

# Boundary conditions and trajectories of diffusion processes

Mark F. Schumaker<sup>a)</sup>

*Department of Mathematics, Washington State University, Pullman, Washington 99164-3113*

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This article constructs trajectories associated with various boundary conditions for the Smoluchowski equation on an interval. Single-particle diffusion processes are first constructed by taking the diffusion limits of random walks. The diffusion limit gives both boundary conditions which enforce the single-particle constraint and properties of underlying trajectories at those boundaries. Mean-field diffusions are then obtained as limits of sums of single-particle processes. The results help to interpret the application of diffusion models to both ion channels and wider pores that facilitate molecular transport across membranes. Potential applications to Brownian dynamics simulations are discussed. © 2002 American Institute of Physics. [DOI: 10.1063/1.1492802]

## I. INTRODUCTION

A traditional approach to the ion channel open pore permeation problem is based on the classical theory of Goldman, Hodgkin, and Katz (GHK theory).<sup>1</sup> Mathematically, this involves the solution of the Smoluchowski equation for the concentration of a diffusing particle on an interval, with boundary conditions specifying that the concentration of the particle at either end is proportional to its concentration in the bulk solutions outside the channel. What is the geometry of the trajectories associated with these boundary conditions? How do the trajectories change when the boundary conditions are modified? A stochastic theory has not been available to answer these questions.<sup>2</sup> This article constructs trajectories associated with four different boundary conditions for the Smoluchowski equation, including those used by GHK theory.

The results help interpret the application of both GHK theory and the more modern Poisson–Nernst–Planck (PNP) theory to ion channels. The latter approach simultaneously solves the Nernst–Planck equation (the first integral of the Smoluchowski equation) with Poisson’s equation for the electrostatic field. GHK and PNP theories are applied to the analysis of K<sup>+</sup> permeation through a synthetic ion channel by Refs. 3 and 4, respectively. In Ref. 4, the boundary conditions on the Nernst–Planck equation are similar to those of GHK theory.

The pores of narrow ion channels such as gramicidin<sup>1</sup> or potassium channels<sup>5</sup> have atomic dimensions and their ion occupancy states are strongly constrained. The applicability of mean-field theories such as GHK or PNP to these systems has recently been challenged.<sup>6,7</sup> This underlines the significance of the single-particle (or single-ion) diffusion theory constructed by Levitt,<sup>8</sup> which is not a mean-field theory. Levitt’s theory describes diffusion in a simplified configuration space of the channel system, analogous to rate theories of ion permeation.<sup>9</sup> This approach has been generalized to construct framework models of permeation — stochastic models designed to incorporate the results of molecular dynamics

simulations.<sup>10,11</sup> This article uses the single-particle theory, as formulated by Ref. 9, to construct the trajectories associated with various boundary conditions, including those of GHK theory.

The results are also applicable to transport through wider pores such as bacterial porins, mitochondrial channels or gap junctions. In these systems, diffusion models may be used to analyze the transport of larger molecules by means of their transient occlusion of ion currents.<sup>12</sup> An analysis based on diffusion equations remains appropriate, as diffusion completely dominates convective flow at reasonable transmembrane pressure differences for pore radii of 1 nm or less.

## II. RESULTS

Let  $x$  be the coordinate parallel to the pore axis of a channel, occupying the interval  $[0,L]$  as sketched in Fig. 1(A). To construct a theory of single-particle diffusion through the channel we first consider a discrete-time, discrete-state random walk on sites  $x_i = iL/n$ ,  $i = 1 \cdots n$  with transition probability from site  $i$  to neighboring site  $j$ <sup>11</sup>

$$k_{ij} = \Delta t \frac{D}{(\Delta x)^2} \exp\left\{\frac{1}{2} \beta [W(x_i) - W(x_j)]\right\}. \quad (1)$$

