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First passage times for multiple particles with reversible target-binding kinetics

Denis S. Grebenkov[a)]

Laboratoire de Physique de la Matière Condensée (UMR 7643), CNRS–Ecole Polytechnique, University Paris-Saclay, 91128 Palaiseau, France and Interdisciplinary Scientific Center Poncelet (ISCP) (UMI 2615 CNRS/IUM/IITP RAS/Steklov MI RAS/Skoltech/HSE), Bolshoy Vlasyevskiy Pereulok 11, 119002 Moscow, Russia

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We investigate the first passage problem for multiple particles that diffuse towards a target, partially adsorb there, and then desorb after a finite exponentially distributed residence time. We search for the first time when *m* particles undergoing such reversible target-binding kinetics are found simultaneously on the target that may trigger an irreversible chemical reaction or a biophysical event. Even if the particles are independent, the finite residence time on the target yields an intricate temporal coupling between particles. We compute analytically the mean first passage time (MFPT) for two independent particles by mapping the original problem to higher-dimensional surface-mediated diffusion and solving the coupled partial differential equations. The respective effects of the adsorption and desorption rates on the MFPT are revealed and discussed. *Published by AIP Publishing.* https://doi.org/10.1063/1.4996395

I. INTRODUCTION

The first-passage phenomena are ubiquitous in nature, with examples ranging from foraging animals in ecology to DNA replication processes in microbiology.[1–4] The overwhelming majority of former works have been focused on the statistics of the first passage time (FPT) of a *single* diffusing particle to a target.[5–18] In particular, the mean FPT was computed for various geometric settings and kinetics (see Ref. 19). In many practical situations, however, an event (e.g., a reaction) is triggered upon the arrival of several particles on the target. For instance, the vesicular transmitter release in neurons is initiated after the arrival of five calcium ions onto the vesicle sensor,[20–22] while the hemoglobin molecule is saturated after the arrival of four oxygen molecules. If the diffusing particles are independent, the knowledge of the FPT distribution for a single particle allows one to deduce the distribution for the maximum of FPTs for many particles, yielding thus the time of the triggered reaction (e.g., the vesicular transmitter release).[23] In practice, however, the particles that have arrived on the target do not stay infinitely long but leave the target after some random residence time. This is a typical feature of reversible reactions when the arrived particle forms a metastable complex with the target molecule that can dissociate later on. The dissociation or desorption mechanism makes the first passage time problem highly nontrivial even for independent particles. For instance, if just two particles are needed to trigger the reaction, the first particle arrived on the target can leave it before the arrival of the second particle. And before the first particle comes to the target again, the second one can leave it, and so on. These random repetitive asynchronized returns to the target have to be accounted for to obtain the first time when both particles are at the target and thus an irreversible reaction or a biophysical event is triggered. We emphasize that the FPT problem with reversible target-binding kinetics is intrinsically a collective multi-particle phenomenon, which is different from FPT problems for Markov switching processes when a diffusing particle can randomly switch between different internal states (e.g., with different diffusivities or target affinities), see Refs. 24–26 and references therein.

In this paper, we investigate the first passage time problem for "impatient" particles with reversible target-binding kinetics. We derive an exact semi-analytical solution of this problem for the simplified case of two particles undertaking one-dimensional diffusion on the interval $(0, L)$ (or between parallel walls separated by a distance L, the lateral motion being irrelevant). More precisely, we compute the mean first time when two particles are simultaneously at the right endpoint (the target). The basic idea is to consider one-dimensional diffusions of two independent particles as a *surface-mediated diffusion* of a single particle inside a square. Although the latter problem has been thoroughly investigated for several geometric configurations,[27–33] the current setting is different and its solution is not yet available. Inspired by former works, we reduce the coupled partial differential equations (PDEs) for the surface-mediated diffusion to a set of linear equations that can be solved either explicitly (in some cases), or approximately, or numerically. This semi-analytical solution allows us to study how the mean first passage time (MFPT) depends on two major parameters of the model: the adsorption rate (or the target reactivity) and the desorption rate (or the mean residence time on the target). Even for this simplified case, the solution is intricate and the MFPT exhibits nontrivial behavior. Note that the theory of many-body diffusion-limited reactions and catalytically activated reactions also employs a mapping of the dynamics

[a)]Electronic mail: denis.grebenkov@polytechnique.edu

of multiple particles onto diffusion in a higher-dimensional space with boundary conditions imposed on the surface of the excluded volume to account for reactions upon particles' encounters (see Refs. 34 and 35 and references therein). However, the reversible target-binding kinetics was ignored in these studies.

The paper is organized as follows. In Sec. II, we formulate the mathematical problem and recall the classical solution for a single particle. These prerequisites will serve as a ground for computing the MFPT for two "impatient" particles in Sec. III. This section presents the main theoretical contribution of the paper. Section IV highlights the respective roles of the finite reactivity and the desorption rate onto the MFPT. Section V concludes the paper by summarizing main results and discussing future perspectives.

