Modeling and simulation of excitation-contraction coupling of fast-twitch skeletal muscle fibers

Monan Wang*, Jiangang Sun and Qiyou Yang

Key Laboratory of Medical Biomechanics and Materials of Heilongjiang Province, Harbin University of Science and Technology, Harbin, Heilongjiang, 150080, China

Abstract.

BACKGROUND: The current excitation-contraction coupling model of fast-twitch skeletal muscle fibers cannot completely simulate the excitation-contraction process.

OBJECTIVE: To solve this problem, this study proposes an excitation-contraction model of fast-twitch skeletal muscle fibers based on the physiological structure and contractile properties of half-sarcomeres.

METHODS: The model includes the action potential model of fast-twitch fiber membranes and transverse tubule membranes, the cycle model of $Ca^{2+}$ in myofibril, the cross-bridge cycle model, and the fatigue model of metabolism.

RESULTS: Finally, detailed analyses of the results from the simulation are conducted using the Simulink toolbox in MATLAB. Two conditions, non-coincidence and coincidence, are analyzed for both the thick and thin myofilaments.

CONCLUSIONS: The simulation results of two groups of models are the same as the previous research results, which validates the accuracy of models.

Keywords: Skeletal muscles, fast-twitch fiber, excitation-contraction coupling, simulation

1. Introduction

At present, the action potential of the sarcolemma and transverse tubule membranes are studied using the Hodgkin-Huxley model and the Goldman-Hodgkin-Katz equation. The inwardly rectifying potassium (Kir) channel, together with the chloride channel (ClC-1), plays a vital role in the skeletal muscle physiology. Current research primarily focuses on the fibrous surface and transverse tubular system (TTS) of amphibians [1], and the measurement of Kir of mammalian skeletal muscle fibers [2–4]. The primary physiological function of mammalian skeletal muscle is to maintain the stability of resting membrane potential and to enable the excitation of electrogenic cells. It is essential to study the properties of Kir in mammalian skeletal muscle fibers to further understand the related muscular diseases in humans [5–7].

In vertebrate skeletal muscle fibers, action potential controls contractile activity by inducing rapid changes of the free $Ca^{2+}$ concentration in the sarcoplasm. $Ca^{2+}$, thus, plays a role in triggering and
regulating skeletal muscle contraction, and its concentration affects contractile force and speed. In order to regulate $Ca^{2+}$ in a myofibril accurately, according to the physiological structure properties of the sarcomere, researchers have used half-sarcomeres and divide its space [8] to analyze the change of $Ca^{2+}$ concentration in the corresponding regions [9–11]. The $Ca^{2+}$ indicator, with low affinity, is microinjected into the sarcoplasm to evaluate the amplitude and time history of regional spatial variation of mean $Ca^{2+}$ concentration [12]. This model can be used to evaluate the movement of $Ca^{2+}$ in myofibrils, the release of $Ca^{2+}$ in sarcoplasmic reticulum, the combination of $Ca^{2+}$ in sarcoplasm, and primary buffers (such as troponin, ATP, parvalbumin, and sarcoplasmic reticulum $Ca^{2+}$ pump). The $Ca^{2+}$ in sarcoplasm is recycled to the sarcoplasmic reticulum by the $Ca^{2+}$ pump.

Skeletal muscle fibers exhibit contractility through the relative sliding of the sarcomere’s thick and thin myofilaments in the myofibril. The sliding process depends on the hydrolysis coupling of ATP and the circulation of the fine filaments, i.e., actin filaments, along the molecules on the head of myosin, forming cross-bridges. In striated muscle fibers, it is believed that tropomyosin and troponin prevent the binding of myosin and actin, which form the cross-bridge circulation and act as doormen. Tropomyosin is the basis of many of actin’s biological activities, and the movement of troponin on the surface of actin is considered critical to the cooperative allosteric regulation of actin. The different positions of the thick and thin myofilaments will affect the speed at which $Ca^{2+}$ and troponin combine and separate [13]. Skeletal muscle fibers become fatigued during the excitation-contraction process, and many factors affect fatigue. Metabolic fatigue is a multi-factored regulation process that includes the accumulation of phosphate, cross-bridge circulation, and reduction of calcium in the sarcoplasmic reticulum [14].

