Uni-directional diffusion flux, Brownian and Langevin simulations

Amit Singer [*]), Zeev Schuss [†])

Department of Mathematics, Tel-Aviv University, Ramat-Aviv, 69978 Tel-Aviv, Israel

Boaz Nadler [§])

Department of Mathematics, Yale University, 10 Hillhouse Avenue P.O. Box 208283, New Haven, Connecticut 06520-8283, USA

The Wiener path integral splits the net diffusion flux into infinite unidirectional fluxes, whose difference is the classical diffusion flux. The infinite unidirectional flux is an artifact of the diffusion approximation to Langevin's equation, an approximation that fails on time scales shorter than the relaxation time $1/\gamma$. The probability of one-dimensional Brownian trajectories that cross a point in one direction per unit time Δt equals that of Langevin trajectories if $\gamma\Delta t = 2$. This result is relevant to Brownian and Langevin dynamics simulation of particles in a finite volume inside a large bath. We describe the sources of new trajectories at the boundaries of the simulation that maintain fixed average concentrations and avoid the formation of spurious boundary layers.

PACS: 31.15.Kb, 02.50.-r
Key words: Wiener's path integral, diffusion, Brownian simulations, Langevin

1 Introduction

The simulation of a test volume in an ionic solution is an important field of chemical physics [1]–[7]. Such a simulation is necessarily limited to a relatively small number of particles, due to computational difficulties. Computer simulations of diffusing particles, such as ions in solution, raise the question of connecting a small discrete simulation volume to a continuum bath. There are many algorithms, procedures and protocols for particles at the interface between the simulation region and the continuum baths (see [8] for a complete list of references on simulations). However, none of them takes into account the actual physics at the interface. The failure of these attempts calls for a theory of the interface that is compatible with the physics and for the design of simulations based on such a theory.

The mathematical model of 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

[*]) e-mail: amits@post.tau.ac.il
[†]) e-mail: schuss@post.tau.ac.il
[§]) e-mail: boaz.nadler@yale.edu

do not reproduce correctly averaged nonlinear response. However, 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.

The boundary fluctuation consists of arrivals of new particles from the bath into, and of the recirculation of particles in and out of the simulation volume. The random motion of the mobile charges brings about fluctuations 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 random influx across the 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 observed 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 random influx with the correct statistical properties of this stochastic process, as mentioned above. Thus the UF is the source strength of the influx, and also the stochastic process that counts the number of trajectories that cross the interface in one direction per unit time. This raises the problem of interface theory in simulations.

This problem arises in predicting the function of protein channels of biological membranes from their structure. They concern both the analytic description of the channel function as well as computer simulations. These problems arise from the molecular level description of the physics of ionic permeation through the channel. The prediction of the properties of ionic channels from their known structure is an interdisciplinary field, that involves biology, chemistry, physics, engineering, computer science, and mathematics. Also the inverse problem, of reverse engineering of the structure from measured channel properties, is a key problem in molecular biophysics.

None of the existing continuum descriptions of ionic permeation captures the rich phenomenology of the patch clamp experiment of Neher and Sakmann [1]. It is therefore necessary to resort to particle simulations of the permeation process. Predicting the function of an ionic channel from its structure by a computer simulation raises the question of connecting a small discrete simulation volume to a continuum bath. Computer simulations are necessarily limited to a relatively small number of particles, due to computational difficulties. Therefore, we analyze both Brownian and Langevin dynamics simulations that describe the motion of mobile ions in solution. Both models reduce the interaction of ions with the solute (water) molecules into friction, a noise term, and a dielectric constant. We consider here simulations of particles that interact with a mean field. We note, however, that the mean field approximation to interacting particles is valid in the bulk at biological concentrations. The channel and its immediate surrounding baths are expected to be within the simulation region.

Our main results are (i) The discovery of the precise range of validity of diffusion theory (Brownian motion) as a description of ionic motion in solution. We found the correct way to use diffusion theory in simulations. Mathematically this is expressed

in the determination of the range of validity of the Smoluchowski approximation to the Langevin equation; (ii) The design of Brownian and Langevin simulations that do not form spurious boundary layers, which are ubiquitous in molecular simulations in biology, chemistry, and physics. This design is based on two new mathematical insights into the theory of diffusion. One is the splitting of the probability flux of the Brownian motion into unidirectional components, which is the result of the definition of probability flux in terms of path integrals. The other is the application of methods of renewal theory to the theory of diffusion.

