Abstract

A Brownian particle with diffusion coefficient $D$ is confined to a bounded domain of volume $V$ in $\mathbb{R}^3$ by a reflecting boundary, except for a small absorbing window. The mean time to absorption diverges as the window shrinks, thus rendering the calculation of the mean escape time a singular perturbation problem. We construct an asymptotic approximation for the case of an elliptical window of large semi axis $a \ll V^{1/3}$ and show that the mean escape time is $E\tau \sim \frac{V}{2\pi Da} K(e)$, where $e$ is the eccentricity of the ellipse; and $K(\cdot)$ is the complete elliptic integral of the first kind. In the special case of a circular hole the result reduces to Lord Rayleigh’s formula $E\tau \sim \frac{V}{4aD}$, which was derived by heuristic considerations. For the special case of a spherical domain, we obtain the asymptotic expansion $E\tau = \frac{V}{4aD} \left[ 1 + \frac{a}{R} \log \frac{R}{a} + O \left( \frac{a}{R} \right) \right]$. This problem is important in understanding the flow of ions in and out of narrow valves that control a wide range of biological and technological function.

1 Introduction

We consider the exit problem of a Brownian motion from a bounded domain, whose boundary is reflecting, except for a small absorbing window. The mean
first passage time to the absorbing window (MFPT), \( E\tau \), is the solution of a mixed Neumann-Dirichlet boundary value problem (BVP) for the Poisson equation, known as the corner problem, which has singularity at the boundary of the hole \([1]-[3]\). The MFPT grows to infinity as the window size shrinks to zero, thus rendering its calculation a singular perturbation problem for the mixed BVP, which we call the narrow escape problem. The narrow escape problem has been considered in the literature in only a few special cases, beginning with Lord Rayleigh (in the context of acoustics), who found the flux through a small hole by using a result of Helmholtz \([6]\). He stated \([7]\) (p.176) “Among different kinds of channels an important place must be assigned to those consisting of simple apertures in unlimited plane walls of infinitesimal thickness. In practical applications it is sufficient that a wall be very thin in proportion to the dimensions of the aperture, and approximately plane within a distance from aperture large in proportion to the same quantity.” More recently, Rayleigh’s result was shown to fit the MFPT obtained from Brownian dynamics simulations \([8]\). Another result was presented in \([9]\), where a two-dimensional narrow escape problem was considered and whose method is generalized here. A related problem is that of escape from a domain, whose boundary is reflecting, except for an absorbing sphere, disjoint from the reflecting part of the boundary \([11, and references therein]\). It differs from the narrow escape problem in that there is no singularity at the boundary and there is no boundary layer. The mixed boundary value problems of classical electrostatics (e.g., the electrified disk problem \([12]\)), elasticity (punch problems), diffusion and conductance theory, hydrodynamics, and acoustics were solved, by and large, for special geometries by separation of variables. In axially symmetric geometries this method leads to a dual series or to integral equations that can be solved by special techniques \([13]-[17]\). The special case of asymptotic representation of the solution of the corner problem for small Dirichlet and large Neumann boundaries was not done for general domains. The first attempt in this direction seems to be \([9]\). The narrow escape problem does not seem to fall within the theory of large deviations \([18]\). It is different from Kolmogorov’s exit problem \([19]\) of a diffusion process with small noise from an attractor of the drift (e.g., a stable equilibrium or limit cycle) in that the narrow escape problem has no large and small coefficients in the equation. The singularity of Kolmogorov’s problem is the degeneration of a second order elliptic operator into a first order operator in the limit of small noise, whereas the singularity of the narrow escape problem is the degeneration of the mixed BVP to a Neumann BVP on the entire boundary. There exist precise asymptotic expansions of \( E\tau \) for Kolmogorov’s exit problem, including error estimates (see, e.g., \([4], [5]\)), which show that the MFPT grows exponentially with decreasing noise. In contrast, the narrow escape time grows algebraically rather than exponentially, as the window shrinks. Our first main result is a derivation of the leading order term in the expansion of the MFPT of a Brownian particle with diffusion.
coefficient $D$, from a general domain of volume $V$ to an elliptical hole of large semi axis $a$ that is much smaller than $V^{1/3}$,

$$E\tau \sim \frac{V}{2\pi Da} K(e),$$

(1.1)

where $e$ is the eccentricity of the ellipse, and $K(\cdot)$ is the complete elliptic integral of the first kind. In the special case of a circular hole (1.1) reduces to

$$E\tau \sim \frac{V}{4aD}.$$  

(1.2)

Equation (1.1) shows that the MFPT depends on the shape of the hole, and not just on its area. This result was known to Lord Rayleigh [7], who considered the problem of the electrified disk (which he knew was equivalent to finding the flow of an incompressible fluid through a channel and to the problem of finding the conductance of the channel), who reduced the problem to that of solving an integral equation for the flux density through the hole. The solution of the integral equation, which goes back to Helmholtz [6] and is discussed in [10], is proportional to $(a^2 - \rho^2)^{-1/2}$ in the circular case, where $\rho$ is the distance from the center of the hole [12]-[14]. Note that equations (1.1) and (1.2) are leading order approximations and do not contain an error estimate. We prove (1.1) by using the singularity properties of Neumann’s function for three-dimensional domains, in a manner similar to that used in [9] for two-dimensional problems. The leading order term is the solution of Helmholtz’s integral equation [6].

Our second main result is a derivation of the second term and error estimate for a ball of radius $R$ with a small circular hole of radius $a$ in the boundary,

$$E\tau = \frac{V}{4aD} \left[ 1 + \frac{a}{R} \log \frac{R}{a} + O\left(\frac{a}{R}\right) \right].$$

(1.3)

Equation (1.3) contains both the second term in the asymptotic expansion of the MFPT and an error estimate. We use Collins’ method [20, 21] of solving dual series of equations and expand the resulting solutions for small $\varepsilon = a/R$. The estimate of the error term, which turns out to be $O(\varepsilon \log \varepsilon)$, seems to be a new result. An error estimate for eq. (1.1) for a general domain is still an open problem. We conjecture that it is $O(\varepsilon \log \varepsilon)$, as is the case for the ball. If the absorbing window touches a singular point of the boundary, such as a corner or cusp, the singularity of the Neumann function changes and so do the asymptotic results. In three dimensions the class of isolated singularities of the boundary is much richer than in the plane, so the methods of [22] cannot be generalized in a straightforward manner to three dimensions. We postpone the investigation of the MFPT to windows at isolated singular points in three dimensions to a future paper. In Section 2 we derive a leading order approximation to the MFPT for a general domain with a general small window.
The leading order term is expressed in terms of a solution to Helmholtz’s integral equation, which is solved explicitly for an elliptical window. In Section 3 we obtain two terms in the asymptotic expansion of the MFPT from a ball with a circular window and an error estimate. Finally, we present a summary and list some applications in Section 4. This is the first paper in a series of three, the second of which considers the narrow escape problem from a bounded simply connected planar domain, and the third of which considers the narrow escape problem from a bounded domain with boundary with corners and cusps on a two-dimensional Riemannian manifold.

