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Mechanochemical model for myosin II dimer that can explain the spontaneous oscillatory contraction of muscle*

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The spontaneous oscillatory contraction (SPOC) of myofibrils is the essential property inherent to the contractile system of muscle. Muscle contraction results from cyclic interactions between actin filament and myosin II which is a dimeric motor protein with two heads. Taking the two heads of myosin II as an indivisible element and considering the effects of cooperative behavior between the two heads on rate constants in the mechanochemical cycle, the present work proposes the tenstate mechanochemical cycle model for myosin II dimer. The simulations of this model show that the proportion of myosin II in different states periodically changes with time, which results in the sustained oscillations of contractive tension, and serves as the primary factor for SPOC. The good fit of this model to experimental results suggests that the cooperative interaction between the two heads of myosin II dimer may be one of the underlying mechanisms for muscle contraction.

Keywords: muscle contraction, spontaneous oscillatory contraction (SPOC), mechanochemical cycle, cooperative behavior

PACS: 87.15.R–, 87.15.A–, 82.39.–K **DOI:** 10.1088/1674-1056/27/11/118702

1. Introduction

Skinned skeletal and cardiac muscle fibers can exhibit the dynamic behavior of spontaneous oscillatory contraction (SPOC), that is, the sarcomere length changes periodically with the saw-tooth waveform.[1–6] The SPOC is considered to be the third state of muscle, which occurs at the activation level that is intermediate between full activation and relaxation.[7] This phenomenon is observed for both skeletal and cardiac muscle in the physiological conditions realized at around pCa$\sim$ 6 (termed Ca-SPOC),[4] or at high concentration of MgADP (ADP: adenosine diphosphate) with MgATP in the absence of Ca^{2+} (termed ADP-SPOC).[5] Besides, even at full activation level with Ca^{2+}, SPOC also occurs by the addition of inorganic phosphate (Pi).[6] In summary, SPOC is a universal phenomenon that occurs under a wide range of conditions.

Some theoretical models for SPOC have been proposed.[8–15] Julicher and Prost[8] presented a physical mechanism which could lead to the oscillatory motion of molecular motors cooperating in large groups when the system was elastically coupled to its environment. Smith and Stephenson[9,10] presented a concrete model based on the experimentally obtained physiological properties of muscle. This model considered the structural and functional factors inherent to the striated muscle, attributing the essential cause of auto-oscillation to the elastic force provided by titin. In recent years, Sato *et al.*[11–13] put forward several similar theories for SPOC. They assumed that the probability of cross-bridge formation was depended on the lattice spacing between the thin and thick filament, while the lattice spacing decreased with the increase of the sarcomere length. Based on the two-state ratchet mode, Li and Wang[14] studied the dynamics of collective myosin II motors. The model results showed that spontaneous oscillations could be generated if the system was elastically coupled to its environment. All the above models help us understand SPOC in different ways, but these theories involve little about the mechanochemical cycle of myosin, failing to exam the dependence of SPOC on the chemical conditions in the experiments. Guo and Luo[15] introduced a chemical kinetic model to describe the muscle contraction and SPOC, considering the dependence of chemical rate constants on the sliding velocity of myofilament and the activation level of muscle. Nevertheless, this model attributed the agent of SPOC to the external factors.

Muscle contraction results from cyclic interactions between the contractile proteins myosin and actin, driven by the turnover of adenosine triphosphate (ATP). Knowing the mechanochemical cycle process of myosin is critical for understanding the mechanism of muscle contraction. Myosin II is a dimeric protein with two heads. The mechanochemical cycle for single myosin head has been intensely studied, but the role of the second head in the myosin II and whether the interhead action will affect the rates in the ATPase cycle

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are still uncertain.[16] Most models for muscle contraction assumed that the two heads of myosin II acted independently from each other, thinking little about the effects of the inter-head action on the mechanochemical cycle. In recent years, however, the single molecular experiments showed that both the inter-molecular force and the external load on molecular motors could greatly affect the rates of the mechanochemical cycle.[17–20] In addition, some experimental results suggested different forms of cooperative behavior between the two heads of myosin II.[21–25] Thus, myosin II dimer may show some different mechanochemical characteristics from a single myosin head.

In this paper, we take into account the effect of cooperativity between the two heads on the rates of the mechanochemical cycle, and propose a mechanochemical model for myosin II. This model gives all possible states of myosin II dimer and the transition between these states. According to mass action law, the proportions of enzyme species (the myosin II dimmers in different states) are calculated. To our surprise, if we assume that the attached myosin heads will help the partner heads rapidly attach to the actin filament,[25] the proportion of myosin II dimers in different states will periodically change with time, which leads to the sustained oscillations of contractive tension and serves as the major contribution to SPOC. As a check on the model, the equation of force balance for SPOC under isotonic conditions is built, by which the time-dependent change in the sarcomere length is calculated. The simulation results are consistent with the experimental observations. This theoretical work may throw some light on further understanding of muscle contraction. Furthermore, since the step manner and cooperating mechanisms of myosin II are different from those of kinesin, myosin V, and cytoplasmic dynein, the present mechanochemical model supplies a new quantitative analysis method to study the mechanism of cooperative behavior in systems of molecular motors.

2. Methods

2.1. The mechanochemical cycle model for myosin II dimer

In order to produce contractive tension, myosin II couples a chemical cycle of ATP hydrolysis to a mechanical actin–myosin interaction. Even at the simplest level, a minimal chemical cycle involves ATP binding, hydrolysis, and subsequent release of Pi and ADP.[26,27] Many models for the mechanochemical cycle of single myosin head have been proposed.[28–31] To study the cooperative interaction between the two myosin heads and the effect of product concentration on SPOC in a simple way, this paper adopts the four-state mechanochemical cycle model for single myosin head, as shown in Fig. 1.