These results have fundamental significance in the mathematical theory of diffusion as a stochastic process. In 1905 Einstein [9] and, independently, in 1906 Smoluchowski [10] offered an explanation of the Brownian motion based on kinetic theory and demonstrated, theoretically, that the phenomenon of diffusion is the result of Brownian motion. Einstein's theory was later verified experimentally by Perrin [11] and Svedberg [12]. That of Smoluchowski was verified by Smoluchowski [13], Svedberg [14], and Westgren [15]. To connect his mathematical theory with the "*irregular movement which arises from thermal molecular movement*", Einstein made the following assumptions [9]: (1) the motion of each particle is independent of the others and (2) "*the movement of one and the same particle after different intervals of time [are] mutually independent processes, so long as we think of these intervals of time as being chosen not too small.*" Thus Einstein's theory is based on the assumption that the diffusing particles are observed intermittently at time intervals that are short, but not too short. Smoluchowski's theory was based on Langevin's more refined description of the Brownian motion [16]. The study of the mathematically idealized Brownian motion (MBM) on short time scales pushes diffusion theory beyond its range of applicability. Thus much of the mathematical phenomenology of the MBM, such as nowhere differentiability, local time, and so on, occurs on time scales that do not correspond to physical diffusion.

2 Statement of the problem

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

$$\frac{\partial p}{\partial t} = -\nabla \cdot J \,. \tag{1}$$

In the diffusion equation, the flux density $J(x,t)$ depends only on position x and time t, and is given by

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

where γ is the friction coefficient (or dynamical viscosity), $\varepsilon = \dfrac{k_B T}{m}$, k_B is Boltzmann's constant, T is absolute temperature, and m is the mass of the diffusing

particle. The external acceleration field is $f(x)$ and $p(x,t)$ is the density (or probability density) of the particles [17]. Writing the FPE in the conservation law form (1), the flux density vector $\boldsymbol{J} = (J_x, J_v)$ is given by

$$\begin{aligned} J_x(x,v,t) &= vp(x,v,t)\,, \\ J_v(x,v,t) &= -\left(\gamma v - f(x)\right) p(x,v,t) - \varepsilon\gamma \nabla_v p(x,v,t)\,. \end{aligned} \tag{3}$$

We interpret $\nabla = (\nabla_x, \nabla_v)$ in (1). While the density $p(x,t)$ in the diffusion equation (1) with (2) is the probability density of the trajectories of the Smoluchowski stochastic differential equation

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

where $w(t)$ is a vector of independent standard Wiener processes (Brownian motions), the density $p(x,v,t)$ in the FPE is the probability density of the phase space trajectories of the Langevin equation

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

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 v at each point x tells the two UFs apart. Thus, in one dimension,

$$\begin{aligned} J_{LR}(x,t) &= \int_0^\infty vp(x,v,t)\,\mathrm{d}v\,, \qquad J_{RL}(x,t) = -\int_{-\infty}^0 vp(x,v,t)\,\mathrm{d}v\,, \\ J_{\mathrm{net}}(x,t) &= J_{LR}(x,t) - J_{RL}(x,t) = \int_{-\infty}^\infty vp(x,v,t)\,\mathrm{d}v\,. \end{aligned} \tag{6}$$

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 [18]. These trajectories cross and recross every point x infinitely many times in any time interval $[t, t+\Delta t]$, giving rise to infinite UFs. However, the net diffusion flux is finite, as indicated in eq.(2). This phenomenon was discussed in detail in [19], 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 UFs measured in diffusion across biological membranes by using radioactive tracer [1] are in effect UFs at absorbing boundaries, because the tracer is a separate ionic species [20].

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 [21]. The "paradox" is resolved by a new

derivation of the FPE for 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. [22, 23, 24, 25]) by the method of M. Kac [26]. The new derivation shows that the path integral definition of UF in diffusion, as first introduced in [19], 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 the Langevin descriptions of the random motion of diffusing particles was hinted at by both Einstein and Smoluchowski. Einstein [9] 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 [10] 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 that $1/\gamma$, which is the same as in Einstein's theory of diffusion [27].

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, for the description 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 UFs 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 Langevin dynamics (LD) in terms of the Wiener path integral, analogous to its definition for the BD in [19]. 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.(26). 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 Section 3, we derive the FPE for the LD (5) from the Wiener path integral. In Section 4, we define the unidirectional probability flux for LD by the path integral and show that is indeed given by (6). In Section 5, we use the results of [21] to calculate explicitly the UF in the Smoluchowski approximation to the solution of the FPE and to recover the flux (2). In Section 6, we use the results of [19] 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 (7), the UFs of LD and BD coincide. In Section 7 we describe the a BD simulation of diffusion between fixed concentrations and give results of simulations. In Section 8 we discuss Langevin trajectories between fixed concentrations. Finally, Section 9 is a summary and discussion of the results.

