Effects of nonequilibrium fluctuations on ionic transport through biomembranes

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We investigate the effects of nonequilibrium flutuations on ionic transport through ion channels in membranes using the concept of localized ratchet. Due to the localization, the ionic population in the binding site can be enhanced or suppressed depending upon ionic potential and its fluctuations, affecting the gating kinetics of the channel. The localized dichotomic fluctuations of ionic potential are shown to give rise to a current reversal differing from the results of periodic ratchets. It is also found that strong correlations between binding energy and membrane potential fluctuations induce resonancelike behaviors in ionic current as the fluctuating rate varies. [S1063-651X(99)17010-7]

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It has been shown that oscillatory or stochastic electric fields may cause directional flow in biochemical cycle and active transport through biomembranes [1–4]. Using irreversible thermodynamics, enzymes have been shown to utilize free energy supplied by external time-dependent perturbations driving the chemical reactions they catalyze away from equilibrium [1]. The random fluctuations of an external electric field can stimulate the pumping mode of Na, K-ATPase, which has been theoretically shown to be a kind of resonance between external field frequency and internal frequency of the membrane proteins in a four-state electroconformational coupling (ECC) model [2]. The same experimental data can be interpreted in terms of much simpler Astumian-Robertson (AR) model for the active kinetics which takes into account two states of the protein only, but including internal fluctuation of membrane potential [3].

In the physics community, nonequilibrium fluctuation (noise)-induced phenomena have recently attracted considerable attention. The thermally driven escape of Brownian particles over fluctuating potential is greatly enhanced if the rate at which the potential fluctuates is commensurate with the escape rate in the absence of the fluctuation, which is called *resonant activation* [5,6]. Another novel phenomenon brought by nonequlibrium flucutation, called *stochastic ratchet* is the occurrence of macroscopic current in a translationally symmetric (periodic) but locally asymmetric structure even though no macroscopic force is acting on average [7]. There are a variety of fluctuations with a wide range of time scales in biological systems due to their complex structures which are flexible and susceptible to external noises. With these fluctuations incorporated into potentials, resonant activation and ratchet can be relevant phenomena behind biological cooperativity.

The ratchet potentials have usually been considered to be of periodic sawtooth-type with two different slopes. A Brownian particle first localized in a potential minimum rearranges itself in a changed potential induced by a nonequilibrium fluctuation. Due to asymmetry of the sawtooth potential, the subsequent distribution rearrangement gives rise to a directed motion. The two cases of nonequilibrium noises of dichotomic type have been considered. One is the fluctuation of force, uniform at any time, which, upon acting on the particle, gives rise to a uniform flux toward the side of lower slope [8]. The other case is the fluctuation of potential. When the potential barrier is fluctuating dichotomically for example, the net flux is induced toward the side of higher slope [8]. In either limit of fast or slow fluctuation, the net flux is reduced to zero. This is due to the fact that for fast fluctuation the net current is the outcome of the average potential and for slow fluctuation it is the average of the current of each individual potential configuration allowed by the fluctuation. But when the flipping (fluctuation) occurs at optimal rates, maximum currents can occur.

In the systems where the translational invariance is broken, it has been shown that the nonequilibrium fluctuations can give rise to a high probability into a desired position [9] and frozen disorders strongly reduce the efficiency of ratchets [10,11]. The ion channels in biological membranes should provide an example of the ratchetlike systems with finite size as well as broken translational symmetry.

Ion channels are the macromolecular structures that play an important role for ionic transport across biomembrane to give rise to neural signal transduction. In crossing the channel, the ions are subject to a potential given by the membrane and other fluctuating background media of dielectric character. Since, in addition, the ion channel has a large number of conformational states undergoing transitions, the backgrounds give rise to nonequilibrium fluctuations with various time scales [12]. The binding sites located in the channel form local potential minima where the ions reside for a while to cross the membrane. Considering only one site of binding with variable widths and depths (interacting ranges and energies), we adopt for analytic simplicity the piecewise linear potential as the ionic potential $U(x)$, defined for the position $0<x<L$ as shown in Fig. 1(a). When the potential difference across the membrane (membrane potential) U_m vanishes, the potential $U(x)$ is symmetric with respect to the binding site, which is assumed to be located at the center, $x=x_2=L/2$ [Fig. 1(b)].