II. MATHEMATICAL PROBLEM AND PREREQUISITES

A. General problem

We start this section by formulating the first passage problem for "impatient" particles with reversible target-binding kinetics in a general situation. For a given Euclidean domain $\Omega_0 \subset \mathbb{R}^d$, let $\Omega_T \subset \Omega_0$ be a target such that its boundary $\partial\Omega_T$ does not intersect the boundary $\partial\Omega_0$ of the domain [Fig. 1(a)]. We consider an ordinary diffusion process inside $\Omega = \Omega_0 \backslash \Omega_T$, started from a point $x \in \Omega$, with a diffusion coefficient D. The boundary $\partial\Omega_0$ is just an outer impermeable wall that keeps the particles inside the domain by reflecting them back into Ω. In turn, when a particle arrives onto the target surface $\partial\Omega_T$, it can be either adsorbed on the target or be reflected back into Ω and resume its diffusion. The probabilities of these two events are determined by the adsorption rate (or the target reactivity) k_{on}. Partial reflections can mimic an energetic barrier at the target, partial reactivity due to heterogeneous distribution of microscopic active/catalytic sites on the target, stochastic gating, conformational incompatibility, recognition phase, or another mechanism that may prevent an immediate adsorption on the target.[18,24,36–43] Once a particle is adsorbed on the target, it remains trapped for a random exponentially distributed time τ, $\mathbb{P}\{\tau \geq t\} = e^{-k_{off} t}$, with a desorption rate k_{off}. After this residence time, the particle is released from the target and resumes its bulk diffusion, until the next arrival on the target, and so on. In the language of reversible kinetics, the adsorption on the target means a formation of a metastable complex that can dissociate with the dissociation rate k_{off}. Given that the first absorption time on the target, the residence time on the target, and the following repeated re-adsorption events are all independent of each other, the first passage properties of such a *single* "impatient" particle are characterized by the distribution $\mathbb{P}_x\{\mathcal{T} \geq t\}$ of the FPT $\mathcal{T}$ to the target. The first-passage problems for such partially reflecting diffusion have been quite well investigated.[44–48]

In this paper, we are interested in the first time $\mathcal{T}_m$ when m independent "impatient" particles that undergo partially reflecting diffusion are simultaneously present on the target. In the special case $k_{off} = 0$, every particle that adsorbs on the target remains there forever, and $\mathcal{T}_m$ is simply the time of the first adsorption of the mth particle onto the target. In other words, $\mathcal{T}_m = \max\{\mathcal{T}^1, \ldots, \mathcal{T}^{(m)}\}$, where $\mathcal{T}^1, \ldots, \mathcal{T}^{(m)}$ are m independent realizations of the first adsorption time to the target. As a consequence, the distribution of $\mathcal{T}_m$ is again reduced to that of $\mathcal{T}$,

$$\mathbb{P}_{x_1,\ldots,x_m}\{\mathcal{T}_m \geq t\} = 1 - \prod_{i=1}^{m} (1 - \mathbb{P}_{x_i}\{\mathcal{T} \geq t\}), \qquad (1)$$

where x_i are the starting positions of particles.

The situation is completely different when the desorption rate k_{off} is nonzero. Even if the particles are independent, the finite residence times they spend on the target result in their temporal coupling, and the distribution of $\mathcal{T}_m$ depends on the first arrival times, the consecutive residence times, and the excursion times in a very intricate way. Although one can still

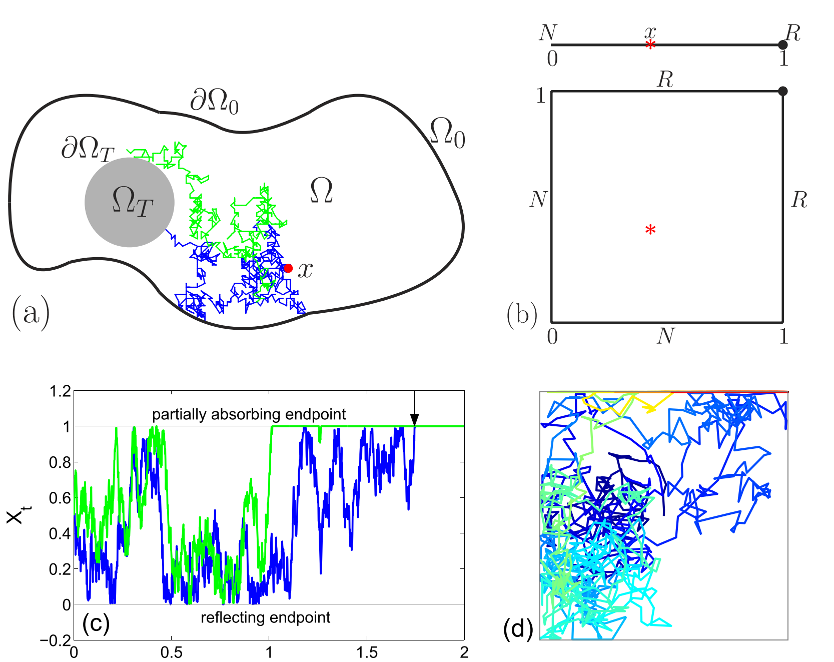

FIG. 1. (a) The first passage time problem for two "impatient" particles that start at x (red circle), diffuse in the domain $\Omega = \Omega_0 \backslash \Omega_T$, and search for a target Ω_T (gray disk). (b) One-dimensional diffusion of two particles on the unit interval and its mapping to surface-mediated diffusion in the unit square, with two fully reflecting edges (N) and two partially absorbing edges (R). The target is located at the corner (1,1). [(c) and (d)] Generated random trajectories of two "impatient" particles on the unit interval, started from $x = 0.5$, with $\kappa = 1$ and $\mu = 1$, plotted as a function of time (c) or in the square (d), with color changing from dark blue at $t = 0$ to dark red at $t = 2$ (dimensionless units, with $L = 1$ and $D = 1$).

rely on the Markovian character and independence of each of these steps, finding the distribution of $\mathcal{T}_m$ even for two particles is a challenging problem that has not found yet an analytical solution, to our knowledge. For these reasons, we restrict the following analysis to the mean FPT for the particular case of the one-dimensional diffusion.

