Letter

Active thermodynamic force driven mitochondrial alignment

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Mitochondria are critical organelles in eukaryotes that produce the energy currency adenosine triphosphate (ATP). In nerve axons, mitochondria are known to align at almost regular intervals to maintain a constant ATP concentration, but little is known about the mechanism. In this Letter, we show theoretically that ATP production and ATP-dependent nondirectional movement of mitochondria are sufficient for alignment, even without an explicit repulsive force between them, or internal mitochondrial states, or memories. This is similar to thermodynamic forces driven by thermal fluctuations, even generated by nonequilibrium processes, and demonstrates the diversity of mechanisms governing the motion of biological matter.

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Understanding how the position of organelles is regulated in eukaryotic cells will be important both biologically and physically. In particular, studying the positioning of mitochondria will be necessary when considering the energetics of the cell [1–4]. The mitochondrion is a fundamental organelle in most eukaryotic cells that produces adenosine triphosphate (ATP) [5,6]. ATP is hydrolyzed and used as an energy source for many processes in the cell, such as the synthesis of biomolecules, signal transduction, and the motility of molecular motors, and then it is essential to transport ATP to its precise location. Since ATP is synthesized by the mitochondria and diffuses, ATP would be concentrated around the mitochondria and its concentration would decrease as the distance from the mitochondria increases by assuming there are ATP sinks throughout the cytoplasm [4]. Mitochondrial positioning is then essential for the proper transport of ATP to its precise location in the cell, but the physical mechanism for this is still unknown.

The importance of mitochondrial positioning may become more critical as the size of the cell increases. In particular, the nerve axons of neurons in animals are quite long, reaching lengths of centimeters in rodents and meters in large mammals [7], while the size of the cell bodies of neurons is typically between a few and several tens of micrometers in diameter [8]. Thus, the positioning of mitochondria within a nerve axon may be essential for the distribution of ATP throughout the axon. Indeed, it has been reported that mitochondria are aligned at nearly equal intervals within a micrometer-to-centimeter-length nerve axon, in several days [2,4]. Mitochondrial alignment requires that mitochondria move away from each other. As for the movement itself, cell biological observations have shown that mitochondria in nerve axons move by axonal transport of kinesin and dynein on microtubules [3,9–11]. Although an agent-based model assuming ATP-dependent changes in internal mitochondrial states and memory of motion has been proposed previously [4], it has failed to derive a sufficient condition for mitochondrial alignment. More importantly, little is known about how the repulsive movement occurs.

In this Letter, we show that, contrary to intuition, direct repulsion between mitochondria is not necessary, and that mitochondrial alignment can arise only from mitochondrial ATP production and ATP concentration-dependent fluctuations in movement without internal mitochondrial states. This may seem strange at first, but as mitochondria approach each other, the increase in local ATP concentration leads to an increase in motion fluctuations and effective repulsion between mitochondria, and then the mitochondria are aligned in a steady state. This mechanism of generating an effective unidirectional force is very similar to the mechanism of the Soret effect [12–14], diffusiophoresis [15–17], or chemophoresis [18–20], where a force is generated that moves particles according to a gradient of temperature, diffusion constant, or adsorptive substance, respectively. This effective unidirectional force, generated only by nondirectional fluctuations in motion, is called the thermodynamic force. Our study shows that even when mitochondria are driven by a nondirectional nonequilibrium force, an effective unidirectional force can be generated by a mechanism similar to the thermodynamic force, and then mitochondrial alignment is achieved.

Here, we consider the movement of mitochondria along one-dimensional microtubules in a nerve axon (Fig. 1). Many

