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Three phase model of the processive motor protein kinesin

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ABSTRACT

Kinesin is a stepping motor that successively produces forward and backward 8-nm steps along microtubules. Under physiological conditions, the steps powering kinesin's motility are biased in one direction and drive various biological motile processes. So far, the physical mechanism underlying the unidirectional bias of the kinesin is not fully understood. Recently, Martin Bier have provided a stepper model [Martin Bier, 2003, Processive motor protein as an overdamped Brownian stepper, Phys. Rev. Lett. 91, 148104], in which the stepping cycle of kinesin includes two distinguished phases: (i) a power stroke phase and (ii) a ratcheted diffusion phase which is characterized as a "random diffusional search". At saturating ATP level, this model can fit the experimental results accurately. In this paper, we'll provide a modified Brownian stepper model, in which the dependence of ATP concentration is considered. In our model, the stepping cycle of kinesin is distinguished into three phases: an ATP-binding phase, a power stroke phase and a ratcheted diffusion phase. This modified model can reconstruct most of the experimental results accurately.

1. Introduction

Molecular motors are biogenic force generators acting in the nanometer range [1]. Linear motors produce sliding movements along filamentous structures called protein tracks; for example, myosin slides along an actin filament [2–4], kinesin [5–9] and dynein [10,11] along a microtubule. Many of the molecular motors have the ability to rotate; for example, the bacterial flagellar motor [12] and F_0F_1-ATP synthase [13]. These movements and forces generated by the motors play essential roles in cellular functions. The linear motor kinesins are widely distributed in almost all eukaryotic cells. These motors are adenosine triphosphate (ATP)-driven walking machines that move in 8-nm steps toward the plus ends of the microtubule, turn over one ATP molecular per step under a range of loads [1,14–16]. Kinesin has two motor domains called heads, each of which includes the ATP- and microtubule-binding sites [17,18]. This motor steps mainly in the forward direction (to the plus end of the microtubule), but occasionally in the backward direction (to its minus end) [19].

The microscopic phase of the processive movement of kinesin has not been well understood. So far, there are mainly two types of models in literature. One type is the thermal ratchet model in which a motor is simply viewed as a Brownian particle moving in two (or more) spatially periodic but asymmetric stochastically switched potentials [20,21], which is more suitable for modeling the processive movement of single-headed motors such as the unconventional single-headed kinesin KIF1A [22]. Another prevailing type of models for conventional kinesin are the hand-over-hand models [15,16,23–27]. In these models, it is supposed that the kinesin dimer maintains continuous attachment to MT by alternately repeating single-headed and double-headed bindings. Recent experiments [15,16] strongly support this type of models by revealing that kinesin walks in an asymmetric hand-over-hand manner and a given head of the dimer is displaced in discrete steps with a mean size of ~16 nm.

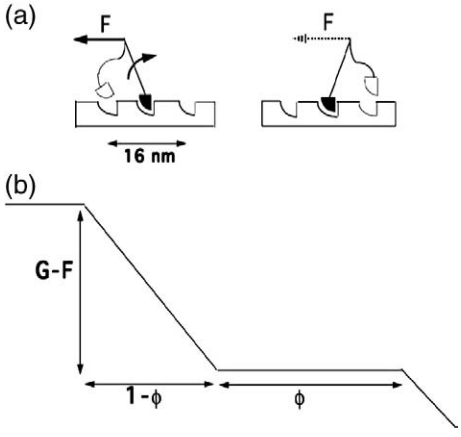

Fig. 1. The setup of the Brownian stepper model provided by Martin Bier. (a) Corresponds to traversing one unit in a 1D reaction space of the two headed motor protein, (b) corresponds to the energy profile along a reaction coordinate, where the power stroke covers a fraction $1-\phi$ of the cycle, the subsequent diffusion covers the remaining ϕ fraction.

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In [28–30], Martin Bier has provided a Brownian stepper model (see Fig. 1), in which two phases are distinguished by the author: (i) a power stroke phase, i.e. the reorientation of the attached head after the anterior head detaches. (ii) A ratcheted diffusion phase, i.e., the detached head is randomly diffusing around the neck linker until it hits the posterior docking site. In saturating ATP level, their model can fit the experimental datapoints accurately. In this paper, we'll provide a more reasonable Brownian stepper model, in which the ATP concentration is included. In this model, the stepping cycle of kinesin is distinguished into three phases: an ATP-binding phase, a power stroke phase and a ratcheted diffusion phase. This modified model can reconstruct most of the experimental results accurately.

