Fluctuation Driven Ratchets: Molecular Motors

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The motion of a heavily damped Brownian particle in a periodic potential subject to a dichotomously fluctuating perturbation is considered. We show that even if the net force is always zero, flow is induced by a fluctuation of the energy barrier, but only at flipping times roughly in between the adiabatic adjustment times on the left and right of the barrier. Predictions of our model are consistent with recent experimental data obtained by Svoboda *et al.* [Nature (London) **365**, 721–727 (1993)] for a single kinesin molecule moving along a biopolymer.

Chemical reactions occur via individual molecular transitions. If the system in which the reaction occurs is large, the effect of this discreteness may be unnoticeable on a macroscopic scale. Nevertheless, local fluctuations always accompany any chemical reaction and are even present at equilibrium. Below we show that nonequilibrium fluctuations brought about by an energy releasing process can be "absorbed" and used to do chemical or mechanical work by an energy requiring process.

The effects of fluctuations on chemical reactions, including enzyme catalysis, have been studied extensively [1–3] in the context of chemical kinetics. In these studies it was shown that zero-average oscillation or fluctuation of the chemical force causes net flux so long as the period of the oscillation, or, equivalently, the correlation time of the fluctuation, is not much shorter than the relaxation time of the reaction. It was also shown that fluctuation of the kinetic barriers of chemical reactions (with the affinity kept zero) can also induce flux [2–4], but at high frequency.

Electric and chemical rectifiers are analogous to Feynman's purely mechanical "ratchet and pawl" engine [5]. Using a potential inspired by Feynman's ratchet, Mag-

nasco [6] recently showed that fluctuations of the force around a zero average can be rectified provided the fluctuations are slow enough (i.e., non-"white"-noise). In the model described by Feynman the pawl moves along a real physical surface consisting of the asymmetric teeth of the ratchet. In such a circumstance it is easy to imagine application of a fluctuating force in either the forward or backward direction. It is much more difficult to imagine a scenario in which the height of the ratchet's teeth fluctuates in time. But such is precisely the mechanical analog of the motion of a Brownian particle on a linear highway with a periodic array of fixed charges where the charge distribution is not symmetric within a period. The binding of a charged ligand, such as ATP (adenosine triphosphate), to the Brownian particle would change the height of the barriers relative to the wells, but would not change the relative heights of the wells.
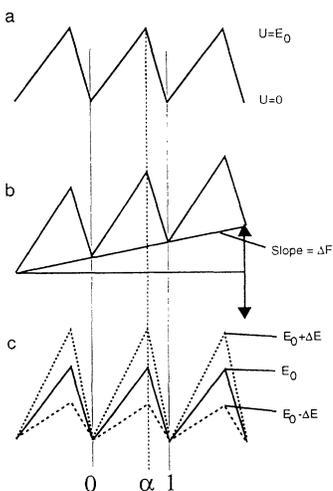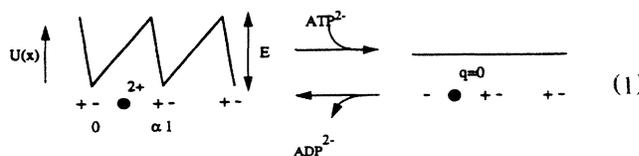
$$ (1) $$

In the case above, if the ball is charged the potential surface has barriers and wells, but when ATP binds the ball becomes neutral and the surface flat.

In this paper we study thermal diffusion on a piecewise linear potential surface where either the force or the barrier height fluctuates between two states. The main point is that fluctuation of the barrier height can cause net flow even though the net macroscopic force is zero at every instant in time. This flow occurs in a frequency band centered around the rate of adiabatic adjustment on the side with the steeper slope.

