Search processes with stochastic resetting and multiple targets

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Search processes with stochastic resetting provide a general theoretical framework for understanding a wide range of naturally occurring phenomena. Most current models focus on the first-passage-time problem of finding a single target in a given search domain. Here we use a renewal method to derive general expressions for the splitting probabilities and conditional mean first passage times (MFPTs) in the case of multiple targets. Our analysis also incorporates the effects of delays arising from finite return times and refractory periods. Carrying out a small-r expansion, where r is the mean resetting rate, we obtain general conditions for when resetting increases the splitting probability or reduces the conditional MFPT to a particular target. This also depends on whether $\pi_{\rm tot} = 1$ or $\pi_{\rm tot} < 1$, where $\pi_{\rm tot}$ is the probability that the particle is eventually absorbed by one of the targets in the absence of resetting. We illustrate the theory by considering two distinct examples. The first consists of an actin-rich cell filament (cytoneme) searching along a one-dimensional array of target cells, a problem for which the splitting probabilities and MFPTs can be calculated explicitly. In particular, we highlight how the resetting rate plays an important role in shaping the distribution of splitting probabilities along the array. The second example involves a search process in a three-dimensional bounded domain containing a set of N small interior targets. We use matched asymptotics and Green's functions to determine the behavior of the splitting probabilities and MFPTs in the small-r regime. In particular, we show that the splitting probabilities and MFPTs depend on the "shape capacitance" of the targets.

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I. INTRODUCTION

A well-known property of a Brownian particle searching for a hidden target in an unbounded domain is that the mean first passage time (MFPT) for target detection is infinite. However, the MFPT can be rendered finite by the introduction of stochastic resetting, whereby the position of the particle is reset to a fixed location at a random sequence of times. The MFPT is also found to be a unimodal function of the mean resetting rate so that the latter can be adjusted to optimize the search time [1–3]. Analogous results have subsequently been obtained for a wide range of stochastic search processes with resetting [4], including nondiffusive processes such as Levy flights [5], velocity jump processes [6,7], and resetting in a potential landscape [8] or in bounded domains [9]. Several authors have focused on extracting universal features of search processes with resetting, deriving general expressions for MFPTs and other statistical quantities [10–14]. Another recent extension has been the inclusion of finite return times [15–17] and refractory periods [18,19].

A common thread through most analytical studies of search processes with stochastic resetting is renewal theory, which exploits the fact that once a particle has returned to its resetting state, it has lost all memory of previous search phases. Often the survival probability with resetting is expressed in terms of the survival probability without resetting using an integral renewal equation, which can then be solved using Laplace transforms [4]. An alternative approach is to decompose the various contributions to the first passage time (FPT) by conditioning on whether or not the searcher resets at least once [11–13,16]. The latter approach does not require Laplace transforms and is particularly useful when incorporating features such as finite return times and search failures.

The renewal method based on conditional expectations has also been applied to other types of FPT problems. For example, consider a Brownian particle diffusing in a bounded domain with one or more pores distributed on the boundary of the domain. Furthermore, suppose that the pores are stochastically gated so that they randomly and independently switch between an open and a closed state. In order to determine the MFPT to escape through an open pore, it is necessary to keep track of all prior visits to each pore when it is in a closed state. The latter can be achieved by conditioning on whether or not the particle hits a closed gate at least once before escaping [20,21], which is the analog of resetting. This is illustrated in Fig. 1(a) for diffusion in an interval. A second example is cytoneme-based morphogen transport [22]. Cytonemes are thin, actin-rich filaments that can dynamically extend up to several hundred microns to form direct cell-to-cell contacts. There is increasing experimental evidence that these direct contacts allow the active transport of morphogen to embryonic cells during development [23–25]. One mechanism of contact-mediated morphogenesis involves cytonemes nucleating from a source cell and dynamically growing and shrinking until connecting with one of a set of target cells [22]. Morphogen is localized at the tip of a growing cytoneme, which is delivered as a morphogen burst when the cytoneme makes temporary

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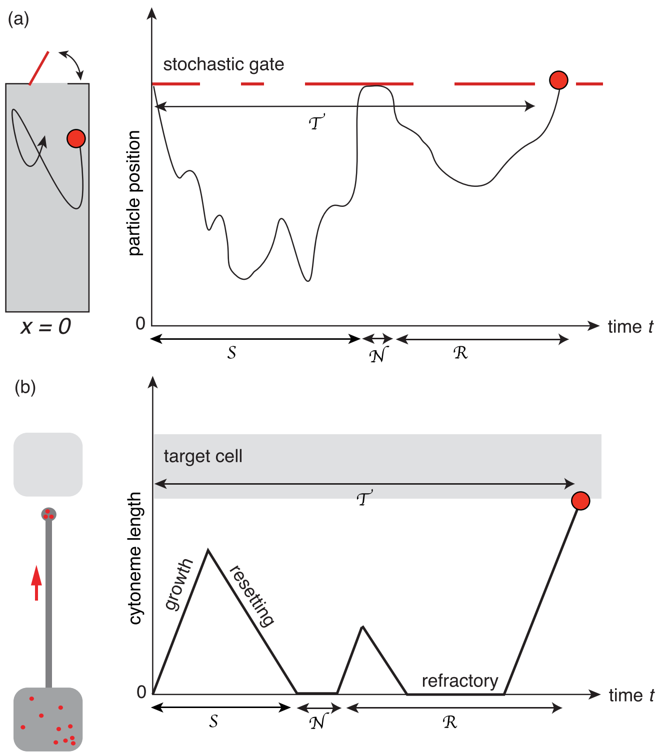

FIG. 1. Examples of conditioning on prior events. (a) Brownian particle diffusing in the interval $[0, L]$ with a stochastic gate at $x = L$ that randomly opens and closes. If the particle reaches the gate when the latter is closed, the process restarts (possibly after a delay due to sticking at the boundary). (b) A cytoneme nucleates from a source cell and grows at a constant speed v_+. Prior to finding a target cell at $x = L$, the cytoneme may randomly switch to a retraction phase (resetting) and return to the origin at a speed V. After a refractory period (nucleation waiting time), a new cytoneme starts to grow and the process repeats. In both examples the FPT can be decomposed as $\mathcal{T} = \mathcal{S} + \mathcal{N} + \mathcal{R}$, where $\mathcal{S}$ is the FPT to return to the start position, $\mathcal{N}$ is a refractory period, and $\mathcal{R}$ is the FPT conditioned on at least one restart. Both $\mathcal{T}$ and $\mathcal{R}$ have the same probability distributions. (More precisely, in the first example, $\mathcal{T}$ and $\mathcal{R}$ are the first return times.)

contact with the target cell before subsequently retracting. The delivery of a single burst can be analyzed in terms of an FPT problem with a sticky (nucleating) boundary at the source cell. This requires conditioning on whether or not the cytoneme returns to the nucleation site at least once before finding a target [see Fig. 1(b)]. The nucleation time is analogous to the refractory period of a resetting process, and the time to retract is analogous to a finite return time.

In this paper, we extend the theory of stochastic processes with resetting and delays to the case of N targets. The major difference from the single target case is that one now has to determine the so-called splitting probabilities π_k, $k = 1, \dots, N$, where π_k is the probability that the particle first finds the kth target. Since, this probability is less than unity due to target competition, it follows that the MFPT to find the kth target is infinite unless it is conditioned on successfully finding the given target, which yields the conditional MFPT. As far as we are aware, the case of multiple targets has not been extensively analyzed in previous work, with the notable exception of Ref. [14], where Laplace transforms are used to determine splitting probabilities for one-dimensional (1D) search processes with instantaneous resetting and the simpler case of search processes with two possible outcomes [7,8,12,13,26]. In Sec. II we introduce the renewal method by considering a single target and calculating the MFPT along identical lines to Ref. [16]. This serves to set up the notation used in subsequent sections. The derivation of the splitting probabilities and conditional MFPTs is carried out in Sec. III using a general resetting time density $\psi(\tau)$. We then show that these statistical quantities can be expressed in terms of Laplace transforms in the case of exponential resetting. In Sec. IV we explore the small-r behavior of the splitting probabilities and conditional MFPTs, where r is the rate of exponential resetting. This allows us to derive general conditions for when resetting increases the splitting probability or decreases the conditional MFPT to a specific target. Defining $\pi_{\rm tot}$ to be the probability that the particle is eventually captured by one of the targets in the absence of resetting, we distinguish between the two cases $\pi_{\rm tot} = 1$ and $\pi_{\rm tot} < 1$. Finally, in Sec. V we illustrate the theory by considering two specific examples. The first involves a cytoneme searching along a 1D array of target cells, a problem for which the splitting probabilities and MFPTs can be calculated explicitly. In particular, we highlight how the resetting rate plays an important role in shaping the distribution of splitting probabilities along the array, which has consequences for the formation of morphogen concentration gradients. The second example concerns a general class of search processes in 3D bounded domains with a set of N small interior targets. Although it is difficult to solve the full problem, we indicate how to obtain approximations in the small-r regime, since these involve moments of the FPT density in the absence of resetting. The latter can be calculated using matched asymptotic expansions and Green's function methods in the limit of small targets. In particular, we show that the splitting probabilities and MFPTs depend on the "shape capacitance" of the targets. (The connection between FPT problems and electrostatics is elucidated in Ref. [27].)

