Diffusion as a chemical reaction: Stochastic trajectories between fixed concentrations

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Stochastic trajectories are described that underly classical diffusion between known concentrations. The description of those experimental boundary conditions requires a phase space using the full Langevin equation, with displacement and velocity as state variables, even if friction entirely dominates the dynamics of diffusion, because the incoming and outgoing trajectories have to be told apart. The conditional flux, probabilities, mean first-passage times, and contents (of the reaction region) of the four types of trajectories—the *trans* trajectories *LR* and *RL* and the *cis* trajectories *LL* and *RR*—are expressed in terms of solutions of the Fokker–Planck equation in phase space and are explicitly calculated in the Smoluchowski limit of high friction. With these results, diffusion in a region between fixed concentrations can be described exactly as a chemical reaction for any potential function in the region, made of any combination of high or low barriers or wells. © *1995 American Institute of Physics.*

I. INTRODUCTION

Diffusion has been analyzed by classical field theory,[1,2] starting with Fick, and also, at higher resolution, by the theory of stochastic processes describing the trajectories of diffusing particles.[3,4] Classical theory is based on the canonical experimental setup for diffusion, where particles diffuse from a region of one concentration to another. Surprisingly, a stochastic theory is not available that describes trajectories in this situation. Theories of stochastic diffusion in the context of chemistry or biology often analyze a restricted case, when particles diffuse over a high barrier. Trajectories diffusing over arbitrary barriers seem not to have been analyzed in this context.

This paper calculates the statistical properties of the random trajectories of diffusion using stochastic differential equations[5–7] to describe the dynamics of ionic motion. The Langevin model is used for the calculation of the probabilities of the four types of trajectories—the *trans* trajectories *LR* and *RL* and the *cis* trajectories *LL* and *RR*—as well as for the calculation of the mean first-passage times and average contents of the reaction region. With this analysis all the statistical properties of the four types of trajectories can be determined for any shape potential function and any friction. In the limit of high friction, reduced problems are derived for each type of trajectory that yield explicit formulas for (conditional) probabilities, contents (of the reaction region), and residence times (i.e., mean first passage times). The *trans* unidirectional components of flux, studied in biology with radioactive tracers for many years, correspond to the conditional probabilities, and are also the (conditional) contents divided by the mean first passage time.

Interestingly, in this setup the velocity distribution of the ions is not Maxwellian, even in the limit of high friction, but rather contains an asymmetric term proportional to flux.

This work started as an attempt to describe the stochastic motion of ions through single biological channels, protein molecules that open to form a pore allowing ions to move across cell membranes.[8] Interestingly, this is the same problem that motivated Fick—who was both a physiologist and physical chemist[8,9]—to invent classical diffusion theory. The biological problem is described at the end of Sec. IX.

II. THE SETUP, FRICTION, AND DIFFUSION

We represent the experimental setup of Fick by a reaction region separating two baths in which concentrations and potentials are maintained fixed. The ions inside (and outside) the reaction region move by diffusion and transport in an electrical field. The electrical field arises from the distribution of charge in the reaction region and at its boundaries, a distribution that must be expected to change as experimental conditions are changed. Thus, the potential function $\Phi(x)$ is expected to vary if the species or concentrations of ions in the baths or the electrical potential there is changed. The diffusion arises from the thermal collisions of the ion with surrounding waters and protein. Motion is collision dominated because the atoms move with thermal velocity (Å/ps) in a liquid with very little empty space; in a typical experiment an ion undergoes hundreds, thousands, or millions of collisions (or more!) as it moves from one boundary at one concentration to another.

Although friction in liquids is characterized by memory kernels, we simplify the calculations by assuming a (position and species dependent) effective friction coefficient, $\beta(x)$ (see Ref. 10). This coefficient would ideally be an output of a numerical simulation of molecular dynamics. The friction coefficient we use is an effective parameter; it is expected to be independent of conditions under a reasonable range of concentrations, electric fields, and temperatures. That is to

say, the structure of the memory kernels is not expected to vary much as the flux is manipulated experimentally by changing concentration, potential, etc. over the pertinent range.

III. THE MATHEMATICAL MODEL AND THE NERNST–PLANCK EQUATION

We present the Nernst–Planck (i.e., Smoluchowski) model so the paper is reasonably self-contained. The reaction region is located on the x-axis between $x=0$ and $x=1$; the bathing solutions are on either side of the reaction region, between $-\infty < x < 0$ and $1 < x < \infty$. The concentration of ions in the reaction region, $\rho(x)$, satisfies the Nernst–Planck equation in Stratonovich form[5,6] (see Appendix A for nondimensionalization)

$$\frac{d}{dx} D(x)\left[\frac{d}{dx}\rho(x) + \frac{1}{\epsilon}\frac{d\Phi(x)}{dx}\rho(x)\right] = 0 \quad \text{for} \quad 0 < x < 1,$$
(3.1)

where $D(x)$ is the diffusion coefficient and ϵ is dimensionless temperature (not necessarily small). Also the concentration of ions in the baths satisfies the three-dimensional Nernst–Planck equation in $-\infty < x < 0$ and $1 < x < \infty$, with $\Phi(x,y,z) \cong \text{const.}$ and $D(x,y,z) = \text{const.}$ In order to avoid solving the Nernst–Planck equation in all three domains simultaneously, we approximate the solution in both baths by constant concentrations. Therefore, the boundary conditions for Eq. (3.1) are

$$\rho(0) = C_L, \quad \rho(1) = C_R.$$
(3.2)

Integrating Eq. (3.1) once, we obtain

$$D(x)\left[\frac{d\rho(x)}{dx} + \frac{1}{\epsilon}\frac{d\Phi(x)}{dx}\rho(x)\right] = -J,$$
(3.3)

where J is the (spatially and temporally constant) flux. Integrating again and using the boundary conditions Eq. (3.2), we obtain

$$\rho(x) = e^{-\Phi(x)/\epsilon}\left\{[C_R e^{\Phi(1)/\epsilon} - C_L e^{\Phi(0)/\epsilon}]\right.$$

$$\left.\times \frac{\int_0^x e^{\Phi(s)/\epsilon}\frac{ds}{D(s)}}{\int_0^1 e^{\Phi(s)/\epsilon}\frac{ds}{D(s)}} + C_L e^{\Phi(0)/\epsilon}\right\}.$$
(3.4)

In particular, if $D(x) \equiv D$, Eq. (3.4) reduces to

$$\rho(x) = \frac{C_R e^{\Phi(1)/\epsilon} - C_L e^{\Phi(0)/\epsilon}}{\int_0^1 e^{\Phi(s)/\epsilon}ds} e^{-\Phi(x)/\epsilon}\int_0^x e^{\Phi(s)/\epsilon}ds$$

$$+ C_L e^{[\Phi(0)-\Phi(x)]/\epsilon}.$$
(3.5)

Using Eq. (3.4) in Eq. (3.3), we obtain

$$J = \frac{C_L e^{\Phi(0)/\epsilon} - C_R e^{\Phi(1)/\epsilon}}{\int_0^1 e^{\Phi(s)/\epsilon}\frac{ds}{D(s)}}.$$
(3.6)

For constant $D(x)=D$, Eq. (3.6) reduces to the well known expression[8]

$$J = D\frac{C_L e^{\Phi(0)/\epsilon} - C_R e^{\Phi(1)/\epsilon}}{\int_0^1 e^{\Phi(s)/\epsilon}ds}.$$
(3.7)

If the concentrations C_L and C_R are time dependent, Eq. (3.7) can be easily generalized by solving the time dependent Nernst–Planck equation.

The stochastic dynamics underlying the Nernst–Planck equation is the *reduced* Langevin equation[4]

$$\beta(x)\dot{x} + \frac{d\Phi(x)}{dx} = \sqrt{2\beta(x)\epsilon}\,\dot{w},$$
(3.8)

where $x(t)$ is the position of the ion at time t, $\Phi(x)$ is the electric potential, $\beta(x)$ is the friction coefficient, ϵ is nondimensional temperature, and $\dot{w}$ is standard Gaussian white noise (see Appendix A). The friction and noise terms in Eq. (3.8) are related by the Einstein fluctuation-dissipation principle.[3–6]

The inhomogeneous boundary condition for the Nernst–Planck equation corresponding to the reduced Langevin equation (3.8) leads to difficulties, because it requires the region outside the channel to be *both* a source (of trajectories entering the channel) and an absorber (of trajectories leaving the channel). In Eq. (3.8), however, all trajectories that originate at the boundary are immediately absorbed there and never get anywhere, an undesirable, presumably unrealistic phenomenon observed directly, at considerable computational cost, in the simulations of Ref. 11.

Exiting and entering trajectories differ only by the sign of their velocities; one is positive and the other negative, but velocity is not a state variable in the reduced Langevin equation (3.8). Obviously, if a stochastic theory is to separate entering from exiting trajectories, it must analyze and describe the velocity of ions as well as their displacement. The distinction between entering (positive velocity at the left boundary $x=0$) and exiting (negative velocity) trajectories cannot be made in the reduced Langevin equation. In contrast, the full Langevin equation[4,6,12,13]

$$\ddot{x} + \beta(x)\dot{x} + \frac{d\Phi(x)}{dx} = \sqrt{2\beta(x)\epsilon}\,\dot{w},$$
(3.9)

describes random ionic trajectories in a phase space with two state variables, displacement, $x(t)$, and velocity, $v \equiv \dot{x}(t)$. Thus, the distinction between entering and exiting trajectories is automatic; one has $v > 0$ at the left entrance and the other has $v < 0$ there. The full Langevin equation describes the underlying dynamics of these trajectories. The Fokker–Planck equation, involving both displacement and velocity, is needed to describe the probability density function of these trajectories, and its evolution. Therefore, we must use the full Fokker–Planck equation rather than the Nernst–Planck to describe diffusion, even if friction is large.

IV. THE LANGEVIN AND FOKKER–PLANCK EQUATIONS; THE NERNST–PLANCK EQUATION RECOVERED

A concentration boundary condition does not imply any particular physical process at the entrance and exit of the reaction region. The ions simply move in and out of a region where friction and potential change from their values in the free solution outside the reaction region. Indeed, in a real experimental situation the concentration is not absolutely fixed at this boundary; rather it is measured and changes are held small enough so they do not matter, as shown by direct experimentation. (In some situations, e.g., currents through biological Ca^{++} channels, significant concentration changes always accompany current flow under realistic conditions.) The trajectories of ions at an edge of the reaction region are complex and oscillate strongly [particularly as friction dominates, $\beta \rightarrow \infty$, and trajectories approach those of Eq. (3.8)] but they are unconstrained by specialized physical structure or experimental apparatus. Some trajectories (the *cis* ones) start at the boundary and end there. (In many situations, most trajectories are of the *cis* type.) Other trajectories (the *trans* ones) enter the reaction region and end on the opposite side. Both sets of trajectories flow without noticeably changing the concentration or potential in the baths because of the experimental apparatus and procedures used to maintain the concentration boundary condition.

A description of the random current requires separate calculation of the properties of incoming and outgoing ions. These ions are distinguished by the different signs of their velocity of motion and so a theory must describe both the position and the velocity of the ion.

velocity can be introduced into the Langevin equation (3.9) explicitly as a second state variable $v(t)$, forming a two-dimensional system

$$\dot{x} = v,$$
$$\dot{v} = -\beta(x)v - \frac{d\Phi(x)}{dx} + \sqrt{2\beta(x)\epsilon}\,\dot{w}(t). \tag{4.1}$$

The random trajectories, $[x(t), v(t)]$, defined by the system Eq. (4.1), describe the motion of the ion in phase space both inside the reaction region and outside, in the baths. The boundaries of the reaction region in phase space are the lines $x=0$, $-\infty < v < \infty$, and $x=1$, $-\infty < v < \infty$. In the real system of baths and reaction region, ions that reach the left end with $v > 0$ enter the reaction region, whereas those that reach this end, coming from the right with $v < 0$, exit the reaction region and diffuse into the external solution. The other end is analogous. The concentration boundary conditions (maintained by experimental apparatus) enforce this behavior. In the bath on the left, that is, for $x < 0$, the ionic motion is described by the Langevin equation (4.1) with $\beta(x)=$const. and $\Phi'(x)=0$, and the experimental apparatus maintains a (nearly) constant concentration of each species and a (nearly) constant electrical potential (analogously on the right). Indeed, these properties are what we mean by "concentration boundary condition."

Inside the reaction region the ionic motion is described by the Langevin equation (4.1) with the friction coefficient

$\beta(x)$ and potential $\Phi(x)$ of the reaction region. That potential function is determined by the spatial distribution of all charge (fixed and mobile, in the reaction region and at the boundaries) and must be expected to change shape if the electrical potential in the baths or the concentrations of ions there are changed. Both $\beta(x)$ and $\Phi(x)$ may undergo a discontinuity at the entrance to the reaction region. However, the random trajectories defined by the Langevin equation remain continuous. They may enter the reaction region on either side and exit on either side with certain probabilities. Thus, no boundary conditions are imposed at the ends of the reaction region.

The stationary joint probability density function of finding a random ionic trajectory at a point (x,v) in phase space is denoted by $p(x,v)$. The marginal probability density of finding an ion at the point x with any velocity, $p(x)$, is given by

$$p(x) = \int_{-\infty}^{\infty} p(x,v)dv. \tag{4.2}$$

If given concentrations, C_L and C_R, are measured at the ends of the reaction region, then

$$p(0) = C_L, \quad p(1) = C_R. \tag{4.3}$$

These are exactly the boundary conditions (3.2) for the Nernst–Planck equation (3.1).

The joint pdf $p(x,v)$ satisfies the stationary Fokker–Planck equation[4–6]

$$\mathscr{L}p(x,v) \equiv -v\,\frac{\partial p}{\partial x} + \beta(x)\epsilon\,\frac{\partial^2 p}{\partial v^2}$$
$$+ \frac{\partial}{\partial v}\left[\beta(x)v + \frac{d\Phi(x)}{dx}\right]p = 0 \tag{4.4}$$

in a large strip $x_L < x < x_R$, $-\infty < v < \infty$, where $x_L \leqslant 0$ and $x_R \geqslant 1$ are points where sources or sinks are placed in order to maintain the fixed concentrations on both sides of the reaction region. Note, however, that no boundary conditions are specified or imposed at the ends of the reaction region, $x=0$ and $x=1$. The properties of the variables at $x=0$ and $x=1$ are derived later as part of the solution to the problem.

The time dependent Fokker–Planck equation is

$$\frac{\partial p(x,v,t)}{\partial t} = \mathscr{L}p(x,v,t). \tag{4.5}$$

Equation (4.4) can also be written in the form of a conservation law

$$-\boldsymbol{\nabla}_{x,v} \cdot \mathbf{J}(x,v) = 0 \quad \text{for } (x,v) \in \mathscr{D}, \tag{4.6}$$

where the probability flux density vector $\mathbf{J}(x,v)$ is defined as usual for this two dimensional problem,[6] by

$$\mathbf{J}(x,v) \equiv \begin{pmatrix} vp(x,v) \\ -[\beta(x)v + \Phi'(x)]p(x,v) - \beta(x)\epsilon\,\dfrac{\partial p(x,v)}{\partial v} \end{pmatrix}. \tag{4.7}$$

Note that $\mathbf{J}(x,v)$ describes the flux of probability; the relation of this flux to the ionic flux through the reaction region remains to be seen.

