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Mapping Intrachannel Diffusive Dynamics of Interacting Molecules onto a Two-Site Model: Crossover in Flux Concentration Dependence

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Abstract

This study focuses on how interactions of solute molecules affect the concentration dependence of their flux through narrow membrane channels. It is assumed that the molecules cannot bypass each other because of their hard-core repulsion. In addition, other short- and long-range solute–solute interactions are included into consideration. These interactions make it impossible to develop an analytical theory for the flux in the framework of a diffusion model of solute dynamics in the channel. To overcome this difficulty, we coarse-grain the diffusion model by mapping it onto a two-site one, where the rate constants describing the solute dynamics are expressed in terms of the parameters of the initial diffusion model. This allows us (i) to find an analytical solution for the flux as a function of the solute concentration and (ii) to characterize the solute–solute interactions by two dimensionless parameters. Such a characterization proves to be very informative as it results in a clear classification of the effects of the solute–solute interactions on the concentration dependence of the flux. Unexpectedly, this dependence can be nonmonotonic, exhibiting a sharp maximum in a certain parameter range. We hypothesize that such a behavior may constitute an element of a regulatory mechanism, wherein maximal flux reports on the optimal solute concentration in the bulk near the channel entrance.

Graphical Abstract

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1. INTRODUCTION

Channel-facilitated transport across cell and organelle membranes and means of its regulation attract a lot of attention from both industry and science. The reason is 2-fold. First, using existing, and finding new low-molecular-weight agents for therapeutic regulation of channels, is of well-recognized practical importance. It is known that approximately 13% of all drugs marketed today act as modifiers of ion channels¹ correcting or alleviating various health problems. Second, ion-selective and metabolite channels of biological membranes offer unique opportunities for studying transport processes at a detailed single-molecule level² and provide important examples of mesoscopic systems that challenge researches with many unsolved problems of solute dynamics under the conditions of nanoscale confinement.^{3–10}

Transport of various solutes through membrane channels is an extremely complex phenomenon.^{11–16} One of the reasons of this complexity is interactions of solute molecules between themselves and with the channel. Here we address the former issue focusing on how it affects the flux dependence on the solute concentration. We will see that the effect can be nontrivial. In particular, the flux can be a nonmonotonic function of the concentration, with a well-pronounced maximum at a certain “optimal” concentration, which is a function of the interaction parameters.

The diffusion model of solute dynamics inside a channel^{17–21} allows formulation of an analytical theory of channel-facilitated transport in two limiting cases of (i) noninteracting solute molecules and (ii) molecules which so strongly repel each other that not more than one molecule is allowed to be in the channel. In applying this model to the analysis of transport under more general assumptions about solute–solute interactions, one faces the problem of more than one diffusing molecule interacting inside the channel, the solution to which is unknown. To bypass this difficulty, we coarse-grain the diffusion model by mapping it onto an effective two-site one, parameters of which are expressed in terms of the parameters of the initial model.²¹

The advantage of the two-site model is that in some cases it allows a relatively simple analytical solution for the solute flux through the channel. Recently, this model was used to analyze different aspects of channel-facilitated transport.^{22–26} To be more specific, in refs

22,23, the authors used the model to study the excluded volume effect on transport (each site cannot be occupied by more than one molecule). Refs 24,25 deal with transport of solutes of two different types, focusing on their cooperation and competition. The closest to the present work is the analysis of the effect of intermolecular interactions on the transport through membrane channels in ref 26. Although both the present study and ref 26 use the same general approach to the problem, there are two main distinctions between the two works:

- (i) While the main focus here is on the flux dependence on solute concentration, ref 26 does not investigate this dependence.
- (ii) In addition, the study in ref 26 assumes equal rates for intersite transitions of solute molecules and for their escape from a singly occupied channel. Here we derive these rates by mapping intrachannel diffusion dynamics onto the two-site model, and it turns out that, for typical channel geometries, the escape rate is much higher than that for intersite jumps (see eqs 1 and 2).

