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Narrow-escape times for diffusion in microdomains with a particle-surface affinity: Mean-field results

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We analyze the mean time t_{app} that a randomly moving particle spends in a bounded domain (sphere) before it escapes through a small window in the domain's boundary. A particle is assumed to diffuse freely in the bulk until it approaches the surface of the domain where it becomes weakly adsorbed, and then wanders diffusively along the boundary for a random time until it desorbs back to the bulk, etc. Using a mean-field approximation, we define t_{app} analytically as a function of the bulk and surface diffusion coefficients, the mean time it spends in the bulk between two consecutive arrivals to the surface and the mean time it wanders on the surface within a single round of the surface diffusion. © *2010 American Institute of Physics*. [doi:10.1063/1.3442906]

I. INTRODUCTION

A generic problem in cellular biochemistry is to estimate the time—the so-called narrow-escape time (NET)—that a randomly moving particle spends in a bounded domain before it escapes through a small window in the domain's boundary. A particle can be an ion, a ligand, a molecule, a protein, etc. A confining domain can be a cell, a microvesicle, a compartment, an endosome, a caveola, a dendritic spine, etc. A variety of processes in which the importance of the NET problem is striking were discussed in Refs. 1–4.

Conventional analytical calculations of the NET rely on the assumption that the confining surface is perfectly reflecting everywhere, except for the escape window—an aperture of typical size a. For the Brownian motion, evaluation of the NET probability density function (PDF) F_t amounts to finding the solution of the diffusion equation with mixed Dirichlet–Neumann boundary conditions.[5]

In three dimensions (3D) one finds[5] (see also Ref. 3) that at sufficiently large times, the probability S_t that the particle has not reached the escape window up to time t obeys

$$S_t \sim \exp\left(-\frac{t}{t_{3D}}\right), \tag{1}$$

where the symbol "∼" signifies that one deals with the leading in time asymptotic behavior and omits the numerical prefactors. The characteristic decay time t_{3D} (the subscript "3D" specifies that the search for the escape window proceeds via the bulk diffusion) in Eq. (1) is given by

$$t_{3D} = \frac{V}{4D_0 a}, \tag{2}$$

where V is the volume of the domain and D_0 is the bulk diffusion coefficient. This result holds for any 3D bounded domain, provided that the boundary is sufficiently smooth and the ratio a/R, where R is the typical size of the domain, is sufficiently small.

The PDF F_t then follows via the relation $F_t = -dS_t/dt$. Hence, t_{3D} in Eq. (2) can be interpreted as the mean time of the first passage to the escape window—the mean NET. Note that the results in Eqs. (1) and (2) have been obtained earlier in Refs. 6–8 and 2 in the special case of a sphere of radius R and the escape window being a geodesic disk of radius a, $a/R \ll 1$.

To get some idea of typical NET scales, consider an example mentioned in Ref. 1—search for the tubule entrance in a vesicle by a diffusive ligand. The vesicle size R and the radius of the tubule entrance a are of orders of 10^{-5} and 10^{-6} cm, respectively, while the ligand diffusion coefficient D_0 is in the range of 10^{-5}–10^{-7} cm^2/s. Thus t_{3D} is of order of 10^{-4}–10^{-2} s, depending on the value of the bulk diffusion coefficient. Of course, one may encounter considerably larger first passage times for larger R or smaller a, as well as under conditions of molecular crowding emerging due to complexity of the cellular environment. In the latter case, an effectively subdiffusive motion can emerge.[4] On the contrary, interactions of particles with molecular motors may induce an effective biased motion and thus reduce the NET.

The analysis based on the "perfectly reflecting wall" assumption misses an important factor. In realistic systems, in addition to the short-range repulsion, there are always some attractive interactions between the surface of the domain and the diffusive particle. Capitalizing on ideas of Adam and Delbrück,[9] set forward for chemoreception (see also the discussion in Ref. 7), one may suppose that if such interactions are sufficiently strong, the actual search for the escape win-

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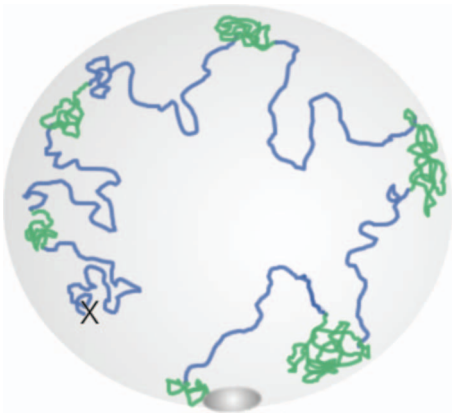

