Diffusive search for diffusing targets with fluctuating diffusivity and gating

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July 2, 2019

Abstract

The time that it takes a diffusing particle to find a small target has emerged as a critical quantity in many systems in molecular and cellular biology. In this paper, we extend the theory for calculating this time to account for several ubiquitous biological features which have largely been ignored in the mathematics and physics literature on this problem. In particular, we allow (i) targets to diffuse on the two-dimensional boundary of the three-dimensional domain, (ii) targets to diffuse in the interior of the domain, (iii) the diffusivities of the searcher particle and the targets to stochastically fluctuate, (iv) targets to be stochastically gated, and (v) the transition times between fluctuations in diffusivity and gating to have effectively any probability distribution. In this general framework, we analytically calculate the leading order behavior of the mean first passage time and splitting probability for the searcher to reach a target as the target size decays, which is the so-called narrow escape limit. To make these extensions, we use a generalized Itô's formula to derive a system of coupled partial differential equations which are satisfied by statistics of the process, where the size of the system and its spatial dimension can be arbitrarily large. We apply matched asymptotic analysis to this system and verify our analytical results by numerical simulation. Our results reveal several new features and generic principles of diffusive search for small targets.

1 Introduction

Over the past decade, there has been a surge of interest from mathematicians and physicists in the so-called narrow escape problem (NEP) [34]. The NEP is to determine the time that it takes a diffusing particle to find a small target on the boundary or in the interior of a bounded domain with a reflecting boundary.

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Mathematically, the NEP typically takes the form of a Poisson equation in two or three space dimensions with mixed Dirichlet/Neumann boundary conditions and/or Dirichlet conditions on holes in the interior of the domain. One then studies how the solution to this partial differential equation (PDE) diverges as the size of the Dirichlet part of the boundary vanishes, which yields the behavior of the mean first passage time (MFPT) for a diffusing "searcher" particle to find a vanishingly small target. Much of the mathematical work has focused on determining how the MFPT depends on geometric features, such as the shape and size of the domain and the shapes and arrangement of the targets.

While the NEP dates back to Helmholtz [33] and Lord Rayleigh [54] in the context of acoustics, the renewed interest stems primarily from applications to molecular and cellular biology (and also ecology [41]). In essence, the NEP finds broad application to biology since the timescale of many biological processes depends on the arrival of diffusing ligands to small (often membrane-bound) proteins (see [4, 16, 32, 34, 35] for more details).

However, previous work on the NEP has largely ignored several biological features, and there is a growing body of experimental evidence indicating that these features play important roles in certain physiological contexts. One such feature is *lateral diffusion*, in which membrane-bound proteins diffuse on a two-dimensional membrane surface [1]. From a mathematical standpoint, calculating the time for a ligand diffusing in a three-dimensional domain to reach targets diffusing on the two-dimensional boundary increases the spatial dimension of the PDE describing the MFPT and effectively makes the diffusion operator anisotropic. By assuming that the membrane-bound proteins are immobile, previous work has avoided such mathematical complications. Nevertheless, the lateral diffusion of membrane components is essential to a variety of physiological processes [58].

Complicating the matter further, not only can target proteins diffuse, but their diffusivity (diffusion coefficient) can stochastically fluctuate between two or more discrete values. For example, AMPA receptors on the post-synaptic membrane alternate within seconds between rapid diffusive and stationary behavior [6], and LFA-1 receptors alternate between fast and slow diffusive states [22, 61]. For LFA-1 receptors, we further note that the random transition times between diffusive states is not exponentially distributed [61]. Due to the prevalence of fluctuating diffusivity in cell biology (sometimes called diffusion heterogeneity), a number of statistical methods have recently been developed to analyze single particle tracking data and detect changes in diffusivity [22, 40, 48, 49, 52, 60, 61]. These methods can also infer parameters, such as the state-dependent diffusivities, the number of diffusive states, and the transition rates between states. Physically, distinct diffusion states typically model either (i) binding/unbinding of the diffusing particle to other molecules that slow its diffusion or (ii) distinct conformational states of a large macromolecule with distinct diffusivities associated with the effective sizes of the conformations (such as globular versus fibrous states) [17, 31, 67].

One final complicating factor is that reactions may be stochastically gated. That is, the diffusing ligand and/or the target may switch between discrete states, with reaction only possible in certain states. For example, enzymes diffusing in the cytoplasm can switch between active and inactive states [53], and transcription factors diffusing in the nucleus bind to DNA promoters with a fluctuating affinity [3]. In the context of cellular transport, molecules with diameter larger than a few nanometers must bind to a molecular chaperone in order to move in and out of the nucleus [24, 63]. Another example is the membrane transport of charged particles through voltage-gated or ligand-gated ion channels that stochastically open and close. For ion channels, we note that the random time between opening and closing is typically not exponentially distributed [30].

Motivated by the aforementioned biological features, in this paper we make several extensions to the NEP. We consider a *searcher* diffusing in a bounded three-dimensional domain with a collection of small *boundary targets* which reside on the domain's two-dimensional boundary and a collection of small *interior targets* that reside in the three-dimensional domain. We make the following extensions, all of which are considered simultaneously. We first allow the boundary targets to diffuse on the surface of the boundary. Second, we allow the interior targets to diffuse in the domain. Third, we allow the diffusivities of the searcher and the targets to stochastically fluctuate. Fourth, we allow the targets to be stochastically gated, meaning they fluctuate between absorbing and reflecting the searcher. Fifth, we do not restrict ourselves to exponentially distributed waiting times between fluctuations in diffusivity and gating, as the random times between these transitions can have any phase probability distribution [50]. Since phase distributions are dense in the set of nonnegative distributions [50], our results hold for effectively any choice of transition time distributions. Furthermore, we do not make any assumptions about the correlations between the diffusive and gating states of the searcher and targets. In this general setup, we analytically calculate the leading order behavior of the MFPT for the searcher to find a target as the target size decays (the narrow escape limit). We also calculate the leading order behavior of the so-called splitting probability, which is the probability that the searcher reaches a given target before any other target. Our results hold for a general class of three-dimensional domains bounded by a smooth level surface of an orthogonal coordinate system, which includes ellipsoids and other solids of revolution [29].

To make these extensions, we use a generalized Itô's formula to derive a large system of coupled PDEs satisfied by the MFPT in a large number of space dimensions. Depending on the number of targets and their fluctuations in diffusivity and gating, the size of the coupled PDE system and its space dimension can each be arbitrarily large. We then apply matched asymptotic analysis to this PDE system in the limit that the targets are small. We derive a similar system and perform similar analysis to analyze the splitting probabilities. Our analytical results are verified by numerical simulations.

We now summarize a few salient features of diffusive search for small targets that emerge from our analysis. First, compared to immobile targets, making the boundary targets diffuse decreases the MFPT by a factor that depends nonlinearly on the ratio of target and searcher diffusivities. Importantly, this factor is independent of the geometry of the domain and the number of targets. Therefore, this factor provides a simple way to quantitatively estimate how target diffusion affects association rates in specific biophysical scenarios, merely requiring one to know approximate target and searcher diffusivities. This analysis also reveals how the diffusivity of a single target may increase the likelihood that the searcher reaches that target before any other target.

Second, making interior targets diffuse also decreases the MFPT by a factor that depends on the ratio of target and searcher diffusivities. We find that interior target diffusion decreases the MFPT more than boundary target diffusion, which reflects the fact that interior targets diffuse in three-dimensions, but boundary targets are restricted to a two-dimensional surface. Third, fluctuations in searcher and interior target diffusivity can often be incorporated by merely assuming a simple averaged diffusivity. In contrast, the effect of fluctuations in boundary target diffusivity is more delicate. Finally, we find that gating affects first passage statistics in a relatively straightforward manner that depends only on the proportion of time that each gate is open.

The rest of the paper is organized as follows. Section 2 summarizes our main results. In section 3, we derive the PDE boundary value problem satisfied by the MFPT and employ matched asymptotic analysis to study its solution. We then study the splitting probability in section 4. We illustrate our general results in some specific examples in section 5, which reveals several general features of diffusive search. We compare our analytical results to numerical simulations in section 6. We conclude by discussing relations to previous work and highlighting future directions.

2 Main results

Consider a *searcher* diffusing with diffusivity $D_0 > 0$ in a bounded, three-dimensional domain $\Omega \subset \mathbb{R}^3$ with smooth boundary $\partial\Omega$. Assume that most of the boundary is reflecting, except for $N^{\mathrm{b}} \geq 1$ small, well-separated disk-shaped *boundary targets* with $\mathcal{O}(\varepsilon)$ radii for $\varepsilon \ll 1$. It is known [19] that the MFPT, T, for the searcher to reach a boundary target has the following asymptotic behavior

$$T \sim \frac{|\Omega|}{\varepsilon D_0 2\pi \sum_{n=1}^{N^{\mathrm{b}}} C_n^{\mathrm{b}}}, \quad \text{as } \varepsilon \to 0, \tag{2.1}$$

where $C_1^{\mathrm{b}}, C_2^{\mathrm{b}}, \dots, C_{N^{\mathrm{b}}}^{\mathrm{b}}$ are the capacitances of the boundary targets, which depend on their relative radii. If instead of boundary targets, the domain Ω contains $N^{\mathrm{i}} \geq 1$ small, well-separated interior targets with $\mathcal{O}(\varepsilon)$ diameters for $\varepsilon \ll 1$, then it is known [18] that the MFPT for the searcher to reach an interior target satisfies

$$T \sim \frac{|\Omega|}{\varepsilon D_0 4\pi \sum_{n=1}^{N^{\mathrm{i}}} C_n^{\mathrm{i}}}, \quad \text{as } \varepsilon \to 0, \tag{2.2}$$

where $C_1^{\mathrm{i}}, C_2^{\mathrm{i}}, \dots, C_{N^{\mathrm{i}}}^{\mathrm{i}}$ are the capacitances of the interior targets, which depend on their shapes and relative sizes. We also note that the probability p_n that the searcher reaches the nth target before any other target is the ratio of capacitances,

$$p_n \sim \frac{C_n^a}{\sum_{k=1}^{N^a} C_k^a}, \quad \text{as } \varepsilon \to 0, \quad a \in \{\mathrm{b}, \mathrm{i}\}, \tag{2.3}$$

for the case of either boundary targets ($a = \mathrm{b}$) or interior targets ($a = \mathrm{i}$) [18]. Equations (2.1), (2.2), and (2.3) assume that the searcher is initially outside an $\mathcal{O}(\varepsilon)$ neighborhood of all the targets. It therefore follows that (2.1), (2.2), and (2.3) are also valid assuming the searcher starts at uniformly distributed initial location, since in that case the probability that the searcher starts in an $\mathcal{O}(\varepsilon)$ of a target is $\mathcal{O}(\varepsilon)$.

We generalize these results to include the possibility that (i) the boundary targets diffuse on the boundary $\partial\Omega$, (ii) the interior targets diffuse in the domain Ω, (iii) the searcher and target diffusivities stochastically fluctuate, and (iv) the boundary and interior targets are stochastically gated, meaning they fluctuate between absorbing and reflecting the searcher. When a target is absorbing, we say it is *open*, and when it is reflecting, we say it is *closed*. We make no assumptions on correlations between these stochastic fluctuations. That is, the gating and diffusivity fluctuations can be independent, perfectly correlated, or have some nontrivial correlations. We suppose the domain $\Omega \subset \mathbb{R}^3$ is bounded by a smooth level surface of an orthogonal coordinate system, which includes ellipsoids and other solids of revolution [29].