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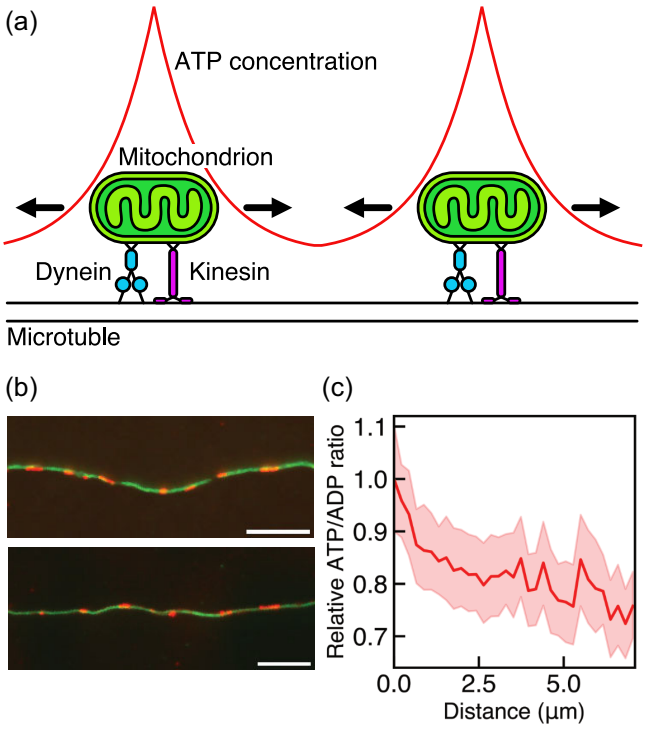

FIG. 1. (a) Schematic representation of the model. We consider one-dimensional dynamics of mitochondria and ATP concentration. Mitochondria produce ATP, and then the gradient of ATP concentration is formed around the mitochondria. Molecular motors, i.e., dynein and kinesin, attach to mitochondria and move on microtubules depending on the ATP concentration. We do not explicitly include the molecular motors in the model and instead represent the mitochondrial movements as a function of ATP concentration. (b) Microscopic images of axons showing mitochondria and tubulin stained with MitoTracker Red CM-H2XRos (red) and antitubulin antibody (green), respectively. Scale bars represent 10 μm. (c) Relative ATP:ADP signal ratio at different distances from a mitochondrion along the axon. The red line and red band represent the mean and 95% confidence interval, respectively. This figure was adopted from Ref. [4].

molecular motors, i.e., dynein and kinesin, move along the microtubules by using chemical energy from ATP [11,21]. Although dynein and kinesin move in opposite directions [22] and have different properties, we assume that they have the same property for simplicity. Since mitochondria are sufficiently large, the thermal noise of their motion is negligible [23]. Indeed, when the ATP synthase is inhibited, mitochondrial movement stops [4]. Instead, mitochondria attach and detach stochastically to molecular motors moving forward or backward, and if we observe their motion on a slower timescale than that of attachment and detachment, mitochondria appear to exhibit a random walk. Indeed, cargoes driven by molecular motors are known to exhibit ballistic motion on the order of a few seconds, but zigzag motion such as the random walk on longer timescales [24]. In contrast, the timescales of the mitochondrial alignments we are interested in are on the order of hours to days [4]. Thus, the timescales of the microscopic motions and the phenomenon of interest are sufficiently different, and we describe our model by the Langevin equation. Furthermore, when a mitochondrion detaches from a molecular motor, it does not move, and we cannot observe the inertia of the movement. We then model the mitochondrial motion as a random walk using the overdamped Langevin equation [25]. Such a formalism is much easier to calculate than the previous discrete model [4].

Molecular motors can only move if they are attached to an ATP molecule [11,21], and then the probability of movement increases with the concentration of ATP. Just as ambient temperature determines the intensity of Brownian motion, ATP concentration determines the intensity of mitochondrial motion. We consider the case where there is no explicit force to align the mitochondria. The equation for the position of the ith mitochondrion is given by

$$\begin{aligned} \frac{dx_i}{dt} &= f[a(x_i)]\eta_i(t), \\ \langle \eta_i(t) \rangle &= 0, \\ \langle \eta_i(t)\eta_j(t') \rangle &= 2\delta_{i,j}\delta(t-t'), \end{aligned} \tag{1}$$

where $a(x_i)$ is the ATP concentration at x_i, and $f(a)$ is an increasing function of a because the probability of moving increases with the concentration of ATP.

Here, we consider the concentration of ATP around the mitochondria. It is natural to assume that the diffusion and consumption of ATP is much faster than the movement of the mitochondria, because ATP is a small molecule and is consumed by too many molecules for various purposes of cellular activity besides molecular motors. Then we assume that the ATP concentration immediately relaxes to the steady state value following the mitochondrial movement. ATP is produced by mitochondria, consumed as an energy source, and diffuses. We assumed that the concentrations of molecules consuming ATP are uniformly distributed in space, and then the consumption of ATP is spatially uniform. We also assumed that the ADP concentration is constant along the axon. Thus, if the consumption of ATP is linearly proportional to its concentration due to mass action, the equation for the ATP concentration a produced by a mitochondrion located at $x = x_i$ is