We study the standard Smoluchowski expansion of the full time dependent Fokker–Planck equation[6] to make the paper reasonably self-contained. Denote the time dependent pdf by $p(x,v,t)$; scale $\beta(x)$ by its maximum, B; write

$$\beta(x) = B\beta_0(x); \tag{4.8}$$

and scale time by $t = Bt'$. For large B the time t' is slow, so that the time dependent Fokker–Planck equation becomes

$$B\beta(x) \frac{\partial}{\partial v}\left(\epsilon \frac{\partial}{\partial v}+v\right)p(x,v,t')+\left[-v\frac{\partial}{\partial x}+\frac{d\Phi(x)}{dx}\frac{\partial}{\partial v}\right]$$

$$\times p(x,v,t')+\frac{1}{B}\left[-\frac{\partial}{\partial t'}p(x,v,t')\right]$$

$$\equiv\left(B\mathscr{L}_0+\mathscr{L}_1+\frac{1}{B}\mathscr{L}_2\right)p(x,v,t')=0, \tag{4.9}$$

where

$$\mathscr{L}_0 p(x,v,t')\equiv\beta_0(x)\frac{\partial}{\partial v}\left(\epsilon\frac{\partial}{\partial v}+v\right)p(x,v,t'), \tag{4.10}$$

$$\mathscr{L}_1 p(x,v,t')\equiv\left[-v\frac{\partial}{\partial x}+\frac{d\Phi(x)}{dx}\frac{\partial}{\partial v}\right]p(x,v,t'), \tag{4.11}$$

and

$$\mathscr{L}_2 p(x,v,t')\equiv-\frac{\partial}{\partial t'}p(x,v,t'). \tag{4.12}$$

Expanding the density in an asymptotic series in negative powers of B,

$$p(x,v,t')=p^0(x,v,t')+\frac{1}{B}p^1(x,v,t')+\frac{1}{B^2}p^2(x,v,t')$$

$$+\cdots, \tag{4.13}$$

we obtain the following hierarchy of equations:

$$\mathscr{L}_0 p^0(x,v,t')=0, \tag{4.14}$$

$$\mathscr{L}_0 p^1(x,v,t')=-\mathscr{L}_1 p^0(x,v,t'), \tag{4.15}$$

$$\mathscr{L}_0 p^2(x,v,t')=-\mathscr{L}_1 p^1(x,v,t')-\mathscr{L}_2 p^0(x,v,t'), \tag{4.16}$$

and so on. From Eq. (4.14) we obtain

$$p^0(x,v,t')=\frac{e^{-v^2/2\epsilon}}{\sqrt{2\pi\epsilon}}P^0(x,t'), \tag{4.17}$$

where $P^0(x,t')$ is yet an undetermined function. The integrable solution of Eq. (4.15) is given by

$$p^1(x,v,t')=\frac{e^{-v^2/2\epsilon}}{\sqrt{2\pi\epsilon}}\left\{-\frac{1}{\beta_0}\left[\frac{\partial P^0(x,t')}{\partial x}\right.\right.$$

$$\left.\left.+\frac{1}{\epsilon}\frac{d\Phi(x)}{dx}P^0(x,t')\right]v+P^1(x,t')\right\}, \tag{4.18}$$

where $P^1(x,t')$ is another undetermined function. Using Eqs. (4.17) and (4.18) in Eq. (4.16) and integrating with respect to v, we obtain

$$\frac{\partial P^0(x,t')}{\partial t'}=\frac{\partial}{\partial x}\left\{\frac{1}{\beta_0(x)}\left[\epsilon\frac{\partial P^0(x,t')}{\partial x}\right.\right.$$

$$\left.\left.+\frac{d\Phi(x)}{dx}P^0(x,t')\right]\right\}. \tag{4.19}$$

Scaling B back into Eq. (4.20) and setting $p(x,t)\equiv P^0(x,t')$, we obtain the Smoluchowski model

$$\frac{\partial p(x,t)}{\partial t}=\frac{\partial}{\partial x}\left\{\frac{1}{\beta(x)}\left[\epsilon\frac{\partial p(x,t)}{\partial x}+\frac{d\Phi(x)}{dx}p(x,t)\right]\right\}. \tag{4.20}$$

Note that Eq. (4.20) has the Stratonovich form.[5,6] In the steady state, we obtain

$$\frac{\partial}{\partial x}\left\{\frac{1}{\beta(x)}\left[\epsilon\frac{\partial p(x)}{\partial x}+\frac{d\Phi(x)}{dx}p(x)\right]\right\}=0, \tag{4.21}$$

where $p(x)\equiv\lim_{t\to\infty}p(x,t)$.

Proceeding as above, we find that $P^1(x,t')=0$. Note that the Smoluchowski equation (4.21) is identical to the stationary Nernst–Planck equation (3.1). Returning to the expansion (4.13), we find that the expansion of the pdf is given by

$$p(x,v,t)\sim\frac{e^{-v^2/2\epsilon}}{\sqrt{2\pi\epsilon}}\left\{p(x,t)-\frac{1}{\beta(x)}\left[\frac{\partial p(x,t)}{\partial x}\right.\right.$$

$$\left.\left.+\frac{1}{\epsilon}\frac{d\Phi(x)}{dx}p(x,t)\right]v+O\left[\frac{1}{\beta^2(x)}\right]\right\}. \tag{4.22}$$

The total probability flux in the x direction is calculated from Eq. (4.7) [see, e.g., Eq. (5.7)] as

$$\mathscr{T}(x,t)\equiv\int_{-\infty}^{\infty}vp(x,v,t)dv$$

$$\sim-\frac{1}{\beta(x)}\left[\epsilon\frac{\partial p(x,t)}{\partial x}+\frac{d\Phi(x)}{dx}p(x,t)\right]$$

$$+O\left[\frac{1}{\beta^2(x)}\right]. \tag{4.23}$$

It follows that away from equilibrium the pdf depends on flux, *no matter what the friction,* so that we obtain an expansion in the Smoluchowski limit (previously derived in another context[14])

$$p(x,v,t)\sim\frac{e^{-v^2/2\epsilon}}{\sqrt{2\pi\epsilon}}\left[p(x,t)+\frac{\mathscr{T}(x,t)v}{\epsilon}+O\left[\frac{1}{\beta^2(x)}\right]\right]. \tag{4.24}$$

Formula (4.24) differs from the usual high friction (Smoluchowski) approximation to the joint pdf $p(x,v,t)$ (see, e.g., Refs. 4, 6, 12, 13). The usual high friction expansion neglects the flux term $\mathscr{T}(x,t)v/\epsilon$ inside the braces of Eq. (4.24). It stops after the first term $p(x,t)$. When the usual approximation to the joint pdf is substituted into the integral in the flux formula (4.23), the resulting flux in the x direction vanishes, no matter what the potential or values of other parameters. Therefore, the usual high friction approximation is valid only when fluxes vanish or are vanishingly small, e.g., at equilibrium or when barriers are sufficiently high that the system is essentially at equilibrium. If, however, a finite

flux is imposed experimentally, *and thus always present no matter what the friction,* as in most laboratory situations, then both terms, viz.,

$$p(x,t)+\frac{\mathcal{T}(x,t)v}{\epsilon},$$

must be retained in Eq. (4.24). The presence of both terms insures that Eq. (4.24) is valid for all values of flux, thus for all barrier shapes. The term $\mathcal{T}(x,t)v/\epsilon$ is responsible for the difference between our analysis, e.g., of chemical reaction, and most earlier work.

Note that Eqs. (4.23) and (4.24) recover the one-dimensional flux of the Nernst–Planck equation (3.1) from the two-dimensional Fokker–Planck equation. The fixed concentration boundary conditions (4.3) give in a straightforward manner the boundary conditions (3.2) for the Smoluchowski equation (4.21).

V. EXIT PROBABILITIES AND EXIT TIMES

One of the goals of this paper is to calculate the statistical properties of each of the four kinds of trajectories, LL, LR, RL, and RR. These trajectories are described by (conditional) probability density functions, their residence times in the reaction region (also called first passage times), and the fluxes of each of the four kinds of trajectories. The relation of these partial fluxes of probability to the flux of ions in the Nernst–Planck equation cannot be assumed; it is one of the outputs of this paper.

In order to calculate the conditional probability $P(L|L)$ of trajectories to exit on the left, given that they entered on the left, we have to isolate the influx of probability from the left from that on the right. Each of these unidirectional probability fluxes (to use the physiologists' words) is further split into its *cis* and *trans* components, into conditional fluxes (to use the probabilists' words), e.g.,

$$\mathcal{T}(L)=\mathcal{T}(L|L)+\mathcal{T}(R|L). \tag{5.1}$$

Here $\mathcal{T}(\cdot)$ describes the flux of probability, not ions. The conditional probability of the *cis* trajectories LL is

$$P(L|L)=\frac{\mathcal{T}(L|L)}{\mathcal{T}(L)}, \quad P(R|L)=1-P(L|L)=\frac{\mathcal{T}(R|L)}{\mathcal{T}(L)}, \tag{5.2}$$

as is obvious by simply counting trajectories. Using similar notation, we obtain

$$P(R|R)=\frac{\mathcal{T}(R|R)}{\mathcal{T}(R)}, \quad P(L|R)=1-P(R|R)=\frac{\mathcal{T}(L|R)}{\mathcal{T}(R)}. \tag{5.3}$$

Thus, the calculation of the exit probabilities of ions that entered on the left consists in splitting the probability influx $\mathcal{T}(L)$ into the *cis* flux $\mathcal{T}(L|L)$ and the *trans* flux $\mathcal{T}(R|L)$, and applying Eqs. (5.2). Next, we must express $\mathcal{T}(L|L)$ and $\mathcal{T}(R|L)$ in terms of the solution of an appropriate boundary value problem. In order to isolate the probability flux entering on the left, we have to eliminate the flux entering on the right. Therefore, we impose a zero-influx condition on the right but we do not impose any boundary condition on the left. Instead, we solve the problem in the interval $x_L<x<1$,

assuming that far away in the solution on the left there is a mechanism that maintains the given concentration there (e.g., a source).

Interestingly, in experiments radioactive tracer is often placed on *just* one side of a reaction region or the other to estimate the ionic fluxes $J(R|L)$ and $J(L|R)$, really the steady state and mean value of the fluxes. In this particular experimental situation, the probability flux and the ionic fluxes coincide, if the incoming flux in both cases is normalized to 1.

We denote by $p(x,v|L)$ the pdf of trajectories that enter the reaction region on the left while the right end is blocked for entering trajectories. The total influx on the left is then

$$\mathcal{T}(L)=\int_0^\infty vp(0,v|L)dv. \tag{5.4}$$

The function $p(x,v|L)$ is the solution of the Fokker–Planck equation (4.4) in the strip $x_L<x<1$, $-\infty<v<\infty$ with the boundary condition

$$\mathcal{T}(1,v|L)\cdot\nu=0 \quad \text{for } v<0, \tag{5.5}$$

where ν is the unit outer normal to the boundary. The boundary condition (5.5) can be written as a condition for the pdf $p(x,v|L)$ as

$$p(1,v|L)=0 \quad \text{for } v<0. \tag{5.6}$$

The *cis* flux $\mathcal{T}(L|L)$ and the *trans* flux $\mathcal{T}(R|L)$ are the conditional effluxes of probability defined in terms of the flux vector $\mathbf{J}(x,v)$ of Eq. (4.7) by

$$\mathcal{T}(L|L)\equiv\int_{-\infty}^0 \mathbf{J}(0,v|L)\cdot\nu dv=-\int_{-\infty}^0 vp(0,v|L)dv, \tag{5.7}$$

$$\mathcal{T}(R|L)\equiv\int_0^\infty \mathbf{J}(1,v|L)\cdot\nu dv=\int_0^\infty vp(1,v|L)dv. \tag{5.8}$$

Similarly, $\mathcal{T}(R|R)$ is calculated from the pdf $p(x,v|R)$ that satisfies the Fokker–Planck equation (4.4) in the strip $0<x<x_R$, $-\infty<v<\infty$ with the boundary condition

$$p(0,v|R)=0 \quad \text{for } v>0. \tag{5.9}$$

As above, we have

$$\mathcal{T}(R|R)\equiv\int_0^\infty \mathbf{J}(1,v|R)\cdot\nu dv=\int_0^\infty vp(1,v|R)dv, \tag{5.10}$$

$$\mathcal{T}(L|R)\equiv\int_{-\infty}^0 \mathbf{J}(1,v|R)\cdot\nu dv=-\int_{-\infty}^0 vp(1,v|L)dv. \tag{5.11}$$

Next, we calculate the conditional residence times, also called mean first passage times (MFPTs), $\bar{\tau}(j|i)$, ($i=L,R$, $j=L,R$), taken by an ion that enters at end i of the reaction region (with velocity pointing into the reaction region) to reach end j of the reaction region (with velocity pointing out of the reaction region), given that it exits there. Note that in general the (unconditional) mean first passage time from i to j is infinite, because there is a finite probability that ions will exit on the other side and so never get to j; that is, the time

they take to get to j is infinite. The contribution of those trajectories to the mean first passage time to reach j is infinite and thus so is the MFPT. The *conditional* MFPT is, however, finite because conditioning selects only those trajectories that do get to j. The infinite MFPT's found in the analytical treatment of the mean flux[11] showed clearly the need for an explicit stochastic analysis of the problem.

Consider the conditional mean time, $\bar{\tau}(L|L)$, taken by an ion that enters the reaction region on the left to exit the reaction region, given that it exits on the left. Note that the trajectories of such ions are conditioned on both end points of their path rather than on just the initial point. Now, to distinguish the two cases, we define the general diffusion (i.e., random) process $[x(t), v(t)]$ and its subset the (doubly) conditioned random process $[x^*(t), v^*(t)]$, with trajectories that begin in the bath on the left with positive velocities having the steady state (but not equilibrium) distribution of that bath, and reach the left end of the reaction region with negative velocities (and therefore leave the reaction region), before they reach the right end. If the random first passage time of any trajectory to the left is called τ_L, and that to the right is called τ_R, the terminal condition is the event $\{\tau_L < \tau_R\}$.

The singly conditioned pdf $p(x, v, t|L)$ is the probability density of finding a trajectory of the (general) process $[x(t), v(t)]$ at the point (x, v) at time t, given that it started on the left. The trajectory can exit either on the left or on the right. On the other hand, the doubly conditioned pdf $p^*(x, v, t|L, L)$ represents the probability density of finding a trajectory of the general process $[x(t), v(t)]$, given that it starts on the left and also ends on the left, that is to say, given that the trajectory is a member of the doubly conditioned class of trajectories, the process $[x^*(t), v^*(t)]$. Note that the trajectories $[x^*(t), v^*(t)]$ form but one of the several classes of trajectories of the unconditional process $[x(t), v(t)]$.

The pdf $p(x, v, t|L)$ is the solution of the time dependent Fokker–Planck equation (4.5) with the boundary condition (5.5). It is shown in Ref. 7, p. 195, pp. 261–263, Eq. (9.1) in particular, that the pdfs of the doubly and singly conditioned processes are related by

$$p^*(x, v, t|L, L) = p(x, v, t|L) \frac{Pr(\tau_L < \tau_R | x, v)}{Pr(\tau_L < \tau_R | L)}. \quad (5.12)$$

The conditional MFPT is given by[7,14,15]

$$\bar{\tau}(L|L) = \int_0^\infty \int_{\mathscr{D}} \int p^*(x, v, t|L, L) dx \, dv \, dt \quad (5.13)$$

$$= \int_0^\infty \int_{\mathscr{D}} \int p(x, v, t|L) \frac{Pr(\tau_L < \tau_R | x, v)}{Pr(\tau_L < \tau_R | L)} dx \, dv \, dt. \quad (5.14)$$

Denoting $P(L|x, v) \equiv Pr(\tau_L < \tau_R | x, v)$ and $P(L|L) = Pr(\tau_L < \tau_R | L)$ [see Eq. (5.2)], we can write Eq. (5.14) as

$$\bar{\tau}(L|L) = \frac{1}{P(L|L)} \int_{\mathscr{D}} \int p(x, v|L) P(L|x, v) dx \, dv. \quad (5.15)$$

We now have to calculate the two probability functions in the double integral. The function $p(x, v|L)$ is the solution

of the boundary value problem (4.4), (5.6) with a line of sources at $x = x_L$. The function $P(L|x, v)$ is the probability that a trajectory starting at (x, v) exits on the left. It follows[5] that $P(L|x, v)$ is the solution of the backward equation

$$v \frac{\partial P(L|x, v)}{\partial x} + \beta(x)\epsilon \frac{\partial^2 P(L|x, v)}{\partial v^2}$$

$$- \left[\beta(x) v + \frac{d\Phi(x)}{dx} \right] \frac{\partial P(L|x, v)}{\partial v} = 0 \quad (5.16)$$

with the boundary conditions

$$P(L|0, v) = 1 \quad \text{for } v < 0,$$
$$P(L|1, v) = 0 \quad \text{for } v > 0. \quad (5.17)$$

The function $P(R|x, v) = 1 - P(L|x, v)$ satisfies the same backward equation,

$$v \frac{\partial P(R|x, v)}{\partial x} + \beta(x)\epsilon \frac{\partial^2 P(R|x, v)}{\partial v^2}$$

$$- \left[\beta(x) v + \frac{d\Phi(x)}{dx} \right] \frac{\partial P(R|x, v)}{\partial v} = 0 \quad (5.18)$$

with the boundary conditions

$$P(R|0, v) = 0 \quad \text{for } v < 0,$$
$$P(R|1, v) = 1 \quad \text{for } v > 0. \quad (5.19)$$

Assuming $\mathscr{T}(L) = 1$, the double integral $\int_{\mathscr{D}} \int p(x, v|L) dx \, dv$ is the contents of the reaction region, because nothing enters on the right. The double integral

$$N(L|L) \equiv \int_{\mathscr{D}} \int p(x, v|L) P(L|x, v) dx \, dv \quad (5.20)$$

is therefore the conditional contents of LL trajectories in the reaction region.

