Cooperative Molecular Motors

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We present a simple stochastical model for motor molecules that cooperate in large groups. This model could apply for actin-myosin motors in muscles and for motility assays with a high concentration of motor molecules. We calculate the dependence of the velocity on the applied force as a function of ATP concentration and show the existence of a dynamical phase transition allowing for spontaneous directed motion even if the system is spatially symmetric. In the symmetric case, the problem is isomorphous to a paramagnet-ferromagnet transition, in the asymmetric case to a liquid-vapor transition.

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Many active processes in biological systems such as muscular contraction, cell motility, and some cellular transport processes are mediated by molecular motors. These motors are protein molecules that can perform mechanical work in the presence of adenosine triphosphate (ATP) as an energy source [1].

Different families of motor proteins have been distinguished that actively slide along rodlike filaments. These filaments play the role of a track to guide the motion. Dyneins and kinesins operate on microtubules while myosins walk along actin filaments. In many cases, these motor molecules do not operate as single particles but cooperate in groups that form a multimotor [1,2].

The most prominent example of a multimotor is the actin-myosin system in muscles [1,3]. Electron microscopy and x-ray diffraction studies of muscle fibers reveal that many myosin molecules are attached to each other with their tails and form myosin filaments. The heads of the myosin molecules are bound to actin filaments. During muscular contraction, the myosin filaments actively slide along actin filaments driven by the chemical energy of ATP. The spacing of actin monomers along the actin filaments bear no special relation with the spacing of myosin molecules in the myosin filament, so that it is a good starting point to consider the motors and track structure as incommensurate [3].

Recent improvements of experimental techniques allow the direct observation of the action of motor proteins [4–6]. In motility assay studies, a glass surface is coated with motor molecules in aqueous solution. Track filaments bound to the motors begin to move along the surface in the presence of ATP [4,6,7]. The sliding velocity can be measured as a function of ATP concentration. However, since the function of motors is not directly observable at molecular scales, the mechanisms of force generation are still not resolved.

Simplified stochastical models have been suggested that give insight in the physical mechanisms important for the force generation of molecular motors. They take into account fluctuations and Brownian motion [2,8–12]. Besides the work of Leibler and Huse [2], who compared the situations of single motors and motors working together in large groups, the previous theoretical work focused on mechanisms for the directed motion of single motor molecules [8–12].

In this Letter, we introduce a theoretical model to describe the cooperative behavior of large ensembles of motors. The motor molecules are described as particles that are attached to a backbone. The model addresses incommensurate or disordered arrangements of particles that correspond to the situations in muscle fibers and motility assays, respectively. The sliding velocity of the backbone along its track is calculated as a function of the external force and the ATP concentration.

We show that the cooperation of a large number of particles can lead to dynamical phase transitions and instabilities that characterize the behavior of such a motor collection. It turns out that cooperating motors can generate a directed force even if the system is symmetric. The direction of motion of a symmetric system is selected by spontaneous symmetry breaking.

We define our model for the most simple case, where particles are rigidly attached to a backbone with fixed spacing s. The position $\hat{x}_i$ of the ith particle reads $\hat{x}_i = is + X$, where X is the position of the backbone along its track. Each particle in the vicinity of the track can be either in a strongly bound state $\sigma = 1$ or in a weakly bound state $\sigma = 2$. The energy of a particle in state σ is given by periodic potentials $W_\sigma(\hat{x}) = W_\sigma(\hat{x} + l)$ with period l. This periodicity reflects the regular surface structure of the track filament formed by subunits of size l. From now on, we use cyclic coordinates $x \equiv \hat{x} \bmod l$ with $0 < x < l$, which describe the particle positions with respect to the potential period.

The system is characterized by distribution functions P and P_σ with $P(x,t) = P_1(x,t) + P_2(x,t)$, which give the probability density to find a particle in state σ at position x at time t. For a finite number N of particles, $P(x,t) \equiv N^{-1}\sum_{i=1}^{N}\delta(x - x_i(t))$. We are interested in the limit of large N. In this limit, P approaches a constant value $P(x,t) = 1/l$ if the structure of motors and track is incommensurate, i.e., the ratio l/s is irrational. The same result holds if the particles are randomly attached to the backbone with a homogeneous distribution.

