Preface

It is a pleasure to welcome all participants of the 6th International Conference on Computational & Mathematical Biomedical Engineering to Sendai. This sixth edition is hosted by one of the most prestigious universities in Japan, Tohoku University.

CMBE is an important forum for sharing progress and knowledge within the community interested in engineering mathematics, computational and experimental methods applied to biomedical problems. This year’s conference has received a large number of abstracts, each of which was peer-reviewed by members of the programme committee and mini-symposia organisers. We would like to thank all the authors and session organisers, committee members and external reviewers for their efforts.

The CMBE19 proceedings will be available to download from the conference website. All authors are invited to submit an extended version of their paper to the ‘International Journal for Numerical Methods in Biomedical Engineering’.

The conference consists of an opening, 2 plenary and 6 keynote lectures, 23 tracks or mini-symposia divided into multiple sessions and 3 standard sessions. Poster abstracts are included in the conference programme and proceedings. CMBE also awards the ‘International Journal for Numerical Methods in Biomedical Engineering (IJNMBE) Best PhD Award in Biomedical Engineering’, in recognition of important contributions to the advancement of computational and/or mathematical biomedical engineering.

Finally, we would like to thank all delegates who attended CMBE19 and made its success.

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Invited Lectures
MODELING SINGLE CELL AND ENDOTHELIAL MONOLAYER MECHANICS DURING METASTATIC CANCER

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SUMMARY

Despite the critical importance of metastasis in cancer, there is much we have to learn about the mechanisms by which a circulating tumor cell enters into the microcirculation, adheres to or becomes lodged in a small capillary, and transmigrates out of the circulation to enter the tissue and become a metastatic tumor. This presentation will address several of these processes through a combination of microfluidic and computational approaches. The computational models are multi-scale in that they involve the macroscopic (continuum) viscoelastic properties of the different cell types as well as cell-cell interactions of adhesion and monolayer junctional dynamics. We address the different cell receptors or internal structure using both discrete and continuum approaches to gain insight into the complex processes comprising the metastatic cascade. These are coupled with microfluidic studies that recreate the microvascular network in the metastatic organ and enable detailed characterization of adhesion and transmigration events. Together, they provide new understanding of these key phenomena.

1 INTRODUCTION

Metastatic cancer, the cause of more than 90% of cancer deaths, remains poorly understood, despite its obvious importance. One reason for this is the difficulty of studying the various stages of the metastatic cascade in vivo, and the lack of comprehensive in vitro or computational models. Here we present several examples focusing on the process by which tumor cells escape from the circulation and invade into the tissue at a metastatic site. We show how the combination of in vitro and computational models can provide new insights into the underlying mechanisms of the disease.

First consider the process by which the circulating tumor cell initiates the process of extravasation, passing across the endothelial barrier. To study this experimentally, we utilize two different microfluidic platforms, both containing an endothelial layer with an internal lumen or fluid space, and bounded externally by an extracellular matrix, either collagen type I or fibrin. In one case, the vessel network emerges from a population of endothelial cells seeded into a fibrin gel, often in co-culture with fibroblasts that help form and maintain the vascular networks. In a second, an endothelial monolayer is seeded on top of a thin, planar collagen gel.

2 THREE MODEL SYSTEMS OF TUMOR CELL EXTRAVASATION

In our first example (Fig. 1A), we obtained time-lapse confocal images of tumor cells that had lodged or adhered to the inside of vessels in the vascular network. In one image from a time-lapse sequence, a tumor cell can be seen in the midst of passing through a gap between endothelial cells.
The nucleus can be seen to be highly deformed, raising questions about the role of nuclear stiffness in transendothelial migration. A 3D continuum model was generated that incorporates the membrane and nucleoplasm of the nucleus, along with adhesions to the ECM and internal contractile elements (Fig. 1B). Results showed that the ability of the cell to transmigrate depends on several factors including the size of the hole in the endothelium, the stiffness of the ECM, and the strength of the contractile force. Estimated values for these parameters supported the hypothesis that tumor cells are capable of undergoing transmigration across a passive endothelial monolayer using actomyosin contractility in the cytoskeletal network [1].

We next asked if it was necessary for the endothelium to relax its tight junctions in order for the tumor cell to gain access to the underlying ECM via invadopodia, or if the natural stochasticity of the monolayer was sufficient to allow this to occur.

Fig. 1. Tumor cell extravasation across an endothelial monolayer. A) Tumor cell (green) in the process of transmigrating across the endothelial wall (pink) of a microvascular network. Note the distortion of the nucleus (blue). B) A Computational model of the extravasation process. (Adapted from [1].)

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Fig. 2. Dynamic gap formation in a planar endothelial monolayer. A) Experimental time-lapse images expressing GFP VE-cadherin. Orange arrows indicate two gaps between endothelial cells. B) One image from a time sequence obtained using a computational model of gap formation. (Adapted from [2].)
To address this question, a planar monolayer system was used, expressing a GFP-labeled VE-cadherin in order to visualize the dynamics of the junctional complexes (Fig. 2A). We found that gaps naturally occurred, especially in the apex regions – those where 3 or more cells joined together – and that these openings occurred with a sufficient frequency and opening size to enable tumor cells to extend invadopodia and gain access to the underlying basement membrane. To explore this further, and investigate the basis for this observation, we developed a discrete model of the monolayer in which the cytoskeleton was represented by a collection of radially oriented filaments connecting to fixed points on the viscoelastic membrane where junctions could stochastically form between neighboring cells (Fig. 2B). Using parameter values largely taken from the literature, we were able to generate results in terms of opening frequency and open time that were in good agreement with the experiments [2]. Of particular note is that only when the known catch-bond behavior of the VE-cadherins was introduced, did the gap size open to a level consistent with the experiments, and eventually close again, suggesting an important role for the adherens junctions in maintaining endothelial barrier integrity [2].

In the process of imaging the planar endothelial monolayer, we observed a phenomenon in which the underlying ECM rapidly (within hours or less) became densified immediately underneath (Fig. 3A), suggesting that the endothelial cells were gathering in and remodeling the local ECM in such a way that it might possibly impair the escape of the tumor cells. In order to study this mechanism further, we modified a Brownian dynamics code that our lab had previously developed to simulate the effect of filopodia that extend a short distance from the basal membrane, adhere to matrix fibers, and pull them toward the cell, rupturing crosslinks between fibers and allowing for plasticity in the ECM (Fig. 3B). Using this code, we were able to capture these dynamic events, providing supporting evidence for the proposed mechanism of the observed matrix densification [3].

3 DISCUSSION

In each of these cases, the coupling of experiment and computation led to new insights not attainable by either alone. Through models such as these, we are gradually building on our understanding of one critical step in the metastatic process, which we hope will lead to new therapeutic approaches.
ACKNOWLEDGEMENTS
This work would not have been possible were it not for a truly exceptional collection of students and postdoctoral researchers, most of whom are recognized as co-authors on the referenced publications. We also gratefully acknowledge financial support from the National Cancer Institute.

REFERENCES
IDENTIFYING PHYSICAL CAUSES OF FAILURE IN BRAIN ANEURYSMS

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SUMMARY

Rupture of cerebral aneurysms is a central cause of subarachnoid hemorrhage, a devastating type of stroke with high mortality and disability rates. However, treatments for unruptured aneurysms have clinical risks that can exceed the risk of rupture. Hence there is a great need to develop reliable methods for assessing rupture risk. Presently, most efforts to improve risk assessment are directed at identifying correlations between outcome (rupture versus non rupture) and patient clinical characteristics, aneurysm geometry, and flow inside the aneurysm. Our group has identified a substantial vulnerable population within the unruptured group with a large heterogeneity in collagen fiber architecture, cellular content and calcifications. These findings motivate our present studies to identify the actual physical causes for wall vulnerability. In this presentation, we discuss recent results in this area using data driven computational simulations to determine conditions that i) enable robust walls, ii) enable sufficient conditions for remodeling and stabilization following subfailure damage or iii) push subfailure damage to catastrophic failure. These studies are driven by data obtained from human aneurysm tissue, analyzed using new bioimaging methodologies that enable mechanical testing simultaneous with imaging of collagen fibers and calcification. New tools for mapping the heterogeneous experimental data for the wall to the 3D reconstructed vascular model make it possible to evaluate the associations between critical aspects of aneurysm wall structure and both hemodynamic and intramural stress.
Coupled Multiphysics Models of Cardiac Hemodynamics: 
From Fundamental Insights to Clinical Translation

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Key words: thrombogenesis, cardiac hemodynamics, heart murmurs

1 INTRODUCTION

The mammalian heart has been sculpted by millions of years of evolution into a flow pump par excellence. During the typical lifetime of a human, the heart will beat over three billion times and pump enough blood to fill over 60 Olympic-sized swimming pools (Mittal 2018). Each of these billions of cardiac cycles is itself a manifestation of a complex and elegant interplay between several distinct physical domains including electrophysiology and mechanics of the cardiac muscles, hemodynamics, and flow-induced movement of the cardiac valves.

Another multiphysics interaction that is key to hemostasis involves hemodynamics and blood biochemistry. The clotting cascade, which is a natural response to injury, is initiated by a sequence of biochemical reactions that are strongly modulated by local flow conditions. In this regard, how the chambers and valves of a healthy heart manage to avoid thrombosis, remains an open question. The presence of heart conditions such as myocardial infarction (MI), cardiomyopathies, valve anomalies and atrial fibrillations, disturb the hemostatic balance and can lead to thrombosis with devastating sequelae such as stroke and MI. Computational models of thrombogenesis in the cardiac system have the potential to provide useful insights into this important phenomenon. (Mittal et al. 2016).

3 RESULTS AND CONCLUSIONS

Figure 1: Coupled chemo-fluidic modeling of thrombogenesis in the left ventricle. Top: Modeling of two patient-specific cases. Bottom: Detailed analysis of flow and coagulation chemistry for one patient specific case.
In the current talk, I will describe a versatile, high-fidelity chemo-fluidic computational model that is formulated to explore a variety of problems related to thrombogenesis in the cardiovascular system. The computational model is applied to the problem of thrombogenesis in the left ventricle (LV) for patient recovery from myocardial infarction. Simulations are conducted for a small cohort of patient-specific models developed from 4D cardiac CT imaging. The simulations suggest a new metric, the E-wave propagation index (EPI), for stratifying the risk of LV thrombogenesis and this metric is validated using a retrospective analysis of a 75-patient cohort. Fig. 1 shows some representative simulations from this study (Seo et al. 2016).

Application of these models to thrombogenesis in transcatheter aortic valves will also be described. This study is motivated by recent clinical studies of bioprosthetic aortic valves based on high-resolution computed tomography (CT) scans that have shown a higher than expected incidence of reduced leaflet motion (RLM) due to early leaflet thrombosis. Although in most cases, the RLM is considered subclinical, the hemodynamic impact and long-term clinical significance of RLM are not yet understood. In our approach, the hemodynamics associated with RLM are investigated using a sharp-interface immersed boundary method-based flow-structure-interaction computational model. A reduced degree-of-freedom model for the leaflet dynamics is employed, which accelerates our ability to examine dominant effects of leaflet motion. Simulations for i) normal, ii) RLM in one, and ii) two leaflets are performed to investigate the effect of RLM on the transvalvular hemodynamics and the implication for the progression of disease. Fig. 2 shows results of simulations for these three valve models.

Finally, the talk will focus on computational modeling of hemoacoustics, i.e. the generation and propagation of heart murmurs. Patterns of blood flow associated with abnormal heart conditions generate characteristic sounds that can be measured on the chest surface using a stethoscope. This technique of `cardiac auscultation' has been used effectively for over a hundred years to diagnose heart conditions. However, the mechanisms that generate heart sounds, as well as the physics of sound transmission through the thorax, are not well understood. I will present a computational method for simulating the physics of heart murmur generation and transmission and will show the use of this model to simulate the murmurs associated with a modeled aortic stenosis. The simulation results are compared with experimental measurements and show good agreement. The present study confirms that the pressure fluctuations on the vessel wall are the source of these heart murmurs, and both compression and shear waves likely play an important role in cardiac auscultation (Seo et al. 2017).

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COMPUTER SIMULATION OF PLATELET ADHESION AND THROMBUS FORMATION

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SUMMARY
The biological function of platelet cell is relatively simple such as adhering to the site of endothelial damage, making aggregates to increase the size of platelet thrombi, providing procoagulant surface to induce activation of coagulation cascade locally, etc. Circulating platelet cell start to adhere immediately to thrombogenic molecules such as von Willebrand factor at site of endothelial injury. A micrometer scale biological phenomena of platelet adhesion could be constructed from nanometer scale of atomic movement with the use of high-performance computers. The growth of platelet thrombi could also be constructed at least partly as the physical events. Quantitative biological experiments provide necessary data to confirm the validity of computer calculation. Computational and mathematical engineering is now become strong tool to understand the mechanism of complex biological phenomena as the integration of simple physical and chemical events.

Key words: platelet, computer simulator, von Willebrand factor, blood flow

1 NUMERICAL SIMULATION OF PLATELET CELL ADHESION, ACTIVATION AND AGGREGATION UNDER BLOOD FLOW CONDITIONS

1.1 Simulation of Platelet Adhesion Under Blood Flow Conditions

Of the important biological function of platelet cells, adhesion at site of endothelial damage is an important initial step leading to the hemostasis and thrombus formation. Previously published biological experimental research revealed that platelet adhesion starts immediately when the endothelial cells were damaged physically or functionally even in the absence of any soluble platelet activating agents. Under blood flow condition, initial adhesion of platelet is mediated exclusively by glycoprotein (GP) Iba binding with von Willebrand factor (VWF). Binding become stabilized by contribution other receptors such as GPIIb/IIIa and GPVI. Under blood flow generating relatively high shear rate greater than 1.500 s\(^{-1}\), platelet cohesion and aggregation are also mediated by the interaction between GPIIb\(_\alpha\) and VWF.

A mathematical simulation model of platelet adhesion and aggregation under blood flow conditions were published previously. These simulators including ours are aim to reproduce platelet adhesion at site of endothelial damage and subsequent local growth of platelet thrombus under various blood flow conditions. Initial adhesion process was modeled as platelet membrane GPIIb\(_\alpha\) binding with exposed VWF. These protein bindings were exerted with viscoelastic spring by Kelvin-Voigt model (Fig. 1, supplemental movie 1). The biological validity of this simulator was established at least partly with comparative biological experiments using flow chamber and human blood. One important factor difficult to incorporate is the role of erythrocytes to generate fluctuating blood flow directed to vessel wall.
A recently developed 10-peta-flops class super computer enable us to mimic the rheological function of erythrocytes assuming blood as Newtonian fluid. Simple simulator enabled to predict accumulation of more platelet around obstacle in the flow route such as stent strut. This technology along with biological experiments provides useful information to predict the shape of stent strut with less thrombogeneity.

1.2 Simulation of von Willebrand factor with platelet GPIIbα

Total number of atoms constructing A1 domain of VWF (ASP506-PRO703), N-terminus GPIIbα (HSE1-PRO265) and surrounding water molecule is 172,934. Current high-performance computers are able to conduct a million of parallel computations. The physical interaction among 172,934 atoms require huge calculation, but the requirement is now within the capacity of current high-performance computer to handle. Classical Newtonian equation of force (F) equals mass (M) x acceleration (A) was applied to predict the physical movement of atoms. To incorporate quantum mechanics (QM) into force field, the chemistry at Harvard Macromolecular Mechanics (CHARMM) force field were used. Fig. 8 shows the snap shot of predicted binding structure of GPIIbα and VWF. With the potential of mean force of structure at various distance between mass center of GPIIbα and VWF, the binding force between GPIIbα and VWF was predicted to be 67 pN. Calculated predictive value was in agreement with the binding force measure by optical tweezers and atomic force microscopy.

1.3 Simulation of platelet interaction with other biologically important system

Upon activation, platelet cells release various bio-chemically active substances locally. These activation-induced local release of various biological substances were modeled as platelet cell simulator. Another important function of activated platelet is local activation of coagulation cascade. This process was also modeled to predict vascular occlusive thrombosis.
3. DISCUSSION
In summary, complexed process of thrombus formation could at least partly reproduced on computer simulation from integration of atomic movement to cellular function. Validation of in silico model with the use of quantitative biological experiments are essential for making computer simulators to be applied in the biological research.
Close collaboration among computer specialists, biomedical research specialists and even medical care profession is crucial.

DISCLOSURE

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COMPUTATIONAL IMAGE ANALYSIS IN BIOMEDICINE:
METHODS AND APPLICATIONS

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SUMMARY

The computational analysis of images, which has become a paramount research topic, is very challenging as it usually comprises complex tasks like as of segmentation, i.e. the detection, of imaged structures, matching and registration, i.e. alignment, of structures, tracking of structures in images, deformation estimation between structures and 3D reconstruction from images. For example, to analyze the behavior of organs from medical image sequences, first the input images should be segmented, then suitable features of the organs under analysis should be extracted and tracked along the sequences and finally, the tracked behavior should be analyzed.

Despite the inherent difficulties, computational methods of image analysis have been more and more used in a wide range of important applications of our society, exceptionally in Biomedicine.

In this talk, computational methods of image analysis that we have developed in order to analyze structures in biomedical images will be introduced; particularly, those developed for image segmentation, matching, registration, tracking and 3D shape reconstruction. Furthermore, their use in several biomedical applications will be presented and discussed.

Keywords: Computer Vision, 3D Vision, Segmentation, Registration, Tracking, Matching, Deformable Models, Stochastic Filters, Volumetric Methods

REFERENCES

COMPUTATIONAL INVESTIGATIONS OF LIVER MULTI-LEVEL HEMODYNAMICS AND FUNCTION: TOWARDS A BETTER UNDERSTANDING OF SURGERY OUTCOMES AND DISEASE PROGRESSION

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SUMMARY

Liver is a key organ of the body, which function might be severely impaired due to disease progression or partial resection (pHx). Both trigger hemodynamics changes, which causes and consequences are still matter of debate. The precise link between liver architecture, perfusion and function remains to be fully elucidated.

First, computational simulations have qualitatively and quantitatively characterized the link between architecture and hemodynamics in the context of pHx, based on multi-level mathematical models of whole-body and hepatic hemodynamics. The hepatic model takes into account a lobe-specific perfusion, with both arterial and portal venous inflows. A dedicated numerical scheme of 1D hemodynamics equations was necessary to handle vessel collapse, which happens during surgery. Second, we characterize such link at different stages of cirrhosis development. For both different mechanisms impacting hemodynamics were studied (organ vascular dilation, liver microcirculation changes, …) : systemic vascular responses seem particularly important to take into account to understand liver hemodynamics changes due to pHx, early days of regeneration and disease progression.

The third piece of the puzzle is function. ICG is an injectable compound, which is a marker of liver function. Its fluorescence dynamics can be interpreted via a dedicated pharmacokinetics model to provide perfusion and function information. Such dynamic signal is a promising way to characterize the liver state.
MATHEMATICAL MODELLING OF TISSUE INVASION AND METASTASIS

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SUMMARY

Tissue invasion and metastasis (the spread of a primary tumour to secondary locations) have been identified as “hallmarks of cancer” [Hanahan, D., Wienberg, R.A. (2000) The Hallmarks of Cancer. Cell, 100, 57-70]. Indeed, the secondary tumours resulting from the metastatic spread—metastases—are the cause of over 90% of all deaths from cancer. Invasion of the surrounding tissue is a complex, multiscale phenomenon involving many inter-related genetic, intra-cellular, cellular and tissue processes at different spatial and temporal scales. Central to invasion is the ability of cancer cells to alter and degrade an extracellular matrix. Combined with abnormal excessive proliferation and migration which is enabled and enhanced by altered cell–cell and cell–matrix adhesion, the cancerous mass can invade the neighbouring tissue. Upon encountering any nearby blood (or lymph) vessels, the cancer cells then interact with endothelial cells and enter the local blood vessel network (intravasation), are carried throughout the blood system, at some later point in time adhere to a blood vessel and exit the network (extravasation) at a distant secondary location of the host body, thereby allowing for the growth of a secondary tumour, or metastasis. In this talk we first present a mathematical model of cancer invasion, where cell–cell and cell–matrix adhesion is accounted for through non-local interaction terms in a system of partial integro-differential equations. The change of adhesion properties during cancer growth and development is investigated here through time-dependent adhesion characteristics within the cell population as well as those between the cells and the components of the extracellular matrix. We then present a novel model of metastatic spread, using a hybrid (discrete-continuum) form of the invasion model, where, in addition to the growth and invasion of a primary tumour (e.g. breast tissue), we consider explicitly different spatial domains representing the secondary locations of metastatic spread (e.g. lung, bone, brain).
ENDOTHELIAL CELL MECHANOSENSING AND ITS ROLE IN VASCULAR PHYSIOLOGY

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SUMMARY

Vascular endothelial cells (ECs) play critical roles in regulating a variety of vascular functions, including maintenance of the vascular tone, blood coagulation and fibrinolysis, and provision of selective permeability to proteins. It has recently become apparent that ECs show alterations in their morphology, functions and gene expression profile in response to exposure to hemodynamic forces, namely, shear stress and stretch [1-3]. These responses also play important roles in maintaining normal circulatory system functions and homeostasis [4], whereas their impairment leads to various vascular diseases, including hypertension, aneurysm and atherosclerosis [5]. The mechanisms underlying the mechanotransduction, however, are not yet clearly understood. Plasma membranes of the ECs have recently been shown to respond differently to shear stress and stretch, by rapidly changing their lipid order, membrane fluidity, and cholesterol content [6, 7]. Artificial lipid-bilayer membranes also show similar changes of the lipid order in response to exposure to shear stress and stretch [6, 7], indicating that these are physical phenomena rather than biological reactions. Such physical changes then activate the membrane receptors and cell responses specific to each type of force [6-8]. These findings suggest that the plasma membranes of ECs act as mechanosensors, and in response to mechanical forces, they show alterations of their physical properties, with modification of the conformation and functions of the membrane proteins, which then trigger activation of the downstream signaling pathways.

Key words: vascular endothelial cells, shear stress, mechanotransduction, plasma membrane

REFERENCES


COMPUTATIONAL TISSUE ENGINEERING:
FROM LIVING IMPLANTS TO VIRTUAL PATIENTS

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SUMMARY

One of the major challenges in Tissue Engineering (TE) is the translation of the increasing biological knowledge on complex cell and tissue behavior into a predictive and robust engineering process. Mastering this complexity is an essential step towards clinical applications of TE. Computational modeling can help in quantifying and optimizing the TE product and process but also in assessing the influence of the in vivo environment on the behavior of the TE product after implantation. In this talk, examples will be shown to demonstrate how computational modeling can contribute in all aspects of the TE product development cycle.

Key words: in silico, tissue engineering, computer modeling

1 INTRODUCTION

The growing field of in silico medicine is focusing mostly on the two largest classes of medicinal products: medical devices and pharmaceuticals. However, also for advanced therapeutic medicinal products, which essentially combine medical devices with a viable cell or tissue part, the in silico approach has considerable benefits. In this talk an overview will be provided of the budding field of in silico regenerative medicine in general and computational bone tissue engineering (TE) in particular. As basic science advances, one of the major challenges in TE is the translation of the increasing biological knowledge on complex cell and tissue behavior into a predictive and robust engineering process. Mastering this complexity is an essential step towards clinical applications of TE. Computational modeling allows to study the biological complexity in a more integrative and quantitative way. Specifically, computational tools can help in quantifying and optimizing the TE product and process but also in assessing the influence of the in vivo environment on the behavior of the TE product after implantation. Examples will be shown to demonstrate how computational modeling can contribute in all aspects of the TE product development cycle: cells, carriers, culture conditions and clinics. Depending on the specific question that needs to be answered the optimal model systems can vary from single scale to multiscale. Furthermore, depending on the available information, model systems can be purely data-driven or more hypothesis-driven in nature. The talk aims to make the case for in silico models receiving proper recognition, besides the in vitro and in vivo work in the TE field.

2. IN SILICO TISSUE ENGINEERING

2.1 Intracellular model of growth plate chondrogenesis: in silico screening

The regulation of the cellular programs is driven by the actions and interactions of numerous biological signaling pathways, making it nearly impossible to predict the biological effects of specific cell culture conditions or screen for druggable target molecules. Based on an extensive literature study, we have proposed a network describing the chondrogenic differentiation process in the growth plate. We have developed a computational strategy allowing the combination of the
advantages of Boolean modeling, having few parameters, with those of differential equation based modeling namely having a continuous level of activity instead of on/off behavior [1-3]. Inference of a micro-array-based network has been performed using a consensus approach based on a variety of inference methods. Comparison to the inferred network confirmed the accuracy of the developed literature-based model and suggested routes for further research. To date, the model has been tested successfully for its predictive capacities in selecting optimal culture strategies for human Periosteal Derived Stem Cells, iPSCs and ATDC5s. This model permits the partial replacement of large-scale screening experiments by an in silico screening experiment, followed by a more targeted in vitro experiment.

2.2 Combining enabling technologies to understand and optimise CaP-driven bone formation
Biological screening experiments for the new biomaterials that are developed every day can be lengthy and costly. We have developed a series of computational models focusing on different types of biomaterials including calcium-phosphate (CaP) based biomaterials and degradable metals. Starting from the data obtained in several screening experiments, simple regression models allowed predicting the experimental outcome for new biomaterials, as long as they were similar to the original sample set [4]. Virtual morphometry and histology permitted further identifying key properties of scaffolds leading to good bone formation with periosteal cells [5]. Finally, mechanistic models were developed to generalize these findings and integrate them in a knowledge-driven platform [6]. The models are currently used as a design tool for the development of optimized CaP-based or biodegradable metal-based structures for 3D printing. The latest model-informed CaP design shows a 5-fold increase in bone formation compared to a clinically used dental biomaterial in an orthotopic rat experiment (publication in preparation).

2.3 Design and optimization of bioreactor culture strategies (including scaffold geometry)
When culturing cells in 3D carrier structures inside a perfusion bioreactor, it is impossible to obtain a real-time, spatially detailed image of the processes that are ongoing inside the bioreactor. Measurements at the in- and outlet of the culture chamber only allow extracting general information. We have developed a series of in silico models that describes in a detailed way the growth of cells inside 3D porous carrier structures during culture in a perfusion bioreactor at various levels of detail (cellular, tissue, organ). These models have been corroborated by comparison with dedicated experiments using periosteal cells seeded on 3D printed titanium scaffold [7-9]. We are now able to model precisely the conditions not only the neotissue as a whole is exposed to during culture, but also individual cells inside the neotissue [10]. In order to perform rigorous optimization of the perfusion regime and the scaffold geometry, a reduced version of the model was created, leading to a 10^5-fold increase in computational efficiency [11]. Multi-objective optimization studies were carried out using, for instance, the criteria of filling speed and culture cost.

2.4 In silico clinical trials related to in vivo bone regeneration treatment
5% of the bone fractures do not heal spontaneously and require additional treatment. Starting during the candidate’s PhD, a computational model was developed describing the spatiotemporal evolution of the most important biological variables during fracture healing. The candidate and her team further refined the description of the angiogenesis process to allow modeling of individual blood vessels [12]. The last years, this model has been applied to investigate specific cases of non-healing fractures, followed by the in silico design of treatment strategies [13]. The latest development in this line is the use of the model to carry out in silico clinical trials investigating the phenotypic variety that exists within the population of young children affected by neurofibromatosis type 1 (NF1). NF1 being a pediatric rare disease, it is impossible to perform controlled trials to investigate the effect of certain treatments. In silico, however, a head-to-head comparison of treated and untreated patients can be performed applying machine learning techniques on the in silico data generated from a population of 200 virtual patients [14,15]. The challenge we are currently addressing is the translation of the identified biomarkers, being in silico model parameters, into patient characteristics that will allow patient stratification prior to invasive treatment. A 3-lineage differentiation test is showing promising results in this direction.
3. DISCUSSION
One of the major challenges influencing the uptake of the models in clinical and regulatory practice is related to building credibility of the digital evidence that these models provide. This credibility building begins with clear (standardized) communication about the models. FDA-USA has published guidelines on how and what model information to include in a regulatory submission. The next step is the verification and validation of the model (V&V40). In the verification step, correspondence is checked between the numerical solution and the mathematical equations making up the model. Afterwards, correspondence between the model outcome and the physical reality needs to be checked (validation). Finally, in an uncertainty quantification analysis, the impact on model output of simplifications and assumptions made during the modeling process is investigated. These guidelines are not only useful to follow in a regulatory setting, but also the academic environment where adherence to the guidelines would mean an increased robustness, reproducibility and industrial uptake of the in silico models.

REFERENCES


Reduced-order modelling for cardiovascular problems I
PATIENT-SPECIFIC CFD MODELLING IN THE THORACIC AORTA THROUGH A LEAST-SQUARE 3-ELEMENT WINDKESSEL APPROACH

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SUMMARY

Computational fluid dynamics in the aorta is currently a well-established methodology. Authors describe many possibilities to prescribe boundary conditions, all of them based on the availability of data. In this article, we propose a tuning method for 3-Element Windkessel based on constrained optimization. Flow data is extracted from PC-MRI whereas pressure wave is adopted from literature. We conclude that this method performs better than using other tuning methods or non-patient-specific data usually available in literature.

Keywords: computational fluid dynamics, thoracic aorta, boundary conditions, lumped parameter models

1 INTRODUCTION

Patient-specific modeling of cardiovascular diseases has been consolidating over the last two decades as a tool for quantitative analysis to elucidate pathological dynamics or even to design new therapies. Computational Fluid Dynamics (CFD) simulations customized in geometries retrieved from patients images are moving from a proof-of-concept stage to the clinical practice. The tailored treatment of boundary data still requires specific investigations due to its major impact in numerical results. On the one hand, one would like to retrieve from specific measures all the data needed by the mathematical model, so to maximize the adherence of the numerical model to the patient-specific data. On the other hand, this is not possible nor appropriate for physical or practical limitations of the measurement process. Devices have limited time and space resolution and measures are typically affected by noise, so they are not complete and trustworthy. In addition, clinical needs require referring to non-invasive and possibly already approved protocols. Different pathologies, diseases, vascular districts and ultimately available measures in this respect lead to different strategies, and the identification of the optimal approach for different problems is far from being reached. In particular, treatment of boundary conditions shows a wide variety of approaches from an extremely simplified stress free approach in the outflow boundaries to sophisticated data assimilation techniques such as Kalman filtering.

The aim of this article is to present and test an algorithm for calibrating boundary conditions in thoracic aortic simulations based on the so-called 3-Element Windkessel model (3WK) [1] and a minimization approach as proposed by [2].

2 METHODOLOGY

Three patients with thoracic aortic aneurysms in the arch were selected from our database. Aortic geometries were reconstructed from thin-cut Computed Tomography Angiography (CTA) from the annulus to the diaphragm including the supraortic vessels. Volume meshing was performed with
VMTK [3], resulting in meshes of an average of 4.5 million tetrahedral elements. In addition, contrast MRI (PC-MRI) was retrospectively reviewed in order to collect flow data in all the aforementioned boundaries. All simulations were run with lifeV finite element library [4].

To test our hypothesis, we ran four sets of simulations with different boundary conditions: *BC1*, where both inflow and 3WK parameters were retrieved from literature [5,6]; *BC2*, where the inflow wave was patient-specific and the outflow parameters were, again, retrieved from literature; *BC3* and *BC4*, where both inflow wave and outflow 3WK were patient specific.

In order to tune the resistances and capacitance in the outlets, we used a constrained optimization procedure as described in [2]. Since the require pressure wave was missing because no catheterization was performed, we assumed a standard one as described in [7] and then adapted to match each patient mean and pulse pressures. The procedure aimed at minimize the difference between the aforementioned pressure wave (or $P_{\text{target}}$) and the resulting pressure wave from applying each flow waveform into a 3WK with varying values of the 3 components (or $P_{\text{estimated}}$). The computational algorithm [8] was based on a nonlinear least-squares problem with bounds on the variables aiming at finding the optimal set of 3WK values that would minimize $P_{\text{target}} - P_{\text{estimated}}$.

Conservation of mass from PC-MRI measurements was not respected neither instantaneously nor by integrating an entire heartbeat. In order to account for this difference in our simulations the 3WK parameters in the descending aorta of *BC3* were tuned by subtracting the supraortic flow to the ascending aortic flow. In *BC4*, the tuning in the descending aorta was made directly with the flow wave retrieved from PC-MRI within its slice.

Velocity and WSS fields were compared qualitatively. Pressure and flow waves in the outputs were compared against their reference counterpart.

### 3 RESULTS

Figure 1 shows the velocity field at the systolic peak considering all the boundary condition strategies for Patient 1.

![Velocity volume rendering in our patient. Each set of boundary conditions results in a different hemodynamic behavior.](image)

Higher velocities towards the supraortic vessels are seen in *BC1* and *BC2*. Conversely, when using patient-specific data, flow is mostly diverted towards the descending aorta (*BC3/BC4*). This is confirmed in Figure 2, where flow distribution is significantly different among tuning strategies. *BC3* and *BC4* show the closest agreement with PC-MRI in terms of flow in most of the vessels. Pressure is better estimated by *BC3*. Analogous results were obtained with the other two patients.
Table 1 summarizes the flow split error between the waves used for the parameter calibration and the flow retrieved from the CFD simulation. Results in the descending aorta (DA) were compared against flow resulting from the consistent mass conservation constraint (DA/Sub) as well as to PC-MRI flow (DA/MRI).

<table>
<thead>
<tr>
<th>Mass Diff</th>
<th>Integral Error</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>74%</td>
<td>99%</td>
<td>20%</td>
</tr>
<tr>
<td>BCT</td>
<td>109 137 2 52</td>
<td>71 82 0 71</td>
<td>117 1 18</td>
<td></td>
</tr>
<tr>
<td>LCCA</td>
<td>172 205 2 52</td>
<td>315 339 2</td>
<td>68 340 0 15</td>
<td></td>
</tr>
<tr>
<td>LSA</td>
<td>94 119 2 52</td>
<td>267 290 0</td>
<td>71 148 2 13</td>
<td></td>
</tr>
<tr>
<td>DA/Sub</td>
<td>39 31 3 14</td>
<td>34 30 1 14</td>
<td>13 0 3</td>
<td></td>
</tr>
<tr>
<td>DA/MRI</td>
<td>6 20 69 51</td>
<td>29 38 95 69</td>
<td>4 19 15</td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Flow split error in all the outflow vessels. The mass difference between descending aortic flow retrieved from PC-MRI and the subtraction of the ascending aortic flow and the supraortic vessels is shown. BC1-BC4: boundary condition schemes. BCT, brachiocephalic trunk; LCCA, left common carotid artery; LSA, left subclavian artery.

4 DISCUSSION

Boundary conditions for computational hemodynamics is an active area of research, where the complexity of choosing a particular scheme is intrinsically related to the availability of the data. Historically, lumped models have been primarily used to assess physiological parameters such as vessel compliance, cardiac output, and peripheral resistance. Then, only in the last decades, lumped models were adapted as boundary condition systems for CFD. Because of their relevance in clinical practice, most of the literature has focused on the quality of the parameter estimation with different methodologies.

In this work, we picked a lumped model (i.e., 3WK) and found its parameters in a least-square fashion rather than relying in their formal definition. Additionally with this method, we also account for the diastolic and systolic pressure, which can be easily known from patient-specific data. As expected, results show that the use of patient-specific data under the optimization strategy work much better than the use of literature data. Furthermore, we found that modifying flow waves a-priori in order to satisfy the conservation of mass, which is one of the modelling assumptions, leads to much better results than using the raw data, even though the mathematical model does not require it.
5 CONCLUSION

To systematically perform CFD simulations in the thoracic aorta, we faced the challenge of assimilating an important quantity of measured data such as PC-MRI flow measurements at the inlet and all the outlets of the domain, as well as the cuff pressure. At a first analysis, retrieved flow data did not satisfy one of our modelling assumptions, which is the conservation of mass. For this reason, we used a 3D/0D multiscale modelling (i.e., 3D incompressible Navier-Stokes equations with rigid wall and 3-element Windkessel models). Additionally, we used a non-linear Least-Square approach to evaluate the 3WK parameters (also known as beat-to-beat parameter estimation). Of note, this surrogate method for data assimilation and boundary condition enforcement has the advantage to be extremely cheap with respect to alternative robust methods such as via a Kalman filter approach. This study also stresses, again, the importance of clinical and patient-specific data for running computational hemodynamics studies.

REFERENCES


FFT BASED 1D BLOOD FLOW SOLVER ACCOUNTING FOR NONLINEARITY AND VESSEL TAPERING AND ITS APPLICATION FOR AAA DETECTION

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SUMMARY

A novel FFT based method is proposed for flow solution in an arterial network. Unlike known FFT based methods, the proposed method can be applied to a network with tapering vessels and vessels with arbitrary aneurysms and stenoses. It also accurately captures the increasing pulse wave velocity (PWV) downstream and steepening of the pulse front. Compared to 1D space-time numerical schemes, the proposed method is fast and robust and correctly accounts for the vessel skin friction through the use of Womersley’s solution. It is a powerful tool to develop non-invasive aortic aneurysm detection methods through the waveform measurement and analysis.

Key words: Fast Fourier Transform (FFT), 1D arterial haemodynamics, perturbation method, aortic aneurysm detection

1 INTRODUCTION

The arterial haemodynamics is influenced essentially by pulse wave propagation phenomena. One of the most effective ways to study wave phenomena in an arterial network is through one-dimensional (1D) flow modelling. At present, the space-time numerical schemes are used for such modelling. However those schemes cannot account correctly for the vessel skin friction in a pulsating flow as the use of Womersley’s solution is too complicated for the 1D space-time approach to handle. Other unsolved issues of 1D space-time approach include difficulties in implementing multi-element windkessel and/or non-reflective outlet boundary conditions, incorporate a robust viscoelastic vessel wall model, curvature of arteries and mass loss in smaller arteries and vessel walls.

An alternative, FFT based, approach is proposed in [1]. It is based on linearisation of the 1D equations and expanding the solution using the Fourier series. The problem of wave propagation in arteries is solved analytically in the frequency domain, separately for every harmonic component. The skin friction can be accurately incorporated via Womersley’s solution. But the method described in [1] has some restrictions. Every vessel is approximated by a uniform pipe and the vessel tapering is not accounted. An aneurysm can be accounted only as a 0D element. Also the linear algebraic equations have to be derived manually and thus the method is not easy to employ on an arbitrary arterial network. Finally, the nonlinear effects are not considered by [1]. Therefore, despite its advantages, it is not competitive against the existing 1D space-time modelling methods.

In the present work, we propose the generalisation of the FFT method by developing an effective and accurate procedure for solving the equations for a tapering vessel or vessel with abnormalities such as aneurysm and stenosis. Also, we account for nonlinear terms in the 1D equation through a nonlinear correction to the linear solution. In addition, in the implementation of the proposed method, the system of algebraic equations for every harmonic component is built automatically for any arbitrary arterial network.
2 METHODOLOGY

The system of PDEs for an arterial network derived in [2] can be written in the form
\[
\frac{\partial q}{\partial t} + \partial \left( \frac{\alpha q^2}{A} \right)/\partial x + (A/\rho) \partial p/\partial x + (2\pi\gamma\nu/A) q = 0, \quad A' \partial p/\partial t + \partial q/\partial x = 0. \tag{1}
\]

Here \(p, q, A\) are the pressure, flow rate and the lumen cross-sectional area, respectively; \(\rho\) and \(\nu\) are the blood density and kinematic viscosity, respectively; \(A' = dA/dp\) can be calculated via the constitutive relation \(A = A(p)\); \(\gamma\) and \(\alpha\) are dimensionless coefficients defined as
\[
\gamma = a|u_r(a)|/\bar{u}, \quad \alpha = \bar{u}^2/(\bar{u})^2 = (1/A\bar{u}^2) \int_S \bar{u}^2 \, dS, \quad \bar{u} = (1/A) \int_S u \, dS
\]
where \(u\) is the flow velocity profile; \(a\) is the lumen radius; subscript \(r\) denotes the partial derivative with respect to \(r\), which is the polar coordinate in the lumen cross-section \(S\).

The equations can be modified and re-written in the matrix form:
\[
Lu = n
\]
where \(L\) is the linear operator, \(u\) is the state vector, and \(n\) is a vector of nonlinear terms:

\[
L = \begin{bmatrix}
\partial / \partial x & (\rho/A_0)(\partial / \partial t) + (2\pi\mu\gamma)/A_0^2 \\
(A_0/(\rho\epsilon_0^2))\partial / \partial t & \partial / \partial x
\end{bmatrix}, \quad u = \begin{bmatrix} p(x,t) \\ q(x,t) \end{bmatrix}
\]

\[
n = \begin{bmatrix}
-(\rho/A_0) \partial \left( \alpha q^2/A \right)/\partial x - (\Delta A/A_0) \partial p/\partial x + ((2\pi\mu\gamma)/A_0) \left( 1/A_0 - 1/A \right) q \\
-\Delta A' \partial p/\partial t
\end{bmatrix}
\]

where \(A_0\) is unperturbed lumen area, \(c_0\) is the pulse wave velocity (PWD) of small amplitude waves, \(\Delta A = A - A_0, \Delta A' = A' - A_0\).

If the nonlinear terms are small, equation (2) can be solved using subsequent approximation (perturbation) method \(u = u^{(1)} + u^{(2)} + \cdots\), where \(u^{(m)}\) satisfies the equation
\[
Lu^{(m)} = n^{(m)}, \quad m = 1, 2, \ldots
\]

where \(n^{(m)}\) are the nonlinear correction terms. Equation (3) is linear for every \(m\). It is homogeneous for \(m = 1: n^{(1)} = 0\). For \(m > 1\) vector \(n^{(m)}\) depends on solutions calculated at previous iterations.

To solve linear PDEs we can apply the direct and inverse Fourier transforms
\[
\begin{bmatrix} P_n(x) \\ Q_n(x) \end{bmatrix} = \frac{1}{T} \int_0^T \begin{bmatrix} p(x,t) \\ q(x,t) \end{bmatrix} e^{-i\omega_n t} \, dt, \quad \begin{bmatrix} p(x,t) \\ q(x,t) \end{bmatrix} = \sum_{n=-\infty}^{+\infty} \begin{bmatrix} P_n(x) \\ Q_n(x) \end{bmatrix} e^{i\omega_n t}
\]

The equations can be modified and re-written in the matrix form:

\[
Lu = n
\]

where \(L\) is the linear operator, \(u\) is the state vector, and \(n\) is a vector of nonlinear terms:

\[
L = \begin{bmatrix}
\partial / \partial x & (\rho/A_0)(\partial / \partial t) + (2\pi\mu\gamma)/A_0^2 \\
(A_0/(\rho\epsilon_0^2))\partial / \partial t & \partial / \partial x
\end{bmatrix}, \quad u = \begin{bmatrix} p(x,t) \\ q(x,t) \end{bmatrix}
\]

\[
n = \begin{bmatrix}
-(\rho/A_0) \partial \left( \alpha q^2/A \right)/\partial x - (\Delta A/A_0) \partial p/\partial x + ((2\pi\mu\gamma)/A_0) \left( 1/A_0 - 1/A \right) q \\
-\Delta A' \partial p/\partial t
\end{bmatrix}
\]

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\]

where \(P_n(x)\) and \(Q_n(x)\) represent the \(n\)th harmonic components, \(T\) is the heartbeat period, \(i\) is the imaginary unity, \(\omega_n = (2\pi/T)n\) is the frequency of \(n\)th harmonic component, \(n = 0, \pm 1, \pm 2, \ldots\).

Applying the direct Fourier transform to (3) we obtain ODEs which for \(m = 1\) are homogeneous
\[
\frac{dP_n}{dx} + i\omega_n \rho \phi^2 \frac{Q_n}{A_0} = 0, \quad \frac{dQ_n}{dx} + i\omega_n A_0 \frac{P_n}{\rho \epsilon_0^2} = 0
\]

where \(\phi(x) = \sqrt{1 - i(2\pi\nu)/\omega_n A_0}\) is a factor responsible for wave decays due to viscous losses.

Solution to ODEs (5) in every vessel can be represented through the transmission matrix which takes the simple form for constant cross-section vessel:
\[
\begin{bmatrix} P_n(x) \\ Q_n(x) \end{bmatrix} = T(x) \begin{bmatrix} P_n(0) \\ Q_n(0) \end{bmatrix} = \begin{bmatrix} \cos kx & -i\tilde{Z} \sin kx \\ -i\tilde{Y} \sin kx & \cos kx \end{bmatrix} \begin{bmatrix} P_n(0) \\ Q_n(0) \end{bmatrix}
\]

where \(k = \omega_n \phi/c_0\) is a complex wavenumber, \(\tilde{Z} = \rho c_0 \phi/A_0\) and \(\tilde{Y} = 1/\tilde{Z}\) are, respectively, the characteristic impedance and compliance in a pipe with viscous losses. Transmission matrix, \(T(x)\) equals to the identity matrix at \(x = 0\), i.e. at the inlet of every vessel.
If the vessel is non-uniform (tapering, for example) then it can be approximated by a sequence of truncated cones. Let \( \{x_0 = 0, x_1, \ldots, x_{N_e-1}, x_N = L \} \) be edge points of the cones where \( N \) is the number of conic elements, \( L \) is the vessel length. Variables \( c, \phi \) and \( k \) can be approximated by

\[
\bar{c}_i \approx \frac{1}{2}(c(x_{i-1}) + c(x_i)), \quad \bar{\phi}_i \approx \frac{1}{2}(\phi(x_{i-1}) + \phi(x_i)), \quad \bar{k}_i \approx \frac{\omega_n}{2} \left( \frac{\phi(x_{i-1})}{c(x_{i-1})} + \frac{\phi(x_i)}{c(x_i)} \right). \tag{7}
\]

Then the transmission matrix of the vessel can be expressed through a product of transmission matrices calculated for every element

\[
\mathbf{T} = \mathbf{T}_N \cdots \mathbf{T}_2 \mathbf{T}_1. \tag{8}
\]

Here \( \mathbf{T}_i \) is the transmission matrix of the \( i \)th conic element

\[
\mathbf{T}_i = \begin{bmatrix}
\frac{a_{i-1}}{a_i} \cos \theta_i + \zeta_i \sin \theta_i & -i \bar{Y}_i [\sin \theta_i - (\zeta_i - \zeta_{i-1}) \cos \theta_i] \\
-i \bar{Y}_i [(1 + \zeta_{i-1} \zeta_i) \sin \theta_i + (\zeta_i - \zeta_{i-1}) \cos \theta_i] & \frac{a_i}{a_{i-1}} (\cos \theta_i - \zeta_i \sin \theta_i)
\end{bmatrix} \tag{9}
\]

where \( a_i = a(x_i), \theta_i = \bar{k}_i h_i, h_i = x_{i-1} - x_i, \zeta_i = \frac{a_i - a_{i-1}}{\bar{k}_i h_i a_i}, \bar{Y}_i = \frac{\pi a_{i-1} a_i}{\rho \bar{c}_i \bar{\phi}_i} = \frac{1}{\bar{Z}_i} \).

Computations show that the conic approximation provides a high accuracy and efficiency in calculation of transmission matrices.

Applying the network inlet, junction and outlet boundary conditions used in 1D modelling, a system of linear algebraic equations can be built for every \( n \)th frequency with respect to inlet flow parameters for every vessel: \( \{P_{nj}(0), Q_{nj}(0)\} \) where \( j \) is a vessel number in the network. Outlet flow parameters for every vessel are represented through the transmission matrix computed. Resolving the system of the equation we enable calculation of \( P_{nj}(x), Q_{nj}(x) \) in any point of \( j \)th vessel through the transmission matrices. After that, performing the inverse FFT, we calculate the waveforms at any point of the network. This will be a solution to a linearised problem.

Now the nonlinear term \( n^{(2)} \) in PDEs (3) can be calculated and we can work with the second iteration in which nonlinear effects already are accounted. Performing FFT we obtain equations (5) with nonzero right hand sides for the nonlinear corrections to the linear solution. Columns of transmission matrix \( T(x) \) represent particular solutions to homogeneous ODEs (5) which can be used in solving inhomogeneous linear ODEs.

### 3 RESULTS AND CONCLUSIONS

To validate the proposed numerical scheme, waveforms have been computed in the arterial network containing 107 blood vessel described in [3]. The comparison of results between the present and numerical computations is shown in Figure 1. Observe that the proposed method gives results very close to that computed by the method used in [4]. There are some small discrepancies near the peak and in the decaying part of the pulse wave, which can be attributed to the computational errors. The numerical model of [4] needs about 300 s to compute the first 3 heartbeat cycles. The proposed method needs only 6 s to compute the correct waveforms, including the nonlinear corrections.

Thus, a novel method, based on the perturbation technique and fast Fourier transform (FFT) in solving the 1D blood flow equations, has been proposed in the present work. The proposed method makes the FFT competitive against traditional space-time numerical schemes in terms of both robustness and speed. In contrast to the FFT approach described in [1], the proposed method can be applied to an arbitrary arterial network, containing tapering vessels, vessels with stenosis and aneurysms, and to a high amplitude waveform in which the nonlinear effects are relevant. As demonstrated by the results, the proposed method is faster than competing methods and it is accurate. It accounts for viscous effects more accurately than any existing space-time methods and more importantly the viscous coefficient, \( \gamma \), is automatically calculated for different flows and physical conditions. The proposed method simplifies boundary conditions required at the terminal vessels. Thus, we believe that this method can be an alternative and potentially a more effective tool for 1D modelling of blood flow in arterial networks.
Figure 1: Pressure waveform (left) and flow rate waveform (right). Computed waveforms at the beginning of aortic arc (green), at the beginning of abdominal aorta (blue) and at the mid-point of the right carotid (red). Waveforms computed by the model in [4] are shown using solid lines and those computed by the proposed method are shown by dashed lines.

Although the proposed method is a substantial improvement to the existing methods, it requires further development in the following area. Further attention is required to deal with viscoelastic effects, blood mass loss due to smaller branches, porous nature of arteries and application to clinical environment.

As it is mentioned in [1], a FFT based approach allows one to rapidly investigate the role of individual physical properties of a cardiovascular system subjected to a pulsatile waveform. The Fourier transform and calculations carried out in frequency domain are the natural ways for dealing with the wave phenomena. Such important concepts as phase and group velocities can be employed in these methods to explain the distinctive features of wave the pulse propagation and reflection. The frequency domain approach has been successfully used in [5] for developing a non-invasive, aortic aneurysm detection method using a waveform analysis.

CONFLICT OF INTEREST

This is to confirm there is no conflict of interest to report.

REFERENCES


A Systematic Comparison between 1-D and 3-D Haemodynamics in Diseased Arterial Models

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SUMMARY

One-dimensional (1-D) models of arterial haemodynamics have received notable attention in the last years. Several studies have assessed the accuracy of the 1-D formulation in the larger systemic arteries under normal physiological conditions. Less attention has been paid to assess this modelling approach under pathological conditions. Here we test arterial 1-D modelling in a series of idealized vasculatures representing the aorta and larger systemic arteries with different sizes of stenoses and/or aneurysms, using 3-D modelling as ground truth. Preliminary results indicate that an energy loss model should be included to improve the accuracy of 1-D model predictions in severe stenoses.

Key words: Haemodynamics, Cardiovascular Disease, Computational Fluid Dynamics, 1-D Arterial Model

1 INTRODUCTION

Computational models are playing an increasingly significant role in current arterial haemodynamics research. They are typically based on the zero-dimensional (0-D), one-dimensional (1-D), or three-dimensional (3-D) formulations, each having its advantages and limitations. Lumped parameter (0-D) models are computationally inexpensive and can provide insights into whole-body haemodynamics, including cardiac dynamics [1]. However, they are not suitable for describing pulse wave propagation and complex flow phenomena in the cardiovascular system. The 1-D formulation, on the other hand, can describe pressure and flow pulse waveforms with a relatively low computational cost [2], [3]. However, the axisymmetric assumption of the 1-D approach makes it difficult to describe complex vascular flow patterns such as secondary flows. The 3-D formulation can simulate pressure and flow pulse waveforms, and complex flow patterns in the arterial network, but this comes at a considerably higher computational cost compared to the 0-D and 1-D approaches [3], [4].

Several studies have compared 1-D and 3-D haemodynamics in the aorta and larger systemic arteries under normal physiological conditions [3], [5]–[7]. However, less attention has been paid to assess the 1-D formulation under pathological conditions. Wan et al. compared haemodynamic data produced by 1-D and 3-D schemes on a patient-specific arterial network with localized changes in luminal cross-sectional area due to the presence of three stenoses in the two iliac arteries and the left superficial femoral artery, and a series of stenoses in the right superficial femoral artery, though they focused on assessing errors in volumetric flow rates rather than pulse waveforms [8]. Stergiopulos, et al. [2], [9] investigated the effects of arterial and aortic stenoses on arterial pulse waveforms, though they only assessed the accuracy of the 1-D model approach by qualitative comparison with previous clinical and experimental studies. In both articles, 1-D model arterial stenoses were described based on empirical data from the in-vivo experiments performed by Young, et al. in the femoral arteries of dogs [10].

The aim of this study is to assess the ability of the 1-D formulation to describe blood pressure, blood flow, and luminal cross-sectional area in diseased arterial vasculatures with localized changes in
geometry and material properties. To achieve this, we compare 1-D and 3-D model predictions of pulse waveforms in a series of idealized compliant arterial models, representing the aorta and larger systemic arteries with different sizes of stenoses and aneurysms, including those shown in Figure 1.

![Diagram of arterial geometries](https://www.nicaedcam.co.uk/solidworks)

Figure 1. Problem descriptions of some of the geometries studied: (a) common carotid artery with a stenosis, (b) abdominal aorta with an aneurysm, and (c) aortic bifurcation with an abdominal aortic aneurysm and a femoral stenosis. $D_{nt}$: normal diameter; $D_{st}$: diameter of the stenosis region; $D_{at}$: diameter of the aneurysm region; $D(x_i)$: transient diameter from normal to either stenosis or aneurysm type; $L_{xi}$: length of the vascular segment; $L_{si}$: length of the stenosis; $L_{ai}$: length of the aneurysms; $h_i$: thickness of the blood vessel wall.

2 METHODOLOGY

Our in-house solver Nektar1D ([http://haemod.uk/nektar](http://haemod.uk/nektar)) was adopted for the 1-D simulations. A full description of the 1-D equations solved by Nektar1D is provided in Reference [11]. The 3-D simulations were carried out using the open source, CFD simulator, CRIMSON ([http://www.crimson.software](http://www.crimson.software)). This uses the 3-D Navier-Stokes equations to compute blood flow and pressure in the fluid domain, and a membrane formulation to solve the 3-D fluid-structure interaction (FSI) problem [12]. Data post-processing to obtain the 3-D model pressure and flow waveforms was performed on ParaView ([https://www.paraview.org](https://www.paraview.org)).

Vascular geometries (e.g. those shown in Figure 1) were designed in 3-D using the commercial software SolidWorks ([https://www.ntcadcam.co.uk/solidworks](https://www.ntcadcam.co.uk/solidworks)). 1-D model geometries were obtained from the centrelines of the 3-D models, with the diameters and wall thickness of the 1-D and 3-D vessels being identical. Stenosis sizes were defined as $(1 - A_s/A_0) \times 100\%$, with $A_s = \pi(D_s/2)^2$ and $A_0 = \pi(D_0/2)^2$, and $D_s$ and $D_0$ as defined in Figure 1.

The 1-D and 3-D formulations used to solve blood flow in each vascular geometry share identical inflow and outflow boundary conditions and have compatible material law. For the 1-D formulation, we adopted the stenosis model proposed by Wan *et al.* [8] to compute energy losses across the narrowing.

Metrics for average, maximum, systolic, and diastolic relative errors were calculated as described in Reference [13]. 1-D model errors for blood pressure and flow were expressed relative to corresponding values obtained from the 3-D simulations.

3 RESULTS AND CONCLUSIONS

Some initial results comparing 1-D and 3-D model blood pressure and flow waveforms in the human common carotid artery are shown in Figure 2. Overall, the 1-D approach is able to capture the main features of the 3-D model pulse waveforms. For moderate stenoses (up to 50%), smaller errors were obtained without considering the energy losses in the 1-D scheme. Whereas, in the case of 75% stenosis, including energy losses in the 1-D scheme reduced relative errors. This result suggests that energy losses in the stenosis should be accounted for the 1-D formulation when investigating severe stenoses.
Figure 2. Comparison of blood pressure (middle) and blood flow (bottom) waveforms at the midpoint (top, red dot) of an idealized model of the human common carotid artery with a stenosis. Results are shown for the 3-D model (red lines), 1-D model without the stenosis model (blue lines), and 1-D model with the stenosis model (black lines). Three stenosis sizes are considered: 25% (left), 50% (middle) and 75% (right). Average (avg), maximum (max), systolic (sys), and diastolic (dias) relative error metrics between 1-D and 3-D results shown each plot (first column: without stenosis model; second column: with stenosis model).

In the presentation, we will systematically investigate different stenosis and aneurysm sizes (by varying the parameters shown in Figure 1) in several vasculatures, such as the ones shown in Figure 1. Furthermore, we are performing in-vitro experiments on the same vasculatures simulated computationally using our existing cardiovascular simulator rig [14]. The aim of these experiments is to refine the calculation of energy losses across different sizes of stenoses and aneurysms for improved 1-D model simulations.

Having a robust 1-D formulation for arterial haemodynamics in diseased vasculatures will allow us to investigate indices of pulse wave analysis for cardiovascular diseases assessment, such as coronary arterial stenosis and abdominal aortic aneurysm. Apart from existing indices, such as FFR for coronary artery stenosis, we aim to use our 1-D model approach to develop new indices; e.g. from peripheral blood vessels where non-invasive measurement are feasible. Having a computational framework that shows a good balance between accuracy and computational cost will enable the creation of database of ‘virtual’ (computed) subjects following our existing approach [15], under cardiovascular diseases conditions for an enhanced study of haemodynamics.

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REFERENCES


INVESTIGATION OF THE EFFECTS OF 0D STENOSIS MODEL AND INFLOW RATE ON PREDICTION ACCURACY OF CEREBRAL HYPERPERFUSION SYNDROME

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SUMMARY

To predict thus avoid cerebral hyperperfusion syndrome (CHS), a potentially life-threatening complication following carotid intervention to open up a stenosis, a non-invasive patient-specific 1D-0D simulation system is developed. In this paper, we conducted pre-operative and pseudo post-operative simulations for two patients, each with three 0D models that give different estimates of the pressure drop across the stenosis, while taking into consideration the effects due to uncertainties in medical data in terms of stenosis ratio and inflow rate, to determine the model-dependent prediction accuracy for CHS. It is found that by selecting the appropriate stenosis model, CHS can be predicted accurately.

Key words: 1D-0D simulation, stenosis model, CHS prediction, medical data uncertainty

1 INTRODUCTION

Cerebral hyperperfusion syndrome (CHS) is a potentially life-threatening complication, often described as an increase of cerebral blood flow >100% compared to baseline [1]. Although rare, it is associated with significant morbidity, including clinical symptoms ranging from severe unilateral headache, to seizures and focal neurologic defects, to intracerebral hemorrhage in its most severe form [2]. It can happen following interventions for carotid artery stenosis, such as carotid endarterectomy [3] and carotid artery stenting (CAS) [4]. As the most commonly used prognostic factor for CHS, cerebrovascular reserve can be assessed through the acetazolamide (ACZ) challenge test [5]. However, since ACZ may lead to side effects [6], non-invasive simulation method has been developed as an alternative for CHS prediction [7]. Yet, uncertainties in medical data present challenges to obtaining accurate prediction results. Zhang [8] quantified the uncertainties of medical data and evaluated their effects on the results of a patient-specific one-dimensional and zero-dimensional (1D-0D) simulation. By applying sensitivity analysis to a patient with potential risk of CHS, who had undergone a staged CAS, the feasibility of the simulation in CHS prediction is confirmed. Okada et al. [9] further investigated the uncertainties in stenosis ratio (SR) and inflow rate on the simulation results with two other patient-specific cases, one with a high SR, the other with a relatively low SR. It is discovered that the simulation method becomes less reliable in case of severe stenosis, which is likely due to the overestimation of pressure drop over the stenosis using the current 0D stenosis model [10]. Given that the selection of an appropriate stenosis model is essential to the accurate prediction of CHS, this paper aims to investigate the prediction accuracy of CHS using three different 0D stenosis models, while taking into consideration the effects due to uncertainties in medical data, in order to determine the most appropriate model among the three and provide hints to 0D stenosis model future improvement.

2 METHODOLOGY
Three-dimensional (3D) models of the patient-specific circle of Willis (CoW) were manually constructed using an image-based vessel shape modeling system (V-Modeler) developed in-house [11]. Patient-specific 1D vessel geometric data were then extracted and input into the 1D-0D simulation along with patient information and other medical measurement data, such as inflow and outflow rates. The 1D-0D simulation consists of pre-operative as well as pseudo post-operative or predictive simulations. In the former, the diameters of the three communicating arteries (DCoA) as well as the peripheral resistances (PR) of distal arteries of the patient-specific CoW were estimated in a way such that the calculated flow rate in each efferent and afferent artery becomes equal to the measured inflow rate using PC-MRA or ultrasound and cerebral flow (CBF) data using SPECT respectively. In the latter, computer-assisted surgery was performed by numerically expanding the stenosis fully such that the stenosis ratio becomes zero (SR=0%), and the adjusted DCoA and PR from the pre-operative simulation were used as input to estimate the increase in CBF after the surgery (ΔQCBF).

Patient-specific 1D-0D simulations along with sensitivity analysis for SR and inflow rate were performed for two case studies. The details are summarized in Table 1 below.

<table>
<thead>
<tr>
<th>PATIENT</th>
<th>CASE 1</th>
<th>CASE 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE/SEX</td>
<td>70 year old male</td>
<td>63 year old male</td>
</tr>
<tr>
<td>STENOSIS</td>
<td>Lt. ICA (NASCET 73%)</td>
<td>Lt. ICA (NASCET 73%)</td>
</tr>
<tr>
<td>SURGERY</td>
<td>Direct CAS</td>
<td>Staged CAS</td>
</tr>
<tr>
<td>SR</td>
<td>66 – 80%</td>
<td>66 – 80%</td>
</tr>
<tr>
<td>INFLOW RATE</td>
<td>±13% (PC-MRA)</td>
<td>±35% (Ultrasound)</td>
</tr>
</tbody>
</table>

In addition, since the selection of an appropriate 0D stenosis model is essential to the accurate prediction of CHS, three models were implemented and compared in conjunction with the sensitivity analysis to allow better prediction accuracy. The three models, which will be discussed in detail later, are respectively the Young’s model [10], a single-step pressure loss model; the Zhang’s model [8], a double-step pressure loss model developed on the basis of Young’s model; and the Bessems’ model [12], a U-shaped pressure loss model.

It needs to be noted that while in Case 2 the patient-specific CoW model is constructed from computed tomography (CT) images, magnetic resonance imaging scans were used in Case 1 instead, which provide only a part of the patient-specific CoW geometry. As such, detailed geometry of the stenosed left ICA is unfortunately unavailable. And its effects on model-dependent simulation results were significant and will be discussed later in the results and conclusions section.

2.1 0D stenosis model

Since 1D stenosis model alone cannot fully account for the pressure loss across a stenosis, an empirical 0D stenosis model was proposed by Young et al. [10], in which the pressure drop is related to flow rate and geometric parameters of the stenosis, calculated by:

\[ \Delta P = \frac{K_v}{A_s D_{a}} \left( Q \right)^2 \left( \frac{A_s}{A_0} - 1 \right) + \frac{K_t}{A_0} \left( \frac{A_s}{A_0} \right) \frac{\rho L_s}{A_0} \dot{Q} \]

where the first term on the right hand side of the equation is a viscous term, the second a nonlinear turbulence term, and the third an unsteadiness term.

\( K_v, K_t, K_u \) are empirically determined coefficients such that \( K_v = 1.0 \) for steady flow, \( K_t = 1.52 \) for unsteady flow (used for simulation), and \( K_u = 1.2 \).

\( K_v \) in the original Young’s model is calculated by

\[ K_v = 32 \left( \frac{0.83 L_s + 1.64 D_s}{A_0} \right) \left( \frac{A_0}{A_s} \right)^2 \]
where the geometric parameters are as shown in Fig. 1(a) below.

![0D stenosis model](image)

Figure 1 0D stenosis model from (a) Young; (b) Zhang

In Zhang’s double-step model, $K_v$ is broken down into more terms which are calculated by

$$K_v = K_{v0} + 2K_{v1},$$

where

$$K_{v0} = 32 \frac{0.83 \frac{L_0}{3} + 1.64D_1}{D_1} \left( \frac{A_1}{A_0} \right)^2$$

$$K_{v1} = 32 \frac{0.83 \frac{L_0}{3} + 1.64D_1}{D_0} \left( \frac{A_1}{A_0} \right)^2$$

The corresponding geometry is shown in Fig. 1(b) above.

In Bessems’ U-shape model, $K_v$ is no longer a constant number, but dependent on the cross-sectional area which is a function of axial location. In other words, the first viscous term for the pressure drop is calculated instead by

$$\int_0^{L_0} 8\pi \mu \frac{Q}{A(x)^2} \, dx$$

3 RESULTS AND CONCLUSIONS

![Figure 2 Sensitivity of CBF increase in ipsilateral middle cerebral artery (MCA) with different 0D stenosis models for (a) Case 1; (b) Case 2](image)

Fig. 2 shows $\Delta Q_{CBF}$ in the ipsilateral middle cerebral artery (MCA) for Case 1 and Case 2, with different 0D stenosis models employed in the pre-operative simulation, while taking into consideration the effects due to uncertainties in SR and inflow rate. The horizontal axis shows the range of SR considered, while the vertical error bars indicate the range of $\Delta Q_{CBF}$ due to uncertainty in inflow rate.

The results of the simulations are summarized as follows:

1. In both Case 1 and Case 2, regardless of the 0D stenosis model used, both the value and the range of $\Delta Q_{CBF}$ increase more than proportionately to SR, which indicates a more than proportionate increase in pressure drop, caused by a combination of effects as described in the previous section, in which the major contribution comes from viscous effects, since velocity gradient increases exponentially with SR:
2. At high SR, overall pressure drop becomes larger than physiologically possible, causing
the simulation to be unstable, from which a convergent result cannot be obtained. This
increase in pressure drop is attributed to not only viscous effects, but mainly turbulence;
3. Mathematically it is understood that Bessem’s model should result in the least pressure
drop over the stenosis due to the more detailed geometry assumed, leading to the general
trend as shown in Case 2. However, results from Case 1 suggest that not using patient-specific geometry for the stenosis part largely influences the pressure drop estimated by 0D stenosis models. In Case 1, literature data were used for the stenosed ICA geometry, in which the stenosis is artificially generated, in a shape similar to that described by Young’s model. As a result, Bessem’s model fails to better describe this simple stenosis geometry, which is the reason for the overestimated pressure drop and ΔQCF thereof;
4. Predictions were relatively accurate since Case 2 had undergone staged CAS fearing the potentially high risk of CHS, just as shown by simulation results in Fig. 2(b). As for Case 1, should medical images of the extracranial portion of the ICAs be readily available, it is possible that the ΔQCF predicted using Bessem’s model will not exceed 100%, providing support to the surgical decision of direct single-stage CAS.

To support the conclusion that Bessem’s model gives the most accurate prediction, more patient-specific simulations to corroborate this finding is necessary. In addition, as the more detailed geometry assumed by Bessem’s model allows better prediction accuracy, it is worthwhile to look into coupling a 3D stenosis model with the current 1D-0D simulation. Future work also remains to improve the stability of the current 1D-0D code, especially at high SR.

REFERENCES

IMPORTANCE OF PRESSURE LOSSES AT ARTERIAL JUNCTIONS UNDER EXERCISE CONDITIONS: A 1D MODELLING STUDY

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SUMMARY
Pressure losses at junctions are often neglected in reduced-order blood flow models; however, they may become significant during exercise owing to increased flow and kinetic energy. Three methods for treating junction flows were compared in a 1D systemic arterial model of resting and exercise conditions: 1) continuity of static and 2) total pressure, and 3) the ‘Unified0D’ method of estimating pressure losses. At rest, all methods provided similar results; during exercise, there were large variable differences in the maximum pressure calculated by the three methods. We conclude that junction pressure losses should be accounted for during increased blood flow conditions.

Key words: exercise, one-dimensional modelling, reduced-order modelling, systemic arteries

1 INTRODUCTION
The arterial circulation has a tree-like structure containing many branching points (junctions) that enable distribution of blood throughout the body. At junctions, blood flow changes direction, giving rise to complex flow patterns such as secondary flows and recirculation zones that cause fluid kinetic energy dissipation and hence pressure loss. Such pressure losses are often neglected in one-dimensional (1D) blood flow models because 1) it is assumed that they are of minor importance and 2) estimation of these losses is challenging without direct measurements or 3D computational fluid dynamics (CFD). In 2015, Mynard and Valen-Sendstad [1] described a unified reduced order (or ‘Unified0D’) model to predict pressure losses at junctions. This technique, which is straightforward to apply in 1D (or 0D) blood flow models, showed surprisingly good agreement (given its simplicity) with CFD in all types of three-branch junction flows and a wide range of Reynold’s numbers, branch angles, and branch diameter ratios.

Using this method, Chnafa et al [2] showed that accounting for junction pressure losses improved estimation of flow split in a reduced order model of cerebral arteries. More broadly, however, it is currently unclear to what extent accounting for these losses will affect data produced by 1D models of the systemic arterial tree. Representing junction losses will likely be important when simulating exercise, which is associated with increased blood flow velocities and hence increased kinetic energy in arteries supplying muscular tissues.

The aims of this study were to 1) develop a 1D systemic arterial model of exercise haemodynamics and 2) evaluate the impact of accounting for pressure losses under resting and exercise conditions, compared with the commonly-used junction models that assume continuity of static or total pressure.

2 METHODOLOGY
The systemic arterial network was extracted from the whole circulation model described in [3] and was modified to include a more complete representation of the leg arteries, where blood flow increases
dramatically during exercise; this involved addition of the circumflex femoral arteries, genicular arteries, and peroneal artery (Figure 1). Without these additions, we found that viscous resistance within the 1D segments under exercise (high flow) conditions led to unrealistically high pressure drops in the leg arteries. Branch angles for all junctions in the model were derived from magnetic resonance angiograms from the OsiriX DICOM image library (Obelix, Cetautomatix, Brebix and Felix), a 3D electronic atlas of cerebral vessels [4] and other literature/atlases. The aortic inlet was coupled to an elastance-based left heart model, similar to that described in [3] but only including the left atrium (LA) and ventricle (LV), with a constant pulmonary venous pressure driving flow into the LA via a small resistance. Three element windkessels formed the terminal outlet boundary conditions. The 1D equations governing velocity, pressure and area were solved as in [3], with viscous resistance estimated via an approximate velocity profile method [5]. A complete description of the model and parameter listing will be published in a subsequent full-length article. Of particular relevance to this paper is that three approaches for treating branch junctions were compared: 1) continuity of static pressure ($p$), 2) continuity of total pressure ($p + \frac{1}{2} \rho u^2$, where $u$ is blood velocity and $\rho$ is blood density) and 3) the Unified0D method [1], which estimates losses based on angles and instantaneous flow and area ratios between branches.

Exercise was modelled by applying the following changes to the reference (i.e. 'resting') simulation: 1) heart rate was increased from 75 to 172 bpm; 2) venous return to the left heart was increased by raising pulmonary venous pressure and reducing inflow resistance; 3) wave speed of all arteries was increased by 24%; 4) reference diameter of leg, arm, face/neck and intercostal arteries were increased by 10-20% (vasodilation); 4) vascular bed resistances were adjusted to achieve a flow distribution typical of high intensity exercise (e.g. [6], with compliances adjusted in a reciprocal manner); 5) LA and LV maximal elastances were increased by a factor of 3 (increased contractility); and 6) LV minimal elastance was reduced by a factor of 0.4 (i.e. increased passive compliance).

3 RESULTS AND CONCLUSIONS

Cardiac output and ascending aortic blood pressure increased from 6.0 L/min and 109/78 mmHg at rest to 20.4 L/min and 158/74 mmHg under exercise conditions. Table 1 shows the blood flow distribution under exercise conditions. Of particular relevance, total leg blood flow increased ~10-fold, to 12.8 L/min (or over 6 L/min per leg), noting that blood flow in one leg can reach 6-10 L/min with exercise [6]. Peak femoral arterial blood velocity increased from 70 to 180 cm/s despite the
Table 1: Blood flows and flow distribution under exercise conditions.

<table>
<thead>
<tr>
<th>Region</th>
<th>Flow (L/min)</th>
<th>% CO</th>
<th>∆rest</th>
<th>Region</th>
<th>Flow (L/min)</th>
<th>% CO</th>
<th>∆rest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>0.69</td>
<td>3.4%</td>
<td>-4%</td>
<td>Spleen</td>
<td>0.09</td>
<td>0.5%</td>
<td>-52%</td>
</tr>
<tr>
<td>Face/Neck</td>
<td>0.60</td>
<td>2.9%</td>
<td>137%</td>
<td>Stomach</td>
<td>0.03</td>
<td>0.1%</td>
<td>-73%</td>
</tr>
<tr>
<td>Shoulders/Arms</td>
<td>2.39</td>
<td>11.7%</td>
<td>258%</td>
<td>Intestines</td>
<td>0.22</td>
<td>1.1%</td>
<td>-60%</td>
</tr>
<tr>
<td>Intercostals</td>
<td>2.27</td>
<td>11.1%</td>
<td>314%</td>
<td>Pelvis</td>
<td>0.22</td>
<td>1.1%</td>
<td>-6%</td>
</tr>
<tr>
<td>Kidneys</td>
<td>0.92</td>
<td>4.5%</td>
<td>-29%</td>
<td>Legs</td>
<td>12.8</td>
<td>62.5%</td>
<td>1016%</td>
</tr>
<tr>
<td>Liver</td>
<td>0.24</td>
<td>1.2%</td>
<td>-18%</td>
<td>Total</td>
<td>20.4</td>
<td>100%</td>
<td>241%</td>
</tr>
</tbody>
</table>

Abbreviations: CO, cardiac output; ∆rest, change in blood flow compared with resting conditions.

Figure 2: Pressure waveforms in the aorta and in two leg arteries under simulated resting (top) and exercise (bottom) conditions. Numbers in blue and red indicate the difference in maximum pressure between static or total pressure continuity models respectively and the UnifiedOD model formulation.

assumed 20% increase in reference diameter.

Figure 2 shows selected pressure waveforms from the network model with parameters representing rest and exercise, while Figure 3 shows differences in maximum pressure between static or total pressure continuity methods and the UnifiedOD method for all network segments. For the resting case, relatively small differences in maximum pressure were observed for static pressure continuity (mean ± SD, -0.2 ± 1.5 mmHg; range -3.2 to 4.7 mmHg) and total pressure continuity (-0.4 ± 1.3 mmHg, -3.6 to 3.2 mmHg), compared with UnifiedOD. Conversely, for the exercise case, substantial and variable differences in maximum pressure were found for both static pressure continuity (0.8 ± 10.1 mmHg, -17.0 to 36.1 mmHg) and total pressure continuity (0.8 ± 7.6 mmHg, -22.0 to 19.0 mmHg), compared with UnifiedOD. In both rest and exercise cases, the absolute difference between static pressure continuity and UnifiedOD (for maximum pressure) was smaller than that between total pressure continuity and UnifiedOD in 43% of segments; hence, there was no clear pattern for either static pressure or total pressure continuity to be closer to UnifiedOD.

In conclusion, we have developed a 1D systemic arterial model that replicates exercise conditions. With this model, we have shown that it is reasonable to neglect pressure losses at junctions during resting conditions. However, the choice of junction model becomes quite important under high flow and kinetic energy conditions such as exercise, where accounting for pressure losses may have a substantial influence on model predictions.
Figure 3: Difference in maximum pressure between junction formulations (open blue circles, static pressure continuity – Unified0D; closed red circles, total pressure continuity – Unified0D). Segment numbers correspond to those in Figure 1.

4 ACKNOWLEDGEMENTS

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REFERENCES


PRENATAL HEMODYNAMIC FEATURES OF THE TERM D-TGA FETUSES WITH CONSTRICTED DUCTUS ARTERIOSUS AND RESTRICTIVE FORAMEN OVALE: A COMPUTATIONAL STUDY

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SUMMARY

We propose for the first time a closed-loop zero- and one-dimensional (0-1D) multiscale fetal circulation model to investigate the impact of ductus arteriosus (DA) constriction and restrictive foramen ovale (FO) on hemodynamic waveform alterations in the term fetus with Dextro-transposition of the great arteries (d-TGA). Our results suggest that DA constriction and restrictive FO result in significant alterations in hemodynamic waveforms, these hemodynamic changes are invaluable in helping obstetricians to evaluate the potential risk and make better-planed perinatal management for fetuses with d-TGA.

Key words: Dextro-transposition of the great arteries, ductus arteriosus constriction, restrictive foramen ovale, multiscale fetal circulation model

1 INTRODUCTION

Dextro-transposition of the great arteries (d-TGA) is one of the most common congenital heart defects, in which the ascending aorta (AAo) and the main pulmonary artery (MPA) are switched, (i.e. the AAo connects to the right ventricle (RV), while the MPA connects to the left ventricle (LV)), as shown in Figure 1. The incidence of d-TGA is approximately 2-5 per 10000 [1-3] with a perioperative mortality rate of about 4% [4].

Figure 1. Schematic representation of the anatomical configuration of (a) a normal and (b) d-TGA fetal circulation. RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle; TV, tricuspid valve; PV, pulmonary valve; MV, mitral valve; AV, aortic valve; FO, foramen ovale; AAo, ascending aorta; MPA, main pulmonary artery; PUV, pulmonary vein; SVC, superior vena cava; IVC, inferior vena cava; DA, ductus arteriosus; AoI, aortic isthmus; DAo, descending aorta.
Abnormalities of the ductus arteriosus (DA) and foramen ovale (FO) frequently accompany with d-TGA [5], which may result in fetal profound hypoxemia and brain anomalies, and even early death of neonates before surgical intervention [5]. Despite advances in the prenatal echocardiographic diagnosis, the d-TGA detection rate remains below 50% [6]. Comprehensive understanding of prenatal hemodynamic features of the d-TGA fetuses associated with the restrictive DA and FO is crucial in helping obstetricians to evaluate the potential risk and make a better-planned preoperative management. To date, however, intrauterine hemodynamic features of the d-TGA fetuses are poorly understood.

The aim of this study is to evaluate prenatal hemodynamic features of the d-TGA fetuses and to find crucial hemodynamic indicators associated with the constricted DA and restrictive FO. To achieve this goal, a closed-loop zero- and one-dimensional (0-1D) multiscale cardiovascular model of a term d-TGA fetus was proposed. With this model, influences of the DA constriction and FO restriction on hemodynamic waveform alterations for term fetuses with d-TGA are analyzed.

2 METHODOLOGY

The developed closed-loop 0-1D multiscale cardiovascular model of a d-TGA fetus at 40 weeks of gestation with a body weight of 3.2kg is shown in Figure 2. The 1D Navier–Stokes equations were used to describe blood flows in the major vessels of the systemic and pulmonary circulations, which could easily integrate the vessel morphology, pulse wave propagation, and hemodynamics of the fetal circulation. And 0D models were used to describe the heart and peripheral vascular beds, which could reproduce the cardiac pumping functions, valve dynamics, and peripheral circulations. For mathematical details, we refer to our previous works [7, 8]. The majority of the fetal cardiovascular model parameters for the d-TGA fetus is estimated from the adult model parameters [7-9], such as \( X = X_{\text{adult}} (W/W_{\text{adult}})^\beta \), where \( X \) is the cardiovascular parameter value, \( W \) is the body weight, and \( \beta \) is the scaling exponent. A set of scaling exponents used to evaluate different kinds of cardiovascular parameters have been defined in our previous study [10]. The rest of the fetal model parameters are defined according to published experimental measurements [3, 11-13], or defined based on empirical estimation. Compared with the normal fetus, the d-TGA fetuses show apparent differences in cardiac valves, FO, and DA sizes, as well as the pulmonary and cerebral vascular resistances [3].

Figure 2. Schematic representation of a closed-loop 0-1D multiscale cardiovascular model of a term fetus with d-TGA. (a) 1D cardiovascular network and terminal connection interface, and (b) 0D model of the heart. \( E \), elastance; \( S \), viscoelasticity; \( B \), Bernoulli resistance; \( L \), inertance of the blood flow; \( C \), vascular compliance; \( R \), vascular resistance.


Figure 3. Effects of DA constriction on hemodynamic waveforms. $A_{DA}$, cross-sectional area of the DA; $A_{DA0}$, cross-sectional area of the DA at normal condition.

Figure 3 shows that the reduced DA size induces 1) a pronounced decrease in the systolic flow but increase in the diastolic flow in the DA, 2) a pronounced increase in the MPA blood pressure, 3) an increased systolic flow in the PV and increased peak late diastolic filling (A-wave) flow in the MV, and even regurgitated flow in the PV and MV in the severe constriction or closure of the DA, 4) a pronounced increase in the LV and LA volumes, and 5) a pronounced decrease in the FO and AoI systolic flow, but increase in the AoI diastolic flow.

Figure 4. Effects of FO restriction on hemodynamic waveforms. $A_{FO}$, cross-sectional area of the FO; $A_{FO0}$, cross-sectional area of the FO at normal condition.

Figure 4 shows that the reduced FO size induces a pronounced 1) decrease in the MV peak early filling (E-wave) and late diastolic filling (A-wave) flow and the PV systolic flow, 2) increase in the AV systolic flow, 3) decrease in the systolic flow but increase in the diastolic flow in the FO, 4)
decrease in the DA systolic flow, 5) increase in the AoI systolic flow. Moreover, our results indicate that the restrictive FO is highly associated with decreased MV E/A ratio and PV peak systolic velocity (PSV) but increased AV PSV and AoI isthmus systolic velocity (ISI) (see Figure 5).

In conclusion, this study highlights the hemodynamic alterations associated with the d-TGA fetus with DA constriction and restrictive FO, and these hemodynamic alterations are invaluable in the prenatal detection of d-TGA and the assessment of the potential d-TGA fetal compromise in combination with the prenatal Doppler ultrasound investigation.

Figure 5. Changes of the TV and MV E/A ratio (a), PV and AV PSV (b), and Aortic ISI associated with the FO size. $A_{FO}$, cross-sectional area of the FO; $A_{FO0}$, cross-sectional area of the FO at normal condition.

REFERENCES

ENERGY-CONSISTENT DISCRETISATION FOR ONE-DIMENSIONAL BLOOD FLOW MODELS

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SUMMARY

The objective of this work is to derive a novel, energy-consistent discretisation for blood flow in the ascending aorta that is suitable to the coupling to an energy-consistent reduced-dimensional nonlinear mechanical model of the heart. The end-goal is to obtain a reliable (i.e. stable and accurate) framework for the modelling of the heart and the ventriculo-vascular coupling, in order to investigate stable inverse problem strategies and obtain patient-specific simulations, and thus accurately estimate some physiological markers, e.g. the dicrotic notch. The model output will be compared with in vivo measurements that we have at our disposal.

Key words: Reduced-order modelling, blood flow modelling, energy-preserving scheme, dicrotic notch

1 INTRODUCTION

The importance of reduced-order (RO) models in clinical applications has been extensively assessed in the last years. This is due to the fact that RO models enable to perform simulations at an acceptable computational cost and are more adequate to the resolution of inverse problems (IP). However, IP strategies may fail if the forward problem lacks of appropriate stability properties. Typically, if filtering strategies are used (as in [2]), the forward model must provide a stable solution, even though it is solved with various sets of parameters and (noisy) feedback terms. In this regard, energy-preserving schemes are ideal to discretise the forward problems, since they are stable and flexible with respect to a variation of parameters and they ensure a reliable control on the behaviour of the solution.

Concerning cardiovascular applications, RO models are nowadays very widespread in the scientific literature for predictions with patient-specific models. Among them, the reduced-dimensional multi-physics beating heart model that has been developed in the Inria research team M\textsuperscript{Ξ}DISIM (see [3]) relies on a strategy introduced in [4] to perform an energy-preserving time discretisation. Note that the main feature of this reduced model is that it preserves all the most important ingredients of a generic three-dimensional model to represent with accuracy a cardiac cavity at a crucial computational gain. Due to model reduction, the local properties are directly translated to the organ level, and detailed anatomical descriptions are not included. Nevertheless, the model can reproduce some significative features of cardiac physiology, e.g. realistic contraction cycle representative of a human left ventricle, and it is possible to retrieve physiological biomarkers that reflect the complex behaviour of a human heart under physiological and some pathological conditions. However, the model proposed in [3] takes into account simple outflow boundary conditions, based on 0D Windkessel models.

In the perspective of extending this model, we present a more advanced approach for the outflow boundary condition. In more detail, the proposed model corresponds to an energy-consistent time discretisation of the nonlinear classical 1D equations of haemodynamics in a generic arterial segment.
2 METHODOLOGY

The approach we propose is based on several considerations. First, we assume a suitable regularity of the solution (i.e., absence of shock waves), that is a reasonable hypothesis for our specific application to blood flow in the arterial system (viscous and laminar flow)

$$
\partial_t A + \partial_s Q = 0, \quad \partial_t Q + \partial_s \frac{Q^2}{A} + \frac{A}{\rho} \partial_s P(A) + K_r \frac{Q}{A} = 0, \quad P(A) = P_{ext} + \psi(A).
$$

(1)

Note that the hypothesis of absence of shock waves is not satisfied when flow in collapsible pipes (e.g., veins) is considered. An essential aspect of our approach is that we start from the energy relation provided in [5, Lemma 2.1] in the continuous framework. Denoting

$$
\varepsilon(t) = \int_0^L e(t, s) ds, \quad \text{with} \quad e = \frac{\rho}{2} A u^2 + \Psi(A) \quad \text{and} \quad \Psi(A) = \int_{A_0}^A \psi(\zeta) d\zeta,
$$

(2)

with $s \in [0, L]$ the abscissa along the arterial segment, it was proved that

$$
\varepsilon(T) + \rho K_r \int_0^T \int_0^L u^2 ds \ dt + \int_0^T Q(P_{tot} - P_{ext}) \bigg|_0^L \ dt = \varepsilon(0) \quad \text{with} \quad P_{tot} = P(A) + \frac{\rho}{2} u^2.
$$

Then, the formulation is based on an adequate change of variables such that the energy density $e(t, s)$ of the system becomes quadratic with respect to these unknowns. More precisely, we define

$$
v = \sqrt{A} u, \quad \Phi(A) = \begin{cases} 
\sqrt{\Psi(A)} & A \geq A_0, \\
-\sqrt{\Psi(A)} & 0 \leq A < A_0.
\end{cases}
$$

If standard tube laws are used, then $\Phi : (A_{min}, +\infty) \rightarrow (\Phi_{min}, +\infty)$ is a smooth invertible function. Then, we retrieve a suitable variational formulation of the problem by algebraic manipulations that require smoothness and positivity properties of the solution. Afterwards, for the sake of robustness we extend the function $\Phi$ as a bijective map from $\mathbb{R}^+$ into $\mathbb{R}$ (see Figure 1). We derive a compatible space discretisation by an appropriate choice of quadrature rule and we recover a semi-discrete energy relation. Finally, we adopt an implicit mid-point time discretisation to guarantee the unconditional stability of the scheme and preserve an energy relation at the fully discrete level. Furthermore, we are able to ensure an overall preservation of the fully discrete energy relation for the model depicted in Figure 2 by an appropriate treatment of the boundary terms – outflow of the heart model and inflow of the haemodynamic model. Note that we interpose a lumped-parameter Windkessel model as a transmission condition between the heart and the vessel models, as shown in Figure 2. In more detail, the diode governs the coupling and decoupling of the two models, representing a simple aortic valve model, whereas $R_v$ is the resistance of the aortic valve, and $C$ is a compliance added for numerical stability reasons.

Figure 1: Left: function $\Psi(\pi R^2)$. Right: function $\Phi(\pi R^2)$. Reference radius set equal to 1 cm.
Figure 2: Schematic representation of the full model under consideration: RO model of the heart (see [3]), simple valve model as a transmission condition, one-dimensional model of blood flow in one arterial segment, standard RCR Windkessel circuit at the outflow of the vessel.

Figure 3: Left: Comparison of the results of six 1D numerical schemes studied in [1] with the 1D scheme proposed in this work in the upper thoracic aorta. Pressure computed at the midpoint of the vessel (in kPa). DCG: discontinuous Galerkin; FEM: Galerkin least-squares finite element method; FVM: finite volume method; LCG: locally conservative Galerkin; McC: finite difference MacCormack method; STM: simplified trapezium rule method; EP: energy-preserving scheme proposed in this work. Right: Inlet blood flow profile used for the simulations.

3 RESULTS AND CONCLUSIONS

A first validation of the one-dimensional blood flow model that we propose in this work consisted in comparing the results of our scheme with those published in the benchmark [1]. To do so, we performed a simulation using the same physical parameters indicated in the cited work for a propagation in the upper thoracic aorta [1, Section 4.1], with an imposed inflow profile. Figure 3 shows the optimal consistency of our results with those published in [1].

Nonetheless, the main motivation of our work is to define a complete RO model for the left ventricle and the ventriculo-vascular coupling in order to obtain a modelling framework that is adapt to inverse problem strategies. The end-goal is to derive patient-specific modelling procedures that give access to physiological markers of great interest for clinical applications, for example the dicrotic notch. This last aspect will be further detailed in the talk. Finally, among the relevant extensions of our work there is the definition of a stable state-observer coupled with a ROUKF (see [2]), aimed at improving the overall stability of the parameter estimation.

REFERENCES


TUNING OF A MULTISCALE STAND-ALONE MODEL FOR PATIENT-SPECIFIC BLOOD FLOW SIMULATIONS IN LARGE ARTERIAL MODELS

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SUMMARY
With the aim to aid medical doctors in diagnosis and treatment of intermediate carotid artery stenoses, the present study proposes a three-step tuning algorithm for the development of patient-specific stand-alone multiscale blood flow models in large arterial geometries. The stand-alone property is achieved by introducing selected inlet and outlet lumped parameter models of the heart and the systemic circulation that would enable fast and reliable estimation of lumped parameters with the potential to predict disease-related flow changes or simulate pathological scenarios including that of hypotensive anesthesia or heart failure caused by coronary artery disease.

Key words: hemodynamics, multiscale modelling, lumped parameter models, parameter estimation

1 INTRODUCTION
The future of human medicine lies in its personalisation and use of non-invasive examination techniques that could alleviate the burden placed on patients, especially the elderly and high-risk ones. In cardiovascular medicine, one of the ways how to achieve a certain degree of personalisation is to introduce patient-specific blood flow models that have the potential to provide clinically valuable results. However, to truly run patient-specific computer simulations that will be able to indicate and possibly also predict disease-related flow changes, and thus, become an integral part of any clinical examination, the mathematical models have to be tuned first to match the individual hemodynamics of each patient.

In this context, the aim of the present study is to propose a tuning algorithm for the personalisation of a stand-alone geometrical multiscale model of arterial blood flow that includes a CT-derived model of large arteries coupled to a lumped parameter (0D) heart model and several outflow Windkessel models, Fig. 1. Note that the stand-alone property is chosen in order to grant the numerical simulations some flexibility regarding possible short- and long-term changes in blood flow of the patient (rest/exercise conditions, pathological changes due to atherosclerosis etc.). The main advantage of the proposed approach is the fact that it is designed purely on the basis of clinical data obtained during standard examinations and medical control, which are mostly non-invasive in nature. The minimum data necessary for the tuning process includes the following (cf. [1]):

- patient’s age and gender at the time of measurement,
- angio-CT scans of the relevant part of the vascular tree,
- flow rate waveforms at all ‘terminal’ vessels of the reconstructed arterial model,
- values of brachial systolic/diastolic pressures (measured, e.g., via the non-invasive cuff-based oscillometry method).

2 METHODOLOGY
To demonstrate the applicability of the tuning algorithm described below, let us first consider a specific example of a stand-alone multiscale arterial blood flow model. For its creation, we used anonymised
clinical data of a 77-year-old male patient provided by the courtesy of the University Hospital in Pilsen, CZ. Following the reconstruction process and data derivation outlined in one of our previous studies [1], the CT-derived arterial model shown in Fig. 1c constitutes an integral part of the blood flow model for the patient who was diagnosed with intermediate left internal carotid artery stenosis. In this case, the presence of the arterial narrowing and its indistinct influence on the downstream hemodynamics are the main motivation for conducting patient-specific blood flow simulations. In other words, the ultimate objective of this study is to provide medical doctors with clinically unavailable information for the assessment of hemodynamic significance of the diagnosed carotid artery stenosis.

Additionally to the 3D arterial model, where the hemodynamics is modelled by means of the incompressible Navier-Stokes equations coupled with the Carreau-Yasuda model for shear-dependent viscosity [2], the blood flow in the remaining (non-reconstructed) cardiovascular system of the patient including his heart is approximated with selected 0D inlet/outlet models displayed in Fig. 1a-b. In the stand-alone blood flow model, these 0D models play a crucial part, seeing as they are responsible for the patient-specific boundary conditions prescribed in the inelastic 3D model. Thus, to get a personalised ‘response’ from these 0D models, their lumped parameters have to be estimated. In this study, this is achieved by the following three-step algorithm that tunes the inlet/outlet 0D models in a sequential manner:

1. **Generation of ‘artificial’ pressure waveform:**
   To avoid identifiability problems during the subsequent estimation processes and also to match the flow condition of the patient (even a hypertensive one), the three-element Windkessel model is utilised to generate the pressure waveform in the ascending aorta. The approach including the derivation of central aortic pressure range, which has to be fitted by the Windkessel model, is described in detail in [1].

2. **Tuning of the 0D heart model:**
   Compared to the outflow Windkessel models, whose lumped parameters will be estimated in the next step, the simple heart model in Fig. 1a is tuned through its time-varying elastance model $E(t)$ that constitutes the basis of the left ventricle performance, and as such is the driving force of the entire 0D model. To match the heart outputs ($Q_{in}, p_{in}$) with the available in-vivo flow rate data and the previously generated pressure waveform in the ascending aorta, the elastance tuning loosely based on the estimation methodology introduced in [3] is carried out via a simple heart-arterial

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**Figure 1:** a) Lumped parameter (0D) model of the heart enhanced with a RLC model of the aorta and b) the three-element Windkessel model connected to the inlet and outlets of the 3D model, respectively; c) patient-specific model of large arteries and its anatomically correct 0D representation made of RL models.
interaction 0D model, where the rest of the stand-alone blood flow model is substituted with the three-element Windkessel model from the first estimation step.

3. Tuning of the outflow Windkessel models:
Considering the complexity of the 3D arterial model shown in Fig. 1c and the potential identifiability problems arising from the number of Windkessel models coupled to each of its 9 outlets (Fig. 1b), it is essential to estimate all the Windkessel parameters (\( R_p, R_d, C_a \)) simultaneously. For this purpose, a sequential estimation approach is chosen that according to the framework introduced in [4] employs the unscented Kalman filter (UKF) for an augmented state-space model. Note that due to minimal computational costs and straightforward implementation, the UKF algorithm [5] is carried out in an anatomically correct 0D representation of the original 3D arterial model apparent from Fig. 1c. The individual steps of the estimation algorithm, as implemented in this study, are described in detail in [1].

After estimating all the necessary lumped parameters, it is finally possible to proceed to the numerical solution of the stand-alone blood flow model. In this study, the obtained governing equations of the geometrical multiscale approach are solved by means of a finite volume solver, whose algorithm was introduced and successfully employed in one of our previous studies [2].

3 RESULTS AND DISCUSSION
For the aforementioned 77-year-old male patient, Figs. 2 and 3 offer a comparison between the original/derived in-vivo data and selected numerical results from the last two steps of the tuning process including the final results obtained through the personalised stand-alone blood flow model.

