Multiscale Modeling of Inherited Cardiomyopathies and Therapeutic Interventions

Model Credibility Plan Overview: NIH U01 HL133359

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Introduction

The multiscale computational model in this project is designed to address how alterations at the molecular level affect cardiac structure and function at the organ level. The developed model will provide a powerful means for predicting how modulations caused by mutations and pharmaceutical therapies alter global cardiac performance. For instance, a recent study demonstrated that a small molecule drug (MK-461) targeted to cardiac myosin was able to prevent the development of hypertrophy in a mouse model. These results provide evidence that the molecular level activity of myosin is the trigger for hypertrophic response and inhibiting myosin activity can prevent the development of hypertrophic cardiomyopathy (HCM). By incorporating myosin-level mechanisms, the multiscale model has the potential to improve our understanding of how molecular forces evolve during familial cardiomyopathies and, more importantly, predict how new classes of targeted drug therapies will affect long-term cardiac remodeling. Each of the investigators associated with this project recognizes the importance of creating models that are robust, well-justified, and appropriately validated. The research plan has been designed so that model development and biological experiments are synergistic and integrated at multiple levels. Sensitivity analysis will be used to identify model parameters that have particularly significant effects. Conversely, parameters that do not materially impact the simulations will be deemphasized as the project gains complexity. To ensure the reproducibility of our model, we will also make our source code, together with model input such as geometry and myofiber field, freely available.

Validation

The multiscale model spans from molecular to organ-level structural scales and encompasses timescales ranging from milliseconds to months. The research plan will produce experimental data at each of these levels, which directly relate to the model parameters (Table 1). The simulations can therefore be validated at each point by comparing computed predictions to analogous measurements. For example, at the cell level, unloaded sarcomere shortening profiles and Ca2+ transients generated by the MyoSim code will be calibrated against experiments from isolated cells to determine parameters such as thin filament cooperativity. At the organ level, P-V loops and myocardial strain patterns generated by ventricular FE models will be calibrated with experimental data from MRI to determine parameters defining the stress-strain relationship, as well as circulatory model parameters. Parameter estimation will be performed using robust numerical optimization techniques, which utilize hybrid methods that perform both global and local searches of the parameter space.

