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Continuum Mechanical Modeling of Cardiac Muscle

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Numerical continuum modeling of muscle is a very interesting research topic. In typical continuum materials, the stress is uniquely determined from the strain. However, this rule no longer applies in muscles undergoing contraction. The actomyosin complexes in muscle [1] constantly change their conformations during the contraction phase of events such as attachment, power strokes of the lever arm, and dissociation (Figure 1A). Furthermore, the rates of the transitions depend on the stain of the lever arm (Figure 1B), which is affected by the continuum muscle contraction. In computer simulations of a beating heart, the modeling of these molecular behaviors is necessary for correctly reproducing the muscle contraction. The contractile force in cardiac cells rises when Ca^{2+} ions are released from the sarcoplasmic reticulum (SR), and relaxes when these ions are sequestered back into the SR. In many earlier studies, the temporal change of contractile force under a given Ca^{2+} transient was computed by a system of ordinary differential equations (ODEs). However, the ODEs cannot easily model the stochastic and cooperative behaviors of actomyosin complexes. For example, in a healthy beating heart, the left ventricular pressure (LVP) (Figure 1C, black line) falls to almost zero at the end-systole, but nearly 10% of the peak Ca^{2+} concentration remains in the cytosol (Figure 1C, red line). Furthermore, the LVP falls much more rapidly than the Ca^{2+} concentration. These quick relaxation properties of cardiac muscle are assumed to originate from the cooperative behavior between the neighboring actomyosin complexes and the stochastic power-stroke mechanism of the myosin lever arms, which depends on the strains in the lever arms. Unless we correctly model these molecular properties, we fail to reproduce the quick relaxation of the cardiac muscle. The consequence is insufficient blood-filling into the ventricular cavity during the diastolic phase.

Multiscale Model

Failed attempts to simulate a beating heart by the existing ODE models have motivated our direct simulations of the individual molecules in our beating heart model. To realize this idea, we couple the macroscopic continuum dynamics by the finite element method (FEM) with the microscopic molecular dynamics by the Monte Carlo (MC) method. These two approaches differ on both spatial and time scales. In our approach [2], we embed the sarcomere model (Figure 1D) of actomyosin complexes (Figure 1A) into each tetrahedral element of the FEM (Figure 1E). Here, we assume that a single sarcomere force represents the contractile tension generated by all cardiac cells in the element. Usually, we set the time step as $\Delta T = 1$ ms in the FEM analysis, and subdivide this value into a finer time step $\Delta t = 10\,\mu$s for the MC analysis.

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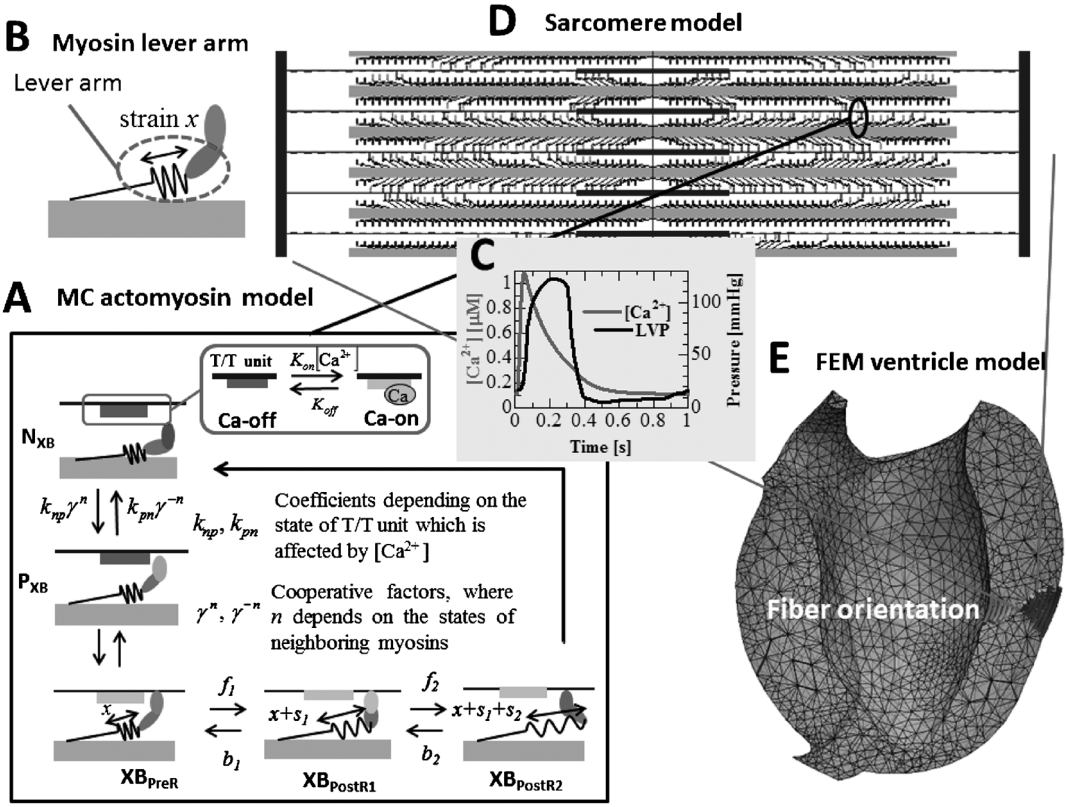