In the case of Fig. 2, the graphs show the evolution of main hemodynamic quantities computed via the tuned heart-arterial interaction 0D model, i.e., results of the 2nd step of the proposed algorithm. As can be noted from these graphs, the 0D heart model can be successfully tuned, but only to a certain degree. The most noticeable differences, which have to be addressed in the future, occur mainly during the early diastole, when the model is unable to correctly capture the pressure decrease and the short backflow phase observed in the ascending aorta of the patient.

Despite the fact that the 0D heart model is probably too simple in structure to accurately approximate the provided hemodynamic data, and thus, will require further modifications, its coupling to the 3D arterial model with tuned outflow Windkessel models can lead to clinically interesting results, Fig. 3. On one hand, the flow rate/pressure waveforms computed by the personalised stand-alone blood flow model seem to contain less noise (smoothed curves) than the ones from the 3rd step of the tuning algorithm (compare the left and right columns in Fig. 3). On the other hand, the imperfection of the coupled 0D heart model leads to unwanted hemodynamic deviations in early diastole including the overall increase in blood pressure.

Regarding the blood flow in the left internal carotid artery, which was of main interest for the diagnosis of the selected patient, it is possible to note that compared to the blood flow in the right counterpart some velocity suppression occurs during the systolic part of the cardiac cycle. Because no exact location for the measured in vivo flow rate waveforms was provided by the medical doctors, we are convinced that, in this case, the waveforms depicts the blood flow not at the outlet of the left internal
carotid artery, as we assumed, but rather near its stenosis, where the presence of jet flow would better explain the shape of the systolic flow rate waveform.

4 ACKNOWLEDGEMENTS

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Modeling blood as living tissue in computational hemodynamics
PATIENT-SPECIFIC FLUID-STRUCTURE INTERACTION
ANALYSES IN ASCENDING THORACIC AORTIC ANEURYSMS
USING SMOOTHED PARTICLE HYDRODYNAMICS COMBINED
WITH 4D MRI

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SUMMARY
An ascending thoracic aortic aneurysm (ATAA) is an asymptomatic localized dilation of the aorta that may be prone to dissection followed by a high mortality rate. So far, in ATAA stress analyses, the mechanical interaction between the red blood cells, white blood cells, and plasma with the thoracic aorta has totally been neglected. This study aims at proposing an interactive patient-specific fluid-structure interaction (FSI) analysis based on smoothed particle hydrodynamics. Velocity vectors are imposed throughout the cardiac cycle using velocity profiles of 4D MRI. The von Mises stresses are calculated and compared in the blood component and the aortic wall.

Key words: Thoracic aorta aneurysm, Blood components, Smoothed particle hydrodynamics.

1 INTRODUCTION
Ascending thoracic aortic aneurysm (ATAA) is a degenerative disease [1] ranked as the 12th leading cause of death in the United States [2]. It has been reported that ATAA rupture or dissection is responsible for ~10,000 deaths in 2014 alone in the United States [3]. Aneurysm formation is associated with wall remodeling, radial enlargement, alteration of the blood hemodynamics, and finally rupture [4]. It has been depicted that degeneration of elastin fibers as a result of aneurysm growth is responsible for weakening of the aortic wall [5]. Therefore, knowledge of the strength [6] and biomechanical behavior [7] of thoracic aortic aneurysms (TAAs) is essential to clinical diagnosis and treatment.

The blood by itself consists of red blood cells (RBCs) and white blood cells (WBCs), in suspension within the plasma with their own molecular weights, constituting ~ 55% of total blood volume [8]. RBCs can tolerate large deformations under external forces allowing them to pass through the capillaries [9]. WBCs are part of our immune system, performing various functions [10]. WBCs are not as deformable as RBCs [11]. To the best authors’ knowledge, numerical modeling of the interaction of RBCs, WBCs, and plasma with an ATAA wall has never been achieved. Therefore, there is a lack of knowledge on the stresses in the components of the blood as well as how ATAAAs affect these interactions. Simulation of blood flow in TAs using smoothed particle hydrodynamics (SPH), which is a particle-based fully Lagrangian mesh-free method, could address this lack. Although so far several studies have been carried out using the SPH method in arteries [12, 13], none of those studies has ever considered the important roles of RBCs, WBCs, and plasma in the calculation of peak wall stresses in ATAAAs.

This study was aimed at addressing this lack by proposing a new stress analysis taking into account the interactions of RBCs, WBCs, and plasma components of the blood with the TA and ATAAAs. This is a first proof of concept study based on a patient-specific aortic model.
2  METHODOLOGY
2.1 Experimental work
TAs of donors from the left ventricle to the abdomen during autopsy of nine healthy and nine aneurysmal male individuals aged 56±10 (Mean±SD) (healthy) and 59±9 (aneurysm) years were collected. All procedures were carried out following agreement of the institutional review board of Basir hospital, Tehran, Iran based on 2008 declaration of Helsinki. The aortic tissues were collected as fresh as possible with less than 5-hour post-mortem. The linear elastic and nonlinear hyperelastic mechanical properties of the ATAs, DTAs, and ATAAAs were measured and incorporated into our model.

2.2 Patient-specific FE model of the aortic wall
The geometrical models were established based on high-resolution contrast-enhanced MRI. The obtained images were imported into the Mimics software (Materialise NV, Leuven, Belgium) to create a surface mesh for a healthy TA. The ATAA geometry was obtained by deforming the healthy geometry to create a realistic ballooned shape in the ascending thoracic aorta. Thereafter, the model was input to Solidworks (Dassault Systèmes, Vélizy-Villacoublay, France) for refinement and conversion to a structured symmetry mesh. The final meshing was achieved in Femap (Siemens PLM Software, Plano, Texas, United States). The model, thereafter, was imported into Abaqus (Dassault Systèmes, Vélizy-Villacoublay, France) for assembly and convergence study (data not reported here). The number of elements (hexahedral)/nodes for TA and ATAA models were 6973/6892 and 8570/5588, respectively. The final FE models are shown in Fig. 1. Eventually, properly assembled and meshed models were run in the explicit dynamics FE code LS-DYNA 970 (LSTC, Livermore, CA, United States). The blood particles were spheres of diameters of 8 and 16 µm for RBCs/plasma and WBCs, respectively.

Fig. 1. Patient-specific geometries of (a) healthy TA and (b) ATAAAs. Cross-sections of each model along with the components of the blood, i.e., RBCs, WBCs, and plasma.

2.3 Blood flow simulations using the smoothed particle hydrodynamics (SPH) technique
A set of particles, representing RBCs, WBCs, and plasma were defined to represent the fluid domain. The blood in healthy ATA/DTA simulations comprised 7374 particles representing RBCs (3319 ~ 45%), WBCs (51 ~ 0.70%), and plasma (4004 ~ 54.30%). The blood in ATAA simulations comprised 8668 particles representing RBCs (3900 ~ 45%), WBCs (62 ~ 0.70%), and plasma (4706 ~ 54.30%). These numbers were chosen through a set of molecular weight pre-simulations. Each group of particles had its own physical properties, which were smoothed out over the particle neighboring, defined such as [14]:

\[ A_i = \sum_j m_j \frac{\delta}{\rho_j} W_{ij} + O(h^2); \quad W_{ij} = W(r_{ij}, h); \quad r_{ij} = r_i - r_j \]  

(1)

where \( A_i, A_j, r_i, \) and \( r_j \) represent any physical property and position of particles ‘i’ and ‘j’; and \( m_j \) and \( \rho_j \) are the mass and density of particle ‘j’, respectively. \( h \) denotes the smoothing length of the kernel function [15, 16]. It is a function of the smoothing length, \( h \), and distance between particles ‘i’ and its neighboring particle ‘j’, \( r_{ij} \).

The physical properties of the blood components, i.e., RBC, WBC, and plasma, were assigned to the model. Particles were defined with a uniform distribution inside the lumen of the models. Since the blood particles in the healthy TA and ATAAAs at their highest velocities moved ~ 40 cm and 26 cm, respectively, some particles leave the domain and this as compensated with an appropriate extension of same length at the inlet.
4D flow magnetic resonance imaging (MRI) is a methodology to measure directly in vivo the time variations of 3D blood flow velocities throughout a complete cardiac cycle. Using this method, the patient-specific time-dependent pulsatile velocity wave-forms of a healthy and a diseased individual were obtained at different anatomical locations of the aorta cycle [17]. The centerline of the aorta was reconstructed and velocity vectors aligned with the centerline were assigned at each cross-section of the aortic wall. This permitted a significant gain of computational cost. A Core i5-4460 CPU@3.20 GHz personal computer with 16.00 GB RAM was used to run the simulations. The simulations were conducted throughout a cardiac cycle (1s) with time steps of 100 µs (10,000 time steps). The simulations of the healthy TA and ATAAAs in the LS-DYNA nonlinear dynamic solver took ~ 79-96 hours.

3 RESULTS AND CONCLUSIONS

3.1 Blood components

FSI simulations permitted to compute von Mises stresses in the components of the blood as well as in the aortic wall throughout a cardiac cycle. The von Mises stresses in all the components of the blood are shown in Fig. 2. They ranged between 6.26 and 6.27 Pa in the healthy TA and they were found to be of 3.92 Pa in ATAA. The results revealed that stresses in the RBCs and WBCs are lower than that of their failure stress values while the stresses in a few plasma particles were higher than that of their failure stress. The results revealed that although the wall material model does not affect the stress values in the components of the blood, the blood particles, especially RBCs, experience higher stress values in the healthy aorta compared to ATAAAs wall, probably because of the smaller diameter. The highest stress values in the components of the blood were located in the aortic arch at post-aneurysmal sites for both the elastic and hyperelastic wall considerations.

Fig. 2. Von Mises stresses in the blood components for the healthy (a) elastic and (b) hyperelastic TA. Similarly, von Mises stresses in the blood components for the (c) elastic and (d) hyperelastic ATAA.

3.2 Aortic wall

The contours of von Mises stresses in the healthy TA and in the ATAA are shown in Fig. 3. The linear elastic wall showed relatively lower stress values than the hyperelastic one. The largest stresses were located in the aortic arch for the healthy TA. Peak von Mises stresses in ATAA ranged between 273.01 and 322.10 kPa and were located mostly at the aneurysmal sites.

Fig. 3. Distribution of von Mises stresses in the wall of (a) elastic and (b) hyperelastic healthy TA as well as (c) elastic and (d) hyperelastic ATAA.

The distribution of pressure in the aortic wall were also calculated. Regardless of the material models, a peak pressure of ~ 21 kPa (157 mmHg) was reached. However, the average pressure was ~ 15 kPa (112 mmHg). The wall shear stress (WSS) distribution was computed for the
elastic and hyperelastic behaviors. The peak WSS were found to be 10.10 and 12.96 Pa for the elastic and hyperelastic ATAA, respectively.

This study is the first complete FSI analysis for an ATAA using the SPH technique. FE models of healthy TA and ATAA were established according to MRI datasets of healthy and diseased human individuals. The stresses in the wall of the aorta and components of the blood were computed and compared. The proposed SPH approach could compute the stresses in the components of the blood in interaction with the healthy and diseased aortic wall. Two types of material models, i.e., elastic and hyperelastic, were used in the simulations, showing that they have a major role onto the wall stress but not on the stresses in the blood components. Future work will aim at developing a new rupture risk assessment for clinicians considering the interactions of the blood components and the aortic wall.

REFERENCES

A REDUCED-ORDER MODEL FOR RED BLOOD CELL DYNAMICS IN BLOOD FLOW

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SUMMARY

Understanding blood rheology plays an essential role in developing new bio-microfluidic systems. Modelling the dynamic behavior of biological cells in blood flow such as red blood cell (RBC) has been a challenge in the past decades due to their complex physics. Several computational methods have been developed to model RBC dynamics but they mostly entail high computational costs. In the present study, we propose a reduced-order model to overcome this limitation by representing RBC as an arrangement of bonded spheres in interaction with the surrounding fluid. The model is implemented in the framework of resolved CFD-DEM. A micro-channel full of suspended RBCs in blood plasma corresponding to hematocrits of 0.15, 0.3 and 0.45 was simulated. The dynamic behavior of RBCs such as deformation, tumbling and etc, as well as the formation of the cell free layer near the channel wall and the velocity are investigated. Accordingly, the change in the apparent viscosity of whole blood is analyzed showing a good agreement with previous literature.

Key words: resolved CFD-DEM, red blood cell (RBC), reduced-order model

1 INTRODUCTION

Blood is an important physiological fluid which is vital for the transportation of oxygen and nutrients to the various parts of the body. Red blood cells (RBCs) are highly deformable in nature with a diameter of 7.82µm and constitute 45% by volume of blood and hence has a major impact on blood flow [1]. Several numerical methods have been developed to deal with RBC dynamics on different scales. Continuum-based approaches and high-resolution mesoscale models [2, 3] proved to be computationally expensive due to the cumbersome fluid-solid interactions and high resolutions involved. Coarse-grained models of RBC diluted the problem to measures of an elastic spring network to represent the RBC membrane [4, 5, 6]. Although the mesoscopic models provided accurate results without compromising computational efficiency, they tend to become expensive when dealing with tube or channels of diameters more than 50µm [7]. Considering this restrictive nature of RBC simulations, Pan et al. devised a low-dimensional model which constituted a ring of spheres connected by wormlike chain (WLC) springs [7]. In the present work, a low-dimensional model similar to that introduced by Pan et al. is presented. The model employs cantilever beams to connect the spheres. It incorporates a velocity-dependent damping of the forces and hence the possibility to consider the viscoelasticity of RBCs. This model is implemented in the framework of resolved CFD-DEM which couples fluid-solid interaction using the immersed boundary method.

2 METHODOLOGY

2.1 Deformable particle model

The reduced-order modelling approach considers geometrical as well as mathematical simplification of the problem. In this model we reduce the complex deformation of a soft particle to the mechanical behaviour of a finite number of spheres interconnected by virtual mathematical bonds represent
cantilever beams as in Figure 1(a). As the spheres translate and rotate, the bonds also deform and transfers and damps inter-sphere forces to control the relative motion of the spheres.

The forces and moments (Figure 1(b)) are calculated incrementally according to the bonded particle model and reads as [8]:

\[ dF^b = K^b v^r \, dt \]  
\[ dM^b = S^b \omega^r \, dt \]  
\[ K^b = \frac{E_b A_b l_b}{l_b}, \quad S^b = \frac{G_b A_b l_b}{l_b} \]  

where \( dF^b \) and \( dM^b \) are the increments in the forces and moments of the bond. \( K^b \) and \( S^b \) are the rigidity terms and \( v^r \) and \( \omega^r \) are the relative linear and angular velocities. \( E_b \) and \( G_b \) are the elastic modulii respectively.

\[ \text{Figure 1: (a) A reduced-order red blood cell; (b) Forces and moments due to the bonds redrawn from [8].} \]

The trajectory of the spheres are solved using Newton’s laws of motion and considering the effects of the bonds the following equations are obtained [8]:

\[ m \frac{d\mathbf{u}_p}{dt} = F^c + F^b + mg + F^c_d + F^b_d + f_{p,f} + \sum_{N_w} f_{p,w} \]  
\[ I_s \frac{d\mathbf{\omega}_p}{dt} = M^c + M^b + M^c_d + M^b_d + r \times \left( \sum_{N_w} f_{p,w} + f_{p,f} \right) \]

where \( m \) and \( I_s \) are the mass and the moment of inertia of each sphere. \( F^c \) and \( F^c_d \) are the contact forces and the damping of the contact forces. Similarly, \( F^b \) and \( F^b_d \) are the bond forces and the damping of the bond forces. The moments due to the contact and the bonds can be recognised in the same manner.

### 2.2 Coupling of fluid-solid interaction

In the two-phase flows, the physics of suspended particles in carrier fluid are strongly coupled. The fluid flow can be described by the incompressible Navier-Stokes equations as:

\[ \rho \frac{\partial \mathbf{u}}{\partial t} + \rho (\mathbf{u} \cdot \nabla) \mathbf{u} = -\nabla p + \mu \Delta \mathbf{u} \]  
\[ \nabla \cdot \mathbf{u} = 0 \]

In the context of resolved CFD-DEM, these two sets of equations are coupled. The particle influence on the fluid flow is introduced by means of forcing terms [9]. The stress tensor \( \sigma \) of the fluid is given by:

\[ \sigma = -pI + \tau \]
where \( p \) is the pressure, \( \tau \) is the deviatoric stress tensor and \( I \) is the identity tensor, which finally yields the interaction force in terms of pressure and viscous forces:

\[
f_{p,f} = \int_{\Omega_S} \left[ \mu \nabla^2 \mathbf{u} - \nabla p \right] d\Omega_S
\]  

(9)

The rotation of the constituent spheres about the centre of mass of the deformable particle is taken into account. Thus, at each instance of time, the deformable particle will be treated as a rigid particle with the a given centre of mass. This yields the velocity of the constituent spheres as:

\[
\mathbf{u}_i = \mathbf{u}_{cm} + \mathbf{r}_i \times \omega_i
\]  

(10)

where \( \mathbf{u}_i \) is the velocity of the constituent sphere, \( \mathbf{u}_{cm} \) is the velocity of the centre of mass, \( \mathbf{r}_i \) is the length vector between the centre of mass and the centroid of the constituent spheres and \( \omega_i \) is the rotation velocity about the centre of mass given by

\[
\omega_i = \frac{\mathbf{r}_i \times \mathbf{u}_i}{|\mathbf{r}_i|^2}
\]  

(11)

Introducing such a rotational velocity as a component of the constituent sphere velocity will enable to introduce a membrane-like rotation for the particle.

### 3 RESULTS AND CONCLUSIONS

The dynamic behaviour of RBCs and their interactions lead to the formation of a cell-free layer (CFL) near the tube walls due to which the apparent viscosity of blood decreases. To analyze these characteristics, the flow of blood with a given hematocrits are observed and the corresponding effects are characterized. In Figure 2(a), a tube of \( D = 20 \mu m \) with \( \text{Hct} = 0.30 \) and the velocity profiles for the flow for \( \text{Hct} = 0.15 \) & 0.3 in a \( 20 \mu m \) tube is shown in Figure 2(b). As the flow progresses, the cells deform and due to their interactions migrate towards the centre of the tube due to which a cell-free layer is formed near the tube wall. With increasing \( \text{Hct} \), the plugging effect of the flow increases due to which the centre-line velocity decreases. The CFL thickness is measured as the position of the outermost RBCs with the radius of the constituent sphere added to it. For \( \text{Hct} = 0.15 \), the CFL is found to be 3\( \mu m \), and for \( \text{Hct} = 0.3 \) it was found to be 2.25\( \mu m \). In the CFL region, the velocity profile follows a parabolic profile as opposed to the almost flat profile at the flow core.

![Diagram](image)

**Figure 2:** (a) Setup for \( D = 20 \mu m \) for \( \text{Hct} = 0.3 \). (b) The velocity profiles for \( \text{Hct} = 0.15 \) & 0.3 compared against Newtonian plasma for \( D = 20 \mu m \). The dotted lines are the location of the cell-free layer.

The apparent viscosity for flow through a tube is given by:

\[
\eta_{app} = \frac{\pi \Delta PD^4}{128QL} = \frac{\Delta PD^2}{32vL}
\]  

(12)
where $L$ is the tube length, $\Delta P$ is the pressure difference and the mean velocity is defined as $\bar{v} = Q/A$. The relative apparent viscosity can be written as:

$$\eta_{rel} = \frac{\eta_{app}}{\eta}$$

with $\eta$ representing the viscosity of plasma. For $H_{ct} = 0.5$, the relative apparent viscosity was found to be 1.33 and that for $H_{ct} = 0.30$ was 1.69. These values agree well with the apparent viscosities that are found by Pan et al [7]. The cell-free layer has lower viscosity compared to the RBC-populated core of the flow, which in turn produces a lubricating effect on the core. With increasing $H_{ct}$, the thickness of the cell-free layer decreases, due to which the lubricating effect decreases and the resistance to the flow also increases as the RBC concentration increases, eventually leading to an increase in the relative apparent viscosity.

REFERENCES


A COMPUTATIONAL MODEL FOR THROMBOSIS FORMATION AND GROWTH IN TYPE B AORTIC DISSECTION

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SUMMARY

We present a recently developed mathematical model for thrombus formation and growth in type B aortic dissection and show how to apply this model for patient-specific predictions. Comparisons of simulation results with clinical follow-up data are made to evaluate the validity and accuracy of the computational model. Factors that influence false lumen thrombosis in aortic dissections are also discussed.

Key words: aortic dissection, thrombus formation, computational model

1 INTRODUCTION

Type B aortic dissection (TBAD) is caused by the formation of a tear in the inner layer of the aortic wall. The thrust of diverted blood causes splitting of the wall layers and leads to the formation of a false lumen. Partial false lumen thrombosis (FLT) was identified as a significant predictor for late complications [1], due to increased false lumen pressure thereby increasing the risk for aortic dilatation and rupture. On the other hand, improved outcomes are associated with complete FLT, which may occur spontaneously in some patients without surgical intervention or can be achieved through thoracic endovascular aortic repair (TEVAR) [2, 3]. Given the importance of FLT in evaluating treatment outcomes for aortic dissection, it would be desirable to be able to predict thrombus formation and growth in dissection false lumen and to identify the anatomical and hemodynamic factors that influence FLT.

We have recently developed a mathematical model suitable for patient-specific prediction of FLT under physiologically realistic flow conditions [4-6]. The model predicts thrombus formation and growth through the evaluation of shear rates, fluid residence time and platelet distribution, based on convection-diffusion-reaction transport equations. It has been applied to medically treated and TEVAR patients with different outcomes over a follow-up period of 2-5 years. For validation purposes, predicted thrombus volume and its variation over time are compared with in vivo data derived from follow-up CT scans.

2 METHODOLOGY

The model consists of the conservation of mass and momentum equations for blood flow and specially formulated transport equations for the formation and growth of thrombus. The latter is based on transport equations for fluid residence time (RT), resting and activated platelets (RP and AP), and a coagulant C. Thrombus formation is tracked through the local concentration of bound platelets (BP), which is used as a surrogate for thrombus. Thrombus growth is predicted through a feedback mechanism which controls the formation of thrombus by allowing BP to accumulate in regions of high concentrations of AP, low shear and high RT, and thrombus growth would be terminated if these conditions were not satisfied. For the transport of coagulant, a shear-stress-dependent flux boundary condition is applied at the wall where thrombus growth can only occur if local time-averaged wall shear stress (TAWSS) is lower than a specified threshold (0.2 Pa in our
Transport within the formed thrombus is also included in the model, where thrombus is treated as a porous medium with its porosity varying between 0.75 for a completely formed thrombus and 1 for no-thrombus. In order to account for the effect of thrombus growth on blood flow, a negative source term proportional to the concentration of BP is introduced in the momentum equation, where this source term represents the resistance imposed by the formed thrombus on blood flow. Details of the mathematical equations and model parameters can be found in [4-6].

3 RESULTS AND CONCLUSIONS

The model described above has been applied to aortic dissection treated by medical therapy alone and patients who underwent TEVAR. Varying degrees of FLT were observed in the follow-ups of these patients, including no FLT, partial and complete FLT. Representative results for a medically treated patient are shown in Figure 1, where changes in false lumen surface over time as a result of thrombus growth can be clearly observed. Comparisons with in vivo data extracted from follow-up CT scans showed good qualitative and quantitative agreement in all cases.

Figure 1: Predicted false lumen surface in a medically treated aortic dissection at different time points from (a) to (d). The false lumen volume is reduced considerably over time due to thrombus formation and growth.

Our results demonstrate that the model is capable of predicting which patients are more likely to develop FLT and to what extent, for both spontaneous and TEVAR-induced thrombosis. We are currently investigating anatomical and stent graft related factors that influence FLT, including the presence and location of reentry tear, the number of side branches perfused by the false lumen, and stent graft length, in an attempt to identify risk factors for incomplete FLT.

REFERENCES

THROMBOSIS SIMULATION FOR NON-NEWTONIAN, PULSATILE FLOW

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SUMMARY

This study investigated the effects of non-Newtonian blood behavior and flow pulsatility on thrombus deposition and growth in a three-dimensional geometry through computational thrombosis simulations. Results from application of the Newtonian, Carreau, and Cross-Power models were compared, which showed that application of the Carreau model provided an accurate prediction in thrombus deposition and growth, where effects of small flow pulsatility may be negligible.

Key words: device-induced thrombosis, numerical simulation, hemodynamics, non-Newtonian

1 INTRODUCTION

Thrombosis is a common complication resulting from implantation of cardiovascular devices. Computational simulation is a powerful tool to provide predictions on thrombus growth in a given geometry and can be used to evaluate the risk of medical devices after implantation. To accurately predict thrombus growth, simulation in a three-dimensional (3D) geometry is necessary.

There have been multiple macroscopic thrombosis models developed. Fogelson (1992), Sorensen et al. (1999a), and Goodman et al. (2005) were the pioneers who simulated thrombosis at a single-scale by coupling the hemodynamics of blood flow with the thrombus growth [4-6]. To further extend the field, Taylor et al. (2016 & 2017) developed a thrombosis model that simulates thrombus deposition and growth in a two-dimensional domain, with spatial and time scales relevant to medical devices [1, 2]. The model assumed thrombosis to predominantly depend on the following species: activated platelets, non-activated platelets, surface adherent platelets, and adenosine diphosphate (ADP). In addition, the fluid velocity field was affected by the forming thrombus and coupled to the simulation. However, the model assumed blood to be Newtonian and flow to be steady, while slight pulsatile flow occurred in the experiments whose data were used for model validation. To introduce and investigate the non-Newtonian and pulsatile flow effects on thrombus deposition and growth, the Carreau and Cross-Power models were added individually to the existing model for comparison.

For the current study, the thrombosis model by Taylor et al. (2016 & 2017) was modified [1, 2] and the non-Newtonian thrombosis simulations under pulsatile flow were performed. The goal was to investigate the effects of non-Newtonian blood behavior and flow pulsatility on thrombus deposition and growth in a 3D geometry.

2 METHODOLOGY

The velocity (\( \mathbf{u} \)) and pressure (\( p \)) fields of laminar fluid flow were solved via the continuity (Eq. 1) and Navier-Stokes equations.

\[
\nabla \cdot \mathbf{u} = 0
\]
To simulate thrombosis, the Navier-Stokes equation was modified into Eq. 2, where Blood viscosity was a shear rate-dependent variable calculated by the Carreau (Eq. 3) and Cross-Power (Eq. 4) models individually.

$$\frac{\partial u}{\partial t} + (u \cdot \nabla) u = -\frac{1}{\rho} \nabla p + \nu \nabla^2 u - \nu F(\varepsilon) u$$  \hspace{1cm} (2)

$$\nu = \nu_{\infty} + (\nu_{0} - \nu_{\infty}) [1 + (k \varepsilon)^{2}]^{\frac{n-1}{2}}$$  \hspace{1cm} (3)

$$\nu = \nu_{\infty} + \frac{(\nu_{0} - \nu_{\infty})}{1 + (n \nu \varepsilon)}$$  \hspace{1cm} (4)

In Eq. 2, the Brinkman term ($\nu F(\varepsilon) u$) was used to couple the velocity field with thrombus growth and $F$ was a function of the platelet aggregation intensity ($\varepsilon$), whose concentration depended on the following species: activated platelets, non-activated platelets, surface adherent platelets, and ADP. These species were calculated in bulk concentrations to match the scale of the system geometry, through a set of convection-diffusion-reaction equations (Eq. 5):

$$\frac{\partial Q}{\partial t} + (u \cdot \nabla) Q = D \nabla^2 Q + R$$  \hspace{1cm} (5)

where $Q$ was a scalar, $D$ was the diffusion coefficient, and $R$ was a source or sink.

The modified computational model was applied to simulate thrombosis in a backward facing step (BFS), an asymmetric expansion. Prior to simulations, a 3D mesh of the geometry was constructed by SolidWorks (Waltham, MA, USA), with dimensions shown in Figure 1. At the inlet, blood flow was set to be fully developed, laminar, and pulsatile with 0.209 m/s amplitude, 15.1 s$^{-1}$ frequency, and a Reynolds number of 490 at peak velocity.

![Figure 1: Dimensions of the backward facing step model used for computational studies. Heights of the channel and size of the step match those of the model used in Taylor et al. (2014) [3].](image)

The computational thrombosis model was applied using OpenFoam (OpenCFD, Ltd, 543 Bracknell, UK) and thrombus growth was simulated for 30 minutes. To validate the results, the simulated thrombus growth was compared with in vitro measurements obtained from magnetic resonance imaging (MRI). In those experiments, bovine blood was circulated through the BFS model, resulting in thrombus growth within the separation region, and the thrombus size was measured at different time points using the MRI scans [3].

### 3 RESULTS AND CONCLUSIONS

The simulation results showed that the thrombus grew at the region where flow separation occurred, which matched the MRI experimental observations [3]. The surface area exposed to blood flow of the simulated thrombus was compared to the in vitro MRI data in Figure 2.
Comparing the results from the Newtonian simulation for steady flow and experimental data, the exposed surface area of the simulated thrombus was greater, roughly by a factor of two. In contrast, the thrombus growth predicted by the non-Newtonian simulations agreed with the experimental data better. Under steady flow, the exposed surface area predicted by the Carreau or Cross-Power model matched the MRI data well. Under pulsatile flow, there was significant increase in thrombus growth after 15 minutes when applying the Cross-Power model, but no significant change when applying the Carreau model.

The results showed that the non-Newtonian assumption for blood improved the existing thrombosis model and provided better prediction on thrombus growth because the non-Newtonian assumption is more sensitive to changes in low shear stress, where the platelets aggregate to form the thrombus. While there was significant change in thrombus growth under pulsatile flow for Newtonian and Cross Power models, the Carreau model was less sensitive to flow pulsatility and its simulation results remained relatively the same. A possible reason is that comparing to the Cross-Power model, the Carreau model results in relatively constant viscosities at low shear rates. Consequently, introduction of small flow pulsatility may not be necessary for more accurate thrombosis simulation when applying the Carreau model. The conclusion could be different when blood flow becomes more pulsatile, affecting the thrombus growth more significantly, which requires further investigation.

REFERENCES

THE EFFECT OF MIXING DEFORMABLE AND STIFFENED RED BLOOD CELLS IN FLOW ON HEMATOCRIT PROFILES AND PLATELET MARGINATION

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SUMMARY

This work probes the effect of red blood cell deformability in whole blood on hematocrit profiles and platelet margination using cell resolved blood flow simulations. We first propose a stiffened red blood cell model and then perform bulk whole blood flow simulations in cylindrical channels with varying mixed stiff-to-healthy red blood cell concentrations. We investigate how different mixtures of stiffened red blood cells present in blood flow impact hematocrit profiles and the transport of platelets.

Key words: hemorheology, red blood cell deformability, margination, lattice Boltzmann

1 INTRODUCTION

Whole blood is complex suspension of cells, and its rheology is highly dependent on the mechanical nature of the cells, red blood cells (RBC) are by far the most numerous cellular component. Along with its population, the RBC’s deformability and bi-concave shape give rise to many effects of whole blood such as shear thinning, the Fåhraeus-Lindqvist effect, and the existence of a red blood cell free layer (CFL). There exist many pathologies that change the deformability of the RBC where stiffened RBCs in the blood stream can lead to vaso-occlusion and loss of nutrient to tissues, like sickle cell anemia [1], malaria, human immunodeficiency virus (HIV), and diabetes [2]. Earlier work by Gutierrez et al. [3] experimentally probed how different RBC rigidities and volume fractions of rigid RBCs impact white blood cell (WBC) margination and adhesion in blood flow. Here we perform cell resolved blood flow simulations to study the role of RBC deformability in the rheology and transport phenomena of whole blood.

The numerical simulations are performed with the validated cell resolved blood flow model HemoCell [4], which is a lattice Boltzmann method (LBM) for the blood plasma, and a discrete element method for the RBC material model that is coupled to the plasma via the immersed boundary method. We study in detail the formation and evolution of RBC hematocrit profiles and platelet margination in pipe geometries with varying stiff-to-healthy RBC populations. Our goal is to study the transport of both RBCs and platelets in idealized geometries which can be followed up with an experiment to measure directly the predicted properties as a result of stiffened RBC fractions in whole blood.
We classify cell stiffness by the elongation index of RBCs in a perfectly sheared environment by measuring both the minor $B$ and major $A$ axes then calculating the elongation index $El = \frac{A - B}{A + B}$. We validate our stiff RBC model by matching the numerical elongation indexes given by HemoCell to the elongation index curves experimentally obtained from the ektacytometer of Gutierrez et al. [3]. In this experiment RBCs are treated with tert-butyl hydroperoxide (TBHP) to induce oxidative stress on cellular membranes which results in a overall stiffened RBC. Treating the RBCs in different concentrations of TBHP results in a range of stiffened RBCs. The elongation curves via ektacytometry are shown as solid lines in Figure 1. The numerical stiff RBC model was achieved by scaling the force coefficients of the validated HemoCell model. In particular we found a combination of scaling the original link $K_l = 15 K_B T$ and bending $K_b = 80 K_B T$ force coefficients of the original HemoCell model [4] along with increasing the interior cytoplasmic viscosity ratio $\Lambda$ [5] results in two stiffened RBC models over a range high shear rates. The link force captures the stretching and compression of the underlying spectrin-network of the RBC and is written as follows.

$$F_{link} = -\frac{K_l * dL}{l} \left[1 + \frac{1}{\tau_l^2 - dL^2}\right]$$  \hspace{1cm} (1)

Here $dL = \frac{L_i - L_0}{L_0}$ is the normal strain defined as the deviation from the equilibrium length $L_0$. The spectrin-network is chosen to reach its persistent length $p = 7.5$ nm at the relative expansion ratio of $\tau_l = 3.0$. The bending force represents the bending response of the membrane arising primarily from the non-zero thickness of the spectrin-network and is calculated between two neighboring surface elements.

$$F_{bend} = -\frac{K_b d\theta}{L_0} \left[1 + \frac{1}{\tau_b^2 + d\theta^2}\right]$$  \hspace{1cm} (2)

Here $d\theta = \theta_i - \theta_0$ and since we chose a lattice fluid resolution of $L_0 = 0.5$ $\mu$m the limiting angle is chosen to be $\tau_b = \frac{\pi}{6}$. For further details of the original HemoCell model please refer to [4]. Implementing the cytoplasmatic viscosity is done by identifying LBM fluid cells which lie inside each RBC and increasing the plasma viscosity [5]. The results of the elongation index matching are shown in the left panel of Figure 1, with a schematic of each cell type shown in the right panel.

![Figure 1: Fit of the numerically stiffened HemoCell model to elongation curves from ektacytometry. The numerical models are shown as the violin plot scattered over the experimental elongation curves shown as lines. For the treated RBCs the red is healthy, green has been treated in 0.5 mM TBHP, and blue with 0.75 mM TBHP. The numerical stiff models are green with scaled link coefficient of $6K_l$ and interior cytoplasmic viscosity ratio of $\lambda = 6.0$, and blue with scaled link $140 K_l$ and bending $500 K_b$ force coefficients. The width of each violin plot highlights the distribution of $El$ measurements taken over a time range of 35 milliseconds, where the error bars show the extrema of the $El$. The right panel is direct output from the simulation which provides a schematic of the ranges of stiffness, following the same color coding of the left panel.](image)
We present two stiffened RBC models. The first stiffened model has modified link coefficient of $K_l = 90 \ K_B T$ and a interior viscosity ratio of $\Lambda = 6$ which matches the 0.5 TMBH experimentally stiffened model. The second stiffer model, shown as a blue violin plot in Figure 1 has modified link and bending force coefficients of $K_l = 2100 \ K_B T$ and $K_b = 40000 \ K_B T$ respectively, this stiffer model matches the experimental 0.75 TBHP stiff cell model. For the bulk pipe flow simulations with mixed stiff-to-healthy populations presented in this abstract we chose the stiffer RBC which matches 0.75 mM TBHP elongation curves.

The mixed stiff-to-healthy populations were first run with the validated two dimensional cell resolved model HemoCell2D [6, 7]. This allowed us to probe a larger set of parameters from which we could chose the interesting cases to simulate in 3D. In 2D we simulated in a periodic straight chamber, with a width of 127 $\mu$m, a 40% hematocrit with stiff-to-healthy RBC ratios of 0, 10, 20, 30, 50, 70, 90, and 100% each over a range of wall shear rates (WSR) of $200 s^{-1}$, $500 s^{-1}$, and $1000 s^{-1}$. These 2D simulations highlight that the greatest effects occur in the 0, 50, and 100% stiff-to-healthy ratio cases. As a result, in 3D, we simulated the 0, 50, and 100% stiff-to-healthy ratio cases in a pipe flow geometry, of radius $R = 50 \mu m$, with a total hematocrit of 30% and wall shear rate of $1000 s^{-1}$. All simulations, both 2D and 3D, were populated with a platelet to RBC (stiff+healthy) ratio of 1:10. A schematic of the 3D 50/50 mixed case is shown in the bottom right panel of Figure 2.

## 3 RESULTS AND CONCLUSIONS

![Figure 2](image-url)

Figure 2: Volume fractions as a function of radial position in the pipe with radius $R = 50 \mu m$, 1000s$^{-1}$ WSR, and 30% total hematocrit cases. The top left panel is the 100% healthy case, the 100% stiff case is in the top right panel, and the 50/50 stiff/healthy mixed case is plotted in the lower left panel. The healthy populations are plotted in red, the stiff populations are plotted in blue, and the platelets are plotted as a grey dashed line. $C_{plt}$ is the normalized platelet volume fraction, and is calculated by measuring the local platelet volume fraction $C_{plt}$ and normalizing to the mean volume fraction of the pipe $C_{plt}$.

We observe in the 2D simulations of varying stiff-to-healthy RBC ratios that the margination of platelets to the vessel walls is greatest in the 100% healthy case and least in the 100% stiff case. Margination gradually increases in all of the intermediate simulations from the 100% stiff to the
100% healthy. This effect is present across all WSR simulations but is greatest in the 1000s$^{-1}$ case. We also observe the decrease of the CFL with the increase of stiffened RBC population. The CFL is measured as the width of a layer from the vessel wall to the position where the RBC volume fraction reaches 5% of the total channel volume fraction for that particular cell type. We attribute this CFL decrease to the lift force felt by the RBCs at the cell wall. The stiffened RBCs have a less net lift force compared to the healthy RBCs, and therefore will overcrowd the vessel walls, which will likely lead in turn to a decrease in platelet margination.

These results are studied and confirmed in greater detail in 3D. Shown in Figure 2 are results of the 3D simulations of the 100% healthy, 50/50 mix and 100% stiff cases with 1000s$^{-1}$ WSR. Platelet volume fraction at the vessel wall decreases from the 100% healthy to the 100% case, with the 50/50 case being the intermediate of the two extremes. This suggests that the margination of platelets decreases as stiff cell volume fraction increases. The 50/50 mix in Figure 2, also highlights the difference in CFL width of the stiff and healthy RBC populations. There exist also a small segregation of healthy and stiff RBCs in the simulations. Here we observe that in a region of radii $R = 8 – 25 \mu m$ stiff RBCs dominate where at larger radii in the region of $R = 25 – 40 \mu m$ healthy cells dominate. This effect maybe due to a shear rate gradient across the diameter of the pipe. At radii closer to the wall we see higher shear rates than those towards the pipe center. Preliminary simulations suggest that cell collisions happen at a much higher rate closer to the wall which may result in the pushing out of stiff RBCs from that region.

The simulations presented here enable the resolution of the individual cells, currently unobtainable by experiment, which allow their movement and emerging rheology to be studied. We report similar behavior to the experiments of Gutierrez et al. with the margination of platelets instead of WBCs and localization of stiff RBCs to the vessel wall.

REFERENCES

NUMERICAL ASSESSMENT OF DEVICE-RELATED THROMBUS FORMATION TRIGGERED BY THE CONTACT SYSTEM

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SUMMARY

Thrombosis is a major concern in blood-contacting medical devices. In the present study, pro-coagulant reactions including the contact activation system are coupled with a fluid solver as well as a recently proposed thrombus formation model. The resulting biochemical/fluid model is applied to a backward facing step configuration, a flow configuration that frequently appears in medical devices. Simulations show that the contact system induces a large concentration of thrombin is the recirculation zone without the need of an a priori knowledge of the thrombus location. Platelets are then chemically activated and generate a thrombus whose position and growth rate are in good agreement with the experimental data available.

Key words: Thrombosis, Contact System, Hemodynamics, Reduced kinetics

1 INTRODUCTION

One of the main problems of blood-contacting devices is thrombus formation which can lead to device malfunction or thromboembolism. Blood clotting in devices is regulated by a series of intertwined biological processes, such as protein adsorption, platelet activity, complement system and coagulation reactions, as reviewed by Gorbet and Sefton [1]. These mechanisms appear due to the presence of the device whose artificial wall lacks the endothelial properties of the vessel. At the material surface, contact activation of factor XII (zymogen of the coagulation cascade) takes place, initiating a cascade of enzymatic reactions [2] that produce thrombin, a key coagulation enzyme that activates platelets and forms fibrin. At the same time, platelet adhesion and activation can also occur at the device surface, as explained by Jaffer et al. [3]. In the last stage of the thrombus formation process, aggregated platelets and polymerized fibrin form a stable clot that may hinder the device performance.

Computational fluid dynamics (CFD) has been used to study the flow in medical devices and evaluate the risk of thrombosis [4]. A straightforward evaluation of thrombosis risk can be performed using specific flow patterns, such as high shear stress leading to platelet activation [5] or stasis which promotes coagulation [6]. Approaches focusing only on flow properties do not allow to study the biochemical processes, which play a major role in thrombus formation [7]. Thus, more exhaustive methods accounting for platelet activity, the coagulation cascade, clot growth and its interaction with the flow have been developed for thrombus triggered by vessel injury [8], [9]. However, only small computational domains (~100 µm) can be considered due to the complexity of these models. Reduced, low-order models accounting for platelet adhesion, activation (by chemical and mechanical pathways) and clot-flow interaction have been developed (Taylor et al. 2016; Wu et al. 2016). Nevertheless, thrombin produced by the coagulation cascade triggered by the contact system has not been considered in a model of thrombus formation in devices. A model that incorporates the contact activation system and the coagulation reactions until thrombin formation coupled with a realistic representation of flow dynamics is thus needed. This is all the more true as
recent clinical studies have pointed at the contact activation phase as a promising therapeutic target providing an anticoagulant strategy without increasing the risk of bleeding [3], [10].

A first step towards this objective was recently presented by Mendez et al. [11] who implemented a surface-mediated thrombin production model in a general purpose computational hemodynamics framework. The model accounts for the interaction of the blood flow with the contact activation system and the rest of the blood coagulation cascade. The objective of the present study is then twofold:

1- couple the framework of [11] to a proper thrombus formation/growth model,
2- assess the resulting pipeline by computing a well-controlled configuration relevant to device-induced thrombus formation.

2 METHODOLOGY

The Navier-Stokes equations are solved along with the Convection-Diffusion-Reaction equations for each chemical species. The set of equations writes:

\[ \nabla \cdot \mathbf{u} = 0 \]  

(1)

\[ \rho \left( \frac{\partial \mathbf{u}}{\partial t} + \mathbf{u} \cdot \nabla \mathbf{u} \right) = - \nabla p + \mu \nabla^2 \mathbf{u} - \mu F(\varepsilon) \mathbf{u} \]  

(2)

\[ \frac{\partial C_i}{\partial t} + \nabla \cdot (C_i \mathbf{u}) = \nabla \cdot (D_i \nabla C_i) + R_i \]  

(3)

where \( \mathbf{u} \) is the velocity field, \( p \) is the pressure field, \( \rho \) stands for the density and \( \mu \) is the dynamic viscosity (both assumed constant-valued). \( C_i \) represents the concentration of species \( i \), \( D_i \) is the diffusion coefficient and \( R_i \) stands for the reaction source term for each of the coagulation factors, as computed from the kinetic model of Chatterjee et al. [12] (53 species, 63 reactions rates). In order to initiate the coagulation reactions by contact activation of factor XII, the proper boundary condition introduced by Mendez et al. [11] is used. This condition relates the species diffusive wall flux to the surface reaction rate of factor XII activation. It reads:

\[ D_{XIIa} \frac{\partial C_{XIIa}}{\partial n} = - k_s C_{XII} \]  

(4)

where \( n \) is the direction normal to the wall and \( k_s \) denotes the surface reaction rate of the \( XII \rightarrow XIIa \) reaction. Furthermore, the thrombus evolution is accounted for thanks to the model proposed by Taylor et al. [13] which considers three biochemical species: non-activated platelets (NP), activated platelets (AP) and Adenosine diphosphate (ADP). Mechanical and chemical activation mechanisms are considered in the model. When a platelet is activated, a certain amount of ADP is released and once a threshold concentration of ADP is reached, chemical activation takes place. As in mechanical activation, chemical activation of platelets also releases ADP and an auto-amplification loop is formed. To quantify thrombus growth, the concept of platelet aggregation intensity \( \varepsilon \) was introduced in [13]. The thrombus frontier corresponds to the surface (line in 2D) where the aggregation intensity reaches a pre-defined threshold value. Production/ destruction of \( \varepsilon \) are also introduced based on the local value of the concentration of activated platelets and viscous shear stress. Finally, the impact of the growing thrombus on the flow is accounted for by considering the thrombus as a porous material and is modeled by adding a Brinkman term in the RHS of the Navier-Stokes equations (see last term of Eq. (2)). The details about the evolution equation of \( \varepsilon \) and the expression of \( F(\varepsilon) \) can be found in Taylor et al., 2016 [13]. The coupling between the approaches developed in [11] and [13] is done by allowing the platelets to be activated by thrombin instead of only ADP. Moreover, given the simplicity of the thrombus model described above, a reduced order kinetic scheme was used for the coagulation cascade which mimics the scheme of Chatterjee et al. [12] at lower cost (5 species and 9 reaction rates).

The framework described above was applied to predict the thrombus growth in a backward facing step geometry (BFS) inspired from the experimental configuration of Taylor et al. 2014 [14]. The
flow equations were solved thanks to the in-house CFD solver YALES2BIO (imag.umontpellier.fr/~yales2bio/) already used by Mendez et al. [11].

3 RESULTS

The flow configuration considered is presented in Figure 1 which also displays a typical map of thrombin concentration after convergence. Note that this result corresponds to the case where the thrombus generation/growth model is switched off. This allows illustrating how the coagulation cascade initiated by the contact system is able to produce thrombin behind the BFS, where the characteristic flow time scale is large enough to allow chemistry to dominate. In the other regions of the flow domain, any thrombin production is washed out before accumulation can occur. Note that the boundary condition Eq. (4) is applied uniformly over all the walls in Fig. 1. This contrasts with conventional in-vivo models in which the reactions are initialized at user-defined injury sites.

![Figure 1](image1.png)

Figure 1: Schematic of the BFS configuration (left) and concentration of thrombin in absence of thrombus formation modeling (right).

When the thrombus generation/growth model is switched on, the computation predicts blood clotting behind the BFS, as observed in the experimental data of Taylor et al. [14]; this is illustrated in Figure 2.

![Figure 2](image2.png)

Figure 2: Longitudinal velocity component after 5 (left) and 20 (right) minutes. The white line is the boundary of the thrombus.

Figure 3 shows that the computed growth of the thrombus is in good agreement with both experimental and computational data. Note however that the evolution of the thrombus is mostly independent (not shown) on the amount of activated platelets injected at the inlet of the flow domain. Indeed, the platelets activation is very efficiently triggered by the thrombin issued by the contact system. This contrasts with the previous study of Taylor et al. 2016 [13] where the background concentration of activated platelet shows a large influence on the non-normalized results.
REFERENCES


USING SUBJECT-SPECIFIC ARTERIAL BLOOD FLOW IN THE MODELLING OF CEREBRAL WATER TRANSPORT

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SUMMARY

This paper investigates the coupling effect between the cerebral blood flow and the cerebrospinal fluid circulation in the brain using a novel three-dimensional multiple-network poroelastic model combined with subject-specific arterial blood flow as boundary conditions. The numerical results demonstrate that in order to capture accurate and realistic fluid transport phenomena in the cerebral environment, multiple communicating fluid compartments need to be considered in one, unified framework. Two coupling mechanisms – coupling between blood and CSF/ISF, and between fluid transport and solid deformation play important roles in this kind of simulation.

Key words: cerebral blood flow, cerebral water transport, poroelasticity, finite element method

1 INTRODUCTION

Blood often transmutes into different fluids in the human body, to adapt and adjust to specific local organ needs. An excellent example of such a process takes place in the brain: there, through a filtration process, blood extravasates to produce interstitial fluid (ISF) and cerebrospinal fluid (CSF) – a markedly clear water-like fluid. The interplay of blood and CSF is central to brain processes and plays an important role in a variety of diseases. Yet, such interplay, in a complex and often deformable environment, poses serious challenges regarding our capacity to model such processes and therefore understand their dynamics.

The Multiple-network PoroElastic Theory (MPET) is a multiple-porosity/multiple-permeability poroelastic model for simulating fluid transport and tissue deformation in tissue - the brain in our case. The brain parenchyma is treated as a deformable solid matrix, permeated by multiple fluid networks [1]. In general, the number of fluid networks can be customised to the specifics of the physiology modelled. For current brain modelling, four coupled fluid networks are considered: an arterial blood network (a), an arteriole/capillary blood network (c), a cerebrospinal fluid/interstitial fluid (CSF/ISF) network (e) and a venous blood network (v). The directional flows between the fluid networks are shown in Figure 1, which connect all four fluid compartments together to form a coupled and integrated fluid domain.

![Figure 1: The four-network poroelastic model (4-MPET) used for mechanistic modelling of the brain.](image)

Figure 1: The four-network poroelastic model (4-MPET) used for mechanistic modelling of the brain.
In this work, the 4-MPET model is used on anatomically realistic brain models. Subject-specific arterial blood flow to the brain are used as boundary conditions in the numerical modelling, with the aim to investigate the coupling effects between cerebral blood flow and CSF/ISF circulation in the cerebral environment.

2 METHODOLOGY

2.1 Governing equations and finite element model

The MPET model incorporates mechanical equilibrium for elastic deformation, mass conservation of fluids and Darcy’s law for fluid flow in a coupled manner. The governing equations of the 4-MPET model are listed as follows, where the primitive variables are the displacement of the parenchymal tissue \( u \) and the pressures of the four fluid networks \( p_i (i = a, c, e, v) \).

\[
G \nabla^2 u + (G + \lambda) \nabla \varepsilon = \alpha_a \nabla p_a + \alpha_c \nabla p_c + \alpha_e \nabla p_e + \alpha_v \nabla p_v
\]

(1)

\[
S_a \frac{\partial p_a}{\partial t} + \alpha_a \frac{\partial \varepsilon}{\partial t} = \frac{k_u}{\mu_a} \nabla^2 p_a + \dot{s}_{c-a}
\]

(2)

\[
S_c \frac{\partial p_c}{\partial t} + \alpha_c \frac{\partial \varepsilon}{\partial t} = \frac{k_c}{\mu_c} \nabla^2 p_c + (\dot{s}_{a-c} + \dot{s}_{e-c} + \dot{s}_{v-c})
\]

(3)

\[
S_e \frac{\partial p_e}{\partial t} + \alpha_e \frac{\partial \varepsilon}{\partial t} = \frac{k_e}{\mu_e} \nabla^2 p_e + (\dot{s}_{c-e} + \dot{s}_{v-e})
\]

(4)

\[
S_v \frac{\partial p_v}{\partial t} + \alpha_v \frac{\partial \varepsilon}{\partial t} = \frac{k_v}{\mu_v} \nabla^2 p_v + (\dot{s}_{c-v} + \dot{s}_{e-v})
\]

(5)

Equation 1 is the equilibrium equation, which describes the momentum balance in the porous medium. Here, \( u \) is the displacement of the tissue; \( p_i \) is the scalar pressure in each fluid network; \( G \) is the shear modulus; \( \lambda \) is the Lamé’s constant; \( \varepsilon \) is the dilatational strain; \( \alpha_i \) is the Biot–Willis coefficient. Equation 2-5 are continuity equations, which describe the mass balance of the four fluid networks, respectively. \( S_i \) is the specific storage for each fluid; \( k_i \) is the permeability; \( \mu_i \) is the viscosity. The \( \dot{s} \) terms on the right-hand side of Equation 2-5 (also demonstrated in Figure 1) define spatially varying source \((\dot{s}_{ij} > 0)\) or sink \((\dot{s}_{ij} < 0)\) terms \([1]\), which are assumed to be driven by local hydrostatic pressure gradients.

Next, the governing equations are discretised by the finite element method and implemented in an in-house Fortran code \([2]\). Both the displacement field \( u \) and the pressures of the four fluid networks \( p_i \) are approximated in the continuous piecewise linear polynomial space. The discretised form of the equilibrium equation is derived from the principle of minimum potential energy,

\[
K u - (Q_a p_a + Q_c p_c + Q_e p_e + Q_v p_v) = F
\]

(6)

where

\[
K = \int_\Omega B^T D B d\Omega
\]

(7)

\[
Q_i = \int_\Omega \alpha_i B^T h d\Omega
\]

(8)

\[
F = \int_\Omega N^T b d\Omega + \int_{\Gamma_N} N^T t_N d\Gamma
\]

(9)

\( K \) is the stiffness matrix; \( Q_i \) is the load on the solid phase contributed from the \( i \)th fluid network; \( b \) is the vector of body force, which is neglected in this paper; and \( t_N \) is the external force acting on the boundary \( \Gamma_N \).

The continuity equations of the fluid networks are discretised using the method of weighted residuals and the continuous Galerkin formulation. The discretised form of the continuity equation of the \( i \)th fluid network is,

\[
A\dot{p} + C p = P
\]

(10)
where

\[
A = S_i \int_\Omega N^T d\Omega \tag{11}
\]

\[
C = \frac{k_i}{\mu_i} \int_\Omega \nabla \Pi N^T d\Omega \tag{12}
\]

\[
P = \int_\Omega \tilde{\Pi} N d\Omega - \int_\Omega \epsilon N d\Omega + \int_{\Gamma_2} q_i N d\Gamma \tag{13}
\]

\(N\) is the continuous piecewise linear polynomial functions; and \(q_i\) is the flux prescribed in the Neumann boundary condition acting on the boundary \(\Gamma_2\). The temporal discretisation of the governing equations is implemented using the method of weighted residuals. An implicit backward Euler scheme is used for time discretisation.

### 2.2 Subject-specific boundary conditions of arterial blood flow

A subject-specific characterisation of the arterial blood supply to the brain is obtained through a combination of ambulatory blood pressure measurements, clinical ultrasound flow measurements and mathematical modelling [3]. These continuous waveforms are fed into the MPET modelling as boundary conditions for the arterial blood compartment at the cortical surface. For each subject, four waveforms are calculated at every time point, which are the internal carotid artery (ICA) blood to the left and right cerebrum (ICA_L and ICA_R), and the vertebral artery (VA) blood to the left and right cerebellum (VA_L and VA_R). In MPET modelling, the cortical surface is divided into four perfusion regions corresponding to the four waveforms (Figure 2). The total amount of arterial blood flow is distributed across each perfusion region and applied as a Neumann boundary condition. This is a simplification of the true cerebral arterial perfusion network of anterior/middle/posterior cerebral arteries extending along the pial surface before dividing into smaller penetrating arteries and arterioles that perfuse the cerebral cortex and deep white matter [3].

![Figure 2: The four perfusion regions on the cortical surface for the subject-specific boundary conditions for the arterial blood compartment (right), and the corresponding waveforms of arterial blood flow profiles (left).](image)

### 3 RESULTS AND CONCLUSIONS

The 4-MPET modelling results of a healthy subject (female, 68 years old) are presented in Figure 3. The data of this subject were obtained from the Lido study, which was approved by the joint ethics committee of the Health Authority Venice 12 and the IRCCS San Camillo (Protocol number 2014.08), and all participants gave informed consent prior to participation in the study. It can be seen from Equation 4 that three source terms can add or remove fluid from the CSF/ISF compartment, which depends on the dilatational/volumetric strain, the pressure gradient between the arteriole/capillary blood and the CSF/ISF compartments, and the pressure gradient between the CSF/ISF and the venous blood compartments, respectively. The contours of these three variables in a horizontal slice are shown in Figure 3b, c and d, together with pressure of the CSF/ISF
compartment (ICP) in Figure 3a. The gradient of ICP in this horizontal slice is less than 0.5 Pa; the value of ICP is relatively higher at the cortical surface and in the periventricular region. This distribution can only be accurately captured by combining the three source terms – the higher magnitude of ICP at the cortical surface is mainly contributed by the source terms driven by pressure gradients between blood and CSF/ISF compartments (Figure 3b and c), whereas the dilatational/volumetric strain from tissue deformation has a major effect on the local high magnitude of ICP in the periventricular region.

Figure 3: MPET modelling results of a healthy subject. a. Intracranial pressure (ICP), i.e. pressure of the CSF/ISF compartment; b. Pressure gradient between the arteriole/capillary blood and the CSF/ISF compartments; c. Pressure gradient between the CSF/ISF and the venous blood compartments; d. Dilatational/volumetric strain.

The numerical results demonstrate that two coupling mechanisms – coupling between blood and CSF/ISF, and between fluid transport and solid deformation, work well in the MPET modelling. In order to capture accurate and realistic fluid transport phenomena in the cerebral environment, multiple communicating fluid compartments need to be considered in one framework. The validation of individual compartments is also necessary (as a way of more accurately depicting the compartmental pressures and strain). In future, more effort needs to be put into refining the underlying physiological mechanisms for the fluid transfer between different fluid compartments. In the current model, this transfer purely depends on hydrostatic pressure gradients, whereas in the biological context it is more likely to be driven by more complicated processes, such as osmotic pressure.

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A PREDICTIVE MULTISCALE FRAMEWORK WITH MACHINE LEARNING METHODS FOR SIMULATING FLOW-INDUCED PLATELET ACTIVATION, AGGREGATION AND ADHESION

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SUMMARY

We present a predictive multiscale framework for simulating flow-induced platelet activation, aggregation and adhesion by coupling Dissipative Particle Dynamics (DPD), Molecular Dynamics (MD), and Coarse-Grained Molecular Dynamics (CGMD). DPD is employed for viscous shear flow around platelets; MD for predicting intra-platelet filopodia formation and microtubular rearrangement; and CGMD to simulate flow-driven platelet aggregation and adhesion mechanisms via receptor-ligand binding. Machine Learning (ML) approaches validate model predictions with in vitro results and adapt temporal scales to diverse spatial scales for more efficient massive simulations. This model is used to predict initial platelet-mediated thrombosis in prosthetic cardiovascular devices and vascular disease processes.

Key words: Predictive Multiscale Modeling; Platelet Activation, Aggregation and Adhesion; Mechanotransduction; Machine Learning.

1 INTRODUCTION

The blood coagulation cascade may be initiated by flow-induced platelet activation, aggregation and adhesion, which prompts clot formation in prosthetic cardiovascular devices and vascular disease processes. Upon activation, platelets undergo complex morphological changes, including cytoskeletal rearrangement and filopodia formation. Activated platelets polymerize fibrinogen into a fibrin network that enmeshes red blood cells. Continuum methods fail to capture the molecular mechanisms involved in morphological changes, while utilizing molecular dynamics is computationally prohibitive. A multiscale approach offers a means to bridge the gap between macroscopic flow and the cellular scales.

Our existing predictive multiscale model is expanded [1] to incorporate a Dissipative Particle Dynamics (DPD) model of viscous blood flow that interfaces with a Coarse-Grained Molecular Dynamics (CGMD) model of mechanobiology-based platelets to simulate their activation via mechanotransduction pathways [2], their aggregation by recruitment of flowing platelets to activated platelets deposited onto blood vessels [3], and their adhesion via vWF-mediated platelet GPIbα binding. In our model, platelets dynamically change their shapes in viscous shear flow and synergistically activate by a biomechanical transductive linkage chain [4]. The CGMD platelet model is embedded in the DPD flow model, with macroscopic dynamic stresses interactively transferred to the platelet model [2]. Hemodynamic stresses that lead to platelet activation and filopodial formation are mapped on the membrane and simultaneously transmitted to its cytoskeleton. Upon activation, platelets with intracellular constituents evolve as they lose their quiescent discoid shape and form filopodia. To simulate platelet recruitment and aggregation, we adopt a molecular-level hybrid force
field consisting of Morse potential and Hooke law for nonbonded and bonded interactions, respectively. This force field is parameterized by correlating with in vitro results such as the platelet contact area and the detachment force between the platelet integrin αIIbβ3 and fibrinogen (Fg) [3]. We extended this model by simulating platelet GPIbα receptor and the von Willebrand factor (vWF) ligand binding near a blood vessel wall under shear stress. The formation and breakage of the GPIbα-vWF bonds are modeled at a 10-nm length scale and simulated at a ns-time scale. We validate this numerical model through the use of shear-based experimental techniques that allow observation and measurement of platelet morphological changes and motions over a wide range of shear stresses (0-30 dyne/cm²) with a ms-time scale image resolution.

2 METHODOLOGY

Our multiple spatiotemporal methods employ a modified DPD to describe viscous blood flow in microchannels and stenoses [5] and a CGMD approach to describe key intra-platelet constituents to model mechanotransduction processes [2] and platelet receptors, including αIIbβ3 and GPIbα.

2.1 Coarse-Graining in Multiple Length Scales by Coupling DPD-CGMD-MD

In the mesoscale, we enhanced the conventional DPD formula by adding a Morse-based repulsive term for favorably producing Poiseuille flow of an incompressible fluid through a stenosis where the compressibility becomes a problem for DPD [5]. A comparative study demonstrates the fluid flow properties of DPD-Morse and DPD fluids through a 67% stenotic microchannel.

In the nanoscale, we built a mechanobiology-based platelet model by describing key intra-platelet constituents and biophysical properties [2]. We modeled a bilayer membrane, an ellipsoid based discoid shape, rigid filamentous actin, and a gel-like cytoplasm using the modified Morse potential [6]. An α-helix structure was used to mimic a protrusible actin filament.

In the microscale, we modeled the formation of αIIbβ3-Fg-αIIbβ3 bonds to simulate recruitment of platelets in aggregation [3] (Fig. 1c); and the formation of GPIbα-vWF bonds to simulate the initiation of platelet adhesion to a vWF-coated blood vessel (Fig. 1d). The platelets' receptor-ligand interactions are described at 10-nm-length, ns-time scales. The platelet membrane has a surface area of 28.6 μm². We defined 67,004 integrin αIIbβ3 receptors represented by particles, while a human platelet surface has 80,000 to 100,000 αIIbβ3 receptors. We also defined 16,751 GPIbα receptors, within the range of 12,000 to 25,000 copies per human platelet.

Spatially, the DPD-CGMD is interfaced by imposing a hybrid force field [1]. In this spatial interface, the Lennard-Jones term helps maintain the cytoskeleton-confined shape and the incompressibility of platelets against the applied shear stress of circumfluent flow. The dissipative and random terms

Fig 1: (a) mechanotransduction of flow stresses in platelets; (b) platelet activation; (c) recruitment and aggregation of unactivated platelets to activated platelets adhered to blood vessel wall; (d) flipping of adhered platelets on the vWF-coated blood vessel wall.
maintain the local flow thermodynamic and mechanical properties, and exchange momentum to express interactions between the platelet and the flow.

2.2 Coarse-Graining in Multiple Time Scales by Adapting Discretization

While Multiscale Modeling (MSM) sufficiently describes details at disparate spatial scales, no effective algorithm exists for adapting vast temporal scales to these diverse spatial scales. We propose a novel state-driven adaptive time-stepping (ATS) scheme [7, 8] that adapts time stepsizes to underlying biophysical phenomena, where mesoscale DPD blood flow is simulated with μs-timescale and microscale CGMD platelet is modeled with ns-to-ps timescales. A machine learning (ML)-based framework trains to adapt the time stepsizes (Fig. 2a). Particle positions and momenta are inputs, and phases are described by the most significant attributes of states from inputs in first two layers-categorized by a neural network and labeled by a two-component vector: time stepsize and state examination frequency . The simulation proceeds with a new time stepsize in steps. The ATS algorithm adjusts time stepsizes at its conclusion. To solve 10-million-particle systems, a numerical experiment using our previous MTS scheme gained 3000x reduction in computing times [7] and its efficiency was further improved by 20–75%, accelerated by our ATS ML scheme for different simulation phases [8]. Conceptually, ATS ML corresponds to coarse-graining in time.

Fig 2: (a) a NN-based ML framework for adapting time stepsizes to platelet dynamics under shear stresses; (b) a NN-based ML framework for predicting contact area during platelet aggregation.

2.3 Model Credibility through Correlation of Model Predictions with In Vitro Results

Whole blood, 30 ml, was obtained from healthy adult donors under Stony Brook University IRB-approved consent and processed to yield isolated platelets, which were reconstituted with red blood cells. This mixture was perfused through 100×1000 µm microchannels pre-coated with 100 µg/ml vWF to induce platelet margination and adhesion. Isolated platelets, 150,000/µl, were perfused at shear stresses 1–10 dyne/cm² to initiate recruitment aggregation, observed at 100× and 200 fps on a DIC microscope and sCMOS camera (Nikon Ti-Eclipse, Andor Zyla). Geometric and physical parameters were extracted, meshed to determine contact area between aggregated platelets, and input into a neural network ML model to predict inter-platelet contact area (Fig. 2b). A feed-forward neural network ML model with 2 hidden layers, each with 10 nodes (Fig. 3b), was trained with 75% of the data at shear stresses of 1, 5 and 10 dyne/cm², with the remaining 25% as test data. Training loss reaches the minimum gradient when training epochs exceed 3000. Independent in vitro experiments at a shear stress of 6.7 dyne/cm² were used to test accuracy. Mean and standard deviation values of normalized contact area model predictions and experimental results (0.094±0.021 and 0.092±0.021, respectively) suggests that our ML model accurately predicts contact area for aggregated platelets and can be used in multiscale modeling to validate in silico results [3].

3 RESULTS AND CONCLUSIONS

Our multiscale model is the first molecular-scale, mechanobiology-based platelet model down to the nm-length, ps-time scales [2]. Membrane Young’s modulus is 31.2 µN/m and shear elastic modulus is 33.0±9.0 µN/m. Cytoplasm viscosity is 4.1 mPa·s. Actin filament stiffness is 56.3±1.0 pN/nm.
Using this model, we simulated flow-induced platelet activation and described the dynamics of varied filopodia formations. Comparative analyses of length and thickness of filopodia show that our model predictions are in agreement with in vitro measurements of flow-induced activated platelets [4]. By extending this model, we modeled the platelet αIIBβ3 receptors to describe aggregation mediated by fibrinogen (Fg). This simulation studies a shear stress of 6.7 dyne/cm² and a shear rate of 619 s⁻¹. As platelets approach, αIIBβ3 and Fg form a bridge (αIIBβ3-Fg-αIIBβ3) which initiates platelet aggregation [3] (Fig. 1c). We also modeled the platelet GPIbα receptors. Ongoing studies employ this model to predict the disassociation of the GPIbα-vWF bonds in the lift-off period of adhered platelets and the re-formation of the GPIbα-vWF bonds as rolling platelets re-attach to the vWF-coated vessel wall under flow conditions (Fig. 1d).

Our simulations do not only agree with in vitro results but also suggest new testable predictions:

- **Platelet Flowing in shear flow**: more rigid platelets overestimate the stress magnitude by 2.77-2.89 times [1]. The elastic 300A-thick membrane deforms due to the surrounding flow, while the gel-like cytoplasm around the filaments further absorbs and reduces mapped stresses, and transduces them to the cytoskeleton.

- **Platelet Activating**: decreasing membrane stiffness plays a key role in promoting the formation of long filopods. Increasing numbers of longer filopods, for highly activated platelets, strongly correlates with microstructural rearrangement and mechanical properties.

- **Platelet Aggregating**: a rigid platelet led to a very significant underestimation of contact area by 89% and detachment force by 91–93%. [3]

Our approach is the first computationally affordable numerical method for simulating platelet activation by highly resolved mapping of mechanical stresses on the cytoskeleton in dynamic flow, and platelet aggregation and adhesion via platelet receptor-ligand binding. Biophysical properties of a platelet are accurately described down to nm-length and ps-time scales. Viscous flow is described at μm-length and ns-time scales. In ongoing studies, a platelet-mediated thrombus growth model under shear is being developed. This thrombus model adapts the molecular-scale properties of our current recruitment aggregation model, thus predicting macro-scale properties using micro-scale principles. Such a model has the advantage of reflecting molecular level changes in receptor-ligand bond formation. We expect our model to be adopted by other fields, including drug delivery, by considering the impact of mechanical events triggering biochemical responses.

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**REFERENCES**


Mathematical and numerical modeling of the heart function I
DEVELOPMENT OF PATIENT-SPECIFIC MODELS OF THE MITRAL VALVE

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SUMMARY
The mitral valve (MV) regulates blood flow into the left ventricle (LV). In situations where the MV fails to fully close the resulting blood regurgitation into the left atrium causes pulmonary congestion, leading to heart failure and/or stroke. There is now agreement that adjunctive procedures are required to treat IMR, yet there is no consensus regarding the best procedure. There is thus an urgent need for quantitative assessments of MV function to better design surgical solutions. We demonstrate state-of-the-art means to produce patient-specific MV computational models to develop quantitatively optimized devices and procedures for MV repair that incorporate LV geometry.

Key words: heart valve, mitral valve, patient specific modeling, computational biomechanics, finite element method

1 INTRODUCTION
Heart valve disease is striking the western world with an ever-increasing prevalence rate. Among the most common valvular lesions, ischemic mitral regurgitation (IMR), appears within one month of infarction in the growing population of patients who have suffered cardiac arrest. While two major surgical solutions for IMR (repair and replacement) have improved significantly over the past three years, there continues to be associated high mortality rates. Consequently, there is an eminent need for improving treatment options to help patients who suffer from MV disorders, especially IMR. It is widely believed that to achieve better patient outcomes, MV treatments need to be tailored to each patients conditions. In the present study, we addressed this issue through developing functionally equivalent models of the chordal structure to build high-fidelity image-based models of the complete MV and in turn simulate MV repair surgery. Our methodology uses only the information that is available prior to surgery and successfully showcases how image-based computational models of the MV can be used to provide additional insight into patient-specific response to annuloplasty repair of the valve.

2 METHODOLOGY
2.1 Simulation methodology
We first developed methodologies to geometrically morph the in vitro geometries to simulate the in vivo configuration using published information on annular geometries. We then applied the same modeling pipeline developed in [1] on five extant micro-CT imaging datasets to independently develop five complete, high-fidelity MV models. We then show how this same pipeline can be directly applied to human imaging data to create patient specific models. Details of how we developed our MV model were presented in [1].

2.2 Extension to Patient specific MV modeling
Three patients were randomly selected from the Cardiothoracic Surgical Trial Network (CTSN) for this study. We processed real-time 3D echocardiographic (rt-3DE) images for these patients from
before and after undergoing the annuloplasty surgery to extract patient-specific leaflet geometries (Figure 1). For each patient, the pre-operative open valve model was converted into a 3D triangulated mesh using Poisson disk resampling and ball pivoting algorithms. The acquired mesh was then morphed to the closed leaflet geometry through a hyperelastic shape-warping technique that enforced the closed leaflet shape through a level-set penalization. Briefly, in this method the ventricular side of the leaflet geometry is first pressurized till the reference open shape transforms to the vicinity of target closed shape. Then, a locally corrective pressure field enforces the final adjustments such that the morphed leaflet mesh from the open state matches the closed leaflet image data. The details of our shape-matching technique including the image processing pipeline, leaflet constitutive relation, and finite element analysis framework can be found in [2]. As the chordal part of MV apparatus cannot be fully resolved via in vivo imaging modalities, we utilized a recently developed functionally equivalent chordal models [3], [4] (Figure 2). To build functionally equivalent chords, at first the open leaflet mesh was uniformly sampled in 3D to acquire a point cloud of the chordal insertions on the leaflet. This point cloud was then mapped to the closed state using the computed registration field. Next, the average papillary muscle (PM) locations also extracted from rt-3DE imaging data were connected to the morphed insertion locations to build single strand chords. The constructed chordal model was then merged with the leaflet geometry, morphed back to the open state, and calibrated to the pre-operative state to build a complete model of the MV apparatus. To predict the effects of annuloplasty repair surgery on each patient, the post-operative valvular configuration was simulated by applying the displacement boundary conditions on the annulus and PM heads (Figure 3).

3 RESULTS AND CONCLUSIONS

The simulation results showed that our modeling approach can be used to reliably predict the closing behavior of the MV following annuloplasty surgery using pre-operative imaging data (Figure 3). In addition, we computed the leaflet deformation fields in the local surface directions which demonstrated the effects of undersized annuloplasty ring on the entire leaflet (Figure 3). Interestingly, the comparison of pre- and post-operative deformation patterns revealed that the circumferential strain and stress decreased significantly in the entire leaflet while radial components of the strain and stress remained mostly the same before and after the annuloplasty repair surgery. We have also integrated...
this technique with complete LV to be able to gain insight into the role of LV geometry on the onset and progress of IMR (Figure 4). Simulating the MV response to surgery from clinical imaging data allows for refinements to treatment planning and optimization of repair surgery procedures. In this study, we presented a pipeline that allows for patient-specific modeling of the MV to predict the valvular response to annuloplasty repair with high predictive power. Our framework only relies on the clinically obtainable imaging data prior to the MV repair operation and thus can be extended into a virtual surgery tool that provides surgeons with additional insight into the patient-specific valvular response to different treatment options.

REFERENCES


Figure 3: the directional strain fields computed for a representative patient in pre- and post-operative states are shown.

Figure 4: the directional strain fields computed for a representative patient in pre- and post-operative states are shown.
THE INVERSE PROBLEM OF CARDIAC MECHANICS - ESTIMATION OF CARDIAC ACTIVE STRESS FROM ENDOCARDIAL MOTION TRACKING

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SUMMARY

The heart acts as the pump of the cardiovascular system due to the active stress developed in individual cardiac muscle cells. The spatio-temporal distribution of this active stress could contain relevant diagnostic information but can currently not be measured in vivo. We introduce a method to estimate dynamic cardiac active stress fields from endocardial surface motion tracking derived from e.g. magnetic resonance imaging data. This ill-posed non-linear problem is solved using Tikhonov regularization in space and time in conjunction with a continuum mechanics forward model. We present a proof-of-concept using data from a biophysically detailed multiscale model of cardiac electromechanics (7649 tetrahedral elements) in which we could accurately reproduce cardiac motion (surface error $<0.4$ mm) and identify non-contracting regions due to myocardial infarction scars (active stress error $<10$ kPa). This inverse method could eventually be used to non-invasively derive personalized diagnostic information in terms of dynamic active stress fields which are not accessible today.

Key words: inverse problem, cardiac mechanics, tikhonov regularization, active stress, tension development

1 INTRODUCTION

The contraction of the heart is driven by the active stress developed in cardiac myocytes and depends on the heart’s geometry, the passive elastomechanical properties of the ventricular wall and its surroundings, and the time course of the blood pressure. Despite their fundamental role for cardiac function (and dysfunction), no method exists so far to measure the dynamic active stress fields. On the other hand, the acquisition of time resolved magnetic resonance image sequences (cine-MRI) in short-axis and multiple long-axes of the heart is part of the regular clinical routine. From these data, the endocardial surfaces can be extracted automatically due to the high contrast between myocardial tissue and blood. Therefore, we hypothesize that it is possible to estimate the active stress field of the ventricles from the endocardial motion if the other variables can either be measured (such as heart geometry), are known a priori (such as typical fiber architecture), or can be estimated (such as passive mechanical properties and blood pressure). In this work, we present a novel method to estimate the dynamic active stress field in the ventricular walls from the motion of the left and right endocardial surfaces based on spatial and temporal Tikhonov regularization [1]. To evaluate this method, we used synthetic data of the surface motion obtained from electromechanical simulations of ventricular contraction. The spatio-temporal distribution of the in vivo active stress development in an individual’s heart could contain valuable diagnostic information facilitating personalized cardiac therapy.
2 METHODOLOGY

A multiscale electromechanical cardiac modeling framework [2] was used to simulate the ventricular contraction (forward simulation) in a whole heart model with four different settings: One for a healthy heart and three with different infarction scars in the left ventricle located anteriorly, posteriorly, and septally. Excitation spread was calculated by solving the monodomain equation on the ventricles. The contraction was driven by a biophysical active stress model of human ventricular cardiomyocytes [3] coupled to the electrophysiological model by ten Tusscher et al. [4]. For the infarction areas, the cells were defined to be passive, i.e. active stress was zero. From the biomechanical simulation results, the motion of the endocardial surface of the ventricles was extracted (target surfaces). These target surfaces could in future be extracted from clinical cine-MRI acquisitions. These data were then used as input for the algorithm to solve the inverse problem, which estimates the active stress field within the ventricular walls for each time step $i$ in such a way that the resulting deformation best matches the input data (inverse solution). The distance between the mesh nodes of the endocardial surfaces of the inverse solution and the target surfaces is iteratively minimized for each time step using a Newton scheme. This distance is described by the field $g_{i,n} \in \mathbb{R}^N$ ($N = 3\bar{N}$ with $\bar{N}$ being the number of endocardial surface nodes) at time step $i$ and iteration $n$. The matrix $A$ is the gradient of the displacement of the mesh nodes on the endocardial surface with respect to $\tau_{i,n}$. Here, $\tau_{i,n} \in \mathbb{R}^M$ is the change of active stress in all $M$ contracting elements:

$$A \tau_{i,n} = g_{i,n},$$  (1)

where

$$A = L \cdot \mathbf{K}_r \in \mathbb{R}^{N \times M}. $$  (2)

Here, $\mathbf{K}_r$ is the gradient of the nodal forces with respect to $\tau_{i,n}$ and $L$ is a reduced inverse of the stiffness matrix considering only the rows related to the $N$ surface nodes. The problem of calculating the particular spatial active stress distribution change $\tau_{i,n}$ that results in a displacement which minimizes $g_{i,n}$ is ill-posed. Therefore, we employed a nonlinear Tikhonov approach with spatial and temporal regularization:

$$(A^T A + \frac{\lambda_1}{\Delta t^2} I + \lambda_2 \Delta_c) \tau_{i,n} = A^T g_{i,n} - \frac{1}{\Delta t^2} (t_{i,n} - 2t_{i-1,n} + t_{i-2,n}) - \lambda_2 \Delta_c t_{i,n}),$$  (3)

where $t_{i,n} \in \mathbb{R}^M$ is the active stress of the contracting elements, i.e. elements within the ventricular wall ($t_{i,n+1} = t_{i,n} + \tau_{i,n}$), $I$ is the $M \times M$ identity matrix, $\Delta_c$ is the discrete Laplace operator, and $\lambda_1$ and $\lambda_2$ are parameters controlling the degree of spatial and temporal regularization, respectively. For each Newton step $n$, equation (3) is solved using LU decomposition.

The heart model used in this study comprised 7649 active elements whereas the target surfaces comprised 900 nodes. The regularization parameters $\lambda_1$ ($1 \times 10^{-20}$) and $\lambda_2$ ($1 \times 10^{-14}$) were set based on initial experience.

3 RESULTS AND CONCLUSIONS

The motion of the heart obtained from the inverse reconstruction matched that of the forward simulation up to a maximum surface error of $<0.4$ mm. (Fig. 1a and 1b). The reconstructed active stress of the inverse solution matched the active stress underlying the forward simulation in terms of spatial distribution and time course during the contraction (Fig. 1c). In the simulation settings with infarction scars, the scar area was clearly identifiable. The reconstructed active stress was significantly reduced and almost zero near the center of the scar area independent of the location of the infarction scar (Fig. 2).

Similar approaches were presented by Balaban, Finsberg et al. [5, 6]. Both studies used a model of the left ventricle only and based their active stress estimation on strain measurements in the 17 AHA segments acquired with echo speckle tracking and not MRI. Both approaches use the sequential quadratic programming algorithm to minimize the misfit between model and measurement data. Our
approach in contrast uses a whole heart model, from which the endocardial surface motion of the left and right ventricle is extracted and serves as input for the non-linear Tikhonov estimation with spatial and temporal regularization spatially resolved on the scale of the individual finite element. Otani et al. proposed a method to estimate active stress from a volumetric displacement field [7]. This approach is different from the one presented here in terms of required input data: we only use the displacement of the endocardial surface, which can be easily extracted from standard cine-MRI data whereas the former study relies on displacement fields covering the whole cardiac wall. Perotti et al. proposed a method similarly relying on full displacement fields to estimate hyperelastic material properties [8].

A limitation of our simulation study is that all other parameters besides the spatio-temporal active stress distribution (fiber orientation, passive mechanical properties, blood pressure, and boundary conditions) were identical for the forward and inverse simulations. Future studies will have to analyze how uncertainties regarding these parameters affect the estimation of the active stress field. Nevertheless, the simulation results are promising and give confidence that this method has the potential to translate endocardial motion extracted from a cine-MRI data stack into a realistic estimation of the cardiac active stress field.

The novel algorithm presented here allowed to reconstruct the spatio-temporal active stress distribution of the ventricles from the motion of the endocardial surfaces accurately. These promising results obtained based on the biophysically detailed forward model need be reproduced using clinical data in the future. If this proves to be possible, our method could be employed to gain novel insight into the role of active stress distribution in pathogenesis of cardiac diseases and its utility for patient stratification in translational studies.
Figure 2: Ventricular contraction was simulated for different infarction setups (left anterior, left posterior, septal). From the simulation results, the surfaces were extracted and used as input for the active stress estimation. Reconstructed and ground truth spatial active stress distributions are compared at representative time steps.

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ACTIVATION-CONTRACTION COUPLING IN A MULTISCALE HEART MODEL

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SUMMARY

Our objective is to integrate detailed muscle contraction models into heart simulations. The originality of our approach is to couple the actin filament activation with a muscle contraction model that takes into account the filament sliding. Our model is derived by modifying the equations of the seminal Huxley’57 model. Coupling it with a simplified whole heart model, we are able to simulate pressure-volume loops. This work may lead to a better understanding of the relevant dynamics of the activation-contraction coupling in the different phases of the heart cycle.

**Key words:** Cardiac muscles, Activation-contraction coupling

1 INTRODUCTION

The cardiac tissue consists of fibre bundles built themselves as the series arrangement of elementary contractile units called sarcomeres. Inside the sarcomere, two lattices of filaments – made of actin and myosin, respectively – slide along each other, generating contraction as the result of the cycling interaction between the myosin protruding heads and the actin binding sites. In rest configuration, the actin sites are unactivated, preventing the myosin heads from attaching. The contraction is triggered by the intracellular release of calcium ions that bind to the actin sites, ultimately allowing myosin attachment (we say that the actin sites are activated). This activation process is known to involve cooperativity mechanisms allowing a sharp tension rise in response to the calcium release [8].

At the organ level, the contraction is regulated by the so-called Frank-Starling mechanism, which consists in having a unique relationship between the end-diastolic volume and the end-systolic pressure. At the microscopic level, this mechanism originates from the variation of the active force developed as a function of the sarcomere stretch. It results from the combination of (i) a variation in the number of myosin heads available for attachment and (ii) a variation in the level of activation of the actin filament.

The modelling of the actomyosin interaction in full actin filament activation conditions has been the topic of extensive works since the seminal paper of Huxley’57 [1, 2, 3, 9, 15]. In parallel, models of the actin filament activation alone have been developed [5], including the cooperativity mechanisms from the seminal Rice’03 model [6]. However, coupling the actin filaments activation models with actomyosin based contraction models considering the filaments relative sliding in the context of whole organ simulation [4, 7] remains a challenge due to computational complexity.

Our approach consists in including the effect of varying filament overlap and actin filament activation into the Huxley’57 model. To overcome the complexity of modelling a spatially distributed actin filament activation and the intermediate stages transforming the binding of calcium into the actin site activation, we consider a phenomenological average level of actin filament activation that can be calibrated on experimental data.
2 METHODOLOGY

Building upon the Huxley’57 model, we consider the population of myosin heads located at a distance \( s \) to the nearest actin site. For a head located at distance \( s \) from the nearest binding site, the dynamics of the probability of being attached \( P_1(s, t) \) is governed by

\[
\partial_t P_1(s, t) + \dot{x}_c \partial_s P_1(s, t) = f(s)(1 - P_1(s, t)) - g(s)P_1(s, t) \tag{1}
\]

where \( \dot{x}_c \) denotes the sliding velocity between actin and myosin filaments. The transition rates \( f \) and \( g \) define the rates of attachment and detachment, respectively. When a myosin head attaches to an actin site, a so-called cross-bridge is formed; its elastic potential energy is denoted by \( w(s) \). The average force per myosin developed in the sarcomere is given by

\[
\tau_c(t) = \frac{1}{d_a} \int_{s^-}^{s^+} \frac{\partial w}{\partial s}(s)P_1(s, t) \, ds, \tag{2}
\]

where \( d_a \) is the distance between two consecutive actin sites and \( s^+ - s^- = d_a \).

In our model, we attribute the variation in the number of myosin heads available for attachment to variations in the degree of filament overlap. These variations are modelled by the parameter \( n_0(t) \).

We consider two distinct pools of myosin heads characterised by the additional discrete variable \( \gamma \). The first pool \( (\gamma = 1) \) contains the heads that are available for attachment; the second pool \( \gamma = 0 \) contains the unavailable heads. We denote by \( n_0(t) \) the ratio of filament overlap.

The conservation of the myosin heads leads to the following dynamics equations

\[
\begin{align*}
\partial_t P_1(s, t, \gamma = 1) + \dot{x}_c \partial_s P_1(s, t, \gamma = 1) + \frac{\dot{n}_0}{n_0} \left[ P_1(s, t, \gamma = 1) - P_1(s, t, \gamma = 0) \right] &= f(s, \gamma = 1)(1 - P_1(s, t, \gamma = 1)) - g(s, \gamma = 1)P_1(s, t, \gamma = 1), \tag{3a} \\
\partial_t P_1(s, t, \gamma = 0) + \dot{x}_c \partial_s P_1(s, t, \gamma = 0) + \frac{\dot{n}_0}{1 - n_0} \left[ P_1(s, t, \gamma = 0) - P_1(s, t, \gamma = 1) \right] &= f(s, \gamma = 0)(1 - P_1(s, t, \gamma = 0)) - g(s, \gamma = 0)P_1(s, t, \gamma = 0), \tag{3b}
\end{align*}
\]

with

\[
|\dot{n}_0| = \begin{cases} n_0 & \text{if } \dot{n}_0 > 0, \\ 0 & \text{otherwise,} \\ -\dot{n}_0 & \text{if } \dot{n}_0 < 0, \\ 0 & \text{otherwise.} \end{cases}
\]

In each equation (3), an additional term in the left-hand side accounts for the flux of myosin heads changing from one pool to the other. The attachment and detachment rates are defined independently in each pool. We will typically choose \( f(\gamma = 0) = 0 \) and \( g(\gamma = 1) = g(\gamma = 0) \).

To take into account the variations of the level of actin filament activation, we introduce a new parameter \( n_a \), which represents the ratio of actin sites that are available for myosin attachment. We assume that the calcium activation results in a uniform distribution of the activated actin sites along the actin filament. Considering that the function \( n_a \) modulates the flux of attachment in a multiplicative manner, the equations (3) become

\[
\begin{align*}
\partial_t P_1(s, t, \gamma = 1) + \dot{x}_c \partial_s P_1(s, t, \gamma = 1) + \frac{\dot{n}_0}{n_0} \left[ P_1(s, t, \gamma = 1) - P_1(s, t, \gamma = 0) \right] &= n_a(C, x_c, t)f(s, \gamma = 1)(1 - P_1(s, t, \gamma = 1)) - g(s, \gamma = 1)P_1(s, t, \gamma = 1), \tag{4a} \\
\partial_t P_1(s, t, \gamma = 0) + \dot{x}_c \partial_s P_1(s, t, \gamma = 0) + \frac{\dot{n}_0}{1 - n_0} \left[ P_1(s, t, \gamma = 0) - P_1(s, t, \gamma = 1) \right] &= n_a(C, x_c, t)f(s, \gamma = 0)(1 - P_1(s, t, \gamma = 0)) - g(s, \gamma = 0)P_1(s, t, \gamma = 0). \tag{4b}
\end{align*}
\]

The calibration of the myosin and actin filament activations functions \( n_0 \) and \( n_a \) are obtained from the experimental data from [13].

First, the ratio of filament overlap \( n_0 \) is determined by the relation between the twitch peak force and the sarcomere length in maximal calcium activation conditions. Secondly, the function \( n_a \) is calibrated with the variations of this relation with the extracellular calcium concentration. Its time dependence is inferred from twitch contractions measured on papillary muscles.
3 RESULTS AND CONCLUSIONS

The results of the calibration are presented in Figure 1 by comparing simulations of the active force with experiments performed in vitro on isolated cardiac muscle cells at constant sarcomere length.

![Figure 1: Calibration with experimental twitch contraction recordings performed on rat cardiac muscles at constant sarcomere length (data from [13]). Note that we corrected the data to remove the passive force that appears as an artefact of the experimental protocol used to maintain the sarcomere length constant throughout the contraction twitch.](image)

We then couple our muscle contraction model to a simplified heart model [12] and simulate pressure-volume loops for various level of preload and after-load. The preliminary results are displayed in Figure 2.

![Figure 2: Pressure-volume loops computed with a simplified heart model coupled with our muscle contraction model.](image)

Our framework thus allows to couple the actomyosin interaction model including the effect of filament sliding with the actin filament calcium-induced activation. Moreover, we are able to integrate it into a whole organ model, opening the door to a detailed analysis of the relevance of the various modelling ingredients in the different phases of the heart cycle. Note also that the coupling with simplified versions of the Rice’03 model [7, 10, 14] could be envisioned in future works to enhance the actin filament activation modelling.

REFERENCES


ACCURATE SIMULATION OF CARDIAC ELECTRO-MECHANICAL ACTIVATION MARKERS

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SUMMARY

Cardiac mechanical activation times derived from recent imaging techniques allow non-invasive estimates of electrical activation and could be used in the study of arrhythmias and reentrant circuits. Here we assess the reliability of mechanical activation time markers derived from fiber and longitudinal strain waveforms, as estimates of the electrical activation time computed from action potential waveforms. The simulations are based on an electro-mechanical Bidomain model including mechano-electric feedbacks. The results show that the mechanical and electrical activation sequences have the same qualitative features and are highly correlated during ectopic endocardial stimulations.

Key words: cardiac electro-mechanical coupling, electrical and mechanical activation times, electromechanical delay, Bidomain model

1 INTRODUCTION

Non-invasive estimates of cardiac electrical activation can be derived from mechanical activation markers in order to determine e.g. the origin of premature ectopic beats during focal arrhythmias or the pathway of reentrant circuits. In this work, we construct some mechanical activation time markers derived from fiber and longitudinal strain waveforms and assess their accuracy in estimating the electrical activation times computed from action potential waveforms. The validation of the reliability of these mechanical activation markers would require the simultaneous measurements of electrical and mechanical activation sequences in vivo. This task is still quite challenging for current experimental technologies, particularly if a high spatial resolution covering the whole ventricular wall is required. Hence, electro-mechanical simulations can be employed in order to assess the reliability of mechanical activation time markers. Some simulation studies have investigated the complex spatio-temporal relationships and differences between the electric cardiac excitation sequence and the subsequent pattern of mechanical myocardial contraction and cardiac electromechanical delay, see e.g. [9, 8, 11, 5]. Here we use a strongly coupled electromechanical Bidomain model composed by four submodels, two for the mechanical activity (passive and active) and two for the electrical one (the Bidomain and ionic models), described in the following Section.

2 METHODS

a) Mechanical model of passive cardiac tissue. We model the cardiac tissue as a non-linear hyperelastic material in the quasi-steady state regime. The material coordinates of the undeformed cardiac domain \(\hat{\Omega}\) are denoted by \(X = (X_1, X_2, X_3)^T\), the spatial coordinates of the deformed cardiac domain \(\Omega(t)\) at time \(t\) by \(x = x(X, t)\), the deformation gradient by \(F(X, t) = \frac{\partial x}{\partial X}\) and the displacement field by \(u(X, t) = x - X\), the Green-Lagrange strain tensor by \(E = \frac{1}{2}(C - I)\) and the Cauchy-Green deformation tensor by \(C = F^T F\). In the Lagrangian framework, after the pull-back
on the reference configuration \( \hat{\Omega} \), we have the equilibrium equation

\[
\text{Div}(FS) = 0 \quad X \in \hat{\Omega},
\]

where the second Piola-Kirchhoff stress tensor \( S \) is given by the sum of passive (\( \text{pas} \)), volumetric (\( \text{vol} \)) and active (\( \text{act} \)) components, i.e. \( S = S_{\text{pas}, \text{vol}} + S_{\text{pas}, \text{act}} \), with \( S_{\text{pas}, \text{vol}} = \frac{\partial W^{\text{vol}}(E)}{\partial E} + \frac{\partial W^{\text{vol}}(E)}{\partial E} \). \( W^{\text{pas}} \) is an exponential strain energy function modeling the passive mechanical behavior of myocardium as a transversely isotropic hyperelastic material. Its analytical expression is derived from the orthotropic law proposed in [6]). We added a volume change penalization term \( W^{\text{vol}} = K(J - 1)^2 \) in order to model the myocardium as a nearly incompressible material; here \( K \) is a positive bulk modulus and \( J = det(F) \).

b) Mechanical model of active tension. The ventricles contraction results from the active tension generated by the myofilaments dynamics activated by calcium. We assume that the generated active tension acts only along the fiber direction, so that the active component is \( S^{\text{act}}(X, t) = JF^{-1}\sigma^{\text{act}}F^{-T} = J\hat{T}_a(X, t)\hat{a}_f \otimes \hat{a}_f \), with \( \hat{a}_f \) the unit vector of fiber direction in the reference configuration. The biochemically generated active tension \( \hat{T}_a(X, t) \) depends on the intracellular calcium concentration \( Ca_t \), the fiber stretch \( \lambda = \sqrt{\hat{a}_f^T C a_f} \), and the stretch-rate \( \frac{df}{dt} \) along the fiber direction \( \hat{T}_a(X, t) = T_a(Ca_t(X, t), \lambda(X, t), \frac{df}{dt}(X, t), \gamma(X, t)) \), and it evolves according to an active tension generation model based on calcium kinetic and myofilament dynamics. In this work, we consider the model considered in Land et al. [10].

c) Bioelectrical model of cardiac tissue: the Bidomain model.

