Tug of war in motility assay experiments

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Abstract
The dynamics of two groups of molecular motors pulling in opposite directions on a rigid filament is studied theoretically. To this end we first consider the behavior of one set of motors pulling in a single direction against an external force using a new mean-field approach. Based on these results we analyze a similar setup with two sets of motors pulling in opposite directions in a tug of war in the presence of an external force. In both cases we find that the interplay of fluid friction and protein friction leads to a complex phase diagram where the force–velocity relations can exhibit regions of bistability and spontaneous symmetry breaking.

Finally, motivated by recent work, we turn to the case of motility assay experiments where motors bound to a surface push on a bundle of filaments. We find that, depending on the absence or the presence of bistability in the force–velocity curve at zero force, the bundle exhibits anomalous or biased diffusion on long-time and large-length scales.

(Some figures in this article are in colour only in the electronic version)

1. Introduction

Molecular motors are proteins which convert chemical energy into mechanical work. In many cases, relating to both in vivo and in vitro situations, they act together in large groups. Among the numerous examples are myosin motors acting in muscles [1], kinesin motors pushing microtubules or myosin motors acting on actin filaments in motility assay experiments (see for example [2, 3]) and the extraction of membrane nanotubes by kinesin motors [4–6]. It is now well established that motors can exhibit a wide range of collective behavior. Many times the collective behavior results in an oscillatory ‘like’ motion [7–11] where the velocity changes abruptly between two distinct values [7, 12].

Frequently the setup is such that the motors all act together in a certain direction. This occurs, for example, in motility assays where the filaments have a well-defined polarity. In some cases, however, the picture is different and two groups of motors pull in opposite directions. This is the case, for example, in muscle contraction, active gels with myosin minifilaments [13–16], contractile ring that forms during cytokinesis, vesicles carried by both kinesin and dynein along microtubule bundles [17] and more. Recently, such a scenario has also been realized in motility assay experiments. In one set of experiments [18] a microtubule is acted upon by both NCD motors and homotetrameric kinesin-5 KLP61F in opposing directions. In another set, bundles of actin filament of opposing polarity are placed on a surface covered with myosin motors [19]. It is very common in such experiments to observe an oscillating-like behavior where a velocity, say of a bundle of filaments, changes between two distinct values.

So far theoretical studies of two classes of motors acting in opposite directions in a tug of war have focused on small groups of processive motors (which hardly detach from their track) acting on a fluid membrane [20] (a more detailed comparison of these results with our results is given below). In this paper we study theoretically a different scenario of a tug of war for non-processive motors acting in large groups on a rigid filament. We focus on motility assay experiments as discussed above, although many of our results can be easily extended to other scenarios. It is the central aim of this paper to analyze the different kinds of behavior that such a system can exhibit. To do this we generalize a discrete model, first introduced in [21], to incorporate two groups of motors pulling on a bundle in opposite directions.

To this end we first revisit the usual scenario where a rigid filament is pulled by a specified number of motors of one type. We analyze the model through a new mean-field approach which allows a straightforward derivation of velocity–force relations, where the force is exerted by some external agent on the filament. Our mean-field approach gives rise to behavior not observed in previous treatments of this system [21–23].
We find four distinct types of force–velocity curves (shown in figures 2(a) and (b)). In particular the force–velocity relation exhibits distinct bistable behavior which result from the viscosity of the fluid and the protein friction. The bistability manifests itself dynamically through an oscillatory-like behavior where the velocity changes between two distinct values. Our analysis illustrates that there is a distinction between bistability which arises due to a ‘fluid’ viscosity studied in [22] from that of one which is caused by protein friction and studied in [24]. The model shows both.

Building on these results we study the case of a bundle of filaments pulled in opposite directions by two groups of motors, with a specified number of each type, and acted upon by an external force (see figure 1 for a setup with no external force). Such a scenario could be realized using single molecule experiments. We find five different types of possible force–velocity relations with as much as four regions of bistability (see figures 4(a) and (b)). Using existing data for myosin we discuss the force–velocity relation expected in a tug of war between two sets of myosin motors. We also present a systematic study of the dynamics of the system which result from the bistability. In the limit \( N \to \infty \) the system can exhibit spontaneous symmetry breaking.

We conclude by considering motility assay experiments. In contrast to the scenario discussed above the number of motors acting in each direction now fluctuates as a function of the location of the bundle on the substrate. Different behavior is found if the system is in a bistable regime or not. When the system is not in a bistable regime, as the size of the bundle increases, its motion becomes irregular (see figure 12). The bundle gets trapped for very long time at specific locations and in a large bundle limit (defined carefully in the text) the mean-square displacement of the bundle grows as \( \log^2(t/t_0) \). Here \( t \) denotes time and \( t_0 \) sets a time scale. Moreover, at locations where the bundle remains trapped it displays an oscillatory-like behavior despite the fact that there is no bistability. When the force–velocity relation is bistable the motion is also irregular. However, now in the large bundle limit the mean-square displacement of the bundle is linear in time (diffusive) and the bundle is expected to have a mean, nonzero, velocity. Our results provide an explanation for the experiments of [19] without resorting to their assumption of cooperative unbinding of the motors.

The structure of the paper is as follows. In section 2 we define the model. In section 3 the model is analyzed using a mean-field approximation. In section 4 the dynamics of the motion are examined. Section 5 studies the case where the number of motors varies randomly in space. In section 6 we compare the results of our model to previous work done on similar setups. Finally we summarize in section 7.

2. The model

The scenario of interest is of two sets of motors pulling in opposite directions on a common backbone—a tug of war. One set pulls in the ‘plus’ direction with a force \( F_+ \), while the other pulls with a force \( F_- \) in the ‘minus’ direction (see figure 1). The motion at low Reynolds number is governed by the force balance equation where the force on the filament is countered by the viscous drag of the filament, namely

\[
\bar{\eta} \nu = F_+ + F_- + F_{\text{ext}}.
\]  

On the left-hand side of the equation \( \bar{\eta} \) is the viscosity and \( \nu \) is the velocity of the filament. On the right-hand side are the forces acting on the filament and we include a possible contribution from an external force, \( F_{\text{ext}} \). We assume a completely rigid filament. To find \( F_{\text{ext}} \), a microscopic model of the motors is needed.

The model we use is based on that introduced in [21]. Illustrated in figure 1, it consists of two motor states denoted by a and d. In the a state the motor is attached to the filament, while in the d state it is detached. The transition rate between states d and a (a and d) is denoted by \( k_d \) and \( k_a \). As shown in figure 1, we assume that when the motor binds to the filament it enters a tense state, where some ‘spring-like’ degree of freedom, \( x \), is extended from an equilibrium position \( x = 0 \). The motor then exerts a force as the spring relaxes and finally completes the cycle by detaching from the filament. In general we expect \( k_d \) to increase with the tension on the motor. Following [21], we take \( k_d = \omega_d \exp(\alpha |x|) \) which is consistent with the usual Kramers form of rates with \( \alpha = K l/k_B T \). Here \( K \) is a spring constant, \( l \) is a microscopic length, \( T \) is the temperature and \( k_B \) is the Boltzmann constant. In addition to being physically motivated, as stressed in [21], simpler forms, for example monotonically decreasing with \( x \), do not yield an oscillating-like behavior which is the focus here. Note that the model considers non-processive motors which often detach. These motors can move backwards often as opposed to processive motors which, in some cases, do so very rarely.

