Counting Translocations of Strongly Repelling Particles through Single Channels: Fluctuation Theorem for Membrane Transport

Alexander M. Berezhkovskii[1] and Sergey M. Bezrukov[2]

[1]Mathematical and Statistical Computing Laboratory, Division of Computational Bioscience, Center for Information Technology, National Institutes of Health, Bethesda, Maryland 20892, USA

[2]Laboratory of Physical and Structural Biology, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland 20892, USA

(Received 6 July 2007; published 24 January 2008)

Transport of strongly repelling particles through a single membrane channel is analyzed assuming that the channel cannot be occupied by more than one particle. An exact solution is found for the Laplace transform of the probability $P_n(t)$ that n particles have been transported in time t. This transform is used to find the flux through the channel and to show that $P_n(t)$ and $P_{-n}(t)$ are related by the fluctuation theorem. The solution is obtained using an observation that $P_n(t)$ is the propagator for a non-Markovian random walk, which can be found by solving a set of integral equations.

DOI: 10.1103/PhysRevLett.100.038104 PACS numbers: 87.15.Ya, 87.16.Uv

In this Letter we analyze transport of solute particles through a single channel in a membrane separating left (L) and right (R) reservoirs. The flux of the solute particles may be driven either by the difference in solute concentrations, c_L and c_R, in the reservoirs, $c_L \neq c_R$, or by a potential drop between the reservoirs, and, of course, both factors may act together. The goal of the theory is to build a bridge establishing a relation between the flux through the channel and a more detailed description of the solute dynamics in the channel and the reservoirs that underlie the transport. We consider solute particles that strongly repel each other and model the repulsion by the requirement that the channel cannot be occupied by more than one particle. Assuming that the channel is empty at $t = 0$ we describe the particle exchange between the reservoirs by the probability $P_n(t)$ that the difference between the number of particles passing from the left reservoir to the right one in time t and the number of particles passing for the same time in the opposite direction is equal to n. One of the main results of this Letter is an exact solution for the Laplace transform of this probability, $\hat{P}_n(s)$, where s is the Laplace parameter. This solution is used to find the flux through the channel and to show that the ratio $P_n(t)/P_{-n}(t)$ obeys the fluctuation theorem. There are several recent papers on the steady-state flux through a singly occupied channel with the major focus on the optimal particle-channel interaction that maximizes the flux driven by the difference in the solute concentrations in the two reservoirs [1–4]. The theory developed in the present Letter leads to an expression for the steady-state flux in the limit $t \to \infty$.

We derive $\hat{P}_n(s)$ in two steps. First, we formulate the problem in terms of a random walk between identical neighboring points of a one-dimensional lattice, which correspond to different numbers of particles transported from the left reservoir to the right one for time t (not to be confused with the site model of the particle intrachannel dynamics):

$$\rightleftarrows -3 \rightleftarrows -2 \rightleftarrows -1 \rightleftarrows 0 \rightleftarrows 1 \rightleftarrows 2 \rightleftarrows 3 \rightleftarrows \quad (1)$$

Second, assuming that the random walk starts from site 0 at $t = 0$ we identify $P_n(t)$ with the random walk propagator, $P_n(t) = P(n, t|0, 0)$, and find $\hat{P}_n(s)$ solving a set of integral equations for this propagator.

The random walk, Eq. (1), is characterized by the probabilities of making a step in the positive and negative directions, W_+ and $W_- = 1 - W_+$, as well as the probability densities for the distributions of the waiting times before the random walk makes a corresponding step, $\chi_+(t)$ and $\chi_-(t)$. To formulate the problem in terms of random walk we derive expressions, which give $W_\pm$ and the Laplace transforms of $\chi_\pm(t)$ as functions of some quantities that characterize motion of the solute particles in the channel and their entrance into the channel from the reservoirs. These relations are another important result of this Letter. We find that $\chi_+(t) = \chi_-(t)$; that is, the distribution of the random walk waiting time is independent of the direction in which a solute passes through the channel. This is done using a recently proven identity of the distributions of the direct translocation times for particles traversing the channel in the opposite directions, which is fulfilled at an arbitrary relation between the translocation probabilities [5]. It is worth mentioning that there is a well-known resemblance between formalisms used to describe channel transport and enzymatic reactions [6]. Therefore, this is not surprising that the invariance of the waiting time distribution with respect to the random walk step direction, derived below, is identical to the result recently obtained by Qian and Xie [7] in their theory of kinetics of enzymatic reactions based on the random walk formalism.