To describe our results, let $J(t) \in \mathcal{J}$ be an irreducible continuous-time Markov jump process on the finite state space $\mathcal{J}$ that governs the searcher and target diffusivities and target gate states (open or closed). That is, each $j \in \mathcal{J}$ corresponds to a searcher diffusivity $D_0(j) > 0$, interior target diffusivities

$$D_1^{\mathrm{i}}(j),\, D_2^{\mathrm{i}}(j),\, \dots,\, D_{N^{\mathrm{i}}}^{\mathrm{i}}(j) \geq 0,$$

boundary target diffusivities

$$D_1^{\mathrm{b}}(j),\, D_2^{\mathrm{b}}(j),\, \dots, D_{N^{\mathrm{b}}}^{\mathrm{b}}(j) \geq 0,$$

interior target gate states

$$S_1^{\mathrm{i}}(j),\, S_2^{\mathrm{i}}(j),\, \dots,\, S_{N^{\mathrm{i}}}^{\mathrm{i}}(j) \in \{0, 1\},$$

and boundary target gate states

$$S_1^{\mathrm{b}}(j),\, S_2^{\mathrm{b}}(j),\, \dots,\, S_{N^{\mathrm{b}}}^{\mathrm{b}}(j) \in \{0, 1\}.$$

For the gate states, $S_n^{\mathrm{i}}(j) = 1$ ($S_n^{\mathrm{i}}(j) = 0$) means that the nth interior target is open (closed) when $J(t) = j$, and similarly for $S_n^{\mathrm{b}}(j)$. We note that any correlations between diffusivity fluctuations and gating are encoded in the dynamics of the jump process $J(t)$. We emphasize that though the time between jumps of $J(t)$ is exponentially distributed, by introducing intermediate states to $J(t)$ we can choose the time between changes in diffusivity and gating to have any phase distribution, which are dense in the set of distributions (see section 3). We further note that the state space of $\mathcal{J}$ can be quite large. For example, if the searcher and targets each switch independently between K diffusivities, and each target opens and closes independently, then the cardinality of the state space is at least $|\mathcal{J}| \geq 2^{N^{\mathrm{i}}+N^{\mathrm{b}}} K^{1+N^{\mathrm{i}}+N^{\mathrm{b}}}$.

In this general setup, we find that the MFPT has the following asymptotic behavior

$$T \sim \frac{|\Omega|}{\varepsilon \sum_{j\in\mathcal{J}} \gamma(j) D_0(j) \Big[2\pi \sum_{n=1}^{N^{\mathrm{b}}} \overline{C}_n^{\mathrm{b}}(j) + 4\pi \sum_{n=1}^{N^{\mathrm{i}}} \overline{C}_n^{\mathrm{i}}(j)\Big]}, \quad \text{as } \varepsilon \to 0, \quad (2.4)$$

where $\{\gamma(j)\}_{j\in\mathcal{J}}$ is the invariant measure of $J(t)$ and

$$\begin{aligned} \overline{C}_n^{\mathrm{b}}(j) &:= S_n^{\mathrm{b}}(j) C_n^{\mathrm{b}} \sqrt{1 + \frac{D_n^{\mathrm{b}}(j)}{D_0(j)}}, \quad n \in \{1, \dots, N^{\mathrm{b}}\}, \\ \overline{C}_n^{\mathrm{i}}(j) &:= S_n^{\mathrm{i}}(j) C_n^{\mathrm{i}} \left(1 + \frac{D_n^{\mathrm{i}}(j)}{D_0(j)}\right), \quad n \in \{1, \dots, N^{\mathrm{i}}\}. \end{aligned} \quad (2.5)$$

Equation (2.4) assumes that the searcher is initially outside an $\mathcal{O}(\varepsilon)$ neighborhood of all the targets. Hence, (2.4) is also valid if the searcher starts at a random initial location, as long as the probability that the searcher starts in an $\mathcal{O}(\varepsilon)$ neighborhood of a target vanishes as $\varepsilon \to 0$ (which includes the case of a uniformly distributed initial location). We comment on the validity of (2.4) in the limit of small or large boundary and interior target diffusivity in the Discussion below. We investigate the implications of (2.4) in several special cases in section 5 below.

The parameters in (2.5) can be interpreted as the effective target capacitances for each state $j \in \mathcal{J}$. To see this, first note that the capacitance is zero if the target is closed ($S_n^{\mathrm{b}}(j) = 0$ or $S_n^{\mathrm{i}}(j) = 0$). Next, if a boundary target diffuses with diffusivity $D_n^{\mathrm{b}}(j) \geq 0$ while the searcher diffuses with diffusivity $D_0(j)$, then the boundary target capacitance increases by the dimensionless factor

$$\sqrt{1 + D_n^{\mathrm{b}}(j)/D_0(j)} \geq 1. \quad (2.6)$$

Effectively, the surface diffusion of the boundary target causes it to occupy a larger area of the boundary. Similarly, if an interior target diffuses with diffusivity $D_n^{\mathrm{i}}(j) \geq 0$ while the searcher diffuses with diffusivity $D_0(j)$, then the interior target capacitance increases by

$$1 + D_n^{\mathrm{i}}(j)/D_0(j) \geq 1. \quad (2.7)$$

Notice that the capacitance increase for a diffusing interior target is larger than for a diffusing boundary target. This reflects the fact that diffusing boundary targets are restricted to the two-dimensional boundary, whereas diffusing interior targets diffuse in the three-dimensional domain.

After interpreting (2.5) as effective target capacitances, the result in (2.4) is quite intuitive. In particular, equations (2.1)-(2.2) imply that the MFPT should be inversely proportional to the product of the searcher diffusivity and the sum of the target capacitances. Equation (2.4) generalizes this point by averaging over the diffusivity/gate states, $j \in \mathcal{J}$, and using the effective capacitances in (2.5).

Furthermore, we show that the probability that the searcher reaches the nth boundary target before any other target is

$$p_n^{\mathrm{b}} \sim \frac{2\pi \sum_{j\in\mathcal{J}} \overline{C}_n^{\mathrm{b}}(j)}{2\pi \sum_{j\in\mathcal{J}} \sum_{n=1}^{N^{\mathrm{b}}} \overline{C}_n^{\mathrm{b}}(j) + 4\pi \sum_{j\in\mathcal{J}} \sum_{n=1}^{N^{\mathrm{i}}} \overline{C}_n^{\mathrm{i}}(j)}, \quad \text{as } \varepsilon \to 0. \tag{2.8}$$

Similarly, the probability that the searcher first reaches the nth interior target is

$$p_n^{\mathrm{i}} \sim \frac{4\pi \sum_{j\in\mathcal{J}} \overline{C}_n^{\mathrm{i}}(j)}{4\pi \sum_{j\in\mathcal{J}} \sum_{n=1}^{N^{\mathrm{b}}} \overline{C}_n^{\mathrm{i}}(j) + 4\pi \sum_{j\in\mathcal{J}} \sum_{n=1}^{N^{\mathrm{i}}} \overline{C}_n^{\mathrm{i}}(j)}, \quad \text{as } \varepsilon \to 0. \tag{2.9}$$

Hence, (2.8)-(2.9) are analogous to (2.3) in that the splitting probability involves the ratio of average effective capacitances. Again, (2.8) and (2.9) assume that the searcher is initially outside an $\mathcal{O}(\varepsilon)$ neighborhood of all the targets (or the probability that the searcher starts in an $\mathcal{O}(\varepsilon)$ neighborhood of a target vanishes as $\varepsilon \to 0$).

3 Mean first passage time

As above, consider a searcher $X(t)$ diffusing in a bounded, three-dimensional domain $\Omega \subset \mathbb{R}^3$. Assume that $N^{\mathrm{i}} \geq 0$ interior targets labeled $Y_1, \dots, Y_{N^{\mathrm{i}}}(t)$ diffuse independently in the domain Ω. In addition, assume that $N^{\mathrm{b}} \geq 0$ boundary targets labeled $Z_1(t), \dots, Z_{N^{\mathrm{b}}}(t)$ diffuse independently on the boundary $\partial\Omega$. To avoid trivialities, we assume that there is at least one target, $N^{\mathrm{i}} + N^{\mathrm{b}} \geq 1$.

3.1 Fluctuations in diffusivity and gating

As above, let $J(t) \in \mathcal{J}$ be a continuous-time Markov jump process controlling the diffusivities and gate states. Let $Q \in \mathbb{R}^{|\mathcal{J}|\times|\mathcal{J}|}$ denote the infinitesimal generator of $J(t)$. That is, the off-diagonal entry $Q(i,j) \geq 0$ of Q gives the rate that $J(t)$ jumps from state $i \in \mathcal{J}$ to state $j \in \mathcal{J}$, and the diagonal entries $Q(j,j)$ are chosen so that Q has zero row sums. Let $\gamma \in \mathbb{R}^{1\times|\mathcal{J}|}$ denote the invariant measure of $J(t)$, which means

$$\gamma Q = 0 \quad \text{and} \quad \sum_{j\in\mathcal{J}} \gamma(j) = 1. \tag{3.1}$$

We assume that $J(t)$ is irreducible with a finite state space, and thus the existence and uniqueness of γ is guaranteed. We note that the property $\gamma Q = 0$ plays a crucial role in our asymptotic analysis below.

Since $J(t)$ is a continuous-time Markov jump process, the time between jumps of $J(t)$ is necessarily exponentially distributed. However, the time between transitions in diffusivity or gating (opening and closing) can be chosen from the class of probability distributions known as phase distributions. Since the probability distribution of any nonnegative random variable can be arbitrarily well approximated by a phase distribution [50], our results hold for effectively any choice of transition time distribution. To make this generalization to non-exponential transition times, one introduces a sequence (or network) of intermediate states to $J(t)$ so that $J(t)$ must traverse these intermediate states before a change in diffusivity or gating occurs (see [50] for details). We note that this basic idea is similar to the well-known "linear chain trick" in ordinary differential equation modeling [21, 36].

We follow [29] and assume that our domain is bounded by the level surface of an orthogonal coordinate system. Specifically, we assume (μ, ν, ω) is an orthogonal coordinate system in $\mathbb{R}^3$ such that fixing μ and varying $\nu \in [0, \nu_0]$ and $\omega \in [0, \omega_0]$ leads to a smooth closed bounded surface in $\mathbb{R}^3$. We define the domain Ω and its boundary $\partial\Omega$ by

$$\begin{aligned}\Omega &:= \{(\mu, \nu, \omega) : \mu \in [0, \mu_0), \nu \in [0, \nu_0], \omega \in [0, \omega_0]\},\\ \partial\Omega &:= \{(\mu, \nu, \omega) : \mu = \mu_0, \nu \in [0, \nu_0], \omega \in [0, \omega_0]\}.\end{aligned}$$

Observe that this implies that the derivative in the direction normal to the surface $\partial\Omega$ is the derivative with respect to μ, denoted as ∂_μ. We denote the scale factors for this coordinate system by $h_\mu(x)$, $h_\nu(x)$, $h_\omega(x)$ for $x \in \mathbb{R}^3$.

We note that this general class of domains includes ellipsoids and all axially symmetric domains [29]. In the Discussion section below, we discuss extending our results to other classes of domains.

The reader may find it useful to keep in mind the special case of a domain Ω that is a sphere of radius $R > 0$, in which case our orthogonal coordinates are the standard spherical coordinates; namely, $(\mu, \nu, \omega) = (r, \theta, \varphi)$, $(\mu_0, \nu_0, \omega_0) = (R, \pi, 2\pi)$, and $(h_\mu(x), h_\nu(x), h_\omega(x)) = (1, r, r\sin(\theta))$.

In this orthogonal coordinate system, the position of the nth boundary target, $Z_n(t) = (\mu_0, \nu_n(t), \omega_n(t)) \in \partial\Omega$, obeys the stochastic differential equations (SDEs),

$$\begin{aligned}\mathrm{d}\nu_n(t) &= \frac{D_n^{\mathrm{b}}(J(t))}{h_\mu h_\nu h_\omega}\partial_\nu\Big(\frac{h_\mu h_\omega}{h_\nu}\Big)\,\mathrm{d}t + \frac{\sqrt{2D_n^{\mathrm{b}}(J(t))}}{h_\nu}\,\mathrm{d}W_{(\nu,n)},\\ \mathrm{d}\omega_n(t) &= \frac{D_n^{\mathrm{b}}(J(t))}{h_\mu h_\nu h_\omega}\partial_\omega\Big(\frac{h_\mu h_\nu}{h_\omega}\Big)\,\mathrm{d}t + \frac{\sqrt{2D_n^{\mathrm{b}}(J(t))}}{h_\omega}\,\mathrm{d}W_{(\omega,n)}, \quad n \in \{1, \dots, N^{\mathrm{b}}\},\end{aligned} \tag{3.2}$$

where $\{W_{(n,\nu)}\}_{n=1}^{N^{\mathrm{b}}}$ and $\{W_{(n,\omega)}\}_{n=1}^{N^{\mathrm{b}}}$ are independent standard Brownian motions. These SDEs can be derived from the formula for the Laplace-Beltrami operator in the (μ, ν, ω) coordinate system (see (3.13) below).