FIG. 1. A path of a diffusing particle starting at point "x" (situated at a distance σ apart from the surface) and leaving the sphere through the escape window placed on the south pole. Excursions in the inner part of the sphere between two consecutive contacts with the surface (Brownian excursions) are marked by a blue color while the excursions along the surface—by a green color.

dow will be a two-stage process, in which the particle will first find the surface of the cell and then will move diffusively along the surface until it finds the escape window. Consequently, one may expect that in this two-stage process the rate at which the escape window is found (and correspondingly, the apparent NET t_{app}) will increase (decrease) by an amount that depends on the surface diffusion coefficient.

It would be even more realistic to suppose that in the presence of particle-surface attractive interactions, the search for the escape window will be an *intermittent* two-stage process:[10–14] A particle approaching the surface will reversibly bind to it (if the barrier against lateral diffusion is smaller than the desorption barrier) and diffuse over the surface for some (random) time T, after which it will desorb back to the inner part of the confining domain, approach it again at some other point, reversibly bind, diffuse, etc. Therefore, as depicted in Fig. 1, a typical particle trajectory will consist of a sequence of surface diffusion tours followed by excursions in the inner part of the domain, i.e., an intermittent combination of diffusion in two and three spatial dimensions. In this case, t_{app} will also acquire a dependence on the mean time τ_s of residence on the surface within each round of surface diffusion. Given that attractive interactions are always present, the result in Eq. (2), based on the assumption of a perfectly reflecting wall, does not provide a reliable estimate of the actual mean NET t_{app}.

In this paper we study analytically, within a mean-field approach, the effect of the particle-surface affinity on the mean NETs. In Sec. II we define our model. In Sec. III we first rederive the result in Eq. (2) in the spirit of the approach discussed by Berg and Purcell[7] in their analysis of diffusive ligand adsorption from the extracellular space by cell bound receptors. Next, we consider a special case of very strong attractive interactions, such that a particle, once it bumps on the surface, stays there for good and wanders along the surface until it finds the escape window. This limit can be thought of as an analog of the Adam–Delbrück two-stage process. Further on, we consider the general case of an intermittent two-stage process. We develop a mean-field approach which allows us to derive a general result for t_{app}, valid for any τ_s. This result represents an interpolation formula from which we recover Eq. (2) when $\tau_s \to 0$ and the result of the Adam–Delbrück-type approach for $\tau_s \to \infty$. Finally, we conclude with a discussion of the overall effect of the particle-surface affinity on the NET.

II. MODEL

We focus here on the simplest geometry in which the bounded domain is a sphere of radius R. We base our approach on the analysis of representative particle's trajectories, rather than on the solution of the diffusion equation with appropriate boundary conditions. Therefore, instead of standard settings "point particle versus window of radius a," we switch here to an equivalent formulation in which the particle has radius a, while the escape window is a point on the surface. Consequently, we stipulate that the particle covers an area πa^2, when it touches the surface. We suppose, as well, that the particle is initially placed at a random position on the surface of a sphere of radius $r_0=R-\sigma$, $\sigma=\gamma a$, where γ is a numerical factor of order of unity; its precise value will be discussed below.

Diffusion coefficient of the particle in the bulk inside the sphere is D_0. When the particle approaches the sphere (i.e., the distance between the particle and the surface of the sphere gets smaller than a), it becomes weakly adsorbed and starts to diffuse, with diffusion coefficient D_s, along the surface of the sphere. At every (arbitrarily small) time step Δt, the particle updates its state: With probability p_d it may detach from the surface and diffuse away, and with probability $1-p_d$ it stays adsorbed and continues diffusion over the surface. The time T of residence on the surface within a single surface diffusion tour is a random variable with distribution

$$P_s(T) = \frac{1}{\tau_s}\exp\left(-\frac{T}{\tau_s}\right), \tag{3}$$

where the mean value

$$\tau_s = \Delta t \frac{1-p_d}{p_d}. \tag{4}$$

Our goal is to define, in this general case, the decay of the probability S_t that the particle has not found the escape window up to time t, from which we will define the tail of the first passage distribution F_t and hence, the characteristic mean NET t_{app}, as a function of τ_s, D_0, D_s, R, and a.

