A new approach to the problem of bulk-mediated surface diffusion

Alexander M. Berezhkovskii,^{1,2} Leonardo Dagdug,^{1,2,a)} and Sergey M. Bezrukov¹

¹*Program in Physical Biology, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland 20892, USA*

²*Mathematical and Statistical Computing Laboratory, Division of Computational Bioscience, Center for Information Technology, National Institutes of Health, Bethesda, Maryland 20892, USA*

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This paper is devoted to bulk-mediated surface diffusion of a particle which can diffuse both on a flat surface and in the bulk layer above the surface. It is assumed that the particle is on the surface initially (at $t = 0$) and at time t , while in between it may escape from the surface and come back any number of times. We propose a new approach to the problem, which reduces its solution to that of a two-state problem of the particle transitions between the surface and the bulk layer, focusing on the cumulative residence times spent by the particle in the two states. These times are random variables, the sum of which is equal to the total observation time t . The advantage of the proposed approach is that it allows for a simple exact analytical solution for the double Laplace transform of the conditional probability density of the cumulative residence time spent on the surface by the particle observed for time t . This solution is used to find the Laplace transform of the particle mean square displacement and to analyze the peculiarities of its time behavior over the entire range of time. We also establish a relation between the double Laplace transform of the conditional probability density and the Fourier-Laplace transform of the particle propagator over the surface. The proposed approach treats the cases of both finite and infinite bulk layer thicknesses (where bulk-mediated surface diffusion is normal and anomalous at asymptotically long times, respectively) on equal footing. © 2015 AIP Publishing LLC. [<http://dx.doi.org/10.1063/1.4928741>]

I. INTRODUCTION

Bulk-mediated surface diffusion is attracting a lot of attention in both theory and experiment due to its well-recognized relevance to a wide variety of processes in nature and technology.^{1–21} This kind of diffusion characterizes the motion of particles on a surface that is in a contact with the bulk in a way that allows for the dynamic partitioning of the particles between the surface-bound and bulk states. As a result, particles intermittently diffuse on the surface and in the bulk. One can envisage a particle that initially undergoes two-dimensional stochastic motion on the surface, then unbinds from it to experience a three-dimensional motion in the adjacent bulk, and then returns to the surface. This may repeat many times, allowing for an accelerated propagation of the particles over the surface when bulk diffusivity is significantly larger than its surface counterpart.

The most well-known example, where bulk-mediated surface diffusion plays an important role, is by now classical studies of the dynamics of gene regulation. Here, the mechanism of dimensionality reduction²² was proposed to explain the association of an *E. coli* lac repressor with its operator site on a DNA chain, which was shown to happen significantly faster than expected for a diffusion-controlled reaction.²³ Richter and Eigen⁷ suggested that the enhancement of the reaction rate can be explained by considering a process in which non-specifically bound proteins not only diffuse in

one dimension along the DNA but also intermittently unbind to undergo bulk diffusion. Their initial treatment was extended in subsequent studies to allow for a more careful consideration of DNA structural features and spatial arrangements^{1–6,8–10} making a quantitative foundation for interpreting experimental findings.^{24–26} One can find a detailed discussion of the problem in a recent review article.²⁰

Our motivation, which adds a couple of relatively new examples to this list, is related to the recent studies of the interaction between certain cytosolic proteins and their membrane-embedded targets, which involves bulk-mediated diffusion over the membrane surface as an essential step. Reconstitution experiments with the voltage dependent anion channel (VDAC) from the outer mitochondrial membrane have demonstrated an unexpected role of the abundant water-soluble protein, dimeric tubulin, in physiological regulation of mitochondrial function.^{27,28} The model, proposed for the VDAC interaction with tubulin and confirmed by a number of specially designed experiments,^{29–31} suggests that the negatively charged disordered tail of tubulin enters the net positively charged VDAC pore and thus blocks it for metabolite transport. Importantly, it was found that this interaction is influenced by the membrane composition, being very sensitive to the lipid species used for bilayer formation in VDAC reconstitution.³² The on-rate of the blockage varied up to 100-fold depending on the particular lipid thus suggesting that tubulin first binds to the membrane and then reaches VDAC via surface diffusion. Another recent example of the membrane-facilitated interaction of a water-soluble cytosolic protein with a membrane target is that of the intrinsically disordered

^{a)}Permanent address: Physics Department, Universidad Autonoma Metropolitana-Iztapalapa, 09340 Mexico City, Mexico.

α -synuclein, implicated in Parkinson disease pathogenesis, with the α -hemolysin channel reconstituted in a planar membrane.³³

This paper deals with bulk-mediated surface diffusion in flat geometry. We consider a point particle that can diffuse both on a flat surface and in the bulk above the surface with diffusivities D_s and D_b , respectively. Initially, the particle is on the surface. It can escape from the surface to the bulk and later return to the surface. Particle diffusion in the bulk is bounded by a flat reflecting “lid” located at distance L from the surface, as shown in Fig. 1. Since the particle can be either on the surface or in the bulk, the particle propagator (Green’s function) has surface and bulk components. The quantities of our interest are the surface component of the propagator, the probability of finding the particle on the surface at time t , and the second moment of the displacement of such a particle. These quantities can be found using the conventional approach, starting with the diffusion equations for the two components of the propagator, which couple through the exchange term that describes dissociation of the particle from the surface and its binding to the surface from the bulk. Such an approach was used in the case of no reflecting lid ($L = \infty$) by Chechkin *et al.*¹⁶

In this paper, we propose a new approach to the problem, which exploits the fact that the particle propagation over the surface is determined by the cumulative times spent by the particle on the surface and in the bulk. These cumulative times are random variables, the sum of which is equal to the total observation time. It is important that these times can be analyzed by considering a relatively simple two-state problem that describes transitions of the particle between the surface and the bulk. The developed formalism is an extension of the formalism proposed to describe diffusion in multilayer media,³⁴ which deals with diffusion without any constraints on the particle position at time t . Here, we modify this formalism to study the particle propagation on condition that the particle is bound to the surface at time t . A similar approach has recently been used to study both unbiased and biased diffusion in three-dimensional comb-like structures.^{35,36}

It is worth noting that the requirement that the particle is bound to the surface at time t makes the particle propagation over the surface qualitatively different from its unconstrained propagation in the lateral direction. In particular, the surface propagation is anomalous diffusion when the bulk layer thickness is infinite (no reflecting lid), whereas the unconstrained lateral propagation is normal diffusion. One of the advantages

of the proposed approach is that it treats the cases of normal and anomalous diffusion (finite and infinite bulk layer thicknesses, respectively) on equal footing.

