Relaxation and fluctuations of the number of particles in a membrane channel at arbitrary particle-channel interaction

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We analyze the relaxation of the particle number fluctuations in a membrane channel at arbitrary particle-channel interaction and derive general expressions for the relaxation time and low-frequency limit of the power spectral density. These expressions simplify significantly when the channel is symmetric. For a square-well potential of mean force that occupies the entire channel, we verify the accuracy of the analytical predictions by Brownian dynamics simulations. For such a channel we show that as the depth of the well increases, the familiar scaling of the relaxation time with the channel length squared is transformed into a linear dependence on the length. © *2008 American Institute of Physics*. [DOI: 10.1063/1.2972981]

I. INTRODUCTION

When a neutral particle enters a wide ion channel the current through the channel decreases since the particle partially blocks it for ion conduction. A classical example is blockage of the maltoporin channel by entering sugar molecules.[1] Such a blockage leads to a decrease in the average current through the channel. Concurrently, because the number of particles in the channel fluctuates around its average value, this also leads to current fluctuations. Analyzing current fluctuations one is able to study the dynamics of particles in the channel.[1–3]

Current fluctuations are characterized by the power spectral density $S(f)$, which is defined as the Fourier transform of the autocorrelation function of the current fluctuations $\langle \Delta I(t) \Delta I(0) \rangle$, where the angular brackets denote the averaging over realizations,

$$S(f) = 4 \int_0^\infty \langle \Delta I(t) \Delta I(0) \rangle \cos(2\pi f t) dt. \quad (1)$$

The present paper is focused on the power spectral density at zero frequency $S(0)$. Our analysis is based on the diffusion model of the particle dynamics in the channel introduced in Ref. 4 and studied in detail both analytically and numerically (see Ref. 5 and references therein). Below we derive $S(0)$ under quite general assumptions about the particle-channel interaction. Earlier we derived $S(f)$ for the entire range of f using a simplified version of the model in which the particle-channel interaction was neglected and the channel was described as a cylindrical tube.[4] Later we generalized this result by allowing the particle to be reversibly trapped by a binding site.[6] The expression for the spectral density derived in Ref. 6 shows how $S(f)$ transforms from the case of no binding studied in Ref. 4 to the Lorentzian form corresponding to the strong-binding limit.[7–9] Here we derive $S(0)$ for a much more general model of the particle intrachannel dynamics.

Our interest to this problem is motivated by experiments with different macromolecular solutes, which have shown that the current fluctuations due to fluctuations in the number of solutes in wide channels, such as alpha-hemolysin, significantly exceed the current fluctuations due to the electrolyte shot noise.[10] This opens an opportunity to study channel-facilitated transport of metabolites and other macromolecules through biological membranes by measuring current fluctuations.[1–3] One can use noise produced by water-soluble polymers (poly(-ethylene glycol)s, PEGs, dextranes, etc.) to study mechanisms of their transport through the channel, their interactions with the channel-forming proteins, and intrachannel diffusion coefficients.[10]

The outline of this paper is as follows. In the next section we briefly summarize a general formalism, which establishes a relation between $S(0)$ and the relaxation time that characterizes the decay of fluctuations of the number of particles in the channel. A general expression for this time is derived in Sec. III on the basis of the diffusion model of the particle intrachannel dynamics. In this section we also demonstrate that the general expressions simplify significantly when the channel is symmetric. In Sec. IV we discuss simple illustrative examples and some tests of the accuracy of our analytical predictions by Brownian dynamics simulations. Some concluding remarks are made in the final section.

