

A framework model based on the Smoluchowski equation in two reaction coordinates

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The general form of the Smoluchowski equation in two reaction coordinates is obtained as the diffusion limit of a random walk on an infinite square grid using transition probabilities that satisfy detailed balance at thermodynamic equilibrium. The diffusion limit is then used to construct a generalization of the single-particle model to two reaction coordinates. The state space includes a square on which diffusion takes place and an isolated empty state. Boundary conditions on opposite sides of the square correspond to transitions between the empty state and the square. The two-dimensional (2D) model can be reduced to a 1D single-particle model by adiabatic elimination. A finite element solution of the 2D boundary value problem is described. The method used to construct the 2D model can be adapted to state spaces that have been constructed by other authors to model K^+ conduction through gramicidin, proton conduction through dioxolane-linked gramicidin, and chloride conduction through the bacterial $H^+ - Cl^-$ antiporter. © 2004 American Institute of Physics. [DOI: 10.1063/1.1785778]

I. INTRODUCTION

Framework models are relatively simple stochastic models designed to incorporate information from detailed computer simulations of biomolecules and use it to calculate properties of the biomolecules over much longer time scales. The one-dimensional single-particle model was developed to model the passage of a single permeant ion through the pore of an ion channel.^{1,2} It requires the specification of a potential of mean force $W(X)$ and diffusion coefficient $D(X)$ as a function of a single reaction coordinate X . The model can be solved analytically for given W and D . Useful analytical solutions can also be constructed for simple networks of coupled one-dimensional state segments and isolated states.³ An application has been made to proton conduction through gramicidin.^{4,5} More recently, a framework model with three reaction coordinates and incorporating potentials of mean force and diffusion coefficients calculated by molecular dynamics has been constructed for K^+ conduction through the KcsA channel.⁶ Brownian dynamics were used to calculate conductances, achieving good agreement with experiment. Although these examples pertain to permeation through narrow ion channels, we anticipate that the framework model approach is more generally applicable to the dynamics of highly constrained molecular systems, with only a few important reaction coordinates.

These framework models are diffusion models. The diffusion approximation may ultimately be justified by a projection of high-dimensional Hamiltonian dynamics to a low dimensional configuration space of slow variables.^{7,8} The projection generally yields a generalized Langevin equation, which simplifies to a classical Langevin equation when there is a large gap in time scales between the slow variables included in the low-dimensional space, and all of the other variables. In practice, the diffusion approximation is assumed by many methods, including the classical theory of Goldman, Hodgkin, and Katz,⁹ Poisson-Nernst-Planck

theory (for example, Ref. 10), and Brownian Dynamics (for example, Refs. 11 and 12).

Recently, several potentials of mean force have been calculated as a function of two or three reaction coordinates. The PMF for K^+ permeation through gramicidin has been calculated as a function of the axial coordinate z along the permeation pathway and the radial distance r from the axis.¹³ The PMF for proton permeation through dioxolane-linked gramicidin dimers has been calculated as a function of the axial z and a backbone coordinate $\alpha - \alpha'$.^{14,15} The PMF for permeation through the bacterial $H^+ - Cl^-$ antiporter¹⁶ has been calculated as a function of the axial coordinates of two chloride ions in the permeation pore.¹⁷ Finally, PMFs for K^+ permeation through the KcsA K^+ channel have been calculated as a function of the axial coordinates of the three ions in the selectivity filter.^{6,18}

In this paper we first describe the Smoluchowski equation and its representation in dimensionless variables. Then the Smoluchowski equation is achieved as the diffusion limit of a random walk on an infinite square lattice with transition probabilities of the form used by Ref. 6. We then construct a generalization of the "single-particle model" with two reaction coordinates, giving a configuration space similar to the two dimensional examples listed above. Despite its name, this model could be straightforwardly modified to include the two-ion PMF described in Ref. 17. Finally, we describe how the two-dimensional model can be solved numerically using the finite element method. Following the results of Ref. 19, we suspect that direct numerical solution of the partial differential equation will be far more efficient than numerical simulation of the underlying trajectories.

II. THE SMOLUCHOWSKI EQUATION

The Smoluchowski equation describes diffusion under the influence of a potential. This has the form of an equation of continuity

$$\partial P / \partial t' = -\nabla' \cdot \mathbf{J}, \quad (1)$$

where the probability current density \mathbf{J} is given by the Nernst-Planck equation

$$\mathbf{J} = -\mathbf{D}[\nabla' P + \beta(\nabla' W)P]. \quad (2)$$

We are concerned with the case of two spatial variables: X and Y and time t' . ∇' is the differential operator with respect to X and Y . $P(X, Y, t')$ is a probability density, $W(X, Y)$ is a potential, $\beta = 1/(k_B T)$, where k_B is Boltzmann's constant, and T is absolute temperature. The diffusion matrix \mathbf{D} must be symmetric, and positive semidefinite.²⁰ For simplicity, we assume \mathbf{D} is positive definite. The solution of the Nernst-Planck equation for $\mathbf{J} = \mathbf{0}$ is proportional to the Boltzmann factor, consistent with statistical mechanics.

Formulas simplify when expressed in terms of dimensionless variables. Let $x = X/L_X$ and $y = Y/L_Y$, where L_X and L_Y are length scales characteristic of the X and Y coordinates. The dimensionless time is $t = t'/t_0$, where t_0 is a characteristic time scale. Let $p(x, y, t) = L_X L_Y P(X, Y, t')$, $w(x, y) = \beta W(X, Y)$, and the dimensionless diffusion matrix

$$\mathbf{d} = t_0 \begin{pmatrix} L_X^{-2} D_1 & L_X^{-1} L_Y^{-1} D_3 \\ L_X^{-1} L_Y^{-1} D_3 & L_Y^{-2} D_2 \end{pmatrix}, \quad (3)$$

where D_1 , D_2 , and D_3 are the respective elements of \mathbf{D} . The elements of the diffusion matrix are defined by²⁰

$$d_{ij}(x_0, y_0) = \lim_{t \rightarrow 0} \langle \Delta \tilde{x}_i \Delta \tilde{x}_j \rangle / (2t), \quad (4)$$

where $\tilde{x}_1 = \tilde{x}$, $\tilde{x}_2 = \tilde{y}$, $\Delta \tilde{x}_i = \tilde{x}_i(t) - \tilde{x}_i(0)$, and $(\tilde{x}(t), \tilde{y}(t))$ is a trajectory of a diffusion process passing through (x_0, y_0) at $t = 0$. $\langle \dots \rangle$ denotes an average over all such trajectories. We also write $d_1 = d_{11}$, $d_2 = d_{22}$ and $d_3 = d_{12} = d_{21}$. In dimensionless variables, the equation of continuity is

$$\partial p / \partial t = -\nabla \cdot \mathbf{j}. \quad (5)$$

The dimensionless probability current density is given by

$$\mathbf{j} = -\mathbf{d}[\nabla p + (\nabla w)p], \quad (6)$$

where ∇ is the differential operator with respect to x and y .

