Site model for channel-facilitated membrane transport: invariance of the translocation time

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Abstract

A particle entering a membrane channel either returns to the initial reservoir from which it entered or goes through to escape on the opposite side. We prove that the probability density of the translocation time is invariant with respect to the direction of passage. This invariance holds at arbitrary asymmetry of the intra-channel potential, i.e., independently of how different the translocation probabilities are in the two directions. Assuming that the particle motion is described as a continuous-time random walk between neighbouring sites representing the channel, we give three proofs of the invariance. The present analysis complements a recent proof of the invariance where we assumed Langevin dynamics of the particle in the channel (Berezhkovskii *et al* 2006 *Phys. Rev. Lett.* **97** 020601).

1. Introduction

This paper is devoted to translocation of charged or neutral particles through channels in biological membranes. A few years ago we discovered a counterintuitive result concerning the average time spent in the channel by translocating particles [1]. We found that this average time is independent of the direction in which the particles go, in spite of the fact that the translocation probabilities in the opposite directions may be quite different. Recently we have shown that the direction-independence of the average transit time is a consequence of the more general property of the particle dynamics in the channel, namely, direction-independence of the probability density for this time. We proved independence of the translocation time probability density of the passage direction for Langevin particles [2], for which diffusion corresponds to a particular case of, so-called, high friction. A few months earlier this property of the probability density of the translocation time was demonstrated by Alvarez and Hajek [3], who described the particle motion in the channel in terms of a one-dimensional discrete-time random walk among

discrete sites representing the channel. The proof given in [3] is based on detailed analysis of the random walk trajectories that traverse the channel in both directions.
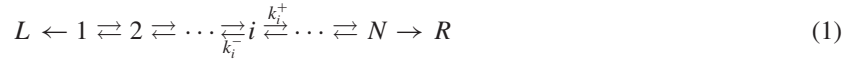
In this paper we also consider the site model of the channel to verify the independence of the translocation time probability density of the passage direction. Assuming that there is only one particle in the channel, we give three new proofs. The first one is based on the fact that the particle propagator satisfies the condition of detailed balance. In fact, this is a discrete version of the proof given in [2]. Our second proof is purely algebraic, while the third one is based on classification of the translocating particle trajectories. The latter generalizes the proof given in [3] to the continuous-time random walk. This proof seems to us more intuitively appealing than the other two proofs since it is based on consideration of the qualitative features of the particle motion in the channel that eventually lead to independence of the translocation time probability density of the passage direction.

Our interest in this subject is motivated by the recent progress in studies of membrane transport at the single-molecule level [4, 5]. Such studies allow analysis of the fine time statistics of individual events of metabolite molecule translocation. Emerging evidence demonstrates the complexity of particle–channel interactions [6] and particle dynamics in the channel [7]. It is quite clear that in addition to ongoing experiments and computer simulations [8, 9], a comprehensive picture of the channel-facilitated transport will necessarily require progress in analytical theory. We hope that the present study is a step in this direction offering a detailed consideration of an overlooked, but important feature of particle motion in the channel.

The outline of the paper is as follows. In the next section we formulate the model and our main statement, which is proved in section 3. Some concluding remarks are given in section 4.

2. The model

Let us assume that the particle motion in the channel can be described as a continuous-time random walk between neighbouring sites as shown in the kinetic scheme

$$L \leftarrow 1 \rightleftarrows 2 \rightleftarrows \cdots \underset{k_i^-}{\overset{}{\rightleftarrows}} i \underset{k_i^-}{\overset{k_i^+}{\rightleftarrows}} \cdots \rightleftarrows N \rightarrow R \tag{1}$$

where k_i^+ and k_i^- are the transition rates from site i to its neighbouring right and left sites, respectively. The channel is represented by N sites while L and R represent the left and right reservoirs separated by the membrane. Particles entering the channel from the left reservoir start from site 1. They either traverse the channel and exit into the right reservoir or return to the left reservoir. Time spent in the channel by a translocating particle will be called 'translocation time'. We denote the probability density of this time by $\varphi_N(t|L \rightarrow R)$, where the subscript N indicates the number of sites representing the channel. Correspondingly, particles entering the channel from the right reservoir start from site N. The probability density of the translocation time for such particles will be denoted as $\varphi_N(t|R \rightarrow L)$. In what follows we prove that

$$\varphi_N(t|L \rightarrow R) = \varphi_N(t|R \rightarrow L) \tag{2}$$

for an arbitrary set of the transition rates $k_i^{\pm}$, $i = 1, 2, \ldots, N$. Importantly, this is true in spite of the fact that the translocation probabilities in the two directions may be quite different.

