The survival probability of diffusion with killing

David Holcman,*† Avi Marchewka,‡ and Zeev Schuss§

October 22, 2018

Abstract

We present a general framework to study the effect of killing sources on moving particles, trafficking inside biological cells. We are merely concerned with 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 killing role. In particular, we study here the survival probability of ions in such environment and we present a general theory to compute the ratio of the number of absorbed particles at specific location to the number of killed particles during their sojourn inside a domain. In the case of a dendritic spine, the ratio is computed in terms of the survival probability of a stochastic trajectory in a one dimensional approximation. We show that the ratio depends on the distribution of killing sources. The biological conclusion follows: changing the position of the pumps is enough to regulate the calcium ions and thus the spine-dendrite communication.

*Department of Mathematics, Weizmann Institute of Science, Rehovot 76100, Israel. D. H. incumbent to the Madeleine Haas Russell Career Development Chair.
†Département de Mathématique et de Biologie, 46, rue d’Ulm 75005 Paris, France.
‡Physics Department, University of North Carolina, Raleigh, NC, USA.
§Department of Mathematics, Tel-Aviv University, Ramat-Aviv 69978, Israel.
1 Introduction

The post-synaptic part of a synapse is usually a dendritic spine, a microstructure located on a dendrite of a neuron (see figure 1). 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 pre-synaptic 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.

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.

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". A killing measure is the probability per unit time and unit length to terminate a trajectory at a given point at a given time. Thus 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 $\tau$.

We need to find the probability $\Pr\{\tau > T \mid y\}$ 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 $y$ in the neck. The ratio

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

is the fraction of absorbed to killed (pumped) particles. We also need to calculate $E[\tau \mid \tau > T, y]$, the mean time to be killed, given that the particle is killed, as well as $E[\tau \mid T > \tau, y]$, 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 the synaptic properties are modified. For example, the biophysical properties of the synapses or the number of channel receptors can be irreversibly changed [10, 8, 9]. 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 [16] 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 figure 1). The measure of this ability is the parameter $R_{\infty}$. When ions leave the spine head and enter the neck, they diffuse and either reach the dendrite (with probability $\Pr\{T > \tau \mid y\}$), or, as mentioned above, are extruded by pump proteins on their way to the dendrite [18, 11].

In a simplified homogenized model proposed in [16], 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 [16] made it possible to predict that changing the length of the spine neck (which occurs under specific conditions, see for example [12]) is sufficient to regulate precisely the number of ions arriving at the dendrite. Spine-dendrite calcium signaling ([13, 11]) 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 $E[t \mid y]$ an ion spends inside the neck can be written as

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

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

The rate $1/E[t \mid y]$ 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
Figure 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 neck length changes dynamically and this is induced by previous calcium ions.

reach the active sites of free enzymes by a Brownian random walk, either the molecules are hydrolyzed or nothing happens (see [15] 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 figure 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 [2]). 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 [1].

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.

2 Killing measure and the survival probability

We consider a Brownian motion (particle) in a cylinder, whose lateral boundary contains many small absorbing hole, one base is reflecting and the other absorbing. This model can be approximated [2] by a one-dimensional Brownian motion on an interval with one reflecting and one absorbing endpoints, 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 $x$ and time $t$ [1].

The survival probability and the pdf of the surviving trajectories can be derived from the Wiener measure [4]. Indeed, for a Brownian trajectory $X(t)$ and the random time at which it is terminated, $\tau$, we denote the (defective) probability density of finding a trajectory at point $x$, given that it starts at $y$, by

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

To derive the joint density of $x(\tau)$ and $\tau$, we can formulate the problem in terms of the Wiener integral with a killing measure. The Wiener density per
unit time of being killed in the time interval \([t, t + \Delta t]\) at a point \(x_N = x\) is

\[
Pr \{ x(\tau) = x, \tau = t \mid x(0) = y \} = \quad (2.1)
\]

\[
\lim_{N \to \infty} \frac{1}{\Delta t} k(x_N, t_N) \Delta t \left[ \left( \frac{1}{2\pi \Delta t} \right)^{N/2} \prod_{j=1}^{N} \exp \left\{ -\frac{(x_j - x_{j-1})^2}{2\Delta t} \right\} \left[ 1 - k(x_{j-1}, t_{j-1}) \Delta t \right] dx_{j-1} \right]
\]

\[
= k(x, t) u(x, t \mid y),
\]

where

\[
\Delta t = \frac{t}{N}, \quad t_j = j \Delta t,
\]

and \(u(x, t \mid y)\) is the solution of the initial value problem

\[
\begin{align*}
&u_t = u_{xx} - k(x, t) u, \text{ for } x \in \mathbb{R}, \ t > 0 \\
&u(x, 0) = \delta(x - y).
\end{align*}
\]

