Biophysical Chemistry 253 (2019) 106221

Contents lists available at ScienceDirect

Biophysical Chemistry

journal homepage: www.elsevier.com/locate/biophyschem

Research Article

A chemical kinetic model for Ca^{2+} induced spontaneous oscillatory contraction of myocardium

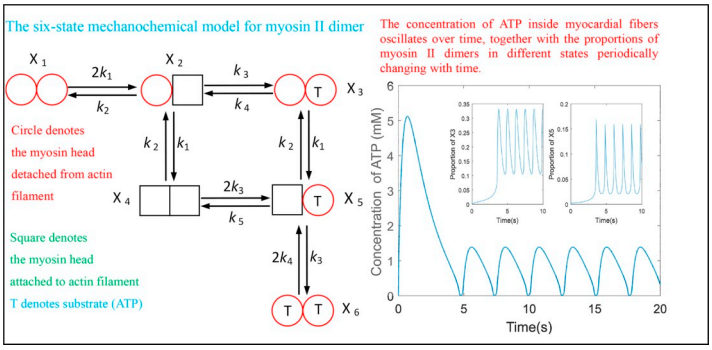
Tala[a], W. Sun[a,b], J.P. Zhang[a], X.Y. Zhao[c], W.S. Guo[a,*]

[a] School of Physical Science and Technology, Inner Mongolia University, 235 West Daxue Street, Hohhot, Inner Mongolia 010021, China
[b] Department of Resource Engineering, Ordos Vocational College, Yikezhao Street, Kangbashi New District, Ordos, Inner Mongolia 017000, China
[c] Department of Statistics and Mathematics, Inner Mongolia University of Finance and Economics, Hohhot, Inner Mongolia 010070, China

HIGHLIGHTS

- The cooperative behavior between the two heads of myosin dimer affects the rates in the mechanochemical cycle.
- The proportions of myosin dimers in different states periodically change with time.
- The concentration of ATP inside myocardial fibers cyclically varies over time.
- The SPOC of muscles may be partly due to chemical oscillation involved in the actomyosin ATPase cycle

GRAPHICAL ABSTRACT



ARTICLE INFO

Keywords:
SPOC (SPontaneous Oscillatory Contraction)
Myosin dimer
Mechanochemical cycle
Reaction-diffusion equation

ABSTRACT

The Ca^{2+} induced Spontaneous Oscillatory Contraction (Ca-SPOC) of cardiac myofibrils oscillate with a period similar to resting heartbeat of several animal species, and its auto-oscillatory properties set the basic rhythm of cardiac contraction. To explain the dynamics of Ca-SPOC, the present paper constructs a novel chemical kinetical model based upon the cooperative behavior between the two heads of myosin II dimer, also considering the reaction-diffusion effect of ATP inside myocardial fibers. The simulation results show that the concentration of ATP inside myocardial fibers oscillates over time under some special conditions, together with the proportions of myosin II dimers in different states periodically changing with time, which contributes to produce the sustained oscillations of contractive tension. These results indicate that the SPOC of muscles may be partly due to chemical oscillation involved in the actomyosin ATPase cycle, which has been ignored by the previous theoretical studies.

1. Introduction

The striated (skeletal and cardiac) muscle usually takes either the contraction or the relaxation state depending on the Ca^{2+} concentration. SPOC (SPontaneous Oscillatory Contraction) is considered to be the third state of striated muscle that exists between the states of relaxation and contraction. Partial activation using precise concentrations of free Ca^{2+} induced spontaneous oscillation of sarcomere length and active tension [1,2], and each sarcomere oscillates with a saw-tooth waveform that consists of a slow shortening phase, followed by a phase of rapid lengthening [3]. This type of oscillation, known as Ca-SPOC, is observed for both skeletal and cardiac muscles without the involvement

* Corresponding author at: School of Physical Science and Technology, Inner Mongolia University, 235 West Street, Hohhot, Inner Mongolia 010021, China.
E-mail address: pygws@imu.edu.cn (W.S. Guo).

https://doi.org/10.1016/j.bpc.2019.106221
Received 2 March 2019; Received in revised form 3 July 2019; Accepted 5 July 2019
Available online 08 July 2019
0301-4622/

of sarcoplasmic reticulum [3,4]. Another type of oscillation, termed ADP–SPOC [5–7], occurs under the steady conditions in the presence of high concentration of ADP and Pi, together with ATP, and in the absence of free Ca2+. The ADP-SPOC is also observed irrespective of muscle type [8].

A. Fabiato and F. Fabiato [8,9] were the first to observe Ca-SPOC in skinned cardiac cells. Ishiwata's group also found the spontaneous tension oscillations in skinned cardiac fibers under partial Ca^{2+}activations [8,10],and suggested that SPOC is a phenomenon inherent to the actomyosin motor itself [11]. D. Sasaki et al. made deep researches about the sarcomeric oscillations in Ca-SPOC of skinned myocardium. They found that the period of sarcomeric oscillation in Ca-SPOC correlated well with that of the resting heartbeat of several animal species [12]. These conclusions indicate that the auto-oscillatory properties of cardiac myofibrils may play a part role in the molecular mechanisms of myocardial beating.

Early experimental and theoretical studies of Ca-SPOC attributed the sarcomeric oscillation to spontaneous release of Ca^{2+} from the sarcoplasmic reticulum (SR), because the SR-dependent oscillations showed several characteristic similarities with Ca-SPOC. However, W.A. Linke confirmed that spontaneous oscillations can occur at partial Ca^{2+} activation in single cardiac myofibrils devoid of SR [10]. Some theories assumed that length-dependent sensitivity of the myofilaments to Ca^{2+} is critical for the oscillations. But more recent experiments showed that thin-filament Ca^{2+} regulation is not a necessary ingredient of the mechanism of SPOC [13]. In recent years, a series of dynamic models were proposed to explain the Ca-SPOC. F. Julicher and J. Prost [14] 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. Using a hydrodynamic approach, S. Günther et al. [15] considered a simple microscopic model of half-sarcomere in which SPOC are a consequence of load dependent detachment rates of molecular motors from filaments. The corresponding model of a chain of sarcomeres can reproduce the phenomenology of waves along muscle fibers. K. Sato et al. [4,16,17] put forward several similar theories for SPOC. They assumed that the probability of cross-bridge formation depends on the lattice spacing between the thin and thick filament, which decreases with an increase in the sarcomere length. All the above models help us understand SPOC in different ways, but these theories involved little about the mechanochemical cycle of myosin, failing to exam the dependence of SPOC on the chemical conditions in the experiments [18].

Some experiments have shown that the concentration of substrate and product in the solution can seriously affect the characteristics of muscle contraction and spontaneous vibration, indicating that the muscle contraction involves profound chemical mechanism. Since these phenomena occur under a fixed chemical condition, the earlier theoretical works considered that SPOC is not driven by the oscillation of chemical parameters, such as concentration of ATP, ADP, Pi or Ca^{2+}, but owes to other factors that contractile apparatus inherently possesses [3]. However, some theoretical and experimental results in recent years have confirmed that the myofilament lattice significantly reduces the diffusion of adenine nucleotides during muscle activation [19–21], and the diffusion effect has never been considered by the earlier studies about SPOC.

Based upon the actomyosin ATPase cycle of single myosin head, this paper proposes a chemical kinetic model for myosin II dimers, in which the cooperativity between two heads of myosin II dimer is fully considered. Taking into account the effect of myofilament lattice on the diffusion of adenine nucleotides, the reaction diffusion equation of ATP inside muscle fibers is also introduced into the numerical calculation of our model. The simulation results showed that both the concentration of ATP and the proportions of myosin II dimers in different states periodically change with time. The oscillation of chemical signals inside myofibrils may be partly responsible for spontaneous oscillatory contraction (Ca-SPOC) of myocardium.

