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Locally and Globally Coupled Oscillators in Muscle

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At an intermediate activation level, striated muscle exhibits autonomous oscillations called SPOC, in which the basic contractile units, sarcomeres, oscillate in length, and various oscillatory patterns such as traveling waves and their disrupted forms appear in a myofibril. Here we show that these patterns are reproduced by mechanically connecting in series the unit model that explains characteristics of SPOC at the single-sarcomere level. We further reduce the connected model to phase equations, revealing that the combination of local and global couplings is crucial to the emergence of these patterns.

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Striated muscle is a biological force generator comprised of a highly periodic pattern of microstructures [Fig. 1(a)]. A basic structural unit is a half-sarcomere (for simplicity, here we call it a sarcomere), which is a barrel-like structure of 1–2 μm in size. The sarcomeres are connected in series to form a linear fiber named a myofibril. The contraction of each sarcomere occurs by the relative sliding of a set of two filaments, named the thick (myosin) and the thin (actin) filaments, which extend from viscoelastic proteinaceous structures, called the M line and the Z line, respectively [Fig. 1(b)]. Catalytic myosin “head” domains extending from the thick filament bind to the adjacent thin filament to form “cross bridges” [1,2] and generate the sliding force between the two filaments using the energy of ATP hydrolysis.

The force-generating activity of each sarcomere is, in general, controlled by the concentration of free Ca\(^{2+}\): the sarcomeres develop force at high and relax at low Ca\(^{2+}\) concentrations. On the other hand, under fixed intermediate activation conditions, such as at pCa \(\sim 6.0\), a remarkable phenomenon, a spontaneous oscillatory contraction termed SPOC [3] occurs in both skeletal [4] and cardiac muscles [5,6]. During SPOC, each sarcomere repeats cycles of submicron-sized length oscillations that are highly stable and comprised of slow shortening and rapid lengthening phases, associated with, respectively, the active force development and relaxation. The pattern of oscillation depends on several physical parameters, such as the number of sarcomeres in the myofibril and the level of activation [3–6]. The fact that SPOC occurs at the fixed chemical conditions suggests that the mechanical property of sarcomeres and local mechanical coupling between the sarcomeres play a crucial role [7].

The SPOC pattern is also affected by the external loading. When the load is maintained constant (isotonic condition), the oscillatory phase of each sarcomere is synchronized in phase [8]. Under auxotonic conditions, where the load is applied by the external spring [Fig. 1(a)], clear traveling (metachronal) waves along the myofibril are observed [3] [Fig. 1(d)]. When the total myofibril length is held constant (isometric condition), the traveling wave tends to be split into several parts [9] [Fig. 1(e)]. In some cases, the out-of-phase synchronization is observed [Fig. 1(f)]. These properties suggest that the global coupling via external load could also be essential. However, the consequences of the local and global couplings between sarcomeres remain largely uncharacterized.

There exist several theoretical models describing SPOC [10–13] that reproduce important features of sarcomere oscillation. The realistic model proposed by Smith and Stephenson [13] is based upon the elasticity of titin, a fibrous protein that connects the end of the thick filament and the Z line. However, our experiments demonstrate that titin is not essential [3]. Other models are either abstract [10] or assume inertia of the external spring or friction from medium [11,12], the contribution of which is in fact very small compared to active and elastic forces. Moreover, more complex and realistic properties of SPOC as described above remain fully unexplained. We recently constructed a unit sarcomere model that can recapitulate the main characteristics of SPOC, including its sawtooth waveform and the phase diagram comprised of relaxation, contraction, and SPOC states [3,14]. In this Letter, we develop a mechanistic model of myofibrils by connecting the unit model and show that it can reproduce various oscillatory patterns of sarcomeres.

The unit model [14] is based on the following three principles: (i) Myosin heads stochastically and independently attach to or detach from the adjacent thin filament (two-state model), and the transition rates depend on the distance between the two filaments, i.e., the lattice spacing [15] [Figs. 1(b) and 1(c) and Eq. (1)]; (ii) the attached heads generate the active sliding force and, simultaneously, the friction [16], and the sum of these two forces is balanced with the externally applied load [Eq. (2)];
We assume that the attachment and detachment rates, \( \alpha(d_i) \) and \( \beta(d_i) \), correspond to full relaxation, whereas sufficiently large \( \alpha(d_i) \) and \( \beta(d_i) \) correspond to full activation.