(2.2)

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

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

(2.3)

\[
u(x, 0 \mid y) = \delta(y - x).
\]

The solution is given by

\[
u(x, t \mid y) = \frac{1}{2\sqrt{\pi Dt}} \exp \left\{ -V_0 t - \frac{(x - y)^2}{4Dt} \right\}. \quad (2.4)
\]

The effect of absorption is expressed through many different features of the Wiener integral. First, the probability per unit time of being killed (absorbed) inside the interval \([a, b]\) at time \(t\) is

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

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

\[
Pr \{ x(\tau) \in [a, b], \tau < t \mid x(0) = y \} = \int_0^t \int_a^b k(x, t) u(x, t \mid y) \, dx \, dt.
\]
The probability of ever being killed in the interval is
\[ \Pr \{ x(\tau) \in [a, b] \mid x(0) = y \} = \int_0^\infty \int_a^b k(x, t) u(x, t \mid y) \, dx \, dt, \]
and the density of ever being killed at \( x \) is therefore
\[ \Pr \{ x(\tau) = x \mid x(0) = y \} = \int_0^\infty k(x, t) u(x, t \mid y) \, dt. \tag{2.5} \]
The survival probability is the probability that the trajectory still exists at time \( t \), that is,
\[ S(t) = \Pr\{\tau > t \mid x(0) = y\} = \int_{\mathbb{R}} u(x, t \mid y) \, dx. \]
For the case \( k(x, t) = V_0 \) eq.(2.4) gives
\[ \Pr\{\tau > t \mid x(0) = y\} = \int_{\mathbb{R}} u(x, t \mid y) \, dx = e^{-V_0 t}. \tag{2.6} \]
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.(2.5), is
\[ P(x \mid y) = V_0 \int_0^\infty \frac{1}{2\sqrt{\pi Dt}} \exp \left\{ -V_0 t - \frac{(x - y)^2}{4Dt} \right\} \, dt \tag{2.7} \]
\[ = \frac{1}{2} \sqrt{\frac{V_0}{D}} \exp \left\{ -\sqrt{\frac{V_0}{D}|x - y|} \right\}. \]
We assume henceforward that the killing measure is time independent.

### 3 Absorption versus killing

We consider now a particle diffusing in a domain \( \Omega \subset \mathbb{R}^n \) with a killing measure \( k(x) \) 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 \( \Omega \) 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 \( x \) where \( k(x) > 0 \), it is terminated with probability 1 the first time it hits \( \partial \Omega_a \). Thus the trajectory may traverse many times killing regions, where \( k(x) > 0 \), but it cannot emerge from the absorbing part of the boundary.
3.1 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 $\tau$, which is the first passage time to $\partial \Omega_a$. We calculate below the probability $\Pr\{T < \tau \mid y\}$, and the conditional distribution $\Pr\{\tau < t \mid \tau < T, y\}$.

We consider the trajectories of the stochastic differential equation

$$dx = a(x) \, dt + B(x) \, dw(t) \quad \text{for } x(t) \in \Omega,$$

(3.1)

where $a(x)$ is a smooth drift vector, $B(x)$ is a smooth diffusion matrix, and $w(t)$ is a vector of independent standard Brownian motions $[1]$. We assume that a killing measure $k(x) \geq 0$ is defined in $\Omega$ and $k(x) > 0$ on a set of positive measure.

