Molecular Motors:
From Individual to Collective Behavior

Frank JÜLICHER[*] and Jacques PROST[**]

Physicochimie Curie, U.M.R. 168, Institut Curie
26 rue d'Ulm, F-75248 Paris Cedex 05, France

We present a simple two state model for the force generation and motion of molecular motors. We discuss the behavior of individual motors and describe how the coupling of motors in large groups can lead to new collective effects like dynamical phase transitions and spontaneous oscillations.

§1. Introduction

The progressive recognition of the ubiquitous role of "molecular motors" in cellular biology has drawn a considerable attention over the last ten years. Their importance in muscular contraction had been recognized early on (see for instance Ref. 1)), but their fundamental role in eucariotic cellular transport is still under active scrutiny. The possibility of developing beautiful experimental techniques, which allows to study the behavior of molecular motors in vitro [2],[3] has drawn a considerable attention.

The Japanese contribution in this field is of prime importance (for instance Ref. 4)). This short note does not aim at a review of the field, but rather at introducing the readers to our theoretical contribution, showing that generic considerations may be helpful for extracting important characteristics of the motor function and moreover for predicting unexpected behavior. [5]-[9] Whether or not, simple theoretical models could be of any use in describing molecular motors is unclear a priori. Indeed, the structure of molecular motors is fairly complex and there are several hundreds of motor proteins classified in three categories (myosins, kinesins and dyneins). They interact specifically with filaments made of other proteins, which have the important characteristic of being periodic and polar. In addition, in vivo, these motor proteins are not the only molecules interacting with the filaments! Under these conditions, it may look useless to attempt any simplified description. However, in all cases, the filaments are periodic and polar, and the motor proteins are enzymes which bind adenosinetriphosphate (ATP) and catalyze its hydrolysis to adenosinediphosphate (ADP). The chemical energy, which results from this hydrolysis, is partially transformed into mechanical work or directed motion along the filament, hence the word "motor".

A faithful description should keep track of all possible conformations of the enzyme in interaction with its substrate (i.e. the filament) and the follow up of

---

the hydrolysis cycle should explain in detail how a net motion results. This is currently beyond the reach of any experimental or theoretical attempt. However, this process extends typically over a ten millisecond time scale. This means that a large number of fluctuations may be integrated out and that a few degrees of freedom only are necessary for the desired description. For instance, temperature may safely be considered to be constant since at such molecular scales (i.e. 1-10 nanometers), any temperature fluctuation is damped out in a few nanoseconds. On a strict chemical basis up to six states seem to be identifiable. [10] This is still too large a number to allow for a simple analysis. We chose to jump to the smallest possible number of states compatible with a "motor" activity: two, in other words the "Ising model" of molecular motors. [6), 11)]

§2. The two state model

The motor proteins are now assumed to exist either in state one or state two. For instance, they could correspond to "ATP bound" and "ATP unbound", which immediately would imply that other stages of the process such as "ADP bound" would have to be short lived compared to the time scale of motion. The states could as well represent conformations of the protein, and ATP hydrolysis could trigger one of the conformational changes. In a given state i ($i = 1, 2$), the protein interacts with the filament, and for any position x along the filament one can define an interaction potential $W_i(x)$. The distance parallel to the filament of a particular point of the protein to an arbitrary origin is denoted by x. Again other degrees of freedom are assumed to reach their local equilibrium (for instance distances orthogonal to the filament). Note that $W_i(x)$ must reflect the period ℓ of the filament and its polarity ($W_i(x + \ell) = W_i(x)$) (see Fig. 1).

