Exact solution to the first-passage problem for a particle with a dichotomous diffusion coefficient

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We consider the problem of first-passage time for reaching a boundary of a particle which diffuses in one dimension and is confined to the region $x \in (0, L)$, with a diffusion coefficient that switches randomly between two states, having diffusivities that are different. Exact analytical expressions are found for the survival probability of the particle as a function of time. The survival probability has a multiexponential decay, and to characterize it, we use the average rate constant k, as well as the instantaneous rate $r(t)$. Our approach can easily be extended to the case where the diffusion coefficient takes n different values. The model should be of interest to biological processes, in which a reactant searches for a target in a heterogeneous environment, making the diffusion coefficient a random function of time. The best example for this is a protein searching for a target site on the DNA.

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I. INTRODUCTION

In a reaction event, particularly in a biological cell, the reactant searches for and finds the target site. In most cases, the process is diffusion-limited: the rate of reaction strongly depends on how fast the reacting molecule can reach the target via diffusion, which has been studied for a long time. Recently there has been considerable interest in problems in which the diffusion process is more complex. For example, the reactants may be coming together by process of subdiffusion, such as in the ring-closing reaction between the two ends of a long polymer molecule [1–3]. Recently there has been ample experimental evidence to suggest that a particle which diffuses in heterogeneous media, such as cytoplasmic environment, exhibits non-Gaussian behavior in its spatial distribution [4,5]. One possible interpretation of such behavior is that due to the structural rearrangement of the medium (e.g., cytoskeleton network) on the observational timescales, the particle experiences different local environments in each of its visits to the target location. As a result, its diffusivity is a random function of time and can be characterized on a longer timescale by its equilibrium (average) value. This idea was introduced by Chubynsky and Slater as the "diffusing diffusivity" model [6] and has been further extended by many groups [7–11]. In Refs. [7,12], the diffusivity is modeled as the square of Ornstein-Uhlenbeck process (OUP), or as a Feller process, which means the diffusivity can take an arbitrary positive value at any time instant. As reported in Refs. [9,13], there are situations where the diffusivity needs to be modeled as a two-state process or dichotomous noise where it can have two values, and it switches between them randomly [3,14]. Of particular interest is the two-state model because it is often used in describing biochemical processes [15–17]. In the literature of nuclear magnetic resonance spectroscopy, it is known as the Kräger [14] model. In the following, we discuss a few specific cases which partially serve as the motivation for our present study.

Gene expression is a complex biochemical process which involves multiple steps. During transcription, the process is initiated only after protein molecules, generally referred to as the transcription factor (TF), bind to a specific DNA sequence known as the promoter. As described in the famous Berg-Hippel facilitated diffusion model [18–22], locating the promoter or the target by a protein molecule consists of a sequence of events involving the excursion of the protein, namely, its three-dimensional (3D) diffusion in cytoplasmic environment, one-dimensional (1D) microhopping along a DNA segment, intersegmental transfer in a DNA loop, and 1D sliding along the DNA chain. Among these, 1D sliding is greatly affected by the heterogeneity, which mainly arises from the variable interaction between protein molecule and the DNA contour (with its varying nucleotide sequence) and the internal fluctuation of DNA. Many studies suggest that during the search, depending on the binding strength of protein-DNA sites, the protein can exist in two different conformations: "search" and "recognition" modes [15,23–25]. Only in the recognition mode can the protein identify a target, but because of the specific binding to a DNA site with a strong interaction it engenders slow diffusive motion. While binding nonspecifically in the search mode, the protein moves faster with a higher diffusivity. Some theoretical studies have shown that under certain conditions conformational transition may assist in searching with a faster rate [26,27]. Another interesting aspect of the investigation into searching is the effect of environmental heterogeneity, specifically here, the internal dynamics of the DNA backbone [28]. Single-molecule experiments on proteins (e.g., LacI repressor or Rad51) diffusing along a linear DNA track have found that binding rate to the target during 1D sliding is much larger than the Smoluchowski limit, and the diffusion coefficients for different trajectories are distributed over a large span, hinting at the heterogeneous nature of the environment [29,30]. Another interesting experiment by Van den Broek *et al.* is on the association of EcoRV enzymes to a

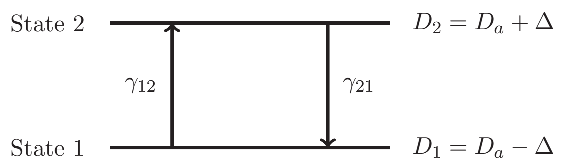

FIG. 1. The switching process and the associated rates.

recognition site along a DNA chain [31]. They observed that the association rate in a coiled DNA is almost twofold higher than the one in a fully stretched DNA configuration. A few groups have analyzed the result theoretically [32–34], and it appears that there are more processes (e.g., intersegmental transfer) involved other than configurational fluctuations of the DNA backbone responsible for the enhancement of the rate. Nonetheless, it is interesting in its own right to understand the impact of heterogeneity induced by internal fluctuations of the DNA chain on the search rate.

In this paper, we therefore revisit the age-old problem of searching, but with a variation. We consider the first-passage problem of a particle diffusing in one dimension confined to some region (bounded or semi-infinite domain) [35,36], with the particle switching randomly between two states having different diffusivities. Note that, in Refs. [37,38], similar studies have been performed where the heterogeneity is incorporated through the OUP model or the Feller process. It is worth mentioning that the present model can be applied to any generic model for heterogeneous media and can easily be extended to any dimensionality.

The plan of the paper is as follows. In Sec. II we discuss the model for diffusivity and formulate the propagator for the dynamical evolution of the probability distribution of the particle. In Sec. III the results for the survival probability, the rate constant, and the absorption rate are discussed. In Sec. III A 2 we consider the case where the particle starts with a definite initial position x_0 at the time $t = 0$ and absorption happens at both the ends. In Sec. III A 3 the case where the initial position is distributed uniformly in the interval $(0, L)$ is considered. In Sec. III B the absorption takes place only at one end. In Sec. III C we consider the case where diffusion is in the semi-infinite interval $(0, \infty)$ with absorption at $x = 0$. In Sec. IV a summary of the findings is provided.

II. MODEL FOR DICHOTOMOUS DIFFUSIVITY AND THE SOLUTION FOR THE FIRST-PASSAGE PROBLEM

Consider a particle undergoing diffusional motion in one dimension, in a region of length L. We assume that the particle can switch between two states, in which its diffusion coefficients are different. So its diffusivity is a stochastic two-value quantity that takes the values D_1 and D_2 with $D_2 > D_1$. It switches between these two values with rate γ_{12} from the state 1 to the state 2 and rate γ_{21} in the opposite direction (see Fig. 1). The instantaneous diffusion coefficient, $D(t)$, at the time t may thus be written as

$$D(t) = D_a + \sigma(t)\Delta, \tag{1}$$

where $D_a = \frac{1}{2}(D_1 + D_2)$, $\Delta = \frac{1}{2}(D_2 - D_1)$, and $\sigma(t)$ is the telegraphic noise, taking the values $\sigma(t) = \pm 1$. The moments of $\sigma(t)$ are given by [39]

$$\bar{\sigma} = \langle \sigma(t) \rangle = \frac{\gamma_{12} - \gamma_{21}}{\gamma_{12} + \gamma_{21}} \tag{2}$$

and

$$\langle \sigma(t_1)\sigma(t_2) \rangle = \bar{\sigma}^2 + \frac{4\gamma_{12}\gamma_{21}}{\gamma^2}\, e^{-\gamma|t_2 - t_1|}, \tag{3}$$

where $\gamma = \gamma_{12} + \gamma_{21}$.

