Developing a Virtual Physiological Mouse model of the heart: Multi-scale coupling is key for controlling ventricular pressure

Sander Land[1], Steven A. Niederer[2], Jan Magnus Aronsen[3], Emil K.S. Espe[3], Lili Zhang[3], William E. Louch[3], Ivar Sjaastad[3], Ole M. Sejersted[3] and Nicolas P. Smith[2]

[1]*University of Oxford,* [2]*King's College London,* [3]*University of Oslo*

Correspondence: sander.land@cs.ox.ac.uk, Wolfson Building, Parks Road, Oxford OX1 3QD, UK

Introduction

Tension generated by cardiac myocytes is known to be influenced by both strain and strain rate at the single cell level. These control mechanisms are of key importance in analyzing how tension generated at the cellular level gives rise to ventricular pressure. However, the underlying biological processes leading to these dependencies remain debated. The mechanisms which determine the coupled electrical and mechanical behaviour of the heart are increasingly being investigated in experimental models which exploit the opportunities provided by genetic manipulation in mice[1]. A Virtual Physiological Mouse heart could be used to interpret the wide range of data from experiments in mice, and improve our understanding of cardiac physiology across species. Even though electromechanical models have been used to investigate the mechanisms of cardiac contraction in a variety of animals such a model of a mouse heart does not yet exist.

Furthermore, both electrophysiological and contraction models are often based on heterogeneous data obtained across a range of species and temperatures, which creates significant limitations[2]. The lack of species and body temperature consistent model is indicative of challenges in identifying model parameters from only cell measurement data. Specifically, many contraction experiments are done at lower temperatures or in skinned preparations[3]. These difficulties with single-cell data further confound determining the influence of length- and velocity dependent feedback on cellular mechanisms for whole organ function.

To address this challenge, we have developed an electromechanical mouse model at body temperature and the physiologically faster 6 Hz heart rate. Using this framework we compare in-silico experiments with recent data and provide a quantitative analysis of deformation dependent electromechanical coupling mechanisms, using experimental data obtained at both the single cell and whole-organ level.

Methods

Our contraction cell model is based on the frameworks by Niederer, Hunter and Smith ("NHS model")[4] and Rice et al.[5], combining the simplicity of the former with the better relaxation kinetics of the latter. Length dependence was modelled as a combination of filament overlap and a shift in calcium sensitivity ('length-dependent activation'). For velocity dependence we use a phenomenological "fading memory" model as in the NHS model, which can reproduce many of the observed effects without being tied to underlying mechanisms. Details of this model are described in Land et al.[6] The original value of the fading memory model's velocity dependence magnitudes A_i were taken from sinusoidal analysis data, in which isometric tension is a dominant factor in determining this parameter. As isometric tension is known to be very low in many single-cell experiments, these parameters were poorly constrained.

The cellular contraction model was coupled to the Li et al. electrophysiological model[7] and embedded in a whole-organ model using methods previously described[8]. For the geometry we use a cubic Hermite mesh based on MRI data (see Fig. 1 (A)). Furthermore we couple the electromechanical model to a full heart cycle model which includes isovolumetric relaxation/contraction, ejection using a Windkessel model, and a simple model of diastole.

Results

Initial results of the whole-organ model showed a striking difference between experimental measurements of ventricular pressure and model predictions, with the latter having a shape similar to single-cell tension transients instead of pressure measurements. Increasing the strength of the aforementioned poorly constrained velocity dependence ($A_1 = -29$ instead of $A_1 = -4$, with $A_2 = -4A_1$ in both cases) significantly reduced these differences. Fig. 1B shows a comparison between pressure transients. Whereas the pressure predicted with a low velocity dependence is very similar to cellular tension transients, increasing velocity dependence results in a flatter, longer, plateau in pressure. While length-dependence does have some effect

as well, the combination of the two length-dependence mechanisms is constrained by experimental data at the cellular level[3]. As shown in Fig. 1C, using a length dependence model closer to that of the NHS model, with the dominant mechanisms being filament overlap rather than length-dependent activation, the pressure transient is more rounded and relaxes more slowly. Table 1 shows the effect of other important parameters, with variations based on how constrained the parameters are by experimental data. These results show the duration of ejection can be significantly influenced by aortic impedance, but this also raises peak systolic pressure further away from experimental data.