II. SEARCH PROCESS WITH STOCHASTIC RESETTING AND A SINGLE TARGET

Consider a particle (searcher) subject to stochastic motion in $\mathcal{U} \subseteq \mathbb{R}^d$. Suppose that there exists some target $\mathcal{U}_0 \subset \mathbb{R}^d$ whose boundary $\partial\mathcal{U}_0$ is absorbing and $\mathbf{x}_r \notin \mathcal{U}_0$. The probability density $p(\mathbf{x}, t|\mathbf{x}_0)$ for the particle to be at position $\mathbf{x}$ at time t, having started at $\mathbf{x}_0$, evolves according to the master equation

$$\frac{\partial p(\mathbf{x}, t|\mathbf{x}_0)}{\partial t} = \mathbb{L} p(\mathbf{x}, t|\mathbf{x}_0), \tag{2.1}$$

where $\mathbb{L}$ is the infinitesimal generator of the stochastic process. This is supplemented by the absorbing boundary condition $p(\mathbf{x}, t|\mathbf{x}_0) = 0$ for all $\mathbf{x} \in \partial\mathcal{U}$. Let $\mathcal{T}(\mathbf{x}_0)$ denote the first passage time to be absorbed by the target, having started at $\mathbf{x}_0$:

$$\mathcal{T}(\mathbf{x}_0) = \inf\{t > 0;\ \mathbf{X}(t) \in \partial\mathcal{U}_0,\ \mathbf{X}(0) = \mathbf{x}_0\}. \tag{2.2}$$

The MFPT can be expressed in terms of a survival probability without resetting, Q_0, which is defined according to

$$T(\mathbf{x}_0)=\mathbb{E}[\mathcal{T}(\mathbf{x}_0)]=\int_0^\infty Q_0(\mathbf{x}_0,t)dt, \tag{2.3}$$

where

$$Q_0(\mathbf{x}_0,t)=\int_{\mathcal{U}\backslash\mathcal{U}_0} p(\mathbf{x},t|\mathbf{x}_0)d\mathbf{x}. \tag{2.4}$$

Now suppose that prior to being absorbed by the target, the particle can reset to a fixed location $\mathbf{x}_r$ at a random sequence of times generated by a probability density $\psi(\tau)$. It follows that $\Psi(\tau)=1-\int_0^\tau \psi(s)ds$ is the probability that no resetting has occurred up to time τ. (In the following we also take $\mathbf{x}_0=\mathbf{x}_r$.) Rather than instantaneously returning to $\mathbf{x}_r$, we assume that the particle switches to a ballistic state in which it returns to $\mathbf{x}_r$ at a constant speed V. (For simplicity, the particle cannot be absorbed by the target when it is in the return phase. One could also consider a more general dynamical model for the return phase as in Refs. [16,17]) In addition, whenever the particle returns to $\mathbf{x}_r$, it is subject to a refractory period before the search begins again. The refractory period is itself a random variable with a corresponding waiting-time density $\phi_{\rm ref}$, which is taken to have a finite mean. We would like to determine the MFPT to be absorbed by the target in the presence of resetting with delays. As recently shown in Ref. [16], this can be achieved using renewal theory, which exploits the fact that once the particle has returned to $\mathbf{x}_r$ it has lost all memory of previous search phases. The latter means that one can condition on whether or not the particle resets at least once, even though a reset event occurs at random times. (In other words, the stochastic process satisfies the strong Markov property.) Here we describe a version of the MFPT derivation carried out in Ref. [16], which is then generalized to the case of multiple targets in Sec. III.

Let $\mathcal{I}(t)$ denote the number of resetting events in the interval $[0,t)$. Consider the following set of first passage times, analogous to the decompositions shown in Fig. 1:

$$\begin{aligned}\mathcal{T}&=\inf\{t>0;\mathbf{X}(t)\in\partial\mathcal{U}_0\},\\ \mathcal{S}&=\inf\{t>0;\mathbf{X}(t)=\mathbf{x}_r,\ \mathcal{I}(t)=1\},\\ \mathcal{R}&=\inf\{t>0;\mathbf{X}(t+\mathcal{S}+\mathcal{N})\in\partial\mathcal{U}_0\}.\end{aligned} \tag{2.5}$$

Here $\mathcal{T}$ is the FPT for finding the target irrespective of the number of resettings, $\mathcal{S}$ is the FPT for the first resetting and return to the reset point $\mathbf{x}_r$ given that the particle is still free, $\mathcal{N}$ is the first refractory time, and $\mathcal{R}$ is the FPT for finding the target given that at least one resetting has occurred. Next we introduce the sets $\Omega=\{\mathcal{T}<\infty\}$ and $\Gamma=\{\mathcal{S}<\mathcal{T}<\infty\}\subset\Omega$. Here Ω is the set of all events for which the particle is eventually absorbed by the target (which has measure one), and Γ is the subset of events in Ω for which the particle resets at least once. It immediately follows that $\Omega\backslash\Gamma=\{\mathcal{T}<\mathcal{S}=\infty\}$, that is, $\Omega\backslash\Gamma$ is the set of all events for which the particle is captured by the target without any resetting. We now use probabilistic arguments to calculate the MFPT $T_r(\mathbf{x}_r)=\mathbb{E}[\mathcal{T}]$ in the presence of resetting, finite return times, and refractory periods.

Following Ref. [16], consider the decomposition

$$T_r(\mathbf{x}_r)=\mathbb{E}[\mathcal{T}]=\mathbb{E}[\mathcal{T}1_{\Omega\backslash\Gamma}]+\mathbb{E}[\mathcal{T}1_\Gamma]. \tag{2.6}$$

The first expectation on the right-hand side can be evaluated by noting that it is the MFPT for capture by the target without any resetting, and the probability density for such an event is $-\Psi(t)\partial_t Q_0(\mathbf{x}_r,t)$. Hence,

$$\begin{aligned}\mathbb{E}[\mathcal{T}1_{\Omega\backslash\Gamma}]&=-\int_0^\infty \tau\Psi(\tau)\frac{\partial Q_0(\mathbf{x}_r,\tau)}{\partial\tau}d\tau\\ &=-\int_0^\infty \psi(\tau)\tau Q_0(\mathbf{x}_r,\tau)d\tau\\ &\quad+\int_0^\infty \Psi(\tau)Q_0(\mathbf{x}_r,\tau)d\tau.\end{aligned} \tag{2.7}$$

We have integrated by parts using $\Psi'(t)=-\psi(t)$ and $\Psi(t)\to 0$ as $t\to\infty$. The second expectation can be further decomposed as

$$\begin{aligned}\mathbb{E}[\mathcal{T}1_\Gamma]&=\mathbb{E}[(\mathcal{S}+\mathcal{N}+\mathcal{R})1_\Gamma]\\ &=\mathbb{E}[\mathcal{S}1_\Gamma]+\tau_{\rm ref}\mathbb{P}[\Gamma]+\mathbb{E}[\mathcal{R}1_\Gamma],\end{aligned} \tag{2.8}$$

where $\tau_{\rm ref}=\int_0^\infty \tau\phi_{\rm ref}(\tau)d\tau$. In order to calculate $\mathbb{E}[\mathcal{S}1_\Gamma]$, we note that the first resetting occurs with probability $\psi(\tau)Q_0(\mathbf{x}_r,\tau)d\tau$ in the interval $[\tau,\tau+d\tau]$. At time τ the particle is at position $\mathbf{X}(\tau)$ and thus takes an additional time $|\mathbf{X}(\tau)-\mathbf{x}_r|/V$ to return to $\mathbf{x}_r$. We thus find that

$$\mathbb{E}[\mathcal{S}1_\Gamma]=\int_0^\infty \psi(\tau)\left(\tau+\frac{\langle|\mathbf{X}(\tau)-\mathbf{x}_r|\rangle}{V}\right)Q_0(\mathbf{x}_r,\tau)d\tau,$$

where $\langle\cdot\rangle$ denotes expectation with respect to the probability density $p(\mathbf{x},t|\mathbf{x}_r)$ evolving according to Eq. (2.1) without resetting and conditioned on survival up to time τ. That is,

$$\langle|\mathbf{X}(\tau)-\mathbf{x}_r|\rangle=\int_{\mathcal{U}\backslash\mathcal{U}_0}|\mathbf{x}-\mathbf{x}_r|\frac{p(\mathbf{x},\tau|\mathbf{x}_r)}{Q_0(\mathbf{x}_r,\tau)}d\mathbf{x}.$$

Hence, defining

$$F(\mathbf{x}_r,\tau)=\int_{\mathcal{U}\backslash\mathcal{U}_0}|\mathbf{x}-\mathbf{x}_r|p(\mathbf{x},\tau|\mathbf{x}_r)d\mathbf{x}, \tag{2.9}$$

we have

$$\mathbb{E}[\mathcal{S}1_\Gamma]=\int_0^\infty \psi(\tau)\left(\tau Q_0(\mathbf{x}_r,\tau)+\frac{F(\mathbf{x}_r,\tau)}{V}\right)d\tau. \tag{2.10}$$

Finally, from the definitions of the first passage times and the effect of resetting,

$$\mathbb{E}[\mathcal{R}1_\Gamma]=T_r(\mathbf{x}_r)\mathbb{P}[\Gamma],\quad \mathbb{P}[\Gamma]=\mathbb{P}[\mathcal{S}<\infty]\mathbb{P}[\mathcal{R}<\infty], \tag{2.11}$$

with

$$P[\mathcal{R}<\infty]=1,\quad \mathbb{P}[\mathcal{S}<\infty]=\int_0^\infty \psi(\tau)Q_0(\mathbf{x}_r,\tau)d\tau. \tag{2.12}$$

Combining Eqs. (2.6)–(2.12) yields the implicit equation

$$\begin{aligned}T_r(\mathbf{x}_r)&=\langle Q_0(\mathbf{x}_r,\tau)\rangle_\Psi+V^{-1}\langle F(\mathbf{x}_r,\tau)\rangle_\psi\\ &\quad+\langle Q_0(\mathbf{x}_r,\tau)\rangle_\psi(\tau_{\rm ref}+T_r(\mathbf{x}_r)),\end{aligned}$$

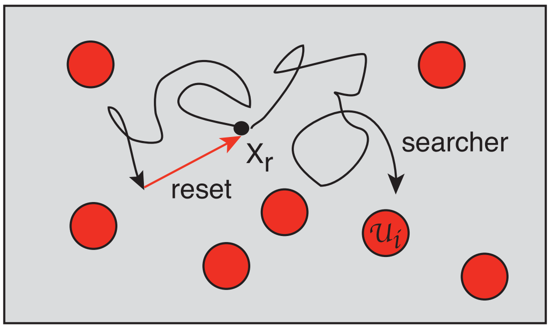

FIG. 2. Particle searching for multiple targets $\mathcal{U}_i \subset \mathcal{U}$, $i = 1, \ldots, N$, and subject to resetting to position $\mathbf{x}_r$ at a rate r.

where

$$\langle f(\tau)\rangle_\psi \equiv \int_0^\infty \psi(\tau)f(\tau)d\tau.$$

Rearranging then yields the following general expression for the MFPT in the presence of resetting and delays:

$$T_r(\mathbf{x}_r) = \frac{\langle Q_0(\mathbf{x}_r,\tau)\rangle_\Psi + \tau_{\rm ref}\langle Q_0(\mathbf{x}_r,\tau)\rangle_\psi + V^{-1}\langle F(\mathbf{x}_r,\tau)\rangle_\psi}{1-\langle Q_0(\mathbf{x}_r,\tau)\rangle_\psi}. \tag{2.13}$$

Assuming constant velocity returns, this result is equivalent to Eq. (5) of Ref. [16]. [It also reduces to Eq. (95) of Ref. [17] in the 1D case with $\tau_{\rm ref} = 0$.] For exponential resetting,

$$\psi(t) = re^{-r\tau}, \quad \Psi(\tau) = e^{-rt},$$

we have

$$T_r(\mathbf{x}_r) = \frac{\widetilde{Q}_0(\mathbf{x}_r, r) + r\tau_{\rm ref}\widetilde{Q}_0(\mathbf{x}_r, r) + r\widetilde{F}(\mathbf{x}_r, r)/V}{1-r\widetilde{Q}_0(\mathbf{x}_r, r)}, \tag{2.14}$$

where $\widetilde{F}(\mathbf{x}_r, r)$ is the Laplace transform of $F(\mathbf{x}_r, \tau)$.