2 General 3D bounded domain

A Brownian particle diffuses freely in a bounded domain $\Omega \subset \mathbb{R}^3$, whose boundary $\partial \Omega$ is sufficiently smooth. The trajectory of the Brownian particle, denoted $x(t)$, is reflected at the boundary, except for a small hole $\partial \Omega_a$, where it is absorbed. The reflecting part of the boundary is $\partial \Omega_r = \partial \Omega - \partial \Omega_a$. The lifetime of the particle in $\Omega$ is the first passage time $\tau$ of the Brownian particle from any point $x \in \Omega$ to the absorbing boundary $\partial \Omega_a$. The MFPT, $v(x) = E[\tau | x(0) = x]$, is finite under quite general conditions [24]. As the size (e.g., the diameter) of the absorbing hole decreases to zero, but that of the domain remains finite, we assume that the MFPT increases indefinitely. A measure of smallness can be chosen as the ratio between the surface area of the absorbing boundary and that of the entire boundary, $\varepsilon = \frac{|\partial \Omega_a|}{|\partial \Omega|} \ll 1$, (see, however, a pathological example in Appendix C). The MFPT $v(x)$ satisfies the mixed boundary value problem [24]

$$\Delta v(x) = -\frac{1}{D}, \quad \text{for} \quad x \in \Omega, \quad (2.1)$$

$$v(x) = 0, \quad \text{for} \quad x \in \partial \Omega_a, \quad (2.2)$$

$$\frac{\partial v(x)}{\partial n(x)} = 0, \quad \text{for} \quad x \in \partial \Omega_r,$$

where $D$ is the diffusion coefficient. According to our assumptions $v(x) \to \infty$ as the size of the hole decreases to zero, e.g., as $\varepsilon \to 0$, except in a boundary layer near $\partial \Omega_a$. Our purpose is to find an asymptotic approximation to $v(x)$ in this limit.
2.1 The Neumann function and integral equations

To calculate the MFPT $v(x)$, we use the Neumann function $N(x, \xi)$ (see [9], [11]), which is a solution of the boundary value problem

$$\Delta_x N(x, \xi) = -\delta(x - \xi), \quad \text{for } x, \xi \in \Omega,$$

(2.3)

$$\frac{\partial N(x, \xi)}{\partial n(x)} = -\frac{1}{|\partial\Omega|}, \quad \text{for } x \in \partial\Omega, \xi \in \Omega,$$

and is defined up to an additive constant. The Neumann function has the form

$$N(x, \xi) = \frac{1}{4\pi|x - \xi|} + v_S(x, \xi),$$

(2.4)

where $v_S(x, \xi)$ is a regular harmonic function of $x \in \Omega$ and of $\xi \in \Omega$. Green’s identity gives

$$\int_\Omega [N(x, \xi)\Delta v(x) - v(x)\Delta N(x, \xi)] \, dx =$$

$$= \int_{\partial\Omega} \left[ N(x(S), \xi)\frac{\partial v(x(S))}{\partial n} - v(x(S))\frac{\partial N(x(S), \xi)}{\partial n} \right] \, dS$$

$$= \int_{\partial\Omega} N(x(S), \xi)\frac{\partial v(x(S))}{\partial n} \, dS + \frac{1}{|\partial\Omega|} \int_{\partial\Omega} v(x(S)) \, dS.$$

On the other hand, equations (2.1) and (2.3) imply that

$$\int_\Omega [N(x, \xi)\Delta v(x) - v(x)\Delta N(x, \xi)] \, dx = v(\xi) - \frac{1}{D} \int_\Omega N(x, \xi) \, dx,$$

hence

$$v(\xi) = \frac{1}{D} \int_\Omega N(x, \xi) \, dx +$$

$$\int_{\partial\Omega} N(x(S), \xi)\frac{\partial v(x(S))}{\partial n} \, dS + \frac{1}{|\partial\Omega|} \int_{\partial\Omega} v(x(S)) \, dS.$$

Note that the second integral on the right hand side of eq.(2.5) is an additive constant. Setting

$$C = \frac{1}{|\partial\Omega|} \int_{\partial\Omega} v(x(S)) \, dS,$$

(2.6)

we rewrite eq.(2.5) as

$$v(\xi) = \frac{1}{D} \int_\Omega N(x, \xi) \, dx + \int_{\partial\Omega} N(x(S), \xi)\frac{\partial v(x(S))}{\partial n} \, dS - C,$$

(2.7)
which is an integral representation of \( v(\xi) \). We define the boundary flux density

\[
g(S) = \frac{\partial v(x(S))}{\partial n},
\]

choose \( \xi \in \partial \Omega_a \), and use the boundary condition (2.2) to obtain the equation

\[
0 = \frac{1}{D} \int_{\Omega} N(x, \xi) \, dx + \int_{\partial \Omega_a} N(x(S), \xi) g(S) \, dS - C,
\]

for all \( \xi \in \partial \Omega_a \). Equation (2.9) is an integral equation for \( g(S) \) and \( C \). To construct an asymptotic approximation to the solution, we note that the first integral in equation (2.9) is a regular function of \( \xi \) on the boundary. Indeed, due to symmetry of the Neumann function, we have from (2.3)

\[
\Delta \xi \int_{\Omega} N(x, \xi) \, dx = -1 \quad \text{for} \quad \xi \in \Omega \tag{2.10}
\]

and

\[
\frac{\partial}{\partial n(\xi)} \int_{\Omega} N(x, \xi) \, dx = -\frac{\vert \Omega \vert}{\vert \partial \Omega \vert} \quad \text{for} \quad \xi \in \partial \Omega. \tag{2.11}
\]

Equation (2.10) and the boundary condition (2.11) are independent of the hole \( \partial \Omega_a \), so they define the integral as a regular function, up to an additive constant, also independent of \( \partial \Omega_a \). The assumption that for all \( x \in \Omega \), away from \( \partial \Omega_a \), the MFPT \( v(x) \) increases to infinity as the size of the hole decreases and eq. (2.6) imply that \( C \to \infty \) as the size of the hole decreases to zero. This means that for \( \xi \in \partial \Omega_a \) the second integral in eq. (2.9) must also become infinite in this limit, because the first integral is independent of \( \partial \Omega_a \). Therefore, the integral equation (2.9) is to leading order

\[
\int_{\partial \Omega_a} N(x(S), \xi) g_0(S) \, dS = C_0 \quad \text{for} \quad \xi \in \partial \Omega_a, \tag{2.12}
\]

where \( g_0(S) \) is the first asymptotic approximation to \( g(S) \) and \( C_0 \) is the first approximation to the constant \( C \). Furthermore, only the singular part of the Neumann function contributes to the leading order, so we obtain the integral equation

\[
\frac{1}{2\pi} \int_{\partial \Omega_a} \frac{g_0(x)}{\vert x - y \vert} \, dS_x = C_0, \tag{2.13}
\]

where \( C_0 \) is a constant, which represents the first approximation to the mean first passage time (MFPT). Note that the singularity of the Neumann function at the boundary is twice as large as it is inside the domain, due to the contribution of the regular part (the “image charge”) and therefore the factor \( \frac{1}{4\pi} \) of equation (2.4) was replaced by \( \frac{1}{2\pi} \). In general, the integral equation (2.13) has no explicit solution, and should be solved numerically.
2.2 Elliptic hole