In Fig. 1, S is substrate (ATP), D is product (ADP), the associated states of myosin heads to thin filament are shown by squares, and the dissociated states by circles. The number 1 denotes the step of myosin heads binding to the actin filament in the absence of ATP, while its reverse process is marked as number 2. The step 1 may be due to the electrostatic force between myosin heads and actin filaments when the binding sites have been active by Ca^{2+} or ADP. The step 2 partly results from the drag force created by the relative sliding between the thin filament and the thick filament.[32] The number 3 denotes the step of ATP binding to the myosin heads and the ATP-myosin complex dissociating from thin filament, and the reversal process of this step is usually negligible in the presence of a sufficiently high ATP concentration. The number 4 denotes the step of power stroke, including the states of ATP hydrolysis and Pi release; the number 6 denotes the step of ADP release; the steps 5 and 7 are the reversal process of 4 and 6, respectively.

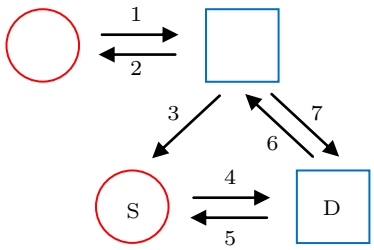


Fig. 1. (color online) The four-state mechanochemical model of single myosin head.

The mechanochemical cycle models of single myosin head neglect the cooperative behavior between the two heads. But different forms of cooperative behavior have been proposed to interpret the experimental results. One type of the cooperative behavior is positive cooperativity, that is, the binding of one head promotes the attachment of the second head. This positive cooperativity helps to explain the apparently faster attachment rate of cross-bridges during muscle stretch and shortening.[25] Based on these facts, this paper takes the two heads as an indivisible whole and proposes a mechanochemical model for myosin II dimer, as shown in Fig. 2.

In Fig. 2, X_i represents the states of myosin dimer, k_i are the rate constants. Since each head of the myosin II dimer has four states (see Fig. 1), the myosin dimer with two heads shares a total of sixteen states, and the sixteen states can be simplified to ten states. From these ten states, four mechanochemical cycles can be constructed, marked as 1, 2, 3, and 4, respectively, which are the same as the cycles shown in Fig. 1. All state transitions (indicated by dotted lines) belonging to cycle 4 are ignored by this paper because the state X_{10} is seldom found in the experiments of muscle contraction.[16] Although there are still various transitions between other states in cycle 4, such as $X_7 \leftrightarrow X_8$ and $X_8 \leftrightarrow X_9$, these state transitions outside of the mechanochemical cycle are insignificant relative to those state transitions within the cycles.

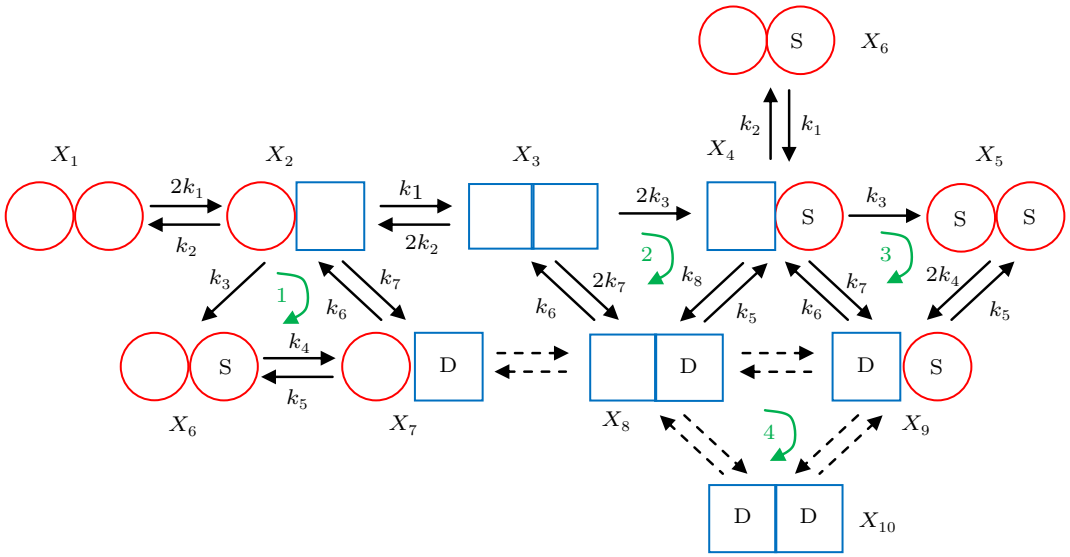


Fig. 2. (color online) The ten-state mechanochemical model for myosin II dimer.

In this model, the cooperative behavior between the two heads is characterized by the effect of inter-head interaction on the rates in the chemical cycle, and it is expressed quantitatively by the ratio of k_8/k_4. Here, the constant k_4 is the binding rate of single myosin head occupied by ATP to thin filament, and k_8 is the association rate of single myosin head while another head has been attached to thin filament. For the mechanochemical cycle model of single myosin head, the value of k_8 is equal to k_4. But in the proposed model for myosin II dimer, the value of k_8 is several times larger than k_4.