Denoting by \( v, u_e, w, c \) the transmembrane potential, the extracellular potential, the gating and ionic concentrations on the deformed configuration and by \( \hat{\nu}, \hat{u}_e, \hat{w}, \hat{c} \) the same quantities on reference configuration, the parabolic-elliptic formulation of the Bidomain model can be written in the Lagrangian framework, after the pull-back on the reference configuration \( \hat{\Omega} \times (0, T) \), as

\[
\begin{aligned}
\left\{ \begin{array}{l}
\left. \frac{cm}{J} \frac{\partial \hat{\nu}}{\partial t} - F^{-T} \nabla \hat{\nu} \cdot \mathbf{V} \right) - \text{Div}(JF^{-1}\hat{D}_iF^{-T}\nabla(\hat{\nu} + \hat{u}_e)) + J_i\chi(v, \hat{w}, \hat{c}, \lambda) = \hat{J}_{i\text{app}}, \\
- \text{Div}(JF^{-1}\hat{D}_iF^{-T} \nabla \hat{\nu}) - \text{Div}(JF^{-1}(\hat{D}_i + \hat{D}_e)F^{-T} \nabla \hat{u}_e) = 0,
\end{array} \right\}
\end{aligned}
\]

where \( \mathbf{V} = \frac{\partial u}{\partial t} \) is the rate of deformation; see [2] for the detailed derivation. \( c_m \) and \( i_{\text{ion}} \) are the membrane capacitance and ionic current per unit volume, respectively. These two partial differential equations (PDEs) are coupled through the reaction term \( i_{\text{ion}} \) with the ordinary differential equations (ODEs) system of the membrane model, given in \( \Omega(t) \times (0, T) \) by

\[
\frac{\partial w}{\partial t} - R_w(v, w) = 0, \quad \frac{\partial c}{\partial t} - R_c(v, w, c) = 0.
\]

The conductivity tensors in the reference configuration are given by \( JF^{-1}\hat{D}_{i,e}(X, t)F^{-T} = \sigma_{i,e} C^{-1} + (\sigma_{f} - \sigma_{i}) \otimes \hat{a}_f \hat{a}_f \). The bioelectrical system (2-3) is completed by prescribing initial conditions on \( \hat{\nu}, w, c \), insulating boundary conditions on \( \hat{u}_e, \hat{\nu} = \hat{\nu} + \hat{u}_e \), and the intracellular and extracellular applied current \( \hat{J}_{i\text{app}} = \hat{J}_{e\text{app}} = \hat{J}_{e\text{app}} \). Since the extracellular potential \( \hat{u}_e \) is defined up to a time dependent constant in space \( R(t) \) determined by the choice of the reference potential, we consider as a reference potential the average of the extracellular potential over the cardiac volume, i.e. we impose \( \int_{\hat{\Omega}} \hat{u}_e(X, t)J(X, t)dX = 0 \).

d) Ionic membrane model and stretch-activated channel current. The ionic current in the Bidomain model (2) is given by \( i_{\text{ion}} = \chi I_{\text{ion}} \), where \( \chi \) is the membrane surface to volume ratio and the ionic current per unit area of the membrane surface. \( I_{\text{ion}} \) is given by the sum \( I_{\text{ion}}(v, w, c, \lambda) = I_{\text{ion}}^m(v, w, c) + I_{\text{sac}} \) of the ionic term \( I_{\text{ion}}^m(v, w, c) \) given by the Faber-Rudy model (FR00) [7] (see also models.cellml.org/cellml), augmented with a stretch-activated current \( I_{\text{sac}} \), see [4] for further details. The FR00 ionic model also specifies the functions \( R_w(v, w) \) and \( R_c(v, w, c) \) in the ODE system (3), consisting of 25 differential equations modeling the dynamics of the ionic currents.
e) Numerical methods, parameters calibration and simulations setup. We consider a left ventricular geometry \( \hat{\Omega} = \Omega(0) \) modeled as a truncated ellipsoid which is the image of a cartesian periodic slab using ellipsoidal coordinates. The cardiac fibers rotate intramurally linearly with the depth for a total amount of 120° proceeding counterclockwise from epicardium to endocardium. Space discretization. We consider an hexahedral structured grid \( T_{hm} \) for the mechanical model (1) and \( T_{he} \) for the Bidomain model (2), where \( T_{he} \) is a refinement of \( T_{hm} \). Time discretization. We consider a semi-implicit splitting method, where the electrical and mechanical time steps could be different. At each time step, we solve i) the ionic model (3) with a first order implicit-explicit (IMEX); ii) the mechanical model (1) and the active tension system to compute the new deformed coordinates \( x^{n+1} \); iii) the electrical model (2) with a first order IMEX method and compute the new electric potentials \( v^{n+1}, u^{n+1}_e \) with an operator splitting method, consisting of decoupling the parabolic from the elliptic equation. In our simulations, the electrical time step size is \( \Delta_e t = 0.05 \) ms, while the mechanical times step is \( \Delta_m t = 0.25 \) ms (see [2] for more details). Computational kernels and parallel solvers. At each time step, the main computational kernels are: i) solving the non-linear system deriving from the discretization of the mechanical problem (1) by a parallel Newton-GMRES-Algebraic Multigrid method; ii) solving the two linear systems deriving from the discretization of the elliptic and parabolic equations in the Bidomain model (2) by a parallel Conjugate Gradient method preconditioned with a Multilevel Additive Schwarz preconditioner. Our parallel simulations have been performed on a Linux cluster using the parallel library PETSc from the Argonne National Laboratory. Initial and boundary conditions. The initial conditions for the electrical model are the resting values for all the potentials and gating variables of the FR00 model, while the boundary conditions for the Bidomain model are for insulated tissue. The mechanical boundary conditions set to zero the total displacement vector at the circumferential basal line meeting the endocardial surface and the third displacement component on the rest of the basal surface. On the endocardial surface, we impose a Neumann boundary condition given by the intracavitary blood pressure, whose dynamics is modeled according to a simple pressure-volume loop model. Electrical and mechanical activation time markers. We measure the strain change with respect to the deformed configuration of the end diastole (the moment when ejection starts), i.e. we compute \( E_{ss}(X,t) := a_s^T E(X,t) a_s - a_s^T E(X,t_{ED}) a_s \), where \( a_s, s = f, l, c, r \) is the unit vector along the fiber, longitudinal, circumferential and radial directions, respectively. At selected nodes \( X \in \hat{\Omega} \), we compute the electrical activation time marker \( AT_e(X) \), defined as the unique instant of maximum time derivative of the transmembrane potential \( \hat{v}(X,t) \) during the upstroke phase of the action potential, and four mechanical activation time markers:

- \( AT_{ta}(X) \), defined as the unique instant when the active tension \( \mathcal{T}_a \) increases above the threshold \( 10\% \max \mathcal{T}_a(X,t) \);
- \( AT_{eff}(X) \), defined as the unique instant when, starting from the onset of myofiber shortening, the fiber strain \( E_{ff}(X,t) \) decreases below the threshold \( \max \mathcal{T}_a E_{ff}(X,t) - 10\%(\max \mathcal{T}_a E_{ff}(X,t) - \min \mathcal{T}_a E_{ff}(X,t)) \);
- \( AT_{ell}(X) \), defined as the unique instant when, starting from the onset of myofiber shortening, the fiber strain \( E_{il}(X,t) \) decreases below the threshold \( \max \mathcal{T}_a E_{il}(X,t) - 10\%(\max \mathcal{T}_a E_{il}(X,t) - \min \mathcal{T}_a E_{il}(X,t)) \).

3 RESULTS AND CONCLUSIONS

Our simulation results show that all the mechanical markers are highly correlated with \( AT_e \) (CC > 0.8). We show in Fig. 1 the regression plots of the electrical and mechanical activation markers considered. \( AT_{ta} \) presents the highest CC = 0.96, whereas \( AT_{eff} \) and \( AT_{ell} \) are comparable, with CC = 0.9. The regression plots in Fig. 1 show that the range of mechanical activation times associated to a specific electrical activation time is large, especially for the middle range of electrical activation times. We plan to run more extensive simulations with additional epicardial and multiple stimulation sites in order to better assess the mechanical markers’ accuracy.

In conclusion, these mechanical activation markers can be used as non-invasive estimates of electrical activation, e.g. to determine the origin of premature ectopic beats during focal arrhythmias or the pathway of reentrant circuits. In order to validate the reliability of these mechanical activa-
Figure 1: Ectopic endocardial stimulation. Regression plots for electrical ($AT_v$) and mechanical ($AT_{eff}$, $AT_{ell}$) activation markers, with their correlation coefficients on the entire ventricular volume.

tion markers, simultaneous measurements of electrical and mechanical activation sequences should be performed in vivo. This task is still quite challenging for current experimental technologies if a high spatial resolution covering the whole ventricular wall is required. Hence, our detailed electromechanical models and simulations can help in assessing the reliability of mechanical activation time markers.

REFERENCES

ASSESSING REGIONAL MYOCARDIAL WORK WITH CARDIAC MECHANICS MODELS PERSONALIZED THROUGH DATA ASSIMILATION

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SUMMARY

A data assimilation technique was utilized to create finite element models of human left ventricles (LV) from a healthy case and a patient suffering from left bundle branch block (LBBB). These models were matched to measured LV volume, regional longitudinal strains, and non-invasive estimates of LV pressure. Model-data mismatch was minimized using a gradient-based optimization technique which required solving the corresponding adjoint equation. The results show an excellent fit between measured and simulated ventricular volumes and strains, and the models were assessed for regional and total myocardial work to give insight into dyssynchronous work dynamics.

Key words: cardiac mechanics, personalized model, data assimilation

1 INTRODUCTION

Patients suffering from left ventricular dyssynchrony, such as in LBBB, may experience inefficient heart function due to uncoordinated contraction of different segments in the heart. Cardiac Resynchronization Therapy (CRT) is a well established treatment option for these patients, however, 30-40\% of patients treated do not respond positively, indicating that the current selection criteria are suboptimal, and that new biomarkers are needed for improving the current clinical practice.

Often in LBBB, septal segments are activated first, and due to the slowing of electrical conduction, this can cause the late-activating lateral wall to stretch. The subsequent contraction of this region then results in a lengthening of the septal segments during systole. This can be identified as wasted work, as the septum is generating force but not aiding to ejection. Recent studies\cite{1} have shown that wasted septal work might be a better predictor for response to CRT, and that the amount of wasted work reflects the potential for recovery. However, myocardial work is difficult to accurately quantify, and methods to calculate regional work quickly and efficiently are needed.

2 METHODOLOGY

We used 4D echocardiographic images provided by Rikshospitalet from one patient diagnosed with left bundle branch block (LBBB) and one healthy volunteer. Briefly, LV endocardial and epicardial surfaces were extracted from the images at the beginning of atrial systole, and left ventricular tetrahedral meshes were created using Gmsh. Myocardial fiber orientations were assigned to the meshes using the Laplace-Dirichlet Rule (LDRB) algorithm \cite{2} with an angle of 60° on the endocardial and −60° on the epicardial surface. In addition, longitudinal strain for each case was measured via speckle tracking echocardiography (SPE) in the 17 AHA segments, and a non-invasive method \cite{3} was used to estimate the LV pressure curve for both subjects.

We then applied a recently developed framework\cite{4} for constraining a mechanical model to these clinical data. This framework employs a gradient-based optimization to estimate passive and active...
mechanical parameters in order to minimize the model-data mismatch through the cardiac cycle. Moreover, the framework utilizes state-of-the-art numerical methods which automatically computes the gradient efficiently by solving the corresponding adjoint equation [5], and thereby can provide these estimates within a reasonable time frame.

These fit models allowed the calculation of regional and total work though integration of work conjugate stress-strain pairs [6]. We computed the full 3D work for each case, as well as work along the fiber direction, where the stress and strain tensors in the calculation were simply interchanged with their respective components. This computed work can be compared against the total mechanical work obtained through integration of the pressure-volume relationship through the cardiac cycle. In order to eliminate geometric considerations, these work calculations were normalized to the total myocardial wall volume to calculate a total mechanical work density (TMWD). This was further normalized across the cardiac cycle time to achieve a total mechanical power density (TMPD) that was comparable between different cases.

3 RESULTS AND CONCLUSIONS

Our data assimilation method produces excellent fit of volume loops and segmental strains for both the healthy and LBBB cases, Figure 1.

Figure 1: Left: Simulated and measured PV loops for the LBBB and normal cases. Right: Comparison between strain measurements in the mid and basal regions from 4D echo and fit model predictions (imaging quality).

The regional stresses that are integrated against strain show a substantial redistribution of stress between the healthy and LBBB cases, Figure 2. The anterior region which was stretched prior to activation shows clear increases in the area of the stress-strain loops. Meanwhile the anteroseptal region and the mid septum are significantly reduced.

Figure 2: Left: Cauchy fiber stress for the normal and LBBB cases at different valvular events (MVC: mitral valve closing, AVO: aortic valve opening, AVC: aortic valve closing, MVO: mitral valve opening). For reference we show the 17 AHA-zone delineation of the left ventricle in the two cases in the bottom panel. Right: Simulated regional fiber stress-strain loops in the mid and basal segments for normal (blue) and LBBB (red).
Integration of conjugate stress-strain pairs then provide a quantification of total myocardial work. This work calculation is presented and compared to the overall mechanical work done on the blood in Table 1. We see in the calculation that the LBBB case performs 20% more work than is needed to expel the blood, indicating that there is significant wasted work being performed during the cardiac cycle. Meanwhile, in the healthy case, both the calculated work done on the fluid and the work done by the myocardium are comparable, indicating that there is little wasted work in the normal function of the ventricle. We are also able to show that work done along the fiber direction in the myocardium makes up about 60% of the total cardiac stroke work.

Table 1: Total mechanical power density (TMPD) computed using the area of the pressure-volume loop normalized to ventricular wall volume (PV area), the full stress and strain tensors (Full), and the fiber component of the stress and strain tensors (Fiber)

<table>
<thead>
<tr>
<th>Case</th>
<th>PV area (kW m(^{-3}))</th>
<th>Full (kW m(^{-3}))</th>
<th>Fiber (kW m(^{-3}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBBB</td>
<td>8.41</td>
<td>10.60</td>
<td>6.42</td>
</tr>
<tr>
<td>Normal</td>
<td>15.79</td>
<td>16.35</td>
<td>9.59</td>
</tr>
</tbody>
</table>

This is further broken down into regional work in Figure 3, and we can see a clear redistribution of work done across the segments. In particular, we can see that the anteroseptal and septal regions in the LBBB patient are not performing the same work as done in the healthy case, and may be targets for treatment such as CRT to renormalize the work performed.

Our results show a promising method for calculating patient specific regional cardiac work in the presence of mechanical dyssynchrony, utilizing a method that is amenable to the time table of clinical decisions. Further work is needed to examine these initial results across a cohort of patients, as well as to test the effect of treatments such as CRT on regional work.

REFERENCES


EFFECT OF FIBROSIS SEVERITY ON ELECTRICAL INSTABILITY AND CONTRACTILE BEHAVIOR: COMPUTATIONAL STUDY

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SUMMARY
This study investigated the electrical instability in computational human heart according to the severity of fibrosis in human atrial model by simulating propagation of the electrical wave. We distributed different amount of fibrosis information randomly to the nodes that made up the computational human atrial model. Fibrosis density and entropy were calculated to quantify the fibrosis spatial pattern. The S1-S2 protocol was implemented to generate a reentrant wave in the atrial model. We compared the electrical instability in normal and when different severity was applied. We concluded that, as the amount of fibrosis severity increases, the electrical propagation becomes chaotic.

Key words: Fibrosis, Reentry, Electrical propagation

1 INTRODUCTION
Cardiac fibrosis occurs with several types of heart diseases, such as ischemic heart disease, inherited mutations and diabetes and is causes morbidity and mortality. Fibrosis mediated scarring and electrical dysfunction often triggers ventricular arrhythmias, which in turn expedites the events towards heart failure and then sudden cardiac death. The predominant cellular mechanism of fibrosis involves the emergence of activated fibroblasts or myofibroblasts.

In previous study, Lim et al. studied the effect of fibrosis severity on ventricular tissue and reported that the conduction velocity in fibrotic tissue was delayed, compared to normal reentrant wave. However, their study was limited to tissue 2D simulation.

In this study, we examined the effect of fibrosis in 3D human atrium on the electrical propagation by using computational human atrial model. To simulate the fibrotic hypertrophy, we distributed fibrosis information quantified using fibrosis density and fibrosis entropy metric values. Here, the simulation study revealed the effect of applying different percentage of fibrosis on the electrical stability.

2 METHODOLOGY
In this study, we used a 3D atrial model which consists of 675923 nodes and 3447823 elements. The computational model is a tetrahedral mesh that represents 3D anatomical model of the human atria. Fibrosis information was distributed randomly in the atrial model.

The action potential model were modified to represent the electrophysiology consequences due to chronic AF condition in non-fibrotic regions and the following modification was applied; 50%, 70% and 50% reduction in $I_{Na}, I_{Ca}$, and $I_{tar}$ respectively. The non-fibrotic chronic AF action potential described above was further modified as follows to represent the chronic AF in fibrotic
regions: 50% reduction in inward rectifier potassium current $I_{K1}$; 50% reduction in L-type calcium current $I_{CaL}$; and 40% reduction in sodium current $I_{Na}$. Furthermore, conductivity values in fibrotic regions were reduced by 30% to mimic the conduction delay due to fibrosis.

Fibrosis Density (FD) and Fibrosis Entropy (FE) were calculated to express the fibrosis information in the atrial model. FD and FE values at each location in the atrial model were calculated based on the characteristics of the local tissue element as well as on those of the surrounding tissue elements. The local FD value in the ith element was calculated as the ratio of all fibrotic tissue elements surrounding the ith element to all elements in the surrounding sub-volume equation (1). The local FE was calculated to indicate the level of disorganization within the surrounding sub-volume and it is expressed using Shannon Entropy equation (2).

$$FD = \frac{F}{N}$$  \hspace{1cm} equation (1)

$$FE = \sum_{i=1}^{N} - p_i \ln(p_i)$$  \hspace{1cm} equation (2)

N was the number of elements within the sub-volume surrounding the element. F was the total number of fibrosis tissue elements surrounding the ith element. Pi was fraction of elements neighboring the ith element that was a different tissue type than the ith element.

3 RESULTS AND CONCLUSIONS

Figure 1 indicates the effect of fibrosis on the stability of electrical stimulation. Figure 1A, shows the sequential plots $V_m$ for generating a re-entrant wave by using S1-S2 protocol. As a result, the electrical propagation in the computational human atrial model gets chaotic as the percentage of fibrosis increase. Fibrosis spatial distribution was quantified using FD and FE metric values. As the amount of severity increased from 10% to 50% as it is shown in figure 1b and figure 1c, the atrial model became more heterogeneous.

Figure 1  (A). Sequence of $V_m$ maps during AF for atrial model with different percentage of fibrosis severity capture at time 7500 ms. (B) Sequence of FD maps showing the spatial distribution of different percentage of fibrosis in the atrial model. (C) Sequence of FE maps showing the spatial distribution of different percentage of fibrosis in the atrial model.

As a conclusion,
REFERENCES


MECHANISTIC INSIGHT INTO THE ACTION POTENTIAL DURATION ALTERNANS USING A PARAMETER SENSITIVITY ANALYSIS TECHNIQUE

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SUMMARY
Alternans is periodic beat-to-beat alternations of myocyte depolarization. This study aims to observe the electrophysiological changes which have the responsibility for the occurrence of APD alternans at slow heart rates by analyzing the cellular parameter sensitivity independently and the combination of several ionic parameter changes at a time. For evaluating alternans, the model was paced from 750 to 180-ms cycle length and the ionic parameters were scaled 50%, 100%, and 150% of the base value. In conclusion, the ionic alterations of calcium and potassium channels contributed to generate APD alternans at slow heart rates.

Key words: action potential duration (APD), alternans, slow heart rates

1 INTRODUCTION
Cardiac alternans is defined as periodic beat-to-beat temporal alternations in the shape of myocyte depolarization. The alternans has been linked to the development of atrial fibrillation (AF) and ventricular arrhythmias. A previous study explains that action potential duration (APD) alternans occurred at slow heart rates in patients experiencing atrial fibrillation, but APD alternans arose only at fast pacing rates in the control subject. In addition, the instability of a cellular mechanism affected the occurrence of APD alternans at pacing rates near rest. Ca\textsuperscript{2+} handling alterations accounted for the initiation and maintenance AF, and the abnormalities of Ca\textsuperscript{2+} cycling underlay ventricular action potential (AP) alternans in heart failure. Chang et al. also conducted a parameter sensitivity analysis of 20 ionic model parameters independently in order to examine which parameter changes affected the occurrence of APD alternans. Then, she revealed APD alternans arose clinically at slow heart rates by only decreasing the ryanodine receptor (RyR) inactivation rate (k\textsubscript{ic\textsubscript{R}}). Moreover, other recent studies revealed Na\textsuperscript{+} channels also played a crucial role in developing arrhythmias.

Instead of only analyzing the parameter sensitivity independently, we therefore also consider to examine the effect of the combinations of several ionic parameter alterations in the ventricular model. Hence, this research aims to observe the electrophysiological changes which play a role for the generation of APD alternans at slow heart rates, using the human ventricular model from Tusscher et al.

2 METHODOLOGY
In this study, we used single-cell analysis in order to understand how the cardiac cellular electrophysiology was affected by the ionic parameter changes. The electrical activity at the cellular level was represented by an ion kinetics model of Tusscher et al. The electrophysiological phenomenon is described by the following equation:

$$\frac{dV}{dt} = \frac{I_\text{ion} + I_\text{stim}}{C_m}$$
where $V$ is membrane potential (mV), $t$ is time (ms), $I_{\text{ion}}$ is the total ionic current of transmembrane (pA/pF), $I_{\text{stim}}$ is the external stimulus current (pA/pF), $C_m$ is the capacitance of cell per unit surface area ($\mu$F/cm$^2$).

The alternans was observed in the single-cell model by applying the clinical pacing protocol from Narayan et al. in order to induce the alternans. First, the single-cell model was paced for 20 beats at 750-ms CL. Then, it was paced for 30 beats at each subsequent CL, starting from 500 ms and decreased in 50-ms steps to 300 ms. From 290-ms to 180-ms CL, the CL was shortened 10-ms steps.

From single-cell simulation, the membrane potential was analyzed to measure action potential duration (APD) alternans. APD was calculated as the time from maximal upstroke velocity to 90% repolarization of membrane potential ($\text{APD}_{90}$). We also computed alternans magnitude (AM) and APD alternans normalized magnitude (ANM). AM was obtained by the mean magnitude of change in APD over the last 10 pairs of beats (11 beats total). ANM was a factor to compare and indicate alternans between cells in varying APD in particular onset CL. ANM was quantified by the dividing AM by the mean APD over the last 10 beats. When ANM was greater than 0.05 (5%), this means that alternans occurred in certain CL. Moreover, alternans onset CL was defined as the longest CL in which ANM value was greater than 0.05.

To analyze the sensitivity of alternans, ten ionic model parameters, which were ionic conductance channels, as shown in Table 1 were tested. Firstly, we examined the sensitivity analysis of cellular parameters which was independently scaled 50%, 100%, and 150% of the original model specified by Tusscher et al. Secondly, we tested the combinations of ten ionic model parameters. Each parameter was scaled 50%, 100% and 150% of the base value of the original model. Among combinations of ten ionic model parameters, 59,049 cases were simulated. Then, ANM values were identified in order to observe the electrophysiological alterations which played a role for the APD alternans onset at slow heart rates, from 350 to 500-ms cycle length (CL).

**Table 1** Table Ionic model parameters used in parameter sensitivity analysis.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$g_{K1}$</td>
<td>Maximal $I_{K1}$ conductance</td>
</tr>
<tr>
<td>$g_{Kr}$</td>
<td>Maximal $I_{Kr}$ conductance</td>
</tr>
<tr>
<td>$g_{Ks}$</td>
<td>Maximal $I_{Ks}$ conductance</td>
</tr>
<tr>
<td>$g_{Na}$</td>
<td>Maximal $I_{Na}$ conductance</td>
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<td>$g_{bNa}$</td>
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<td>Maximal $I_{CaL}$ conductance</td>
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</tr>
<tr>
<td>$g_{pK}$</td>
<td>Maximal $I_{pK}$ conductance</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ORI</th>
<th>ANM</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.050001</td>
</tr>
<tr>
<td>B</td>
<td>0.050002</td>
</tr>
<tr>
<td>C</td>
<td>0.0500101</td>
</tr>
<tr>
<td>D</td>
<td>0.0500124</td>
</tr>
<tr>
<td>E</td>
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</tr>
<tr>
<td>F</td>
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</tr>
<tr>
<td>G</td>
<td>0.0500264</td>
</tr>
<tr>
<td>H</td>
<td>0.0500273</td>
</tr>
<tr>
<td>I</td>
<td>0.0500302</td>
</tr>
<tr>
<td>J</td>
<td>0.0500303</td>
</tr>
</tbody>
</table>
Figure 1 Mean APD and alternans onset cycle length (CL) of the original model and ten parameter-combination cases where ANMs were the lowest values. The ten simulated cases can be seen in Table 2.

Figure 1 shows the comparisons of mean APD and alternans onset cycle length for the original model of Tusscher et al. and ten parameter-combination cases which generated the lowest ANM values among the whole simulated cases (see Table 2). The mean APD and onset CL of the original model was 220 and 280 ms, respectively. Case A produced the longest CL when the alternans occurred, at 500 ms. In the case C and G, conversely, the alternans began at 280 ms which was the same CL as that of in the original case.

Table 2 Simulation cases of the combination of ten ionic parameters which were scaled 50%, 100%, and 150% of the original model. These were the cases which produced the ten smallest ANM values among the whole simulation.

<table>
<thead>
<tr>
<th>Case</th>
<th>Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>gK1</td>
</tr>
<tr>
<td>ORI</td>
<td>100%</td>
</tr>
<tr>
<td>A</td>
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</tr>
<tr>
<td>B</td>
<td>150%</td>
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<tr>
<td>C</td>
<td>150%</td>
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<tr>
<td>D</td>
<td>150%</td>
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<td>E</td>
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<td>F</td>
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<td>100%</td>
</tr>
<tr>
<td>J</td>
<td>100%</td>
</tr>
</tbody>
</table>

In conclusion, APD alternans is the beat-to-beat oscillations in the shape of cardiac electrical signals. This also has been associated with cardiac arrhythmia, leading to cardiac arrest. The electrophysiological mechanism underlies the occurrence of APD alternans at slow heart rates in the ventricular model. Based on the results, we found that ionic conductances of potassium and
calcium channels could contribute to the generation of APD alternans at slow heart rates, from 350 to 500 ms. Moreover, the longer the alternans onset cycle length (CL), the more severe the ventricular arrhythmia. This is because the longer onset cycle length means the earlier alternans began in the simulation. Thus, when the alternans onset cycle length was longer, the ventricles were more susceptible and vulnerable due to cellular alterations in the model.

REFERENCES

COMPUTATIONAL FRAMEWORK FOR ELECTROPHYSIOLOGY PROBLEMS AND ITS APPLICATION TO SCROLL WAVES AND ECG MODELING

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SUMMARY

This work develops a computational framework for cardiac electrophysiology modeling. The framework is based on open-source packages: Ani3D, INMOST, CVODE. We use the P1 finite element method on unstructured tetrahedral meshes for solving PDEs arising in bidomain/monodomain equations. We employ parallelization technologies to reduce the computational time. As an application example, we consider modeling of scroll waves and rotor filaments in anisotropic human cardiac tissue and calculate ECG graphs. This are the main stages in the study of ECG dependency on different scroll wave types and arrhythmia regimes.

Key words: electrophysiology, bidomain model

1 INTRODUCTION

Computationally efficient numerical models of cardiac electrophysiology attract ever-growing attention. They are used in clinical applications, such as predictions of severity and duration of arrhythmias under certain conditions, defibrillation therapy optimization, selection of the best treatment scenario and minimization of the reoperation probability among others. In the clinical study it is extremely hard to obtain the detailed picture of cardiac electrical activity and to separate the relative roles of different involved processes. In-vitro studies are complicated by scarcity of human material (donor hearts). Thereby numerical simulations help to complement in-vivo and in-vitro experiments [1]. Systems of monodomain and bidomain equations are considered to be the most appropriate descriptions of electrical activity in cardiac tissues. The bidomain model is a system of two partial differential equations describing the evolution of the intracellular and extracellular potentials coupled at each point in space to a system of ordinary differential equations which describe transmembrane ionic current density.

The solution of bidomain equations may be split into two steps: the solution of coupled parabolic and elliptic PDEs (sequentially or fully implicitly) and the solution of nonlinear systems of ODEs. The finite element method is used conventionally for the spatial discretization of the monodomain and bidomain PDEs. The size of ODE systems depends on a cell model and usually is not large, but it must be solved for each mesh node. The numerical solution of monodomain and bidomain equations on high-resolution meshes is computationally expensive in 3D. Moreover, usually one needs to perform hundreds of simulations with various model parameters. Thereby the corresponding computational frameworks should take advantage of High Performance Computing architectures.

This work develops a computational framework for modeling of the cardiac electrophysiology based on open-source packages. Verification of the framework was conducted on a series of benchmarks proposed in the literature [2]. As an application example, we consider modeling of scroll waves and rotor filaments in anisotropic human cardiac tissue and their correlation with ECG graphs.
The important part of heart work is the orderly propagation of the electrical signal, the wave of excitation passing through cardiac tissue, which subsequently triggers ordered contraction of myocytes. Abnormal propagation of the electrical excitation (e.g. due to local inhomogeneities) may produce scroll waves rotating around filament, that is a geometrical place of singularity points. Investigation of filament’s parameters (such as curvature, “tension”, trajectory etc.) gives important information about dynamics of the scroll wave. The latter is hypothesized to underlie ventricular fibrillation, the leading cause of sudden cardiac death. Modeling of scroll waves plays the role of the intermediate step in our current research which is aimed at study of ECG picture dependency on different arrhythmia regimes such as number of rotors, their drift and mutual arrangement. Thus it becomes possible to explore the impact of ionic model parameters on ECG types and classify them.

2 METHODOLOGY

2.1 Governing equations

Let $\Omega$ represent a 3D domain with piecewise smooth boundary $\partial \Omega$. The basic bidomain equations associate the intracellular potential $\phi_i$ and the extracellular potential $\phi_e$ defined in $\Omega$, through the transmembrane current density. The transmembrane voltage $v = \phi_i - \phi_e$ and $\phi_e$ satisfy the equations in $\Omega$:

\[
\chi \left( C_m \frac{\partial v}{\partial t} + I_{ion}(u, v) \right) - \nabla \cdot \left( \sigma_i \nabla (v + \phi_e) \right) = I_i, \\
\nabla \cdot \left( (\sigma_1 + \sigma_e) \nabla \phi_e + \sigma_i \nabla v \right) = -I_{total}, \\
\frac{\partial u}{\partial t} = f(u, v),
\]

where $C_m$ is the cell membrane capacitance, $\chi$ is the membrane surface-to-volume ratio, $I_i$ and $I_e$ are an intra- and extracellular volume current density stimulus, $I_{total} = I_i + I_e$, $\sigma_1$ and $\sigma_e$ are the intra- and extracellular conductivity tensors, respectively. We use anisotropic conductivity tensors with their principal axes aligned with fiber orientation to account the role of electrical properties of myocyte fibers. The current density in the ionic channels $I_{ion}$ is defined by a function $f$ of a vector of state variables $u \equiv u(t, x)$ defined by a system of nonlinear ODEs. For the human heart we employ O’Hara-Rudy model.

Having the extracellular potentials $\phi_e$ in the heart $\Omega$, we can solve forward ECG problem, i.e. compute extracellular potentials $\phi_e$ in the whole body $T$:

\[
-\nabla (\sigma_e \nabla \phi_e) = 0, \quad \text{in } T \setminus \Omega,
\]

where $\phi_e$ is continuous in $T$. The problem is solved with zero Neumann boundary condition.

2.2 Numerical methods

The core tool of the computational framework is Ani3D (Advanced Numerical Instruments) package [3]. It provides tools for usage of anisotropic grids and tensors, which are crucial in real heart modeling due to the essential anisotropic features of the myocardial tissue, and offers advanced finite element discretizations on tetrahedral meshes. To calculate the ionic current density from a system of ODEs, we use CVODE software [4] and CellML repository [5]. In general, solution of systems of ODEs is the most computationally expensive part. In order to parallelize all computations, we apply Ani3D-extension of parallel platform INMOST [6, 7] and OpenMP technology.

The S1-S2 protocol of stimulation was used to induce scroll wave reentry on ventricles, see Figure. 1, left. We varied the parameters of O’Hara-Rudy model to get different topological types of scroll wave filaments. It is well known that filament trajectory evolves due to variation of ionic conductances [8]. In present work we consider the impact of $I_{Na}$ (fast inward sodium current), $I_{Ca,L}$ (L-type calcium current), $I_{Kr}$ (rapid delayed rectifier potassium current) and $I_{KATP}$ (ATP-dependent potassium current).
3 RESULTS AND CONCLUSIONS

Numerical experiments shows that increase in $I_{Na}$ conductance causes increase in tissue excitability. $I_{Ca,L}$ and $I_{Kp}$ mainly affect on repolarization time while activated $I_{Katp}$ reproduces ischemic conditions. We calculated ECG for different types of scroll waves, see Figure 1, right. Investigation of ECG dependencies on scroll-wave types is our current research.

We presented the new electrophysiological parallel computational framework based on the open-source packages and applied it in modeling of scroll-waves on cardiac tissue and calculation of ECG. The code uses anisotropic conductivity tensors and adaptive unstructured meshes. The Ani3D framework allows us to extend our electrophysiological solver to electromechanical problems and other multiphysics cardiac problems as well.

![Figure 1: Scroll wave on human ventricles (left) and distribution of potentials on the body surface and electrode positions used for computation of the leads (right)](image_url)

REFERENCES


Coronary blood flow modelling for fractional flow reserve prediction
ON BOUNDARY CONDITIONS IN COMPUTATION OF CT-BASED FFR: A STUDY INTEGRATING PET PERFUSION IMAGES IN CFD

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SUMMARY

Sensitivity of CT-based fractional flow reserve (FFR) calculation to inflow and outflow boundary conditions (BCs) was investigated. The inflow investigation focused on the impact of flow pulsatility, and the outflow investigation was on the effect of using patient-specific myocardial perfusion downstream to each coronary branch. The FFRs were computed for 12 patients with various degree of stenosis. CFD simulations using 3D patient-specific anatomical models with patient-specific inflow and outflow conditions indicated that the type of inflow BCs (steady/pulsatile) does not have a significant impact on computed FFRs. The FFRs derived from the two outflow BCs – determined from only vessel morphology and from myocardial perfusion – agreed in general but the difference is larger for severely diseased patients, potentially misleading the treatment. The sensitivity of FFR computations to BCs were shown not too high in general but there are some exceptions where extra care may need to be in place.

Key words: CT-based computation of FFR, flow pulsatility, patient-specific outflow

1 INTRODUCTION

Coronary artery disease (CAD) is the leading cause of death globally. For example, it is associated with 19% of deaths in Europe [1]. The most common form of CAD is myocardial ischemia caused by atherosclerotic narrowing in the epicardial vessels, i.e. stenosis. Fractional flow reserve (FFR), a risk indicator based on pressure drop across a stenosis, was proposed and proven as an effective method to assess the functional severity of a stenosis for clinical decision making how the stenosis should be treated [2]. While FFR is mostly calculated using intra-coronary pressure from invasive catheterization, an alternative approach using medical-image-based 3D anatomical models and computational fluid dynamics (CFD) has become a common method to non-invasively assess the severity [3].

Although the computational approach has become reasonably mature and now a variety of non-invasive FFR calculation methods – combining different imaging modalities [4-6] – exist, assumptions are inevitable in computational models which introduce uncertainties. Typical challenge can be found with boundary conditions. For example, in well-defined simulations where boundary conditions are known from invasive measurements, it was shown that FFR is not affected by the difference between steady and pulsatile flow conditions [7]. However, in practice, such a complete set of data is not always available. We therefore examined the impact of various inflow as well as outflow boundary conditions on computation of FFR, in practical scenarios, to shed light on the requirements for those conditions to ensure adequate model representation. In particular, we made a unique attempt to incorporate patient-specific outflow conditions by incorporating positron emission tomography (PET) images.
2 METHOD

2.1 Patients
This study included 13 lesions from 12 patients (7 male, 5 female, age: 61.7±12.2 years) of various levels of angiographically determined epicardial stenosis (7 mild, 3 intermediate and 3 severe case). All patients underwent 4D CTCA for anatomical assessment and ⁸²Rb PET perfusion imaging to identify ischaemic regions in the myocardium. The study was carried out in accordance with the recommendations of the South East Research Ethics Research Committee (Aylesford, Kent, UK) with written informed consent from all subjects, in accordance with the Declaration of Helsinki.

2.2 General analysis approach
CTCA images were segmented to produce 3-D anatomical models of the aortic root and coronary arteries, which were then meshed using tetrahedral and prism elements, in the order of 10⁶ elements per model, using Simpleware ScanIP (Synopsys, CA, USA). The blood flow in the anatomical models were computed using a commercial CFD package ANSYS CFX 17.0 (ANSYS, Inc. Cannonsburg, USA). The flow was assumed to be laminar and blood was modelled as homogenous and Newtonian fluid with its density and dynamic viscosity 1060 kg/m³ and 0.004 Pa s, respectively. The vessel wall was approximated as rigid wall, where non-slip boundary conditions were applied, and cardiac-induced wall motion was not incorporated. Once the resulting pressure profiles across the stenosed branch is computed, ratio of the pressure downstream to the stenosis to that at the coronary ostium was calculated as FFR. In the pulsatile simulations, the lowest FFR – typically appears during the diastole – was taken as the value for the patient.

2.3 Inflow boundary conditions
The acquired CT was time series with one image set per every 10% of cardiac cycle, enabling segmentation of the LV cavity at multiple points over time. The aortic outflow waveform was estimated by calculating the temporal variation of the cavity volume across the cycle assuming the flow in the diastolic phase to be zero. Both pulsatile and steady flow simulations were carried out. For the steady state simulations, the patient-specific stroke volume per cardiac cycle (i.e. mean flow rate from the LV) was used as inflow condition.

2.4 Outflow boundary conditions
At the distal end of each branch in the 3D models, two types of boundary conditions were considered: morphology-based boundary condition (MBC) and perfusion-based (i.e. patient-specific) boundary condition (PBC). In either case, the actual outflow boundary conditions were given using 2-element Windkessel model where resistance and compliance are defined at each outlet (Figure 1). In MBC, a conventional approach, the downstream resistances were determined using a structured tree model [8] representing a peripheral vascular tree. In practice, the branching structure of the vasculature and diameter of each segment were defined using Murray’s law and empirical branch ratio 9:6 [8]. The total resistance of the ‘generated’ vascular tree till the cut-off diameter of 50 μm was calculated for each outlet. Compliance parameter at each outlet was calculated by setting the time constant (=1/RC) equal to 0.063 s following the literature [9]. To model physiological diastolic-dominant flow in the left coronary tree, a typical left-ventricular pressure waveform was applied across the capacitance component of the Windkessel. The resistances for coronary outlets were then adjusted such that the total coronary flow accounts for 5% of the total aortic inflow and the aortic pressure pulse falls within the patient-specific systolic and diastolic brachial pressures (mean pressure was used in steady state simulations). Even after this, the resistance at the end still depends on the diameter of each outlet of reconstructed 3D model.

For the PBC, the resistance adjustment was done further for each outlet, such that the flow ratio between different coronary branches follow the proportion of blood perfusion around the corresponding outlets based on the PET images. To achieve this, CT and PET images were first co-registered using anatomical landmarks, and then the PET image intensities were sampled (representing perfusion in ml/100ml/min), around the anatomical model outlets using a sampling sphere of 20 mm diameter. Here, as in the MBC, the total coronary flow is assumed to be 5% of the
Calculation of FFR requires the hyperaemic state, i.e. increased flow under administration of vasodilatory drug adenosine. Conventionally with MBC, hyperaemic state is represented by reduction of peripheral resistance to 30% of its original. We varied the resistance reduction from 30% to 90% of the original, in order to investigate the sensitivity of FFR to the degree of hyperaemia. With PBC, hyperaemic resistances were determined based on PET images acquired during adenosine administration, i.e. patient-specific hyperaemic state was incorporated with PBC. Here, resulting hyperaemic coronary flow is not 5% of the total aortic input any more.

3 RESULTS, DISCUSSION AND CONCLUSIONS

3.1 Impact of inflow boundary conditions – pulsatile vs steady

FFR values calculated pulsatile and steady inflow conditions are compared first, for randomly selected 4 patients with various degree of diseases (trivial-severe). The results are summarised in Table 1. Here, only MBC was used for the outflow. The FFRs under the two inflow conditions are generally in good agreement, i.e. FFR is nearly independent of the boundary conditions. Further investigation on the flow rates through various branches revealed that the flow rates through the stenosed branches are closely matched between the two simulation types while the difference in the healthy branch flows tend to be higher. The stenosis limits the flow in the branch and hence the influence of time-dependent variation of the flow is limited.

3.2 Impact of outflow boundary conditions – morphology-based vs perfusion-based

Knowing from the previous section that the steady flow can be used to sufficiently evaluate FFR, the results obtained with MBC and PBC for 11 vessels are compared while keeping inflow condition steady. All FFRs obtained with various boundary conditions are presented in Figure 2.

The range of FFR with the variable MBC, also shown in Figure 2, demonstrates that the variability of FFR is small (<0.03) for patients with high FFR, i.e. the less diseased patients. The range becomes much larger towards the patients with lower overall FFR, 0.22 at the maximum for LAD of Patient 12. The FFRs derived with patient-specific outflow (PBC) fell within the range of FFRs with variable MBC for most of the patients. For Patient 7 and 12 (LAD), FFR ranges are large but the entire ranges are below the 0.8 threshold, i.e. they would be in the ‘diseased’ category anyways.

3.3 Conclusions

We conducted a series of computational FFR analysis using various inflow and outflow boundary condition to investigate their impact on the FFR derivation. The FFRs computed with the different boundary conditions agreed in general, i.e. the sensitivity of FFR computation to boundary conditions is not very high. However, the models with PET-based outflow condition revealed that there are some cases in which conventional boundary condition underestimate the functional severity of a stenosis, potentially placing the patient in different diagnostic category. The proposed method to derive a range of potential FFR for a patient, by varying peripheral resistance over a physiologically possible range, gave an additional insight into the sensitivity of FFRs. The method could potentially compensate the lack of perfusion data in analysis and may provide additional diagnostic indications.
Table 1. Comparison of FFRs obtained from two types of inflow boundary conditions.

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulsatile FFR</td>
<td>0.59</td>
<td>0.84</td>
<td>0.80</td>
<td>0.94</td>
</tr>
<tr>
<td>Steady-MBC FFR</td>
<td>0.60</td>
<td>0.86</td>
<td>0.80</td>
<td>0.96</td>
</tr>
</tbody>
</table>

CT (grayscale) and PET (colour) images co-registered

3D model and boundary conditions

Typical pressure profile obtained with PBC (left) and MBC (right) with arrows indicating the stenosis

Figure 1. Analysis overview and a typical computational results.

Figure 2. The FFRs of patients ordered in reference to the value of FFR. The bars indicate the range of FFRs obtained using the various MBCs, with the conventional (MBC 30%) marked as a diamond, and the PBC marked as cross. Patient numbers are shown on the plot as reference. Patient 12 had stenosis in 2 vessels (LAD and LCx).

REFERENCES

COMBINING REDUCED-ORDER MODELS AND DEEP LEARNING
FOR FAST AND ACCURATE FRACTIONAL FLOW RESERVE
PREDICTION

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SUMMARY
A reduced-order model for coronary circulation is combined with deep neural networks for fast and accurate Fractional Flow Reserve prediction. Neural networks are trained with a database containing solutions obtained with a three-dimensional model of patient-specific coronary arterial networks extracted from 63 patients with suspected Coronary Artery Disease. We explore different strategies to incorporate information from 3D simulations into reduced-order models and discuss the implications of using deep learning in the context of development of clinical decision tools based on reduced-order models.

Key words: Fractional Flow Reserve, reduced-order model, coronary flow, deep learning

1 INTRODUCTION
Fractional Flow Reserve (FFR) is an index used to characterize the functional significance of coronary artery stenoses [1]. Besides the proven validity of FFR in the clinical context [2], it remains an invasive procedure with associated risks. This fact has motivated the search for non-invasive tests to reduce the number of patients with negative FFR outcome. Coronary Computed Tomography Angiography (CCTA) has been proposed as a candidate. CCTA is very selective in terms of true positives (patients that later show functional significant lesions in FFR assessment), while its performance to detect true negatives is poor [3]. Non-invasive CCTA-derived FFR has emerged as a possible response to the need for reducing false positive CCTA recommendations, with many methods proposed over the past decade [4]. We aim at reducing discrepancies of reduced-order model predicted pressure drops versus results obtained with a model that considers 3D incompressible Navier-Stokes equations to describe blood flow in coronary arteries. To do so we learn discrepancy functions by training neural networks on a 3D simulation database.

2 METHODOLOGY

Patients and data acquisition 63 patients with suspected stable CAD were recruited as part of an ongoing clinical trial at St. Olavs hospital, Trondheim, Norway [5]. For each patient CCTA was acquired, along with other relevant measurements. See [6] for full details.

3D model 3D simulations are performed considering segmented coronary trees as rigid domains with a prescribed pressure as inlet boundary condition and either prescribed flows (via prescribed
parabolic velocity profile) or lumped-parameter models attached to each network outlet. A full description of the underlying mathematical models and their numerical treatment is provided in [6] and references cited therein. We performed several 3D simulations for each patient, normally more than 6, using different modelling assumptions, all deriving in physiological flows for baseline and hyperemic conditions. Hyperemic conditions are situations in which peripheral coronary resistance is reduced by injecting a vasodilatory drug, such as adenosine. FFR is measured under these hypothetical maximal flow conditions. FFR predictions obtained using the 3D model will be denoted FFR\textsubscript{3D}.

**Reduced-order model** Segmentation of coronary vessels is performed using the open-source software ITK-SNAP [7]. Surface mesh processing, addition of flow extensions and 3D meshing is performed using the open-source library Vascular Modeling ToolKit [8]. Centerlines are masked differentiating bifurcation areas, healthy vessels and stenoses. The proposed pipeline for constructing a 1D-0D domain from 3D segmentations is explained in detail in [6]. In healthy vessels blood flow is modelled according to a 1D steady state blood flow model [6]. Assuming positive flow, \( Q > 0 \), pressure drop across a stenotic vessel can be modelled as

\[
\Delta P_{0D} = a_{0D} Q + b_{0D} Q^2,
\]

with parameters

\[
a_{0D} = \frac{K_v \mu}{A_0 D_0}, \quad b_{0D} = \frac{K_l \rho}{2 A_0^2} \left( \frac{A_0}{A_s} - 1 \right)^2,
\]

where \( A_0 \) and \( A_s \) represent the normal and stenotic diameters, respectively. Similarly, \( D_0 \) and \( D_s \) represent the normal and stenotic segments, respectively. Furthermore, \( K_v \) and \( K_l \) are empirical coefficients, with \( K_v = 32 \left( 0.83 L_s + 1.64 D_s \right) \cdot \left( A_0/A_s \right)^2 / D_0 \), \( K_l = 1.52 \) [9], whereas \( L_s \) is the length of the stenosis. \( \mu \) and \( \rho \) are the blood viscosity and density, respectively.

Normally (1) will reproduce pressure drops registered in 3D simulations, \( \Delta P_{3D} \), with a certain error, so that a discrepancy function can be defined

\[
e_{\Delta P_{3D}} = e_{\Delta P_{0D}}(Q; a_{0D}, b_{0D}, p) = \Delta P_{3D} - \Delta P_{0D}(Q; a_{0D}, b_{0D}),
\]

with \( p = \{ p_1, p_2, \ldots, p_n \} \), a set of parameters not considered by the reduced-order stenosis model. Noting that for 3D simulations we have available sets of pairs \( (Q, \Delta P_{3D}) \) for each patient and thus for each stenosis detected, we can perform a least square fitting for each stenosis in order to retrieve \( a_{3D} \) and \( b_{3D} \). Since the original work concerning this stenosis model [9] considered a step reduction in vessel diameter from the healthy to the stenotic regions, we assess the impact of considering the actual geometry of the stenotic area. If \( A_{3D}(s) \) is the cross-section of a vessel at intrinsic coordinate \( s \), then an alternative coefficient \( \hat{a}_{0D} \) is computed as

\[
\hat{a}_{0D} = \int_{L_s} \frac{8\pi \mu}{A_{3D}^2} ds,
\]

noting that \( \hat{a}_{0D} \) is simply the viscous pressure drop over the stenotic segment for a parabolic velocity profile, divided by \( Q \).

**Machine learning** We learn discrepancy function (3) from 3D simulation results by using fully connected feed-forward neural networks. Neural network training and evaluation is performed using the high-level neural network API Keras [10] to interact with TensorFlow machine learning implementations [11]. Candidate parameters are extracted from 3D segmentations and stored as centerline attributes. Results shown here are for a feed-forward neural network consisting of 2 hidden layers of 50 neurons using ReLU activation function. The TensorFlow optimizer Adam was used. The input layer has input features \( f = \{ Q, R_{\text{pro}} , R_s, R_{\text{dist}}, L_s, b_{0D}, \kappa, SF, EX, R_{\text{maxIns}} \} \), where \( R_{\text{pro}} \) is the proximal reference radius, \( R_s \) is the minimum diameter, \( R_{\text{dist}} \) is the distal reference radius, \( L_s \) is the stenosis length, \( b_{0D} \) is given in (2), \( \kappa \) is average curvature in stenotic area, \( SF \) is average shape factor computed as ratio between minimum and maximum diameter, \( EX \) is an eccentricity index and...
Figure 1: Scatter and Bland-Altman plots of $a_{3D}$ vs. $a_{0D}$ (first row), $a_{3D}$ vs. $\hat{a}_{0D}$ (second row). Units for $a$ are mmHg ml$^{-1}$ s. In Bland-Altman plot black horizontal line denotes the bias and dashed lines represent the limits of agreement.

$R_{\text{maxIns}}$ is maximum inscribed sphere radius at minimum diameter location. The output layer is composed by a single neuron with linear activation function and the neural network output is $e_{\Delta P_{3D}}^{DL}$. The 63 patients where split into learning and validation groups on a patient basis, with 55% patients in the learning and 45% patients in the testing group. The python package scikit-learn was used for patient splitting ensuring similar FFR distributions in both groups [12]. The learning group was subdivided into a training dataset (70%) and a validation dataset (30%). During the training procedure the neural network parameters are learned from training data, while validation data is used to determine when the learning process stopped, prevent overfitting and for hyperparameter space optimization. FFR predictions obtained using the reduced-order model will be denoted $FFR_{RO}$, while predictions obtained using the reduced-order model in combination with neural networks will be denoted $FFR_{DL}^{RO}$.

3 RESULTS AND CONCLUSIONS

Figure 1 depicts scatter and Bland-Altman plots for $a_{3D}$ versus $a_{0D}$ and for $a_{3D}$ versus $\hat{a}_{0D}$, showing a significant improvement in the agreement between the reducer-order model parameter and the one computed from 3D simulations by using (4) instead of expression in (2).

We consider 745 stenoses masked as such by our stenosis detection algorithm (see [6]) for deep learning purposes. Results shown here are for test patient group (29 patients and 47 FFR measurements), i.e. for patients not used in the training of neural networks. Figure 2 depicts scatter and Bland-Altman plots for $FFR_{3D}$ versus $FFR_{RO}$ and for $FFR_{3D}$ versus $FFR_{DL}^{3D}$. Results show a significant improvement in the agreement of reduced-order model predictions versus results obtained using the 3D model. In fact for $FFR_{3D} - FFR_{RO}$ we have a bias (standard deviation) of -0.054 (0.042), while for $FFR_{3D} - FFR_{DL}^{RO}$ we have a bias (standard deviation) of -0.010 (0.033).

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Figure 2: Scatter and Bland Altman plots of FFR$_{3D}$ vs. FFR$\text{RO}$ (top row) and FFR$_{3D}$ vs. FFR$\text{DL}$ (bottom row). In Bland-Altman plot black horizontal line denotes the bias and dashed lines represent the limits of agreement.


BRANCH FLOW ALLOCATION METHOD AND ITS APPLICATION IN THE CALCULATION OF FRACTIONAL FLOW RESERVE IN STENOTIC CORONARY ARTERY

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SUMMARY

Coronary branch flow allocation methods based on volume-flow relationship and diameter-flow relationship was employed for the numerical simulation of fractional flow reserve (FFR). The values of simulated FFR based on CT images (FFR_{CT}) for 16 patients were compared with clinical measured FFR. The results showed that the FFR_{CT} demonstrates 80% of consistency with the clinical data. The coronary branch flow allocation method can be applied to calculate the value of clinical non-invasive FFR_{CT}.

Key words: Fractional flow reserve, Hemodynamics, Numerical simulation

1 INTRODUCTION

The main two clinical diagnosis procedures for coronary artery stenosis are morphological approach based on Computed Tomography Angiography (CTA) and functional approach based on Fractional Flow Reserve (FFR). FFR has been regarded as the gold standard because of its high accuracy for the assessment of myocardial ischemia. FFR determines the likelihood that the stenosis impedes oxygen delivery to the heart muscle, and it is defined as ratio of the pressure after (distal to) a stenosis to the pressure before (proximal to) the stenosis. There is no absolute cut-off point at which FFR becomes abnormal; rather, there is a smooth transition, with a large grey zone of insecurity. In clinical trials, a cut-off point of 0.75 to 0.80 has been used; higher values indicate a non-significant stenosis, whereas lower values indicate a significant lesion. However, the application of this gold standard has been restricted owning to its invasiveness, high risk, and high cost.

Fortunately, computational fluid dynamics (CFD) can provide an efficient solution for the non-invasive calculation of FFR based on CTA images (for short, FFR_{CT}). Recently, FFR_{CT} has attracted much attention from worldwide [1-3]. However, the accuracy of FFR_{CT} restricts its application in ordinary clinics. One of the main factors influencing the calculation accuracy of FFR_{CT} is the boundary condition of flow rate in CFD simulation [4,5].

It has been long recognized that many physiological variables depend on body size. The standard way of expressing such a relationship is by using a scaling law:

\[ y = aM^b \]  

(1)

where \( y \) is any measurable quantity of interest, \( M \) is body mass, and \( a \) and \( b \) are coefficients. With regard to the application of this scaling law in the calculation of flow rate in coronary artery, West

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et al proposed the space-filling fractal networks of branching tubes [6], and the following allometric scaling law was satisfied:

\[ Q = a M_{myo}^b \]  

where \( Q \) stands for the flow rate in coronary artery, and \( M_{myo} \) stands for the myocardial mass which is proportional to the volume of coronary branches according to the structure-function relationship. Then,

\[ Q = a V^b \]  

where \( V \) is the volume of coronary branches.

According to the Poisseulle’s law which describes the flow rate in a tube [7,8], the relationship between flow rate and caliber radius satisfies the following equation:

\[ Q = \frac{\pi r^4}{128 \eta} \]  

where \( \eta \) is the viscosity of blood, \( r \) is the radius of vessel, \( b \) is a constant. Thus, the flow rate in coronary artery branches can be allocated according to the volume of coronary branches or the radius (of diameter) of vessel [9,10].

The purpose of this paper is to employ the coronary blood flow allocation methods based on volume-flow relationship (Eq. (3)) and diameter-flow relationship (Eq. (4)) to set the boundary condition in the numerical simulation of FFR\textsubscript{CT} and compare their application feasibility.

2 METHODOLOGY

According to the specific inclusion and exclusion criteria, 16 patients with 20 stenotic lesions in coronary artery were enrolled. All these subjects underwent CTA and FFR procedures. The 3D models of coronary artery tree were reconstructed by using Mimas10.0 (Materialise’s Interactive Medical Image Control System; Materialise, Leuven, Belgium) based on CTA images. Those branches with the diameter \( \geq 1 \) mm were preserved in medical image processing. The volumes and diameters of the coronary arteries were measured. ANSYS Workbench14.0 (ANSYS, Inc., Canonsburg, PA, USA) was employed to perform the finite element analysis of hemodynamics [11,12].

Different numbers of element (i.e. 330631, 743015, 1115723) were tested for the mesh independency. The size of element number around 750 thousands was selected for the model discretization after comparing the relative errors between neighboring meshing sizes.

The blood flow was assumed as incompressible steady Newtonian fluid flow with the density of 1050 kg/m\(^3\) and the viscosity of 0.0035 Pa·s. The fluid-structure interaction between blood flow and coronary vessel wall was neglected, and thus the arterial wall was regarded as a rigid wall where the no-slip condition was satisfied.

The coronary flow rate can be estimated by using the following empirical formula [13]:

\[ Q_{cor} = 0.003HR[-0.568\ln(HR) + 3.246]P_d(W_l/0.85)^{0.75} \]  

where \( Q_{cor} \) is the coronary flow rate during hyperemia, \( HR \) is the heart rate, \( P_d \) is the mean aortic diastolic pressure, and \( M_L \) is the mass of left ventricle which can be measured according to CTA.

The allocation of flow rate can be accomplished based on two approaches [14-16]. The first one is according to the volume-flow relationship, i.e. the flow rate is proportional to the volume of the corresponding coronary branches: \( Q \propto V \). As shown in Fig.1, \( Q_0 = Q_1 + Q_2; Q_1 = Q_{11} + Q_{12}; Q_2 = Q_{21} + Q_{22}; Q_1 : Q_2 = V_1^{0.75} : V_2^{0.75}; Q_{11} : Q_{12} = V_{11}^{0.75} : V_{12}^{0.75}; Q_{21} : Q_{22} = V_{21}^{0.55} : V_{22}^{0.75} \) ……The second one is according to the diameter-flow relationship, i.e. the flow rate is proportional to the cubic of diameter of the corresponding coronary branches: \( Q \propto d^3 \). As shown in Fig.1, \( Q_1 : Q_2 = d_1^3 : d_2^3; Q_{11} : Q_{12} = d_{11}^3 : d_{12}^3; Q_{21} : Q_{22} = d_{21}^3 : d_{22}^3 \) ……

The flow rate at each terminal branch was assigned as the outlet boundary condition. The mean value of aortic diastolic pressure at the root of coronary artery was assigned as the inlet boundary condition.
The simulation of hemodynamics in the patient-specific models was performed by using ANSYS Workbench.

3 RESULTS

The relative errors between the FFR$_{CT}$ based on CFD simulation and the invasively measured FFR were obtained. These relative errors are 10.47% and 11.76% respectively based on volume-flow relationship and diameter-flow relationship. They are different but similar. This difference may be induced both from the neglect of branches with the diameter less than 1 mm and from the subjective operation of 3D model reconstruction and smoothing.

The diagnostic accuracies of FFR$_{CT}$ obtained from volume-flow relationship and diameter-flow relationship are 65% and 85% respectively as illustrated in Tab.1 and Tab. 2. The large difference may be resulted from the fact that the volume-flow relationship is more sensitive to the grey zone of insecurity (with FFR\leq 0.80 as threshold).

| Tab.1 Diagnostic accuracy of FFR$_{CT}$ based on volume-flow relationship |
|-----------------------------|-------------|-------------|
|                            | FFR\leq 0.80 | FFR > 0.80  |
| FFR$_{CT}$                 |             |             |
| \leq 0.80                  | 2           | 1           |
| > 0.80                     | 6           | 11          |

| Tab.2 Diagnostic accuracy of FFR$_{CT}$ based on diameter-flow relationship |
|-----------------------------|-------------|-------------|
|                            | FFR\leq 0.80 | FFR > 0.80  |
| FFR$_{CT}$                 |             |             |
| \leq 0.80                  | 6           | 1           |
| > 0.80                     | 2           | 11          |

Bland-Altman method was used to evaluate the consistency of FFR$_{CT}$ and FFR. The 95% confidence interval between FFR$_{CT}$ and FFR is nearly around [-0.2, +0.2], and most of the data fall within the interval, which indicates that FFR$_{CT}$ and FFR have good consistency (Fig. 2). The consistency is larger than 80%.

![Fig.2 Bland-Altman diagrams. (a) Volume-flow approach; (b) diameter-flow approach](image-url)
4 CONCLUSIONS

In summary, this work employed the coronary blood flow allocation methods based on volume-flow relationship and diameter-flow relationship to set the boundary condition in the numerical simulation of $F_{\text{FFR}_{CT}}$ and compare their application feasibility. The results demonstrated good consistency between the non-invasive value of $F_{\text{FFR}_{CT}}$ and the invasive value of FFR even though there are large errors between the diagnostic accuracies of these two methods. The coronary branch flow allocation method can be applied to calculate the value of clinical non-invasive $F_{\text{FFR}_{CT}}$. Of note, the volume-flow relationship proposed in cited paper is for cumulative quantities. Thus, this approach features low accuracy for the calculation of $F_{\text{FFR}_{CT}}$. Further in-depth research works are needed to modify, verify and clarify its application in the calculation of $F_{\text{FFR}_{CT}}$.

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IMPACT OF A PRESSURE WIRE AND UPSTREAM PLAQUE ON MYOCARDIAL BRIDGING

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SUMMARY

In epicardial coronary artery, the vessel is exposed to the myocardium. However, the segment tunneling through the heart muscle is myocardial bridging (MB). Due to the heart compression force, a narrowing is present in systole, which may lead to severe ischemia. Fractional flow reserve (FFR) is an index to evaluate the severity of the stenosis of coronary arteries. A baseline model of MB has been created via fluid-structure interaction study. By inserting a pressure wire and adding an upstream plaque, the values of FFR decreased, while the combination effect of these two factors is not additive.

Key words: myocardial bridging, pressure wire, upstream plaque, fractional flow reserve

1 INTRODUCTION

In healthy individuals, epicardial coronary artery is exposed to the myocardium. Myocardial bridging (MB) is present when a segment of a major epicardial coronary artery tunnels through the heart muscle. MB is an inborn abnormality and is generally confined to the middle of the left anterior descending coronary artery (LAD). MB presents as a dynamic stenosis, and the mechanisms are quite different compared with atherosclerosis which is also called fixed plaque. In systole, a narrowing appears in MB due to the heart compression force, while in diastole the same artery remains uncompressed and normal.

The incidence that has been reported varies from 1.5 to 16% when assessed by coronary angiograph, but in some autopsy series, it is as high as 80% [1]. Interestingly, based on the clinical angiography, a fixed plaque is frequently found proximal to MB [2]. In addition, symptomatic patients who have MB as their only cardiac abnormality may present with myocardial ischemia, acute coronary syndromes, transient ventricular dysfunction or even death [2].

Fractional flow reserve (FFR) has been proposed to more accurately evaluate the severity of the coronary narrowing [3]. FFR is simplified as a ratio of distal pressure (P_d) to aortic pressure (P_a). The unitless index ranges from 0 to 1 and a smaller value indicates a more severe MB. In clinics, the sensor mounted on the guiding catheter records P_a in the coronary ostium and a pressure wire is introduced to record P_d at the distal end of stenosis [4]. A real-time value of FFR is then shown on the monitor screen.

To the best of our knowledge, few researches have investigated the fluid-structure interaction (FSI) characteristics of MB by computational fluid dynamics (CFD) study. In this article, a baseline model of MB with 30% compression ratio has been generated via FSI analysis. By inserting a pressure wire and adding a 50% upstream plaque, the separate and combine effects of these two factors have been identified.
2 METHODOLOGY

The numerical procedures were computed in commercial software – COMSOL Multiphysics 5.3. Figure 1 is the illustration of the ideal baseline model. A three-dimensional geometry is created by revolving the sketch along z axis. The diameter (D) of the blood flow domain is 3 mm and the wall thickness is 0.5 mm [5]. The total length of the model is 48D with a stress zone simulating the region of MB. The fluid domain is assumed to be viscous, laminar and Newtonian. The density was set as 1050 kg/m3 [6] and the viscosity was set as 0.00365 Pa·s [7]. The arterial wall domain is assumed to be linear elastic. The Young’s modulus is 3E+6 Pa and the Poisson’s ratio is 0.2 [8].

![Figure 1. Schematic illustration of the baseline model.](image)

A force function was applied to the middle MB zone to mimic the systolic heart compression force [9]:

\[
f(z) = 250 \times e^{(4D)^2} \times (N)
\]

In order to explore the influences of the pressure wire and upstream plaque, a probe was inserted from the center of the inlet to the position of measuring Pd – 10D down the MB. In addition, a 50% diameter stenosis was created in the upstream segment. The radius of the pressure wire is 0.18 mm, and it is assumed as a tiny metal for the simplification. The length of the plaque is 2D, and it is positioned at the entrance of the MB. For all the models, a pressure of 90 mmHg was prescribed at the inlet, while a flow rate of 2.8 ml/s was prescribed at the outlet. The value of P_a was set as 90 mmHg as well. Navier-Stokes equations were solved in steady state and the two-way coupled FSI was simulated in the software.

3 RESULTS AND DISCUSSION

Meshing convergence study has been performed in the baseline model. The value of P_d is sensitive and significant to this research. Therefore, it was selected as the parameter in the convergence study. The elements with a size of 1E+5 and 1E+6 were drawn in COMSOL, and the outcomes of P_d were 11217 Pa and 11216 Pa, respectively. The main difference is minor, and the meshing size of 1E+5 was selected to obtain the mesh independent results.

Due to the external force applied to the stress zone, a narrowing is computed in the baseline model (Figure 2). The compression ratio of the MB model is around 30% and the value of FFR in the baseline model is 0.93.

Stefan et al. concluded that a low but increasing wall shear stress (WSS) may contribute to the atherosclerotic plaque formation proximal to MB [10]. However, the visualized post-processing contours were not presented in the publications. Figure 2 shows the WSS distributions of the 30% MB case. In the middle of the bridge, WSS is larger than 10 Pa. And the high WSS may have a protective role from the atherosclerosis generation. In the downstream segment, the value of WSS remains low yet stable. However, a low WSS and an increase in local wall tension and stretch in the upstream segment may induce endothelial injury and subsequent thrombus formation, which
corresponds to the conclusion in [10]. In the following part, the impact of an atherosclerotic plaque on MB would be identified.

**Figure 2.** WSS distributions of the baseline model.

Figure 3 represents the pressure distributions in the central plane of the probe- and plaque-included models with a presented length of 20D in the middle. The value of FFR decreases from 0.93 to 0.88 if introducing a pressure wire in the baseline MB model. The value of FFR is decreased to 0.88 as well with only an upstream plaque, while it reduces to 0.77 if adding both. Interestingly, the combination effect of these two factors is not additive, which is actually larger than the impact of each separate factor.

**Figure 3.** Pressure distributions of the blood flow domain in a central plane. (A) representing the model only inserting a pressure wire; (B) representing the model only adding a 50% upstream plaque; (C) denoting the MB model with both probe and plaque. The length presented in the contours is only 20D in the middle of the models.

Park et al. found that the frequency of visual-functional mismatch between angiography and FFR is high [11]. The reasons may lie in the degrees of stenosis, lesion length, different lesion shape, plaque eccentricity, surface roughness and various shapes of plaque rupture. Based on the results above, pressure wire could contribute significantly to the FFR value. Clinically, the pressure wire is
a significant tool to measure the pressure. However, the elimination of the probe in numerical study may result in a higher FFR value falsely, even if its radius is very small.

4 CONCLUSION

A 30% MB model has been created via FSI study and by analysing the WSS distributions, a plaque proximal to MB is prone to be formed. The values of FFR are decreased after adding a pressure wire and a 50% upstream plaque in the baseline model. However, the combination effect of these two factors is not additive, and it is larger than the linear effect. In CFD study, pressure wire could contribute significantly to FFR estimation. Therefore, its inclusion in FFR prediction methods has to be considered seriously.

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HYPEREMIA MODEL IN FFR SIMULATIONS

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SUMMARY

Fractional flow reserve (FFR) measured during invasive coronary angiography is the gold standard for decision making in coronary revascularization. FFR is calculated as a ratio between average pressure distal to the stenosis and average aortic pressure in the case of maximum possible hyperemia. There are different approaches to simulate hyperemic state in coronary hemodynamics. In this work we compare two models of hyperemic state and demonstrate that they can have a drastic effect on FFR estimation.

Key words: coronary circulation, fractional flow reserve, hyperemia, vasodilatation

1 INTRODUCTION

Coronary heart disease takes one of the leading places among the causes of death of patients of working age. Actual approaches to the treatment of the disease involve a detailed assessment of coronary blood flow. Fractional flow reserve (FFR) measured during invasive coronary angiography is the gold standard for decision making in coronary revascularization [3]. The integration of computational fluid dynamics and quantitative anatomic and physiologic modeling now enables simulation of patient-specific hemodynamic parameters from coronary computed tomography (CT) datasets.

There exist several computed FFR (cFFR) methodologies based on reduced order models [5, 2, 4]. Each of the methodologies consists of CCTA image segmentation algorithm, choice of boundary condition, wall-state equation, model of the stenosis and many other aspects. In this work we investigate one particular aspect: model of hyperemia. It is not exactly clear how to change model parameters to simulate hyperemic state. We investigate two hyperemia models. The first one is based on the reduction of peripheral resistance. The second one increases diameters of the coronary arteries. We compare their performance by estimating FFR on a number of cases.

2 METHODOLOGY

The 1D model [4] is based on equations of mass and momentum conservation

\[
\frac{\partial A_k}{\partial t} + \frac{\partial (A_k u_k)}{\partial x} = 0,
\]

\[
\frac{\partial u_k}{\partial t} + \frac{\partial (u_k^2/2 + p_k/\rho)}{\partial x} = -\frac{8\pi \mu u_k}{A_k},
\]

where \(k\) is the index of the vessel, \(t\) is the time; \(x\) is the distance along the vessel, \(\rho\) is the blood density (constant), \(A_k(t, x)\) is the vessel cross-section area, \(p_k\) is the blood pressure, \(u_k(t, x)\) is the linear velocity averaged over the cross-section, \(\mu\) is the blood viscosity.

Constitutive law ("wall-state equation") for the material of the vessel wall is

\[
p_k(A_k) - p_{sk} = \rho_\text{w} c_w^2 f(A_k),
\]

where \(p_{sk}\) is the reference pressure. The function \(f(A_k)\) represents the wall-stress equilibrium condition.
where $\rho_w$ is vessel wall density (constant),

$$f(A_k) = \begin{cases} 
\exp\left(\frac{A_k}{A_{0k}} - 1\right) - 1, & A_k/A_{0k} > 1 \\
\ln A_k/A_{0k}, & A_k/A_{0k} \leq 1,
\end{cases} \quad (4)$$

$p_{sk}$ is the myocardium pressure, $A_{0k}$ is the unstressed cross-sectional area, $c_k$ is the parameter of the vessel wall elasticity.

The model is modified by active vessel wall response (autoregulation) function according to [6]. Autoregulation is a response of the arteries wall elasticity to changes in blood pressure. Increase in blood pressure leads to increased stiffness of the vessel wall.

At the aortic root the blood flow is prescribed

$$u(t, 0) A(t, 0) = Q_H(t) \quad (5)$$

Each terminal artery with an index $k$ is connected to the venous pressure $p_{veins} = 12$ mm Hg through the hydraulic resistance $R_k$

$$p_k(A_k(t, \tilde{x}_k)) - p_{veins} = R_k A_k(t, \tilde{x}_k) u_k(t, \tilde{x}_k). \quad (6)$$

Parameters $R_k$ are adjusted to reproduce the arterio-venous pressure drop.

Stenosis is included as a separate vessel with smaller diameter. We assume that degree of stenosis, its length and location are known either from clinicians or medical imaging software. We utilize MultiVox medical imaging package developed in Moscow State University.

Values of unstressed cross-sectional areas $A_{0k}$ and vessels’ lengths can be acquired from CT-images [4]. We take into account that cross-sectional areas on CT-images are not unstressed and thus some corrections to $A_{0k}$ values are needed. Elasticity parameters $c_k$ can be assigned to the network with the help of pulse wave velocity studies [1]. Resistances $R_k$ are adjusted to reproduce the arterio-venous pressure drop. Baseline values of parameters can be changed based on patient-specific data, e.g. blood pressure measurements.

### 2.1 Hyperemia models

We consider two hyperemia models.

In model A we simulate the hyperaemic conditions by performing a 20% reduction of $c_k$ in (4) and halving $R_k$ in (6). Autoregulation is switched off which leads to additional increase in blood flow. This provides a 2-3-fold increase of the coronary blood flow.

In model B we start by artificially removing all stenoses from the model. After that we gradually increase diameters of all coronary vessels. The goal is to provide calculated FFR higher than 0.95 in all vessels. After that we introduce all stenoses back by reducing diameters by the same percentage. We also reduce $c_k$ by 20% and disable the autoregulation.

### 3 RESULTS AND CONCLUSION

We compare results of two models on 10 patients. CT-scans and measured FFR were provided by Swansea University Medical School. Figure 1 shows comparison between invasive FFR and CT-derived FFR.

Model B shows much better results. The mean absolute difference for model A is 0.29 and for model B is 0.05. It should be noted that results for Model A were calculated blindly while results for model B were acquired through a correction of Model A. It is clear that Model A produced systematic underestimation of FFR. We assume that the main reason is the quality of CT data. A significant number of vessels are not represented for each patient. As a result the blood flow in stenosed areas can be increased and FFR decreased. By increasing diameters in Model B we compensate for the absence of smaller coronary vessels.
Model A have a better physiological grounding. Hyperemic state occurs due to vasodilatation of small vessels. It leads to decrease in peripheral resistance. However, model B provides $\text{FFR} \geq 0.95$ in healthy vessels. We suggest that hyperemia model does not have to represent physiological changes in properties of the vessel. It can also be derived from functional parameters and hemodynamic indices, such as FFR.

REFERENCES


IMPACT OF BASELINE CORONARY FLOW AND ITS DISTRIBUTION ON FRACTIONAL FLOW RESERVE PREDICTION

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SUMMARY

Model-based prediction of Fractional Flow Reserve (FFR) in the context of stable Coronary Artery Disease (CAD) diagnosis requires a number of modeling assumptions to be made. One of these assumptions, present in most modeling approaches proposed so far, is the definition of a baseline coronary flow, i.e. total coronary flow at rest prior to the administration of any drug needed to perform invasive measurements. Here we explore the impact of several approaches available in the literature to estimate and distribute baseline coronary flow using a reduced-order model.

Key words: Fractional Flow Reserve, reduced-order model, coronary flow

1 INTRODUCTION

Fractional Flow Reserve (FFR) is an index to characterize the functional significance of coronary artery stenoses [1]. Besides the proven validity of FFR as a diagnostic tool for stable CAD [2], it remains an invasive procedure with associated risks. This fact has motivated the search for non-invasive tests to reduce the number of patients with negative FFR outcome. Coronary Computed Tomography Angiography (CCTA) has been proposed as a candidate and is gaining more popularity in clinical use [3]. CCTA has shown to be very selective in terms of correctly identifying CAD (true positives), while its performance to exclude CAD (true negatives) is worse [4]. In this context, non-invasive CCTA-derived FFR has emerged and has the potential to reduce the number of unnecessary invasive procedures, with many methods proposed over the past decade [5]. Such methods aim at predicting FFR by using non-invasive information only, and have already shown potential to be used as a screening tool in addition to standard CCTA assessment. These methods share some common general steps that are necessary for FFR prediction: (i) define the computational domain of coronary vessels; (ii) define a mathematical model for fluid mechanics valid in domain defined in (i); (iii) define boundary conditions; (iv) solve the mathematical model; (v) evaluate predicted FFR at desired locations. However, the way each of these steps is performed varies greatly. In this paper we address two aspects of this pipeline. First we consider steps (ii) and (iv), working on the improvement and validation of a reduced-order model for the coronary circulation that allows for fast and accurate FFR prediction. Next we focus on step (iii), investigating the impact of several approaches for baseline coronary flow determination and flow distribution proposed so far in the literature on FFR prediction.

2 METHODOLOGY

Patients and data acquisition  63 patients with suspected stable CAD were recruited as part of an ongoing clinical trial at St. Olavs hospital, Trondheim, Norway [7]. For each patient the following data was acquired: CCTA, Left ventricle mass (LVM), Ultrasound-derived Cardiac Output (CO),
Reduced-order model  Segmentation of coronary vessels is performed using the open-source software ITK-SNAP [8]. Surface mesh processing, addition of flow extensions and 3D meshing is performed using the open-source library Vascular Modeling ToolKit (VMTK) [9]. Centerlines are masked differentiating bifurcation areas, healthy vessels and stenoses. Here we propose to modify the domain definition reported in [6] as follows: (i) the spacing between nodes is reduced from 0.5 mm to 0.125 mm; (ii) an additional criteria for masking stenotic regions based on the gradient of the radius in the longitudinal direction is added. In [6], a detected stenosis was marked until the estimated stenosis degree (SD) was below 12%. Here we require that SD > 12% ∨ |dr/dx| < 0.05.

In healthy vessels, blood flow is modeled according to a 1D steady state blood flow model, while at stenoses, pressure drop is modeled using a well-known algebraic model [10]. Two alternative modeling setups are considered: prescribed flow rate at outlets or resistive elements coupled to outlets. Full details on the mathematical models and corresponding numerical treatment are given in [6].

3D simulations are used to validate the reduced-order model proposed in [6] and improved in this work. These simulations are performed considering segmented coronary trees as rigid domains with a prescribed pressure as inlet boundary condition and either prescribed flows or lumped-parameter models attached to each network outlet. A full description of the underlying mathematical models and their numerical treatment is provided in [6] and references cited therein.

To predict FFR the following pipeline is followed: (i) define total baseline coronary flow; (ii) distribute flow among network outlets; (iii) perform simulation with prescribed inlet pressure and outlet flows; (iv) compute equivalent outlet resistance and reduce to simulate effect of vasodilatory adenosine injection; (v) perform hyperemic simulation with reduced resistances. Predictions obtained with the reduced-order and 3D model are called FFR_{RO} and FFR_{3D} respectively.

Baseline flow determination and distribution  In this work we explore a number of methods to estimate baseline coronary flow, q. In selecting the methods to use we sought to include methods that...
use different types of data. In particular, we included methods that rely on cardiac output estimation, as well as methods that use left ventricle mass and a method based on population studies. US $\tilde{q}_{\text{Guyton}}$ is computed taking 4.5% [12] of Ultrasound-derived CO. $\tilde{q}_{\text{DeSimone}}$ is computed using HR and estimated SV [11]. $\tilde{q}_{\text{Kishi}}$ is computed from LVM and constant myocardial perfusion rate [13]. $\tilde{q}_{\text{Sharma}}$ is computed from LVM and HR × SBP dependent myocardium perfusion rate [14]. $\tilde{q}_{\text{Sharma}}$ and $\tilde{q}_{\text{Kishi}}$ are corrected flows from original values assuming that Total Myocardial Mass (TMM) is 2.4 LVM and not 1.5 LVM as suggested in original works. This new constant was determined from considerations made from our patients’ LVMs and references on TMM normal values. Baseline coronary flow was distributed among outlets using Murray’s law applied either at outlets (Distal Murray (DM)) or at each branching point of the network, starting from the root (Proximal Murray (PM)), or using Transluminal Attenuation Gradient (TAG) as proposed in [13]. We also considered a prescribed flow splitting between left and right coronary branches [15] or we applied flow distribution to both coronary branches simultaneously.

Table 3: Comparison of FFR_{RO} vs FFR_{m} for coupled branches treatment. For each column representing different accuracy measures, we have highlighted the best (red), second best (blue) and third best (green) measures. a and b are coefficients for linear fitting: FFR_{RO} = a FFR_{m} + b, while r is Pearson’s correlation coefficient.

<table>
<thead>
<tr>
<th>Baseline flow</th>
<th>Flow distribution</th>
<th>a</th>
<th>b</th>
<th>r</th>
<th>FFR_{RO} − FFR_{m}</th>
<th>Acc</th>
<th>Sen</th>
<th>Spe</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>US $\tilde{q}_{\text{Guyton}}$</td>
<td>DM</td>
<td>0.67</td>
<td>0.31</td>
<td>0.55</td>
<td>-0.04 (0.15)</td>
<td>80.00</td>
<td>54.55</td>
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<td>75.00</td>
<td>81.48</td>
</tr>
<tr>
<td></td>
<td>p. Murray</td>
<td>0.63</td>
<td>0.34</td>
<td>0.53</td>
<td>-0.04 (0.15)</td>
<td>78.10</td>
<td>48.48</td>
<td>91.67</td>
<td>72.73</td>
<td>79.52</td>
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<tr>
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<td>TAG</td>
<td>0.87</td>
<td>0.11</td>
<td>0.61</td>
<td>-0.01 (0.16)</td>
<td>86.67</td>
<td>78.79</td>
<td>90.28</td>
<td>78.79</td>
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<tr>
<td></td>
<td>DM</td>
<td>0.76</td>
<td>0.22</td>
<td>0.54</td>
<td>-0.02 (0.17)</td>
<td>82.86</td>
<td>66.67</td>
<td>90.28</td>
<td>78.86</td>
<td>85.53</td>
</tr>
<tr>
<td></td>
<td>PM</td>
<td>0.70</td>
<td>0.26</td>
<td>0.52</td>
<td>-0.01 (0.16)</td>
<td>81.90</td>
<td>63.64</td>
<td>90.28</td>
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<td>0.29</td>
<td>0.54</td>
<td>-0.04 (0.15)</td>
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<td>91.67</td>
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<tr>
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<td>PM</td>
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<td>0.53</td>
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<td>77.14</td>
<td>42.42</td>
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<td>0.02 (0.17)</td>
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<td>93.06</td>
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<td>90.14</td>
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<td>DM</td>
<td>0.68</td>
<td>0.30</td>
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<td>-0.04 (0.15)</td>
<td>82.86</td>
<td>63.64</td>
<td>91.67</td>
<td>77.78</td>
<td>84.62</td>
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<tr>
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<td>0.51</td>
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<td>87.62</td>
<td>78.79</td>
<td>91.67</td>
<td>81.25</td>
<td>90.41</td>
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</tbody>
</table>

3 RESULTS AND CONCLUSIONS

Figure 1 shows scatter and Bland-Altman plots for a comparison of FFR predicted by 3D and reduced-order models, while numerical values of the comparison is given in Table 1, which is also reporting indexes on the agreement of predicted FFR by the reduced-order model versus results obtained using 3D simulations. Comparison of reduced-order model predicted FFR and 3D model predicted FFR versus invasive measurements are also shown. We observe that errors introduced by the reduced-order model are small compared to errors made in invasive FFR prediction and that the diagnostic accuracy of reduced-order model results is very similar to that of results obtained using a 3D model.

Predicted average flows, as well as average myocardium perfusion rates are in line with reference physiological values of 250 ml/min and 0.8 ml/g/min [12] for approaches using our TMM to LVM re-
lation (TMM = 2.4 LVM) and where flow is not derived from perfusion rates, i.e. $q^{\text{US}}_{\text{Guyton}}, q^{\text{DeSimone}}_{\text{Guyton}}, q_{\text{Sakamoto}}$ and $q_{\text{Sharma}}$, see Table 2.

Table 3 shows accuracy indexes for predicted FFR with respect to invasive FFR for all possible combinations of baseline flow determination and flow distribution strategies. TAG flow distribution outperforms other flow distribution strategies in all cases considered, in line with results obtained in [13]. The best performing method has the setting: coupled branches treatment, $q^{\text{US}}_{\text{Guyton}}$ and TAG flow distribution. Of course this optimal configuration is only valid for our dataset and modeling framework and will not necessarily apply in a different context. However, we note that error standard deviation changes across all different setups remained rather invariant. This means that no patient-specific method considered here was able to significantly improve results. Considerations on the construction of each of these baseline flow determination methods support this observed fact. Significant improvement of results will be obtained by intervening in other modeling aspects that are known to be relevant such as vessel geometry and modeling of baseline to hyperemic peripheral resistance dynamics.

REFERENCES


IN VITRO EXPERIMENTAL INVESTIGATION OF INTERMEDIATE CORONARY LESION USING POROUS TERMINAL IMPEDANCE

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²Biomedical Engineering Group, Zienkiewicz Centre for Computational Engineering, College of Engineering, Swansea University, Swansea SA2 8PP, UK.

SUMMARY

In this work, the experimental investigation of Fractional Flow Reserve (FFR) in the intermediate coronary lesion is carried out using porous medium impedance to resemble microvasculature resistance. Different combination of the porous medium is introduced, and a comparative study is performed to investigate the influence on the FFR value and determine the best one which will closely resemble microvascular resistance.

Key words: Fractional flow reserve, coronary lesion, porous terminal impedance.

1 INTRODUCTION

Coronary heart disease (CHD) is the most commonly encountered heart disease responsible for approximately 20 percent of all deaths in the world. In mild cases of CHD, medication is often preferred. However, in a large number of cases, CHD falls between mild and severe. This poses a problem for clinicians in choosing the right course of action. Fractional flow reserve (FFR) is the pressure drop across a coronary stenosis that is used as a clinical measure to determine the severity of CHD [1]. FFR is defined as the ratio of distal pressure ($p_d$) to proximal pressure ($p_p$) of the stenotic lesion which can be written as

$$FFR = \frac{p_d}{p_p}$$

The present technique followed to diagnose the patients for finding out the severity of stenosis is invasive. FFR is computed using a catheter which is inserted into patient’s blood vessel and it is taken to the stenosed location for investigation. Eventually the values of pressures are measured across the stenosis to quantify the severity of stenosis. However due to its invasive nature, FFR can be associated with medical complications, such as coronary dissections, and is not entirely suitable for the follow-up of medically treated stenoses, in addition to cost implications [2]. Now-days, a Computed Tomography Angiogram (CTA) is performed on patients, which obtains 3D images of the moving heart and bigger arterial vessels. This 3D image is reconstructed, and numerical simulations are performed on the generated 3D model of arteries to predict the FFR value. This procedure does not involve any risk as this is non-invasive. Though the 3D modeling predicts FFR value close to that of the value obtained using the catheterization procedure, the time taken for simulations is enormous because it incorporates the solution of full 3D transient Navier Stokes equations in the entire domain. Efforts are being made to reduce the computational time. The experimental set-up is an approximation to the human systemic circulation and it can reproduce pulse waveforms with significant physiological
features in the vascular model. However, waveforms become less physiological as we march towards the periphery. This is due to the use of the simple resistance boundary conditions, which reflect any incoming wave without smoothing them. In most of the experimental studies to date, the terminal end is either linearly tapered or had constant cross-section for the smallest branches [3, 4].

The motivation lies in the improvement of the in-vitro measurement technique of FFR in coronary arteries. The experimental investigation of FFR in the intermediate coronary lesion is carried out using porous medium to resemble microvasculature resistance. Different combination of the porous medium is introduced and a comparative study is performed to understand the influences on the FFR value.

2 METHODOLOGY

The experimental setup of flow through coronary artery has been developed in the present study and it is shown in Fig.1. The components used in the experiment are a pulsatile pump, silicon tubes, patient-specific stenosed vascular tree, pressure sensors, and porous resistance section. Water-glycerol at specific ratio is used as blood mimicking fluid [4]. The pressure sensor is calibrated using a two-point calibration technique. The pulsatile pump creates physiological flow relevant for mammalian blood circulation. The patient-specific coronary tree is generated form CT scan data and printed as a 3-D model. The Y-connector is used for insertion of wire catheter and it is taken to the stenosed region for measurement of the pressure in proximal and distal location. Bridge amplifier is used for amplification of the pressure signals. Data acquisition system (DAQ) is used for data visualization of the measured data. The porous resistance section is introduced for mimicking the microvascular resistance. Repeatability of the flow measurement was ascertained from experiment carried over a three-month period.

Figure 1: Schematic drawing of the experimental set-up
3 RESULT AND CONCLUSIONS

Figure 2: Pressure signal recorded before section B

The methodology for carrying out in vitro experimentation of stenosed coronary artery is proposed in this work using porous terminal impedance. Figure 2 shows the pressure signal which is recorded before section B using pressure probe. Different combination of piecewise section having different porosity is introduced to mimic vascular resistance. This may be the stepping stone of using porous medium experimentally for representing vascular resistance in the systemic circulation more accurately.

The opted porous medium which is close to the approximation of the human vascular resistance, and it gives enough information about the geometric influence of coronary artery. In future, by creating porous medium to the different arterial models can group together to find out the best vascular resistance model using machine learning.

REFERENCES

A VESSEL LENGTH METHOD TO COMPUTE CORONARY FRACTIONAL FLOW RESERVE FROM COMPUTED TOMOGRAPHY IMAGES

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SUMMARY

The fractional flow reserve (FFR) is an index to evaluate the functional severity of coronary stenosis. To obtain non-invasively the coronary FFR value, this method uses the vessel length-based lumped parameter model of the coronary vascular system. We also exclude aortic part in the computational domain of the computational fluid dynamics model for efficient computation. The computed FFR (CT-FFR) was compared with clinically measured results for validations of this method. Simulation results show that the diagnostic accuracy, sensitivity, and specificity of non-invasive FFR on a per-vessel basis were 85.8%, 86.2%, and 85.5%, respectively, for CT-FFR ≤ 0.80.

Keywords: fractional flow reserve, vessel length method, coronary artery

1 INTRODUCTION

Fractional flow reserve (FFR) is a hyperemic pressure ratio-derived index to estimate stenosis severity in coronary artery as the gold diagnostic standard. In spite of recent progress in patients specific method of computed FFR (CT-FFR), there are still many unresolved problems. Especially, complicated model structure to simulate the patient-specific model of CT-FFR is a typical example. This study aims to propose a simple and efficient method of CT-FFR based vessel length approach, and we validate its clinical performance. This method couples computed tomography (CT)-derived 3D computational fluid dynamics (CFD) model with vessel length based lumped parameter models (LPM). Moreover, the computational domain of CFD doesn’t include the aortic part for efficient computation. For clinical validation of the present method, we simulate computed FFRs of 117 patients and compared the results with clinically measured FFR values.

2 METHODOLOGY

In this work, pulsatile flows were simulated to obtain non-invasively the coronary FFR values by using a multi-scale coronary modeling coupling computational fluid dynamics (CFD) with the lumped parameter model (LPM) of the cardiovascular system in Figure 1. This method uses patient-specific coronary arteries for the CFD model and includes only the vessel length-based LPM of the coronary vascular system for boundary conditions. The simulations of the multi-scale modeling were performed using Navier-Stokes solver based on a segregated finite element scheme [1-3]. Measured blood pressure data was employed as an inlet boundary condition for the
CFD model, and we couple CFD outlet with LPM of the microvascular system of a coronary system for the specification of the outlet boundary condition of the CFD model. To calculate the LPM parameters such as resistances and capacitances, we employed the novel vessel-length based method [3-5].

![Figure 1. Procedure for computed CT-FFR](image)

To establish the LPM parameter, we first obtained each summed length of left anterior descending vessels (LAD), left circumflex vessels (LCX), and right coronary vessels (RCA). We expressed as the resistances of LAD, LCX, and RCA with the assumption that a longer coronary artery has more daughter branches and thus fed more heart mass than a shorter one [3-5]. A detailed explanation is shown in our previous papers [2-5]. In the equations, resistance, denoted as ‘R’, are inversely proportional to vessel length, l, indicating that longer vessel length induces less resistance and thus more blood flow.

\[
R_{\text{LAD}} = \frac{k}{l_{\text{LAD}}} \\
R_{\text{LCX}} = \frac{k}{l_{\text{LCX}}} \\
R_{\text{RCA}} = \alpha \frac{k}{(1-l_{\text{RCA}})/l_{\text{RCA}}} + \frac{k}{l_{\text{RCA}}} \
\quad (\alpha > 1)
\]

In the equations, resistance, denoted as ‘R’, are inversely proportional to vessel length, l, indicating that longer vessel length induces less resistance and thus more blood flow. Here, \( \alpha \) is set to be 3.45, reducing the effect of the RCA vessel length feeding RV muscle on RCA flow. ‘k’ is the proportional constant derived from the pressure-flow rate relation as explained in our previous paper [4] (Equation 4).

\[
k = \frac{\Delta P}{Q} \left\{ l_{\text{LAD}} + l_{\text{LCX}} + \frac{(1-l_{\text{RCA}})/l_{\text{RCA}}}{(1-l_{\text{RCA}})/l_{\text{RCA}} + \alpha} \right\}
\]

In the above equation, the Q and \( \Delta P \) are the total flow rate to coronary arteries and the pressure difference between the aorta and coronary veins, respectively. Schematic of the present vessel length method to estimate LPM resistance is shown in Figure 2.
3 RESULTS AND CONCLUSIONS

We validated this method in terms of a patient-specific coronary model was constructed from CT images, and the computed FFR (CT-FFR) was compared with clinically measured FFR results. The diagnostic performance of the present vessel length method was evaluated in susceptible coronary artery disease. For this purpose, 117 Patients who had undergone computed tomography images (CT) for suspected coronary artery disease (CAD). FFRs were clinically measured in 218 vessels by using guide catheter-wire as reference standard from 4 medical institutions (Ulsan University Hospital, Ulsan, Korea; Seoul National University Hospital, Seoul, Korea; Keimyung University Dongsan Medical Center, Daegu, Korea; Inje University Ilsan Paik Hospital, Goyang, Korea). The coronary computed tomography angiography (CCTA) images were analyzed in a blinded fashion by an independent core laboratory in accordance with the Society of Cardiovascular Computed Tomography guidelines on CCTA interpretation [7]. The CT-FFR and clinically measured FFR correlated well (r = 0.76, p <0.001) with slight underestimation by CT-FFR of 0.014, p = 0.007. With a vessel length based computational fluid dynamics, the diagnostic accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of non-invasive FFR on a per-vessel basis were 85.8%, 86.2%, 85.5%, 79.8%, and 90.3%, respectively, for CT-FFR ≤ 0.80 in Table 1. A high area under the receiver operating characteristic curve (AUC) for CT-FFR was 0.93. Therefore, non-invasive FFR (CT-FFR) method showed good diagnostic performance for the detection of functionally significant coronary artery disease.

Table 1. Diagnostic performance of computed CT-FFR

<table>
<thead>
<tr>
<th>Measure</th>
<th>Per-vessel (n = 218)</th>
<th>Per-patient (n = 117)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>CT-FFR ≤ 0.8 (95% CI)</td>
<td>CT-FFR ≤ 0.8 (95% CI)</td>
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<tr>
<td>Accuracy</td>
<td>86 (81–90)</td>
<td>86 (79–92)</td>
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<tr>
<td>Sensitivity</td>
<td>86 (79–94)</td>
<td>93 (87–99)</td>
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<td>Specificity</td>
<td>86 (80–92)</td>
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<td>PPV</td>
<td>80 (72–88)</td>
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<td>LR−</td>
<td>0.10 (0.10–0.27)</td>
<td>0.10 (0.04–0.23)</td>
</tr>
</tbody>
</table>

Cl = confidence interval; CT-FFR = FFR from computed tomography; LR+ = positive likelihood ratio; LR− = negative likelihood ratio; NPV = negative predictive value; PPV = positive predictive value.

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Standard Session I
MECHANICAL FEEDBACK AND COOPERATIVITY IN A THEORETICAL MODEL OF AIRWAY SMOOTH MUSCLE CELL–MATRIX ADHESION

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SUMMARY

The generation of contractile force by airway smooth muscle cells, via intracellular acto-myosin crossbridge dynamics, and its transmission to the extra-cellular matrix (ECM), through integrin-mediated cell-ECM adhesions, are key processes that regulate bronchoconstriction in asthma. In this study we develop a multiscale model coupling these two processes and investigate their modulation by oscillatory loading. Parameter exploration uncovers regions of bistability and hysteresis that arise due to shared loading between integrin bonds and intracellular crossbridges. The findings could help explain the transient bronchodilatory effect of a deep breath observed in asthmatics compared to a more sustained effect in normal subjects.

Key words: asthma, deep inspiration, bistability, integrins, crossbridges

1 INTRODUCTION

Bronchoconstriction, a narrowing of the airways characteristic of asthma, is regulated by two key processes: the generation of contractile force (via actomyosin crossbridges within airway smooth muscle (ASM) cells) and the transmission of this contractile force to the surrounding extracellular matrix (via integrin-mediated adhesions). In several experimental studies, deep inspirations (DIs) have been observed to reverse bronchoconstriction in healthy subjects, but this reversal was transient or not seen in asthmatics [1–3]. The mechanisms underlying this result are currently unknown. Motivated by these observations, previous research has focussed on understanding how contractile force generation is modulated by oscillatory loading. However, integrins are well-known to respond to environmental fluctuations, and are therefore also an important factor to consider. In this study, we develop a theoretical model to study how both crossbridges and integrins respond to oscillatory loading of the ECM. Using the model, we investigate the mechanical coupling between the two processes and suggest bistability (which arises due to mechanical cooperativity) as a possible mechanism behind differing responses to DIs.

