Collective Motions of Molecular Machines under Non-equilibrium Condition with Chemo-mechanical Coupling

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Abstract—A physical mechanism of alternate motion of the double-headed processive motor is considered. Incorporating recent experimental observations, we introduce a model with load dependent transitions between states of motors. Our model explains the mechanism how randomly fluctuating motions can be converted into clocklike alternate motions. We investigate conditions under which the double-headed motor works as a collectively working processive motor.

1. Introduction

The processive motor, like kinesin or myosin V, is the most sophisticated enzyme protein to work as a single molecule, which has two motor domains moved alternately and walks along a rail protein[1]. Remarkable nature of the processive motor is the step which is tightly coupled to a chemical reaction cycle and maintained for several μm's until detachment occurs. Although the physical mechanism of this nature, which is called "processivity", has been studied in many experiments and models, the cooperative mechanism working between two heads is still not understood.

In the recent experiment by Uemura *et. al.*, the unbinding force of single kinesin-microtubule complexes was measured[2]. They showed that the binding affinity of ADP for kinesin depends on the direction of applied load along the microtubule. This result indicates that the enzyme activity of the motor is controlled by the internal strain, and hence the cooperativity of two motor domains can be generated. To understand the mechanism of the alternate motion, we extend the flashing ratchet model[3] by introducing load dependence of state transitions.

2. Model

We consider a double-headed motor which is composed of a bead particle and two motor particles ("heads") as shown in Fig.1. The bead particle diffuse on a flat potential and the motor particles diffuse on a potential $W(x_i, \theta_i)$, where x_i is the position and θ_i is the state of the motor particle ($i = 1, 2$). These particles are coupled by springs with the elastic constant K. An external load $-F$ is exerted on the bead particle, then equations of motions are expressed
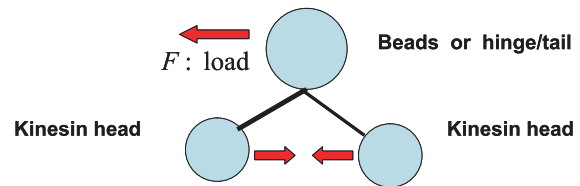

Figure 1: A model of double-headed motor, kinesin.

by following Langevin equations:

$$\gamma_0 \dot{x}_0 = -\sum_{i=1}^{2} K(x_0 - x_i) - F + R_0(t), \tag{1}$$

$$\gamma_i \dot{x}_i = -\frac{\partial}{\partial x_i} W_{\theta_i}(x_i) - K(x_i - x_0) + R_i(t), \tag{2}$$

where the natural length of the spring is assumed to be zero, γ_i is the viscosity coefficient, $R_i(t)$ is the white Gaussian noise with zero mean and the time correlation $\langle R_i(t)R_i(t')\rangle = 2\gamma_i k_B T \delta(t - t')$, where k_B is the Boltzmann constant and T is the absolute temperature. The subscript i here denotes the bead particle when $i = 0$ and the ith motor particle otherwise. Then we assume that the motor particles independently experience transitions between two states as shown in Fig.2.

Transition rates are supposed to depend on the force exerted to each motor particle $f_i = -K(x_i - x_0)$ and to be expressed as following Arrhenius type equations[4]:

$$k_0(x_i, f_i) = \tilde{k}_0(x_i) \cdot \frac{1}{z(s_0)} e^{\frac{f_i s_0}{k_B T}}, \tag{3}$$

$$k_1(x_i, f_i) = \tilde{k}_1(x_i) \cdot \frac{1}{z(s_1)} e^{-\frac{f_i s_1}{k_B T}}, \tag{4}$$