The evolution of the probability density function (PDF) $P(x, t)$ for the particle is described by the diffusion equation

$$\frac{\partial P(x,t)}{\partial t} = D(t)\frac{\partial^2 P(x,t)}{\partial x^2}. \tag{4}$$

The above can be written using the operator notation as

$$\frac{\partial}{\partial t}|P(t)\rangle = -D(t)\hat{\mathcal{H}}|P(t)\rangle, \tag{5}$$

with $\mathcal{H} = -\frac{\partial^2}{\partial x^2}$. The solution of the equation, formally, is

$$|P(t)\rangle = e^{-\int_0^t ds D(s)\hat{\mathcal{H}}}|P(0)\rangle, \tag{6}$$

where $|P(t)\rangle$ denotes the state of the system at the time t, defined such that $\langle x|P(t)\rangle = P(x,t)$. The operator $\hat{\mathcal{H}}$ is Hermitian, and it has a complete set of orthonormal eigenfunctions $|m\rangle$ with real eigenvalues, determined by the boundary conditions imposed on the problem. From Eq. (6) we get

$$\begin{aligned} P(x,t) = \langle x|P(t)\rangle &= \langle x|e^{-\int_0^t ds D(s)\hat{\mathcal{H}}}|P(0)\rangle \\ &= \int dx_i\, \langle x|e^{-\int_0^t ds D(s)\hat{\mathcal{H}}}|x_i\rangle\langle x_i|P(0)\rangle \\ &= \int dx_i\, G(x,t|x_i,0)P(x_i,0). \end{aligned} \tag{7}$$

In the second step of the above, we use the resolution of identity: $\int dx_i|x_i\rangle\langle x_i| = 1$, and in the last step, the propagator $G(x,t|x_i,0)$ is defined by $G(x,t|x_i,0) = \langle x|e^{-\int_0^t ds D(s)\hat{\mathcal{H}}}|x_i\rangle$. Using the property of completeness, i.e., $\sum_{m=1}^{\infty}|m\rangle\langle m| = 1$, the propagator can be rewritten as

$$\begin{aligned} G(x,t|x_i,0) &= \sum_{m=1}^{\infty}\langle x|m\rangle e^{-\int_0^t ds D(s)\lambda_m}\langle m|x_i\rangle \\ &= \sum_{m=1}^{\infty}\phi_m^*(x_i)e^{-\lambda_m\int_0^t ds D(s)}\phi_m(x). \end{aligned} \tag{8}$$

$\phi_m(x) = \langle x|m\rangle$ is the mth eigenfunction in position space, and its conjugate, $\phi_m^*(x) = \langle m|x\rangle$. As the diffusivity $D(s)$ is a random function of time, one needs to take the average of Eq. (8) over all realizations of $D(s)$, which we shall indicate as $\langle\cdots\rangle_{D(s)}$. The averaged propagator is

$$G(x,t|x_i,0) = \sum_{m=1}^{\infty}\phi_m^*(x)\big\langle e^{-\lambda_m\int_0^t ds D(s)}\big\rangle_{D(s)}\phi_m(x_i). \tag{9}$$

Hereafter, with the notation $G(x,t|x_i,0)$ and $P(x,t)$, we refer to the ensemble-averaged propagator [Eq. (9)] and PDF [obtained from Eq. (7) using the propagator given in Eq. (9)], respectively.

III. SURVIVAL PROBABILITY AND AVERAGE RATE IN A FINITE DOMAIN

A. Survival with absorption at both ends

1. The propagator

We now consider the model known as the Oster-Nishijima model [40], in which the particle diffuses in one dimension, with its position $x \in [0, L]$. The particle is absorbed whenever it reaches the boundaries of this region. This means that the probability distribution $P(x,t)$ obeys the boundary conditions

$$P(0,t) = P(L,t) = 0. \tag{10}$$

In this case, the normalized eigenfunctions are

$$\phi_m(x) = \sqrt{\frac{2}{L}}\sin\left(\frac{m\pi x}{L}\right), \tag{11}$$

with $m = 1, 2, 3, \dots$ and associated eigenvalues are given by

$$\lambda_m = \frac{m^2\pi^2}{L^2}. \tag{12}$$

So from Eq. (9), the propagator is

$$G(x,t|x_i,0) = \frac{2}{L}\sum_{m=1}^{\infty}\sin\left(\frac{m\pi}{L}x\right)\left\langle e^{-\lambda_m\int_0^t ds D(s)}\right\rangle_{D(s)} \times \sin\left(\frac{m\pi}{L}x_i\right). \tag{13}$$

It is easy to see that the above analysis is valid even in cases where there is reflection at one end, rather than being absorbed. All that one needs to do is to modify the eigenfunctions and eigenvalues of the operator $\hat{\mathcal{H}}$ so as to suit the problem.

2. The particle starts at x_0

Here we take the particle to be initially located at x_0, so that the probability distribution of its initial position x_i is given by $P(x_i, 0) = \delta(x_i - x_0)$. The survival probability $\mathcal{S}(t)$ of the particle after a time t is then given by

$$\mathcal{S}(t) = \int_0^L dx\, P(x,t) \tag{14}$$

$$= \frac{2}{L}\sum_{m=1}^{\infty}\int_0^L dx \sin\left(\frac{m\pi}{L}x\right)\langle e^{-\lambda_m\int_0^t dsD(s)}\rangle_{D(s)} \times \int_0^L dx_i \sin\left(\frac{m\pi}{L}x_i\right)\delta(x_i - x_o)$$

$$= \frac{4}{\pi}\sum_{m=0}^{\infty}\frac{\sin\left[\frac{(2m+1)\pi}{L}x_o\right]}{2m+1}\left\langle e^{-\lambda_{2m+1}\int_0^t dsD(s)}\right\rangle_{D(s)}. \tag{15}$$

For the dichotomous noise, the quantity $\langle e^{-\lambda\int_0^t dsD(s)}\rangle_{D(s)}$ for constant λ can be easily found as demonstrated in the Appendix (see also Refs. [14,41,42]). The method given in the Appendix is valid, even for the most general case where the diffusion coefficient takes n different values $D_1, D_2, \dots, D_n$. For a dichotomous diffusion coefficient, it is given by

$$\langle e^{-\lambda\int_0^t dsD(s)}\rangle_{D(s)} = \frac{1}{2}\left(1 - \frac{\theta_3}{\theta_2}\right)e^{-(\theta_1+\theta_2)t} + \frac{1}{2}\left(1 + \frac{\theta_3}{\theta_2}\right)e^{-(\theta_1-\theta_2)t}, \tag{16}$$

where $\theta_1 = D_a\lambda + \frac{1}{2}(\gamma_{12} + \gamma_{21})$, $\theta_2 = \frac{1}{2}\sqrt{[2\lambda\Delta + (\gamma_{21} - \gamma_{12})]^2 + 4\gamma_{12}\gamma_{21}}$, and $\theta_3 = \frac{1}{2}(\gamma_{12} + \gamma_{21}) - \frac{\gamma_{12}-\gamma_{21}}{\gamma_{12}+\gamma_{21}}\lambda\Delta$.

Now we define dimensionless variables by $\bar{t} = tD_a/L^2$, $\bar{\gamma} = \gamma L^2/D_a$, $\bar{\gamma}_{12} = \gamma_{12}/\gamma$, $\bar{\gamma}_{21} = \gamma_{21}/\gamma$, $\bar{\Delta} = \Delta/(D_a\bar{\gamma})$, $\bar{x}_0 = x_0/L$ and use Eqs. (15) and (16) to get the expression for the survival probability as a function of the dimensionless variable $\bar{t}$:

$$\mathcal{S}(\bar{t}) = \frac{4}{\pi}\sum_{m=0}^{\infty}\frac{\sin[(2m+1)\pi\,\bar{x}_o]}{2m+1}\left[\frac{1}{2}\left(1 - \frac{\bar{\theta}_3}{\bar{\theta}_2}\right)e^{-(\bar{\theta}_1+\bar{\theta}_2)\bar{t}} + \frac{1}{2}\left(1 + \frac{\bar{\theta}_3}{\bar{\theta}_2}\right)e^{-(\bar{\theta}_1-\bar{\theta}_2)\bar{t}}\right]. \tag{17}$$