The SDE describing the position of the searcher $X(t) \in \overline{\Omega} \subset \mathbb{R}^3$ is simplest to express in Cartesian coordinates,

$$\mathrm{d}X(t) = \sqrt{2D_0(J(t))}\,\mathrm{d}\mathbf{W}_0(t) + \mathbf{n}(X(t))\,\mathrm{d}L_0(t), \tag{3.3}$$

where $\mathbf{W}_0(t)$ is an independent $\mathbb{R}^3$-valued standard Brownian motion, $\mathbf{n} : \partial\Omega \mapsto \mathbb{R}^3$ is the inner normal field, and $L_0(t)$ is the local time [38] of $X(t)$ on $\partial\Omega$. The local time is the time that $X(t)$ spends on $\partial\Omega$. More precisely, $L_0(t)$ is non-decreasing and increases only when $X(t)$ is on $\partial\Omega$ and $L_0(0) = 0$. The significance of the local time term in (3.3) is that it forces X to reflect from $\partial\Omega$ in the normal direction and thus ensures that $X(t) \in \overline{\Omega}$ for all $t \geq 0$. Similarly, the interior target positions satisfy

$$\mathrm{d}Y_n(t) = \sqrt{2D_n^{\mathrm{i}}(J(t))}\,\mathrm{d}\mathbf{W}_n(t) + \mathbf{n}(Y_n(t))\,\mathrm{d}L_n(t), \quad n \in \{1, \ldots, N^{\mathrm{i}}\}, \tag{3.4}$$

where $\mathbf{W}_n(t)$ is an independent $\mathbb{R}^3$-valued standard Brownian motion and $L_n(t)$ is the local time of $Y_n(t)$ on $\partial\Omega$.

We point out that (3.2)-(3.4) imply that the paths of the searcher and the targets are noninteracting. However, we emphasize that the diffusivities in (3.2)-(3.4) can change when the Markov process $J(t)$ jumps. Hence, the searcher and target paths may be correlated since their diffusivities can depend on the common jump process $J(t)$.

3.2 PDE boundary value problem for the MFPT

We are interested in the first time that the searcher reaches a small neighborhood of an open target. The region near the interior targets is the union,

$$\cup_{n=1}^{N^{\mathrm{i}}} \Omega_n^{\varepsilon}(Y_n(t)), \tag{3.5}$$

where

$$\Omega_n^{\varepsilon}(y) := \{x \in \Omega : \varepsilon^{-1}(x - y) \in \Omega_n\}, \tag{3.6}$$

where $\Omega_n \subset \mathbb{R}^3$ is a bounded, connected open set containing the origin with smooth boundary for each $n \in \{1, \ldots, N^{\mathrm{i}}\}$ and $\varepsilon \ll 1$. We emphasize that since the target positions are stochastic processes, the region in (3.5) is also stochastic.

The region of the boundary near the boundary targets is

$$\cup_{n=1}^{N^{\mathrm{b}}} \Gamma(Z_n(t), \varepsilon a_n), \tag{3.7}$$

where for a point $z = (\mu_0, \nu_z, \omega_z) \in \partial\Omega$, we let $\Gamma(z, \varepsilon a) \subset \partial\Omega$ denote the small disk-like region,

$$\Gamma(z, \varepsilon a) := \{(\mu_0, \nu, \omega) : (h_\nu(z)(\nu - \nu_z))^2 + (h_\omega(z)(\omega - \omega_z))^2 \leq (\varepsilon a)^2\}, \tag{3.8}$$

and $\varepsilon \ll 1$. We note that if Ω is a sphere of radius $R > 0$, then $\Gamma(z, \varepsilon R)$ is the spherical cap centered at $z \in \partial\Omega$ with curved surface area $2\pi R^2(1 - \cos(\varepsilon)) = \pi(\varepsilon R)^2 + \mathcal{O}(\varepsilon^4)$.

Let $S^{\rm i}(j) \subset \{1,\dots,N^{\rm i}\}$ denote the set of indices of interior targets that are open when $J(t) = j \in \mathcal{J}$,

$$S^{\rm i}(j) := \{n : S^{\rm i}_n(j) = 1\}.$$

For boundary targets, we similarly define $S^{\rm b}(j) := \{n : S^{\rm b}_n(j) = 1\}$. Define the stopping time

$$\tau := \inf\Big\{t \geq 0 : X(t) \in \big\{\cup_{n\in S^{\rm i}(J(t))}\,\Omega^{\varepsilon}_n(Y_n(t))\big\} \cup \big\{\cup_{n\in S^{\rm b}(J(t))}\,\Gamma(Z_n(t),\varepsilon a_n)\big\}\Big\}, \tag{3.9}$$

which is the first time the searcher reaches an open target (boundary or interior), and the corresponding MFPT,

$$T_j(x,\mathbf{y},\mathbf{z}) := \mathbb{E}[\tau | X(0) = x, \mathbf{Y}(0) = \mathbf{y}, \mathbf{Z}(0) = \mathbf{z}, J(0) = j], \tag{3.10}$$

which is the MFPT conditioned on the initial conditions $X(0) = x \in \overline{\Omega}$,

$$\begin{aligned}
\mathbf{Y}(0) &= (Y_1(0),\dots,Y_{N^{\rm i}}(0)) = (y_1,\dots,y_{N^{\rm i}}) = \mathbf{y} \in (\overline{\Omega})^{N^{\rm i}},\\
\mathbf{Z}(0) &= (Z_1(0),\dots,Z_{N^{\rm b}}(0)) = (z_1,\dots,z_{N^{\rm b}}) = \mathbf{z} \in (\partial\Omega)^{N^{\rm b}},
\end{aligned}$$

and $J(0) = j \in \mathcal{J}$.

Putting these functions in a vector $\mathbf{T}(x,\mathbf{y},\mathbf{z}) = \{T_j(x,\mathbf{y},\mathbf{z})\}_{j\in\mathcal{J}} \in \mathbb{R}^{|\mathcal{J}|}$, we claim that

$$-\mathbf{1} = \big(\mathcal{L} + Q\big)\mathbf{T}, \quad x \in \Omega\backslash\{\cup_{n\in S^{\rm i}(j)}\Omega^{\varepsilon}_n(y_n)\},\ \mathbf{y} \in (\Omega)^{N^{\rm i}},\ \mathbf{z} \in (\partial\Omega)^{N^{\rm b}}, \tag{3.11}$$

where $\mathbf{1} \in \mathbb{R}^{|\mathcal{J}|}$ is the vector of all 1's, $\mathcal{L}$ is the differential operator

$$\mathcal{L} := \mathbf{D}_0\Delta_x + \sum_{n=1}^{N^{\rm i}} \mathbf{D}^{\rm i}_n \Delta_{y_n} + \sum_{n=1}^{N^{\rm b}} \mathbf{D}^{\rm b}_n \mathbb{L}_{z_n}, \tag{3.12}$$

where

$$\begin{aligned}
\mathbf{D}_0 &:= \operatorname{diag}(D_0(j)) \in \mathbb{R}^{|\mathcal{J}|\times|\mathcal{J}|},\\
\mathbf{D}^{\rm i}_n &:= \operatorname{diag}(D^{\rm i}_n(j)) \in \mathbb{R}^{|\mathcal{J}|\times|\mathcal{J}|}, \quad n \in \{1,\dots,N^{\rm i}\}\\
\mathbf{D}^{\rm b}_n &:= \operatorname{diag}(D^{\rm b}_n(j)) \in \mathbb{R}^{|\mathcal{J}|\times|\mathcal{J}|}, \quad n \in \{1,\dots,N^{\rm b}\}
\end{aligned}$$

are diagonal matrices, Δ_x is the Laplacian acting on $x \in \mathbb{R}^3$, and $\mathbb{L}_z$ is the Laplace-Beltrami operator

$$\mathbb{L}_z := \frac{1}{h_\mu h_\nu h_\omega}\Big[\partial_\nu\Big(\frac{h_\mu h_\omega}{h_\nu}\partial_\nu\Big) + \partial_\omega\Big(\frac{h_\mu h_\nu}{h_\omega}\partial_\omega\Big)\Big] \tag{3.13}$$

acting on $z = (\mu_0,\nu,\omega) \in \partial\Omega$. Furthermore, T_j satisfies

$$\begin{aligned}
T_j &= 0, \quad x \in \big\{\cup_{n\in S^{\rm i}(j)}\,\Omega^{\varepsilon}_n(y_n)\big\} \cup \big\{\cup_{n\in S^{\rm b}(j)}\,\Gamma(z_n,\varepsilon a_n)\big\},\\
\partial_{\mu_x} T_j &= 0, \quad x \in \partial\Omega\backslash\big\{\cup_{n\in S^{\rm b}(j)}\,\Gamma(z_n,\varepsilon a_n)\big\},\\
\partial_{\mu_{y_n}} T_j &= 0, \quad y_n \in \partial\Omega, \quad n \in \{1,\dots,N^{\rm i}\},
\end{aligned} \tag{3.14}$$

where ∂_{μ_x} denotes differentiation in $x \in \mathbb{R}^3$ in the direction normal to the boundary $\partial\Omega$.

We now use the generalized Itô's formula to verify (3.11) and (3.14). Suppose a function $\mathbf{T}(x, \mathbf{y}, \mathbf{z}) = \{T_j(x, \mathbf{y}, \mathbf{z})\}_{j \in \mathcal{J}}$ satisfies (3.11) and (3.14). Let $T(x, \mathbf{y}, \mathbf{z}, j)$ denote $T_j(x, \mathbf{y}, \mathbf{z})$ and let $\mathbb{E}_0$ denote expectation conditioned on

$$X(0) = x, \quad \mathbf{Y}(0) = \mathbf{y}, \quad \mathbf{Z}(0) = \mathbf{z}, \quad J(0) = j.$$

By the generalized Itô's formula[1], we have that

$$\begin{aligned}
&\mathbb{E}_0\Big[T(X(\min\{t,\tau\}), \mathbf{Y}(\min\{t,\tau\}), \mathbf{Z}(\min\{t,\tau\}), J(\min\{t,\tau\}))\Big] - T(x, \mathbf{y}, \mathbf{z}, j) \\
&= \mathbb{E}_0\Big[\int_0^{\min\{t,\tau\}} (\mathcal{L} + Q) T(X(s), \mathbf{Y}(s), \mathbf{Z}(s), J(s))\,\mathrm{d}s\Big] \\
&\quad + \mathbb{E}_0\Big[\int_0^{\min\{t,\tau\}} \partial_{\mu_z} T(X(s), \mathbf{Y}(s), \mathbf{Z}(s), J(s))\,\mathrm{d}L_0(s)\Big] \\
&\quad + \sum_{n=1}^{N^{\mathrm{i}}} \mathbb{E}_0\Big[\int_0^{\min\{t,\tau\}} \partial_{\mu_{y_n}} T(X(s), \mathbf{Y}(s), \mathbf{Z}(s), J(s))\,\mathrm{d}L_n(s)\Big].
\end{aligned} \tag{3.15}$$

By the definition of τ in (3.9) and the equations satisfied by $\mathbf{T}$ in (3.11) and (3.14), we have that (3.15) reduces to

$$\begin{aligned}
&\mathbb{E}_0\Big[T(X(\min\{t,\tau\}), \mathbf{Y}(\min\{t,\tau\}), \mathbf{Z}(\min\{t,\tau\}), J(\min\{t,\tau\}))\Big] - T(x, \mathbf{y}, \mathbf{z}, j) \\
&= -\mathbb{E}_0[\min\{t,\tau\}].
\end{aligned} \tag{3.16}$$

We then recover (3.10) after taking $t \to \infty$ in (3.16) and using that $\tau < \infty$ almost surely.

