A whole-heart model of multiscale soft tissue mechanics and fluid structure interaction for clinical applications (Whole-Heart-FSI)

University of Glasgow, EPSRC Established Fellowship

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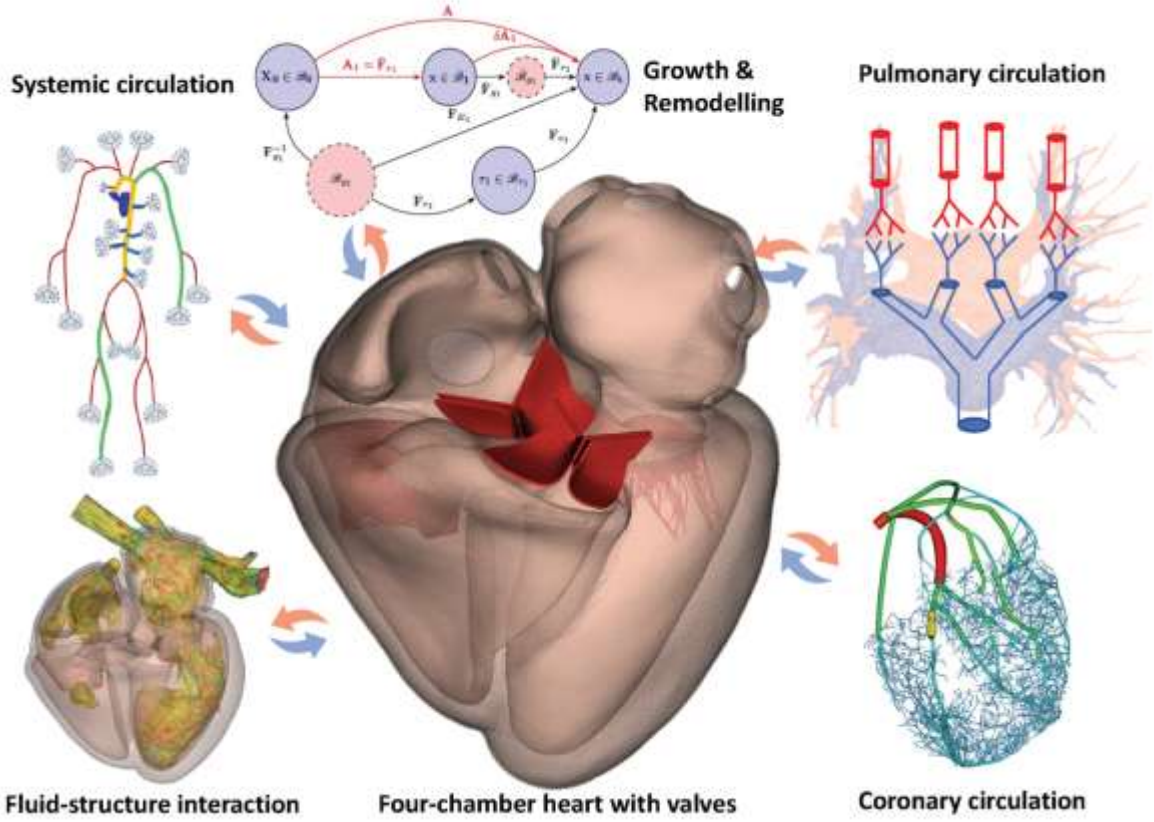

A: From proposal to interview:

I didn't have courage to apply for the EPSRC Fellowship until I met Kate Reading at the EPSRC HIVE workshop in Glasgow in 2017. Kate, who oversees the Healthcare Technology Fellowship scheme, happened to be in our discussion group and was delighted to hear my interest. I submitted the outline proposal, that provided the focus and qualification assessment, and had a go-ahead response a week later. However, I still couldn't find energy to write a full proposal in my already busy life, being focused on the SofTMech Centre mid-term review and the SofTMech-MP international centre-to-centre proposal. In May 2018, I sat next to Prof. Alain Goriely, one of the mid-term review external assessors, at the post mid-review dinner, who had just obtained his EPSRC Established Career Fellowship and kindly encouraged me to apply too. That was the final boost I needed.

I started to set a hour a day to work on it, imaging that I had a "student" who would knock at my door every day. This approach was inspirated by the book "Bird by Bird" by Anne Lamott, which describes how one may complete a daunting task, like shooting a treeful of birds, bird by bird at a time. This strategy worked and I gradually became eager to meet the "student" everyday. A few months later, I submitted my full proposal, Whole Heart-FSI.

