Channel-facilitated membrane transport: Transit probability and interaction with the channel

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Transport of metabolites between cells and between subcellular compartments is facilitated by special protein channels that form aqueous pores traversing biological membranes. Accumulating evidence demonstrates that solute-specific channels display pronounced binding to the corresponding solutes. In this paper we rationalize this observation by showing that a wide and deep potential well inside the channel is able to greatly increase the transit probability of the particle through the channel. Using a one-dimensional diffusion model with radiation boundary conditions, we give exact analytical expressions for the particle translocation probabilities. We also run Brownian dynamics simulations to verify the model and the quantitative predictions of our theory. [DOI: 10.1063/1.1475758]

I. INTRODUCTION

It is now well established that transport of various metabolites across cellular and organelle membranes occurs through protein channels.[1] Therefore one of the main goals of membrane biophysics is to understand how these channels work. Here we study a fragment of this general problem, namely, how does solute-channel interaction influence the probability that the solute, having entered the channel, will traverse the membrane?

Accumulating evidence suggests that metabolite-specific channels have evolved to bind corresponding metabolite molecules. For example, it is long recognized that the sugar-specific channel, maltoporin, shows pronounced interactions with penetrating sugars.[2,3] The binding is so strong that recently it has become possible to observe the time-resolved events of single sugar molecule translocation through the channel pore.[4,5] Another recent example[6] illustrates the importance of solute-channel interactions in antibiotic translocation through bacterial general porin, OmpF. Interestingly, in this case it is not the bacterial channel that has evolved to bind an antibiotic molecule (antibiotics kill bacteria); it is the attacking organisms, molds, which have evolved to produce antibiotics that effectively penetrate bacterial walls.

In this article we study how the interaction with the channel influences the translocation of a metabolite molecule, assuming that its size is small compared to the channel length. A similar problem concerning ion translocation was recently addressed using the Fokker–Planck equation in phase space.[7] Our theory, which permits us to avoid some difficulties inherent to this approach, is developed in the framework of a one-dimensional diffusion model with the radiation boundary conditions. Previously,[8] we derived these boundary conditions to study particle number fluctuations in a simple case of a cylindrical channel. We found an expression for the radiation parameter (rate constant) in terms of the channel radius and the diffusion constant in the bulk outside the channel. We used this model to analyze spectral characteristics of particle number fluctuations and showed excellent agreement between theory and computer simulations that did not contain any adjustable parameters.

One of the main results of the present study is general exact expressions for the translocation probabilities for particles that enter the channel from either side of the membrane. They are derived in Sec. III and given by Eq. (3.14). Detailed analysis of these expressions is performed in Sec. IV. It shows that the presence of a deep potential well that occupies most of the channel length makes the translocation more probable. To test our theory we run Brownian dynamics simulations as described in Sec. V. We found excellent agreement between the translocation probabilities predicted by the theory and obtained in simulations. Some important factors determining the efficiency of the channel, but omitted in our analysis, are discussed in the concluding section.

II. THE MODEL

Consider a particle that enters a membrane channel from the left at $t=0$. Sometime later this particle will escape the channel either on the same or opposite side of the membrane.

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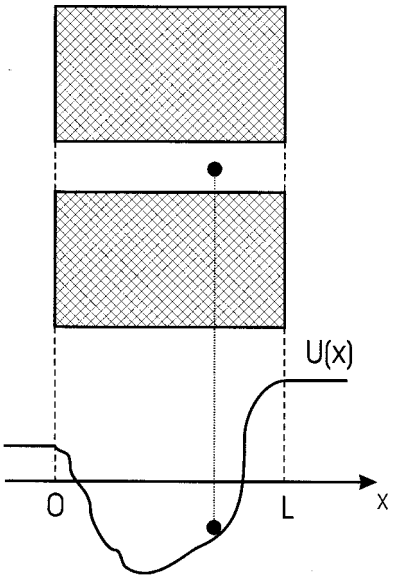

FIG. 1. A sketch of the system under study. Brownian particles wander freely in two reservoirs connected by a cylindrical channel of length L and radius a. The black circle represents a particle diffusing in the channel. There is no interaction between particles; any number of them can be in the channel simultaneously.