Here $\bar{\theta}_1 = (2m+1)^2\pi^2 + \frac{\bar{\gamma}}{2}$, $\bar{\theta}_2 = \frac{1}{2}\sqrt{[2(2m+1)^2\pi^2\bar{\Delta}\bar{\gamma} + \bar{\gamma}(\bar{\gamma}_{21} - \bar{\gamma}_{12})]^2 + 4\bar{\gamma}^2\bar{\gamma}_{12}\bar{\gamma}_{21}}$ and $\bar{\theta}_3 = \frac{\bar{\gamma}}{2} - (2m+1)^2\pi^2\bar{\Delta}\bar{\gamma}(\bar{\gamma}_{12} - \bar{\gamma}_{21})$. Equation (17) shows that the probability density decays in a multiexponential fashion. Therefore, we calculate the average rate constant $\bar{k}$ for absorption, defined by [40]

$$\bar{k} = \frac{1}{\int_0^\infty d\bar{t}\,\mathcal{S}(\bar{t})}. \tag{18}$$

Note that the first-passage time ($\bar{t}_{FP}$) is related to $\bar{k}$ by $\bar{t}_{FP} = 1/\bar{k}$. It is also useful to define a time-dependent rate $r(t)$ by

$$r(t) = -\frac{\partial\mathcal{S}(t)}{\partial t}. \tag{19}$$

a. Constant diffusivity. For normal diffusion, diffusion coefficient $D(\bar{t}) = \bar{D}_0$, which is a constant, the survival probability, from Eq. (17), is given by (the subscript 0 is used for the normal diffusion case)

$$\mathcal{S}_0(\bar{t}) = \frac{4}{\pi}\sum_{m=0}^{\infty}\frac{\sin[(2m+1)\pi\,\bar{x}_o]}{2m+1}e^{-(2m+1)^2\pi^2\bar{D}_0\bar{t}}. \tag{20}$$

So the time-averaged rate constant $\bar{k}_0$, defined by $\bar{k}_0^{-1} = \int_0^\infty d\bar{t}\mathcal{S}_0(\bar{t})$ can be written as

$$\frac{1}{\bar{k}_0} = \frac{1}{\bar{D}_0}\frac{4}{\pi^3}\sum_{m=0}^{\infty}\frac{\sin[(2m+1)\pi\bar{x}_o]}{(2m+1)^3}. \tag{21}$$

For $\bar{x}_0 = 1/2$, the sum can be exactly evaluated and is found to be $\bar{k}_0 = 8\bar{D}_0$. The average rate is proportional to the diffusion coefficient, as expected.

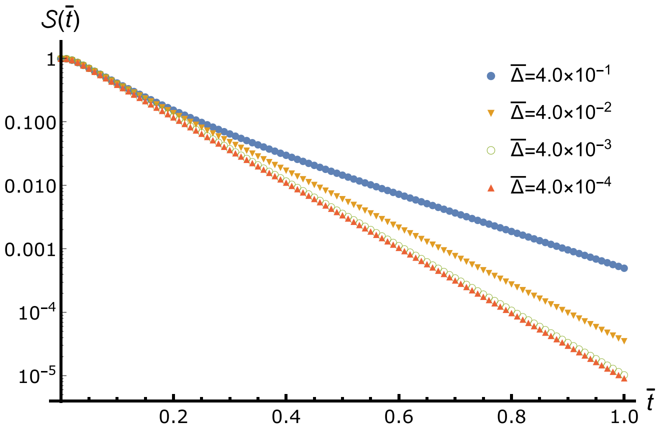

FIG. 2. The survival probability $\mathcal{S}(\bar{t})$ of a particle starting at $\bar{x}_0 = 1/2$ (at the center of the box), plotted as a function of time $\bar{t}$ on logarithmic scale for different values of $\bar{\Delta}$ taking the mean diffusivity constant at $\bar{D} = 1.20$. The plots are obtained using Eq. (22) by summing numerically the eigenmodes up to $m = 300$. The values of Poisson rates are taken as $\bar{\gamma}_{12} = 3/4,\ \bar{\gamma}_{21} = 1/4$.

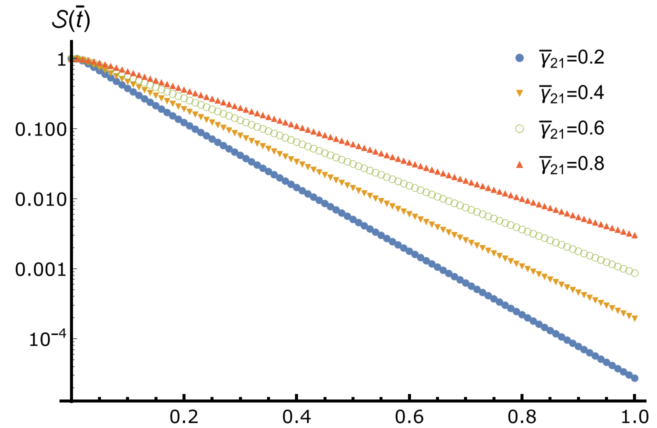

FIG. 3. The plot of survival probability $\mathcal{S}(\bar{t})$ on logarithmic scale as a function of time $\bar{t}$ for different values of $\bar{\gamma}_{21}$ taking the initial position of the particle at $\bar{x}_0 = 1/2$. The values of the parameters used for the numerical computation of Eq. (22) are $\bar{\Delta} = 1/20$, $\bar{\gamma} = 10$.

b. Dichotomous diffusivity. For dichotomous diffusivity, by virtue of Eq. (17), the survival probability can be written explicitly as

$$\mathcal{S}(\bar{t}) = \frac{4}{\pi}\sum_{m=0}^{\infty}\frac{\sin[(2m+1)\pi\,\bar{x}_o]}{2m+1}\left\{\frac{1}{2} - \frac{\frac{\bar{\gamma}}{2} - (2m+1)^2\pi^2\bar{\Delta}\bar{\gamma}(\bar{\gamma}_{12}-\bar{\gamma}_{21})}{\sqrt{[2(2m+1)^2\pi^2\bar{\Delta}\bar{\gamma} + \bar{\gamma}(\bar{\gamma}_{21}-\bar{\gamma}_{12})]^2 + 4\bar{\gamma}^2\bar{\gamma}_{12}\bar{\gamma}_{21}}}\right\}$$
$$\times\, e^{-\left\{2m+1)^2\pi^2 + \frac{\bar{\gamma}}{2} + \frac{1}{2}\sqrt{[2(2m+1)^2\pi^2\bar{\Delta}\bar{\gamma} + \bar{\gamma}(\bar{\gamma}_{21}-\bar{\gamma}_{12})]^2 + 4\bar{\gamma}^2\bar{\gamma}_{12}\bar{\gamma}_{21}}\right\}\bar{t}}$$
$$+ \frac{4}{\pi}\sum_{m=0}^{\infty}\frac{\sin[(2m+1)\pi\,\bar{x}_o]}{2m+1}\left\{\frac{1}{2} + \frac{\frac{\bar{\gamma}}{2} - (2m+1)^2\pi^2\bar{\Delta}\bar{\gamma}(\bar{\gamma}_{12}-\bar{\gamma}_{21})}{\sqrt{[2(2m+1)^2\pi^2\bar{\Delta}\bar{\gamma} + \bar{\gamma}(\bar{\gamma}_{21}-\bar{\gamma}_{12})]^2 + 4\bar{\gamma}^2\bar{\gamma}_{12}\bar{\gamma}_{21}}}\right\}$$
$$\times\, e^{-\left\{(2m+1)^2\pi^2 + \frac{\bar{\gamma}}{2} - \frac{1}{2}\sqrt{[2(2m+1)^2\pi^2\bar{\Delta}\bar{\gamma} + \bar{\gamma}(\bar{\gamma}_{21}-\bar{\gamma}_{12})]^2 + 4\bar{\gamma}^2\bar{\gamma}_{12}\bar{\gamma}_{21}}\right\}\bar{t}}. \tag{22}$$

We compare this with the case of normal diffusion having a diffusion coefficient which is the average value of $D(t)$ for switching diffusion as given by $\langle D(t)\rangle = D_a + \langle\sigma\rangle\Delta$. We denote the average diffusivity as $\bar{D}$ after redefining it as $\bar{D} = \langle D(t)\rangle/D_a = 1 + \bar{\Delta}\bar{\gamma}(\bar{\gamma}_{12} - \bar{\gamma}_{21})$. So the value of $\bar{D}_0$ is taken to be $\bar{D}_0 = \bar{D} = 1 + \bar{\Delta}\bar{\gamma}(\bar{\gamma}_{12} - \bar{\gamma}_{21})$. Note that the relation $D_2 \geqslant D_1 \geqslant 0$ ensures that $\bar{\Delta}\bar{\gamma} \leqslant 1$.

