

Identity of Distributions of Direct Uphill and Downhill Translocation Times for Particles Traversing Membrane Channels

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We study the distribution of direct translocation times for particles passing through membrane channels connecting two reservoirs. The direct translocation time is a conditional first-passage time defined as the residence time of the particle in the channel while passing to the other side of the membrane directly, i.e., without returning to the reservoir from which it entered. We show that the distributions of direct translocation times are identical for translocation in both directions, independent of any asymmetry in the potential across the channel and, hence, the translocation probabilities.

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The transport of ions, metabolites, and other large molecules across cell and organelle membranes is in many cases controlled by membrane proteins that form solute-specific channels [1]. Together with active transport [2], passive diffusion of molecules facilitated by channels is now recognized as one of the major mechanisms of metabolic regulation. A complex interplay of position-dependent forces acting on a translocating molecule determines the transport rates and channel selectivity for different solutes.

The constructive role of attractive interactions between the particle and the pore was recently analyzed in the framework of a one-dimensional diffusive model of the channel transport [3] and it was shown that, rather counter-intuitively, the average direct translocation time in the presence of an arbitrary potential is independent of the direction in which the particle goes [4]. For example, for ions going through a channel in the presence of an external voltage (Fig. 1) the “uphill” and “downhill” average direct translocation times are equal even though the uphill translocation probability is much smaller than the downhill one. A special case of such direction invariance has been discussed in Ref. [5] in the context of rate calculations for fluctuating barriers where the independence of the mean instanton time of the travel direction was demonstrated.

In the present study we prove a more general statement. This Letter deals specifically with the direct translocation time of ions, metabolites, and macromolecular solutes through channels in membranes and, more generally, the direct translocation time between two arbitrary hypersurfaces in configuration space. The direct translocation time is defined as the time it takes for a particle entering the channel on one side to exit the channel on the opposite side without returning to the reservoir from which it entered. This time is a conditional first-passage time which should not be confused with the unconditional one [6]. We show

that the distributions of the uphill and downhill direct translocation times are the same, and that this is an almost immediate consequence of detailed balance or microscopic reversibility.

We begin by assuming that the dynamics of the particle in the channel can be described by a one-dimensional Langevin equation. As we discuss at the end, the main result can readily be generalized to other dynamics and higher dimension. We will show that the probability densities of the uphill and downhill direct translocation times are equal

$$\varphi(t|x_L \rightarrow x_R) = \varphi(t|x_R \rightarrow x_L), \quad (1)$$

where x_L and x_R are the left and right boundaries of the channel (Fig. 1). For a particle of mass m moving in the channel the Langevin equation is

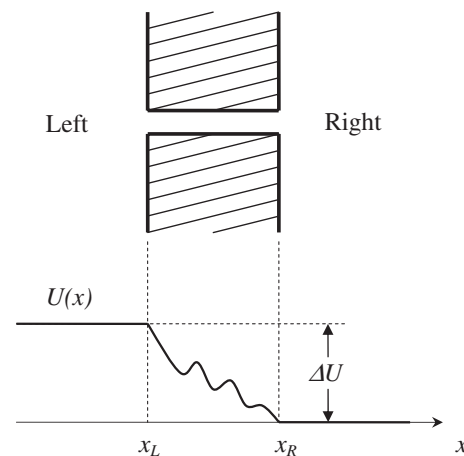


FIG. 1. Membrane channel and the potential of mean force, $U(x)$, along the channel axis; ΔU is the potential drop across the channel.

$$m\ddot{x} + \zeta\dot{x} + U'(x) = f(t). \quad (2)$$

Here $U(x)$ is the potential of mean force along the channel axis, ζ is the friction coefficient, and $f(t)$ is a Gaussian delta-correlated random force with zero mean related to the friction coefficient by the fluctuation-dissipation relation $\langle f(t)f(t') \rangle = 2k_B T \zeta \delta(t-t')$, where k_B and T are the Boltzmann constant and the absolute temperature. One can find a discussion of ion transport through membrane channels based on the one-dimensional Langevin equation in Ref. [7].