Our goal is to calculate probabilities of both outcomes for particles that enter the channel from both sides.

We will model the particle motion in the channel by one-dimensional diffusion on the interval $(0,L)$ (see Fig. 1). The interaction of the particle with the channel will be taken into account by assuming that (a) the diffusion occurs in the potential $U(x)$, and (b) the diffusion coefficient $D(x)$ depends on particle position x. The behavior of the particle in the channel is described by the propagator or Green function, $G(x,t|x_0)$, which is the probability density to find the particle at point x at time t assuming that at $t=0$ the particle position was $x=x_0$. The propagator satisfies the diffusion (Smoluchowski) equation

$$\frac{\partial G}{\partial t}=\frac{\partial}{\partial x}\left\{D(x)e^{-\beta U(x)}\frac{\partial}{\partial x}[Ge^{\beta U(x)}]\right\}, \tag{2.1}$$

where $\beta=(k_BT)^{-1}$, k_B and T are the Boltzmann constant and absolute temperature, with the initial condition

$$G(x,0|x_0)=\delta(x-x_0). \tag{2.2}$$

Boundary conditions imposed at the channel ends describe escape of the particle from the channel. They have the form of radiation boundary conditions

$$\begin{aligned}\frac{\partial}{\partial x}[Ge^{\beta U(x)}]|_{x=0}&=\frac{k_0}{D(0)}e^{\beta U(0)}G(0,t|x_0),\\ -\frac{\partial}{\partial x}[Ge^{\beta U(x)}]|_{x=L}&=\frac{k_L}{D(L)}e^{\beta U(L)}G(L,t|x_0),\end{aligned} \tag{2.3}$$

where k_0 and k_L are the rate constants characterizing the efficiency of the escape ($k=\infty$ and $k=0$ correspond to absorbing and reflecting end points, respectively).

III. TRANSLOCATION PROBABILITIES

Using the propagator one can find the survival probability $S(t|x_0)$, which is the probability for a particle that started at position $x=x_0$, has not escaped from the channel by time t,

$$S(t|x_0)=\int_0^L G(x,t|x_0)dx. \tag{3.1}$$

The probability density for the particle lifetime in the channel is given by

$$\varphi(t|x_0)=-\frac{dS(t|x_0)}{dt}=-\int_0^L\frac{\partial G(x,t|x_0)}{\partial t}dx. \tag{3.2}$$

Integrating both sides of the diffusion equation in Eq. (2.1) with respect to x from 0 to L and using the boundary conditions in Eq. (2.3), one finds

$$\begin{aligned}\varphi(t|x_0)&=k_0G(0,t|x_0)+k_LG(L,t|x_0)\\&=f_0(t|x_0)+f_L(t|x_0).\end{aligned} \tag{3.3}$$

This gives $\varphi(t|x_0)$ as a sum of two probability fluxes, $f_0(t|x_0)=k_0G(0,t|x_0)$ and $f_L(t|x_0)=k_LG(L,t|x_0)$, that escape the channel from the two ends at time t. The total probabilities for the particle to escape through the left and right ends of the channel, denoted as $P_0(x_0)$ and $P_L(x_0)$, are

$$\begin{aligned}P_0(x_0)&=\int_0^\infty f_0(t|x_0)dt=k_0\int_0^\infty G(0,t|x_0)dt,\\P_L(x_0)&=\int_0^\infty f_L(t|x_0)dt=k_L\int_0^\infty G(L,t|x_0)dt.\end{aligned} \tag{3.4}$$