Equation (1) is the time evolution equation for the fraction of myosin heads attached to the thin filament, \( P_i \), which includes both the active force-generating state and the attached state that only contributes to passive force generation. Here, the subscript \( i \) denotes quantities of the \( i \)th sarcomere. Let the total number of sarcomeres be \( N \).

The force balance along the long axis of the myofibril is given by

\[
\frac{dP_i}{dt} = \alpha(d_i)(1 - P_i) - \beta(d_i)P_i.
\]  

(iii) the force balance in the short axis perpendicular to the myofibril’s long axis is also taken into account [Eq. (4)]. [For more details on (ii) and (iii), see Supplemental Material, Text 1 [17]]. Since the parameters of the unit model describe the fundamental properties of the sarcomere structure, we can easily extend it to the myofibril model:

\[
\frac{dP_i}{dt} = \alpha(d_i)(1 - P_i) - \beta(d_i)P_i.
\]  

\[
a \frac{d\xi_i}{dt} - \eta_m \frac{\xi_i}{s_0} \sum_{i} \frac{d\xi_i}{dt} - F_{ex} = 0.
\]  

where \( \xi_i \) is the length of overlap between the thick and thin filaments, which can be described as \( SL_i = SL(0) - \xi_i \) (\( SL_i \) is the length of the \( i \)th sarcomere and \( SL(0) \) is the length at no overlap). Here, \( \xi_i P_i/s_0 \) is the total number of cross bridges, and \( s_0 \) is the interval between the adjacent myosin heads along each thick filament. The first and second terms in Eq. (2) represent, respectively, the averaged active sliding force and the passive friction force generated by cross bridges [16], where \( a \) and \( \eta_m \) are positive constants (see the Supplemental Material, Text 1 for details [17]). All sarcomeres bear the same external force \( F_{ex} \) because they are connected in series and both their inertia and the friction between sarcomeres and the surrounding medium (water) are negligible compared to the forces considered here. Whereas the form of \( F_{ex} \) depends on the type of the external load (isotonic, auxotonic, or isometric), it is expressed as

\[
F_{ex} = F_0 + K \sum_{i=1}^{N} (\xi_i - \bar{\xi}).
\]  

Here, \( F_0 \) is a given constant force, and \( \bar{\xi} \) is a stationary solution of Eqs. (1), (2), and (4) for \( \xi_i \) at \( F_{ex} = F_0 \). \( K \) is a spring constant of the external spring, and the position of one end of the spring \( X_0 \) is given as \( X_0 = N(SL(0) - \bar{\xi}) + F_0/K \). The cases of \( K \to 0 \), a finite \( K \), and \( K \to \infty \) in Eq. (3)
correspond to the isotonic, auxotonic, and isometric conditions, respectively.

The force balance along the short axis of a myofibril is given by

$$k_i(l_i(\xi_i) - d_i) + k_m P_i \xi_i (l_m - d_i) - \eta_d \frac{dd_i}{dt} + V(d_{i-1}, d_i, d_{i+1}) = 0. \quad (4)$$

The first term is the force generated by the filament lattice. We assume that the lattice has a linear stiffness $k_i$ and generates elastic force as it separates from the equilibrium spacing $l_i$ attained under the relaxing conditions [Fig. 1(d)]. It has been experimentally established that the interfilament distance at the equilibrium attained under the relaxing conditions decreases on increasing $SL$ [18]; therefore, we simply put $l_i(\xi_i) = l_{o0} + l_{s1} \xi_i$ with positive constants $l_{o0}$ and $l_{s1}$. The second term is the average force exerted by cross bridges, approximated by the elastic force produced by a linear spring with spring constant $k_m$ and natural length $l_m$ (for more details, see the Supplemental Material, Text 1 [17]). The third term $\eta_d \frac{dd_i}{dt}$ is the friction force due to the viscoelasticity of the filament lattice; $\eta_d$ is assumed to be small.

