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 \( \theta_i \) 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 by following Langevin equations:

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

\[
\gamma_i \dot{x}_i = - \frac{\partial}{\partial x_i} W_0(x_i) - K(x_i - x_0) + R_i(t),
\]

where the natural length of the spring is assumed to be zero, \( \gamma_i \) 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 \( i \)th 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]:

\[
k_0(x_i, f_i) = \tilde{k}_0(x_i) \cdot \frac{1}{z(s_0)} e^{-s_0 \frac{f_i}{k_B T}},
\]

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

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 tranition 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 particle (open circle) and two motor particles (filled circle) are elastically coupled. Each motor particle moves on the individual potential which is switched between two states. One is the symmetric potential with period $L$ and energy height $\Delta E$ ($\theta=0$, the attached state), the other is the flat potential ($\theta=1$, 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 ($\theta=0$) and loosely coupled state ($\theta=1$) 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 $\theta=0$ state to the $\theta=1$ 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 potential minimum ("binding site");

$$k_{\theta}(x,f) = \begin{cases} k_{0,1} & (0 \leq \xi_i \leq d, L - d \leq \xi_i < L) \\ 0 & (\text{otherwise}) \end{cases}, \quad (5)$$

where $k_0$ and $k_1$ are constants, $L$ is the potential period, $\xi_i = x_i \text{mod} L$, and $d$ satisfies $0 < d < \frac{L}{2}$. Additionally, motor particles are assumed not occupy the same binding site simultaneously. On these assumptions, numerical simulations 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 equations (2.3)~(2.5).

With positive values of $s_0$ and $s_1$, the double-headed motor 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 diffusionally motion where both heads are in detached state and undergo free Brownian motions. Because we are interested only in the alternate motion, 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: Virtual potential surfaces for a single head motor as a function of position coordinate $x$ and reaction coordinate $\phi$.

Figure 4: An example of trajectories of the motor. Two motor particles (upper black and gray lines) shows alternate 8nm step and the bead particle (lower black line, 16nm shifted down the position from its original position) shows 8nm or 4nm steps. 4nm step can be observed when the duration in the state which both heads are attached to the track is considerable. $s_0 = s_1 = 2.5\text{nm}$, $k_0 = 0.97/s$, $k_1 = 190/s$. 

$\Delta E$ is $0.02 \text{pNms/nm}$, $K$ is $2 \text{pN/nm}$.
these parameters, we can evaluate the performance of the double-headed motor as a processive motor. The coupling ratio \( c \) is expressed by

\[
e = V \tau_{cycle}/L,
\]

where \( V \) is the mean velocity and \( \tau_{cycle} \) 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

\[
l_{mr} = V \tau_{me},
\]

where \( \tau_{me} \) 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 satisfy the local detailed balance when the system approaches to the equilibrium condition. The transition probabilities are defined as follows:

\[
k_0(x,f) = \hat{k}_0(x)e^{\frac{-W_0(x)}{k_BT}},
\]

\[
k_1(x,f) = \hat{k}_1(x)e^{\frac{-W_1(x)}{k_BT}}.
\]

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

\[
k_0(x,f) = k_1(x,f) \exp\left[\frac{W_0(x) - W_1(x)}{k_BT}\right] \exp\left[\frac{f(s_0 + s_1)}{k_BT}\right],
\]

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

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

\[
\Omega(x,f) = k_0(x,f) - k_1(x,f) \exp\left[\frac{W_0(x) - W_1(x) + f(s_0 + s_1)}{k_BT}\right]
\]

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:

\[
k_0(x,f) = [\alpha(x)\mu_{ATP}/k_BT + \varphi(x)]e^{W_0(x) + f s_0}/k_BT,
\]

\[
k_1(x,f) = [\alpha(x)\varphi_{ADP}/k_BT + \omega(x)]e^{W_1(x) - f s_1}/k_BT,
\]

where \( \alpha(x) \) represents the transitions induced by the chemical reaction, and the \( \varphi(x) \) denotes the thermal excitation. A simple calculation leads to

\[
\Omega(x,f) = \alpha(x)e^{W_0(x) + \mu_{ATP} + f s_0}/k_BT \left( 1 - e^{-\Delta\mu/k_BT} \right),
\]

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, \( \Delta\mu \rightarrow 0 \), \( \Omega(x,f) \) 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 \( k_0 \) and the attachment rate \( k_1 \) have to satisfy. In the equilibrium the condition \( k_0 < k_1 \) need to be satisfied by the fact

\[
\Omega = k_0 - k_1 e^{(W_0-W_1)/k_BT} = 0.
\]

Therefore in general, if \( W_0 < W_1 \) is the case, \( k_0 < k_1 \) thus \( k_0 < k_1 \) follows. In the present work, we performed numerical simulation under this condition. We employed a rather strong condition, \( k_0 < k_1 \). This situation is expected when the hydrolysis term become dominant term in the transition 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 tail 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 \( k_0 \) and \( k_1 \) 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 \( k_0 \). 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 \( k_0 \) and \( k_1 \) 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 5](image)

**Figure 5:** (a) The coupling ratio as a function of $s_0$ and $s_1$. Solid curves represent fitting curves denoted by $m_1+m_2(1-e^{-m_3s_0})$, where $m_1$, $m_2$, $m_3$ are fitting parameters. Here the parameters; $\kappa_0=0.42$/s, $\kappa_1=210$/s. (b) The mean run length as a function of $\kappa_0$ and $\kappa_1$. Solid lines represent functions proportional to $\kappa_0^{-1}$. Here the parameters; $s_0 = s_1=2.5$nm.

**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 $\kappa_0$ and $\kappa_1$, 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 $\kappa_0$ and $\kappa_1$ 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**