Several methods have been developed to estimate diffusion coefficients from simulations as a function of one reaction coordinate. $\langle \Delta x(t)^2 \rangle$ has been calculated from unrestrained molecular dynamics trajectories.²¹ The diffusion coefficient was estimated from the slope of the second moment as a function of t . The effect of a biasing potential can be taken into account^{22,23} by studying the slope of $\langle [x(t) - \langle x(t) \rangle]^2 \rangle$. This approach assumes a uniform drift, but trajectory segments can be taken from a localized region of space to estimate a local diffusion coefficient. It appears straightforward to generalize these methods to calculate the elements of \mathbf{d} defined by Eq. (4). Another method involves confining a trajectory to a neighborhood of a given point in the state space by introducing a Hook's law potential. The diffusion coefficient can then be deconvoluted from the restrained trajectories though an analysis of a generalized Langevin equation.^{4,24,25} This method assumes the validity of the generalized Langevin equation,²⁶ but has the important

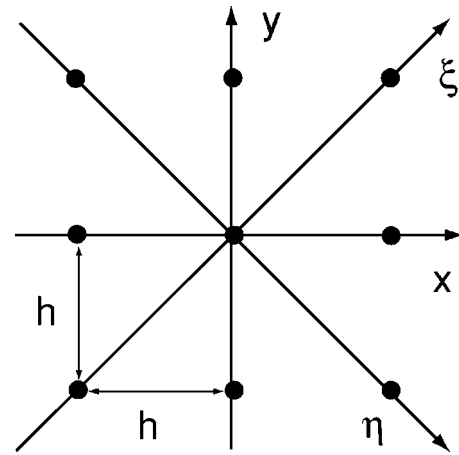


FIG. 1. Infinite square grid with spacing h on which a random walk is defined that is used to obtain the Smoluchowski equation in the diffusion limit. A walker at the central node (i, j) can make a transition to any of the eight nearest neighbors shown. Directions corresponding to increasing values x , y , ξ , and η are shown.

advantage of disentangling the diffusion coefficient even in the presence of a rapidly varying potential of mean force. It would be very useful to generalize it to two or more reaction coordinates.

III. DERIVATION OF THE SMOLUCHOWSKI EQUATION

Consider a discrete-time random walk on the infinite square grid of Fig. 1. A walker at the central node (i, j) can make a transition to any one of eight nearest neighbors. Let h be the grid spacing. Put $x = ih$ and $y = jh$. The relationship between the probability that node (i, j) is occupied, $q_{i,j}(t)$, and the density $p(x, y, t)$ is

$$q_{i,j}(t) = p(x, y, t)h^2. \quad (7)$$

The increase of $q_{i,j}(t)$ over one time step is equal the flow of probability into (i, j) from surrounding nodes:

$$q_{i,j}(t + \Delta t) - q_{i,j}(t) = \Delta t h^2 (T_1 + T_2 + T_3 + T_4). \quad (8)$$

We use the diffusive scaling $\Delta t = \Delta \tau h^2$, where $\Delta \tau$ may be chosen so that transition probabilities never exceed one. Terms on the right-hand side of Eq. (8) are

$$\begin{aligned} \Delta t h^2 T_1 = & q_{i+1,j}(t)k_{(i+1,j) \rightarrow (i,j)} + q_{i-1,j}(t)k_{(i-1,j) \rightarrow (i,j)} \\ & - q_{i,j}(t)[k_{(i,j) \rightarrow (i+1,j)} + k_{(i,j) \rightarrow (i-1,j)}], \end{aligned} \quad (9)$$

$$\begin{aligned} \Delta t h^2 T_2 = & q_{i,j+1}(t)k_{(i,j+1) \rightarrow (i,j)} + q_{i,j-1}(t)k_{(i,j-1) \rightarrow (i,j)} \\ & - q_{i,j}(t)[k_{(i,j) \rightarrow (i,j+1)} + k_{(i,j) \rightarrow (i,j-1)}], \end{aligned} \quad (10)$$

$$\begin{aligned} \Delta t h^2 T_3 = & q_{i+1,j+1}(t)k_{(i+1,j+1) \rightarrow (i,j)} \\ & + q_{i-1,j-1}(t)k_{(i-1,j-1) \rightarrow (i,j)} - q_{i,j}(t) \\ & \times [k_{(i,j) \rightarrow (i+1,j+1)} + k_{(i,j) \rightarrow (i-1,j-1)}], \end{aligned} \quad (11)$$

$$\begin{aligned} \Delta t h^2 T_4 = & q_{i+1,j-1}(t) k_{(i+1,j-1) \rightarrow (i,j)} \\ & + q_{i-1,j+1}(t) k_{(i-1,j+1) \rightarrow (i,j)} - q_{i,j}(t) \\ & \times [k_{(i,j) \rightarrow (i+1,j-1)} + k_{(i,j) \rightarrow (i-1,j+1)}]. \end{aligned} \quad (12)$$

Transition probabilities are given by the following formulas,^{2,5,6,27} which are consistent with the Boltzmann factor under detailed balance:

$$k_{(i,j) \rightarrow (i+1,j)} = \Delta t d(1,0) h^{-2} e^{[w(x,y) - w(x+h,y)]/2}, \quad (13)$$

$$k_{(i,j) \rightarrow (i-1,j)} = \Delta t d(-1,0) h^{-2} e^{[w(x,y) - w(x-h,y)]/2}, \quad (14)$$

$$k_{(i,j) \rightarrow (i,j+1)} = \Delta t d(0,1) h^{-2} e^{[w(x,y) - w(x,y+h)]/2}, \quad (15)$$

$$k_{(i,j) \rightarrow (i,j-1)} = \Delta t d(0,-1) h^{-2} e^{[w(x,y) - w(x,y-h)]/2}, \quad (16)$$

$$k_{(i,j) \rightarrow (i+1,j+1)} = \Delta t d(1,1) h^{-2} e^{[w(x,y) - w(x+h,y+h)]/2}, \quad (17)$$

$$\begin{aligned} k_{(i,j) \rightarrow (i-1,j-1)} = & \Delta t d(-1,-1) h^{-2} \\ & \times e^{(w(x,y) - w(x-h,y-h))/2}, \end{aligned} \quad (18)$$

$$k_{(i,j) \rightarrow (i+1,j-1)} = \Delta t d(1,-1) h^{-2} e^{[w(x,y) - w(x+h,y-h)]/2}, \quad (19)$$

$$k_{(i,j) \rightarrow (i-1,j+1)} = \Delta t d(-1,1) h^{-2} e^{[w(x,y) - w(x-h,y+h)]/2}. \quad (20)$$

The transition probability $k_{(i+1,j) \rightarrow (i,j)}$ can be obtained from Eq. (14) with the replacements $i \rightarrow i+1$, $x \rightarrow x+h$, and $d(-1,0) \rightarrow d(1,0)$; other cases are similar. The exponential factors will be expanded in Taylor series. For example

$$\begin{aligned} e^{[w(x,y) - w(x+h,y)]/2} = & 1 - w_x(x,y)h/2 + \epsilon_1(x,y)h^2 \\ & + O(3), \end{aligned} \quad (21)$$

where

$$\epsilon_1(x,y) = -w_{xx}(x,y)/4 + w_x(x,y)^2/8, \quad (22)$$

and the symbol $O(n)$ refers to terms of order h^n or higher. The diffusion factors are $d(\Delta i, \Delta j)$, where $(\Delta i, \Delta j)$ is the displacement from the central node (i, j) . These factors are given by

$$d(1,0) = [d_1(x,y) + d_1(x+h,y)]/2 - \Delta d, \quad (23)$$

$$d(-1,0) = [d_1(x,y) + d_1(x-h,y)]/2 - \Delta d, \quad (24)$$

$$d(0,1) = [d_2(x,y) + d_2(x,y+h)]/2 - \Delta d, \quad (25)$$

$$d(0,-1) = [d_2(x,y) + d_2(x,y-h)]/2 - \Delta d, \quad (26)$$

$$d(1,1) = [d_3(x,y) + d_3(x+h,y+h)]/4 + \Delta d/2, \quad (27)$$

$$d(-1,-1) = [d_3(x,y) + d_3(x-h,y-h)]/4 + \Delta d/2, \quad (28)$$

$$d(1,-1) = -[d_3(x,y) + d_3(x+h,y-h)]/4 + \Delta d/2, \quad (29)$$

$$d(-1,1) = -[d_3(x,y) + d_3(x-h,y+h)]/4 + \Delta d/2. \quad (30)$$

Equations (23)–(26) are similar in form to the average diffusion coefficients given by Ref. 6, but with Δd subtracted. While the diagonal elements d_1 and d_2 of a positive definite diffusion matrix are positive, the cross diffusion d_3 may be negative. The value of the parameter Δd will not change the Smoluchowski equation derived below from the diffusion limit of the random walk. However, for some $h > 0$ (assum-

ing the continuity of d_1 , d_2 , and d_3), Δd can be adjusted so that the transition probabilities are all positive as long as the following diagonal dominance criterion is satisfied at each point (x, y) :

$$d_1, d_2 > |d_3|. \quad (31)$$

This may be compared with the requirement that d be positive definite

$$d_1 > 0, \quad (32a)$$

and

$$d_1 d_2 > d_3^2. \quad (32b)$$

Diagonal dominance guarantees positive definiteness, but the converse is not true. Adjustment of the diffusion factors using Δd does not give a representation of every diffusion matrix in terms of a random walk, but a larger set of diffusions can be represented than would be case for $\Delta d = 0$. In future work, this will allow us to make contact with methods based on trajectories, i.e., Brownian dynamics.

