Channel-Facilitated Molecular Transport across Membranes: Attraction, Repulsion, and Asymmetry

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Transport of molecules across membrane channels is investigated theoretically using exactly solvable discrete stochastic site-binding models. It is shown that the interaction potential between molecules and the channel has a strong effect on translocation dynamics. The presence of attractive binding sites in the pore accelerates the particle current for small concentrations outside the membrane, while for large concentrations, surprisingly, repulsive binding sites yield the most optimal transport. In addition, the asymmetry of the interaction potential also strongly influences the channel transport. The mechanism underlying these phenomena is discussed using the details of particle dynamics at the binding sites.

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Membrane proteins support and regulate fluxes of ions and molecules that are critical for cell functioning [1]. Molecular transport across membrane pores is characterized by high efficiency, selectivity, and robustness in the response to fluctuations in the cellular environment; however, the mechanisms of these processes are still not well understood [1–3]. Membrane channel proteins, that use the energy of adenosine triphosphate hydrolysis to move particles against external free-energy gradients, are known as active transporters. There are experimental and theoretical arguments that suggest that high selectivity in these proteins is reached via specific interactions at the narrowest part of the pore [2], although recent experiments indicate that nonspecific interactions with the whole channel are also important [4]. It was assumed earlier that the membrane proteins with large water-filled pores move molecules in a passive transport mode by using simple diffusion, and that they have relatively low efficiency and selectivity. However, recent experiments show that permeating molecules interact strongly with large membrane pores leading to very efficient and highly selective transport [5–9].

To understand the facilitated transport phenomena in large membrane pores several theoretical approaches have been presented [10–15]. A continuum model that describes the motion of a single molecule in the channel as one-dimensional diffusion along the potential of mean forces with a position-dependent diffusion constant [12–14] has investigated the most efficient permeation dynamics, and it was shown that there is an optimum attraction between the channel and the translocating molecule that creates the maximal flux. However, a uniform potential along the entire channel with the attraction magnitude of $6–8k_BT$ has been assumed in the calculations that reproduce the experimentally measured currents. The structure of membrane channel proteins is very complex [2], and the realistic free-energy potential of interaction must have a very rough landscape. Recent molecular dynamics simulations of glycerol translocation through aquaglyceroporin GlpF [16] calculate a potential of mean force that shows several relatively weak $(2–6k_BT)$ but strongly localized sites. In a different approach, a macroscopic version of Fick's law has been used to analyze the molecular transport through the channels [15], and it was concluded that in the idealized model any interaction would lead to the amplification of molecular flow. However, this conclusion is rather unphysical since a binding site with infinite attraction would block the molecular traffic through the pore, contradicting this prediction. Potentials of interaction between the channels and permeating molecules, determined in experiments and from computer simulations [16,17], are generally asymmetric with multiple weakly attractive and repulsive binding sites. Although the coupling between nonequilibrium fluctuations and asymmetric potentials of interaction has been discussed recently [18], a full theoretical description of the effect of attractions and repulsions, and of the asymmetry of the interaction potential, on

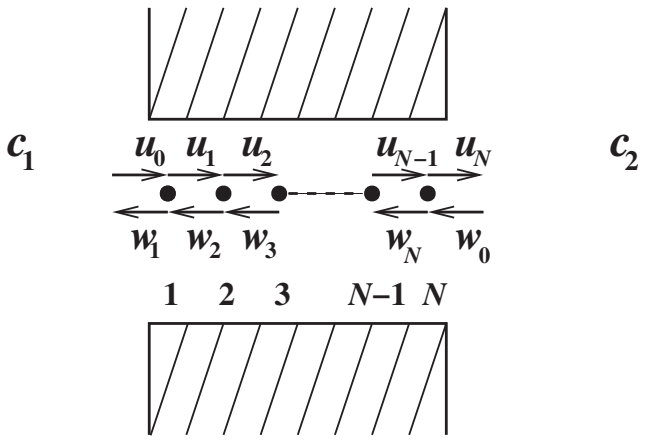

FIG. 1. A general kinetic scheme for a stochastic model of membrane transport with N binding sites. A membrane separates two chambers with concentrations c_1 and c_2. A particle can enter the channel from the left with the rate $u_0 = k_{on}c_1$ or from the right with the rate $w_0 = k_{on}c_2$, and it leaves the pore with rates $u_N = w_1 = k_{off}$. At the site j the particle jump forward and backward with rates u_j and w_j, respectively.

the molecular currents through the biological pores is not available. In this Letter I present a theoretical analysis of channel-facilitated transport using simple discrete stochastic models with multiple binding sites that allow one to calculate dynamic properties exactly. It is found that, depending on the concentrations outside the membrane, attractive or repulsive binding sites can increase molecular fluxes, and that the translocation dynamics is strongly influenced by the asymmetry of the potential.

