Properties of tug-of-war model for cargo transport by molecular motors

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Molecular motors are essential components for the biophysical functions of the cell. Current quantitative understanding of how multiple motors move along a single track is not complete, even though models and theories for a single motor mechanochemistry abound. Recently, Müller *et al.* have developed a tug-of-war model to describe the bidirectional movement of the cargo [Proc. Natl. Acad. Sci. U.S.A. **105**, 4609 (2008)]. They found that the tug-of-war model exhibits several qualitative different motility regimes, which depend on the precise value of single motor parameters, and they suggested that the sensitivity can be used by a cell to regulate its cargo traffic. In the present paper, we will carry out a detailed theoretical analysis of a special case of tug-of-war model: in which the numbers of the two different motor species which bound to the cargo tend to infinite. Through the analysis, all the stable, i.e., biophysically observable, steady states and their stability domains can be obtained. Depending on values of the several parameters, the tug-of-war model exhibits uni-, bi-, or tristability. The steady-state movement of the cargo, which is transported by two different molecular motor species, is determined by the initial numbers of the motors which bound to the track.

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I. INTRODUCTION

Molecular motors, including biological motor proteins such as kinesin [1–4], dynein [5,6], mysion [7–9] and F_0F_1-adenosine triphosphate (ATP) synthase [10], are mechanochemical force generators which convert chemical or biochemical energy in the form of chemical potential into mechanical work in thermal environment [11]. Many biological motor proteins can move processively. For example, myosin slides along an actin filament, kinesin and dynein along microtubule (MT). All of them are ATP-driven "directional walking machines" [12,13]: kinesin moves toward the plus end of the MT and dynein toward the minus end. In comparison with the macroscopic engines driven by Carnot cycles, molecular motors have a high energy efficiency at about 50%, while the energy efficiency of a car is about 15%–20% [5,14,15]. Furthermore, the velocities of molecular motors are also fast with mean velocity be at about several hundreds nanometers per second [16]. However, the most significant difference between the molecular motors and the macroscopic engines is that the former are moving in a thermal noise dominated environment [17]. So the movement of the molecular motors should be described stochastically rather than determinately. Being able to convert and harvest energy with high efficiency on a mesoscopic scale makes molecular motors an exciting area of scientific research with potentially great innovative applications for energy production.

Great progress has been made in recent years in modeling the movement of molecular motors including the mean-field methods [11,18,19], the Langevin stochastic dynamic methods [20,21], and discrete stochastic methods [22–26]. However, the existing models for a single molecular motor are not sufficient in predicting the recent experimental results: it is found that bidirectional motion of the cargo, which is carried by motor proteins, exhibits different patterns in different stages of embryonic development [27]. Following these recent experimental results [28–30], Lipowsky and his coworkers [31–35] have developed the tug-of-war model for describing the movement of the cargo carried by processive motors such as kinesin and dynein. In their model, the experimentally known single motor properties are taken into account, so it is consistent with almost all experimental observations and can make quantitative predictions for bidirectional transport of the cargo. Since cargo movement carried by a single motor protein via an elastic tether has been extensively studied in the past [36,37], the focus of tug-of-war model is not on the detailed movement of cargo carried by a single motor per se, rather, it concerns with the competition and cooperation of multiple motors on a single track (see the schematic depiction in Fig. 1).

One of the interesting cases of tug-of-war model is that: in which the cargo is attached by a great deal of molecular

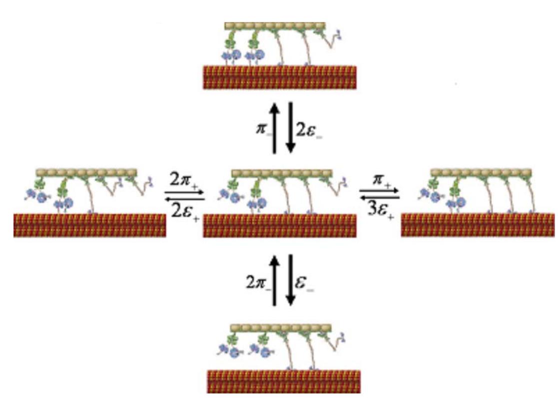

FIG. 1. (Color online) Schematic depiction of tug-of-war model: a cargo with $N_+=3$ plus motors (kinesin) and $N_-=2$ motors (dynein) is pulled by a fluctuating number of motors bound to the microtubule.

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TABLE I. Single-motor parameters for kinesin 1 and cytoplasmic dynein ([31] and references therein).

Parameter	Symbol	Kinesin 1	Dynein
Stall force	F_s	6 pN	1.1 pN
Detachment force	F_d	3 pN	0.75 pN
Unbinding rate	ϵ_0	1 s^{-1}	0.27 s^{-1}
Binding rate	π_0	5 s^{-1}	1.6 s^{-1}
Forward velocity	v_F	1 μm/s	0.65 μm/s
Superstall velocity amplitude	v_B	6 nm/s	72 nm/s

motors, i.e., the number $N_+(N_-)$ of plus (minus) motors, which bound to the cargo, tends to infinite. Detailed analysis of this special case is helpful to understand the properties of tug-of-war model and consequently the principle of cargo movement transported by different molecular motor species. In the present paper, we will give a mathematical analysis of this special case. Through detailed analysis, we find that the steady-state movement of cargo is determined by the initial numbers of the two motor species which bound to the track of movement. Biophysically, the steady state is the only state that can be observed experimentally and Monte Carlo simulations indicate the transition time from the initial state to the steady state is very short (see Figs. 7 and 8). Through the discussion in this paper, we can find that the movement of the cargo has at most three stable steady states, which is determined by the single motor parameters and external force. If there exists two or three stable steady states, then many parameters of plus and minus motors have at least one critical point. The movement of cargo would change from one stable steady state to another if one of the parameters jumps from one side of its critical point to another side. Certainly, for small motor numbers N_+ and N_- cases, there are some differences because it is more easy for the cargo movement to stochastically jump from one steady state to another (see Fig. 8). In the following, we first introduce the tug-of-war model and then give detailed discussion gradually.