The transition probability function of $x(t)$ satisfies the Fokker-Planck equation

$$\frac{\partial p(x,t \mid y)}{\partial t} = \mathcal{L} p(x,t \mid y) - k(x)p(x,t \mid y) \quad \text{for } x, y \in \Omega,$$

(3.2)

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

$$\mathcal{L} p(x,t \mid y) = \sum_{i,j=1}^{n} \frac{\partial^2 \sigma_{ij}(x)p(x,t \mid y)}{\partial x^i \partial x^j} - \sum_{i=1}^{n} \frac{\partial a^i(x)p(x,t \mid y)}{\partial x^i},$$

(3.3)

and

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

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

$$\mathcal{L} p(x,t \mid y) = -\nabla \cdot J(x,t \mid y),$$

(3.4)

where the components of the flux density vector $J(x,t \mid y)$ are defined as

$$J^i(x,t \mid y) = -\sum_{j=1}^{n} \frac{\partial^2 \sigma_{ij}(x)p(x,t \mid y)}{\partial x^i} + a^i(x)p(x,t \mid y).$$

(3.5)

The initial and boundary conditions for the Fokker-Planck equation (3.2) are

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

(3.6)

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

(3.7)

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

(3.8)
The transition pdf \( p(x, t \mid y) \) is actually the joint pdf
\[
p(x, t \mid y) \, dx = \Pr \{ x(t) \in x + dx, \, T > t, \, \tau > t \mid y \},
\]
that is, \( p(x, t \mid y) \) 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 \( x \).

We begin by showing that
\[
\Pr \{ T < \tau \mid y \} = \int_0^\infty \int_\Omega k(x) p(x, t \mid y) \, dx \, dt
\]
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 \( x \) can be represented by the limit as \( N \to \infty \) of
\[
\Pr \left\{ x_N(t_{j,N}) \in \Omega, \, x_N(t_{2,N}) \in \Omega, \ldots, x_N(t) = x, \, t \leq T \leq t + \Delta t \mid x(0) = y \right\} = \\
\left[ \int_\Omega \cdots \int_\Omega \frac{dy_j}{\sqrt{(2\pi\Delta t)^n \det \sigma(x)(t_{j-1,N})}} \right] \\
\times \exp \left\{ -\frac{1}{2\Delta t} \left[ y_j - x(t_{j-1,N}) - a(x(t_{j-1,N})) \Delta t \right]^T \sigma^{-1}(x(t_{j-1,N})) \right\} \\
\times \left[ y_j - x(t_{j-1,N}) - a(x(t_{j-1,N})) \Delta t \right] \left[ 1 - k(x(t_{j,N}) \Delta t) \right] \right] k(x) \Delta t,
\]
where
\[
\Delta t = \frac{t}{N}, \quad t_{j,N} = j \Delta t,
\]
and
\[
x(t_{0,N}) = y
\]
in the product. The limit is the Wiener integral defined by the stochastic differential equation (3.1), with the killing measure \( k(x) \) and the absorbing boundary condition [19]. In the limit \( N \to \infty \) the integral (3.11) converges to the solution of the Fokker-Planck equation (3.2) in \( \Omega \) with the initial and boundary conditions (3.6) and (3.7). Integrating over \( \Omega \) with respect to \( x \) and from 0 to \( \infty \) with respect to \( t \), we obtain, in view of (3.9), the representation (3.10).

A second derivation begins with the integration of the Fokker-Planck equation (3.2),
\[
1 = \int_0^\infty \int_{\partial \Omega} J(x, t \mid y) \cdot \nu(x) \, dS_x \, dt + \int_0^\infty \int_\Omega k(x) p(x, t \mid y) \, dx \, dt.
\]
We write

\[ J(t \mid y) = \oint_{\partial \Omega} \mathbf{J}(x, t \mid y) \cdot \mathbf{\nu}(x) \, dS_x \]  

(3.13)

and note that this is the absorption probability current on \( \partial \Omega \). Therefore, in view of the boundary conditions (3.7), (3.8), \( \int_0^\infty J(t \mid y) \, dt \) 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. (3.12) as

\[ \int_0^\infty J(t \mid y) \, dt = 1 - \int_0^\infty \int_\Omega k(x)p(x, t \mid y) \, dx \, dt \]

we obtain (3.14).

