Survival probability of diffusion with trapping in cellular neurobiology

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The problem of diffusion with absorption and trapping sites arises in the theory of molecular signaling inside and on the membranes of biological cells. In particular, this problem arises in the case of spine-dendrite communication, where the number of calcium ions, modeled as random particles, is regulated across the spine microstructure by pumps, which play the role of killing sites, while the end of the dendritic shaft is an absorbing boundary. We develop a general mathematical framework for diffusion in the presence of absorption and killing sites and apply it to the computation of the time-dependent survival probability of ions. We also compute the ratio of the number of absorbed particles at a specific location to the number of killed particles. We show that the ratio depends on the distribution of killing sites. The biological consequence is that the position of the pumps regulates the fraction of calcium ions that reach the dendrite.

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I. INTRODUCTION

The post-synaptic part of a synapse is usually a dendritic spine, a microstructure located on a dendrite of a neuron (see Fig. 1) [1–4]. The spine geometry consists of a nearly spherical head connected to the dendrite by a narrow cylindrical neck. Calcium ions enter the spine head through glutamate gated channels following the release of glutamate neurotransmitters by the presynaptic terminal. The communication between a dendritic spine and the dendrite depends on the ability of the calcium ions to pass through the cylindrical neck to the dendrite. When ions enter the neck, they diffuse and either reach the dendrite or are extruded on their way to the dendrite by pump proteins located on the lateral surface of the neck [1,5]. The number of calcium ions that arrive at the dendrite and the calcium contents of the spine are regulated by the geometry of the neck and by the contents of the spine. The contents include organelles, such as the endoplasmic reticulum, calcium buffer proteins such as calmodulin, calcium stores, actin-myosin proteins, and pumps on the spine membrane. In this paper, we focus on the role of the spine neck in spine-dendrite communication, which is an area of intense experimental research (see, e.g., Refs. [1,3]). We adopt a simplified one-dimensional model of the diffusive motion of calcium ions in the neck, in which the termination of ionic trajectories by pumps is described as "killing," while termination in the dendrite is described as "absorption." The killing measure (the probability per unit time and unit length to terminate a trajectory at a given point at a given time) has been introduced into the chemical reaction literature in Ref. [6] (see also Refs. [7–10]).

An ion can pass through a killing site many times without being terminated. In contrast, an absorbing boundary terminates the trajectory with probability 1 the first time the trajectory gets there. Thus we distinguish between two random times on a trajectory, the time to be killed, denoted T, and the time to be absorbed, denoted τ. We need to find the probability $\Pr\{\tau > T|\boldsymbol{y}\}$ of an ion getting killed (pumped out) in the neck before it is absorbed at the boundary (the dendrite), given that it started at a point $\boldsymbol{y}$ in the neck. The ratio

$$R_\infty = \frac{\Pr\{\tau < T|\boldsymbol{y}\}}{\Pr\{\tau > T|\boldsymbol{y}\}}$$

is the fraction of absorbed to killed (pumped) particles. We also need to calculate $E[T|\tau > T, \boldsymbol{y}]$, the mean time to be killed, given that the particle is killed, as well as $E[\tau|T > \tau, \boldsymbol{y}]$, the mean time to absorption, given that the particle is absorbed. An application of our model in neurobiology concerns calcium regulation in the dendritic spine and in the dendrite. In dendrites of neurons, ions are constantly exchanged between compartments and when the concentration of calcium ions in the dendritic shaft rises above a threshold value, some specific cascades of chemical reactions are initiated that can lead to a new physiological stage, where

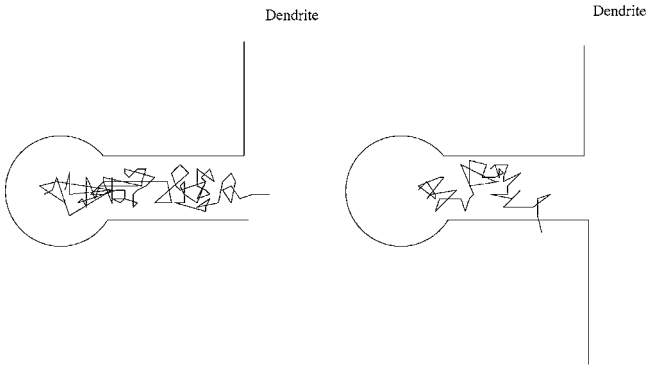

FIG. 1. Extrusion of an ion from the spine neck. A dendritic spine is a microstructure located on the dendrite of neurons, consisting of a round head connected to the dendrite through a cylindrical neck. Its function is still unclear. After ions enter through the head, either they are pumped out (right figure) or they reach the dendrite (left picture). The number of ions reaching the dendrite is regulated by the number and the distribution of pumps and the length of the spine neck.

the synaptic properties are modified. For example, the biophysical properties of the synapses or the number of channel receptors can be irreversibly changed [4,11,12]. The process that consists of changing the synaptic properties is known as synaptic plasticity. Today, the mechanisms of induction of synaptic changes are still unclear, but it has been demonstrated recently [13] that the induction process can be affected by the dynamics of the spine-dendrite coupling. The communication between a dendritic spine and the dendrite depends on the ability of the ions to pass through the cylindrical neck of the spine (see Fig. 1). The measure of this ability is the parameter R_∞. When ions leave the spine head and enter the neck, they diffuse and either reach the dendrite (with probability $\Pr\{T>\tau|\mathbf{y}\}$), or, as mentioned above, are extruded by pump proteins on their way to the dendrite [1,5]. In a simplified homogenized model proposed in Ref. [13], the number of ions filtered by the neck has been estimated and compared with experimental results. This number depends on the distribution of pumps along the neck and on the efficiency of the pumping process. The precise comparison with experimental data in Ref. [13] made it possible to predict that changing the length of the spine neck (which occurs under specific conditions, see, for example, Ref. [3]) is sufficient to regulate precisely the number of ions arriving at the dendrite. Spine-dendrite calcium signaling ([1,5]) and its regulation through specific microstructures, such as the spine neck, is crucial for the induction of synaptic plasticity, which underlies learning and memory. The mean time $E[t|\mathbf{y}]$ an ion spends inside the neck can be written as

$$E[t|\mathbf{y}] = E[t|\tau<T,\mathbf{y}]\Pr\{\tau<T|\mathbf{y}\} + E[t|T<\tau,\mathbf{y}]\Pr\{T<\tau|\mathbf{y}\}$$
$$= E[\tau|\tau<T,\mathbf{y}]\Pr\{\tau<T|\mathbf{y}\} + E[T|T<\tau,\mathbf{y}]\Pr\{T<\tau|\mathbf{y}\}.$$