When the hole $\partial \Omega_a$ is an ellipse, the solution of the integral equation (2.13) is known \cite{7, 16}. Specifically, assuming the ellipse is given by

$$\frac{x^2}{a^2} + \frac{y^2}{b^2} = 1, \quad z = 0, \quad (b \leq a),$$

the solution is

$$g_0(x) = \frac{\tilde{g}_0}{\sqrt{1 - \frac{x^2}{a^2} - \frac{y^2}{b^2}}}, \quad (2.14)$$

where $\tilde{g}_0$ is a constant (to be determined below). The proof, originally given in \cite{6}, is reproduced in Appendix B. To determine the value of the constant $\tilde{g}_0$, we use the compatibility condition

$$\int_{\partial \Omega_a} g_0(x) dS_x = \frac{|\Omega|}{D}, \quad (2.15)$$

obtained from the integration of eq.\,(2.11) over $\Omega$. Using the value

$$\int_{\partial \Omega_a} g_0(x) dS_x = \int_{-a}^{a} dx \int_{-b\sqrt{1 - \frac{x^2}{a^2}}}^{b\sqrt{1 - \frac{x^2}{a^2}}} \frac{\tilde{g}_0 dy}{\sqrt{1 - \frac{x^2}{a^2} - \frac{y^2}{b^2}}} = 2\pi ab\tilde{g}_0 \quad (2.16)$$

and the compatibility condition (2.15), we obtain

$$\tilde{g}_0 = \frac{|\Omega|}{2\pi Da b}. \quad (2.17)$$

Hence, by equation (B.3), the leading order approximation to $C$ is

$$C_0 = \frac{1}{2\pi} \int_{\partial \Omega_a} g_0(x) dS_x = \frac{|\Omega|}{2\pi Da} K(e), \quad (2.18)$$

where $K(\cdot)$ is the complete elliptic integral of the first kind, and $e$ is the eccentricity of the ellipse,

$$e = \sqrt{1 - \frac{b^2}{a^2}}. \quad (2.19)$$

In other words, the MFPT from a large cavity of volume $|\Omega|$ through a small elliptic hole is to leading order

$$E\tau(a, b) \sim \frac{|\Omega|}{2\pi Da} K(e). \quad (2.20)$$
For example, in the case of a circular hole, we have $e = 0$ and $K(0) = \frac{\pi}{2}$, so that

$$E\tau(a,a) \sim \frac{|\Omega|}{4Da} = O\left(\frac{1}{\varepsilon}\right),$$

(2.21)

provided

$$\frac{|\Omega|^{2/3}}{|\partial\Omega|} = O(1) \quad \text{for} \quad \varepsilon \ll 1.$$

Equation (2.21) was used in [8], [23]. If the mouth of the channel is not circular, the MFPT is different. Equation (2.21) indicates that a Brownian particle that tries to leave the domain “sees” finer details in the geometry of the hole and the domain than just the quotient of the surface areas. The additional geometric features contained in the MFPT are illustrated by the two interesting limits $e \ll 1$, where the ellipse is almost circular, and $1 - e \ll 1$, where the ellipse is squeezed. In the case $e \ll 1$, we use the expansion of the complete elliptic integral of the first kind [26]

$$K(e) = \frac{\pi}{2} \left\{ 1 + \left(\frac{1}{2}\right)^2 e^2 + \left(\frac{1}{2} \cdot \frac{3}{4}\right)^2 e^4 + \left(\frac{1}{2} \cdot \frac{3}{4} \cdot \frac{5}{6}\right)^3 e^6 + \cdots \right\}.$$  

(2.22)

In the second limit $1 - e \ll 1$, we find from the asymptotic behavior [26]

$$\lim_{e \to 1} \left[ K(e) - \frac{1}{2} \log \frac{16}{1 - e} \right] = 0 $$

(2.23)

that

$$E\tau \sim \frac{|\Omega|}{4\pi a} \log \frac{16}{1 - e}, \quad \text{for} \quad 1 - e \ll 1.$$  

(2.24)

The area of the hole is given by

$$S = \pi ab = \pi a^2 \sqrt{1 - e^2},$$  

(2.25)

or equivalently

$$a = \sqrt[4]{\frac{S^{1/2}}{\pi^{1/2} (1 - e^2)^{1/4}}},$$  

(2.26)

and the MFPT has the asymptotic form

$$E\tau \sim \frac{4\sqrt{2} |\Omega| (1 - e)^{1/4}}{4\sqrt{\pi S}} \log \frac{16}{1 - e}, \quad \text{for} \quad 1 - e \ll 1.$$  

(2.27)
3 Explicit computations for the sphere

The analysis of Section 2 is not easily extended to the computation, or even merely the estimation of the next term in the asymptotic approximation of the MFPT. The explicit results for the particular case of escape from a ball through a small circular hole gives an idea of the order of magnitude of the second term and the error in the asymptotic expansion of the MFPT. If the domain $\Omega$ is a ball, the method of [13]-[15], [20], and [21] can be used to obtain a full asymptotic expansion of the MFPT. We consider the motion of a Brownian particle inside a ball of radius $R$. The particle is reflected at the sphere, except for a small cap of radius $a = \varepsilon R$ and surface area $4\pi R^2 \sin^2 \frac{\varepsilon}{2}$, where it exits the ball. We assume $\varepsilon \ll 1$. The MFPT $v(r, \theta, \phi)$ satisfies the mixed boundary value problem for Poisson’s equation in the ball [24],

\[
\Delta v(r, \theta, \phi) = -1, \quad \text{for } r < R, \quad 0 \leq \theta \leq \pi, \quad 0 \leq \phi < 2\pi,
\]

\[
v(r, \theta, \phi) \bigg|_{r=R} = 0, \quad \text{for } 0 \leq \theta < \varepsilon, \quad 0 \leq \phi < 2\pi,
\]

\[
\frac{\partial v(r, \theta, \phi)}{\partial r} \bigg|_{r=R} = 0, \quad \text{for } \varepsilon \leq \theta \leq \pi, \quad 0 \leq \phi < 2\pi,
\]

The diffusion coefficient has been chosen to be $D = 1$. Due to the cylindrical symmetry of the problem, the solution is independent of the angle $\phi$, that is, $v(r, \theta, \phi) = v(r, \theta)$, so the system (3.1) can be written as

\[
\Delta v(r, \theta) = -1, \quad \text{for } r < R, \quad 0 \leq \theta \leq \pi,
\]

\[
v(r, \theta) \bigg|_{r=R} = 0, \quad \text{for } 0 \leq \theta < \varepsilon,
\]

\[
\frac{\partial v(r, \theta)}{\partial r} \bigg|_{r=R} = 0, \quad \text{for } \varepsilon \leq \theta \leq \pi,
\]

where the Laplacian is given by

\[
\Delta v(r, \theta) = \frac{1}{r^2} \frac{\partial}{\partial r} \left( r^2 \frac{\partial v}{\partial r} \right) + \frac{1}{r^2 \sin \theta} \frac{\partial}{\partial \theta} \left( \sin \theta \frac{\partial v}{\partial \theta} \right).
\]

The function $f(r, \theta) = \frac{R^2 - r^2}{6}$ is the solution of the boundary value problem

\[
\Delta f = -1, \quad \text{for } r < R,
\]

\[
f \bigg|_{r=R} = 0.
\]
In the decomposition \( v = u + f \), the function \( u(r, \theta) \) satisfies the mixed Dirichlet-Neumann boundary value problem for the Laplace equation

\[
\Delta u(r, \theta) = 0, \quad \text{for} \quad r < R, \quad 0 \leq \theta \leq \pi,
\]

\[
u(r, \theta)
\]

\[
\left. \frac{\partial u(r, \theta)}{\partial r} \right|_{r=R} = \frac{R}{3}, \quad \text{for} \quad \varepsilon \leq \theta \leq \pi.
\]

