Diffusion in multilayer media: Transient behavior of the lateral diffusion coefficient

Alexander M. Berezhkovskii[a] and George H. Weiss

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

A general formalism for treating lateral diffusion in a multilayer medium is developed. The formalism is based on the relation between the lateral diffusion and the distribution of the cumulative residence time, which the diffusing particle spends in different layers. We exploit this fact to derive general expressions which give the global and local time-dependent diffusion coefficients in terms of the average cumulative times spent by the particle in different layers and the probabilities of finding the particle in different layers, respectively. These expressions are used to generalize two recently obtained results: (a) A solution for the short-time behavior of the lateral diffusion coefficient in two layers separated by a permeable membrane obtained by a perturbation theory is extended to the entire range of time. (b) A solution for the time-dependent diffusion coefficient of a ligand, which repeatedly dissociates and rebinds to sites on a planar surface, obtained under the assumption that the medium above the surface is infinite, is generalized to allow for the medium layer of finite thickness. For the latter problem we derive an expression for the Fourier-Laplace transform of the propagator in terms of the double Laplace transform of the probability density of the cumulative residence time spent by the ligand in the medium layer. [DOI: 10.1063/1.2188394]

I. INTRODUCTION

In the present paper we analyze the lateral diffusion of a particle in a multilayer medium whose geometry is as shown in Fig. 1. The diffusion coefficient in this system will be assumed to be a function of the particle z coordinate only, $D(z)$, and independent of its lateral coordinate x. The particle transfers between layers due to its motion along the z coordinate. As a result, its lateral diffusion coefficient changes at random times which are determined by the z-coordinate motion. In consequence, the diffusion coefficient varies as a function of time from its value in the initial layer in which the particle is found to its final long-time asymptotic value given by the equilibrium average of $D(z)$.

The present analysis is devoted to a study of the transient behavior of the lateral diffusion coefficient. Our approach to the problem is based on the relation between the lateral diffusion and the distribution of the cumulative residence times, which the diffusing particle spends in different layers. We utilize the fact that particle motion along the z coordinate is assumed to be unaffected by its lateral diffusion. Because of this, the problem of lateral diffusion can be reduced to that of deriving probabilities for finding the particle in different layers at time t, a one-dimensional problem which can be solved with relative ease.

Our interest in lateral diffusion was stimulated by recent papers published by Sen[1] and Lieto *et al.*[2] The first, among other interesting results, derives the short-time behavior of

the mean-squared displacement in the lateral direction in a two-layer system separated by a permeable membrane as a function of membrane permeability. The second deals with the lateral diffusion of a ligand which repeatedly dissociates and rebinds to sites on a planar surface. The authors derived an expression for the time-dependent lateral diffusion coefficient as a function of the concentration of the binding sites on the surface and the rate constants that characterize ligand binding and dissociation of the ligand-site complexes.

Other motivating factors for the present analysis are recent experiments on morphogen transport in development, where locally secreted growth factors spread through the tissue and activate cell surface receptors to control gene expression in target cells as discussed by Vincent and Dubois.[3] In particular, recent experimental studies of pattern formation in the *Drosophila* wing imaginal disk suggested the mechanism in which secreted ligand moves by a combination of extracellular diffusion and cell surface transport mediated by cell surface molecules[4] (proteoglycans). The simplest model of this mechanism leads to the problem considered in this paper.

In the next section we develop a general formalism allowing us to express the mean-squared displacement and time-dependent diffusion coefficient in terms of the probabilities of finding the particle in different layers, and the average cumulative residence times spent by the particle in these layers. This formalism is used to generalize the results obtained in Refs. 1 and 2 in Secs. III and IV. In Sec. III we generalize the short-time solution for the lateral diffusion coefficient obtained by Sen[1] using the perturbation theory. Our solution allows one to find the behavior of the time-

[a]Permanent address: Karpov Institute of Physical Chemistry, Ul. Vorontsovo Pole 10, Moscow 103064, Russia. Electronic mail: berezh@mail.nih.gov
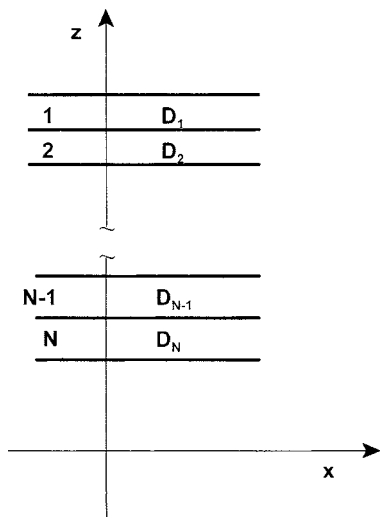
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FIG. 1. Schematic representation of an N-layer system with diffusion constants, $D_1, \ldots, D_N$.

dependent diffusion coefficient over the entire range of time by inverting a Laplace transform. In Sec. IV we generalize the solution obtained by Lieto et al.[2] assuming that the layer of the medium above the surface is infinite. We give a solution for the case of an arbitrary layer thickness. The final section generalizes the formalism to express the propagator in the system studied in Ref. [2] in terms of the probability density of the cumulative residence time, which the diffusing ligand spends in the bulk layer of the medium.

II. DEVELOPMENT OF FORMALISM

We consider the lateral diffusion of a particle in the multilayer medium shown in Fig. 1. The cumulative residence times spent by the particle in layers $1, 2, \ldots, N$ will be denoted by $\tau_1, \tau_2, \ldots, \tau_N$, respectively. By convention the initial position of the diffusing particle is at $x = 0$. The lateral propagator of the particle is given by

$$g(x|\tau_1, \tau_2, \ldots, \tau_N) = \frac{1}{\sqrt{4\pi \sum_{j=1}^{N} D_j \tau_j}}$$
$$\times \exp\left[-\frac{x^2}{4 \sum_{j=1}^{N} D_j \tau_j} \right], \quad (2.1)$$

where x is the value of the lateral coordinate at time t. This time is obviously related to the τ_i by

$$t = \sum_{j=1}^{N} \tau_j. \quad (2.2)$$

For a given trajectory of the particle along the z coordinate, $z(\tau)$, with $0 \leq \tau \leq t$, the lateral propagator can be written in generalized form as

$$g(x|t|\{z(\tau)\}) = \frac{1}{\sqrt{4\pi \int_0^t D(z(\tau)) d\tau}}$$
$$\times \exp\left[-\frac{x^2}{4 \int_0^t D(z(\tau)) d\tau} \right] \quad (2.3)$$

from which we can immediately infer that $\langle x(t) \rangle = 0$.

