Effect of binding on escape from cavity through narrow tunnel

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When a diffusing particle escapes from a spherical cavity through a narrow, not too long tunnel, the escape kinetics is essentially single-exponential. The presence of reversible binding sites on the cavity wall leads to retention of the particle in the system and converts the single-exponential kinetics into bi-exponential. We develop a theory that describes these effects. The theory shows how the delay time and the average number of binding events depend on the geometric and kinetic parameters of the system. To study the effect of the cavity shape, we also analyze the kinetics when the particle escapes from a cylindrical cavity with reversible binding sites. [<http://dx.doi.org/10.1063/1.3697972>]

I. INTRODUCTION

In this paper we develop a theory of diffusional escape of a particle from a cavity through a narrow tunnel (Fig. 1) in the presence of particle-binding sites on the cavity surface. We were stimulated to develop such a theory by a recent simulation study of diffusion and retention of Ca^{2+} -calmoduline-dependent protein kinase II (CaMKII) in dendritic spines.¹ Among other things, the authors studied “the impact of binding sites” on the escape rate. One of their findings is a transition from single-exponential to double-exponential kinetics with the decrease of the CaMKII dissociation rate from the site. The authors indicated that there is a lack of a theory treating the effect of binding on the escape kinetics. Here, we fill in the gap and develop such a theory by generalizing the theory of escape from a cavity through a narrow tunnel in the absence of binding sites developed in Ref. 2. One can find detailed discussion of the role of escape of CaMKII from dendritic spines in the induction of long-term potentiation in Ref. 1 and references therein.

The geometry of the system studied in this paper is schematically shown in Fig. 1. Following Ref. 1, we model the spine as a spherical head of radius R connected to the dendrite by a narrow cylindrical neck of length L and radius a . CaMKII is modeled as a point Brownian particle. It is assumed that initially the particle is in the spine head. The first passage of the particle to the boundary separating the spine neck from the dendrite (shown in Fig. 1 by the dashed line) is considered as its escape from the spine. Binding sites located on the head surface reversibly bind the particle. This leads to the slowdown of the escape kinetics. Our analysis of the effect of binding on the kinetics is based on the theory developed in Ref. 2. Therefore, we first briefly discuss this theory. Then we consider its generalization that treats the kinetics in the presence of the binding sites.

II. THEORY

Consider a particle diffusing in the system shown in Fig. 1 in the absence of the binding sites. The particle starts in the cavity (spine head) and is eventually trapped by the spine-dendrite boundary. To reach the boundary the particle has to enter the tunnel (spine neck). A distinctive feature of the spine morphology studied in Ref. 1 is that the neck radius is small compared to the radius of the head, $a \ll R$ and; therefore, the time required for the particle to find the tunnel entrance significantly exceeds its equilibration time in the isolated cavity. As a consequence, the particle survival probability in the cavity without entering the tunnel, $P(t)$, decays as a single exponential, $P(t) = e^{-k_{cav}t}$, and, hence, satisfies the rate equation

$$\dot{P}(t) = dP(t)/dt = -k_{cav}P(t), \quad (1)$$

where the rate constant $k_{cav} = 4aD_{cav}/V_{cav}$ is the inverse mean particle lifetime in the cavity, D_{cav} is the particle diffusion coefficient in the cavity, and $V_{cav} = 4\pi R^3/3$ is the cavity volume. One can find rigorous derivations of Eq. (1) in Refs. 3(a) and 3(b), and its back-of-the-envelope derivation and numerical test in Ref. 3(c).

Upon entering the tunnel, the particle either comes back to the cavity or escapes to the dendrite (is trapped by the neck-dendrite boundary at the opposite end of the tunnel). We denote the probabilities of the two outcomes by $1 - W$ and W , respectively. When the tunnel is not too long, the time spent by the particle in the tunnel is much smaller than the searching time for the tunnel entrance. As a consequence, the particle survival probability in the spine, $S(t)$, satisfies

$$\dot{S}(t) = -k_{out}S(t), \quad (2)$$

where the rate constant k_{out} is $k_{out} = Wk_{cav}$. The trapping probability, W , for a particle entering the tunnel from the cavity is given by⁴ $W = [1 + 4LD_{cav}/(\pi aD_{tun})]^{-1}$, where D_{tun} is the particle diffusion coefficient in the tunnel. Using this we can write the rate constant k_{out} as

$$k_{out} = \frac{\pi a^2 D_{tun}}{[1 + \pi a D_{tun}/(4L D_{cav})] L V_{cav}}. \quad (3)$$

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FIG. 1. Schematic representation of a dendritic spine connected to a dendrite. The dashed line shows the boundary separating the spine neck from the dendrite.

When $a \ll L$, the second term in the square brackets can be neglected and Eq. (3) takes the form $k_{out} = \pi a^2 D_{tun} / (L V_{cav})$ suggested earlier.⁵ In the opposite limiting case of very short tunnel, $L \ll a$, $W \approx 1$, and $k_{out} \approx k_{cav}$. Solving Eq. (2) with the initial condition $S(0) = 1$, we find that the particle survival probability in the spine decays as a single exponential, $S(t) = e^{-k_{out}t}$. One can find detailed discussion of escape from a cavity through a narrow tunnel in the absence of binding sites in Ref. 2, including numerical tests that show excellent agreement between the analytical and numerical results.

