the aortic valve (left) a normal case, (middle) patient 1, (right) patient 2

The pressure drop across the left and right leaflet of each aortic valve. From the state flow simulation results of the two patient cases and the normal case, we extracted node pressure value, and then calculated the node mean pressure of each leaflet surface (Table 1). Compared with the normal case, the difference of pressure drop across the left and right leaflet between of the two patient cases were 94Pa and 413Pa respectively.

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3.2 Discussion

In this paper, we measured the angles between the aortic valve orifice and the ascending aortic axes from the CTA image of two collected patient cases with aortic insufficiency after arterial switch operation, and then created three flow field model of aortic valve, namely a normal case and two patient cases. We investigated the flow field in terms of the flow pattern and the pressure difference across leaflets.

From the flow resistance perspective, local resistance increases is caused by main flowing direction change because of the angle between the aortic valve orifice and the ascending aortic axes. In the follow-up study, quantitative calculation for the relationship between energy loss through the aortic valve and the orifice direction will be planned.

From the mechanism of valve closure as a result of flow deceleration, Flow velocity on the region behind the valve leaflets is lower than it between left and right leaflets. Decelerating flows between left and right leaflets have little effect on the region behind the valve leaflets, thus generate reverse pressure drop. Leaflets cannot stand any pressure drop. So decelerating flow pushes the leaflets into the left ventricle, and releases the pressure drop across the leaflet at the same time. Compared with normal case, the angles between the aortic valve orifice and the ascending aortic axes result in the change of pressure distribution on the two sides of leaflet surface for the two patient cases. The difference of pressure drop across the left and right leaflet increases with the angles between the
aortic valve orifice and the ascending aortic axes. It suggest that further research is need to quantify the relationship between pressure drop across leaflets for patient cases and leaflet dynamics behavior. We suspect that the difference of pressure drop across the left and right leaflets may cause leaflet mismatch during closure, and then result in aortic valve insufficiency.

Research limitations: In this paper, we only simulated steady flow in the opening state of aortic valve and analyzed flow pattern and the difference of pressure difference across the open valve between the left and right leaflet. Further study will be needed to investigate effect of aortic valve orifice direction on closing process of aortic valve with the fluid structure coupled simulation.

3.3 Conclusions
In this paper, we created three geometrical models of open aortic valve based on CTA images of a normal case and two patient cases with neo-aortic valve insufficiency after arterial switch operation. and then investigated the flow pattern and difference of pressure drop across the left and right leaflets from the results of computational fluid dynamics through solving the steady flow. From the mechanism of valve closure as a result of flow deceleration, compared with normal case, aortic valve orifice direction increase the difference of pressure drop across the left and right leaflets. Further research will evaluate the axial displacement, contact force and coaptation of leaflets with the fluid structure coupled method. We suspect that the difference of pressure drop may cause leaflet mismatch during closure, and then result in aortic valve insufficiency.

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ACKNOWLEDGE

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CENTRAL BLOOD PRESSURE ESTIMATION: A REDUCED ONE-DIMENSIONAL MODEL OF THE AORTIC CIRCULATION

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SUMMARY

We present a one-dimensional (1-D) model of the 116 larger arteries in the systemic circulation to investigate how peripheral vessels affect the central (aortic) blood pressure waveform. This is achieved following two model reduction approaches based on (i) the calculation of outflow boundary conditions of the reduced model from the flow distribution of the complete model; and (ii) the systematic lumping of peripheral 1-D model vessels. Both methods aim to preserve the total resistance and compliance of the original model. Results are presented for a population of virtual subjects which enables us to assess the impact of individual model parameters on the aortic pressure waveform.

Key words: patient-specific modelling, 1-D blood flow modelling, haemodynamics

1 INTRODUCTION

The aortic or central blood pressure (CBP) waveform provides clinically relevant information for the diagnosis, prognosis and treatment of hypertension, which is related to cardiovascular diseases such as heart failure, stroke and coronary artery disease. In the clinic, CBP can only be accurately assessed via invasive procedures which rely on pressure-sensing wires or cardiac catheters. Magnetic resonance imaging (MRI) offers non-invasive, accurate measurements of aortic geometry and blood flow waveforms. Approximate measurements of peripheral pressure can be obtained non-invasively through tonometry. Patient-specific blood flow modelling can be used to estimate the CBP waveform from these non-invasive measurements.

One-dimensional (1-D) blood flow modelling can simulate pulse waves in the arterial system. A number of \textit{in vivo} \cite{1, 2, 3, 4}, \textit{in vitro} \cite{5, 6, 7, 8, 9}, and 3-D numerical \cite{10, 11} studies have shown that 1-D modelling can accurately reproduce the main features of the pressure, flow and area waveforms. This work uses a coupled 1-D/0-D model of the arterial system composed of the 116 larger arteries of the systemic circulation. Arteries are represented as 1-D segments and outflow boundary conditions are represented by 0-D lumped parameter models of the perfusion of more peripheral vessels. The numerical simulations are run in Nektar1D, a validated computational framework of arterial haemodynamics \cite{12}.

The aim of this work is to show how a 1-D model of aortic blood flow is able to accurately estimate CBP for a population of 22 virtual patients. As an input to the model, flow and pressure waveforms are measured at locations which are commonly measured \textit{in vivo} (aorta, carotid and brachial arteries).

2 METHODOLOGY

In order to assess the effect which more peripheral arteries have on the CBP waveform, we perform a model reduction on a 116-artery model, created using the clinical data collected in \cite{13}. The resulting
reduced model only includes the thoracic aorta and the three supraortic arteries. This model reduction is performed following two different approaches: (i) based on the peripheral outflow distribution at terminal vessels and (ii) through a systematic lumping of peripheral 1-D vessels which preserves the total resistance and compliance of the original model, as described in Epstein’s paper [14].

2.1 Model reduction based on the peripheral outflow distribution

We choose our boundary conditions based on the flow distribution at the outlet of each terminal vessel. Our boundary conditions are represented by 0-D models known as three-element Windkessel models which account for peripheral compliance and resistance. Terminal vascular compliance is assumed to be proportional to mean outflow: larger peripheral arteries should accommodate larger volumes of blood. Vascular resistance is assumed to be inversely proportional to mean outflow: smaller peripheral arteries should offer a greater resistance to flow.

2.2 Model reduction based on a systematic lumping of 1-D vessels

Following this approach, 1-D vessels are lumped into two-element Windkessel models. At bifurcations, these parallel 0-D models are combined to form a new three-element Windkessel model which is connected to the outlet of the parent vessel. Epstein’s 1-D model reduction method was originally applied to both a model of the 55 larger systemic arteries and an extended 67-artery model. In the current work, this method is modified to account for anastomosis in the arteries of the hands and the brain of the 116-artery model.

![Figure 1](image)

**Figure 1**: Virtual database methodology applied to the 116-artery model. Modified from [15].

Using the 116-artery model as the baseline, we have created a virtual population of 22 virtual healthy subjects following Willemet’s approach [15] as shown in Figure 1. Parameters for these virtual subjects are varied within healthy ranges observed in the clinical literature. Non-physiological results for blood pressure and flow are filtered out. Each physiological virtual subject model is reduced follow-
ing previous reduction approaches. A local sensitivity analysis on the virtual population allows us to analyse the accuracy of the reduced aortic model for a range of individual model parameter variations.

3 RESULTS AND CONCLUSIONS

Results suggest that the reduced model captures best the CBP waveform by adjusting the net peripheral resistance, \( R_T \). This reduction follows the peripheral outflow distribution approach (Section 2.1) for the determination of the 0-D model parameters. Figure 2 shows the comparison between the simulation results for the baseline 116-artery model and the reduced model.

<table>
<thead>
<tr>
<th>Parameter change</th>
<th>Ascending Aorta ( P ) (kPa)</th>
<th>Descending Aorta ( P ) (kPa)</th>
<th>Descending Aorta ( Q ) (mL/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline ( C_T, R_T )</td>
<td>![GraphAscendingAortaBaselineReduced]</td>
<td>![GraphDescendingAortaBaselineReduced]</td>
<td>![GraphDescendingAortaBaselineReduced]</td>
</tr>
<tr>
<td>Baseline ( R_T )</td>
<td>![GraphAscendingAortaBaselineReduced]</td>
<td>![GraphDescendingAortaBaselineReduced]</td>
<td>![GraphDescendingAortaBaselineReduced]</td>
</tr>
<tr>
<td>Baseline ( C_T )</td>
<td>![GraphAscendingAortaBaselineReduced]</td>
<td>![GraphDescendingAortaBaselineReduced]</td>
<td>![GraphDescendingAortaBaselineReduced]</td>
</tr>
</tbody>
</table>

Figure 2: Baseline model and reduced model (flow distribution-based reduction): pressure at the ascending and descending aorta and flow at the descending aorta. Top: original model parameter values are used in the reduced model; middle: adjusted total compliance (\( C_T \)); bottom: adjusted net peripheral resistance (\( R_T \)).

After the in silico validation of the aortic model using virtual patients, we will work on the in vivo validation. Patient-specific model parameters are found using in vivo aortic geometry and luminal cross-sectional area, aortic flow waves, and peripheral blood pressures. The geometry of the aorta and the supra-aortic arteries, as well as the aortic flow, is obtained from MRI data. Non-invasive pressure measurements are obtained from tonometry data.

4 ACKNOWLEDGMENTS

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REFERENCES


A NOVEL FLUID-SOLID-GROWTH-TRANSPORT (FSGT) FRAMEWORK FOR MODELLING THE EVOLUTION OF INTRACRANIAL ANEURYSM DISEASE

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SUMMARY

Computational models of intracranial aneurysm (IA) evolution do not explicitly represent endothelial cells (ECs). Here, we extend an IA Fluid-Solid-Growth framework to model Transport and to explicitly represent the morphology of the endothelium; we consider the competing influences of both cyclic deformation and wall shear stress to guide EC shape and alignment. We then establish a model which links EC morphology to EC permeability and the growth of the aneurysm. We envisage improved modelling of the role of the endothelium may help to differentiate between stable IAs and those likely to rupture.

Key words: intracranial aneurysm, endothelial cells, permeability, wall shear stress, cyclic stretch

1 INTRODUCTION

IA detection is increasing due to improved imaging facilities in hospitals, and the cost of this disease is increasing. Hence there is an urgent need to revolutionise IA management and treatment, e.g., by developing: diagnostic tools to distinguish stable IAs from those likely to rupture, therapeutic approaches to stabilise IAs, and clinical tools to personalise, evaluate and optimise treatment strategies. Computational modelling can assist in achieving these goals.

It is widely accepted that the flow environment plays an influential role on aneurysm progression and its fate. However, the mechanobiological mechanisms that links flow related stimuli to the fate of the IA remain unclear. Moreover, the cells that sense the flow-related stimuli (wall shear stress and cyclic deformation) are not explicitly represented. Consequently, models are limited in their predictive abilities. Here we propose a novel fluid-solid-growth-transport (FSGT) framework enriched with an explicit representation of the endothelial morphology. We assume that the permeability is related to the morphology of endothelial cells (ECs). This approach enables us to link IA evolution to EC morphology.