The equations of motion for P_σ read

$$\partial_t P_1 + v\,\partial_x P_1 = -\omega_1(x)P_1 + \omega_2(x)P_2\,, \tag{1}$$

$$\partial_t P_2 + v\,\partial_x P_2 = \omega_1(x)P_1 - \omega_2(x)P_2\,. \tag{2}$$

Here, $\omega_1(x)$ and $\omega_2(x)$ denote the transition rates between the two states. The velocity of the backbone $v \equiv \partial_t X$ is determined by the relation $f_{\mathrm{ext}} = \lambda_0 v - f$, which expresses the externally applied force per particle f_{ext} in terms of the force per particle

$$f \equiv -\int_0^l dx\,(P_1\,\partial_x W_1 + P_2\,\partial_x W_2)\,, \tag{3}$$

exerted by the potentials. The friction force $\lambda_0 v$ is due to viscous damping with damping coefficient λ_0.

Transitions between the two states are (i) thermal transitions, which obey detailed balance, and (ii) ATP driven excitations, which do not obey detailed balance and which drive the active motion of the motors. We write $\omega_1(x) = \omega_2(x)\exp\{[W_1(x) - W_2(x)]/T\} + \Omega\Theta(x)$, where T denotes temperature [9]. The excitation amplitude Ω is proportional to the concentration of ATP and $\Theta(x)$ describes the x dependence of ATP excitations. For $\Omega = 0$, detailed balance is preserved.

Using the relation $P_2 = -P_1 + 1/l$, which is valid for an incommensurate or disordered system, the probability distribution in the steady state obeys

$$v\,\partial_x P_1 = -[\omega_1(x) + \omega_2(x)]P_1 + \omega_2(x)/l\,. \tag{4}$$

It is of pedagogical value to solve (4) in a power expansion as a function of v,

$$P_1 = \sum_{n=0}^{\infty} v^n P_1^{(n)} \quad \text{with } P_1^{(n)} = -\frac{1}{\omega_1 + \omega_2}\,\partial_x P_1^{(n-1)} \tag{5}$$

and $P_1^{(0)} = \omega_2/(\omega_1 + \omega_2)l$. The equation for v is then

$$f_{\mathrm{ext}} - f_\Omega^{(0)} = (\lambda_0 + f_\Omega^{(1)})v + \sum_{n=2}^{\infty} f_\Omega^{(n)} v^n, \tag{6}$$

with $f_\Omega^{(n)} = \int_0^l P_1^{(n)}\partial_x(W_1 - W_2)\,dx$.

If detailed balance is preserved ($\Omega = 0$, absence of ATP) $f_\Omega^{(0)} = 0$, $f_\Omega^{(1)} > 0$, there is no spontaneous motion, friction is increased. If detailed balance is broken, two important features appear: (i) $f_\Omega^{(0)}$ becomes different from zero; the system can set itself into motion spontaneously. This appearance of a self-propelling force has already been discussed in the framework of single motors [8,9]. (ii) $f_\Omega^{(1)}$ can become negative. This is a qualitatively new feature stemming from the "cooperativity" of motors. To better understand the implications of this sign change, we consider first a symmetric track filament. Under such circumstances, Eq. (6) reads to relevant order (with the condition of no external force $f_{\mathrm{ext}} = 0$),

$$-(\lambda_0 + f_\Omega^{(1)})v = v^3 f_\Omega^{(3)} + O(v^5)\,. \tag{7}$$

If $\lambda_0 + f_\Omega^{(1)} > 0$, the only solution is $v = 0$. If $\lambda_0 + f_\Omega^{(1)} < 0$, the system bifurcates towards a moving solution [see Fig. 1(a)] with

$$v = \pm\left(\frac{1}{f_\Omega^{(3)}}\,\frac{\partial f^{(1)}_{(\Omega=\Omega_c)}}{\partial\Omega}\,(\Omega - \Omega_c)\right)^{1/2}, \tag{8}$$

where Ω_c is the critical excitation rate for which $\lambda_0 + f_{\Omega_c}^{(1)} = 0$. The solution with $v = 0$ is stable for $\Omega < \Omega_c$ and becomes unstable for $\Omega > \Omega_c$. In the latter case, starting with $v = 0$, any small perturbation grows in time because the force f exerted by the potentials acts to increase the velocity. Eventually the system reaches a state with constant velocity v as given by (8). This state is stable with respect to small perturbations. The direction of motion is selected randomly as a result of fluctuations via spontaneous symmetry breaking. With an external force, the problem is formally equivalent to that

