On the narrow escape problem

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March 5, 2013

Contents

1 Introduction

The narrow escape problem, which goes back to Rayleigh [1945], deals with the escape time (ET) of a Brownian particle from a bounded domain with reflecting boundaries except for a small absorbing part, a narrow escape window. It is a ubiquitous topic in physics, biophysics, physical chemistry and physiology, where the absorbing boundary can represent a target protein channel for ions on a cellular membrane [Holcman and Schuss, 2004], a neurotransmitter receptor in a neuronal synapse [Schuss et al., 2007] or a target enzyme for substrate molecules in a microdomain [Holcman and Schuss, 2005], just to name a few. The problem of calculating the mean escape time (MET), or mean first passage time (MFPT), of a particle through a target site, can be transformed into a Poisson equation in the domain with mixed Neumann-Dirichlet boundary conditions [Schuss, 1980]. As such, it relates to the spectrum of the Laplacian, its Dirichlet and Neumann Green's functions, electrostatic capacities of surfaces and multipole expansions of potentials, all known topics in classical electrostatics and hydrodynamics [Ward and Keller, 1993; Jackson, 1998; Singer et al., 2006].

This article is meant to (1), give a conceptual and mathematical introduction to the narrow escape problem, (2), present, derive and elaborate on some of the frequently used principles and tools and (3), illustrate the application of the theory to some physical problems.

1.1 Article contents

In section 1 I derive a hierarchy of boundary value problems for the moments of the distribution of escape times, the first term of which is often used to explicitly calculate the mean escape time from bounded domains. As a demonstrative example, I then use this hierarchy to find leading order approximations, for all moments of the capture time by traps within an arbitrary three-dimensional domain with reflecting boundary. Finally, I briefly show how the narrow escape problem relates to the spectral properties of the Laplacian.

In section 2 I introduce multipole expansions for the far-field approximation of potentials generated by compactly supported sources. The leading order expansion term, the so called *monopole moment*, is then used to define the famous *electrostatic capacity* of an arbitrary domain. The latter is an intrinsic geometric property related to the Green's functions of the Laplace operator, that mediates the effects of window shape on escape times.

In section 3 I comment on work performed by Cheviakov et al. [2010], who provide a three-term expansion for the mean escape time from the unit ball, through several small windows on its boundary. I introduce the so called *surface Neumann Green's function* and provide an alternative derivation for it for the three-dimensional unit ball, to the one given by the original authors. I then look at the famous electrified disk problem of electrostatics, which appears in the derivation of the leading order boundary layer expansion term for the MET. Finally, I show how the total electrostatic capacity of a cluster of escape windows can be estimated, a task one is faced with when windows are at very small distances to one another.

In section 4 I demonstrate how the narrow escape theory can be applied to certain statistical mechanical and biophysical problems. Specifically, I relate the narrow escape problem to (1), the thermodynamic equilibration of two connected chambers, (2), enzymatic reaction rates in microdomains and (3), ion-diffusion rates in dendritic spines.

1.2 Problem statement

Consider a bounded domain $\Omega \subseteq \mathbb{R}^n$ with boundary $\partial\Omega = \partial\Omega_r \cup \partial\Omega_a$, where $\partial\Omega_a$ shall have non-zero surface area. $\partial\Omega_r$ will be the reflecting part of the domain's boundary, impermeable to Brownian particles that are reflected upon hitting it. $\partial\Omega_a$ represents one or more target sites at which particles are absorbed or equivalently, *windows* through which diffusing particles can exit the domain Ω. It might correspond to internal *holes* in Ω or *apertures* on its outer wall. Consider particle trajectories satisfying in Ω the Langevin equation of motion

$$d\mathbf{X}(t) = \mathbf{v}(\underline{\mathbf{X}}(t)) + \sqrt{2D}d\mathbf{W}(t), \tag{1.1}$$

with smooth drift $\mathbf{v}$, constant diffusion coefficient $D > 0$ and start position $\mathbf{X}(0) = \underline{\mathbf{x}}_o \in \Omega$. $\mathbf{W}(t)$ is the n-dimensional Wiener process. Figure 1.1 illustrates this context. The behavior of $\underline{\mathbf{X}}(t)$ near the boundary $\partial\Omega$ will be described in detail in section 1.3 below. The narrow escape problem deals with the distribution of the random escape time $T(\mathbf{x}_o)$ through $\partial\Omega_a$, of a particle starting at $\mathbf{x}_o \in \Omega$, in the case

where $\partial\Omega_a$ becomes very small. Naturally, great interest is devoted to the asymptotic behavior of the mean escape time (MET), $\mathbb{E}T(\mathbf{x}_o)$. The scaling parameter $\varepsilon \ll 1$ is usually taken to be the *radius* of the absorbing windows.

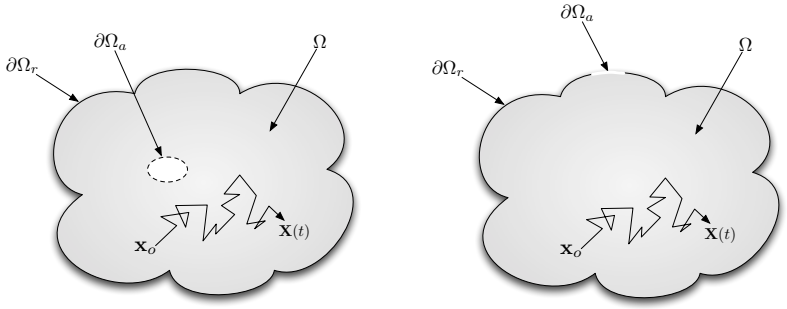

Figure 1.1: On the mean escape time (MET) of a diffusing particle in a domain Ω. The particle, subject to Brownian motion and drift as given in (1.1), may only escape from a window $\partial\Omega_a$.

Let $p(t_o, \mathbf{x}_o, t, \mathbf{x})$ be the transition probability density (more correctly, measure) for the process (1.1) from $\mathbf{x}_o \in \Omega$ at time t_o to $\mathbf{x} \in \mathrm{cl}(\Omega)$ at time $t \geq t_o$, where $\mathrm{cl}(\Omega)$ denotes the topological closure of Ω. Since (1.1) is time homogeneous, the transition probability of the process is stationary, i.e., $p(t_o, \mathbf{x}_o, t, \mathbf{x}) = r(t - t_o, \mathbf{x}_o, \mathbf{x})$ for some function r. At any moment $t \geq 0$,

$$q(t, \mathbf{x}_o) := 1 - \int_\Omega r(t, \mathbf{x}_o, \mathbf{x})\ d\mathbf{x} \tag{1.2}$$

is the probability of the particle having escaped the domain by time t, given that it started at $\mathbf{x}_o \in \Omega$. From basic probability theory, one knows that the MET is given by

$$\mathbb{E}T(\mathbf{x}_o) = u(\mathbf{x}_o) := \int_0^\infty (1 - q(t, \mathbf{x}_o))\ dt \tag{1.3}$$

whenever it exists, that is

$$u(\mathbf{x}_o) = \int_0^\infty \int_\Omega r(t, \mathbf{x}_o, \mathbf{x})\ d\mathbf{x}\ dt. \tag{1.4}$$

Note that, assuming $u(\mathbf{x}_o) < \infty$, the two integrals in (1.4) are interchangeable. The existence of the MET presumes that the mass of the distribution $r(t, \mathbf{x}_o, \cdot)$ in Ω tends to 0 quickly enough as $t \to \infty$. This is, for $\partial\Omega_a$ having non-zero surface measure and a divergence-free vector field $\mathbf{v}$, a reasonable assumption I shall make [Schuss, 1980]. The average MET from Ω (i.e., assuming a uniform probability distribution of the start position) is then given by

$$\overline{u} := \frac{1}{|\Omega|} \int_\Omega u(\mathbf{x}_o)\ d\mathbf{x}_o, \tag{1.5}$$

where $|\Omega|$ is the volume of Ω.

1.3 A boundary value problem for the MET

As it turns out, $u(\mathbf{x}_o)$ satisfies a Poisson equation with respect to the start position $\mathbf{x}_o \in \Omega$, with mixed Dirichlet-Neumann boundary conditions [Schuss, 1980; Singer and Schuss, 2006; Schuss et al., 2007]. The derivation outlined below, includes a detailed definition of the process $\mathbf{X}(t)$ near the boundary $\partial\Omega$ and is inspired by Schuss [1980, §5.3 and §5.4]. Once on the absorbing boundary $\partial\Omega_a$, the particle is assumed to halt, so that

$$p(t_o, \mathbf{x}_o, t, \mathbf{x}) = \delta(\mathbf{x} - \mathbf{x}_o), \quad t \geq t_o,\ \mathbf{x}_o \in \partial\Omega_a,\ \mathbf{x} \in \mathrm{cl}(\Omega). \tag{1.6}$$

The behavior of the Markov process $\mathbf{X}$, after reaching the reflecting boundary at $\mathbf{y} \in \partial\Omega_r$ is defined as follows: Introduce the local coordinates $\boldsymbol{\zeta} = \mathbf{f}(\mathbf{x})$ in a neighborhood $\mathcal{U}$ of $\mathbf{y}$ (with $\mathbf{f}$ a diffeomorphism),

such that $\partial\Omega_r \cap \mathcal{U}$ corresponds to the hyperplane $\{\zeta_1 = 0\}$ and $\mathcal{U} \cap \Omega$ corresponds to $\zeta_1 > 0$. Extend the vector field $\mathbf{v}$ to $\mathcal{U} \cap (\mathbb{R}^n \setminus \Omega)$ by reflection in the hyperplane $\{\zeta_1 = 0\}$. Let $\widetilde{\mathbf{X}}$ be the extension of the process $\mathbf{X}$ to $\mathcal{U} \cap \mathbb{R}^n$, satisfying (1.1). Now extend $\mathbf{X}$ as the reflection of $\widetilde{\mathbf{X}}$ in the hyperplane $\{\zeta_1 = 0\}$ back into $\mathcal{U} \cap \Omega$. Since the reflection is instantaneous and both $\mathbf{X}, \widetilde{\mathbf{X}}$ are Markovian with almost surely continuous paths, this local definition of the reflection is independent of the exact choice of $\mathbf{f}$ and indeed adequate to define the process $\mathbf{X}$. See figure 1.2 for a supportive illustration.

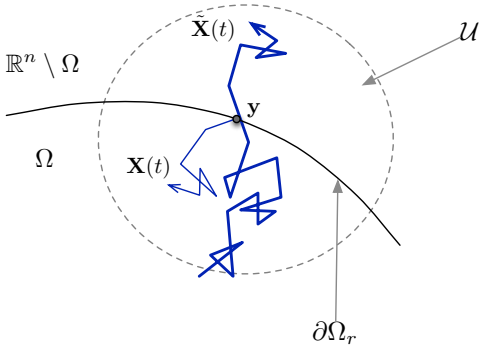

Figure 1.2: On the definition of the reflected Brownian process within Ω.

Let $\widetilde{p}(t_o, \mathbf{x}_o, t, \mathbf{x})$ be the transition density of the non-reflected process $\widetilde{\mathbf{X}}$. Because of reflection, for $\mathbf{x}_o, \mathbf{x} \in \mathcal{U} \cap \Omega$ one has

$$p(t_o, \mathbf{x}_o, t, \mathbf{x}) = \widetilde{p}(t_o, \mathbf{x}_o, t, \mathbf{x}) + \widetilde{p}(t_o, \mathbf{x}_o, t, \overline{\mathbf{x}}), \tag{1.7}$$

where $\overline{\mathbf{x}} \in \mathbb{R}^n \setminus \Omega$ is the reflection of $\mathbf{x}$ in $\partial\Omega_r$. By symmetry about $\partial\Omega_r$, one knows that $\widetilde{p}(t_o, \mathbf{x}_o, t, \overline{\mathbf{x}}) = \widetilde{p}(t_o, \overline{\mathbf{x}}_o, t, \mathbf{x})$, where $\overline{\mathbf{x}}_o \in \mathbb{R}^n \setminus \Omega$ is the reflection of $\mathbf{x}_o$ in $\partial\Omega_r$. In local coordinates thus

$$p(t_o, \zeta_1, \zeta_2, \dots) = \widetilde{p}(t_o, \zeta_1, \zeta_2, \dots) + \widetilde{p}(t_o, -\zeta_1, \zeta_2, \dots), \tag{1.8}$$

so that

$$\frac{\partial}{\partial \zeta_1} p(t_o, \zeta_1, \zeta_2, \dots)\big|_{\zeta_1 = 0} = 0. \tag{1.9}$$

Consequently, p satisfies the boundary condition

$$\partial_{\mathbf{n}_{\mathbf{x}_o}} p(t_o, \mathbf{x}_o, t, \mathbf{x})\big|_{\mathbf{x}_o \in \partial\Omega_r} = 0. \tag{1.10}$$

The transition density $p(t_o, \mathbf{x}_o, t, \mathbf{x})$ satisfies the *Kolmogorov backward equation*

$$\partial_{t_o} p(t_o, \mathbf{x}_o, t, \mathbf{x}) = -D\Delta_{\mathbf{x}_o} p(t_o, \mathbf{x}_o, t, \mathbf{x}) - \mathbf{v}(\mathbf{x}_o)\nabla_{\mathbf{x}_o} p(t_o, \mathbf{x}_o, t, \mathbf{x}). \tag{1.11}$$

By time homogeneity, $p(t_o, \mathbf{x}_o, t, \mathbf{x}) = r(t - t_o, \mathbf{x}_o, \mathbf{x})$, so that (1.11) translates to

$$\partial_t r(t, \mathbf{x}_o, \mathbf{x}) = D\Delta_{\mathbf{x}_o} r(t, \mathbf{x}_o, \mathbf{x}) + \mathbf{v}(\mathbf{x}_o)\nabla_{\mathbf{x}_o} r(t, \mathbf{x}_o, \mathbf{x}). \tag{1.12}$$

Using (1.12) in (1.4), yields

$$\begin{aligned}
D\Delta_{\mathbf{x}_o} u(\mathbf{x}_o) &= \int_0^\infty \int_\Omega D\Delta_{\mathbf{x}_o} r(t, \mathbf{x}_o, \mathbf{x})\ d\mathbf{x}\ dt \\
&= \int_0^\infty \int_\Omega \left[\partial_t r(t, \mathbf{x}_o, \mathbf{x}) - \mathbf{v}(\mathbf{x}_o)\nabla_{\mathbf{x}_o} r(t, \mathbf{x}_o, \mathbf{x})\right]\ d\mathbf{x}\ dt \\
&= \int_\Omega \left[r(\infty, \mathbf{x}_o, \mathbf{x}) - r(0, \mathbf{x}_o, \mathbf{x})\right]\ d\mathbf{x} - \int_0^\infty \int_\Omega \mathbf{v}(\mathbf{x}_o)\nabla_{\mathbf{x}_o} r(t, \mathbf{x}_o, \mathbf{x})\ d\mathbf{x}\ dt \\
&= -\int_\Omega \delta(\mathbf{x} - \mathbf{x}_o)\ d\mathbf{x} - \mathbf{v}(\mathbf{x}_o)\nabla_{\mathbf{x}_o} \int_0^\infty \int_\Omega r(t, \mathbf{x}_o, \mathbf{x})\ d\mathbf{x}\ dt \\
&= -1 - \mathbf{v}(\mathbf{x}_o)\nabla_{\mathbf{x}_o} u(\mathbf{x}_o).
\end{aligned} \tag{1.13}$$

Note that use has been made of the fact that $r(\infty, \mathbf{x}_o, \mathbf{x}) = 0$ and $r(0, \mathbf{x}_o, \mathbf{x}) = \delta(\mathbf{x} - \mathbf{x}_o)$. Furthermore, using the boundary conditions (1.6) and (1.10) in (1.4) gives the corresponding boundary conditions for $u(\mathbf{x}_o)$. I summarize

$$\begin{aligned} &D\Delta_{\mathbf{x}_o} u(\mathbf{x}_o) + \mathbf{v}(\mathbf{x}_o)\nabla_{\mathbf{x}_o} u(\mathbf{x}_o) = -1, \\ &\partial_{\mathbf{n}} u\big|_{\partial\Omega_r} = 0, \\ &u\big|_{\partial\Omega_a} = 0. \end{aligned} \tag{1.14}$$

Solving (1.14) gives the MET $u(\mathbf{x}_o)$ for any particle starting at $\mathbf{x}_o \in \Omega$.