Because the nonequilibrium fluctuation in the systems with no translational symmetry can induce the localization of Brownian particles as mentioned before, it can be inferred that the ionic population in binding sites of ion channel can be enhanced or suppressed by the fluctuations. It has been shown that the ionic population in the binding sites can influence channel function by interacting with channel

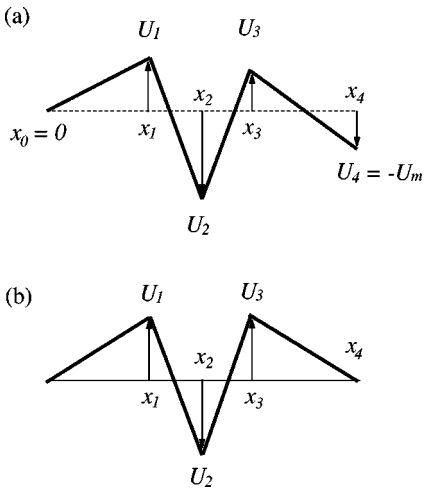

FIG. 1. (a) Model potential $U(x)$ of ion with a binding site at the center of channel. It is characterized by the barrier height U_1, U_3 and binding depth U_2 as well as the membrane potential U_m. (b) The $U(x)$ is taken to be symmetric in the absence of membrane potential ($U_m=0$).

structure [13–18]. For example, the permeant ions prevent the channel from closing by entropic interaction [13–16]. Therefore, there is a good possibility that the fluctuations affect the gating kinetics of the channels via pumping ions into or out of the binding site.

In this paper, we study the changes of ionic concentration at the binding site and current in ion channels induced by nonequilibrium fluctuations. The equation of motion for an ion in the channel is the overdamped Langevin equation,

$$\gamma\dot{x} = -\frac{\partial U(x)}{\partial x} + \xi(t) + F(x,t), \tag{1}$$

where $\xi(t)$ is the thermal noise, white and Gaussian, related to the damping coefficient γ via the fluctuation-dissipation theorem,

$$\langle \xi(t)\xi(0)\rangle = 2\gamma k_B T \delta(t). \tag{2}$$

With this noise only, the system approaches the equilibrium at long times. By the additional nonequilibrium fluctuation, $F(x,t)$, however, the system is driven out of the equilibrium. We consider the nonequilibrium fluctuation to be modeled as dichotomic noise which flips between two states with rate f. One case we study is the fluctuation of the membrane potential (U_m) i.e., the uniform force acting on the ion in the region, $0<x<L$. The other case is the local potential fluctuations which are manifested in the barrier heights, U_1 and U_3, and the binding depth U_2, due to the local fluctuations of electric fields on the ion induced by the backgrounds.

In both cases, the force on ions in each region fluctuates between $F_i+\Delta F_i$ and $F_i-\Delta F_i$ where i denotes each linear region (x_{i-1},x_i), $i=1,\ldots,4$. One can set up the Fokker-Planck equations equivalent to the Langevin equations in each region as follows:

$$\frac{\partial}{\partial t}P_i^{\pm}(x,t) = \frac{1}{\gamma}\frac{\partial}{\partial x}\left(-(F_i \pm \Delta F_i) + k_B T\frac{\partial}{\partial x}\right)P_i^{\pm}(x,t) - fP_i^{\pm}(x,t) + fP_i^{\mp}(x,t). \tag{3}$$

Here $P_i^{\pm}(x,t)$ is the probability density at t in region i that the particle is at position x under the force with $\pm$ signs, f is the flipping rate of the fluctuation.