Conservation of probability gives Eq. (8). Dividing this by $\Delta t h^2$ obtains

$$[p(x,y,t+\Delta t) - p(x,y,t)]/\Delta t = T_1 + T_2 + T_3 + T_4. \quad (33)$$

This form leads to the Smoluchowski equation in the limit $h \rightarrow 0$. Expand the expression for T_1 , Eq. (9), by substituting from Eqs. (13) and (14) (replacing $i \rightarrow i+1$ or $i \rightarrow i-1$ as necessary) and then expanding the exponentials. This gives

$$\begin{aligned} T_1 = & p(x+h,y,t) d(1,0) h^{-2} [1 + w_x(x+h,y)h/2 \\ & + \epsilon_1(x+h,y)h^2 + O(3)] + p(x-h,y,t) d(-1,0) \\ & \times h^{-2} [1 - w_x(x-h,y)h/2 + \epsilon_1(x-h,y)h^2 + O(3)] \\ & - p(x,y,t) \{ d(1,0) h^{-2} [1 - w_x(x,y)h/2 + \epsilon_1(x,y)h^2 \\ & + O(3)] + d(-1,0) h^{-2} [1 + w_x(x,y)h/2 \\ & + \epsilon_1(x,y)h^2 + O(3)] \}. \end{aligned} \quad (34)$$

A. The diffusive component

We first analyze the diffusive component of the expression for T_1 given above. The result will then be used to deduce the form of the diffusive components of T_2 , T_3 , and T_4 from Eq. (33). Let $T_1(m)$ denote the component in T_1 of order h^m . From Eq. (34)

$$\begin{aligned} T_1(-2) = & d(1,0) h^{-2} [p(x+h,y,t) - p(x,y,t)] \\ & + d(-1,0) h^{-2} [p(x-h,y,t) - p(x,y,t)]. \end{aligned} \quad (35)$$

Expand $d(1,0)$ and $d(-1,0)$, using Eqs. (23) and (24), and rearrange terms to obtain

$$\begin{aligned} T_1(-2) = & [d_1(x,y)/2 - \Delta d] h^{-2} [p(x+h,y,t) \\ & + p(x-h,y,t) - 2p(x,y,t)] + [d_1(x+h,y)/2] \\ & \times h^{-2} [p(x+h,y,t) - p(x,y,t)] + [d_1(x-h,y)/2] \\ & \times h^{-2} [p(x-h,y,t) - p(x,y,t)]. \end{aligned} \quad (36)$$

In the diffusion limit obtain

$$\begin{aligned} \lim_{h \rightarrow 0} T_1(-2) &= (d_1/2 - \Delta d)p_{xx} + d_{1,x}p_x + d_1p_{xx}/2 \\ &= [(d_1 - \Delta d)p_x]_x. \end{aligned} \quad (37)$$

By symmetry, the corresponding result for $T_2(-2)$ is

$$\lim_{h \rightarrow 0} T_2(-2) = [(d_2 - \Delta d)p_y]_y, \quad (38)$$

where a subscript x or y denotes partial differentiation and $d_{1,x} = (\partial/\partial x)d_1$.

A very similar argument by symmetry can be made to obtain expressions for $T_3(-2)$ and $T_4(-2)$. Consider the variables ξ and η illustrated in Fig. 1

$$\xi = (x + y)/2, \quad (39)$$

$$\eta = (x - y)/2. \quad (40)$$

If $f(x, y)$ is a differentiable function, the chain rule gives

$$f_\xi = f_x + f_y, \quad (41)$$

$$f_\eta = f_x - f_y, \quad (42)$$

where ξ or η as subscripts denote partial differentiation. Then by analogy with the previous results, but taking into account the forms of $d(1,1)$, $d(-1,-1)$, $d(1,-1)$, and $d(-1,1)$, Eqs. (27)–(30):

$$\lim_{h \rightarrow 0} T_3(-2) = [(d_3/2 + \Delta d/2)p_\xi]_\xi, \quad (43)$$

$$\lim_{h \rightarrow 0} T_4(-2) = [(-d_3/2 + \Delta d/2)p_\eta]_\eta. \quad (44)$$

These formulas can also be obtained by a direct analysis of T_3 and T_4 which is similar to, but more tedious than, that for T_1 . Using Eqs. (41) and (42), we obtain

$$\begin{aligned} \lim_{h \rightarrow 0} T_3(-2) + T_4(-2) &= \Delta d(p_{xx} + p_{yy}) + 2d_3p_{xy} \\ &\quad + d_{3,x}p_y + d_{3,y}p_x. \end{aligned} \quad (45)$$

Combining the results of Eqs. (37), (38), and (45) there finally obtains

$$\lim_{h \rightarrow 0} [T_1(-2) + T_2(-2) + T_3(-2) + T_4(-2)] = \nabla \cdot (d\nabla p). \quad (46)$$

The right-hand side is the diffusive component of the Smoluchowski equation, Eqs. (5) and (6).

B. The drift component

The drift component of T_1 corresponds to the $O(-1)$ terms. From Eq. (34)

$$\begin{aligned} T_1(-1) &= d(1,0)h^{-1}[w_x(x+h,y)p(x+h,y,t) \\ &\quad + w_x(x,y)p(x,y,t)]/2 - d(-1,0)h^{-1} \\ &\quad \times [w_x(x-h,y)p(x-h,y,t) \\ &\quad + w_x(x,y)p(x,y,t)]/2. \end{aligned} \quad (47)$$

Expand $d(1,0)$ and $d(-1,0)$ and rearrange terms to get

$$\begin{aligned} T_1(-1) &= [d_1(x,y)/2 - \Delta d](2h)^{-1}[w_x(x+h,y) \\ &\quad \times p(x+h,y,t) - w_x(x-h,y)p(x-h,y,t)] \\ &\quad + (4h)^{-1}[d_1(x+h,y)w_x(x+h,y) \\ &\quad \times p(x+h,y,t) - d_1(x-h,y)w_x(x-h,y) \\ &\quad \times p(x-h,y,t)] + (4h)^{-1}w_x(x,y)p(x,y,t) \\ &\quad \times [d_1(x+h,y) - d_1(x-h,y)]. \end{aligned} \quad (48)$$

Let $h \rightarrow 0$ and rearrange to obtain

$$\begin{aligned} \lim_{h \rightarrow 0} T_1(-1) &= (d_1w_xp)_x - \Delta d(w_xp)_x \\ &= [(d_1 - \Delta d)w_xp]_x. \end{aligned} \quad (49)$$

The corresponding result for $T_2(-1)$ is

$$\lim_{h \rightarrow 0} T_2(-1) = [(d_2 - \Delta d)w_y p]_y. \quad (50)$$

By analogy with the previous results, and taking into account the forms of $d(1,1)$, $d(-1,-1)$, $d(1,-1)$, and $d(-1,1)$:

$$\lim_{h \rightarrow 0} T_3(-1) = [(d_3/2 + \Delta d/2)w_\xi p]_\xi, \quad (51)$$

$$\lim_{h \rightarrow 0} T_4(-1) = [(-d_3/2 + \Delta d/2)w_\eta p]_\eta. \quad (52)$$

Using the transformation formulas for derivatives with respect to ξ and η , Eqs. (41) and (42), obtain

$$\begin{aligned} \lim_{h \rightarrow 0} [T_3(-1) + T_4(-1)] \\ = \Delta d[(w_xp)_x + (w_y p)_y] + [(d_3w_xp)_y + (d_3w_y p)_x]. \end{aligned} \quad (53)$$

Combining the results of Eqs. (49), (48), and (53)

$$\begin{aligned} \lim_{h \rightarrow 0} [T_1(-1) + T_2(-1) + T_3(-1) + T_4(-1)] \\ = \nabla \cdot [d(\nabla w)p]. \end{aligned} \quad (54)$$

The right-hand side is the drift component of the Smoluchowski equation, Eqs. (5) and (6).