B. One-dimensional problem

We consider one-dimensional diffusion of a particle on an interval $(0, L)$ of length L. We assume that the left endpoint $x = 0$ is fully reflecting whereas the right endpoint $x = L$ is a partially absorbing target. For a single particle started from $x \in (0, L)$, the distribution of the first passage time $\mathcal{T}$ to the target, $S(t, x) = \mathbb{P}_x\{\mathcal{T} \geq t\}$, also known as the survival probability up to time t, satisfies the following PDEs:[49]

$$\partial_t S(t; x) - D\partial_x^2 S(t; x) = 0 \quad (0 < x < L), \tag{2a}$$
$$\partial_x S(t; x) = 0 \quad (x = 0), \tag{2b}$$
$$D\partial_x S(t; x) + k_{\rm on} S(t; x) = 0 \quad (x = L), \tag{2c}$$

subject to the initial condition $S(0; x) = 1$. This problem can be easily solved by integrating the spectral expansion of the propagator,

$$S(t; x) = \sum_{n=0}^{\infty} e^{-Dt\alpha_n^2/L^2} u_n(x) \int_0^L dx'\, u_n(x'), \tag{3}$$

where α_n^2/L^2 and $u_n(x)$ are the eigenvalues and eigenfunctions of the Laplace operator $-\partial_x^2$ on $(0, L)$ with Neumann-Robin boundary conditions at endpoints 0 and L, respectively,

$$u_n(x) = \sqrt{2/L}\, e_n \cos(\alpha_n x/L) \qquad (n = 0, 1, 2, \ldots). \tag{4}$$

Here α_n are solutions of the equation

$$\alpha_n \sin\alpha_n = \kappa \cos\alpha_n \tag{5}$$

and

$$e_n = \left(\frac{\kappa + \alpha_n^2}{\kappa^2 + \kappa + \alpha_n^2}\right)^{1/2} \tag{6}$$

are the normalization constants, with

$$\kappa = \frac{k_{\rm on} L}{D} \tag{7}$$

being the dimensionless reactivity. One can show that for any $n = 0, 1, 2, \ldots$, there is only one solution of Eq. (5) on the interval $[\pi n, \pi(n + 1/2)]$, the endpoints of this interval corresponding to the Neumann ($\kappa = 0$) and Dirichlet ($\kappa = \infty$) limiting cases, respectively. Using the identities

$$\sin\alpha_n = \frac{\kappa(-1)^n}{\sqrt{\alpha_n^2 + \kappa^2}}, \qquad \cos\alpha_n = \frac{\alpha_n(-1)^n}{\sqrt{\alpha_n^2 + \kappa^2}}, \tag{8}$$

one writes the survival probability from Eq. (3) as

$$S(t; x) = 2\sum_{n=0}^{\infty} e^{-Dt\alpha_n^2/L^2} \frac{(-1)^n \kappa \sqrt{\kappa^2 + \alpha_n^2}}{\alpha_n(\kappa^2 + \kappa + \alpha_n^2)} \cos(\alpha_n x/L). \tag{9}$$

From the survival probability, one also obtains the MFPT,

$$\langle \mathcal{T} \rangle_x = \int_0^\infty dt\, t\, (-\partial_t S(t; x)) = \frac{L^2 - x^2}{2D} + \frac{L^2}{\kappa D}. \tag{10}$$

The first term represents the MFPT to a fully absorbing target, whereas the second term accounts for eventual reflections on a partially absorbing target.

III. SEMI-ANALYTICAL SOLUTION

The trajectories of two independent particles on the interval $(0, L)$ can be seen as two coordinates of a single particle undergoing a surface-mediated diffusion in the square $(0, L) \times (0, L)$. The two edges of the square, $\{0\} \times (0, L)$ and $(0, L) \times \{0\}$, are fully reflecting whereas the two other edges are partially absorbing [Fig. 1(b)]. When such a particle is adsorbed on one of partially absorbing edges, it performs one-dimensional diffusion along this edge. This represents the situation when one of two original particles is adsorbed (and thus does not move), while the other keeps diffusing. Diffusion along the edge continues for a random exponentially distributed time τ (controlled by the desorption rate $k_{\rm off}$) and then desorbs from the edge and resumes its two-dimensional diffusion in the square. However, before the desorption event, the adsorbed particle can manage to reach the partially absorbing endpoint of the edge [i.e., to reach the corner (L, L) of the square]. The adsorption at the corner corresponds precisely to the event when two original particles are present at the target. In other words, we consider a particle started from a point (x,y) inside the square Ω and search for the MFPT $t(x,y)$ to the corner (L, L) of the square for a surface-mediated diffusion with partially reactive boundary characterized by dimensionless reactivity κ and desorption rate $k_{\rm off}$.