3. Three proofs of equality (2)

3.1. Definitions

To prove equality (2) we introduce the propagator $G_N(i, t|j)$, which is the probability that the particle occupies site i at time t on condition that it started from site j at $t = 0$,

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$i, j = 1, 2, \ldots, N$. The probability flux formed by the particles which translocate from left to right for time t, $f_N(t|L \to R)$, is given by

$$f_N(t|L \to R) = k_N^+ G_N(N, t|1). \tag{3}$$

We use this flux to find the translocation probability, $P_N(L \to R)$,

$$P_N(L \to R) = \int_0^\infty f_N(t|L \to R) \, \mathrm{d}t = k_N^+ \int_0^\infty G_N(N, t|1) \, \mathrm{d}t \tag{4}$$

and the probability density of the translocation time

$$\varphi_N(t|L \to R) = \frac{f_N(t|L \to R)}{P_N(L \to R)} = \frac{G_N(N, t|1)}{\int_0^\infty G_N(N, t|1) \, \mathrm{d}t}. \tag{5}$$

Correspondingly, the probability density of the translocation time in the opposite direction is

$$\varphi_N(t|R \to L) = \frac{G_N(1, t|N)}{\int_0^\infty G_N(1, t|N) \, \mathrm{d}t}. \tag{6}$$

3.2. Proof 1

This proof is based on the fact that the propagators $G_N(N, t|1)$ and $G_N(1, t|N)$ are related by the condition of detailed balance. To formulate this condition, consider an auxiliary random walk obtained from the walk in equation (1) by putting $k_1^- = k_N^+ = 0$, that converts sites 1 and N into reflecting boundaries (RB). In this case the particle never escapes from the channel. We denote the propagator for this random walk by $G_N^{RB}(i, t|j)$. As $t \to \infty$, the propagator $G_N^{RB}(i, t|j)$ approaches the equilibrium probability of finding the particle on site i, $P_N^{RB}(i|\text{eq})$,

$$\lim_{t \to \infty} G_N^{RB}(i, t|j) = P_N^{RB}(i|\text{eq}). \tag{7}$$

The propagator $G_N^{RB}(i, t|j)$ and the equilibrium probability $P_N^{RB}(i|\text{eq})$ are related by the relationship

$$G_N^{RB}(i, t|j) P_N^{RB}(j|\text{eq}) = G_N^{RB}(j, t|i) P_N^{RB}(i|\text{eq}) \tag{8}$$

which is the condition of detailed balance for the random walk between the reflecting boundaries. As shown in appendix A, the propagator $G_N(i, t|j)$ satisfies the condition of detailed balance of the same form:

$$G_N(i, t|j) P_N^{RB}(j|\text{eq}) = G_N(j, t|i) P_N^{RB}(i|\text{eq}). \tag{9}$$

We use this to prove equality (2). To do this consider the ratio of the probability densities defined in equations (5) and (6):

$$\frac{\varphi_N(t|L \to R)}{\varphi_N(t|R \to L)} = \frac{G_N(N, t|1)}{G_N(1, t|N)} \frac{\int_0^\infty G_N(1, t|N) \, \mathrm{d}t}{\int_0^\infty G_N(N, t|1) \, \mathrm{d}t}. \tag{10}$$

One can check that the ratio is equal to unity using the relation in equation (9), so that the two probability densities are equal.

3.3. Proof 2

In this proof we use the Laplace transform of the propagator

$$\hat{G}_N(i, s|j) = \int_0^\infty \mathrm{e}^{-st} G_N(i, t|j) \, \mathrm{d}t \tag{11}$$

and the definitions of the probability densities given in equations (5) and (6) to write the equality (2) in the form

$$\hat{G}_N(1, 0|N)\hat{G}_N(N, s|1) = \hat{G}_N(N, 0|1)\hat{G}_N(1, s|N). \tag{12}$$

By explicit calculation one can check that this is true for $N = 1$ and 2. To prove this in general we derive some relations between the propagator describing the particle motion in the N-site channel and the propagator $G_{N-1}(i, t|j)$, $i, j = 1, 2, \ldots, N - 1$, that describes motion of the particle in the $(N - 1)$-site channel which is obtained by putting $k_N^+ = \infty$ in the kinetic scheme shown in equation (1).