The rate $1/E[t|\mathbf{y}]$ is the total probability flux out of the neck. This is a measurable quantity that can be used to prove that ions diffusing into the dendrite originate in the spine head. Indeed, calcium that enters the spine head through the glutamate gated channels at the top of the spine head takes much longer to reach the dendrite than calcium that enters through voltage gated channels. This is due to the much faster propagation of the membrane depolarization than movement by diffusion. In a biological context the final distribution of particles between absorption and killing indicates the future changes in the steady properties of the synapse. This is a general principle in cell biology regulation. It is fundamental for the homeostasis of a living cell to regulate the number of proteins or small molecules it contains and to maintain this number constant in the absence of external input. This is, for example, achieved through an equilibrium between synthesis and hydrolysis mechanisms. At a molecular level, when molecules reach the active sites of free enzymes by a Brownian random walk, either the molecules are hydrolyzed or nothing happens (see Ref. [14] for a stochastic description) and after some time, the molecules are absorbed or enter different organelles. This is what happens in signal transduction, as in synapses of neurons or in sensor cells. In some cases, the stability and the function of the cell depends on the efficiency of such dynamical processes. In addition, the geometry of the cell participates in the regulation of the number of particles, such as ions, that reach specific locations. In the present work, we are interested in estimating the probability that an ion survives in a medium containing many pumps. We compute the probability to arrive at a specific location before being killed (see Fig. 1) as a function of structure and pump distribution. In the case of a dendritic spine, we assume that the cylindrical neck can be approximated by a one-dimensional interval, and the computations are given in a one-dimensional model. The one-dimensional approximation is valid when the radius of the spine neck is sufficiently small, otherwise, the small pumps cannot affect the normal diffusion process (see Ref. [15]). We will see that various pump distributions affect the concentration of ions in the neck; we compare a uniform distribution along the spine neck, modeled as a constant killing rate, to an accumulation of pumps in "hot spots" at some specific locations (for example, at the base of the dendritic spine). In either case, we estimate the flux of ions into the dendrite. The reduced one-dimensional model of Brownian motion with killing and absorption is investigated in various types of killing sets. It is of interest to determine the influence of spatial distribution of the killing measure on the global survival probability of the population. Absorption and killing are expressed differently in the Fokker-Planck equation (FPE) for the transition probability density function (pdf) of the Brownian motion. While total absorption at the boundary is expressed as a homogeneous Dirichlet boundary condition, killing appears as a reaction term in the FPE [16]. Our main results are general expressions for the probabilities, ratio, and mean times in general, and in particular, we give explicit expressions as functions of the geometry and distribution of killing sites in the one-dimensional model. We also provide a biological interpretation of the results.

II. KILLING MEASURE AND THE SURVIVAL PROBABILITY

We consider a Brownian motion (particle) in a cylinder, whose lateral boundary contains many small absorbing holes, one base is reflecting and the other absorbing. This model can be approximated [15] by a one-dimensional Brownian motion on an interval with one reflecting and one absorbing endpoint, and a killing measure inside the interval. The strength of the killing measure is related to the absorption flux of the three-dimensional Brownian motion through the small holes on the boundary of the cylinder. The killing measure $k(x,t)$ is the probability per unit time and unit length that the Brownian trajectory is terminated at point x at time t [16]. The survival probability and the pdf of the surviving trajectories can be derived from the Wiener measure [17]. Indeed, the joint (defective) probability density of finding a trajectory at point x and the distribution of the random time at which it is terminated τ is

$$u(x,t|y)dx = \Pr\{x(t) \in x+dx, \tau>t|x(0)=y\},$$

which is the solution of the boundary value problem [6]

$$u_t = u_{xx} - k(x,t)u, \quad \text{for } x \in \mathbb{R}, \quad t > 0,$$

$$u(x,0) = \delta(x-y). \tag{1}$$

In the case that $k(x,t)=V_0$ and the diffusion coefficient is D, we have

$$\frac{\partial u(x,t|y)}{\partial t} = D\frac{\partial^2 u(x,t|y)}{\partial x^2} - V_0 u(x,t|y), \quad \text{for } x \in \mathbb{R}, \quad t > 0,$$

$$u(x,0|y) = \delta(y-x). \tag{2}$$

The solution is given by

$$u(x,t|y) = \frac{1}{2\sqrt{\pi D t}}\exp\left\{-V_0 t - \frac{(x-y)^2}{4Dt}\right\}. \tag{3}$$

The probability per unit time of being killed inside the interval $[a,b]$ at time t is

$$\Pr\{x(\tau) \in [a,b], \tau = t | x(0) = y\} = \int_a^b k(x,t)u(x,t|y)dx,$$

while the probability of being killed in the interval before time t is

$$\Pr\{x(\tau) \in [a,b], \tau < t | x(0) = y\} = \int_0^t \int_a^b k(x,t)u(x,t|y)dx\,dt.$$

The probability of ever being killed in the interval is

$$\Pr\{x(\tau) \in [a,b] | x(0) = y\} = \int_0^\infty \int_a^b k(x,t)u(x,t|y)dx\,dt,$$

and the density of ever being killed at x is therefore

$$\Pr\{x(\tau) = x | x(0) = y\} = \int_0^\infty k(x,t)u(x,t|y)dt. \tag{4}$$

The survival probability is the probability that the trajectory still exists at time t, that is,

$$S(t) = \Pr\{\tau > t | x(0) = y\} = \int_{\mathbb{R}} u(x,t|y)dx.$$

For the case $k(x,t)=V_0$ Eq. (3) gives

$$\Pr\{\tau > t | x(0) = y\} = \int_{\mathbb{R}} u(x,t|y)dx = e^{-V_0 t}. \tag{5}$$

This is exactly the rate at which particles disappear from the medium. The rate is exponential, so that out of N_0 initial independent Brownian particles in $\mathbb{R}$ the expected number of particles that have disappeared by time t is $N_0(1-e^{-V_0 t})$. The probability of being killed at point x, given by Eq. (4), is

$$P(x|y) = V_0 \int_0^\infty \frac{1}{2\sqrt{\pi D t}}\exp\left\{-V_0 t - \frac{(x-y)^2}{4Dt}\right\}dt$$
$$= \frac{1}{2}\sqrt{\frac{V_0}{D}}\exp\left\{-\sqrt{\frac{V_0}{D}}|x-y|\right\}. \tag{6}$$

We assume henceforward that the killing measure is time independent.