Adapting the technique developed in Refs. 27–30, we also introduce two MFPTs $t_1(x)$ and $t_2(y)$ to the corner (L, L) for the case when the particle starts on the partially absorbing edges. These MFPTs satisfy the coupled PDEs with appropriate boundary conditions,

$$D(\partial_x^2 + \partial_y^2) t(x, y) = -1, \tag{11a}$$
$$D\partial_x^2 t_1(x) + k_{\rm off}(t(x, L) - t_1(x)) = -1, \tag{11b}$$
$$D\partial_y^2 t_2(y) + k_{\rm off}(t(L, y) - t_2(y)) = -1, \tag{11c}$$
$$(\partial_x t(x, y))_{x=0} = 0, \tag{11d}$$
$$(\partial_y t(x, y))_{y=0} = 0, \tag{11e}$$
$$L(\partial_x t(x, y))_{x=L} - \kappa(t_2(y) - t(L, y)) = 0, \tag{11f}$$
$$L(\partial_y t(x, y))_{y=L} - \kappa(t_1(x) - t(x, L)) = 0, \tag{11g}$$
$$L(\partial_x t_1(x))_{x=L} + \kappa t_1(L) = 0, \tag{11h}$$
$$L(\partial_y t_2(x))_{y=L} + \kappa t_2(L) = 0, \tag{11i}$$
$$(\partial_x t_1)_{x=0} = 0, \tag{11j}$$
$$(\partial_y t_2)_{x=0} = 0. \tag{11k}$$

Equation (11a) is the standard Poisson equation for the MFPT in the square. The second and third Poisson equations on two partially absorbing edges account for the desorption mechanism controlled by the desorption rate $k_{\rm off}$. The Neumann boundary conditions [(11d), (11e), (11j), and (11k)] ensure reflections at two reflecting edges and at the reflecting endpoint of two other edges. Equations (11f) and (11g) describe the exchange between the bulk and the partially absorbing edges. Finally, the Robin boundary conditions (11h) and (11i) mimic partial adsorptions at the endpoints of the two edges.

First, we aim to solve Eq. (11b) with boundary conditions (11h) and (11j). For this purpose, we rewrite this equation as

$$(\mu - L^2\partial_x^2)t_1(x) = \frac{L^2}{D} + \mu\, t(x,L), \tag{12}$$

with

$$\mu = \frac{k_{\rm off}L^2}{D}, \tag{13}$$

and use the eigenfunctions in Eq. (4) of the Laplace operator $-\partial_x^2$ on $(0, L)$ with Neumann-Robin boundary conditions at endpoints 0 and L. This is a natural choice to ensure the boundary conditions (11h) and (11j). Expanding $t_1(x)$ onto the complete basis of these eigenfunctions,

$$t_1(x) = \frac{L^2}{D}\sum_{n=0}^{\infty} b_n \cos(\alpha_n x/L), \tag{14}$$

substituting this expansion into Eq. (12), multiplying by $\cos(\alpha_n x/L)$, and integrating over $(0, L)$, one expresses the coefficients b_n as

$$b_n = \frac{2e_n^2}{\mu+\alpha_n^2}\int\limits_0^1 dx\, \cos(\alpha_n x)\Big(1 + \frac{D}{L^2}\mu\, t(xL,L)\Big). \tag{15}$$

Next, we search for the MFPT $t(x,y)$ in a form

$$t(x,y) = \frac{(L^2-x^2)+(L^2-y^2)}{4D} + \frac{L^2}{D}\sum_{n=0}^{\infty} c_n\Big\{\cos(\alpha_n x/L)\cosh(\alpha_n y/L) + \cosh(\alpha_n x/L)\cos(\alpha_n y/L)\Big\}, \tag{16}$$

where α_n are determined as solutions of Eq. (5). The first term provides the particular solution of the inhomogeneous equation (11a), whereas the sum is a general solution of the homogeneous (Laplace) equation $D\Delta t = 0$ that satisfies Eqs. (11d) and (11e). The unknown coefficients c_n will be chosen to satisfy the remaining conditions. Note that we set the same coefficient in front of two terms in the sum due to the symmetry of the problem: $t(x,y) = t(y,x)$.

Substituting $t(x,L)$ from Eq. (16) into Eq. (15), one gets

$$b_n = \frac{2e_n^2}{\mu+\alpha_n^2}\Bigg\{\frac{\sin\alpha_n}{\alpha_n} + \mu\frac{\sin\alpha_n - \alpha_n\cos\alpha_n}{2\alpha_n^3} + c_n\mu\frac{\cosh\alpha_n}{2e_n^2} + \mu\sum_{k=0}^{\infty} c_k\cos\alpha_k \frac{\alpha_k\sinh\alpha_k\cos\alpha_n + \alpha_n\sin\alpha_n\cosh\alpha_k}{\alpha_k^2+\alpha_n^2}\Bigg\}, \tag{17}$$

where we used the identity

$$\int\limits_0^1 dx\, \cos(\alpha x)\cosh(\beta x) = \frac{\beta\sinh\beta\cos\alpha + \alpha\sin\alpha\cosh\beta}{\beta^2+\alpha^2}. \tag{18}$$