The Gaussian form of the propagator implies that the mean-squared displacement in the lateral direction is

$$\overline{\Delta x^2(t|\{z(\tau)\})} = 2 \int_0^t D(z(\tau)) d\tau. \quad (2.4)$$

Averaging this expression over all possible trajectories of the particle that start from $z(0) = z_0$ we obtain

$$\langle \Delta x^2(t|z_0) \rangle = 2 \int_0^t \langle D(z(\tau)) \rangle d\tau, \quad (2.5)$$

where the average $\langle D(z(t)) \rangle$ is expressed in terms of the propagator in the z direction, $G(z, t|z_0)$, as

$$\langle D(z(t)) \rangle = \int D(z) G(z, t|z_0) dz. \quad (2.6)$$

The propagator $G(z, t|z_0)$ is defined so that $G(z, t|z_0) dz$ is the probability of finding the particle between z and $z + dz$ at time t conditional on the particle being initially at $z = z_0$. The motion of the particle along the z coordinate may be described using different languages, e.g., diffusion, random walk, etc. Two examples of the z-coordinate motion are considered in Secs. III and IV. Eventually, we find for the mean-squared displacement in the x direction

$$\langle \Delta x^2(t|z_0) \rangle = 2 \int_0^t \int D(z) G(z, \tau|z_0) dz d\tau. \quad (2.7)$$

Equation (2.7) is a general expression encompassing both a continuous variation of the diffusion coefficient and the discrete layer description when one assumes that $D(z)$ is piecewise constant as is the case in the representation of the propagator in Eq. (2.1). Let the jth layer be defined by the z coordinates of its boundaries which we denote by $(z_{j,\min}, z_{j,\max})$. The probability that the particle is in layer j at time t can be expressed in terms of the propagator $G(z, t|z_0)$ as

$$P_j(t|z_0) = \int_{z_{j,\min}}^{z_{j,\max}} G(z, t|z_0) dz \quad (2.8)$$

so that, in the case of discrete layers, we can decompose Eq. (2.7) into the sum

$$\langle \Delta x^2(t|z_0) \rangle = 2 \sum_{j=1}^{N} D_j \int_0^t d\tau \int_{z_{j,\min}}^{z_{j,\max}} G(z, \tau|z_0) dz$$
$$= 2 \sum_{j=1}^{N} D_j \int_0^t P_j(\tau|z_0) d\tau. \quad (2.9)$$

The time integral on the right-hand side of this equation is

the average cumulative residence time spent by the particle in layer j, similar to that in Ref. 5,

$$\bar{\tau}_j(t|z_0) = \int_0^t P_j(\tau|z_0)d\tau, \tag{2.10}$$

so that the expression for $\langle \Delta x^2(t|z_0) \rangle$ is a direct and intuitively appealing generalization of the relation $\langle \Delta x^2(t) \rangle = 2Dt$ as follows:

$$\langle \Delta x^2(t|z_0) \rangle = 2\sum_{j=1}^N D_j \bar{\tau}_j(t|z_0). \tag{2.11}$$

We now consider the time-dependent diffusion coefficient. There are two definitions of this function to be referred to as $D_{\text{global}}(t|z_0)$ and $D_{\text{local}}(t|z_0)$. Their definitions are

$$D_{\text{global}}(t|z_0) = \frac{1}{2t}\langle \Delta x^2(t|z_0) \rangle = \sum_{j=1}^N D_j \bar{P}_j(t|z_0), \tag{2.12}$$

$$D_{\text{local}}(t|z_0) = \frac{1}{2}\frac{d}{dt}\langle \Delta x^2(t|z_0) \rangle = \sum_{j=1}^N D_j P_j(t|z_0), \tag{2.13}$$

where $\bar{P}_j(t|z_0)$ is the average probability of finding the particle in layer j,

$$\bar{P}_j(t|z_0) = \frac{1}{t}\int_0^t P_j(\tau|z_0)d\tau = \frac{\bar{\tau}_j(t|z_0)}{t}. \tag{2.14}$$

The two diffusion coefficients, $D_{\text{global}}(t|z_0)$ and $D_{\text{local}}(t|z_0)$, are related and equal to one another at both short and long times, but differ at intermediate times. At short times both are equal to the diffusion constant of the particle in the layer in which the particle is found initially. At long times the probabilities $P_j(t|z_0)$ tend to their equilibrium values, which we write as P_j^{eq}. In consequence, the two diffusion coefficients approach the asymptotic value D_{eff} given by

$$D_{\text{eff}} = \sum_{j=1}^N D_j P_j^{\text{eq}}. \tag{2.15}$$

The two diffusion coefficients in Eqs. (2.12) and (2.13) are related by

$$D_{\text{global}}(t|z_0) = \frac{1}{t}\int_0^t D_{\text{local}}(\tau|z_0)d\tau, \tag{2.16}$$

from which the identity of their behaviors at short and long times is immediately evident.

In the following two sections the formalism developed in the present section will be applied to the problems raised in Ref. 1 and 2, which are related to two-layer systems. The present work generalizes some of the results given in those papers.

III. LATERAL DIFFUSION IN TWO LAYERS SEPARATED BY A MEMBRANE

In this section we analyze lateral diffusion in two layers of thicknesses L_1 and L_2, respectively, separated by a membrane of permeability κ as shown in Fig. 2. We follow Ref. 1 in assuming that the initial coordinate z_0 is uniformly distrib-
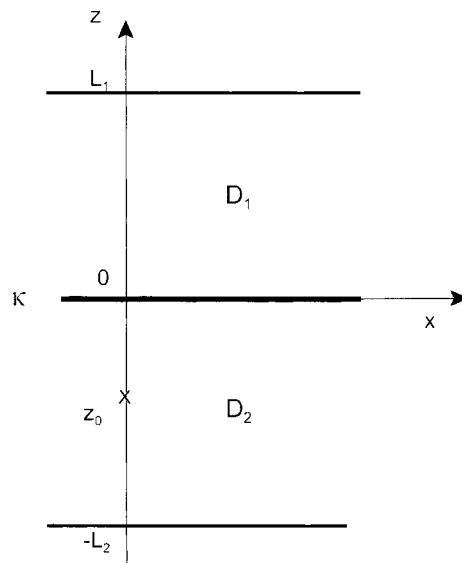

FIG. 2. A schematic representation of a two-layer system. The layers are assumed to be separated by an infinitely thin membrane of permeability κ. The initial z coordinate of the particle, z_0, is uniformly distributed over z in the lower layer of thickness L_2.

uted over z in the second layer. Our analysis generalizes the analysis of the lateral diffusion by Sen,[1] who, among other things, derived the short-time behavior of the lateral diffusion coefficient.