II. TUG-OF-WAR MODEL

The tug-of-war model is first developed by Lipowsky's study group [31–35] to study the bidirectional transport of the cargo, in which the cargo is attached with N_+ plus and N_- minus motors. Particularly, if $N_+=0$ or $N_-=0$, it recovers the usual model for cooperate transport by a single motor species [33,38]. In this model, each motor species is characterized by six parameters, which can be measured in single molecular experiments (see Table I): (i) stall force F_s (pN), (ii) detachment force F_d (pN), (iii) unbinding rate ϵ_0 (s^{-1}), (iv) binding rate π_0 (s^{-1}), (v) forward velocity v_F (μm/s), and (vi) superstall velocity amplitude v_B (nm/s). The motors bind to or unbind from a MT in a stochastic fashion, so that the cargo is pulled by $n_+\le N_+$ plus and $n_-\le N_-$ minus motors, where n_+ and n_- fluctuate with time (see Fig. 1).

In the tug-of-war model, it is assumed that, at every time t, the state of cargo with N_+ plus and N_- minus motors firmly attached to it is fully characterized by numbers n_+ and n_- of plus and minus motors that are bound to the MT. The state of cargo changes when a plus or a minus motor binds or unbinds to/from the MT (see Fig. 1). The probability $p(n_+,n_-,t)$ to have n_+ plus and n_- minus motors that are bound to MT at time t can be described by the following master equation:

$$\begin{aligned}\frac{dp(n_+,n_-,t)}{dt} &= [N_+-(n_+-1)]\pi_+ p(n_+-1,n_-,t)\\ &\quad + (n_++1)\epsilon_+(n_++1,n_-)p(n_++1,n_-,t)\\ &\quad + [N_--(n_--1)]\pi_- p(n_+,n_--1,t)\\ &\quad + (n_-+1)\epsilon_+(n_+,n_-+1)p(n_+,n_-+1,t)\\ &\quad - [(N_+-n_+)\pi_+ + n_+\epsilon_+(n_+,n_-) + (N_--n_-)\pi_-\\ &\quad + n_-\epsilon_-(n_+,n_-)]p(n_+,n_-,t), \quad 1\le n_+\le N_+\\ &\quad -1 \text{ and } 1\le n_-\le N_--1, \end{aligned} \tag{1}$$

where $\pi_+(\pi_-)$ is the binding rate of a single plus (minus) motor to the MT, which depends only weakly on the load [33] and therefore is taken equal to zero-load binding rate $\pi_{0+}(\pi_{0-})$. $\epsilon_+(\epsilon_-)$ is the unbinding rate of a single plus (minus) motor from the MT, which increases exponentially with the applied force F:

$$\epsilon_\pm(F) = \epsilon_{0\pm}\exp(|F|/F_{d\pm}) \tag{2}$$

as measured for kinesin [16], where F_d is the detachment force. The governing equations for $n_+=0,N_+$ or $n_-=0,N_-$ are similar to Eq. (1) except $\pi_+(N_+,n_-)=\pi_-(n_+,N_-)=0$ and $\epsilon_+(0,n_-)=\epsilon_-(n_+,0)=0$.

Under the assumptions that the motors act independently and feel each other only due to two effects, (i) opposing motors act as load and (ii) identical motors share this load, Lipowsky and co-workers gave the following relation (see [34]):

$$n_+F_+ = -n_-F_- \equiv F_c \tag{3}$$

where $F_+(-F_-)$ is the load felt by each plus (minus) motor. Equations (2) and (3) imply

$$\epsilon_\pm(n_+,n_-) = \epsilon_{0\pm}\exp[|F_c|/n_\pm F_{d\pm}]. \tag{4}$$

Here, the cargo force F_c is determined by the condition that plus motors, which experience the force F_c/n_+, and minus motors, which experience the force $-F_c/n_-$, move with the same velocity v_c, which is the cargo velocity:

$$v_c(n_+,n_-) = v_+(F_c/n_+) = -v_-(-F_c/n_+). \tag{5}$$

The same as in [31], the following piecewise linear force-velocity relation of a single motor is used in this paper:

$$v(F) = \begin{cases} v_F(1-F/F_s) & \text{for } F\le F_s\\ v_B(1-F/F_s) & \text{for } F\ge F_s, \end{cases} \tag{6}$$

where v_B is the absolute value of the superstall velocity amplitude, v_F is the zero-load forward velocity, and F_s is the stall force.

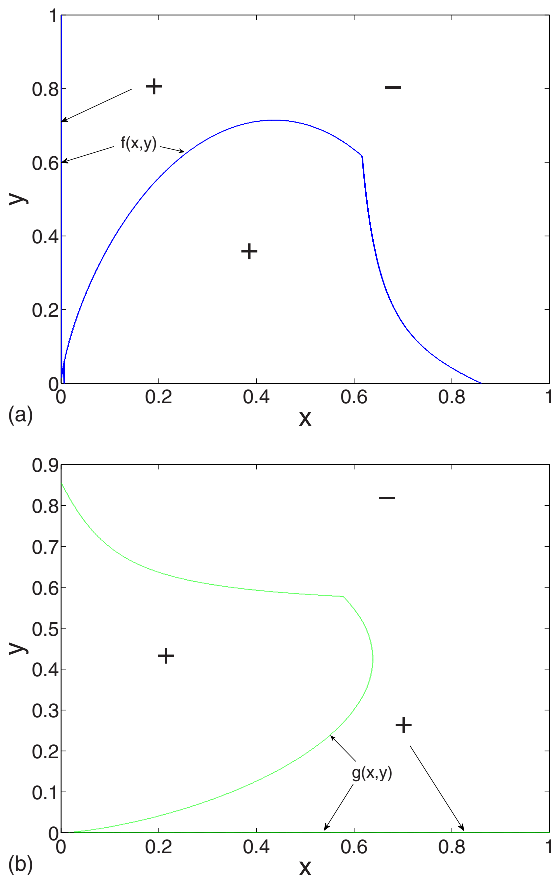

FIG. 2. (Color online) The figures of functions $f(x,y)=0, g(x,y)=0$. The "+" ("−") means the function f (or g) is positive (negative) in the corresponding subdomains. The parameters used in the figures are $F_{s+}=1.1, F_{d+}=0.82, \epsilon_{0+}=0.26, \pi_+=1.6, V_{F+}=550, V_{B+}=67, F_{s-}=1.1, F_{d-}=0.75, \epsilon_{0-}=0.27, \pi_-=1.6, V_{F-}=650, V_{B-}=72, F_{ext}=0$.

