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Effects of Tropomyosin Stiffness on Cardiac Thin Filament Activation using Stochastic Computational Model

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Abstract

In this paper, a coarse-graining mathematical model is given to study cardiac muscle contraction. The model is derived to simulate tropomyosin (Tm) oscillations over the surface of actin filament during cardiac thin filament activation. The model is stochastic in nature and is based on Langevin dynamics principle. The model links the atomistic energy landscape of the Tm-actin interactions in the thin-filament regulatory unites (RUs) to sarcomere-level activation dynamics. The proposed approach provides a more detailed molecular connection between Tm dynamic modes of oscillations, Tm- actin energy landscape, and force-Ca2+ sensitivity of the sarcomere. Furthermore, the model is kept flexible enough such that it can be developed further to investigate how, for example, Tm mutations modify the Tm-actin interaction-energy landscape that regulates the Tm positioning and mobility on the surface of actin filaments.

Keywords: cardiac mechanics, thin filament, tropomyosin, computational medicine, Langevin dynamics, stochastic differential equations.

1 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 the sarcomere 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. Many of these mutations have found to be distributed on residues located on the tropomyosin-actin interface and some may modify the interaction activation energy landscape that regulates the tropomyosin positioning and mobility on the surface of actin filaments. These mutations and post-translational modifications influence not only the tropomyosin dynamics but affects myofilament Ca2+ sensitivity and alter cooperative interactions [1–5].

Tropomyosin (Tm) is an important protein for regulating cardiac contraction. When Tm gets activated, it oscillates in the azimuthal direction over actin surface. These dynamical motions of Tm are believed to play an important role in regulating muscle contraction [6–9]. Computational models including the Markov Chain Monte Carlo MCMC-based algorithms were proposed in several myofilament mechanistic models [10–13] 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 [14].

In this paper, a multi-scale modelling approach to link atomistic molecular simulations of protein-protein (i.e., Tm-actin) interactions in the thin filament regulatory unit to the sarcomere level activation dynamics is proposed. More specifically, we propose to use Langevin dynamics based on stochastic theory to capture large scale oscillations. This computational method approach provides more accurate modelling of the myofilament biophysics and can be used to predict the effects of point mutations on the sarcomere contraction.

2 Methods

A mathematical model that can describe the azimuthal oscillations of the Tm molecules over the surface of the actin filament during thin filament activation is given in this section. The model is derived based on using N-coupled Brownian bodies to approximate a one-half sarcomere, where each body indicates a Tm molecule that is associated with a single functional (RU). A total of N = 26 coupled RUs was used, each RU is comprised of seven-actin monomers, troponin complex (Tn), Tm, and S1 subunit of myosin. Consider analysing the situation when the tropomyosin (Tm) molecule moves azimuthally over the surface of the actin filament during the thin filament activation process. These movements eventually lead to global conformational changes that uncover the myosin-binding sites, hence facilitating muscle contraction. It should be noted that Tm molecule is normally modelled as a flexible coil composed of 26-functional regulatory units (RUs) which are interconnected in a flexible coil model, see Fig1. The equation that governs the dynamics of this motion can be derived from

