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Theory of single-file multiparticle diffusion in narrow pores

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Single-file diffusion of multiple strongly interacting particles in a one-dimensional pore is described within a general analytical framework. The theory accounts for nonequilibrium conditions, explicit particle-particle interactions, external potential acting on the particles and the fluctuations of the number of particles due to their exchange with external equilibrium reservoirs. It is shown that the problem can be reduced to a closed hierarchical set of partial differential equations of increasing dimensionality, which can be solved numerically. Our framework allows computing any macroscopic characteristic of multiparticle diffusion in the pore. It is shown that the pore occupancy probabilities and the current are rational functions of external concentrations in the steady state. The theory is tested on a simplified model of the narrow rigid pore inspired by the selectivity filter of biological ion channel. Perspectives and limitations of the theory are discussed.

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I. INTRODUCTION

The narrow nanoscale pores, which conduct ions or other small molecules, constitute a significant challenge for physical modeling. Such pores exhibit a range of unique properties, which are never observed in macroscopic pores or bulk liquids. Particularly, the particles in very narrow nanoscale pores cannot pass by each other (single-file motion). The pore can also be long enough to accommodate more than one particle at the same time. The examples of such nanopores, which are very important for practical applications, are the ion channels of biological membranes [1–3] and carbon nanotubes [4,5]. The ion channels span the membranes and connect two solutions with very different electrochemical potentials of the permeating ions. Thus they function in strongly nonequilibrium conditions. The same is true for possible applications of the carbon nanotubes as transport channels or nanopipettes. The macroscopic flux of the permeating particles through these objects is of great importance for practical applications.

Despite the fact that the narrow pores with multiple occupancy are known for many years, there is no universally accepted dedicated physical theory of these objects. Narrow pores are routinely studied by molecular dynamics (MD) [6–8] or Brownian dynamics (BD) [7,9–11] simulations. In these approaches the motion equations of individual particles in the pore and in the adjacent regions of solutions are solved numerically and the properties of the channel are obtained as time averages over simulated trajectories. This approach is very effective in revealing fine details of interactions inside the channel and provided invaluable insight into the functioning of the biological ion channels. Despite current limitations imposed by the computer power and certain methodological issues successful attempts are made to predict the current through the channels using MD [12] and BD [7,11]. It is obvious that these limitations would be eventually eliminated by rapid advance in computer hardware and simulation software.

However, it is often desirable to have more general theoretical picture of the physical processes in the narrow pores with multiple occupancy. Although the general theory is unable to describe particular molecular system at the same level of details as atomistic simulations, it can complement them in many important aspects:

(1) the theory is independent on atomistic design of particular object. Thus it can describe universal principles of the diffusion in narrow pores in any natural or artificial system.

(2) The theory provides conceptual overview of possible phenomena in the pores, which may or may not be observed in particular system in particular conditions;

(3) the necessary conditions for particular type of behavior could be formulated;

(4) very wide range of pore parameters and external conditions could be studied;

(5) macroscopic characteristics of the pore (such as particle density, current or distribution of occupancy states) could be computed for the objects, which are either not suitable for atomistic simulations or does not justify such time-consuming modeling; and

(6) the theory could be used as an "ideal reference" for simulations or experimental studies. Deviations of the experimental data from the predictions of the theory could be more valuable for analysis than the experimental data themselves.

It is necessary to note that any general theory could not be immediately applied to real complicated molecular systems. However, the parameters obtained from real systems could be used to obtain an idealized and simplified model of particular object.

Several approaches to analytical description of the narrow pores exist. The discrete description is utilized in the so-called "rate theories" [3,13,14], which are very popular and widespread in the ion channel science. In this approach multiple ions can reside in the binding sites inside the channel and move by jumping over the energy barriers between the sites. The rate theories can predict many characteristics of the real channels, but possess several drawbacks. These models are usually phenomenological. The heights of the energy barriers between the binding sites are often hard to estimate especially if the number of sites is large. The continuous diffusion of ions in the realistic energy profiles cannot be described if the profiles lack pronounced binding sites or possess wide and deep energy wells containing several ions. In the majority of rate theories the interaction between the ions is treated at the level of so-called "kinematics interaction," which means that no more than one ion can occupy the binding site. Such description is usually oversimplified and becomes inadequate if the ions interact strongly at short distances inside deep and wide energy well.

The continuous description is used in the classical theories of the ion diffusion based on the Poisson-Boltzmann or the Poisson-Nernst-Planck equations. The discrete nature of the permeating particles is averaged out in these theories and the macroscopic characteristics of the system are considered. Although these theories are often successful for large macroscopic pores, they are unable to predict many properties of the very narrow pores which contain several ions [11,15,16]. Recently these theories were revised in the case of confined geometries. In the work [17] the diffusion of particles in the narrow pore is reduced to the hierarchical system of the Poisson-Nernst-Planck-like equations. This theory is build in terms of effective concentrations and leads to the infinite hierarchy of multiparticle equations, which resembles the Bogolyubov-Born-Green-Kirkwood-Yvon (BBGKY) chain of equations. Although this theory is quite general and robust, it does not lead to the closed system of equations (additional considerations should be used to close the system).

Another continuous approach is based on the multidimensional Fokker-Plank equations, which describe the evolution of the particle density distribution for each of the possible pore occupancies. These equations could be obtained as a continuous limit of the rate theory approach, when the number of discrete binding sites approaches infinity [14], or as continuous representation of the stochastic Langevin equations [18]. This description is detailed enough to account explicitly for the complex energy profiles inside the pore and for explicit particle-particle interactions. Therefore, this approach is promising for creating robust, general and detailed analytical theory of the diffusion in the narrow pores. Present work is also based on the formalism of the multidimensional Fokker-Plank equations.

One of the problems, which arise in the analytical theories in general and in the theories based on the Fokker-Plank equations in particular, is the choice of the boundary conditions. The boundary conditions depend on the model of the pore boundary and the details of particle exchange events adopted in the theory. It is obvious that the particle, which leaves the pore, can reenter it with certain probability, which decreases with time and depends on the diffusion coefficient and the properties of the transition region between the pore and the bulk solution (the vestibule). As a consequence effective concentration of particles in the vicinity of the channel entrance differs from the concentration in the bulk solution [19]. The microscopic kinetic balance at the pore boundary is usually considered in order to describe complex events particle escape and reentrance. This method is the most straightforward, but it leads to complex boundary conditions, which contain unknown kinetic constants. The complexity of such boundary conditions is shown in details in the work of Stephan *et al.* [14], where the microscopic rate constant theory for the channel with multiple occupancy was developed systematically and transformed to the system of the Fokker-Planck equations in continuous limit [14]. The equations for n and $n+1$ particles are coupled by means of unknown kinetic parameters of the channel boundaries. The boundary conditions are quite nontrivial in the case of two particles and become extremely complex in the general case. As a result the pores with more then two ions are not considered [14]. Another example of complex boundary conditions, which contain the current through the channel, can be found in the work [19]. In the present work an explicit microscopic description of the ion exchange events is avoided, which greatly simplifies boundary conditions and puts our framework apart from existing analytical theories.

Another problem of analytical theories is that the equation can only be written for given number of particles, while this number fluctuates in real pore. Thus, different occupancy states of the pore and transitions between them should be taken into account. In the pioneering work of Levitt [20] this problem was first addressed in the case of the single-ion channel, which can exists in the states with and without an ion. The empty channel is modeled by a single state, which is associated with the ion exchange events at both sides of the channel. In the work [19] this scheme was improved by eliminating unphysical correlations between the exit of the ion from one side of the channel and its reentrance from the other side. Despite successful application to Gramicidin channel [21] this approach was not generalized to the channels with multiple occupancy. The ion exchange with external solutions is mimicked by the empty state and the corresponding kinetic constants in this approach. Thus the weights of the occupancy states depend on unknown kinetic parameters, which is not always acceptable. Another approach to the problem of variable pore occupancy is developed in the works of Nelson [22] and Roux [23] where the properties of the channel are expressed as the weighted averages over occupancy states. The corresponding occupancy states theory of Nelson [22] is a purely phenomenological kinetic theory. It is based on common structural features of two biological channels (the gramicidin A channel and the KcsA channel selectivity filter), which limits its generality. The statistical theory of Roux [23], being quite general, is formulated for equilibrium conditions, thus the current through the channel and other nonequilibrium properties cannot be computed. Despite the limitations, these theories demonstrate that the averaging over discrete occupancy states is a very effective way of describing channels with fluctuating number of particles. In the present work we generalized this approach to the case of nonequilibrium conditions and used it in our analytical framework.

It is possible to conclude that a general theory of multiparticle diffusion in narrow pores is highly demanded now. The goal of this work is development of such general theory of the multiparticle single-file diffusion. The distinctive features of our theory are the following:

(1) our theory is based on the very basic principles of nonequilibrium statistical physics and the theory of probability. It is built in the bottom-up manner with minimal and controllable assumptions and maximal generality in mind;

(2) it describes one-dimensional single-file diffusion of multiple particles in a narrow pore in nonequilibrium condi-

tions. The effects of different particle concentrations and the external electrostatic potential are taken into account;

(3) the particles move in an arbitrary potential, created by the pore walls, and interact strongly by means of an arbitrary repulsive interaction potential;

(4) Any nonequilibrium macroscopic characteristic of the pore (such as the current or the mean occupancy) can be computed if the external conditions and the interaction potentials inside the pore are known;

(5) the problem is reduced to a closed set of simple partial differential equations of increasing dimensionality. The number of equations is limited and equal to the maximal number of particles, which can reside in the pore. This set can be solved numerically for any number of particles, which is only limited by the computer time and memory; and

(6) the fluctuations of the number of particles, which occur due to exchange between the pore and external solutions, are taken into account without explicit modeling of complex kinetics of the particle exchange events and the pore vestibules. It is assumed that the correlations between the particles, which remain in the pore and the particle, which crosses the pore boundary are lost immediately upon escape. This leads to convenient factorization of the probability density functions and allows considering the solutions as ideal thermal bathes. This assumption leads to very simple and natural boundary conditions and allows computing the probabilities of the occupancy states without additional assumptions and parameters. More complex models of the pore vestibules may be used if necessary.

Our theory is tested by applying it to the simplified model of the single-file pore with rigid structure inspired by the selectivity filter of the KcsA ion channel, which was developed in our previous works [24,25]. The pore is considered rigid in the sense that there are no motions in the pore wall with the characteristic times larger then the characteristic particle passage time. It is necessary to emphasize that this model is nothing more than simple, general and convenient playground for testing our theoretical developments. It has no relation to real ion channel except the dimensions and the qualitative shape of the energy profile. It is chosen as a test case because of its simplicity and immediate compatibility with the formalism developed in this work. The results obtained with this model should not be compared with real ion channels in realistic conditions. Since this work presents the method in development, no attempts were made to build more realistic models of real ion channels or other single-file pores. The macroscopic characteristics of this simplified model are obtained in a wide range of parameters and compared to the results of earlier studies [25]. The predictions of our theory correlate very well with earlier results obtained by other techniques. This confirms the correctness of our theoretical framework.

II. THEORY

A. Formulation of the problem and the basic assumptions

Let us consider a system, which consists of two reservoirs of particles G_1 and G_2 and a narrow channel G_{Ch}, which connects them. The motion of particles in the channel is one dimensional and single-file (the particles do not pass by each other). The particles move along the coordinate $x \in (-L;L)$, where points $\pm L$ correspond to the ends of the channel. The particles interact strongly with each other and with the channel structure. The number of particles in the channel fluctuates in time due to exchange with the reservoirs. Not more than M particles can reside in the channel at the same time.

There are fixed concentrations of particles c_1' and c_2' in the reservoirs (in $1/\text{Å}^3$ units). They correspond to "one-dimensional concentrations" c_1 and c_2 (in $1/\text{Å}$ units) on the channel boundaries,

$$c_{1,2} = c_{1,2}' S \tag{1}$$

where S is the effective cross section of the channel on its boundaries. We will use the term "concentration" for $c_{1,2}$ hereafter for the sake of simplicity. The electrostatic potentials in the reservoirs are $-\psi$ and ψ, respectively. The reservoirs are considered to be in thermodynamic equilibrium.

It is assumed that there is no correlation between the motion of particles in the channel and in the reservoirs. This assumption is the key point of our theory. It presumes that the particle, which crosses the pore boundary and escapes to the reservoir, loses all correlations with the particles, which remain in the pore immediately. This means that the probability of reentry of the escaped particle is the same as the probability of entry of any other particle from the reservoir (the particle has no memory). As a result the reservoirs do not "feel" the presence of the pore and could be considered as ideal heat bathes with given concentrations of particles. The basic assumption of the immediate loss of correlations at the pore boundary allows describing this boundary in the model-free manner but the models of the pore vestibules could also be incorporated if necessary. This basic assumption can also be derived from dynamic equations in certain conditions as it is shown in Appendix B.

