Dynamic Instabilities in Assemblies of Molecular Motors with Finite Stiffness

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We propose a two-state "soft-motor" model for the collective behavior of molecular motors which takes into account both the internal motor stiffness and the periodic interaction with the filament. As in the Prandtl-Tomlinson model of tribology, the important parameter of the model is the pinning parameter, which compares the stiffness of the motors to the stiffness of the potential. The model predicts dynamic instabilities in two disconnected regions of parameter space. These parameter ranges correspond to two existing theories of motor assemblies, the rigid two-state model and the crossbridge model. The model also predicts a discontinuity of the slope of the force-velocity relation at small velocities.

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In cells, chemical energy is constantly consumed and partly converted into mechanical work by motor proteins [1]. In contradistinction to passive matter, living matter can display spontaneous periodic activity, which has important physiological functions. Examples include spontaneous oscillations of the mechanosensory hair bundle in the inner ear, the beating of cilia and muscle cell oscillations (reviewed in [2,3]). Oscillatory instabilities could emerge from the interaction with regulatory proteins or from specific geometrical constraints [3], but recent experiments suggest that the oscillatory behavior can be an intrinsic property of molecular motor assemblies working against an elastic load [4].

Such instabilities are predicted by existing models where the motors act collectively because they are tightly bound together [5–8]. In these theories, the instability mechanism is linked to the breaking of the detailed balance condition (which reflects energy consumption), and to the generation of a force that amounts to a negative friction at low velocities. Oscillatory behavior occurs in the presence of a weak elastic load. Another collective effect arises under force clamp condition and at low noise level: the motion can switch between phases of opposite velocities. This phenomenon is called "bidirectional motion" [9,10]. Existing theories can be classified into two seemingly unrelated categories: the crossbridge model and the rigid two-state model [5–7]. In crossbridge or "power-stroke" models [1,11], the motors are described as flexible springs, their heads bind to specific attachment sites and remain stuck until unbinding. The motors switch between well-defined conformational states. The dynamic instability is associated to a variation of the unbinding rate with spring tension [5,6]. In the rigid two-state model [7,8], the centers of mass of the motors are described as particles rigidly linked to a common backbone. The particles switch between two states where they experience the periodic interaction potential of the filament. This model can also lead to dynamic instabilities if the transition rates break detailed balance.

We propose here a "soft-motor" model which takes into account both the flexibility of the motors and the periodic interaction potential due to the filament. This model exhibits a nontrivial stability diagram with two separated unstable regions at high and low motor stiffness. It therefore predicts that a molecular motor assembly can undergo a dynamic instability either by increasing or by decreasing the motor stiffness. An important parameter of the soft-motor model is the pinning parameter a which compares the stiffness of the motors to the stiffness of the periodic potential. This parameter has not yet been introduced for molecular motor assemblies but it controls the transition to solid friction in the Prandtl-Tomlinson model of tribology [12], which can be seen as the single state version of the soft-motor model. Although no solid friction is predicted in the soft-motor model, a generic discontinuity of the slope of the force-velocity relation at small velocities is predicted which is a signature of the solid friction. The soft-motor model also enables to make a link between the existing theories of molecular motor assemblies considered so far as unrelated. At low values of the pinning parameter, the model reduces to the rigid two-state model while for strong pinning, the predicted behavior of an assembly of motors is very similar to that of the "crossbridge" model. The very rapid stretching of the motor

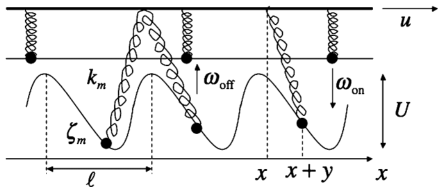

FIG. 1. Schematic representation of the soft-motor model (see text).

spring upon sliding down the potential after attachment plays the role of the power stroke.

The model.—A schematic representation of the soft-motor model is sketched on Fig. 1. It considers a collection of N motors, modeled as springs of stiffness k_m tightly linked to a common rigid backbone moving at a velocity $u(t)$. The motors interact with a fixed filament. We call x the position of the attachment point of a given motor on the backbone in the reference frame of the filament at time t, and y the elongation of the spring. The motors are either in an "attached" or a "detached" state. In the attached state, the motors interact with the filament via a potential $W(x + y)$ which is periodic with amplitude U and period ℓ, to reflect the periodicity of the filament.

