How Interactions Control Molecular Transport in Channels

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Abstract The motion of molecules across channels and pores is critically important for understanding mechanisms of many cellular processes. Here we investigate the mechanism of interactions in the molecular transport through nanopores by analyzing exactly solvable discrete stochastic models. According to this approach the channel transport is viewed as a set of chemical transitions between discrete states. It is shown that the strength and spatial distribution of molecule/channel interactions can strongly modify the particle current. Our analysis indicates that the most optimal transport is achieved when the binding sites are near the entrance or exit of the pore depending on the sign of interaction potential. In addition, the role of intermolecular interactions during the channel transport is studied, and it is argued that an increase in the flux can be observed for some optimal interaction strength. The mechanisms of these phenomena are discussed.

Keywords Molecular transport · Discrete stochastic models · Nanopores · Intermolecular interactions

1 Introduction

The role of biological channels is to support cellular processes by regulating fluxes of molecules and ions in both directions [1, 2]. It is known that transport across membrane protein pores is fast, efficient, selective, and their functioning is robust with respect to strong non-equilibrium fluctuations in the cellular environment [2]. These observations are especially surprising since in many cases the molecular translocation does not involve the use of metabolic energy or conformational changes [4]. Understanding molecular mechanisms of channel transport is one of the most fundamental problems in biology.

When molecules enter into the channel their motion is slowed down mostly due to entropic barriers, and additional forces are needed to overcome these barriers. In cellular systems electric fields and/or chemical interactions are used to speed up translocation. There are
increasing experimental evidences that high efficiency, speed and selectivity of many biological and artificial channels is a result of complex processes that involve molecule/pore and intermolecular interactions [3–15]. Recent high-resolution experiments on polypeptide translocations through protein nanopores [14, 15] started to probe the effect of molecule/pore interactions at the single-molecule level. It was found that changing the location of the binding site in the pore significantly modified the polypeptide flux across the channel. However, a comprehensive description of the role of interactions in the transport through the pores is still not available due to the biochemical and biophysical complexity of the translocation machinery and due to the lack of structural information [4, 14, 15].

To uncover mechanisms of molecular transport across the nanopores several theoretical methods have been proposed [16–26]. The continuum models of the channel transport view the translocation as one-dimensional motion in an effective potential created by interactions with nanopores and with other molecules [18–22]. Interactions are typically modeled as square well potentials that occupy the whole volume of the pore. A different approach utilizes discrete-state stochastic models in which the translocation dynamics is analyzed as set of chemical transitions between specific binding sites in the channel [23–26]. By mapping the discrete-state model of molecular transport across the channel to a single-particle hopping along a periodic lattice, a full dynamic description of permeation through the pore can be obtained for arbitrary sets of parameters [23, 24]. Theoretical calculations also show that both continuum and discrete approaches are closely related, and the results obtained by these approaches can be mapped into each other [20, 22].

Current theoretical models provide a reasonable description of some features of transport processes in the nanopores [18–26]. However what mechanisms control molecular permeation through channels is still an open question. In this paper, we analyze theoretically the effect of interactions on the molecular transport across channels. Specifically, we address the question of how the translocation dynamics is modified by the strength and spatial distribution of the binding sites, and also by the intermolecular interactions.

2 Theoretical Model

2.1 Molecule/Channel Interactions

We consider transport of molecules through nanopore as an effective one-dimensional motion along the discrete lattice of binding sites as illustrated in Fig. 1. There are $N$ binding