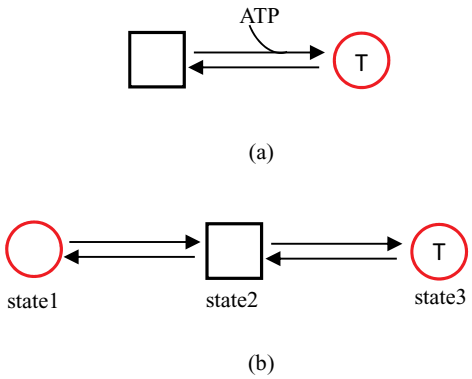


Fig. 1. Diagram of the three-state mechanochemical cycle for one head of myosin. Each square or circle indicates one myosin head. Square, the myosin head attached to actin filament; circle, the myosin head detached from actin filament. T is substrate (ATP).

2. Method

2.1. The six-state mechanochemical model for myosin II dimer

The force for muscle contraction is generated by the interaction of actin (thin) filament and myosin heads, and every head is governed by the four-state mechanochemical cycle described by the Lymn-Taylor model [22]. A simplified version of Lymn-Taylor cycle is the two-state model, i.e., only the attached and detached states of myosin heads are considered, shown as Fig. 1a.

Here, the associated states of myosin heads to thin filament are shown by squares, and dissociated states by circles. T denotes substrate (ATP). The two-state model is widely used to explain the muscle contraction and SPOC, but it is too simple to investigate the effect of Ca^{2+} on force development during muscle contraction. In addition, the two-state model fails to examine the step of nucleotide-free myosin head dissociating from thin filament, which is outside the ATP hydrolysis cycle [23]. To study Ca-SPOC with a simple but complete model, this paper provides the three-state mechanochemical cycle for single myosin head, as shown in Fig. 1b.Where, the process, state 1 → state 2, may be due to the electrostatic force between myosin heads and actin in the absence of ATP, which is regulated through a translocation of tropomyosin by the troponin complex in response to Ca^{2+} [24], while the reverse process, state 2 → state 1, may result from the drag force occurred by the relative sliding between the thin filament and the thick filament [25].

Myosin II is a dimeric protein with two heads. Some experimental results suggested different forms of cooperative behavior between the two heads of myosin [26–28]. One type of the cooperative behavior is positive cooperativity, that is, binding of one head promotes attachment of the second head [28]. Based on these facts, this paper takes the two heads as an indivisible whole and proposes a six-state mechanochemical model for myosin II dimer, shown in Fig. 2.

Here, X_i (i = 1–6) represent the states of myosin dimer, k_i (i = 1–6) are the rate constants. Since each head of the myosin II dimer has three states (see Fig. 1b), the myosin dimer with two heads shares a total of nine states, and the nine states can be simplified to six states X_1~X_6.

The constants k_1 is related to the level of muscle activation and is determined by the concentration of Ca^{2+}, while k_2 is the rate of actomyosin detachment induced by the drag force resulting from the relative sliding between the thin filament and the thick filament. The variable k_3 is the first-order rate constant of ATP binding to myosin , and $k_3 = K_3[ATP]$, where $K_3$is the second-order rate constant of ATP binding to myosin.

The constants k_4 is the binding rate of single myosin head occupied by ATP to thin filament, and k_5 is the binding rate of one myosin head

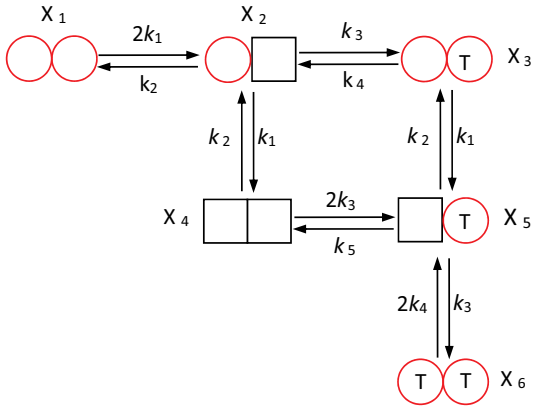


Fig. 2. The six-state mechanochemical model for myosin II dimer. X_i (i = 1–6) represent the states of myosin dimer, k_i (i = 1–6) are the rate constants.

to thin filament while another head has been attached to thin filament (see Fig. 1b). The cooperative behavior between the two heads is characterized by the effect of inter-head interaction on the binding rates in the chemical cycle, and it is expressed quantitatively by the ratio of k_5/k_4. Some experimental results suggested that binding of one head promotes attachment of the second head during muscle stretch and shortening. Therefore, the rate k_5 may be several times of k_4. This is the remarkable difference between the mechanochemical cycle model for myosin II dimer proposed in this paper and those models for single myosin head, in which the value of k_5 is equal to k_4.

2.2. Dynamic analysis for this model

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

$$\begin{aligned}
\frac{dx_1}{dt} &= -2k_1x_1 + k_2x_2 \quad (1.1)\\
\frac{dx_2}{dt} &= 2k_1x_1 - (k_1 + k_2 + k_3)x_2 + k_4x_3 + k_2x_4 \quad (1.2)\\
\frac{dx_3}{dt} &= k_3x_2 - (k_1 + k_4)x_3 + k_2x_5 \quad (1.3)\\
\frac{dx_4}{dt} &= k_1x_2 - (k_2 + 2k_3)x_4 + k_5x_5 \quad (1.4)\\
\frac{dx_5}{dt} &= k_1x_3 + 2k_3x_4 - (k_2 + k_3 + k_5)x_5 + 2k_4x_6 \quad (1.5)\\
\frac{dx_6}{dt} &= k_3x_5 - 2k_4x_6 \quad (1.6)
\end{aligned} \tag{1}$$

Here, x_i is the proportion of myosin II dimer in different states. The adenine nucleotides are transported through striated muscle fibers during muscle activation, and the myofilament lattice significantly reduces the diffusion of adenine nucleotides [19–21]. According to Fick's law and chemical reaction kinetics theory (see Appendix A), the value of y([ATP], the average concentration of ATP in the local neighborhood of myosin active sites) can be calculated approximately by the following equation

$$\frac{dy}{dt} = \frac{D}{r^2}(a - by) - cK_3y(x_2 + 2x_4 + x_5) \tag{2}$$

In Eq. (2) , D is the diffusion coefficient, r is the radius of myofilament, a is the concentration of ATP in solution, by is the minimum concentration of ATP in the center of myofilament, c is the concentration of myosin in muscle, $K_3$is the second-order rate constant of ATP binding to myosin. As a result of diffusion effect, the value of by must be less than that of y. Thus, the ratio coefficient $b$ranges from zero to one.