3 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

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

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

$$\begin{aligned} &\mathrm{Prob}\,\{x(t+\Delta t) = x, v(t+\Delta t) = v\} = p(x, v, t+\Delta t) = \\ &= o(\Delta t) + \frac{1}{\sqrt{4\varepsilon\gamma\pi\Delta t}} \int_a^b \int_{-\infty}^{\infty} p(\xi, \eta, t)\delta(x - \xi - \eta\Delta t)\times \\ &\qquad \times \exp\left\{-\frac{[v - \eta - [-\gamma\eta + f(\xi)]\Delta t]^2}{4\varepsilon\gamma\Delta t}\right\} \mathrm{d}\xi\,\mathrm{d}\eta\,. \end{aligned} \tag{12}$$

To understand (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 FPE from eq.(12). Integration with respect to ξ gives

$$p(x,v,t+\Delta t) = o(\Delta t) + \frac{1}{\sqrt{4\varepsilon\gamma\pi\Delta t}} \int_{-\infty}^{\infty} p(x-\eta\Delta t,\eta,t)\times \\ \times \exp\left\{-\frac{[v-\eta-[-\gamma\eta+f(x-\eta\Delta t)]\Delta t]^2}{4\varepsilon\gamma\Delta t}\right\} \mathrm{d}\eta\,. \tag{13}$$

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

$$p(x,v,t+\Delta t) = \frac{1}{\sqrt{2\pi}(1-\gamma\Delta t+o(\Delta t))} \int_{-\infty}^{\infty} \mathrm{e}^{-u^2/2}\,\mathrm{d}u \times \\ \times p\Big(x - v(1+\gamma\Delta t)\Delta t + o(\Delta t), \\ v(1+\gamma\Delta t) + u\sqrt{2\varepsilon\gamma\Delta t} - f(x)\Delta t(1+\gamma\Delta t) + o(\Delta t), t\Big)\,. \tag{14}$$

Abbreviating $\tilde{x} = x - v(1+\gamma\Delta t)\Delta t + o(\Delta t)$, $\tilde{v} = v(1+\gamma\Delta t) + u\sqrt{2\varepsilon\gamma\Delta t} - f(x)\Delta t(1+\gamma\Delta t) + o(\Delta t)$ and re-expanding in powers of Δt, we get

$$p\,(\tilde{x},\tilde{v},t) = p(x,v,t) - v\Delta t\frac{\partial p(x,v,t)}{\partial x} + \\ + \frac{\partial p(x,v,t)}{\partial v}\left(v\gamma\Delta t + u\sqrt{2\varepsilon\gamma\Delta t} - f(x)\Delta t + o(\Delta t)\right) + \\ + \varepsilon\gamma u^2\Delta t\frac{\partial^2 p(x,v,t)}{\partial v^2} + o(\Delta t)\,,$$

so (14) gives

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

Dividing by Δt and taking the limit $\Delta t \to 0$, we obtain the FPE

$$\frac{\partial p(x,v,t)}{\partial t} = -v\frac{\partial p(x,v,t)}{\partial x} + \frac{\partial}{\partial v}\left[\left(\gamma v - f(x)\right)p(x,v,t)\right] + \varepsilon\gamma\frac{\partial^2 p(x,v,t)}{\partial v^2}\,, \tag{15}$$

which is the conservation law (1) with the flux components (3). The UF $J_{LR}(x,t)$ is usually defined as the integral of $J_x(x,v,t)$ over the positive velocities [21, and references therein], that is,

$$J_{LR}(x,t) = \int_0^\infty vp(x,v,t)\,\mathrm{d}v\,. \tag{16}$$

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

4 The unidirectional flux of the Langevin equation

The instantaneous unidirectional probability flux from left to right at a point x is defined as the probability per unit time (Δt), of Langevin trajectories that are to the left of x at time t (with any velocity) and propagate to the right of x 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

$$\begin{aligned} J_{LR}(x,t) = \lim_{\Delta t\to 0}\frac{1}{\Delta t}\int_{-\infty}^{x}\mathrm{d}\xi\int_{x}^{\infty}\mathrm{d}x\int_{-\infty}^{\infty}\mathrm{d}\eta\int_{-\infty}^{\infty}\mathrm{d}v\,\frac{1}{\sqrt{4\varepsilon\gamma\pi\Delta t}}p(\xi,\eta,t)\times \\ \times\delta(x-\xi-\eta\Delta t)\exp\left\{-\frac{\left(v-\eta-[-\gamma\eta+f(\xi)]\Delta t\right)^2}{4\varepsilon\gamma\Delta t}\right\}. \end{aligned} \tag{17}$$

Integrating with respect to v eliminates the exponential factor and integration with respect to ξ fixes ξ at $x-\eta\Delta t$, so

$$\begin{aligned} J_{LR}(x,t) &= \lim_{\Delta t\to 0}\frac{1}{\Delta t}\int\int_{x-\eta\Delta t<x}p(x-\eta\Delta t,\eta,t)\,\mathrm{d}\eta\,\mathrm{d}x = \\ &= \lim_{\Delta t\to 0}\frac{1}{\Delta t}\int_0^\infty d\eta\int_{x-\eta\Delta t}^{x}p(u,\eta,t)\,\mathrm{d}u \\ &= \int_0^\infty \eta p(x,\eta,t)\,\mathrm{d}\eta\,. \end{aligned} \tag{18}$$

The expression (18) is identical to (16).

