Kernel representations for flux and concentration in ion channel models with time-varying concentrations

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This paper explores stochastic models for the study of ion transport in biological cells. It considers one-dimensional models with time-varying concentrations at the boundaries. The average concentration and flux in the channel are obtained as kernel representations, where the kernel functions have a probabilistic interpretation which contributes to a better understanding of the models. In particular, the kernel representation is given for the flux at a boundary point, providing a correct version of a representation found in the literature. This requires special attention because one of the kernel functions exhibits a singularity. This kernel representation is feasible due to the linearity of the system that arises from the assumed independence between ions. © *2006 American Institute of Physics*. [DOI: 10.1063/1.2363187]

I. INTRODUCTION

The transport of ions between the interior and the exterior of biological cells plays an important role in the function of the cells and hence in many processes of biological interest. This transport of ions takes place through aqueous pores (channels) formed by proteins embedded in a lipid bilayer membrane, which is essentially impermeable to ions. Ions diffuse and drift in the aqueous pore, formed by these proteins, between the interior and exterior baths due to concentration and potential gradients. Ions diffuse from regions of high concentration to regions of low concentration according to Fick's law[1,2] in the absence of electric fields. They drift due to electric fields caused by fixed charges in the channel walls, charges from the other ions in the channel, the dielectric properties of the channel, and the transmembrane potential, according to Ohm's law.[1,2]

Among the most common approaches to modeling ion transport one can find molecular dynamics simulations,[3–8] Brownian dynamics simulations,[3–13] the reaction-rate models,[2,3,14,15] and Nernst-Planck (NP) electrodiffusion models.[2–5,7,8,14–18] This paper uses models along the lines of both the reaction-rate and the NP electrodiffusion theories to represent the dynamics of ion diffusion across a channel between two baths. These models can be easily simulated and compared with experimental results.

At any given time, the ion can be located in the channel or in either one of the baths, but it cannot be located in the membrane because the membrane is assumed impermeable to ions. The flux from one bath to the other is usually the experimentally observable quantity, so the system can be considered to be one dimensional. Throughout the remainder of this paper, the exterior and interior baths are referred to as the left and right baths, respectively. This system is depicted in Fig. 1.

The remainder of the paper is organized as follows. Section II concerns discrete state models and Sec. III concerns the diffusion (continuous) analogs. Section II A discusses a discrete model to represent the dynamics of a single ion that diffuses within the channel between the two baths. The continuous limit of this model under the appropriate scaling describes a diffusion model governed by the reduced Langevin dynamics, and the probability density of the limit process satisfies the Smoluchowski equation. This diffusion limit is described in Sec. III A. Section II B describes a discrete model for a system with multiple noninteracting ions and time-varying concentrations at the boundaries. This model is based on the single ion model of Sec. II A. The average concentration and flux are obtained as kernel representations, where the kernel functions have a probabilistic interpretation. Section III B then describes the diffusion limit of this model for a system with multiple noninteracting ions. In particular, the kernel representation is given for the flux at the right boundary, providing a correct version of the representation in Ref. 19. This requires special attention because one of the kernel functions exhibits a singularity due to the infinite unidirectional flux of the reduced Langevin model. Section IV briefly discusses the kernel representation for the full Langevin model. Section V discusses connections between the discrete state model used in this paper and the theory of Brownian dynamics simulations. Finally, Sec. VI gives some discussion on the results of this paper.

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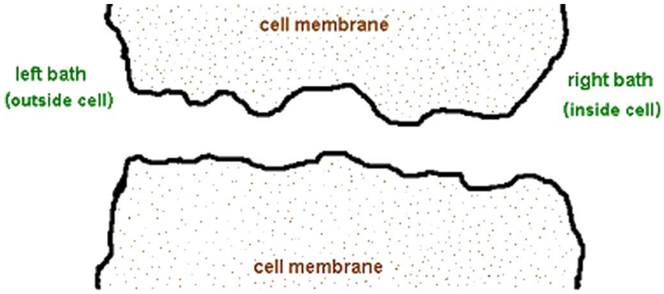

FIG. 1. System model.

II. DISCRETE MODELS

This section considers one-dimensional discrete models for ion transport between two baths with time-varying concentrations. Section II A suggests a one-dimensional model to represent the dynamics of an excursion of a single ion inside the channel. This model is then used in Sec. II B to describe a system with multiple ions and time-varying concentrations at the boundaries. The average concentration and flux in this system with multiple ions are obtained as kernel representations, where the kernel functions have a probabilistic interpretation. These representations aide in obtaining the average concentration and flux for the diffusion models, particularly for the flux at the boundaries. Simulations of these models are simple to implement and their results can be compared to the experimentally measurable flux.