It can be shown (see Appendix B) that rather than calculating the double integral in Eq. (5.15), the conditional MFPT, $\bar{\tau}(L|L)$, can be calculated from the solution of the following boundary value problems. First, calculate $p(x, v|L)$ from the boundary value problem (4.4), (5.6), as described above, then calculate the solution to another boundary value problem, now with $p(x, v|L)$ as a *source* density, for an unknown quantity $q(x, v|L)$,

$$\mathscr{L} q(x, v|L) = -p(x, v|L) \quad \text{for } (x, v) \in \mathscr{D} \quad (5.21)$$

with the boundary conditions

$$q(0, v|L) = 0 \quad \text{for } v > 0,$$
$$q(1, v|L) = 0 \quad \text{for } v < 0. \quad (5.22)$$

Then, according to Eqs. (5.15) and (5.7) we have the nearly symmetrical equation

$$\bar{\tau}(L|L) = \frac{\int_{-\infty}^0 v q(0, v|L) dv}{\int_{-\infty}^0 v p(0, v|L) dv} = \frac{-\int_{-\infty}^0 v q(0, v|L) dv}{\mathscr{T}(L|L)}. \quad (5.23)$$

In view of Eq. (5.7), Eqs. (5.15) and (5.23) can be written as

$$\mathcal{T}(L|L) = \frac{N(L|L)}{\bar{\tau}(L|L)}, \tag{5.24}$$

in analogy with the unconditional formula given in Refs. 4, 13, and 15.

The other conditional mean first passage times can be calculated from

$$\bar{\tau}(R|L) = \frac{1}{P(R|L)} \int_{\mathscr{D}} \int p(x,v|L)P(R|x,v)dx\,dv, \tag{5.25}$$

where $P(R|x,v)$ is the probability that a trajectory starting at (x,v) exits on the right,

$$\bar{\tau}(R|R) = \frac{1}{P(R|R)} \int_{\mathscr{D}} \int p(x,v|R)P(R|x,v)dx\,dv, \tag{5.26}$$

and

$$\bar{\tau}(L|R) = \frac{1}{P(L|R)} \int_{\mathscr{D}} \int p(x,v|R)P(L|x,v)dx\,dv. \tag{5.27}$$

VI. CIS AND TRANS PROBABILITIES AND FLUXES

We turn now to the large friction expansion of the pdf $p(x,v|L)$ considered in Sec. V. The large friction expansion of the pdf $p(x,v|L)$ is not as obvious as that of $p(x,v)$ in Sec. IV. The difference between the expansions arise from the boundary conditions and their interpretation. Since no restrictions were imposed at the boundary on entering and exiting trajectories in the treatment of Sec. IV, no boundary layers arise in the Smoluchowski expansion (4.13)–(4.22). In contrast, in Sec. V a boundary condition (5.6) is used to separate unidirectional probability fluxes, and so a boundary layer is present at $x=1$. A similar situation was considered in Refs. 16, 14, and 17.

Now, we further split the unidirectional probability fluxes into their cis and trans components. In particular, to split the incoming flux from the left into its components, we simply take the flux of the Fokker–Planck equation, with the boundary condition (5.6) at $x=0$ that the Smoluchowski expansion (4.22) produces, and split it into its cis and trans components. Specifically, the solution is given in the strip $0<x<1$, $-\infty<v<\infty$ by the expansion

$$p(x,v|L) = \frac{e^{-v^2/2\epsilon}}{\sqrt{2\pi\epsilon}} \left[p(x|L) + \text{b.l.}(x,v) + \frac{\mathcal{T}v}{\epsilon} + \text{h.o.t.} \right], \tag{6.1}$$

with the following notation: b.l.(x,v) means the value at the point (x,v) of the boundary layer formed at $x=1$, h.o.t. means "higher order terms in powers of $1/B$." The reduced density, $p(x|L)$, is the solution of the Smoluchowski equation

$$\frac{d}{dx} \left(\frac{1}{\beta(x)} \{ [\Phi'(x)p(x|L)]' + \epsilon p''(x|L) \} \right) = 0$$

$$\text{for } 0<x<1 \tag{6.2}$$

with an absorbing condition at the right end point. [The right end point for $p(x|L)$ is actually located at $x_R^* = 1 + O(1/\beta)$.[14,16,17]] The boundary layer, b.l.(x,v) that arises from the boundary condition at $x=1$, is transcendentally small at $x=0$,[14,17] because the reaction region $[0,1]$ is much longer than the boundary layer on the right. Near $x=0$ the boundary layer function (from the other side) b.l.(x,v), is a smooth function. The probability current (i.e., the probability flux) of $p(x|L)$, denoted $\mathcal{T}$, is constant in the interval $0<x<1$. This gives

$$p(x|L) = \frac{\mathcal{T}}{\epsilon} e^{-\Phi(x)/\epsilon} \int_x^1 \beta(s)e^{\Phi(s)/\epsilon}ds, \tag{6.3}$$

so that

$$p(0|L) = \frac{\mathcal{T}}{\epsilon} e^{-\Phi(0)/\epsilon} \int_0^1 \beta(x)e^{\Phi(x)/\epsilon}dx. \tag{6.4}$$

Now, the incoming probability current on the left (none flows on the right!) is given by

$$\mathcal{T}(L) = \int_0^\infty v p(x,v|L)dv = \sqrt{\frac{\epsilon}{2\pi}} p(0|L)$$

$$+ \int_0^\infty \text{b.l.}(0,v)v\,dv + \frac{\mathcal{T}}{2}, \tag{6.5}$$

and the outgoing flux on the left is given by

$$\mathcal{T}(L|L) = -\int_{-\infty}^0 v p(x,v|L)dv$$

$$= \sqrt{\frac{\epsilon}{2\pi}} p(0|L) - \int_{-\infty}^0 \text{b.l.}(0,v)v\,dv - \frac{\mathcal{T}}{2}. \tag{6.6}$$

Neglecting the contribution of the remote boundary layer, as we may, and using Eqs. (6.1) and (6.4), we obtain

$$\mathcal{T}(L) = \frac{\mathcal{T}}{\sqrt{2\pi\epsilon}} e^{-\Phi(0)/\epsilon} \int_0^1 \beta(x)e^{\Phi(x)/\epsilon}dx + \frac{\mathcal{T}}{2}. \tag{6.7}$$

The trans flux is given by

$$\mathcal{T}(R|L) = \mathcal{T}(L) - \mathcal{T}(L|L) = \mathcal{T}. \tag{6.8}$$

Now, by Eq. (5.2),

$$P(R|L) = \frac{\mathcal{T}(R|L)}{\mathcal{T}(L)}$$

$$= \frac{\mathcal{T}}{\frac{\mathcal{T}}{\sqrt{2\pi\epsilon}} e^{-\Phi(0)/\epsilon}\int_0^1 \beta(x)e^{\Phi(x)/\epsilon}dx + \frac{\mathcal{T}}{2}}$$

$$= \frac{1}{\frac{1}{\sqrt{2\pi\epsilon}} e^{-\Phi(0)/\epsilon}\int_0^1 \beta(x)e^{\Phi(x)/\epsilon}dx + \frac{1}{2}}. \tag{6.9}$$

If the incoming probability flux $\mathcal{T}(L)$ is normalized to 1, then $\mathcal{T} = P(R|L)$. This gives

$$\mathscr{T} = \frac{1}{\frac{1}{\sqrt{2\pi\epsilon}} e^{-\Phi(0)/\epsilon} \int_0^1 \beta(x) e^{\Phi(x)/\epsilon} dx + \frac{1}{2}}. \qquad (6.10)$$

It should be noted that $\mathscr{T}$ does not necessarily represent the physical ionic current, because in the physical problem there are no boundary conditions at the ends of the reaction region that correspond to the no flux conditions introduced in the mathematics to define and separate the unidirectional probability fluxes.

In the limit of large β, we obtain

$$P(R|L) = \sqrt{2\pi\epsilon} \, \frac{e^{\Phi(0)/\epsilon}}{\int_0^1 \beta(x) e^{\Phi(x)/\epsilon} dx}. \qquad (6.11)$$

Similarly,

$$P(L|R) = \sqrt{2\pi\epsilon} \, \frac{e^{\Phi(1)/\epsilon}}{\int_0^1 \beta(x) e^{\Phi(x)/\epsilon} dx}. \qquad (6.12)$$

Trajectories must go either to the left or right—they are not stored in the channel—and so the probabilities of *cis* trajectories are simply the complement of the *trans* probabilities, as mentioned previously in Eqs. (5.2) and (5.3),

$$P(L|L) = 1 - P(R|L) \qquad (6.13)$$

and

$$P(R|R) = 1 - P(L|R). \qquad (6.14)$$

Nernst–Planck flux in terms of conditional exit probabilities

It has always been intuitively clear that a relation should exist between the unidirectional fluxes of the flux formula (3.6) and the conditional probabilities of the trajectories that carry that flux. However, the proper stochastic definition of those unidirectional fluxes and conditional probabilities was not clear (see Ref. 11) and so the implementation of the intuition was not known.

Our analysis shows that the conditional fluxes (i.e., the unidirectional fluxes of ions) are proportional to the conditional exit probabilities (6.11) and (6.12), the proportionality constant being the concentration at the source of the trajectories. In particular, the Nernst–Planck flux formula Eq. (3.6) can be written as

$$J = \alpha [C_L P(R|L) - C_R P(L|R)], \qquad (6.15)$$

where the numerical factor α is given by

$$\alpha = \sqrt{\frac{1}{2\pi\epsilon}}. \qquad (6.16)$$

The net ionic flux from left to right, Eq. (3.6), is therefore the difference between the probability fluxes, normalized by the concentrations on both sides of the reaction region. [If C_L, C_R are time dependent, Eq. (6.15) can be generalized by solving the time dependent Smoluchowski equations (4.20) and (3.7).]

Simulations show [Ref. 11, Eq. (7.5)] that the flux formula Eq. (3.6) can be expressed in terms of the relative numbers of random trajectories that start inside the reaction re-

gion at a distance Δx from an absorbing boundary and make it across the reaction region to the other boundary. These numbers were related to an analytical expression [Ref. 11, Eq. (2.24)] that was derived from the Nernst–Planck model. Equation (6.15) provides a probabilistic derivation of both the analytical and statistical results of Ref. 11.

Physiologists have estimated the components ("unidirectional fluxes") of the (mean steady-state) net flux by placing radioactive tracer on one side of a system or the other since radioactive isotopes became available in the 1940s. Thus, the physiologists' unidirectional fluxes correspond precisely to one set of trajectories, described by one set of conditional probabilities, or the other, as they should if the probabilistic and tracer analysis consider the same trajectories, albeit in quite different experimental and theoretical traditions. Note, however, that physiologists have usually ignored the existence of *cis* fluxes and their contribution to open-channel noise (see Sec. IX), perhaps because their mean value is zero in the steady-state measured in traditional experiments.

VII. RESIDENCE TIMES (MFPTs)

The conditional mean first passage times $\bar{\tau}(i|j)$, $(i = L, R, \; j = L, R)$ can also be calculated in the large friction limit. We use the approximation Eq. (6.1) with Eq. (6.3) for $p(x, v|L)$ in the double integral in Eq. (5.15). The large friction approximation to $P(R|x, v)$ is found directly from the backward equation (5.18). Using the expansion

$$P(R|x, v) = P^0(R|x, v) + \frac{1}{B} P^1(R|x, v) + \cdots, \qquad (7.1)$$

we find that $P^0(R|x, v)$ is independent of v [we denote it by $P^0(R|x)$] and that it satisfies the reduced backward equation

$$\epsilon \frac{d^2 P^0(R|x)}{dx^2} - \Phi'(x) \frac{dP^0(R|x)}{dx} = 0 \qquad (7.2)$$

with the boundary conditions

$$P^0(R|0) = 0, \;\; P^0(R|1) = 1. \qquad (7.3)$$

Thus,

$$P^0(R|x) = \frac{\int_0^x e^{\Phi(s)/\epsilon} ds}{\int_0^1 e^{\Phi(s)/\epsilon} ds}. \qquad (7.4)$$

Next, we combine the expression (5.25) for $\bar{\tau}(R|L)$ and the expression (6.11) for $P(R|L)$; the expressions (6.1) and (6.3) for $p(x, v|L)$; and the expressions (7.1) and (7.4) for $P(R|x)$, and write

$$\bar{\tau}(R|L) = \frac{1}{\epsilon \int_0^1 e^{\Phi(s)/\epsilon} ds} \int_0^1 e^{-\Phi(x)/\epsilon}$$
$$\times \left[\int_x^1 \beta(s) e^{\Phi(s)/\epsilon} ds \int_0^x e^{\Phi(s)/\epsilon} ds \right] dx \qquad (7.5)$$

after normalizing the entrance probability flux density $v p(x, v|L)$ by $\mathscr{T}(L) = 1$. Similarly, we obtain

$$\bar{\tau}(L|L) = \frac{\mathscr{T}}{\epsilon(1 - \mathscr{T}) \int_0^1 e^{\phi(x)/\epsilon} dx} \int_0^1 e^{-\Phi(x)/\epsilon} ds$$

$$\times \left[\int_x^1 \beta(s) e^{\Phi(s)/\epsilon} ds \int_x^1 e^{\Phi(s)/\epsilon} ds \right] dx, \quad (7.6)$$

where $\mathscr{T}$ is given by Eq. (6.10). In particular, for a free particle (no external field) with large constant friction [$\beta(x)$ = const. $\gg 1$] we obtain

$$\bar{\tau}(L|L) = \frac{1}{3} \sqrt{\frac{2\pi}{\epsilon}}. \quad (7.7)$$

The mean time an ion spends in the reaction region, given that it entered on the left, is given by

$$\bar{\tau}(L) = \bar{\tau}(L|L) P(L|L) + \bar{\tau}(R|L) P(R|L)$$

$$= \int_{\mathscr{D}} \int p(x,v|L) [P(L|x,v) + P(L|x,v)] dx \, dv$$

$$= \int_{\mathscr{D}} \int p(x,v|L) dx \, dv. \quad (7.8)$$

Using the same approximations as above, we find that

$$\bar{\tau}(L) = \sqrt{\frac{2\pi}{\epsilon}} \frac{\int_0^1 e^{[\Phi(0)-\Phi(x)]/\epsilon} \int_x^1 \beta(s) e^{\Phi(s)/\epsilon} ds \, dx}{\int_0^1 \beta(x) e^{\Phi(x)/\epsilon} dx}. \quad (7.9)$$

In particular, for a free particle,

$$\bar{\tau}(L) = \frac{1}{2} \sqrt{\frac{2\pi}{\epsilon}}. \quad (7.10)$$

We observe that as the friction $\beta(x) \to \infty$ [see Eq. (4.8)], the *trans* probability $P(R|L)$ vanishes and the *trans* time $\bar{\tau}(R|L)$ becomes infinite. Obviously, $P(L|L) \to 1$, but $\bar{\tau}(L|L)$ remains finite, namely,

$$\lim_{\beta(x)\to\infty} \bar{\tau}(L|L) = \mathscr{T}_\infty \int_0^1 e^{-\Phi(x)/\epsilon} ds$$

$$\times \left[\int_x^1 \beta_0(s) e^{\Phi(s)/\epsilon} ds \int_x^1 e^{\Phi(s)/\epsilon} ds \right] dx, \quad (7.11)$$

where

$$\mathscr{T}_\infty = \sqrt{\frac{2\pi}{\epsilon}} \frac{e^{\Phi(0)/\epsilon}}{\int_0^1 \beta_0(t) e^{\Phi(x)/\epsilon} dx \int_0^1 e^{\Phi(x)/\epsilon} dx}. \quad (7.12)$$

In the large friction limit, the mean time that an ion entering on the left spends in the reaction region is given by

$$\lim_{\beta(x)\to\infty} \bar{\tau}(L) = \sqrt{\frac{2\pi}{\epsilon}} \frac{\int_0^1 e^{[\Phi(0)-\Phi(x)]/\epsilon} \int_x^1 \beta_0(s) e^{\Phi(s)/\epsilon} ds dx}{\int_0^1 \beta_0(x) e^{\Phi(x)/\epsilon} dx}. \quad (7.13)$$

The (apparently paradoxical) finite value of $\bar{\tau}(L|L)$ and of $\bar{\tau}(L)$ even in the large friction limit can be understood as follows. Consider the simplest example of an overdamped free particle, with constant friction β, that enters the reaction region on the left with positive velocity v_0. On the average, it will penetrate into the reaction region a distance $x_0 = v_0/\beta$.[18] The mean time for a Brownian particle with diffusion coefficient D to exit the interval $[0,1]$ from an ini-

tial point x_0 is $x_0(1-x_0)/D$.[5] Since D is inversely proportional to β,[18] we find that the mean exit time remains finite even as $\beta \to \infty$.

