Dynamic transitions in coupled motor proteins

Evgeny B. Stukalin and Anatoly B. Kolomeisky

Department of Chemistry, Rice University, Houston, Texas 77005, USA
(Received 16 September 2005; published 24 March 2006)

The effect of interactions on dynamics of coupled motor proteins is investigated theoretically. A simple stochastic discrete model, which allows one to calculate explicitly the dynamic properties, is developed. It is shown that there are two dynamic regimes, depending on the interaction between the particles. For strong interactions the motor proteins move as one tight cluster, while for weak interactions there is no correlation in the motion of the proteins, and the particle separation increases steadily with time. The boundary between the two regimes is specified by a critical interaction that has a nonzero value only for the coupling of the asymmetric motor proteins, and it depends on the temperature and transition rates. At the critical interaction there is a change in slope for the mean velocities and a discontinuity in the dispersions of the motor proteins as a function of interactions.

Motor proteins are active enzyme molecules that are important for molecular transport, force generation, and transfer of genetic information in biological systems [1–3]. They move along the rigid linear tracks by utilizing the energy of hydrolysis of ATP or related compounds, and the chemical energy is transferred into the mechanical work with a high efficiency. However, the mechanisms of the mechanochemical coupling in the motor proteins are not fully understood [2].

Structural and biochemical studies of the motor proteins reveal that they consist of many domains [2–5], and frequently these subunits also have enzymatic activity. For example, for the multidomain helicase RecBCD [6], which corrects DNA breaks by unwinding the double-stranded DNA [7–10], it was found experimentally that it moves *significantly* faster than the individual subunits RecB and RecD which also work as helicase motor proteins [9]. The coordination and interaction between the internal domains might change significantly the dynamic properties of enzymes [11,12]. Motor proteins in cells frequently work in large groups [2,3], although the mechanism of such multiparticle coordinated motion is not well understood. In recent *in vivo* experiments [13] the transport of organelles by kinesin and dynein motor proteins, which move in opposite directions, has been investigated, and it was shown that they do not work against each other. Motor proteins moving in different directions coordinate the overall transport of vesicles and organelles. These experimental findings suggest that the interdomain coupling and interactions between different proteins have a strong effect on functioning of these biological molecules. However, theoretical understanding of these phenomena is still limited [2,14,15]. Recently, we proposed a simplified theoretical approach to explain the dynamic properties of multidomain motor proteins by accounting for the interactions [15], and it was successfully applied to understand the dynamics of single RecBCD helicases. The purpose of this work is to investigate the general effect of interactions inside the motor proteins and between the molecules on dynamics for more realistic biological transport models.

We assume that there are two interacting particles that move along parallel tracks, as shown in Fig. 1. This model describes the motion of helicases with two active subunits on different DNA strands [15], or it might correspond to the transport of two interacting motor proteins (kinesins, dyneins) on parallel filaments (microtubules). The positions of the particles A and B are defined by integers l and m, respectively, on the corresponding lattices. It is assumed that the
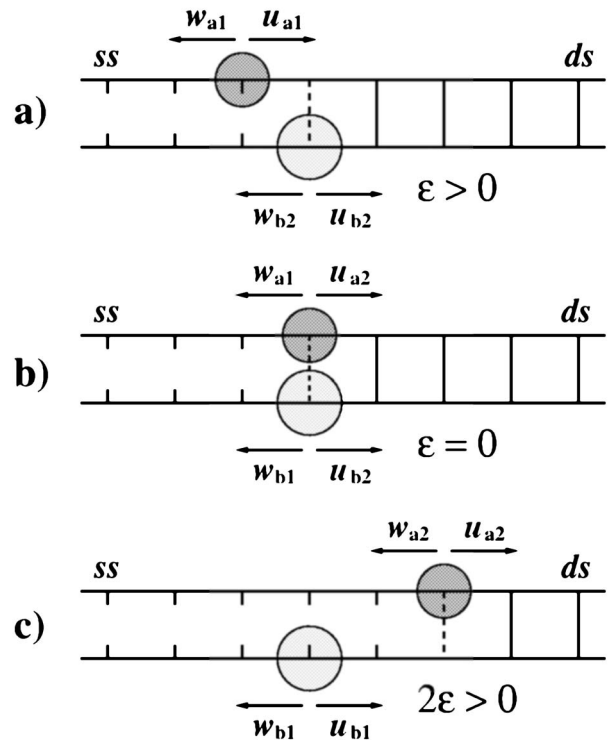