In the two-layer system the expression for $D_{\text{local}}(t|z_0)$ in Eq. (2.13) takes the form

$$D_{\text{local}}(t|z_0) = D_1 P_1(t|z_0) + D_2 P_2(t|z_0)$$
$$= D_1 + (D_2 - D_1)P_2(t|z_0). \tag{3.1}$$

We assume that the separating membrane is located at $z=0$ and that the particle is initially uniformly distributed in the layer whose boundaries are $z=-L_2$ and $z=0$. We will use the notation

$$\bar{h}(t) = \frac{1}{L_2}\int_{-L_2}^0 h(t|z_0)dz_0 \tag{3.2}$$

to denote the average of an arbitrary function $h(t|z_0)$ with respect to z_0. In terms of this notation we can express the average of Eq. (3.1) as

$$\bar{D}_{\text{local}}(t) = D_1 + (D_2 - D_1)\bar{P}_2(t). \tag{3.3}$$

Thus, the value of $\bar{P}_2(t)$ determines $\bar{D}_{\text{local}}(t)$.

Let $P_{12}(t)$ be the probability that the particle is in layer 1 at time t given that it was at $z=0$ initially, that is, it was just slightly below the interface in layer 2 at $t=0$. In addition, let $\varphi_{\text{FP}}(t|z_0)$ be the probability density for the first-passage time from z_0 to the separating membrane at $z=0$. Using these two functions we can write the probability $P_2(t|z_0)$ as

$$P_2(t|z_0) = 1 - \int_0^t P_{12}(t-\tau)\varphi_{\text{FP}}(\tau|z_0)d\tau. \tag{3.4}$$

Since $\bar{\varphi}_{\text{FP}}(t)$ is the averaged value of $\varphi_{\text{FP}}(t|z_0)$, it follows that $\bar{P}_2(t)$ satisfies

$$\bar{P}_2(t) = 1 - \int_0^t P_{12}(t-\tau)\bar{\varphi}_{FP}(\tau)d\tau. \tag{3.5}$$

The last equation is in convolution form, which suggests dealing with it by means of Laplace transforms. Denote the Laplace transform of an arbitrary function $h(t)$ by $\hat{h}(s)$, so that the Laplace transform of Eq. (3.5) is

$$\hat{\bar{P}}_2(s) = \frac{1}{s} - \hat{P}_{12}(s)\hat{\bar{\varphi}}_{FP}(s). \tag{3.6}$$

The Laplace transform $\hat{\bar{\varphi}}_{FP}(s)$ is derived in Appendix A and found to be

$$\hat{\bar{\varphi}}_{FP}(s) = f\left(\frac{L_2^2 s}{D_2}\right), \tag{3.7}$$

where the function $f(\xi)$ is

$$f(\xi) = \frac{\tanh(\sqrt{\xi})}{\sqrt{\xi}}. \tag{3.8}$$

The function $P_{12}(t)$ can be found in terms of the solution to the two-state non-Markovian model described by the kinetic scheme

$$1 \underset{\varphi_2(t)}{\overset{\varphi_1(t)}{\rightleftarrows}} 2, \tag{3.9}$$

where $\varphi_1(t)$ and $\varphi_2(t)$ are probability densities for individual sojourn times in layers 1 and 2, respectively, for the particle entering the corresponding layer. The required Laplace transforms are derived in Appendix B, where they are shown to be

$$\hat{\varphi}_i(s) = \frac{1}{1 + s\bar{t}_i f(L_i^2 s/D_i)}, \quad i = 1,2, \tag{3.10}$$

where the $\bar{t}_i = L_i/\kappa$ are the mean sojourn times in each of the layers. A knowledge of the two Laplace transforms is required for a derivation of the Laplace transform of $P_{12}(t)$.

The function $P_{12}(t)$ can be found either by enumerating all trajectories or else by solving an integral equation satisfied by this function. In the second case we observe that the probability that a sojourn in layer 1 lasts for a time greater than t is

$$\Phi_1(t) = \int_t^\infty \varphi_1(\tau)d\tau, \tag{3.11}$$

whose Laplace transform is $\hat{\Phi}_1(s) = [1 - \hat{\varphi}_1(s)]/s$. There are two possible scenarios in which the particle can be found in layer 1 at time t, having been just near the separating membrane in layer 2 at $t=0$. Either the particle enters layer 1 at time τ and remains there through the time $t-\tau$ or else it remains in layer 1 for some shorter time before reentering layer 2, so that the process begins over again. This is described by the integral equation

$$P_{12}(t) = \int_0^t \left[\Phi_1(t-\tau) + \int_0^{t-\tau} P_{12}(t-\tau-\tau')\varphi_1(\tau')d\tau'\right]$$
$$\times \varphi_2(\tau)d\tau, \tag{3.12}$$

which can be solved in the Laplace transform domain. That solution is found to be

$$\hat{P}_{12}(s) = \frac{[1 - \hat{\varphi}_1(s)]\hat{\varphi}_2(s)}{s[1 - \hat{\varphi}_1(s)\hat{\varphi}_2(s)]}. \tag{3.13}$$

On substituting the expressions in Eq. (3.10) for the $\hat{\varphi}_i(s)$ into this relation we find

$$\hat{P}_{12}(s) = \frac{\bar{t}_1 f(L_1^2 s/D_1)}{s[\bar{t}_1 f(L_1^2 s/D_1) + \bar{t}_2 f(L_2^2 s/D_2) + s\bar{t}_1\bar{t}_2 f(L_1^2 s/D_1)f(L_2^2 s/D_2)]}. \tag{3.14}$$

Since $\hat{\bar{\varphi}}_{FP}(s)$ is known from Eq. (3.7) and $\hat{P}_{12}(s)$ from Eq. (3.14), the function $\hat{\bar{P}}_2(s)$ can be found from their combination in Eq. (3.6) as follows:

$$\hat{\bar{P}}_2(s) = \frac{1}{s}\left[1 - \frac{\bar{t}_1 f(L_1^2 s/D_1)f(L_2^2 s/D_2)}{\bar{t}_1 f(L_1^2 s/D_1) + \bar{t}_2 f(L_2^2 s/D_2) + s\bar{t}_1\bar{t}_2 f(L_1^2 s/D_1)f(L_2^2 s/D_2)}\right]. \tag{3.15}$$