5 The Smoluchowski approximation to the unidirectional current

The following calculations were done in [21] 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

$$p(x,v,t)\sim\frac{\mathrm{e}^{-v^2/2\varepsilon}}{\sqrt{2\pi\varepsilon}}\left\{p(x,t)-\frac{1}{\gamma}\left[\frac{\partial p(x,t)}{\partial x}-\frac{1}{\varepsilon}f(x)p(x,t)\right]v+O\left(\frac{1}{\gamma^2}\right)\right\}, \tag{19}$$

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

$$\gamma\frac{\partial p(x,t)}{\partial t}=\varepsilon\frac{\partial^2 p(x,t)}{\partial x^2}-\frac{\partial}{\partial x}\left[f(x)p(x,t)\right]. \tag{20}$$

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

$$\begin{aligned}J_{LR}(x,t)&=\int_0^\infty vp(x,v,t)\,\mathrm{d}v=\\&=\int_0^\infty v\frac{\mathrm{e}^{-v^2/2\varepsilon}}{\sqrt{2\pi\varepsilon}}\left\{p(x,t)-\frac{1}{\gamma}\left[\frac{\partial p(x,t)}{\partial x}-\frac{1}{\varepsilon}f(x)p(x,t)\right]v+O\left(\frac{1}{\gamma^2}\right)\right\}\mathrm{d}v=\\&=\sqrt{\frac{\varepsilon}{2\pi}}p(x,t)-\frac{1}{2\gamma}\left[\varepsilon\frac{\partial p(x,t)}{\partial x}-f(x)p(x,t)\right]+O\left(\frac{1}{\gamma^2}\right).\end{aligned} \tag{21}$$

Similarly, the UF from right to left is

$$\begin{aligned}J_{RL}(x,t)&=-\int_{-\infty}^0 vp(x,v,t)\,\mathrm{d}v=\\&=\sqrt{\frac{\varepsilon}{2\pi}}p(x,t)+\frac{1}{2\gamma}\left[\varepsilon\frac{\partial p(x,t)}{\partial x}-f(x)p(x,t)\right]+O\left(\frac{1}{\gamma^2}\right).\end{aligned} \tag{22}$$

Both UFs in (21) and (22) are finite and proportional to the marginal density at x. The net flux is the difference

$$J_{\mathrm{net}}(x,t)=J_{LR}(x,t)-J_{RL}(x,t)=-\frac{1}{\gamma}\left[\varepsilon\frac{\partial p(x,t)}{\partial x}-f(x)p(x,t)\right], \tag{23}$$

as in classical diffusion theory [21], [28].

6 The 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 [17]

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

As in Section 4, the unidirectional probability current (flux) density at a point x can be expressed in terms of a path integral as

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

where

$$\begin{aligned}J_{LR}(x,t,\Delta t)&=\sqrt{\frac{\gamma}{4\pi\varepsilon\Delta t}}\int_0^\infty\mathrm{d}\xi\int_\xi^\infty\mathrm{d}\zeta\,\exp\left\{-\frac{\gamma\zeta^2}{4\varepsilon}\right\}\times\\&\times\left\{p\left(x,t\right)-\sqrt{\Delta t}\left[-\frac{\zeta f(x)}{2\varepsilon}p\left(x,t\right)+\left(\zeta-\xi\right)\frac{\partial p(x,t)}{\partial x}\right]+O\left(\frac{\Delta t}{\gamma}\right)\right\}.\end{aligned}$$

It was shown in [19] that

$$J_{LR}(x,t,\Delta t)=\sqrt{\frac{\varepsilon}{\pi\gamma\Delta t}}\,p(x,t)+\frac{1}{2\gamma}\left(f(x)p(x,t)-\varepsilon\frac{\partial p(x,t)}{\partial x}\right)+O\left(\frac{\sqrt{\Delta t}}{\gamma^{3/2}}\right). \quad (26)$$

