Diffusion-limited binding to a site on the wall of a membrane channel

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(Received 15 August 2006; accepted 16 November 2006; published online 27 December 2006)

The authors develop a theory of diffusion-controlled reactions with a site located on the wall of a cylindrical membrane channel that connects two reservoirs containing diffusing particles which are trapped by the site at the first contact. An expression for the Laplace transform of the rate coefficient, $k(t)$, is derived assuming that the size of the site is small compared to the channel radius. The expression is used to find the stationary value of the rate coefficient, $k(\infty)$, as a function of the length and radius of the channel, the radius of the site, and its position inside the channel (distances from the two ends of the channel) as well as the particle diffusion constants in the bulk and in the channel. Their derivation is based on the one-dimensional description of the particle motion in the channel, which is generalized to include binding to the site into consideration. The validity of the approximate one-dimensional description of diffusion and binding was checked by three-dimensional Brownian dynamics simulations. They found that the one-dimensional description works reasonably well when the size of the site does not exceed 0.2 of the channel radius. © *2006 American Institute of Physics*. [DOI: 10.1063/1.2409682]

I. INTRODUCTION

This paper deals with binding of diffusing particles to a site located on the wall of a membrane channel, as shown in Fig. 1. The major step of our analysis is mapping of the three-dimensional problem of the particle diffusion in the channel onto a one-dimensional one. We assume that the size of the site is small compared to the channel radius and describe binding in terms of absorption by a δ sink with a prescribed trapping rate which is a function of both the size of the site and the channel radius. This approximation is checked by three-dimensional Brownian dynamics simulation in Sec. III after we formulate the problem in the next section. Comparison shows that the approximation works reasonably well when the ratio of the size of the site to the channel radius is small enough.

We use this approximation in Sec. IV to find the Laplace transform of the time-dependent rate coefficient, $k(t)$. This function characterizes survival probability, $S(t)$, of the site, which is assumed to annihilate at the first contact with the particle,

$$S(t) = \exp\left[-c\int_0^t k(t')dt'\right], \tag{1.1}$$

where c is the particle concentration in the two reservoirs separated by the membrane. Our solution shows how the rate coefficient and, hence, $S(t)$ depend on the geometric parameters of the site and of the channel as well as on the location of the site inside the channel.

Our interest in this problem is motivated by recent progress in studies of transport through large membrane channels.[1–3] Compared with ion-selective channels of neurophysiology large channels seem to serve a different purpose than just to conduct small ions. These channels are rather pathways for metabolites and macromolecules such as proteins and nucleic acids, and their function is to regulate metabolite fluxes across the cell and organelle membranes. One of the new developments in studies of large channels is based on the idea that by measuring the current carried by small ions, one can access the transport of larger molecules through their occlusion of the current.[4] These transient occlusions generate measurable excess noise and in many cases can be resolved as single-molecular events reporting on partitioning and dynamics of molecules within the confines of the channel pores.

One of the mechanisms that affect the occlusion of the small ion current is binding of the large solutes to their high affinity sites on the channel wall forming proteins. In the previous study[5] we analyzed the diffusion-controlled binding assuming that the site is large in the sense that its size is comparable with the channel radius. In this case a particle reaching the channel cross section containing the site is trapped with probability close to unity. Therefore, this cross section can be considered as a perfectly absorbing boundary for the diffusing solute. However, recent experiments complemented by molecular dynamics simulations[6] have demonstrated that the sites can be relatively small, so that the particle reaching the cross section of the channel where the site is located has a good chance to avoid contacting the site and to escape from the channel. A similar situation is realized for protons that protonate residues lining the channel pore.[7]

With this in mind, in the present paper we extended the analysis given in Ref. 5 for large binding sites. Here we consider a model in which the cross section containing the

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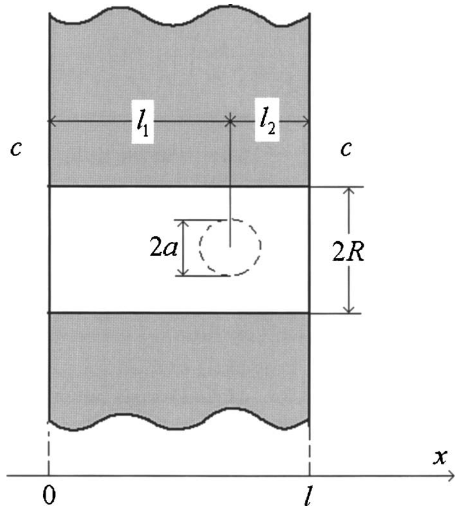

FIG. 1. Circular binding site of radius a on the wall of the cylindrical channel of radius R. The channel connects two reservoirs separated by a membrane of thickness l. The reservoirs contain diffusing particles at concentration c. The site is located at distance l_1 from the left entrance into the channel and distance $l_2=l-l_1$ from the right entrance.

site is not necessarily perfectly absorbing. The trapping rate in this cross section is now a free parameter of the model. The solution obtained in Ref. 5 is recovered from the solution derived below in the limiting case of infinitely high trapping rate, which corresponds to the perfectly absorbing cross section.