where s_0 and s_1 are characteristic lengths of the detachment reaction and the attachment reaction respectively. The normalization factor $z(s)$ is calculated so that the integration of the force dependent term about the Gaussian distribution of the distance $x_i - x_0$ is equal to 1. These parameters s_0 and s_1 represent characteristic lengths of internal fluctuation which is related to the affinity of nucleotides to motor domain to induce transition. The state trantion of molecular motor is better understood if the potential surface is considered in the space of position coordinate and reaction coordinate as shown in Fig. 3. When ATP is attached to the motor there is a high energy barrier between tightly binded
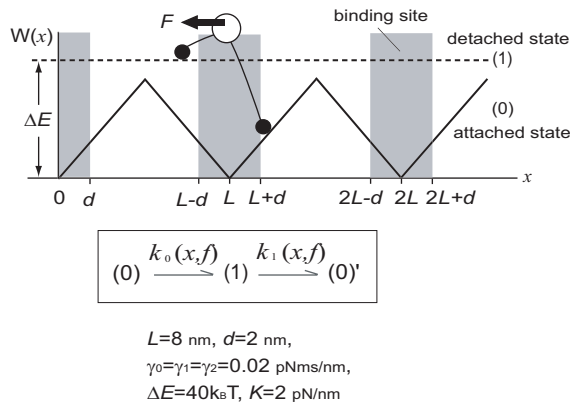
Figure 2: The schematic view of our model. A bead parti-
cle (open circle) and two motor particles (filled circle) are
elastically coupled. Each motor particle moves on the indi-
vidual potential which is switched between two states. One
is the symmetric potential with period L and energy height
ΔE (θ=0, the attached state), the other is the flat potential
(θ=1, the detached state). State transitions are assumed to
take place only when the motor particle is on the binding
site (shaded region). Parameter values are set as shown in
the lower right of this figure.

state ($\phi = 0$) and loosely coupled state ($\phi = 1$) as shown
in Fig. 3a. However, if the ATP is hydrolyzed the energy
barrier is highly reduced and the motor utilizes chemical
potential of ATP hydrolysis to detach from the $\phi = 0$ state
to the $\phi = 1$ state where the motor easily diffuse by the
thermal noise.

State transitions are assumed to take place only when the
motor particle is on the localized region around the poten-
tial minimum ("binding site");

$$\tilde{k}_{0,1}(x_i) = \begin{cases} \kappa_{0,1} & (0 \le \xi_i \le d, L - d \le \xi_i < L) \\ 0 & (otherwise) \end{cases}, \quad (5)$$

where κ_0 and κ_1 are constants, L is the potential period,
$\xi_i = x_i \bmod L$, and d satisfies $0 < d < \frac{L}{2}$. Additionally, mo-
tor particles are assumed not occupy the same binding site
simultaneously. On these assumptions, numerical simula-
tions are performed by integrating equations (2.1) and (2.2)
using an Euler scheme, and then state transitions of two
motor particles are independently calculated using equa-
tions (2.3)~(2.5).

With positive values of s_0 and s_1, the double-headed mo-
tor can show two types of motions. One is the alternate
motion where each step is tightly coupled to one transition
cycle (Fig.4), the other is the diffusional motion where both
heads are in detached state and undergo free Brownian mo-
tions. Because we are interested only in the alternate mo-
tion, here we observe the double-headed motor except in
the diffusional motion. In the numerical simulations we
calculate two parameters; the coupling ratio and the mean
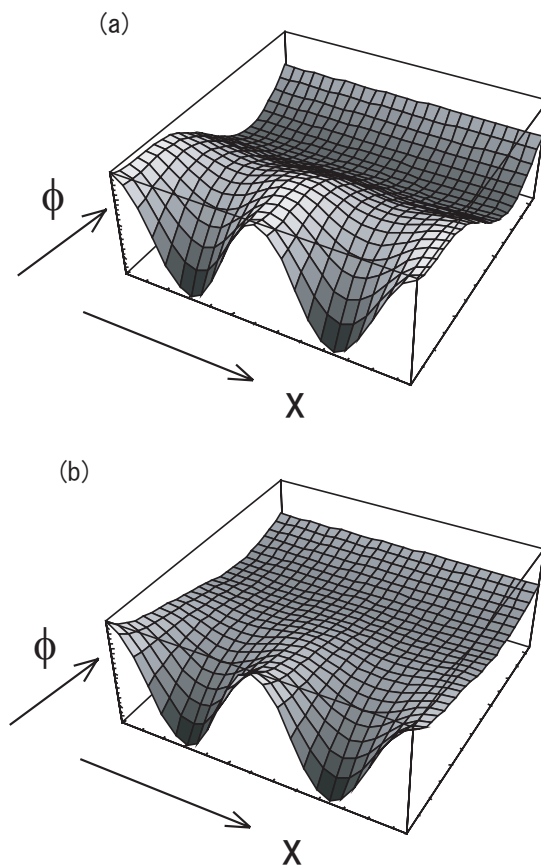run length, which characterize the alternate motion. Using