The setup for the problem is as follows: We have a periodic piecewise linear potential as in Fig. 1. In order to get fluctuation induced flow it is essential that one side is steeper than the other, i.e., that $\alpha \neq \frac{1}{2}$. In this Letter we take $a > \frac{1}{2}$. In an overdamped environment and after scaling the viscosity away and putting the energy in units of kT the motion on a potential like the one in Fig. 1 is described by the following Langevin equation:

FIG. 1. The piecewise linear potential (a) and the types of fluctuations that we study: the fluctuating force (b) and the fluctuating barrier (c).

$$\dot{x} = -\frac{\partial}{\partial x}U(x,t) + \xi(t) ,$$

where ξ represents the Gaussian white-noise term. The potential undergoes a dichotomous Markovian fluctuation and we study two cases.

(i) Fluctuating force

$$\frac{\partial}{\partial x}U(x,t) = \frac{\partial}{\partial x}U(x) + \Delta F(t) .$$

Here the net force $\Delta F(t)$ fluctuates according to Markovian kinetics between $+\Delta F$ and $-\Delta F$ [cf. Fig. 1(b)]. For $F = -\partial U/\partial x$, which represents the local force on the particle, we find that on $(0,a)$ the force fluctuates between $F_1^+ = -E_0/a - \Delta F$ and $F_1^- = -E_0/a + \Delta F$, and on $(a,1)$ between $F_2^+ = E_0/(1-a) + \Delta F$ and $F_2^- = E_0/(1-a) - \Delta F$.

(ii) Fluctuating barrier

$$\frac{\partial}{\partial x}U(x,t) = \frac{\partial}{\partial x}[U(x) + \Delta u(x,t)] .$$

Here the potential at any x fluctuates symmetrically around $U(x)$ and $\Delta u(x,t)$ can take the values $+\Delta u(x)$ and $-\Delta u(x)$ [cf. Fig. 1(c)]. We see that the force F now fluctuates between $F_1^+ = -(E_0 + \Delta E)/a$ and $F_1^- = -(E_0 - \Delta E)/a$ on the interval $(0,a)$ and between $F_2^+ = (E_0 + \Delta E)/(1-a)$ and $F_2^- = (E_0 - \Delta E)/(1-a)$ on the interval $(a,1)$. Note that we have $\Delta u(0) = \Delta u(1) = 0$ and $U(x,t) = U(x+1,t)$. Ajdari and Prost recently suggested a method for dielectrophoretic separation with fluctuating barriers and without a macroscopic driving field [7].

Going from the Langevin to the associated Fokker-Planck equation [8] for the probability density distribution we find

$$\frac{\partial}{\partial t}\begin{bmatrix} P_i^+(x,t) \\ P_i^-(x,t) \end{bmatrix} = \begin{bmatrix} -\gamma - F_i^+ \partial_x + \partial_{xx} & \gamma \\ \gamma & -\gamma - F_i^- \partial_x + \partial_{xx} \end{bmatrix}$$

$$\times \begin{bmatrix} P_i^+(x,t) \\ P_i^-(x,t) \end{bmatrix} , \qquad (2)$$

where $i = 1$ represents the system on the interval $(0,a)$ and $i = 2$ represents the system on $(a,1)$. γ is the flipping rate of the fluctuation. The quantities $P^+(x,t)$ and $P^-(x,t)$ are the probabilities at any time t to find the barrier at the $+$ or $-$ configuration, respectively, and the particle at position x. From conservation of probability ($\partial_t P = -\partial_x J$, where $P = P^+ + P^-$) it is inferred that a stationary solution $P(x,t) = P(x)$ implies a constant flux J. Stationarity means that the left-hand side of (2) equals zero. In that case one can solve for $P(x)$ from two coupled second order linear homogeneous equations. One of the eigenvalues of system (2) is zero, so the solution is of the following form:

$$P_i^\pm(x) = A_i^\pm e^{\lambda_1^{(i)}x} + B_i^\pm e^{\lambda_2^{(i)}x} + C_i^\pm e^{\lambda_3^{(i)}x} + D_i^\pm . \qquad (3)$$

Solving for the sixteen coefficients is a matter of linear algebra. Substituting (3) in the differential equations (2)

and demanding that for every $\exp(\lambda_k^{(i)}x)$ the coefficient be identically zero fixes the ratios A_i^+/A_i^-, B_i^+/B_i^-, and C_i^+/C_i^- and leads to $D_i^+ = D_i^-$. The remaining 8 degrees of freedom can be fixed by demanding that the probability density $P^\pm(x)$ and the flux $J^\pm(x) = (F^\pm - d/dx)P^\pm(x)$ both be continuous at the points $x = 0/1$ and $x = a$ and by normalizing the total probability on one period to be 1.