There are no energy barriers between the channel and the reservoirs, so the exchange of particles between the channel and the reservoirs is purely diffusive. Let us assume that the volumes of the reservoirs are V_1 and V_2 and the total number of particles in the system $G = G_1 \cup G_{Ch} \cup G_2$ is $N \gg M$ (these auxiliary quantities will vanish later in the thermodynamic limit).

All energies are in the k_BT units, where k_B is the Boltzmann constant, T is the absolute temperature. All quantities in the theory are assumed to be dependent on time. In the expressions where the arguments are omitted for compactness the parameter t is also omitted. Steady state quantities are marked explicitly. Our task is to find such nonequilibrium quantities of the channel as the distribution of the particle density along the channel, the current, the mean occupancy, etc., as functions of particle concentrations in reservoirs and external potentials.

B. Outline of the theory

The main difficulty of describing our system is that the number of particles in the channel is variable, while all conventional dynamic equations and relations of the statistical physics, which describe nonequilibrium systems, operate with a fixed number of particles. The idea of our theoretical development is to present the distribution function of our system as a series in discrete channel occupancies. Such decomposition is straightforward at equilibrium [23], but becomes nontrivial in our case. The outline of the theoretical development is the following:

(1) the N-particle distribution function of the whole system $F(x_1,\dots,x_N;t)$ is constructed taking into account the properties of the reservoirs. Hereafter $x_1,\dots,x_N$ are the coordinates of particles, t is the time;

(2) the probabilities w_n of the occupancy states with n particles inside the channel are found $(0 \le n \le M)$;

(3) the partial distribution functions $f_m^{(n)}(x_1,\dots,x_m;t)$ of m $(m \le n)$ particles in the channel, which contains n particles are found. All quantities of the reservoirs except $c_{1,2}$ and ψ vanish at this step after transition to the thermodynamic limit;

(4) it is shown that any property of the channel can be obtained as a series in channel occupancies. They depend on unknown n-particle distribution functions inside the channel $\phi^{(n)}(x_1,\dots,x_n;t)$; and

(5) it is shown that the distribution functions $\phi^{(n)}(x_1,\dots,x_n;t)$ are the solution of the hierarchical set of partial differential equations, which is obtained from the Langevin equation of motion of the particles inside the channel.

C. Multiparticle distribution function of the whole system

Let $x_1,x_2,\dots,x_N$ be the coordinates of N identical particles located in the whole region $G=G_1 \cup G_{Ch} \cup G_2$. x_i's are assumed to be the vectors in the reservoirs and the scalars in the channel. It is obvious that $N=\bar{N}_1+\bar{N}_{Ch}+\bar{N}_2$, where $\bar{N}_i$ is the average number of particles in the region i. Thus, the concentrations are $c_i=\frac{\bar{N}_i}{V_i}$. Let us construct the N-particle distribution function $F(x_1,\dots,x_N;t)$ of the whole system G.

The role of the reservoirs in our system is only to provide the equilibrium heat baths with constant concentrations of particles. Thus we assume the simplest possible model of the reservoirs with independent particles (which do not interact or interact in the mean field approximation) so that the multiparticle distribution function is factorized in the reservoirs. The distribution function (not normalized) of any particle i in any of the reservoirs can be written as

$$\tilde{\varphi}(x_i) = \lambda_1\chi_1(x_i) + \lambda_2\chi_2(x_i), \tag{2}$$

where

$$\chi_j(x_i) = \begin{cases} 1, & if\ \ x_i \in G_j \\ 0, & if\ \ x_i \notin G_j \end{cases} \qquad \mathrm{j} = 1,2,Ch \tag{3}$$

is the auxiliary function which selects one of the regions, $\lambda_i=e^{\mu_i}$ is the absolute chemical activity, μ_i is the chemical potential in the ith region. The chemical activity is proportional to concentration $\lambda_i=\vartheta \cdot c_i$, where ϑ is the coefficient of chemical activity. Since the model of the reservoirs is arbitrary, it is possible to assume that $\vartheta \equiv 1$, which is always true for the solutions of independent particles. In the steady state theory arbitrarily values of ϑ could be used (see Appendix A). Equation (2) can be rewritten as

$$\tilde{\varphi}(x_i) = c_1\chi_1(x_i) + c_2\chi_2(x_i). \tag{4}$$

It is not possible to factorize the distribution function in the region G_{Ch}, thus the multiparticle distribution functions of n ions, which reside in the channel $\phi^{(n)}(x_1,\dots,x_n;t)$ should be introduced $(\phi^{(0)} \equiv 1)$. The general distribution function $F(x_1,\dots,x_N;t)$ can be written then as a sum over the states with a fixed number of particles in the channel,

$$F(x_1,\dots,x_N;t) = Z^{-1}\sum_{n=0}^{M}\frac{1}{n!}\sum_{\substack{i_{1,2\dots n}=1\\(i_1\neq i_2\neq\dots i_n)}}^{N} \times \phi^{(n)}(x_{i_1},\dots,x_{i_n};t)\prod_{\substack{k=1\\(k\neq i_{1,2\dots n})}}^{N}\tilde{\varphi}(x_k), \tag{5}$$

where Z is the normalization factor. We assume that all particles in the system are physically indistinguishable but assigned unique numbers to aid subsequent derivations. The notation x_{i_j} here and below means that the particle with number i_j resides in jth place inside the channel counting from the left boundary. The factor $1/n!$ appears because the function $\phi^{(n)}(x_1,\dots,x_n;t)$ is defined symmetric (invariant by swapping the coordinates of each two particles).

If the ith particle reaches the boundary of the channel $(x_i=\pm L)$, then it is considered to be in the corresponding reservoir. By definition, it loses interaction with other particles in the channel (no correlations of motion between particles inside the channel and in the reservoirs), thus

$$\begin{aligned}\phi^{(n)}(x_1,\dots,x_n;t)\big|_{x_i=\mp L} &= \tilde{\varphi}(x_i)\big|_{x_i=\mp L} \\ &\times \phi^{(n-1)}(x_1,\dots x_{i-1},x_{i+1}\dots x_{n-1};t) = c_{1,2} \\ &\times \phi^{(n-1)}(x_1,\dots x_{i-1},x_{i+1}\dots x_{n-1};t).\end{aligned} \tag{6}$$

Expression (6) is fundamental for subsequent derivations. It represents the boundary conditions for functions $\phi^{(n)}(x_1,\dots,x_n;t)$ for any n.

The normalization factor Z is

$$\begin{aligned}\mathrm{Z} &= \int_G dx_1,\dots,\int_G dx_N\Bigg[\sum_{n=0}^{M}\frac{1}{n!}\sum_{\substack{i_{1,2\dots n}=1\\(i_1\neq i_2\neq\dots i_n)}}^{N} \times \phi^{(n)}(x_{i_1},\dots,x_{i_n};t)\prod_{\substack{k=1\\(k\neq i_{1,2\dots n})}}^{N}\tilde{\varphi}(x_k)\Bigg] \\ &= \sum_{n=0}^{M} C_N^n p^{(n)}[(\bar{N}_1+\bar{N}_2)]^{N-n},\end{aligned} \tag{7}$$

where $C_N^n = \frac{N!}{(N-n)!n!}$;

$$p^{(n)} = \int_{-L}^{L} dx_1, \ldots, \int_{-L}^{L} dx_n \phi^{(n)}(x_1, \ldots, x_n; t), \tag{8}$$

is the norm of $\phi^{(n)}(x_{i_1}, \ldots, x_{i_n}; t)$, $p^{(0)} \equiv 1$.

Taking into account that $N \gg n$, $\frac{N!}{(N-n)!} \approx N^n$, and $\bar{N}_1 + \bar{N}_2 \approx N$, we obtain

$$Z = N^N \sum_{n=0}^{M} \frac{p^{(n)}}{n!} \tag{9}$$

Inserting Eq. (9) into Eq. (5) yields:

$$F(x_1, \ldots, x_N; t) = \sum_{n=0}^{M} \frac{1}{N^n n!} \sum_{\substack{i_{1,2\ldots n}=1 \\ (i_1 \neq i_2 \neq \ldots \neq i_n)}}^{N} \frac{\phi^{(n)}(x_{i_1}, \ldots, x_{i_n}; t)}{\sum_{m=0}^{M} \frac{p^{(m)}}{m!}} \prod_{\substack{k=1 \\ (k \neq i_{1,2\ldots n})}}^{N} \varphi(x_k) \tag{10}$$

where $\varphi(x_i) = \frac{\tilde{\varphi}}{N} = \frac{c_1\chi_1(x_i) + c_2\chi_2(x_i)}{N}$ is the normalized distribution function of the particle located outside the channel.

Distribution function (10) can be rewritten in a more convenient form

$$F(x_1, \ldots, x_N; t) = \sum_{n=0}^{M} w_n \Phi^{(n)}(x_1, \ldots, x_N; t), \tag{11}$$

where

$$w_n = \frac{\frac{p^{(n)}}{n!}}{\sum_{m=0}^{n_{\max}} \frac{p^{(m)}}{m!}} \tag{12}$$

is the probability of the occupancy state with n ions in the channel (see the proof below);

$$\Phi^{(n)}(x_1, \ldots, x_N; t) = \frac{1}{N^n p^{(n)}} \sum_{\substack{i_{1,2\ldots n}=1 \\ (i_1 \neq i_2 \neq \ldots i_n)}}^{N} \left[\phi^{(n)}(x_{i_1}, \ldots, x_{i_n}; t) \prod_{\substack{k=1 \\ (k \neq i_{1,2\ldots n})}}^{N} \varphi(x_k) \right] \tag{13}$$

is the N-particle partial, not normalized distribution function, which corresponds to the configuration with any n particles inside the channel and the other $N-n$ particles in the reservoirs.

D. Probabilities of the occupancy states

Let us introduce the function

$$Q_n(x_1 \ldots x_N) = \sum_{i_{1,2,\ldots,n}=1}^{N} \frac{1}{n!} \left\{ \prod_{\substack{k=1 \\ (i_1 \neq i_2 \neq \ldots i_n)}}^{n} \chi_{Ch}(x_{i_k}) \cdot \prod_{\substack{j=1 \\ (j \neq i_{1,2\ldots k=1})}}^{N} [\chi_1(x_j) + \chi_2(x_j)] \right\}, \tag{14}$$

which is equal to unity when exactly n ions are located inside the channel and equal to zero otherwise. The probability of the configuration with any n ions inside the channel can be written as the average of Eq. (14) with distribution function (11),

$$\langle Q_n \rangle \equiv \int_G dx_1 \ldots \int_G dx_N Q_n(x_1, \ldots, x_N) F(x_1, \ldots, x_N; t). \tag{15}$$

Substituting Eqs. (14) and (11) into Eq. (15), we obtain after some transformations $\langle Q_n \rangle = w_n$, where w_n is given by Eq. (12). Thus, we proved that the weights w_n are the probabilities of the occupancy states with n ions in the channel.

Let us test the correctness of our derivations by considering the simplest limiting case of the free (not interacting) particles, equal concentrations $c_1 = c_2 = c_{Ch}$ and $M \gg 1$. In this case $p^{(m)} = (c_{Ch} V_{Ch})^m = (\bar{n}_{Ch})^m$, where $\bar{n}_{Ch}$ is the average number of particles in the channel, V_{Ch} is the "volume" of the channel. As a result, the Eq. (12) transforms to the well-known Poison distribution

$$w_n = \frac{\frac{(\bar{n}_{Ch})^n}{n!}}{\sum_{m=0}^{M} \frac{(\bar{n}_{Ch})^m}{m!}} \approx \frac{(\bar{n}_{Ch})^n}{n!} e^{-\bar{n}_{Ch}},$$

as it was expected.

E. Partial distribution functions in the channel

In principle, distribution function (11) can be used to find the statistical averages of all properties of the channel; however, it depends on the coordinates of a very large number of particles in the reservoirs and the number of particles N. The dependence of the statistical averages on the coordinates of particles in the reservoirs should obviously vanish in the thermodynamic limit. Let us show this by considering an arbitrary function $B(x_1, \dots, x_M)$, which depends on the coordinates of M particles inside the channel. Such function should be built taking into account possible permutations of N particles between the channel and the reservoirs [26],

$$B(x_1, \dots, x_M;t) = \sum_{m=0}^{M} \frac{1}{m!} \sum_{\substack{k_1=1 \\ (k_1 \neq \dots}}^{N} \cdots \sum_{\substack{k_m=1 \\ \dots \neq k_m)}}^{N} b(x_{k_1}, \dots, x_{k_m};t), \tag{16}$$

where $b(x_{k_1}, \dots, x_{k_m})$ is symmetric with respect to permutations of any pair of its arguments and cannot be written as a sum of other functions, which depend on less then m variables [26].