It should be noted that in our situation, in general, the usual rate kinetics adopted in ECC and AR models should not be applied since the nonequilibrium fluctuations and/or crossing dynamics can be fast so that the particle within the well is not in quasiequilibrium. The rate kinetics fails to give a correct description if the flipping time (f^{-1}) is not much longer than the ionic relaxation time τ_D, comparable to L^2/D where $D=k_BT/\gamma$ (diffusion constant), because the fast fluctuation drives the ions in the well away from quasiequilibrium [6]. If we take the values as $L=5$ nm and $D=10^{-11}\sim 10^{-9}$ m^2/s, which is smaller than in the bulk because of restricted space inside the pore [19], the τ_D is of order of $10^{-8}\sim 10^{-6}$ s. This suggests that the rate kinetics has a limited validity for the ionic transport under the nonequilibrium fluctuation with the flipping rate $f=10^6$ Hz associated with stimulating the pumping mode of Na, K-ATPase [2]. Moreover, it is not legitimate to use the rate kinetics for the case where the barrier height is not high enough for ions in the well to be equilibrated. The description of Fokker-Planck equation should have more general validity for the wide range of flipping rate and in the low barrier cases.

After converting to dimensionless units $x/L\to x$, $(k_BT/\gamma L^2)t\to t$, $(\gamma L^2/k_BT)f\to f$, and $(F_i\pm\Delta F_i/k_BTL)\to F_i\pm\Delta F_i$, we get the following Fokker-Planck equation:

$$\frac{\partial}{\partial t}P_i^{\pm}(x,t) = \frac{\partial}{\partial x}\left(-(F_i\pm\Delta F_i) + \frac{\partial}{\partial x}\right)P_i^{\pm}(x,t) - fP_i^{\pm}(x,t) + fP_i^{\mp}(x,t). \tag{4}$$

In terms of the new functions, $P_i(x,t)=P_i^+(x,t)+P_i^-(x,t)$ and $Q_i(x,t)=P_i^+(x,t)-P_i^-(x,t)$, the equation can be written as

$$\frac{\partial}{\partial t}P_i(x,t) = \frac{\partial}{\partial x}\left(-F_iP_i - \Delta F_iQ_i + \frac{\partial}{\partial x}P_i\right), \tag{5}$$

$$\frac{\partial}{\partial t}Q_i(x,t) = \frac{\partial}{\partial x}\left(-F_iQ_i - \Delta F_iP_i + \frac{\partial}{\partial x}Q_i\right) - 2fQ_i. \tag{6}$$

The stationary solution of $P_i(x,t)$, the total probability density, is of interest. Below we obtain stationary solutions satisfying $(\partial/\partial t)P_i=0$ and $(\partial/\partial t)Q_i=0$, and thus

$$-F_iP_i - \Delta F_iQ_i + \frac{\partial}{\partial x}P_i = -J, \tag{7}$$

$$\frac{\partial}{\partial x}\left[-F_iQ_i - \Delta F_iP_i + \frac{\partial}{\partial x}Q_i\right] - 2fQ_i = 0, \tag{8}$$

where J is the stationary current which is defined as $(\partial/\partial t)P=-(\partial/\partial x)J$. After eliminating $Q_i(x)$ in the above equations, we obtain the following linear ordinary differential equation for $P_i(x)$:

$$\left\{\frac{\partial^3}{\partial x^3}-2F_i\frac{\partial^2}{\partial x^2}+(F_i^2-\Delta F_i^2-2f)\frac{\partial}{\partial x}+2fF_i\right\}P_i(x)=2fJ. \tag{9}$$

We write the solution of the form

$$P_i(x)=\sum_{j=1}^{3} C_{ij}e^{\lambda_{ij}x}+J/F_i \tag{10}$$

and, by Eq. (7),

$$Q_i(x)=\frac{1}{\Delta F_i}\sum_{j=1}^{3}(-F_i+\lambda_{ij})C_{ij}e^{\lambda_{ij}x}. \tag{11}$$

where λ_{ij} is the jth root of the characteristic equation in region i that follows from Eq. (9).