This enables us to find both the long- and short-time behaviors of the probability of interest by passing to the limits $s \to 0$ or $s \to \infty$, respectively. In the first case we find

$$\hat{\bar{P}}_2(s) \approx P_2^{eq}/s, \quad s \to 0, \tag{3.16}$$

where the equilibrium probability P_2^{eq} is found to be

$$P_2^{eq} = \frac{\bar{t}_2}{\bar{t}_1 + \bar{t}_2} = \frac{L_1}{L_1 + L_2}. \tag{3.17}$$

Hence it follows that $\bar{D}_{local}(t) \to D_{eff}$ as $t \to \infty$, where

$$D_{\text{eff}} = \frac{D_1 L_1 + D_2 L_2}{L_1 + L_2}. \tag{3.18}$$

Similarly, the large-s behavior of $\hat{\bar{P}}_2(s)$ determines the short-time behavior of $\bar{P}_2(t)$. Since

$$\hat{\bar{P}}_2(s) \approx \frac{1}{s}\left(1 - \frac{\kappa}{L_2 s}\right), \quad s \to \infty \tag{3.19}$$

the short-time expression for this probability is

$$\bar{P}_2(t) \approx 1 - \frac{\kappa t}{L_2}, \quad t \to 0 \tag{3.20}$$

and therefore

$$\bar{D}_{\text{local}}(t) \approx D_2 + (D_1 - D_2)\frac{\kappa t}{L_2}, \quad t \to 0, \tag{3.21}$$

which is the result derived by Sen.[1]

Equation (3.18) and (3.21) give long- and short-time behaviors of the diffusion coefficient. To find $\bar{D}_{\text{local}}(t)$ over the

entire range of time one has to use Eq. (3.3) with $\bar{P}_2(t)$ as found by numerically inverting the transform $\hat{\bar{P}}_2(s)$ in Eq. (3.15). Furthermore, $\bar{D}_{\text{global}}(t)$ can be found from the relation in Eq. (2.16). The short-time behavior of $\bar{D}_{\text{global}}(t)$ can be obtained using Eq. (2.16) with the approximation to $\bar{D}_{\text{local}}(t)$ shown in Eq. (3.21). This leads to

$$\bar{D}_{\text{global}}(t) \approx D_2 + (D_1 - D_2)\frac{\kappa t}{2L_2}, \quad t \to 0. \tag{3.22}$$

On comparing the expressions in Eqs. (3.21) and (3.22) one can see the difference between the two diffusion coefficients at short times.

To conclude this section we consider the case in which there is no membrane separating the two layers, corresponding to the limit $\kappa \to \infty$. The expression for D_{eff} given in Eq. (3.18) is independent of κ, while the short-time behavior in Eq. (3.20) cannot be correct in the limit $\kappa \to \infty$. However, if one passes to that limit in Eq. (3.15) one finds that $\hat{\bar{P}}_2(s)$ takes the form

$$\hat{\bar{P}}_2(s) = \frac{1}{s}\left[1 - \frac{\sqrt{D_1 D_2}\,\tanh\sqrt{L_1^2 s/D_1}\,\tanh\sqrt{L_2^2 s/D_2}}{L_2\sqrt{s}(\sqrt{D_1}\,\tanh\sqrt{L_1^2 s/D_1} + \sqrt{D_2}\,\tanh\sqrt{L_2^2 s/D_2})}\right]. \tag{3.23}$$

At large s this can be approximated by

$$\hat{\bar{P}}_2(s) \approx \frac{1}{s}\left[1 - \frac{\sqrt{D_1 D_2}}{\sqrt{s}L_2(\sqrt{D_1} + \sqrt{D_2})}\right], \quad s \to \infty. \tag{3.24}$$

From this we infer the short-time limiting behavior

$$\bar{P}_2(t) \approx 1 - \frac{2\sqrt{D_1 D_2 t}}{\sqrt{\pi}L_2(\sqrt{D_1} + \sqrt{D_2})}, \quad t \to 0, \tag{3.25}$$

which means that

$$\bar{D}_{\text{local}}(t) \approx D_2 + \frac{2(\sqrt{D_1} - \sqrt{D_2})}{\sqrt{\pi}L_2}\sqrt{D_1 D_2 t}, \quad t \to 0. \tag{3.26}$$

This implies that in the short-time limit $\bar{D}_{\text{local}}(t) - D_2$ is proportional to t when there is a separating membrane between the two layers and to $t^{1/2}$ in the absence of a membrane.

IV. ALTERNATING SURFACE AND BULK DIFFUSIONS OF A LIGAND

In this section we generalize the analysis of lateral diffusion of a ligand as originally studied by Lieto et al.[2] That model consists of a ligand which can diffuse either on a planar surface or in an infinite medium above the surface. Our formalism will be applied to a situation in which the infinite medium is replaced by a finite medium of arbitrary thickness, L. Figure 3 illustrates the resulting system. The upper boundary of the medium layer is chosen to be a re-

flecting boundary for the diffusing ligands. We will assume, in agreement with the analysis in Ref. 2, that the ligand is initially on the surface which contains a concentration B of binding sites. Ligand-site association and dissociation of the ligand-site complexes will be described by the rate constants k_a and k_d, respectively. Ligand diffusion constants on the surface and in the bulk will be denoted by D_1 and D_2, respectively. The corresponding notations in Ref. 2 are D_A and D_C.

The diffusion coefficient $D_{\text{local}}(t)$ is again given by the expression in Eq. (3.3), where the Laplace transform of $\bar{P}_2(t)$ is that given in Eq. (3.6). However, because the two-layer system studied in the previous section now is a single-layer system, we can set $\hat{\bar{\varphi}}_{\text{FP}}(s) = 1$ in Eq. (3.6) and replacing $\hat{\bar{P}}_2(s)$ by $\hat{P}_2(s)$ we can write
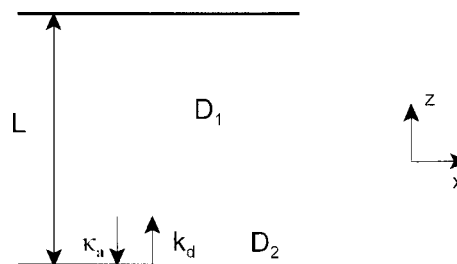