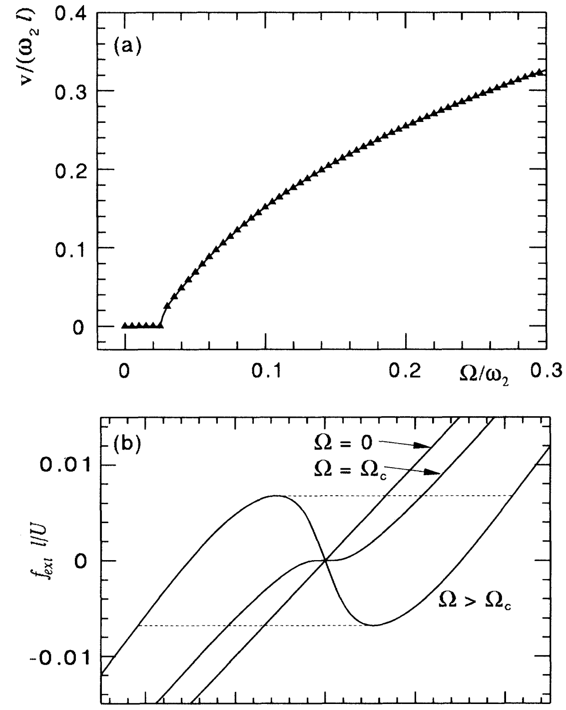

FIG. 1. (a) Spontaneous velocity v as a function of the excitation amplitude Ω for a symmetric potential as shown in Fig. 2(b) with $d/l = 0.1$ and $\lambda_0\omega_2 l^2/U = 0.1$. (b) External force f_{ext} as a function of the velocity v for the same system and $\Omega = 0$, $\Omega/\omega_2 = \Omega_c/\omega_2 \simeq 0.026$ and $\Omega/\omega_2 = 0.1$.

of a magnetization in the presence of a magnetic field close to a paramagnetic-ferromagnetic critical point [see Fig. 1(b)].

The general case of an asymmetric filament is now equivalent to that of a liquid-vapor critical point. The velocity corresponds to the density, the excitation amplitude to temperature, and the force to pressure. The critical point v_c, f_c, Ω_c can be defined in exactly the same way as in the case of fluids, and the velocity in its vicinity obeys the standard mean field laws $[|v - v_c| \propto (f_{\text{ext}} - f_c)^{1/3}, \Omega = \Omega_c; |v - v_c| \propto (\Omega - \Omega_c)^{1/2}, f_{\text{ext}} = f_c]$.

We postpone for a more detailed article the corresponding discussion and prefer to illustrate these considerations on a simple example. We choose a piecewise linear potential W_1, a constant W_2, and a piecewise constant rate of ATP excitations as described in Fig. 2. For simplicity, we assume that ω_2 is constant, and we look at the limit of small temperatures compared to the potential barriers $T \ll U$. In this limit, $\omega_1(x) = \Omega\Theta(x)$, and thermal excitations are neglected. The (f_{ext}, v) diagram is plotted in Fig. 3(a) for an asymmetric track filament and different values of Ω: For $\Omega < \Omega_c$, v increases monotonously as a function of f_{ext}. The effective friction coefficient $\lambda \equiv \partial f_{\text{ext}}/\partial v$ is everywhere positive. For $\Omega = \Omega_c$, v increases monotonously as a function of f_{ext} but at the critical point $\partial f_{\text{ext}}/\partial v = \partial^2 f_{\text{ext}}/\partial v^2 = 0$. For $\Omega > \Omega_c$, the function $v(f_{\text{ext}})$ is multivalued in a certain region, like a van der Waals isotherm below the critical temperature: the two steady states with $\partial f_{\text{ext}}/\partial v > 0$ are stable, the intermediate one with $\partial f_{\text{ext}}/\partial v < 0$ is unstable.