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 \( x \) over \( \Omega \) and with respect to \( t \) from 0 to \( t \). It is given by

\[
\Pr\{T < t \mid \tau > T, y\} = \frac{\Pr\{T < t, \tau > T \mid y\}}{\Pr\{\tau > T \mid y\}} = \frac{\int_0^t \int_\Omega k(x)p(x, s \mid y) \, dx \, ds}{\int_0^\infty \int_\Omega k(x)p(x, s \mid y) \, dx \, ds}.
\]  

(3.14)

Hence

\[
E[T \mid T < \tau, y] = \frac{\int_0^\infty \int_0^t \int_\Omega k(x)p(x, s \mid y) \, dx \, ds \, dt}{\int_0^\infty \int_\Omega k(x)p(x, s \mid y) \, dx \, ds}.
\]  

(3.15)

Equivalently,

\[
E[T \mid T < \tau, y] = \frac{\int_0^\infty \int_\Omega k(x)p(x, s \mid y) \, dx \, ds \, dt}{\int_0^\infty \int_\Omega k(x)p(x, s \mid y) \, dx \, ds},
\]  

(3.16)

which can be expressed in terms of the Laplace transform

\[
\hat{p}(x, q \mid y) = \int_0^\infty p(x, s \mid y)e^{-qs} \, ds
\]
as

\[
E[T \mid T < \tau, y] = -\frac{\int_{\Omega} k(x)\hat{p}(x, q \mid y) \, dx}{\int_{\Omega} k(x)\hat{p}(x, q \mid y) \, dx}
\]

\[
= -\frac{\partial}{\partial q} \left( \ln \left\{ \int_{\Omega} k(x)\hat{p}(x, q \mid y) \, dx \right\} \right) \bigg|_{q=0}.
\]

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

\[
\Pr \{ \tau < t \mid T > \tau, y \} = \frac{\int_{0}^{t} J(s \mid y) \, ds}{1 - \int_{0}^{\infty} \int_{\Omega} k(x)p(x, s \mid y) \, dx \, ds}.
\]

Thus the mean time to absorption in \( \partial \Omega_a \) of trajectories that are absorbed is given by

\[
E[\tau \mid T > \tau, y] = \int_{0}^{\infty} \Pr \{ \tau > t \mid T > \tau, y \} \, dt
\]

\[
= \frac{\int_{0}^{\infty} sJ(s \mid y) \, ds}{1 - \int_{0}^{\infty} \int_{\Omega} k(x)p(x, s \mid y) \, dx \, ds}.
\]

The survival probability is given by

\[
S(t \mid y) = \int_{\Omega} p(x, t \mid y) \, dx.
\]

### 3.2 An application: a “hot spot” killing in a finite interval

We provide here first an explicit estimation of the survival probability when the killing measure is a Dirac killing at a single point in a finite interval and second, we estimate the conditional mean first passage time to exit before being killed.

#### 3.2.1 Explicit decay of the survival probability

To compare the survival probability of Brownian motion with and without a Dirac killing at a point \( x_1 \) in the interval \([0, \pi]\) with absorbing boundaries, we
consider the solution of the boundary value problem

\[
\frac{\partial u(x, t \mid x_1)}{\partial t} = D \frac{\partial^2 u(x, t \mid x_1)}{\partial x^2} - V \delta(x - x_1) u(x, t \mid x_1) \text{ on } \mathbb{R} \quad (3.21)
\]

\[
u(x, 0 \mid x_1) = \delta(x - y).
\]

\[
u(0, t \mid x_1) = u(\pi, t \mid x_1) = 0,
\]

and we denote by \( G \) the Green function of the free particle problem, where \( V = 0 \), then

\[
G(x, t \mid y) = \frac{2}{\pi} \sum_{n=1}^{\infty} \sin nx \sin ny e^{-n^2 t}.
\]

Therefore the survival probability of Brownian motion in the interval is

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

Using the Laplace transform, the solution \( u(x, t \mid y) \) of (3.21) with \( V > 0 \) is given by

\[
\hat{u}_V(x, q \mid y) = \hat{G}(x, q \mid y) - \frac{V \hat{G}(x, q \mid x_1)}{1 + V \hat{G}(x_1, q \mid x_1)} \hat{G}(x_1, q \mid y), \quad (3.22)
\]

where

\[
\hat{G}(x, q \mid y) = \frac{2}{\pi} \sum_{n=1}^{\infty} \frac{\sin nx \sin ny}{q + n^2}. \quad (3.23)
\]

