

Dynamics of the tug-of-war model for cellular transport

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The transport of organelles and other cargoes in living cells has been described by a kinetic tug-of-war model advanced by Müller, Klumpp, and Lipowsky, in which, as a function of time, t , a team of $n_+(t) = 0, 1, \dots, N_+$ molecular motors may attach a cargo to a filamentous track and pull it towards the plus end in competition with $n_-(t) = 0, 1, \dots, N_-$ motors that pull towards the opposite end. In recent work [Y. Zhang, *Phys. Rev. E* **79**, 061918 (2009)] this model was analyzed for $N_+, N_- \gg 1$, establishing the existence, depending on the motor parameters and the ratio $\nu = N_+/N_-$, of system states with either one, two, or three distinct stable stationary modes of motion. Here, adopting a theoretical perspective, we study the parametric and ν dependence of the transitions between these mono-, bi-, or tristable system states and examine their associated trajectories and domains of attraction in the flow space, (n_+, n_-) , of the attached motor numbers. Various sequences of winning, losing, and “stalemate” or close-to-motionless modes are uncovered. When, as realistic, N_+ and N_- are of order 2 to 10, fluctuations will move the system from one of two or three modes of motion to another mode. An analysis of the associated probability fluxes demonstrates that the mean time between mode-to-mode transitions increases exponentially with N_+ and N_- . The overall stall force, i.e., the externally imposed load under which the mean cargo velocity vanishes, is similarly elucidated and shown to vary strongly but *sublinearly* with N_+ and N_- , as well as depending in a less than transparent manner on other model parameters beyond the stall forces of the individual + and – motors.

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I. INTRODUCTION

The study of the ways in which a cell moves and of its ongoing internal motions [1], is a central aspect of cell biology. A basic conceptual approach to this topic, eloquently expounded by Howard [2,3], might be termed “mechanomolecular,” or even “mechanobiomolecular;” it finds roots in early theories of muscle: see [2]. Recognizing, in particular, the stochastic fluctuations of molecular processes at physiological temperature, a systematic and effectively parallel theoretical approach has been developed by Jülicher and Prost [4,5] and their coworkers (see, e.g., [6,7]). In one aspect, this involves what are sometimes termed “continuum ratchets” [8]. Oster and co-workers, adopting a still more detailed mechanical outlook, have studied a variety of cellular mechanisms: see, e.g., [9,10]. On the other hand, as noted by Kolomeisky and Widom [8,11], a simpler, and from a molecular viewpoint, more concrete approach invokes discrete stochastic, chemical kinetic models which must, however, now entail an *explicit* mechanical element at the single molecule level [8,12]. Such modeling might be termed “chemomechanical” or “chemobiomechanical.”

An important cellular process is the transport of organelles and vesicles of various sorts along cytoskeleton tracks within a live cell [1,2,13–16]. Such movements are typically accomplished by *teams* of more than a single motor protein, such as kinesins and dyneins [8,17–19], that bind to the cargo and then tow it along a microtubule. The different approaches sketched above, which, naturally, are complementary to some extent, have been brought to bear on this

topic [20–22]. In particular, Müller, Klumpp, and Lipowsky [23–26] have recently devised a chemobiomechanical model to describe the stochastic “tug-of-war” that arises when *competing teams* of motors engage a cargo; that can result in abrupt switching from steady motion in one direction to similar motion in the opposite sense [14,25–30]. It is notable that a predicted feature of these models, namely, a “slow mode” that can appear when the opposing efforts of the two teams almost balance, has been seen in subsequent experiments by Soppina *et al.* [29,30]. Accordingly, it seems useful from a general theoretical viewpoint to study the properties of the tug-of-war family of models in some detail.

To that end a recent theoretical analysis used a mean field or large motor-numbers approach [25,26]. The results established that the tug-of-war models may, indeed, realize states with either one, two, or three distinct stationary modes of motion, which depend on the parameters of the two types of motor protein and on the ratio, $\nu = N_+/N_-$, of the available number N_+ , of plus-end directed motors, to the number N_- , of minus-end motors. The specific numbers $n_+(t) (\leq N_+)$ and $n_-(t) (\leq N_-)$ of motors that, at time t , attach cargo to the polar track fluctuate stochastically; but for large N_+ and N_- , the stationary motion of the cargo is determined by the initial values $n_+(0)$ and $n_-(0)$. The more detailed study that is reported here uncovers transition points between the distinct monostable, bistable, or tristable states of the system for large N_+ and N_- as the motor parameters (see Sec. II below) and the ratio ν are varied. Indeed, our calculations indicate that the variation of almost any of the parameters can yield transitions as the examples presented in Sec. III illustrate.

On the other hand, for the ranges of N_+ and N_- encountered in real living cells (say 2–10 [24,26]) fluctuations between the different modes of motion, each with a characteristic mean velocity V along the track, must arise. Indeed,

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TABLE I. Single-motor parameters and the values adopted to model kinesin 1 and cytoplasmic dynein: see [23] and references therein.

Parameter	Symbol	Kinesin 1	Dynein
Attachment rates	$k_+^{\text{on}}, k_-^{\text{on}}$	5 s^{-1}	1.6 s^{-1}
Detachment rates at zero load	$k_{0+}^{\text{off}}, k_{0-}^{\text{off}}$	1 s^{-1}	0.27 s^{-1}
Detachment force	F_d^+, F_d^-	3 pN	0.75 pN
Zero-load speed	V_F^+, V_F^-	$1 \text{ } \mu\text{m/s}$	$0.65 \text{ } \mu\text{m/s}$
Stall force	F_S^+, F_S^-	6 pN	1.1 pN
Superstall speed amplitude	V_B^+, V_B^-	6 nm/s	72 nm/s

these have been observed experimentally [29,30] and are readily demonstrated in Monte Carlo simulations [25]. An immediate question to ask is “What values of N_+ , N_- are large enough to justify the mean-field approach?” To answer this question, Sec. IV presents a study of the probability flux between different stationary modes of motion as a function of the motor numbers N_+ and N_- . The results indicate that the mean residence times in a particular stationary mode, which is proportional to the inverse of an associated probability flux, can be well approximated by $A(\nu)e^{B(\nu)N_+}$. Roughly speaking, we find that the fluctuations of the cargo motion as it is transported by the cooperation of kinesin and dynein teams, as described by the parameters in Table I, can be neglected when $N_+, N_- > 5$. However, if the opposing motors are more closely matched, $N_+, N_- > 10$ may well be needed.

The stall force of the cargo under an externally imposed load is discussed in Sec. V and found to depend strongly and in a nonobvious fashion on the values of N_+ and N_- . Finally, in Sec. VI the results are briefly summarized and some open questions are noted.

Before proceeding, however, it should be noted that the tug-of-war models as formulated below have not been established as an adequate description of the *in vitro* or *in vivo* experiments that are currently being undertaken and that may be anticipated [14–16,27–31]. In particular, in a notable recent experiment by Diehl and coworkers [31] precisely two kinesin 1 motors were attached to a DNA scaffold at a separation of 50 nm. The observed motion was interpreted [31] as indicating significant communication and, indeed, “interference,” between the two motors in ways that are not explicitly represented in the tug-of-war models studied here.

II. TUG-OF-WAR MODEL AND MEAN FIELD LIMIT

To start we recapitulate here and discuss briefly the definition and basic properties of the tug-of-war model devised by Lipowsky and coworkers [23–26]. The cargo is moved with velocity $V_C(t)$ at time t along a polar track by two teams of motors bound to it, namely, N_+ plus-end directed motors and N_- minus-end directed motors. Whereas N_+ and N_- will be supposed fixed, the numbers $n_+(t)$ and $n_-(t)$ that attach the cargo to the track vary stochastically. The corresponding rates are specified by the properties of the individual motors. For each motor species this requires (at least) six parameters. These are listed in Table I and their meaning and significance are explained forthwith.

Table I also lists numerical values for the 12 parameters required to characterize kinesin 1 and cytoplasmic dynein. These were originally chosen by Müller *et al.* [23] on the basis of evidence then available. It must be strongly emphasized, however, that these specific parameter values, particularly those for dynein, are subject to modification as observational data for the individual motor proteins are improved. In particular, the stall force for cytoplasmic dynein is listed in Table I as $F_S^- = 1.1 \text{ pN}$ in accord with experiments by Malik *et al.* [32]. On the other hand this particularly low value must surely be revised since Higuchi and coworkers [33] report a value of $F_S^- = 7\text{--}8 \text{ pN}$, while Gennerich *et al.* conclude $F_S^- = 6.9 \pm 1.0 \text{ pN}$ [34]; indeed, these values exceed that listed in Table I for kinesin 1! Consequently, in our present theoretical study we have utilized the values in Table I *purely* as illustrative of the different types of phenomena the tug-of-war models may exhibit and to provide some sense of plausible, realistic numerical values and their parameter dependence. Thus, specific numerical results should *not*, without verifying their sensitivity to the parameter assignments, be taken as more than qualitative or semiquantitative predictions, if indeed, as much as that.

To be specific regarding the motor parameters, note that (i) fixed independent attachment or “on” rates k_+^{on} and k_-^{on} are postulated together with (ii) detachment or “off” rates $k_+^{\text{off}}(F)$ and $k_-^{\text{off}}(F)$ that are supposed to depend on the load force, F , felt by the individual motor according to

$$k_{\pm}^{\text{off}}(F) = k_{0\pm}^{\text{off}} \exp(|F|/F_d^{\pm}), \quad (1)$$

where the important detachment forces, F_d^+ and F_d^- , likewise characterize the individual + and – motors (see Table I). A load-dependence for the on rates might also be considered but seems likely (as discussed in [26], supporting info.) to be less significant. It is worth remarking that this load dependence of the detachment rates represents, from a cellular perspective, a crucial component of the mechanical control system since, as emphasized by Howard [3], it provides direct and rapid feedback to the system. However, the basic tug-of-war models we analyze below lack the explicit elastic elements or “spring” identified by Jülicher and colleagues (see [7]) as essential for controlled stable mechanical oscillations as seen, for example, in the beating of cilia [3,35,36] and in mitotic spindle movement [37,38].