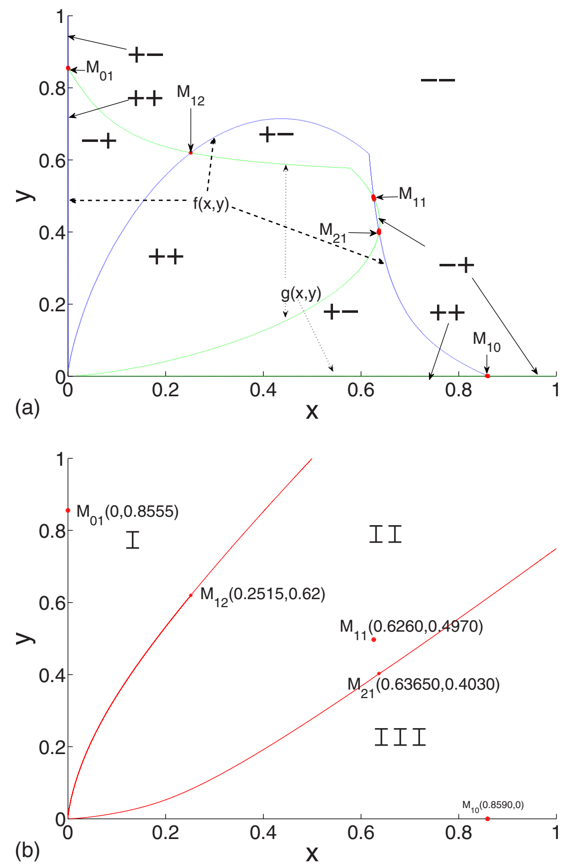

FIG. 3. (Color online) The steady states of system (22), where the unstable steady states (M_{12} and M_{21}) are denoted by "*" and the stable steady states are denoted by "⊛." If the initial state $P_0(x_0,y_0)$ lies in the subdomain I (II or III), then the final state is the stable steady state M_{01} (M_{11} or M_{10}). The parameters used in the figures are the same as in Fig. 2.

III. VELOCITY OF CARGO AND UNBINDING RATES OF MOTORS

For the convenience of the following analysis, we give the formulations of cargo velocity and unbinding rates of plus and minus motors in this section.

(i) In case of "stronger plus motors," i.e., $n_+F_{s+}>n_-F_{s-}$, Eqs. (5) and (6) lead to the cargo force and velocity:

$$F_c(n_+,n_-) = \frac{v_{F+}+v_{B-}}{v_{F+}/n_+F_{s+}+v_{B-}/n_-F_{s-}},$$

$$v_c(n_+,n_-) = \frac{n_+F_{s+}-n_-F_{s-}}{n_+F_{s+}/v_{F+}+n_-F_{s-}/v_{B-}}. \tag{7}$$

Using Eqs. (4) and (7), the unbinding rates of plus and minus motors are

$$\epsilon_\pm(n_+,n_-) = \epsilon_{0\pm}\exp\left(\frac{n_\mp F_{s+}F_{s-}(v_{F+}+v_{B-})}{(n_+F_{s+}v_{B-}+n_-F_{s-}v_{F+})F_{d\pm}}\right)$$
$$=: \epsilon_{0\pm}\exp\left(\frac{n_\mp}{(an_++bn_-)F_{d\pm}}\right), \tag{8}$$

where

$$a=\frac{v_{B-}}{F_{s-}(v_{F+}+v_{B-})},\quad b=\frac{v_{F+}}{F_{s+}(v_{F+}+v_{B-})}. \tag{9}$$

Let $x=n_+/N_+$, $y=n_-/N_-$, and $c=N_+/N_-$, then

$$\epsilon_+(x,y) = \epsilon_{0+}\exp\left(\frac{y}{(acx+by)F_{d+}}\right),$$

$$\epsilon_-(x,y) = \epsilon_{0-}\exp\left(\frac{cx}{(acx+by)F_{d-}}\right). \tag{10}$$

(ii) In case of "stronger minus motors," i.e., $n_+F_{s+}<n_-F_{s-}$, the cargo force and velocity are