FIG. 3. A schematic representation of a bulk medium layer of thickness L above a surface which reversibly binds ligands with an effective bimolecular trapping rate κ_a and a unimolecular dissociation rate k_d.

$$\hat{P}_2(s) = \frac{1}{s} - \hat{P}_{12}(s). \tag{4.1}$$

The transform $\hat{P}_{12}(s)$ is that given in Eq. (3.13), where the value of $\hat{\varphi}_1(s)$ is to be taken from Eq. (3.10) with $\kappa = \kappa_a = k_a B$, which is the effective trapping rate of the ligand by the surface with binding sites. Furthermore, by the assumption of first-order kinetics for dissociation, $\varphi_2(t) = k_d \exp(-k_d t)$, the transform $\hat{\varphi}_2(s)$ is

$$\hat{\varphi}_2(s) = \frac{k_d}{k_d + s}. \tag{4.2}$$

Substituting the results just mentioned into the expression for $\hat{P}_2(s)$ in Eq. (4.1) we find

$$\hat{P}_2(s) = \frac{1 + s\bar{t}_1 f(L^2 s/D_1)}{s[1 + (s + k_d)\bar{t}_1 f(L^2 s/D_1)]}$$

$$= \frac{1 + (\sqrt{D_1 s}/\kappa_a)\tanh(\sqrt{L^2 s/D_1})}{s[1 + [(s + k_d)/\kappa_a]\sqrt{D_1/s}\tanh(\sqrt{L^2 s/D_1})]}, \tag{4.3}$$

where $\bar{t}_1 = L/\kappa_a$ and we have used the formula for $f(\xi)$ given in Eq. (3.8).

While Eq. (4.3) cannot be inverted in any simple closed form, approximations can be found in different limiting cases. The equilibrium value P_2^{eq} is found by expanding Eq. (4.3) around $s = 0$ and retaining the term proportional to s^{-1}. In this way it is found that

$$P_2^{eq} = \frac{1}{1 + k_d\bar{t}_1} = \frac{k_a}{k_a + k_d L} = \frac{B}{B + K_d L}, \tag{4.4}$$

where we have introduced the equilibrium dissociation constant $K_d = k_d/k_a$. The two diffusion coefficients, $D_{local}(t)$ and $D_{global}(t)$, vary from the same initial value, D_2, to the asymptotic value D_{eff}, which is

$$D_{eff} = \frac{D_1 K_d L + D_2 B}{K_d L + B}. \tag{4.5}$$

As $L \to \infty$, $P^{eq} \to 0$ as seen from Eq. (4.4) and $D_{eff} \to D_1$ as seen from the previous equation.

The Laplace transform in Eq. (4.3) can be inverted in the two limits, $L \to 0$ and $L \to \infty$. The first of these limits is defined more precisely by the requirement that the characteristic intralayer relaxation time, L^2/D_1, is much smaller than the characteristic association time, $\bar{t}_1 = L/\kappa_a$. When this condition holds we can approximate $f(L^2 s/D_1)$ by 1 that leads to

$$\hat{P}_2(s) = \frac{1 + s\bar{t}_1}{s[1 + (k_d + s)\bar{t}_1]}. \tag{4.6}$$

The corresponding approximation to $P_2(t)$ is then found to be

$$P_2(t) = P_2^{eq} + P_1^{eq} \exp\left[-(1 + k_d\bar{t}_1)\frac{t}{\bar{t}_1}\right], \tag{4.7}$$

where P_2^{eq} and $P_1^{eq} = 1 - P_2^{eq}$ are the equilibrium probabilities of finding the ligand on the surface and in the layer, respectively. If we substitute this approximation into the result for $D_{local}(t)$ in Eq. (3.1) we find

$$D_{local}(t) = D_{eff} + (D_2 - D_1)P_1^{eq} \exp\left[-(1 + k_d\bar{t}_1)\frac{t}{\bar{t}_1}\right]$$

$$= D_{eff} + (D_2 - D_{eff})\exp\left[-(1 + k_d\bar{t}_1)\frac{t}{\bar{t}_1}\right]. \tag{4.8}$$

On making use of the relation between $D_{global}(t)$ and $D_{local}(t)$ in Eq. (2.16) we also obtain

$$D_{global}(t) = D_{eff} + (D_2 - D_{eff})$$

$$\times \frac{\bar{t}_1\{1 - \exp[-(1 + k_d\bar{t}_1)(t/\bar{t}_1)]\}}{(1 + k_d\bar{t}_1)t}. \tag{4.9}$$

Another limit in which the transform in Eq. (4.3) can be inverted in closed form is $L \to \infty$, the semi-infinite space analyzed in Ref. 2. In this limit Eq. (4.3) reduces to the form

$$\hat{P}_2(s) = \frac{(\kappa_a/\sqrt{D_1}) + \sqrt{s}}{\sqrt{s}(s + \kappa_a\sqrt{s/D_1} + k_d)}. \tag{4.10}$$

This transform can be inverted by means of relations from Ref. 6. Using the relation between $D_{local}(t)$ and $P_2(t)$ given in Eq. (3.3) one finds $D_{local}(t)$ which we write in terms of the notation introduced in Ref. 2. The result for $D_{local}(t)$ can be written in terms of the function $w(i\eta)$ defined as

$$w(i\eta) = \exp(\eta^2)\text{erfc}(\eta), \tag{4.11}$$

where $\text{erfc}(\eta)$ is the complementary error function.[6] The expression is

$$D_{local}(t) = D_1 + \frac{D_2 - D_1}{b_1 - b_2}[(b + b_1)w(-ib_1\sqrt{k_d t})$$

$$- (b + b_2)w(-ib_2\sqrt{k_d t})], \tag{4.12}$$

where the dimensionless parameters b, b_1, and b_2 are defined by

$$b = \frac{\kappa_a}{\sqrt{D_1 k_d}} = \frac{B}{K_d}\sqrt{\frac{k_d}{D_1}}, \quad b_{1,2} = \frac{1}{2}(-b \pm \sqrt{b^2 - 4}). \tag{4.13}$$

By invoking the relation between $D_{global}(t)$ and $D_{local}(t)$ given in Eq. (2.16) we find

$$D_{\text{global}}(t) = D_1 + \frac{(D_2 - D_1)}{k_d t}\left\{ 2b\sqrt{\frac{k_d t}{\pi}} - b^2 + 1 \right.$$

$$+ \frac{1}{(b_1 - b_2)}[[(b^2 - 1)b_2 + b]w(-ib_1\sqrt{k_d t})$$

$$\left. - [(b^2 - 1)b_1 + b]w(-ib_2\sqrt{k_d t})]\right\}, \qquad (4.14)$$

which is the result for the time-dependent diffusion coefficient derived by Lieto et al.[2] The values of both $D_{\text{local}}(t)$ and $D_{\text{global}}(t)$ given in Eqs. (4.12) and (4.14) vary with time from D_2 to D_1 as t varies from 0 to ∞.