The function $V$ defines the strength of the interaction between the adjacent sarcomeres through the lattice spacing. By regarding the sarcomeres as being coupled mutually through the elastic springs with stiffness $k_{MZ}$ and assuming that the mechanical properties of $M$ and $Z$ lines are the same, we take the following form of $V$:

$$V(d_{i-1}, d_i, d_{i+1}) = k_{MZ}(d_{i-1} - d_i) + (d_{i+1} - d_i). \quad (5)$$

Summarizing all the facts noted above, Eqs. (1), (2), and (4) are rewritten in a concise form:

$$\frac{d}{dt}\begin{pmatrix} P_i \\ \xi_i \\ d_i \end{pmatrix} = \begin{pmatrix} \alpha(d_i)(1 - P_i) - \beta(d_i)P_i \\ (\alpha \xi_i P_i - F_0 s_0)/\eta_m \xi_i P_i \\ (k_i(l_i(\xi_i) - d_i) + k_m P_i \xi_i (l_m - d_i)/s_0)/\eta_d \\ + k_{MZ}\begin{pmatrix} 0 \\ 0 \\ d_i + d_{i+1} - 2d_i/\eta_d \end{pmatrix} \\ + K \left( \sum_{i=1}^N (\xi_i - \xi_{i}) s_0/\eta_m \xi_i P_i \right) \end{pmatrix}. \quad (6)$$

This equation includes both local and global couplings. Indeed, the second and third terms on the right-hand side become, respectively, the second derivative and the integration terms in some continuous limits. If we put $N = 1$, $k_{MZ} = 0$, $K = 0$, and $\eta_d \to +0$, the connected model comes to the unit model.

The unit model shows supercritical Hopf bifurcation with the control parameters $\alpha_1$ (activation level) and $F_0$ (constant external force) [14]. If we set $\alpha_1$ and $F_0$ to any values within the oscillation region, aside from the vicinity of the bifurcation points, the system undergoes auto-oscillations showing sawtooth waveforms. In the subsequent analysis we use the values $(\alpha_1, F_0) = (19, 20)$, but any set of values within the parameter region of the auto oscillation yields essentially the same results (for the units of time and length, see the Supplemental Material, Table 1 [17]).

In the connected model [Eq. (6)], the additional control parameters are $N$ and $K$. We take the Neumann boundary conditions expressed as $d_0 = d_N$ and $d_{N+1} = d_N$. The initial condition is described in the legend of Fig. 3. The simulation time is much longer than the oscillation period to identify the final state of the system. If the final state is stationary, the phase of the $i$th sarcomere $\phi_i$ is written as $\phi_i = \omega t + \phi_i$, with constants $\omega$ and $\phi_i$. We term $\phi_i$ the relative phase difference”, and its profile identifies the type of the oscillation pattern. Figure 2 shows different oscillation patterns (the corresponding spatial profiles of $\phi_i$ are shown in the Supplemental Material, Fig. 1 [17]).

The phase diagram for the oscillation patterns against $N$ and $K$ (Fig. 3) reveals several significant features. At small $K$ (the isotonic condition) the oscillatory units are in-phase synchronized, which is consistent with the experimental results [8]. At $K$ greater than the characteristic value $K'$, this in-phase synchronization becomes unstable, and traveling waves emerge [Fig. 2(b)]. Since the locally coupled identical and linearly connected oscillators do not show traveling waves under Neumann boundary conditions.

FIG. 2 (color). Examples showing typical spatiotemporal patterns of SL oscillations. (a), (b), (c), and (d) show, respectively, in-phase synchronization, traveling waves, disrupted traveling waves, and out-of-phase synchronization. The values of $N$ and $K$ used in each simulation are $N = 24$ and $K = 0.01, 0.18, 0.7, 3.75$, respectively, and the values of the other parameters are indicated in the legend of Fig. 3. It is to be noted that the SPOC period largely depends on $\eta_m$ as shown in Eq. (2), that is, the larger the value of $\eta_m$, the longer the SPOC period (see Fig. 8A in [14] for model simulation, and Figs. 3 and 4 in [3] for experimental results). The movies are shown in the Supplemental Material, Movie 2 [17].
[19], the appearance of traveling waves may be due to the
clock of global coupling. As $K$ increases, a different
oscillatory pattern is observed, which we call “the disrupted
traveling waves” [Fig. 2(c)]. Its characteristic is
the existence of finite phase gaps between the traveling wave
domains [Fig. 2(c) and see Supplemental Material, Fig. 1(c)
[17]]. To the best of our knowledge, this oscillatory pattern
has never been reported before in the system of coupled
identical oscillators. As $K$ increases further, we enter the
region of out-of-phase oscillation [Fig. 2(d)] and then con-
traction region (without oscillation) at any $N$ (Fig. 3). The
connected model predicts the existence of nonstationary
states at small $N$, which should be experimentally con-
firmed. With the exception of the yellow region in Fig. 3,
all types of oscillatory patterns have been experimentally
observed [3]. Several of those are shown in Figs. 1(d)–1(f),
and the Supplemental Material [17].