In general, the protein is not in mechanical equilibrium at position x and experiences a force $-\partial_x W_i(x)$ from the filament. Furthermore, at any given time and loca-
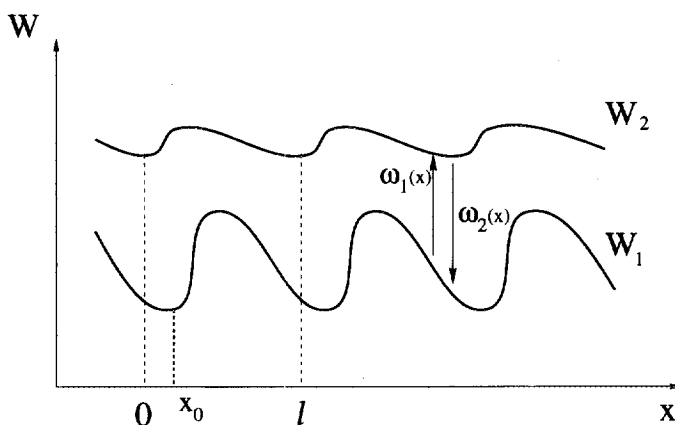

Fig. 1. Schematic picture of the two ℓ-periodic asymmetric potentials. Although the two potentials are flat on large scale, motion is expected when the ratio of transition rates ω_1/ω_2 is driven away from its equilibrium value.

tion x during a time interval dt, a protein in state 1 has a probability $P_{21} = \omega_1(x)dt$ to switch to state 2, a protein in state 2 has a probability $P_{12} = \omega_2(x)dt$ to switch to state 1. (Note that $\omega_1(x)$ and $\omega_2(x)$ are periodic with the filament period ℓ.) The stochastic description is simplest in the Fokker-Planck representation, where $P_i(x,t)$ is the probability density for the motor to be at location x, time t, in state i. The equations read:

$$\partial_t P_1 + \partial_x J_1 = -\omega_1(x)P_1 + \omega_2(x)P_2 , \tag{2·1}$$

$$\partial_t P_2 + \partial_x J_2 = \omega_1(x)P_1 - \omega_2(x)P_2 . \tag{2·2}$$

The currents J_i result either from Brownian motion, or from the force $(-\partial_x W_i(x) + f_{\text{ext}})$ experienced by the protein (f_{ext} being imposed by external means):

$$J_i = \mu_i[-k_B T \partial_x P_i - P_i \partial_x W_i + P_i f_{\text{ext}}] . \tag{2·3}$$

On general grounds, one can write:

$$\begin{aligned}
\omega_1(x) &= \left(\alpha(x)e^{\frac{\mu_{\text{ATP}}}{k_B T}} + \omega(x)\right) e^{\frac{W_1(x)}{k_B T}} , \\
\omega_2(x) &= \left(\alpha(x)e^{\frac{\mu_{\text{ADP}}+\mu_{\text{P}}}{k_B T}} + \omega(x)\right) e^{\frac{W_2(x)}{k_B T}} .
\end{aligned} \tag{2·4}$$

Here, μ_{ATP}, μ_{ADP} and μ_{P} are the chemical potentials of ATP, ADP and phosphate. $\alpha(x)$ and $\omega(x)$ are unknown functions, which again must reflect the symmetry properties of the filaments (i.e. periodic and polar). In equilibrium $\mu_{\text{ATP}} = \mu_{\text{ADP}} + \mu_{\text{P}}$, and detailed balance $\omega_1(x) = \omega_2(x) \exp[\frac{W_1(x)-W_2(x)}{k_B T}]$ holds. The quantity

$$\Omega(x) = \omega_1(x) - \omega_2(x) \exp\left[\frac{W_1(x) - W_2(x)}{k_B T}\right] \tag{2·5}$$

measures the local deviation from detailed balance. For $\mu_{\text{ATP}} - \mu_{\text{ADP}} - \mu_{\text{P}} \gg k_B T$, $\Omega(x)$ is simply proportional to the ATP concentration.

Using (2·1), (2·2) and (2·3), it is possible to show that in order to get a deterministic motion over large scales, one needs:[6] (i) the breaking of detailed balance ($\Omega \neq 0$), i.e., energy consumption, (ii) the polarity of the filament. The absence of either of these requirements destroys any motion. The dependence of the velocity on Ω is summarized in Fig. 2. The solid line corresponds to $\Omega = $ const, whereas the dotted one corresponds to $\Omega(x) \sim \sum_n \delta(x - x_0 + n\ell)$ (i.e., state changes are only allowed at particular positions $x = x_0 + n\ell$).