A. Single ion

This section suggests a one-dimensional discrete model to represent an excursion of an ion that diffuses within the channel between the two baths. The appropriately scaled limit of this model yields a diffusion model with reduced Langevin dynamics. This model is applicable to systems where the concentrations are low enough that there is at most one ion inside the channel at any given time or to single ion occupancy channels such as the gramicidin channel.[20] This model is then used in Sec. II B as a building block for a model with multiple noninteracting ions.

The space discretization is done by dividing the channel into $N \geqslant 1$ sites labeled $1, \ldots, N$ and considering the outer and inner baths as sites 0 and $N+1$, respectively. Figure 2 depicts this discretization.

The dynamics of the ion are represented by a discrete time Markov chain X on $1, \ldots, N$ killed at the boundaries.

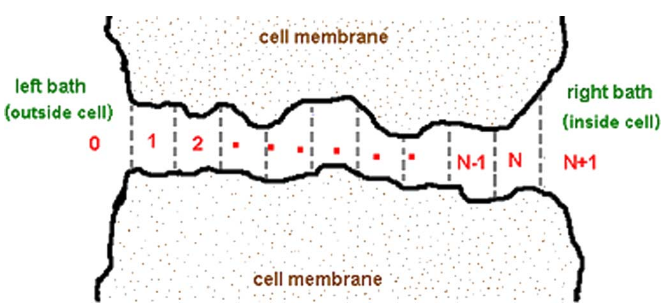

FIG. 2. Discrete model.

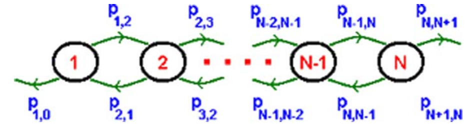

FIG. 3. Birth-death process on $\{1, \ldots, N\}$ killed at the boundaries. Self-loops are omitted.

The process being killed at the boundaries means that the excursion ends when the ion reaches one of the baths. In reality, an ion can exit the channel to a bath, and then reenter the channel. Thus, a single ion can have many excursions into the channel, and the model of this section describes one such excursion. Because an excursion is terminated upon reaching a bath, for a fixed time m and a fixed initial site i fixed, the distribution of the process $P(m,i,j) := P^i[X_m = j]$ as a function of j can add up to less than 1. For example, given that the ion is at site 1 at some time k, the ion next jumps towards state 0 with some nonzero probability and vanishes, in which case the Markov process is said to be killed at time $k+1$. An excursion of an ion entering from the left starts at state 1, and an excursion of an ion entering from the right starts at state N.

For sites $i, j \in \{1, \ldots, N\}$, the one-step transition probability $p_{i,j}$ is the probability the ion is at site j after one time step, given that it is at state i at the beginning of the time step. Assume that the ion can jump only to neighboring sites, i.e., $p_{i,j} = 0$ for $j \notin \{i-1, i, i+1\}$. This is reasonable in high friction with a small enough time step. Also assume that $p_{i,j} > 0$ whenever $|i-j| = 1$. This type of Markov chain is depicted in Fig. 3 and is known as a birth-death process killed at the boundaries.

Given a potential function and a diffusion coefficient for the channel, one can find sets of transition probabilities for this discrete model such that its diffusion limit satisfies the Smoluchowski equation with the given potential function and diffusion coefficient. One such set of transition probabilities is utilized in Sec. III A, and other choices are considered in Refs. 21 and 22.

The distribution of the process, $P(m,i,j)$, is sufficient to obtain the kernel representations for the average concentration and flux in these discrete models. However, in order to obtain the correct representation of the average flux at the ends of the channel in the diffusion limit models, it helps to know when the ion reaches the boundaries. Let T_0 be the killing time at the left boundary, i.e., it is the time at which the ion jumps from site 1 into the left bath, where the process X is immediately killed. If X is never killed at the left boundary (in particular, if it is killed at the right boundary) then $T_0 = \infty$. Similarly, let T_{N+1} be the killing time at the right boundary.

For an initial site $i \in \{1, \ldots, N\}$ and a time $m \geqslant 0$, let the left boundary-hitting time distribution, denoted by Q_L, be defined as

$$Q_L(i,m) = P^i[T_0 = m]. \tag{1}$$

Therefore, for a fixed initial site i, $Q_L(i,m)$ is the probability that the ion jumps into the left bath, where the process X is killed, during time step m given that it started at site i. Similarly, let the right boundary-hitting time distribution be defined as

$$Q_R(i,m) := P^i[T_{N+1} = m]. \tag{2}$$

For a fixed initial site i, the ion can reach either boundary with positive probability, therefore $Q_R(i,m)$ and $Q_L(i,m)$ are defective probability distributions as functions of m, meaning that for fixed initial site i, the sum over time m is less than 1.

