Walking motion of an overdamped active particle in a ratchet potential

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Abstract An active particle can convert its internal energy into mechanical work. We study a generalized energy-depot model of an overdamped active particle in a ratchet potential. Using well-known biological parameters for kinesin-1 and modeling ATP influx as a pulsed energy supply, we apply our model to the molecular motor system. We find that our simple model can capture the essential properties of the kinesin motor such as forward stepping, stalling, backward stepping, dependence on ATP concentration, and stall force. Our model might be quite universal in the sense that it is able to describe dynamics of various types of motors as long as realistic parameters for each motor species are adopted.

Keywords Active particle · Kinesin · Energy depot model

1 Introduction

Motions of active particles have been studied intensively in connection with swarm dynamics of fishes, small insects, microorganisms [1–4], and self-organized motions of

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molecular motors and micro/nano-robots [5–9]. As a model to describe these self-propelling processes, an energy depot model was introduced by Schweitzer et al. [10, 11]. Recently, it was found that an active particle with a generalized energy depot exhibits stepping motion similar to that observed in processive molecular motors [12]. It raises an immediate question whether this stepping motion can be sustained in the presence of the ratchet potential, which simulates the role of cytoskeletal filaments for molecular motors. In this paper, we examine this question using processive kinesin as an example, adopting biological parameters obtained from experiments.

Conventional kinesin, kinesin-1, walks processively along a microtubule toward the plus end (defined as ‘forward’) [13–15] generating 6–8 pN per step [16] by consuming one adenosine-triphosphate (ATP) [17, 18] and transports vesicles and organelles [19–28]. One of the interesting observations is the backward moonwalking of kinesin [25, 26, 28–34] under a backward load much larger than the stall force. There are reports that backward steps are related to ATP synthesis [33, 35] or ATP hydrolysis [31–34]. Another interesting question to be answered is why N-terminal kinesins move toward the microtubule plus ends, whereas C-terminal kinesins move toward the minus ends [27].

Although recent experiments on kinesin motors have produced detailed microscopic information on the dynamics of kinesin at the single molecule level, no simple and manageable physical model that can handle various dynamic features mentioned above has yet emerged. A new model, which is flexible enough to accommodate collective behavior of molecular motors [36–40] and to design characteristics of nano and micro-motors, would be anticipated [41, 42].

Recently, we have shown that an active particle model with a generalized energy depot produces the molecular motor-like walking motion under certain conditions [12]. This result motivated us to apply the generalized energy depot model to a kinesin motor walking along a microtubule in a biological environment. For this purpose, it is necessary to include an interaction between the kinesin molecule and the microtubule in an overdamped environment. The interaction between kinesin and microtubule can be described by an asymmetric ratchet potential [38, 39] since the microtubule could be considered as an asymmetric and periodic structure. It is worthwhile mentioning that our model could show a processive stepping motion without the asymmetric ratchet potential [12]. Hence, introducing the ratchet potential is not essential for processive stepping motion but rather to describe the existence of microtubule. The overdamping environment is introduced by neglecting the inertia of kinesin, since the mass of kinesin is very small. The energy supply from the ATP hydrolysis is modeled as a time-dependent energy pulse. We also introduce an external force against the forward motion of kinesin.

In Section 2, we briefly describe our generalized energy depot model of a Brownian particle. In Section 3, detailed applications to the system of a kinesin motor on a microtubule are discussed in an overdamped limit. In this case, the inertia term can be safely neglected. In Section 4, the results of numerical simulations are presented by choosing parameters realistically whenever possible. One of our results shows that the directionality of the active particle depends on its internal mechanism of energy conversion. This indicates that the present model is consistent with the experimental observation that the direction of kinesin movement depends on the kinesin species. Another result is the prediction of stalling force of 6 pN, which is also in good agreement with the known experimental value. We find that our simple and rather abstract model can successfully capture essential properties of kinesin. Concluding remarks follow in Section 5.