III. ABSORPTION VERSUS KILLING

We consider now a particle diffusing in a domain $\Omega \subset \mathbb{R}^n$ with a killing measure $k(\boldsymbol{x})$ and an absorbing part $\partial\Omega_a \subset \partial\Omega$ of the boundary $\partial\Omega$. Thus the trajectory of the particle can terminate in two ways: it can either be killed inside Ω or absorbed in $\partial\Omega_a$. The difference between the killing and the absorbing processes is that while the trajectory has a finite probability of not being terminated at points $\boldsymbol{x}$, where $k(\boldsymbol{x})>0$, it is terminated with probability 1 the first time it hits $\partial\Omega_a$. Thus the trajectory may traverse many times killing regions, where $k(\boldsymbol{x})>0$, but it cannot emerge from the absorbing part of the boundary.

A. Definition and basic equations

We define two random termination times defined on the trajectories of the diffusion process: the time to killing, denoted T, and the time to absorption in $\partial\Omega_a$, denoted τ, which is the first passage time to $\partial\Omega_a$. We calculate below the probability $\Pr\{T<\tau|y\}$, and the conditional distribution $\Pr\{\tau < t | \tau < T, y\}$. We consider the trajectories of the stochastic differential equation

$$d\boldsymbol{x} = \boldsymbol{a}(\boldsymbol{x})dt + \boldsymbol{B}(\boldsymbol{x})d\boldsymbol{w}(t) \text{ for } \boldsymbol{x}(t) \in \Omega, \tag{7}$$

where $\boldsymbol{a}(\boldsymbol{x})$ is a smooth drift vector, $\boldsymbol{B}(\boldsymbol{x})$ is a smooth diffusion matrix, and $\boldsymbol{w}(t)$ is a vector of independent standard Brownian motions [16]. We assume that a killing measure $k(\boldsymbol{x}) \geqslant 0$ is defined in Ω and $k(\boldsymbol{x})>0$ on a set of positive measure. The transition probability function of $\boldsymbol{x}(t)$ satisfies the Fokker-Planck equation

$$\frac{\partial p(\boldsymbol{x},t|\boldsymbol{y})}{\partial t} = \mathcal{L}p(\boldsymbol{x},t|\boldsymbol{y}) - k(\boldsymbol{x})p(\boldsymbol{x},t|\boldsymbol{y}) \text{ for } \boldsymbol{x},\boldsymbol{y} \in \Omega, \tag{8}$$

where the forward operator $\mathcal{L}$ is defined by

$$\mathcal{L}p(\boldsymbol{x},t|\boldsymbol{y}) = \sum_{i,j=1}^n \frac{\partial^2 \sigma^{i,j}(\boldsymbol{x})p(\boldsymbol{x},t|\boldsymbol{y})}{\partial x^i\,\partial x^j} - \sum_{i=1}^n \frac{\partial a^i(\boldsymbol{x})p(\boldsymbol{x},t|\boldsymbol{y})}{\partial x^i} \tag{9}$$

and

$$\boldsymbol{\sigma}(\boldsymbol{x}) = \frac{1}{2}\boldsymbol{B}(\boldsymbol{x})\boldsymbol{B}^T(\boldsymbol{x}).$$

The forward operator $\mathcal{L}$ can also be written in the divergence form

$$\mathcal{L}p(\boldsymbol{x},t|\boldsymbol{y}) = -\boldsymbol{\nabla}\cdot\boldsymbol{J}(\boldsymbol{x},t|\boldsymbol{y}), \tag{10}$$

where the components of the flux density vector $\boldsymbol{J}(\boldsymbol{x},t|\boldsymbol{y})$ are defined as

$$J^i(\boldsymbol{x},t|\boldsymbol{y}) = -\sum_{j=1}^{n} \frac{\partial \sigma^{i,j}(\boldsymbol{x}) p(\boldsymbol{x},t|\boldsymbol{y})}{\partial x^i} + a^i(\boldsymbol{x}) p(\boldsymbol{x},t|\boldsymbol{y}). \quad (11)$$

The initial and boundary conditions for the Fokker-Planck equation (8) are

$$p(\boldsymbol{x},0|\boldsymbol{y}) = \delta(\boldsymbol{x}-\boldsymbol{y}) \quad \text{for} \quad \boldsymbol{x},\boldsymbol{y} \in \Omega, \quad (12)$$

$$p(\boldsymbol{x},t|\boldsymbol{y}) = 0 \quad \text{for} \quad t>0,\ \boldsymbol{x} \in \partial\Omega,\ \boldsymbol{y} \in \Omega_a, \quad (13)$$

$$\boldsymbol{J}(\boldsymbol{x},t|\boldsymbol{y}) \cdot \boldsymbol{\nu}(\boldsymbol{x}) = 0 \quad \text{for} \quad t>0,\ \boldsymbol{x} \in \partial\Omega - \partial\Omega_a,\ \boldsymbol{y} \in \Omega. \quad (14)$$

The transition pdf $p(\boldsymbol{x},t|\boldsymbol{y})$ is actually the joint pdf

$$p(\boldsymbol{x},t|\boldsymbol{y})d\boldsymbol{x} = \Pr\{\boldsymbol{x}(t) \in \boldsymbol{x}+d\boldsymbol{x}, T>t, \tau>t|\boldsymbol{y}\}, \quad (15)$$

that is, $p(\boldsymbol{x},t|\boldsymbol{y})$ is the probability density that the trajectory survived to time t, i.e., was neither killed nor absorbed in $\partial\Omega_a$, and is located at $\boldsymbol{x}$. We begin by showing that

$$\Pr\{T<\tau|\boldsymbol{y}\} = \int_0^\infty \int_\Omega k(\boldsymbol{x}) p(\boldsymbol{x},t|\boldsymbol{y}) d\boldsymbol{x} dt \quad (16)$$