FIG. 1. Schematic view of the motion of two interacting motor proteins. Transition rates u_{ai} and w_{ai} ($i=1$ or 2) describe the motion of the particle A (small circles), while u_{bi} and w_{bi} are the transition rates for the particle B (large circles). The first subscripts a and b for all transition rates refer to the particles A and B, respectively. The second subscripts 1 describe the trailing subunit, while the second subscripts 2 are for the leading particle. Any configuration is specified by the integers l and m for the positions of the particle A and B, correspondingly. The energy of interaction in the configuration (l,m) is equal to $|l-m|\varepsilon \geq 0$.

interaction between particles favors compact vertical configurations, while the potential energy of the nonvertical configurations is larger, $U(l,m) = U_0 + \varepsilon|l-m|$, where the parameter $\varepsilon \geqslant 0$ specifies the coupling. This potential seems realistic for the motion of some helicases [6], where at each step of the leading subunit the bond between two strands of DNA should be broken, and it leads to approximately linear dependence of the interaction energy on the distance between the subunits. In addition, in the transport of motor proteins (kinesins, dyneins, myosins) along parallel filaments (actin filaments, microtubules) an effectively linear potential of interactions might appear as a result of complex interactions with the molecular tracks and/or motor protein's cargo. Note that in contrast to the previous theoretical approach [15], in this more realistic model of the biological transport the particles are allowed to move without any restrictions on distances between them.

We introduce $P(l,m;t)$ as the probability to find the system in the configuration where A is at the position l on the first track and B is at the position m on another track at time t. The dynamics of the system is described by a set of transition rates that depend not only on the particle type, but also on the position of the particles. For configurations $(l \pm k, l)$ $[k \geqslant 1]$, the trailing particle can move forward (backward) with a rate u_{j1} (w_{j1}), where $j = a$ or b corresponds to the particle A or B, respectively. At the same time, the leading particle can jump forward (backward) with a rate u_{j2} (w_{j2}). For the vertical configurations (l,l) each particle can hop forward with the rate u_{j2} or it can move backward with the rate w_{j1}; see Fig. 1. Note that in our model the transition rates do not depend on the particle separation $k = |l-m|$, but only on the "type" of transition: where it leads to a more (k decreases) or less compact (k increases) configuration. This is a property of the linear potential of interaction, which leads to the energy difference between two consecutive configurations being equal to ε, independent of the particle separation k. The transition rates are related via the detailed balance relations

$$\frac{u_{j1}}{w_{j1}} = \frac{u_j}{w_j}\exp(+\varepsilon/k_B T), \quad \frac{u_{j2}}{w_{j2}} = \frac{u_j}{w_j}\exp(-\varepsilon/k_B T), \quad (1)$$

with $j = a$ or b, and where u_j and w_j are the hopping rates in the case of no interaction between the particles ($\varepsilon = 0$).

The dynamics of the system is governed by a set of master equations for the probability distribution function $P(l,m;t)$,

$$\frac{dP(l,l;t)}{dt} = u_{a1}P(l-1,l;t) + w_{a2}P(l+1,l;t)$$

$$+ u_{b1}P(l,l-1;t) + w_{b2}P(l,l+1;t)$$

$$- (u_{a2} + w_{a1} + u_{b2} + w_{b1})P(l,l;t); \quad (2)$$

$$\frac{dP(l,l-k;t)}{dt} = u_{a2}P(l-1,l-k;t) + w_{a2}P(l+1,l-k;t)$$

$$+ u_{b1}P(l,l-1-k;t) + w_{b1}P(l,l+1-k;t)$$

$$- (u_{a2} + w_{a2} + u_{b1} + w_{b1})P(l,l-k;t); \quad (3)$$

$$\frac{dP(l-k,l;t)}{dt} = u_{a1}P(l-1-k,l;t) + w_{a1}P(l+1-k,l;t)$$

$$+ u_{b2}P(l-k,l-1;t) + w_{b2}P(l-k,l+1;t)$$

$$- (u_{a1} + w_{a1} + u_{b2} + w_{b2})P(l-k,l;t). \quad (4)$$

At all times these probabilities satisfy the normalization condition $\sum_{l=-\infty}^{+\infty}\sum_{m=-\infty}^{+\infty} P(l,m;t) = 1$. The solutions of the master equations can be found be summing over all integers l and m at the fixed particle separation k. Defining new functions