The currently existing excitation-contraction model of fast-twitch muscle fibers cannot simulate the excitation-contraction process completely. To solve this problem, this study proposes an excitation-contraction model for fast-twitch skeletal muscle fibers based on the physiological structure and contractile properties of the half-sarcomere. The study is structured as follows: (1) establishment of an action potential model for fast-twitch muscle fiber membranes and transverse tubule membranes; (2) establishment of the cycle model of $Ca^{2+}$ in myofibril; (3) establishment of the cross-bridge cycle model and the fatigue model of metabolism in half-sarcomeres; and (4) analysis of the results from the excitation-contraction model simulation.

2. Methods

2.1. Modeling of the skeletal fast muscle fiber membrane potential

A two-compartment model was used to simulate the action potential of skeletal fast muscle fibers. The total ionic current on the surface of the muscle fibers is calculated by adding Na$^+$ current ($I_{\text{Na},s}$), K$^+$ delayed rectifier current ($I_{\text{DR},s}$), K$^+$ inward rectifier current ($I_{\text{IR},s}$), Cl$^-$ current ($I_{\text{Cl},s}$), and Na$^+$–K$^+$ current ($I_{\text{NaK},s}$), as shown by Eq. (1):

$$I_{\text{ionic},s} = I_{\text{Na},s} + I_{\text{DR},s} + I_{\text{IR},s} + I_{\text{Cl},s} + I_{\text{NaK},s}$$

Due to the difference between ion channel densities in the T tube and myolemma, the ratio of T tube membrane density to myolemma channel density can be represented by $\eta$. The calculation of ionic current ($I_{\text{ionic},t}$) on the T tube per unit area is then shown by Eq. (2) as:

$$I_{\text{ionic},t} = \eta_{\text{Na}}g_{\text{Na},t}(J_{\text{Na},t}/75) + \eta_{\text{DR}}g_{\text{DR},t}(J_{\text{K},t}/50) + \eta_{\text{IR}}g_{\text{IR},t}(J_{\text{K},t}/50) + \eta_{\text{Cl}} g_{\text{Cl},t}(J_{\text{Cl},t}/75) + \eta_{\text{NaK}}g_{\text{NaK},t}f_t, \tag{2}$$
where \( g_{Na,t} \) is the \( Na^+ \) channel conductance, \( g_{DR,t} \) is the \( K^+ \) channel conductance, \( g_{IR,t} \) is the \( K^+ \) inward rectifier channel conductance, and \( g_{Cl,t} \) is the \( Cl^- \) channel conductance.

The changes in concentration of \( Na^+ \) in cells, \( Na^+ \) in T tube, and \( Na^+ \) in intercellular space are shown in Eqs (3)–(5), using time as the basis. Similarly, the changes in concentration (with respect to time) of \( K^+ \) in cells, \( K^+ \) in T tube, and \( K^+ \) in intercellular space can be obtained.

\[
\frac{dNa_i}{dt} = \frac{-f_T(I_{Na,t} + 3I_{NaK,t} + I_{rest}) - I_{Na,s} + 3I_{NaK,s} + I_{rest}}{1000F\xi_1} \tag{3}
\]

\[
\frac{dNa_t}{dt} = \frac{I_{Na,t} + 3I_{NaK,t} + I_{rest}}{1000F\xi_1} - \frac{Na_t - Na_e}{\tau_{Na_1}} \tag{4}
\]

\[
\frac{dNa_e}{dt} = \frac{I_{Na} + 3I_{NaK} + I_{rest}}{1000F\xi_3} - \frac{Na_t - Na_e}{\tau_{Na_2}} \tag{5}
\]

In Eqs (2)–(5), \( f_T \) represents the proportion of fiber occupied by the T tube, \( \xi_1 \) represents the ratio of volume to surface area of the T tube, \( \xi_2 \) represents the ratio of volume to surface area of cells, \( \xi_3 \) represents the ratio of volume to surface area of intercellular space, \( \tau_{Na_1} \) represents diffusion time constant of the T tube, and \( \tau_{Na_2} \) represents the diffusion time constant of intercellular space.