Our results derived to this point allow us to examine the transient behavior of the diffusion coefficients in the two limiting cases based on the layer thickness. Equations (4.8) and (4.9) represent these diffusion coefficients in the thin layer regime, i.e., $L \ll D_1/\kappa_a$, while Eqs. (4.12) and (4.14) give the solutions for $D_{\text{local}}(t)$ and $D_{\text{global}}(t)$ in the infinite thickness limit. Intermediate values of L can only be dealt with by numerically inverting the Laplace transform of $\hat{P}_2(s)$ given in Eq. (4.3). After that $D_{\text{local}}(t)$ can be found by means of Eq. (3.1) and then used in Eq. (2.16) to obtain the remaining function $D_{\text{global}}(t)$.

Our final comment relates to the equality $\kappa_a = k_a B$. When analyzing ligand binding to the sites on the surface one has to deal with an unsolvable diffusion problem. The point is that the boundary conditions on the surface are nonuniform: partially absorbing on the sites and reflecting on the rest of the surface. Moreover, the sites are randomly distributed over the surface. There is an approximation that allows one to overcome the difficulty. The trick, called boundary homogenization, is based on the replacement of the nonuniform boundary condition on the surface by a uniform radiation boundary condition in which the effective trapping rate is equal to κ_a. This converts the original unsolvable diffusion problem to a solvable one. Boundary homogenization of surfaces randomly covered by absorbing disks has been recently discussed in Ref. 7. As shown in that reference the relation $\kappa_a = k_a B$ is a special limiting case of a general formula for κ_a. The relation is applicable in the limit when $B \to 0$.

V. GENERALIZATIONS

The results obtained in previous sections can also be derived by other methods. Our formalism demonstrates the relation between lateral diffusion and the cumulative residence times spent by the diffusing particle in different layers. To further illustrate this point we now derive an expression for the Fourier-Laplace transform of the lateral propagator for the problem considered in the previous section. We give the propagator in terms of Laplace transforms of the probability densities for particle lifetimes in the bulk and on the surface. The derived expression is then used to find the effective-medium approximation for the propagator. Finally, we discuss further generalizations of the formalism.

To initiate our analysis consider particle trajectories that are initially at $x_0 = 0$ on the surface and spend a time τ out of

the total observation time t in the bulk layer. The lateral propagator based on these trajectories is a special case of the propagator in Eq. (2.1) and is explicitly

$$g(x|\tau, t - \tau|2) = \frac{\exp\{-x^2/4[D_1\tau + D_2(t - \tau)]\}}{\sqrt{4\pi[D_1\tau + D_2(t - \tau)]}}. \qquad (5.1)$$

The complete lateral propagator is the average of $g(x|\tau, t - \tau|2)$ taken over all trajectories that reach the point x at time t.

It follows from Eq. (5.1) that the average taken with respect to trajectories is equivalent to an average with respect to the time spent in the bulk, τ. To evaluate the average we assume that $D_1 > D_2$ and define a probability density $f(\tau|t|2)$, so that $f(\tau|t|2)d\tau$ is the fraction of trajectories that are originally on the surface and spend a time between τ and $\tau + d\tau$ out of the observation time t in the bulk. This function allows us to write the propagator as

$$g(x, t|2) = \int_0^t g(x|\tau, t - \tau|2)f(\tau|t|2)d\tau. \qquad (5.2)$$

Its Fourier transform with respect to x is given by

$$g(k, t|2) = \int_{-\infty}^{\infty} g(x, t|2)e^{ikx}dx$$

$$= \int_0^t e^{-k^2[D_1\tau + D_2(t - \tau)]}f(\tau|t|2)d\tau. \qquad (5.3)$$

A function which will be needed for our further analysis is the double Laplace transform of $f(\tau|t|2)$ defined as

$$\hat{f}(\lambda|\sigma|2) = \int_0^{\infty} e^{-\sigma t}dt \int_0^t e^{-\lambda\tau}f(\tau|t|2)d\tau. \qquad (5.4)$$

Having this transform allows us to write the Laplace transform of $g(k, t|2)$ as

$$\hat{g}(k, s|2) = \int_0^{\infty} e^{-st}g(k, t|2)dt$$

$$= \hat{f}(\lambda = (D_1 - D_2)k^2|\sigma = s + D_2 k^2|2), \qquad (5.5)$$

where $D_1 > D_2$. This establishes a relation between the Fourier-Laplace transform of the lateral propagator and the double Laplace transform of the probability density of the cumulative residence time in the bulk layer of the medium, which is one of the main results of the paper.

Now we derive an expression for $\hat{f}(\lambda|\sigma|2)$ in terms of the Laplace transforms of the probability densities, $\varphi_i(t)$, $i = 1, 2$, which describe the dynamics of the two-state system shown in Eq. (3.9). To do this we introduce the probability density $f(\tau|t|1)$ for the time spent in the bulk by a particle that escapes from the surface at $t = 0$ conditional on the observation time being equal to t. If we further define the survival probability in state i, which is the probability that the duration of a single sojourn in state i lasts longer than t, i.e.,

$$\Phi_i(t) = \int_t^\infty \varphi_i(\tau')d\tau', \quad i = 1,2, \tag{5.6}$$

we can then write a coupled pair of integral equations for functions $f(\tau|t|1)$ and $f(\tau|t|2)$ as follows:

$$f(\tau|t|1) = \Phi_1(t)\delta(t-\tau) + \int_0^t \varphi_1(t')f(\tau-t'|t-t'|2)dt',$$

$$\tag{5.7}$$

$$f(\tau|t|2) = \Phi_2(t)\delta(\tau) + \int_0^t \varphi_2(t')f(\tau|t-t'|1)dt'.$$

These may be solved by means of the double Laplace transform defined in Eq. (5.4), which transforms the set of equations above to the following:

$$\hat{f}(\lambda|\sigma|1) = \hat{\Phi}_1(\lambda+\sigma) + \hat{\varphi}_1(\lambda+\sigma)\hat{f}(\lambda|\sigma|2),$$

$$\tag{5.8}$$

$$\hat{f}(\lambda|\sigma|2) = \hat{\Phi}_2(\sigma) + \hat{\varphi}_2(\sigma)\hat{f}(\lambda|\sigma|1).$$