by two different derivations. First, assume that the entire boundary is absorbing, that is, $\partial\Omega_a = \partial\Omega$. Then the probability density of surviving up to time t and being killed at time t at point $\boldsymbol{x}$ can be represented by the limit as $N\to\infty$ of

$$\begin{aligned}
&\Pr\{\boldsymbol{x}_N(t_{1,N}) \in \Omega, \boldsymbol{x}_N(t_{2,N}) \in \Omega, \ldots, \boldsymbol{x}_N(t) \\
&\quad = \boldsymbol{x}, t \leqslant T \leqslant t+\Delta t | \boldsymbol{x}(0) = \boldsymbol{y}\} \\
&\quad = \Bigg[\int_\Omega \int_\Omega \cdots \int_\Omega \prod_{j=1}^{N} \frac{d\boldsymbol{y}_j}{\sqrt{(2\pi\Delta t)^n \det \boldsymbol{\sigma}(\boldsymbol{x})(t_{j-1,N})}} \\
&\qquad \times \exp\Bigg\{ -\frac{1}{2\Delta t} \{\boldsymbol{y}_j - \boldsymbol{x}(t_{j-1,N}) \\
&\qquad - \boldsymbol{a}[\boldsymbol{x}(t_{j-1,N})]\Delta t\}^T \boldsymbol{\sigma}^{-1}[\boldsymbol{x}(t_{j-1,N})] \\
&\qquad \times \{\boldsymbol{y}_j - \boldsymbol{x}(t_{j-1,N}) - \boldsymbol{a}[\boldsymbol{x}(t_{j-1,N})]\Delta t\} \Bigg\} \\
&\qquad \times \{1 - k[\boldsymbol{x}(t_{j,N})\Delta t]\} \Bigg] k(\boldsymbol{x})\Delta t, \quad (17)
\end{aligned}$$

where

$$\Delta t = \frac{t}{N}, \quad t_{j,N} = j\Delta t$$

and

$$\boldsymbol{x}(t_{0,N}) = \boldsymbol{y}$$

in the product. The limit is the Wiener integral defined by the stochastic differential equation (7), with the killing measure $k(\boldsymbol{x})$ and the absorbing boundary condition [18]. In the limit $N\to\infty$ the integral (17) converges to the solution of the Fokker-Planck equation (8) in Ω with the initial and boundary conditions (12) and (13). Integrating over Ω with respect to $\boldsymbol{x}$ and from 0 to ∞ with respect to t, we obtain, in view of Eq. (15), the representation (16). A second derivation begins with the integration of the Fokker-Planck equation (8),

$$1 = \int_0^\infty \oint_{\partial\Omega} \boldsymbol{J}(\boldsymbol{x},t|\boldsymbol{y}) \cdot \boldsymbol{\nu}(\boldsymbol{x}) dS_x dt + \int_0^\infty \int_\Omega k(\boldsymbol{x}) p(\boldsymbol{x},t|\boldsymbol{y}) d\boldsymbol{x} dt. \quad (18)$$

We write

$$J(t|\boldsymbol{y}) = \oint_{\partial\Omega} \boldsymbol{J}(\boldsymbol{x},t|\boldsymbol{y}) \cdot \boldsymbol{\nu}(\boldsymbol{x}) dS_x \quad (19)$$

and note that this is the absorption probability current on $\partial\Omega$. Therefore, in view of the boundary conditions (13) and (14), $\int_0^\infty J(t|\boldsymbol{y})dt$ is the total probability that has ever been absorbed at the boundary $\partial\Omega_a$. This is the probability of trajectories that have not been killed before reaching $\partial\Omega_a$. Writing Eq. (18) as

$$\int_0^\infty J(t|\boldsymbol{y})dt = 1 - \int_0^\infty \int_\Omega k(\boldsymbol{x}) p(\boldsymbol{x},t|\boldsymbol{y}) d\boldsymbol{x} dt,$$

we obtain Eq. (16). The probability distribution function of T for trajectories that have not been absorbed in $\partial\Omega_a$ is found by integrating the Fokker-Planck equation with respect to $\boldsymbol{x}$ over Ω and with respect to t from 0 to t. It is given by

$$\begin{aligned}
\Pr\{T<t|\tau>T,\boldsymbol{y}\} &= \frac{\Pr\{T<t,\tau>T|\boldsymbol{y}\}}{\Pr\{\tau>T|\boldsymbol{y}\}} \\
&= \frac{\int_0^t \int_\Omega k(\boldsymbol{x}) p(\boldsymbol{x},s|\boldsymbol{y}) d\boldsymbol{x} ds}{\int_0^\infty \int_\Omega k(\boldsymbol{x}) p(\boldsymbol{x},s|\boldsymbol{y}) d\boldsymbol{x} ds}. \quad (20)
\end{aligned}$$

Hence

$$E[T|T<\tau,\boldsymbol{y}] = \frac{\int_0^\infty \int_t^\infty \int_\Omega k(\boldsymbol{x}) p(\boldsymbol{x},s|\boldsymbol{y}) d\boldsymbol{x}\, ds\, dt}{\int_0^\infty \int_\Omega k(\boldsymbol{x}) p(\boldsymbol{x},s|\boldsymbol{y}) d\boldsymbol{x}\, ds}. \quad (21)$$

Equivalently,

$$E[T|T<\tau,\boldsymbol{y}] = \frac{\int_0^\infty s \int_\Omega k(\boldsymbol{x}) p(\boldsymbol{x},s|\boldsymbol{y}) d\boldsymbol{x}\, ds\, dt}{\int_0^\infty \int_\Omega k(\boldsymbol{x}) p(\boldsymbol{x},s|\boldsymbol{y}) d\boldsymbol{x}\, ds}, \quad (22)$$

which can be expressed in terms of the Laplace transform

$$\hat{p}(\boldsymbol{x},q|\boldsymbol{y}) = \int_0^\infty p(\boldsymbol{x},s|\boldsymbol{y}) e^{-qs} ds$$

as

$$E[T|T<\tau,\mathbf{y}] = -\left.\frac{\int_\Omega k(\mathbf{x})\frac{\partial}{\partial q}\hat{p}(\mathbf{x},q|\mathbf{y})d\mathbf{x}}{\int_\Omega k(\mathbf{x})\hat{p}(\mathbf{x},q|\mathbf{y})d\mathbf{x}}\right|_{q=0}$$
$$= -\left.\frac{\partial}{\partial q}\left(\ln\left\{\int_\Omega k(\mathbf{x})\hat{p}(\mathbf{x},q|\mathbf{y})d\mathbf{x}\right\}\right)\right|_{q=0}. \quad (23)$$