We describe the entrance of the particles into the channel from the reservoirs as first order processes characterized by the rate constants, $k_{\text{in}}^I = k_{\text{on}}^I c_I$, $I = L, R$. Then the probability density of the channel lifetime in the "empty state," $\varphi_{\text{emp}}(t)$, is given by $\varphi_{\text{emp}}(t) = k_{\text{in}} \exp(-k_{\text{in}} t)$, where $k_{\text{in}} = k_{\text{in}}^L + k_{\text{in}}^R$, and the probabilities of the particle entrance into the channel from the left and right reservoirs, $P_{\rm in}^L$ and $P_{\rm in}^R$, are $P_{\rm in}^L = k_{\rm in}^L/k_{\rm in}$ and $P_{\rm in}^R = k_{\rm in}^R/k_{\rm in}$. When the potential drop is localized on the membrane, the bimolecular rate constants, $k_{\rm on}^I$, are given by the Hill formula for the trapping rate by an absorbing circular disk on the otherwise reflecting planar wall [8] or its modification for noncircular absorbers [9]. The fate of the particle in the channel depends on the side from which it enters. A particle entering the channel from the left reservoir comes back with probability $P_{L\to L}$ and passes to the right reservoir with probability $P_{L\to R} = 1 - P_{L\to L}$. Corresponding return and translocation probabilities for particles entering the channel from the right reservoir are $P_{R\to R}$ and $P_{R\to L}$. The probability densities of the lifetime in the channel for returning and traversing particles are denoted as $\varphi_{L\to L}(t)$, $\varphi_{R\to R}(t)$, $\varphi_{L\to R}(t)$, and $\varphi_{R\to L}(t)$. Recently, using several different models of the particle dynamics in the channel, it has been shown [5] that the probability densities $\varphi_{L\to R}(t)$ and $\varphi_{R\to L}(t)$ are identical, $\varphi_{L\to R}(t) = \varphi_{R\to L}(t) = \varphi_{\rm tr}(t)$, independently of how different the translocation probabilities, $P_{L\to R}$ and $P_{R\to L}$, are.

We begin with finding probabilities W_+ and W_-. Consider the total number of entrances into the channel, N, for sufficiently long time, so that the number of transitions in each direction is much greater than unity. N is the sum of the numbers of entrances into the channel from the left and right reservoirs, $N = N_L + N_R$, where, on average, $N_I = P_{\rm in}^I N$, $I = L, R$. The numbers of the $L \to R$ and $R \to L$ transitions are given by $N_{L\to R} = P_{L\to R}N_L = P_{\rm in}^L P_{L\to R}N$ and $N_{R\to L} = P_{R\to L}N_R = P_{\rm in}^R P_{R\to L}N$. The probability W_+ is the fraction of the $L \to R$ transitions out of the total number of transitions,

$$W_+ = \frac{N_{L\to R}}{N_{L\to R} + N_{R\to L}} = \frac{P_{\rm in}^L P_{L\to R}}{P_{\rm in}^L P_{L\to R} + P_{\rm in}^R P_{R\to L}} = \frac{k_{\rm on}^L c_L P_{L\to R}}{k_{\rm on}^L c_L P_{L\to R} + k_{\rm on}^R c_R P_{R\to L}}. \tag{2}$$

Respectively, the probability W_- is

$$W_- = \frac{N_{R\to L}}{N_{L\to R} + N_{R\to L}} = \frac{P_{\rm in}^R P_{R\to L}}{P_{\rm in}^L P_{L\to R} + P_{\rm in}^R P_{R\to L}} = \frac{k_{\rm on}^R c_R P_{R\to L}}{k_{\rm on}^L c_L P_{L\to R} + k_{\rm on}^R c_R P_{R\to L}}. \tag{3}$$