Similarly,

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

where

$$\begin{aligned}J_{RL}(x,t,\Delta t)&=\sqrt{\frac{\gamma}{4\pi\varepsilon\Delta t}}\int_0^\infty \mathrm{d}\xi\int_\xi^\infty \mathrm{d}\zeta\,\exp\left\{-\frac{\gamma\zeta^2}{4\varepsilon}\right\}\times\\ &\times\left\{p\,(x,t)+\sqrt{\Delta t}\left[-\frac{\zeta f(x)}{2\varepsilon}p\,(x,t)+(\zeta-\xi)\,\frac{\partial p(x,t)}{\partial x}\right]+O\left(\frac{\Delta t}{\gamma}\right)\right\}= \quad (27)\\ &=\sqrt{\frac{\varepsilon}{\pi\gamma\Delta t}}\,p(x,t)-\frac{1}{2\gamma}\left(f(x)p(x,t)-\varepsilon\frac{\partial p(x,t)}{\partial x}\right)+O\left(\frac{\sqrt{\Delta t}}{\gamma^{3/2}}\right).\end{aligned}$$

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

$$\begin{aligned}J_{\mathrm{net}}(x_1,t)&=\lim_{\Delta t\to 0}\left\{J_{LR}(x_1,t,\Delta t)-J_{RL}(x_1,t,\Delta t)\right\}=\\ &=-\frac{1}{\gamma}\left[\varepsilon\frac{\partial}{\partial x}p(x,t)-f(x)p(x,t)\right],\end{aligned} \quad (28)$$

which is identical to (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 infinitely many times in any time interval $[t,t+\Delta t]$ [29]. Obviously, such a vacillation creates infinite UFs.

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

$$\gamma\Delta t=2 \quad (29)$$

in equations (26) and (27) gives (21) and (22). This means that the diffusion approximation to the FPE on time scales shorter than $1/\gamma$ gives rise to non-physical artifacts, however, it is valid on longer time scales. The unidirectional flux in a simulation of diffusion agrees with that of the FPE only if (29) holds, otherwise, the unidirectional fluxes are missed, though the net flux is still correct.

7 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: (i) According to the dynamics (4), new trajectories that are started at $x(-\Delta t) = 0$ move to $x(0) = \sqrt{\frac{2\varepsilon}{\gamma}}|\Delta w|$; (ii) The dynamics progresses according to the Euler scheme $x(t + \Delta t) = x(t) + \sqrt{\frac{2\varepsilon}{\gamma}}\Delta w$; (iii) The trajectory is terminated if $x(t) > 1$ or $x(t) < 0$. The parameters are $\varepsilon = 1$, $\gamma = 1000$, $\Delta t = 1$. We ran 10,000 random trajectories and collected their statistics with the results shown in Figure 1.

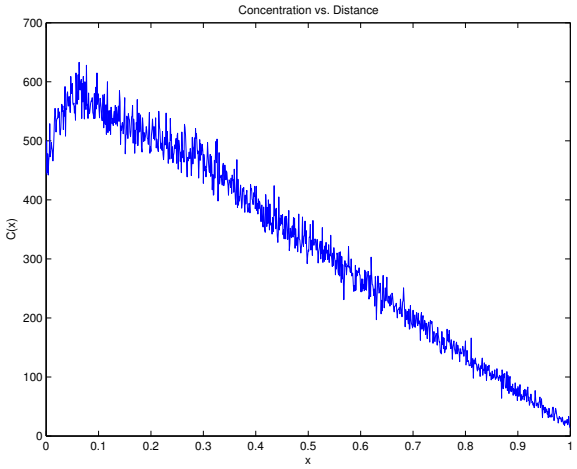

Fig. 1. The concentration profile of Brownian trajectories that are initiated at $x = 0$ with a normal distribution, and terminated at either $x = 0$ or $x = 1$.

The simulated 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 [30]. 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

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

where $\sigma^2 = \dfrac{2\varepsilon\Delta t}{\gamma}$ and C is determined by the normalization condition $\int_0^\infty f(x)\,\mathrm{d}x = 1$. This gives

$$f(x) = \sqrt{\frac{\pi}{2\sigma}}\,\mathrm{erfc}\left(\frac{x}{\sqrt{2}\sigma}\right). \tag{30}$$

Rerunning the simulation with the entrance pdf $f(x)$, we obtained the expected linear concentration profile, without any depletion layers (see Figure 2).

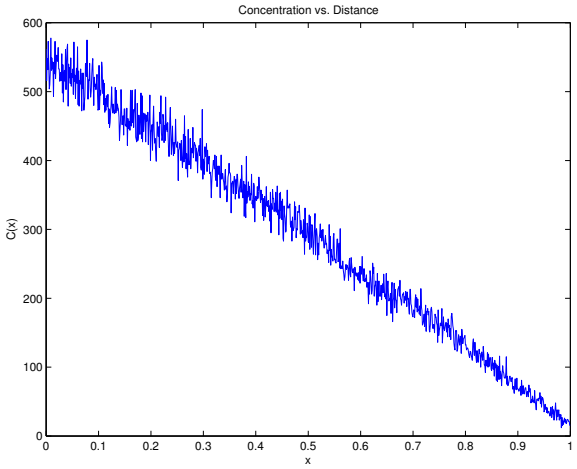

Fig. 2. The concentration profile of Brownian trajectories that are initiated at $x = 0$ with the residual of the normal distribution, and terminated at either $x = 0$ or $x = 1$.