Both the particle translocation probability and the distribution of the direct translocation times can be expressed in terms of the propagator $G(x, v, t|x_0, v_0)$ defined as the probability density of finding the particle at point x with velocity v at time t conditional on the particle being at point x_0 with velocity v_0 at $t = 0$, $x_L < x, x_0 < x_R$. The propagator satisfies the Klein-Kramers equation [8]

$$\frac{\partial G}{\partial t} = -v \frac{\partial G}{\partial x} + \frac{U'(x)}{m} \frac{\partial G}{\partial v} + \frac{\zeta}{\beta m^2} \frac{\partial}{\partial v} \times \left[e^{-\beta m v^2/2} \frac{\partial}{\partial v} (e^{\beta m v^2/2} G) \right], \quad \beta = (k_B T)^{-1} \quad (3)$$

with the initial condition $G(x, v, 0|x_0, v_0) = \delta(x - x_0)\delta(v - v_0)$ and absorbing boundary conditions at the channel ends. It is assumed that particles leaving the channel instantly become indistinguishable from other particles of the reservoir. Therefore, only direct translocations contribute into the translocation process. The motion of diffusing particles at the channel boundaries is examined

in Refs. [3,4]. Diffusion corresponds to the high-friction limit of the Langevin dynamics, and it can be shown that Eq. (1) is true in this case.

Consider particles that enter the channel from the left. We assume that particles in the reservoirs are in thermal equilibrium and that there is no hydrodynamic flow through the channel. The flux entering the channel is given by $c_L \int_0^\infty v_L p_{\text{eq}}(v_L) dv_L$, where c_L is the particle concentration in the left reservoir and $p_{\text{eq}}(v_L)$ is the Maxwell distribution. The velocity distribution of the entering particles is $p(v_L) = \beta m v_L \exp(-\beta m v_L^2/2) H(v_L)$, where $H(z)$ is the Heaviside step function. When a particle enters the channel at x_L with an initial velocity v_L , the flux escaping at x_R at time t , $f(t|x_L \rightarrow x_R|v_L)$, is given by

$$f(t|x_L \rightarrow x_R|v_L) = \int_0^\infty v_R G(x_R, v_R, t|x_L, v_L) dv_R. \quad (4)$$

Averaging this flux over the initial distribution of v_L we obtain

$$f(t|x_L \rightarrow x_R) = \int_0^\infty f(t|x_L \rightarrow x_R|v_L) p(v_L) dv_L. \quad (5)$$

This flux, in turn, can be used to find the translocation probability, $P(x_L \rightarrow x_R)$,

$$P(x_L \rightarrow x_R) = \int_0^\infty f(t|x_L \rightarrow x_R) dt \quad (6)$$

and the probability density of the direct translocation time from left to right

$$\varphi(t|x_L \rightarrow x_R) = \frac{f(t|x_L \rightarrow x_R)}{P(x_L \rightarrow x_R)} = \frac{\int_0^\infty dv_L \int_0^\infty dv_R v_R G(x_R, v_R, t|x_L, v_L) v_L \exp(-\beta m v_L^2/2)}{\int_0^\infty dt \int_0^\infty dv_L \int_0^\infty dv_R v_R G(x_R, v_R, t|x_L, v_L) v_L \exp(-\beta m v_L^2/2)}. \quad (7)$$

Similarly, the probability density of the direct translocation time from right to left is given by

$$\varphi(t|x_R \rightarrow x_L) = \frac{\int_{-\infty}^0 dv_L \int_{-\infty}^0 dv_R v_L G(x_L, v_L, t|x_R, v_R) v_R \exp(-\beta m v_R^2/2)}{\int_0^\infty dt \int_{-\infty}^0 dv_L \int_{-\infty}^0 dv_R v_L G(x_L, v_L, t|x_R, v_R) v_R \exp(-\beta m v_R^2/2)}. \quad (8)$$

To prove that the probability densities in Eqs. (7) and (8) are equal, we use the fact that the propagators $G(x_R, v_R, t|x_L, v_L)$ and $G(x_L, v_L, t|x_R, v_R)$ satisfy the condition of detailed balance which is proved below

$$G(x_R, v_R, t|x_L, v_L) \exp\left\{-\beta\left[\frac{m v_L^2}{2} + U(x_L)\right]\right\} = G(x_L, -v_L, t|x_R, -v_R) \exp\left\{-\beta\left[\frac{m v_R^2}{2} + U(x_R)\right]\right\}. \quad (9)$$

To derive the equality in Eq. (1) we (i) multiply both numerator and denominator by $\exp[-\beta U(x_L)]$ in Eq. (7) and by $\exp[-\beta U(x_R)]$ in Eq. (8), (ii) change variables of integration $v_L \rightarrow -v_L$ and $v_R \rightarrow -v_R$ in Eq. (8), and (iii) invoke the condition of detailed balance, Eq. (9).

