Multiscale Model of Cardiac Muscle Contraction using Langevin Dynamics and Biological Elastic Network Analysis

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Abstract. In this paper, a multiscale model of cardiac thin filament activation and sarcomere contraction is proposed. The model is derived such that it links atomistic molecular scale data of sarcomere protein-protein interactions to the cellular scale. More specifically, we propose to use (i) an elastic network modeling method to solve for the small scale oscillations of tropomyosin protein dynamics on the surface of actin filament, (ii) Langevin dynamics simulations based on stochastic theory to capture large scale oscillations. These two computational methods provide more accurate modeling of the cardiac contraction biophysics and can be used to predict the effects of point mutations on the cardiac contraction.

Introduction

Cardiac diseases are the leading cause of death worldwide. Many of the inherited cardiac phenotype diseases such as hypertrophic and dilated cardiomyopathies are linked to missense mutations in sarcomeric regulatory (tropomyosin, actin, troponin, myosin) proteins. These mutations and post-translational modifications influence not only the molecular contraction dynamics, but also affect cellular-tissue wall mechanics interactions, which in turn affect heart pumping efficiency. The majority of these mutations has found to be distributed on residues located on the tropomyosin-actin interface and many may modify the interaction energy landscape that regulates the Tm positioning and mobility on the surface of actin filaments. These mutations and post-translational modifications influence not only the Tm dynamics, but affects myofilament Ca^{2+} sensitivity and alter cooperative interactions between actin, Tm, troponin-complex and myosin [1].

Tropomyosin (Tm) is an important protein for regulating cardiac contraction. When Tm gets activated, it oscillates in the azimuthal direction over actin surface. The Tm dynamical motions are believed to play an important role in regulating muscle contraction [2]. Computational models including the Markov Chain Monte Carlo MCMC -based algorithms were proposed in several myofilament mechanistic models [3] in order to understand intrinsic mechanism by which the Tm oscillates between the B-C-M states. Although the MCMC computational models were able to predict with acceptable degrees of accuracy the angular positions events of Tm. Yet, the applicability of MCMC simulations in describing how Tm alternates between angular locations is limited. Most importantly, they cannot be used to time-track the intrinsic Tm dynamic motions between regulatory positions or simulate mutation effects, which is a process that requires molecular and stochastic multiscale high fidelity simulations [4].

Results and discussion

The results using Langevin dynamics stochastic simulations will be used to understand how the Tm molecule fluctuates over the actin filament as a function of the azimuthal angle. The results using protein elastic network model will be used to show the dominant eigen values of these oscillations. Both results will help to better understand the role of Tm dynamics during the cardiac thin filament activation process.

References

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