1.4 Boundary value problems for higher ET moments

In a similar way as for the MET, $\mathbb{E}T(\mathbf{x}_o)$, boundary value problems can be derived for all higher raw moments of $T(\mathbf{x}_o)$. Its central moments can then easily be expressed in terms of its raw moments. From basic probability theory one knows that

$$\begin{aligned} \mathbb{E}(T^m(\mathbf{x}_o)) = u_m(\mathbf{x}_o) &:= \int_0^\infty \mathcal{P}(T^m(\mathbf{x}_o) > t)\ dt \\ &= \int_0^\infty \left[1 - q(\sqrt[m]{t}, \mathbf{x}_o)\right]\ dt \\ &= m \int_\Omega \int_0^\infty t^{m-1} r(t, \mathbf{x}_o, \mathbf{x})\ dt\ d\mathbf{x} \end{aligned} \tag{1.15}$$

for $m \in \mathbb{N}$, whenever $\mathbb{E}(T^m(\mathbf{x}_o))$ exists. Applying the Kolmogorov backward equation (1.12) to (1.15) for $m \geq 2$ yields

$$\begin{aligned} D\Delta_{\mathbf{x}_o} u_m(\mathbf{x}_o) =& m \int_\Omega \int_0^\infty t^{m-1} D\Delta_{\mathbf{x}_o} r(t, \mathbf{x}_o, \mathbf{x})\ dt\ d\mathbf{x} \\ =& m \int_\Omega \int_0^\infty t^{m-1} \left[\partial_t r(t, \mathbf{x}_o, \mathbf{x}) - \mathbf{v}(\mathbf{x}_o)\nabla_{\mathbf{x}_o} r(t, \mathbf{x}_o, \mathbf{x})\right]\ dt\ d\mathbf{x} \\ =& -m(m-1) \int_\Omega \int_0^\infty t^{m-2} r(t, \mathbf{x}_o, \mathbf{x})\ dt\ d\mathbf{x} - \mathbf{v}(\mathbf{x}_o)\nabla_{\mathbf{x}_o} u_m(\mathbf{x}_o) \\ =& -m u_{m-1}(\mathbf{x}_o) - \mathbf{v}(\mathbf{x}_o)\nabla_{\mathbf{x}_o} u_m(\mathbf{x}_o). \end{aligned} \tag{1.16}$$

Using the boundary conditions (1.6) and (1.10) in (1.15), gives the corresponding boundary conditions for $u_m(\mathbf{x}_o)$. One thus obtains the infinite hierarchy of boundary value problems

$$\begin{aligned} &D\Delta_{\mathbf{x}_o} u_m(\mathbf{x}_o) + \mathbf{v}(\mathbf{x}_o)\nabla_{\mathbf{x}_o} u_m(\mathbf{x}_o) = -m u_{m-1}(\mathbf{x}_o), \quad m \in \mathbb{N}, \\ &\partial_{\mathbf{n}} u_m\big|_{\partial\Omega_r} = 0, \quad u_m\big|_{\partial\Omega_a} = 0 \end{aligned} \tag{1.17}$$

for all raw moments $u_m(\mathbf{x}_o)$ of $T(\mathbf{x}_o)$, where I set $u_0 := 1$. In principle, (1.17) allows for the calculation of all moments $u_1(\mathbf{x}_o), u_2(\mathbf{x}_o), \ldots$ in a sequential manner. Notice that (1.14) is just the first term ($m = 1$) in the hierarchy (1.17).

1.5 Example: Reflecting domain with interior traps (3D)

I demonstrate the application of the hierarchy (1.17) to the narrow escape problem for a three-dimensional domain $\widetilde{\Omega} \subseteq \mathbb{R}^3$ with reflecting boundary and N interior, small, disjoint traps $\Omega_1, .., \Omega_N \subseteq \widetilde{\Omega}$. In the notation introduced in section 1.2, $\Omega := \widetilde{\Omega} \setminus \bigcup_{i=1}^N \mathrm{cl}(\Omega_i)$, $\partial\Omega_r = \partial\widetilde{\Omega}$ and $\partial\Omega_a = \bigcup_{i=1}^N \partial\Omega_i$. I consider the limit where the traps converge to single points, i.e., $\Omega_j = \mathbf{x}_j + \varepsilon\Omega_{oj}$ with $\varepsilon \to 0^+$, for fixed $\mathbf{x}_j \in \widetilde{\Omega}$ and certain open sets $\Omega_{oj} \subseteq \mathbb{R}^3$ that include the origin. I consider the escape time $T(\mathbf{x}_o)$ through (or *first capture time* by) any of the traps, of a Brownian particle with no drift, starting at $\mathbf{x}_o \in \Omega$. See figure 1.3 for a supporting illustration.

Using the method of matched asymptotic expansions to solve (1.14), Cheviakov and Ward [2011, §3.1] have shown the MET to behave as

$$u(\mathbf{x}_o) \sim \frac{|\widetilde{\Omega}|}{4\pi N \overline{C} D\varepsilon} \left[1 - 4\pi\varepsilon \sum_{j=1}^N C_j G(\mathbf{x}_o, \mathbf{x}_j) + \frac{4\pi\varepsilon}{N\overline{C}} \cdot p_c(\mathbf{x}_1, .., \mathbf{x}_N)\right] + \mathcal{O}(\varepsilon), \tag{1.18}$$

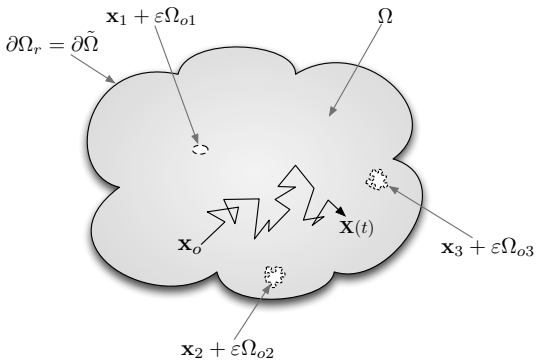

Figure 1.3: On the narrow escape problem in a three-dimensional domain with interior traps.

at least when starting in the outer region $|\mathbf{x}_o - \mathbf{x}_j| \gg \mathcal{O}(\varepsilon)\ \forall j$. Here, C_j are the electrostatic capacities of the scale invariant Ω_{oj} (see section 2.2), $\overline{C} := (C_1 + \cdots + C_N)/N$, $G(\mathbf{x}, \mathbf{y})$ is the Neumann Green's function for the trap-free domain $\widetilde{\Omega}$ and $p_c(\mathbf{x}_1, .., \mathbf{x}_N)$ is a function of the trap centers $\mathbf{x}_j$ [Cheviakov and Ward, 2011, eqs. (2.23b) & (2.26a)]. Inserting (1.18) into (1.17) yields the boundary value problem

$$\begin{aligned} &D\Delta_{\mathbf{x}_o} u_2(\mathbf{x}_o) = -\frac{2\varkappa}{\varepsilon} + \mathcal{O}(1), \\ &\partial_{\mathbf{n}} u_2\big|_{\partial\Omega_r} = 0, \quad u_2\big|_{\partial\Omega_a} = 0 \end{aligned} \tag{1.19}$$

for the second moment $u_2(\mathbf{x}_o) := \mathbb{E}T^2(\mathbf{x}_o)$, where I abbreviate $\varkappa := \frac{|\widetilde{\Omega}|}{4\pi N\overline{C}D}$. Rescaling $u_2 =: \widetilde{u}_2/\varepsilon$ translates (1.19) into

$$\begin{aligned} &\frac{D}{2\varkappa}\Delta_{\mathbf{x}_o}\widetilde{u}_2(\mathbf{x}_o) = -1 + \mathcal{O}(\varepsilon), \\ &\partial_{\mathbf{n}}\widetilde{u}_2\big|_{\partial\Omega_r} = 0, \quad \widetilde{u}_2\big|_{\partial\Omega_a} = 0. \end{aligned} \tag{1.20}$$

Notice that (1.20) has the same structure as (1.14), modulo an additional source term of order $\mathcal{O}(\varepsilon)$ and a modified diffusion coefficient. One can therefore adopt the asymptotic methods used by Cheviakov and Ward [2011] and approximate $\widetilde{u}_2(\mathbf{x}_o)$ in the outer region, at least up to an error of order $\mathcal{O}(\varepsilon)$. Specifically, one finds

$$\widetilde{u}_2(\mathbf{x}_o) \sim \frac{2\varkappa|\widetilde{\Omega}|}{4\pi N\overline{C}D\varepsilon}\left[1 - 4\pi\varepsilon\sum_{j=1}^{N} C_j G(\mathbf{x}_o, \mathbf{x}_j) + \frac{4\pi\varepsilon}{N\overline{C}}\cdot p_c(\mathbf{x}_1, .., \mathbf{x}_N)\right] + \mathcal{O}(\varepsilon), \tag{1.21}$$

so that

$$u_2(\mathbf{x}_o) \sim \frac{2\varkappa^2}{\varepsilon^2}\left[1 - 4\pi\varepsilon\sum_{j=1}^{N} C_j G(\mathbf{x}_o, \mathbf{x}_j) + \frac{4\pi\varepsilon}{N\overline{C}}\cdot p_c(\mathbf{x}_1, .., \mathbf{x}_N)\right]. \tag{1.22}$$

The same methodology can be applied at every iteration in the hierarchy (1.17) to obtain all raw moments

$$\mathbb{E}T^m(\mathbf{x}_o) = u_m(\mathbf{x}_o) \sim \frac{m!\varkappa^m}{\varepsilon^m} + \mathcal{O}(\varepsilon^{1-m}), \quad m \in \mathbb{N}. \tag{1.23}$$

The central moments are thus, to leading order, given by

$$\begin{aligned} \mathbb{E}(T(\mathbf{x}_o) - u(\mathbf{x}_o))^m &\sim \sum_{k=0}^{m}\binom{m}{k}\left(\mathbb{E}T^k(\mathbf{x}_o)\right)\cdot\left(-u(\mathbf{x}_o)\right)^{m-k} \\ &\sim \frac{\varkappa^m}{\varepsilon^m}\sum_{k=0}^{m}\binom{m}{k}(-1)^{m-k}k! \\ &\sim \frac{\varkappa^m}{\varepsilon^m}\cdot(!m), \end{aligned} \tag{1.24}$$

where $!m$ denotes the subfactorial, or derangement, of m [Graham et al., 1994, p. 195]. Notice that by (1.23), $\mathbb{E}T^m(\mathbf{x}_o) \sim m!\cdot(\mathbb{E}T(\mathbf{x}_o))^m$ as $\varepsilon \to 0^+$, as is the case for an exponential distribution. This suggests that the escape times $T(\mathbf{x}_o)$ are approximately exponentially distributed, at least when starting in the outer region. This prediction is further elaborated on in section 1.7.

1.6 Spectral analysis of escape times

I shall from now on consider Brownian particles without drift, i.e., with equation of motion (1.1) where $\mathbf{v} \equiv 0$, in a domain as described in section 1.2. Let $\rho(0, \mathbf{x})$ be the probability density of their initial position in the domain Ω. Consider the symmetric differential operator $D\Delta$, acting on smooth scalar fields f in Ω with boundary conditions

$$f\big|_{\partial\Omega_a} = 0, \quad \partial_{\mathbf{n}} f\big|_{\partial\Omega_r} = 0. \tag{1.25}$$

Then the (non-normalized) probability density $\rho(t, \mathbf{x})$ of the particle position at time t and point $\mathbf{x} \in \Omega$, satisfies the Fokker-Planck equation [Frank, 2005] $\partial_t \rho = D\Delta\rho$ and the boundary conditions (1.25). Now suppose the Laplacian Δ has on Ω the complete orthonormal system of eigenfunctions $\Phi_1(\mathbf{x}), \Phi_2(\mathbf{x}), \ldots$ with corresponding eigenvalues $0 > \lambda_1 \geq \lambda_2 \geq \ldots$, that is $\Delta\Phi_n = \lambda_n \Phi_n$ and $\int_\Omega \Phi_n \Phi_m = \delta_{nm}$ for all $n, m \in \mathbb{N}$. Note that by the assumptions made in 1.2 and the symmetry of Δ, all eigenvalues of Δ are indeed real and strictly negative. Then $\rho(t, \mathbf{x})$ can formally be written as

$$\rho(t, \mathbf{x}) = \sum_{n=1}^{\infty} \alpha_n \Phi_n(\mathbf{x}) \cdot e^{D\lambda_n t}, \tag{1.26}$$

with the Fourier coefficients $\alpha_n \in \mathbb{C}$ given by

$$\alpha_n = \int_\Omega \rho(0, \mathbf{x}) \Phi_n(\mathbf{x}) \, d\mathbf{x} = \langle \rho(0, \cdot), \Phi_n \rangle \,. \tag{1.27}$$

Then similar to (1.2),

$$q(t) := 1 - \int_\Omega \rho(t, \mathbf{x}) \, d\mathbf{x} = 1 - \sum_{n=1}^{\infty} \langle \rho(0, \cdot), \Phi_n \rangle \cdot \langle 1, \Phi_n \rangle \cdot e^{D\lambda_n t} \tag{1.28}$$

gives the cumulative probability of the particle having escaped the domain by time $t \geq 0$. Hence, similar to (1.3), the sum

$$\sum_{n=1}^{\infty} \frac{1}{-D\lambda_n} \cdot \langle \rho(0, \cdot), \Phi_n \rangle \cdot \langle 1, \Phi_n \rangle \tag{1.29}$$

gives the mean escape time from Ω, for the initial distribution $\rho(0, \mathbf{x})$. In particular, for $\rho(0, \mathbf{x}) = \delta(\mathbf{x} - \mathbf{x}_o)$ one obtains

$$u(\mathbf{x}_o) = \sum_{n=1}^{\infty} \frac{1}{-D\lambda_n} \cdot \Phi_n(\mathbf{x}_o) \cdot \langle 1, \Phi_n \rangle \,. \tag{1.30}$$

Similarly, the average MET from Ω is obtained for an initial uniform distribution $\rho(0, \mathbf{x}) = |\Omega|^{-1}$, that is

$$\overline{u} = \frac{1}{D\,|\Omega|} \cdot \sum_{n=1}^{\infty} \frac{\langle 1, \Phi_n \rangle^2}{-\lambda_n}. \tag{1.31}$$

It should be kept in mind that the eigenvalues λ_n as well as eigenfunctions Φ_n strongly depend on the geometry of Ω and $\partial\Omega_a$.