Note that

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

According to equation (3.20), the survival probability \( S_V(t \mid y) \) is given by

\[
S_V(t \mid y) = \int_0^\pi u_V(x, t \mid y) \, dx \quad (3.24)
\]

and the Laplace transform is

\[
\hat{S}_V(t \mid y) = \int_0^\pi \hat{u}_V(x, t \mid y) \, dx. \quad (3.25)
\]
Using (3.22), we find that the survival probabilities, without and with the Dirac killing, differ by
\[ \hat{S}_0(q \mid y) - \hat{S}_V(q \mid y) = \frac{V \hat{G}(x_1, q \mid y)}{1 + V \hat{G}(x_1, q \mid x_1)} \hat{S}_0(q \mid x_1). \] (3.26)

To compute \( \hat{S}_0(q \mid y) \), we use the formula
\[ S_u(q \mid z) = \sum_{n=1}^{\infty} \frac{\cos(nz)}{n^2 + q} = \begin{cases} \left( \frac{\cosh(\sqrt{q}z)}{\tanh(\sqrt{q}\pi)} - \frac{1}{\sqrt{q}\pi} \right) \frac{\pi}{2\sqrt{q}}, & \text{for } q \geq 0 \\ \left( -\frac{\cos(\sqrt{-q}z)}{\tan(\sqrt{-q}\pi)} + \frac{1}{\sqrt{-q}\pi} \right) \frac{\pi}{2\sqrt{-q}}, & \text{for } q < 0 \end{cases} \]
when \( x, y \in ]0, \pi[ \). Then,
\[ \hat{G}(x, q \mid y) = \frac{S_u(q \mid x - y) - S_u(q \mid x + y)}{\pi}. \]

Thus
\[ \hat{S}_0(q \mid y) = \int_0^{\pi} \frac{1}{2\sqrt{q}} \left( \frac{\cosh(\sqrt{q}(x - y))}{\tanh(\sqrt{q}\pi)} - \frac{\cosh(\sqrt{q}(x + y))}{\tanh(\sqrt{q}\pi)} \right) dx \]
\[ = \frac{1}{2q \tanh(\sqrt{q}\pi)} \left[ \sinh(\sqrt{q}(x - y)) - \sinh(\sqrt{q}(x + y)) \right]_0^{\pi}. \]

From a Taylor expansion around \( q = 0 \), we obtain that
\[ \hat{S}_0(q \mid y) = \frac{Q(y)}{6\pi} + O(\sqrt{q}), \quad (3.27) \]
where \( Q(y) = -3\pi^2y - \pi3y^2 + y^3 \), and similarly
\[ \hat{S}_0(q \mid x_1) = \frac{Q(x_1)}{6\pi} + O(\sqrt{q}). \] (3.28)

We conclude that in a bounded interval, the decay rate for the survival probability of a free particle is exponential with a rate constant \( \frac{6\pi}{Q(y)} \), which depends on the initial position of the particle and is given by
\[ S_0(t \mid y) \sim \exp \left\{ -\frac{6\pi t}{Q(y)} \right\} \quad \text{for } t \gg 1. \]

For a given \( V > 0 \), equation (3.26) contains the term \( \frac{V \hat{G}(x_1, q \mid y)}{1 + V \hat{G}(x_1, q \mid x_1)} \), which is 1 at \( q = 0 \), and at the first order approximation, when \( y \neq x_1 \),
\[ \hat{S}_V(q \mid y) = \hat{S}_0(q \mid y) - S_0(q \mid x_1) = \frac{Q(y)}{6\pi} - \frac{Q(x_1)}{6\pi} + O(\sqrt{q}). \] (3.29)
We conclude that the strength $V$ does not enter the first approximation of the survival probability, but the decay rate constant is bigger than in pure diffusion. More specifically, we obtain that

$$S_V(t | y) \sim \exp \left\{ -\frac{6\pi t}{Q(y) - Q(x_1)} \right\} \text{ for } t \gg 1. \quad (3.30)$$

The potential strength $V$ enters in the next term in the expansion of $S_V$.