The comparison of these curves with experiments confirms the notion of "active sites" used by biologists: indeed no maximum of the velocity as a function of ATP concentration has ever been found, which implies that the conformational changes are allowed only at very localized places of the filament. A more detailed description of this point, and of the mechanisms involved in the motion generation may be found in Refs. 6) and 9).
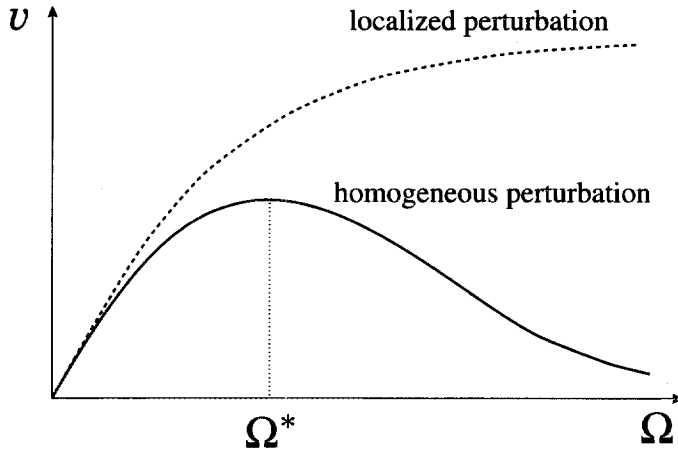
Fig. 2. Schematic diagram of the spontaneous average velocity v (for zero external force $f_{\text{ext}} = 0$) of the particle as a function of Ω which measures the departure from equilibrium and is related to the fuel concentration.

§3. Collective behavior

In muscles, but also in "motility assays" and presumably in many other circumstances, motors do not act as independent units, but as collections. A subtle difference between "rowers" (i.e., motors designed to operate in groups like myosins) and "porters" (i.e., motors designed to work individually like kinesins), has been introduced by Leibler and Huse: [12], [13] "rowers" spend most of their time in a state unbound to the filament, whereas "porter" spend most of their time in the bound state. In the spirit of our two state model, we raised a different kind of question: following the simple logic outlined above, can one expect any original feature from the conjunction of many motors operating together? For instance, a non-interacting spin will never show any phase transition, whereas spin collections can undergo a large variety of phase transitions depending on their interactions. Actually, we expect the same to be true for coupled molecular motors. [7]

The interaction between motors could be quite complex, but the possibility for dynamical phase transition is best evidenced in the simple case where the motors are rigidly connected to each other, and either randomly spaced or with a period incommensurate with that of the filament. This is the case in "motility assays" where motors are bound to a substrate and also in muscles where they are connected together through the entanglements of their stems. A schematic representation is given in Figs. 3(a) and (b). Under those conditions, the equations for the two-state model become simply

$$\partial_t P_1 + v \partial_\xi P_1 = -\omega_1(\xi) P_1 + \omega_2(\xi) P_2 ,$$
$$\partial_t P_2 + v \partial_\xi P_2 = \omega_1(\xi) P_1 - \omega_2(\xi) P_2 , \tag{3.1}$$