![Fig. 1] A schematic picture of the discrete stochastic model with $N$ binding sites for the translocation through the pore. A dashed box indicates the volume of the channel.
sites in the channel, and concentrations of molecules to the left or right of the channel are equal to \(c_1\) and \(c_2\), respectively. The molecule can move into the channel from the left (right) with the rate \(u_0 = k_{on}c_1\) \((w_0 = k_{on}c_2)\); and the particle can move out of the channel with rates \(w_1\) and \(u_N\); see Fig. 1. In the nanopore the molecule at the site \(j\) \((j = 1, 2, \ldots, N)\) can jump forward (backward) with the rate \(u_j\) \((w_j)\). First, we consider the situation when only one particle can be found in the channel. The probability to find a molecule at site \(j\) at time \(t\) is given by a function \(P_j(t)\), and the translocation dynamics is fully described by a set of master equations,

\[
\frac{d P_j(t)}{dt} = u_{j-1}P_{j-1}(t) + w_{j+1}P_{j+1}(t) - (u_j + w_j)P_j(t),
\]

for \(j = 1, \ldots, N\); while \(P_0(t) = P_{N+1}(t) = 1 - \sum_{j=1}^{N} P_j(t)\) describes the completely empty channel at the time \(t\) \([23, 24]\). We have shown earlier \([23, 24]\) that this model with \(N\) binding sites can be solved exactly at \(t \to \infty\) by mapping it into a single-particle random walk model on an infinite periodic lattice (with a period equal to \(N + 1\)). The size of the period is equal to \(N + 1\) because there are \(N\) states inside the channel and one state outside of the channel \([23, 24]\). Specifically, for the uniform channel with a simplifying assumption of zero particle concentration to the right of the pore \((w_0 = 0)\) the expression for the particle current is given by

\[
J_0(N) = \frac{uu_0}{(N + 1)\left(u + \frac{N}{2}u_0\right)},
\]

where \(u_j = w_j = u\) \((j = 1, \ldots, N)\). To quantify the effect of interactions we assume that in one of the binding sites, say \(k\)-th, the particle interacts with the pore with potential \(\varepsilon\) that differs from other sites. The case of \(\varepsilon > 0\) corresponds to attractive interactions, while negative \(\varepsilon\) describe the repulsive binding site. The transition rates near the special binding site must satisfy the detailed balance conditions \([23, 24]\) which lead to

\[
\frac{u_k'}{w_k'} = \frac{u_{k-1}}{w_k} x, \quad \frac{u_k'}{w_{k+1}'} = \frac{u_k}{w_{k+1}} x^{-1},
\]

where \(u_{k-1}, u_k, w_k\) and \(w_{k+1}\) correspond to the uniform channel without special interactions, and we define \(x = \exp(\varepsilon/k_B T)\). The corresponding explicit expressions for transition rates can now be written as \([27]\),

\[
u_k' = u_k x^{\theta-1}, \quad w_k' = w_k x^{\theta-1}, \quad w_{k+1}' = w_{k+1} x^\theta,
\]

where the coefficient \(\theta\) \((0 \leq \theta \leq 1)\) describes how the potential modifies the corresponding transition rates \([23, 24, 27]\). Now flux in the channel with the binding site at the position \(k\) is equal to

\[
J_k(N) = \frac{uu_0}{u[2x^{-\theta} + N - 1] + u_0[2(k - 1)x^{-\theta} + x^{1-\theta} + (N - k)x + \frac{N(N-1)}{2} - k + 1]}.
\]

The effect of interactions can be better understood by analyzing the dimensionless ratio of particle currents,

\[
\frac{J_k(N)}{J_0(N)} = \frac{(N + 1)((u/u_0) + \frac{N}{2})}{(u/u_0)[2x^{-\theta} + N - 1] + [2(k - 1)x^{-\theta} + x^{1-\theta} + (N - k)x + \frac{N(N-1)}{2} - k + 1]}.
\]
This function provides a convenient measure of how the positioning of the special binding site changes the particle current in comparison with the uniform channel without special binding sites.

The curves presented in Fig. 2 show the effect of the special binding site location on particle fluxes. For attractive interactions the most optimal current is reached when the binding site is the last one \( k = N \), while it is better to have the repulsive site at the entrance \( k = 1 \) to accelerate the transport. It can be shown rigorously from (6) that \( \frac{\partial J_k(N)}{\partial k} > 0 \) for positive \( \epsilon \), and \( J_k(N) \) is always a decreasing function for negative \( \epsilon \).

