# BROWNIAN SIMULATIONS AND UNI-DIRECTIONAL FLUX IN DIFFUSION

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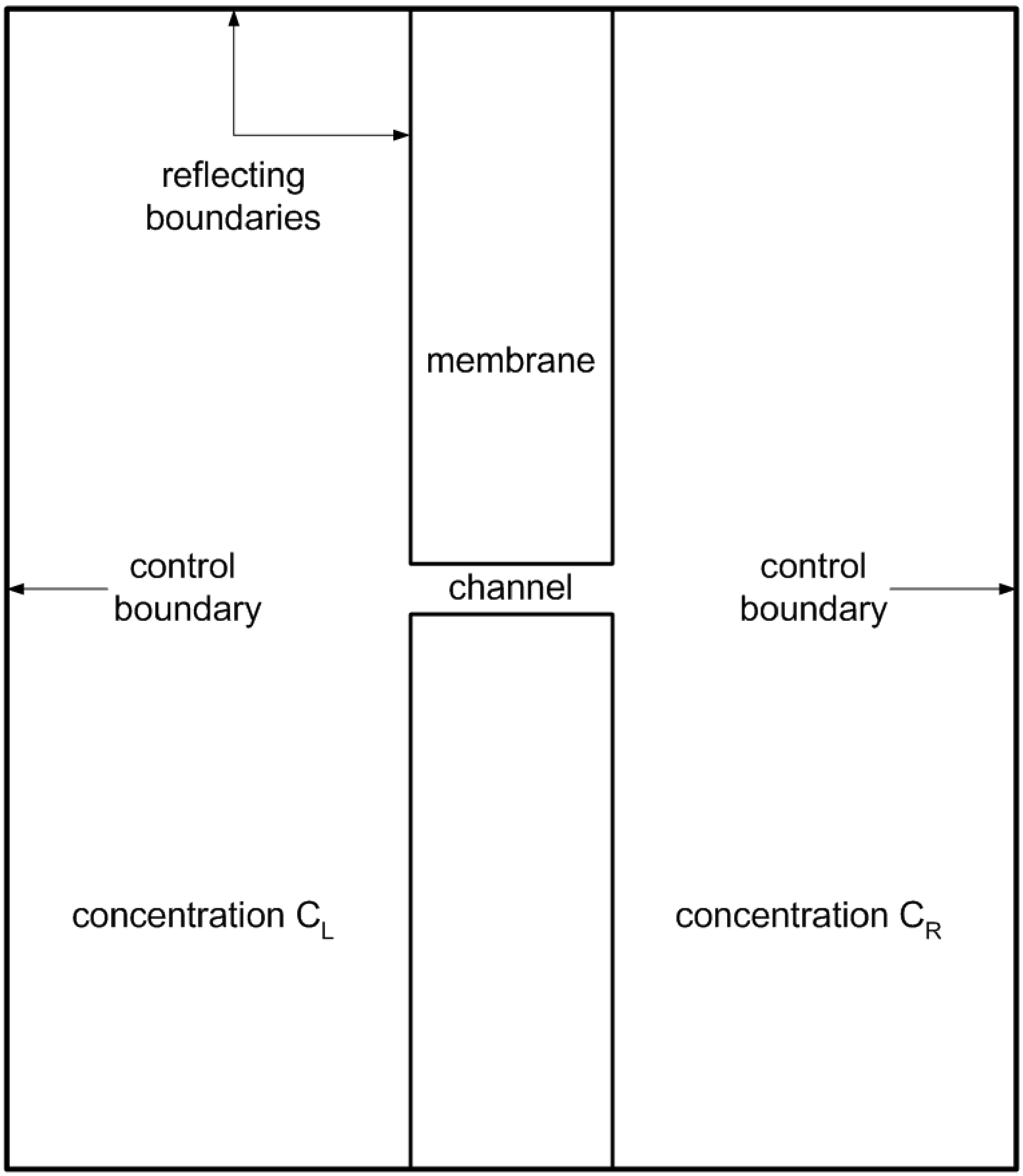
## Introduction

• Numerical simulations of protein channels of biological membranes require connections of a small discrete simulation volume to large baths that are maintained at fixed concentrations and voltages.

• The continuum baths are connected to the simulation through interfaces, located in the baths sufficiently far from the channel. Average boundary concentrations have to be maintained at their values in the baths by injecting and removing particles at the interfaces.

# The Physical Setup



## Motivation

• The interface is an imaginary wall, which the physical trajectories of the diffusing particles cross and recross any number of times.

• The efflux of simulated trajectories through the interface is seen in the simulation, however, the influx of new trajectories, which is the unidirectional flux (UF) of diffusion, has to be calculated so as to reproduce the physical conditions.

• The UF is the source strength of the influx, and also the number of trajectories that cross the interface in one direction per unit time.

• The classical diffusion equation defines net diffusion flux, but not unidirectional fluxes.

## Outline

- The stochastic formulation of classical diffusion in terms of the Wiener process leads to a Wiener path integral, which can split the net flux into unidirectional fluxes.