where (3.1) holds for any motor, provided the coordinate x_n of motor n is mapped on a reference period, via the transformation $\xi = x_n \bmod \ell$, with $0 \le \xi < \ell$.
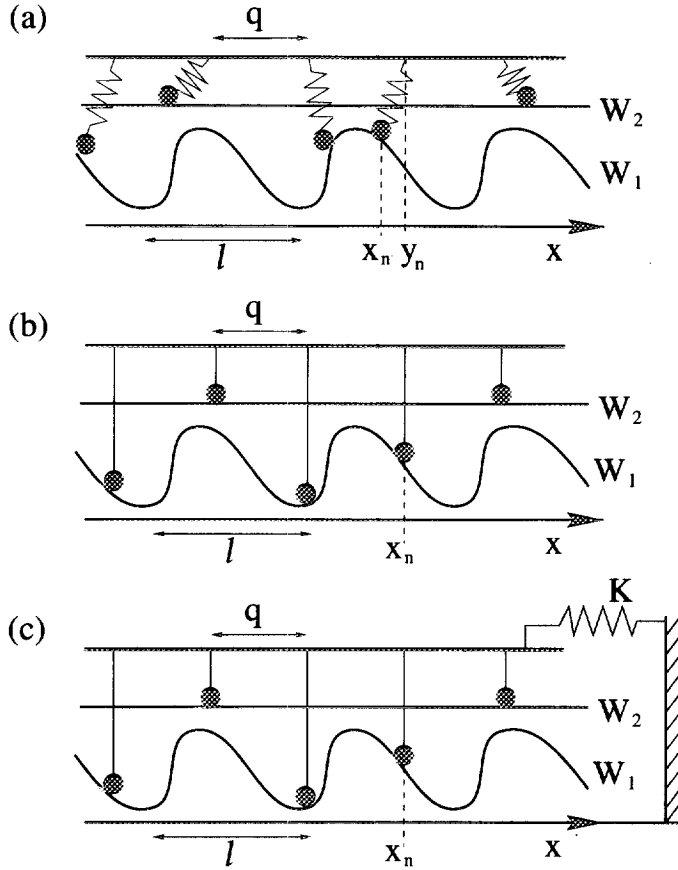
Fig. 3. (a) Schematic representation of a two-state many-motor system. Particles are attached periodically with spacing q via springs to a backbone at positions y_n. Particle positions are denoted by x_n. The potentials W_1 and W_2 are ℓ-periodic. (b) Rigid coupling of particles with $y_n = x_n$. (c) Rigid system coupled elastically to the environment via an elastic element K.

The velocity v, common to all motors, is determined by a global force balance:

$$v = \mu(f_{\text{ext}} + f) \ . \tag{3.2}$$

For a very large number of motors, (3.2) can be expressed "per motor", in which case μ is a passive friction per motor, f_{ext} the external force per motor, and the internal force f given by

$$f = -\int_0^\ell d\xi \left(P_1 \partial_\xi W_1(\xi) + P_2 \partial_\xi W_2(\xi) \right) \ . \tag{3.3}$$

The details of the arguments have been given in Ref. 7): this system of equations involves the existence of a dynamical critical point and a regime of first order transitions. A typical force/velocity diagram reveals a structure very reminiscent of a pressure/volume isotherm of a liquid-vapor system (Fig. 4). For excitation parameters $\Omega < \Omega_c$, there is a one to one relation between external force and velocity, but for $\Omega > \Omega_c$, three velocities correspond to one external force (two stable, and one
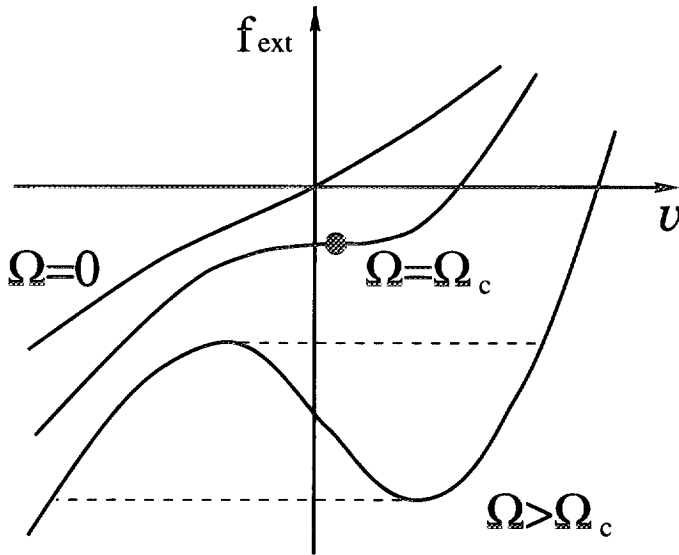
Fig. 4. External force f_{ext} as a function of velocity v for an *asymmetric* system, for different values
of the excitation amplitude Ω. A critical point exists for $\Omega = \Omega_c$. For $\Omega > \Omega_c$, the velocity
shows instabilities and discontinuities as a function of the force f_{ext}.

unstable) just as in a Van der Waals pressure/volume isotherm. The prediction here
is that one could very well find experimental situations in which motor collections
might either go in one direction or its opposite for the same external force and same
filament direction. This putative surprising behavior may be traced down to the
existence in the model of a symmetry breaking transition, when the filament is itself
symmetrical.

