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

Yunxin Zhang∗†‡

Abstract

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, M.J.I. Müller et al. have developed a tug-of-war model to describe the bidirectional movement of the cargo (PNAS(2008) 105(12) P4609-4614). 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 the sensitivity can be used by a cell to regulate its cargo traffic. In the present paper, we will carry out a further detailed theoretical analysis of the tug-of-war model. All the stable, i.e., biophysically observable, steady states and their stability domains can be obtained. Depending on values of the several parameters, tug-of-war model exhibits either uni-, bi- or tristability. In large motor number case, the steady state movement of the cargo, which is transported by two molecular motor species, is determined by the initial numbers of the motors which bound to the

∗School of Mathematical Sciences, Fudan University, Shanghai 200433, China
†Shanghai Key Laboratory for Contemporary Applied Mathematics, Fudan University
‡Centre for Computational Systems Biology, Fudan University (E-Mail: xyz@fudan.edu.cn)
track. For small motor number case, the movement of cargo may jump from one of the stable steady state to another.

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\section{Introduction}

Molecular motors, including biological motor proteins such as kinesin \cite{1,2,3,4}, dynein \cite{5,6}, myosin \cite{7,8,9} and $F_{0}F_{1}$-ATP synthase \cite{10}, are mechanochemical force generators which convert chemical or biochemical energy in the form of chemical potential into mechanical work in thermal environment \cite{11}. The mechanochemical process is accomplished by individual macromolecules, immersed in an aqueous solution with the chemical potential, moving along a linear track. Many biological motor proteins move processively. For example, myosin slides along an actin filament, kinesin and dynein along microtubule (MT). All of them are adenosine triphosphate (ATP)-driven “directional walking machines” \cite{12,13}: Kinesin moves towards the plus end of the MT and dynein towards 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\% \cite{5,14,15}. Furthermore, the velocities of molecular motors are also fast with mean velocity be at about several hundreds nanometers per second \cite{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 \cite{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 \[18, 19, 11\], the Langevin stochastic dynamic methods \[20, 21\] and discrete stochastic methods \[22, 23, 21, 25, 26\]. 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, 29, 30]), Lipowsky and his coworkers have developed the tug-of-war model for describing the movement of the cargo carried by processive motors, such as kinesin and dynein ([31, 32, 33, 34, 35]). 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).

In the present paper, we will give a further comprehensive mathematical analysis of tug-of-war model. 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. At the same time, Monte Carlo simulations indicate the transition time from the initial state to the steady state is very short (see Figs. 7, 8). Theoretically, the movement of the cargo has at most three stable steady states. 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. In the following, we firstly introduce the tug-of-war model, and then give the detailed discussion gradually.
Figure 1: 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.

2 The tug-of-war model

The tug-of-war model is developed by Reinhard Lipowsky’s study group ([31, 32, 33, 34, 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 Tab. 1): (i) stall force $F_S$ (pN) (ii) detachment force $F_d$ (pN) (iii) unbinding rate $\epsilon_0$ ($s^{-1}$) (iv) binding rate $\pi_0$ ($s^{-1}$) (v) forward velocity $v_F$ ($\mu$m/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 $n_+ \leq N_+$ plus and $n_- \leq N_-$ minus motors, where $n_+$ and $n_-$ fluctuate with time (see Fig. 1).

In tug-of-war model, it is assumed that, at every time $t$, the state of cargo with
| Parameter                              | Symbol | Kinesin 1 | Dynein   |
|---------------------------------------|--------|-----------|----------|
| Stall force                           | $F_s$  | 6pN       | 1.1pN    |
| Detachment force                      | $F_d$  | 3pN       | 0.75pN   |
| Unbinding rate                        | $\epsilon_0$ | $1s^{-1}$ | $0.27s^{-1}$ |
| Binding rate                          | $\pi_0$ | $5s^{-1}$ | $1.6s^{-1}$ |
| Forward velocity                      | $v_F$  | 1$\mu$m/s | 0.65$\mu$m/s |
| superstall velocity amplitude        | $v_B$  | 6nm/s     | 72nm/s   |