In the presence of binding sites on the head surface, the particle can be in two states, bound and unbound. Let k_b and k_d be the binding and dissociation rate constants, respectively. The former is a function of the number of binding sites, their mutual location and trapping efficiency, which can be found by means of boundary homogenization. To study the transition between single- and double-exponential kinetics due to the presence of the binding sites, we use these rate constants to write the evolution equations for the probabilities $P_b(t)$ and $P_u(t)$ of finding the particle in bound and unbound states at time t ,

$$\dot{P}_b(t) = k_b P_u(t) - k_d P_b(t), \quad (4)$$

$$\dot{P}_u(t) = k_d P_b(t) - (k_b + k_{out}) P_u(t). \quad (5)$$

Solving these equations with the initial conditions $P_b(0) = 0$ and $P_u(0) = 1$, we find the particle survival probability in the spine, $S(t) = P_b(t) + P_u(t)$,

$$S(t) = \frac{1}{\lambda_1 - \lambda_2} [(\lambda_1 - k_b - k_d) e^{-\lambda_1 t} + (k_b + k_d - \lambda_2) e^{-\lambda_2 t}], \quad (6)$$

where λ_1 and λ_2 are given by

$$\lambda_{1,2} = \frac{1}{2} \left[k_b + k_d + k_{out} \pm \sqrt{(k_b + k_d + k_{out})^2 - 4k_d k_{out}} \right]. \quad (7)$$

As might be expected, the survival probability is double-exponential. It becomes single-exponential in two limiting cases: (a) $S(t) \approx e^{-k_{out}t}$ when $k_b \rightarrow 0$, $k_d \rightarrow \infty$ (no binding limit), and (b) $S(t) \approx e^{-k_d k_{out} t / (k_b + k_{out})}$ when $k_b \rightarrow \infty$, $k_d \rightarrow 0$ (strong binding limit). At first glance, it may seem that the rate equations, Eqs. (4) and (5), provide an inaccurate description of the problem. However, this is not true. As shown in Ref. 6, this description is quite precise.

The mean particle lifetime in the spine, τ , is given by $\tau = \int_0^\infty S(t) dt$. We can write this time as a sum of the mean lifetime in the absence of binding sites, k_{out}^{-1} , and a delay time $\Delta\tau$ due to the particle binding to the sites, $\tau = k_{out}^{-1} + \Delta\tau$. Using $S(t)$ in Eq. (6) we find that the delay time is

$$\Delta\tau = k_b / (k_d k_{out}). \quad (8)$$

Using $\Delta\tau$ and the mean particle lifetime in the bound state, k_d^{-1} , we can find the average number n_b of binding events before the particle escapes from the spine

$$n_b = k_d \Delta\tau = k_b / k_{out}, \quad (9)$$

To study the effect of the spine morphology on the mean particle lifetime in the spine, τ , and the average number of binding event, n_b , the authors of Ref. 1 ran simulations in the cylindrical geometry mimicking the filopodial spine.⁷ Now we show how the theory can be developed in this case, by modeling the spine as a cylinder of length L and radius a . The end of the cylinder contacting the dendrite is considered as a perfectly absorbing boundary. We assume that the particle starts from the opposite end of the cylinder, where the binding sites are located, so that this end is a reversible trap for the particle. This is essentially the model of filopodial spine studied in Ref. 1. We find τ and n_b for this model using an effective one-dimensional description of the particle motion in a cylindrical cavity.

The particle propagator in the unbound state, $g(x, t)$, satisfies the diffusion equation,

$$\frac{\partial g(x, t)}{\partial t} = D \frac{\partial^2 g(x, t)}{\partial x^2}, \quad 0 < x < L, \quad (10)$$

with boundary conditions $g(0, t) = 0$ and $-D \partial g(x, t) / \partial x|_{x=L} = \kappa g(L, t) - k_d P_b(t)$, where D is the particle diffusion coefficient, κ is the rate of its trapping by the binding sites, and $P_b(t)$ is the probability of finding the particle in the bound state at time t , which satisfies

$$\dot{P}_b(t) = \kappa g(L, t) - k_d P_b(t). \quad (11)$$

Solving Eqs. (10) and (11) with the initial conditions $g(x, 0) = \delta(x - L)$, $P_b(0) = 0$, we find the mean particle lifetime in the spine $\tau = \int_0^\infty S(t) dt$, where $S(t)$ is the particle survival probability in the spine given by $S(t) = \int_0^L g(x, t) dx + P_b(t)$. The result is

$$\tau = \frac{L^2}{2D} + \frac{\kappa L}{D k_d}. \quad (12)$$

In the absence of binding sites ($\kappa = 0$), Eq. (12) reduces to the known result, $\tau|_{\kappa=0} = L^2 / (2D)$. Equation (12) shows that $\tau = \tau|_{\kappa=0} + \Delta\tau$, where $\Delta\tau = \kappa L / (D k_d)$ is the delay time due to particle trapping by the binding sites. We use this

to find the average number n_b of binding events before the particle escapes from the spine

$$n_b = k_d \Delta \tau = \kappa L / D. \quad (13)$$

To summarize, motivated by a recent simulation study of impact of binding on CaMKII diffusion and retention in dendritic spines,¹ we show how the problem can be treated analytically. To be more specific, we have developed a theory of the effect of binding on the escape from a cavity through a narrow tunnel (Fig. 1) and from a cylindrical spine with no cavity. This is an extension of the general escape theory in the absence of binding sites developed in Ref. 2. Finally, we mention recent papers^{6,8} on the particle first passage to a small spot on the wall of a spherical cavity by intermittent bulk and surface diffusion. The difference between these papers lies in how they describe particle binding to and dissociation from the cavity wall. In Ref. 6, it is assumed that the wall is partially absorbing and after dissociation the particle is just near the wall, while Ref. 8 assumes that the wall is perfectly absorbing and the dissociation is a non-local process. Our analysis is close to that in Ref. 6, in which one can find more detailed discussion of the relation between the papers.

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