The outline of this paper is as follows. A general theory is developed in Section III, after we specify the model in Section II. Sections IV and V are devoted to the probability of finding the particle on the surface at time t and the mean square displacement in time t , conditional on that the particle is on the surface at time t , respectively. In Section VI, we establish a relation between the Fourier-Laplace transform of the particle propagator over the surface and the double Laplace transform of the conditional probability density of the cumulative time spent on the surface by a particle observed for time t , which starts on the surface at $t = 0$ and is bound to the surface at time t . Some concluding remarks are made in Sec. VII.

II. MODEL

Consider a particle performing intermittent bulk-surface diffusion in the flat geometry schematically shown in Fig. 1. Its bulk-surface transitions are described by the kinetic scheme

It is assumed that the particle survival probability on the surface (s), $S_s(t)$, decays as a single exponential,

$$S_s(t) = e^{-kt}, \quad (2.2)$$

where k is the rate constant, which is the inverse mean particle lifetime on the surface. The probability density of this lifetime, $\varphi_s(t)$, is

$$\varphi_s(t) = -\frac{dS_s(t)}{dt} = ke^{-kt}. \quad (2.3)$$

The efficiency of the particle binding to the surface from the bulk is characterized by the binding rate κ that enters into the radiation boundary condition on the surface for the bulk component of the particle propagator (see Fig. 1 and Appendix A). One can find the probability density of the particle lifetime in the bulk (b), $\varphi_b(t)$, by solving a one-dimensional diffusion problem in the direction normal to the surface. For the sake of completeness, the solution is provided in Appendix A, where an expression for the Laplace transform of this probability density is derived. (The Laplace transform of function $f(t)$, denoted by $\hat{f}(s)$, is defined as $\hat{f}(s) = \int_0^\infty e^{-st} f(t) dt$, where s is the Laplace parameter.) As shown in Appendix A, $\hat{\varphi}_b(s)$ is given by

$$\hat{\varphi}_b(s) = \frac{\kappa}{\kappa + \sqrt{sD_b} \tanh(L\sqrt{s/D_b})}. \quad (2.4)$$

In the case of no reflecting lid ($L \rightarrow \infty$), this expression simplifies and takes the form

$$\hat{\varphi}_b(s) = \frac{\kappa}{\kappa + \sqrt{sD_b}}. \quad (2.5)$$

Finally, we mention that when the particle spends time t on the surface, its surface propagator, $g_s(\mathbf{r}, t)$, which is the probability density of the displacement $\mathbf{r}$ in time t , is

$$g_s(\mathbf{r}, t) = \frac{1}{4\pi D_s t} e^{-r^2/(4D_s t)}, \quad (2.6)$$

FIG. 1. Schematic representation of the geometry analyzed in the paper.

where $r = |\mathbf{r}|$. The mean square displacement of such a particle, $\langle r^2(t) \rangle_s$, is given by

$$\begin{aligned} \langle r^2(t) \rangle_s &= \iint r^2 g_s(\mathbf{r}, t) d\mathbf{r} \\ &= \frac{1}{2D_s t} \int_0^\infty r^3 e^{-r^2/(4D_s t)} dr = 4D_s t. \end{aligned} \quad (2.7)$$

Correspondingly, when the particle spends time t in the bulk, its bulk lateral (b, l) propagator, $g_{b,l}(\mathbf{r}, t)$, and the mean square displacement in the lateral direction, $\langle r^2(t) \rangle_{b,l}$, respectively, are

$$g_{b,l}(\mathbf{r}, t) = \frac{1}{4\pi D_b t} e^{-r^2/(4D_b t)} \quad (2.8)$$

and

$$\begin{aligned} \langle r^2(t) \rangle_{b,l} &= \iint r^2 g_{b,l}(\mathbf{r}, t) d\mathbf{r} \\ &= \frac{1}{2D_b t} \int_0^\infty r^3 e^{-r^2/(4D_b t)} dr = 4D_b t. \end{aligned} \quad (2.9)$$

In the rest of the paper, bulk-mediated surface diffusion is analyzed in the framework of the model described above.

III. GENERAL THEORY

Consider a particle observed for time t , focusing on those realizations of the particle trajectory, which spent a cumulative time τ on the surface and, respectively, time $t - \tau$ in the bulk, $0 \leq \tau \leq t$. The lateral (l) propagator, due to such realizations of the particle trajectory, denoted by $G_l(\mathbf{r}, t|\tau)$, is given by

$$\begin{aligned} G_l(\mathbf{r}, t|\tau) &= \iint g_{b,l}(\mathbf{r} - \mathbf{r}', t - \tau) g_s(\mathbf{r}', \tau) d\mathbf{r}' \\ &= \frac{1}{4\pi [D_s \tau + D_b(t - \tau)]} e^{-r^2/\{4[D_s \tau + D_b(t - \tau)]\}}. \end{aligned} \quad (3.1)$$

The cumulative time τ is a random variable. Therefore, to find the propagator of interest for a particle that starts on the surface at $t = 0$ and is bound to the surface at time t , we have to average the propagator in Eq. (3.1) over τ .

To this end, we introduce the conditional probability density $\nu_s(\tau|t)$ of the cumulative time τ spent by the particle on the surface, on the condition that it is on the surface at $t = 0$ and at time t . The product $\nu_s(\tau|t)d\tau$ is the fraction of such realizations of the particle trajectory, which start on the surface, where they spend the cumulative time between τ and $\tau + d\tau$, and are bound to the surface at time t . The integral of $\nu_s(\tau|t)$ over τ from zero to t is the probability of finding the particle on the surface at time t , denoted by $P_s(t)$,

$$P_s(t) = \int_0^t \nu_s(\tau|t) d\tau. \quad (3.2)$$

This is the normalization condition for the conditional probability density $\nu_s(\tau|t)$. Eventually, the propagator of interest, denoted by $G(\mathbf{r}, t)$, is given by

$$G(\mathbf{r}, t) = \int_0^t G_l(\mathbf{r}, t|\tau) \nu_s(\tau|t) d\tau. \quad (3.3)$$

As follows from Eqs. (3.1) and (3.2), the integral of this propagator over $\mathbf{r}$ is the probability $P_s(t)$ of finding the particle on

the surface at time t ,

$$\iint G(\mathbf{r}, t) d\mathbf{r} = \int_0^t \nu_s(\tau|t) d\tau = P_s(t). \quad (3.4)$$

