Forced to cooperate

Summary

The heart is a pump that propels blood throughout the body. This pump function is enabled by the rhythmic contraction and relaxation of the cardiac muscle developing tension in the cardiac walls. The most basic functional unit of muscle, called the sarcomere, is responsible for the active generation of force through biophysical interactions between thick and thin filaments. Myosin heads that protrude from the thick filaments can attach to myosin binding sites on thin filaments, forming cross-bridges (XB) that can generate force. At rest, binding sites on the thin filaments are blocked. Electrical signals initiate depolarization of myocardial cells, triggering the release of calcium into the intracellular space. Muscle is activated when a calcium ion (Ca^{2+}) binds to a molecule called troponin, triggering conformational changes of the thin filament that result in the unblocking of the binding sites.

It has been shown that slight increases in the intracellular calcium concentration result in disproportionately large increases in tension. While it is widely accepted that the disproportionate increase in tension is due to cooperativity, the mechanism is debated. In this thesis, we propose a novel, physics- and chemistry-based mechanism of cooperativity in the cardiac sarcomere and develop a computational model to test it. Because the model is made to understand clinically relevant questions, it is built up and validated step by step for its eventual implementation within a model of the closed-loop circulation.

Groups have performed experiments in which isolated cardiac muscle cells were skinned and placed in a bath containing specific concentrations of ions. The muscle cells developed tension while their length was held constant, and the developed steady-state tension was recorded. The experiment was conducted multiple times with different calcium concentrations resulting in a group of data points that characterized the relationship between calcium concentration and tension for a given

sarcomere length. The calcium-tension relationship from these experiments is typically fitted with a sigmoidal curve. The curve generally has a steep upslope in tension with small changes in calcium concentration, implying cooperativity. In **Chapter 2**, we present our novel hypothesis for the mechanism of cooperativity in the cardiac sarcomere. We hypothesize that high mechanical tension in the thin filament hinders the release of calcium from the troponin complex, thus hindering deactivation of the muscle. We propose that a baseline level of chemical cooperativity intrinsic to the thin filament is boosted by mechanical tension. Based on our hypothesis, we have developed a computational model of mechano-chemical interactions in the cardiac sarcomere, called MechChem. We utilized the MechChem model to mimic the conditions in the steady-state isometric contraction experiments. The MechChem model produced calcium-tension curves that fit experimental data better than the typically used sigmoidal curve, so our hypothesis could not be disproved. In addition, simulation results provided a potentially testable hypothesis because our model predicted the existence of a spatial heterogeneity in XB binding, with more XBs forming in areas of the thin filament under greater tension.

The ability of the MechChem model to successfully reproduce data from skinned muscle cell experiments provided the motivation to develop the model further. In a physiological situation, the calcium concentration in the intracellular space does not remain constant but rises and falls in time. The increase in calcium concentration triggers contraction, and the subsequent decrease results in relaxation. In **Chapter 3**, we extended the MechChem model to include transient changes in calcium concentration. Additionally, we introduced a model of the cross-bridge cycle in which myosin heads can cycle between an attached, force-generating state and a detached, non-force-generating state. We utilized the model to mimic isometric twitch experiments in which the sarcomere length was held constant while the calcium concentration changed in time. Experiments have shown that the duration of the relaxation phase of contraction increases with greater developed peak tension during a twitch. MechChem simulation results suggest that the prolongation of the relaxation

phase at higher tension is a result of the tighter binding of a calcium ion to troponin in areas under higher tension, thus delaying the deactivation of troponin.

In **Chapter 4**, we extended the MechChem model further to include the ability of the sarcomere to shorten. Model simulations were performed where the initial sarcomere length was set, and the sarcomere contracted against various afterloads. When the sarcomere generated enough tension to overcome the afterload, it would shorten. When it no longer developed enough tension, the afterload would cause relengthening of the sarcomere, mimicking isotonic twitch experiments. Model-generated results were strikingly similar to experimental results. This was the final developmental step before the model was ready to be integrated within a whole-heart model.

In **Chapter 5**, the MechChem model was integrated within the CircAdapt model of the heart with its closed-loop circulation. The combined model was utilized in an attempt to understand the connection between cross-bridge kinetics and whole-heart function of heart failure patients with left bundle branch block (LBBB) before and after cardiac resynchronization. Our results suggested that while regional ventricular tissue deformation patterns appeared more synchronous and uniform in patients with a reduced cross-bridge cycling rate, their potential for improved outcome after cardiac resynchronization is significantly compromised. In addition, the simulated patterns of left ventricular mechanical discoordination in the electrically dyssynchronous heart showed the same typical characteristics as observed clinically in patients. These results suggest that the integration of the MechChem model within the CircAdapt framework is a promising advancement in multi-scale modeling of cardiovascular dynamics. Moving forward, the integrated model will be a powerful hypothesis-generating tool when understanding cellular level mechanical dysfunction in relation to whole-heart hemodynamics.