III. SPLITTING PROBABILITIES AND CONDITIONAL MFPTs FOR MULTIPLE TARGETS

Now suppose that there are N targets $\mathcal{U}_i$, $i = 1, \ldots, N$, as shown in Fig. 2. First, consider the case without resetting ($r = 0$). Let $\mathbf{J}(\mathbf{x}, t|\mathbf{x}_r)$ denote the probability flux of the stochastic search process without resetting such that Eq. (2.1) becomes

$$\frac{\partial p(\mathbf{x}, t|\mathbf{x}_r)}{\partial t} = \mathbb{L}p(\mathbf{x}, t|\mathbf{x}_r) = -\nabla\cdot\mathbf{J}(\mathbf{x}, t|\mathbf{x}_r), \tag{3.1}$$

supplemented by the absorbing boundary conditions

$$p(\mathbf{x}, t|\mathbf{x}_r) = 0, \quad \mathbf{x}\in\partial\mathcal{U}_a = \bigcup_{j=1}^N \partial\mathcal{U}_j \tag{3.2}$$

and the initial condition $p(\mathbf{x}, 0|\mathbf{x}_r) = \delta(\mathbf{x}-\mathbf{x}_r)$. Let $\mathcal{T}_k(\mathbf{x}_r)$ denote the FPT that the particle is captured by the kth target, with $\mathcal{T}_k(\mathbf{x}_r) = \infty$ indicating that it is not captured. Define $\Pi_k(\mathbf{x}_r, t)$ to be the probability that the particle is captured by the kth target after time t, given that it started at $\mathbf{x}_r$,

$$\Pi_k(\mathbf{x}_r, t) = \mathbb{P}[t < \mathcal{T}_k(\mathbf{x}_r) < \infty] = \int_t^\infty J_k(\mathbf{x}_r, t)dt', \tag{3.3}$$

where

$$J_k(\mathbf{x}_r, t) = -\int_{\partial\mathcal{U}_k} \mathbf{J}(\mathbf{y}, t|\mathbf{x}_r)\cdot d\mathbf{y}. \tag{3.4}$$

The negative sign indicates that the flux is into domain $\mathcal{U}_k$.

The splitting probability $\pi_k(\mathbf{x}_r)$ and conditional MFPT $T_k(\mathbf{x}_r)$ to be captured by the kth target are then

$$\pi_k(\mathbf{x}_r) = \Pi_k(\mathbf{x}_r, 0) = \int_0^\infty J_k(\mathbf{x}_r, t)dt \tag{3.5}$$

and

$$T_k(\mathbf{x}_r) = \mathbb{E}[\mathcal{T}_k|\mathcal{T}_k < \infty] = \frac{1}{\pi_k(\mathbf{x}_r)}\int_0^\infty \Pi_k(\mathbf{x}_r, t)dt. \tag{3.6}$$

The total probability of being captured by one of the targets, $\pi_{\rm tot}(\mathbf{x}_r)$, is

$$\pi_{\rm tot}(\mathbf{x}_r) := \sum_{k=1}^N \pi_k(\mathbf{x}_r).$$

We allow for the possibility that $\pi_{\rm tot}(\mathbf{x}_r) < 1$, which holds in the case of diffusion in an unbounded domain, for example. This should be distinguished from the notion of failure to find a particular target due to absorption by another target. The former type of failure disappears when resetting is included, whereas the latter persists. Finally, note that integrating Eq. (3.1) with respect to $\mathbf{x}$ and t implies that the survival probability up to time t is

$$\begin{aligned} Q_0(\mathbf{x}_r, t) &= \int_{\mathcal{U}\backslash\mathcal{U}_a} p(\mathbf{x}, t|\mathbf{x}_r)d\mathbf{x} \\ &= 1-\pi_{\rm tot}(\mathbf{x}_r) + \sum_{k=1}^N \Pi_k(\mathbf{x}_r, t). \end{aligned} \tag{3.7}$$

We now extend the renewal method introduced in Sec. II to calculate the splitting probability $\pi_{r,k}(\mathbf{x}_r)$ and conditional MFPT $T_{r,k}(\mathbf{x}_r)$ to be captured by the kth target in the presence of resetting. Consider the following set of first passage times, which are the multitarget analogs of equation (2.5):

$$\begin{aligned} \mathcal{T}_k &= \inf\{t \geqslant 0; \mathbf{X}(t)\in\partial\mathcal{U}_k\}, \\ \mathcal{S} &= \inf\{t \geqslant 0; \mathbf{X}(t) = \mathbf{x}_r,\ \mathcal{I}(t) = 1\}, \\ \mathcal{R}_k &= \inf\{t \geqslant 0; X(t+\mathcal{S}+\mathcal{N})\in\partial\mathcal{U}_k\}. \end{aligned}$$

Here $\mathcal{T}_k$ is the FPT for finding the kth target irrespective of the number of resettings, $\mathcal{S}$ is the FPT for the first resetting and return to $\mathbf{x}_r$ without being captured by any target, $\mathcal{N}$ is the first refractory time, and $\mathcal{R}_k$ is the FPT for finding the kth target given that at least one resetting has occurred. Next we define the sets

$$\Omega_k = \{\mathcal{T}_k < \infty\}, \quad \Gamma_k = \{\mathcal{S} < \mathcal{T}_k < \infty\} \subset \Omega_k,$$

where Ω_k is the set of all events for which the particle is eventually absorbed by the kth target without being absorbed by any other target, and Γ_k is the subset of events in Ω_k for which the particle resets at least once. It immediately follows that

$$\Omega_k\backslash\Gamma_k = \{\mathcal{T}_k < \mathcal{S} = \infty\},$$

where $\Omega_k\backslash\Gamma_k$ is the set of all events for which the particle is captured by the kth target without any resetting.

A. Splitting probabilities

The splitting probability $\pi_{r,k}(\mathbf{x}_r)$ can be decomposed as

$$\pi_{r,k}(\mathbf{x}_r) := \mathbb{P}[\Omega_k] = \mathbb{P}[\Omega_k\backslash\Gamma_k] + \mathbb{P}[\Gamma_k]. \tag{3.8}$$

We note that the probability that the particle is captured by the kth target in the interval $[\tau, \tau + d\tau]$ without any returns to $\mathbf{x}_r$ is $\Psi(\tau)J_k(\mathbf{x}_r, \tau)d\tau$, with $J_k(\mathbf{x}_r\tau)$ given by Eq. (3.4). Hence,

$$\begin{aligned}\mathbb{P}[\Omega_k\backslash\Gamma_k] &= \int_0^\infty \Psi(\tau)J_k(\mathbf{x}_r, \tau)d\tau \\ &= -\int_0^\infty \Psi(\tau)\frac{d\Pi_k(\mathbf{x}_r, \tau)}{d\tau}d\tau \\ &= \pi_k(\mathbf{x}_r) - \int_0^\infty \psi(\tau)\Pi_k(\mathbf{x}_r, \tau)d\tau, \end{aligned}\tag{3.9}$$

after integrating by parts. Next, from the definitions of the first passage times, we have

$$\mathbb{P}[\Gamma_k] = \mathbb{P}[\mathcal{S} < \infty]\mathbb{P}[\mathcal{R}_k < \infty], \tag{3.10}$$

and memoryless return to $\mathbf{x}_r$ implies that $\mathbb{P}[\mathcal{R}_k < \infty] = \pi_{r,k}(\mathbf{x}_r)$. In addition,

$$\begin{aligned}\mathbb{P}[\mathcal{S} < \infty] &= \int_0^\infty \psi(\tau)Q_0(\mathbf{x}_r, \tau)d\tau \\ &= 1 - \pi_{\text{tot}}(\mathbf{x}_r) + \sum_{k=1}^N \int_0^\infty \psi(\tau)\Pi_k(\mathbf{x}_r, \tau)d\tau. \end{aligned}\tag{3.11}$$

We have used the fact that the probability of resetting in the time interval $[\tau, \tau + d\tau]$ is equal to the product of the reset probability $\psi(\tau)d\tau$ and the survival probability $Q_0(\mathbf{x}_r, \tau)$ that the particle has not been captured by a target up to time τ. Hence, Eq. (3.10) becomes

$$\mathbb{P}[\Gamma_k] = \pi_{r,k}(\mathbf{x}_r)\langle Q_0(\mathbf{x}_r, \tau)\rangle_\psi. \tag{3.12}$$

Combining Eqs. (3.9) and (3.12) yields the implicit equation

$$\pi_{r,k}(\mathbf{x}_r) = \langle \Lambda_k(\mathbf{x}_r, \tau)\rangle_\psi + \langle Q_0(\mathbf{x}_r, \tau)\rangle_\psi \pi_{r,k}(\mathbf{x}_r),$$

which, upon rearranging, leads to the following result:

$$\pi_{r,k}(\mathbf{x}_r) = \frac{\pi_k(\mathbf{x}_r) - \langle \Pi_k(\mathbf{x}_r, \tau)\rangle_\psi}{\langle Q_0(\mathbf{x}_r, \tau)\rangle_\psi}. \tag{3.13}$$