The conditional probability density of the cumulative time is determined by the dynamics of the particle bulk-surface transitions. Therefore, $\nu_s(\tau|t)$ can be found by solving a two-state problem, described by the kinetic scheme in Eq. (2.1). The solution, obtained in Appendix B, provides the double Laplace transform of $\nu_s(\tau|t)$, denoted by $\hat{\nu}_s(\sigma, s)$ and defined as

$$\begin{aligned} \hat{\nu}_s(\sigma, s) &= \int_0^\infty e^{-st} dt \int_0^t e^{-\sigma\tau} \nu_s(\tau|t) d\tau \\ &= \int_0^\infty \int_0^\infty e^{-(st+\sigma\tau)} \nu_s(\tau|t) d\tau dt, \end{aligned} \quad (3.5)$$

where in the second double integral we have used the fact that $\nu_s(\tau|t) = 0$, when $\tau > t$. The solution gives $\hat{\nu}_s(\sigma, s)$ in terms of the Laplace transforms of the probability densities of the particle lifetimes in the two states,

$$\hat{\nu}_s(\sigma, s) = \frac{1 - \hat{\varphi}_s(s + \sigma)}{(s + \sigma)(1 - \hat{\varphi}_s(s + \sigma)\hat{\varphi}_b(s))}. \quad (3.6)$$

The Laplace transform of the probability density $\varphi_s(t)$, Eq. (2.3), is given by

$$\hat{\varphi}_s(s) = \frac{k}{s + k}. \quad (3.7)$$

Using this and the expression for $\hat{\varphi}_b(s)$ in Eq. (2.4), we obtain

$$\begin{aligned} \hat{\nu}_s(\sigma, s) &= \frac{1}{s + \sigma + k(1 - \hat{\varphi}_b(s))} \\ &= \frac{\kappa + \sqrt{sD_b} \tanh(L\sqrt{s/D_b})}{(s + \sigma)\kappa + (s + \sigma + k)\sqrt{sD_b} \tanh(L\sqrt{s/D_b})}. \end{aligned} \quad (3.8)$$

As follows from Eq. (3.2), the Laplace transform of the probability $P_s(t)$ of finding the particle on the surface at time t is related to $\hat{\nu}_s(\sigma, s)$ by

$$\hat{P}_s(s) = \hat{\nu}_s(\sigma = 0, s). \quad (3.9)$$

Substituting here $\hat{\nu}_s(\sigma, s)$ in Eq. (3.8), we obtain

$$\begin{aligned} \hat{P}_s(s) &= \frac{1}{s + k(1 - \hat{\varphi}_b(s))} \\ &= \frac{\kappa + \sqrt{sD_b} \tanh(L\sqrt{s/D_b})}{s\kappa + (s + k)\sqrt{sD_b} \tanh(L\sqrt{s/D_b})}. \end{aligned} \quad (3.10)$$

An alternative derivation of this expression is given in Appendix C. Using Eqs. (3.1)–(3.3), one can establish a relation between the second moment of the displacement, $\langle r^2(t) \rangle$, and the mean cumulative time, $\langle \tau(t) \rangle$, spent by the particle on the surface,

$$\begin{aligned} \langle r^2(t) \rangle &= \iint r^2 G(\mathbf{r}, t) d\mathbf{r} \\ &= 4[D_s \langle \tau(t) \rangle + D_b(tP_s(t) - \langle \tau(t) \rangle)], \end{aligned} \quad (3.11)$$

where the mean cumulative time is defined as

$$\langle \tau(t) \rangle = \int_0^t \tau \nu_s(\tau|t) d\tau. \quad (3.12)$$

In our analysis, we use the Laplace transform of the mean cumulative time, denoted by $\langle \hat{\tau}(s) \rangle$, that can be found by means of the relation

$$\langle \hat{\tau}(s) \rangle = - \frac{\partial \hat{v}_s(\sigma, s)}{\partial \sigma} \Big|_{\sigma=0}, \quad (3.13)$$

which follows from the definitions in Eqs. (3.12) and (3.5). Substituting here $\hat{v}_s(\sigma, s)$ in Eq. (3.8), we arrive at

$$\langle \hat{\tau}(s) \rangle = \left[\frac{\kappa + \sqrt{s D_b} \tanh(L \sqrt{s/D_b})}{s \kappa + (s + k) \sqrt{s D_b} \tanh(L \sqrt{s/D_b})} \right]^2 = (\hat{P}_s(s))^2. \quad (3.14)$$

Using this, one can write the Laplace transform of the mean square displacement $\langle r^2(t) \rangle$, Eq. (3.11), as

$$\langle \hat{r}^2(s) \rangle = 4 \left[(D_s - D_b) (\hat{P}_s(s))^2 - D_b \frac{d\hat{P}_s(s)}{ds} \right]. \quad (3.15)$$

This and Eq. (3.14) establish simple relations between the Laplace transforms of the mean square displacement of the particle and the mean cumulative time, on the one hand, and the Laplace transform of the probability of finding the particle on the surface given in Eq. (3.10), on the other. It is important that the latter can be easily found by solving the two-state problem, Eq. (2.1), as shown in Appendix C.

IV. PROBABILITY $P_s(t)$

In this section, we use the Laplace transform in Eq. (3.10) to analyze the probability $P_s(t)$ of finding the particle on the surface at time t . Function $P_s(t)$ describes relaxation of this probability from unity at $t = 0$ to its equilibrium value, P_s^{eq} , as $t \rightarrow \infty$. The latter is given by

$$P_s^{eq} = \lim_{t \rightarrow \infty} P_s(t) = \lim_{s \rightarrow 0} s \hat{P}_s(s) = \frac{\kappa}{\kappa + kL}, \quad (4.1)$$

where we have used $\hat{P}_s(s)$ in Eq. (3.10). The expression in Eq. (4.1) shows that P_s^{eq} vanishes in the absence of the lid ($L = \infty$),

$$\lim_{L \rightarrow \infty} P_s^{eq} = 0. \quad (4.2)$$

In this case, the small- s asymptotic behavior of the Laplace transform $\hat{P}_s(s)$, Eq. (3.10), has the form

$$\hat{P}_s(s)|_{L=\infty} \approx \frac{\kappa}{k \sqrt{s D_b}}, \quad s \rightarrow 0. \quad (4.3)$$