This elegant form is a suggestion of Roux.<sup>13</sup>  $D$  is a diffusion coefficient and  $\Delta x = L/n$  is the interval between the sites, where a diffusion will be constructed on  $0 \leq x \leq L$ .  $W(x)$  is a potential of mean force, which is identical to the Helmholtz free energy,<sup>14</sup> and  $\beta = 1/k_B T$ . The random walk satisfies detailed balance at thermodynamic equilibrium. At any steady state, the net probability flux into site  $i$  is zero:

$$P_i(k_{i,i-1} + k_{i,i+1}) = P_{i-1}k_{i-1,i} + P_{i+1}k_{i+1,i}, \quad (2)$$

where  $P_i$  is the probability the walker is at  $x_i$ . The diffusion limit corresponds to  $n \rightarrow \infty$ . The time step  $\Delta t$  is scaled  $\Delta t = \Delta \tau / n^2$ , where  $\Delta \tau$  is independent of  $n$ . This scaling keeps transition probabilities bounded on taking the limit.  $\Delta \tau$  can then be chosen so that the probability of movement never exceeds one. Assuming the channel has cross-section  $A$ , the relationship between probability and concentration is  $P_i = C_i A \Delta x$ . Expand the right-hand side of Eq. (1) in powers

<sup>a)</sup>Electronic mail: schumaker@wsu.edu

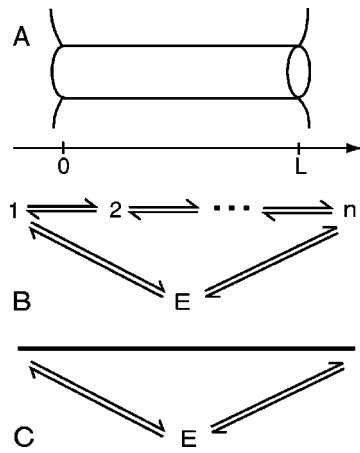


FIG. 1. (A) Sketch of a channel in a biological membrane.  $x$  is the coordinate parallel to the pore axis. The pore occupies the interval  $0 \leq x \leq L$ . (B) State diagram of the random walk used to construct a single-particle diffusion. (C) State diagram for a single-particle diffusion process with exponential boundary conditions.

of  $1/n$ , insert the result into Eq. (2), recognize finite difference approximations for derivatives and take the limit  $n \rightarrow \infty$  to obtain the steady state Smoluchowski equation:

$$0 = \frac{d^2 C}{dx^2} + \frac{d}{dx} \beta W'(x) C(x). \quad (3)$$

For simplicity,  $A$  and  $D$  have been assumed constant. The Smoluchowski equation may be integrated once to give the Nernst-Planck equation

$$J = -DA \left[ \frac{dC}{dx} + \beta W'(x) C \right], \quad (4)$$

where  $J$  is probability flux. This is where continuum models of ion permeation often begin.<sup>1</sup>

The point of the random walk construction is to obtain boundary conditions for the Smoluchowski equation that give single-particle diffusion. Introduce the empty state  $E$  to give the state diagram of Fig. 1(B). Transition probabilities to and from the empty state are defined by<sup>9</sup>

$$k_{E1} = \Delta t C_I A D L^{-1} \kappa_I^{-1} e^{\beta[\Psi_I - W(0)]}, \quad (5)$$

$$k_{1E} = \Delta t D L^{-2} n \kappa_I^{-1}, \quad (6)$$

$$k_{En} = \Delta t C_{II} A D L^{-1} \kappa_{II}^{-1} e^{-\beta W(L)}, \quad (7)$$

$$k_{nE} = \Delta t D L^{-2} n \kappa_{II}^{-1}. \quad (8)$$

$\Psi_I$  is the applied electrical potential on side I of the channel and the potential on side II is taken to be zero by convention.  $C_I$  and  $C_{II}$  are bulk concentrations of permeant particles on side I and side II of the channel, respectively, and  $\kappa_I$  and  $\kappa_{II}$  are dimensionless constants. Dwell times in the empty state follow a geometric distribution. Assuming that the system is in the empty state at time  $t=0$ , the probability that the system remains in the empty state after  $s$  time steps is  $(1 - (k_{E1} + k_{En}))^s$ . Write the elapsed time in the empty state  $t = s\Delta t$  and take the limit  $n \rightarrow \infty$ , or equivalently  $\Delta t \rightarrow 0$ . The geometric distribution converges to an exponential distribution with mean time in the empty state

$$\bar{t} = \Delta t / (k_{E1} + k_{En}). \quad (9)$$

Rates of transitions into sides I and II of the channel are controlled by  $\kappa_I$  and  $\kappa_{II}$ .