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 Figure 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.(26)-(27). 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 $\Delta t \to 0$. The key to this remedy is the calculation of the UF in diffusion.

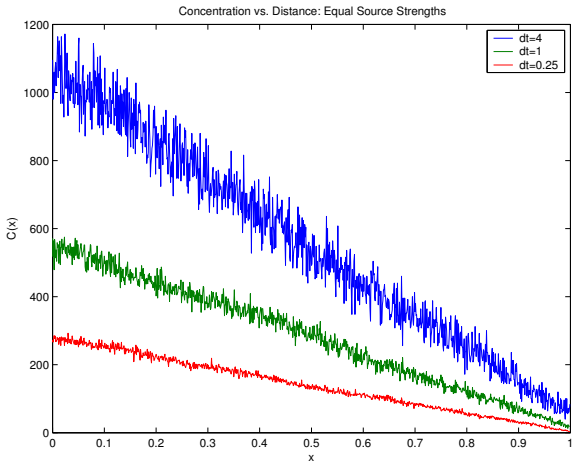

Fig. 3. The concentration profile of Brownian trajectories that are initiated at $x = 0$ and terminated at either $x = 0$ or $x = 1$. Three different time steps ($\Delta t = 4, 1, 0.25$) were used, but the injection rate of new particles remained constant. Refining the time step decreases the concentration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

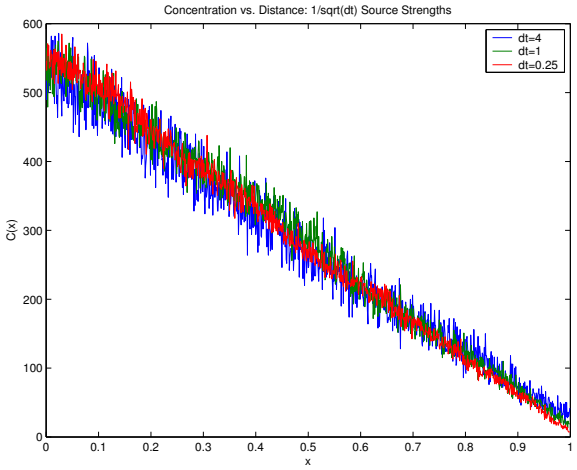

Fig. 4. The concentration profile of Brownian trajectories that are initiated at $x = 0$ and terminated at either $x = 0$ or $x = 1$. Three different time steps ($\Delta t = 4, 1, 0.25$) are shown, and the injection rate of new particles is proportional to $1/\sqrt{\Delta t}$. Refining the time step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

8 Langevin trajectories between fixed concentrations

The expansion (19) gives the stationary pdfs of velocities of the particles crossing the interface into the given volume as

$$\begin{aligned} p_L(v) &\sim \frac{\frac{\mathrm{e}^{-v^2/2\varepsilon}}{\sqrt{2\pi\varepsilon}}\left\{1+\frac{\mathcal{J}v}{\varepsilon C_L}\right\}}{\frac{1}{2}+\frac{\mathcal{J}}{C_L\sqrt{2\pi\varepsilon}}} \quad \text{for} \quad v>0\,, \\ p_R(v) &\sim \frac{\frac{\mathrm{e}^{-v^2/2\varepsilon}}{\sqrt{2\pi\varepsilon}}\left\{1-\frac{\mathcal{J}v}{\varepsilon C_R}\right\}}{\frac{1}{2}+\frac{\mathcal{J}}{C_R\sqrt{2\pi\varepsilon}}} \quad \text{for} \quad v<0\,, \end{aligned} \tag{31}$$

where $\mathcal{J}$ is the net probability flux through the channel. The source strengths (unidirectional fluxes at the interfaces) are given by (27) as

$$\begin{aligned} J_L &= \sqrt{\frac{\varepsilon}{2\pi}}C_L - \frac{\mathcal{J}}{2} + O\left(\frac{1}{\gamma^2}\right), \\ J_R &= \sqrt{\frac{\varepsilon}{2\pi}}C_R + \frac{\mathcal{J}}{2} + O\left(\frac{1}{\gamma^2}\right). \end{aligned}$$

Therefore Langevin trajectories should be injected at the boundaries of the simulation at rates given by the source strengths and their velocities should be chosen according to the densities (31) [31].