2 METHODOLOGY

We begin by overviewing the computational framework (see Figure 1). It is based on the existing FSG framework [1] that models the fluid and solid mechanics of arterial wall and explicitly links mechanical stimuli to growth and remodelling (G&R) of the arterial constituents. We make further improvement by coupling the FSG with a model of chemical transport [2] to form a novel FSG Transport (FSGT) framework.
Figure 1: Workflow of the FSGT framework: (a) structural model of arterial wall (b) Computational Fluid dynamics (CFD) and transport simulations (c) results from mechanical, (CFD) and transport simulations provide inputs to the G&R algorithms; (d) chemical and mechanical stimuli are inputs to growth and remodeling algorithms which update the constitutive model of the tissue.

3 RESULTS AND DISCUSSION

We model the morphology of ECs subject to competing WSS and CS stimuli [3,4] and illustrate the predicted EC distribution on a patient-specific aneurysm. Simple hypotheses linking EC permeability to EC morphology are proposed and influence on IA evolution is simulated.

This approach enables IA evolution to be intimately linked to the morphology of the endothelium. We envisage that if we can predict EC morphology and its relationship to the remodeling of IA tissue, this may assist in stratifying those IAs that are stable from those that require interventional treatment.

REFERENCES

A CONSTRAINED MIXTURE MODEL OF THE LEFT VENTRICLE AND ITS APPLICATION TO SIMULATING MYOCARDIAL INFARCTION

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SUMMARY
Myocardial infarction results in a change to the mechanical environment of the left ventricle (LV). Consequently, following an MI, both the localised infarct region and the LV will remodel. Computational models may help us to predict whether the remodelling will have a deleterious impact on LV mechanical function. We model the left ventricle as a nonlinear elastic spherical membrane using a constrained mixture approach. Constituents are configured in the loaded configuration to optimise the mechanical function of the heart. First, we illustrate a conceptual model of the healthy ventricle and its adaption to altered mechanical loading. We then consider its application to simulate myocardial infarction: an immediate loss of myocytes is prescribed and we simulate the growth and remodelling of the infarct.

Key words: growth and remodelling, cardiac biomechanics, myocardial infarction

1 INTRODUCTION
Coronary heart disease is the leading cause of mortality, both within the UK and worldwide, accounting for about 20% of all deaths each year. One of the most common outcomes of coronary heart disease is myocardial infarction (MI), which may lead to heart failure. To prevent chronic heart failure from developing, adequate measures must be taken as soon as possible after an MI. Untreated, or unsuccessfully treated, MI may lead to extensive fibrous scarring, with expansion of the infarct region, hypertrophy of remote myocardium and overall ventricular dilatation. Consequences of this adverse remodelling process include loss of cardiac function, manifest as reduced ejection fraction and lethal arrhythmias, such as ventricular fibrillation, resulting in cardiac arrest. In addition to goals of improved quality of life and life expectancy for people suffering from MI, there are economic demands to make diagnosis and treatment more cost-effective. Unfortunately, as the processes underlying heart function are extremely complicated, experimental approaches alone cannot identify key fundamental mechanisms of the disease that often operate simultaneously. Mathematical modelling may provide insight into LV remodelling post MI and predict the long term change to LV mechanical function. This may lead to the development of new therapeutic strategies[1] and assist in stratification of management of the disease.

2 METHODOLOGY
We model the left ventricle as non-linear elastic spherical membrane, e.g. see [2, 3]; the tissue is modelled as a constrained mixture consisting of ground matrix, collagen and cardiac myocytes. The
The governing equation for mechanical equilibrium is:

\[ p = \frac{2H}{R^3} \left( m_e^{GM} \sigma_e^{GM}(\lambda) + m_m^{M} \sigma_m^{M}(\lambda^{M}) + m_c^{C} \sigma_c^{C}(\lambda^{C}) \right) \]  

(1)

where \( m^J \) represents mass density ratios of the constituents (\( J = GM, M, C \)) and \( \sigma^J \) denotes the Cauchy stresses experienced by the collagen(C), myocytes(active & passive) (M) and the ground matrix(GM); \( \lambda^{M} \) and \( \lambda^{C} \) denote the stretches of the myocytes and collagen; \( H \) and \( R \) denote the unloaded thickness and radius of the sphere.

The mechanical response of the ground matrix is defined relative to the unloaded configuration of the ventricle whereas collagen and myocytes are assumed to be configured in the loaded configuration such that the left ventricle achieves an optimum mechanical function. The loaded configuration is characterized by four states during the pressure-volume relationship (see Fig. 1). For simplicity, we assume that optimum mechanical function is achieved by configuring the constituents relative to one of these four states. More specifically, we assume:

- cardiac myocytes are configured with at attachment stretch (\( \lambda_{AT}^M > 1 \)) at end diastole so that they can achieve maximum active stress. The value of this stretch can be inferred from force-length relationship data for a myocyte.
- collagen is configured to act as a protective sheath against over distension. More specifically, we suppose that it is configured to achieve a maximum (attachment) stretch, (\( \lambda_{AT}^C > 1 \)), during the cardiac cycle.

![Figure 1](image.png)

**Figure 1:** (a) A representation of the changes in the pressures and volumes within the left ventricle over a cardiac cycle.

Given that collagen and myocytes are configured in the loaded configuration they have distinct natural reference configurations at which they begin to bear passive load. These are related to the unloaded matrix stretch (configuration \( \Omega_0 \), see Fig. 2) via their recruitment stretches, i.e.

\[ \lambda_R^{J} = \lambda/\lambda_{AT}^{J} \quad (J = M, C) \]  

(2)

The heart tissue may remodel in response to perturbations to its mechanical environment. We simulate remodelling the reference configurations of the constituents so that they maintain their preferred homeostatic stretches in the loaded configuration, i.e.

\[ \frac{d\lambda_R^{C}}{dt} = \alpha_C \left( \max(\lambda^{C}|\Omega_A,\Omega_B,\Omega_C,\Omega_D) - \lambda_{AT}^{C} \right) \quad ; \quad \frac{d\lambda_R^{M}}{dt} = \alpha_M \left( \frac{\lambda^{M}|\Omega_A - \lambda_{AT}^{M}}{\lambda_{AT}^{M}} \right) \]  

(3)

where, \( \alpha_C, \alpha_M \) are remodelling rate parameters.
Similarly, the mass-density of collagen can adapt:

$$\frac{dm^C}{dt} = \xi m^C \left( \max(\lambda^C|_C, \lambda^A|_A) - \lambda^C_{AT} \right)$$

where $\xi > 0$ is a growth factor.

To simulate myocardial infarction, we prescribe an instantaneous complete loss of myocytes, i.e.,

$$m^C(t = 0^+) = 0$$

and allow the collagen to adapt.

### 3 RESULTS AND CONCLUSIONS

Figure 3 illustrates the pressure-volume loop for our conceptual model of the left ventricle. This illustrative mathematical model is used to explore hypotheses for how constituents/myocytes are configured during the cardiac cycle and how the scar region evolves following a MI. Results obtained with a prescribed degradation of myocytes, indicative of an infarction are shown in Figure 4. Interestingly, we observe that the assumption of constant collagen attachment stretch gives rise to an unrealistic remodelled thickness of the infarct and hence a more sophisticated constitutive model for growth and remodelling of the collagen microstructure is required. Following Aparicio et al [4], we sophisticate the model to incorporate a triangular distribution function for the collagen attachment stretches. We simulate the remodelling of the attachment stretch distribution: this enables the collagen to bear more load for a given mass and yields results consistent with in vivo observations for evolving thickness of the infarct region.
Figure 4: Results illustrating a case of myocyte degradation leading to an increase in the constituent stretches and collagen deposition in response to the increased stretches

4 ACKNOWLEDGEMENTS

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REFERENCES


INTRAOCULAR PRESSURE ESTIMATION USING PRINCIPAL COMPONENT ANALYSIS OF TONOMETRIC RESULTS

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SUMMARY

Estimation of the intraocular pressure (IOP) is the main tool used for the detection of glaucoma which is the main cause of blindness in the world. In the present study, a new methodology to determine IOP based on tonometric pressure, whole cornea deformation during tonometry, and initial corneal geometry is proposed. The data collected during tonometry is subjected to a principal component analysis (PCA) which in turn allows the estimation not only of the IOP but also the instantaneous modulus of elasticity (E) of the corneal tissue. The data used for the PCA analysis was numerically obtained by means of the computational simulation of the cornea deformation during tonometry. The proposed methodology was computationally validated with excellent agreement between estimated and actual values of IOP and E.

Key words: Intraocular Pressure, Elastic Modulus, Tonometry, Principal Component Analysis.

1 INTRODUCTION

Despite the development of different techniques and procedures, the correct measurement of the intraocular pressure remains as one of the main challenges in ophthalmology, since IOP is the main tool for the diagnosis of glaucoma. Several new devices have been developed trying to get a better estimation of the IOP [1]. However, these new devices have been calibrated using the Goldmann Applanation Tonometer which does not consider the influence of several corneal geometric and mechanical parameters [2]. There have been also many attempts to obtain equations to correct Goldmann measurements using computational tools such as finite element analysis [3][4].

In the present work, computational simulations of tonometry are performed, then the displacements of different points of the cornea and the corneal geometric parameters are analyzed using a principal components approach in order to determine the relationship of these parameters and the actual intraocular pressure. Then, a simple mathematical model is proposed to estimate the IOP and the instantaneous elastic modulus of the cornea based on the principal components analysis.

2 METHODOLOGY

The computational simulations were performed using the commercial finite elements analysis software (Abaqus/CAE) to evaluate the interaction between the cornea and a rigid element used as the tonometer. The axisymmetric model of the cornea considered a central thickness of 0.51mm, a posterior radius of 6mm, and an anterior radius of 7.1mm (Fig. 1). The cornea mechanical behavior was assumed to be linear elastic, and the interaction between the two elements was made using ‘surface-to-surface contact’ interaction neglecting the friction effect.
Computational simulations were performed for different combinations of intraocular pressure and modulus of elasticity, and considering the same geometric model shown in Fig. 1. Each simulation consisted of two steps, first the intraocular pressure is applied in the cornea posterior face, and then the rigid element is moved producing the cornea deformation. The displacement of six reference fixed points over cornea surface (figure 1) are obtained from the simulations.

The data considered for the Principal Component Analysis were: actual intraocular pressure, modulus of elasticity, initial corneal central thickness and anterior curvature, along with the displacements of the six reference points and the tonometric pressure. This type of analysis allows a dimensional reduction to a vectorial space using two main PCA components. This new representation exhibits a unique and distinguishable behavior for each pressure level and elastic modulus as can be seen in Fig. 2a where each marker type represent a pressure level and lines represent the same elastic modulus value.