Figure 1 Multiscale modeling. A: MC model of the actomyosin complex. The contraction force is contributed by three attached states (XB_{PreR}, XB_{PostR1} and XB_{PostR2}). The transitions between N_{XB} and P_{XB} are influenced by the states of the T/T unit above the myosin head through the coefficients K_{np}, K_{pn} and the states of the neighboring myosins through the cooperative factors γ^n, γ^{-n} ($\gamma=40$). B: Myosin lever arm. C: Transients of the averaged Ca^{2+} concentration over the ventricle (red lines) and the left ventricular pressure (LVP: black line). D: Sarcomere model composed of actomyosin complexes. E: FEM ventricle model showing the twisted fiber orientations along the transmural line.

Coupling of Molecules and Continuum

In our approach, the macroscopic active stress tensor $\boldsymbol{S}_{act}$ in the finite element time interval $[T, T+\Delta T]$ is implicitly determined, ensuring compatibility between the molecular and continuum virtual works as shown in Figure 2.

To account for the state transitions of the actomyosin complexes during this time interval, we relate the strain rates on three scales (actomoysin complex, sarcomere and continuum). In the FEM analysis, the stress under contractile tension T_f is represented by the second Piola-Kirchhoff stress tensor:

$$\boldsymbol{S}_{act}=\frac{T_f}{\lambda}\boldsymbol{f}\otimes\boldsymbol{f}=\sum_{i,j}\frac{T_f}{\lambda}f_i f_j \boldsymbol{e}_i\otimes\boldsymbol{e}_j, \tag{1}$$

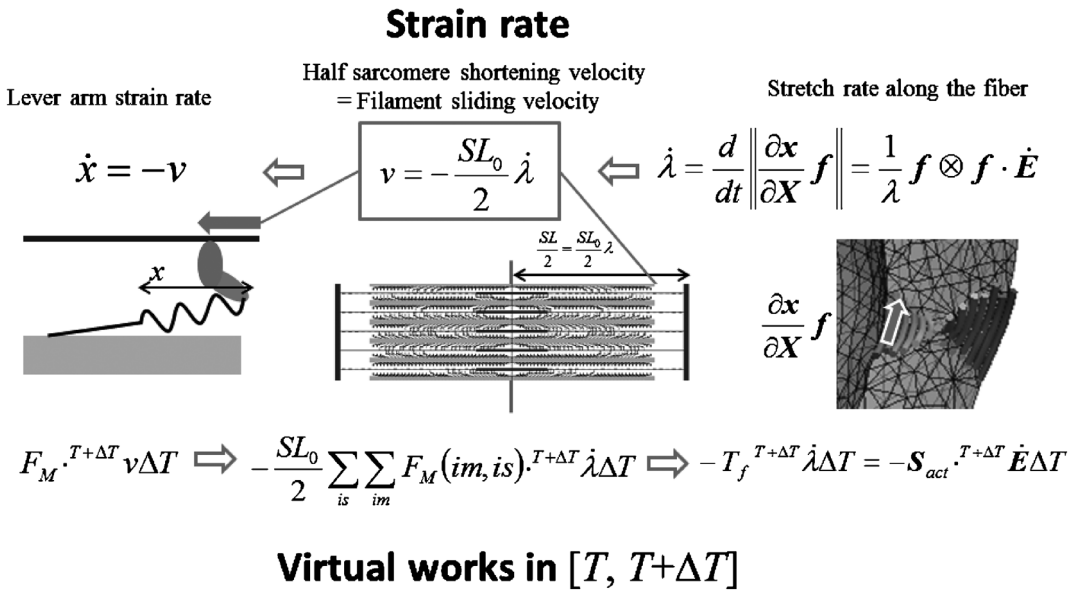

Figure 2 Strain rates in the model (top) and the virtual works (bottom) on the three scales: the actomoysin complex, the sarcomere and the continuum.