The statistical average of Eq. (16) reads as

$$\begin{aligned} \langle B \rangle &= \sum_{m=0}^{M} \int_G dx_1 \cdots \int_G dx_N \frac{1}{m!} \sum_{\substack{k_1=1 \\ (k_1 \neq \dots}}^{N} \cdots \sum_{\substack{k_m=1 \\ \dots \neq k_m)}}^{N} b(x_{k_1}, \dots, x_{k_m};t) F(x_1, \dots, x_N;t) \\ &= \sum_{m=0}^{M} C_N^m \int_{G_{Ch}} dx_1 \cdots \int_{G_{Ch}} dx_m b(x_1, \dots, x_m;t) \int_G dx_{m+1}, \dots, \int_G dx_N F(x_1, \dots, x_N;t) \end{aligned} \tag{17}$$

because the number of identical terms in the sum $\sum_{\substack{k_1=1 \\ (k_1 \neq \dots}}^{N} \cdots \sum_{\substack{k_m=1 \\ \dots \neq k_m)}}^{N}$ is $\frac{N!}{(N-m)!}$.

It is obvious that

$$\begin{aligned} &\int_G dx_{m+1} \dots \int_G dx_N F(x_1, \dots, x_N;t) \\ &\quad = \sum_{n=0}^{M} w_n \left\{ \int_G dx_{m+1} \dots \int_G dx_N \Phi^{(n)}(x_1, \dots, x_N;t) \right\}. \end{aligned} \tag{18}$$

Inserting Eq. (13) into Eq. (18) yields

$$\begin{aligned} &\int_G dx_{m+1} \dots \int_G dx_N \Phi^{(n)}(x_1, \dots, x_N;t) \\ &\quad = \int_G dx_{m+1} \dots \int_G dx_N \left\{ \sum_{\substack{i_{1,2\dots n}=1 \\ (i_1 \neq i_2 \neq \dots i_n)}}^{N} \right. \\ &\qquad \times \left. \left[\phi^{(n)}(x_{i_1}, \dots, x_{i_n};t) \prod_{\substack{k=1 \\ (k \neq i_{1,2\dots n})}}^{N} \varphi(x_k) \right] \Big/ N^n p^{(n)} \right\} \end{aligned} \tag{19}$$

This expression is not zero only if the coordinates of m particles $(x_1, \dots, x_m)$, which are not integrated over, are the arguments of $\phi^{(n)}(x_{i_1}, \dots, x_{i_n};t)$. Let us call these m particles "fixed particles," while all other particles will be called "free particles" (these terms do not mean that the particles are physically constrained by any means). The number of permutations of the free particles between the channel and the reservoirs is $\frac{(N-m)!}{(N-n)!}$, while the number of permutations between the fixed and free particles inside the channel is $\frac{n!}{(n-m)!}$. Thus, Eq. (19) can be rewritten as

$$\begin{aligned} &\int_G dx_{m+1} \dots \int_G dx_N \Phi^{(n)}(x_1, \dots, x_N;t) \\ &\quad = \frac{(N-m)!}{(N-n)!} \frac{n!}{(n-m)!} \int_G dx_{m+1} \dots \int_G dx_N \\ &\qquad \times \left\{ \phi^{(n)}(x_1, \dots, x_n;t) \prod_{k=n+1}^{N} \varphi(x_k) / N^n p^{(n)} \right\}. \end{aligned}$$

Taking into account that $C_N^m \frac{(N-m)!}{(N-n)!} \frac{n!}{(n-m)!} \frac{1}{N^n} \approx \frac{1}{m!} \frac{n!}{(n-m)!}$, average (17) can be written as

$$\begin{aligned} \langle B \rangle &= \sum_{m=0}^{M} \frac{1}{m!} \sum_{n=m}^{M} w_n \int_{-L}^{L} dx_1 \cdots \int_{-L}^{L} dx_m b(x_1, \dots, x_m;t) \\ &\quad \times \left\{ \frac{n!}{(n-m)!} \int_{-L}^{L} dx_{m+1} \cdots \int_{-L}^{L} dx_n \left[\frac{\phi^{(n)}(x_1, \dots, x_n;t)}{p^{(n)}} \right] \right\}. \end{aligned}$$

This form does not contain the number of particles N and can be used in the thermodynamic limit $N\to\infty$, $\frac{\bar{N}_1}{V_1}\to c_1$, and $\frac{\bar{N}_2}{V_2}\to c_2$. The final expression for the average of B can be written in a more convenient form as

$$\langle B\rangle = \sum_{m=0}^{M}\frac{1}{m!}\sum_{n=m}^{M} w_n\int_{-L}^{L}dx_1\ldots\int_{-L}^{L}dx_m b(x_1,\ldots,x_m;t) \times f_m^{(n)}(x_1,\ldots,x_m;t) \tag{20}$$

where w_n is defined by Eq. (12);

$$f_m^{(n)}(x_1,\ldots,x_m;t) = \frac{n!}{(n-m)!}\int_{-L}^{L}dx_{m+1}\cdots \times\int_{-L}^{L}dx_m\left[\frac{\phi^{(n)}(x_1,\ldots,x_n;t)}{p^{(n)}}\right] \tag{21}$$

is the well-known m-particle partial distribution function of the system (the channel in our case), which contains n particles [26].

Expressions (12), (20), and (21) depend on the coordinates of particles in the channel only. They provide full statistical description of the diffusion through the channel and can be used to compute all desirable statistical averages providing that the functions $\phi^{(n)}(x_1,\ldots,x_n;t)$ are known.

F. Macroscopic properties of the channel

Once the distribution functions $\phi^{(n)}(x_1,\ldots,x_n;t)$ are found as described below, the macroscopic properties of the channel could be computed.

1. Distribution of particle density

The density of particles at point z for some microscopic configuration of ions x can be written as $\rho(z,x_1,\ldots,x_n) = \sum_{i=1}^{M}\delta(z-x_i)$, where x_i are instantaneous positions of the particles dependent on time. Substituting this expression to Eq. (20) in place of b we get the steady state distribution of the particle density along the channel,

$$\rho(z;t) = \langle\rho(z,\vec{x})\rangle = \sum_{n=1}^{M} w_n f_1^{(n)}(x_1) = \sum_{n=1}^{M} n\cdot w_n\int_{-L}^{L}dx_2\cdots\int_{-L}^{L}dx_n\left[\frac{\phi^{(n)}(x_1,\ldots,x_n;t)}{p^{(n)}}\right]. \tag{22}$$

2. Current

The flux of particles through the channel with fixed number of particles n and known particle density $\rho(z;t)$ is [18]

$$j(z;t) = -D\left[\frac{\partial U(z)}{\partial z} + \frac{\partial}{\partial z}\right]\rho(z;t), \tag{23}$$

where $U(z;t) = U_0(z) + \int_{-L}^{L}dz' V(z-z')\rho(z';t)$ is the total energy of the particle at point z, which interacts with the particle density $\rho(z;t)$. This flux can be written as

$$j(z;t) = -De^{-U(z;t)}\frac{\partial\theta(z;t)}{\partial z},$$

where $\theta(z;t) = e^{U(z;t)}\rho(z;t)$. For any instantaneous macroscopic configuration of n particles the density is $\rho_n(z,x_1,\ldots,x_n) = \sum_{i=1}^{n}\delta(z-x_i)$; thus, the instantaneous microscopic current is

$$j^{(n)}(z,x_1,\ldots,x_n) = -De^{-U(z;t)}\frac{\partial}{\partial z}\left[e^{U(z;t)}\sum_{i=1}^{n}\delta(z-x_i)\right]. \tag{24}$$

Averaging Eq. (24) with the normalized symmetric distribution function $\frac{\phi^{(n)}(x_1,\ldots,x_n;t)}{p^{(n)}}$ we get the time-dependent current through the channel containing exactly n particles in the cross-section z,

$$J^{(n)}(z;t) \equiv \langle j^{(n)}(z,x)\rangle = -D\int_{-L}^{L}dx_1,\ldots,dx_n e^{-U(z;t)}\frac{\partial}{\partial r} \times\left[e^{U(z;t)}\sum_{i=1}^{n}\delta(z-x_i)\right]\frac{\phi^{(n)}(x_1,\ldots,x_n;t)}{p^{(n)}},$$

or, after some transformations,

$$J^{(n)}(z;t) = -D\left[\frac{n}{p^{(n)}}\int_{-L}^{L}dx_2\ldots dx_n \times e^{-U_n(z,x_2,\ldots,x_n)}\frac{\partial v^{(n)}(z,x_2,\ldots,x_n;t)}{\partial z}\right]. \tag{25}$$

In the steady state the current is obviously the same for each cross section of the channel, therefore Eq. (25) is in fact independent of z. For the sake of simplicity, we will compute the current at $z=-L$. The full steady state current through the channel with fluctuating occupancy is [according to Eq. (20)]

$$J \equiv \langle j(-L,\vec{x})\rangle = \sum_{n=1}^{M} w_n\cdot J^{(n)}(-L)$$

or, taking into account Eq. (35)

$$J = -\frac{D}{\sum_{m=0}^{M}\frac{p^{(m)}}{m!}}\sum_{n=1}^{M}\left[\frac{1}{(n-1)!}\int_{-L}^{L}dx_2,\ldots,dx_n \times e^{-U_n(-L,x_2,\ldots,x_n)}\left.\frac{\partial v^{(n)}(z,x_2,\ldots,x_n)}{\partial z}\right|_{z=-L}\right]. \tag{26}$$

3. Mean occupancy

The mean occupancy is computed trivially as

$$n_{mean} = \sum_{n=1}^{M} n\cdot w_n. \tag{27}$$

G. Concentration dependencies of the channel properties in the steady state

As it is shown in Appendix A, the functions $\phi^{(n)}$ and $p^{(n)}$ could be written as n-th degree polynomial functions of concentrations c_1 and c_2 in the steady state [formulas (A4) and (A5) respectively], Unknown functions $g_k^{(n)}$, $k=0,1,\ldots,n$ in Eqs.(A4) and (A5) and are independent on concentrations and should be found separately. As a result, the concentration dependence of any steady state channel property could be determined explicitly providing that $g_k^{(n)}$ are known. Particularly, the occupancy probabilities w_n are

$$w_n(r_1,r_2)=\frac{\frac{1}{n!}\sum_{k=0}^{n}a_k^{(n)}r_1^{n-k}r_2^{k}}{\sum_{m=0}^{M}\sum_{k=0}^{m}\frac{1}{m!}a_k^{(m)}r_1^{m-k}r_2^{k}}, \tag{28}$$

where $r_1=c_1e^{U_0(-L)}$ and $r_2=c_2e^{U_0(L)}$.

Taking into account $a_0^{(0)}=1$, which is obvious from Eq. (A5), we get the system of linear equations for $a_k^{(n)}$,

$$\sum_{k=0}^{n}a_k^{(n)}r_1^{n-k}r_2^{k}=n\,!\,\frac{w_n(r_1,r_2)}{w_0(r_1,r_2)}. \tag{29}$$

The steady state current though the channel in a configuration with particular occupancy n could be written, taking into account Eqs. (A2) and (A5) and (25), as

$$J^{(n)}=-D\left[\frac{n}{\sum_{k=0}^{n}a_k^{(n)}r_1^{n-k}r_2^{k}}\sum_{k=1}^{n}\int_{-L}^{L}dx_2,\ldots,dx_n\right.\\ \left.\times e^{-U_n(z,x_2,\ldots,x_n)}\frac{\partial g_k^{(n)}(z,x_2,\ldots,x_n)}{\partial z}r_1^{n-k}r_2^{k}\right]\Bigg|_{z=-L}. \tag{30}$$

Equation (30) could be written as a system of linear equations for $\alpha_k^{(n)}$

$$\sum_{k=1}^{n}\alpha_k^{(n)}r_1^{n-k}r_2^{k}=(n-1)\,!\,\frac{-J^{(n)}(r_1,r_2)}{D}\cdot\frac{w_n(r_1,r_2)}{w_0(r_1,r_2)},$$

$$\alpha_k^{(n)}=\int_{-L}^{L}dx_2,\ldots,dx_ne^{-U_n(z,x_2,\ldots,x_n)}\frac{\partial g_k^{(n)}(z,x_2,\ldots,x_n)}{\partial z}. \tag{31}$$

Thus, in order to find the concentration dependence of w_n in the steady state conditions one should compute the set of functions $w_n(r_1,r_2)$ by solving Eq. (29) numerically for different pairs of concentrations (exact values of concentrations do not matter). Inserting these values into the system of linear Eq. (29) for each $n=1,\ldots,M$ one can compute the set of coefficients $a_k^{(n)}$. The concentration dependence of J could be found in the same way by computing $J^{(n)}(r_1,r_2)$ for several different pairs of concentrations for each $n=1,\ldots,M$ and finding the set of coefficients $\alpha_k^{(n)}$.