Eq. (1) is a 6th-order equation and is not convenient for kinetic analysis. To simplify the system, we divide the above chemical reactions into fast and slow process, and use the quasi-equilibrium assumptions for the fast reaction to simplify the equations. In Eq. (1), with respect to the rate constants k_1, k_2, k_4, and k_5, the rate k_3 is a time-dependent variable that approaches zero at some point. Therefore, the differential equations with k_3 as the coefficient, such as (1.3), (1.5) and (1.6), are treated as slow reaction, while the differential Eqs. (1.1), (1.2), (1.4) are processed in the fast reaction. As a result of quasi-equilibrium hypothesis,

$$\begin{aligned}
\frac{dx_1}{dt} &= 2k_1x_1 + k_2x_2 = 0\\
\frac{dx_2}{dt} &= 2k_1x_1 - (k_1 + k_2 + k_3)x_2 + k_4x_3 + k_2x_4 = 0\\
\frac{dx_4}{dt} &= k_1x_2 - (k_2 + 2k_3)x_4 + k_5x_5 = 0
\end{aligned} \tag{3}$$

Solve the Eq. (3),we get

$$\begin{aligned}
x_1 &= \frac{k_2}{2k_1}\cdot\frac{(k_2 + 2k_3)k_4x_3 + k_2k_5x_5}{k_3(2k_1 + k_2 + 2k_3)}\\
x_2 &= \frac{k_4(k_2 + 2k_3)x_3 + k_2k_5x_5}{k_3(2k_1 + k_2 + 2k_3)}\\
x_4 &= \frac{k_1k_4x_3 + k_5(k_1 + k_3)x_5}{k_3(2k_1 + k_2 + 2k_3)}
\end{aligned} \tag{4}$$

As $x_1 + x_2 + x_3 + x_4 + x_5 + x_6 = 1$, so

$$\begin{aligned}
x_6 &= 1 - x_1 - x_2 - x_3 - x_4 - x_5\\
&= 1 - \frac{2k_1 + k_2}{2k_1}\cdot\frac{(k_2 + 2k_3)k_4x_3 + k_2k_5x_5}{k_3(2k_1 + k_2 + 2k_3)} - x_3 - \frac{k_1k_4x_3 + (k_1 + k_3)k_5x_5}{k_3(2k_1 + k_2 + 2k_3)} - x_5\\
&= 1 - Ax_3 - Bx_5
\end{aligned} \tag{5}$$

In which,

$$A = 1 + \frac{(2k_1 + k_2)(k_2 + 2k_3)k_4 + 2k_1^2k_4}{2k_1k_3(2k_1 + k_2 + 2k_3)}$$

$$B = 1 + \frac{(2k_1 + k_2)k_2k_5 + 2k_1(k_1 + k_3)k_5}{2k_1k_3(2k_1 + k_2 + 2k_3)}$$

Substituting Eqs. (4) and (5) into Eqs. (1.3) and (1.5), then

$$\begin{aligned}
\frac{dx_3}{dt} &= k_3x_2 - (k_1 + k_4)x_3 + k_2x_5\\
&= \frac{k_4(k_2 + 2k_3)x_3 + k_2k_5x_5}{(2k_1 + k_2 + 2k_3)} - (k_1 + k_4)x_3 + k_2x_5\\
&= -\left(k_1 + \frac{2k_1k_4}{2k_1 + k_2 + 2k_3}\right)x_3 + \left(k_2 + \frac{k_2k_5}{2k_1 + k_2 + 2k_3}\right)x_5
\end{aligned} \tag{6}$$

$$\begin{aligned}
\frac{dx_5}{dt} &= k_1x_3 + 2k_3x_4 - (k_2 + k_3 + k_5)x_5 + 2k_4x_6\\
&= k_1x_3 + \frac{2k_1k_4x_3 + 2k_5(k_1 + k_3)x_5}{2k_1 + k_2 + 2k_3} - (k_2 + k_3 + k_5)x_5 + 2\\
&\quad k_4(1 - Ax_3 - Bx_5)\\
&= 2k_4 + \left(k_1 + \frac{2k_1k_4}{2k_1 + k_2 + 2k_3} - 2k_4A\right)\\
&\quad x_3 + \left[\frac{2k_5(k_1 + k_3)}{2k_1 + k_2 + 2k_3} - (k_2 + k_3 + k_5) - 2k_4B\right]x_5\\
&= 2k_4 + \left(k_1 + \frac{2k_1k_4}{2k_1 + k_2 + 2k_3} - 2k_4A\right)\\
&\quad x_3 - \left(k_2 + k_3 + \frac{k_2k_5}{2k_1 + k_2 + 2k_3} + 2k_4B\right]x_5
\end{aligned} \tag{7}$$

The reaction diffusion equation of ATP (Eq. (2)) is expressed as

$$\frac{dy}{dt} = \frac{D}{r^2}(a - by) - cK_3y(x_2 + 2x_4 + x_5)$$
$$= \frac{D}{r^2}(a - by) - cK_3y\left[\frac{k_4(k_2 + 2k_3)x_3 + k_2k_5x_5 + 2k_1k_4x_3 + 2k_5(k_1 + k_3)x_5}{k_3(2k_1 + k_2 + 2k_3)} + x_5\right]$$
$$= \frac{D}{r^2}(a - by) - cK_3y\left(\frac{k_4x_3 + k_5x_5}{k_3} + x_5\right)$$
$$= \frac{D}{r^2}(a - by) - (k_4x_3 + k_5x_5)c - cK_3yx_5 \qquad (K_3y = k_3) \tag{8}$$

If the diffusion process of ATP inside myofilaments is not considered, the concentration of ATP will be constant and $dy/dt = 0$. The present model is further simplified to a two-dimensional system consisting of the variables x_3 and x_5. Now, let us solve the equilibrium point of the two-dimensional system and analyzes the conditions for the existence of the periodic solution.

The equilibrium point of the system (x_3*, x_5*) can be derived from $dx_3/dt = 0$ and $dx_5/dt = 0$, that is

$$x_3^* = \frac{2k_4}{\left(k_2 + k_3 + \frac{k_2k_5}{2k_1 + k_2 + 2k_3} + 2k_4B\right)E + 2k_4A - k_1 - \frac{2k_1k_4}{2k_1 + k_2 + 2k_3}}$$
$$x_5^* = Ex_3^* \qquad \left(E = \frac{k_1(2k_1 + k_2 + 2k_3 + 2k_4)}{k_2(2k_1 + k_2 + 2k_3 + k_5)}\right) \tag{9}$$

For a given ATP concentration, all rates k_i in Eq. (1) are constant, and the two-dimensional system x_3-x_5 has a unique equilibrium point. The rank of the linearized matrix at the equilibrium point (x_3*, x_5*) is

$$\tau = \frac{\partial}{\partial x_3}\left[-\left(k_1 + \frac{2k_1k_4}{2k_1 + k_2 + 2k_3}\right)x_3 + \left(k_2 + \frac{k_1k_5}{2k_1 + k_2 + 2k_3}\right)x_5\right]\Bigg|_{(x_3^*, x_5^*)}$$
$$+ \frac{\partial}{\partial x_5}\left[2k_4 + \left(k_1 + \frac{2k_1k_4}{2k_1 + k_2 + 2k_3} - 2k_4A\right)\right.$$
$$\left.x_3 - \left(k_2 + k_3 + \frac{k_2k_5}{2k_1 + k_2 + 2k_3} + 2k_4B\right)x_5\right]\Bigg|_{(x_3^*, x_5^*)}$$
$$= -\left(k_1 + \frac{2k_1k_4}{2k_1 + k_2 + 2k_3}\right) - \left(k_2 + k_3 + \frac{k_2k_5}{2k_1 + k_2 + 2k_3} + 2k_4B\right) < 0 \tag{10}$$

In order to quantitatively discuss the influence of the reaction diffusion of ATP on the periodic solution of Eq. (1), the Eqs. (6)–(8) need to be further simplified. Make a quasi-equilibrium assumption for Eq. (6), that is, let $dx_3/dt = 0$, then $x_3 = x_5/E$, and Eqs. (7) and (8) can be converted into

$$\frac{dx_5}{dt} = 2k_4 + \left[\frac{1}{E}\left(k_1 + \frac{2k_1k_4}{2k_1 + k_2 + 2k_3} - 2k_4A\right) - \left(k_2 + k_3 + \frac{k_2k_5}{2k_1 + k_2 + 2k_3} + 2k_4B\right)\right]x_5 \tag{11}$$

$$\frac{dy}{dt} = \frac{D}{r^2}(a - by) - \left(\frac{k_4}{E} + k_5\right)x_5c - cK_3yx_5 \tag{12}$$

3. Results and discussion

3.1. The proportion of myosin dimer in different states

To analyze the cooperative effects of the two heads of myosin II dimer, the proportions of myosin dimer in different states are 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 value of k_1 is taken as $3\,s^{-1}$, while $k_2$changes in the range of $1\,s^{-1}$ to $40s^{-1}$ with various muscle active conditions [29,30]. The actual value k_2 employed in our model is $10s^{-1}$. The rate of k_3 is the result of multiplying K_3 by y, namely, $k_3 = K_3y$. The value of K_3 is about

Table 1
Model parameters.