Assuming that the potential drop between the two reservoirs is localized on the membrane we use the condition of detailed balance

$$k_{\rm on}^L P_{L\to R} \exp(-\beta U_L) = k_{\rm on}^R P_{R\to L} \exp(-\beta U_R), \tag{4}$$

where U_L and U_R are the potential energies of a solute particle in the left and right reservoirs, respectively, and $\beta = (k_B T)^{-1}$ with k_B and T denoting, respectively, the Boltzmann constant and the absolute temperature, to write W_+ and W_- in terms of the affinity, $A(c_L/c_R, \Delta U)$, defined as $\beta A(c_L/c_R, \Delta U) = \ln(c_L/c_R) + \beta \Delta U$, with $\Delta U = U_L - U_R$ [10]. The result is

$$W_\pm = \frac{1}{1 + \exp[\mp \beta A(c_L/c_R, \Delta U)]}. \tag{5}$$

It shows how the probabilities W_+ and W_- depend on the external parameters c_L, c_R, and ΔU. In the absence of the potential drop between the reservoirs the probabilities W_+ and W_- are given by $W_\pm = c_{L,R}/(c_L + c_R)$, while for equal concentrations in the reservoirs these probabilities are $W_\pm = [1 + \exp(\mp \beta \Delta U)]^{-1}$. Naturally, $W_+ = W_- = 1/2$ at equilibrium.

Next we proceed to the probability densities $\chi_+(t)$ and $\chi_-(t)$ that characterize the distributions of the waiting times before the random walk makes a step in the positive or negative direction, respectively. Consider all possible realizations leading to the $L \to R$ transition. Note that a particle entering the channel from the right reservoir must return since we count only realizations that lead to the $L \to R$ transition, while a particle entering from the left reservoir may either pass through the channel or come back. With this in mind we can write an integral equation, which takes all these possibilities into account:

$$W_+\chi_+(t) = \int_0^t dt_1 \varphi_{\rm emp}(t_1)\Big[P_{\rm in}^R P_{R\to R} W_+ \int_0^{t-t_1} \varphi_{R\to R}(t_2)\chi_+(t-t_1-t_2)dt_2 + P_{\rm in}^L\Big(P_{L\to R}\varphi_{L\to R}(t-t_1) + P_{L\to L}W_+ \int_0^{t-t_1} \varphi_{L\to L}(t_2)\chi_+(t-t_1-t_2)dt_2\Big)\Big]. \tag{6}$$

The first term in the square brackets, which is proportional to $P_{\rm in}^R$, is due to nontranslocating trajectories of the particles entering the channel from the right reservoir. The second term, proportional to $P_{\rm in}^L$, is due to the particles entering the channel from the left reservoir. Solving Eq. (6) we find the Laplace transform of $\chi_+(t)$ denoted by $\hat\chi_+(s)$,

$$\hat\chi_+(s) = \frac{(P_{\rm in}^L P_{L\to R} + P_{\rm in}^R P_{R\to L})\hat\varphi_{\rm emp}(s)\hat\varphi_{L\to R}(s)}{1 - [P_{\rm in}^L P_{L\to L}\hat\varphi_{L\to L}(s) + P_{\rm in}^R P_{R\to R}\hat\varphi_{R\to R}(s)]\hat\varphi_{\rm emp}(s)}. \tag{7}$$

Respectively, the Laplace transform of $\chi_-(t)$ is given by

$$\hat\chi_-(s) = \frac{(P_{\rm in}^L P_{L\to R} + P_{\rm in}^R P_{R\to L})\hat\varphi_{\rm emp}(s)\hat\varphi_{R\to L}(s)}{1 - [P_{\rm in}^L P_{L\to L}\hat\varphi_{L\to L}(s) + P_{\rm in}^R P_{R\to R}\hat\varphi_{R\to R}(s)]\hat\varphi_{\rm emp}(s)}. \tag{8}$$

Using the fact that $\varphi_{L\to R}(t) = \varphi_{R\to L}(t) = \varphi_{\rm tr}(t)$ [5], we arrive at an important conclusion that the probability densities $\chi_+(t)$ and $\chi_-(t)$ are also identical, $\chi_+(t) = \chi_-(t) = \chi(t)$, and, hence, the probability density of the waiting time between successive steps of the random walk is independent of the step direction. The Laplace transform of $\chi(t)$ is

$$\hat{\chi}(s) = \frac{(P_{\rm in}^L P_{L\to R} + P_{\rm in}^R P_{R\to L})\hat{\varphi}_{\rm emp}(s)\hat{\varphi}_{\rm tr}(s)}{1 - [P_{\rm in}^L P_{L\to L}\hat{\varphi}_{L\to L}(s) + P_{\rm in}^R P_{R\to R}\hat{\varphi}_{R\to R}(s)]\hat{\varphi}_{\rm emp}(s)}. \quad (9)$$

Equations (5) and (9) are important results of our analysis since they establish the relation between the parameters of the random walk in Eq. (1) $W_\pm$ and $\hat{\chi}(s)$, on one hand, and quantities that characterize dynamics of the solute particles in the channel and their entrance into the channel from the reservoirs, on the other hand.