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

$N_+$ 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 bound motors at time $t$ can be described by the following Master equation:

$$\frac{dp(n_+, n_-, t)}{dt} = [N_+ - (n_+ - 1)]\pi_+ p(n_+ - 1, n_-, t)$$

$$+ (n_+ + 1)\epsilon_+(n_+ + 1, n_-)p(n_+ + 1, n_-, t)$$

$$+ [N_- - (n_- - 1)]\pi_- p(n_+, n_- - 1, t)$$

$$+ (n_- + 1)\epsilon_-(n_+, n_- + 1)p(n_+, n_- + 1, t)$$

$$- [(N_+ - n_+)\pi_+ + n_+\epsilon_+(n_+, n_-)]p(n_+, n_-, t)$$

$$- [(N_- - n_-)\pi_- + n_-\epsilon_-(n_+, n_-)]p(n_+, n_-, t)$$

$$1 \leq n_+ \leq N_+ - 1 \quad \text{and} \quad 1 \leq n_- \leq N_- - 1$$

(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 $F$:

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

as measured for kinesin [39], where $F_d$ is the detachment force. The governing equations for $n_+ = 0, N_+$ or $n_- = 0, N_-$ are similar as (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 coworkers gave the following relation (see [34])

$$
n_+ F_+ = -n_- F_- \equiv F_c \quad (3)
$$

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

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

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:

$$
v_c(n_+, n_-) = v_+(F_c/n_+) = -v_-(F_c/n_-) \quad (5)
$$

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

$$
v(F) = \begin{cases} 
v_F(1 - F/F_s) & \text{for } F \leq F_s \\
v_B(1 - F/F_s) & \text{for } F \geq F_s \end{cases} \quad (6)
$$

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

3 The velocity of cargo and unbinding rates of motors

For the convenience of analysis in the following sections, we give the formulations of velocity of cargo 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) (6) lead to the cargo force and velocity:

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

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

(7)

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

$$\epsilon_{\pm}(n_+, n_-) = \epsilon_{0\pm} \exp \left( \frac{n_{\mp} F_{s+} F_{s-} (v_{F+} + v_{B-})}{(n_+ F_{s+} + v_{B-} + n_- F_{s-} - v_{F+}) F_{q\pm}} \right)$$

$$= : \epsilon_{0\pm} \exp \left( \frac{n_{\mp}}{(an_+ + bn_-) F_{q\pm}} \right)$$

(8)

where

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

(9)

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

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

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

(10)

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

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

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

$$= -\frac{yF_{s-} - xcF_{s+}}{xcF_{s+}/v_{B+} + yF_{s-}/v_{F-}}$$

(11)

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

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

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

(12)

in which

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

(13)
The splitting boundary of case (I) and case (II) is \( n_+ F_{s+} = n_- F_{s-} \), i.e. \( y = x c F_{s+} / F_{s-} \).

### (III) If an external force \( F_{ext} \) is present, here \( F_{ext} \) is taken to be positive if it points into the minus direction, then the force balance (3) becomes

\[
n_+ F_+ = -n_- F_+ F_{ext}
\]

In case of \( n_+ F_{s+} - F_{ext} > n_- F_{s-} \), carrying through the same calculation as for the case without external force leads to the velocity of cargo

\[
v_c(n_+, n_-) = \frac{n_+ F_{s+} - n_- F_{s-} - F_{ext}}{n_+ F_{s+}/v_{F+} + n_- F_{s-}/v_{B-}}
\]  

(14)

The corresponding unbinding rates of the plus and minus motors are

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

(15)

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

\[
v_c(n_+, n_-) = \frac{n_+ F_{s+} - n_- F_{s-} - F_{ext}}{n_+ F_{s+}/v_{B+} + n_- F_{s-}/v_{F-}}
\]  

(16)

and the unbinding rates of plus and minus motors are

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

(17)

Similarly, the splitting boundary of case (III) and case (IV) is \( n_+ F_{s+} = n_- F_{s-} + F_{ext} \), i.e. \( y = x c F_{s+} / F_{s-} - F_{ext} / N_- F_{s-} \).

### (V) More generally, if there exists an external force \( F_{ext} \) and the friction coefficient of cargo is \( \gamma \), then in the case of \( n_+ F_{s+} - F_{ext} > n_- F_{s-} \), the velocity of the cargo is

\[
v_c(n_+, n_-) = \frac{n_+ F_{s+} - n_- F_{s-} - F_{ext}}{n_+ F_{s+}/v_{F+} + n_- F_{s-}/v_{B-} + \gamma}
\]  

(18)

and the unbinding rates of plus and minus motors are

\[
\epsilon_+(x, y) = \epsilon_{0+} \exp \left( \frac{y + a (F_{ext} + \gamma v_c)/N_-}{(acx + by) F_{d+}} \right) \\
\epsilon_-(x, y) = \epsilon_{0-} \exp \left( \frac{cx - b (F_{ext} + \gamma v_c)/N_-}{(acx + by) F_{d-}} \right)
\]

(19)
On the other hand, if $n_+ F_{s+} - F_{ext} < n_- F_{s-}$, then the velocity of cargo is