The load-speed relations for single + and – motor proteins in the tug-of-war models are taken (iii) to obey the piecewise linear relations

$$V_{\pm}(F) = V_F^{\pm} [1 - (F/F_S^{\pm})] \quad \text{for } 0 \leq F \leq F_S^{\pm}, \quad (2a)$$

$$= V_B^{\pm} [1 - (F/F_S^{\pm})] \quad \text{for } F \geq F_S^{\pm}, \quad (2b)$$

$$= V_F^{\pm} \quad \text{for } F \leq 0, \quad (2c)$$

with corresponding zero-load speeds $V_F^{\pm}$ and stall forces $F_S^{\pm}$ [39,40]. This representation of the velocity-load relations for individual motor proteins is a caricature of the more complex relations actually observed: see [8,12,17,18,23]. Nevertheless, it serves to capture the most essential features discovered experimentally including, in the last relation, the re-

sponse to *assisting* loads: see also [41]. Furthermore, as demonstrated by Müller (see [26], Sec. 3.3), many properties of the tug-of-war models do not depend strongly on the precise form of the force-velocity relations, as long as the velocity decreases monotonically as the imposed load increases and then exhibits slow backwards motion under superstall loads. Thus to avoid further complications, we adopt these simple linear force-velocity relations for this study. More realistic forms, however, present no serious obstacles for most of the analysis presented below.

Although in reality the cargo, specifically when an endosome [29] or a mitochondrion [30], has been observed to undergo stretching, it is supposed (iv) that all the individual motor velocities, V_+ and $-V_-$, match the cargo velocity V_C . Finally, for simplicity, the model assumes (v) that the instantaneous load is shared *equally* between the $n_+(t)$ plus-end directed motors that happen to be attached to the track at time t and, likewise for the $n_-(t)$ attached minus-end directed motors. A more realistic treatment would allow for *unequal*, stochastic load sharing [42] although it seems reasonable to anticipate that this would be significant only for detailed fluctuation effects.

The model assumptions now imply

$$V_C(n_+, n_-) = V_+(F_{\text{car}}/n_+) = -V_-[(F_{\text{car}} - F_{\text{ext}})/n_-], \quad (3)$$

where F_{car} denotes the load on the cargo defined by

$$F_{\text{car}} := n_+ F_+ = -n_- F_- + F_{\text{ext}}, \quad (4)$$

where F_+ and F_- are the loads felt by each individual $+$ and $-$ motor, respectively, while F_{ext} denotes an externally imposed load that opposes plus-end directed motion; all the loads are defined to be positive when directed towards the minus end of the track. For simplicity, we will assume here and in Secs. III and IV that the external load F_{ext} vanishes. In that case the assumption Eq. (2c) for assisting loads, plays no role. However, when in Sec. V, we discuss the cargo stall forces, it does enter in an essential manner.

Finally, the independence of the individual motors and their shared load implies the overall detachment rates

$$\epsilon_{\pm}(n_+, n_-) = k_{0\pm}^{\text{off}} n_{\pm} \exp(|F_{\text{car}}|/n_{\pm} F_d^{\pm}), \quad (5)$$

with corresponding overall attachment rates

$$\pi_{\pm}(n_+, n_-) = k_{\pm}^{\text{on}} (N_{\pm} - n_{\pm}). \quad (6)$$

If $p(n_+, n_-; t)$ denotes the probability of finding n_+ and n_- motors attached to the track at time t , the behavior of the system is, thus, described by the master equation

$$\begin{aligned} (d/dt)p(n_+, n_-; t) = & \pi_+(n_+ - 1, n_-)p(n_+ - 1, n_-; t) \\ & + \epsilon_+(n_+ + 1, n_-)p(n_+ + 1, n_-; t) \\ & + \pi_-(n_+, n_- - 1)p(n_+, n_- - 1; t) \\ & + \epsilon_-(n_+, n_- + 1)p(n_+, n_- + 1; t) \\ & - [\pi_+(n_+, n_-) + \pi_-(n_+, n_-)] \\ & + \epsilon_+(n_+, n_-) + \epsilon_-(n_+, n_-) p(n_+, n_-; t), \end{aligned} \quad (7)$$

for $1 \leq n_+ \leq N_+ - 1$ and $1 \leq n_- \leq N_- - 1$, and similar equations

can be given for $n_+ = 0$, N_+ , and $n_- = 0$ or N_- . In proceeding to analyze the model one must recognize two distinct situations between which the system may switch stochastically [23–25]. The first is:

A. Plus-motors winning: i.e., $n_+ F_S^+ > n_- F_S^-$

The cargo load and velocity are then

$$F_{\text{car}}(n_+, n_-) = \frac{V_F^+ + V_B^-}{V_F^+/n_+ F_S^+ + V_B^-/n_- F_S^-}, \quad (8)$$

$$V_C(n_+, n_-) = \frac{n_+ F_S^+ - n_- F_S^-}{n_+ F_S^+/V_F^+ + n_- F_S^-/V_B^-}, \quad (9)$$

while the detachment rates may be written [25]

$$k_{\pm}^{\text{off}}(n_+, n_-) = k_{0\pm}^{\text{off}} \exp[n_{\mp}/(an_+ + bn_-)F_d^{\pm}], \quad (10)$$

where the load distribution parameters are

$$a = \frac{V_B^-}{F_S^-(V_F^+ + V_B^-)}, \quad b = \frac{V_F^+}{F_S^+(V_F^+ + V_B^-)}. \quad (11)$$

For discussing the mean-field limit for large N_+ and N_- we set

$$y = n_+/N_+, \quad z = n_-/N_-, \quad \nu = N_+/N_-, \quad (12)$$

and then have

$$\begin{aligned} k_+^{\text{off}}(y, z) &= k_{0+}^{\text{off}} \exp\left[\frac{z}{(a\nu y + bz)F_d^+}\right], \\ k_-^{\text{off}}(y, z) &= k_{0-}^{\text{off}} \exp\left[\frac{\nu y}{(a\nu y + bz)F_d^-}\right], \end{aligned} \quad (13)$$

with, from Eq. (9), a complementary expression for $V_C(x, y)$.

The second situation is:

B. Minus-motors winning: i.e., $n_+ F_S^+ < n_- F_S^-$

The appropriate expressions for the cargo load and the velocity then become

$$F_{\text{car}}(n_+, n_-) = \frac{V_B^- + V_F^+}{V_B^-/n_+ F_S^- + V_F^+/n_- F_S^+}, \quad (14)$$

$$V_C(n_+, n_-) = -\frac{zF_S^- - y\nu F_S^+}{y\nu F_S^+/V_B^- + zF_S^-/V_F^+}, \quad (15)$$

while the detachment rates of the plus and minus motors are now

$$\begin{aligned} k_+^{\text{off}}(y, z) &= k_{0+}^{\text{off}} \exp\left[\frac{z}{(\bar{a}\nu y + \bar{b}z)F_d^+}\right], \\ k_-^{\text{off}}(y, z) &= k_{0-}^{\text{off}} \exp\left[\frac{\nu y}{(\bar{a}\nu y + \bar{b}z)F_d^-}\right], \end{aligned} \quad (16)$$

with modified load distribution parameters

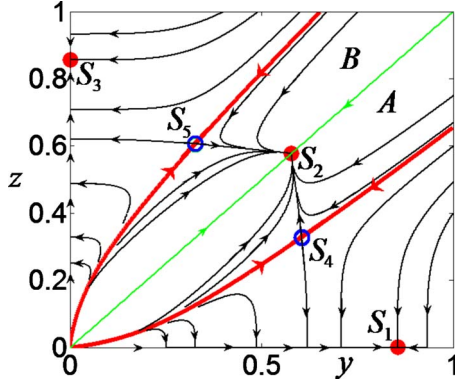


FIG. 1. (Color online) The flow diagram in the (y, z) or $(n_+/N_+, n_-/N_-)$ phase plane for a completely symmetric tug-of-war model with $N_+ = N_-$ (or $\nu = 1$) and the $+$ and $-$ motor parameters exactly matched. The parameters used in this figure are those adopted for cytoplasmic dynein: see Table I. There are three stable stationary modes of motion, labeled S_1 , S_2 , and S_3 , corresponding to a steady positive velocity, to perfect balance with zero velocity, and to a steady negative velocity. In addition there are two *unstable* modes of motion, S_4 and S_5 , marked by open circle. The two thicker (red) trajectories separating the three subdomain basins of attraction are symmetric about the line $z = y$ (or $n_+ = n_-$) which separates the plus-motor winning sector A, below the line, from the complementary sector B, above: see Eq. (18).

$$\bar{a} = \frac{V_F^-}{F_S^-(V_B^+ + V_F^-)}, \quad \bar{b} = \frac{V_B^+}{F_S^+(V_B^+ + V_F^-)}. \quad (17)$$

The boundary separating sectors **A** and **B** in the “phase plane” (n_+, n_-) or (y, z) [see Fig. 1] is simply

$$n_+ F_S^+ = n_- F_S^- \quad \text{or} \quad z = \nu_{AB} y, \quad (18)$$

with $\nu_{AB}/\nu \equiv F_S^+/F_S^-$. For the symmetric tug-of-war model illustrated in Fig. 1 the **AB** boundary is simply the diagonal axis $y = z$; but see also Figs. 3, 5, and 6 below.

Mean-field limit

Finally, in the limit when N_+ and N_- become large, the variables y and z become continuous and we obtain [24–26] the deterministic flow equations

$$\frac{dy}{dt} = k_+^{\text{on}} - y[k_+^{\text{on}} + k_+^{\text{off}}(y, z)] =: f(y, z),$$

$$\frac{dz}{dt} = k_-^{\text{on}} - z[k_-^{\text{on}} + k_-^{\text{off}}(y, z)] =: g(y, z). \quad (19)$$

Clearly, steady modes of cargo motion are found by solving the equations $f(y, z) = g(y, z) = 0$ to find the fixed points, (y^*, z^*) , of the flows. A completely symmetric case with $N_+ = N_-$ or $\nu = 1$ is illustrated in Fig. 1 which exhibits five fixed points (with values listed in Table II). Three of these, labeled S_1 , S_2 , and S_3 , correspond to stable stationary modes of motion with cargo velocities $V_1 = V_0$, $V_2 = 0$ and $V_3 = -V_0$ (with, for the values adopted in the figure, $V_0 = 650$ nm/s). The stability of these modes is ensured by the validity of the standard inequalities

$$\left. \frac{\partial f}{\partial y} \right|_* + \left. \frac{\partial g}{\partial z} \right|_* < 0, \quad (20)$$

$$\left. \frac{\partial f}{\partial y} \right|_* \left. \frac{\partial g}{\partial y} \right|_* - \left. \frac{\partial f}{\partial z} \right|_* \left. \frac{\partial g}{\partial x} \right|_* < 0,$$

which specify that the real parts of the eigenvalues of the Jacobean matrix at (y^*, z^*) should be negative.