We evaluate the sum in Eq. (22) numerically by taking the first 300 eigenstates. Plots of the resultant survival probabilities as functions of time are given in Figs. 2–4. In Fig. 2 the small $\bar{\Delta}$ value corresponds to the case where the difference in the diffusion coefficients between the two states is small and the system approaches normal diffusion. The chance of survival is the least in this case. The multiexponentiality is clearer in the case where the value of $\bar{\Delta}$ is larger. In Fig. 3 the survival probabilities are plotted for different values of the Poisson rate $\bar{\gamma}_{21}$. Note that $\bar{\gamma}_{12} + \bar{\gamma}_{21} = 1$. For larger values of $\bar{\gamma}_{21}$, the particle spends more time in the state with lower diffusivity, and hence the mean diffusivity $\bar{D}$ has lower values. Consequently, the particle has higher survival probabilities. The effect of initial position is illustrated in Fig. 4. Evidently, the chance of survival is smaller if the particle initially starts nearer to a sink.

By virtue of Eqs. (18) and (22), the mean rate constant, $\bar{k}$, can be calculated, and it reads

$$\frac{1}{\bar{k}} = \frac{4}{\pi}\sum_{m=0}^{\infty}\frac{\sin[(2m+1)\pi\bar{x}_o]}{2m+1}\,\frac{(2m+1)^2\pi^2[1-\bar{\Delta}\bar{\gamma}(\bar{\gamma}_{12}-\bar{\gamma}_{21})] + \bar{\gamma}}{\left[(2m+1)^2\pi^2 + \frac{\bar{\gamma}}{2}\right]^2 - \left[(2m+1)^2\pi^2\bar{\Delta}\bar{\gamma} + \frac{\bar{\gamma}}{2}(\bar{\gamma}_{21}-\bar{\gamma}_{12})\right]^2 - \bar{\gamma}^2\bar{\gamma}_{12}\bar{\gamma}_{21}}. \tag{23}$$

The above sum is evaluated numerically and is plotted in Figs. 5–7. From Fig. 5, one finds that $\bar{k} < \bar{k}_0$, indicating that the average rate of absorption is smaller when the diffusivity fluctuates. Figure 6 shows that the rate constant $\bar{k}$ decays

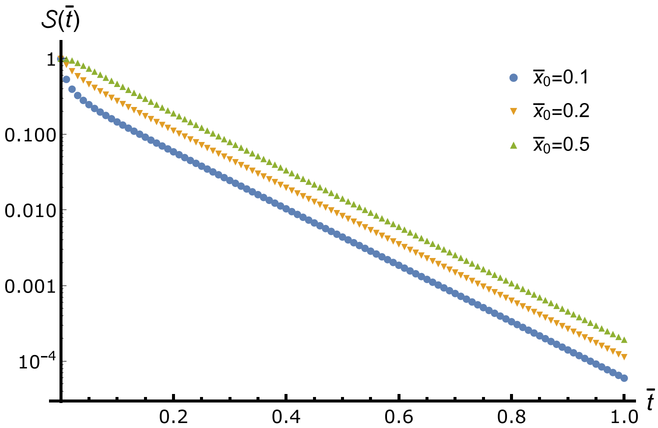

FIG. 4. Logarithmic plot of survival probability as a function of time $\bar{t}$ for different values of initial position $\bar{x}_0$ for a fixed mean diffusivity of $\bar{D} = 1.10$. The other parameters used for the numerical computation of Eq. (22) are $\bar{\Delta} = 1/20,\ \bar{\gamma}_{12} = 3/5$.

monotonically with $\bar{\Delta}$ for $\bar{\gamma}_{21} \geqslant \bar{\gamma}_{12}$. This is because of the decrease in the mean diffusivity of the particle. Figure 7 demonstrates the dependence of initial position $\bar{x}_0$ on $\bar{k}$. The minimum of $\bar{k}$ occurs at $\bar{x}_0 = 1/2$ irrespective of the values of Poisson rates. Interestingly, the rate constant $\bar{k}$ can be evaluated exactly if $\bar{x}_0 = 1/2$. In this case Eq. (23) simplifies to

$$\begin{aligned}\frac{1}{\bar{k}} &= \frac{4}{\pi}\sum_{m=0}^{\infty}\frac{(-1)^m}{2m+1}\,\frac{(2m+1)^2\pi^2[1-\bar{\Delta}\bar{\gamma}(\bar{\gamma}_{12}-\bar{\gamma}_{21})]+\bar{\gamma}}{(2m+1)^2\pi^2[(1-\bar{\Delta}^2\bar{\gamma}^2)(2m+1)^2\pi^2+\bar{D}\bar{\gamma}]}\\
&= \frac{4}{\pi}\sum_{m=0}^{\infty}\frac{(-1)^m}{2m+1}\,\frac{1-\bar{\Delta}\bar{\gamma}(\bar{\gamma}_{12}-\bar{\gamma}_{21})}{(1-\bar{\Delta}^2\bar{\gamma}^2)(2m+1)^2\pi^2+\bar{D}\bar{\gamma}}\\
&\quad+\frac{4}{\pi^3}\sum_{m=0}^{\infty}\frac{(-1)^m}{(2m+1)^3}\,\frac{\bar{\gamma}}{(1-\bar{\Delta}^2\bar{\gamma}^2)(2m+1)^2\pi^2+\bar{D}\bar{\gamma}}\\
&= \frac{1}{8\bar{D}}+\frac{4\bar{\Delta}^2\bar{\gamma}\bar{\gamma}_{12}\bar{\gamma}_{21}}{\bar{D}^2}\left\{1-\operatorname{sech}\left[\sqrt{\frac{\bar{D}\bar{\gamma}}{4(1-\bar{\Delta}^2\bar{\gamma}^2)}}\right]\right\}. \qquad (24)\end{aligned}$$

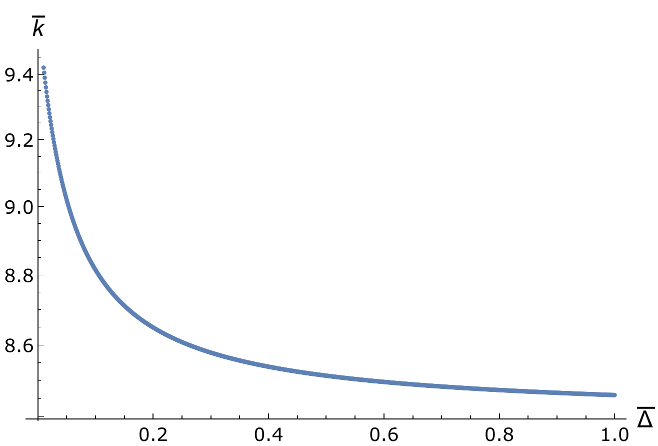

FIG. 5. Plot of the average rate constant $\bar{k}$ against $\bar{\Delta}$ for a particle starting at the position $\bar{x}_0 = 1/2$, and diffusing inside the bounded region with two absorbing boundaries at $x = 0$ and $x = L$. The mean diffusivity is kept fixed at $\bar{D} = 1.20$, and $\bar{\gamma}_{12} = 3/4$. The rate constant decreases as $\bar{\Delta}$ increases.

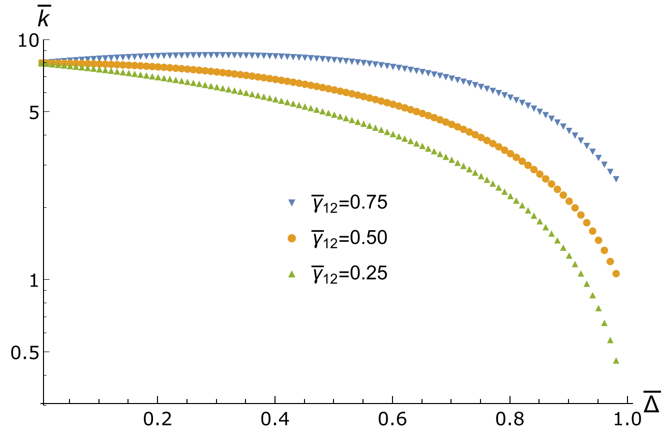

FIG. 6. Logarithmic plot of $\bar{k}$ as a function of $\bar{\Delta}$ for different values of $\bar{\gamma}_{12}$ considering the initial position of the particle at $\bar{x}_0 = 1/2$ and $\bar{\gamma} = 1$. Its motion is restricted to the domain $x \in [0, L]$ in the presence of two absorbing boundaries.

Clearly for $\bar{D} = \bar{D}_0,\ \bar{k} < \bar{k}_0$.