1.7 Poissonian escape through small apertures

In the case where the aperture $\partial\Omega_a$ becomes vanishingly small, i.e., $|\partial\Omega_a| \to 0$, the eigenvalues λ_n and eigenfunctions Φ_n approximate the spectrum and eigenfunctions of Δ in a completely reflecting domain ($\partial\Omega_r = \partial\Omega$). In particular, $\lambda_1 \to 0$ and $\Phi_1 \to 1/\sqrt{|\Omega|}$, so that $\langle 1, \Phi_n \rangle \to \delta_{1n} \cdot \sqrt{|\Omega|}$. In that case, the average MET behaves asymptotically as $\overline{u} \sim -1/(D\lambda_1)$ and determining it constitutes a singular perturbation problem [Cheviakov et al., 2010; Cheviakov and Ward, 2011]. In fact, by (1.28) the cumulative probability of escape by time t behaves asymptotically as

$$q(t) \sim 1 - e^{D\lambda_1 t}. \tag{1.32}$$

Hence, for small $\partial\Omega_a$ we expect escape times to be approximately exponentially distributed with rate $-D\lambda_1$ [Grigoriev et al., 2002; Schuss et al., 2007], as already seen in example 1.5.

This result has an intuitive explanation: As the escape window becomes very small, particle escape becomes a rare event, in the sense that the involved time scales are much larger than the time scales involved in the relaxation of the distribution within the domain. Thus, the probability $S(t_1, t_2)$ of the particle remaining in Ω during the time interval $[t_1, t_2]$, provided it was in Ω at t_1, only depends on the difference $t_2 - t_1$ but not on the initial particle position, i.e., $S(t_1, t_2) = S(t_2 - t_1)$. On the other hand, $S(0, t_1 + t_2) = S(0, t_1) \cdot S(t_1, t_2)$, so that $S(t_1 + t_2) = S(t_1)S(t_2)$. Hence $S(t) = e^{-kt}$ for some rate $k > 0$, that is, particle escape is a Poissonian process.

For verification purposes, I implemented Monte Carlo simulations of Brownian trajectories within the three-dimensional unit sphere. The otherwise reflecting sphere boundary included a small circular window through which particles could escape (cf. section 3). I performed a statistical analysis of the observed escape times, when the start positions were uniformly distributed in the domain. The discrete processes were adaptations of standard schemes (cf. [Glasserman, 2003, §3] and [Kroese et al., 2011, §5.10]), with the reflections evaluated on the piecewise linearly interpolated sample paths. All random numbers were generated using the libc pseudo-random generator [Apple Inc., 2011]. Normally distributed numbers were generated using the Box-Muller transform [Gentle, 2003, §5.2.1]. The source code can be obtained from the author upon request. Figure 1.4(a) shows an example realization of a Brownian particle trajectory that eventually escapes the domain. Figure 1.4(b) shows the empirical distribution of escape times from the same domain, obtained from a large number of trials. As can be seen, escape times are very close to exponentially distributed. Starting all simulations at a fixed point within the sphere (but not to close to the window), does not qualitatively change the outcome. This pattern verifies the predictions made above.

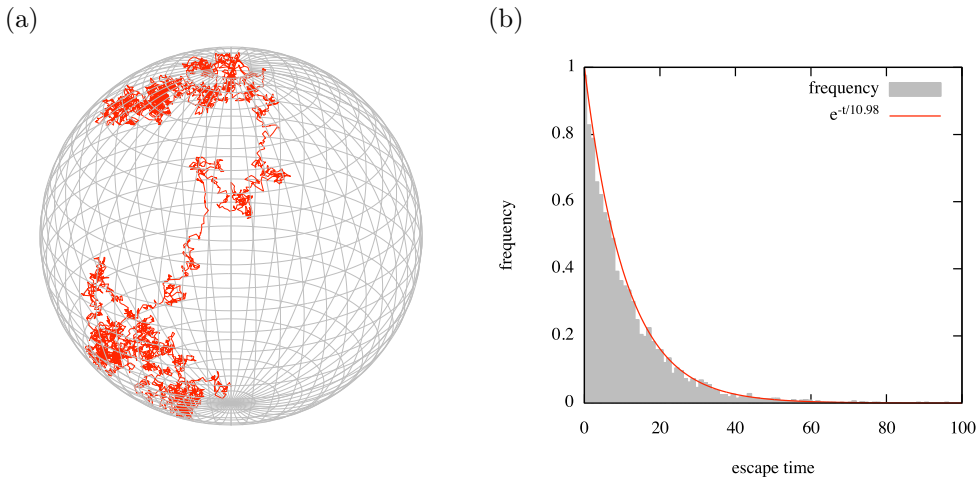

Figure 1.4: (a) Example simulation of Brownian motion within the three-dimensional unit ball with a small circular window on the top. The particle starts near the bottom and eventually escapes through the window. (b) Empirical escape time frequency (normalized to maximum 1) from the same domain, obtained from a Monte Carlo simulation of 5000 sample paths. The path start positions were uniformly distributed in the domain. The estimated MET was 10.98. The red, solid curve shows the theoretical density of the exponential distribution with the same mean for comparison, normalized to maximum 1. Both for (a) and (b), window radius $\varepsilon = 0.1$, $D = 1$ and time step was 10^{-7}.

It should be noted that for non-zero drift $\mathbf{v} \neq 0$, as would be the case for particles moving within a potential well, the principal eigenfunction Φ_1 does not necessarily approach a constant (cf. [Singer and Schuss, 2006, eq. (12)]). In that case, the approximation (1.32) is no longer valid and escape times are no longer exponentially distributed.

2 Electrostatic capacity and multipole expansions

Electrostatic capacity, defined below, is an intrinsic geometric property of bounded domains in $\mathbb{R}^n$, that is deeply connected to the Green's functions of the Laplace operator. As such, it appears in several physical and mathematical theories, such as electrostatics and mean escape time theory for diffusing particles [Swanson, 1963; Ozawa, 1983; Jackson, 1998; Singer et al., 2006]. I give here an introduction to electrostatic capacities, and more broadly, multipole expansions for far-field potentials, from an electrostatic point of view. Of course, the results are generic and equally applicable to the narrow escape problem, as required for example by matched asymptotic expansion techniques [Cheviakov et al., 2010; Cheviakov and Ward, 2011]. I refer to sections 1.5, 3.2, 3.3 and 4.2 for example applications.

2.1 Multipole expansions in free space (nD)

I begin with the multipole expansion of an electrostatic potential $U(\mathbf{x})$, generated by a compactly supported charge distribution $\zeta(\mathbf{x})$ in free space $\mathbb{R}^n$ (where $n \geq 3$). Specifically, let $U : \mathbb{R}^n \to \mathbb{R}$ be the solution of the Poisson equation with natural boundary conditions

$$\Delta U(\mathbf{x}) = -\zeta(\mathbf{x}), \quad U(\infty) = 0. \tag{2.1}$$

The question I wish to answer is simple to state: Can one find an asymptotic far-field expansion for the potential U, in which each expansion term splits into a term characterizing the source ζ and a term only depending on $\mathbf{x}$? One has

$$U(\mathbf{x}) = -\int_{B_R} G(\mathbf{x}, \mathbf{y})\zeta(\mathbf{y})\, d\mathbf{y}, \tag{2.2}$$

where $B_R \supseteq \operatorname{supp}\zeta$ is any fixed ball of radius $R > 0$ enclosing the support of ζ, and

$$G(\mathbf{x}, \mathbf{y}) := -\frac{1}{\alpha(n)} \frac{1}{|\mathbf{x} - \mathbf{y}|^{n-2}} \tag{2.3}$$

is the free-space Dirichlet Green's function for Δ (cf. [Evans, 2010, p. 22]). The coefficient $\alpha(n)$ is the volume of the unit ball in $\mathbb{R}^n$, multiplied by $n(n-2)$. Denote $f(\mathbf{x}, \mathbf{z}) := G(\mathbf{x}, |\mathbf{x}|\,\mathbf{z})$. Then by Taylor,

$$f(\mathbf{x}, \mathbf{z}) = \sum_{m=0}^{N} \frac{1}{m!} \partial_{z^{i_1}..z^{i_m}} f(\mathbf{x}, 0) \cdot z^{i_1} \cdot .. \cdot z^{i_m} + R_N(\mathbf{x}, \mathbf{z}), \tag{2.4}$$

where the error $R_N(\mathbf{x}, \mathbf{z})$ can be estimated by Lagrange as

$$|R_N(\mathbf{x}, \mathbf{z})| \leq \frac{1}{(N+1)!} \sup_{|\mathbf{w}| \leq \varepsilon} \left\| \partial^{N+1}_{\mathbf{z}^{N+1}} f(\mathbf{x}, \mathbf{w}) \right\| \cdot \varepsilon^{N+1}, \tag{2.5}$$

as long as $|\mathbf{z}| \leq \varepsilon$. Here, $\|\cdot\|$ denotes the operator norm induced by the norm of the underlying linear space. Note that in (2.4) I use Einstein's summation convention and each index i_k runs from 1 to n. Notice that one has

$$\partial_{z^{i_1}..z^{i_m}} f(\mathbf{x}, \mathbf{z}) = |\mathbf{x}|^m \, \partial_{y^{i_1}..y^{i_m}} G(\mathbf{x}, \mathbf{y})\big|_{\mathbf{y}=|\mathbf{x}|\mathbf{z}}. \tag{2.6}$$

For the special Green's function (2.3) one furthermore finds

$$\left\| \partial^m_{\mathbf{y}^m} G(\mathbf{x}, \mathbf{y}) \right\| \in \mathcal{O}(1/\,|\mathbf{x}|^{n-2+m}) \tag{2.7}$$

as $\mathbf{x} \to \infty$, as long as $\mathbf{y} \in \mathcal{O}(1)$. Using estimate (2.7) in (2.5), turns (2.4) into the asymptotic approximation

$$G(\mathbf{x}, \mathbf{y}) = f\left(\mathbf{x}, \frac{\mathbf{y}}{|\mathbf{x}|}\right) = \sum_{m=0}^{N} \frac{1}{m!} \partial_{y^{i_1}..y^{i_m}} G(\mathbf{x}, 0) \cdot y^{i_1} \cdot .. \cdot y^{i_m} + \mathcal{O}(1/\,|\mathbf{x}|^{n+N-1}) \tag{2.8}$$

as $\mathbf{x} \to \infty$, uniformly in $\mathbf{y} \in B_R$. Consequently, (2.2) expands to

$$U(\mathbf{x}) = -\sum_{m=0}^{N} \frac{1}{m!} \partial_{y^{i_1}..y^{i_m}} G(\mathbf{x}, 0) \cdot \int_{B_R} \zeta(\mathbf{y}) \cdot y^{i_1} \cdot .. \cdot y^{i_m}\, d\mathbf{y} + \mathcal{O}(1/\,|\mathbf{x}|^{n+N-1}), \tag{2.9}$$

as $\mathbf{x} \to \infty$. For translation invariant kernels like (2.3), i.e., $G(\mathbf{x}, \mathbf{y}) = G(\mathbf{x}-\mathbf{y})$, one has $\partial_{y^{i_1}..y^{i_m}} G(\mathbf{x}, 0) = (-1)^m \partial_{i_1..i_m} G(\mathbf{x})$, so that (2.9) takes the form

$$U(\mathbf{x}) = -\sum_{m=0}^{N} \frac{(-1)^m}{m!} \partial_{i_1..i_m} G(\mathbf{x}) \cdot \int_{B_R} \zeta(\mathbf{y}) \cdot y^{i_1} \cdot .. \cdot y^{i_m} \, d\mathbf{y} + \mathcal{O}(1/|\mathbf{x}|^{n+N-1}). \tag{2.10}$$

It should be noted that (2.9) is valid for any differential operator $\mathcal{L}$ other than Δ (though possibly with a different error estimate), provided an error estimate such as (2.7) can be made. Similarly, (2.10) is valid for any translation invariant differential operator $\mathcal{L}$ other than Δ, provided an error estimate such as (2.7) can be made. Also note that in physics literature, the expansion (2.10) is often written in a slightly different but equivalent form (for $n = 3$), namely

$$U(\mathbf{x}) = -\sum_{m=0}^{N} \frac{(-1)^m}{m!} \cdot \frac{x^{i_1} \cdot .. \cdot x^{i_m}}{|\mathbf{x}|^{2N+1}} \int_{B_R} \zeta(\mathbf{y}) \cdot |\mathbf{y}|^{2N+1} \, \partial_{i_1..i_m} G(\mathbf{y}) \, d\mathbf{y} + \mathcal{O}(1/|\mathbf{x}|^{N+2}). \tag{2.11}$$

From (2.10) and (2.3) one has in particular

$$U(\mathbf{x}) = \frac{1}{\alpha(n)\,|\mathbf{x}|^{n-2}} \int \zeta(\mathbf{y}) \, d\mathbf{y} + \frac{(n-2)}{\alpha(n)} \cdot \frac{\mathbf{x}}{|\mathbf{x}|^n} \int \zeta(\mathbf{y})\mathbf{y} \, d\mathbf{y} + \mathcal{O}(1/|\mathbf{x}|^n), \tag{2.12}$$

with $\int \zeta(\mathbf{y}) \, d\mathbf{y}$ and $\int \zeta(\mathbf{y})\mathbf{y} \, d\mathbf{y}$ as the so called *monopole* and *dipole moments* of the charge distribution ζ, respectively. Note that the monopole moment is simply the total charge.