Based on the PCA results the following methodology is proposed to estimate not only the actual IOP but also the instantaneous modulus of elasticity of the cornea:

1. Generation of a database of simulation results subjected to PCA considering different corneal geometries, intraocular pressures, and corneal mechanical properties.

2. In the ophthalmologist office and for the specific patient, perform tonometric measurement and determination of the displacements of the reference points of the patient cornea. With these data calculate the corresponding values for the two main principal components. This point correspond to TP in Fig. 2a and 2b.

3. Identify lines with constant value of pressure (lines L01 and L23 in figure 2b) and constant elastic modulus (lines L02 and L13 in Fig. 2b) nearest to the TP point in the new PCA space.

4. Finally, interpolate for the point TP between constant pressure and constant elastic modulus lines to estimate the actual intraocular pressure and instantaneous modulus of elasticity.

3 RESULTS AND CONCLUSIONS

In order to validate the proposed methodology, 18 computational simulations were performed with different combinations of IOP and modulus of elasticity. Then, the corresponding PCA analysis was
performed to generate a simple database in the new space. For the validation, seven pairs of IOP and E were selected and computational simulations were performed. The corresponding results for these 7 simulations represent the data that would be taken at the ophthalmologist office. Then, using the created database and following steps 3 and 4 of the proposed methodology, an estimation of the IOP and corneal instantaneous E were obtained. The results are summarized in Table 1. These results show a maximum error of 2% for elastic module and 3.97% for IOP.

Based on the obtained results, the following preliminary conclusions can be drawn in the present study:

- Tonometry may be enhanced in order to obtain additional data that can be processed using principal component analysis. The output of the PCA provides new information that can be used for a better estimation of the IOP.

- The proposed methodology for the evaluation of IOP and corneal modulus of elasticity, based on the PCA of the data that can be taken from tonometry, provided good estimations.

- In order to improve the accuracy of the proposed methodology a richer database should be built considering a wider range of IOP, modulus of elasticity, and corneal geometries.
<table>
<thead>
<tr>
<th>ELASTIC MODULUS [kPa]</th>
<th>IOP [kPa] (mmHg)</th>
<th>ELASTIC MODULUS [kPa]</th>
<th>IOP [kPa] (mmHg)</th>
<th>ELASTIC MODULUS</th>
<th>IOP</th>
</tr>
</thead>
<tbody>
<tr>
<td>625</td>
<td>1.67 (12.52)</td>
<td>625.2</td>
<td>1.6705 (12.523)</td>
<td>0.03</td>
<td>2.19</td>
</tr>
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<td>612.8</td>
<td>2.2843 (17.127)</td>
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</tbody>
</table>

Table 1: Validation results.

REFERENCES


INTERACTION BETWEEN NUCLEOSIDE DIPHOSPHATE KINASE AND GRAPHENE OXIDE AND ITS IMPACT ON CARDIOVASCULAR DISEASES

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SUMMARY

Here we report possibly for the first time the computational understanding of the interactions between Graphene Oxide (GO) and the enzyme Nuclear Diphosphate Kinase (NDPK) and its implications. Nucleoside Diphosphate Kinase is responsible for suppressing the formation of the second messenger cAMP during heart failure [1]. However, cAMP signal transduction can potentially compensate for the NO production that was being inhibited due to the damage of the coronary endothelium during heart failure[6]. Using NAMD simulations and VMD analysis, it is observed that graphene oxide has the potential to approach and bind to the active site of NDPK.

Keywords: Nucleoside Diphosphate Kinase (NDPK), Graphene Oxide, Nanotechnology, Nanoscale Molecular Dynamics (NAMD), Visual Molecular Dynamics (VMD)

1 INTRODUCTION

Here we report possibly for the first time the computational understanding of the interactions between the nanomaterial Graphene Oxide (GO) and the enzyme Nuclear Diphosphate Kinase (NDPK) and its implications. Nanoscale Molecular Dynamics (NAMD) and Visual Molecular Dynamics (VMD) are currently being used to run simulations and analyze the interactions between NDPK and GO. The simulations have run for 4.22 ns out of the ongoing 120 ns, and it is being observed whether or not GO is attracted to the active site of the enzyme. Graphene oxide is being used because of its excellent biocompatibility, high water dispersibility, and large surface area [4]. NDPK has numerous roles in the body, such as activating G-proteins and transferring a phosphate from ATP to GDP (resulting in ADP and GTP). It also plays a role in cell proliferation, development, signal transduction, endocytosis, etc. Normally, increased activity of NDPK yields the synthesis of the second messenger cyclic adenosine monophosphate (cAMP). [2] However, during heart failure, NDPK suppresses cAMP formation due to altered signal transduction pathways via G-proteins. To help prevent heart failure, the body produces Nitric Oxide (NO) which helps the veins and arteries to dilate so that blood can flow through the body. NO is produced by the body in the endothelium that lines the walls of blood vessels. However, during
heart failure, the lining is damaged, inhibiting the production of NO [5]. cAMP signal transduction pathways have the potential to produce NO after the endothelium lining is in the process of being damaged. Therefore, when NDPK suppresses cAMP during heart failure, it in turn inhibits the production of nitric oxide—which is crucial for a healthy heart. Using NAMD simulations and analysis using VMD, it is observed that graphene oxide has the potential to be attracted to the active site of NDPK. If graphene oxide binds itself to the active site of NDPK (located at the amino acid histidine 118), it can cease the enzyme’s function, lower the rate of reaction, and potentially affect heart failure. If not binding directly to the active site, it also has the potential to bind on other portions of NDPK, blocking other substrates.

2 METHODOLOGY

Simulations using NAMD 2.12 were carried out to analyze the interaction between the enzyme NDPK and the graphene oxide. The PDB file for NDPK was gathered from PDB.org and the graphene oxide related files were developed by the authors. Simulations are on the process of being run for 120 ns. Extreme Science and Engineering Discovery Environment (XSEDE) which is supported by the National Science Foundation, is providing the computing resources for this project [4]. So far, the simulation has been run for 4.22 nanoseconds. VMD 1.9.2 is being used to analyze the results.

3 FINDINGS AND ARGUMENT: The Last 85 Frames of the Simulation are Shown

![Interaction energy (Van Der Waals) between graphene oxide and the NDPK](image1)

![RMSD analysis of NDPK over time](image2)

**Figure 1:** (a) Interaction energy (Van Der Waals) between graphene oxide and the NDPK. A large, negative interaction energy signifies great attraction. Although this is the interaction energy between the center of mass of the enzyme and the graphene oxide as opposed to between the histidine and graphene oxide, strong attraction towards the protein could also mean that the graphene oxide inhibits other substrates from approaching/interacting with the protein. (b) RMSD analysis of NDPK over time is showing a potential for stable adsorption on the surface of the graphene oxide sheet after 4.22 ns.
This project is ongoing, and the plan is to continue this simulation for 120 ns. However, so far it can be observed that attraction exists between the enzyme and graphene oxide, and that the distance between the graphene oxide and histidine 118 (the active site of the enzyme) is decreasing. Also, interaction energy is negative, indicating that attraction between the enzyme and graphene oxide exists. Lastly, the RMSD of NDPK over time shows a potential for stable adsorption on the surface of the graphene oxide molecule after 4.22 ns. The principle in this abstract, can be used wherever NDPK is present in the body or where controlling it is an issue. Graphene oxide can also be used with other proteins and enzymes and the implications can be studied.

4 ACKNOWLEDGEMENTS AND FUNDING

This work used the Extreme Science and Engineering Discovery Environment (XSEDE), which is supported by National Science Foundation grant number MCB170002. We would also like to acknowledge Christopher N. Hill of the MIT Department of Earth, Atmospheric, and Planetary Sciences, and Scott Yockel of the Harvard University FAS Research Computing department for computational help.

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MODELING DIFFUSION IN THE EXTRACELLULAR SPACE OF THE BRAIN

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SUMMARY

Using publicly available electron microscopy (EM) reconstructions of extracellular space, we create a finite element model of extracellular diffusion and use it to estimate how geometric tortuosity varies with tunnel volume fraction. Estimates are compared to existing estimates from a Monte Carlo model and found to agree well.

Key words: diffusion, tortuosity, extracellular space

1 INTRODUCTION

Diffusion in the extracellular space (ECS) of the brain is important for signaling between neurons, but is also crucial for homeostasis, energy supply and clearance of waste products. As the ECS is highly tortuous and the extracellular volume fraction varies regionally, it may be that the brain controls rates of diffusion by varying the shape of the ECS [2]. This can be achieved by changing the concentrations of ions in the ECS, which has been shown to happen between sleep and awake states [1], as well as pathological activity such as epileptogenesis [3].

2 METHODOLOGY

The ECS is very convoluted. Even though it in volume makes up about 20% of the parenchyma, the open space between adjacent membranes is typically very small, in the order of tens of nanometers. Cells swell when the brain is prepared for EM reconstructions, and high-quality images with a realistic extracellular volume fraction is not easily accessible. This is a challenge for modeling ECS-sensitive phenomena which cannot really be overcome without advances in imaging techniques.

In [4], reconstructions with realistic extracellular volumes are created from the raw EM reconstruct by a computational algorithm which adds extracellular volume between cell membranes. An example of their reconstructed ECS is shown in figure 2, revealing the intricate nature of the ECS and the high mesh resolution required to accurately represent it. Further, they study extracellular diffusion using a Monte-Carlo model. This yields estimates of geometric tortuosity, a measure of hindrance to diffusion.

In this work, we create a finite element model of extracellular diffusion using the Poisson equation, and compare our derived tortuosities to the tortuosities derived by the Monte-Carlo model in [4]. Simulations are carried out using the FEniCS software suite [5].

3 RESULTS AND CONCLUSIONS

Our estimates of tortuosity are very close to those of [4], yielding an estimate of the tortuosity of about 1.2 in the arguably most physiologically reasonable cases. The fact that the finite element and
Figure 1: A sample mesh generated from the ECS reconstructions in [4].

Figure 2: Streamlines from diffusion simulations. Note the intertwined path taken by particles, a consequence of the tortuous nature of the ECS.

Monte-Carlo models correspond closely is reassuring, providing further evidence of the claim that geometric tortuosity has a nonnegligible dependence on the lacunarity of the ECS.

Further, to provide insight into this relationship, we repeat our experiments in idealized geometries in which lacunarity is the only parameter varying to demonstrate that the observed dependence of tortuosity on lacunarity is not an artifact of the reconstruction process.