Using the definitions introduced above one can check that

$$P_0(x_0)+P_L(x_0)=\int_0^\infty\varphi(t|x_0)dt=1. \tag{3.5}$$

It is convenient to introduce an auxiliary function $F(x|x_0)$, defined as

$$F(x|x_0)=\int_0^\infty G(x,t|x_0)dt. \tag{3.6}$$

Then we can write the probabilities in Eq. (3.4) as

$$P_0(x_0)=k_0F(0|x_0),\quad P_L(x_0)=k_LF(L|x_0). \tag{3.7}$$

Using Eqs. (2.1)–(2.3) one can check that $F(x|x_0)$ satisfies

$$\frac{d}{dx}\left\{D(x)e^{-\beta U(x)}\frac{d}{dx}[e^{\beta U(x)}F(x|x_0)]\right\}=-\delta(x-x_0), \tag{3.8}$$

with the boundary conditions

$$\begin{aligned}\frac{d}{dx}[e^{\beta U(x)}F(x|x_0)]|_{x=0}&=\frac{k_0}{D(0)}e^{\beta U(0)}F(0|x_0),\\-\frac{d}{dx}[e^{\beta U(x)}F(x|x_0)]|_{x=L}&=\frac{k_L}{D(L)}e^{\beta U(L)}F(L|x_0).\end{aligned} \tag{3.9}$$

One can find $F(x|x_0)$ from Eqs. (3.8) and (3.9) and then the probabilities using Eq. (3.7). This leads to

$$P_0(x_0)=\frac{\tilde{k}_0\left[1+\tilde{k}_L\int_{x_0}^{L}e^{\beta U(y)}\frac{dy}{D(y)}\right]}{\tilde{k}_0+\tilde{k}_L+\tilde{k}_0\tilde{k}_L\int_0^L e^{\beta U(y)}\frac{dy}{D(y)}},$$

$$P_L(x_0)=\frac{\tilde{k}_L\left[1+\tilde{k}_0\int_{0}^{x_0}e^{\beta U(y)}\frac{dy}{D(y)}\right]}{\tilde{k}_0+\tilde{k}_L+\tilde{k}_0\tilde{k}_L\int_0^L e^{\beta U(y)}\frac{dy}{D(y)}}, \tag{3.10}$$

where we have introduced the notations

$$\tilde{k}_0=k_0e^{-\beta U(0)},\quad \tilde{k}_L=k_Le^{-\beta U(L)}. \tag{3.11}$$

The probabilities in Eq. (3.10) satisfy the normalization condition in Eq. (3.5).

In this paper we are interested in translocation probabilities, that can be easily obtained from the general expressions in Eq. (3.10). For particles that enter the channel from the left ($x_0=0$) and right ($x_0=L$) these probabilities, respectively, are

$$P_L(0)=\frac{\tilde{k}_L}{\tilde{k}_0+\tilde{k}_L+\tilde{k}_0\tilde{k}_L\int_0^L e^{\beta U(y)}\frac{dy}{D(y)}},$$

$$P_0(L)=\frac{\tilde{k}_0}{\tilde{k}_0+\tilde{k}_L+\tilde{k}_0\tilde{k}_L\int_0^L e^{\beta U(y)}\frac{dy}{D(y)}}. \tag{3.12}$$

It is convenient to introduce a notation for the potential-energy difference along the channel

$$\Delta U=U(L)-U(0). \tag{3.13}$$

In addition, for certainty we take $U(0)=0$. This allows us to write the translocation probabilities in the form

$$P_L(0)=\frac{k_Le^{-\beta\Delta U}}{k_0+k_Le^{-\beta\Delta U}+k_0k_Le^{-\beta\Delta U}\int_0^L e^{\beta U(y)}\frac{dy}{D(y)}},$$

$$P_0(L)=\frac{k_0}{k_0+k_Le^{-\beta\Delta U}+k_0k_Le^{-\beta\Delta U}\int_0^L e^{\beta U(y)}\frac{dy}{D(y)}}. \tag{3.14}$$

The translocation probabilities in Eq. (3.14) can be used to find the probabilities that particles do not translocate and escape the channel through the same end where they entered. The nontranslocation probabilities are

$$P_0(0)=1-P_L(0),$$
$$P_L(L)=1-P_0(L). \tag{3.15}$$

The probabilities given in Eqs. (3.14) and (3.15) are one of the main results of this paper.