As in the case of Brownian simulations, new trajectories have to be injected into the simulation volume Ω with displacements and velocities as though the simulation extends outside Ω, consistently with the scheme (10), (11), because the interface is a fictitious boundary. The scheme (10), (11) 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 (10), (11),

$$\begin{aligned} &\Pr\{x(t')=x, v(t')=v \,|\, x(t)=\xi, v(t)=\eta\} = \\ &\quad = \frac{\delta(x-\xi-\eta\Delta t)}{(4\pi\varepsilon\gamma\Delta t)^{3/2}} \exp\left\{-\frac{|v-\eta-(\gamma v - f(\xi))\Delta t|^2}{4\varepsilon\gamma\Delta t}\right\} + o(\Delta t)\,. \end{aligned} \tag{32}$$

The stationary pdf $p(\xi, \eta)$ of such a bath point is given in (19). The conditional probability of such a landing is

$$\Pr\{x, v \,|\, x\in\Omega, \xi\in B\} = \frac{\displaystyle\int_{\mathbb{R}^3} \mathrm{d}\eta \int_B \mathrm{d}\xi \Pr\{v(t')=v, x(t')=x \,|\, \xi, \eta\} p(\xi,\eta)}{\Pr\{x\in\Omega, \xi\in B\}}\,, \tag{33}$$

where the denominator is a normalization constant such that

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

Thus the first point of a new trajectory is chosen according to the pdf (33) and the subsequent points are generated according to (10), (11), that is, with the transition pdf (32), until the trajectory leaves Ω. By construction, this scheme recovers the joint pdf (19) 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

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

which means that γ is sufficiently large, the flux term in eq.(19) is negligible relative to the concentration term. The concentration term is linear with slope $\mathcal{J}$ and thus can be approximated by a constant, so that $p(\xi) = p(0) + O\left(\gamma^{-1}\right)$ in the left bath. Actually, the value of $p(0) \neq 0$ is unimportant, because it cancels out in the normalized pdf (33), which comes out to be

$$\begin{aligned} \Pr\{x, v \,|\, x > 0, \xi < 0\} = {} & \frac{\exp\left\{-\dfrac{v^2}{2\varepsilon[1 + (\gamma\Delta t)^2]}\right\}}{2\varepsilon\Delta t\sqrt{1 + (\gamma\Delta t)^2}} \times \\ & \times \operatorname{erfc}\left(\sqrt{\frac{1 + (\gamma\Delta t)^2}{4\varepsilon\gamma\Delta t}}\left(\frac{x}{\Delta t} - v\frac{1 - \gamma\Delta t}{1 + (\gamma\Delta t)^2}\right)\right) . \end{aligned} \tag{34}$$

In the limit $\Delta t \to 0$ we obtain from eq.(34)

$$\Pr\{x, v \,|\, x > 0, \xi < 0\} \to \frac{2\delta(x)H(v)}{\sqrt{2\pi\varepsilon}} \, \mathrm{e}^{-v^2/2\varepsilon} \,, \tag{35}$$

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 (31). Note, however, that injecting trajectories by any Markovian scheme, with the limiting distribution (35) and with any time step Δt, creates a boundary layer [32].

A 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 $x = 0$ (red) and once with the pdf (34) (blue) shows that a boundary layer is formed in the former, but not in the latter (see Figure 5).

An alternative way to interpret eq.(34) is to view the simulation (10), (11) 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

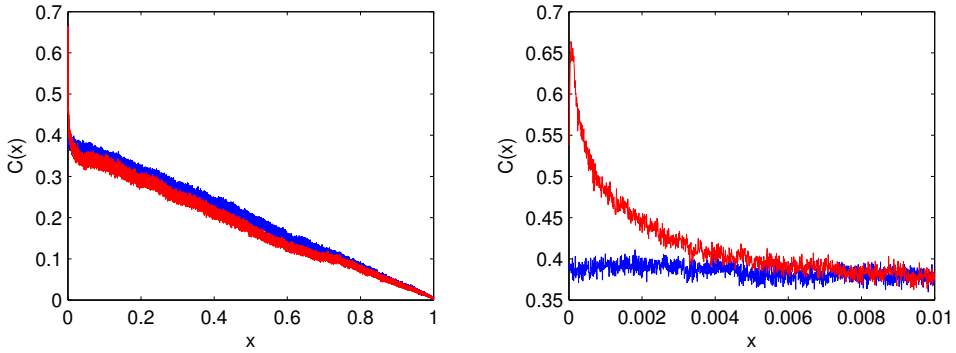

Fig. 5. Left panel: Concentration against displacement of a LD simulation with injecting particles according to the residual distribution (34) (blue), and according to the Maxwellian velocity distribution (35) exactly at the boundary (red). The two graphs are almost identical, except for a small boundary layer near $x = 0$ in red. Right panel: Zoom in of the concentration profile in the boundary layer $x < 0.01 = \sqrt{\varepsilon}/\gamma$.

boundary, the time of insertion has 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 (34).