For future reference, I would like to point out the following rule for translation invariant G: From (2.2) one has

$$\nabla_{\mathbf{x}} U(\mathbf{x}) = -\int_{B_R} \mathbf{F}(\mathbf{x}-\mathbf{y}) \zeta(\mathbf{y}) \, d\mathbf{y}, \tag{2.13}$$

where $\mathbf{F}(\mathbf{x}) := \nabla_{\mathbf{x}} G(\mathbf{x})$ is the gradient of G. For many Green's functions G (as is the case with (2.3)), the vector-valued kernel $\mathbf{F}$ is again suitable for a similar multipole expansion, this time on a component-by-component basis. This leads to an expansion similar to (2.10), namely

$$\nabla_{\mathbf{x}} U(\mathbf{x}) \sim -\sum_{m=0}^{N} \frac{(-1)^m}{m!} \nabla_{\mathbf{x}} \partial_{i_1..i_m} U(\mathbf{x}) \cdot \int_{B_R} \zeta(\mathbf{y}) \cdot y^{i_1} \cdot .. \cdot y^{i_m} \, d\mathbf{y} + \dots. \tag{2.14}$$

2.2 Electrostatic capacity in free space (3D)

Now consider the related Dirichlet problem

$$\Delta U\big|_{\mathbb{R}^3 \setminus \mathrm{cl}(\Omega)} = 0, \quad U\big|_{\partial\Omega} = U_o, \quad U(\infty) = 0, \tag{2.15}$$

where $\Omega \subseteq \mathbb{R}^3$ is a bounded open set with smooth boundary. W.l.o.g. I assume that Ω includes the origin. I also assume that $\mathbb{R}^3 \setminus \mathrm{cl}(\Omega)$ is connected. The function $U_o : \partial\Omega \to \mathbb{R}$ gives the potential on $\partial\Omega$. Using a separation of variables ansatz in spherical coordinates $(\rho, \vartheta, \varphi)$, one obtains the fundamental solutions for the Laplace operator and finds that U must be of the form

$$U(\rho, \vartheta, \varphi) = \sum_{l=0}^{\infty} \sum_{m=-l}^{l} A_l^m \cdot \rho^{-(l+1)} \cdot Y_l^m(\vartheta, \varphi) \tag{2.16}$$

for suitable coefficients $A_l^m \in \mathbb{C}$, where Y_l^m are the spherical harmonics of degree l and order m [Courant and Hilbert, 1966, §V.8 & VII.5]. By the orthogonality relation $\int_{S^1} Y_l^m Y_{l'}^{m'} \, dS = \delta_{ll'}\delta_{mm'}$, one has

$$A_l^m = R^{(l-1)} \int_{\partial B_R} U(\rho, \vartheta, \varphi) \cdot Y_l^m(\vartheta, \varphi) \, dS(\vartheta, \varphi) \tag{2.17}$$

for any ball B_R of radius $R > 0$ enclosing the domain $\partial\Omega$. In particular,

$$U(\rho, \vartheta, \varphi) \sim \frac{1}{4\pi\rho} \cdot \frac{1}{R} \int_{\partial B_R} U \, dS + \mathcal{O}(\rho^{-2}) \tag{2.18}$$

as $\rho \to \infty$. Now recall that for harmonic functions $U : \mathbb{R}^3 \setminus B_R \to \mathbb{R}$ one has $R^{-1}\int_{\partial B_R} U\ dS = \int_{\partial B_R} \partial_{\mathbf{n}} U\ dS$, where $\mathbf{n}$ is the unit normal vector on ∂B_R pointing into B_R. Thus, any one of the integrals below

$$\frac{1}{4\pi R}\int_{\partial B_R} U\ dS = \frac{1}{4\pi}\int_{\partial B_R} \partial_{\mathbf{n}} U\ dS = \frac{1}{4\pi}\int_{\partial\Omega} \partial_{\mathbf{n}} U\ dS =: \frac{1}{4\pi} Q(\Omega, U_o) \tag{2.19}$$

is independent of R (provided $\Omega \subseteq B_R$), and only depends on the geometry of Ω and the potential field U_o on $\partial\Omega$.

For the special case where U_o is constant on $\partial\Omega$, one has $Q(\Omega, U_o) = U_o Q(\Omega, 1)$, as becomes apparent from the original boundary value problem (2.15). The value $C(\Omega) := \frac{1}{4\pi} Q(\Omega, 1)$ is called the *electrostatic capacity* of the domain Ω [Jackson, 1998; Cheviakov and Ward, 2011]. Note that the asymptotic scaling

$$U(\mathbf{x}) \sim U_o C(\Omega)\, |\mathbf{x}|^{-1} + \dots \tag{2.20}$$

as $\mathbf{x} \to \infty$, can and is often being used as an alternative defining property of the capacity $C(\Omega)$.

This name *electrostatic capacity* is due to the following physical interpretation: Let Ω represent a perfect electric conductor kept at constant potential $U_o \in \mathbb{R}$. Recall that the interior of a conductor is charge-free and that $\sigma := \partial_{\mathbf{n}} U\big|_{\partial B_R}$ is the per-surface charge density on the conductor surface [Jackson, 1998]. Hence, $Q(\Omega, U_o) = \int_{\partial\Omega} \sigma\ dS$ is the total charge stored on the conductor surface $\partial\Omega$, while the electrostatic capacity $C(\Omega)$ is simply the ratio of total charge $Q(\Omega, U_o)$ over the scaled potential $4\pi U_o$. This interpretation is also retrieved when comparing (2.18) and (2.12). Indeed, if U is the solution of (2.1) in $\mathbb{R}^3$ for a suitable charge distribution ζ supported in the (non-conducting) domain Ω, and such that $U\big|_{\partial\Omega} \equiv U_o$: const, one again obtains

$$Q(\Omega, U_o) = \int_\Omega \zeta(\mathbf{y})\ d\mathbf{y}, \quad C(\Omega) = \frac{1}{4\pi U_o}\int_\Omega \zeta(\mathbf{y})\ d\mathbf{y}. \tag{2.21}$$

It is noteworthy that (2.19) readily yields the electrostatic capacity of a three-dimensional ball B_R of radius R, namely $C(B_R) = R$. In fact, Szegö [1930] shows that the ball has the smallest electrostatic capacity among all domains with same volume and smooth boundary. It should be pointed out that in contemporary physics literature, the electrostatic capacity differs from the above definition by a factor 4π [Jackson, 1998]. Finally, I mention that a similar notion of capacity exists for bounded domains in $\mathbb{R}^2$, called the *logarithmic capacity* [Ward et al., 1993; Coombs et al., 2009].

2.3 Electrostatic capacity and multipole expansions in half-space (nD)

While the electrostatic capacity defined in section 2.2 concerns the boundaries of domains in $\mathbb{R}^3$, an analogous and equally important concept exists for open surfaces. A special case of importance to the narrow escape problem, is that of a flat, bounded, $(n-1)$-dimensional surface in $\mathbb{R}^n$. Specifically, consider the following mixed Dirichlet-Neumann problem in the half-space $\mathbb{R}^n_* := \{\mathbf{x} = (x_1, .., x_n) \in \mathbb{R}^n : x_n > 0\}$:

$$\Delta U\big|_{\mathbb{R}^n_*} = 0, \quad U\big|_{\partial\Omega_d} = U_o, \quad \partial_{x_n} U\big|_{\partial\Omega_r} = 0, \quad U(\infty) = 0, \tag{2.22}$$

where $\partial\Omega_d \subseteq \{x_n = 0\}$ is a bounded $(n-1)$-dimensional open set with smooth boundary and $\partial\Omega_r := \{x_n = 0\} \setminus \partial\Omega_d$. $U_o : \partial\Omega_d \to \mathbb{R}$ is some smooth function. Notice that the solution to (2.22) is exactly the solution to the Dirichlet problem

$$\Delta U\big|_{\mathbb{R}^n \setminus \partial\Omega_d} = 0, \quad U\big|_{\partial\Omega_d} = U_o, \quad U(\infty) = 0, \tag{2.23}$$

restricted to $\mathbb{R}^n_*$, since then by reflection symmetry $\partial_z U\big|_{\partial\Omega_r} = 0$. Recall the Neumann Green's function

$$G_h(\mathbf{x}, \mathbf{y}) := -\frac{1}{\alpha(n)}\left[\frac{1}{|\mathbf{x}-\mathbf{y}|^{n-2}} + \frac{1}{|\mathbf{x}-\overline{\mathbf{y}}|^{n-2}}\right] \tag{2.24}$$

for the half-space $\mathbb{R}^n_*$, where $\overline{\mathbf{y}} := (y_1, .., y_{n-1}, -y_n)$ is the reflection of $\mathbf{y}$ by the hyperplane $\{x_n = 0\}$. One has the representation

$$U(\mathbf{x}) = -\int_{\partial\Omega_d} G_h(\mathbf{x}, \mathbf{y}) \cdot \partial_{\mathbf{n}} U(\mathbf{y})\ dS(\mathbf{y}) = -\int_{\partial\Omega_d} G(\mathbf{x}, \mathbf{y}) \cdot 2\partial_{\mathbf{n}} U(\mathbf{y})\ dS(\mathbf{y}), \tag{2.25}$$

where G is the free-space Dirichlet Green's function defined in (2.3) and $\mathbf{n} = (0, .., 0, -1)^T$ is the unit normal vector on $\{x_n = 0\}$ pointing out of $\mathbb{R}^n_*$, $\partial_{\mathbf{n}}$ evaluated in $\mathrm{cl}(\mathbb{R}^n_*)$. Comparing (2.25) to (2.2) allows for the following interpretation: Define $\zeta(\mathbf{y}) := 2\partial_{\mathbf{n}} U(\mathbf{y}) \cdot \delta(y_n)$, then U is just the restriction to half-space of the whole-space solution to (2.1). Hence, $\sigma := 2\partial_{\mathbf{n}} U\big|_{\partial\Omega_d}$ is the per-surface charge density on the conducting electrified sheet $\partial\Omega_d$, such that $\partial\Omega_d$ is at potential U_o. The factor 2 stems from the fact that the sheet charge is shared equally among both sides of the sheet. Eq. (2.25) shows that solving (2.22) is equivalent to finding the appropriate charge density on the sheet surface. One can easily adopt the multipole expansion (2.10) introduced in section 2.1 to obtain

$$U(\mathbf{x}) = -\sum_{m=0}^{N} \frac{(-1)^m}{m!} \partial_{i_1..i_m} G(\mathbf{x}) \cdot \int_{\partial\Omega_d} 2\partial_{\mathbf{n}} U(\mathbf{y}) \cdot y^{i_1} \cdot .. \cdot y^{i_m} \, dS(\mathbf{y}) + \mathcal{O}(1/|\mathbf{x}|^{n+N-1}) \tag{2.26}$$

as $\mathbf{x} \to \infty$, where the summation indices i_k now run from 1 to $(n-1)$. In particular

$$U(\mathbf{x}) \sim \frac{1}{\alpha(n)|\mathbf{x}|^{n-2}} \int_{\partial\Omega_d} 2\partial_{\mathbf{n}} U(\mathbf{y}) \, dS(\mathbf{y}) + \frac{(n-2)}{\alpha(n)} \cdot \frac{\mathbf{x}}{|\mathbf{x}|^n} \int_{\partial\Omega_d} \mathbf{y} 2\partial_{\mathbf{n}} U(\mathbf{y}) \, dS(\mathbf{y}) + \mathcal{O}(1/|\mathbf{x}|^n) \tag{2.27}$$

as $\mathbf{x} \to \infty$. Now let $U_o \in \mathbb{R}$ be constant on $\partial\Omega_d$. Similar to the free-space case (2.15), one calls the coefficient

$$C(\partial\Omega_d) := \frac{1}{\alpha(n) U_o} \int_{\partial\Omega_d} 2\partial_{\mathbf{n}} U \, dS, \tag{2.28}$$

which is independent of $U_o \neq 0$, the *electrostatic capacity* of the domain $\partial\Omega_d$. It is the total charge stored on a thin, flat, conducting sheet $\partial\Omega_d$ that is at potential U_o. Note that the asymptotic scaling

$$U(\mathbf{x}) \sim U_o C(\partial\Omega_d) |\mathbf{x}|^{2-n} + \dots \tag{2.29}$$

as $\mathbf{x} \to \infty$, can be used as an alternative defining property of the capacity $C(\partial\Omega_d)$ [Cheviakov et al., 2010].

3 On the narrow escape problem for the unit ball (3D)

In this section I comment on the recent work by Cheviakov et al. [2010], who provide a three-term expansion for the mean escape time through several small windows on the boundary of the three-dimensional unit ball. I elaborate on three concepts appearing in the original article: (1), The surface Neumann Green's function, (2), the so called electrified disk problem in electrostatics and (3), the electrostatic capacity of window clusters and their effects on the MET.

3.1 On the surface Neumann Green's function

In section 1.5 I considered the escape times of diffusing particles from a three-dimensional domain Ω through small interior traps $\Omega_1, .., \Omega_N \subseteq \widetilde{\Omega}$, where $\Omega = \widetilde{\Omega} \setminus \bigcup_{j=1}^N \mathrm{cl}(\Omega_j)$. We have seen that higher order corrections to the MET, as given by (1.18), depend explicitly on the trap positions $\mathbf{x}_j$ and the geometry of $\widetilde{\Omega}$. This dependence is encoded in the Neumann Green's function $G(\mathbf{x}, \mathbf{x}_j)$ for the Laplace operator in $\widetilde{\Omega}$. For fixed $\mathbf{x}_j \in \widetilde{\Omega}$, $G(\mathbf{x}, \mathbf{x}_j)$ is the solution to the stationary diffusion equation

$$\begin{aligned} &\Delta_{\mathbf{x}} G(\mathbf{x}, \mathbf{x}_j) = |\widetilde{\Omega}|^{-1} - \delta(\mathbf{x} - \mathbf{x}_j), \quad \mathbf{x} \in \widetilde{\Omega}, \\ &\partial_{\mathbf{n}_{\mathbf{x}}} G(\mathbf{x}, \mathbf{x}_j) = 0, \quad \mathbf{x} \in \partial\widetilde{\Omega}, \\ &\int_{\widetilde{\Omega}} G(\mathbf{x}, \mathbf{x}_j) \, d\mathbf{x} = 0 \end{aligned} \tag{3.1}$$

in $\widetilde{\Omega}$, with an interior source localized at $\mathbf{x}_j \in \widetilde{\Omega}$. In the limit where $\mathbf{x}_j \to \partial\widetilde{\Omega}$ and the absorbing boundaries $\partial\Omega_j$ become part of $\partial\widetilde{\Omega}$, the original expansion (1.18) is no longer valid. Nonetheless, one might expect a certain similarity to (1.18), if the free-space electrostatic capacities C_j of the traps are replaced by their half-space capacities introduced in section 2.3 and G is replaced by the so called *surface Neumann Green's function* $G_{\mathrm{s}}(\mathbf{x}, \mathbf{x}_j)$. This was demonstrated by Singer et al. [2006] and Cheviakov et al. [2010] for circular windows on a sphere, as well as by Singer et al. [2008] for a circular window on the surface of an arbitrary domain.