VIII. HIGH BARRIERS

The traditional analysis of chemical kinetics (Ref. 4) uses rates to describe flux over large barriers, and so we should specialize our results to that case. We consider, without loss of generality, the unidirectional flux into $C_R = 0$, for the overdamped (Smoluchowski) case of high friction, putting a source at $x = x_L$ and an absorbing boundary at $x = 1$. The Smoluchowski equation is given by

$$\frac{d}{dx} \left(\frac{1}{\beta(x)} \{ [\Phi'(x) p(x|L)]' + \epsilon p''(x|L) \} \right) = -\delta(x - x_L), \quad (8.1)$$

with the boundary condition

$$p(1|L) = 0. \quad (8.2)$$

The solution of Eqs. (8.1), (8.2) is

$$p(x|L) = \frac{\mathscr{T}}{\epsilon} e^{-\Phi(x)/\epsilon} \int_x^1 \beta(s) e^{\Phi(s)/\epsilon} H(s - x_L) ds, \quad (8.3)$$

where $H(x)$ is the Heaviside step function. Now, we assume that the potential $\Phi(x)$ forms a well with its bottom at $x = 0$, say, and with a top at a point $x = x_C$, where $0 < x_C < 1$. Small ϵ represents a high barrier.

Assuming a constant concentration, C_L, at $x = 0$, we get from Eq. (8.3) in the limit of small ϵ

$$\mathscr{T} = \frac{C_L \omega_C}{\beta(0) \sqrt{2\pi\epsilon}} e^{-\Delta\Phi/\epsilon}, \quad (8.4)$$

where the barrier height is given by

$$\Delta\Phi \equiv \Phi(x_C) - \Phi(0)$$

and

$$\omega_C \equiv \sqrt{-\Phi''(x_C)},$$

see Ref. 11.

This equation is *not* identical to Kramers' formula[4] because that traditional result expresses the flux in terms of the total population of reactant molecules rather than their concentration. The reactant population is the integral of $p(x|L)$ in the reactant well, that is,

$$N_L \equiv \int_{x_L}^{x_C} p(x|L) dx.$$

Using Eq. (8.3), we obtain Kramers' result,[4]

$$\mathscr{T} = \frac{N_L \omega_0 \omega_C}{2\pi\beta(0)} e^{-\Delta\Phi/\epsilon}, \quad (8.5)$$

where

$$\omega_0 \equiv \sqrt{\Phi''(0)}.$$

It is interesting to calculate the conditional MFPTs in the limit of a high barrier. Assuming for simplicity that $\beta(x) = \beta$ = const., we obtain for $\epsilon \ll 1$ (see Appendix C),

$$\bar{\tau}(R|L) \sim \frac{\pi}{2\sqrt{\frac{8}{2\pi}-1}} \frac{\beta}{\omega_C^2} \tag{8.6}$$

and

$$\bar{\tau}(L|L) \sim \frac{2\pi}{\omega_0}. \tag{8.7}$$

It is remarkable that the conditional MFPTs are independent of the barrier height in this limit. But the conditional mean first-passage time $\bar{\tau}(R|L)$ [of Eq. (8.6)] is a property of just those trajectories that cross the barrier and make it to the other side. The other trajectories—the LL ones—do not cross the barrier at all; they exit at the absorbing boundary after their (conditional mean) first-passage time $\bar{\tau}(L|L)$, cf. Eq. (8.7).

IX. SUMMARY AND DISCUSSION

A. Flux and high friction

In this paper, we show that the full Langevin equation, rather than the reduced Smoluchowski equation, is needed to describe ions diffusing from one concentration to another, whatever the friction. Even if ionic motion along the trajectories of the Langevin equation (3.9) is grossly overdamped, the system is not in equilibrium because flux is present. The velocity distribution is not Maxwellian [see Eq. (4.24)], but rather contains an asymmetric term, proportional to the flux of ions. In addition, the displacement and velocity of overdamped ions are not independent, as is the case in equilibrium or nearly equilibrium systems (e.g., systems with high barriers), but rather significantly correlated. [Indeed, that is why flux flows in the consistent treatment of high friction given in Eqs. (4.23) and (4.24).] It follows that the joint probability density function of displacement and velocity does not factor into a solution of the Smoluchowski (Nernst–Planck) equation multiplied by a Maxwellian density of velocities (that has zero net flux), as is usually stated.[4,6,13]

Obviously, a theory that implies zero flux should not be used to predict flux. The traditional Smoluchowski limit implies a Maxwellian distribution of velocities and zero flux. It cannot consistently describe a finite flux. It should not be used to describe experiments performed away from equilibrium, in which flux is present.

B. Chemical reaction as a diffusion

Our analysis shows that diffusion between concentration boundary conditions can be described as a chemical reaction, without approximation, no matter what the shape of the potential barrier between reactant and product, because each unidirectional flux in Eq. (6.15) and Eq. (3.6) is strictly proportional to the concentration at its source, for a potential barrier of any shape. Thus, each unidirectional flux—and their difference the net flux—follow the law of mass action (if barriers are independent of concentration) no matter what the shape of the potential barrier that limits conversion (i.e., diffusion) from reactant to product, if they flow between regions of fixed concentrations.

Chemistry is built upon the idea of a reaction, in the simplest case $\mathbf{A} \rightleftharpoons \mathbf{B}$, where a boldface uppercase letter, e.g., $\mathbf{A}$, represents the concentration of species A, $\mathbf{B}$ likewise, and $\rightleftharpoons$ represents the process converting A to B. In the simplest case, the process is described by the law of mass action, giving a rate of reaction (i.e., rate of change of concentration of product $\mathbf{B}$) described by a rate constant, independent of time and concentration of A and B. The simplest case is the paradigm of a chemical reaction; it is the archetype that is taught in elementary courses, and it is the mold into which other more complex cases are cast.

The idea of a chemical reaction is generalized in physical chemistry into a process in a multidimensional phase space, in which the movement of a particle along the reaction path, over barriers and through wells of potential, describes the conversion of A to B, and the concentrations of A and B generally appear as boundary conditions. In most cases, this generalization has been studied in the limit of high barriers, because the species A and B are well defined in that case, and the analysis of the conversion process is dramatically simplified if flux is determined only at one location, the top of a barrier (see Sec. VIII). One difficulty with the high barrier approximation, however, is that it implies a near equilibrium, nearly no flux system. Another is that it tends to obscure the role of boundary conditions, namely the concentrations of reactant A and product B. If of interest, the effect of boundary conditions and flux must be reinstated later, after they have been approximated away, and that is difficult to do without introducing inconsistencies.

The analysis presented here gives boundary conditions and partial differential equations equal weight, thereby increasing the reality and complexity of the mathematical analysis. Nonetheless, analytical expressions for the flux are derived with simple physical and stochastic meaning; the approximation of high barriers can still be invoked, but now after the problem has been solved and the role of boundary conditions and flux has been displayed explicitly and consistently.

To our surprise, this approach, that starts by making a simple problem complex (because it does not assume large barriers), leads eventually to a simple result, valid under a range of conditions including large barriers. In fact, the flux formula Eq. (6.15), true for all shapes and sizes of potential barriers, is so simple that further approximation seems unnecessary, and unwise. For example, $\alpha P(B|A)C_A$ is the (unidirectional) flux of $A \rightarrow B$ and $\alpha P(A|B)C_B$ is the flux of $B \rightarrow A$, with the obvious change of notation from location to species. Indeed, the chemical reaction

$$A \underset{k_b}{\overset{k_f}{\rightleftharpoons}} B, \tag{9.1}$$

provides an irresistible generalization of the idea of rate "constant" to chemical reactions with concentration boundary conditions and arbitrary potential barriers, using the obvious definitions $k_f = \alpha P(B|A)$ and $k_b = \alpha P(A|B)$.

With this generalization, the law of mass action (with rate constant independent of concentration) will be true *even if barriers are low*, if concentrations at the boundaries are maintained and the barriers are independent of concentration.

Of course, the same chemical reaction does *not* follow simple rate laws if other boundary conditions are imposed. For example, if the same chemical reaction (i.e., a stochastic process with the same dynamics, with the same profile of potential barriers, same diffusion coefficients and so on, differing only in its behavior at the boundaries of the system) is studied after a sudden change of concentration of species **A**, the time course of the relaxation of concentration of **A** or **B** will not in general be exponential (if barriers are low for example) and simple rate laws do not apply. The law of mass action does not apply in its simplest formulation. We see then that the experimental imposition of concentration boundary conditions may lead to significant simplification in analysis, e.g., in the case of small barriers.

Our version of the law of mass action may be useful in a number of other cases as well as in the case of small barriers (1) when the other approximations of high barrier theory (e.g., location away from the boundary) are not appropriate; (2) when the dependence on boundary conditions is itself of practical interest (as in the biological application); (3) when species are not well determined, for example, when an intermediate species lying "between" *A* and *B* is observed experimentally and that species does not lie between two high barriers.

C. Numerical simulations

The explicit formulas for the conditional probabilities, fluxes, contents, and residence times given in this paper are valid when friction is large. In many applications, however, closed form expressions for the solution of the Fokker–Planck equation, or its approximation, are not available, for example, if the system is not overdamped, if ions interact directly with each other, or if the Fokker–Planck equation is coupled to other differential equations, e.g., to the Poisson equation determining the electrostatic potential. In these cases, numerical simulations of trajectories or numerical solutions of the partial differential equations are needed.

Even in the most general case, the conditional probabilities, fluxes, contents, and residence times given in this paper (and the relations among them) remain well defined. The probability measures can be estimated from numerical simulations of ion dynamics if analysis is not practicable. The formulation presented here allows much more efficient simulations of trajectories than used previously[11] because all trajectories are used to estimate parameters.

When simulating the Langevin equation, trajectories have to be started at $x = 0$ and $v > 0$, and at $x = 1$ and $v < 0$. The velocities v should be chosen at random, from the nonequilibrium distribution Eq. (6.1), cf. Eq. (4.24). Whenever a trajectory exits the strip domain, it should be terminated.

The following data should be recorded and processed according to the formulas of Sec. V:

(1) The number of RL, LR, LL, and RR trajectories.
(2) The duration of the trajectory.
(3) The exit point of the trajectory, that is, L or R, and v at the exit point.

Even in the general case, where dynamics are complex and do not follow the Langevin equation, diffusion can still be treated as a chemical reaction with no approximation, provided that the potential functions and diffusion coefficients are not significant functions of the concentration of reactant or product. If they are significant functions, the representation of the system as a chemical reaction will probably mislead more than inform and so should be replaced by direct consideration of the experimental observables, e.g., concentrations and fluxes in traditional experiments.

D. Biological applications

This work was motivated by the biological problem that interested Fick, the motion of ions across biological membranes. In the biological context (of, for example, ion permeation through channels in membranes[8]), barriers cannot be assumed large because many channels are selected by evolution to pass large currents and fluxes;[19] concentration boundary conditions are unavoidable (in contrast to chemical problems, where concentration boundary conditions are often obscured by high barriers); and stochastic properties are routinely measured. Thus, we are forced to a stochastic theory of ionic permeation, the first installment of which is presented here; the stochastic analysis of diffusion between concentration boundary conditions.

Ionic channels determine the diffusive flows in the biological systems that originally interested Fick. Before channels were studied individually, macroscopic currents were usually interpreted as flows through a fixed area of homogeneous membrane. We now know that ions flow through individual protein molecules—ion channels—that can open and close. The number of open channels is anything but fixed; the phenomenon of gating, and thus the time dependent phenomena of channels, arise from changes in the number of open channels and thereby in the area of membrane through which current flows. Traditional interpretations of macroscopic currents must be discarded, because the macroscopic currents come from a varying number of channels; traditional theories can be retained, but now as descriptions of flow through one protein molecule, a single open channel.

A single open channel is a unique object for investigation. It is a single protein molecule performing a natural function of great biological and medical significance, fully as important for the life of cells as the catalytic functions of most proteins (i.e., enzymes). The mechanism of channel function is much simpler than of enzymes, because covalent bonds do not change as ions permeate channels. For millenia (at least since Aristotle), a goal of biological research has been the prediction of function, given structure. For nearly a century and a half, ever since molecules were discovered and kinetic theory was invented, biologists have dreamed of predicting function from atomic structure, using physical theory. Channels are a more promising subject for such research than any class of proteins of comparable biological and medical importance, in the opinion of at least one of us.[19]

E. Open channel noise and the counter model

Current flow through a single open channel is noisy, so characteristically noisy that it begs for a stochastic description and identification, if not analysis. A stochastic theory of

open channel noise has been presented by Frehland and co-workers[20] and has been used to interpret experimental results[21-23] in normal conditions and when "slow ions" (i.e., blockers) are present. This theory, however, describes the movement of ions in solution by Eyring's rate theory, originally derived to describe the flux of atoms in gas phase chemical reactions, occurring without friction or interatomic collisions. Rate theory can be reworked into a transition state theory useful in condensed phases, like liquids or proteins where friction and interatomic collisions dominate kinetics,[24] but the theory, reworked or not, requires potential barriers to be large and far removed from the ends of the channel [see, e.g., Eq. (8.4)]; in either case the role of concentration gradients is obscured, even though concentrations have prominent effect in diffusion and biological phenomena.

The traditional description of ionic flow by the Nernst–Planck equation with prescribed concentration boundary conditions gives an expression for the net ionic flux as a function of the concentrations and the potential in the channel [see Eq. (3.6)]. This function depends linearly on the concentrations and depends exponentially on the values of the potential at the endpoints (and on its exponential integral). Thus, for example, if the values of the potential at the endpoints are equal, exchanging the concentrations reverses the flux.

There are several properties of the ionic current measured in real single channels that are hard to accommodate in Nernst–Planck theories. These include current fluctuations, nonlinear dependence of the flux on concentration (saturation), blocking of the channel by slow ions, properties of ratios of unidirectional fluxes, asymmetry of channel phenomena, and so on (Ref. 8, pp. 374–389). In addition, Nernst–Planck models exclude the notion of a channel that admits one ion at a time (a single ion channel).

In order to account for these phenomena in single ion channels, we are analyzing a stochastic model, in which the channel is viewed as a paralyzable counter, similar to the Geiger counter of radioactive decays. In this model a single ion channel is "paralyzed" for the time it is occupied by an ion. The randomness of the model arises because the motion of an ion inside the channel is diffusive and therefore random, so are the time spent in the channel and the time to the arrival of the next ion to the channel; and also ions can enter and exit the channel on either side with certain probabilities.

The random times the channel is occupied or empty account for the fluctuations in open channel current seen experimentally, as they do in theories of shot noise. The finite time that an ion has to spend inside the channel before exiting accounts for the saturation in flux as concentration is increased. It also accounts for blocking of the channel by slow ions.