Parameter	Value	Source(Ref.)
k_1	$3\,s^{-1}$	
k_2	$10s^{-1}$	[29,30]
K_3	$5000\,mM^{-1}.s^{-1}$	[30–33]
k_4	$25\,s^{-1}$	[30,34]
k_5	$200\,s^{-1}$	
D	$50\sim200\mu m^2.s^{-1}$ 10^{-8}–$10^{-9}\,m^2.s^{-1}$	[20,21]
r	50–100 μm	[12]
a	5 mM	[12]
b	0.1	
c	0.5 mM	[35]

$1 \times 10^6 \sim 8 \times 10^6 M^{-1}s^{-1}$, and the concentration of adenine nucleotides is usually reported in unit of mM. As a result, the rate K_3 ranges from 1000 to 8000 $mM^{-1}s^{-1}$ [30–33].

In this model, the cooperative behavior between two myosin 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_5/k_4. The value of k_4 is taken as $25\,s^{-1}$, and the ratio k_5/k_4 is in the range of 5–10 [30,34].

Inside myofibrils (1–2 μm in diameter) and small myocardial fibers (no more than 20 μm in diameter) [20,21], the diffusion coefficient of ATP is about $50\sim200\mu m^2.s^{-1}$. During the SPOC of the muscle, the speed of ATP diffusion may be greatly increased due to the rapid sliding of a large number of thick and thin filaments in the muscle fibers. Based on this assumption, the diffusion coefficient of ATP inside myocardial fibers (about 80–200 μm in diameter) is taken as 10^{-8}–$10^{-9}\,m^2/s$ (similar to the diffusion coefficient of small molecules in solution). Referring to the related literature [12,20,21,36], the value of D/r^2 range from 1 to $200\,s^{-1}$ in our calculation. The concentrations of ATP in solution, a, is 5 mM, while the ratio coefficient $b$varies between 0.1 and 0.3. The concentration of myosin in skeletal muscle, c, is about 0.15–0.5 mM [35].

Substituted the parameter values above into Eqs. (1)–(2), the numerical solution of x_i versus t are given in Fig. 3.

The numerical simulation results show that the proportions of myosin dimers in different states, x_i, periodically change with time. During the process of SPOC, due to the fast relative sliding between thick and thin filaments, the lever arm of myosin swings quickly and the contractive force is generated only at the moment when the power stroke is produced. Thus, the muscle contraction force is proportional to

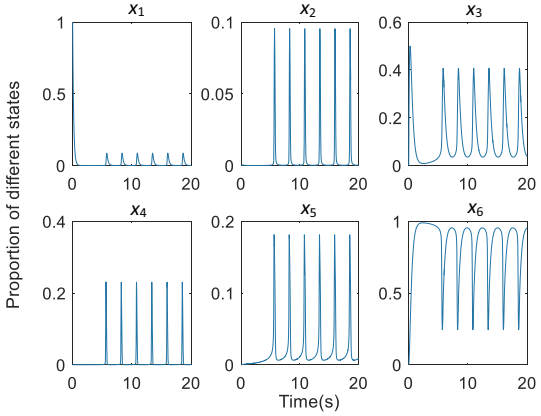


Fig. 3. The proportions of myosin dimer in different states. The values of rate constant: $k_1 = 3\,s^{-1}$, $k_2 = 10s^{-1}$, $K_3 = 5000\,mM^{-1}\,s^{-1}$, $k_4 = 25\,s^{-1}$, $k_5 = 200\,s^{-1}$, $D/r^2 = 5\,s^{-1}$, a = 5 mM, b = 0.1,c = 0.5 mM. The initial values of x_i and y are $x_1(0) = 1$, $x_2(0) = 0$, $x_3(0) = 0$, $x_4(0) = 0$, $x_5(0) = 0$, $y(0) = 0$ mM, respectively.

the number of power strokes, which is mainly decided by x_3 and x_6 in the given activation level. As a result, the contractive force cyclically changes with time, and this is partly responsible for SPOC.

The movement of single myosin head has a certain vibrational characteristic, which is manifested by Brownian motion. In the presence of ATP, the random thermal diffusion behavior of myosin head may occur if the head and the actin filament are in a weakly bound state. Myosin binds to actin filaments in a forward or backward direction, creating a backward or forward tension [37]. The Brownian motion of a single myosin molecule, however, is insufficient to form spontaneous vibration. The literature [38] studied the interaction between a "rod fiber" (consisting of a small amount of myosin II) and an actin filament, and found the relative displacement vibration between the two kinds of filaments, indicating the systems composed of small amount of myosin heads and an actin filament is enough to produce spontaneous vibration. However, the waveform of its spontaneous vibration is not regular, cluttered and not periodic. This means that the regular periodic waves of SPOC are determined by the structure of the muscle itself. In general, the SPOC of muscles is not only the embodiment of the working characteristics of single myosin II molecule, but also the result of collective cooperation of a large number of molecules. The muscle structure modulates the pattern of collective collaboration.

3.2. The time-dependent change in the concentration of ATP

To our surprise, at a given concentration of substrate outside the muscle fibers, the concentration of the ATP inside myofilament changes periodically with time, as shown in Fig. 4a.

In most of the SPOC experiments, the concentration of the ATP in solution outside of myofilament was fixed to a certain value. Therefore, The previous theoretical studies on SPOC have always taken the concentration of the ATP inside the myofibrils as a fixed value. In recent years, however, experimental and theoretical studies shown that the lattice structure of sarcomere seriously affects the diffusion process of nucleotides. So, the previous works on SPOC may neglect the reaction diffusion process of ATP from solution to myofibrils. Based on the diffusion and consumption process of ATP in myofilament, the reaction diffusion equation of ATP was established in this paper. Numerical results show that the concentration of ATP in the myofibrils changes periodically with time. This conclusion needs to be verified experimentally.

In order to investigate whether the reaction diffusion process of ATP inside muscle fibers is a common phenomenon during SPOC, the present work studied the effects of radius (r) of muscle fibers (or myofibril), ATP concentration, and diffusion coefficient (D) on chemical oscillations.

In the literature [6] that studied the spontaneous tension oscillation in skinned bovine cardiac muscle, the wide of cardiac muscle fibers was about 40–80 μm, and the concentration of ATP ([ATP]) was 1–2 mM. Based on these data, we calculated the time-dependent change of [ATP] inside muscle fibers, shown as Fig. 4b, in which $D/r^2 = 20s^{-1}$, a = 1 mM. This calculation result indicates that the chemical oscillation can be induced in thinner muscle fibrils at lower concentration of ATP.

W.A. Linke et al. [10] observed the phenomenon of SPOC in single isolated cardiac myofibril (about 1–2 μm in diameter) at intermediate activation level (pCa 6.0, [ATP] = 4 mM). According to these experimental data and Eq. (2), the change of [ATP] over time was calculated, as shown in Fig. 4c. Obviously, the concentration of ATP is uniform in the single myofibril and does not change with time. In other words, there is no chemical oscillation occurred inside the single myofibril, although the spontaneous sarcomeric oscillations can be observed under this chemical condition. So, the periodic change of [ATP] is not the necessary condition and essential cause of SPOC, but merely a regulatory factor.