According to the mass action law, the set of chemical dynamics equations describing the graph in Fig. 2 can be written as

$$\begin{aligned}
\frac{\mathrm{d}x_1}{\mathrm{d}t} &= -2k_1x_1 + k_2x_2,\\
\frac{\mathrm{d}x_2}{\mathrm{d}t} &= 2k_1x_1 - k_2x_2 - k_1x_2 + 2k_2x_3 - k_3x_2 + k_6x_7 - k_7x_2,\\
\frac{\mathrm{d}x_3}{\mathrm{d}t} &= k_1x_2 - 2k_2x_3 - 2k_3x_3 + k_6x_8 - 2k_7x_3,\\
\frac{\mathrm{d}x_4}{\mathrm{d}t} &= k_1x_6 - k_2x_4 + 2k_3x_3 - k_3x_4 - k_8x_4 + k_5x_8 + k_6x_9 - k_7x_4,\\
\frac{\mathrm{d}x_5}{\mathrm{d}t} &= k_3x_4 - 2k_4x_5 + k_5x_9,\\
\frac{\mathrm{d}x_6}{\mathrm{d}t} &= k_3x_2 + k_2x_4 - k_1x_6 - k_4x_6 + k_5x_7,\\
\frac{\mathrm{d}x_7}{\mathrm{d}t} &= k_4x_6 - k_5x_7 - k_6x_7 + k_7x_2,\\
\frac{\mathrm{d}x_8}{\mathrm{d}t} &= 2k_7x_3 - k_6x_8 + k_8x_4 - k_5x_8,\\
\frac{\mathrm{d}x_9}{\mathrm{d}t} &= -k_6x_9 + k_7x_4 + 2k_4x_5 - k_5x_9,
\end{aligned} \tag{1}$$

where x_i is the proportion of various myosin dimer states and satisfies the following equation:

$$x_1 + x_2 + x_3 + x_4 + x_5 + x_6 + x_7 + x_8 + x_9 = 1. \tag{2}$$

2.2. The reaction diffusion equation of ATP inside myofilament

The adenine nucleotides are transported through skeletal muscle fibers during muscle activation, and the myofilament lattice significantly reduces the diffusion of adenine nucleotides.[33–35] As a result, from the outside of myofilament to the center of myofilament, the ATP concentration varies from place to place. Due to the reaction–diffusion effect, the concentration of ATP inside myofilament may change with time. Thus, the average concentration of ATP in the local neighborhood of myosin active sites, y, is a time-dependent variable. Since the influence of myofilament lattice on the diffusion process is very complex, it is difficult to establish the reaction–diffusion equation accurately. The focus of this paper is to study the effect of cooperation between two myosin heads on the mechanochemical cycle. Therefore, the detailed analysis of the diffusion process is not conducted, but only a relatively simple mathematical expression is given below.

The diffusion effect of ATP is mainly reflected in the radial direction of muscle fibers. According to Fick's law, the diffusion of ATP follows the equation

$$J = -D\frac{\partial u}{\partial x}. \tag{3}$$

Here, J is the diffusion flux which measures the amount of diffusion material substance per unit cross-sectional area perpendicular to the diffusion direction, D is the diffusion coefficient, and $\partial u/\partial x$ is the concentration gradient at this cross-section.

Assuming that the volume of myofilaments is V, the side area is A, and the average concentration of ATP in myofilament is y, then the amount of ATP diffused into the muscle

fiber per unit time is

$$\frac{\partial(\mathrm{ATP})}{\partial t} = \frac{\partial(yV)}{\partial t} = JA = -DA\frac{\partial u}{\partial x}. \tag{4}$$

From Eq. (4), it can be derived that

$$\frac{\partial y}{\partial t} = -\frac{A}{V}D\frac{\partial u}{\partial x}. \tag{5}$$

If the shape of the myofilament is a cylinder with a length of l and a radius of r, then

$$\frac{\partial y}{\partial t} = -\frac{A}{V}D\frac{\partial u}{\partial x} = -\frac{2\pi rl}{\pi r^2 l}D\frac{\partial u}{\partial x} = -\frac{2D}{r}\frac{\partial u}{\partial x}. \tag{6}$$

There is still no experimental data on the concentration gradient of ATP diffusion in the muscle fibers. For the sake of simplicity, we assume that the concentration gradient is equal everywhere inside the muscle fibers, position-independent, but only as a function of the average ATP concentration y. So

$$\frac{\partial u}{\partial x} = \frac{u_2(y) - u_1(y)}{x_2 - x_1}, \tag{7}$$

where $u_1(y)$ is the concentration of ATP in the solution outside the myofilament, $u_2(y)$ is the concentration of ATP in the center of myofilaments, and $x_2 - x_1$ is the distance that ATP diffuses within the myofilaments. Because the average ATP concentration y is independent of the variable x, equation (6) can be written as

$$\frac{\partial y}{\partial t} = \frac{\mathrm{d}y}{\mathrm{d}t} = \frac{2D}{r}\frac{u_1(y) - u_2(y)}{x_2 - x_1} = \frac{2r}{x_2 - x_1}\frac{D}{r^2}(u_1(y) - u_2(y)). \tag{8}$$

In the experiments of SPOC, the concentration of ATP outside the myofilaments is constant. Here, suppose its value is a mM. The ATP concentration in the center of myofilaments is less than the average concentration of ATP due to the reaction–diffusion effect. For simplicity, let us set $u_2(y) = by$, where b is the scaling factor between 0 and 1. Thus, due to the diffusion effect, the change in the concentration of ATP per unit time satisfies the following equation:

$$\frac{\mathrm{d}y}{\mathrm{d}t} = \frac{2r}{x_2 - x_1}\frac{D}{r^2}(a - by). \tag{9}$$

Considering that the values of $x_2 - x_1$ and r are in the same order of magnitude, if the diffusion coefficient D is properly chosen, equation (9) can be simplified to

$$\frac{\mathrm{d}y}{\mathrm{d}t} = \frac{D}{r^2}(a - by). \tag{10}$$

Equation (10) indicates the amount of ATP that diffuses into the myofilament per unit time.