Separation of variables suggests that

\[
u(r, \theta) = \sum_{n=0}^{\infty} a_n \left( \frac{r}{R} \right)^n P_n(\cos \theta),
\]

where \( P_n(\cos \theta) \) are the Legendre polynomials, and the coefficients \( \{a_n\} \) are to be determined from the boundary conditions

\[
u(r, \theta)
\]

\[
\left. \frac{\partial u(r, \theta)}{\partial r} \right|_{r=R} = \sum_{n=0}^{\infty} a_n P_n(\cos \theta) = 0, \quad \text{for} \quad 0 \leq \theta < \varepsilon,
\]

\[
\left. \frac{\partial u(r, \theta)}{\partial r} \right|_{r=R} = \sum_{n=1}^{\infty} n a_n P_n(\cos \theta) = \frac{R^2}{3}, \quad \varepsilon \leq \theta \leq \pi.
\]

Equations (3.4), (3.5) are dual series equations of the mixed boundary value problem at hand, and their solution results in the solution of the boundary value problem (3.2). Dual series equations of the form

\[
\sum_{n=0}^{\infty} a_n P_n(\cos \theta) = 0, \quad \text{for} \quad 0 \leq \theta < \varepsilon,
\]

\[
\sum_{n=0}^{\infty} (2n + 1)a_n P_n(\cos \theta) = G(\theta), \quad \text{for} \quad \varepsilon \leq \theta \leq \pi
\]

are solved in [13, eqs.(5.5.12)-(5.5.14), (5.6.12)]. However, the dual series equations (3.6)-(3.7) are different from equations (3.4)-(3.5). The factor \( 2n+1 \) that appears in equation (3.6) is replaced by \( n \) in equation (3.5). What seems as a slight difference turns out to make our task much harder. The factor \( 2n+1 \) fits much more easily into the infinite sums (3.6)-(3.7), because it is the normalization constant of the Legendre polynomials.

### 3.1 Collins’ method

The solution of dual relations of the form (3.5) (see [13, (5.6.19)-(5.6.20)]) is discussed in [20], [21]. Specifically, assume that for given functions \( G(\theta) \) and
$F(\theta)$ we have the representation
\[
\sum_{n=0}^{\infty} (1 + H_n) b_n T_{m+n}^{-m}(\cos \theta) = F(\theta), \quad \text{for} \quad 0 \leq \theta < \varepsilon,
\]
\[
\sum_{n=0}^{\infty} (2n + 2m + 1) b_n T_{m+n}^{-m}(\cos \theta) = G(\theta), \quad \text{for} \quad \varepsilon < \theta \leq \pi,
\]
where $T_{m+n}$ are Ferrer’s associated Legendre polynomials [27], [28] and \{H\} is a given series that is $O(n^{-1})$ as $n \to \infty$. Then for $m = 0$, we have
\[
\sum_{n=0}^{\infty} (1 + H_n) b_n P_n(\cos \theta) = F(\theta), \quad \text{for} \quad 0 \leq \theta < \varepsilon, \quad (3.8)
\]
\[
\sum_{n=0}^{\infty} (2n + 1) b_n P_n(\cos \theta) = G(\theta), \quad \text{for} \quad \varepsilon < \theta \leq \pi. \quad (3.9)
\]
Setting $a_0 = b_0$, $a_n = \frac{2n + 1}{2n} b_n$, $n \geq 1$ in equations (3.4)-(3.5) results in
\[
\sum_{n=0}^{\infty} (1 + H_n) b_n P_n(\cos \theta) = 0, \quad \text{for} \quad 0 \leq \theta < \varepsilon, \quad (3.10)
\]
\[
\sum_{n=0}^{\infty} (2n + 1) b_n P_n(\cos \theta) = \frac{2R^2}{3} + b_0, \quad \text{for} \quad \varepsilon \leq \theta \leq \pi. \quad (3.11)
\]
Equations (3.10)-(3.11) are equivalent to (3.8)-(3.9) with $H_0 = 0$, $H_n = \frac{1}{2n}$, $n \geq 1$, $F(\theta) = 0$, and $G(\theta) = \frac{2R^2}{3} + b_0$. Collins’ method of solution consists in finding an integral equation for the function
\[
h(\theta) = \sum_{n=0}^{\infty} (2n + 1) b_n P_n(\cos \theta), \quad \text{for} \quad 0 \leq \theta < \varepsilon,
\]
so that
\[
b_n = \frac{1}{2} \int_{0}^{\varepsilon} h(\alpha) P_n(\cos \alpha) \sin \alpha \, d\alpha + \frac{1}{2} \int_{\varepsilon}^{\pi} G(\alpha) P_n(\cos \alpha) \sin \alpha \, d\alpha.
\]
Substituting into equation (3.8), with $F(\theta) \equiv 0$, we find for $0 \leq \theta < \varepsilon$ that
\[
0 = \frac{1}{2} \int_{0}^{\varepsilon} h(\alpha) \sum_{n=0}^{\infty} (1 + H_n) P_n(\cos \alpha) P_n(\cos \theta) \sin \alpha \, d\alpha
\]
\[
+ \frac{1}{2} \int_{\varepsilon}^{\pi} G(\alpha) \sum_{n=0}^{\infty} (1 + H_n) P_n(\cos \alpha) P_n(\cos \theta) \sin \alpha \, d\alpha. \quad (3.12)
\]
3.2 The asymptotic expansion

To facilitate the calculations, we consider first the case $H_n = 0$ for all $n$. Then we will show that the leading order term obtained for this case is the same as that for the case $H_n \neq 0$. In the latter case, we obtain the first correction to the leading order term and an estimate on the remaining error.

3.2.1 The leading order term when $H_n \equiv 0$

We will now sum the series (3.12) in the case $H_n \equiv 0$. First, we recall Mehler’s integral representation for the Legendre polynomials [26], [29],

$$P_n(\cos \theta) = \frac{\sqrt{2}}{\pi} \int_0^\theta \frac{\cos(n + \frac{1}{2})u du}{\sqrt{\cos u - \cos \theta}},$$  \hspace{1cm} (3.13)

and the identity [13]

$$\sqrt{2} \sum_{n=0}^\infty P_n(\cos \alpha) \frac{\cos \left(n + \frac{1}{2}\right) u}{\sqrt{\cos u - \cos \alpha}} = \frac{H(\alpha - u)}{\sqrt{\cos u - \cos \alpha}},$$ \hspace{1cm} (3.14)

where $H(x)$ is the Heaviside unit step function. Then we obtain for $u < \theta < \varepsilon < \alpha$,

$$\frac{1}{2} \int_{\theta}^{\pi} G(\alpha) \sum_{n=0}^\infty P_n(\cos \alpha)P_n(\cos \theta) \sin \alpha d\alpha =$$

$$= \frac{1}{2} \int_{\varepsilon}^{\pi} G(\alpha) \sum_{n=0}^\infty P_n(\cos \alpha) \sqrt{2} \frac{1}{\pi} \int_0^\theta \frac{\cos(n + \frac{1}{2})u du}{\sqrt{\cos u - \cos \theta}} \sin \alpha d\alpha$$

$$= \frac{1}{2\pi} \int_0^\theta \frac{du}{\sqrt{\cos u - \cos \theta}} \int_{\varepsilon}^{\pi} G(\alpha) \sin \alpha d\alpha \sqrt{\cos u - \cos \alpha}.$$ \hspace{1cm} (3.15)