To analyze the model we employ a mean-field approximation. This is done by writing self-consistent equations for the force generated by the motors and the transition rates. To this end we relate the displacement \( x \) (of the ‘spring-like’ degree of freedom) to the velocity of the filament, \( \nu \). We expect the approach to hold for a large number of motors, when the fluctuations in the velocity are negligible. The self-consistent equations are obtained as follows. We
denote the velocity of the filament by \( v \), the time since the motor attached to the filament by \( t \) and the initial extension of the spring after attaching to the filament by \( x_0 \). Since \( v \) is taken to be constant the rate \( k_0(x) \), which depends on the extension of the spring \( x \), can be expressed using \( x_0 \), \( v \) and \( t \), namely \( k_0(x_0, v, t) = k_0(x) = k_0(x_0 - vt) \). The probability density of detaching at time \( t \) is then

\[
p(t, v, x_0) = \exp \left( - \int_0^t k_0(x_0, v, t') \, dt' \right) k_0(x_0, v, t).
\] (2)

To derive this expression it is convenient to discretize time into infinitesimal intervals of size \( dt \). The probability of detaching at each interval is \( k_d(t, v, x_0) \). Therefore the probability of remaining attached in the interval \( dt \) is \( 1 - k_d(t, v, x_0) \). Combining these to express \( p(t, v, x_0) \) one obtains

\[
p(t = n \cdot dt, v, x_0) = k_0(x_0 - n v \cdot dt) \prod_{j=1}^{n-1} (1 - k_0(x_0 - j v \cdot dt) \, dt),
\] (3)

which reduces to (2) in the limit \( dt \to 0 \).

Using this, a self-consistent detachment rate, \( k_d(v) \), which approximates the detachment rate for a given \( v \) by a single time scale can be defined through

\[
\frac{1}{k_d(v)} = \int dx_0 q(x_0) \int_0^\infty dt' \, p(x_0, v, t')
\] (4)

Here \( q(x_0) \) is the probability density of the springs attaching to the filament with an extension \( x_0 \). The self-consistent rates can be easily obtained for different choices of \( q(x_0) \) numerically. An example of \( 1/k_d(v) \) obtained numerically is shown in figure A1 (for a similar approximation in a different context see [25]).

We find that for generic choices \( 1/k_d(v) \) is peaked around some value \( v = v_0 \) and decays monotonically to zero on both sides of the peak. Fast velocities (positive or negative) imply a fast growth of \( k_d(x) \). This in turn makes \( k_d(v) \) larger.

The peak around the finite value of \( v_0 \) results from the finite positive average of \( q(x_0) \) which is assumed. Namely, if a motor attaches at a positive initial extension \( x_0 \) then for a positive velocity \( |x| = |x_0 - vt| \) first decreases up to time \( t = x_0/v \) and then begins to increase. On the other hand for a negative velocity \( |x| \) increases monotonically with \( |v| \). Since the detachment rate increases with \( |x| \) this causes a peak in the function \( k_d(v) \), which is located generically at a positive \( v_0 \) (for more details see appendix A).

Moreover, we find that the exact form of the function is unimportant for the qualitative results expected from such a simple model [26] (this will become evident later). To this end, we use a simplified analytical form, \( k_d(v) = \kappa (|v - v_0|^3/W + 1) \), which captures all the important features of the exact form derived by the procedure above. Here \( \kappa \) is the binding rate at \( v = v_0 \) and \( W \) is a scale parameter with units of velocity squared. A similar procedure is used to define \( k_s \). Since in the detached state the spring is not stretched, it is easy to see that the above procedure leads to an attachment rate which is independent of \( v \) (see also [21, 23]).

Next, we need to specify the force exerted by the motor. This force, of course, varies with time. Within our approach we replace the time-dependent force by its average, \( f(v) \), over the attachment time to the filament \( 1/k_d(v) \). While this can be done formally it is easy to see that to linear order in \( v \), \( f(v) = G - \gamma v \). Positive velocities tend to initially release the tension in the spring decreasing the force. The term \( \gamma v \) is the leading order behavior of a friction which is commonly termed protein friction [23]. This arises due to the energy dissipated when a tense motor unbinds. To see this, consider motors that are unable to actively generate force, so that \( G = 0 \). Clearly, \(-\gamma v \) is the force (friction) resulting from the elastic element of the bound motors being stretched by an external force. In general \( \gamma \) can have a non-trivial, details-sensitive, dependence on the velocity. However for large velocities motors are quickly detached from the filament and the effect of the friction becomes less important. This will be shown in the treatment of the collective behavior of the motors presented below.

Before turning to the two sets of motors problem it will be useful to first analyze the single set problem, \( F_\pm = 0 \), as our solution for the two set problem relies on it.

3. Mean-field analysis

3.1. One set of motors

In this section we will examine the case where a single set of motors operates against an external force, namely \( F_\pm = 0 \). In principle, since the model constitutes a one-step process over the number of motors in the a state, \( N_s \), a formal solution may be written for the steady state. However, it is more instructive to examine a mean-field solution that is easily generalized to two sets of motors. Based on the rates defined above it is straightforward to write mean-field equations for \( P_i = N_i/N \), the fraction of motors in each state

\[
\frac{\partial t}{\partial t} P_a = P_d k_a - k_d(v) P_a.
\] (5)

Here \( N_i \) is the number of motors in state \( i = d, a \) and \( N \) is the total number of motors. Note that a single motor is coupled to the rest of the motors through the rate \( k_d(v) \) which has a non-trivial dependence on the velocity, \( v \). The mean-field approximation, on the top of the approximations described above, neglects correlations between \( k_d(v) \) and \( P_a \). Furthermore, since the motors are identical the same equation holds for all motors.

The stationary solution of these equations is easily solved and along with the normalization condition \( P_d + P_a = 1 \) yields

\[
P_a(v) = \left( 1 + \frac{k_a(v)}{k_d(v)} \right)^{-1}.
\] (6)

Note that the expression depends on \( v \), the velocity of the filament. To obtain \( v \) as a function of, say \( f_\text{ext} = F_\text{ext}/N \), one then uses the solution self-consistently in the force balance equation, setting \( F_\pm = N_s f(v) \). To a first approximation we take \( f \) proportional to the length of the filament. Assuming the motors are evenly spaced out the overall viscosity can be expressed using the total number of motors \( N \) and \( \eta \), the viscosity per unit distance between motors, such that \( f = N \eta \). This results in

\[
f_\text{ext}(v) = \eta v + (\gamma v - G) P_a(v),
\] (7)
with $P_a(v)$ given in (6). The right-hand side of the equation is a sum of three terms. The first, due to the viscosity of the filament, is monotonic in $v$. The second results from the protein friction and the third from the force exerted by the motors. The last two terms multiply $P_a(v)$ which due to the functional form of $k_d(v)$ is a non-monotonic function of $v$. As we show this implies that in some ranges of the parameters there is a region of $f_{\text{ext}}$ where there are three velocity solutions for a given choice of $f_{\text{ext}}$. Following [12] we take this as evidence for bistability. In fact, we demonstrate below that the competition between the three terms, with two non-monotonic, can lead to a rather rich behavior with four distinct phases. For now we focus on the steady-state solutions. Later on we analyze the dynamics which arise in the bistable regimes.

3.2. Phase diagram

In this section we classify the different possible force–velocity curves. Asymptotically, for large $f_{\text{ext}}$ most of the motors are detached and the velocity is roughly $v \simeq f_{\text{ext}}/\eta$. For smaller forces, depending on the parameter values, the contribution from the non-monotonic terms can be important. We find four distinct regimes which qualitatively depend on $\gamma$, $G$ and $\eta$ as follows:

(i) Large $\eta$, small $\gamma$ and small $G$—no bistable regime. Here the first term in (7) dominates due to the large viscosity so that the velocity changes monotonically with the external force. The stall force, defined as $v(f_{\text{ext}}) = 0$ occurs for $f_{\text{ext}} < 0$, or in other words the velocity is positive when there is no external force acting on the motors (see figure 2(a)).