We conclude that the concentration dependencies of all channel properties could be determined analytically if the corresponding coefficients are pre-computed numerically. The cost of this pre-computation is negligible in comparison to the time of numerical computation of all concentration dependencies.

H. *n*-particle distribution functions of the channel

The n-particle distribution functions in the channel $\phi^{(n)}(x_1,\ldots,x_n;t)$ are the only remaining unknown components in our theory. It is necessary to note that these functions are defined for the channel which is attached to the reservoirs but contains exactly n particles all the time. The fluctuations of the number of particles in the system are described by occupancy probabilities w_n, which weigh the contributions of the corresponding occupancy states. The probabilities w_n depend on $\phi^{(n)}(x_1,\ldots,x_n;t)$ [see Eqs. (12) and (8)] so that our initial problem is now reduced to finding $\phi^{(n)}(x_1,\ldots,x_n;t)$ for $0<n\leqslant M$.

The task of finding the functions $\phi^{(n)}(x_1,\ldots,x_n;t)$ is independent from the general theory developed above and depends on the physical processes inside the channel and its molecular design. It is obvious that dynamic equations of individual particles inside the channel should be solved to get these functions. Therefore the strategy of finding $\phi^{(n)}(x_1,\ldots,x_n;t)$ and necessary additional assumptions depend on the specific system under study, while other parts of the theory remain completely general. In this work we develop the technique, which allows finding steady state properties of the channel where the motion of particles is stochastic and overdamped.

The motion of n particles inside the channel is governed by their interaction with the channel structure, particle-particle interactions and the external field. The particles move in the potential $U_n(\vec{x},\psi)$, $\vec{x}=\{x_1,x_2,\ldots,x_n\}$ created by the channel walls and the external field ψ. The potential U_n is assumed to be smooth enough. Interaction between the particles i and j is described by the potential $V(x_i-x_j)$. Let us assume that the motion of particles in the channel is stochastic and overdamped. In this case it can be described by the set of Langevin equations

$$\dot{x}_i=-D\frac{\partial U_n(x_1,\ldots,x_n)}{\partial x_i}+\sqrt{2D}\xi_i(t), \tag{32}$$

where $i=1,n$;

$$U_n(x_1,\ldots,x_n)=\sum_{i=1}^{n}U_0(x_i)+\sum_{\substack{i,j=1\\(i>j)}}^{n}V(x_i-x_j) \tag{33}$$

is the total potential of n particles; D is the diffusion coefficient; ξ_i is the white noise, $\langle\xi_i\rangle=0$, $\langle\xi_i\cdot\xi_j\rangle=\delta_{i,j}$; U_0 is the single-particle energy profile created by the pore walls (see Sec. II for details).

It is necessary to note that the diffusion coefficient D is the one-dimensional property, which is not directly related to the diffusion coefficient in bulk solution. D is a free parameter in our model. D could also be considered variable along the pore and written as $D(x)$ if necessary. However, we assumed that D is a constant in the sake of simplicity.

The equation for the n-particle distribution function, which corresponds to set (32), is the n-dimensional Focker-Planck equation [18],

$$\frac{\partial \phi^{(n)}(x_1,\ldots,x_n,t)}{\partial t} = D\sum_{i=1}^{n}\frac{\partial}{\partial x_i}\left[\frac{\partial U_n(x_1,\ldots,x_n)}{\partial x_i}\phi^{(n)}(\vec{x},t) + \frac{\partial \phi^{(n)}(x_1,\ldots,x_n,t)}{\partial x_i}\right] \qquad (34)$$

where $x_{1,\ldots,n}\in[-L,L]$. The distribution function is defined on the n-dimensional hypercube $\mathfrak{R}_n$.

In principle it is possible to solve the set of time-dependent Eq. (34); however, the steady state ($\frac{\partial\phi^{(n)}(x_1,\ldots,x_n;t)}{\partial t}=0$) is considered in this work. Thus the time dependence is absent hereon in all expressions. The set of Eq. (34) is subject to the boundary conditions [Eq. (6)]. These boundary conditions are recursive—the solution of the n-dimensional problem serves as a boundary conditions for the $(n+1)$-dimensional one. Thus the solution of the whole problem is achieved as a consecutive solution of the Eqs. (34) of growing dimensionality for $n=1,\ldots,M$. It is important to note that Eqs. (34) become interdependent because of the boundary conditions [Eq. (6)] only. There are no terms in (34), which describe the interchange between the occupancy states with different n. The proof of this nontrivial fact is given in Appendix B.

It is obvious that the Eq. (34) cannot be solved analytically. Numerical solution is also nontrivial and depends strongly on the nature of functions U_0 and V. In the majority of real systems the particle-particle interaction is repulsive and discontinuous at zero distance (i.e., Coulomb or van der Waals interactions). As a result, the function $\phi^{(n)}$ grows rapidly in certain regions of the configuration space, which makes the numerical solvers unstable. In order to overcome this difficulty and to simplify the equations, let us define a new function,

$$v_n(x_1,\ldots,x_n) = e^{U_n(x_1,\ldots,x_n)}\phi^{(n)}(x_1,\ldots,x_n). \qquad (35)$$

In equilibrium $\phi^{(n)}(x_1,\ldots,x_n)=\text{const}\cdot e^{-U_n(x_1,\ldots,x_n)}$ and $v_n(x_1,\ldots,x_n)=\text{const}$. In the nonequilibrium conditions the function v contains the nonequilibrium part of the distribution function. It is possible to say that the function v is related to local entropy, while the term $\exp(U_n(x_1,\ldots,x_n))$ is related to energy.

Equation (34) can be written in terms of the functions v in the steady state as

$$\sum_{i=1}^{n}\frac{\partial}{\partial x_i}\left[e^{-U_n(x_1,\ldots,x_n)}\frac{\partial}{\partial x_i}v_n(x_1,\ldots,x_n)\right]=0, \qquad n=1,\ldots,M. \qquad (36)$$

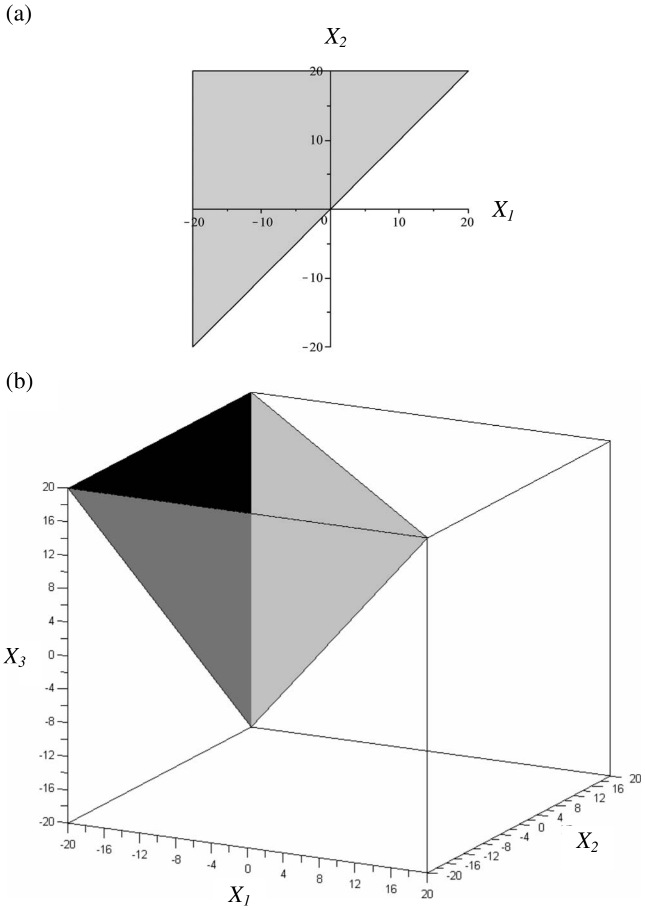

FIG. 1. The main region in the (a) two-dimensional and (b) three-dimensional cases. The main region is shaded in (a). In (b) the main region is inside the shaded polyhedron.

They are subject to the recursive boundary conditions

$$v_n(-L,x_2\ldots x_n) = r_1 v_{n-1}(x_2\ldots x_n), \quad v_n(x_1\ldots x_{n-1},L) = r_2 v_{n-1}(x_1\ldots x_{n-1}) \qquad (37)$$

where $r_1=c_1e^{U_0(-L)}$ and $r_2=c_2e^{U_0(L)}$;

$$v_1(x) = r_1 + (r_2-r_1)\int_{-L}^{x}e^{U_0(x')}dx'\int_{-L}^{L}e^{U_0(x)}dx \qquad (38)$$

is the analytical solution in the case $n=1$.

Equation (36) can be written in the compact operator form as

$$\Delta v_n(x_1,\ldots,x_n) = \nabla U(x_1,\ldots,x_n)\cdot\nabla v_n(x_1,\ldots,x_n). \qquad (39)$$

The ith particle is always confined by the region $x_{i-1}\le x_i\le x_{i+1}$; therefore, the hypercube $\mathfrak{R}_n$ can be divided into $n!$ equivalent regions, which differ by the exchange of a pair of variables. Thus, it is possible to find the function v in the "main" region $-L\le x_1\le x_2\le\ldots\le x_{n-1}\le x_n\le L$ only and expand it to the whole hypercube by exchanging the corresponding pairs of coordinates. The main regions in the cases of two and three dimensions are shown in Fig. 1.

It is possible to show that v_n is somewhat similar to a harmonic function in the main region. It contains no local minima or maxima and reaches the extremal values on the boundary of the main region. Thus, v_n is limited, smooth and monotonous in the main region along all its coordinates. This greatly simplifies the numerical solution.

Numerical solution

Although the system of Eqs. (39) with boundary conditions (37) looks very compact and elegant, it is still very challenging for numerical solution. The principal difficulty is the fact that the elliptic partial differential equations (PDEs) of growing dimensionality should be solved in succession. Simple iterative finite-difference methods of solving elliptic PDEs become too slow for us already for $n=2$. The convergence properties of simple numerical solvers are very different for different dimensionality of the problem, while in our case the method should be convergent for all dimensionalities from 1 to M. Another difficulty is the finite-difference approximation of the first derivatives in Eq. (39). The terms $\partial U_n(\vec{x})/\partial x_i$ could be fast changing, which requires very fine grids and prevents us from using fast multigrid techniques [27].

In order to overcome these difficulties, we transform our boundary problem into an equivalent variation problem. The minimization of the functional

$$Q=\int_G dx_1,\ldots,x_n\cdot\exp[-U_n(x_1,\ldots,x_n)](\nabla v)^2, \tag{40}$$

is equivalent to solving the Dirichlet problem defined by Eqs. (39) and (37).

Indeed, the Euler-Lagrange equation for $R=\exp(-U_n(x_1,\ldots,x_n))(\nabla v)^2$ is

$$\frac{\partial R}{\partial v}-\sum_{i=1}^{n}\frac{\partial}{\partial x_i}\frac{\partial R}{\partial\left(\dfrac{\partial v}{\partial x_i}\right)}=0,$$

which leads, after some transformations, to Eq. (39).

Let us define the finite-difference approximation of functional (40):

$$Q=\sum_{\substack{i_1,i_2\ldots i_n=2\\ i_1<i_2<\ldots<i_n}}^{K-1} E_{i_1i_2\ldots i_n}\frac{1}{2}\sum_{k=1}^{n}\left[\left(\frac{v_{i_1\ldots i_k+1\ldots i_n}-v_{i_1\ldots i_k\ldots i_n}}{h}\right)^2+\left(\frac{v_{i_1\ldots i_k\ldots i_n}-v_{i_1\ldots i_k-1\ldots i_n}}{h}\right)^2\right] \tag{41}$$

where K is the number of discrete points along each of n coordinates; $E_{i_1i_2\ldots i_n}=e^{-U_n(x_{i_1},x_{i_2},\ldots x_{i_n})}$; $h=x_{i+1}-x_i$ is the discrete step. The points x_i, $1<i<K$ are inner points of the grid while the points $x_1=-L$, $x_K=L$ correspond to the boundary conditions. We used the mean of the forward and backward approximations of the first derivatives to make the expression symmetric. This simplifies subsequent derivations.