The outline of the article is as follows. The two-site model that we use to derive an expression for the steady-state flux and its relation to the diffusion model of the solute intrachannel dynamics are discussed in Section 2. In Section 3, we derive and analyze the expression for the steady-state flux of the interacting solute molecules focusing on the flux concentration dependence. Some concluding remarks are made in Section 4. The Appendix provides a detailed discussion of the mapping of solute diffusion dynamics in the channel onto the two-site model.

2. MODEL

Consider a single solute molecule inside a two-site channel. The dynamics of such a molecule are schematically illustrated by Figure 1. It is characterized by four rate constants which describe transitions between the two channel sites, α_1 and α_2 , and the escape from the channel to the left and right reservoirs, $k_{\text{off}}^{(1)}$ and $k_{\text{off}}^{(2)}$, respectively. The relations between these rate constants and parameters of the diffusion model that describes solute dynamics in the channel as one-dimensional diffusion in the potential of mean force are established in ref 21. To make the present article self-contained, an alternative derivation of these relations is given in the Appendix.

For the sake of simplicity, we consider transport through a symmetric cylindrical channel for which $\alpha_1 = \alpha_2 = \alpha$ and $k_{\text{off}}^{(1)} = k_{\text{off}}^{(2)} = k_{\text{off}}$. In this special case, the expressions giving the rate constants in terms of the channel length, l , radius, a , and the solute diffusivities inside the channel, D_{ch} , and in the bulk, D_{b} , which may be different, are (see the Appendix)

$$\alpha = \frac{2D_{\text{ch}}}{l^2} \quad (1)$$

and

$$k_{\text{off}} = \frac{8D_b}{\pi al} \quad (2)$$

These expressions show that in the absence of solute molecule interactions with the channel walls, except for possible hydrodynamic hindrance reducing the solute intrachannel diffusivity, k_{off} significantly exceeds a for long narrow channels, $l \gg a$.

We study transport driven by the solute concentration difference on the two sides of the membrane, assuming that the solute concentrations in the left and right reservoirs, respectively, are $c_L = c$ and $c_R = 0$. The solute entrance into the empty channel is described by the influx, $k_H c$, where

$$k_H = 4aD_b \quad (3)$$

is the Hill rate constant.²⁷

We will consider transport of hard-core solute molecules which cannot bypass each other inside the channel. This implies that each channel site cannot be occupied by more than one molecule. As a consequence, the channel can be in one of the four states shown in Figure 2, which illustrates the kinetic scheme of interstate transitions. Additional (to the hard-core repulsion) short-range interactions of solute molecules inside the channel affect the rate constant k_{off} . We denote the rate constant describing the escape of a molecule from the channel occupied by two molecules by k'_{off} . Solute repulsion/attraction results in the increase/decrease of this rate constant compared to k_{off} .

The second molecule can enter the channel only when the first molecule occupies site 2. Long-range interactions of a molecule inside the channel with molecules in the bulk affect the influx. The corresponding influx is denoted by $k'_H c$: $k'_H > k_H$, when the long-range interactions are attractive, and $k'_H < k_H$, when these interactions are repulsive.

The model described above is used to study how these interactions affect the steady-state flux through the channel.

3. STEADY-STATE FLUX

To analyze the steady-state flux, consider the steady-state probabilities of finding the channel in each of the four states shown in Figure 2, which are denoted by P_{00} , P_{10} , P_{01} , and P_{11} . Here the first and last probabilities are those for the empty channel, P_{00} , and for the channel occupied by two molecules, P_{11} , whereas P_{10} and P_{01} are the probabilities of finding the channel occupied by one molecule located on site 1 or site 2, respectively (see Figure 2). The four probabilities satisfy a system of linear equations

$$k_H c P_{00} - (\alpha + k_{\text{off}}) P_{10} + \alpha P_{01} + k'_{\text{off}} P_{11} = 0 \quad (4)$$

$$\alpha P_{10} - (\alpha + k_{\text{off}} + k'_H c) P_{01} + k'_{\text{off}} P_{11} = 0 \quad (5)$$

$$k'_H c P_{01} - 2k'_{\text{off}} P_{11} = 0 \quad (6)$$

$$P_{00} + P_{10} + P_{01} + P_{11} = 1 \quad (7)$$

where the first three equations are balance equations at steady state, and the last equation is the normalization condition.