III. INSTRUCTIVE EXAMPLES

To gain a better sense of the range and nature of the behavior of the tug-of-war model as the parameters vary, many examples have been studied within the mean-field limit. Some of these are presented here starting with the parameters adopted for kinesin and dynein (see Table I) but as the ratio $\nu = N_+/N_-$ is varied. First, as shown in Fig. 2, we present the steady stable mode velocities as a function of ν . Evidently, the system undergoes sharp transitions from *bistability* below $\nu_{c1} = 0.262$ to *tristability* up to the second critical value $\nu_{c2} = 0.276$ beyond which bistability is restored. The subsequent plots in Fig. 3, and in Figs. 5 and 6 below, illustrate the nature of the flows arising in the different *states*.

It is perhaps worth mentioning that from the viewpoint of the theory of dynamical systems and vector fields, the transitions in the flow fields arising as parameters are varied—such as occurring at the values ν_{c1} and ν_{c2} marked by dotted lines in Fig. 2—represent *bifurcations* that may be systematically classified and are characterized by specific names [43]. For the interested reader, the appropriate terms are presented in the caption for Fig. 2 and in those for Figs. 7–10, below.

In Fig. 3 an immediate issue requiring comment—also evident in Fig. 1—is the seemingly nonanalytic sharp right-angle turns of the flow trajectories as they appear to reach the y and z axes. Thereupon the flows proceed, it seems, directly

TABLE II. The five fixed points of the completely symmetric tug-of-war model with the parameters adopted for dynein as listed in Table I. Note that $y = n_+/N_+$ and $z = n_-/N_-$.

	S_1	S_2	S_3	S_4	S_5
y^*	0.8556	0.5775	2.430×10^{-6}	0.6052	0.3275
z^*	2.430×10^{-6}	0.5775	0.8556	0.3275	0.6052

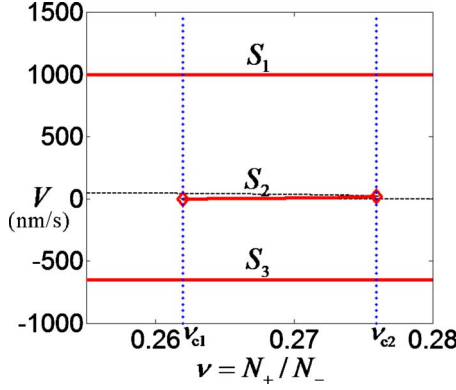


FIG. 2. (Color online) Variation of the stable mode velocities with the ratio ν for the kinesin+dynein tug-of-war model with the parameters listed in Table I. A (2, 3, 2) state sequence is exhibited as ν increases. Note that the velocity of the “stalemate” or almost unmoving mode, S_2 , increases slightly with ν . The transitions at ν_{c1} and ν_{c2} , leading to the appearance and disappearance of the slow mode S_2 , represent saddle-node bifurcations [43].

along the axes to the appropriate fixed points, S_1 or S_3 as the case may be. Indeed, it appears graphically that these two stable fixed points, which correspond to either the + or – team decisively winning (losing) respectively, are located precisely on the axes.

However, such nonanalytic behavior is illusory. Firstly, as seen from Table II, for the dyneinlike symmetrical tug-of-war, the winning/losing fixed points, while very close to the axes, do *not* actually lie *on* them. The reason for the graphical illusion lies, first, in the small values of the dimensionless products aF_d^- and bF_d^+ which both take the value 0.068 for the symmetrical dyneinlike model while, for the kinesin+dynein model, from the parameters in Table I we find $aF_d^- = 4.58 \times 10^{-2}$ and $bF_d^+ = 4.6 \times 10^{-3}$. Secondly, by Eq. (19)

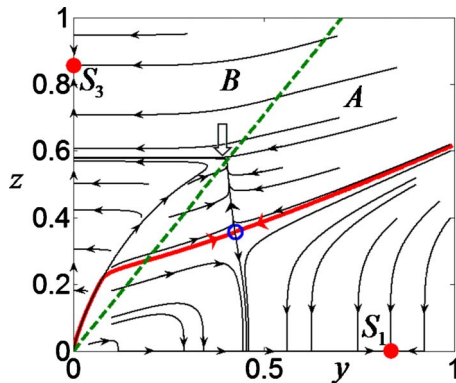


FIG. 3. (Color online) Flow diagram for the kinesin+dynein model as in Fig. 2 for the ratio $\nu = 0.260 < \nu_{c1}$. Note the two stable fixed points, shown as solid circles, representing modes S_1 and S_3 , and an unstable saddle point marked by an open circle. The open arrowhead indicates a region where, although remaining smooth, the directions of the flow change rapidly with y and z ; this reflects a “nearby” pair of fixed points, one stable, one unstable that are realized when ν exceeds ν_{c1} : see Fig. 5 below. The dashed line of slope $\nu_{AB} = 1.4182$ represents the **AB** boundary specified by Eq. (18).

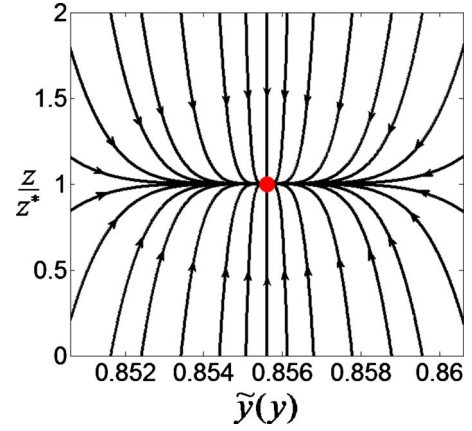


FIG. 4. (Color online) Detail of the flow trajectories near the stable fixed point S_1 at $y^* = 0.8556$ of the flows in Fig. 1 for the symmetric model. Note that the scale of the flows is set by $z^* = 2.43 \times 10^{-6}$. The apparent right angle trajectories seen near the axes in Figs. 1 and 3 are, in fact, smooth but rapid changes in direction. Furthermore, there are no flows along the $z=0$ axis. To obtain this plot the nonlinear variable $\tilde{y}(y) \equiv y^* + (1-y^*)w(y)$ with $w(y) = \pm [|y-y^*|/(1-y^*)]^\Lambda$ was introduced. Then, in order to capture the essence of the actual asymptotic behavior, namely, $(z-z^*) \sim \pm |y-y^*|^\lambda$ with $\lambda \approx 3.52 \times 10^5$, the parameter Λ is chosen as $20\lambda = 7.04 \times 10^4$. For the kinesin+dynein model in Fig. 3 one has $\lambda \approx 1.37 \times 10^8$.

the fixed point conditions $f(x^*, y^*) = g(x^*, y^*) = 0$ for S_1 , the plus-winning mode, yield, first

$$y_1^* \simeq k_+^{\text{on}} / (k_+^{\text{on}} + k_{0+}^{\text{off}}), \quad (21)$$

and hence, with the aid of Eq. (13), the result

$$z_1^* \simeq (k_-^{\text{on}} / k_{0-}^{\text{off}}) \exp(-1/aF_d^-), \quad (22)$$

where the dominating exponential factor derives from the basic assumption Eq. (1).

For the complementary, minus-winning mode S_3 , one similarly finds

$$y_3^* \simeq (k_+^{\text{on}} / k_{0+}^{\text{off}}) \exp(-1/bF_d^+), \quad (23)$$

$$z_3^* \simeq k_-^{\text{on}} / (k_-^{\text{on}} + k_{0-}^{\text{off}}). \quad (24)$$

These estimates lead, in turn, to the numerical values in Table II for the symmetrical model; however, the even smaller values $z_1^* = 1.95 \times 10^{-9}$ and $y_3^* = 5.41 \times 10^{-95}$ result from the kinesin+dynein parameters assigned in Table I.

On reflection, it is evident that these extremely small fixed point values derive principally from the assumption [embodied in the force-velocity relation (2) and the corresponding parameter values in Table I] that the superstall velocities of both + and – motors, while negative, are very small (relative to the low-load velocities). They remain so even under significantly large loads. As illustrated in Fig. 4, a suitable nonlinearly rescaled depiction of the flows near the fixed point S_1 makes it clear that, within the mean-field continuous-variable limit, the flows close to the axes always remain fully analytic.

It is also evident that the extraordinarily small deviations of the fixed points from the axes, of order 10^{-9} or less, can have no physical significance for the tug-of-war models with, as in reality, $N_+, N_- \lesssim 10^2$ or, even, 10^3 . Rather, while the dynamics of the winning team of, say, plus motors may possibly be described by a continuous variable $y = n_+(t)/N_+$, the losing team needs to be described for $z \lesssim 10^{-2}$ or 10^{-3} by small discrete values $n_-(t) = 0, 1, 2, \dots$ which will, further, be subject to fluctuations about their small mean values.

A second point worthy of mention concerns the **AB** boundary, $z = \nu_{AB}y$ [see Eq. (18)] shown as a dashed line in Figs. 3, 5, and 6. This divides the (y, z) plane into two regions, **A** (below) and **B** (above), in which the detachment rates k_+^{off} and k_-^{off} have distinct analytic forms. One might, in general, expect the rates to jump on crossing the boundary; but a careful study using Eqs. (11) and (13), with Eqs. (16)–(18), reveals that the rates vary continuously while their gradients, $(\partial k_+^{\text{off}}/\partial y)$, etc., undergo jumps. Consequently, on crossing from one side to the other, the trajectories and their slopes almost always remain continuous while in general, their *curvatures* vary discontinuously. However, since the jumps are comparatively small and because the off-rate amplitudes, $k_{0\pm}^{\text{off}}$, are small relative to the $k_{\pm}^{\text{on}}$, the curvature changes are generally inconsequential and not evident graphically.

Nevertheless, a full analysis reveals that if there is a point on a flow trajectory with a slope discontinuity, it must be a fixed point, (y^*, z^*) , lying on the **AB** boundary and corresponding to a zero velocity or “tie mode.” If such a point does exist, its coordinates are given by

$$y^* = k_+^{\text{on}} / \{k_+^{\text{on}} + k_{0+}^{\text{off}} \exp[\nu_{AB}/(a\nu + b\nu_{AB})F_d^+]\},$$

$$z^* = k_-^{\text{on}} / \{k_-^{\text{on}} + k_{0-}^{\text{off}} \exp[\nu/(a\nu + b\nu_{AB})F_d^-]\}. \quad (25)$$

For the symmetric tug-of-war model, indeed, there is such a fixed point as can be seen in Fig. 1. The fact that the two trajectories incoming from the **A** and **B** sectors, above and below the symmetric boundary $y=z$, meet at a clearly evident sharp angle is an example of this exceptional case [with coordinates given by $\nu = \nu_{AB} = 1$ in Eq. (25)].