Inverting this Laplace transform, we find the long-time asymptotic behavior of the probability $P_s(t)$ in the absence of the lid

$$P_s(t)|_{L=\infty} \approx \frac{\kappa}{k \sqrt{\pi D_b t}}, \quad t \rightarrow \infty. \quad (4.4)$$

Thus, the long-time behavior of the probability $P_s(t)$ is qualitatively different, depending on whether the bulk layer thickness is finite or infinite. However, the short-time behavior of this probability is universal, in the sense that it is independent of the bulk layer thickness. This is a consequence of the fact that the particle is unaware of the layer thickness when time is short enough. One can find the short-time behavior of $P_s(t)$ by inverting the large- s asymptotic form of $\hat{P}_s(s)$. As

FIG. 2. The time dependences of the probability $P_s(t)$ of finding the particle on the surface at time t . The dependences are obtained by numerically inverting the Laplace transform in Eq. (3.10) using the Stehfest algorithm. The main panel illustrates variation of $P_s(t)$ as the bulk layer thickness changes from $L = 1$ to $L = \infty$, at $D_b = k = \kappa = 1$; the values of L are given above the curves. The inset illustrates variation of $P_s(t)$ at $L = \infty$ as D_b changes from 0.1 to 10, at $k = \kappa = 1$; the values of D_b are given above the curves. All the parameter values are given in dimensionless units.

follows from Eq. (3.10), this asymptotic form is given by

$$\hat{P}_s(s) \approx \frac{1}{s} - \frac{k}{s^2} + \frac{k\kappa}{s^{5/2}\sqrt{D_b}}, \quad s \rightarrow \infty. \quad (4.5)$$

Inverting this Laplace transform, we obtain

$$P_s(t) \approx 1 - kt + \frac{4k\kappa}{3\sqrt{\pi D_b}} t^{3/2}, \quad t \rightarrow 0. \quad (4.6)$$

Here, the first two terms on the right-hand side are due to those realizations of the particle trajectory, which do not escape from the surface to the bulk layer during time t . The third term is due to those realizations of escaped trajectories that return to the surface during this time.

The time dependences of the probability $P_s(t)$ of finding the particle on the surface at time t are illustrated in Fig. 2. The curves are obtained by numerically inverting the Laplace transform in Eq. (3.10). The main panel shows $P_s(t)$ for several values of the bulk layer thickness, $L = 1, 2, 5$, and ∞ , assuming that all other parameters are equal to unity, $D_b = k = \kappa = 1$, where all the parameters are given in dimensionless units. The inset shows the dependence $P_s(t)$ in the absence of the reflecting lid ($L = \infty$) at three values of the bulk diffusivity, $D_b = 0.1, 1$, and 10 , assuming that $k = \kappa = 1$. One can see (1) that $P_s(t)$ decreases as L increases (main panel) and (2) that the increase in D_b accelerates the decay of $P_s(t)$ (inset).

V. MEAN SQUARE DISPLACEMENT

In this section, we analyze the time dependence of the mean square displacement $\langle r^2(t) \rangle$. The focus is on how this dependence changes as a function of the bulk layer thickness L and the diffusivity ratio D_b/D_s . For such an analysis, according to Eq. (3.11), we need to know two functions: the probability $P_s(t)$ of finding the particle on the surface at time t and the mean cumulative time $\langle \tau(t) \rangle$, spent by the particle on the surface, on condition that the particle starts from the

surface at $t = 0$ and is bound to the surface at time t . We begin with the long-time asymptotic behavior of $\langle r^2(t) \rangle$. After that, we discuss the dependence $\langle r^2(t) \rangle$ at short times and illustrate its time behavior over the entire time range.

A. Long-time behavior

As $t \rightarrow \infty$, the probability $P_s(t)$ of finding the particle on the surface approaches its equilibrium value P_s^{eq} , given by Eq. (4.1). When L is finite, the Laplace transform of the mean cumulative time, Eq. (3.14), in the small- s limit takes the form

$$\langle \hat{\tau}(s) \rangle \approx \frac{1}{s^2} (P_s^{eq})^2, \quad s \rightarrow 0. \quad (5.1)$$

Inverting this Laplace transform, we find the long-time behavior of the mean cumulative time,

$$\langle \tau(t) \rangle \approx t (P_s^{eq})^2, \quad t \rightarrow \infty. \quad (5.2)$$

Substituting this into Eq. (3.11), we obtain that $\langle r^2(t) \rangle$ at long times is proportional to time and can be written in the conventional form as

$$\langle r^2(t) \rangle = 4D_{eff}t, \quad t \rightarrow \infty. \quad (5.3)$$

Here, D_{eff} is the effective diffusivity given by

$$D_{eff} = P_s^{eq} D_{eff}^{conv}, \quad (5.4)$$

where D_{eff}^{conv} is the conventional (*conv*) effective diffusivity. The latter describes effective diffusion of the particle in the absence of the constraint that the particle should be on the surface at time t ,

$$D_{eff}^{conv} = D_s P_s^{eq} + D_b P_b^{eq}, \quad (5.5)$$

where P_b^{eq} is the equilibrium probability of finding the particle in the bulk layer above the surface,

$$P_b^{eq} = 1 - P_s^{eq} = \frac{kL}{\kappa + kL}. \quad (5.6)$$

The expression in Eq. (5.4) gives the effective diffusivity as a product of two factors, the equilibrium probability of finding the particle on the surface and the conventional effective diffusivity. The former, P_s^{eq} , monotonically decreases as L increases, approaching zero as $L \rightarrow \infty$, Eq. (4.1). The behavior of the second factor, D_{eff}^{conv} , depends on whether D_b is larger than D_s or not. When $D_b < D_s$, both P_s^{eq} and D_{eff}^{conv} are monotonically decreasing functions of L , and hence D_{eff} also monotonically decreases with L . The situation changes when $D_b > D_s$, which is frequently the case. Here, D_{eff}^{conv} monotonically increases with L , approaching its upper limit D_b , as $L \rightarrow \infty$. The competition of the two factors may lead to a non-monotonic L -dependence of the effective diffusivity D_{eff} . This happens when $D_b > 2D_s$.