Summing both sides of Eq. (3.13) implies that $\sum_{k=1}^N \pi_{r,k}(\mathbf{x}_r) = 1$. In other words, in the presence of reset, the particle is captured by one of the targets with probability 1. Note that the splitting probability $\pi_{r,k}(\mathbf{x}_r)$ is independent of the refractory periods and finite return times. However, implicit in the calculation of $\pi_{r,k}(\mathbf{x}_r)$ is the assumption that the particle returns to $\mathbf{x}_r$ and then escapes from the refractory state in a finite time. In the particular case of exponential resetting, Eq. (3.13) becomes

$$\pi_{r,k}(\mathbf{x}_r) = \frac{\pi_k(\mathbf{x}_r) - r\widetilde{\Pi}_k(\mathbf{x}_r, r)}{1 - r\widetilde{Q}_0(\mathbf{x}_r, r)}. \tag{3.14}$$

B. Conditional MFPTs

The conditional MFPT $\mathbb{E}[\mathcal{T}_k 1_{\Omega_k}] = \pi_{r,k}T_{r,k}$ can be analyzed along similar lines to the splitting probability by introducing the decomposition

$$\mathbb{E}[\mathcal{T}_k 1_{\Omega_k}] = \mathbb{E}\big[\mathcal{T}_k 1_{\Omega_k\backslash\Gamma_k}\big] + \mathbb{E}[\mathcal{T}_k 1_{\Gamma_k}]. \tag{3.15}$$

The first expectation can be evaluated by noting that it is the MFPT for capture by the kth target without any resetting, and the probability density for such an event is $\Psi(\tau)J_k(\mathbf{x}_r, \tau)d\tau$. Hence,

$$\begin{aligned}\mathbb{E}\big[\mathcal{T}_k 1_{\Omega_k\backslash\Gamma_k}\big] &= \int_0^\infty \tau\Psi(\tau)J_k(\mathbf{x}_r, \tau)d\tau \\ &= -\int_0^\infty \tau\Psi(\tau)\frac{d\Pi_k(\mathbf{x}_r, \tau)}{d\tau}d\tau \\ &= -\int_0^\infty \tau\psi(\tau)\Pi_k(\mathbf{x}_r, \tau)d\tau \\ &\quad + \int_0^\infty \Psi(\tau)\Pi_k(\mathbf{x}_r, \tau)d\tau. \end{aligned}\tag{3.16}$$

The second expectation can be further decomposed as

$$\begin{aligned}\mathbb{E}\big[\mathcal{T}_k 1_{\Gamma_k}\big] &= \mathbb{E}\big[(\mathcal{S} + \mathcal{N} + \mathcal{R}_k)1_{\Gamma_k}\big] \\ &= \mathbb{E}\big[\mathcal{S}1_{\Gamma_k}\big] + \tau_{\text{ref}}\mathbb{P}[\Gamma_k] + \mathbb{E}\big[\mathcal{R}_k 1_{\Gamma_k}\big] \\ &= \mathbb{E}\big[\mathcal{S}1_{\Gamma_k}\big] + (\tau_{\text{ref}} + T_{r,k})\mathbb{P}[\Gamma_k], \end{aligned}\tag{3.17}$$

with $\mathbb{P}[\Gamma_k]$ given by Eq. (3.12). Again, $\mathcal{N}$ denotes the random time spent in the refractory state at $\mathbf{x}_r$ before switching back to the search phase, with $\mathbb{E}[\mathcal{N}] = \tau_{\text{ref}}$, and we have used the result $\mathbb{E}[\mathcal{R}_k 1_{\Gamma_k}] = T_{r,k}\mathbb{P}[\Gamma_k]$. The latter follows from the fact that return to $\mathbf{x}_r$ restarts the stochastic process without any memory.

In order to calculate $\mathbb{E}[\mathcal{S}1_{\Gamma_k}]$, it is necessary to incorporate the time of return following the first resetting event along the lines of Sec. II. The first return is initiated before being captured by a target with probability $\psi(\tau)Q_0(\mathbf{x}_r, \tau)d\tau$ in the interval $[\tau, \tau + d\tau]$. At time τ the particle is at position $\mathbf{X}(\tau)$ and thus takes an additional time $|\mathbf{X}(\tau) - \mathbf{x}_r|/V$ to return to $\mathbf{x}_r$. Using the fact that $\mathbb{P}[\mathcal{R}_k < \infty] = \pi_{r,k}$, we have

$$\begin{aligned}&\mathbb{E}\big[\mathcal{S}1_{\Gamma_k}\big] \\ &\quad = \pi_{r,k}(\mathbf{x}_r)\int_0^\infty \psi(\tau)\left(\tau + \frac{\langle|\mathbf{X}(\tau) - \mathbf{x}_r|\rangle}{V}\right)Q_0(\mathbf{x}_r, \tau)d\tau\end{aligned}$$

where $\langle\cdot\rangle$ denotes expectation with respect to the probability density $p(\mathbf{x}, t|\mathbf{x}_r)$ evolving according to Eq. (3.1) without resetting and conditioned on survival up to time τ. Hence, we have

$$\mathbb{E}[\mathcal{S}1_\Gamma] = \pi_{r,k}(\mathbf{x}_r)\int_0^\infty \psi(\tau)\left(\tau Q_0(\mathbf{x}_r, \tau) + \frac{F(\mathbf{x}_r, \tau)}{V}\right)d\tau \tag{3.18}$$

where $F(\mathbf{x}_r, \tau)$ is given by Eq. (2.9) for p evolving according to (3.1) and $\mathcal{U}_0$ replaced by $\mathcal{U}_a$.

Combining Eqs. (3.15)–(3.18) yields an implicit equation of the form

$$\begin{aligned}\pi_{r,k}(\mathbf{x}_r)T_{r,k}(\mathbf{x}_r) &= -\langle\tau\Pi_k(\mathbf{x}_r, \tau)\rangle_\psi + \langle\Pi_k(\mathbf{x}_r, \tau)\rangle_\Psi \\ &\quad + \pi_{r,k}(\mathbf{x}_r)(\langle\tau Q_0(\mathbf{x}_r, \tau)\rangle_\psi + V^{-1}\langle F(\mathbf{x}_r, \tau)\rangle_\psi) \\ &\quad + (\tau_{\text{ref}} + T_{r,k}(\mathbf{x}_r))\pi_{r,k}(\mathbf{x}_r)\langle Q_0(\mathbf{x}_r, \tau)\rangle_\psi.\end{aligned}$$

Rearranging then yields the conditional MFPT

$$\pi_{r,k}(\mathbf{x}_r)T_{r,k}(\mathbf{x}_r) = \frac{-\langle \tau\Pi_k(\mathbf{x}_r,\tau)\rangle_\psi + \langle \Pi_k(\mathbf{x}_r,\tau)\rangle_\Psi + \pi_{r,k}(\mathbf{x}_r)(\langle[\tau+\tau_{\rm ref}]Q_0(\mathbf{x}_r,\tau)\rangle_\psi + V^{-1}\langle F(\mathbf{x}_r,\tau)\rangle_\psi)}{1-\langle Q_0(\mathbf{x}_r,\tau)\rangle_\psi}, \tag{3.19}$$

with

$$\langle Q_0(\mathbf{x}_r,\tau)\rangle_\psi = 1-\pi_{\rm tot}(\mathbf{x}_r) + \sum_{k=1}^N \langle \Pi_k(\mathbf{x}_r,\tau)\rangle_\psi.$$

In the particular case of exponential resetting, Eq. (3.19) can be expressed in terms of Laplace transforms according to

$$\pi_{r,k}(\mathbf{x}_r)T_{r,k}(\mathbf{x}_r) = \frac{\widetilde{\Pi}_k(\mathbf{x}_r,r) + r\widetilde{\Pi}_k'(\mathbf{x}_r,r) + \mathcal{B}(r)\pi_{r,k}(\mathbf{x}_r)}{1-r\widetilde{Q}_0(r)}, \tag{3.20}$$

where a prime denotes differentiation with respect to r,

$$\mathcal{B}(r) = \frac{1-\pi_{\rm tot}}{r} - r\sum_{k=1}^N \frac{d\widetilde{\Pi}_k(r)}{dr} + r\frac{\widetilde{F}(r)}{V} + \tau_{\rm ref} r\widetilde{Q}_0(r), \tag{3.21}$$

and

$$r\widetilde{Q}_0(r) = 1-\pi_{\rm tot} + r\sum_{k=1}^N \widetilde{\Pi}_k(r). \tag{3.22}$$

IV. SMALL-r EXPANSION

Let us now focus on the case of exponential resetting at a rate r. One of the major reasons that search processes with stochastic resetting are of interest is that in cases where the MFPT is infinite in the limit $r\to 0$ (no resetting), one typically finds that there exists an optimal resetting rate r^* that minimizes the MFPT [4]. This reflects the fact that the MFPT is also infinite in the limit $r\to\infty$, since the searcher resets to $\mathbf{x}_r$ so often that it never has a chance to reach a target. Here we explore the limit $r\to 0$ further by carrying out small-r expansions of the various Laplace transforms appearing in Eqs. (3.14) and (3.20). For notational simplicity, we drop the explicit dependence on the reset position $\mathbf{x}_r$.