2.2. Modeling of calcium cycling in skeletal fast muscle fiber

We divided the sarcomere into six geometric regions, which are \( V_1 \), \( V_2 \), \( V_3 \), \( V_4 \), \( V_5 \), and \( V_6 \), as shown in Fig. 1. \( V_1 = 5.5\% V \), \( V_2 = 3.5\% V \), \( V_3 = 6\% V \), \( V_4 = 85\% \left( 1 - \frac{0.75}{l_x} \right) V \), \( V_5 = 85\% \left( \frac{1.75}{l_x} - 1 \right) V \), and \( V_6 = 85\% \left( 1 - \frac{1}{l_x} \right) V \).

A 10-state model is used to describe the release process from the T tube voltage to the Reynolds channel. The ten states consist of five states of four voltage sensor molecules and two states of a Reynolds channel (including five closed states \( C_0 - C_4 \) and five open states). Based on the division of the half-sarcomere regions and the \( Ca^{2+} \) cycle, the change in \( Ca^{2+} \) concentration in \( V_1 \)–\( V_6 \) regions are analyzed, as shown in Eqs (6)–(11), and the model’s parameters are shown in Table 1:
2.3. Modeling of the cross-bridge dynamic in skeletal fast muscle fiber

A 6-state model is used when $Ca^{2+}$ and troponin combine in the non-coincidence region ($V_4$), and the binding site of free troponin ($T_0$) is shown in Eq. (12):

$$T_0 = T_{tot} - Ca_4^T - Ca_4^T - D_0 - D_1 - D_2$$  (12)
In the non-coincidence region \((V_4)\) the function of combining \(Ca^{2+}\) and troponin, \(F_1(Ca_4, T_n)\), is calculated according to Eq. (13):

\[
F_1(Ca_4, T_n) = k_{on}^{T} Ca_4 T_0 - k_{off}^{T} Ca_4 + k_{on}^{T} Ca_4 T_0 - k_{off}^{T} Ca_4 + k_{on}^{T} Ca_4 D_0 - k_{off}^{T} D_1 + k_{on}^{T} Ca_4 D_1 - k_{off}^{T} D_2
\]

(13)

In the coincidence region \((V_5)\), an 8-state model is used. During the process of cross-bridge cycling, the binding site of free troponin \((T_0)\) is shown in Eq. (14):

\[
T_0 = T_{tot} - Ca_4^T - Ca_5^T - D_0 - D_1 - D_2 - A_1 - A_2
\]

(14)

In the coincidence region \((V_5)\), during the process of cross-bridge cycling, the function of combining \(Ca^{2+}\) and troponin, \(F_2(Ca_5, T_n)\), is calculated according to Eq. (15), and the model’s parameters are shown in Table 2.

\[
F_2(Ca_5, T_n) = k_{on}^{T} Ca_5 T_0 - k_{off}^{T} Ca_5 + k_{on}^{T} Ca_5 T_0 - k_{off}^{T} Ca_5 + k_{on}^{T} Ca_5 D_0 - k_{off}^{T} D_1 + k_{on}^{T} Ca_5 D_1 - k_{off}^{T} D_2
\]

(15)

2.4. The fatigue modeling of metabolism in skeletal fast muscle fiber

During the cross-bridge cycle, when the cross-bridge attains a strong binding state from a weak binding state, the ATP will be hydrolyzed to generate ADP and \(P_i\). When the product of solubilities of \(P_{SR}\) and \(Ca_1\) in sarcoplasmic reticulum exceeds 6 mM, it is considered that the \(P_i\) in sarcoplasm goes through the passive channel and is transported to the sarcoplasmic reticulum, at a speed ranging from 30 to 170 \(\mu\)m/s, and combines with \(Ca^{2+}\) in the sarcoplasmic reticulum to generate precipitation. A \(P_{i}\) of 20 mM can reduce 29% of \(Ca^{2+}\) released by sarcoplasmic reticulum. When the muscle fiber contraction ends, \(P_i\) in sarcoplasm can slowly be removed, and the sarcoplasm would then recover to a resting state of 3 mM.