The stochastic model of the ionic current requires the stochastic description of the ionic trajectories presented here. The stochastic analysis of an ionic channel as a counter of ions will be given in a separate publication.[25]

ACKNOWLEDGMENTS

APPENDIX A: NONDIMENSIONALIZATION

We introduce the following notation. The two sources are placed at the origin and at d. We assume that the motion of an ion of mass m and total charge ze, where z is the valence of the ion, diffusing in a liquid bath, can be described by the Langevin equation

$$m\frac{d^2\tilde{x}}{d\tilde{t}^2} + m\tilde{\beta}(\tilde{x})\frac{d\tilde{x}}{d\tilde{t}} + ze\frac{d\tilde{\Phi}(\tilde{x})}{d\tilde{x}} = \sqrt{2mkT\tilde{\beta}(\tilde{x})}\frac{d\tilde{w}}{d\tilde{t}},$$

(A1)

where $\tilde{\beta}(\tilde{x})$ is the state dependent friction coefficient (per unit mass), k Boltzmann's constant, T is absolute temperature, and $\tilde{w}$ is standard Brownian motion. The function $\tilde{\Phi}(\tilde{x})$ represents the electric potential in the reaction region. We introduce dimensionless variables according to Table I. Note that the dimensionless length of the reaction region is 1. The scaling factor for the potential, $\Delta\Phi$, was chosen to represent the barrier height, if one is well defined. Otherwise it is the thermal energy. This scaling is necessary to keep track of the various orders of magnitude in the Fokker–Planck equation when we use the high friction expansion in Secs. VI and VII. Following earlier practice,[5,15] we use ϵ to describe nondimensional temperature; it need not be small.

APPENDIX B: CALCULATION OF THE CONDITIONAL MFPT FROM BOUNDARY VALUE PROBLEMS

The conditional contents, $N(L|L)$, of LL trajectories in the channel is given by the double integral Eq. (5.20) if $\mathcal{T}(L)=1$, as mentioned in Sec. V. We show below that

$$N(L|L) = -\int_{-\infty}^{0} vq(0,v|L)dv,$$

(B1)

where $q(x,v|L)$ is the solution of the boundary value problem Eqs. (5.21) and (5.22).

First, we observe that according to Ref. 15, the probability of exit at $x=0$, given the initial point (x,v) in $\mathcal{D}$, is the total efflux of probability on the left in a stationary problem with a source at (x,v) and no influx at $x=0$ and $x=1$. That is,

$$Pr(\tau_L < \tau_R | x,v) \equiv P(L|x,v) = -\int_{-\infty}^{0}\eta p(0,\eta|x,v)d\eta,$$

(B2)

where $P(L|x,v)$ is as defined in Sec. V, and $p(\xi,\eta|x,v)$ is the solution of the boundary value problem

$$\mathcal{L}_{\xi,\eta}\,p(\xi,\eta|x,v) = -\delta(\xi-x)\delta(\eta-v)$$

for $(\xi,\eta) \in \mathcal{D}$ and $(x,v) \in \mathcal{D}$ (B3)

with the no influx boundary conditions

$$p(0,\eta|x,v) = 0 \quad \text{for} \quad \eta > 0$$

(B4)

$$p(1,\eta|x,v) = 0 \quad \text{for} \quad \eta < 0.$$

(B5)

TABLE I. Symbols and nondimensionalization.

Name	Dimensional	Dimensionless
Proton charge	e (Coulombs)	
Position	$\tilde{x}$ (m)	$\tilde{x}=xd$
Length of reaction region	d (m)	1
Scaling factor	$\Delta\Phi$ (J/kg)	see below[a]
Electric potential	$\tilde{\Phi}(\tilde{x})$ (J/Coulomb)	$\dfrac{ez}{m}\tilde{\Phi}(\tilde{x})=\Phi(x)\cdot\Delta\Phi$
Time	$\tilde{t}$ (s)	$\tilde{t}=\dfrac{d}{\sqrt{\Delta\Phi}}t$
Absolute temperature	kT (J)	$\epsilon=\dfrac{kT}{m\Delta\Phi}$
Friction coefficient	$\tilde{\beta}(\tilde{x})$ (1/s)	$\tilde{\beta}(\tilde{x})=\dfrac{\beta(x)}{d}\sqrt{\Delta\Phi}$
Diffusion coefficient	$\tilde{D}(\tilde{x})=\dfrac{kT}{m}\tilde{\beta}(\tilde{x})$ (m/s)	$D(x)=\dfrac{\epsilon}{\beta(x)}$
Concentration in bath	$\tilde{C}_{L(R)}$ (#/m³)	$\tilde{C}_{L(R)}=\pi a^2 d C_{L(R)}$
Concentration in reaction region	$\tilde{\rho}(\tilde{x})$ (#/m³)	$\tilde{\rho}(\tilde{x})=\tilde{C}_L\rho(x)$
Source strength	$\tilde{c}_{L(R)}$ (#/s)	$c_{L(R)}=\dfrac{d}{\sqrt{\Phi}}\tilde{c}_{L(R)}$
Flux	$\tilde{\mathbf{J}}$ (#/m² s)	$\mathbf{J}=\dfrac{\pi a^2 d}{\sqrt{\Delta\Phi}}\tilde{\mathbf{J}}$

[a]Scaling factor for electric potential $\Delta\Phi=\max\{kT/m, ez/m[\max\Phi(x)-\min\Phi(x)]\}$.

From the definition Eqs. (5.20) and (B2), it follows that

$$N(L|L)=-\int_{\mathscr{D}}\int\left[p(x,v|L)\int_{-\infty}^{0}\eta p(0,\eta|x,v)d\eta\right]dx\,dv$$

$$=-\int_{-\infty}^{0}\eta q(0,\eta|L)d\eta,$$

where we define

$$q(\xi,\eta|L)\equiv\int_{\mathscr{D}}\int p(x,v|L)p(\xi,\eta|x,v)dx\,dv.$$

Applying the forward operator $\mathscr{L}$ [in the variables (ξ,η)] to $q(\xi,\eta|L)$ and noting that it can be exchanged with the double integral because it acts on nonintegrated variables, we obtain from Eq. (B3),

$$\mathscr{L}_{\xi,\eta}q(\xi,\eta|L)=-\int_{\mathscr{D}}\int p(x,v|L)\delta(\xi-x)$$

$$\times\delta(\eta-v)dx\,dv$$

$$=-p(\xi,\eta|L),\qquad\text{(B6)}$$

which is Eq. (5.21). The boundary conditions Eq. (5.22) follow from Eqs. (B4) and (B5).

APPENDIX C: THE CONDITIONAL MFPT FOR HIGH BARRIERS

With the assumptions of Sec. IX, we have to evaluate $\bar{\tau}(R|L)$ from Eq. (7.5) in the limit $\epsilon\ll1$. First, we note that in this limit

$$I\equiv\int_0^1 e^{\Phi(s)/\epsilon}ds\sim\frac{\sqrt{2\pi\epsilon}}{\omega_C}e^{\Phi(x_C)/\epsilon}.\qquad\text{(C1)}$$

Next, we define

$$\Psi(x)\equiv\int_0^x e^{\Phi(s)/\epsilon}ds$$

and note that $\Psi(1)=I$. For $\beta(x)=\beta=$ const.,

$$\bar{\tau}(R|L)=\frac{\beta}{\epsilon I}\int_0^1 e^{-\Phi(x)/\epsilon}[I-\Psi(x)]\Psi(x)dx.\qquad\text{(C2)}$$

Asymptotically, $\Psi(x_C)\sim\frac{1}{2}I$ and so, for simplicity, we assume the exact equality

$$\Psi(x_C)=\tfrac{1}{2}I.\qquad\text{(C3)}$$

Then, the integrand in Eq. (C2) peaks at x_C. Indeed, writing the exponent of the integrand in the form

$$U(x)\equiv\frac{-\Phi(x)}{\epsilon}+\log[I-\Psi(x)]+\log\Psi(x),\qquad\text{(C4)}$$

we find that

$$U'(x)=\frac{-\Phi'(x)}{\epsilon}+\frac{\Psi'(x)}{\Psi(x)}-\frac{\Psi'(x)}{I-\Psi(x)},$$

$$U''(x)=\frac{-\Phi''(x)}{\epsilon}+\frac{\Psi''(x)}{\Psi(x)}-\frac{\Psi'^2(x)}{\Psi^2(x)}-\frac{\Psi''(x)}{I-\Psi(x)}$$

$$-\frac{\Psi'^2}{[I-\Psi(x)]^2}.$$

Setting $x=x_C$ in Eq. (C5), noting that $\Phi'(x_C)=0$, and using Eq. (C3), we find that $U'(x_C)=0$. Furthermore, using Eq. (C1), we find that

$$U''(x_C)=\frac{\omega_C^2}{\epsilon}\left(1-\frac{8}{2\pi}\right)\equiv-\frac{\omega'^2}{\epsilon},\qquad\text{(C5)}$$

where

$$\omega'\equiv\omega_C\sqrt{\frac{8}{2\pi}-1}.\qquad\text{(C6)}$$

It follows that the integral in Eq. (C2) can be calculated by the Laplace method,[26] yielding Eq. (8.6).

The asymptotic calculation of $\bar{\tau}(L|L)$ is simpler, because the integrand in Eq. (7.6) is maximal at $x=0$. Assuming that $\Phi(x)$ has a local minimum at $x=0$, using the Laplace expansion, and Eq. (C1), we obtain Eq. (8.7).

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Comment on Nadler, Schuss, Singer (2005) and Singer and Schuss (2005)

Bob Eisenberg April 16 2010

The boundary layer that is the problem in the Eisenberg, Klosek, Schuss paper is not a practical problem because measurements should not and usually are not taken at the absorbing electrode. Rather a "four electrode arrangement" is used, as is described in electrochemistry textbooks: a separate pair of electrodes are used to measure potential that carry no current at all. These simply report the electrical potential at some location away from the absorbing electrode. Precautions are taken that the concentrations used in analyzing experiments also do not include the boundary layer at the absorbing boundary.

A significant difficulty with the EKS, NSS and SS papers is—as it is in all these treatments (Eisenberg 2006)—the cavalier treatment of charged solutes as if they do not generate an electrical potential. The papers in this group do not compute the potential from the charge distribution. Thus, the boundary layers and behaviors reported would in practice be expected to be very different for solutions of ions like NaCl, or solutions with mixed monovalent and divalent ions.

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A NOTE ON THE NON-DIMENSIONALIZATION IN EKS*

Boaz Nadler
September 1998

We start from the dimensional equation

$$m\ddot{\tilde{x}} + \tilde{\beta}\dot{\tilde{x}} + ze\frac{d\tilde{\phi}}{d\tilde{x}} = \sqrt{2\tilde{\beta}kT}\dot{\tilde{w}} \tag{1}$$

In this equation, $\tilde{w}$ is *dimensional*, with dimension $[\sec^{1/2}]$. We scale the variables in the following way,

$$\tilde{x} = Lx, \quad \tilde{\phi} = \frac{kT}{ez}\phi, \quad \tilde{t} = \frac{L}{\sqrt{kT/m}}t, \quad \tilde{\beta} = \frac{\sqrt{kT/m}}{L}\beta. \tag{2}$$

Insertion of this scaling into the dimensional equation, and use of the scaling identity $w_1(\alpha t) = \sqrt{\alpha}w_2(t)$ for Gaussian noise, yields the non-dimensional equation,

$$\frac{d^2x}{dt^2} + \beta\frac{dx}{dt} + \frac{d\phi}{dx} = \sqrt{2\beta}\dot{w}. \tag{3}$$

In this equation $\dot{w}$ denotes *non-dimensional* standart white noise.

We now consider the value of the non-dimensional parameter β. From the scaling we have that

$$\beta = L\sqrt{\frac{m}{kT}}\tilde{\beta} = \frac{L}{D}\sqrt{\frac{kT}{m}} \tag{4}$$

With a typical value of $L = 30\mathring{A}$ for the length of the channel, $D = 10^{-10}\text{m/s}^2$ for the diffusion coefficient, and $m = 60m_p$, where m_p is the proton's mass, we obtain that $\beta = 6100$.

We now compute the average non-dimensional time to enter the channel, assuming free diffusion outside. This dimensional time is given by

$$\tau_{arrival} = \frac{1}{2\pi\rho Dr_{ch}} \tag{5}$$

Thus the non dimensional time is given by

$$t_{arrival} = \frac{\sqrt{kT/m}}{L}\tau_{arrival}. \tag{6}$$

With typical values $\rho = 100\text{mM}$, $r_{ch} = 3\mathring{A}$, and $D = 10^{-10}\text{m/s}^2$, we obtain that in non dimensional units, $t_{arrival} = 6000$, i.e. of the order of β.

*Eisenberg, R. S., Klosek, M. M., and Schuss, Z. (1995) Diffusion as a chemical reaction: Stochastic trajectories between fixed concentrations. J. Chem. Phys. 102, 1767-1780.

Langevin Trajectories between Fixed Concentrations

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We consider the trajectories of particles diffusing between two infinite baths of fixed concentrations connected by a channel, e.g., a protein channel of a biological membrane. The steady state influx and efflux of Langevin trajectories at the boundaries of a finite volume containing the channel and parts of the two baths is replicated by termination of outgoing trajectories and injection according to a residual phase space density. We present a simulation scheme that maintains averaged fixed concentrations without creating spurious boundary layers, consistent with the assumed physics.

Introduction.—We consider particles that diffuse in a domain Ω connecting two regions, where fixed, but possibly different, concentrations are maintained by connection to practically infinite reservoirs. This is the situation in the diffusion of ions through a protein channel of a biological membrane that separates two salt solutions of different fixed concentrations [1].

Continuum theories of such diffusive systems describe the concentration field by the Nernst-Planck equation with fixed boundary concentrations [1–4]. On the other hand, the underlying microscopic theory of diffusion describes the motion of the diffusing particles by Langevin's equations [2,4–6]. This means that on a microscopic scale there are fluctuations in the concentrations at the boundaries. The question of the boundary behavior of the Langevin trajectories (LT), corresponding to fixed boundary concentrations, arises both in theory and in the practice of particle simulations of diffusive motion [7–14].

When the concentrations are maintained by connection to infinite reservoirs, there are no physical sources and absorbers of trajectories at any definite location in the reservoir or in Ω. The boundaries in this setup can be chosen anywhere in the reservoirs, where the average concentrations are effectively fixed. Nothing unusual happens to the LT there. Upon reaching the boundary they simply cross into the reservoir and may cross the boundary back and forth any number of times. Limiting the system to a finite region necessarily puts sources and absorbers at the interfaces with the baths, as described in [15].

The boundary behavior of diffusing particles in a finite domain Ω has been studied in various cases, including absorbing, reflecting, sticky boundaries, and many other modes of boundary behavior [16,17]. In [18] a sequence of Markovian jump processes is constructed such that their transition probability densities converge to the solution of the Nernst-Planck equation with given boundary conditions, including fixed concentrations and sticky boundaries. Brownian dynamics simulations with different boundary protocols seem to indicate that density fluctuations near the channels are independent of the boundary conditions, if the boundaries are moved sufficiently far away from the channel [19]. However, as shown in [20], many boundary protocols for maintaining fixed concentrations lead to the formation of spurious boundary layers, which in the case of charged particles may produce large long range fluctuations in the electric field that spread throughout the entire simulation volume Ω. The analytic structure of these boundary layers was determined in [21,22], following several numerical investigations (e.g., [23]).

It seems that the boundary behavior of LT of particles diffusing between fixed concentrations has not been described mathematically in an adequate way. From the theoretical point of view, the absence of a rigorous mathematical theory of the boundary behavior of LT diffusing between fixed concentrations, based on the physical theory of the Brownian motion, is a serious lacuna in classical physics.

It is the purpose of this Letter to analyze the boundary behavior of LT between fixed concentrations and to design a Langevin simulation that does not form spurious boundary layers. We find the joint probability density function of the velocities and locations, where new simulated LT are injected into a given simulation volume, while maintaining the fixed concentrations. As the time step decreases the simulated density converges to the solution of the Fokker-Planck equation (FPE) with the imposed boundary conditions without forming boundary layers.