3. Uniform initial density

We now consider the situation where the particle is initially uniformly distributed over the region $x \in [0, L]$, i.e., $P(x, t = 0) = \frac{1}{L}[\Theta(x) - \Theta(x - L)]$, where $\Theta(x)$ is the Heaviside step function. Using Eq. (7), the PDF can be expressed as

$$\begin{aligned}P(x,t) &= \frac{2}{L}\sum_{m=1}^{\infty}\sin\left(\frac{m\pi}{L}x\right)\langle e^{-\lambda_m\int_0^t dsD(s)}\rangle_{D(s)}\\
&\quad\times\int_0^L dx_i\,\sin\left(\frac{m\pi}{L}x_i\right)P(x_i,0)\\
&= \frac{4}{\pi L}\sum_{m=0}^{\infty}\frac{\sin\left[\frac{(2m+1)\pi}{L}x\right]}{2m+1}\langle e^{-\lambda_{2m+1}\int_0^t dsD(s)}\rangle_{D(s)}. \qquad (25)\end{aligned}$$

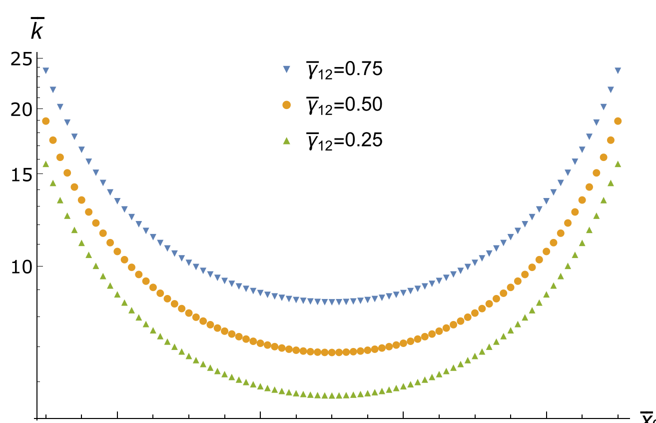

FIG. 7. Logarithmic plot of rate constant $(\bar{k})$ as a function of initial position of the particle $\bar{x}_0$ for different values of $\bar{\gamma}_{12}$, considering the absorption occurs at $x = 0$ and $x = L$. The other parameters are set to $\bar{\Delta} = 0.4,\ \bar{\gamma} = 1.0$.

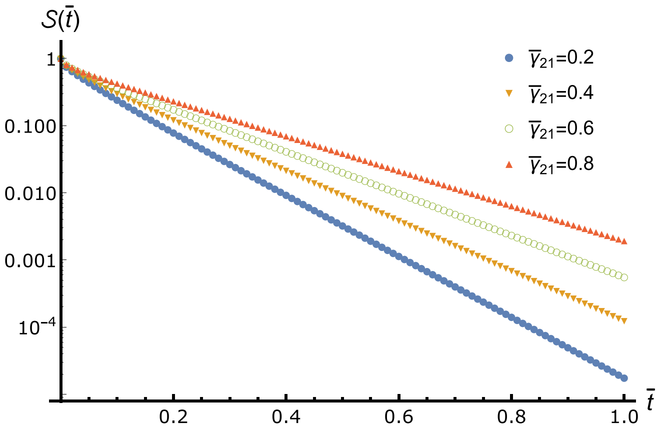

FIG. 8. Logarithmic plot of survival probability, $\mathcal{S}(\bar{t})$, as a function of time $\bar{t}$ for different values of $\bar{\gamma}_{21}$ for the case where the particles are assumed to be uniformly distributed initially over the entire box. The plots are obtained upon performing the numerical summation of Eq. (28) up to the eigenmodes $m = 300$ by taking the values of parameters as $\bar{\gamma} = 10$, $\bar{\Delta} = 1/20$.

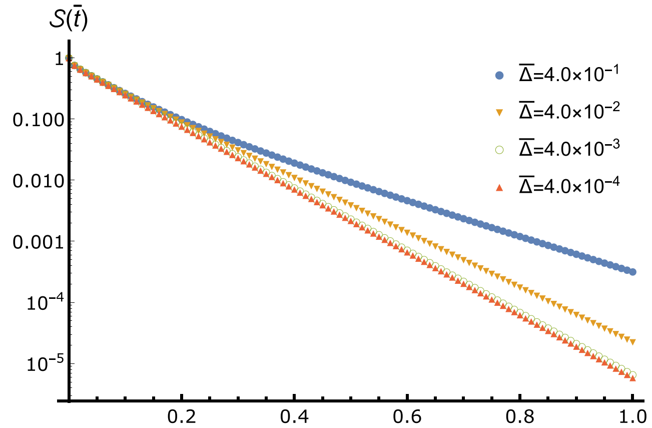

FIG. 9. Plots for uniform initial density. Logarithmic plot of survival probability, $\mathcal{S}(\bar{t})$, as a function of time $\bar{t}$ for different values of $\bar{\Delta}$. The plots are obtained upon performing the numerical summation of Eq. (28) up to the eigenmodes $m = 300$. The values of other parameters used for the computation are $\bar{\gamma}_{12} = 3/4$, $\bar{D} = 1.20$.

The survival probability within the bounded domain can be calculated by integrating the density over whole space and is given by

$$\begin{aligned}\mathcal{S}(t) &= \int_0^L dx\, P(x,t)\\ &= \frac{4}{\pi L}\sum_{m=0}^{\infty}\langle e^{-\lambda_{2m+1}\int_0^t ds D(s)}\rangle_{D(s)}\int_0^L dx\,\frac{\sin\left[\frac{(2m+1)\pi}{L}x\right]}{2m+1}\\ &= \frac{8}{\pi^2}\sum_{m=0}^{\infty}\frac{1}{(2m+1)^2}\langle e^{-\lambda_{2m+1}\int_0^t dsD(s)}\rangle_{D(s)}.\end{aligned} \tag{26}$$

Henceforth, we express the survival probability in terms of dimensionless variables as defined in the previous case.

Normal diffusion. Let us first consider the case where diffusivity is a constant and is denoted by $\bar{D}_0$:

$$\mathcal{S}_0(\bar{t}) = \frac{8}{\pi^2}\sum_{m=0}^{\infty}\frac{1}{(2m+1)^2}e^{-(2m+1)^2\pi^2\bar{D}_0\bar{t}}. \tag{27}$$

Dichotomous diffusivity. For switching diffusion, Eq. (26) becomes

$$\begin{aligned}\mathcal{S}(\bar{t}) = \frac{8}{\pi^2}\sum_{m=0}^{\infty}\frac{1}{(2m+1)^2}&\left[\frac{1}{2}\left(1-\frac{\bar{\theta}_3}{\bar{\theta}_2}\right)e^{-(\bar{\theta}_1+\bar{\theta}_2)\bar{t}}\right.\\ &\left.+\frac{1}{2}\left(1+\frac{\bar{\theta}_3}{\bar{\theta}_2}\right)e^{-(\bar{\theta}_1-\bar{\theta}_2)\bar{t}}\right].\end{aligned} \tag{28}$$

We evaluate Eq. (28) numerically by summing the eigenmodes up to $m = 300$, and the results are pictorially depicted in Fig. 8 and 9. From Fig. 8 one can see that the chances of survival increase with the higher values of $\bar{\gamma}_{21}$, consistent with the previous case (see Sec. IIIA2). Also, its dependency on $\bar{\Delta}$ for the system with a fixed average diffusivity is similar to the previous one, as shown in Fig. 9.