$$\frac{\partial a(x,t)}{\partial t} = p_a\delta(x-x_i) + D_a\frac{\partial^2 a}{\partial x^2} - d_a a, \tag{2}$$

where p_a, D_a, and d_a are the production rate, diffusion constant, and consumption rate of ATP, respectively. When the ATP concentration at $x = \infty$ and $-\infty$ is 0 [26], the steady state ATP concentration produced by one mitochondrion is

$$a_i^* = a_0 e^{-\sqrt{\frac{d_a}{D_a}}|x-x_i|}, \tag{3}$$

where a_0 is given by $a_0 = p_a/d_a$. This is consistent with the previous experimental observation [see Fig. 1(c) and Ref. [4]]. Since Eq. (2) is linear, the concentration of ATP produced by different mitochondria can be linearly superposed, and the ATP concentration is given by

$$a^* = a_0 \sum_{i=1}^{N} e^{-\sqrt{\frac{d_a}{D_a}}|x-x_i|}, \tag{4}$$

where N is the number of mitochondria.

First, we show that there is an effective repulsive force between mitochondria. For simplicity, we consider the interaction between two mitochondria, one of which is fixed at $x = 0$. If the position of the freely moving mitochondrion is $x = x_1$, the ATP concentration at this location is given as the sum of the ATP produced by the fixed and moving mitochondria as $a(x_1) = a_0 + a_0 \exp(-\sqrt{\frac{d_a}{D_a}}|x_1|)$. Then, the dynamics of the freely moving mitochondrion is given by

$$\frac{dx_1}{dt} = f\left[a_0\left(1 + e^{-\sqrt{\frac{d_a}{D_a}}|x_1|}\right)\right]\eta_1(t). \tag{5}$$

From the above equation, we solve the Fokker-Planck equation by considering the above equation as the Stratonovich stochastic differential equation as

$$\begin{aligned}\frac{dP(x_1,t)}{dt} &= \frac{\partial}{\partial x_1}\left[f[a(x_1)]\frac{\partial}{\partial x_1}\{f[a(x_1)]P(x_1,t)\}\right] \\ &= -\frac{df(a)}{da}\frac{\partial}{\partial x_1}\left\{\frac{da(x_1)}{dx_1}f[a(x_1)]P(x_1,t)\right\} \\ &\quad + \frac{\partial^2}{\partial x_1^2}\{f[a(x_1)]^2P(x_1,t)\} \\ &= \pm a_0\sqrt{\frac{d_a}{D_a}}\frac{df(a)}{da}\frac{\partial}{\partial x_1}\left\{e^{-\sqrt{\frac{d_a}{D_a}}|x_1|}f[a(x_1)]P(x_1,t)\right\} \\ &\quad + \frac{\partial^2}{\partial x_1^2}\{f[a(x_1)]^2P(x_1,t)\},\end{aligned} \tag{6}$$

where if $x_1 > 0$ or <0, a sign of the first term is positive or negative, respectively. The first and second terms in the above equation indicate an anisotropic flow and an isotropic diffusion, respectively. Although no explicit force is added to the mitochondrion as in Eq. (1), there is an effective force between mitochondria due to the existence of an ATP concentration gradient similar to the thermodynamic force. Here, $f(a)$ is an increasing function of a, and then $\frac{df(a)}{da}$ is positive. Hence, the first term works to increase the distance between two mitochondria, i.e., the active thermodynamic force between two mitochondria works as a repulsive force.

We confirmed that this repulsive force can drive the alignment of mitochondria. As shown in Fig. 2, initially all mitochondria are randomly distributed. When the positions of two or more mitochondria were close, the local ATP concentration around each mitochondrion was increased, and these positions fluctuated intensely. Then, these mitochondria moved away from each other with high probability, and after they separated and isolated, the ATP concentration around a mitochondrion decreased (see also the Supplemental Movie [27]). Therefore, the fluctuation of the position of the mitochondria also decreased, and the mitochondria were kept apart for a long time. That is, the mitochondria moved away from each other autonomously and were almost equally spaced without the explicit repulsion force between them.