I consider the transport of particles through a cylindrical membrane channel as shown in Fig. 1. The molecule enters the pore from the left (right) chamber that has a concentration c_1 (c_2) with the rate $u_0 = k_{on}c_1$ ($w_0 = k_{on}c_2$), and it leaves the channel to the left (right) with the rate $w_1 = k_{off}$ ($u_N = k_{off}$). It is assumed that individual particles do not interact with one another, and, that there are N binding sites in the channel. A particle at site j ($j = 1, 2, \ldots, N$) jumps to the right (left) with the rate u_j (w_j). Defining $P_j(t)$ as a probability of finding the molecule at the binding site j at time t, the translocation dynamics can be described by a set of master equations,

$$\frac{dP_j(t)}{dt} = u_{j-1}P_{j-1}(t) + w_{j+1}P_{j+1}(t) - (u_j + w_j)P_j(t), \tag{1}$$

where $j = 1, 2, \ldots, N$ and $P_0(t) \equiv P_{N+1}(t) = 1 - \sum_1^N P_j(t)$ is the probability of finding the channel empty at time t [14]. The discrete stochastic model with N binding sites can be solved exactly by mapping it into a single-particle hopping model along the periodic infinite one-dimensional lattice with $N + 1$ states per period [19,20]. This mapping can be understood by considering multiple identical channels arranged sequentially and keeping the concentration gradient across each period as $\Delta c = c_1 - c_2$. Then dynamic properties of channel-facilitated transport model can be calculated exactly. Specifically, the particle current J for the system shown in Fig. 1 with N identical sites without interactions ($u_j = w_{j+1} = \alpha$ for $j = 1, 2, \ldots, N - 1$) is given by [19,20]

$$J_0 = \frac{k_{on}(c_1 - c_2)}{2[1 + \frac{k_{on}(c_1+c_2)N}{2k_{off}}][1 + \frac{k_{off}(N-1)}{2\alpha}]}. \tag{2}$$

For the channel with a fixed length the transition rate $\alpha \propto N$ because the mean distance between two neighboring binding sites is inversely proportional to N. Then for $N \gg 1$, as expected, the molecular flux is $J_0 \propto 1/N$ [10].

To investigate the effect of interactions in membrane transport the simplest model with only $N = 1$ binding site is analyzed. First suppose that the energy of the binding ssite is equal to $-\varepsilon$; i.e., $\varepsilon > 0$ corresponds to an attractive site, while negative ε describes a repulsive site. The transition rates are related to the interaction potential via the detailed balance conditions

$$\begin{aligned} \frac{u_0(\varepsilon)}{w_1(\varepsilon)} &= \frac{u_0(\varepsilon = 0)}{w_1(\varepsilon = 0)}x, \\ \frac{u_1(\varepsilon)}{w_0(\varepsilon)} &= \frac{u_1(\varepsilon = 0)}{w_0(\varepsilon = 0)}(1/x), \quad \text{with} \quad x = \exp(\varepsilon/k_BT), \end{aligned} \tag{3}$$

and they can be written as follows [20],

$$\begin{aligned} u_0(\varepsilon) &= u_0x^{\theta_1}, & w_1(\varepsilon) &= w_1x^{\theta_1-1}, \\ u_1(\varepsilon) &= u_1x^{\theta_2-1}, & w_0(\varepsilon) &= w_0x^{\theta_2}, \end{aligned} \tag{4}$$

where the interaction-distribution coefficients $0 \le \theta_i \le 1$ describe how the potential effects the transition rates. Coefficients θ_i give relative distances between free-energy minima and transition states for the corresponding transformations. For simplicity, it is assumed that $\theta_1 = \theta_2 = \theta$. Then the particle current is equal to

$$J = \frac{(u_0u_1 - w_0w_1)x^\theta}{(u_0 + w_0)x + (u_1 + w_1)} = \frac{k_{on}(c_1 - c_2)x^\theta}{2 + \frac{k_{on}(c_1+c_2)}{k_{off}}x}. \tag{5}$$