Finally, in comparing Fig. 3 with Fig. 6, we note that although the system exhibits bistability for both $\nu < \nu_{c1}$ and $\nu > \nu_{c2}$, the domain of attraction for forward motion is significantly larger in the latter case.

The (V, ν) phase diagram shown in Fig. 2 reveals a (2,3,2), i.e., bistable-to-tristable-to-bistable sequence of system states. It is natural to enquire if other types of sequence can be realized in tug-of-war models. Indeed they can if one chooses to vary other parameters! Thus Fig. 7 displays a $(V, F_d^+ = F_d^-)$ phase diagram for a symmetric model in which one sees the state stability sequence (2,3,1), i.e., ending in a monostable state. To provide further analytic insight, this diagram includes the velocities of the *unstable* stationary modes of motion illustrating the phenomenon of loss of a mode when a pair of stationary points, one stable, one unstable, coalesce. The resulting “critical points” are marked by diamonds. Biophysically the behavior seen may be interpreted as a result of having raised the detachment forces F_d^+ and F_d^- so high as to ensure a stalemate or tie of zero motion

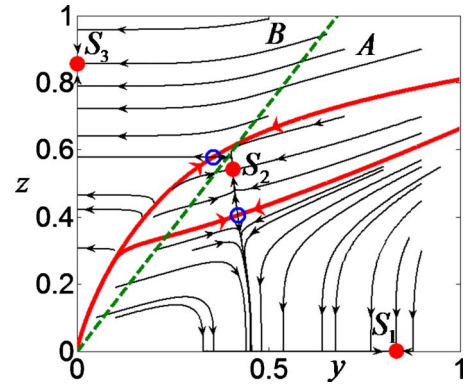


FIG. 5. (Color online) Flow diagram as in Fig. 3 but for the parameter value $\nu = 0.270$. Now there are three stable fixed points, corresponding to the modes of motion S_1 , S_2 , and S_3 and, in addition, two unstable saddle points marked by open circles. The straight dashed line represents the **AB** boundary $z = \nu_{AB}y$; see Eq. (18).

of the balanced teams. Thus the larger are the F_d , the harder it is to detach a motor from the track by increasing load. When a motor is easily detached, only two modes of motion are realized corresponding to one or the other team winning, because, compared to the detachment force, the force exerted by the two teams is relatively large [29]. On the other hand, when it is hard to detach a motor from the track, only the low-velocity tie mode can be achieved in the tug-of-war.

Fig. 8 demonstrates again a (2,3,2) stability sequence but now for an asymmetric model in a (V, k_+^{on}) diagram. As in Fig. 2, the velocity of the slow-moving mode changes slightly with the parameter k_+^{on} . But it is clear that overall the system behavior may be summarized, using a convenient notation [23,24], as $(+-) \Rightarrow (+0-) \Rightarrow (+-)$ in contrast to the sequence $(+-) \Rightarrow (+0-) \Rightarrow (0)$ in Fig. 7. The interesting feature is that, when there are three modes of motion, the velocity of the almost matched stable mode may not be zero. Although this may seem to contradict natural intuition, the phenomenon has, in fact, been observed both in the *in vivo* and *in vitro* experiments [29,30] and, of course, can be checked by Monte Carlo simulations for the tug-of-war model.

A more complex three-step (2,3,2,1) sequence in a (V, F_d^+) diagram is displayed in Fig. 9. In further contrast to Fig. 7,

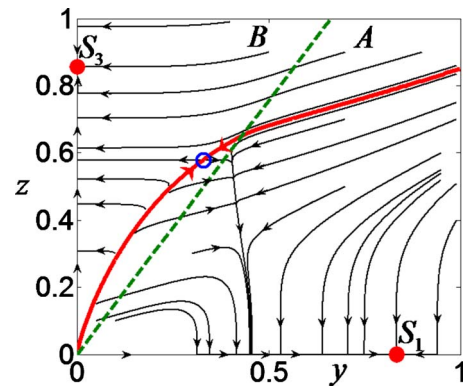


FIG. 6. (Color online) Flow diagram as in Fig. 5 but for $\nu = 0.277$ for which case there are again only two stable fixed points, labeled S_1 and S_3 and one unstable saddle point (open circle).

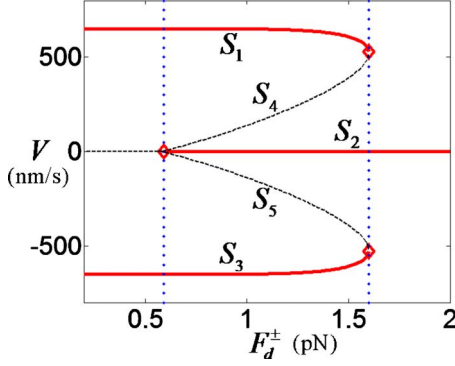


FIG. 7. (Color online) Transitions between bistable, tristable, and monostable system states for a symmetric model ($\nu=1$) as the detachment force varies from the value $F_d^+ = 0.75$ pN adopted for dynein, all the other parameters being fixed as listed for dynein in Table I. The bold curves depict the variation of the velocities of the stable modes of steady motion as in Fig. 2, while the dashed lines correspond to *unstable* stationary modes as seen in Figs. 1, 3, 5, and 6. The stationary mode S_2 appears at a subcritical pitchfork bifurcation while S_1 and S_3 terminate at saddle-node bifurcations [43].

the monostable state achieved for large F_d^+ now contains a single (+) mode corresponding to rapid plus-end directed motion. As mentioned above, a large F_d^+ means that a plus-end motor is difficult to detach from the track. Thus, it is not difficult to understand these results: when F_d^+ is much smaller than $F_d^- (=0.75$ pN), the plus-end team cannot match the opposing team to achieve a stalemate, low-velocity mode. But when F_d^+ is close to F_d^- , the two teams can achieve a balance, so there are three modes of motion. On increasing F_d^+ , the minus team becomes too weak to match the plus team, while when F_d^+ is large enough, the plus-end motors cannot be detached and so the cargo moves only towards the plus end of the track.

In Fig. 10, the stall force F_S^+ for one team of otherwise fully symmetric motors is varied with $\nu=1$. One finds that a strongly *asymmetric* bistable state of form (+,0) is realized which transforms via a (+0-) state to a more typical bistability state (+-). An unusual feature of this diagram is the

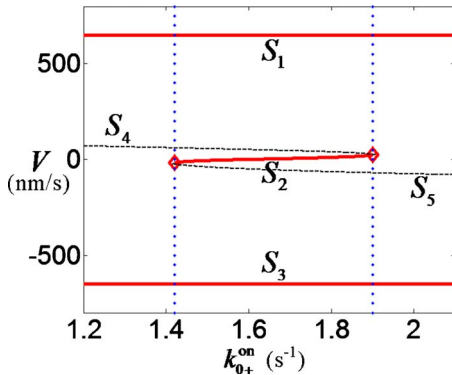


FIG. 8. (Color online) Transitions as in Fig. 7 for a symmetric tug-of-war model using the parameters adopted for dynein (see Table I) except that the symmetry has been broken by varying the on-rate amplitude k_0^+ from the dynein value $k_0^- = 1.6$ s⁻¹. As in Fig. 2 the slow mode S_2 is bounded by two saddle-node bifurcations.

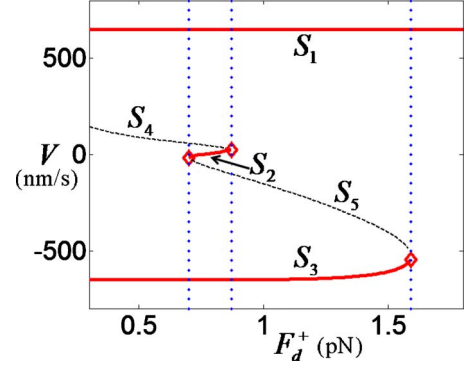


FIG. 9. (Color online) Transitions as in Figs. 7 and 8 for a symmetric dynein-type model (Table I) but with the symmetry broken by varying the detachment force F_d^+ from the dynein value $F_d^+ = 0.75$ pN. The sequence of *four* distinct system states seen is $(+-) \Rightarrow (+0-) \Rightarrow (+-) \Rightarrow (+)$. All three transitions represent saddle-node bifurcations.

“collision,” at the point marked by a cross close to $F_S^+ = 1.47$ pN, of the locus of the low-velocity stable mode, labeled S_2 , with the positive-velocity unstable mode, S_4 , as the critical point at $F_S^+ = 1.8$ pN (marked by a diamond) is approached. This behavior results from the close-to-symmetric underlying model. As inspection of the sequential set of trajectories shown in Fig. 11 reveals, there is always a trajectory on the diagonal $z=y$. Furthermore, when $\nu=1$ with $F_d^+ = F_d^- \equiv F_d$, $k_+^{\text{on}} = k_-^{\text{on}} \equiv k^{\text{on}}$, and $k_{0+}^{\text{off}} = k_{0-}^{\text{off}} \equiv k^{\text{off}}$, there is likewise a stationary mode given by

$$y^* = z^* = k^{\text{on}} / \{k^{\text{on}} + k^{\text{off}} \exp[1/(a+b)F_d]\}. \quad (26)$$

Consequently, if we also have, as here, $V_B^+ = V_B^-$ and $V_F^+ = V_F^-$ with F_S^- fixed, the coordinates $y^* = z^*$, and the corresponding stability depends smoothly via the expression Eq. (11) [or Eq. (17)] for the coefficients a and b (or $\bar{a}$ and $\bar{b}$) in Eq. (26),

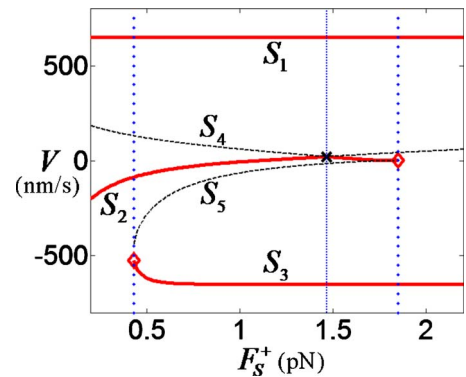


FIG. 10. (Color online) Transitions as in previous figures for a symmetric dynein-type model with the stall force F_S^+ departing from the adopted dynein value $F_S^- = 1.1$ pN. Note the novel state sequence, with a strongly asymmetric bistability state (+0) transforming to (+0-). At the special “collision point” (marked by a cross) the stable mode S_2 meets (and exchanges stability) with the unstable mode S_4 . This represents a transcritical bifurcation [43]. The remaining two transitions (terminating the unstable mode S_5) correspond to saddle-node bifurcations.