The steady-state flux J between the two reservoirs is given by (see Figure 2)

$$J = k_{\text{off}} P_{01} + k'_{\text{off}} P_{11} \quad (8)$$

One can find this flux by substituting into the above equation the probabilities P_{01} and P_{11} obtained by solving eqs 4–7. The result is

$$J = \frac{1}{F(c)} k'_{\text{off}} \alpha k_H c (2k_{\text{off}} + k'_H c) \quad (9)$$

where $F(c)$ is a quadratic function of the solute concentration given by

$$F(c) = 2k_{\text{off}}^2 k'_{\text{off}} + k_{\text{off}} k'_{\text{off}} (4\alpha + 2k_H c + k'_H c) + k'_{\text{off}} k_H c (4\alpha + k'_H c) + \alpha k_H k'_H c^2 \quad (10)$$

The solute–solute interactions can be neglected as $c \rightarrow 0$. In this limiting case, the flux in eq 9 reduces to that for noninteracting point particles

$$J = \frac{\alpha k_H c}{k_{\text{off}} + 2\alpha}, c \rightarrow 0 \quad (11)$$

To characterize the strength of the short-range and long-range solute–solute interactions, we introduce two dimension-less parameters, ε and μ , and write the rate constants k'_{off} and k'_H as

$$k'_{\text{off}} = k_{\text{off}}/\varepsilon, k'_H = \mu k_H \quad (12)$$

The case of $\mu = \varepsilon = 1$ corresponds to noninteracting hard-core particles. Respectively, $\varepsilon < 1$ and $\varepsilon > 1$ correspond to short-range repulsion and attraction, and $\mu < 1$ and $\mu > 1$ correspond to long-range repulsion and attraction between the hard-core molecules. Indeed, when $\varepsilon < 1$ ($\varepsilon > 1$), $k'_{\text{off}} < k_{\text{off}}$ ($k'_{\text{off}} > k_{\text{off}}$) because the two molecules inside the channel repel (attract) each other. When $\mu < 1$ ($\mu > 1$), $k'_H < k_H$ ($k'_H > k_H$) because of repulsive (attractive) interactions of the molecule inside the channel with molecules in the bulk decreasing (increase) the influx, $k'_H c$.

Some of the regimes allowed by the present model may seem to involve contradictory assumptions. For example, the regime of long-range repulsion between the solute molecules and, simultaneously, their short-range attraction in the channel. However, such “oppositely directed” interactions are possible. The situation here is analogous to well-known cooperative binding of molecules of the same charge to various proteins, including ion channels.²⁸

Using ε and μ , we can write the flux in eq 9 as

$$J(\varepsilon, \mu) = \frac{1}{G(c|\varepsilon, \mu)} k_{\text{off}} a k_H c (2k_{\text{off}} + \mu k_H c) \quad (13)$$

Where

$$G(c|\varepsilon, \mu) = 2k_{\text{off}}(k_{\text{off}} + 2a)(k_{\text{off}} + k_H c) + \mu k_H c (k_{\text{off}}^2 + k_{\text{off}} k_H c + \varepsilon a k_H c) \quad (14)$$

These expressions show that the flux is a monotonically decreasing function of ε ; i.e., the decrease of short-range repulsion (or the increase of short-range attraction) leads to the decrease of the flux at fixed μ and c . The μ -dependence of the flux at fixed ε and c is more complex. As follows from eqs 13 and 14, the flux monotonically increases with μ when $(\varepsilon/2 - 1)cV_{\text{ch}} < 2$, where $V_{\text{ch}} = \pi a^2 l$ is the channel volume, and we have used the relation $k_H/k_{\text{off}} = V_{\text{ch}}/2$, and monotonically decreases with μ when $(\varepsilon/2 - 1)cV_{\text{ch}} > 2$. The flux is independent of μ , i.e., independent of the strength of the long-range interactions when parameter ε and the concentration satisfy $(\varepsilon/2 - 1)cV_{\text{ch}} = 2$.