The time-averaged rate constant for normal diffusion can be calculated as

$$\bar{k}_0^{-1} = \int_0^{\infty} d\bar{t}\,\mathcal{S}_0(\bar{t}) = \frac{1}{\bar{D}_0}\frac{8}{\pi^4}\sum_{m=0}^{\infty}\frac{1}{(2m+1)^4} = \frac{1}{12\bar{D}_0}. \tag{29}$$

For switching diffusion, the rate constant is computed as

$$\begin{aligned}\bar{k}^{-1} &= \int_0^{\infty} dt\,\mathcal{S}(t) = \frac{8}{\pi^2}\sum_{m=0}^{\infty}\frac{1}{(2m+1)^2}\int_0^{\infty} d\bar{t}\left[\frac{1}{2}\left(1-\frac{\bar{\theta}_3}{\bar{\theta}_2}\right)e^{-(\bar{\theta}_1+\bar{\theta}_2)\bar{t}}+\frac{1}{2}\left(1+\frac{\bar{\theta}_3}{\bar{\theta}_2}\right)e^{-(\bar{\theta}_1-\bar{\theta}_2)\bar{t}}\right]\\ &= \frac{8}{\pi^2}\sum_{m=0}^{\infty}\frac{1}{(2m+1)^2}\frac{(2m+1)^2\pi^2[1-\bar{\Delta}\bar{\gamma}(\bar{\gamma}_{12}-\bar{\gamma}_{21})]+\bar{\gamma}}{(2m+1)^2\pi^2[(1-\bar{\Delta}^2\bar{\gamma}^2)(2m+1)^2\pi^2+\bar{D}\bar{\gamma}]}.\end{aligned} \tag{30}$$

The sum is evaluated numerically, and the rate is plotted in Figs. 10 and 11. Like the previous case, the rate constant $\bar{k}$ becomes smaller with increasing $\bar{\Delta}$. Equation (30) can also be computed analytically, and it reads

$$\begin{aligned}\bar{k}^{-1} &= \frac{8}{\pi^2}\sum_{m=0}^{\infty}\frac{1}{(2m+1)^2}\frac{1-\bar{\Delta}\bar{\gamma}(\bar{\gamma}_{12}-\bar{\gamma}_{21})}{(1-\bar{\Delta}^2\bar{\gamma}^2)(2m+1)^2\pi^2+\bar{D}\bar{\gamma}}+\frac{8}{\pi^4}\sum_{m=0}^{\infty}\frac{1}{(2m+1)^4}\frac{\bar{\gamma}}{(1-\bar{\Delta}^2\bar{\gamma}^2)(2m+1)^2\pi^2+\bar{D}\bar{\gamma}}\\ &= \frac{1}{12\bar{D}}+\frac{4\bar{\Delta}^2\bar{\gamma}\bar{\gamma}_{12}\bar{\gamma}_{21}}{\bar{D}^2}\left\{1-\sqrt{\frac{4(1-\bar{\Delta}^2\bar{\gamma}^2)}{\bar{D}\bar{\gamma}}}\tanh\left[\sqrt{\frac{\bar{D}\bar{\gamma}}{4(1-\bar{\Delta}^2\bar{\gamma}^2)}}\right]\right\}.\end{aligned} \tag{31}$$

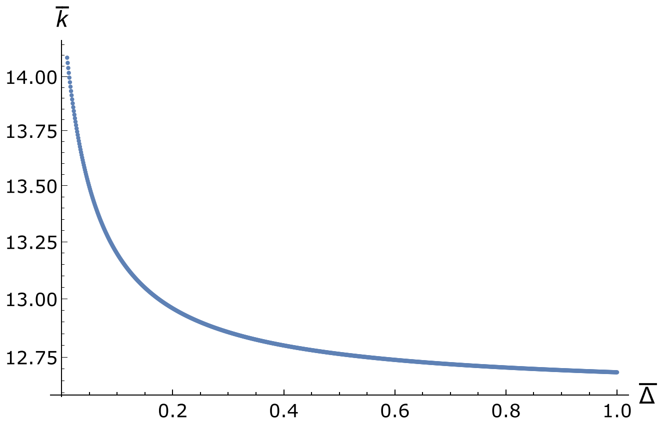

FIG. 10. The average rate $\bar{k}$ is plotted on logarithmic scale as a function of $\bar{\Delta}$, taking $\bar{\gamma}_{12} = 3/4$. The particles are assumed to have a mean diffusivity $\bar{D} = 1.20$ and were initially uniformly distributed over the entire bounded region $x \in [0, L]$.

Notice that $\bar{k}^{-1} > \bar{k}_0^{-1}$ for the case where $\bar{D}$ is taken to be equal to $\bar{D}_0$. Clearly, the rate constant is maximum for normal diffusion,

B. Survival in a finite region with absorption at one end

Here we consider that the Brownian particle is confined in a box of length L with an absorbing boundary at $x = 0$ and a reflecting one at $x = L$, and the particle is initially present at a position, $x = x_0$. Mathematically speaking, $P(x = 0, t) = 0$, $\frac{dP(x,t)}{dx}|_{x=L} = 0$, $P(x, t = 0) = \delta(x - x_0)$.

So the propagator can be given as

$$G(x,t|x_i,0) = \frac{2}{L}\sum_{m=0}^{\infty}\sin\left[\frac{(2m+1)\pi}{2L}x_i\right]\sin\left[\frac{(2m+1)\pi}{2L}x\right] \times \langle e^{-\lambda_{2m+1}\int_0^t ds D(s)}\rangle_{D(s)}, \quad (32)$$

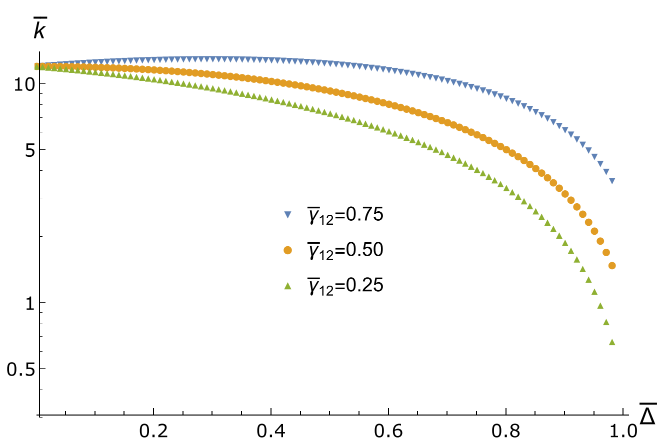

FIG. 11. Logarithmic plot of average rate $\bar{k}$ as a function of $\bar{\Delta}$ for different values of $\bar{\gamma}_{12}$, taking $\bar{\gamma} = 1$. The particles are assumed to have initial uniform distribution inside a box having two absorbing boundaries at $x = 0$ and $x = L$.

where $\lambda_{2m+1} = \frac{(2m+1)^2\pi^2}{4L^2}$, and $m = 0, 1, 2, \ldots$. The survival probability can be computed as

$$\begin{aligned} \mathcal{S}(t) &= \frac{2}{L}\sum_{m=0}^{\infty}\int_0^L dx\sin\left[\frac{(2m+1)\pi}{2L}x\right]\langle e^{-\lambda_{2m+1}\int_0^t dsD(s)}\rangle_{D(s)} \\ &\quad\times\int_0^L dx_i\sin\left[\frac{(2m+1)\pi}{2L}x_i\right]\delta(x_i - x_0) \\ &= \frac{4}{\pi}\sum_{m=0}^{\infty}\frac{\sin\left[\frac{(2m+1)\pi}{2L}x_0\right]}{2m+1}\langle e^{-\lambda_{2m+1}\int_0^t dsD(s)}\rangle_{D(s)}. \end{aligned} \quad (33)$$

Notice that Eq. (33) has exact same expression as Eq. (15) with the only difference in the box length being doubled, which is very much evident as the particle is now being absorbed only at a single boundary after reflected back from the other end. A similar argument can be established for the situation where the particle was initially uniformly distributed inside the box. Therefore, for the present case, both Eqs. (23) and (31) hold true with L being replaced by $2L$.

C. Diffusion in the semi-infinite region with absorption at $x = 0$

1. Initial position at x_0

Now we consider the case where the particle diffuses in a semi-infinite region $x \in [0, \infty)$ with an absorbing boundary at $x = 0$. The initial position is taken to be $x_0 > 0$. The eigenfunctions appropriate for this problem are $\phi_\kappa(x) = \sqrt{\frac{2}{\pi}}\sin(\kappa x)$, which obey the normalization condition, $\int_0^\infty d\kappa\,\phi_\kappa(x)\,\phi_\kappa(x') = \delta(x - x')$, and are eigenfunctions of the operator, $-D\frac{\partial^2}{\partial x^2}$, with the eigenvalue $D\kappa^2$. Using these and following Eq. (9), we get

$$G(x,t|x_i,0) = \frac{2}{\pi}\int_0^\infty d\kappa\,\sin(\kappa x)\sin(\kappa x_i)\langle e^{-\kappa^2\int_0^t dsD(s)}\rangle_{D(s)}. \quad (34)$$

So the survival probability is given by

$$\begin{aligned} \mathcal{S}(t) &= \int_0^\infty dx_i\int_0^\infty dx\,G(x,t|x_i,0)\,P(x_i,0) \\ &= \frac{2}{\pi}\int_0^\infty d\kappa\frac{\sin(\kappa x_o)}{\kappa}\langle e^{-\kappa^2\int_0^t dsD(s)}\rangle_{D(s)}. \end{aligned} \quad (35)$$