We begin with the propagator $G_N(N, t|1)$, which satisfies

$$G_N(N, t|1) = k_{N-1}^+ \int_0^t G_N(N, t - t_1|N)G_{N-1}(N - 1, t_1|1) \, dt_1. \tag{13}$$

The propagator $G_N(N, t|N)$, respectively, satisfies

$$G_N(N, t|N) = e^{-k_N t} + k_N^- k_{N-1}^+ \int_0^t dt_1 \, e^{-k_N t_1} \int_0^{t-t_1} G_N(N, t - t_1 - t_2|N)$$
$$\times G_{N-1}(N - 1, t_2|N - 1) \, dt_2, \tag{14}$$

where $k_N = k_N^+ + k_N^-$. Solving these equations we find a relation between the Laplace transforms of the propagators $\hat{G}_N(N, s|1)$ and $\hat{G}_{N-1}(N - 1, s|1)$. The relation is

$$\hat{G}_N(N, s|1) = \frac{k_{N-1}^+ \hat{G}_{N-1}(N - 1, s|1)}{s + k_N - k_N^- k_{N-1}^+ \hat{G}_{N-1}(N - 1, s|N - 1)}. \tag{15}$$

Next we find the Laplace transform of the propagator $G_N(1, t|N)$, which satisfies

$$G_N(1, t|N) = k_N^- \int_0^t e^{-k_N t_1} \Bigg[G_{N-1}(1, t - t_1|N - 1)$$
$$+ k_{N-1}^+ \int_0^{t-t_1} G_N(1, t - t_1 - t_2|N)G_{N-1}(N - 1, t_2|N - 1) \, dt_2 \Bigg] dt_1. \tag{16}$$

Solving this we obtain a relation between the Laplace transforms of the propagators $\hat{G}_N(1, s|N)$ and $\hat{G}_{N-1}(1, s|N - 1)$. The relation is

$$\hat{G}_N(1, s|N) = \frac{k_N^- \hat{G}_{N-1}(1, s|N - 1)}{s + k_N - k_N^- k_{N-1}^+ \hat{G}_{N-1}(N - 1, s|N - 1)}. \tag{17}$$

Using the Laplace transforms in equations (15) and (17), we find that the products of the propagators on the left- and right-hand sides of equation (12), respectively, are

$$\hat{G}_N(1, 0|N)\hat{G}_N(N, s|1)$$
$$= \frac{k_N^- k_{N-1}^+ \hat{G}_{N-1}(1, 0|N - 1)\hat{G}_{N-1}(N - 1, s|1)}{[k_N - k_N^- k_{N-1}^+ \hat{G}_{N-1}(N - 1, 0|N - 1)][s + k_N - k_N^- k_{N-1}^+ \hat{G}_{N-1}(N - 1, s|N - 1)]} \tag{18}$$

and

$$\hat{G}_N(N, 0|1)\hat{G}_N(1, s|N)$$
$$= \frac{k_N^- k_{N-1}^+ \hat{G}_{N-1}(N - 1, 0|1)\hat{G}_{N-1}(1, s|N - 1)}{[k_N - k_N^- k_{N-1}^+ \hat{G}_{N-1}(N - 1, 0|N - 1)][s + k_N - k_N^- k_{N-1}^+ \hat{G}_{N-1}(N - 1, s|N - 1)]}. \tag{19}$$

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Comparison shows that the equality (12) is fulfilled when the propagator describing the particle motion in the fictitious $(N-1)$-site channel satisfies

$$\hat{G}_{N-1}(1,0|N-1)\hat{G}_{N-1}(N-1,s|1) = \hat{G}_{N-1}(N-1,0|1)\hat{G}_{N-1}(1,s|N-1). \tag{20}$$

This is the analogue of equality (12) for the $(N-1)$-site channel. Repeating this procedure we eventually find that the equality (12) is fulfilled because it is true for the corresponding fictitious two-site channel, for which $\hat{G}_2(2,s|1) = k_1^+/D(s)$ and $\hat{G}_2(1,s|2) = k_2^-/D(s)$, where $D(s) = (k_1^+ + k_1^- + s)(k_2^+ + k_2^- + s) - k_1^+ k_2^-$. Thus, we have proved the equality (12) and, hence, the identity of the probability densities of the forward and backward translocation times in equation (2) for an arbitrary set of the transition rates $k_i^{\pm}$, $i = 1, 2, \ldots, N$.