IV. CONSTRUCTION OF THE 2D SINGLE-PARTICLE MODEL

This section constructs a model for single-particle diffusion through a pore with two reaction coordinates which generalizes the single-particle model in one reaction coordinate.^{1,2} A state diagram of the random walk used to construct the two-dimensional (2D) model is shown in Fig. 2(a). The random walk takes place on an $n \times n$ square lattice with grid spacing $h = 1/n$. The state diagram of the 2D model obtained in the diffusion limit $n \rightarrow \infty$ is shown in Fig. 2(b). This diagram consists of the unit square, parametrized by x and y , and an additional state E , which represents the empty pore.

In the interior of the lattice in Fig. 2(a), define the random walk with the same transition probabilities as used to derive the Smoluchowski equation on the infinite square grid

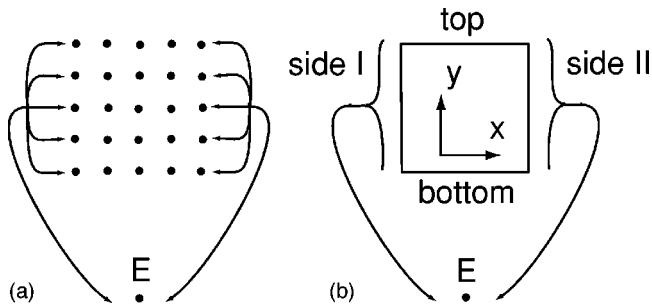


FIG. 2. (a) Random walk used to construct the 2D single-particle model. The walk takes place on an $n \times n$ square lattice. Transitions can be made between grid points in columns 1 and n and the empty state E. (b) State diagram of the 2D single-particle model, obtained as the diffusion limit of the random walk. The Smoluchowski equation describes the diffusion process on the square domain. Transitions can be made between sides I and II and the empty state.

in Sec. III. This section defines transition probabilities on the boundaries of the square, and then takes the diffusion limit to obtain a boundary value problem.

A. Reflecting boundaries

Figure 3 shows a closeup of the top boundary of the square lattice in Fig. 2(a), centered on a grid point (i, n) in the top boundary row n . Transitions can be made between this point and its five nearest neighbors with the same transition probabilities as used in the interior of the lattice. The rate of increase of $q_{i,n}$ must equal the flow of the probability into (i, n) from surrounding nodes, giving Eq. (8) with $j = n$. $\Delta t h^2 T_1$ is still given by Eq. (9), with $j = n$, but the following new definitions are obtained:

$$\Delta t h^2 T_2 = q_{i,n-1}(t)k_{(i,n-1) \rightarrow (i,n)} - q_{i,n}(t)k_{(i,n) \rightarrow (i,n-1)}, \quad (55)$$

$$\Delta t h^2 T_3 = q_{i-1,n-1}(t)k_{(i-1,n-1) \rightarrow (i,n)} - q_{i,n}(t)k_{(i,n) \rightarrow (i-1,n-1)}, \quad (56)$$

$$\Delta t h^2 T_4 = q_{i+1,n-1}(t)k_{(i+1,n-1) \rightarrow (i,n)} - q_{i,n}(t)k_{(i,n) \rightarrow (i+1,n-1)}. \quad (57)$$

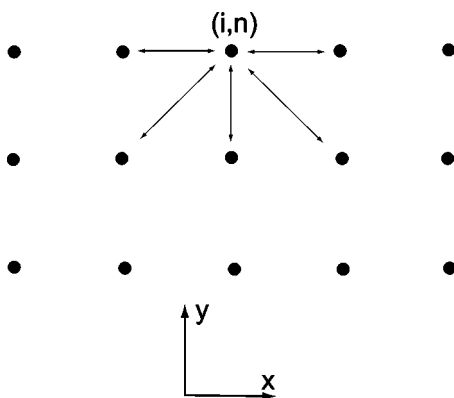


FIG. 3. Closeup of a portion of the square lattice used to construct the 2D single-particle model, centered on the node (i, n) . The walker can make a transition to and from any of the five nearest neighbors. Those transitions are governed by the same transition probabilities as would apply to the corresponding transitions to and from an interior node.

The Smoluchowski equation obtained in the preceding section came from conservation of probability, rewritten as Eq. (33). However, in the present case this will not lead to a finite limit as $h \rightarrow 0$, since some of the terms required to construct second differences are missing. Instead, multiply Eq. (33) by h . In the limit $h \rightarrow 0$, the left-hand side goes to zero and we will obtain the boundary condition from the limit of $h(T_1 + T_2 + T_3 + T_4)$.

The definition of T_1 has not been changed, and Eq. (49) shows that its limit is finite. As a result

$$\lim_{h \rightarrow 0} h T_1 = 0. \quad (58)$$

To obtain an expression for $h T_2$ from Eq. (55) that may be analyzed in the limit $h \rightarrow 0$, put $x = ih$ and $y = jh = 1$ and express $q_{i,j}(t)$ in terms of the density $p(x, y, t)$. Replace the transition probabilities with their definitions and then expand the exponentials giving

$$h T_2 = d(0, -1) \{ [p(x, 1-h, t) - p(x, 1, t)] / h - w_y(x, 1-h) \times p(x, 1-h, t) / 2 - w_y(x, 1) p(x, 1, t) / 2 + O(1) \}. \quad (59)$$

Expand $d(0, -1)$ and let $h \rightarrow 0$ to obtain

$$\lim_{h \rightarrow 0} h T_2 = -[d_2(x, 1) - \Delta d] [p_y(x, 1, t) + w_y(x, 1) p(x, 1, t)]. \quad (60)$$

By analogy with this result, taking into account the forms of $d(-1, -1)$ and $d(1, -1)$, and also taking into account that T_4 orders terms in the opposite sense with respect to the η axis as T_2 and T_3 do with respect to the y and ξ axes, we have

$$\lim_{h \rightarrow 0} h T_3 = -[d_3(x, 1) / 2 + \Delta d / 2] [p_\xi(x, 1, t) + w_\xi(x, 1) p(x, 1, t)], \quad (61)$$

$$\lim_{h \rightarrow 0} h T_4 = [-d_3(x, 1) / 2 + \Delta d / 2] [p_\eta(x, 1, t) + w_\eta(x, 1) p(x, 1, t)]. \quad (62)$$

Combining the results of Eqs. (58), (60), (61), and (62) gives

$$\lim_{h \rightarrow 0} h(T_1 + T_2 + T_3 + T_4) = \mathbf{j}(x, 1, t) \cdot \hat{\mathbf{e}}_y, \quad (63)$$

where \mathbf{j} is given by Eq. (6) and $\hat{\mathbf{e}}_y$ is the unit vector in the y direction. Multiplying both sides of Eq. (33) by h and letting $h \rightarrow 0$, finally obtains the boundary condition

$$\mathbf{j} \cdot \hat{\mathbf{e}}_y = 0, \quad (64)$$

where $\mathbf{j} = \mathbf{j}(x, 1, t)$ on the top boundary of the unit square in Fig. 2(b). Treatment of the bottom boundary is similar, and Eq. (64) is obtained for $\mathbf{j} = \mathbf{j}(x, 0, t)$.