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NUMERICAL MODELING OF LEAFLETS FOR ARTIFICIAL AORTIC VALVES WITH SPH METHOD

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SUMMARY

Nowadays, Transcatheter aortic valve implantation (TAVI) is one of the least invasive methods of replacing dysfunctional aortic valve for people who because of weak health cannot qualify for open heart surgery. In this method, the artificial low-profile balloon-expandable aortic valve is implanted using a catheter, which is inserted into a large blood vessel. The shape of expandable stents and leaflets differs from those mounted by open heart valve surgery. And as there is not much space, reducing the size of the aortic valve is very important. The Fluid-Structure Interaction between blood and leaflets in aortic valve is a complex phenomenon. Therefore, it is quite difficult to account for many variables and to keep the reasonable time of solution. For these reasons a simple model was created, where blood was assumed to behave like Newtonian fluid modelled by smoothed particle hydrodynamic elements (SPH). The geometry of the model was simplified: reduced to two rigid tubes with different diameters and leaflets mounted between them. The numerical model was generated in Matlab in a form of mathematical functions. LS-Dyna input *.k file with specified geometry and material models is received as an output from the function file. Soft tissue properties are taken from tests carried out in strength testing machine. Procedure and results from tensile and indentation tests were presented in publication [5, 6].

Key words: aortic valve leaflets, computational fluid dynamics, sph

1 INTRODUCTION

The purpose of this article is to analyze the influence of constraints on kinematic parameters of aortic valve leaflets during cardiac cycle [14]. Various models of aortic valve leaflet geometry generation have been described so far [1, 4], and they are basically either spherical, cylindrical or planar [10]. According to the literature, in human biological leaflets the angle between the leaflet and horizontal plane inclosure of leaflets is between 19 and 29 deg. In commercial artificial low profile aortic valves stents are shorter and the angle is lower. A more thorough study of commercial aortic valves reveals a noticeable change in the way of fixing leaflets with a stent: before there were straight lines and nowadays there is a function of the second degree. The intention of authors was to investigate how it changed kinematic characteristics of aortic valve leaflets during closure and opening.

Fig.1. Geometry of leaflets in Matlab and LS Prepost generated automatically by function file
2 NUMERICAL MODEL

Various methods are used in Computational Fluid Mechanics for flow modeling of aortic valve flow. The inclusion of Fluid Structure Interaction FSI significantly complicated, as models can be 2- [11], or 3-dimensional [12, 13]. In our case, the first attempt was to implement the model in commercial code software - Ansys CFX. However, in CFD module there is a weak two-way connection, what leads to instabilities in fluid and structural domains with the same density. In Ansys, the Immersed Solid Method is implemented, but forces and torques on immersed solids are usually underestimated. That is why the next attempt was done in engineering software LS-Dyna to assess the possibility of using other methods. Very promising was *ICFD incompressible fluid solver with the Fractional Step (partitioned) method used to uncouple fluid and solid equations. Fluid and solid geometry must match at the interface, but mesh can be different. Unfortunately, this method is time-consuming because of large displacements of leaflets and the needed remeshing of fluid domain. To speed up simulations and keep fluid domain in a model of aortic valve leaflets far away from remeshing, the Smoothed Particle Hydrodynamics (SPH) [20] was selected. In this meshless method, the motion of a set of particles is specified by general conservation equations. Its implementation is in explicit finite element code LS-Dyna [19, 21], and examples of applying SPH method in heart valves simulation can be found in the literature [7, 18].

![Fig.2. Stress distribution in leaflets during Diastole](image)

Results depend on a number of smoothed particles and on how many finite elements are on leaflets after discretization. The geometry of aortic valve leaflets was generated from mathematical functions in Matlab, where numbers of nodes, lines, and constraints were specified. By implementation of LS-Dyna *.k syntax into a Matlab function file, a parametrical model ready for use in the future optimization process was received.

In SPH method, there is no direct method of application of boundary condition in a form of pressure. Therefore, applying blood flow by velocity or force from aorta and stroke volume from the left ventricle (fig.3) is necessary. It can be called Piston like method.

![Fig. 3. Left ventricle volume and piston location along z-axis](image)
According to stroke volume curve presented in fig. 3, diastole during which heart fills with blood takes 0.5 sec, while the time of systole during which blood is ejected is equal to 0.3 sec. End diastolic volume is 132 ml, stroke volume is 72 ml and end systolic volume 60 ml.

3 RESULTS AND CONCLUSIONS

During opening and closure of leaflets, the maximum stress appears in locations where each leaflet form commissure [3]. The size of commissure and shape of leaflets must be optimal to ensure sufficient coaptation depth and to keep the stress of material below yield stress [2, 15, 16, 17]. The numerical model presented above can serve as a tool for selection of optimal leaflet shape for various materials.

Acknowledgments

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Computational Prediction of the Effects of the Intra-aortic Balloon Pump on Heart Failure with Valvular Regurgitation Using a 3D Cardiac Electromechanics Model

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SUMMARY

IABP is normally contra-indicated in significant aortic regurgitation (AR). It causes and aggravates pre-existing AR while performing well in the event of mitral regurgitation (MR). Nevertheless, a question of clinical significance arises since the AR can co-exist with an intra-aortic balloon pump (IABP). This study computationally proved the reason for the clinical contra-indication of IABP in AR patients.

Key words: intra-aortic balloon pump, aortic regurgitation, mitral regurgitation, 3D electromechanical model, stroke volume, ventricular workload

1 INTRODUCTION

An intra-aortic balloon pump (IABP) is used to increase myocardial oxygen perfusion, while simultaneously increasing cardiac output and decreasing the workload of the ventricle. This is realized via counter-pulsation of the IABP. Extant research indicates that valve regurgitation; i.e., backward flow in the heart when a cardiac valve does not close completely, has a significant effect on the cardiac function [1]. Heart valves are located between the atria and the ventricles (the mitral and tricuspid valves), and between the ventricles and the aortas (the aortic and pulmonary aortic valves). The most common heart valve diseases include aortic and mitral insufficiencies. Cardiac responses such as cardiac output and blood pressure vary according to the type of valve that is affected and the severity of the regurgitation. This can also affect the efficacy of the IABP function when patients are treated with IABP therapy [2]. IABP is normally contra-indicated in significant aortic regurgitation (AR). It causes and aggravates pre-existing AR while performing well in the event of mitral regurgitation (MR) [3]. Nevertheless, a question of clinical significance arises since the AR can co-exist with the IABP.

Indirect parameters such as the mean systolic pressure, product of heart rate and peak systolic pressure, and pressure-volume are used to quantify the effect of IABP on ventricular workload. However, to-date no studies have quantified the reduction in workload with IABP directly since experimental methods for documenting and evaluating myocardial energy consumption throughout the ventricular volume are hampered by low spatiotemporal resolution. Computational modeling is an alternative approach to overcome this limitation. Previously, a computational model of IABP support was developed using a three-dimensional electromechanical model of failing ventricles in conjunction with a lumped model of the circulatory system [4, 5]. Furthermore, a 3D electromechanical model of failing ventricles with mitral and aortic valve regurgitations was also developed [6]. These models enabled the quantification of changes in the local contractile energy consumption of the myocardium. In this study, IABP function was incorporated into the electromechanical model of a ventricle with mitral and aortic valve regurgitation with a lumped model of the circulatory system.

The goal of this study involved examining the effect of IABP therapy on ventricular mechanics under valvular insufficiency by using a computational model of the heart. For this purpose, the 3D electromechanical model of the failing ventricles used in previous studies was coupled with a lumped-parameter model of valvular regurgitation and the IABP-treated vascular system.
2 METHODOLOGY

Ventricular electromechanics model

An MRI-based electromechanical model of the failing canine ventricles developed by previous studies was used to achieve the goals of this study [7]. The ventricular geometry and fiber and laminar sheet architecture of the model were constructed from high-resolution MRI and diffusion tensor MRI scans of canine ventricles involved in heart failure (HF). The model consisted of coupled electrical and mechanical components and a lumped-parameter representation of the circulatory system.

Model of IABP function

Given the inflation and deflation of an IABP balloon inside a systemic artery, the cycle of its inflation and deflation was modeled as a time-varying compliance with respect to the systemic artery. A harmonic waveform was used for the time-varying compliance of the systemic artery to generalize the patterns of inflation and deflation of an IABP. The harmonic waveforms for the compliance of the artery were expressed as follows:

\[ C_{SA, IABP}(t) = C_{SA} \times SF_{IABP}(t) \]  
\[ SF_{IABP}(t) = (1 - sf) + sf \times \cos\left(\frac{2\pi t}{BCL} - \phi\right) \]

where, \( C_{SA, IABP} \) denotes the time-varying compliance of the systemic arteries with the IABP, \( C_{SA} \) denotes the compliance of the systemic arteries without the IABP, \( SF_{IABP} \) denotes a scale factor for the IABP, \( sf \) denotes the level of the scale factor, \( BCL \) denotes the cycle length of the ventricle and the time shift between the ventricular contraction cycle and the IABP inflation cycle. The \( sf \) represents a major parameter, which is proportional to the stroke volume of IABP and related to the pumping compliance of IABP. First, several \( sf \) parameter values such as 0.05, 0.1, 0.15, 0.2, 0.25, and 0.30 were applied to obtain appropriate model parameters of the IABP function. The \( sf \) parameter was selected as 0.2, and this reduced the \( C_{SA, IABP} \) value to 60% of the maximum value. The pumping phase was set as 3.66 radians (350 ms shifted from the end-diastole), instead of the end-systole because the phase exhibited the maximum efficiency in terms of the volume of pumping blood during inflation as indicated by a previous study [5].

Model of valve regurgitation

Two additional branches were added to both the aortic and the mitral compartments in the lumped-parameter model to model MR and AR. One of the branches had a forward diode to represent forward flow, and the other branch had a backward diode to represent leakage flow. The diodes had different resistance values.

\[ Q_{MI} = \begin{cases} \frac{P_{LA} - P_{LV}}{R_{MI}} & \text{when } P_{LA} > P_{LV} \\ \frac{P_{LA} - P_{LV}}{R_{MI, Leak}} & \text{when } P_{LA} \leq P_{LV} \end{cases} \]
\[ Q_{AO} = \begin{cases} \frac{P_{LV} - P_{AO}}{R_{AO}} & \text{when } P_{LV} > P_{AO} \\ \frac{P_{LV} - P_{AO}}{R_{AO, Leak}} & \text{when } P_{LV} \leq P_{AO} \end{cases} \]

where \( Q \), \( P \), and \( R \) denote the flow rate (mL/min), pressure (mmHg), and flow resistance (mmHg\,min/mL), respectively, and the subscripts \( MI, AO, LV, LA, \) and \( Leak \) represent mitral valve, aortic valve, left ventricle (LV), left atrium, and leakage, respectively. A scale factor for leakage blood flow through the valves was introduced to quantify the severity of regurgitation. Several SF parameters such as 2%, 4%, 6%, 8%, and 10% were applied to consider the variation of regurgitation fraction from weak valvular insufficiency to severe valvular insufficiency.

Simulation protocol

For all the simulations, the duration of the entire cardiac cycle was set as 600 ms. The severity of the regurgitation was varied from 0% (baseline state) to 10% (severe regurgitation) in 2%
increments. For each case, the simulation was executed for 20 s, to ensure that the cardiovascular responses such as blood pressure, flow, and volume reached nearly steady state in each compartment for a given degree of regurgitation.