II. FORMULATION OF THE PROBLEM

Consider two reservoirs separated by a membrane of thickness l. Reservoirs contain diffusing particles that can go from one reservoir to another through a cylindrical channel of radius R in the separating membrane. On the channel wall there is a circular binding site of radius a, $a \ll R$, which instantly loses its trapping ability (annihilate) when binding the first particle that reaches the site. This site is located at distances l_1 and $l_2=l-l_1$ from the left and right entrances into the channel, respectively, as shown in Fig. 1. We assume that when the channel arises at $t=0$ it is free from the particles which are uniformly distributed in the two reservoirs. The survival probability of the site given in Eq. (1.1) is the probability that no particle has reached the site by time t. Our goal is to find the rate coefficient $k(t)$ which is a function of the geometric parameters a, R, l, and l_1 as well as the diffusion constants of the particle in the channel, $D_{\rm ch}$, and in the bulk, D_b.

To begin with, we note that the product $ck(t)$ is a time-dependent flux of the particles through the perfectly absorbing circular sink of radius a located on the channel wall exactly like the binding site. To find this flux one has to solve the three-dimensional diffusion problem in the two reservoirs and in the channel with absorbing boundary condition on the sink and to match the solutions at the channel entrances. This program is too complicated to be carried out. However, an approximate but quite accurate technique has been found to handle such problems.[8] The idea is to describe the three-dimensional diffusion in the channel as one-dimensional one with radiation boundary conditions at the channel ends that characterize the efficiency of escape from the channel of a particle approaching the channel boundary. Several problems, in which diffusion in the channel contacting with a bulk plays a crucial role, have been studied using this approach.[5,8,9] The results derived on the basis of the one-dimensional approximation were compared with those obtained in three-dimensional Brownian dynamics simulations. Excellent agreement was found between theoretically predicted and numerically obtained results.

Now we generalize the one-dimensional description of the particle motion in the channel so as to take trapping of diffusing particles by a small absorbing spot into account. Let the x axis be directed along the channel and normal to the membrane and $p(x,t)$ be the one-dimensional density of the particles at point x of the channel, $0<x<l$, at time t. We assume that this function satisfies the diffusion equation

$$\frac{\partial p}{\partial t} = D_{\rm ch}\frac{\partial^2 p}{\partial x^2} - \kappa_a \delta(x-l_1)p, \quad 0<x<l, \tag{2.1}$$

in which the sink term describes absorption of the particles by the spot. Taking advantage of the fact that the spot is small compared to the channel radius, $a \ll R$, we approximate the shape of the sink term by the δ function. The sink strength or trapping efficiency, κ_a, is taken to be equal to

$$\kappa_a = \frac{4D_{\rm ch}a}{\pi R^2}. \tag{2.2}$$

In the next section we demonstrate that this description of trapping by a small circular absorber leads to the theoretical predictions which are in good agreement with the results found in three-dimensional Brownian dynamics simulations. We explain our choice of κ_a in Eq. (2.2) after we discuss boundary conditions imposed at the channel ends.

It has been shown in Ref. 8 that the end points $x=0$ and $x=l$, as viewed from the channel, can be regarded as partially absorbing boundaries. The efficiency of escape from the channel of a particle that approaches the boundary is characterized by the trapping rate entering into the boundary conditions (BCs), $\kappa_{\rm BC}$, which is given by[8]

$$\kappa_{\rm BC} = \frac{4D_b}{\pi R}. \tag{2.3}$$

To write the boundary conditions we introduce fluxes of particles that enter the channel from the left (L) and right (R) reservoirs at time t, $J_{L,R}(t)$. The boundary conditions can be written as

$$D_{\rm ch} \left.\frac{\partial p(x,t)}{\partial x}\right|_{x=0} = \kappa_{\rm BC}p(0,t) + J_L(t), \tag{2.4a}$$

$$-D_{\rm ch} \left.\frac{\partial p(x,t)}{\partial x}\right|_{x=l} = \kappa_{\rm BC}p(l,t) + J_R(t). \tag{2.4b}$$