The next section obtains the average concentration and flux in a system with multiple noninteracting ions as kernel representations, where the kernel functions are the distributions P, Q_R, and Q_L. These distributions can also be used to obtain several quantities of interest for ion channels, such as the crossing probabilities and the mean crossing time.[21]

B. Multiple ions

This section describes a discrete system with multiple noninteracting ions. Situations in which there is no interaction among the ions in the channel can be associated with dilute solutions or solutions with high electric permittivity, where the interaction among ions becomes negligible. The average concentration and flux in the channel are obtained as kernel representations with a probabilistic interpretation. The relation between the diffusion limit model of this discrete model with multiple ions and Nernst-Planck electrodiffusion theory is discussed in Sec. III B.

This noninteracting model assumes that the ions in the channel move independently of each other. The dynamics of each ion are described by the single ion excursion models of Sec. II A. It remains to describe the specifics of the entrance process. Define time step $m \geqslant 0$ as the time interval $[m,m+1)$ and assume that the system is initialized at time 0. Let $C_L(m)$ and $C_R(m)$ be the concentration or the expected number of ions at the left and right baths, respectively, at the beginning of time step m. These ions might be ions that have entered (and exited) the channel before. During time step m, each one of the ions at the left bath enters the channel, into site 1, with probability p_R. Similarly, each one of the ions at the right bath enters the channel, into site N, with probability p_L. On average, $C_L(m)p_R$ ions enter the channel from the left bath and $C_R(m)p_L$ ions enter the channel from the right bath during time step m. The initial concentration is assumed to be given as $C_0(i)$ for site $i \in \{1,\ldots,N\}$. If the channel is empty at time zero then $C_0(i) \equiv 0$ for $i \in \{1,\ldots,N\}$.

The noninteraction among ions allows the superposition of the contributions from each ion to both flux and concentration. The average concentration of ions at site $j \in \{1,\ldots,N\}$ at the beginning of time step $m \geqslant 0$, denoted by $C(j,m)$, has three components. It has a contribution from the ions that were initially in the channel, from ions that entered from the left bath, because the initial time step 0 up to the current time step m, and from ions that entered from the right bath because the initial time step 0 up to the current time step m, yielding

$$\begin{aligned} C(j,m) = &\sum_{i=1}^{N} C_0(i)P(m,i,j) \\ &+ \sum_{b=0}^{m-1} C_L(b)p_R P(m-b-1,1,j) \\ &+ \sum_{b=0}^{m-1} C_R(b)p_L P(m-b-1,N,j). \end{aligned} \tag{3}$$

Each ion that does enter the channel contributes to the average concentration at site j and time step m, through the probability of being at site j at time step m without having reached the boundaries, where it is killed. Recall that an ion may reenter the channel many times. The model does not keep track of which ions entering the channel were in the channel previously. Equation (3) is the kernel representation of the concentration, where the kernel functions have the probabilistic interpretation of being the distribution of the Markov chain X, which is killed at the boundaries.

The average flux at site $j \in \{1,\ldots,N\}$ during time step $m \geqslant 0$, denoted by $F(j,m)$, is defined as the average number of ions jumping from site j into site $j+1$ during time step m minus the average number ions jumping from site $j+1$ into site j during the same time step, i.e., it is the average flux over an imaginary line between sites j and $j+1$. This can be expressed as

$$F(j,m) = \begin{cases} C(j,m)p_{j,j+1} - C(j+1,m)p_{j+1,j}, & j \in \{1,\ldots,N-1\} \\ C(N,m)p_{N,N+1} - C_R(m)p_L, & j = N, \end{cases} \tag{4}$$

whose kernel representation for $j \in \{1,\ldots,N-1\}$ is obtained by substituting (3) into (4),

$$\begin{aligned} F(j,m) = &\sum_{i=1}^{N} C_0(i)(p_{j,j+1}P(m,i,j) - p_{j+1,j}P(m,i,j+1)) + p_R\sum_{b=0}^{m-1} C_L(b)(p_{j,j+1}P(m-b-1,1,j) - p_{j+1,j}P(m-b-1,1,j+1)) \\ &+ p_L\sum_{b=0}^{m-1} C_R(b)(p_{j,j+1}P(m-b-1,N,j) - p_{j+1,j}P(m-b-1,N,j+1)). \end{aligned} \tag{5}$$

Each ion contributes to the flux at site j during time step m through how more likely it is to reach site j at the beginning of time step m and jump right, without reaching the boundaries, than to reach site $j+1$ and jump left, without reaching the boundaries. The kernel functions are proportional to the distribution of X.