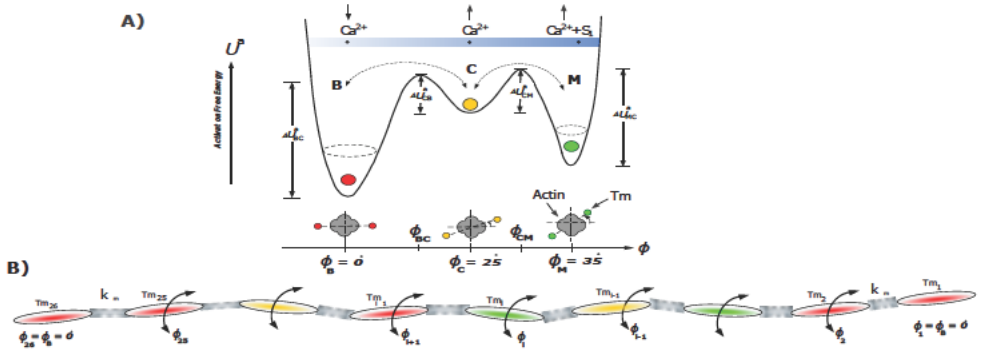

Figure 1: Schematic diagram of the model components. (A) The structure of myofilament main regulatory proteins such as the tropomyosin protein and the associated B-C-M conformational positions and (B) Activation osciallatory dynamics of tropomyosin as governed by a multi-well activation energy potential.

finding the total Hamiltonian (H) quantity of the system. The Hamiltonian of this system can be given as

$$H = \frac{\lambda}{2}\left(\frac{d\phi_i}{dt}\right)^2 + U_i{}^a(\phi_i) + U^e(\phi_1, \phi_2, ...\phi_{26}), \qquad i = 1:26 \quad RUs \tag{1}$$

where ϕ_i is the azimuthal angle, λ is the damping coefficient. U_i^a is an activation potential energy for each RU which can be reconstructed using the Brownian dynamic simulations. The term $U^e(\phi_1, \phi_2, ...\phi_{26})$ represents the stored elastic mechanical energy in the coupled RUs.

Now, using Hamiltonian principles and in the presence of thermal fluctuations, the equations that govern the motions of Tm molecules between B-C-M equilibrium states can be derived from the momentum balance along the reaction direction ϕ_i . Specifically, these equations can be derived by using the canonical form of Brownian dynamics of an overdamped system, which gives rise to the Langevin stochastic dynamics as

$$\lambda\frac{d\phi_i}{dt} + \frac{d}{d\phi_i}[U_i^a(\phi) + U^e(\phi_i)] = \sqrt{2\lambda k_B T}\Gamma_i(t)\ , \phi(t=0) = \phi_B \tag{2}$$

subjected to the following conditions; (i) $\phi(t=0) = \phi_B$, , (ii) $\langle\Gamma(t)\rangle = 0$ and (iii) $\langle\Gamma(t_1)\Gamma(t_2)\rangle = \delta(t_1 - t_2) \qquad \forall\, t \in (0, t_f)$. Where ϕ is the azimuthal angle, λ is the damping coefficient, k_B is the Boltzmann constant, T is the surrounding temperature in kelvin.

The elastic energy of the Tm molecule can be given as

$$U^e = \frac{1}{2}K_{Tm}[{\phi_2}^2 + (\phi_3 - \phi_2)^2 + (\phi_4 - \phi 3)^2 + ... + (\phi_{25} - \phi_{24})^2 + {\phi_{25}}^2] \tag{3}$$

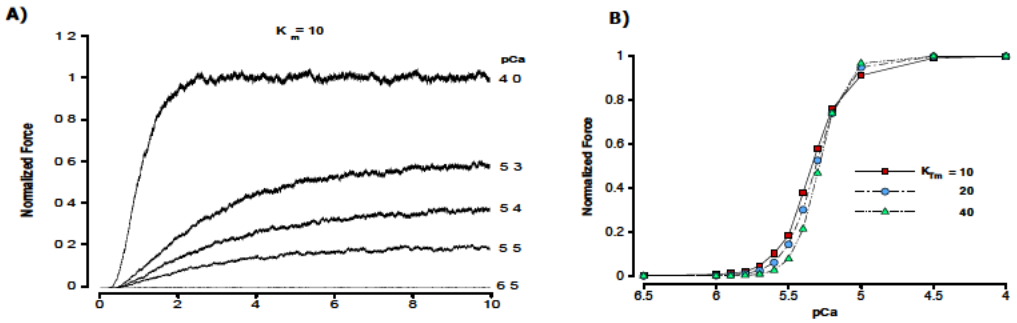

Figure 2: Force development as a result of sarcomere contraction. (A) Time-force development at different levels of Ca^{2+} concentration and for a Tm stiffness $K_{Tm} = 10$ (pN . nm/rad). (B) The effects of Tm stiffness on the force-pCa sensitivity relationship.