Now we will prove that the condition of detailed balance in Eq. (9) is valid in the presence of absorbing boundary conditions at the channel ends. Note that both propagators in Eq. (9) can be considered as sums over trajectories which start from the two ends at $t = 0$ and leave the

channel at time t , with specified initial and final velocities. For each trajectory contributing into the propagator $G(x_R, v_R, t|x_L, v_L)$ there exists its time-reversed counterpart that contributes into $G(x_L, -v_L, t|x_R, -v_R)$ and vice versa. Let $\{x_f(t'), v_f(t')\}$, $0 \leq t' \leq t$, be a trajectory contributing into $G(x_R, v_R, t|x_L, v_L)$ and $\{x_r(t'), v_r(t')\}$ be its time-reversed counterpart, i.e., $x_r(t-t') = x_f(t')$ and $v_r(t-t') = -v_f(t')$. We will show that realization probabilities for these trajectories, $W(\{x_f, v_f\})$ and $W(\{x_r, v_r\})$, satisfy

$$W(\{x_f, v_f\}) \exp\left[-\beta\left[\frac{m}{2}v_L^2 + U(x_L)\right]\right] = W(\{x_r, v_r\}) \exp\left[-\beta\left[\frac{m}{2}v_R^2 + U(x_R)\right]\right]. \quad (10)$$

Since the propagators are weighted sums over trajectories, the condition of detailed balance in Eq. (9) is a consequence of Eq. (10).

To find the weights $W(\{x_f, v_f\})$ and $W(\{x_r, v_r\})$ we use the Harmonic Oscillator Bath approach to the stochastic dynamics suggested by Zwanzig [9]. According to this approach, different stochastic trajectories $\{x(t'), v(t')\}$ correspond to different initial conditions of the Hamiltonian system formed by the bath oscillators and the system under consideration which bilinearly couples with the oscillators. The oscillators are described by their positions, $\{q_j\}$, and velocities, $\{\dot{q}_j\}$, $j = 1, 2, \dots$. The total energy of the entire system, E , is

$$E = \frac{m}{2}v^2 + U(x) + E_{\text{osc}}(\{q_j, \dot{q}_j\}|x), \quad (11)$$

where $E_{\text{osc}}(\{q_j, \dot{q}_j\}|x)$ is the oscillator bath energy which depends on x as a parameter

$$E_{\text{osc}}(\{q_j, \dot{q}_j\}|x) = \sum_j \frac{m_j}{2} [\dot{q}_j^2 + \omega_j^2(q_j - \lambda_j x)^2]. \quad (12)$$

Let $\{q_{j,f}(0)\}$ and $\{\dot{q}_{j,f}(0)\}$ be the set of initial conditions for the bath oscillators that leads to the trajectory $\{x_f(t'), v_f(t')\}$, $0 \leq t' \leq t$. The realization probability of this trajectory is the Maxwell-Boltzmann probability of the corresponding set of initial conditions for the bath oscillators assuming that $x_f(0) = x_L$

$$W(\{x_f, v_f\}) = Z^{-1} \exp[-\beta E_{\text{osc}}(\{q_{j,f}(0), \dot{q}_{j,f}(0)\}|x_L)], \quad (13)$$

where Z is the partition function of the oscillator bath. When the trajectory reaches the channel boundary at time t , $x_f(t) = x_R$, the bath oscillators have their final positions, $\{q_{j,f}(t)\}$, and velocities, $\{\dot{q}_{j,f}(t)\}$. We use this information to construct the initial conditions for the bath oscillators, which will lead to the time-reversed trajectory $\{x_r(t'), v_r(t')\}$: $q_{j,r}(0) = q_{j,f}(t)$, $\dot{q}_{j,r}(0) = -\dot{q}_{j,f}(t)$. The realization probability for the reversed trajectory is the Maxwell-Boltzmann probability of the initial conditions $\{q_{j,r}(0), \dot{q}_{j,r}(0)\}$ for the bath oscillators assuming that $x_r(0) = x_R$

$$W(\{x_r, v_r\}) = Z^{-1} \exp[-\beta E_{\text{osc}}(\{q_{j,r}(0), \dot{q}_{j,r}(0)\}|x_R)], \quad (14)$$

where we have used the fact that $E_{\text{osc}}(\{q_{j,r}(0), \dot{q}_{j,r}(0)\}|x_R) = E_{\text{osc}}(\{q_{j,f}(t), \dot{q}_{j,f}(t)\}|x_R)$.

The realization probabilities in Eqs. (13) and (14) satisfy the relation in Eq. (10). This follows from the fact that the energies $mv_L^2/2 + U(x_L) + E_{\text{osc}}(\{q_{j,f}(0), \dot{q}_{j,f}(0)\}|x_L)$ and $mv_R^2/2 + U(x_R) + E_{\text{osc}}(\{q_{j,f}(t), \dot{q}_{j,f}(t)\}|x_R)$ are equal be-

cause they are the same total energy of the isolated Hamiltonian system at times 0 and t . Thus, we have proved the relation in Eq. (10) and, hence, the condition of detailed balance in Eq. (9).