To evaluate the results of numerical simulations of
Eq. (6), we reduce the connected model to phase equations
by means of the standard reduction method [20,21]. Let
$(P^{(0)}(t), \xi^{(0)}(t), d^{(0)}(t))$ be the $T$-periodic solution of Eq. (6)
for $k_{MZ} = 0$ and $K = 0$, and $\phi_i(P_i, \xi_i, d_i)$ be the phase of
the $i$th sarcomere, satisfying $d\phi_i/dt = \omega_0 = 2\pi/T$ in
the absence of coupling [20,21]. The reduction theory states
that if the interactions between the oscillatory units are
sufficiently weak, the evolution equation of the coupled
system is written only in terms of $\phi$’s. Hence,

$$
\frac{d\phi_i}{dt} = \omega_0 + k_{MZ}(B(\phi_i - \phi_{i+1}) + B(\phi_i - \phi_{i-1}))
+ K \sum_{j=1}^{N} A(\phi_i - \phi_j).
$$

(A and $B$ are coupling functions given by $A(\phi) = (1/T) \times
\int_0^T dt Z_2(t)(\xi - \xi^{(0)}(t - \phi/\omega_0))s_0/\eta_m \xi^{(0)}(t)P^{(0)}(t)$
and $B(\phi) = (1/T) \int_0^T dt Z_2(t)(d^{(0)}(t - \phi/\omega_0) - d^{(0)}(t))/\eta_d$,
where $Z_2(t) = \delta \phi/\delta \xi|_0$ and $Z_3(t) = \delta \phi/\delta d|_0$.). With
the symbol $\bullet$ denoting their values at $(P, \xi, d) =
(P^{(0)}(t), \xi^{(0)}(t), d^{(0)}(t))$. The phase sensitivity $Z$ in the inte-
grands of $A$ and $B$ are numerically calculated from the
Malkin theory [22]. Equation (7) shows that only the relative
coupling strength $K/k_{MZ}$ and the two coupling
functions $A$ and $B$ determine the final state of Eq. (6). The
explicit forms of $A$ and $B$ for the case $(\alpha_1, F_0) = (19, 20)$
are given in Fig. 4. The signs of $B'(0)$ (negative) and $A'(0)$
(positive) indicate that with respect to small phase differ-
ences the local interaction is “attractive” and the global
interaction is “repulsive.” This result reflects that the lattice
spacing in the adjacent sarcomeres tends to be equal and the
external spring tends to keep the total myofibril length
constant. To see how the value of $K^*$, above which the

![FIG. 3 (color). Phase diagram of the SL oscillation patterns in
the steady state under auxotonic conditions obtained from the
connected model. A: $K$, the total number of sarcomeres, $N$. Ordinate,
the ratio of the spring constant of the external spring, $K$,
to the stiffness of the Z (or M) line, $k_{MZ}$. $KN^3/k_{MZ}$. The color
region indicates the steady state of SL: in-phase synchronization
(white), traveling wave (blue), disrupted traveling wave (red), out-
of-phase synchronization (green), nonstationary (yellow), and con-
traction without oscillation (black). Typical oscillation patterns
occurring to the markers (a)–(d) are shown in Fig. 2. In general,
the final state depends on the initial conditions (e.g., SLt, and
its distribution), the dependence of which is indicated by the two-color
circles where the proportion of each color indicates the probability
of the appearance of the two states. The initial conditions used here
are given by adding random numbers $\delta \in [-0.0001, 0.0001]$ to a
stationary solution $(P, \xi, d) = (0.18, 1.08, 25.1)$. When the initial
randomness is increased to, for example, $\delta \in [-0.01, 0.01]$, the
contraction region (black) at larger $N$ values becomes the out-of-
phase oscillations (green), while the other states are essentially
unaltered. $c^*$ is $\log(-\pi^2 B'(0)/A'(0))$. The parameters
are $\alpha_1 = 19$, $F_0 = 20$, $\beta_0 = 20$, $k_{MZ} = 0.5$, $\eta_d = 0.0005$, $k_m = 1$, $s_0 = 0.01$,
$l_m = 23$, $l_i = 60$, $\eta_m = 1.5$, $d_0 = 25.3$, $SL^{(0)} = 3.6$, $l_o = 23$,
$l_{rl} = 2.53$, and $a = 1$, which are nondimensionalized such that $k_m$
the force and length along the short axis (1 a.u.) $nm^{-1}$ and $a$ the
force along the long axis (1 pN) are unity. In addition, the unit
time is chosen as 1 s, and the unit lengths for the short and long axes
are chosen as 1 nm (for $d$, $l_m$, and $l_i$) and 1 $\mu$m (for $s_0$ and SL),
respectively. (For more details see the Supplemental Material, Table 1
[17]).)