Define J_0 as the molecular flux in the system without interactions ($\varepsilon = 0$), then the ratio of currents is given by

$$\frac{J}{J_0} = \frac{[k_{on}(c_1 + c_2) + 2k_{off}]x^\theta}{2k_{off} + k_{on}(c_1 + c_2)x}. \tag{6}$$

The molecular flux depends strongly on the interaction strength at the binding site, as shown in Fig. 2. For strong attractions and repulsions the current decreases, while for intermediate interaction strengths the molecular flow increases significantly, reaching a maximum value at ε^*,

$$\varepsilon^* = k_BT \ln\left[\frac{\theta}{(1-\theta)}\frac{2k_{off}}{k_{on}(c_1 + c_2)}\right]. \tag{7}$$

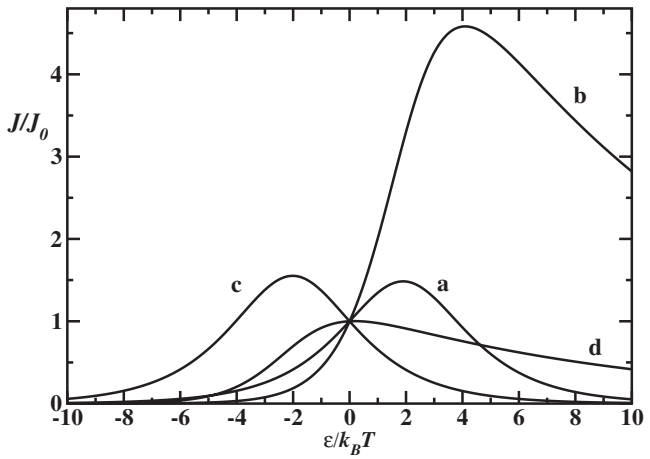

FIG. 2. Relative currents as a function of the interaction strength for the model with $N = 1$ binding site for different concentrations. The transitions rates $k_{on} = 15\ \mu M^{-1}\,s^{-1}$ and $k_{off} = 500\ s^{-1}$ are taken from Ref. [9]. For all calculations $c_2 = 0$ is assumed. Different curves correspond to calculations using Eq. (6) with (a) $c_1 = 10\ \mu M$ and $\theta = 0.5$; (b) $c_1 = 10\ \mu M$ and $\theta = 0.9$; (c) $c_1 = 500\ \mu M$ and $\theta = 0.5$; and (d) $c_1 = 500\ \mu M$ and $\theta = 0.9$.

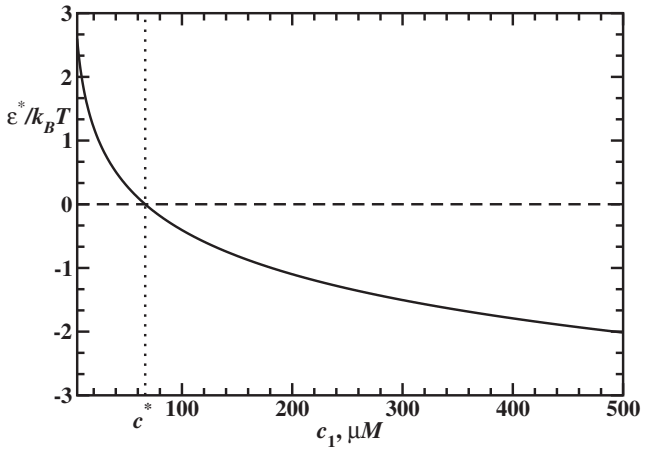

FIG. 3. The most optimal interaction as a function of the external molecular concentration c_1 ($c_2 = 0$ and $\theta = 0.5$ are assumed).