Similarly,

$$\frac{1}{2} \int_{0}^{\varepsilon} h(\alpha) \sum_{n=0}^\infty P_n(\cos \alpha)P_n(\cos \theta) \sin \alpha d\alpha =$$

$$= \frac{1}{2\pi} \int_0^\theta \frac{du}{\sqrt{\cos u - \cos \theta}} \int_{u}^{\varepsilon} h(\alpha) \sin \alpha d\alpha.$$ \hspace{1cm} (3.16)

Hence,

$$\int_0^\theta \frac{du}{\sqrt{\cos u - \cos \theta}} \int_{u}^{\varepsilon} h(\alpha) \sin \alpha d\alpha =$$

$$- \int_0^\theta \frac{du}{\sqrt{\cos u - \cos \theta}} \int_{\varepsilon}^{\pi} G(\alpha) \sin \alpha d\alpha.$$ \hspace{1cm} (3.17)
Equation (3.17) means that the Abel transforms of two functions are the same, so that

\[ \int_0^\varepsilon h(\alpha) \sin \alpha \, d\alpha = \int_0^\varepsilon G(\alpha) \sin \alpha \, d\alpha, \]  

(3.18)

because the Abel transform is uniquely invertible. Equation (3.18) is an Abel-type integral equation, whose solution is given by

\[ h(\theta) \sin \theta = \frac{1}{\pi} \frac{d}{d\theta} \int_\theta^\varepsilon \frac{\sin u \, du}{\sqrt{\cos \theta - \cos u}} \int_\varepsilon^\pi \frac{G(\alpha) \sin \alpha \, d\alpha}{\sqrt{\cos u - \cos \alpha}}, \]  

(3.19)

or

\[ h(\theta) = -\frac{2}{\sin \theta} \frac{d}{d\theta} \int_\theta^\varepsilon \frac{H(u) \sin u \, du}{\sqrt{\cos \theta - \cos u}}, \]  

(3.20)

where

\[ H(u) = -G(u, \varepsilon), \]  

(3.21)

and

\[ G(u, \varepsilon) = \frac{1}{2\pi} \int_\varepsilon^\pi \frac{G(\theta) \sin \theta \, d\theta}{\sqrt{\cos u - \cos \theta}}. \]  

(3.22)

The dual integral equations (3.10)-(3.11) define \( G(\theta) = \frac{2R^2}{3} + b_0 \), so that

\[ G(\psi, \phi) = \frac{1}{2\pi} \int_\phi^\pi \left( \frac{2R^2}{3} + b_0 \right) \frac{\sin \theta \, d\theta}{\sqrt{\cos \psi - \cos \theta}}, \]  

(3.23)

\[ = \left( \frac{2R^2}{3} + b_0 \right) \frac{1}{\pi} \sqrt{\cos \psi - \cos \theta} \bigg|_{\theta=\phi}^\pi 
\]

\[ = \left( \frac{2R^2}{3} + b_0 \right) \frac{1}{\pi} \left( \sqrt{2 \cos \psi} - \sqrt{\cos \psi - \cos \phi} \right), \quad \text{for} \quad \psi < \phi. \]

In particular, setting \( n = 0 \) in equation (3.12) and using equation (3.20), gives

\[ b_0 = \frac{1}{2} \int_0^\varepsilon h(\alpha) \sin \alpha \, d\alpha + \frac{1}{2} \int_\varepsilon^\pi \left( \frac{2R^2}{3} + b_0 \right) \sin \alpha \, d\alpha \]  

(3.24)

\[ = \sqrt{2} \int_0^\varepsilon H(\psi) \cos \frac{\psi}{2} \, d\psi + \left( \frac{2R^2}{3} + b_0 \right) \cos^2 \frac{\varepsilon}{2}. \]
Integrating equation $\text{(3.23)}$, we obtain

\[
\sqrt{2} \int_{0}^{\varepsilon} G(\psi, \varepsilon) \cos \frac{\psi}{2} d\psi = (3.25)
\]

\[
= \left( \frac{2R^2}{3} + b_0 \right) \frac{\sqrt{2}}{\pi} \int_{0}^{\varepsilon} \left( \sqrt{2} \cos \frac{\psi}{2} - \sqrt{\cos \psi - \cos \varepsilon} \right) \cos \frac{\psi}{2} d\psi
\]

\[
= \frac{2R^2}{3} + b_0 \left( \varepsilon + \sin \varepsilon \right) - \left( \frac{2R^2}{3} + b_0 \right) \frac{4}{\pi} \int_{0}^{\varepsilon} \sin \frac{\varepsilon}{2} \frac{s^2 ds}{\sqrt{\sin^2 \frac{\varepsilon}{2} - s^2}}
\]

\[
= \frac{2R^2}{3} + b_0 \left( \varepsilon + \sin \varepsilon \right) - \left( \frac{2R^2}{3} + b_0 \right) \sin^2 \frac{\varepsilon}{2}.
\]

Combining equations (3.24) and (3.25) gives

\[
b_0 = \frac{2R^2}{3} \left( \frac{\pi}{\varepsilon + \sin \varepsilon} - 1 \right) = \frac{2R^2}{3} \left( \frac{\pi}{2\varepsilon} + O(1) \right) = \frac{|\Omega|}{4a} \left( 1 + O \left( \frac{a}{R} \right) \right), \quad (3.26)
\]

where $|\Omega| = \frac{4\pi R^3}{3}$ is the volume of the ball, and $a = R\varepsilon$ is the radius of the hole.

### 3.2.2 The case $H_n \neq 0$

The asymptotic expression (3.26) for $b_0$, was derived under the simplifying assumption that $H_n \equiv 0$. However, we are interested in the value of $b_0$ which is produced by the solution of the dual series equations (3.10)-(3.11), where $H_n = \frac{1}{2n}$. We sum the series (3.12) by the identities

\[
\frac{1}{2} \int_{0}^{\varepsilon} h(\alpha) \sum_{n=0}^{\infty} H_n P_n(\cos \alpha) P_n(\cos \theta) \sin \alpha d\alpha
\]

\[
= \frac{1}{2} \int_{0}^{\varepsilon} h(\alpha) \sum_{n=0}^{\infty} H_n \frac{\sqrt{2}}{\pi} \int_{0}^{\alpha} \frac{\cos(n + \frac{1}{2})v}{\sqrt{\cos v - \cos \alpha}} \frac{\sqrt{2}}{\pi} \int_{0}^{\theta} \frac{\cos(n + \frac{1}{2})u}{\sqrt{\cos u - \cos \theta}} \sin \alpha d\alpha
\]

\[
= \frac{1}{2\pi} \int_{0}^{\varepsilon} h(\alpha) \sin \alpha d\alpha \int_{0}^{\alpha} \frac{dv}{\sqrt{\cos v - \cos \alpha}} \int_{0}^{\theta} \frac{K(u, v)}{\sqrt{\cos u - \cos \theta}}
\]

\[
= \frac{1}{2\pi} \int_{0}^{\theta} \frac{du}{\sqrt{\cos u - \cos \theta}} \int_{0}^{\varepsilon} K(u, v) dv \int_{v}^{\varepsilon} \frac{h(\alpha) \sin \alpha d\alpha}{\sqrt{\cos v - \cos \alpha}}. \quad (3.27)
\]
where
\[ K(u, v) = \frac{2}{\pi} \sum_{n=0}^{\infty} H_n \cos \left( n + \frac{1}{2} \right) u \cos \left( n + \frac{1}{2} \right) v \] (3.28)
\[ = -\frac{\cos \left( \frac{1}{2} (v + u) \right)}{2\pi} \log 2 \left| \sin \frac{1}{2} (v + u) \right| -\frac{\cos \left( \frac{1}{2} (v - u) \right)}{2\pi} \log 2 \left| \sin \frac{1}{2} (v - u) \right| \\
+ \frac{v + u - \pi}{4\pi} \sin \frac{1}{2} (v + u) + \frac{v - u - \pi}{4\pi} \sin \frac{1}{2} (v - u). \]