To demonstrate this, we use the relations in Eqs. (4.1) and (5.6) to write the effective diffusivity, Eq. (5.4), in terms of the system parameters,

$$D_{eff} = \frac{\kappa (D_s \kappa + D_b k L)}{(\kappa + k L)^2}. \quad (5.7)$$

One can see that, when $D_b > 2D_s$, D_{eff} first increases with L , reaches a maximum, and then decreases, approaching zero as

$L \rightarrow \infty$. Hence, when $D_b > 2D_s$, there is an optimal bulk layer thickness L^* that maximizes the effective diffusivity,

$$L^* = \frac{\kappa}{k} \left(1 - \frac{2D_s}{D_b} \right). \quad (5.8)$$

The optimal layer thickness, considered as a function of the ratio D_b/D_s , is always smaller than its maximum value κ/k , approaching this value from below as $D_b/D_s \rightarrow \infty$. The maximum value of the effective diffusivity at fixed values of the parameters k , κ , D_s , and D_b is independent of k and κ and given by

$$D_{eff, \max} = D_{eff}|_{L=L^*} = \frac{D_b^2}{4(D_b - D_s)}. \quad (5.9)$$

The L -dependence of the effective diffusivity, Eq. (5.7), is illustrated in Fig. 3.

In the absence of the reflecting lid ($L = \infty$), the mean square displacement $\langle r^2(t) \rangle$ has qualitatively different asymptotic long-time behavior, compared to that in Eq. (5.3). In this case, as $t \rightarrow \infty$, the probability $P_s(t)|_{L=\infty}$ tends to zero, Eq. (4.4), whereas the mean cumulative time approaches a constant value. To show this, we use the Laplace transform of the mean cumulative time, Eq. (3.14), which, in the absence of the lid, reduces to

$$\langle \hat{\tau}(s) \rangle|_{L=\infty} = \left[\frac{\kappa + \sqrt{s D_b}}{s(\kappa + \sqrt{s D_b}) + k\sqrt{s D_b}} \right]^2. \quad (5.10)$$

The leading term of the small- s expansion of $\langle \hat{\tau}(s) \rangle|_{L=\infty}$ is

$$\langle \hat{\tau}(s) \rangle|_{L=\infty} \approx \frac{\kappa^2}{s k^2 D_b}, \quad s \rightarrow 0. \quad (5.11)$$

Inverting this Laplace transform, we find that, as $t \rightarrow \infty$, the mean cumulative time spent by the particle on the surface, conditional on that the particle is on the surface at time t , approaches a constant value given by

$$\lim_{t \rightarrow \infty} \langle \tau(t) \rangle|_{L=\infty} = \frac{\kappa^2}{k^2 D_b}. \quad (5.12)$$

As a consequence, the mean square displacement in Eq. (3.11) reduces to

FIG. 3. The L -dependence of the effective diffusivity, Eq. (5.7), at different values of the diffusivity ratio $D_b/D_s = 1, 2, 4, 8$, and 16 , from bottom to top.

$$\langle r^2(t) \rangle|_{L=\infty} = 4D_b t P_s(t)|_{L=\infty} = \frac{4\kappa}{k} \sqrt{\frac{D_b t}{\pi}}, \quad t \rightarrow \infty, \quad (5.13)$$

where we have used the long-time asymptotic behavior of the probability $P_s(t)|_{L=\infty}$ given in Eq. (4.4).

The expression for the mean square displacement in Eq. (5.13) describes anomalous subdiffusion, $\langle r^2(t) \rangle \propto t^\alpha$, with the exponent $\alpha = 1/2$. This expression also shows that the anomalous subdiffusion is due to vanishing probability of finding the particle on the surface at time t . As follows from Eq. (5.13), the ratio $\langle r^2(t) \rangle|_{L=\infty} / P_s(t)|_{L=\infty}$ grows linearly with time at long times,

$$\frac{\langle r^2(t) \rangle|_{L=\infty}}{P_s(t)|_{L=\infty}} = 4D_b t, \quad t \rightarrow \infty, \quad (5.14)$$

as in the case of regular diffusion. The fact that this ratio contains D_b and does not contain D_s is not surprising. The reason is that the particle spends almost all observation time t in the bulk and only vanishingly small fraction of this time on the surface.

Based on the above analysis, we can write a simple universal formula for the long-time behavior of the mean square displacement,

$$\langle r^2(t) \rangle = 4D_{eff}^{conv} t P_s(t), \quad t \rightarrow \infty, \quad (5.15)$$

which is also supported by common sense arguments. This formula describes the mean square displacement in both cases of normal (finite L) and anomalous (infinite L) diffusion, where $\langle r^2(t) \rangle$ is given by Eqs. (5.3) and (5.13), respectively.

B. Short-time behavior

While the long-time behavior of the mean square displacement, $\langle r^2(t) \rangle$, is a function of L , its short-time behavior is L -independent, since the particle is unaware of the bulk layer thickness when time is short enough. According to Eq. (3.11), to obtain this asymptotic behavior, we need to know the short-time behaviors of the probability $P_s(t)$ of finding the particle on the surface at time t and of the mean cumulative time $\langle \tau(t) \rangle$. The former is given by Eq. (4.6). We find the latter by inverting the large- s asymptotic form of its Laplace transform, Eq. (3.14). This asymptotic form is given by

$$\langle \hat{\tau}(s) \rangle = \frac{1}{s^2} - \frac{2k}{s^3} + \frac{2k\kappa}{s^{7/2}\sqrt{D_b}}, \quad s \rightarrow \infty. \quad (5.16)$$

Inverting this Laplace transform, we obtain

$$\langle \tau(t) \rangle = t - kt^2 + \frac{16k\kappa}{15\sqrt{\pi D_b}} t^{5/2}, \quad t \rightarrow 0. \quad (5.17)$$

Substituting the limiting forms of $P_s(t)$, Eq. (4.6), and $\langle \tau(t) \rangle$, Eq. (5.17), into Eq. (3.11), we arrive at

$$\langle r^2(t) \rangle = 4 \left[D_s t (1 - kt) + (4D_s + D_b) \frac{4k\kappa}{15\sqrt{\pi D_b}} t^{5/2} \right], \quad t \rightarrow 0. \quad (5.18)$$

Here, the first term in the square brackets is due to those realizations of the particle trajectory that do not escape from the surface during time t . The second term is due to such

realizations of the trajectory that escape from the surface and later come back.

C. Entire time range

One can find the mean square displacement $\langle r^2(t) \rangle$ over the entire time range by substituting into Eq. (3.11) $P_s(t)$ and $\langle \tau(t) \rangle$ obtained by numerically inverting the Laplace transform of these functions given by Eqs. (3.10) and (3.14), respectively. This can be done for arbitrary values of the system parameters D_s , D_b , L , k , and κ , including the case of anomalous diffusion ($L = \infty$).