Finally, we substitute $t(x, y)$ from Eq. (16) and $t_1(x)$ from Eq. (14) into Eq. (11g) to get

$$\kappa t_1(x) = (L\partial_y t + \kappa t)_{y=L} = -\frac{L^2}{2D} + \kappa\frac{L^2-x^2}{4D} + \frac{L^2}{D}\sum_{n=0}^{\infty} c_n\cos(\alpha_n x/L)(\alpha_n\sinh\alpha_n + \kappa\cosh\alpha_n), \tag{19}$$

where we used Eq. (5) to check that the contribution from the last term in Eq. (16) vanishes. We multiply the above relation by $\cos(\alpha_n x/L)$ and integrate over $(0, L)$ to get

$$\kappa b_n = e_n^2\Big(-\frac{\sin\alpha_n}{\alpha_n} + \frac{\sin\alpha_n - \alpha_n\cos\alpha_n}{\alpha_n^3}\Big) + c_n(\alpha_n\sinh\alpha_n + \kappa\cosh\alpha_n). \tag{20}$$

From Eqs. (17) and (20), one can express the coefficients c_n

$$c_n e_n^{-2}\alpha_n^2\cosh\alpha_n\Big(\kappa + (\mu+\alpha_n^2)\frac{\tanh\alpha_n}{\alpha_n}\Big) - 2\kappa\mu\sum_{k=0}^{\infty} c_k\cos\alpha_k\frac{\alpha_k\sinh\alpha_k\cos\alpha_n + \alpha_n\sin\alpha_n\cosh\alpha_k}{\alpha_k^2+\alpha_n^2} = \frac{\sin\alpha_n}{\alpha_n}(\mu + 2\alpha_n^2 + \kappa). \tag{21}$$

Using Eqs. (5) and (8) and setting

$$\tilde{c}_n = c_n(\kappa\cosh\alpha_n + \alpha_n\sinh\alpha_n)\cos\alpha_n, \tag{22}$$

one can rewrite Eq. (21) as

$$\tilde{c}_n(\kappa^2+\kappa+\alpha_n^2)\Big(1 + \frac{\mu\sinh\alpha_n}{\alpha_n(\kappa\cosh\alpha_n + \alpha_n\sinh\alpha_n)}\Big) - 2\kappa\mu\sum_{k=0}^{\infty}\frac{\tilde{c}_k}{\alpha_k^2+\alpha_n^2} = \frac{\kappa}{\alpha_n^2}(\mu + 2\alpha_n^2 + \kappa). \tag{23}$$

This equation should be satisfied for any $n = 0, 1, 2, \ldots$. The solution of this infinite set of linear equations yields the coefficients $\tilde{c}_n$ and thus c_n that fully determine the MFPT $t(x, y)$ via Eq. (16). This is our exact semi-analytical solution of the problem. Note that Eq. (11f) is automatically satisfied due to the symmetry.

IV. DISCUSSION

In this section, we study the dependence of the MFPT on two major parameters of the model: the dimensionless reactivity κ [given by Eq. (7)] and the dimensionless desorption rate μ [given by Eq. (13)]. In general, the set of linear equations in Eq. (23) of linear equations on $\tilde{c}_n$ can be truncated and solved numerically by inverting the underlying matrix. The fast decay of the coefficients $\tilde{c}_n$ with n allows one to get accurate results with moderate truncation sizes and thus very rapidly. In the following illustrations, the numerical inversion was performed for the truncated system with 1000 equations but much smaller truncation sizes could be used. In Subsections IV A–IV D, we discuss two exact solutions for $\mu = 0$ (Sec. IV A) and for $\kappa = \infty$ (Sec. IV B), an explicit approximate solution for moderate μ (Sec. IV C) and the asymptotic behavior for large μ and small κ (Sec. IV D).

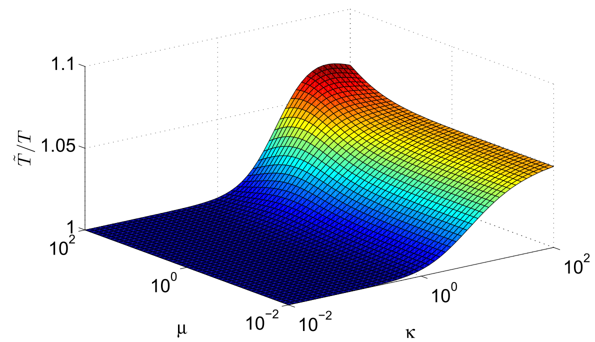

FIG. 2. The ratio $\tilde{T}/T$ as a function of κ and μ.

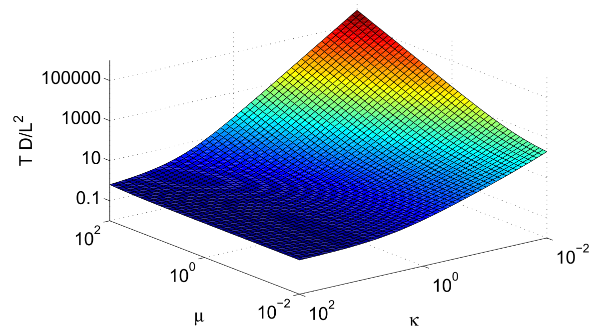

FIG. 3. The global MFPT T as a function of κ and μ.