The flux at the right boundary $(j=N)$ for $m>0$ can be obtained by substituting (3) into (4),

$$F(N,m) = \sum_{i=1}^{N} C_0(i)P(m,i,N)p_{N,N+1} + p_R\sum_{b=0}^{m-1} C_L(b)P(m-b-1,1,N)p_{N,N+1} + p_L\left(\sum_{b=0}^{m-1} C_R(b)P(m-b-1,N,N)p_{N,N+1} - C_R(m)\right). \tag{6}$$

This kernel representation of the flux at the right boundary is well defined in these discrete models. However, its diffusion limit is not well defined when the boundary concentrations are not constant because the kernel function in the third summation becomes nonintegrable in the limit. For this reason, we rearrange (6) so that the diffusion limit of each term is well defined. As shown in Sec. III B, the following variation of (6) suffices:

$$\begin{aligned}F(N,m) &\overset{(a)}{=} \sum_{i=1}^{N} C_0(i)P(m,i,N)p_{N,N+1} + p_R\sum_{b=0}^{m-1} C_L(b)P(m-b-1,1,N)p_{N,N+1} \\ &\quad + p_L\left(\sum_{b=0}^{m-1} C_R(b)P(m-b-1,N,N)p_{N,N+1} - C_R(m)\sum_{m=0}^{\infty}(Q_R(N,m)+Q_L(N,m))\right) \\ &\overset{(b)}{=} \sum_{i=1}^{N} C_0(i)Q_R(i,m+1) + p_R\sum_{b=0}^{m-1} C_L(b)Q_R(1,m-b) \\ &\quad + p_L\sum_{b=0}^{m-1}(C_R(b)-C_R(m))Q_R(N,m-b) - p_LC_R(m)\sum_{b=m+1}^{\infty} Q_R(N,b) - p_LC_R(m)\sum_{b=0}^{\infty} Q_L(N,b).\end{aligned} \tag{7}$$

Equality (a) follows because $\Sigma_{m=0}^{\infty}(Q_R(N,m)+Q_L(N,m))=1$, and equality (b) follows because $Q_R(i,0)=0$ and $Q_R(i,m)=P(m-1,i,N)p_{N,N+1}$.

Notice that the kernel functions for the flux at the right boundary are the boundary-hitting time distributions, instead of the distribution of the Markov chain itself. The diffusion limits of these representations for the average concentration and flux are well defined and are given in Sec. III B.

III. DIFFUSION MODELS

This section considers the diffusion limit of the discrete models of Sec. II. Section III A deals with the limit of the model of Sec. II A for an excursion of a single ion. This limit model describes a diffusion model with reduced Langevin dynamics whose propagator satisfies the Smoluchowski equation. Section III B then addresses the limit of the multiple noninteracting ion model of Sec. II B. This limit model is consistent with Nernst-Planck electrodiffusion theory. The kernel representations for the average concentration and flux in the diffusion limit model are obtained as limits of their discrete analogs. Special attention is required to represent the flux at the boundaries because one of the kernel functions exhibits a singularity in this reduced Langevin regime.

A. Single ion

This section describes the diffusion process that arises as the appropriately scaled limit of the discrete single ion excursion model of Sec. II A. Let the space step size Δx satisfy $\Delta x = L_c/N$, where L_c is the length of the channel and N is a large integer. Let the time step size Δt be such that

$$\lim_{\Delta x,\Delta t\to 0} \frac{(\Delta x)^2}{\Delta t} = G > 0 \tag{8}$$

and consider the scaled process $\widetilde{X}$ defined by

$$\widetilde{X}_t := \Delta x X_{\lfloor t/\Delta t\rfloor}.$$

If the scaled process has limiting drift and diffusion functions, then, under regularity assumptions, the scaled process converges to a diffusion process.[23–25] This diffusion process can be used to model the dynamics of a single ion excursion inside the channel in continuous space. These dynamics are of the reduced Langevin type.

Models of ion transport as an electrodiffusion process establish a relation between the electric potential function and the drift experienced by the ions. Also, estimates on the diffusion coefficient are known for some channels. Therefore, it is useful to establish a relation between the parameters of the electrodiffusion process (drift and diffusion functions) and the parameters of the discrete system (one-step transition probabilities).

Given the friction coefficient γ and the potential function U (which imparts a drift μ on the ions) of the channel of interest, one can choose the one-step transition probabilities for the discrete model such that the propagator $p(x,t|x_0)$ of the diffusion limit process satisfies the Smoluchowski equation,[26–28]

$$\frac{\partial p(x,t|x_0)}{\partial t} = \frac{\partial}{\partial x}\left(D(x)e^{-\beta U(x)}\frac{\partial}{\partial x}(p(x,t|x_0)e^{\beta U(x)})\right)$$
$$= -\frac{\partial}{\partial x}(\mu(x)p(x,t|x_0)) + \frac{\partial^2}{\partial x^2}(D(x)p(x,t|x_0)), \tag{9}$$

where $D=k_BT/m\gamma$ and $\mu=-\beta D(\partial U/\partial x)+(\partial D/\partial x)$.