It can be shown[8] that the boundary conditions more accurate than Eqs. (2.4) are non-Markovian but reduces to Eqs. (2.4) on times larger than R^2/D_b. In our further analysis we will neglect details of the kinetics occurring on such times. Then the fluxes $J_{L,R}(t)$ can be set equal to their stationary value, $4D_bRc$, which is the stationary flux of the particles to a per-

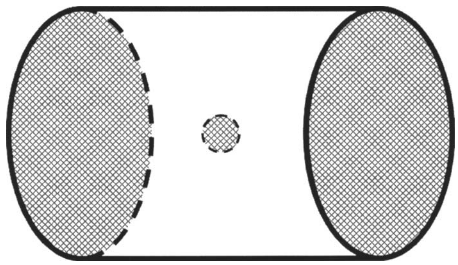

FIG. 2. Cylindrical cavity of unit radius, $R=1$, and length l containing a perfectly absorbing disk of radius a located on the cavity wall at equal distance from both ends of the cylinder, which are also perfectly absorbing surfaces, used in our Brownian dynamics simulations. The absorbing surfaces are crosshatched in the figure. A special feature of our simulations is that near the absorbing surfaces we used 100 times smaller time step than in the rest of the cavity volume. The regions where the smaller time step was used are thin slabs of thickness of 0.1 near the two absorbing ends of the cylinder and the rectangular parallelepiped of the height of 0.1 and the square in the basis of the size $2(a+0.1)$ surrounding the absorbing disk. The parallelepiped was located so that the center of its basis touched the wall of the cylinder just at the point where the center of the disk was located. In simulations the particle initial positions were uniformly distributed over the cross section of the cylinder that passed through the center of the disk perpendicular to the cavity axis.

fectly absorbing disk of radius R on the otherwise perfectly reflecting planar wall.[10]

To explain our choice of the expression for the sink strength in Eq. (2.2) consider a particle diffusing in the channel with the absorbing spot on the wall assuming that the particle cannot escape from the channel because the exits are closed by reflecting lids. The average lifetime of such a particle, i.e., its mean first passage time to the spot, is given by[11]

$$\tau_{3D} = \frac{V_{ch}}{4D_{ch}a} = \frac{\pi R^2 l}{4D_{ch}a}, \quad (2.5)$$

where $V_{ch}=\pi R^2 l$ is the volume of the channel and the subscript 3D indicates that this estimation of the lifetime is based on the three-dimensional consideration. We can also estimate this lifetime in the framework of the one-dimensional description. When the sink strength is small in the sense that the average lifetime of the particle is much greater than the average equilibration time which is of the order of l^2/D_{ch}, the lifetime is given by

$$\tau_{1D} = \frac{l}{\kappa_a}, \quad (2.6)$$

where the subscript 1D indicates that this estimation is obtained in the framework of the one-dimensional description. One can see that our choice of κ_a in Eq. (2.2) leads to identity of the lifetimes in Eqs. (2.5) and (2.6), $\tau_{3D}=\tau_{1D}$.

In Sec. IV we use the one-dimensional description of the particle diffusion and trapping in the channel to derive the Laplace transform of the rate coefficient, $k(t)$. However, first we discuss the numerical test of the approximate one-dimensional description in the following section.

III. NUMERICAL TEST OF THE APPROXIMATION

To check the accuracy of our approximate one-dimensional description of diffusion and binding in the channel, we ran Brownian dynamics (BD) simulations in the geometry shown in Fig. 2 and compared the results found in simulations with those predicted on the basis of the one-dimensional description. In our simulations particles diffused in the cylindrical cavity of radius $R=1$ and length l that contained a perfectly absorbing circular disk of radius a on its wall which was otherwise perfectly reflecting. The disk was located on equal distance from either end of the cylinder, which was also perfectly absorbing surfaces. Particles were initially uniformly distributed over the cross section of the cylinder that passed through the center of the disk perpendicular to the wall. The particle trajectory was terminated at the moment when it reached the disk or the channel ends for the first time.

TABLE I. The fraction of trajectories trapped by the disk, $f_{disk}^{(BD)}$, found in simulations for several values of the parameters l and a, which are given in the first row and the first column of the table, respectively.

	10	20	30
0.05	0.142	0.245	0.321
0.10	0.2471	0.4105	0.5008
0.15	0.343	0.515	0.616
0.20	0.409	0.591	0.682

In simulations we ran $N=50\,000$ trajectories and recorded whether the trajectory crossed the disk or the channel ends and the lifetime t_i for each trajectory, $i=1,2,\ldots,N$. We used these data to find the fraction of the trajectories trapped by the disk, $f_{disk}^{(BD)}$, and the average lifetime of the particles, $\bar{t}_{BD}$. This was done for $l=10,20,30$ and $a=0.05, 0.10, 0.15, 0.20$, assuming that the particle diffusion coefficient was equal to one-half, $D=1/2$. The results are shown in Tables I and II. As might be expected, the probability that the particle is trapped by the disk increases with the disk size and with the length of the cavity. The average lifetime of the particle increases with the length of the cavity and decreases when the disk size increases.