The minimum of Q is reached when $\frac{\partial Q}{\partial v_{i_1i_2\ldots i_n}}=0$ at all inner points of the n-dimensional grid. Trivial but lengthy transformations lead to the following relation, which minimizes Eq. (41):

$$v_{i_1i_2\ldots i_n}=\frac{E_{i_1i_2\ldots i_n}\sum_{k=1}^{n}\sum_{\alpha=\pm1}v_{i_1\ldots i_k+\alpha\ldots i_n}+\sum_{k=1}^{n}\sum_{\alpha=\pm1}E_{i_1\ldots i_k+\alpha\ldots i_n}\cdot v_{i_1\ldots i_k+\alpha\ldots i_n}}{2nE_{i_1i_2\ldots i_n}+\sum_{k=1}^{n}\sum_{\alpha=\pm1}E_{i_1\ldots i_k+\alpha\ldots i_n}}. \tag{42}$$

If relation (42) is satisfied at each inner point of the grid then $v_{i_1i_2\ldots i_n}$ is the finite-difference solution of variation problem (40) and corresponding boundary problem (39). It is important that relation (42) applied iteratively is a smoothing operation. The value of v at each point is set to the weighted average of v at adjacent points in each subsequent iteration and thus smooths the high-frequency fluctuations of v. This allows us to use Eq. (42) as an iterative smoother in the multigrid algorithm [27].

We apply a modified full multigrid technique [27] to find the solution. Our method implements the first stage of the standard full multigrid algorithm. We start with the coarsest grid with three points in each dimension and applied Eq. (42) to a single inner point to find the exact solution. Then the solution is interpolated to a finer grid with 5 points in each dimension using the distributive stencil generalized to the n-dimensional case [27]. The approximate solution is refined by applying Eq. (42) iteratively until the convergence criterion is met. This solution is interpolated to a finer grid and the procedure is repeated until the solution on the finest grid is obtained.

This technique is very stable and fast and allows us to avoid problems with the fast-growing derivatives. It is implemented as a FORTRAN 90 program, which handles the problem of arbitrary dimensionality limited by the available computer memory only (the execution time grows exponentially with the increase of dimensionality). We do not analyze the convergence properties of this method and do not intend to reach arbitrary precision. Thus all computations presented in this work should be addressed as semiquantitative to avoid problems in interpretation caused by possible numerical errors.

It is necessary to note that the technique presented here is only one of the possible ways to solve the set of Eq. (39). All the results of our theory stand regardless of the numerical

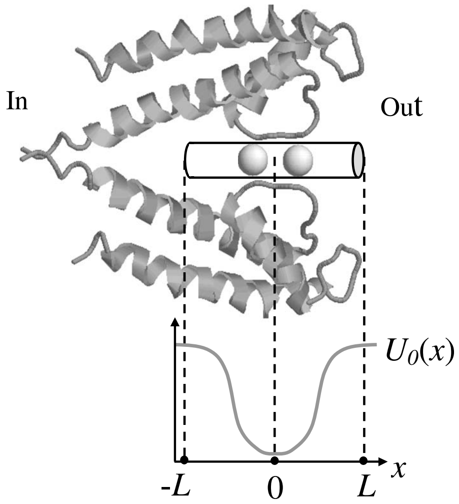

FIG. 2. Relationship between the model and the real structure of KcsA channel. The channel is shown in cartoon representation. Two out of four subunits are shown for clarity.

procedure used to find the functions $v^{(n)}$. More robust and precise technique could be implemented in the future.

I. Application to the simplified model of the single-file pore

In order to test our general theory we have to apply it to some model system, which is sufficiently simple and well studied to serve as a testing ground. We utilized the simplified model of the single-file pore inspired by the selectivity filter of KcsA ion channel developed in our previous works [24,25].

The KcsA potassium channel is now a classical object for ion channel modeling and simulations [6–8]. However, the real channel is too complex and shows too complicated behavior to be used as a test case for validating our theoretical framework. Particularly, the channel structure is not rigid in the sense that there are complex slow gating motions, with the time scales much larger than the ion passage time. Our theory currently operates with rigid pores only (the pores, which lack motions slower than the ion passage time). Thus we designed an extremely simplified "cartoon model" of the selectivity filter of the channel, which is the most structured part of the structure. This model has no relation to real channel except the dimensions and the shape of the single-ion energy profile. Thus, the results described below should not be related to real channel. They only serve as a validation of our theoretical developments against the data obtained on the same model in our previous works [24,25]. The relation between the mode and the structure of the real channel is shown in Fig. 2.

The simplicity of the chosen model makes it very convenient for testing our theoretical framework. In this model the one-dimensional motion of ions is described in terms of the single-ions energy profile U_0 and the ion-ion interaction potential V, which makes the application of our theory straightforward.

The shape of the single-ion energy profile U_0 could be deduced from MD simulations of the KcsA channel. The inverted bell-like shape of this profile is well established now [24]. However, the depth of the profile is a matter of debates [24]. It was shown in our previous works [24,25] that the profiles obtained in MD simulations could be approximated by the inverted Gaussian curve

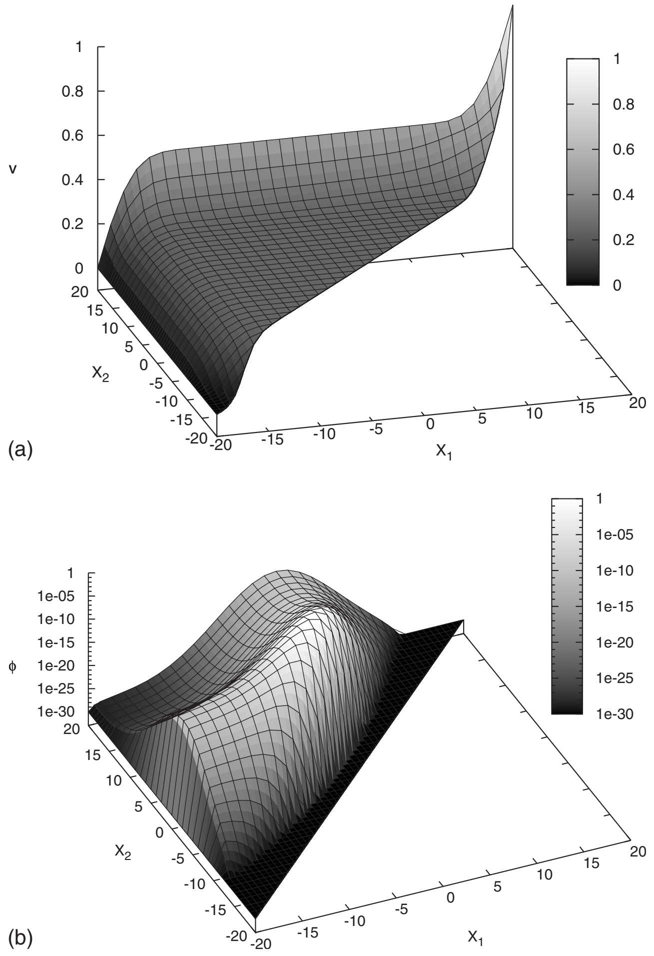

FIG. 3. Functions (a) v and (b) ϕ (normalized) for $n=2$, $c_1=10^{-4}$ Å^{-1}, $c_2=0$ Å^{-1}, $A=43.0$ k_BT, $d=3.0$ Å, and $\psi=0$ mV. The function ϕ is extremely sharp (note the log scale), while the function v is very smooth and monotonous. Coordinates x_1 and x_2 are in Å.

$$U_0(x) = -A\,\exp(x^2/s^2) + x\psi/L, \tag{43}$$

where A is the depth of the single-ion energy profile; s is the half-width of this profile. The second term describes the transmembrane electrostatic potential in the linear approximation (see Sec. III for the rationale).

The ion-ion electrostatic interactions in the selectivity filter of real channel are screened significantly by the water molecules, which reside between the ions, and the pore walls. Although the details of this screening can be very complex, it is obvious that the screening is strongly distance-dependent and cannot be described by a uniform dielectric constant. In our model the ion-ion interactions are approximated by the shielded Coulomb interaction

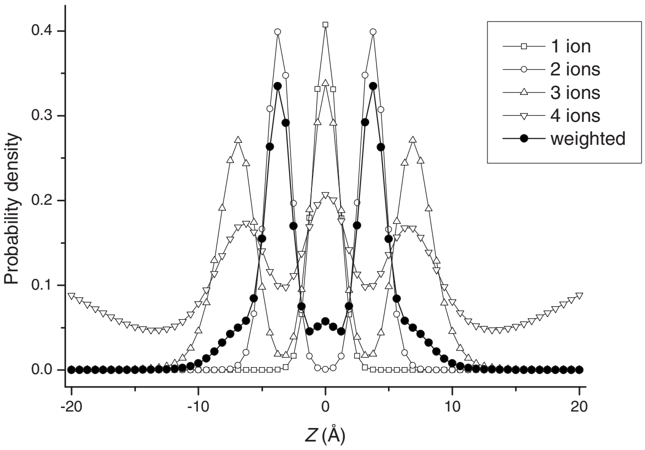

FIG. 4. The distribution of ionic density in different occupancy states and weighted distribution obtained by formula (22). The parameters are $c_1 = c_2 = 10^{-4}$ Å^{-1}, $A = 43.0$ $k_B T$, and $d = 3.0$ Å. Mean occupancy of the channel is $n_{mean} = 2.08$.

$$V(r) = \frac{b}{r}\exp\left(-\frac{r}{d}\right)$$

where d is the shielding constant; b is the constant, which converts the electrostatic energy to the $k_B T$ units. This interaction should be considered as the simplest reasonable approximation of the real ion-ion interaction. The empirical constant d allows us to vary the amount of screening in the selectivity filter.

The values of empirical constants are $b = 566.2$, $s = 9$ Å, and $L = 20$ Å [24,25]. Free parameters A and d are varied. It is established in experiments and simulations that the selectivity filter of the KcsA channel contains 2 or 3 ions in physiological conditions [1,3,28]. Following these evidence the configurations up to $M = 4$ were considered to cover the whole range of possible channel occupancies. As it is said in the Formulation, the "concentrations" c_1 and c_2 are in 1/Å units. In order to relate them to real concentrations c_1' and c_2' the cross sections of the channel boundaries S and S_2 should be known [see Eq. (1)]. In addition, in the case of our model of the KcsA channel c_2' is not the concentration in the intracellular solution, but that in the so-called central cavity of the channel. Finding the exact relations between c_1 and c_2 and real concentrations is not in the scope of this work.

1. Distribution functions v and ϕ

Figure 3 shows the distribution functions v and ϕ in the two-dimensional case ($n = 2$). It is clearly seen that the function v is monotonous in both coordinates and very smooth. In contrast, the function ϕ is extremely fast changing (note the log scale). This difference demonstrates the advantage of computing smooth function v numerically, which allows us to avoid instabilities and minimize numerical errors.

2. Distribution of the particle density for different occupancy states

Figure 4 shows the distributions of the ionic density for different occupancy states and the weighted steady state distribution. It is clearly seen that the distributions have the number of peaks, which corresponds to the number of ions for occupancies $n = 1,2,3$. For the occupancy $n = 4$ there are three peaks of the particle density inside the channel and a substantial density near the ends of the channel. This means that the energy well in the channel ($A = 43$ $k_B T$) is too shallow to accommodate four ions, thus the excessive ion is located near one of the vestibules. Indeed, the weight w_4 of the four-ion configuration in this case is negligible. The weighted density is formed mainly by the configurations with 2 and 3 ions. Since the mean number of ions is 2.08 the state $n = 2$ dominates in the weighted density.

It is clear that the shape of the weighted density depends strongly on the weights of particular configurations and can be different for different parameter values. The distributions shown in Fig. 4 are in fact equilibrium distributions (the membrane potential is zero and the concentrations are equal), however the weighted distribution can only be obtained when the probabilities of all occupancy states are computed. In nonequilibrium conditions the distributions become asymmetric and the positions and shapes of the maxima change, however the qualitative picture remains the same.

3. Barrierless conduction

The distinctive feature of the KcsA channel, which was revealed in the MD simulations, is so-called knock-on barrier-less conduction. The occupancy states with 2 and 3 ions in the selectivity filter of a real channel have almost identical energies. The filter contains 2 ions most of the time. When the third ion enters the filter, the two ions move in a concerted way forming the triple occupancy state. Then the ion from the other side of the filter moves toward the end and escapes to opposite solution restoring the state with double occupancy. The whole process is almost isoenergetic, thus the current in this regime reaches the maximum. It was shown in our previous work [24] that the barrier-less conduction is a quite general mechanism, which could be observed in very simplified models. Here we studied it using our theory. Taking into account simplified nature of the model used here the results should not be directly related to real channel. However qualitative comparison of general physical mechanisms is possible and shows that our theory is able to describe fundamental physical principles of diffusion in the narrow pores.