Boundary conditions of the Smoluchowski equation corresponding to these exponentially distributed dwells are obtained by balancing flux into and out of sites 1 and  $n$  of the random walk. This gives

$$P_1(k_{1E} + k_{12}) = P_2 k_{21} + P_E k_{E1}, \quad (10)$$

and a similar equation on side II. Insert definitions for transition probabilities, take the limit  $n \rightarrow \infty$ , and use Eq. (4) to obtain the boundary conditions:

$$C(0) = P_E e^{\beta[\Psi_I - W(0)]} C_I - \kappa_I L (AD)^{-1} J, \quad (11)$$

$$C(L) = P_E e^{-\beta W(L)} C_{II} + \kappa_{II} L (AD)^{-1} J. \quad (12)$$

To solve the Smoluchowski equation, multiply Eq. (4) by an integrating factor and integrate to get

$$L J h(x) = -DA [C(x) e^{\beta W(x)} - C(0) e^{\beta W(0)}], \quad (13)$$

where

$$h(x) = L^{-1} \int_0^x e^{\beta W(x')} dx'. \quad (14)$$

Set  $x=L$  and simplify the right-hand side of Eq. (13) using the boundary conditions to obtain the solution<sup>9</sup>

$$J_{\text{exp}}(C_I, C_{II}) = (AD/L) P_E (C_I e^{\beta \Psi_I} - C_{II}) R^{-1}, \quad (15)$$

$$R = h(L) + \kappa_I e^{\beta W(0)} + \kappa_{II} e^{\beta W(L)}. \quad (16)$$

The probability of the empty state is obtained from

$$P_E = 1 - \int_0^L A C(x) dx, \quad (17)$$

where the concentration  $C(x)$  of diffusers in the pore is first obtained by substituting Eq. (11) into Eq. (13). Then Eq. (17) gives

$$P_E = (1 + F)^{-1}, \quad (18)$$

where  $F = F_{Eq} + F_{NE}$  and

$$F_{Eq} = A C_I e^{\beta \Psi_I} \int_0^L e^{-\beta W(x)} dx, \quad (19)$$

$$F_{NE} = A R^{-1} (C_{II} - C_I e^{\beta \Psi_I}) \int_0^L (h(x) + \kappa_I e^{\beta W(0)}) e^{-\beta W(x)} dx. \quad (20)$$

At equilibrium  $\Psi_I$  is given by the Nernst Eq.<sup>1</sup> and  $F = F_{Eq}$ .

The subscript on  $J$  in Eq. (15) emphasizes that this single-particle process has exponentially distributed dwell times in the empty state. We refer to these as *exponential* boundary conditions. The domain of this diffusion process is the state diagram shown in Fig. 1(C). Figure 2(A) shows a simulation of a diffusion process with exponential boundary conditions generated by iterating the random walk on the state diagram of Fig. 1(B).

Physically, dwell times in the empty state will be distributed exponentially if the probability of entrance does not depend on the time that has elapsed since a particle last exited the channel.<sup>15</sup> This will be a good approximation when the mean time between entrances is much longer than the time scale associated with channel relaxation after a particle exits, a condition that will be satisfied at sufficiently low permeant particle concentrations in the bulk solutions. The complicated dynamics of the particle entrance process then determine only the mean time before entrance. Note that the exponential distribution refers to entrances associated with *distinct* particles. It does not capture the highly correlated motions of a single particle which may cross an arbitrary threshold several times in the process of entering a pore. The exponential distribution of distinct arrivals by noninteracting diffusers has been rigorously established.<sup>16</sup>