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II. GENERAL FORMALISM

Consider the electric current carried by electrolyte ions through the channel in the absence of nonconducting particles, I_0. We assume that the decrease in the current due to the presence of the particles in the system is proportional to the number of the particles in the channel. This assumption holds true for wide channels and sufficiently low concentrations of the particles. Denoting this number at time t by $N(t)$ we can write the instantaneous value of the current $I(t)$ as

$$I(t) = I_0[1 - \alpha N(t)], \tag{2}$$

where α is a constant. Then the average value of the current, $\langle I\rangle = \langle I(t)\rangle$, is

$$\langle I\rangle = I_0[1 - \alpha N_{\mathrm{eq}}], \tag{3}$$

where $N_{\mathrm{eq}} = \langle N(t)\rangle$ is the average number of the particles in the channel, which can be found from the equilibrium distribution. The current fluctuation, $\Delta I(t) = I(t) - \langle I\rangle$, is proportional to the fluctuation of the number of particles in the channel, $\Delta N(t) = N(t) - N_{\mathrm{eq}}$,

$$\Delta I(t) = -\alpha I_0 \Delta N(t). \tag{4}$$

From this it follows that $S(0)$ is given by

$$S(0) = 4\int_0^\infty \langle \Delta I(t)\Delta I(0)\rangle dt = 4\alpha^2 I_0^2 \int_0^\infty \langle \Delta N(t)\Delta N(0)\rangle dt. \tag{5}$$

Note that since $S(0)$ is proportional to α^2, the power spectral density does not change even when α is negative so that the current through the channel, Eq. (2), increases due to the particle entrance.

We define the conditional average of $\Delta N(t)$, $\langle \Delta N(t)\rangle_{\mathrm{cond}}$, as the fluctuation of the number of particles in the channel at time t on condition that the fluctuation at $t=0$ was $\Delta N(0)$ and the particles were distributed in the channel according to the Boltzmann law. Assuming that the particles inside the channel do not interact with each other we can write $\langle \Delta N(t)\rangle_{\mathrm{cond}}$ in terms of the single-particle relaxation function $R(t)$ as

$$\langle \Delta N(t)\rangle_{\mathrm{cond}} = \Delta N(0) R(t). \tag{6}$$

Then we have

$$\langle \Delta N(t)\Delta N(0)\rangle = N_{\mathrm{eq}} R(t), \tag{7}$$

where we have used the fact that the equilibrium distribution of the number of noninteracting particles in the channel is the Poisson one and, hence, $\langle \Delta N^2\rangle = N_{\mathrm{eq}}$. Eventually we can write $S(0)$ in Eq. (5) as

$$S(0) = 4\alpha^2 I_0^2 N_{\mathrm{eq}} \tau_{\mathrm{rel}}, \tag{8}$$

where we have introduced the relaxation time τ_{rel} defined by

$$\tau_{\mathrm{rel}} = \int_0^\infty R(t) dt. \tag{9}$$

In what follows we derive an expression for τ_{rel} in the framework of the diffusion model of the particle dynamics in the channel mentioned above.

III. RELAXATION TIME

The diffusion model describes particle motion in the channel as one-dimensional diffusion along the channel axis coinciding with the x-axis of the coordinate system. Diffusion occurs in the potential of mean force $U(x)$ with a position-dependent diffusion coefficient $D_{\mathrm{ch}}(x)$, which are assumed to be independent of the number of particles in the channel. The particle propagator $G(x,t|x_0)$ satisfies the Smoluchowski equation

$$\frac{\partial G}{\partial t} = \frac{\partial}{\partial x}\left\{ D_{\mathrm{ch}}(x) p_{\mathrm{eq}}(x) \frac{\partial}{\partial x}[p_{\mathrm{eq}}^{-1}(x) G] \right\}, \quad x_L < x < x_R, \tag{10}$$

where x_L and x_R are positions of the left and right boundaries of the channel and $p_{\mathrm{eq}}(x)$ is the intrachannel Boltzmann distribution,

$$p_{\mathrm{eq}}(x) = \frac{\exp[-U(x)/(k_B T)]}{\int_{x_L}^{x_R} \exp[-U(y)/(k_B T)] dy}, \quad x_L < x < x_R, \tag{11}$$

with the standard notations, k_B and T, for the Boltzmann constant and absolute temperature. The propagator reduces to the delta function at $t=0$, $G(x,0|x_0) = \delta(x - x_0)$, $x_L < x_0 < x_R$, and satisfies radiation boundary conditions at the channel ends,

$$D_{\mathrm{ch}}(x_L) p_{\mathrm{eq}}(x_L) \left.\frac{\partial}{\partial x}\{p_{\mathrm{eq}}^{-1}(x) G\}\right|_{x=x_L} = \kappa_L G|_{x=x_L},$$