To maintain the stationary state of constant but nonuniform concentrations, we impose the boundary conditions at both sides of membrane located at $x=0$ and $x=1$,

$$P_1(0)=A_{in}C_{in}/N_{tot}, \tag{12}$$

$$P_4(1)=A_{out}C_{out}/N_{tot}, \tag{13}$$

where C_{in} and C_{out} are ionic concentration in bulks, A_{in} and A_{out} denote the cross-sectional area of the channel inside and outside of membrane, and N_{tot} is the total number of ions in the system including the bulk. Moreover, since the bulk concentrations do not depend on the configuration (+ or −) of the fluctuation, $P_1^+(0)=P_1^-(0)$ and $P_4^+(1)=P_4^-(1)$, which gives us

$$Q_1(0)=0, \tag{14}$$

$$Q_4(1)=0. \tag{15}$$

If we further note that $P_i(x)$ and $Q_i(x)$ have to be continuous at any x, we obtain the following boundary conditions:

$$P_i(x_i)=P_{i+1}(x_i), \tag{16}$$

$$Q_i(x_i)=Q_{i+1}(x_i). \tag{17}$$

Applying the continuity of $P_i(x)$, $Q_i(x)$, and the probability currents, J_Q defined as $(\partial/\partial t)Q_i=-(\partial/\partial x)J_Q$, to Eq. (6), we can find additional boundary conditions,

$$Q'_{i+1}(x_i)-Q'_i(x_i)=\{(F_{i+1}-F_i)Q_i(x_i)+(\Delta F_{i+1}-\Delta F_i)P_i(x_i)\}, \tag{18}$$

where the prime denotes position derivative.

What remains to be done is to solve the linear equations with 13 unknowns using the above 13 boundary conditions, for ionic population $c_i(x)=N_{tot}P_i(x)$ and current $N_{tot}J$, with the parameters relevant to the real channel. We define

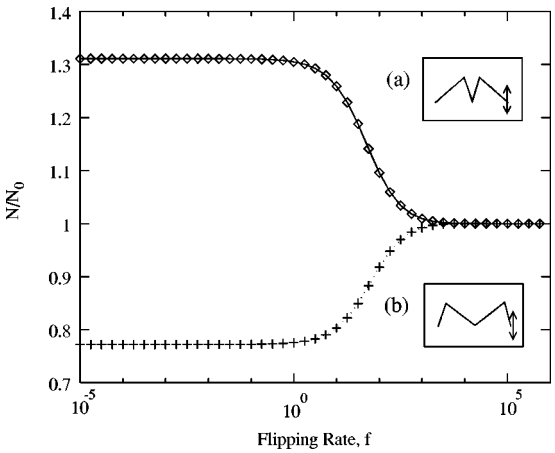

FIG. 2. Enhancement and suppression of ionic population by membrane potential fluctuations with slow flipping; (a) is for $x_1/x_2=0.9$ (narrow binding site) and (b) is for $x_1/x_2=0.1$ (wide binding site); $U_m=0$, $C_{in}=C_{out}$, $U_1=U_3=8$, $U_2=0$, $x_2=0.5$, $x_2-x_1=x_3-x_2$, $\Delta U_m=2$, $\Delta U_1=\Delta U_2=\Delta U_3=0$.

the ratio of the number of ions in the binding in the presence of the fluctuation to that without it and j, the normalized current,

$$N/N_0=\frac{\int_{x_1}^{x_2}dx\,c_2(x)+\int_{x_2}^{x_3}dx\,c_3(x)}{\int_{x_1}^{x_2}dx\,c_2^0(x)+\int_{x_2}^{x_3}dx\,c_3^0(x)}, \tag{19}$$

$$j=\frac{N_{tot}J}{A_{in}C_{in}}, \tag{20}$$

where the superscript 0 indicates no fluctuation. The ratio N/N_0 is expected to go to unity as flipping rate of any fluctuationis goes to infinity because ions feel only average potential, which is exactly the potential in the absence of fluctuation. For the same reason, a fast nonequilibrium fluctuation around an equilibrium yields no net current.

