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Force-velocity relations of a two-state crossbridge model for molecular motors

A. VILFAN¹, E. FREY² and F. SCHWABL¹

¹*Institut für Theoretische Physik, Technische Universität München
D-85747 Garching, Germany*

²*Physics Department, Harvard University - Cambridge, MA02138, USA*

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Abstract. – We discuss the force-velocity relations obtained in a two-state crossbridge model for molecular motors. They can be calculated analytically in two limiting cases: for a large number and for one pair of motors. The effect of the strain-dependent detachment rate on the motor characteristics is studied. It can lead to linear, myosin-like, kinesin-like and anomalous curves. In particular, we specify the conditions under which oscillatory behavior may be found.

Understanding the molecular mechanism underlying biological motors has recently attracted increasing interest in biology as well as in physics [1]. Motor proteins such as myosin, kinesin and dynein moving along molecular tracks are involved in a wide range of processes essential for life, *e.g.*, cell division, muscle contraction, and intracellular transport of organelles. For many decades exclusively data from physiological measurements on muscles [2] provided experimental information for modeling molecular motors [3, 4]. In recent years, a variety of *in vitro* techniques allowed the observation of single motor proteins [5] and gave new insights into the basic principles underlying their operation. Not only new theoretical models for single-molecule motors [6-9] were inspired by these experiments, but also new models for cooperative motors [10, 11].

The theoretical models can follow two different goals. Either they are designed to fit as many physiological experiments as possible by including many (up to six) different states, or one uses simplified models (mostly with two states: attached and detached) in order to extract the generic features of motion generation and classify the motors according to their properties [10, 11]. Latter models fall into two classes, one using a specific conformational change (power stroke) in the motor molecule [10], the other a ratchet mechanism [12, 11]. A striking result of the ratchet models was the prediction of spontaneous oscillations of cooperative motors [13], which might explain the oscillatory behavior of muscles [14].

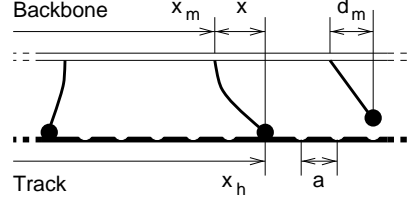


Fig. 1. – Schematic model for the motor heads running along a molecular track.

Here we discuss the force-velocity relations of a two-state power-stroke model with strain-dependent detachment rates. Depending on the functional form of these rates, the model can show a much greater variety of phenomena than previously discussed [3, 10]. These include linear, hyperbolic, anomalous or kinesin-like force-velocity relations. In the two-state model each motor molecule has two long-living states: attached and detached. This corresponds to the model described by Leibler and Huse [10] when only the time limiting steps important for mechanical properties are taken into account. Two-state models have also been used previously for myosin [3] and kinesin [7, 8] as well as in ratchet models [11, 15]. We generalize the two-state model by introducing arbitrarily strain-dependent transition rates and discrete binding sites. Both extensions are crucial for a qualitative and quantitative explanation of experiments.