First, note that from the definition of $\Pi_k(t)$ we have

$$\widetilde{\Pi}_k(r) = \frac{\pi_k - \widetilde{J}_k(r)}{r}. \tag{4.1}$$

Since the probability flux J_k is the moment generator of the FPT density into the kth target, it has the Taylor-series expansion with respect to r

$$\widetilde{J}_k(r) = \widetilde{J}_k(0) + r\widetilde{J}_k'(0) + \frac{r^2}{2}\widetilde{J}_k''(0) + o(r^2)$$
$$= \pi_k - r\pi_k T_k + \frac{r^2}{2}\pi_k T_k^{(2)} + o(r^2),$$

where

$$T_k^{(2)} = \int_0^\infty t^2 J_k(t)dt. \tag{4.2}$$

Substituting into Eq. (4.1) implies that

$$r\widetilde{\Pi}_k(r) = r\pi_k T_k - \frac{r^2}{2}\pi_k T_k^{(2)} + o(r^2), \tag{4.3}$$

and hence

$$\lim_{r\to 0} r\widetilde{\Pi}_k(r) = \Pi_k(\infty) = 0,$$
$$\lim_{r\to 0} \widetilde{\Pi}_k(r) = \pi_k T_k,$$
$$\lim_{r\to 0} r\widetilde{\Pi}_k'(r) = 0.$$

Using these limits we can obtain small-r approximations of the splitting probabilities and conditional MFPTs. First, from Eqs. (3.14) and (3.22) we have

$$\pi_{r,k} = \frac{\pi_k - r\widetilde{\Pi}_k(r)}{\pi_{\rm tot} - r\sum_{l=1}^N \widetilde{\Pi}_l(r)}$$
$$= \frac{\pi_k - r\pi_k T_k + o(r)}{\pi_{\rm tot} - r\sum_{l=1}^N \pi_l T_l + o(r)}. \tag{4.4}$$

Thus,

$$\lim_{r\to 0}\pi_{r,k} = \frac{\pi_k}{\pi_{\rm tot}}.$$

In the case $\pi_{\rm tot}=1$,

$$\pi_{r,k} = \pi_k + r\pi_k\left(\sum_{l=1}^N \pi_l T_l - T_k\right) + o(r), \tag{4.5}$$

which implies that a low resetting rate will increase the probability of finding the kth target provided that

$$T_k < \sum_{l=1}^N \pi_l T_l. \tag{4.6}$$

This is the multitarget extension of the result previously obtained for Bernouilli trials in Ref. [13].

It immediately follows from Eq. (3.21) that if there is a nonzero probability of failure in the absence of resetting ($\pi_{\rm tot}<1$), then $\mathcal{B}(r)\to\infty$ as $r\to 0$ and hence

$$\lim_{r\to 0}\pi_{r,k}T_{r,k} = \infty, \tag{4.7}$$

implying that the MFPT is a nonmonotonic function of r. Now suppose that $\pi_{\rm tot}=1$. Applying the series expansion, (4.3), then gives

$$\pi_{r,k}T_{r,k} = \pi_k T_k + r\left(\pi_k T_k\sum_{l=1}^N \pi_l T_l - \pi_k T_k^{(2)} + \mathcal{B}_0\pi_k\right) + o(r), \tag{4.8}$$

where

$$\mathcal{B}_0 = \frac{1}{2}\sum_{k=1}^N \pi_k T_k^{(2)} + \frac{\widetilde{F}(0)}{V} + \tau_{\rm ref}\left[\sum_{l=1}^N \pi_l T_l\right]. \tag{4.9}$$

Hence,

$$\lim_{r\to 0}\pi_{r,k}T_{r,k}=\pi_k T_k. \tag{4.10}$$

Let us define

$$\langle T\rangle=\sum_{k=1}^{N}\pi_k T_k,\quad \sigma^2(T)=\sum_{k=1}^{N}\pi_k T_k^{(2)}-\langle T\rangle^2, \tag{4.11}$$

where $\langle T\rangle$ is the unconditional MFPT in the absence of resetting, and $\sigma^2(T)$ is the corresponding variance. Summing both sides of Eq. (4.8), we see that

$$\sum_{k=1}^{N}\pi_{r,k}T_{r,k}$$
$$=\langle T\rangle+\frac{r}{2}\left(\langle T\rangle^2-\sigma^2(T)+\frac{2\widetilde{F}(0)}{V}+2\tau_{\rm ref}\langle T\rangle\right)+o(r). \tag{4.12}$$

This implies that adding a low rate of resetting reduces the unconditional MFPT if and only if the coefficient of variation (CV) satisfies

$$\langle T\rangle^2-\sigma^2(T)+\frac{2\widetilde{F}(0)}{V}+2\tau_{\rm ref}\langle T\rangle<0. \tag{4.13}$$

This is a generalization of the condition obtained in Ref. [12] for instantaneous resetting, which is recovered by taking $\tau_{\rm ref}=0$ and $V\to\infty$:

$$\text{CV}:=\frac{\sigma(T)}{\langle T\rangle}>1. \tag{4.14}$$

If we only include the effects of refractory periods, then we have a quadratic in $\langle T\rangle$ and the condition becomes

$$\langle T\rangle<\sqrt{\tau_{\rm ref}^2+\sigma^2(T)}. \tag{4.15}$$

Finally, returning to Eq. (4.8) and ignoring any delays, we have

$$\begin{aligned}\pi_{r,k}T_{r,k}&=\pi_k T_k+r\big(\pi_k T_k\langle T\rangle-\pi_k T_k^{(2)}\big)\\&\quad+\frac{r}{2}(\sigma^2(T)-\langle T\rangle^2)\pi_k+o(r),\end{aligned} \tag{4.16}$$

Hence, the conditional MFPT of the kth target will be increased by resetting if

$$T_k\langle T\rangle-T_k^{(2)}+\tfrac{1}{2}(\sigma^2(T)+\langle T\rangle^2)<0. \tag{4.17}$$

V. EXAMPLES

We now illustrate the above theory by considering two examples of search processes with stochastic resetting and multiple targets. The first is a 1D application to cytoneme-based morphogen transport, for which the splitting probabilities and MFPTs can be calculated explicitly. The second is a general class of search processes in 3D bounded domains with a set of N small interior targets. Although it is difficult to solve the full problem, one can explore the behavior in the small-r regime along the lines of Sec. IV.

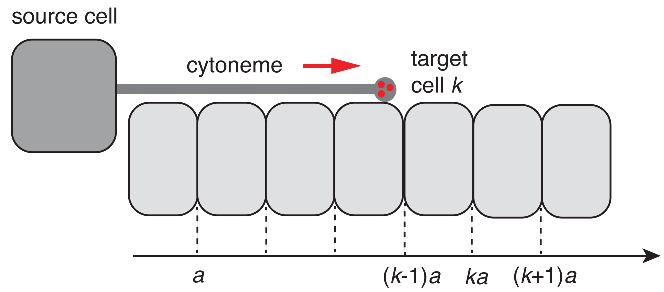

FIG. 3. Semi-infinite array of partially absorbing target cells and a source cell at the origin $x=0$. Each target cell is of width a and the cytoneme can be captured by the kth target cell at a rate κ if $(k-1)a<X(t)<ka$.

A. Directed search along an array of targets

As our first example, consider a simplified version of the cytoneme-based morphogen transport model introduced in Ref. [22], which we map onto a search process with stochastic resetting. Consider a source cell with a single cytoneme nucleation site and a semi-infinite array of target cells as shown in Fig. 3. The kth target cell has width a and its distal end is at a distance ka from the source cell. Whenever a cytoneme nucleates from the source cell, it grows along the surface of the array at a constant speed v_+ and can be captured by the kth target at a rate κ when $X(t)\in((k-1)a,ka)$. (In this example, the targets are only partial absorbers, but the general analysis in Sec. III still applies.) The resetting dynamics of the cytoneme is as shown in Fig. 1(b) for a single target. That is, prior to finding one of the target cells, the cytoneme may randomly switch to a retraction phase (resetting) and return to the origin at a speed V. After a refractory period (nucleation waiting time), a new cytoneme starts to grow and the process repeats. We take

$$\phi_{\rm res}(t)=\frac{1}{\tau_{\rm ref}}e^{-t/\tau_{\rm ref}}.$$

(Some of the model parameters can be inferred from experimental studies of cytoneme-based transport in zebrafish [24]. For example, $a\sim 10$ μm, $v_+\sim 0.01$–0.1 μm/s, and $\tau_{\rm ref}\sim 30$–60 s.)

Let $p_n(x,t)$ be the probability density that at time t the particle (cytoneme tip) is at $X(t)=x$ and in either the search state ($n=+$) or the return state ($n=-$). Similarly, let $P_0(t)$ denote the probability that the particle is in the refractory state at time t. The corresponding master equation with resetting takes the form

$$\frac{\partial p_+}{\partial t}=-v_+\frac{\partial p_+}{\partial x}-rp_+-\kappa p_+,\quad x\in(0,\infty), \tag{5.1a}$$

$$\frac{\partial p_-}{\partial t}=v_-\frac{\partial p_-}{\partial x}+rp_+,\quad x\in(0,\infty), \tag{5.1b}$$

$$\frac{dP_0}{dt}=v_-p_-(0,t)-\eta P_0(t), \tag{5.1c}$$

together with the boundary condition

$$v_+p_+(0,t)=\eta P_0(t). \tag{5.1d}$$

(Here we drop the explicit dependence on $x_0=x_r=0$.)

Following the general framework in Sec. III, we first analyze the search process without resetting. In this case, the probability flux into the kth target at time t is

$$J_k(t) = \kappa \int_{(k-1)a}^{ka} p_+(x,t)dx$$
$$= \kappa \int_{(k-1)a}^{ka} \delta(x - v_+t)e^{-\kappa t}dx = \kappa\chi_k(t)e^{-\kappa t}, \quad (5.2)$$

where $\chi_k(t) = 1$ if $(k-1)a/v_+ < t < ka/v_+$ and is 0 otherwise. The splitting probability that the particle is captured by the kth target is

$$\pi_k = \int_0^\infty J_k(y,t')dt' = \kappa \int_0^\infty \chi_k(t)e^{-\kappa t}$$
$$= e^{-\kappa(k-1)a/v_+} - e^{-\kappa ka/v_+}. \quad (5.3)$$

Here $e^{-\kappa(k-1)a/v_+}$ is the probability of reaching the kth target without being captured by any upstream targets, so π_k is the probability that the particle is captured by the kth target before passing to the $(k+1)$th target. It immediately follows that $\sum_{k=1}^\infty \pi_k = 1$. The probability $\Lambda_k(t) = \pi_k - \Pi_k(t)$ that the particle is captured by the kth target before time t is

$$\Lambda_k(t) = \int_0^t J_k(t')dt' = H(t-\tau_k)[e^{-\kappa t} - e^{-\kappa ka/v_+}]$$
$$+ H(t-\tau_{k-1})[e^{-\kappa(k-1)a/v_+} - e^{-\kappa t}], \quad (5.4)$$

where $H(t)$ is the Heaviside function. Laplace transforming then gives

$$\widetilde{\Lambda}_k(s) = \left(\frac{1}{s} - \frac{1}{s+\kappa}\right)(e^{-(s+\kappa)(k-1)a/v_+} - e^{-(s+\kappa)ka/v_+}). \quad (5.5)$$

Substituting Eqs. (5.3) and (5.5) into Eq. (3.14) then yields the splitting probability $\pi_{r,k}$ under resetting:

$$\pi_{r,k} = \frac{r\widetilde{\Lambda}_k(r)}{r\sum_{l=1}^\infty \widetilde{\Lambda}_l(r)} = e^{-(r+\kappa)(k-1)a/v_+} - e^{-(r+\kappa)ka/v_+}. \quad (5.6)$$

Suppose that we write $\pi_{r,k} = \pi_r(ka)$. In Fig. 4 we show sample plots of the splitting probability function $\pi_r(L)$ as a function of the distance L from the source cell with $a = 1$ and $\kappa = 1$. It can be seen that the splitting probability is an exponentially decreasing function of L. Moreover, the steepness of the exponential gradient is an increasing function of r and a decreasing function of v_+. Consequently, $\pi_{r,k}$ is a unimodal function of r for targets close to the origin and a monotonically decreasing function of r at more distal target locations.