(ii) Small $\eta$, small $\gamma$ and large $G$—single bistable regime at $f_{\text{ext}} < 0$. Here the third term, due to the force exerted by the motors, is large enough so that its non-monotonic behavior becomes important. This is seen in figure 2(b) where the force–velocity curve shows a region with three possible values of $v$ for a given value of $f_{\text{ext}}$. In particular there is a region where $\partial_v f_{\text{ext}}(v) < 0$ for one solution and $\partial_v f_{\text{ext}}(v) > 0$ for the other two solutions. Since $\partial_v f_{\text{ext}}(v) < 0$ implies a negative mobility, namely increasing the force leads to a decrease in the velocity, this suggests that the solution is unstable. The difference between the two stable solutions is manifested through the number of motors in state $a$. The solution with the larger velocity has more motors in the attached state enabling it to counter the external force. The solution with the smaller velocity has most of the motors detached, resulting in a negative velocity. This can be seen by setting $\gamma = 0$ in (7) and is illustrated in figure 2(d) where we plot $P_a(f_{\text{ext}})$.

(iii) Small $G$, small $\eta$ and large $\gamma$—single bistable regime at $f_{\text{ext}} > 0$. Here only the second non-monotonic contribution due to protein friction induces a bistable regime. This occurs as long as $\eta$ is not too small so that the non-monotonic behavior due to the force exerted by the motors becomes unimportant. Now the force–velocity curve has a single bistable region located at $f_{\text{ext}} > 0$ while the velocity varies continuously for $f_{\text{ext}} < 0$ (see figure 2(a)). Unlike (ii) both stable solutions have a positive velocity.

(iv) Small $\eta$, large $\gamma$ and large $G$—two bistable regimes. Here both non-monotonic terms, due to the protein friction and the force exerted by the motors become important. Interestingly, this can lead to two distinct regions of bistability. In contrast to the bistable region due to the force exerted by the motors (ii), in the additional bistable region both of the stable solutions have a positive velocity. This is illustrated in figure 2(b) where it is seen that increasing $\gamma$ adds a second bistable regime located at positive forces.

For the specific choice we make here for $k_d(v)$ the results can be understood as follows. Due to the symmetric choice of the rate $k_d(v)$, the fraction of attached motors has the property $P_a(v + v_0) = P_a(-v + v_0)$. Therefore, the force of the motors can be expressed in terms of symmetric and anti-symmetric functions relative to $v_0$, namely

$$(G - \gamma v) P_a(v) = P_a(v)(G - v_0 \gamma) - \gamma P_a(v)(v - v_0). \quad (8)$$

The first term on the right-hand side is symmetric with a single extremum and therefore contributes a single non-monotonic region. The second term on the right-hand side is anti-symmetric and has two extrema located symmetrically around $v_0$ contributing two bistable regions. Note that when $G = w_0/\gamma$ there is only an antisymmetric contribution. We stress that while this argument is specific for our choice of $k_d(v)$ the general structure is unchanged for other choices of non-symmetric $k_d(v)$.

The different parameters can in principle be controlled, to some extent, experimentally to observe possible transitions between the different regimes. For example, $\eta$ can be controlled by the density of motors along the filament and $\gamma$ can be controlled to some extent by the ATP concentration. It is well known that increasing ATP concentration increases the unbinding rate [27]. Therefore large values of $\gamma$ would correspond to small unbinding rates of the motors and hence small ATP concentration. $G$ might be tuned by changing the neck region of the motor. In figure 2(c) we illustrate two transitions controlled by the viscosity $\eta$—one from two bistable regimes to a non-bistable regime and one from a single bistable regime to a non-bistable regime. The filled areas represent ranges of $f_{\text{ext}}$ for which there is bistable behavior for the first transition (blue) and the second transition (red). For every value of $\eta$, the region is calculated from the two adjacent extrema of the mean-field $f_{\text{ext}}$. For large enough viscosity $\eta$, the velocity $v$ changes continuously with the external force, $f_{\text{ext}}$. As $\eta$ is decreased beyond a threshold value a bistable region emerges and the range of force values it encompasses grows.

It is interesting and surprising that the simple model presented above accounts well for the measured force–velocity curves for myosin II (which is a much more complicated system). In figure 3 we show a fit of the mean-field solution to the data of [11] along with numerical simulations of the model. In contrast to the mean-field solution, the experimental and numerical data show that the positive velocity branch is stable up to a certain force. In other words, up to this force the motion of the filament with negative velocity is hardly observed. We shall return to this point. It results from the dynamical
aspects which are not captured by the mean-field solution that will be discussed in a separate section and appears in our numerical simulations of the model (shown in the figure). To fit the data we used $k/k_a = 1/10, G = 4.5 \text{ pN}, v_0 = 1.5 \mu\text{m s}^{-1}, \gamma = 0.28 \text{ pN s} \mu\text{m}^{-1}, W = 16(\mu\text{m s}^{-1})^2$ and $\eta = 0.006 \text{ pN s} \mu\text{m}^{-1}$, which are in the range of values measured independently in [27] and [28] (see also references within). The experiments were performed using an external voltage and we rely on their conversion between voltage and force per motor. While in [11] the points with negative velocity are quoted to be stable, our model predicts them to result from the motion of the filament in two opposite directions. Clearly more data are needed in this region to improve the fit. Moreover the fit can be improved by using more elaborate forms for $k_a(v)$ or models with more internal states.

Finally, we note that the above analysis interpolated between two regimes which were previously studied. In one class of models a joint rod and protein friction term was accounted for in the formulation of the first term on the right-hand side of (7) [22]. In another class of models only protein friction in the form of the second term on the right-hand side of (7) was considered [21]. We show that both lead to distinct bistable regimes which can lead to a richer behavior than previously discussed. Our focus in the paper, however, is a tug-of-war scenario. As we illustrate, using the approach developed above, the analysis becomes straightforward.

3.3. Two sets of motor engaged in a tug of war

We now turn to discuss the possible force–velocity curves for two sets of motors pulling one against another in a tug of war. Again we focus on the steady-state mean-field predictions and later discuss dynamical aspects. The setup we consider is as follows. Two (or several) connected actin filaments of opposite polarity form a bundle which is set on a substrate of motors. In this section we assume that the number of motors which operate on the bundle is constant. Thus, the filament (or filaments) with positive polarity is acted upon by $N^+$ motors pulling in the positive direction while the filament (or filaments) with negative polarity is acted upon by $N^-$ motors pulling in the negative direction (see figure 1).

Motivated by the experiments of [19], and for simplicity, we assume that both sets of motors, pulling in opposite directions, are identical. The definition of the rates of the model then follows as above but now with a modified force balance equation, which accounts for both sets of motors. Defining $N^+_a$ ($N^-_a$) to be the number of attached motors pulling in the positive (negative) direction the force balance equation now reads

$$\eta v = N^+_a f^+_a + N^-_a f^-_a + \overline{F}_{ext},$$

$$\eta v(N^+ + N^-) = N^+_a(G - \gamma v) - N^-_a(G + \gamma v) + \overline{F}_{ext}. \tag{9}$$

Here $N^+ + N^-$ is the total number of motors, $N^+_a f^+_a = N^+_a(G - \gamma v)$ is the force produced by the motors pulling in the positive direction and $N^-_a f^-_a = -N^-_a(G + \gamma v)$ is the force produced by the motors pulling in the negative direction. Finally $\overline{F}_{ext}$ is an external force (the overline is used to distinguish this from the case of a single set of motors). As in the previous section the total viscosity is taken to be proportional to the total number of motors.