I was interviewed in January 2019 by a Maths panel in Swindon. The interview was scheduled for 4pm; I was the last one of the day, but I had flown to Swindon the day before to be on the safe side. At noon, I got an unexpected call to see if I could make the interview at 1pm – someone else was delayed. Luckily, I was only 15min away. The interview went very well, the panel with a well-balanced expertise knew what to ask, and I knew how to answer, having rehearsed several times beforehand. Although the project is heavily focused on mathematical modelling, there is also a statistics element, with Prof. Dirk Husmeier as my collaborator. I didn't think the panel would ask me questions on the statistics, but when all the questions were exhausted and I faced a smiling panel, someone asked a statistical question. My mind went blank, but I gave my best honest reply. I left with an uneasy feeling, but later Dirk told me it was exactly the right answer. After an anxious waiting, I got the fellowship and started in October, 2019.

B. The research theme and progress

So what is the Whole-Heart-FSI? The project is driven by the fact that cardiovascular disease is the leading cause of disability and death in the UK and worldwide. The British Heart Foundation estimates cardiovascular disease has a £19bn annual economic impact. Mathematical and image-based modelling of the heart has greatly advanced our understanding of heart function and promises to support diagnosis and treatment decision. However, clear gaps and challenges exist in current heart modelling, particularly for understanding the structural impairment where mechanics plays a major role. The ambitious aim of my project is to model the whole heart with four chambers, connected to all the circulatory systems incorporating fluid-structure interaction (FSI). This is in contrast to most of the heart studies that focus on the left ventricle only, which excludes interactions between chambers, cardiac tissues and flows. In addition, many medical treatments for heart problems are aimed to restore the pump function or electrophysiology behaviour of the heart. However, diastolic heart failure often occurs with normal ejection fraction, so there are no recommended treatment options, despite several different structural cardiac abnormalities often leading to this type of heart failure. For example, mitral regurgitation, a leakage of blood from the left ventricle retrogradely passing through mitral valve into the left atrium, can induce lung congestion, right heart overload and eventual heart failure. Myocardial infarction, more commonly known as heart attack, accounting for 4/5 of all cardiac deaths, can lead to heart failure despite immediate treatments, while congenital heart disease, caused by inborn developmental error, gives rise to complex blood flow physiology patterns both within the heart and systemic and pulmonary circulations, and remains relatively under-evaluated with respect to the natural history of disease and therapeutic intervention.

Sustained heart diseases such as heart attack can give rise to abnormal fluid dynamics linked to thrombosis in the left atrium appendix, as found in most of the heart failure cases in a clinical trial by GlaxoSmithKline plc. The right ventricle has a complex geometry and contractile pattern that is distinct from the left ventricle. This renders it challenging to quantify the performance using standard clinical investigion tools. The inability to model the

complete heart limits the application into pulmonary hypertension, right ventricle disease and congenital heart disease. Including all the four chambers within the Whole Heart-FSI we see as an essential advance that will improve our understanding of cardiac functioning in its totality.

Research on heart disease induced growth is still at its infancy, and a framework for multiscale soft tissue modelling that accounts for cellular changes is yet to be developed. Importantly, the change in the tissue properties is a critical determinant of heart function. Prolonged activation of inflammation increases protease activity and is associated with enhanced dilative remodelling, whereas increased matrix deposition results in a stiffer ventricle and thus diastolic dysfunction. The challenge of heart modelling is inherently patient-specific; however, most existing models are too simplified for clinical needs, yet too computationally intensive to provide real-time diagnosis support. Addressing these issues will make a difference in clinical translation. By combining the state-of-the art Mathematical modelling with Statistical emulation applied to the whole heart, we are trying to take a significant step in this direction.

C. The progress – and unexpected challenges

Two years into the project, progress has been made along six parallel threads.