2. Three phase model of kinesin

Our three phase model can be described as following (see Fig. 2): In the first phase, one head is in nucleotide-free state and attached to microtubule, whereas the other head is in ADP state and diffuses on the basis of the partner head. The detached head traps ADP and cannot bind microtubule until ATP binds to the attached one [5,18]. The dwell time t_1 of this phase is determined by ATP concentration [ATP] and ATP-binding rate k_1: $t_1 = 1/k_b = 1/k_1[\mathrm{ATP}]$ [31]. The experimental data from different groups leads to slightly different values for the ATP-binding rate k_1 [32], for example, $k_1 = 2\ (\mu\mathrm{M\ s})^{-1}$ in [6] and $k_1 = 1.8\ (\mu\mathrm{M\ s})^{-1}$ in [31]. As ATP binds to the attached head, microtubule activation of the kinesin ATPase occurs, which accelerate the ADP release of the detached head. ATP binding to the holdfast head acts as a gate that allows the other head to begin a diffusional search for its next binding site [6]. This is the beginning of the second phase.

In the second phase, the neck linker of the ATP bounded head, i.e. the residues of the neck bridging the catalytic core and the subsequent coiled-coil dimerization domain, would be immobilized onto the catalytic core towards the microtubule plus end, which is termed as neck linker "docking". Docking of neck linker of the holdfast head (i.e. the trailing head) then allows the releasing of ADP and binding to microtubule of the tethered head (i.e. the leading head). In this phase, the center of mass of

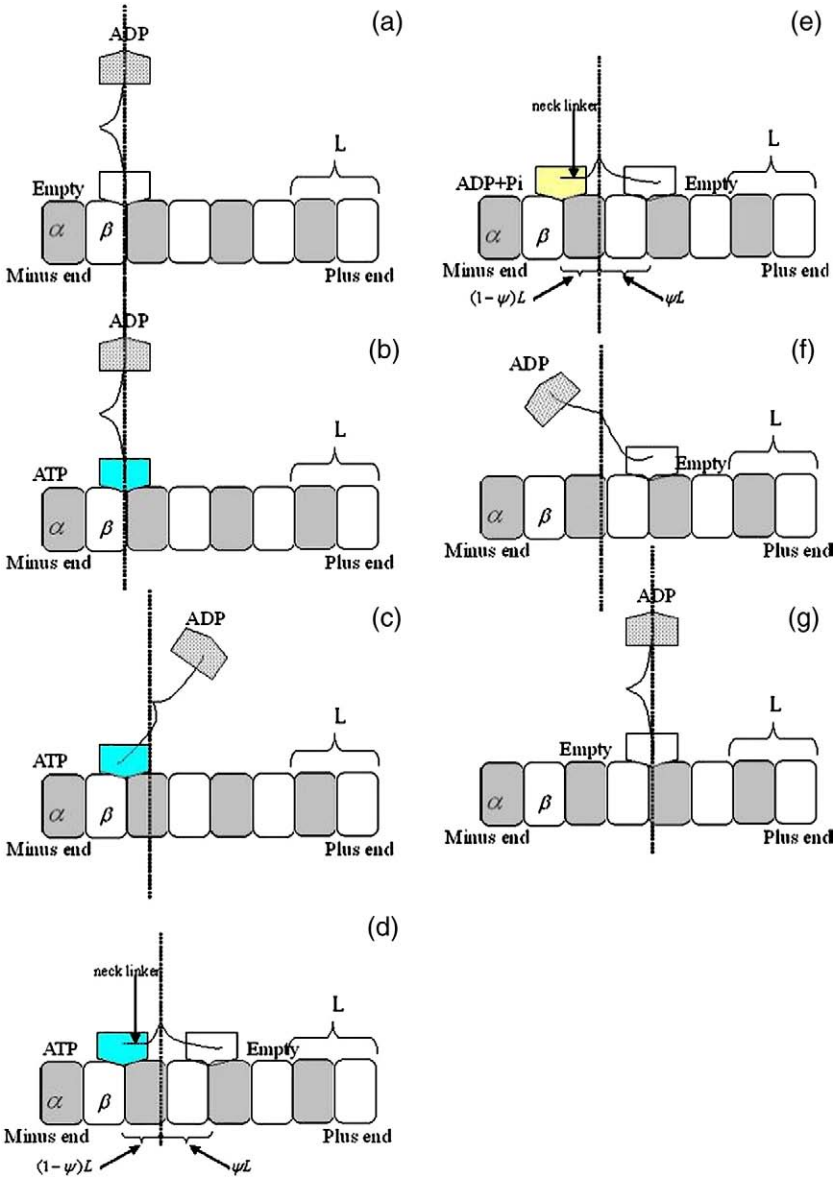

Fig. 2. Schematic illustration of the three phase model, the vertical dotted line is the position of the center of mass. (a) The cycle begin with one nucleotide-free head (trailing head) binding to microtubule and one ADP binding head (leading head) diffusing freely on the basis of the trailing head. (b) (c) After ATP binding to the trailing head, its neck linker begins to dock, allowing the leading head releasing ADP and diffusing to the plus end. (d) The center of mass of the motor moves $(1-\psi)L$ forward, and the leading head binds to the next binding site. (e) After the leading head binding to microtubule, ATP is hydrolyzed at the trailing head. (f) Once Pi is released, the trailing head is detached. (g) After the detachment, the trailing head begins to diffuse. This diffusion is regarded as one that between a reflecting barrier and an absorbing barrier. In this process, the center of mass of the motor moves ψL forward.