Now consider a channel subject to  $m$  independent single-particle processes of the type described above, each with bulk concentrations  $C_I/m$  and  $C_{II}/m$ . Letting  $m \rightarrow \infty$ , particle entrances into the channel are described by a Poisson process. Entrances occur with exponentially distributed waiting times, but regardless of the occupation state of the channel. We refer to these as Poisson boundary conditions. From Eqs. (18)–(20),  $P_E \rightarrow 1$  as  $C_I/m, C_{II}/m \rightarrow 0$ . From Eq. (15), the flux is then given by

$$J_{Poi}(C_I, C_{II}) = \lim_{m \rightarrow \infty} m J_{\text{exp}}(C_I/m, C_{II}/m) \quad (21)$$

$$= (AD/L)(C_I e^{\beta \Psi_I} - C_{II}) R^{-1}. \quad (22)$$

The last expression is also the solution of the Smoluchowski equation with the boundary conditions obtained by replacing  $P_E \rightarrow 1$  in Eqs. (11) and (12).

A special case of Poisson boundary conditions is obtained by extending the domain of the Nernst–Planck equation to  $(-\infty, \infty)$ , where the intervals  $(-\infty, -a)$  and  $(L + a, \infty)$  correspond to bulk regions on either side of the membrane.<sup>8</sup> Hemispherical endcaps of radius  $a$  on either side of the pore mediate a transition to spherical symmetry. Assuming  $W(x) = \Psi_I$  for  $x \leq 0$  and  $W(x) = 0$  for  $x \geq L$ , and performing integrals over the bulk regions assuming spherical symmetry, one obtains the flux  $J$  in the form of Eqs. (15) and (16) with  $P_E = 1$  and  $\kappa_I = \kappa_{II} = A/(2\pi aL)$ , where we have assumed that the diffusion coefficients of the permeant particle have the same value in the channel and the bulk. This example illustrates the correspondence of the terms proportional to  $\kappa_I$  and  $\kappa_{II}$  to the resistance offered by the bulk solution to the current flow.

In general, the denominator  $R$  in Eqs. (15) and (16) may be interpreted as the sum of three dimensionless series resistances. Terms proportional to  $\kappa_I$  and  $\kappa_{II}$  correspond to access resistances of the bulk solutions, and the term proportional to  $h(L)$  corresponds to the resistance of the channel. Figure 2(B) shows a simulation of a diffusion process with Poisson boundary conditions.

The interpretation of  $\kappa_I$  and  $\kappa_{II}$  as corresponding to access resistance is interesting in connection with the radiation boundary conditions used to compute the spectral density of ion conduction noise associated with the escape of larger