2 The generalized energy depot model

A Brownian particle moving in an external potential $U(x)$ is governed by the Langevin equation,

$$m \frac{dv}{dt} = -\mu_0 v - \frac{dU}{dx} + s\zeta, \quad (1)$$

where m is the mass, v the velocity of the particle, μ_0 the friction coefficient, and $s = \sqrt{2\mu_0 k_B T}$ with T being the temperature and k_B being the Boltzmann constant by the fluctuation-dissipation theorem. The random function $\zeta(t)$ is Gaussian white noise satisfying $\langle \zeta(t) \rangle = 0$ and $\langle \zeta(t)\zeta(t') \rangle = \delta(t - t')$.

If the Brownian particle can absorb energy from its environment, store the energy in its internal depot as an internal energy, and convert the internal energy into mechanical energy, then the motion of the Brownian particle is called active [11]. The energy balance equation for the internal depot $e(t)$ can be generally described as [11, 12]

$$\frac{de}{dt} = q(x, t) - ce - d(x, v)e, \quad (2)$$

where $q(x, t)$ is the energy influx to the depot from the environment, c the rate of internal dissipation of the depot assumed constant, and $d(x, v)$ the conversion rate of the internal energy into mechanical energy. Consequently, the Langevin equation for an active Brownian particle is written as

$$\begin{aligned} m \frac{dv}{dt} &= -\mu_0 v - \frac{dU}{dx} + f_{active} + s\zeta \\ &= -\mu v - \frac{dU}{dx} + s\zeta, \end{aligned} \quad (3)$$

where $f_{active} = d(x, v)e/v$ and $\mu = \mu_0 - d(x, v)e/v^2$.

It is convenient to rewrite the equations using dimensionless parameters marked with upper bars such as

$$\bar{x} = x/L, \quad \bar{t} = t/\tau, \quad \bar{e} = e/E, \quad \bar{U} = U/E, \quad \text{and} \quad \bar{\zeta} = \sqrt{\tau}\zeta, \quad (4)$$

where L , τ , and E denote the length, time, and energy scales, respectively. These scales will be defined using relevant parameters of the system considered. Hence, the equations of motion for an active Brownian particle can be rewritten as

$$\bar{m} \frac{d\bar{v}}{d\bar{t}} = -\bar{\mu} \bar{v} - \frac{\partial \bar{U}}{\partial \bar{x}} + \bar{s} \bar{\zeta}, \quad (5)$$

$$\frac{d\bar{e}}{d\bar{t}} = \bar{q} - \bar{c}\bar{e} - \bar{d}\bar{e}, \quad (6)$$

where $\bar{\mu} = \mu L^2/(E\tau)$.

In the next section, the generalized energy depot model is applied specifically to a system of a kinesin motor on a microtubule using realistic biological parameters for two-headed kinesin. Furthermore, we note that, although energy is a continuous quantity, the energy supply $q(x, t)$ in a system of kinesin motor is treated as a pulse-like quantity to reflect the energy input from ATP hydrolysis.

3 Model for kinesin motor on microtubule

In the previous work [12], it was shown that an active particle described by the generalized energy depot model can execute a stepping motion with a non-zero mass. The conversion rate $d(x, v)$ played a crucial role in the dynamics of the active particle and the stepping motion appeared when a velocity-dependent conversion rate was considered as

$$d(v) = a_1 v + a_2 v^2 + a_3 v^3 + a_4 v^4. \quad (7)$$

A constant term is not considered in the above expression since the constant contribution can be absorbed by c , the rate of internal dissipation in the energy balance (2). The effects of coefficients a_i have been discussed systematically in the previous work [12]. Motivated from the result of stepping motion, we study whether our simple model could describe realistic molecular motors.