$$F_c(n_+,n_-) = -\frac{v_{B+}+v_{F-}}{v_{B+}/n_+F_{s+}+v_{F-}/n_-F_{s-}},$$

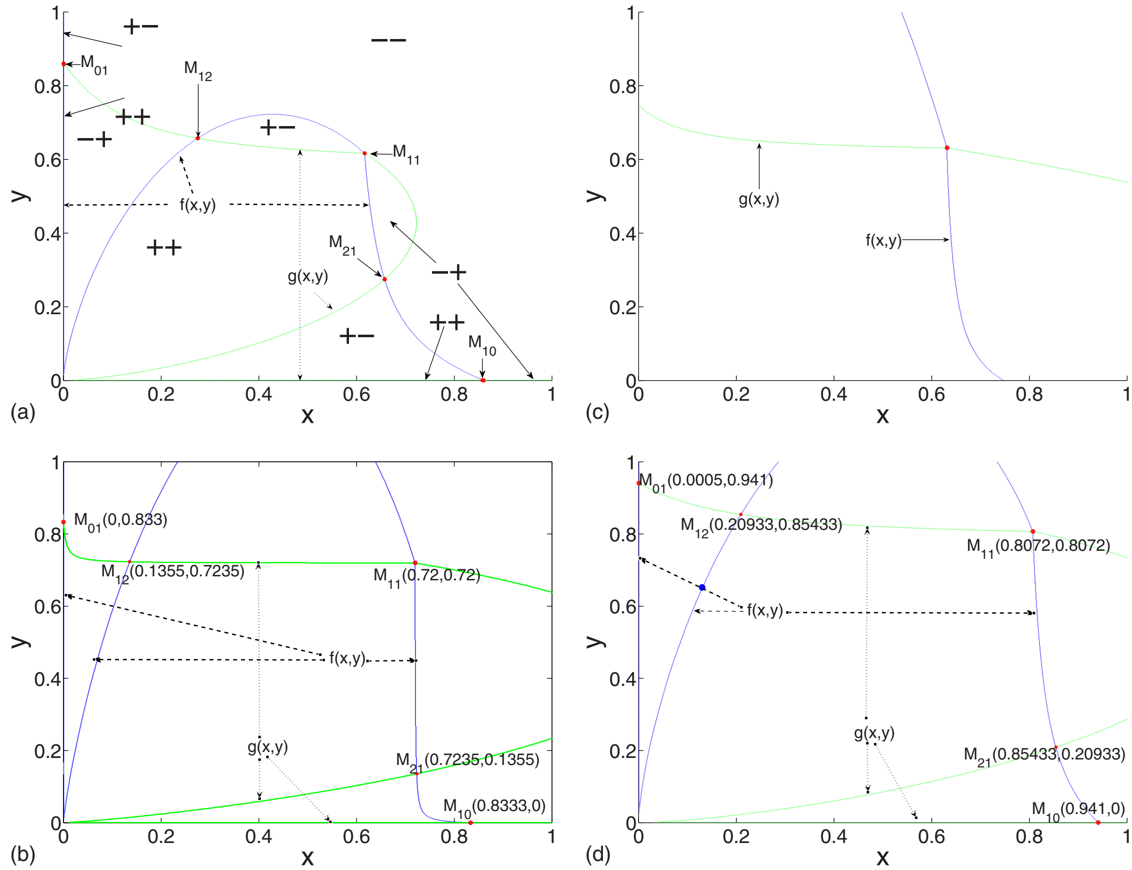

FIG. 4. (Color online) Figures of $f(x,y)=0, g(x,y)=0$ for symmetric tug-of-war model, in which plus and minus motors have the same parameters. The unstable steady states are denoted by "*" and the stable steady states are denoted by "⊛." The parameters used in this figures are $F_s=1.1, F_d=0.82, \epsilon_0=0.26, \pi=1.6, V_F=550, V_B=67, F_{ext}=0$ (a); $F_s=2, F_d=3, \epsilon_0=1, \pi=5, V_F=1000, V_B=6, F_{ext}=0$ (b); $F_s=0.45, F_d=0.82, \epsilon_0=0.54, \pi=1.6, V_F=550, V_B=67, F_{ext}=0$ (c); $F_s=1.1, F_d=0.82, \epsilon_0=0.1, \pi=1.6, V_F=550, V_B=67, F_{ext}=0$ (d).

$$\begin{aligned} v_c(n_+,n_-) &= -\frac{n_-F_{s-}-n_+F_{s+}}{n_+F_{s+}/v_{B+}+n_-F_{s-}/v_{F-}} \\ &= -\frac{yF_{s-}-xcF_{s+}}{xcF_{s+}/v_{B+}+yF_{s-}/v_{F-}}. \end{aligned} \tag{11}$$

Similar as in (i), the unbinding rates of plus and minus motors are

$$\epsilon_+(x,y) = \epsilon_{0+}\exp\left(\frac{y}{(\bar{a}cx+\bar{b}y)F_{d+}}\right),$$

$$\epsilon_-(x,y) = \epsilon_{0-}\exp\left(\frac{cx}{(\bar{a}cx+\bar{b}y)F_{d-}}\right), \tag{12}$$

in which

$$\bar{a} = \frac{v_{F-}}{F_{s-}(v_{B+}+v_{F-})}, \quad \bar{b} = \frac{v_{B+}}{F_{s+}(v_{B+}+v_{F-})}. \tag{13}$$

The splitting boundary of case (i) and case (ii) is $n_+F_{s+} = n_-F_{s-}$, i.e., $y=xcF_{s+}/F_{s-}$. (iii) If an external force F_{ext} is present (F_{ext} is taken to be positive if it points into the minus direction), then force balance (3) becomes

$$n_+F_+ = -n_-F_- + F_{ext}.$$

If $n_+F_{s+}-F_{ext}>n_-F_{s-}$, by similar calculation as in the case without external force leads to the following formulation of cargo velocity:

$$v_c(n_+,n_-) = \frac{n_+F_{s+}-n_-F_{s-}-F_{ext}}{n_+F_{s+}/v_{F+}+n_-F_{s-}/v_{B-}}. \tag{14}$$

The corresponding unbinding rates of plus and minus motors are

$$\epsilon_+(x,y) = \epsilon_{0+}\exp\left(\frac{y+aF_{ext}/N_-}{(acx+by)F_{d+}}\right),$$

$$\epsilon_-(x,y) = \epsilon_{0-}\exp\left(\frac{cx-bF_{ext}/N_-}{(acx+by)F_{d-}}\right). \tag{15}$$

(iv) If an external force F_{ext} is present and $n_+F_{s+}-F_{ext} < n_-F_{s-}$, then the formulation of cargo velocity is

$$v_c(n_+,n_-) = \frac{n_+F_{s+}-n_-F_{s-}-F_{ext}}{n_+F_{s+}/v_{B+}+n_-F_{s-}/v_{F-}} \tag{16}$$