3.3 Matched asymptotic analysis of MFPT PDE

For $\varepsilon \ll 1$, we expect that $\mathbf{T}$ has a boundary layer for x in a neighborhood of $\{\cup_{n=1}^{N^{\mathrm{i}}} y_n\} \cup \{\cup_{n=1}^{N^{\mathrm{b}}} z_n\}$, so we introduce the outer expansion

$$\mathbf{T} = \varepsilon^{-1} T^{(0)} \mathbf{1} + \mathbf{T}^{(1)} + \cdots, \tag{3.17}$$

where $T^{(0)} \in \mathbb{R}$ is a constant and $\mathbf{T}^{(1)} \in \mathbb{R}^{|\mathcal{J}|}$ is a function. Plugging (3.17) into (3.11) and (3.14) yields

$$\begin{aligned}
-\mathbf{1} &= (\mathcal{L} + Q)\mathbf{T}^{(1)}, \quad x \in \Omega \backslash \{\cup_{n \in S^{\mathrm{i}}(j)} \{y_n\}\}, \, \mathbf{y} \in \Omega^{N^{\mathrm{i}}}, \, \mathbf{z} \in (\partial\Omega)^{N^{\mathrm{b}}}, \\
\partial_{\mu_x} \mathbf{T}^{(1)} &= 0, \quad x \in \partial\Omega \backslash \{\cup_{n \in S^{\mathrm{b}}(j)} \{z_n\}\} \\
\partial_{\mu_{y_n}} \mathbf{T}^{(1)} &= 0, \quad y_n \in \partial\Omega, \quad n \in \{1, \ldots, N^{\mathrm{i}}\}.
\end{aligned} \tag{3.18}$$

[1] Itô's formula is the stochastic version of the chain rule [51]. The generalized Itô's formula applies to SDEs with random switching. For more information, see Lemma 3 on page 104 of [59] or Lemma 1.9 on page 49 of [46].

Comparing (3.18) to (3.14), notice that the targets have shrunk to points from the perspective of the outer solution. We now approximate the solution to (3.11) and (3.14) in the inner region near each y_n and z_n to determine the singular behavior of $\mathbf{T}^{(1)}$ as either $x \to y_n$ or $x \to z_n$.

3.3.1 Behavior near boundary targets

To determine the behavior of the jth component of $\mathbf{T}^{(1)}$ (denoted by $T_j^{(1)}$) in the inner region near $z_n = (\mu_0, \nu_n, \omega_n) \in \partial\Omega$ for $n \in S^{\mathrm{b}}(j)$, we introduce the local coordinates

$$\eta := \varepsilon^{-1} h_\mu(z_n)(\mu_0 - \mu), \tag{3.19}$$

$$s_1 := \varepsilon^{-1} \xi_n(j) h_\nu(z_n)(\nu - \nu_n), \tag{3.20}$$

$$s_2 := \varepsilon^{-1} \xi_n(j) h_\omega(z_n)(\omega - \omega_n), \tag{3.21}$$

where $\xi_n(j)$ is the dimensionless constant

$$\xi_n(j) := \sqrt{\frac{D_0(j)}{D_0(j) + D_n^{\mathrm{b}}(j)}} \in (0, 1]. \tag{3.22}$$

We then define the inner solution,

$$w((\eta, s_1, s_2), \mathbf{y}, \mathbf{z}) :=$$
$$T_j\big((\mu_0 - \varepsilon(h_\mu(z_n))^{-1}\eta, \nu_n + \varepsilon(\xi_n(j)h_\nu(z_n))^{-1}s_1, \omega_n + \varepsilon(\xi_n(j)h_\omega(z_n))^{-1}s_2\big), \mathbf{y}, \mathbf{z}\big).$$

We note that the local coordinates (η, s_1, s_2) and the inner solution w depend on the indices n and j, but we have suppressed this dependence to simplify notation.

By our choice of $\xi_n(j)$ in (3.22), a straightforward calculation shows that the jth component of the differential operator $\mathcal{L}$ in (3.12) expressed in local coordinates is

$$(\mathcal{L})_j = \varepsilon^{-2} D_0(j)\Big[\partial_{\eta\eta} + \partial_{s_1 s_1} + \partial_{s_2 s_2}\Big] + \mathcal{O}(\varepsilon^{-1}).$$

Therefore, substituting the inner expansion

$$w = \varepsilon^{-1} w^{(0)} + w^{(1)} + \cdots,$$

into (3.11) yields the leading order inner problem,

$$\begin{aligned} (\partial_{\eta\eta} + \partial_{s_1 s_1} + \partial_{s_2 s_2}) w^{(0)} &= 0, \quad \eta > 0,\ s_1 \in \mathbb{R},\ s_2 \in \mathbb{R}, \\ \partial_\eta w^{(0)} &= 0, \quad \text{on } \eta = 0,\ s_1^2 + s_2^2 \geq (\xi_n(j) a_n)^2, \\ w^{(0)} &= 0, \quad \text{on } \eta = 0,\ s_1^2 + s_2^2 \leq (\xi_n(j) a_n)^2. \end{aligned} \tag{3.23}$$

The matching condition is that the near-field behavior of the outer expansion as $x \to z_n$ must agree with the far-field behavior of the inner expansion as $\rho \to \infty$, where

$$\rho := \sqrt{\eta^2 + s_1^2 + s_2^2}.$$

That is,

$$\varepsilon^{-1}T^{(0)} + T_j^{(1)} + \cdots \sim \varepsilon^{-1}w^{(0)} + w^{(1)} + \cdots, \quad \text{as } x \to z_n,\ \rho \to \infty. \tag{3.24}$$

Hence, the leading order matching condition is that $w^{(0)} \sim T^{(0)}$ as $\rho \to \infty$. Therefore, we set $w^{(0)} = T^{(0)}(1 - w_c)$, where w_c satisfies the well-known electrified disk problem from electrostatics,

$$\begin{aligned} (\partial_{\eta\eta} + \partial_{s_1 s_1} + \partial_{s_2 s_2})w_c = 0, &\quad \eta > 0,\ s_1 \in \mathbb{R},\ s_2 \in \mathbb{R}, \\ \partial_\eta w_c = 0, &\quad \text{on } \eta = 0,\ s_1^2 + s_2^2 \geq (\xi_n(j)a_n)^2, \\ w_c = 1, &\quad \text{on } \eta = 0,\ s_1^2 + s_2^2 \leq (\xi_n(j)a_n)^2, \\ w_c \to 0, &\quad \text{as } \rho \to \infty. \end{aligned} \tag{3.25}$$

The solution w_c is known explicitly [23], but we need only the far-field behavior,

$$w_c \sim \xi_n(j) C_n^{\mathrm{b}} \rho^{-1}, \quad \text{as } \rho \to \infty, \tag{3.26}$$

where $C_n^{\mathrm{b}} = 2a_n/\pi$ is the capacitance of a disk of radius $a_n > 0$. It follows that

$$w^{(0)} \sim T^{(0)}\Big(1 - \xi_n(j) C_n^{\mathrm{b}} \rho^{-1}\Big), \quad \text{as } \rho \to \infty. \tag{3.27}$$

Plugging this into the matching condition yields that $T_j^{(1)}$ has the following singular behavior as $x \to z_n$ for $n \in S^{\mathrm{b}}(j)$,

$$T_j^{(1)} \sim \frac{-\xi_n(j) C_n^{\mathrm{b}} T^{(0)}}{\big[(h_\mu(z_n)(\mu_0 - \mu))^2 + (\xi_n(j) h_\nu(z_n)(\nu - \nu_n))^2 + (\xi_n(j) h_\omega(z_n)(\omega - \omega_n))^2\big]^{\frac{1}{2}}}. \tag{3.28}$$

The singular behavior in (3.28) can be written in distributional form as

$$\begin{aligned} \partial_{\mu_x} T_j^{(1)} &= -2\pi T^{(0)} \sum_{n \in S^{\mathrm{b}}(j)} \frac{C_n^{\mathrm{b}}}{\xi_n(j)} \frac{\delta(\nu - \nu_n)\delta(\omega - \omega_n)}{h_\nu(z_n) h_\omega(z_n)}, \quad x \in \partial\Omega, \\ \partial_{\mu_{y_n}} T_j^{(1)} &= 0, \quad y_n \in \partial\Omega, \quad n \in \{1, \ldots, N^{\mathrm{i}}\}, \end{aligned} \tag{3.29}$$

for each $j \in \mathcal{J}$. In order to see that (3.29) is the distributional form of (3.28) for the PDE (3.18), assume that a set of functions $\{f_j\}_{j \in J}$ satisfy (3.18) and (3.29). To determine the behavior of f_j as $x \to z_n \in \partial\Omega$ for $n \in S^{\mathrm{b}}(j)$, we let $0 < \bar{\varepsilon} \ll 1$ and define

$$\begin{aligned} &g((\bar{\eta}, \bar{s}_1, \bar{s}_2), \mathbf{y}, \mathbf{z}) := \\ &f_j\big((\mu_0 - \bar{\varepsilon}(h_\mu(z_n))^{-1}\bar{\eta}, \nu_n + \bar{\varepsilon}(\xi_n(j) h_\nu(z_n))^{-1}\bar{s}_1, \omega_n + \bar{\varepsilon}(\xi_n(j) h_\omega(z_n))^{-1}\bar{s}_2), \mathbf{y}, \mathbf{z}\big), \end{aligned}$$

for $\bar{\eta} > 0, \bar{s}_1 \in \mathbb{R}, \bar{s}_2 \in \mathbb{R}$. If we then expand g as $g = \bar{\varepsilon}^{-1} g_0 + g_1 + \cdots$, it follows from a calculation similar to the one that led to (3.23) that g_0 satisfies

$$(\partial_{\bar{\eta}\bar{\eta}} + \partial_{\bar{s}_1 \bar{s}_1} + \partial_{\bar{s}_2 \bar{s}_2}) g_0 = 0, \quad \bar{\eta} > 0,\ \bar{s}_1 \in \mathbb{R},\ \bar{s}_2 \in \mathbb{R}. \tag{3.30}$$

Furthermore, the following boundary condition follows immediately from (3.29) and the definition of g,

$$\partial_{\bar{\eta}} g((\bar{\eta}, \bar{s}_1, \bar{s}_2), \mathbf{y}, \mathbf{z}) = \bar{\varepsilon}^{-1} 2\pi T^{(0)} \xi_n(j) C_n^{\mathrm{b}} \delta(\bar{s}_1)\delta(\bar{s}_2),$$

and therefore,

$$\partial_{\bar{\eta}} g_0 = 2\pi T^{(0)} \xi_n(j) C_n^{\mathrm{b}} \delta(\bar{s}_1)\delta(\bar{s}_2), \quad \bar{\eta} = 0, \bar{s}_1 \in \mathbb{R}, \bar{s}_2 \in \mathbb{R}. \tag{3.31}$$

The solution to (3.30) and (3.31) is

$$g_0 = -T^{(0)} \xi_n(j) C_n^{\mathrm{b}} \rho^{-1}.$$

Matching the far-field behavior of $\bar{\varepsilon}^{-1} g_0$ with the near-field behavior of f_j implies that f_j has the singular behavior in (3.28) as $x \to z_n$.