We now show that the identity of the distributions of the uphill and downhill direct translocation times, Eq. (1), is an almost immediate consequence of microscopic time reversibility. Up to now we dealt with the one-dimensional motion of the particle in the potential $U(x)$ on the interval $x_L \leq x \leq x_R$. Let us now consider the particle motion over the entire range of the x coordinate assuming that this motion occurs in the potential $V(x)$ which is identical to $U(x)$ for $x_L \leq x \leq x_R$ and tends to infinity as $|x| \rightarrow \infty$ so that $\int_{-\infty}^{\infty} \exp[-\beta V(x)] dx$ is finite. Figure 2 illustrates the difference between $V(x)$ and $U(x)$. The point is that the probability densities $\varphi(t|x_L \rightarrow x_R)$ and $\varphi(t|x_R \rightarrow x_L)$ can be determined from infinitely long equilibrium trajectories of particles that move in the potential $V(x)$. Such trajectories cross the interval (x_L, x_R) many times and the probability densities can be found from the fragments that traverse the interval without returning to the entrance point. The velocity distributions of particles entering the channel from the two sides are identical to the velocity distributions of particles crossing x_L and x_R found from the equilibrium trajectories. The identity of the probability densities of the direct translocation times, Eq. (1), is a consequence of the fact that for each trajectory fragment going from left to right there exists its ‘‘mirror image’’ obtained by inverting the sign of the particle velocity at each point of the interval, which goes from right to left, and vice versa (Fig. 3).

The above analysis can be readily generalized to more complex dynamics [like generalized Langevin dynamics or continuous-time random walks on a one-dimensional lattice [10]], channel geometries, and higher dimensions to

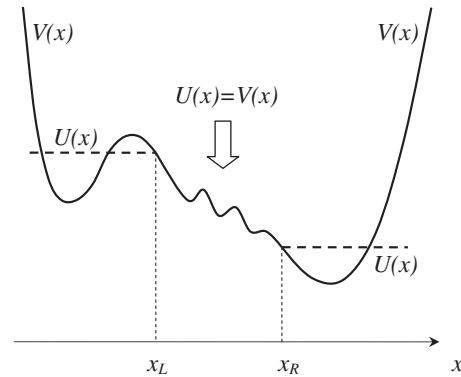


FIG. 2. Auxiliary potential $V(x)$ is identical to $U(x)$ on the interval corresponding to the channel, $x_L \leq x \leq x_R$, and tends to infinity as $|x| \rightarrow \infty$.

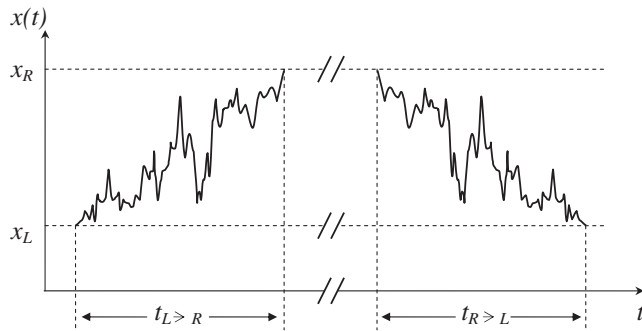


FIG. 3. Fragment of an equilibrium trajectory that goes from left to right and its mirror image that goes from right to left. The direct translocation times $t_{L \rightarrow R}$ and $t_{R \rightarrow L}$ are equal.

include, e.g., protein and solvent coordinates. In essence, microscopic reversibility combined with averaging over equilibrium trajectories ensures that the direct translocations in the forward direction and their mirror images, the direct translocations in the backward direction, appear with equal probability. Specifically, if one defines “entrance” and “exit” to a channel as crossing certain surfaces, then the distributions of the direct translocation times from left to right and from right to left are identical for any three-dimensional membrane channel in the presence of an arbitrary external potential. Time-reversal symmetry has been used explicitly in transition path sampling [11].

Identity of the distributions of the direct uphill and downhill translocation times proved in the present Letter is a crucial step in constructing a comprehensive theory of counting single-molecule translocations through single membrane channels [12]. Among the possibilities of experimental verification of our results, we would like to indicate digital video microscopy of colloidal particles [13] and single-molecule protein folding experiments [14]. Such experimental “tests” would touch upon Loschmidt’s paradox by demonstrating directly that system trajectories are microscopically time reversible, even if the macroscopic system satisfies the Second Law.

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Note added.—Independence of the direct translocation time distribution of the passage direction is discussed in a recent paper [15] published after the present manuscript

was submitted. The analysis in Ref. [15] is based on a discrete time random walk model of the particle motion in the channel. When the number of sites modeling the channel tends to infinity and the interval between successive steps of the random walk tends to zero in an appropriate way, this model corresponds to diffusion of the particle in the channel, which is the high-friction limit of our more general description.

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