The *model* is defined as follows. N motors are positioned with their roots on a stiff backbone (the effects of an elastic backbone have been studied in [16]) and can attach to the molecular track (actin or tubulin) as shown in fig. 1. Let x_h denote the position of a (free or bound) head and x_m the position of its root at the backbone. $x = x_h - x_m$ then denotes the strain on a head. Deformations of a head can be described in terms of a harmonic potential $\mathcal{H} = U(x - x_d)$ with $U(x) \equiv \frac{1}{2}k_m x^2$. After attaching to or detaching from the track, a conformational change in the head, described by shifting the potential by the distance d_m , takes place, *i.e.* $x_d = 0$ in the attached (A) state and $x_d = d_m$ in the detached (D) state. This is the *first spatial asymmetry* in our model and constitutes the basic mechanism for the generation of directed motion. We assume that the transitions between the two states occur stochastically with characteristic times t_a and t_d . We assume that the overall attachment rate t_d^{-1} of a free head is constant, but its distribution to the single binding sites proportional to their Boltzmann weights $W_i \propto \exp[-\beta U(ia - x_m - d_m)]$, where a denotes the separation between the binding sites ($a = 5.5$ nm on actin and 8 nm on tubulin [17]) [18]. The normalization reads $\sum_i W_i = 1$. Such behavior can be expected for example if some reaction has to take place before a free head comes into the affine state, which then quickly attaches to the track. The same assumption has also been used in [8] and in a slightly modified way in [7]. However, other scenarios which include a position-dependent attachment rate are conceivable as well [3, 19]. An experimental estimate for the amplitude of thermal fluctuations of a free myosin head with data from ref. [20] ($k_m = 0.4$ pN/nm, $d_m = 10$ nm) gives $\sigma = \sqrt{k_B T / k_m} \approx 0.3 d_m$. While we assumed a constant attachment rate t_d^{-1} , there is strong experimental evidence [21, 22] for a strain-dependent detachment rate t_a^{-1} of myosin.

We will show that different functions $t_a(x)$ describing strain-dependence of the detachment rate lead to various interesting phenomena, which are the main topic of our discussion. In generally $t_a(x)$ will be an asymmetric function, thus bringing a *second asymmetry* into the model. The *duty ratio* (the fraction of time a motor spends in the attached state) [23] is given as $\eta(v = 0) = t_a(d_m) / (t_a(d_m) + t_d)$ at zero velocity.

We start our analysis by considering a large group of N rigidly coupled independent motors,

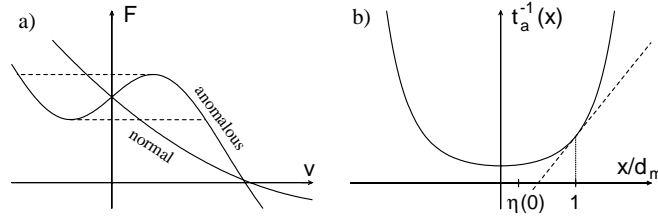


Fig. 2. – a) Examples of a normal and an anomalous F - v relation, leading to oscillating behavior. b) A graphical representation of the criterion for the occurrence of oscillations. If the tangent to the detachment rate as a function of x/d_m in the point 1 crosses the x -axis on the right of the point given by the duty ratio at zero velocity $\eta(0)$, the force-velocity relation is anomalous with a hysteresis around $v = 0$.

a situation typical for the actin-myosin motor in muscles. Then the velocity fluctuations resulting from the stochastic operation of single motors can be neglected. We set up a Master equation for the probability density $\Phi_a(x, t)$ for a motor being attached with strain x at time t and probability $\Phi_d(t)$ for a motor being detached. We also need the probability density $P(x, x_m)$ that a motor at x_m attaches with strain x on it. This will in general depend on the actual position of the motor head x_m with respect to the binding sites ($x_i = ia$), which is again correlated with the detachment positions. However, this correlation vanishes either for a strain-independent detachment rate or if the motors have a low duty ratio (they spend most of the time in the detached state), which is the case for myosin [24]. In this case we can replace $P(x, x_m) \equiv \sum_i W_i \delta(x + x_m - ia)$ by its average $P(x) = \int_{i_0 a}^{(i_0+1)a} dx_m P(x, x_m)/a$

$$P(x) = \frac{1}{a} \frac{e^{-\beta U(x-d_m)}}{\sum_j e^{-\beta U(x-d_m+ja)}}, \quad (1)$$

which is always normalized to 1. The probability Φ_d and probability density Φ_a obey the following Master equations:

$$(\partial_t - v\partial_x) \Phi_a(x, t) = \frac{\Phi_d(t)}{t_d} P(x) - \frac{\Phi_a(x, t)}{t_a(x)}, \quad \partial_t \Phi_d(t) = -\frac{\Phi_d(t)}{t_d} + \int_{-\infty}^{\infty} dx \frac{\Phi_a(x, t)}{t_a(x)}, \quad (2)$$

with normalization $\Phi_d(t) + \int_{-\infty}^{\infty} \Phi_a(x, t) dx = N$. The force produced by the group of motors is given by $F(t) = \int_{-\infty}^{\infty} dx \Phi_a(x, t) \partial_x U(x)$.