Figure 3: Vertual potential surfaces for a single head motor
as a function of position coordinate x and reaction coordi-
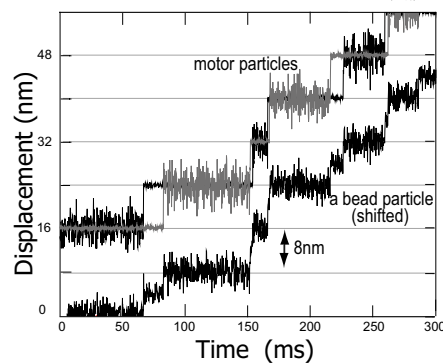nate ϕ.

Figure 4: An example of trajectories of the motor. Two
motor particles (upper black and gray lines) shows alter-
nate 8nm step and the bead particle (lower black line, 16nm
shifted down the positioin from its original position) shows
8nm or 4nm steps. 4nm step can be observed when the du-
ration in the state which both heads are attached to the track
is considerable. $s_0 = s_1 = 2.5$nm, $\kappa_0 = 0.97$/s, $\kappa_1 = 190$/s.

663

these parameters, we can evaluate the performance of the double-headed motor as a processive motor. The coupling ratio c is expressed by

$$c = V\tau_{\text{cycle}}/L, \tag{6}$$

where V is the mean velocity and τ_{cycle} is the average turnover time of one transition cycle. The value of c represents conversion efficiency of the transition cycle into the forward step. Namely, when $c = 1$, the forward step and the transition cycle are in one-to-one ratio and, when $c = 0$, the motor generates alternate but no directional motion. Additionally, $c = \frac{1}{2}$ is the ideal limit in flashing ratchet model with asymmetric on/off potentials because the probability of a forward step per one transition cycle never exceed $\frac{1}{2}$. Next we consider a carrying capacity of the motor by defining the mean run length as

$$l_{\text{mr}} = V\tau_{\text{mr}}, \tag{7}$$

where τ_{mr} is the average run time until both heads are detached simultaneously. The double-headed motor can be said to work not as a Brownian motor, but as a processive motor when l_{mr} is more than order of magnitude larger than L.

3. Local deviation from detailed balance

Here we note that the system with chemo-mechanical coupling has to satify the local detailed balance when the system aproaches to the equilibrium condition. The transition probabilities are defined as follows;

$$k_0(x_i, f_i) = \hat{k}_0(x_i)e^{f_i s_0/k_B T}, \tag{8}$$
$$k_1(x_i, f_i) = \hat{k}_1(x_i)e^{-f_i s_1/k_B T}. \tag{9}$$

If no energy is supplied to the system, the detailed balance has to be satisfied;

$$k_0(x, f) = k_1(x, f)\exp\left[\frac{W_0(x) - W_1(x)}{k_B T}\right]\exp\left[\frac{f(s_0 + s_1)}{k_B T}\right],$$
$$= k_1(x, f)\exp\left[\frac{U_0(x, f) - U_1(x, f)}{k_B T}\right], \tag{10}$$

where we denote modified potentials due to external force as $U_i(x, f) \equiv W_i(x) \pm f s_i$.