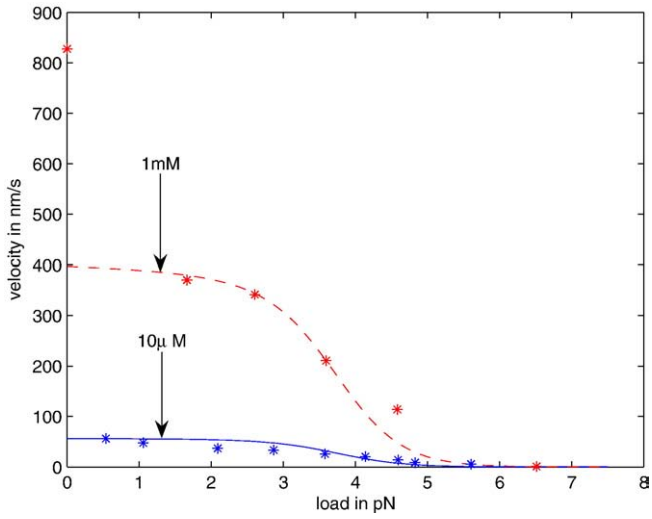

Fig. 3. Load–velocity diagram for the motion of kinesin on microtubule. The datapoints are from Ref. [6]. The two curves are obtained by the theoretical formulation (4), where the dashed red one corresponds to [ATP]=1 mM and the solid blue one corresponds to [ATP]=10 M. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

kinesin and cargo moves $l_z=(1-\psi)L$ forward, where l_z is the length of the zippered neck linker, $L=8.2$ nm is the stepsize of kinesin and $1-\psi$ is the fraction of the stepsize occupied in this phase. Since the movement of the motor protein is coupled with the ATP catalysis, it is reasonable to relate the fraction $1-\psi$ of the mechanical cycle to the fraction $1-\phi$ of the chemical reaction cycle (see Fig. 1). Different from Martin Bier's model, in this phase, the motor moves $l_z=(1-\psi)L$ forward (see Fig. 2), but not L (see Fig. 1). It is well known that the energy G consumed in this process is about 5–6 k_BT (k_B is the Boltzmann constant, T absolute temperature) [7,14,33]. The distance l_z moved in this phase is about 2.4–3 nm [7,14,33]. From mutagenesis studies one knows the neck linker zippered length lies within 5–10 residues [34–36], i.e. 1.8–3.6 nm. Specially, $l_z=2.52$ nm, i.e. 7 residues is used in [37]. The dwell time t_2 of this phase is mainly determined by the neck linker "docking", which can be described as power stroke [28–30]. Under the assumption that the power stroke is a completely smooth linear downslide [29], the force driving the motor protein down this power stroke section equals $F_{ps}=G/(1-\psi)L$. The time to complete this power stroke phase thus equals

$$t_2=\frac{\xi(1-\psi)L}{F_{ps}-f_{ext}}=\frac{\xi(1-\psi)L}{\frac{G}{(1-\psi)L}-f_{ext}}=\frac{k_BT(1-\psi)^2L^2}{D(G-f_{ext}(1-\psi)L)} \quad (1)$$

where ξ is the friction, f_{ext} is the external load. If we take k_BT to be the unit of energy and $F_{ext}=f_{ext}L/k_BT$ to be the dimensionless force, the dwell time of the second phase is $t_2=(1-\psi)^2L^2/(G-F_{ext}(1-\psi))D$.