In order to calculate the conditional MFPTs using the general formula, Eq. (3.20), we also need to determine the function F of Eq. (2.9) and its Laplace transform. The probability density without resetting evolves according to the single equation

$$\frac{\partial p}{\partial t} = -v_+\frac{\partial p}{\partial x} - \kappa p, \quad x \in (0,\infty). \quad (5.7)$$

This has the solution

$$p(x,t) = \delta(x - v_+t)Q_0(t), \quad (5.8)$$

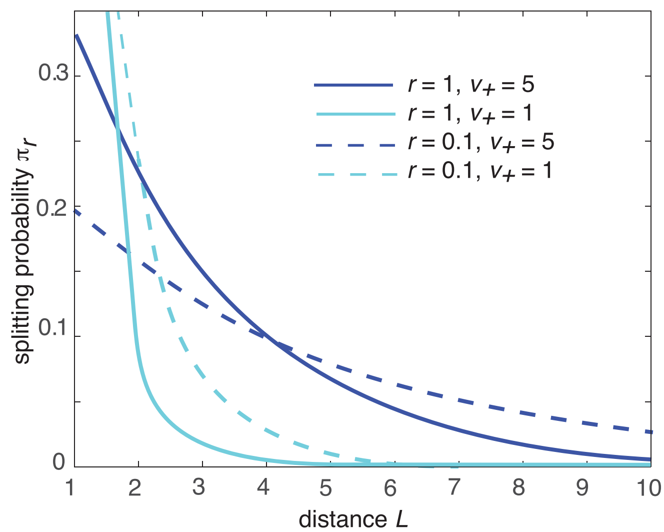

FIG. 4. Plot of splitting probability $\pi_r(L)$ as a function of distance from the source cell for various speeds v_+ and exponential resetting rates r. Here $\pi_r(ka) = \pi_{r,k}$ with $a = 1$.

where $Q_0(t)$ is the survival probability (starting at the origin),

$$Q_0(t) = 1 - \sum_{k=1}^\infty \Lambda_k(t) = e^{-\kappa t}.$$

It follows that

$$F(t) = \int_0^\infty xp(x,t)dx = v_+tQ_0(t). \quad (5.9)$$

Laplace transforming then gives

$$\widetilde{F}(r) = -v_+\frac{d\widetilde{Q}_0(r)}{dr} = \frac{v_+}{(r+\kappa)^2}.$$

Substituting Eqs. (5.3), (5.5), and (5.10) into the general expression, Eq. (3.20), for the MFPT reduces to

$$\pi_{r,k}T_{r,k} = \frac{-\widetilde{\Lambda}_k(r) - r\widetilde{\Lambda}_k'(r) + \mathcal{B}(r)\pi_{r,k}}{\kappa/(r+\kappa)},$$

where

$$\mathcal{B}(r) = \frac{r}{(r+\kappa)^2}\left(1 + \frac{v_+}{V}\right) + \frac{r\tau_{\rm ref}}{r+\kappa}. \quad (5.10)$$

Example plots of the MFPT as a function of the distance L and resetting rate r are shown in Figs. 5 and 6, respectively. We see that when $\pi_{\rm tot} = 1$, the MFPT is an increasing function of r. This suggests that resetting is not necessary for the given search process. However, as shown in Fig. 4, r has a strong effect on the spatial variation of the splitting probability. This has important implications for the role of cytoneme-based morphogenesis in generating morphogen gradients, which we explore further elsewhere.

The assumption that $\pi_{\rm tot} = 1$ may also fail to hold due to the cytoneme nucleating in the wrong orientation, for example. In this case, the inclusion of resetting results in MFPTs that are unimodal functions of r. Another way to include the possibility of failure is to discount any trajectories that are captured beyond the Nth target cell. This means that in the absence of resetting, the probability of failure is $e^{-\kappa a/v_+}$.

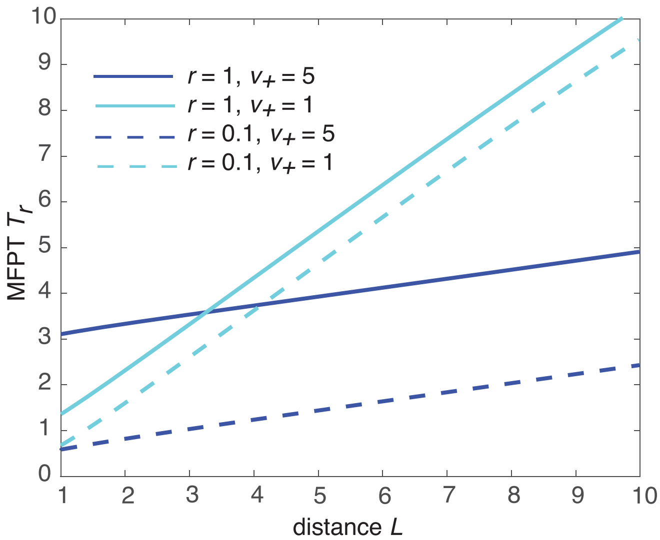

FIG. 5. Plot of conditional MFPT $T_r(L)$ as a function of distance from the source cell for various speeds v_+ and exponential resetting rates r. Here $T_r(ka) = T_{r,k}$ with $a = 1$, $V = 1$, and $\tau_{\rm ref} = 1$.

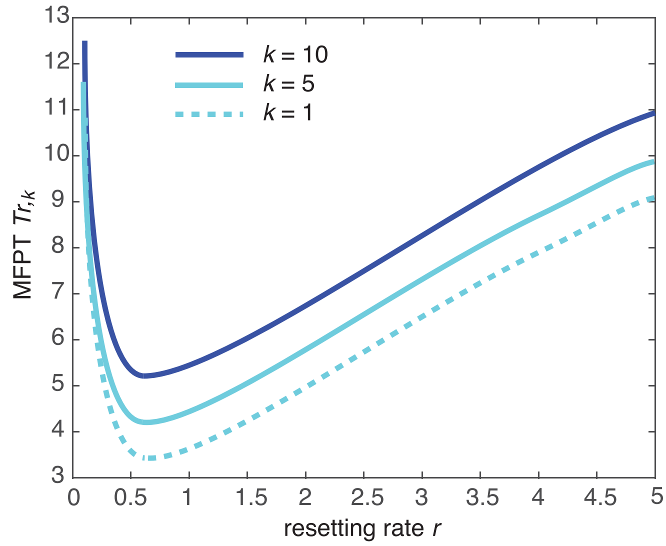

FIG. 7. Plot of conditional MFPT $T_{r,k}$ as a function of resetting rate r for various targets k and $V = 1$. In contrast to Fig. 6, capture by any target $k > 10$ is treated as a failure so $\pi_{\rm tot} < 1$. Other parameters are $v_+ = 5$ and $\tau_{\rm ref} = 1$.

Repeating the above analysis and plotting the resulting conditional MFPTs, it can be shown that the conditional MFPTs are now unimodal functions of r. This is illustrated in Fig. 7.

B. Three-dimensional diffusion in a bounded domain with small interior traps: Small-*r* expansion

As our second example, consider a Brownian particle diffusing in a 3D bounded domain $\mathcal{U}$ with N small traps in the interior of the domain. In the absence of resetting, the probability density evolves according to the diffusion equation

$$\frac{\partial p(\mathbf{x}, t|\mathbf{x}_0)}{\partial t} = D\nabla^2 p(\mathbf{x}, t|\mathbf{x}_0) = -D\nabla \cdot \mathbf{J}(\mathbf{x}, t|\mathbf{x}_0), \quad (5.11)$$

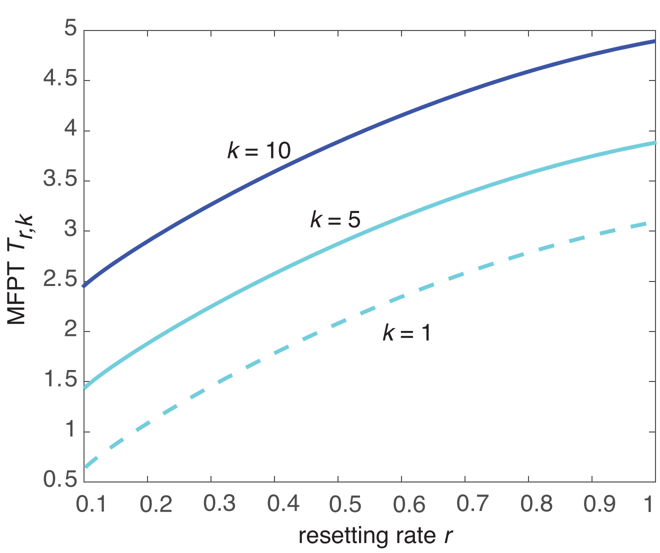

FIG. 6. Plot of conditional MFPT $T_{r,k}$ as a function of resetting rate r for various target cells. Other parameters are $v_+ = 5$, $V = 1$, $\tau_{\rm ref} = 1$.

with a reflecting boundary condition on the exterior of the domain

$$\partial_n p(\mathbf{x}, t|\mathbf{x}_0) = 0, \quad \mathbf{x} \in \partial\mathcal{U}, \quad (5.12)$$

where ∂_n denotes the outward normal derivative, and absorbing boundary conditions on the trap boundaries,

$$p(\mathbf{x}, t|\mathbf{x}_0) = 0 \quad \mathbf{x} \in \partial\mathcal{U}_a = \bigcup_{j=1}^{N} \partial\mathcal{U}_j. \quad (5.13)$$

Each trap is assumed to have a size $|\mathcal{U}_j| = \epsilon^3|\mathcal{U}|$ with $\mathcal{U}_j \to \mathbf{x}_j \in \mathcal{U}$ uniformly as $\epsilon \to 0$, $j = 1, \ldots, N$. The traps are also taken to be well separated in the sense that $|\mathbf{x}_i - \mathbf{x}_j| = O(1)$, $j \neq i$, and $\mathrm{dist}(x_j, \partial\mathcal{U}) = O(1)$.