3.4. Proof 3

Equality (2) might look counterintuitive at first sight. Indeed, in the case of large transmembrane electric fields acting on charged particles, the translocation probabilities in the two directions can be different by orders of magnitude. Under these conditions it may seem surprising that the two time distributions are identical. To make this identity more intuitively appealing, we give another proof which is based on the consideration of trajectories contributing into $\varphi_N(t|L \to R)$ and $\varphi_N(t|R \to L)$. We note that all trajectories of particles translocating from left to right can be classified depending on how many loops of a particular type the trajectory has. Denoting different classes of trajectories by α we can write the flux $f_N(t|L \to R)$ as a sum of contributions $f_N^{(\alpha)}(t|L \to R)$ due to the trajectories belonging to different classes α:

$$f_N(t|L \to R) = \sum_\alpha f_N^{(\alpha)}(t|L \to R). \tag{21}$$

Correspondingly, the translocation probability $P_N(L \to R)$ can be written as

$$P_N(L \to R) = \sum_\alpha P_N^{(\alpha)}(L \to R) \tag{22}$$

where the contribution $P_N^{(\alpha)}(L \to R)$ is given by

$$P_N^\alpha(L \to R) = \int_0^\infty f_N^{(\alpha)}(t|L \to R)\,\mathrm{d}t. \tag{23}$$

Next we introduce the relative weights of the contributions due to the trajectories belonging to different classes α, $w_N^{(\alpha)}(L \to R)$, defined by

$$w_N^{(\alpha)}(L \to R) = \frac{P_N^{(\alpha)}(L \to R)}{P_N(L \to R)} \tag{24}$$

and the probability densities of the translocation time for each class of the trajectories, $\varphi_N^{(\alpha)}(t|L \to R)$, defined as

$$\varphi_N^{(\alpha)}(t|L \to R) = \frac{f_N^{(\alpha)}(t|L \to R)}{P_N^{(\alpha)}(L \to R)}. \tag{25}$$

This allows us to write the probability density $\varphi_N(t|L \to R)$ as a weighted sum of $\varphi_N^{(\alpha)}(t|L \to R)$:

$$\varphi_N(t|L \to R) = \sum_\alpha w_N^{(\alpha)}(L \to R)\varphi_N^{(\alpha)}(t|L \to R). \tag{26}$$

For any trajectory of a particle translocating from left to right there exists its time-reversed counterpart of a particle translocating from right to left and vice versa. Therefore, the

classification of the forward trajectories is also applicable to the backward ones. This implies that we can rewrite the relations given in equations (21)–(26) replacing $L \to R$ by $R \to L$ and present the probability density $\varphi_N(t|R \to L)$ as a weighted sum:

$$\varphi_N(t|R \to L) = \sum_\alpha w_N^{(\alpha)}(R \to L)\varphi_N^{(\alpha)}(t|R \to L). \tag{27}$$

Next we note that the probability densities $\varphi_N^{(\alpha)}(t|L \to R)$ and $\varphi_N^{(\alpha)}(t|R \to L)$ are equal:

$$\varphi_N^{(\alpha)}(t|L \to R) = \varphi_N^{(\alpha)}(t|R \to L) \tag{28}$$

since the probability density for the particle lifetime on a site is independent of the direction in which the particle makes a step. For site i this probability density is $k_i \exp(-k_i t)$, where $k_i = k_i^+ + k_i^-$. In addition, the relative weights $w_N^{(\alpha)}(L \to R)$ and $w_N^{(\alpha)}(R \to L)$ are also equal:

$$w_N^{(\alpha)}(L \to R) = w_N^{(\alpha)}(R \to L) \tag{29}$$

since topologically identical trajectories equally contribute into both weights: the weight $w_N^{(\alpha)}(R \to L)$ is formed by trajectories which are time-reversed counterparts of the trajectories contributing into $w_N^{(\alpha)}(L \to R)$ and vice versa. As a consequence, probability densities (27) and (28) are equal and, hence, equality (2) is fulfilled.