Assume that the one-step transition probabilities of the discrete model are of the following form for site $i \in \{1,\ldots,N\}$:

$$p_{i,i+1} = \frac{\Delta t}{2\Delta x}\mu_i + \frac{\Delta t}{(\Delta x)^2}D_i, \tag{10}$$

$$p_{i,i-1} = -\frac{\Delta t}{2\Delta x}\mu_i + \frac{\Delta t}{(\Delta x)^2}D_i, \tag{11}$$

where $D_i=D(i\Delta x)$, $\mu_i=\mu(i\Delta x)$, and Δx, Δt are small enough to keep $p_{i,i+1}$ and $p_{i,i-1}$ between 0 and 1. Other choices of one-step transition probabilities can be found in Refs. 21, 22, and 29. To keep continuity at the boundaries let

$$p_R = \frac{\Delta t}{2\Delta x}\mu_0 + \frac{\Delta t}{(\Delta x)^2}D_0, \tag{12}$$

$$p_L = -\frac{\Delta t}{2\Delta x}\mu_{N+1} + \frac{\Delta t}{(\Delta x)^2}D_{N+1}. \tag{13}$$

Then, under the scaling given by (8) with $G \geqslant \max_{x\in[0,L_c]}3D(x)$,

$$(\Delta x)X_{[t/\Delta t]} \Rightarrow W_t,$$

where "$\Rightarrow$" denotes convergence in distribution and W is a diffusion process on $(0,L_c)$ which is killed at the boundaries and satisfies the Smoluchowski equation (9).[23–25] In particular, one can obtain an electrodiffusion process if the potential function U is proportional to the external electric potential.

For $y\in(0,L_c)$ and $t\geqslant 0$, the propagator of W is defined as

$$p(x,t|y) := \frac{P^y[W_t \in dx]}{dx}, \tag{14}$$

for $x\in(0,L_c)$.

Therefore, for t,y fixed, $p(x,t|y)dx$ is the probability that W is in $(x,x+dx)$ at time t given that it started at y. If $p(x,t|y)>0$ then it is possible that W has not reached the boundaries by time t, because it would be immediately killed there. The probability that W has already reached the boundaries by time t can be nonzero. Therefore, for t,y fixed, $p(x,t|y)$ is a probability density as function of x whose integral over x is less than 1.

For the remainder of this section, let $\rightarrow$ denote the limit as $\Delta x,\Delta t\rightarrow 0$, $m\Delta t\rightarrow t$, $i\Delta x\rightarrow y$, and $j\Delta x\rightarrow x$ for $i,j \in\{1,\ldots,N\}$, $m\geqslant 0$, $x,y\in(0,L_c)$, and $t\geqslant 0$. The scaled limit of the distribution of the discrete process X corresponds to the density of the diffusion process W, i.e.,

$$\frac{P(m,i,j)}{\Delta x} \rightarrow p(x,t|y). \tag{15}$$

The distribution dies quickly at the boundaries but it remains nonzero under the following scaling:

$$\frac{P(m,1,j)}{(\Delta x)^2} \rightarrow g(x,t|0), \tag{16}$$

$$\frac{P(m,N,j)}{(\Delta x)^2} \rightarrow -g(x,t|L_c), \tag{17}$$

where

$$g(x,t|y) := \frac{\partial p(x,t|y)}{\partial y}.$$

Let T_0 be the killing time at the left boundary; i.e., it is the time at which W exits the interval $(0,L_c)$ through the left boundary, where it is immediately killed. If W is never killed at the left boundary (in particular, if it is killed at the right boundary) then $T_0=\infty$. Similarly, let T_{L_c} be the killing time at the right boundary.

The scaled limits of the boundary-hitting time distributions of the discrete process X are equivalent to the boundary-hitting time densities of the diffusion process W, i.e.,

$$\frac{Q_R(j,m)}{\Delta t} \rightarrow q_R(x,t) := \frac{P^x[T_{L_c}\in dt]}{dt}, \tag{18}$$

$$\frac{Q_L(j,m)}{\Delta t} \rightarrow q_L(x,t) := \frac{P^x[T_0\in dt]}{dt}. \tag{19}$$

The boundary-hitting time distributions also die quickly at the boundaries but they remain nonzero under the following scaling:

$$\frac{Q_R(1,m)}{\Delta x\Delta t} \rightarrow k_R(0,t), \tag{20}$$

$$\frac{Q_R(N,m)}{\Delta x\Delta t} \rightarrow -k_R(L_c,t), \tag{21}$$

$$\frac{Q_L(N,m)}{\Delta x\Delta t} \rightarrow -k_L(L_c,t), \tag{22}$$

where

$$k_R(x,t) := \frac{\partial q_R(x,t)}{\partial x},$$

$$k_L(x,t) := \frac{\partial q_L(x,t)}{\partial x}.$$

The next section obtains the average concentration and flux in this diffusion limit model as kernel representations, where the kernel functions are the densities p, q_R, q_L, and their derivatives. These densities can be used to obtain several quantities of interest for ion channels, such as the crossing probabilities and the mean crossing time.[21]

B. Multiple ions

This section discusses the diffusion limit of the noninteracting model of Sec. II B. It is assumed here that the limit process exists and that it can be considered simply as the aggregation of independent diffusion processes, where each process corresponds to the diffusion model of Sec. III A. The existence of such a limit process can be shown,[30] but it is beyond the scope of this paper. The average concentration and flux are obtained as kernel representations by taking the limit of their discrete analogs under the diffusion scaling. Special attention is required at the boundaries because one of the kernel functions has a singularity.