$$D_{\mathrm{ch}}(x_R) p_{\mathrm{eq}}(x_R) \left.\frac{\partial}{\partial x}\{p_{\mathrm{eq}}^{-1}(x) G\}\right|_{x=x_R} = -\kappa_R G|_{x=x_R}, \tag{12}$$

where the rate constants κ_L and κ_R are given in terms of the channel radius $r_{\mathrm{ch}}(x_{L,R})$ and the particle diffusion coefficient in the bulk, D_b, by[4]

$$\kappa_{L,R} = \frac{4 D_b}{\pi r_{\mathrm{ch}}(x_{L,R})}. \tag{13}$$

The probability of the particle survival in the channel for time t on condition that the particle starts from x_0, $S(t|x_0)$, is given by

$$S(t|x_0) = \int_{x_L}^{x_R} G(x,t|x_0) dx. \tag{14}$$

The relaxation function $R(t)$ is the equilibrium average of $S(t|x_0)$,

$$R(t) = \int_{x_L}^{x_R} S(t|x_0) p_{\mathrm{eq}}(x_0) dx_0. \tag{15}$$

Substituting this into Eq. (9) we find that the relaxation time can be written as

$$\tau_{\mathrm{rel}} = \langle \tau(x_0)\rangle_{\mathrm{eq}} = \int_{x_L}^{x_R} \tau(x_0) p_{\mathrm{eq}}(x_0) dx_0, \tag{16}$$

where $\tau(x_0)$ is the average lifetime in the channel for a particle which starts from x_0,

$$\tau(x_0) = \int_0^\infty S(t|x_0)dt. \tag{17}$$

This time considered as a function of x_0 satisfies the adjoint Smoluchowski equation,[11,12]

$$\frac{d}{dx_0}\left[D_{\rm ch}(x_0)p_{\rm eq}(x_0)\frac{d\tau(x_0)}{dx_0}\right] = -p_{\rm eq}(x_0), \tag{18}$$

with the boundary conditions

$$D_{\rm ch}(x_L)\left.\frac{d\tau(x_0)}{dx_0}\right|_{x=x_L} = \kappa_L\tau(x_L),$$

$$D_{\rm ch}(x_R)\left.\frac{d\tau(x_0)}{dx_0}\right|_{x=x_R} = -\kappa_R\tau(x_R). \tag{19}$$

Solving this equation we find

$$\tau(x_0) = \frac{1+\kappa_L F_L(x_0)+\kappa_R' F_R(x_0)+\kappa_L\kappa_R' F_{LR}(x_0)}{\kappa_L'+\kappa_R'+\kappa_L'\kappa_R'\int_{x_L}^{x_R}\frac{dz}{D_{\rm ch}(z)p_{\rm eq}(z)}}, \tag{20}$$

where $\kappa_{L,R}' = \kappa_{L,R}p_{\rm eq}(x_{L,R})$ and functions $F_L(x_0)$, $F_R(x_0)$, and $F_{LR}(x_0)$ are given by

$$F_L(x_0) = \int_{x_L}^{x_0}\frac{dz}{D_{\rm ch}(z)p_{\rm eq}(z)}\int_z^{x_R}p_{\rm eq}(y)dy, \tag{21}$$

$$F_R(x_0) = \int_{x_0}^{x_R}\frac{dz}{D_{\rm ch}(z)p_{\rm eq}(z)}\int_{x_L}^{z}p_{\rm eq}(y)dy, \tag{22}$$

and

$$\begin{aligned}F_{LR}(x_0) = &\left[\int_{x_L}^{x_0}\frac{dz}{D_{\rm ch}(z)p_{\rm eq}(z)}\right]\\ &\times\left[\int_{x_L}^{x_R}\frac{dz}{D_{\rm ch}(z)p_{\rm eq}(z)}\int_{x_L}^{z}p_{\rm eq}(y)dy\right]\\ &-\left[\int_{x_L}^{x_R}\frac{dz}{D_{\rm ch}(z)p_{\rm eq}(z)}\right]\\ &\times\left[\int_{x_L}^{x_0}\frac{dz}{D_{\rm ch}(z)p_{\rm eq}(z)}\int_{x_L}^{z}p_{\rm eq}(y)dy\right].\end{aligned} \tag{23}$$