We first focus on the internal dynamics of a given motor located at position x at time t and that has been attached for a time τ. We call $y(x, \tau, t)$ the elongation of its spring. Force balance on the motor head involves the friction force due to the sliding velocity between motor head and filament with friction coefficient ζ_m, the interaction between motor and filament and the elastic force of the spring:

$$\zeta_m[\partial_t y + \partial_\tau y + u(t)(\partial_x y + 1)] = -k_m y - W'(x + y). \tag{1}$$

We assume that the viscous friction on the motor in the detached state is very low and that the relaxation time of the spring in this state is much smaller than any other time scale, so that the motor springs in the detached state are not stretched. We also neglect thermal noise and assume that motors bind with no elongation: $y(x, \tau = 0, t) = 0$.

In the limit of a large number of motors $N \gg 1$, we define the density $p(x, \tau, t)$ of motors at position x (modulo ℓ) that have been attached for a time τ, at time t. The detachment rate $\omega_{\mathrm{off}}(x + y, y)$ depends both on the position of the motor head on the filament $x + y$ and on the elongation y itself, and the attachment rate $\omega_{\mathrm{on}}(x)$ only depends on the position x. The rate functions $\omega_{\mathrm{on}}(x)$ and $\omega_{\mathrm{off}}(x + y, y)$ are periodic in x. The rates are of the order of a typical inverse transition time $t_m \sim 10^{-3}$ s and they do not satisfy detailed balance. Motor conservation imposes that

$$\partial_t p + \partial_\tau p + u(t)\partial_x p = -\omega_{\mathrm{off}}(x + y, y)p + \omega_{\mathrm{on}}(x)\delta(\tau)n_d, \tag{2}$$

where $n_d(x, t)$ is the density of detached motors at position x. We consider motors which are distributed either randomly or periodically with a spacing incommensurate with the period of the filament, so that $n_d(x, t) + \int_0^\infty d\tau p(x, \tau, t) = 1/\ell$.

The force exerted by the motors on the backbone is $F_m = N k_m \int_0^\infty d\tau \int_0^\ell dx y(x, \tau, t) p(x, \tau, t)$. Except for symmetric potentials and transition rates, it is finite at vanishing velocity. The backbone has therefore a spontaneous velocity under vanishing external force. At constant velocity u, the force reaches a steady state. We define the effective friction coefficient as the slope of the force-velocity relation at small velocity: $\xi_{\mathrm{eff}} = -(\partial_u F_m)_{u=0}$. A negative value of this friction coefficient is a signature of a dynamic instability [6,7], which leads to oscillations or bidirectional motion. In the following, we focus on the effective friction coefficient ξ_{eff} and determine the regions of parameter space where it is negative.

Adiabatic approximation.—The various regimes of the theory can be discussed by introducing the dimensionless parameter $\epsilon = (\zeta_m/k_m)/t_m$, which compares the characteristic time of spring elongation with the characteristic attachment-detachment time. In the case $\epsilon \gg 1$, once they are attached, the motors behave as "stuck" to the filament. They elongate by $\delta y \simeq -u/\omega_{\mathrm{off}}$ before detaching and dissipating the stored elastic energy. This process generates a positive effective friction coefficient first introduced in Ref. [13] under the name of "protein friction." Therefore, in the regime $\epsilon \gg 1$, no instability can exist.

In the limit $\epsilon \ll 1$, the elongation y evolves much faster than the density p. This suggests an "adiabatic" approximation. All the motors attached at a given position x reach almost "instantaneously" an elongation y_0 satisfying the static mechanical equilibrium

$$k_m y_0 + W'(x + y_0) = 0. \tag{3}$$

This equation does not always have a single solution $y_0(x)$. The second important dimensionless parameter of the theory is the pinning parameter, defined as $a = |\min[W''(x)/k_m]|$. The value of this parameter determines the number of solutions to Eq. (3) depending on whether $a < 1$ or $a > 1$. In the following, the regime associated to soft motors ($a < 1$) is called "weak pinning regime," whereas the regime associated to stiff motors ($a > 1$) is called "strong pinning regime."