The scaled limits of the initial and boundary concentrations are assumed to be given by

$$c_0(x) = \lim_{\substack{\Delta x,\Delta t\to 0\\ j\Delta x\to x}} \frac{C_0(j)}{\Delta x}, \tag{23}$$

$$c_R(t) = \lim_{\substack{\Delta x,\Delta t\to 0\\ m\Delta t\to t}} \frac{C_R(m)}{\Delta x}, \tag{24}$$

$$c_L(t) = \lim_{\substack{\Delta x,\Delta t\to 0\\ m\Delta t\to t}} \frac{C_L(m)}{\Delta x}. \tag{25}$$

Then, the average concentration in the diffusion model can be obtained as the scaled limit of the average concentration in the discrete model (3) for $x \in (0,L_c)$ and $t>0$,

$$\begin{aligned} c(x,t) = \lim_{\substack{\Delta x,\Delta t\to 0\\ j\Delta x\to x, m\Delta t\to t}} \frac{C(j,m)}{\Delta x} &= \int_0^{L_c} c_0(y)p(x,t|y)dy \\ &+ D(0)\int_0^t c_L(t-s)g(x,s|0)ds - D(L_c) \\ &\times \int_0^t c_R(t-s)g(x,s|L_c)ds, \end{aligned} \tag{26}$$

which is a kernel representation. The kernel functions are the density of the diffusion process W killed at the boundaries, and the derivative of the density evaluated at the boundaries.

Similarly, the kernel representation of average flux in the diffusion model can be obtained from the scaled limit of the flux in the discrete model (5) for $x \in (0,L_c)$ and $t>0$ as

$$\begin{aligned} J(x,t) = \lim_{\substack{\Delta x,\Delta t\to 0\\ j\Delta x\to x, m\Delta t\to t}} \frac{F(j,m)}{\Delta t} &= \mu(x)\int_0^{L_c} c_0(y)p(x,t|y)dy - \int_0^{L_c} c_0(y)\frac{\partial}{\partial x}(D(x)p(x,t|y))dy + D(0)\mu(x)\int_0^t c_L(t-s)g(x,s|0)ds \\ &- D(0)\int_0^t c_L(t-s)\left.\frac{\partial}{\partial x}(D(x)g(x,s|y))\right|_{y=0} ds - D(L_c)\mu(x)\int_0^t c_R(t-s)g(x,s|L_c)ds + D(L_c)\int_0^t c_R(t-s) \\ &\times \left|\frac{\partial}{\partial x}(D(x)g(x,s|y))\right|_{y=L_c} ds. \end{aligned} \tag{27}$$

The concentration, given by (26), can be continuously extended to $[0,L_c]$, but the flux, given by (27), cannot be extended because the result would be ill defined due to the singularity of one of the kernel functions involved. The kernel function in the last term in (27) is $O(t^{-3/2})$,[21] which is not integrable around $t=0$. This singularity is present only if the boundary concentrations are not constant. It is also not present in the full Langevin regime, as explained in Sec. IV. For this reason, the kernel representation of the average flux at the right boundary in the diffusion model has to be obtained separately as the scaled limit of the average flux at the right boundary of the discrete model (7) for $t>0$ as

$$\begin{aligned} J(L_c,t) = \lim_{\substack{\Delta x,\Delta t\to 0\\ N\Delta x\to L_c, m\Delta t\to t}} \frac{F(N,m)}{\Delta t} &= \int_0^{L_c} c_0(y)q_R(y,t)dy + D(0)\int_0^t c_L(t-s)k_R(0,s)ds \\ &- D(L_c)\int_0^t (c_R(t-s)-c_R(t))k_R(L_c,s)ds + D(L_c)c_R(t)\int_t^\infty k_R(L_c,s)ds + D(L_c)c_R(t)\int_0^\infty k_L(L_c,s)ds, \end{aligned} \tag{28}$$

where the kernel functions are the boundary-hitting time densities of the diffusion process W and their derivatives at the boundaries.

A kernel representation for the average flux at the right boundary is obtained in Ref. 19 but a singularity in one of the kernel functions causes the representation to be ill defined. The kernel function $k_R(L_c,t)$ is not integrable around $t=0$. This singularity is missed in Ref. 19 and hence the representation obtained there, which includes this nonintegrable kernel function, is ill defined. The factor $c_R(t-s)-c_R(t)$, which goes to zero as s goes to zero, in the third integral in (28) takes care of this singularity and hence (28) is a well defined kernel representation for the average flux at the right boundary.