where the unit vector $\boldsymbol{f} = \sum_{i=1}^{3} f_i \boldsymbol{e}_i$ denotes the fiber orientation at the material point $\boldsymbol{X}$, and λ denotes the stretch along the fiber orientation $\boldsymbol{f}$ given by

$$\lambda = \left\| \frac{\partial \boldsymbol{x}}{\partial \boldsymbol{X}} f \right\| = \sqrt{\sum_{i,j,k=1}^{3} \frac{\partial x_k}{\partial X_i}\frac{\partial x_k}{\partial X_j} f_i f_j}\,.$$

The insertion of λ into the denominator of (1) is justified by the infinitesimal relationship $T_f \delta\lambda = \boldsymbol{S}_{act} \cdot \boldsymbol{\delta E}$, where $\boldsymbol{E}$ is the Green-Lagrange strain tensor. The contractile tension T_f is computed by summing the molecular forces produced by the actomyosin complexes arranged along the actin filaments in the sarcomere model:

$$T_f = \frac{R_S}{SA_0}\frac{2}{ns}\sum_{is=1}^{ns}\sum_{im=1}^{nm} F_M(im, is).$$

Here, SA_0 (= 1000 nm^2) is the cross sectional area of a single actin filament, R_S denotes the volume ratio of the sarcomere (= 0.5), and nm (= 38) is the number of myosin molecules surrounding the binding sites arranged along one of the two spirals in the actin filament. ns is the number of actin filament samples in the sarcomere model. The force generated by an individual myosin molecule is given by

$$F_M(im, is) = \frac{\Delta t}{\Delta T}\sum_{k=1}^{nt} \delta_{A,k}(im, is) k_M{}^{T+k\Delta t} x(im, is),$$

where the FEM time step interval $[T, T+\Delta T]$ is subdivided into nt MC time steps. $\delta_{A,k}$ takes 1 in the attached case and 0 in the detached case for $k = 1, \cdots, nt$. k_M denotes the spring constant of the

myosin lever arm, and ${}^{T+k\Delta t}x$ is the strain of the myosin lever arm at time $T+k\Delta t$. This strain is a function of the initial strain at the attachment (x_{init}) under the thermal fluctuation, the power stroke from the latest attachment from t_A to $T+k\Delta t$ (${}^{T+k\Delta t}x_{PS}$), and the length change due to the filament sliding:

$$ {}^{T+k\Delta t}x(im, is) = x_{init} + {}^{T+k\Delta t}x_{PS} + \frac{SL_0}{2}\left\{\int_{\min(t_A, T)}^{T} \dot{\lambda} dt + {}^{T+\Delta T}\dot{\lambda}(T+k\Delta t - \max(t_A, T))\right\}. \quad (2) $$

Here, $SL_0/2$ is the unloaded half-sarcomere length that relates the muscle stretch rate along the fiber orientation ($\dot{\lambda}$) to the shortening velocity of the sarcomere ($-SL_0\dot{\lambda}/2$).

x_{PS} is incremented by the working stroke size s during the forward transition from the pre-power stroke to the post-stroke state, and decremented by s in the reversal stroke from the post-stroke to the pre-stroke state. The rate constants of the forward (f) and backward (b) transitions between the pre- and post-stroke states, are determined as it follows the relationship given by the statistical equilibrium:

$$ \frac{f(x)}{b(x)} = \exp\left(-\frac{E_{Post} - E_{\mathrm{Pre}} + k_M((x+s)^2 - x)^2/2}{kT}\right), \quad (3) $$

where k and T denote the Boltzmann constant and the temperature, respectively, and E_{Pre} and E_{Post} are the free energies of the myosin head in the pre- and post-stroke states, respectively. The difference $E_{Post} - E_{\mathrm{Pre}}$ corresponds to the partial transfer of the chemical energy obtained by ATP hydrolysis to the mechanical stress energy generated by the strain increment s. At the current FEM step in $[T, T+\Delta T]$, the filament sliding contribution (third term in the right hand side of (2)) is computed by implicitly assuming the stretch rate $\dot{\lambda}$ at $T+\Delta T$. Through this implicit scheme, we can correctly incorporate the temporal stiffness into the Jacobian matrix, and hence stabilize the Newton-Raphson (NR) iteration in the FEM analysis within a reasonable time step ΔT. Note that the NR steps iteratively reuse the computational results obtained in the MC steps.