The conditional distribution of the first passage time to the boundary of trajectories, given that they are absorbed, is

$$\Pr\{\tau<t|T>\tau,\mathbf{y}\} = \frac{\int_0^t J(s|\mathbf{y})ds}{1-\int_0^\infty\int_\Omega k(\mathbf{x})p(\mathbf{x},s|\mathbf{y})d\mathbf{x}ds}. \quad (24)$$

Thus the mean time to absorption in $\partial\Omega_a$ of trajectories that are absorbed is given by [19]

$$E[\tau|T>\tau,\mathbf{y}] = \int_0^\infty \Pr\{\tau>t|T>\tau,\mathbf{y}\}dt$$
$$= \frac{\int_0^\infty sJ(s|\mathbf{y})ds}{1-\int_0^\infty\int_\Omega k(\mathbf{x})p(\mathbf{x},s|\mathbf{y})d\mathbf{x}ds}. \quad (25)$$

The survival probability is given by

$$S(t|\mathbf{y}) = \int_\Omega p(\mathbf{x},t|\mathbf{y})d\mathbf{x}. \quad (26)$$

B. Killing at hot spots (trapping) in a finite interval

We derive explicit estimates of the survival probability with a Dirac killing measure and of the conditional mean time to absorption (before being killed) in a finite interval.

1. Explicit decay of the survival probability in one dimension

To compare the survival probability of Brownian motion with and without a Dirac killing (a trap or hot spot) at a point x_1 in the interval $[0,\pi]$, with absorbing boundaries, we write the boundary value problem (8)–(13) as

$$\frac{\partial u(x,t|x_1,y)}{\partial t} = D\frac{\partial^2 u(x,t|x_1,y)}{\partial x^2} - V\delta(x-x_1)u(x,t|x_1,y)$$
$$\text{for}\quad 0<x<\pi,$$
$$u(x,0|x_1,y) = \delta(x-y),$$
$$u(0,t|x_1,y) = u(\pi,t|x_1,y) = 0 \quad (27)$$

and recall that the Green function of the free particle problem, where $V=0$, is

$$G(x,t|y) = \frac{2}{\pi}\sum_{n=1}^\infty \sin nx \sin nye^{-n^2t}.$$

Therefore the survival probability of Brownian motion in the interval is

$$S_0(t|y) = \int_0^\pi G(x,t|y)dx = \frac{4}{\pi}\sum_{n=1}^\infty \frac{\sin(2n-1)y}{2n-1}e^{-(2n-1)^2t}.$$

Using the Laplace transform, the solution $u(x,t|x_1,y)$ of Eq. (27) with $V>0$ is given by

$$\hat{u}_V(x,q|x_1,y) = \hat{G}(x,q|y) - \frac{V\hat{G}(x,q|x_1)}{1+V\hat{G}(x_1,q|x_1)}\hat{G}(x_1,q|y), \quad (28)$$

where

$$\hat{G}(x,q|y) = \frac{2}{\pi}\sum_{n=1}^\infty \frac{\sin nx \sin ny}{q+n^2}. \quad (29)$$

Note that

$$\hat{S}_0(q|y) = \int_0^\pi \hat{G}(x,q|y)dx = \frac{4}{\pi}\sum_{n=1}^\infty \frac{\sin(2n-1)y}{(2n-1)[q+(2n-1)^2]}.$$

According to Eq. (26), the survival probability $S_V(t|y)$ is given by

$$S_V(t|x_1,y) = \int_0^\pi u_V(x,t|x_1,y)dx \quad (30)$$

and the Laplace transform is

$$\hat{S}_V(q|y) = \int_0^\pi \hat{u}_V(x,q|x_1,y)dx. \quad (31)$$

Using Eq. (28), we find that the survival probabilities, without and with the Dirac killing, differ by

$$\hat{S}_0(q|y) - \hat{S}_V(q|x_1,y) = \frac{V\hat{G}(x_1,q|y)}{1+V\hat{G}(x_1,q|x_1)}\frac{4}{\pi}$$
$$\times\sum_{n=1}^\infty \frac{\sin(2n-1)x_1}{(2n-1)[q+(2n-1)^2]}. \quad (32)$$

The difference $\hat{S}_0(q|y)-\hat{S}_V(q|x_1,y)$ has no poles other than the zeros of $1+V\hat{G}(x_1,q|x_1)$, which are written as $q=-\xi^2$, where ξ is the smallest positive root of the equation (see Appendix I)

$$\sin\xi(\pi-x_1)\sin\xi x_1 = -\frac{\xi\sin\xi\pi}{V}. \quad (33)$$

For small V, we have

$$q = -1 - V\frac{2}{\pi}\sin(\pi - x_1)\sin x_1 + O(V^2). \tag{34}$$

The result (34) means that killing is most effective when the killing site is in the middle of the interval.

For large V and $x_1 > \pi/2$, we have

$$q = -\left(\frac{\pi}{x_1}\right)^2 + \frac{2\pi^2}{x_1^3}\frac{1}{V} + O\left(\frac{1}{V^2}\right), \tag{35}$$

which means that for large killing V the decay rate is the same as that in the interval enclosed between the killing site x_1 and the more distant endpoint of the interval $[0,\pi]$, with absorbing boundaries. Note that the decay rate in this case is independent of the initial point y. See Appendix I for details.

2. The conditional Mean First Passage Time (MFPT) $E[T|T<\tau,y]$

We use Eq. (23) to write the conditional MFPT $E[T|T<\tau,y]$ as

$$\begin{aligned} E[T|T<\tau,y] &= -\left.\frac{\partial}{\partial q}\ln\{\hat{p}(x_1,q|y)\}\right|_{q=0} \\ &= \frac{x_1 y(x_1^2+y^2+2\pi^2)-\pi(x_1^3+y^3)}{6(\pi-x_1)y} \\ &\quad\times\frac{\pi}{\pi+V(\pi-x_1)y} \end{aligned} \tag{36}$$

(see Appendix II for details).