The flux from one bath to the other is usually the experimentally observable quantity, and the kernel representation given here for the flux at the right boundary can be compared to available experimental results and used as an estimate in general.

IV. KERNEL REPRESENTATIONS FOR FULL LANGEVIN DYNAMICS

The singularities we encountered are associated with the reduced Langevin dynamics, for which the unidirectional fluxes are infinite.[31] In contrast, unidirectional fluxes for the full Langevin dynamics are finite.[31] Here we briefly discuss kernel representations under full Langevin dynamics.

Let $p(x,v,t|y,\eta)$ denote the joint density of the position and velocity (x,v) at time t for an ion released at time zero at y with initial velocity η, with absorption at the boundaries. The integral of the density function over all (x,v) is thus the probability the ion has not been absorbed by time t. This joint density function satisfies a forward evolution equation as described in Ref. 31.

For $x\in[0,L_c]$ and $v\in(-\infty,\infty)$, let $c(x,v,0)$ be the initial concentration of ions inside the channel at x with velocity v. For $t\geq 0$ and $v\in[0,\infty)$, let the boundary concentration of ions at the left bath with velocity v be given by $c(0,v,t)$. Similarly, for $t\geq 0$ and $v\in(-\infty,0]$, let the boundary concentration of ions at the right bath with velocity v be given by $c(L_c,v,t)$. For $x\in[0,L_c]$, $v\in(-\infty,\infty)$, and $t\geq 0$, let $c(x,v,t)$ denote the concentration in the two-dimensional phase space (x,v) at time t. Then by the law of total probability,

$$\begin{aligned}c(x,v,t) &= \int_0^{L_c} dy \int_{-\infty}^{\infty} d\eta c(y,\eta,0)p(x,v,t|y,\eta)\\ &\quad + \int_0^t ds \int_0^{\infty} d\eta c(0,\eta,s)\,\eta p(x,v,t-s|0,\eta)\\ &\quad + \int_0^t ds \int_{-\infty}^{0} d\eta c(L_c,\eta,s)\,\eta p(x,v,t-s|L_c,\eta).\end{aligned} \tag{29}$$

The term $c(0,\eta,s)\eta p(x,v,t-s|0,\eta)$ in (29) represents the flux of velocity v ions entering from the left at time s. There are no singularities, even as x approaches the boundaries, if the given boundary conditions are continuous.

Then, the flux at x at time time t is given by

$$\begin{aligned}J(x,t) &= \int_{-\infty}^{\infty} vc(x,v,t)dv\\ &= \int_0^{L_c} dy \int_{-\infty}^{\infty} d\eta c(y,\eta,0)r(x,t|y,\eta)\\ &\quad + \int_0^t ds \int_0^{\infty} d\eta c(0,\eta,s)\,\eta r(x,t-s|0,\eta)d\eta\\ &\quad + \int_0^t ds \int_{-\infty}^{0} d\eta c(L_c,\eta,s)\,\eta r(x,t-s|L_c,\eta)d\eta\end{aligned}$$

where $r(x,t|y,\eta)=\int_{-\infty}^{\infty} vp(x,v,t|y,\eta)dv$.

In this full Langevin regime, the unidirectional fluxes are finite,[31] and hence one can rewrite the flux in terms of the unidirectional fluxes, as $J(x,t)=J_{LR}(x,t)-J_{RL}(x,t)$, where $J_{LR}(x,t)$ is the unidirectional flux from left to right and $J_{RL}(x,t)$ is the unidirectional flux from right to left. This decomposition into the unidirectional flux contributions is particularly helpful at the boundary because, on one hand, the flux entering the channel is completely determined by the specified boundary conditions,

$$J_{LR}(0,t) = \int_0^{\infty} vc(0,v,t)dv \quad \text{and}$$

$$J_{RL}(L_c,t) = \int_{-\infty}^{0} vc(L_c,v,t)dv.$$

On the other hand, the flux leaving the channel is determined by the solution to (29),

$$J_{RL}(0,t) = \int_{-\infty}^{0} vc(0,v,t)dv \quad \text{and}$$

$$J_{LR}(L_c,t) = \int_0^{\infty} vc(L_c,v,t)dv$$

V. RELATION TO SIMULATION AND BROWNIAN DYNAMICS

We would like to warn the reader that this paper is concerned with relationships among statistical averages for noninteracting particles. There are several issues associated with simulations that are not addressed by those relationships. We comment on some of them in this section. The channel model used in this paper is doubly discrete (DD)—it is a version of the reduced Langevin equation, or Smoluchowski equation, discretized in both time and space. An advantage of the DD model is that transition probabilities for constant drift and diffusion terms can be written explicitly, so that singular limiting behavior can be explored, and density evolution can be carried out numerically in a simple fashion.[21] A related model is that of Brownian dynamics (BD), useful for simulations. A particle in a BD simulation also moves in discrete time steps, but the jumps are continuous with a Gaussian density. The BD and DD models can be conceptually related to each other by supposing that $\hat{\Delta}t=K\Delta t$, where $\hat{\Delta}t$ is the time step size for the BD model, Δt is the time step size for the DD model, and K is a large positive integer constant. By the central limit theorem, the sum of K steps for the DD model is roughly equivalent to a single Gaussian distributed step for the BD model. Thus, BD simulations can be much more efficient than simulations based on the DD model, because of the speedup factor K.