### 3.2.2 Computation of the conditional MFPT $E[T | T < \tau, y]$

The conditional MFPT $E[T | T < \tau, y]$ is computed by using expression (3.17) as follows. Equation (3.17), corresponding to the killing measure $V \delta(x - x_1)$, gives

$$E[T | T < \tau, y] = -\frac{\partial}{\partial q} \ln \{\hat{p}(x_1, q | y)\} \bigg|_{q=0}. \quad (3.31)$$

The Laplace transform of equation (3.21) with absorbing boundary conditions is given by

$$\hat{u}(x, q | y) = -\frac{2V}{\pi} \int_1^{+\infty} \frac{\sin nx \sin ny}{q + n^2} \hat{u}(x_1, q | y) + \hat{G}(x, q | y), \quad (3.32)$$

which gives for $x = x_1$,

$$\hat{u}(x_1, q | y) = \frac{\hat{G}(x_1, q | y)}{1 + \frac{2V}{\pi} \sum_1^{+\infty} \frac{\sin nx_1 \sin ny}{q + n^2}}, \quad (3.33)$$

and

$$\frac{\partial}{\partial q} \ln \hat{p}(x_1, q | y) = \frac{\partial}{\partial q} \ln \hat{G}(x_1, q | y) - \frac{\partial}{\partial q} \ln \left( 1 + \frac{2V}{\pi} \sum_1^{+\infty} \frac{\sin nx_1 \sin ny}{q + n^2} \right)$$

$$= \alpha(x_1 | y) + \beta(x_1 | y)$$

with

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

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

\[ = \frac{2V \sum_{n=1}^{+\infty} \sin n x_1 \sin n y}{1 + 2V \sum_{n=1}^{+\infty} \frac{\sin n x_1 \sin n y}{n^2}}. \]

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

\[ \frac{2}{\pi} \sum_{n=1}^{\infty} \frac{\sin n x_1 \sin n y}{n^2} = \frac{(\pi - x_1)y}{\pi} \]

\[ \frac{2}{\pi} \sum_{n=1}^{\infty} \frac{\sin n x_1 \sin n y}{n^4} = \frac{x_1 y (x_1^2 + y^2 + 2\pi^2) - (x_1^3 + y^3)}{6\pi^4}. \]

so that finally, we obtain

\[ E[T \mid T < \tau, y] = -\alpha(x_1 \mid y, ) + \beta(x_1 \mid y) \]

\[ = \frac{x_1 y (x_1^2 + y^2 + 2\pi^2) - (x_1^3 + y^3)}{6(\pi - x_1) y} \frac{\pi}{\pi + V(\pi - x_1)y}. \]

### 3.3 Ratio measuring the distribution of particles

According to the Fokker-Planck equation (3.2), 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

\[ R(t) = \frac{\int_{\partial \Omega_\omega} J(x, t \mid y) \cdot \nu(x) \, dS_x}{\int_{\Omega} k(x) p(x, t \mid y) \, dx}. \]  

(3.34)

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

\[ R_\infty = \frac{\int_{0}^{\infty} \int_{\partial \Omega_\omega} J(x, t \mid y) \cdot \nu(x) \, dS_x \, dt}{\int_{\Omega} k(x) p(x, t \mid y) \, dx \, dt} = \frac{\int_{\partial \Omega_\omega} J(x \mid y) \cdot \nu(x) \, dS_x}{\int_{\Omega} k(x) G(x \mid y) \, dx}, \]  

(3.35)
where $G(x \mid y)$ is defined by the equation

$$- \rho(y) = \mathcal{L}G(x \mid y) - k(x)G(x \mid y) \quad \text{for } x, y \in \Omega$$

(3.36)

with the forward operator $\mathcal{L}$ defined in eq. (3.3), $\rho(y)$ is the initial density, and $J(x \mid y)$ is the flux density vector at point $x$, computed with respect to the function $G(x \mid y)$. When $\rho(y) = \delta(y)$, $G$ is the standard Green function with boundary conditions given by equation (3.7).