Similarly,
\[ \frac{1}{2} \int_{\pi}^{\pi} G(\alpha) \sum_{n=0}^{\infty} H_n P_n(\cos \alpha) P_n(\cos \theta) \sin \alpha \, d\alpha \]
\[ = \frac{1}{2\pi} \int_{\pi}^{\pi} G(\alpha) \sin \alpha \, d\alpha \int_{\pi}^{\alpha} \frac{dv}{\cos v - \cos \alpha} \int_{0}^{\theta} \frac{K(u, v) \, du}{\cos u - \cos \theta} \\
= \frac{1}{2\pi} \int_{0}^{\theta} du \frac{1}{\cos u - \cos \theta} \int_{\pi}^{\alpha} G(\alpha) \sin \alpha \, d\alpha \int_{0}^{\alpha} \frac{K(u, v) \, dv}{\cos v - \cos \alpha}. \] (3.29)
Substituting equations (3.15), (3.16), (3.27), and (3.29) into equation (3.12) yields
\[ 0 = \frac{1}{2\pi} \int_{0}^{\theta} du \frac{1}{\cos u - \cos \theta} \int_{u}^{\pi} h(\alpha) \sin \alpha \, d\alpha \int_{0}^{\alpha} \frac{K(u, v) \, dv}{\cos u - \cos \alpha} \\
+ \frac{1}{2\pi} \int_{0}^{\theta} du \frac{1}{\cos u - \cos \theta} \int_{\pi}^{\pi} \frac{h(\alpha) \sin \alpha \, d\alpha}{\cos u - \cos \alpha} \int_{0}^{\theta} \frac{K(u, v) \, dv}{\cos v - \cos \alpha} \\
+ \frac{1}{2\pi} \int_{0}^{\theta} du \frac{1}{\cos u - \cos \theta} \int_{\pi}^{\alpha} G(\alpha) \sin \alpha \, d\alpha \int_{\pi}^{\alpha} \frac{K(u, v) \, dv}{\cos v - \cos \alpha} \\
+ \frac{1}{2\pi} \int_{0}^{\theta} du \frac{1}{\cos u - \cos \theta} \int_{\pi}^{\alpha} G(\alpha) \sin \alpha \, d\alpha \int_{0}^{\theta} \frac{K(u, v) \, dv}{\cos v - \cos \alpha}, \]
which is again an Abel-type integral equation. Inverting the Abel transform [30], we obtain
\[ 0 = \frac{1}{2\pi} \int_{u}^{\pi} \frac{h(\alpha) \sin \alpha \, d\alpha}{\cos u - \cos \alpha} + \frac{1}{2\pi} \int_{0}^{\theta} \frac{K(u, v) \, dv}{\cos v - \cos \alpha} \\
+ \frac{1}{2\pi} \int_{\pi}^{\alpha} \frac{G(\alpha) \sin \alpha \, d\alpha}{\cos u - \cos \alpha} + \frac{1}{2\pi} \int_{\pi}^{\alpha} \frac{K(u, v) \, dv}{\cos v - \cos \alpha}. \] (3.30)
Setting
\[ H(u) = \frac{1}{2\pi} \int_0^\varepsilon \frac{h(\alpha) \sin \alpha d\alpha}{\sqrt{\cos u - \cos \alpha}}, \]  
(3.31)
we invert the Abel transform \((3.31)\) to obtain
\[ h(\theta) = -\frac{2}{\sin \theta} \frac{d}{d\theta} \int_\varepsilon^\theta \frac{\sin u H(u) du}{\sqrt{\cos \theta - \cos u}}. \]  
(3.32)
Writing
\[ J(u) = H(u) + G(u, \varepsilon), \]  
(3.33)
equation \((3.30)\) becomes
\[ J(u) + \int_0^\varepsilon K(u, v)J(v) dv = M(u), \]  
(3.34)
where the free term \(M(u)\) is given by
\[ M(u) = -\int_\varepsilon^\pi K(u, v)G(v, v) dv. \]  
(3.35)
Equation \((3.34)\) is a Fredholm integral equation for \(J\).

3.2.3 The second term and the remaining error: \(L^2\) estimates

Equations \((3.24)\), \((3.25)\), and \((3.33)\) give that
\[ b_0 + \frac{2R^2}{3} = \frac{2R^2}{3} \frac{\pi}{\varepsilon + \sin \varepsilon} + \frac{\sqrt{2\pi}}{\varepsilon + \sin \varepsilon} \int_0^\varepsilon J(u) \cos \frac{u}{2} du, \]  
(3.36)
where \(J\) is the solution of the Fredholm equation \((3.34)\). In this section we show that
\[ \frac{\sqrt{2\pi}}{\varepsilon + \sin \varepsilon} \int_0^\varepsilon J(u) \cos \frac{u}{2} du = \left( b_0 + \frac{2R^2}{3} \right) \left( \varepsilon \log \frac{1}{\varepsilon} + O(\varepsilon) \right), \]
therefore the last term in eq.\((3.36)\) should be considered a small correction to the leading order term \(\frac{2R^2}{3} \frac{\pi}{\varepsilon}\), obtained in Section 3.2.2. This confirms the intuitive results of \([8], [23]\) and gives an estimate on the error term. Due to the logarithmic singularity of the function \(K(u, v)\) (see \((3.28)\)) the operator \(K\), defined by
\[ Kf(u) = \int_0^\varepsilon K(u, v)f(v) dv, \]  
(3.37)
maps \(L^2[0, \varepsilon]\) into \(L^2[0, \varepsilon]\). In Appendix A we derive the estimate
\[ \|K\|_2 \leq \frac{\sqrt{30}}{2\pi} \varepsilon \log \frac{1}{\varepsilon}, \]  
(3.38)
for \(\varepsilon \ll 1\). Better estimates can be found; however we settle for this rough estimate that suffices for our present purpose.
3.2.4 Estimate of $\|J\|_2$

In terms of the operator $K$, equation (3.34) can be written as

$$J = M - KJ. \quad (3.39)$$

The triangle inequality yields

$$\|J\|_2 \leq \|M\|_2 + \|KJ\|_2 \leq \|M\|_2 + \|K\|_2 \|J\|_2, \quad (3.40)$$

which together with the estimate (3.38) gives

$$\|J\|_2 \leq \frac{\|M\|_2}{1 - \|K\|_2} \leq \left(1 + \varepsilon \log \frac{1}{\varepsilon}\right) \|M\|_2 \text{ for } \varepsilon \ll 1. \quad (3.41)$$