We also calculated these quantities in the framework of the one-dimensional (1D) description in Appendix A, where we found that

$$f_{disk}^{(1D)} = \frac{1}{1+(\pi R^2/al)} \quad (3.1)$$

and

$$\bar{t}_{1D} = \frac{l^2}{8D(1+(al/\pi R^2))}. \quad (3.2)$$

The ratios of the theoretically predicted and numerically obtained values of f_{disk} and $\bar{t}$ are given in Tables III and IV.

TABLE II. The average lifetime of the particle, $\bar{t}_{BD}$, found in simulations for several values of the parameters l and a, which are shown in the first row and the first column of the table, respectively.

	10	20	30
0.05	21.378	75.784	153.199
0.10	18.728	59.319	112.164
0.15	16.182	48.206	86.839
0.20	14.755	40.888	71.175

TABLE III. The ratio of the theoretically predicted probability of the particle trapping by the disk, $f_{\rm disk}^{(1D)}$ in Eq. (3.5), to the value of this probability found in simulations, $f_{\rm disk}^{\rm (BD)}$, for several values of the parameters l and a, which are given in the first row and the first column of the table, respectively.

	10	20	30
0.05	0.97	0.98	1.01
0.10	0.98	0.95	0.98
0.15	0.94	0.95	0.96
0.20	0.95	0.95	0.96

One can see that deviations of these ratios from unity are less than 10% even when the disk size is as large as 0.2.

Another comparison of the prediction based on the one-dimensional description with the result found in three-dimensional Brownian dynamics simulations is presented in Fig. 3, which shows logarithm of the particle survival probability as a function of time for $a=0.05$ and $l=30$. The solid curve was obtained by inverting numerically the Laplace transform of the survival probability, $\hat{S}_{\rm 1D}(s)$, derived in Appendix A and given in Eq. (A6), while the crosses represent the survival probability $S_{\rm BD}(t)$ found in simulations. One can see that the two survival probabilities are very close to one another on times smaller than 900 dimensionless units. The difference between $S_{\rm BD}(t)$ and $S_{\rm 1D}(t)$ on these times is smaller than 4%. On larger times the difference becomes significant because of the poor statistics. The point is that the survival probability at $t=900$ is less than 2×10^{-3}. Therefore the number of trajectories with the lifetimes greater than 900 in our simulations was less than 100 that is definitely not enough for finding a reliable value of the survival probability.

To summarize, comparison with three-dimensional Brownian dynamics simulations discussed in this section shows that the approximate one-dimensional description of diffusion and binding in the channel works reasonably well when the binding site is not too large. This is important since this approximation allows one to convert unsolvable three-dimensional problems into one-dimensional ones which can be solved with relative ease.

IV. RATE COEFFICIENT

In this section we discuss the rate coefficient, $k(t)$, which determines the survival probability of the binding site, Eq. (1.1). Our analysis is based on the one-dimensional model formulated in Eqs. (2.1)–(2.4). It is assumed that when the channel is formed at $t=0$, it is free from diffusing particles. Therefore, we will solve Eq. (2.1) with the initial condition $p(x,0)=0$.

TABLE IV. The ratio of the theoretically predicted average lifetime of the particle, $\bar{t}_{\rm (1D)}$ in Eq. (3.8), to the value of this lifetime found in simulations, $\bar{t}_{\rm BD}$, for several values of the parameters l and a, which are given in the first row and the first column of the table, respectively.

	10	20	30
0.05	1.01	1.00	0.99
0.10	1.01	1.03	1.03
0.15	1.05	1.06	1.07
0.20	1.04	1.08	1.09

To find the rate coefficient we need to know the flux through the sink, which is given by $\kappa_a p(l_1,t)$. Then the rate coefficient can be found by means of the relation

$$k(t) = \frac{1}{c}\kappa_a p(l_1,t). \tag{4.1}$$

As derived in Appendix B the Laplace transform of $k(t)$ can be written in terms of functions $P(x)$ and $Q(x)$ defined as

$$P(x) = \sqrt{sD_{\rm ch}}\cosh\left(x\sqrt{\frac{s}{D_{\rm ch}}}\right) + \kappa_{\rm BC}\sinh\left(x\sqrt{\frac{s}{D_{\rm ch}}}\right), \tag{4.2}$$

$$Q(x) = \sqrt{sD_{\rm ch}}\sinh\left(x\sqrt{\frac{s}{D_{\rm ch}}}\right) + \kappa_{\rm BC}\cosh\left(x\sqrt{\frac{s}{D_{\rm ch}}}\right). \tag{4.3}$$