As $D_{\rm ch}(x)\to\infty$ (fast intrachannel equilibration) $\tau(x_0)$ becomes independent of x_0 and is given by

$$\tau(x_0) = \frac{1}{\kappa_L'+\kappa_R'}. \tag{24}$$

In the opposite limit of very slow intrachannel diffusion, which is equivalent to the limit when $\kappa_L,\kappa_R\to\infty$, $\tau(x_0)$ in Eq. (20) reduces to the mean first passage time from x_0 to the channel ends, $\tau_{\rm FP}(x_0)$,

$$\tau_{\rm FP}(x_0) = \frac{F_{LR}(x_0)}{\int_{x_L}^{x_R}\frac{dz}{D_{\rm ch}(z)p_{\rm eq}(z)}}. \tag{25}$$

Averaging $\tau(x_0)$ in Eq. (20) according to Eq. (16) we arrive at

$$\tau_{\rm rel} = \langle\tau(x_0)\rangle_{\rm eq} = \frac{1+\kappa_L'G_L+\kappa_R'G_R+\kappa_L'\kappa_R'G_{LR}(x_0)}{\kappa_L'+\kappa_R'+\kappa_L'\kappa_R'\int_{x_L}^{x_R}\frac{dz}{D_{\rm ch}(z)p_{\rm eq}(z)}}, \tag{26}$$

where

$$G_L = \int_{x_L}^{x_R}\frac{dz}{D_{\rm ch}(z)p_{\rm eq}(z)}\left[\int_z^{x_R}p_{\rm eq}(y)dy\right]^2, \tag{27}$$

$$G_R = \int_{x_L}^{x_R}\frac{dz}{D_{\rm ch}(z)p_{\rm eq}(z)}\left[\int_{x_L}^{z}p_{\rm eq}(y)dy\right]^2, \tag{28}$$

and

$$\begin{aligned}G_{LR} = &\left[\int_{x_L}^{x_R}\frac{dz}{D_{\rm ch}(z)p_{\rm eq}(z)}\int_z^{x_R}p_{\rm eq}(y)dy\right]\\ &\times\left[\int_{x_L}^{x_R}\frac{dz}{D_{\rm ch}(z)p_{\rm eq}(z)}\int_{x_L}^{z}p_{\rm eq}(y)dy\right]\\ &-\left[\int_{x_L}^{x_R}\frac{dz}{D_{\rm ch}(z)p_{\rm eq}(z)}\right]\\ &\times\left\{\int_{x_L}^{x_R}\frac{dz}{D_{\rm ch}(z)p_{\rm eq}(z)}\left[\int_z^{x_R}p_{\rm eq}(y)dy\right]\right.\\ &\left.\times\left[\int_{x_L}^{z}p_{\rm eq}(y)dy\right]\right\}.\end{aligned} \tag{29}$$

The expression in Eq. (26), which gives the relaxation time at arbitrary particle-channel interaction, is one of the main results of this paper. Substituting this relaxation time into Eq. (8) one obtains a general expression for the power spectral density of fluctuations of the ion current through the channel at zero frequency, $S(0)$.

The expression for $\tau(x_0)$, Eqs. (20)–(23), significantly simplifies for a symmetric (sym) channel, i.e., when $\kappa_L=\kappa_R=\kappa$ and both $U(x)$ and $D_{\rm ch}(x)$ are symmetric functions of x about the center of the channel located at $x=x_c=(x_L+x_R)/2$. In this case $\tau_{\rm sym}(x_0)$ is given by

$$\tau_{\rm sym}(x_0) = \tau_{\rm FP}^{\rm (sym)}(x_0)+\frac{1}{2\kappa'}, \tag{30}$$

where $\kappa' = \kappa p_{\rm eq}(x_L) = \kappa p_{\rm eq}(x_R)$ and $\tau_{\rm FP}^{\rm (sym)}(x_0)$ is the mean first passage time for the symmetric channel given by