B. Entrance and exit on sides I and II

Figure 4 shows a closeup of the left-hand boundary of the square domain in Fig. 2(a), which we call side I. The figure is centered on grid point $(1, j)$. Transitions can be made between this point and one of its five nearest neighbors

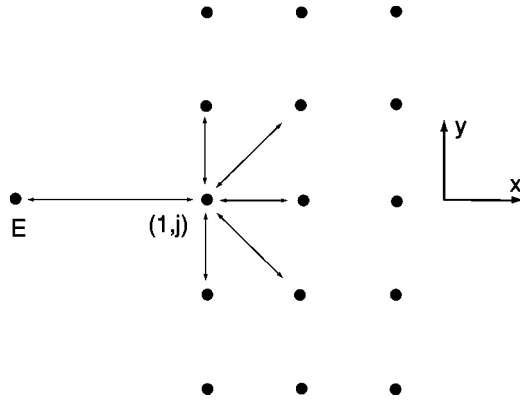


FIG. 4. Closeup of a portion of the square lattice centered on node $(1,j)$. The walker can make a transition to and from the any of the five nearest neighbors on the lattice and, in addition, the empty state E . Transitions to and from the lattice neighbors are governed by the same transition probabilities as would apply to corresponding transitions to and from an interior node. Transition probabilities to and from the empty state are given by Eqs. (80) and (81).

in the square domain and also to and from the empty state E . The rate of increase of $q_{1,j}(t)$ must equal the flow of probability into $(1,j)$ from surrounding nodes, giving

$$q_{1,j}(t + \Delta t) - q_{1,j}(t) = \Delta t h^2 (T_1 + T_2 + T_3 + T_4 + T_5), \quad (65)$$

where $\Delta t h^2 T_2$ is given by Eq. (10), with $i=1$, but the following new definitions are obtained:

$$\Delta t h^2 T_1 = q_{2,j}(t) k_{(2,j) \rightarrow (1,j)} - q_{1,j}(t) k_{(1,j) \rightarrow (2,j)}, \quad (66)$$

$$\Delta t h^2 T_3 = q_{2,j+1}(t) k_{(2,j+1) \rightarrow (1,j)} - q_{1,j}(t) k_{(1,j) \rightarrow (2,j+1)}, \quad (67)$$

$$\Delta t h^2 T_4 = q_{2,j-1}(t) k_{(2,j-1) \rightarrow (1,j)} - q_{1,j}(t) k_{(1,j) \rightarrow (2,j-1)}, \quad (68)$$

$$\begin{aligned} \Delta t h^2 T_5 &= q_E(t) k_{E \rightarrow (1,j)} - q_{1,j}(t) k_{(1,j) \rightarrow E}, \\ &= q_E(t) k_{E \rightarrow (1,j)} - p(h,y,t) h^2 k_{(1,j) \rightarrow E}. \end{aligned} \quad (69)$$

Rewrite Eq. (65) as

$$[p(h,y,t + \Delta t) - p(h,y,t)] h / \Delta t = h (T_1 + T_2 + T_3 + T_4 + T_5), \quad (70)$$

and consider the terms hT_i in the limit $h \rightarrow 0$.

Substituting the definitions of the transition probabilities into Eq. (66) and then expanding the exponentials, we obtain

$$\begin{aligned} hT_1 &= h^{-1} d(1,0) \{ p(2h,y,t) [1 + w_x(2h,y)h/2 + O(2)] \\ &\quad - p(h,y,t) [1 - w_x(h,y)h/2 + O(2)] \}. \end{aligned} \quad (71)$$

Let $h \rightarrow 0$ to give

$$\lim_{h \rightarrow 0} hT_1 = [d_1(0,y) - \Delta d] [p_x(0,y,t) + w_x(0,y)p(0,y,t)]. \quad (72)$$

Since we have the full, symmetrical, expression for T_2 , which has a finite limit as $h \rightarrow 0$, Eq. (50), it follows that

$$\lim_{h \rightarrow 0} hT_2 = 0. \quad (73)$$

By analogy with the formula for hT_1 , and taking into account the forms of $d(-1,-1)$ and $d(1,-1)$, we have

$$\begin{aligned} \lim_{h \rightarrow 0} hT_3 &= [d_3(0,y)/2 + \Delta d/2] \\ &\quad \times [p_\xi(0,y,t) + w_\xi(0,y)p(0,y,t)], \end{aligned} \quad (74)$$

$$\begin{aligned} \lim_{h \rightarrow 0} hT_4 &= [-d_3(0,y)/2 + \Delta d/2] [p_\eta(0,y,t) \\ &\quad + w_\eta(0,y)p(0,y,t)]. \end{aligned} \quad (75)$$

In order that the flow of probability between the unit square of Fig. 2(b) and the empty state be finite and nonzero, we require $\lim hT_5$ to be finite and nonzero. From the last expression of Eq. (69), noting that $\lim q_E$ and $\lim p$ will also be finite and nonzero

$$k_{E \rightarrow (1,j)} \propto \Delta t h, \quad (76)$$

$$k_{(1,j) \rightarrow E} \propto \Delta t h^{-1}. \quad (77)$$

At thermodynamic equilibrium, the probability of node (i,j) in Fig. 2(a) is proportional to the Boltzmann factor

$$q_{i,j} = q_0 e^{-w(x,y)} \quad (78)$$

for $q_0 \propto h^2$. Then detailed balance gives

$$k_{E \rightarrow (1,j)} / k_{(1,j) \rightarrow E} \propto h^2 e^{-w(h,y)}. \quad (79)$$

A similar requirement holds on side II.

The following formulas for entrance and exit transition probabilities satisfy these requirements and are analogous to the formulas for entrance and exit rates of the single-particle model in one reaction coordinate.^{1,2} Let $\psi_I = \beta \Psi_I$ denote the dimensionless applied potential on side I, where the applied potential on side II is zero by convention.

$$k_{E \rightarrow (1,j)} = \Delta t h \kappa_I^{-1} c_I, \quad (80)$$

$$k_{(1,j) \rightarrow E} = \Delta t h^{-1} \kappa_I^{-1} e^{w(h,y) - \psi_I}, \quad (81)$$

$$k_{E \rightarrow (n,j)} = \Delta t h \kappa_{II}^{-1} c_{II}, \quad (82)$$

$$k_{(n,j) \rightarrow E} = \Delta t h^{-1} \kappa_{II}^{-1} e^{w(1,y)}. \quad (83)$$

Compared with the 1D model described in the references, factors dependent on the potentials w and ψ_I are moved to the exit transition probabilities, a convention which seems to be appropriate for modeling proton entrance into and exit from gramicidin.²⁸ In general, the division of potential factors between entrance and exit transition probabilities is model dependent and should, ideally, be determined by molecular dynamics or similar detailed molecular simulations. The analogy with the formulas for the 1D single-particle model is closest with the definitions $c_R = ALC_R$, for $R \in \{I, II\}$, and $t_0 = L^2/D$. Parameters used in the 1D model are A , the pore cross section L , the pore length D , the effective diffusion coefficient associated with entrance and exit, and C_R , the concentration of permeant ion on side R . κ_I and κ_{II} control the distribution of waiting times in the empty state; see Sec. V B below.

Inserting the definitions, Eqs. (80) and (81) into Eq. (69), we obtain

$$\lim_{h \rightarrow 0} hT_5 = q_E(t) \kappa_I^{-1} c_I - p(0, y, t) \kappa_I^{-1} e^{w(0, y) - \psi_I}. \quad (84)$$

Combining the results of Eqs. (72)–(75) and $\lim_{h \rightarrow 0} hT_5$ from Eq. (84), we obtain

$$\begin{aligned} \lim_{h \rightarrow 0} h(T_1 + T_2 + T_3 + T_4 + T_5) \\ = d_1(0, y)[p_x(0, y, t) + w_x(0, y)p(0, y, t)] \\ + d_3(0, y)[p_y(0, y, t) + w_y(0, y)p(0, y, t)] \\ + q_E(t) c_I \kappa_I^{-1} - p(0, y, t) \kappa_I^{-1} e^{w(0, y) - \psi_I}. \end{aligned} \quad (85)$$

Let $h \rightarrow 0$ in Eq. (70) to obtain the boundary condition on side I. A similar analysis yields the boundary condition on side II. These are

$$p(0, y, t) e^{w(0, y) - \psi_I} = q_E(t) c_I - \kappa_I \mathbf{j}(0, y, t) \cdot \hat{\mathbf{e}}_x, \quad (86)$$

$$p(1, y, t) e^{w(1, y)} = q_E(t) c_{II} + \kappa_{II} \mathbf{j}(1, y, t) \cdot \hat{\mathbf{e}}_x. \quad (87)$$

To summarize, the single-particle model solves the Smoluchowski equation on the unit square shown in Fig. 2(b). The Smoluchowski equation combines the equation of continuity, Eq. (5), and the Nernst-Planck equation, Eq. (6). The boundary condition on the top and bottom of the unit square is Eq. (64), corresponding to reflection of trajectories. The boundary conditions on sides I and II are given by Eqs. (86) and (87). Figure 2(b) is a representation of the state space. Since the system must be in some state, these equations must be combined with the normalization criterion

$$q_E(t) + \int_0^1 \int_0^1 p(x, y, t) dx dy = 1. \quad (88)$$

Normalization makes the boundary conditions on sides I and II nonlocal,^{29,30} since they refer to a quantity q_E which depends on the integral of p over the unit square.