2 METHODOLOGY

The mathematical model (sketched in Fig. 1) consists of three elements in series representing the ECM, integrins and the ASM cell. Within the cell, we consider a passive stiffness as well as parallel contractile units that are governed by the well-established Huxley–Hai–Murphy (HHM) model [4]. The HHM model is an advection–reaction system where myosin crossbridges undergo transitions between four states, accounting for phosphorylation and dephosphorylation of the crossbridges and their attachment and detachment to actin filaments. Transition rate functions are governed by local kinetics, and contractile force is generated by crossbridges in the attached states. Similarly, we consider local binding and rupture kinetics of integrins, adapting a formulation from
our previous model of cell–matrix adhesion dynamics [5]. These elements are coupled to, and respond to, mechanical loading, which is applied via an oscillatory displacement condition to the ECM (LT, Fig. 1b).

3 RESULTS AND CONCLUSIONS

Due to load-dependent unbinding of integrins and crossbridges, we find that both force transmission and force generation are affected by increasing amplitudes of oscillatory loading (Fig. 2). Moreover, there is a close mechanical coupling between the two processes from which a regulatory mechanism appears to emerge due to negative feedback: integrins and crossbridges have a competing effect on cell deformation, and a decrease in integrin density promotes crossbridge attachment. For intermediate amplitudes of loading we observe a region of bistability where shared loading and cooperativity between integrins can allow an initially high adhesion state to persist. This is analogous to a result reported in our earlier study [5], in which only integrin dynamics were modelled. However, in this fully-coupled model, we observe an additional region (Fig. 3) due to a similar cooperativity between crossbridges. The different regions are attainable as a dimensionless parameter \( \beta \), which describes the relative strengths of the crossbridges and integrins, varies; for low \( \beta \), integrin cooperativity is dominant; for high \( \beta \), crossbridge cooperativity dominates. In both cases, the existence of bistability has interesting consequences. We find that large perturbations in oscillation amplitude (representing DIs) can result in a dramatic reduction in the total contractile force transmitted to the ECM. When bistability is present, this reduction can either persist or recover depending on where the unperturbed oscillation amplitude lies relative to the bistable region. Specifically, if this unperturbed amplitude is bistable, a permanent switch in behaviour is possible. It has been observed that DIs can reverse bronchoconstriction in non-asthmatics but not in asthmatics, and we propose that an underlying bistability could explain this.

Motivated by understanding the role of both actomyosin crossbridges and integrins in regulating bronchoconstriction, we developed a mathematical model of their combined responses to oscillatory loading. By coupling local binding kinetics to higher scale relative motion, we demonstrate the existence of mechanical feedback and mechanical cooperativity. To our knowledge, interacting crossbridge and integrin dynamics have not been considered at this level of
A consequence of the mechanical cooperativity is the existence of bistability under certain parameter regimes. In these cases, it is possible to see a permanent switch in qualitative behaviour where large amplitude perturbations lead to reduced levels of total contractile force. Our mathematical model therefore predicts results of clinical significance: we propose that bistability could be a mechanism underlying experimental observations on the bronchodilatory effect of deep inspirations in non-asthmatics. Moreover, the model provides insight into parameters that influence the bistability; for example, we have observed that an increase in passive cell stiffness results in a narrower bistable region, which could be relevant to understanding the ineffectiveness of DIs at reversing bronchoconstriction in asthmatics. In summary, our work highlights the importance of considering both contractile force generation and contractile force transmission, generates hypotheses for the differing responses to DIs in asthmatics and non-asthmatics, and suggests bistability and mechanical cooperativity as important directions for future experimental study.

REFERENCES

THREE-DIMENSIONAL STRESS DISTRIBUTIONS IN PASSIVE AND ACTIVE STATES ACCOUNTING FOR CIRCUMFERENTIAL AND AXIAL RESIDUAL STRAINS OF ARTERY

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SUMMARY

Three-dimensional strain and stress distributions in passive and smooth muscle constricted states were analyzed considering circumferential and axial residual strains. Experimental data of a common carotid artery of rabbit were used to obtain material parameters for passive and active strain energy functions.

Key words: artery, residual strain, stress distribution

1 INTRODUCTION

It is well known that arteries are subject to residual stress. In earlier studies, the residual stress in the arterial ring relieved by a radial cut has been considered in stress analysis [1]. However, it has been found that axial strips sectioned from arteries also curled into arcs, showing that the axial residual stresses were relieved from the arterial walls [2]. The combined relief of circumferential and axial residual stresses must be considered to accurately analyze stress and strain distributions under physiological loading conditions. In the present study, a mathematical model of a stress-free configuration of artery was proposed using the Riemannian geometry [3]. Stress analysis for an arterial wall under unloaded and physiologically loaded conditions was performed using an exponential type strain energy function for the passive state and a strain energy function for the state with constricted smooth muscle induced with noradrenaline of $10^{-5}$ M.

2 METHODOLOGY

2.1 Kinematics

Let $\mathcal{B}$ denote a set of material points considered and $E^3$ the three-dimensional Euclidean space. We shall call a map $\chi$ from $\mathcal{B}$ into $E^3$ a configuration of $\mathcal{B}$. We introduce a curvilinear coordinate system $\left\{x^i; g_{ij}\right\}$ where $i,j$ are integers 1, 2, and 3, $x^i$ denote coordinates and $g_{ij}$ components of a metric tensor for $E^3$. For a material point $p \in \mathcal{B}$, $\chi$ is defined as a map $p \mapsto x$ where $x = (x^1, x^2, x^3)$. A configuration for the unloaded state is denoted by $\kappa$. For the unloaded state we introduce a curvilinear coordinate system $\left\{\xi^a; \gamma_{ab}\right\}$. The material point $p \in \mathcal{B}$ is mapped as $\xi = (\xi^1, \xi^2, \xi^3) = \kappa(p)$. In general, the unloaded material body $\kappa(\mathcal{B})$ with a metric tensor $\gamma_{ab}$ has residual stress. However, a metric tensor with components $\eta_{ab}$ may be defined over $\kappa(\mathcal{B})$ to obtain the stress-free state. In this case the infinitesimally small distance $ds$ between two points in the stress-free configuration can be determined with

$$ds^2 = \eta_{ab} d\xi^a d\xi^b.$$
shall call the body $\kappa(\beta)$ with a metric tensor $\eta_{ab}$ a Riemannian stress-free configuration. The Riemannian stress-free configuration may not be generally Euclidean because the Riemann-Christoffel tensor may not vanish in the body $\kappa(\beta)$ with the metric tensor $\eta_{ab}$. Because we treated a thick-walled cylindrical vessel, a cylindrical coordinate system $x^1 = \theta$, $x^2 = z$, and $x^3 = r$ with components of a metric tensor $g_{11} = g_{22} = r^2$, $g_{23} = g_{33} = 1$, and $g_{ij} = 0 (i \neq j)$ was adopted. For the unloaded configuration $\kappa$, a cylindrical coordinate system $\xi^1 = \theta$, $\xi^2 = \zeta$, and $\xi^3 = \rho$ with $\gamma_{11} = \gamma_{22} = \rho^2$, $\gamma_{22} = \gamma_{44} = 1$, $\gamma_{33} = \gamma_{55} = 1$, and $\gamma_{ab} = 0 (a \neq b)$ was adopted. If there is no residual stress, $\kappa(\beta)$ with a metric tensor $\eta_{ab}$ is considered a stress-free reference configuration but there exists residual stress the metric tensor becomes $\eta_{ab}$ that is different from $\gamma_{ab}$. The covariant components of the Riemann-Christoffel tensor for the stress-free configuration are expressed as follows:

$$R_{a[pqr]} = \frac{1}{2} \left( \frac{\partial^2 \eta_{av}}{\partial \xi^p \partial \xi^v} + \frac{\partial^2 \eta_{pv}}{\partial \xi^a \partial \xi^v} - \frac{\partial^2 \eta_{au}}{\partial \xi^p \partial \xi^v} - \frac{\partial^2 \eta_{uv}}{\partial \xi^a \partial \xi^v} \right) + \eta^{\kappa} (\Gamma_{a[pq]} - \Gamma_{apq} \Gamma_{dvp})$$

where $\eta^{\kappa}$ represent the reciprocal components of the metric tensor. In the three-dimensional space, distinct covariant components of the Riemann-Christoffel tensor $R_{1212} = R_{3333} = R_{0000}$, $R_{2323} = R_{0000}$, $R_{1213} = R_{3330}$, $R_{2123} = R_{0030}$, $R_{3132} = R_{0030}$ may not vanish [4]. Therefore, we may check these components to know whether the Riemannian stress-free configuration is Euclidean or not. If there is a global Euclidean stress-free configuration, all components vanish everywhere.

2.2 Stress-free configuration of artery

**STRESS-FREE CONFIGURATION**

![Stress-Free Configuration Diagram](image)

**UNLOADED CONFIGURATION**

![Unloaded Configuration Diagram](image)

Fig. 1 Schematic drawings of local stress-free and unloaded configurations for artery.

From Fig. 1, the stretch ratios of the unloaded state with reference to the local stress-free configurations are provided as follows:

$$\Lambda_\theta = \frac{2\pi \rho}{\Theta_u \rho} = \frac{2\pi \rho}{\psi_{\phi} S} \left( R_s \leq R \leq R_u, \ \rho_s \leq \rho \leq \rho_u \right)$$

$$\Lambda_\zeta = \frac{l_u}{\psi_{\phi} S} = \frac{\gamma_{zz}}{\eta_{zz}} \left( S \leq S \leq S \right)$$

$$\Lambda_\rho = \frac{d \rho}{d R} = \frac{d \rho}{d S} = \sqrt{\frac{\gamma_{\rho \rho}}{\eta_{\rho \rho}}} \left( R - R_s = S - S \right)$$

(2)
It should be noted that the stretch ratio in the radial direction in the local stress-free configurations is common. The product of three principal stretch ratios is 1 based on the incompressibility of arterial wall, i.e., we obtain the following equation:

\[ \Lambda_\theta \Lambda_z \Lambda_\rho \frac{2\pi \rho}{\Theta_\rho R \Psi_\rho S} \frac{d\rho}{dR} = 1 \quad (S = S_r + R_i - R) \]  

(3)

From the above equation, we obtain the following relation:

\[ \rho = \sqrt{\frac{\Theta_\rho \Psi_\rho}{6\pi l_w}} \left[ -2R^3 + 3(R_i + S_r)R^2 - (R_i + 3S_r)R_i^2 \right] + \rho_i^2 \]

(4)

where the angles are expressed in radian and we imposed a boundary condition \( \rho_i = \rho(R_i) \). It is easily demonstrated that \( \rho \) increases as \( R \) increases for \( R \in [R_i, R_f] \). The components of the metric tensor for the Riemannian stress-free configuration are provided from Eq. (2):

\[ \eta_{zz} = \left( \frac{\Theta_\rho R}{2\pi} \right)^2, \quad \eta_{z\theta} = \left( \frac{\Psi_\rho S}{l_w} \right)^2, \quad \eta_{\rho\rho} = \left( \frac{dR}{d\rho} \right)^2, \quad \eta_{\theta\theta} = 0 \quad (\alpha \neq \beta) \]

(5)

Is the coordinate system for the Riemannian stress-free configuration \( \{ \xi^\alpha; \eta_{\alpha\beta} \} \) Euclidean? We calculated 6 components of the Riemann-Christoffel tensor. The component of \( R_{\xi\xi\xi} \) does not vanish and the other 5 components vanish. Therefore, the Riemannian stress-free configuration \( \kappa(\xi) \) with the metric tensor \( \eta_{\alpha\beta} \) is non-Euclidean.

### 2.3 Strain energy functions for passive and active stresses

For the passive state of the artery, the following strain energy function [5] was adopted:

\[ W_{\text{passive}} = \frac{\mu}{2}(I - 3) + \frac{k_1}{k_2} (\exp Q - 1), \quad Q = k_2[(1 - \zeta)(I - 3)^2 + \zeta(K - 1)^2] \]

(6)

where \( \mu \) and \( k_i \) are constants with the dimension of energy density, \( k_2 \), and \( \zeta \in [0,1] \) denote nondimensional values, respectively. The invariants are expressed as follows:

\[ I = \lambda_\theta^2 + \lambda_z^2 + \lambda_\rho^2, \quad K = \lambda_\theta^2 \cos^2 \varphi + \lambda_z^2 \sin^2 \varphi \]

(7)

where \( \varphi \) and \( \pi - \varphi \) denote mean angles of fibers against the circumferential direction with bimodal distribution although \( \varphi \) was not determined by a histological observation. Here, let \( \lambda_i \) \((i = \theta, z, r)\) denote the stretch ratio of a current configuration in each direction with reference to the Riemannian stress-free configuration:

\[ \lambda_\theta = \Lambda_\theta \tilde{\lambda}_\theta, \quad \lambda_z = \Lambda_z \tilde{\lambda}_z, \quad \lambda_r = \Lambda_\rho \tilde{\lambda}_r \]

(8)

where \( \tilde{\lambda}_i \) represent the stretch ratios of a current configuration \( \chi \) with reference to the unloaded state.

A strain energy function for active stress [6] was modified as follows:

\[ W_{\text{active}} = \frac{C}{2} \tanh(a_\theta \lambda_\theta^2 + a_z \lambda_z^2 + a_r \lambda_r^2 - a) \]

(9)
where $C$ represents a constant with energy density dimension and depends on concentration of vasoactive agonist, and $a_i$ and $a$ are nondimensional constants, respectively. The total stress under the activated state is derived from the sum of the passive and active strain energy functions as follows:

$$W_{\text{total}} = W_{\text{passive}} + W_{\text{active}}$$

(10)

### 3 RESULTS AND CONCLUSIONS

Outer radius vs intraluminal pressure and axial force vs intraluminal pressure relationships of artery were well fitted to the experimental results for the passive and active conditions using Cauchy stresses derived from the present strain energy functions:

$$P_i = \int_0^r (\sigma_{\theta\theta} - \sigma_{rr}) \frac{dr}{r}, \quad F_z = 2\pi \int_0^r \left[ \sigma_{zz} - (\sigma_{\theta\theta} + \sigma_{rr}) / 2 \right] r dr$$

(11)

![Fig. 2](image)

**Fig. 2** Outer radius vs intraluminal pressure (a) and axial force vs intraluminal pressure (b). Curves were calculated considering circumferential and axial residual strains.

Material parameters of the strain energy functions were estimated by nonlinear regression. Distributions of stretch ratios and stresses were computed considering (1) only circumferential residual strain and (2) both circumferential and axial residual strains. The difference between the results on the assumptions (1) and (2) was not so large. However, the axial stretch ratio was constant through the arterial wall on the assumption (1) and it increased from the inner surface to the outer surface through the arterial wall on the assumption (2).

### REFERENCES


MODELLING THE DEFORMATION BEHAVIOR OF STOMATOCYTE, DISCOCYTE AND ECHINOCYTE RED BLOOD CELL MORPHOLOGIES DURING OPTICAL TWEEZERS STRETCHING

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SUMMARY

A coarse-grained (CG) red blood cell (RBC) membrane model is used to investigate the deformation behavior of stomatocyte, discocyte and echinocyte morphologies during optical tweezers stretching. First, the numerically predicted discocyte deformation behavior is validated against analogous experimental observations, and then the numerically predicted stomatocyte and echinocyte deformation behavior is compared to the discocyte deformation behavior. The findings indicate that the CG-RBC membrane model is capable of accurately predicting the deformation behavior of stomatocyte, discocyte and echinocyte RBC morphologies during optical tweezers stretching, and an applicable tool to investigate the evolution of RBC behavior and membrane properties for different morphologies.

Key words: Red Blood Cell, Optical Tweezers Stretching, Stomatocyte, Echinocyte

1 INTRODUCTION

The RBC morphology affects its deformability, and optical tweezers stretching experiments can be used to investigate the global deformability of different RBC morphologies. Many optical tweezers stretching investigations have been conducted experimentally and numerically to study the discocyte RBC deformation behavior [1-3], but limited studies have been conducted on stomatocyte and echinocyte morphologies. Consequently, there is limited understanding of the influence of different RBC morphologies on its deformability and membrane mechanical properties. Improved understanding on above aspects during RBC morphology transformation can assist in identifying membrane structural modifications during in-vitro RBC storage and hematological disorders [4-6], which lead to RBC morphological changes and reduced deformability. In this study, a CG-RBC membrane model is proposed to investigate the global deformation behavior of different RBC morphologies.

2 METHODOLOGY

The coarse-grained RBC (CG-RBC) membrane model is built by a 2D triangulated network of \(N_v (= 2,562)\) vertices having \(N_t (= 5,120)\) triangular elements and \(N_s (= 7,680)\) adjacent vertex-vertex connections. The triangulated network is composed of only 12 vertices (=0.47%) having 5 adjacent vertex-vertex connections, whereas all the remaining membrane vertices (=99.53%) have 6 adjacent vertex-vertex connections. Therefore, the CG-RBC membrane has high quality of triangulation, and the effects of inhomogeneity can be considered minimal. The RBC membrane free energy is the collective contribution of in-plane stretching energy \(E_{\text{Stretching}}\), out-of-plane bending energy
(\(E_{\text{Bending}}\)), and constraints of reference cell surface area (\(E_{\text{Surface Area}}\)) and cell volume (\(E_{\text{Volume}}\)). \(E_{\text{Stretching}}\) is estimated based on the coarse-graining approach implemented by Fedosov et al. [3], and is given by

\[
E_{\text{Stretching}} = \sum_{j \in 1 \ldots N} \frac{k_p T l_{\text{max}} (3 x_j^2 - 2 x_j^3)}{4 p (1 - x_j)} + \frac{k_p}{(m - 1) t_j^m - 1}
\]

where, \(l_j\) is the length of \(j^{th}\) link, \(k_p\) is the Boltzmann constant, \(T (= 296.15 K)\) is the absolute temperature, \(l_{\text{max}}\) is the maximum link extension, \(p\) is the persistence length, \(k_p\) is the power function coefficient, and \(m (= 2)\) is an exponent such that \(m > 0\). \(x_j\) is defined as \(x_j = l_j / l_{\text{max}}\). Following the CG-RBC membrane model [3], the membrane shear modulus \([\mu_0 (= 4.0 \mu N m^{-1})]\) [3, 6] can be expressed as:

\[
\mu_0 = \frac{\sqrt{3} k_p T}{4 p l_{\text{eq}} x_0} \left(\frac{x_0}{2 (1 - x_0)}\right)^3 \left(1 - \frac{1}{4 (1 - x_0)^2} + \frac{1}{4}\right) + \frac{\sqrt{3} k_p (m + 1)}{4 l_0^m + 1}
\]

where, \(l_0\) is the equilibrium length of spectrin link and defined as \(x_0 = l_0 / l_{\text{max}} (= 0.45)\). The parameters \(k_p\) and \(p\) can be estimated for a given \(\mu_0\) and \(x_0\) using Equation (1) and Equation (2) at the equilibrium state of specified cytoskeletal reference state. \(E_{\text{Bending}}\) is estimated based on a discrete approximation of the Helfrich energy model [7] for a zero spontaneous membrane curvature, and is given by

\[
E_{\text{Bending}} = 2 \kappa \sum_{j \in 1 \ldots N} \frac{M_j^2}{\Delta A_j}
\]

where \(\kappa (= 2.5 \times 10^{-19} N m)\) [6, 8] is the bending modulus, \(M_j\) is the membrane curvature at the triangle-pair that shares the \(j^{th}\) link, and \(\Delta A_j\) represents the surface area associated with the \(j^{th}\) link. \(M_j\) and \(\Delta A_j\) are given by

\[
M_j = \frac{1}{2} l_j \theta_j
\]

\[
\Delta A_j = \frac{1}{3} (A_{T1} + A_{T2})
\]

where \(\theta_j\) is the angle between outward normal vectors to the triangles sharing \(j^{th}\) link, and \(A_{T1}\) and \(A_{T2}\) are the planer area of \(T1\) and \(T2\) triangles respectively that share the \(j^{th}\) link. \(E_{\text{Surface Area}}\) and \(E_{\text{Volume}}\) are estimated according to Equation (6) and Equation (7) [3, 9], and the first part of Equation (6) represents the total surface area constraint whereas the second part represents the triangular element surface area constraint.

\[
E_{\text{Surface Area}} = \frac{1}{2} k_A \left(\frac{A - A_0}{A_0}\right)^2 A_0 + \sum_{k \in 1 \ldots N} \frac{1}{2} k_a \left(\frac{A_k - A_{k,0}}{A_{k,0}}\right)^2 A_{k,0}
\]

\[
E_{\text{Volume}} = \frac{1}{2} k_v \left(\frac{V - V_0}{V_0}\right)^2 V_0
\]

where, \(A_0 (= 140.0 \mu m^2)\) is the reference membrane surface area [4, 5], \(A\) is the instantaneous membrane surface area, \(A_{k,0}\) is the reference area of \(k^{th}\) triangle, \(A_k\) is the instantaneous area of \(k^{th}\) triangle, \(V_0 (= 93.48 \mu m^3)\) is the reference cell volume [4, 5] and \(V\) is the instantaneous cell volume. \(k_A (= 1.0 \times 10^{-3} N m^{-1})\), \(k_a (= 5.0 \times 10^{-5} N m^{-1})\) and \(k_v (= 100.0 N m^{-2})\) represent the total surface area, local surface area and volume constraint coefficients, respectively. A bilayer-coupling model (BCM) based approach is used to obtain stomatocyte, discocyte and echinocyte morphologies, and to the membrane energy through bilayer-leaflet-area-difference \(E_{\text{Area-difference}}\) and total-membrane-curvature constraints \(E_{\text{Total-curvature}}\). \(E_{\text{Area-difference}}\) to maintain a reference bilayer-leaflet-area-difference \((\Delta A_0)\) is given by

\[
E_{\text{Area-difference}} = \frac{1}{2} \pi \kappa_{ad,0} \left(\frac{\Delta A - \Delta A_0}{A}\right)^2 A
\]

where, \(\kappa_{ad} (= 300.0 \kappa)\) is the bilayer-leaflet-area-difference constraint coefficient, \(D_0 (= 2.0 nm)\) is the monolayer thickness, and \(\Delta A\) is the instantaneous bilayer-leaflet-area-difference which is estimates as follows.

\[
\Delta A = 2 D_0 \sum_{j \in 1 \ldots N} M_j
\]

\(\Delta A_0/A_0(\%) = 0.105, 0.120\) and \(0.190\) for stomatocyte, discocyte and echinocyte morphologies, respectively. \(E_{\text{Total-curvature}}\) to maintain a reference total-membrane-curvature \((C_0)\) is given by
\[ E_{\text{Total-curve}} = \frac{1}{2} \frac{k_C}{D_0^2} \left( \frac{C - C_0}{A} \right)^2 A \]  

(10)

where \( k_C \) is the total-membrane-curvature constraint coefficient, and \( C \) is the instantaneous total-membrane-curvature which is estimated as follows.

\[ C = 2D_0 \sum_{j \in 1 \ldots N_3} |M_j| \]  

(21)

\( C_0 / A_0 \) for stomatocyte, discocyte and echinocyte morphologies, respectively. Therefore, the total free energy (\( E \)) of the RBC membrane is given by

\[ E = E_{\text{Stretching}} + E_{\text{Bending}} + E_{\text{Surface Area}} + E_{\text{Volume}} + E_{\text{Area-difference}} + E_{\text{Total-curve}} \]  

(12)

The optical tweezers stretching forces from \( 0 \rightarrow 200 \, \text{pN} \) is applied to the opposite ends of the cell [2, 3] along the principle axis of inertia through silica beads of \( 4.2 \, \mu m \) in diameter at \( 2.0 \, \mu m \) contact diameter, and stretched. The methodology of optical tweezers stretching implementation is adopted from Fedosov et al. [3], and the stable equilibrium RBC configuration is obtained at the minimum membrane free energy configuration under the externally applied stretching forces.

3 RESULTS AND CONCLUSIONS

The global cell deformability is numerically investigated for stomatocyte, discocyte and echinocyte morphologies through optical tweezers stretching deformation. Figure 1 presents the RBC membrane vertex points subjected to stretching force through attached silica beads of same size and at equal contact diameter. The contact area between RBC membrane and silica beads is similar for the stomatocyte and discocyte morphologies, whereas it is lower for the echinocyte. The spicules on the echinocyte cell surface reduce the contact between RBC membrane and beads, resulting in lower contact area.

Figure 1: Optical tweezers stretching implementation on (a) stomatocyte, (b) discocyte and (c) echinocyte morphologies

The variation of axial (\( D_A \)) and transverse (\( D_T \)) cell diameters [2, 3] at equilibrium is monitored at stretching forces analogous to optical tweezers stretching experiments by Suresh et al. [1]. The equilibrium stomatocyte, discocyte and echinocyte cell morphologies at 100 pN stretching force are presented in Figure 2. The stomatocyte and echinocyte morphologies have conserved their morphology characteristics during optical tweezers stretching, though the biconcave discocyte shape has lost its biconcavity. Figure 3 presents the percentage change in \( D_A \) and \( D_T \) cell diameters for stomatocyte and discocyte at similar \( \mu_0 \) and \( \kappa \) [10], along with analogous experimental observations by Suresh et al. [1]. The discocyte stretching response agrees with experimental observations, and has a maximum deviation of \( \sim 10.0 \% \) with respect to analogous experimental stretching, whereas the stomatocyte stretching response indicates higher global deformability than the discocyte. The echinocyte morphology shows the experimentally observed stiffer nature [11] at a membrane shear modulus above \( 2.5 \mu_0 \), which is comparable to experimental estimations [12].

Figure 2: Morphology deformation of (a) stomatocyte, (b) discocyte and (c) echinocyte RBCs under 40 pN optical tweezers stretching force

In conclusion, the study investigates the deformation behavior of stomatocyte, discocyte and echinocyte morphologies under optical tweezers stretching, using a coarse-grained red blood cell membrane model that agrees well with analogous experimental observations. Therefore, the current
model is an applicable tool to further investigate the evolution of RBC behavior and membrane properties for different morphologies.

Figure 3. Numerically predicted change in $D_A$ and $D_T$ cell diameters for stomatocyte and discocyte morphologies at similar $\mu_0$ and $\kappa$ versus experimentally observed change in $D_A$ and $D_T$ for discocyte morphology by Suresh et al. [1]

REFERENCES

LIGHT PROPAGATION MODELS OF THE HUMAN NECK FOR PHOTOACOUSTIC IMAGING OF THYROID CANCER

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SUMMARY
We numerically investigated light propagation in the human neck model using the radiative transfer equation (RTE) and diffusion equation (DE), and influences of the light propagation models on pressure propagation for applications to photoacoustic imaging of the thyroid cancer. The DE results deviated from the RTE results especially around the trachea (void region) and near the source position. However, the difference around the trachea less influenced pressure propagation because little photoacoustic pressure was generated in the trachea. The results suggest the applicability of the DE around the trachea, although the RTE-calculation is necessary near the light source.

Key words: quantitative photoacoustic tomography, light and pressure propagation models

1 INTRODUCTION
Photoacoustic tomography (PAT) enables non-invasive imaging of various kinds of tissue volumes and organs in high resolution based on the photoacoustic effect. Moreover, quantitative PAT (qPAT) has been extensively discussed, which relies on the mathematical models of light and pressure propagation and reconstructs a spatial distribution of the optical absorption coefficient. Recently, PAT has been applied to thyroid cancer imaging, and it can improve image qualities of the thyroid compared with the conventional ultrasound tomography [1]. Hence, it is expected that qPAT can offer further improvement of the imaging qualities. For the application of qPAT to the thyroid cancer imaging, one needs accurate and efficient models of light and pressure propagation in the human neck.

A light propagation model for qPAT is usually in the steady-state because the time-scale of light propagation in the order of pico-second is much faster than that of pressure propagation in the order of micro-second. The radiative transfer equation (RTE) can provide accurate descriptions of light propagation in a length scale of the mean-free path. Because of its integro-differential form with a multi-variable function, however, the numerical calculation of the RTE suffers from the high computational loads. To reduce computational loads, the photon diffusion equation (DE) has been widely used [2], which is the diffusion approximation of the RTE. Nevertheless, the DE is invalid at several conditions such as a region near the source position and void region where light is less scattered and absorbed. As a first step toward a construction of the accurate and efficient model of light propagation in the 3D human neck, it is significant to examine light propagation in a 2D human neck model based on the RTE and DE. Recently, light propagation in the 2D human neck model was numerically investigated using the time-dependent RTE [3] for diffuse optical tomography. Then, the complicated light propagation in the human neck was observed mainly due to a difference of the optical properties between the trachea (void region) and the other tissue regions; and refractive-index mismatch
at the trachea boundary. Meanwhile, few investigation is reported for numerical calculation of light propagation in the human neck using the steady-state RTE.

In this paper, we numerically investigated light propagation in the 2D human neck model using the steady-state RTE and DE. Also, we examined influences of the light propagation models on pressure propagation.

2 NUMERICAL MODELS AND CALCULATION METHODS

2.1 Human neck model

We used the 2D human neck model, constructed in our previous research from MR image of adult woman as shown in Fig. 1(a). The human neck consists of a background tissue, trachea, spine, spinal cord, blood vessels, and absorber. The absorber, which is a model of the thyroid cancer, is located between the front surface of the neck and trachea: widths in $x$- and $y$-axis are approximately 1.0 cm and 0.3 cm, respectively; and its absorption coefficient was set as 1.0 cm$^{-1}$ and the other optical properties are the same as the background tissue. The optical properties of the human neck model except the absorbers were referred to [3]. For the finite element analysis, triangular elements meshes in the human neck model were generated by Gmsh with a homogeneous mesh size of 0.1 cm.

The light source was located at the front surface of the neck, $(x, y) = (6.7 \text{ cm}, 12.4 \text{ cm})$ as shown in Fig. 1(b). The curved detector array for photoacoustic pressure was considered at the front surface of the neck as shown in Fig. 1(b), which is based on the geometry of the measurement setup [1].

2.2 Radiative transfer equation

In 2D, the steady-state RTE is formulated as

$$\Omega \cdot \nabla I(r, \Omega) + \mu_t(r) I(r, \Omega) = \mu_s(r) \int_{S^2} d\Omega' \Theta(\Omega' \cdot \Omega') I(r, \Omega') + q(r, \Omega),$$  

where $I(r, \Omega)$ in J \cdot cm$^{-1}$ \cdot rad$^{-1}$ represents the light intensity as a function of spatial location $r = (x, y)$ in cm for a 2D Cartesian coordinate system and angular direction, $\Omega$; $\mu_t = \mu_a + \mu_s$; $\mu_a(r)$ and $\mu_s(r)$ in cm$^{-1}$ are the absorption and scattering coefficients, respectively; $\Theta(\Omega', \Omega)$ in rad$^{-1}$ is a phase function with $\Omega'$ and $\Omega$ denoting the incident and scattered directions, respectively; and $q(r, \Omega)$ in J \cdot cm$^{-2}$ \cdot rad$^{-1}$ is a source term. For the formulation of $\Theta(\Omega' \cdot \Omega')$, we employed the 2D Heney-Greenstein phase function, which specifies anisotropy of light scattering by the anisotropic parameter $g$. For simplicity, $q(r, \Omega)$ was set as an isotropic point source. As a boundary condition, we considered the refractive-index mismatch at the external neck and trachea boundaries.

In the RTE calculation, we employed the finite element and discrete ordinates methods. The streamline upwind/Petrov-Galerkin method was employed for spatial discretization and the extended trapezoidal rule for angular discretization, where the total number of angular direction was 48. The discrete form of the RTE was solved iteratively by Bi-CGSTAB method in the C++ programming language. The tolerance error was $10^{-16}$. The implementation scheme for the refractive-index mismatched...
boundary condition was referred to [4]. The numerical schemes of the RTE were verified by the analytical solution of the RTE in a homogeneous medium and that of the DE in a homogeneous circular medium.

2.3 Diffusion equation

The steady-state DE is given by

$$-\nabla \cdot D(r) \nabla \Phi(r) + \mu_a(r) \Phi(r) = q_0(r),$$

where $\Phi(r) = \int d\Omega I(r, \Omega)$ represents the optical energy density in $J \cdot cm^{-1}$; $D(r) = [2\mu_s(r)(1 - g(r))]^{-1}$ the diffusion coefficient; and $q_0$ an isotropic source term.

We implemented the Robin boundary condition, which is the diffusion approximation of the refractive-index mismatched boundary condition. We employed the Galerkin method for the finite element calculations. The other details were the same as the RTE calculation.

2.4 Photoacoustic wave equation

When thermal and stress confinements are satisfied, pressure propagation is given by the photoacoustic wave equation (PWE):

$$\left( \nabla^2 - \frac{1}{v_s^2} \frac{\partial^2}{\partial t^2} \right) p(r, t) = -\beta C_p H(r) \frac{\partial}{\partial t} \delta(t),$$

where $p(r, t)$ in Pa represents photoacoustic pressure, $v_s$ in $cm \cdot \mu s^{-1}$ the speed of sound, $\beta$ in $K^{-1}$ the thermal coefficient of volume expansion and $C_p$ in $J \cdot kg \cdot cm^{-3}$ the specific heat capacity at constant pressure, and $\delta(t)$ the Dirac delta function. Also, $H(r) = \mu_a(r) \Phi(r)$ in $J \cdot cm^{-2}$ represents the heat function generated from the optical absorption. The initial pressure is given as $\Gamma(r) \mu_a(r) \Phi(r)$, with the Grüneisen parameter, $\Gamma = \beta v_s^2 / C_p$. In the PWE calculation, we employed the k-Wave solver under an absorbing boundary condition [5]. The k-Wave solver requires three acoustic properties; $(v_s, \Gamma, \rho)$ in $kg \cdot m^{-3})$. Here, the three acoustic properties of the trachea (air) and the other tissue regions were set as $(3.53 \times 10^{-4}, 0.40, 1.14)$ and $(1.52 \times 10^{-2}, 0.20, 9.93 \times 10^2)$, respectively.

3 NUMERICAL RESULTS AND CONCLUSIONS

3.1 Light propagation in the human neck

In this subsection, we discuss the spatial distributions of the optical energy density, $\Phi(r)$, calculated by the RTE and DE as shown in Figs. 2(a) and (b). Local absorption by the blood vessels was observed for both the light propagation models. Also, light penetration inside the neck was enhanced due to the trachea (void region) for both the models. Nevertheless, the DE results deviated from the RTE results around the trachea and near the source position. This is because of a breakdown of the diffusion approximation around the regions; and because of the difference in the trachea boundary treatments between the RTE and DE: the precise treatment for the RTE while no treatment for the DE.
3.2 Pressure propagation in the human neck

We examined the influence of the difference in the light propagation models on the pressure propagation in the human neck. Figure 3 shows the temporal profiles of photoacoustic pressure at the detectors, D1 to D4, based on the RTE and DE with/without absorbers, respectively. The profiles resulted in accumulations of a bipolar pulse generated at each position, and its positive and negative peak values were determined by $\Gamma \mu_a \Phi$. Hence, the pressure generated inside the trachea was negligibly low while the pressure generated around the light source and absorbers were high; e.g., in D1, the broad positive peak approximately from 12.0 to 13.0 $\mu$s and the sharp peak at 13.7 $\mu$s come from the light absorbers and source, respectively. Additionally, due to a difference in the acoustic properties between the trachea and other tissue region, the pressure reflected at the trachea boundary and its phase was reversed. As shown in Fig. 3, the existence of the absorbers strongly influenced the profiles for both the light propagation models. Meanwhile, a difference in the models for the trachea less influenced pressure propagation. These results suggest the applicability of the DE around the trachea as a light propagation model, although the RTE-calculation is necessary near the light source.

4 ACKNOWLEDGEMENTS

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REFERENCES


COMPREHENSIVE BIOMECHANISM OF IMPACT RESISTANCE IN THE CAT’S PAW PAD

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SUMMARY

In this paper, we investigated the impact resistance biomechanism of the cat’s paw pad, using mechanical testing, section staining technique, micro-CT scanning, and finite element analysis. The results showed that the adipose compartment, which comprises adipose tissue enclosed within collagen septa, in the subcutaneous tissue presents an ellipsoid-like structure, and we further interpreted the energy absorption biomechanism of the paw pad during impact. This comprehensive study can accordingly provide new inspirations of shock-absorbing composite materials in engineering.

Key words: paw pad, impact resistance, ellipsoid-like structure, biomechanism

1 INTRODUCTION

Cats are generally acknowledged to have extraordinary athletic ability, especially in jumping, through natural selection. When striking the ground, they can land smoothly, without any injury, though they are subjected to large impact forces, as high as several times their body weight [1]. It is believed that the paw pads play a protective and load-bearing role during landing since they are the only body parts that touch the ground. Indeed, most sporty members of the Felidae family (including cats, tigers, leopards and so on) are extant representatives of the padded foot. The cat paw pad consist of digital and metacarpal pads, which are usually located beneath distal interphalangeal joints and metacarpophalangeal joints, respectively [2]. It is logical to argue that cats mainly rely on the metacarpal pads to absorb impact energy because they have relatively long carpals and tarsals as well as large metacarpal pads.

In the past few decades, a large number of studies have been done on the mechanical properties of human heel pads, revealing the nonlinear, visco-elastic mechanical behavior [3-5]. Moreover, the heel pad comprises adipose tissue enclosed within collagen septa, forming many small compartments, which are considered to be many small hydrostatic systems [6, 7]. Ker et al. [8] found that mechanical properties of heel pads are almost impervious to strain rate and temperature, suggesting that there is no bulk fluid flow between the small compartments. Therefore, the compartment can be regarded as filled with fluid and the total volume remains unchanged, but deformation occurs during load-bearing. Nevertheless, there have been few systematic studies on the biomechanical behaviour of cat paw pads. Alexander et al. [9] conducted the numerical simulation and in vitro dynamic compression tests on the paw pads of some mammals, and argued that the paw pads should have a variable mechanical property, so as to prevent the excessive ground peak reaction force and enhance stability and robustness under vibration. Chi, K.J. [10] investigated a large number of studies on functional morphology and biomechanics of mammalian footpads, and concluded that the footpads should have a certain flexibility, stiffness and damping, in order to absorb energy, transfer the ground reaction force and maintain stability, respectively.
However, to our knowledge, there were lack of comprehensive and comparative studies on cats’ paw pads and no quantitative investigation of the micromechanics of paw pads has been published. The objective of this paper is therefore to study the comprehensive biomechanism of impact resistance in the cat’s paw pad. In this study, a mechanical testing system was used to observe the macroscopic mechanical properties at different vibration frequencies, and the microstructure were investigated using section staining technique and micro-CT scanning. Finite element (FE) models of ellipsoid-like and cylindrical (for control) adipose compartments, which are considered to be small hydrostatic systems, were established to study energy absorption mechanism. The results of this study will help to interpret and understand the impact resistance biomechanism of cat paw pads. A more practical motivation for this study is to provide useful information for the future development of impact resistant biomaterials.

2 METHODOLOGY

2.1 Ethical statement

All experimental procedures were approved by the Science and Ethics Committee of Beihang University.

2.2 Mechanical testing

Five metacarpal pads were subjected to dynamic compressive tests, using Instron E10000 test machine. The actuator was made to move up and down sinusoidally under position control, so that fluctuating compressive forces acted on the pads. The loading frequencies were 0.11 Hz, 1.1 Hz, 11 Hz, respectively. Forces and displacements were recorded as outputs, and each test was allowed to run for at least 5 cycles, before a record was made.

2.3 Histological examination

The metacarpal pad specimens were fixed in 10% neutral buffered formalin for 48 hours and then cut into twenty 1-mm-thick slices in the sagittal and transverse planes. The 1-mm-thick slices were washed in distilled water, dehydrated with alcohol and embedded in paraffin for 3 hours at 60°C. The paraffin tissue blocks were cut into 10-µm-thick slices and then stained with haematoxylin and eosin stain for histological examination.

2.4 Micro-CT scanning

The metacarpal pad specimens were scanned by micro-CT (Skyscan1272, Skyscan, Belgium) at a spatial resolution of 8 μm. The scanned Dicom images were then imported to Mimics for threshold segmentation, and the analysis area was selected for 3D reconstruction.

2.5 Finite element analysis

In this paper, we established ellipsoid shell and cylindrical shell (for control) models with a thickness of 1mm, which had the same volumes. Moreover, the shell models were filled with incompressible water, which therfore were considered to be hydrostatic systems. Based on the previous cat jumping experiment, a sinusoidal force with a frequency of 1Hz was applied to the top of the two models. The effective stresses, maximum displacements and shape change of the two models in the whole fluid-solid coupling analysis step were recorded and analyzed.

3 RESULTS AND CONCLUSIONS

The mechanical tests on paw pads showed that stiffness increased roughly in proportion to strain. It could be predicted that the ground reaction force, however large, can not reduce the pad thickness zero. Besides, the behaviour the energy dissipation and stiffness at any particular load, changed little over a wide range of frequencies, appears similar to rubbery polymers. Moreover, mechanical
properties were almost impervious to strain rate, suggesting that there was no bulk fluid flow between the small compartments. The adipose compartment of cats therefore can also be regarded as a model, which is filled with fluid and fixed volume, but shape deformation occurs during load-bearing.

Histologically, it was found that there were many collagen fibers, elastic fibers, and fat cells in the subcutaneous tissue, resulting in a large number of adipose compartments surrounded by collagenous membranes. Furthermore, after micro-CT scanning and 3D reconstruction, we found that the adipose compartment presented an ellipsoid-like structure, with a decreasing area from the middle to the two ends.

Additionally, the finite element results showed that the ellipsoid-like structure had larger displacement in the early stage of impact, which could absorb more energy and prevent instability at touchdown, while the cylindrical structure was more resistant to deformation. Moreover, the effective stress of the ellipsoid-like compartment decreased gradually from both ends to the middle, making it change to a cylindrical shape, which had greater resistance to deformation, so we speculated that this is the reason why the macroscopic stiffness increased with increasing time after contact.

The results of this study can provide biological inspiration for impact resistant foot pad to reduce human lower limbs injuries during landing. It should be noted that, in this study, we ignored the interplay between the adipose compartments, while in fact, the space arrangement of compartments would affect the energy absorption and shape change of pads during impact, so further study is warranted.

REFERENCES

PIXEL-REGION-DISSIMILARITY-BASED LEVEL SET METHOD
FOR IMAGE SEGMENTATION

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SUMMARY
Image segmentation plays an important role in medical image processing. There are various methods including the variational method, the Mixture Gaussian model, and so on to accomplish the work. In this article, we are willing to separate gray matter from MRI image. Since the results obtained from Chan-Vese model did not satisfy our purpose, we propose the pixel-region-dissimilarity functional to accomplish it. Finally, the simulation results show that our method is more robust than Chan-Vese model.

Key words: Image segmentation, Variational method, Level set model

1 INTRODUCTION
Image segmentation occurs in several areas. To deal with the problem, not only did the statistic method but the variational method was proposed.

In 2001, Chan and Vese [3] have proposed the energy functional for image segmentation. In their method, they asked the pixel values in each region be constant after proposed, which the result image is known as piecewise constant image. In the functional, with level set for defining regions and the difference between pixel value and the mean pixel value of regions. Their purpose is to find the level set function which minimize the functional. [4] [5]

Besides, there are other methods which based on minimizing the dissimilarity measurement in each regions. For example, the model proposed by L.Bertelli [6] which based on Chan-Vese functional and used pairwise similarity between data points in the functional. Nevertheless, this model needed $O(n^2)$ spaces in RAM for storing similarity matrix, where $n$ is the number of total pixels in image and spent much CPU time for computing.

2 METHODOLOGY
In [2] [3], the energy functional proposed by Chan and Vese is stated as follow.

$$E^{CV} (\phi) = \lambda_1 \int_{\phi>0} |I_r(x) - c_1|^2 dx + \lambda_2 \int_{\phi<0} |I_r(x) - c_2|^2 dx + \eta \cdot \text{length}(\phi = 0),$$
where
\[
\phi(x) = \begin{cases} 
> 0 & x \in \Omega_1 \\
0 & x \in \Omega_1 \cap \Omega_2 \\
< 0 & x \in \Omega_2 
\end{cases}
\]
is the level set function. \(I, I_r\) represent the image after processed, and raw image respectively. \(c_1, c_2\) are the mean of pixel values in the regions where \(\phi > 0\), and \(\phi < 0\) respectively.

Since the result Fig.2, which is performed by the Chan-Vese method is sensitive to noise, we proposed the pixel-region-dissimilarity functional.

First, we measure the dissimilarity of pixel to region
\[
M_{\alpha,\beta}(I_r(x), c_i) = \frac{\alpha + \beta |I_r(x) - c_i|^2}{\sum_{i=1}^{N} \alpha + \beta |I_r(x) - c_i|^2}, \quad i \in \{1, 2, 3...N\},
\]
where \(\Omega = \bigcup_{i=1}^{N} \Omega_i\), \(\alpha\) and \(\beta\) are dissimilarity coefficients; \(N\) is the number of regions to be segmented; \(c_i\) is the mean of pixel values in region \(\Omega_i\). In order to make the dissimilarity near contour to \(\frac{1}{2}\), we set \(\alpha\) as \(\frac{1}{2}\) and \(\beta\) as \(\frac{1}{1+|\nabla I_r(x)|^2}\). To interpret the meaning of the dissimilarity measurement, if \(|\nabla I_r(x)|\) is large, which means that the pixel \(I_r(x)\) is near the contour, where \(\beta\) is small, therefore the dissimilarity measurement will be \(\frac{1}{2}\).

Based on the dissimilarity function above, we propose a level set based energy functional.
\[
E_{\alpha,\beta}(\phi) = \gamma_1 \int_{\phi > 0} M_{\alpha,\beta}(I_r(x), c_1)dx + \gamma_2 \int_{\phi < 0} M_{\alpha,\beta}(I_r(x), c_2)dx + \eta length(\phi = 0),
\]
which is equivalent to
\[
E_{\alpha,\beta}(\phi) = \gamma_1 \int_{\Omega} M_{\alpha,\beta}(I_r(x), c_1)H(\phi)dx + \gamma_2 \int_{\Omega} M_{\alpha,\beta}(I_r(x), c_2)(1-H(\phi))dx + \eta \int_{\Omega} \delta(\phi)\nabla H(\phi)|dx,
\]
where \(H\) is the Heaviside function and we use smooth functions to approximate it.
\[
H_\epsilon(x) = \frac{1}{2} + \frac{1}{\pi} \arctan(x)\epsilon).
\]

By calculus of variations and the steepest descent method, we derived the following evolution equation,
\[
\frac{\partial \phi}{\partial t} = -\delta_\epsilon(\phi) \left[ \gamma_1 M_{\alpha,\beta}(I_r(x), c_1) - \gamma_2 M_{\alpha,\beta}(I_r(x), c_2) + \eta \kappa(\phi) \frac{\nabla \phi}{|\nabla \phi|} \right],
\]
where
\[
\delta_\epsilon(x) = H_\epsilon'(x) = \frac{1}{\pi} \frac{\epsilon}{x^2 + \epsilon^2}.
\]

Next, we use finite difference method to get the following scheme:
\[
\frac{\phi_{i,j}^{t+1} - \phi_{i,j}^{t}}{\Delta t} = -\delta_\epsilon(\phi_{i,j}^{t}) \left[ \gamma_1 M(I_{r_{i,j}}, c_1) - \gamma_2 M(I_{r_{i,j}}, c_2) + \eta \kappa(\phi) \right].
\]

As \(\beta = \frac{1}{1+|\nabla I_r(x)|^2}\) in dissimilarity function, we use central difference method to calculate \(|\nabla I_r|\).
\[
|\nabla I_{r_{i,j}}| = \frac{(I_{r_{i,j+1}} - I_{r_{i,j-1}})^2 + (I_{r_{i+1,j}} - I_{r_{i-1,j}})^2}{4}
\]
and \(\kappa(\phi)\) is the curvature of the level set \(\phi\), with the details of discretization are given in [3].
\[
M(I_{r_{i,j}}, c_k) = \frac{1}{2} + \frac{1}{1 + |\nabla I_{r_{i,j}}|^2} |I_{r_{i,j}} - c_k|^2
\]
\[
= \frac{1}{2} + \frac{1}{1 + |\nabla I_{r_{i,j}}|^2} |I_{r_{i,j}} - c_k|^2
\]
for \(k \in \{1, 2\}\).
3 RESULTS AND CONCLUSIONS

For numerical stimulation, we set $\Delta t = 1$, $h = 0.5$, $\gamma_1 = \gamma_2 = 10^{-2}$, $\eta = 10^{-5}$. As the change of $c_i$ is less than $10^{-5}$, the process will stop. The result is given below:

![Results and Conclusions](image)

Figure 1: Results of different methods.

![Local Performance](image)

Figure 2: Local performance of Chan-Vese and the proposed method.

<table>
<thead>
<tr>
<th>Method</th>
<th>Iteration</th>
<th>CPU time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chan-Vese method</td>
<td>77</td>
<td>11.83</td>
</tr>
<tr>
<td>Proposed method with $\alpha = \frac{1}{2}$, $\beta = \frac{1}{1 +</td>
<td>\nabla I_r(x)</td>
<td>^2}$</td>
</tr>
</tbody>
</table>

Table 1: Result information

In our purpose, we are willing to separate gray matter from raw image, which is colored in shin color. From the results above, we can see the result boundary obtained from our method between gray matter and the other is clearer than Chan-Vese method.

Even though our method costs much time and more iterations than Chan-Vese method, the result zero level set which is the contour does fit better then the result of Chan-Vese method.

Overall, in this article, we proposed a energy functional which chose the pixel-region- dissimilarity function rather than the difference between pixel and the mean of pixel values in each region. Then after applying the calculus of variation to the functional for optimizing, an evolution equation will be...
derived and using the finite difference method to accomplish the process. Finally, this method will be used for further problems and aim to reconstruct the brain surface in our future work.

REFERENCES


DEVELOPMENT OF FAST DATA PROCESSING SOLUTION TO DETERMINE LOCATION OF CONTACT BETWEEN TOTAL HIP REPLACEMENT BEARINGS

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SUMMARY

Total hip replacement (THR) positioning is crucial for the overall performance of the device. Associated contributors to failure include edge contact, where contact falls partially on the rim of the acetabular cup. This current study focused on the solution development for fast biomechanical data processing for establishing the risk of edge contact from a patient-specific perspective. The results of this study suggest that the solution can be used to identify patients at most risk for further \textit{in vitro} or \textit{in silico} tests. The solution can also be used to assist in optimum surgical positioning identification.

Key words: surgical positioning, patient biomechanics, edge contact

1 INTRODUCTION

Although THR surgery is considered one of the most successful orthopaedic interventions, failures which require revision surgery still occur. One of the known contributors to the failure of THR is edge contact, where the acetabular cup and the femoral head remain concentric but contact falls partially on cup rim. Failures associated with edge contact include rim damage \cite{1} and lysis, from increased wear, due to altered loading and torques \cite{2}. Edge contact, or dislocation in worst case, can be reduced with well-planned surgical positioning of the THR components. Lewinnek et al. \cite{3} proposed the use of ‘safe-zones’ measured on the anterior-posterior standing radiographs which was based on dislocation and impingement data. Since, many studies showed that these zones are not always suitable as the patient-specific functional cup orientation during daily activities is not taken into account \cite{4}. Previous \textit{in vitro} \cite{5} and \textit{in silico} studies \cite{6}, using mechanical joint simulators and finite element analysis respectively, have covered the implications of component malpositioning from device-specific perspective. However, these did not include patient-specific information such as contact force and pelvic motions. One of the reasons being the infeasibility of these pre-clinical tests for large parametric studies in terms of time and associated costs. Therefore the aim of current study was to develop a solution for highlighting the risk of edge contact from patient-specific perspective for large THR patient cohorts.

2 METHODOLOGY

To establish the risk of edge contact the proximity of contact area to acetabular rim was measured. To ensure fast data processing, minimising the use of FEA, the contact area was assumed to remain circular and not to change shape in the event of edge contact. The main solution algorithm was developed using MATLAB R2017a (\copyright\ The MathWorks, Inc., US). The flow-chart in figure 1b describes solution steps.

Location of the contact: Output and input data

The output of the developed algorithm consisted of the angles measured through the activity cycle. Two angles were measured, one from the pole of the acetabular cup to the centre of the contact and
second from the pole of the cup to the furthest edge of the contact area. Both are presented in the figure 1a and referred to as centre proximity angle and proximity angle respectively. The cup and head were assumed to remain concentric throughout the cycle according to the definition of edge contact.

The algorithm was tested using biomechanical gait data acquired from HIP98 database [7] for one patient, walking at self-selected speed. The data in the database was collected using bespoke instrumented THR implant and Vicon (Oxford Metrics plc, UK) motion marker system. For the solution development the data was extracted in the laboratory coordinate system, defined by inferior-superior (IS), medial-lateral (ML) and anterior-posterior (AP) axes shown in figure 1a. The data used for current study included hip-joint contact force vector components, locations of hip-joints centres, pelvis centre defined by L5-S1 vertebrae junction, and pelvic angles around ML and AP axes. The cup orientation was defined in laboratory coordinate system described in HIP98[7] database.

Centre proximity angle and proximity angle calculation

To find both aforementioned angles, equations for spherical cap, circular segment and angle between two vectors were used [8]. Three vectors were defined for the calculation with initial point at the origin of the cup 1a. These were contact centre, cup pole and contact area edge vectors. The direction of contact centre vector, was defined by three contact force components for each gait cycle point. The cup pole vector direction was determined by the position of the acetabular cup. The contact area edge vector direction was defined by the location of the furthest point of contact area from the cup pole for each gait cycle point. The centre proximity angle, $\theta$, was found through dot product of the cup pole, $\vec{Y}$, and contact centre angle, $\vec{X}$ (Eq. 1).

$$\theta = \cos^{-1} \left( \frac{\vec{X} \cdot \vec{Y}}{|X||Y|} \right) \tag{1}$$

To identify proximity angle, $\alpha$, the relationship between contact area and contact force was used in the algorithm. The magnitude of the contact area was represented by surface area of the spherical cap of the cup, $S_{\text{cap}}$. Knowing cap base radius, $r_{\text{cap}}$, and radius of acetabular cup, $R_{\text{cup}}$ the angle $\alpha$ was found. The cap base radius was derived from equation 2b.

$$\alpha = \sin^{-1} \left( \frac{r_{\text{cap}}}{R_{\text{cup}}} \right), \text{where} \tag{2a}$$

$$S_{\text{cap}} = \pi \left( r_{\text{cap}}^2 + \left( \frac{S_{\text{cap}}}{2\pi R_{\text{cup}}} \right)^2 \right) \tag{2b}$$
Cup orientation

To set up the stationary acetabular cup orientation the supporting algorithm was developed and based on the quaternion definition. The cup orientation was set using cup pole vector, and modified using two clinically relevant positions, inclination and version. Initial position of the cup was such that inclination and version axes aligned with AP and IS axes of the laboratory coordinate system respectively. The inclination was applied first, followed by version. To generate new vector position, $\vec{v}_{\text{new}}$, an angle $\gamma$, was applied by conjugation of cup defining vector, $\vec{v}$ and quaternion, $q$, representing the rotation through the angle around desired axis, $[u_x, u_y, u_z]$ (eq. 3).

$$\vec{v}_{\text{new}} = q \ast \vec{v} \ast q^{-1}$$

where

$$q = \cos \frac{\gamma}{2} + (u_x \hat{i} + u_y \hat{j} + u_z \hat{k}) \sin \frac{\gamma}{2}$$

FEA contact area

The relationship between contact force and contact area was established using FEA software, ABAQUS/CAE 6.14 (Dassault Systemes, France). This allowed to derive equation describing the relationship which was used in the main solution algorithm for variable contact force magnitudes. The THR model was represented by a hollow sphere with a rigid ball contacting inner wall. This allowed for maintenance of contact area circularity. The contact forces were applied between 0.2kN and 5kN based on forces reported in HIP98 database [7]. Elastic modulus was set to 1GPa, poisson’s ratio was set to 0.4, radial clearance was set to 0.5mm and cup diameter was set to 32mm [6, 7]. These settings broadly represent ceramic-on-polyethylene THR. The resultant contact force was applied vertically along the IS axis. The choice of mathematical functions to represent the relationship were exponential, Fourier series, Gaussian, linear, polynomial and power-law fitting models. The curve-fit displaying lowest root mean squared error was chosen, which in this case was power-law function (eq. 4).

$$\text{Contact Area}[mm^2] = 113 \ast \text{Contact Force}[kN]^{0.5}$$

Pelvic motion addition

Pelvic motion addition was separated into two parts. First, the dynamic pelvic coordinate system was generated for each gait cycle point, then the force vector was expressed in that system. Two methods of dynamic coordinate system construction were considered to accommodate for different data types. One method used hip joint and pelvic centre locations data and second method used measured pelvis angles. For the first method hip joint and pelvic centre was used as reference points for dynamic co-ordinate system generation based on axes definitions. ML$_{\text{dynamic}}$ axis was defined as the one connecting the left and right hip joint centres. The IS$_{\text{dynamic}}$ axis, was set to be perpendicular to ML$_{\text{dynamic}}$ axis and coincide with L5-S1 junction projection on the AP$_{\text{dynamic}}$ plane. And the AP$_{\text{dynamic}}$ axis, was set to be perpendicular to those defined previously.

For the second method the algorithm was designed so the rotation around each axis was applied to the coordinate system iteratively. The initial position of the pelvic dynamic coordinate system was assumed to be identical to the global coordinate system. The first test of the algorithm revealed that variation in order of applied angles results in different final positions of the coordinate system. This was attributed to the fact that the rotations in vivo are happening simultaneously, in other words they all happen as one rotation around some dynamic axis. To achieve the simultaneity, for each time step the three angles were set to be applied in small steps per gait cycle point. Number of suitable iterations, 10, was derived by testing the final positions of test vector with variable order of pelvic angle application. The angles were applied using quaternion definition described previously.

To suit both methods instead of rotating the cup defining vectors through the gait cycle, the force vector was rotated in relation to the motion of pelvis. To achieve that the force vector was translated into the dynamic pelvic coordinate system. The combination of three projections would give coordinate of three-dimensional projection of the force vector in dynamic pelvic coordinate system. For each gait cycle point, force unit vector was projected on each axis of dynamic coordinate system in isolation.
using dot product rule (Eq. 1) where axis, $Y$ must be a unit vector and $X$ is force vector. The new force unit vector was composed from $[\cos \theta_{ML}, \cos \theta_{AP}, \cos \theta_{SI}]$ according to direction cosines rule [8] where $\theta_{axis}$ is angle between force unit vector and coordinate system axis.

3 RESULTS AND CONCLUSIONS

The output for two cases using joint locations and angles is presented in figure 2. The angle around IS axis was not available for this database, hence the first method represents the contribution of all three pelvic motions and second method contribution of two motions. The case with no pelvic motion is also presented. From the figure it can be seen that pelvic motion as a gait feature affects the risk of edge contact. Developed solution can be used to establish the patient-specific biomechanical activity features which contribute to the risk of edge contact. Identified features could then be used in vivo and in silico pre-clinical tests. The algorithm has been successfully used to process 80 cases for parametric patient-specific study by Vasiljeva et al., [9]. In total data processing time took less than 24 hours. Similar to figure 2, the study by Vasiljeva et al., [9] revealed the importance of pelvic motions in consideration for component positioning, as well as the main motion features contributing to that effect.

REFERENCES

BIOMECHANICAL MODELS COUPLED TO TGF-β ACTIVATION IN THE ASTHMATIC AIRWAY

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SUMMARY

Asthma is a highly prevalent disease characterised by inflammation, airway hyper-responsiveness and airway remodelling. Current evidence suggests that bronchoconstriction, induced by airway smooth muscle cell (ASM) contraction, activates the pro-remodelling cytokine transforming growth factor β (TGF-β). This may further stimulate ASM contraction and proliferation. We hypothesise that accumulation of ASM and extracellular matrix (ECM) may be due to the up-regulation of TGF-β activation. We develop and validate a mathematical model of TGF-β activation that aims to recapitulate experimental results and ultimately provide insight into mechanisms that may operate in the asthmatic airway in vivo.

Key words: airway biomechanics, TGF-β, mechanotransduction, hyperelasticity

1 INTRODUCTION

Around 300 million individuals worldwide suffer from asthma [1], and it is estimated that over 250,000 of these people die prematurely each year as a result [2]. Asthma is the most prominent chronic disease among children, and yet despite its prevalence, the causes of asthma remain poorly understood [3].

Asthma is characterised by long-term recurrent episodes of intense inflammation, airway hyper-responsiveness, and airway remodelling. Airway hyper-responsiveness refers to excessive bronchoconstriction (narrowing of the airway) due to rapid contraction of ASM in response to a relatively low dose of contractile agonist [3]. Chronic inflammation causes swelling of the airway tissue and activation of contractile agonists which induce bronchoconstriction, resulting in overall restricted pulmonary function. Airway remodelling refers to the persistent structural changes to airway constituents that occur due to inflammatory injury repair, tissue thickening, and scarring [4]. Until recently, airway remodelling has been predominantly attributed to chronic inflammation. However, current experimental evidence suggests that bronchoconstriction-induced airway narrowing may play a key role in promoting remodelling [1]. Tissue strain induced by bronchoconstriction activates the regulatory cytokine TGF-β by unfolding a protein complex that stores the latent form of the molecule which is anchored to the ECM by transmembrane receptors known as integrins [5]. Preliminary experiments by our collaborators in the Division of Respiratory Medicine [6], indicate that cyclic stretching of precision-cut lung slices (PCLS) increases TGF-β activation. Activation of TGF-β may further stimulate contraction and proliferation of ASM, and deposition and remodelling of the ECM, thereby significantly affecting airway mechanics. In the healthy airway, regulatory mechanisms terminate this process, thereby maintaining homeostasis [7]. We hypothesise that in asthma there is a loss of this homeostatic state, resulting in excessive contraction of the ASM and accumulation of ECM proteins, further up-regulating TGF-β production through a positive mechanotransductive feedback loop. However, the mechanisms underlying cell-mediated TGF-β activation during an asthmatic exacerbation are not clear.
In this study we develop a biomechanical model of the PCLS experiment [6] to quantify mechanical stress experienced by the airway wall constituents in response to cyclic stretching and the consequent activation of TGF-β. In particular, we carefully assess the applicability of various simplifying assumptions of the PCLS geometry to determine the most appropriate representation for use in future modelling efforts.

2 METHODOLOGY

We have developed a biomechanical model of TGF-β activation that couples subcellular mechanotransductive signalling pathways to nonlinear hyperelastic models of airway mechanics. We use constrained mixture theory [8] to model an airway within the PCLS as a mixture of an active contractile ASM component and a passive nonlinear, incompressible, fibre-reinforced hyperelastic ECM component [9]. Contractile force generation is assumed to occur in the direction of the ASM bundle orientation and is driven by active TGF-β. ECM strain-stiffening occurs in the direction of the collagen fibre orientation and accounts for the recruitment of collagen fibres (from a crimped to uncrimped configuration) when stretched [2].

TGF-β activation is governed by an ordinary differential equation (ODE) model describing the rate of change of active TGF-β incorporating non-mechanical basal activation, contraction-driven mechanical activation, TGF-β-ASM binding, and natural degradation. Changes to the mechanical properties of the tissue, along with TGF-β-induced ASM contraction, generate differences between the stress states of the two hyperelastic constituents. Stress drives mechanical activation and leads to further activation of TGF-β in a positive feedback loop once a required stress threshold between the ASM and ECM constituents is surpassed (representing the strain which unlocks the complex encapsulating TGF-β).

We assume the deformation of the PCLS is axisymmetric, torsion free and under plane stress and is driven by applied displacement boundary conditions at the outer radius provided from the in vitro experiments [6]. Hence, the inner radius, upper and lower surfaces of the PCLS are free boundaries. Therefore, assuming there are no body forces acting on the tissue, we balance linear momentum subject to a zero radial stress inner boundary and an outer boundary with prescribed displacement conditions. To permit analysis of our hyperelastic model, we assume a deformation of the form

\[ r = \hat{r}(R), \quad \theta = \Theta, \quad z = \lambda_z(R)Z \]  

(1)

where \( R, \Theta \) and \( Z \) represent the reference configuration in cylindrical co-ordinates. Additionally, we apply two simplifying limits. Our first simplification (‘membrane model’) to the PCLS description is a membrane of infinitesimal thickness (setting \( \lambda_z(R) = 1 \) in 1). Axisymmetry allows us to describe the deformation of the membrane solely in terms of the radius, and thus our membrane approximation reduces the PCLS description to the simplest one spatial dimension form. Incompressibility requires the deformation to satisfy the equation

\[ \frac{dr}{dR} = \frac{R}{r}. \]  

(2)

Radial deformation \( r \) is dictated by the displacement outer boundary. We use the balance of linear momentum equations, the Cauchy Stress tensor and the inner boundary condition to determine the tissue pressure

\[ p = \frac{2W_1R^2}{r^2} - \int_{R_{in}}^{R} \frac{2}{R'} \left( W_1 + W_4 - \frac{W_1R'^4}{r^4} \right) dR'. \]  

(3)

The constituent and tissue stress components follow directly from pressure.

Our second approximation (‘finite thickness model’) to the PCLS description exploits the assumption that the thickness of the PCLS \( h \) is very small relative to the outer radius of the PCLS \( R_{out} \). We introduce asymptotic expansions for each of the variables and Cauchy stress components, via a small parameter \( \epsilon = \frac{h}{R_{out}} \ll 1 \), to determine the leading order and order \( \epsilon \) deformation. At leading order, plane stress and incompressibility reduce the balance of linear momentum equations to two coupled
ODEs

\[
\frac{dr^{(0)}}{dR} = \frac{R}{r^{(0)}\lambda_z^{(0)}} , \quad (4a)
\]

\[
\frac{d\lambda_z^{(0)}}{dR} = \frac{R}{R^2 + 2r^{(0)}\lambda_z^{(0)}} \left( 2\lambda_z^{(0)} - \frac{R^2}{r^{(0)}^2} \left( 1 + \frac{W_4^{(0)}}{W_1} \right) \lambda_z^{(0)} \frac{r^{(0)} \lambda_z^{(0)}^2}{R^2} \right) , \quad (4b)
\]

presenting a boundary value problem that is to be solved subject to the inner and outer boundary conditions. We satisfy zero radial stress at the inner radius with the leading order relation

\[
\lambda_z^{(0)}(R_{in}) = R_{in}^2 r^{(0)}_2 \lambda_z^{(0)}(R_{in}) . \quad (5)
\]

In Matlab, we use the solvers bvp4c and fsolve to solve (4) numerically subject to the known boundary condition at the outer radius while satisfying the constraint imposed by (5) at the inner radius. The leading order Cauchy stress components for the whole tissue and each of the constituents follow directly. Following the same methodology as above, we obtain the order \(\epsilon\) Cauchy stress components.

We assess the accuracy of these approximations by comparing our solutions to a full three-dimensional model simulated in the nonlinear finite element software FEBio \[10\]. Thereafter, we couple both of our PCLS approximation models to our TGF-\(\beta\) activation ODE and simulate TGF-\(\beta\)-mediated contraction and the subsequent change in effective mechanical properties as TGF-\(\beta\) progresses. Qualitative and quantitative comparisons are made between solutions from the approximations.

### 3 RESULTS AND CONCLUSIONS

Exploration of the passive tissue mechanics in our membrane and finite thickness model, prior to coupling to our TGF-\(\beta\) ODE model, reveal significant qualitative and quantitative differences in the distributions of stress within the constituents which are sensitive to the magnitude of ASM contractile force, the stiffness of ECM relative to that of ASM, and the amount of applied stretch. Importantly, the membrane model is constrained at the inner radius to deform according to the outer radial boundary condition as the deformation is entirely determined by satisfying incompressibility in response to the prescribed displacement. Thus, the presence of contractile force increases the stress within the tissue as any further deformation is not permitted by incompressibility. In contrast, the finite thickness model deforms in response to ASM contraction by contracting radially at the inner radius (Figure 1(iv)) and thinning axially at the outer radius (Figure 1(v)). In this instance, the finite thickness model allows the tissue to deform to resolve stresses, as observed in the FEBio model. As a result we see that the magnitude of Von Mises stress is larger in the membrane model than in the finite thickness model and FEBio model (Figure 1(iii)). As expected, increasing the contraction strength increases the overall stress state in both approximations and FEBio model and accentuates the deformation in the finite thickness and FEBio model.

We couple our PCLS model approximations to our ODE model and simulate the mechanical activation of TGF-\(\beta\) in the absence of stretch, in the presence of a fixed 15% stretch, and under cyclic stretching. We find that TGF-\(\beta\)-induced ASM contraction and ECM strain stiffening increases TGF-\(\beta\) activation as the PCLS deforms (Figure 1(vi)). These results highlight the underlying mechanisms of mechanotransductive activation feedback due to airway deformation and is captured by both simplified PCLS models. Qualitatively, our results resemble experimentally observed behaviour and indicate that axisymmetric cyclic stretching increases TGF-\(\beta\) activation over the absence of stretch (Figure 1(vii)). Our findings suggest that exaggerated airway deformations and stiffening ECM, experienced in the asthmatic airway, are expected to give rise to further elevated levels of TGF-\(\beta\). We intend to couple our FEBio model to our ODE model in order to compare our current results.

Additional experiments in which 5, 10, 20 and 25% stretches are applied to PCLS will enable further validation of our coupled model of stress-induced TGF-\(\beta\) activation in vitro. Thereafter, we aim to extend our model towards an in vivo description of the resultant ASM accumulation, ECM deposition and corresponding modification to effective mechanical properties in response to contraction-induced
TGF-β activation. These predictions will be validated against measurements of airway remodelling obtained from a series of experiments in Ovalbumin- and Methacoline-challenged mice and will provide insight into mechanisms that may operate in the asthmatic airway in vivo.

Figure 1: Plots (i,ii) Cauchy stress components $\sigma$ and (iii) Von Mises stress for the PCLS tissue, stretched by 15%, plotted as functions of the deformed radius $r$, (iv) radial deformation $r$ and (v) axial deformation $z$ of the PCLS, stretched by 15%, plotted as functions of the undeformed radius in the reference configuration $R$, (vi) concentration of active TGF-β within the PCLS in the absence of stretch, presence of a fixed 15% stretch and cyclic stretching to a maximum of 15%. FEBio, FT and Membrane denote the FEBio, finite thickness and membrane model results respectively. All quantities are dimensionless.

REFERENCES


Reduced-order modelling for cardiovascular problems II
COMPUTATIONAL ANALYSIS OF THE PATHOLOGICAL CEREBRAL CIRCULATION BY THE REDUCED ORDER METHODS

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SUMMARY

We perform a computational analysis of the cerebral circulation in the case of the atherosclerosis and vascular tortuosity on the basis of patient data and anatomical features of the Circle of Willis.

Key words: cerebral circulation, atherosclerosis, Circle of Willis, 1D haemodynamics

1 INTRODUCTION

The two pathological factors play an important role in the development of insufficiency in the cerebral circulation, which is atherosclerosis and tortuosity of the carotid and vertebral arteries (CVA). Both factors produce energy losses and downstream velocity decrease. The individual anatomical features of the Circle of Willis (CW) impose additional variability in the analysis of possible side-effects. In this work, we perform computational analysis of cerebral blood flow (CBF) as a function of these factors. The possible side-effect of the pathological tortuosity (PT) is the blood flow decrease during the low-flow conditions. This pathology is observed in 30\% cases of the deaths from stroke. CW plays an important role during the atherosclerosis disease as it helps to redistribute and compensate CBF through the brain via collateral flow. A lot of people have anatomical variations, which are the absence of some part of the CW. It complicates the computational analysis of the CBF based on CTA and ultrasound velocity measurements. In this work, we use 1D model of haemodynamics and compare several lumped models of atherosclerosis. We also propose a lumped model of PT. The 1D structure of the vascular network is produced by the specific set of algorithms which takes CTA data and produces 1D graph [1, 2]. Our results include a computational study of the CBF variations scenarios accounting for the typical anatomical features of CW and stenosis placement. We also present a computational analysis of the CBF with the PT in the low-flow conditions due to hypotension.

2 METHODOLOGY

2.1 1D network model of the blood flow

The modern 1D approaches and reviews can be found in [3, 4]. Our 1D hemodynamics model is based on the model of viscous incompressible fluid in a network of elastic tubes [5].

\[
\frac{\partial \vec{V}}{\partial t} + \frac{\partial \vec{F}}{\partial x} = \vec{G},
\]

where \( t \) is the time; \( x \) is the distance along the vessel counted from the vessel junction point; \( \rho \) is the blood density (constant); \( A(t, x) \) is the vessel cross-section area; \( p \) is the blood pressure; \( u(t, x) \) is
the linear velocity averaged over the cross-section; \( f_{tr} \) is the friction force.

\[
p(A_k) - p_\ast = \rho_w c^2 f(A),
\]

where \( \rho_w \) is vessel wall density (constant);

\[
f(A_k) = \begin{cases} 
\exp\left(\frac{A_k}{A_{0k}} - 1\right) - 1, & A_k/A_{0k} > 1 \\
\ln A_k/A_{0k}, & A_k/A_{0k} \leq 1,
\end{cases}
\]

\( k \) is the index of the vessel; \( p_{ak} \) is pressure in the tissues surrounding the vessel; \( A_{0k} \) is the unstressed cross-sectional area. \( c_k \) is the velocity of small disturbances propagation in the vessel wall, which defines elastic properties of the wall. At the entry point of the aorta, the blood flow \( Q_H(t) \) is assigned. At the junctions of arteries to the continuity of the total pressure is imposed

\[
p_i(A_i(t, \bar{x}_i)) + \frac{\rho u_i^2(t, \bar{x}_i)}{2} = p_j(A_j(t, \bar{x}_j)) + \frac{\rho u_j^2(t, \bar{x}_j)}{2},
\]

where \( i, j \) are indices of the vessels; \( \bar{x} \) is the coordinate of boundary point of the vessel. Each terminal artery is connected to the venous pressure \( p_{veins} = 12 \text{ mm Hg} \) through a hydraulic resistance \( R_k \)

\[
p_k(A_k(t, \bar{x}_k)) - p_{veins} = R_k A_k(t, \bar{x}_k) u_k(t, \bar{x}_k).
\]

To complete the system we add the mass conservation and compatibility conditions of (1) (see [6]).

### 2.2 Atherosclerosis

Atherosclerosis plaques are simulated by different models. In the first model we introduce a separate vessel with decreased diameter, which is calculated basing on the degree of the stenosis \( \alpha \)

\[
d_{sten} = d_{non-sten}(1 - \alpha),
\]

where \( d_{sten} \) is the diameter in the stenosed part, \( d_{non-sten} \) is the diameter in an adjacent region. Parameter \( \alpha \) is determined from the CTA data. In the other models the plaques are simulated as specific pressure drop \( \Delta p \) or \( \frac{dP}{dx} \) conditions:

\[
\Delta p = \frac{288 \rho}{2 Re A_s^2} Q^2,
\]

\[
\Delta p = (R_1 + R_2)Q + (K_1 + K_2)Q^2,
\]

\[
\Delta p = \frac{K_v \mu}{2 \pi R^3} Q + \frac{K_l \rho}{2 A_0} \left( \frac{A_0}{A_s} - 1 \right)^2 Q |Q| + \frac{K_u \rho l_s}{A_0} \frac{dQ}{dt},
\]

\[
\frac{dp}{dx} = \left( \frac{8 \rho Q^2 B_1 B_2}{\pi^2 R^5} \right) \frac{dR}{dx} - \frac{60 \mu Q B_3}{\pi R^4},
\]

where \( Q = uA \) is a flow rate, \( Re \) is Reynolds number, \( R_1, R_2, K_1, K_2, B_1, B_2, K_u, K_l, K_t \) are constants, \( \rho \) is blood density, \( R \) is diameter of the vessel. Formula (7) is considered in [7], (8) in [8], (9) in [9, 10, 11], (10) in [12].

### 2.3 Pathological tortuosity

To account for the PT we modify friction force as

\[
f_{fr} = -\frac{4 \pi \mu}{A_k^2} \left( \frac{A_k}{A_0} + \frac{A_0}{A_k} \right) \left( 1 + \alpha_{fr} \kappa_k(x_k) \right), \kappa = \left| \frac{d^2 r(s)}{ds^2} \right|,
\]

where \( \kappa \) is a local curvature of the vessel, \( r(s) \) is a 3D curve equation, which is derived from CTA data, \( 0 \leq s \leq 1 \) is a parameter along the curve, \( \alpha_{fr} \) is parameter (constant), which is set according to the experiments [13]. In [11] we suppose that additional friction force occurs due to the Coriolis force
and centripetal force effect, which is proportional to the local curvature of the vessel. In the case of
the straight artery, the curvature $\kappa$ equals to zero and $11$ becomes the friction force for the straight
vessel, e.g. [5]. In the cases of the kinking and coiling PT we introduce a node with the empirical
pressure drop conditions

$$\Delta p = k_b \frac{U^2}{2},$$

(12)

$U$ is the upstream velocity; $k_b$ is the energy loss coefficient, which approximately can be set according
to the experiments in the rigid tubes [14]. It should be studied in the details in future work.

3 RESULTS AND CONCLUSIONS

3.1 Anatomical variations of the CW and atherosclerosis

To study the effect of the CW variations we attach the typical networks of the CW to the patient net-
works of the CVA closed CW, absence of the anterior communicating artery (ACoA), absence of the
right posterior communicating artery (RPCoA), absence of the right and left posterior communicating
arteries (RPCoA and LPCoA), absence of the RPCoA and absence of the ACoA, absence of the RP-
CoA and LPCoA and absence of the ACoA. We consider the effect of the atherosclerosis disease of
LICA, RICA, LVA and RVA to the blood flow through the main arteries supplying the brain (LMCA,
RMCA, LPCA, RPCA). Here we denote RICA and LICA as right and left internal carotid artery, RVA
and LVA as right and left vertebral artery, RMCA and LMCA as right and left middle cerebral artery,
RPCA and LPCA as right and left posterior cerebral artery, RPCoA as anterior communicating artery,
ACA as anterior cerebral artery. In all cases we observe, that, in the absence of atherosclerosis, the blood flow in the main arter-
ies is the same as in the case of the full CW. Anatomical structure of the CW substantially affects the
blood flow in the main arteries supplying the brain during atherosclerosis disease. In some cases, we
observe a noticeable but small decrease in the blood flow of about 2%-3%. One should pay attention
to these cases, since the more severe stenoses or intensive blood flow due to physical activity, mental
stress, hypertension, et. al. may cause a pronounced effect. In some cases removal of the stenosis
improves blood supply in one region but decreases it in another. This can lead to negative side-effects
of the possible treatment.

3.2 Pathological tortuousity

To study the effect of the PT we insert different types of the PT into RICA. We consider the straight
case (no tortuosity), C-type, S-type, kinking or coiling type and general case according to the patient
data (see table 1). The total length of the tortuous region remains the same in all cases. All values are
shown for the peak of the systole. We observe almost the same velocity drop and substantially greater
pressure drop in the case of PT relative to the straight case. It results in the blood flow redistribution:
The blood flow in the collateral path (LICA) increases, while the flow through the RICA decreases.
The pressure in the CW decreases. This effect is more pronounced in the case of the hypotension.

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for collecting the data and R. Pryamonosov for processing CTA data.
### Table 1: Blood flow in CVA in normal and hypotension conditions (stroke volume 55 ml and 45 ml.)

<table>
<thead>
<tr>
<th></th>
<th>Straight</th>
<th>Coiling</th>
<th>S-type</th>
<th>C-type</th>
<th>Patient</th>
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<tr>
<td>Pressure before tortuosity, mmHg</td>
<td>124/101</td>
<td>124/101</td>
<td>124/101</td>
<td>124/101</td>
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<tr>
<td>Pressure before tortuosity, mmHg</td>
<td>111/90</td>
<td>110/90</td>
<td>97/79</td>
<td>100/81</td>
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<tr>
<td>Pressure drop, mmHg</td>
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<td>14/11</td>
<td>27/22</td>
<td>24/20</td>
<td>24/20</td>
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<tr>
<td>Velocity before tortuosity, cm/s</td>
<td>50/40</td>
<td>48/40</td>
<td>42/34</td>
<td>42/34</td>
<td>44/36</td>
</tr>
<tr>
<td>Velocity after tortuosity, cm/s</td>
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<td>40/34</td>
<td>34/26</td>
<td>39/28</td>
<td>36/28</td>
</tr>
<tr>
<td>Velocity drop, cm/s</td>
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<td>8/6</td>
<td>8/8</td>
<td>6/6</td>
<td>8/8</td>
</tr>
<tr>
<td>$Q_{RICA}$ (tortuosity), ml/s</td>
<td>1.15/0.94</td>
<td>1.15/0.93</td>
<td>0.88/0.7</td>
<td>0.97/0.77</td>
<td>0.97/0.77</td>
</tr>
<tr>
<td>$Q_{LICA}$, ml/s</td>
<td>1.08/0.86</td>
<td>1.08/0.86</td>
<td>0.92/0.89</td>
<td>0.96/0.88</td>
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<tr>
<td>$Q_{ACA}$, ml/s</td>
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<td>1.08/0.87</td>
<td>0.92/0.73</td>
<td>0.96/0.76</td>
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<td>$P_{ACA}$, mmHg</td>
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<td>76/63</td>
<td>78/62</td>
<td>78/63</td>
</tr>
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</table>

### REFERENCES


APPLYING DIRECTOR THEORY TO THE MODELLING OF FLUID FLOW IN STRAIGHT AND CURVED PIPES

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SUMMARY

This work involves applying director theory to the modelling of fluid flow in straight and curved pipes. Director theory assumes that the velocity of the fluid can be approximated by a summation of weighting functions multiplied by vectors that are dependent on the coordinate following the centre-line of the pipe. The aim is to investigate whether this could be a useful approach for modelling blood flow in the human cardiovascular system. The approach allows for a more realistic geometric model than classical 1D approaches, but is computationally cheaper than full 3D simulations.

Key words: director theory, fluid, modelling, cardiovascular

1 INTRODUCTION

This work is about applying director theory (also known as Cosserat theory) to the modelling of fluid flow in pipes. The motivation behind this project is to explore if director theory could help the modelling of blood flow in the human cardiovascular system become a viable clinical tool. While it is possible to reconstruct 3D computational models of individual patients using non-invasive medical imaging techniques, only a section of this can be used for 3D CFD simulations, otherwise the computational effort becomes too great. This can be coupled with 1D modelling for the arterial branching. The aim is to find a good balance between computational cost and accuracy. The director theory approach is computationally cheaper than full 3D modelling but retains more information about the geometry of the pipes than classical 1D models.

2 METHODOLOGY

The idea behind director theory is to assume that the velocity of the fluid flow can be approximated by a series expansion of shape functions, which are generally polynomials of the cross-sectional coordinates, multiplied by vectors (called director velocities) that depend only on the coordinate following the centreline of the pipe and on time, as shown by Eq. (1). Integrated versions of the conservation of momentum and ‘director momentum’ equations are imposed.

\[ \mathbf{v}(\zeta^1, \zeta^2, \zeta^3) = \sum_{N=1}^{K} \lambda_N^{\zeta^1} (\zeta^1, \zeta^2) \mathbf{w}_N^{\zeta^3}(\zeta^3, t) \] (1)

There are a number of advantages to the director theory approach. The system of equations is closed at each order, meaning that no assumptions need to be made about the form of the nonlinear and viscous terms. It is a hierarchical theory, so the accuracy can be improved, at the cost of the simplicity of the equations. The theory allows for the description of curvature and torsion, as well as non-circular cross-sections. This results in a more accurate solution of the flow field as compared to classical 1D
models which are effectively straight rods. Preliminary discussion and comparison of director theory to classical 1D models are outlined in Robertson and Sequeira [1].

We began following the work of Caulk and Naghdi [2], taking a director approach to modelling fluid flow in a straight cylindrical pipe, where the radius of the pipe could vary along the coaxial direction. Satisfying boundary, incompressibility and integrated (over the cross-section) versions of the momentum equations, leads to a system of six partial differential equations dependent on the coaxial coordinate and time. These equations can be simplified for particular geometries or conditions, which in some cases leaves a system which can be solved analytically.

Then we began applying the theory to curved pipes, starting with a toroidally curved pipe, initially following the work of Green et al [3], later diverging from their approach in how the appropriate equations of motions are derived. We set up a local coordinate system that follows the curve of the pipe. The shape functions are assumed to be of polynomial form. To determine their exact form, the velocity expansion, for a chosen order, is substituted into incompressibility and boundary condition equations. The shape functions for \( N = 1 \) to \( N = 6 \) are shown in Fig. 2. As can be seen, cross-sectional flow does not enter until the sixth order. Once the shape functions have been determined, the director velocities are determined through the satisfaction of the integrated momentum equations. We employ Powell’s hybrid method to find solutions to these equations.

![Figure 1: The shape functions for order \( N = 1 \) to \( N = 6 \) in each of the \( \zeta^i \) directions.](image-url)
3 RESULTS AND CONCLUSIONS

In the most simple case of a straight cylindrical pipe of constant cross-section, following the work of Caulk and Naghdi, we were able to recover the Poiseuille solution through the director theory approach. We were also able to recover a decaying swirling solution in the straight pipe as seen in Fig. 2. This shows the advantage of the director theory approach over classical 1D modelling, where it is not possible to capture flow in the cross-section.

![Figure 2: Decaying swirling solution in a straight pipe.](image)

In the toroidally curved pipe, the flow field from our solutions, which can be seen in Fig. 3, matches the flow field from a 3D simulation created using STAR-CCM+. This is with a curvature ratio of 0.01 and a Reynolds number of approximately 2.

![Figure 3: Solution for a toroidally curved pipe of curvature ratio 0.01.](image)

Figures 4 - 6 show the contours of the velocity in the $\zeta^3$, $\zeta^1$ and $\zeta^2$ directions respectively in a cross-section of the toroidal pipe. The left images are from a 3D simulation created using STAR-CCM+. The right images are the solutions obtained through the director theory approach.

![Figure 4: Coaxial velocity contours in the cross-section of the pipe. Left: STAR-CCM+ simulation. Right: director theory approach.](image)
This provides a promising start to applying this approach to curved pipes. We can now begin to look at increasing the complexity of the curvature and including torsion into this theory, with the hope of building up to realistic geometries for blood vessels.

4 ACKNOWLEDGEMENTS

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REFERENCES


SIMPLE METRICS DISCRIMINATES PRECLINICAL DIASTOLIC DYSFUNCTION PATIENTS FROM CONTROL ONES

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SUMMARY

We present a novel index to discriminate patients with preclinical diastolic dysfunction (PDD) from control (C) ones. We use data of pressure waveforms (PWF) of 20 patients with PDD and data of PWF of 20 patients with normal diastolic dysfunction used as control. We find that, most of the abnormality of the PDD group is in the systolic portion of the waveform. We then use data of inflow signals for the same two cohorts of patients as input to a reduced 1-D model to study mechanisms. Our results suggest that simple metrics can be used to characterize the PWF and distinguish between certain medical conditions and a control group.

Key words: In-vivo pressure data, In-vivo flow data, Preclinical diastolic dysfunction, Pressure waveforms, Pressure decomposition, 1-D arterial haemodynamics; Generalized Darcy’s model.

1 INTRODUCTION

The pulse wave generated by the contraction of the left ventricle propagates in the arterial tree and is 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. Several studies have address the study of the shapes with different metrics [1]. The amount of indices that have been introduced in the literature is very large and introduction of new indices may only be relevant in the context of a specific medical condition.

Preclinical Diastolic Dysfunction has been broadly defined as a condition in subjects with left ventricular diastolic dysfunction, without the diagnosis of congestive heart failure, and with normal systolic function [2]. Even though PDD remains poorly understood, it has clinical significance, since PDD has been shown to progress to overt heart failure (HFpEF) [2].

In this work, we introduce an index that discriminates between PWF of patients with PDD, from that ones belonging to a control group. We use in-vivo PWF data measured of 20 patients with PDD and of 20 patients without this disease used as control. We have determined the value of our index in different time intervals of the PWF and found that most of the abnormality comes from the systolic portion of the waveform.

We then have used flows measured in-vivo in the aorta in the same two cohorts of patients to model pressure waveforms with a reduced 1-D analytical model [3] that has been assessed with 3-D numerical schemes [4]. Our analytical index, obtained from the modeled analytical PWF, also discriminates from the two cohorts of patients in the systolic part of the PWF.

Our aim is to show that simple metrics to characterize the PWF, can distinguish between certain medical conditions and a control group.
2 METHODOLOGY

2.1 Study Population

Two groups of patients were chosen from those recruited to be evaluated for hypertension at Guy’s and St Thomas’ Hypertension Clinic. Although subjects were referred for evaluation of hypertension, many of them were normotensive.

Left ventricular diastolic dysfunction leading to heart failure with preserved ejection fraction is a major clinical problem. $E/E'$ measurement, which is the ratio of the early diastolic velocity on transmitral Doppler ($E$) and the early diastolic velocity of mitral valve annulus obtained from tissue Doppler ($E'$), is one of the best imaging markers for evaluation of diastolic dysfunction. The $E/E'$ ratio has been shown as a good predictor of left ventricular diastolic dysfunction. In this work the $E/E'$ ratio was therefore used to define PDD.

Table 1 shows population characteristics: age, sex, body mass index (BMI), and characteristic values of the PWF: peripheral systolic blood pressure (pSBP) and diastolic blood pressure (DBP). As it can be appreciated in the Table, Group 1, used as Control, has small values of $E/E'$, while Group 2, corresponding to patients with PDD has relatively large values of $E/E'$.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1 (Control)</th>
<th>Group 2 (PDD)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>48.2 ± 15.4</td>
<td>48.3 ± 15.4</td>
<td>0.59</td>
</tr>
<tr>
<td>Sex, male %</td>
<td>55</td>
<td>45</td>
<td>0.53</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.9 ± 5.7</td>
<td>27.0 ± 4.1</td>
<td>0.60</td>
</tr>
<tr>
<td>pSBP, mmHg</td>
<td>131.5 ± 17.3</td>
<td>132.5 ± 15.8</td>
<td>0.59</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>77.6 ± 11.8</td>
<td>81.3 ± 10.6</td>
<td>0.12</td>
</tr>
<tr>
<td>$E/E'$</td>
<td>5.2 ± 0.8</td>
<td>8.0 ± 1.2</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Table 1: Population characteristics. P value for sex has been obtained with a $\chi^2$ test.

2.2 Hemodynamic Measurements

Hemodynamic measurements were performed as previously described in [5]: ‘Radial and carotid pressure waveforms were obtained by applanation tonometry performed by an experienced operator using the SphygmoCor system (AtCor, West Ryde, New South Wales, Australia). Approximately 10 cardiac cycles were obtained and ensemble averaged. Waveforms that did not meet the in-built quality control criteria in the SphygmoCor system were rejected. Brachial BP was measured in triplicate by a validated oscillometric method (Omron 705CP; Omron Healthcare, Japan) and used to calibrate radial waveforms and thus to obtain a mean arterial pressure through integration of the radial waveform. Carotid waveforms were calibrated from mean arterial pressure and diastolic brachial BP on the assumption of equality of these pressures at central and peripheral sites [6]. Ultrasound imaging was performed by an experienced operator using the Vivid-7 ultrasound platform (General Electric Healthcare, Little Chalfont, United Kingdom). Velocity above the aortic valve was recorded using pulsed wave Doppler obtained from an apical 5-chamber view. All ultrasound measurements were averaged over at least 3 cardiac cycles.’

2.3 Index for the average concavity of the PWF

The second derivative of a function is related to the concavity of the graph. A function that is convex (concave up) has a positive second derivative, while a function that has a negative second derivative is concave down, normally called concave. Indices using the second derivative in time had been used previously by Takazawa (see for example [7]), who studied particular points in the curve of the second derivative in time, and found relations between the values at those particular points. Here we propose a new index consisting of the average concavity of the PWF graph, in a certain time interval. We compute it by performing the time average of the second derivative in time of the PWF.
on that interval. Since to study PDD we are mainly interested in the systolic part of the waveform, we compute our averaged concavity index including a minus sign as

\[ C = - < \frac{d^2p}{dt^2} > |_{R_i} \]  

Figure 1 shows a typical pressure vs time PWF in which we have indicated 4 non-exclusive intervals. We have defined three intervals in the systolic portion of the waveform, all of them starting from the point where \( dp/dt \) is maximum, which is related to heart contractility [8]. The first interval, \( R_1 \), ends at \( p_1 \), a point associated with peak myocardial wall stress [9]; the second one, \( R_2 \), goes to the time of maximum value of the PWF, the third one, \( R_3 \), ends at the time of the dicrotic notch. Finally, interval, \( R_4 \), is defined in the diastolic part of the PWF. It starts at the diastolic peak and ends in the the last value of pressure measured for the cycle.

2.4 Reduce Modeling. Analysis of PWF obtained from measured inflows

We have used the analytical 1-D model presented in [3, 10] to model PWF. We have taken flows measured in-vivo in the aorta as inflows and modeled PWF for the two cohorts of patients. We have analyzed the same ranges of the PWF than for the in-vivo PWF. Examples of in-vivo flows, in-vivo PWF and modeled PWF, for extreme values of \( E/E' \), are shown in Fig. 2.

3 RESULTS AND CONCLUSIONS

Figure 3 shows a BoxPlot analysis of the average concavity index, \( C \), for the in-vivo PWF. The index measured in the systolic part of the PWF, namely, in ranges \( R_1 \), \( R_2 \), and \( R_3 \), presents paired-P values, \( pP < 0.05 \). This indicates that \( C \) is a reasonable index to discriminate between the two cohorts of patients. These results are mainly -but not exclusively- determined by the maximum value of \( dp/dt \), which also presents \( pP < 0.05 \) (see Fig. 4). This will be further explained during the presentation. On the contrary, in the diastolic part of the PWF, the index \( C \) measured in interval \( R_4 \), does not discriminate between the two cohorts of patients.

According to [2], a better characterization of PDD is needed, to identify risk factors for progression to overt heart failure, and to identify pertinence of therapeutic interventions to delay the progression to HFpEF. Our index \( C \), obtained from both, the in-vivo and the modeled analytical PWF, discriminates the two cohorts of patients in the systolic part of the PWF, indicating that this simple metrics, can distinguish between PDD and a control group. Modeled data will be analyzed during the presentation.

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$R_1 \ pP = 0.017$

Control: $8744 \pm 2645 \ \frac{\text{mmHg}}{s}$
PDD: $6982 \pm 2934 \ \frac{\text{mmHg}}{s}$

$R_2 \ pP = 0.005$

Control: $6209 \pm 3920 \ \frac{\text{mmHg}}{s}$
PDD: $3361 \pm 1817 \ \frac{\text{mmHg}}{s}$

$R_3 \ pP = 0.041$

Control: $2319 \pm 617 \ \frac{\text{mmHg}}{s}$
PDD: $1971 \pm 650 \ \frac{\text{mmHg}}{s}$

$R_4 \ pP = 0.259$

Control: $-51 \pm 93 \ \frac{\text{mmHg}}{s}$
PDD: $-76 \pm 68 \ \frac{\text{mmHg}}{s}$

Figure 3: Box-plots of index $C$ for Control an PDD patients, obtained from in-vivo measurements.

Figure 4: $dp/dt_{max}$ for in-vivo PWF, $pP = 0.004$.


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ASSESSMENT OF A SIMPLIFIED METHOD FOR THE CALCULATION OF CORONARY FLOW RESERVE WITH THE HELP OF CFD SIMULATIONS

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SUMMARY

This paper aims at analysing a simplified method for the calculation of coronary flow reserve (CFR) in stenosed coronary arteries. CFD computations were performed to test the reliability of the model with patient-specific models and measured pressure data. In this project nine patients were included in a retrospective manner. Although the model uses some rudimentary assumptions and just a few geometrical data, a strong and significant correlation ($p < 0.0001; r = 0.9775$) was found between the results of the numerical and the model approach.