According to Eq. (1), the amount of ATP consumed by myosin heads per unit time should be expressed as

$$\frac{\mathrm{d}y}{\mathrm{d}t} = ck_3(x_2 + 2x_3 + x_4) = cK_3y(x_2 + 2x_3 + x_4). \tag{11}$$

Here, c is the concentration of myosin in muscle, k_3 is the first-order rate constant of ATP binding to myosin, and K_3 is the second-order rate constant of ATP binding to myosin. So, k_3 is the result of multiplying K_3 by y, namely, $k_3 = K_3y$. Combining Eqs. (10) and (11), the value of y can be calculated approximately by the following equation:

$$\frac{\mathrm{d}y}{\mathrm{d}t} = \frac{D}{r^2}(a - by) - cK_3y(x_2 + 2x_3 + x_4). \tag{12}$$

2.3. The force equation of SPOC under isotonic condition

The SPOC is often studied under isotonic and isometric conditions. Yasuda *et al.* made a deep research into SPOC and got the time-dependent change in the sarcomere length (SL) under the isotonic condition.[1] To check the proposed mechanochemical model of myosin dimer, the present work establishes the kinetic equation describing the force balance along the myofilament, as shown by

$$F + \eta\frac{\mathrm{d}l}{\mathrm{d}t} + F_\mathrm{k} - F_\mathrm{ex} = 0, \tag{13}$$

where F is the muscle contraction force that can be expressed as follows:

$$F = \beta nF_0. \tag{14}$$

Here, F_0 is the force generated by a power stroke, and n is the number of power strokes produced by lots of myosin heads in one sarcomere. Because not all the power strokes will occur at the same time, the macroscopic muscle contraction force F is not equal but proportional to nF_0. The proportionality coefficient between F and nF_0 is β.

In Eq. (14), the number of power strokes n can be written as

$$n = q(x_4 + x_5 + x_6)(l_\mathrm{m} - l)/s_0. \tag{15}$$

Here, l is the sarcomere length changing with time, l_m is a constant equal to the sarcomere length without overlap between the thick and thin filaments, $l_\mathrm{m} - l$ stands for the overlap length, s_0 is the average interval between the adjacent myosin heads along the thick filament, and $x_4 + x_5 + x_6$ represents the fraction of myosin heads in the pre-power-stroke state. The probability of cross-bridge formation, q, is closely related to the sarcomere length l.[11] In most cases, the longer the sarcomere length l, the bigger the value of q. For simple, this paper assumes that the probability of cross-bridge formation is directly proportional to the square of l/l_0, that is

$$q = q_0(l/l_0)^2, \tag{16}$$

where l_0 is the sarcomere length in the relaxed state, and q_0 is the probability of cross-bridge formation corresponding to the length of l_0.

The second term in Eq. (13), $\eta\frac{\mathrm{d}l}{\mathrm{d}t}$, represents the friction force due to the relative sliding of the thin and thick filaments, where η is the fiction coefficient.[36]

The last two terms in Eq. (13), $F_{\rm k}$ and $F_{\rm ex}$, represent the passive force originated from the elastic element in the myofibril and the external force, respectively. $F_{\rm ex}$ is a constant at the isotonic condition. According to the literatures,[37,38] $F_{\rm k}$ can be expressed as a function of l

$$F_{\rm k}=\frac{1}{3}\left(18l^3-115l^2+255l-188\right). \tag{17}$$

Substituting Eqs. (14) and (17) into Eq. (13), it is deduced that

$$\frac{{\rm d}l}{{\rm d}t}=-\beta nF_0/\eta+\left(F_{\rm ex}-\frac{1}{3}\left(18l^3+115l^2-255l+188\right)\right)\Big/\eta. \tag{18}$$

Equation (18) gives the time-evolution relationship for the SL under the isotonic condition.

3. Results and discussion

3.1. The proportions of myosin II dimer in different states

To analyze the cooperative effects of the two heads of myosin II dimer, the proportion of myosin II dimer in different states is numerically calculated for given specified rate constants. Table 1 shows the experimentally measured and estimated range of rates for the steps in the mechanochemical cycle and the actual values employed in our model analyses.

The constants k_1 and k_2 are related to the level of muscle activation, which depends on the concentration of ADP and Ca^{2+}. The value of k_1 is taken as 0.1 s^{-1}, while k_2 changes with various muscle active conditions.[39,40] The actual value k_2 employed in our model is 0.5 s^{-1}.

The rate k_3 is the first-order rate constant of ATP binding to myosin, and K_3 is the second-order rate constant of ATP binding to myosin. So, $k_3 = K_3 y$, where y is the average concentration of ATP inside the myofilament. The rate constant K_3 is about 1×10^6 $M^{-1}\cdot s^{-1}$–8×10^6 $M^{-1}\cdot s^{-1}$,[40–43] and the concentration of adenine nucleotides is usually reported in units of mM. As a result, the rate K_3 ranges from 1000 $mM^{-1}\cdot s^{-1}$ to 8000 $mM^{-1}\cdot s^{-1}$.

The constant k_4 is the binding rate of single myosin head occupied by ATP to thin filament, and k_8 is the association rate of single myosin head while another head has been attached to thin filament, as shown in Fig. 2. Some experimental results suggested that the binding of one head promotes the attachment of the second head during muscle stretch and shortening. Therefore, the rate k_8 may be several times of k_4. In this work, the value of k_4 is taken as 22 s^{-1} [40,44] and the ratio k_8/k_4 is in the range of 5–10.

The rate constant k_5 is determined by the inverse process of ATP hydrolysis, and the rate of 1 s^{-1}–10 s^{-1} for k_5 is adopted by this work.[40,42–44] The constants k_6 and k_7 are related to the reversible steps of ADP release. In the experimental research by Yasuda *et al.*, the concentration of ADP is 4 mM. As the second-order rate constant of ADP binding to myosin (K_2) is about 1×10^5 $M^{-1}\cdot s^{-1}$–5×10^5 $M^{-1}\cdot s^{-1}$,[41,44] the rates of 800 s^{-1} and 200 s^{-1} are used for k_6 and k_7, respectively.[40,46]

Table 1. Model parameters.