The mean square displacement is a monotonically increasing function of time. Its growth rate, denoted by $4D_{eff}(t)$,

$$\frac{d \langle r^2(t) \rangle}{dt} = 4D_{eff}(t), \quad (5.19)$$

where $D_{eff}(t)$ is the time-dependent effective diffusivity, shows a rich behavior. As time increases from zero to infinity, $D_{eff}(t)$ varies from D_s at $t = 0$ to its long time asymptotic behavior given by

$$D_{eff}(t) = D_{eff}^{conv} \frac{d(t P_s(t))}{dt}, \quad t \rightarrow \infty. \quad (5.20)$$

In the rest of this section, we discuss the time dependence of the ratio $D_{eff}(t)/D_s$. The Laplace transform of the ratio $D_{eff}(t)/D_s$ is related to the Laplace transform of the mean square displacement by the relation

$$\frac{\hat{D}_{eff}(s)}{D_s} = \frac{s \langle \hat{r}^2(s) \rangle}{4D_s}. \quad (5.21)$$

Inverting this numerically, one can find $D_{eff}(t)/D_s$ at arbitrary values of the problem parameters. The focus is on how this time dependence changes when we change the bulk layer thickness, L , and the ratio of the bulk and surface diffusivities, D_b/D_s .

Since the particle escapes from the surface, the ratio $D_{eff}(t)/D_s$ always monotonically decreases from unity at short times. If the bulk and surface diffusivities are equal, $D_b = D_s$, the ratio $D_{eff}(t)/D_s$ is identical to the probability of finding the particle on the surface at time t ,

$$\frac{D_{eff}(t)}{D_s} = P_s(t), \quad (5.22)$$

whose time-dependent behavior at several values of L is illustrated in Fig. 2. As follows from Eq. (5.7), the ratio exceeds unity as $t \rightarrow \infty$, when the inequality

$$\frac{D_b}{D_s} > 2 + \frac{kL}{\kappa} \quad (5.23)$$

is fulfilled. As a consequence, in such a case, $D_{eff}(t)/D_s$ is a non-monotonic function of time, having a minimum at short times. However, the ratio may have a non-monotonic time behavior even when the inequality in Eq. (5.23) is violated. This happens when the diffusivity ratio D_b/D_s is large enough.

The time behavior of the ratio $D_{eff}(t)/D_s$ is illustrated in Figs. 4 and 5, taking that $k = \kappa = 1$ in dimensionless units. Figure 4 shows the ratio in the absence of the reflecting lid ($L = \infty$) for $D_b/D_s = 1, 30, 60, 90$, and 120. One can see that

FIG. 4. The time dependences of the effective diffusivity, $D_{\text{eff}}(t)$, in the absence of the reflecting lid ($L = \infty$) at different values of D_b , which are given near the curves. The dependences are obtained by numerically inverting the Laplace transform in Eq. (5.21), using the Stehfest algorithm, with $D_s = k = \kappa = 1$ (in dimensionless units).

while the ratio monotonically decreases with time at $D_b/D_s = 1$, at higher values of D_b/D_s , $D_b/D_s = 30, 60, 90$, and 120 , the situation is qualitatively different. The ratio first decreases and reaches a minimum, then it increases and reaches

FIG. 5. The time dependences of the effective diffusivity, $D_{\text{eff}}(t)$, at $D_b = 30$ (panel (a)) and $D_b = 120$ (panel (b)) for different values of the bulk layer thickness L , which are given near the curves. The dependences are obtained by numerically inverting the Laplace transform in Eq. (5.21), using the Stehfest algorithm, with $D_s = k = \kappa = 1$. All the parameter values are given in dimensionless units.

a maximum, and then it decreases again approaching its long-time asymptotic behavior given by (see Eq. (5.13) with $k = \kappa = 1$)

$$\frac{D_{\text{eff}}(t)}{D_s} = \frac{1}{2D_s} \sqrt{\frac{D_b}{\pi t}}, \quad t \rightarrow \infty. \quad (5.24)$$

Figure 5(a) shows the time dependence of the ratio $D_{\text{eff}}(t)/D_s$ for several values of the bulk layer thickness, $L = 0.1, 0.2, 1, 5, 10, 15$, and ∞ , at a fixed value of $D_b/D_s = 30$. While at $L = 0.1, 0.2, 1, 5, 10$, and 15 the dependences have only one extremum, a minimum at short times, at $L = \infty$, the dependence has two extrema, a short time minimum and a maximum at later times. Finally, at $L = 25$, the dependence has three extrema. At relatively short times, this dependence is practically indistinguishable from that at $L = \infty$ and has two extrema, a minimum and a maximum. The difference between the two dependences manifests itself at more later times, where the dependence at $L = 25$ has the second minimum. Similar time dependences are shown in Fig. 5(b) for $D_b/D_s = 120$ and $L = 30, 40, 60, 90$, and ∞ . A distinctive feature of the dependences at $L = 40, 60$, and 90 is that they have three extrema: two minima separated by a maximum, while other curves have one ($L = 30$) or two ($L = \infty$) extrema. To summarize, the time dependence $D_{\text{eff}}(t)/D_s$ has three extrema when both D_b/D_s and L are large enough.

VI. THE PROPAGATOR

In this section, we establish a relation between the Fourier-Laplace transform of the propagator $G(\mathbf{r}, t)$, Eq. (3.3), and the double Laplace transform of the conditional probability density $v_s(\tau|t)$ of the cumulative time τ spent by the particle on the surface, on the condition that it is on the surface at $t = 0$ and at time t .

