Forced to cooperate

DOI:
10.26481/dis.20181109ld

Valorisation

Cardiovascular dysfunction is a leading cause of death in the western world according to the World Health Organization. Despite centuries of research, there still remain gaps in the current understanding of the cardiovascular system. In order to understand the complexities of cardiac function in both healthy and pathological situations, computational models have been developed to mimic various biophysical aspects of the circulation.

Of the various aspects of the circulation, this thesis centers on the development of a novel computational model of the most basic functional unit of the contractile system, called the sarcomere. The computational model presented in this thesis, the MechChem model, was built for its eventual use in understanding clinically relevant problems in the human heart. The emphasis on clinical translation means that this project was specifically designed with valorisation in mind. This chapter will focus on the valorisation opportunities originating from the research presented in this thesis.

Knowledge transfer

Knowledge gained through research, whether the data is positive or negative, is valuable to the scientific community. Distribution of knowledge can save both time and money. If knowledge and data are freely available, the number of experiments repeated by different research groups could potentially be decreased. Additionally, the distribution of knowledge allows others to build on existing ideas and hypotheses. Hence, knowledge transfer for further utilization is a key aspect of valorisation. To this end, the work described in this thesis has been presented at international conferences and workshops. Furthermore, each of the chapters (Chapter 2- 5) detailing the buildup of the MechChem model as well as its application have been accepted for publication in scientific journals with the purpose of making the studies available to the scientific community.

In addition to the publication of the central hypotheses and results in this work, the source code of the computational models described in this thesis has been made openly available online. Chapter 2 details our novel hypothesis of cooperative activation in the cardiac sarcomere. The availability of the source code makes it possible for other groups to utilize the model that represents the main hypothesis underlying MechChem with their own contraction models. Chapter 3 builds on the MechChem model by adding a simplified contraction model for which the source code is also freely available online. This work can also be utilized by other groups wishing to insert a simplified contraction model in a larger model of the heart. Overall, the availability of the source code provides possibilities for others to build on the work presented in this thesis, thus increasing the possible knowledge gained from this work.

Prior to the development of the MechChem model, a relatively simple model of the closed-loop circulation, called CircAdapt, has been developed at Maastricht University. The model is composed of various modules that represent the components of the circulation. A user-friendly interface, developed previously for use of the CircAdapt model as an educational tool, is freely available on www.circadapt.org. This educational tool enables real-time beat-to-beat simulation of various hemodynamic signals, and its interface allows easy modification of model parameters. As a result, one can learn about cardiac physiology by tweaking different properties of the circulation. The educational tool is part of the medical curriculum in Maastricht University. In the future, the MechChem model may be included in the educational tool. This would allow students to better understand properties of the heart at the tissue level and how they determine regional myocardial mechanics, which can be measured clinically using echocardiographic deformation (or strain) imaging. Regional myocardial strain patterns provide information on regional tissue properties such as myocardial stiffness and contractility that can be utilized to pinpoint the underlying causes of cardiac dysfunction. Further, this information may provide insight to which treatment option to choose. Hence, the addition of the MechChem model to the CircAdapt educational tool, and further the medical curriculum, may help future clinicians gain deeper understanding of the cardiac abnormalities they will eventually treat. Because the additional knowledge gained through the use of the MechChem model benefits clinicians, it will also benefit the patients who will be receiving treatments.

Benefits of a model-based approach

When integrated in a multi-scale model of the human heart and circulation, such as CircAdapt, the well-validated MechChem model provides the ideal environment for *in silico* cardiovascular research. As such, it can be utilized as a hypothesis-generating tool. The *in silico* development of a more targeted hypothesis and study design prior to animal experimentation can reduce the number of animals necessary for research. In addition to the potential reduction in animals used for experiments due to computational modeling, the cost will also be reduced, allowing allocation of financial resources to further research projects.

While computational modeling can potentially decrease the number of experiments necessary on animals, it also provides a platform to isolate and change specific parameters in a simple and fast way that may not be possible in an animal model. The study presented in Chapter 5 of this thesis is an example of the latter. We changed a single parameter to allow us to understand the effect of a reduced rate of cross-bridge cycling, independent of any other interactions, on mechanical dyssynchrony in patients with dyssynchronous heart failure. To perform the same reduction in rate of contraction in animals, a certain drug may need to be administered or animals would need to be bred to have specific traits. Utilizing a computational model also allows the changes to be made in a short period of time, thereby saving time to generate results. Reduction in the intervention on animals, in addition to saving time and money, may also reduce ethical concerns. A computational model can be pushed to absolute extremes without any inhumane actions. While computational modeling cannot replace experiments on animals in the foreseeable future, it can reduce the amount of experiments that need to be performed by helping to create a more targeted hypothesis for experimentation.

Clinical applications

In this thesis (Chapter 5), we have utilized the MechChem model embedded in the CircAdapt model of the closed-loop circulation to understand a clinical problem. Previous studies have shown that the deformation pattern of tissue in the septal wall of the heart can serve as an indication for whether a heart failure patient will respond favorably to cardiac resynchronization therapy. In our study in Chapter 5, we tried to understand the underlying mechanisms responsible for the different septal deformation patterns in a specific cardiac abnormality known as left bundle branch block. The results in Chapter 5 are hypothesis-generating and also have potential clinical applicability. It may be possible to utilize the model in the future to understand septal strain patterns in the individual heart failure patient with the possibility to aid in the determination and personalization of therapy. The study presented in Chapter 5 was a first test of the multi-scale CircAdapt-MechChem model, but the potential impact will be broader. As the model is validated and improved, it may be utilized to study a wider range of cardiac abnormalities. The model could be made available to clinicians to help them make decisions regarding patient prognosis and treatment options. The model can be fed personalized information such as ECG-based activation times as well as tissue deformation patterns in different segments of the heart. Hence, the model has the potential to affect treatment in the clinic by aiding the clinician with decision-making, eventually improving the standard of care that patients receive.