3.3.2 Behavior near interior targets

To determine the behavior of $T_j^{(1)}$ in the inner region near $y_n \in \Omega$ for $n \in S^{\mathrm{i}}(j)$, we introduce the local coordinate

$$\tilde{x} := \varepsilon^{-1}(x - y_n), \tag{3.32}$$

and the inner solution

$$u(\tilde{x}, \mathbf{y}, \mathbf{z}) := T_j(y_n + \varepsilon \tilde{x}, \mathbf{y}, \mathbf{z}).$$

Expanding the inner solution,

$$u = \varepsilon^{-1} u^{(0)} + u^{(1)} + \cdots,$$

and noting that $\Delta_x = \varepsilon^{-2}\Delta_{\tilde{x}}$ and $\Delta_{y_n} = \varepsilon^{-2}\Delta_{\tilde{x}}$, we obtain the leading order inner problem

$$\begin{aligned} \Delta_{\tilde{x}} u^{(0)} &= 0, \quad \tilde{x} \notin \Omega_n, \\ u^{(0)} &= 0, \quad \tilde{x} \in \overline{\Omega}_n. \end{aligned}$$

The matching condition is

$$\varepsilon^{-1} T^{(0)} + T_j^{(1)} + \cdots \sim \varepsilon^{-1} u^{(0)} + u^{(1)} + \cdots, \quad \text{as } x \to y_n,\ |\tilde{x}| \to \infty, \tag{3.33}$$

and thus $u^{(0)} \sim T^{(0)}$ as $|\tilde{x}| \to \infty$. Therefore, we write

$$u^{(0)} = T^{(0)}(1 - u_c), \tag{3.34}$$

where u_c satisfies

$$\begin{aligned} \Delta_{\tilde{x}} u_c &= 0, \quad \tilde{x} \notin \Omega_n, \\ u_c &= 1, \quad \tilde{x} \in \overline{\Omega}_n, \\ u_c &\to 0, \quad \text{as } |\tilde{x}| \to \infty. \end{aligned} \tag{3.35}$$

The problem (3.35) has been well-studied in the field of electrostatics, and it is known that the solution has the following far-field behavior [37],

$$u_c \sim C_n^{\mathrm{i}} |\tilde{x}|^{-1} + \mathcal{O}(|\tilde{x}|^{-2}), \quad \text{as } |\tilde{x}| \to \infty, \tag{3.36}$$

where C_n^{i} is the capacitance of Ω_n. The capacitance is determined by the shape of Ω_n and can be calculated analytically for certain shapes. For example, if Ω_n is a sphere of radius $a > 0$, then $C_n^{\mathrm{i}} = a$. See Table 1 in [18] for other examples in which the capacitance can be calculated analytically.

Using the matching condition (3.33), the form of $u^{(0)}$ in (3.34), and the far-field behavior in (3.36), it follows that $T_j^{(1)}$ has the singular behavior

$$T_j^{(1)} \sim \frac{-T^{(0)} C_n^{\mathrm{i}}}{|x - y_n|}, \quad \text{as } x \to y_n \text{ if } n \in S^{\mathrm{i}}(j). \tag{3.37}$$

3.3.3 Determining $T^{(0)}$

Recall that $\gamma \in \mathbb{R}^{1 \times |\mathcal{J}|}$ is the invariant distribution of the jump process $J(t)$ and thus satisfies (3.1). Therefore, multiplying the PDE in (3.18) on the left by γ yields the scalar PDE,

$$-1 = \sum_{j \in \mathcal{J}} \gamma(j) \left[D_0(j) \Delta_x + \sum_{n=1}^{N^{\mathrm{i}}} D_n^{\mathrm{i}}(j) \Delta_{y_n} + \sum_{n=1}^{N^{\mathrm{b}}} D_n^{\mathrm{b}}(j) \mathbb{L}_{z_n} \right] T_j^{(1)}, \tag{3.38}$$

which is satisfied at $x \in \Omega \backslash \{\cup_{n \in S^{\mathrm{i}}(j)} \{y_n\}\}$, $\mathbf{y} \in \Omega^{N^{\mathrm{i}}}$, $\mathbf{z} \in (\partial\Omega)^{N^{\mathrm{b}}}$. In light of the singular behavior in (3.37), we decompose $T_j^{(1)}$ into

$$T_j^{(1)} = T_{j,\mathrm{reg}}^{(1)} - \sum_{n \in S^{\mathrm{i}}(j)} \frac{T^{(0)} C_n^{\mathrm{i}}}{|x - y_n|}, \quad j \in \mathcal{J},$$

where $\{T_{j,\mathrm{reg}}\}_{j \in \mathcal{J}}$ satisfy (3.38) at $x \in \Omega$, $\mathbf{y} \in \Omega^{N^{\mathrm{i}}}$, $\mathbf{z} \in (\partial\Omega)^{N^{\mathrm{b}}}$, and $T_{j,\mathrm{reg}}$ is bounded as $x \to y_n$ for all $n \in \{1, \dots, N^{\mathrm{i}}\}$. Using the identity

$$\Delta_a \big(|a - b|^{-1} \big) = -4\pi \delta(a - b), \quad a, b \in \mathbb{R}^3,$$

it follows that

$$\begin{aligned} -1 = &\sum_{j \in \mathcal{J}} \gamma(j) \left[D_0(j) \Delta_x + \sum_{n=1}^{N^{\mathrm{b}}} D_n^{\mathrm{i}}(j) \Delta_{y_n} + \sum_{n=1}^{N^{\mathrm{i}}} D_n^{\mathrm{b}}(j) \mathbb{L}_{z_n} \right] T_j^{(1)} \\ &- 4\pi T^{(0)} \sum_{j \in \mathcal{J}} \gamma(j) \sum_{n \in S^{\mathrm{i}}(j)} (D_0(j) + D_n^{\mathrm{i}}(j)) C_n^{\mathrm{i}} \delta(x - y_n), \quad x \in \Omega, \mathbf{y} \in \Omega^{N^{\mathrm{i}}}, \mathbf{z} \in (\partial\Omega)^{N^{\mathrm{b}}}. \end{aligned} \tag{3.39}$$

Integrating (3.39) over $\Omega \times (\Omega)^{N^{\mathrm{b}}} \times (\partial\Omega)^{N^{\mathrm{b}}}$ yields

$$
\begin{aligned}
&- |\partial\Omega|^{N^{\mathrm{i}}} |\Omega|^{N^{\mathrm{b}}+1} = \sum_{j\in\mathcal{J}} \gamma(j) \Big[D_0(j) \int \Delta_x T_j^{(1)} \,\mathrm{d}x \,\mathrm{d}\mathbf{y} \,\mathrm{d}S_{\mathbf{z}} \\
&+ \sum_{n=1}^{N^{\mathrm{i}}} D_n^{\mathrm{i}}(j) \int \Delta_{y_n} T_j^{(1)} \,\mathrm{d}x \,\mathrm{d}\mathbf{y} \,\mathrm{d}S_{\mathbf{z}} + \sum_{n=1}^{N^{\mathrm{b}}} D_n^{\mathrm{b}}(j) \int \mathbb{L}_{z_n} T_j^{(1)} \,\mathrm{d}x \,\mathrm{d}\mathbf{y} \,\mathrm{d}S_{\mathbf{z}} \Big] \\
&- 4\pi T^{(0)} |\partial\Omega|^{N^{\mathrm{i}}} |\Omega|^{N^{\mathrm{b}}} \sum_{j\in\mathcal{J}} \gamma(j) \sum_{n\in S^{\mathrm{i}}(j)} (D_0(j) + D_n^{\mathrm{i}}(j)) C_n^{\mathrm{i}},
\end{aligned}
\tag{3.40}
$$

where $\mathrm{d}S_{\mathbf{z}} = \mathrm{d}S_{z_1} \cdots \mathrm{d}S_{z_{N^{\mathrm{b}}}}$ and $\mathrm{d}S_{z_n} = h_\nu(z_n) h_\omega(z_n) \mathrm{d}\omega_n$ is the surface element. Now, the divergence theorem implies that

$$
\begin{aligned}
\int_\Omega \Delta_x T_j^{(1)} \,\mathrm{d}x &= \int_{\partial\Omega} \partial_{\mu_x} T_j^{(1)} \,\mathrm{d}S_x, \\
\int_\Omega \Delta_{y_n} T_j^{(1)} \,\mathrm{d}y_n &= \int_{\partial\Omega} \partial_{\mu_{y_n}} T_j^{(1)} \,\mathrm{d}S_{y_n}, \quad n \in \{1, \dots, N^{\mathrm{i}}\},
\end{aligned}
\tag{3.41}
$$

and

$$
\int_{\partial\Omega} \mathbb{L}_{z_n} T_1 \,\mathrm{d}S_{z_n} = 0 \quad n \in \{1, \dots, N^{\mathrm{b}}\},
\tag{3.42}
$$

since $\mathbb{L}$ is the Laplace-Beltrami operator and $\partial\Omega$ is a closed manifold. Combining (3.40) with (3.41)-(3.42) and (3.29) yields

$$
\begin{aligned}
T^{(0)} &= |\Omega| \left\{ \sum_{j\in\mathcal{J}} \gamma(j) \Big[2\pi D_0(j) \sum_{n\in S^{\mathrm{b}}(j)} \frac{C_n^{\mathrm{b}}}{\xi_n(j)} + 4\pi \sum_{n\in S^{\mathrm{i}}(j)} (D_0(j) + D_n^{\mathrm{i}}(j)) C_n^{\mathrm{i}} \Big] \right\}^{-1} \\
&= |\Omega| \left\{ \sum_{j\in\mathcal{J}} \gamma(j) D_0(j) \Big[2\pi \sum_{n=1}^{N^{\mathrm{b}}} \overline{C}_n^{\mathrm{b}}(j) + 4\pi \sum_{n=1}^{N^{\mathrm{i}}} \overline{C}_n^{\mathrm{i}}(j) \Big] \right\}^{-1},
\end{aligned}
\tag{3.43}
$$

where we have defined

$$
\begin{aligned}
\overline{C}_n^{\mathrm{b}}(j) &:= S_n^{\mathrm{b}}(j) C_n^{\mathrm{b}} \sqrt{1 + \frac{D_n^{\mathrm{b}}(j)}{D_0(j)}}, \quad n \in \{1, \dots, N^{\mathrm{b}}\}, \\
\overline{C}_n^{\mathrm{i}}(j) &:= S_n^{\mathrm{i}}(j) C_n^{\mathrm{i}} \left(1 + \frac{D_n^{\mathrm{i}}(j)}{D_0(j)} \right), \quad n \in \{1, \dots, N^{\mathrm{i}}\},
\end{aligned}
$$

which can be interpreted as effective capacitances depending on the state $j \in \mathcal{J}$. Combining (3.43) with (3.17) thus yields the leading order MFPT for the searcher to find an open target, assuming the particle starts outside an $\mathcal{O}(\varepsilon)$ neighborhood of every target. It follows that (3.43) is also the leading order MFPT for a random initial location for the searcher, as long as the probability that the searcher starts in an $\mathcal{O}(\varepsilon)$ neighborhood of a target vanishes as $\varepsilon \to 0$. Of course, this includes a uniformly distributed initial location.

4 Splitting probability

In the previous section, we calculated the expected amount of time it takes for the searcher to find an open target. In this section, we calculate the probability that the searcher first reaches a specific open target before reaching any other open target. For concreteness, we calculate the probability that the searcher first reaches boundary target $n_0 \in \{1, \dots, N^{\mathrm{b}}\}$. Calculating the probability that the searcher first reaches a specific interior target is similar.