3.2.5 Estimate of $\|M\|_2$

We proceed to find an estimation for $\|M\|_2$. First, we prove that the kernel satisfies the identity

$$\int_0^\pi K(u, v) \cos \frac{v}{2} dv = 0, \quad \text{for all } u. \quad (3.42)$$

Indeed, by changing the order of summation and integration, we obtain

$$\int_0^\pi K(u, v) \cos \frac{v}{2} dv = \frac{1}{\pi} \sum_{n=1}^\infty \frac{1}{n} \cos \left(n + \frac{1}{2}\right) u \int_0^\pi \cos \left(n + \frac{1}{2}\right) v \cos \frac{v}{2} dv \quad (3.43)$$

Equations (3.23), (3.35), and (3.42) imply that

$$M(u) = \frac{\sqrt{2}}{\pi} \left(\frac{2R^2}{3} + b_0\right) \int_0^\varepsilon K(u, v) \cos \frac{v}{2} dv. \quad (3.44)$$

The estimate (3.38) gives

$$\|M\|_2 \leq \frac{\sqrt{2}}{\pi} \left(\frac{2R^2}{3} + b_0\right) \|K\|_2 \varepsilon \leq \frac{\sqrt{15}}{\pi^2} \left(\frac{2R^2}{3} + b_0\right) \varepsilon^{3/2} \log \frac{1}{\varepsilon}. \quad (3.45)$$

Combining the estimates (3.41) and (3.45), we obtain for $\varepsilon \ll 1$

$$\|J\|_2 \leq \frac{4}{\pi^2} \left(\frac{2R^2}{3} + b_0\right) \varepsilon^{3/2} \log \frac{1}{\varepsilon} = \left(\frac{2R^2}{3} + b_0\right) O\left(\varepsilon^{3/2} \log \varepsilon\right). \quad (3.46)$$
3.2.6 The second term and error estimate

The Cauchy-Schwartz inequality implies that

\[
\frac{\sqrt{2\pi}}{\varepsilon + \sin \varepsilon} \left| \int_0^\varepsilon J(u) \cos \frac{u}{2} \, du \right| \leq \left( \frac{2R^2}{3} + b_0 \right) \varepsilon \log \frac{1}{\varepsilon},
\]

(3.47)

for \( \varepsilon \ll 1 \), which together with (3.36) gives

\[
b_0 = \frac{\pi R^2}{3\varepsilon} (1 + O(\varepsilon \log \varepsilon)) = \frac{|\Omega|}{4a} (1 + O(\varepsilon \log \varepsilon)).
\]

(3.48)

To obtain the explicit expression for the term \( O(\varepsilon \log \varepsilon) \), we write the Fredholm integral equation (3.34) as

\[(I + K)J = M.\]

(3.49)

The estimate (3.38) implies that \( \|K\|_2 < 1 \) for sufficiently small \( \varepsilon \), hence

\[J = M + O(\|K\|_2\|M\|_2).\]

(3.50)

Thus, using equation (3.44) and the estimates (3.38) and (3.45), we write the last term in equation (3.36) as

\[
\int_0^\varepsilon J(u) \cos \frac{u}{2} \, du = \int_0^\varepsilon M(u) \cos \frac{u}{2} \, du + O(\varepsilon\|K\|_2\|M\|_2) =
\]

\[
\frac{\sqrt{2}}{\pi} \left( b_0 + \frac{2R^2}{3} \right) \left[ \int_0^\varepsilon \int_0^\varepsilon K(u,v) \cos \frac{u}{2} \cos \frac{v}{2} \, du \, dv + O(\varepsilon^3 \log^2 \varepsilon) \right].
\]

Equation (3.28) gives the double integral as

\[
\int_0^\varepsilon \int_0^\varepsilon K(u,v) \cos \frac{u}{2} \cos \frac{v}{2} \, du \, dv = \frac{1}{\pi} \varepsilon^2 \log \frac{1}{\varepsilon} + O(\varepsilon^2),
\]

hence

\[
\frac{\sqrt{2\pi}}{\varepsilon + \sin \varepsilon} \int_0^\varepsilon J(u) \cos \frac{u}{2} \, du = \left( b_0 + \frac{2R^2}{3} \right) \left[ \varepsilon \log \frac{1}{\varepsilon} + O(\varepsilon) \right].
\]

Now it follows from equation (3.36) that

\[
b_0 = \frac{|\Omega|}{4a} \left[ 1 + \varepsilon \log \frac{1}{\varepsilon} + O(\varepsilon) \right].
\]

(3.52)
3.3 The MFPT

Using the explicit expression (3.52), we obtain the MFPT from the center of the ball as

\[ v \bigg|_{r=0} = u \bigg|_{r=0} + \frac{R^2}{6} = b_0 + \frac{R^2}{6} = \frac{|\Omega|}{4a} \left[ 1 + \varepsilon \log \frac{1}{\varepsilon} + O(\varepsilon) \right]. \]  

(3.53)

This is also the averaged MFPT for a uniform initial distribution,

\[ E\tau = \frac{1}{|\Omega|} \int_{0}^{2\pi} d\phi \int_{0}^{\pi} \sin \theta \, d\theta \int_{0}^{R} v(r, \theta) r^2 \, dr = \frac{|\Omega|}{4a} \left[ 1 + \varepsilon \log \frac{1}{\varepsilon} + O(\varepsilon) \right]. \]

4 Summary and applications

The narrow escape problem for a Brownian particle leads to a singular perturbation problem for a mixed Dirichlet-Neumann (corner) problem with large Neumann part and small Dirichlet part of the boundary. The corner problem, that arises in classical electrostatics (e.g., the electrified disk), elasticity (punch problems), diffusion and conductance theory, hydrodynamics, acoustics, and more recently in molecular biophysics, was solved hitherto mainly for special geometries. In this paper, we have constructed a leading order asymptotic approximation to the MFPT in the narrow escape problem for a general smooth domain and have derived a second term and an error estimate for the case of a sphere. Our derivation makes Lord Rayleigh’s qualitative observation into a quantitative one. Our leading order analysis of the general case uses the singularity property of the Neumann function for a general domain in \( \mathbb{R}^3 \). The special case of the sphere is analyzed by a method developed by Collins and yields a better result. A different approach to the calculation of the MFPT would be to use singular perturbation techniques. The vanishing escape time at the boundary would then be matched to the large outer escape time of order \( \varepsilon^{-1} \) by constructing a boundary layer near the boundary. The analysis of the MFPT to a small window at an isolated singular point of the boundary is postponed to a future paper. Brownian motion through narrow regions controls flow in many non-equilibrium systems, from fluidic valves to transistors and ion channels, the protein valves of biological membranes \( [31] \). Indeed, one can view an ion channel as the ultimate nanovalve—nearly picovalve—in which macroscopic flows are controlled with atomic resolution. In this context, the narrow escape problem appeared in the calculation of the equilibration time of diffusion between two chambers connected by a capillary \( [23] \). The equilibration time is the reciprocal of the first eigenvalue of the Neumann problem in this domain, which depends on the MFPT of a Brownian motion in each chamber to the narrow connecting channel. The first eigenfunction is constructed by piecing together the eigenfunctions of the narrow escape problem in each
chamber and in the channel so that the function and the flux are continuous across the connecting interfaces. It was assumed in [23] that the flux profile in the connecting hole was uniform. The structure of the flux profile, which is proportional to \((a^2 - \rho^2)^{-1/2}\), has been observed by Rayleigh in 1877 [7]. Rayleigh first assumed a radially uniform profile of flux and then refined the profile of flux going through the channel, allowing it to vary with the radial distance from the center of the cross section of the channel, so as to minimize the kinetic energy. A calculation of the equilibration time was carried out in [32] by solving the same problem, and gave a result that differs from that of [7], which was obtained by heuristic means, by less than two percent. A different approximation, based on the Fourier-Bessel representation in the pore, was derived in [15]. Another application of the narrow escape problem concerns ionic channels [31], and particularly particle simulations of the permeation process [33]-[37] that capture much more detail than continuum models. Up to now, computer simulations are inefficient because an ion takes so long even to enter a channel and then so many of the ions return from where they came. From the present analysis, it becomes clear why ions take so long to enter the channel. According to (1.2) the mean time between arrival of ions at the channel is