In Fig. 2 the flux as a function of the flipping rate γ is shown for both the fluctuating force (top) and the fluctuating barrier (bottom). In both cases there is no flux as $\gamma \to \infty$ (i.e., for non-time-correlated noise). This is because after a flip of the potential surface the probability distribution does not have enough time to adjust to the new potential; i.e., the adiabatic adjustment time is longer than the average flipping time $1/\gamma$, and the system effectively "feels" the average potential. Figure 2 also shows how in the low frequency limit of the fluctuating force case there is a flux. Magnasco treated this case extensively in a recent issue of this journal [6] and derived an expression in terms of system parameters for the flux by assuming the system to be adiabatic at all times, calculating the flux in each of the two states and averaging.

In that same issue we studied a special case of a problem originally proposed by Doering and Gadoua [9] and presented results concerning the mean first passage time over a ramp with a fluctuating slope [10]. We found that the characteristic time for adiabatic adjustment on an interval was of the same order of magnitude as the mean first passage time over a ramp with zero slope of the length of that interval. With the viscosity absorbed in the time and the energy in units of kT the mean square distance diffused in time t is given by $\overline{d^2} = 2t$. For the data we used in Fig. 2 the longer slope has a length of almost 1; we see that the inflection point of the sigmoid at the top of Fig. 2 is indeed around $\ln\gamma = 1$, i.e., a flipping time
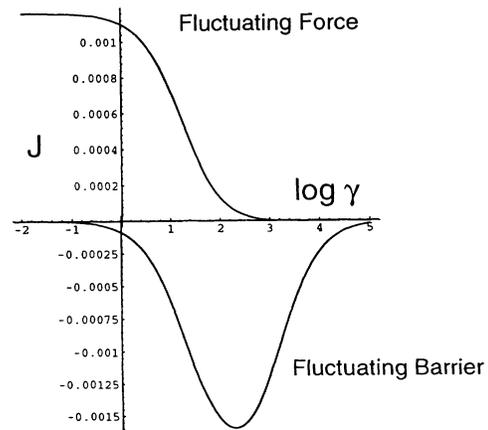

FIG. 2. The flux along the x axis for both systems presented in Fig. 1: (Top) the fluctuating force with $a = \frac{10}{11}$, $E_0 = 10$, and $\Delta F = 1$, and (bottom) the fluctuating barrier with $a = \frac{10}{11}$, $E_0 = 10$, and $\Delta E = 1$.

of order 1.

The explanation for the shape of the curve at the bottom of Fig. 2 is more subtle. There is of course no flux for any constant potential surface if $U(0) = U(1)$. Thus in the low frequency limit, where the flux is the average of the $+$ and $-$ flux, the net flux is zero. The interval with nonzero flux occurs because adiabatic adjustment on the steeper slope is faster by a factor $[a/(a-1)]^2$. We expect flux to occur in the regime where the flipping time is longer than the characteristic time for adiabatic adjustment on the steeper slope and shorter than the characteristic time for adiabatic adjustment on the longer slope. This means in our case that $2/a^2 < \gamma < 2/(1-a)^2$ is the interval where there is a nonzero turnover each time the barrier jumps to the other state. Taking into account that the flux is this turnover multiplied by γ we find for the interval of nonzero flux the following estimate:

$$2 \ln \left[\frac{2}{a^2} \right] < \ln \gamma < 2 \ln \left[\frac{2}{(1-a)^2} \right].$$

This estimate corresponds well with what is observed on the bottom of Fig. 2. It is worth noting that this interval does not depend on E_0 or ΔE. We furthermore observe that a maximal flux occurs when $\gamma \approx 2/(1-a)^2$; this is precisely the time it takes to diffuse a distance $1-a$ over a flat ramp and, according to a conjecture we made in our previous paper [10], the time for adiabatic adjustment on the steeper slope. Interestingly, the sign of the flux induced by a fluctuating barrier is opposite that induced by a fluctuating force. Recently Doering, Horsthemke, and Riordan [11] have shown that depending on the statistics of a fluctuating force, the first correction in an expansion away from the white-noise limit can have either sign.