Recall the stopping time τ in (3.9) and define the splitting probability,

$$p_j(x, \mathbf{y}, \mathbf{z}) := \mathbb{P}\big(X(\tau) \in \Gamma(Z_{n_0}(\tau), \varepsilon a_{n_0}) \,|\, X(0) = x, \mathbf{Y}(0) = \mathbf{y}, \mathbf{Z}(0) = \mathbf{z}, J(0) = j\big).$$

Similar to the previous section, one can use Itô's formula to show that the vector $\mathbf{p}(x, \mathbf{y}, \mathbf{z}) = \{p_j(x, \mathbf{y}, \mathbf{z})\}_{j \in \mathcal{J}}$ satisfies

$$\begin{aligned} (\mathcal{L} + Q)\mathbf{p} &= 0, \quad x \in \Omega \backslash \{\cup_{n \in S^{\mathrm{i}}(j)} \Omega_n^\varepsilon(y_n)\}, \, \mathbf{y} \in \Omega^{N^{\mathrm{i}}}, \, \mathbf{z} \in (\partial\Omega)^{N^{\mathrm{b}}}, \\ p_j &= 1, \quad n_0 \in S^{\mathrm{b}}(j), \, x \in \Gamma(z_{n_0}, \varepsilon a_{n_0}), \\ p_j &= 0, \quad x \in \{\cup_{n \in S^{\mathrm{b}}(j), n \neq n_0} \Gamma(z_n, \varepsilon a_n)\} \cup \{\cup_{n \in S^{\mathrm{i}}(j)} \Omega_n^\varepsilon(y_n)\}, \\ \partial_{\mu_x} p_j &= 0, \quad x \in \partial\Omega \backslash \big\{ \cup_{n \in S^{\mathrm{b}}(j)} \Gamma(z_n, \varepsilon a_n) \big\}, \\ \partial_{\mu_{y_n}} p_j &= 0, \quad y_n \in \partial\Omega, \quad n \in \{1, \dots, N^{\mathrm{i}}\}. \end{aligned} \tag{4.1}$$

As in the previous section, we use the method of matched asymptotic expansions to approximate $\mathbf{p}$. In the outer region, we introduce the outer expansion,

$$\mathbf{p} = p^{(0)}\mathbf{1} + \varepsilon \mathbf{p}^{(1)} + \cdots,$$

where $p^{(0)} \in \mathbb{R}$ is a constant and $\mathbf{p}^{(1)} \in \mathbb{R}^{|\mathcal{J}|}$ is a function. Plugging this expansion into (4.1) yields

$$\begin{aligned} (\mathcal{L} + Q)\mathbf{p}^{(1)} &= 0, \quad x \in \Omega \backslash \{\cup_{n \in S^{\mathrm{i}}(j)} \{y_n\}\}, \, \mathbf{y} \in (\Omega)^{N^{\mathrm{i}}}, \mathbf{z} \in (\partial\Omega)^{N^{\mathrm{b}}}, \\ \partial_{\mu_x} p_j^{(1)} &= 0, \quad x \in \partial\Omega \backslash \{\cup_{n \in S^{\mathrm{b}}(j)} \{z_n\}\}, \\ \partial_{\mu_{y_n}} p_j^{(1)} &= 0, \quad y_n \in \partial\Omega, \quad n \in \{1, \dots, N^{\mathrm{i}}\}. \end{aligned} \tag{4.2}$$

To determine the behavior of the jth component of $\mathbf{p}^{(1)}$ (denoted by $p_j^{(1)}$) in the inner region near $z_n = (\mu_0, \nu_n, \omega_n)$ for $n \in S^{\mathrm{b}}(j)$, we define the inner solution,

$$w((\eta, s_1, s_2), \mathbf{y}) :=$$
$$p_j\big((\mu_0 - \varepsilon(h_\mu(z_n))^{-1}\eta, \nu_n + \varepsilon(\xi_n(j)h_\nu(z_n))^{-1}s_1, \omega_n + \varepsilon(\xi_n(j)h_\omega(z_n))^{-1}s_2), \mathbf{y}\big),$$

as a function of the local coordinates (η, s_1, s_2) in (3.19).

As above, substituting the inner expansion

$$w = w^{(0)} + \varepsilon w^{(1)} + \cdots,$$

into (4.1) yields the leading order inner problem,

$$\begin{aligned}(\partial_{\eta\eta}+\partial_{s_1s_1}+\partial_{s_2s_2})w^{(0)}&=0,\quad \eta>0,\ s_1\in\mathbb{R},\ s_2\in\mathbb{R},\\ \partial_\eta w^{(0)}&=0,\quad \text{on } \eta=0,\ s_1^2+s_2^2\geq(\xi_n(j)a_n)^2,\\ w^{(0)}&=\delta_{nn_0},\quad \text{on } \eta=0,\ s_1^2+s_2^2\leq(\xi_n(j)a_n)^2,\end{aligned}\tag{4.3}$$

where $\delta_{nn_0}=0$ if $n\neq n_0$ and $\delta_{n_0n_0}=1$.

Using the matching condition

$$p^{(0)}+\varepsilon p_j^{(1)}+\cdots\sim w^{(0)}+\varepsilon w^{(1)}+\cdots,\quad \text{as } x\to z_n,\ \rho\to\infty,\tag{4.4}$$

we have that the leading order inner solution near z_n is

$$w^{(0)}=p^{(0)}+(\delta_{nn_0}-p^{(0)})w_c,$$

where w_c is as in (3.25). Using (3.26), it follows that

$$w^{(0)}\sim p^{(0)}+(\delta_{nn_0}-p^{(0)})\xi_n(j)C_n^{\mathrm{b}}\rho^{-1},\quad \text{as } \rho\to\infty.\tag{4.5}$$

Plugging this into the matching condition yields that $p_j^{(1)}$ has the following singular behavior as $x\to z_n$ for $n\in S^{\mathrm{b}}(j)$,

$$p_j^{(1)}\sim\frac{(\delta_{nn_0}-p^{(0)})\xi_n(j)C_n^{\mathrm{b}}}{[(h_\mu(z_n)(\mu_0-\mu))^2+(\xi_n(j)h_\nu(z_n)(\nu-\nu_n))^2+(\xi_n(j)h_\omega(z_n)(\omega-\omega_n))^2]^{\frac{1}{2}}}.\tag{4.6}$$

To determine the behavior of $p_j^{(1)}$ in the inner region near $y_n\in\Omega$ for $n\in S^{\mathrm{i}}(j)$, we define the inner solution

$$u(\tilde{x},\mathbf{y},\mathbf{z}):=p_j(y_n+\varepsilon\tilde{x},\mathbf{y},\mathbf{z}).$$

where the local coordinate $\tilde{x}$ is as in (3.32). Expanding the inner solution,

$$u=u^{(0)}+\varepsilon u^{(1)}+\cdots,$$

we obtain the leading order inner problem

$$\begin{aligned}\Delta_{\tilde{x}}u^{(0)}&=0,\quad \tilde{x}\notin\Omega_n,\\ u^{(0)}&=0,\quad \tilde{x}\in\overline{\Omega}_n.\end{aligned}$$

Using the matching condition,

$$p^{(0)}+\varepsilon p_j^{(1)}+\cdots\sim u^{(0)}+\varepsilon u^{(1)}+\cdots,\quad \text{as } x\to y_n,\ |\tilde{x}|\to\infty,\tag{4.7}$$

it follows that

$$u^{(0)}=p^{(0)}(1-u_c),\tag{4.8}$$

where u_c satisfies (3.35). Using (3.36) and (4.7)-(4.8), it follows that $p_j^{(1)}$ has the singular behavior

$$p_j^{(1)} \sim \frac{-p^{(0)} C_n^{\mathrm{i}}}{|x-y_n|}, \quad \text{as } x \to y_n \text{ if } n \in S^{\mathrm{i}}(j). \tag{4.9}$$

As above, we multiply the PDE in (4.2) on the left by $\gamma \in \mathbb{R}^{1\times|\mathcal{J}|}$ and write the singular behavior in (4.6) and (4.9) in distributional form to obtain

$$\begin{aligned}0 = &\sum_{j\in\mathcal{J}} \gamma(j) \left[D_0(j)\Delta_x + \sum_{n=1}^{N^{\mathrm{i}}} D_n^{\mathrm{i}}(j)\Delta_{y_n} + \sum_{n=1}^{N^{\mathrm{b}}} D_n^{\mathrm{b}}(j)\mathbb{L}_{z_n} \right] p_j^{(1)} \\ &- 4\pi p^{(0)} \sum_{j\in\mathcal{J}} \gamma(j) \sum_{n\in S^{\mathrm{i}}(j)} (D_0(j) + D_n^{\mathrm{i}}(j)) C_n^{\mathrm{i}} \delta(x-y_n), \quad x \in \Omega, \mathbf{y} \in \Omega^{N^{\mathrm{i}}}, \mathbf{z} \in (\partial\Omega)^{N^{\mathrm{b}}},\end{aligned} \tag{4.10}$$

and

$$\begin{aligned}\partial_{\mu_x} p_j^{(1)} &= 2\pi \sum_{n\in S^{\mathrm{b}}(j)} (\delta_{nn_0} - p^{(0)}) \frac{C_n^{\mathrm{b}}}{\xi_n(j)} \frac{\delta(\nu-\nu_n)\delta(\omega-\omega_n)}{h_\nu(z_n)h_\omega(z_n)}, \quad x \in \partial\Omega, \\ \partial_{\mu_{y_n}} p_j^{(1)} &= 0, \quad y_n \in \partial\Omega, \quad n \in \{1,\dots,N^{\mathrm{i}}\},\end{aligned} \tag{4.11}$$

Integrating (4.10) and using the divergence theorem and (4.11) implies that

$$p^{(0)} = \frac{\sum_{j\in\mathcal{J}} \gamma(j)\overline{C}_{n_0}^{\mathrm{b}}(j)}{\sum_{j\in\mathcal{J}} \gamma(j) \sum_{n=1}^{N^{\mathrm{b}}} \overline{C}_n^{\mathrm{b}}(j) + 2\sum_{j\in\mathcal{J}} \gamma(j) \sum_{n=1}^{N^{\mathrm{i}}} \overline{C}_n^{\mathrm{i}}(j)}. \tag{4.12}$$

A similar calculation shows that the probability of reaching interior target $n_0 \in \{1,\dots,N^{\mathrm{i}}\}$ before any other interior or boundary target converges as $\varepsilon \to 0$ to

$$\frac{2\sum_{j\in\mathcal{J}} \gamma(j)\overline{C}_{n_0}^{\mathrm{i}}(j)}{\sum_{j\in\mathcal{J}} \gamma(j) \sum_{n=1}^{N^{\mathrm{b}}} \overline{C}_n^{\mathrm{b}}(j) + 2\sum_{j\in\mathcal{J}} \gamma(j) \sum_{n=1}^{N^{\mathrm{i}}} \overline{C}_n^{\mathrm{i}}(j)}. \tag{4.13}$$

The expressions (4.12)-(4.13) for the splitting probabilities are valid when $\varepsilon \ll 1$, assuming the searcher starts outside an $\mathcal{O}(\varepsilon)$ neighborhood of every target. Therefore, (4.12)-(4.13) are also valid for a random initial location for the searcher, as long as the probability that the searcher starts in an $\mathcal{O}(\varepsilon)$ neighborhood of a target vanishes as $\varepsilon \to 0$ (which is the case for a uniformly distributed initial location).

5 Examples

In this section, we apply our general results from the previous two sections to several specific examples. In addition to illustrating our results, this section reveals several general features of diffusive search for small targets.

Example 1 (Boundary targets with constant diffusivity)**.** Assume that there are $N^{\mathrm{b}} = N > 0$ boundary targets and no interior targets, $N^{\mathrm{i}} = 0$. If the targets are immobile ($D_n^{\mathrm{b}} = 0$, $n \in \{1, \dots, N\}$) and always open, and the searcher has constant diffusivity $D_0 > 0$, then (3.43) implies that the MFPT for the searcher to reach a target is

$$T \sim \frac{|\Omega|}{2\pi\varepsilon D_0 \sum_{n=1}^{N} C_n^{\mathrm{b}}}, \quad \text{as } \varepsilon \to 0,$$

which recovers a known result [29]. If we now suppose that each boundary target diffuses with constant diffusivity $D > 0$, then (3.43) implies that the MFPT is

$$T \sim \frac{\xi|\Omega|}{2\pi\varepsilon D_0 \sum_{n=1}^{N} C_n^{\mathrm{b}}}, \quad \text{as } \varepsilon \to 0, \tag{5.1}$$

where ξ is the dimensionless factor,

$$\xi := \sqrt{\frac{D_0}{D_0 + D}} \in (0, 1). \tag{5.2}$$

Hence, making the boundary targets diffuse has the relatively simple leading order effect of shrinking the MFPT for immobile targets by the factor $\xi \in (0, 1)$.