The result is

$$\hat{k}(s) = \frac{4D_b R\kappa_a[P(l_1)+P(l_2)]}{s[(\kappa_a/\sqrt{sD_{\rm ch}})P(l_1)P(l_2)+P(l_1)Q(l_2)+P(l_2)Q(l_1)]}. \tag{4.4}$$

These expressions together with those in Eqs. (2.2) and (2.3) determine $\hat{k}(s)$ as a function of the geometric parameters a, R, l, and l_1, as well as the diffusion constants $D_{\rm ch}$ and D_b. This is one of the main results of the present paper. The Laplace transform in Eq. (4.4) is too complicated to be inverted analytically, but it can be easily inverted numerically. This allows one to find transient behavior of $k(t)$ from zero at

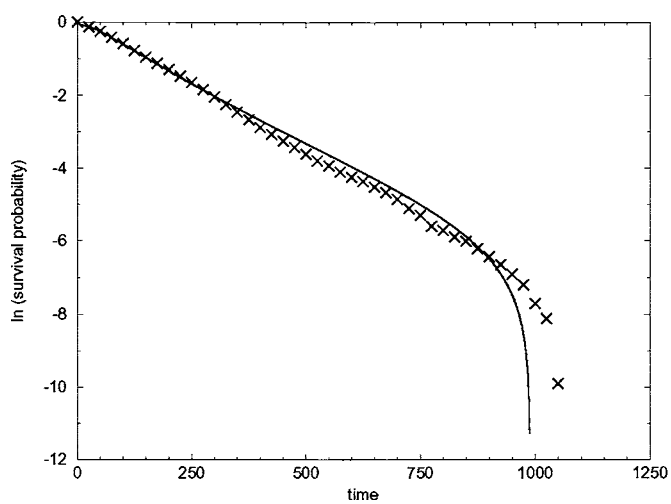

FIG. 3. Logarithm of the particle survival probability in the cylindrical cavity of unit radius, $R=1$, and length $l=30$ containing a perfectly absorbing disk of radius $a=0.05$ located on the cavity wall at equal distances from both ends of the cylinder, which are also perfectly absorbing surfaces, as a function of the dimensionless time. Crosses represent logarithm of the survival probability found in simulations, while the solid curve is obtained by numerically inverting the Laplace transform in Eq. (A6). In simulations the particle initial positions were uniformly distributed over the cross section of the cylinder that passed through the center of the disk perpendicular to the cavity axis.

$t=0$ to its stationary value which is reached as $t\to\infty$, $k_{st}=k(\infty)$. The latter can be found from the small-s asymptotic behavior of $\hat{k}(s)$,

$$k_{st}=\lim_{s\to 0} s\hat{k}(s). \tag{4.5}$$

We use k_{st} found by means of this relation to analyze how the stationary rate coefficient depends on the geometric and kinetic parameters of the problem.

Using the results in Eqs. (4.2) and (4.3) and the relations in Eqs. (2.2) and (2.3), we obtain

$$k_{st}=\frac{4D_bR(2+\lambda)}{(1+\nu\lambda)[1+(1-\nu)\lambda]+(\pi R^2/4al)\lambda(2+\lambda)}, \tag{4.6}$$

where

$$\lambda=\frac{4D_bl}{\pi D_{ch}R}, \quad \nu=\frac{l_1}{l}, \tag{4.7}$$

correspondingly, $1-\nu=l_2/l$. This stationary rate coefficient can be written in the form that has a transparent interpretation,

$$k_{st}=4D_bR[W(l_1)+W(l_2)]. \tag{4.8}$$

Here $4D_bR$ is the Hill formula[10] for the stationary trapping rate by a perfectly absorbing circular disk of radius R (entrance into the channel) located on the otherwise perfectly reflecting planar wall, while $W(l_1)$ and $W(l_2)$ are the probabilities to be trapped by the absorbing spot on the channel wall for particles entering the channel through the left and right ends, respectively.