Now we proceed to the propagator, $P(n, t|0, 0) = P_n(t)$. Introducing the survival probability of the random walk on a site, $S(t) = \int_t^\infty \chi(t')dt'$, we can write an integral equation for the propagator

$$P_n(t) = \delta_{n0}S(t) + \int_0^t S(t-t')[W_+J_{n-1}(t') + W_-J_{n+1}(t')]dt', \quad (10)$$

where δ_{ij} is the Kronecker delta and $J_n(t)$ is the probability flux escaping from site n at time t. This flux satisfies

$$J_n(t) = \delta_{n0}\chi(t) + \int_0^t \chi(t-t')[W_+J_{n-1}(t') + W_-J_{n+1}(t')]dt'. \quad (11)$$

To solve these equations we introduce two generating functions $F_P(\varphi, t) = \sum e^{{\rm i}n\varphi}P_n(t)$ and $F_J(\varphi, t) = \sum e^{{\rm i}n\varphi}J_n(t)$. First we use Eq. (11) to find the Laplace transform of $F_J(\varphi, t)$ and then Eq. (10) to find the Laplace transform of $F_P(\varphi, t)$:

$$\hat{F}_P(\varphi, s) = \frac{1-\hat{\chi}(s)}{s}[1 + (W_+e^{i\varphi} + W_-e^{-i\varphi})\hat{F}_J(\varphi, s)] = \frac{1-\hat{\chi}(s)}{s[1-\hat{\chi}(s)(W_+e^{i\varphi} + W_-e^{-i\varphi})]}. \quad (12)$$

From this we obtain the Laplace transform of the propagator in terms of W_+ and W_- and $\hat{\chi}(s)$:

$$\hat{P}_n(s) = \frac{1}{2\pi}\int_{-\pi}^{\pi} e^{-{\rm i}n\varphi}\hat{F}_P(\varphi, s)d\varphi = \left(\frac{W_+}{W_-}\right)^{n/2}\left[\frac{2\sqrt{W_+W_-}\hat{\chi}(s)}{1+\sqrt{1-4W_+W_-[\hat{\chi}(s)]^2}}\right]^{|n|} \times \frac{1-\hat{\chi}(s)}{s\sqrt{1-4W_+W_-[\hat{\chi}(s)]^2}}. \quad (13)$$

One can see that $\hat{P}_n(s)$ satisfies $W_-^n\hat{P}_n(s) = W_+^n\hat{P}_{-n}(s)$ and, hence, the probability $P_n(t)$ obeys the fluctuation theorem [11] which for the nonequilibrium steady state under consideration has the form

$$\frac{P_n(t)}{P_{-n}(t)} = \left(\frac{W_+}{W_-}\right)^n = \left(\frac{k_{\rm on}^L c_L P_{L\to R}}{k_{\rm on}^R c_R P_{R\to L}}\right)^n = \exp[n\beta A(c_L/c_R, \Delta U)], \qquad t > 0. \quad (14)$$

In the absence of the potential drop between the reservoirs Eq. (14) reduces to the relation $P_n(t)/P_{-n}(t) = (c_L/c_R)^n$ discussed by Qian and Xie in the context of kinetics of enzymatic reactions [7]. When the concentrations in the reservoirs are equal and the transport is due to the potential drop, Eq. (14) takes the form $P_n(t)/P_{-n}(t) = \exp(n\beta\Delta U)$. It is interesting that the fluctuation theorem in Eq. (14) is true not only for solute particles that strongly repel each other. It can be shown that Eq. (14) is also true for non-interacting solutes so that the channel can be occupied by an arbitrary number of particles [12].

The average number of particles transported from the left reservoir to the right one in time t, $\langle n(t)\rangle$, is given by

$$\langle n(t)\rangle = \sum_{n=-\infty}^{\infty} nP_n(t). \quad (15)$$

The Laplace transforms of $\langle n(t)\rangle$ and of the flux through the channel at time t, $j(t)$, defined as $j(t) = d\langle n(t)\rangle/dt$, can be readily obtained using $\hat{P}_n(s)$ in Eq. (13):

$$\hat{j}(s) = s\langle\hat{n}(s)\rangle = (W_+ - W_-)\frac{\hat{\chi}(s)}{1-\hat{\chi}(s)} = \tanh\left(\frac{\beta A(c_L/c_R, \Delta U)}{2}\right)\frac{\hat{\chi}(s)}{1-\hat{\chi}(s)}. \quad (16)$$