Key words: CFR, FFR, CFD, TIMI-frame count

1 INTRODUCTION

Coronary artery disease (CAD) is a major health problem in modern populations and the main cause of death worldwide. Coronary stenosis occurs when a narrowing due atherosclerosis develops in the blood supplying arteries of the heart. As the number one public health concern, it is an extensively researched area and in the recent decades a number of newly discovered diagnostic methods emerged. The most recognised and recommended diagnostic measure is called invasive fractional flow reserve (FFR), which is the ratio of the cycle averaged pressures measured distally and proximally to the stenosis. Another widely used quantity in conjunction with FFR is the coronary flow reserve (CFR). By definition it is the ratio of the cycle averaged flow rates in the diseased artery during hyperaemia and rest. Currently, the invasive measurement of FFR is favoured by the European guidelines, and the value of 0.8 is considered as a threshold for the decision for intervention [4]. Although previous studies [3] have reported that FFR guided decision-making improves the subsequent medical outcome, above the threshold value a non-negligible risk of events can arise. This indicates a need to understand the various perceptions of the hemodynamic environment both in terms of pressure and flow field. A better understanding of the underlying phenomena could lead to better decisions for deferral or intervention which, in return could reduce the number of unnecessary interventions [1, 2, 3].

The purpose of this study was to delve deeper into the idea behind a simplified method that aims at quantifying the coronary flow reserve (CFR). The method uses the intracoronary blood pressure measurements and geometrical data, derived from angiographic images. To assess the reliability of the method, we compared the model results with patient-specific computational fluid dynamics (CFD) simulations.

2 METHODOLOGY

In this retrospective study nine patients (6 LAD, 1 CX and 2 RCA) were included. Invasive FFR measurements were carried out using a pressure wire (St. Jude Medical, St. Paul, Minnesota). Hyperaemic condition was induced by the administration of intracoronary adenosine. Proximal (aorta) and distal pressure traces were recorded for about 30-40 seconds from the starting point of the adenosin administration until the re-stabilisation of the resting condition.
2.1 Simple model

A dedicated software was used to reconstruct the angiographic images in 3D (QAngio XA Research Edition 1.0, Medis Specials bv, Leiden). The target vessels were further analysed to determine the geometric parameters depicted in Figure 1 such as cross-sectional areas and vessel segment lengths. In recent studies a good agreement was found between the total pressure loss measured by a pressure wire and an approximated pressure loss calculated by simplified equations [5, 6, 7, 8]. In general the total pressure loss of any flow resistance, like an (coronary) arterial segment can be calculated as the sum of two terms, a linear viscous friction and a quadratic flow separation term as follows:

$$\Delta p_{\text{Total}} = fQ + sQ^2$$

According to Figure 1, we can decompose a target vessel into three consecutive segments. Each of these segments have an average cross-sectional area and length that can be used to calculate the linear loss terms as a Hagen-Poiseuille pressure loss, assuming steady flow:

$$f = f_{\text{prox}} + f_{\text{sten}} + f_{\text{dist}}; f_{\text{segment}} = \frac{8\pi\mu L_{\text{segment}}}{A_{\text{segment}}^2}$$

where $\mu$ is the dynamic viscosity. The flow separation loss can be assessed by a Borda-Carnot type pressure loss. In this term only the exit loss due to the sudden cross-section expansion was taken into account and the entrance loss was neglected. Furthermore the remaining term uses the "minimal lumen area" for the estimation of flow separation related losses [9].

$$s = k_{\text{sep}} \rho \frac{1}{0.266} \left( \frac{1}{A_{\text{MLA}}} - \frac{1}{A_d} \right)^2 \text{ and } k_{\text{sep}} = 1.21 + 0.08 \left( \frac{L_p}{2D_{\text{ref}}} \right)$$

where the function $k_{\text{sep}}$ and the constant values are empirically determined and $D_{\text{ref}}$ is the reference diameter [9]. Rearranging Eqs. (1) we can calculate the flow rates (hyperaemic and resting) from the measured pressure differences and geometric data derived from the angiographic images. Then the CFR can be calculated by the definition.

2.2 CFD simulations

3D CFD analysis was carried out using a commercial finite volume solver (ANYSY CFX 17.2 ANSYS Inc, Canonsburg, USA) for all patient-specific geometries. First, 3D angiographic reconstructions were pre-processed then imported to ANSYS for numerical meshing and computation. The numerical meshes consisted 1.5 to 2 million cells on average with an appropriate number of boundary
layers adjacent to the wall. Both in the unsteady and steady state simulations the vessel wall was assumed to be rigid and the blood to be a Newtonian fluid. Spatial discretisation was set to be of second order and a convergence criterion of $10^{-6}$ was prescribed. In the steady state computations the hyperaemic and resting cycle averaged pressure differences were imposed as boundary conditions (total pressure difference on the inlet and static 0 Pa pressure on the outlet). The unsteady simulations utilised the measured aorta and distal pressure wave-forms on the inlet and the outlet boundaries respectively. According to this work-flow four computations were concluded for each geometry and the CFR values were then calculated from both the steady state and unsteady approaches (see Figure 2.)

![Diagram showing unsteady and steady state calculations](image)

Figure 2: The four computations from the patients specific data. Left: the unsteady calculations using the measured pressure waveforms. Right: the steady calculations using the cycle averaged pressures.

## 3 RESULTS

Simple statistical analysis was used to assess the correlation between CFR values calculated with the simplified method and CFD. A strong and significant correlation ($p < 0.0001; r = 0.9775$) was found between the simplified method and the steady state results. Interestingly, for those subjects with a CFR value lower than 2.0 (below the recognised threshold value) an even stronger relationship was found ($p < 0.00005; r = 0.992$). Based on the Bland-Altman analysis noticeable difference only occurs with the patients with non significant lesions (CFR is higher than 2.0). A less significant ($p < 0.0005$), yet still strong correlation ($r = 0.9342$) was found between the two CFD approaches.

![Graph showing correlation between simple method and steady state CFD results](image)

![Bland-Altman analysis results](image)

Figure 3: Left: Correlation between the simple method and the steady state CFD results. Right: Result of the Bland-Altman analysis.
4 CONCLUSIONS

The results of this investigation show that the simple model could be used to determine the coronary flow reserve. Overall, these results indicate that the estimation for CFR could be adequate, but caution must be exercised. Though the correlation analysis show a significant relationship on the level of flow rates non-negligible differences can exist. Since the simplified model applies just a few geometrical data, the flow rate estimation will be accurate in only those lesions which are relatively straight and symmetric (as the model considers a Borda-Carnot expansion). However, since the main goal of the current study was to determine the validity of this model for CFR estimation - which is defined as a ratio - the actual values in the nominator and denominator of the fraction do not have to be considered.

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REFERENCES


MATHEMATICAL MODELLING OF FLUID FLOW IN A JUNCTION OF THIN CHANNELS WITH APPLICATION TO HEMODYNAMICS

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SUMMARY
Development of adequate 1D models of circulatory blood system meets several serious obstacles and we will discuss some questions related to bifurcation nodes of the arterial tree, blood flow in capillaries and vessels with elastic walls. Using dimension reduction procedure, we propose a 1D model for the capillary system as a fractal graph whose edges are supplied with differential structure. We analyze the influence of defects of the vessel’s wall near the bifurcation point on the pressure drop matrix whose elements are included in the modified Kirchhoff transmission conditions. We exploit a 2D model describing the elastic behavior of the wall of a curved flexible vessel which takes interaction with surrounding muscle tissue and the fluid flow into account and we study the Stokes flow in this vessel.

Key words: hemodynamics, fluid mechanics, dimension reduction, asymptotic analysis

1 INTRODUCTION
Blood vessels form one of the most complicated and important systems in the human body, the circulatory system. It is exposed to various risks and is poorly amenable to medical treatment. The mathematical modelling of blood transport in arteries, veins, capillaries and other blood vessels is a classical problem which is still very relevant today, see, i.e., [1, 2].

We are interested in modelling the whole circulatory system, taking into account not just the blood vessels themselves, whose walls consist of several layers of anisotropic material, but also the interaction of the vessels with both the surrounding muscle material and the blood flow within.

During the past 30 years, considerable progress has been made in developing various asymptotic methods for problems in elasticity theory and hydrodynamics. These include the method of dimension reduction, which replaces a higher-dimensional model by another one of lower dimension. Another group of methods concerns so-called singular perturbed domains, which often involve the interaction of models of different limit dimensions in applications (cf. [3], [4] and many others).

One of the main goals of our research is to bring these modern asymptotic methods to bear on the modelling of the circulatory system with the aim of proposing a 1D model for the whole circulatory system which takes into account elastic properties of vessels and their interaction with surrounding muscle material.

2 METHODOLOGY
There is a lot of works dealing with flows on networks; see, i.e., the survey paper [5]. We consider blood flow in a vessel with an attached capillaries. The novelty of our study is to model the capillary
system as a fractal graph described by a set of scaling factors and the corresponding self-reproducing solutions for blood flow in such a fractal structure [6]. A fractal graph whose edges are supplied with ordinary differential equations obtained by the dimension reduction procedure from a 3D model of blood flow in thin vessels. The Kirchhoff transmission conditions must be satisfied at each interior vertex. The geometry and physical parameters of this system are described by a finite number of the scaling factors which allow the system to have self-reproducing solutions. Namely, these solutions are determined by the factors values on a certain fragment of the fractal graph and are extended to its rest part by virtue of these scaling factors. The main result is the existence and uniqueness of self-reproducing solutions, whose dependence on the scaling factors of the fractal graph is also studied. As a corollary we obtain a relation between the pressure and flux at the junction, where the capillary system is attached to the blood vessel. This relation leads to the Robin boundary condition at the junction and this condition allows us to solve the problem for the flow in the blood vessel without solving it for the attached capillary system.

We also consider a bifurcation of an artery. The blood flow is modelled using the standard Navier-Stokes equations. The influence of defects of the vessel’s wall near the bifurcation point on the pressure drop matrix is analyzed [8]. This is achieved by using classical shape optimization techniques. We calculate the material derivative in the case of oblong plaques or aneurysms (see Fig.1, a and b) and the topological derivative in the case of localized ones (see Fig.1, c and d). The pressure drop matrix was introduced in [9] as an integral characteristic of a junction of several pipes with absolutely rigid walls. It appears that the elements of this matrix are included in the modified Kirchhoff transmission conditions, which describe more adequately the total pressure loss at the bifurcation point of the flow passed through the corresponding junction of the pipes, see [10], [11].

In the paper [11] a 1D model of a fluid flow at a junction of thin vessels with rigid walls was developed. In particular, a new transmission condition at the bifurcation point was derived, which can be considered as a modification of the classical Kirchhoff condition. Clearly, the total flux at the bifurcation point is zero but continuity of the pressure is not so obvious. In fluid mechanics, one uses the total pressure loss in the flow passing the bifurcation point, see [7, 12]. An appropriate object to describe this pressure loss is the pressure drop matrix, elements of which are involved in the modified Kirchhoff conditions. This modification improves the model in several directions. First, the discrepancy of the approximation of 3D model by the 1D one is $O(e^{-\frac{h}{\rho}})$, where $h$ is the thickness of the vessel and $\rho$ is a positive constant. We remind that the application of the classical Kirchhoff conditions brings the discrepancy $O(h^3)$ for the velocities and $O(h)$ for the pressure. This difference is essential if we deal with a large system with many bifurcations. Second, the modified transmission conditions depend on the geometry of the bifurcation region.

We consider the Stokes system in an unbounded domain with cylindrical outlets to infinity and prove...
the unique solvability of the problem. For obtaining the asymptotic behavior of the solution we exploit special homogeneous solutions to the Stokes problem with non-zero flux and with a linear growth in the pressure at infinity. As a consequence, we obtain a definition of the symmetric pressure drop matrix $Q$, which plays a crucial role in the functioning of the bifurcation node.

We analyze the influence of certain defects (e.g., plaques, aneurysms) in the bifurcation node and close to it on the matrix $Q$. Using asymptotic analysis of elliptic boundary value problems in regularly (or singularly) perturbed domains we find the increments of the pressure drop matrix and also determine their signs.

We present a 2D model describing the elastic behavior of the wall of a curved flexible vessel. The wall has a laminate structure consisting of several anisotropic layers of varying thickness and is assumed to be much smaller in thickness than the radius of the channel which itself is allowed to vary. Our 2D model takes the interaction of the wall with any surrounding or supporting material and the fluid flow. The curvature and twist of the vessels axis as well as the anisotropy of the laminate wall present the main challenges in applying the dimension reduction procedure so plenty of examples of canonical shapes of pipes and their walls are supplied with explicit systems of differential equations in [14].

We use an existing 2D model of the vessel wall along with Navier-Stokes equations to model the flow through the channel while taking factors, namely, surrounding muscle tissue and presence of external forces other than gravity into account, see [15].

3 RESULTS AND CONCLUSIONS

A fractal graph model for capillaries is constructed. We proved the existence and uniqueness of self-reproducing solutions, whose dependence on the scaling factors of the fractal graph has also been studied.

We have considered a bifurcation of an artery. The influence of defects of the vessel’s wall near the bifurcation point on the pressure drop matrix has been analyzed. In reality the boundary layer phenomena predicts fast local changes to both velocity and pressure inside the bifurcation. Thus it is not appropriate for a 1D model to assume a continuous pressure. We present a modification to the classic Kirchhoff conditions, with a symmetric pressure drop matrix, that is more suitable for 1D flow models. An asymptotic analysis, that has been carried out previously shows that the new transmissions conditions has an exponentially small error.

The modified transmission conditions take the geometry of the bifurcation into account and can treat two outlets differently. The conditions can also be written in a form that is suitable for implementation in a finite difference solver. Also, by appropriate choice of the pressure drop matrix we show that the new transmission conditions can produce head loss coefficients similar to experimentally obtained ones, see [12].

To study the fluid-structure interaction we have presented and exploited 2D model of the elastic pipe shell while linearized Navier-Stokes equations are used to model the flow through the channel. Surrounding muscle tissues and presence of external forces other than gravity are taken into account. The model is obtained via a dimension reduction procedure based on the assumption of thinness of the vessel relative ti its length. Results of numerical simulations are presented to highlight the influence of different factors on the blood flow [13]. Asymptotic analysis gives us the leading order terms constituting the Stokes flow in this model [15].

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INVESTIGATING UTERINE ARTERY DOPPLER WAVEFORMS IN PREGNANCY USING CARDIOVASCULAR NETWORK MODELS

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SUMMARY

Doppler waveforms in the uterine arteries are clinically used to monitor the development of the placenta. Various indices have been developed based on these waveforms that are used as indicators for poor placental development. However, these indices are still not well understood. This study presents a framework that is used to create personalized computational models of the maternal cardiovascular system. A base-line 1D computational cardiovascular flow model is optimized toward a range of non-invasive clinical measurements for a group of 4 patients. The model manages to predict the characteristics in the shapes of the uterine waveforms. These modelling results will allow for a more detailed analysis of the mechanistic pathways that lead to changes in the waveforms.

Key words: Utero-ovarian model, Pregnancy, Optimisation, Maternal Circulation

1 INTRODUCTION

The maternal cardiovascular system undergoes significant physiological changes through the different stages of pregnancy. There is an increased arterial compliance of 35% [1], a decrease of total resistance of the peripheral beds, whilst can be an increase of cardiac output of up to 40%. Furthermore, the mean arterial blood pressure typically decreases early in pregnancy and the development of the placenta and fetus require a significant increase of blood supply to the uterus. This increase requires the utero-ovarian vascular beds to adapt appropriately and if this does not happen it can lead to some pregnancy related pathologies [2]. Various indices are used clinically [3] to assess the development of the utero-ovarian system and placenta during pregnancy, which are based on the doppler waveforms in the uterine arteries. However, there is only a limited knowledge on the mechanistic pathways that cause these indices to change.

In this work we aim to develop a framework that can be used to generate personalized cardiovascular models based on a range of non-invasive clinical measurements. These models can then be used to study the specific relations between the maternal systemic circulation and their utero-ovarian circulation. The study presents the optimization procedure required and shows the preliminary result on 4 patients, two of whom were known to develop pre-eclampsia later on in pregnancy.

2 METHODOLOGY

As a basis for the personalized models we chose our previously developed model [3,4,5]. This model is closed-loop and includes 513 1D vessels (systemic and pulmonary arteries and veins), 61 0D vascular beds and an elastance-based heart model with 4 heart valves. The model also contains a utero-ovarian network model with 20 arcuate branching off the uterine arteries and a further 50
radial/spiral arteries. Through an optimization procedure this “template” model is personalized towards the measurements of each patient.

Patient data was collected with NHS REC approval (11/NW/0426), and all patients were identified through the translational research clinics at St Mary’s Hospital, Manchester, UK. The clinical data used for the optimization in this study is given in Table 1.

Table 1: Patient data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Blood pressure (mmHg)</th>
<th>Heart rate (bpm)</th>
<th>Cardiac output (litres/minute)</th>
<th>Pulse Wave Velocity (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>103 65</td>
<td>109</td>
<td>6.1</td>
<td>7.7</td>
</tr>
<tr>
<td>2</td>
<td>131 93</td>
<td>104</td>
<td>7.3</td>
<td>9.4</td>
</tr>
<tr>
<td>3</td>
<td>124 78</td>
<td>89</td>
<td>3.5</td>
<td>7.3</td>
</tr>
<tr>
<td>4</td>
<td>136 92</td>
<td>108</td>
<td>7.3</td>
<td>6.6</td>
</tr>
</tbody>
</table>

In addition to this data, the uterine Doppler waveforms are also included. The optimization procedure has 2 stages:

1. Changes to the peripheral bed resistances, systemic arterial areas and total blood volume to reproduce blood pressures, heart rate and cardiac output with the model. After this stage the flow waveform at the aortic root (and therefore the cardiac output) is fixed in stage 2 where an open arterial system network (no veins or pulmonary circulation) will be used.
2. Further optimization will be performed similar to stage 1, but now the compliance of the systemic arteries and areas of the utero-ovarian system will be tuned until the blood pressures, pulse wave velocity and doppler waveforms are the same as the measurements.

At this point a personalized model of the patient has been created.

3 RESULTS AND CONCLUSIONS

Preliminary results of the framework look promising. For all four patients the algorithm framework converges to a solution within 1% of the measured parameters. Although the optimization towards the peak systolic and end diastolic velocities in the uterine artery is imposed in the algorithm the remainder of the waveform shape is not. However, due to the integration of the varied range of non-invasive measurements a similarly shape features of the velocity waveform is reproduced using the model as is shown in Figure 1 for patient 2.

![Figure 1: Doppler waveform for patient 2 as predicted by the model (left) against the Doppler waveform measured (right).](image)

Some preliminary information resulting from the models is displayed in Table 2. This shows that the adaptation of the systemic arterial areas and compliances results in the same values for the pulse wave velocity as measured. Furthermore, the optimization shows that the areas of the systemic arteries for the first 2 patients, who developed pre-eclampsia later in pregnancy, is larger than for the latter 2 patients. However, this trend could not be observed in the prediction of the arcuate artery size. Further research on larger numbers of patients is required to study the findings.
from the computational models in more detail, but will help in understanding the mechanistic pathways through which pathologies in pregnancy influence the measurements.

Table 2: Some parameters resulting from the personalized models for the 4 patients

<table>
<thead>
<tr>
<th>patient</th>
<th>PWV model</th>
<th>Scaling parameter for area of arteries</th>
<th>Arcuate artery diameters (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7.701</td>
<td>1.31</td>
<td>4.95</td>
</tr>
<tr>
<td>2</td>
<td>9.318</td>
<td>1.69</td>
<td>1.94</td>
</tr>
<tr>
<td>3</td>
<td>7.256</td>
<td>0.44</td>
<td>2.69</td>
</tr>
<tr>
<td>4</td>
<td>6.605</td>
<td>0.56</td>
<td>1.67</td>
</tr>
</tbody>
</table>

REFERENCES


BLOOD FLOW REDUCED-ORDER MODELING ACROSS MACROSCOPIC THROUGH MESOSCOPIC SCALES

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SUMMARY

We propose a hemodynamic reduced-order model bridging macroscopic and mesoscopic blood flow circulation scales from small arteries to capillaries. Representative network geometries are generated by means of stochastic growth algorithms constrained by statistical morphological and topological principles and are mathematically described by graphs. Different compliant structural models with respect to pressure loads are used depending on vessel walls thicknesses and structures. Nonlinear rheological properties of blood are also included in the model. Dynamic network responses are computed for different conditions. The computational model quantifies small-scale flow pulsatility, which has wide-ranging physiological influences.

Key words: microcirculation, reduced-order modeling, multi-scale, pulsatility

1 INTRODUCTION

Microcirculation plays a central role in the regulation of many important physiological mechanisms of the circulatory system. It is the main site of exchange between the blood and the tissues but it also acts as a regulating factor, reorganizing the blood flow according to the metabolic activity or the development of certain pathologies. Microvascular structure is highly complex and represents an important ‘mesoscale’ in physiological systems, functionally bridging higher and lower scales. An example of this relationship between scales involves the transition from pulsatile (in large arteries) to steady pressure (in capillaries). The mechanisms behind this peripheral dampening are influenced by several factors such as wave travel, damping and reflections due to the impedance mismatch, but they are less well understood when microvascular diseases are observed in association with end-organ damage.

Despite tremendous progress, reliable microcirculation structure and function \textit{in vivo} measurements remain difficult to collect for healthy and diseased tissues. Theoretical and numerical models are therefore needed to understand the microcirculation processes and to establish quantitative relationships with phenomena occurring on these large and small scales. Numerical modeling of large-scale microvascular architecture and its coupling with micro-flow and blood transport by means of three-dimensional models is currently out of reach because of the complexity and dimensionality of the computational domain. One-dimensional reduced-order models (ROM) are commonly used to simulate convection-dominated blood flow for which pulse waves propagate in a network of distributed large compliant arteries \cite{2, 1, 3}. These models predict spatio-temporal evolution of averaged hemodynamic quantities such as flow rates, cross-sectional areas or blood pressures with satisfactory accuracy.

While different type of ROM have been developed in order to model circulation at smaller scales, such as multi-compartment representations, very few topologically/geometrically-detailed network-based ROM attempts exist \cite{5, 7}. They have made progress in understanding microcirculation phenomena, but their reliability and use are still limited, mainly because they are not yet capable of encapsulating...
all of the submodels necessary to microcirculation across multiple scales. For instance, microvascular scales are often dissociated from those of the systemic circulation. Other reasons include the fact that the compliance of the structure and its dynamic interactions with the blood flow are often neglected to model networks formed of rigid vessels and subjected to stationary flows instead. This is detrimental to the study of the benefit of flow pulsatility to the microcirculation [6]. Moreover, computational domains representing large-scale microvascular network structures of the microcirculation of healthy or diseased tissues are difficult to construct. Indeed, these highly distributed and space-filling structures bear a high degree of spatial heterogeneity in architecture and topology. The approach used in this work relies on the ex novo generation of vasculature across all scales (down to the capillaries size) by means of mathematical algorithms. In this case, care has to be taken in order to avoid a numerical difficulty related to the unavoidable need for pruning of the macro/mesoscale network due to the unmanageable number of vessels generated.

In the following we briefly describe how we address these numerical challenges.

2 METHODOLOGY

In this work, we rely on the inherited framework of hemodynamics one-dimensional time-dependant ROM, commonly used to simulate convection-dominated blood flow for which pulse waves propagate in large elastic arteries. We show that it is possible to enrich this ROM and extend its capability toward microcirculation at mesoscopic scales both in terms of modeling and computational efficiency. For the computational domain, we first propose a method to generate realistic vessel trees ex novo – organized into small arteries, arterioles all the way down capillaries (draining venules and veins are voluntarily not included and are replaced by appropriate boundary conditions) – by means of stochastic growth mathematical algorithms (statistically) constrained by some realistic morphological and topological principles. Moreover, due to computational cost constraints we have developed several truncation strategies to efficiently prune the network and provide calibrated boundary conditions in place of the missing branches such that the simulation in the reduced domain produces a realistic response. Fig. (1) shows an example of a truncated network of $O(5000)$ vessels generated according to that pathway and ranging from macroscopic (here $D_0 = 1mm$) to mesoscopic $D_{\text{min}} = 8.5\mu m$ scales. Color shading relates to diameter sizes. Zoomed-up inset plot is also included in order to reveal the fine details of the large network all the way down to capillaries (represented in red).

The vascular tree is mathematically described by a graph of blood vessels: i.e. a network of thin, deformable, and axisymmetric arterial segments filled with blood, taken as an incompressible non-Newtonian fluid. The hemodynamics ROM formulation is based on the conservation of mass and momentum equations and a tube law (e.g. linear elasticity model) and takes the form of a nonlinear system of equations with cross-sectional averaged quantities varying in time and along a single axial coordinate along the arterial centerline. The modeling of the mechanical properties of the vessels has to differentiate among the different scales of the network. Therefore, vessel walls thicknesses and structures of arteries, arterioles and capillaries being quite different in terms of their response to pressure loads, we adopt in this work different structural models in order to address the specifics of the wall thickness-to-radius ratios [4].

The vessel wall motion induced by the transmural pressure is described by a linear elasticity relation, based on the reference unloaded state:

$$p = p_{\text{ref}} + \beta (A - \sqrt{A_{\text{ref}}}),$$

where the $\beta$ parameter may encompass a vector of parameters describing the mechanical properties of the membrane, related to the distensibility of the vessel: $\beta = 2/D\sqrt{A}$, and $A$ refers to the cross-sectional lumen area. Causin et al. [4] have identified two cases:

- Thick-walled case: vessel wall thickness is significant, e.g. $h \sim 35\% D$, in this case:

$$p_{\text{ref}} = \frac{2(R_{\text{ref}} + h_{\text{ref}})^2}{(1 - \nu)R_{\text{ref}}^2 + (1 + \nu)(R_{\text{ref}} + h_{\text{ref}})^2} p_{\text{ext}},$$

$$\beta = \frac{E((R_{\text{ref}} + h_{\text{ref}})^2 - R_{\text{ref}}^2)}{(1 - \nu)R_{\text{ref}}^2 + (1 + \nu)(R_{\text{ref}} + h_{\text{ref}})^2} \frac{1}{R_{\text{ref}} \sqrt{\pi}}.$$  

(2)
Geometries measured in vivo noted \((R_d, h_d)\) do not correspond to unloaded conditions. In practice, an inverse problem has to be solved, whose unknowns are \((R_{ref}, h_{ref}, p_t)\). As we do not rely on medical imaging and measurements, we assume without loss of generality that the measured configuration corresponds to zero transmural pressure, i.e. \(A_d = A_{\Delta p_t=0}, h_d = h_{\Delta p_t=0}\). Under this assumption, the problem may be inverted:

\[
R_{ref} = \frac{R_{\Delta p_t=0}}{1 - \frac{1}{E_p} p_{ext}}, \quad h_{ref} = \sqrt{R_{ref}^2 + h_{\Delta p_t=0}(h_{\Delta p_t=0} + 2R_{\Delta p_t=0}) - R_{ref}}.
\]

- Thin-walled case: i.e. \(h < 10\%D\), which often leads to the following implicit simplification: \(h \ll D\). Expressions in Eq. (2) simplify to: \(p_{ref} = p_{ext}\) so the transmural pressure is null \(\Delta p_t = 0\), the reference surface becomes \(A_{ref} = A_{\Delta p_t=0}, h_{ref} = h_{\Delta p_t=0}\) and \(\beta = \frac{E h_{\Delta p_t=0}}{(1-\nu^2)\sqrt{\pi R_{\Delta p_t=0}^2}}\).

In the simulations, structural model is selected from the above based on vessel wall thickness. Finally, the complex nonlinear rheological properties of blood (i.e. Fähraeus-Lindqvist effect, Fähraeus effect, and plasma skimming effects) are significant in the microcirculation and must be addressed in the modeling effort. In this solver, we have accounted for some of the blood rheology effects through the parametric calculation of a dynamic macroscopic description of the apparent blood flow viscosity, which impacts the friction term in the momentum equation balance of our model.

We adopt a discontinuous Galerkin (DG) method with a spectral/spatial discretization which has proven its efficiency for simulating hemodynamics in large- and medium-sized pulsatile arteries. In its original form, it relies on explicit schemes for time-integration. While this kind of schemes performs well under convective stability constraint of CFL-type, it is more strongly impacted by the diffusive stability constraint in case of low Reynolds and Womersley numbers creeping flows typically encountered in the smaller vessels of the microcirculation. In this work, we have alleviated these constraints and have adapted the implementation to make the time-advancing computationally tractable at all scales.

3 RESULTS AND CONCLUSIONS

The new implementation of the numerical scheme makes feasible the simulation of networks with \(\mathcal{O}(10^4)\) vessels, thanks to the rapid convergence properties exhibited by spectral elements method. The proposed reduced-order model was used to simulate the blood flow for fifteen cardiac cycles in a compliant vasculature network ranging from macro to mesoscale differing by more than two orders of magnitude, cf. Fig. 1. The inflow rate was setup to 1.74 ml·min⁻¹. Calibrated Windkessel-type boundary conditions are applied at the free ends of the network. Computer time to complete one cardiac cycle (with \(\Delta t = 0.3\mu s\)) was 5 hours for an Intel Xeon E5 CPU having 3.7GHz clock frequency and 16Gb DDR3 of RAM. The initial results of this application have been encouraging and dynamical effects related to the coupling between the non-Newtonian blood rheology and the pulsatility of the flow are well captured by the model. The entire tree was well perfused according to the mean flow observation. The simulation generated an unsteady flow rate from 29 \(\mu l\cdot s^{-1}\) at the main feeding artery to 0.1 \(nl\cdot s^{-1}\) in capillaries. Averaged (over space-time) pressure statistics plotted against vessel diameters, show a strong decline from the main feeding artery to the capillaries, while mean pressure variability is largest in arterioles. The dynamic characteristics of the pressure signals, captured by the pressure pulsatility index (not represented here) show a strong variation with a decay of pulsatility with one order of magnitude difference from central to most distal regions. In conclusion, the model may serve as a useful tool for the investigation of pulsatility dependent microvascular physiology. Current work involve multiscale modeling and simulation on larger networks with larger main feeding arteries. Preliminary work has also been pursued to include passive circulation transport, e.g. for completing the blood rheology model. Some effort will be made in the future to complement the model in order to also include the network of venules draining the vasculature through converging bifurcations.
Figure 1: Pseudo-3D view of a graph representing a compliant vasculature network ranging from macroscopic (main feeding artery $1\text{mm}$ in yellow color) to mesoscopic (capillaries: $8.5\mu\text{m}$ in red color) scales, with 5299 vessels (435 small arteries, 4548 arterioles and 312 capillaries) (left) and corresponding statistical distribution of averaged blood pressure ($\text{mmHg}$) vs. vessel diameter ($\mu\text{m}$) (right).

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A REDUCED ORDER MODELING METHOD FOR CARDIOVASCULAR FLOW

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SUMMARY

In this work we have developed a novel distributed lumped parameter model to study global hemodynamics of the cardiovascular system at a fraction of the computational cost of 1D, 2D, and 3D modeling. The proposed framework is fully automated and only requires the 3D segmented geometry. This framework provided consistent prediction with 3D simulations for a broad range of vascular models.

Key words: reduced order modeling, lumped parameter models, image-based simulations

1 INTRODUCTION

Image-based computational fluid dynamics (CFD) is widely used to simulate blood flow and pressure in arterial networks. These simulations have become increasingly powerful to understand normal and pathological physiology, and improve clinical decisions. However, CFD simulations are computationally expensive and prone to numerical instabilities. These factors have limited the broader adoption of image-based CFD and its use in parametric analyses. Reduced-order modeling (ROM) of blood flow provides the ability to study global hemodynamics of large cardiovascular networks at a fraction of the computational effort of CFD. This is valuable when multiple simulations are required, such as for data assimilation, optimization, parameter tuning, and uncertainty analysis, or for timely decision support in clinical deployment. We have developed a novel distributed lumped parameter (DLP) framework to compute temporal flow and pressure waveforms in cardiovascular applications. To evaluate the accuracy of the proposed DLP methodology, we have applied this framework to diverse range of healthy and diseased patient-specific cardiovascular anatomies including aortic, aorto-femoral, cerebrovascular, coronary, pulmonary and congenital heart disease models (a total of 24, 4 of each type), and have compared the DLP results to those from 3D time-dependent (3Dt) CFD simulations.

2 METHODOLOGY

Here we describe how to construct a DLP model from an image-based 3D geometry by assigning a resistance to each vascular segment considering various sources of energy dissipation.

Viscous and curvature effects: The energy dissipation due to blood viscosity is taken into account by modifying the well-known Poiseuille resistance \(R_p = \frac{8 \mu}{\pi r^4}\). First, an integral form of this equation is used to consider the spatial variation of vessel radius along the vessel length. Next, because secondary flows in a curved vessel cause extra viscous dissipation than for the same flow in a straight vessel, the
energy dissipation due to vessel curvature is considered by using an analytical model relating the viscous friction factor of a curved vessel to that of a straight vessel [1]. These two considerations lead to the following formula:

\[
R_v = \frac{8 \mu}{\pi} \int_0^L 0.1033K^2 \left( 1 + \frac{1.729}{K^2} - \frac{1.315}{K^{1.5}} \right) \frac{1}{r^4} \, dx
\]

where \( K = Re(a/R)^{1/2} \) is the Dean number, \( Re \) is the Reynolds number, \( a \) is the vessel radius, and \( R \) is the vessel curvature.

**Sudden expansion effect:** The energy loss at sudden expansions is modeled by using a semi-empirical model as [2]:

\[
R_s = \sum_{i=1}^{n} \rho K_I \left( \frac{A_{0,i}}{A_{n,i}} - 1 \right)^2 |Q_i|, \quad K_I = 1.52
\]

where \( A_s \) and \( A_0 \) are minimum and nominal cross-sectional areas of the artery, respectively. \( n \) is the number of expansions in each artery.

**Bifurcation effect:** A nonlinear resistance \( (R_b) \) is added in series to the resistances due to viscous and sudden expansion effects of a child branch, based on a semi-empirical model [3]:

\[
R_b = \frac{\rho}{2} \frac{Q_{dat}^2}{A_{dat}^2} \left( 1 + \frac{\lambda_j^2 \psi_j^2 - 2 \lambda_j \psi_j \cos(\phi_j)}{Q_{dat}^2} \right), \quad \lambda_j = \frac{Q_{j}}{Q_{dat}}, \quad \psi_j = \frac{A_{dat}}{A_j}
\]

where \( Q_{dat} \) and \( A_{dat} \) are the flow rate and the cross-sectional area of the datum supplier at the bifurcation junction, respectively. \( \phi_j \) is defined based on empirical observations as \( \phi_j = 3(\pi - \theta_j)/4 \), where \( \theta_j \) is the angle between a datum supplier and its child branch.

**Pulsatility effect:** The effect of changes in velocity profile is considered by changing the viscous resistance based on the Womersley number. This is done by numerically calculating velocity profiles from the Womersley solution, and computing the radial derivative at the vessel wall to obtain a modified viscous friction factor and a modified \( R_v \) accordingly.

We developed an automated framework (described in Figure 1) to compute flow rate and pressure using the DLP model.

3 RESULTS AND CONCLUSIONS

To evaluate the proposed DLP framework, we present three comparisons. First, we calculated relative errors between the mean values of the temporal flow rate and pressure from the DLP model against 3Dt CFD simulations at the inlet and outlets of each model. Second, for perspective, we compared the results from the 3Dt CFD with a DLP model where a Poiseuille resistance is assigned to each vascular segment by considering the averaged vessel radius and neglecting other sources of dissipation. Finally, the temporal flow and pressure waveforms from the DLP model are compared with their CFD counterparts in several locations. We note that the DLP model is in no way tuned to the CFD results—it is based only on the image segmentation geometry and is fully automated. To ensure a consistent comparison between the DLP and 3Dt CFD modeling, consistent boundary conditions are employed at inlets and outlets. Due to limited space, we only present the results for 4 coronary models, although more models and other vascular domains have been considered.
Four patient-specific anatomical models of the aorta and major coronary arteries are shown in Figure 2. This set is relatively broad; **Model C** is “healthy” with no stenosis, **Models B and D** have mild stenoses in the left and right coronary arteries, respectively, and **Model A** has a severe (~80%) and a mild (~50%) stenosis in a left coronary artery. In all cases, aortic flow was prescribed at the inlet, an RCR Windkessel of the systemic circulation was coupled at the aortic outlet, and coronary-specific lumped-parameter networks that consider the time-dependent intramyocardial pressure were coupled at the coronary outlets.

**Figure 2.** Four coronary models and illustration of errors of mean flow rate (left panel) and pressure (middle panel) between the DLP model \( Q_{3D}, P_{3D} \) and the 3Dt CFD simulation \( Q_{3D}, P_{3D} \). Right panel depicts mean pressure errors between the 3Dt CFD and a DLP model assigning a Poiseuille resistance to each vascular segment \( P_{pOis} \).
As shown in Figure 2, the mean values of the pressure error are 4.9%, 2.6%, 0.7% and 1.0% for Models A, B, C, and D, respectively. The maximum error of ~10% is observed for one of the coronary branches of Model A. For perspective, the right panel in Figure 2 plots error from assigning simple Poiseuille resistances to each vascular segment, which demonstrates significantly higher errors, and hence, the significant improvement of the DLP framework in predicting hydrodynamic effects. Figure 3 presents more detailed comparison of the DLP results against those from 3Dt CFD, demonstrating that the DLP model can accurately predict pressure waveforms at different locations of the coronary artery tree of Model A, including at f and g that are downstream branches of the complex stenotic region.

![Figure 3](image)

Figure 3. Color contours of early diastolic pressure and velocity of the coronary Model A and examples of comparison of temporal flow rate and pressure waveforms from the DLP model (“0D”) and the 3Dt CFD simulations (“3D”) at the boundaries.

We have presented a DLP framework to predict temporal flow and pressure waveforms in 3D vasculature models. This framework is fully automated based on image geometry, and generally requires ~1/1000 of the computational cost compared to 3Dt CFD simulations. Although not shown here due to space, this framework has been applied to a range of vascular models, demonstrating, to the best of the authors' knowledge, one of the most comprehensive comparisons of a ROM to a 3Dt CFD standard. The proposed DLP framework provided consistent prediction with 3Dt CFD simulations with mean errors <7% for all models (including aforementioned non-coronary domains) spanning a reasonably broad range of geometrical and physical characteristics; for example, key parameters such as area reduction ratio \(1 - \frac{A_s}{A_0}\), mean curvature ratio \(\alpha/R\), Reynolds \((Re)\) and Womersley \((\alpha)\) spanned on the order of ~50-90%, ~0-0.5, ~100-3000 and ~1-20, respectively, in models considered. To provide more general insight into the contribution of each sources of energy dissipation, we note that the modification due to flow separation at sudden expansions has the highest contribution to accurately predict flow and pressure distributions. Viscous resistance modified by curvature/pulsatility effect has the second highest contribution in energy losses. Finally, the modification introduced by bifurcation effects appears to improve the accuracy of the ROM for cases with more than ~20 junctions such as pulmonary models.

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Clinical application of computational biomechanics I
COMPUTATIONAL MODELING OF BRAIDED STENT BASED ON COROTATIONAL BEAM ELEMENT FORMULATION

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SUMMARY
This study proposes a computational model of the braided stent for investigating the mechanism of insufficient stent expansion during deployment. Wires constituting the stent are explicitly modeled by Kirchhoff’s rod theory and its mechanical behavior is precisely treated by corotational beam element formulation. The equation of motion of the stent is solved by a step-by-step manner with considering frictional contacts between wires. A numerical example of the stent deployment into an artery demonstrated that insufficient stent expansion locally occurred in both end portions, which may be caused by the local equilibrium between elastic energies stored in wires and frictional resistances.

Key words: Braided stent, Corotational beam element, Frictional contact, Finite element method

1 INTRODUCTION
The braided stent is a popular endovascular device for treatment of cerebral aneurysms. This stent has woven mesh design made of braided metallic wires for satisfying both high flexibility and low porosity as compared with the laser-cut stent, and thus its deployment into parent arteries of the aneurysm acts to not only assist the coil embolization to prevent coil protrusion but also provide flow diversion effect. However, it is commonly known that stent deployment in the inappropriate conditions leads to the insufficient stent expansion [1] and its mechanism is still poorly clarified. Understanding of the mechanism of the insufficient stent expansion in the mechanical viewpoint may be feasible to improve more reasonable stent design which minimizes the risk of the insufficient expansion and determine the appropriate procedure of the stent deployment in individual patients.

The present study proposes a computational model of the braided stent to deepen our understanding of the mechanism of the insufficient stent expansion. Metallic wires constituting the braided stent are explicitly represented and these mechanical behaviors including large deflection are precisely expressed by the method of corotational beam element formulation [2]. Mechanical interactions between wire-wire, wire-catheter and wire-aneurysm are also treated with considering frictions. Numerical example exhibits overall procedure of the stent deployment from the stent packing into the catheter to the stent deployment into an idealized straight artery.

2 METHODOLOGY
2.1 Stent modeling
We modeled the braided stent as a set of thin slender wires modeled by Kirchhoff’s rod theory (Fig. 1) and solved these mechanical equilibrium state with considering these frictional contacts. The elastic energy of the wire per unit length \( U \) is derived by integrating the axial stretching/compression, bending and torsional elastic energies, given by

\[
U = \frac{1}{2} k_s e^2 + k_t (\kappa_1 - \kappa_0^1)^2 + k_b (\kappa_2 - \kappa_0^2)^2 + k_b (\kappa_3 - \kappa_0^3)^2, \tag{1}
\]
where $k_s$, $k_t$ and $k_b$ is the axial, torsional and flexural rigidities, $\varepsilon$ is the axial strain, $\kappa_1$, $\kappa_2$ and $\kappa_3$ is the degree of twist and curvatures and $\kappa_1^0$, $\kappa_2^0$ and $\kappa_3^0$ is those in the reference state. Based on the minimum energy principle, the stress resultants of the beam can be decomposed to be axial force $n$, torque $m_1$ and bending moments $m_2$ and $m_3$ from the elastic energy shown in the eq.1, given by

$$
n = k_s\varepsilon, \quad m_1 = k_t(\kappa_1 - \kappa_1^0), \quad m_2 = k_b(\kappa_2 - \kappa_2^0), \quad m_3 = k_b(\kappa_3 - \kappa_3^0).$$

(2)

Each wire was discretized to be a set of two-node beam elements (Fig. 1(top-left)). Orthonormal triad of unit vectors is assigned on each node to express rotational degree of freedom. The element coordinate system is also assigned on each element as the rotating frame. Stress resultants of the beam element are calculated by discretizing the eq. 2 in this element coordinate system and transformed to the global coordinate system with considering finite rotation of the beam element by the idea of corotational beam element formulation [2]. Contacts between wire-wire, wire-aneurysm wall and wire-catheter are detected by the method of our previous study [3] and contact forces are treated with considering frictions. Linear visco-elastic model is applied to represent the repulsive force on the normal direction and Coulomb’s friction model is used to express friction force. An arterial wall and catheter are assumed to be rigid for simplicity. Following the resultant force of the wires and contact forces, stent motion during deployment into arteries is expressed by solving the equation of motion, given by

$$
\mathbf{M}\ddot{\mathbf{U}} + \mathbf{C}\dot{\mathbf{U}} + \mathbf{F}_{int}(\mathbf{U}) = \mathbf{F}_{ext}(\mathbf{U}),
$$

(3)

where $\mathbf{M}$ is the mass matrix, $\mathbf{C}$ is the damping matrix calculated by Rayleigh ansatz, $\mathbf{F}_{int}$ is the internal force calculated as the stress resultants, $\mathbf{F}_{ext}$ is the contact force and $\mathbf{U}$ is the displacement vector of stent nodes. Dot shows derivative with respect to time. The eq. 3 is solved by explicit predictor-corrector scheme with adaptive time stepping [4].

Figure 1: Geometry of the braided stent consisting of thin slender wires. Wires are modeled by Kirchhoff’s theory of rod and discretized as a set of beam elements treated by the corotational beam element formulation.

### 2.2 Numerical example

We conducted a numerical example of the stent deployment into an idealized straight artery with the diameter of 4 mm. The braided stent with the outer diameter of 5 mm and total length of 33 mm was constructed (Fig. 1). The stent consisted of 24 metallic wires with the diameter of 0.04 mm and the shape at the reference state was set to be a single helical shape with constant curvatures ($=0.2$) and torsion ($=0.2$). Wires were modeled to be made from Co-Cr alloy with Youngs modulus of 225 GPa and shear modulus of 95 GPa. Friction coefficient of the wire-wire contact was set to be 0.8 whereas wire-arterial wall and wire-catheter were set to be 0.1 and 0.01 not to disturb numerical solution.
Before the stent deployment into the artery, the stent was placed in the straight catheter with a diameter of 0.7 mm by compressing wires towards the central axis of the stent in the quasi-static manner. The catheter and the stent inside the catheter were set on the center-line of the artery. Nodes of the proximal end of the stent was fixed only on the longitudinal direction and the stent deployment was represented by pulling the catheter from the distal to the proximal side.

3 RESULTS AND CONCLUSIONS

Figure 2 shows snapshots of the deployment process of the braided stent from the catheter into the artery. Although the stent was self-expanded uniformly to the arterial wall from the distal to the proximal end, insufficient expansion occurred in both end portions. Stent diameter after deployment along the longitudinal axis of the artery is shown in Fig. 3. Diameters approached to the arterial diameter (4 mm) in almost all portions, whereas diameters of both end portions were approximately 25% lower than other portions. This local insufficient expansion is consistent with the clinical observation in the braided stent deployment [3].

To interpret the mechanism of this local insufficient expansion in mechanical viewpoint, we assessed the bending and torsional energies stored in wires before and after deployment (Fig. 4). Before deployment, although both energies were nearly constant in almost all portions of the stent, locally small in both end portions. After deployment, although the bending energy decreased one order of magnitude, these values were still higher than the torsional energy. Its values was also locally small in both end portions, while local maximum and plateau was found at the distal and proximal portion where the local minimum of the stent diameter occurred (Fig. 3). These results suggest that the bending energy stored in both end portions are relatively small before deployment, and then releases of the bending energy is disturbed by the frictional resistances exerted on wires and causes local insufficient expansions at both end portions.

The present study develops a computational model of the braided stent with considering mechanical behaviors of constituting wires and these mechanical interactions. Numerical example successfully demonstrated stent self-expansion procedure in an idealized straight artery whereas local insufficient expansion occurred in both end portions of the stent. Obtained results suggest that this insufficient expansion may be caused by the local equilibrium between elastic energies stored in wires and frictional resistances. From this speculation, systematic studies about the geometric and mechanical characteristics of wires using proposed computational model may be feasible to design a mechanically appropriate stent which minimizes the risk of the insufficient expansion.

![Figure 2: Snapshots of the stent deployment at the process of 0%, 25%, 75% and 100%.](image1)

![Figure 3: Stent diameter along the longitudinal axis of the artery after deployment. Origin (z=0) is assigned on the proximal end of stent and the position is normalized by the stent length.](image2)
Figure 4: Bending and torsional energies stored in wires along the longitudinal axis of the stent before deployment (inner catheter, left) and after deployment (right). The origin ($z=0$) is assigned on the proximal end of the stent and the position is normalized by the stent length. Local maximum and plateau in distal and proximal portion are shown in black arrows.

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REFERENCES

COMPUTATIONAL MODELLING OF THROMBOLYSIS IN ISCHEMIC STROKE

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SUMMARY

We present a recently developed multi-level computational framework for the simulation of clot lysis under conditions mimicking intravenous thrombolytic therapy for the treatment of acute ischemic stroke. We show how the model can be applied to clinically relevant scenarios in order to assess the therapeutic efficacy and risk for hemorrhagic complications. Opportunities and challenges involved in further improvement and application of the model are also discussed.

Key words: thrombolysis, ischemic stroke, multi-level model

1 INTRODUCTION

The presence of occluding blood clots can prevent blood from reaching vital organs and tissues, causing life-threatening events such as acute myocardial infarction and stroke. Blood clots can be either removed surgically by means of mechanical thrombectomy or dissolved through thrombolytic therapy which involves intravenous infusion of a clot lysis agent, such as recombinant tissue-type plasminogen activator (t-PA) [1]. However, thrombolytic therapy is not always effective and may cause serious complications such as intracranial hemorrhage (ICH) in some patients [2].

Multiple factors can influence the efficacy of thrombolytic therapy; these include drug dose and its administration mode, the location and size of the clot, as well as clot composition and its properties. Thrombolysis is a complex process that involves interactions among multi-level physical and biochemical phenomena, such as pharmacokinetics (PK) and pharmacodynamics (PD) of the drug, lysis protein kinetics and fibrinolytic reactions, blood flow and drug transport. We have recently developed a multi-level computational model for thrombolysis that can be applied to clinically relevant settings [3, 4]. The model has been applied to clots of varying location, length and properties in anatomically realistic cerebral arteries. It has also been used to evaluate the influence of dose regimen on lysis completion time and the risk for ICH.

2 METHODOLOGY

Figure 1 gives an overview of the computational model which combines a 3-D thrombolysis model with a compartmental model. The 3-D thrombolysis model couples blood flow, drug transport and the dissolution of fibrin fibers, whilst the compartmental model describes the dynamic interactions of lysis proteins in plasma during intravenous infusion of t-PA. The temporal variations of lysis proteins obtained from the compartmental model are used as input to the 3-D thrombolysis model. The thrombolysis model consists of modified equations for the conservation of mass and momentum for blood flow, transport equations for essential proteins involved in fibrinolysis (t-PA, plasminogen, plasmin and anti-plasmin), and a set of fibrinolytic reaction equations to evaluate the degradation of fibrin binding sites. Physiological outflow boundary conditions are applied at all model outlets. Details of the mathematical equations and model parameters can be found in [4].
Figure 1: Overview of the computational model for thrombolysis. Here the 3-D geometry represents the internal carotid artery bifurcation consisting of a normal anterior cerebral artery and an occluded middle cerebral artery (extracted from [4]).

3 RESULTS AND CONCLUSIONS

The model described above has been applied to a variety of settings relevant to acute ischemic stroke, with the occluding clot being located in the M1 segment of the middle cerebral artery (MCA) and the M2 inferior branch, respectively, together with different clot lengths and properties. The influence of dose regimens is also investigated by varying the t-PA dose, bolus-infusion delay time and bolus-infusion ratio. The effectiveness of the treatment is evaluated through the lysis rate and lysis completion time, while the risk for hemorrhagic complications is assessed by monitoring the plasma concentration of fibrinogen. Clinical studies have shown that low levels of fibrinogen concentration in plasma are associated with increased risk of ICH [5].

Our results demonstrate that clot size has a strong influence on lysis completion time and that this effect becomes more pronounced as the initial clot volume increases. For the same clot size, complete lysis takes longer time to achieve for clots located in the M2 segment than in the M1 segment. In addition, finer clots with a smaller fiber radius dissolve more slowly than coarse clots due to slower t-PA penetration in the clots. Furthermore, increasing t-PA dose can cause a rapid reduction in plasma fibrinogen level, indicative of increased risk of ICH, without necessarily improving the lysis completion time, whereas bolus-infusion delays can substantially increase the time required to achieve recanalization.

REFERENCES

PATIENT-SPECIFIC CT-BASED ACTIVE/PASSIVE FSI MODELS FOR LEFT VENTRICLE IN HYPERTROPHIC OBSTRUCTIVE CARDIOMYOPATHY

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SUMMARY

To further understand the mechanisms of systolic anterior motion in hypertrophic obstructive cardiomyopathy, three-dimensional patient-specific passive/active fluid structure interaction models were developed to investigate the hemodynamic statuses before and after surgical septal myectomy in the left ventricle at pre-SAM time point. It was both found in active and passive models that mean value of maximum pressure difference on coapted MVL were relatively high pre-operatively, but decreased significantly after successful septal myectomy. The difference of the simulation results between passive and active models were also compared in this study. Our results indicated that the passive model may be used as good approximations to active models to perform mechanical analysis for left ventricle with clinical implementation potential. Prospective and large-scale studies are needed to further validate our findings.

Key words: fluid-structure interactions, passive model, active model, left ventricle, hypertrophic obstructive cardiomyopathy, systolic anterior motion

1 INTRODUCTION

Hypertrophic cardiomyopathy (HCM) occurs in about 1 of every 500 adults in the general population [1]. It’s been reported that left ventricular outflow tract obstruction (LVOTO) is observed in 70% patients with HCM [2, 3]. Systolic anterior motion (SAM) of the mitral valve (MV) is the dominant cause of dynamic outflow tract obstruction in most patients with hypertrophic obstructive cardiomyopathy (HOCM). Currently, the hemodynamic mechanisms of SAM remain unclear.

Several heart models have been proposed in the literature to assess the hemodynamics and gain insights of myocardial function in heart and become increasingly important in cardiovascular research [4, 5]. The application of computational approaches may be a valuable tool to investigate the mechanisms of SAM and possibly improve the surgical outcome through virtual planning. In this study, we developed patient-specific computed-tomography (CT) based 3D fluid-structure interactions (FSI) models for the left ventricle of 6 HOCM patients. Both the passive and active FSI models were constructed to investigate the hemodynamic statuses before and after surgical septal myectomy. The simulation results between passive and active models were also compared.
2 METHODOLOGY

2.1 Data acquisition

6 patients with HOCM receiving septal myectomy at Fuwai Hospital were recruited in this study. The patients were divided into two groups with Group 1 (Patient No. 1-5) with satisfactory surgery outcomes, and Group 2 (Patient NO. 6) with unsatisfactory surgery outcome. The investigation was approved by the review board on human subject research (Fuwai Hospital, Chinese Academy of Medical Sciences), and informed consent was obtained. ECG-gated cardiac CT scans were performed at every 5% RR interval in the cardiac cycle. The beginning time of SAM ranged from 5% to 8% RR interval in the cardiac cycle in all these 6 patients. Therefore, to investigate the mechanisms of the initiation of SAM, the pre- and post-operative CT images of patients’ LV at the pre-SAM time point (5% RR interval) were selected to construct the geometry model. For each patient, there were around 130 slices with 0.625 mm slice thickness covering the left ventricle, and one slice out of every 4 slices were used to construct the 3D FSI models. Patient-specific heart rate and blood pressure (arm cuff pressure measurements) at the time of the CT examinations were used in the simulation. The patient-specific LV volume, LV pressure and the left ventricular outflow tract (LVOT) velocity at pre-SAM time obtained from echo and MRI data were used to verify the simulation results.

2.2 Passive/Active FSI Models

The material property of the LV was assumed to be hyperelastic, isotropic, incompressible and homogeneous. The modified non-linear Mooney-Rivlin model was used to describe the material properties with constants chosen to match the measured patient-specific volume at the end of isovolumic systole phase. Blood flow in the LV was assumed to be laminar, Newtonian, viscous and incompressible. The Navier-Stokes equation with Arbitrary Lagrangian Eulerian formula was used as the governing equation. The fluid and structure models were coupled through their interfaces at which the No-slip boundary conditions and natural force boundary conditions were specified [6-9]. The fully coupled FSI model was solved by ADINA using unstructured finite elements and the Newton-Raphson iteration method.

The passive model treated the left ventricle muscle as passive material. The left ventricle was inflated/deflated by specify the pressure conditions on inlet (mitral valve) and outlet (aortic valve) in the cardiac cycle [8]. In active model, the active contraction of LV from the end of the isovolumic systole to the pre-SAM time point was implemented by specifying the pressure conditions at the outlet and outer boundary of LV (epicardium) [9]. The simulation results between passive and active models were compared by paired t-test.

3 RESULTS AND CONCLUSIONS

There were 12 active and 12 passive FSI models constructed based on in vivo pre- and post-operative CT Images from 6 patients. Figure 1 presented LV 3D geometry, and the numerical simulation results of 3D velocity vector flow, the pressure difference on the coapted MVL, and the shear stress distribution on the MVL obtained from an active FSI models.
3.1 Pressure difference on the coapted MVL were found significantly decreased after successful surgery

To assess the driving force of SAM, the pre- and post-operative pressure difference on coapted MVL were analyzed. It was found that the mean value of maximum pressure difference was relatively high pre-operatively, but decreased significantly after successful septal myectomy (pre-op: 4.30 ± 1.88 mmHg versus post-op: 0.57 ± 0.36 mmHg, n=5, p =0.002) in active models (Fig. 2a). While the maximum pressure difference on coapted MVL remains still high (pre-op: 6.65 mmHg versus post-op: 4.39 mmHg, n=1) after failed surgery (SAM was not eliminated after the surgery). The same trend was found in passive model pre-op: 2.44 ± 1.30 mmHg versus post-op: 0.29 ± 0.24 mmHg, n=5, p =0.007) (Fig.2b), although the pressure values in passive models were significantly lower than those obtained from active models.

3.2 The Difference of computational results between active and passive model

The maximum pressure values at pre-SAM time point on mitral valve leaflet (MVL) in passive model (83.2±11.8 mmHg) is only 1.2% less than that in active model (82.1±11.6 mmHg, p<0.0001). The difference of mean pressure on MVL between active and passive model is not significant (80.7±11.4 vs. 82.5±11.7 mmHg, p<0.0001). The maximum and mean value of shear stress on MVL between active and passive models were not significant (11.8±8.0 vs 11.3±7.7 dyn/cm², p=0.0005; 5.0±2.6 vs. 4.7±2.3 dyn/cm², p<0.0001).

There were statistical significant difference found in stress values between active and passive models. The maximum value of maximum principle stress (Stress-P1) in passive models were...
40.7% higher than that in active models (130.0±100.3 vs. 92.4±74.9 kPa, p<0.0001), while the maximum strain value in passive models were only 3.88% less than that from passive models (0.109±0.032 vs. 0.105±0.003, p<0.0001).

3.3 Discussion and conclusions.

The septal myectomy (Morrow procedure) is the gold standard treatment for HOCM patients [10]. The procedure is still challenging since the inadequate excision cannot abolish SAM, while excessive myectomy may produce complete heart block or ventricular septal defect. The application of numerical simulations may implement the numerical resection. The pressure distributions on MVL and the fluid flow pattern may also be numerically obtained and analyzed to predict if the “resection” is sufficient to eliminate SAM. The resection region can be numerically adjusted for optimal surgical strategy.

While the mechanisms driving the left ventricle motion in passive model is different from real heart motion, the passive models can still simulate the left ventricle motion, deformation, and fluid flow with proper pressure conditions, and found the similar results with active models which might elucidate the mechanisms for SAM. Comparing to active models, the passive models decrease the complexity of the modeling construction and the difficulty of convergence significantly. Therefore, passive model may be used as good approximations to active models to perform mechanical analysis for left ventricle with clinical implementation potential. Prospective and large-scale studies are needed to further validate our findings.

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SUMMARY

Babies affected by non-syndromic craniosynostosis experience premature ossification of one or more sutures. Scaphocephaly (long and narrow head, caused by ossification of the sagittal suture) affects 1.7 every 2000 births. These patients are treated within the first 6 months by means of metallic distractors (stainless steel springs) which help reshaping the calvarium in a minimally invasive manner. Nitinol has the potential to allow for a more controlled effect thanks to its superelastic properties. We hereby present the design of a new distractor which was tested in-silico in a virtual population.

Key words: craniosynostosis, spring cranioplasty, nitinol

1 INTRODUCTION

Sagittal craniosynostosis consists of premature ossification of the sagittal suture, occurring during the first few months of life, which leads to head deformity with subsequent brain growth restriction. Extensive surgery is necessary to perform head reshaping and improve aesthetic appearance: more recently, Spring Assisted Cranioplasty (SAC) has been introduced as a less invasive alternative. SAC entails skull incisions to free the fused suture and insertion of two metallic distractors (springs) which promote gradual cranial reshaping (figure 1A). SAC has proved safe and effective in treating scaphocephaly [1]: advantages include a reduce morbidity, hospital stay as well as need for transfusion. Main criticism of this technique is the sudden spring expansion occurring in theatre: over 50% of the opening occurs on table and over 75% occurs within the first day after insertion [2]. High forces are experienced by patient calvarium and the other sutures are likely to rupture. Numerical modelling can be used to predict the effect of springs: our group validated a finite element model by means of on-table 3D scanning [3]. Nitinol is an equiatomic nickel-titanium (NiTi) alloy exhibiting shape memory effect (SME) as well as superelastic properties: our group designed an alternative to current stainless steel (SS) springs using shape memory alloys (SMA) and investigated its potential by means of in-silico modelling in a retrospective patient population.

2 METHODOLOGY

2.1 Patient population

Preoperative computed tomography (CT) images were retrieved for 10 patients: (age = 5.5 ± 1.2 months): SCANIP (Synopsis, Mountain View CA) was used to create 3D models of each patient calvarium (skull and sutures, figure 1B) by means of automatic segmentation; each model was afterwards discretized using linear tetrahedral elements. A logarithmic growth curve was used to account
for patient growth between the time of CT and the time of surgical procedure (1.6 ± 0.8 months) retrieved using a separate population of 24 patients [4] and used to scale the calvarium of each patient of the study. ANSYS was used for simulation of spring expansion using a previously validated methodology [3] (figure 1C): data relative to spring model and osteotomy size and locations, retrieved during surgery, were used to simulate spring positioning. A viscoelastic material model was used to model skull reshaping due skull-spring interaction [5]. Data relative to spring expansion at the time of surgery, at follow-up 1 (on day 1) and at follow up 2 (on day 28 ± 12) were retrieved from surgical notes and x-ray measurements and used to tune the model.

2.2 Prototyping

A first prototype of a nitinol spring, with similar shape and dimensions to the device currently implanted (figure 2A) was firstly internally prototyped and - afterwards - manufactured (figure 2B) by an external company (Nordson Medical, OH). Mechanical tests on the prototype - performed in a range of deformation similar to those reported for the present spring [2] were performed to assess the capability of the new prototype to exert constant force during the unloading phase (figure 2C) at body temperature. A finite element model was tuned (figure 2D) in order to extract material properties of this NiTi alloy. Such results were afterwards employed to perform further design of other prototypes by mean of design of experiments: spring thickness and spring height were varied and the effect on the distraction plateau value was investigated. Three further models were produced, having

Figure 1: A) Sample of patient affected by scaphocephaly, top and right view (top); patient calvarium after insertion of cranioplasty springs. B) Patient population used in this study. C) Pre-operative CAD model (left) with simulated spring expansion (centre) and superimposition of the deformed model with the x-ray scan (right)

Figure 2: A) sample of SS spring; B) first prototype of NITI spring; C) mechanical testing of NITI spring; D) Finite Element Modelling for material tuning; E) SS spring force-opening diagram, showing steep spring force decay in the region of interest; F) NITI spring force-opening diagram showing a wide plateau in the region of interest.
Figure 3: A) comparison of skull reshaping on-table and at 1 day FU for SS and NITI spring; B) Comparison of on-table spring opening in the population when the SS and NITI springs are virtually implanted; C) comparison of on-table suture strain for SS and NITI spring on a sample patient.

3 RESULTS AND CONCLUSIONS

Each patient model was scaled using the growth curve to compensate for head growth between the time of CT scan and surgery. Three prototypes were produced, having the same geometry but wire thickness equal to 1.5mm, 2.0mm and 2.25mm (NITI10, NITI 20, NITI225): these prototypes had plateau forces equal to 2.47N, 6.13N, 8.83N respectively. While current spring models exhibit a sharp decrease in force soon after insertion (figure 2E), the NITI spring exhibits a lower force at insertion which remains virtually constant afterwards (figure 2F). Simulation in the patient group showed that NiTi exhibit a lower on-table opening ($p < 0.01$, figure 3A, 3C) but eventually fully open. Analysis of spring kinematics showed a nearly twofold increase in creep time constant ($\tau_{SS} / \tau_{NITI}$), showing a more gentle effect. Strain levels on the coronal suture were $30.7\% \pm 16.2\%$ lower when a NiTi string was virtually implanted (figure 3B). This work presents a design framework for a new prototype of craniofacial distractor for the treatment of scaphocephaly, manufactured and tested in-silico: virtual NiTi spring implantation showed a different distraction kinematics with a more gentle effect on the calvarium at the time of implantation. The new device will allow for a better interaction between distractor and skull, by exerting a constant low force on the patient calvarium while achieving the same amount of distraction: in-vivo studies will assess the effect on cranial reshaping as well as patient safety.

REFERENCES


FLUID–STRUCTURE INTERACTION MODELING OF TRANSCATHETER HEART VALVES

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SUMMARY

In this work, we develop and apply a novel immersogeometric fluid–structure interaction (FSI) framework for the modeling and simulation of the transcatheter aortic valve replacement. To account for physiological realism, methods are proposed to model and couple the main components of the system, including the arterial wall, blood flows, heart valve leaflets, and the frame. In the simulation, the transcatheter heart valve (THV) is crimped and deployed into the aorta to study the radial outward force and friction force between the aortic wall and the THV frame. The FSI results of this work help better understand the anchoring ability of the THV.

Key words: fluid–structure interaction, transcatheter aortic valve replacement, immersogeometric analysis, isogeometric beams and shells

1 INTRODUCTION

Percutaneous interventions, such as transcatheter aortic valve replacement (TAVR), have emerged as minimally invasive alternatives to surgical treatment of various valvular diseases [1]. A prosthetic aortic valve is deployed through a catheter and anchored to the aortic annulus over the calcified leaflets, displacing the diseased valve and assuming its role. TAVR offers many advantages, including less postoperative pain, faster rehabilitation, and better performance in terms of pressure gradients and orifice areas. The safe anchoring of the transcatheter heart valve (THV) in the patients anatomy is a key to a successful TAVR procedure. The fully expanded frame of most THVs is designed to be oversized with respect to the diameter of the aortic annulus. The oversizing degree after a TAVR procedure depends on the stiffness and elasticity of the surrounding anatomy and the mechanical properties of the THV. To estimate the oversizing degree prior to the implantation and to obtain permission to market, in vitro measurement of the radial outward force is the current standard to evaluate the THV [2]. For the purpose of improving THV designs and pre-operative planning, computational simulations of TAVR provide an effective way to study the interaction between the THV and the host tissue.

The ultimate goal of this work is to be able to compare the coefficient of friction with conditions of patient-specific aortic roots in order to estimate the possibility of migration of specific sizes of THVs. In order to study the coefficient of friction, which is necessary for THV anchoring, information on both radial outward force and friction force is needed. To achieve this goal, we propose methods to geometrically model a THV using an isogeometric analysis (IGA)-based parametric design platform and develop a fluid–structure interaction (FSI) framework for TAVR simulation. The THV is modeled based on a 26 mm CoreValve with three main components: the frame, the skirt, and the leaflets. The coupling among the components introduces major challenges in accurately simulating such a system. The THV frame is modeled using an extension of the isogeometric Bernoulli beam formulation proposed by [3]; the method is extended in order to handle complex geometries. We also propose penalty methods to couple adjacent patches between the skirt and leaflets, and the skirt and frame. With the proposed technology, we simulate the coupled dynamics of the aortic root, the THV, and the surrounding blood flow under physiological conditions to study the radial outward force and friction force between the aortic wall and THV frame.

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2 METHODOLOGY

2.1 FSI problem

The THV and ascending aorta at time \( t \) are modeled as elastic structures occupying region \( (\Omega_s)_t \), coupled to blood flow through \( (\Omega_f)_t \) by kinematic and traction compatibility conditions at the fluid–structure interface \( (\Gamma_1)_t \). The blood flow within \( (\Omega_f)_t \) is assumed to be incompressible and Newtonian. This coupled partial differential equation (PDE) system can be expressed in weak form as: Find a fluid velocity \( \mathbf{u}_f \in S_u \), fluid pressure \( p \in S_p \), structure displacement \( \mathbf{y} \in S_y \), and a fluid–solid interface traction \( \lambda \in S_t \) such that for all \( \mathbf{w}_f \in V_u \), \( q \in V_q \), \( \mathbf{w}_s \in V_y \), and \( \delta \lambda \in \mathcal{V}_t \),

\[
B_t(\{\mathbf{w}_f, q\}, \{\mathbf{u}_f, p\}) - F_t(\{\mathbf{w}_f, q\}) + B_s(\mathbf{w}_s, \mathbf{y}) - F_s(\mathbf{w}_s) \\
+ \int_{\Gamma_1} (\mathbf{w}_f - \mathbf{w}_s) \cdot \delta \mathbf{y} \; d\Gamma + \int_{\Gamma_1} \delta \lambda \cdot (\mathbf{u}_f - \mathbf{u}_s) \; d\Gamma \\
+ \int_{\Gamma_1} (\mathbf{w}_f - \mathbf{w}_s) \cdot \beta (\mathbf{u}_f - \mathbf{u}_s) \; d\Gamma = 0, \\
\]

where \( S_{(\cdot)} \) and \( \mathcal{V}_{(\cdot)} \) are trial solution and test function spaces and \( B_t \), \( B_s \), \( F_t \), and \( F_s \) are variational forms defining the fluid and structure subproblems, \( \mathbf{u}_f \) is the material time derivative of \( \mathbf{y} \), and \( \beta \) is a penalty parameter. The additional terms integrated over \( \Gamma_1 \) enforce the fluid–structure coupling conditions on the fluid–structure interface.

The FSI model can be separated into fluid and structure sub-problems. The fluid sub-problem is described by the Navier–Stokes equations of incompressible flows and the ALE formulation proposed in [4] is employed. For the structure sub-problems, we separate the structure terms into multiple parts. This distinction can be formalized by introducing superscripts “so”, “sh”, and “be” to denote the solid, shell, and beam, respectively. The THV frame is modeled using isogeometric Kirchhoff–Love thin shell proposed by [5]. The artery wall is modeled as a hyperelastic solid, subject to damping forces proposed in [6]. The THV frame is modeled using isogeometric Bernoulli beams as discussed in the next section.

2.1.1 Isogeometric Bernoulli beams for THV frame

The frame is fabricated with thin, long wires which are modeled as isogeometric Bernoulli beams proposed by [3] with cubic NURBS curves. We apply this theory to the complex geometry of the THV frame. The beam subproblem is as follows:

\[
P_{sb}(\mathbf{w}_s, \mathbf{y}) - F_{sb}(\mathbf{w}_s) = \\
\int_{(L_{be})_0} \mathbf{w}_s \cdot \rho_{be} A \frac{\partial^2 \mathbf{y}}{\partial t^2} \; dL + \int_{(L_{be})_0} \int_{A} \delta \mathbf{E} : \mathbf{S} \; dA \; dL \\
- \int_{(L_{be})_0} \mathbf{w}_s \cdot \rho_{be} \mathbf{A} e \; dL - \int_{(L_{be})_0} \mathbf{w}_s \cdot \mathbf{h}_{net} \; dL, \\
\]

where \( (L_{be})_t \) and \( (L_{be})_0 \) are the center line of the beam in the current and reference configurations, respectively, \( \rho_{be} \) is the beam density, and \( A \) is the cross sectional area of the beam.

The design procedure for generating the frame consists of the definition of the NURBS curve and the definition of the cross-sectional profile along the curve. Since the frame is assumed to be perfectly radially symmetric, we generate the first NURBS curve and determine the rest by symmetrical cloning. The cross-sectional profile is defined by two local unit vectors that are simultaneously perpendicular to the tangent of the curve at each location over the entire NURBS curve. Since Bernoulli theory is applied, the cross sections must remain the same throughout, thus we define the same cross-sectional profile along the entire curve. In this work, the St. Venant–Kirchhoff material model is applied to the beam.
2.2 Immersogeometric FSI framework

We develop and apply a novel immersogeometric FSI framework for the modeling and simulation of TAVR. Immersogeometric analysis is a computational technique that directly captures the design geometries in an unfitted analysis mesh. The methods make beneficial use of isogeometric analysis to discretize both the structural and fluid mechanics subproblems. To account for physiological realism, methods are proposed to model and couple the main components of the system, including the arterial wall, blood flow, heart valve leaflets, and the frame.

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 as both 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 [7]. The motion of the fluid–solid interface provides the boundary conditions for solving the linear elastostatic problem for the fluid mesh motion.

The THV is immersed into a moving blood-flow domain. The immersogeometric FSI problem is formulated using an augmented Lagrangian approach, which was originally proposed in [8] to handle boundary-fitted mesh computations with nonmatching fluid–structure interface discretizations and was extended to immersed FSI problems in [9].

2.2.1 Shell–shell and shell–beam coupling

To couple the structural motions of the leaflets and the skirt, we employ a penalty approach to eliminate displacements and rotations at the coupled patch interfaces. The displacement penalty term added to $B_{sh}^s(w_s, y)$ is given as,

$$ + \int_{\mathcal{L}^{AB}} \alpha_d (w^A_s - w^B_s) \cdot (y^A - y^B) \, d\mathcal{L} .$$

$L^{AB}$ denotes the patch interface, $y^A$ and $y^B$ are the displacements of the corresponding points on surface patches $S^A$ and $S^B$, respectively, and $\alpha_d$ is a penalty parameter of large magnitude. We use this penalty formulation for the coupling between the shell and beam as well.

For the rotational continuity between the the leaflets and the skirt, the rotational penalty virtual work [10] is added to $B_{sh}^s(w_s, y)$ and is given as,

$$ + \int_{\mathcal{L}^{AB}} \alpha_r \left( \left( \cos \phi - \cos \hat{\phi} \right) \left( \delta \cos \phi - \delta \cos \hat{\phi} \right) + \left( \sin \phi - \sin \hat{\phi} \right) \left( \delta \sin \phi - \delta \sin \hat{\phi} \right) \right) \, d\mathcal{L} ,$$

where $\phi$ and $\hat{\phi}$ are the angles between the surfaces before and after deformation, respectively, $\delta$ denotes the variation, and $\alpha_r$ is the penalty parameter of large magnitude.

3 RESULTS AND CONCLUSIONS

A comprehensive TAVR system, the 26 mm CoreValve, is simulated to study the radial outward force and the friction force between the aortic wall and the THV frame. Several cardiac cycles are computed until a time-periodic solution is achieved. With the information of both forces, the coefficient of friction, which is necessary for THV anchoring, is evaluated over a cyclic period. By comparing the coefficient of friction with the patient-specific conditions of the aortic root, the possibility of migration of specific sizes of THVs is estimated. The TAVR FSI results are shown in Figure 1. Figures 1a and 1b show the TAVR after deployment and the functionality of the leaflets. The static force required for safe anchoring is plotted in Figure 1c. The coefficient of static friction is depicted in Figure 1d, which is defined by the ratio of the friction force to the radial force. The results indicate that the minimum of the friction coefficient, 0.18, is necessary to anchor the TAVR without migration.
Figure 1: TAVR FSI simulation results. (a) Volume rendering of the velocity field at fully opened and closed configurations. (b) Top view of the THV at fully opened and closed configurations. (c) Distribution of static friction force at fully opened and closed configurations. (d) Coefficient of static friction during a cardiac cycle.

REFERENCES


EFFECT PREDICTION OF CARDIAC RESYNCHRONIZATION THERAPY USING A PATIENT-SPECIFIC HEART SIMULATOR

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SUMMARY
The objective of this study was to evaluate the capability of patient-specific simulation models for predicting the response to cardiac resynchronization therapy (CRT). We created patient-specific heart models with realistic three-dimensional morphology based on clinical data recorded before treatment for nine patients with heart failure and conduction block treated using biventricular pacing. Each model was tailored to reproduce the surface electrocardiography, echocardiography, and hemodynamic measurements of each patient. We then performed CRT simulation on each heart model according to the actual pacing protocol without changing any baseline parameters of the heart model, and compared the responses with clinical data. The best correlation was obtained between the maximum value of the time derivative of ventricular pressure and the clinically-observed improvement in ejection fraction. The patient-specific, multi-scale heart simulation successfully predicted the response to CRT by reproducing the complex pathophysiology of the heart. With further verification, this technique may be a useful tool in clinical decision making.

Key words: pacemakers, heart failure, conduction, hemodynamics

1 INTRODUCTION
The extensive clinical and basic studies have examined the factors involved in the therapeutic response of individual patients treated with cardiac resynchronization therapy (CRT). However, a significant proportion (\(\geq 30\%\)) of patients do not benefit from this invasive therapy. To solve this problem, computer simulations of CRT have been widely used to study the underlying mechanisms\cite{1,2}.

We have developed a multi-scale, multi-physics three-dimensional heart simulator in which propagation of excitation, contraction and relaxation, development of pressure, and blood flow are reproduced based on molecular models of the cardiac excitation-contraction process\cite{3,4}. We also succeeded in simulating the patient-specific body surface electrocardiogram (ECG)\cite{5}. By applying these technologies, we created a tailor-made simulation model of the heart to determine if the effects of CRT could be predicted in a canine model of heart failure with left bundle branch block\cite{6}. Further, we extended this approach to test the capability of our simulator as a tool for patient-specific evaluation of pathophysiology in a retrospective study. In that study, we created patient-specific models of the failing heart with dyssynchrony, and performed CRT simulations according to the actual pacing
Tailor-made cardiac resynchronization therapy (CRT) simulation. SR: sarcoplasmic reticulum

Figure 1: Tailor-made cardiac resynchronization therapy (CRT) simulation. SR: sarcoplasmic reticulum

The simulation results of CRT effects correlated well with the clinical parameters that reflect the therapeutic effect. Thus, we demonstrated the utility of patient-specific CRT simulation and its possible application in future clinical practice.

2 METHODOLOGY

The outline of our multi-scale, multi-physics heart simulator and its personalization technique are shown below (Fig. 1). Methodological details are as previously reported [7].

(1) Patient-specific three-dimensional finite element (FE) models of the ventricles and upper body (torso) were reconstructed from multi-slice computed tomography or magnetic resonance imaging data.

(2) These ventricular models with realistic morphology and fiber structure were subdivided into FEs, and the electrophysiological models representing endocardial, M, or epicardial cells were implemented to these elements with sarcomere models.

(3) The standard 12-lead ECGs recorded from patients before CRT were reproduced by the simulator by identifying the earliest activation sites and the timing of activation in an iterative manner.

(4) Each model was tailored to reproduce the hemodynamics measurements of each patient. Simultaneously, the lumped parameter models of the systemic and pulmonary circulations and time-varying elastance models of the atria were connected to the FE heart model, and the parameters were adjusted for each patient.

(5) CRT simulation was performed for each heart model without changing any parameters of the heart or circulation determined for the baseline simulation. The positions of the pacing leads were estimated from biplane chest radiography or CT images if available, and then adjusted to reproduce the 12-lead ECG under pacing.

From the simulation results, we calculated QRS width, left ventricular (LV) ejection fraction (EF), and the maximum value of the time derivative of LV pressure (dP/dtmax). Clinical outcome was evaluated according to the improvement in EF indicated on the ultrasonographic cardiogram.

3 RESULTS AND CONCLUSIONS

An example of the simulated and actual ECGs before and after CRT for the standard 12 leads are shown in Fig. 2A. The simulated ECGs agreed well with the actual recordings by reproducing the
Figure 2: Simulated effects of CRT (modified from [7]). (A) Standard 12-lead electrocardiogram (ECG) before (left) and after (right) CRT. In each panel, ECGs are compared between simulation (in silico, right column) and actual recordings (in vivo, left column). (B) Time-lapse images of the propagation of excitation and contraction before (top row) and after (bottom row) CRT. Numbers at the bottom indicate the time after the onset of excitation (in milliseconds). (C) Left ventricular (LV) pressure-volume relationships before (block line) and after (red line) CRT. (D) The time derivative of LV pressure before (block line) and after (red line) CRT.

wide QRS pattern before treatment. The corresponding excitations and contractions in these ECGs are shown in Fig. 2B. Whereas the excitation propagated only from the right heart before treatment (Fig. 2B, top row), biventricular pacing excited both ventricles from the apical side, so that the right ventricular outflow became the last part to be excited (Fig. 2B, bottom row). The electromechanical simulation coupled with the systemic and pulmonary circulations allowed evaluation of the hemodynamic consequences of CRT. CRT increased the EF with a concomitant rise in end-systolic pressure, indicating improved contractility (end-systolic elastance) (Fig. 2C). This improvement was further substantiated by the increase in dP/dtmax (Fig. 2D).

In the nine patients studied, CRT increased the EF by 8.7±5.7% (range -19% to 41%) according to the clinical records. Simulated improvements in EF by CRT (ΔEFsim) weakly correlated with the clinically observed improvements in EF (Fig. 3A). The simulated improvements were also much smaller than those seen clinically. However, there was a tighter correlation of the clinically observed improvement in EF and the simulated increase in dP/dtmax (ΔdP/dtmax sim) (Fig. 3B). These data suggest that dP/dtmax (r=0.94) is a better predictor of CRT responses than EF (r=0.59). Although the simulation effectively reproduced the clinical changes in QRS duration, the clinical and simulated changes in QRS duration (ΔQRSsim and ΔQRSclin) did not correlate with the clinical improvement in EF (Fig. 3C and D). This discrepancy between electrical and mechanical improvements in dyssynchrony is consistent with earlier clinical observations.

Multi-scale, tailor-made heart simulation can reproduce most of the pathophysiology of the failing heart and responses to CRT, thereby providing mechanistic insight into the pathophysiology of heart failure with conduction block. Although this was a retrospective study with a limited number of subjects, the predictive ability of this simulation technique warrants further examination with regard to future clinical applications.
Figure 3: Predictive ability of biomarkers (modified from [7]). (A) Clinically observed improvement in the ejection fraction ($\Delta$EFclin) versus simulated improvement at maximum dP/dt ($\Delta$P/dtmax sim). (B) Clinically observed improvement in the ejection fraction ($\Delta$EFclin) versus simulated improvement in the ejection fraction ($\Delta$EF sim). (C) Clinically observed improvement in the ejection fraction ($\Delta$EFclin) versus simulated narrowing of the QRS ($\Delta$QRSsim). (D) Clinically observed improvement in the ejection fraction ($\Delta$EFclin) versus clinically observed narrowing of the QRS ($\Delta$QRSclin).

REFERENCES


Mathematical and numerical modeling of the heart function II
A HYPERELASTIC IMMERSED BOUNDARY FINITE ELEMENT MODEL OF THE HUMAN HEART

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SUMMARY
We construct a fluid–structure interaction model of the entire adult human heart. The model includes descriptions of the great vessels, the four heart chambers, and the four valves. Fluid and solid mechanics are approximated with the immersed boundary finite element method. In this approach, the solid displacements and forces are approximated on a Lagrangian finite element mesh, and the fluid velocity and pressure are approximated on a fixed Cartesian grid. Blood flow is described by a Newtonian fluid. The heart walls, valves, and vessels are viscoelastic materials, where the solid component of the stress comes from a hyperelastic strain energy. We construct fiber fields on most of the structures to account for the anisotropic responses of the tissues. These fiber fields are generated using a rule–based Poisson interpolation approach. Contraction of the heart chambers is described using a uniform asynchronous active tension function. Atrial contraction is followed by ventricular systole. The model is coupled to realistic loading conditions that describe both diastolic filling and the afterload experienced during ventricular systole.

Key words: immersed boundary, finite element, cardiovascular modeling.

1 INTRODUCTION

The immersed boundary method is a general framework for fluid–structure interaction, in which the solid is described in Lagrangian coordinates and the fluid is described in Eulerian coordinates. This approach was developed by Peskin for heart valve modeling [6, 5]. The method is appealing for problems with structures undergoing large deformations because the fluid and solid discretizations are not required to conform at their interface.

In this paper, we use a version of the immersed boundary method called the immersed boundary finite element method to construct a model of the adult human heart. We use a variant of this approach introduced by Boffi et al. [4], and a numerical discretization introduced by Griffith and Luo [3].
2 METHODOLOGY

The equations of motion for the fluid–structure problem are derived by Boffi et al. [4]:

\[
\rho \left( \frac{\partial \mathbf{u}(x,t)}{\partial t} + \mathbf{u}(x,t) \cdot \nabla \mathbf{u}(x,t) \right) = -\nabla p(x,t) + \mu \nabla^2 \mathbf{u}(x,t) + \mathbf{f}(x,t),
\]

\[\nabla \cdot \mathbf{u}(x,t) = 0,\]

\[\mathbf{f}(x,t) = \int_U \nabla \mathbf{X} \cdot \mathbf{P}_e(\mathbf{X},t) \delta(x - \chi(\mathbf{X},t)) \, d\mathbf{X},\]

\[\frac{\partial \chi}{\partial t}(\mathbf{X},t) = \int_\Omega \mathbf{u}(x,t) \delta(x - \chi(\mathbf{X},t)) \, d\mathbf{X},\]

In the above equations we denote the fluid velocity with \( \mathbf{u} \), the pressure with \( p \), the density with \( \rho \), and the viscosity with \( \mu \). Equations (1)–(2) represent the balance of momentum for a continuum – fluid and solid – under incompressible motion. The tensor \( \mathbf{P}_e \) is the first Piola–Kirchhoff elastic stress, which appears via (3) as a force density in the momentum equation; it represents the force the solid exerts on the fluid. We assume the solids can be described as hyperelastic materials immersed in fluid. Thanks to this immersion in the fluid, the heart wall, the valves, and the vessels are actually viscoelastic. In fact, the stress in the solid region can be described as the sum of an elastic and a viscous components. The elastic component of the stress is computed from a pseudo-strain energy density \( W \):

\[ \mathbf{P}_e = \frac{\partial W}{\partial \mathbf{F}}, \]

where \( \mathbf{F} \) is the deformation gradient, which maps the reference configuration of the solid to its deformed state. The viscous component of the stress is inherited by the fluid permeating the solid region. Finally, equation (4) states that the solid moves with the background fluid velocity.

These equations are approximated numerically using a staggered Cartesian grid for the fluid variables and a finite element mesh for the solid displacements and forces. In particular, the force densities appearing in (3) are projected onto the basis functions defined on the volumetric finite element mesh. For details on this numerical method, we refer to Griffith and Luo [3].

The geometry of the heart model, except for the valves, is derived from computed tomography data of a healthy adult human heart. Since CT data does not provide enough resolution to accurately segment valves, their geometries are idealized. On the left of Figure 1, we show the meshed heart and great vessel geometries with the underlying Cartesian fluid grid. On the right, we show the location of the valves with respect to the heart geometry.

Figure 1: Visualization of the heart, great vessel, and idealized valve geometries. In the figure on the left, the AMR fluid grid is also depicted.
The myocardial wall, the vessel walls and the valves have an anisotropic mechanical response. To model this behavior, we consider fiber reinforced strain energy densities. Specifically, for the valves, we use the Holzapfel and Ogden constitutive law [1]:

$$W_{\text{HO}}(I_1, I_{4s}, I_{4t}, I_{8fs}) = \frac{a}{2b} \exp \left( b \left( I_1 - 3 \right) \right) + \sum_{i=fs} \frac{ai}{2bi} \left( \exp \left( b_i (I_{4i} - 1)^2 \right) - 1 \right) + \frac{af_s}{2bf_s} \left( \exp \left( b_{fs} I_{8fs}^2 \right) - 1 \right).$$

In this model, the valves have two orthogonal directions described by circumferential and radial fiber fields. For the myocardium we also use the model by Holzapfel and Ogden [1] where one of the two families of fibers represent the collagen structure of the muscle. For the heart walls we have also considered a Fung-type Guccione model [2]:

$$W_{\text{myo}}(F) = \frac{c}{2} \left( \exp Q - 1 \right),$$

$$Q = b_f \tilde{E}_{11}^2 + b_t (\tilde{E}_{22}^2 + \tilde{E}_{33}^2 + \tilde{E}_{12}^2 + \tilde{E}_{13}^2 + \tilde{E}_{23}^2 + \tilde{E}_{32}^2).$$

Figure 2 shows the circumferential fibers for the aortic valve on the left, and the fibers for the heart myocardium on the right. These vector fields are computed by solving a sequence of harmonic problems on the finite element mesh.

![Figure 2: A visualization of the fiber vector fields for the aortic valve on the left and the heart myocardium on the right.](image)

3 RESULTS AND CONCLUSIONS

We present some preliminary results for ventricular systole in Figure 3 as well as an entire cardiac cycle in Figure 4. Figure 3 displays the displacement of the heart myocardium along with the magnitude of the fluid velocity on a slice through the ascending aorta. We can see that there is substantial flow through the aorta during ventricular systole.

![Figure 3: Snapshots in time of the flow through the aorta during ventricular systole. Time increases from left to right.](image)

Figure 4 shows displacement of the valves and heart myocardium. We see closure of the mitral and tricuspid valves and a corresponding opening of the aortic and pulmonary valves during ventricular systole. We remark that proper functioning of the valve models is necessary to capture the phases...
Figure 4: Snapshots in time of a cardiac cycle. The left figure is the initial configuration. The middle figure depicts closure of the mitral and tricuspid valves, and the right figure shows opening of the aortic and pulmonary valves.

of the ventricular beat, in particular the isovolumic phase. The opening exercises and closing of the valves is dictated by the ventricular pressures, atrial pressures, and aorta and pulmonary artery pressures.

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MODELING PATIENT-SPECIFIC LEFT-VENTRICULAR BLOOD FLOW AND MITRAL VALVE DYNAMICS

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SUMMARY

This abstract describes a method for modeling patient-specific left-ventricular blood flow and mitral valve dynamics. We aim to build a model that produces realistic flows under physiological pressures and can be constructed without excised specimens. Patient-specific left-ventricular geometry and deformation through the cardiac cycle are measured from MRI scans. We construct model mitral valves using a design-based methodology, in which we compute the loads the valve must support, then assign model geometry and material properties accordingly. The system is then simulated with blood using the immersed boundary method. With this model, we aim to study macro-scale cardiac flows and pathophysiology.

Key words: left-ventricular blood flow, mitral valve modeling, fluid-structure interaction

1 INTRODUCTION

The primary goal of this study is to build patient-specific mathematical models of the left heart that produce physiological flows when driven by physiological pressures over multiple cardiac cycles. This model will include valves that qualitatively match the anatomy of real valves, and heart walls with experimentally measured, patient-specific geometry and prescribed deformations.

Modeling of heart mechanics is fundamentally challenging; one must consider detailed anatomy, biomechanics, and specialized numerical methods for fluid-structure interaction appropriate for large deformations and complex geometries. Heart valve tissue is fibrous; its material response is highly nonlinear, anisotropic and heterogeneous. Valve closure is “especially challenging to simulate because it fundamentally involves a delicate balance between the fluid dynamics and elasticity of the valve’s leaflets” [1]. Novel modeling techniques using design-based elasticity have proven effective at overcoming these challenges [2]. Heart valves undergo large, rapid deformations and self-contact through the cardiac cycle; ventricular geometry is wavy and changes rapidly with muscle contractions, causing the blood domain to rapidly change in size and topology. Numerical techniques such as the immersed boundary method [3] are necessary to simulate these complicated physical situations.

This model will include a unique combination of components to test valve function and be amenable to answering questions on disease physiology. Existing models from other groups include left ventricular muscle mechanics, but do not attempt to achieve patient-specific deformations [4], or model muscle and electrical heart activity, but do not model fluid or valve mechanics [5]. For example, it has been proposed that a large vortex is shed from the mitral valve leaflets and that this supports valve closure. We seek to confirm or refute this hypothesis. We will also investigate the mechanics of a heart condition called hypertrophic cardiomyopathy.
2 METHODOLOGY

To predict the hemodynamics of a particular individual, we will extract their ventricular geometry by segmentation of MRI scan images. We perform image segmentation in our in-house, open-source tool SimVascular to extract the geometry of the ventricular surface for each patient [6, 7]. We hand-draw contours for all relevant portions of the anatomy, including with the endocardial surface of the left ventricle and a portion of the left atrium, the papillary muscles and the aorta. These contours are then lofted into a three dimensional model that represents the boundary of the blood domain in our simulations, see Figure 1.

Figure 1: Image segmentation contours showing the endocardium of the left ventricle and its papillary muscles (left), contours of the left atrium, left ventricle and aorta segmented from multiple MRI orientations (center), resulting three dimensional model (right).

To model the mitral valve, we use a design-based approach in which we compute the model geometry and tensions that are needed to support a pressure load when the valve is closed, and then assign material properties such that these tensions can be generated by uniform strain. This model was originally developed in [8, 2]. We do not rely on measured geometry or material properties of an excised specimen. Our goal is to build the model valve as much as possible from first principles, formulated as differential equations for the closed, pressurized valve.

To construct the model, we assume that the valve is composed of two leaflets, which are made up of fibers that exert tension only in the fiber directions, and which support a static, uniform pressure load $p$. We represent the leaflets as an unknown parametric surface, $X(u, v) : \Omega \subset \mathbb{R}^2 \to \mathbb{R}^3$. In this formulation, there are two families of fibers, one running along the curves $v = \text{constant}$, and the other along the curves $u = \text{constant}$. Let subscripts denote partial derivatives, $\| \cdot \|$ denote the Euclidean norm, $X_u / \|X_u\|$ and $X_v / \|X_v\|$ the unit tangents to each fiber family, and $S, T$ the tension in each family. We then derive the following nonlinear partial differential equation for the equilibrium of the leaflets, in which derivatives of tensions support a pressure:

$$0 = p(X_u \times X_v) + \frac{\partial}{\partial u} \left( S \frac{X_u}{\|X_u\|} \right) + \frac{\partial}{\partial v} \left( T \frac{X_v}{\|X_v\|} \right),$$

(1)

To close equation 1, and avoid use of a reference configuration that was not available, we specify the maximum tension, and defined $S$ and $T$ such that the tension goes smoothly to zero as the lengths of fibers go to zero. Equation 1 then becomes

$$0 = p(X_u \times X_v) + \frac{\partial}{\partial u} \left( \alpha \left( 1 - \frac{1}{1 + \|X_u\|^2 / a^2} \right) \frac{X_u}{\|X_u\|} \right) + \frac{\partial}{\partial v} \left( \beta \left( 1 - \frac{1}{1 + \|X_v\|^2 / b^2} \right) \frac{X_v}{\|X_v\|} \right),$$

(2)
where $\alpha, \beta$ are the maximum tensions and $a, b$ can be tuned to influence fiber spacing. We specify that the chordae tendineae also exert tension; their equilibrium is represented by a discrete system of nonlinear equations. We then discretize and solve this nonlinear PDE simultaneously with the discrete equilibrium equations in the chordae, coupling the free edge of the valve to the chordae at locations corresponding to where real chordae attach. The mitral valve skeleton, which is treated as a boundary condition when solving equation 2, is segmented from MRI data so that the valve fits in the model heart of this individual. From the solution of these equations, the closed model valve geometry emerges, along with the highly heterogeneous tensions the valve must support during closure.

To simulate the valve with fluid, we treat every link in the discretized model as a nonlinear spring. The solution of equation 2 specifies a length $L$ and tension $\tau$ of each link in the model expected during valve closure, and we use this information to generate a constitutive law for the valve. We assume that all links in the model have uniform strain of $E_0 = 0.16$, then solve $E_0 = L/R - 1$ to determine a rest length $R$ for the link. We set the stiffness for each link such that the required tension is achieved at this strain. This newly specified constitutive law is applicable throughout the cardiac cycle and suitable for use in simulations with fluid. Note that equation 2 is solved solely to generate the model and plays no further role.

Finally, using the immersed boundary method [3], we simulate the model left ventricle and mitral valve with fluid. All simulations are run with the fluid solver IBAMR [9]. To drive the simulation, we prescribe a time-dependent pressure difference across the mitral valve as boundary conditions at the aorta and left atrium. Valve motion is passive and elastic, determined by the constitutive law as described above and through its coupling to the fluid. We prescribe the location of the left ventricular wall with a penalty method. For a point $X$ in the structure domain and its desired location $X_{\text{target}}$, a force $F = -\kappa(X - X_{\text{target}})$, where $\kappa$ is a penalty spring constant, approximately enforces its position.
Note that is a model of a static, heart-shaped test chamber and does not yet include ventricular motion.

3 RESULTS AND FUTURE WORK

Preliminary flows of the mitral valve in a patient-specific geometry are shown in Figure 2. In future work, motion of the geometry will be controlled with prescribed displacement. We use image registration techniques to extract the motion of an individuals left ventricle from time-resolved MRI scans [10]. An aortic valve model is under development using similar methods to that of the mitral valve. When these techniques succeed, we will apply them to study the physiology of hypertrophic obstructive cardiomyopathy (HOCM) and its surgical treatment. In individuals with HOCM, the ventricular septum thickens, blocking the outflow of blood from the left ventricle, increasing risk of sudden cardiac death and eventually leading to heart failure [11]. The mechanics of HOCM, however, are not well understood. We seek to study the mechanisms of its pathophysiology and provide quantitative information on their causes.