C. The ratio of absorption to killing

According to the Fokker-Planck equation (8), the time-dependent ratio $R(t)$ of the absorbed particles (particles leaving the domain, before being killed) to the killed particles at time t can be defined as

$$R(t) = \frac{\int_{\partial\Omega_a} \boldsymbol{J}(\boldsymbol{x},t|\boldsymbol{y})\cdot\boldsymbol{\nu}(\boldsymbol{x})}{\int_\Omega k(\boldsymbol{x})p(\boldsymbol{x},t|\boldsymbol{y})d\boldsymbol{x}}. \tag{37}$$

More interestingly, we can define a steady state ratio R_∞, which is the total number of absorbed particles to the total number of killed particles after infinite time, by the expression

$$R_\infty = \frac{\int_0^\infty\int_{\partial\Omega_a}\boldsymbol{J}(\boldsymbol{x},t|\boldsymbol{y})\cdot\boldsymbol{\nu}(\boldsymbol{x})dS_{\boldsymbol{x}}dt}{\int_0^\infty\int_\Omega k(\boldsymbol{x})p(\boldsymbol{x},t|\boldsymbol{y})d\boldsymbol{x}dt} = \frac{\int_{\partial\Omega_a}\boldsymbol{J}(\boldsymbol{x}|\boldsymbol{y})\cdot\boldsymbol{\nu}(\boldsymbol{x})dS_{\boldsymbol{x}}}{\int_\Omega k(\boldsymbol{x})G(\boldsymbol{x}|\boldsymbol{y})d\,x}, \tag{38}$$

where $G(\boldsymbol{x}|\boldsymbol{y})$ is defined by the equation

$$-\rho(\boldsymbol{y}) = \mathcal{L}G(\boldsymbol{x},|\boldsymbol{y}) - k(\boldsymbol{x})G(\boldsymbol{x}|\boldsymbol{y}) \text{ for } \boldsymbol{x},\boldsymbol{y}\in\Omega \tag{39}$$

with the forward operator $\mathcal{L}$ defined in Eq. (9), $\rho(\boldsymbol{y})$ is the initial density, and $\boldsymbol{J}(\boldsymbol{x}|\boldsymbol{y})$ is the flux density vector at point $\boldsymbol{x}$, computed with respect to the function $G(\boldsymbol{x}|\boldsymbol{y})$. When $\rho(\boldsymbol{y})=\delta(\boldsymbol{y})$, G is the standard Green function with boundary conditions given by Eq. (13). We can define another ratio of interest: in a permanent regime, when a flux enters the domain through a part of the boundary, it is partitioned into the flux of absorbed and killed particles. When a steady state regime is achieved, we can define the ratio R_s as above. We denote by $\partial\Omega_i$ the part of the boundary, where a steady flux enters the domain. The steady state Fokker-Planck equation becomes

$$0 = \mathcal{L}p(\boldsymbol{x}|\boldsymbol{y}) - k(\boldsymbol{x})p(\boldsymbol{x}|\boldsymbol{y}) \text{ for } \boldsymbol{x},\boldsymbol{y}\in\Omega, \tag{40}$$

where the forward operator $\mathcal{L}$ is defined by Eq. (9) and the boundary conditions are

$$p(\boldsymbol{x}|\boldsymbol{y}) = 0 \quad \text{for } \boldsymbol{x}\in\partial\Omega,\boldsymbol{y}\in\Omega_a,$$

$$\boldsymbol{J}(\boldsymbol{x}|\boldsymbol{y})\cdot\boldsymbol{\nu}(\boldsymbol{x}) = 0 \text{ for } \boldsymbol{x}\in\partial\Omega-\partial\Omega_a-\partial\Omega_i,\boldsymbol{y}\in\Omega, \quad t>0,$$

$$\boldsymbol{J}(\boldsymbol{x}|\boldsymbol{y})\cdot\boldsymbol{\nu}(\boldsymbol{x}) = -\Phi(\boldsymbol{x}) \text{ for } \boldsymbol{x}\in\partial\Omega_i.$$

The time-independent flux is $\Phi(\boldsymbol{x})\geqslant 0$. The external steady state flux of absorbed particles is

$$J_a = \int_{\partial\Omega_a}\boldsymbol{J}(\boldsymbol{x}|\boldsymbol{y})\cdot\boldsymbol{\nu}(\boldsymbol{x})dS_{\boldsymbol{x}}. \tag{41}$$

The total inward flux is

$$J_i = \int_{\partial\Omega_i}\boldsymbol{J}(\boldsymbol{x}|\boldsymbol{y})\cdot\boldsymbol{\nu}(\boldsymbol{x})dS_{\boldsymbol{x}} = \int_{\partial\Omega_i}\Phi(\boldsymbol{x})dS_{\boldsymbol{x}}. \tag{42}$$

We define the ratio R_s as

$$\begin{aligned} R_s &= \frac{\int_{\partial\Omega_a}\boldsymbol{J}(\boldsymbol{x}|\boldsymbol{y})\cdot\boldsymbol{\nu}(\boldsymbol{x})dS_{\boldsymbol{x}}}{\int_\Omega k(\boldsymbol{x})p(\boldsymbol{x}|\boldsymbol{y})d\,x} \\ &= \frac{\int_{\partial\Omega_i}\Phi(\boldsymbol{x})dS_{\boldsymbol{x}} - \int_\Omega k(\boldsymbol{x})p(\boldsymbol{x}|\boldsymbol{y})d\boldsymbol{x}}{\int_\Omega k(\boldsymbol{x})p(\boldsymbol{x}|\boldsymbol{y})d\boldsymbol{x}}. \end{aligned} \tag{43}$$

The second part of the identity is a consequence of conservation of matter.