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

(20)

and the unbinding rates of plus and minus motors are

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

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

(21)

The splitting boundary of these two cases is also

$$n_+ F_{s+} = n_- F_{s-} - F_{ext},$$

i.e.

$$y = xc F_{s+}/F_{s-} - F_{ext}/N_- F_{s-}.$$ 

4 The dynamics of motor numbers $n_+$ and $n_-$

For the sake of convenience, let

$$
\begin{align*}
& r_+ \equiv r_+(n_+, n_-) := (N_+ - n_+)\pi_+ \\
& s_+ \equiv s_+(n_+, n_-) := n_+\epsilon_+(n_+, n_-) \\
& r_- \equiv r_-(n_+, n_-) := (N_- - n_-)\pi_- \\
& s_- \equiv s_-(n_+, n_-) := n_-\epsilon_-(n_+, n_-)
\end{align*}
$$

(22)

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

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

(23)

In the limit $\Delta t \to 0$, (23) leads to

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

(24)

Similarly, the dynamics of minus motor number is

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

(25)

9
Figure 2: 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.

So $x = \frac{n_+}{N_+}, \ y = \frac{n_-}{N_-}$ satisfy

$$\begin{cases} 
\frac{dx}{dt} = \pi_+ - x[\pi_+ + \epsilon_+(x, y)] := f(x, y) \\
\frac{dy}{dt} = \pi_- - y[\pi_- + \epsilon_-(x, y)] := g(x, y)
\end{cases} \tag{26}$$

As we all know, the steady state solutions $(x^*, y^*)$ of the system (26), 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

$$\begin{bmatrix}
\frac{\partial f}{\partial x}(x^*, y^*) & \frac{\partial f}{\partial y}(x^*, y^*) \\
\frac{\partial g}{\partial x}(x^*, y^*) & \frac{\partial g}{\partial y}(x^*, y^*)
\end{bmatrix} \tag{27}
$$

are nonpositive. It is to say that

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

$$\frac{\partial f}{\partial x}(x^*, y^*)\frac{\partial g}{\partial y}(x^*, y^*) - \frac{\partial f}{\partial y}(x^*, y^*)\frac{\partial g}{\partial x}(x^*, y^*) \geq 0 \tag{28}$$

To better understanding, the figures of functions $f(x, y) = 0, g(x, y) = 0$ are plotted in figure 2. In view of conditions (28), to initial values $x_0 = \frac{n_+}{N_+}, y_0 = \frac{n_-}{N_-}$, if the point $P_0(x_0, y_0)$ lies in the subdomain I (II or III), then the final state is
Figure 3: The steady states of system (26). Where the unstable steady states are denoted by “∗”, 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 $M_{10}$).

stable steady state $M_{01}$ ($M_{11}$ or $M_{10}$) (see Fig. 3). Theoretically, $y_{M_{10}} \neq 0$, $x_{M_{01}} \neq 0$, but they are small than the accuracy of the numerical calculation used in this paper, so we simply regard them as 0.

To further understand the properties of the stable steady state points, the figures of $f(x, y) = 0$ and $g(x, y) = 0$ with different values of parameters $F_{s+}, F_{s-}, F_{d+}, F_{d-}, v_{B+}, v_{B-}, v_{F+}, v_{F-}, \pi_+, \pi_-, \epsilon_{0+}, \epsilon_{0-}$ and $c = N_+/N_-$ are plotted in Fig. 4 and 5, 6. From the figures, one can find that system (26) might have one, two or three stable steady states, which depends on the values of the parameters. Given the initial value $(x_0, y_0)$, the final steady state can be determined using the similar method as in Fig. 3 (Right). 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.

Obviously, 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
Figure 4: 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 “∗”, the stable steady states are denoted by “◦”. 
Figure 5: Asymmetric tug-of-war model: In this case, the system might have one, two or three stable steady states.

Figure 6: Tug-of-war model with external force $F_{ext}$: In this case, the system might have two or three stable steady states.
Figure 7: For large motor numbers $N_+, N_-$ cases, the steady states is determined by the theoretical steady state $n^*_+ \approx N_+ x^*, n^*_- \approx N_- y^*$. **Left:** $(n_+(0)/N_+, n_-(0)/N_-)$ lie in subdomain (II); **Middle:** $(n_+(0)/N_+, n_-(0)/N_-)$ lie in subdomain (III); **Right:** $(n_+(0)/N_+, n_-(0)/N_-)$ lie in subdomain (I).

or plus), and 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.