Parameter	Value	Ref.
k_1	0.1 s^{-1}	[45]
k_2	0.5 s^{-1}	[39], [40]
K_3	5000 $mM^{-1}\cdot s^{-1}$	[40]–[43]
k_4	22 s^{-1}	[40], [44]
k_5	10 s^{-1}	[40], [42]–[44]
k_6	800 s^{-1}	[40], [46]
k_7	200 s^{-1}	[41], [44]
k_8	200 s^{-1}	
D	100–200 $\mu m^2\cdot s^{-1}$	[34], [35]
r	1–2 μm	[1]
a	0.2 mM	[1]
b	0.1	
c	0.5 mM	[47]
l_0	1.8–2.2 μm	[48], [49]
s_0	14.34 nm	[50]
$l_{\rm m}$	3.87 μm	[48], [49]
F_0	5.5 pN	[51]
η	0.1 pN·s·m^{-1}	[36]
q_0	0.2	[11]
β	0.1	[52]

The diffusion coefficient of small molecules in solution is around 10^{-8} m^2/s–10^{-9} m^2/s, and the radius of myofilament used in experiments is in the ranges of 10^{-5} m–10^{-6} m. Referring to the related literature,[1,34,35] the value of D/r^2 ranges from 10 to 100 in our calculation. The concentration of ATP in solution, a, is 200 μM, while the ratio coefficient b varies between 0.1 and 0.3. The concentration of myosin in skeletal muscle, c, is about 0.15 mM–0.5 mM.[47]

Substituting the above parameter values into Eqs. (1) and (12), the numerical solution of x_i versus t is given in Fig. 3.

The numerical simulation results show that the proportion of myosin II dimers in different states, x_i, periodically changes with time. The muscle contraction force is proportional to the number of power strokes, which is mainly decided by x_5 and x_6 in the given activation level. Thus, the force cyclically changes with time, and this is the basic reason for SPOC. It is also found that all the values of x_i tend to be constants if the rate of k_4 is equal to k_8. This brings about the conclusion that one of the necessary conditions for SPOC is $k_8 > k_4$. The significant difference between k_4 and k_8 is the key factor that results in the remarkable nonlinear behavior in the muscle system. This suggests that the inter-head cooperative behavior may play a critical role in muscle contraction.

The simulation results also show that the concentration of the ATP around the local area of active site changes periodically with time, as shown in Fig. 4. In most of the experiments to study SPOC, the concentration of the ATP in solution

outside of myofilament was fixed to a certain value. The previous theoretical studies about SPOC, therefore, have never taken the concentration of the ATP as a variable. These theories may ignore the diffusion of the ATP from the solution to myofibril. Considering the diffusion and the consumption of ATP inside myofilament, this paper establishes the reaction–diffusion equation about ATP. The numerical results indicate that the concentration of ATP inside myofilament periodically varies over time. This is a new discovery that needs to be validated.

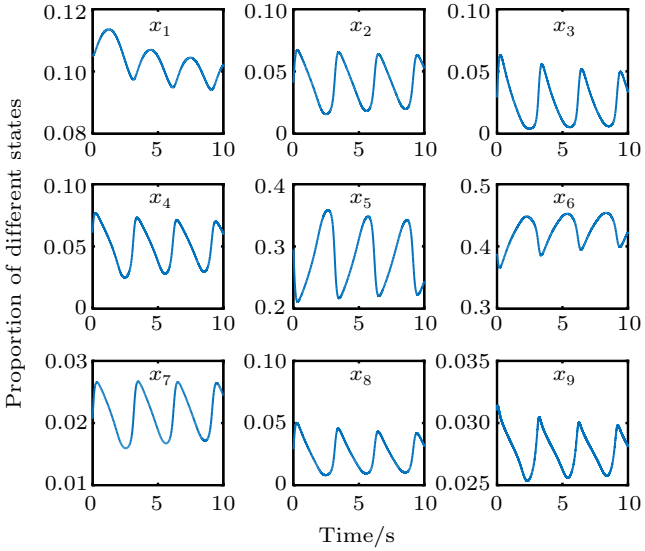


Fig. 3. (color online) Proportion of myosin II dimer in different states. The values of rate constants are $k_1 = 0.1$ s^{-1}, $k_2 = 0.5$ s^{-1}, $K_3 = 5000$ mM^{-1}·s^{-1}, $k_4 = 22$ s^{-1}, $k_5 = 10$ s^{-1}, $k_6 = 800$ s^{-1}, $k_7 = 200$ s^{-1}, $k_8 = 200$ s^{-1}, $D/r^2 = 80$, $a = 0.2$ mM, $b = 0.1$, and $c = 0.5$ mM. The initial values of x_i are $x_1(0) = 0.105$, $x_2(0) = 0.041$, $x_3(0) = 0.029$, $x_4(0) = 0.061$, $x_5(0) = 0.295$, $x_6(0) = 0.388$, $x_7(0) = 0.021$, $x_8(0) = 0.029$, and $x_9(0) = 0.031$; $y(0) = 0.039$ mM.

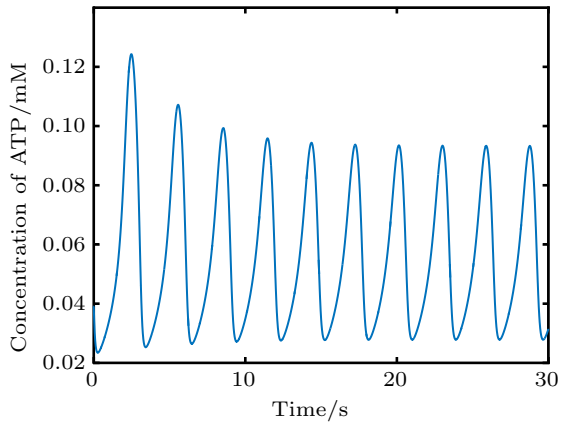


Fig. 4. (color online) The time-dependent change in ATP concentration.