and the unbinding rates of plus and minus motors are

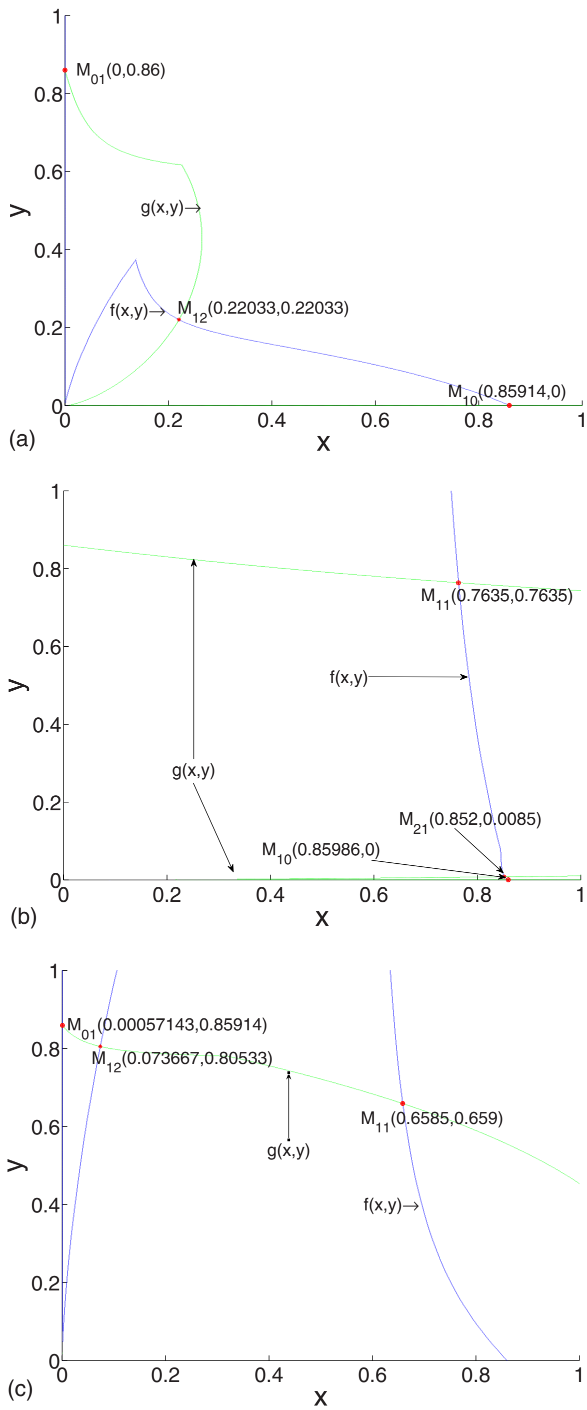

FIG. 5. (Color online) Asymmetric tug-of-war model: system (22) might have one, two, or three stable steady states. The parameters used in the figures are $F_{s+}=3, F_{d+}=0.82$, $\epsilon_{0+}=0.26$, $\pi_+=1.6$, $V_{F+}=550$, $V_{B+}=67, F_{s-}=1.1, F_{d-}=0.82, \epsilon_{0-}=0.26, \pi_-=1.6, V_{F-}=550$, $V_{B-}=67, F_{ext}=0$ (a); $F_{s+}=0.1, F_{d+}=0.82, \epsilon_{0+}=0.26, \pi_+=1.6, V_{F+}=550$, $V_{B+}=67, F_{s-}=1.1, F_{d-}=0.82, \epsilon_{0-}=0.26, \pi_-=1.6, V_{F-}=550, V_{B-}=67, F_{ext}=0$ (b); $F_{s+}=1.1, F_{d+}=0.82, \epsilon_{0+}=0.26, \pi_+=1.6, V_{F+}=550$, $V_{B+}=67$, $F_{s-}=0.45$, $F_{d-}=0.82$, $\epsilon_{0-}=0.26, \pi_-=1.6, V_{F-}=550$, $V_{B-}=67, F_{ext}=0$ (c).

$$\epsilon_+(x,y) = \epsilon_{0+} \exp\left(\frac{y + \bar{a}F_{ext}/N_-}{(\bar{a}cx + \bar{b}y)F_{d+}}\right),$$

$$\epsilon_-(x,y) = \epsilon_{0-} \exp\left(\frac{cx - \bar{b}F_{ext}/N_-}{(\bar{a}cx + \bar{b}y)F_{d-}}\right). \tag{17}$$

It can be easily verified that the splitting boundary of case (iii) and case (iv) is $n_+F_{s+}=n_-F_{s-}+F_{ext}$, i.e., $y=xcF_{s+}/F_{s-}-F_{ext}/N_-F_{s-}$.

More generally, if there exists an external force F_{ext} and nonzero friction coefficient γ, the formulations of cargo velocity and unbinding rates also can be obtained by the similar methods as in (iii) and (iv).

IV. DYNAMICS OF MOTOR NUMBERS n_+ AND n_-

For the sake of convenience, let

$$\begin{cases} r_+ \equiv r_+(n_+,n_-) := (N_+ - n_+)\pi_+ \\ s_+ \equiv s_+(n_+,n_-) := n_+\epsilon_+(n_+,n_-) \\ r_- \equiv r_-(n_+,n_-) := (N_- - n_-)\pi_- \\ s_- \equiv s_-(n_+,n_-) := n_-\epsilon_-(n_+,n_-) \end{cases} \tag{18}$$

and $\lambda=r_++r_-+s_++s_-$. During time interval $(t,t+\Delta t)$, the increase in plus motor number is

$$n_+(t+\Delta t) - n_+(t) = \left(\frac{r_+}{\lambda} - \frac{s_+}{\lambda}\right)\int_0^{\Delta t} \lambda e^{-\lambda}dt = \frac{r_+ - s_+}{\lambda}(1 - e^{-\lambda\Delta t}) \tag{19}$$

In the limit $\Delta t \to 0$, Eq. (19) leads to

$$\frac{dn_+}{dt} = r_+ - s_+ = (N_+ - n_+)\pi_+ - n_+\epsilon_+(n_+,n_-). \tag{20}$$

Similarly, the dynamics of minus motor number is

$$\frac{dn_-}{dt} = r_+ - s_+ = (N_- - n_-)\pi_- - n_-\epsilon_-(n_+,n_-). \tag{21}$$

So the variables $x=n_+/N_+, y=n_-/N_-$ satisfy

$$\begin{cases} \dfrac{dx}{dt} = \pi_+ - x[\pi_+ + \epsilon_+(x,y)] := f(x,y) \\ \dfrac{dy}{dt} = \pi_- - y[\pi_- + \epsilon_-(x,y)] := g(x,y). \end{cases} \tag{22}$$