Once the solution is found, we can also calculate the *global* MFPT by averaging over the starting points. One can consider either two particles started uniformly and independently, or two particles started from the same position that is uniformly distributed. We define respectively

$$\tilde{T} = \frac{1}{L^2} \int_0^L dx \int_0^L dy\, t(x,y), \tag{24a}$$

$$T = \frac{1}{L} \int_0^L dx\, t(x,x). \tag{24b}$$

Substituting Eq. (16) into these expressions, we get

$$\tilde{T} = \frac{L^2}{D}\left(\frac{1}{3} + \sum_{n=0}^{\infty} \frac{2\tilde{c}_n}{\alpha_n^3} \frac{\kappa \sinh \alpha_n}{\kappa \cosh \alpha_n + \alpha_n \sinh \alpha_n}\right), \tag{25a}$$

$$T = \frac{L^2}{D}\left(\frac{1}{3} + \sum_{n=0}^{\infty} \frac{\tilde{c}_n}{\alpha_n^2}\right). \tag{25b}$$

Figure 2 shows that $\tilde{T}$ and T are very close to each other for a broad range of parameters κ and μ. We will thus focus on the simpler expression (25b).

Figure 3 shows the global MFPT T as a function of κ and μ. One can note that (i) as $\kappa \to \infty$, T approaches a constant that is independent of μ; and (ii) T diverges as $\mu \to \infty$ or/and $\kappa \to 0$. In Subsections IV A—IV D, we investigate different limiting cases.

A. Uncoupled particles (μ = 0)

When $\mu = 0$, the nondiagonal terms in Eq. (23) vanish, and its solution is

$$\tilde{c}_n = \frac{\kappa(2\alpha_n^2 + \kappa)}{\alpha_n^2(\kappa^2 + \kappa + \alpha_n^2)}. \tag{26}$$

As a consequence, we get the exact explicit MFPT,

$$t(x,y) = \frac{2L^2 - x^2 - y^2}{4D} + \frac{L^2}{D} \sum_{n=0}^{\infty} \frac{\kappa(2\alpha_n^2 + \kappa)}{\alpha_n^2(\kappa^2 + \kappa + \alpha_n^2)\cos \alpha_n} \frac{\cos(\alpha_n x/L)\cosh(\alpha_n y/L) + \cos(\alpha_n y/L)\cosh(\alpha_n x/L)}{\kappa \cosh \alpha_n + \alpha_n \sinh \alpha_n}. \tag{27}$$

It is instructive to compare this solution to the conventional way of obtaining the MFPT for uncoupled particles which relies on Eq. (1), into which the survival probability from Eq. (9) is substituted,

$$\begin{aligned} t(x,y) &= \int_0^\infty dt\, t\,(-\partial_t \mathbb{P}_{x,y}\{\mathcal{T}_2 \ge t\}) \\ &= \frac{2L^2}{D} \sum_{n=0}^{\infty} \frac{C_n}{\alpha_n^2} (\cos(\alpha_n x/L) + \cos(\alpha_n y/L)) \\ &\quad - \frac{4L^2}{D} \sum_{n_1,n_2=0}^{\infty} \frac{C_{n_1} C_{n_2}}{\alpha_{n_1}^2 + \alpha_{n_2}^2} \cos(\alpha_{n_1} x/L)\cos(\alpha_{n_2} y/L), \end{aligned} \tag{28}$$

where

$$C_n = \frac{(-1)^n \kappa \sqrt{\alpha_n^2 + \kappa^2}}{\alpha_n(\alpha_n^2 + \kappa + \kappa^2)} \tag{29}$$

are the coefficient in Eq. (9). The two representations in Eqs. (27) and (28) are equivalent, though our formula (27) is simpler, as it does not involve the double sum. We stress that the dependence of the MFPT on κ is not explicit and highly nontrivial even for uncoupled particles. In turn, the global MFPT from Eq. (25b),

$$T = \frac{L^2}{D}\left(\frac{1}{3} + \sum_{n=0}^{\infty} \frac{\kappa(2\alpha_n^2 + \kappa)}{\alpha_n^4(\kappa^2 + \kappa + \alpha_n^2)}\right), \tag{30}$$

can be computed explicitly using the identity (see the Appendix)

$$\sum_{k=0}^{\infty} \frac{1}{z^2 + \alpha_k^2} = \frac{(1+\kappa)\sinh z + z\cosh z}{2z(z \sinh z + \kappa \cosh z)}. \tag{31}$$

After simplifications, one gets

$$T = \frac{L^2}{2D}\left(1 + \frac{3}{\kappa}\right). \tag{32}$$

For comparison, the global MFPT for a single particle, which is obtained by integrating Eq. (10), is $\frac{L^2}{3D}(1 + \frac{3}{\kappa})$.