### 5 Comparison with Monte Carlo simulations

Due to the above discussion, in large motor numbers limit $N_+, N_- \to \infty$, the movement of the cargo might have one, two or three stable steady states. The final steady state is determined by the initial motor numbers $n_+(0) = N_+ x_0$ and $n_-(0) = N_- y_0$ (see Fig. 7). For example, in case of Fig. 3 (right), if $(n_+(0)/N_+, n_-(0)/N_-)$ lies in subdomains (II), the final steady state would be $n^*_+ \approx N_+ x_{M_{11}}, n^*_- \approx N_- y_{M_{11}}$.

However, if the numbers $N_+, N_-$ of molecular motors, which attached to the cargo, is finite or even small, the steady states numbers $n^*_+$ and $n^*_-$ might be different with the theoretical values $N_+ x^*$ and $N_- y^*$. Theoretically, if $M_i(x_i, y_i)(i = 1, 2$ or $3$) are the stable steady points of the system (26), which can be regarded as the large motor numbers limit of (24) (25), then steady state numbers $n^*_+$ and $n^*_-$ would lie in the
Figure 8: For small motor numbers $N_+, N_-$, the final motor numbers $n_+, n_-$ can change from one stable steady state to another. **Left:** The final motor numbers $n_+, n_-$ change from $N_+ x_{M11}$, $N_- y_{M11}$ to $N_+ x_{M10}$, $N_- y_{M10}$. **Right:** The final motor numbers $n_+, n_-$ change from $N_+ x_{M01}$, $N_- y_{M01}$ to $N_+ x_{M11}$, $N_- y_{M11}$.

neighborhoods of the theoretical values $N_+ x_i$ and $N_- y_i$. But, in small $N_+, N_-$ cases, the steady state motor numbers $n_+^a$ and $n_-^a$ 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 stepsize of the system (26) are $\Delta x = 1/N_+$, $\Delta y = 1/N_-$. So the smaller of motor numbers $N_+, N_-$, the 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

$$p_{S}^{12} = \prod_{(S_i, S_{i+1}) \in S_R} \frac{\pi_{i+}}{\pi_{i+} + \epsilon_{i+} + \pi_{i-} + \epsilon_{i-}} \prod_{(S_j, S_{j+1}) \in S_L} \frac{\epsilon_{j+}}{\epsilon_{j+} + \epsilon_{j+} + \pi_{j-} + \epsilon_{j-}} \prod_{(S_k, S_{k+1}) \in S_U} \frac{\pi_{k-}}{\pi_{k+} + \epsilon_{k+} + \pi_{k-} + \epsilon_{k-}} \prod_{(S_l, S_{l+1}) \in S_D} \frac{\epsilon_{l-}}{\epsilon_{l+} + \epsilon_{l+} + \pi_{l-} + \epsilon_{l-}}$$

(29)
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 $n_+(P_2) = n_+(P_1) - 1, n_-(P_2) = n_-(P_1) + 1$, $(P_1, P_2) \in S_D$ 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 states to the neighborhood of another stable steady states. From these transition probabilities, we can know more details about the steady state movement of the cargo in this small $N_+, N_-$ cases.

6 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 states of the movement of the cargo is determined by initial numbers of the plus and minus motors which are bound to the microtubule. Certainly, the velocity and direction of the movement are also determined by other several parameters, such as $N_\pm, F_\pm, \pi_\pm, \epsilon_{0\pm}, F_d\pm, v_F\pm, v_B\pm, F_{\text{ext}}, \gamma$. 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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Properties of tug-of-war model for cargo transport by molecular motors

Yunxin Zhang*†‡

Abstract

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, M.J.I. Müller et al. have developed a tug-of-war model to describe the bidirectional movement of the cargo (PNAS(2008) 105(12) P4609-4614). 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 the sensitivity can be used by a cell to regulate its cargo traffic. In the present paper, we will carry out a further detailed theoretical analysis of the tug-of-war model. All the stable, i.e., biophysically observable, steady states and their stability domains can be obtained. Depending on values of the several parameters, tug-of-war model exhibits either uni-, bi- or tristability. In large motor number case, the steady state movement of the cargo, which is transported by two molecular motor species, is determined by the initial numbers of the motors which bound to the

*School of Mathematical Sciences, Fudan University, Shanghai 200433, China
†Shanghai Key Laboratory for Contemporary Applied Mathematics, Fudan University
‡Centre for Computational Systems Biology, Fudan University (E-Mail: xyz@fudan.edu.cn)
track. For small motor number case, the movement of cargo may jump from one of the stable steady state to another.