$$\tau_{\rm FP}^{\rm (sym)}(x_0) = \tau_{\rm FP}^{\rm (sym)}(x_c) - \int_{x_c}^{x_0}\frac{dz}{D_{\rm ch}(z)p_{\rm eq}(z)}\int_{x_c}^{z}p_{\rm eq}(y)dy, \tag{31}$$

with

$$\tau_{\rm FP}^{\rm (sym)}(x_c) = \int_{x_c}^{x_{R,L}}\frac{dz}{D_{\rm ch}(z)p_{\rm eq}(z)}\int_{x_c}^{z}p_{\rm eq}(y)dy. \tag{32}$$

Equation (30) shows that $\tau_{\rm sym}(x_0)$ is simply a sum of two times which correspond to the limits of very fast and very slow intrachannel equilibration. This is a unique property of symmetric channel, which does not work in the general case, Eq. (20).

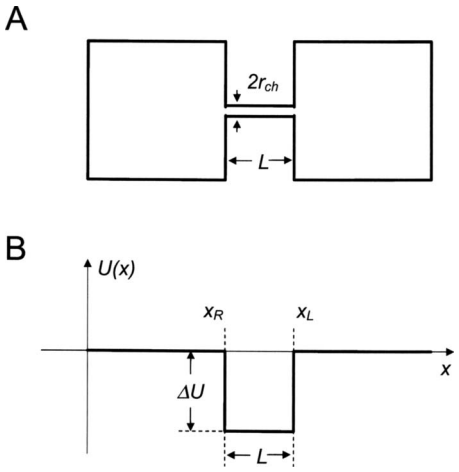

FIG. 1. (A) Cylindrical channel connecting two reservoirs. (B) The profile of the potential of mean force used in Brownian dynamics simulations.

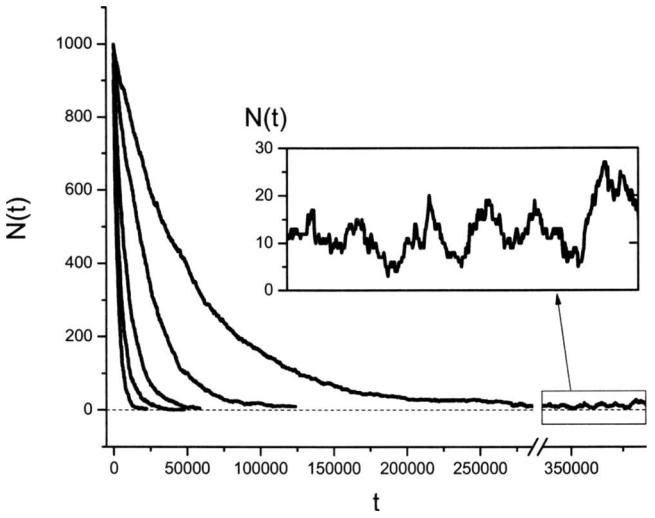

FIG. 2. Relaxation of the particle number in the channel obtained in Brownian dynamics simulations for a channel with $L=50$ and $r_{ch}=5.5$. The channel connects two cubic reservoirs of side length of 200. The total number of particles in the system is 1000. Initially all the particles are uniformly distributed in the channel. The tracks correspond to the increasing well depths ΔU of the square-well potential of mean force [Fig. 1(b)], $\Delta U/(k_BT)=0$, 1, 2, 3, and 4 from left to right, correspondingly. The inset shows a fragment of the track corresponding to stationary equilibrium fluctuations in the number of particles at $\Delta U/(k_BT)=4$.