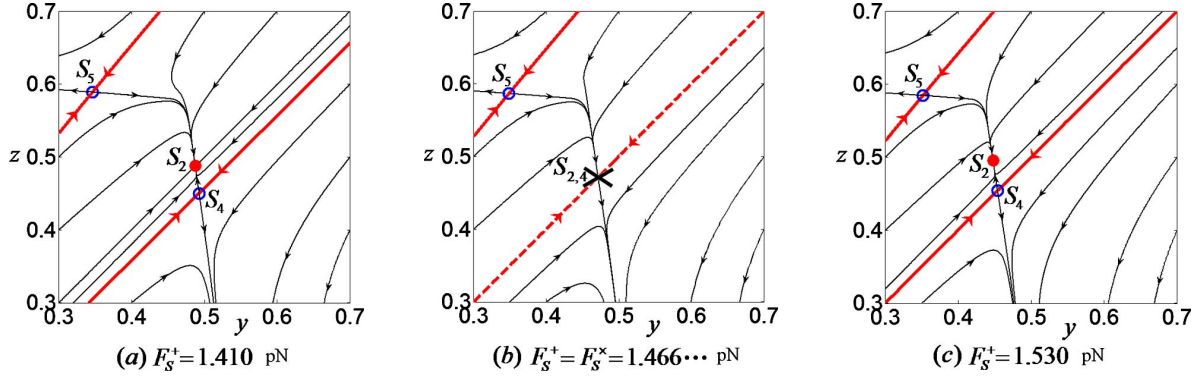


FIG. 11. (Color online) The central region of the (y, z) flow diagram for the system in Fig. 10 for the successive values of the parameter F_S^+ showing the coalescing of the stable mode (solid circle) with the unstable mode (open circle) at the special value $F_S^+ = F_S^*$ (marked by a cross) where the transcritical bifurcation is realized. For $F_S^+ < F_S^*$ the stable mode lies on the trajectory $z=y$ while for $F_S^+ > F_S^*$, the unstable mode lies on this axis.

on the parameter F_S^+ . Furthermore, one finds that the stability of this mode changes when the determinant

$$D(F_S^+) = \begin{vmatrix} (\partial f / \partial y) & (\partial f / \partial z) \\ (\partial g / \partial y) & (\partial g / \partial z) \end{vmatrix} \quad (27)$$

vanishes. This, in turn leads to the condition which yields the collision point value $F_S^+ = F_S^* = 1.46677 \dots \text{pN}$. At this point, in fact, the stable and unstable modes S_2 and S_4 coalesce as illustrated in Fig. 11.

Finally, it may be remarked that the motility modes for large or small values of the various motor parameters are readily found theoretically. For example, as the ratio $\nu = N_+/N_-$ becomes large there is only one stable fixed point described by

$$y^* \approx k_+^{\text{on}} / (k_+^{\text{on}} + k_{0+}^{\text{off}}), \quad (28)$$

$$z^* \approx (k_-^{\text{on}} / k_{0-}^{\text{off}}) \exp(-1/aF_d^-),$$

which corresponds to a balance with respect to binding and unbinding of plus-end motors which then dominate. Naturally, there is a complementary result when $\nu \rightarrow 0$. Similar results can be obtained for other parameters of the model within the mean-field limit.

IV. MODE-TO-MODE TRANSITION RATES

As pointed out previously [25], the results derived via the mean-field analysis are valid only for sufficiently large motor numbers N_+ and N_- . Conversely, when N_+ and N_- are small, the motion of the cargo will fluctuate and, as observed in [29,30], may change from one state identified as stable in the mean-field limit to another. Here, we investigate numerically the *probability fluxes* between distinct, otherwise stable stationary states, that arise this way. The method used here is a combination of mean field theory (using basins of attractions to obtain boundaries between different modes of motion) and the stochastic model [using the Master equation to obtain the probabilities $p(n_+, n_-)$]. The results demonstrate that the mean transition times between states increase exponentially as the numbers of motors involved increase [44,45]. Put oth-

erwise, the more motors engaged in the transportation process, the more steadily will the cargo move along its track.

The first and crucial issue for a fluctuating system of relatively few motors is to identify suitable boundaries in the (n_+, n_-) plane across which to calculate probability fluxes. To this end it is appropriate, at least when N_+ and N_- are only moderately small, to examine the flow fields in the corresponding mean-field limit that embodies the same ratio $\nu = N_+/N_-$. Consider, thus, the (y, z) plane as depicted for example, in Figs. 1, 3, 5, and 6 above. As clear from these figures, the flow plane is, for fixed ν and a given set of motor parameters, divided up into two or into three distinct *basins of attraction*, say $\mathbf{D}_1$ and $\mathbf{D}_2$ or $\mathbf{D}_1$, $\mathbf{D}_2$, and $\mathbf{D}_3$, each associated with the corresponding stable fixed points, S_1 and S_2 or S_1 , S_2 , and S_3 . See Fig. 12 for the case $\nu=1$ with $N_+ = N_- = 15$. (As evidenced by Fig. 9, there can also be models exhibiting only a single fixed point with a basin of attraction encompassing the whole flow plane; but in such cases the issue of transition fluxes is clearly moot.)

If, for $N_+, N_- \gg 1$, the initial values $[y(0), z(0)]$ lie in the basin $\mathbf{D}_i$, the expected stationary motion of the cargo corre-

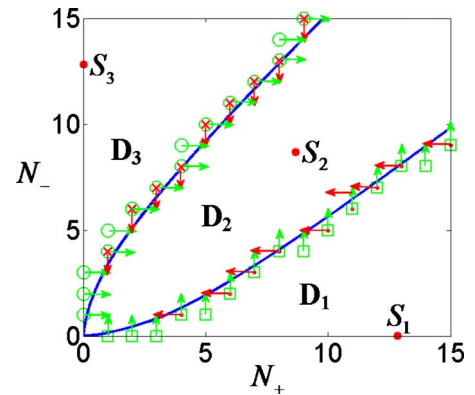


FIG. 12. (Color online) Examples of boundaries $\mathbf{B}_{ij}^U$, $\mathbf{B}_{ij}^D$, $\mathbf{B}_{ij}^L$, and $\mathbf{B}_{ij}^R$ for a symmetric dynein-type model as in Fig. 1 with $N_+ = N_- = 15$. The bonds identified by “O” with (green) right pointing arrows belong to B_{32}^R , those identified by “x” with (red) down pointing arrows belong to B_{32}^D , the squares “□” with (green) upwards arrows belong to B_{12}^U , while those marked “●” with (red) left pointing arrows specify B_{12}^L .

sponds to mode $S_i(y_i^*, z_i^*)$. For finite motor numbers, however, the maximal points (n_+, n_-) of the probability distribution $p(n_+, n_-)$ will, in general, differ somewhat from the mean field values $(N_+ y_i^*, N_- z_i^*)$. Correspondingly, the basins of attraction may also differ to some extent from the mean-field expectations. Nevertheless, for N_+ and N_- finite but sufficiently large, the deviations from the basins predicted by mean-field analysis will not be significant. Accordingly, we will accept as a leading approximation, the mean-field basins. This will surely be satisfactory for large enough motor numbers but the numerical results for small N_+, N_- might not be fully adequate.

Examination of the flows in Figs. 1, 3, 5, and 6 demonstrates that, especially, in asymmetric models with three mean-field stable states, the shapes of the basins $\mathbf{D}_i$ may be fairly complex. One also sees that the boundaries $\mathbf{B}_{ij}$, separating basins $\mathbf{D}_i$ and $\mathbf{D}_j$ are determined by the separating trajectories or separatrices that flow into the appropriate saddle points describing *unstable* stationary modes of motion, such as labeled S_4 and S_5 in Fig. 1 (and likewise in Figs. 3, 5, and 6). Given a boundary $\mathbf{B}_{ij}$, the probability flux from mode S_i to S_j is thus measured by the flux through $\mathbf{B}_{ij}$. Hence we calculate the flux via the expression

$$J_{ij} \simeq \sum_{(n_+/N_+, n_-/N_-) \in \mathbf{B}_{ij}^R} \pi_+(n_+, n_-) p(n_+, n_-) + \sum_{(n_+/N_+, n_-/N_-) \in \mathbf{B}_{ij}^L} \epsilon_+(n_+, n_-) p(n_+, n_-) + \sum_{(n_+/N_+, n_-/N_-) \in \mathbf{B}_{ij}^U} \pi_-(n_+, n_-) p(n_+, n_-) + \sum_{(n_+/N_+, n_-/N_-) \in \mathbf{B}_{ij}^D} \epsilon_-(n_+, n_-) p(n_+, n_-), \quad (29)$$

where, as illustrated in Fig. 12 for the symmetric model $N_+ = N_- = 15$, the boundaries are identified by those sets of directed lines or “bonds” labeled R, L (right, left) or U, D (up, down), that link adjacent points of the $N_+ \times N_-$ discrete grid of values of $n_+(t)$ and $n_-(t)$ and intersect the limiting mean-field boundaries between the corresponding mean-field basins of attraction $\mathbf{D}_i$ and $\mathbf{D}_j$ [recall that the transition rates $\pi_+(n_+, n_-)$, etc. are defined in Eqs. (5)–(7) above]. Thus, more formally by identifying the boundary bonds, we can write

$$\begin{aligned} \mathbf{B}_{ij}^R &= \left\{ \left(\frac{n_+}{N_+}, \frac{n_-}{N_-} \right) \in \mathbf{D}_i \quad \text{and} \quad \left(\frac{n_+ + 1}{N_+}, \frac{n_-}{N_-} \right) \in \mathbf{D}_j \right\}, \\ \mathbf{B}_{ij}^L &= \left\{ \left(\frac{n_+}{N_+}, \frac{n_-}{N_-} \right) \in \mathbf{D}_i \quad \text{and} \quad \left(\frac{n_+ - 1}{N_+}, \frac{n_-}{N_-} \right) \in \mathbf{D}_j \right\}, \\ \mathbf{B}_{ij}^U &= \left\{ \left(\frac{n_+}{N_+}, \frac{n_-}{N_-} \right) \in \mathbf{D}_i \quad \text{and} \quad \left(\frac{n_+}{N_+}, \frac{n_- + 1}{N_-} \right) \in \mathbf{D}_j \right\}, \\ \mathbf{B}_{ij}^D &= \left\{ \left(\frac{n_+}{N_+}, \frac{n_-}{N_-} \right) \in \mathbf{D}_i \quad \text{and} \quad \left(\frac{n_+}{N_+}, \frac{n_- - 1}{N_-} \right) \in \mathbf{D}_j \right\}. \end{aligned} \quad (30)$$