IV. DISCUSSION

We begin our discussion of the translocation probabilities in Eq. (3.14) with an observation that the ratio of these probabilities does not depend on the potential profile $U(x)$ and depends only on the potential difference ΔU:

$$\frac{P_L(0)}{P_0(L)}=\frac{k_L}{k_0}e^{-\beta\Delta U}. \tag{4.1}$$

The translocation probabilities reach their maximum values when a deep potential well occupies the entire channel so that the integral in Eq. (3.14) can be neglected. The maximum values are

$$P_L^{\max}(0)=\frac{k_Le^{-\beta\Delta U}}{k_0+k_Le^{-\beta\Delta U}},\quad P_0^{\max}(L)=\frac{k_0}{k_0+k_Le^{-\beta\Delta U}}. \tag{4.2}$$

The translocation probabilities take these maximum values when intrachannel equilibration occurs much faster than all other processes. This happens when $D(x)\to\infty$.

Next, we indicate that in the limiting case of the membrane of zero thickness ($L=\Delta U=0$) separating two identical solutions ($k_0=k_L$) our theory recovers the trivial result

$$P_L(0)=P_0(L)=\tfrac{1}{2}. \tag{4.3}$$

When $\Delta U=0$ and $k_0=k_L=k$, the translocation probabilities are equal to one another and given by

$$P_0(L)=P_L(0)=P_{\mathrm{tr}}=\frac{1}{2+k\int_0^L e^{\beta U(y)}\frac{dy}{D(y)}}. \tag{4.4}$$

In the absence of the potential and for position-independent diffusion coefficient, $D(x)=\mathrm{const}=D$, the translocation probability in Eq. (4.4) takes the form

$$P_{\mathrm{tr}}=\frac{1}{2+\frac{k}{D}L}. \tag{4.5}$$

Previously, we found that for a cylindrical channel of radius a the rate constant is given by[8]

$$k=\frac{4D_b}{\pi a}, \tag{4.6}$$

where D_b is the particle diffusion constant in the bulk which in general may differ from the diffusion constant D in the channel. Substituting this k into Eq. (4.5), we obtain

$$P_{\mathrm{tr}}=\frac{1}{2+\frac{4D_bL}{\pi Da}}. \tag{4.7}$$

For a long narrow channel ($L\gg a$) this translocation probability takes the form

$$P_{\mathrm{tr}}\approx\frac{\pi Da}{4D_bL}\ll 1. \tag{4.8}$$

Thus, the probability of translocation through a narrow cylindrical channel in the absence of attractive potential is very small.

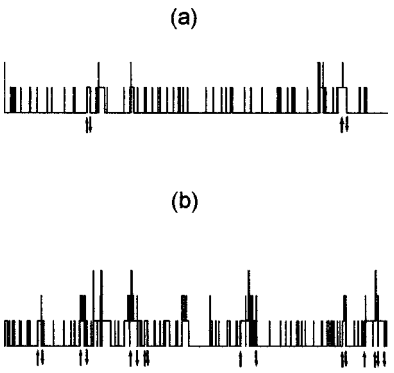

FIG. 2. The record of the number of particles in the channel in the absence of a potential well (panel a) and in the presence of the well of dimensionless depth $\beta U_0 = \ln 5$ that occupies the entire channel, $l = 198$ (panel b). The events corresponding to particle's passage through the channel are marked by the pairs of upward and downward arrows. Most of the particles leave the channel from the same opening they enter. One can see that the translocation is more probable in the presence of the potential well.

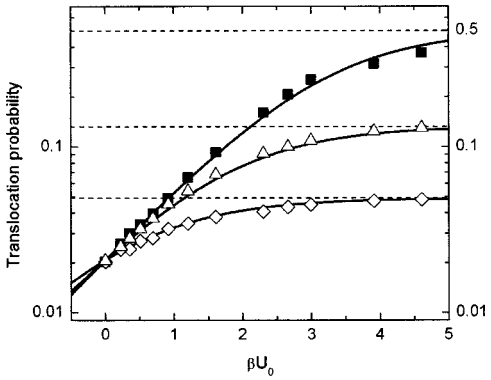

FIG. 3. The translocation probability as a function of the dimensionless well depth for wells of the length $l = 198$, 176, and 120, from top to bottom. The solid curves are drawn according to Eq. (4.10). The horizontal dashed lines correspond to the limiting values in Eq. (4.11).