3.5. Illustration

Substituting the definition of $w_N^{(\alpha)}(L \to R)$ given in equation (24) and the definition of $w_N^{(\alpha)}(R \to L)$,

$$w_N^{(\alpha)}(R \to L) = \frac{P_N^{(\alpha)}(R \to L)}{P_N(R \to L)} \tag{30}$$

into equation (29), we find that the ratio $P_N^{(\alpha)}(L \to R)/P_N^{(\alpha)}(R \to L)$ is independent of α and is given by

$$\frac{P_N^{(\alpha)}(L \to R)}{P_N^{(\alpha)}(R \to L)} = \frac{P_N(L \to R)}{P_N(R \to L)}. \tag{31}$$

To illustrate this relation we consider a two-site model described by the kinetic scheme

$$L \underset{k_1^-}{\leftarrow} 1 \underset{k_2^-}{\overset{k_1^+}{\rightleftarrows}} 2 \overset{k_2^+}{\to} R. \tag{32}$$

The probabilities that the particle occupying site i, $i = 1, 2$, makes a step to the left, Φ_i^-, or to the right, Φ_i^+, are given by $\Phi_i^\pm = k_i^\pm/k_i$. In the two-site model only simple two-step (step forward, step backward) loops are possible. We classify all translocating trajectories by the number of loops which the trajectory has, taking α equal to the number of loops, $\alpha = 0, 1, 2, \ldots$. Then the translocation probabilities $P_2^{(\alpha)}(L \to R)$ and $P_2^{(\alpha)}(R \to L)$ are given by

$$P_2^{(\alpha)}(L \to R) = \Phi_1^+ \Phi_2^+ (\Phi_1^+ \Phi_2^-)^\alpha \tag{33}$$

and

$$P_2^{(\alpha)}(R \to L) = \Phi_1^- \Phi_2^- (\Phi_1^+ \Phi_2^-)^\alpha. \tag{34}$$

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$$P_2^{(2)}(L \to R) = \Phi_1^+ \Phi_2^+ \left(\Phi_1^+ \Phi_2^- \right)^2$$

$$P_2^{(1)}(L \to R) = \Phi_1^+ \Phi_2^+ \Phi_1^+ \Phi_2^-$$

$$P_2^{(0)}(L \to R) = \Phi_1^+ \Phi_2^+$$

$$L \leftarrow 1 \leftrightarrows 2 \to R$$

$$P_2^{(0)}(R \to L) = \Phi_1^- \Phi_2^-$$

$$P_2^{(1)}(R \to L) = \Phi_1^- \Phi_2^- \Phi_1^+ \Phi_2^-$$

$$P_2^{(2)}(R \to L) = \Phi_1^- \Phi_2^- \left(\Phi_1^+ \Phi_2^- \right)^2$$
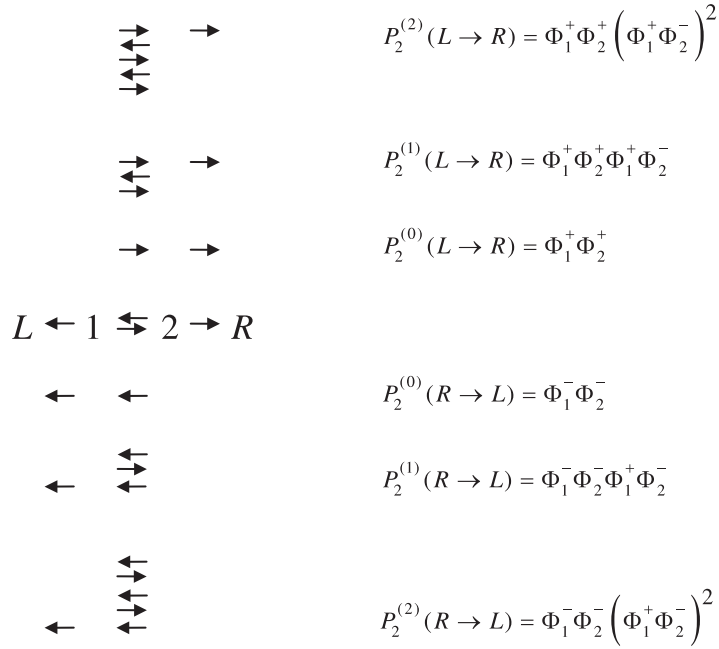
Figure 1. Three simplest classes of translocating trajectories and probabilities of their realizations in kinetic scheme (32).