K. Yasuda et al. [36] used a microscopy system to investigate the length-tension relation of SPOC in a single skeletal myofibril (1–2 μm in diameter) at a high ADP-to-ATP ratio. They founded that the SPOC of single myofibril can be generated even if the concentration of ATP is very low ([ATP] = 0.1–0.2 mM). In order to test whether there is a chemical oscillation inside myofibril at low concentration of ATP, the

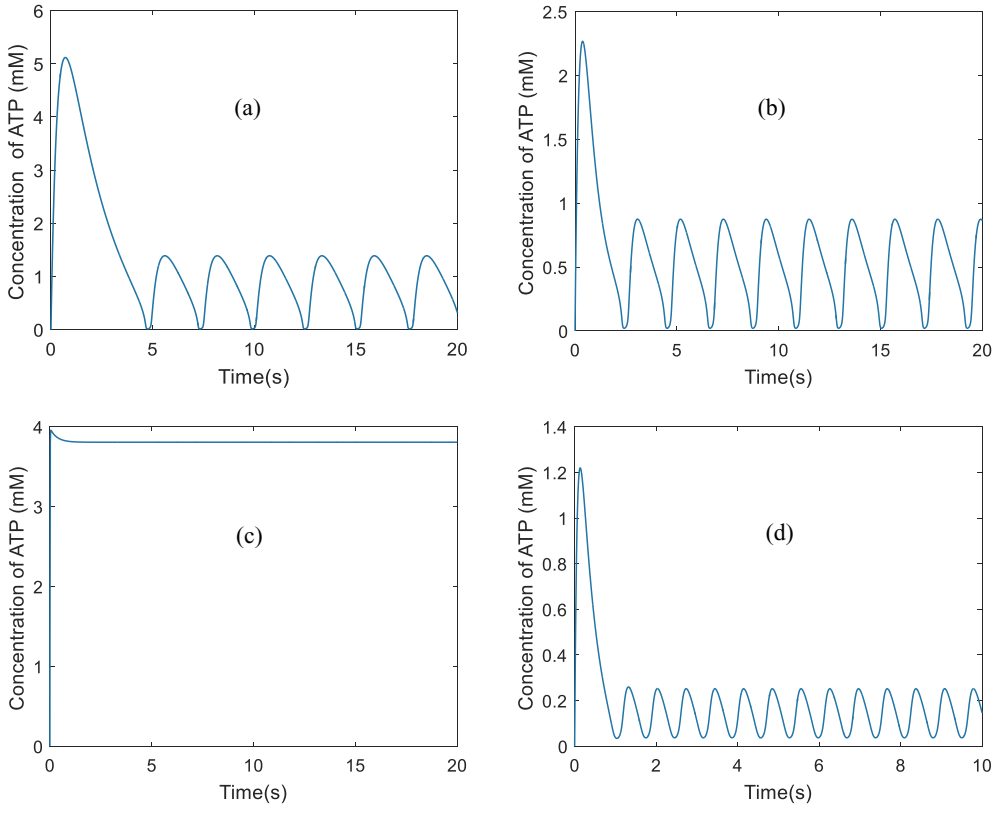


Fig. 4. The oscillation of ATP concentration inside muscle fiber or myofibril. (a) The values of rate constants and the initial values of x_i and y are as same as those in Fig. 3. $D/r^2 = 5\,s^{-1}$, a = 5 mM. (b) The simulation result of skinned bovine cardiac muscle fiber (r = 20–50 μm). $K_3 = 3000\,mM^{-1}\,s^{-1}$, $k_4 = 18\,s^{-1}$, $D/r^2 = 20s^{-1}$, a = 1 mM, b = 0.15. (c) and (d) The oscillation of ATP concentration in single rabbit cardiac myofibrils (r = 1 μm). $K_3 = 5000\,mM^{-1}\,s^{-1}$, $k_4 = 29\,s^{-1}$, $D/r^2 = 150\,s^{-1}$. In Fig. 4c, a = 4 mM, b = 1, while a = 0.2 mM, b = 0.1 in Fig. 4d.

relationship between [ATP] and time was calculated according to Eq. (2). The simulation result (see Fig. 4d) shows that there is a reaction diffusion process inside a single myofibril, when the concentration of ATP outside the myofibril is low. In spite of the diameter of a single myofibril is very thin (1–2 μm), it contains thousands of thick and thin filaments, which is expected to result in the concentration gradient of ATP in myofibrils. This conclusion may have been overlooked by the previous theoretical studies.

Through lots of simulations, we found that chemical oscillations occur only when the velocity of ATP flowed into muscle fibers ($D/r^2 \cdot a$) is approximately equal to the rate (k_4) of hydrolysis of ATP by myosin heads. This conclusion is logical. It indicates that the balance between the supply and consumption of ATP in the muscle fibers is the necessary condition for generating stable chemical oscillations; while the cooperation between the two heads of myosin (the difference between k_5 and k_4) leads to periodic oscillations near the equilibrium state.

In the above calculations, the diffusion coefficient of ATP in myofibrils (1–2 μm in diameter) was in the range of 50~200$\mu m^2/s$ [20,21], but the value of diffusion coefficient in muscle fibers (80–200 μm in diameter) was adjusted by us to 10^{-8}–10^{-9} m^2/s. We think the rapid sliding between a large number of thick and thin filaments in the muscle fibers may greatly increase the speed of ATP diffusion during SPOC. If the relative sliding between lots of myofilaments does not affect the diffusion coefficient of ATP, then the Eq. (2) needs to be modified to more accurately describe the diffusion of ATP inside myocardial fibers.

In order to make dynamic analysis with the simplified Eqs. (6)–(8), the parameter values in Table 1 are substituted into these equations for numerical calculation. The simulation results are shown in the Fig. 5, from which it can be seen that the simplified Eqs. (6)–(8) has a periodic solution, similar to the calculation results of the Eq. (1). They differ only in the period and amplitude of the oscillation. Therefore, it is feasible to use the simplified equations to analyze the conditions under which various states produce oscillations.

If the diffusion process of ATP inside myofibrils is not considered, the concentration of ATP will be constant. In this case, the Eqs. (6)–(8) can be simplified to the two-dimensional system composed of x_3 and x_5. Since the rank of the linearized matrix at the equilibrium point (x_3^*, x_5^*) is less than zero (see Eq. (10)), the two-dimensional system does not have a periodic solution near the equilibrium point. In other words, in the present model shown in Fig. 2, the reaction diffusion process of ATP inside the muscle fiber is one of the necessary conditions for the spontaneous vibration of the sarcomere, and the chemical oscillation may be partly responsible for SPOC of striated muscle.

To discuss the influence of the reaction diffusion of ATP on the periodic solution of Eq. (1), we substitute the values of the parameters in the Table 1 into Eqs. (11) and (12) for numerical calculation. The results show that x_5 and y have no periodic solutions. So, the system described by Eq. (1) cannot be simplified to a two-dimensional planar system for dynamic analysis.

3.3. The periods of SPOC in different animal myocardiums

The experiments about SPOC of several animal myocardial fibers performed by D. Sasaki et al. showed that the periods of sarcomere length vibration in different animal species are different, which are inversely proportional to their respective heart rates. Fig. 6a shows the relationship between the period of Ca-SPOC and the period of the resting heartbeat [12]. There was a good correlation between them with the correlation coefficient of 0.94. The different resting heartbeats of several animal species are due to the different expression of myosin heavy chain isoforms (MHC) in animal myocardium [7]. The expression types of MHC in mammalian hearts are α-MHC and β-MHC, resulting in three different types of myosin, V1 (αα), V2 (αβ) and V3 (ββ). All mammalian species express different proportions of MHC. For example, V1 (αα) is expressed in mice and rats with fast heart rate in animals, and V3 (ββ) is expressed in a large mammal (e.g., human) with a slow heart rate of V3 (ββ).