Figure 1 Transmural distribution of myocardial contractile ATP consumption rate and tension and blood pressure in the LV, aorta, and LA under 10% AR and 10% MR conditions in the control and IABP therapy groups

3 RESULTS AND CONCLUSIONS

In this study, the effect of IABP on heart failure with valvular regurgitation (AR and MR) was quantitatively examined by using a sophisticated computational model of IABP-implanted ventricles. The main findings were follows:

1. IABP therapy was disturbed in terms of reducing the myocardial tension generation and contractile ATP consumption by valvular regurgitation, particularly in the AR condition.
2. The IABP worsened the problem of ventricular expansion induced due to the regurgitated blood volume during the diastole under the AR condition.
3. When the severity of valvular regurgitation increased, the stroke volume and ejection fraction (which are important indices for estimating cardiac pumping function) decreased. The IABP enabled the increase in stroke volume in the AR condition, but reduced stroke volume even further in a severe MR condition.
4. The IABP reduced LV stroke work in the AR condition, MR condition, and the no regurgitation condition. Therefore, the IABP helped the ventricle to pump blood and reduced the ventricular workload.
5. Contractile myocardial ATP consumption increased according to the severity of the AR and MR, but the IABP reduced the contractile myocardial ATP consumption. The IABP retrenched biological energy in pumping blood in the AR and MR conditions as well as in the no regurgitation condition.

The computational model of cardiac electromechanics proposed in this study was used to quantitatively predict the effect of IABP function on the cardiovascular responses of patients with AR and MR conditions. The IABP could partially perform its role in the MR condition. However, it was disturbed by the AR and worsened the cardiovascular responses that followed the AR. Therefore, this study computationally proved the reason for the clinical contra-indication of IABP in AR patients.
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ROLE OF RADIAL COLLAGEN FIBERS IN OPTIC NERVE HEAD BIOMECHANICS

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SUMMARY

We recently identified a layer of radial collagen fibers of 60-180 µm thick in the most anterior region of the peripapillary sclera in sheep eyes [1]. Our goal was to determine the biomechanical role of these radial fibers. Towards this goal, we constructed seven generic models of the posterior eye with various scleral collagen fiber orientations. Results showed that radial fibers can have the positive effect of decreasing the strain in the neural tissues within the canal, but that this comes at the expense of a slight increase in the strain within the lamina cribrosa. A combination of circumferential and radial fibers can better protect the optic nerve head tissues from mechanical insult than each alone.

Key words: collagen, sclera, optic nerve head

1 INTRODUCTION

Glaucoma is the second leading cause of blindness worldwide [2]. It is characterized by irreversible damage to the retinal ganglion cell (RGC) axons within the optic nerve head (ONH), where the axons pass through the lamina cribrosa (LC) and exit the eye. Although the causes of RGC degeneration in glaucoma are not completely understood, elevated intraocular pressure (IOP) has been identified as a primary risk factor for the development and progression of glaucomatous optic neuropathy. It has been hypothesized that the loss of RGC axons in glaucoma is due to the IOP-induced mechanical deformation within the ONH. As the principal load-bearing tissue of the eye, the sclera provides the ONH with mechanical support during IOP elevations. The sclera is a complex structure with various collagen fiber orientations, and its mechanical behavior is anisotropic and nonlinear. A ring of circumferentially aligned collagen fibers surrounding the scleral canal has been reported in rat, monkey and human eyes [3-5]. Finite element (FE) modeling has been used to evaluate the role of the sclera and its structure on the biomechanical environment of the ONH [6, 7]. These studies have demonstrated that a sclera with circumferential fibers surrounding the canal results in lower IOP-induced deformations within the LC, compared with a simpler isotropic sclera.

Recently, using polarized light microscopy, we reported a layer of radial collagen fibers, 60-180 µm thick, in the most anterior region of the peripapillary sclera of sheep [1], humans and monkeys [8]. The radial fibers extended at least 3 mm from the canal. These radial fibers have also been observed utilizing wide-angle x-ray scattering [9], but their biomechanical role and how they affect ONH and LC biomechanics remains unknown.

Our goal in this work was to determine the biomechanical role of these fibers. Towards this goal, we constructed seven generic models of the posterior eye with various scleral collagen fiber orientations. We hypothesize that radial fibers may stabilize the posterior eye in a different way than circumferential fibers, and further that a combination of both fiber types can better protect the ONH tissues from mechanical insult than each alone.
2 METHODOLOGY

The posterior eye was simplified as a portion of a sphere with an inner radius of 12 mm, thickness of 0.4 mm and arc length of 5 mm (Fig. 1). For computational simplicity, only one-fourth of the volume was modeled and symmetric boundary conditions were applied on the two symmetry planes. The model was partitioned into four layers along the thickness direction and five sections along the radial direction. The section closest to the axis of symmetry represented the scleral canal containing the LC (top two layers) and neural tissues (bottom two layers). All other sections were modeled as the sclera with predefined collagen fiber orientations in different layers.

![Diagram](image.png)

**Fig. 1** Generic models of the posterior eye. Left: model geometry. Right: the seven models with various scleral collagen fiber orientations. For clarity, fiber orientations are shown on the symmetry plane only. Three types of fiber orientations were assigned: radial fibers, shown in yellow and a “-” symbol, circumferential fibers, shown in green with a “*” symbol, and transversely isotropic fibers, which are random in the sclera plane, shown in grey with the “#” symbol. Models #4-7 varied in the ratio of circumferential to radial fibers in the innermost section, as indicated by Protrusion ratio in the insert on the bottom right.

All tissues were modeled as hyperelastic fiber-reinforced composites. The strain energy function for the fibers was defined using an exponential-power law, while the ground material was modeled as a Mooney-Rivlin solid. Fiber alignment was described by a 2D \( \pi \)-periodic von-Mises distribution with fibers confined within the plane tangent to the scleral surface. Material properties of the sclera and neural tissues were fit to experimental data obtained from the literature [10, 11]. The stiffness of the LC (i.e., fiber stiffness, 1\(^{st}\) Mooney-Rivlin constant and bulk modulus of the ground material) was assumed one-fourth of that of the sclera due to the lack of experimentally measured LC properties.

Three types of scleral collagen fiber orientations were considered: random, circumferential (tangent to the scleral canal boundary) and radial (perpendicular to the scleral canal boundary). Seven models with different combinations of fiber orientations were then created. In Model #1, the fibers were randomly distributed in the sclera plane, representing a transversely isotropic sclera. In Model #2, circumferential fibers were added to the section adjacent to the scleral canal. In Model #3, only radial fibers were added to the top layer of the sclera. In Models #4-7, both circumferential and radial fibers were added and four protrusion ratios of radial fibers were considered: 0, 0.5, 0.9 and 1. The protrusion ratio (range 0-1) was defined as the ratio of the length of the protrusion portion of radial fibers (with respect to the boundary of the circumferential ring) to the thickness of the circumferential ring. Based on our observation, a protrusion ratio of 0.9 was closest to the physiologic case [1].
For each model, an IOP of 50 mmHg was applied to the inner surface of the sphere. A uniform outward boundary pressure of 800 mmHg (16× IOP) was applied to the side surface to mimic the hoop stresses induced by IOP. The nodes at the top edge of the side surface were constrained along the y-direction to prevent rigid-body displacement. The model was discretized into 27,909 nodes and 24,000 elements (23,760 8-noded hexahedral elements and 240 6-noded pentahedral elements). All models were solved using FEBio v2.3.0. Scleral canal expansion (SCE) and posterior laminar displacement (PLD) were defined as outputs of the FE simulations. SCE was calculated as the change in the canal size (anterior surface). PLD was calculated as the difference in the anterior-posterior displacement between the center of the LC and the edge of the scleral canal (posterior surface). Finally, we examined the distributions of maximum principal strain (MPS) in the ONH.

3 RESULTS AND CONCLUSIONS

Fig. 2 illustrates the effects of collagen fiber orientation on SCE and PLD. SCE was smallest in the case with circumferential fibers alone (Model #2), and largest in the case with radial fibers alone (Model #3). The opposite trend was found for PLD, indicating that constraints on SCE may induce posterior bowing of the LC. A combination of both fiber types (Models #4-7) was able to decrease the large SCE induced by radial fibers and PLD by circumferential fibers, and the extent was determined by the protrusion ratio of radial fibers.

Fig. 3 illustrates the effects of collagen fiber orientation on the distributions of MPS in the ONH. Circumferential fibers alone (Model #2) decreased the peak strain in the LC by 13% as compared with the isotropic model, demonstrating their ability to limit IOP-induced strain in the LC. This is consistent with previous findings [6, 7]. Interestingly, circumferential fibers alone (Model #2) increased the peak strain in the neural tissues by 4%. The increased strain in the neural tissues was caused by the increased PLD, which squeezed the neural tissues underneath the LC. Radial fibers alone effectively reduced the strain in the neural tissues; however, this was at the expense of increasing the strain in the LC (Model #3). A combination of both fiber types (Models #4-7) was able to substantially decrease the strain in the neural tissues (up to 19%) without increasing the strain in the LC too much (less than 12%), as compared with circumferential fibers alone.

In summary, we have demonstrated that radial fibers stabilized the posterior eye in a different way than circumferential fibers. Radial fibers can mitigate large LC posterior bowing which caused by circumferential fibers, and thus reduce the strain in the neural tissues. However, this was at the expense of increasing the strain in the LC. A combination of both fiber types can make the posterior eye more stable, and thus better protect the ONH tissues from mechanical insult than each alone.

Fig. 2 Effects of collagen fiber orientation on scleral canal expansion (SCE, top left) and posterior laminar displacement (PLD, top right). Bottom: demonstration of seven models with different scleral collagen fiber orientations. Radial fibers alone induced largest SCE, while circumferential fibers alone induced largest PLD. A combination of both fiber types (Models #4-7) was able to achieve moderate magnitudes of SCE and PLD.
Fig. 3  Effects of collagen fiber orientation on the distributions of maximum principal strain in the ONH. Circumferential fibers alone (Model #2) decreased the peak strain in the LC by 13%, but increased the peak strain in the neural tissues by 4%. Radial fibers alone (Model #3) effectively reduced the peak strain in the neural tissues, at the expense of increasing the peak strain in the LC. A combination of both fiber types (Models #4-7) was able to substantially decrease the strain in the neural tissues (up to 19%) without increasing the strain in the LC too much (less than 12%).

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MECHANICAL RESPONSE AND FIBER REMODELING IN ELASTASE-INDUCED RABBIT ANEURYSMS

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SUMMARY

The abnormal hemodynamics generated in cerebral aneurysms are believed to play a central role in progressive wall degradation that can lead to rupture. While elastase induced aneurysm models in rabbits have been used for device development, they have rarely been used to study wall degradation and the effect of hemodynamics. Here, we evaluated changes in walls of rabbit aneurysms, 8 and 12 weeks after creation. Walls remodeled in response to increased axial load in a manner that varied through the thickness. The rabbit model can potentially be used to evaluate the effect of altered hemodynamics on wall changes and assess pharmacological treatments for this disease.