Next, suppose that the N boundary targets have potentially differing diffusivities $D_1, \dots, D_N$. For simplicity, assume the targets have the same size ($a_n = a > 0$, $n \in \{1, \dots, N\}$). Then, (4.12) implies that the probability that the searcher first reaches boundary target n_0 is

$$p \sim \frac{(\xi_{n_0})^{-1}}{\sum_{n=1}^{N} (\xi_n)^{-1}}, \quad \text{as } \varepsilon \to 0, \quad \text{where } \xi_n := \sqrt{\frac{D_0}{D_0 + D_n}}. \tag{5.3}$$

This equation reveals that differing surface diffusivity of targets could be a mechanism for regulating the flux to each target.

Example 2 (Interior targets with constant diffusivity)**.** Assume that there are $N^{\mathrm{i}} = N > 0$ interior targets and no boundary targets, $N^{\mathrm{b}} = 0$. If the targets are immobile ($D_n^{\mathrm{i}} = 0$, $n \in \{1, \dots, N\}$) and always open, and the searcher has constant diffusivity $D_0 > 0$, then (3.43) implies that the MFPT for the searcher to reach a target is

$$T \sim \frac{|\Omega|}{4\pi\varepsilon D_0 \sum_{n=1}^{N} C_n^{\mathrm{i}}}, \quad \text{as } \varepsilon \to 0,$$

which recovers a known result [18]. If we now suppose that each interior target diffuses with constant diffusivity $D > 0$, then (3.43) implies that the MFPT is

$$T \sim \frac{|\Omega|}{4\pi\varepsilon (D_0 + D) \sum_{n=1}^{N} C_n^{\mathrm{i}}} = \frac{\xi^2|\Omega|}{4\pi\varepsilon D_0 \sum_{n=1}^{N} C_n^{\mathrm{i}}}, \quad \text{as } \varepsilon \to 0, \tag{5.4}$$

where ξ is as in (5.2).

Interpreting the first expression in (5.4), we see that making the interior targets diffuse with diffusivity $D > 0$ is (to leading order) equivalent to making the targets immobile and increasing the searcher diffusivity to $D_0 + D$. Comparing (5.1) to the second expression in (5.4), we see that making boundary targets diffuse shrinks the MFPT by ξ, whereas making interior targets diffuse has the stronger effect of shrinking the MFPT by ξ^2. It is not surprising that making interior targets diffuse has a stronger effect on the MFPT compared to making boundary targets diffuse, since diffusing boundary targets are restricted to a two-dimensional surface.

Analogous to Example 1, suppose the N interior targets have potentially differing diffusivities $D_1, \ldots, D_N$, and for simplicity, assume the targets have the same size and shape ($\Omega_n = \Omega_m \in \mathbb{R}^3$ for all $n, m \in \{1, \ldots, N\}$). Then, (4.12) implies that the probability that the searcher first reaches interior target n_0 is

$$p \sim \frac{(\xi_{n_0})^{-2}}{\sum_{n=1}^{N} (\xi_n)^{-2}}, \quad \text{as } \varepsilon \to 0, \tag{5.5}$$

where ξ_n is as in (5.3). Comparing (5.5) to (5.3), we see that differing interior target diffusivities have a stronger effect on splitting probabilities compared to differing boundary target diffusivities.

Example 3 (Fluctuating diffusivity and searcher/target correlations)**.** Assume that there is one boundary target and zero interior targets, and that the boundary target is always open. Suppose that the boundary target diffusivity fluctuates between slow and fast diffusivities, $D^- < D^+$, and similarly suppose that the searcher diffusivity fluctuates between $D_0^- < D_0^+$. For simplicity, assume that the target and the searcher each spend an equal proportion of time in their respective slow and fast states. In order to minimize the MFPT, how should the fluctuations in diffusivity be correlated? That is, should the searcher diffuse fast when the target diffuses fast or should the searcher diffuse fast when the target diffuses slowly?

To answer this question, we apply (3.43) which reveals that if the searcher diffuses fast (slowly) when the target diffuses fast (slowly), then the MFPT is

$$T \sim \frac{|\Omega|}{\pi \varepsilon C^{\mathrm{b}} \Big(D_0^+ \sqrt{1 + D^+/D_0^+} + D_0^- \sqrt{1 + D^-/D_0^-} \Big)}, \quad \text{as } \varepsilon \to 0. \tag{5.6}$$

In the opposite situation, in which the searcher diffuses fast (slowly) when the target diffuses slowly (fast), the MFPT is

$$T \sim \frac{|\Omega|}{\pi \varepsilon C^{\mathrm{b}} \Big(D_0^+ \sqrt{1 + D^-/D_0^+} + D_0^- \sqrt{1 + D^+/D_0^-} \Big)}, \quad \text{as } \varepsilon \to 0. \tag{5.7}$$

It is straightforward to check that the MFPT in (5.6) is less than the MFPT in (5.7). Thus, the MFPT is minimized by coupling fast (slow) searcher diffusion with fast (slow) boundary target diffusion.

We now investigate the analogous question for interior targets. Suppose that there is one interior target and zero boundary targets. As above, suppose the boundary target diffusivity fluctuates between $D^- < D^+$ and the searcher diffusivity fluctuates between $D_0^- < D_0^+$, spending an equal proportion of time in each diffusive state. Equation (3.43) implies that the MFPT is

$$T \sim \frac{|\Omega|}{2\pi C^{\mathrm{i}}(D_0^+ + D_0^- + D^+ + D^-)}, \quad \text{as } \varepsilon \to 0, \tag{5.8}$$

regardless of the correlations between searcher and target diffusivity. That is, in contrast to the result for boundary targets, correlations between searcher and interior target diffusivities have no leading order effect on the MFPT.

Example 4 (Fluctuations in diffusivity)**.** First assume that all of the targets are immobile ($D_n^{\mathrm{i}} = D_n^{\mathrm{b}} = 0$) and always open. Then, (3.43) implies that the MFPT is

$$T \sim |\Omega| \Big\{ \varepsilon \overline{D}_0 \Big[2\pi \sum_{n=1}^{N^{\mathrm{b}}} C_n^{\mathrm{b}} + 4\pi \sum_{n=1}^{N^{\mathrm{i}}} C_n^{\mathrm{i}} \Big] \Big\}^{-1}, \quad \text{as } \varepsilon \to 0,$$

where

$$\overline{D}_0 := \sum_{j \in \mathcal{J}} \gamma(j) D_0(j)$$

is the average searcher diffusivity. Hence, for the purpose of calculating the leading order MFPT, the fluctuating searcher diffusivity can be replaced by a constant, average searcher diffusivity.

Similarly, if we also allow the interior targets to diffuse with fluctuating diffusivity, then (3.43) implies that the MFPT is

$$T \sim |\Omega| \Big\{ \varepsilon \Big[\overline{D}_0 2\pi \sum_{n=1}^{N^{\mathrm{b}}} C_n^{\mathrm{b}} + 4\pi \sum_{n=1}^{N^{\mathrm{i}}} (\overline{D}_0 + \overline{D}_n^{\mathrm{i}}) C_n^{\mathrm{i}} \Big] \Big\}^{-1}, \quad \text{as } \varepsilon \to 0,$$

where

$$\overline{D}_n^{\mathrm{i}} := \sum_{j \in \mathcal{J}} \gamma(j) D_n^{\mathrm{i}}(j), \quad n \in \{1, \dots, N^{\mathrm{i}}\},$$

is the average diffusivity of the nth interior target. That is, the fluctuating searcher and interior target diffusivities can be replaced by their average diffusivities.

However, if we allow the boundary targets to diffuse with fluctuating diffusivity, then (3.43) implies that we cannot merely replace the fluctuating boundary target diffusivity by their average diffusivity (even if the searcher diffuses with constant diffusivity). This is because $\xi_n(j)$ in (3.22) is a nonlinear function of $D_n^{\mathrm{i}}(j)$.

Example 5 (Gating independent of fluctuations in diffusivity)**.** Suppose that the target gating is independent of fluctuations in searcher and target diffusivity. This implies that the Markov jump process $J(t) \in \mathcal{J}$ can be decomposed into two independent Markov jump processes, $J_{\mathrm{g}}(t) \in \mathcal{J}_{\mathrm{g}}$ and $J_{\mathrm{d}}(t) \in \mathcal{J}_{\mathrm{d}}$, that respectively control the gating and diffusivity fluctuations, and the state space of $J(t)$ is the Cartesian product $\mathcal{J} = \mathcal{J}_{\mathrm{g}} \times \mathcal{J}_{\mathrm{d}} = \{(j_{\mathrm{g}}, j_{\mathrm{d}}) : j_{\mathrm{g}} \in \mathcal{J}_{\mathrm{g}}, j_{\mathrm{d}} \in \mathcal{J}_{\mathrm{d}}\}$. Furthermore, it is straightforward to show that the invariant measure of $J(t)$ is the product measure $\gamma(j_{\mathrm{g}}, j_{\mathrm{d}}) = \gamma_{\mathrm{g}}(j_{\mathrm{g}})\gamma_{\mathrm{d}}(j_{\mathrm{d}})$, where $\gamma_{\mathrm{g}} \in \mathbb{R}^{1\times|\mathcal{J}_{\mathrm{g}}|}$ and $\gamma_{\mathrm{d}} \in \mathbb{R}^{1\times|\mathcal{J}_{\mathrm{d}}|}$ are the unique invariant measures of $J_{\mathrm{g}}(t)$ and $J_{\mathrm{d}}(t)$, respectively.

Therefore, (3.43) implies that the MFPT is

$$T \sim |\Omega| \Big\{ \varepsilon \sum_{j_{\mathrm{d}} \in \mathcal{J}_{\mathrm{d}}} \gamma_{\mathrm{d}}(j_{\mathrm{d}}) D_0(j_{\mathrm{d}}) \Big[2\pi \sum_{n=1}^{N^{\mathrm{b}}} P_n^{\mathrm{b}} C_n^{\mathrm{b}} \Big(1 + \frac{D_n^{\mathrm{b}}(j_{\mathrm{d}})}{D_0(j_{\mathrm{d}})}\Big)^{1/2} + 4\pi \sum_{n=1}^{N^{\mathrm{i}}} P_n^{\mathrm{i}} C_n^{\mathrm{i}} \Big(1 + \frac{D_n^{\mathrm{i}}(j_{\mathrm{d}})}{D_0(j_{\mathrm{d}})}\Big) \Big] \Big\}^{-1}, \quad \text{as } \varepsilon \to 0, \tag{5.9}$$

where $P_n^{\mathrm{b}} \in (0,1]$ (respectively $P_n^{\mathrm{i}} \in (0,1]$) is the proportion of time that the nth boundary (respectively interior) target is open,

$$P_n^{\mathrm{b}} := \sum_{j_{\mathrm{g}} \in \mathcal{J}_{\mathrm{g}}} \gamma_{\mathrm{g}}(j_{\mathrm{g}}) S_n^{\mathrm{b}}(j_{\mathrm{g}}), \quad P_n^{\mathrm{i}} := \sum_{j_{\mathrm{g}} \in \mathcal{J}_{\mathrm{g}}} \gamma_{\mathrm{g}}(j_{\mathrm{g}}) S_n^{\mathrm{i}}(j_{\mathrm{g}}).$$

In words, (5.9) implies the simple and intuitive result that the capacitance of each target is merely reduced by the proportion of time that that target is open. If each target is open the same proportion of time $P \in (0,1]$, then (5.9) implies that the MFPT is

$$T \sim P^{-1} T_{\mathrm{open}}, \quad \text{as } \varepsilon \to 0,$$

where T_{open} is the MFPT in the case that the targets are always open.

