Chemically Driven Motility of Brownian Particles

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A simple model is devised to show that an enzymatic Brownian particle in a *static* electric field can undergo directional movement when coupled with a *nonequilibrium* chemical reaction which the particle catalyzes, if at least one of the intermediate states of the catalytic cycle is charged. The direction of the movement depends not only on the asymmetry of the electric field, but also on the direction of the chemical reaction and the mechanism of the catalytic cycle. The Brownian particle can also move against an external load and thus do mechanical work. This study suggests that enzyme molecules could be separated based on their enzymatic activities. The formalism developed in this paper can be extended and applied to biological motors. [S0031-9007(96)00487-5]

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Recently the directional movement of Brownian particles in a periodic potential has attracted considerable attention [1–7]. It is known that the long-time movement of a Brownian particle is not directionally biased in the presence of a periodic potential if the potential is *static*. But, if the potential is asymmetric within a period and is randomly or regularly switched on and off (so that the force acting on the particles fluctuates), then a net directional movement of the particle can be achieved [1–5]. As in other cases of external fluctuation-induced free energy transduction [8–12], energy from a fluctuating force field is thus found to be able to do mechanical work. Experiments using oscillating electric fields have not only confirmed the existence of directional movement but also shown that particles with different charges or electric properties could be separated [3,4]. In this Letter, we demonstrate with a simple model that a Brownian particle can execute directional movement in a *static* (*nonfluctuating*) periodic electric field when coupled with a nonequilibrium chemical reaction. In other words, the free energy of a nonequilibrium chemical reaction can be directly transduced by a Brownian particle to do mechanical work. The general principle of the model can be tested experimentally and should prove useful in biomolecular separation. Moreover, the formalism developed here can be generalized and used for analyzing the motility of single biological motors *in vitro*, where the effect of Brownian motion may be important.

As shown in Fig. 1(a), the Brownian particle E is considered as an enzyme that catalyzes the breakdown of AB into A^+ and B^-. For simplicity, we consider only the reduced scheme in Fig. 1(b). However, the general conclusions discussed below are expected to be applicable to Fig. 1(a) or other more complicated kinetic schemes. The chemical reaction ($AB \rightarrow A^+ + B^-$) is assumed to be inhibited in the absence of E and the concentrations of AB, A^+, and B^- in solution are assumed to be time independent. We want to study the movement of this chemi-

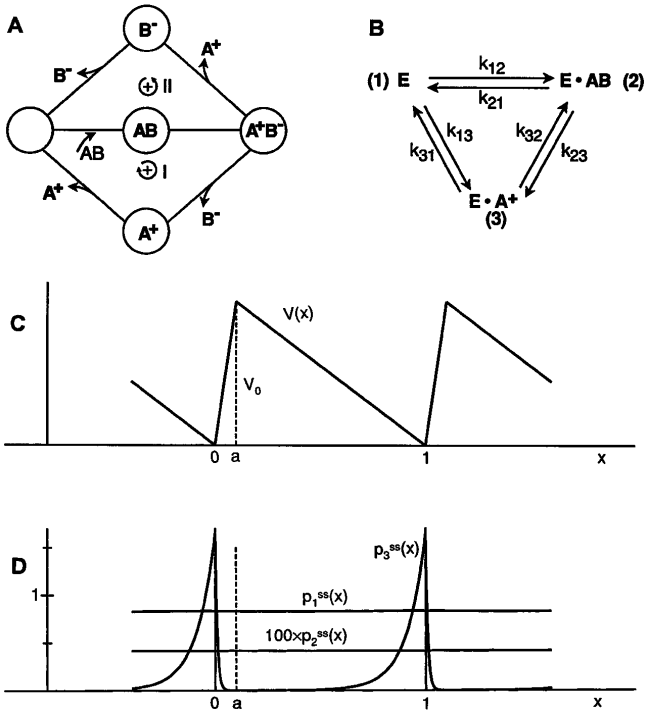

FIG. 1. (a) A kinetic mechanism for the reaction $AB \leftrightarrow A^+ + B^-$ which is catalyzed by the enzymatic Brownian particle (symbolized by a circle). (b) The reduced kinetic scheme after neglecting cycle II and assuming that the bond-breaking step is much faster then the binding of AB to the Brownian particle, which is denoted as E (to emphasize its enzymatic character). This three-state scheme is used for all the results reported here. (c) A periodic piece-linear potential $V(x)$ that is assumed to act on the enzymatic Brownian particle only when it is in state 3. The potential is asymmetric when $a \neq 1/2$. (d) The steady-state probabilities calculated using parameters in Table I and $[AB]/[AB]^{eq} = 10$.