The surface Neumann Green's function is the solution to the stationary diffusion equation

$$\begin{aligned} &\Delta_{\mathbf{x}} G_{\mathrm{s}}(\mathbf{x},\mathbf{x}_j) = |\widetilde{\Omega}|^{-1}, \quad \mathbf{x}\in\widetilde{\Omega},\\ &\partial_{\mathbf{n}_{\mathbf{x}}} G_{\mathrm{s}}(\mathbf{x},\mathbf{x}_j) = \delta_{\mathrm{s}}(\mathbf{x}-\mathbf{x}_j), \quad \mathbf{x}\in\partial\widetilde{\Omega},\\ &\int_{\widetilde{\Omega}} G_{\mathrm{s}}(\mathbf{x},\mathbf{x}_j)\, d\mathbf{x} = 0 \end{aligned} \tag{3.2}$$

in $\widetilde{\Omega}$, with a surface source localized at $\mathbf{x}_j \in \partial\widetilde{\Omega}$. Here, δ_{s} is the two-dimensional surface δ-distribution on $\partial\widetilde{\Omega}$. Note that (3.2) is the fundamental solution to the Neumann problem

$$\Delta U\big|_{\widetilde{\Omega}} = \text{const}, \quad \partial_{\mathbf{n}} U\big|_{\partial\widetilde{\Omega}} = \sigma, \tag{3.3}$$

for any given surface source density $\sigma : \partial\widetilde{\Omega} \to \mathbb{R}$. That is to say that, one has the representation

$$U(\mathbf{x}) = \overline{U} + \int_{\partial\widetilde{\Omega}} G_{\mathrm{s}}(\mathbf{x},\mathbf{y})\sigma(\mathbf{y})\, dS(\mathbf{y}), \quad \mathbf{x}\in\widetilde{\Omega}\cup\partial\widetilde{\Omega}, \tag{3.4}$$

for any U solving (3.3), where $\overline{U} := |\widetilde{\Omega}|^{-1}\int_{\widetilde{\Omega}} U$.

The surface Neumann Green's function has been used to calculate the exterior magnetic field of the Sun, based on the estimated normal field component normal to the Sun's surface [Schmidt, 1964; Sakurai, 1982]. It's singularity behavior has also been investigated in connection with the exterior magnetic field generated by magnetic fluxons on superconductor boundaries [Silbergleit et al., 2003]. It turns out that, apart from the Newtonian singularity $\frac{1}{4\pi|\mathbf{x}-\mathbf{y}|}$, the surface Neumann Green's function $G_{\mathrm{s}}(\mathbf{x},\mathbf{y})$ has an additional logarithmic singularity as $\mathbf{x}\to\mathbf{y}$ [Popov, 1992]. Such sub-dominant singularities become important when calculating higher order expansion terms in narrow escape problems [Cheviakov et al., 2010] or the interaction of magnetic vortices in superconductors [Silbergleit et al., 2003].

I shall give here a rough derivation of the surface Neumann Green's function for the three-dimensional unit ball $\widetilde{\Omega} = \{\mathbf{x}\in\mathbb{R}^3 : |\mathbf{x}|<1\}$. The latter appears in the three-term expansion of the MET from the unit ball, provided by Cheviakov et al. [2010]. The derivation is based on the hints given by Kellogg [1929] in an exercise on Neumann Green's functions. I begin by noting that (3.4) also holds if one replaces G_{s} by G, but a priori only for $\mathbf{x}\in\widetilde{\Omega}$. This implies that $G(\mathbf{x},\mathbf{y}) = G_{\mathrm{s}}(\mathbf{x},\mathbf{y})$ whenever $\mathbf{x}\in\widetilde{\Omega}$ and $\mathbf{y}\in\partial\widetilde{\Omega}$. Since no singularities in $\mathbf{x}\in\mathrm{cl}(\widetilde{\Omega})$ are expected away from $\mathbf{y}$, one can safely conclude that in fact $G(\mathbf{x},\mathbf{y}) = G_{\mathrm{s}}(\mathbf{x},\mathbf{y})$ whenever $\mathbf{y}\in\partial\widetilde{\Omega}$ and $\mathbf{x}\in\mathrm{cl}(\widetilde{\Omega})\setminus\{\mathbf{y}\}$.

Kellogg [1929, p. 247, Exercise 4] proposes a solution to the Neumann problem

$$\begin{aligned} &\Delta_{\mathbf{x}} G_o(\mathbf{x},\mathbf{y}) = -\delta(\mathbf{x}-\mathbf{y}), \quad \mathbf{x},\mathbf{y}\in\widetilde{\Omega}\\ &\partial_{\mathbf{n}_{\mathbf{x}}} G_o(\mathbf{x},\mathbf{y}) = -|\partial\widetilde{\Omega}|^{-1}, \quad \mathbf{x}\in\partial\widetilde{\Omega},\ \mathbf{y}\in\widetilde{\Omega}, \end{aligned} \tag{3.5}$$

where $|\partial\widetilde{\Omega}| = 4\pi$, in the form

$$G_o(\mathbf{x},\mathbf{y}) := \frac{1}{4\pi\,|\mathbf{x}-\mathbf{y}|} + \frac{1}{4\pi\,|\mathbf{y}|\,|\mathbf{x}-\overline{\mathbf{y}}|} + \frac{1}{4\pi}\ln\left[\frac{2}{1-\mathbf{x}\cdot\mathbf{y}+|\mathbf{y}|\,|\mathbf{x}-\overline{\mathbf{y}}|}\right], \quad \mathbf{x}\in\mathrm{cl}(\widetilde{\Omega}), \tag{3.6}$$

where $\overline{\mathbf{y}} := \mathbf{y}/|\mathbf{y}|^2$ and $\mathbf{x}\cdot\mathbf{y}$ denotes the scalar product. Note that such a G_o is sometimes also referred to as Neumann Green's function, or *Green's function of the second kind*. The Laplacian $\Delta_{\mathbf{x}}$ of the first term in (3.6) gives $-\delta(\mathbf{x}-\mathbf{y})$. It is also easy to see that the second term is harmonic in $\mathbf{x}\in\widetilde{\Omega}$, since $\overline{\mathbf{y}}\notin\widetilde{\Omega}$. Showing that the 3rd term is harmonic is a lengthy but straightforward calculation, which can be verified using computer algebra systems such as Mathematica [Wolfram Research, 2010]. It is also straightforward (albeit tedious) to show that G_o satisfies the boundary condition in (3.5). Observing that

$$|\mathbf{y}|\,|\mathbf{x}-\overline{\mathbf{y}}| = \sqrt{1+|\mathbf{x}|^2\,|\mathbf{y}|^2 - 2\,|\mathbf{x}|\,|\mathbf{y}|\cos\theta}, \tag{3.7}$$

where θ is the angle between $\mathbf{x}$ and $\mathbf{y}$, convinces that $G_o(\mathbf{x},\mathbf{y}) = G_o(\mathbf{y},\mathbf{x})$. The Neumann Green's function G, defined by (3.1), can be obtained by letting

$$G(\mathbf{x},\mathbf{y}) := G_o(\mathbf{x},\mathbf{y}) + R(\mathbf{x},\mathbf{y}), \tag{3.8}$$

with the regular part $R(\mathbf{x},\mathbf{y})$ solving the boundary value problem

$$\begin{aligned}
&\Delta_{\mathbf{x}} R(\mathbf{x},\mathbf{y}) = |\widetilde{\Omega}|^{-1}, \quad \mathbf{x},\mathbf{y}\in\widetilde{\Omega},\\
&\partial_{\mathbf{n}_{\mathbf{x}}} R(\mathbf{x},\mathbf{y}) = |\partial\widetilde{\Omega}|^{-1}, \quad \mathbf{x}\in\partial\widetilde{\Omega},\ \mathbf{y}\in\widetilde{\Omega},\\
&\int_{\widetilde{\Omega}} R(\mathbf{x},\mathbf{y})\ d\mathbf{x} = -\int_{\widetilde{\Omega}} G_o(\mathbf{x},\mathbf{y})\ d\mathbf{x}, \quad \mathbf{y}\in\widetilde{\Omega}
\end{aligned} \tag{3.9}$$

for every $\mathbf{y}\in\mathrm{cl}(\widetilde{\Omega})$. The symmetry of $G(\mathbf{x},\mathbf{y})$ in its two arguments (cf. [Pozrikidis, 2011, §2.2.5]) implies a similar symmetry of $R(\mathbf{x},\mathbf{y})$. I thus make the ansatz

$$R(\mathbf{x},\mathbf{y}) := \alpha(|\mathbf{x}|^2+|\mathbf{y}|^2)+\beta(|\mathbf{x}|+|\mathbf{y}|)+\gamma, \tag{3.10}$$

for suitable constants $\alpha,\beta,\gamma\in\mathbb{R}$. The faith in such a simple ansatz stems from the high symmetry of the domain $\widetilde{\Omega}$, and is justified in retrospect. The first two conditions in (3.9) are satisfied for $\alpha = 1/(6|\widetilde{\Omega}|)$ and $\beta = 0$, so that

$$G(\mathbf{x},\mathbf{y}) = \frac{1}{4\pi\,|\mathbf{x}-\mathbf{y}|} + \frac{1}{4\pi\,|\mathbf{y}|\,|\mathbf{x}-\overline{\mathbf{y}}|} + \frac{1}{4\pi}\ln\left[\frac{2}{1-\mathbf{x}\cdot\mathbf{y}+|\mathbf{y}|\,|\mathbf{x}-\overline{\mathbf{y}}|}\right] + \frac{1}{6|\widetilde{\Omega}|}(|\mathbf{x}|^2+|\mathbf{y}|^2)+\gamma \tag{3.11}$$

The constant γ has to be chosen such that the integral $\int_{\widetilde{\Omega}} G(\mathbf{x},\mathbf{y})\ d\mathbf{x}$ vanishes for all $\mathbf{y}$. Of course, this is only possible if the integral itself is independent of $\mathbf{y}$. This is in fact the case, as was demonstrated by Cheviakov and Ward [2011, Lemma A.1]. Hence, γ can be calculated by setting $\mathbf{y}=0$ and demanding that $\int_{\widetilde{\Omega}} G(\mathbf{x},0)\ d\mathbf{x} = 0$, which quickly gives $\gamma = -7/(10\pi)$. Result (3.11) is the same as obtained by Cheviakov and Ward [2011, eq. (2.26a)], using an expansion of the subdominant part of G into Legendre polynomials. Finally, one concludes that

$$G_{\mathrm{s}}(\mathbf{x},\mathbf{y}) = \frac{1}{2\pi\,|\mathbf{x}-\mathbf{y}|} + \frac{1}{4\pi}\ln\left[\frac{2}{1-\mathbf{x}\cdot\mathbf{y}+|\mathbf{x}-\mathbf{y}|}\right] + \frac{1}{8\pi}(|\mathbf{x}|^2+1) - \frac{7}{10\pi}, \tag{3.12}$$

gives the surface Neumann Green's function of the three-dimensional unit ball, when $\mathbf{y}\in\partial\widetilde{\Omega}$ and $\mathbf{x}\in\mathrm{cl}(\widetilde{\Omega})\backslash\{\mathbf{y}\}$. The representation (3.12) can alternatively be derived using a suitable expansion into Legendre polynomials, as shown by Cheviakov et al. [2010, Lemma 2.1].