For this most optimal interaction strength the corresponding most efficient relative current is

$$\left(\frac{J}{J_0}\right)^* = (1-\theta)\left[1+\frac{k_{\rm on}(c_1+c_2)}{2k_{\rm off}}\right] \times \left[\frac{\theta}{(1-\theta)}\,\frac{2k_{\rm off}}{k_{\rm on}(c_1+c_2)}\right]^{\theta}. \quad (8)$$

It can be shown that the largest increase in the relative current can be achieved when $\theta \to 1$, producing

$$\left(\frac{J}{J_0}\right)^* = \left[1+\frac{2k_{\rm off}}{k_{\rm on}(c_1+c_2)}\right]. \quad (9)$$

This effect can be estimated explicitly by using the transition rates $k_{\rm off} \simeq 500\ {\rm s}^{-1}$ and $k_{\rm on} \simeq 15\ \mu{\rm M}^{-1}\,{\rm s}^{-1}$ found from experiments on maltodextrin translocation through maltoporin channels [9]. For concentrations of a few μM, Eq. (9) predicts about 100 times increase in the molecular fluxes over $\varepsilon = 0$ case.

The optimal interaction ε^* depends on the concentrations outside the membrane pore as illustrated in Fig. 3. Our analysis shows that the presence of an attractive site leads to molecular flux increases for small concentrations c_1, while for large concentrations the presence of a repulsive site increases the particle current. There is a critical concentration, c^* (for every fixed c_2), that separates the two regimes. The fact that a repulsive binding site leads to current increase seems, at first, surprising, and it has not been predicted in previous theoretical approaches [10–15]. However, these observations can be understood as follows: Suppose that the concentration on the right of the membrane is zero (see Fig. 1), i.e., $c_2 = 0$ (although our arguments can be generalized). It can be shown that the current across the membrane can be viewed as a ratio $J = \Pi/\tau$ between the effective probability to translocate the pore and the mean residence time that a particle spends in the channel [21]. In the present case $\Pi = 1$, and the current is inversely proportional to the time [21],

$$\tau = \frac{1}{u_0 x^\theta} + \frac{1}{u_1 x^{\theta-1}} + \frac{w_1}{u_0 u_1 x^\theta} = \frac{2}{k_{\rm on} c_1 x^\theta} + \frac{x^{1-\theta}}{k_{\rm off}} = \frac{1}{x^\theta}\left(\frac{2}{k_{\rm on}c_1} + \frac{x}{k_{\rm off}}\right). \quad (10)$$

This expression can be understood as a sum of two contributions, namely, the effective times to enter the binding site and to leave it. The conditions for optimal transport correspond to the situation when these two terms are approximately equal. Then the increase in c_1 lowers the value of the most optimal interaction, and for large concentrations the repulsive binding site provides the most efficient translocation. It is suggested that in the general case of an interaction potential with N binding sites the most optimal transport is achieved when the effective times to enter and to leave the strongest attractive or repulsive sites balance each other.

The potential of interaction between the solute and the channel is generally asymmetric [16,17]. To study this property we examine a discrete stochastic model with $N = 2$ binding sites. The asymmetry is introduced by assuming that energies of two consecutive binding sites are $-\varepsilon$ and 0 or 0 and $-\varepsilon$, respectively. If the interaction is on the first binding site, the particle current is given by [20]

$$J_1 = \frac{k_{\rm on}(c_1-c_2)}{\left[1+\frac{k_{\rm on}c_1}{k_{\rm off}} + x^{-\theta}\left(1+\frac{k_{\rm off}}{\alpha}+\frac{k_{\rm on}c_2}{k_{\rm off}}+\frac{k_{\rm on}c_2}{\alpha}\right) + x^{1-\theta}\left(\frac{k_{\rm on}c_2}{k_{\rm off}}+\frac{k_{\rm on}c_1}{\alpha}\right) + x\frac{k_{\rm on}c_1}{k_{\rm off}}\right]}, \quad (11)$$

while for the case when the interaction is on the second binding site one finds

$$J_2 = \frac{k_{\rm on}(c_1-c_2)}{\left[1+\frac{k_{\rm on}c_2}{k_{\rm off}} + x^{-\theta}\left(1+\frac{k_{\rm off}}{\alpha}+\frac{k_{\rm on}c_1}{k_{\rm off}}+\frac{k_{\rm on}c_1}{\alpha}\right) + x^{1-\theta}\left(\frac{k_{\rm on}c_1}{k_{\rm off}}+\frac{k_{\rm on}c_2}{\alpha}\right) + x\frac{k_{\rm on}c_2}{k_{\rm off}}\right]}, \quad (12)$$