In the weak pinning regime $a < 1$, Eq. (3) has only one solution, so that all the motors attached in x have the same elongation $y_0^+(x)$. The adiabatic approximation of Eq. (1) is

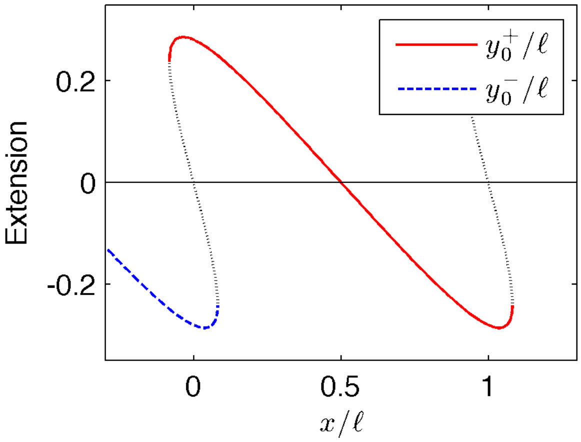

FIG. 2 (color online). Functions $y_0^+(x)$ and $y_0^-(x)$ for a sinusoidal potential with $a = 1.8$.

then $y(x,\tau) \simeq y_0^+(x)$. The situation is different in the strong pinning regime $a > 1$. As shown in Fig. 2, two possible equilibrium elongations $y_0^+(x)$ and $y_0^-(x)$ satisfy Eq. (3). For each position x, two populations of motors coexist, with the two possible elongations. The motors with elongation $y_0^-(x)$ attached when they were facing the potential well to the left of their current position, and their head is still "pinned" in this potential well. Conversely, the motors with elongation $y_0^+(x)$ attached at later time, while they were facing the potential well in front of their current position. As $x - u\tau$ is the position of the head just after attachment, this leads to the following adiabatic approximation of Eq. (1): $y(x,\tau) \simeq y_0^-(x)$ if $x - u\tau < 0$, $y(x,\tau) \simeq y_0^+(x)$ if $x - u\tau > 0$ (we have defined here the position $x = 0$ as the maximum of the potential, and considered positions x between 0 and ℓ [14]).

Within these adiabatic approximations, the explicit calculation from Eq. (2) leads to an effective friction coefficient valid in the limit $\epsilon \to 0$:

$$\xi_{\rm eff} = \frac{Nk_m}{\ell}\int_0^\ell dx \frac{y_0^+}{\omega_{\rm on} + \tilde{\omega}_{\rm off}} \frac{d}{dx}\left(\frac{\omega_{\rm on}}{\omega_{\rm on} + \tilde{\omega}_{\rm off}}\right) + \xi_2, \tag{4}$$

where $\tilde{\omega}_{\rm off}(x) = \omega_{\rm off}(x + y_0^+(x), y_0^+(x))$. The friction coefficient ξ_2 vanishes if $a < 1$ and depends only on the values of the transition rates at the maximum of the potential if $a > 1$:

$$\xi_2 = \frac{Nk_m}{\ell}\left[\frac{\omega_0 y^+}{(\omega_0 + \omega^+)\omega^+} - \frac{\omega_0 y^-}{(\omega_0 + \omega^-)\omega^-}\right] + \frac{Nk_m y^+ \omega_0^2(\omega^+ - \omega^-)(\omega_0 + \omega^- + \omega^+)}{\ell\omega^+\omega^-(\omega_0 + \omega^-)(\omega_0 + \omega^+)^2}, \tag{5}$$

with $y^+ = y_0^+(0)$, $y^- = y_0^-(0)$, $\omega^+ = \omega_{\rm off}(y^+, y^+)$, $\omega^- = \omega_{\rm off}(y^-, y^-)$, and $\omega_0 = \omega_{\rm on}(0)$. A necessary condition for the coefficient $\xi_{\rm eff}$ to be negative is that the transition rates break detailed balance.

The friction coefficient ξ_2 is positive and corresponds to the concept of protein friction [13]. It does not vanish even if the transition rates are uniform, as it is mostly due to the attachment-detachment cycles of the motors. In the vicinity of the critical value of the pinning parameter, $a \to 1^+$, ξ_2 vanishes as $\sqrt{a-1}$. Because the expression of the friction coefficient ξ_2 is not symmetric with respect to the exchange between (y^+, ω^+) and (y^-, ω^-), the soft-motor model generically predicts a discontinuity of the slope of the force-velocity relation at small velocities. The crossbridge model can lead to such a discontinuity only if singular transition rate functions are used [15].

Localized attachment.—In order to make precise predictions, we now make a specific choice of the transition rate functions: we consider the case where the unbinding rate depends only on the elongation y and where the binding rate is infinite over a small region of size $d \ll \ell$ centered around a position $x_{\rm on}$, and vanishes outside this region. This mimics the simple picture of an attachment site. The effective friction coefficient at leading order in d is then

$$\xi_{\rm eff} \simeq -Ndk_m y_0'(x_{\rm on}) \frac{\omega_{\rm off}(y_{\rm on}) - y_{\rm on}\omega_{\rm off}'(y_{\rm on})}{2\ell\omega_{\rm off}^2(y_{\rm on})}, \tag{6}$$

where we have called $y_{\rm on} = y_0(x_{\rm on})$ the motor elongation after attachment and where the primes denote derivatives.