4 ACKNOWLEDGEMENTS

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REFERENCES


ESTIMATION OF A COMPATIBLE CARDIAC CONDUCTION SYSTEM FROM DISCRETE ENDOCARDIAL TIME SAMPLES

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SUMMARY
Reconstructing a patient-compatible Purkinje Network from electroanatomical maps is a challenging task, that could help improve models for electrophysiology simulation. In this study, we present a method to build a Purkinje network from estimated Purkinje-myocardial junctions, that is compatible with patient’s electroanatomical map with an average error below 1ms. We carry out a simulation study to show the effect of PMJ density on the estimated times and Purkinje network morphology.

Key words: cardiac conduction system, inverse estimation, electrophysiology personalization

1 INTRODUCTION

The reconstruction of the ventricular cardiac conduction system (CCS) from patient-specific data is a challenging problem [1, 2]. High-resolution imaging techniques have allowed only the segmentation of proximal sections of the CCS from images acquired ex-vivo [6]. Some methods have already been presented to estimate the Purkinje Network (PKN) from electro-anatomical maps (EAMs) [4, 3]. In this paper, we present an algorithm that estimates a set of Purkinje-myocardial junctions (PMJs) from EAMs, and builds a PKN compatible with the location and activation time of PMJs. The algorithm is tested on several PKN configurations, with simulated and clinical data. The results show that the set of PMJs built explains the observed activation map for different synthetic CCS configurations. The average error in the predicted activation time is below the amplitude of the error in the data.

2 MATERIAL AND METHODS

An EAM was acquired at Bordeaux University Hospital using the CARTO system (Webster Biosense) from a patient showing idiopathic ventricular fibrillation. Each sample acquired was postprocessed to obtain the local activation time (LAT) as the maximum negative deflection in monopolar and bipolar signals, and subsequently performing a manual validation, and filtering of samples that do not show spatio-temporal correspondence.

2.1 Algorithm

The goal of the algorithm is to find the PKN branching configuration that is able to reach all the estimated PMJs minimizing both the estimated LAT at the PMJ and the length of the whole PKN.
Table 1: Estimation of the PKN directly from the real PMJs.

<table>
<thead>
<tr>
<th>Name</th>
<th>PMJs</th>
<th>PMJs&lt;4.0</th>
<th>PMJs&lt;1.0</th>
<th>Error at PMJs</th>
<th>Distance error</th>
<th>Error at mesh</th>
</tr>
</thead>
<tbody>
<tr>
<td>PK6</td>
<td>1224</td>
<td>96.32%</td>
<td>84.23%</td>
<td>0.69 ± 0.6 ms</td>
<td>0.87 ± 1.32 mm</td>
<td>0.52 ± 0.3 ms</td>
</tr>
<tr>
<td>PK3</td>
<td>831</td>
<td>94.83%</td>
<td>79.42%</td>
<td>0.72 ± 0.6 ms</td>
<td>1.76 ± 2.61 mm</td>
<td>0.63 ± 0.5 ms</td>
</tr>
<tr>
<td>PK11</td>
<td>442</td>
<td>96.83%</td>
<td>88.20%</td>
<td>0.65 ± 0.6 ms</td>
<td>1.19 ± 1.39 mm</td>
<td>0.63 ± 0.5 ms</td>
</tr>
<tr>
<td>PK4</td>
<td>362</td>
<td>95.86%</td>
<td>78.45%</td>
<td>0.70 ± 0.6 ms</td>
<td>1.53 ± 1.58 mm</td>
<td>0.65 ± 0.5 ms</td>
</tr>
<tr>
<td>PK15</td>
<td>206</td>
<td>95.63%</td>
<td>80.58%</td>
<td>0.81 ± 0.7 ms</td>
<td>1.89 ± 2.06 mm</td>
<td>0.72 ± 0.8 ms</td>
</tr>
</tbody>
</table>

We build the estimated PKN iteratively. An initial branch \( \Xi_0 \), corresponding to the His bundle and Left Bundle Branch (LBB), is built before the algorithm generates any further branch. The initial branch starts always from a location determined by the user and expands to the apex through the septal wall following the shortest path [3]. Then, we process the PMJs ordered by LAT, starting by the earliest one. Therefore, we start building the PKN from the region closer to the LBB, which is expected to show smaller LAT errors due to the shorter path from the Atrioventricular Node (AVN). After step \( i \), we have processed \( i - 1 \) PMJs in \( \Theta \) and have built an estimated tree \( \Xi^{i-1} \) that connects them. We pick \( \theta_i \) and solve the Eikonal problem on \( \Omega \) starting from \( \theta_i \) to obtain the distance from the estimated PMJ to all the vertices on \( \Xi^{i-1} \). Then, we try to connect the PMJ \( \theta_i \) with \( \Xi \) using a geodesic that ends at a point \( \xi_i \in \Xi^{i-1} \). The connection point is chosen so that it minimizes the difference between the activation time of \( \theta_i \) through \( \Xi \) and the value of \( t_i \). We use the constraint that the path cannot intersect the PKN created so far. We only connect \( \theta_i \) with a new branch if the error is below a threshold. Once the iteration ends with the last \( \theta_n \), the process is restarted trying to connect the disregarded PMJs to the estimated PKN, using a larger threshold. The algorithm stops when all the PMJs have been connected to \( \Xi \) or when the error threshold reaches a predefined bound.

2.2 Experimental setup

We have built a series of synthetic PKNs on the geometry of a left ventricular endocardium reconstructed from MRI, using the stochastic method described in [5], and have generated the corresponding tissue activations. More information about the different PKN generated and some images can be found in [1]. For the evaluation of the algorithm, we have performed two sets of experiments. First, we have used the actual PMJs of each PKN to build an estimated PKN and compare it with the original. Second, we have simulated an EAM acquisition registering the activation time, according to the different PKNs, at a number of measurement points uniformly distributed. A Gaussian error is added to the actual LAT on the measurement points. We estimate the PMJs from this information using [1], which are used as the input data for our algorithm. In order to have a quantitative assessment of the algorithm we consider several measures of quality, summarized in Tables 1 and 2. We have considered: the number of nodes in \( \Theta \) that have been successfully connected to \( \Xi \) (error < 4.0ms); the mean absolute error of the activation time at PMJs \( \theta_i \) according to the activation resulted from the propagation through the estimated PKN and a given conduction velocity, in ms; the average distance from the estimated branches and the real branches per branch subsegment.

3 RESULTS AND CONCLUSIONS

For the estimation of PKNs, we compared the results using real (Table 1) and estimated PMJs (Table 2) as input to the algorithm. As expected, the real PMJs yield smaller errors, and the PKN structure is better reproduced (see Fig. 1). The difference in LAT at PMJs when using the real PMJs is below 1ms for all scenarios, as it is the average errors after propagating the signal to all mesh nodes. The average distances between tree segments is less than 1mm, due to the close match of real and estimated PKNs in most tree sections. In addition, around 95% of the PMJs can be connected to the three with an error...
Figure 1: Graphical results for PK11 and $\sigma = 0.5$. The original PKN is depicted as a tubular structure in grey color, while PMJs are represented with spheres. First row correspond to estimated PKNs using the real PMJs, while second row are the PKN estimated from estimated PMJs (also included). PMJs in (b) and (f) are color coded to show the error (ms) when the estimated PKN is used. PKN in (c) and (d) show the differences in angle (degrees) between the real and the estimated PKN branches, while (d) and (h) show the distance (mm) between the elements of the real and the estimated PKN.

<table>
<thead>
<tr>
<th>Name</th>
<th>PMJs</th>
<th>CV</th>
<th>PMJs$&lt;4.0$</th>
<th>PMJs$&lt;1.0$</th>
<th>Error at PMJs</th>
<th>Distance error</th>
<th>Error at mesh</th>
</tr>
</thead>
<tbody>
<tr>
<td>PK6</td>
<td>114</td>
<td>1.1</td>
<td>76.32%</td>
<td>62.28%</td>
<td>0.79 ± 0.9ms</td>
<td>2.20 ± 2.7mm</td>
<td>1.67 ± 1.8ms</td>
</tr>
<tr>
<td>PK3</td>
<td>95</td>
<td>1.2</td>
<td>77.89%</td>
<td>60.00%</td>
<td>0.66 ± 0.7ms</td>
<td>2.11 ± 2.4mm</td>
<td>1.20 ± 1.4ms</td>
</tr>
<tr>
<td>PK11</td>
<td>111</td>
<td>1.0</td>
<td>81.98%</td>
<td>63.96%</td>
<td>0.76 ± 0.8ms</td>
<td>1.92 ± 1.8mm</td>
<td>1.40 ± 1.4ms</td>
</tr>
<tr>
<td>PK4</td>
<td>99</td>
<td>1.0</td>
<td>85.86%</td>
<td>69.70%</td>
<td>0.72 ± 0.6ms</td>
<td>2.17 ± 2.1mm</td>
<td>1.18 ± 1.2ms</td>
</tr>
<tr>
<td>PK15</td>
<td>83</td>
<td>1.1</td>
<td>79.52%</td>
<td>57.83%</td>
<td>0.72 ± 0.5ms</td>
<td>3.09 ± 3.6mm</td>
<td>1.38 ± 1.6ms</td>
</tr>
</tbody>
</table>

Table 2: Estimation of PKN from estimated PMJs and error $\sigma = 0.5$ms. Conduction velocities (CV) in m/s.

below 4.0ms. When estimated PMJs are used to build the PKN, the conduction velocity in the PKN has to be estimated. Since we only have a subset of the PMJs, the algorithm tends to overestimate the conduction velocity (see Table 2 (CV)), where most cases have values above the real value of 1.0m/s. The percentage of estimated PMJs successfully connected to the PKN decreases, due to errors in their location and activation time (note that error was inserted in the samples as described in [1]), but it is always above 75%. Although errors at PMJs are still below 1ms in all scenarios, the average error across the mesh increases to around 1.3ms due to the underestimation in the overall number of PMJs. The same explanation applies to the increase in distance error, since the low number of PMJs and associated branches in the estimated PKN leads to larger distances to the real PKN.

The estimation of PKN was carried out in an exemplary patient, based on the EAM data collected from the LV endocardium. The electrical signals were filtered and processed to detect LATs. A total of 210 samples manually validated, and projected to a reference endocardial surface mesh, were used as an input for the algorithm. The conduction velocities (CV) that produced a meaningful PKNs were in the range between 2.5 and 4.0 m/s, which are within a physiological range, although overestimation was expected since only a total of 22 PMJs was estimated. This low number was obtained because estimated PMJs were discarded if they did not meet criteria related to correlation with sample points. Best case was obtained using a CV of 3m/s (see Table 3), with a full connection of PMJs and an average error of 0.27ms at PMJs. Since we do not have ground truth data for LAT at all the mesh point (CARTO data is interpolated), we could not obtain the associated error. The structure of the estimated PKN changed depending on the CV used, as can be observed in Fig. 2, since the path...
Figure 2: PKN Estimated from patient’s EAM using different conduction velocities (CVs). CVs were (a) 2.5m/s, (b) 3.0m/s, (c) 3.2m/s, and (d) 4.0m/s. As can be observed, the structure of the PKN and the errors at the PMJs change depending on the conduction velocity chosen.

<table>
<thead>
<tr>
<th>CV (m/s)</th>
<th>PMJs&lt;4.0</th>
<th>PMJs&lt;1.0</th>
<th>Error at PMJs</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5</td>
<td>100.0%</td>
<td>72.2%</td>
<td>0.33 ± 0.5ms</td>
</tr>
<tr>
<td>3.0</td>
<td>100.0%</td>
<td>83.3%</td>
<td>0.27 ± 0.3ms</td>
</tr>
<tr>
<td>3.2</td>
<td>95.5%</td>
<td>50.0%</td>
<td>0.99 ± 1.5ms</td>
</tr>
<tr>
<td>3.5</td>
<td>94.4%</td>
<td>38.9%</td>
<td>0.69 ± 1.19ms</td>
</tr>
<tr>
<td>4.0</td>
<td>100.0%</td>
<td>54.6%</td>
<td>0.64 ± 1.0ms</td>
</tr>
</tbody>
</table>

Table 3: Estimation of the PKN from EAM data.

length from the atrio-ventricular node to a given PMJ is affected by this parameter. Overall, the errors obtained at PMJs are small enough to apply this method to estimate the PKN for patient-specific cardiac modeling. Due to the under estimation of PMJs, the CV in PKN is expected to be overestimated, as well as the overall activation of the endocardium. One of the most important drawbacks of the method is the dependence on the estimation of LATs at PMJs, which have to be carefully reviewed to avoid spatio-temporal inconsistent maps.

REFERENCES


EFFECTS OF MYOFIBRE ARCHITECTURE ON BIVENTRICULAR BIOMECHANICS: A SIMULATION STUDY

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SUMMARY

Personalized computational cardiac modelling can provide unique insights on heart function both physiologically and pathologically. Myofibre architecture is one of the essential components when constructing realistic cardiac biomechanical models. Although ex vivo myofibre datasets are available, many computational studies still use rule-based myofibre reconstruction. In this study, we develop a bi-ventricle neonatal porcine model with myofibres reconstructed by mapping an ex vivo myofibre dataset through a large deformation deformorphic metric mapping (LDDMM) approach, we further compare this model with a corresponding model based on a rule-based approach using the same ex vivo dataset. Our results show that incorporating a realistic myofibre structure can produce larger stroke work, higher ejection fraction and apical twist. The LDDMM-based model outcome is closer to the healthy range compared to the rule-based myofibre reconstruction. This highlights the importance of a realistic myofibre architecture in personalized ventricular modelling.

Key words: bi-ventricular model, myofibre architecture, biomechanics, LDDMM

1 INTRODUCTION

Cardiac diseases remain a major public healthy burden, especially the adverse remodelling of cardiac function after acute myocardial infarction (MI). Studies have demonstrated that mechanical stresses and strains in myocardium can have great effects on pathological processes [7]. The three-dimensional (3-D) spatial architecture of myofibres plays a very important role in heart function, influencing electrical propagation, myocardial expansion in diastole and contraction in systole. 3-D finite element (FE) mechanics models of the heart have been extensively used to investigate regional myofibre strains and stresses in normal and abnormal function [7, 9]. To include myofibres into the computational models, two different approaches have been widely used in the literature, one approach is directly mapping myofibres from ex vivo datasets to the computational models, for example the model reconstructed directly from diffusion-tensor magnetic resonance imaging (DT-MRI) datasets [9] or using atlas-based methods to warp the DT-MRI data into the models. The other approach is the rule-based method in which myofibres rotates from endocardium to epicardium with prescribed angles, varied linearly in most of studies [10].

Based on a rule-based approach for myofibre reconstruction in a left ventricle (LV) model, Wang et al. [10] found that changes in myofibre rotation angle can dramatically affect the stress and strain distributions during diastole. Later, using a bi-ventricular model, Patil et al. [8] also demonstrated that changes in myofibre angle can significantly affect myofibre stress-strain distribution within the LV wall in diastole. In a recent study, Gil et al [4] compared three different myofibre architectures in an electromechanics bi-ventricular model, one is from a DT-MRI dataset, the other two are reconstructed using a rule-based approach with histologically measured myofibre angles. Their results showed that the model with realistic myofibre structure from DT-MRI produces functional scores much closer to healthy ranges than rule-based approaches.
In this study, we develop a neonatal bi-ventricle porcine model to compare ex vivo DT-MRI myofiber architecture with two different simplifications based on a rule-based approach [10]. The first simplification uses AHA17 segments to reconstruct myofibres with different fibre angles at each segment, a further simplification is made by also assigning the same fibre rotation angles in the whole ventricle.

2 METHOD

A bi-ventricular model is reconstructed from a 3-D computed tomography (CT) data of a neonatal porcine heart. Details of the data acquisition can be found in [1]. The 3D CT data is first segmented using Seg3D\(^1\), then the boundary contours are exported into SolidWorks (Dassault Systemes, MA USA) for the 3-D geometry reconstruction, and finally meshed with ICEM (ANSYS, Inc. PA USA) as shown in Fig. 1(a). A DT-MRI dataset from an ex-vivo canine heart, publicly available from the Cardiovascular Research Grid \(^2\), is used in this study to provide the myofibre architectures in the left ventricle (Fig. 1(b)), details of the ex vivo DT-MRI dataset can be found in [6].

Deformetrica\(^3\), an open-source software for statistical analysis of 2D and 3D shape data based on large deformation diffeomorphic metric mapping (LDDMM) framework [3], is used to map the myofibre architecture from the DT-MRI dataset to the bi-ventricular model. Because Deformetrica can only map different surface meshes, we first register the endocardial surfaces between the bi-ventricular model and the DT-MRI dataset, then register the epicardial surfaces. Denoting the displacements when warping the DT-MRI dataset to the computational model on the endocardial surface as \(u_{\text{endo}}^{\text{LDDMM}}\) and \(u_{\text{epi}}^{\text{LDDMM}}\) for the epicardial surface, we interpolate warping displacements from the endocardial and epicardial surfaces into the inner wall by solving a Poisson system (Eq. 1) in Fenics\(^4\),

\[
\begin{align*}
\nabla^2 u &= 0, \\
\quad u &= u_{\text{endo}}^{\text{LDDMM}} \quad \text{at endocardial surface,} \\
\quad u &= u_{\text{epi}}^{\text{LDDMM}} \quad \text{at epicardial surface,} \\
\frac{\partial u}{\partial N} &= 0 \quad \text{at basal plane,}
\end{align*}
\]  

(1)

where \(N\) is the surface normal. The mapped myofibre direction (\(f_{\text{bi-ven}}\)) in the bi-ventricular model is then \(f_{\text{bi-ven}} = F f_{\text{DT-MRI}}\), in which \(f\) is myofibre direction, and \(F\) is the deformation gradient from the DT-MRI dataset to the bi-ventricular model, obtained by solving Eq.(1). Fig. 1(c) illustrates the mapped fibre architecture in the neonatal porcine bi-ventricular model.

After mapping the ex vivo myofibre dataset, the average fibre angles are calculated for the endocardium (\(\theta_{\text{ave}}^{\text{endo}}\))) and epicardium (\(\theta_{\text{ave}}^{\text{epi}}\)), then for each segment of the AHA-17 division (Fig. 1(d)). Because the DT-MRI dataset does not measure myofibres in the right ventricle, we assume myofibres in the right ventricle (RV) vary linearly from endocardium with \(\theta_{\text{ave}}^{\text{endo}}\) to epicardium with \(\theta_{\text{ave}}^{\text{epi}}\). Three cases are considered. Case 1: the bi-ventricular model with the DT-MRI mapped myofibre architecture, shown in Fig. 1(f); case 2: myofibre rotates linearly at each LV segment according to the average myofibre angle for each segments, shown in Fig. 1(e); and case 3: Myofibre rotates linearly between endocardium and epicardium from \(\theta_{\text{ave}}^{\text{endo}}\) to \(\theta_{\text{ave}}^{\text{epi}}\) (Fig. 1(g)). A rule-based approach [10] is used in cases 2 and 3 to construct myofibres. Note case 2 has heterogeneous myofibre organization in the whole LV, but homogeneous one within each segment, while case 3 has the same myofibre rotation across the whole LV. No dispersion is included in cases 2 and 3. The sheet angle is assumed to be zero for the three cases.

The Cauchy stress tensor \(\sigma\) is additively decomposed into two components, the passive part \(\sigma^p\) and the active part \(\sigma^a\). The passive behaviour of the tissue is described using a reduced HO model proposed by [5],

\[
\psi = \frac{a}{2b} \exp[b(I_1-3)] + \sum_{i=f,n} \frac{a_i}{2b_i} \{\exp[b_i(\max(I_{4i})-1)^2]-1\} + \sum_{i,j=f,n} \frac{a_{ij}}{2b_{ij}} \{\exp(b_{ij}I_{8ij}^2)-1\} + \frac{1}{D} (\frac{J^2 - 1}{2} - \ln(J))
\]

(2)

\(^1\)http://www.sci.utah.edu/cibc-software/seg3d.html

\(^2\)http://cvrgrid.org/data/ex-vivo

\(^3\)http://www.deformetrica.org/

\(^4\)https://fenicsproject.org/
Figure 1: Neonatal bi-ventricle model construction with myofibers. (a) the bi-ventricle model built from a 3D CT data, (b) the ex vivo DT-MRI dataset, (c) LDDMM-mapped myofibers in the bi-ventricle model, (d) AHA17 divisions, (e) the bi-ventricle model with myofibre constructed using a rule-based approach for each segment (case 2), (f) the bi-ventricle model with LDDMM-mapped myofibres (case 1), (g) the bi-ventricle model with rule-based approach (case 3), and (h) the FE bi-ventricle model with lumped circulation systems, $C$ represents compliance, and $R$ represents flow resistance.

where $a, b, a_i, b_i, a_{ij}, b_{ij}$ are material constants, $I_4 = \text{trace}(F^T F)$, $I_4f = f_0 \cdot (F^T F f_0)$, $I_4n = n_0 \cdot (F^T F n_0)$, $I_{8fs} = f_0 \cdot (F^T F s_0)$, $I_{8fn} = f_0 \cdot (F^T F n_0)$, $f_0$, $s_0$ and $n_0$ are the myofibre, sheet and sheet-normal directions at reference state, $J = \text{det} F$, and $1/D$ is the bulk modulus. We assume the active tension $T_a$ is generated only along the myofibre direction, a time-varying elastance model of active tension development is used for modelling active force $T_a$, and $\sigma_a = T_a \otimes f$ [9]. The FE model of heart is coupled to lumped models of pulmonary and systemic circulatory systems that are realised through a combination of surface-based fluid cavities and fluid exchanges (Fig. 1(h)). Explicit Abaqus (Dassault Systemes, MA USA) is used for the bi-ventricular model simulation, its implementation is based on the development of the SIMULIA LivingHeart project. A 8 mmHg end-diastolic pressure for the LV and 4 mmHg for the RV are assumed for all cases, parameters in Eq.(2) are determined from the experimental study of [1].

3 RESULTS

Fig. 2 (a) shows the pressure-volume loops among the three models. Although all the cases experience the same end-diastolic pressure with same material properties, it can be found that case 1 with LDDMM mapped myofibres has a slightly larger end-diastolic volume and contracts more in systole with a much smaller end-systolic volume, around 1.3 mL compared to the rule-based cases (around 1.45 mL). Similar results can be found for the right ventricle, a much smaller end-systolic volume is achieved in case 1. The difference between the cases 2 and 3 is minor. Fig. 2 (b) summarizes the ejection fractions for both the LV and RV, higher ejection fractions (EF) can be found in case 1 with LDDMM mapped fibres than other two cases, around 5% more in LV and 3% more in RV. In fact, LV EFs in cases 2 and 3 are both less than 50%, which suggests the LV pump function is suboptimal. The apical twists during systole with respect to end-diastole are shown in Fig. 2(c), the peak twist angle from case 1 is around 11°, which is within the reported ranges in healthy hearts $(10.2 \pm 7.6^\circ)$ [2], and higher than the values from case 2 (8°), and case 3 (7°).

Figure 3 shows the peak systolic myofibre stress distributions for the three cases. In case 1, high myofibre stress can be found at both the endocardial and epicardial surfaces, while for cases 2 and 3, myofibre stress in the endocardial surface is much higher than other regions. Among the three cases, case 1 experiences higher myofibre stress than other two cases, partially because the larger end-diastolic volume (Fig. 2(a)) results in a higher active tension generation according to the “Frank-Starling” law. Moreover, stress pattern in case 1 is much more heterogeneous than the distributions.
4 CONCLUSION

In this study, we have developed a neonatal bi-ventricular computational model with mapped myofibre architecture from an ex vivo DT-MRI dataset using a LDDMM approach. Different approximations of myofibre architecture are compared in terms of cardiac pump function. Our results show that using realistic myofibre architecture can produce better cardiac work, higher ejection fraction and larger apical twist compared to the simplified rule-based myofibres, even though they all are derived from the same DT-MRI dataset. Our results suggest that it is necessary to incorporate realistic myofibre architecture if personalized ventricular models are needed.

Acknowledgement We are grateful for the funding provided by the UK EPSRC (EP/N014642/1). D. Guan also acknowledges funding from the Chinese Scholarship Council and the fee waiver from the University of Glasgow. Thanks also extend to all members of the Living Heart Project.

REFERENCES


SIMULATION OF ELECTRICAL CARDIOVERSION IN TP06 MYOCARDIAL MODEL INFLUENCED BY CLASS III AND IV ANTI-ARRHYTHMIC DRUGS

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SUMMARY

Computer-based simulations of cardiac arrhythmia treatment are of great interest. In this paper, we propose a spatially adaptive stimulation method and a pacing period assimilation algorithm, which avoid forming new spiral waves on the electrode. We model the myocardium affected by verapamil, amiodarone and L-type Ca-channel blockade and try to supersede the spiral wave by pacing from a linear electrode. Pacing periods and induced drift velocities are compared between these cases.

Key words: low-voltage cardioversion, ionic currents, spiral waves, anti-arrhythmia pacing

1 INTRODUCTION

Computer-simulated therapy for life-threatening arrhythmias caused by spiral waves is intensively studied during the last decades. A number of methods for managing the cardiac arrhythmias exist. One of them is low-voltage cardioversion (LVC), or overdrive pacing, which was originally described for chemical active media [6]. Here, an electrode is placed in the myocardium and initiates waves with a shorter period than that of arrhythmia. In some cases, this procedure has been shown to remove spiral waves from the heart, thus stopping cardiac arrhythmia.

We studied the LVC method using a stimulation from point electrodes, which is usually implemented in practice, as well as from a linear electrode [3, 2]. These electrodes create new plane waves. However, if the stimulation zone crosses a spiral wave sleeve, new spiral waves can appear through a mechanism similar to the S1S2 protocol [9]. This phenomenon leads to worsened arrhythmia and complicates the theoretical study of induced drift; therefore, it is important to develop a stimulation algorithm that avoids the appearance of new spiral waves.

In this paper, we proposed two new stimulation algorithms. The first one is based on the idea that each stimulus is applied to a part of the electrode, and the second one helps the medium assimilate the short stimulation period. We studied these algorithms in a 2D TP06 heart muscle model [10]. Electrical properties of cardiac tissue were changed using two anti-arrhythmic drugs—verapamil and amiodarone—and the L-type Ca-channel blockade. We found the parameters of these stimulation algorithms that provide safe and effective LVC. The drift velocity was measured in the successful LVC cases. The advantage of our algorithms is that they allow to avoid new spiral waves when using linear electrodes. The L-type Ca-channel blockade and verapamil adversely affected the LVC, and amiodarone usage showed promising results.

2 MATERIALS AND METHODS

The mathematical models and numerical methods that we used are described in detail in [4]; here, we briefly specify their main features. We solved the monodomain reaction-diffusion system [10] in a
2D anisotropic homogeneous rectangle 3:1 with no-flux boundary conditions. Tissue anisotropy was described via fibres directed parallel to the X-axis. The tissue’s anisotropy ratio along and across the fibres was 3 for wave speeds and 9 for diffusion coefficients.

We modelled the effects of anti-arrhythmic drugs of Classes III and IV—verapamil, amiodarone and a CaL-blocker—using approaches proposed in [1, 5, 8]. We multiplied both gCaL and gKr by 0.25, 0.5, and 0.75 to model the verapamil effect and denote these cases as ver25, ver50, and ver75, respectively. We used the same coefficients for gCaL to model the L-type Ca-channel blocker, cases gCaL25, gCaL50, gCaL75. Finally, we simulated amiodarone in low (1 µM, amio1) and high (3 µM, amio3) concentrations, as proposed in [8]. The case with normal currents was denoted as norm.

We stimulated a 2.5 mm-wide area at the left side of the domain and called this zone electrode.

The partial differential equations were integrated using the explicit Euler method and the finite difference approach. Table 1 shows the simulation parameters. We used the initial conditions and S1S2 protocol in such a way that a sole spiral wave rotated in the domain. We checked that the spiral wave did not drift.

| Table 1: Mesh, stimulation and diffusion parameters |
|-----------------------------------------------|----------|
| Spatial grid size $dr$ along the fibres, mm  | 0.25     |
| Time step $dt$, ms                           | 0.02     |
| Stimulation current $I_{st}$, $\mu$A/cm²   | −50      |
| Stimulation duration $t_{stim}$, ms          | 1.5      |
| Diffusion coefficient $D$ along the fibres, mm²/ms | 0.154 |
| Integration domain size $L$, mm              | 100      |
| External stimulation beginning $t_0$, ms     | 2000     |
| Potential level $u^*$, mV, for tip search    | 0        |
| Time frame $\Delta t$, ms, for tip search    | 10       |

For the external pacing, we found a stimulation period $T_0$ so that the wave train expanded, occupied a sufficient area, made no new spiral waves and did not cause the original spiral wave drift yet. Then, the stimulation period gradually changed to a target period $T_{stim} \in [T_{refr}, T_{sw}]$, where $T_{refr}$ is the minimal stimulation period caused by cardiac tissue refractoriness and $T_{sw}$ is the spiral wave period. This algorithm allowed us to avoid break-up caused by the stimulation with a constant period $T_{stim}$.

We tried to find appropriate $T_0$ values for all the model variants and succeeded in all cases except for $amio3$, $ver25$ and $gCaL25$. For those cases, we used a spatially adaptive stimulation.

The adaptive algorithm finds and stimulates ‘safe’ electrode subzones where there is no wave back front. An electrode point $r$ is ‘safe’ if its potential $u(r) > u_{top}$ or $u(r) < u_{low}$, where $u_{top}$ and $u_{low}$ are parameters of the algorithm. The first inequality shows that the cell is in the excited and absolute refractory state and the second one, the excitable state. In this way, we do not stimulate cells in the relative refractory state. The algorithm parameters were $u_{top} = −13$ mV and $u_{low} = −50$ mV. Figure 1 shows a pattern 10 ms after an adaptive stimulus ($gCaL75$ case). For better representation, the anisotropic rectangle was stretched and shown as an isotropic square.

3 RESULTS AND CONCLUSIONS

As mentioned above, we found $T_0$ stimulation periods for $norm$, $amio1$, $ver50$, $ver75$, $gCaL50$, $gCaL75$ cases first. Starting from there, we changed the periods gradually until we faced a Mobitz pattern, dynamical instability or pacing ineffectiveness. In the three other cases, we tried to use the adaptive algorithm and succeeded in the $amio3$ case. Therefore, we found intervals of effective stimulation periods (IESP) for seven cases. The spiral wave disappeared after it approached the boundary.

We also tried to use our spatially-adaptive algorithm in all other cases, succeeding in cases $ver75$, $ver50$, $gCaL75$ and $gCaL50$.

Results for the both algorithms are shown in Table 2. Stimulation periods in brackets are relative to the spiral wave periods; they are shown to compare different cases. The most successful are cases
amio1, amio3 and norm. Successful period intervals were found in cases ver75, gCaL50 and gCaL75, but they are short compared to amiodarone and norm cases.

Table 2: Parameters and characteristics of LVC in the myocardial models

<table>
<thead>
<tr>
<th>Variant</th>
<th>( T_{sw} ), ms</th>
<th>min. effective ( T_{stim} ), ms (rel. period)</th>
<th>max. effective ( T_{stim} ), ms (rel. period)</th>
<th>IESP, ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>norm</td>
<td>237.6</td>
<td>227 (0.955)</td>
<td>235 (0.989)</td>
<td>8</td>
</tr>
<tr>
<td>amio1</td>
<td>250</td>
<td>239 (0.956)</td>
<td>248.5 (0.994)</td>
<td>9.5</td>
</tr>
<tr>
<td>amio3</td>
<td>257.5</td>
<td>245 (0.951)</td>
<td>255 (0.99)</td>
<td>10</td>
</tr>
<tr>
<td>ver25</td>
<td>243.5</td>
<td>-</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>ver50</td>
<td>237</td>
<td>233 (0.983)</td>
<td>233 (0.983)</td>
<td>0</td>
</tr>
<tr>
<td>ver75</td>
<td>238</td>
<td>229 (0.962)</td>
<td>234 (0.983)</td>
<td>5</td>
</tr>
<tr>
<td>gCaL25</td>
<td>205</td>
<td>-</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>gCaL50</td>
<td>215</td>
<td>209.5 (0.974)</td>
<td>212 (0.986)</td>
<td>2.5</td>
</tr>
<tr>
<td>gCaL75</td>
<td>225</td>
<td>218 (0.969)</td>
<td>221 (0.982)</td>
<td>3</td>
</tr>
</tbody>
</table>

We measured the spiral wave drift velocity \( \vec{V} = (V_x, V_y) \) in the effective LVC cases. Figure 2 presents \( V_x \) depending on the relative stimulation period. Generally, the lower the period, the higher the \( V_x \).

In the gCaL50 case, the spiral wave drift was irregular and drift velocity was inconstant, making it impossible to measure precisely. The drift velocity \( V_y \) component was parallel to the electrode; since it did not depend on the changed ionic currents, we do not show its plot.

Note that the induced drift in cases gCaL50, \( T_{stim} = 212 \) ms and ver50, \( T_{stim} = 233 \) ms was toward the electrode. The drift was so slow that the spiral did not disappear during one minute.

During all experiments with stimulation periods lower than IESP, except norm and amio1, we observed dynamic instability as a result of interaction of the waves. In some cases, when plane waves from the electrode reached the spiral wave, the core moved toward the electrode. Additionally, couples of spiral waves sometimes arose in zone of contact between the plane and spiral waves. Such instability led to fibrillation and made further LVC treatment ineffective. A similar phenomenon was observed [11] but still requires further investigations.

The spiral wave in ver25 broke up without the external pacing. In gCaL25, the spiral wave meandered and the pacing was unsuccessful. All attempts caused multiple additional spiral waves.

Our spatially-adaptive algorithm enables us to stimulate an area without the threat of spiral waves occurrence and fibrillation. The anti-arrhythmic drugs are intended to suppress arrhythmias; how-
ever, only some of them showed a positive effect on the LVC. The overdrive pacing in the cardiac tissue influenced by the L-type calcium-channel blockade and verapamil caused spiral wave breakup. However, amiodarone slightly increased LVC effectiveness.

Previously, we did not observe dynamic instability in Aliev–Panfilov and Luo–Rudy I cardiac tissue models [2, 3]. Such instability in the TP06 model may explain the failure of electrotherapy on patients; thus it is important to use realistic models.

Mechano-electrical feedback can play a significant role in spiral wave drift and, therefore, in overdrive pacing. Thus, one future direction for our research includes simulations of the mechanical activity of the myocardium. Also we plan to study LVC in 3D heart models.

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OPTIMAL BOUNDARY CONDITIONS IN FLUID SIMULATIONS FOR PREDICTING OCCLUDER-RELATED THROMBUS FORMATION IN THE LEFT ATRIA

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SUMMARY

Several modelling approaches to simulate blood flow patterns in the left atria (LA) have recently been proposed, especially to better understand the relation between left atrial appendage morphology and the risk of thrombus formation in atrial fibrillation patients. Most studies are based on Computational Fluid Dynamics (CFD) but there is not a consensus on the boundary conditions (BC) which provide more realistic simulations due to the lack of shared ground-truth data. In this work, we study the influence of adding localized deformation in the LA wall using dynamic meshes comparing to assuming rigid walls, as well as different BC configurations using a real case.

Key words: Atrial Fibrillation, Computational Fluid Dynamics, Dynamic Meshes, Thrombus Formation

1 INTRODUCTION

In clinical practice, atrial fibrillation (AF) is the most common arrhythmia. This abnormality in the heart rhythm can lead to stroke and heart failure constituting a public health problem, specially after some studies predicted that in Europe. AF will affect 17.9 million by 2060 [1]. It is known that haemodynamics plays a key role in thrombus formation, which later, could lead to stroke. In clinical practice blood flow can be assessed from Transesophageal Echocardiographic (TEE) images, but only on a given 2D point of view, which is insufficient. Advanced imaging techniques provide blood velocity 3D data but currently with low spatial resolution and limited accuracy near to the wall and to assess vortex formation or stagnations.

Computational Fluid Dynamics (CFD) is a good complement to imaging for obtaining personalized blood flow information due to the increasing computational power available these days and recent streamlining of patient-specific geometrical mesh generation processes. In addition, velocity and pressure are estimated over time on each 3D point of the geometrical domain of interest. In CFD fluid dynamics are solved using the Navier-Stokes equations, but the domain is rigid. This assumption can be a limitation when studying highly deformable structures such as the atria. More realistic coupling between mechanics and fluid (e.g. with Fluid Structure Interaction and Arbitrary Lagrangian-Eulerian schemes), leading to deformable meshes, are becoming available but nowadays these methods are still very expensive computationally.

Several researchers have used CFD to study thrombus formation in AF patients. They argue that the lack of left atrial movement in these patients justified the assumption of rigid walls [2-6]. Others have tried to impose wall deformation as constraints to the left atrial boundaries [7,8]. Additionally, there is not a consensus on the optimal boundary conditions (BC) such as velocity and pressure profiles at inlets/outlets of the domain to make simulations physiologically meaningful and closer to imaging observations. In this work, we study the influence of applying localized left atrial wall deformation and different inlet/outlet boundary conditions configurations (three different ones) to predict thrombus formation and find optimal device positioning, which is an important issue.
nowadays [10]. The different simulation scenarios are tested on data of an atrial fibrillation patient acquired at Hospital Clínic de Barcelona that had a thrombus formed after the implantation of a left atrial appendage occluder (LAAO) device.

2 METHODOLOGY

The analyzed patient underwent a LAAO implantation (Amplatzer Amulet, Abbot, Eschborn, Germany) following the recommended medical guidelines. However, this patient kept generating a thrombus at the base of the device after the intervention. When anticoagulants were given to the patient, the thrombus disappeared but, as soon as the treatment was stopped, the thrombus consistently re-generated again. This case is then ideal to assess if simulations provide in silico indices related to thrombus formation since an exhaustive follow-up was performed using echocardiography and Computed Tomography (CT) scans.

To study the hemodynamics on this patient, we firstly extracted the left atrial geometry from a CT image of the patient, using semi-automatic segmentation tools available in the Open Source 3D Slicer software1. Details on the meshing pipeline can be found in [4]. The ventricular systole and diastole were considered to last 0.40 s and 0.60 s, respectively.

Several simulations were run with three different BC scenarios: 1) Rigid walls, velocity outlet profile at the mitral valve (MV) and pressure inlet at pulmonary veins (PV), as in [2,3]; 2) Rigid walls, velocity inlet profile at the PV while MV was defined as a wall during systole and as a pressure outlet in diastole [4-6]; and 3) deforming walls with dynamic meshes such as in [7,8], and inlet/outlet configuration like in Scenario 2. A longitudinal deformation of the MV surface boundary was applied, together with a diffusion-based smoothing scheme. Ansys Software 19.2 (academic research CFD solver)2, was used to simulate the strain rate of the LA. The MV movement profile was extracted from the study of Varonesi et al. [11].

Fluid simulation results with the different BC scenarios were then post-processed to estimate the Endothelial Cell Activation Potential (ECAP) index, proposed by Diachille et al. [9], which has high values associated to low velocities and high flow complexity, i.e. in regions with higher risk of thrombus formation.

3 RESULTS AND CONCLUSIONS

In this work, we mainly show results in the systolic phase of the cardiac cycle since the different BC scenarios will produce similar behaviour at diastole as has been verified in our simulations. Figure 1 depicts the simulated velocity maps with the different BC scenarios at time step: 0.35 s (systole). In Scenario 1 (left in Figure 1), there is zero velocity going through the MV during systole; following mass continuity law, there is not any velocity entering into the system. Scenario 2 (middle in Figure 1) seems to solve this problem since a velocity profile is imposed at the inlets (i.e. PV), thus producing more reasonable velocity magnitude values entering the system (red areas in Figure 1). However, as the MV is defined as a static wall in systole, there is not flow exiting the domain nor cavity volume increase, thus leading to a flow stagnation in the lower part of the LA (dark blue regions next to the MV in Figure 1, middle). It can be observed that the BC of Scenario 3 (right in Figure 1), including MV ring displacement, generate simulations where blood flow reaches all parts of the LA, which is a more realistic behaviour that the other two scenarios.

1 https://www.slicer.org/

2 https://www.ansys.com/products/fluids/ansys-fluent
In Figure 2, the LA geometry of the studied patient after LAAO implantation is presented using two different BC: Scenario 1 and Scenario 3 described above. As it can be seen, the chosen BC scenario directly affects the ECAP index and the estimation of thrombus risk. The lack of LA wall movement and velocities entering into the cavity through the PV produce very low velocity values inside the LA that leads to an ECAP overestimation (red areas in the first column, top row of Figure 2). This overestimation does not correspond to the velocity maps, where no vortex is generated on the location where the thrombus was found outside the device (see laminar flow in second and third columns, top row, of Figure 2). Thus, the high ECAP values are due to the lack of circulation inside the LA, not due to the low velocity vortices (see reference [9] to see how ECAP is computed). In contrast, the BC in Scenario 3, including a deforming wall behaviour, produce reasonable ECAP values (order of magnitude such as in [9]), as can be seen in Figure 2 (first column, bottom row). Most importantly, high ECAP values are found exactly where the thrombus was formed, according to the visual inspection of echocardiography data of this patient (red-green areas in ECAP map; first column, bottom row of Figure 2). This is confirmed when observing the blood flow streamlines (second and third columns, bottom row, of Figure 2) of the simulation, where a vortex is generated due to a misplacement of the LAAO device.
In several LA fluid modelling works, the impairment of wall movement in AF patients has been used as an argument for using CFD rather than more complex fluid-structure approaches. From a computational point of view, this reasoning is understandable since FSI-like schemes require expensive computational resources. In AF patients, especially in more severe ones (i.e. persistent), left atrial active contraction is severely reduced. However, this does not imply a total absence of LA wall movement because there is a passive longitudinal movement mainly produced by the left ventricle. Furthermore, the blood flowing from the pulmonary veins to the mitral valve, filling the left atria, also induces a LA volume increase that should affect its wall movement.

In this paper, we have compared different BC scenarios, including one (Scenario 3) where the longitudinal movement of the MV is incorporated, following data found in the literature [11]. According to our preliminary experiments, the absence of LA wall movement induces smaller velocities than the ones measures from imaging during systole, especially at the inferior part of the LA [12]. These low velocities can lead to an overestimation of indices for risk of thrombus formation (e.g. ECAP) due to its dependence on velocity, especially in systole. These problems are not relevant in diastole since the opening of the MV ensures flow going out of the system, leading to more reasonable flow patterns and velocities. The BC in Scenario 3 (i.e. including deforming walls) seem to overcome all these issues and provide realistic haemodynamics over the whole cardiac cycle. This has been demonstrated by the ability of the simulations to localize where the thrombus was created in a patient after the implantation of a LAAO device. The inspection of the simulations with our clinical collaborators helped to identify the misplacement of the device as well as the optimal settings to avoid thrombus formation.

REFERENCES

STRUCTURALLY-DRIVEN CONSTITUTIVE MODELLING OF PASSIVE MYOCARDIUM IN HEART FAILURE

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SUMMARY

Most constitutive models of passive myocardium are formulated based on the functional form of non-linear stress-strain data. Although such constitutive models can reproduce the overall mechanical behaviour of myocardium, they generally do not reflect the microstructural and material changes that occur as myocardium progressively remodels during growth or disease. The present study proposes a novel structurally-motivated constitutive model of passive myocardium that directly links quantitative characteristics of myocardial collagen organisation to the mechanical function of the heart. As such, it provides insight into the biophysical relationship between structure and function of the myocardium.

Key words: cardiac modelling, tissue mechanics, collagen morphology, heart failure

1 INTRODUCTION

Heart failure (HF) is one of the most deadly and costly conditions in the developed world, despite the wide variety of research in medicine and improvements in clinical management. The pathological process of HF is associated with microstructural remodelling that leads to changes in ventricular geometry and impaired cardiac function. The role of myocardial microstructural remodelling in the mechanics of failing hearts remains poorly understood. Structurally-based constitutive modelling can aid in the understanding of the mechanisms of mechanical dysfunction during HF, and thus help to pave the way towards more effective treatments that target these underlying mechanisms of HF. In the present study, we propose a new structurally-motivated constitutive model of passive myocardium that biophysically links the observed changes in myocardial collagen organisation, acquired using confocal microscopy, to left ventricular (LV) mechanical function obtained from ex vivo chamber compliance measurements.

2 METHODOLOGY

2.1 Quantifying cardiac structural remodelling from imaging data

In vivo cardiac magnetic resonance imaging (MRI) and extended-volume confocal microscopy were used to quantify the remodelling of the LV geometry and myocardial microstructure, respectively, of 12-month-old spontaneously hypertensive rat (SHR) and an age-matched Wistar-Kyoto (WKY) rat as control. In vivo cardiac MRI images were processed using in-house software to construct three-dimensional (3D) LV geometry at all frames of the cardiac cycle. Surface points were generated from the 3D LV geometry at diastasis and used to customise a single-element, thick-walled, truncated axisymmetric prolate spheroidal model (Fig.1a).
Extended-volume confocal images, taken from the LV midwall, were acquired at a resolution of 1 μm per voxel edge, with a total imaging volume of 400 μm x 400 μm x 200 μm (Fig.1b). Given that the collagen network is the predominant structural component of the cardiac extracellular matrix, and the major stress-bearing component of the myocardium, a robust method to quantify collagen morphology from confocal images is important for understanding the role of collagen organisation in cardiac mechanical properties.

![Figure 1: (a) 3D LV FE models constructed from subject-specific in vivo MRI data at diastasis. (b) Confocal image volumes: myocytes have variable intensity, while collagen appears bright.](image)

The collagen network was segmented from the confocal images using a customised pipeline [1]. As collagen morphology is described at a local level, a number of regions-of-interest were extracted from the 3D segmented images for shape quantification. A representative collagen shape was then computed by averaging inertia matrices of segmented collagen structures (Fig.2a). As the eigenvalues \((\lambda_\alpha, \lambda_\beta, \lambda_\gamma)\) of the lumped inertia matrix indicate the collagen shape while the eigenvectors carry the orientations, two morphological parameters \((E = \frac{\lambda_\beta}{\lambda_\alpha} \text{ and } A = \frac{\lambda_\gamma}{\lambda_\alpha})\) based on the eigenvalues were used to quantify the morphological differences between healthy and diseased hearts. Eigenvalues denote the largest, middle, and smallest eigenvalues, respectively, and are constrained by the fact that \(\lambda_\alpha \geq \lambda_\beta \geq \lambda_\gamma > 0\). Such morphological parameters allow the collagen network to be represented in a continuum sense (Fig.2b).

### 2.2 Quantifying cardiac functional remodelling

*Ex vivo* LV compliance measurements were used to characterise passive ventricular function by attaching the excised hearts to a Langendorff apparatus, and a saline-filled balloon catheter was inserted into the LV via the mitral valve. The balloon was inflated by plunging fluid to a maximum pressure of 30 mmHg, and then deflating. Pressure was measured using a differential pressure transducer connected to a side port in the balloon catheter. Compliance (the inverse of stiffness) was measured as the change in volume over the change in pressure. LV passive compliance, as a function of filling pressure, was then used to determine trends of LV chamber stiffness between healthy and diseased hearts independent of changes in LV size.
2.3 A structurally-driven model for passive myocardium

Bearing in mind the local organisation \((\alpha, \beta, \gamma)\) of the representative collagen structure (Fig.2), we represented myocardial tissue as an incompressible material with an exponential strain-energy function \(W\) with terms of Green-Lagrange strain tensors \(E_{ij}\) referred to the local collagen coordinate system.

\[
W = \frac{a}{b} V_f \left[ e^b Q - 1 \right],
\]

\[
Q = E_{\alpha\alpha}^2 + E_{\beta\beta}^2 + A_\alpha + E_{\gamma\gamma}^2 + 2 \left[ E_{\alpha\beta}^2 + A_\alpha E_{\gamma\gamma}^2 + E_{\alpha\gamma}^2 + A_\beta E_{\beta\gamma}^2 \right]
\]

where \(E\), \(A\) and \(V_f\) (collagen volume fraction) are directly quantified from the confocal images and used to reproduce the anisotropic nature of the myocardium. The remaining two parameters, \(a\) (stiffness-like parameter) and \(b\) (dimensionless nonlinearity parameter), are determine the overall stiffness of the myocardium and the nonlinear nature of the passive mechanical response, respectively. This constitutive equation was then integrated into a finite element (FE) model of the LV (Fig.1a) using in-house FE analysis software. Myocyte orientations in both SHR and WKY rat FE models were set to vary from \(+60^\circ\) at the endocardium to \(-70^\circ\) at the epicardium, while the sheetlet orientation was fixed at \(+30^\circ\) with respect to the short-axis plane in concordance with previous studies [2, 3]. Passive inflation of the LV was simulated by kinematically constraining the LV base and applying cavity pressures over the endocardial surfaces of the models. The pressure was applied homogeneously and increased in increments from 0 mmHg to 15 mmHg to span the range of physiological filling pressures. LV compliance was derived from the model-predicted pressure-volume curves to mimic the experimentally-derived compliance data. The material parameters \((a, b)\) were identified using a nonlinear least-squares algorithm that minimised the differences between model-predicted and experimentally measured compliance data for both healthy and diseased hearts.

3 RESULTS AND CONCLUSIONS

To link the observed differences in cardiac microstructure and ventricular mechanical function, we built LV FE models (Fig. 1a) from \textit{in vivo} cardiac MRI data. Microstructural data from the confocal images (Fig. 1b; Table. 1) were integrated into the LV mechanics models using Eq.1. A single pair of fitted constitutive parameters \((a\approx 139.6\ \text{kPa},\ b\approx 49.6)\) were estimated to best fit the \textit{ex vivo} LV...
compliance data for both animals simultaneously (Fig. 3). This approach mechanistically linked the observed LV geometric and microstructural remodelling to explain the differences in passive LV mechanical function.

![Graph showing compliance data for WKY and SHR hearts](image)

Figure 3. Model predictions of LV compliance (lines) versus experimental data (symbols) for 12-month-old diseased SHR (red) and age-match WKY rat heart (blue) as control. While subject specific geometric models (derived from in vivo MRI) and myocardial microstructural parameters (derived from confocal images) were used for each case, a single set of fitted material parameters (a= 139.6 kPa, b= 49.6) were used for both hearts.

Table 1: Microstructural parameters $V_f$, $E$ and $A$, quantified directly from myocardial confocal images (Fig.1a) for diseased SHR and WKY rat heart as control.

<table>
<thead>
<tr>
<th>Animal</th>
<th>$V_f$</th>
<th>$E$</th>
<th>$A$</th>
</tr>
</thead>
<tbody>
<tr>
<td>WKY</td>
<td>0.06</td>
<td>0.7</td>
<td>0.2</td>
</tr>
<tr>
<td>SHR</td>
<td>0.11</td>
<td>0.8</td>
<td>0.4</td>
</tr>
</tbody>
</table>

In this study, we have developed a new structurally-based constitutive model of passive myocardium to investigate the underlying biomechanical mechanisms of HF. Providing insight into the biophysical links between myocardial microstructure and ventricular function remodelling will advance our understanding HF pathophysiology and hence help to pave the way towards more effective treatments.

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In-vivo characterization and imaged-based modeling of tissue biomechanics
A CLINICALLY APPLICABLE STRATEGY FOR ESTIMATION OF IN VIVO VENTRICULAR WALL ELASTICITY

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SUMMARY

A clinically applicable approach to estimate the in vivo elastic material properties of the heart wall is presented. This strategy utilizes a patient-specific bi-ventricle mechanical model within an optimization-type inverse problem solution procedure that accounts for the rigid body motion of the heart to estimate elastic properties from untagged cardiac images and corresponding hemodynamic measurements. An example is examined of applying this inverse solution procedure to actual clinical patient data, including standard clinical imaging and interventricular pressure measurement. The results show that the inverse solution procedure can obtain a consistent estimate for the elastic properties of the heart wall.

Key words: inverse material characterization, clinical, heart wall

1 INTRODUCTION

Measures of myocardial stiffness have been identified as important features of a variety of cardiovascular diseases, such as myocardial infarction and diastolic heart failure [1]. One specific example is pulmonary hypertension (PH), which is a deadly cardio-pulmonary illness that is clinically characterized by a hemodynamic state of elevated mean pulmonary arterial pressure [2]. A particular observation relating to the effects of PH on the human heart is that PH substantially changes the mechanical properties of the heart, especially the right ventricle (RV). Although this link between mechanics and PH is clear, more detailed quantitative studies are necessary before specific features of mechanical property changes can be available for improved diagnosis and prognosis. Moreover, to study the in vivo mechanical property changes of the RV, a reliable method is necessary to quantify these mechanical properties from standard clinically available patient data. Towards addressing this challenge, an inverse problem solution technique is being developed, and will be presented herein, to estimate the mechanical material properties of the heart wall from clinically attainable cardiac medical images (e.g., CMRI) and measurable hemodynamics. This approach includes a bi-ventricle (i.e., left and right ventricle combined geometries only) computational representation of the passive mechanics of the heart combined with a shape-matching optimization-based inverse solution estimation procedure that includes a registration strategy to account for any rigid rotation and translation of the heart during passive function. The following details the inverse solution estimation procedure, which is followed by application of the estimation procedure to a clinical example to evaluate the solution capabilities.

2 METHODOLOGY

The overall inverse solution procedure utilized herein is based upon ongoing work of the authors to develop a shape-based strategy to inversely estimate mechanical properties of biological structures,
particularly focused on the human heart [3]. The solution procedure follows the standard pattern of a PDE-constrained optimization method for estimation of inverse problem solutions [4]. In particular, in this work a bi-ventricle representation of the heart is generated from the patient imaging data. Then, finite element analysis is used to estimate the passive diastolic process by applying the patient-specific pressure change between beginning and end diastole to the interventricular walls for a given estimate of the ventricular wall material parameters. Lastly, the shape of the ventricle(s) estimated by the finite element analysis is compared to the shape of the ventricle(s) extracted from the patient imaging data. If the comparison of the shape is sufficient, then the estimated properties are accepted as the estimate of the actual in vivo mechanical properties. Alternatively, if the shape comparison is not yet sufficient, the estimated parameters are updated (corresponding to a standard optimization procedure), and the process is repeated from the point of simulating diastole with the bi-ventricle model.

For the present study, the standard transversely isotropic Fung-type model for myocardium was used as the constitutive model in the bi-ventricle finite element analysis. In this representation, there are two key material parameters to determine (which were the unknowns in the inverse problem): (1) the stiffness parameter, $C_0$, and (2) the nonlinearity parameter, $B_0$. A standard gradient-based interior point optimization method was used to minimize the objective function to estimate the material parameters. Of particular importance to the present development is the strategy used to compare the estimated ventricular shape and the target shape at end diastole extracted from the patient’s imaging data (i.e., the optimization objective function).

### 2.1 Objective Function

In order to have an approach to utilize standard clinical imaging data (e.g., without tagging) most directly, the strategy proposed is to compare shape, rather than displacement or strain, which would require additional pre-processing to obtain. For the study herein, the standard Hausdorff distance was applied for this shape comparison. Moreover, since the focus of the application of interest (PH) is on the RV, only the RV shape, specifically the RV endocardial surface (RVES), was used as the target shape extracted from the medical images. However, prior to calculating the Hausdorff distance, it is necessary to account for the potential of organ-level rotation and translation, so that only the deformation of the ventricle is compared, not its rigid motion. Therefore, the process to evaluate the objective function includes an iterative closest point rigid registration step to remove this rotation and translation. Fig. 1 shows a flowchart for this approach that was used to compare the RV shape estimated by the bi-ventricle finite element analysis to the target RV shape.

![Flow chart for the method to quantitatively compare the estimated and target RVES shapes.](image-url)
3 RESULTS AND CONCLUSIONS

3.1 Clinical Data Acquisition

Cardiovascular magnetic resonance (CMR) images from a randomly chosen patient who underwent both CMR and right heart catheterization within a 2-day period were utilized in this study. Images were acquired using a 1.5-Tesla Siemens Magnetom Espree (Siemens Medical Solutions, Erlangen, Germany) equipped with a 32-channel cardiac coil. Standard breath-held cine imaging was acquired with steady-state free precession in the short axis orientation spanning the base to apex (6 mm slice thickness, 4 mm skip). Typical imaging parameters included 30 phases per R-R interval, matrix 256 by ~144, flip angle 51 deg, TE 1.11 ms, acceleration factor 3.

4.1 Inverse Estimation of Passive Elastic Properties

The inverse solution procedure defined was applied five separate times, with a different randomly generated starting estimate of the two material parameters each time to evaluate the consistency of the result. The results were found to be highly consistent for this example patient, with each inverse estimation providing nearly identical material parameter estimates. The average estimate of the two material parameters were: $C_0 = 1.15 \text{ kPa}$ and $B_0 = 9.6$. These parameters are well within the normal range of stiffness and nonlinearity terms reported in the literature. More importantly, Fig. 2 shows the final RVES shape predicted by the finite element analysis with the estimated material parameters in comparison to the target RVES shape from the medical images by overlapping the corresponding point cloud representations.

![Fig.2 Comparison of the point cloud representations of the RVES shape from the inversely estimated material parameters and the RVES shape extracted from the clinical imaging data.](image)

The material properties estimated by the inverse solution procedure clearly produce an RVES shape at the end of the simulated diastolic process that qualitatively matches well with the RVES shape extracted from the clinical imaging data at end diastole.

To further examine the behavior of the inverse problem, each of the two material parameters were varied in a feasible range, and the optimization objective function (i.e., the Hausdorff distance) was calculated for each combination of material parameters. Fig. 3 shows a plot of this Hausdorff distance for each combination of the stiffness and nonlinearity material parameters.

![Fig.3 Hausdorff distance between the target RVES shape and the simulated RVES shape with various combinations of the stiffness and nonlinearity parameters.](image)
What is particularly significant is that the objective function surface is smooth and convex. Therefore, it is not surprising that the inverse solution estimation procedure consistently estimated nearly the same parameters each time. However, there is a “trough” in the objective function surface where a relatively large range of parameter combinations provided a similarly low error estimation. Although this was not an issue for the current test, there could be some concern that if a similar trough exists for other cases, that there may be situations where a unique (or nearly unique) solution cannot be obtained from the inverse estimation process.

The results indicate that potential exists to use the proposed method for inversely estimating the in vivo elastic material properties of the heart wall with standard clinical cardiac imaging and hemodynamic data. Yet, work still remains to further evaluate and develop the proposed approach. In addition to examining more test cases, a particularly important future development is to incorporate more realistic material properties and boundary conditions.

REFERENCES


3D INELASTIC MODEL FOR LUNG IMAGE REGISTRATION

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SUMMARY

For several years, different methods of image registration have been used to provide additional insight in the non-invasive study of lung mechanics, which may lead to a better diagnostic of diseases. Nevertheless, the vast majority of current models, are not capable to account for sliding, which results in misleading biomechanical estimations, particularly in discontinuity regions. In this work, we present a novel inelastic image registration model capable of handling discontinuities. Our model was evaluated using both synthetic and lung CT images, and presented lower registration errors than the competition, encouraging its applicability in the biomechanical analysis of lungs.

Key words: lung image registration, tissue sliding, regional lung stress/strain

1 INTRODUCTION

To date, many deformable image registration (DIR) models have been developed to study organ biomechanics. The basic idea of DIR models is to estimate an optimal transformation between different images, such that all points from one image are mapped into another. For its applicability, DIR methods have been used to estimate deformation mechanisms in lungs (figure 1) and many studies \([1, 2, 3]\) have provided solid evidence that volumetric deformation between healthy and disease subjects are distinct, supporting the idea that regional lung deformation can be beneficially used towards disease diagnosis.

![Figure 1: Biomechanical example using DIR models](image_url)

In particular, the deformation mechanisms involved in the kinematics of lungs are genuinely complicated, where lobar and pleural sliding is a constant and intrinsic component of lung deformation. In recent years, only a few group of DIR models have been developed that actually accounts for discontinuities \([4, 5, 6]\), however in general most DIR models assume a smooth and continuous deformation mapping field which restrain them from capturing sliding inside the lung and on its boundaries. This issue results in registration errors, which has a direct impact on the mechanical estimations of regional lung deformation.

In this work we present a novel inelastic DIR model that incorporates a dissipative component in its formulation, which in turn allow us to capture sliding during the process of image registration.
2 METHODOLOGY

For convenience and due to its close relation to nonlinear continuum mechanics [7], we formulated our inelastic DIR model as an energy minimization functional. For the sake of simplicity, a similarity measure based in the sum of squared differences (SSD) is used in our model. On the other hand, the penalty term is expressed such that the deformation tensor may be decomposed into an elastic component and a dissipative component, in order to capture sliding mechanisms. This concept has been extensively used in modeling plastic failure, where a shear deformation drives a plastic behavior [8]. Consequently, at the material level, the model rely on its internal variables, which by definition depend on the flow rule and hardening law according a Von Mises model.

The registration model is formulated in such a way that the optimal transformation is defined in terms of a displacement field \(\mathbf{u}\), which is further decomposed into a displacement field \(\mathbf{\eta}\) that belongs to the \(\mathbb{RM}\) (rigid-body motion) space and a displacement field \(\bar{\mathbf{u}}\) that is orthogonal to the \(\mathbb{RM}\) space. Finally the model is defined as:

\[
\min_{\bar{\mathbf{u}} \in \mathbb{RM}^\perp} \max_{\rho \in \mathbb{RM}} \min_{\mathbf{\eta} \in \mathbb{RM}} \Pi[\bar{\mathbf{u}}, \rho, \mathbf{\eta}] = \alpha D[\bar{\mathbf{u}}, \mathbf{\eta}] + \hat{L}_n(\chi_{n+1}) - <\bar{\mathbf{u}}, \rho> \tag{1}
\]

where \(D\) stands for the image similarity term, \(\alpha > 0\) is a weighting parameter, \(\hat{L}\) is the discrete Lagrangian which depends on the state variables \(\chi_{n+1}\) at time \(t_{n+1}\). At last, \(\rho\) is a Lagrange multiplier that removes the compatibility requirement and delivers a well-posed problem that guarantees a unique solution [9].

The numerical solution of 1 is obtained by means of a standard gradient-descent method and the continuous formulation is discretized using 1st order tetrahedral finite elements.

2.1 Materials

The inelastic DIR model was implemented on two datasets: i) a 2D chessboard-like synthetic dataset, both in a reference configuration and a deformed state resembling a dislocation and ii) a free-access clinical dataset [10](DIR-Lab) including 10 3D lung CT images at total lung capacity (TLC) and functional residual capacity (FRC). The clinical dataset also includes 300 landmarks in each configuration, that will allow us to evaluate the performance of the model.

2.2 Experiments

To assess the influence of incorporating sliding constraints and the importance of handling discontinuities in image registration, we compared our inelastic DIR model against a fully elastic finite element (FE) model and an open source state-of-the-art registration tool known as Niftyreg [11]. Using the synthetic dataset, we computed the residual sum of squared differences (RSS) as a metric of evaluation between the reference and the resampled images. On the other hand, for the clinical dataset we used the Target Registration Error (TRE) as a metric of evaluation. The TRE was defined as the Euclidean distance between landmarks in the floating image and those in the reference image, displaced by the deformation mapping field. Our results were compared to those reported in [6].

3 RESULTS

For the case of the synthetic dataset, in terms of the RSS error our proposed inelastic model outperformed both the elastic FE model and the NiftyReg model, showing an error of \(RSS = 0.29\) for the inelastic model, \(RSS = 2.27\) for the elastic FE model and \(RSS = 2.63\) for the NiftyReg model.

By visual inspection on a 2D lung CT slice, we could observe that the inelastic model was able to adequately capture sliding mechanisms whilst the elastic model fail to do so.

This was also verified by the fact that our inelastic model showed a TRE of 11.76 using several landmarks positioned in the ribs, while in the elastic FE model the TRE was 193.73 and in the NiftyReg model the TRE was 83.49.
4 CONCLUSIONS

In this work we presented a novel model for non-rigid image registration, that is able to account for tissue sliding in lung images, without any a-priori knowledge of the spatial location of the discontinuities.

Future steps are focussed on improving the computational time needed to solve these problems.

REFERENCES


FINITE ELEMENT MODELING OF PELVIS FOR TREATMENT OF SACROILIAC JOINT DYSFUNCTION


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SUMMARY

The pelvis can be subjected to dysfunctions such as the sacroiliac joint disease which is an abnormal motion of the sacroiliac joint. This disease can lead to heavy consequences, from pain to complete immobility of certain part of the body. In this study, finite element models of the pelvis with sacroiliac joint fixations were developed and used to compare different configurations of fixations and improve posterior fixations so that results can come closer to anterior fixations. Stress distribution of the pelvis bones and sacroiliac joint cartilage were evaluated.

Key words: finite element analysis, sacroiliac joint disease, anterior and posterior fixations

1 INTRODUCTION

The human pelvis is the set of bones of the waist located between the spine and the lower limbs. In some cases, the pelvis can be subjected to dysfunctions such as the sacroiliac joint disease which is an abnormal motion of the sacroiliac joint leading to heavy consequences, from pain to complete immobility of certain part of the body. Fusion surgeries have been employed to insert implants to fix the joint, stimulate its ossification and minimize the motion between the different bones [1, 2]. Anterior fusion surgery, fixations are placed from the front side of the body. It is a strong fixation with significantly reduced pain. It is however intrusive due to the presence of many organs, and difficult to perform. Posterior fusion surgery, fixations are placed from the back. Few organs are present, so it is easier to perform. However, clinical results show that remaining pain is recurrent, and fixations are considered weaker than the front side. In this study, we focus on the effect of fixations on the pelvis and sacroiliac joint by finite element analysis in order to evaluate quantitatively each fixation’s efficiency and improve posterior fixations to make their efficacy closer to standard anterior fixations.

2 METHODOLOGY

The finite element model based on Hammer et al. [3] comprises the sacrum, the left and right hip bones, the pubic symphysis, the different surrounding ligaments (springs) as well as the left and right sides’ sacroiliac joint cartilage and ligament (Fig. 1). Fixations using rods, screws, cages and rods are placed on the left side of the pelvis. The different loadings correspond to different human postures. The Sacral Slope (SS), angle between the horizontal and the tangent to the surface of the
Fig. 1 Finite element model of the pelvis with the different types of fixations. (N) Without fixation, (P) posterior fixation with 3 screws and 1 rod, (P+C1) model P with a cage in configuration 1, (P+C2) model P with a cage in configuration 2, (A) anterior fixation with 5 screws and 1 plate.

Fig. 2 Stress distribution within the left sacroiliac joint cartilage for different fixation and human postures.

first vertebrae of the sacrum in the pelvis, permits to differentiate the different postures. Four postures are considered: Standing SS 35°, Sitting SS 5°, 20° and 35°.

3 RESULTS AND CONCLUSIONS

Stress distribution within the left sacroiliac joint cartilage for each type of fixation and different human postures is shown in Fig. 2. Regarding to the stress concentration, anterior fixation (A) is better than posterior one P. The screw arrangements that worked the best in previous studies (A) do not always obtain the same efficiency for some specific loadings such as Sitting SS 5°, showcasing a real problem for the sacroiliac joint dysfunction treatment. The insertion of a cage can globally decrease the stress distribution in the sacroiliac joint, resulting in better stabilization of the joint. The direction of the cage can also play a significant role and better results are obtained when the longitudinal axis of the cage gets closer to the perpendicular of the sacroiliac joint’s normal axis (C1). In summary, finite element analysis permits the evaluation and comparison of fixations’ efficiency, facilitating the improvement of surgery’s implants.

REFERENCES

MECHANICAL HOMEOESTASIS IN A MORPHOELASTIC MECHANOBIOLOGICAL MODEL OF AIRWAY REMODELLING

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SUMMARY

In healthy tissues cells establish a homoeostatic mechanical state through phenotypic changes, and modifications to their environment (a well-studied phenomenon in arteries). In airways, however, limited knowledge of airway composition and mechanics means that this is poorly understood, and cannot be directly measured. We therefore develop a theoretical–experimental approach, combining mechanical testing, imaging and mathematical modelling. We characterise in detail the composition and mechanics of murine airways, and employ these data within our mathematical model to propose a mechanotransductive cellular response by which homoeostasis is maintained. Our results have important implications for pathological conditions such as asthmatic airway remodelling.

Key words: asthma, mechanical homoeostasis, airway remodelling, morphoelasticity

1 INTRODUCTION

Asthma is a disease of varying severity, typically characterised by inflammation, airway hyperresponsiveness, and airway remodelling. The inter-relationship of these characteristics with regard to pathogenesis and severity remains unknown. With a recently developed morphoelastic mechanobiological model [2], we have shown that increased airway smooth muscle cell (ASMC) hyper-responsiveness to contractile agonists may exacerbate inflammation-driven remodelling via a novel mechanotransductive feedback mechanism. It is well known, however, that biological tissues in normal conditions, establish a mechanical homoeostatic state \textit{in vivo}, in which cells maintain an ideal level of mechanical stress by altering both their mass and their surrounding ECM structure and content. We hypothesise that airway remodelling is a result of perturbations from such a mechanically homoeostatic state.

While the discovery of residual stresses allows computation of homoeostatic stress in arteries, much less is known about the airways—in particular, such residual stresses have not been observed experimentally. Furthermore very little is known about the mechanical properties and microstructural arrangement of the constituents comprising the airway wall, since few mechanical studies have been performed on airways. Our premise is that in normal airways, dynamic balances between stress-dependent cell proliferation, apoptosis, and manipulation of the extracellular matrix, allows a homoeostatic state of mechanical stress to be achieved such that there is no airway remodelling (i.e. the airway wall thickness remains unchanged). Crucially, this homoeostatic stress state cannot be measured directly. In this study we therefore combine mechanical testing, imaging approaches and mathematical modelling to provide new understanding of airway mechanical homoeostasis and for understanding the alterations that could lead to pathological conditions such as asthmatic airway remodelling.

We first determine the structure–function relationship of normal (non-remodelled) murine airways through matched mechanical testing and measurements of airway composition. These data are then used within our previously developed model [2] to determine mechanotransductive regimes that lead
to a mechanically homoeostatic state, under various parameter regimes. Insights from this study will ultimately allow us to test our hypothesis that airway remodelling occurs as a result of dysregulation of processes that normally maintains this state.

2 METHODOLOGY

2.1 Experimental methods

Lungs were harvested from 8-week old C-57 mice (n = 6), and small airways (<100 microns) were dissected from the lung following sacrifice and mounted on a wire myograph for ring testing. The airway was stretched by separating the two wires, and force and length were recorded. Following testing, the airways were fixed in 2% paraformaldehyde, and then immunohistochemistry and laser-scanning microscopy were used to quantify the volume of constituents in the airway wall. The airways were stained for cell nuclei (DAPI), f-actin, and phalloidin, and imaged via combined confocal/two-photon emission microscopy.

2.2 Mathematical model

We adapt our previous model [2] to investigate the hypothesis that tissue stresses beyond a certain ‘homoeostatic’ range lead to mechanotransductive airway remodelling by influencing cell proliferation and ECM deposition. We model the airway wall as an axisymmetric cylinder, composed of a mixture of proliferating, contractile ASMCs and ECM (the dynamics of which are governed by a set of time-dependent coupled mass balance ODEs). The cylinder is represented as a multi-phase, hyperelastic material reinforced with two families of fibers [1], and accommodates strain stiffening, airway smooth muscle contraction, inflation pressures, and the contractile agonist activation. Passive mechanical properties are fitted to the data obtained in §2.1 using the lsqcurvefit function in MATLAB and the default ‘trust region reflective’ algorithm.

We define the stress along a given fibre direction,

\[ \tau = \frac{1}{2} \sum_{j=1,2} T : m_c^{(j)} \otimes m_c^{(j)}, \]  

(1)

to govern stress-driven proliferation, apoptosis and degradation, where \( T \) is the Cauchy stress tensor and \( m_c^{(j)} \) is the (circumferentially-oriented) contractile ASMC fibers. In particular, we assume that cells undergo a switch to a proliferative (respectively, apoptotic) phenotype in response to local fibre stress via a smoothed switch function, so that the rate of cell proliferation is described by a function of the form:

\[ c_p(\tau) = \frac{1}{2} (\tanh(\alpha(\tau - \tau_0 - \Delta \tau_0)) + 1), \]  

(2)

where \( \tau_0 \) and \( \Delta \tau_0 \) denote the position and width of the homoeostatic stress window, and \( \alpha \) determines the steepness of the curve. A similar function describes apoptosis; see Fig. 2(A).

Overall airway remodelling is reflected by the radial motion of the airway walls (the homoeostatic equilibrium reflects a state of internal dynamic equilibrium). The fully coupled system of equations consisting of mass balance, balance of linear momentum, and incompressibility is solved numerically as a boundary value problem to determine stress values (\( \tau_0, \Delta \tau_0 \)) that lead to neither airway wall growth or atrophy. This computation is carried out for parameter values and airway geometries for each of the specimens described in §2.1.

3 RESULTS AND CONCLUSIONS

The force-displacement data obtained from the wire myograph were converted to stress-strain curves (Fig. 1(A)). The same airway segments tested mechanically were then imaged to obtain the volume fractions of the tissue constituents (Fig. 1(B). By using this combined mechanical testing-imaging approach, we were able to fit our mechanical model to the experimental data and thereby determine...
Figure 1: (A) Stress-strain curves for 6 murine airways. (B) 2D projection of 3D volume of the airway wall (based on stacks of images from combined confocal/two-photon emission microscope), showing the mechanically-dominant constituents: actin (yellow), elastin (red) and collagen (green) for representative specimen. (C) ASM and ECM volume fractions as functions of airway radius extracted from image stacks in (B).

Figure 2: (A) Rates of cell proliferation (red curve) and apoptosis (blue curve) as functions of the fibre stress $\tau$, parametrised by $\tau_0$ and $\Delta \tau_0$, reflecting a homoeostatic stress window. (B) Velocity at the inner radius resulting from the solution of the boundary value problem described above for a set $(\tau_0, \Delta \tau_0)$ parameter values. Regions of parameter space in which thickening of the airway wall occurs is indicated by positive velocity contours and atrophy by negative velocity contours, with a region in between in which there is zero growth.

the parameters that characterise the mechanical properties of the airway wall tissue for each of the above specimens as well as the constituent volume fractions (Fig. 1(C)).

A parameter exploration study is performed over a range of candidate stress values for each specimen, and the growth velocity is computed, revealing the ranges that result in zero growth; a representative case is shown in Fig. 2(B).

By combining mechanical testing and imaging, with our mathematical model of growth and remodelling, we have developed a novel method for determining mechanical homoeostasis in the airway wall, information that is not available experimentally. In particular this study provides possible homeostatic stress values for given applied pressures and tissue constitutions. We can thus use these computed mechanically homoeostatic states as initial conditions in time-dependent growth simulations (see e.g. [2]) to test the hypothesis that perturbations to this state (through inflammatory challenges or bronchoconstrictive events) result in airway remodelling.

REFERENCES

FINITE ELEMENT BIOMECHANICAL INVESTIGATIONS OF PATHOLOGICAL EFFECTS ON ORGAN-LEVEL TRICUSPID VALVE FUNCTION

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SUMMARY

Current clinical methods of assessing tricuspid valve function provide key information about the valve’s geometry, but very limited information about the valve’s mechanical environment. The objective of this work is to address this gap through development of a finite element framework that provides insight into the effect of common functional tricuspid regurgitation pathologies on the valve’s biomechanical function. This framework quantifies key clinically-relevant geometrical values, such as the leaflet tenting area, and other engineering mechanics metrics. Results from this study are expected to significantly aide the clinical setting in assessing and treating functional tricuspid regurgitation.

Key words: finite element modeling, the tricuspid valve, functional tricuspid regurgitation

1. INTRODUCTION

The tricuspid valve (TV) is located in the right side of the heart and facilitates the unidirectional blood flow from the right atrium to the right ventricle. Functional tricuspid regurgitation (FTR) occurs when alterations to the TV geometry hinder the TV from preventing the undesired backflow of blood into the right atrium during systole. FTR has been historically under-treated in the clinical setting due to assumptions that FTR will naturally regress after treatment of left-sided lesions [1]. A recent study has contradicted this assumption and demonstrated that FTR will continue to worsen after the repair and often worsen the overall prognosis [2]. The focus on the TV has thus increased in the past 5-10 years with emphases on more accurate assessment of FTR and determination of optimal treatment time. However, as Dreyfus et al. [3] pointed out, proper assessment of FTR can be difficult, especially when dealing with less than moderate FTR. Also, clinical assessment of FTR relies on medical imaging modalities, such as 2D/3D echocardiography, that shows key information about the TV geometry but no information about the underlying TV mechanical environment. Therefore, the objective of this study is to develop a finite element framework for the TV that provides enhanced information about key clinically-relevant geometrical and mechanical quantities considering various pathologies associated with FTR.

2. METHODOLOGY

2.1 Finite Element Model

The finite element (FE) model geometry was generated in two steps. First, the leaflet geometry was created using a previously-published parametric model for the TV [4] and was represented by cubic B-spline surfaces and curves. Values defining the key parameters of the TV were sourced from [5]. Second, the TV annulus and chordae tendineae geometries were obtained from micro-CT imaging data of an ovine TV fixed in the closed position. These geometries were then combined, and finite element meshes were created in ABAQUS CAE (Fig. 1).
2.2 Finite Element Simulations of TV Systolic Closure

FE simulations were performed using the ABAQUS/Explicit dynamic solver (Dassault Systèmes). In this study, both the valvular annulus and papillary muscle tips were assumed to be fixed. A transvalvular pressure of 25 mmHg and 40 mmHg was applied to the ventricular side of the leaflets for 0.4 seconds to mimic TV systolic closure for healthy and pulmonary hypertension conditions, respectively. The nonlinear mechanical behavior of TV leaflets was modeled by an isotropic solid under the hyperelasticity framework with a strain energy density [5]:

\[
\psi = c_0 (I_1 - 3) + c_1 (e^{2(I_1-3)} - 1) - \frac{p}{2} (I_3 - 1),
\]

where \(c_0, c_1,\) and \(c_2\) are the material constants, \(I_1\) and \(I_3\) are the first and third invariants of the right Cauchy-Green deformation tensor \(C,\) and \(p\) is the penalty parameter for enforcing the incompressibility condition. The chordae tendineae were idealized by means of 3D trusses and assumed to be nonlinearly elastic with a Young’s modulus of 40 MPa and a Poisson’s ratio of 0.30.

A series of FE numerical studies were performed to investigate the effect of various pathologies typically associated with FTR on geometrical and mechanical values: (i) pulmonary hypertension (PH), (ii) annulus dilation (AD) with a flattened annulus, and (iii) papillary muscle (PM) displacement considering a flattened annulus. To create the FE model associated with the AD scenario, displacement boundary conditions were first applied to the annulus of the healthy FE model corresponding to a non-uniform dilation of the annulus away from the septum [6]. A similar method was used for the PM displacement scenario using values obtained from in vivo imaging [7].

2.3 Post-Processing of the FE Simulation Results

FE Simulation results from the health and different diseased scenarios were post-processed using ParaView (Kitware) to quantify key geometrical and mechanical quantities, including the von Mises stress and the Green-Lagrangian strain. As for the geometrical evaluations, clinically-relevant metrics were quantified for the coaptation between each leaflet: the leaflet tenting height, the tenting area, and the coaptation height (Fig. 2a). Three slices were made to represent the coaptation of the leaflets (Fig. 2b) for making comparisons of these geometrical values between simulation scenarios.
3. RESULTS AND DISCUSSIONS

FE predicted von Mises stress and maximum in-plane Green strain of the healthy TV at systolic closure are depicted in Figures 3a-b, whereas the comparisons of these two mechanics-related metrics between any two of the simulation scenarios are summarized in Figure 3c. Our numerical results show the central belly leaflet stress for all three TV leaflets ranges from 70-125 kPa, while the strain ranges from 0.30-0.60. These stress values, as well as the values for the other simulation scenarios, fall under the maximum in-vivo stress of ~125 kPa previously reported in literature [8]. As for the comparison between simulation scenarios, pulmonary hypertension resulted in the largest changes in both the von Mises stress (+65%) and Green strain (+14%), followed by the annulus dilation (+13% and +12%), and then papillary muscle displacement (-8% and +7%).

Figure 3: FE results of systolic closure of the healthy TV: (a) von Mises stress, and (b) maximum in-plane Green-Lagrangian strain. (c) Comparisons of von Mises stress and Green-Lagrangian strain between healthy and diseased TVs.

Results of the geometrical quantities are shown in Figure 4. The TV with pulmonary hypertension shows a consistent trend of decreasing tenting area (14 – 40%), decreasing tenting height (6 – 26%), and increasing coaptation height (3 – 4%) for all three coaptation slices. The trends of the results associated with AD and PM displacement disease scenarios are less consistent with the changes in geometric metrics compared to the pulmonary hypertension scenario. On average, changes resulting from PM displacement are ~42% greater than AD displacement, except for the tenting area of the CVPS coaptation where AD has a 32% greater effect.

Figure 4: Results of the clinically-relevant geometrical values for the three coaptation slices.
This study has, for the first time, used a FE framework to provide a quantitative evaluation of the effect of pathologies associated with FTR on the biomechanical function of the TV. Results from this study largely agree with a previous study by Casa et al. [9] in which they used an in-vitro system to assess the effect of PH, AD, and PM displacement on the TV biomechanical function. Differences are likely related to the selection of geometry as Casa et al., used excised porcine valves whereas this study used a parametric representation of the leaflets from previous literature. Furthermore, we also considered a flattened annulus geometry for the AD and PM displacement scenarios, which previous literature suggests occurs during the progression of FTR.

Findings from this preliminary numerical study could help better understand how PH, AD, and PM displacement affect the TV function. TV closure index (TV leaflet length / TV tenting area) is currently used as a marker for PH [10], and this could be further expanded upon. Moreover, the present work provides a new avenue for computational modeling of the TV, which could significantly benefit the clinical setting. For example, extensions of the current work refining the material model and including a patient’s geometry could aid with the assessment of a valve’s status. Insight from this patient-specific model would help with decisions about the need for TV repair at the time of cardiac surgery for other lesions. Furthermore, the framework could be extended to guide development of patient-specific therapeutics such as the annuloplasty ring.

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REFERENCES

SPATIALLY RESOLVED DISTENSIBILITY OF AORTIC WALLS DETERMINED FROM 4D ULTRASOUND MEASUREMENTS

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SUMMARY

AAA rupture risk prediction suffers from a lack of indices, which are precise in the individual case. 4D ultrasound imaging provides temporally and spatially resolved strain fields of the aneurysm wall. Using the pulse pressure, we have determined the spatially resolved distensibility for healthy and diseased aortic walls. The spatial heterogeneity of the distensibility distribution is significantly increased in aneurysms, an increase that is not correlated with the maximum diameter. This index might provide additional information for AAA rupture risk prediction.

Key words: ultrasound elastography, aneurysm, distensibility

1 INTRODUCTION

Abdominal aortic aneurysms (AAA) are a degenerative disease of the human aortic wall that may lead to weakening and eventually rupture of the wall with high mortality rates. Since the currently established criterion for surgical or endovascular treatment of the disease is imprecise in the individual case and treatment is not free of complications, the need for additional patient-individual biomarkers for short-term AAA rupture risk as basis for improved clinical decision making is widely acknowledged. Time resolved 3D ultrasound combined with speckle tracking algorithms is a novel non-invasive medical imaging technique that provides full-field displacement and strain measurements of aortic and aneurysmal wall motion [1]. This is patient-individual information that has not been used so far to assess wall strength and rupture risk. In the current study we have used 4D ultrasound strain imaging to compute the spatially resolved distensibility distribution in three patient groups: young volunteers < 60 y. o. without known cardiovascular diseases, aged arteriosclerotic patients > 60 y. o. without AAA, and AAA patients. We have correlated the observed changes in the distribution of local elastic properties with the aortic diameter within each group.

2 METHODOLOGY

For this study, 4D ultrasound and blood pressure data of 61 patients and volunteers presented at the Clinics for Vascular and Endovascular Surgery of the University Hospital Frankfurt am Main were evaluated. The study was approved by the local ethics committee. Patient data are divided into three groups: “young” patients < 40 y.o. without known cardiovascular risk factors (n = 19), “elderly” patients > 60 y.o. without AAA (n = 20), and AAA patients > 60 y.o. (n = 22). Local distensibilities were determined for wall areas of 2 - 10 mm² based on local circumferential strains and pulse pressure. Mean and maximum distensibilities as well as indices for the local variations of the distensibility distribution (local distensibility ratio, heterogeneity index) have been determined.
3 RESULTS AND CONCLUSIONS

Mean distensibility is significantly decreasing from young (3.83 [2.82, 5.87] 10⁻³ mmHg⁻¹) to elderly (0.67 [0.39, 0.87] 10⁻³ mmHg⁻¹) and AAA (0.27 [0.20, 0.54] 10⁻³ mmHg⁻¹). Mean and maximum distensibility are inversely correlated and the heterogeneity of the elastic properties is correlated positively with the aortic diameter in the young group. In contrast, no correlation between any distensibility distribution index with diameter is observed in the aged or diseased group. Both indices characterising the heterogeneous elastic properties are significantly increasing from young through elderly to AAA.

The size and distribution of local distensibilities provides information on the mechanical properties of the aortic and aneurysmal wall. Since it depends on geometrical information (local diameter), local distensibility is not a ‘proper’ material parameter. However, in the case of aged and pathologic aortic walls this dependency is negligible compared to the changes in the aortic stiffness. We propose that the heterogeneous distribution is indicative of microstructural changes in the aortic wall. Therefore, the variable distribution of distensibilities might be a candidate biomarker to classify aneurysms with respect to their rupture risk. Since it is not correlated with the maximum aneurysm diameter, it could provide additional individual information to the established criterion for treatment.

REFERENCES

New CFD tools for clinical medicine
PATHOPHYSIOLOGY OF CARDIOVASCULAR DISEASE AND COMPUTATIONAL FLUID DYNAMICS MODELING IN AORTIC DISEASES

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SUMMARY

In recent years, computational fluid dynamics (CFD) has attracted considerable attention in cardiovascular medicine. In addition to traditional assessment based on anatomical information, the CFD-based approach provides an opportunity to gain novel insights into vascular pathophysiology by exploring the relationship between structure and biomechanical forces in flow dynamics. As CFD modeling is widely used in clinical situations, it is very important for clinicians to understand the basic principles, benefits, limitations, and pitfalls of CFD modeling. Also, mathematician need to understand the essential cardiovascular pathophysiology which is tightly associated with vascular hemodynamics and fluid-structure interaction surrounding vascular lumen.

In this topic, we present an overview of CFD modeling and its application to pathophysiology of aortic diseases, and primarily to aortic aneurysms.

Key words: Clinical medicine, Mathematical modeling, Medical imaging, Cardiovascular disease

1 INTRODUCTION

Currently, computational fluid dynamics (CFD) has become a widely adopted methodology for solving complex problems in many modern engineering fields. The CFD-based approach is used for understanding the relationship between structure and flow by solving systems of partial differential equations to simulate fluid flow. Advances in medical imaging and computational methods provide an opportunity to apply the CFD-based approach in clinical medicine. Cardiovascular imaging is one of the most common medical applications of CFD modeling. CFD modeling is essentially studied by applied mathematicians and engineers who are specialists in fluid mechanics. In addition to the knowledge about CFD modeling itself, it is also crucial to know essential cardiovascular pathophysiology to understand the relationship between and the effects of hemodynamics on the structure (vessel wall) and the resulted pathophysiological reaction of the vessel.

In this paper, we present an overview of cardiovascular pathophysiology focusing on the aortic disease, and primarily to aortic aneurysms, and discuss how hemodynamic phenomenon effects on the vessel wall to understand pathophysiological mechanism.

CFD modeling and its application to aortic diseases, and primarily to aortic aneurysms.

2 CLINICAL SIGNIFICANCE OF CFD MODELING FOR AORTIC ANEURYSMS

For many years, the size of the aorta has been the principle decision making criteria for intervention of an aortic aneurysm. Many guidelines for the treatment of aortic aneurysms advocate a maximal aortic diameter and clinical risk factors as the determination of the timing for intervention (1). Many studies have suggested that some small aortic aneurysms may rupture prior to reaching 55 mm of maximum short diameter, which is the suggested threshold size for surgical
intervention (4), whereas many aneurysms larger than the threshold never rupture. Therefore, appropriate predictors for the risk of rupture and the progression of an aneurysm, other than aortic size, would improve current treatment strategies by providing appropriative timing for intervention, while also reducing the expense and risk of unnecessary intervention.

One goal of CFD modeling in cardiovascular medicine is to understand the relationships between anatomical geometry (i.e., vascular anatomy), local hemodynamics (blood flow), fluid-structure interaction (FSI) including stress and pressure on the vessel wall, and the vascular pathology (development and progression of atherosclerosis, aneurysm, dissection, etc.). Several studies have suggested that hemodynamic forces may provide one of the most significant biomechanical effects underlying aneurysm development (2). As measurement of in vivo hemodynamics assessment can be difficult and invasive, researchers are gradually focusing on the assessment of hemodynamics, using non-invasive CFD modeling to predict the risk of future rupture for aneurysms.

3 HEMODYNAMIC FORCES RELEVANT TO AORTIC PATHOLOGY

Clinical and experimental observations have indicated that various biomechanical conditions interactively influence the progression of an aortic aneurysm (3)(4).

3.1 Wall shear stress
Wall shear stress (WSS), which is the tangential force of blood flowing on the endothelial surface of blood vessels, is the most significant of the hemodynamic forces in a blood vessel. The interactions of pulsatile blood flow with arterial structures generate complex hemodynamic forces on the vessel wall that exhibit spatial and temporal variation (5). Endothelial cellular responses to these physical stimuli influence vessel wall homeostasis. Constant laminar blood flow with tangential WSS protects the vascular endothelium (6). After fluctuations of WSS promote changes in biochemical signals, the biophysiological characters of vessel wall starts to degenerate. The degeneration of vessel wall will directly lead to the initiation and progression of some cardiovascular diseases, including aortic aneurysm and coronary artery disease.

3.2 Oscillatory shear index
OSI is another significant hemodynamic parameter used to assess WSS in that it has the time-averaged magnitude of WSS in the denominator. OSI quantifies the fluctuations of WSS from the primary flow direction during the cardiac cycle. For example, blood flow with fluctuations possesses a high OSI even though its time-averaged WSS is low. Fluctuations of WSS disturb the vessel wall homeostasis and may induce aortic pathologie.

3.2 Vessel wall strain and distensibility
Recently, several researchers investigated other biomechanical forces aside from WSS for predicting the risk of rupture. Di Martino et al. reported that maximum tissue stiffness was inversely correlated with wall strength, suggesting lower stiffness as a possible predictor of aneurysm rupture (7). Also, Wilson et al. suggested that distensibility at baseline and the change of the aorta during follow-up were correlated with the risk of rupture, in addition to the diastolic pressure and larger parameter. Several ultrasound studies reported assessment of local wall strain of the whole abdominal aortic aneurysm in vivo. Satriano et al. proposed a 3D image-based approach to compute aortic wall strain maps in vivo, which was used for various imaging modalities. In terms of CFD, Stevens et al. used a CFD method to assess how a change of flow-related biomechanical properties affects the wall stress and the related wall strain (8). Although further clinical studies are required, such hypotheses regarding vessel wall strain and wall distensibility would add more insight in predicting the precise risk for aneurysm rupture. Figure 4 illustrates the interrelationship between flow, WSS, OSI, and pressure on the vessel wall (i.e., distention force).

4 REGIONAL HEMODYNAMIC DIFFERENCES RELEVANT TO AORTIC ANEURYSMS

Few studies have investigated regional pathogenic risks of aortic pathologies. Even in different regions in the aorta that have the same diameter, the behavior of aortic dilatation differs depending on the location in the aorta. Usually, the abdominal aorta has a marked predilection for aneurysmal dilatation when compared to the thoracic aorta, where the infrarenal aorta is the most common site
of aortic aneurysm formation. Different hemodynamic influences present along the length of the aorta may work in concert with other regional factors to explain this preferential distribution (3). Region-specific structural differences are well recognized along the aorta. For example, the elastin–collagen ratio declines along the length of the aorta, reducing elasticity and wall motion. Reduced distal aortic elasticity, in combination with augmented pressure due to pulse wave reflections from aortic bifurcation and other downstream arteries, may increase wall strain and aneurysm susceptibility.

Most relevant to aortic disease pathophysiology, and its predilection for the distal aortic segment, is the marked difference between aortic WSS in the proximal and distal aorta. In proximal aortic segments, flow is antegrade throughout the cardiac cycle, providing continuous antegrade laminar WSS (3). As discussed above, constant laminar blood flow with normal WSS regulates homeostasis of the vascular endothelium (6). In general, the time-averaged WSS is high, while the OSI is low in the distal thoracic aortic arch because of uniform laminar flow. In contrast, many experimental and numerical studies have indicated that multiple secondary reverse flows with vortex formation were observed in the late systolic and diastolic phases during the cardiac cycle, while they were not observed in the thoracic and proximal aorta (3). As a result, the time-averaged WSS is low and the OSI is high in the distal abdominal aorta when compared with proximal aorta. These distinct regional differences in hemodynamic influences may account for some component of the differential aneurysm risk noted between the thoracic and abdominal aortic segments. Furthermore, there is individual variation in the location of aneurysmal formation among patients. Although the infrarenal aorta is the most common site of aortic aneurysm formation, some patients have an aneurysm in the distal aortic arch or in the thoraco-abdominal junction. Differences of anatomical geometry (shape of the aorta) can generate patient-specific flow patterns and FSIs during the cardiac cycle. CFD modeling improves our understanding of variation in the location of aneurysmal formation among individual patients.

5 CONCLUSIONS

The advancement of CFD modeling has presented a unique opportunity to provide new insights into vascular hemodynamics in the assessment of cardiovascular diseases. Patient-specific CFD modeling has the potential to provide a comprehensive understanding of the interaction between vascular morphology, blood flow, and FSI. Information about biomechanical forces in aortic pathologies may help to predict the risk of aortic aneurysm and to select appropriate treatment.

REFERENCES

OUTLET BOUNDARY CONDITIONS FOR THE NAVIER–STOKES EQUATIONS

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SUMMARY

We propose an energy-stable outlet boundary condition for the incompressible Navier–Stokes equations. The condition is a generalization of the standard free-traction condition. We also consider a penalty approximation, a kind of the nonlinear Robin condition, to deduce a suitable formulation for numerical computations. We examine their effectiveness using some numerical examples.

Key words: Navier-Stokes equations, variational inequality, penalty method

1 INTRODUCTION

When conducting numerical simulation of real-world flow problems, we often encounter issues related to artificial boundary conditions. A typical and important example is the blood flow problems in large arteries, where the blood is assumed to be a viscous incompressible fluid (cf. \cite{1}, \cite{2}). Blood vessels are modeled as branched pipes as shown for illustration in Fig. 1. A velocity profile at the inlet boundary \(S\) can be given. The flow is presumed to be a perfect non-slip on the wall \(C\). Consequently, the blood flow simulation is highly dependent on the choice of artificial boundary conditions posed on the outlet boundary \(\Gamma\).