where the same coefficients θ are assumed in both cases. The ratio of these two currents is plotted in Fig. 4. It deviates from unity for all interactions except $\varepsilon = 0$. Generally, for $\varepsilon < 0$ we have $J_1/J_2 > 1$, while for attractive interactions the current ratio is always less than unity. Thus putting the binding site at different positions along the channel changes the molecular flux across the membrane. This surprising observation can be explained by looking at the dynamics of particle translocation. Consider the repulsive interaction at the first binding site. After the particle passes the binding site it has a low probability to come back from the second site since the barrier is high. As a result, the overall translocation time is low and the translocation current is large. However, when

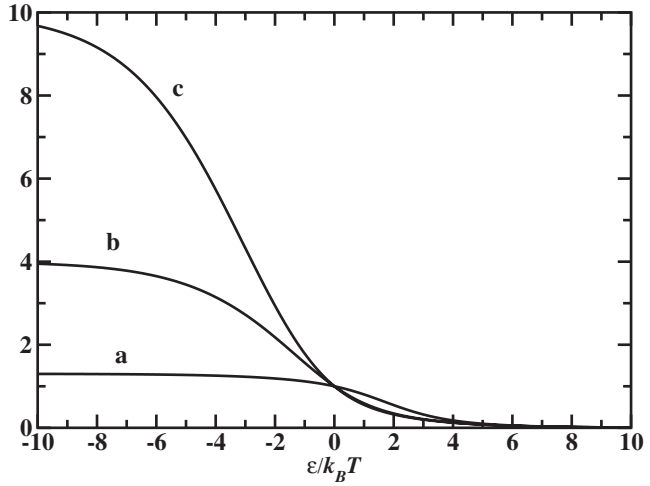

FIG. 4. The ratio of two currents as a function of the interaction strength for two models with $N = 2$ binding sites. The transitions rates $k_{on} = 15\ \mu M^{-1} s^{-1}$ and $k_{off} = 500\ s^{-1}$ are taken from Ref. [9]. For all calculations $c_2 = 0$, $\theta = 0.5$, and $\alpha = k_{off}$ are assumed. Different curves correspond to different concentrations: (a) $c_1 = 10\ \mu M$; (b) $c_1 = 100\ \mu M$; and (c) $c_1 = 300\ \mu M$.

the repulsive interaction is at the second binding site, the situation is different. After reaching the binding site the particle has a high probability to return to the first site, and many attempts to cross the second binding site will be made before successfully passing through the channel. As a result, the overall translocation time is high, leading to small molecular fluxes across the pore.

In conclusion, we have presented discrete-state stochastic models of translocation of molecules across membrane pores, that allow one to calculate explicitly the dynamical properties of the system. The conditions for the most optimal channel transport have been discussed and it has been shown that the strength of interactions at the binding sites strongly influences the translocation dynamics. For small concentrations outside the membrane attractive sites yield the largest particle current, while repulsive binding sites produce the most efficient transport for large external concentrations. It is argued that optimal conditions are achieved when the mean times to enter attractive or repulsive sites are balanced by the corresponding times to leave these positions. To the best of our knowledge, this Letter is the first that suggests that repulsive interactions might be favorable for translocations across the channels. Our method has also been used to investigate the effect of asymmetry on membrane transport by putting a strong interaction site at different positions in the channel. The asymmetry gives different free-energy landscapes, thus producing different currents. This suggests that asymmetry in the interaction potential controls the overall membrane transport, even without coupling to nonequilibrium fluctuations [18]. The theoretical analysis presented supports the idea that interactions between the molecules and the entire channel are important for membrane transport [4]. Our calculations indicate that the mechanism of high selectivity and efficiency of membrane channels is due to the interaction potential between molecules and the channel, and it is suggested that evolution has tuned this potential to create the most optimal molecular transport [6]. It is important to note, however, that our model is rather oversimplified and many important factors of translocation dynamics, such as interactions between molecules and the three-dimensional nature of the channels and corresponding potentials, are neglected. Nevertheless, one may expect that the main physical principles of translocation across membrane pores presented in this Letter remain generally valid. It will be important to investigate the validity of our predictions by analyzing more realistic models of membrane transport.

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