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1 Introduction

Molecular motors, including biological motor proteins such as kinesin \cite{1,2,3,7}, dynein \cite{4,5}, myosin \cite{6,7,8} and \( F_0F_1-\text{ATP synthase} \) \cite{9}, are mechanochemical force generators which convert chemical or biochemical energy in the form of chemical potential into mechanical work in thermal environment \cite{10}. The mechanochemical process is accomplished by individual macromolecules, immersed in an aqueous solution with the chemical potential, moving along a linear track. Many biological motor proteins move processively. For example, myosin slides along an actin filament, kinesin and dynein along microtubule (MT). All of them are adenosine triphosphate (ATP)-driven “directional walking machines” \cite{11,12}: Kinesin moves towards the plus end of the MT and dynein towards 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\% \cite{4,13,14}. Furthermore, the velocities of molecular motors are also fast with mean velocity be at about several hundreds nanometers per second \cite{15}. 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 \cite{16}. 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 [17, 18, 10], the Langevin stochastic dynamic methods [19, 20] and discrete stochastic methods [21, 22, 23, 24, 25]. 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 ([25]). Following these recent experimental results ([26, 27, 28]), Lipowsky and his coworkers have developed the tug-of-war model for describing the movement of the cargo carried by processive motors, such as kinesin and dynein ([29, 30, 31, 32, 33]). 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 ([29, 30], 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).

In the present paper, we will give a further comprehensive mathematical analysis of tug-of-war model. 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. At the same time, Monte Carlo simulations indicate the transition time from the initial state to the steady state is very short (see Figs. 7, 8). Theoretically, the movement of the cargo has at most three stable steady states. 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. In the following, we firstly introduce the tug-of-war model, and then give the detailed discussion gradually.
Figure 1: 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.

2 The tug-of-war model

The tug-of-war model is developed by Reinhard Lipowsky’s study group ([29, 30, 31, 32, ?]) 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 ([31, 33]). In this model, each motor species is characterized by six parameters, which can be measured in single molecular experiments (see Tab. [1]): (i) stall force $F_S$ (pN) (ii) detachment force $F_d$ (pN) (iii) unbinding rate $\epsilon_0$ ($s^{-1}$) (iv) binding rate $\pi_0$ ($s^{-1}$) (v) forward velocity $v_F$ ($\mu m/s$) 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 $n_+ \leq N_+$ plus and $n_- \leq N_-$ minus motors, where $n_+$ and $n_-$ fluctuate with time (see Fig. [1]).

In tug-of-war model, it is assumed that, at every time $t$, the state of cargo with
Table 1: Single-motor parameters for kinesin 1 and cytoplasmic dynein ([29] and references therein).

| Parameter                        | Symbol | Kinesin 1 | Dynein |
|----------------------------------|--------|-----------|--------|
| Stall force                      | $F_s$  | 6pN       | 1.1pN  |
| Detachment force                 | $F_d$  | 3pN       | 0.75pN |
| Unbinding rate                   | $\epsilon_0$ | $1s^{-1}$ | $0.27s^{-1}$ |
| Binding rate                     | $\pi_0$ | $5s^{-1}$ | $1.6s^{-1}$ |
| Forward velocity                 | $v_F$  | 1$\mu$m/s | 0.65$\mu$m/s |
| superstall velocity amplitude    | $v_B$  | 6nm/s     | 72nm/s |

$N_+$ 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 bound motors at time $t$ can be described by the following Master equation:

$$
\frac{dp(n_+, n_-, t)}{dt} = [\pi_0 - (n_+ - 1)\epsilon_0]p(n_+ - 1, n_-, t) + (n_+ + 1)\epsilon_0(n_+, n_+ - 1)p(n_+ + 1, n_-, t) + [\pi_0 - (n_- - 1)\epsilon_0]p(n_+, n_-, t) + (n_- + 1)\epsilon_0(n_+, n_- + 1)p(n_+, n_- + 1, t) - [(n_+ - n_+)\pi_0 + n_+\epsilon_0(n_+, n_-)]p(n_+, n_-, t) + (n_- - n_)\epsilon_0(n_+, n_-)p(n_+, n_-, t) + (n_+ + 1)\epsilon_0(n_+, n_- + 1)p(n_+, n_- + 1, t)
$$

(1)

where $\pi_0 (\pi_0)$ is the binding rate of a single plus (minus) motor to the MT, which depends only weakly on the load ([31]) 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 $F$:

$$
\epsilon_{\pm}(F) = \epsilon_{0\pm} \exp(|F|/F_{d\pm})
$$  \hspace{1cm} (2)

as measured for kinesin [34], where $F_d$ is the detachment force. The governing equations for $n_+ = 0, N_+$ or $n_- = 0, N_-$ are similar as (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 coworkers gave the following relation (see [32])

$$
n_+ F_+ = -n_- F_- \equiv F_c
$$  \hspace{1cm} (3)