We computed the current and the mean occupancy in the channel varying the well depth A from 1 to 79 $k_B T$ and the shielding constant d from 1.5 to 10 Å. The results are shown in Fig. 5. It is clearly seen that the current depends dramatically on the parameters. In general, the current decreases with the increase of the well depth and the shielding. There are three well-defined ridges of large current, which look like "fingers" in the contour plot [Fig. 3(a)]. The current in the "valleys" between the ridges is much smaller.

The mean occupancy increases with the increase of A and decrease of d, which allows more ions to reside in the channel. This increase is stepwise. There are four well-defined step-shaped plateaus, which correspond to $n_{mean} = 1,2,3,4$, respectively, [Fig. 3(b)]. The transitions between the plateaus are rather sharp, which means that the occupancy changes

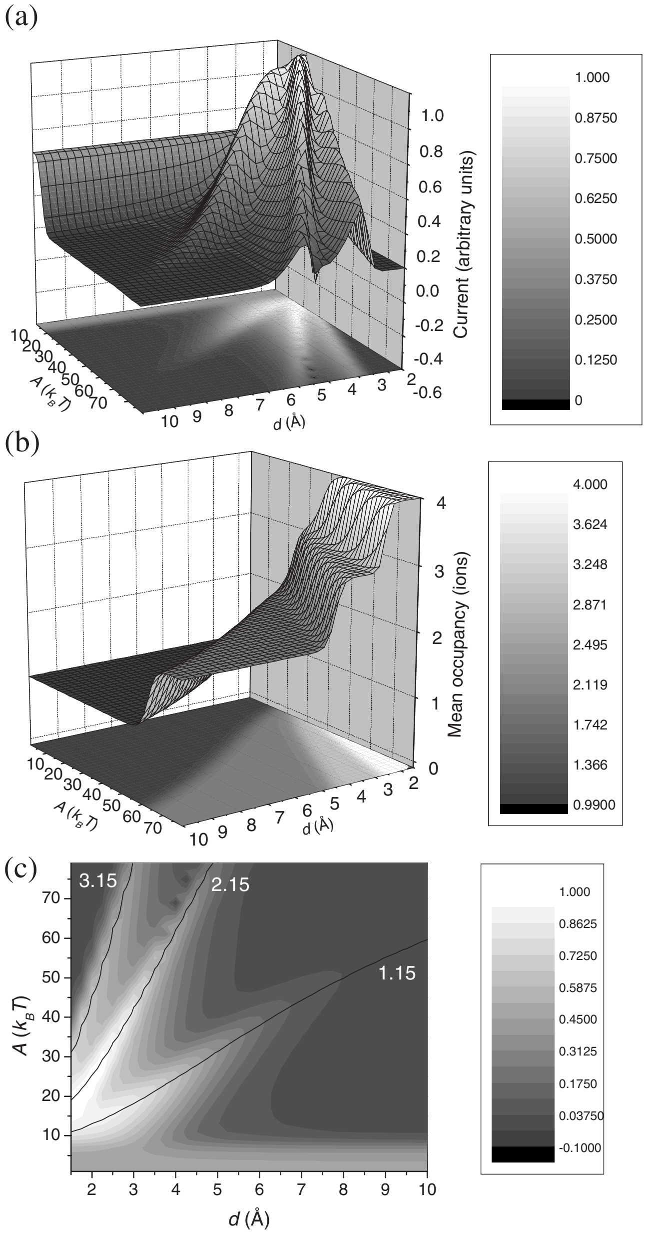

FIG. 5. The (a) current and the (b) mean occupancy as a function of the well depth A and the shielding constant d. (c) shows the isolines of mean occupancy (solid black lines), which correspond to the ridges of maximal current, superimposed to the contour plot of the current. The values of the isolines are shown.

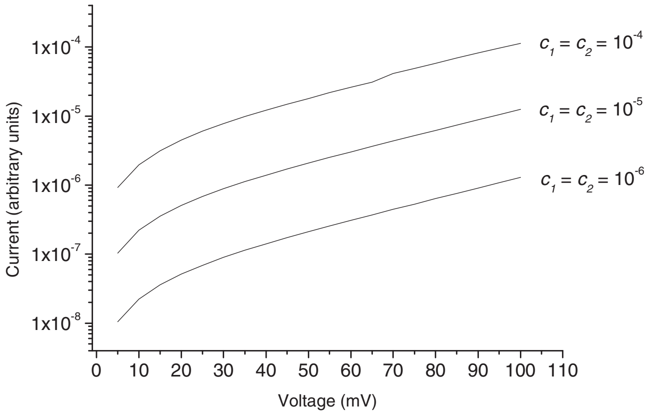

FIG. 6. Current-voltage relationships for $A=43.0\ k_BT$, $d=3.0$ Å, and indicated values of concentrations (in Å^{-1} units).

abruptly in a narrow domain of parameters. Comparison of Figs. 5(a) and 5(b) shows that the transitions between the states with different occupancy roughly correspond to the ridges of maximal current. Figure 5(c) shows this correlation in details. The isolines of the mean occupancy are parallel to the ridges of maximal current. The isolines, which correspond to the highest points of the ridges are $n_{mean}=1.15$, 2.15, and 3.15, respectively. These isolines match the ridges extremely well, which can be explained as follows. The maximal current is observed when n ions reside in the channel most of the time and the $n+1$ ion comes to facilitate the knock-on conduction. This is only possible if the probability of the state with $n+1$ ions is small enough. Indeed, the mean occupancy of, say, 2.5 means that the third ion enters the channel and remains there for a long time. In this case the current would necessarily be small. At the same time the $n+1$th ion should enter the channel sufficiently often to maintain a large current. The interplay of these two factors lead to some optimal mean occupancy of the channel, which appears to be 0.15 larger than the corresponding dominant number of ions in the channel for given parameters.

These results are consistent with the results of Brownian dynamics simulations from our previous work [25] and confirm the validity of our theory.

4. Current-voltage dependence

The current-voltage dependencies of the model pore in the case of equal concentrations c_1 and c_2 are shown in Fig. 6.

The possible difference between our results and these experimental findings is explained by the fact, that we model only the selectivity filter of the channel in very simplified way, while the shape of the current-voltage relationship is likely to depend on the other parts of the real channel. Particularly, existence of the energy barriers, which are absent in our simple model, may change the shape of the current-voltage relationships dramatically.

5. Concentration dependencies

The concentration dependencies of the mean occupancy and the occupancy probabilities w_n are shown in Fig. 7. The zero occupancy can only be reached for zero concentrations, which is never possible in real system. The single occupancy dominates for very small concentrations up to $c=10^{-10}$. With the further increase in concentration the double occupancy becomes dominant. It is interesting to note that the double occupancy dominates in a very broad range of concentrations (from $c=10^{-9}$ to $c=10^{-4}$). This correlates very well with the experimentally determined double occupancy of the selectivity filter of the KcsA channel in a broad range of conditions. The triple occupancy dominates for still larger concentrations but in a much more narrow domain. Finally, the probability of the state with four ions in the channel becomes significant for extremely large concentrations, which are unlikely to be observed in real system.

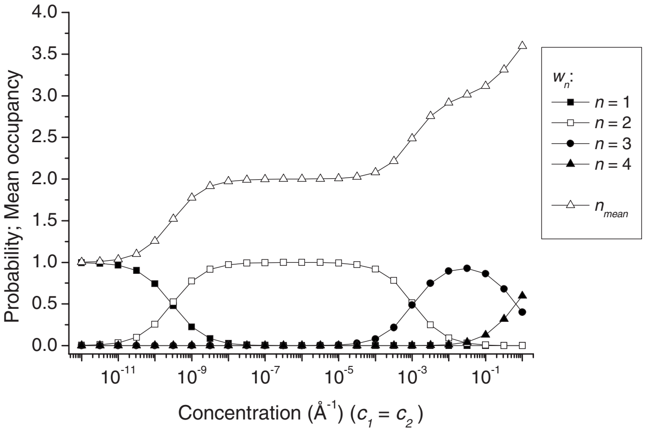

FIG. 7. Concentration dependencies of the mean occupancy and the occupancy probabilities w_n.

III. DISCUSSION

The problem of diffusion of multiple strongly interacting particles in the channels in nonequilibrium conditions is rarely considered analytically. If such problem arise in practice it is usually addressed by direct numerical simulation of motion of particles (numerical solution of the motion equations). The examples of this approach are the molecular dynamics and Brownian dynamics simulations of diffusion of water and ions in narrow pores [4,29] and biological ion channels [6,9,30]. Such simulations become defacto standard for the systems with multiparticle diffusion. They provide significant insight into the functioning of the ion channels. However, they cannot substitute the robust analytical theory in terms of understanding the fundamental physical phenomena in narrow pores with single-file diffusion. Such theory can serve as a solid basis for comparison and evaluation of various simulation techniques and can reduce the computational burden dramatically in the cases when atomistic details are not important.

In this work we developed an analytical theory of the multiparticle single-file diffusion in the external potential in nonequilibrium conditions. The theory is constructed in a bottom-up manner from the very basic principles of statistical physics and probability theory. The unique feature of our approach is that we take into account the fluctuations of the number of particles in the system due to the exchange with external reservoirs. This is vital because the number of particles in nanopores is usually very small (of order of unity), therefore each exchange event changes the system dramatically. Our theory is mainly targeted to such systems with a small number of particles. Although it can be used for any number of particles, various mean-field approaches may be simpler and computationally more efficient if the number of particles is large.

The exchange of particles between a one-dimensional pore and three-dimensional reservoirs is rather hard to model. There are some transition regions (the vestibules) at the ends of real pores where the motion of particles changes gradually from one-dimensional to three-dimensional and the interactions between the particles decrease. Modeling of the vestibules requires additional parameters, which are hard to justify in the general theory. That is why we used the simplest model of "sharp" channel boundaries (without explicit vestibules). The correlations between the particles in the channel and the particle, which escapes beyond the boundary, are lost immediately in this model. This assumption is a key point of our theory. It is definitely an oversimplification; however, it allows to build an elegant and tractable theory without any additional assumptions about the pore vestibules and the details of the particle exchange events. This puts our theory apart of other similar works, where the exchange events at the pore boundary are described using either unknown microscopic kinetic constants or explicit models of the vestibules. In term of the general theoretical framework our single controllable assumption about the loss of correlation at the boundary is preferable in comparison to the introduction of unknown adjustable parameters, which depend on multiple and uncontrollable assumptions about the pore vestibules. Explicit model of the vestibules can also be incorporated into our framework if necessary (see Appendix B); however, detailed analysis of this possibility is beyond the scope of the current work.

Our theoretical framework could be subdivided into two parts. The first part is the statistical physics derivations, which result in expressions (12), (20), and (21). These expressions allow us to determine any time-dependent macroscopic characteristic of the channel if the concentrations c_1 and c_2, the membrane potential ψ and the distribution functions $\phi^{(n)}$ are known. According to Eq. (20), any macroscopic property of the channel can be obtained by averaging the corresponding property over all possible occupancy states. The probabilities of the occupancy states in our theory are computed using the same hierarchical system of the Fokker-Plank equations for $\phi^{(n)}$ Eq. (34), which is used to compute all other macroscopic parameters of the system. No additional parameters are needed. This is in contrast to the works [19–21], where the probabilities of the occupancy states depend on additional kinetic parameters at the channel boundaries. Our approach of subdividing the general distribution function into the weighted terms, which correspond to different occupancy states, is conceptually similar to the averaging over occupancy states in the works [22,23]. In contrast to these works we generalized this approach to the nonequilibrium system.

The second part of the theory is rather independent from the first one. In this part the n-particle distribution functions $\phi^{(n)}$ are found from dynamic equations, which are transformed to a hierarchical system of Fokker-Planck Eq. (34). This system is similar (but not identical) to the systems obtained in [14] or [17]. In contrast to these works, there are no additional terms containing higher order functions $\phi^{(n+1)}$ in the equation for $\phi^{(n)}$. Thus, Eq. (34) is not coupled explicitly. The only way of coupling is the hierarchical set of boundary conditions [Eq. (6)]. These boundary conditions are very simple and natural—the solution of the n-dimensional equation serves as a boundary condition for the next $n+1$ dimensional equation. In contrast to [14,19] there are no kinetic parameters of the particle exchange events in the boundary conditions. This greatly simplifies the equations and eliminates adjustable parameters, which are hard to estimate.