In the present model shown in Fig. 2, the rate constant k_4 is related to enzyme activity of ATP, ie, increasing the value of k_4 helps to increase the binding rate of myosin to actin filaments. As α-MHC has higher ATPase activity than β-MHC, the value of k_4 in mice and rats must be larger than that of pig and cow. The numerical calculation results show that the period of Ca-SPOC decreases as the value of k_4 increases (see Fig. 6b). This conclusion is consistent with the experimental data shown in Fig. 6a.

3.4. The cooperative effect between two myosin heads on SPOC

In this paper, 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_5/k_4. For the mechanochemical cycle model of single myosin head, the value of k_4 is equal to k_5. But in the present model for myosin II dimer, the value of k_5 is several times more than k_4. In order to investigate the cooperative effect between two myosin heads on SPOC, the change in period of Ca-SPOC with the value of k_5 at $k_4 = 25\,s^{-1}$ is calculated, as shown in Fig. 7, from which we can see that the period of Ca-SPOC decreases approximately linearly with the ratio of k_5/k_4.

It is also found that all the values of x_i tend to be constants if the rate of k_5 is equal to k_4. This brings about the conclusion that one of necessary condition for SPOC is $k_5 > k_4$. The significant difference between k_4 and k_5 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 presented model assumes that there is a certain cooperative mechanism between the two heads of myosin II dimer when the concentration of Ca^{2+} is at a medium value. If the muscle is in relaxation

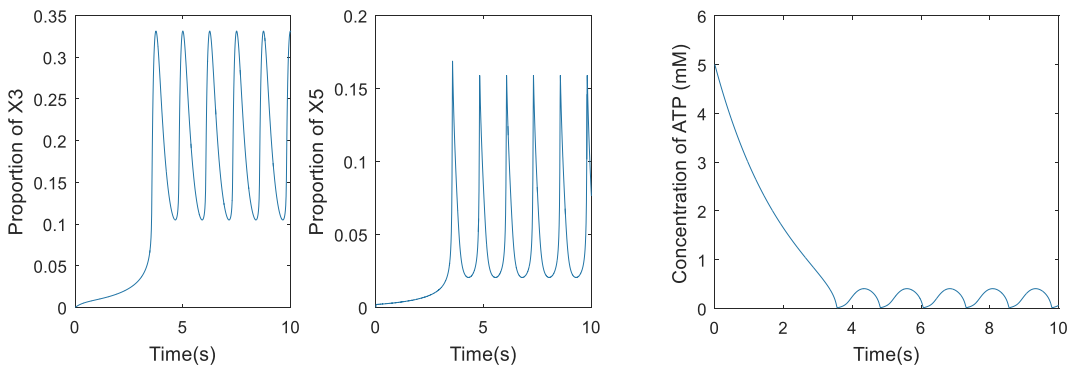
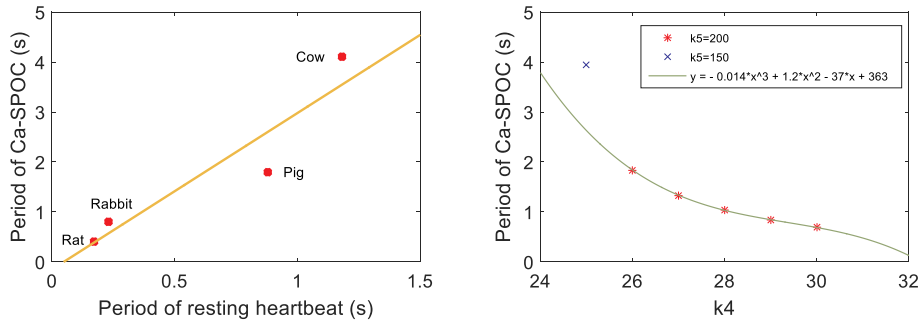


Fig. 5. The simulation results for the simplified equations. The values of k_i are as same as those in Fig. 3, the initial values of x_i and y are $x_3(0) = 0$, $x_5(0) = 0$, $y(0) = 5$ mM, respectively.



(a) (b)

Fig. 6. (a) The relationship between the period of Ca-SPOC and the period of the resting heartbeat [12]. (b) the import of $k_4$on the period of Ca-SPOC.

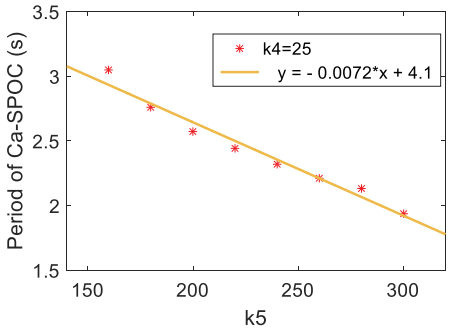


Fig. 7. The change in period of Ca-SPOC with the value of k_5 at $k_4 = 25$.

state, the concentration of Ca^{2+} inside the myofilaments will be very low, and most of the binding sites on the actin filament are blocked, and only one head of myosin II dimer can bind to actin filament. On the contrary, when muscle is in contraction state, the concentration of Ca^{2+} is very high and most of the binding sites on the actin filament are activated. In this case, the two heads of myosin dimer may bind to the actin filament at the same time. In general, the cooperativity between the two myosin heads is not obvious or does not exist when the muscle is under contraction or relaxation state. Therefore, the proposed mechanochemical cycle model of myosin II dimer is more suitable for explaining the third state of striated muscle (SPOC) that exists between the states of relaxation and contraction.

3.5. The effect of Ca^{2+} and ADP on SPOC

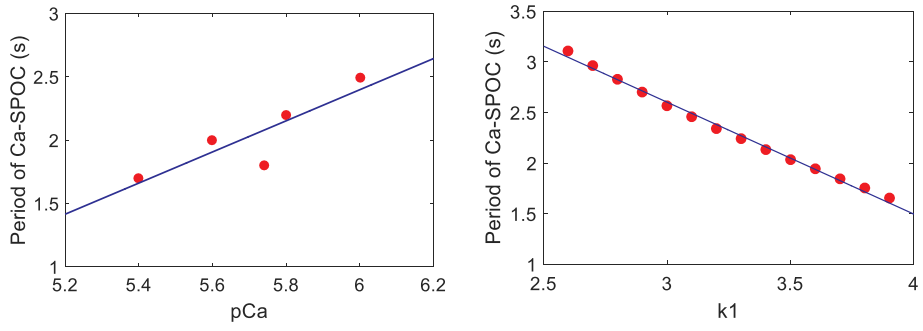
D. Sasaki et al. studied Ca-SPOC under physiological condition and analyzed the oscillation characteristics of Ca-SPOC in several types of animal myocardium. It was observed by phase contrast microscopy that periodic oscillations of sarcomere can be reproduced over a wide range of pCa values. The relationship between the period of Ca-SPOC and pCa was investigated in porcine myocardium [12], shown in Fig. 8 (a), from which it can be derived that the period of Ca-SPOC positively correlated with pCa with the correlation coefficient of 0.87.

As a further check on our model, we test the dependence of SPOC on the concentration of Ca^{2+} ($[Ca^{2+}]$). The influence of $[Ca^{2+}]$ on the activation level of muscle contraction is characterized by the parameter, k_1, which is involved in the transition processes, $X_1 \rightarrow X_2$, $X_2 \rightarrow X_4$ and $X_3 \rightarrow X_5$. The contractive force during SPOC is mainly determined by the proportions of the state X_3 and X_6 (x_3 and x_6) in Fig. 2. Here, the period of x_i at different value of k_1 was calculated, shown as Fig. 8b. The simulation results show that the period of x_i decreases linearly with the increase of k_1. This indicates that the parameter k_1 in our model is proportional to the value of pCa.