In order to consider an interaction between the kinesin molecule and the microtubule, various types of asymmetric periodic potentials have been proposed [38–49]. Here we adopt a simple and typical asymmetric ratchet potential. Kinesin often carries vesicles, organelles, or cargoes while walking along a microtubule. Such a load is considered as a constant external force in our model for simplicity and the constant load can be generated by a force-feedback trap in experiments. Adopting the asymmetric ratchet potential $U_r(x)$ and an external force f_{load} in our model, the total potential $U(x)$ for the system of a kinesin motor on a microtubule can be expressed as

$$-\frac{dU}{dx} = -\frac{dU_r}{dx} + f_{load}. \quad (8)$$

The asymmetric ratchet potential $U_r(x)$ is described as

$$\begin{cases} \frac{U_0}{bL}(x - nL) & \text{if } nL \leq x \leq (n+b)L \\ \frac{U_0}{L-bL}((n+1)L - x) & \text{if } (n+b)L \leq x \leq (n+1)L \end{cases} \quad (9)$$

where b is the asymmetric parameter to be fixed at $1/3$ for simulation, $L (= 8 \text{ nm})$ is the distance between kinesin binding sites on the microtubule, which will be the length scale for the dimensionless parameter, and n runs as $0, 1, 2, \dots$ as shown in Fig. 1.

Fig. 1 Sketch of the asymmetrical ratchet potential representing the interaction between kinesin and microtubule: $U_r(x)$ (above) and sketch of the time-dependent energy influx supplied by the ATP hydrolysis: $q(t)$ (below)

It is well known that the two-headed kinesin motor walks along the microtubule with 8-nm step size, spending about 30 ms, on average, for each step and using around $25 k_B T$ released from the hydrolysis of one ATP [17, 18, 46, 47, 50]. This information can be used to define the energy flux $q(x, t)$ into the depot. In this model, we consider a time-dependent pulse-like energy flux $q(t)$ with randomness such as

$$q(t) = \begin{cases} q_0 r & \text{if } n\tau \leq t < (n + \gamma)\tau \\ 0 & \text{if } (n + \gamma)\tau \leq t < (n + 1)\tau \end{cases} \quad (10)$$

where n runs as $0, 1, 2, \dots$ as shown in Fig. 1. Here $q_0 = 25k_B T/\gamma\tau$, $\tau (= 30 \text{ ms})$ is the time for one step, γ is an adjustable parameter to make $\gamma\tau$ the actual energy-supply time, and r is a random number to control the effect of ATP concentration. In most of the previous models, q was assumed constant [11, 12]. However, the fact that energy is supplied only during the ATP hydrolysis process, taking about 7 ms [29, 46], while walking one step takes about 30 ms, motivates us to use the above pulse-like energy supply. The pulse-like energy influx implies that the time for energy supply is much shorter than that for one-step walking. We would like to point out that this is not the real situation, since ATP does not bind in regular time intervals. However, the regularly pumped energy supply in time seems to be sufficient to understand whether our generalized model of an active particle can describe the motions of molecular motors on cytoplasmic filaments. The analysis of an active Brownian motion using stochastic pulse-wise energy influx has been reported by another group [51]. Furthermore, binding of ATP to kinesin and the occurrence of hydrolysis depend on the concentration of ATP. The random number r will be generated such that $r = 1$ always for 100% ATP supply, which represents saturation. On the other hand, for 50% of ATP supply, we generate $r = 1$ in half the total occurrences and $r = 0$ in the other half. Here, we note that limping, or asymmetric walking motion, studied in some literature [24, 30] can readily be included in our model using different values of τ for even and odd steps. We do not consider the motor unbinding from the microtubule in this model.