V. PROPERTIES OF THE 2D SINGLE-PARTICLE MODEL

A. Thermodynamic equilibrium

At thermodynamic equilibrium, the probability density on the unit square in Fig. 2(b) is independent of time and satisfies the Boltzmann distribution

$$p(x, y) = p_0 e^{-w(x, y)}, \quad (89)$$

the continuous analog of Eq. (78). Inserting this into the Nernst Planck equation, Eq. (6), gives the condition for detailed balance

$$\mathbf{j}(x, y) \equiv \mathbf{0}. \quad (90)$$

The boundary conditions on sides I and II, Eqs. (86) and (87), become

$$p(0, y) e^{w(0, y) - \psi_I} = q_E c_I, \quad (91)$$

$$p(1, y) e^{w(1, y)} = q_E c_{II}. \quad (92)$$

Substituting the form of the Boltzmann distribution for p , dividing Eq. (92) by Eq. (91), and then solving for ψ_I obtains the Nernst equation

$$\psi_I = \ln(c_{II}/c_I). \quad (93)$$

Inserting the Boltzmann form into Eq. (91) and solving for p_0 gives

$$p_0 = q_E c_I e^{\psi_I}. \quad (94)$$

Insert the Boltzmann form into the normalization condition, Eq. (88), and then use Eq. (94) to substitute for p_0 . Solve for q_E to get

$$q_E = \left(1 + c_{II} \int_0^1 \int_0^1 e^{-w(x, y)} dx dy \right)^{-1}, \quad (95)$$

generalizing a result for the 1D single-particle model,¹ and consistent with the results of a statistical mechanical study of single-particle channels.³¹

B. Waiting times in the empty state

Let $f(t, t_0)$ be the probability that the empty state is occupied continuously until time t , given that it was occupied at a previous time t_0 . Then

$$f(t + \Delta t, t_0) - f(t, t_0) = -f(t, t_0) \sum_{j=1}^n (k_{E \rightarrow (1, j)} + k_{E \rightarrow (n, j)}), \quad (96)$$

where the transition probabilities are given by Eqs. (80) and (82). Divide by Δt and let $\Delta t \rightarrow 0$ to give

$$(\partial/\partial t)f(t, t_0) = -(c_I \kappa_I^{-1} + c_{II} \kappa_{II}^{-1})f(t, t_0), \quad (97)$$

with the solution

$$f(t, t_0) = e^{-(c_I \kappa_I^{-1} + c_{II} \kappa_{II}^{-1})(t - t_0)}. \quad (98)$$

The 1D single-particle model also has an exponential distribution of waiting times in the empty state.¹

C. Exact reduction to the 1D single-particle model

An exact reduction of the 2D single-particle model to a 1D model proved useful for checking the algorithm for the numerical solution described in Sec. VI. Suppose that the cross diffusion $d_3 = 0$ and that d_1 , d_2 and w are independent of y . Consider an initial value problem for the 2D single-particle model with initial condition $p(x, y, 0)$ independent of y . Then there are no terms in the Smoluchowski equation, Eqs. (5) and (6), the boundary conditions, Eqs. (64), (86), and (87), or the normalization condition, Eq. (88), which would break the initial homogeneity in y . Introduce the reduced probability density and current

$$\bar{p}(x, t) = \int_0^1 p(x, y, t) dy, \quad (99)$$

$$J(x, t) = \int_0^1 j_1(x, y, t) dy. \quad (100)$$

Integrate the first component of Eq. (6) with respect to y and note that $j_2 = 0$. Substitute the result into Eq. (5) to obtain a Smoluchowski equation for the reduced density,

$$\bar{p}_t = [d_1(\bar{p}_x + \bar{w}_x \bar{p})]_x, \quad (101)$$

where subscripts x and t denote partial derivatives and $\bar{w}(x) = w(x, y)$. Integrate Eqs. (86) and (87) over y to obtain boundary conditions for the reduced problem on sides I and II

$$\bar{p}(0, t) e^{\bar{w}(0) - \psi_I} = q_E(t) c_I - \kappa_{IJ} \mathcal{J}(0, t), \quad (102)$$

$$\bar{p}(1, t) e^{\bar{w}(1)} = q_E(t) c_{II} + \kappa_{II} \mathcal{J}(1, t). \quad (103)$$

Integrating over the normalization condition, Eq. (88),

$$q_E(t) + \int_0^1 \bar{p}(x, t) dx = 1. \quad (104)$$

Equations (101)–(104) give a time-dependent single-particle model.

D. Reduction to 1D by adiabatic elimination

The 2D single-particle model may also be used to illustrate the elimination of a fast variable to obtain an effective 1D model. This is known as adiabatic elimination and underlies the projection that sometimes allows processes involving many degrees of freedom to be usefully described in terms of a few reaction coordinates. Assume the cross diffusion $d_3 = 0$. The Smoluchowski equation, Eqs. (5) and (6), can then be written in the form

$$p_t = [d_1(p_x + w_x p)]_x + \zeta [d_2(p_y + w_y p)]_y, \quad (105)$$

where we have made the replacement $d_2 \rightarrow \zeta d_2$. Assuming that d_1 and d_2 are constant, the results of Refs. 20 and 32 apply directly. In the limit $\zeta \rightarrow \infty$, the probability density in the slow variable x satisfies a Smoluchowski equation in one spatial variable with an averaged potential \bar{w} ,

$$\bar{p}_t = [d_1(\bar{p}_x + \bar{w}_x \bar{p})]_x, \quad (106)$$

where

$$\bar{w}_x(x) = \int_0^1 w_x(x, y) p_0(x, y) dy \quad (107)$$

and p_0 is the equilibrium probability density in y , with x regarded as a parameter,

$$p_0(x, y) = e^{-w(x, y)} / \int_0^1 e^{-w(x, y')} dy'. \quad (108)$$

$-\bar{w}_x$ is the mean force acting on the particle in the direction of the slow variable, formed by averaging over the equilibrium distribution of the fast variable. In this sense, the result is a mean field theory. The potential w can be written

$$\bar{w}(x) = -\ln \left(\int_0^1 e^{-w(x, y)} dy \right). \quad (109)$$

Appropriate boundary conditions for the reduced 1D single-particle model may be obtained from the diffusion limit of the random walk whose state diagram is depicted by Fig. 1 of Ref. 2. To specify the entrance rates for the reduced model, note that the distribution of 2D model entrances from the empty state is independent of ζ . The total rate of entrance into side I or II from the empty state is obtained by summing Eqs. (80) and (82) over j , obtaining

$$k_{E \rightarrow I} = \Delta t \kappa_I^{-1} c_I, \quad (110)$$

$$k_{E \rightarrow II} = \Delta t \kappa_{II}^{-1} c_{II}. \quad (111)$$

The exit rates for the reduced model are obtained by averaging over the equilibrium distribution of the fast variable. Using

$$\int_0^1 e^{w(x, y)} p_0(x, y) dy = e^{\bar{w}(x)} \quad (112)$$

to compute the average of the exit rates given by Eqs. (81) and (83), we obtain

$$k_{I \rightarrow E} = \Delta t h^{-1} \kappa_I^{-1} e^{\bar{w}(h) - \psi_I}, \quad (113)$$

$$k_{II \rightarrow E} = \Delta t h^{-1} \kappa_{II}^{-1} e^{\bar{w}(1)}. \quad (114)$$