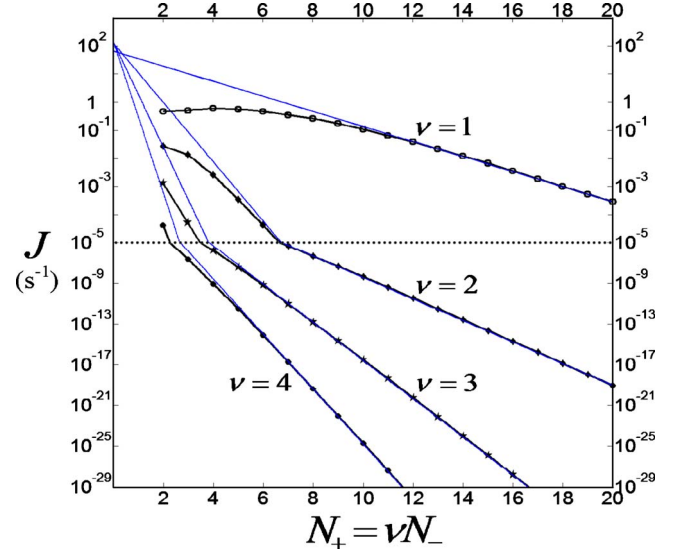


FIG. 13. (Color online) Probability fluxes as a function of motor number for symmetric dyneinlike tug-of-war models with $\nu := N_+/N_- = 1, 2, 3$, and 4. Note the break in the logarithmic flux scale at $J = 10^{-5} \text{ s}^{-1}$ marked by the horizontal dotted line. The parameters of the straight line fits shown are given in Table III.

Then, to obtain these discrete boundary sets, $\mathbf{B}_{ij}^R, \dots$, the mean-field boundaries of the different basins $\mathbf{D}_i$ ($1 \leq i \leq 2$ or 3) are needed. As observed, these may be calculated by solving the differential equation

$$dz/dy = g(y, z)/f(y, z), \quad (31)$$

for the separating trajectories that flow into the unstable modes or saddle points at which the conditions Eq. (20) are violated [46].

On this basis various special cases have been studied as a function of N_+ and N_- to provide some insights into the various probability fluxes. Of course, the expected lifetime for transitions out of a state vary as the reciprocal of the probability fluxes.

A. Fully symmetric dynein-type model: $\nu = N_+/N_- = 1$

In this case, as depicted in Fig. 1, there are three basins of attraction, $\mathbf{D}_1$, $\mathbf{D}_2$, and $\mathbf{D}_3$, but only the fluxes $J_{21} = J_{23}$ are relevant since direct transitions between modes S_1 and S_3 are most improbable. The data from $N_+ = N_- = 2$ up to 20 are shown in Fig. 13: see the plot labeled $\nu = 1$. At first there is little strong variation, but it is evident that for $N_+ = N_- \geq 10$ the fluxes decay rapidly; indeed the results are rather well fit by the general expression

$$J(N_+, N_-) \approx A(\nu) e^{-B(\nu) N_+}, \quad (32)$$

with $A(1) = 66.52 \text{ s}^{-1}$ and $B(1) = 0.2686$: see also Table III.

B. Symmetric dynein-type model for $\nu > 1$

When $\nu = 2, 3, \dots$ or, equivalently, $\nu = \frac{1}{2}, \frac{1}{3}, \dots$, the motility phase diagrams and flow fields (which resemble Figs. 2, 3, and 6) display only two basins of attraction separated by a

TABLE III. Parameters for fitting the probability fluxes for the symmetric dyneinlike models to the form (32): see Fig. 13.

	$\nu=1$	$\nu=2$	$\nu=3$	$\nu=4$
$A(\nu)$ (s^{-1})	66.52	132.9	156.6	170.4
$B(\nu)$	0.2686	0.5285	0.6259	0.6761

single curvilinear mean-field boundary. As evident from Fig. 13 (see the plots labeled $\nu=2, 3$, and 4) the fluxes are orders of magnitude smaller than for $N_+=N_-$, i.e., $\nu=1$. Furthermore the exponential form Eq. (32) provides a good description down to values of $N_+ \gtrsim 5$. The appropriate parameters are listed in Table III.

C. Asymmetric kinesin+dynein model

Using the parameters of Table I one finds that for $\nu=1, 2, 3, 4$ and the reciprocals $\frac{1}{2}, \frac{1}{3}, \frac{1}{4}$, there are just two stationary states and, again, only one mean-field boundary. For $N_+ \gtrsim 10$, the fluxes are again well fit by Eq. (32) but with the parameters presented in Table IV.

Cargo detachment

Finally, we address the rate of total detachment of the cargo from the track, i.e., transitions to the state with $n_+=n_-=0$. For even moderate values of N_+ and N_- the cargo seldom detaches completely from the track. Indeed, for large values of N_+ and N_- , one sees from Eq. (19) that $(y, z) = (0, 0)$ cannot be a steady mode of motion. But for small motor numbers, detachment is possible; indeed, being detached can be regarded as a special mode of cargo motion. Furthermore, the rate of detachment relates to many significant biophysical properties of cargo transport, such as the mean velocity, mean run length, etc. At steady state, the flux of detachment of the cargo can be calculated from [47]

$$J_d = k_{0+p}^{\text{off}}(1, 0) + k_{0-p}^{\text{off}}(0, 1) = (N_+ k_+^{\text{on}} + N_- k_-^{\text{on}}) p(0, 0). \quad (33)$$

This has been done for the specific models described above. By fitting to Eq. (32) we find a fair description for $N_+ \gtrsim 9$ is given by the parameter values listed in Table V.

V. STALL FORCE OF THE CARGO

Measurements of the velocities of single motor protein molecules *in vitro* under controlled, steady external loads have proved most informative: see, e.g., [17, 18]. A prime observable is then the *stall force*, F_S , which brings the mean velocity, $\bar{V}(F_{\text{ext}})$, of the motor on the track to zero. This

TABLE V. Detachment fluxes as fitted to relation (32) for $\nu=1, 2, 3$.

		$\nu=1$	$\nu=2$	$\nu=3$
Symmetry	$A(\nu)$ (s^{-1})	9.262	29.68	44.24
	$B(\nu)$	0.8174	0.822	0.8256
Asymmetry	$A(\nu)$ (s^{-1})	7.925	55.80	81.88
	$B(\nu)$	0.7504	0.7643	0.7686

feature of individual motors is, of course, embodied in the tug-of-war models via the relations (2) and the parameters F_S^+ and F_S^- . It should be noticed, that the expressions (2) allow, albeit in approximate form, for reverse or “backward” velocities under superstall loads as observed experimentally (and treated theoretically in, e.g., [41]). It is thus appropriate to consider similar observations on cargoes pulled by teams of motors under external loads and to enquire what the tug-of-war models may predict for such experiments. In this situation, as mentioned in Sec. II, the responses embodied in the relation (2) for *assisting* loads must also be employed.

The most appropriate definition of the stall force for the cargo is not *a priori* obvious; but it seems reasonable to retain as a definition of the stall force (see, e.g., [8].) that fixed, steady externally imposed load under which the mean value of the fluctuating velocity of the cargo vanishes [48–51]. Recall that the external load, F_{ext} , enters via Eqs. (3) and (4) in Sec II. A little reflection, however, reveals that there are now, in fact, two distinct, oppositely directed, stall forces that must be considered, namely, the plus-end stall force F_C^+ , under which the mean positive velocity of the cargo is reduced to zero from a *positive zero-load* mean velocity, and the complementary minus-end stall force F_C^- , which reduces the negative mean velocity of the cargo to zero starting from a *negative average zero-load* velocity. On the basis of our definition, one easily finds that the stall forces F_C^+ and F_C^- of a completely symmetric tug-of-war model are both zero. More generally, when the mean zero-load velocity is positive, so is the plus-end stall force, F_C^+ , while the minus-end stall force is identically zero. Conversely, when the zero-load velocity is negative, the minus-end stall force F_C^- is positive but the plus-end stall vanishes.

To obtain the cargo stall forces F_C^+ and F_C^- it is necessary to construct an expression for the mean stationary cargo velocity

$$\bar{V}_C(F_{\text{ext}}) = \sum_{n_+=0}^{N_+} \sum_{n_-=0}^{N_-} p_{\infty}(n_+, n_-) V_C(n_+, n_-), \quad (34)$$

where the individual state velocities $V_C(n_+, n_-)$ were introduced in Eqs. (9) and (15) while the stationary state prob-

TABLE IV. Parameters for the probability fluxes for the kinesin+dynein models.

	$\nu=4$	$\nu=3$	$\nu=2$	$\nu=1$	$\nu=1/2$	$\nu=1/3$	$\nu=1/4$
$A(\nu)$ (s^{-1})	43.47	4.919	3.063	1.850	3.284	14.528	4.513
$B(\nu)$	0.8323	0.5326	0.7988	0.754	0.7451	0.7516	0.8341

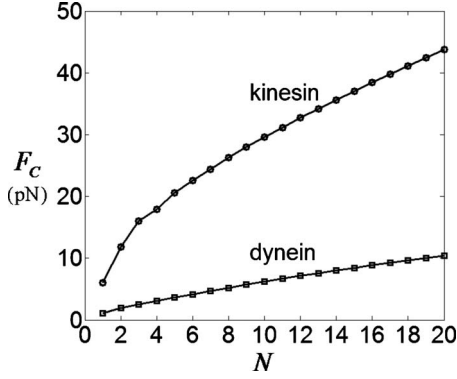


FIG. 14. The cargo stall force, $F_C(N)$, for a cargo towed by N motors of a single species using the model parameters in Table I.

abilities, $p_\infty(n_+, n_-)$, follow from the master equation (7). Then the equations $\bar{V}_C(F_C^+) = 0$ or $\bar{V}_C(F_C^-) = 0$ must be solved. This can be achieved numerically for specific models specified by, say, the motor numbers N_+ and N_- when the individual motor parameters are fixed as, e.g., in Table I. However, it is instructive to examine some cases analytically to demonstrate concretely the general conclusion, namely, that there are no simple or obvious results. Rather it transpires that in general all the parameters affect the values of F_C^+ and F_C^- .