3.2 The electrified disk problem

In view of the intermediate result (2.16) in [Cheviakov et al., 2010], I shall elaborate on the so called *electrified disk problem* of electrostatics in the half-space $\mathbb{R}^3_* := \{\mathbf{x}=(x_1,x_2,x_3)\in\mathbb{R}^3 : x_3>0\}$. I shall work in cylindrical coordinates (ρ,φ,z). We seek a solution to the boundary value problem

$$\Delta w_c\big|_{\mathbb{R}^3_*} = 0, \quad w_c\big|_{\partial\Omega_d} = 1, \quad \partial_z w_c\big|_{\partial\Omega_r} = 0, \quad w_c(\infty) = 0, \tag{3.13}$$

where $\partial\Omega_d\subseteq\{z=0\}$ is a two-dimensional, bounded domain (e.g. a thin disk) at *potential* 1 and $\partial\Omega_r := \{z=0\}\setminus\partial\Omega_d$. Notice that this is the three-dimensional version of the general problem (2.22) studied in section 2.3. A separation of variables ansatz $w_c(\rho,\varphi,z) = R(\rho)\Phi(\varphi)Z(z)$ yields a complete set of fundamental solutions for (3.13). From (3.13) one obtains

$$\frac{R'}{\rho R} + \frac{R''}{R} + \frac{\Phi''}{\rho^2\Phi} + \frac{Z''}{Z} = 0, \tag{3.14}$$

with the conditions

$$R(\infty) = Z(\infty) = 0, \quad \Phi(\varphi+2\pi) = \Phi(\varphi), \quad R(0)\in\mathbb{R}. \tag{3.15}$$

Eq. (3.14) implies

$$\frac{R'}{\rho R} + \frac{R''}{R} + \frac{\Phi''}{\rho^2\Phi} = -\frac{Z''}{Z} = -\varkappa^2 \tag{3.16}$$

for some constant $\varkappa>0$, so that

$$Z(z) = \mathrm{const}\cdot e^{-\varkappa z}. \tag{3.17}$$

Note that any other eigenvalue choice on the RHS of (3.16) would not allow for solutions $Z(z)$ compatible with the boundary condition $Z(\infty) = 0$. Consequently,

$$\frac{\rho R'}{R} + \frac{\rho^2 R''}{R} + \varkappa^2\rho^2 = -\frac{\Phi''}{\Phi} =: \lambda \tag{3.18}$$

for some constant $\lambda \in \mathbb{R}$. The case $\lambda < 0$ is discarded, since it only allows for the non-periodic solutions $\Phi(\varphi) = Ae^{\sqrt{-\lambda}\varphi} + Be^{-\sqrt{-\lambda}\varphi}$ $(A, B \in \mathbb{R})$. In case $\lambda = 0$, $\Phi(\varphi) = \text{const}$ is the only periodic solution. In case $\lambda > 0$, one obtains

$$\Phi(\varphi) = A\cos(\sqrt{\lambda}\varphi) + B\sin(\sqrt{\lambda}\varphi), \tag{3.19}$$

while the periodicity of Φ demands that $\lambda = n^2$ for some $n \in \mathbb{N}$. Hence, R satisfies

$$\rho^2 R'' + \rho R' + (\varkappa^2\rho^2 - n^2)R = 0. \tag{3.20}$$

Temporarily rescaling $r := \varkappa\rho$ turns (3.20) into Bessel's differential equation

$$r^2\partial_r^2 R + r\partial_r R + (r^2 - n^2)R = 0 \tag{3.21}$$

of order $n \in \mathbb{N}_0$ [Abramowitz and Stegun, 1964]. Its only solution not singular at the origin is given by the Bessel function J_n of the first kind and order n, i.e., $R(\rho) = \text{const}\cdot J_n(\varkappa\rho)$. Note that also $J_n(\infty) = 0$, in accordance with (3.15). One concludes that the general solution to (3.13) is formally given by

$$w_c(\rho,\varphi,z) = \sum_{n=0}^{\infty}\int_0^\infty e^{-\varkappa z}\cdot J_n(\varkappa\rho)\cdot\big[A(\varkappa,n)\cos(n\varphi) + B(\varkappa,n)\sin(n\varphi)\big]\ d\varkappa, \tag{3.22}$$

with the coefficients $A(\varkappa,n),\ B(\varkappa,n) \in \mathbb{R}$ chosen such that the boundary conditions (3.13) are satisfied. As adumbrated, I shall consider the special case of an electrified disk $\partial\Omega_d = \{z = 0,\ \rho \le a\}$ of radius $a > 0$. Then w_c is axially symmetric, $w_c = w_c(\rho, z)$, and thus of the form

$$w_c(\rho,\varphi,z) = \int_0^\infty f(\mu)\cdot e^{-\mu z/a}\cdot J_0\left(\mu\rho/a\right)\ d\mu, \tag{3.23}$$

for a suitable spectrum $f(\mu)$. Note that in (3.23) I introduced the rescaled variable $\mu := a\varkappa$. The boundary conditions (3.13) translate to

$$\begin{aligned}\int_0^\infty f(\mu)\cdot J_0(\mu\xi)\ d\mu &= 1, \quad 0 \le \xi \le 1,\\ \int_0^\infty \mu f(\mu)\cdot J_0\left(\mu\xi\right)\ d\mu &= 0, \quad \xi > 1.\end{aligned} \tag{3.24}$$

Now recall the two identities

$$\begin{aligned}\int_0^\infty \frac{\sin\mu}{\mu}\cdot J_0(\mu\xi)\ d\mu &= \frac{\pi}{2}, \quad 0 \le \xi \le 1,\\ \int_0^\infty \sin\mu\cdot J_0\left(\mu\xi\right)\ d\mu &= 0, \quad \xi > 1,\end{aligned} \tag{3.25}$$

satisfied by the Bessel function J_0 [Abramowitz and Stegun, 1964, eqs. (11.4.35), (11.4.38), (5.2.26)]. I mention that these integrals appear as early as 1873 in electrostatic theory [Weber, 1873]. Hence, setting $f(\mu) := \frac{2\sin\mu}{\pi\mu}$ satisfies (3.24). One concludes that

$$w_c(\rho, z) = \frac{2}{\pi}\int_0^\infty \frac{\sin\mu}{\mu}\cdot e^{-\mu z/a}\cdot J_0\left(\mu\rho/a\right)\ d\mu, \tag{3.26}$$

indeed as given by Cheviakov et al. [2010, eq. (2.16)]. An alternative approach to solving (3.13) is provided by Fabrikant [1989, §1.4]. Using the representation (3.26), a multipole expansion as described in section 2.3 can now be derived for w_c. Observe that

$$\partial_z w_c(\rho, z)\big|_{z=0} = -\frac{2}{a\pi}\int_0^\infty \sin\mu\cdot J_0\left(\mu\rho/a\right)\ d\mu = -\frac{2}{\pi}\frac{1}{\sqrt{a^2-\rho^2}}, \tag{3.27}$$

where in the last step I used [Abramowitz and Stegun, 1964, eq. (11.4.38)]. Inserting (3.27) into the expansion (2.27), yields the approximation

$$\begin{aligned} w_c(\mathbf{x}) \sim & \frac{1}{\pi^2 |\mathbf{x}|} \int_0^{2\pi} \int_0^a \frac{\rho}{\sqrt{a^2-\rho^2}} \, d\rho \, d\varphi \\ & + \frac{\mathbf{x}}{\pi^2 |\mathbf{x}|^3} \cdot \int_0^{2\pi} \int_0^a \rho^2 \frac{\cos\varphi \cdot \mathbf{e}_1 + \sin\varphi \cdot \mathbf{e}_2}{\sqrt{a^2-\rho^2}} \, d\rho \, d\varphi + \mathcal{O}(1/|\mathbf{x}|^3) \\ \sim & \frac{2}{\pi |\mathbf{x}|} \int_0^a \frac{\rho}{\sqrt{a^2-\rho^2}} \, d\rho \\ & + \frac{\mathbf{x}}{\pi^2 |\mathbf{x}|^3} \cdot \int_0^a \frac{\rho^2}{\sqrt{a^2-\rho^2}} \int_0^{2\pi} [\cos\varphi \cdot \mathbf{e}_1 + \sin\varphi \cdot \mathbf{e}_2] \, d\varphi \, d\rho + \mathcal{O}(1/|\mathbf{x}|^3) \\ \sim & \frac{2a}{\pi |\mathbf{x}|} + \mathcal{O}\big(|\mathbf{x}|^{-3}\big) \end{aligned} \tag{3.28}$$

as $\mathbf{x} \to \infty$. Note that the dipole moment vanishes due to the disk's radial symmetry. Comparing (3.28) to (2.29), shows that $2a/\pi$ is exactly the electrostatic capacity of the disk $\partial\Omega_d$. One should appreciate how multipole expansion methods can readily give an asymptotic expansion for $w_c(\mathbf{x})$ without an analytic expression for (3.26), only requiring the surface charge density $\partial_{\mathbf{n}} w_c\big|_{\partial\Omega_d}$.

3.3 On the electrostatic capacity of a cluster of circular windows

Calculating the electrostatic capacity of bounded surfaces, as defined in sections 2.2 and 2.3, is an integral part of estimating mean escape times in the narrow escape problem. Even leading order expansion terms depend on the capacities of available escape windows, which are assumed to be well-distanced. On the other hand, when windows are clustered together at distances of order $\mathcal{O}(\varepsilon)$, one needs to treat each cluster as a single, possibly complex window [Holcman and Schuss, 2008; Cheviakov et al., 2010; Cheviakov and Ward, 2011]. Due to mutual polarization effects between proximate surfaces, solving the Laplace equation (2.23) for surfaces composed of multiple disjoint sub-surfaces $\partial\Omega_d^j$, is a non-trivial task. Fabrikant [1988] gives a method for estimating the total capacity $C(\partial\Omega_d)$ of such a compound surface $\partial\Omega_d = \bigcup_{j=1}^N \partial\Omega_d^j$, when $\partial\Omega_d \subseteq \partial\mathbb{R}^3_*$ consists of multiple disjoint discs. More precisely, he provides a parametrized algebraic system relating disk charges to disk potentials, where the parameters of the system are unknown but nonetheless within known bounds. I briefly recall his results and show how these can be used to obtain lower and upper bounds for $C(\partial\Omega_d)$. I then use these estimates to demonstrate the effects of window clustering on the mean escape time of Brownian particles from the three-dimensional unit ball.

Consider N disjoint disks $\partial\Omega_d^1, .., \partial\Omega_d^N \subseteq \partial\mathbb{R}^3_*$ of radii $a_1, .., a_N > 0$, centered at $\mathbf{x}_1, .., \mathbf{x}_N \in \partial\mathbb{R}^3_*$, at given potentials $U_1, .., U_N \in \mathbb{R}$ and with unknown total surface charges $Q_1, .., Q_N$, respectively. Recall that the Q_j are defined in section 2.3 as

$$Q_j := \int_{\partial\Omega_d^j} 2\partial_{\mathbf{n}} U \, dS, \tag{3.29}$$

where $\mathbf{n} = (0, 0, -1)^T$ denotes the unit normal vector on $\partial\mathbb{R}^3_*$ out of $\mathbb{R}^3_*$, $\partial_{\mathbf{n}}$ evaluated in $\mathrm{cl}(\mathbb{R}^3_*)$, and U solves the boundary value problem

$$\Delta U\big|_{\mathbb{R}^3 \setminus \partial\Omega_d} = 0, \quad U(\infty) = 0, \quad U\big|_{\partial\Omega_d^j} = U_j, \quad j = 1, .., N. \tag{3.30}$$

By Fabrikant [1988, eq. (24)] one knows that

$$\sum_{j=1}^N Q_j \arcsin \frac{a_k}{b_{jk}} = 4\pi a_k U_k, \quad k = 1, .., N, \tag{3.31}$$

where $b_{kk} := a_k$ and every other b_{jk} $(j \neq k)$ is the distance $|\mathbf{y}_{jk} - \mathbf{x}_k|$ of the centre $\mathbf{x}_k$ of disk $\partial\Omega_d^k$ to some unknown point $\mathbf{y}_{jk}$ within disk $\partial\Omega_d^j$. The latter originates from an application of the first mean value theorem to surface integrals over $\partial\Omega_d^j$. More precisely, $\mathbf{y}_{jk}$ is chosen such that

$$\int_{\partial\Omega_d^j} \eta_j(\mathbf{y}) \arcsin \frac{a_k}{|\mathbf{y} - \mathbf{x}_k|} \, dS(\mathbf{y}) \overset{!}{=} Q_j \arcsin \frac{a_k}{b_{jk}}, \quad j \neq k, \tag{3.32}$$

where $\eta_j := 2\partial_{\mathbf{n}} U\,|_{\partial\Omega_d^j}$ is the surface charge density on $\partial\Omega_d^j$. Note that for (3.32) one assumes that η_j does not change sign on $\partial\Omega_d^j$. A justification for this assumption is given below. The restriction

$$|\mathbf{x}_j - \mathbf{x}_k| - a_j \leq b_{jk} \leq |\mathbf{x}_j - \mathbf{x}_k| + a_j, \tag{3.33}$$

in conjunction with (3.31), provides in principle a means for estimating the possible charges Q_j.

Now let $U_1 = \cdots = U_N = 1$. Then (3.31) can be written in the matrix form

$$\mathbb{M} \cdot \mathbf{Q} = 4\pi\mathbf{a}, \tag{3.34}$$

where $\mathbb{M} \in \mathbb{R}_+^{N\times N}$ and $\mathbf{Q}, \mathbf{a} \in \mathbb{R}_+^N$ are defined as

$$\mathbb{M} := \begin{pmatrix} \arcsin\frac{a_1}{b_{11}} & \dots & \arcsin\frac{a_1}{b_{N1}} \\ \vdots & \ddots & \vdots \\ \arcsin\frac{a_N}{b_{1N}} & \dots & \arcsin\frac{a_N}{b_{NN}} \end{pmatrix}, \quad \mathbf{a} := \begin{pmatrix} a_1 \\ \vdots \\ a_N \end{pmatrix}, \quad \mathbf{Q} := \begin{pmatrix} Q_1 \\ \vdots \\ Q_N \end{pmatrix}. \tag{3.35}$$

Since (3.30) always has a solution, $\mathbf{Q}$ exists as a solution to (3.34). By (2.28), the electrostatic capacity of the cluster $\partial\Omega_d$ is given by

$$C(\partial\Omega_d) = \frac{1}{4\pi}\sum_{j=1}^{N} Q_j. \tag{3.36}$$

Keep in mind that $\mathbb{M}$ generally depends on the radii $a_1, .., a_N$ and centers $\mathbf{x}_1, .., \mathbf{x}_N$ through (3.32). Also note that by the maximum/minimum principle of harmonic functions and the boundary conditions (3.30), the potential U only takes on values within the interval $[0, 1]$. Since $U|_{\partial\Omega_d^j} = 1\ \forall j$, one concludes that $\partial_{\mathbf{n}} U|_{\partial\Omega_d^j} \geq 0$, i.e., the surface charge densities η_j are indeed all non-negative, as assumed in (3.32). Note that this conclusion critically depends on the fact that all disks share the same, non-negative potential. As the charges Q_j are non-negative, (3.36) can be written as

$$C(\partial\Omega_d) = \frac{1}{4\pi}\left\|\mathbf{Q}\right\|_{L^1}, \tag{3.37}$$

where $\|\cdot\|_{L^1}$ denotes the L^1-norm in $\mathbb{R}^N$. From (3.34) one can estimate

$$\left\|\mathbf{Q}\right\|_{L^1} \geq \frac{4\pi\left\|\mathbf{a}\right\|_{L^1}}{\|\mathbb{M}\|}, \tag{3.38}$$

where $\|\mathbb{M}\|$ is the operator norm induced by $\|\cdot\|_{L^1}$. Recall that

$$\|\mathbb{M}\| = \max_{1\leq j\leq N}\sum_{k=1}^{N}|M_{kj}|. \tag{3.39}$$

Denote by $l_{jk} := |\mathbf{x}_k - \mathbf{x}_j|$ the center-to-center distances between disks. Then by (3.33) one can estimate

$$|M_{kj}| \leq \arcsin\frac{a_k}{l_{jk} - a_j}, \quad j \neq k. \tag{3.40}$$

Combining (3.37), (3.38), (3.39) and (3.40), one finally obtains the lower bound

$$C(\partial\Omega_d) \geq \frac{\sum_{j=1}^{N} a_j}{\frac{\pi}{2} + \max\limits_{1\leq j\leq N}\sum\limits_{k\neq j}\arcsin\frac{a_k}{l_{jk} - a_j}}. \tag{3.41}$$