$$P_{0,0}(t) = \sum_{l=-\infty}^{+\infty} P(l,l;t), \quad P_{0,k}(t) = \sum_{l=-\infty}^{+\infty} P(l,l-k;t),$$

$$P_{1,k}(t) = \sum_{l=-\infty}^{+\infty} P(l-k,l;t), \quad (5)$$

it can be shown then that in the stationary-state limit

$$P_{0,k} = P_{0,0}(\beta_0)^k, \quad P_{1,k} = P_{0,0}(\beta_1)^k, \quad (6)$$

where

$$\beta_0 = \frac{u_{a2} + w_{b1}}{u_{b1} + w_{a2}}, \quad \beta_1 = \frac{u_{b2} + w_{a1}}{u_{a1} + w_{b2}}. \quad (7)$$

These auxiliary functions play a critical role in our analysis. When $\beta_0 < 1$ and $\beta_1 < 1$, using the conservation of probability, we obtain

$$P_{i,k} = \frac{(1-\beta_0)(1-\beta_1)}{1 - \beta_0\beta_1}(\beta_i)^k, \quad i = 0,1. \quad (8)$$

This means that the vertical configuration ($k=0$) is the most probable one, and the probabilities of the less compact configurations are exponentially decreasing functions of the particle separation k. In this regime the particles A and B correlate their motion. From the knowledge of the stationary probabilities and the transition rates, the dynamic properties of the system, such as the mean velocity V and dispersion (effective diffusion constant) D of the center of mass, can be calculated as

$$V_{\text{c.m.}} = \frac{1}{1 - \beta_0\beta_1}[(u_{a2} - \beta_0 w_{a2})(1-\beta_1)$$

$$+ (u_{b2} - \beta_1 w_{b2})(1-\beta_0)], \quad (9)$$

and

$$D_{\text{c.m.}} = \frac{1}{1 - \beta_0\beta_1}\left[\left(\frac{1}{2}(u_{a2} + \beta_0 w_{a2}) - \frac{(A_0 + w_{a2})(u_{a2} - \beta_0 A_0)}{u_{b1} + w_{a2}}\right)\right.$$

$$\times (1-\beta_1) + \left(\frac{1}{2}(u_{b2} + \beta_1 w_{b2})\right.$$

$$\left.\left. - \frac{(A_1 + w_{b2})(u_{b2} - \beta_1 A_1)}{u_{a1} + w_{b2}}\right)(1-\beta_0)\right] \quad (10)$$

where the coefficients A_i are given by

$$A_0 = \frac{\beta_1(u_{a1} - u_{a2}) + \beta_0\beta_1 w_{a2} - w_{a1}}{1 - \beta_0\beta_1},$$

$$A_1 = \frac{\beta_0(u_{b1} - u_{b2}) + \beta_0\beta_1 w_{b2} - w_{b1}}{1 - \beta_0\beta_1}. \tag{11}$$

The dynamic properties of the individual particles coincide with the dynamic properties of the center of mass of the motor protein cluster, and it can be shown that the average distance L between the particles is always finite (in units of lattice spacings),

$$L = \frac{1}{1 - \beta_0\beta_1}\left(\frac{\beta_0(1 - \beta_1)}{1 - \beta_0} + \frac{\beta_1(1 - \beta_0)}{1 - \beta_1}\right). \tag{12}$$

The situation is different when at least one of $\beta_i > 1$ ($i=0$ or 1). Then from Eq. (6) it can be concluded that less compact configurations (large k) dominate the steady-state dynamics of the system. In this regime the particles A and B move independently from each other with mean velocities (assuming A is the leading particle)

$$V_A = u_{a2} - w_{a2}, \quad V_B = u_{b1} - w_{b1}, \tag{13}$$

and dispersions

$$D_A = (u_{a2} + w_{a2})/2, \quad D_B = (u_{b1} + w_{b1})/2. \tag{14}$$

The dynamic properties of the center of mass of the motor protein cluster are given by

$$V_{\text{c.m.}} = \tfrac{1}{2}(V_A + V_B), \quad D_{\text{c.m.}} = \tfrac{1}{4}(D_A + D_B). \tag{15}$$

Furthermore, the average particle-particle separation L is steadily increasing with time.