Again we treat these equations within a mean-field approach replacing $N^+_a$ by $N^\pm P^\pm_a$. Here $P^+_a$ ($P^-_a$) is the fraction of motors in the attached state pulling in the positive (negative) direction. Clearly, these satisfy (6) so that $P^+_a(v)$ and $P^-_a(v)$ are related through $P^+_a(v) = P^-_a(-v)$. Using this with the expression for $f_{ext}(v)$ defined in (7) the force–velocity relation takes the form

$$\overline{F}_{ext}(v) = N^+ f^+_a(v) - N^- f^-_a(-v). \tag{10}$$

Note that the relation only relies on the anti-symmetric nature of the force exerted by the motors and additivity of

Figure 2. Results for a single set of motors. (a) Force–velocity curve of types (i) and (iv). Here $\eta = 0.1 \text{ pN s} \mu\text{m}^{-1}$. (b) Force–velocity curves of types (ii) and (iii). Here $\eta = 0.01 \text{ pN s} \mu\text{m}^{-1}$. (c) Bistable ranges of $f_{ext}$ as a function of $\eta$ (shown in blue and red). (d) Fraction of attached motors with parameters as in (b). In (a) and (b) the dotted line signifies the regions of the solutions where $\partial_v f_{ext}(v) < 0$. In all figures $k_a/k = 1/5, G = 5 \text{ pN}, W = 10(\mu\text{m s}^{-1})^2, v_0 = 2 \mu\text{m s}^{-1}$. $\gamma$ is given in the graph in units of $\text{pN s} \mu\text{m}^{-1}$.

Figure 3. A fit of the theory to experimental data. Solid dots (●) are data extracted from [11]. The solid line presents the results of the mean-field theory and empty circles (○) represent the average velocity obtained from the simulations of the model using the fitted parameters of the mean-field results. The dashed line represents the predictions for tug of war between two equally sized groups of myosin motors.
the viscous terms. In the following we consider the case 
\(N^+ = N^- \equiv N\), for which \(F_{\text{ext}}(v = 0) = 0\). For this case the 
force–velocity curves, in terms of the normalized external force 
\(\frac{F_{\text{ext}}(v)}{N}\), are independent of \(N\). Therefore the 
force–velocity curves can be easily obtained using (10) by 
creating antisymmetric combinations of the curves obtained 
for one set of motors.

3.4. Phase diagram

By following the above procedure we find four distinct generic 
structures for the force–velocity curve. Similar to the one 
motor case these arise from an interplay of the various viscous 
terms and the force exerted by the motors. In contrast to the 
single motor case the generic curves cannot be easily classified 
according to the values of the viscosities and the force exerted 
by the motors.

(I) **Monotonic force–velocity curve.** Here the force–velocity 
curve does not have any bistable regions (see figure 4(a)). 
Such behavior can arise under several situations. The 
simplest one involves an antisymmetric combination of a 
monotonic force–velocity curve for a single set of motors 
(regime (i) of the previous section). However under 
certain conditions it might also occur by antisymmetric 
combinations of any of the other regimes. This will occur 
when the non-monotonic regime of one curve is weak 
sufficient so that when a monotonic contribution is added to 
it, it becomes monotonic. In all these cases, in the absence 
of an external force the average velocity of the rod is zero.

(II) **Single oscillating regime, centered around** \(F_{\text{ext}} = 0\). 
This can occur only when we combine single motor 
curves from regime (ii) or regime (iv) of the previous 
section. The latter combination requires that the non-
monotonic behavior due to the protein friction is canceled 
by the antisymmetric combination. In this case at zero 
external force the system exhibits two stable solutions 
with velocities equal in magnitude but with opposite sign 
(see figure 4(a)). For the solution with positive velocity 
\(N^+_a > N^-_a\), while for solutions with negative velocity 
\(N^-_a < N^+_a\) (see figure 4(d)). Note that similar force– 
velocity curves have also been shown to exist theoretically 
for completely symmetric motors [12].

(III) **Two non-monotonic regimes.** This occurs when single 
motor force–velocity curves from regime (ii) or regime 
(iv) of the previous section are combined. Now the force–velocity 
curve has two symmetric bistable regions at positive and negative forces (see figure 4(b)). In the 
absence of any external force there is a single solution 
with zero velocity. In this case the fraction of attached 
motors \(P^+_a\) is equal and relatively large.

(IV) **Three bistable regimes.** This can occur only by combining 
force–velocity curves from regime (iv) of the previous 
section. Now there is one bistable regime around zero 
external force and two antisymmetric bistable regimes at 
positive and negative external forces.

(V) **Four bistable regimes.** As evident from the above 
constructions it is also possible to find regimes where 
there are four bistable regimes by suitable combinations 
of curves for one set of motors. Two are at small positive 
and negative values of the forces and two are at large ones. 
In fact, in some cases, the two small force regimes may 
be located one on the top of the other. This leads to a 
regime around zero force with four stable velocities. By 
explicitly plotting the curves we find that both of these 
require a careful fine tuning of parameters. We therefore 
do not expect them to appear under generic conditions.

The transitions into the bistable regimes as a function of 
viscosity are illustrated in figure 4(c) for various parameters. 
Again we see that increasing the viscosity smooths out the 
force–velocity curve until it becomes completely monotonic. 
In addition \(P^+_a(F_{\text{ext}})\) is seen to have a complex structure, as 
drawn in figure 4(d), with the same number of bistable regions 
as the force–velocity curve.

In the case of two equally sized groups of motors, a simple 
criterion for bistability at \(F_{\text{ext}} = 0\) can be found from the results 
for a force–velocity curve of a single set of motors. This is 
done by requiring a negative mobility at zero velocity. Namely, 
\(\Delta_{v}F_{\text{ext}}|_{v=0} < 0\), which can be rewritten using (10) 
\(\Delta_{v}F_{\text{ext}}|_{v=0} = 2\Delta_{v}F_{\text{ext}}(v)|_{v=0} < 0\). 
(11)

Namely, the slope of the single motor set force–velocity 
curve at stall force has to be negative. On a single set of motors this 
could be measured from the slope of the force in constant 
velocity experiments [24] around zero velocity. Constant 
velocity experiments are required as the zero velocity solution 
might be unstable and would therefore not appear in constant 
force experiments.

We now turn to discuss the case where \(N^+ \neq N^-\). The 
force–velocity curves are once again found using the
We now discuss the dynamics of two sets of motors pulling antisymmetric combinations of the single force–velocity curves (see equation (10)). When this is done the force–velocity curve is no longer antisymmetric. Changing the ratio $N^+ / N^-$ leads to a continuous change of the force–velocity curve as shown in figure 5. As expected, as the ratio of the number of motors increases, the curves change continuously from the behavior of two sets of motors to that of a single set of motors. In general this leads to a loss of possible bistable regions of the force–velocity curve.

Finally, we note that using the parameters from the fit of figure 3 it is possible to predict the force–velocity curve for two groups of myosin motors (consider all the reservations stated above). We expect a force–velocity curve of type (II), namely at zero force there are two possible velocities. Note, however, that care must be taken with this conclusion since we applied a specific (simple) model to fit the experimental data. For a clear conclusion the procedure explained above should be performed on data using constant velocity experiments (for example, using single molecule techniques).

4. Dynamics

We now discuss the dynamics of two sets of motors pulling oppositely in a tug of war. As above we assume a setup where $N^+$ motors pull against $N^-$ motors. We focus on the generic case (as we argue below) that $N^+ \approx N^-$ and $f_{\text{ext}}$ is small. The more conventional setup of disordered motility assays will be discussed in the following section.

The mean-field treatment of above does not account for the dynamics, and only provides possible steady-state solutions. To account for the dynamics we expand the master equation of the process in powers of $1/N^2$ into a Fokker–Planck equation. These results, and all other numerical results presented in the paper, are verified using Monte Carlo simulations, described in appendix B.