For a constant positive velocity we have to find stationary solutions of eq. (2):

$$\Phi_a(x) = \frac{N \int_{-\infty}^{\infty} dy G(x, y) P(y)}{vt_d + \int_{-\infty}^{\infty} dx' \int_{-\infty}^{\infty} dy G(x', y) P(y)}, \quad G(x, y) = \exp \left[- \int_x^y \frac{dx'}{vt_a(x')} \right] \theta(y - x). \quad (3)$$

$G(x, y)$ is a Green's function which can be interpreted as the probability that a motor which got bound to the track with strain y still remains bound when its strain reaches x .

For a harmonic potential $U(x)$ and a strain-independent detachment rate ($t_a(x) \equiv t_a$) one always gets a linear force-velocity relation $F/N = t_a k_m (d_m - vt_a)/(t_a + t_d)$. It neither depends on temperature nor on the distance between the binding sites. More complex functions $t_a(x)$ of course lead to other forms of the force-velocity relations. They can be classified into two groups: the normal ones with a monotonously decreasing force for an increasing velocity and the anomalous ones, showing hysteretic behavior (fig. 2a)). The reason why anomalous relations are interesting is that they allow two different velocities for the same external force.

For instance, in a harmonic external potential this leads to spontaneous oscillations if the hysteresis spreads over $v = 0$. Such oscillations were first proposed in a two-state ratchet model by Jülicher and Prost [13,11]. Here we show how such a mechanism can be implemented in crossbridge model.

Upon neglecting the discreteness of the binding sites and thermal fluctuations, a simple *sufficient* algebraic criterion for the occurrence of these oscillations can be derived. The zero-velocity point certainly lies in a hysteretic range if the slope of the force-velocity relation is positive there. Due to the simplification mentioned above, we set $P(y) = \delta(y - d_m)$ in eq. (3) and calculate the derivative

$$\left. \frac{dF}{dv} \right|_{v=0} = N \frac{k_m t_a^2(d_m)}{t_d + t_a(d_m)} \left(-1 + \frac{t_d}{t_d + t_a(d_m)} d_m t_a(d_m) \frac{d}{dx} t_a^{-1}(x) \Big|_{x=d_m} \right). \quad (4)$$

If its value is positive, the force-velocity relation certainly shows anomalous behavior. A graphical representation of this criterion is shown in fig. 2.

The force-velocity relation as calculated by now describes the mean force a group of motors produces when moving with a given constant velocity. However, the situation is usually reversed and one is interested in the mean velocity at a constant force. Of course, both situations are equivalent in the limit of large N . But for a finite N the motion actually occurs stepwise. This raises the question, how the motors remember on which limb of the hysteresis they currently move. The quantity that actually distinguishes between both limbs is the number of currently attached motors. Together with the external force it uniquely defines the velocity. This follows from the fact that the force per attached motor decreases monotonously with increasing velocity (fig. 3), as can be seen from eq. (3). In a finite system the number of motors fluctuates and if it passes a threshold value the velocity jumps from one stable state into the other. The probability for such jumps is highest if the original state is close to the edge of the hysteresis and the number of motors low.

An example of a function always leading to a *normal* F - v relation is $t_a(x) = \exp[\alpha x]$. It states that the lifetime of the attached state is larger for those heads that have just gone through the power stroke and produce maximum force than for those which have already done their work and now pull backwards. This idea has already been used by A. F. Huxley [3]. Such a dependence is needed for an explanation of the approximately hyperbolic force-velocity dependence in muscle systems. Physiological data by Hill [2] are perfectly fitted within the above analytic results by choosing $\alpha d_m = 0.55$ and $t_d \gg t_a^0$. Quantized binding sites and thermal fluctuations are found to play only a minor role (their neglect leads to almost the same curve with $\alpha d_m = 0.58$).