TABLE I. Parameters of the model used in the calculations. Detailed balance dictates that $k_{21}\alpha_{32}\alpha_{13}/\alpha_{12}k_{23}k_{31} = K$.

$k_{12} = \alpha_{12}[AB] = 0.02[AB]$	$k_{21} = 20.0$
$k_{23} = 20.0$	$k_{32} = \alpha_{32}[B^-](x) = 0.2[B^-](x)$
$k_{31} = 1.0$	$k_{13} = \alpha_{13}[A^+](x) = 0.1[A^+](x)$
$\langle[A^+]\rangle = 1.0$	$\langle[B^-]\rangle = 1.0$
$K = 1.0$	$[AB]^{\mathrm{eq}} = 1.0$
$a = 0.1$	$V_0 = 10.0$
$[A^+](x) = \langle A^+\rangle \exp(-V)/\langle\exp(-V)\rangle^*$	$[B^-](x) = \langle B^-\rangle \exp(V)/\langle\exp(V)\rangle$
$[AB]^{\mathrm{eq}}_{\mathrm{loc}} = [AB]^{\mathrm{eq}}/\langle\exp[-V(x)]\rangle\langle\exp[V(x)]\rangle = 4.54 \times 10^{-3}$	

*Angular brackets signify taking average over one period of the potential.

cally coupled Brownian particle E when it is interacting with a periodic and asymmetric potential as that in Fig. 1(c). Let us assume that the particle E is influenced by the potential $V(x)$ only in state 3 [this occurs naturally if $V(x)$ is an electric potential]. In general $V(x)$ can be viewed as a potential of mean force or a free energy function (see below). For this part of the paper, $V(x)$ is taken as an electric potential. Thus the concentrations of the ionic species A^+ and B^- adopt Boltzmann distributions: $[A^+](x) = \langle[A^+]\rangle \exp[-V(x)]/\langle\exp[-V(x)]\rangle$ and $[B^-](x) = \langle[B^-]\rangle \exp[V(x)]/\langle\exp[V(x)]\rangle$, where the angular brackets $\langle\ \rangle$ represent averaging over one period. As a result, two pseudo-first-order rate constants (k_{13} and k_{32}; see Table I) are x dependent. The local equilibrium concentration of AB, $[AB]^{\mathrm{eq}}_{\mathrm{loc}} = K[A^+](x)[B^-](x)$, where K is the equilibrium constant of the chemical reaction in solution, is x independent. Note that if $V(x)$ were absent, the equilibrium concentration of AB would be $[AB]^{\mathrm{eq}} = K\langle[A^+]\rangle\langle[B^-]\rangle$, which is higher than $[AB]^{\mathrm{eq}}_{\mathrm{loc}}$. The chemical reaction is out of equilibrium when $[AB] \neq [AB]^{\mathrm{eq}}_{\mathrm{loc}}$.

The probabilities $p_i(x,t)$ of finding E at x and in state i at time t obey the diffusion-reaction equations [13],

$$\partial p_i/\partial t = -\partial u_i/\partial x + \sum_{j\neq i} k_{ji}p_j - p_i \sum_{j\neq i} k_{ij}\,, \quad (1)$$