It is well know that the steady-state solutions (x^*,y^*) of system (22), which satisfy $f(x^*,y^*)=0$ and $g(x^*,y^*)=0$, are stable if and only if the real parts of the two eigenvalues of the following matrix:

$$\begin{bmatrix} \dfrac{\partial f}{\partial x}(x^*,y^*) & \dfrac{\partial f}{\partial y}(x^*,y^*) \\ \dfrac{\partial g}{\partial x}(x^*,y^*) & \dfrac{\partial g}{\partial y}(x^*,y^*) \end{bmatrix} \tag{23}$$

are nonpositive, i.e.,

$$\frac{\partial f}{\partial x}(x^*,y^*) + \frac{\partial g}{\partial y}(x^*,y^*) \le 0,$$

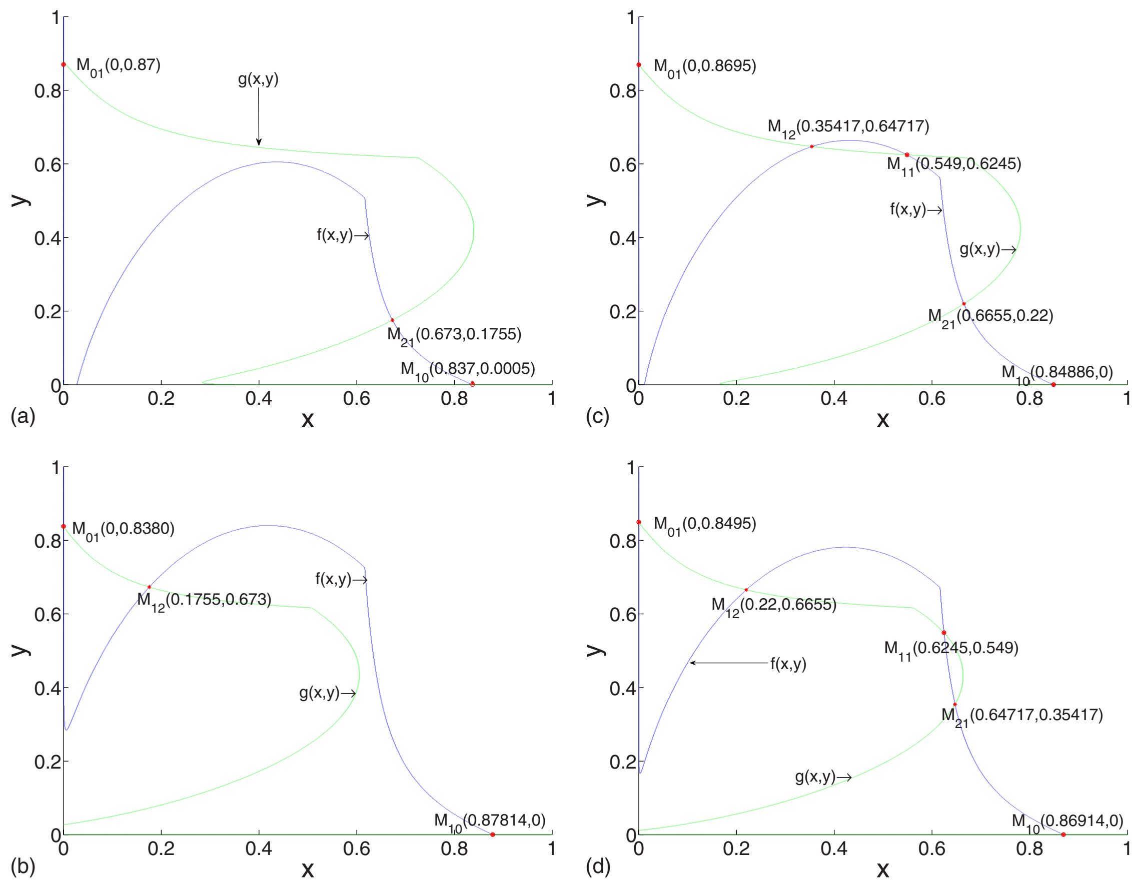

FIG. 6. (Color online) Tug-of-war model with external force F_{ext}: system (22) might have two or three stable steady states. The parameters used in the figures are $F_{s+}=F_{s-}=1.1, F_{d+}=F_{d-}=0.82, \epsilon_{0+}=\epsilon_{0-}=0.26, \pi_+=\pi_-=1.6, V_{F+}=V_{F-}=550, V_{B+}=V_{B-}=67$ and $F_{ext}=6$ (a), $F_{ext}=-6$ (c), $F_{ext}=3$ (b), $F_{ext}=-3$ (d).

$$\frac{\partial f}{\partial x}(x^*,y^*)\frac{\partial g}{\partial y}(x^*,y^*) - \frac{\partial f}{\partial y}(x^*,y^*)\frac{\partial g}{\partial x}(x^*,y^*) \geq 0. \qquad (24)$$

To better understand the properties of functions $f(x,y)=0$ and $g(x,y)=0$, their figures are plotted in Fig. 2.

Due to the stable conditions (24), given initial values $x_0 = n_+/N_+$ and $y_0=n_-/N_-$, if the point $P_0(x_0,y_0)$ lies in the subdomain I (II or III), then the final state would be stable steady state M_{01} (M_{11} or M_{10}) (see Fig. 3). Theoretically, $y_{M_{10}}\neq 0$ and $x_{M_{01}}\neq 0$, but they are smaller than the accuracy of the numerical calculation used in this paper, so we simply regard them as 0.

To further understand properties of the stable steady-state points, the figures of $f(x,y)=0$ and $g(x,y)=0$ with different values of parameters F_{s+},F_{s-}, F_{d+},F_{d-}, v_{B+}, v_{B-}, v_{F+}, v_{F-}, π_+,π_-, $\epsilon_{0+},\epsilon_{0-}$, and $c=N_+/N_-$ are plotted in Figs. 4–6.