B. Fully absorbing target ($\kappa = \infty$)

The division of Eq. (23) by κ^2 removes again the non-diagonal terms in the limit $\kappa \to \infty$, yielding an explicit solution

$$\tilde{c}_n = \frac{1}{\alpha_n^2} \tag{33}$$

from which

$$c_n = \frac{(-1)^n}{\alpha_n^3 \cosh \alpha_n}, \tag{34}$$

where $\alpha_n = \pi(n + 1/2)$. As expected, when the target is perfectly absorbing, a particle released after some residence time is immediately re-adsorbed, so that the result does not depend on μ. We then get

$$t(x, y) = \frac{2L^2 - x^2 - y^2}{4D} + \frac{L^2}{D} \sum_{n=0}^{\infty} \frac{(-1)^n}{\alpha_n^3} \frac{\cos(\alpha_n x/L)\cosh(\alpha_n y/L) + \cos(\alpha_n y/L)\cosh(\alpha_n x/L)}{\cosh \alpha_n}. \tag{35}$$

We also obtain the global MFPT,

$$T = \frac{L^2}{D}\left(\frac{1}{3} + \sum_{n=0}^{\infty} \frac{1}{\alpha_n^4}\right) = \frac{L^2}{2D}. \tag{36}$$

C. General approximate solution

In general, finding the exact explicit solution of Eq. (23) remains problematic. When μ is not too large, an approximate solution can be obtained within "a diagonal approximation" that was shown to be efficient for finding the MFPT for other surface-mediated diffusions.[27–30] This approximation consists in neglecting all non-diagonal elements in the matrix form of these linear equations. A straightforward application of this approximation to Eq. (23) would yield a rather complicated approximation of a limited practical use. To get a more convenient approximation, we use the identity (see the Appendix),

$$\sum_{n=0}^{\infty} \frac{1}{(z^2 + \alpha_n^2)(\kappa^2 + \kappa + \alpha_n^2)} = \frac{\sinh z}{2z\kappa(z \sinh z + \kappa \cosh z)}. \tag{37}$$

Denoting

$$\hat{c}_n = \tilde{c}_n(\kappa^2 + \kappa + \alpha_n^2), \tag{38}$$

Eq. (23) can be rewritten as

$$\hat{c}_n - 2\kappa\mu \sum_{k=0}^{\infty} \frac{\hat{c}_k - \hat{c}_n}{(\alpha_n^2 + \alpha_k^2)(\kappa^2 + \kappa + \alpha_k^2)} = \frac{\kappa}{\alpha_n^2}(\mu + 2\alpha_n^2 + \kappa). \tag{39}$$

The diagonal approximation applied to this form of linear equations consists in neglecting the sum that yields a simple approximate solution

$$\tilde{c}_n \approx \frac{\kappa(\mu + 2\alpha_n^2 + \kappa)}{\alpha_n^2(\kappa^2 + \kappa + \alpha_n^2)}. \tag{40}$$

Substituting this approximation into Eq. (25b) and calculating the series by using Eq. (37), we get an explicit approximation for the global MFPT,

$$T_{\rm app} = \frac{L^2}{D} \frac{(\kappa + 3)(\mu + 3\kappa)}{6\kappa^2} = \frac{L^2}{2D}\left(1 + \frac{3D}{Lk_{\rm on}}\right)\left(1 + \frac{k_{\rm off}L}{3k_{\rm on}}\right). \tag{41}$$

This approximation is one of the main practical results of the paper that illustrates the influence of the reversible binding to the target onto the MFPT through the second factor [note that the first factor is the MFPT for uncoupled particles, see Eq. (32)]. The approximation becomes exact in the limit $\mu \to 0$ [see Eq. (32)] and in the limit $\kappa \to \infty$ [see Eq. (36)].

Figure 4 illustrates the quality of this approximation. As expected, the approximation is very accurate for small μ. Even for large μ, one also gets accurate results whenever $\kappa \ll 1$ or $\kappa \gg 1$. The worst situation corresponds to large μ and $\kappa \sim 1$. Note also that $T_{\rm app}$ turns out to be the upper bound for T.

D. Asymptotic behavior for large μ and small κ

Given that the regime of large μ is not easily accessible from the analysis of Eq. (23), we provide below some probabilistic arguments to estimate the MFPT. Since the starting point does not matter in this regime, we do not distinguish MFPT and global MFPT. More precisely, we consider the asymptotic behavior for large μ and small κ. In this case, the mean time of each bulk excursion for each particle is large [being of the order of $L^2/(D\kappa)$, see Eq. (10)], whereas the mean residence time on the target, $1/k_{\rm off}$, is small. Let us consider the history of arrivals of one pre-selected particle on the target. The second particle needs to arrive on the target during short residence periods of the first particle. The probability of finding the second particle at the target is approximately the ratio of the residence and excursion times, i.e., κ/μ. On average, one needs approximately $1/(\kappa/\mu)$ trials for this rare event to occur. Since the duration of one trial is dominated by the excursion time, the MFPT is of the order

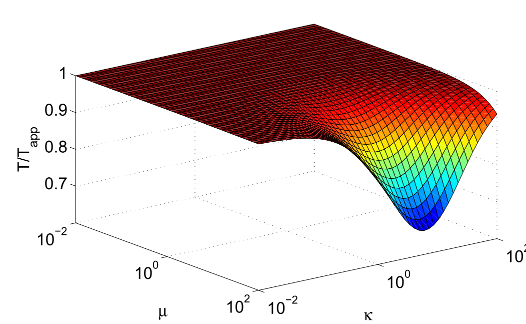

FIG. 4. The global MFPT T divided by its approximation $T_{\rm app}$ from Eq. (41) as a function of κ and μ.

of $(\mu/\kappa)\ L^2/(D\kappa)$. Alternatively, one could select the second particle and estimate the probability of arrivals of the first particle. These two equivalent considerations halve the MFPT, yielding

$$T \simeq \frac{L^2}{D}\frac{\mu}{2\kappa^2} \qquad (\mu \gg 1,\ \kappa \ll 1). \tag{42}$$

Note that the approximation in Eq. (41) predicts the correct asymptotic behavior $\mu/(2\kappa^2)$ for large μ and small κ, and its agrees well with the exact solution (see Fig. 4).