$$u_i = -\partial p_i/\partial x - z_i p_i dV/dx\,, \quad (2)$$

$i = 1, 2$, and 3, where z_i are used to select the state in which the potential is active ($z_1 = z_2 = 0$ and $z_3 = 1$). For convenience, the quantities x, t, V, and k_{ij} have been made dimensionless. They are related to the corresponding physical quantities (signified by a bar over each symbol) through $x = \bar{x}/L$, $t = D\bar{t}/L^2$, $V = \bar{V}/k_BT$, and $k_{ij} = L^2\bar{k}_{ij}/D$, where L is the length of the period of the potential, D is the diffusion constant of the particle, and k_BT is the product of Boltzmann's constant and the temperature. By summing over the three states in Eq. (1), one has $\partial p(x,t)/\partial t = -\partial u/\partial x$ where $p(x,t) = \sum_i p_i(x,t)$ and $u = \sum_i u_i$. At steady state, $\partial p(x,t)/\partial t = 0$. This implies that u is either zero or a constant quantity that is independent of x. Since $V(x)$ is periodic, both p_i and u_i are also periodic at steady state. It can be shown [14] that if the steady-state probabilities $p_i^{\mathrm{ss}}(x)$ of Eq. (1) satisfy the normalization condition

$$\sum_i \int_0^1 p_i^{\mathrm{ss}}(x)\,dx = 1\,, \quad (3)$$

then this constant u is equal to the *long time velocity* of the Brownian particle. The rate of breakdown of AB at steady state can be evaluated as

$$J = \int_0^1 [k_{12}p_1^{\mathrm{ss}}(x) - k_{21}p_2^{\mathrm{ss}}(x)]\,dx\,. \quad (4)$$

Identical results for J can be obtained using either of the other two sides of the catalytic cycle in Fig. 1(b). The rate of dissipation of chemical free energy is $J\Delta G$, where $\Delta G = \ln([AB]/[AB]^{\mathrm{eq}})$ and $[AB]^{\mathrm{eq}}$ is the equilibrium concentration of AB.

The steady-state solutions of Eqs. (1) and (2) were obtained numerically using the finite-difference method and the steady-state probabilities thus obtained were then used to calculate u and J from Eqs. (2) and (4). The parameters used in the calculations for the model in Fig. 1(b) are shown in Table I. For illustration, the periodic steady-state probabilities evaluated from Eq. (1) for $[AB]/[AB]^{\mathrm{eq}} = 10$ are displayed in Fig. 1(d). Within each period, all three probabilities depend on x, but the dependence of $p_i^{\mathrm{ss}}(x)$ and $p_2^{\mathrm{ss}}(x)$ on x is barely discernible in the scale of the figure. The particle velocity u and AB breakdown rate J calculated for the model are shown in Fig. 2 as functions of $[AB]$. Several interesting features can be seen. First, when the chemical reaction is in equilibrium, i.e., $[AB] = [AB]^{\mathrm{eq}}_{\mathrm{loc}}$, the particle has no net movement, consistent with thermodynamics. When $[AB] > [AB]^{\mathrm{eq}}_{\mathrm{loc}}$, particle E has a net movement toward the less tilted side of the asymmetric potential [toward the right in Fig. 1(c)], just as in external-fluctuation driven systems [1–4]. However, when $[AB] < [AB]^{\mathrm{eq}}_{\mathrm{loc}}$, the direction of the movement is reversed. Thus, in contrast to the external-fluctuation driven case, the movement direction of a chemically driven Brownian particle is not solely determined by the asymmetry of the potential. Second, as $[AB]$ increases above $[AB]^{\mathrm{eq}}_{\mathrm{loc}}$, initially both u and J increase. However, u rises to a maximum and then decays to an asymptotic value at large $[AB]$, while J increases monotonically and saturates at large $[AB]$. Third, values of J calculated for $V(x)$ with parameters $a = 0.1$ and $V_0 = 10$ are similar to those without the potential and thus are insensitive to the potential. Fourth,