D. The one-dimensional case

The fluxes R_∞ and R_s can be explicitly evaluated in one dimension for a finite interval. The ratio R_s was computed in Ref. [13] in the case of an interval $[0,L]$, when the killing measure was uniformly distributed. We assume now that the inward flux at $x=L$ is a constant Φ and at $x=0$ an absorbing boundary condition is given. We consider here the case where the killing is a Dirac $k(x)=k\delta(x-x_1)$ located at a single point x_1, and k is a constant. This case can be viewed as a simplified model of calcium flow in a narrow and long neck of a dendritic spine with a cluster of pumps at x_1. The

particles are only driven by diffusion, so the steady state equation (40) becomes

$$D\frac{\partial^2 p(x)}{\partial x^2} - k\delta(x-x_1)p(x) = 0 \quad \text{for} \quad 0 < x < L,$$

$$\frac{\partial p(L)}{\partial x} = \Phi,$$

$$p(0) = 0,$$

and the ratio is

$$R_s = \frac{D\dfrac{\partial p(0)}{\partial x}}{kp(x_1)}. \tag{44}$$

An explicit computation of $p(x)$ gives

$$Dp'(L) = -\frac{D\Phi}{1+\dfrac{k}{D}(L-x_1)},$$

$$kp(x_1) = \frac{k\Phi(x_1-L)}{1+\dfrac{k}{D}(L-x_1)},$$

and

$$R_s = \frac{D}{k(L-x_1)}. \tag{45}$$

The result can be generalized to the case of a two hot spots in a straightforward manner.

The ratio R_s decays as

$$R_s \sim \frac{1}{\cosh(cL)} \quad \text{for} \quad L \to \infty \quad (c = \text{const})$$

if the killing measure is uniform in the interval $[0,L]$ [13]. This decay, compared to Eq. (45), shows that any redistribution of the killing sites affects the ratio (see discussion in Sec. IV). In the same spirit, we give an explicit expression for R_∞ in the case of a finite interval $[0,L]$, where particles are free to leave the domain at the points 0 and L. We assume that initially the particles are located at a point x_1. Here the killing occurs at the point $y<x_1$. Green's function for this problem, defined in Eq. (39), is the solution of the boundary value problem

$$D\frac{\partial^2}{\partial x^2}G(x|y) - k(x)G(x|y) = -\delta(x_1) \quad \text{for} \quad x,y \in [0,L],$$

$$G(0|y) = 0, \quad G(L|y) = 0.$$

An explicit solution of this problem gives the ratio R_∞ as given by

$$R_\infty = \frac{(L-x_1)k}{D\left(1+\dfrac{L-y}{y} - k\dfrac{y-x_1}{D}\right)}.$$

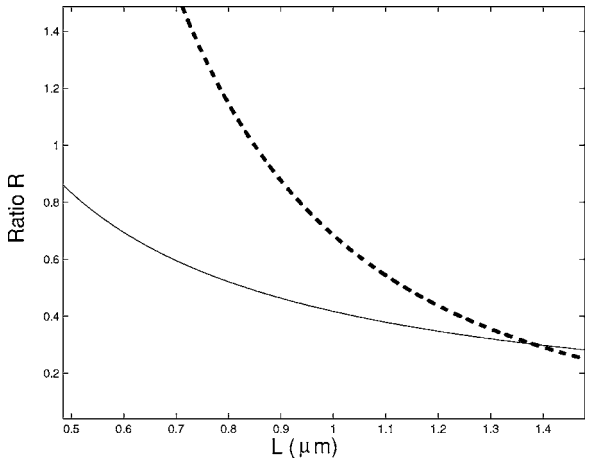

FIG. 2. Ratio of "absorbed" to "killed" particles, R_s, versus the length of the spine neck, L, for two types of pump distribution. Dashed curve: uniform distribution of pumps. Plain curve: all pumps are accumulated near the base of the spine neck.

IV. CONCLUSIONS, APPLICATIONS, AND PERSPECTIVE

We have provided in this paper a general mathematical framework for the computation of the distribution of "killed" and "absorbed" particles, after they flow into a bounded domain. The ratios R_∞ or R_s of "absorbed" to "killed" particles are in general difficult quantities to estimate analytically. However, in one dimension the explicit dependence of the ratio on the geometry can be computed; we analyzed here two extreme distributions: a uniform distribution and a Dirac killing measure. Formulas (45) and $1/\cosh(cL)$ ($c=\text{const}$) of Ref. [13] prove that the ratios depend on the killing distribution. For a general three-dimensional domain, R_s can only be estimated in asymptotic cases, where the absorbing boundary occupies a small portion of the boundary or when the support of the killing measure is small (see Refs. [20–23]). To illustrate the effect of the pump distribution on the ratio R_s, we have plotted in Fig. 2 two ratios associated with two types of distributions. The numbers relevant to the figure are $N=10$ pumps located on the spine neck (see Ref. [13]), a diffusion constant $D=400\ \mu\text{m}^2/\text{s}$, and extrusion rate $\chi=16.6\ \text{s}^{-1}$. For these values, we get the ratio $k/D=N\chi/D=2.4$. We assume that most of the pumps are accumulated near $x_1=0$, close to the bottom of the spine neck. When the pumps are uniformly distributed, the ratio is given by $R_s(L)=1/[\cosh(bL)-1]$, where $b=\sqrt{N\chi/D}=1.55$. The curve representing R_s for a uniform distribution is in dashed line. For a spine of neck length of 1.4 μm, there is an inversion in the dominant ratio of extrusion. For example, for a spine length of 1 μm, when the pumps are uniformly distributed, $R_s=0.4$, which corresponds to ten absorbed ions, four arrive at the dendrite. If the pumps are accumulate at the base of the neck, the ratio is about 0.7, corresponding to seven ions arriving at the dendrite and ten are absorbed. It is interesting to note that changing the pump distribution can have such effect. In the general context of microstructures in biological systems, the ratio R_s provides information about the total distribution of particles. When the killing measure is redistributed and a critical value of the ratio R_s is attained, new biophysical processes can be initi-