III. NET PROBLEM WITH A PARTICLE-SURFACE AFFINITY

As the first step, we rederive the results in Eqs. (1) and (2), adapting to the NET problem the approach discussed by Berg and Purcell[7] within the context of chemoreception. Next, we will extend the developed approach over the case when a particle has an affinity to the surface and may diffuse along the surface.

A. NET problem with a perfectly reflecting wall revisited

Let $p_d \equiv 1$ so that the boundary of the sphere is perfectly reflecting. A given path of a particle during time t can be then viewed as a sequence of N Brownian excursions—3D loops connecting the points where the particle has touched the surface; of course, N is a realization-dependent random variable. These excursions correspond to the parts of the path marked in blue in Fig. 1; since we focus on the case $p_d \equiv 1$, the "green" parts should shrink to single points on the sphere.

Note that the term "touching the surface," as well as the hypothetical path depicted in Fig. 1 should be viewed with an appropriate caution. As a matter of fact, the total number of distinct encounters of a point particle with the surface during a finite time interval is infinite in the limit of continuous diffusion. To avoid this confusing behavior, one has to introduce a finite cutoff distance of order of a realistic particle radius.

Further on, not all encounters with the surface can be considered as independent tries in search for the escape window, but only those Brownian excursions whose ends on the surface are separated by a distance greater than a; shorter Brownian excursions should be removed and *considered as* a single try. This circumstance has been discussed in Ref. 7. Of course, this criterion is rather ambiguous and does not define the precise value of the cutoff distance. In this regard, we define a Brownian excursion as a part of a particle trajectory which starts at a distance $\sigma = \gamma a$ away from the surface and ends up on the surface without ever crossing it. In doing so, we consider γ as a fitting parameter which will be chosen afterward in order to match the exact result in Eq. (2).

The probability of not hitting the escape window in a single random encounter with the surface is $1-\pi a^2/4\pi R^2$. If the contacts with the surface can be taken as independent tries, we may estimate the probability that a given path, starting at a random location on the surface of a sphere of radius $R-\sigma$, has not found the escape window as a product $(1-[a^2/4R^2])^N$. Consequently, the survival probability S_t will be given by

$$S_t = \sum_{N=0}^{\infty} P_t(N)\left(1-\frac{a^2}{4R^2}\right)^N, \tag{5}$$

where $P_t(N)$ is the probability that the particle "touched" the surface exactly N times within time interval t.

Suppose now that a particle starting at $t=0$ at distance σ apart from the surface of the sphere touches the surface for the first time at $t=\tau_1$, for the second time at $t=\tau_1+\tau_2$, etc. Then, the probability distribution $P_t(N)$ can be defined as

$$P_t(N) = E_\tau\left\{\theta\left(t-\sum_{k=1}^{N}\tau_k\right)\theta\left(\sum_{k=1}^{N+1}\tau_k - t\right)\right\}, \tag{6}$$

where the symbol $E_\tau\{\cdots\}$ denotes averaging with respect to the distribution of τ-variables, while $\theta(x)$ is the Heaviside theta function which is defined as $\theta(x)=1$ if $x>0$ and zero otherwise.

Using the following representation of the rectangular function:

$$\theta(t-A)\,\theta(B-t) = \mathcal{L}^{-1}\left\{\frac{\exp(-\lambda A)-\exp(-\lambda B)}{\lambda}\right\}, \tag{7}$$

$\mathcal{L}^{-1}\{\cdots\}$ being the inverse Laplace transformation with respect to the parameter λ, we perform averaging over the distribution $P(\tau)$ of independent, identically distributed τ-variables and find that $P_t(N)$ obeys

$$P_t(N) = \mathcal{L}^{-1}\left\{\frac{\phi_\lambda^N}{\lambda}(1-\phi_\lambda)\right\}, \tag{8}$$

where

$$\phi_\lambda = \int_0^\infty d\tau \exp(-\lambda\tau)P(\tau) \tag{9}$$

is the moment-generating function of the τ-variables. One may readily notice that $P_t(N)$ in Eq. (8) is normalized, $\Sigma_N P_t(N)=1$.