For a similar upper bound, one has to consider the inverse $\mathbb{M}^{-1}$. I shall do so for the simple case of 3 equally sized disks of radius a, located on $\partial\mathbb{R}_*^3$ so that all three center-to-center distances are equal to $l > 2a$ (see figure 3.1). Then by permutation symmetry, all three surface charge densities η_j are equal, modulo a suitable rotation of 120° or 240°. Therefore (3.32) gives the same $b_{jk} =: b$ for all $j \neq k$. The matrix $\mathbb{M}$ thus takes the form

$$\mathbb{M} = \frac{\pi}{2}\begin{pmatrix} 1 & \varkappa & \varkappa \\ \varkappa & 1 & \varkappa \\ \varkappa & \varkappa & 1 \end{pmatrix}, \tag{3.42}$$

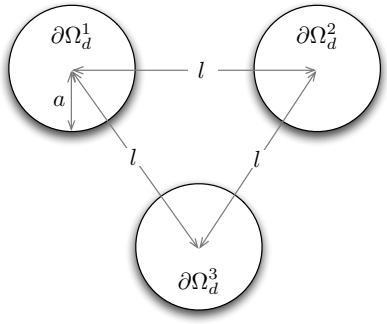

Figure 3.1: On estimating the electrostatic capacity of a three-disk cluster.

where I abbreviate $\varkappa := \frac{2}{\pi}\arcsin\frac{a}{b}$. One then easily finds $Q_j = \frac{8a}{1+2\varkappa}$ $\forall j$ and finally, using (3.37),

$$C(\partial\Omega_d) = \frac{6a}{\pi(1+2\varkappa)}. \tag{3.43}$$

Note that $C(\partial\Omega_d^j) = 2a/\pi$ is the electrostatic capacity of any one of the individual disks $\partial\Omega_d^j$, as demonstrated in section 3.2. Result (3.43) shows that the compound capacity $C(\partial\Omega_d)$ of the three disks is strictly less than the sum of their individual capacities. Using (3.33) and (3.43), one can estimate

$$\frac{6a}{\pi + 4\arcsin\frac{a}{l-a}} \le C(\partial\Omega_d) \le \frac{6a}{\pi + 4\arcsin\frac{a}{l+a}}. \tag{3.44}$$

As expected, $C(\partial\Omega_d) \sim 6a/\pi = \sum_{j=1}^3 C(\partial\Omega_d^j)$ as $l \gg a$, while in the extreme case of adjacent disks ($l = 2a$), (3.44) gives

$$\frac{2a}{\pi} \le C(\partial\Omega_d) < \frac{2a}{\pi}\cdot 2.094. \tag{3.45}$$

Hence, clustering the disks together reduces their joint capacity by somewhere between 30% and 67%, compared to the case where they are well separated.

As shown by Cheviakov et al. [2010, §2.2], the MET of a Brownian particle from the unit ball through N small windows on its boundary, is asymptotically $\tau \sim 2\pi\left[3D\varepsilon(C_1 + .. + C_N)\right]^{-1}$ as $\varepsilon \to 0^+$. Here, $C_1, .., C_N$ are the electrostatic capacities of the windows in the inner coordinates. In particular, in the case of three well-separated circular windows of radius $\varepsilon \ll 1$, one has $C_j = 2/\pi$ and thus $\tau \sim \pi^2/(9D\varepsilon)$. On the other hand, when the three windows are clustered together with a center-to-center distance $l = l_o\varepsilon$ ($l_o \ge 2$), one is effectively left with a single window in the shape of a three-disk cluster with capacity $C = 6\left[\pi(1+2\varkappa)\right]^{-1}$, where $\varkappa = \frac{2}{\pi}\arcsin\frac{1}{b}$ and b is between $l_o{-}1$ and $l_o{+}1$. Hence, $\tau \sim (1{+}2\varkappa)\cdot\pi^2/(9D\varepsilon)$. This suggests that window clustering, while preserving the total window area, can significantly increase the MET. Similar effects have been found by Holcman and Schuss [2008].

4 Some applications of the narrow escape theory

This section demonstrates three recent applications of the narrow escape theory to statistical mechanical and biophysical problems: (1), the relaxation rate of two connected gas chambers to thermodynamic equilibrium, (2), enzymatic reaction rates in microdomains and (3), calcium ion diffusion rates in dendritic spines.

4.1 Equilibration of two chambers connected through a narrow aperture

A ubiquitous problem in physical chemistry and physiology, is determining the relaxation dynamics of gas or fluid chambers connected through a network of thin capillaries [Perkins and Johnston, 1963; Burganos, 1993; Karlsson et al., 2005]. In case of diffusing Brownian particles, the relaxation time of the system is connected to the mean first passage times to the capillary aperture in the different chambers, as shall be illustrated in the following simple example [Dagdug et al., 2003]. I consider two chambers of volumes $V_1, V_2 \subseteq \mathbb{R}^3$ with smooth boundary, separated by an impermeable membrane with a narrow circular

aperture of radius $\varepsilon > 0$. Note that in this simple case, the capillary length is zero. For sufficiently small ε, the relaxation rate to equilibrium particle distribution is typically limited by the bottleneck imposed by the low flux through the aperture. One is thus often interested in the number of particles N_1, N_2 in the two chambers (with $N := N_1 + N_2$ fixed), and the rate at which these reach their equilibrium distribution. Grigoriev et al. [2002] have shown that individual particles approach the aperture from within chamber $i \in \{1, 2\}$ in exponentially distributed time at a rate $k_i \sim 4\varepsilon D/V_i$, at least in the limit $\varepsilon \to 0$. This rate is independent of their start position when the latter is not to close to the aperture (cf. section 1.7).

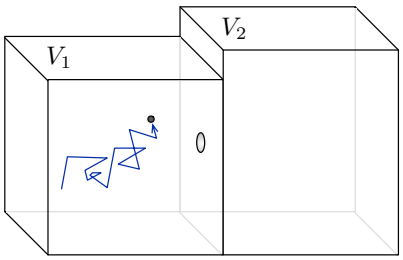

Figure 4.1: Two gas chambers connected through a small aperture: Particles follow independent Brownian trajectories and occasionally switch chambers.

It should be mentioned that a common implicit assumption at this point, is that of non-interacting and independently diffusing particles. In reality of course, it is their very interaction and collisions that generate their Brownian-like motion [Roy, 2001]. The assumption of independent particle trajectories is indeed an old standing issue in statistical mechanics and goes by names such as the *propagation of molecular chaos* [Hollinger, 1962; Dawson, 1983; Acebrón et al., 2005]. It becomes explicit in the derivation of evolution equations for the one-particle densities in kinetic gas theory, when particle correlations are ignored in the so called BBGKY hierarchy for the n-particle densities [Wilmanski, 2008, §7.2].

For $N \gg 1$, particles reach the aperture from chamber i at a rate $N_i(t) \cdot k_i$. Once at the aperture, they may end up in the interior of either chamber with probability $1/2$, while the time scales associated with this transition are negligible compared to the longer time scale $1/k_i$. Hence, in the deterministic limit and for $\varepsilon \ll \operatorname{diam} V_i$,

$$\dot{N}_1(t) \approx -\frac{k_1}{2} N_1(t) + \frac{k_2}{2} N_2(t), \tag{4.1}$$

where conservation of particles means $N_2 = N - N_1$. It is straightforward to see that (4.1) has the solution

$$N_i(t) \approx N_i^{\mathrm{eq}} + \exp\left[-2tDr \cdot \left(\frac{1}{V_1} + \frac{1}{V_2}\right)\right] \cdot \left[N_i(0) - N_i^{\mathrm{eq}}\right], \quad t \geq 0,\ i = 1, 2, \tag{4.2}$$

where $N_i^{\mathrm{eq}} := NV_i/(V_1 + V_2)$ are the equilibrium particle counts in the two chambers. Thus, in the limit $\varepsilon \to 0^+$, relaxation proceeds exponentially with a time constant scaling as $\mathcal{O}(1/\varepsilon)$.

4.2 Michaelis-Menten kinetics in microdomains

A potential application of narrow escape time theory is to chemical reaction rates in microdomains, when only a low number of substrates or enzymes is involved. I shall adopt the formalism introduced by Holcman and Schuss [2005] and Schuss et al. [2007] for microdomain chemical kinetics, to derive a formula for the stationary enzymatic reaction rate in a reflecting microdomain Ω. I assume the domain to contain a low but constant concentration of substrate and enzyme molecules. This is often a reasonable assumption for biological microdomains (e.g. cell organelles) with semipermeable membranes, submerged into a constant solution. My results reproduce the known Michaelis-Menten formula for enzymatic kinetics [Michaelis and Menten, 1913].

I assume that each of the $S \in \mathbb{N}$ substrate molecules moves within Ω in a Brownian manner without drift. I assume that each of the $E \in \mathbb{N}$ enzymes defines a small, static sub-domain Ω_o, upon the entrance of which a substrate molecule is captured and forms an enzyme-substrate complex. Such a complex either releases a target product(s) at rate $\nu > 0$ or the original, untransformed substrate at a backward rate $\mu > 0$. See figure 4.2 for a supporting illustration. The scaling parameter shall be the electrostatic

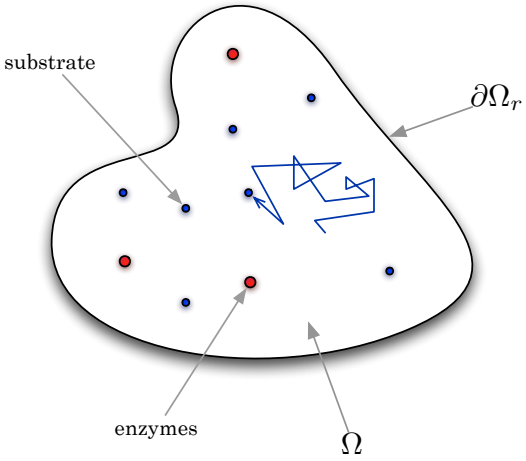

Figure 4.2: On enzymatic kinetics in microdomains.

capacity $\varepsilon > 0$ of the enzyme's capture domain Ω_o, defined in 2.2, while I assume that enzyme molecules are well separated. Recall that for a spherical Ω_o, ε is equal to its radius.

If $p_k(t)$ denotes the probability of k enzyme-substrate complexes being present at time t, then the target production rate is $V(t) = \nu \sum_{k=1}^{E} k p_k(t)$. The expected first passage time of a substrate molecule to one of n available enzyme sites, can be shown to scale asymptotically as

$$\tau \sim \frac{|\Omega|}{4\pi n D \varepsilon}, \quad \text{as } \varepsilon \to 0^+, \tag{4.3}$$

as long as the particle does not start in the proximity of any of the enzymes [Cheviakov and Ward, 2011, §3.1]. Note that in this approximation, τ is independent of the enzyme positions. Based on the above postulates, it is straightforward to find a master equation for the probability distribution $\{p_k(t)\}_{k=0}^{E}$, namely

$$\begin{aligned}
&\dot{p}_k(t) = S\varkappa\varepsilon(E-k+1)\cdot p_{k-1}(t) + (k+1)\mu \cdot p_{k+1}(t) - [S\varkappa\varepsilon(E-k) + k\mu]\cdot p_k(t), \quad 1 \le k < E,\\
&\dot{p}_0(t) = \mu \cdot p_1(t) - S\varkappa\varepsilon E \cdot p_0(t),\\
&\dot{p}_E(t) = S\varkappa\varepsilon \cdot p_{E-1}(t) - E\mu \cdot p_E(t),
\end{aligned} \tag{4.4}$$

where $\varkappa := 4\pi D/|\Omega|$. The stationary distribution $\{\overline{p}_k\}_{k=0}^{E}$ is then determined by the algebraic system

$$\begin{aligned}
&\overline{p}_1 = \frac{\varkappa}{\mu} SE\varepsilon \cdot \overline{p}_0,\\
&\overline{p}_{k+1} = \frac{1}{(k+1)\mu}\Big[[S\varkappa\varepsilon(E-k) + k\mu]\cdot \overline{p}_k - S\varkappa\varepsilon(E-k+1)\cdot \overline{p}_{k-1}\Big], \quad 1 \le k < E,\\
&\overline{p}_E = \frac{S\varkappa\varepsilon}{E\mu}\cdot \overline{p}_{E-1}.
\end{aligned} \tag{4.5}$$

Using the first two equations in (4.5), one finds by mathematical induction that

$$\overline{p}_n = \left(\frac{S\varkappa\varepsilon}{\mu}\right)^n \cdot \binom{E}{n} \cdot \overline{p}_0, \quad n = 0, .., E. \tag{4.6}$$

Notice that (4.6) also satisfies the 3rd equation in (4.5). The condition $\sum_{k=0}^{E} \overline{p}_k = 1$ determines $\overline{p}_0$ as

$$\overline{p}_0 = \left(1 + \frac{S\varkappa\varepsilon}{\mu}\right)^{-E}, \tag{4.7}$$

where I used the binomial theorem $(x+1)^E = \sum_{n=0}^{E} \binom{E}{n} x^n$. Using (4.6) with (4.7), one finds the expected stationary production rate to be

$$\overline{V} = \nu \left(1 + \frac{S\varkappa\varepsilon}{\mu}\right)^{-E} \sum_{n=0}^{E} \binom{E}{n} n \left(\frac{S\varkappa\varepsilon}{\mu}\right)^n = \frac{\nu E \cdot S}{\frac{\mu}{\varkappa\varepsilon} + S}, \tag{4.8}$$

whereas I used the fact that

$$Ex(1+x)^{E-1} = x\frac{d}{dx}(1+x)^E = \sum_{n=0}^{E}\binom{E}{n}nx^n. \tag{4.9}$$

One thus retrieves the famous Michaelis-Menten formula for the equilibrium production rate

$$\overline{V} = \frac{\nu E \cdot S}{\frac{\mu|\Omega|}{4\pi D\varepsilon} + S}, \tag{4.10}$$

at least asymptotically as $\varepsilon \to 0^+$. Notice how the half-saturation constant depends on the enzyme's shape and size through its capacity ε, as well as on the domain volume $|\Omega|$. For low concentrations $S \approx 0$ or small $\varepsilon \approx 0$, $\overline{V}$ is approximately $\frac{4\pi D\varepsilon}{\Omega} \cdot \frac{\nu}{\mu} \cdot ES$, that is, given by a mass action law. On the other hand, for $S \to \infty$, $\overline{V} \approx \nu E$ only depends on the enzyme's concentration.