3.1. Two Limiting Cases.

- (1) For noninteracting (ni) hard-core particles, $\mu = \varepsilon = 1$, the flux in eq 13 reduces to

$$J_{\text{ni}} = \frac{k_{\text{off}} \alpha k_{\text{H}} c (2k_{\text{off}} + k_{\text{H}} c)}{2k_{\text{off}}^3 (4\alpha + 3k_{\text{H}} c) + k_{\text{off}} k_{\text{H}} c (4\alpha + k_{\text{H}} c) + \alpha k_{\text{H}}^2 c^2} \quad (15)$$

This describes a monotonically increasing sublinear concentration dependence of the flux, which saturates to

$$J_{\text{ni}}^{\text{max}} = \frac{k_{\text{off}} \alpha}{k_{\text{off}} + \alpha}, c \rightarrow \infty \quad (16)$$

1. (2) In the case of strong long-distance repulsion (sldr), $\mu = k'_{\text{H}} = 0$, the channel is singly occupied, and we have

$$J_{\text{sldr}} = \frac{k_{\text{off}} \alpha k_{\text{H}} c}{(k_{\text{off}} + 2\alpha)(k_{\text{off}} + k_{\text{H}} c)} \quad (17)$$

This flux is also monotonic and sublinear in concentration. As $c \rightarrow \infty$, it approaches its maximum value given by

$$J_{\text{sldr}}^{\text{max}} = \frac{k_{\text{off}} \alpha}{k_{\text{off}} + 2\alpha}, c \rightarrow \infty \quad (18)$$

As might be expected, $J_{\text{ni}} > J_{\text{sldr}}$ for all concentrations.

3.2. General Case.

Analysis of eqs 13 and 14 in the general case of arbitrary interactions between the solute molecules brings about rich behavior of the flux as a function of the concentration, a feature that may seem unexpected for such a simple model. Specifically, it turns out that at sufficiently strong short-range interactions, the flux can be nonmonotonic and has a maximum at a certain concentration.

Using eqs 13 and 14, it can be shown that the straight line

$$\varepsilon = 2 + \frac{\mu}{2} \frac{k_{\text{off}}}{\alpha} \quad (19)$$

separates the regions of the (μ, ε) plane with different types of the flux dependence on the solute concentration. The flux is a monotonic function of the concentration, if $\varepsilon < 2 + \mu k_{\text{off}} / (2\alpha)$, and has a maximum when $\varepsilon > 2 + \mu k_{\text{off}} / (2\alpha)$. As the strength of long-range interactions increases, the flux can demonstrate a superlinear dependence at low

concentrations. As follows from eqs 13 and 14, the concentration dependence of the flux is sublinear when $\mu < 2 + k_{\text{off}}/\alpha$ and superlinear when $\mu > 2 + k_{\text{off}}/\alpha$. Regions in the (μ, ε) plane of different flux behaviors are shown in Figure 3. At $\varepsilon < 2$, the flux always increases with concentration monotonically; at $\varepsilon > 2$ (strong short-range attraction), the flux exhibits a maximum. Correspondingly, at $\mu < 2$, the flux is always sublinear in the concentration; at $\mu > 2$ (strong long-range attraction), the flux is superlinear.

The 3D plot in Figure 4 shows the concentration dependence of the flux for different values of the dimensionless parameter ε at $\mu = 3 \times 10^{-3}$ (strong long-range repulsion). It is seen that this dependence changes from monotonically increasing at small ε to the one displaying a crossover behavior at large ε corresponding to a strong short-range attraction between solutes in the channel. The most interesting effect in the flux concentration dependence is the nonmonotonic behavior found for strong short-range attractions. The flux not only saturates but is impeded by the increasing particle bulk concentration after it reaches a maximum at some “optimal” concentration.