	Ejection	Peak SP	ESP	SV
Experimental PV data	43 ms	43 ms	43 ms	43 ms
Default $A_1 = -4$	27.3 ms	27.3 ms	27.3 ms	27.3 ms
High velocity dependence $A_1 = -29$	↑ 10.8 ms	↑ 10.8 ms	↑ 10.8 ms	↑ 10.8 ms
Aortic impedance Z +50%	↑ 3.8 ms	↑ 3.8 ms	↑ 3.8 ms	↑ 3.8 ms
End-diastolic-pressure +0.1 kPa	↑ 0.5 ms	↑ 0.5 ms	↑ 0.5 ms	↑ 0.5 ms
Fiber stiffness C_2 -12.5%	↑ 0.3 ms	↑ 0.3 ms	↑ 0.3 ms	↑ 0.3 ms

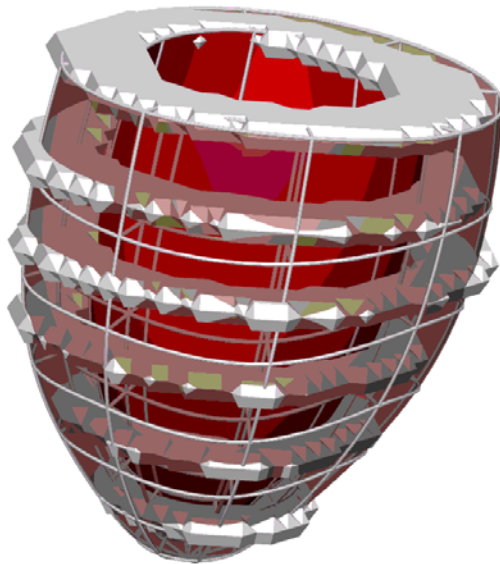
Table 1: Summary of parameter sensitivity results at the whole organ level. Results shown for duration of ejection, peak systolic pressure (SP), end systolic pressure (ESP) and stroke volume (SV) for parameters involved in length- and velocity dependence, as well as some others which have the greatest effect on ejection time.