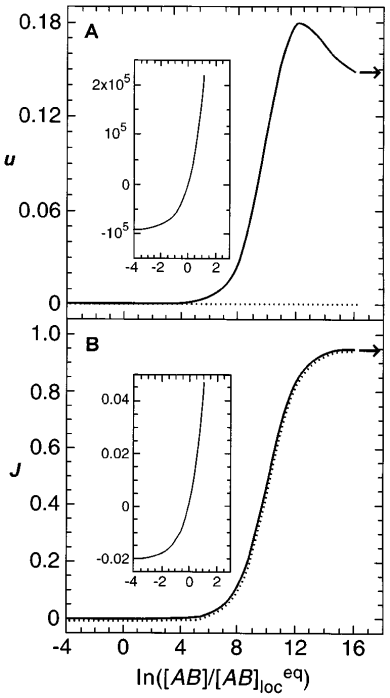

FIG. 2. (a) The velocity u of the Brownian particle as a function of the concentration of AB calculated from Eq. (2) using the steady-state probabilities as shown in Fig. 1(d). (b) The breakdown rate J of AB as a function of $[AB]$, calculated from the steady-state probabilities using Eq. (4). The dotted curves represent the results in the absence of the potential. Arrows indicate the asymptotic values at large $[AB]$. Magnified views for small values of $[AB]$ are shown in the insets. The parameters used in obtaining the curves are listed in Table I (in particular, $[AB]^{\rm eq}_{\rm loc} = 4.54 \times 10^{-3}$).

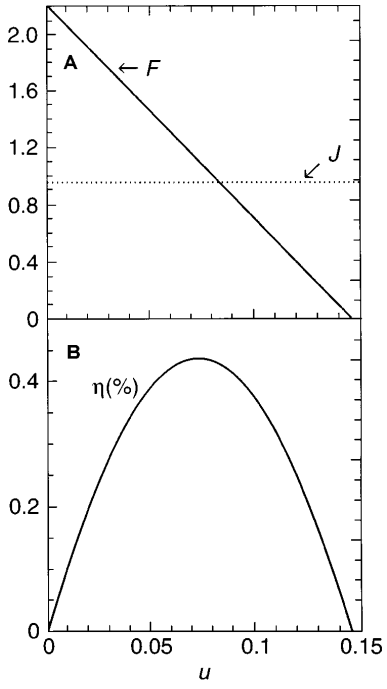

FIG. 3. (a) The external load F (solid curve) and the AB breakdown rate J (dashed curve) as functions of the velocity u of the Brownian particle. (b) The efficiency η of free-energy transduction as a function of u. All the curves are obtained using the parameters in Table I and $[AB]/[AB]^{\rm eq} = e^{20}$.

u and J change signs simultaneously at $[AB] = [AB]^{\rm eq}_{\rm loc}$ and hence a change in the direction of the chemical reaction results in a change in the direction of the particle movement.

The existence of directional movement means that the chemically driven Brownian particle can carry an external load and do mechanical work. By adding a term $-Fp_i$ to the right-hand side of Eq. (2) and calculating u as a function of the external load F, one can obtain the force-velocity curve. The result for the present model with the parameter set of Table I and $[AB]/[AB]^{\rm eq} = e^{20}$ is shown in Fig. 3(a). There is an apparent linear relationship between F and u for loads less than the isometric force $F_{\rm iso}$, the value of F at which $u = 0$. Meanwhile, J is almost constant. The efficiency of free-energy transduction, $\eta = Fu/J\Delta G$, is shown in Fig. 3(b) as a function of the velocity u. For the particular parameter set, the maximum efficiency is small ($\sim 0.5\%$).

We have demonstrated here that an enzyme molecule is able to use the thermal Brownian motion and the free energy of the chemical reaction it catalyzes to move unidirectionally in a spatially periodic and asymmetric electric potential, even against an external load. It is important to point out that in order to generate biased movement the particle has to oscillate between charged and uncharged states (so that the interaction between the particle and the potential field fluctuates). However, although it is a *necessary* condition, oscillation between charged and uncharged states is not a *sufficient* condition for the biased movement to occur; the driving chemical reaction has to be out of equilibrium. To our knowledge, this is the first model with an *explicit* mechanism that displays how scalar chemical free energy is converted into vectorial mechanical energy.

The validity of this model can be tested by adapting a similar setup used for studying external-fluctuation driven mobility [3,4]. The results obtained in our study suggest that, in addition to charges and sizes, biomolecules can be separated according to enzymatic activities or mechanisms. In principle, molecules with different enzymatic activities or mechanisms can be separated in the presence of a static periodic and asymmetric *electric* potential by adding different substrates. Whether this is a feasible experiment remains to be investigated.