An other qualitatively new behavior is expected whenever the filament is con-
nected to the rigid structure, not only via the motors, but also in series with them
via a passive elastic element or spring (Fig. 3(c)). For small spring constants, it is
easy to understand that the filament will now oscillate, under appropriate circum-
stances. Let us prepare the system under conditions such that the spring is not
stressed ($f_{\text{ext}} = 0$) and that $\Omega = 0$. At time $t = 0$, we stimulate ATP consumption
in such a way that $\Omega > \Omega_c$. The filament, then, starts moving and while extending
the spring develops gradually a force which opposes the motion. The filament veloc-
ity decreases along the right branch of the lower curve of Fig. 4 ($\Omega > \Omega_c$), until it
reaches the minimum velocity. Then, an instability sets in, since any further decrease
of the velocity corresponds to no other solution than that of the left branch. On that
branch, the direction of the velocity is such that the spring extension and with it the
absolute value of the external force decrease. The system now follows the left branch
of the v/f_{ext}, curve. This goes on, as long as the velocity reaches the local maximum
on the left branch. Now, no further increase is possible and the system jumps back
on the right branch of the curve. This is a standard mechanism for oscillations of
relaxation. A more elaborate analysis gives access to transients, phase diagrams,
etc. [8] Typical curves representing displacement of the filament as a function of time
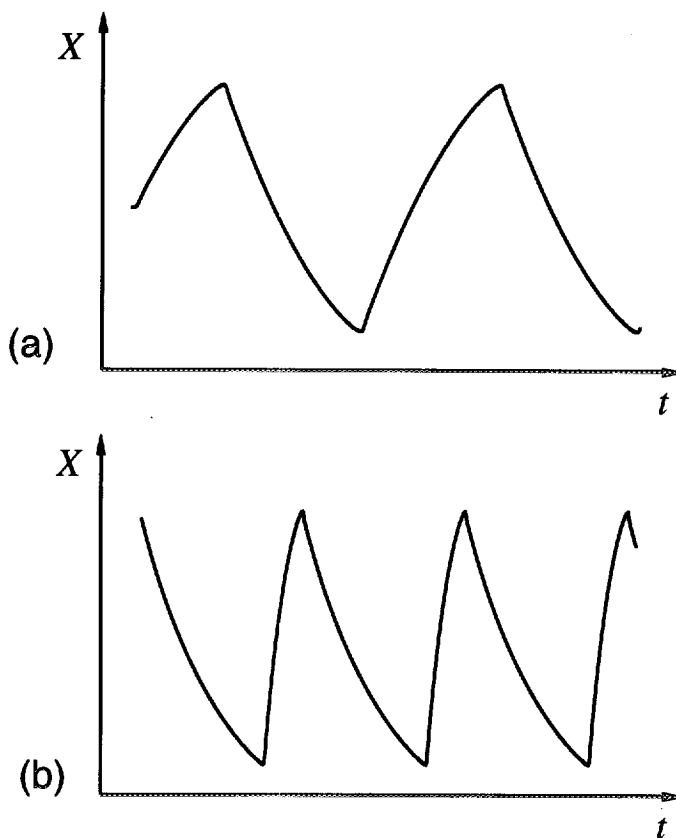
Fig. 5. (a) Spontaneous oscillations of a symmetric collective system coupled via an elastic element to its environment. The oscillations show characteristic cusps at the maximum and the minimum where the sliding velocity changes discontinuously corresponding to the instabilities in the force-velocity curve. (b) For an asymmetric system, the broken symmetry is reflected on the oscillation curve.

are displayed in Fig. 5. The existence of both the velocity discontinuity, and the oscillations when a spring is added, is robust in that refinements of the model such as additional elastic elements as shown in Fig. 3(a), do not destroy collective effects, provided "reasonable" order of magnitudes are used. One exception to this robustness: if the state changes occur in the vicinity of a maximum of $W_i(x)$ (instead of a minimum), the system is stabilized. In this case, discontinuities and oscillations are suppressed.