- These unidirectional fluxes are infinite, though the net flux is finite and agrees with classical theory.

- The infinite unidirectional flux is an artifact caused by replacing the Langevin dynamics with its Smoluchowski approximation, which is classical diffusion.

- The probability of Brownian trajectories that cross an interface in one direction in unit time $\Delta t$ equals that of the probability of the corresponding Langevin trajectories if $\gamma\Delta t = 2$.

- The unidirectional flux is proportional to the concentration and inversely proportional to $\sqrt{\Delta t}$ to leading order.

## Net Flux

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

$$\frac{\partial p}{\partial t} = -\nabla \cdot \boldsymbol{J}.$$

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

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

where $\gamma$ 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 $\boldsymbol{f}(\boldsymbol{x})$ and $p(\boldsymbol{x}, t)$ is the density (or probability density) of the particles.

## Net Flux cont.

The flux density in the FPE is given by where the net probability flux density vector has the components

$$\begin{aligned} J_{\boldsymbol{x}}(\boldsymbol{x},\boldsymbol{v},t) &= \boldsymbol{v}p(\boldsymbol{x},\boldsymbol{v},t) \\ J_{\boldsymbol{v}}(\boldsymbol{x},\boldsymbol{v},t) &= -\left(\gamma\boldsymbol{v}-\boldsymbol{f}(\boldsymbol{x})\right)p(\boldsymbol{x},\boldsymbol{v},t) \\ &\quad -\varepsilon\gamma\nabla_{\boldsymbol{v}}p(\boldsymbol{x},\boldsymbol{v},t). \end{aligned}$$

$\boldsymbol{J}$ is a *net flux density* vector. Splitting of $\boldsymbol{J}$ into into two unidirectional components across a given surface, such that the net flux $\boldsymbol{J}$ is their difference is pretty obvious in the FPE, because the velocity $\boldsymbol{v}$ at each point $\boldsymbol{x}$ tells the two UFs apart. Thus, in one dimension,

$$\begin{aligned} J_{LR}(x,t) &= \int_0^\infty vp(x,v,t)\,dv, \\ J_{RL}(x,t) &= -\int_{-\infty}^0 vp(x,v,t)\,dv \\ J_{\text{net}}(x,t) &= J_{LR}(x,t)-J_{RL}(x,t) \\ &= \int_{-\infty}^\infty vp(x,v,t)\,dv. \end{aligned}$$

## Infinite UFs

In contrast, the net flux $J(x,t)$ in the DE cannot be split this way, because velocity is not a state variable. How to split the net flux?

The trajectories of a diffusion process do not have well defined velocities, because they are nowhere differentiable with probability 1.

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.

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 are in effect UFs at absorbing boundaries, because the tracer is a separate ionic species.

## An Apparent Paradox

An apparent paradox arises in the Smoluchowski approximation of the FPE by the DE. Using the path integral to define the UF of the Langevin trajectories, it can be shown that their UFs are those given before. These expressions remain finite in the Smoluchowski limit $\gamma \to \infty$.

In contrast, the path integral definition of the UF of the Smoluchowski (Brownian) trajectories gives infinite UFs for all $\gamma$.

## Short Time Discrepancy

The discrepancy between the Einstein and the Langevin descriptions of the random motion of diffusing particles was hinted at by both Einstein and Smoluchowski.

Einstein 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.

Smoluchowski 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.

## Langevin Dynamics

The Langevin equation

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

is rewritten as the phase space system

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

This means that in time $\Delta t$ the dynamics progresses, more or less, according to

$$\begin{aligned} x(t+\Delta t) &= x(t) + v(t)\Delta t, \\ v(t+\Delta t) &= v(t) + [-\gamma v(t) + f(x(t))]\Delta t \\ &\quad + \sqrt{2\varepsilon\gamma}\,\Delta w, \end{aligned}$$

where $\Delta w \sim \mathcal{N}(0, \Delta t)$. This means that

$$p(x, v, t+\Delta t) = \frac{1}{\sqrt{4\varepsilon\gamma\pi\Delta t}} \int\int p(\xi, \eta, t)\delta(x - \xi - \eta\Delta t) \times \exp\left\{-\frac{[v - \eta - [-\gamma\eta + f(\xi)]\Delta t]^2}{4\varepsilon\gamma\Delta t}\right\} d\xi\, d\eta.$$

## The Fokker-Planck Equation

Using the path integral formulation we derive the Fokker-Planck equation

$$\begin{aligned}\frac{\partial p(x,v,t)}{\partial t} &= -v\frac{\partial p(x,v,t)}{\partial x} \\ &\quad +\frac{\partial}{\partial v}\left[(\gamma v - f(x))\,p(x,v,t)\right] \\ &\quad +\varepsilon\gamma\frac{\partial^2 p(x,v,t)}{\partial v^2}\end{aligned}$$