Key words: elastase-induced aneurysm, fiber remodeling, failure testing

1 INTRODUCTION

An intracranial aneurysm (IA) is most commonly a saccular enlargement in the wall of a cerebral artery. Aneurysm rupture is associated with high morbidity and mortality and hence there is a pressing need to better understand disease progression and to identify clinically useful metrics for assessment of rupture risk. It is commonly accepted that stress factors such as abnormal hemodynamics can lead to wall degradation that sometimes present in the clinic as changes to the aneurysm shape and size. However, in most cases, such longitudinal information is not available, and aneurysm size is used for risk assessment. Human intracranial aneurysm samples can be obtained following treatment by surgical clipping and have provided valuable information about the heterogeneity in the aneurysm wall among patients (e.g. [1-2]). Recent studies have addressed the relationship between hemodynamics and changes to the aneurysm wall [3-5]. A challenge is that harvested aneurysm tissue from patients only represents one time point in the pathology. Animal models for IAs provide a means of studying the evolving aneurysm wall.

In this work, we evaluate temporal changes in mechanical properties and collagen fiber remodeling in an elastase-induced aneurysm model in rabbit [6]. As in an evolving cerebral aneurysm, the rabbit aneurysm wall experiences changing tensile loads during progression and must adapt its extracellular matrix. In the rabbit model, as for human aneurysms, this remodeling must occur under conditions of abnormal blood flow. Here, we analyze the changing collagen architecture and mechanical properties in the wall of the rabbit model using multi-photon microscopy.

2 METHODOLOGY

Nine elastase-induced aneurysms were created as described in [8]. Briefly, the sac of the model aneurysm is formed using elastase incubation and vessel ligation in the right common carotid artery. Aneurysms were harvested 8 weeks (n=4) and 12 weeks (n=5) after creation and control
vessels were harvested at that time. All aneurysms and control artery were mechanically tested using a custom-built uniaxial loading system compatible with the multiphoton microscope (MPM, Olympus FV1000 MPE, Tokyo, Japan), enabling simultaneous mechanical testing and MPM imaging of elastin and collagen fibers (Figure 1), [10]. To have a more comprehensive understanding of the fiber structure across the wall, samples were also imaged from both luminal and abluminal sides in the unloaded state.

Uniaxial failure tests were conducted in samples cut parallel to the longitudinal axis of the aneurysm sac. Mechanical changes were expected to be most evident in this direction due to increased load bearing following vessel ligation. To increase the likelihood of failure in the field of view and obtain a more uniform stress-strain distribution, samples were cut into dogbone shapes, Figure 1(b), before testing. Assuming an isochoric deformation, current cross sectional areas were calculated from the stretch and unloaded cross sectional area. The Cauchy stress was then calculated from external load and current area.

![Figure 1](image)

Figure 1. (a) Experimental uniaxial tensile system seen under multiphoton microscope. (b) Tissue specimen before and after cutting into dogbone shape (decrements in scale bar are 1 mm) with region of MPM imaging shown. (c) Representative 500 micron square MPM image.

3 RESULTS AND CONCLUSIONS

3.1 Mechanical Response

Seven samples failed in the middle region, while two failed near the clamp and were excluded from the study. The loading curves for the uniaxial failure tests of these seven samples are shown in Figure 2. The control artery (orange curve) is the most elastic and weakest of all the samples. This is consistent with the lower axial load in the control artery compared with the aneurysm. Both the 8 week (dashed) and 12 week (solid) samples display heterogeneity in the mechanical behavior. In all cases, the toe region of the aneurysms is substantially shorter than the control artery. The shortened toe region is consistent with the lack of internal elastic lamina in the aneurysm tissue. Four aneurysms show substantially increased ultimate stress compared with the control artery, suggesting fiber remodeling in adaptation to the increased axial load.

![Figure 2](image)

Figure 2. Cauchy stress versus stretch for uniaxial failure testing
3.2 Collagen fibers in control artery during axial loading

In the unloaded control artery (λ=1), medial collagen fibers were circumferentially oriented, Figure 3(a). There is little change in their orientation with increasing stretch even at stretches as high as 2.4. Furthermore, the wavy nature of the fibers remains at this stretch, suggesting fibers are not load bearing. In contrast, at λ=2.4, adventitial fibers are straightened and aligned in the axial (loading) direction, suggesting they are load bearing.

![Collagen fibers in control artery](image)

Figure 3. (a) MPM image stacks in control artery from lumenal side, showing media collagen at different stretch levels; (b) MPM image stacks of adventitia fibers at elevated stretch.

3.3 Collagen fibers in the unloaded aneurysm wall

Representative projected stacks of MPM images of adventitial collagen are shown in Figure 4. The adventitial collagen of all aneurysm samples and the control artery were wavy and collected in bundles. Some samples showed a more distributed orientation throughout the adventitial layer while others were circumferentially aligned (for example H629).

![Collagen fibers in the unloaded aneurysm wall](image)

Figure 4. Image stacks of adventitial collagen: 4 cases of aneurysm and 1 case of control artery.

In contrast, the collagen fibers in the unloaded medial layer of the aneurysm samples show gross qualitative differences with the control artery. The medial layer is now composed of two or more distinct regions. The innermost region (closest to the adventitia) has fibers with a stronger SHG signal compared with the control artery and was seen in all nine cases, Figure 5. The medial layer has adapted to the increased axial load, showing collagen fibers with a wider distribution of fiber angles compared with the control artery. Interior to this region is a layer more similar in fiber diameter and SHG intensity to the control artery. In some arteries, there is an additional inner layer displaying disorganized collagen fibers.

3.3 Collagen recruitment in the aneurysm wall during load bearing

Collagen recruitment for a representative sample under axial load is shown in Figure 5. As for Figure 6, this is the inner most region of the medial layer, with strong SHG signal. Unlike the control artery, the collagen fibers in this layer reorient and align in the axial direction with increasing axial load enabling the medial layer to contribute to axial load bearing. Two of the 8 week and one of the 12 weeks samples had substantially lower ultimate stress than other aneurysm walls, Figure 2. The adventitia fibers of these three weak samples were aligned in the circumferential direction, and therefore not well suited to contribute to axial load bearing.
Additional explanations for the reduced strength and this adventitial reorientation are under investigation.

Figure 6. Inner region of medial layer in aneurysm wall, showing stronger SHG signal and more distributed fiber angle compared with the control artery.

Figure 5. Response of remodeled fiber to axial loading, case H629.

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In this article, we investigate the design parameters of the material properties used in grips that will ensure development of uniaxial stress state within a tissue sample and failure of the tissue in the region where uniaxial conditions prevail based on a finite element model created to mimic experimental result.

**Key words:** cerebral arterial tissue, uniaxial testing, grip design, finite element method

### 1 INTRODUCTION

Uniaxial testing is the most popular method for the evaluation of biomechanical properties of soft tissue. In this method, a tissue specimen is fixed between two grips and stretched with a known displacement in one direction while the load borne by the specimen is recorded. The load-displacement data provides the constitutive behavior of the tissue. Often, the specimen is also stretched until failure to ascertain the uniaxial strength of the tissue. For accurate evaluation of the material properties, however, uniform stress transmission within the tissue needs to be attained. The fixity at the tissue-grip interface is known to give rise to localized stress concentrations or even tissue damage that may provide erroneous uniaxial data. The standard practice to alleviate this problem is to attach the tissue to pieces of an intervening material, typically sandpaper or cardboard, glued to the metallic grips [1, 2]. However, no analysis exists in the literature to ascertain whether this arrangement results in uniform stress distribution in the vicinity of the grips. In addition, the effect of material properties of the intervening material on the tissue stress distribution is also not quantified. In this abstract, we present a detailed computational study of the effect of grip design on the stress state of the soft tissue specimen. We developed an image derived finite element model of a dog bone shaped cerebral arterial wall tissue specimen attached to steel grips through a thin layer of soft material. The grips were first clamped to the specimen with a specified displacement, and then uniaxial displacement was applied to one of the clamps. The property of the intervening layer was parametrically varied to observe its effect on the stress field within the specimen and the evolution of tissue damage that would lead to tissue failure. We computationally found that insertion of a soft rubber layer between the steel grips and cerebral artery tissue specimen resulted in uniform uniaxial stress near the midlength of the specimen, while no stress concentration was observed near the grips. In addition, damage was also localized in the midregion of the specimen. These results are expected to provide guidelines for proper design of grips for the uniaxial testing apparatus for testing of soft tissues in general, and cerebral arterial wall tissue in particular.

### 2 METHODOLOGY

A finite element model was created from the micrographs of the uniaxial test apparatus along with a rabbit cerebral artery wall tissue specimen of dimensions 7.1 mm X 2 mm X 0.25 mm. The tissue was attached to the steel grips by 3 mm X 10 mm pieces of soft material layer of 0.787 mm thickness. Steel grips were modeled as 5 mm X 10 mm X 1.5 mm blocks. Due to the symmetry of
the geometry, only one-fourth of the entire set-up with appropriate boundary conditions along the
symmetry planes was considered. The model was meshed with 14,149 hexahedral elements using
Trelis (http://www.csimsoft.com/, American Fork, UT). The tissue constitutive response was
modeled using isotropic, nonlinear hyperelastic material model given by [3]. The model
parameters, α and β, were calibrated against experimental stress-strain curve data from uniaxial
failure tests of rabbit cerebral artery from Robertson and Sang [4]. The failure of the tissue was
modeled using an isotropic damage model, [5], with two parameters, ξ_{max} and ι. For the best fit
between experimental curves and theoretical model predicted curves (R^2=0.9898), α = 0.455 MPa,
β = 0.531 MPa, ξ_{max}=0.9, and ι=5 MPa. Steel was modeled as a compressible neoHookean material
with λ = 104 GPa and μ = 69.2 GPa. The intervening layer was also modeled as a compressible
neoHookean material, and its material parameters were varied from that of steel: Case 1, a cloth
tape: Case 2 (McMaster-Carr, #77195A1), and a foam tape: Case 3 (McMaster-Carr, #7626A213).
These three cases were chosen to represent the effect of a highly stiff, a moderately soft, and a very
soft layer of material, respectively. The tape material parameters were estimated to be λ = 170 MPa
and μ = 682 MPa for Case 2 and λ = 22.3 MPa and μ = 14.8 MPa for Case 3. The interface
between the tissue and the grips were provided with special, zero thickness interfacial elements [6]
that could simulate the contact and frictional slipping between two domains. To mimic the
experimental loading conditions, the grips were first clamped on the specimen with a clamp
displacement of 62.5 μm normal to the specimen face applied over 2000 load steps. The grip at the
right end was then kept fixed while the grip to the left end was provided with a boundary
displacement of 3.5 mm in the axial direction of the tissue applied over another 2000 load steps.
The finite element simulations were performed using a custom nonlinear finite element code
developed in our lab. The details of our custom finite element software can be found in [7].