The trapping probabilities $W(l_1)$ and $W(l_2)$ are given by

$$W(l_1)=W_{cs}(l_1)K, \quad W(l_2)=W_{cs}(l_2)K. \tag{4.9}$$

Here $W_{cs}(x)$ is the trapping probability found assuming that the entire cross section (cs) of the channel perpendicular to its axis and located at distance x from its entrance is perfectly absorbing,

$$W_{cs}(x)=\left[1+\left(1-\frac{x}{l}\right)\right]^{-1}. \tag{4.10}$$

The factor K in Eq. (4.9) is the probability to be trapped by the absorbing spot on the channel wall for a particle that starts from the cross section passing through the center of the spot perpendicular to the channel axis; the particle starting position is uniformly distributed over the cross section. The factor K is given by

$$K=\left[1+\frac{\pi R^2}{4al}\lambda(2+\lambda)W_{cs}(l_1)W_{cs}(l_2)\right]^{-1}. \tag{4.11}$$

Thus, the stationary rate coefficient in Eq. (4.8) can be written as

$$k_{st}=4D_bR[W_{cs}(l_1)+W_{cs}(l_2)]K. \tag{4.12}$$

Putting here $K=1$ we recover k_{st} derived earlier in Ref. 5 assuming that the entire cross section is perfectly absorbing.

Alternatively, the stationary rate coefficient in Eq. (4.6) can be written in the Collins-Kimball form,[12]

$$k_{st}=\frac{(4D_{ch}a)k_{cs}}{4D_{ch}a+k_{cs}}. \tag{4.13}$$

Here $4D_{ch}a$ is the Hill formula[10] for the small perfectly absorbing disk on the wall of the channel and k_{cs} is a sum of two rate coefficients each of which has the Collins-Kimball form,

$$k_{cs}=k_{cs}(l_1)+k_{cs}(l_2), \tag{4.14}$$

where $k_{cs}(x)$ is the stationary rate coefficient in situation when the entire cross section located at distance x from the channel entrance is perfectly absorbing, given by[5]

$$k_{cs}(x)=\frac{(4D_bR)(\pi R^2D_{ch}/x)}{4D_bR+\pi R^2D_{ch}/x}. \tag{4.15}$$

Assuming that in Eq. (4.13) $4D_{ch}a\gg k_{cs}$ we obtain $k_{st}=k_{cs}$ and recover the expression for k_{st} derived in Ref. 5.

Expressions in Eqs. (4.8) and (4.13) can be used to write the stationary flux of the particles into the absorbing spot on the channel wall, f_{st}, in the two forms,

$$f_{st}=4D_bR[W(l_1)+W(l_2)]c \tag{4.16}$$

and

$$f_{st}=\frac{(4D_{ch}a)k_{cs}}{4D_{ch}a+k_{cs}}c, \tag{4.17}$$

which allow different interpretations. The flux in Eq. (4.16) is a sum of two fluxes each of which is a product of the stationary flux to the channel entrance, $4D_bRc$, and the decreasing factor $W(l_i)$, $i=1,2$, due to the fact that the binding site is hidden in the channel. The expression in Eq. (4.17) may be interpreted as the Hill formula for the stationary flux to the absorbing disk on the channel wall, $4D_{ch}ac_{eff}$, which contains the effective concentration c_{eff} of the particles,

$$c_{eff}=\frac{k_{cs}}{4D_{ch}a+k_{cs}}c, \tag{4.18}$$

which is smaller than the particle concentration c in the reservoirs.

As might be expected, the stationary rate coefficient monotonically decreases, as the site moves into the channel, and reaches its minimum value when $l_1=l_2=l/2$, i.e., $\nu=1/2$. One can see this from Eq. (4.6). The decrease of k_{st} may be characterized by the ratio $k_{st}|_{\nu=1/2}/\,k_{st}|_{\nu=0}$ which is given by

$$\frac{k_{st}|_{\nu=1/2}}{k_{st}|_{\nu=0}}=\frac{1+\lambda+(\pi R^2/4al)\lambda(2+\lambda)}{1+\lambda+(1/4)\lambda^2+(\pi R^2/4al)\lambda(2+\lambda)}, \tag{4.19}$$

where the ratio is small and the decrease is significant when $\lambda\gg 1$. This may be due to either because $D_{ch}\ll D_b$ or because of $L\gg R$, and, of course, both factors may contribute.

V. CONCLUDING REMARKS

The present paper is devoted to kinetics of diffusion-controlled binding to a small circular site located on the wall of a cylindrical membrane channel. One of the main results of our analysis is the expression for the Laplace transform of the rate coefficient, Eq. (4.4), which determines the survival probability of the binding site, Eq. (1.1). We use this expression to find the stationary value of the rate coefficient reached as $t \to \infty$. Different representations of this quantity are given in Eqs. (4.6), (4.8), (4.12), and (4.13). They show how the stationary trapping rate depends on the geometric and kinetic parameters of the system. These parameters are the length and radius of the channel, the radius of the site, and the distances from its center to the channel ends, which determine the location of the site inside the channel, as well as the diffusion constants of the particles in the channel and in the bulk outside the channel. Although the theory is developed assuming that the site radius is much smaller than the radius of the channel, it turns out that when the radius of the site formally tends to infinity we recover the result derived for large binding sites in Ref. 5.