Two limits are of interest. For stiff motors ($a \ll 1$), $y_{\rm on}$ vanishes and we obtain $\xi_{\rm eff} \simeq NdW''(x_{\rm on})/[2\ell\omega_{\rm off}(0)]$. This friction coefficient can be negative if $W''(x_{\rm on}) < 0$, i.e., if $x_{\rm on}$ is close to the maximum of the potential. This can happen only for an active system where detailed balance is broken, as already discussed for the rigid two-state model [8,16]. The second limit is that of very soft motors ($a \gg 1$) where $\xi_{\rm eff} \simeq Ndk_m[\omega_{\rm off}(y_{\rm on}) - y_{\rm on}\omega_{\rm off}'(y_{\rm on})]/[2\ell\omega_{\rm off}^2(y_{\rm on})]$. In this case, the friction is negative if the unbinding rate depends on elongation. This expression is very similar to that of the friction coefficient calculated for a crossbridge model [6]. The rapid movement of the motors towards the bottom of the potential just after attachment plays the role of the "power-stroke." Equation (6) makes clear that two regimes of instability are accessible in the soft-motor model, and establishes a link between the two types of models that generate oscillations of molecular motors: rigid two-state models [7,8] and models with force-dependent unbinding rates [5,6,17,18].

Stability diagram.—The analytical expressions of the effective friction $\xi_{\rm eff}$ have been obtained in the limit $\epsilon \to 0$. For finite values of ϵ, we have calculated $\xi_{\rm eff}$ numerically. We have studied a slightly different case where the binding rate is a regular function with a localized maximum (defined in the caption of Fig. 3). We looked for the instability boundaries where $\xi_{\rm eff}$ changes sign. The results are reported in Fig. 3 as a stability diagram in a plane (a, ϵ). There are two disconnected regions of instability, corresponding to stiff motors and soft motors, respectively. The stability limits along the a axis are very well described by the results obtained with the adiabatic approximation. Note that the topology of the stability diagram depends on the particular choice of the transition rates; the instability associated with soft motors does not exist if the attachment rate is uniform (whatever the potential shape or the dependence on elongation of the unbinding rate).

Link with the Prandtl-Tomlinson model.—The single state version of our theory ($\omega_{\rm off} = 0$) corresponds to the overdamped athermal Prandtl-Tomlinson model of tribology [12]. In this model, the pinning parameter plays a key role and monitors the transition to solid friction: a discontinuity in the force-velocity-relation appears when $a > 1$. Solid friction though does not exist in the soft-motor model since the time to wait before the system reaches the solid friction force varies as $1/|u|$, and is larger than t_m in the limit of small velocities. Solid friction is replaced by the protein friction ξ_2, which vanishes at the elastic instability

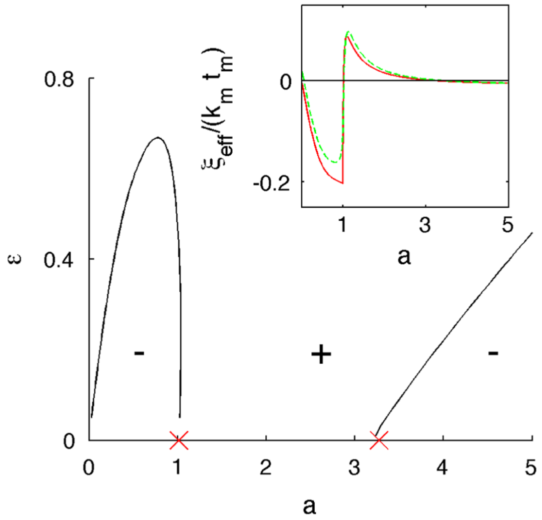

FIG. 3 (color online). Stability diagram. The black line separates the stable zone (where $\xi_{\text{eff}} > 0$, marked "+") from the unstable zones (where $\xi_{\text{eff}} < 0$, marked "–"). It is determined numerically for $W(x) = (U/2)\cos(2\pi x/\ell)$, $\omega_{\text{off}}(y) = 0.15 t_m^{-1}(1 + (\alpha y)^2/2)$, and $\omega_{\text{on}} = 0.05 t_m^{-1}\{-0.5 + 1/[1 - 0.95\cos(2\pi(x - x_{\text{on}})/\ell)]\}$, $\alpha = 10/\ell$ and $x_{\text{on}} = 0.85\ell$. The red crosses indicate the values of a where the friction coefficient given by Eq. (4) vanishes (limit $\epsilon = 0$). Inset: variation of the effective friction coefficient with the pinning parameter a, for $\epsilon = 0$ (continuous red line) and $\epsilon = 0.0885$ (dashed green line).