The following clarifies how flux can occur when $a \neq \frac{1}{2}$. Consider the system depicted under (1) and let the forward and backward rate constant both be equal to γ. We let E be sufficiently large, such that the probability distribution when the barriers are up can be reasonably assumed to consist of delta functions at $-1, 0, 1, 2$, etc. If the barrier moves to the down configuration at $t = 0$, then each of the spikes will start to diffuse. The spike at $t = 0$ diffuses according to

$$P(0|x;t) = \frac{1}{2\sqrt{\pi t}} e^{-x^2/4t}. \tag{4}$$

After $1/\gamma$ units of time the probability to be to the right of a is $\int_a^\infty P(0|x;1/\gamma)dx$ and the probability to be to the left of $-(1-a)$ is $\int_{-\infty}^{-(1-a)} P(0|x;1/\gamma)dx$. When the barrier goes up again the difference of these two integrals is the amount of probability that will be caught in the well as $x = -1$. Substituting the expression (4) for $P(0|x;1/\gamma)$ one finds for the flux

$$J(\gamma) = \frac{1}{4}\gamma \left\{ \mathrm{erfc}\left[\frac{a}{2}\sqrt{\gamma} \right] - \mathrm{erfc}\left[\frac{1-a}{2}\sqrt{\gamma} \right] \right\}.$$

This function describes a function like the one on the bottom of Fig. 2 and the agreement between this function and an exact solution as in (3) gets better for higher values of E in (1). A similar mechanism was discussed by Ajdari and Prost [7].

We have a mechanism here to transduce chemical energy into mechanical energy and a simple model for motor proteins. An interesting feature of our model is that it stops transducing energy at zero temperature, whereas with a ratchet of the type discussed by Magnasco flux can still occur at zero temperature for large enough fluctuation amplitude. It is also worth noting that the potential in our model is truly periodic everywhere and at all times.

In the case of the motion of a motor protein along a biopolymer, one way a fluctuation is brought about is by the repeated binding of ATP and release of ADP. To see whether the mechanism we have proposed can generate biologically significant flux we have to undo the scaling (the coefficient of friction β is absorbed in the time, $kT = 1$, and the period L of the potential is the unit of distance) of our units. With J_{sim} being the result of our simulation and using Einstein's formula, $D = kT/\beta$, for the relation between the coefficient of friction and the diffusion coefficient, we have for the flux $J = J_{\text{sim}}(D/L)$. If d is the length of the part of the period with the steeper slope, then we have for the flipping time t_{max} at which a maximum flux occurs $t_{\text{max}} = d^2/2D$. Interestingly, with this simple model we can within an order of magnitude account for experimental data recently obtained by Svoboda et al. [12]. These authors followed a single kinesin molecule moving along microtubule. They reported the stepwise motion that our model predicts and a step length corresponding to the electron microscopically observed period along the microtubule of $L = 8$ nm. Varying the ATP concentration they found maximal average speed of 300–500 nm/s and, in that case, measured a force of 5 pN necessary to stop the motion of the kinesin. Going back to (dimensionless) Eq. (2) and substituting realistic values for a fluctuating barrier of $E_0 = \Delta E = 4$ (which corresponds to a fluctuation between a flat potential and barriers of $8kT$) and $a = \frac{7}{8}$, we obtain for the maximal flux $J_{\text{sim}} \approx 1$. This flux can be stopped with a constant force of about 2 (a factor $\zeta \approx 2$ more than it would take to stop a flux of 1 on a flat ramp because most of the motion takes place during the half of the time when the barrier is down). Going back now to the experiment of Svoboda et al. and taking the ratio of stopping force and average speed and multiplying it with our guess of $1/\zeta = \frac{1}{2}$ (which means that we assume that the barriers are up half the time) we find an estimate for the friction coefficient between kinesin and microtubule of $\beta \approx 6 \times 10^{-6}$ Ns/m. Putting this value and $L = 8$ nm in our model and realizing that $a = \frac{7}{8}$ implies $d = 1$ nm, we arrive at $t_{\text{max}} \approx 7 \times 10^{-4}$ s for the flipping time at maximal flux. Assuming that the turnover of one ATP brings about two flips [i.e., one forward and one backward transition in (1)], we find that about 700 ATPs per second are consumed when one kinesin moves at maximal speed,