First consider the fluctuation of membrane potential, ΔU_m, around the equilibrium state, $U_m=0$ with $C_{in}=C_{out}$, where the potential barriers are symmetric about the position of the binding site, x_2. In Fig. 2, it is shown that the localized potential with broken translational symmetry can alter the ionic population under nonequilibrium fluctuations. We can see for this case that slow fluctuations (small f) in membrane potential increase the ionic population for narrow binding site (a), decrease it for wide binding site (b). The slow membrane potential(force) fluctuation induces directed current and thus enhancement and suppression of the ionic population at the binding site. Whether the ionic population increases or not is determined by the direction of the current, which depends on the local shape of asymmetric potential. As can be inferred from the result of a ratchet with fluctuating force, the binding site narrow (wide) enough to produce the potential well of high (low) slope in the range $x_1<x<x_3$ induces the nonstationary current into (out of) it.

Figure 3 concerns the situation where the two barriers fluctuate simultaneously. The enhancement or suppression of the population is observed depending upon the width of the

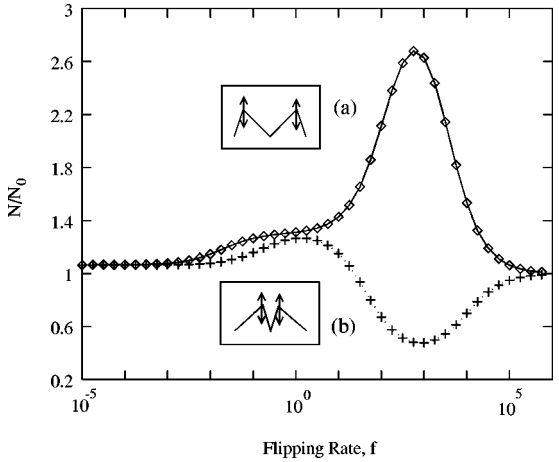

FIG. 3. Enhancement and suppression of ionic population by two barrier fluctuations; (a) is for $x_1/x_2=0.1$ (wide binding site) and (b) is for $x_2/x_1=0.9$ (narrow binding site); $U_m=0$, $C_{in}=C_{out}$, $U_1=U_3=8$, $U_2=0$, $\Delta U_m=0$, $\Delta U_1=\Delta U_2=2$, $\Delta U_2=0$, $x_2=0.5$, $x_2-x_1=x_3-x_2$.

binding site and time scale of fluctuations, which is entirely different from the above result of membrane potential fluctuation. The results of periodic ratchet potentials [8] explain that the moderately fast potential fluctuations make the ionic population increase for wide binding site and decrease for narrow binding site. But, a difference lies in that in our case there exists a range of small flipping rate where the ionic population is enhanced for either case, resulting from the nature of localized ionic potential with a broken transitional symmetry.

In the above case there is no net current due to inversion symmetry of the system. However, if we allow only one barrier to fluctuate while keeping the other to be fixed, we find that a net current of different direction does occur depending upon the flipping rate (Fig. 4). The ionic population has nearly the same feature (Fig. 5) as found in the case of two barrier fluctuations. While the current peak induced by fast flipping can be observed as in periodic ratchets, the current reversal by slow flipping is a novel pheonomenon due to broken-translational symmetry, which gives rise to ionic imbalance between binding site and bulk, and local fluctuation

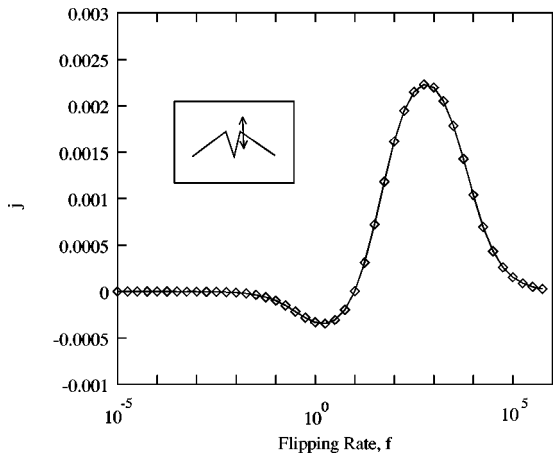

FIG. 4. Induced currents by one barrier fluctuation; the situation is the same as Fig. 3 except for $\Delta U_1=0$.