Validation

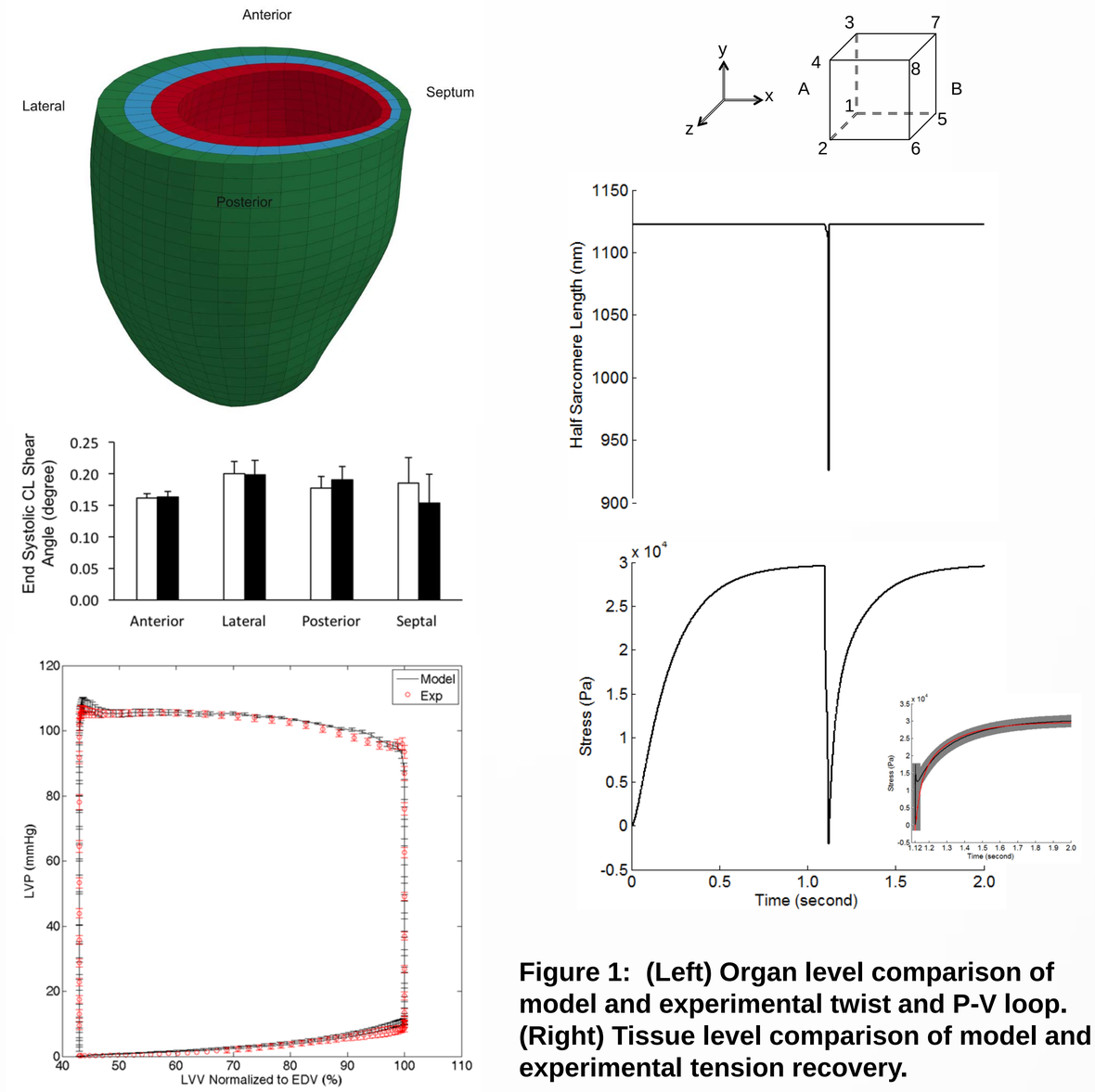

Figure 1: (Left) Organ level comparison of model and experimental twist and P-V loop. (Right) Tissue level comparison of model and experimental tension recovery.

Sensitivity

At present, the research team will employ variance-based methods, which not only assess the influence of individual parameters on model results, but also coupled interactions between parameters. In this technique, simulations will be conducted over a discrete set of parameter combinations (since the parameter space is large), in order to build a piecewise hypersurface that can be analyzed more efficiently with Monte Carlo methods. This approach will allow us to determine which parameters exert the largest influence on clinically-relevant model predicted quantities such as ejection fraction, wall thickness, and circumferential strain.

Structural level	Time scale	Experiments	Date types	Modeling approach	Associated model parameters
Molecular	ms	Stopped flow kinetics; in vitro motility assays; gel electrophoresis; Western blotting	Myosin function, protein isoforms, posttranslational modifications	MyoSim	Myosin rate constants
Cells	ms to s	Unloaded sarcomere shortening profiles, Ca^{2+} transients	Cell-level contractility	MyoSim	Molecular parameters plus thin filament on/off rates, cooperativity, and titin-mediated stiffness
Tissue	ms to s	Histology, Force, tension-pCa tension recovery kinetics, force-velocity curves	Fiber disarray, tissue-level contractility	Small-scale FE system	Cell-level parameters plus collagen-based stiffness
Organ	ms to s (single cardiac cycle)	DENSE MRI, diffusion tensor MRI, pressure catheterization	Ventricular function and geometry, fiber orientation	Organ-scale FE systems	Passive parameters, active force scaling coefficient, Windkessel model parameters
Organ/ Cells	Days to months	Repeat experiments over serial time course	Ventricular geometry/ cell morphology	Growth and remodeling FE systems	Growth tensor F^g; rate constants for sarcomere deposition and removal

Table 1: Validation at multiple temporal and spatial levels