Multiscale modeling of inherited arrhythhmias

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Abstract

Mutations in genes associated to the LQT syndrome render the heart at high risk for the incidence of life threatening arrhythmias. In general the fatal event takes a long time to develop, with a cumulative probability of cardiac death that may reach 80% for symptomatic individuals. Despite this high risk, the therapeutic options are limited. If one of the few drug treatments is not efficient the only alternative is an implantable cardiac defibrillator which has numerous side effects, e.g., pain, false positives, and adverse tissue remodeling.

While protein defects render the myocardium at high risk for cardiac death, there still need a specific trigger to initiate the fatal event. Indeed the lack of knowledge of the nature of this trigger makes this condition difficult to treat. As a matter of fact, clinicians are facing a great individual variability in response to treatment.

Our ultimate goal is through multiscale modeling predict the conditions of initiation of these arrhythmias based on data collected non-invasively on specific patients. Our governing hypothesis is that in LQT2 and LQT3 substrates, a premature beat is generated at zones displaying a steep transitions in protein expressions when traveling impulses cross them along a specific orientation. This makes the arrhythmia dependent upon the origin of the cardiac beat.

We simulate cardiac excitation in portions of the right and left ventricular walls of pig and human hearts. Excitation is modeled with the Bidomain formalism incorporating a detailed cell model (includes calcium cycling). The system of equations is solved with a finite element method at resolutions of 100 μm and 100 μs in space and time respectively. The excitation model includes an accurate, image based, description of the geometry and microanatomy (cardiac fibers and lamina) of the myocardial wall. The associated matrix system is solved with a Dual conjugate gradient method that we recently introduced. The simulations are carried out on massively parallel computers of the Texas advanced computer center (TACC).

Cellular (pig) data and epifluorescence measurements during excitation in slabs excised from the ventricular free walls of the pig are used to validate our excitation model. Then adjustments are made to make the excitation model representative of human excitation. Our plans include the generation of voltage clamp data in cell expression systems in a manner to incorporate the kinetics associated to LQT2 and LQT3 mutations in the excitation model. Indeed we take advantage of nonlinear estimation methods we develop and alleviate all limitations associated to nonlinear least square fitting.

At this stage of development we show that the wavefront orientation within the myocardial wall may change abruptly, and that in some regions the sequence of excitation in zones displaying steep transitions in protein expression may favor the initiation of a premature beat.

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