As discussed in the previous section, in order to have the dimensionless equations of motion, we introduce the length, time, and energy scales as $L = 8 \text{ nm}$, $\tau = 30 \text{ ms}$, and $E = 25k_B T$, respectively. Considering that the molecular motors are highly overdamped, we neglect the inertia term. Hence the dimensionless equations of motion for the system of kinesin on a microtubule are

$$0 = -\bar{\mu}\bar{v} - \frac{d\bar{U}_r}{d\bar{x}} + \bar{f}_{load} + \bar{s}\bar{\zeta}, \quad (11)$$

$$\frac{d\bar{e}}{d\bar{t}} = \bar{q}(\bar{t}) - \bar{c}\bar{e} - \bar{d}(\bar{v})\bar{e}. \quad (12)$$

Equation (11) is a stochastic first-order differential equation. The relations between the dimensionless parameters and the original parameters and their numerical values are summarized in Table 1. We use a typical value of the friction coefficient of a motor

Table 1 Relations between the dimensional and dimensionless parameters

Dimensional parameter	Dimensionless parameter
$\mu_0 = 6 \text{ pN}\cdot\text{ms}/\text{nm}$	$\bar{\mu}_0 = L^2\tau^{-1}E^{-1}\mu_0 = 0.12$
$s = 7 \text{ pN}\sqrt{\text{ms}}$	$\bar{s} = L\tau^{-\frac{1}{2}}E^{-1}s = 0.1$
$U_0 = 7.5 k_B T$	$\bar{U}_0 = E^{-1}U_0 = 0.3$
$f_{load}^{stall(exp)} = 7 \text{ pN}$	$\bar{f}_{load}^{stall(exp)} = LE^{-1}f_{load}^{stall(exp)} = 0.55$
$q_0 = E/(\gamma\tau) = 25 k_B T/\text{ms}$	$\bar{q}_0 = \tau E^{-1}q_0 = 30$
$c = 0.17/\text{ms}$	$\bar{c} = \tau c = 5$

Note that $L = 8 \text{ nm}$, $\tau = 30 \text{ ms}$, $E = 25 k_B T = 25 \times 4.1 \text{ pN}\cdot\text{nm}$, and $\gamma = 1/30$

protein μ_0 [38, 47]. Using μ_0 at room temperature, the stochastic intensity is determined by $s = \sqrt{2\mu_0 k_B T}$. It is suggested that the magnitude of the ratchet potential energy U_0 might be roughly from one quarter to half of the energy supply [50]. We adopt $U_0 = 0.3E$. We simulate the model for several different values of load. The internal dissipation rate c of the depot is roughly determined to have 50% efficiency of kinesin motor.

4 Results of numerical simulations

For numerical simulation, we use the realistic values of biological parameters obtained by experiments as listed in Table 1 [25, 52] except for the stall force. The stall force will be obtained in our simulation and compared to the experimental value in Table 1 [25]. The dimensionless random noise $\bar{s}$ is estimated as 0.1 at room temperature, and after simulations it turned out not to affect significantly the dynamics of the system in the presently chosen parameters. Hence we investigate the dynamics in the deterministic manner ignoring the random noise effect in this study. However, we note that there is another stochastic contribution in the walking motion of the two-headed kinesin other than the thermal one. It is conjectured that in the waiting state, the head containing ADP diffuses between forward and backwards sites [26]. This stochastic diffusion is expected to contribute much more significantly than the thermal fluctuation. We do not include this contribution in the present study due to lack of quantitative information. The most important and crucial parameters for observing the walking motion in our model are $\bar{a}_1$, $\bar{a}_2$, $\bar{a}_3$, and $\bar{a}_4$, consisting of the dimensionless conversion rate $\bar{d}$ of internal energy into mechanical work. We search for relevant values of these parameters which show the forward and backward walking motions in a consistent way.

Equation (11) leads to a cubic equation for $\bar{v}$. We solve the cubic equation numerically and find the solution, $\bar{v}_s(\bar{x}, \bar{e})$. The ordinary differential equations are written as

$$\frac{d\bar{x}}{d\bar{t}} = \bar{v}_s(\bar{x}, \bar{e}), \quad (13)$$

$$\frac{d\bar{e}}{d\bar{t}} = \bar{q}(\bar{t}) - \bar{c}\bar{e} - \bar{d}(\bar{v}_s(\bar{x}, \bar{e}))\bar{e}. \quad (14)$$

Numerical integrations of (13) and (14) result in expressions for $\bar{x}(\bar{t})$ and $\bar{e}(\bar{t})$.