To evaluate $P(\tau)$, and hence, ϕ_λ, consider the following auxiliary problem—the survival of a particle (whose initial location is uniformly distributed on the surface of a sphere of radius $R-\sigma$), which diffuses with diffusion coefficient D_0 within a sphere of radius R whose surface is perfectly adsorbing. Green's function $G_\tau(r|r_0=R-\sigma)$ solution of this problem is given by[15]

$$G_\tau(r|r_0) = \frac{1}{2\pi R}\sum_{n=1}^{\infty}\frac{\sin\left(\frac{\pi n r}{R}\right)}{r}\frac{\sin\left(\frac{\pi n r_0}{R}\right)}{r_0} \times \exp\left(-\left(\frac{\pi n}{R}\right)^2 D_0\tau\right). \tag{10}$$

Integrating over the angular variables and r we find S_τ—the probability that such a particle survives until time τ, from which we get the desired PDF $P(\tau)=-dS_\tau/d\tau$ that the first encounter with the surface occurred exactly at time moment τ,

$$P(\tau) = \frac{2\pi D_0}{R^2-\sigma R}\sum_{n=1}^{\infty} n\sin\left(\frac{\pi n\sigma}{R}\right)\exp\left(-\left(\frac{\pi n}{R}\right)^2 D_0\tau\right). \tag{11}$$

Note that the distribution in Eq. (11) has been previously obtained in Ref. 16 within a different context.

Before we proceed further, several remarks concerning the PDF in Eq. (11) are to be made. The distribution $P(\tau)$ involves three different time scales. The smallest one corresponds to the most probable value $\sim\sigma^2/D_0$, which means that most of the time the particle simply bounces onto the surface almost immediately without leaving it for any considerable distance. Further on, at intermediate scales the distribution $P(\tau)$ has a "fat" algebraic tail $P(\tau)\sim\tau^{-3/2}$. In this regime $P(\tau)$ describes the probability for a random walk, commencing at a plane bounding an infinite 3D system, to return back to the plane for the first time after time τ. As a matter of fact, the mean τ—the mean length of Brownian excursions τ_b—is dominated by this very regime,

$$\tau_b = \int_0^\infty d\tau \tau P(\tau) = \frac{R\sigma}{3D_0}\left(1 - \frac{\sigma}{2R}\right) \approx \frac{R\sigma}{3D_0} \tag{12}$$

and is R/σ times larger than the most probable return time. Finally, at times of order R^2/D_0, finite-size effects dominate and the distribution $P(\tau)$ decays exponentially with time.

Consequently, the moment-generating function of a random variable τ obeys

$$\phi_\lambda = \frac{R}{R-\sigma}\frac{\mathrm{sh}((R-\sigma)\sqrt{\lambda/D_0})}{\mathrm{sh}(R\sqrt{\lambda/D_0})}, \tag{13}$$

from which equation we find that at sufficiently large times t, the distribution function $P_t(N)$ follows:

$$P_t(N) \sim \frac{\sqrt{5\sigma}}{2\sqrt{\pi RN}}\exp\left(-\frac{5\sigma}{4RN}\left(N - \frac{3D_0 t}{\sigma R}\right)^2\right). \tag{14}$$

This distribution is centered around the mean value $\bar{N}=t/\tau_b$ and, at fixed t, decays exponentially with N on both sides of the $\bar{N}$.

Now, the asymptotic decay form of S_t in Eq. (5) can be determined in two different ways. We can either convert the sum into an integral and use the asymptotic distribution in Eq. (14), or perform summation exactly and then invert the Laplace transform in the asymptotic limit $t\to\infty(\lambda\to 0)$. We proceed with the latter scenario. Plugging $P_t(N)$ given by Eq. (8) into Eq. (5) and performing summation over N, we get

$$S_t = \mathcal{L}^{-1}\left\{\frac{(1-\phi_\lambda)}{\lambda\left(1-\left(1-\frac{a^2}{4R^2}\right)\phi_\lambda\right)}\right\}. \tag{15}$$

In the large-t limit, the integral in Eq. (15) is dominated by the behavior of ϕ_λ in the vicinity of $\lambda=0$. Expanding

$$1-\left(1-\frac{a^2}{4R^2}\right)\phi_\lambda \approx \frac{a^2}{4R^2} - \frac{R\sigma}{3D_0}\lambda, \tag{16}$$

we find that the asymptotic behavior of S_t in Eq. (15) follows

$$S_t \sim \exp\left(-\frac{3D_0 a}{4\gamma R^3}t\right). \tag{17}$$

Choosing now $\gamma=\pi/4$, we see that the latter decay form coincides with the result in Eqs. (1) and (2). Consequently, we may interpret t_{3D} in Eq. (2) as

$$t_{3D} = \frac{4R^2}{a^2}\tau_b, \tag{18}$$

where the first multiplier determines the mean number of independent tries necessary to find the location of the escape window, while the second factor is the mean time separating independent tries—the mean length of a Brownian excursion.