The Fourier transform of the propagator $G(\mathbf{r}, t)$, denoted by $G(\mathbf{q}, t)$, is defined as

$$G(\mathbf{q}, t) = \iint e^{i\mathbf{q}\mathbf{r}} G(\mathbf{r}, t) d\mathbf{r}. \quad (6.1)$$

Using Eq. (3.3), we can write $G(\mathbf{q}, t)$ in terms of the Fourier transform of the lateral propagator $G_l(\mathbf{r}, t|\tau)$, which is denoted by $G_l(\mathbf{q}, t|\tau)$,

$$G(\mathbf{q}, t) = \int_0^t G_l(\mathbf{q}, t|\tau) v_s(\tau|t) d\tau. \quad (6.2)$$

As follows from Eq. (3.1), this Fourier transform is given by

$$G_l(\mathbf{q}, t|\tau) = \iint e^{i\mathbf{q}\mathbf{r}} G_l(\mathbf{r}, t|\tau) d\mathbf{r} = e^{-(D_s \tau + D_b(t-\tau))q^2}, \quad (6.3)$$

where $q = |\mathbf{q}|$. Substituting this expression for $G_l(\mathbf{q}, t|\tau)$ into Eq. (6.2), we obtain

$$G(\mathbf{q}, t) = e^{-D_b q^2 t} \int_0^t e^{-(D_s - D_b)q^2 \tau} v_s(\tau|t) d\tau. \quad (6.4)$$

The Fourier-Laplace transform of the propagator $G(\mathbf{r}, t)$, denoted by $\hat{G}(\mathbf{q}, s)$, is the Laplace transform of $G(\mathbf{q}, t)$

$$\hat{G}(\mathbf{q}, s) = \int_0^\infty e^{-st} G(\mathbf{q}, t) dt. \quad (6.5)$$

Substituting here $G(\mathbf{q}, t)$ in Eq. (6.4), we arrive at

$$\hat{G}(\mathbf{q}, s) = \int_0^\infty e^{-(s+D_b q^2)t} dt \int_0^t e^{-(D_s-D_b)q^2 \tau} v_s(\tau|t) d\tau. \quad (6.6)$$

Comparison with Eq. (3.5) shows that, when $D_s > D_b$, Eq. (6.6) establishes the relation between the Fourier-Laplace transform of the propagator $G(\mathbf{r}, t)$ and the double Laplace transform of the conditional probability density $v_s(\tau|t)$ of the cumulative time spent by the particle on the surface

$$\hat{G}(\mathbf{q}, s) = \hat{v}_s((D_s - D_b)q^2, s + D_b q^2), \quad D_s > D_b. \quad (6.7)$$

When $D_s < D_b$, by replacing τ in the second integral in Eq. (6.6) by $\tau' = t - \tau$, $\hat{G}(\mathbf{q}, s)$ can be written as

$$\hat{G}(\mathbf{q}, s) = \int_0^\infty e^{-(s+D_s q^2)t} dt \int_0^t e^{-(D_b-D_s)q^2 \tau'} v_s(t - \tau'|t) d\tau'. \quad (6.8)$$

Function $v_s(t - \tau|t)$ is the conditional probability density of the cumulative time τ spent in the bulk by the particle observed for time t , on the condition that the particle is on the surface at $t = 0$ and at time t . Denoting this conditional probability density by $v_b(\tau|t)$, we have

$$v_b(\tau|t) = v_s(t - \tau|t). \quad (6.9)$$

Using this, we can write Eq. (6.8) as

$$\hat{G}(\mathbf{q}, s) = \int_0^\infty e^{-(s+D_s q^2)t} dt \int_0^t e^{-(D_b-D_s)q^2 \tau} v_b(\tau|t) d\tau. \quad (6.10)$$

The double Laplace transform of $v_b(\tau|t)$, denoted by $\hat{v}_b(\sigma, s)$, is defined in the same way as the double Laplace transform of $v_s(\tau|t)$ in Eq. (3.5),

$$\begin{aligned} \hat{v}_b(\sigma, s) &= \int_0^\infty e^{-st} dt \int_0^t e^{-\sigma \tau} v_b(\tau|t) d\tau \\ &= \int_0^\infty \int_0^\infty e^{-(st+\sigma \tau)} v_b(\tau|t) d\tau dt. \end{aligned} \quad (6.11)$$

Comparison of Eqs. (6.10) and (6.11) shows that

$$\hat{G}(\mathbf{q}, s) = \hat{v}_b((D_b - D_s)q^2, s + D_s q^2), \quad D_b > D_s. \quad (6.12)$$

Thus, the Fourier-Laplace transform of the propagator $G(\mathbf{r}, t)$ can be found using functions $\hat{v}_s(\sigma, s)$ or $\hat{v}_b(\sigma, s)$, Eqs. (6.7) and (6.12), depending on whether D_s is larger than D_b or not. It is important that functions $\hat{v}_s(\sigma, s)$ or $\hat{v}_b(\sigma, s)$ can be obtained by solving a two-state problem. When the two diffusion coefficients are equal, $D_s = D_b = D$, Eqs. (6.8) and (6.10) reduce to

$$\hat{G}(\mathbf{q}, s) = \int_0^\infty e^{-(s+Dq^2)t} P_s(t) dt = \hat{P}_s(s + Dq^2). \quad (6.13)$$

Respectively, the propagator $G(\mathbf{r}, t)$ in this case is

$$G(\mathbf{r}, t) = \frac{1}{4\pi Dt} e^{-r^2/(4Dt)} P_s(t), \quad (6.14)$$

as might be expected based on common sense arguments.

VII. CONCLUDING REMARKS

In this paper, we propose a new approach to the problem of bulk-mediated surface diffusion. The approach is based on the observation that bulk-mediated particle propagation over the surface is determined by the cumulative residence times spent by the particle on the surface and in the bulk. With this in mind, we focus our analysis on the cumulative times spent by the particle in the two states. These times are random variables, the sum of which is equal to the total observation time. Therefore, the key quantity in our approach is the probability density $v_s(\tau|t)$ of the cumulative time τ spent by the particle on the surface, on condition that the particle, observed for time t , starts on the surface at $t = 0$ and is bound to the surface at time t .

It is important that it is possible to find an exact solution for the double Laplace transform of $v_s(\tau|t)$, given in Eq. (3.8), by analyzing the two-state problem of the particle transitions between the surface and the bulk layer above the surface, Eq. (2.1). With this solution in hand, one can easily determine the probability of finding the particle on the surface at time t , as well as the mean square displacement of such a particle in time t , as discussed in Sections IV and V, respectively. Moreover, there is a simple relation between the Fourier-Laplace transform of the particle propagator on the surface and the double Laplace transform of $v_s(\tau|t)$, derived in Section VI. The proposed approach is applicable for all values of the problem parameters, the dissociation and binding rate constants, k and κ , the surface and bulk diffusivities, D_s and D_b , and the bulk layer thickness L (see Fig. 1). In particular, it allows one to analyze the cases of normal and anomalous diffusion (finite and infinite L , respectively) in the framework of the same formalism, over the entire range of time including transient behavior in both regimes.