We search for a set of $\{\bar{a}_1, \bar{a}_2, \bar{a}_3, \bar{a}_4\}$, which generates the forward-stepping motion when there is no opposing load, and obtain $\{-10, 1, 0, 0.1\}$. There are no reasons to have only one set of $\bar{a}$ values for the description of motor dynamics in our model. However, the nonlinearity and complexity of $d(v)$ prevent us from pinpointing the physical meaning of each parameter, $\bar{a}_i$. Understanding the detailed meaning of our model will be our next step. In this report, we emphasize that our generalized active particle model could capture the essential features of a biological motor.

Figure 2 shows walking motions in the absence of any load. We simulate the directionality and the dependence on ATP concentration of the motion. Figure 2a and b are for 100% chance of ATP binding, which represents an ATP concentration at saturation. On the other hand, Fig. 2c and d correspond to 50% chance of ATP binding, which represents an ATP concentration lower than saturation. We observe that the kinesin motor moves faster at higher concentration, as observed in experiments. It is interesting that processive backward steps are observed when only $\bar{a}_4$ changes sign from positive to negative, while processive forward steps are observed for positive $\bar{a}_4$. When the velocity is not so fast, the directionality

Fig. 2 Processive forward and backward steps when $\tilde{f}_{load} = 0$ at two different ATP concentrations: **a** $\tilde{a}_4 = 0.1$ and 100% chance of ATP binding, **b** $\tilde{a}_4 = -0.1$ and 100% chance of ATP binding, **c** $\tilde{a}_4 = 0.1$ and 50% chance of ATP binding, **d** $\tilde{a}_4 = -0.1$ and 50% chance of ATP binding

of the active particle is determined by the linear term. However, when the particle speeds up, the v^4 -term dominates and determines the direction of motion. This result implies that the directionality comes from the internal mechanism ($d(v)$) of the active particle. This particle-dependent behavior supports the observation that the speed is negative in some particular family of kinesin motors [3, 53, 54]. It also indicates that our model is suitable to study not only N-terminal kinesins moving towards the microtubule plus ends but also C-terminal kinesins moving towards the minus ends [27]. Moreover, since our model considers energy supply by ATP hydrolysis, the result of processive backward steps with consuming one ATP and moving 8 nm at each step supports strongly that backward steps are triggered by ATP hydrolysis instead of ATP synthesis [25, 29, 34].

Since the present model successfully simulates the kinesin's walking motion without load at different ATP concentrations, we now test whether the model can produce a consistent walking motion and stalling behavior under load. In Figs. 3 and 4, the effects of the opposing load are simulated at 100% and 50% chances of ATP binding, respectively. When the load is not strong enough, such as $\tilde{f}_{load} = -0.3$, which corresponds to $f_{load} \simeq -3.8$ pN, the forward stepping motions are not changed whether the ATP concentration is saturated or not, as shown in Figs. 3a and 4a. This result agrees with the experiment [29],

Fig. 3 Dependence of motions on the opposing load $\tilde{f}_{load}$ at 100% chance of ATP binding: **a** $\tilde{f}_{load} = -0.3$ ($f_{load} = -3.8$ pN), **b** $\tilde{f}_{load} = -0.5$ ($f_{load} = -6.8$ pN), **c** $\tilde{f}_{load} = -0.6$ ($f_{load} = -7.7$ pN)

which reported that almost all steps are forward at loads lower than 4 pN. At high loads, such as $\tilde{f}_{load} = -0.6$, which corresponds to $f_{load} \simeq -7.7$ pN, our model shows backward slippages as shown in Figs. 3c and 4c. The velocity of the backward slippages at full energy supply in Fig. 3c is slower than the velocity at half of maximal energy supply in Fig. 4c, as expected. Figure 3b shows that the active particle does not move backwardly even with $\tilde{f}_{load} = -0.5$, which corresponds to $f_{load} \simeq -6.8$ pN, if the energy is fully supplied, whereas Fig. 4b shows again backward slippages, if the energy supply is half that shown in Fig. 3b.