To this end, the simplest cases to consider are when only one species of motor is available, i.e., N_+ with $N_- = 0$ or vice versa. This situation was originally addressed by Klump and Lipowsky but without allowing for reverse velocities under superstall loads [41,52,53]. Following their approach, we obtain, for the simplest nontrivial case, namely, $N_+ = 2$ ($N_- = 0$), the equation

$$2k_{0+}^{\text{off}} \exp(F_C^+/2F_d^+) V_B^+ [1 - (F_C^+/F_S^+)] + k_+^{\text{on}} V_F^+ [1 - (F_C^+/2F_S^+)] = 0, \quad (35)$$

which evidently depends on all the single motor parameters rather than simply on F_S^+ as might have been guessed. (For a more detailed analysis see the supplemental material [54]). Furthermore, one can see that while, as expected, one

does have $F_C^+(N_+=2) > F_S^+ \equiv F_C^+(N_+=1)$, the cargo stall force is actually *less* than $2F_S^+$. In the special case in which the detachment force becomes large ($F_d^+ \rightarrow \infty$) so that the unbinding rate ϵ_+ in Eq. (5) becomes independent of the external load, Eq. (35) can be solved explicitly to yield

$$F_C^+(N_+=2) - F_S^+ = F_S^+ k_+^{\text{on}} V_F^+ / (k_+^{\text{on}} V_F^+ + 4k_{0+}^{\text{off}} V_B^+). \quad (36)$$

Indeed, this result for $F_d^+ \rightarrow \infty$ can be extended to yield a general, but fairly complicated result for $F_C^+(N_+)$. In the special case $V_B^+ = V_F^+$ one can then further establish the bound

$$F_C^+(N_+) \leq (N_+ + 1) F_S^+ p (1 - q^{N_+}) / [1 - q^{N_+} (pN_+ + 1)], \quad (37)$$

where $p = 1 - q = k_+^{\text{on}} / (k_+^{\text{on}} + k_{0+}^{\text{off}})$. (Of course, the corresponding results apply for $N_- \geq 1$ with $N_+ = 0$.)

This bound suggests a linear relation between F_C^+ and N_+ (or F_C^- and N_-). But the numerical results shown in Fig. 14 display a significant *sublinear* dependence for both kinesin and dynein models [52]. Indeed, when the numerics are extended to (unphysical) values of N_+, N_- of order 10^2 , a power law with exponent close to 0.75 provides a reasonable fit to F_C^+ for both models. Perhaps also surprising is that while, by Table I, the single-molecule stall force for kinesin is about 5.5 times that for dynein, this factor exceeds the cargo stall force ratio $F_C^{\text{kin}} / F_C^{\text{dyn}} \approx 3.75$, observed for large motor numbers, by 40 to 50%.

When one comes to competing teams (with $N_+, N_- \geq 1$) the general analytical expressions are rather intractable although for $N_+ = N_- = 1$ explicit results can be usefully examined. Then one readily sees [54] that $F_C^+(N_+ = N_- = 1)$ bears no simple relation to $(F_S^+ - F_S^-)$ as might have been hoped. On the other hand, as seen in Fig. 15(a), the dependence of the stall force F_C^+ on N_+ for fixed values of $N_- = 1, 5, \dots$, resembles the single-species sublinear results of Fig. 14 but with monotonically lower values as N_- increases. Note, in particular, that the differences $F_C^+(N_+ + 1) - F_C^+(N_+)$ are much smaller than F_S^+ . At first sight, a somewhat surprising feature of Fig. 15(a) is that for sufficiently many competing motors, specifically for $N_- \geq 10$ (using Table I parameters), the stall force F_C^+ sticks at a zero value until N_+ exceed a positive threshold, $N_+^0(N_-)$. However, these threshold values are rela-

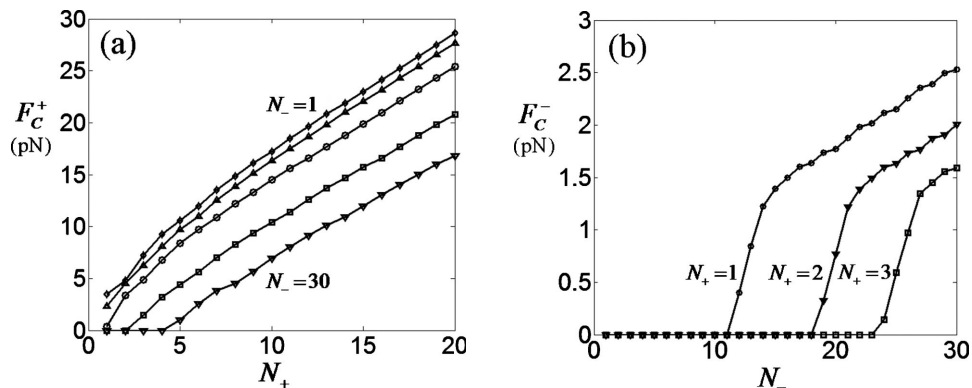


FIG. 15. Dependence of the stall forces F_C^+ and F_C^- for the kinesin+dynein model (see Table I) on the corresponding motor numbers, N_+ and N_- , with fixed competing numbers. In (a) the specified numbers, N_- , of competing minus-end motors are, reading from the top downwards, 1, 5, 10, 20, and 30.

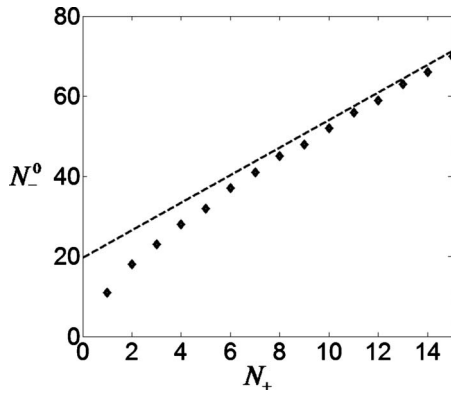


FIG. 16. The threshold number, $N_-^0(N_+)$, of dynein motors which are needed to stall the motion of cargo attached to N_+ kinesin motors. The dashed straight line is merely an aid to assessing the sublinear character of the N_-^0 plot.

tively small. Thus, for $N_- = 30$ one might have guessed, from the ratio $F_S^+/F_S^- \approx 5$, that 6 or 7 plus-end motors would be needed to provide a positive mean motion and nonzero stall force; but as the figure reveals, 5 or more motors suffices.

The situation appears rather different, indeed, when, as in Fig. 15(b), one examines the cargo stall force that pertains to the weaker team of motors, namely, F_C^- . In this case the thresholds, $N_-^0(N_+)$, are much larger and enter even for $N_+ = 1$. Furthermore, on passing the threshold the cargo stall forces increase rather rapidly for the first few values of N_- exceeding N_-^0 . They remain, however, significantly lower than the F_C^+ stall force in accord with expectations based on the small ratio $F_S^-/F_S^+ \approx 0.2$. Thereafter, however, the plots of $F_C^-(N_-)$ at fixed N_+ , increase roughly linearly (at least up to $N_- \approx 60$). As to the threshold values themselves, one sees from Fig. 16 that they grow steadily but sublinearly.

The overall behavior is somewhat paradoxical in that whereas intuitively one kinesin motor could be balanced by about five dyneins, this impression proves quite misleading for small values of N_+ . Indeed, from Fig. 15(b) one sees that about eleven dyneins are needed to stall one kinesin when $N_+ = 1$, while eighteen or so suffice when $N_+ = 2$. On the other hand, from Fig. 16 one concludes that for large N_+ , in the range above 10, four or five dyneins are able to achieve an effective balance. If, experimentally, methods could be devised to control the cargo-bound motor numbers, these feature of the stall force, $F_C^-(N_+, N_-)$, could be valuable in testing the validity of the tug-of-war models, in sharpening the parameter values, and in improving details.

VI. CONCLUDING REMARKS

The tug-of-war models we have studied above were first formulated succinctly by Müller *et al.* [23,24] although, as indicated in our Introduction, earlier treatments [3–12] involving many of the modeling aspects, must not be overlooked. In the first studies [23,24] a stochastic treatment was developed, employing a master equation, and numerical calculations were undertaken. Different modes of motion were identified via peaks in the stationary probability distribu-

tions. Furthermore, changes of state, depending on parameter choices, from $(+, -)$ to $(+, 0, -)$ directed motions, etc., were observed.

Subsequently, the large-motor-number limit or mean-field theory was introduced and developed by one of us [25] and independently addressed by Müller [26]. Initially, however, the approach was employed mainly to examine basic properties of the dynamics. In the present article, we have examined various further aspects within the mean-field limit. In particular, we have exposed the various types of transition induced between different numbers of stationary modes of motion when motor parameters are varied. The results indicate, indeed, that changes in most of the parameters generate sharp bifurcations or transition points. An interesting feature uncovered is that, in many cases, there are three stationary modes of motion but none of the corresponding velocities actually vanishes. In other words, the cargo always moves with some nonzero mean velocity, even in an almost balanced or low-velocity stalemate mode. This phenomena has been experimentally observed in recent studies: see Figs. 1 and 2 in [29], and Figs. 2 and 3 in [30].

However, to judge the value and range of validity of the mean-field analysis, it is important to study the stochastically induced transitions between different modes of motion. Thus we have shown that for finite N_+ and N_- the average times, $t_{\pm}$, the cargo spends in $+$ or $-$ unidirectional motion (which times we identify as proportional to the inverse probability fluxes between the different stationary mean-field modes) increase exponentially with the total number of available motors. Thus, when more motors are involved, the cargo moves more deterministically even though the maximum cargo speed does not change significantly. Furthermore, we find that the lifetime of the cargo on the track prior to detachment likewise increases exponentially with N_+ and N_- . This issue has also been addressed recently by Müller *et al.* [45] using a stochastic approach. Although the criteria for specifying probability fluxes differs somewhat from ours [46], the exponential dependence on motor numbers is confirmed.

Experimentally, it should be relatively easy to measure the stall force of a cargo under an externally imposed load. Although appropriate or optimal definitions are not obvious (as are discussed briefly in Section V), the numerical calculations of Lipowsky *et al.* [53] indicate an increase of stall force with motor number, although a simple linear relationship is *not* realized. Our analytic and numerical results demonstrate, in fact, that the stall force is never a simple linear function of N_+ and N_- , rather a sublinear dependence is revealed. Unfortunately, therefore, it is not straightforward to determine the motor numbers observationally by measuring the stall force of a cargo, contrary to what has been suggested in some reports in recent experimental studies [16,49]. Moreover, it may transpire that the tug-of-war models overlook important mechanistic details of cellular cargo motion. For example, the intermolecular interactions between the different motors might play a role [30,31] and the elasticity of the links between the cargo and the motors might be significant [49]. To address such questions, further measurements under varying experimental conditions should be of assistance. An initial approach would be to measure the stalling force distributions [48] of cargoes when

moved in environments with only a single available motor species: according to the underlying single-species model, differences between adjacent peaks or maxima in the distributions as the numbers of motors attached rises should not be constant but, rather, decrease somewhat.