As we show below two generic behaviors which depend on the presence of bistability in the mean-field solution are found. When there is no bistability (regimes (I) and (III)), as intuitively clear, the motion on long-time scales is biased diffusion. The bias vanishes for $N^+ = N^-$ at $f_{\text{ext}} = 0$, while for $N^+ \neq N^-$ the bias vanishes for a nonzero value of $f_{\text{ext}}$. Note however, that on short time scales the motion may display an oscillatory-like behavior as seen in figure 11(b). The velocity distribution function cannot be fitted using a single Gaussian function (see in figure 11(a)).

When a bistability is present (regimes (II) and (IV)) the behavior is more interesting. We find stochastic transitions between the two mean-field solutions. The motion on each of the two mean-field solutions is biased diffusion with the bias dictated by the corresponding velocity. Each is characterized by an average dwell time, $\tau_+$ and $\tau_-$, for positive and negative velocities, respectively. These are defined by the average time during which one solution changes to the other. Of course on long-time scales the behavior is still biased diffusion. The analysis below shows that the average dwell times increase exponentially with the number of motors. The prefactor in the exponential depends on the exact value of the external force. (This is very similar to the exponential time scales found for the symmetric motors in [12].) For $N^+ = N^- = N$ the ratio of the dwell times, $\tau_+ / \tau_-$ is exponentially large (small) in the number of motors for $f_{\text{ext}} > 0$ ($f_{\text{ext}} < 0$), namely $\tau_+ / \tau_- \sim \exp(\theta N f_{\text{ext}})$ where $\theta$ is a positive constant. This implies that for a large number of motors the transition between the two branches becomes very sharp. Specifically, in the $N \to \infty$ limit at $f_{\text{ext}} = 0$ right–left symmetry of the system spontaneously breaks. As discussed in [12] a similar picture also holds for a single set of motors around the force regime exhibiting bistability. Note that when no bistable region is present the corresponding dwell times of the oscillations-like behavior (see figure 11(b)) has a weak dependence on the number of motors.

To derive these results we start by analyzing the case of a single set of motors which is then easily generalized to two sets of motors. Our model for one set of motors is a one-step process [29] with $N$ distinct states defined by the number of attached motors, $N_g$. The transition rate from a state with $N_g$ motors to one with $N_g + 1$, is given by $g_{N_g} = k_d(N - N_g)$. The transition from $N_g$ to $N_g - 1$ is given by $r_{N_g} = N_k d(v)$. The master equation then reads

$$
\dot{p}(N_g) = -(r_{N_g} + g_{N_g})p(N_g) + r_{N_{g+1}}p(N_{g+1}) + g_{N_{g-1}}p(N_{g-1}).
$$

where $p(N_g)$ is the probability of having $N_g$ motors attached. Next, we define $q = N_g / N$ so that for every $N_g$ takes values in the range $0–1$. For brevity we use the operator $E$, defined through its operation on a function $f(q)$, namely $E f(q) = f(q + 1/N)$ and $E^{-1} f(q) = f(q - 1/N)$. It is easy to see that the master equation using these notations is given by

$$
\dot{p}(q) = (E - 1) p(q) r(q) + (E^{-1} - 1) p(q) g(q),
$$

with $r(q) = r(Nq)$ and $g(q) = g(Nq)$. Next, the operator $E$ is expanded in powers of $1/N$ [29] keeping terms up to second order so that: $E = 1 + \frac{1}{N} \partial_q + \frac{1}{2 N^2} \partial_q \partial_{qq}$ and $E^{-1} = 1 - \frac{1}{N} \partial_q + \frac{1}{2 N^2} \partial_q \partial_{qq}$. This gives the Fokker–Planck equation

$$
\dot{p}(q) = -\partial_q F_q p(q) + \frac{1}{2N} \partial_q q (D_q p(q)).
$$

The right-hand side of the equation has two terms: a drift term defined through

$$
F_q = \frac{1}{N} (g(q) - r(q)) = k_d (1 - q) - q k_d(v).
$$
which for a constant $f_{ext}$ is independent of $N$. Note that requiring $F_q = 0$ yields the steady-state mean-field equations. Therefore, the previous mean-field solutions serve as extrema of the effective potential of the Fokker–Planck equation. It is easy to verify that solutions which satisfy $\delta_t f_{ext} < 0$ (negative mobility) correspond to maxima while those with $\delta_t f_{ext} > 0$ (positive mobility) correspond to minima. The second term is a diffusive term, with

$$D_q = \frac{1}{N}(g_{Nq} + r_{Nq}) = k_q(1 - q) + qk_d(v),$$

(16)

independent of $N$ for a constant $f_{ext}$. In both the expressions of $F_q$ and $D_q$ the velocity is given by the force balance equation: $\eta v = q(G - \gamma v) + f_{ext}$. Note the overall $1/N$ term multiplying the diffusive term. A standard Kramers analysis [29] implies that the time needed to cross the barrier from one minima to the other is given by $\tau \sim \exp(\alpha N)$ where $\alpha$ is a positive constant which depends on the functional form of $D_q$ and $F_q$. The analysis shows, similar to [12], that the time increases exponentially with $N$.

Next we extend the above analysis to two sets of motors. We focus on the case $f_{ext} = 0$. Repeating the same procedure used to obtain (14) but now with the two coordinates $q = N^+ / N^*$ and $s = N^- / N^*$, one obtains

$$\delta_q p = -\partial_q(F_q p) - \partial_q(F_s p) + \frac{1}{2N^+} \partial_q^2(D_q p) + \frac{1}{2N^-} \partial_q^2(D_s p).$$

(17)

$F_q$ and $D_q$ are defined as above and $F_s$ and $D_s$ are given by

$$F_q = k_q(1 - q) + qk_d(-v),$$

$$D_q = k_q(1 - q) + qk_d(v).$$

(18)

On the right-hand side of (17) there are now two drift terms and two diffusive terms, one for each direction. This equation is augmented by $\eta(N^+ + N^-) v = qN^*(G - \gamma v) - sN^*(G + \gamma v)$. To analyze the equations we consider first the case $N^* = N^-$. In this case it easy to see that, due to the symmetry of the force balance equation, $F_q$, $F_s$, $D_q$ and $D_s$ become independent of $N^\pm$. As in the case of a single set of motors, the steady-state mean-field solution corresponds to $F_q = 0$ and $F_s = 0$.

The effective force field may have either one or two stable stationary points that correspond to the number of stable mean-field solutions (we ignore the rare possibility of four bistable regimes). We begin by discussing the latter and argue that it leads to ‘oscillations’ between the two solutions. In figure 6(a) the effective ‘force field’ caused by $F_q$ and $F_s$ for general values of $s$ and $q$ is shown. One can clearly see two stable minima and a single stationary unstable point (saddle point). The trajectories $\delta q = F_q(q, s)$ and $\delta s = F_s(q, s)$ are exact in the limit $N^\pm \to \infty$. It is straightforward to argue using standard methods [29] that $\tau_+ = \tau_- = \exp(\beta N^+) = \exp(\beta N^-)$. Here $\beta$ is a positive constant and $\tau_+$ and $\tau_-$ are the typical dwell times in the minima corresponding to the motors pulling to the right and left, respectively.

Generically $N^+$ and $N^-$ are not equal. In particular one expects for a typical bundle, composed of a random assortment of filaments with opposite polarity (see figure 1), $N^+ - N^- \sim \sqrt{N^+ + N^-}$. In this limit the mean-field solutions are modified from the case $N^* = N^-$ by terms of the order $1/\sqrt{N^+ + N^-}$, vanishing in the large $N^\pm$ limit. In contrast, we find that the dwell times are very sensitive to the difference in the number of motors of each type. In particular we find $\tau_+/\tau_- \sim \exp(\beta N^+ - \beta N^-)$. Namely, when oscillations are present a small relative difference in the number of motors can lead to a strong asymmetry in the dwell times.