The assumption of the "sharp" boundary allows writing continual Eq. (34) immediately instead of deriving them from the microscopic transition rate schemes (which should be done separately for each channel occupancy [14]). Such schemes become very complex already for three particles in the pore [14], while our equations are written in general form for any number of particles. In contrast to [17] our system of equation is closed. The number of equations in the system is equal to the maximal number of particles M, which can reside in the pore. This number is always limited by the physical length of the pore and the particle-particle repulsion in the sense that the probability of the occupancy of the state $M+1$ is negligible.

We show that the problem of finding $\phi^{(n)}$ could be reduced to a hierarchical system of simple partial differential equations of increasing dimensionality in the steady state. This system can be solved numerically by various techniques, which should be chosen taking into account the specific features of the studied system. The numerical method used to solve this system is designed with arbitrary dimensionality of equations and numerical efficiency in mind. Specific features of the equations prevent us from using standard numerical algorithms with known convergence properties. The algorithm used in this work is a modification of the multigrid technique adapted for the optimization problem, which is equivalent to our equations. It is fast and stable; however, its precision and convergence properties are uncertain. Analysis of the latter is not in the scope of this work. No quantitative comparison with experimental data is made in this work; thus, this uncertainty is acceptable for us. More robust computational techniques will be developed in the future.

It is shown that such steady state macroscopic characteristics of the channel as the current and the occupancy probabilities are analytical rational functions of concentrations. The coefficients of these functions could be easily computed numerically. Thus, the concentration dependencies could be obtained in a wide range of parameters at low computational cost.

The single-particle energy profile U_0 is an important quantity in our theory. U_0 is an effective (free) energy of the particle at certain position of the pore caused by the interaction of the particle with the pore wall. The permeating particles interact with the pore wall and cause polarization and rearrangements in its structure. These changes, in turn, lead to the changes of the energy profile for permeating particles. The details of this complex mutual influence depend on the characteristic time of the particle passage through the pore τ and the characteristic times of structural relaxations in the pore wall. If all motions of the pore wall relax faster then τ, then the structure of the pore wall and the particle density in the pore become self-consistent. In this case U_0 accounts for this self-consistency in the mean-field-like manner. All self-consistent rearrangements of the structure, which follow the passage of the particle are averaged in U_0 (the average particle moves in the effective mean-field potential U_0). Thus, it is possible to say that the pore wall is effectively "rigid" (U_0 does not change in time in the steady state) if there are no motions in the pore wall with the characteristic times larger then τ.

U_0 is also averaged over local motions of the pore wall independent on the interaction with the permeating particles, which are faster then τ. It also incorporates the effect of the external electric field and other external conditions on the pore structure. The single-particle energy profile is not "microscopic" quantity but a kind of effective mean-field potential. Such averaged nature of U_0 allows computing it in MD simulations of real channels [30].

It is obvious that U_0 can depend on the pore occupancy and external conditions, so, strictly speaking, the single-particle energy profile should be written as $U_0^{(n)}(x_i,\psi,c_1,c_2)$. However, in this work we assume that U_0 is independent on the channel occupancy and external conditions in the sake of simplicity. Such dependence could be introduced trivially by writing $U_0^{(n)}(x_i,\psi,c_1,c_2)$ instead of $U_0(x_i)$ in all corresponding formulas. In this case U_0 should be computed for each value of the external parameters and each pore occupancy by means of, i.e., MD simulations.

Description of the transmembrane electrostatic potential is one of the most challenging issues in the ion channel modeling. In principle our theory is not limited by any particular way of computing electrostatic potential. The potential $U_n(\vec{x},\psi)$ in Eq. (32) may incorporate any approach of evaluating electrostatic interactions such as explicit solution of the Poisson equations in the pore. However, simplified model of electrostatic interactions is often desirable because of either prohibitively large computational intensity of solving the Poisson equations or the need of simple analytical formulas. The simplest and widely used Goldman approximation presumes that the transmembrane potential drops linearly across the pore. It is definitely an oversimplification if *all* electrostatic interactions in the pore are described by the Goldman approximation. However, this is not the case in our theory.

Let us consider the electrostatic potential E acting on the individual ion in the pore. This potential for the ion i could be written as

$$E_i = E_{ion-ion} + E_{env-ion} + E_{dir}, \tag{44}$$

where $E_{ion-ion}$ is the potential caused by all other ions in the pore; E_{dir} is the "direct" transmembrane potential, which would act on the ion in the absence of other charges and polarizable environment; $E_{env-ion}$ is the electrostatic potential caused by all other charges in the system except the ions in the pore and the polarizable environment. $E_{ion-ion}$ is included into the particle-particle interactions V in Eq. (33); thus, $E_{ion-ion}=\sum_{j\neq i}^{n}V(x_i-x_j)$, where n is the number of ions in the pore. It is obvious that in the absence of charges and polarization effects the transmembrane potential drops linearly, thus E_{dir} is described perfectly by the Goldman approximation $E_{dir}(x)=x_i\psi/L$. $E_{env-ion}$ includes the influence of the static charges in the pore wall, the changes in the channel structure caused by the transmembrane potential ψ and various polarization effects. According to the definition given above the contributions, which constitute $E_{env-ion}$ are partially included into U_0 in the self-consistent manner, thus, $E_{env-ion}=U_0(x_i,\psi)+E_{corr}$, where E_{corr} is the correction, which cannot be described by the self-consistent mean-field potential U_0. Substituting corresponding terms into Eq. (44) we get

$$E_i = U_0(x_i, \psi) + \sum_{j \neq i}^{n} V(x_i - x_j) + x_i \psi / L + E_{corr}.$$

The linear term could be incorporated into U_0 as it is done in Eq. (43) for convenience.

If E_{corr} is small, then total electrostatic potential is described exhaustively by V, U_0 and.the linear Goldman term, which describes direct influence of the transmembrane potential on the ion.

Thus, the Goldman approximation is valid for *the part* of the electrostatic potential, which is not covered explicitly by V and U_0. The quality of this approximation depends on E_{corr} (approximation becomes exact if E_{corr} is negligible). The magnitude of E_{corr} should be estimated for each particular system.

Our theory was applied to the simplified model of the narrow pore, which was inspired by a real object (the selectivity filter of KcsA potassium channel). We have obtained macroscopic properties of this model channel (current and mean occupancy) in a wide range of model parameters. Predictions of our theory are consistent with the results of our previous works where the properties of the channel where computed by the Brownian dynamics simulations [25]. Although the model of the channel used in this work is very simplified, it provides some insights into the physical principles of the barrier-less conduction mechanism, which is postulated for real channels. It is shown that the knock-on conduction is possible if the weight of the occupancy state with $n+1$ ions in the channel containing n ions most of time is ~ 0.15 (for concentrations $c_1 = c_2 = 10^{-4}$ Å^{-1}). This value is a compromise between the large number of permeation events and the small residence time of the $n+1$ ion in the channel during each of these events. It is remarkable that the weight of the $n+1$ occupancy state is the same for all "ridges" of current, which correspond to predominant occupancies $n=1,2,3$ [Fig. 5(c)].

The concentration dependence of the mean channel occupancy show that there are steps of constant occupancy corresponding to $n=1,2,3$. The width of the steps depends on the parameters of the single-ion energy profile. In the case of parameters, which are closest to the selectivity filter of a real KcsA channel ($d=3$ Å, $A=43$ $k_B T$), the double occupancy dominates in a very broad range of concentrations (Fig. 7). This correlates very well with the fact that two ions occupy the selectivity filter in a broad range of conditions including the crystal structure [1].

It is necessary to note, however, that the model used in this work should only be considered as an oversimplified cartoon of the KcsA selectivity filter, designed for testing purposes. Thus only very general qualitative comparison of results with the real channel is possible. The goal of this work is not to study the KcsA channel or any other particular object, but to develop and validate the theoretical framework. The similarities in behavior of our model and real channel show similarities of general physical principles, which govern their functioning, and should not be overestimated.

A. Limitations

There are several limitations of our theoretical framework. The first and the most important is the "sharp" boundary between the channel and the reservoirs, where all correlations between the particles inside and outside the channel are lost. As it was shown above, this assumption allows overcoming numerous conceptual and technical problems, which were revealed in the previous works in this field. However, our assumption may be oversimplified for particular systems. In reality, there is always a transition region ("vestibule"), where the interactions of particles change gradually. More realistic model of the vestibules can be employed for specific systems. Appendix B describes in details the derivation of our boundary conditions and shows the way of introducing more complicated models of the vestibules if such complication is justified.

Another limitation is the usage of the Langevin (or corresponding Fokker-Plank) equations for modeling the motion of multiple, strongly interacting particles in the channel. This implies that the motion of each particle is an independent Markov process, which is not necessarily the case. In principle, any other non-Markovian description can be used to find the distribution functions ϕ inside the channel if this is justified by the nature of the studied system.

Finally, the external electrostatic potential is assumed to be linear inside the channel (the Goldman approximation [3]). As it is described above the large part of the nonlinearity of the electrostatic potential may be incorporated into the single-particle energy profile, however the importance of remaining effects is uncertain. More robust description should employ evaluation of the electrostatic field inside the channel using the Poisson or Poisson-Boltzmann equations.

We do not discuss the limitations of the very simplified model of the KcsA channel used in this work to evaluate and to test our theory. This model was discussed in details in our previous works [24,25].

B. Perspectives

Although our theory is quite general, it can be extended to account for some commonly observed special cases of multiparticle diffusion. Simultaneous diffusion of particles of several different kinds can be described. Different single-particle energy profiles U_0 and different interactions V could be assigned for the particles of different kind. Such approach can be used to model the motion of water molecules and ions in the ion channels in a more realistic way.

The single-file motion of particles in the channel is not necessarily strictly one-dimensional. The particles can have limited mobility in the directions perpendicular to the channel axis. Such mobility can be different in different parts of the pore (depending on the pore radius and the properties of the channel walls). Such mobility could be taken into account in several different ways including introduction of the entropic term to the single-particle energy profile or explicit introduction of additional degrees of freedom.

The interactions between the channel structure and the diffusing particles can be considered explicitly (particle-conformational interaction). It was shown that such interaction can lead to very interesting self-organization phenomena [31–35], thus such studies are very promising.

Our approach can be combined with the MD simulations of the ion channels. It is well-known that equilibrium distributions of ions in the ions channels cannot be computed by MD due to the limited simulation time scale. However, the single-ion energy profiles can be obtained easily [30]. Application of our theory allows obtaining ionic charge density in the channel from rather short MD simulations. This could help to bridge the gap between the MD simulations time scale (hundreds of nanoseconds) and the time scale of the most interesting channel gating events (milliseconds).

IV. CONCLUSION

We developed a general analytical framework which describes single-file diffusion of multiple strongly interacting particles in nonequilibrium conditions. The model takes into account the external potential action on the diffusing particles and the fluctuations of the number of particles due to their exchange with external reservoirs. The model is constructed in a bottom-up manner from the very basic principles of statistical physics and probability theory. It is shown that the problem can be reduced to a hierarchical system of elliptic partial differential equations of increasing dimensionality, which can be solved numerically. Our framework allows us to compute any macroscopic characteristics of the single-file multiparticle diffusion, including the current and the occupancy probabilities. It is shown that the occupancy probabilities and the current are rational functions of external concentrations.

The theory is tested on a model of the narrow pore inspired by the selectivity filter of biological ion channel. The macroscopic characteristics of the model channel are obtained in a wide range of parameters. Obtained data correlate very well with the data of earlier studies performed on the same model, which serves as a validation of our theoretical framework.

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APPENDIX A: ANALYTICAL CONCENTRATION DEPENDENCIES IN THE STEADY STATE

In this appendix the analytical concentration dependencies of the steady state channel properties are obtained. It is also shown that the function $\phi^{(n)}$ is a homogeneous function of degree n for $c_{1,2}$ in the steady state.