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

$$
\epsilon_{\pm}(n_+, n_-) = \epsilon_{0\pm} \exp[F_c/n_\pm F_{d\pm}]
$$  \hspace{1cm} (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:

$$
v_c(n_+, n_-) = v_+(F_c/n_+) = -v_-(-F_c/n_-)
$$  \hspace{1cm} (5)

The same as in [29], the following piecewise linear force-velocity relation of a single motor is used in this paper:

$$
v(F) = \begin{cases} 
v_F(1 - F/F_s) & \text{for } F \leq F_s \\
v_B(1 - F/F_s) & \text{for } F \geq F_s
\end{cases}
$$  \hspace{1cm} (6)

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

3 The velocity of cargo and unbinding rates of motors

For the convenience of analysis in the following sections, we give the formulations of velocity of cargo 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) (6) lead to the cargo force and velocity:

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

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

\[
\epsilon_\pm(n_+, n_-) = \epsilon_{0\pm} \exp \left( \frac{n_\pm F_{s+} F_{s-}(v_{F+} + v_{B-})}{(n_+ F_{s+} v_{B-} + n_- F_{s-} v_{F+}) F_d} \right)
\]
\[
= : \epsilon_{0\pm} \exp \left( \frac{n_\pm}{(an_+ + bn_-) F_d} \right)
\]

where

\[
a = \frac{v_{B-}}{F_{s-}(v_{F+} + v_{B-})} \quad b = \frac{v_{F+}}{F_{s+}(v_{F+} + v_{B-})}
\]

Let \( x = n_+/N_+ \), \( y = n_-/N_- \) and \( c = N_+/N_- \), then

\[
\epsilon_+(x, y) = \epsilon_{0+} \exp \left( \frac{y}{(ac x + by) F_d} \right)
\]
\[
\epsilon_-(x, y) = \epsilon_{0-} \exp \left( \frac{cx}{(ac x + by) F_d} \right)
\]

(II) In case of “stronger minus motors”, i.e. \( n_+ F_{s+} < n_- F_{s-} \), the cargo force and velocity are:

\[
F_c(n_+, n_-) = -\frac{v_{B+} + v_{F-}}{v_{B+}/n_+ F_{s+} + v_{F-}/n_- F_{s-}}
\]
\[
v_c(n_+, n_-) = -\frac{n_- F_{s-} - n_+ F_{s+}}{n_+ F_{s+}/v_{B+} + n_- F_{s-}/v_{F-}}
\]
\[
= -\frac{y F_{s-} - x c F_{s+}}{x c F_{s+}/v_{B+} + y F_{s-}/v_{F-}}
\]

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

\[
\epsilon_+(x, y) = \epsilon_{0+} \exp \left( \frac{y}{(\bar{a} c x + by) F_d} \right)
\]
\[
\epsilon_-(x, y) = \epsilon_{0-} \exp \left( \frac{cx}{(\bar{a} c x + by) F_d} \right)
\]

in which

\[
\bar{a} = \frac{v_{F-}}{F_{s-}(v_{B+} + v_{F-})} \quad \bar{b} = \frac{v_{B+}}{F_{s+}(v_{B+} + v_{F-})}
\]
The splitting boundary of case (I) and case (II) is \( n_+ F_{s+} = n_- F_{s-} \), i.e. \( y = x c F_{s+} / F_{s-} \).

(III) If an external force \( F_{ext} \) is present, here \( F_{ext} \) is taken to be positive if it points into the minus direction, then the force balance becomes

\[
n_+ F_+ = -n_- F_+ F_{ext}
\]

In case of \( n_+ F_{s+} - F_{ext} > n_- F_{s-} \), carrying through the same calculation as for the case without external force leads to the velocity of cargo

\[
v_c(n_+, n_-) = \frac{n_+ F_{s+} - n_- F_{s-} - F_{ext}}{n_+ F_{s+}/v_{F+} + n_- F_{s-}/v_{F-}}
\]

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

\[
v_c(n_+, n_-) = \frac{n_+ F_{s+} - n_- F_{s-} - F_{ext}}{n_+ F_{s+}/v_{B+} + n_- F_{s-}/v_{B-} + \gamma}
\]