V. CONCLUSIONS

We considered the first passage time problem for multiple "impatient" particles that search for a target, partially adsorb on the target, and then desorb after a random residence time due to reversible target-binding kinetics. We were interested in characterizing the first time when m independent diffusing particles are simultaneously present at the target. The desorption mechanism leads to intricate temporal coupling even between independent particles. In order to reveal the respective roles of the finite reactivity of the target ($k_{\rm on}$) and the desorption rate ($k_{\rm off}$) onto the mean FPT, we simplified as much as possible the geometric domain, focusing on two independent particles undergoing one-dimensional diffusion on the interval (or between parallel walls). Mapping this problem onto surface-mediated diffusion in the square, we managed to obtain a semi-analytical solution of the underlying coupled PDEs. The obtained formula for the MFPT exhibits an analytical dependence on the starting point but requires a numerical solution of the system of linear equations on the coefficients. The fast decay of the coefficients allows one to get very accurate results with moderate truncation sizes. Moreover, for moderate desorption rates, we derived an explicit approximate solution for the MFPT. In particular, the approximation in Eq. (41) for the global MFPT helps to grasp the respective roles of the two major parameters of the model. We also showed that small reactivity or large desorption rate can increase the MFPT by many orders of magnitude, playing thus an important role in the analysis of chemical and biochemical reactions that involve several reactants. The reversible binding to the target (accounted for through the desorption rate $k_{\rm off}$) had been largely ignored in former studies of the MFPT.

The proposed derivation can potentially be extended to many particles but the analysis becomes substantially more cumbersome. For instance, one-dimensional diffusion of three independent particles can be mapped onto surface-mediated diffusion in a cube, which has three reflecting and three partially absorbing faces. Once a particle is adsorbed on such a face, it starts two-dimensional diffusion on that face, which has two reflecting and two partially absorbing edges. One can write the coupled PDEs for seven MFPTs to the corner (L, L, L): one for the starting point in the cube, three for the starting point in each of three faces, and three for the starting point in each of three edges. Although the solution seems to be feasible, the derivation is rather involved. An extension to a larger number of particles would result in even a larger system of coupled PDEs.

The main idea of mapping the first passage time problem for multiple particles onto surface-mediated diffusion is not limited to one-dimensional diffusion considered in this paper. For instance, the trajectories of two independent particles diffusing in a three-dimensional domain Ω can be considered as coordinates of surface-mediated diffusion in the six-dimensional domain $\Omega \times \Omega$. While chances of getting the semi-analytical solution of this problem remain elusive in general, our results can potentially be extended to rotation-invariant domains. This problem will be addressed in a future work.

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APPENDIX: DERIVATION OF SUMMATION IDENTITIES

We briefly discuss the derivation of the identities (31) and (37) that we used to compute the global MFPT and to get an approximate solution for the coefficients $\tilde{c}_n$. In general, such identities can be derived as partial fraction expansions of appropriate meromorphic functions over their poles (Mittag-Leffler's theorem in complex analysis). For the considered model of one-dimensional diffusion, a simpler and straightforward derivation comes from the Laplace transformation of the survival probability. It is elementary to derive the solution of the Laplace-transformed diffusion equation, $(p - D\partial_x^2)\tilde{S}(p,x) = 1$ for $0 < x < 1$, subject to the boundary conditions (2b) and (2c),

$$\tilde{S}(p;x) = \frac{1}{p}\left(1 - \frac{\kappa\cosh(x\sqrt{\frac{p}{D}})}{\kappa\cosh(L\sqrt{\frac{p}{D}}) + L\sqrt{\frac{p}{D}}\sinh(L\sqrt{\frac{p}{D}})}\right). \tag{A1}$$

The comparison of this relation to the Laplace transform of the survival probability in Eq. (9) yields the identity

$$\sum_{n=0}^{\infty} \frac{1}{(\kappa^2+\kappa+\alpha_n^2)(\alpha_n^2+z^2)}\frac{\cos(\alpha_n x)}{\cos\alpha_n} = \frac{1}{2z^2\kappa}\left(1 - \frac{\kappa\cosh(xz)}{\kappa\cosh z + z\sinh z}\right), \tag{A2}$$

where we set $z = L\sqrt{p/D}$ and $L = 1$, and used Eq. (8). This identity is valid for any positive z and κ, and any x between 0 and 1. Setting $x = 1$, one gets immediately Eq. (37). Taking twice the derivative with respect to x at $x = 1$ and setting $z \to 0$, one finds

$$\sum_{n=0}^{\infty} \frac{1}{\kappa^2+\kappa+\alpha_n^2} = \frac{1}{2\kappa}. \tag{A3}$$

Finally, rewriting the first factor in the left-hand side of Eq. (A2) as the sum of two partial fractions, setting again $x = 1$, and using Eq. (A3), one derives Eq. (31).

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