In equilibrium $r_1 = r_2 = r$ and $\nu_n(x_1, \ldots, x_n) = r^n$, according to Eq. (37). Let us determine the dependence of $\upsilon_n(x_1, \ldots, x_n)$ on $r_{1,2}$ in nonequilibrium conditions using the Green's function formalism. Let us note that the operator $\mathbb{R} = \sum_{i=1}^{n} \frac{\partial}{\partial x_i} [e^{-U_n(x_1,\ldots,x_n)} \frac{\partial}{\partial x_i}]$ in Eq. (36) is a linear Hermitian operator. The solution of the Dirichlet problem (39) $\mathbb{R}\upsilon_n(x_1, \ldots, x_n) = 0$ with the boundary conditions [Eq. (37)] is [36]:

$$\upsilon_n(x) = r_1 \int_{(x_1=-L)} G_n^{(-1)}(x, \omega_1) \upsilon_{n-1}(\omega_1) d\omega_1 + r_2 \int_{(x_n=L)} G_n^{(+1)}(x; \omega_2) \upsilon_{n-1}(\omega_2) d\omega_2, \quad \text{(A1)}$$

where $G_n^{(\mp 1)}(x; \omega)$ are Green functions of the second kind defined as

$$G_n^{(-1)}(x, \omega_1) = -\left. \frac{\partial \mathbb{Q}(x, x')}{\partial e^{(-)}} \right|_{x' = (-L, \omega_1)}$$

and

$$G_n^{(+1)}(x, \omega_2) = -\left. \frac{\partial \mathbb{Q}(x, x')}{\partial e^{(+)}} \right|_{x' = (L, \omega_2)},$$

where $\vec{e}^{(\mp)}$ are the normals to hyperplains $x_1 = -L$ and $x_n = L$, respectively; $\mathbb{Q}(x, x')$ is the Green function of the first kind, which satisfy the equation $\mathbb{R}\mathbb{Q}(x, x') = \delta(x - x')$; $\omega_1 = (x_2, \ldots, x_n)$, $\omega_2 = (x_1, \ldots, x_{n-1})$.

If $r_1 = r_2$ then

$$\int_{(x_1=-L)} G_n^{(-1)}(x, \omega_1) d\omega_1 + \int_{(x_n=L)} G_n^{(+1)}(x, \omega_2) d\omega_2 = 1.$$

Applying Eq. (A1) recursively for $n-1, n-2, \ldots, 3, 2$ and substituting expression for $\upsilon_1(x)$ we obtain the polynomial dependence on $r_{1,2}$

$$\upsilon^{(n)}(x) = \sum_{k=0}^{n} g_k^{(n)}(x) r_1^k r_2^{n-k}, \quad \text{(A2)}$$

where

$$g_k^{(n)}(x) = \sum_{\substack{i_1, \ldots, i_n = \pm 1 \\ i_1 + i_2 + \ldots + i_n = n - 2k}} \int_{(x_1=-L)} d\xi_1, \ldots, d\xi_n G_n^{(i_n)}(x, \xi_n) \times G_{n-1}^{(i_{n-1})}(\xi_n, \xi_{n-1}) \cdot \ \ldots \ \cdot G_1^{(i_1)}(\xi_2, \xi_1)$$

is independent of $r_{1,2}$,

$$\sum_{k=0}^{n} g_k^{(n)}(x) = 1. \quad \text{(A3)}$$

Using Eq. (A2) one can write the functions ϕ and p as polynomials in $r_{1,2}$

$$\phi^{(n)}(x) = e^{-U_n(x)} \sum_{k=0}^{n} g_k^{(n)}(x) r_1^{n-k} r_2^k, \quad \text{(A4)}$$

$$p^{(n)} = \sum_{k=0}^{n} a_k^{(n)} r_1^{n-k} r_2^k, \quad \text{(A5)}$$

where $a_k^{(n)} = \int_{-L}^{L} dx_1, \ldots, dx_n e^{-U_n(x)} g_k^{(n)}(x)$.

Thus the function $\phi^{(n)}$ is a homogeneous function of degree n for $r_{1,2}$ (or $c_{1,2}$). As a result arbitrary coefficient of chemical activity ϑ could be retained in the theory starting from formula (4) but only in the steady state. This coefficient will vanish in the subsequent transformations, however we do not show this here.

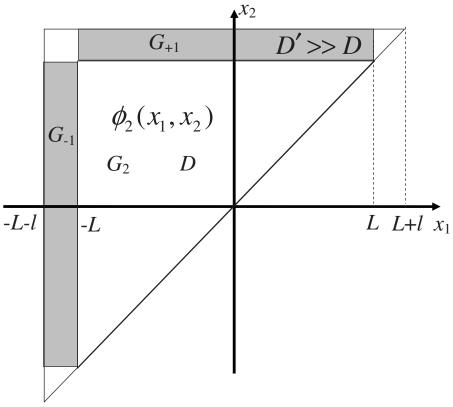

FIG. 8. The scheme of transition regions for Appendix B.

APPENDIX B: BOUNDARY CONDITIONS OF EQ. (34)

In this appendix the boundary conditions [Eq. (6)] for Eq. (34) are derived from explicit description of the channel vestibules (transition regions near the ends of the channel). It is shown which physical approximations lead to the boundary conditions [Eq. (6)] if they are not treated as assumption. It is also shown that n-dimensional Eq. (34) reduces to the $n-1$ dimensional equation of the same form (without any additional terms) if one of the particles reaches the channel boundary.

Let us consider the case $n=2$ in the sake of simplicity. There are transition regions (channel vestibules) of length l between the channel and the reservoirs, which extend from $-L-l$ to $-L$ and from L to $L+l$, respectively. The vestibules correspond to the areas G_{-1} and G_{+1} in the main region of the configurational space (Fig. 8). In the region G_{-1} the first ion is located in the left vestibule while the second ion resides inside the channel. In the region G_{+1} the second ion is located in the right vestibule while the first ion resides inside the channel.

Relaxation of any fluctuation in the reservoirs should be much faster than that inside the channel (the Boltzmann distribution is maintained inside the reservoirs regardless of any exchange events between the channel and the reservoirs). This means that effective diffusion coefficient in the reservoirs in much larger than that inside the channel. We assume that this is also true in the transition regions and effective diffusion coefficient in G_{-1} and G_{+1} is

$$D' \gg D. \tag{B1}$$

It is necessary to emphasize that effective diffusion coefficient D' is computed as a one-dimensional property (by analogy with D), while the vestibules are essentially three dimensional. Thus there is no contradiction between Eq. (50) and the fact that real three dimensional diffusion coefficient in the bulk solution and in the narrow pore could be of the same order of magnitude.

We further assume that $U_0(x) \approx 0$ in G_{-1} and G_{+1}. This means that the channel structure does not influence the motion of ions in the vestibules significantly. If this is not so, the vestibules should be shifted further toward bulk solutions.

Under these assumptions two-dimensional Eq. (34) in all regions reads as

$$\frac{\partial \phi^{(2)}(x_1,x_2;t)}{\partial t} = D(x_1)\frac{\partial}{\partial x_1}\left[\frac{\partial U_2(x_1,x_2)}{\partial x_1}\phi^{(2)} + \frac{\partial \phi^{(2)}}{\partial x_1}\right] + D(x_2)\frac{\partial}{\partial x_2}\left[\frac{\partial U_2(x_1,x_2)}{\partial x_2}\phi^{(2)} + \frac{\partial \phi^{(2)}}{\partial x_2}\right] \tag{B2}$$

where

$$D(x_i) = \begin{cases} D, x_i \in (-L,L) \\ D' \gg D, x_i \in [-(L+l),-L] \cup [L,L+l] \end{cases}.$$

The distribution function and the normal component of the flux should be continuous at the boundaries between the channel and the vestibules [18]; thus,

$$\phi^{(2)}(x_1,x_2;t)|_{x_{1,2}=\pm(L-0)} = \phi^{(2)}(x_1,x_2;t)|_{x_{1,2}=\pm(L+0)} \tag{B3}$$

$$-D\left[\frac{\partial U_2(x_1,x_2)}{\partial x_{1,2}}\phi^{(2)}(x_1,x_2;t) + \frac{\partial \phi^{(2)}(x_1,x_2;t)}{\partial x_{1,2}}\right]\Bigg|_{\pm(L-0)} = -D'\frac{\partial \phi^{(2)}(x_1,x_2;t)}{\partial x_{1,2}}\Bigg|_{\pm(L+0)} \tag{B4}$$

Taking into account Eq. (B1) the distribution function in the region G_{+1} could be written in adiabatic approximation as $\phi_2(x_1,x_2;t) \approx \varphi_{+1}(x_2;t)\phi^{(1)}_{+1}(x_1;t)$, where $\varphi_{+1}(x_2;t)$ is the distribution function of the second particle, which is located in the right vestibule. $\varphi_{+1}(x_2;t)$ is in the local steady state for any position of the slowly moving first particle; thus, two dimensional Fokker-Plank Eq. (B2)transforms to two independent equations for $\varphi_{+1}(x_2;t)$ and $\phi^{(1)}_{+1}(x_1;t)$. The relaxation of $\varphi_{+1}(x_2;t)$ is fast, so only the local steady state value $\varphi^{(\infty)}_{+1}(x_2;t)$ is of interest. Taking into account $U_0(x) \approx 0$ in G_{+1} we get

$$\varphi^{(\infty)}_{+1}(x_2;t) = c_2 - [\phi^{(1)}_{+1}(L-0,t) - c_2]\frac{x_2-L-l}{l},$$

$$x_2 \in (L,L+l).$$

It is clear that

$$\frac{\partial \varphi_{+1}(x_2;t)}{\partial x_2}\Bigg|_{x_2=L+0} = \frac{[\phi^{(1)}_{+1}(L-0,t) - c_2]}{l} \tag{B5}$$

is independent of x_2.

The equation for slowly changing function $\phi^{(1)}_{+1}(x_1;t)$ is

$$\frac{\partial \phi^{(1)}_{+1}(x_1;t)}{\partial t} = D\frac{\partial}{\partial x_1}\left[\frac{\partial U_0(x_1)}{\partial x_1}\phi^{(1)}_{+1}(x_1;t) + \frac{\partial \phi^{(1)}_{+1}(x_1;t)}{\partial x_1}\right]. \tag{B6}$$

According to Eq. (B3),

$$\phi_2(x_1,x_2;t)|_{x_2=L-0} = \phi^{(1)}_{+1}(x_1;t)\cdot\varphi^{(\infty)}_{+1}(x_2;t)|_{x_2=L+0} \tag{B7}$$

at the channel boundary. Substituting Eq. (B5) into Eq. (B4) yields

$$-D\left[\frac{\partial U_2(x_1,x_2)}{\partial x_2}\phi^{(2)}(x_1,x_2;t)+\frac{\partial \phi^{(2)}(x_1,x_2;t)}{\partial x_2}\right]\Bigg|_{x_2=L-0}$$
$$=-D'\frac{\partial \varphi_{+1}(x_2;t)}{\partial x_2}\Bigg|_{x_2=L+0}\cdot \phi^{(1)}_{+1}(x_1;t)$$
$$=-\frac{D'}{l}[\varphi_{+1}(L+0,t)-c_2]\phi^{(1)}_{+1}(x_1;t).$$

The left-hand side of this expression is independent on D', thus in the limit $D' \to \infty$ $\varphi^{(\infty)}_{+1}(L+0,t)\to c_2$ to ensure that the right hand side is also independent on D'. According to Eq. (B7) this yields $\phi^{(2)}(x_1,x_2;t)|_{x_2=L-0}=\phi^{(1)}_{+1}(x_1;t)\cdot c_2$. The same considerations apply to the left boundary of the channel, thus $\phi^{(2)}(x_1,x_2;t)|_{x_i=\mp L}=c_{1,2}\cdot\phi^{(1)}_{\mp 1}(x_1;t)$ if $D'\to\infty$.

Let us write the general distribution function of a single particle inside the channel at point x, while other particle is located in one of the vestibules as

$\phi^{(1)}(x;t)=\phi^{(1)}_{+1}(x;t)+\phi^{(1)}_{-1}(x;t)$. This function, Eq. (B6) for the region G_{+1} and the equation for the region G_{-1} analogous to Eq.(B6) yields the equation for the distribution function of a single particle inside the channel

$$\frac{\partial \phi^{(1)}(x;t)}{\partial t}=D\frac{\partial}{\partial x}\left[\frac{\partial U_1(x)}{\partial x}\phi^{(1)}(x;t)+\frac{\partial \phi^{(1)}(x;t)}{\partial x}\right]. \tag{B8}$$

The solution of this equation is the boundary condition for initial Eq. (34) (with two particles inside the channel)

$$\phi^{(2)}(x_1,x_2;t)|_{x_{1,2}=\mp L}=c_{2,1}\cdot\phi^{(1)}(x_{2,1};t). \tag{B9}$$

The development presented above is easily generalized to the case $n>2$. In general case (B8) transforms to Eq. (34) while Eq. (B9) transforms to Eq. (6).

Thus, it is shown that hierarchical boundary conditions [Eq. (6)] correspond to the situation when effective diffusion coefficient in the channel vestibules is very large in comparison to its value inside the channel. It is also shown that n-dimensional Eq. (34) transforms to the same $n-1$ dimensional equation at the channel boundary if Eq. (6) is valid.

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