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 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 [10–12].

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) in order to extract the generic features of motion generation and classify the motors according to their properties [10,12]. Latter models fall into two classes, one using a specific conformational change (power stroke) in the motor molecule [13], the other a ratchet mechanism [14]. A striking result of the ratchet models was the prediction of spontaneous oscillations of cooperative motors [15,16], which might explain the oscillatory behavior of muscles [17].

Here we discuss the force-velocity relations of a two-state 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 [16,17]. 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 [1,2,11]. 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. Let $x_a$ denote the position of a (free or bound) head and $x_m$ the position of its root at the backbone, as sketched in Fig. 1. Deformations of one head can then be described in terms of a harmonic potential $H = U(x_a - x_m - x_d)$ with $U(x) \equiv \frac{1}{2} k_m x^2$. After attaching to or detaching from the fiber, a conformational change in the head, described by shifting the potential by the distance $d_a$, takes place, i.e. $x_d = 0$ in the attached (A) state and $x_d = d_a$ 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 $t_d$. While the attachment rate $t_a^{-1}$ can be assumed to be constant, there is strong experimental evidence [16,17] for a strain-dependent detachment rate $t_d^{-1}$ of myosin.

We will show that different functions $t_a(x)$ describing strain-dependence of the detachment rate leads 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 binding sites are discrete with a separation of $a = 5.5$ nm on actin (8 nm on tubulin [18]). Before binding to a site, the head position fluctuates due to thermal motion. We assume that even in the affine state there is a time scale separation between the diffusion and the...
attachment time of the free head. This leads to the probability that a head positioned at \( x_0 \) binds to site \( i \) given by the Boltzmann weight \( W_i \propto \exp[-\beta U(-x_0 + ia)] \) [19]. An experimental estimate for the amplitude of thermal fluctuations of a free myosin head with data from Ref. [20] \((k_m = 0.4\text{ pN}/\text{nm}, d_m = 10\text{ nm})\) gives \( \sigma = \sqrt{k_B T/k_m} \approx 0.3\ d_m \).

We start our analysis by considering a large group of \( N \) rigidly coupled independent motors, a situation typical for the actin-myosin motor in muscles. Then the fluctuations resulting from the stochastic operation of single motors can be neglected. We set up a Master equation for the probability densities \( \Phi_a(x, t) \) for a motor being attached at \( x \) at time \( t \) and \( \Phi_d(t) \) for a motor being detached. We also need the probability density \( P(x, x_m) \) that a motor at \( x_m \) attaches at a distance \( x \) from its root.

This will depend on the actual position of the motor head \( x_m \) with respect to the binding sites \((x_i = ia)\). But, since generically myosin remains in the detached state for a relatively long time we may assume the root position before attachment to be completely random with respect to the discrete binding sites and replace \( P(x, x_m) \) by its average \( P(x) = \int_0^a dx_m P(x, x_m)/a \). Then, \( P(x) \) becomes

\[
P(x) = \frac{1}{a} \sum_j e^{-\beta(U(x-d_m)} \frac{e^{-\beta(U(x-d_m))}}{\sum_j e^{-\beta(U(x-d_m+j\alpha)}}, \tag{1}
\]

and the probability densities \( \Phi_a \) and \( \Phi_d \) obey the following Master equations

\[
(\partial_t - v\partial_x) \Phi_a(x, t) = \frac{\Phi_d(t)}{t_d} P(x) - \frac{\Phi_a(x, t)}{t_a(x)}, \tag{2}
\]

\[
\partial_t \Phi_d(t) = -\frac{\Phi_d(t)}{t_d} + \int dx \frac{\Phi_a(x, t)}{t_a(x)},
\]

with normalization \( \Phi_d(t) + \int \Phi_a(x, t)dx = N \). The force produced by the group of motors is given by \( F(t) = \int dx \Phi_a(x, t)\partial_x U(x) \).

![Image](Fig. 2)  

**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 right of the point given by the duty ratio (d.r.) at zero velocity (as shown above), the force-velocity relation is anomalous with a hysteresis around \( v = 0 \).

For a constant positive velocity we have to find stationary solutions of Eq. [2]

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

\( G(x, y) \) is a Green’s function which can be interpreted as the probability that a motor which got bound to the fiber at position \( y \) still remains bound when its position reaches \( x \).

For a harmonic potential \( U(x) \) and a strain-independent detachment rate one 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 hysteric behavior (Fig. 2). 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 J"ulicher and Prost [11,13,14]. 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. [2] and calculate the derivative

\[
\frac{dF}{dv} \bigg|_{v=0} = N \frac{k_m t_a'(d_m)}{t_d + t_a(d_m)} \left( -1 \right. \\
\left. + \frac{t_d}{t_d + t_a(d_m)} d_{m} t_a'(d_m) \frac{d}{dx} t_a^{-1}(x) \bigg|_{x=d_m} \right). \tag{4}
\]

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. As a consequence the duty ratio becomes lower at higher velocities. 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 $t_d \gg \tau_d^0$. 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 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 $v \to -\infty$. 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 (including low Ca$^{2+}$ concentration, which indeed means a low duty-ratio) [4]. However, other explanations which suppose that the oscillations are induced by the regulatory system are possible as well [21].

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 [22]. Although it is not yet completely clear how the two kinesin heads “walk” along the protofilaments [23], there are good arguments to use a model with 8 nm periodicity [24] 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 [25]. The velocity decreases with increasing load almost linearly [26]. Above the stall force kinesin shows back-and-forth movement, but does not walk backwards [27]. Forward loads can increase the velocity many times [27].

From the fluctuation analysis [28,29] 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 [30] ($r \approx 0.5$) is not a priori inconsistent with a model where only one of both symmetries is present (e.g. 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 [27] additionally implies that one of these both 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 [8] 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 $N \to \infty$, 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 unprobable, we take only the attachment rate at the front (f) or rear (r) side of the other head into account: $R_{a/f}^i = \mathcal{N} \exp[\pm \beta k_m a(d_m - F/k_m)/2]$; $\mathcal{N}$ is chosen such that both rates add up to $t_{d}^{-1}$. The respective detachment
rates are $R_d^{1/2} = t^{-1/2}((\pm a + F/k_m)/2)$. This gives
\[ v(F) = \frac{a/2}{t_d + 1/(R_d' + R_d^0)} \left( \frac{R_d' - R_d^{1/2}}{R_d' + R_d^0} + \frac{R_d^{1/2} - R_d^0}{R_d' + R_d^0} \right). \]

The linear force-velocity curve has led some authors [24,22] 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. [12,20] (Fig. 4) with extensions similar to those in Ref. [27]. Fig. 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 is $P_L = t_d/t_a(F/k_m)$, yielding 5% at zero load and saturating ATP concentration, somewhat higher than comparable observations (1.3%) [24].

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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