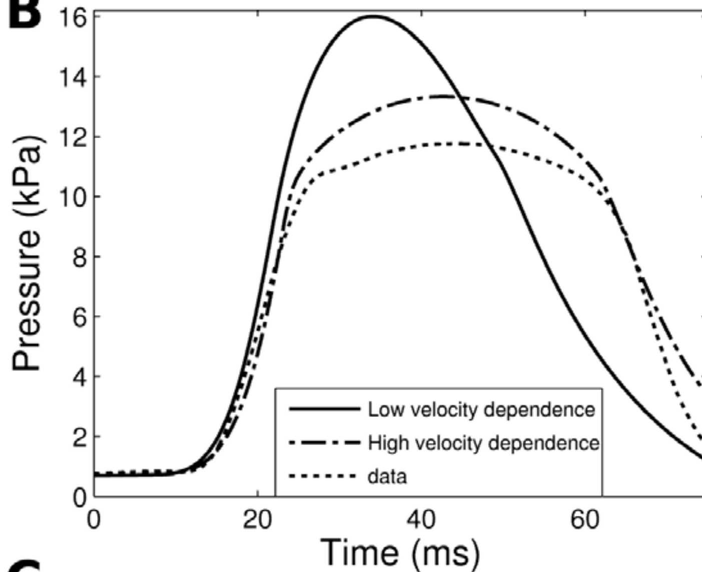
Discussion and Conclusions

To investigate electromechanical coupling, we have developed a computational model, which can reproduce the fast contraction and relaxation kinetics observed in mouse hearts. Our model is data-driven and based mainly on experiments performed at body temperature. Using this model, we have shown that running whole-organ simulations can assist in the inference of aspects of length- and velocity dependent feedback at the cellular scale, for which data is still insufficient or contradictory. Most importantly, we were able to use emergent function in whole-organ simulations to show the importance of a stronger velocity-dependent effect on tension in reproducing pressure transients seen in vivo. Introducing such a stronger velocity dependence resulted in a longer duration of ejection, with a lower and extended pressure plateau during ejection, rather than a pressure transient which is similar to single-cell tension transients. Results from a detailed parameter sensitivity analysis show that this is a necessary change to explain pressure transients, as other parameters in the model are either constrained from experimental data or do not explain differences between model results and experimental data. The flatter plateau in pressure transients is mainly a velocity-dependent effect: when the aortic valve opens there is a phase of fast shortening which slows further generation of tension. At the end of ejection, tension is briefly increased by the 'B process' known from sinusoidal analysis[9], resulting in higher pressures at the end of ejection. The decrease in tension as the effects of this process end, combined with the faster relaxation due to length dependent (de)activation at a shorter sarcomere length, likely leads to the high dP/dt_{min} values seen.

Whereas previous studies using electromechanical models have usually been based on a few results or required large supercomputing facilities, the smaller organ size combined with efficient computational methods[8] have allowed us to easily obtain hundreds of whole-organ simulations, making the mouse an effective computational model as well. Furthermore modelling cardiac function at a higher heart rate and physiological temperature allowed for more quantitative comparison with data from in vivo measurements compared to previous murine models at low temperatures or pacing frequencies, as differences between models and experiments cannot simply be rationalised by appealing to temperature differences. Using more physiological conditions has already shown that previous contraction models do not always handle relaxation well at these pacing frequencies, which can easily go unnoticed when running simulations at 1 Hz or comparing to experimental data obtained at lower temperatures. As models progress towards simulating increasingly physiological cases, they can reveal gaps in our current understanding of cardiac physiology. An example of this relevant to the current study is the difference seen between model and experiments during late IVR and the rate of relaxation, which is still to be fully explained.

In conclusion, we have developed the first electromechanical model of the mouse heart, allowing in-silico investigation of many experiments done in these animals. This framework has already shown potential for improving our understanding of cardiac function at both the single-cell and whole-organ level, by revealing the role of coupling mechanisms in explaining the striking differences between the shapes of cellular tension and ventricular pressure transients.





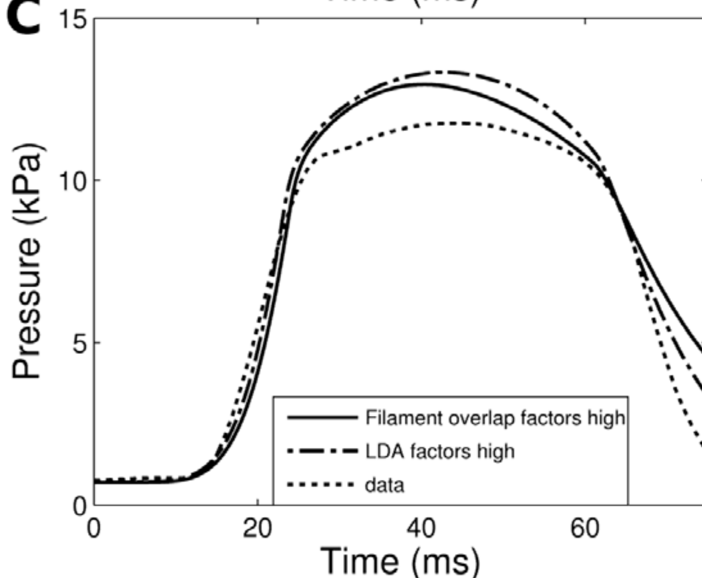


Fig. 1: Whole-organ simulation. Panel (A) shows the mesh used in simulations (red), which was generated from MRI data (white). Panel (B) shows a comparison of pressure transients with low and high velocity dependence. Panel (C) shows a comparison of length-dependence mechanisms, with either the filament overlap or length-dependent activation being the dominant mechanism.

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