In the absence of resetting, the FPT problem in the case of small targets can be analyzed using matched asymptotic expansions and Green's function methods [28–31]. That is, the splitting probabilities π_k, conditional MFPTs T_k, and higher-order moments such as $T_k^{(2)}$ satisfy time-independent boundary value problems that can be solved by constructing an inner or local solution valid in an $O(\epsilon)$ neighborhood of each target and then matching to an outer or global solution that is valid away from each neighborhood. A more challenging problem is to solve the full time-dependent problem, which is necessary in order to determine the splitting probabilities $\pi_{r,k}$ and MFPTs $T_{r,k}$ in the presence of resetting [see Eqs. (3.14) and (3.20)]. However, it is possible to use the results of asymptotic analysis in the small-r limit, since the resulting expansions involve moments of the FPT density without resetting [see Eqs. (4.4) and (4.8)]. We illustrate the basic idea by showing how to calculate π_k along the lines of Ref. [29] and then simply quote the analogous results for T_k and $T_k^{(2)}$.

First, it is well known that $\pi_k(\mathbf{x})$ satisfies the boundary value problem

$$\nabla^2\pi_k(\mathbf{x}) = 0, \quad \mathbf{x} \in \mathcal{U}\backslash\mathcal{U}_a; \quad \partial_n\pi_k(\mathbf{x}) = 0, \quad \mathbf{x} \in \partial\mathcal{U}, \tag{5.14a}$$

with

$$\pi_k(\mathbf{x}) = 1, \quad \mathbf{x} \in \partial\mathcal{U}_k; \quad \pi_k(\mathbf{x}) = 0, \quad \mathbf{x} \in \bigcup_{j\neq k}\partial\mathcal{U}_j. \tag{5.14b}$$

In the outer region, which is outside an $O(\epsilon)$ neighborhood of each trap, π_k is expanded as

$$\pi_k = \pi_k^{(0)} + \epsilon\pi_k^{(1)} + \epsilon^2\pi_k^{(2)} + \dots.$$

Here $\pi_k^{(0)}$ is an unknown constant, and

$$\nabla^2\pi_k^{(n)}(\mathbf{x}) = 0,\ \mathbf{x} \in \mathcal{U}\backslash\{\mathbf{x}_1, \dots, \mathbf{x}_N\},$$
$$\partial_n\pi_k(\mathbf{x}) = 0,\ \mathbf{x} \in \partial\mathcal{U} \tag{5.15}$$

for $n = 1, 2$, together with certain singularity conditions as $\mathbf{x} \to \mathbf{x}_j$, $j = 1, \dots, N$. The latter are determined by matching to the inner solution. In the inner region around the jth trap, we introduce the stretched coordinates $\mathbf{y} = \epsilon^{-1}(\mathbf{x} - \mathbf{x}_j)$ and set $u_k(\mathbf{y}) = \pi_k(\mathbf{x}_j + \epsilon\mathbf{y})$. Expanding the inner solution as

$$u_k = u_k^{(0)} + \epsilon u_k^{(1)} + \dots,$$

we find that

$$\nabla_{\mathbf{y}}^2 u_k^{(0)}(\mathbf{y}) = 0,\ \mathbf{y} \notin \mathcal{U}_k, \quad u_k^{(0)}(\mathbf{y}) = \delta_{j,k}, \mathbf{y} \in \partial\mathcal{U}_j;$$
$$\nabla_{\mathbf{y}}^2 u_k^{(1)}(\mathbf{y}) = 0,\ \mathbf{y} \notin \mathcal{U}_k, \quad u_k^{(1)}(\mathbf{y}) = 0, \mathbf{y} \in \partial\mathcal{U}_j. \tag{5.16}$$

Finally, the matching condition is that the near-field behavior of the outer solution as $\mathbf{x} \to \mathbf{x}_j$ should agree with the far-field behavior of the inner solution as $|\mathbf{y}| \to \infty$, which is expressed as

$$\pi_k^{(0)} + \epsilon\pi_k^{(1)} + \epsilon^2\pi_k^{(2)} + \dots \sim u_k^{(0)} + \epsilon u_k^{(1)} + \dots.$$

The details of the matching process can be found in [29]. Here we just indicate the steps. First, $\pi_k^{(0)} \sim u_k^{(0)}$ so that we can set $u_k^{(0)}(\mathbf{y}) = \pi_k^{(0)} + (\delta_{j,k} - \pi_k^{(0)})w(\mathbf{y})$, with $w(\mathbf{y})$ satisfying the boundary value problem

$$\nabla_{\mathbf{y}}^2 w(\mathbf{y}) = 0, \quad \mathbf{y} \notin \mathcal{U}_k; \quad w(\mathbf{y}) = 1, \quad \mathbf{y} \in \partial\mathcal{U}_j;$$
$$w(\mathbf{y}) \to 0 \quad \text{as} \quad |\mathbf{y}| \to \infty. \tag{5.17}$$

This is a well-known problem in electrostatics and has the far-field behavior

$$w(\mathbf{y}) \sim \frac{C_j}{|\mathbf{y}|} + \frac{\mathbf{P}_j \cdot \mathbf{y}}{|\mathbf{y}|^3} + \dots \quad \text{as} \quad |\mathbf{y}| \to \infty, \tag{5.18}$$

where C_j is the capacitance and $\mathbf{P}_j$ the dipole vector of an equivalent charged conductor with the shape $\mathcal{U}_j$. (Here C_j has the units of length.) It now follows that $\pi_k^{(1)}$ satisfies Eq. (5.15) together with the singularity condition

$$\pi_k^{(1)}(\mathbf{x}) \sim \left(\delta_{j,k} - \pi_k^{(0)}\right)\frac{C_j}{|\mathbf{x} - \mathbf{x}_j|} \quad \text{as} \quad \mathbf{x} \to \mathbf{x}_j.$$

In other words, $\pi_k^{(1)}$ satisfies the inhomogeneous equation

$$\nabla^2\pi_k^{(1)}(\mathbf{x}) = -4\pi\sum_{j=1}^N \left(\delta_{j,k} - \pi_k^{(0)}\right)C_j\delta(\mathbf{x} - \mathbf{x}_j), \quad \mathbf{x} \in \mathcal{U};$$
$$\partial_n\pi_k^{(1)}(\mathbf{x}) = 0, \quad \mathbf{x} \in \partial\mathcal{U}. \tag{5.19}$$

This can be solved in terms of the Neumann Green's function

$$\nabla^2 G(\mathbf{x}; \mathbf{x}') = \frac{1}{|\mathcal{U}|} - \delta(\mathbf{x} - \mathbf{x}'),$$
$$\mathbf{x} \in \mathcal{U}; \quad \partial_n G = 0, \quad \mathbf{x} \in \partial\mathcal{U}; \tag{5.20a}$$
$$G(\mathbf{x}, \mathbf{x}') = \frac{1}{4\pi|\mathbf{x} - \mathbf{x}'|} + R(\mathbf{x}, \mathbf{x}'),$$
$$\int_{\mathcal{U}} G(\mathbf{x}, \mathbf{x}')d\mathbf{x} = 0, \tag{5.20b}$$

with $R(\mathbf{x}, \mathbf{x}')$ corresponding to the regular part of the Green's function. Given G, the solution can be written as

$$\pi_k^{(1)}(\mathbf{x}) = 4\pi\sum_{j=1}^N \left(\delta_{j,k} - \pi_k^{(0)}\right)C_j G(\mathbf{x}, \mathbf{x}_j) + \chi_k, \tag{5.21}$$

with unknown constant

$$\chi_k = \frac{1}{|\mathcal{U}|}\int_{\mathcal{U}} \pi_k^{(1)}(\mathbf{x})d\mathbf{x}. \tag{5.22}$$

In order to fully specify the $O(1)$ and $O(\epsilon)$ contributions to the splitting probability π_k we have to determine the constants $\pi_k^{(0)}$ and χ_k. The first follows immediately from integrating Eq. (5.19) over the domain $\mathcal{U}$ and imposing the reflecting boundary condition. This yields the solvability conditions $\sum_j(\delta_{j,k} - \pi_k^{(0)})C_j = 0$, so that

$$\pi_k^{(0)} = \frac{C_k}{N\overline{C}}, \quad \overline{C} = \frac{1}{N}\sum_{j=1}^N C_j. \tag{5.23}$$