3.2. The time-dependent changes in sarcomere length

The time-dependent changes in sarcomere length are calculated by Eq. (18). The parameter values employed in Eq. (18) are shown in Table 1. The values of l_m, l_0, and s_0, taken from rabbit psoas, are 3.87 μm–3.89 μm, 1.8 μm–2.2 μm, and 14.34 nm, respectively.[48–50] The force generated by a single myosin head, F_0, is about 5 pN–6 pN.[51] The external force, F_{ex}, ranges from 1.83 N/m^2–3.27 × 10^4 N/m^2 in the experiment by Yasuda *et al.*, corresponding to about 15 pN–25 pN for a single thin filament (the number of which is 1.2×10^{15}/m^2 in myofibril[53]). The friction coefficient, η, is taken as 0.1 pN·s·m^{-1}–1.1 pN·s·m^{-1} in our simulation.[36] The value of the probability of cross-bridge formation at relaxation, q_0, is taken as 0.2.[11] Referring to the experimental value of duty ratio,[52] the value of 0.1 for β is used.

Substituting the above related parameter values into Eq. (18), the numerical simulation of SL versus t at F_{ex} = 19 pN, 21 pN, and 23.5 pN are given in Fig. 5. The SL–time relationship displays as the saw-tooth waveform, the period of which is about 3 s and does not rely on the external force, while the amplitude of oscillation decreases with the increase of the external force. These results are similar to the experimental observations shown in Fig. 4 of the literature.[1]

In the process of muscle contraction, the lattice spacing between the thin and thick filaments varies with the sarcomere length. So the cross-bridge formation probability coupling to the muscle structure is not a constant. If the coupling effect is not taken into account, the value of q will hold as a constant q_0 and will never change with the sarcomere length. On this occasion, the numerical simulation shows that the range of SL oscillation will be quite different from the experimental data, or the distortion in wave shape of SPOC may be observed. It implies that the coupling relation between the muscle structure and the probability of cross-bridge formation is an important element for SPOC, but not the intrinsic factor.

In addition, the simulation results show that the term F_k in Eq. (17), the passive force originated from the elastic element, is not essential to SL oscillation, although the value of F_k can influence the amplitude of SL oscillation. This conclusion is consistent with the related experimental observations.

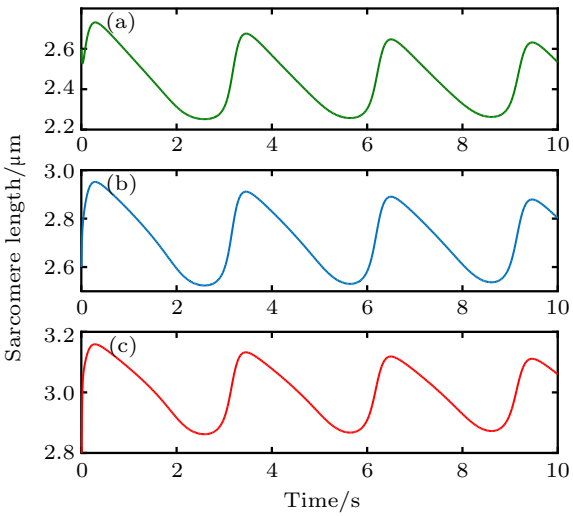


Fig. 5. (color online) The time-dependent sarcomere length during isotonic SPOC under different external loads. The average external loads are (a) 19 pN, (b) 21 pN, and (c) 23.5 pN. The initial values of x_i and y are the same as those in Fig. 3.

As a further check on our model, we test the dependence of SPOC on the concentration of ADP ([ADP]), that is, the change in SL–time relationship with the parameters of k_1 and k_7. The parameter k_7, the result of multiplying [ADP] and K_2 (the second-order rate constant of ADP binding to myosin), characterizes the influence of [ADP] on the transition processes, $X_2 \to X_7$, $X_3 \to X_8$, and $X_4 \to X_9$. The parameter primarily reflects the effect of [ADP] on the activation level of muscle contraction, but the relationship between and [ADP] is too complicated to give a quantitative analysis about them.

The simulation results show that the wave form, amplitude, and period of SPOC are influenced by [ADP]. Both the amplitude and the period decrease with the increase of k_7, accompanied by the change of oscillation from the saw-tooth waveform to the triangular type. A similar tendency is also observed when k_1 is increased, because the increase in the ADP concentration may also change the activation level of muscle contraction.

The force equation (18) is just suitable to calculate the time-dependent changes in sarcomere length under isotonic condition. Since the intrinsic factor for SPOC is the chemical oscillation induced by the cooperative operation of two myosin heads, it is reasonable to believe that the local SPOC wave may occur in some sarcomeres even when the total length of myofibrils is fixed, and the oscillatory contractions can propagate to the adjacent sarcomere, forming a traveling wave along the myofibril. Therefore, the present cooperative model for myosin dimer can explain the intrinsic reason for SPOC under both isotonic and isometric conditions. But a more precise equation should be established to describe the force balance under the isometric condition.

3.3. The various conditions for SPOC to occur

In our model, the level of muscle activation, the cooperative effect between the two heads of myosin, and the concentrations of ATP and ADP are important conditions for spontaneous oscillation of muscle contraction.

The level of muscle activation is determined by the concentration of Ca^{2+} or ADP in solution and is expressed mainly by the rate constant k_1. When the rate of k_1 is relatively larger or smaller, the muscle is in a contracted or relaxed state. Conversely, only when the value of k_1 is moderate, the sustained oscillations of contractive tension may be generated. Therefore, muscle activation at a moderate level is the basic condition for SPOC.