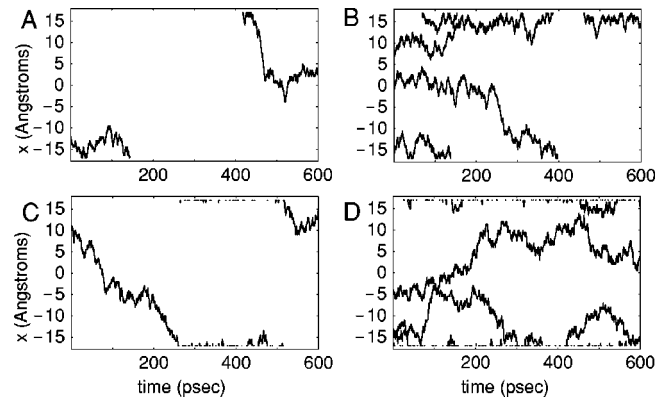


FIG. 2. Diffusing particle trajectories through a channel with various boundary conditions. Parameters model  $K^+$  transport through a synthetic ion channel (Ref. 3). The pore length  $L = 34 \text{ \AA}$ ; the ordinate shows the pore extended over the interval  $[-L/2, L/2]$ . The cross section  $A = \pi r^2$  with radius  $r = 6.5 \text{ \AA}$ , diffusion coefficient  $D = 0.2 \text{ \AA}^2/\text{ps}$  and capture radius  $a = 4 \text{ \AA}$ . For simplicity,  $W = \Psi_I = 0$ .  $C_I = C_{II} = 1 \text{ M}$ . Trajectories are simulated on the state diagram of Fig. 1 (B) using  $n = 69$  sites. (A) Exponential boundary conditions. The simulations use  $\kappa_I = \kappa_{II} = A/(2\pi aL)$  giving  $\bar{t} = 165 \text{ ps}$ . (B) Poisson boundary conditions.  $\bar{t} = 165 \text{ ps}$ . Boundary conditions are simulated using  $m = 40$  processes with exponential boundary conditions scaled according to the right-hand side of Eq. (21). (C) Levitt boundary conditions. (D) Goldman–Hodgkin–Katz boundary conditions simulated using  $m = 40$  processes with Levitt boundaries.

diffusing molecules from channels.<sup>17</sup> Set  $W' = 0$  in Eq. (4) and  $C_I = C_{II} = 0$  in Eqs. (11) and (12) to obtain

$$C(0) = \kappa_I L dC/dx, \quad (23)$$

$$C(L) = -\kappa_{II} L dC/dx. \quad (24)$$

Nonzero values of  $\kappa_I$  and  $\kappa_{II}$  corresponding to access resistance refer to trajectories outside the pore. Molecules that are well separated from the pore do not occlude ion currents. Thus, appropriate values of  $\kappa_I$  and  $\kappa_{II}$  must refer to components of escaping trajectories in the immediate vicinity of the pore.

To continue the construction of trajectories associated with boundary conditions, consider the single-particle diffusion process obtained from the random walk construction by using the entry and exit rates  $k'_{E1} = nk_{E1}$ ,  $k'_{1E} = nk_{1E}$ ,  $k'_{En} = nk_{En}$  and  $k'_{nE} = nk_{nE}$  instead of those defined by Eqs. (5)–(8). Instead of the Eqs. (11) and (12), one obtains the boundary conditions

$$C(0) = P_E e^{\beta[\Psi_I - W(0)]} C_I, \quad (25)$$

$$C(L) = P_E e^{-\beta W(L)} C_{II} \quad (26)$$

which were originally proposed by Levitt,<sup>8</sup> and we refer to these as Levitt boundary conditions. The corresponding flux is

$$J_{\text{Lev}}(C_I, C_{II}) = ADL^{-1} P_E (C_I e^{\beta \Psi_I} - C_{II}) h(L)^{-1}. \quad (27)$$

Terms in the denominator proportional to  $\kappa_I$  and  $\kappa_{II}$  and modeling access resistance are not present. The mean time in the empty state of the random walk is now

$$\bar{t} = \Delta t / (k'_{E1} + k'_{En}) \propto n^{-1}, \quad (28)$$

and  $\bar{t} \rightarrow 0$  as  $n \rightarrow \infty$ . However,  $P_E$  is given by Eqs. (18)–(20) with  $\kappa_I = \kappa_{II} = 0$  and remains positive. Figure 2(C) shows a simulation. The empty state is associated with a density of transitions to and from the boundaries of the pore.

Finally consider  $m$  independent processes with Levitt boundary conditions, each with bulk concentrations  $C_I/m$  and  $C_{II}/m$ . Taking the limit  $m \rightarrow \infty$  obtains the flux

$$J_{\text{GHK}}(C_I, C_{II}) = \lim_{m \rightarrow \infty} m J_{\text{Lev}}(C_I/m, C_{II}/m) \quad (29)$$

$$= ADL^{-1}(C_I e^{\beta \Psi_I} - C_{II}) h(L)^{-1}. \quad (30)$$

$J_{\text{GHK}}$  is the solution of the Nernst–Planck equation with boundary conditions specifying that  $C(0)$  and  $C(L)$  are proportional to the bulk concentrations at their respective sides of the channel [Eqs. (25) and (26) with  $P_E \rightarrow 1$ ]. This is the case of the traditional Goldman–Hodgkin–Katz theory of ion permeation<sup>1</sup> and we refer to these as GHK boundary conditions. Figure 2(D) shows an example of particle trajectories. As with Levitt boundary conditions,  $\bar{t} = 0$ .