(V) More generally, if there exists an external force \( F_{ext} \) and the friction coefficient of cargo is \( \gamma \), then in the case of \( n_+ F_{s+} - F_{ext} > n_- F_{s-} \), the velocity of the cargo is

\[
v_c(n_+, n_-) = \frac{n_+ F_{s+} - n_- F_{s-} - F_{ext}}{n_+ F_{s+}/v_{F+} + n_- F_{s-}/v_{F-}}
\]

and the unbinding rates of plus and minus motors are

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

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

Similarly, the splitting boundary of case (III) and case (IV) is \( n_+ F_{s+} = n_- F_{s-} + F_{ext} \), i.e. \( y = x c F_{s+}/F_{s-} - F_{ext}/N_- F_{s-} \).
On the other hand, if \( n_Fs_+ - F_{ext} < n_Fs_- \), then the velocity of cargo is

\[
v_c(n_+, n_-) = \frac{n_Fs_+ - n_Fs_- - F_{ext}}{n_Fs_+/v_B + n_Fs_-/v_F + \gamma} \tag{20}
\]

and the unbinding rates of plus and minus motors are

\[
\begin{align*}
\epsilon_+(x, y) &= \epsilon_{0+} \exp \left( \frac{y + \bar{a}(F_{ext} + \gamma v_c)/N_-}{(\bar{a}cx + \bar{b}y)F_d^+} \right) \\
\epsilon_-(x, y) &= \epsilon_{0-} \exp \left( \frac{cx - \bar{b}(F_{ext} + \gamma v_c)/N_-}{(\bar{a}cx + \bar{b}y)F_d^-} \right) \tag{21}
\end{align*}
\]

The splitting boundary of these two cases is also \( n_Fs_+ = n_Fs_- + F_{ext} \), i.e.

\[
y = xcs_Fs_+/F_s_- - F_{ext}/N_Fs_-.
\]

4 The dynamics of motor numbers \( n_+ \) and \( n_- \)

For the sake of convenience, let

\[
\begin{align*}
    r_+ &\equiv r_+(n_+, n_-) := (N_+ - n_+)\pi_+ \\
    s_+ &\equiv s_+(n_+, n_-) := n_+\epsilon_+(n_+, n_-) \\
    r_- &\equiv r_-(n_+, n_-) := (N_- - n_-)\pi_- \\
    s_- &\equiv s_-(n_+, n_-) := n_-\epsilon_-(n_+, n_-)
\end{align*} \tag{22}
\]

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

\[
n_+(t + \Delta t) - n_+(t) = \left( \frac{r_+}{\lambda} - \frac{s_+}{\lambda} \right) \int_0^{\Delta t} \lambda e^{-\lambda t} dt = \frac{r_+ - s_+}{\lambda} \left( 1 - e^{-\lambda \Delta t} \right) \tag{23}
\]

In the limit \( \Delta t \to 0 \), (23) leads to

\[
\frac{dn_+}{dt} = r_+ - s_+ = (N_+ - n_+)\pi_+ - n_+\epsilon_+(n_+, n_-) \tag{24}
\]

Similarly, the dynamics of minus motor number is

\[
\frac{dn_-}{dt} = r_+ - s_+ = (N_- - n_-)\pi_- - n_-\epsilon_-(n_+, n_-) \tag{25}
\]
So \( x = n_+/N_+ \), \( y = n_-/N_- \) satisfy

\[
\begin{align*}
\frac{dx}{dt} &= \pi_+ - x[\pi_+ + \epsilon_+(x, y)] := f(x, y) \\
\frac{dy}{dt} &= \pi_- - y[\pi_- + \epsilon_-(x, y)] := g(x, y)
\end{align*}
\]

(26)

As we all know, the steady state solutions \((x^*, y^*)\) of the system (26), 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

\[
\begin{bmatrix}
\frac{\partial f}{\partial x}(x^*, y^*) & \frac{\partial f}{\partial y}(x^*, y^*) \\
\frac{\partial g}{\partial x}(x^*, y^*) & \frac{\partial g}{\partial y}(x^*, y^*)
\end{bmatrix}
\]

(27)

are nonpositive. It is to say that

\[
\frac{\partial f}{\partial x}(x^*, y^*) + \frac{\partial g}{\partial y}(x^*, y^*) \leq 0
\]

(28)

To better understanding, the figures of functions \(f(x, y) = 0\), \(g(x, y) = 0\) are plotted in figure 2. In view of conditions (28), to initial values \(x_0 = n_+/N_+, y_0 = n_-/N_-\), if the point \(P_0(x_0, y_0)\) lies in the subdomain I (II or III), then the final state is
Figure 3: The steady states of system (26). Where the unstable steady states are denoted by “∗”, 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 $M_{01} (M_{11} \text{ or } M_{10})$.

stable steady state $M_{01} (M_{11} \text{ or } M_{10})$ (see Fig. 3). Theoretically, $y_{M_{10}} \neq 0$, $x_{M_{01}} \neq 0$, but they are small than the accuracy of the numerical calculation used in this paper, so we simply regard them as 0.