Trajectories, fluxes, and boundary concentrations.—We assume fixed concentrations C_L and C_R on the left and right interfaces between Ω and the baths B, respectively, with all other boundaries of Ω being impermeable walls, where the normal particle flux vanishes. We assume that the particles interact only with a mean field, whose potential is $\Phi(x)$, so the diffusive motion of a particle in the channel and in the reservoirs is described by the Langevin equation (LE)

$$\ddot{x} + \gamma(x)\dot{x} + \nabla_x\Phi(x) = \sqrt{2\gamma(x)\varepsilon}\dot{w},$$
$$x(0) = x_0, \qquad v(0) = v_0, \tag{1}$$

where $\gamma(x)$ is the (state-dependent) friction per unit mass, ε is a thermal factor, and $\dot{w}$ is a vector of standard independent Gaussian δ-correlated white noises [6].

The probability density function (PDF) of finding the trajectory of the diffusing particle at location x with velocity v at time t, given its initial position, satisfies the FPE in the bath and in the reservoirs,

$$\frac{\partial p}{\partial t} = -v \cdot \nabla_x p + \gamma(x)\varepsilon\Delta_v p$$
$$+ \nabla_v \cdot [\gamma(x)v + \nabla_x\Phi(x)]p, \tag{2}$$
$$p(x, v, 0|x_0, v_0) = \delta(x - x_0, v - v_0).$$

In the Smoluchowski limit of large friction the stationary solution of (2) admits the form [5]

$$p(x, v) = \frac{e^{-|v|^2/2\varepsilon}}{(2\pi\varepsilon)^{3/2}}\left\{p(x) + \frac{J(x) \cdot v}{\varepsilon} + O\left(\frac{1}{\gamma^2}\right)\right\} \tag{3}$$

where the flux density vector $J(x)$ is given by

$$J(x) = -\frac{1}{\gamma(x)}\left\{\varepsilon\nabla p(x) + p(x)\nabla\Phi(x)\right\} + O\left(\frac{1}{\gamma^2}\right),$$

and $p(x)$ satisfies

$$-\nabla \cdot J(x) = \nabla \cdot \frac{1}{\gamma(x)}\{\varepsilon\nabla p(x) + p(x)\nabla\Phi(x)\} = 0.$$

In one dimension, the stationary PDFs of velocities of the particles crossing the interface into the given volume are

$$p_L(v) \sim \frac{\frac{e^{-v^2/2\varepsilon}}{\sqrt{2\pi\varepsilon}}\{1 + \frac{Jv}{\varepsilon C_L}\}}{\frac{1}{2} + \frac{J}{C_L\sqrt{2\pi\varepsilon}}} \quad \text{for } v > 0,$$
$$\tag{4}$$
$$p_R(v) \sim \frac{\frac{e^{-v^2/2\varepsilon}}{\sqrt{2\pi\varepsilon}}\{1 - \frac{Jv}{\varepsilon C_R}\}}{\frac{1}{2} + \frac{J}{C_R\sqrt{2\pi\varepsilon}}} \quad \text{for } v < 0,$$

where J is the net probability flux through the channel. The source strengths (unidirectional fluxes at the interfaces) are given by [5]

$$J_L = \sqrt{\frac{\varepsilon}{2\pi}}C_L - \frac{J}{2} + O\left(\frac{1}{\gamma^2}\right),$$
$$\tag{5}$$
$$J_R = \sqrt{\frac{\varepsilon}{2\pi}}C_R + \frac{J}{2} + O\left(\frac{1}{\gamma^2}\right).$$

Application to simulation. —Langevin simulations of ion permeation in a protein channel of a biological membrane have to include a part of the surrounding bath, because boundary conditions at the ends of the channel are unknown. The boundary of the simulation has to be interfaced with the bath in a manner that does not distort the physics. This means that new LT have to be injected into the simulation at the correct rate and with the correct distribution of displacement and velocity, for otherwise, spurious boundary layers will form [20].

Consider a single simulated trajectory that jumps according to the discretized LE (1)

$$x(t + \Delta t) = x(t) + v(t)\Delta t,$$
$$v(t + \Delta t) = v(t)(1 - \gamma\Delta t) - \nabla_x\Phi(x(t))\Delta t \tag{6}$$
$$+ \sqrt{2\varepsilon\gamma}\Delta w(t),$$

where Δw is normally distributed with zero mean and variance Δt. The trajectory is terminated when it exits Ω for the first time. The problem at hand is to determine an injection scheme of new trajectories into Ω such that the interface concentrations are maintained on the average at their nominal values C_L and C_R and the simulated density profile satisfies (3).

To be consistent with (3), the injection rate has to be equal to the unidirectional flux at the boundary (5). New trajectories have to be injected with displacement and velocity as though the simulation extends outside Ω, consistently with the scheme (6), because the interface is a fictitious boundary. The scheme (6) can move the trajectory from the bath B into Ω from any point $\xi \in B$ and with any velocity η. The probability that a trajectory, which is moved with time step Δt from the bath into Ω or from Ω into the bath, will land exactly on the boundary is zero. It follows that the PDF of the point (x, v), where the trajectory lands in Ω in one time step, at time $t' = t + \Delta t$, say, given that it started at a bath point (ξ, η) (in phase space) is, according to (6),

$$\Pr\{x(t') = x, v(t') = v|x(t) = \xi, v(t) = \eta\}$$
$$= \frac{\delta(x - \xi - \eta\Delta t)}{(4\pi\varepsilon\gamma\Delta t)^{3/2}}$$
$$\times \exp\left\{-\frac{|v - \eta + (\gamma\eta + \nabla\Phi(\xi))\Delta t|^2}{4\varepsilon\gamma\Delta t}\right\} + o(\Delta t). \tag{7}$$

The stationary PDF $p(\xi, \eta)$ of such a bath point is given in (3). The conditional probability of such a landing is

$$\Pr\{x, v|x \in \Omega, \xi \in B\} = \frac{\int_{\mathbb{R}^3} d\eta \int_B d\xi \Pr\{v(t') = v, x(t') = x|\xi, \eta\}p(\xi, \eta)}{\Pr\{x \in \Omega, \xi \in B\}}, \tag{8}$$

where the denominator is a normalization constant such that

$$\int_{\mathbb{R}^3} dv \int_\Omega dx \Pr\{x, v|x \in \Omega, \xi \in B\} = 1.$$

Thus the first point of a new trajectory is chosen according to the PDF (8) and the subsequent points are generated according to (6), that is, with the transition PDF (7), until the trajectory leaves Ω. By construction, this scheme

recovers the joint PDF (3) in Ω, so no spurious boundary layer is formed.

As an example, we consider a one-dimensional Langevin dynamics simulation of diffusion of free particles between fixed concentrations on a given interval. Assuming that in a channel of length L

$$\frac{(C_L - C_R)\sqrt{\varepsilon}}{\gamma L} \ll C_L,$$

$$\Pr\{x, v | x > 0, \xi < 0\} = \frac{\exp\{-\frac{v^2}{2\varepsilon[1+(\gamma\Delta t)^2]}\}}{2\varepsilon\Delta t\sqrt{1+(\gamma\Delta t)^2}} \times \text{erfc}\left(\sqrt{\frac{1+(\gamma\Delta t)^2}{4\varepsilon\gamma\Delta t}}\left(\frac{x}{\Delta t} - v\frac{1-\gamma\Delta t}{1+(\gamma\Delta t)^2}\right)\right). \qquad (9)$$

In the limit $\Delta t \to 0$ we obtain from Eq. (9)

$$\Pr\{x, v | x > 0, \xi < 0\} \to \frac{2\delta(x)H(v)}{\sqrt{2\pi\varepsilon}} e^{-v^2/2\varepsilon}, \qquad (10)$$

where $H(v)$ is the Heaviside unit step function. This means that with the said approximation, LT enter at $x = 0$ with a Maxwellian distribution of positive velocities. Without the approximation the limiting distribution of velocities is (4). Note, however, that injecting trajectories by any Markovian scheme, with the limiting distribution (10) and with any time step Δt, creates a boundary layer [20].

A Langevin dynamics (LD) simulation with $C_L \neq 0$, $C_R = 0$, and the parameters $\gamma = 100$, $\varepsilon = 1$, $L = 1$, $\Delta t = 10^{-4}$ with 25000 trajectories, once with a Maxwellian distribution of velocities at the boundary $x = 0$ (bottom trace on the left panel and top trace on the right panel, red online) and once with the PDF (9) (top trace on the left panel and bottom trace on the right panel, blue online) shows that a boundary layer is formed in the former, but not in the latter (see Fig. 1).

An alternative way to interpret Eq. (9) is to view the simulation (6) as a discrete time Markovian process $(x(t), v(t))$ that never enters or exits Ω exactly at the boundary. If, however, we run a simulation in which particles are inserted at the boundary, the time of insertion has

which means that γ is sufficiently large, the flux term in Eq. (3) is negligible relative to the concentration term. The concentration term is linear with slope J and thus can be approximated by a constant, so that $p(\xi) = p(0) + O(\gamma^{-1})$ in the left bath. Actually, the value of $p(0) \neq 0$ is unimportant, because it cancels out in the normalized PDF (8), which comes out to be

to be random, rather than a lattice time $n\Delta t$. Thus the time of the first jump from the boundary into the domain is the residual time $\Delta t'$ between the moment of insertion and the next lattice time $(n + 1)\Delta t$. The probability density of jump size in both variables has to be randomized with $\Delta t'$, with the result (9).

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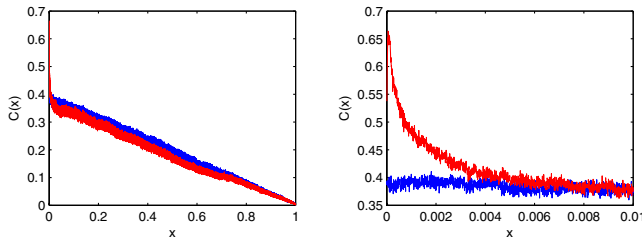[14] W. Im, S. Seefeld, and B. Roux, Biophys. J. **79**, 788 (2000).

FIG. 1 (color online). Left panel: Concentration against displacement of a LD simulation with injecting particles according to the residual distribution (9) (top trace, blue online), and according to the Maxwellian velocity distribution (10) exactly at the boundary (bottom trace, red online). The two graphs are almost identical, except for a small boundary layer near $x = 0$ in the residual distribution. Right panel: Zoom in of the concentration profile in the boundary layer $x < 0.01 = \sqrt{\varepsilon}/\gamma$.

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Brownian simulations and unidirectional flux in diffusion

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The prediction of ionic currents in protein channels of biological membranes is one of the central problems of computational molecular biophysics. Existing continuum descriptions of ionic permeation fail to capture the rich phenomenology of the permeation process, so it is therefore necessary to resort to particle simulations. Brownian dynamics (BD) simulations require the connection of a small discrete simulation volume to large baths that are maintained at fixed concentrations and voltages. The continuum baths are connected to the simulation through interfaces, located in the baths sufficiently far from the channel. Average boundary concentrations have to be maintained at their values in the baths by injecting and removing particles at the interfaces. The particles injected into the simulation volume represent a unidirectional diffusion flux, while the outgoing particles represent the unidirectional flux in the opposite direction. The classical diffusion equation defines net diffusion flux, but not unidirectional fluxes. The stochastic formulation of classical diffusion in terms of the Wiener process leads to a Wiener path integral, which can split the net flux into unidirectional fluxes. These unidirectional fluxes are infinite, though the net flux is finite and agrees with classical theory. We find that the infinite unidirectional flux is an artifact caused by replacing the Langevin dynamics with its Smoluchowski approximation, which is classical diffusion. The Smoluchowski approximation fails on time scales shorter than the relaxation time $1/\gamma$ of the Langevin equation. We find that the probability of Brownian trajectories that cross an interface in one direction in unit time Δt equals that of the probability of the corresponding Langevin trajectories if $\gamma \Delta t = 2$. That is, we find the unidirectional flux (source strength) needed to maintain average boundary concentrations in a manner consistent with the physics of Brownian particles. This unidirectional flux is proportional to the concentration and inversely proportional to $\sqrt{\Delta t}$ to leading order. We develop a BD simulation that maintains fixed average boundary concentrations in a manner consistent with the actual physics of the interface and without creating spurious boundary layers.

I. INTRODUCTION

The prediction of ionic currents in protein channels of biological membranes is one of the central problems of computational molecular biophysics. None of the existing continuum descriptions of ionic permeation captures the rich phenomenology of the patch clamp experiments [1]. It is therefore necessary to resort to particle simulations of the permeation process [2–7]. Computer simulations are necessarily limited to a relatively small number of mobile ions, due to computational difficulties. Thus a reasonable simulation can describe only a small portion of the experimental setup of a patch clamp experiment: the channel and its immediate surroundings. The inclusion in the simulation of a part of the bath and its connection to the surrounding bath are necessary, because the conditions at the boundaries of the channel are unknown, while they are measurable in the bath, away from the channel.

Thus the trajectories of the particles are described individually for each particle inside the simulation volume, while outside the simulation volume they can be described only by their statistical properties. It follows that on one side of the interface between the simulation and the surrounding bath the description of the particles is discrete, while a continuum description has to be used on the other side. This poses the fundamental question of how to describe the particle trajectories at the interface, which is the subject of this paper.

We address this problem for Brownian dynamics (BD) simulations, connected to a practically infinite surrounding bath by an interface that serves as both a source of particles that enter the simulation and an absorbing boundary for particles that leave the simulation. The interface is expected to reproduce the physical conditions that actually exist on the boundary of the simulated volume. These physical conditions are not merely the average electrostatic potential and local concentrations at the boundary of the volume, but also their fluctuation in time. It is important to recover the correct fluctuation, because the stochastic dynamics of ions in solution are nonlinear, due to the coupling between the electrostatic field and the motion of the mobile charges, so that averaged boundary conditions do not reproduce correctly averaged nonlinear response. In a system of noninteracting particles incorrect fluctuation on the boundary may still produce the correct response outside a boundary layer in the simulation region [8].

The boundary fluctuation consists of arrival of new particles from the bath into the simulation and of the recirculation of particles in and out of the simulation. The random motion of the mobile charges brings about the fluctuation in both the concentrations and the electrostatic field. Since the simulation is confined to the volume inside the interface, the new and the recirculated particles have to be fed into the simulation by a source that imitates the influx across the

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interface. The interface does not represent any physical device that feeds trajectories back into the simulation, but is rather an imaginary wall, which the physical trajectories of the diffusing particles cross and recross any number of times. The efflux of simulated trajectories through the interface is seen in the simulation; however, the influx of new trajectories, which is the unidirectional flux (UF) of diffusion, has to be calculated so as to reproduce the physical conditions, as mentioned above. Thus the UF is the source strength of the influx and also the number of trajectories that cross the interface in one direction per unit time.

The mathematical problem of the UF begins with the description of diffusion by the diffusion equation. The diffusion equation (DE) is often considered to be an approximation of the Fokker-Planck equation (FPE) in the Smoluchowski limit of large damping. Both equations can be written as the conservation law

$$\frac{\partial p}{\partial t} = -\boldsymbol{\nabla} \cdot \boldsymbol{J}. \qquad (1)$$

The flux density $\boldsymbol{J}$ in the diffusion equation is given by

$$\boldsymbol{J}(\boldsymbol{x},t) = -\frac{1}{\gamma}[\varepsilon \boldsymbol{\nabla} p(\boldsymbol{x},t) - \boldsymbol{f}(\boldsymbol{x})p(\boldsymbol{x},t)], \qquad (2)$$

where γ is the friction coefficient (or dynamical viscosity), $\varepsilon = k_B T/m$, k_B is Boltzmann's constant, T is absolute temperature, and m is the mass of the diffusing particle. The external acceleration field is $\boldsymbol{f}(\boldsymbol{x})$ and $p(\boldsymbol{x},t)$ is the density (or probability density) of the particles [9]. The flux density in the FPE is given by where the net probability flux density vector has the components

$$J_x(\boldsymbol{x},\boldsymbol{v},t) = \boldsymbol{v}p(\boldsymbol{x},\boldsymbol{v},t),$$

$$J_v(\boldsymbol{x},\boldsymbol{v},t) = -[\gamma\boldsymbol{v} - \boldsymbol{f}(\boldsymbol{x})]p(\boldsymbol{x},\boldsymbol{v},t) - \varepsilon\gamma\boldsymbol{\nabla}_v p(\boldsymbol{x},\boldsymbol{v},t). \qquad (3)$$

The density $p(\boldsymbol{x},t)$ in the diffusion equation (1) with (2) is the probability density of the trajectories of the Smoluchowski stochastic differential equation

$$\dot{\boldsymbol{x}} = \frac{1}{\gamma}\boldsymbol{f}(\boldsymbol{x}) + \sqrt{\frac{2\varepsilon}{\gamma}}\,\dot{\boldsymbol{w}}, \qquad (4)$$

where $\boldsymbol{w}(t)$ is a vector of independent standard Wiener processes (Brownian motions).

