# 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)

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

where $D(x)$ is the diffusion coefficient and $\epsilon$ 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

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

Integrating Eq. (3.1) once, we obtain

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

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

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

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

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

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

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

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

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

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

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

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]

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

where $x(t)$ is the position of the ion at time $t$, $\Phi(x)$ is the electric potential, $\beta(x)$ is the friction coefficient, $\epsilon$ 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]

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

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, $\beta \to \infty$, 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.

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

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

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

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

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

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

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]

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

in a large strip $x_L < x < x_R$, $-\infty < v < \infty$, where $x_L \leq 0$ and $x_R \geq 1$ 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

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

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

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

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

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

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

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

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 $\nu$ 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

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

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

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

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

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

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 $\tau_L$, and that to the right is called $\tau_R$, 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

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

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

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

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

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

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

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

and the outgoing flux on the left is given by

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

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

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),

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

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

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

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

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

It should be noted that $\mathcal{T}$ 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 $\beta$, we obtain

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

Similarly,

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

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),

$$P(L|L) = 1 - P(R|L) \tag{6.13}$$

and

$$P(R|R) = 1 - P(L|R). \tag{6.14}$$

### 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

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

where the numerical factor $\alpha$ is given by

$$\alpha = \sqrt{\frac{1}{2\pi\epsilon}}. \tag{6.16}$$

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 $\Delta x$ 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

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

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

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

with the boundary conditions

$$P^0(R|0) = 0, \quad P^0(R|1) = 1. \tag{7.3}$$

Thus,

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

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

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

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

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

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

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

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

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

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

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

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

Using the same approximations as above, we find that

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

In particular, for a free particle,

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

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,

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

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

where

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

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

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

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 $\beta$, 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 $\beta$,[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

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

with the boundary condition

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

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

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

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 $\epsilon$ represents a high barrier.

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

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

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]

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

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 $\beta(x) = \beta = \text{const.}$, 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 over-damped 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]

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## 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

$$m \frac{d^2\tilde{x}}{d\tilde{t}^2} + m\tilde{\beta}(\tilde{x}) \frac{d\tilde{x}}{d\tilde{t}} + ze \frac{d\tilde{\Phi}(\tilde{x})}{d\tilde{x}} = \sqrt{2mkT\tilde{\beta}(\tilde{x})} \frac{d\tilde{w}}{d\tilde{t}}, \tag{A1}$$

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 $\epsilon$ 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

$$N(L|L) = -\int_{-\infty}^{0} v q(0,v|L) dv, \tag{B1}$$

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 $\mathscr{D}$, 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,

$$Pr(\tau_L < \tau_R | x,v) \equiv P(L|x,v) = -\int_{-\infty}^{0} \eta p(0,\eta|x,v) d\eta, \tag{B2}$$

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

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

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

with the no influx boundary conditions

$$p(0,\eta|x,v) = 0 \quad \text{for } \eta > 0 \tag{B4}$$

$$p(1,\eta|x,v) = 0 \quad \text{for } \eta < 0. \tag{B5}$$

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) | $\frac{ez}{m}\tilde{\Phi}(\tilde{x})=\Phi(x)\cdot\Delta\Phi$ |
| 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 $(\xi,\eta)$] 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),

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

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

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

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

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

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.,

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

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

$$\Psi(x_C)=\frac{1}{2}I. \tag{C3}$$

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

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

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

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

where

$$\omega'\equiv\omega_C\sqrt{\frac{8}{2\pi}-1}. \tag{C6}$$

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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