To analyze how the translocation probability depends on the potential $U(x)$, we use Eq. (4.4), where we take $D(x) = \text{const} = D$ and

$$U(x) = \begin{cases} 0, & 0 < x < x_1, x_2 < x < L, \\ -U_0, & x_1 \leqslant x \leqslant x_2. \end{cases} \tag{4.9}$$

This potential has three parameters: the well depth, U_0, and length, $l = x_2 - x_1$, as well as the position of the well center, $(x_1 + x_2)/2$. The translocation probability in this case is given by

$$P_{\text{tr}} = \frac{1}{2 + \dfrac{4D_b}{\pi D a}[L - l(1 - e^{-\beta U_0})]}, \tag{4.10}$$

where we have used the expression for k in Eq. (4.6). From Eq. (4.10) one can see that P_{tr} does not depend on where the well is located. For deep wells, $\beta U_0 \gg 1$, P_{tr} becomes independent of the well depth and is given by

$$P_{\text{tr}} \approx \frac{1}{2 + \dfrac{4D_b}{\pi D a}(L - l)}. \tag{4.11}$$

The translocation probability approaches its maximum value, 0.5, as $l \to L$, so that a deep well occupies the entire channel. This conclusion can also be drawn from the more general expression in Eq. (4.4), as well as from the expressions in Eq. (4.2).

V. SIMULATIONS

To test the theory we performed Brownian dynamics simulations for a channel with radius $a = 5.5$ and length $L = 200$ in conditional dimensionless units, taking equal diffusion constants in the channel and in the bulk, $D = D_b$ (for more details see Ref. 8). For the sake of simplicity we used the square-well potential in Eq. (4.9) symmetric about the channel center, i.e., $x_1 = (L - l)/2$, $x_2 = (L + l)/2$, where l is the length of the well. The translocation probability was calculated for $l = 120$, 176, and 198 at several values of the dimensionless well depth βU_0. Figure 2 shows records of the number of particles in the channel for the well with $l = 198$ and $\beta U_0 = 0$ and $\ln 5$ [panels (a) and (b), respectively]. One can see that the number of successful attempts to pass through the channel in panel (b) is greater than that in panel (a) as the presence of the potential well facilitates passage of the particles.

The translocation probability was calculated as a ratio of the number of particles that passed through the channel to the total number of particles that entered the channel. The results presented in Fig. 3 show that the translocation probability increases as the well depth grows approaching the limiting value in Eq. (4.11). At a fixed well depth the probability increases as the well length grows. The results found in simulations are in excellent agreement with the predictions of our theory given in Eq. (4.10).

VI. CONCLUDING REMARKS

In this paper we have developed a theory to relate metabolite-channel interaction to the translocation probability of single metabolites. Our theory completely neglects competition among different molecules. In reality, a metabolite molecule passing through a channel acts as a ''stopper'' for other molecules[9] because the molecules cannot jump one over the other. Therefore, for the efficient work of the channel it is required that the molecules do not spend too much time in the channel. This means that a channel with a very deep potential well occupying the entire channel will not be efficient in spite of its high translocation probability. Thus, depending on metabolite concentration, there is an ''optimal potential well'' that makes the channel most efficient. The metabolite translocation probability through this channel would be sufficiently high while metabolite lifetime in the channel would not be too long.

Here we have studied translocation probabilities of neutral molecules. In principle, the same approach can be used to analyze translocation of ions. However, in the case of ions it is not obvious that the problem can always be reduced to a one-dimensional one. If such a reduction is justified, our

theory can be applied after the corresponding potential $U(x)$ is precalculated.

In conclusion, it would be interesting to generalize our analysis to the case of multichannel membrane and to develop a general approach of the type of Siegel's theory,[10] in which he considers transport across laterally homogeneous membranes. We will address this problem in our forthcoming work.

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