In the third phase, ATP hydrolysis and Pi release results in the weakening of electrostatic binding force between the trailing head and the binding site of microtubule. Driven by the internal elastic force and torque, the trailing head is then detached from microtubule and diffuse to its equilibrium position. The dwell time t_3 of this phase is mainly determined by diffusion. In this phase, the center of mass of kinesin and cargo moves $l_d=\psi L$ forward. The diffusion in this phase can be regarded as a random walk between a reflecting barrier and an absorbing barrier [30]. So the dwell time in this phase is $t_3=(\psi L)^2/2D$. In conclusion, for the entire catalytic cycle, we obtain a duration of

$$T=t_1+t_2+t_3=\frac{(1-\psi)^2L^2}{(G-F_{ext}(1-\psi))D}+\frac{(\psi L)^2}{2D}+\frac{1}{k_1[ATP]}. \quad (2)$$

Before we derive the formulation of the average velocity of kinesin, there is a complication we have to take care of. It appears that, in practice, 5% to 10% kinesin's steps are backward [31]. Recently, the backstepping of the motors had been resolved with great accuracy (see [6] and [7,33,14]). For example, Taniguchi et al. [7] find $P_f/P_b=e^{\frac{Gk_BT-f_{ext}(d_f-d_b)}{k_BT}}$ where Gk_BT is the free energy difference between the backward and forward direction barrier, d_f, d_b are the forward and backward characteristic distances respectively, P_f, P_b are the probabilities of forward and backward stepping. In this research, we use $d_b=0$ [7] and $d_f=(1-\psi)L$, which implies $P_f/P_b=e^{G-(1-\psi)F_{ext}}$ (where $F_{ext}=f_{ext}L/k_BT$ and the energy G is expressed in units of k_BT). Furthermore, Taniguchi et al. [7] also find the ratio of forward movement to detachment is $P_f/P_b=k_f^0e^{\frac{f_{ext}(d_d-d_f)}{k_BT}}/k_d^0$, where d_d is the characteristic distance of detachment, k_f^0, k_d^0 are the rate constants of forward movement and detachment f d respectively at zero load. Let $d_d=0$ [7], one obtains $P_f/P_d=k_f^0e^{-F_{ext}(1-\psi)}/k_d^0$. In view of $P_f+P_b+P_d=1$, we obtain

$$P_f=\frac{1}{1+e^{(1-\psi)F_{ext}-G}+\frac{k_d^0}{k_f^0}e^{(1-\psi)F_{ext}}} \quad P_b=\frac{e^{(1-\psi)F_{ext}-G}}{1+e^{(1-\psi)F_{ext}-G}+\frac{k_d^0}{k_f^0}e^{(1-\psi)F_{ext}}}. \quad (3)$$

In the computer simulation, we use $k_d^0=0.14$ and $k_f^0=544$ [7]. Finally, we obtain the average velocity of kinesin

$$v=(P_f-P_b)\frac{L}{T}=\frac{1-e^{(1-\psi)F_{ext}-G}}{1+e^{(1-\psi)F_{ext}-G}+\frac{k_d^0}{k_f^0}e^{(1-\psi)F_{ext}}}\frac{1}{\frac{(1-\psi)^2}{G-F_{ext}(1-\psi)}+\frac{\psi^2}{2}+\frac{1}{k_1[ATP]}\frac{D}{L^2}}\frac{D}{L}. \quad (4)$$

The stall force of kinesin is $f_s=Gk_BT/(1-\psi)L$ (in units of pN).

The load–velocity data (star points) that Carter and Cross recorded [6] and the theoretical curves according to Eq. (4) are shown in Fig. 3. In the computer simulation, we use $G=6k_BT$, $D=7.5\times10^{-16}$ m^2/s, $L=8.2$ nm, $k_1=2(\mu M\ s)^{-1}$, $d_d=d_b=0$, $d_f=3$ nm (i.e. $1-\psi=3/8.2$), $k_d^0=0.14$, $k_f^0=544$, $T=300$. In Fig. 3, the dashed red curve is corresponding to [ATP]=1 mM, the blue solid curve is corresponding to [ATP]=10 μM.

3. Concluding remarks and discussion

In this research, the movement of the motor protein kinesin is modeled by three phase model. The cycle of kinesin movement begins with one nucleotide-free head attaching to the microtubule and one ADP trapped head diffusing freely on the basis of the another one. In the first phase, the kinesin waits until ATP is bound to the attached head (trailing head). After ATP binding, its neck linker docked, which allowing the leading head releasing ADP and binding to microtubule. In this phase, the center of mass of kinesin moves $l_z=(1-\psi)L$ forward. This phase is regarded as power stroke. When the leading head has bound to microtubule, the ATP bound to the trailing head begins to hydrolyze. ATP hydrolysis and Pi release result in the weakening of binding force between the trailing head and the binding site. From the internal force and torque, the trailing head is then detached from microtubule. After detachment, the trailing head diffuses to its equilibrium position. In this phase, the center of mass of kinesin moves ψL forward. This phase is regarded as random walk between a reflecting barrier and an absorbing barrier.

Though it is very difficult to be detected experimentally [6], there are previous reports of substeps [38,39] and several models predict substeps [40–42]. From the three phase model, the movement of kinesin includes two substeps: the power stroke which covers 3 nm and the diffusion which covers 5.2 nm. The substeps 3 nm and 5.2 nm are the same as the experimental results in [38].

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