The density $p(\boldsymbol{x},\boldsymbol{v},t)$ is the probability density of the phase space trajectories of the Langevin equation

$$\ddot{\boldsymbol{x}} + \gamma\dot{\boldsymbol{x}} = \boldsymbol{f}(\boldsymbol{x}) + \sqrt{2\varepsilon\gamma}\,\dot{\boldsymbol{w}}. \qquad (5)$$

In practically all conservation laws of the type (1) J is a *net flux density* vector. It is often necessary to split it into two unidirectional components across a given surface, such that the net flux J is their difference. Such splitting is pretty obvious in the FPE, because the velocity $\boldsymbol{v}$ at each point $\boldsymbol{x}$ tells the two UF's apart. Thus, in one dimension,

$$J_{LR}(x,t) = \int_0^\infty vp(x,v,t)dv, \quad J_{RL}(x,t) = -\int_{-\infty}^0 vp(x,v,t)dv,$$

$$J_{\text{net}}(x,t) = J_{LR}(x,t) - J_{RL}(x,t) = \int_{-\infty}^\infty vp(x,v,t)dv. \qquad (6)$$

In contrast, the net flux $J(x,t)$ in the DE cannot be split this way, because velocity is not a state variable. Actually, the trajectories of a diffusion process do not have well-defined velocities, because they are nowhere differentiable with probability 1 [10]. These trajectories cross and recross every point x infinitely many times in any time interval $[t,t+\Delta t]$, giving rise to infinite UF's. However, the net diffusion flux is finite, as indicated in Eq. (2). This phenomenon was discussed in detail in [11], where a path integral description of diffusion was used to define the UF. The unidirectional diffusion flux, however, is finite at absorbing boundaries, where the UF equals the net flux. The UF's measured in diffusion across biological membranes by using radioactive tracer [1] are in effect UF's at absorbing boundaries, because the tracer is a separate ionic species [12].

An apparent paradox arises in the Smoluchowski approximation of the FPE by the DE; namely, the UF of the DE is infinite for all γ, while the UF of the FPE remains finite, even in the limit $\gamma \to \infty$, in which the solution of the DE is an approximation of that of the FPE [13]. The "paradox" is resolved by a new derivation of the FPE for Langevin dynamics (LD) from the Wiener path integral. This derivation is different than the derivation of the DE or the Smoluchowski equation from the Wiener integral (see, e.g., [17–20]) by the method of Kac [21]. The new derivation shows that the path integral definition of UF in diffusion, as first introduced in [11], is consistent with that of UF in the FPE. However, the definition of flux involves the limit $\Delta t \to 0$, that is, a time scale shorter than $1/\gamma$, on which the solution of the DE is not a valid approximation to that of the FPE.

This discrepancy between the Einstein and Langevin descriptions of the random motion of diffusing particles was hinted at by both Einstein and Smoluchowski. Einstein [14] remarked that his diffusion theory is based on the assumption that the diffusing particles are observed intermittently at short time intervals, but not too short, while Smoluchowski [15] showed that the variance of the displacement of Langevin trajectories is quadratic in t for times much shorter than the relaxation time $1/\gamma$, but is linear in t for times much longer than $1/\gamma$, which is the same as in Einstein's theory of diffusion [16].

The infinite unidirectional diffusion flux imposes serious limitations on BD simulations of diffusion in a finite volume embedded in a much larger bath. Such simulations are used, for example, in simulations of ion permeation in protein channels of biological membranes [1]. If parts of the bathing solutions on both sides of the membrane are to be included in the simulation, the UF's of particles into the simulation have to be calculated. Simulations with BD would lead to increasing influxes as the time step is refined.

The method of resolution of the said "paradox" is based on the definition of the UF of the LD in terms of the Wiener path integral, analogous to its definition for the BD in [11]. The UF $J_{LR}(x,t)$ is the probability per unit time Δt of trajectories that are on the left of x at time t and are on the right of

x at time $t+\Delta t$. We show that the UF of BD coincides with that of LD if the time unit Δt in the definition of the unidirectional diffusion flux is exactly

$$\Delta t = \frac{2}{\gamma}. \tag{7}$$

We find the strength of the source that ensures that a given concentration is maintained on the average at the interface in a BD simulation. The strength of the left source J_{LR} is to leading order independent of the efflux and depends on the concentration C_L, the damping coefficient γ, the temperature ε, and the time step Δt, as given in Eq. (27). To leading order it is

$$J_{LR} = \sqrt{\frac{\varepsilon}{\pi\gamma\Delta t}} C_L + O\left(\frac{1}{\gamma}\right). \tag{8}$$

We also show that the coordinate of a newly injected particle has the probability distribution of the residual of the normal distribution. Our simulation results show that no spurious boundary layers are formed with this scheme, while they are formed if new particles are injected at the boundary. The simulations also show that if the injection rate is fixed, there is depletion of the population as the time step is refined, but there is no depletion if the rate is changed according to Eq. (8).

In Sec. II, we derive the FPE for the LD (5) from the Wiener path integral. In Sec. III, we define the unidirectional probability flux for LD by the path integral and show that is indeed given by Eqs. (6). In Sec. IV, we use the results of [13] to calculate explicitly the UF in the Smoluchowski approximation to the solution of the FPE and to recover the flux (2). In Sec. V, we use the results of [11] to evaluate the UF of the BD trajectories (4) in a finite time unit Δt. In the limit $\Delta t \to 0$ the UF diverges, but if it is chosen as in Eq. (7), the UF's of LD and BD coincide. In Sec. VI we describe the a BD simulation of diffusion between fixed concentrations and give results of simulations. Finally, Sec. VII is a summary and discussion of the results.

II. DERIVATION OF THE FOKKER-PLANCK EQUATION FROM A PATH INTEGRAL

The LD (5) of a diffusing particle can be written as the phase space system

$$\dot{x} = v, \quad \dot{v} = -\gamma v + f(x) + \sqrt{2\varepsilon\gamma}\, \dot{w}. \tag{9}$$

This means that in time Δt the dynamics progresses according to

$$x(t+\Delta t) = x(t) + v(t)\Delta t + o(\Delta t), \tag{10}$$

$$v(t+\Delta t) = v(t) + [-\gamma v(t) + f(x(t))]\Delta t + \sqrt{2\varepsilon\gamma}\,\Delta w + o(\Delta t), \tag{11}$$

where $\Delta w \sim \mathcal{N}(0, \Delta t)$; that is, Δw is normally distributed with mean 0 and variance Δt. This means that the probability density function evolves according to the propagator

$$\text{Prob}\{x(t+\Delta t)=x, v(t+\Delta t)=v\}$$

$$= p(x,v,t+\Delta t) = o(\Delta t) + \frac{1}{\sqrt{4\varepsilon\gamma\pi\Delta t}}$$

$$\times \int_a^b \int_{-\infty}^\infty p(\xi,\eta,t)\,\delta(x-\xi-\eta\Delta t)$$

$$\times \exp\left\{-\frac{[v-\eta-[-\gamma\eta+f(\xi)]\Delta t]^2}{4\varepsilon\gamma\Delta t}\right\} d\xi\, d\eta. \tag{12}$$

To understand Eq. (12), we note that given that the displacement and velocity of the trajectory at time t are $x(t)=\xi$ and $v(t)=\eta$, respectively, then according to Eq. (10), the displacement of the particle at time $t+\Delta t$ is deterministic, independent of the value of Δw, and is $x=\xi+\eta\Delta t+o(\Delta t)$. Thus the probability density function (pdf) of the displacement is $\delta(x-\xi-\eta\Delta t+o(\Delta t))$. It follows that the displacement contributes to the joint propagator (12) of $x(t)$ and $v(t)$ a multiplicative factor of the Dirac δ function. Similarly, Eq. (11) means that the conditional pdf of the velocity at time $t+\Delta t$, given $x(t)=\xi$ and $v(t)=\eta$, is normal with mean $\eta+[-\gamma\eta+f(\xi)]\Delta t+o(\Delta t)$ and variance $2\varepsilon\gamma\Delta t+o(\Delta t)$, as reflected in the exponential factor of the propagator. If trajectories are terminated at the ends of an finite or infinite interval (a,b), the integration over the displacement variable extends only to that interval.

The basis for our analysis of the UF is the following new derivation of the Fokker-Planck equation from Eq. (12). Integration with respect to ξ gives

$$p(x,v,t+\Delta t)$$

$$= o(\Delta t) + \frac{1}{\sqrt{4\varepsilon\gamma\pi\Delta t}} \int_{-\infty}^\infty p(x-\eta\Delta t,\eta,t)$$

$$\times \exp\left\{-\frac{[v-\eta-[-\gamma\eta+f(x-\eta\Delta t)]\Delta t]^2}{4\varepsilon\gamma\Delta t}\right\} d\eta. \tag{13}$$

Changing variables to

$$-u = \frac{v-\eta-[-\gamma\eta+f(x-\eta\Delta t)]\Delta t}{\sqrt{2\varepsilon\gamma\Delta t}}$$

and expanding in powers of Δt, the integral takes the form

$$p(x,v,t+\Delta t) = \frac{1}{\sqrt{2\pi}[1-\gamma\Delta t+o(\Delta t)]}$$

$$\times \int_{-\infty}^\infty e^{-u^2/2} du\, p(x-v(1+\gamma\Delta t)\Delta t$$

$$+ o(\Delta t), v(1+\gamma\Delta t)+u\sqrt{2\varepsilon\gamma\Delta t}$$

$$- f(x)\Delta t(1+\gamma\Delta t)+o(\Delta t), t). \tag{14}$$

Reexpanding in powers of Δt, we get

$p(x - v(1 + \gamma\Delta t)\Delta t + o(\Delta t), v(1 + \gamma\Delta t) + u\sqrt{2\varepsilon\gamma\Delta t}$

$\qquad - f(x)\Delta t(1 + \gamma\Delta t) + o(\Delta t), t)$

$\qquad = p(x, v, t) - v\Delta t \dfrac{\partial p(x, v, t)}{\partial x} + \dfrac{\partial p(x, v, t)}{\partial v}[v\gamma\Delta t + u\sqrt{2\varepsilon\gamma\Delta t}$

$\qquad - f(x)\Delta t + o(\Delta t)] + \varepsilon\gamma u^2 \Delta t \dfrac{\partial^2 p(x, v, t)}{\partial v^2} + o(\Delta t),$

so Eq. (14) gives

$$p(x, v, t + \Delta t) - \dfrac{p(x, v, t)}{1 - \gamma\Delta t} = -\dfrac{1}{1 - \gamma\Delta t} v\Delta t \dfrac{\partial p(x, v, t)}{\partial x}$$

$$+ \dfrac{\Delta t}{1 - \gamma\Delta t} \dfrac{\partial p(x, v, t)}{\partial v}[v\gamma - f(x)]$$

$$+ \dfrac{\varepsilon\gamma\Delta t}{1 - \gamma\Delta t} \dfrac{\partial^2 p(x, v, t)}{\partial v^2} + O(\Delta t^{3/2}).$$

Dividing by Δt and taking the limit $\Delta t \to 0$, we obtain the Fokker-Planck equation in the form

$$\dfrac{\partial p(x, v, t)}{\partial t} = -v \dfrac{\partial p(x, v, t)}{\partial x} + \dfrac{\partial}{\partial v}\{[\gamma v - f(x)]p(x, v, t)\}$$

$$+ \varepsilon\gamma \dfrac{\partial^2 p(x, v, t)}{\partial v^2}, \qquad (15)$$

which is the conservation law (1) with the flux components (3). The UF $J_{LR}(x_1, t)$ is usually defined as the integral of $J_x(x_1, v, t)$ over the positive velocities ([13], and references therein)—that is,

$$J_{LR}(x_1, t) = \int_0^\infty v p(x_1, v, t) dv. \qquad (16)$$

To show that this integral actually represents the probability of the trajectories that move from left to right across x_1 per unit time, we evaluate below the probability flux from a path integral.

III. UNIDIRECTIONAL FLUX OF THE LANGEVIN EQUATION

The instantaneous unidirectional probability flux from left to right at a point x_1 is defined as the probability per unit time (Δt), of Langevin trajectories that are to the left of x_1 at time t (with any velocity) and propagate to the right of x_1 at time $t + \Delta t$ (with any velocity), in the limit $\Delta t \to 0$. This can be expressed in terms of a path integral on Langevin trajectories on the real line as

$$J_{LR}(x_1, t) = \lim_{\Delta t \to 0} \dfrac{1}{\Delta t} \int_{-\infty}^{x_1} d\xi \int_{x_1}^\infty dx \int_{-\infty}^\infty d\eta \int_{-\infty}^\infty dv \dfrac{1}{\sqrt{4\varepsilon\gamma\pi\Delta t}}$$

$$\times p(\xi, \eta, t)\delta(x - \xi - \eta\Delta t)$$

$$\times \exp\left\{-\dfrac{\{v - \eta - [-\gamma\eta + f(\xi)]\Delta t\}^2}{4\varepsilon\gamma\Delta t}\right\}. \qquad (17)$$

Integrating with respect to v eliminates the exponential fac-

tor, and integration with respect to ξ fixes ξ at $x - \eta\Delta t$, so

$$J_{LR}(x_1, t) = \lim_{\Delta t \to 0} \dfrac{1}{\Delta t} \int\int_{x - \eta\Delta t < x_1} p(x - \eta\Delta t, \eta, t) d\eta\, dx$$

$$= \lim_{\Delta t \to 0} \dfrac{1}{\Delta t} \int_0^\infty d\eta \int_{x_1 - \eta\Delta t}^{x_1} p(u, \eta, t) du$$

$$= \int_0^\infty \eta p(x_1, \eta, t) d\eta. \qquad (18)$$

Expression (18) is identical to Eq. (16).

IV. SMOLUCHOWSKI APPROXIMATION TO THE UNIDIRECTIONAL CURRENT

The following calculations were done in [13] and are shown here for completeness. In the overdamped regime, as $\gamma \to \infty$, the Smoluchowski approximation to $p(x, v, t)$ is given by

$$p(x, v, t) \sim \dfrac{e^{-v^2/2\epsilon}}{\sqrt{2\pi\epsilon}}\left\{p(x, t) - \dfrac{1}{\gamma}\left[\dfrac{\partial p(x, t)}{\partial x} - \dfrac{1}{\epsilon}f(x)p(x, t)\right]v\right.$$

$$\left. + O\left(\dfrac{1}{\gamma^2}\right)\right\}, \qquad (19)$$

where the marginal density $p(x, t)$ satisfies the Fokker-Planck-Smoluchowski equation

$$\gamma\dfrac{\partial p(x, t)}{\partial t} = \varepsilon\dfrac{\partial^2 p(x, t)}{\partial x^2} - \dfrac{\partial}{\partial x}[f(x)p(x, t)]. \qquad (20)$$

According to Eqs. (16) and (19), the UF is

$$J_{LR}(x_1, t) = \int_0^\infty v p(x_1, v, t) dv = \int_0^\infty v\dfrac{e^{-v^2/2\epsilon}}{\sqrt{2\pi\epsilon}}\left\{p(x, t)\right.$$

$$\left. - \dfrac{1}{\gamma}\left[\dfrac{\partial p(x, t)}{\partial x} - \dfrac{1}{\epsilon}f(x)p(x, t)\right]v + O\left(\dfrac{1}{\gamma^2}\right)\right\} dv$$

$$= \sqrt{\dfrac{\varepsilon}{2\pi}}p(x_1, t) - \dfrac{1}{2\gamma}\left[\varepsilon\dfrac{\partial p(x, t)}{\partial x} - f(x)p(x, t)\right]$$

$$+ O\left(\dfrac{1}{\gamma^2}\right). \qquad (21)$$

Similarly, the UF from right to left is

$$J_{RL}(x_1, t) = -\int_{-\infty}^0 v p(x_1, v, t) dv = \sqrt{\dfrac{\varepsilon}{2\pi}}p(x_1, t)$$

$$+ \dfrac{1}{2\gamma}\left[\varepsilon\dfrac{\partial p(x, t)}{\partial x} - f(x)p(x, t)\right] + O\left(\dfrac{1}{\gamma^2}\right). \qquad (22)$$

Both UF's in Eqs. (21) and (22) are finite and proportional to the marginal density at x_1. The net flux is the difference

$$J_{net}(x_1,t) = J_{LR}(x_1,t) - J_{RL}(x_1,t)$$

$$= -\frac{1}{\gamma}\left[\varepsilon\frac{\partial p(x,t)}{\partial x} - f(x)p(x,t)\right], \qquad (23)$$

as in classical diffusion theory [13,22].