To see this dependence we consider the case $N^\pm = N(1 \pm \epsilon)$ with $\epsilon$ of the order $1/\sqrt{N}$. The force-balance equation now gives $v$ an explicit dependence on the values of $N_+$ and $N_-$. This in turn leads to corrections of the order of $\epsilon$ to both $F_q$ and $F_s$, which are easily found to first order in $\epsilon$

$$\delta F_q = - \epsilon 2q \frac{\kappa}{W} (v - v_0) \delta v,$$

$$\delta F_s = - \epsilon 2s \frac{\kappa}{W} (v + v_0) \delta v,$$

(19)

$$\delta v = \left[ G_q + G_s - \frac{(q - s)^2 G_F}{2q + \gamma q + \gamma s} \right].$$

The contributions of these terms, as seen in figure 6(b), increase the transition probability from one minimum to the second and decrease the transition in the opposite direction (depending on the sign of $\epsilon$). The analysis follows as
above [29] and we find \( \tau_+ \propto \exp(\alpha N + \kappa \epsilon N) \) and \( \tau_- \propto \exp(\alpha N - \epsilon N) \) with \( \alpha, \kappa \) and \( \chi \) positive constants. This implies that

\[
\frac{\tau_+}{\tau_-} \sim \exp((\kappa + \chi)\epsilon N),
\]

so that the ratio of the dwell times increases exponentially with the difference between the number of motors of each type. Note that the analysis relies on a relative small difference in the number of motors and in general holds as long as \( \epsilon \) is small. When this is not the case the results might change. In particular, the mean-field solutions, as discussed in the previous section, might not show a bistable behavior. To verify the predicted behavior we have carried out numerical simulations. In figure 7 we plot the ratio \( \tau^+/\tau^- \) and show that indeed it behaves as discussed above.

A similar effect occurs when \( N^+ = N^- = N \) and an external force is added. To first order in \( F_{\text{ext}} \) the effective forces \( F_q(s, q) \) and \( F_q(s, -q) \) have the additional terms

\[
\delta F_q = -2q \frac{\kappa}{W} (v - v_0) \frac{\tau_{\text{ext}}}{2\eta + \gamma s + s q},
\]

\[
\delta F_q = -2s \frac{\kappa}{W} (v + v_0) \frac{\tau_{\text{ext}}}{2\eta + s q + s q}.
\]

It is straightforward to argue that \( \tau_+ / \tau_- \propto \exp(\theta N \tau_{\text{ext}}) \), where \( \theta \) is a positive constant. This is seen in figures 8 and 9. Note that this implies that for large \( N^+ \) the velocity, \( \nu(F_{\text{ext}}) \), switches sharply between the positive and negative mean-field branches (see figure 3). In the limit \( N \to \infty \) at \( \tau_{\text{ext}} = 0 \) the system exhibits spontaneous breaking of the symmetry between the two directions of motion.

We now turn to discuss the case where there is no bistable region and \( N^+ = N^- \). Since there is only one steady-state mean-field solution, the effective force field has only one stationary point. Clearly, the motion on long-time scales is therefore diffusive. However, on short time scales the motion may display a weak oscillatory-like behavior. Figure 10 shows an effective force field that leads to this behavior. At the vicinity of the stationary point the force on the constant \( q + s \) line is smaller than the force on the

Figure 7. The ratio of the dwell times, \( \tau_+ / \tau_- \), in a bistable region when \( N^+ \neq N^- \) and there is no external force as obtained from numerical simulations. To a good approximation \( \tau_+ / \tau_- \propto \exp(\alpha N^+ - \alpha N^-) \), where \( \alpha \) is a positive constant. Here \( \kappa / k_i = 1 \), \( W = 10 \, (\mu \text{m s}^{-1})^2 \), \( v_0 = 3 \, \mu \text{m s}^{-1} \), \( G = 5 \, \text{pN} \), \( \eta = 0.0125 \, \text{pN s \mu m}^{-1} \) and \( \gamma = 0.125 \, \text{pN s \mu m}^{-1} \).

Figure 8. The ratio of dwell times, \( \tau_+ / \tau_- \), in a bistable region as a function of \( N^+ + N^- \). For \( N^+ = N^- \) and a constant \( F_{\text{ext}} \) as obtained from numerical simulations. To a good approximation, \( \tau_+ / \tau_- \propto \exp(\theta F_{\text{ext}} N) \). Here \( k_i / \kappa = 1 \), \( W = 10 \, (\mu \text{m s}^{-1})^2 \), \( v_0 = 2.5 \, \mu \text{m s}^{-1} \), \( G = 5 \, \text{pN} \), \( \eta = 0.01 \, \text{pN s \mu m}^{-1} \), \( \gamma = 0.5 \, \text{pN s \mu m}^{-1} \) and \( F_{\text{ext}} = 0.12 \, \text{pN} \).

Figure 9. The ratio of dwell times in a bistable region for a constant \( N = N^+ = N^- \) as a function of \( F_{\text{ext}} \) as obtained from numerical simulations. To a good approximation, \( \tau_+ / \tau_- \propto \exp(\theta F_{\text{ext}} N) \). All the parameters are the same as in figure 8 except for \( v_0 = 3 \, \mu \text{m s}^{-1} \).

Figure 10. The effective force field when there is a single steady-state mean-field solution plotted in the \( q, s \) plane. Note that there is only one stationary stable point. The shape of the effective force field induces anticorrelation between \( q \) and \( s \). The parameters are the same as in figure 6(a) except for \( \eta = 0.01 \, \text{pN s \mu m}^{-1} \) and \( \gamma = 2.5 \, \text{pN s \mu m}^{-1} \).

\( q = s \) direction. This induces anticorrelations between \( q \) and \( s \) which increase the probability to find a nonzero velocity. Typical traces of the displacement of the bundle, \( x(t) \), appear almost bidirectional and the velocity distribution deviates from a Gaussian distribution as seen in figure 11(a). Note that for other choices of parameters, \( q \) and \( s \) can be positively correlated, yielding a Gaussian distribution. Finally, as clearly
that in general the motor distribution is expected to be random this implies moved around by motors which are bound to a substrate. Since of the filament. In typical motility assays the filament is was taken to be a constant independent of the displacement. So far the number of motors pulling in each direction.

5. Disorder

In summary, irrespective of the presence of the bistability in the mean-field solution for fixed $N^+$ and $N^-$, the motion on long-times and large-length scales is biased diffusion. When bistability is present the motion will exhibit oscillations in the sense described above and the crossover to the final biased diffusive behavior is expected to occur on time scales which are exponentially large in the number of motors.

Two extreme cases may be considered:

(a) $N^\pm$ is only time dependent. This could result, for example, from extremely flexible motors and a bundle composed of a fine mesh of filaments. This allows each motor to bind to a positive and negative filament with equal probability. The motion in this case on long-time scales and large-length scales will clearly be biased diffusion with the average velocity determined by the average of $N^+ - N^-$. A nonzero average $N^+ - N^-$ could result, for example, from a difference in the amount of filaments of each polarity which compose a bundle. To conclude, in this case the additional randomness does not change the qualitative motion however it could change the diffusion constant and the bias.

(b) $N^\pm$ is only $x$ dependent. Here $x$ denotes the location of the center of mass of the bundle. This can occur, for example, if each motor can bind only to one of the directions—either the plus oriented filaments or the negative oriented filaments and will naturally be the case when the bundle of the filaments in each direction is so thick that a motor can bind only to a filament of a given direction (or if the flexibility of the tail is limited). This coupled to inhomogeneities of the motor density is likely to lead to an $x$ dependent $N^\pm$ (see figure 1 where $N^\pm$ is the integral of the motor density beneath the plus and minus filaments, respectively).