As follows from Eq. (30) the relaxation time for a symmetric channel, $\tau_{\mathrm{rel}}^{(\mathrm{sym})}$, is given by

$$\tau_{\mathrm{rel}}^{(\mathrm{sym})}=\langle\tau_{\mathrm{FP}}^{(\mathrm{sym})}(x_0)\rangle_{\mathrm{eq}}+\frac{1}{2\kappa'}, \tag{33}$$

where $\langle\tau_{\mathrm{FP}}^{(\mathrm{sym})}(x_0)\rangle_{\mathrm{eq}}$ is the equilibrium average of $\tau_{\mathrm{FP}}^{(\mathrm{sym})}(x_0)$,

$$\langle\tau_{\mathrm{FP}}^{(\mathrm{sym})}(x_0)\rangle_{\mathrm{eq}}=\int_{x_L}^{x_R}\tau_{\mathrm{FP}}^{(\mathrm{sym})}(x_0)p_{\mathrm{eq}}(x_0)dx_0$$
$$=\int_{x_L}^{x_R}\frac{dz}{D_{\mathrm{ch}}(z)p_{\mathrm{eq}}(z)}\left[\int_{x_c}^{z}p_{\mathrm{eq}}(y)dy\right]^2. \tag{34}$$

One can see that the expressions giving the relaxation time for a symmetric channel, Eqs. (33) and (34), are much simpler than their counterparts in the general case, Eqs. (26)–(29). The result in Eq. (33) was reported earlier in Ref. 4 without a derivation.

IV. ILLUSTRATIVE EXAMPLES

To illustrate general expressions derived in the last section, consider a symmetric cylindrical channel of radius r_{ch} and length L in the case when intrachannel potential is a square well of depth ΔU that occupies the entire channel (Fig. 1). For such a channel

$$\kappa'=\frac{4D_b}{\pi r_{\mathrm{ch}}L}\exp\left(-\frac{\Delta U}{k_BT}\right). \tag{35}$$

Assuming that $D_{\mathrm{ch}}(x)$ is a constant, $D_{\mathrm{ch}}(x)=D_{\mathrm{ch}}$, we use Eq. (34) to find that $\langle\tau_{\mathrm{FP}}^{(\mathrm{sym})}(x_0)\rangle_{\mathrm{eq}}=L^2/(12D_{\mathrm{ch}})$. As a result, the relaxation time in Eq. (33) takes the form

$$\tau_{\mathrm{rel}}^{(\mathrm{sym})}=\frac{L^2}{12D_{\mathrm{ch}}}+\frac{\pi r_{\mathrm{ch}}L}{8D_b}\exp\left(\frac{\Delta U}{k_BT}\right). \tag{36}$$

One can see that in the absence of the particle attraction to the channel, $\Delta U=0$, the relaxation time for a long channel, $L\gg r_{\mathrm{ch}}$, is close to the averaged mean first passage time to the channel ends [the first term on the right-hand side of Eq. (36)]. In the opposite limit, $\Delta U\gg k_BT\ln[D_bL/D_{\mathrm{ch}}r_{\mathrm{ch}}]$, the rate limiting step is the particle escape from the deep potential well. In this case τ_{rel} is close to the second term on the right-hand side of Eq. (36).

To check the validity of the analytical results derived in the framework of the approximate one-dimensional description of the particle intrachannel dynamics, we ran three-dimensional Brownian dynamics simulations in the geometry shown in Fig. 1. In our simulations two cubic reservoirs of the side length of 200 were connected by a cylindrical channel of radius $r_{\mathrm{ch}}=5.5$ and lengths $L=25$, 50, and 100. The dimensionless well depth $\Delta U/(k_BT)$ of the attractive square-well potential that occupied the entire channel was taken to be equal to $\Delta U/(k_BT)=0$, 1, 2, 3, and 4. The particles were allowed to diffuse freely with the same diffusion coefficient in the reservoirs and in the channel, $D_b=D_{\mathrm{ch}}=0.125$. The time step was equal to unity. When a trajectory step intersected either of the channel openings from inside, the particle was randomly allowed to exit the channel with probability $\exp[-\Delta U/(k_BT)]$. With probability $1-\exp[-\Delta U/(k_BT)]$ the particle position was left unchanged.

In our numerical experiments all particles, $N=1000$, were uniformly distributed in the channel at $t=0$ while the reservoirs were empty. In the course of the simulations we monitored the number of the particles in the channel, $N(t)$, as a function of time. Typical curves are shown in Fig. 2. The curves describe the decay of $N(0)=1000$ to its equilibrium value. More precisely, as $t\to\infty$ the curves describe equilibrium fluctuations of $N(t)$ around their equilibrium values. The relaxation curves, examples of which are shown in Fig. 2, were then averaged over five independent simulation runs. The resulting averaged relaxation curves were used to find τ_{rel} as the area under the curve, Eq. (9). We compare theoretical predictions for τ_{rel} to the numerical results in Fig. 3. One can see an excellent agreement between the two.