Our analysis is based on an approximate one-dimensional description of the particle motion in the channel suggested in Ref. 8. To derive the results we have extended the formalism so as to include trapping of the particles by the binding site into consideration. To check the accuracy of our approximate one-dimensional approach we compare theoretical predictions derived in the framework of the one-dimensional description with the results obtained in three-dimensional Brownian dynamics simulations. There is a good agreement between the predicted and simulated results when the radius of the site does not exceed 0.2 of the channel radius. This agreement may be considered as a justification of the approximate one-dimensional approach which has been used in Sec. IV when finding the solution for the Laplace transform of the rate coefficient.

The fact that the site is hidden in the membrane channel leads to a decrease of the binding rate compared to the situation where the same site is exposed on the membrane surface. For the first time this effect was studied by Samson and Deutch[13] in their theory of diffusion-controlled reactions with buried active sites. Samson and Deutch analyzed enzyme kinetics in situation where the active site of the enzyme was a small spherical cap buried inside an inert sphere that represented the enzyme molecule. In Ref. 5 the result for the stationary trapping rate derived in that paper for large binding sites hidden in membrane channels is compared with the stationary trapping rate given by the Samson-Deutch theory[13] in the corresponding limiting case. A special feature of kinetics analyzed in the present paper is that the binding site is small compared to the channel radius. Therefore, the particle reaching the cross section of the channel containing the site has a good chance to avoid being trapped and to escape from the channel.

Finally, we note that the results obtained in the present paper for circular binding sites can be easily generalized to the case of noncircular sites. This can be done by prescribing the noncircular site an effective radius, a_{eff}, given by $a_{\mathrm{eff}} = [AP/(2\pi^2)]^{1/3}$, where A and P are the area and perimeter of the site. Justification for this prescription is given in Ref. 14.

ACKNOWLEDGMENTS

The authors are grateful to Sergey Bezrukov and Attila Szabo for numerous very helpful discussions of the problem and related issues. This study was supported by the Intramural Research Program of the NIH, Center for Information Technology. One of the authors (L.D.) also thanks the Camachos Foundation for partial support.

APPENDIX A: f_{disk} AND $\bar{t}$ FROM 1D DESCRIPTION

The key function of this description is the particle propagator $G(x,t|l/2)$, which satisfies

$$\frac{\partial G}{\partial t} = D\frac{\partial^2 G}{\partial x^2} - \kappa\delta(x-l_1)G, \quad 0 < x < l, \tag{A1}$$

where D is the particle diffusion constant and the sink strength κ is given by Eq. (2.2) in which D_{ch} is replaced by D. The propagator also satisfies the initial condition $G(x,0|l/2)=\delta(x-l/2)$, and absorbing boundary conditions at $x=0$ and $x=l$, $G(0,t|l/2)=G(l,t|l/2)=0$. Solving the problem by the Laplace transformation method we find that the Laplace transform of the propagator is given by

$$\hat{G}(x,s|l/2) = A \times \begin{cases} \sinh\left(x\sqrt{\dfrac{s}{D}}\right), & 0 < x < \dfrac{l}{2} \\ \sinh\left((l-x)\sqrt{\dfrac{s}{D}}\right), & \dfrac{l}{2} < x < l, \end{cases} \tag{A2}$$

where the factor A is

$$A = \left[2\sqrt{sD}\cosh\left(\frac{l}{2}\sqrt{\frac{s}{D}}\right) + \kappa\sinh\left(\frac{l}{2}\sqrt{\frac{s}{D}}\right)\right]^{-1}. \tag{A3}$$

We use the Laplace transform of the propagator to find the fraction of the particle trajectories trapped by the sink, $f_{\mathrm{disk}}^{(1\mathrm{D})}$,

$$f_{\mathrm{disk}}^{(1\mathrm{D})} = \kappa\int_0^\infty G(l/2,t|l/2)dt = \kappa\hat{G}(l/2,0|l/2). \tag{A4}$$

Using the Laplace transform in Eq. (A2) and the relation $\kappa = 4Da/(\pi R^2)$ we obtain the result in Eq. (3.1). Survival probability of the particle, $S_{1\mathrm{D}}(t)$, is given by

$$S_{1\mathrm{D}}(t) = \int_0^t G(x,t|l/2)dx. \tag{A5}$$

We can find its Laplace transform using the transform in Eq. (A2). The result is

$$\hat{S}_{1\mathrm{D}}(s) = 2A\sqrt{\frac{D}{s}}\left[\cosh\left(\frac{l}{2}\sqrt{\frac{s}{D}}\right) - 1\right]. \tag{A6}$$

The average lifetime of the particle, $\bar{t}_{1\mathrm{D}}$, is related to the transform $\hat{S}_{1\mathrm{D}}(s)$ by the relation $\bar{t}_{1\mathrm{D}}=\hat{S}_{1D}(0)$, which leads to the result in Eq. (3.2).