The calculation of χ_k is more involved, since it is obtained by imposing a solvability condition on the $O(\epsilon^2)$ contribution $\pi_k^{(2)}$. This requires matching $\pi_k^{(2)}$ with the far-field behavior of $u_k^{(1)}$, which is itself found by matching $u_k^{(1)}$ with the near-field behavior of $\pi_k^{(1)}$. The final result is [29]

$$\pi_k(\mathbf{x}) \sim \frac{C_k}{N\overline{C}} + 4\pi\epsilon C_k\left[G(\mathbf{x}, \mathbf{x}_k) - \frac{1}{N\overline{C}}\sum_{j=1}^N C_j G(\mathbf{x}, \mathbf{x}_j)\right]$$
$$+ \epsilon\chi_k + o(\epsilon), \tag{5.24}$$

where

$$\chi_k = -\frac{4\pi C_k}{N\overline{C}}\left[\sum_{j=1}^N \mathcal{G}_{kj}C_j - \frac{1}{N\overline{C}}\sum_{i=1}^N C_i\mathcal{G}_{ij}C_j\right], \tag{5.25a}$$

with $\mathcal{G}_{ij} = G(\mathbf{x}_i, \mathbf{x}_j)$ for $i \neq j$, and $\mathcal{G}_{ii} = R(\mathbf{x}_i, \mathbf{x}_i)$. Note that

$$\sum_{k=1}^N \chi_k = 0.$$

An analogous asymptotic analysis can be used to determine the conditional MFPTs T_k and second moments $T_k^{(2)}$ [31]. First, T_k satisfies a boundary value problem of the form

$$\nabla^2(\pi_k(\mathbf{x})T_k(\mathbf{x})) = -\frac{\pi_k(\mathbf{x})}{D}, \quad \mathbf{x} \in \mathcal{U}\backslash\mathcal{U}_a, \tag{5.26a}$$

$$\partial_n(\pi_k(\mathbf{x})T_k(\mathbf{x})) = 0, \quad \mathbf{x} \in \partial\mathcal{U}, \tag{5.26b}$$

$$\pi_k(\mathbf{x})T_k(\mathbf{x}) = 0, \quad \mathbf{x} \in \partial\mathcal{U}_k, \tag{5.26c}$$

$$\pi_k(\mathbf{x})T_k(\mathbf{x}) \to 0, \quad \mathbf{x} \in \partial\mathcal{U}_j, \quad j \neq k. \tag{5.26d}$$

Matching the asymptotic expansions of the inner and outer solutions of Eqs. (5.26) one finds that [31]

$$\pi_k(\mathbf{x})T_k(\mathbf{x}) \sim \frac{C_k}{N\overline{C}}\frac{|\mathcal{U}|}{4\pi\epsilon DN\overline{C}} \times \left[1-4\pi\epsilon\sum_{j=1}^N C_jG(\mathbf{x},\mathbf{x}_j)+\frac{4\pi\epsilon}{N\overline{C}}\sum_{i,j=1}^N C_i\mathcal{G}_{ij}C_j\right] + \frac{\chi_k|\mathcal{U}|}{4\pi DN\overline{C}} + o(1). \tag{5.27}$$

In addition,

$$T_k(\mathbf{x}) \sim \frac{|\mathcal{U}|}{4\pi\epsilon DN\overline{C}} - \frac{|\mathcal{U}|}{D}G(\mathbf{x},\mathbf{x}_k) + \frac{|\mathcal{U}|}{D(N\overline{C})^2}\sum_{i,j=1}^N C_i\mathcal{G}_{ij}C_j + o(1). \tag{5.28}$$

Second, $T_k^{(2)}$ satisfies the boundary value problem

$$\nabla^2\big(\pi_k(\mathbf{x})T_k^{(2)}(\mathbf{x})\big) = -\frac{2\pi_k(\mathbf{x})T_k(\mathbf{x})}{D}, \quad \mathbf{x} \in \mathcal{U}\backslash\mathcal{U}_a, \tag{5.29a}$$

$$\partial_n\big(\pi_k(\mathbf{x})T_k^{(2)}(\mathbf{x})\big) = 0, \quad \mathbf{x} \in \partial\mathcal{U}, \tag{5.29b}$$

$$\pi_k(\mathbf{x})T_k^{(2)}(\mathbf{x}) = 0, \quad \mathbf{x} \in \partial\mathcal{U}_k, \tag{5.29c}$$

$$\pi_k(\mathbf{x})T_k^{(2)}(\mathbf{x}) \to 0, \quad \mathbf{x} \in \partial\mathcal{U}_j, \quad j \neq k. \tag{5.29d}$$

Again matching the asymptotic expansions of the inner and outer solutions one finds that [31]

$$\pi_k(\mathbf{x})T_k^{(2)}(\mathbf{x}) \sim \frac{C_k}{N\overline{C}}\frac{2|\mathcal{U}|^2}{(4\pi\epsilon DN\overline{C})^2} \times \left[1-4\pi\epsilon\sum_{j=1}^N C_jG(\mathbf{x},\mathbf{x}_j)+\frac{4\pi\epsilon}{N\overline{C}}\sum_{i,j=1}^N C_i\mathcal{G}_{ij}C_j\right] + \frac{\mu_k|\mathcal{U}|}{2\pi\epsilon DN\overline{C}} + o(1/\epsilon), \tag{5.30}$$

where

$$\mu_k = \frac{C_k}{N\overline{C}}\frac{|\mathcal{U}|}{D(N\overline{C})^2}\sum_{i,j=1}^N C_i\mathcal{G}_{ij}C_j + \frac{\chi_k|\mathcal{U}|}{4\pi DN\overline{C}}. \tag{5.31}$$

Note that the leading-order contributions to $\pi_k(\mathbf{x})$, $\pi_k(\mathbf{x})T_k(\mathbf{x})$, and $\pi_kT_k^{(2)}(\mathbf{x})$ are independent of the initial position $\mathbf{x}$ and the locations $\mathbf{x}_j$ of the targets.

We can now analyze how resetting affects the search process in the small-r regime using the results in Sec. IV and setting $\mathbf{x} = \mathbf{x}_r$. First, from Eqs. (5.24), (5.27), and (5.30), we have the leading-order approximations

$$\langle T\rangle \sim \frac{|\mathcal{U}|}{4\pi\epsilon ND\overline{C}} \times \left[1-4\pi\epsilon\sum_{j=1}^N C_jG(\mathbf{x}_r,\mathbf{x}_j)+\frac{4\pi\epsilon}{N\overline{C}}\sum_{i,j=1}^N C_i\mathcal{G}_{ij}C_j\right],$$

$$\sigma^2(T) \sim \frac{|\mathcal{U}|^2}{(4\pi\epsilon ND\overline{C})^2} + \frac{|\mathcal{U}|^2}{2\pi\epsilon D^2(N\overline{C})^3}\sum_{i,j=1}^N C_i\mathcal{G}_{ij}C_j.$$

Recall from Eq. (4.6) that resetting will increase the splitting probability to the kth target provided that $T_k < \langle T\rangle = \sum_{k=1}^N \pi_lT_l$. We thus obtain the leading-order condition

$$\overline{C}G(\mathbf{x}_r,\mathbf{x}_k) > \frac{1}{N}\sum_{j=1}^N C_jG(\mathbf{x}_r,\mathbf{x}_j). \tag{5.32}$$

This condition will clearly be satisfied if $\mathbf{x}_r \approx \mathbf{x}_k$. Next, recall from Eq. (4.14) that resetting will decrease the unconditional MFPT provided that $\sigma^2(T) > \langle T\rangle^2$. In the limit $\epsilon \to 0$, this reduces to the condition

$$\sigma^2(T) - \langle T\rangle^2 \sim \frac{|\mathcal{U}|^2}{2\pi\epsilon(DN\overline{C})^2}\sum_{j=1}^N C_jG(\mathbf{x}_r,\mathbf{x}_j) > 0.$$

Note that these results can only be established if one includes next-to-leading-order contributions to $\langle T\rangle$ and $\sigma^2(T)$. They depend on the capacitances C_j, the positions $\mathbf{x}_j$ of the targets, and the Green's function of the diffusion equation without resetting.

VI. DISCUSSION

In this paper we have derived general expressions for the splitting probabilities and conditional MFPTs for a search process with stochastic resetting, delays, and multiple targets. We obtained these results using a renewal method that involves conditioning the search process on whether or not at least one resetting occurs. Such an approach has previously been applied to a range of FPT problems with or without resetting [11–13,16,20–22]. Indeed, we showed how various results from these previous studies can be recovered in particular limits. One focus of our analysis was to determine the behavior of the search process in the small-r regime, which provides insights into whether or not the introduction of resetting can be beneficial [11–13]. We derived conditions for when resetting increases (decreases) the splitting probability (conditional MFPT) based on the splitting probabilities and first and second moments of the conditional FPT densities without resetting. This was subsequently applied to the general problem of search in a 3D bounded domain with a set of small targets in the interior of the domain. In particular, we showed how asymptotic analysis can be used to calculate the effects of resetting in the small-r regime. A natural extension would be to consider the search for small targets in a 2D domain, where one would need to take into account the fact that the 2D Neumann Green's function has logarithmic singularities [32]. Another extension would be to consider absorbing targets located on the boundary rather than the interior of the search domain.

We also explored a practical application of the theory to a problem in developmental cell biology, namely, the search-and-capture of cytonemes during morphogenesis. In this case, resetting plays an important role in determining the distribution of splitting probabilities across a set of target cells. This suggests that multiple rounds of search-and-capture events could generate a morphogen concentration gradient that depends on r. Indeed, suppose that each time a cytoneme finds a target, it delivers a packet of morphogen to the target and then retracts back to its nucleation site, after which another round of search-and-capture occurs. Assuming that packets degrade at a constant rate γ, the mean number of packets present within the kth target in the long-time limit will be $\overline{M}_k = \pi_k/(\gamma\langle T\rangle)$. That is, the mean time between capture events is the unconditional MFPT $\langle T\rangle$ and the fraction of these that deliver a packet to the kth target over many trials is given by the splitting probability π_k. Thus $\pi_k/\langle T\rangle$ is the mean rate of delivery of resources to the kth target, which is balanced by the degradation rate at steady state. This result, as well as higher-order moments of the resource distribution, can be obtained more rigorously by extending our recent work on queuing theory and search processes with stochastic resetting [33] to the case of multiple targets [34]. Another natural extension would be to consider cytonemes growing and retracting in higher-dimensional spaces in order to deliver morphogen to target cells arranged in 2D or 3D arrays.

Finally, the example of cytoneme-based morphogenesis suggests a more general class of search-and-capture problems, in which the interior of the search domain is partitioned into a set of partially absorbing targets. Such a scenario has a number of other applications in cell biology, including the active motor-driven transport of vesicles to synaptic targets in the axons of neurons. Analogous to cytoneme-based transport, the splitting probabilities would determine the steady-state distribution of synaptic resources along the axon. There are also higher-dimensional versions of active vesicular transport, involving molecular motors moving along cytoskeletal networks within the cell body.

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