The cooperative effect between the two heads of myosin dimer is reflected by the ratio of k_8/k_4. A large number of simulations show that the steady state solutions of Eq. (1) will be constant and the sarcomere length will not change with time if the double-headed cooperative effect is not taken into account, even though the muscle activation is under a moderate level. On the contrary, if we assume that there is significant cooperativity between the two heads ($k_8/k_4 > 5$), the periodic solutions can be obtained from the differential equations; thereby the time-dependent change in sarcomere length is also observed. Therefore, in our model, the cooperative mechanism between myosin heads serves as the primary factor for SPOC.

The concentration of ATP and ADP in the solution is the external condition at which the muscle produces spontaneous vibration. The concentration of ATP determines the value of the parameter a, and thus the value of the rate k_3 can be calculated; the concentration of ADP determines the value of k_7 while affecting the value of k_1. The rest of the rate constants k_2, k_4, k_5, k_6, and the value of parameter c, are constant for the given experimental conditions. Some experimental observations show that the concentration ratio of ATP to ADP ([ATP]/[ADP]) has a great influence on SPOC. By the numerical simulations, we find that increasing the concentration of ADP (i.e., increasing the rate of k_7) at a given ATP concentration ([ATP] $= a$ mM) gradually changes the period and the amplitude of SOPC until the vibration disappears. This conclusion is consistent with the observed phenomenon in the experiments.

The reaction–diffusion effect of ATP inside muscle fibers is also a necessary condition for SPOC. Without considering the reaction–diffusion effect, the average value of ATP concentration near the active sites of myosin, y, should be assumed as a constant, then the steady-state solutions of the differential equations are also constant and do not change with time. In this case, the muscle will be in a contracted or relaxed state. However, the reaction–diffusion equation (12) has a periodic solution only if the cooperative effect between myosin heads is fully considered ($k_8 > k_4$). Therefore, the time-dependent change in the average value of ATP concentration inside the muscle fibers is the result of the double-head cooperative mechanism rather than the cause of SPOC.

4. Conclusion

The conditions for SPOC to occur are very extensive. It means that SPOC is the characteristic of the dynamic system determined by the muscle structure and the mechanochemical cycle of myosin. Based on the idea that the cooperative behavior between the two heads of myosin II dimer may affect the rate in the mechanochemical cycle, this paper proposes a kinetic model for myosin II dimer to describe the spontaneous oscillatory contraction of myofibrils. The chemical kinetic analysis for the model indicates that the coordination of two heads leads to the cyclic change in the proportions of myosin dimer in different states. As a result, the contractive force also periodically changes with time, which is the intrinsic cause of SPOC. This kind of remarkable nonlinear behav-

ior derived from the mechanochemical model for myosin II dimer suggests that the inter-head cooperative behavior may play a critical role in the muscle contraction. Although some mechanochemical models have been proposed to explain the cooperative behavior between the two heads of processive motors, such as myosin V, kinesin, and dynein, the cooperative mechanisms of these motors are obviously different from that of myosin II, which works in a collective and collaborative manner.[54] Thus, the mechanochemical model established by this paper may supply a new quantitative analysis method to study the cooperative characteristics of molecular motor systems.

The present work also investigates the effect of muscle structure on SPOC. The simulation results show that the muscle structure could significantly affect the waveform and amplitude characteristics of SPOC. During muscle contraction, the lattice spacing between the thin and thick filaments varies with the sarcomere length, corresponding to the change in the cross-bridge formation probability. So, the coupling relation between the muscle structure and the cross-bridge formation is an important factor for SPOC. Furthermore, the passive force originated from the elastic element in the myofibril helps to keep the amplitude of SPOC in a reasonable range, although the passive force is not a necessary condition for SPOC.

Considering that the myofilament lattice can significantly reduce the diffusion of adenine nucleotides, this paper establishes the reaction–diffusion equation about ATP. It is unexpected that the concentration of ATP inside myofilament periodically changes with time. Since the SPOC phenomena occur under a fixed chemical condition, early theoretical studies have considered that SPOC is not driven by the oscillation of chemical parameters, such as the concentration of ATP, Pi, or Ca^{2+}, but owes to other factors that contractile apparatus inherently possesses. These theoretical studies may ignore the diffusion of adenine nucleotides from the solution to myofibril. Further research is needed to tell whether the oscillation of chemical parameters plays an important role in the occurrence of SPOC.