This model can also be used to qualitatively analyze the effect of ADP concentration on SPOC. In the experiments performed by D. Sasaki et al. [12], the initial concentration of ADP in the solution was zero. Therefore, the value of k_4 in our model was mainly taken from the release rate of ADP, and the step of ADP binding to myosin was not considered. If the concentration of ADP is increased in the solution, the step of ADP release will be suppressed, and thus the value of k_4 will decrease. Numerical simulations show that the period of SPOC will increase with the decrease of k_4. As the purpose of this paper was to examine the characteristics of Ca-SPOC, the step of Pi release was ignored in the present mechanochemical model, so it is difficult to analyze the effect of Pi on SPOC. An improved version of our model may have more value for theoretical researches.

4. Conclusion

The spontaneous oscillatory contraction of myofibrils (SPOC) can be



(a) (b)

Fig. 8. Effect of Ca^{2+} on the period of Ca-SPOC. (a) The relationship between the period of Ca-SPOC and pCa in porcine myocardium [12]. (b) the change in the period of Ca-SPOC with the parameter k_1.

observed under various chemical conditions. Therefore, the phenomenon of SPOC contains a profound chemical dynamics mechanism. To explain the chemical properties of Ca-SPOC, the present work takes the two heads of myosin as an indivisible whole and proposes a six-state chemical kinetic model for myosin II dimer. The chemical dynamics analysis for the model indicates that the coordination of two heads leads to the cyclic change in the proportion of myosin dimer in different states. As a result, the contractive force will periodically change with time, which is partly responsible for SPOC. It is also found that the concentration of ATP inside myofibrils periodically changes with time under specific condition, even if the concentration of ATP outside myofibrils is set to a fixed value. This unexpected result has never been mentioned in previous studies. It means that the chemical oscillation inside muscle fibers may play an important role in the spontaneous oscillatory contraction of myocardium.

The cooperative behavior between multiple heads of linear molecular motors is one of the basic working characteristics. Based on the cooperative characteristics among molecular motors, many models have been proposed to explain their mechanical properties. Since the step manner and cooperating mechanisms of myosin II are different from those of kinesin, myosin V, and cytoplasmic dynein, the present chemical model supplies a new quantitative analysis method to study the mechanism of cooperative behavior in systems of molecular motors.

Authors' contributions

Conceived and designed the model: Tala and W. S. Guo. Mathematical calculation:W. Sun. Analyzed the data: Tala, X. Y. Zhao and J. P. Zhang. Paper writing: Tala, W. Sun, X. Y. Zhao and J. P. Zhang.

Declaration of Competing Interest

The authors declare no competing financial interests.

Acknowledgment

This work was supported by National Natural Science Foundation of China (30860075), and Research Program of Science and Technology at Universities of Inner Mongolia Autonomous Region (NJZY19007, NJZC17458, NJZY16493).

Appendix: The reaction-diffusion equation of ATP inside myofilament [18]

The myofilament lattice significantly reduces the diffusion of adenine nucleotides from the outside of myofilament to the center of myofilament. 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

$$J = -D\cdot\frac{\partial u}{\partial x} \tag{S1}$$

Here, J is the diffusion flux, D is the diffusion coefficient, and $\partial u/\partial x$ is the concentration gradient at this cross-section.

Assuming that the volume of muscle fiber is V, the side area is A, and the average concentration of ATP in muscle fiber is y, then the amount of ATP diffused into the muscle fiber per unit time is

$$\frac{\partial(ATP)}{\partial t} = \frac{\partial(y\cdot \mathrm{V})}{\partial t} = J\cdot \mathrm{A} = -D\cdot \mathrm{A}\cdot\frac{\partial u}{\partial x} \tag{S2}$$

From Eq. (S2), it can be derived that

$$\frac{\partial y}{\partial t} = -\frac{\mathrm{A}}{\mathrm{V}}\cdot D\cdot\frac{\partial u}{\partial x} \tag{S3}$$

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

$$\frac{\partial y}{\partial t} = -\frac{\mathrm{A}}{\mathrm{V}}\cdot D\cdot\frac{\partial u}{\partial x} = -\frac{2\pi rl}{\pi r^2 l}\cdot D\cdot\frac{\partial u}{\partial x} = -\frac{2D}{r}\cdot\frac{\partial u}{\partial x} \tag{S4}$$

It is difficult to give an accurate mathematical expression for $\partial u/\partial x$. In a simple way, this paper assumes that $\partial u/\partial x$ is position-independent, but only as a function of the average ATP concentration$y$. So

$$\frac{\partial u}{\partial x} = \frac{u_2(y) - u_1(y)}{d_2 - d_1} \tag{S5}$$

where $u_1(y)$ is the concentration of ATP in the solution outside the muscle fiber, $u_2(y)$ is the concentration of ATP in the center of muscle fiber, and $d_2 - d_1$ is the distance that ATP diffuses within the muscle fiber. Because the average ATP concentration y is independent of the variable x, Eq. (S4) can be written as

$$\frac{\partial y}{\partial t} = \frac{dy}{dt} = \frac{2D}{r}\cdot\frac{u_1(y) - u_2(y)}{d_2 - d_1} = \frac{2r}{d_2 - d_1}\cdot\frac{D}{r^2}(u_1(y) - u_2(y)) \tag{S6}$$

In the experiments of SPOC, the concentration of ATP outside the muscle fiber is constant, a mM. Due to the reaction-diffusion effect, the ATP concentration in the center of muscle fiber is less than the average concentration of ATP. Let us set $u_2(y) = by$, where b is the scaling factor between 0 and 1. Thus, the change in the concentration of ATP per unit time satisfies the following equation:

$$\frac{dy}{dt} = \frac{2r}{d_2 - d_1}\cdot\frac{D}{r^2}(a - by) \tag{S7}$$

As the values of $d_2 - d_1$ and r are in the same order of magnitude, if the diffusion coefficient D is properly chosen, Eq. (S7) can be simplified to

$$\frac{dy}{dt} = \frac{D}{r^2}(a - by) \tag{S8}$$

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

$$\frac{dy}{dt} = ck_3(x_2 + 2x_4 + x_5) = cK_3y(x_2 + 2x_4 + x_5) \tag{S9}$$

Here, c is the concentration of myosin in muscle. Combining Eqs. (S8) and (S9), the value of y can be calculated approximately by the following equation:

$$\frac{dy}{dt} = \frac{D}{r^2}(a - by) - cK_3y(x_2 + 2x_4 + x_5) \tag{S10}$$

References

[1] D.G. Stephenson, D.A. Williams, Calcium-activated force responses in fast- and slow-twitch skinned muscle fibres of the rat at different temperatures, J. Physiol. 317 (1981) 281.
[2] S. Ishiwata, K. Yasuda, Mechano-chemical coupling in spontaneous oscillatory contraction of muscle, Phase Transit. 45 (1993) 105–136.
[3] S. Ishiwata, Y. Shimamoto, N. Fukuda, Contractile system of muscle as an auto-oscillator, Prog. Biophys. Mol. Biol. 105 (2011) 187–198.
[4] K. Sato, M. Ohtaki, Y. Shimamoto, S. Ishiwata, A theory on auto-oscillation and contraction in striated muscle, Prog. Biophys. Mol. Biol. 105 (2011) 199–207.
[5] N. Okamura, S. Ishiwata, Spontaneous oscillatory contraction of sarcomeres in skeletal myofibrils, J. Muscle Res. Cell Motility 9 (1988) 111–119.
[6] N. Fukuda, H. Fujita, T. Fujita, S.I. Ishiwata, Spontaneous tension oscillation in skinned bovine cardiac muscle, Pflugers Arch. 433 (1996) 1–8.
[7] D. Sasaki, H. Fujita, N. Fukuda, S. Kurihara, S. Ishiwata, Auto-oscillations of skinned myocardium correlating with heartbeat, J. Muscle Res. Cell Motil. 26 (2005) 93–101.
[8] J.E. Wolfe, S. Ishiwata, F. Braet, R. Whan, Y. Su, S. Lal, C.G.D. Remedios, SPontaneous Oscillatory Contraction (SPOC): auto-oscillations observed in striated muscle at partial activation, Biophys. Rev. 3 (2011) 53–62.
[9] A. Fabiato, F. Fabiato, Myofilament-generated tension oscillations during partial calcium activation and activation dependence of the sarcomere length-tension relation of skinned cardiac cells, J. General Physiol. 72 (1978) 667–699.
[10] W.A. Linke, M.L. Bartoo, G.H. Pollack, Spontaneous sarcomeric oscillations at intermediate activation levels in single isolated cardiac myofibrils, Circ. Res. 73 (1993) 724.
[11] H. Fujita, S. Ishiwata, Spontaneous oscillatory contraction without regulatory proteins in actin filament-reconstituted Fibers, Biophys. J. 75 (1998) 1439–1445.
[12] D. Sasaki, N. Fukuda, S. Ishiwata, Myocardial sarcomeres spontaneously oscillate with the period of heartbeat under physiological conditions, Biochem. Biophys. Res. Commun. 343 (2006) 1146–1152.
[13] P.P. de Tombe, A. Belus, N. Piroddi, B. Scellini, J.S. Walker, A.F. Martin, C. Tesi, C. Poggesi, Myofilament calcium sensitivity does not affect cross-bridge activation-relaxation kinetics, Am. J. Physiol. Regul. Integr. Comp. Physiol. 292 (2007) R1129.
[14] F. Julicher, J. Prost, Spontaneous oscillations of collective molecular motors, Phys. Rev. Lett. 78 (1997) 4510–4513.
[15] S. Günther, K. Kruse, Spontaneous waves in muscle fibres, New J. Phys. 9 (2009) 417.
[16] K. Sato, Y. Kuramoto, M. Ohtaki, Y. Shimamoto, S. Ishiwata, Locally and globally coupled oscillators in muscle, Phys. Rev. Lett. 111 (2013).
[17] K. Nakagome, K. Sato, S.A. Shintani, S. Ishiwata, Model simulation of the SPOC wave in a bundle of striated myofibrils, Biophys. Physicobiol. 13 (2016) 217–226.
[18] W. Sun, X.Y. Zhao, J.P. Zhang, et al., Mechanochemical model for myosin II dimer that can explain the spontaneous oscillatory contraction of muscle, Chin. Phys. B 27 (2018) 5.
[19] P.R. Shorten, J. Sneyd, A mathematical analysis of obstructed diffusion within skeletal muscle, Biophys. J. 96 (2009) 4764–4778.
[20] P.M. Kekenes-Huskey, T. Liao, A.K. Gillette, J.E. Hake, Y. Zhang, A.P. Michailova, A.D. McCulloch, J.A. McCammon, Molecular and subcellular-scale Modeling of nucleotide diffusion in the cardiac Myofilament lattice, Biophys. J. 105 (2013) 2130–2140.
[21] A. Illaste, M. Laasmaa, P. Peterson, M. Vendelin, Analysis of molecular movement reveals lattice like obstructions to diffusion in heart muscle cells, Biophys. J. 102 (2012) 739–748.
[22] R.W. Lymn, E.W. Taylor, Mechanism of ATP Hydrolysis by actomyosin, Biochemistry 10 (1971) 4617–4624.
[23] M.J. Greenberg, G. Arpağ, E.M. Ostap, A perspective on the role of myosins as mechanosensors, Biophys. J. 110 (2016) 2568–2576.
[24] C. Risi, J. Eisner, B. Belknap, D.H. Heeley, H.D. White, G.F. Schröder, V.E. Galkin, Ca^{2+}-induced movement of tropomyosin on native cardiac thin filaments revealed by cryoelectron microscopy, Proceedings of the National Academy of Sciences of the United States of America, 114 2017, p. 6782.
[25] K. Tawada, K. Sekimoto, A physical model of ATP-induced actin-myosin movement in vitro, Biophys. J. 59 (1991) 343–356.
[26] E. Brunello, M. Reconditi, R. Elangovan, M. Linari, Y.-B. Sun, T. Narayanan, P. Panine, G. Piazzesi, M. Irving, V. Lombardi, Skeletal muscle resists stretch by rapid binding of the second motor domain of myosin to actin, Proc. Natl. Acad. Sci. U. S. A. 104 (2007) 20114–20119.
[27] N. Albet-Torres, M.J. Bloemink, T. Barman, R. Candau, K. Frolander, M.A. Geeves, K. Golker, C. Herrmann, C. Lionne, C. Piperio, S. Schmitz, C. Veigel, A. Mansson, Drug effect unveils inter-head Cooperativity and strain-dependent ADP release in fast skeletal Actomyosin, J. Biol. Chem. 284 (2009) 22926–22937.
[28] A. Mansson, Actomyosin-ADP states, Interhead Cooperativity, and the force-velocity relation of skeletal muscle, Biophys. J. 98 (2010) 1237–1246.
[29] G.H. Lan, S.X. Sun, Dynamics of myosin-driven skeletal muscle contraction: I. steady-state force generation, Biophys. J. 88 (2005) 4107–4117.
[30] D.D. Hackney, F. Tamanoi, D.S. Sigman, Energy Coupling and Molecular Motors, Elsevier Academic Press, 2003.
[31] J.E. Baker, C. Brosseau, P.B. Joel, D.M. Warshaw, The biochemical kinetics underlying actin movement generated by one and many skeletal muscle myosin molecules, Biophys. J. 82 (2002) 2134–2147.
[32] M. Kaya, Y. Tani, T. Washio, T. Hisada, H. Higuchi, Coordinated force generation of skeletal myosins in myofilaments through motor coupling, Nat. Commun. 8 (2017).
[33] F.C. Minozzo, D. Altman, D.E. Rassier, MgADP activation contributes to force enhancement during fast stretch of isolated skeletal myofibrils, Biochem. Biophys. Res. Commun. 463 (2015) 1129–1134.
[34] M. Linari, M. Caremani, V. Lombardi, A kinetic model that explains the effect of inorganic phosphate on the mechanics and energetics of isometric contraction of fast skeletal muscle, Proc. Royal Soc. B Biol. Sci. 277 (2010) 19–27.
[35] Z.H. He, G.J.M. Stienen, J.P.F. Barends, M.A. Ferenczi, Rate of phosphate release after photoliberation of adenosine 5 '-triphosphate in slow and fast skeletal muscle fibers, Biophys. J. 75 (1998) 2389–2401.
[36] K. Yasuda, Y. Shindo, S. Ishiwata, Synchronous behavior of spontaneous oscillations of sarcomeres in skeletal myofibrils under isotonic conditions, Biophys. J. 70 (1996) 1823–1829.
[37] T. Yanagida, Y. Ishii, Single molecule detection, thermal fluctuation and life, Proc. Jpn. Acad. 93 (2017) 51–63.
[38] K. Motoshi, H. Hideo, Nonlinear elasticity and an 8-nm working stroke of single myosin molecules in myofilaments, Science 329 (2010) 686–689.