The above analysis assumes that solute molecules do not interact with the channel walls. In reality, this is not necessarily the case.^{11–16} Attraction to the channel walls makes the channel a trap for solute molecules and leads to the decrease of the escape rate constant k_{off} . As discussed in the Appendix, at the pronounced attractive interactions between the solute and the channel walls, this rate constant may be smaller than its counterpart α , describing intersite jumps. This is in contrast to the case of no interaction, where k_{off} is typically greater than α (see eqs 1 and 2). Solute attraction to the channel walls in combination with strong short-range solute–solute attraction may result in a sharp peak in the concentration dependence of the flux, as illustrated in Figure 5. The sharpness of the peak depends on the interaction strength: the higher ε , the sharper the peak. We hypothesize that this phenomenon may be used by nature as a sensory mechanism of a regulatory circuit, wherein an “optimal” solute concentration is reported upon by maximizing the transmembrane flux of the molecules.

4. CONCLUSIONS

In summary, a simple two-site model of channel-facilitated membrane transport explored in the present work allows for a description of not only flux saturation with the solute concentration but also more subtle effects, such as super-linearity and crossover behavior. This is a consequence of accounting for long-range and short-range interactions between the solute molecules by two dimensionless parameters, ε and μ , which describe the effect of the interactions on the rate constants, eq 12.

Finally, we note that the advantage of the two-site model analyzed above is that it allows for an analytical solution for the steady-state flux of the interacting solute molecules through a membrane channel, eqs 9 and 13. This solution was used to study the concentration dependence of the flux. We believe that the qualitative pattern of how the interactions affect this dependence is universal in the sense that it is not a specific feature of the two-site model. It would be interesting to check this prediction numerically for other models of the dynamics of interacting solutes in the channel.

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APPENDIX: MAPPING THE INTRACHANNEL DIFFUSION DYNAMICS ONTO A TWO-SITE MODEL

The diffusion model^{17–21} describes the motion of a solute molecule in the channel as one-dimensional diffusion along the channel axis (chosen as the x -coordinate) in the potential of mean force, $U(x)$, which can include both energetic and entropic contributions. According to this model, the molecule propagator (Green's function) in the channel, denoted by $G(x, t | x_0)$, satisfies

$$\frac{\partial G}{\partial t} = \frac{\partial}{\partial x} \left\{ D(x) e^{-\beta U(x)} \frac{\partial}{\partial x} [e^{\beta U(x)} G] \right\} \quad (\text{A.1})$$

subject to the initial condition, $G(x, 0 | x_0) = \delta(x - x_0)$, and the boundary conditions at the left (L) and right (R) channel ends, located at x_L and x_R , respectively

$$D(x_L) e^{-\beta U(x_L)} \frac{\partial}{\partial x} [e^{\beta U(x)} G] \Big|_{x=x_L} = \kappa_L G \Big|_{x=x_L} \quad (\text{A.2})$$

and

$$-D(x_R) e^{-\beta U(x_R)} \frac{\partial}{\partial x} [e^{\beta U(x)} G] \Big|_{x=x_R} = \kappa_R G \Big|_{x=x_R} \quad (\text{A.3})$$

The rate constants κ_L and κ_R , entering the boundary conditions, are^{29,30}

$$\kappa_L = \frac{4D_b}{\pi a_L}, \kappa_R = \frac{4D_b}{\pi a_R} \quad (\text{A.4})$$

In the above equations, $\beta = (k_B T)^{-1}$, where k_B and T are the Boltzmann constant and absolute temperature; $D(x)$ is the molecule diffusivity in the channel, which may depend on x and differs from its bulk counterpart D_b ; and a_L and a_R are the channel radii at x_L and x_R , respectively.