6 Numerical simulation

We perform Monte Carlo simulations to verify the predicted MFPTs derived above. In all numerical results discussed, 10^4 trajectories were simulated. For each trajectory, a single searcher particle is initialized to a position uniformly within the domain Ω and evolves with (unless noted) diffusivity $D_0 = 1$. This update step uses an Euler-Maruyama scheme [39] with varying time step ranging from 10^{-3} to 10^{-7} depending on how far the particle is from the nearest target or boundary. The interior targets are also initialized uniformly within the domain and evolve by standard diffusion updated with the Euler-Maruyama scheme. The boundary targets are initialized uniformly on $\partial\Omega$. The SDEs (3.2) provide the evolution of the centers of the boundary targets, written in the orthogonal coordinates. When the searcher hits the boundary of the domain, a check is made whether a boundary target is encountered. If not, the interior particle is reflected off the normal direction of the surface at the point of intersection, and repeated until this procedure places the particle within the domain. Reflection of interior targets is handled in the same manner. When the searcher encounters either type of target, the trajectory is terminated and the time is recorded. Interior targets are taken to be spheres and boundary targets are circular, each with radius ε. More precisely, for interior targets we take $\Omega_n = \{x \in \mathbb{R}^3 : |x| = 1\}$ in (3.6) for $n \in \{1, \dots, N^{\mathrm{i}}\}$, and boundary targets are defined in (3.7)-(3.8) with $a = 1$.

Examples 1 and 2 above discuss the first scenario of interest for numerical simulation: how target diffusivity influences the MFPT with varying number of interior and boundary targets with constant diffusivity, D. We take the domain to be a unit sphere and the target size to be $\varepsilon = .025$. The results of these Monte Carlo simulations, compared with the predicted formulae (5.1) and (5.4), are in Fig. 1a. Indeed, we see a strong agreement between the predicted dependence on D for interior, boundary, and mixed target scenarios.

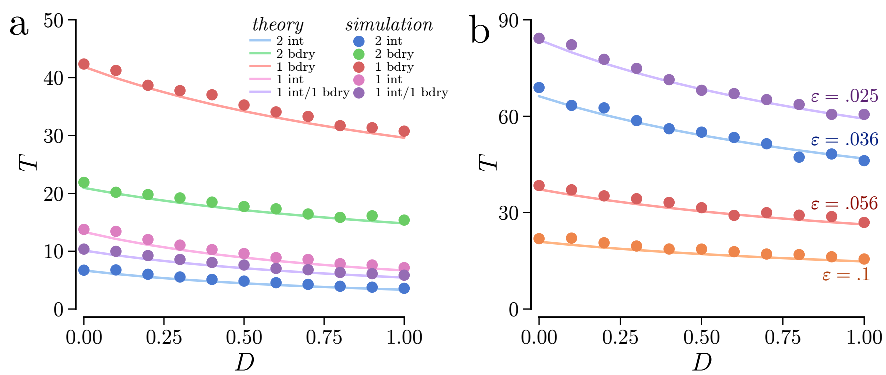

Figure 1: Mean first passage times with constant searcher and target diffusivity. **a:** MFPT (T) for a particle in a spherical domain as a function of target diffusivity D, for varying types and numbers of targets. **b:** MFPT (T) plotted against target diffusivity D for a single boundary target on the surface of a non-spherical (ellipsoidal) domain and varying ε.

We also performed simulations in an ellipsoid domain Ω with standard parameterization

$$x = a \sin\theta \cos\phi, \quad y = b \sin\theta \sin\phi, \quad z = c\cos\theta, \tag{6.1}$$

with $\theta \in [-\pi/2, \pi/2]$, $\phi \in [-\pi, \pi]$, and $a = 2$, $b = 1$, $c = 1$. In these simulations, we kept the diffusivity of the searcher constant ($D_0 = 1$) and varied the size ε and diffusivity D of the boundary target. The results of these simulations are in Fig. 1b, along with the predicted values in (5.1), and we again see excellent agreement between the simulations and the predicted values.

We also used Monte Carlo simulations to verify the MFPT in scenarios in which the searcher and targets switch diffusivities. Taking the domain to be a unit sphere, we follow Example 3 above by having a single interior or boundary target with $\varepsilon = 10^{-1.5}$ which switches between a slow and a fast diffusivity ($D^- = 0.05$ and $D^+ = 2$) at rate $\lambda > 0$. In addition, the searcher switches between diffusivities $D_0^- = 0.1$ and $D_0^+ = 1$. The results of these simulations are in Fig. 2, where we consider the MFPT T to a single boundary or single interior target as a function of the switching rate λ.

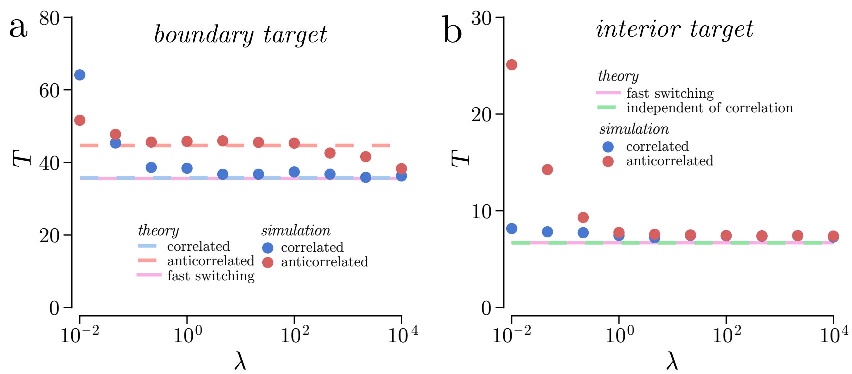

Figure 2: Mean first passage time for switching searcher and target diffusivities. **a:** MFPT (T) as a function of switching rate λ of searcher and one boundary target. The curves are (5.6) and (5.7). **b:** MFPT (T) as a function of switching rate λ of searcher and one interior target. The curves are (5.8). In both plots, the correlated scenario has the searcher and target switch between slow/slow and fast/fast states, whereas anticorrelated switches between slow/fast and fast/slow.

In one set of simulations, which we denote *correlated*, the searcher and the target is initialized (with equal probability) to both be in their slow state or both in their fast state, so the state of the system is either (D_0^-, D^-) or (D_0^+, D^+). At rate λ, the whole system switches between these two states, causing both the searcher and target to switch from slow to fast (or vice versa). In the *anticorrelated* scenario, the searcher is initialized to a diffusivity and targets are initialized to the opposite, so the states of the systems now become and (D_0^-, D^+) or (D_0^+, D^-). Again, at rate λ, the whole system switches between these two states. We plot these Monte Carlo simulations for a boundary target against the predictions in (5.6) and (5.7) in Fig. 2a. We also note that in the fast switching limit (large λ), the switching diffusivities can be replaced with average diffusivities $\bar{D}_0, \bar{D}$ in the constant diffusivity prediction (5.1). We see that for these chosen parameters, in the slow switching scenario, the correlated scenario produces the largest MFPT. However, as the switching rate increases, the theory values become accurate and remain accurate over several orders of magnitude. As predicted, the performance reverses with switching: the anticorrelated scenario performs worse than the correlated. As λ becomes large, both correlated and anticorrelated converge to the fast switching limit, which closely matches the correlated prediction.

We repeat this same setup for a single interior target, the results of which can be seen in Fig. 2b. Here, the theory suggests that the correlated and anticorrelated scenarios should be indistinguishable with both having a MFPT predicted by (5.8). Indeed, we see that for sufficiently fast switching, the prediction holds and the two different correlation scenarios are indistinguishable, illustrating a fundamental difference between switching interior and boundary targets.

7 Discussion

We have extended the narrow escape problem to include diffusing boundary targets, diffusing interior targets, stochastically fluctuating searcher and target diffusivities, and stochastically gated targets. We make no assumptions on correlations between changes in diffusivity and gating, and thus they can be independent, perfectly correlated, or have some nontrivial correlations. Furthermore, the time between transitions in diffusivity or gating can have any phase distributions. Since phase distributions are dense in the set of nonnegative distributions [50], our results hold for effectively any choice of transition time distributions.

Our analysis is in the narrow escape (small target) limit. Note that our results ((2.4), (2.8), and (2.9)) remain valid if take the limit of small boundary and/or interior target diffusivities, as the factors in (2.6) and (2.7) reduce to unity if $D_n^{\mathrm{b}}/D_0 \to 0$ and $D_n^{\mathrm{i}}/D_0 \to 0$, respectively. However, our results do not in general remain valid if we take the limit of large diffusivity of targets. To see this, note that the MFPT formula in (2.4) vanishes if $D_n^{\mathrm{b}}(j)/D_0(j) \to \infty$, but the MFPT in this limit should actually correspond to the case of a perfectly absorbing boundary (see [44] for more on this phenomenon).

Our work is related to a number of prior studies. The method of matched asymptotic analysis that we employ relies on the theory of strong localized perturbations [66]. More specifically, the methods that we employ for diffusive targets follow the methods used in [18] for immobile interior targets and the methods used in [19] for immobile boundary targets.

Other works that study diffusive search for diffusive targets include [7, 8, 26, 27, 47, 55, 62, 65]. In contrast to these previous works which consider searchers and targets both diffusing in the same space dimension (which is typically one space dimension), we considered searchers diffusing in three dimensions and boundary targets diffusing in two dimensions (and interior targets diffusing in three dimensions). To our knowledge, the only prior work that considers such inter-dimensional reactions of searchers diffusing in three dimensions and targets diffusing in two dimensions is our recent work [44], where we show how receptor lateral diffusion and cell rotational diffusion modify Berg and Purcell's classic results [5] in chemoreception.

In the context of molecular and cellular biology, several recent works study the MFPT of a searcher to reach a target, where the searcher diffusivity stochastically fluctuates [12, 13, 14, 28, 56, 57]. In contrast to our present work, these prior works consider only two possible diffusivities for the searcher and a single immobile target. In further contrast, [13, 28] consider one-dimensional or spherically symmetric spatial domains. Moreover, [28, 56, 57] consider fluctuations in diffusivity and gating assuming that the states of the diffusivity and the gate are perfectly correlated. Additional prior studies of diffusive search for stochastically gated targets includes [2, 9, 10, 11]. In most of this prior work, there is only a single target [9, 11, 13, 28, 56, 57]. In the references which consider multiple gated targets, the gate states are either perfectly correlated [2] or independent [10]. All of this prior work assumes that the time between fluctuations in diffusivity and/or gating is exponentially distributed.

We have followed [29] in assuming that our three-dimensional spatial domain Ω is bounded by the level surface of an orthogonal coordinate system. This class of domains is quite general, as it includes all axially symmetric domains. Furthermore, this assumption allows our calculations regarding diffusing boundary targets and the behavior of the MFPT and splitting probabilities to be quite explicit. Nevertheless, we suspect that our results can be extended to any domain with a smooth boundary. Indeed, our results immediately apply to domains with smooth boundaries if we have only interior targets ($N^{\mathrm{b}} = 0$).

Furthermore, we found that the leading order behavior of the MFPT and splitting probabilities depends only on the volume of the domain and is otherwise independent of the geometry of the domain. To determine how the geometry of the domain influences the MFPT and splitting probabilities at higher orders, one would need more detailed information about a certain Green's function corresponding to that domain. Indeed, using detailed information about certain Green's functions for spherical domains, previous authors have determined two or three term asymptotic expansions for MFPTs to small targets in various scenarios [18, 19, 20, 29].

An additional interesting and biologically motivated future direction would be to extend our results to space-dependent diffusivities. Alternatively, one could seek to extend our results to space-dependent transition rates between spatially constant diffusivities. Indeed, very recent experimental work has revealed the critical role that such space-dependent transition rates play in the formation of protein concentration gradients in developing cells [15, 25, 67] (see also [43]). The notion that space-dependent transition rates between spatially constant diffusivities could yield space-dependent diffusivities was proposed and analyzed in [12, 14] (see also [45]), along with the resulting Itô-Stratonovich dilemma for continuous stochastic processes with multiplicative noise [42, 64].

Acknowledgments

SDL was supported by the National Science Foundation (DMS-1814832 and DMS-1148230). The support and resources from the Center for High Performance Computing at the University of Utah are gratefully acknowledged.

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