The same *formalism* described in this paper [as those in Eqs. (1)–(4)] can be obtained for the so-called "cross-bridge" *models* of biological motors. In biological motors, the crossbridge (the head) of a motor not only is the site of chemical catalysis but also can attach (bind) to a specific binding site on a subunit of the polymer. Force is generated between the motor and the polymer only when the crossbridge is attached. That is, some or all of the states of the catalytic cycle of the crossbridge can bind

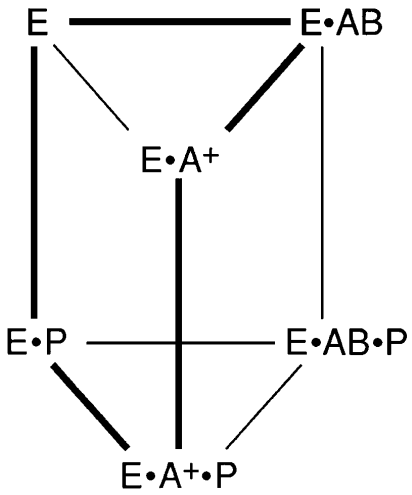

FIG. 4. A kinetic model for biological motors. The upper triangle represents the original catalytic cycle of the motor in solution [Fig. 1(b)], while the lower one represents the one when the motor is attached to the polymer (P). If the dominant cycle of the model is assumed to be the one shown in heavy lines and if states EA^+ and EP are assumed to be transient intermediates, then the original six-state model can be reduced to a three-state model similar to that shown in Fig. 1(b) with state 3 representing the attached EA^+P state.

to the polymer and form attached (force-generating) states as shown in Fig. 4. As discussed by Hill [15], the force generated by a crossbridge in state i can be evaluated as $F_i = -dA(x)/dx$ where x measures the relative distance between the motor and the binding site on a polymer subunit and $A_i(x)$ is the *basic free energy* of the crossbridge in state i. $A_i(x)$ is x dependent only when state i is an attached state and its value is completely determined by the transition rate constants of the given model [15]. When the binding sites on the polymer are linearly and regularly spaced, each $A_i(x)$ in the model becomes periodic and equations similar to those in Eqs. (1)–(4) can be obtained immediately for biological motors if $z_i V$ in Eq. (2) is replaced with $A_i(x)$. In other words, the movement of a single Brownian motor on a periodic polymer can be evaluated theoretically for any kinetic model using the same numerical procedure presented here.

Finally, if the kinetic model in Fig. 4 contains only one dominant cycle as shown in the diagram and states EA^+ and EP are assumed to be transient intermediates (low concentrations), then the original six-state model can be reduced to a three-state one similar to that in Fig. 1(b). Thus it is interesting to compare the calculations done in this paper with those measured for the kinesin-microtubule system [16,17]. The dimensionless quantities F, J, and u are related to the corresponding physical quantities through $F = L\overline{F}/k_BT$, $J = L^2\overline{J}/D$, and $u = L\overline{u}/D$. Taking $T = 300$ K and $L = 8$ nm (the subunit length), fixing D at 6.73×10^{-11} cm^2 s^{-1} so that $\overline{J}$ equals the rate of ATP hydrolysis ($\sim$100 s^{-1}) [18], and using the data in Fig. 3(a), one finds the calculated isometric force and maximum velocity (when $F = 0$) to be 1.14 pN and 0.12 μm s^{-1}, respectively. The measured values are 4–5 pN and 0.5–0.6 μm s^{-1}, respectively [16,17].

In summary, chemically coupled Brownian particles can be made to move unidirectionally in a static periodic potential. The direction of movement depends on the direction of the chemical reaction and the kinetic mechanism of the catalytic cycle, as well as the asymmetry of the potential. The formalism developed in the present paper is applicable to crossbridge models and therefore is useful in modeling the motility of single biological motors in *in vitro* measurements, where thermal Brownian motion may contribute to the movement of the motor.

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