In the construction of the process with Poisson (or GHK) boundary conditions as a limit of processes with exponential (or Levitt) boundary conditions, each of the latter processes is associated with bulk permeant particle concentrations  $C_I/m$  and  $C_{II}/m$ . The probability that the pore of a process with exponential boundary conditions is not occupied has the form  $P_E = (1 + F/m)^{-1}$ , where  $F$  is independent of  $m$ . The probability that  $m$  such processes each have an unoccupied pore is  $(1 + F/m)^{-m}$ . Taking the limit  $m \rightarrow \infty$ , we obtain the probability that the pore with Poisson boundary conditions is not occupied

$$Q_0 = \lim_{m \rightarrow \infty} P_E (C_I/m, C_{II}/m)^m = e^{-F}. \quad (31)$$

The probability that the pore with Poisson boundary conditions is occupied by  $d$  diffusers is

$$Q_d = \lim_{m \rightarrow \infty} \binom{m}{d} (1 - P_E)^d P_E^{m-d} = (F^d/d!) e^{-F}. \quad (32)$$

Note that

$$\sum_{d=0}^{\infty} Q_d = e^{-F} \sum_{d=0}^{\infty} F^d/d! = 1. \quad (33)$$

At equilibrium,  $F = F_{E,q}$  and these expressions agree with statistical mechanics.

### III. SUMMARY AND DISCUSSION

This article has constructed trajectories associated with four different boundary conditions for the Smoluchowski equation on the interval. Levitt and exponential boundary conditions model single-particle diffusions, or, more generally, diffusions in which the occupation number of particles in an interval can change by only one. Levitt boundary conditions are obtained by scaling the random walk transition probability from the pore to the empty state diffusively, as  $n^2$ . They are appropriate when access resistance is negligible — for example, when modeling diffusive transport between the ends of a single-particle interval and an immediately adjacent region.<sup>18</sup> Exponential boundary conditions are ob-

tained by scaling the transition probabilities between the pore and empty state with one less power of  $n$  than for Levitt boundaries. Trajectories enter the pore with exponentially distributed waiting times at either end of the interval, and the mean time before entrance at a given end models access resistance between that end and a separated bath. GHK and Poisson boundary conditions model mean-field diffusions and should be used only when the assumption of independent trajectories within a pore is reasonable. Particle transitions between the interval and the empty state are similar to those of Levitt and exponential boundaries, respectively, but take place regardless of occupation number. GHK boundaries are then appropriate when access resistance is negligible. Poisson boundaries model access resistance and could be used to incorporate this into one dimensional PNP models.

Brownian dynamics simulations of ion permeation suggest that the mean-field approximation breaks down when the pore radius is less than a debye length,<sup>6,7</sup> a condition that holds for most biological ion channels. However, the random walks used to construct the boundary conditions can themselves be viewed as discrete-time Brownian dynamics simulations on a one dimensional lattice. Rules for interactions between random walkers could be included to obtain algorithms reminiscent of one dimensional Brownian dynamics simulations of ion permeation through gramicidin<sup>19</sup> and potassium channels.<sup>20</sup> The four cases of boundary conditions described above would correspond to different rules for introducing or removing walkers at the endmost lattice sites.

These endmost sites bear some resemblance to buffer zones used in three dimensional simulations of ion permeation through OmpF porin.<sup>21,22</sup> In those zones, Monte Carlo moves based on the grand canonical ensemble were used to introduce and remove ions. This treatment assumes that ion concentrations in the physical system are close to thermodynamic equilibrium at the location of the buffer zones in the simulations. This assumption appears to be well justified under the conditions of the porin simulations, which achieved very good agreement with experiment. However, the Grand Canonical Monte Carlo boundary conditions might underestimate access resistance in other cases. If the one dimensional random walk construction presented above could be generalized to provide boundary conditions for three dimensional regions, the generalization would also provide alternative rules for introducing and removing ions, directly incorporating access resistance, in Brownian dynamics simulations.

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