References

[1] Yasuda K, Shindo Y and Ishiwata S 1996 *Biophys. J.* **70** 1823
[2] Wolfe J E, Ishiwata S, Braet F, Whan R, Su Y, Lal S and dos Remedios C G 2011 *Biophys. Rev.* **3** 53
[3] Kagemoto T, Li A, dos Remedios C G and Ishiwata S 2015 *Biophys. Rev.* **7** 15
[4] Sasaki D, Fukuda N and Ishiwata S 2006 *Biochem. Biophys. Res. Commun.* **343** 1146
[5] Shimamoto Y, Kono F, Suzuki M and Ishiwata S 2007 *Biophys. J.* **93** 4330
[6] Shimamoto Y, Suzuki M and Ishwata S 2008 *Biochem. Biophys. Res. Commun.* **366** 233
[7] Ishiwata S, Shimamoto Y and Fukuda N 2011 *Prog. Biophys. Mol. Biol.* **105** 187
[8] Uuml F and Prost L 1997 *Phys. Rev. Lett.* **78** 4510
[9] Smith D A and Stephenson D G 1994 *J. Muscle Res. Cell Motil.* **15** 369
[10] Smith D A and Stephenson D G 2009 *Biophys. J.* **96** 3682
[11] Sato K, Ohtaki M, Shimamoto Y and Ishiwata S 2011 *Prog. Biophys. Mol. Biol.* **105** 199
[12] Sato K, Kuramoto Y, Ohtaki M, Shimamoto Y and Ishiwata S 2013 *Phys. Rev. Lett.* **111** 108104
[13] Nakagome K, Sato K, Shintani S A and Ishiwata S 2016 *Biophys. Physicobiol.* **13** 217
[14] Li J F, Wang Z Q, Li Q K, Xing J J and Wang G D 2016 *Chin. Phys. B* **25** 118701
[15] Guo W S, Luo L F and Li Q Z 2002 *Chem. Phys. Lett.* **363** 471
[16] Mansson A, Rassier D and Tsiavaliaris G 2015 *Biomed Res. Int.* 245154
[17] Dogan M Y, Can S, Cleary F B, Purde V and Yildiz A 2015 *Cell Rep.* **10** 1967
[18] Cleary F B, Dewitt M A, Bilyard T, Htet Z M, Belyy V, Chan D D, Chang A Y and Yildiz A 2014 *Nat. Commun.* **5** 4587
[19] Trivedi D V, Muretta J M, Swenson A M, Davis J P, Thomas D D and Yengo C M 2015 *Proc. Natl. Acad. Sci. USA* **112** 14593
[20] Zhao X Y, Sun W, Zhang J P, Tala and Guo W S 2014 *Biochem. Biophys. Res. Commun.* **453** 686
[21] Conibear P B and Geeves M A 1998 *Biophys. J.* **75** 926
[22] Brunello E, Reconditi M, Elangovan R, Linari M, Sun Y B, Narayanan T, Panine P, Piazzesi G, Irving M and Lombardi V 2007 *Proc. Natl. Acad. Sci. USA* **104** 20114
[23] Jung H S, Komatsu S, Ikebe M and Craig R 2008 *Mol. Biol. Cell* **19** 3234
[24] Albet-Torres N, Bloemink M J, Barman T, Candau R, Frolander K, Geeves M A, Golker K, Herrmann C, Lionne C, Piperio C, Schmitz S, Veigel C and Mansson A 2009 *J. Biol. Chem.* **284** 22926
[25] Mansson A 2010 *Biophys. J.* **98** 1237
[26] Kull F J and Endow S A 2013 *J. Cell Sci.* **126** 9
[27] Geeves M A 2016 *Biopolymers* **105** 483
[28] Lymn R W and Taylor E W 1971 *Biochemistry* **10** 4617
[29] Spudich J A 1994 *Nature* **372** 515
[30] Kuehner S and Fischer S 2011 *Proc. Natl. Acad. Sci. USA* **108** 7793
[31] Mijailovich S M, Nedic D, Svicevic M, Stojanovic B, Walklate J, Ujfalusi Z and Geeves M A 2017 *Biophys. J.* **112** 984
[32] Gorga J A, Fishbaugher D E and VanBuren P 2003 *Biophys. J.* **85** 2484
[33] Shorten P R and Sneyd J 2009 *Biophys. J.* **96** 4764
[34] Illaste A, Laasmaa M, Peterson P and Vendelin M 2012 *Biophys. J.* **102** 739
[35] Kekenes-Huskey P M, Liao T, Gillette A K, Hake J E, Zhang Y, Michailova A P, McCulloch A D and McCammon J A 2013 *Biophys. J.* **105** 2130
[36] Bormuth V, Varga V, Howard J and Schaeffer E 2009 *Science* **325** 870
[37] Linke W A, Ivemeyer M, Mundel P, Stockmeier M R and Kolmerer B 1998 *Proc. Natl. Acad. Sci. USA* **95** 8052
[38] Linke W A, Stockmeier M R, Ivemeyer M, Hosser H and Mundel P 1998 *J. Cell Sci.* **111** 1567
[39] Lan G H and Sun S X 2005 *Biophys. J.* **88** 4107
[40] Hackney D D, Tamanoi F and Sigman D S 2003 *Energy Coupling and Molecular Motors* (San Diego: Elsevier Academic Press)
[41] Baker J E, Brosseau C, Joel P B and Warshaw D M 2002 *Biophys. J.* **82** 2134
[42] Kaya M, Tani Y, Washio T, Hisada T and Higuchi H 2017 *Nat. Commun.* **8** 16036
[43] Minozzo F C, Altman D and Rassier D E 2015 *Biochem. Biophys. Res. Commun.* **463** 1129
[44] Linari M, Caremani M and Lombardi V 2010 *Proc. R. Soc. B* **277** 19
[45] Smith D A and Geeves M A 1995 *Biophys. J.* **69** 538
[46] Canepari M, Maffei M, Longa E, Geeves M and Bottinelli R 2012 *Exp. Physiol.* **97** 873
[47] He Z H, Stienen G J M, Barends J P F and Ferenczi M A 1998 *Biophys. J.* **75** 2389
[48] Joumaa V, Leonard T R and Herzog W 2008 *Proc. R. Soc. B* **275** 1411
[49] Pavlov I, Novinger R and Rassier D E 2009 *Am. J. Physiol. Cell Physiol.* **297** C1211
[50] Linari M, Brunello E, Reconditi M, Fusi L, Caremani M, Narayanan T, Piazzesi G, Lombardi V and Irving M 2015 *Nature* **528** 276
[51] Piazzesi G, Reconditi M, Linari M, Lucii L, Bianco P, Brunello E, Decostre V, Stewart A, Gore D B and Irving T C 2007 *Cell* **131** 784
[52] Finer J T, Simmons R M and Spudich J A 1994 *Nature* **368** 113
[53] Higuchi H, Nakauchi Y, Maruyama K and Fujime S 1993 *Biophys. J.* **65** 1906
[54] Lin L F, Zhou X W and Ma H 2013 *Acta Phys. Sin.* **62** 240501 (in Chinese)