![FIG. 4 (color). Phase-coupling functions obtained from
Eq. (6). The parameters and the conditions are the same as in
Fig. 3. $A(\phi)$ (red) and $B(\phi)$ (blue) are those for the global
and local couplings, respectively.](108104-4)
in-phase state is destabilized, is determined and how the traveling waves arise for $K > K^*$, we take a continuous limit in Eq. (7) assuming that $N$ is infinitely large. Introducing $x = i/N$, $\phi(x, t) = \phi_i(t)$, $\dot{k}_{MZ} = \dot{k}_{MZ}/N^2$ and $\dot{K} = KN$ into Eq. (7), we obtain

$$
\frac{\partial \phi}{\partial t} = \omega_0 + \dot{k}_{MZ}\left(-\frac{\partial^2 \phi}{\partial x^2}\right) + \dot{K} \int_0^1 A(\phi(x, t) - \phi(x', t)) dx',
$$

(8)

where we expand the local coupling in terms of $x$ derivatives of $\phi$ up to the leading term. $(\partial \phi/\partial x)^2$ has been dropped because $|B''(0)| \ll |B'(0)|$. Linearizing Eq. (8) in $\phi$ gives

$$
\frac{\partial \phi}{\partial t} = (\omega_0 + \dot{K} + \dot{k}_{MZ}(-B'(0)\partial^2 \phi/\partial x^2) + \dot{K} A'(0)(\phi(x, t) - \phi(x', t)) dx')
$$

from which we obtain the critical value $K^* = -\pi^2 k_{MZ} B'(0)/N^2 A'(0)$ with the first destabilized mode $\cos \pi x$. The value of $K^*$ is in good agreement with that of the numerical simulations of Eq. (6) for large $N$ (Fig. 3). To find the stationary state for $K > K^*$, we write $\phi(x, t)$ as $\phi(x, t) = \omega t + \dot{\phi}(x)$ and substitute it into Eq. (8). This gives an integro-differential equation for $\dot{\phi}$:

$$
\frac{\partial^2 \dot{\phi}}{\partial x^2} = \left[\dot{k}_{MZ}\int_0^1 A(\phi(x) - \phi(x')) dx'\right] + (\omega_0 - \omega)\dot{K} B'(0).
$$

To understand qualitatively the nature of the stationary solution of this equation, we tentatively put $A(\phi) = \sin \phi$ preserving the repulsiveness of $A$. Then, the above equation becomes equivalent to the equation of motion for a pendulum under gravitational force, if we regard $x$ as time. $\omega$ is given as $\omega = \omega_0$ and $\dot{\phi}(x)$ is given as the inverse of an elliptic function that is a monotonous function of $x$, implying a traveling wave. In the real case of $A$ containing higher harmonics, the solution is more complicated, but qualitatively remains the same: $\omega (> \omega_0)$ is uniquely determined, and $\dot{\phi}(x)$ is a monotonous function of $x$.

In the present model, we assumed that the cross bridge is an independent force generator. Recently, Plaçais et al. reported that the actomyosin system composed of a small number of molecules can oscillate spontaneously under loading [24], suggesting that the actomyosin complexes function cooperatively [25]. Thus, it will be worth studying whether the cooperativity is involved in the fine mechanism of SPOC.

Here, we have demonstrated that the system where basic oscillatory units are connected in series has the local-global coupling, producing various oscillation patterns. One point to be emphasized is that the common force acting on each unit works as a “repulsive global” coupling, and this type of interaction enhances the inhomogeneity of the system. In SPOC, this effect breaks the spatial uniformity of the system and, with the attractive local coupling, produces traveling or disrupted traveling waves. In the field of coupled oscillators, several studies [26] examined simultaneous local and attractive global couplings. Our observation that the mechanical coupling can as well produce repulsive global coupling may stimulate the investigation of this type of coupled systems.

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[17] See Supplemental Material at http://link.aps.org/supplemental/10.1103/PhysRevLett.111.108104 for the forces generated by cross bridges (Text 1), experimental conditions (Text 2), the units of parameters (Table 1), and movies.
[23] We have also noted that the disrupted traveling wave reflects characteristic properties of $A$ and $B$ and their balance. The detailed study will be presented elsewhere.