From the figures, one can find that system (22) might have one, two, or three stable steady states, which depends on the values of different parameters. Given initial value (x_0,y_0), the final steady state can be determined using the similar method as in Fig. 3(b). One can be easily know that, almost all of the parameters used in the tug-of-war model have one or two critical points, the final stable steady state would change if one of the parameters jumps from one side of its critical points to another side. For $N_+=0$ or $N_-=0$ (i.e., $c=0$ or $c=\infty$), the tug-of-war model is reduced to the usual model for cooperate transport by a single motor species (minus or plus). In these cases, the only stable steady state is $\pi_+/(\pi_++\epsilon_{0+})$ for plus motor species or $\pi_-/(\pi_-+\epsilon_{0-})$ for minus motor species. The average velocity of the cargo at steady state is $v_c=v_c(x^*,0)=v_{F+}$ if $c=\infty$, and $v_c=v_c(0,y^*) =-v_{B-}$ if $c=0$, which are the velocities of a single motor.

V. COMPARISON WITH MONTE CARLO SIMULATIONS

From the above discussion, we can know that, in large motor numbers limit $N_+,N_-\to\infty$, the movement of cargo might have one, two, or three stable steady states. The final steady state is determined by the initial numbers $n_+(0) =N_+x_0$ and $n_-(0)=N_-y_0$ of the motors which bind to MT (see Fig. 7). For example, in the case of Fig. 3(b), if $[n_+(0)/N_+,n_-(0)/N_-]$ lies in subdomains (II), the final steady state would be $n_+^s\approx N_+x_{M_{11}},n_-^s\approx N_-y_{M_{11}}$.

However, if the numbers N_+,N_- of molecular motors, which firmly attached to the cargo, are finite or even small, the steady-state numbers n_+^s and n_-^s might deviate from the theoretical values N_+x^* and N_-y^*. Theoretically, if $M_i(x_i,y_i)(i=1,\ 2,\ \text{or}\ 3)$ are the stable steady points of system (22), which can be regarded as the large motor numbers

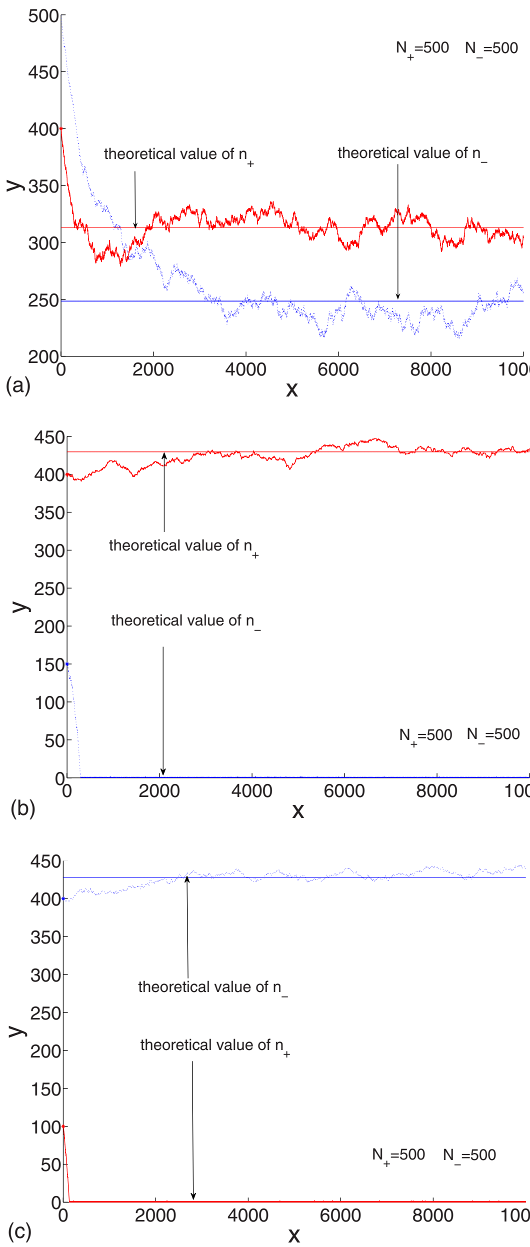

FIG. 7. (Color online) For large motor numbers N_+ and N_- cases, the final steady state of cargo movement can be determined by the theoretical results $n_+^s \approx N_+ x^s, n_-^s \approx N_- y^s$. (a) $[n_+(0)/N_+, n_-(0)/N_-]$ lies in subdomain (II); (b) $[n_+(0)/N_+, n_-(0)/N_-]$ lie in subdomain (III); (c) $[n_+(0)/N_+, n_-(0)/N_-]$ lie in subdomain (I). The parameters used in the figures are $F_{s+}=1.1, F_{d+}=0.82, \epsilon_{0+}=0.26$, $\pi_+=1.6$, $V_{F+}=550$, $V_{B+}=67$, $F_{s-}=1.1$, $F_{d-}=0.75$, $\epsilon_{0-}=0.27$, $\pi_-=1.6$, $V_{F-}=650$, $V_{B-}=72, F_{ext}=0$. The initial values of n_+ and n_- are denoted by "*."

limit of Eqs. (20) and (21), then steady-state numbers n_+^s and n_-^s would lie in the neighborhoods of the theoretical values $N_+ x_i$ and $N_- y_i$. But, in small N_+, N_- cases, the steady-state motor numbers n_+^s and n_-^s can jump easily from the neighborhood of one of the theoretical stable steady-state point $(N_+ x_i, N_- y_i)$ to the neighborhood of another theoretical stable steady-state point $(N_+ x_j, N_- y_j)$ (see Fig. 8). For finite motor numbers N_+, N_-, the step size of system (22) are $\Delta x = 1/N_+$, $\Delta y = 1/N_-$. So the smaller of motor numbers N_+, N_-, the