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(x \mid y) - k(x)p(x \mid y) \quad \text{for } x, y \in \Omega,$n

(3.37)

where the forward operator $\mathcal{L}$ is defined by (3.3) and the boundary conditions are

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

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

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

The time independent flux is $\Phi(x) \geq 0$. The external steady state flux of absorbed particles is

$$J_a = \int_{\partial\Omega_a} J(x \mid y) \cdot \nu(x) dS_x.$$n

(3.38)

The total inward flux is

$$J_i = \int_{\partial\Omega_i} J(x \mid y) \cdot \nu(x) dS_x = \int_{\partial\Omega_i} \Phi(x) dS_x.$$n

(3.39)

We define the ratio $R_s$ as

$$R_s = \frac{\int_{\partial\Omega_a} J(x \mid y) \cdot \nu(x) dS_x}{\int_{\partial\Omega_i} \Phi(x) dS_x - \int_{\Omega} k(x)p(x \mid y) dx} = \frac{\int_{\partial\Omega_i} \Phi(x) dS_x - \int_{\Omega} k(x)p(x \mid y) dx}{\int_{\Omega} k(x)p(x \mid y) dx}. (3.40)$$n

The second part of the identity is a consequence of conservation of matter.
3.4 The one-dimensional case

The fluxes $R_\infty$ and $R_s$ can be explicitly evaluated in dimension 1, when the domain is a finite interval. The ratio $R_s$ was computed in \[16\] in the case of an interval $[0,L]$, when the killing measure was uniformly distributed.

We assume now that the inward flux at $x = 0$ is a constant $\Phi$ and at $x = L$ 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. The particles are only driven by diffusion, so the steady state equation (3.37) becomes

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

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

$$p(0) = 0$$

and the ratio is

$$R_s = \frac{D \frac{\partial p}{\partial x}(0)}{kp(x_1)}. \quad (3.41)$$

From an explicit computation of $p(x)$, one can derive that

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

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

and

$$R_s = \frac{D}{k(L-x_1)}. \quad (3.42)$$

The result can be generalized to the case of a two hot spots in a straightforward manner. When killing occurs uniformly, the ratio $R_s$ decays as function of $L$ like the function $\frac{1}{\cosh(cL)}$, $(c = \text{const.})$ \[16\]. This decay, compared to the decay of equation (3.42), shows that any redistribution of the killing affects this ratio, which is discussed in the conclusion section.

In the same spirit, we give an explicit expression for $R_\infty$ in the case of a finite interval $[0, L]$, where particles are free to leave the domain at the points
0 and $L$. Initially, we assume that the particles are located at a point $x_1$. Here the killing occurs at the point $y < x_1$. In that case the Green function $G(x \mid y)$, defined by (3.36), is the solution of
\begin{equation}
-\delta(x_1) = D \frac{\partial^2}{\partial x^2} G(x \mid y) - k(x)G(x \mid y) \quad \text{for } x, y \in [0, L]
\end{equation}

\begin{align*}
G(0 \mid y) &= 0 \\
G(L \mid y) &= 0
\end{align*}

and by solving this equation, the ratio $R_\infty$ is given by
\begin{equation}
R_\infty = \frac{(L - x_1)k}{D \left( 1 + \frac{L - y}{y} - k \frac{y - x_1}{D} \right)}.
\end{equation}

4 Conclusions, applications, and perspective

We have provided in this paper a general mathematical framework to compute the distribution of “killed” and “absorbed” particles, after they flow into a bounded domain. The ratios $R_\infty$ or $R_s$ of “killed” to “absorbed” particles are in general difficult quantities to estimate analytically. However, in one dimension the exact dependency of the ratio on the geometry can be computed; we analyzed here two extreme distributions: a uniform distribution and a Dirac killing measure. Formulas (3.42) and $1/\cosh(cL)$, ($c = \text{const.}$) of [16] prove that the ratios depend on the killing distribution. For a general three-dimensional domain, $R_\infty$ 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 [14]).

In the general context of microstructures in biological systems, the ratio $R_\infty$ provides information about the total distribution of particles. When the killing measure is redistributed and a critical value of the ratio $R_\infty$ is attained, new biophysical processes can be initiated 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 to a specific compartment.