The existence of unstable steady states leads to discontinuities of v as a function of f_{ext} as follows: first, we look at the load-free velocity (i.e., $f_{\text{ext}} = 0$). If a load is applied, i.e., $f_{\text{ext}} < 0$, v decreases. The maximal load $|f_{\max}|$ the collection of motors can carry is determined at the minimum of the function $f_{\text{ext}}(v)$. If this load is exceeded, i.e., $|f_{\text{ext}}| > |f_{\max}|$, the system changes its direction of motion discontinuously. For reverse motion, a similar instability occurs at the maximum of $f_{\text{ext}}(v)$. These discontinuities are indicated in Fig. 3(a) for $\Omega/\omega_2 = 0.02$ by horizontal lines. This instability occurs for finite velocity. The system therefore becomes unstable before the motion is stopped: It cannot be reversed continuously by applying an external force. In an experimental situation this instability would look like a sudden "rip-off" of the track filament from the motors as soon as a critical load is reached.

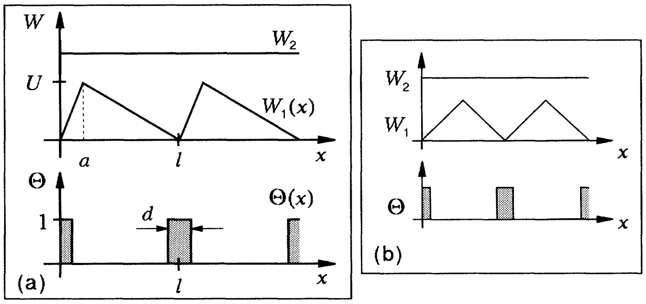

FIG. 2. Schematic diagrams of the potentials $W_1(x)$, $W_2(x)$, and the rate of ATP excitations $\Omega\Theta(x)$ for an asymmetric system (a) and a symmetric system (b). The potentials are characterized by the amplitude U, the period l, and the asymmetry parameter a/l of the sawtooth potential W_1. ATP excitations occur only within an interval of width d, centered at the potential minimum where $\Theta(x) = 1$.