In figure 1 we show three simplest classes of trajectories, with $\alpha = 0, 1, 2$, corresponding to translocations in both directions, and give probabilities of their realizations. Using the expressions given in equations (33) and (34) we find that

$$P_2(L \to R) = \sum_{\alpha=0}^{\infty} P_2^{(\alpha)}(L \to R) = \frac{\Phi_1^+ \Phi_2^+}{\Phi_1^- + \Phi_1^+ \Phi_2^+} \tag{35}$$

and

$$P_2(R \to L) = \sum_{\alpha=0}^{\infty} P_2^{(\alpha)}(R \to L) = \frac{\Phi_1^- \Phi_2^-}{\Phi_2^+ + \Phi_1^- \Phi_2^-}. \tag{36}$$

Alternatively, one can derive these expressions solving the rate equations as shown in appendix B. Using the expressions given in equations (33)–(36) and the fact that the denominators in equations (35) and (36) are identical, one can check that the relation (31) is fulfilled for any α.

4. Concluding remarks

In the present paper we have proved independence of the translocation time probability density of the passage direction for particles going through membrane channels. We describe the particle motion in the channel as a continuous-time random walk between neighbouring sites with arbitrary transition rates. Therefore the invariance of the translocation time probability density with respect to the passage direction holds independently of how different the translocation probabilities in the two directions are.

The proofs given in the present paper for the random walk model of the particle motion in the channel complement the proof given in [2], where the motion was described in terms of the

Langevin dynamics. Based on this, we believe that the property of the particle dynamics in the channel analysed in the present paper and in [2, 3] is quite general and equation (2) is true for any model of the particle motion in the channel independently of the strength of the external field as well as the nature of the particle–channel interaction.

Acknowledgments

Appendix A. Condition of detailed balance

Consider a continuous-time random walk between N sites assuming that the walking particle occupying site i can be trapped with the trapping rate γ_i $i = 1, 2, \ldots, N$. The propagator $G(i, t | j)$ (we omit subscript N in this appendix) satisfies an evolution equation of the form

$$\frac{\mathrm{d}G(i, t | j)}{\mathrm{d}t} = \sum_{k=1}^{N} (K_{ik} - \Gamma_{ik}) G(k, t | j) \tag{A.1}$$

and the initial condition $G(i, 0 | j) = \delta_{ij}$, where K_{ij} and Γ_{ij} are $N \times N$ matrices of transition and trapping rates, respectively. The matrix element K_{ij} with $i \neq j$ is the rate constant for transition $j \to i$, and $K_{jj} = -\sum_{i=1, i \neq j}^{N} K_{ij}$. Matrix elements Γ_{ij} are given by $\Gamma_{ij} = \gamma_j \delta_{ij}$. For the random walk considered in the main body of the text $\gamma_1 = k_1^-$, $\gamma_2 = \gamma_3 = \cdots = \gamma_{N-1} = 0$, and $\gamma_N = k_N^+$. Matrix elements of the transition rate matrix are $K_{ij} = k_{i-1}^+ \delta_{ji-1} - k_i \delta_{ij} + k_{i+1} \delta_{ji+1}$, where $k_i = k_i^- + k_i^+$.

Because of the trapping the particle survival probability tends to zero as $t \to \infty$. When all trapping rates are equal to zero, the particle never dies and the propagator describes relaxation to the steady-state distribution which is assumed to be the equilibrium one, $P(i | \mathrm{eq})$,

$$\lim_{t \to \infty} G(i, t | j)|_{\mathrm{no\ trapping}} = P(i | \mathrm{eq}). \tag{A.2}$$

Matrix elements of the transition rate matrix and $P(i | \mathrm{eq})$ are related by the condition of detailed balance:

$$K_{ij} P(j | \mathrm{eq}) = K_{ji} P(i | \mathrm{eq}). \tag{A.3}$$

The goal of this appendix is to show that the propagator $G(i, t | j)$ satisfies the condition of detailed balance that has the form

$$G(i, t | j) P(j | \mathrm{eq}) = G(j, t | i) P(i | \mathrm{eq}) \tag{A.4}$$

similar to that in equation (A.3).