To state the problem more specifically, let \(\Omega \subset \mathbb{R}^d\), \(d = 2, 3\), be a bounded domain and let the boundary \(\partial \Omega\) be composed of three parts \(S, C\) and \(\Gamma\). Those \(S, C\) and \(\Gamma\) are assumed to be smooth surfaces, although the whole boundary \(\partial \Omega\) itself is not smooth. Then, for \(T > 0\), we consider the Navier-Stokes equations

\[
\begin{align*}
  u_t + (u \cdot \nabla) u &= \nabla \cdot \sigma(u, p) + f & \text{in } \Omega \times (0, T), \quad (1a) \\
  \nabla \cdot u &= 0 & \text{in } \Omega \times (0, T), \quad (1b) \\
  u &= b & \text{on } S \times (0, T), \quad (1c) \\
  u &= 0 & \text{on } C \times (0, T), \quad (1d) \\
  u|_{t=0} &= u_0 & \text{on } \Omega \quad (1e)
\end{align*}
\]

for velocity \(u = (u_1, \ldots, u_d)\) and pressure \(p\) with the density \(\rho = 1\) and the kinematic viscosity \(\nu\) of the viscous incompressible fluid under consideration. Therein, \(\sigma(u, p) = (\sigma_{ij}(u, p))_{ij} = -pI + 2\nu D(u)\) denotes the stress tensor, where \(D(u) = (D_{ij}(u))_{ij} = \frac{1}{2} (\nabla u + \nabla u^T)\) is the deformation-rate tensor and \(I\) is the identity matrix. The prescribed functions \(f = f(x, t)\) and \(u_0 = u_0(x)\) respectively denote the external force and initial velocity. Moreover, \(b = b(x, t)\) denotes the prescribed inflow velocity with \(b|_{\partial S} = 0\).

A setting of the boundary condition on \(\Gamma\) is not a trivial task, because the flow distribution and pressure field are unknown. They cannot be prescribed in many simulations. As a common outflow boundary...

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condition, the free-traction condition or the so-called do-nothing condition

\[ \tau(u, p) = 0 \quad \text{on} \quad \Gamma \]

is still frequently used today, where \( \tau(u, p) = \sigma(u, p) n \) denotes the traction vector on \( \partial\Omega \) and \( n \) the outward normal vector to \( \partial\Omega \). Although this condition is enough for many problems, it sometimes causes serious numerical instability near \( \Gamma \); see [3, Remark 4.1] for example. Actually, from the perspective of mathematics, energy inequality is not guaranteed under (2). It is a shortcoming of employing (2). To describe this issue, we take a reference flow \((g, \pi)\) satisfying \( g = b \) on \( S \) and \( g = 0 \) on \( C \). Using this, we will find \((u, p)\) of the form \( u = U + g, \quad p = P + \pi \).

Then, the energy inequality for (1) reads as

\[
\sup_{t \in [0, T]} \| U \|_{L^2(\Omega)}^2 + 2\nu \int_0^T D_{ij}(U)D_{ij}(U) \leq C,
\]

where \( C \) denotes a positive constant depending only on \( f, u_0, b \) and \( T \). This inequality is of use. It plays a crucial role in the construction of a solution of the Navier–Stokes equations as just discussed herein. Furthermore, it is associated with the stability of numerical schemes from the viewpoint of numerical computation. That is, it is preferred that the energy inequality is not spoiled after discretizations. However, the energy inequality (3) is not certain to hold under (2) even for the continuous case. With this connection, F. Boyer, F. Bruneau and P. Fabrie proposed and studied a class of nonlinear boundary conditions that ensure energy inequality (see [4], [5], [6]). A typical outflow condition they proposed is given as

\[
\tau(u, p) = -\frac{1}{2}[u_n]_+ U + 2\nu D(g)n \quad \text{on} \quad \Gamma,
\]

where \([s]_+ = \max\{0, \pm s\}\) and \( s = [s]_+ - [s]_- \).

As a matter of fact, a similar boundary condition is successfully applied in actual computations, i.e., in blood flow simulation for thoracic arteries. Bazilevs et al. [3, §4] employed the following condition. First, they introduced a regularized traction vector

\[ \tilde{\tau}(u, p) = \tau(u, p) + [u_n]_- u \]

and considered the resistance boundary condition

\[ \tilde{\tau}(u, p) \cdot n + R \int_\Gamma u_n \, d\Gamma + p_0 = 0, \quad \tilde{\tau}(u, p) - [\tilde{\tau}(u, p) \cdot n]n = 0 \quad \text{on} \quad \Gamma, \]
where \( R \) and \( p_0 \) are prescribed constants that control the average of the flow rate across \( \Gamma \) (see [7], [8]). This condition is equivalently written

\[
\tau(u, p) = -[u_n]_+ - \left( R \int_{\Gamma} u_n \, d\Gamma + p_0 \right) n. \tag{5}
\]

If \( b = 0 \) (then we can take \( g = 0 \) and \( \pi = 0 \)), we derive the energy inequality under this condition. They offered several numerical results for medical problems and gave no mathematical considerations. On the other hand, Labeur and Wells [9] considered fundamentally the same condition as (5) with \( R = p_0 = 0 \), where they studied energy stable hybrid discontinuous finite element method but did not discuss about the well-posedness of the continuous problem.

Those previous works suggest the importance of controlling the flow-direction near the outlet boundary for stable numerical computations and that the energy inequality is a key property to ascertain whether the flow-direction is suitable or not. Therefore, it is worthwhile considering flow-direction boundary conditions, such as (4) and (5), from the perspective of numerical analysis. Furthermore, few works examine those boundary conditions from the perspective of pure analysis.

The condition (4) is useful, but it presents a few difficulties. Consequently, a non-trivial relationship is assumed between the traction \( \tau(u, p) \) and the velocity \( u \) in (4). We must determine the reference velocity \( g \) before computation. However, it is not readily apparent that the condition (5) is suitable for the case \( b \neq 0 \).

In the present paper, we propose a new boundary condition (see [10], [11]). To control the flow direction at \( \Gamma \), we pose a unilateral boundary condition of Signorini’s type

\[
\left\{ \begin{array}{l}
  u_n \geq 0, \\
  \tau_n(u, p) \geq 0, \ u_n \tau_n(u, p) = 0, \ \tau_T(u) = 0
\end{array} \right. \quad \text{on } \Gamma, \tag{6}
\]

where

\[
\tau_n(u, p) = \tau(u, p)n, \quad \tau_T(u) = \tau(u, p) - \tau_n(u, p)n.
\]

Under this condition, the solution of (1) satisfies the energy inequality (see Theorem ??). It is indeed a generalization of the free-traction condition (2). Namely,

- if \( u_n > 0 \) on \( \omega \subset \Gamma \), then \( \tau_n(u, p) = 0 \) on \( \omega \);
- if \( u_n = 0 \) on \( \omega \subset \Gamma \), then \( \tau_n(u, p) \geq 0 \) on \( \omega \).

Condition (6) is described in terms of inequalities so that it cannot be directly applied to numerical calculations. However, we can use its penalty approximation

\[
\tau_n(u, p) = \frac{1}{\varepsilon} [u_n]_- + \tau_T(u) = 0 \quad \text{on } \Gamma, \tag{7}
\]

where \( 0 < \varepsilon \ll 1 \) is the penalty parameter. After introducing a \( C^1 \) regularization of \([\cdot]_-\), we can solve (1) with (7) by using, for example, Newton’s iteration. We do not need to introduce the reference velocity \( g \) for computation. Moreover, the condition (7) is closely related with (5) in a certain sense. Namely, although \( \varepsilon \) is originally defined as a positive constant, we set it as a function:

\[
\frac{1}{\varepsilon} = [u_n]_-.
\]

Then, (7) implies

\[
\tau_n(u, p) = [u_n]^2 = -[u_n]_- u_n, \quad \tau_T(u) = 0.
\]

Hence, as for the normal component, (7) and (5) are equivalent for \( R = p_0 = 0 \), which suggests that (5) is of use for the case \( b \neq 0 \). This is another motivation for studying (7).

In this paper, we describe the mathematical formulation and examine their effectiveness using some numerical examples.
REFERENCES


NUMERICAL INVESTIGATION OF THERMO-FLUID DYNAMICS IN SUBJECT-SPECIFIC HUMAN EYES USING THE GENERALIZED POROUS MEDIUM APPROACH

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SUMMARY

The present work elaborates the application of the generalized porous medium model to the study of heat and fluid flow in healthy and glaucomatous eyes of different subject specimens, considering the presence of ocular cavities and porous tissues. The dependence of TM porosity and permeability on Intraocular Pressure (IOP) has been analysed in detail, and the differences between healthy and glaucomatous eye conditions have been highlighted. The physiological conditions of patients have been found to have a significant influence on the thermo-fluid dynamic phenomena. The results clearly indicate that porosity and permeability of Trabecular Meshwork (TM) are two important parameters that affect eye pressure distribution.

Key words: Generalised porous medium model; Eye modeling; Intraocular Pressure (IOP); Patient oriented

1 INTRODUCTION

Glaucoma is a major eye disease which leads to the optic nerve damage resulting in visual impairment. The survey of World Health Organisation (WHO) has shown that 60 million of the world population suffers from this ocular malady. Elevated IntraOcular Pressure (IOP) and distension of cornea at the Anterior Chamber (AC) of eye are the primary stages of glaucoma infected patient. The medical physicians have found that lowering IOP at the anterior segment of eye is the better way to cure glaucoma.

Aqueous Humor (AH) is a transparent fluid inside the AC, secreted by the ciliary body, has an important role in regulating the IOP conditions which determines the physiological state of the ocular cavities. AH drains into AC, undergoes free convection due to hydrostatic pressure difference induced by the gravitational force and the thermal gradients at the ocular regions. Based on the in-vivo and in-vitro studies, it has been found out that AH exits through the ocular porous tissue, Trabecular Meshwork (TM), experiences a higher outflow resistance due to TM with a consequent increase in IOP. Also, in some cases, the over secretion of ciliary body accumulates the AH at the AC inducing an abnormal higher pressure condition at ocular cavities despite having a lower TM resistance. Therefore, the complex mechanisms at the AC due to AH and TM makes the problem challenging in assessing the physiological condition of the eye.
In the current study, the authors have developed a transient Generalized porous medium model incorporated in finite volume based software, OpenFOAM to understand the interaction of AH flow and TM porous structure and its effect on IOP inside the patient-specific 3D AC domain which is obtained through reconstruction of 2D AC images arranged at different angles [1].

2 MATHEMATICAL MODEL AND NUMERICAL METHODOLOGY

Laminar, incompressible fluid flow has been considered in this work for AH, in order to model its velocity and temperature inside the anterior chamber of human eyes by solving the generalised porous medium model [2,3]. Buoyancy effects have been incorporated via the Boussinesq approximation, relating density variations to temperature differences in cornea, lens and iris, obtaining a mixed convection flow regime. The conservation equations of the generalised porous medium model in indicial notation can be written as:

Continuity equation:

\[ \frac{1}{\varepsilon} \frac{\partial u_i}{\partial x_i} = 0 \]

Momentum equation:

\[
\frac{\rho_f}{\varepsilon} \left( \frac{\partial u_i}{\partial t} + \frac{\partial}{\partial x_j} (u_i u_j) \right) = \frac{1}{\varepsilon} \frac{\partial}{\partial x_i} \left( \rho_f \varepsilon \right) + \frac{\mu}{\varepsilon^2} \frac{\partial^2 u_i}{\partial x_i^2} - \frac{1.75}{\sqrt{150}} \frac{\rho_f}{\sqrt{\kappa}} \frac{|V|}{\varepsilon^{3/2}} u_i + \left( \rho_{ref} - \rho_f \right) g Y_i
\]

Energy equation

\[
\left[ \varepsilon \left( \rho c_p \right)_f - (1 - \varepsilon) \left( \rho c_p \right)_s \right] \frac{\partial T}{\partial t} + \left( \rho c_p \right)_f u_i \frac{\partial T}{\partial x_i} = k \frac{\partial^2 T}{\partial x_i^2}
\]

The generalised porous medium model (1-3) is very useful in problems where a porous medium interacts with a free fluid, such as the present case where ocular cavities are in contact with porous tissues. In fact, the model approaches the Navier-Stokes equations when permeability, \( \kappa \), goes to infinity and porosity, \( \varepsilon \), approaches unity. However, when permeability assumes a finite value and porosity is smaller than one, the model describes heat and fluid flow in porous tissues.

3 COMPUTATIONAL DOMAIN AND BOUNDARY CONDITIONS

The present numerical procedure aims at predicting the AH thermo-fluidic phenomena inside the anterior section of human eye and conventional TM outflow pathways by means of GPM model. In order to reproduce the actual eye dimensions of human subject-specimen, the stacks of 2D AC tomographic images arranged at different angles have been reconstructed to extract the 3D computational domain by employing SART technique as shown in figure 1. The SART techniques allows to extract the actual AC of a subject-specimen with specific attention in capturing the ocular tissue contours (iris, cornea), the gap between lens and iris which provide the AH ingress secreted from the ciliary body.

Figure 1. 3D reconstruction of the 2D AC eye images.
Four subject-specimens are used in this study and their health conditions are categorised on the basis of IOP measured in clinical trials, out of which three eyes glaucomatous (GE1, GE2, GE2) while the fourth one is a Healthy Eye (HE). Moreover, the glaucomatous eyes are actually diagnosed with uveal glaucoma, a condition due to the inflammation of TM cells and as a consequence, there is an increase in TM resistance to AH flow which leads to a higher IOP at AC. Since the extracted computational domain consists of only AC, lens, iris and inlet, conventional AH outflow pathways comprising TM, SC and CC are modelled as shown in figure 2. The AH formed by the ciliary process flow through the space between the lens and iris, exit at the CC which serves as the outlet. The width of TM at the anterior and posterior portion is 70µm and 100µm, respectively and a Schlemm’s Canal (SC) with an average diameter of 125µm has been modelled at the top of TM [4].

![Figure 2. Computational domain of glaucomatous eye, GE1](image)

AH is secreted by the ciliary body, which is represented in the present model by a small inlet section in the anterior segment of the eye, between iris and lens, as shown in Figure 2. A nominal volumetric flow rate of 2.5 µL/min is assigned at the inlet section. The Schlemm’s Canal (SC) and Collector Channels (CC) are subject to an episcleral venous pressure of 10.5 mm Hg. Lens, iris and cornea are assumed to be impermeable walls, where no slip boundary conditions are imposed. The temperature of the outer surface of cornea is set at 27°C, while the temperature of lens and iris are set to normal human body temperature of 37°C. Appropriate permeability values, depending on the health condition of human eye, are used for the porous tissue that represents the TM.

### 3 RESULTS AND CONCLUSIONS

The permeability and porosity parameters in the eye model are calibrated in the numerical model based on the IOP of the four subject-specimens measured in the clinical trials. These are reported as follows:

<table>
<thead>
<tr>
<th>Eye specimen</th>
<th>IOP (mmHg)</th>
<th>Permeability ($m^2$), $\kappa$</th>
<th>Porosity, $\varepsilon$</th>
</tr>
</thead>
<tbody>
<tr>
<td>GE1</td>
<td>47</td>
<td>$4 \times 10^{-17}$</td>
<td>0.05</td>
</tr>
<tr>
<td>GE2</td>
<td>33</td>
<td>$3 \times 10^{-15}$</td>
<td>0.10</td>
</tr>
<tr>
<td>GE3</td>
<td>30</td>
<td>$1 \times 10^{-15}$</td>
<td>0.12</td>
</tr>
<tr>
<td>HE</td>
<td>13</td>
<td>$1 \times 10^{-16}$</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Tabel 1. IOP, permeability and porosity values of four subject-specimens

The flow fields inside the computational domains of the four subject specimens are plotted for supine and standing positions. The temperature difference among the cornea, iris and lens generates AH vortex patterns inside the AC of subject specimens which differs between supine and standing position. It is interesting to note that the velocity magnitudes at the supine positions have lower velocity values with respect to the standing positions as shown in Figure 3. Moreover, the
glaucomatous eyes (GE1, GE2, GE3) have velocities which are lower in magnitude as compared to the healthy eyes (HE). This is due to the higher IOP values for the glaucomatous eyes.

Figure 3. Velocity fields of the four subject specimens between supine position (left) and standing position (right)

The following conclusions are drawn from the study.
1. The TM porous parameters, i.e. porosity and permeability, have a relevant role in determining the physiological conditions of the different subject specimens.
2. Glaucomatous eyes (GE1, GE2 and GE3) exhibit a lower AH velocity magnitude with respect to healthy eyes, due to higher IOP, affecting the normal biological function of the eye.
3. The heat and mass transfer phenomena are substantially different for the glaucomatous eyes when compared to the healthy eyes.

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REFERENCES


GEOMETRICAL CHARACTERISTIC STUDY FOR CARDIOVASCULAR DISEASES

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SUMMARY

In this paper, we introduce a geometrical characterization of blood vessels, which vary widely among individuals. Differences in the vessel morphology can produce different flow characteristics, stress distributions, and ultimately different outcomes. We present numerical simulations for blood flows related to aortic aneurysms to understand a relationships between aorta morphology and blood flow characteristics.

Key words: blood flow, geometrical characteristics, wall shear stress

1 INTRODUCTION

Our target is blood flows in the human aorta. Aortic aneurysm and aortic dissections persist as life-threatening hazards. Although patient-specific simulations are common in biomedical engineering field and extremely useful for grasping the flow/stress distributions and for patient-specific treatment planning, they remain insufficient to elucidate the general mechanisms of a targeted disease. We introduce a geometrical characterization of blood vessels, which vary widely among individuals. Differences in the vessel morphology can produce different flow characteristics, stress distributions, and ultimately different outcomes. Therefore, the characterization of the morphologies of these vessels poses an important clinical question.

2 METHODOLOGY

Figure 1 shows one of our geometrical representations. Left shows the original vessel and the centerline of it, where the centerline is represented by NURBS interpolation. In the central figure, the number of control points for NURBS is decreased, and in the right figure, we obtain original and coarse-grained centerlines.

Fig. 1 Geometrical representations
3 RESULTS AND CONCLUSIONS

Figure 2 shows wall shear stress distributions for original and coarse-grained shapes averaged over the one heart period. Then, integration of wall shear stress is computed for original and coarse-grained shapes as follows.

\[ \bar{\sigma}(s) = \int_{\Gamma(s)}^{\Gamma} |\sigma| dt \, d\Gamma \]

where \( s \) is the length along the centerline and \( \Gamma(s) \) is a cross-section of the vessel wall at \( s \). Figure 3 shows \( \bar{\sigma}(s) \) for original and coarse-grained shapes, where red curves show the original and blue show the coarse-grained shapes.

In the cases which show large differences in the descending aorta, aneurysms occurred also in the descending aorta. This result can provide information for understating the characteristic difference between individuals.

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REFERENCES

ZERO-STRESS-STATE ESTIMATION IN MEDICAL-IMAGE BASED ARTERIAL MODELING

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SUMMARY

An extension of the initial-guess design for the arterial integration-point-based zero-stress state (IP-BZSS) estimation method is evaluated. The new method has two features. a) An IPB shell-like coordinate system, which increases the scope of the design to general parametrization in the computational space. b) Analytical solution of the force equilibrium in the normal direction, based on the Kirchhoff–Love shell model, which places proper constraints on the design parameters. The evaluation is based on comparing the maximum principal stretches for the initial guess and converged solution.

Key words: Patient-specific arterial FSI, Image-based geometry, Aorta, Zero-stress state, Isogeometric wall discretization, T-spline basis functions, Integration-point-based zero-stress state, Shell-model-based initial guess

1 INTRODUCTION

A method for estimation of the element-based ZSS was introduced in [1]. The method has been applied to coronary arterial dynamics computation with medical-image-based time-dependent anatomical models in [2]. The method has three main components. 1. An iterative method, which starts with a calculated initial guess, is used for computing the ZSS such that when a given pressure load is applied, the image-based target shape is matched. 2. A method for straight-tube segments is used for computing the element-based ZSS so that we match the given diameter and longitudinal stretch in the target configuration and the “opening angle.” 3. An element-based mapping between the artery and straight-tube is extracted from the mapping between the artery and straight-tube segments. The version of the method with NURBS wall discretization was introduced in [3, 4]. In the method introduced in [5], the estimation is based on T-spline wall discretization and is in the form of integration-point-based ZSS (IPBZSS). The IPBZSS is a convenient representation of the ZSS because with isogeometric discretization, especially with T-spline discretization, specifying conditions at integration points is more straightforward than imposing conditions on control points. In the extension of IPBZSS introduced in [6], the method introduces a new design procedure for the ZSS initial guess to increase the scope and robustness. The procedure has two features. a) An IPB shell-like coordinate system, which increases the scope of the design to general parametrization in the computational space. b) Analytical solution of the force equilibrium in the normal direction, based on the Kirchhoff–Love shell model, which places proper constraints on the design parameters. Here we evaluate how the new design procedure for the ZSS initial guess performs. We first present 3D computations with a Y-shaped tube, then a 3D computation where the target geometry is coming from medical images of a human aorta. To evaluate the new design of the ZSS initial guess, we show the differences between the initial guess and converged ZSS in terms of principal stretches and curvature changes.
2 RESULTS AND CONCLUSIONS

In Figure 1, we compare, in terms of the difference between the maximum principal stretches from the ZSS initial guess and converged ZSS, the earlier way [5], which is based on given design parameters (stretches and the opening angle), and the new design [6], which is based on the force equilibrium in the normal direction. The maximum principal stretch for the ZSS initial guess is indicated by \((\lambda_1)^0\), and for the converged ZSS by \((\lambda_1)^\infty\). In Figure 2, we compare the earlier and new ways, again in terms of the difference between the maximum principal stretches from the ZSS initial guess and converged ZSS. With the new design, initial-guess and converged stretches are very close in most regions. The regions with more differences are mostly saddle points, which are difficult to represent by the force equilibrium in the normal direction only.
Figure 2: Patient-specific aorta geometry. The difference $|1 - (\lambda_1)^0/(\lambda_1)^\infty|$ from the earlier (top) and new (bottom) designs.
REFERENCES


NUMERICAL STUDY OF BLOOD FLOW FOR SHUNT MODEL USING STABILIZED FINITE ELEMENT APPROACH

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SUMMARY

In this paper, we present a hemodynamics simulation for a radial artery–cephalic vein shunt for hemodialysis. Three-dimensional shunt geometry is extracted from CT scans. For this study, blood is regarded as a Newtonian fluid that is governed by incompressible Navier-Stokes (N–S) equations. N–S equations are discretized using SUPG/PSPG stabilized finite element approximations. Our aim is to ascertain wall shear stress distributions and vortex structures related to the energy dissipation patterns.

Key words: shunt model, vortex structures, wall shear stress

1 INTRODUCTION

Hemodialysis is the treatment modality of choice for patients with chronic kidney disease (CKD). For dialysis patients, arteriovenous fistula (AVF) is regarded as well-functioning vascular access. For efficient and successful hemodialysis, vascular access is constructed by connecting the radial artery and cephalic vein through a surgical procedure. The objective of this study is to investigate the detailed flow patterns and wall shear stress distributions using the stabilized finite element approach. From patient-specific CT scans, an external surface of the concerned flow geometry is extracted. Vascular Modeling Toolkit (vmtk) [1] is used to derive a centerline associated with the flow geometry, which facilitates generation of the geometry mesh.

2 METHODOLOGY

2.1 Blood viscosity

Hematocrit ($H_{ct}$), the volume fraction of red blood cells, plays a crucially important role in defining blood viscosity ($\mu$), as discussed in [2]. Its value is given as

$$\mu = \mu_p \left( \frac{1}{1 - \alpha H_{ct}} \right) \quad \text{for} \quad H_{ct} < 5\%, \quad (1)$$

which is valid for non-effective interactions between cells. In the equation, $\mu_p$ represents the plasma viscosity; $\alpha$ denotes a shape parameter. If $H_{ct} > 5\%$, then the value of parameter $\alpha$ is expressed as

$$\alpha = 0.076 \exp \left[ 2.49 H_{ct} + \frac{1107}{T} \exp(-1.69 H_{ct}) \right] \quad \text{for} \quad H_{ct} < 60\% \quad \text{at} \quad T = 310^9 K. \quad (2)$$
2.2 Governing equations

Letting $\Omega \times (0, T) \subset \mathbb{R}^{nd} \times (0, T)$ be the spatial time domain where $nd$ represents the number of space dimensions, then governing is done using unsteady, incompressible N–S equations as

$$\rho (\partial_t \vec{u} + \vec{u} \cdot \nabla \vec{u}) = -\nabla p + \mu \nabla^2 \vec{u} \quad \text{in} \quad \Omega \times (0, T)$$

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

where $\rho$, $\vec{u}$, $p$ and $\mu$ respectively denote the blood density, velocity vector, pressure, and viscosity.

2.3 Finite element formulation

For discretizing the governing equations above, we used the streamline upwind Petrov–Galerkin (SUPG) / pressure stabilizing Petrov–Galerkin (PSPG) developed by Tezduyar et al. [3]. Spatial domain $\Omega$ is discretized into the elements $\Omega_e$, $e = 1, 2, \cdots, n_{el}$. Letting $S_u$ and $V_u$ respectively stand for the trial and test function spaces for velocity and letting $S_p$ and $V_p$ be the trial and test function spaces for pressure, we can express the stabilized finite element formulation of equations (1)–(2) with the SUPG/PSPG stabilization terms as shown below.

Find $\vec{u}^h \in S_u$ and $p^h \in S_p$ such that $\forall \vec{u}^h \in V_u$ and $\forall q^h \in V_p$:

$$\int_{\Omega} \vec{w}^h \cdot (\partial_t \vec{u}^h + \vec{u}^h \cdot \nabla \vec{u}) d\Omega - \int_{\Omega} (\nabla \cdot \vec{u})^h d\Omega + \int_{\Omega} 1/Re \nabla \vec{w}^h \nabla^2 \vec{u}^h d\Omega + \sum_{e=1}^{n_{el}} \int_{\Omega_e} \tau (\vec{w}^h \cdot \nabla \vec{u}^h) (\partial_t \vec{u}^h + \vec{u}^h \cdot \nabla \vec{u}^h + \nabla p^h) d\Omega = 0$$

SUPG term

$$\int_{\Omega} q^h \nabla \cdot \vec{w}^h d\Omega + \sum_{e=1}^{n_{el}} \int_{\Omega_e} \tau q^h \cdot (\partial_t \vec{u}^h + \vec{u}^h \cdot \nabla \vec{u}^h + \nabla p^h) d\Omega = 0$$

PSPG term

In that equation, $\tau$ is the stabilization parameter given as

$$\tau = \left[ \left( \frac{2}{\Delta t} \right)^2 + \left( \frac{2||\vec{w}^h||}{h_e} \right)^2 + \left( \frac{4}{Re h_e^2} \right)^2 \right]^{1/2}.$$  

Here, $Re$ is the Reynolds number, $||\vec{w}^h||$ is the norm of local velocity vector, element length $h_e$ is taken from [3], and $\Delta t$ is the time step. Therefore, discretization of the N–S equations by stabilized finite element method engenders a large and sparse non-symmetric system of linear equations that is solved using the GPBi-CG algorithm discussed in [4].

3 NUMERICAL RESULTS AND CONCLUSIONS

For numerical simulations, an extracted geometry from CT scans is used to draw a centerline and to generate the boundary layer mesh as shown in Figure 1. To compute blood flow patterns and wall shear stress distributions, we consider the pulsatile velocity profile for the inflow boundary while various flow rates are used for outflow boundaries. This report describes different blood flow streamlines through Figures 2 - 3 with velocity magnitudes. We note the strong presence of vortices at the bifurcation site for high viscosity and similar flow pattern for low viscosity with different flow rates. Along similar lines, we observe the dependence of wall shear stress distributions on $H_{ct}$ and flow rate, as depicted in the Figures 4 - 5. When viscosity is low, the wall shear stress distributions are similar for different flow rates, although the different flow rates show different wall shear stress distributions in high-viscosity cases. Therefore, different features of flow patterns and wall shear stress distributions are observed for different hematocrit levels and for different flow rates.
Figure 1: Boundary layer mesh for shunt geometry (Left: centerline, Right: finite element mesh)

Figure 2: Blood flow patterns at maximum inflow velocity with flow rate vein : artery = 75 : 25 (Left: $H_{ct} = 20\%$, Right: $H_{ct} = 45\%$)

Figure 3: Blood flow patterns at maximum inflow velocity with flow rate vein : artery = 90 : 10 (Left: $H_{ct} = 20\%$, Right: $H_{ct} = 45\%$)

Figure 4: Wall shear stress distributions at maximum inflow velocity with flow rate vein : artery = 75 : 25 (Left: $H_{ct} = 20\%$, Right: $H_{ct} = 45\%$)
Figure 5: Wall shear stress distributions at maximum inflow velocity with flow rate vein : artery = 90 : 10
(Left: Hct = 20%, Right: Hct = 45%)

REFERENCES

Artificial intelligence and machine learning in biomedical engineering: methods and applications
COMBINING MACHINE LEARNING AND COMPUTATIONAL MECHANICS TO FIND SOLUTION TO BIOMEDICAL ENGINEERING PROBLEMS - FRACTIONAL FLOW RESERVE (FFR)

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SUMMARY

In this work how machine learning can be combined with computational engineering to find solutions to real practical problems of clinical interest has been discussed. The potential uses of machine learning in the context of approximate solution to differential equations with the application to cardiovascular problems is discussed. The paper also discusses the use of synthetic data generated to use in the training of machine learning algorithms and parameter identification. The fractional flow reserve is used as an example to demonstrate the use of machine learning in computational bioengineering.

Key words: Fractional flow reserve, artificial intelligence, passive digital twin

1 INTRODUCTION

Fractional flow reserve, a technique used to measure pressure difference across a coronary artery stenosis in coronary catheterization, is a decisive factor used by cardiologists to evaluate the risk of performing a percutaneous coronary intervention to treat an individual suffering from carotid artery stenosis. The conventional invasive method used to determine FFR involves insertion of a catheter, using a sheath and a guidewire, through the femoral or radial artery and guiding the wire with pressure sensor tip to the coronary arteries. Recent development of passive but non-invasive FFR measuring technique [1, 2, 3], using computational fluid dynamics, has given rise to a quick, low-cost approach for screening of patients. It has also provided a promising platform for artificial intelligence to be introduced and used as an alternative but robust tool to calculate FFR.

Passive digital twin is a concept of replicating a human digitally using obtained data, such as Computed tomography scans, and creation of an off-line model to study various aspects of the body. In the present study, discussions have been limited to replication of coronary circulation for measurement of FFR, the parameter of interest (see Fig1).

In this work, we propose a method to predict FFR value by coupling CT scan and a passive coronary digital twin model using machine learning. The method was developed primarily in three steps, 1) Development of a passive digital twin model of the cardiovascular system, capable of mimicking the coronary arterial system with geometrical and haemodynamic parameters close to that of the actual human subject, 2) Generation of a massive virtual database for FFR results, covering a wide range of various physiological and stenotic parameters, with the help of the digital twin model developed, 3) Training of a machine learning algorithm using the virtual database generated and then enhancing the prediction capability with transfer learning technique using the few actual patient FFR results.

1.1 Machine learning in fractional flow reserve

Machine learning is currently one of the most sought after technique in biomedical engineering because of its overwhelming capability to accurately predict values and categorize health conditions
in problems where mathematical approximations cannot provide acceptable results. Given the wide prevalence of cardiovascular diseases and its link to 7.2 million deaths\[^4\] in the world, an interest amongst academics and industry to use artificial intelligence in treatment can be anticipated. In the case of FFR, Itu \textit{et al}\[^5\] used machine learning to predict FFR values. A multilayered perceptron model, trained using a database of 12,000 virtual patients developed using a one dimensional haemodynamic model, was used in their work. A variation in anatomical parameters of the coronary arteries and the resulting haemodynamic parameters were used to train their machine learning model. The scope for using not just the anatomical parameters but also the cardiac parameters of the human subject, such as cardiac output, downstream resistance and ejection fraction, to increase the accuracy of prediction still exists. The work presented in this paper proposes a novel digital twin model that utilizes the power of machine learning to incorporate hemodynamic conditions arising not only because of the anatomy of coronary arteries but also cardiac condition of the subject.

2 METHODOLOGY

2.1 Passive Digital Twin

The passive digital twin proposed in this work primarily consists of two components, a machine learning (ML) model and a one dimensional systemic circulation model.

2.1.1 Machine learning for estimating cardiac outflow

The ML model is used to predict cardiac outflow parameters such as ejection fraction and cardiac output by using input parameters such as systolic and diastolic blood pressure, age, weight, height, pre-existing cardiac diseases and so on. The output from the ML model and other haemodynamic conditions is replicated in the systemic circulation model by varying parameters such as elastance curve of the heart and resistances. Anatomy of the arteries used in the systemic circulation model is varied using relations obtained from literature to make the geometry used more patient oriented.

2.1.2 One dimensional haemodynamic model

The haemodynamic model adopted in this work, is a modified version of the model proposed by Mynard and Smolich \[^6\]. A large number of alternative models can be found in references \[^7\]. In this work, only the coronary arterial system is of interest. The model considers major vessels in the systemic arteries as 1-D vessel segments. The inlet of the aorta is connected to a two chamber 0-D heart model, while the outlet of peripheral vessels connects to a three element Windkessel model, which accounts for the micro-circulation.

Blood flow in the 1-D vessel is governed by the non-linear set of equations, eq 1 and 2. An assumption of a flat velocity profile is used for the convective acceleration term, and a profile with boundary layer
is chosen for the viscous friction term. A viscoelastic constitutive law is chosen for the walls, which consists of a power law model for the elastic term and a Voigt model for the viscous wall term (Eqs. 3, 4). The wave speed from eq. 3 is used to find the time required for the pulse to reach the carotid arteries. The majority of vascular beds in this model are treated using three element Windkessel models, which are constructed using 1) lumped compliances on the arterial side, 2) characteristic impedances coupling any number of connecting 1-D arteries to the lumped parameter microvasculature, and 3) a constant vascular bed resistance to represent downstream resistance from the micro-circulation. These vascular beds have been incorporated in all microvasculature beds except the liver and myocardium. For a detailed discussion of the vascular bed modelling of liver and myocardium, see Mynard et al. [8].

A 0-D or lumped model of heart is used in this model. Lagrange multipliers have been used to connect 1-D vessels. The connectivity between 1-D and 0-D models is performed by sharing a pressure node. The system of equations are solved using the methodology in [9] are:

\[
\frac{\partial A}{\partial P} \frac{\partial P}{\partial t} + \frac{\partial Q}{\partial x} = 0, \quad (1)
\]

\[
\frac{\rho}{A} \frac{\partial Q}{\partial t} + \frac{\rho}{A} \frac{\partial}{\partial x} \left( \frac{Q^2}{A} \right) + \frac{\partial P}{\partial x} = -\frac{22\pi \mu Q}{A^2}, \quad (2)
\]

\[
P - P_{ext} = \frac{2\rho c_0^2}{b} \left[ \left( \frac{A}{A_0} \right)^{b/2} - 1 \right] + \frac{\Gamma}{A \sqrt{A}} \frac{\partial A}{\partial t} + P_0, \quad (3)
\]

\[
b = \frac{2\rho c_0^2}{P_0 - P_{collapse}}, \quad (4)
\]

where \( Q \) is the flow rate, \( P \) is the total pressure, \( A \) is the arterial cross sectional area, \( t \) is the time, \( x \) is the coordinate axis, \( \rho \) is the density of blood, \( \mu \) is the dynamic viscosity of the blood, \( c \) is the intrinsic wave speed and \( \Gamma \) is the viscoelastic parameter. The subscripts \( ext, 0 \) and \( collapse \) represent respectively external, stress free and collapse.

### 2.2 Virtual Database

Using the above developed passive digital twin model, a massive database of 20,000 virtual patients was generated. The anatomical conditions, such lengths and diameters of the coronary arteries and the aortic root, and cardiac conditions, varied using parameters such as age, weight, height and so on, were varied using random function. This lead to the generation of a database having a large set of varying patient parameters.
2.3 Neural Network to predict FFR

A neural network, Multilayer Perceptron, comprising of 5 hidden layers was used to predict FFR value in a particular coronary artery. All hidden layers used 'Tanh' activation function, except for the final layer which used 'sigmoid' function. The input consisted of 45 parameters, such as cardiac output, vessel radius at the occlusion and location of occlusion (see Fig 2).

3 RESULTS AND CONCLUSIONS

The methodology proposed in this work using artificial intelligence was able to produce results with levels of accuracy as high as 89%, when observed on synthetic data. This model has now the potential to be tested and re-calibrated in clinical environments. The levels of accuracy may come down by a marginal amount when used by clinicians, which will account for actual patient data, but a re-calibration of the machine learning model using transfer learning technique can enhance the accuracy, potentially much higher than the above observed value.

REFERENCES


BRAIN LOCAL STRUCTURE INFERENCEROUS USING DIFFUSION MRI AND DEEP NEURAL NETWORKS

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SUMMARY

Diffusion MRI, a dataset of diffusion weighted images acquired with multiple directions and strengths of the gradient field, can characterize the local properties of microstructures in living organisms, by using parameters of various signal models. Conventionally, such local properties were obtained through parameter fitting for the signal models. Recent reports revealed that machine learning approaches, such as deep regression neural networks, are promising for inferring the parameters. In this short paper, the basics of diffusion MRI and parameter inference by using deep neural networks are introduced and the characteristics of the approach are discussed.

Key words: diffusion MRI, synthetic Q-space learning, deep neural networks

1 INTRODUCTION

In neuroscience and related clinical researches, diffusion MRI (dMRI) is widely used. A dataset of dMRI includes the signals of diffusion-weighted images (DWI) obtained using various directions and strengths of the gradient field, so-called motion probing gradient (MPG), to form a q-space [1]. The data can be used to quantify the local characteristics of microstructures in the living organisms, such as the brain white matter, by using model parameters such as diffusion anisotropy. Various signal models, including the most popular diffusion tensor imaging (DTI) [2], have been employed for characterizing tissue properties, and the parameters have been obtained conventionally through fitting. Recently, machine learning approaches have been used to infer the dMRI parameters [3-5]. Golkov et al. [5] inferred several model parameters by using multi-layer perceptron (MLP), and this approach is called q-space learning. In the study, training datasets were prepared using the fitting results of real dMRI data. However, such an approach suffers from a lack of variation in training and the absence of a gold standard. Instead, the synthetic q-space learning proposed by Ye [6] uses only synthetic training datasets generated from signal model equations, and has achieved promising results. Furthermore, it has been revealed that the noise level should be matched among the training and test data to obtain optimal robustness in dMRI parameter inference [7], which is called as noise level matching (NLM).

In this paper, the dMRI basics and parameter inference by using deep neural networks are introduced and the characteristics of the approach are discussed by using the signal model examples of DTI [2], diffusional kurtosis imaging (DKI) [8], and neurite orientation dispersion diffusion imaging (NODDI) [9].

2 METHODOLOGY

2.1 Diffusion MRI signal models

(1) Diffusion Tensor Imaging: The DTI model [2] quantifies anisotropic diffusion by a 2nd-order symmetric tensor \( D \), and is often applied to the estimation of fiber orientation. In the model, DWI signal \( S \) along direction \( g \) is approximated with the diffusion coefficient represented by a quadratic form of \( g \) and \( D \) as follows:
\[
\frac{S}{S_0} \equiv \exp(-bg^T Dg) \, .
\]

Note that \( S_0 \) is a baseline DWI signal when \( b = 0 \), and \( b \) is the so-called b-value that contains the magnitude of the MPG [1] and physical constants such as the gyromagnetic ratio of a proton. The parameters inferred for DTI here are mean diffusivity \( MD \) and fractional anisotropy \( FA \), which are derived from eigenvalues of \( D \) [1].

(2) Diffusional Kurtosis Imaging: This model can quantify the non-Gaussian nature of the water diffusion due to microstructural constraints [8]. The signal model equation is in an extended form of the 1D Gaussian description of the Stejskal–Tanner model [10] with an additional parameter of diffusional kurtosis \( K \) as follows:

\[
\frac{S}{S_0} \equiv \exp(-bD + D^2K/6)
\]

where \( D \) is the diffusion coefficient. This DKI model is designed to measure diffusion along a specific direction of the MPG. In three measurements of signals, parameter inference is an even-determined problem, and its closed-form solution is given [8]. For more than three measurements, parameter fitting, such as through the least square method, is employed and a generalized closed form is available [11]. In this paper, \( D \) and \( K \) inferred by MLP are shown.

(3) Neurite Orientation Dispersion Diffusion Imaging: The NODDI [9] model quantifies three elements of the signals by water diffusion, and isotropic and anisotropic components consisting of intracellular and extracellular diffusion as follows:

\[
\frac{S}{S_0} \equiv F_{iso}E_{iso} + (1 - F_{iso})(F_{ic}E_{ic} + (1 - F_{ic})E_{ec}) \, .
\]

\( F \) and \( E \) represent the signal fraction and the normalized signal of the three elements, respectively. The intracellular signal component \( E_{ic} \) represents the degree of angular variation of neurites approximated by Watson distribution and its central orientation. The maps of two fractional parameters, \( F_{iso} \) and \( F_{ic} \), and a parameter of neurites orientation dispersion, \( OD \), inferred by neural network are shown in this paper.

2.2 Implementation of multi-layer perceptron

As in the previous study [5], MLP was employed for the regression-based inference of the parameters of dMRI. As described in the next section, dMRI data acquisition simulation was performed to yield 14 diffusion measurements for DTI, five for DKI, and 73 for NODDI, including one baseline signal \( S_0 \) for each model. The log-input of the normalized signal \( \log(S/S_0) \) was used instead of the signal \( S \). Consequently, the numbers of inputs were 13 for DTI, four for DKI, and 72 for NODDI. The numbers of units in the hidden layer were 256 for DTI, 128 for DKI, and 400 for NODDI without dropout. The output was singular in all models. In summary, unit numbers of 13-256-256-256-1 for DTI, 4-128-128-128-1 for DKI, and 72-400-400-400-1 for NODDI were used in this study. For activation, the ReLU function was used. The Keras environment on the front-end of TensorFlow was used. The training parameters were Normal for initialization and Adam for optimization, with 100 epochs, a batch size of 10,000, and other default settings of the Keras regressor.

2.3 Synthetic data for training

First of all, the signal model parameters were randomly generated in a uniform distribution within a pre-determined range [7] to simulate the dMRI signal acquisition. The parameters \( \lambda_1, \lambda_2, \lambda_3, D, \) and \( K \) were determined in slightly wider ranges than those in the range of clinical data reported in the literature. For the DTI model, elements to compose the diffusion tensor, such as eigenvalues, \( \lambda_1, \lambda_2, \) and \( \lambda_3, \) and eigenvectors \( e_1, e_2, \) and \( e_3 \) were generated first. The diffusion tensor was then obtained.

After generating the model parameters, dMRI signals were obtained using the model equations. The measurement of dMRI signal sets was simulated for each model. For the DTI model, a single b-value of 1000 \( s/mm^2 \), with 13 directions of MPG vectors, was used in addition to randomly generating the baseline signal \( S_0 \) within the range 500–8000. Similarly, four signals with \( b \) \( (s/mm^2) = 0, 311, 1244, \) and 2800 were generated for the DKI model. For the NODDI model, \( b=700 \) in 24 directions of the MPG, and \( b=2000 \) in 48 directions were simulated in addition to \( S_0 \).
Finally, the generated signals were contaminated with artificial noise. Because MRI signals are formed as magnitudes of complex values, the noise distribution is not simple-additive Gaussian but appeared as Rician [12]. A simple model for such noise is expressed as follows [8]:

\[ S_{\text{measured}} = \sqrt{S^2 + \eta^2}. \]  \hspace{1cm} (4)

The zero-mean Gaussian noise term \( \eta \) with standard deviation \( \sigma \) was determined randomly according to the baseline signal level \( S_0 \) by using various levels of ratios: \( \sigma/S_0 \) for NLM[7].

3 RESULTS AND CONCLUSIONS

Fig. 1 shows examples of dMRI parameter inference for healthy volunteer datasets. The DTI dataset was in a matrix size 95×95×58, with an isovoxel resolution of 2 mm, with a single baseline measurement and 13 directions of the MPG at 1000 s/mm². For DKI, a matrix size 64×64×43, isovoxel resolution of 3 mm, and four b-values identical to the synthetic data were used. The MPG direction representing a patient anterior–posterior orientation was used for the diffusion measurement; \( g=\langle -0.03,0.94,-0.33 \rangle \). For the NODDI, a sample dataset available on the website of the NODDI MATLAB toolbox [13] was used, with a matrix size 128×128×50. The q-space settings were identical to those of the synthetic data.

![Diffusion MRI parameter maps](image)

Fig 1 diffusion MRI parameter maps by conventional fitting (upper), and by deep neural network (lower). From left, DTI: \( D \), DTI: \( FA \), DKI: \( D \), DKI: \( K \), NODDI: \( F_{iso} \), NODDI: \( F_{ic} \), and NODDI: \( OD \).

As shown in the figure, neural network yields similar or better parameter inference results in comparison with the conventional fitting approaches. Especially, diffusional kurtosis parameter map was greatly improved. As a major advantage of the Q-space learning by using neural network, the processing speed can be considered. Though it takes up to several hours with conventional approaches to obtain the NODDI parameters, the neural network yielded the parameter maps within a few minutes with a standard PC workstation. In addition, the synthetic learning approach has the advantages whereby the quantity and quality of training data are fully controllable, and the gold standard of the parameters is clearly defined. Beyond these advantages, the importance of NLM should be considered to obtained better results [7]. However, it is often difficult to determine the noise level from clinical data. This can be a potential disadvantage for the neural network with the NLM. Future studies cover such investigation of methodology for automatic NLM according to each clinical data set.

In summary, this paper introduced the dMRI basics and examples of parameter inference by using deep neural networks for the signal model examples of DTI, DKI, and NODDI. By comparing with conventional approaches, the advantages of deep neural networks were also shown.

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PREDICTING VENTRICULAR FIBRILLATION BASED ON QRS COMPLEX SHAPE USING ARTIFICIAL NEURAL NETWORK

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SUMMARY

Ventricular fibrillation (VF) can cause rapid heart rate and then death in the absence of immediate treatment. Several studies have achieved promising performances in predicting VF using heart rate variability (HRV) features. However, as VF is life threatening heart condition, its prediction performance needs further improvement. We extracted the features from 2 min long HRV and ECG signals (QRS signed area and R-peak amplitude) to predict VF occurrence before its onset. Based on artificial neural network, the prediction accuracies obtained for HRV features, QRS complex shape features, and combination of both were 72%, 98.6%, and 99.83%, respectively.

Key words: Ventricular fibrillation, heart rate variability, artificial neural network

1 INTRODUCTION

Ventricular tachyarrhythmia (VTA) causes rapid heart rate and then eventually death in the absence of immediate medical intervention [1]. As majorities of sudden cardiac deaths (SCD) occur because of VTA [1], early prediction of VTA is important to save patients’ lives. VTA contains different types of arrhythmias which includes ventricular tachycardia (VT) and ventricular fibrillation (VF). Because measuring and analyzing ECG signals are efficient ways to identify electrical conduction malfunctions in the heart, such as arrhythmia, previous studies have attempted to predict the occurrence of VT, VF, or both by investigating electrocardiography (ECG) [2]-[4].

Previous studies focused on prediction of VTA using HRV analysis on or prior to the event using VTA and control HRV features. Multilayer perceptron (MLP) neural network with principal component analysis (PCA) used to predict SCD early in patients with sustained VTA using classical features (time and frequency features) and time-frequency features [5]. Experimental results showed that the combination of time-frequency and nonlinear features can predict VTA with high accuracies [6]. Artificial neural network (ANN) models have been frequently applied to deal with complexities of the features extracted from HRV [6]. Recently, features extracted from respiratory rate variability (RRV) along with HRV features were used to improve the performance of VT prediction several minutes before its onset [1].

Several studies showed promising performances of predicting VTA by using HRV, RRV, other features, and their combination [1], [6]. However, they did not consider QRS complex features; QRS complex represents the ventricular depolarization process [7]. When ventricles make reentrant waves due to ectopic focus or other reasons, the cardiac electrical wave pattern can affect the QRS shape and from which important features can be extracted. If more emphasis is put on feature extraction from QRS complex, performance of predicting VT/VF could be improved significantly.

The aim of this study is to investigate the feasibility of the features from QRS complex shape on early prediction of VF as compared to traditional HRV features. To this end, we extracted two features such as QRS complex signed area and R-peak amplitude, and investigated the prediction
performance of VF using ANN, expecting an increased prediction performance using the features from QRS complex.

2 METHODOLOGY

2.1 Dataset

We used freely available databases in PhysioNet [8], such as Creighton University (CU) ventricular tachyarrhythmia (CUDB) [9], normal datasets from paroxysmal atrial fibrillation (PAF) prediction challenge database (PAFDB) [10] and MIT-BIH normal sinus rhythm database (NSRDB) [8]. The sampling frequencies were 250Hz for CUDB and 128Hz the other two databases. Even though there were 35 recordings in CUDB, seven recordings were not considered because some of them had only VT events (not VF event) and some others are shorter than the required data length (> 150s). Thus, a total of 27 recordings were used for data analysis. The control group consisted of 28 subjects (22 subjects who did not have fibrillation events from PAFDB and 6 subjects from normal sinus rhythm database – NSRDB).

2.2 Preprocessing

The databases in PhysioNet [8] for our study contained both raw ECG signals and their corresponding HRV signals. The R-peak to R-peak intervals (RR) were produced by reading the annotation files in PhysioNet [8] that were annotated by Cardiologists. We have divided the signal into two parts: required time and forecast time. The required time represents the time period used for feature extraction between 150 and 30s before the VF onset time. The forecast time indicates the time period between 30 and 0s (VF onset time). Using the required time data, we can predict the occurrence of VF before the forecast time.

2.3 Feature extraction

The features consist of 11 HRV features (4 features in time domain, 4 features in frequency domain, 3 features using Poincare nonlinear) and 4 QRS complex features (in time domain). The desired features for the investigation were extracted from the required time between 150 and 30s before VF onset. The QRS complex signed area and R-peak amplitude were computed using a function known as ECG-derived Respiratory (EDR) from PhysioNet matlab toolbox [11].

2.4 Proposed method

The architecture of our ANN is fully connected network structure consisting of three layers: an input layer with nodes representing input variables to the problem, a hidden layer containing nodes to help capture the nonlinearity in the data, and an output layer with a node representing the dependent variable [12],[13]. Both input and hidden layers use rectified linear unit (RELU) [14] activation function and the output layer uses sigmoid activation function[15]. Activation functions basically decide which neurons should be activated or deactivated [16]. The hidden layer consists of six neurons which were selected by trial and error experimentation. We implemented three ANN models with three different input parameters (i) 11 HRV features, (ii) only 4 QRS shape features, and (iii) 11 HRV and 4 QRS complex shape features. The input parameters were standardized and shuffled before they were used in the network. To avoid overfitting, the models were evaluated 10 times with 10-fold cross validation.

3 RESULTS AND CONCLUSIONS

Table 1 summarizes the performance of 3 ANNs with different feature types; HRV vs. QRS vs. their combination. 11 HRV features obtained 72% prediction accuracy. The sensitivity and specificity were 65.68% and 98.44%, respectively. When using 4 features extracted from QRS complex signed area and R-peak amplitude, the prediction performance improved dramatically. The accuracy, sensitivity, and specificity were 98.6%, 98.4%, and 99.04%, respectively. By adding 4 features extracted from QRS complex signed area and R-peak amplitude to the 11 HRV features, the prediction accuracy was slightly improved to 99.83%, but which was not significant. The result
shows that the QRS complex shape features extracted from the ECG have significant impact in predicting VF before its occurrence in terms of its performance. The ANN with 11 HRV features has the lowest area under curve (AUC) value (0.71). When using 4 QRS complex shape features, the AUC reaches 0.99. By combining both HRV features and QRS complex shape features the AUC improved to 1.

Table 1. The results for the ANNs in predicting VF 30 seconds before its occurrence.

<table>
<thead>
<tr>
<th>ANN with</th>
<th>Input Parameters</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Accuracy (%)</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRV</td>
<td>11</td>
<td>65.68</td>
<td>98.44</td>
<td>72 ± 18.2</td>
<td>0.71</td>
</tr>
<tr>
<td>QRS signed area +</td>
<td>4</td>
<td>98.4</td>
<td>99.04</td>
<td>98.6 ± 4.7</td>
<td>0.99</td>
</tr>
<tr>
<td>R-peak Amplitude</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HRV + QRS signed</td>
<td>15</td>
<td>99.47</td>
<td>100</td>
<td>99.83 ± 1.7</td>
<td>1.0</td>
</tr>
<tr>
<td>area + R-peak</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amplitude</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Our result shows that features extracted from HRV have important information to predict the occurrence of VF before several minutes. However, one study revealed that the performance of using only HRV features can be improved by adding RRV features [1]. Therefore, we investigated that only QRS complex shape or combined with HRV can improve the performance of predicting VF, and our study shows that the features extracted from QRS complex shape could have significant effect on predicting VF.

The main limitation of our study is the small number of the datasets and the short length of the signals before the VF occurs. To implement this study for clinical purpose, our ANN model needs to be trained using more datasets.
REFERENCES


PROOF OF CONCEPT FOR MACHINE LEARNING APPLICATION 
TO ARTERIAL DISEASE DETECTION

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SUMMARY
This proof of concept (PoC) aims to assess the ability of a machine learning classifier to predict the presence of a stenosis or an aneurysm within a simple three-vessel arterial system. It is found that using virtual patients, a machine learning classifier could detect stenosis with a maximum accuracy of 77\% for healthy patients and 61\% for unhealthy patients. Aneurysm detection was worse with 62\% of healthy patients and 61\% of unhealthy patients classified correctly.

Key words: Arterial disease, machine learning, virtual patient database, one dimensional pulse wave propagation model.

1 INTRODUCTION
Cardiovascular disease is a general term given to conditions relating to the heart and blood vessels. When this disease effects the arterial system it is referred to as arterial disease. While there are many forms of arterial disease, two of the most common are stenosis and aneurysm. A stenosis is a narrowing of an arterial vessel. The prevalence of stenosis has been recorded to be between 1.9\% and 18.83\% within different arterial vessels and different demographics [1, 2]. The second common form of arterial disease is aneurysm. An aneurysm is a localised weakening of an arterial vessel wall, causing the vessel to bulge. This bulge will gradually grow over time until, if left untreated, it may eventually rupture. As with stenosis, aneurysm may be referred to by several different names, depending on the location of the disease. The most common form of arterial aneurysm is abdominal aortic aneurysm (AAA), with a prevalence of 4.8\% [3].

It has been shown that changes to the cross sectional area of an arterial vessel, whether this is an enlargement due to aneurysm or reduction due to stenosis, will cause changes to the pressure-flowrate waveforms of the blood passing through that vessel [4–7]. This suggests that it should be possible to predict the presence of a stenosis or aneurysm within an arterial network using pressure-flowrate measurements.

If a large database of pressure-flowrate measurements taken from patients of known arterial health is available, it should be possible for a machine learning (ML) classifier to be trained to distinguish between healthy and unhealthy patients. A direct prediction of a patients health could then be made by using pressure-flowrate measurements, bypassing the need for physical models and making the proposed method both inexpensive and near instantaneous. This PoC will make a first step in assessing the possibility of using ML to predict arterial disease. Two virtual patient databases containing healthy and unhealthy patients, similar to that presented in [8], are created as a surrogate to a real cohort. This virtual population is then be used to train a series of ML classifiers to detect arterial disease and test their performance.
2 METHODOLOGY

As opposed to using measurements taken from real patients to train and test the ML classifiers, virtual patients are created using a physical model. The physical model used to create virtual patients is a one dimensional pulse wave propagation model [9]. By considering each vessel as a deforming tube, and considering only mean values at each cross section, a system of two governing equations can be derived. These equations are derived from conservation of mass and momentum by assuming that blood is incompressible, and the tube walls are impermeable. The derivation of these equations can be found in [10]. The resulting system is described by:

$$\frac{\partial A}{\partial t} + \frac{\partial (UA)}{\partial x} = 0,$$

(1)

$$\frac{\partial U}{\partial t} + U \frac{\partial U}{\partial x} + \frac{1}{\rho} \frac{\partial P}{\partial x} = \frac{f}{\rho A},$$

(2)

where $f$ is the frictional force per unit length and is given by:

$$f(x, t) = -2(\zeta + 2)\mu \pi U.$$ 

(3)

In the above equations $P(x, t)$, $A(x, t)$, and $U(x, t)$ denote the pressure, area, and velocity of blood flow at location and time $x$ and $t$ respectively. $\rho$ is density of blood, $\mu$ is the dynamic viscosity of blood, and $\zeta$ is a constant dependent on a chosen velocity profile (in this PoC $\zeta = 9$). To complete this system a third relationship is included, a mechanical model for the displacement of the vessel walls [9]:

$$P - P_{ext} = P_d + \beta \sqrt{A} - \sqrt{A_d},$$

(4)

where

$$\beta = Eh^4 \frac{4}{3} \pi .$$

(5)

Here, $P_{ext}$ represents the external pressure, $P_d$ represents the diastolic pressure, $A_d$ represents the diastolic area, $E$ represents the vessel walls Young’s modules, and $h$ represents the wall thickness.

This system of equations has been previously used and tested extensively [9–14]. The physical system described by equations (1)-(4) is numerically solved using a discontinuous Galerkin scheme [10]. The input into the arterial system is a prescribed volumetric flow rate. The terminal boundaries of the three vessel system are represented by a three element Windkessel models [15]. The configuration of the three elements within this system is shown in Figure 1, and the coupling of boundary conditions to this 1D model is visualised in Figure 2.

![Figure 1: The configuration of the three elements within the Windkessel model are shown [9]. $Q_{1D}$ and $P_{1D}$ are the volumetric flow rate and pressure at the terminal boundary of the 1D system respectively.](image)

To generate patients, it is assumed that across a large population all patient parameters are independent and normally distributed. The mean value for each parameter is being taken from literature [9] and the standard deviation is set to 20% of the mean. Values for each patient parameter are then sampled from these created distributions. For simplicity all virtual patients are limited to having a maximum of one diseased vessel. The health of each patient is generated so that 50% of patients are healthy, and there is an equal number of aortic, first iliac, and second iliac diseased patients.

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As two different diseases, stenosis and aneurysm, are being examined two different virtual patient databases (VPDs) are created. One VPD is being created containing healthy and stenosed patients, and the other with healthy and aneurysm patients. Each VPD has been created so that it contains 3,888 healthy patients and 1,296 with disease in each of the three vessels. The output of the numerical model is the pressure and flowrate at each discrete time point throughout the arterial network. As the pressure and flowrates are periodic it would seem natural to represent the time domain results using a Fourier series. Using this representation will allow for the pressure and flow rates to be described to a high level of completeness in much fewer dimensions. It was found that including up to the 5th order Fourier series coefficient could accurately reproduce the pressure-flowrate waveforms. For this PoC, measurements of pressure and flow are limited to being taken at the inlet and two outlets of the system, shown in Figure 2 by $P_1$, $Q_1$, $P_2$, $Q_2$, $P_3$, $Q_3$ respectively.

A logistic regression algorithm, which is a supervised ML algorithm [17], is used in this study. This algorithm classifies test patients by analysing the relationship between a series of measured inputs and a known output for a large number of observed events. These measurements from observed events can be expressed as $D = \{(x_i, y_i) | i = 1...m\}$. Here $x_i$ represents the vector of measurements taken from event $i$, $y_i$ represents the correct classification of event $i$, and $m$ represents the total number of observed events. It is known that changes to pressure and flowrate within an arterial network between two time points can be decomposed into a forward and backward propagating waveform [18]. Classifiers will be trained using vectors of measurements, $x_i$, consisting of both raw pressure-flowrate measurements and forward-backward propagating pressure-flowrate measurements.

3 RESULTS AND CONCLUSIONS

There are 63 possible combinations of input measurements that can be created from the three locations at which pressure-flowrate measured are taken. Classifiers are trained using each of the two VPDs for each possible combination of pressure-flowrate measurements. The healthy and unhealthy classification accuracy for each measurement combination is recorded. It was found, as expected, that best results were achieved when using pressure and flowrate measurements at all three locations. The results achieved with this combination of input parameters are shown in Table 1. While these results show promise, they are reliant on the use of invasive measurements (either pressure measurements, or material properties required to obtain forward-backward propagating waveforms).
<table>
<thead>
<tr>
<th>Measurement form</th>
<th>Pressure and flowrate %</th>
<th>Only flowrate %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Healthy</td>
<td>Unhealthy</td>
</tr>
<tr>
<td><strong>Stenosis</strong></td>
<td>72.88</td>
<td>52.54</td>
</tr>
<tr>
<td>Raw</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forward-backward</td>
<td>77.56</td>
<td>61.67</td>
</tr>
<tr>
<td><strong>Aneurysm</strong></td>
<td>53.88</td>
<td>55.73</td>
</tr>
<tr>
<td>Raw</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forward-backward</td>
<td>62.64</td>
<td>61.00</td>
</tr>
</tbody>
</table>

Table 1: Classifier results using pressure-flowrate measurements at all three locations and only flowrate at all three locations.

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Clinical application of computational biomechanics II
COMPLEX CARDIAC SURGERY AND FLUID MECHANICS OF BLOOD FLOW: ROLE OF MATHEMATICAL AND PHYSIOLOGICAL THEOREMS IN ADULT CONGENITAL HEART SURGERY.

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SUMMARY

Recent progress in perioperative patient managements in cardiology, surgical indications and optimal surgical procedures are standardized and are determined based on statistical data. However, some patients with complicated heart anatomy and function are still challenging, and they require fluid dynamical analysis in the determination of therapeutic strategies due to the shortage of experience or data with relatively short history in cardiac surgery. Blood flow imaging such as 4D flow MRI provides information of cardiac function and workload, which are essential for decision making of patients. CFD modeling with physiologically defined boundary conditions plays an essential role in surgical planning, when combined with CG. We discuss the role of fluid mechanics in complex cardiac surgery in an era of data science and statistical evidence.

Key words: Cardiac Surgery, 4D flow MRI, CFD modeling

1 INTRODUCTION

Recent progress in computer sciences and technology has brought advances in medical imaging, and with the combination of theorem of fluid mechanics, several novel blood flow imaging tools are generated and industrialized [1], [2]. Phase contrast MRI (PC-MRI) detects the blood flow velocity distribution of the magnetic gradient fields [1], and reconstruction of all directions of PC-MRI provides 3D flow streamline with pulsatility, which is known as 4D flow MRI [2]. In addition to in-vivo flow visualization of patients' heart and vessels, 4D flow MRI provides information of cardiac function, cardiac output valve regurgitation volume, and cardiac workload, which is defined by a viscous dissipation term of fluid flow, which is called flow energy loss (EL).

Computational fluid dynamics can be applied to medical images and it can realize blood flow in the cardiovascular system, when combined with physiologically appropriate boundary conditions in the cardiovascular system. In addition, when combined with 3D computer graphics (CG), it plays a role of
surgical planning for the choice of optimal surgical procedures with an information of postoperative “virtualized” hemodynamics.

Recent progress in clinical practice has promoted standardization of cardiovascular medicine and surgery, and statistical evidences with sufficient clinical datasets guided to sophisticated clinical guidelines. However, even today, several complicated cases especially in reoperation in late-term after the repair of congenital heart diseases, called adult congenital heart surgery, are still lack in sufficient data and are challenging [3], because of the complicated heart anatomy and hemodynamics, and because of the shortage of history in cardiac surgery and experiences compared with long patients follow up periods. We introduce, at first, blood flow imaging methods based on 4D flow MRI and CFD modeling, and then discuss their practical role in the determination of surgical indication through a few case presentations.

2 METHODOLOGY in 4D FLOW MRI and CFD MODELING

In 4D flow MRI, we take systematic data acquisition with multislice sagittal SSPF (steady state free procession) and PC-MRI without using any contrast medium under free breath. In addition to the right and left ventricular chamber size and contraction as usual cardiac MRI, flow rate and valve regurgitation, flow streamlines are visualized [2]. Moreover, hemodynamic parameters including flow energy loss (EL) is defined as the following term.

\[ \int dt \int \frac{1}{2} \mu \left( \frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i} \right)^2 dv \]

where \( u_i \) and \( x_i \) are flow velocity vector component, and Cartesian coordinate of arbitrary direction \( i \), respectively, and \( \mu \) is a viscosity. This term is an alternative of total pressure loss under specific boundary conditions, which are compatible to physiology of peripheral vessels [1]. This parameter is known as cardiac workload, a predictor of ventricular deterioration [4]. In addition to examine the alignment of the flow streamlines, we calculated a parameter named helicity \( \mathbf{u} \cdot \nabla \times \mathbf{u} \), which is conceptually equivalent as cross-linking number of the streamlines [1].

In CFD modeling, boundary conditions in inlets and outlets are essential to realize physiological flow. We define outlet boundary conditions as the following rule.

(1) In aortic flow simulation, outlet boundary conditions are defined as pressure including reflection wave from the peripheral tissue, vascular inertance, and autonomic nerve regulation.

\[ P_{\text{outlet}} = P_{\text{measure}} - Z_0 Q - L \frac{dQ}{dt} \pm RH(Q_{\text{out}} - Q) \]

where \( Z_0 \) is a characteristic impedance of aorta, and \( L \), and \( R \) indicate vascular inertance and resistance, respectively. \( H(x) \) is a Heaviside function that regulate switch of a nerve system.

(2) In a system that does not matter stenosis or perfusion pressure difference between outlets, outlet boundary condition is defined as pressure.

\[ P_{\text{outlet}} = P_{\text{measure}} - Z_0 Q - L \frac{dQ}{dt} \]

(3) In a system that does matter stenosis and perfusion pressure difference between outlets, time varying impedance that reflect peripheral perfusion capacity is given \( R(t) \). Especially in coronary arterial system, time averaged impedance depends on the estimated perfused myocardial muscle volume obtained from 3D CT images for realize the perfusion capacity of the coronary arterial system. Each myocardial voxel is attributed to the nearest coronary branch.

Finite volume method is applied to calculate Navier-Stokes equation with a Newtonian incompressible fluid with constant viscosity scheme other than aortic flow, in which RNG (renormalization group) k-epsilon model is applied to realize flow of high Reynolds number flow [6]. In a virtualized surgery in a computer, we combined computer graphics (CG) to create a geometry of postoperative state to predict hemodynamics after each surgical procedure.
3 VALIDATIONS and APPLICATIONS

4D flow MRI has an advantage in the examination of diseases in complex 3D anatomy such as congenital heart disease [3]. In addition, flow EL is a sensitive parameter to estimate cardiac workload, and useful for the indication or postoperative evaluation of the heart valve disease [3]. As a comparative study between 4D flow MRI and CFD calculation, we performed voxel by voxel validation of flow velocity vector inside the aorta [6]. It has both meanings of qualitative validation (whether CFD models with these boundary conditions can realize actual blood flow in human beings), and quantitative validation (the evaluation of measurement error in magnetic resonance). Among the turbulent models including LES (large eddy simulation), RNG k-epsilon has best agreement to the 4D flow MRI vector inside the aortic flow [6].

4D flow MRI visualized and quantified disturbed turbulent flow pattern in a diseased valve. Even though helical spiral flow pattern was observed both in bicuspid aortic valve and in bioprothetic valve, helicity, the cross-linking number is quite different between them. EL in healthy, bicuspid valve, and bioprothetic valve case was 1.86, 3.92, and 2.43 mW respectively. This bicuspid valve case had stenosis with valve regurgitation, and he was indicated valve surgery. Helicity is a kind of dissipative quantity with viscous property like EL, as its time change described below becomes negative under the traction free and surface normal boundary conditions in inlets and outlets of the vessels.

\[
\frac{\partial}{\partial t} \left( \bar{u} \cdot \bar{\omega} \right) = - \int_{\partial D} \left( \bar{u} \cdot \bar{\omega} \right) n - \rho \left( - \frac{1}{2} \bar{\omega} \left| \bar{\omega} \right|^2 \right) n dA - \mu \int_{D} \left( \frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i} \right) \frac{\partial u_k}{\partial x_l} dV
\]

MRI has an advantage in the evaluation of the right ventricle (RV), we visualized pulmonary regurgitation (PR) of a 54-year-old female after the repair of tetralogy of Fallot, a congenital heart disease. 4D flow MRI quantifies the regurgitation volume and flow EL in the RV and pulmonary circulation. The patient recovered from RV failure after the pulmonary valve replacement with a bioprothetic valve. Flow EL decreased after the surgery [3].

CFD calculation has good agreement with measured flow with transit time flowmeter even in small size vessels such as coronary arteries. As an application of our CFD system of coronary artery and aortic root, we performed virtualized surgery before actual operation of an adult congenital case. A 38-year-old female with restenosis in the ascending aorta after the repair of supravalvular stenosis when she was 8 years old. Severe stenosis inside the aorta caused hypertrophy of the left ventricular muscle and diffuse dilatation of the coronary arteries. Two CFD simulation models with in-situ coronary reconstruction and coronary arterial bypass grafting (CABG) procedures are created to
avoid postoperative ischemia to the hypertrophied ventricular muscle after the reduction of the perfusion pressure inside dilated coronary arteries with the stenosis release. Flow acceleration with pressure drop in systole was released irrespective of the coronary artery reconstruction procedures, but in diastole, low perfusion pressure and small amount of coronary arterial flow were found in CABG reconstruction especially in diastole in left coronary arterial branches. Therefore, we selected in-situ reconstruction of coronary arteries with root replacement, and postoperative course was uneventful, and the patient discharged 2 weeks after the operation.

In conclusion, even in an era of data science with abundant data for statisticians, some cases in adult congenital heart disease have still shortage of experiences or accumulated data with short history for optimization of therapy; therefore, fluid dynamics with flow measurement and calculation plays an essential role in the determination of surgical indication and in optimization of the procedures. 4D flow MRI is a powerful tool to derive several hemodynamic parameters to avoid ventricular function, and CFD modeling with CG is a powerful tool for surgical planning.

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PRIMARY STABILITY OF CEMENTLESS ACETABULAR CUP IMPLANTS: A NUMERICAL STUDY

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SUMMARY

Biomechanical phenomena occurring at the bone-implant interface during the press-fit insertion of acetabular cup (AC) implants are still poorly understood due to multiscale complexity. This work presents a finite element study of the biomechanical behavior of the AC implant during the press-fit insertion and pull-out processes as a function of the bone Young’s modulus $E_b$, the diametric interference fit (IF) and the friction coefficient at bone-implant interface $\mu$. The numerical model is validated by comparison with experimental results obtained from an \textit{in vitro} test. Proposed parametric studies may be useful to understand the biomechanical determinant of the AC implant primary stability and could help surgeons making better decisions on the choice of the implant roughness and the interference fit used for a specific patient’s bone quality.

Key words: Bone implant interface, primary stability, FE analysis

1 INTRODUCTION

Within the last thirty years, total hip arthroplasty has become a common surgical intervention. Nevertheless, surgical failures still occur, leading to dramatic consequences for patients and important costs for the healthcare system. Aseptic loosening is one of the most common causes of failure and it is often related to the implant primary stability. Cementless acetabular cup (AC) implant surgery has become more and more employed over the past decade because of various drawbacks associated with cemented implants. AC implants are inserted using the press-fit technique, where the implant primary stability is obtained by slightly oversizing the AC implant compared to the host bone cavity. The AC implant is then inserted into the bone cavity using impacts produced by a surgical hammer. The pre-stressed state of the bone-implant system is responsible for the AC implant primary stability. The AC implant primary stability refers to the quality of the implant mechanical fixation obtained during the surgery, which is due to residual stresses localized mostly at the AC implant rim [1,2,3]. Different pull-out tests [4,5] have been carried out \textit{in vitro} or \textit{ex vivo} in order to assess the AC implant primary stability. However, the dependence of the primary stability of the cementless acetabular cup implants on the geometrical and physical properties at bone-implant interface have not been carefully instigated.

The aim of this study is to provide a better understanding of the phenomena occurring at the bone-implant interface and of the determinants of the biomechanical behavior of cementless AC implant. To do so, geometrically nonlinear finite element analyses of a 2-D axisymmetric model were performed to simulate the quasi-static insertion and pull-out process of the AC implant in bone. A parametric study has been carried out to investigate the effects of the interference fit, the friction coefficient and bone properties on the pull-out force, \textit{i.e} the force neccesary to move the AC out of the bone cavity host.
2 METHODOLOGY

A 2-D axisymmetric finite element (FE) model aiming to simulate the AC implant quasi-static biomechanical behavior by reproducing the implant press-fit configuration and a pull-out test, was employed. For the simulation of the mechanical problem of the insertion and pull-out of an AC implant, the system was considered as nonlinear geometrically elastic solids under quasi-static loading conditions.

Figure 1 presents the in vitro test for determining the pull-out force on a bovine femur sample (a) and the corresponding geometrical model (b). Three domains may be distinguished in this model: the ancillary (stainless steel), the AC implant (titanium alloy TiAl6V4) and the bone sample (trabecular bone). All of them are considered as isotropic elastic materials with the same Poisson coefficient of 0.3. The Young modulus of the ancillary and the AC implant are 210 GPa and 113 GPA, respectively. The Young modulus of the bone (E_b) varies in the range of 0.1-1 GPa with reference value 0.2 GPa. The contact condition between the AC implant and the bone is modeled by the static Coulomb’s friction law. The friction coefficient \( \mu \) at the bone-implant interface varies in the range of 0-1 with a reference value \( \mu^* = 0.3 \).

The finite mesh consists of about 2500 quadrilateral Lagrange element and 200 contact elements, leading to a global system with about 15000 degrees of freedom. For this study, numerical analyses were carried out using Ansys® Workbench software (v. 17.0, Canonsburg, US).

In this axisymmetric model, symmetric conditions are imposed at left-hand surface of all sub-domain. The bottom surface of the bone sample is fixed. A vertical quasi-static displacement \( U_0(t) \) applied at the top surface of the ancillary which consists of 3 sub-steps: (i) an insertion phase, in which a linearly decreasing displacement (from 0 to \( d_0 \)) is imposed, (ii) a holding phase, in which the displacement is kept to be constant (\( d_0 \)); and (iii) a pull-out phase, in which a linearly increasing displacement is imposed (from \( d_0 \) to 0) until the implant was completely detached from bone tissue (Figure 2(a)). At each imposed displacement increment, the vertical reaction force at the upper surface of the ancillary (denoted by \( R_a \)) (which also represents the vertical force applied to the implant) may be...
calculated (Figure 2(b)). The maximum value of the imposed displacement \(d_0\) is chosen in such a way that the force \(R_a\) reaches a controlled value \(F_0\). As it can be seen in the Figure 2(b), this numerical test allows to determine the pull-out force (PO force) which defined by the maximum value of the reaction force \(R_a\).

![Figure 2(a)](image1)

**Figure 2 (a) Imposed displacement (b) reaction force at the upper at the surface of the ancillary**

### 3 RESULTS AND CONCLUSIONS

Different parameters, such as the friction coefficient \(\mu\), the bone Young’s modulus \(E_b\) and the interference fit IF (corresponding to the difference between the implant and the bone cavity nominal diameters) were varied within their physiological ranges, and their influence on the primary stability was investigated. The numerical model was first validated and collated through a comparison with experimental results obtained from an *in vitro* test, which allows us to determine a reference configuration with the parameter set: \(\mu^* = 0.3\), \(E_b^* = 0.2\) GPa and \(IF^* = 1\) mm for an insertion force \(F_0 = 2.5\) kN (see Fig. 3c). In the reference configuration, a maximal contact pressure \(t_N = 10.7\) MPa was found to be localized at the peri-equatorial rim of the acetabular cavity good agreement with previous works [1,2,5].

Parametric studies were carried out by fixing 2 parameters among \((E_b, IF, \mu)\) and varying the third one. The results of pull-out forces computed in three cases are presented in Figure 3, showing that the pull-out force is a concave function with respect to \(\mu\) (or to \(E_b\), or to \(IF\), respectively). These curves allow us to determine the optimal friction coefficient \(\mu = 0.6\) (or \(E_b = 0.35\) GPa, or \(IF = 1.4\) mm, respectively) to obtain the maximum PO force in each situation. The results may be useful to understand the biomechanical determinant of the AC implant primary stability and could help surgeons making better decisions on the choice of the implant roughness and the interference fit used for a specific patient’s bone quality.
Figure 3: (a) Variation of the PO force as a function of the friction coefficient $\mu$ for constant values of $E_b = 0.2\text{GPa}$ and $IF=1\text{ mm}$; (b) Variation of the PO force as a function of the bone Young’s modulus $E_b$ for constant values of $\mu=0.3$ and $IF=1\text{ mm}$; Variation of the PO force as a function of the interference fit $IF$ for constant values of $\mu=0.3$ and $E_b=0.2\text{GPa}$. The press-fitting force is taken equal to 2.5 kN.

The present study investigates the dependence of the AC implant primary stability on its environment including the interference fit, the friction coefficient and bone properties. This study emphasizes the existence of an optimal primary stability condition, which depends in a coupled manner on the friction coefficient, on the stiffness properties and on the bone cavity under-reaming.

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REFERENCES

HEMODYNAMIC EFFECTS OF ENHANCED EXTERNAL COUNTERPULSATION ON CEREBRAL ARTERIES: A MULTISCALE STUDY

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SUMMARY

Clinical questions about optimal mode of enhanced external counterpulsation (EECP) for stroke patients remain to be answered. A 0D/3D geometric multiscale model of the cerebral artery was established to investigate the acute and long-term hemodynamic effects of EECP. Results show that the pressure amplitude and pressurization duration have different impacts on hemodynamic effects in the EECP treatment. With the increasing pressure amplitude applied, hemodynamic effects of cerebral artery improved slightly. Nevertheless, hemodynamic effects improved significantly with increasing pressurization duration. Long pressurization duration resulted in the better hemodynamic effects for stroke patients.

Key words: enhanced external counterpulsation, cerebral artery, geometric multiscale model, hemodynamic effects

1 INTRODUCTION

Enhanced external counterpulsation (EECP) is an effective method for treating patients with cerebral ischemic stroke. The hemodynamics is the major contributing factor in the treatment of EECP. For stroke patients, EECP can effectively increase blood perfusion in the brain and alleviate the symptoms of ischemia in real time [1, 2], which is the acute hemodynamic effect of treatment. In addition, by accelerating blood flow, EECP significantly improves the wall shear stress (WSS) in cerebral arteries. For stenotic cerebral arteries, vascular endothelial cells (VECs) of stenosis are constantly exposed to a high WSS environment during long-term application of EECP [3], which effectively inhibits atherosclerosis development and promotes benign remodeling of blood vessels. The treatment effect of EECP acting on VECs is the long-term hemodynamic effect. However, different counterpulsation modes may lead to different acute and long-term hemodynamics, thus result in different treatment effects. Three questions about regarding appropriate counterpulsation modes to optimize the hemodynamic effects remain to be answered in clinical treatment: 1) During counterpulsation, should the same pressure applied to three parts be maintained? 2) How can the pressure amplitude applied to each part be adjusted? 3) How can the pressurization duration of counterpulsation be adjusted? By focusing on the concerns of clinical application, this study first used hemodynamic geometric multiscale numerical simulation to investigate the acute and long-term hemodynamic effects on cerebral arteries of different counterpulsation modes.

2 METHODOLOGY

A 0D/3D geometric multiscale model of the cerebral artery was established as shown in Fig. 1. The closed-loop 0D model of blood circulatory system was set up referring to previous studies [4, 5]. Based on the computed tomography angiography (CTA) images of a cerebral artery, the 3D model...
was reconstructed using 3D remodeling tools such as Mimics and FreeForm Modeling Plus. The structure at coupling interface of 0D/3D model was designed according to previous study [6]. Numerical simulations were conducted using the CFX module of ANSYS to obtain the acute hemodynamic indicators, including mean arterial pressure (MAP) and cerebral blood flow (CBF), and the long-term hemodynamic indicator of local cerebral artery, including wall shear stress (WSS). The counterpulsation was achieved by applying pressure on the calves, thighs and buttocks modules in the 0D model. Different counterpulsation modes, including different pressure amplitudes (150-260 mmHg) and pressurization durations (0.5, 0.6 and 0.7 s), were applied to investigate the responses of hemodynamics which impact the acute and long-term treatment effects. Vascular collapse and automatic regulation mechanism of cerebral blood flow were considered during counterpulsation.

Figure 1 The geometric multiscale model of the cerebral artery with three inlets and six outlets. In the 0D module, the voltage sources $P_{e}$ in artery and vein units were used to simulate the pressure provided by the counterpulsation cuff, which exist in $A8-A13$ and $V8-V13$ only. The diodes in $V8-V13$ were used to simulation the venous valve of the lower limbs. In the 3D module, $RICA$ and $LICA$ are right and left internal carotid arteries, respectively, $BA$ is basilar artery, $b$ and $c$ are anterior cerebral arteries, $a$ and $d$ are middle cerebral artery, $e$ and $f$ are posterior cerebral arteries.

3 RESULTS AND CONCLUSIONS

Variations on the pressure amplitude and pressurization duration have different impacts on hemodynamic effects in the EECP treatment. Fig. 2 shows there was little difference between the hemodynamics of the same or different pressure amplitudes applied to calves, thighs and buttocks. With the increase in the same pressure amplitude applied to the three parts, the MAP and CBF improved slightly when the pressure amplitude was less than 200 mmHg as shown in Fig. 3, which was consistent with clinical data [7]. Nevertheless, the hemodynamics showed a significant impact
by pressurization duration. The simulation waveforms of the aortic pressure and CBF under different pressurization durations are shown in Fig. 4. Fig. 5 shows the WSS contours of cerebral artery at the maximum flow moments during systole and diastole under three pressurization durations. As the results show, the MAP, CBF and WSS improved significantly with increasing pressurization duration, and the highest WSS of the cerebral artery in both systole and diastole was observed for the mode of pressure release at 0.7 s.

Figure 2 The variations of MAP and CBF by each pressure amplitude difference between the calves, thighs and buttocks.

Figure 3 The MAP and CBF under different pressure amplitudes

Figure 4 The simulation waveforms of aortic pressure and CBF under three pressurization durations
It can be concluded that when the EECP was applied to patients with cerebral ischemic stroke, the same pressure amplitude could be adopted in three parts. Patients will not benefit much more from EECP treatment by excessively increasing the pressure amplitude. However, during clinical operation, pressurization duration should be tried to increase in a cardiac circle to optimize the hemodynamics as much as possible, thus acquiring the better acute and long-term treatment effect.

REFERENCES

IN-SILICO DEVELOPMENT OF NOVEL DEVICES TO TREAT CEREBRAL BIFURCATION ANEURYSMS

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SUMMARY

Cerebral bifurcation aneurysms remain hard to treat with conventional therapeutic device options despite bifurcation cases constituting the majority of the cerebral aneurysms presented clinically. The design of novel flow-diverter devices to treat these challenging cases can be greatly enhanced with in-silico simulation of device deployment and flow-diverting capacity with CFD. Two novel device designs are explored in this study and show positive results from virtual treatment of a number of bifurcation aneurysms, when compared to conventional devices.

Key words: medical devices, CFD, aneurysms, flow-diverter

1 INTRODUCTION

Cerebral aneurysms are a localized weakening and ballooning of the vessel wall in the arteries that supply the brain with blood. Aneurysms that grow and are at risk of rupture must be treated to prevent further complications or life-threatening hemorrhage [1]. Minimally-invasive treatment options are very attractive for cerebral aneurysms, and lesions have been successfully isolated with both coils and low-porosity stents, commonly known as flow-diverters [2].

The majority of cerebral aneurysms occur at vessel bifurcations [1, 3]. Despite significant innovation in cerebral aneurysm treatment in the past two decades, only a small number of dedicated devices are available to specifically treat bifurcation aneurysms—and even fewer treatment options are available for wide-necked lesions. In all of these cases the treatment devices are designed to be placed within the delicate aneurysm dome (e.g. WEB, Artisse or Medina devices) or to jail a daughter vessel with low-porosity mesh as in the case of a conventional flow-divertor (e.g. SILK, PED, FRED or SURPASS devices). Treatment failures from poor device-aneurysm compliance, aneurysm neck remnants or occluded daughter vessels have been reported in both types of device [4, 5, 6, 7].

Consequently, there is a strong desire to develop a dedicated flow-diverter device to treat cerebral bifurcation aneurysms without unnecessarily restricting the blood supply to daughter vessels or requiring the device to be placed within the delicate aneurysm sack. In this study a computational pipeline to design and test novel flow-diverter devices is showcased and two candidate devices (the Sphere [8] and the eCLIPs [9, 10]) are investigated further. In both cases these novel devices are compared to a conventional flow-diverter deployed to treat the same aneurysm geometries.

2 METHODOLOGY

Five cerebral bifurcation aneurysm geometries were selected for virtual deployment and CFD simulation by the relevant clinical teams. The selected geometries consisted of three internal carotid
terminus aneurysms and two basilar tip aneurysms with maximum aneurysm dome and neck diameters varying from 4.2 to 13.4mm and 3.3 to 6.4mm respectively.

Simplified wireframe versions of the treatment devices were deployed manually into each aneurysm geometry. The devices were deployed without considering material properties but instead the placement was achieved by minimizing the local curvature of each device element. Conventional flow-diverter devices were deployed using a previously detailed fast-deployment algorithm also built on minimizing local deformation [11]. The wireframe devices were then fleshed with thickness appropriate for each device and trimmed in extraneous areas (those far from the aneurysm neck or daughter vessel lumen) to increase subsequent computational efficiency.

Each aneurysm geometry with each device deployed was meshed in CFD-VisCART (ESI Group, Paris) to a previously investigated level of mesh independence and exported to CFD-ACE+ Multiphysics Suite (ESI Group, Paris) for computational fluid dynamics calculations. Transient CFD simulations were performed corresponding to three cardiac cycles with blood velocity and waveforms taken from population-average values for the relevant arterial segments. Blood was modelled as a Newtonian fluid with the Navier-Stokes equations solved using the finite volume method and second-order interpolations in both space and time. Simulations were run on 32-64 cores with convergence at each timestep seen in fewer than 50 iterations and overall solution times of 72-96 hours.

Post-processing of results was conducted in CFD-VIEW (ESI Group, Paris) and included interrogating reductions in aneurysm flowrate, mean aneurysm velocity, and spatially-averaged aneurysm wall shear stress (WSS)—all factors linked with aneurysm occlusion by thrombosis—as well as reductions in peak aneurysm WSS and velocity—factors associated with reduced rupture risk [12, 13].

![Figure 1](image-url)
3 RESULTS AND CONCLUSIONS

The performance of each novel flow-diverting device was compared to a conventional flow-diverter device across the five aneurysm geometries investigated. Reductions in metrics associated with aneurysm thrombosis such as aneurysm inflow and mean WSS were similar across the devices pointing towards a similar potential for successful lesion isolation. Devices with finer pore structures (smaller mesh) were shown to be more effective at reducing jets of flow entering the aneurysm dome, which could offer additional therapeutic benefit by reducing rupture risk.

Subtle flow features were revealed by the CFD simulations including concentrations of outflow at the aneurysm neck after conventional device deployment, as well as substantially different degrees of performance with flow-diverters deployed in either left-hand or right-hand bifurcation branches. Additionally, the sensitivity to device deployment position in the novel designs was evaluated with a subset of aneurysm geometries. These simulations showed little variation in device performance (<5% change in reduction metrics) and add robustness to the in-silico predictions of performance.

Overall a large range of flow patterns, aneurysm inflow rates, velocities and WSS distributions were seen across the aneurysm geometries, which reinforces the need for patient-specific considerations in treatment planning and device selection. Finally, the biochemical processes leading to successful aneurysm isolation, including thrombus initiation and growth, are not modelled explicitly in this case due to their immense complexity. However, by comparing novel devices to established treatment options, where the clinical performance is well-documented, the potential of a novel design can be rapidly and confidently evaluated—and be used to inform subsequent design decisions.

REFERENCES

EVALUATION OF WRIST INSTABILITY USING 3D RECONSTRUCTED BIOMEDICAL IMAGES AND COMPUTATIONAL SIMULATION

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SUMMARY

Delay in treatment of wrist pain and instability due to inconsistent diagnosis on clinical examination often leads to poor clinical outcomes. We propose a new diagnosis method using 3D reconstructed biomedical images and computational simulation based on change of synovial fluid pressure can improve the accuracy and consistency of clinical diagnosis on wrist pain and instabilities. The proposed method was validated by showing that the change of simulated and experimental synovial fluid pressure was 110Pa and 225Pa. Furthermore, the simulated synovial fluid pressure was found to resemble the experimental results within 1 cycle of radioulnar deviation.

Key words: wrist pain, synovial fluid, computed tomography

1 INTRODUCTION

Wrist pain may be caused by trauma, degeneration and inflammation. Traumatic wrist pain and loss of function can be due to acute injury, chronic repetitive injury, fractures of carpal bones or ligamentous injuries. The latter may be partial or complete, with complete injuries resulting in instability and pain. Degeneration problem associated with bony swellings, ganglion cyst formation, deformities and old fractures of the distal radius or wrist bones can result in osteoarthritis or post-traumatic arthritis. Inflammation as result of rheumatoid arthritis can also cause wrist pain and instabilities.

Diagnosis of wrist pain and instabilities can be performed by taking a careful history and performing a meticulous physical examination. In particular, the wrist instabilities are classified as static or dynamic [1]. Static instabilities can be diagnosed on plain X-rays scanned through abnormal carpal angles or carpal alignment. However, dynamic instabilities may not be seen on routine radiographic examinations. Therefore, it will lead to inconsistent diagnosis on clinical examination.

Invasive diagnosis of wrist instabilities by using wrist arthroscopy remains the gold standard if the cause of wrist pain is unknown, especially the wrist pain continues for several months despite nonsurgical treatment. The procedure includes the insertion of a small camera fixed to the end of a narrow tube through a small incision directly into the back of the wrist joint. Several small incisions allow the surgeon to see the ligaments and cartilage of each bone. However, the associated risks of this procedure include but not limited to infection, additional trauma to nerves, tendons or cartilage and highly operator dependent.

Recent studies on four-dimensional Computed Tomographic (CT) imaging wrist [2, 3], synovial fluid kinematics at the scapholunate joint [4], twist X-ray dynamic scapholunate instability [5] and

In this paper, we present a new diagnosis method of wrist pain and instabilities using the 3 dimensional (3D) reconstructed biomedical images and investigate the synovial fluid dynamics and its influence on wrist kinematics based on computational simulation approach. We hypothesize that using 3D biomedical images and computational simulation based on the change of synovial fluid pressure can address the current challenges while improve the accuracy and consistency of diagnosed results on wrist pain and instabilities.

2 METHODOLOGY

In this section, we present the dynamic CT scans for image segmentation, 3D model reconstruction of wrist and computational simulation of scapholunate (SL) joint with the presence of synovial fluid.

2.1 Motion simulation of cadaveric wrist and synovial fluid pressure measurement

Following the approval of the Institutional Review Board, a cadaveric right-handed wrist with no clinical history of wrist injury was used. As shown in Figure 1(a), the fresh-frozen cadaveric hand was thawed to room temperature and passively moved in radioulnar deviation with a frequency of 60 cycles per minute, at 10° of radial and 20° of ulnar deviation, using a custom-made motorized jig. In order to capture the kinematics of the carpal bones, the cadaveric wrist was subjected to gated-CT scanning (Somatom Definition, Siemens Healthcare, Forchheim, Germany) while undergoing the radioulnar deviation.

The same setup was adopted to measure the pressure change of synovial fluid. As shown in Figure 1(b), the cadaveric hand was fixed at neutral position. At first, any intact synovial fluid was aspirated from the SL joint by insertion of a needle into the SL joint, with the aid of an ultrasound system (ACUSON P300, Siemens Healthcare, California, USA). One ml of commercially available synovial fluid (SYNVISC® Hylan G-F 20, Genzyme Biosurgery, New Jersey, USA) was injected into the SL joint, so as to simulate synovial fluid accumulation under osteoarthritic conditions. The same needle was connected to a pressure transducer via a rigid tube primed with saline solution. Three independent sets of synovial fluid pressure were measured for 8s each with interval break of refilling the tube.

![Figure 1.](image)

Figure 1. (a) Dynamic CT scan; (b) experimental setup of cadaveric hand in radioulnar deviation.

2.2 3D reconstructed model of cadaveric wrist

As shown in Figure 2(a) and 2(b), the CT images were then processed using image processing software (Mimics, Materialise NV, Leuven, Belgium) and 3D models of the scaphoid and lunate (Figure 1(c)) were constructed through semi-automatic segmentation process.

After importing the scaphoid and lunate into SolidWorks (Dassault Systèmes SolidWorks Corp., Concord, MA, USA), a fluid volume was obtained by extruding from the surface of both solid
bodies. This fluid volume in between the two bones is known as the synovial fluid. As shown in Figure 2(c), the synovial fluid has a volume of 104.83 mm$^3$.

2.3 Computational simulation

Fluid-structure interaction (FSI) is a multi-physics coupling between both fluid dynamics and structural mechanics disciplines. Recent advancements in computer resources have allowed the development of robust and effective approaches for complex problems. This led to an increased interest in utilizing FSI to solve complex fluid and solid interaction problems [7]. In this study, we employed FSI analysis based on ANSYS, WORKBENCH (ANSYS Inc., Pennsylvania, USA) to investigate the complex interaction between the synovial fluid and the scaphoid and lunate.

In brief, the synovial fluid was assumed to be Newtonian fluid and the scaphoid and lunate were formulated as linear elastic material. A prescribed rotation and linear velocities of scaphoid, obtained from our kinematic study of wrist motion after the image segmentation, were tabulated as the boundary conditions of the study. Tetrahedral element meshing was applied to the fluid domain while the hexahedron mesh was applied on the scaphoid and lunate. A 2-way FSI using “System Coupling” was established to interact the transient structural system of scaphoid and lunate with the fluent system of synovial fluid.

3 RESULTS AND CONCLUSIONS

The experimental results were presented in Figure 3(a). Pressure was initially recorded as 0 Pa after the signals were processed with a high pass digital filter. When the cadaveric hand moved from the radial deviation towards ulnar deviation (from first to second dot), synovial fluid pressure reduced to its minimum point and then increased back to 0 Pa as the motion simulator approached the preset maximum ulnar deviation angle of 20° and the motion became momentarily zero. When the cadaveric hand moved back to radial deviation (from second to third dot), synovial fluid pressure increased to its maximum point and then decreased back to 0 Pa again after the cycle was completed.

The simulated synovial fluid pressure was found to resemble the experimental results within 1 cycle (see Figure 3(b)). There are 1 peak and 1 trough of synovial pressure corresponding to the previously described maximum and minimum point. The peak of synovial fluid pressure obtained from the simulation is 377 Pa while the peak pressure obtained from the experiments ranged from 165 to 225 Pa. The trough of synovial pressure obtained from the simulation and experiments is 47 Pa and 0 to 24 Pa. This accounts for the pressure change of synovial fluid as 118 Pa and 225 Pa for simulation and experiments.

The change from the peak to trough of synovial pressure is abrupt. This implies a sudden change of relative motion between the scaphoid and lunate, in which the synovial fluid pressure increases and then decreases abruptly, as a result of the narrowing of scapholunate gap during radioulnar deviation [8].
In conclusion, we presented the first 3D computational model of wrist joint which was validated by measuring the synovial fluid pressure change undergone radioulnar deviation.

![Figure 3(a)](image)

Figure 3(a) Three sets of synovial fluid pressure measurements across 8s of data; (b) Comparison between synovial fluid pressure obtained from FSI simulation and experimental data.

REFERENCES


A COMPUTATIONAL STUDY OF FRACTIONAL FLOW RESERVE AND INSTANTANEOUS WAVE-FREE RATIO ON PATIENT-SPECIFIC CORONARY NETWORK MODELS

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\textsuperscript{3}Derriford Hospital and Peninsula Medical School, Plymouth Hospitals NHS Trust, Plymouth, UK

SUMMARY

In this work we compare computational methodologies for conventional fractional flow reserve, diastolic fractional flow reserve, and instantaneous wave-free ratio, using coronary networks extracted from coronary computed tomography angiography. Both diastolic fractional flow reserve and instantaneous wave-free ratio show excellent correlation with the conventional fractional flow reserve measurement. The predicted cut-off point for end-diastolic FFR is approximately 0.8, which is the same as conventional FFR. For the instantaneous wave-free ratio, the cut-off point is predicted to be 0.907. Both of these cut-off points are in agreement with those chosen by clinicians when assessing a stenotic lesion.