4.3 Calcium diffusion in dendritic spines

Dendritic spines are protrusions from neuronal dendrites, consisting of a more or less bulbous spine head and a small, narrow neck connecting the head to the parent dendrite (see figure 4.3). They receive excitatory input from axons connected to the spine head [Yuste and Bonhoeffer, 2004], and their synaptic plasticity is believed to play a fundamental role in learning and memory processes [Segal, 2005]. Recent research has tried to describe the electrophysiology of spines and in particular calcium ion dynamics using a Langevin description of their microscopic motion [Berry et al., 2000; Holcman et al., 2004; Schuss et al., 2007], providing an alternative to the historical cable-theory approach [Koch and Poggio, 1983].

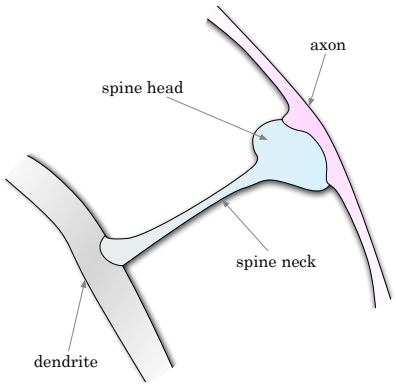

Figure 4.3: Illustration of a dendritic spine, connecting a neuron's dendrite to a nearby axon.

I give here a simple example of how the narrow escape theory can be used to estimate the rate of Calcium ion traversal from the spine head to the parent dendrite [Schuss et al., 2007]. I approximate the spine neck $\mathcal{N}$ by a narrow cylinder of constant radius ε and length L. The spine head is modeled by a domain Ω with reflective boundary everywhere, except for a narrow aperture connecting it to the neck. Upon the entrance of the neck, a calcium ion cannot return to the head. Calcium ions follow a purely Brownian motion with constant diffusion coefficient D and no drift. This approximation ignores any alternative ion pathways and potential barriers present in real spines [Segal, 2005]. I take $D = k_B T/(m\gamma)$, where T is the interior spine temperature, m is the reduced ion mass and γ is the dynamical viscosity [Holcman et al., 2004].

The mean time τ a calcium ion will spend in the spine, can be decomposed into the mean first passage time τ_{h} from within the spine head to the small absorbing neck aperture, and the expected time τ_{n} it takes to traverse the spine neck and reach the dendritic shaft. By Grigoriev et al. [2002], asymptotically $\tau_{\mathrm{h}} \sim |\Omega|/(4\varepsilon D)$ as $\varepsilon \to 0$. For τ_{n}, I shall consider the transition probability $p(t, \mathbf{x})$ from the neck entrance to any other point $\mathbf{x} \in \mathcal{N}$ within the neck at time t, introduced in 1.2. It satisfies the boundary value

problem [Schuss, 1980]

$$\begin{aligned} &\partial_t p(t,\mathbf{x}) = D\Delta p(t,\mathbf{x}), \\ &p(t,\mathbf{x}) = 0, \quad \mathbf{x}\in\partial\mathcal{N}_a, \quad \partial_{\mathbf{n}} p(t,\mathbf{x}) = 0, \quad \mathbf{x}\in\partial\mathcal{N}_r, \end{aligned} \tag{4.11}$$

where $\partial\mathcal{N}_a$ is the aperture connecting the spine neck to the dendrite and $\partial\mathcal{N}_r = \partial\mathcal{N}\backslash\partial\mathcal{N}_a$ is the remaining, reflecting neck boundary. I introduce cylindrical coordinates (ρ,φ,z), such that z is along the neck's long axis. See figure 4.4 for a supporting illustration.

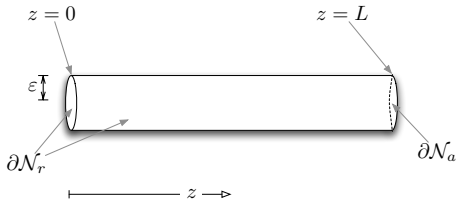

Figure 4.4: On the derivation of the mean traversal time τ_{n} of a cylindrical spine neck.

I introduce the (non-normalized) *cross-section average*

$$\overline{p}(t,z) := \int_0^{2\pi}\int_0^{\varepsilon} \rho\cdot p(t,\rho,\varphi,z)\; d\rho\; d\varphi \tag{4.12}$$

at time t and distance z from the spine neck entrance. Inserting (4.12) into the PDE (4.11) yields

$$\begin{aligned} \partial_t\overline{p}(t,z) =& D\int_0^{2\pi}\int_0^{\varepsilon} \rho\cdot\Delta p(t,\rho,\varphi,z)\; d\rho\; d\varphi \\ =& D\int_0^{2\pi}\int_0^{\varepsilon} \partial_\rho\left(\rho\partial_\rho p\right)\; d\rho\; d\varphi + D\int_0^{\varepsilon}\frac{1}{\rho}\underbrace{\int_0^{2\pi}\partial_\varphi^2 p\; d\varphi}_{0}\; d\rho + D\int_0^{2\pi}\int_0^{\varepsilon}\rho\partial_z^2 p\; d\rho\; d\varphi \\ =& D\int_0^{2\pi}\varepsilon\underbrace{\partial_\rho p\big|_{\rho=\varepsilon}}_{0}\; d\varphi + D\int_0^{2\pi}\int_0^{\varepsilon}\rho\partial_z^2 p\; d\rho\; d\varphi \\ =& D\cdot\partial_z^2\overline{p}(t,z). \end{aligned} \tag{4.13}$$

It is also clear that the boundary conditions (4.11) imply the boundary conditions

$$\overline{p}(t,L) = 0, \quad \partial_z\overline{p}(t,0) = 0. \tag{4.14}$$

Inserting (4.12) into (1.4), shows that the mean traversal time, starting anywhere on the neck's entrance, is given by

$$\tau_{\mathrm{n}} = \int_0^{\infty}\int_0^{L}\overline{p}(t,z)\; dz\; dt. \tag{4.15}$$

Hence, the calculation of τ_{n} reduces to solving the one-dimensional mean escape time problem (1.14), that is

$$\begin{aligned} &D\partial_z^2 u(z) = -1, \quad z\in[0,L], \\ &u(L) = 0, \quad \partial_z u(0) = 0. \end{aligned} \tag{4.16}$$

It is easy to see that (4.16) has solution $u(z) = (L^2 - z^2)/(2D)$, so that $\tau_{\mathrm{n}} = u(0) = L^2/(2D)$. One concludes that the mean escape time of a Calcium ion from the spine head to the dendrite, is given by

$$\tau \sim \frac{m\gamma}{2k_B T}\cdot\left[\frac{|\Omega|}{2\varepsilon} + L^2\right], \tag{4.17}$$

at least asymptotically as $\varepsilon\to 0$.

References

Abramowitz, M., Stegun, I., 1964. Handbook of Mathematical Functions. Applied mathematics series, Dover Publications.

Acebrón, J.A., Bonilla, L.L., Vicente, C.J.P., Ritort, F., Spigler, R., 2005. *The Kuramoto model: A simple paradigm for synchronization phenomena.* Rev. Mod. Phys. 77, 137–185.

Apple Inc., 2011. *Random, part of bsd libc.* Standard C Library, Darwin 10.8.0.

Berry, R., Rice, S., Ross, J., 2000. Physical Chemistry. Topics in Physical Chemistry Series, Oxford University Press.

Burganos, V.N., 1993. *Monte carlo simulation of gas diffusion in regular and randomized pore systems.* The Journal of chemical physics 98, 2268.

Cheviakov, A., Ward, M., 2011. *Optimizing the principal eigenvalue of the laplacian in a sphere with interior traps.* Mathematical and Computer Modelling 53, 1394–1409.

Cheviakov, A., Ward, M., Straube, R., 2010. *An asymptotic analysis of the mean first passage time for narrow escape problems: Part II: The sphere.* Multiscale Modeling & Simulation 8, 836–870.

Coombs, D., Straube, R., Ward, M., 2009. *Diffusion on a sphere with localized traps: Mean first passage time, eigenvalue asymptotics, and fekete points.* SIAM Journal on Applied Mathematics 70, 302–332.

Courant, R., Hilbert, D., 1966. Methods of mathematical physics. Number v. 1 in Methods of Mathematical Physics, Interscience Publ.

Dagdug, L., Berezhkovskii, A.M., Shvartsman, S.Y., Weiss, G.H., 2003. *Equilibration in two chambers connected by a capillary.* The Journal of chemical physics 119, 12473.

Dawson, D.A., 1983. *Critical dynamics and fluctuations for a mean-field model of cooperative behavior.* J. Stat. Phys. 31, 29–85.

Evans, L., 2010. Partial Differential Equations. Graduate Studies in Mathematics, American Mathematical Society. 2 edition.

Fabrikant, V., 1988. *Potential of several arbitrarily located disks.* J. Austral. Math. Soc. Ser. B 29, 342–351.

Fabrikant, V., 1989. Applications of potential theory in mechanics: a selection of new results. Mathematics and its applications, Kluwer Academic Publishers.

Frank, T., 2005. Nonlinear Fokker-Planck Equations: Fundamentals and Applications. Springer, New York. 2 edition.

Gentle, J., 2003. Random Number Generation and Monte Carlo Methods. Statistics and Computing, Springer.

Glasserman, P., 2003. Monte Carlo Methods in Financial Engineering. Applications of Mathematics Series, Springer.

Graham, R.L., Knuth, D.E., Patashnik, O., 1994. Concrete Mathematics. Addison-Wesley. 2 edition.

Grigoriev, I.V., Makhnovskii, Y.A., Berezhkovskii, A.M., Zitserman, V.Y., 2002. *Kinetics of escape through a small hole.* The Journal of chemical physics 116, 9574.

Holcman, D., Schuss, Z., 2004. *Escape through a small opening: receptor trafficking in a synaptic membrane.* Journal of statistical physics 117, 975–1014.

Holcman, D., Schuss, Z., 2005. *Stochastic chemical reactions in microdomains.* Journal of Chemical Physics 122, 114710.

Holcman, D., Schuss, Z., 2008. *Diffusion escape through a cluster of small absorbing windows.* Journal of Physics A: Mathematical and Theoretical 41, 155001.

Holcman, D., Schuss, Z., Korkotian, E., 2004. *Calcium dynamics in dendritic spines and spine motility.* Biophysical journal 87, 81–91.

Hollinger, H., 1962. *Molecular chaos and the boltzmann equation.* J. Chem. Phys. 36, 3208.

Jackson, J.D., 1998. Classical Electrodynamics. Wiley. 3rd edition.

Karlsson, A., Sott, K., Markström, M., Davidson, M., Konkoli, Z., Orwar, O., 2005. *Controlled initiation of enzymatic reactions in micrometer-sized biomimetic compartments.* The Journal of Physical Chemistry B 109, 1609–1617.

Kellogg, O., 1929. Foundations of Potential Theory. Dover books on physics and chemistry, Dover.

Koch, C., Poggio, T., 1983. *A theoretical analysis of electrical properties of spines.* Proceedings of the Royal Society of London. Series B. Biological Sciences 218, 455–477.

Kroese, D., Taimre, T., Botev, Z., 2011. Handbook of Monte Carlo Methods. Wiley Series in Probability and Statistics, Wiley.

Michaelis, L., Menten, M.L., 1913. *Die Kinetik der Invertinwirkung.* Biochem. z 49, 352.

Ozawa, S., 1983. *Electrostatic capacity and eigenvalues of the laplacian.* J. Fac. Sci. Univ. Tokyo 30, 2.

Perkins, T., Johnston, O., 1963. *A review of diffusion and dispersion in porous media*. SPE Journal 3, 70–84.

Popov, I.Y., 1992. *Extension theory and localization of resonances for domains of trap type.* Mathematics of the USSR-Sbornik 71, 209.

Pozrikidis, C., 2011. Introduction to Theoretical and Computational Fluid Dynamics. OUP USA.

Rayleigh, J.W.S.B., 1945. The Theory of Sound. Dover, New York. 2 edition.

Roy, S., 2001. Thermal Physics And Statistical Mechanics. Basic physics through problems series, New Age International.

Sakurai, T., 1982. *Green's function methods for potential magnetic fields.* Solar Physics 76, 301–321.

Schmidt, H.U., 1964. *On the observable effects of magnetic energy storage and release connected with solar flares*, in: Hess, W.N. (Ed.), Aas-nasa symposium on the physics of solar flares, NASA-SP-50, pp. 107–114.

Schuss, Z., 1980. Theory and applications of stochastic differential equations. Wiley Series in Probability and Statistics - Applied Probability and Statistics Section, Wiley.

Schuss, Z., Singer, A., Holcman, D., 2007. *The narrow escape problem for diffusion in cellular microdomains.* Proceedings of the National Academy of Sciences 104, 16098–16103.

Segal, M., 2005. *Dendritic spines and long-term plasticity.* Nature Reviews Neuroscience 6, 277–284.

Silbergleit, A., Mandel, I., Nemenman, I., 2003. *Potential and field singularity at a surface point charge.* Journal of Mathematical Physics 44, 4460–4466.

Singer, A., Schuss, Z., 2006. *Activation through a narrow opening*. Physical Review E 74, 020103.

Singer, A., Schuss, Z., Holcman, D., 2008. *Narrow escape and leakage of brownian particles*. Physical Review E 78, 051111.

Singer, A., Schuss, Z., Holcman, D., Eisenberg, R., 2006. *Narrow escape, Part I*. Journal of Statistical Physics 122, 437–463.

Swanson, C., 1963. *Asymptotic variational formulae for eigenvalues.* Canad. Math. Bull 6, 15–25.

Szegö, G., 1930. *Über einige Extremalaufgaben der Potentialtheorie.* Mathematische Zeitschrift 31, 583–593.

Ward, M., Heshaw, W., Keller, J., 1993. *Summing logarithmic expansions for singularly perturbed eigenvalue problems.* SIAM Journal on Applied Mathematics 53, 799–828.

Ward, M.J., Keller, J.B., 1993. *Strong localized perturbations of eigenvalue problems.* SIAM Journal on Applied Mathematics 53, 770–798.

Weber, H., 1873. *Ueber die besselschen functionen und ihre anwendung auf die theorie der elektrischen ströme.* Journal für die reine und angewandte Mathematik 75, 75–105.

Wilmanski, K., 2008. Continuum Thermodynamics: Foundations. Series on Advances in Mathematics for Applied Sciences, World Scientific.

Wolfram Research, I., 2010. Mathematica. Wolfram Research, Inc., Champaign, Illinois. version 8.0 edition.

Yuste, R., Bonhoeffer, T., 2004. *Genesis of dendritic spines: insights from ultrastructural and imaging studies.* Nature Reviews Neuroscience 5, 24–34.