The random walk also requires specification of transition probabilities in the interior of the occupied segment²⁷

$$k_{i \rightarrow i+1} = \Delta t d_1 h^{-2} e^{[\bar{w}(x) - \bar{w}(x+h)]/2}, \quad (115)$$

$$k_{i \rightarrow i-1} = \Delta t d_1 h^{-2} e^{[\bar{w}(x) - \bar{w}(x-h)]/2}, \quad (116)$$

where $x = ih$. The Smoluchowski equation [Eq. (106)] and the following single-particle boundary conditions may then be obtained from the diffusion limit of the random walk:

$$\bar{p}(0, t) e^{\bar{w}(0) - \psi_I} = \bar{q}_E(t) c_I - \kappa_{IJ} \mathcal{J}(0, t), \quad (117)$$

$$\bar{p}(1, t) e^{\bar{w}(1)} = \bar{q}_E(t) c_{II} + \kappa_{II} \mathcal{J}(1, t). \quad (118)$$

These have the same form as Eqs. (102) and (103). A normalization condition of the form of Eq. (104), but involving \bar{q}_E and \bar{p} , also applies. For a case at steady state, numerical integration confirms that the 2D probability density of Eq. (105), averaged over y , converges to the density of the reduced model of Eq. (106) as $\zeta \rightarrow \infty$.³³

VI. NUMERICAL SOLUTION OF THE TIME-INDEPENDENT BOUNDARY VALUE PROBLEM

The Smoluchowski equation combines the equation of continuity, Eq. (5), and the Nernst-Planck equation, Eq. (6). The corresponding time-independent equation is

$$\nabla \cdot [d(\nabla p + (\nabla w)p)] = 0. \quad (119)$$

This is solved on the unit square in Fig. 2(b). The boundary condition on the top and bottom is Eq. (64), corresponding to reflection of trajectories. The boundary conditions on sides I and II are given by Eqs. (86) and (87). The probability density p , empty state probability q_E , and current \mathbf{j} are all assumed to be independent of time. The probability density and current are coupled by the time-independent version of the normalization condition given by Eq. (88). Normalization makes the boundary conditions on sides I and II nonlocal, since they refer to a quantity q_E , which depends on the integral of p over the unit square.

The boundary value problem was solved using the finite element method.^{34,35} An advantage of this popular method is its natural handling of the boundary conditions. Beginning with Eq. (119), we multiply by an arbitrary test function $-u(x, y)$ and integrate over the region to obtain

$$-\int_0^1 \int_0^1 u \nabla \cdot [d(\nabla p + (\nabla w)p)] dx dy = 0. \quad (120)$$

Applying Green's first identity to the first term in this integral, we obtain

$$-\int_B u(d\nabla p) \cdot \mathbf{n} ds + \int_0^1 \int_0^1 \nabla u \cdot (d\nabla p) - u \nabla \cdot [d(\nabla w)p] dx dy = 0, \quad (121)$$

where B is the boundary of the unit square, and \mathbf{n} is an outward unit normal to the boundary. The integral over the boundary is broken into four pieces corresponding to the four sides. Then the integral for each side is modified in accordance with the boundary condition for that side. For example, the integral on the right-hand boundary (side II) is

$$-\int_0^1 u(1,y)(d\nabla p)(1,y) \cdot \hat{\mathbf{e}}_x dy \\ = -\int_0^1 u(1,y)[d_1(1,y)p_x(1,y) + d_3(1,y)p_y(1,y)] dy. \quad (122)$$

The boundary condition for the right side (side II) is the

time-independent version of Eq. (87). Expanding $\mathbf{j}(1,y) \cdot \hat{\mathbf{e}}_x$ using Eq. (6) and rearranging terms, we can rewrite the boundary condition as

$$-[d_1(1,y)p_x(1,y) + d_3(1,y)p_y(1,y)] \\ = [d_1(1,y)w_x(1,y) + d_3(1,y)w_y(1,y) \\ + \kappa_{II}^{-1} e^{w(1,y)}] p(1,y) - c_{II} \kappa_{II}^{-1} q_E. \quad (123)$$

Substituting Eq. (123) into Eq. (122), we find that the right-hand side of Eq. (122) can be replaced by

$$\int_0^1 [d_1(1,y)w_x(1,y) + d_3(1,y)w_y(1,y) \\ + \kappa_{II}^{-1} e^{w(1,y)}] p(1,y) u(1,y) dy - c_{II} \kappa_{II}^{-1} q_E \int_0^1 u(1,y) dy. \quad (124)$$

Making similar replacements in the left, top, and bottom portions of the boundary integral, we find that Eq. (121) is equivalent to

$$a(p,u) = q_E L(u), \quad (125)$$

where

$$a(p,u) = \int_0^1 \int_0^1 \nabla u \cdot (d\nabla p) - u \nabla \cdot (p d\nabla w) dx dy + \int_0^1 [d_3(x,1)w_x(x,1) + d_2(x,1)w_y(x,1)] p(x,1) u(x,1) dx \\ - \int_0^1 [d_3(x,0)w_x(x,0) + d_2(x,0)w_y(x,0)] p(x,0) u(x,0) dx + \int_0^1 [d_1(1,y)w_x(1,y) + d_3(1,y)w_y(1,y) \\ + \kappa_{II}^{-1} e^{w(1,y)}] p(1,y) u(1,y) dy - \int_0^1 [d_1(0,y)w_x(0,y) + d_3(0,y)w_y(0,y) - \kappa_I^{-1} e^{w(0,y) - \psi_I}] p(0,y) u(0,y) dy$$

and

$$L(u) = c_I \kappa_I^{-1} \int_0^1 u(0,y) dy + c_{II} \kappa_{II}^{-1} \int_0^1 u(1,y) dy.$$

In the finite-element approximation, the function p is assumed to be a linear combination of a finite set of piecewise polynomial basis functions ϕ_1, \dots, ϕ_n :

$$p(x,y) = \sum_{j=1}^n c_j \phi_j(x,y). \quad (126)$$

We used piecewise bilinear "tent" functions.^{34,35} Substituting this form into Eq. (125), and using the basis functions also as test functions, we obtain the system of n linear equations

$$\sum_{j=1}^n c_j a(\phi_j, \phi_i) = q_E L(\phi_i), \quad i = 1, \dots, n, \quad (127)$$

which can be solved for c_1, \dots, c_n .

In a normal finite element analysis, the solution of Eq. (127) yields p , by substituting the c_j values into Eq. (126). However, we have the complication of not knowing q_E . We therefore solve the related system

$$\sum_{j=1}^n \hat{c}_j a(\phi_j, \phi_i) = L(\phi_i), \quad i = 1, \dots, n, \quad (128)$$

in which q_E is replaced by 1. Letting

$$\hat{p}(x,y) = \sum_{j=1}^n \hat{c}_j \phi_j(x,y),$$

we have

$$p(x,y) = q_E \hat{p}(x,y). \quad (129)$$

Let

$$I_{\hat{p}} = \int_0^1 \int_0^1 \hat{p}(x,y) dx dy. \quad (130)$$

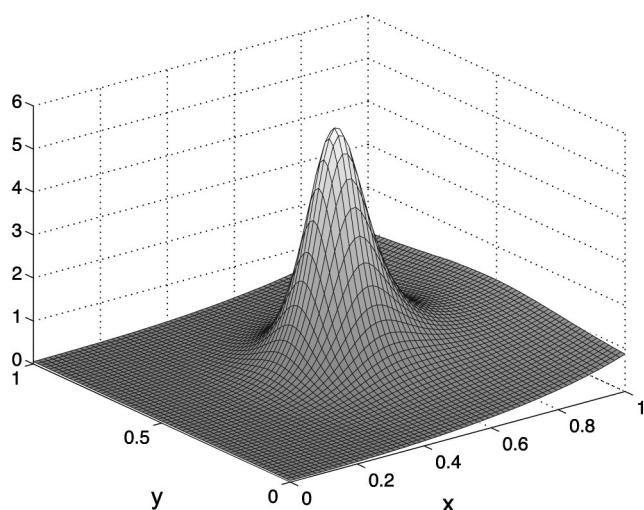


FIG. 5. The density $p(x,y)$ from the numerical solution of the time-independent boundary value problem described in Sec. VI.