Since the Laplace transform of $\Phi_i(t)$ is

$$\mathcal{L}\{\Phi_i(t)\} = \frac{1 - \hat{\varphi}_i(s)}{s}, \tag{5.9}$$

we can eliminate $\hat{f}(\lambda|\sigma|1)$ and write the complete solution for $\hat{f}(\lambda|\sigma|2)$ as

$$\hat{f}(\lambda|\sigma|2) = \frac{\lambda + \sigma - \hat{\varphi}_2(\sigma)[\lambda + \sigma\hat{\varphi}_1(\lambda+\sigma)]}{\sigma(\lambda+\sigma)[1 - \hat{\varphi}_2(\sigma)\hat{\varphi}_1(\lambda+\sigma)]}. \tag{5.10}$$

This last equation can be used to find $\hat{g}(k,s|2)$ in Eq. (5.5) in terms of Laplace transforms of the $\varphi_i(t)$ as follows:

$$\hat{g}(k,s|2) = \frac{s + D_1k^2 - \hat{\varphi}_2(s+D_2k^2)[(s+D_2k^2)\hat{\varphi}_1(s+D_1k^2) + (D_1-D_2)k^2]}{(s+D_1k^2)(s+D_2k^2)[1 - \hat{\varphi}_1(s+D_1k^2)\hat{\varphi}_2(s+D_2k^2)]}. \tag{5.11}$$

When the Fourier parameter k is set equal to zero, $\hat{g}(0,s|2) = 1/s$ as required by the conservation of probability. In the small-s and small-k regime we can introduce the approximation

$$\hat{\varphi}_i(s+D_ik^2) \approx 1 - \bar{t}_i(s+D_ik^2), \tag{5.12}$$

where $\bar{t}_1 = L/\kappa_a$ as in Eq. (4.3) and $\bar{t}_2$ is the reciprocal of the dissociation rate, $\bar{t}_2 = 1/k_d$. This approximation is used to find the effective-medium approximation for the propagator by expanding Eq. (5.11) and retaining the lowest order terms in s and k^2. In this way we find

$$\hat{g}_{EM}(k,s|2) = \frac{1}{s + D_{eff}k^2}, \tag{5.13}$$

where D_{eff} is the effective diffusion constant given by

$$D_{eff} = \frac{D_1\bar{t}_1 + D_2\bar{t}_2}{\bar{t}_1 + \bar{t}_2}, \tag{5.14}$$

which is identical to D_{eff} in Eq. (4.5). Inverting the transform in Eq. (5.13) we may write

$$g_{EM}(x,t|2) = \frac{1}{\sqrt{4\pi D_{eff}}}\exp\left(-\frac{x^2}{4D_{eff}t}\right), \tag{5.15}$$

which describes the lateral diffusion after many transitions have been made between the bulk layer and the surface.

Finally, we give an explicit formula for the propagator $\hat{g}(k,s|2)$ in the simplest case of a thin bulk layer. Here $\varphi_1(t)$ becomes a single exponential and its Laplace transform takes the form

$$\hat{\varphi}_1(s) = \frac{1}{1 + s\bar{t}_1}. \tag{5.16}$$

Using this and the expression for $\hat{\varphi}_2(s)$ in Eq. (4.2) we can find the double transform in Eq. (5.10) as follows:

$$\hat{f}(\lambda|\sigma|2) = \frac{\bar{t}_1 + \bar{t}_2 + (\lambda+\sigma)\bar{t}_1\bar{t}_2}{\bar{t}_1(\lambda+\sigma) + \bar{t}_2\sigma + \sigma(\lambda+\sigma)\bar{t}_1\bar{t}_2}. \tag{5.17}$$

Inverting this transform (one can find some details of the inversion in Ref. 8) we find, for the probability density,

$$f(\tau|t|2) = \delta(\tau)e^{-t/\bar{t}_2} + \frac{1}{\bar{t}_2}\left[I_0\left(2\sqrt{\frac{\tau(t-\tau)}{\bar{t}_1\bar{t}_2}}\right)\right.$$
$$\left. + \sqrt{\frac{(t-\tau)\bar{t}_2}{\pi\bar{t}_1}}I_1\left(2\sqrt{\frac{\tau(t-\tau)}{\bar{t}_1\bar{t}_2}}\right)\right]$$
$$\times e^{-\tau/\bar{t}_1 - (t-\tau)/\bar{t}_2}H(t-\tau), \tag{5.18}$$

where the $I_n(y)$ are modified Bessel functions of the first kind[6] of order n and $H(y)$ is the Heaviside step function.

Using $\hat{\varphi}_1(s)$ in Eq. (5.16) and $\hat{\varphi}_2(s)$ in Eq. (4.2) we can write the propagator in Eq. (5.11) as

$$\hat{g}(k,s|2)$$

$$= \frac{\bar{t}_1 + \bar{t}_2 + (s+D_1k^2)\bar{t}_1\bar{t}_2}{(s+D_1k^2)\bar{t}_1 + (s+D_2k^2)\bar{t}_2 + (s+D_1k^2)(s+D_2k^2)\bar{t}_1\bar{t}_2}. \tag{5.19}$$

This transform of the propagator can be used to find the Laplace transform of the mean-squared displacement

$$\mathcal{L}\{\langle\Delta x^2(t)\rangle\} = -\left.\frac{\partial^2 \hat{g}(k,s|2)}{\partial k^2}\right|_{k=0}$$

$$= 2\frac{D_1\overline{t}_1 + D_2\overline{t}_2 + sD_2\overline{t}_1\overline{t}_2}{s^2(\overline{t}_1 + \overline{t}_2 + s\overline{t}_1\overline{t}_2)}. \tag{5.20}$$

This yields for the Laplace transform of $D_{\text{local}}(t)$

$$\hat{D}_{\text{local}}(s) = \frac{s}{2}\mathcal{L}\{\langle\Delta x^2(t)\rangle\} = \frac{D_1\overline{t}_1 + D_2\overline{t}_2 + sD_2\overline{t}_1\overline{t}_2}{s(\overline{t}_1 + \overline{t}_2 + s\overline{t}_1\overline{t}_2)}. \tag{5.21}$$

The inverse of this transform is just the value of $D_{\text{local}}(t)$ given in Eq. (4.8).