A characteristic of BD simulation involving a boundary is that the steady state density exhibits a spurious boundary layer, unless the step size distribution for particles entering the channel is suitably selected.[31] It is shown in Ref. 31 that if the step size of particles entering the region of simulation is taken to be the renewal density associated with the Gaussian step size distribution, then the spurious boundary layer in steady state is eliminated. The work (Ref. 32) gives an entrance distribution for simulations based on the full Langevin equation, in which both the position and velocity of particles are tracked. Such a spurious boundary layer does not arise in the DD model. For example, if the drift is zero and the boundary concentrations and diffusion coefficient are constant, then the steady state density for the DD model is exactly linear. This is consistent with the renewal theory based insight of Ref. 31, because the renewal distribution corresponding to the ± 1 step sizes of the DD model is step size 1 with probability 1.

Another property of BD simulations is that the intensity of particles entering the boundary is typically proportional to $1/\sqrt{\hat{\Delta}t}$ or, equivalently, the mean number of particles injected per time step is proportional to $\sqrt{\hat{\Delta}t}$.[31] The same scaling is used in the DD model. Specifically, (8) and (23) show that the mean number of particles introduced at the left boundary at a time step j, namely, $C_0(j)p_R$, is proportional to $\sqrt{\Delta t}$. Because $\hat{\Delta}t = K\Delta t$, a simulation of DD requires the introduction of $\sqrt{K}$ times more particles per unit time than BD simulation, even though the average number of particles in the system for the BD and DD models are the same. An explanation is that many particles enter and depart the DD system in fewer than K time steps and hence do not show up in the BD simulation.

Simulations with boundaries require stochastic models of the sources of particles at the boundaries. The models used influence stochastic fluctuations of current.[33,34] Such considerations are beyond the scope of this paper. Because our model involves noninteracting particles, the concentrations at the boundaries and within the channel are statistical averages, which are valid for any stochastic model for ion sources with the specified means. Accurate models for ion sources should be rather bursty, because an ion near the boundary will typically enter and exit many times. A method for reintroducing ions based on full Langevin dynamics is given in Ref. 35. Radiation boundary conditions have also been explored in the literature[26,27,34] instead of the absorption boundary used in this paper and in Refs. 31, 32, and 36 among others. The work (Ref. 36) explores the use of renewal processes as sources of particles from constant concentration baths at the boundaries. It is shown that even the time-varying statistical averages (but not the steady state averages) are influenced by the choice of distribution used in the renewal sources. However, if stationary renewal sources are used, such that the time of arrival of the first particle to enter the system has the stationary residual renewal distribution, all choices of interarrival times with the same mean would yield the same equations for the time-varying statistical mean concentration.

VI. DISCUSSION

A noninteracting model with time-varying concentrations at the boundaries is considered both in discrete space and in continuous space. The average concentration and flux are obtained as kernel representations, where the kernel functions have a probabilistic interpretation. In the reduced Langevin regime, the kernel functions are the transition density and boundary-hitting time densities, as well as their derivatives, of the stochastic process that is used to model the motion of single ions. Special attention is required to represent the flux at the boundaries in the diffusion model because one of the kernel functions exhibits a singularity due to the infinite unidirectional flux of the reduced Langevin regime. This singularity is only of concern when dealing with time-varying concentrations. The flux at the right boundary is addressed in Ref. 19, but the given solution is ill defined due to a singularity in the kernel representation obtained. The kernel representations given in this paper are well defined. Kernel representations for the concentration and flux inside the channel and at the boundaries are also given for full Langevin dynamics. The kernel functions in this representation are well defined because of the finiteness of the unidirectional fluxes in the full Langevin regime.

Simulations of the models presented here are simple to implement and the flux obtained from them can be compared to the experimentally measurable flux.

The diffusion limit of these noninteracting models is consistent with Nernst-Planck electrodiffusion theory, so the concentration and the flux can be represented by partial differential equations with appropriate initial and boundary conditions. Interaction among ions can be incorporated into the model, as suggested in Ref. 21, and the diffusion limit of an open interacting model could be investigated to obtain representations in terms of partial differential equations that can be used to obtain quantities of interest such as concentration, flux, and distribution of trans path duration.

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