To coarse-grain the intrachannel diffusion dynamics and to map it onto the two-site model described by the kinetic scheme schematically shown in Figure 1, we have to express the

rate constants α_1 , α_2 , $k_{\text{off}}^{(1)}$, and $k_{\text{off}}^{(2)}$ in terms of the parameters of the diffusion dynamics. For this purpose, consider a solute molecule that starts from the left channel end, $x_0 = x_L$. To find expressions for α_1 and $k_{\text{off}}^{(1)}$, we use eq A.1 with a partially absorbing (radiation) boundary condition at $x = x_L$, eq A.2, and perfectly absorbing boundary conditions at $x = x_R$ eq A.3 with $\kappa_R = \infty$, which leads to $G(x_R, t | x_L) = 0$. Solving eq A.1 with these initial and boundary conditions, we find the splitting probabilities for the molecule to be trapped by the right boundary at $x = x_R$, P_+ , and to escape from the channel through the left boundary, $P_- = 1 - P_+$, as well as the mean molecule lifetime, τ_L . The results are

$$P_+ = \frac{1}{1 + \kappa_L e^{-\beta U(x_L)} \int_{x_L}^{x_R} e^{\beta U(y)} D^{-1}(y) dy} \quad (\text{A.5})$$

$$P_- = 1 - P_+ = \kappa_L e^{-\beta U(x_L)} \int_{x_L}^{x_R} e^{\beta U(y)} D^{-1}(y) dy P_+ \quad (\text{A.6})$$

$$\tau_L = \int_{x_L}^{x_R} \left(\int_x^{x_R} e^{\beta U(y)} D^{-1}(y) dy \right) e^{-\beta U(x)} dx P_+ \quad (\text{A.7})$$

Next, we compare these quantities with their counterparts given by the two-site model. Specifically, when a molecule starts from site 1, it either jumps to site 2 or escapes from the channel. The splitting probabilities for the two processes, P_{jump} and $P_{\text{esc}} = 1 - P_{\text{jump}}$, respectively, and the molecule mean lifetime on the site, τ_1 , are given by

$$P_{\text{jump}} = \alpha_1 \tau_1, P_{\text{esc}} = k_{\text{off}}^{(1)} \tau_1, \tau_1 = \frac{1}{k_{\text{off}}^{(1)} + \alpha_1} \quad (\text{A.8})$$

Finally, we find the rate constants $k_{\text{off}}^{(1)}$ and α_1 , assuming that both models predict the same values for the mean lifetime and the splitting probabilities. This leads to

$$k_{\text{off}}^{(1)} = \frac{P_-}{\tau_L} = \frac{\kappa_L e^{-\beta U(x_L)} \int_{x_L}^{x_R} e^{\beta U(y)} D^{-1}(y) dy}{\int_{x_L}^{x_R} \left(\int_x^{x_R} e^{\beta U(y)} D^{-1}(y) dy \right) e^{-\beta U(x)} dx} \quad (\text{A.9})$$

and

$$\alpha_1 = \frac{P_+}{\tau_L} = \frac{1}{\int_{x_L}^{x_R} \left(\int_x^{x_R} e^{\beta U(y)} D^{-1}(y) dy \right) e^{-\beta U(x)} dx} \quad (\text{A.10})$$

Similar calculations result in the following expressions for the rate constants $k_{\text{off}}^{(2)}$ and α_2 :

$$k_{\text{off}}^{(2)} = \frac{\kappa_R e^{-\beta U(x_R)} \int_{x_L}^{x_R} e^{\beta U(y)} D^{-1}(y) dy}{\int_{x_L}^{x_R} \left(\int_{x_L}^x e^{\beta U(y)} D^{-1}(y) dy \right) e^{-\beta U(x)} dx} \quad (\text{A.11})$$

and

$$\alpha_2 = \frac{1}{\int_{x_L}^{x_R} \left(\int_{x_L}^x e^{\beta U(y)} D^{-1}(y) dy \right) e^{-\beta U(x)} dx} \quad (\text{A.12})$$

Equations A.9–A.12 provide the desirable expressions for the rate constants α_1 , α_2 , $k_{\text{off}}^{(1)}$, and $k_{\text{off}}^{(2)}$ in terms of the parameters of the diffusion dynamics. One can find an alternative derivation of these expressions in ref 21.