For normal diffusion, $D(s)$ is constant and is equal to D_0. So the survival probability in Eq. (35) reduces to

$$\mathcal{S}_0(t) = \frac{2}{\pi}\int_0^\infty d\kappa\,D_0\sin(\kappa x_o)\,e^{-\kappa^2 D_0 t} = \mathrm{erf}\left(\frac{x_0}{2\sqrt{D_0 t}}\right). \quad (36)$$

Therefore, the instantaneous rate can be obtained as

$$\begin{aligned} r_0(t) &= -\frac{\partial\mathcal{S}_0(t)}{\partial t} = \frac{2}{\pi}\int_0^\infty d\kappa\,D_0\kappa\,\sin(\kappa x_o)\,e^{-\kappa^2 D_0 t} \\ &= \frac{x_o\,e^{-\frac{x_0^2}{4D_0 t}}}{\sqrt{4\pi D_0 t^3}}. \end{aligned} \quad (37)$$

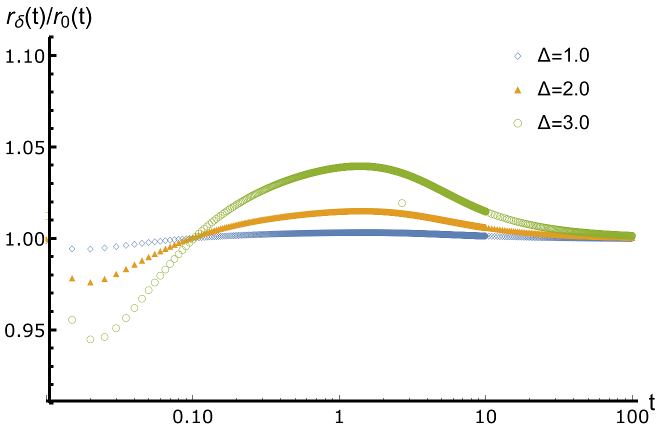

FIG. 12. The rate for switching diffusion divided by that for normal diffusion is plotted in log-linear scale as a function of time for different Δ values for the case where the particle was initially at a position $x_0 = 1.0$ and is diffusing in the semi-infinite region $x \in [0, \infty)$. The parameters used for the numerical computation are $\langle D(t)\rangle = D_0 = 10,\ \gamma_{12} = 3/4,\ \gamma_{21} = 1/4$.

For switching diffusion, the rate can be computed by virtue of Eqs. (19) and (35), and it reads

$$r_\delta(t) = \frac{2}{\pi}\int_0^\infty d\kappa \frac{\sin(\kappa x_o)}{\kappa}\left[\frac{(\Theta_1+\Theta_2)}{2}\left(1-\frac{\Theta_3}{\Theta_2}\right)e^{-(\Theta_1+\Theta_2)t} + \frac{(\Theta_1-\Theta_2)}{2}\left(1+\frac{\Theta_3}{\Theta_2}\right)e^{-(\Theta_1-\Theta_2)t}\right], \tag{38}$$

where $\Theta_1 = D_a\kappa^2 + \frac{1}{2}(\gamma_{12}+\gamma_{21})$, $\Theta_2 = \frac{1}{2}\sqrt{[2\kappa^2\Delta + (\gamma_{21}-\gamma_{12})]^2 + 4\gamma_{12}\gamma_{21}}$ and $\Theta_3 = \frac{1}{2}(\gamma_{12}+\gamma_{21}) - \frac{\gamma_{12}-\gamma_{21}}{\gamma_{12}+\gamma_{21}}\kappa^2\Delta$.

We evaluate Eqs. (38) and (37) numerically at different times and plot the results as a ratio of two rates in Figs. 12 and 13. For comparison, the value of average diffusivity for switching diffusion, $\langle D(t)\rangle$ is taken the same as D_0. At the initial stages, the rate for switching diffusion is considerably lower than that for normal diffusion. But at some intermediate stages, the absorption happens at a greater rate for switching case. The extent at which rate is diminished or enhanced strongly depends on the strength of noise, Δ. Also, in the same way, the proximity of particles to a sink affects the rate. After a long time, the two rates become equal.

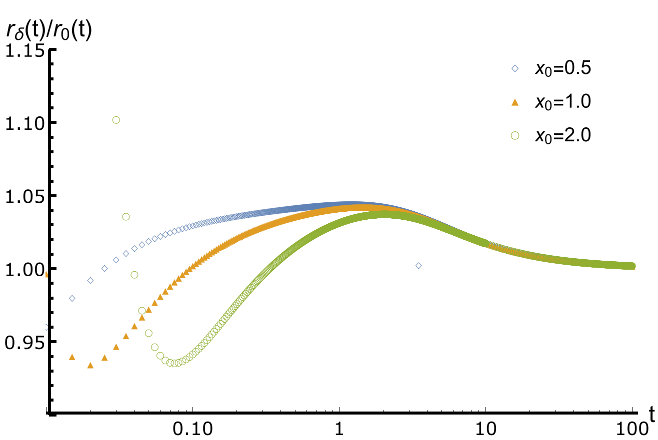

FIG. 13. Log-linear plot of the ratio of rates for switching and normal diffusion as a function of time t for different initial positions of the particle diffusing in the semi-infinite region $x \in [0, \infty)$. The parameters used for the numerical computation are given by the set $\{\langle D(t)\rangle = D_0 = 10,\ \Delta = 3.0,\ \gamma_{12} = 3/5,\ \gamma_{21} = 2/5\}$.

2. *Uniform initial density*

In a semi-infinite region, like the previous case, the propagator is given by Eq. (34). Using this, and upon doing the nondimensionalization of the parameters, the total number $\mathcal{N}(t)$ of particles at the time t can be expressed as

$$\mathcal{N}(t) = \int_0^\infty dx_i \int_0^\infty dx\, G(x,t|x_i,0)\,P(x_i,0) = -\frac{4\delta_o}{\pi}\int_0^\infty \frac{d\kappa}{\kappa^2}\left\langle e^{-\kappa^2\int_0^t ds\, D(s)}\right\rangle_{D(s)}, \tag{39}$$

where δ_o is the initial density per unit length. Note that this integral is infinity, due to the divergence at $\kappa = 0$, which is not surprising, as there are infinite number of particles. However, the rate at which the particles are removed can easily be calculated by differentiating this with respect to t, as shown below.

For normal diffusion, $D(s)$ is set to D_0, and therefore, the rate can be obtained, using Eq. (39), as

$$r_0(t) = -\frac{\partial\mathcal{N}_0(t)}{\partial t} = \frac{4\delta_o D_0}{\pi}\int_0^\infty d\kappa\, e^{-\kappa^2 D_0 t} = 2\delta_o\sqrt{\frac{D_0}{\pi t}}. \tag{40}$$

For switching diffusion, one can compute the absorption rate, $r(t)$, by virtue of Eqs. (19) and (39), and it can be written as

$$r_c(t) = \frac{4\delta_o}{\pi}\int_0^\infty \frac{d\kappa}{\kappa^2}\left[\frac{(\Theta_1+\Theta_2)}{2}\left(1-\frac{\Theta_3}{\Theta_2}\right)e^{-(\Theta_1+\Theta_2)t} + \frac{(\Theta_1-\Theta_2)}{2}\left(1+\frac{\Theta_3}{\Theta_2}\right)e^{-(\Theta_1-\Theta_2)t}\right]. \tag{41}$$

Equations (40) and (41) are evaluated numerically, and their ratio is plotted as a function of time t in Fig. 14. It can be noted that in Eq. (41), the term on the right-hand side is well behaved near $\kappa = 0$, the $1/\kappa^2$ term is canceled by the κ^2-like behavior of the term inside the square bracket. From Fig. 14, one can see that for normal diffusion, the particle is absorbed at a much faster rate in shorter timescales. But at intermediate times, the rate in the case of dichotomous diffusivity is larger because there is a higher probability of the particle surviving compared to the normal case. The enhancement of rate occurs at comparatively larger extent if Δ has large values. In the long-time limit, the rate $r(t)$ approaches to $r_0(t)$.