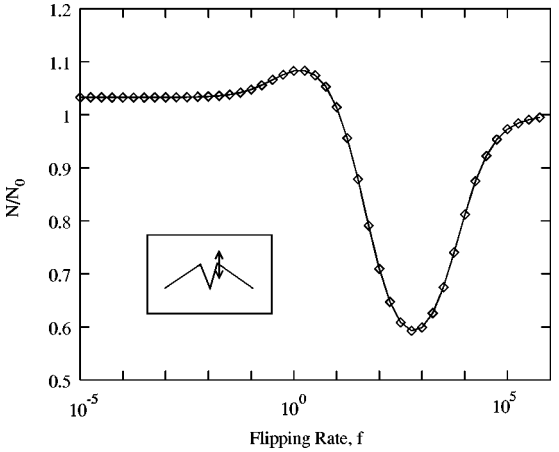

FIG. 5. Enhancement and suppression of ionic population by one barrier fluctuation; the situation is the same as the previous figure.

of the barrier. Because of this reversal current, the increase of ionic population in binding site takes place in Fig. 3(b).

Although we have considered two cases of fluctuations separately, in real situation, however, they occur in correlated manners. As the conformation of the voltage-gated ion channel depends upon the direction of applied field, so does the shape of ionic potential. This asymmetric field dependency does bring the local fluctuations of the potential in strong correlation with the fluctuation of the membrane potential, U_m. In the case of periodic ratchet, the correlated fluctuation between force and potential tops cannot be distinguished from the correlation with potential bottoms. However, in our situation, the correlation between force and potential barriers (tops) and binding energy (bottom) give rise to quite distinct features in ionic population and current. Figures 6 and 7 represent the behaviors of the ionic population and current for the case where the membrane potential fluctuates around $U_m=0$ synchronously with the barrier heights U_1 and U_3. We find that the ionic population gets the maximum at an optimal flipping rate while the current decreases monotonically as the flipping rate decreases. The maximum population is a kind of resonance explained as follows: while

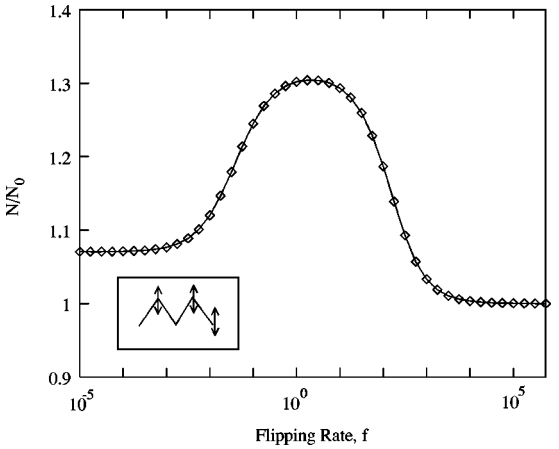

FIG. 6. Change of ionic population in the binding site induced by fluctuating barrier heights correlated with fluctuating membrane potential; $x_1/x_2=0.5$, $U_m=0$, $C_{in}=C_{out}$, $U_1=U_3=8$, $U_2=0$, $\Delta U_m=2$, $\Delta U_1=\Delta U_2=2$, $\Delta U_2=0$, $x_2=0.5$, $x_2-x_1=x_3-x_2$.

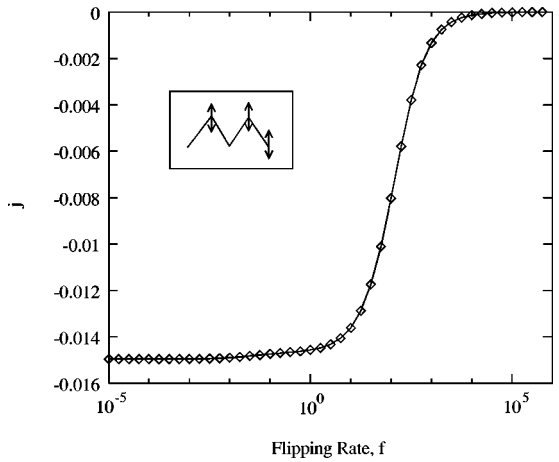

FIG. 7. Change of ionic current induced by fluctuating barrier heights correlated with fluctuating membrane potential; the situation is the same as the previous figure.