V. UNIDIRECTIONAL CURRENT IN THE SMOLUCHOWSKI EQUATION

Classical diffusion theory, however, gives a different result. In the overdamped regime the Langevin equation (9) is reduced to the Smoluchowski equation [9]

$$\gamma\dot{x} = f(x) + \sqrt{2\varepsilon\gamma}\,\dot{w}. \qquad (24)$$

As in Sec. III, the unidirectional probability current (flux) density at a point x_1 can be expressed in terms of a path integral as

$$J_{LR}(x_1,t) = \lim_{\Delta t\to 0} J_{LR}(x_1,t,\Delta t), \qquad (25)$$

where

$$J_{LR}(x_1,t,\Delta t)$$

$$= \sqrt{\frac{\gamma}{4\pi\varepsilon\Delta t}}\int_0^\infty d\xi \int_\xi^\infty d\zeta \exp\left\{-\frac{\gamma\zeta^2}{4\varepsilon}\right\}\Bigg\{p(x_1,t)$$

$$-\sqrt{\Delta t}\left[-\frac{\zeta f(x_1)}{2\varepsilon}p(x_1,t) + (\zeta - \xi)\frac{\partial p(x_1,t)}{\partial x}\right] + O\left(\frac{\Delta t}{\gamma}\right)\Bigg\}. \qquad (26)$$

It was shown in [11] that

$$J_{LR}(x_1,t,\Delta t)$$

$$= \sqrt{\frac{\varepsilon}{\pi\gamma\Delta t}}p(x_1,t) + \frac{1}{2\gamma}\left(f(x_1)p(x_1,t) - \varepsilon\frac{\partial p(x_1,t)}{\partial x}\right)$$

$$+ O\left(\frac{\sqrt{\Delta t}}{\gamma^{3/2}}\right). \qquad (27)$$

Similarly,

$$J_{RL}(x_1,t) = \lim_{\Delta t\to 0} J_{RL}(x_1,t,\Delta t),$$

where

$$J_{RL}(x_1,t,\Delta t)$$

$$= \sqrt{\frac{\gamma}{4\pi\varepsilon\Delta t}}\int_0^\infty d\xi \int_\xi^\infty d\zeta \exp\left\{-\frac{\gamma\zeta^2}{4\varepsilon}\right\}\Bigg\{p(x_1,t)$$

$$+ \sqrt{\Delta t}\left[-\frac{\zeta f(x_1)}{2\varepsilon}p(x_1,t) + (\zeta - \xi)\frac{\partial p(x_1,t)}{\partial x}\right] + O\left(\frac{\Delta t}{\gamma}\right)\Bigg\}$$

$$= \sqrt{\frac{\varepsilon}{\pi\gamma\Delta t}}p(x_1,t) - \frac{1}{2\gamma}\left(f(x_1)p(x_1,t) - \varepsilon\frac{\partial p(x_1,t)}{\partial x}\right)$$

$$+ O\left(\frac{\sqrt{\Delta t}}{\gamma^{3/2}}\right). \qquad (28)$$
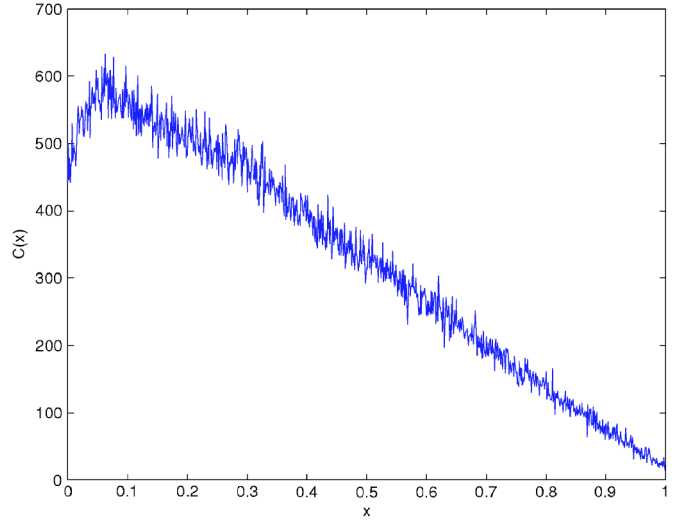

FIG. 1. The concentration profile of Brownian trajectories that are initiated at $x=0$ with a normal distribution and terminated at either $x=0$ or $x=1$.

If $p(x_1,t)>0$, then both $J_{LR}(x_1,t)$ and $J_{RL}(x_1,t)$ are infinite, in contradiction to the results (21) and (22). However, the net flux density is finite and is given by

$$J_{net}(x_1,t) = \lim_{\Delta t\to 0}\{J_{LR}(x_1,t,\Delta t) - J_{RL}(x_1,t,\Delta t)\}$$

$$= -\frac{1}{\gamma}\left[\varepsilon\frac{\partial}{\partial x}p(x_1,t) - f(x_1)p(x_1,t)\right], \qquad (29)$$

which is identical to Eq. (23).

The apparent paradox is due to the idealized properties of the Brownian motion. More specifically, the trajectories of the Brownian motion, and therefore also the trajectories of the solution of Eq. (24), are nowhere differentiable, so that any trajectory of the Brownian motion crosses and recrosses the point x_1 infinitely many times in any time interval $[t,t+\Delta t]$ [23]. Obviously, such a vacillation creates infinite UF's.

Not so for the trajectories of the Langevin equation (9). They have finite continuous velocities, so that the number of crossing and recrossing is finite. We note that setting $\gamma\Delta t=2$ in Eqs. (27) and (28) gives Eqs. (21) and (22).

VI. BROWNIAN SIMULATIONS

Here we design and analyze a BD simulation of particles diffusing between fixed concentrations. Thus, we consider the free Brownian motion [i.e., $f=0$ in Eq. (4)] in the interval $[0,1]$. The trajectories were produced as follows: (a) According to the dynamics (4), new trajectories that are started at $x(-\Delta t)=0$ move to $x(0)=(\sqrt{2\varepsilon/\gamma})|\Delta w|$. (b) The dynamics progresses according to the Euler scheme $x(t+\Delta t)=x(t)+(\sqrt{2\varepsilon/\gamma})\Delta w$. (c) The trajectory is terminated if $x(t)>1$ or $x(t)<0$. The parameters are $\varepsilon=1$, $\gamma=1000$, and $\Delta t=1$. We ran 10 000 random trajectories and constructed the concentration profile by dividing the interval into equal parts and recording the time each trajectory spent in each bin prior to termination. The results are shown in Fig. 1. The simulated
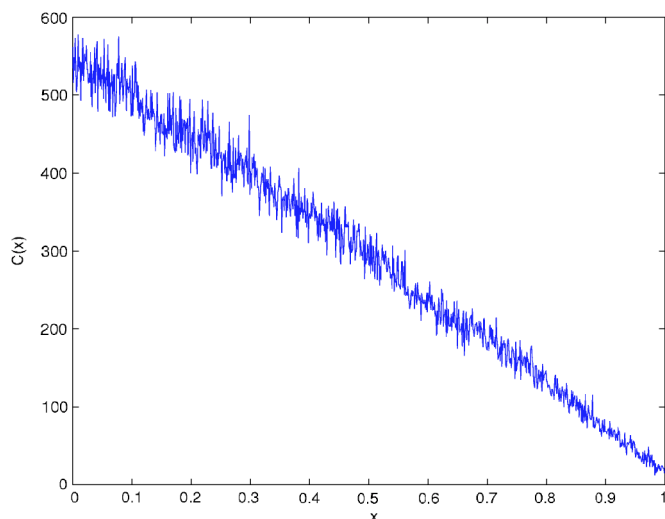
FIG. 2. The concentration profile of Brownian trajectories that are initiated at $x=0$ with the residual of the normal distribution and terminated at either $x=0$ or $x=1$.

FIG. 3. (Color online) The concentration profile of Brownian trajectories that are initiated at $x=0$ and terminated at either $x=0$ or $x=1$. Three different time steps ($\Delta t=4,1,0.25$) were used, but the injection rate of new particles remained constant. Refining the time step decreases the concentration profile.

concentration profile is linear, but for a small depletion layer near the left boundary $x=0$, where new particles are injected. This is inconsistent with the steady-state DE, which predicts a linear concentration profile in the entire interval $[0,1]$. The discrepancy stems from part (a) of the numerical scheme, which assumes that particles enter the simulation interval exactly at $x=0$. However, $x=0$ is just an imaginary interface. Had the simulation been run on the entire line, particles would hop into the simulation across the imaginary boundary at $x=0$ from the left, rather than exactly at the boundary. This situation is familiar from renewal theory [24]. The probability distribution of the distance an entering particle covers, not given its previous location, is not normal, but rather it is the residual of the normal distribution, given by

$$f(x) = C \int_{-\infty}^{0} \exp\left\{-\frac{(x-y)^2}{2\sigma^2}\right\} dy, \qquad (30)$$

where $\sigma^2=2\varepsilon\Delta t/\gamma$ and C is determined by the normalization condition $\int_0^\infty f(x)dx=1$. This gives

$$f(x) = \sqrt{\frac{\pi}{2\sigma}}\,\mathrm{erfc}\left(\frac{x}{\sqrt{2}\sigma}\right). \qquad (31)$$

Rerunning the simulation with the entrance pdf $f(x)$, we obtained the expected linear concentration profile, without any depletion layers (see Fig. 2). Injecting particles exactly at the boundary makes their first leap into the simulation too large, thus effectively decreasing the concentration profile near the boundary.

Next, we changed the time step Δt of the simulation, keeping the injection rate of new particles constant. The population of trajectories inside the interval was depleted when the time step was refined (see Fig. 3). A well-behaved numerical simulation is expected to converge as the time step is refined, rather than to result in different profiles. This shortcoming of refining the time step is remedied by replacing the constant-rate sources with time-step-dependent
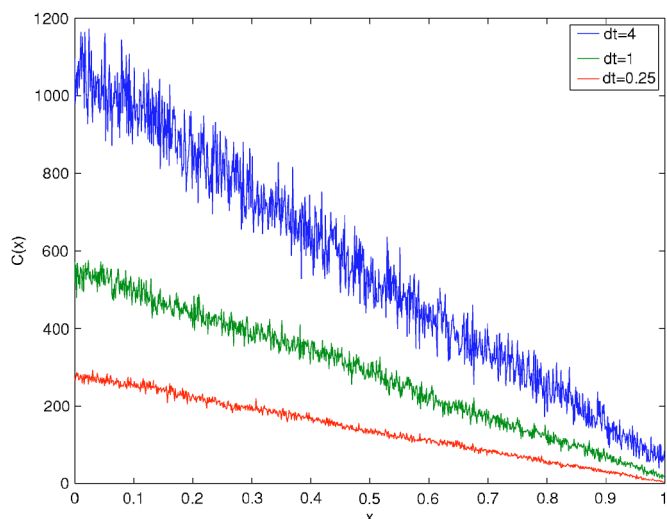
sources, as predicted by Eqs. (27) and (28). Figure 4 describes the concentration profiles for three different values of Δt and source strengths that are proportional to $1/\sqrt{\Delta t}$. The concentration profiles now converge when $\Delta t \rightarrow 0$. The key to this remedy is the calculation of the UF in diffusion.

VII. SUMMARY AND DISCUSSION

Both Einstein [14] and Smoluchowski [15] (see also [16]) pointed out that BD is a valid description of diffusion only at times that are not too short. More specifically, the Brownian
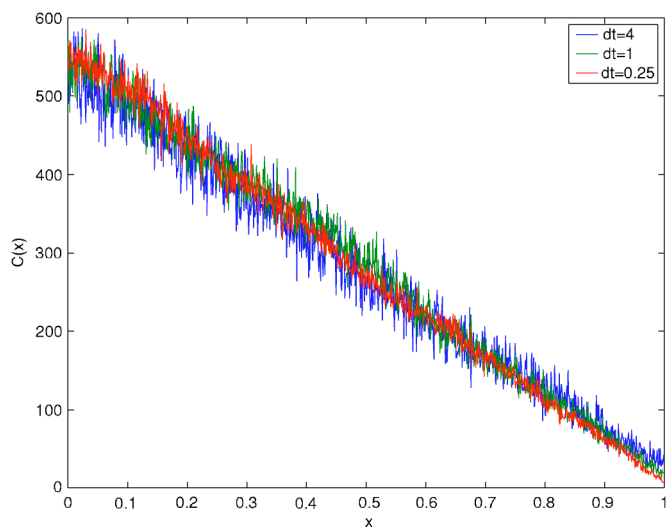

FIG. 4. (Color online) The concentration profile of Brownian trajectories that are initiated at $x=0$ and terminated at either $x=0$ or $x=1$. Three different time steps ($\Delta t=4,1,0.25$) are shown, and the injection rate of new particles is proportional to $1/\sqrt{\Delta t}$. Refining the time step does not alter the concentration profile.

approximation to the Langevin equation breaks down at times shorter than $1/\gamma$, the relaxation time of the medium in which the particles diffuse.

In a BD simulation of a channel the dynamics in the channel region may be much more complicated than the dynamics near the interface, somewhere inside the continuum bath, sufficiently far from the channel. Thus the net flux is unknown, while the boundary concentration is known. It follow that the simulation should be run with source strengths (27) and (28):

$$ J_{LR} \sim \sqrt{\frac{\varepsilon}{\pi\gamma\Delta t}}C_L + \frac{1}{2}J_{\text{net}}, \quad J_{RL} \sim \sqrt{\frac{\varepsilon}{\pi\gamma\Delta t}}C_R - \frac{1}{2}J_{\text{net}}. $$

However, J_{net} is unknown, so neglecting it relative to $(\sqrt{\varepsilon/\pi\gamma\Delta t})C_{L,R}$ will lead to steady-state boundary concentrations that are close, but not necessarily equal, to C_L and C_R. Thus a shooting procedure has to be adopted to adjust the boundary fluxes so that the output concentrations agree with C_L and C_R, and then the net flux can be readily found.

According to Eqs. (27) and (28), the efflux and influx remain finite at the boundaries and agree with the fluxes of LD if the time step in the BD simulation is chosen to be $\Delta t = 2/\gamma$ near the boundary. If the time step is chosen differently, the fluxes remain finite, but the simulation does not recover the UF of LD. At points away from the boundary, where correct UF's do not have to be recovered, the simulation can proceed in coarser time steps.

The above analysis can be generalized to higher dimensions. In three dimensions the normal component of the UF vector at a point x on a given smooth surface represents the number of trajectories that cross the surface from one side to the other, per unit area at x in unit time. Particles cross the interface in one direction if their velocity satisfies $v \cdot n(x) > 0$, where $n(x)$ is the unit normal vector to the surface at x, thus defining the domain of integration for Eq. (6).

The time course of injection of particles into a BD simulation can be chosen with any interinjection probability density, as long as the mean time between injections is chosen so that the source strength is as indicated in Eqs. (27) and (28). For example, these times can be chosen independently of each other, without creating spurious boundary layers.

ACKNOWLEDGMENTS

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