IV. CONCLUSION

We have found the exact solution for the survival probability of a particle with a dichotomous diffusion coefficient. It is found that the survival probability, in general, is larger if the diffusion coefficient switches, in comparison with the case where the diffusion coefficient has a constant value which is the average value of $D(t)$. Similar results have been previously reported in the case of "diffusing diffusivity" model [37,38],

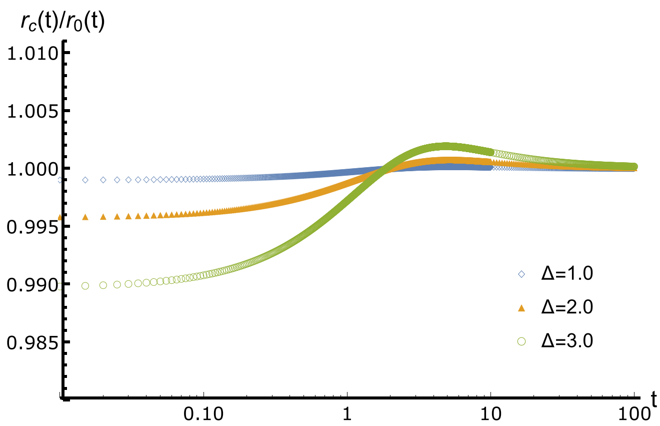

FIG. 14. The rate for switching diffusion divided by that for normal diffusion is plotted as a function of time t in the log-linear scale for different values of Δ. The particles are assumed to have initial uniform distribution over the entire semi-infinite region $x \in [0, \infty)$. The other parameters are $\{\langle D(t)\rangle = D_0 = 10,\ \gamma_{12} = 3/4,\ \gamma_{21} = 1/4\}$.

and so it may hold true for any generic system which transits among multiple states with different diffusivities.

Consequently, the rate constant for absorption strongly depends on Δ—the separation between the diffusion coefficients. We have explored the effects of various parameters in the dynamics which can provide suitable conditions for an optimal reaction strategy. This study may be extended to model several two-state processes, for example, target search in the context of gene expression, stochastic gating in ion channels, and conformational switching of a polymer.

APPENDIX: EVALUATION OF THE AVERAGE $I(t) = \langle \exp[-\lambda \int_0^\tau d\tau_1 D(\tau_1)]\rangle$

The probability of finding the particle in a state with diffusion coefficient D_i at the time t will be denoted by $P_i(t)$. The column matrix $\boldsymbol{P}(t) = \binom{P_1(t)}{P_2(t)}$ obeys the equation

$$\frac{d\boldsymbol{P}(t)}{dt} = -\boldsymbol{\gamma}\boldsymbol{P}(t), \tag{A1}$$

where the rate matrix $\boldsymbol{\gamma}$ is defined by

$$\boldsymbol{\gamma} = \begin{pmatrix} \gamma_{12} & -\gamma_{21} \\ -\gamma_{12} & \gamma_{21} \end{pmatrix}. \tag{A2}$$

The solution of Eq. (A1) is given by

$$\boldsymbol{P}(t) = \boldsymbol{U}(t)\boldsymbol{P}(0), \tag{A3}$$

where $\boldsymbol{U}(t) = \exp(-t\boldsymbol{\gamma})$. We now proceed to the evaluation of $I(t)$. On expanding the exponential as a series, we get

$$I(t) = \sum_{n=0}^{\infty} \frac{(-\lambda)^n}{n!} \int_0^t dt_1 \int_0^t dt_2 \cdots \int_0^t dt_n \times \langle D(t_1)D(t_2)\cdots D(t_n)\rangle, \tag{A4}$$

which may be rewritten as

$$I(t) = \sum_{n=0}^{\infty} (-\lambda)^n \int_0^t dt_1 \int_0^{t_1} dt_2 \cdots \int_0^{t_{n-1}} dt_n \times \langle D(t_1)D(t_2)\cdots D(t_n)\rangle. \tag{A5}$$

Defining the diffusivity matrix $\boldsymbol{D}$ by

$$\boldsymbol{D} = \begin{pmatrix} D_1 & 0 \\ 0 & D_2 \end{pmatrix}, \tag{A6}$$

we can write this series as

$$I(t) = \sum_{n=0}^{\infty} (-\lambda)^n \int_0^t dt_1 \int_0^{t_1} dt_2 \cdots \int_0^{t_{n-1}} dt_n \boldsymbol{F}\boldsymbol{U}(t-t_1) \times \boldsymbol{D}\boldsymbol{U}(t_1-t_2)\boldsymbol{D}\cdots\boldsymbol{U}(t_{n-1}-t_n)\boldsymbol{D}\boldsymbol{P}_{eq}, \tag{A7}$$

where the row matrix $\boldsymbol{F} = (1, 1)$. The column matrix $\boldsymbol{P}_{eq} = \frac{1}{\gamma_{12}+\gamma_{21}}\binom{\gamma_{21}}{\gamma_{12}}$ is the equilibrium value of $\boldsymbol{P}$. Note that this implies that the initial value of the diffusion coefficient can be any one of the two possibilities, with probabilities given by the equilibrium distribution. Introducing the time-ordering operator $\hat{T}$ which arranges times in the quantities that follow it in the decreasing order, which is popularly used in quantum mechanical time evolution problems, we may write this as

$$I(t) = \boldsymbol{F}\hat{T}\left\{\boldsymbol{U}(t)\exp\left[-\lambda\int_0^t d\tau \boldsymbol{D}(\tau)\right]\right\}\boldsymbol{P}_{eq}, \tag{A8}$$

where $\boldsymbol{D}(\tau) = \boldsymbol{D}$ is actually time independent, but the argument τ is necessary for the purpose of time ordering. The time dependence may be omitted once this ordering has been done. On differentiating the matrix $\boldsymbol{M}(t) = \hat{T}\{\boldsymbol{U}(t)\exp[-\lambda\int_0^t d\tau \boldsymbol{D}(\tau)]\}$ with respect to t, we find

$$\frac{d\boldsymbol{M}(t)}{dt} = -(\boldsymbol{\gamma} + \lambda\boldsymbol{D})\boldsymbol{M}(t). \tag{A9}$$

On using $\boldsymbol{M}(0) = \boldsymbol{I}$, the 2×2 identity matrix, we find

$$\boldsymbol{M}(t) = e^{-t(\boldsymbol{\gamma}+\lambda\boldsymbol{D})}, \tag{A10}$$

which when used in Eq. (A8) gives

$$I(t) = \boldsymbol{F}e^{-t(\boldsymbol{\gamma}+\lambda\boldsymbol{D})}\boldsymbol{P}_{eq}. \tag{A11}$$

Using $\boldsymbol{V}$, the matrix of eigenvectors of the matrix $\boldsymbol{\gamma} + \lambda\boldsymbol{D}$, with the corresponding diagonal eigenvalue matrix $\boldsymbol{\theta}$, obeying $(\boldsymbol{\gamma} + \lambda\boldsymbol{D})\boldsymbol{V} = \boldsymbol{V}\boldsymbol{\theta}$ we can write the above as

$$I(t) = \boldsymbol{F}\boldsymbol{V}e^{-t\boldsymbol{\theta}}\boldsymbol{V}^{-1}\boldsymbol{P}_{eq}. \tag{A12}$$

Note that Eq. (A12) is quite general and is applicable even a more general situation where the diffusion coefficient takes on n different values, $D_1, D_2, \ldots, D_n$. In the case that we consider, $n = 2$, and the values of the eigenvalues are

$$\theta_1 = \frac{1}{2}[(D_1 + D_2)\lambda + \gamma_{12} + \gamma_{21}],$$
$$\theta_2 = \frac{1}{2}\sqrt{[(D_2 - D_1)\lambda + (\gamma_{21} - \gamma_{12})]^2 + 4\gamma_{12}\gamma_{21}}. \tag{A13}$$

Finding the corresponding eigenvectors and using them as well, Eq. (A12) leads to

$$I(t) = \frac{1}{2}\left(1 - \frac{\theta_1 - \lambda D_{eq}}{\theta_2}\right) e^{-(\theta_1+\theta_2)t} + \frac{1}{2}\left(1 + \frac{\theta_1 - \lambda D_{eq}}{\theta_2}\right) e^{-(\theta_1-\theta_2)t}, \tag{A14}$$

where $\langle D(t)\rangle = \boldsymbol{FDP}_{eq} = \frac{\gamma_{12}D_2+\gamma_{21}D_1}{\gamma_{12}+\gamma_{21}}$.

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