## The unidirectional flux of the Langevin equation

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

$$\begin{aligned} J_{LR}(x_1,t) &= \lim_{\Delta t\to 0}\frac{1}{\Delta t}\int_{-\infty}^{x_1} d\xi \int_{x_1}^{\infty} dx \int_{-\infty}^{\infty} d\eta \int_{-\infty}^{\infty} dv \\ &\quad \times \frac{1}{\sqrt{4\varepsilon\gamma\pi\Delta t}} p(\xi,\eta,t)\delta(x-\xi-\eta\Delta t) \\ &\quad \times \exp\left\{-\frac{[v-\eta-[-\gamma\eta+f(\xi)]\Delta t]^2}{4\varepsilon\gamma\Delta t}\right\}. \end{aligned}$$

## The unidirectional flux of the Langevin equation

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

$$\begin{aligned} & J_{LR}(x_1, t) \\ &= \lim_{\Delta t \to 0} \frac{1}{\Delta t} \int\int_{x-\eta\Delta t < x_1} p(x - \eta\Delta t, \eta, t)\, d\eta\, dx \\ &= \lim_{\Delta t \to 0} \frac{1}{\Delta t} \int_0^\infty d\eta \int_{x_1 - \eta\Delta t}^{x_1} p(u, \eta, t)\, du \\ &= \int_0^\infty \eta p(x_1, \eta, t)\, d\eta. \end{aligned}$$

## The Smoluchowski approximation to the unidirectional current

In the overdamped regime, as $\gamma \to \infty$, the Smoluchowski approximation to $p(x,v,t)$ is given by

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

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

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

## The Smoluchowski approx. Cont.

The UF is

$$J_{LR}(x_1,t) = \int_0^\infty vp(x_1,v,t)\,dv$$

$$= \int_0^\infty v\frac{e^{-v^2/2\epsilon}}{\sqrt{2\pi\epsilon}}\,dv \times$$
$$\left\{p(x,t) - \frac{1}{\gamma}\left[\frac{\partial p(x,t)}{\partial x} - \frac{1}{\epsilon}f(x)p(x,t)\right]v + O\left(\frac{1}{\gamma^2}\right)\right\}$$
$$= \sqrt{\frac{\varepsilon}{2\pi}}p(x_1,t) - \frac{1}{2\gamma}\left[\varepsilon\frac{\partial p(x,t)}{\partial x} - f(x)p(x,t)\right]$$
$$+O\left(\frac{1}{\gamma^2}\right).$$

Similarly, the UF from right to left is

$$J_{RL}(x_1,t) = -\int_{-\infty}^0 vp(x_1,v,t)\,dv$$
$$= \sqrt{\frac{\varepsilon}{2\pi}}p(x_1,t) + \frac{1}{2\gamma}\left[\varepsilon\frac{\partial p(x,t)}{\partial x} - f(x)p(x,t)\right]$$
$$+O\left(\frac{1}{\gamma^2}\right).$$

## The Smoluchowski approx. Cont.

Both UFs in are finite and proportional to the marginal density at $x_1$.

The net flux is the difference

$$\begin{aligned} J_{\text{net}}(x_1,t) &= J_{LR}(x_1,t) - J_{RL}(x_1,t) \\ &= -\frac{1}{\gamma}\left[\varepsilon\frac{\partial p(x,t)}{\partial x} - f(x)p(x,t)\right], \end{aligned}$$

as in classical diffusion theory.

## The unidirectional current in the Smoluchowski equation

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

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

The unidirectional probability current (flux) density at a point $x_1$ can be expressed in terms of a path integral as

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

where

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

$$\times \Bigg\{ p\,(x_1, t)$$

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

$$+ O\left(\frac{\Delta t}{\gamma}\right)\Bigg\}.$$

## The unidirectional current in the Smoluchowski equation - Cont.

Integration yields

$$J_{LR}(x_1,t,\Delta t) = \sqrt{\frac{\varepsilon}{\pi\gamma\Delta t}}\, p(x_1,t)$$
$$+\frac{1}{2\gamma}\left(f(x_1)p(x_1,t) - \varepsilon\frac{\partial p(x_1,t)}{\partial x}\right) + O\left(\frac{\sqrt{\Delta t}}{\gamma^{3/2}}\right).$$

Similarly,

$$J_{RL}(x_1,t,\Delta t) = \sqrt{\frac{\varepsilon}{\pi\gamma\Delta t}}\, p(x_1,t)$$
$$-\frac{1}{2\gamma}\left(f(x_1)p(x_1,t) - \varepsilon\frac{\partial p(x_1,t)}{\partial x}\right) + O\left(\frac{\sqrt{\Delta t}}{\gamma^{3/2}}\right).$$

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 LD UFs. However, the net flux density is finite

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

## Application to Simulation

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

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

However, $J_{\text{net}}$ 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.

## Summary

Net fluxes of BD and LD are finite and equal.

The UFs of LD are finite, but the UFs of BD are infinite and diverge as $1/\sqrt{\Delta t}$.

Refining the numerical time step of BD requires increasing the sources strength. The constant LD UFs should not be used (causes depletion of particles from the simulation).

For $\gamma \Delta t = 2$ the UFs of LD and BD are equal.