This expression is another important result of our analysis since it allows one to find transient behavior of $j(t)$ from zero at $t = 0$ to its steady-state value, j_{ss}, given by the asymptotic long-time behavior of $j(t)$. The steady-state flux can be found from the small-s expansion of $\hat{j}(s)$ using the relation $\hat{\chi}(s) \approx 1 - \tau_\chi s$, $s \to 0$,

$$j_{ss} = \frac{d\hat{j}(s)}{ds}\bigg|_{s=0} = \frac{W_+ - W_-}{\tau_\chi} = \frac{1}{\tau_\chi}\tanh\left(\frac{\beta A(c_L/c_R, \Delta U)}{2}\right), \qquad t \gg \tau_\chi, \quad (17)$$

where τ_χ is the mean time between successive translocations through the channel. This time can be expressed in terms of the mean lifetimes in the channel of translocating and returning particles, $\tau_{\rm tr}$, $\tau_{L\to L}$, and $\tau_{R\to R}$,

$$\tau_\chi = \tau_{\rm tr} + \frac{1 + k_{\rm on}^L c_L P_{L\to L}\tau_{L\to L} + k_{\rm on}^R c_R P_{R\to R}\tau_{R\to R}}{k_{\rm on}^L c_L P_{L\to R} + k_{\rm on}^R c_R P_{R\to L}}. \quad (18)$$

Equation (17) has a transparent physical interpretation: The flux is the product of the average number of transitions between the reservoirs per unit time, $1/\tau_\chi$, and the probability that the transition occurs in the $L \to R$ direction, $(W_+ - W_-)$.

Using Eqs. (2), (3), and (18) we can write j_{ss} in Eq. (17) as

$$j_{ss} = \frac{k_{\rm on}^L c_L P_{L\to R} - k_{\rm on}^R c_R P_{R\to L}}{1 + k_{\rm on}^L c_L \tau_{\rm inside}^L + k_{\rm on}^R c_R \tau_{\rm inside}^R}, \quad (19)$$

where $\tau_{\rm inside}^L$ and $\tau_{\rm inside}^R$ are the average lifetimes in the channel of the particles entering from the left and right reservoirs, $\tau_{\rm inside}^L = P_{L\to L}\tau_{L\to L} + P_{L\to R}\tau_{\rm tr}$ and $\tau_{\rm inside}^R = P_{R\to R}\tau_{R\to R} + P_{R\to R}\tau_{\rm tr}$. To our knowledge this expression for the steady-state flux through a singly occupied channel was first suggested on the basis of physically appealing arguments in [1] and derived in [4]. The theory above shows how the expression in Eq. (19) can be obtained analyzing the time-dependent behavior of the flux $j(t)$. In the absence of the potential drop between the reservoirs the flux in Eq. (19) can be written as

$$j_{ss}^{(0)} = \frac{k_{\rm on}^L P_{L\to R}^{(0)}(c_L - c_R)}{1 + k_{\rm on}^L c_L \tau_{\rm inside}^L + k_{\rm on}^R c_R \tau_{\rm inside}^R}. \quad (20)$$

When the solute concentrations in the reservoirs are equal, $c_L = c_R = c$, and the transport is due to the potential drop, Eq. (19) reduces to

$$j_{ss}|_{c_L=c_R=c} = \frac{c(k_{\rm on}^L P_{L\to R} - k_{\rm on}^R P_{R\to L})}{1 + c(k_{\rm on}^L \tau_{\rm inside}^L + k_{\rm on}^R \tau_{\rm inside}^R)}. \quad (21)$$

Linearizing the right-hand side of this expression with respect to the potential drop one recovers the Ohm law for the channel.

In summary, we have shown that the probability density of time between successive particle translocations from one reservoir to the other is independent of the direction in which the particle goes, and we derived an expression for the Laplace transform of this function as well as the expressions for the probabilities of the $L \to R$ and $R \to L$ transitions. These expressions are given in terms of quantities that characterize motion of the particles in the channel and in the reservoirs, Eqs. (5) and (9). We use these expressions to derive the Laplace transform of the probability, $P_n(t)$, Eq. (13). We demonstrate that $P_n(t)$ satisfies the fluctuation theorem, Eq. (14), and we use its Laplace transform to find the flux of the particles between the reservoirs, Eqs. (17) and (19). General relations derived in this Letter are model independent in the sense that they remain unchanged whatever model of the solute dynamics in the channel is used. Different models simply lead to different expressions for the probabilities and lifetimes that describe the particle's life in the channel. For the diffusion model of the particle motion in the channel [13] one can find explicit expressions for all the quantities appearing in our analysis in Ref. [14]. These expressions show how these quantities depend on the solute-channel interaction, which implicitly includes the dependence on the shape and the size of the translocating particles, as well as the channel geometry. Finally it might be interesting to apply the same ideas to transport through confined quantum systems with Coulomb or van der Waals blockades [15].