In **Thread I**, we extended the left ventricle model to include the mitral valve model, and then added the left atrium model, linked with the pulmonary circulation. In collaboration with Mark Danton (consultant cardiac surgeon), we obtained interesting new results about these sub-systems of the heart, that have been presented at various conferences, workshops, and published [1]. We are now building the whole heart model consisting of the four cardiac chambers, the left and right atria and ventricles, based on a mesh downloaded from Zenodo (https://doi.org/10.5281/zenodo. 3890034), and are adding all the heart valves, and the systemic and pulmonary circulations. The coronary circulation will also be included. Including the coronary circulation will greatly expand the clinical applications of the model. For example, the prognosis of myocardial infarction, typically caused by acute obstruction of a dominant coronary artery, relies on a rapid recovery of the coronary microcirculation. However, this requires that the heart wall itself is modelled as poroelastic material first, which is addressed in **Thread II.**

Thread II is to model cardiac perfusion with improved numerical efficiency. The computational framework we developed is published in [2], and the new numerical methods developed are due to be submitted. Currently we are coupling the heart model with a detailed coronary network model, with application to human heart diseases. This work is in collaboration with Colin Berry the cardiologist, as well as Boyce Griffith from University of North Carolina at Chapel Hill, Jack Lee from UCL and Mette Olufsen from NC State University.

Thread III is to deal with the growth and remodelling of the cardiac tissue. Heart evolves with time; this process is faster when diseased. Modelling this requires new mathematical theory. One approach is to introduce a so-called growth tensor in the framework of the volumetric growth theory. However, most existing theories evaluate the growth tensor in the undeformed and unloaded configuration, which is not appropriate as tissues adapt to changes in real time. We have developed a new theory that allows the growth tensor to be defined in

the current loaded configuration, and able to produce residual strain that is consistent with experimental observation [3]. We also estimated the growth tensor from imaging of an infarcted human heart in a first natural history of the disease [4].

Thread IV is to carry out a detailed energy budget analysis of FSI within the heart, in collaboration with Dr. Peter Stewart. The model has first been applied to flow through a collapsible channel, a prototypical system for investigating FSI, that exhibits fascinating physical behaviour including multiple steady and oscillatory solutions. In particular, we have revealed an entirely new mechanism for self-excited oscillation from an inflated basic state, which may have relevance to aneurysms. These studies are published in journals such as *JFM* [5-7].

Thread V: In collaboration with Dr. Hao Gao, we have improved the modelling of the myocardium by adding details of the cellular level. The heart muscle cells (myocytes) in the myocardium and the scaffold (collagen network) have very delicate structures to maximize the pumping function. Existing studies usually consider main features (i.e. average muscle orientations), but miss features like dispersion. In this Thread both the passive and active heart muscle models include the myocyte and collagen dispersions, and the work is published in *R Soc Open Science* [8] and *JEM* [9].

Thread VI focuses on Statistics analysis. Mathematical models of the heart based on continuum mechanics are computationally expensive and reconstructing a patient-specific heart geometry can take days or weeks, involve tedious manual input. To make a heart model work requires lengthy computational time since the mathematical model needs to be run thousands of times as part of optimisation algorithm to match the patient data. Because of those difficulties, we have not seen many biomechanical heart models adopted in the clinics. To overcome those obstacles, we must make use of advanced statistical inference approaches and artificial intelligence to accelerate the clinical translation of models. In a series of past studies [10-11], we have demonstrated that a computationally cheap statistical surrogate model can be derived from the computationally expensive mathematical model can be replaced by without compromising the accuracy. In this project, led by Dirk, we have also successfully adapted "deep learning" techniques based on convolutional neural networks to learn heart geometry directly from the heart scans without manual interventions [12]. We have observed three orders of magnitude acceleration when inferring heart muscle stiffness using surrogate modelling, reducing the computational time to less than 15 mins. Currently, we are applying the cutting-edge mathematical models in real-time prediction and assessment of the heart function with sound uncertainty quantification.

The unexpected: Covid-19 made it impossible to travel and to visit the international labs of our project partners. We did run one online workshop, but we have not been able to make full use of face-to-face talks with our collaborators, and important experimental data still cannot be produced. On the other hand, Covid-19 has also provided new challenges, and our clinicians have embarked on new research on the correlations between Covid and MI, as well as on new drugs on MI. We therefore have applied for an IAA project to ensure that our models can be translated to these clinically orientated projects. We already have acquired 1000+ heart scans from healthy controls, myocardial infarction patients, and COVID-19 patients. This calls for more man power and statistical input.

Finally, I must say that the project relies on successful collaborations with international collaborators as well as clinicians. They all provided excellent support. The project also greatly benefits from the strong link to the SofTMech Centre. Indeed, we were able to extend the Statistics RA contract from two years to four years, with SofTMech-Hub's funding, so that the statistical analysis can start in year two, rather that in year four. The regular online communications between all RAs and CIs within the SofTMech Centre have made the research productive and enjoyable, even under the difficult situation. Looking ahead, the road is long, the tasks are challenging, but there is direction, adaptation, and progress.

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