B. NET problem with particle-surface affinity: Adam–Delbrück-type two-stage process

In this subsection we consider an opposite extreme case, i.e., that of $p_d=0$, so that once a particle happens to approach the surface of the domain, it stays there for good and wanders along the surface until it finds the escape window. In a sense, this is an idealized situation. Indeed, in this case the barrier against the desorption should be infinitely large, and consequently, the barrier against the lateral diffusion should be infinitely large too, effectively suppressing the movement of the particle along the surface.

Neglecting the time τ_b it will take, on average, for the particle to arrive for the first time at some random point on the surface of the domain, we write the probability that a particle diffusing along the surface with diffusion coefficient D_s would not find the escape window until time t as

$$S_t = \left(1 - \frac{A(t)}{4\pi R^2}\right), \tag{19}$$

where $A(t)$ is the mean area swept on the surface of a sphere of radius R by a diffusive disk of radius a until time t—a two-dimensional analog a Wiener sausage.[17] This area is defined by a series[18]

$$\left(1 - \frac{A(t)}{4\pi R^2}\right) = \left(1 - \frac{a^2}{4R^2}\right)\sum_{k=1}^{\infty} a_k \exp\left[-\nu_k(\nu_k+1)\frac{D_s t}{R^2}\right], \tag{20}$$

where

$$a_k = \frac{1}{1-x_0}\left(\int_{x_0}^1 dx P_{\nu_k}(x)\right)^2 \Bigg/ \int_{x_0}^1 dx P_{\nu_k}^2(x), \tag{21}$$

$P_\nu(x)$ being the Legendre functions, while $x_0=-1+a^2/2R^2$ and ν_k are the roots (numbered in the ascending order) of the equation

$$P_{\nu_k}(x_0) = 0. \tag{22}$$

Note that the expansion in Eq. (20) differs by a factor $(1-[a^2/4R^2])$ from the formal solution of the trapping problem on the surface of a sphere.[18] This difference originates from different initial conditions. Namely, in our case a particle can be initially located at any point on the surface (including the area covered by the trap, in which case it disappears instantaneously—this corresponds to finding the escape window at a first try), while in the situation studied in Ref. 18 the particle starts from a random point somewhere outside the trap.

The leading asymptotic behavior of S_t in Eq. (19) is dominated by the smallest root ν_1 of Eq. (22). Hence, the asymptotic behavior of S_t is

$$S_t \sim \exp\left(-\frac{t}{t_{2D}}\right), \tag{23}$$

with

$$t_{2D} = \frac{R^2}{\nu_1(\nu_1+1)D_s}, \tag{24}$$

where the subscript "2D" signifies that the search for the escape window proceeds in this case via the surface diffusion.

When $a/R \ll 1$, for the smallest root one gets $\nu_1 \approx 1/(2\ln(2R/a))$ and, consequently, t_{2D} obeys, in the leading order in a/R,[18]

$$t_{2D} \approx \frac{2R^2}{D_s}\ln\left(\frac{2R}{a}\right). \tag{25}$$

This result has been also obtained in Refs. 1 and 7 and earlier by Bloomfield and Prager[19] in their calculation of the attachment rate of tail fibers to bacteriophages. Note that $t_{2D} \sim R^2 \ln(R)$ and thus should be much larger than $\tau_b \sim R$, which describes the mean time necessary to reach the surface of the domain. This means that it was quite legitimate to discard this contribution in our analysis.

C. NET problem with particle-surface affinity: An intermittent two-stage process

We turn finally to the general case when the detachment probability $0 < p_d < 1$ so that a particle, when touching the surface, will remain weakly adsorbed and wander on the surface for some random time T, then detach and diffuse in the bulk, reattach to the surface, etc.