In the biologcal systems the detailed balance is broken most of the time by hydrolysis of ATP. That enables the system to generate mtion against external forces. Let us define a quantity characterize the local deviation from the detailed balance:

$$\Omega(x, f) = k_0(x, f) - k_1(x, f)\exp\left[\frac{W_0(x) - W_1(x) + f(s_0 + s_1)}{k_B T}\right]. \tag{11}$$

We assume that every hydrolysis event triggers transition of the motor from the state 0 to 1, and detachment of ADP

triggers transition from the state 1 to 0. Therefore the transition probabilities are modified due to chemical potential and the external force as follows;

$$k_0(x, f) = [\alpha(x)e^{\mu_{ATP}/k_B T} + \omega(x)]e^{(W_0(x) + f s_0)/k_B T},$$
$$k_1(x, f) = [\alpha(x)e^{(\mu_{ADP} + \mu_P)/k_B T} + \omega(x)]e^{(W_1(x) - f s_1)/k_B T},$$

where $\alpha(x)$ represents the transitions induced by the chemical reaction, and the $\omega(x)$ denotes the thermal excitation.

A simple calculation leads to

$$\Omega(x, f) = \alpha(x)e^{(W_0(x) + \mu_{ATP} + f s_0)/k_B T}(1 - e^{\Delta\mu/k_B T}), \tag{12}$$

where $\Delta\mu \equiv \mu_{ATP} - \mu_{ADP} - \mu_P$ denotes the energy release by an event of ATP hydrolysis. Note that in the limit of equilibrium condition, $\Delta\mu \to 0$, $\Omega(x, f)$ vanishes linearly with $\Delta\mu$. Thus the local detailed balance is satisfied.

By considering the case of no external force, we can deduce the relation that the detachment rate κ_0 and the attachement rate κ_1 have to saisify. In the equilibrium the condition $k_0 < k_1$ need to be satisfied by the fact

$$\Omega = k_0 - k_1 e^{(W_0 - W_1)/k_B T} = 0. \tag{13}$$

Therefore in general, if $W_0 < W_1$ is the case, $k_0 < k_1$ thus $\kappa_0 < \kappa_1$ follows. In the present work, we performed numerical simulation under this condition. We employed a rather strong condition, $\kappa_0 \ll \kappa_1$. This situation is expected when the hydrolysis term become dominant term in the ransition rate.

4. Result

First we show in Fig.5a the coupling ratio as a function of s_0 and s_1. The coupling ratio increases with s_0 and saturates to a constant value, which increases with s_1 and approaches to 1. Because s_0 and s_1 causes asymmetry in the detachment and attachment motion respectively, the initial increase in c is due to the increase of detachment probability of the trail head when both heads are in the attached state and the increase in the saturating value is due to the increase of probability of forward step when one of the heads is in detached state. We can say from this result that the transitions of two heads are converted into the cooperative alternate motions when enough large values of s_0 and s_1 are assigned. Next, the mean run length l_{mr} as a function of κ_0 and κ_1 are shown in Fig.5b. When we set values of s_0 and s_1 so that the forward step and the transition cycle is in one-to-one ratio, the mean run length decreases inversely to κ_0. This decrease in l_{mr} is due to the increase in the rate of detachment of both heads. The alternate motion can be said to become dominant against the Brownian motion when we set values of rate coefficients κ_0 and κ_1 so that the alternate step is maintained over long distance compared to step size L.

