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Multi-Scale Modeling of Excitation-Contraction Coupling in the Normal and Failing Heart

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Abstract— **Here we describe new computational models of cardiac electromechanics starting from the cellular scale and building to the tissue, organ and system scales. We summarize application to human genetic diseases (LQT1 and LQT3) and to modeling of congestive heart failure.**

I. Introduction

THE excitation-contraction coupling properties of cardiac myocytes isolated from different regions of the mammalian ventricular walls vary considerably, but their effects on integrated ventricular electromechanical function is poorly understood. By using multi-scale models of ventricular electromechanics, we have investigated the consequences of these regional cellular heterogeneities on integrated ventricular function. Multi-scale models have also been useful for elucidating the determinants of ventricular dysfunction in congestive heart failure. We are now testing the ability of these models to predict patient-specific responses to heart failure therapy.

II. Cellular Systems Models

We developed a detailed model of excitation-contraction coupling model with region-dependent parameters for epicardial, mid-myocardial and endocardial myocytes [1, 2]. See Figure 1. We found that heterogeneities in ion currents and calcium handling were not sufficient to explain all the observed differences in single cell twitch dynamics. However, by allowing a higher ratio of fast to slow myosin isoforms in the epicardial myocytes, closer agreement with experimental observations could be achieved [2].

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III. Tissue Models

Incorporating these cell models into three-dimensional models of ventricular action potential propagation, we gained new insights into the mechanisms of arrhythmia formation due to mutations in genes associated with the LQT1 [3] and LQT3 [4] variants of long-QT syndrome. In LQT1, sympathetic stimulation resulted in action potential prolongation mediated by phosphorylation via PKA of the L-type calcium channel that was not compensated for by increased IKs in mutant heart. Conversely in LQT3, associated with mutations in the SCN5A gene, model results suggested that cholinergic activity might increase arrhythmia risk [5].

IV. Organ Models

The effects of heterogeneous excitation-contraction coupling properties of cardiac myocytes (See II. Cellular Systems Models) on ventricular function are uncertain. We embedded the cell-level excitation-contraction coupling model with region-dependent parameters within a simple finite element model of left ventricular geometry to study effects of electromechanical heterogeneity on local myocardial mechanics and global hemodynamics [6]. This model was compared with one in which heterogeneous myocyte parameters were assigned randomly throughout the mesh while preserving the total amount of each cell subtype. The two models displayed nearly identical transmural patterns of fiber and cross-fiber strains at end systole, but showed clear differences in fiber strains at earlier points during systole. Hemodynamic function, including peak left ventricular pressure, maximum rate of left ventricular pressure development, and stroke volume were essentially identical in the two models. These results suggest that in the intact ventricle heterogeneously distributed myocyte subtypes primarily impact local deformation of the myocardium, and that these effects are greatest during early systole.

V. Heart Failure Models

We also modeled ventricular electromechanics in the dyssynchronous failing dog heart and examined the relative impact of dilation, negative inotropy, negative lusitropy and electrical dyssynchrony on regional function and on clinical indices of regional function. To quantify the severity of regional cardiac dysfunction in heart failure patients, investigators have proposed clinical indices of mechanical

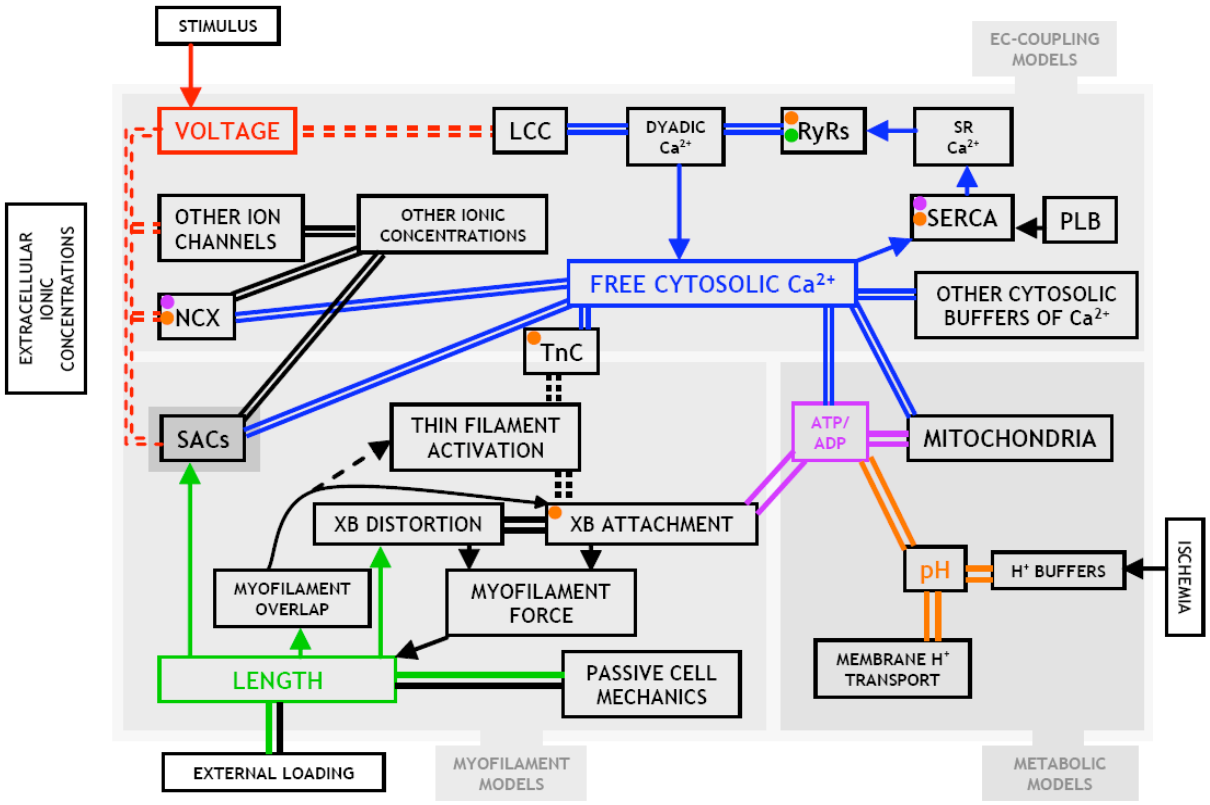

Fig. 1. Schematic of integrated excitation-contraction coupling model of the cardiac myocyte.

dyssynchrony (Dyssynchrony of contraction (DOC)) and dyskinesis (Circumferential Uniformity Ratio Estimate (CURE) and Internal Stretch Fraction (ISF)). The analysis suggested that there are significant interactions between dilation and asynchronous activation affecting regional mechanics: the non-uniformity of fiber shortening throughout the left ventricle during ejection is more sensitive to an asynchronous pattern of activation in a dilated heart than in a normal-sized heart. The clinical indices of regional function CURE and ISF – but not DOC – were sensitive to this interaction. Therefore, CURE and ISF are better measures of dispersion of regional function, whereas DOC is not. These results might explain the good reflection of ISF with contractile capacity that can be recruited by cardiac resynchronization therapy [7] as only a dilated heart has the best potential to remodel reversely significantly.

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