Statistical properties also showed that mitochondria move away from each other without explicit repulsive forces. When there is no interaction between mitochondria, their position is completely random. Then the distribution of the distance between two neighboring mitochondria in a steady state follows the exponential distribution: In the limit of infinite system size, keeping the ratio N/L, where L is the system size, the frequency of mitochondrial existence is described by a Poisson process, where on average Nx/L mitochondria appear for every fixed distance x. Thus, a probability distribution of the distance between two adjacent mitochondria at a steady state is given by $N\exp(-Nx/L)/L$, where the probability decreases monotonically with x. In fact, if $f(a)$ is given as a constant independent of a, i.e., each mitochondrion exhibits the random walk independent of the ATP concentration, the distribution of the distance between two adjacent mitochondria was well fitted to the exponential distribution (see gray and black dashed lines in Fig. 3), and no peaks appear at points where the distance is not zero.

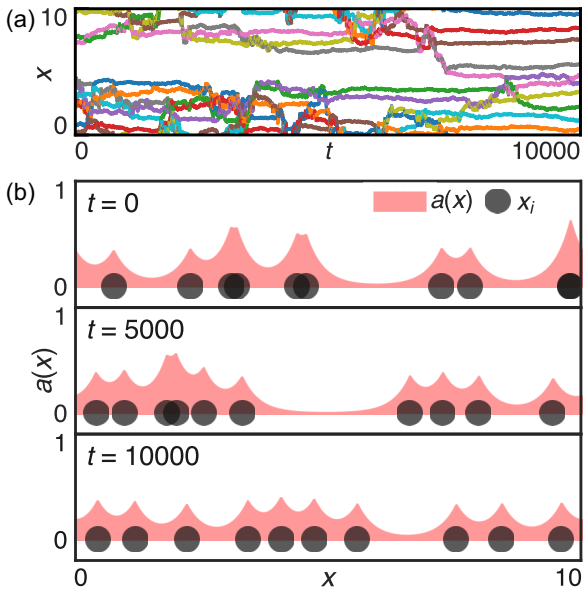

FIG. 2. Time evolution of mitochondrial positions. (a) Each line corresponds to the time evolution of the position of a different mitochondrion. At $t = 0$, the position of each mitochondrion was randomly distributed. (b) Snapshots of mitochondrial positions and ATP concentration. The black circles are the mitochondrial positions, and the red area is the ATP concentration. We set N to 10, L to 10, a_0 to 0.3, and d_a/D_a to 9.0 [28]. We numerically solved the dynamics under the periodic boundary condition. See also the Supplemental Movie [27].

In contrast, when $f(a)$ was given as an increasing function of a, i.e., the intensity of the fluctuation of the mitochondrial position depended on the local ATP concentration, the distribution of the distance between two adjacent mitochondria at a steady state was no longer fitted by the exponential function, but showed the peak at points where the distance is not zero. Although the peak still appeared when $f(a)$ was a linear function of a, the peak was less obvious because its position was close to the origin and its height was not as high (see the green line in Fig. 3). The peak appeared more obvious when $f(a)$ was a higher-order equation for a with the same parameter set (see blue and red lines in Fig. 3). This is because the higher the order of $f(a)$ for a, the greater the difference in the magnitude of the fluctuations when a mitochondrion exists alone compared to in the vicinity of other mitochondria. Thus, the thermodynamic repulsive force between mitochondria will

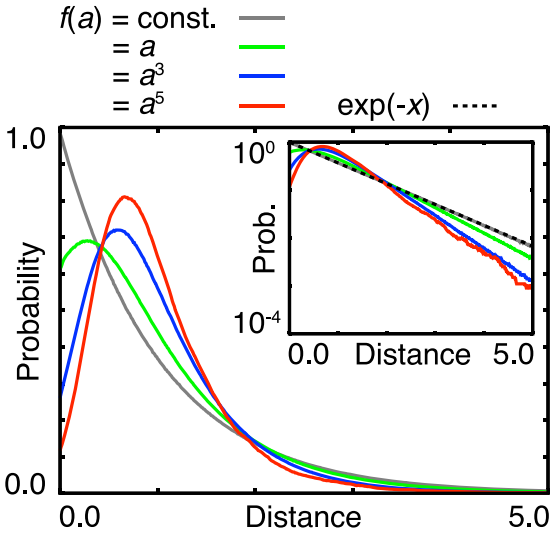

FIG. 3. Probability distribution of the distance between two adjacent mitochondria at steady state. The gray, green, blue, and red solid lines are for cases where $f(a)$ is given as constant, a, a^3, and a^5, respectively. The black dashed line is the analytically derived distribution without an interaction between mitochondria. To obtain the distribution, we set N to 100 and L to 100, the same ratio N/L as in Fig. 2. Other parameters are the same as in Fig. 2. Inset: The distribution is plotted with a logarithmic scale.

also be greater since $f(a)$ is of higher order. Indeed, the repulsive force between two mitochondria is greater if $f(a)$ is of higher order than a, as can be seen from Eq. (6). In any case, if the magnitude of the fluctuations in mitochondrial position depends positively on the ATP concentration, the mitochondria will align at a steady state even if there is no explicit repulsive force between them.