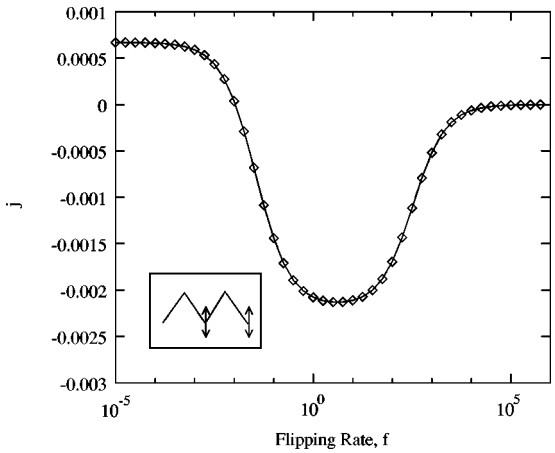

FIG. 9. Change of ionic current vs flipping rate induced by fluctuating binding energy correlated with fluctuating membrane potential; the situation is the same as the previous figure.

the lowering of the barrier height (U_2) due to the fluctuation facilitates the ion to cross, but the subsequent raising of another barrier height (U_3) can forbid the ion to escape from the binding site if the flipping rate happens to be comparable with the escape rate. The current increases monotonically as the flipping rate decreases because for low flipping rate both barrier heights can remain lower for the duration longer than the crossing time.

Figures 8 and 9 depict the case where the membrane potential fluctuation, same as above, is accompanied with the binding depth (U_2) fluctuation. In contrast to the preceding results, while the ionic population becomes the maximum for a low flipping rate, there is an optimal flipping rate that minimizes the ionic population and at the same time maximizes the current in the direction opposite to current attained at low frequencies. The reason for the maximal population for a low flipping rate is argued as follows: when the binding energy changes due to the fluctuation, ΔU_2 , it incurs the populational change in accordance with the Arrhenius factor, which yields overall enhancement beyond N_0 by the factor $\frac{1}{2}(e^{\Delta U_2}+e^{-\Delta U_2})$, which is larger than unity. When the flipping is optimal, however, there exist the resonancelike behaviors in current as well as in ionic population where the flipping of electric field becomes efficient in pumping ions out of shallow binding site. This novel phenomenon takes place by the cooperative activity of the localization of potential, thermal noise, and the membrane potential and binding energy fluctuations.

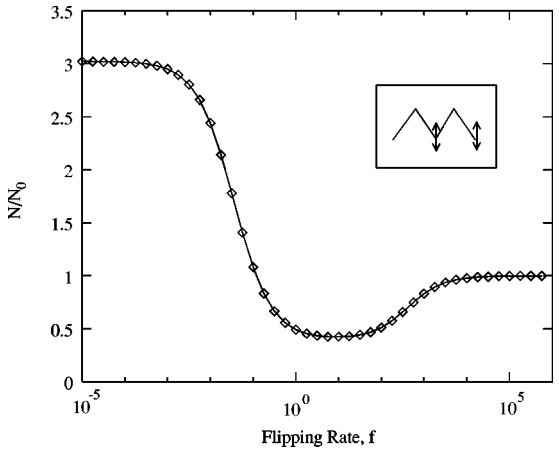

FIG. 8. Change of ionic population in the binding site induced by fluctuating binding energy correlated with fluctuating membrane potential; $U_m=0$, $C_{in}=C_{out}$, $\Delta U_m=2$, $\Delta U_1=\Delta U_3=0$, $\Delta U_2=-2$, $U_1=U_3=8$, $U_2=0$, $x_1/x_2=0.5$, $x_2=0.5$, $x_2-x_1=x_3-x_2$.

The above mentioned maximum current for some range of the flipping rate features also in some theoretical models using chemical kinetics. The ECC model, which considers four conformational states, exhibits the current resonance between the flipping rate and the internal frequency of the protein [2]. This result, however, is attibutable to macromolecular conformational transitions the model assumes, which is significantly different from our situation. The AR model of two conformational states interprets the results of ECC model for the case where the intrinsic fluctuation of membrane potential exists [3]. In this model, however, the fluctuation of external electric field is statistically uncorrelated with the intrinsic fluctuation. On the other hand, the nonmonotonic dependence of current on the flipping rate presented in this paper is brought by strong correlation between the fluctuations from external electric field and internal binding energy. This suggests another new mechanism by which the enhancement of ionic current takes place in the presence of the membrane potential with a fluctuation of suitable time scale.