In reality it is probable that the situation is a mix with both a time and an $x$ dependence with sensitivity to the details of both the structure of the bundles and the elasticity of the motor tail. In such a case, as evident below, the $x$ dependence will dominate. Finally we note that other possible forms of disorder are possible such as the motor parameters. These again can be classified as cases (a) and (b) above. In case (a) this disorder will be washed out and will not influence the motion up to a redefinition of the average velocity and diffusion constant. When the disorder is frozen in space (case (b)) it will lead to an increase of magnitude in the random-forcing field due to the force exerted by the motors. As will become clear this will only enhance the behavior found when $N^+$ and $N^-$ are location dependent.

We now turn to analyze case (b) in detail. In this case $N^\pm(x)$ has an explicit $x$ dependence and the motion is more interesting. Numerics show that the bundle appears to be trapped for long times at certain locations (see figure 12 for a sample trajectory). Note that when this happens the motion of
the bundle appears oscillatory like even if there is no bistability (see figure 12, green (C)). Specifically, $N^+(x)$ and $N^-(x)$ are now random variables with averages $\bar{N}^+(x)$ and $\bar{N}^-(x)$, respectively. The overline denotes an average over $x$ locations (or equivalently an average over disorder realizations). We comment that in actual experiments it is more likely that a bundle composed of many randomly oriented filaments will not be symmetrical, namely $N^+(x) \neq N^-(x)$. Therefore $N^+(x) - N^-(x)$, which signifies the overall polarity of the bundle, is expected from the central limit theorem to scale as $\sqrt{\ell}$, where $\ell$ is the overall length of the bundle. When $N^+ \neq N^-$, as discussed above (at low Reynolds numbers the velocity is proportional to the applied force), there is a nonzero mean velocity implying that $N^+ - N^-$ acts as an effective force. The random $N^+(x) - N^-(x)$ thus induces a random effective force field for the motion of the center of mass of the bundle. Note that this effective force field also fluctuates with time due to the stochastic attachment and detachment of the motors. The local time average of this force is expected to grow monotonically with $N^+(x) - N^-(x)$.

We expect for such problems, that on large-scale lengths and long times, the system can be described by a single Brownian particle diffusing in an effective random-forcing field. This problem has been studied extensively in the past [30] and one finds four prominent types of behavior:

1. $\mu > 2$, $\langle x(t) \rangle \sim t$ and $\langle x(t)^2 \rangle - \langle x(t) \rangle^2 \sim t$.
2. $1 < \mu < 2$, $\langle x(t) \rangle \sim t$ and $\langle x(t)^2 \rangle - \langle x(t) \rangle^2 \sim t^{2/\mu}$.
3. $0 < \mu < 1$, $\langle x(t) \rangle \sim t^\mu$ and $\langle x(t)^2 \rangle - \langle x(t) \rangle^2 \sim t^\mu$.
4. $\mu = 0$, Sinai diffusion, $F_0 = 0$, $\langle x(t) \rangle = 0$ and $\langle x(t)^2 \rangle \sim \log^\gamma (t/t_1)$.

The exponent $\mu = 2F_0D/\sigma$ is related to $F_0$, the average force acting on the particle, $D$, the diffusion constant in the absence of disorder and $\sigma$ is defined through the correlation $F(x)F(x') = \sigma \delta(x - x')$. The overline denotes an average over disorder realizations, angular brackets denote an average over histories of the system with a given realization of disorder and $\langle f(x) \rangle = F(x) + F_0$ is the force acting on the particle at $x$ with the choice $F = 0$. Anomalous dynamics occur for $\mu < 2$ and more prominently for $\mu < 1$, and result from particles being trapped in rare deep wells, created by the random-forcing field, for exponentially long times in the depth of the well [30].

To check if this straightforward analogy holds we account for disorder by defining a model, illustrated in figure 13, where $N^\pm(x)$ are random variables that depend on $x$, the location of the center of mass of the bundle. To generate a random motor landscape the motors are equally spaced, separated by the distance $\Delta$. on a one dimensional lattice and assigned a random pulling direction that does not change with time. We consider a bundle composed of two groups of filaments with opposite polarities. The plus filament has a length of $L_+$ and the minus filament $L_-$. Therefore the probability that a motor has a plus/minus pulling direction is $p_\pm = L_\pm/\ell$, where $\ell = L_+ + L_-$. It is easy to verify that the average polarity is $\bar{N}^+(x) - \bar{N}^-(x) \propto L_+ - L_-$. Note that since the motors are equally spaced the bundle is always subject to a constant number of motors $N^+(x) + N^-(x)$ proportional to $\ell$.

An example of a realization of a motor landscape is shown in figure 13(A). The resulting $N^+(x) - N^-(x)$, shown in figure 13(B), is due to the distribution of the motors below the bundle. As discussed above this is expected to lead to random location-dependent forcing on the bundle.

We now turn to consider how a typical bundle will behave. A typical bundle composed of many filaments is expected to have an average polarity $\bar{N}^+(x) - \bar{N}^-(x) \propto \sqrt{\ell}$. For this reason we set $\bar{N}^+(x) - \bar{N}^-(x) \propto \sqrt{\sigma^2 + \sigma^2}$. Using Monte Carlo simulations and averaging over many realizations of disorder we verify that indeed the behavior is similar to the motion of a single Brownian particle in a random-forcing energy landscape and we are able to extract the exponent $\mu$ for different parameters from data over a few decades. We are interested in the dependence of $\mu$ on the bundle lengths $\ell$ in the bistable and non-bistable regime.

The scale of the effective random-forcing energy landscape is set by the distance between adjacent motors $\Delta$. The resulting effective potential is therefore expected to be proportional to $\Delta$. In simulations $\mu$ can be adjusted by varying $\Delta$ while keeping all other parameters constant. This, however, may be difficult to achieve in experiments since $\Delta$ is controlled by the motor density. To keep all other parameters constant the size of the bundle and the viscosity must therefore also be scaled. Nonetheless, the motor density is related to $\mu$.  

![Figure 13](image-url)

Figure 13. (A) The model we use to capture the effects of disorder. The bundle (yellow) is set on a surface of random motors with either a plus or minus pulling direction. In case (a) the pulling direction at each site changes randomly with time. In case (b) the pulling direction is chosen randomly and does not change with time. (B) $N^+ - N^-$ as a function of the location of $x$, the center of mass of the bundle (case (b)).

The length of the bundle here is 8 units of $\Delta$, the distance between adjacent motors. Note that $N^+ - N^-$ is not shown at the edges due to the finite length of the motor landscape.
When bistability is present the force–velocity curve (see figure 4, regimes (II) and (IV)). Two different behavior when bistability is present or absent in obtain \( \mu, \Delta = 0.25 \mu m \) is the spacing between adjacent motors. In the inset \( \mu \) is shown as a function of \( N^+ + N^- \). Here \( k/k_a = 2, W = 10 (\mu m s^{-1})^2, v_0 = 2.5 \mu m s^{-1}, G = 5 \) pN, \( \eta = 0.0125 \) pN s \( \mu m^{-1} \) and \( \gamma = 1 \) pN s \( \mu m^{-1} \).

The results are given in figure 14 and figure 15. We find two different behavior when bistability is present or absent in the force–velocity curve (see figure 4, regimes (II) and (IV)). When bistability is present \( \mu \) grows with \( N^+ + N^- \). Therefore in a motility assay experiment we expect that larger bundles will have larger \( \mu \) (see figure 14). On long-time scales and large-length scales the motion will be a biased diffusion. On the other hand when no bistability is present \( \mu \) grows with \( N^+ + N^- \). Therefore in a motility assay experiment we expect that larger bundles will have larger \( \mu \) (see figure 14). Parameters are the same as in figure 14 except for \( v_0 = 1 \mu m s^{-1} \).