9 Summary and discussion

Both Einstein [9] and Smoluchowski [10] pointed out that BD is a valid description of diffusion only at times that are not too short. More specifically, the Brownian 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 (26), (27),

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

However, $J_{\rm net}$ is unknown, so neglecting it relative to $\sqrt{\frac{\varepsilon}{\pi\gamma\Delta t}}\, C_{L,R}$ 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 (26) and (27), 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 $\Delta t = \frac{2}{\gamma}$ 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 UFs 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 inter injection probability density, as long as the mean time between injections is chosen so that the source strength is as indicated in (26) and (27). For example, these times can be chosen independently of each other, without creating spurious boundary layers.

This research was partially supported by research grants from the US-Israel Binational Science foundation, the Israel Science Foundation, DARPA, NSF and NIH.

References

[1] B. Hille: *Ionic Channels of Excitable Membranes*, Sinauer Associates Inc., Sunderland, 3rd ed., 2001, pp. 1–814.

[2] W. Im and B. Roux: J. Mol. Bio. **322** (2002) 851.

[3] W. Im and B. Roux: J. Mol. Bio. **319** (2002) 1177.

[4] M. Schumaker: J. Chem. Phys. **117** (2002) 2469.

[5] B. Corry, M. Hoyles, T. W. Allen, M. Walker, S. Kuyucak and S.H. Chung: Biophys. J. **82** (2002) 1975.

[6] S. Wigger-Aboud, M. Saraniti and R.S. Eisenberg: Nanotech **3** (2003) 443.

[7] T.A. van der Straaten, J. Tang, R.S. Eisenberg, U. Ravaioli and N.R. Aluru: J. Computational Electronics **1** (2002) 335.

[8] Naeh T.: *Simulation of ionic solution*, Ph.D. dissertation, Department of Mathematics, Tel-Aviv University, 2001.

[9] A. Einstein: Ann. d. Physik **17** (1905) 549; See also *Investigations on the Theory of the Brownian Movement*, Dover, 1956.

[10] M.R. von Smolan Smoluchowski: Rozprawy Kraków **A46** (1906) 257; see also Ann. d. Physik **21** (1906) 756.

[11] J. Perrin: C.R. Paris **146** (1908) 967.

[12] T. Svedberg: Z. Elektrochemie **12** (1906) 853.

[13] M.R. von Smolan Smoluchowski: Wien. Ber. **123** (1914) 2381.

[14] T. Svedberg: Zeits. f. physik Chemie **77** (1911) 147.

[15] A. Westgren: Arkiv for Matematik, Astronomi, och Fysik **11** (1916), **13, 14** (1918).

[16] P. Langevin: C.R. Paris **146** (1908) 530.

[17] Z. Schuss: *Theory and Applications of Stochastic Differential Equations*, Wiley, NY, 1980.

[18] A. Dvoretzky, P. Erdös and S. Kakutani: in *Proc. Fourth Berkeley Symp. on Math. Stat. and Probability II*, pp.103-116. Univ. of Calif. Press 1961.

[19] A. Marchewka and Z. Schuss: Phys. Rev. A **61** (2000) 052107.

[20] D.P. Chen and R.S. Eisenberg: Biophys. J. **65** (1993) 727.

[21] R.S. Eisenberg, M.M. Kłosek and Z. Schuss: J. Chem. Phys. **102** (1995) 1767.

[22] H. Kleinert: *Path Integrals in Quantum Mechanics, Statistics, and Polymer Physics*, World Scientific, NY 1994.

[23] L.S. Schulman: *Techniques and Applications of Path Integrals*, Wiley, NY 1981.

[24] F. Langouche, D. Roekaerts and E. Tirapegui: *Functional Integration and Semiclassical Expansions*, (Mathematics & Its Applications), D. Reidel, Dodrecht, 1982.

[25] M. Freidlin: *Functional Integration and Partial Differential Equations*, (Annuals of Mathematics Studies, 109), Princeton, NJ, 1985.

[26] M. Kac, *Probability and Related Topics in the Physical Sciences*, Interscience, NY, 1959.

[27] S. Chandrasekhar: Rev. Mod. Phys. **15** (1943) 1; also in N. Wax, ed.: *Selected Papers on Noise and Stochastic Processes*, Dover, New York, 1954.

[28] C.W. Gardiner: *Handbook of Stochastic Methods*, 2-nd edition, Springer, NY, 1985.

[29] K. Itô and H.P. McKean, Jr.: *Diffusion Processes and their Sample Paths*, Springer, NY, 1996.

[30] S. Karlin and H.M. Taylor: *A First Course in Stochastic Processes*, Academic Press, NY, 1975.

[31] B. Nadler, Z. Schuss and A. Singer: Phys. Rev. Lett. **94** (2005) 218101.

[32] A. Singer, Z. Schuss, B. Nadler and R.S. Eisenberg: Phys. Rev. E **70** (2004) 061106.