A framework for anti-arrhythmic drugs testing using a multi-scale computational heart employing Alya Red

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Abstract

Multi-scale computational models are becoming an easy, affordable and useful tool to understand the effects of drugs in the human heart. Detailed, accurate computational models will surely become a useful framework to advance the testing of various drugs in a controlled, analytic fashion in humans, previous to clinical tests. In this work, we establish a framework where we can systematically generate simulations to test the interaction of various channel blocks caused by various drugs. In particular, for the moment, we focus on the sodium channel, the rapid potassium current and the L-type calcium current using a human, transmurally heterogeneous cell model at a normal and heart failure state in a healthy heart's anatomy. Here, we present a general pathway to drug testing using a multi-scale, finite element, high performance computational platform called Alya Red[1, 3].

Mathematical modeling is useful to understand biological systems that are as complicated as the heart. Describing the heart in a quantitative manner can be used to evaluate our understanding of key biological processes that interact in complex manners, thus predicting or explaining some of the clinical physiology or pathology that might have not been evident otherwise.

Simulating a heart beat is a complex problem with multiple strongly coupled scales spanning several orders of magnitude: from the descriptions of cellular ion channels, the arrangement of cells into a spatial description, generally known as myofibre orientation; and up to the geometry of the cardiac chambers. The multi-scale nature of the simulation requires the use of finite elements to compute the solution of ordinary and partial differential equations on a highly refined domain. Therefore, high performance computing is the most adequate framework and tool for solving highly detailed simulations aimed at understanding cardiac physiology.

Here we present a framework to use a multi-scale, coupled electro-mechanics model in order to simulate the effect of anti-arrhythmic drugs in the human heart. The various components of the model need to be carefully pre-processed, for example, to indicate the various regions to establish the heterogeneity of the tissue. This includes not only transmural heterogeneity, but the existence of ischemic or scarred tissue, if included in the simulation protocol. We employ one human biventricular geometry obtained from the John Hopkins Database, including its diffusion tensors to estimate the fiber orientations. The mesh obtained contains approximately 35 million tetrahedral elements, that are coupled in a one-to-one fashion between the electric and mechanic problem. The main setup for this problem, is the varying initial conditions to be set for each of the simulations. It is important to reduce the number of beats to simulate, due to the intensive computations required by the problem. We include a pre-process stage within the computational framework, where the relevant initial conditions are calculated in a single cell at a steady state, then the full 3D model can automatically run with the given necessary initial conditions to provide the important data required after a single beat, or after computing only a few beats.

With this, we can generate various different cases, parting from the anatomy of the human heart in healthy and diseased states. Then by just indicating the heart rate, the cell state (normal or on heart failure), the drug blocking effect on a particular channel and the dosis, we can perform a complete analysis of various possible responses to the therapy, where we can observe the interaction of the varying substrate characteristics and the existence of early afterdepolarisations, torsades-des-pointes and pro-arrhythmic effects.

Keywords: Cardiac computational modelling, multi-scale, arrhythmias, etc.

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