§4. Discussion

The "Ising-like" two state model described here, allows not only to confirm in a "blind" way the notion of active sites, but also to predict two original types of behavior: (i) regions of phase space where filaments with the same polarity and under the action of the same external force, can go in opposite directions; (ii) regions of phase space where filaments should oscillate provided they are connected to a spring.

The first proposition can be tested using appropriate motility assays.[14] Filaments are forced to follow straight trajectories given by linear grooves imposed on the substrate, and the external force is induced by a d.c. electric field. The force/velocity curve observed in such experiments shows a discontinuity and hysteresis compatible with the above prediction. The direct visual observation of this phenomenon near "stall" conditions is quite revealing: some filaments may be seen moving both "forward" and "backward" as a function of time keeping the external force constant. This behavior is expected in the case of a first order transition, with fluctuations observable in a finite size system. Whether the actual mechanism at work corresponds exactly to the theory or not, is unimportant: the main point of the model is that generically one may expect discontinuous behavior in motor collections. This implies the existence of mechanical thresholds which might be taken advantage of by nature.

The second proposition could be tested in the same type of experimental set-up by adding a proper spring. This has not been achieved yet. However, elastic elements are naturally included in muscles, and oscillatory muscles do exist. They are generically classified as "synchronous muscles", which follow a periodic signal sent by nerves, or as "asynchronous muscles", the oscillations of which bare no connection whatsoever with any nerve signal.[15] The first case clearly involves calcium release and is not a natural candidate for our prediction, but the second case (which corresponds to wasps and bees) could well be explained (in a generic sense) by our analysis. Moreover, beautiful experiments show that in the absence of any external solicitations, muscular cells not designed by nature for oscillations, do oscillate provided they are in the right region of phase space.[16] The observed elongation versus time curve, is very reminiscent of the curve shown in Fig. 5(b) ! Thus, even though the above described analysis is highly idealized, it contains enough richness to allow for predictions which seem to be experimentally relevant.

References

1) A. F. Huxley and R. Niedegerke, Nature **173** (1954), 971.
2) S. J. Kron and J. A. Spudich, Proc. Natl. Acad. Sci. USA **83** (1986), 6272.
3) Y. Harada, A. Noguchi, A. Kishino and T. Yanagida, Nature **326** (1987), 805.
4) A. Ishijima, T. Doi, K. Sakurada and T. Yanagida, Nature **352** (1991), 301.
5) A. Ajdari and J. Prost, C.R. Acad. Sci. Paris **II315** (1992), 1635.
6) J. Prost, J. F. Chauwin, L. Peliti and A. Ajdari, Phys. Rev. Lett. **72** (1994), 2652.
7) F. Jülicher and J. Prost, Phys. Rev. Lett. **75** (1995), 2618.
8) F. Jülicher and J. Prost, Phys. Rev. Lett. **78** (1997), 4510.
9) F. Jülicher, A. Ajdari and J. Prost, Rev. Mod. Phys. **69** (1997), 1269.
10) T. L. Hill, Prog. Biophys. Mol. Biol. **28** (1974), 267.
11) C. S. Peskin, G. B. Ermentrout and G. F. Oster, *Cell Mechanics and Cellular Engineering*, ed. V. Mow et al. (Springer, New-York, 1994).
12) S. Leibler and D. Huse, C.R. Acad. Sci. Paris **III313** (1991), 27.
13) S. Leibler and D. Huse, J. Cell Biol. **121** (1993), 1357.
14) D. Riveline, A. Ott, F. Jülicher, D. A. Winkelmann, O. Cardoso, J. J. Lacapere, S. Magnusdottir, J. L. Viovy, L. Gorre-Talini and J. Prost, preprint.
15) J. W. S. Pringle, in *Insect Flight Muscle*, ed. R. T. Tregear (North-Holland, Amsterdam, 1977), p. 177.
16) K. Yasuda, Y. Shindo and S. Ishiwata, Biophys. J. **70** (1996), 1823.