Key words: haemodynamic modelling, coronary arteries, ffr, ifr

1 INTRODUCTION

Fractional flow reserve (FFR) is the current gold standard of care for assessing the functional consequences of an obstructive lesion in a coronary artery \[1\]. FFR is an invasive procedure performed during coronary angiography that requires the insertion of a catheter and guide-wire from the femoral artery to the coronary arteries. A pressure-sensitive wire is used to measure the pressure ratio of the pressure distal to a stenosis to the pressure in the aorta. The technique relies on administering a hyperaemic drug (typically adenosine) to the patient, which causes an increase in blood flow through the coronary arteries by reducing the downstream resistance in the coronary vascular bed, and also increases the patient’s cardiac output. The pressure ratio is used to estimate the functional impact and severity of a stenotic lesion. An FFR-guided strategy has been shown to reduce unnecessary stenting, improve overall treatment outcomes, and is cost saving when compared to quantitative coronary angiography alone \[2\]. Nevertheless, alternative diagnosis strategies continue to be developed and tested in order to further reduce costs and improve patient outcomes, particularly as the number of cases involving coronary heart disease is increasing worldwide \[3\].

Diastolic FFR (d-FFR) refers to a collection of FFR variations which includes: full-diastolic FFR, where the mean FFR of diastole is used; mid-diastole, where the FFR is recorded at a single time point in mid-diastole; and end-diastole, where FFR is measured at a single time point at end-diastole. The most promising of these is end-diastole, which has been shown to have a better correlation than conventional FFR \[4\] when compared to FFR as measured using flow-probes. However, end-diastolic FFR has not been tested in many clinical studies. In addition, d-FFR is still performed under hyperaemia, and thus still requires adenosine (or other drugs) to be administered, which can have dangerous side-effects in some patients. This motivated the development of a technique called the instantaneous wave-free ratio (iFR) that can be performed during resting conditions. iFR has been shown to have a similar diagnostic accuracy as conventional FFR \[5\], and has been proposed as part of a hybrid approach which involves both FFR and iFR.
Computed FFR (cFFR) based on reduced-order modelling have compared well with 3D modelling techniques [6, 7], and have been shown to be accurate when compared to the invasive clinical FFR measurements [8]. Thus the modelling approach implemented in this work is based on reduced-order modelling, as simulations can be performed in seconds, rather than hours (for 3D). Currently the cut-off point of FFR and d-FFR is generally considered to be 0.8, while for iFR there has been no consistent threshold found with ranges between 0.83 [9] and 0.92 [11] being given in clinical studies. This variability in the diagnostic threshold supports the use of a computational model to help in its determination by overcoming the variability of surgical techniques. Furthermore, by utilising the same inlet boundary conditions for each patient geometry using the mean cardiac output of a population, the changes in FFR and iFR are primarily dependant on the geometry. The purpose of this work is to compare cFFR, d-FFR, and ciFR methods in a computational framework which could be used to estimate the correct cut-off points of both end-diastolic FFR and iFR. Invasive FFR measurements and CCTA data are utilised to extract geometry and to validate the 1D FFR framework before comparing cFFR with ciFR. In the remainder of the paper the computational end-diastolic FFR prediction will be referred to as dFFR.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Resting</th>
<th>Hyperaemic</th>
<th>Patient Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic pressure (mmHg)</td>
<td>115</td>
<td>115</td>
<td>Stenosis no.</td>
</tr>
<tr>
<td>Diastolic pressure (mmHg)</td>
<td>74</td>
<td>70</td>
<td>No. FFR &lt; 0.8</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>5.19</td>
<td>7.6</td>
<td>No. FFR ≥ 0.8</td>
</tr>
<tr>
<td>Heart rate (BPM)</td>
<td>65</td>
<td>90</td>
<td>Diagnostic accuracy FFR (%)</td>
</tr>
</tbody>
</table>

Table 1: Parameters for resting and hyperaemic conditions and patient characteristics and diagnostic accuracy of model FFR against clinical invasive FFR measurements

2 METHODOLOGY

The modelling methodology implemented in this work is described in [8], and involves the one-dimensional haemodynamic equations given by: the continuity equation

\[
C_a \frac{\partial P}{\partial t} + \frac{\partial Q}{\partial x} = 0,
\]

where \( C_a \) is the vessel compliance, \( P \) is the mean hydrostatic pressure in a cross section, and \( Q \) is the volumetric flow rate; and the momentum equation

\[
\rho \frac{\partial Q}{\partial t} + \rho \frac{\partial}{\partial x} \left( \frac{Q^2}{A} \right) + \frac{\partial P}{\partial x} = \frac{22 \mu \pi Q}{A^2},
\]

where \( \rho \) is the density of blood, \( A \) is the cross-sectional area of the vessel, \( \mu \) is the blood viscosity. The inlet boundary condition is a defined flow rate, which is generated by utilising the initial and adaptive parameter estimation technique developed in [13]. The estimated parameters and patient characteristics in implemented in this study are described in Table 1. The outlet boundary condition is a lumped-parameter model that includes interaction a lumped-parameter heart model [8]. The haemodynamic equations are solved using a implicit sub-domain collocation scheme [12].
2.1 FFR, dFFR, and iFR

Conventional FFR, dFFR, and iFR, are all measurements involving the ratio of the pressure proximal \( P_p \) to a stenosis (usually aortic pressure), and the pressure distal \( P_d \) to a stenosis. The ratio of \( P_d/P_p \) is used for all cases. The main differences between these methods are as follows: (1) Conventional FFR and dFFR are measured under hyperaemic conditions, which requires a drug such as adenosine to be administered; (2) Conventional FFR is the mean of the pressure ratio \( P_d/P_p \) over a cardiac cycle, while dFFR the instantaneous time point at the end of diastole; (3) iFR is performed under resting conditions, and is the mean of the pressure ratio \( P_d/P_p \) during the wave-free period, which is shown in Figure 1 as the grey shaded region.

Table 2: Diagnostic performance of ciFR compared with cFFR.

<table>
<thead>
<tr>
<th>diagnostic accuracy (%)</th>
<th>sensitivity (%)</th>
<th>specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>93.33</td>
<td>100</td>
<td>91.67</td>
<td>75.00</td>
<td>1</td>
</tr>
</tbody>
</table>

3 RESULTS AND CONCLUSIONS

The main results are shown in Figure 2 and Table 2. The dFFR correlation with FFR is excellent, having a Pearson correlation coefficient of 0.9941. This would be expected as they are both performed during identical hyperaemic conditions (in a clinical setting), and hence are performed during the same computational simulation. This indicates that the value of dFFR, is almost identical to that of conventional FFR, thus making the cut-off point for determining whether a stenosis is functionally significant the same at around 0.8. The correlation of iFR to conventional FFR is still excellent, with a Pearson correlation coefficient of 0.92. The computation of iFR is performed on the same patient geometry as in the FFR and dFFR cases, but simulates resting conditions. The chosen clinical cut-off point of 0.9 for iFR, seems to be quite close, as the mean difference in iFR and conventional FFR is shown in Figure 2d to be 0.1070; indicating that for this small cohort, assuming a linear relation between FFR and iFR, is 0.9070. In order to improve this estimation, a larger cohort will be tested in
future research.

4 ACKNOWLEDGEMENTS

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REFERENCES


Mathematical and numerical modeling of the heart function III
Computational modeling of valve sounds from prosthetic aortic valves

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Summary
Transvalvular flows and hemodynamically generated heart sounds in prosthetic aortic valves in normal valve as well as valves with leaflet thrombosis are studied via computational models to explore auscultation-based detection of early leaflet thrombosis. Fluid-structure-interaction simulations of transvalvular flows are performed by a sharp-interface immersed boundary method with an efficient reduced degree-of-freedom model for the dynamics of the valve leaflets. The valve sounds are predicted by using a Green's function-based method. Various degrees of reduced leaflet motions are considered, and the characteristics of the systolic murmur associated with leaflet thrombosis are investigated.

Key words: heart sound, hemodynamics, phonocardiography, murmur

1 Introduction
Aortic valve replacement is a procedure to treat aortic valve problems such as severe aortic stenosis or aortic insufficiency. Transcatheter aortic valve replacement (TAVR) with bioprosthetic valves has become highly prevalent because of its minimally invasive nature. One recently reported problem in the aortic valve replacement with bioprosthetic valves is early leaflet thrombosis and resulting reduced leaflet motion (RLM) [1,2]. While leaflet thrombosis significantly increases the risk of thromboembolic events, RLM associated with early leaflet thrombosis is usually clinically silent, and therefore difficult to detect. It has been shown that the RLMs due to early leaflet thrombosis can be resolved by anticoagulation [1], which implies that early detection and timely treatment are crucial for preventing the progression of leaflet thrombosis and resolving the risk of thromboembolism. At the current time, the only method to detect sub-clinical RLM is high-resolution cardiac computed tomography (CT) scan [1,2], but persistent monitoring for leaflet thrombosis is not possible via this imaging modality.

One possible alternative diagnostic method for the early detection of sub-clinical RLM is auscultation – the diagnosis based on heart sounds. Auscultation has been used in the diagnosis of cardiovascular diseases for nearly 150 years. In particular, aortic diseases such as aortic valve stenosis can be identified by “murmurs” generated by abnormal blood flow pattern [3]. The auscultation is non-invasive and inexpensive, and thus very appropriate for the routine check-up and proactive monitoring. Since RLM will change the blood flow pattern, it should generate characteristic murmurs that can be used for the early detection of RLM caused by leaflet thrombosis. The key question is what feature of the murmur provides diagnosis of the RLM with high sensitivity and specificity. In the present study, we investigate the characteristics of murmur sounds associated with the RLMs via computational modeling of transvalvular hemodynamics and murmur generation.

For the computational modeling of transvalvular flow with normal and various abnormal prosthetic aortic valves, an efficient and easy-to-handle fluid-structure-interaction (FSI) model can facilitate the analysis. In the present study, we employ a simplified FSI model that requires fewer number of parameters and lower computational cost for the efficient hemodynamic simulation of aortic valves.
This model is focused on resolving the kinematics of leaflet motions and the associated transvalvular hemodynamics rather than the detailed structural dynamics of the valve.

The prediction and analysis of the murmurs caused by the RLMs is done by using a Green’s function based analysis [4] which relates the hemodynamic pressure fluctuation and the murmur signal. The advantage of this approach is the quick turn-around time, which allows us to study the correlations between the various types of RLMs and the resulting murmurs. This study will provide fundamental knowledge and data that support the development of auscultation technique for the early detection of the RLM.

2 METHODOLOGY

In this study, a canonical model of aorta and prosthetic aortic valve are employed for the investigation of transvalvular flow and hemodynamic sound. The aorta model is based on the data presented by Reul et. al.[5] and we considered a simple and generic bioprosthetic valve model.

2.1 Reduced degree-of-freedom valve model

The simplified, reduced degree-of-freedom (DOF) valve dynamics model is employed in this study. In this model, the valve displacement ($d_v$) is decomposed into a time coefficient and a spatial vector;

$$d_v(t, \mathbf{x}) = c(t) \hat{b}(\mathbf{x})$$

(1)

and the spatial vector, $b$ is prescribed by using the fully opened and fully closed valve geometries. The time coefficient, $c$ then represents the degree of opening. By integrating a simplified equation of motion over the entire leaflet surface, and applying the decomposition, Eq. (1), one can obtain the equation for the time coefficient, $c$:

$$\frac{d^2 c}{dt^2} = \frac{\Delta p}{\alpha} \int \frac{d S}{a \hat{b} \cdot \hat{n}} - K (c - c_o)$$

(2)

where $\Delta p$ is the local trans-leaflet pressure difference, $\alpha$ is a mass coefficient, and $K$ is a stiffness coefficient. The resulting model has two parameters ($\alpha, K$) and 1 DOF ($c$) for each leaflet but can still resolve the large-scale features of the leaflet motion by coupling with the full fluid dynamics equations. This model is computationally very efficient because only one ordinary differential equation needs to be solved for each leaflet.

2.2 Flow solver

The flow simulation for the FSI modeling is performed by a highly versatile, fully parallelized in-house immersed boundary, incompressible flow solver “ViCar3D” that computes flow with complex moving/deforming bodies [6]. The solver models flow via direct numerical simulation (DNS) as well as large-eddy simulation (LES) and employs an efficient, Bi-Conjugate Gradient (BiCG) solver for the pressure that scales well on up to about 1000 processors [7]. The solver has been extensively validated for a variety of laminar/turbulent flows and FSI problems and employed for a wide range of studies of cardiac hemodynamics, including modeling of hemodynamics in the left ventricle with natural and prosthetic mitral valves. The flow through the aorta and valve model is driven by the prescribed, time-dependent blood flow rate at the aortic root.

2.3 Murmur prediction

In previous studies [8,9], it has been shown that the primary source of murmur is the hemodynamic pressure fluctuation on the vessel wall. It is also shown that the murmur signal represented by the surface acceleration on the epidermal surface is related to the pressure force on the vessel wall by the Green's function, and the murmur signal predicted by the free-space Green's function agrees very well with the full 3D direct simulation results as well as the experimental measurements for the frequency range lower than $O(1000)$Hz [9]. In this study, therefore, the systolic murmur generated by the transvalvular flows are efficiently predicted by using the free-space Green's
function. The aorta wall is divided into 400 patches, and the murmur generated by the pressure force on each patch are superposed by the following equation:

\[
a_i(\tilde{y}, \omega) = 2 \sum_k (-\omega)^2 G(x_k, \omega) F_{\omega} \omega, \quad F_{\omega} \omega = n_j(\tilde{x}_j) P(x, \omega) \Delta \omega
\]  

(3)

where \(a\) is the surface acceleration on the epidermal surface (chest surface), \(y\) is the position vector to the measurement point, \(G\) is the Green's function, \(r\) is the vector from the source to measurement point, \(P\) is the hemodynamic pressure on the lumen wall, \(x\) is the position vector to the source point on the lumen wall, \(n\) is the unit normal vector of the vessel wall segment, \(\Delta A\) is the area of the segment, and \(\omega\) is the angular frequency. The measurement point is set 10 cm apart from the lumen wall. The murmur signal is analyzed based on the surface acceleration normal to the epidermal surface.

3 RESULTS AND CONCLUSIONS

Simulations are performed for the cases with a baseline normal valve model (Base), RLM on 1 leaflet (RLM1), and RLM on 2 leaflets (RLM2). For the leaflets with reduced motion, the stiffness coefficient, \(K\) is increased by 10 times to model thrombotic leaflets. The instantaneous 3D vortical structures at peak systole are shown in Fig. 1A for three cases. The figure shows a vortex ring generated with the valve opening and the subsequent complex vortex structures due to flow separation. It is observed that the presence of RLM tilts the direction of main aortic jet toward the wall opposite to the leaflet with reduced motion, and this generates bigger and stronger flow separation. It should be noted that the current RLM cases can be considered sub-clinical as the pressure drop across the valve remains below 10 mmHg. The root-mean-squared wall pressure fluctuations through one cardiac cycle are calculated and plotted in Fig. 1B and strong pressure fluctuations are measured just downstream of the sinus region. With RLMs, the pressure fluctuation increases especially on the aortic lumen downstream of the leaflet with reduced motion, and this makes the wall pressure fluctuation circumferentially asymmetric.

The murmur signals predicted by Eq. (3) are presented in Figs. 2 and 3. Figure 2 shows time histories of the epidermal surface accelerations for three cases. For the baseline case, the first strong peak is associated with valve opening and the other strong peak noted by 'S2' is associated with valve closing. The mid-systolic murmur is marked by 'M', but it is quite weak for the baseline case. For the RLM1 case, one leaflet does not fully open and closes earlier than the other two leaflets, and this generates multiple closing sounds (marked by 'S2'). The systolic murmur marked by 'M' is noticeably stronger than the baseline case. For the RLM2 case, two leaflets show limited opening and earlier closing and this also generates a split 'S2' peak. The mid-systolic murmur in the RLM2 case is much stronger than the other two cases. Figure 3 shows time-frequency spectrograms of the murmur signals. The figure clearly shows that the RLM increases the intensity of the mid-systolic murmur and extends its frequency contents. The present simulation results show
that the RLM modifies the S2 timing and increases the intensity and frequency range of the mid-systolic murmur.

Fig. 2: Time series of the predicted murmur signal (acceleration on the epidermal surface). M: mid-systolic murmur, S2: signal associated with the valve closing. Base: baseline normal, RLM1: RLM on 1 leaflet, RLM2: RLM on 2 leaflets.

Fig. 3: Time-frequency spectrogram of the predicted murmur signal. Base: baseline normal, RLM1: RLM on 1 leaflet, RLM2: RLM on 2 leaflets.

The current work shows the viability of using auscultation to detect valve anomalies such as early leaflet thrombosis. Furthermore, the current approach of using computational models with simple leaflet dynamics models is effective in enabling an exploration of the physics of this problem.

REFERENCES

CARDIAC ELECTROMECHANICS: MULTISCALE MODELING, COUPLING SCHEMES, AND NUMERICAL SIMULATION

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SUMMARY
We consider the mathematical and numerical modeling of cardiac electromechanics with application to the left ventricle of the human heart. We proceed by integrating state–of–the–art models for the electrophysiology of the tissue, mechanical activation at the cellular level, and the passive mechanical response of the muscle, thus yielding a coupled electromechanical problem within the active strain paradigm. We consider the spatial approximation of the Partial Differential Equations therein involved by means of the Finite Element method and the time discretization by Backward Differentiation Formulas. We numerically solve the coupled electromechanics problem by exploiting both monolithic and staggered approaches, for which we verify, compare, and critically discuss their accuracy properties and computational efficiency in simulating the whole cardiac cycle. In addition, we develop a multiscale model for cardiac electromechanics that accounts for microscopic active force generation at the cellular level within the active stress paradigm; with this aim, we exploit model order reduction techniques based on Machine Learning algorithms to enable efficient numerical simulations of multiscale electromechanics. Finally, we present several numerical results of the electromechanics problem in the human left ventricle obtained in the high performance computing framework.

Key words: cardiac modeling, electromechanics, numerical approximation, numerical simulation

1 INTRODUCTION
Mathematical and numerical modeling of the heart function are challenging tasks, mainly due to the multiphysics and multiscale nature of the problem at hand. A meaningful and accurate electromechanical model should therefore be able to represent the multiple interactions among the core models: electrophysiology, force generation at the cellular level, and passive and active mechanics at the macroscopic tissue level. At the same time, the model should be able to capture the broad range of spatio–temporal scales characterizing the myocardium along the heartbeat [4].

The focus of this work is twofold. First, we address the numerical coupling of core models concurring to the overall heart function, in particular regarding cardiac electromechanics, for which we review and analyze monolithic and partitioned strategies; for the latter, we show that computational efficiency can be enhanced by means of staggered strategies that enable using different time step sizes for solving electrophysiology and mechanical core models. Then, we consider models for active force generation at microscales of the cardiac tissue; these are meant to be exploited for multiscale numerical simulations of cardiac electromechanics.

2 METHODOLOGY
2.1 Core models for cardiac electromechanics
We model cardiac electrophysiology by means of the monodomain equation coupled with suitable ionic models for describing the complex electro–chemical interactions occurring at the cellular level.
In particular, we consider for the latter the phenomenological Bueno–Orovio model for its simplicity and meaningfulness. This yields a system of differential problems coupling PDEs and ODEs [2].

The macroscopic mechanical model takes into account for several features of the myocardium. The passive response of the muscle to external forces is modeled through the momentum conservation equation characterized by means of the Holzapfel–Ogden strain energy function with penalization terms accounting for moderate compressibility of the tissue. We model instead active mechanics, driven by the action potential and intracellular Calcium concentration, within the active strain paradigm; with this aim, we use a recently developed transmurally heterogeneous orthotropic activation model [1].

2.2 Numerical approximation and coupling

We use the Finite Element Method for the spatial discretization of the PDEs involved in the differential model and Backward Differentiation Formulas for the time discretization. We consider both fully implicit and semi–implicit schemes; the latter are obtained by means of suitable extrapolation of the primary variables from those computed at the previous time instances. Essential elements of our computational approach are: i) the generation of physically meaningful fibers and collagen sheets to feed the electrophysiology and, above all, the mechanical models; ii) the use of a numerical algorithm for the definition of the prestress state of the myocardium as geometries acquired from medical images (MRI) do not correspond to the stress free configuration [2].

After full discretization of the core cardiac models, we face the issue of addressing their numerical coupling. The monolithic strategy calls for solving at each time instance the fully coupled problem corresponding to cardiac electromechanics; typically, this involves a huge set of non linear equations. When using the Newton method, this boils down to repeatedly solving huge linear systems, which require suitable preconditioning strategies, especially in the high performance computing framework. With this aim, we use a block Gauss–Seidel preconditioner [2] with Multigrid or Additive Schwarz preconditioners for the blocks corresponding to the electrophysiology or mechanical core models.

Concerning instead the partitioned strategy for the numerical coupling of cardiac electromechanics, we proceed by splitting the electrophysiology solver from the mechanics one. This strategy enables using different time discretization schemes for the two core models, other than allowing different time step sizes for their approximation; this leads to the so–called staggered schemes. We systematically use the latter for cardiac electromechanics to enhance the computational efficiency of our solver [3]. Indeed, we typically use a small time step size for solving the electrophysiology model, while a (much) larger one for the mechanics.

2.3 Modeling of active force generation in the cardiac tissue

The mathematical modeling of the complex phenomena behind the active contraction of cardiomyocytes is crucial for understanding heart function as it represents the natural bridge between electro-
physiology and mechanics at the tissue level. Available force generation models can be classified in: i) phenomenological models (like those previously considered in the active strain approach) and ii) microscale models, which describe in detail the phenomena taking place at the subcellular scale [7, 8]. The latter are however very involved and lead to overwhelming computational costs in simulations of the whole heart function.

Mathematical models of the Calcium–driven activation of the cardiac tissue are typically based on Markov Chains describing the state transition of the so–called regulatory units, namely troponin and tropomyosin. The centrality of the phenomenon of cooperativity between adjacent units typically calls using the time–consuming Monte Carlo method that may require several hours of computing time for simulating a cardiac cycle for a single filament of a cardiomyocyte. To overcome this issue, we developed in [5] a model for the cardiac tissue activation, with explicit spatial representation of nearest–neighborhood interactions of regulatory units. Under the assumption of conditional independence of specific sets of events, we have derive an equation describing the time evolution of joint probabilities of triplets of adjacent units. The associated Fokker–Planck equation, featuring $10^{21}$ variables, can thus be reduced to a system of ODEs with slightly less than $2^{199}$ variables, which yields a reduction of computational costs of a factor $1/10^{4}000$. This reduced model is able of reproducing physiological force–calcium and force–length relationships, other than highlighting qualitative and quantitative agreement with experimental measurements under dynamic conditions.

Still, multiscale electromechanical simulations namely call for solving the previous microscale force generation model at each quadrature node of the computational mesh used for the macroscopic mechanical model. This motivates using model order reduction (MOR) methods to further reduce the computational complexity of the previous force activation model with $2^{200}$ variables. We develop in [6] a data–driven MOR technique exploiting machine learning algorithms. More specifically, we build our reduced model as a maximum–likelihood problem, in which we look for the model that minimizes, in a class of candidate models, the error on the available input–output pairs. We represent candidate models by means of Artificial Neural Networks (ANNs), which we train to learn the dynamics of the original active force generation model from the training input-output data. We show that this reduced model based on ANN is able to reproduce the results of the $2^{200}$ variables model with an error lower than 2% and requiring negligible computational times to simulate a cardiac cycle. The reduced model is thus particularly suitable for the multiscale numerical simulation of cardiac electromechanics in the myocardium.

3 RESULTS AND CONCLUSIONS

We numerically solve the cardiac electromechanical model for both idealized and patient–specific left ventricle geometries for which provide and compare clinically meaningful indicators like the pressure–volume loops. Figs. 1 and 2 highlight the numerical solution at different times of systole for a patient–specific left ventricle. We analyze the computational efficiency of our monolithic and partitioned (staggered) strategies and we compare the numerical results in terms of accuracy.

Moreover, we perform numerical simulations of cardiac electromechanics by exploiting our multi-
scale models for active force generation in the sarcomere, including the reduced model based on ANNs. We show that these models are particularly suitable for efficiently simulating mechanical contraction and relaxation driven by electrophysiology within the active stress paradigm and are thus enabling factors for multiscale cardiac modeling.

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INVESTIGATING THE PRO- AND ANTI-ARRHYTHMIC PROPERTIES OF HUMAN INDUCED PLURIPOTENT STEM CELL-DERIVED CARDIOMYOCYTES IN POST-INFARCTION PATIENT HEARTS: A MODELING STUDY

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SUMMARY
Post-myocardial infarction patients are at an increased risk for lethal arrhythmias. Introduction of human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) into the infarcted tissue has emerged as a possible therapy to recover the electrical and mechanical function of the injured tissue. However, recent studies have shown that hiPSC-CMs can have pro-arrhythmic properties. The goal of this study is to use patient-specific cardiac modeling to investigate the therapeutic potential of hiPSC-CMs and determine the properties and conditions that contribute to their pro-arrhythmogenicity.

Key words: cardiac electrophysiology, stem cell, arrhythmia

1 INTRODUCTION
Cardiac arrest remains the leading cause of death in the United States. Approximately two-thirds of these victims have a prior myocardial infarction (MI) [1]. MI results from obstruction of cardiac blood vessel that lead to hypoxia, ischemia, and cell death in tissue downstream from the site of block. The remodeled tissue results in loss of mechanical function that contributes to impairment of cardiac function.

The decreased blood flow also induces various levels of electrophysiological remodeling within the infarcted tissue [2]. A gray zone (GZ) of myocardium near the infarct experiences decreased perfusion which results in cellular electrical remodeling. While the GZ remains viable, it exhibits reduced excitability, longer action potential durations (APD), and redistribution of gap junction channels that result in altered conductivity. These remodeled cells facilitate arrhythmia induction by serving as sites of conduction block and reentry formation.

Recently, advances in cell and tissue engineering have resulted in the possibility of treating post-MI patients using human induced pluripotent stem cell derived cardiomyocytes (hiPSC-CMs). In animal studies, incorporation of hiPSC-CMs in infarcted tissue have been shown to significantly improve cardiac mechanical function [3]. However, it remains technically challenging to produce fully mature hiPSC-CMs that replicates the electrophysiological characteristics of ventricular myocytes. In general, hiPSC-CMs produced in the laboratory exhibit longer APDs, decreased excitability, and exhibit automaticity. These properties could lead to arrhythmia induction when implanted in hearts.

Anatomically realistic and biophysically detailed multiscale computer models of the heart are playing an increasingly important role in advancing our understanding of integrated cardiac function in health and disease. Clinical use of such methods has so far been limited due to the infancy of the research and the lack of validation. Such methods, however, are growing in popularity and becoming more widespread, at least in clinical research. We have previously demonstrated, retrospectively, that computational simulations using personalized virtual heart models can be used to predict arrhythmic risk in patients with infarcted tissue [4]. The goal of this study is to use patient-specific models of post-MI ventricles to explore, in-silico, the pro and anti-arrhythmic properties of hiPSC-CMs.
2 METHODOLOGY

2.1. Patient-specific post-MI ventricular models

The reconstruction of the patient-specific models used in this study have been previously described in [4]. Briefly, patients with chronic MI underwent contrast-enhanced MRI prior to implantation of implantable cardioverter-defibrillators (ICD). The first step in creating the model was to segment the images to separate the ventricles from the surrounding torso (Figure 1A). In brief, the myocardium was labeled by fitting closed splines through a set of landmark points placed semi-automatically along the epicardial and endocardial boundaries of the ventricles in the image. The placement of landmark points was performed manually for a number of slices that were evenly distributed in the image. The landmark points for the volume in between these slices were obtained automatically by interpolating the manually identified points, using spherical harmonic analysis.

Within the cardiac tissue, three distinct regions were further identified: the uninjured myocardium, and two regions within the infarct, an irreversibly injured central scar zone and a partially viable gray zone (GZ). Gray-level thresholding of the MRI scan was used to distinguish between the two regions in the infarct.

With tissue segmentation complete, the commercial software Tarantula was used to create the finite element mesh of the heart and the surrounding volume (Figure 2A). The resulting mesh consisted of ~5 million nodes and ~30 million tetrahedral elements with an average edge length of 400um. This resolution was sufficient to represent structural details while keeping the model computationally manageable. Finally, fiber orientations were assigned to each element of the mesh using a rule-based approach.

Two patients from the published cohort were used for this study. Patient 1 had an arrhythmic event as recorded by the ICD 3 years post-implantation while Patient 2 had no recorded arrhythmic events.

Figure 1: A) MRI with splines to segment cardiac surfaces and reconstructed FEM model. B) Action potential traces of normal myocardium (TT) and representative hiPSC-CMs with varying levels of gK1 expression.

2.2. Electrophysiological Properties and Stimulation Protocol

The myocardium was assumed anisotropic. Normal conductivity values were used for the non-infarct tissue. GZ conductivity values were assigned based on previous studies reporting a 90% decrease in transverse coupling. The infarct scar was assumed nonexcitable.

The ionic kinetics in the normal and GZ myocardium were represented by the ten Tusscher human ventricular model [5]. Membrane kinetics in the GZ was modified based on data from literature. Previous studies of GZ in infarcted hearts have reported a reduction in peak sodium current to 38% of the normal value [6]; in peak L-type calcium current to 31% of normal [7]; and in peak potassium currents IKr and IKs to 30 and 20% of the maximum [8], respectively. These modifications result in longer APD and decreased excitability compared to the normal myocardium (Figure 2A).
Mathematical description of current flow in cardiac tissue was based on the monodomain representation.

To examine the arrhythmogenic propensity of the infarct substrate, an aggressive pacing protocol was delivered from 19 sites in the heart. For each site, pacing commenced at a cycle length of 600 ms for five beats (S1); 450ms after the last S1, 6 stimuli were delivered at progressively shorter coupling intervals, starting at 190ms and decreasing in steps of 10ms. The induced activity was monitored for additional 2.5 s.

2.3. Simulation of hiPSC-CM Therapy

To simulate stem cell therapy, all the elements marked as scar or GZ were replaced with a formulation of hiPSC-CM model developed by Paci et al [9]. To investigate the role of different maturation states of the hiPSC-CM, the maximum conductance of the fast sodium current and the IK1 current were increased up to 10x of the published baseline values. Figure 1B shows representative traces of the APs for the cases when gNa=1 and gK1=1,2,3,4,5. The stimulation protocol was repeated to determine the arrhythmic propensity of the heart.

3 RESULTS AND CONCLUSIONS

Figure 2: A) Successful induction of arrhythmia in Patient 1. B) Isochrones during pacing showing no induction of reentrant circuit in Patient 2.

In the MI hearts without hiPSC-CM therapy, aggressive pacing from the apex resulted in successful induction of arrhythmia in Patient 1. Figure 2 shows the resulting reentrant circuit after pacing from a site near the base of the LV (blue star). The simulations show that the decreased excitability, longer APD, and reduced conduction velocity in the GZ promote conduction block and reentry formation. On the other hand, aggressive pacing from any of the 19 sites resulted in no reentry induction in Patient 2. This is due to the smaller GZ volume present in Patient 2 compared to Patient 1 which resulted in more uniform conduction during the pacing protocol. The simulation outcomes matched the clinical presentation of both patients.

Figure 3 shows the vulnerability grid for each patient heart after replacement of all infarcted tissue with hiPSC-CMs. Incorporation of hiPSC-CMs with baseline values of gNa=1 and gK1=1 resulted in arrhythmia induction in both patient hearts. Arrhythmia initiation and maintenance is similar to conditions described in Patient 1. The longer APD, elevated resting membrane potential, and decreased conduction velocity within the regions seeded with hiPSC-CMs resulted in conduction block and reentry formation. As gNa and gK1 were increased, the hearts became non-inducible for reentry.

These results demonstrate the importance of maturation of the hiPSC-CMs prior to implantation in patient hearts. The current formulation of the hiPSC-CM had significantly lower expressions of gK1 and gNa that resulted in pro-arrhythmic action potential phenotypes. Thus, rather than being therapeutic, incorporation of these cells in the infarcted region resulted in reentry induction even in hearts where reentry was not inducible (Patient 2). Both gNa and gK1 had to be increased to critical
levels in order to suppress the pro-arrhythmic qualities of the hiPSC-CMs. However, the difference in critical levels between Patients 1 and 2 is a patient-specific difference in response to the therapy. This is probably due to differences in ventricular and infarct geometries.

In conclusion, this study shows that computational models of the heart can be used to investigate the conditions necessary in order to suppress the pro-arrhythmic properties of hiPSC-CM therapy. Furthermore, these results show how simulations can be used to guide further development of this promising therapy.

![Vulnerability grids for each patient after hiPSC-CM therapy.](image)

**Figure 3: Vulnerability grids for each patient after hiPSC-CM therapy.**

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**REFERENCES**

THE ROLE OF THE PURKINJE NETWORK IN COMPUTATIONAL MODELS OF PATHOLOGICAL SCENARIOS

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SUMMARY

We consider electro-physiology and electro-mechanical models for the cardiac function with inclusion of detailed Purkinje fibers. We study the effect of such inclusion on pathological scenarios such as the left bundle branch block, the Wolff Parkinson White syndrome, the presence of scars.

**Key words:** Computational electro-physiology, Purkinje network, left bundle branch block

1 INTRODUCTION

Computational modeling is effectively used to have a description of the electrical activity in the heart. For instance, there could be the interest in studying how a pathological condition of the electrical conduction influences the mechanical contraction of the ventricles. A crucial role in the propagation of the electrical potential in the heart is played by the Purkinje fibers. This is a complex network of cardiac cells located on the endocardium specialized in the fast conduction of electrical signals in the ventricles, in order to guarantee its coordinated contraction [7]. This network could play an important role in pathological conditions. For example, in the left bundle branch block (LBBB), the Purkinje system of the left ventricle is interrupted and the signal enters through the septum. However, due to the antidromic propagation, i.e. the activation of the network due to a stimulus coming from the myocardium, it could be possible that the network is activated by the signal entering in the left ventricle through the septum, thus influencing the overall excitation and contraction. Other examples are provided by the Wolff Parkinson White syndrome, where again the network is antidromically activated by the anomalous path characterizing this pathology, and the presence of scars due to myocardial infarcts, where the propagation of the Purkinje cells is heavily limited.

2 METHODOLOGY

The mathematical model couples the bidomain equations for the electrophysiology [2], an active strain formulation for the active mechanics [6] together with the orthotropic model for the passive one [4], and the 1D monodomain equation in the Purkinje network [1, 9, 8, 5]. The Purkinje network is obtained by personalizing a fractal network by using measured data of endocardial activation times. Patient specific geometries are used to simulate the pathological scenarios described above.

The electromechanical coupled problem in the myocardium reads [3, 5]:

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For each \( t \in (0, T) \), find \( v_m, w_m, u_{e,m}, d, \gamma_f \) such that

\[
J_{\chi m} \left( C_m \frac{\partial v_m}{\partial t} + I_{\text{ion}}^m (v_m, w_m) \right) - \nabla_0 \cdot \left( J F^{-1} D_{i,m} F^{-T} \nabla_0 v_m \right) \]

\[
- \nabla_0 \cdot \left( J F^{-1} D_{e,m} F^{-T} \nabla_0 u_{e,m} \right) - J F^{-1} (D_{i,m} + D_{e,m}) F^{-T} \nabla_0 u_{e,m} = 0 \quad \text{in} \quad \Omega_0, \quad (1a) 
\]

\[
- \nabla_0 \cdot \left( J F^{-1} D_{e,m} F^{-T} \nabla_0 v_m \right) - \nabla_0 \cdot \left( J F^{-1} (D_{i,m} + D_{e,m}) F^{-T} \nabla_0 u_{e,m} \right) = 0 \quad \text{in} \quad \Omega_0, \quad (1b) 
\]

\[
\frac{\partial w_m}{\partial t} + f_m (v_m, w_m) = 0 \quad \text{in} \quad \Omega_0, \quad (1c) 
\]

\[
\rho \frac{\partial^2 d}{\partial t^2} - \nabla_0 \cdot P(d, \gamma_f) = 0 \quad \text{in} \quad \Omega_0, \quad (1d) 
\]

\[
\mu_A w_m^3 \frac{\partial \gamma_f}{\partial t} - \varepsilon \Delta_0 \gamma_f = \Phi(w_m^3, \gamma_f, d) \quad \text{in} \quad \Omega_0, \quad (1e) 
\]

where (1a)-(1b) are the bidomain problem for the transmembrane potential \( v_m \) and the extracellular potential \( u_{e,m} \), (1c) is the ODE system for the gating variables \( w_m \), (1d) the mechanical problem for the myocardium, (1e) represents the dynamics of the local stretching \( \gamma_f \) which links the electrical and the mechanical problem providing the active contraction. Here, \( I_{\text{ext}} \) accounts for the coupling with the Purkinje network monodomain problem at the Purkinje-muscle junctions (PMJ) located in \( s_j \):

\[
I_{\text{ext}} = \sum_{j=1}^{N} \frac{1}{A_j} I_{\mathcal{B}_j(s_j)} \varphi_j, 
\]

where \( \mathcal{B}_r(s_j) \) is a ball with center in \( s_j \), \( A_j \) its volume, \( I \) is the characteristic function, and

\[
\varphi_j = \frac{v_m^+(g_j) + v_m^-(g_j)}{2} - \frac{1}{A_{r \mathcal{B}_j}} \int_{\mathcal{B}_j} v_m \, dx, \quad j = 1, \ldots, N, \quad t \in (0, T], 
\]

represent the current at the \( j \)th PMJ. On the other side, the \( \varphi_j \)’s provide the Neumann data for the Purkinje network at the PMJ. For a detailed description of the monodomain Purkinje problem, we refer the reader to [8, 5].

3 RESULTS AND CONCLUSIONS

The numerical results show the importance of including the Purkinje network in the computational models. For example, we found that the Purkinje network is activated also in LBBB owing to the signal coming from the septum and entering the network. The latter brings the signal to the free wall of the left ventricle in a faster way than in absence of the network. In Figure 1, we report for the LBBB simulation the evolution of the Purkinje network and transmembrane potentials in a realistic scenario for three different time steps. From the middle figure, we can observe that the electrical signal reaches the free wall through the activated Purkinje network and not through the contiguous myocardial regions.

For the WPW syndrome, we found that the propagation is strongly influenced by the network which is activated by the anomalous signal. Finally, we observe as expected that the decreased conductivity of the network in presence of the scars induces anomalous electric patterns.
Figure 1: Evolution of the Purkinje network and transmembrane potentials for three different time steps represented in the deformed domain.

REFERENCES


TOWARDS AUTOMATED BIOMECHANICAL ANALYSIS OF PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY

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SUMMARY

Hypertrophic cardiomyopathy (HCM) is the most common genetic heart disease. Due to heterogeneity in the disease phenotype, outcomes range from sudden cardiac death to heart failure to a normal life expectancy. Personalized cardiac modelling has the potential to be a useful tool with which to stratify HCM patients into groups based on risk of cardiac events. Employing automated methods of segmentation and model customization can bring personalized models (for HCM and other pathologies) into common clinical practice. This initial study presents a semi-automated pipeline for rapid model generation and simulation of a cardiac cycle in an HCM cohort.

Key words: personalized modelling, deep learning, hypertrophic cardiomyopathy, clinical translation

1 INTRODUCTION

Hypertrophic cardiomyopathy (HCM), a genetic disease characterised by an abnormal thickening of the ventricular myocardium, affects up to 1 in 200 people [1]. Outcomes for patients range from heart failure and sudden cardiac death to survival to normal life expectancy. Clinical challenges in HCM include patient risk stratification (heart failure and sudden cardiac death) as well as drug or surgical (myectomy or alcohol septal ablation) therapy planning. HCM patients are typically monitored throughout life, using medical imaging – such as magnetic resonance imaging (MRI) – to identify and track regions of hypertrophy over time. Paradoxically, despite clear evidence of genetic mutations, the presentation (e.g. hypertrophy location and symptomatic heart failure progression) within patients varying widely even when HCM is familial. While typically viewed as disease of the left ventricle, right ventricular functional indices, such as contractile reserve [13], have been shown to be impaired in HCM as well, suggesting the condition impacts the function of both ventricular chambers. With enhanced imaging capabilities, computational models provide a unique tool that can be developed in order to study the mechanics of HCM hearts, potentially uncovering new markers with which clinicians can use to stratify patients into risk groups and plan therapy.

A key factor hindering progress is the model generation process. Typically, patient-specific modelling requires time-consuming manual segmentation of the myocardium from short and long axis images by an expert. In this talk, we present an automated pipeline and analysis tools for simulating the biventricular heart beat in HCM patients. Using new deep learning algorithms [3, 4, 5, 6], trained on large data sets, enables rapid automated segmentation of cardiac anatomy. From these segmentations, new tools can be used to create computational meshes which can be customized to the short and long axis segmentations of the myocardium to provide a patient-specific models. With appropriate boundary conditions [15], material stiffness [8, 9] and active tension parameters [10, 14] are determined to make personalized biomechanical models robustly and efficiently.
2 METHODOLOGY

We have implemented a semi-automated pipeline for the generation of personalized models from short and long axis cardiac MR images, collected during a standard clinical imaging protocol in an HCM cohort.

2.1 MR Data Collection and Analysis

Images have been acquired in 30 patients with HCM ranging from mild to severe. A balanced fast free echo sequence was used to collect cine images at 14 short axis slice locations and three long-axis imaging planes including four, three and two-chamber views on a Philips Achieva 3T scanner. Images were acquired at 30 time points in the cardiac cycle.

2.2 Deep Learning Segmentation

A fully-convolutional network with a 17 convolutional layer VGG-like architecture was used for the automatic segmentation of the LV myocardium, blood-pool and RV over the cardiac cycle for all short axis images. Similarly, another VGG network was used to automatically segment the LV myocardium and blood-pool at end-diastole for long axis slices [4, 7]. Each convolutional layer of the network is followed by batch normalisation and ReLU, except the last one, which is followed by the softmax function. In the case of the SA stack, each slice is segmented independently, i.e. in 2D. Short and long axis networks were trained using a cohort of 200 subjects including healthy and HCM patients.

2.3 Biventricular Model Fitting

Prior to fitting the biventricular model, positions of the mitral, aortic and tricuspid valves were selected from the four-, three- and two-chamber long axis images. Additionally, the position of the LV apex was chosen from the four-chamber long axis slice. Finally, an RV wall thickness was defined since segmentations are only obtained for the RV blood pool and not the RV epicardium. Using a set RV wall thickness, the RV epicardial contours were defined at a given distance, normal to the RV endocardial contours.

Given the short axis contours, long axis contours, valve points, apex and RV insertion points (defined as the intersection points between the RV free wall and the LV epicardial contours), a biventricular model was fitted to the data using the two-step iterative method developed in [2] (see Figure 1). Briefly, a series of stiff linear least squares fits with high D-affine regularization weight was performed to provide an adequate first solution. For each iteration, the Jacobians on $4 \times 4 \times 4$ Gaussian quadrature points were calculated. If all positive, the model was updated, the regularization weight was decreased and another iteration was performed. If not, the model was not updated and another optimization step was performed using diffeomorphic constraints based on the magnitude of the displacement.

Figure 1: Left: Neural network segmentation of the LV blood pool, LV myocardium and RV blood pool. Middle and right: A biventricular mesh fitted to the patient data.
2.4 Modelling Cardiac Mechanics

With patient-specific models generated, simulations of the full cardiac cycle will be presented, extending the methods in [14, 15] to the biventricular case. Novel boundary conditions are introduced to model the influence of the epicardial surface as well as valve plane motion through the use of data-derived boundary energies, rather than Dirichelet conditions. Using Windkessel models to account for the pressure volume relationship throughout the cardiac cycle, we introduce a new addition to cope with the potential outflow obstruction that is typically found in patients. A new extension of the Holzapfel-Ogden model accounting for viscoelasticity is introduced, representing the viscous losses observed in experimental data. Passive and active parameters will be personalized by finding the best match between the geometric data from MR images and model results. A purely mechanical rather than electro-mechanical model is used.

3 RESULTS AND CONCLUSIONS

Biventricular models were fit to the image datasets, with a representative five cases at end-diastole and end-systole. The entire process, including manual selection of valve points, model fitting and mesh generation, can be completed for a single patient in less than 25 minutes on a personal laptop (32 GB RAM, 2.1 GHz Intel core i7 CPU). Errors were calculated between the contour points (from segmentations) and their corresponding fitted surfaces as a measure of the relative fit (Figure 2). RMS errors, averaged over all five cases, were 2.154 mm and 1.667 mm at end-diastole and end-systole, respectively.

Figure 2: Boxplots of absolute errors for each patient at end-diastole (top) and end-systole (bottom) for short axis (SA), long axis (LA), left ventricular (LV), right ventricular (RV), epicardial (Epi) and endocardial (Endo) contours.

Biomechanical models are then presented, with personalization, boundary conditions and viscoelastic simulations highlighted. This initial study presents a semi-automated pipeline for generating efficient patient-specific biventricular models.

REFERENCES


UNCERTAINTY QUANTIFICATION IN CARDIAC ELECTROPHYSIOLOGY DISEASE MODELING

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SUMMARY

We present a computationally efficient framework to perform sensitivity analysis and uncertainty quantification in cardiac electrophysiology, aimed at better understanding the mechanisms behind cardiac rhythm disorders. To this goal, we develop a data-model integration strategy based on efficient reduced-order numerical solvers combined with uncertainty quantification techniques. Numerical experiments dealing with pathological cases, such as tachycardia, illustrate the ability of the pipeline in estimating which parameters and which interactions among them generate a pathological condition.

Key words: Cardiac electro-physiology, uncertainty quantification, patient-specific modelling

1 INTRODUCTION

Numerical modeling of the heart function is becoming a recognized tool of clinical utility, which improves the understanding of possible causes of cardiac dysfunctions and enables the diagnosis and optimal therapy design. Several PDE models and numerical methods for their approximation, such as the finite element method, have been developed to describe single (and coupled) functionalities, e.g. cardiac electrophysiology, tissue mechanics and hemodynamics [5].

Physical indices and outputs of clinical interest can be directly approximated through the numerical solution of the cardiac mathematical models for a given set of parametrized inputs. These model parameters, characterizing both physical and/or geometrical configurations of the system, show a considerable intra- and extra-subject variability and are affected by numerous sources of uncertainty that arise from both experimental variability and lack of knowledge.

Large-scale clinical data are nowadays available, providing detailed information about the function and dysfunction of the heart. Their integration within mathematical models brings promising opportunities towards better understanding cardiac diseases. In this context, the development of new efficient data-model integration methods, ranging from data assimilation and uncertainty quantification techniques to sensitivity analysis, is crucial in order to provide fast and reliable answers to clinical questions.

2 METHODOLOGY

We develop a computationally efficient framework to perform uncertainty quantification (UQ) in cardiac electrophysiology in order to improve the ability of cardiac models to reproduce both physiological and pathological patient-specific behaviors. Numerical models for electrophysiology, obtained from the discretization of nonlinear parametrized coupled system of ordinary and partial differential equations (PDEs), are inevitably affected by uncertainty, e.g., in (i) the computational domain, (ii) physical coefficients and (iii) boundary conditions. We address a complete UQ pipeline, including: (i) a variance-based sensitivity analysis for the selection of the most relevant input parameters; (ii) forward UQ (or uncertainty propagation) to investigate the impact of intra-subject variability on clinically relevant outputs related to the cardiac action potential; (iii) backward UQ (or parameter and state estimation and data assimilation) in view of both model calibration and personalization.
A complete characterization of the role and importance of the input parameters is paramount in order to adopt a parameterized model as an approximation of the physical phenomenon of interest: sensitivity analysis quantifies the effects of parameters variation on the outputs of interest, providing a criterium to rank the most influential input parameters. In this work we consider a variance-based global sensitivity analysis which describes the amount of output variance generated from the variation of a single parameter and also from interactions among the parameters.

Since the knowledge on the parameter values of cardiac electrophysiology models is limited, it is crucial to understand how input uncertainties are propagated to the outputs (forward UQ) and to develop methods for estimating patient-specific parameters from noisy measurements (backward UQ). Bayesian methods provide a rigorous framework for the solution of backward UQ problems and data-assimilation. Sampling algorithms, such as the Markov chain Monte Carlo (MCMC) [3] or the (ensemble) Kalman filter [2], enable to estimate the distribution of quantities of interest (model parameters, state of a system) from noisy (non)-invasive clinical measurements.

Both UQ and sensitivity analysis exploit stochastic (Monte Carlo) sampling techniques, thus implying overwhelming computational costs because of the huge amount of queries to the high-fidelity electrophysiology coupled PDE-ODEs model. To mitigate this computational burden, we replace the high-fidelity model with computationally less expensive projection-based local reduced-order model. This latter provides a low-dimensional approximation obtained by reducing the number of equations and of the corresponding unknowns involved in it. Reduced solutions can be expressed as linear combinations of problem-specific basis functions obtained from processing a precomputed database of high-fidelity solutions. However, the nonlinear nature of the problem and the presence of moving fronts in the solution make the application of standard ROM techniques very problematic. For this reason, we adopt local ROM built through a k-means clustering in the state space of the snapshots for both the solution and the nonlinear term [1].

3 RESULTS AND CONCLUSIONS

Numerical experiments dealing with both physiological and pathological cases illustrate the ability of the UQ pipeline based on reduced-order models to realize a cost-effective-but still accurate-methodology [4]. We consider the monodomain model to describe the action potential dynamic, coupled with the Aliev-Panfilov model to characterize the ionic activity through the cell membrane. In order to reproduce a pathological electrical activity such as tachycardia we consider the so-called S1-S2 stimulation protocol formed by a first train of physiological beats (S1), followed by a second premature stimulus (S2). The effect of the S2 stimulus depends on several parameters, such as the time interval between S1 and S2 stimuli, the area of the stimulated region and the recovery properties of the tissue. These parameters variations produce three possible outcomes:

- tissue refractoriness, i.e. the S2 stimulus is delivered when the tissue is not yet excitable;
- sustained reentries, in the form of two reentrant circuits around each singularity (figure of eight);
- non-sustained reentry, in the form of an extra tissue activation without reentrant circuits.

In this context, the activation map represents an output of clinical interest which can be numerically approximated at each point of the computational mesh. This map is obtained by evaluating the local activation time (LAT), that is, the time when the maximum negative slope of the electrical deflection is measured. We apply the proposed reduced-order UQ framework in order to investigate the sensitivity of the activation map with respect to variations of input parameters and we simulate several UQ propagation scenarios in order to assess the risk of sustained reentries.

4 ACKNOWLEDGMENTS

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Application of CT-Image based finite element method to orthopaedic biomechanics problems
A SUBJECT-SPECIFIC FINITE ELEMENT STUDY OF PROXIMAL FEMUR STRENGTH AFTER CAM RESECTION FOR FEMORO-ACETABULAR IMPINGEMENT.

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SUMMARY

Purpose of the present study was to evaluate the effect of cam resection on the mechanical strength of proximal femur using subject-specific finite element analysis (FEA). The finite element femur models were constructed from computed tomography scan data which were acquired pre- and postoperatively; therefore, the femur models represented the shape of the original femur, including cam lesion and the bone resection site. The result from our FEA suggests that there is a risk of femoral neck fracture after arthroscopic cam resection, particularly when the resected lesion is located distally.

Key words: Finite element analysis, Femoro-acetabular impingement, Arthroscopic cam resection

1 INTRODUCTION

An insufficiency fracture of the femoral neck is relatively rare, but it is a severe complication associated with osteochondroplasty for femoro-acetabular impingement (FAI) [1]. Several previous studies have assessed the fracture risk in femurs after osteochondroplasty [2][3][4]. However, the results of those studies were based on simulative operations in computer, which were different from actual bone property after osteochondroplasty. To investigate the mechanical strength property of femoral neck arthroscopic osteochondroplasty, we adopted finite element analysis (FEA) and a subject-specific model using postoperative computed tomography (CT) data. We constructed 3-dimensional finite element (FE) models of the femur from computed tomography (CT) images obtained before and after osteochondroplasty. Therefore, our FE models of postoperative femurs simulated the area and geometry of bone resection that had been performed in real surgery. Additionally, to clarify which aspect of bone resection would affect postoperative femur strength, we analyzed the geometry of the resected area using the same CT images used to render the FE models.

2 METHODOLOGY

2.1 Subject

All experimental procedures were approved by our institutional review board. Eighteen subjects (14 men and 4 women) who had received arthroscopic cam resection for cam-type FAI at our institution were included in the present study. The diagnosis of cam-type FAI was based on alpha angle threshold ≥55°.

2.2 Finite Element Analysis

We constructed FE models of the proximal half of the operated side of the femur from pre- and postoperative CT data sets of our 18 subjects using Mechanical Finder Ver. 7.0 (RCCM Inc. Japan).
Thus, 36 femur models were generated for FEA in our study. We used a first order 4-nodal tetrahedral element was used to construct our finite element models, and three nodal shell elements (which were placed on the outer surface of the model) were used to simulate the thin cortical bone layer of the femoral head and neck lesion. The material properties of the femurs were calculated based on the original CT dataset and mapped to the FE models. A load was applied to the head of the femur model from 20° relative to the femoral axis, simulating joint reactive force in single leg stance. We increased the load until at least 15 contiguous shell elements failed [5], and the load at this stage was defined as a predictable fracture load. The location of the failed shell element was considered the predictable fracture location.

2.3 Three-dimensional image analyses

The same CT data sets used in FE modeling were analyzed using an image analyzer (Ziostation®, Ziosoft, Inc. Japan). We obtained double oblique multiple planar reconstruction images of the pre- and postoperative femur and defined 4 planes (S1-S4) perpendicular to the femoral neck axis at points that divided the femur head radius into quarters (Figure □). Pre- and postoperative images in the same plane were superimposed (Figure 3) to measure the resected depth and area of the plane. Data analyses: All statistical analysis in this study was performed using R version 3.0.2. Linear regression models were used to compare the predictable fracture load from our FEA and the resected depth and area measured in our image analysis. Pearson’s correlation coefficient values between the fracture load and measured values (i.e., the depth and area) were calculated for five slices as indicated in Figure 3.

![Figure 3: (A) Diagram showing reference plane setting. Four lines perpendicular to the femoral neck axis (S1-S4) represent locations of each reference plane. r: radius of the best fit circle to femoral head intersection. Gray area represents difference between pre- and postoperative cross section of proximal femur (resected bone). (B) Oblique sagittal image of femoral neck at S4 reference plane. Cross section of pre- and postoperative femoral neck was drawn in gray and white, respectively. The bone resection depth was calculated by [(A)/B] (%). The dark gray area represents the cross-sectional area of the bone resection.](image)

3 RESULTS AND CONCLUSIONS

A maximum 30% decrease in the simulated fracture load was observed in 18 postoperative femur models; however, 8 postoperative femur models needed more than 90% of the preoperative fracture load to cause fracture (15 contiguous shells failed) somewhere in the femur model (Figure 4). The correlation between fracture load and measurements at the bone resection site was significant in the (S4) plane correspond to head neck junction (p<0.05).

Both the percentage depth ($R^2=0.60, p<0.01$) and area ($R^2=0.60, p<0.01$) of the bone resection site correlated strongly with postoperative changes in the simulated fracture load ($R^2=0.60, p<0.01$). There was a similar relationship between percentage depth of bone resection in the S3 plane ($R^2=0.48, p<0.01$). However, coefficient of determination for resected area ($R^2 =0.38$) was below the level of significance and inconclusive. In the S2 plane, which was set more proximal to the femoral head center, we found no correlation between bone resection measurements and
postoperative changes in the simulated fracture load. The resected bone volume did not correlate with the postoperative changes in the simulated fracture load ($R^2=0.05$, $p=0.4$).

A representative postoperative finite element model constructed after fracture simulation are shown in Figure 4.

![Figure 4](image)

**Figure 4.** Representative femur model (28 yrs. male) showing the location of yielded shell elements (white area), which are the simulated fracture. Dotted line indicates the area of bone resection.

Because of the nature of computer simulation study, the main results of our study were based on assumptions and simplification of the actual conditions. For example, we adopted only one loading scenario (single leg stance) replicating mechanical test conducted in previous studies [3], and evaluation of femur strength was only based on relative strength calculations.

In some cases, surgeons would perform aggressive bone resection of head-neck junction area to avoid unfavourable outcome due to under-resection of cam lesion [6]. Surgeons should also be cautious about the risk of over-resection at femoral head-neck junction which would lead to postoperative femoral neck fracture. The result from our biomechanical study using FEA suggest that the risk of femoral neck fracture after arthroscopic cam resection, particularly when the resected lesion is located distally.

**REFERENCES**


STRESS DISTRIBUTION IN THE CORACOID GRFT AFTER LATARJET PROCEDURE: THE RELATIONSHIP TO THE SITE OF OSTEOLYSIS

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SUMMARY

Latarjet procedure has been widely used for the anterior shoulder instability. However, osteolysis of the grafted coracoid was occasionally seen after this procedure. To clarify its pathophysiology, we investigated the stress distribution pattern in the grafted coracoid. The results of the present study clearly demonstrated that the proximal half of the coracoid graft represented significantly lower equivalent stress than the distal half (p = 0.0059). In particular, the lowest equivalent stress was seen in the proximal-medial-superficial part. We assumed that the osteolysis might start from the proximal-medial-superficial part of the coracoid graft, which gradually extend to its proximal half.

Key words: Latarjet procedure, Osteolysis, Stress shielding, finite element method

1 INTRODUCTION

Latarjet procedure has been widely used for the anterior shoulder instability with a large glenoid defect. It is well known that the successful anterior stabilization could be achieved by this procedure even in the contact sports athletes [1]. However, osteolysis of the grafted coracoid was occasionally seen after Latarjet procedure [2]. To clarify the pathophysiology of postoperative osteolysis, we attempted to investigate the stress distribution pattern in the grafted coracoid using 3-dimensional finite element (FE) method.

2 METHODOLOGY

2.1 Modeling

CT-DICOM data of the contralateral healthy shoulder in 10 patients with unilateral anterior shoulder instability (9 males and 1 female, age: 17–49) were used for the present study. Three dimensional finite element models of the glenohumeral joint was developed using software, Mechanical Finder (ver. 9.0, RCCM, Japan). In each shoulder, a 25% bony defect was created in the anterior glenoid cavity, where coracoid process was transferred using two half-thread screws. Articular cartilage was modeled to cover the joint surface of the glenoid as well as the humeral head to recreate their contact and the friction coefficient was determined as 0. In the present study, the arm position was determined as 0-degree abduction (Fig. 1). The Young’s modulus of bone was automatically calculated by its CT number and its Poisson’s ratio was determined based on the mass density. As for the cartilages, the Young’s modulus and the Poisson’s ratio were determined as 35.0 MPa and 0.45, respectively. While medial margin of the scapula was completely constrained, a
standard compressive load (50 N) toward the center of the glenoid was applied to the lateral wall of the greater tuberosity. A tensile load (20 N) was also applied to the tip of the coracoid process along the direction of conjoint tendon.

2.2 Analysis and data interpretation

Then, elastic analysis was performed and the distribution pattern of Drucker-Prager equivalent stress was investigated in each model. In particular, mean equivalent stress in the proximal half of the grafted coracoid was compared to the distal half. To further localize the stress distribution pattern inside the coracoid bone graft, it was divided into 8 parts (proximal/distal, medial/lateral and superficial/deep) and the mean equivalent stress in each part was compared.

2.3 Statistical analysis

For statistical analyses, Wilcoxon matched-pairs signed rank test was used to compare the mean equivalent stress between proximal and distal halves and repeated measures one-way ANOVA followed by Dunnett’s multiple comparisons test was used for the comparison among 8 parts of coracoid bone graft.

3 RESULTS AND CONCLUSIONS

The proximal half of the coracoid graft represented significantly lower equivalent stress than the distal half (p = 0.0059). Among 8 parts in the coracoid graft, the lowest equivalent stress was seen in the proximal-medial-superficial part. Statistically, the mean equivalent stress in this part was significantly lower than that in the distal parts (p < 0.05, Table 1).

In the clinical practice, Di Giacomo et al reported that the proximal and superficial zone of the coracoid graft was most involved in osteolysis after Latarjet procedure [2]. The results of the present study were consistent with their findings. Biomechanically, the distal half of the coracoid graft was exposed to the tensile load of the conjoint tendon and a compressive load was applied to its lateral parts due to the contact with the humeral head. A compressive load was also applied to the deep parts of the coracoid graft due to contact with the glenoid neck. As a result, stress shielding was the most evident in the proximal-medial-superficial part of the coracoid graft. Based on the results of the present study, we assumed that the osteolysis might start from the proximal-medial-superficial part of the coracoid graft, which gradually extend to its proximal half.

<table>
<thead>
<tr>
<th>Part of the coracoid</th>
<th>Mean equivalent stress ($\times 10^3$ MPa)</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lateral</td>
<td>Superficial</td>
<td>138.1</td>
</tr>
<tr>
<td></td>
<td>Deep</td>
<td>230.7</td>
</tr>
<tr>
<td>Medial</td>
<td>Superficial</td>
<td>118.6</td>
</tr>
<tr>
<td></td>
<td>Deep</td>
<td>148.3</td>
</tr>
<tr>
<td>Distal</td>
<td>Superficial</td>
<td>247.4</td>
</tr>
<tr>
<td></td>
<td>Deep</td>
<td>270.8</td>
</tr>
<tr>
<td></td>
<td>Superficial</td>
<td>203.2</td>
</tr>
<tr>
<td></td>
<td>Deep</td>
<td>211.8</td>
</tr>
</tbody>
</table>

Table 1: Mean equivalent stress in each part of grafted coracoid
REFERENCES


MICROSCOPIC STRAIN ANALYSIS IN COLLAGEN FIBER IN PERI-IMPLANT BONE USING MICRO-CT AND STITCHED SHG IMAGES

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SUMMARY

Bone consists of mineralized collagen fiber, water and protein at the nanoscale. Downscaling multiscale analysis by finite element analysis (FEM) based on the micro-CT images and second harmonic generation (SHG) images is adopted to study the stress and strain distribution considering the collagen fibers in the newly peri-implant bone. SHG image-stitching technique has been achieved to obtain accurate positions and to analyze large regions. The result indicates that the analyzed region close to the neck of the implant is mainly under compression, and the strain concentration is observed in the collagen-rich region.

Key words: micro-CT images, SHG images, collagen fibers, multiscale analysis

1 INTRODUCTION

According to the hierarchical structure of bone [1] (Figure 1), there are two types of bone: the trabecular bone that is porous and the cortical bone that is condense. Osteon is the unit of the cortical bone, which is in the cylinder shape with lamella arranged concentrically. Lamellas are formed with collagen fibers arranged parallelly, whose unit is collagen fibril composed of collagen molecules and biological apatite. With micro-meter resolution, osteons, lamellas and collagen fibers can be observed in the SHG images.

After the dental implant is planted, osseointegration process happens and results in the direct attachment of the newly grown bone to the implant [2]. Observed from the SHG images, the newly grown bone is supposed to be the cortical bone, whose nanostructure is of great interest to dentists. Therefore in this study, the numerical approach is applied to understand the correlation between the loading conditions and nanostructure of collagen fiber in the peri-implant bone. This is so far the first attempt to use both micro-CT images and SHG images in the finite element analysis.
2 METHODOLOGY

The specimen is a mandible with two screw-vent 4 × 10 mm implants planted for 22 years. The mandible and two implants were scanned by micro-CT imaging technique separately, whose resolution is 90 μm × 90 μm × 50 μm. Each micro-CT image covers region of 45 mm².

2.1 SHG imaging technique and image stitching

The SHG apparatus (Figure 2) includes a multiphoton confocal microscopy system (A1R+MP, Nikon, Japan) with an excitation laser (Mai Tai eHP). The minimum dimension of the observed objective is about 350 μm, which allows to observe osteons, lamellas and collagen fibers. The resolution of SHG images is 0.83 μm × 0.83 μm × 20 μm and each discrete image covers region of 0.83 mm².

The discrete SHG images allows to only observe a small region ranging from 0.5 mm² to 1 mm² depending on the image resolution. Locating the 3D structure based on such discrete SHG images is inaccurate without reference system. Therefore image-stitching technique (Figure 3) is applied. With the stitched SHG images, the implant bed can be used as the reference system to locate the region of interest (ROI) for analysis. One stitched SHG image consists of 323 discrete images and five stitched images were obtained.

2.2 Downscaling computational method

In this study, downscaling computational method is adopted to study the mechanical behavior of nanostructure of collagen fibers. Models at three scales are created (Figure 3). The macroscopic model (Figure 3(a)) is created using micro-CT images, which includes both the mandible and implants and whose mesh size is 0.09 mm. A cubic bone region (mesoscopic model in Figure 3(b))
near the neck of the dental implant is separated from the macroscopic model and meshed with elements of 0.009mm. The 3D structure of collagen fibers is constructed with the stitched SHG images. A collagen region of 0.025mm$^3$ (Figure 3(c)) at the same location is extracted, whose vacant space is filled with bone. The microscopic model is created by meshing both the bone and collagen fibers with elements of 0.002mm.

The boundary condition (Figure 3(a)) for the macroscopic model followed previous research [3]: mesiodistal surfaces of the mandible are completely constrained, and a prescribed displacement of 250nm was applied on the top of two implants in the implant axial direction. Meanwhile based on Specified Boundary Method (SBM) [4], the boundary conditions for the mesoscopic model and microscopic model are the interpolated displacement obtained from macroscopic model and mesoscopic model. In the numerical simulation, both the bone and the collagen fiber were set to be isotropic material.

![Three-scale analysis](image)

**Figure 3 Three-scale analysis**

### 3 RESULTS AND CONCLUSIONS

Several ROIs near the dental implant have been analyzed with the downscaling computation method. The result of one ROI close to the neck of the implant is selected to present. A comparison of the histogram of principle stress ratio ($\sigma_1/\sigma_3$) of the macroscopic model and microscopic model is presented in Figure 4. When the ratio is smaller than 0.7, the element is assumed to be subjected to compression. In the macroscopic model, 92% of the bone in the ROI is under compression. And in the microscopic model, 90% of bone is under compression, which matches the result of macroscopic model. Meanwhile, 68% of collagen fiber is under compression and 12% of collagen fibers is under large tension. In the contour of minimum principle strain of microscopic model (Figure 5), the strain of bone is lower than the collagen fiber and strain concentration occurs in the collagen rich region.

In the future, different angle force [3] will be imposed on the implants in the macroscopic model to compare the strain distribution in the collagen fibers (Figure 6). Furthermore, more ROIs near the dental implant will be analyzed to obtain more understanding in the structure of collagen fibers of the peri-implant bone.
Figures:

- Figure 4: Histogram of principle stress ratio
- Figure 5: Results of minimum principle strain of macroscopic model and microscopic model
- Figure 6: Loading conditions in the future plan

REFERENCES


STRESS AND PERIPROSTHETIC BONE MINERAL DENSITY CHANGES AFTER IMPLANTATION OF TWO DIFFERENT ZWEYMULLER TYPE STEMS

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SUMMARY

We analyzed equivalent stress with CT-based finite element analysis and bone mineral density by dual-energy X-ray absorptiometry in the femur after implantation of two different Zweymuller type stems. There was no significant difference in equivalent stress in a standing position between the two stems. The change rate of bone mineral density in the proximal lateral part was significantly different. The rotational force may cause the discrepancy between equivalent stress and bone mineral density changes.

Key words: finite element analysis, total hip arthroplasty, Zweymuller stem

1 INTRODUCTION

Implantation of total hip arthroplasty (THA) components caused a significant change of stress environments. Several studies have reported that bone mineral density (BMD) decreases after THA, especially in the proximal femur¹⁻³. This phenomenon is explained as an adaptive remodeling response of bone tissue to a significant change in its stress environments.

Minimally-invasive THA has been widely established and several implants have been adapted to minimally-invasive THA. SL-PLUS MIA stem (Smith & Nephew Orthopaedics AG) is a modified implant of Zweymuller type SL-PLUS standard stem (Smith & Nephew Orthopaedics AG). The major change is an omission of the trochanteric wing, which enables a bone-sparing and may lead to changes of femoral stress distribution and rotational stability. The change of stress distribution in the femur could affect BMD after THA.

In the present study, we constructed finite element (FE) models of femurs and stems and analyzed equivalent stress in the femur. In addition, we measured BMD in the femur by dual-energy X-ray absorptiometry (DEXA) after THA. The purpose of this study was to investigate the equivalent stress in the femur and to compare the relationships between equivalent stress and BMD changes after implantation of two different Zweymuller type stems.

2 METHODOLOGY

This study included twenty-one cases (18 women and 3 men) who underwent primary cementless THA with SL-PLUS MIA stem or SL-PLUS standard stem. Eleven cases received SL-PLUS MIA stem and ten cases received SL-PLUS standard stem. Zones were defined according to Gruen's system (zones 1–7)⁴.

Computed-tomography (CT) images of the femur were taken before and at 1 week after surgery. FE models of the femur and stem were constructed from CT data by Mechanical Finder (Research Center of Computational Mechanics Inc., Tokyo, Japan), software that creates FE models showing individual bone shape and density distribution. The FE models of the femur consisted of approximately 200,000 elements, in addition to 50,000 elements for the prosthesis. The mechanical properties of the bone were determined from CT density values, using the equations proposed by Keyak et al.⁵. The elastic modulus of the stem was 109.0 GPa and Poisson ratio was 0.28. One loading condition in a standing position was simulated. Equivalent stress was analyzed in zones 1 to 7 and compared with the DEXA data.
3 RESULTS AND CONCLUSIONS

FE studies revealed that there was no significant difference in equivalent stress between SL-PLUS MIA stem and SL-PLUS standard stem (Figure 1). BMD was maintained after THA in zones 3, 4, and 5, whereas BMD decreased in zones 2, 6, and 7. In zone 1, BMD decreased in SL-PLUS MIA stem by 14%, while BMD was maintained in SL-PLUS standard stem (Table 1).

In this study we confirmed that the postoperative equivalent stress in the femur did not change significantly between SL-PLUS MIA stem and SL-PLUS standard stem in the standing position.

![Figure 1. Equivalent stress in the preoperative and postoperative femur.](image)

Table 1. Change rate of BMD at 1year after THA

<table>
<thead>
<tr>
<th>Zone</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>SL-PLUS MIA stem (%)</td>
<td>86</td>
<td>87</td>
<td>96</td>
<td>99</td>
<td>101</td>
<td>84</td>
<td>65</td>
</tr>
<tr>
<td>SL-PLUS standard stem (%)</td>
<td>99</td>
<td>86</td>
<td>98</td>
<td>100</td>
<td>100</td>
<td>79</td>
<td>65</td>
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</table>

REFERENCES

BIOMECHANICAL ANALYSIS OF COMPRESSIVE FRACTURE DUE TO FEMORAL HEAD NECROSIS

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SUMMARY

CT-image based finite element method was applied to analyze the mechanism of compressive fracture of femoral head with necrosis. An artificial ellipsoid model of necrosis with reduced Young’s modulus was inserted into a realistic model of hip joint and mechanical analysis with damage mechanics was conducted to reproduce the fracture behavior of femoral head as cumulative damaged elements. The results clearly indicated that the compressive fracture of diseased head is initiated with microscopic damage formation along the boundary zone between the necrosis and healthy bone.

Key words: CT-FEM, Hip joint, Damage mechanics

1 INTRODUCTION

Femoral head necrosis is characterized as initiation and accumulation of necrosis tissues due to ischemicence. Increase of necrosis tissues finally results in compressive fracture of femoral head and for the worst cases, total hip arthroplasty (THA) is applied to recover the biomechanical function of hip joint. Biological mechanisms of femoral head necrosis have thoroughly been investigated and however, the mechanical mechanism of the compressive fracture of femoral head has not been clarified yet [1,2].

CT- image based finite element method (CT-FEM) has been utilized to analyze different kinds of mechanical problems related to bones and joints in the orthopaedic field [3-5]. Recently, bone mineral density (BMD) can be estimated from CT values of the images and furthermore, Young’s modulus can be evaluated from BMD on the basis of empirical formulae [6,7].

In the present study, a three-dimensional realistic hip joint models were constructed by using CT-images of three patients and then an artificial ellipsoid model of necrosis tissue was inserted into the femoral head of each models. Finite element analysis with damage mechanics was then performed to understand the mechanism of compressive fracture of the head caused by the ellipsoid necrosis.

2 MODELLING AND ANALYSIS

CT-images of three patients, 79 and 61 y.o. females and 55 y.o. male, were used to construct 3D hip joint models. An ellipsoid necrosis model with the major axis of 12 mm and the minor axis of 5 mm was inserted into the femoral head of each models so that 25% of the ellipsoid was exposed on the surface of the head as shown in Fig.1. Cartilage model was also inserted between the femoral head and the pelvis. The complete model is shown in Fig.1 with the boundary condition. Vertical load of maximum 1800 N was distributed on the upper edge of the pelvis and the load was applied by 10 steps from 180 to 1800 N. The side edges of the pelvis were fixed in the X and Y directions and the bottom edge of femur (condylar surface) was totally fixed as shown in Fig.1.
Young’s modulus and the yield strength of bone were estimated using Keyak’s method with use of bone mineral density evaluated from CT values. Poisson’s ratio was set to 0.4. Young’s modulus and Poisson’s ratio of the necrosis model were set to 13 kPa and 0.4, respectively. Yield strength of the necrosis model was chosen to be 1 kPa. Young’s modulus, Poisson’s ratio and yield strength of the cartilage model were set to 520 kPa, 0.4 and 20.6 kPa, respectively.

Damage mechanics was introduced into CT-FEM to express cumulative fracture of bone and necrosis tissue. Their tensile deformation behaviors are assumed to be linear elastic and tensile fracture of an element takes place when the principal stress reaches the critical value which is equal to 0.8 x yield strength. On the contrary, their compressive deformation behaviors are assumed to be elastic-plastic and the yielding of an element takes place when the equivalent stress reaches the yield strength and furthermore the compressive fracture of the element occurs when the minimum principal strain reaches its critical value.

3 RESULTS AND DISCUSSION

Distribution patterns of the minimum principal stress at 180 N are shown in Fig.2. The negative values correspond to compressive stress. It is clearly seen that high compressive stress generated in the interfacial region between the necrosis and the normal bone. This is thought to be caused by the stress concentration due to the difference of Young’s modulus. Distribution patterns of damaged elements in 79 y.o. model are shown in Fig.3. The yellow and red elements correspond to compressive yielding and fracture, respectively. The blue elements express tensile fracture. It is seen that damages initiated in the interfacial region between the necrosis and the normal bone at the low level of applied load. Damaged elements accumulated and created a donut-like shape as the applied load increased as shown in Fig.B. Further increase of applied load resulted in the progress of damage formation towards the center of the necrosis as shown in Fig.C.

Accumulation of fracture elements is shown in Fig.4. It is obviously seen that increasing number of fracture elements in 79 y.o. model is much higher than the other two models. It is worth noting that
the volumes of pelvis and femur of 79 y.o. model are 262 and 344 cm³, while the volumes of 61 and 55 y.o. models are 292/408 cm³ and 350/544 cm³, respectively. Thus, the bone volumes of 79 y.o. model are smaller than the others and therefore, much higher stress is generated, resulting in the larger number of fracture elements.

![Fig.4 Accumulation of fracture elements in three models](image)

Mechanism of compressive fracture of femoral head due to necrosis is proposed as follows:
1) When compressive load is applied on the upper surface of the necrosis region, it tends to extend towards the circumference due to Poisson's effect.
2) Such deformation of the necrosis is restrained by the surrounding cancellous bone tissue which has much higher elastic modulus than that of the necrosis tissue.
3) Therefore, high concentration of compressive stress generates along the interface region between the necrosis and the cancellous bone.
4) Fracture of the necrosis tissue takes place in the interfacial region due to such stress concentration and gradually progresses towards the center of the necrosis region. Finally, compressive fracture of the whole necrosis region takes place.

REFERENCES

BONE STRENGTH OF FOREARM DIAPHYSEAL RECOVERS IN THREE MONTHS AFTER PLATE REMOVAL

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\textsuperscript{2}Department of Bioenvironmental Medicine, Chiba University
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SUMMARY

Open reduction internal fixation using plates is a commonly accepted method to diaphysis forearm fractures in adults. However, in some patient after plate removal, refracture occur because of bone atrophy. We investigated forearm bone strength change after plate removal using computed tomography based specimen-specific finite element model. The bone strength would be decrease after plate fixation and it would recover three months after plate removal. It may be necessary for patients to restrict activities such as sports and work for about three months until bone strength recovers.

Key words: forearm diaphysis, bone strength, finite element analysis

1 INTRODUCTION

Open reduction internal fixation using compression plates is a commonly accepted method of management of diaphysis forearm fractures in adults. Previous study demonstrated that the bone strength of forearm resulted in atrophy, in the long-term period after surgery \cite{1}. Therefore, in some patient after plate removal, refracture occur. However, it is not known when the bone strength recovers. The aim of this study was to investigate forearm bone strength change after plate removal using computed tomography (CT) based specimen-specific finite element model (FEM).

2 METHODOLOGY

In this study we included 13 forearm fracture with 7 patients managed by locking plates. Computed tomographic imaging of both forearms was performed at before plate remove and 1, 3, 6 months after plate remove to assess local bone mineral density and to predict bone strength. We created 3-dimensional FEM at each period employing Mechanical Finder software from CT data using a previously reported protocol. \cite{2} We calculated ratios of fractured to contralateral forearm strength. Bone strength of fractured to contralateral ratios were compared between before plate remove and 1, 3, 6 months after plate remove.

3 RESULTS AND CONCLUSIONS

Mean patient age at plate remove was 33.5years. The mean period of plate fixation was 33.2 months. The mean bone strength of healthy contralateral side was 7910.2N. The mean strength of injury side before plate remove and 1,3,5 months after plate remove were 4093.1N, 4178.3, 6139.7, 7220.7N, respectively. And injury-healthy ratios were 49.0\%, 62.7\%, 88.0\%, 95.2\%, respectively. Compared with the healthy side, the bone strength before removal plate was significant decrease. And the bone strength three months after plate removal was significant recovered. This study demonstrated bone strength would be decrease after plate fixation and it would recover three months after plate removal. It may be necessary for patients to restrict activities such as sports and work for about three months until bone strength recovers.

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Session in honor of Prof. Rainald Lohner
60th birthday
NUMERICAL SIMULATION OF INCOMPRESSIBLE FLOWS IN TIME-DEPENDENT DOMAINS AND HEMODYNAMIC APPLICATIONS

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SUMMARY

We present a stable finite-element scheme for simulation of incompressible flows in time-dependent domains. The time step is independent of the mesh size, and only one linear system is solved on each time step. We consider fluid-structure interaction (FSI) and Navier-Stokes equations in time-dependent domains and provide stability analysis for both problems and convergence analysis for the second problem. The properties of the scheme are shown on several benchmarks and hemodynamic applications.

Key words: fluid-structure interaction, incompressible Navier-Stokes, moving domain, finite elements

1 METHODOLOGY

We present a stable finite-element scheme for simulation of incompressible flows in time-dependent domains. The time step is independent of the mesh size, and only one linear system is solved on each time step. We consider fluid-structure interaction (FSI) and Navier-Stokes equations in time-dependent domains and provide stability analysis for both problems and convergence analysis for the second problem. The properties of the scheme are shown on several benchmarks [1, 2, 3, 4] and hemodynamic applications.

2 RESULTS AND CONCLUSIONS

We address 2D and 3D flows in blood vessels with nonlinear hyperelastic models of vessel wall. In Figure 1 the left picture shows the 2D computational domain for a vessel with aneurysm [5], the right picture presents a snapshot of the pressure wave propagation in an elastic tube with circular cross-section [8]. In Figure 2 we demonstrate the 3D flow for periodic interaction between a viscous incompressible fluid and a nonlinear solid filament in a 3D setting for which experimental data are collected using phase-contrast magnetic resonance imaging [8]. We also present in Figure 3 simulation of an incompressible flow in a model of the left ventricle of the human heart, where the ventricle wall dynamics is reconstructed from a sequence of contrast enhanced Computed Tomography images [6, 7].

We thank Victoria Salamatova (Sechenov University) for fruitful discussions. The work was supported by the Russian Foundation for Basic Research, grant 18-31-20048.
Figure 1: Left: the computational domain for the 2D model aneurysm. Right: pressure wave propagation in a 3D elastic tube at $t = 0.008s$: middle cross-section velocity field, pressure distribution, velocity vectors and 10-fold enlarged structure displacement.

Figure 2: Snapshot of the flow at $t = 1.153s$ of Phase II of experiment [4]: streamlines colored by the velocity magnitude.

Figure 3: Snapshots of the computational mesh and the velocity field during systolic phase of a human left ventricle.
REFERENCES


MODELING ENDOVASCULAR PROCEDURES FOR INTRACRANIAL ANEURYSMS

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SUMMARY

This article summarizes methods and tools developed for modeling endovascular procedures for the treatment of intracranial aneurysms, and their application to the evaluation of devices and treatment options. In particular, we focus on immersed boundary methods for unstructured grids, device deployment tools and techniques, and porous media. Applications include flow diverting stents, intrasaccular devices and devices with semi-permeable membranes used for bifurcation aneurysms.

Key words: flow diversion, intrasaccular devices, immersed methods

1 INTRODUCTION

Most intracranial aneurysms are treated with surgical clipping or endovascular coiling. However, large, wide-necked aneurysms are difficult to treat with these approaches. Clipping requires complete exposure of the aneurysm neck and often placement of several clips to isolate the aneurysm from the circulation, and access to certain locations may also be problematic. Coiling can be problematic in wide-necked aneurysms since the coil mass can protrude into the parent artery, and large aneurysms also have high rates of coil compaction and recanalization. Thus, other techniques and devices have been explored over the years. Most of these techniques rely on the concept of flow diversion, i.e. if the flow to the aneurysm is sufficiently reduced, the aneurysm will thrombose and therefore will be excluded from the circulation.

Image-based computational fluid dynamics (CFD) is useful to analyze the effect of some of these devices and procedures on patient-specific geometries, as well as to associate these effects with treatment outcomes in order improve the device design or better plan the treatment of individual patients. However, the simulation of blood flows in aneurysms that have been treated with endovascular devices is challenging because of two main issues. First, the creation of geometric models of the devices after they have been deployed into the patient-specific vascular geometry is a challenging task. Secondly, the need to take into account the geometries of these devices, which often involve many thin wires, makes the grid generation process problematic.

Different approaches have been used to tackle these problems [1-3]. In this article, we summarize our strategies and tools for modeling a variety of endovascular devices, and their application to the evaluation of different devices and their outcomes.

2 METHODOLOGY

2.1 Vascular Modeling

Patient-specific models of the aneurysm and parent artery are created from 3D rotational angiography (3DRA) images acquired prior to the aneurysm treatment [4]. The vascular models are
truncated perpendicularly to the vessels axes, and include as much as possible of the proximal part of the parent artery in order to adequately represent the blood flow to the aneurysm [5]. Unstructured grids are generated using advancing front methods [4] with a minimum resolution of 0.2 mm.

2.2 Device Modeling

Models of endovascular devices are created by first deploying a cylindrical surface (i.e. support surface) within the vascular model. For this purpose, first the skeleton of the vascular model is extracted and the cylindrical surface is created along the skeleton. The surface is then expanded under internal elastic forces that try to recover the reference diameter of the device and contacts with the vascular walls that prevent the surface from expanding beyond the vessel boundaries. Once the surface has been deployed, the device design is mapped to the cylindrical surface, taking into account changes in the device characteristics (e.g. angles between wires) due to foreshortening effects [6]. A similar procedure is used for deploying intrasaccular devices, but in this case, the cylindrical surface is expanded along a skeleton that extends into aneurysm. These procedures have been implemented into a graphical tool that allows the user to interactively place an endoluminal or intrasaccular device within a vascular model. This tool also allows the user to use 2D angiography images acquired immediately after implantation of the device to guide the virtual deployment process [7].

Endovascular devices such as flow diverting (FD) stents and intrasaccular devices that consist in a set of braided wires are then represented as a collection of overlapping spheres. The spheres diameter matches the thickness of the device wires.

2.3 Flow Modeling

Blood is modeled as an incompressible Newtonian fluid and the unsteady Navier-Stokes equations are solved with finite element methods on unstructured grids under pulsatile flow conditions [4]. To model the post-implantation conditions, the endovascular devices represented as a collection of overlapping spheres are embedded in the CFD mesh. The spheres are used to identify which mesh elements are cut by the endovascular device wires. These elements are then adaptively refined, and the process is repeated until the mesh contains about 4-5 elements across the device wires. Immersed boundary methods on unstructured grids are then used to solve the Navier-Stokes equations by imposing no-slip boundary conditions at the intersections of the device wires and the mesh elements [3]. This approach is quite flexible and allows the representation of quite complex devices in an automatic manner. The only drawback is that the resulting meshes after adaptive refinement can be quite large, especially for devices with large numbers of thin wires (e.g. 100-200 million elements for WEB intrasaccular devices).

3 RESULTS AND CONCLUSIONS

In what follows we describe examples from our previous work of the use of computational models of cerebral aneurysms with implanted endovascular devices to analyze a variety of treatment options and devices.

3.1 Flow Diverting Stents

The tools and techniques described above have been applied to the study of flow diverting stents. First, we studied the effects of device foreshortening and showed that implantation of devices with reference diameters larger than the parent artery (which is typically done to ensure good wall apposition) can reduce the hemodynamic performance of the device [6]. Secondly, we compared the device characteristics after implantation and flow conditions between the computational models and direct measurements in rabbit models [8]. This study showed that the geometric characteristics of the device model agreed with those of the actual device measured ex-vivo, and that flow conditions obtained with the CFD model agreed with in-vivo Doppler ultrasound measurements [8]. Next, we compared flow conditions created immediately after treatment of aneurysms with flow diverters in a group of aneurysms that were completely occluded at follow-up against another
group that remained open (incomplete occlusion). This analysis was carried out with both rabbit [9] and human [10] data. The results indicated that the mean aneurysm velocity and inflow rate were significantly lower in the incomplete occlusion groups, and that these variables could be used to discriminate between complete and incomplete occlusions.

3.2 Bifurcation Aneurysms

The treatment of bifurcation aneurysms with flow diverters present additional challenges and questions. For example, in a recent study we investigated whether the effects of deploying a single flow diverter for the treatment of aneurysms at the bifurcation of the internal carotid artery (ICA) [11]. In this case there are two alternatives: a) place the FD from the ICA to the middle cerebral artery (MCA), and b) place the FD from the ICA to the anterior cerebral artery (ACA). We investigated whether the flow in the jailed artery was reduced and which alternative would produce a larger reduction in the aneurysm flow conditions. The results indicate that there is virtually no change in the flow rate to the jailed artery (keeping the resistance of the distal vascular beds fixed), and that redirecting the flow towards the MCA yields slightly larger hemodynamic reductions in the aneurysm.

3.3 Y-Stenting

Another alternative that has been tried for bifurcation aneurysms is the use of Y-stenting technique, which consists in placing two stents from the parent artery into each of the two daughter branches. The methodology described above was used to analyze the effects of Y-stenting of MCA aneurysms using two Enterprise stents. The results indicate that Y-stenting can be an effective flow diversion technique for this type of aneurysm.

3.4 Intrasaccular Devices

Since endoluminal FD require dual antiplatelet therapy and are difficult to use for bifurcation aneurysms, new intrasaccular devices have been developed. These devices consist in a single or dual compartments of braided wires of 20-40 µm that are deployed within the aneurysm cavity. In a recent study we showed that the computational models are capable of reproducing flow features observable in-vivo with angiography [7]. A second study showed that aneurysms that remained open after treatment with intrasaccular devices had larger inflow rates and mean velocity than those that occluded immediately [12]. These results are consistent with those of FD devices previously described.

3.4 Devices with Semi Porous Membranes

Finally, we applied the methodology to the study of the flow effects of devices that consist in a stent-like structure with an attached semi-permeable membrane that limits the flow into the aneurysm (e.g. pCANVAS device). To model these devices, a surface representing the membrane was created across the aneurysm orifice. Mesh elements crossed by this surface were identified and adaptively refined. Then, elements within a certain distance from the surface were identified and assigned to a porous material. The porosity parameter of the semi-permeable membrane thus modeled were estimated so that the average reduction in the mean aneurysm velocity coincided with experimental results obtained with angiography [13]. A pilot study with data from 8 aneurysms treated with the pCANVAS device indicate that if the membrane is perfectly deployed across the aneurysm orifice, there are no differences in the intra-aneurysmal flow conditions of complete and incompletely occluded aneurysms. Thus this suggests that in incompletely occluded aneurysms the device may not have been ideally placed.

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DEVELOPMENT AND APPLICATION OF A COUPLED CFD-CSD METHODOLOGY; ON THE OCCASION OF PROF. RAINALD LÖHNER’s 60th BIRTHDAY

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SUMMARY

This paper describes Prof Löhner’s development and application of a coupled computational Fluid Dynamics (CFD) and Computational Structural Dynamics (CSD) methodology. Development was initiated in the early 1990’s, when both technologies reached a mature state. Loose coupling of codes was chosen, to preserve and maintain investments. The initial effort coupled FEFLO, Löhner’s CFD code, with LLNL’s DYAN3D. However, the need to accurately model structural failure via cracking, rather than element erosion, led to the development of an in-house structural code, ASICSD. Sample of the extensive application of the combined methodologies will be described.

Key words: coupled CFD-CSD methodologies, blast wave, structural response

1 INTRODUCTION

While previous efforts have been devoted to coupling of CFD and CSD for modeling structural elastic response, our focus has been on modeling blast wave loading on structures and the resulting structural plastic deformation, specifically for protection of facilities against terrorist attacks. Modeling of such events requires the accurate modeling of several complex physical mechanisms relating to fluid and structural dynamics, such as explosive detonation, blast wave propagation, steel cased weapon break-up and target structural response to blast, fragment and debris loading. Clearly, these require coupling of CFD and CSD methodologies. This requirement has been around for a long time, however, only in the early 1990’s it was felt that the state-of-the-art in CFD and CSD modeling is mature and stable enough to enable methodology coupling. To couple the codes, Prof. Löhner developed a general loose coupling algorithm, called FEMAP [1], with the objective of general coupling of fluid dynamics, structural dynamic, thermal dynamics, as well as radiation codes. The approach taken is to treat each code as a library and pass information from one to another in a conservative form.

The first coupled code developed [2], used FEFLO as the fluid code. FEFLO has been tested and validated by then extensively for at least a decade [3]. The CSD code was LLNL’s developed DYNA3D [4]. For certain class of problems, such as blast loading on steel panels or concrete walls, results were encouraging. However, when applied to modeling of cased weapon detonation/fragmentation, results were disappointing. DYNA3D eroded failed elements, generating erroneous rarefaction waves, as well as forming crude opening of the cracks. At this point Prof. Löhner and Dr Soto initiated the development of ASICSD (described below), which models accurately crack opening and relief of the internal high pressure detonation products [5].

The next major methodology evolution was the transition from a glued mesh approach (i.e., identical fluid and structural surfaces), to the embedded mesh approach [6] (where the structure is
“floating” through the fluid model). This major change was necessitated by the modeling of CSD surfaces (plates) failing in contact, due to: 1. the large number of expensive (CPU) local and global remeshings; and 2. formation of negative CFD elements. The CSD contact algorithm is typically based on modeling CSD initial surface penetration, followed by an application of a restoring force. Unfortunately, the penetration process creates CFD negative elements. An example is shown in [2], where the simulations required immense CPU investment, resulting from frequent remeshing due to surface folding and penetration. Another reason for switching to the embedded approach is shown in Fig 1, which shows a cased weapon breaking to hundreds of fragments. Under the high internal detonation pressure, the weapon case breaks to hundreds/thousands of fragments. The need to individually form a mesh about each and every one of these CSD surfaces (for the glued approach), and model the bodies propagation over distances of several meters, forced hundreds of local and global remeshings, and the cost became unattainable [7], forcing up to shift to the embedded approach. Further improvements included the development of the adaptive embedded approach [6,8], the inclusion of particles, reactive or inert [9] within the coupled methodology, as well as an innovative node balancing scheme to model reactive flows [10].

While the final paper will describe several applications of the coupled methodology, in this abstract we include just one simulation that demonstrates several of the capabilities develop by Prof. Löchner.

2 METHODOLOGY

The CFD methodology used here is FEFLO [11], a general-purpose CFD code based on the following general principles:
- Use of unstructured grids (automatic grid generation and mesh refinement);
- Finite element discretization of space;
- Separate flow modules for compressible and incompressible flows;
- Arbitrary Lagrangian-Eulerian formulation for body-fitted moving grids;
- Embedded formulation for complex/dirty geometries;
- Edge-based data structures for speed;
- Optimal data structures for different supercomputer architectures;
- Continuous updated shock-capturing and high order schemes (including DG [12]); and
- Bottom-up coding from the subroutine level to assure an open-ended, expandable architecture.

The code has had a long history of relevant applications and has been validated repeatedly [2, 13]. FEFLO has been ported to both shared memory and distributed memory machines.

The CSD code, ASICSD [5], is an unstructured, explicit finite element code, designed to model large structural deformations. It includes a good data base for non-linear materials with elasto-plastic compartmental laws with rupture. The code incorporates a large library of materials and various equations-of-state, and many kinematic options such as slidelines and contacts. The code is fully parallelized and has been extensively validated [5].

Coupling between all modules is provided by FEMAP, via a loose-coupling approach. The embedded approach is used to couple the CFD and CSM module [1].

3 RESULTS AND CONCLUSIONS

Figure 2 shows the test configuration, which consisted of a disposable burst room composed of two culvert sections. A reusable thick reinforced concrete closure panel with a doorway is placed at the far end to provide confinement and controlled venting of the structure. The permanent portion of the test structure is designed to study the failure of the first wall, propagation of blast and debris into the second bay, and progressive loading and failure of the second wall. The facility incorporates two replaceable test walls, loaded with load beams to ensure full enclosure during the test. This constitutes a severe test of the coupled methodology as it requires accurate modeling of several physical processes as well as several coupled numerical schemes. The controlling physical mechanisms include: detonation wave initiation, detonation wave propagation through the explosive, charge case expansion under the extreme load, case cracking, break-up and formation of fragments, detonation products expansion through the forming cracks, and detonation products and...
case fragments impact on the facility walls, wall response and failure, and blast wave as well as secondary debris (ejecta, dust, rebars and other first wall debris) impact on the next-layer of walls, and their response.

The study incorporated comparison of predicted and measured pressure and impulse time histories at several locations, as well as measured and predicted walls response (acceleration and deflection) for the two test walls, obtained when incorporating dust production from the culverts in the simulation [14]. Figure 3a shows a comparison for stations 1 and 2 (symmetric) in the detonation room. The experimental data is in black, the blast wave results without including dust effect (i.e., modeling the culvert as rigid) is in green, while the predicted results including dust is in red. The difference between the predictions is strikingly evident at about 10 ms, when the reflected shock from the room far end attempted to propagate towards the test walls. The reflected wave then encountered several hundred kilograms of fine dust and was damped (i.e., significant energy loss) due to: 1) thermal (internal) energy loss as the dust particles internal energy increases due to heating by the hot detonation products; and 2) drag damping (kinetic energy loss), as the blast wave accelerates the slower particles.

The results including the dust effects yield a more accurate blast wave energy damping, not just for a station in the blast room (Fig 3a) but also for two stations in the bay room: station 8 located on the ceiling, and station 10, located on test wall 2 (Figs 3b and 3c, respectively). Finally, the accurate pressure environment prediction resulted in a accurate structural response prediction. Figures 4a and 4b show comparisons of measured and predicted accelerations and displacements for test walls 1 and 2, respectively. Very good agreement is demonstrated both in terms of wall acceleration and displacement.
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