Consider a path starting at a random point on the surface of a sphere of radius $R - \pi a/4$ and suppose that this path touched the surface of the sphere at time moment τ_1, then wandered along the surface for a random time T_1, detached from the surface at time moment $\tau_1 + T_1$, subsequently returned to the surface at time moment $\tau_1 + T_1 + \tau_2$, etc. Then, assuming that subsequent visits of the surface can be considered as independent tries in search for the exit, the probability S_t that the escape window has not been found by such a path comprising N rounds of Brownian excursions followed by subsequent surface diffusion tours, can be written as

$$S_t = P_t(N=0) + \sum_{N=1}^{\infty} E_{\tau,T}\left\{\prod_{k=1}^{N}\left(1 - \frac{A(T_k)}{4\pi R^2}\right)\theta \times \left(t - \sum_{k=1}^{N}\tau_k + \sum_{k=1}^{N-1} T_k\right)\theta\left(-t + \sum_{k=1}^{N+1}\tau_k + \sum_{k=1}^{N} T_k\right)\right\}, \tag{26}$$

where now the symbol $E_{\tau,T}\{\cdots\}$ denotes the averaging with respect to both the distribution of τ-variables, Eq. (11), and the distribution of T-variables, Eq. (3).

Note that Eq. (26) tacitly assumes that each surface diffusion tour is an independent try in search for the escape window, which manifests itself in the decoupling of the average of the product into the product of average values. This is, of course, an uncontrollable assumption.

On one hand, the distribution $P(d)$ of the distance d between the point where the particle detaches from the surface and the point where it reattaches to the surface again after an excursion in the bulk is given by the Poisson kernel for a three-dimensional ball:[20] $P(d) \sim (1/d^3)$. This is a broad distribution, such that the areas visited on the surface in two consecutive surface diffusion tours will not, on average, significantly overlap.

On the other hand, the surface of the domain is of a finite extent and one will certainly have an oversampling—some parts of the surface will be visited many times before the escape window is found. This will incur some correlations in the search process since the true survival probability S_t accounts only for the actual area swept on the surface by a particle up to time t, and counts multiple visits to the same place as a single try. In this sense, Eq. (26) defines a lower bound on the true survival probability, precisely in the same way as the Rosenstock (or Smoluchowski) approximation defines a rigorous lower bound on the decay function for the trapping problem (see, e.g., Ref. 21).

Consequently, decoupling of correlations defines a rigorous lower bound on the mean NET. Given that, as we proceed to show, t_{app} obtained via such a mean-field approach entails exact results for $\tau_s \to 0$ and $\tau_s \to \infty$, one may judge that it is a useful and plausible approximation. A further discussion of this matter goes beyond the scope of the current paper and will be addressed both analytically and numerically elsewhere.[22]

Using the Laplace transform representation of the rectangular function, Eq. (7), we may conveniently rewrite Eq. (26) and perform straightforwardly averaging over the distributions of τ- and T-variables. In doing so, we get

$$S_t = \mathcal{L}^{-1}\left\{\frac{1-\phi_\lambda}{\lambda} + \frac{\phi_\lambda(F_0 - \phi_\lambda F_\lambda)}{\lambda(1-\phi_\lambda F_\lambda)}\right\}, \tag{27}$$

where ϕ_λ is defined in Eq. (13) and

$$F_\lambda = \frac{1}{\tau_s}\int_0^\infty dT\left(1 - \frac{A(T)}{4\pi R^2}\right)\exp\left(-\frac{T}{\tau_s} - \lambda T\right). \tag{28}$$

Explicitly, F_λ is given by a series

$$F_\lambda = \left(1 - \frac{a^2}{4R^2}\right)\sum_{k=1}^{\infty} a_k\left(1 + \nu_k(\nu_k+1)\frac{D_s\tau_s}{R^2} + \tau_s\lambda\right)^{-1}. \tag{29}$$

Consider now the behavior of the coefficients in this series in more detail. First, for small a/R a good approximate solution of Eq. (22) is $\nu_k = k - 1 + 1/(2\ln(2R/a))$,[18] and thus the roots of Eq. (22) grow linearly with k. Second, in the leading order in a/R, $a_k = \delta_{k,1}$, where $\delta_{k,1}$ is the Kronecker delta ($a_k = 1$ for $k=1$ and zero otherwise), correction terms to this dependence are of order of $(a/R)^2 f_k$, where f_k is a rapidly decaying function of k. All this permits us, so far as we are interested in the small-λ (large-t) limit, is to consider only the first term in the series in Eq. (29) and skip the remaining terms, giving

$$F_\lambda \sim \left(1 - \frac{a^2}{4R^2}\right)\left(1 + \nu_1(\nu_1+1)\frac{D_s\tau_s}{R^2} + \tau_s\lambda\right)^{-1}. \tag{30}$$