Beating Heart Simulation Results

Figure 3 shows the behavior of the sarcomere model (Figure 3B) embedded in the inner layer of the left ventricular free wall (Figure 3A). At the end-systolic phase (range surrounded by the broken lines in Figure 3D, E and F), the relative frequency of the backward to forward transitions increases (Figure 3F) as the sarcomere shortening decelerates (Figure 3E: black line), and the sarcomere contraction finally ends. A quick stretch (Figure 3E: black line) immediately follows the increased frequency of backward transitions (Figure 3F: red line). Together with cooperation among the neighboring myosin molecules, these backward transitions quickly reduce the blood pressure (Figure 3D: red line), facilitating the quick filling of blood into the left ventricle (Figure 3D: black line). Figure 3G presents the contours of the arm strain distribution. In the post stroke state (XB_{PostR2}), the center of the distribution shifts to larger strains towards the end-systolic phase. Such a distribution shift has a major impact on balancing the frequencies of the forward and backward transitions determined by (3).

We are currently developing more detailed molecular models under the post-K supercomputer

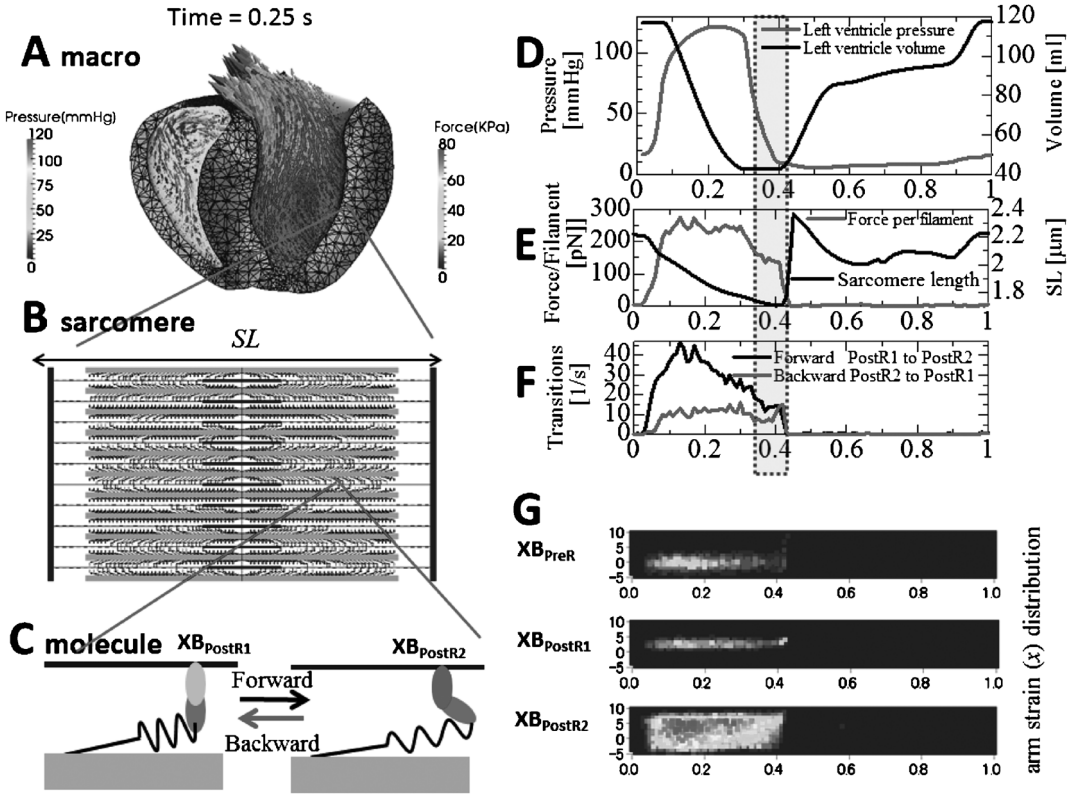

Figure 3 Simulation results of a beating heart. Distribution of the contractile tension T_f (A) and the cross bridges in the sarcomere model embedded in the inner layer (B) at $T = 0.25$ s. Also shown are the time transients of the left ventricular pressure and volume (D), the sarcomere force and length (E), the frequencies of the forward and backward transitions (F), and the strain distributions in the lever arms of the sarcomere model embedded in the inner layer (G).

project*1. This study will provide insights into the molecular-level mechanisms that control the state transitions. Such a study is necessary for linking various mutants of contractile proteins with heart failures.

References

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[2] Washio T, Yoneda K, Okada J, Kariya T, Sugiura S, Hisada T. Ventricular fiber optimization utilizing the branching structure. Int J Numer Method Biomed Eng. 2016; 32(7): e02753.

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