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- [1] D. Bray, *Cell Movements: From Molecules to Motility*, 2nd ed. (Garland, New York, 2001).
 - [2] J. Howard, *Mechanics of Motor Proteins and the Cytoskeleton* (Sinauer Associates and Sunderland, MA, 2001).
 - [3] J. Howard, *Annu. Rev. Biophys.* **38**, 217 (2009).
 - [4] F. Jülicher and J. Prost, *Phys. Rev. Lett.* **75**, 2618 (1995).
 - [5] F. Jülicher, A. Ajdari, and J. Prost, *Rev. Mod. Phys.* **69**, 1269 (1997).
 - [6] S. Camalet, F. Jülicher, and J. Prost, *Phys. Rev. Lett.* **82**, 1590 (1999).
 - [7] T. J. Mitchison and H. M. Mitchison, *Nature (London)* **463**, 308 (2010).
 - [8] A. B. Kolomeisky and M. E. Fisher, *Annu. Rev. Phys. Chem.* **58**, 675 (2007).
 - [9] T. Elston and G. Oster, *Biophys. J.* **73**, 703 (1997).
 - [10] H.-Y. Wang, T. Elston, A. Mogilner, and G. Oster, *Biophys. J.* **74**, 1186 (1998).
 - [11] A. B. Kolomeisky and B. Widom, *J. Stat. Phys.* **93**, 633 (1998).
 - [12] M. E. Fisher and A. B. Kolomeisky, *Proc. Natl. Acad. Sci. U.S.A.* **96**, 6597 (1999).
 - [13] R. D. Vale, *Cell* **112**, 467 (2003).
 - [14] D. B. Hill, M. J. Plaza, K. Bonin, and G. Holzwarth, *Eur. Biophys. J.* **33**, 623 (2004).
 - [15] C. Kural, H. Kim, S. Syed, G. Goshima, V. I. Gelfand, and P. R. Selvin, *Science* **308**, 1469 (2005).
 - [16] G. T. Shubeita, S. L. Tran, J. Xu, M. Vershinin, S. Cermelli, S. L. Cotton, M. A. Welte, and S. P. Gross, *Cell* **135**, 1098 (2008).
 - [17] N. J. Carter and R. A. Cross, *Nature (London)* **435**, 308 (2005).
 - [18] S. M. Block, *Biophys. J.* **92**, 2986 (2007).
 - [19] A. Gennerich and R. D. Vale, *Curr. Opin. Cell Biol.* **21**, 59 (2009).
 - [20] M. Badoual, F. Jülicher, and J. Prost, *Proc. Natl. Acad. Sci. U.S.A.* **99**, 6696 (2002).
 - [21] E. B. Stukalin, H. Phillips, and A. B. Kolomeisky, *Phys. Rev. Lett.* **94**, 238101 (2005).
 - [22] S. Klumpp and R. Lipowsky, *Proc. Natl. Acad. Sci. U.S.A.* **102**, 17284 (2005).
 - [23] M. J. I. Müller, S. Klumpp, and R. Lipowsky, *Proc. Natl. Acad. Sci. U.S.A.* **105**, 4609 (2008).
 - [24] M. J. I. Müller, S. Klumpp, and R. Lipowsky, *J. Stat. Phys.* **133**, 1059 (2008).
 - [25] Y. Zhang, *Phys. Rev. E* **79**, 061918 (2009).
 - [26] In independent work, cited in [24], M. J. I. Müller, has also explored the large (N_+ , N_-) or mean-field limit: see M. J. I. Müller, Ph.D. thesis, University of Potsdam, 2008; <http://opus.kobv.de/ubp/volltexte/2008/1871/>. To the degree that her results overlap those reported in [25], they are fully consistent; but they do not extend to the further results reported here.
 - [27] X. Nan, P. A. Sims, P. Cheng, and X. S. Xie, *J. Phys. Chem. B* **109**, 24220 (2005).
 - [28] V. Levi, A. S. Serpinskaya, E. Gratton, and V. Gelfand, *Biophys. J.* **90**, 318 (2006).
 - [29] V. Soppina, A. K. Rai, A. J. Ramaiya, P. Barak, and R. Mallik, *Proc. Natl. Acad. Sci. U.S.A.* **106**, 19381 (2009).
 - [30] A. Gennerich and D. Schild, *Phys. Biol.* **3**, 45 (2006).
 - [31] A. R. Rogers, J. W. Driver, and M. R. Diehl, *Phys. Chem. Chem. Phys.* **11**, 4882 (2009).
 - [32] R. Mallik, B. C. Carter, S. A. Lex, S. J. King, and S. P. Gross, *Nature (London)* **427**, 649 (2004).
 - [33] S. Toba, T. M. Watanabe, L. Yamaguchi-Okimoto, Y. Y. Toyoshima, and H. Higuchi, *Proc. Natl. Acad. Sci. U.S.A.* **103**, 5741 (2006).
 - [34] A. Gennerich, A. P. Carter, S. L. Reck-Peterson, and R. D. Vale, *Cell* **131**, 952 (2007).
 - [35] I. H. Riedel-Kruse, A. Hilfinger, J. Howard, and F. Jülicher, *HFSP J.* **1**, 192 (2007).
 - [36] A. Hilfinger, A. K. Chattopadhyay, and F. Jülicher, *Phys. Rev. E* **79**, 051918 (2009).
 - [37] S. W. Grill, K. Kruse, and F. Jülicher, *Phys. Rev. Lett.* **94**, 108104 (2005).
 - [38] J. Pecreaux, J.-C. Röper, K. Kruse, F. Jülicher, A. A. Hyman, S. W. Grill, and J. Howard, *Curr. Biol.* **16**, 2111 (2006).
 - [39] The linear form Eq. (2a) was introduced independently by Grill *et al.* [37] in their treatment of mitotic spindle oscillations; however, the attachment and detachment rates of the force generating motors there, were related to an elastic linker length rather than directly to the load acting.
 - [40] In their initial study, S. Klumpp and R. Lipowsky [22] used the linear force-velocity relation $V(F_{\text{ext}}) = V_F[1 - (F_{\text{ext}}/F_S)]$ for $0 \leq F_{\text{ext}} \leq F_S$ as in Eq. (2a) but, in place of Eq. (2b) took $V(F_{\text{ext}}) = 0$ for $F_{\text{ext}} > F_S$. For assisting loads, i.e., when $F_{\text{ext}} < 0$, they employed Eq. (2c).
 - [41] D. Tsygankov and M. E. Fisher, *Proc. Natl. Acad. Sci. U.S.A.* **104**, 19321 (2007); *J. Chem. Phys.* **128**, 015102 (2008).
 - [42] A. Kunwar and A. Mogilner, *Phys. Biol.* **7**, 016012 (2010).
 - [43] J. Guckenheimer and P. Holmes, *Nonlinear Oscillations, Dynamical System, and Bifurcations of Vector Fields* (Springer-

Verlag, New York, 1983).

- [44] In recent work by Müller *et al.* [45] (which the authors kindly communicated to us prior to publication) this principal conclusion regarding the exponential dependence of the probability fluxes or transition times is also found. However, as we explain further below, their calculational approach differs significantly from ours and is, we believe, of more limited applicability.
- [45] M. J. I. Müller, S. Klumpp, and R. Lipowsky, *Biophys. J.* **98**, 2610 (2010).
- [46] We comment now that rather than identifying the underlying basins of attraction separating the distinct modes of motion, as we have done, Müller *et al.* [45] consider only the overall switch times between uniform plus-end directed motion and the reverse. To that end, they calculate the probability flux across what we have, in Sec. II, termed the **AB** boundary in the (y, z) or (n_+, n_-) flow plane: see again Figs. 1, 3, 5, and 6, here the strict linearity of this boundary, defined by Eq. (18), is evident. In some cases the difference between this **AB** boundary and what we believe is a more appropriate boundary specification, may not be very significant numerically. But in other cases, such as seen in Figs. 3 and 6, where there are, indeed, only two stable states, the differences are much greater. While in Fig. 5, where there are *three* states stable in the mean field limit, it seems evident *a priori* that the **AB** boundary represents a less than optimal choice for of a locus across which to compute relevant fluxes.
- [47] The formulation used here is also employed in [45] but the fits reported in Table V provide a concrete numerical picture.
- [48] Another possible definition, favored in some experimental studies (see, e.g., [16,49–51]), follows the motion of the cargo in a fixed harmonic trap and records what might be termed a “stalling distribution,” in which a mean velocity of zero is considered to be observed but under fluctuations in position and, hence, in the force actually imposed by the trap. While this is an experimentally convenient procedure in that it avoids the use of a “force clamp,” which, with suitable feedback, imposes a steady load force, it seems somewhat less definitive for characterizing the intrinsic system behavior. In particular, an element of judgment is involved in deciding that, in a specific run, a further forward step and, hence “stalling” under a *greater mean load* will not eventually be realized as the mean velocity smoothly decreases with load. Conversely, by unequivocally identifying mean *backwards* motion, as in the experiments of Carter and Cross [17] on kinesin, the value of the stall force (including a clear upper bound) is more convincingly established.
- [49] A. Kunwar, M. Vershinin, J. Xu, and S. P. Gross, *Curr. Biol.* **18**, 1173 (2008).
- [50] A. Yildiz, M. Tomishige, A. Gennerich, and R. D. Vale, *Cell* **134**, 1030 (2008).
- [51] C. Cho, S. L. Reck-Peterson, and R. D. Vale, *J. Biol. Chem.* **283**, 25839 (2008).
- [52] More recently Lipowsky *et al.* [53] have extended their calculations utilizing Eq. (2b) for superstall loads. They note that the cargo stall force, $F_C(N)$, for a single motor species is substantially smaller than $NF_C(1)=NF_S$, the sum of the individual stall force, but do not report the significant sublinear variation we find: see Fig. 14.
- [53] R. Lipowsky, J. Beeg, R. Dimova, S. Klumpp, and M. J. I. Müller, *Physica E (Amsterdam)* **42**, 649 (2010), this article also contains a review from the authors’ perspective of the tug-of-war model.
- [54] See supplementary material at <http://link.aps.org/supplemental/10.1103/PhysRevE.82.011923> for describing analysis of stall forces in the tug-of-war models.