transition $a = 1$ as $\xi_2 \sim \sqrt{a - 1}$ (Fig. 3, inset). The elastic instability transition is associated to a sharp disappearance of the instability corresponding to stiff motors in the example of Fig. 3. The discontinuity of the slope of the force-velocity relation is another signature of the transition to solid friction. If ω_{off} tends to zero at fixed ω_{on}, ξ_2 becomes infinite, corresponding to the solid friction (in the absence of thermal fluctuations).

Concluding remarks.—We have proposed a two-state soft-motor model to describe the collective properties of molecular motor assemblies. The model emphasizes the role of the pinning parameter a, which had not been recognized yet in molecular motor theories. In the strong pinning regime, hysteresis in the motor head position leads to a term akin to the so-called protein friction, which replaces the solid friction of the Prandtl-Tomlinson model. Another consequence of this hysteresis is the generic discontinuity of the slope of the force-velocity relation at small velocities. We also found an unexpected stability diagram with two disconnected regions of dynamic instability. A strong prediction is therefore that a molecular motor assembly is unstable either at very high or at very low motor stiffness. These two limits correspond to the two existing theories of molecular motor assemblies, the crossbridge model and the rigid two-state model. Although these theories have up to now been considered as incompatible, our model shows they are governed by the same underlying physics in two different limits.

Comparison to experiments requires the knowledge of the pinning parameter. For myosin motors, it can be estimated as follows. Recent experimental values give $\ell \simeq 6$ nm and $k_m \simeq 2$ pN/nm [19]. The critical pinning parameter at the elastic instability transition $a = 1$ would be obtained for a sinusoidal potential of amplitude $U^* \simeq 4$ pN $\cdot$ nm $\simeq k_B T$. It is commonly assumed that the potential amplitudes are rather of the order of $10 k_B T$. This leads to a pining parameter a of the order of 10. Myosin motors should therefore rather be described by crossbridge models than by the rigid two-state model. For other motors systems, however, both limits could be accessible.

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[1] J. Howard, *Mechanics of Motor Proteins and the Cytoskeleton* (Sinauer Associates, Sunderland, MA, 2001).
[2] T. Guérin, J. Prost, P. Martin, and J.-F. Joanny, Curr. Opin. Cell Biol. **22**, 14 (2010).
[3] A. Vilfan and E. Frey, J. Phys. Condens. Matter **17**, S3901 (2005).
[4] P.-Y. Plaçais, M. Balland, T. Guérin, J.-F. Joanny, and P. Martin, Phys. Rev. Lett. **103**, 158102 (2009).
[5] C. J. Brokaw, Proc. Natl. Acad. Sci. U.S.A. **72**, 3102 (1975).
[6] A. Vilfan, E. Frey, and F. Schwabl, Europhys. Lett. **45**, 283 (1999).
[7] F. Jülicher and J. Prost, Phys. Rev. Lett. **78**, 4510 (1997).
[8] F. Jülicher and J. Prost, Phys. Rev. Lett. **75**, 2618 (1995).
[9] D. Riveline *et al.*, Eur. Biophys. J. **27**, 403 (1998).
[10] M. Badoual, F. Jülicher, and J. Prost, Proc. Natl. Acad. Sci. U.S.A. **99**, 6696 (2002).
[11] A. F. Huxley, Prog. Biophys. Biophys. Chem. **7**, 255 (1957).
[12] M. H. Müser, M. Urbakh, and M. O. Robbins, Adv. Chem. Phys. **126**, 187 (2003).
[13] K. Tawada and K. Sekimoto, J. Theor. Biol. **150**, 193 (1991).
[14] We restrict the discussion to potentials with first and third derivatives vanishing at the same points. We do not expect this assumption to be crucial.
[15] T. L. Daniel, A. C. Trimble, and P. B. Chase, Biophys. J. **74**, 1611 (1998).
[16] For rigid motors, friction can be negative either if the motors detach at the bottom of the potential, or if they attach at the top of the potential.
[17] S. Günther and K. Kruse, New J. Phys. **9**, 417 (2007).
[18] S. W. Grill, K. Kruse, and F. Jülicher, Phys. Rev. Lett. **94**, 108104 (2005).
[19] A. Lewalle *et al.*, Biophys. J. **94**, 2160 (2008).