When (i) channels are cylindrical and (ii) there are no interactions of the solute molecules with the channel walls, the potential of mean force vanishes, $U(x) = 0$, and the intrachannel diffusivity is position-independent, $D_{\text{ch}}(x) = \text{const} = D_{\text{ch}}$. As a consequence, eqs A.9–A.12 simplify and reduce to

$$\alpha_1 = \alpha_2 = \alpha = \frac{2D_{\text{ch}}}{l^2} \quad (\text{A.13})$$

and

$$k_{\text{off}}^{(1)} = k_{\text{off}}^{(2)} = k_{\text{off}} = \frac{8D_{\text{b}}}{\pi al} \quad (\text{A.14})$$

These expressions for the rate constants are used in the main text, eqs 1 and 2.

Expressions for $k_{\text{off}}^{(1)}$ and $k_{\text{off}}^{(2)}$ in eqs A.9 and A.11 with κ_L and κ_R given by eq A.4 are applicable when the potential of mean force $U(x)$ smoothly approaches its bulk values on the two sides of the membrane. Some models assume that the channel is a trap for diffusing solutes, and to escape from the channel, a solute molecule has to climb the barriers, U_L and

U_R , at the left and right channel ends, respectively. In this case, $U(x_L)$ and $U(x_R)$ in eqs A.9 and A.11 are the energies of a solute molecule in the channel. In addition, the right-hand sides of the expressions for κ_L and κ_R in eq A.4 should be multiplied by the factors $\exp(-\beta \Delta U_{L,R})$. For a cylindrical channel with a rectangular potential well of depth U occupying the entire channel, the escape rate constant is given by

$$k_{\text{off}} = \frac{8D_b}{\pi a l} e^{-\beta \Delta U} \quad (\text{A.15})$$

This rate constant may be well below α in eq A.13, in contrast to k_{off} in eq A.14, which is greater than α for typical channel geometries.

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Figure 1.

A solute molecule (shown as a black circle) in a two-site channel can either jump between the sites or leave the channel. The model assumes that all transitions are Markovian and characterized by site-dependent rate constants, α_1 , α_2 , $k_{off}^{(1)}$, and $k_{off}^{(2)}$. The channel site numbers, 1 and 2, are shown in the upper left corners of each box.

Figure 2.

Transitions of solute molecules (black circles) between the four states of a symmetric two-site channel when the solute concentrations on the left and right sides of the membrane, respectively, are $c_L = c$ and $c_R = 0$. The channel site numbers, 1 and 2, are shown in the upper left corners of each box.

Figure 3.

Regions in the (μ, ε) plane with different flux dependences on the solute concentration. According to eqs 13 and 14, at different strengths of short-range and long-range interactions between solutes, characterized by dimensionless parameters ε and μ , respectively, the flux can exhibit four qualitatively different patterns of behavior, changing from sublinear to superlinear and from monotonic to that with a maximum. Note that $\varepsilon=1$ separates regions of short-range attraction and repulsion, while $\mu=1$ separates regions of long-range attraction and repulsion.

Figure 4.

Dependence of the flux, eq 13, on the solute concentration c at different strengths of intrachannel short-range attraction between solute molecules, characterized by the dimensionless parameter ε , eq 12. Other parameters are $\alpha = 1$, $k'_{\text{off}} = 1$, $k_{\text{H}} = 10^4$, and $k'_{\text{H}} = 30$ ($\mu = 3 \times 10^{-3}$, strong long-range repulsion).

Figure 5.

Flux as a function of the solute concentration, eq 13, in the regime of strong particle–channel attraction and particle–particle short-range attraction characterized by the dimensionless parameter ε . The values of this parameter are $\varepsilon = 10^2, 3 \times 10^2, 10^3, 3 \times 10^3$, and 10^4 from the bottom to top curves. Other parameters are $\alpha = 10^3$, $k'_{\text{off}} = 10^{-2}$, and $k_{\text{on}} = k'_{\text{on}} = 10^3 (\mu = 1)$.