Figure 1. Solid model of experimental setup: top (left) and side (right) views of mesh geometry.
Represented is steel (grey), intervening layer (black), and tissue (pink).

3 RESULTS

We simulated the uniaxial test of the cerebral arterial tissue specimen and recorded the evolution of
stress and damage distribution within the tissue. Figure 2 shows the Cauchy stress field within the
entire specimen in the axial direction for an applied stretch of 1.7. Stress at the ends regions of the
specimen where the grips attach to the tissue is lower than that in the region between the tissues for
all the cases. However, the stress distribution in the specimen between the grips was significantly
altered by the mechanical properties of the intervening material at the grip. Very stiff intervening
layer (Case 1) resulted in very high stress concentration in the tissue near the grips, while the mid
region was subjected to an average stress of about 7 MPa. Introduction of cloth tapes (Case 2) did
not mitigate the stress concentration near the grips appreciably. The tissue midregion stress also
remained similar to Case 1. In comparison, the tissue clamped with the soft foam tape (Case 3)
exhibited less stress localization in the vicinity of the grips. In addition, average stress in the
specimen midregion increased to about 8 MPa.
Next, we studied the evolution of damage for the three cases mentioned above. Figure 3 shows the damage distribution within the tissue specimen between the grips at an applied stretch of 1.9. The damage contours clearly show that the tissue specimen was likely to fail at the middle when it is attached to the grips with very soft layer (Case 3). For all other cases, damage accumulation near the grips was comparable to that in the middle signifying an equal probability of specimen failure near the grips and the middle region.

4 DISCUSSION

While the soft tissue specimen is typically attached to the metallic grips with a piece of cardboard or sand paper to ensure uniform stress distribution, whether this approach actually results in such distribution is not known. In this abstract we presented a computational study of the uniaxial test taking into account the specimen as well as the grip. We introduced a thin layer at the interface of the grip and the specimen and endowed this layer with material properties of different materials. For all the cases, axial stress in the portion of the tissue that was attached to the grips was lower than the rest of the specimen denoting a part of the load was transmitted by the grip assembly in that region. However, beyond the grips there was a jump in stress in the tissue denoting the load was borne alone by the specimen. The stiffness mismatch between the tissue material and the intervening layer material resulted in stress concentration near the grips. We found that a soft foamy layer reduced the magnitude of the stress concentration appreciably. In addition, the foamy layer resulted in a damaged region at the middle at higher applied stretch signifying failure of the specimen near the middle. Figures 2 and 3 together show that for the dogbone shaped specimen attached to the grips by foam tapes, the evolution of axial stress and ensuing damage was uniform.
at the midregion and thus represented proper uniaxial response of the tissue. We believe that the lower stiffness mismatch between the foam layer and the tissue was responsible for this desirable behavior. We anticipate that intervening layer material properties need to be tailored for different tissue specimens, but the guiding principle will be the attainment of a low stiffness mismatch between the tissue and the attaching layer at the grip.

Our study has several limitations. The material was assumed to be isotropic and homogeneous. However, actual arterial tissue is highly anisotropic and heterogeneous. Different stresses may arise within different layers of the tissue. In addition, localized stress concentrations can occur in the sites of heterogeneities in the specimen thus initiating failure from these points. These effects were not included in our model. However, our simulations reveal an overall guideline for the grip design for uniaxial tests. Further, we did not consider any friction at the interface between the tissue and the intervening layer at the grip. We applied a clamping displacement sufficient to prevent the tissue slippage from the clamp.

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REFERENCES


DATA ASSIMILATION FOR CARDIAC ELECTRICAL DYNAMICS

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SUMMARY

Many simplified models have been developed over the years to represent the complex cardiac cell dynamics. In this manuscript we present a unified version of a four variables model which parameters are calculated to reproduce the dynamics of other more complex models as well as experimentally measured action potential shapes, action potential restitutions and conduction velocity restitutions. This condensed model includes in one single set of equations, previous models, such as a human ventricular cells for normal and Brugada syndrome and new experimentally driven models for rabbit and pig cardiac cells.

Key words: cardiac cell models, cardiac biomechanics, translational cardiac modelling

1 INTRODUCTION

The study of cardiac arrhythmias using mathematical models has two main challenges. First, to describe realistic electrophysiological dynamics of cardiac cells\cite{1}, and second to develop fast computational methods that are able to simulate these models fast from single cell to full 3D tissue\cite{2–5}. Numerous cardiac cell models have been developed since the first model of Purkinje cells developed by Denis Noble in 1962\cite{6}, that range from 2 variables\cite{7,8} to models with very large number of variables. (E.g. human ventricles such as the TNNP with 19\cite{9}, O’Hara et al. with 41\cite{10}, and the Iyer et al with 67\cite{11}. Many of these complex models have been shown to actually fail to reproduce some physiological dynamics when coupled in tissue or paced at fast cycle lengths\cite{12–15}. So simple 4 variable models have been developed that have been able to reproduce the dynamics of other more complex models\cite{13,16} as well as the cell physiology of experimental data\cite{17,18}.

2 METHODOLOGY

We combine previous versions of 4 variable models\cite{13,16–18} into one set of equations and include new fits to rabbit and pig ventricular cells. Furthermore we developed a single code using WebGL for this model with all the variations in parameter to reproduce: 1) Normal Human ventricular cells for Epi, Endo and Mid-myocardium\cite{13}. 2) Reproduce the human ventricular cells for the TNNP model\cite{13}. 3) Human ventricular cells with Brugada syndrome\cite{16}. 4) Dog right atria and pulmonary veins\cite{17}. 5) Human atria models for 5 different patients\cite{18}. 6) Rabbit ventricle cells with two different drugs (DAM and CytoD) and 7) Pig ventricular cells.

The models are solved using the explicit Euler method with time steps of 0.05ms and a spatial resolution of 0.025cm using WebGL. WebGL allows to download the code using any browser, which will automatically run the code on the machine that downloads the file and run it on that machine’s GPU. So there is no need to compile any code, and the program is machine independent as it can run on windows, Linux and/or Mac. The fact that it runs on the machine’s graphic card, means that it runs in parallel and with an efficiency that can be comparable to real time.
The model’s equations are given below.

\[
\begin{align*}
\partial_t u &= \nabla \cdot \left(D \nabla u\right) - \left(J_{f1} + J_{so} + J_{si}\right) \\
\partial_t v &= \left[1 - H(u - \theta_v)\right]\left(v_{\infty} - v\right)/\tau_{v^-} - H(u - \theta_v)v/\tau_{v^+} \\
\partial_t w &= \left[1 - H(u - \theta_w)\right]\left(w_{\infty} - w^{\text{aux}}\right)/\tau_{w^-} - H(u - \theta_w)w/\tau_{w^+} \\
\partial_t s &= \left\{1 + \tanh(k_s(u - u_a))/2 - s\right\}/\tau_s
\end{align*}
\]

(1)

\[
\begin{align*}
J_{f1} &= -vH(u - \theta_v)(u - \theta_v)/(u_u - u)/\tau_{f1} \\
J_{so} &= (u - u_a)[1 - H(u - \theta_{so})]/(1 - \beta_s v)/\tau_s + H(u - \theta_{so})/\tau_{so} \\
J_{si} &= -\gamma_s H(u - \theta_{si})ws/\tau_{si} \\
&\quad - (1 - \gamma_s)(1 + \tanh[k_s(u - \theta_{si})])w/\tau_{si}'
\end{align*}
\]

(2)

\[
\begin{align*}
\tau_{v^-} &= \left[1 - H(u - \theta_v)\right]\tau_{v^-} + H(u - \theta_v)^{-}\tau_{v^-} \\
\tau_{w^-} &= \tau_{w^-} + (\tau_{w^-} - \tau_{w^-})/2 \\
\tau_{w^+} &= \tau_{w^+} + (\tau_{w^+} - \tau_{w^+})/2 \\
\tau_s &= \left[1 - H(u - \theta_s)\right]\tau_s + H(u - \theta_s)\tau_s \\
\tau_{so} &= \tau_{so} + (\tau_{so} - \tau_{so})/2 \\
\tau_{si} &= \tau_{si} + (\tau_{si} - \tau_{si})/2 \\
\tau_{si}' &= \alpha_{si}[1 + \exp[k_{si}(u - \theta_{si})]]/\left\{1 - \tanh[k_{si}(u - \theta_{si})]\right\}
\end{align*}
\]

(3)

\[
\begin{align*}
v_{\infty} &= 1 - H(u - \theta_{v\infty}) \\
w_{\infty} &= \left[1 - H(u - \theta_{w\infty})\right](1 - u)/\tau_{w\infty} + H(u - \theta_{w\infty})w_{\infty}^{\text{aux}}
\end{align*}
\]

(4)

(5)

(6)

(7)

Where, equation 1 is the voltage equation in space and includes a Laplacian term for the diffusion in tissue and the summ of three currents. One fast inward representing the Sodium currents, one slow outward representing the Calcium currents and one slow inward representing the potassium currents (given by equations 5-6). Equations 2-4 are for the other 3 variables of the model which in addition to the voltage, they are “v” a gate variable for sodium, “w” and “s” two calcium gate variables. Equations 8-15 indicate time constants for the dynamics of the 3 gate variables and equations 16 and 17 provide the steady state values for the “v” and “w” gates.

3 RESULTS AND CONCLUSIONS

The final model is available at [http://chaos.gatech.edu/2D_4V_Master_Model_01_08_2017/](http://chaos.gatech.edu/2D_4V_Master_Model_01_08_2017/) for two dimensional simulations on a tissue of size 13x13cm². The program allows to initiate plane waves and spiral waves by exciting inside the tissue with the mouse. Furthermore all the different models are available and the parameters can be change during the simulation at any time. Figure 1 shows an example of a spiral wave initiated using the parameters for the Human epicardium cell model[13]. The figure shows also the voltage signal from one pixel in time and all the menus that can be used during the simulations. They also include stimulations on the tissue by using the mouse or a particular position in space with a given period.
3.4 Conclusion
We have condensed in a single model the dynamics of several cardiac systems. From Human ventricle and atrial models to animal models such as rabbit, dogs and pigs. This model reproduces these different cell dynamics by changing the various parameters in the model. Furthermore, the model can be simulated in two dimensional tissues in near real time using GPU processors and via the web by programming it in WebGL. This is the first time the dynamics of many different cell types can be studied by practically anyone by only using our code that is machine independent.