With this in mind we symmetrize the evolution operator on the right-hand side of equation (A.1) by writing the propagator as

$$G(i, t | j) = \sqrt{P(i | \mathrm{eq})} f(i, t | j). \tag{A.5}$$

Function $f(i, t | j)$ satisfies an evolution equation of the form

$$\frac{\mathrm{d}f(i, t | j)}{\mathrm{d}t} = \sum_{k=1}^{N} (H_{ik} - \Gamma_{ik}) f(k, t | j) \tag{A.6}$$

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where H_{ij} is given by

$$H_{ij} = K_{ij}\sqrt{\frac{P(j|\mathrm{eq})}{P(i|\mathrm{eq})}} = K_{ij}\sqrt{\frac{K_{ji}}{K_{ij}}}. \tag{A.7}$$

The initial condition for equation (A.6) is

$$f(i,0|j) = \frac{1}{\sqrt{P(j|\mathrm{eq})}}\delta_{ij}. \tag{A.8}$$

One can see that $H_{ij} = H_{ji}$. Thus, the evolution operator on the right-hand side of equation (A.6) is symmetric. Using its eigenfunctions, $\varphi_n(i)$, that satisfy

$$\sum_{j=1}^{N}(H_{ij} - \Gamma_{ij})\varphi_n(j) = \varepsilon_n\varphi_n(i), \qquad n = 1, 2, \ldots, N \tag{A.9}$$

we can write the eigenfunction expansion of the propagator $g(i,t|j)$ corresponding to the evolution equation (A.6):

$$g(i,t|j) = \sum_{1}^{N}\varphi_n(i)\varphi_n(j)\exp(\varepsilon_n t). \tag{A.10}$$

We use this propagator to find the solution for $f(i,t|j)$ and then for the propagator $G(i,t|j)$. The result is

$$G(i,t|j) = \sqrt{P(i|\mathrm{eq})}\,g(i,t|j)\frac{1}{\sqrt{P(j|\mathrm{eq})}}. \tag{A.11}$$

This expression for the propagator together with the expression in equation (A.10) allows one to check that $G(i,t|j)$ satisfies the condition of detailed balance in equation (A.4).

Appendix B. Translocation probabilities for the two-site model

For the two-site model described by kinetic scheme (32) the translocating flux $f_2(t|L \rightarrow R)$ is given by

$$f_2(t|L \rightarrow R) = k_2^+ G_2(2,t|1). \tag{B.1}$$

The propagator $G_2(i,t|1)$, $i = 1, 2$, can be found by solving the equations

$$\frac{\mathrm{d}G_2(1,t|1)}{\mathrm{d}t} = -k_1 G_2(1,t|1) + k_2^- G_2(2,t|1). \tag{B.2}$$

$$\frac{\mathrm{d}G_2(2,t|1)}{\mathrm{d}t} = k_1^+ G_2(1,t|1) - k_2 G_2(2,t|1) \tag{B.3}$$

with the initial condition $G_2(i,t|1) = \delta_{i1}$. Solving these equations we find that the Laplace transform of the flux is

$$\hat{f}_2(s|L \rightarrow R) = \frac{k_1^+ k_2^+}{(s + k_1)(s + k_2) - k_1^+ k_2^-}. \tag{B.4}$$

We use this transform to find the translocation probability

$$P_2(L \rightarrow R) = \hat{f}_2(0|L \rightarrow R) = \frac{k_1^+ k_2^+}{k_1 k_2 - k_1^+ k_2^-} \tag{B.5}$$

which is identical to the expression in equation (35). Following the same way one can derive

$$P_2(R \rightarrow L) = \frac{k_1^- k_2^-}{k_1 k_2 - k_1^+ k_2^-} \tag{B.6}$$

which is identical to the expression in equation (36).

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