The formalism just developed can be generalized to be applied to particles which annihilate with the rates γ_1 and γ_2 in the bulk layer and on the surface, respectively. The propagator in Eq. (5.1) then is changed to

$$g(x|\tau, t-\tau|2)$$

$$= \frac{\exp\{-\{x^2/4[D_1\tau + D_2(t-\tau)]\} - \gamma_1\tau - \gamma_2(t-\tau)\}}{\sqrt{4\pi[D_1\tau + D_2(t-\tau)]}}. \tag{5.22}$$

The Fourier transform of this propagator averaged over τ is

$$g(k,t|2) = \int_0^t \exp\{-[(D_1k^2 + \gamma_1)\tau + (D_2k^2 + \gamma_2)$$

$$\times (t-\tau)]\}f(\tau|t|2)d\tau. \tag{5.23}$$

This has the same form as Eq. (5.3) provided that D_i in that formula is replaced by $D_i + \gamma_i/k^2$. The Fourier-Laplace transform now replaces Eq. (5.5) by

$$\hat{g}(k,s|2) = \hat{f}(\lambda = (D_1 - D_2)k^2 + \gamma_1 - \gamma_2|\sigma = s + D_2k^2$$

$$+ \gamma_2|2). \tag{5.24}$$

The same replacement can be used to generalize the expression in Eq. (5.11), which gives $\hat{g}(k,s|2)$ in terms of the Laplace transforms of the probability densities $\varphi_i(t)$, $i=1,2$. The generalized expression can be used to find the effective-medium approximation for the propagator analogous to one in Eq. (5.13), inverting which we find

$$g_{\text{EM}}(x,t|2) \approx \frac{1}{\sqrt{4\pi D_{\text{eff}}t}}\exp\left(-\frac{x^2}{4D_{\text{eff}}t} - \gamma_{\text{eff}}t\right), \tag{5.25}$$

in which $\gamma_{\text{eff}} = (\gamma_1\overline{t}_1 + \gamma_2\overline{t}_2)/(\overline{t}_1 + \overline{t}_2)$ is the effective annihilation rate.

The formalism in this section is easily modified so as to be applicable to problems in photon migration, in which one wants to estimate the width of one of the layers in a two phase medium with different optical parameters. This forms the basis of some applications of optical imaging.[9]

In summary, our analysis exploits the relation between the lateral diffusion in a multilayer medium and the distribution of cumulative residence times spent by the diffusing particle in different layers. Based on this relation we have derived general expressions for the global and local time-dependent lateral diffusion coefficients given in Eqs. (2.12) and (2.13). These expressions were then used to generalize

results for the time-dependent lateral diffusion coefficient recently obtained by Sen[1] and Lieto *et al.*[2] In addition, for the problem considered in Ref. 2 we show that the Fourier-Laplace transform of the lateral propagator can be expressed in terms of the double Laplace transform of the probability density of the residence time.

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APPENDIX A: DERIVATION OF THE LAPLACE TRANSFORM IN EQUATION (3.7)

Consider a particle diffusing along the z axis on an interval of length L. The interval is terminated by reflecting and absorbing points located at $z=L$ and $z=0$, respectively. Let $S(t|z_0)$ be the probability that the particle has not been absorbed by time t conditional on its being at z_0 at $t=0$. The probability density for the first-passage time to the absorbing point is

$$\varphi_{\text{FP}}(t|z_0) = -\frac{\partial S(t|z_0)}{\partial t}. \tag{A1}$$

The survival probability satisfies the backward diffusion equation

$$\frac{\partial S(t|z_0)}{\partial t} = D\frac{\partial^2 S(t|z_0)}{\partial z_0^2} \tag{A2}$$

subject to the initial condition $S(0|z_0)=1$ together with the boundary conditions

$$S(t|0) = \left.\frac{\partial S(t|z_0)}{\partial z_0}\right|_{z_0=L} = 0. \tag{A3}$$

Solving the problem in the Laplace transform domain one can find $\hat{S}(s|z_0)$ and then the transform of $\varphi_{\text{FP}}(t|z_0)$. This leads to

$$\hat{\varphi}_{\text{FP}}(s|z_0) = \frac{\cosh(\sqrt{s/D}(L-z_0))}{\cosh(\sqrt{s/D}L)}. \tag{A4}$$

When this is averaged with respect to a uniform distribution of z_0 according to Eq. (3.2), one finds the relation in Eq. (3.7).

APPENDIX B: DERIVATION OF $f(z)$ IN EQUATION (3.10)

We analyze a one-dimensional system similar to that in Appendix A, except that now $z=0$ is a partially absorbing point and $z=L$ is fully reflecting. Green's function of a particle that starts from the radiation boundary ($z=0$) at $t=0$, $G(z,t|0)$, satisfies

$$\frac{\partial G(z,t|0)}{\partial t} = D\frac{\partial^2 G(z,t|0)}{\partial z^2} \tag{B1}$$

together with the initial condition $G(z,0|0) = \delta(z)$ and the boundary conditions

$$\frac{\partial G(z,t|0)}{\partial z}\bigg|_{z=L} = 0, \qquad \frac{\partial G(z,t|0)}{\partial z}\bigg|_{z=0} = \frac{\kappa}{D}G(0,t|0). \tag{B2}$$

The probability density for a sojourn time on the interval, $\varphi(t)$, is equal to the flux escaping through the partially absorbing point at $t > 0$ conditional on the particle entering the interval through this point at $t=0$. That is to say

$$\varphi(t) = \kappa G(0,t|0). \tag{B3}$$

The resulting equation for Green's function in the Laplace transform domain is again a simple second-order differential equation, solving which one can eventually find the Laplace transform of $\varphi(t)$ as follows:

$$\hat{\varphi}(s) = \left[1 + \frac{\sqrt{sD}}{\kappa}\tanh\left(L\sqrt{\frac{s}{D}}\right)\right]^{-1}. \tag{B4}$$

Moments of the sojourn time can be calculated directly from this formula. The mean sojourn time is found to be

$$\bar{t} = \int_0^\infty t\varphi(t)dt = -\left.\frac{d\hat{\varphi}(s)}{ds}\right|_{s=0} = \frac{L}{\kappa}. \tag{B5}$$

This allows us to write the expression for $\hat{\varphi}(s)$ in the form

$$\hat{\varphi}(s) = \left[1 + s\bar{t}\frac{\tanh(L\sqrt{s/D})}{L\sqrt{s/D}}\right]^{-1}, \tag{B6}$$

which is the formula in Eq. (3.10).

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