APPENDIX B: LAPLACE TRANSFORMS OF $k(t)$

The one-dimensional density $p(x,t)$ can be written as a sum of two terms,

$$p(x,t) = p_L(x,t) + p_R(x,t), \tag{B1}$$

where $p_L(x,t)$ and $p_R(x,t)$ are due to the particles entering the channel through the left and right ends, respectively. These functions can be written in terms of the particle propagator in the channel, $G(x,t|x_0)$, which satisfies

$$\frac{\partial G}{\partial t} = D_{\rm ch}\frac{\partial^2 G}{\partial x^2} - \kappa_a \delta(x-l_1)G, \quad 0 < x < l, \tag{B2}$$

with the initial condition $G(x,0|x_0)=\delta(x-x_0)$ and the boundary conditions

$$\left[D_{\rm ch}\frac{\partial G}{\partial x} - \kappa_{\rm BC}G\right]\Bigg|_{x=0} = \left[D_{\rm ch}\frac{\partial G}{\partial x} + \kappa_{\rm BC}G\right]\Bigg|_{x=l} = 0. \tag{B3}$$

The expression for $p_L(x,t)$ and $p_R(x,t)$ in terms of the propagator and the fluxes entering the channel from the left and right reservoirs, $J_L(t)$ and $J_R(t)$, are

$$p_L(x,t) = \int_0^t G(x,t-t'|0)J_L(t')dt' \tag{B4}$$

and

$$p_R(x,t) = \int_0^t G(x,t-t'|l)J_R(t')dt'. \tag{B5}$$

Using Eqs. (4.1) and (B1) we can write $k(t)$ as a sum,

$$k(t) = k_L(t) + k_R(t), \tag{B6}$$

where

$$k_L(t) = \frac{\kappa_a}{c}p_L(l_1,t) = \frac{\kappa_a}{c}\int_0^t G(l_1,t-t'|0)J_L(t')dt' \tag{B7}$$

and

$$k_R(t) = \frac{\kappa_a}{c}p_R(l_1,t) = \frac{\kappa_a}{c}\int_0^t G(l_1,t-t'|l)J_R(t')dt'. \tag{B8}$$

Replacing fluxes $J_L(t)$ and $J_R(t)$ by their stationary value $4D_bRc$ we arrive at

$$k_L(t) = 4D_bR\kappa_a\int_0^t G(l_1,t-t'|0)dt' \tag{B9}$$

and

$$k_R(t) = 4D_bR\kappa_a\int_0^t G(l_1,t-t'|l)dt'. \tag{B10}$$

Eventually the Laplace transforms of the rate coefficients $k_L(t)$ and $k_R(t)$ are given by

$$\hat{k}_L(s) = \frac{4D_bR\kappa_a}{s}\hat{G}(l_1,s|0), \quad \hat{k}_R(s) = \frac{4D_bR\kappa_a}{s}\hat{G}(l_1,s|l). \tag{B11}$$

The propagator $G(x,t|0)$ satisfies Eq. (B2) with the boundary conditions in Eq. (B3) and the initial condition $G(x,0|0)=\delta(x)$. One can find $\hat{G}(l_1,s|0)$ solving this equation. The result is

$$\hat{G}(l_1,s|0) = \frac{P(l_2)}{(\kappa_a/\sqrt{sD_{\rm ch}})P(l_1)P(l_2) + P(l_1)Q(l_2) + P(l_2)Q(l_1)}, \tag{B12}$$

with $P(x)$ and $Q(x)$ given in Eqs. (4.2) and (4.3). The propagator $G(x,t|l)$ also satisfies Eq. (B2) with the boundary conditions in Eq. (B3) but the initial condition for this propagator is $G(x,0|l)=\delta(x-l)$. The Laplace transform of this propagator at $x=l_1$ is given by

$$\hat{G}(l_1,s|l) = \frac{P(l_1)}{(\kappa_a/\sqrt{sD_{\rm ch}})P(l_1)P(l_2) + P(l_1)Q(l_2) + P(l_2)Q(l_1)}. \tag{B13}$$

Finally, one can obtain the expression for $\hat{k}(s)$ in Eq. (4.4) by Laplace transforming Eq. (B6) and using the results in Eqs. (B11)–(B13).

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