6. On the relation to other models

It is interesting to compare our results with two related works. In [22] many rigidly coupled motors were modeled using a ratchet model on a symmetric potential. This amounts to non-directional rigidly coupled motors. The model also may exhibit oscillating-like behavior at zero applied external force. In another work a tug of war between two processive groups of motors pulling on a liquid membrane was considered [20]. This model also showed an oscillating-like behavior at zero applied force. While our model is different from both (it considers two non-processive motors coupled rigidly) the behavior is not too different than the two models discussed above.

Clearly an important similarity between the models is the dependence of the detachment rates on the applied force. This dependence is similar despite apparent different implementations. In the model of [22] this occurs effectively through the ratchet model while in the model of [20] and in our model this is done explicitly. The presence of such detachment rates naturally leads (even without an active force generating element, see [24]) to bistable stick-slip motion displayed by all models.

Despite the similarities there are also important differences between the models. For example, in [22] only one possible bistable region is discussed. While their model does not have an explicit difference between protein friction and fluid friction we believe that it should display behavior which is as rich as we discuss. Note that the behavior of the two models on a disordered substrate which was not elaborated on is expected to be different. The model studied in [20] is somewhat different. The motors are processive. The force–velocity curve of the motors used in [20] assumes that the motors share the load equally (note that this is not expected to be true in fluid membranes [6]). We believe that the important difference between this model and ours is the processivity of the motors. This allows them to hold a stable configuration where the two groups work against each other with an average zero velocity. Indeed in their model such behavior is observed even in the presence of two other stable solutions with positive and negative velocities. Note that in the analysis of [31] where a single group of motors working against an external force is studied no bistability is observed. We believe this to be the result of considering only attached vesicles where at least one motor is bound to the track. We expect bistability to occur if this is relaxed.

7. Conclusions

The paper focused on the dynamics of motors in a tug-of-war situation which are coupled by a rigid backbone. Using a steady-state mean-field solution of a model introduced in [21]
we characterized different possible force–velocity relations which in many cases exhibit regions of bistability. The implications for motility assays were then discussed.

It is interesting to compare our results to recent motility assays on myosin motors with a setup very similar to that we consider [19]. In the experiments bundles of actin indeed exhibit trapping for long periods of time at specific locations. When trapped they exhibit an oscillating-like behavior between two velocities. This agrees well with our prediction for a random-forcing energy landscape.

Furthermore, in [19] they studied bundles trapped in such minima and considered the dependence of the average dwell time in each velocity as a function of the number of motors. The experiments show a weak dependence on the number of motors, which in [19] was explained by cooperative unbinding of the motors. As shown in figure 12, in a minima of the random-forcing energy landscape, as intuitively clear, the motion of the bundle exhibits an oscillating-like behavior. Moreover, when the force–velocity relation exhibits no bistability the dwell time in each velocity has a very weak dependence on the number of motors (see figure 16). This provides an alternative explanation of the experimental results. This conclusion could possibly be verified by single molecule experiments of the force–velocity curve of a single set of motors under the experimental settings of [19]. (We note that our analysis of figure 3 suggests a bistable behavior for myosin. However, as stated above, care has to be taken since a specific model was assumed in fitting the experimental data of [11] and the exact setup in [11] and [19] is somewhat different.) For a clear analysis constant velocity experiments have to be carried out followed by the analysis we describe. In figure 17 we show the average dwell time when a bistability is present in the force–velocity curve. There the behavior is distinct and the dwell time in each velocity has a strong exponential dependence on the number of motors. Note that the dwell time in figures 16 and 17 in principle depends on the realization of disorder and the local structure of the effective potential well.

Finally, we note that using the techniques described above it is straightforward to derive the behavior of motors of different types each pulling in an opposite direction.

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Appendix A. Estimating $k_d(v)$

Here we illustrate in more detail the derivation of the self-consistent detachment rate $k_d(v)$ using (4). The idea is closely related to an approximation scheme carried out in [25]. First we show in figure A1 a numerical solution obtained using $k_d = \omega_{k0} \exp (\alpha |x|)$ and $q(x_0)$ chosen as a delta function located at a position which insures the motor moves forward on average. As can be seen $1/k_d(v)$ is sharply peaked around a positive velocity. The intuitive reason for this peak is stated in the main text. Clearly, a more general $q(x_0)$ will have a similar structure as long as it has a mean which insures the motors move forward. This can be seen formally by noting that the delta function solution serves as a Greens function for a general $q(x_0)$.

Here we argue that $1/k_d(v)$ is peaked around a positive velocity as long as $q(x_0)$ has a mean which is positive. To do this we denote $\tilde{t}(v) \simeq 1/k_d(v)$ the average attachment time and by $\tilde{x}_0$ the average initial extension. Recalling that $k_d = \omega_{k0} \exp (\alpha |x|)$ we replace $|x|$ with $|\tilde{x}_0 - v\tilde{t}(v)|$ and obtain

$$\tilde{t}(v) \exp (\alpha |\tilde{x}_0 - v\tilde{t}(v)|) = 1/\omega_{k0}.$$  \hfill (A.1)

Note that if $|v|$ is large then $\tilde{t}(v)$ must be small in order to compensate for the large exponent. Next we expand this expression to first order in $v$ and obtain

$$\tilde{t}(v) \simeq 1/\omega_{k0} \exp (-|\tilde{x}_0|) (1 \pm \alpha v/\omega_{k0} \exp (-|\tilde{x}_0|)).$$  \hfill (A.2)

where the positive sign corresponds a positive $\tilde{x}_0$ and the minus sign corresponds to a negative $\tilde{x}_0$. Namely, when $\tilde{x}_0$ is positive $\tilde{t}(v) \big|_{v=0}$ is positive and the maximum of $\tilde{t}(v)$ is located at $v > 0$.

We stress that the results in the paper, as evident from the analysis, are insensitive to the exact form of $k_d(v)$ and therefore choose a particularly simple form.
Appendix B. Simulations

Monte Carlo simulations are employed to verify mean-field results and test our arguments. We use a standard Gillespie [32] algorithm. In each time step one transition occurs, namely one of $N^+ + N^−$ motors will either detach or attach. Since transition times are Poissonian the probability for each transition is proportional to its respective rate. Next, the advancement time is chosen from an exponential distribution, with a time constant proportional to its respective rate. Once these two steps are completed the velocity and the rates are recalculated and the whole cycle is repeated.

The case of disorder the definition of the rates and the algorithm are mostly unchanged. The only difference is that one needs to account for the changes in $N^±(x)$. This is done by modifying only the number of detached motors $N^0_−(x)$ as the bundle moves along the motor landscape. The results are not expected to change due to this approximation even under a more detailed model as long as most of the motors remain in the detached state.

Throughout the paper $x(t)$ is sampled at time steps of $dt = 100/κ$ and the length of the simulations is $10^6/κ$ unless specified otherwise.

Appendix C. Dwell time measurements

In several parts of the paper the dwell times, $τ_+$ and $τ_−$, are estimated in the bistable region from the numerical simulations. These are extracted from the autocorrelation function of $N^+ − N^−$ which we observe to decay exponentially as, $\exp(−t/T)$ with $T$ a time scale. In general $τ_± ≠ T_±$ and $1/T = 1/τ_+ + 1/τ_−$. To find $τ_+$ and $τ_−$ independently we calculate numerically the ratio of the time spent in the positive and in the negative velocity which yields $τ_+/τ_−$. Then together with the expression for $1/T$, $τ_+$ and $τ_−$ are obtained.

Note that when there is disorder the autocorrelation tail may not be purely exponential because of the local motor landscape. In this case the dwell time can be found directly from $x(t)$. It is given by the average time it takes the velocity to switch signs. This method is useful when there is a single dwell time, namely $\tau_{ext} = 0$ and $N^+ = N^−$.

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