We are grateful to Attila Szabo for numerous enlightening discussions of different aspects of the problem. Attila drew our attention to the results by Qian and Xie [7] and to the resemblance between transport through a singly occupied channel and enzymatic reaction [6]. He pointed out that there should be a fluctuation theorem for channel-facilitated membrane transport since such a theorem does exist for the kinetics of enzymatic reactions. We are also grateful to Chris Jarzynski and members of his group for a very helpful discussion of different questions related to the fluctuation theorem. This study was supported by the Intramural Research Program of the NIH, Center for Information Technology and National Institute of Child Health and Human Development.

[1] A. M. Berezhkovskii and S. M. Bezrukov, Biophys. J. **88**, L17 (2005); Chem. Phys. **319**, 342 (2005).
[2] W. R. Bauer and W. Nadler, Proc. Natl. Acad. Sci. U.S.A. **103**, 11446 (2006).
[3] A. B. Kolomeisky, Phys. Rev. Lett. **98**, 048105 (2007).
[4] S. M. Bezrukov, A. M. Berezhkovskii, and A. Szabo, J. Chem. Phys. **127**, 115101 (2007).
[5] A. M. Berezhkovskii, G. Hummer, and S. M. Bezrukov, Phys. Rev. Lett. **97**, 020601 (2006); J. Alvarez and B. Hajek, Phys. Rev. E **73**, 046126 (2006); A. M. Berezhkovskii and S. M. Bezrukov, J. Phys. Condens. Matter **19**, 065148 (2007).
[6] T. L. Hill, Biochemistry **14**, 2127 (1975).
[7] H. Qian and X. S. Xie, Phys. Rev. E **74**, 010902(R) (2006).
[8] T. L. Hill, Proc. Natl. Acad. Sci. U.S.A. **72**, 4918 (1975).
[9] O. K. Dudko, A. M. Berezhkovskii, and G. H. Weiss, J. Chem. Phys. **121**, 1562 (2004).
[10] L. E. Reichl, *A Modern Course in Statistical Physics* (University of Texas Press, Austin, 1980).
[11] D. J. Evans and D. J. Searles, Phys. Rev. E **50**, 1645 (1994); Adv. Phys. **51**, 1529 (2002); G. Gallavotti and E. G. D. Cohen, Phys. Rev. Lett. **74**, 2694 (1995); J. Stat. Phys. **80**, 931 (1995); J. Kurchan, J. Phys. A **31**, 3719 (1998); J. L. Lebowitz and H. Spohn, J. Stat. Phys. **95**, 333 (1999); C. Maes, J. Stat. Phys. **95**, 367 (1999); C. Jarzynski and D. K. Wojcik, Phys. Rev. Lett. **92**, 230602 (2004); P. Gaspard, J. Chem. Phys. **120**, 8898 (2004); D. Andrieux and P. Gaspard, J. Chem. Phys. **121**, 6167 (2004); J. Stat. Mech. P01011 (2006); U. Seifert, Europhys. Lett. **70**, 36 (2005); R. van Zon, S. Ciliberto, and E. G. D. Cohen, Phys. Rev. Lett. **92**, 130601 (2004); R. D. Astumian, Phys. Chem. Chem. Phys. **9**, 5067 (2007).
[12] A. M. Berezhkovskii and S. M. Bezrukov (to be published).
[13] S. M. Bezrukov, A. M. Berezhkovskii, M. A. Pustovoit, and A. Szabo, J. Chem. Phys. **113**, 8206 (2000).
[14] A. M. Berezhkovskii, M. A. Pustovoit, and S. M. Bezrukov, J. Chem. Phys. **116**, 9952 (2002); **119**, 3943 (2003).
[15] L. S. Kuzmin, P. Delsing, T. Claeson, and K. K. Likharev, Phys. Rev. Lett. **62**, 2539 (1989); K. Capelle, M. Borgh, K. Karkkainen, and S. M. Reimann, Phys. Rev. Lett. **99**, 010402 (2007).