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REFERENCES


A NEW RABBIT MODEL FOR INVESTIGATION OF HUMAN INTRACRANIAL ANEURYSMS

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SUMMARY
A novel bifurcation rabbit model was designed to eliminate retrograde flow. In this work, we use computational fluid dynamic simulations to investigate the ability of this new rabbit model to create flow patterns relevant to human intracranial aneurysm (IA). The flow types generated in the new rabbit model are found to be highly relevant clinically. In particular, two of the most common flow types found in human cerebral aneurysms can be generated using this model. The new fully-prograde model thus has great potential for studying the role of adverse hemodynamics in aneurysm wall degradation.

Key words: intracranial aneurism, elastase-induced rabbit aneurysm, CFD

1 INTRODUCTION

The abnormal flow within a cerebral aneurysm is believed to play an important role in the degradation of the extracellular matrix. Correlations have been sought between rupture and hemodynamic characteristics such as wall shear stress magnitude (WSSM); in other studies, the relationship between global flow metrics and changes to the aneurysm wall were sought [1-2]. More recently, efforts have been made to identify a connection between local hemodynamics and wall degradation, investigating the stability of flow patterns, regions of impingement, inflow jet size, wall shear stress (WSS), and the formation of multiple vortices [3-9]. A general conclusion is that aneurysms with simple stable flow patterns and large impingement region are safer than those with complex unstable flow patterns and small impingement region [5]. Flow patterns have been classified into four different types based on their stability and complexity [9]: a single stationary vortex, Type I, multiple stationary vortices, Type II, a single stationary vortex plus a secondary transient vortex, only visible during part of the cardiac cycle, Type III, and multiple transient vortices that constantly change orientation and impingement region, Type IV, which have been found to represent 44%, 19%, 17%, and 20% of the population, respectfully.

Animal models of cerebral aneurysms have been introduced and used for devise design and to understand the impact of the abnormal flow in the cerebral aneurysm on wall remodeling [10,11]. An elastase induced rabbit model for cerebral aneurysms has been shown to generate a range in values of pressure, WSS, and OSI that are typical for human IAs [12]. However, these sidewall models only generate Type I and III flows which contain a partially retrograde component.

In this study, we utilize computational modeling to analyze a novel bifurcation-like rabbit aneurysm model that was previously developed at the Mayo Clinic. This model eliminates retrograde flow using a surgically created arteriovenous fistula distal to the aneurysm which produces a “high flow” as opposed to the slower, partially retrograde flow “low flow”. We extensively evaluate this model in silico to determine the flow types that can be generated in this model as well as the robustness of
this model to geometric perturbations. This latter point is important for understanding whether it is possible to create an animal model with a desired flow type on demand. We found the novel rabbit aneurysm model has the ability to generate clinically important flow types not previously seen in the side wall rabbit model.

2 METHODOLOGY

Three rabbit models were considered in this study - two new high flow bifurcation models as well as a modification of the low flow, side wall model. The aneurysms for Cases 1 and 2 were created in the proximal LCCA following distal ligation and elastase exposure. The RCCA was attached directly to the venous system in order to create a fully pro-grade flow condition which is more similar to arterial flow in cerebral arteries. Case 3 is a sidewall aneurysm, obtained by ligating the RCCA without the AVF. Retrograde flow is generated in Case 3 during part of the cardiac cycle. The 3D computational models of the rabbit vasculature or Cases 1-3 were reconstructed using a commercial package (MIMICS; Materialise, Leuven, Belgium) and used for the CFD studies. To test the sensitivity of the flow fields to geometric variation, two in silico modifications (one “bottle-necked” and one “inclined”) were created. The bottle-necked aneurysm was created by both widening the sac diameter and narrowing the neck region; the inclined aneurysm was created by re-orientating the angle of the neck plane with respect to the parent vasculature. The flow type for each case was determined based on the definition published in [9], in which flow patterns in the IA were classified based on complexity and stability.

Blood was modeled as an incompressible Newtonian fluid with viscosity 0.0035 Pa s and density1050 kg/m^3. A uniform velocity profile was prescribed due to the proximity of the aneurysms to the heart [13]. The numerical results of the unsteady 3D Navier-Stokes equation were obtained using an edge-based finite element scheme in the CFD code Feflo [8]. Time varying velocity boundary conditions were prescribed at the boundaries of the fluid domain based on in vivo ultrasound measurements, with the notable exception of the descending artery, where a pressure boundary condition was used. Each cardiac cycle was discretized by 100 timesteps and the domain discretized with linear tetrahedral mesh elements with near-uniform edge lengths of approximately 0.015 cm.

3 RESULTS AND CONCLUSIONS

Streamlines were used to classify flow type during systole and diastole, Figure 1. Cases 1 and 2, with the fully high flow condition, both gave a Type II flow. In contrast, Case 3 generated a Type III flow. To further assess the impact of the flow condition, a low flow condition was prescribed in Case 1 and compared with results for the same model with the high flow condition, Figure 2. The effect of aspect ratio on flow type was explored by morphing the original high aspect ratio aneurysm for Case 1 into a low aspect ratio (AR) bifurcation aneurysm, Figure 3. This change from high to low aspect ratio, shift the flow type from type II to type I flow. The robustness of the flow type for Case 1 was evaluated by modifying the original geometry, Figure 4. The flow type was unchanged, despite modifications to the sac geometry as well as changes in orientation of the aneurysm sac relative to the parent artery.

In this study, new rabbit models developed by the Kallmes group were investigated in silico. The new high flow bifurcation model was found capable of generating both Type I and Type II flows in low and high aspect ratio sacs, respectively. Furthermore, the high flow conditions generated using the AVF eliminate the retrograde flow found in low flow models which is a flow conditions unrealistic in physiological cerebral circulation. Additionally the type II flow was found to be robust to perturbations in sac geometry and sac orientation relative to the parent vasculature. This new model effectively extends the repertoire of relevant flow types possible from the rabbit animal model. In the future, the study of sensitivity to geometric variations can be extended. Thus, this new rabbit model has potential to serve as a powerful tool in relating more adverse hemodynamics to wall structure/content.
Figure 1: Comparison of velocity magnitude and streamlines between bifurcation model (Cases 1, 2), and sidewall model (Case 3).

Figure 2: Comparison of different flow conditions for fully pro-grade high flow and partially retro-grade low flow in Case 1.

Figure 3: Assessment of the change in flow streamlines for high aspect ratio (HAR) versus low aspect ratio (LAR) sac geometries for Case 1. The flow type was seen to shift from a Type 2 flow (HAR) to a Type 1 flow (LAR).

Figure 4: Robustness of Case 1 to permutations in geometry. Modification A (Mod A): the sac diameter was widened and the neck region narrowed. Modification B (Mod B): the angle between the plane of the neck centerline and the parent vessel was altered. The flow type remained unchanged relative to the original model shown in row 3 (Case 1).

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between Human and Rabbit Saccular Aneurysms.

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EMOTION ANALYSIS USING ELECTRODERMAL SIGNALS AND SPIKING NEURAL NETWORK

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SUMMARY

Emotion is a psycho-physiological process that is characterized by behavior, perception, attention and decision making. Assessment of emotional states is important in the field of cognitive neurological disorders and clinical conditions. Analysis of Electrodermal Activity (EDA) signals is a popular technique to identify different emotional states. EDA is a non-invasive technique that records the skin conductance. In this work, an attempt has been made to differentiate various emotional states using EDA signals and Spiking Neural Network (SNN). The signals are obtained from a publicly available DEAP database. SNNs are brain-inspired feature learning and classification architecture. This methodology is able to learn and predict the arousal-valence levels for emotion classification. The result shows that SNNs are able to classify different emotional states. It is also found that the SSN is able to achieve an average recognition accuracy of 73.75% on the arousal dimensions and 71% on the valence dimensions. This method appears to be useful in analysis of EDA signals for classification of emotional states.

Key words: Spiking neural network, Electrodermal activity signals, emotion, valence, arousal, classification

1 INTRODUCTION

Emotions play an important role in addressing the peculiar behavior of individual human being. It affects psychological and physiological responses such as social behavior, facial expressions, nervous system activity and other biological system. Assessment of emotions is a challenging task [1]. An Emotional state can be described in two-dimensional valence-arousal space using Russell scales [2]. Generally, Emotions can be differentiated through analysis of facial expressions or through physiological signals such as Electrocardiogram (ECG), Electroencephalogram (EEG) and Electrodermal Activity (EDA). EDA signals are considered as the most reliable biomarker for the reliable quantification of emotions [3]. In this work, an attempt has been made to classify EDA signals in arousal-valence scale to identify various emotions using Spiking Neural Network (SNN).

2 METHODOLOGY

For this study, EDA signals are obtained from the DEAP database with valence-arousal scale [2]. The database consist of physiological signals from 32 subjects using audio-visual stimuli. EDA signals are divided into sixty segments, normalized and randomly sampled to obtain even distribution of training samples. Leave-one-out cross validation is used for testing the emotional state classification.

2.1 Spiking Neural Network

SNN are brain inspired artificial neural networks that are used for modeling, learning and classification. SNN uses spiking neurons for approximate continuous functions in the analysis. The spiking neurons represent the inherent dynamic nature that is characterized by the internal state with time. Spikes trains are generated for the given input using leaky integrate and fire model [4]. Synapses are encoded with information between the neuron. A presynaptic neuron uses spikes train to communicate with postsynaptic neurons. Unsupervised learning is used to set the initial
connection weights in synaptic neurons. Supervised learning is used in SNN to minimize the residual error between the input and output spikes. The spiking neuron dynamics in SNN can be represented as [4]:

\[ V(t) = \sum_k w_{kj} \sum_r R(t - t_{kr}) + V_{rest} \]

where \( w_{kj} \) is the initial synaptic weight of neuron and \( t_{kr} \) is the neuron’s presynaptic spike. The resting potential of the \( V^\text{th} \) node is given by \( V_{rest} \) which is initially set as 0.

The action potential of the \( k^\text{th} \) neuron is initiated if the potential of neuron is higher than the threshold at a given instant of time \( t^{in} \)

\[ V(t^{in}) \geq \text{threshold and } \frac{dV(t^{in})}{dt} > 0 \]

After the synaptic node is fired, a spike is generated and the membrane voltage is reset to its initial state. The potential of the node is initially at resting level for a time period also known as refractory period [4]. The performance of SNN is dependent on the firing rate of synaptic neuron which is governed by different learning rules.

3 RESULTS AND CONCLUSIONS

A representative EDA signal which is divided into equal segments is shown in Fig. 1(a). This step is performed to obtain the higher number of signal samples to enhance performance. Fig. 1(b) shows the synaptic weights of the SNN before the learning process. It represents the initial connection weights of a spiking neuron. The synaptic weights of SNN after the learning process are shown in Fig. 1(c). The x-axis represents the signal sample numbers and the y-axis represents the weight learned in the learning process.

The classification accuracy of SNN in classifying arousal and valence dimensions of the signal are 73.75% and 71%, respectively. It is observed that the recognition rate of arousal dimension is higher than that of valence dimension. It may be due to stimulus-specific response in EDA signals.

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