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AN IN-SILICO FRAMEWORK FOR CARDIAC DRUG TESTING: HYPERTROPHIC CARDIOMYOPATHY TISSUE MODEL AND THE EFFECTS OF RANOLAZINE ON THE ELECTRO-MECHANIC RESPONSE OF THE VENTRICULAR SEPTUM.

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A multi-scale, multi physics, massively parallel program, called Alya Red [1], has been used to develop an insilico drug-testing framework for high throughput screening of the electro-mechanic effect of drugs at the tissue and organ level. Alya Red is a finite-element, high performance computational platform capable of solving tightly coupled electro-mechanic models from the cell to the tissue level.

Hypertrophic cardiomyopathy (HCM) is the most common monogenic cardiac disorder encountered in the clinic, and is also the most common cause of arrhythmic sudden cardiac death in young athletes [2]. We aim to simulate the electro-mechanic phenotype and understand the arrhythmogenicity of the HCM heart and explore the use of the late sodium blocker ranolazine as a pharmacological treatment to HCM.

The anatomy employed for this preliminary study is a segment of the ventricular septum of a human biventricular geometry obtained from the John Hopkins Database, including its diffusion tensors to define the fiber orientations. The human cell model of electrophysiology employed includes the late sodium channel [3]. Data relative to the electrophysiologic characteristics and pharmacologic responsiveness of human tissue with hypertrophic cardiomyopathy (HCM) was obtained from isolated cells from the septum of from patients with HCM [2]. The cells in the septum were modeled as M cells, but modified to mimic the electrical remodeling due to the HCM. The excitation-contraction and material models used correspond to [4] and [5] respectively.

HCM was modeled by increasing the INaL current. We also tested an increase in Ca(2+) (I(CaL)) currents and decreased repolarizing K(+) currents, related to enhanced Ca(2+)/ calmodulin kinase II (CaMKII) activity [6]. Single cell simulations were set up to reproduce the experimental measurements of action potential duration (APD) and increased INaL current [2]. The model was then incorporated and run in 3-D simulations on a mesh with 52K elements. S1-S2 restitution protocol was performed on the virtual wedge to obtain the restitution curves for both the HCM tissue and after the exposure to ranolazine.

Results in the virtual wedge show the changes on the restitution curves due to the HCM, and to the administration of ranolazine. This preliminary study helps us validate the capabilities of our framework to test drugs and their effect on the electro-mechanics of the myocardium. The future work involves the use of full bi-ventricular anatomies to observe the overall response of the HCM biventricular organ.

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