3. Results and discussion

3.1. Analysis of the simulated excitation-contraction model of skeletal fast muscle fiber in conditions of non-coincidence of the thick and thin myofilaments

When skeletal fast muscle fibers are in a resting state, the number of ions in the myofibril remain constant, and their concentrations are shown in Table 3. Calsequestrin in the sarcoplasmic reticulum combines a large amount of calcium ions to be stored. Magnesium ions in sarcoplasm combine at most of
Table 3
Ion concentration in the myofibril at resting

| Ions                              | Concentration | Unit |
|-----------------------------------|---------------|------|
| Calsequestrin (sarcoplasmic reticulum) | 31000         | µM   |
| $Ca^{2+}$ (sarcoplasmic reticulum) | 1500          | µM   |
| $Ca^{2+}$ (sarcoplasm)            | 0.05          | µM   |
| $Mg^{2+}$ (sarcoplasm)            | 1000          | µM   |
| ATP (sarcoplasm)                  | 8000          | µM   |
| Parvalbumin (sarcoplasm)          | 1500          | µM   |
| Troponin (sarcoplasm)             | 240           | µM   |

Table 4
The percentage of ions in the binding site at resting

| Ions                              | $Ca^{2+}$ | $Mg^{2+}$ |
|-----------------------------------|-----------|-----------|
| Calsequestrin (sarcoplasmic reticulum) | 54.55%    | –         |
| Troponin (sarcoplasm)             | 7.1%      | –         |
| Parvalbumin (sarcoplasm)          | 41%       | 54.1%     |
| ATP (sarcoplasm)                  | –         | 90.9%     |

Fig. 2. Release rate of calcium ion in terminal cistern.

the ATP binding sites. The percentages of calcium and magnesium ions in binding sites, respectively, are shown in Table 4.

When a single action potential is transmitted to the transverse tubule membranes, the dihydropyridine voltage receptor (DHPR) on the transverse tubule membranes is coupled to the Reynolds channel on the terminal cistern to control the release of $Ca^{2+}$ on the terminal cistern. According to the mathematical model established in this study, a simulation module is built in Simulink to simulate the release of $Ca^{2+}$ on the terminal cistern membrane under the control of a single action potential. The simulation results are shown in Fig. 2. The terminal cistern began to release the $Ca^{2+}$ 1.4 ms after the action potential was generated, the peak value of the release flow was 204 µM/ms, and the time corresponding to the peak value was 2.8 ms. The simulation results were the same as the mean value detected by Baylor et al., upon calculation of the $Ca^{2+}$ fluorescence in 11 muscle fibers. When $Ca^{2+}$ was released into the sarcoplasm, it bound to the binding sites of the buffer in the sarcoplasm, such as ATP and parvalbumin. In the V4 region, besides ATP and parvalbumin, troponin was also included. Considering the V4 region as an example,
Fig. 3. The simulation module of the binding of calcium ion and troponin.

The simulation process carried out in Simulink can be described as follows: (1) In the V4 region, the calcium ion and troponin are bound with a 6-state model; (2) a blank model editing window is opened in Simulink; (3) the corresponding modules are created; (4) the parameters of the module are set and the values are shown in Table 4; and (5) the modules are connected, as shown in Fig. 3. The simulation processes for the other regions are similar to those employed for the V4 region. The modules built in Simulink are connected to form the excitation-contraction model of fast-twitch skeletal muscle fibers when non-coincidence of the thick and thin myofilaments occur. The module system is shown in Fig. 4. The system parameters of the model are set, the start time of the simulation is set to 0, the stop time of the simulation is set to 30, and the type is set to Variable-step [15].

The simulation results showed that the concentrations of calcium ions in V3, V4, and V5 regions...
increased after 1.4 ms, and the concentrations of free calcium ions in V3 reached a peak value of 24 µM at 3.5 ms. With the diffusion of free calcium ions, the concentrations of calcium ions in V4 and V5 also reached peak values. When the action potential was stopped, the calcium pump began to transport the calcium ions from the sarcoplasm to the sarcoplasmic reticulum, which led to the decrease of the calcium ion concentration in the sarcoplasm, upon which it attained resting state. As shown in Fig. 5, Baylor and Hollingworth measured the change of calcium ion concentration by injecting the calcium ion indicator, furaptra, into the fast-twitch muscle fibers of mice. The peak value of free calcium ion concentration measured was 17 µM, and the time corresponding to the peak value was 4.2 ms. Baylor’s simulation by a multi-compartment model showed that the average free calcium ion concentration in sarcoplasm was 16.3 µM, and the corresponding time was 3.5 ms. The simulation results in this study show that the average free calcium ion concentration in sarcoplasm is 16 µM, and the time corresponding to the peak value is 3.2 ms. The free $Ca^{2+}$ concentration amplitude in this study are similar to the experimental results and Baylor’s simulation results, and the time taken for free calcium ion concentration to reach the
Fig. 5. The average concentration of free calcium ions in sarcoplasm.