These observations can be understood in the following way. Putting the attractive binding site near the exit increases the probability of finding the particle here, which leads to higher chances to complete the translocation by exiting to the right. The repulsive site at the entrance serves as a barrier for the particles that already passed it, lowering the probability of unsuccessful excursions without the translocation. These results are in full agreement with recent single-molecule experiments on translocation of polypeptides [14, 15]. In these experiments the mutation in the biological nanopore that increased the molecule/pore interaction have led to faster transport when the mutation site was near the exit. These theoretical results might also explain why so many biological channels have their binding sites at the entrance and/or at the exit positions. To have special bindings at these locations will optimize the overall fluxes [28]. Our results can be easily extended to more complex potential with several attractive and repulsive sites, and it can be shown that the most optimal flux is reached when repulsive sites cluster together near the entrance, while attractive sites tend to stay closer to the exit.

The strength of interactions can also affect the flux through the nanopore as shown in Fig. 3, in agreement with previous theoretical findings for the channel-facilitated molecular transport [18–24]. For any set of parameters there is an optimal interaction strength \( \epsilon^* \) that can be obtained from the condition \( \frac{\partial J_k(N)}{\partial \epsilon} (\epsilon^*) = 0 \), yielding the following equation,

\[
2\theta \left[ \frac{u}{u_0} + k - 1 \right] = (1 - \theta)x + (N - k)x^{1+\theta}.
\]
Specifically, for the most optimal site \( k = N \) (for attractive interactions) we have the following expression for the most optimal interaction strength,

\[
\varepsilon^* = k_B T \ln \left[ \frac{2\theta}{1 - \theta} \left( \frac{u}{u_0} + N - 1 \right) \right].
\]

(8)

It is interesting to note that the optimal interaction in this case is an increasing function of the size of the channel (or the number of binding sites \( N \)). For arbitrary position of the special binding site, from (7) it can be shown that for \( \theta = 0 \) we have \( \varepsilon^* = -\infty \) for any position of the binding site, while for \( \theta = 1 \) one can obtain

\[
\varepsilon^* = \frac{1}{2} k_B T \ln \left[ \frac{2(u/u_0 + k - 1)}{N - k} \right].
\]

(9)

It suggests that distribution factors \( \theta \) are very important for molecular transport across membrane channels.

2.2 Intermolecular Interactions

During the translocation across the channels more than one molecule can be found inside the nanopores and interactions between them might become important for the transport [25, 26]. Previous theoretical treatments considered the effect of the particle crowding [25, 26], but only hard-core exclusion interactions have been assumed and correlations in channel occupation have also been neglected. However, since the molecular permeation through the pores can be viewed effectively as one-dimensional systems the effect of intermolecular interactions and particle correlations could be significant. To investigate explicitly the effect of intermolecular interactions we consider a specific \( N = 2 \) model without molecule/pore interactions, as specified above, but allowing more than one particle to be found in the pore. This simple model can serve as a good testing ground for underlying complex transport phenomena. There is an energy cost associated with finding two particles next to each other. The configuration with 2 particles has an energy \( \varepsilon \), with \( \varepsilon > 0 \) (\( \varepsilon < 0 \)) describing attractive (repulsive) interactions. There are four possible configurations in the channel as plotted in Fig. 4. We label them as \((i, j)\) with \( i, j = 0 \) (\( i, j = 1 \)) for the empty (occupied) site. It should
be noted that the rate to enter the half-filled configuration $u_1$ and the exit rate from the fully occupied state $u_2$ are related via the detailed balance,

$$\frac{u_1}{u_2} = \frac{u_0}{u} x,$$

with $x = \exp(\epsilon/k_B T)$. The case $\epsilon = 0$ corresponds to the situation analyzed in Refs. [25, 26]. This allows us to write explicit expressions,