ated that affect irreversibly the physiological properties of the microstructure. Indeed, if enough particles enter the structure and stay sufficiently long, they bind to a large number of molecules. When a critical number of bonds are made, a cascade of chemical reactions is initiated. Thus a threshold can be reached by simply redistributing the killing measure. The implementation of these changes at a molecular level is yet to be identified. The mean conditional time of being absorbed before killing, $E(T|\tau<T)$, reveals not only the time spent inside the structure, but also how long it takes on the average for particles to arrive at a specific compartment. The spine-dendrite communication can be described in terms of quantities such as R_s and $E(T|\tau<T)$. First, the regulation of calcium ions that reach the dendrite can be achieved by various mechanisms. One possibility to decrease R_s is to increase the length of the neck, which really occurs *in vitro* experiments [13]. In that case, if the distribution of the killing measures is scaled with the dilation of the neck, the ratio R_s changes, with no need to change the total killing measure (e.g., the number of pumps). A second possibility is to redistribute the killing measure in a way that affects the ratio R_s, as shown in our computations (e.g., from uniform to accumulation at a hot spot). We can predict from expression (45), that moving all the calcium pumps at the bottom of the spine neck reduces the number of ions arriving at the dendrite. Finally, the number of pumps can also be changed. All possibilities are expected to be observed and any particular choice should be understood in the context of its function. We expect that the distribution of pumps across the spine neck to be highly dynamic and driven by the mean electrical activity of the dendrite. In particular, we may wonder how such distribution changes in the wake of applying protocols such as long term potentiation (LTP), which lead to long term changes at the synapse level [4]. No results seem to be known about the effect of LTP on the pump redistribution in spines. In reality, as studied in Ref. [5], the movement of ions inside the spine neck is not purely Brownian, but has a drift component, which affects the dynamics and changes the ratio. The mean time $E(\tau|\tau>T)$ to arrive at the dendrite was used in Ref. [13] to confirm that calcium ions arriving at the dendrite originate at the spine head (not in external sources). This result is derived by comparing the experimental time scale with $E(\tau|\tau>T)$. The mean time $E(\tau|\tau>T)$ is thus a fundamental parameter in the context of spine-dendrite communication, because it measures the mean time calcium ions enter the dendrite, and is related to the induction time of cascades of reactions, involved in modifying the synaptic weight. Changing the $E(\tau|\tau>T)$ is a part of the spine regulation process. This can be achieved by various ways: changing the spine neck length, changing the number of pumps and their distribution. Various biological investigations (see, for example, Ref. [1]) are dedicated to the elucidation of how such regulation is achieved at a biochemical level. Finally, the present computations assume that the neck width is small. If this is not the case, the one-dimensional approximation of the cylinder is no longer valid and pumps become insignificant.

APPENDIX A

We provide here the details of the computations used in Sec. III B 1. The function $\hat{G}(x_1,q|x_1)$ is given by

$$\hat{G}(x_1,q|x_1)=\frac{2}{\pi}\sum_{n=1}^{\infty}\frac{\sin nx_1\sin nx_1}{q+n^2}. \tag{A1}$$

For $a\in\mathbb{R}$, we will use the following identity:

$$\frac{\pi\cos(ax)}{2\sin(ax)}=\frac{1}{2a}+\sum_{n=1}^{\infty}\frac{(-1)^n a\cos(ax)}{a^2-n^2}\quad\text{for}\quad -\pi<x<\pi, \tag{A2}$$

where x is replaced by $x-\pi$. If we denote by F the function,

$$F(z)=\sum_{n=1}^{\infty}\frac{\cos(nx)}{q+n^2}, \tag{A3}$$

then by Eq. (A2),

$$F(z)=-\frac{1}{2q}-\frac{\pi\cos[\sqrt{-q}(z-\pi)]}{2\sqrt{-q}\sin(\sqrt{-q}\pi)}. \tag{A4}$$

Finally,

$$\begin{aligned}\hat{G}(x_1,q|x_1)&=\frac{F(0)-F(2x_1)}{\pi}\\&=\frac{\cos[\sqrt{-q}(2x_1-\pi)]-\cos[\sqrt{-q}(\pi)]}{2\sqrt{-q}\sin(\sqrt{-q}\pi)}.\end{aligned} \tag{A5}$$

Remark. The expansion of the zeros for V small and V large in Sec. III B 1 are obtained by a regular perturbation in term of the potential and the inverse of the potential.

APPENDIX B

We provide here the details of the computations used in Sec. III B 2. The Laplace transform of Eq. (27) with absorbing boundary conditions is given by

$$\hat{u}(x,q|y)=-\frac{2V}{\pi}\sum_{1}^{+\infty}\frac{\sin nx\sin ny}{q+n^2}\hat{u}(x_1,q|y)+\hat{G}(x,q|y), \tag{B1}$$

which gives for $x=x_1$

$$\hat{u}(x_1,q|y)=\frac{\hat{G}(x_1,q|y)}{1+\frac{2V}{\pi}\sum_{1}^{\infty}\frac{\sin nx_1\sin ny}{q+n^2}} \tag{B2}$$

and

$$\begin{aligned}&\frac{\partial}{\partial q}\ln\hat{p}(x_1,q|y)\\&\quad=\frac{\partial}{\partial q}\ln\hat{G}(x_1,q|y)-\frac{\partial}{\partial q}\ln\left(1+\frac{2V}{\pi}\sum_{1}^{+\infty}\frac{\sin nx_1\sin ny}{q+n^2}\right)\\&\quad=\alpha(x_1|y)+\beta(x_1|y)\end{aligned}$$

with

$$\alpha(x_1|y) = \left.\frac{\partial}{\partial q}\ln\hat{G}(x_1,q|y)\right|_{q=0} = -\frac{\sum_{n=1}^{\infty}\frac{\sin nx_1\sin ny}{n^4}}{\sum_{n=1}^{\infty}\frac{\sin nx_1\sin ny}{n^2}}$$

and

$$\beta(x_1|y) = -\left.\frac{\partial}{\partial q}\ln\left(1+\frac{2V}{\pi}\sum_{1}^{+\infty}\frac{\sin nx_1\sin ny}{q+n^2}\right)\right|_{q=0} = \frac{\frac{2V}{\pi}\sum_{n=1}^{\infty}\frac{\sin nx_1\sin ny}{n^4}}{1+\frac{2V}{\pi}\sum_{1}^{+\infty}\frac{\sin nx_1\sin ny}{n^2}}.$$

For $x_1, y \in]0,\pi[$, it is well known that

$$\frac{2}{\pi}\sum_{n=1}^{\infty}\frac{\sin nx_1\sin ny}{n^2} = \frac{(\pi-x_1)y}{\pi},$$

$$\frac{2}{\pi}\sum_{n=1}^{\infty}\frac{\sin nx_1\sin ny}{n^4} = \frac{x_1y}{6\pi}(x_1^2+y^2+2\pi^2) - \frac{(x_1^3+y^3)}{6},$$

hence

$$E[T|T<\tau,y] = -\alpha(x_1|y)+\beta(x_1|y) = \frac{x_1y(x_1^2+y^2+2\pi^2)-\pi(x_1^3+y^3)}{6(\pi-x_1)y} \times \frac{\pi}{\pi+V(\pi-x_1)y},$$

which is Eq. (36).

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