A function that can lead to an *anomalous* F - v relation is $t_a(x) \propto \exp[-2|x|/d_m]$, as shown in fig. 3. For a sufficiently low duty ratio $\eta(0)$ the point $v = 0$ lies within a hysteresis and is unstable if the force is held constant. Instead, a positive finite solution is possible or a negative with $v \rightarrow -\infty$. To obtain the latter from our equations, an infinitesimally small friction term has to be added. Now if one lets such a group pull against a harmonic spring with the other end fixed, the extension of the spring oscillates in a sawtooth-like manner with flat ascending slopes (motors working against the spring force) and very steep descending slopes (the spring force pulling motors backwards). Very similar behavior has been observed in muscles under some conditions [14].

So far, our discussion has focused on situations where motors are operating in large groups. There is, however, a second scenario, where only a few molecular motors cooperate at a time, *e.g.*, when kinesin transports vesicles along microtubules. Modeling them is guided by the following experimental observations: A kinesin molecule with two heads can move over long distances without detaching from the microtubule [25]. Although it is not yet completely clear

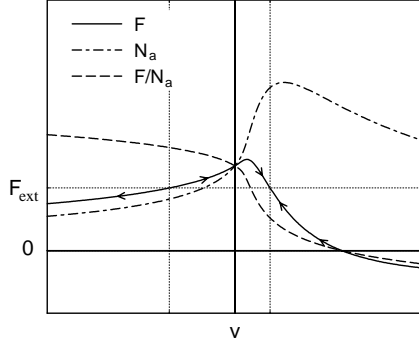


Fig. 3

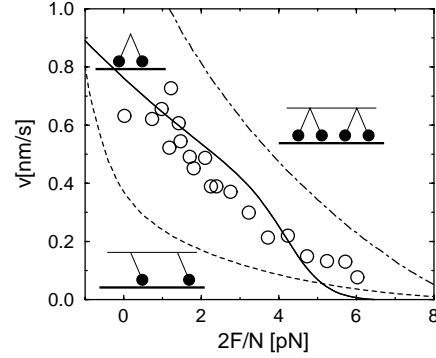


Fig. 4

Fig. 3. – An example of the F - v curve for $t_a(x) \propto \exp[-2|x|/d_m]$ and a low duty ratio. The solid line shows the mean force motors would produce at a given velocity. The dot-dashed line shows the mean number of attached motors and the dashed one the mean force per attached motor. Seeking for the velocity at a given force one obtains a stable (higher v) and an unstable (lower v) solution. A third solution is always $v \rightarrow -\infty$, but to obtain it one has to include an infinitesimally small friction term.

Fig. 4. – Force-velocity curves for kinesin. Experimental data from ref. [25] at saturating ATP concentration and the theoretical curve for $\alpha = 0.5 \text{ nm}^{-1}$, $t_d = 3 \text{ ms}$, $t_a^0 = 700 \text{ ms}$, $d_m = 4 \text{ nm}$ and $k_m = 1.1 \text{ pN/nm}$. The middle curve shows the result for one double-headed molecule, the upper one for many coupled double-headed molecules and the lower one for many single-headed molecules. These two curves were obtained from a Monte Carlo simulation since the assumptions leading to eq. (1) are not valid any more.

how the two kinesin heads “walk” along the protofilaments [26], there are good arguments to use a model with 8 nm periodicity [27] where each binding site can be occupied only with one head at a time. Single-headed kinesin can move microtubules if cooperating in larger groups, but not as fast as double-headed [28]. The velocity decreases with increasing load almost linearly [25, 29]. Above the stall force kinesin shows back-and-forth movement, but does not walk backwards [30]. Forward loads can increase the velocity many times [30].