The boundary between two dynamic regimes is determined by the condition $\beta_0 = 1$ and $\beta_1 < 1$, or $\beta_1 = 1$ and $\beta_0 < 1$. Using the detailed balance (1), it can be argued that

$$u_{j1} = u_j \gamma^{1-\theta_{j1}}, \quad w_{j1} = w_j \gamma^{-\theta_{j1}},$$

$$u_{j2} = u_j \gamma^{-\theta_{j2}}, \quad w_{j2} = w_j \gamma^{1-\theta_{j2}}, \tag{16}$$

where $\gamma = \exp(\varepsilon/k_B T)$, and $j = a$ or b. The coefficients θ_{ji} are energy-distribution factors that determine the effective splitting of the interaction energy between the forward and backward transitions [2,14,15]. In the simplest approximation, we assume that all energy-distribution factors are approximately equal to each other, $0 \leq \theta_{ji} \approx \theta \leq 1$, because they describe similar transitions in the motion of the individual motor proteins [15]. More general situation with state-dependent energy-distribution factors can also be analyzed. Substituting Eq. (16) into the expressions (7), we obtain

$$\beta_0 \gamma = (\beta_1 \gamma)^{-1} = (u_a + w_b)/(u_b + w_a). \tag{17}$$

Then the boundary between two dynamic regimes corresponds to the critical value of the interaction energy,

$$\varepsilon_c = k_B T \left| \ln\left(\frac{u_a + w_b}{u_b + w_a}\right) \right| \geq 0. \tag{18}$$

It is important to note that the critical interaction depends on temperature, and in the transport of the identical particles
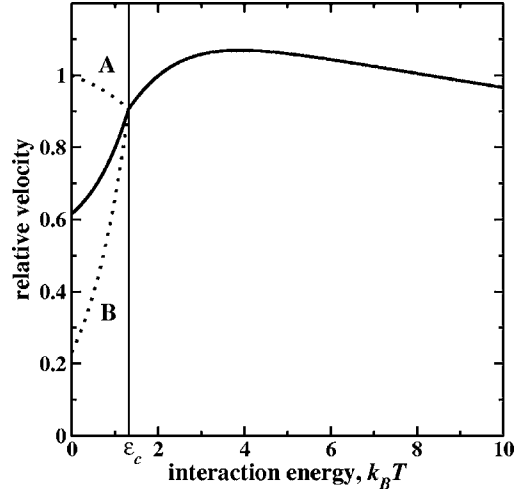

FIG. 2. Relative velocities (with respect to the motion of a free particle A) for the coupled motor proteins as a function of the interaction energy. Solid line corresponds to the relative velocity of the center of mass of the particles, while the dotted lines are the relative velocities of the individual particles below the critical interaction. The parameters used for calculations are $u_a=4$, $w_a=0.1$, $u_b=1$, $w_b=0.1$, and $\theta=0.02$.

($A=B$) it is always zero. The dynamic transition can only be observed for the coupling of the asymmetric motor proteins.

The existence of two dynamic regimes in the transport of interacting asymmetric motor proteins can be understood as follows. Consider the configuration where the particle A is k sites ahead of the particle B and $\varepsilon=0$. The effective rate of the transition to configurations where two particles are separated by $k+1$ sites is equal to $u_a + w_b$, while the effective rate for $k+1 \rightarrow k$ transition is $u_b + w_a$. The free energy change of making the particle configuration less compact ($k \rightarrow k+1$) can be written as $\Delta G(0) = -k_B T \ln\left(\frac{u_a+w_b}{u_b+w_a}\right) < 0$ [2,16], assuming that $u_a + w_b > u_b + w_a$. If there is interaction between the particles, then the free energy change increases, $\Delta G(\varepsilon) = \Delta G(0) + \varepsilon$. The boundary between two regimes corresponds to $\Delta G(\varepsilon_c) = 0$, and it leads to $\varepsilon_c = |\Delta G(0)|$. Thus, for strong interactions ($\varepsilon > \varepsilon_c$), it is energetically unfavorable to make less compact configurations. The particles cannot run away from each other, and they move as one tightly coupled cluster. For weak interactions ($\varepsilon < \varepsilon_c$), the favorable free energy change of making a less compact particle configuration cannot be compensated by the energy of interaction. As a result, the distance between particles grows linearly with time, and they move in uncorrelated fashion. The dynamic properties of interacting motor proteins are different in the two regimes, as shown in Figs. 2 and 3. The mean velocity of the center of mass changes the slope at the critical energy of interaction, while the mean velocities of the individual particles converge to a single value (Fig. 2). The effect of the interaction is much stronger for the dispersions. There is a jump in the mean dispersion of the center of mass at the transition, and the mean dispersions of the individual particles do not converge to a single value (Fig. 3). This discontinuity in the dispersions is a striking feature of the transition. It can also be hypothesized that this dynamic transition might work in
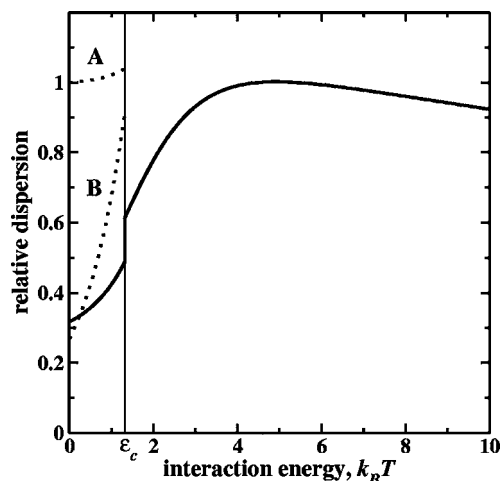
FIG. 3. Relative dispersions (with respect to the motion of a free particle A) for coupled motor proteins as a function of the interaction energy. Solid line corresponds to the relative dispersion of the center of mass of the particles, while the dotted lines are the relative dispersions of the individual particles below the critical interaction. The parameters used for calculations are the same as in Fig. 2.