To find the stall force and force dependence of the velocity, we plotted the velocity-force curves in Fig. 5 by simulating 100 times at each point with two different energy supplies. Stalling at which the velocity of the kinesin becomes zero occurs at $\tilde{f}_{load} = -0.49$ for full supply of energy and $\tilde{f}_{load} = -0.47$ for half supply of energy in our model. These values are close enough to claim that the stall force in our model does not depend on the ATP concentration sensitively. The corresponding stall force in real dimension is about 6 pN, which is comparable with the experimental value of 6–7 pN [16, 21, 29]. When the load is less than 4 pN, the average velocity does not depend on the load, but does depend on the ATP concentration. These results are in good agreement with the experimental reports.

Fig. 4 Dependence of motions on the opposing load $\tilde{f}_{load}$ at 50% chance of ATP binding:

a $\tilde{f}_{load} = -0.3$ ($f_{load} = -3.8$ pN), **b** $\tilde{f}_{load} = -0.5$ ($f_{load} = -6.8$ pN), **c** $\tilde{f}_{load} = -0.6$ ($f_{load} = -7.7$ pN)

Fig. 5 We simulate 100 times at each point with two different ATP supplies. Converting into real dimensions, we present the average and the square root of variance in velocity versus force of load. In the region of zero velocity, simulations with refined parameters are performed

5 Conclusions

In this paper, we have presented a simple physical model that can reproduce the salient points of the complicated walking motion of kinesin based on the generalized energy depot model of active particles. In the generalized energy depot model, one can control the motion of a particle through energy influx and internal energy conversion. For the kinesin motor system, we introduced pulse-like energy supplies and a specific velocity-dependent conversion rate function of internal energy into mechanical work. For the numerical simulation, we used experimentally known values of biological parameters for two-headed kinesin by designing the model so that the kinesin makes an 8-nm-wide step, consuming one ATP in the absence of load.

In our model, kinesin exhibited forward or backward stepping motion along the microtubule depending on the internal mechanism of the molecular motor in the absence of load. This result implies that the directionality of the kinesin motor could be determined by the intrinsic properties of kinesin consistent with observations. Through the processive backward steps in the absence of loads, our model supports the hypothesis that backward stepping is based on ATP hydrolysis. The kinesin motor is known to keep walking forward under loads less than 4 pN and stall at about 7 pN. It is also known that the stall force is not sensitive to the ATP concentration. Our model has produced all these properties qualitatively well, including the velocity-force curves for the saturating and non-saturating ATP concentrations.

Even though our simple model can capture the essential features of the kinesin motor successfully, our model does not describe the stochastic stepping, the ratio of forward to backward steps, and force-dependence of the dwell time between steps. Moreover, we do not understand the physical meaning of a_i in the internal energy conversion rate $d(v)$ and also the meaning of the internal energy depot for kinesin or any molecular motors. Efforts to understand these points will be our future work. If we succeed in analyzing the internal energy conversion mechanism more concisely, then the generalized active Brownian particle model [55] seems to describe the dynamics of various molecular motors as long as the realistic biological parameters for each motor species are adopted. For instance, our model can be readily applied to the walking motion of cytoplasmic dynein on microtubules alone or in tandem [56]. The collective operation of molecular motors can also be studied by our model using a synchronized energy supply $q(x, t)$ for the synchronized operation of coupled kinesin motors. Another interesting application of the present model is to the walking mechanism of micro or nano-robots since our model can generate diverse motions by controlling the energy influx $q(x, t)$ and the conversion rate $d(x, v)$ of an internal energy into mechanical energy.

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