Here, we show that nondirectional fluctuations in mitochondrial movement and mitochondrial ATP production are sufficient to align mitochondria along a nerve axon. This suggests that mitochondrial function itself is linked to patterning, and that no special function such as signaling between mitochondria is required for equispaced patterning. In addition, it has been observed experimentally that the movement of mitochondrial position in nerve axons is initially strong, but as it gradually approaches the equispaced pattern, the movement becomes weaker [4], as we observed in Fig. 2. For this gradual fixation, the nonlinear dependence of the fluctuation of the mitochondrial movement on the ATP concentration will play an important role: The stronger the nonlinearity of the dependence of the fluctuations on the ATP concentration, the greater the relative difference in the fluctuations is when the mitochondria are close together and when they are far apart, and the less likely they are to move when the mitochondria are aligned. Since multiple molecular motors are known to act in concert for cargo transport [22,29–31], the ATP concentration dependence of mitochondrial fluctuations would inevitably be nonlinear. In the future, such nonlinearity will be validated both experimentally and theoretically using more microscopic models. Note that even after alignment, the fluctuations continue, albeit weakly. Therefore, in the real system, after the initial alignment by a mechanism we propose here, there may be a mechanism to further fix the position of the mitochondria. Indeed, some mechanisms have been proposed to arrest mitochondria after positioning [3,32,33].

Mitochondrial alignment is thought to be physiologically important for maintaining a uniform ATP concentration in cells [4]. The mechanism proposed here shows that mitochondria move to autonomously resolve deviations in ATP concentration without any special mechanism. Moreover, it has long been known that mitochondria move in the direction of lower ATP concentrations in a nerve axon [1]. Our results are in good agreement with this observation. Although we consider a one-dimensional system here because the nerve axon is pseudo-one-dimensional, the mechanism presented will also work for higher-dimensional systems. Therefore, the proposed mechanism can be used to achieve a uniform intracellular ATP concentration in different cells, even beyond the nerve axon. Furthermore, a similar mechanism may work for the uniform distribution of organelles other than mitochondria and molecules. This study will provide an important basis for future discussions of the distribution of substances within cells.

In this Letter, we have shown that nondirectional motion due to nonequilibrium processes, not thermal noise, can generate unidirectional motion of biological matter. This is more as thermodynamic forces driven by thermal fluctuations than the motion of active matter, and we term this active thermodynamic force. In fact, Eq. (1) contains neither interaction terms between mitochondria nor ATP gradient-dependent terms, unlike many equations describing active matter [34,35]. This fundamental equation contains only the ATP concentration-dependent fluctuation as the Brownian particle in the thermal gradient. Although the equations governing motion are so simple, by combining them with nonequilibrium reactions that change the chemical field, we found that interactions between biological matter can occur through the active thermodynamic force. This result reminds us of the diversity of mechanisms governing the motion of biological matter. Our study will be a pioneering step in understanding the motion of biological materials due to active thermodynamic forces driven by nonequilibrium processes, and it is expected that both experiment and theory will reveal in further studies that a variety of processes are driven by similar mechanisms.

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[27] See Supplemental Material at http://link.aps.org/supplemental/10.1103/PhysRevResearch.6.L022024 for the movie of the dynamics of mitochondria and ATP distribution. The parameters utilized in this movie are identical to those presented in Fig. 2.

[28] Although the actual decay rate of ATP and the rate of diffusion of ATP within the cell are not known, only two parameters are important in the model: $\sqrt{d_a/D_a}$, the characteristic length of decrease of the ATP concentration, and L/N, the average interval of mitochondrial positions. Both the former and latter have a dimension of length, and then finally the ratio of those is a unique parameter, which determines the behavior of the system. Those two values are the same order, as shown in Figs. 1(b) and 1(c), and then we used the same order parameters in numerical experiments.

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