REGULATORY MECHANISMS IN CARDIAC ACTIVE MECHANICS: FROM MICROSCALE MODELS TO MULTISCALE NUMERICAL SIMULATIONS

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Introduction

Cardiac muscle contraction is driven by subcellular processes that convert chemical energy into mechanical work. These processes are influenced by a complex network of regulatory and feedback mechanisms (e.g. calcium-driven regulation, length-dependent activation and force-velocity relationship), which play essential roles in the organ-level cardiac function (e.g. Frank-Starling mechanism). However, studying the fibers stretch-rate feedback (SRF) through numerical simulations poses numerous challenges, both at the modeling and methodological levels [1,2]. For this reason, the mathematical models proposed in the literature in the past have always - to the best of our knowledge - ignored this feedback. As a matter of fact, the effects of SRF on the overall cardiac function are still poorly understood.

Methods

We present a mathematical model of sarcomeres, based on a biophysically detailed description of troponin-tropomyosin complexes and cross-bridge dynamics. Remarkably, the model explicitly encodes the calcium-driven cooperative activation of the thin filament and the force-velocity relationship within a computationally tractable framework. We are thus able, for the first time, to simulate sarcomere contraction in a computational time that is suitable for multiscale simulations and with an explicit representation of the main proteins. Then, we propose two numerical schemes that allow to cure non-physical oscillations occurring in the numerical solution due to the presence of the SRF. These schemes address instabilities issues arising from the coupling of the microscale force generation model with the tissue mechanics and the blood circulation models, respectively.

Results

We are able to reproduce the healthy cardiac function for all the heart chambers, in terms of pressure-volume loops, time evolution of pressures, volumes and fluxes, and three-dimensional cardiac deformation, with excellent matching with cardiac physiology. Our results show that, when neglecting the SRF in the simulation, the fluxes across the semilunar valves largely exceed the physiological range. Moreover, we show that, thanks to the introduction of our stabilization terms, we are able to remove the non-physical oscillations that would otherwise affect the numerical solution.

Discussion

Our results allow to investigate the effects of the SRF on the cardiac organ-level function. This feedback, originating from the microscale force-velocity relationship of sarcomeres, reduces the active force in regions where fibers are rapidly shortening. The macroscopic effect is a homogenization of fibers shortening velocity that, from a hemodynamic perspective, results into a smoothing of the ejected blood flux. Hence, we postulate that the SRF, despite originating at the microscale, plays a crucial role in the macroscopic regulation of blood fluxes. However, if not properly managed at the numerical level, this feedback produces non-physical oscillations that may lead the numerical simulation to fail. Thus, the interplay between accurate mathematical models and efficient and stable numerical methods is of utmost importance to reproduce the heart physiology.

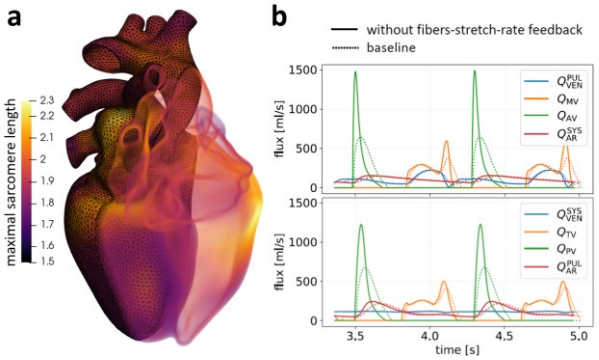

Figure 1: (a) Results of a four-chamber electromechanical simulations, highlighting the heterogeneous space distribution of the fibers elongation. (b) Blood fluxes across cardiac valves with and without fibers SRF.

References

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