Now suppose that the nonequilibrium fluctuations occur around the Nernst equilibrium, with

$$U_m=-\ln\frac{A_{in}C_{in}}{A_{out}C_{out}} \tag{21}$$

and no net current. Figure 10 shows that more currents in the direction of higher potential (current reversal) are generated as U_m increases. Figure 10(d) depicts the case with $U_m=3$ (equivalent to 75 mV approximately), a value close to the rest membrane potential typical of biomembranes. It is worthwhile to investigate how the fluctuation of binding can be correlated with the mechanism of ion pumps of generating the uphill current in real biomembranes.

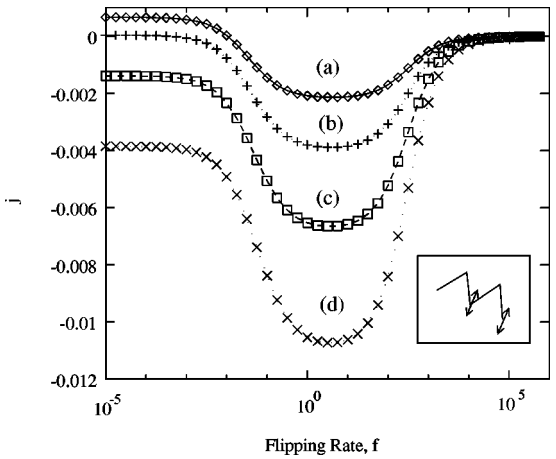

FIG. 10. Behaviors of ionic current induced by the fluctuating binding site strongly correlated with the fluctuating membrane potential in various Nernst equilibrium conditions. The (a) is the same as in Fig. 9. The situation is the same except for $U_m=1$ (b), 2 (c), 3 (d), and $A_{in}C_{in}/A_{out}C_{out}=e^{-U_m}$.

The relevant parameters for biological transport are $L=5$ nm (thickness of biomembranes), $U_{1,3}=5\sim10k_BT$ (barrier height), $U_m=10\sim100$ mV (membrane potential), and $D=10^{-11}\sim10^{-9}$ m^2/s (diffusion constant). The dimensionless parameters employed in this paper, $U_1=U_3=8$, $U_m=0\sim3$, and $\Delta U_m=2$ are in the above range. The range of the flipping rate where the fluctuation-driven phenomena occur in our results is $10^4\sim10^{11}$ Hz, which is obtained by multiplying the dimensionless flipping rate by D/L^2 ($10^5\sim10^7$ Hz). In particular, the current induced by the fluctuation in Figs. 9 and 10 occurs in the range of $10^4\sim10^9$ Hz, which covers the optimal frequency, 10^6 Hz for the pumping mode of Na, K-ATPase [2].

In summary, we have investigated the behaviors of ion channels subject to nonequilibrium fluctuations using the idea of the localized ratchet systems. It has been shown that the fluctuations facilitate the increase or decrease of ions in the binding site due to the localization, depending upon the shape of ionic potential, membrane potential, as well as their fluctuations, and the time scales. These effects appear to be relevant to the real situations where the permeant ions affect strongly the gating kinetics of ion channels by interacting with channel structure. Because of broken translational symmetry, the local barrier fluctuations for the case of narrow binding site give rise to the increase of ionic population and the current in a direction opposite to what is expected from the theory of periodic ratchets. Among many features, we mention that the strong correlation between the fluctuations of membrane potential and binding energy cooperates with thermal noise and localized ionic potential to induce the behaviors including the maximum current reversals for optimal flippings. For the full description of the nonequilibrium fluctuation-induced effects on ion transport, the interaction between the ion and the channel structure, which has been developed in our previous work [16] and other references [17,18], has to be incorporated into our theoretical investigation.

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