considerably more than one ATP per step. $J_{sim} \approx 1$, $\beta \approx 6 \times 10^{-6}$ Ns/m, and $L = 8$ nm furthermore leads to $J \approx 100$ nm/s, only a factor of 4 smaller than the speed that Svoboda et al. [12] measured. Refinements are possible that make our model of barrier fluctuation driven motion along a biopolymer more biologically realistic. For instance, letting forward and backward transition rates in (1) be different allows for $\zeta \neq \frac{1}{2}$. It is then possible for the model at the observed ratio of stopping force and average speed and $L = 8$ nm to generate the observed flux of 400 nm/s with an ATP turnover of only 200 s^{-1}.

We have shown that zero-average random fluctuations of a barrier height or a net force can cause a particle on a nonsymmetric periodic potential to move uphill against a constant applied force. This means that the system is able to absorb energy from the source of the fluctuations and use it to do work. But we know that energy cannot be absorbed from equilibrium fluctuations, and therefore it becomes important to question what the critical distinctions between equilibrium and nonequilibrium (energy driven) fluctuations are. One difference, emphasized by Magnasco [6], is the time correlation of the fluctuation — we usually model equilibrium fluctuations as white noise, noise with a correlation time that approaches zero. In our model very high frequency fluctuations, which also have a correlation time approaching zero, do not induce net flux. Can this be the only difference? If so, we are led to the conclusion expressed by Magnasco—that a nonsymmetric system can extract energy from the time-correlated noise in a bath without "paying" for it. Yet, there is one additional assumption that is implicit in both the Langevin noisy force, and in the dichotomous noise used by Magnasco, and by us among many others. That is that the fluctuations do not depend on the state of the system. For every force, there is an equal and opposite reaction force, so, when is it appropriate to ignore the effect of the system on the source of the noise? Consider a broader model for a noise influenced process in terms of two coupled stochastic differential equations, one for the evolution of the system variable, and one for the evolution of the noise process:

$$\dot{x} = -\frac{\partial}{\partial x} U_1(x) + f(x,n) + X + \xi(t) ,$$

$$\dot{n} = -\frac{\partial}{\partial n} U_2(n) + g(x,n) + N + \xi^*(t) .$$

In the above equations, $U_1(x)$ and $U_2(n)$ are the periodic potentials on which x and n move, and X and N represent the driving forces for the system x and noise n evolution,

respectively. We have separated these so that $\int_0^{L_1} \partial U_1 = \int_0^{L_2} \partial U_2 = 0$, where L_1 and L_2 are the periods of $U_1(x)$ and $U_2(n)$, respectively. The coupling between the system x and noise n is through the functions f and g. If $\partial f/\partial n = -\partial g/\partial x$ the vector field (f,g) is curl free and describes motion in a potential. If X and N are both zero, detailed balance holds and there is no flux along x. The noise process still produces fluctuation, but the feedback between x and n is reciprocal and no power transfer occurs. This has been called endogenous noise [3]. If N is not zero, the fluctuations are driven by a nonequilibrium force, and, depending on the symmetry of the potential U_1 the interaction $f(n,x)$ may cause flux along the coordinate x. If N is very large, $g(n,x)$ can be neglected in the second equation to very good approximation, yielding effectively state independent noise (or autonomous noise [3]). Dichotomous noise arises if $f(n,x)$ can take on only two values, depending on n. In the case shown under (1), N represents the ΔG of hydrolysis of ATP. Only if the barrier fluctuation is negligible compared to this ΔG can we consider the noise autonomous.

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