From the fluctuation analysis [31, 32] it is quite certain that both the process of attachment and of detachment include an asymmetry between the forward and the backward direction (a new head attaches in front of the other one and the rear head detaches more probably than the front one). The low variance [33] ($r \approx 0.5$) is not *a priori* inconsistent with a model where only one of both symmetries is present (one where steps with 8 nm and 0 nm occur with equal probabilities), but then everything else in the duty cycle including the dwell times would have to be completely deterministic, which does not seem realistic. The behavior at superstall forces [30] additionally implies that one of both these asymmetries remains over the whole force range, while the other one reverses at higher forces. In our discussion we restrict ourselves to a model in which the attachment asymmetry gets reversed with increasing load while the detachment asymmetry remains. This approach has already been used by Peskin and Oster [7] and in a similar way by Duke and Leibler [8]. This, however, does not mean that we consider the other case less realistic.

The central result is again the force-velocity relation. Because the velocity is not temporally constant as for $N \rightarrow \infty$, it has to be calculated directly from transition rates for a constant force. Since an attachment two sites away from the other head is very improbable, we take only the attachment rate at the front (f) or rear (r) side of the other head into account:

$R_a^{f/r} = \mathcal{N} \exp[\pm \beta k_m a (d_m - F/k_m)/2]$; \mathcal{N} is chosen such that both rates add up to t_d^{-1} . The respective detachment rates are $R_d^{f/r} = t_a^{-1}((\pm a + F/k_m)/2)$. This gives

$$v(F) = \frac{a/2}{t_d + 1/(R_d^f + R_d^r)} \left(\frac{R_d^r - R_d^f}{R_d^r + R_d^f} + \frac{R_a^f - R_a^r}{R_a^f + R_a^r} \right). \quad (5)$$

The linear force-velocity curve has led some authors [26, 25] to the conclusion that there is no strain-dependence of the detachment rates. This conclusion, however, is only valid in a model with continuous binding sites [10]. Taking into account discrete binding sites actually leads to a nonlinear, S-shaped curve if the detachment rates are strain-independent. Again the simplest choice is $t_a(x) = \exp[\alpha x]$. Using a reasonable set of parameters the model is able to reproduce the nearly linear dependence reported in refs. [25, 29] (fig. 4) with extensions similar to those in ref. [30]. Figure 4 further shows the velocity for a large number of coupled double-headed and single-headed kinesin molecules. When comparing them to experiments care has to be taken since the pairs are in reality coupled elastically to the backbone, which leads to lower velocities. Beside that both curves depend very sensitively on the choice of $t_a(x)$. Nevertheless, they show clearly that the “repulsion” between heads already causes a significant velocity difference between single- and double-headed kinesin.

Another quantity of interest is the probability for the whole molecule detaching from the microtubule during one step, *i.e.* $P_L = t_d/t_a(F/k_m)$, yielding 5% at zero load and saturating ATP concentration, somewhat higher than comparable observations (1.3%) [28].

In summary, we have shown that a generalized two-state crossbridge model for molecular motors can lead to a much larger variety of phenomena than previously discussed. We have found analytical results in two limiting cases: for a large number of rigidly coupled motors and for one pair. In the first case we show how different functions describing the strain-dependence of the detachment rate result in linear, hyperbolic or even anomalous force-velocity relations and give a simple algebraic criterion for the latter. Discrete binding sites play only a minor role. For one pair of motors force-velocity relations as measured on kinesin can be reproduced. They depend crucially on the displacement between the binding sites. The model also shows a significant difference between single- and double-headed kinesin when operating in large groups.

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- [33] An important feature of the stochastic trajectory is the variance of displacement [31, 32]. The quantity $r = \frac{d}{dt} \langle (x(t) - \langle x(t) \rangle)^2 \rangle / \langle v \rangle a$ is a measure for the randomness of the movement. Its value is 1 for a Poisson stepper and 0 for a deterministic process. A two-state model can reach a minimum of $r = 0.5$. The parameters used above lead to $r = 0.62$ at zero load, which is not far from the experimental value $r = 0.52 \pm 0.2$ [31, 32].