We think that one of the most interesting results obtained in the paper is the non-monotonic L -dependence of the long-time plateau value of the effective diffusivity, when $D_b > 2D_s$. As a consequence, there exists an optimal layer thickness, which makes the bulk-mediated surface propagation of the particles the most efficient. Also of importance is the existence of a universal formula for the long-time behavior of the mean square displacement, given in Eq. (5.15), which describes this quantity in both normal and anomalous diffusion regimes, where the displacement is proportional to t and $\sqrt{t}$, respectively. Another interesting result of this work is complex non-monotonic behavior of the time-dependent effective diffusivity shown in Figs. 4 and 5.

Although this study is devoted to bulk-mediated diffusion in flat geometry, the proposed approach can be easily extended to the case of cylindrical geometry considered by Chechkin *et al.*^{14,15} To do this, one only has to replace the Laplace transform of the probability density $\varphi_b(t)$ of the particle lifetime in the bulk layer given in Eq. (2.4) for flat geometry by its counterpart for cylindrical geometry. The latter can be derived in the same way as we have used in Appendix A to derive $\hat{\varphi}_b(s)$ for flat geometry.

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APPENDIX A: LAPLACE TRANSFORM OF THE PROBABILITY DENSITY $\varphi_b(t)$

To find the Laplace transform of the probability density $\varphi_b(t)$ of the particle lifetime in the bulk (see Fig. 1), consider a particle that dissociates from the surface at $t = 0$. The particle lifetime in the bulk is determined by its diffusion in the z -direction which is normal to the surface located at $z = 0$. The particle propagator in the z -direction, $G_n(z, t)$, satisfies the diffusion equation

$$\frac{\partial G_n(z, t)}{\partial t} = D_b \frac{\partial^2 G_n(z, t)}{\partial z^2}, \quad 0 < z < L \quad (\text{A1})$$

subject to the initial condition

$$G_n(z, 0) = \delta(z) \quad (\text{A2})$$

and the boundary conditions

$$D_b \frac{\partial G_n(z, t)}{\partial z} \Big|_{z=0} = \kappa G_n(0, t), \quad \frac{\partial G_n(z, t)}{\partial z} \Big|_{z=L} = 0. \quad (\text{A3})$$

The probability density $\varphi_b(t)$ is the probability flux escaping from the interval $0 < z < L$ through the partially absorbing boundary at $z = 0$ at time t ,

$$\varphi_b(t) = \kappa G_n(0, t). \quad (\text{A4})$$

As follows from Eqs. (A1)-(A3), the Laplace transform of the propagator, denoted by $\hat{G}_n(z, s)$, satisfies the equation

$$s\hat{G}_n(z, s) - \delta(z) = D_b \frac{d^2 \hat{G}_n(z, s)}{dz^2}, \quad 0 < z < L \quad (\text{A5})$$

subject to the boundary conditions

$$D_b \frac{d\hat{G}_n(z, s)}{dz} \Big|_{z=0} = \kappa \hat{G}_n(0, s), \quad \frac{d\hat{G}_n(z, s)}{dz} \Big|_{z=L} = 0. \quad (\text{A6})$$

Solving Eq. (A5) with the boundary conditions in Eq. (A6), one can find the Laplace transform of the propagator at $z = 0$, $\hat{G}_n(0, s)$. Then, one can use Eq. (A4) to find the Laplace transform of the probability density by the relation

$$\hat{\varphi}_b(s) = \kappa \hat{G}_n(0, s). \quad (\text{A7})$$

Following this way, one arrives at the expression for $\hat{\varphi}_b(s)$ given in Eq. (2.4) of the main text.

APPENDIX B: DERIVATION OF THE EXPRESSION FOR $\hat{\nu}(\sigma, s)$ IN EQ. (3.6)

The conditional probability density $\nu(\tau|t)$ of the cumulative time τ spent by the particle on the surface on condition that the particle is observed for time t , and that it is on the surface

initially ($t = 0$) and at time t , satisfies

$$\begin{aligned} \nu(\tau|t) &= S_s(t)\delta(\tau - t) + \int_0^t \varphi_s(t_1)dt_1 \\ &\times \int_0^{t-t_1} \varphi_b(t_2)\nu(\tau - t_1|t - t_1 - t_2)dt_2. \end{aligned} \quad (\text{B1})$$

The first term on the right-hand side of this equation is due to those realizations of the particle trajectory that do not escape from the surface during the observation time t . The second term is due to those realizations that escape from the surface to the bulk for the first time at time t_1 and then return to the surface at time $t_1 + t_2$. After the double Laplace transformation, defined in Eq. (3.5), Eq. (B1) takes the form

$$\hat{\nu}(\sigma, s) = \hat{S}_s(s + \sigma) + \hat{\varphi}_s(s + \sigma)\hat{\varphi}_b(s)\hat{\nu}(\sigma, s). \quad (\text{B2})$$

Solving this linear equation, and using the relation $\hat{S}_s(s) = (1 - \hat{\varphi}_s(s))/s$, which follows from the definition of $\varphi_s(t)$ in Eq. (2.3), one obtains the expression for $\hat{\nu}(\sigma, s)$ in terms of the Laplace transforms of the probability densities of the particle lifetimes on the surface and in the bulk, $\hat{\varphi}_s(s)$ and $\hat{\varphi}_b(s)$, respectively, given in Eq. (3.6).

APPENDIX C: ALTERNATIVE DERIVATION OF THE EXPRESSION FOR $\hat{P}_s(s)$ IN EQ. (3.10)

The probability $P_s(t)$ of finding the particle on the surface at time t can be written as the sum of two terms

$$P_s(t) = S_s(t) + \int_0^t \varphi_s(t_1)dt_1 \int_0^{t-t_1} \varphi_b(t_2)P_s(t - t_1 - t_2)dt_2, \quad (\text{C1})$$

where the first term is the probability that the particle has not escaped from the surface in time t , and the second term is the probability that the particle escaped from the surface at least once and later came back. After the Laplace transformation, Eq. (C1) takes the form

$$\hat{P}_s(s) = \hat{S}_s(s) + \hat{\varphi}_s(s)\hat{\varphi}_b(s)\hat{P}_s(s). \quad (\text{C2})$$

Solving this linear equation, we obtain

$$\hat{P}_s(s) = \frac{\hat{S}_s(s)}{1 - \hat{\varphi}_s(s)\hat{\varphi}_b(s)}. \quad (\text{C3})$$

Using here the relation $\hat{S}_s(s) = (1 - \hat{\varphi}_s(s))/s$, and the expression for the Laplace transform $\hat{\varphi}_s(s)$ in Eq. (3.7), we recover the expression for $\hat{P}_s(s)$ in Eq. (3.10).

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