Independently we use Brownian dynamics simulations to

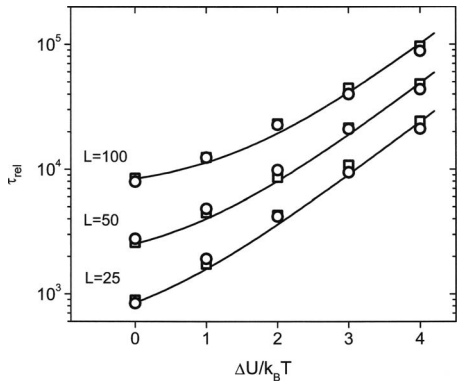

FIG. 3. Relaxation time τ_{rel} found numerically by two methods as the area under the relaxation curves (squares) and from the power spectral density $S_{\delta N}(0)$ as the ratio $S_{\delta N}(0)/(4N_{eq})$ (circles). The solid curves are τ_{rel} predicted by Eq. (36) with $D_b=D_{ch}=0.125$ and $r_{ch}=5.5$.

compute the power spectral density of the equilibrium fluctuations of the number of particles in the channel at zero frequency, $S_{\delta N}(0)$,

$$S_{\delta N}(0) = 4\int_0^\infty \langle \Delta N(t)\Delta N(0)\rangle dt. \tag{37}$$

This quantity is related to the relaxation time by the relationship

$$S_{\delta N}(0) = 4N_{eq}\tau_{rel} \tag{38}$$

as follows from Eq. (8) with $\alpha=I_0=1$. In Fig. 3 we use circles to show τ_{rel} found as the ratio $S_{\delta N}(0)/(4N_{eq})$. One can see a very good agreement between τ_{rel} found by the two different methods.

When particles entering the channel are polymers, the decrease in the channel conductance produced by one "particle" is proportional to the polymer chain length N_p,[13] i.e., α in Eq. (2) is proportional to N_p. Moreover, both the average number of the polymers in the channel and the relaxation time are functions of N_p, $N_{eq}=N_{eq}(N_p)$ and $\tau_{rel}=\tau_{rel}(N_p)$. Thus, in this case the spectral density in Eq. (8) is also a function of N_p having the form, $S(0)\propto N_p^2 N_{eq}(N_p)\tau_{rel}(N_p)$. The dependence $N_{eq}(N_p)$ approaches zero for sufficiently large N_p as polymers with large N_p do not enter the channel. As a consequence, the product $N_p^2 N_{eq}(N_p)$ is a bell-shaped function of N_p. This leads to a bell-shaped dependence of the experimentally observed spectral density $S(0)$,[10] in which the shape and position of the maximum may be significantly modified by the N_p-dependence of the relaxation time.

V. CONCLUDING REMARKS

In the present study we have extended our previous work on fluctuations in the number of particles in a cylindrical channel to the case of arbitrary interactions between the particles and the channel. Although the corresponding power spectral densities are rather complex and differ from simple Lorentzian spectra, the low-frequency asymptote $S(0)$—sometimes the only part of the spectrum available in experiment—can be calculated using the potential of mean force of the particle and its intrachannel diffusion coefficient. Time-dependent behavior of the fluctuations characterized by $S(0)$ can be linked to the relaxation: as shown in Eq. (8), $S(0)$ is proportional to the relaxation time τ_{rel} defined in Eq. (9). In the case of a square-well potential occupying the entire channel, the expression for τ_{rel} has a simple form, Eq. (36), which shows that as the depth of the potential well increases, the dependence of the relaxation time on the channel length undergoes transition from the usual quadratic dependence to the linear one. We hope that these analytical results will be useful in interpreting experiments on channel-facilitated particle transport through biological membranes as well as for understanding noise phenomena in synthetic nanopores and nanofluidic devices.[14–17]

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