Fig. 6. Changes in the concentration of the free troponin binding sites and the binding of troponin and calcium ions in V4.

peak value is slightly smaller than that in Baylor’s study. The small size of the half-sarcomere used in this model may have led to the free calcium ion concentration in the sarcoplasm reaching the peak value more quickly. In the region of V4, Ca\textsuperscript{2+} binds to troponin. Since the thick and thin myofilaments do not overlap, there is no cross-bridge activation, and the 6-state model is used to combine Ca\textsuperscript{2+} and troponin. The simulation results of the binding of Ca\textsuperscript{2+} and troponin in region V4 are shown in Fig. 6. With the combination of Ca\textsuperscript{2+} and troponin, the concentration of tropomyosin-binding site of free troponin decreased, and its lowest value was approximately 170 µM, which was 71% of the concentration of free binding site of troponin in the resting state. The concentration of combining Ca\textsuperscript{2+} and troponin increased, and its maximum value was found to be 70 µM, which was 29% of the combination of calcium ions and troponin at resting state, and the corresponding time was 7 ms. Zot et al. simulated the combination of Ca\textsuperscript{2+} and troponin, and the peak value of free troponin binding site was 75% of that in its resting state. The peak value of the combination of calcium ion and troponin was 25% of that in its resting state, and the time corresponding to the peak value was 10 ms. In comparison to the simulation results of Zot et al. [16], the peak value obtained in this study is slightly higher, and the time corresponding to the peak value is a little shorter. However, the time corresponding to the peak value in this study is closer to that of
Fig. 7. Changes in the concentration of troponin and tropomyosin regulated the units in V4.

Fig. 8. Changes in the concentration of troponin and tropomyosin regulated the units.

Baylor et al. The simulation results of the relationship between troponin and tropomyosin regulated unit concentration is shown in Fig. 7. Only a small number of tropomyosin structures have conformational changes when a single action potential is stimulated.

3.2. Simulation analysis of the excitation-contraction model of skeletal fast muscle fiber in the condition of coincidence of the thick and thin myofilaments

When the half-sarcomere’s length was $l_x \in [1.1, 1.75] \, \mu m$, the thick and thin myofilaments coincided. With the shortening of the half-sarcomere, the number of the coincident thick and thin myofilaments increased; at that time, the structure of the half-sarcomere was divided into 6 regions. In region $V_4$, a 6-state model was used when $Ca^{2+}$ and troponin combines. In region $V_5$, due to the coincidence of thick and thin myofilaments, when troponin was combined with two $Ca^{2+}$ ions, the cross-bridge was activated, so an 8-state model was used in this region.

When $l_x = 1.1 \, \mu m$, the thick and thin myofilaments coincided completely. The conformations of troponin and tropomyosin regulated units are changed by the binding of $Ca^{2+}$ and troponin during a single
contraction. The head of myosin (cross bridge) on the thick myofilament binds to the myosin-binding site on the thin myofilament, actin, by hydrolyzing ATP. The simulation results of the combination of $Ca^{2+}$ and troponin, and cross-bridge activation are shown in Fig. 8. In comparison to Fig. 7, the concentration of troponin and tropomyosin regulated units increased, and the combination of myosin to actin changed the rate of binding and separation of $Ca^{2+}$ and troponin. This promoted the conformation change of tropomyosin and decreased the rate of separation of $Ca^{2+}$ and troponin. The result was consistent with that of Zot’s. The simulation results of the degree of cross-bridge activation are shown in Fig. 9. The degree $A_2$ of cross-bridge activation represents the intensity of the excitation-contraction of the skeletal fast muscle fibers. The simulation results of ATP hydrolysis are shown in Fig. 10, with the circulation of the cross-bridge, and the phosphoric acid produced by hydrolysis of ATP accumulating continuously.

When the length of the half-sarcomere is $l_x \in (1.1, 1.75)$, the model can be used to simulate the change of free calcium ion concentration in the sarcoplasm, the degree of cross-bridge activation, and the $P_i$ produced by ATP hydrolysis in the conditions of different degrees of coincidence of thick and thin myofilaments.
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Conflict of interest

None to report.

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