cells as a controlling mechanism that switches off the protein function at undesirable conditions.

For illustration consider a simplified model of the interacting motor proteins that can only step forward, i.e., $w_a = w_b = 0$. This model seems reasonable for the description of RecBCD transport [15], since the experiments indicate that the backward transition rates are small [17]. Assuming that A moves faster than B, the critical interaction can be written as $\varepsilon_c = k_B T \ln(u_a/u_b)$. For RecBCD proteins, where the transition rates for subunits can be approximated as $u_a = 300$ and $u_b = 73$ base pairs (bp)/s [15], the critical interaction is $\varepsilon_c \approx 1.4 k_B T$. Theoretical analysis [15] estimates the energy of interaction between the subunits in RecBCD as $\approx 6 k_B T$, implying that this motor protein moves in the strong coupling regime, in agreement with experiments [7–10]. Using Eqs. (9)–(11), it can be shown that for large interactions the dynamic properties of the system are given by

$$V_{\text{c.m.}}(\varepsilon \geqslant \varepsilon_c) = \frac{(u_a + u_b)\gamma^{-\theta}}{1 + \gamma^{-1}},$$

$$D_{\text{c.m.}}(\varepsilon \geqslant \varepsilon_c) = V_{\text{c.m.}}\left(1 - \frac{2}{\gamma(1 + \gamma^{-1})^2}\right). \quad (19)$$

In the weak coupling regime, from the expressions (13)–(15) it can be derived that

$$V_{\text{c.m.}}(\varepsilon \leqslant \varepsilon_c) = (u_a + u_b \gamma)\gamma^{-\theta}, \quad D_{\text{c.m.}}(\varepsilon \leqslant \varepsilon_c) = V_{\text{c.m.}}/8. \quad (20)$$

The jump in the dispersions at the critical interaction is equal to

$$\Delta D = (u_a/4)(u_a/u_b)^{-\theta}\left(2\frac{u_a^2 + u_b^2}{(u_a + u_b)^2} - 1\right) > 0. \quad (21)$$

Although for this simplified model the dispersion jump is always positive, in general this discontinuity might have any sign.

The presented theoretical analysis is based on a simplified picture that neglects many important features of the biological transport. The intermediate biochemical states, sequence dependence, and protein flexibility have not been taken into account in this approach. However, it is expected that these phenomena will not change the main prediction of our analysis—the existence of the dynamic transitions specified by interactions between the particles. The most crucial assumption in our approach is the use of the linear potential of interactions. An important question is if the predicted dynamic transitions will survive for more realistic potentials, but the linear coupling can be experimentally observed, for example, by exerting forces on two motor proteins by optical traps [11,17], while keeping the difference between the forces constant at all times.

In summary, the effect of interactions in motor proteins is investigated by analyzing explicitly a simple stochastic model. Using the exact formulas for the dynamic properties, it is shown that there are two dynamic regimes for asymmetric motor proteins depending on the coupling energy. Below the critical interaction the particles do not correlate with each other, while above the critical interaction the particles move as a tight cluster. The origin of these phenomena is the balance between the chemical free energy change and the change in the energy of interactions. It is suggested that the dynamic transitions might play an important role in the functioning of proteins. This theoretical approach proposes a new way of investigating and controlling biological transport processes at the nanoscale level.

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