$$u_1 = u_0 x^{\theta}, \quad u_2 = u x^{\theta-1},$$

where the coefficient $0 \leq \theta \leq 1$ again specifies how the inter-particle interaction modifies these entrance and exit rates. We can define $P(i,j,t)$ as the probability to find channel in the state $(i,j)$ at time $t$, and temporal evolution of the system dynamics can be found by analyzing corresponding master equations:

$$\frac{dP(0,0;t)}{dt} = u P(0,1;t) + u P(1,0;t) - u_0 P(0,0;t),$$

$$\frac{dP(1,0;t)}{dt} = u_0 P(0,0;t) + u_2 P(1,1;t) + u P(0,1;t) - 2u P(1,0;t),$$

$$\frac{dP(0,1;t)}{dt} = u P(1,0;t) + u_2 P(1,1;t) - (2u + u_1) P(0,1;t),$$

$$\frac{dP(1,1;t)}{dt} = u_1 P(0,1;t) - 2u_2 P(1,1;t).$$

Solving these equations at large times ($\frac{dP(i,j;t)}{dt} \rightarrow 0$) yields the expression for the molecular flux,

$$J_2 = \frac{3u u_0 (u + \frac{u_0}{2} x^{\theta})}{3u^2 + \frac{u_0^2}{2} (x + x^{\theta}) + u u_0 (3 + x^{\theta}/2)},$$

In the limit of $\epsilon \rightarrow -\infty$ only a single molecule can be found in the channel and (13), as expected, reduces to (2) for $N = 2$,

$$J_1 = \frac{u u_0}{3(u + u_0)}.$$
The effect of intermolecular interactions on the channel fluxes, as shown in Fig. 5, is rather complex. For $\theta = 0$ the flux is always a decreasing function of the interaction, and the single-particle transport is the most optimal. For $\theta = 1$ the trend is reversed: the stronger the interaction, the larger the molecular flux. However, for intermediate values of $0 < \theta < 1$ (which is probably a more realistic situation) a non-monotonous dependence is observed with the flux reaching a maximum at some optimal interaction strength. The optimal interaction could be positive or negative depending on the parameters of the system. For attractive interactions the presence of the particle in the channel stimulates the entrance of another particle into the pore, but it also slows down exiting of both particles from the channel. For repulsive interactions partially-filled channels serve as a barrier for the particle to enter lowering the particle flux through the system. But simultaneously the entering particle accelerates the exiting of the particle already inside increasing the particle current. The combination of these processes explains the complex behavior in the channel with multiple particles.

3 Summary and Conclusions

To summarize, we have investigated the effect of interactions on the molecular transport across channels. Using exactly-solvable discrete stochastic models, we have shown that the strength of the interaction, as well as the spatial distribution, are important parameters that can effectively control molecular translocations through nanopores. It was found that the largest particle current can be achieved when attractive sites are near the exit of the channel, while the most optimal position of repulsive sites are near the entrance. We have argued that the mechanism of how the interaction affect the transport across the channel is based on controlling local concentration of particles in the channel. Special binding sites might serve as local traps or barrier, modifying the overall dynamics. Attractive sites increase the probability to find the particles at these binding sites, while the repulsive sites work as barriers preventing particles already in the channel from moving back. Our theoretical picture agrees well with single-molecule experiments on translocation of polypeptides and it allows to explain these observations [14, 15]. In addition, presented theoretical conclusions also agree with experimental observations on maltoporin channels [8]. One could argue
that our theoretical approach might also explain observed distributions of binding sites in real biological channels [28]. However, it should be noted that biological transport systems might not be optimized with the respect of the particle current. But our method still allows to analyze microscopic details of molecular transport across channels.

In addition, we have studied the role of intermolecular interactions in the transport through nanopores. It was found that at some interaction strength the particle flux can be increased to reach the maximum level. The complex behavior could be explained by the fact that particles already in the channel might catalyze or inhibit the entrance into the channel of other particles. The discussed model presents a convenient theoretical framework for investigating complex transport phenomena in biological and artificial channels, and it might also serve as a first step for further studies that must include more realistic structural and biochemical information.

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