Finally, notice that the first term in Eqs. (26) and (27) decays rapidly in the time t domain, compared to the second one (indeed, its characteristic decay time is just τ_b) and thus its contribution is negligible in the large-t limit, we get

$$S_t \sim \mathcal{L}^{-1}\left\{\left(\frac{3D_0(a^2 + 4\nu_1(\nu_1+1)D_s\tau_s)}{12D_0R^2\tau_s + \pi a R^3} + \lambda\right)^{-1}\right\}, \tag{31}$$

which describes the asymptotic behavior of the survival probability in the limit $\lambda \to 0$.

IV. RESULTS AND DISCUSSION

Inverting Eq. (31), we obtain our main results,

$$S_t \sim \exp\left(-\frac{t}{t_{\rm app}}\right), \tag{32}$$

where

$$t_{\rm app} = \frac{12D_0R^2\tau_s + \pi aR^3}{3D_0(a^2 + 4\nu_1(\nu_1+1)D_s\tau_s)} \tag{33}$$

is the mean NET for diffusion in a sphere with particle-surface affinity. Note that for $\tau_s \to 0$ we recover the exact result in Eq. (2), while for $\tau_s \to \infty$ we find from Eq. (33) the exact result in Eq. (24), specific for the Adam–Delbrück-type two-stage search process.

It is expedient to cast the result in Eq. (33) into a physically meaningful form, using the characteristic times introduced in Eqs. (4), (12), and (24),

$$t_{\rm app} = \frac{\tau_b + \tau_s}{\dfrac{a^2}{4R^2} + \dfrac{\tau_s}{t_{\rm 2D}}}. \tag{34}$$

This equation has a transparent physical meaning: The numerator on the right-hand-side of Eq. (34) defines the overall time spent, on average, in a single Brownian excursion in the bulk followed by a surface diffusion tour, while the denominator defines the average fraction of the sphere surface covered within a single tour of surface diffusion. Therefore, $t_{\rm app}$ equals the time consumed by a Brownian excursion and a single surface diffusion tour, times the number of tries necessary to cover the whole surface. Note that essentially the same argument have been used in Refs. 23 and 24 to estimate the first passage time for search by a diffusive protein for a specific binding site on a DNA molecule.

Further on, we rewrite Eq. (34) formally as

$$t_{\rm app} = t_{\rm 3D}\left(1 + \frac{\tau_s}{\tau_b}\right) \Big/ \left(1 + \frac{4R^2}{a^2}\frac{\tau_s}{t_{\rm 2D}}\right). \tag{35}$$

One notices next that $t_{\rm app}$ is a monotonically increasing (decreasing) function of τ_s if $t_{\rm 2D} > t_{\rm 3D}$ ($t_{\rm 2D} < t_{\rm 3D}$). Consequently, $t_{\rm app} > t_{\rm 3D}$ when

$$\frac{D_0}{D_s} > \frac{\pi}{3}\nu_1(\nu_1+1)\frac{R}{a}. \tag{36}$$

Typically, D_s is less by two or three orders of magnitude than D_0 (may be even less under the conditions of molecular crowding[25]), which means that the ratio on the left hand side of the inequality in Eq. (36) is of order of 10^2–10^3. For the example, mentioned in Sec. I, search for the tubule entrance in a vesicle by a diffusive ligand, one has $R/a \sim 10^1$ so that the right hand side of Eq. (36) is of order of unity and the inequality in Eq. (36) evidently fulfills. This means that for this example the particle-surface affinity will generally lead to *larger* mean NETs, compared to the estimate based on the assumption of a perfectly reflecting wall. To inverse the inequality, one will need the ratio R/a to be of order of 10^3–10^4, which may be realized, say, for catalytic reactions in microporous media (R being the radius of a pore and a—radius of a catalytic site). In this case, indeed, one may expect that particle-surface affinity will reduce the effective times of the first passage to the catalytic site and thus enhance the reaction rate.

Finally, we recall that Eq. (33) defines a rigorous lower bound on the actual mean NET for any τ_s. This is, however, a mean-field result and, in view of the importance of the problem, it would be highly desirable to study the NET problem with a particle-surface affinity within a more elaborate/exact approach accompanied by numerical simulations. These investigations are currently underway.[22]

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