The spine-dendrite communication can be described in terms of quantities such as $R_\infty$ 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 $R_\infty$ is to increase the length of the neck, which really occurs in vitro experiments [12]. In that case, if the distribution of the killing measures is scaled with the dilation of the neck, the ratio $R_\infty$ 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 $R_\infty$, as shown in our computations (e.g., from uniform to accumulation at a hot spot). We can predict from expression (3.42), 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 LTP (Long Term Potentiation), which lead to long term changes at the synapse level [10]. No results seem to be known about the effect of LTP on the pump redistribution in spines. In reality, as studied in [13], 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 $E(\tau \mid \tau > T)$ to arrive at the dendrite was used in [16] 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 $E(\tau \mid \tau > T)$. The mean time $E(\tau \mid \tau > T)$ 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 $E(\tau \mid \tau > T)$ 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 [11]) 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.

References

[1] Z. Schuss, *Theory and Applications of Stochastic Differential Equations*, Wiley Series in Probability and Statistics. John Wiley Sons, Inc., New York, 1980.
[2] D. Holcman, A. Singer, Z. Schuss, “Diffusion in a cylinder with many small absorbers on the boundary” (preprint).

[3] G.C. Papanicolaou, S.R.S. Varadhan, “Diffusion in regions with many small holes”, Stochastic Differential Systems, pp.190–206, Lecture Notes in Control and Information Sci., 25, Springer, Berlin-New York, 1980.

[4] H.P. McKean, Jr. and K. Itô, Diffusion Processes and their Sample Paths, Springer Verlag Paperback, 1996

[5] Handbook of Mathematical Functions with Formulas, Graphs, and Mathematical Tables, M. Abramowitz and I.A. Stegun, eds. John Wiley & Sons, Inc., New York; National Bureau of Standards, Washington, DC, 1984.

[6] S. Karlin and M.A. Taylor, A Second Course in Stochastic Processes, Academic Press, Inc., New York-London, 1981.

[7] A. Papoulis, Probability, Random Variables and Stochastic Processes with Errata Sheet,

[8] D. Choquet, A. Triller, “The role of receptor diffusion in the organization of the postsynaptic membrane”, Nat. Rev. — Neurosci. 4 (4), pp.251-65 Review (2003).

[9] A.J. Borgdorff, D. Choquet, “Regulation of AMPA receptor lateral movements”, Nature 417 (6889), pp.649-53 (2002).

[10] R.C. Malenka, R. Nicoll, “Long-Term Potential-A Decade of progress?” Nature 285, pp.1870-1873 (1999).

[11] B.L. Sabatini, M. Maravall, and K. Svoboda, “Ca^{2+} signalling in dendritic spines”, Curr. Opin. Neurobiol. 11 (3). pp.349-356 (2001).

[12] Korkotian E, Segal M. “Spike-associated fast contraction of dendritic spines in cultured hippocampal neurons”, Neuron. 2001 Jun;30(3):751-8.

[13] D. Holcman, Z. Schuss, E. Korkotian, “Calcium dynamics in dendritic spines and spine motility”, Biophys J. 2004 Jul;87(1):81-91.

[14] D. Holcman, Z. Schuss, “Escape through a small opening: receptor trafficking in a synaptic membrane”, J. of Statistical Physics 117 (5/6) Dec. (2004)p 191-230.

[15] D. Holcman, Z. Schuss, “Stochastic Chemical Reactions in Micro-domains”, Journal of Chemical Physics, 122, 1-2005.
[16] E. Korkotian, D. Holcman, M. Segal, “Dynamic Regulation of Spine-Dendrite Coupling in Cultured Hippocampal Neurons”, *Euro. J. of Neuroscience*, Nov; 20(10):2649-63. 2004.

[17] B. Hille, *Ionic Channels of Excitable Membranes*, Third Edition, Sinauer Inc, Massachusetts, 2001.

[18] T. Naeh, M.M. Klosek, B. J. Matkowsky, and Z. Schuss, “A direct approach to the exit problem”, *SIAM J. Appl. Math.* **50**, 595 (1990).

[19] H. Kleinert, *Path Integrals in Quantum Mechanics, Statistics, and Polymer Physics*, World Scientific, NY 1994.