The thermal fluctuations $\Gamma_i(t)$ term is modelled using a Gaussian white noise distribution, which has a zero mean and satisfies the fluctuation-dissipation theorem. To implement this model and track each Tm-body oscillations between the B, C, and M states as a function of time, numerical integration to the systems of stochastic ordinary differential equations (SODEs), Eq.(3) is required.

3 Results

A one-dimensional crystal composed of a total number of 26 RUs (i.e., 26 Tm-Brownian bodies) is considered. The angle of the first and last Tm molecules are used to specify the system boundary conditions, where both are set in the blocked state for all the simulation time. It should be noted that the energetic barriers between the equilibrium B-C-M states have been found to strongly depend on the location of the critical roots of the activation free-energy profile, Fig1 A. This implies that the location of these critical roots implicitly represents the effects of free Ca2+ concentrations on the energy barriers. Once the activation free-energy profile is available and an expression for the elastic energy of the system under consideration is obtained.

The coupled SODEs derived in equation (2) can be integrated numerically using the Euler-Maruyama numerical method. To calculate the force development at different levels of Ca2+ concentrations, a one-dimensional crystal composed of 26 RUs is considered. The angles of the first and last Tm molecules are used to specify the system boundary conditions, in which both are set in the blocked state for all simulation times. In Fig. 2A, a sample result of force-time development of the myofilament at different calcium concentration (pCa) values and at Tm stiffness $K_{Tm} = 10$ (pN.nm/rad) is given. The steady state values of these time traces are then obtained. The simulations are obtained at different values of $K_{Tm} = 10, 20, 40$ (pN.nm/rad), to show the effects of Tm stiffness of the steepness of the force-pCa relationships. The results have shown that Tm stiffness can change the force-Ca2+ sensitivity, hence can affect the cooperativity (Hill index) of this relationship, see Fig. 2B.

4 Conclusions and Contributions

In this study, an accurate stochastic ordinary differential equations (SODEs) myofilament model based on Langevin dynamics is derived. The Langevin component of the model could predict the spatiotemporal dynamics of Tm angular movements between the B-C-M equilibrium positions as a result of thermal fluctuations. The model extends our previous myofilament studies, which use Markov-type simulation and nonlinear dynamics to track Tm conformational changes and motions between the B-C-M states [14–18]. The model allows us to accurately simulate steady- state force-pCa relationships and study the effects of Tm stiffness on the cooperative activation. In terms of myofilament cooperativity, the mathematical description of the model includes two sources of cooperativity. The first arises from Ca2+ binding to TnC, which affects the energetic barrier between the B and C states. The second arises from the nearest-neighbor interactions (RU-RU cooperativity), which are represented by using an elastic distortion energy.

In conclusion, the presented coarse-graining mathematical model herein is derived to study Tm oscillations over the surface of actin filament during cardiac muscle contraction using Langevin dynamics simulations. The model links the atomistic energy landscape of the Tm-actin interactions in the thin-filament RU to sarcomere-level activation dynamics. The proposed multiscale approach provides a more detailed molecular connection between Tm dynamic modes of motions, Tm- actin energy landscape, and force-Ca2+ sensitivity of the sarcomere. Furthermore, the model is kept flexible enough such that it can be developed further to investigate how, for example, Tm mutations modify the Tm-actin interaction-energy landscape that regulates the Tm positioning and mobility on the surface of actin filaments. Therefore, this Langevin modelling approach may offer an enhanced mechanistic methodology to describe cardiac muscle contraction in both healthy and diseased subjects. The main contribution of this mathematical modeling approach is the capability of linking the Tm-actin molecular energy landscape interactions to thin-filament scale activation using Langevin dynamics. The underlying idea of this study is based on fundamental theories explaining the molecular interactions of myofilament proteins during cardiac muscle activation.

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