To further understand the properties of the stable steady state points, the figures of $f(x, y) = 0$ and $g(x, y) = 0$ with different values of parameters $F_{s+}, F_{s-}, F_{d+}, F_{d-}, \nu_{B+}, \nu_{B-}, \nu_{F+}, \nu_{F-}, \pi_{+}, \pi_{-}, \epsilon_{0+}, \epsilon_{0-}$ and $c = N_+/N_-$ are plotted in Fig. 4 and 5. From the figures, one can find that system (26) might have one, two or three stable steady states, which depends on the values of the parameters. Given the initial value $(x_0, y_0)$, the final steady state can be determined using the similar method as in Fig. 3 (Right). 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.

Obviously, 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...
Figure 4: 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 "∗", the stable steady states are denoted by "●".
Figure 5: Asymmetric tug-of-war model: In this case, the system (26) might have one, two or three stable steady states.

Figure 6: Tug-of-war model with external force $F_{ext}$: In this case, the system (26) might have two or three stable steady states.
Figure 7: For large motor numbers $N_+, N_-$ cases, the steady states is determined by the theoretical steady state $n_+^s \approx N_+ x^s$, $n_-^s \approx N_- y^s$. \textbf{Left:} $(n_+(0)/N_+, n_-(0)/N_-)$ lie in subdomain (II); \textbf{Middle:} $(n_+(0)/N_+, n_-(0)/N_-)$ lie in subdomain (III); \textbf{Right:} $(n_+(0)/N_+, n_-(0)/N_-)$ lie in subdomain (I).

or plus), and 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.

5 Comparison with Monte Carlo simulations

Due to the above discussion, in large motor numbers limit $N_+, N_- \to \infty$, the movement of the cargo might have one, two or three stable steady states. The final steady state is determined by the initial motor numbers $n_+(0) = N_+ x_0$ and $n_-(0) = N_- y_0$ (see Fig. 7). For example, in case of Fig. 3 (right), 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 attached to the cargo, is finite or even small, the steady states numbers $n_+^s$ and $n_-^s$ might be different with the theoretical values $N_+ x^s$ and $N_- y^s$. Theoretically, if $M_i(x_i, y_i)(i = 1, 2$ or $3)$ are the stable steady points of the system (26), which can be regarded as the large motor numbers limit of (24) (25), then steady state numbers $n_+^s$ and $n_-^s$ would lie in the
Figure 8: For small motor numbers $N_+, N_-$, the final motor numbers $n_+, n_-$ can change from one stable steady state to another. **Left:** The final motor numbers $n_+, n_-$ change from $N_+x_{M_11}, N_-y_{M_11}$ to $N_+x_{M_{10}}, N_-y_{M_{10}}$; **Right:** The final motor numbers $n_+, n_-$ change from $N_+x_{M_{01}}, N_-y_{M_{01}}$ to $N_+x_{M_{11}}, N_-y_{M_{11}}$.

neighborhoods of the theoretical values $N_+x_i$ and $N_-y_i$. But, in small $N_+, N_-$ cases, the steady state motor numbers $n^*_+$ and $n^*_-$ 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 stepsize of the system (26) are $\Delta x = 1/N_+, \Delta y = 1/N_-$. So the smaller of motor numbers $N_+, N_-$, the 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

$$ p^{12}_S = \prod_{(S_i, S_{i+1}) \in S_R} \frac{\pi_{i+}}{\pi_{i+} + \epsilon_{i+} + \pi_{i-} + \epsilon_{i-}} \prod_{(S_j, S_{j+1}) \in S_L} \frac{\epsilon_{j+}}{\pi_{j+} + \epsilon_{j+} + \pi_{j-} + \epsilon_{j-}} \prod_{(S_k, S_{k+1}) \in S_U} \frac{\pi_{k-}}{\pi_{k-} + \epsilon_{k+} + \pi_{k-} + \epsilon_{k-}} \prod_{(S_l, S_{l+1}) \in S_D} \frac{\epsilon_{l-}}{\pi_{l+} + \epsilon_{l+} + \pi_{l-} + \epsilon_{l-}} $$

(29)
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 states to the neighborhood of another stable steady states. From these transition probabilities, we can know more details about the steady state movement of the cargo in this small $N_+, N_-$ cases.

6 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 states 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 a critical point, 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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