The load dependence of the speed of processive motor has been measured experimentally by Nishiyama et al..
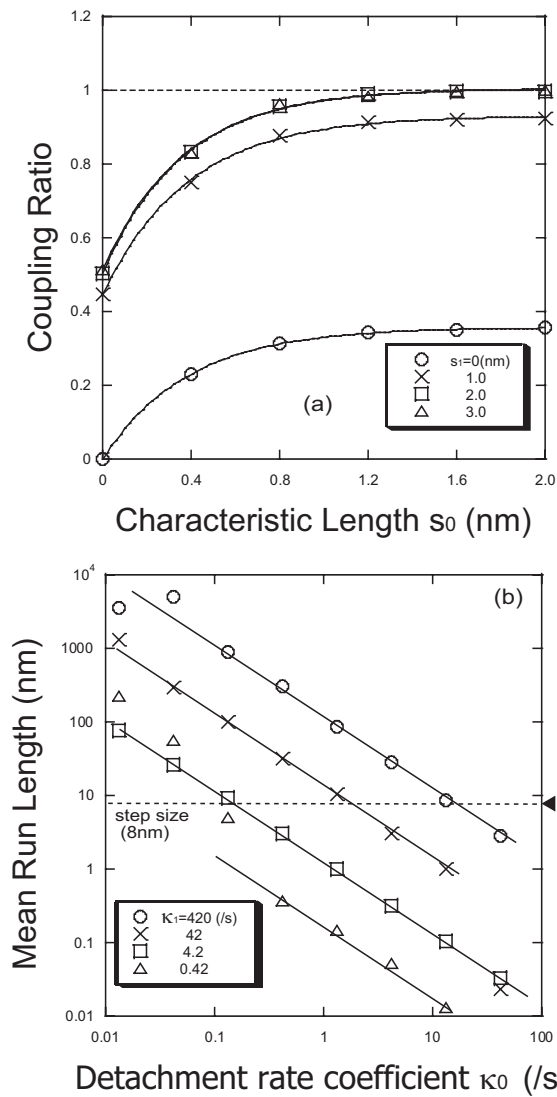
Here we also measured the load dependence of the speed in the numerical simulation. The obtained result (Fig. 6) reasonably agree with the experimental results.
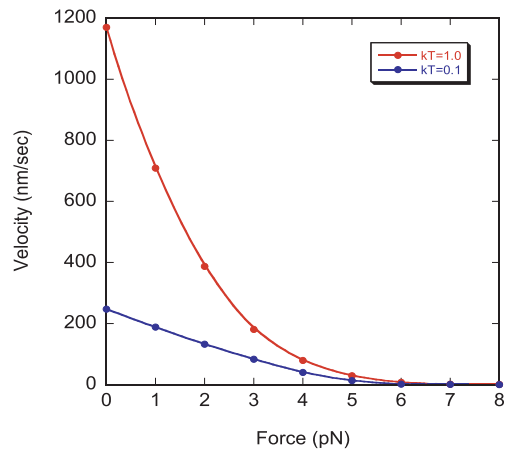
Figure 6: Speed of a two head motor as a function of loads.

As we see above, the double-headed motor can show the processive motion. There are four important factors for the processivity: characteristic lengths s_0 and s_1, which contribute to the coupling ratio, and transition rate coefficients κ_0 and κ_1, which contribute to the mean run length. When these parameters are assigned to proper values, the Brownian motion of coupled particles are converted into the clocklike motion. The values of κ_0 and κ_1 found in this work quantitatively agree with experimental observations[5]. The necessary value of s_0 and s_1 for the processivity is about 2nm, which is much smaller than the step size (8nm). This indicates that a small conformational change of the motor domain caused by external load induces regulated reactions. Thus coordination of two heads through the load dependent transitions is the essential mechanism to make a processive motor. The "lever action" of motor is not necessarily required.

References

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Figure 5: (a) The coupling ratio as a function of s_0 and s_1. Solid curves represent fitting curves denoted by $m_1 + m_2(1 - e^{-m_3 s_0})$, where m_1, m_2, m_3 are fitting parameters. Here the parameters; κ_0=0.42/s, κ_1=210/s. (b) The mean run length as a function of κ_0 and κ_1. Solid lines represent functions proportional to κ_0^{-1}. Here the parameters; $s_0 = s_1$=2.5nm.