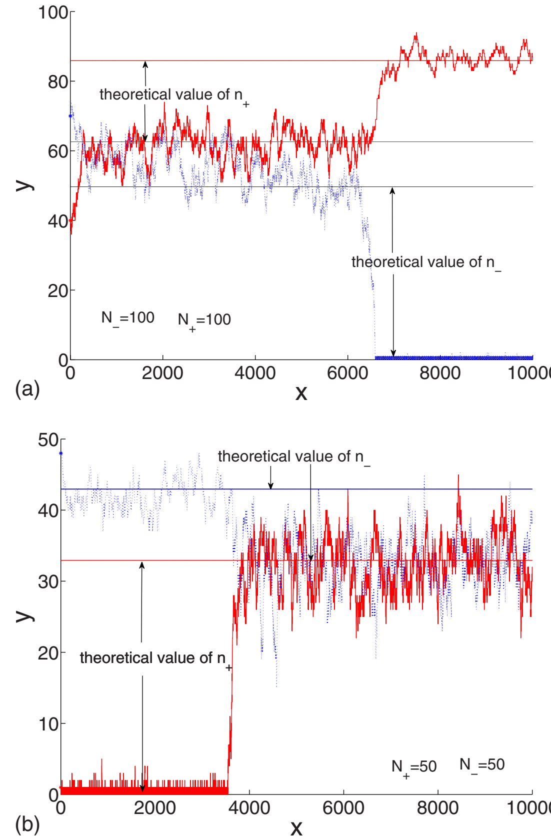

FIG. 8. (Color online) For small motor numbers N_+, N_-, the final motor numbers n_+, n_- can jump from the neighborhood of one stable steady state to another. (a) the final motor numbers n_+, n_- jump from $N_+ x_{M_{11}}$, $N_- y_{M_{11}}$ to $N_+ x_{M_{10}}$, $N_- y_{M_{10}}$; (b) the final motor numbers n_+, n_- jump from $N_+ x_{M_{01}}$, $N_- y_{M_{01}}$ to $N_+ x_{M_{11}}$, $N_- y_{M_{11}}$. The parameters used in (a) are $F_{s+}=1.1$, $F_{d+}=0.82, \epsilon_{0+}=0.26$, $\pi_+=1.6$, $V_{F+}=550$, $V_{B+}=67$, $F_{s-}=1.1$, $F_{d-}=0.75$, $\epsilon_{0-}=0.27, \pi_-=1.6, V_{F-}=650, V_{B-}=72, F_{ext}=0, N_+=N_-=100$. The parameters used in (b) are $F_{s+}=1.1, F_{d+}=0.82, \epsilon_{0+}=0.26, \pi_+=1.6, V_{F+}=550, V_{B+}=67$, $F_{s-}=0.45$, $F_{d-}=0.82, \epsilon_{0-}=0.26, \pi_-=1.6, V_{F-}=650, V_{B-}=72, F_{ext}=0, N_+=N_-=50$. The initial values of n_+ and n_- are denoted by "*."

easier for motor numbers n_+, n_- to jump from one of the steady subdomains I, II, or III to another. Intuitively, the probability that $(n_+/N_+, n_-/N_-)$ lies in the neighborhood of the stable steady-state point M_i is proportional to the area of M_i's steady subdomain. Mathematically, the probability of motor numbers n_+, n_- change from $n_+^{(1)}, n_-^{(1)}$ to $n_+^{(2)}, n_-^{(2)}$ along trajectory S is

$$p_S^{12} = \left[\prod_{(S_i, S_{i+1}) \in S_R} \frac{\pi_{i+}}{\pi_{i+} + \epsilon_{i+} + \pi_{i-} + \epsilon_{i-}} \right] \times \left[\prod_{(S_j, S_{j+1}) \in S_L} \frac{\epsilon_{j+}}{\pi_{j+} + \epsilon_{j+} + \pi_{j-} + \epsilon_{j-}} \right] \times \left[\prod_{(S_k, S_{k+1}) \in S_U} \frac{\pi_{k-}}{\pi_{k+} + \epsilon_{k+} + \pi_{k-} + \epsilon_{k-}} \right] \times \left[\prod_{(S_l, S_{l+1}) \in S_D} \frac{\epsilon_{l-}}{\pi_{l+} + \epsilon_{l+} + \pi_{l-} + \epsilon_{l-}} \right], \quad (25)$$

where $S_L \cup S_R \cup S_U \cup S_D = S$, $(P_1, P_2) \in S_R$ if and only if $n_+(P_2) = n_+(P_1) + 1, n_-(P_2) = n_-(P_1)$, $(P_1, P_2) \in S_L$ if and only if $n_+(P_2) = n_+(P_1) - 1, n_-(P_2) = n_-(P_1)$, $(P_1, P_2) \in S_U$ if and only if $n_+(P_2) = n_+(P_1), n_-(P_2) = n_-(P_1) + 1$, $(P_1, P_2) \in S_D$ if and only if $n_+(P_2) = n_+(P_1), n_-(P_2) = n_-(P_1) - 1$. So, theoretically, we can obtain the probability that motor numbers n_+, n_- change from the neighborhood of one stable steady state to the neighborhood of another stable steady state. From these transition probabilities, we can know more details about the steady-state movement of the cargo in the small N_+, N_- cases.

VI. CONCLUSION AND REMARKS

In this paper, the steady-state properties of the recent tug-of-war model, which is provided by Lipowsky *et al.* to model the movement of cargo, which is transported by two motor species in the cell, is discussed. Biophysically, the stable steady states are the most important states because the transition time to the stable steady state, as illustrated in this paper, is very short (see Figs. 7 and 8), so almost all of the data are measured in stable steady states. Through the discussion in this paper, we can know that the final steady state of the movement of the cargo is determined by initial numbers of the plus and minus motors which are bounded to the microtubule. Certainly, the velocity and direction of the movement are also determined by other several parameters, such as $N_\pm, F_{s\pm}, \pi_\pm, \epsilon_{0\pm}, F_{d\pm}, v_{F\pm}, v_{B\pm}, F_{ext}, \gamma$. One can also find that almost each of the parameters has critical points, which determine the stable steady velocity and direction of the cargo. It is most probable that many of the parameters, including the numbers N_+ and N_- of plus and minus motors which are tightly attached to the cargo, and the initial binding numbers $n_+(0)$ and $n_-(0)$, can be determined by the biochemical environment and properties of the cargos, so some of which can be transported from the plus end to the minus end, and others can be transported reversely.

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