Substituting this into the time-independent version of the normalization condition Eq. (88), using Eq. (129), we find that $q_E(1 + I_{\hat{p}}) = 1$, so that

$$q_E = 1/(1 + I_{\hat{p}}). \quad (131)$$

Substituting this value of q_E into Eq. (129), we obtain $p(x,y)$.

An example was constructed using the potential

$$w(x,y) = b[f(r) - 1] + \psi_I(1 - x), \quad (132)$$

with $f(r) = r^2/(a^2 + r^2)$ and $r^2 = (x - 0.5)^2 + (y - 0.5)^2$. Parameter values were $a = 0.2$, $b = 4$, and $\psi_I = 4$. The elements of the diffusion matrix were $d_1(x,y) = 2[2 - f(r)]$, $d_2(x,y) = 2 - f(r)$, and $d_3(x,y) = [2 - f(r)]/2$. The numerically computed steady probability density on the unit square is shown in Fig. 5. The finite element method was compared with a direct numerical solution of the random walk which approximates the 2D single-particle model at steady state, giving a very similar result. This second method will be discussed in a forthcoming paper.

VII. SUMMARY AND DISCUSSION

The method we have used to construct a two-dimensional framework model can be adapted to state spaces that have been constructed by molecular dynamics simulations for K^+ conduction through gramicidin,¹³ proton conduction through dioxolane linked gramicidin dimers^{14,15} and chloride conduction through the bacterial $H^+ - Cl^-$ antiporter.¹⁷ More generally, the framework model method should be applicable to state spaces constructed for highly constrained biomolecular systems, that is, having only a few important reaction coordinates. The framework model receives estimates of the potential of mean force and elements of the diffusion matrix from detailed molecular simulations, and can then compute conductances and other properties of the experimental system very rapidly, allowing detailed comparison with experiment. It will be important to develop methods for estimating the off-diagonal elements of the diffusion matrix from the simulations. The square geometry of

the state space representing the pore, Fig. 2(b), may not be an important limitation since an effective state space with ragged boundaries can be defined between high potential walls. We anticipate that the methods we have used to construct framework models with two reaction coordinates on a square lattice can be generalized to construct models with three reaction coordinates on a cubic lattice. These methods could then be applied to recent models of conduction through the selectivity filter of the KcsA potassium channel.^{6,18}

For large problems, the most time consuming step of the finite element method for solving the framework model is the solution of the linear system of Eq. (128). Using the sparse data structure and the direct method of solving linear systems provided in MATLAB (Ref. 36) on a modern desktop computer (1.7 GHz Pentium IV), we have solved a linear system with $n = 27\,000$ unknowns and a half bandwidth of about 900. The solution took 80 s and required 400 MB of memory. For very large problems, iterative methods are more efficient.³⁷ Using MATLAB's implementation of the iterative method BiCGSTAB with no preconditioner, we have solved a linear system with $n = 125\,000$ unknowns and a half bandwidth of about 2500. The solution took 55 s and required 25 MB of memory. These solutions were computed to approximately ten digits accuracy.

¹P. McGill and M. F. Schumaker, *Biophys. J.* **71**, 1723 (1996).

²M. F. Schumaker, *J. Chem. Phys.* **117**, 2469 (2002).

³E. J. Mapes and M. F. Schumaker (unpublished).

⁴M. F. Schumaker, R. Pomès, and B. Roux, *Biophys. J.* **79**, 2840 (2000).

⁵M. F. Schumaker, R. Pomès, and B. Roux, *Biophys. J.* **80**, 12 (2001).

⁶S. Bernèche and B. Roux, *Proc. Natl. Acad. Sci. U.S.A.* **100**, 8644 (2003).

⁷B. J. Berne and R. Pecora, *Dynamic Light Scattering* (Wiley, New York, 1976), Chap. 11.

⁸B. Roux, T. Allen, S. Bernèche, and W. Im, *Q. Rev. Biophys.* **37**, 15 (2004).

⁹B. Hille, *Ionic Channels of Excitable Membranes*, 2nd ed. (Sinauer, Sunderland, Massachusetts, 1992).

¹⁰D. Chen, J. Lear, and B. Eisenberg, *Biophys. J.* **72**, 97 (1997).

¹¹T. W. Allen and S. H. Chung, *Biochim. Biophys. Acta* **1515**, 83 (2001).

¹²R. J. Mashl, Y. Tang, J. Schnitzer, and E. Jakobson, *Biophys. J.* **81**, 2473 (2001).

¹³T. W. Allen, O. S. Andersen, and B. Roux, *Proc. Natl. Acad. Sci. U.S.A.* **101**, 117 (2004).

¹⁴C.-H. Yu, S. Cukierman, and R. Pomès, *Biophys. J.* **84**, 816 (2003).

¹⁵C.-H. Yu and R. Pomès, *J. Am. Chem. Soc.* **125**, 13890 (2003).

¹⁶A. Accardi and C. Miller, *Nature (London)* **427**, 803 (2004).

¹⁷J. Cohen and K. Schulten, *Biophys. J.* **86**, 836 (2004).

¹⁸S. Bernèche and B. Roux, *Nature (London)* **414**, 73 (2001).

¹⁹Y. Song, Y. Zhang, T. Shen, C. G. Bajaj, J. A. McCammon, and N. A. Baker, *Biophys. J.* **86**, 2017 (2004).

²⁰H. Risken, *The Fokker-Planck Equation*, 2nd ed. (Springer, Berlin, 1989) Secs. 4.7 and 8.3.

²¹S. W. Chiu, J. A. Novotny, and E. Jakobsson, *Biophys. J.* **64**, 98 (1993).

²²W. Im and B. Roux, *J. Mol. Biol.* **319**, 1177 (2002).

²³G. R. Smith and M. S. P. Sansom, *Biophys. J.* **75**, 2767 (1998).

²⁴S. Crouzy, T. B. Woolf, and B. Roux, *Biophys. J.* **67**, 1370 (1994).

²⁵J. E. Straub, M. Borkovec, and B. J. Berne, *J. Chem. Phys.* **89**, 4833 (1988).

²⁶B. J. Berne, M. Borkovec, and J. E. Straub, *J. Phys. Chem.* **92**, 3711 (1988).

²⁷N. Agmon and J. J. Hopfield, *J. Chem. Phys.* **78**, 6947 (1983).

²⁸J. A. Gowen, J. C. Markham, S. E. Morrison, T. A. Cross, D. D. Busath, E. J. Mapes, and M. F. Schumaker, *Biophys. J.* **83**, 880 (2002).

²⁹C. V. Pao, *J. Comput. Appl. Math.* **136**, 227 (2001).

³⁰H.-M. Yin, *J. Math. Anal. Appl.* **294**, 712 (2004).

³¹B. Roux, *Biophys. J.* **77**, 139 (1999).

³²K. Kaneko, *Prog. Theor. Phys.* **66**, 129 (1981).

³³M. F. Schumaker (unpublished).

- ³⁴R. Wait and A. R. Mitchell, *Finite Element Analysis and Applications* (Wiley, New York, 1985).
- ³⁵O. C. Zienkiewicz and R. L. Taylor, *The Finite Element Method*, 5th ed. (Butterworth-Heinemann, Boston, 2000).

- ³⁶MATLAB is a registered trademark of the MathWorks, Inc.
- ³⁷A. Greenbaum, in *Iterative Methods for Solving Linear Systems*, Frontiers in Applied Mathematics, Vol. 17, edited by H. T. Banks (SIAM, Philadelphia, 1997).