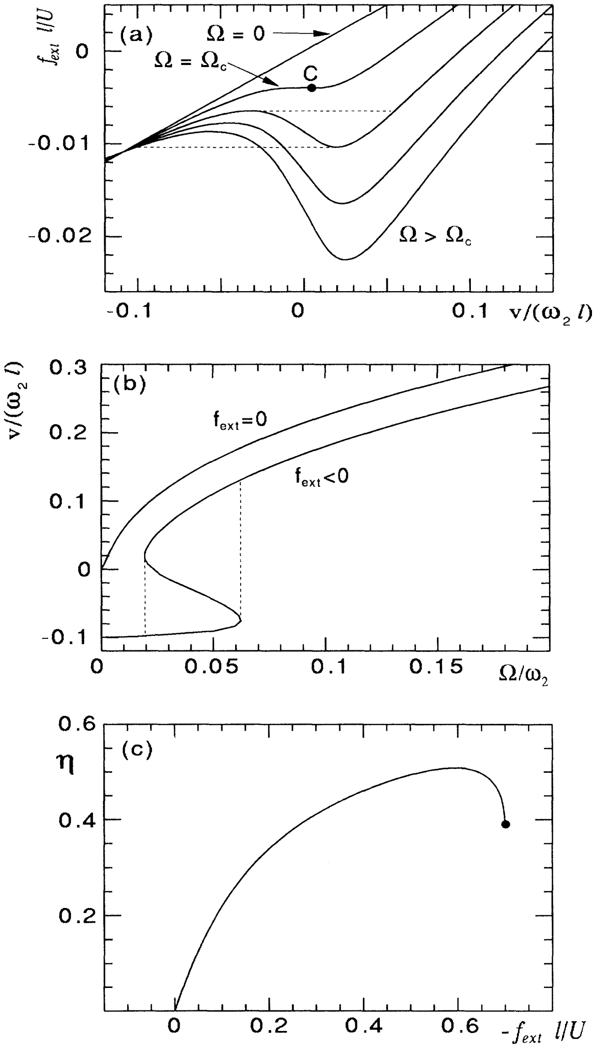

FIG. 3. (a) External force f_{ext} as a function of the velocity v for an asymmetric potential as shown in Fig. 2(a) with $d/l = a/l = 0.1$ and $\lambda_0\omega_2 l^2/U = 0.1$. The curves correspond to $\Omega/\omega_2 = 0$, 0.009, 0.02, 0.03, and 0.04, from top to bottom. Note the critical isoexcitation (equivalent to critical isotherm) for $\Omega/\omega_2 = \Omega_c/\omega_2 = 0.009$, which includes the critical point C with critical values $v_c/\omega_2 l \simeq 0.005$, $f_c l/U \simeq -0.004$. (b) Sliding velocity v as a function of Ω for $f_{\text{ext}} = 0$ (top) and $f_{\text{ext}} l/U = -0.01$ (bottom). (c) Efficiency η as a function of f_{ext} for $\Omega/\omega_2 = 10$ and $\Delta G = U$.

The velocity v for an asymmetric track filament is displayed as a function of the excitation amplitude Ω in Fig. 3(b). With no load, the motors begin to move for arbitrarily small Ω and reach for large Ω a maximal velocity $v/\omega_2 l \simeq 1.94$. With a constant load $f_{\mathrm{ext}} l/U = -0.01$, the system slides backwards for small Ω. If Ω is increased, the direction of motion changes discontinuously at $\Omega/\omega_2 \simeq 0.063$. For decreasing Ω, this instability occurs for $\Omega/\omega_2 \simeq 0.02$. The sliding velocity as a function of Ω is hysteretic.

An important property of the system is its efficiency $\eta \equiv \mathcal{W}/\mathcal{Q}$. Here, $\mathcal{W} \equiv -f_{\mathrm{ext}} l$ is the mechanical work performed during one potential period and

$$\mathcal{Q} \equiv \Omega \, \Delta G \, \frac{l}{v} \int_0^l dx \, P_1(x) \Theta(x) \tag{9}$$

is the energy consumption per particle along one potential period. The energy cost of exciting a particle to state $\sigma = 2$ is denoted by ΔG.

The efficiency η is displayed as a function of the load in Fig. 3(c). For increasing load, the efficiency reaches a maximum where $\eta \simeq 0.51$. It decreases again before the maximal load $|f_{\mathrm{ext}}| = |f_{\max}|$ is attained and the system becomes unstable.

In the examples, as shown in Figs. 1 and 3, thermal excitations are neglected. The critical point still exists if thermal excitations are taken into account, but its location in the $(f_{\mathrm{ext}}, v, \Omega)$ coordinate system varies with temperature.

The results discussed so far have been obtained with the assumption that the motors are rigidly coupled. This is equivalent to a mean field theory, which neglects fluctuations of the positions of individual particles. These fluctuations can be taken into account by elastically coupling the particles to the backbone via a spring with elastic modulus c. It can be shown that for sufficiently large values of c this generalized model exhibits the same qualitative behavior as the rigid model described here [13].

In summary, we have shown that a large number of particles, which are coupled together by a rigid backbone and which move in periodic potentials, can form a very efficient motor. This efficiency comes from the fact that no diffusive steps are required as a result of the cooperativity of the system. This cooperativity leads to the existence of instabilities and dynamical phase transitions. In the symmetric case, the transition is isomorphous to a paramagnet-ferromagnet transition, in the asymmetric case to a liquid-vapor transition. As a consequence, the velocity as a function of the applied load shows discontinuities and hysteretic behavior. In particular, the motion cannot be stopped or reversed continuously by increasing the load. An important result is the generation of a directed force and directed motion even if the system is symmetric. This behavior differs fundamentally from that of single particles where the spatial asymmetry of the system is essential.

The mechanisms for spontaneous symmetry breaking and directed motion that we propose here are not restricted to biological motors and ATP excitations. They could also be implemented in a physical system and driven by other types of excitation processes. If our model is relevant for biological motors, the characteristic behavior as described for asymmetric potentials should be observable in motility assay experiments with a high concentration of motor molecules.

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