\[
\bar{\tau} = \frac{E\tau}{N} = \frac{1}{4DaC}, \tag{4.1}
\]

where \(N\) is the number of ions in the simulation and \(C\) is their concentration. A coarse estimate of \(\bar{\tau}\) at the biological concentration of 0.1Molar, channel radius \(a = 20\text{Å}\), diffusion coefficient \(D = 1.5 \times 10^{-9}\text{m}^2/\text{sec}\) is \(\bar{\tau} \approx 1\text{nsec}\). In a Brownian dynamics simulation of ions in solution with time step which is 10 times the relaxation time of the Langevin equation to the Smoluchowski (diffusion) equation at least 1000 simulation steps are needed on the average for the first ion to arrive at the channel. It should be taken into account that most of the ions that arrive at the channel do not cross it [38].

The narrow escape problem comes up in problems of the escape from a domain composed of a big subdomain with a small hole, connected to a thin cylinder (or cylinders) of length \(L\). If ions that enter the cylinder do not return to the big subdomain, the MFPT to the far end of the cylinder is the sum of the MFPT to the small hole and the MFPT to the far end of the narrow cylinder. The latter can be approximated by a one-dimensional problem with one reflecting and one absorbing endpoint. If the domain has a volume \(V\), the approximate expression for the MFPT is

\[
E\tau \approx \frac{V}{4\varepsilon D} + \frac{L^2}{2D}. \tag{4.2}
\]

This method can be extended to a domain composed of many big subdomains with small holes connected by narrow cylinders. The case of one sphere of volume \(V = \frac{4\pi R^3}{3}\), with a small opening of size \(\varepsilon\) connected to a thin cylinder
of length $L$ is relevant in biological micro-structures, such as dendritic spines in neurobiology. Indeed, the mean time for calcium ion to diffuse from the spine head to the parent dendrite through the neck controls the spine-dendrite coupling. This coupling is involved in the induction of processes such as synaptic plasticity. Formula 4.2 is useful for the interpretation of experiments and for the confirmation of the diffusive motion of ions from the spine head to the dendrite.

Another significant application of the narrow escape formula is to provide a new definition of the forward binding rate constant in micro-domains. Indeed, the forward chemical constant is really the flux of particles to a given portion of the boundary, depending on the substrate location. Up to now, the forward binding rate was computed using the Smoluchowski formula, which corresponds to the absorption flux of particles in a given sphere immersed in an infinite medium. The formula applies when many particles are involved. But to model chemical reactions in micro-structures, where a bounded domain contains only a few particles that bind to a given number of binding sites, the forward binding rate,

$$k_{\text{forward}} = \frac{1}{\bar{\tau}},$$

has to be computed with $\bar{\tau}$ given in eq. 4.1.

A Estimate of $\|K\|_2$

A.1 Estimate of the kernel

A rough estimate of the kernel, for $0 \leq u, v \leq \varepsilon$, is obtained from equation 3.28 as

$$K^2(u, v) \leq \frac{5}{4\pi^2} \cos \frac{1}{2}(v + u) \left( \log 2 \left| \sin \frac{1}{2}(v + u) \right| \right)^2 + \frac{5}{4\pi^2} \cos \frac{1}{2}(v - u) \left( \log 2 \left| \sin \frac{1}{2}(v - u) \right| \right)^2.$$

Furthermore,

$$\int_0^\varepsilon \cos \frac{1}{2}(v + u) \left( \log 2 \left| \sin \frac{1}{2}(v + u) \right| \right)^2 du = \int_{2\sin^2 \frac{1}{2}v}^{2\sin^2 \frac{1}{2}(v + \varepsilon)} (\log x)^2 dx \leq 2 \left( \sin \frac{1}{2}(v + \varepsilon) - \sin \frac{1}{2}v \right) \left( \log 2 \left| \sin \frac{1}{2}v \right| \right)^2 \leq \varepsilon \cos \frac{1}{2}v \left( \log 2 \left| \sin \frac{1}{2}v \right| \right)^2,$$

and

$$\int_0^\varepsilon \varepsilon \cos \frac{1}{2}v \left( \log 2 \sin \frac{1}{2}v \right)^2 dv = \varepsilon \int_{2\sin^2 \frac{1}{2}\varepsilon}^{2\sin^2 \frac{1}{2}(v + \varepsilon)} (\log x)^2 dx \leq 2\varepsilon^2 \log^2 \varepsilon.$$
Similarly,

\[
\int_0^\varepsilon \cos \frac{1}{2}(v-u) \left( \log \left| 2 \sin \frac{1}{2}(v-u) \right| \right)^2 dv = \\
\int_0^{2 \sin \frac{1}{2} \varepsilon} (\log x)^2 \, dx + \int_0^{2 \sin \frac{1}{2} (\varepsilon-u)} (\log x)^2 \, dx \leq \\
2u \log^2 u + 2(\varepsilon-u) \log^2 (\varepsilon-u).
\]

It follows that

\[
\int_0^\varepsilon \left( 2u \log^2 u + 2(\varepsilon-u) \log^2 (\varepsilon-u) \right) \, du \leq 4 \varepsilon^2 \log^2 \varepsilon,
\]

because \( u \log u \) is an increasing function in the interval \( 0 \leq u \leq e^{-2} \). Altogether, we obtain

\[
\|K\|_2 \leq \frac{\sqrt{30}}{2\pi} \varepsilon \log \frac{1}{\varepsilon} \quad \text{for} \quad \varepsilon \ll e^{-2}, \tag{A.1}
\]

which is (3.38).

\section*{B Elliptic hole}

We present here, for completeness, Lure’s \cite{16} solution to the integral equation (2.13) in the elliptic hole case. We define for \( y = (x,y) \)

\[
L(y) = 1 - x^2/a^2 - y^2/b^2 \quad (b \leq a)
\]

and introduce polar coordinates in the ellipse \( \partial \Omega_a \)

\[
x = y + (\rho \cos \theta, \rho \sin \theta),
\]

with origin at the point \( y \). The integral in eq. (2.13) takes the form

\[
\int_{\partial \Omega_a} \frac{g_0(x)}{|x-y|} \, dS_x = \int_0^{2\pi} d\theta \int_0^{\rho_0(\theta)} \frac{\tilde{g}_0 \, d\rho}{\sqrt{L(x)}}, \tag{B.1}
\]

where \( \rho_0(\theta) \) denotes the distance between \( y \) and the boundary of the ellipse in the direction \( \theta \). Expanding \( L(x) \) in powers of \( \rho \), we find that

\[
L(x) = 1 - \frac{(x + \rho \cos \theta)^2}{a^2} - \frac{(y + \rho \sin \theta)^2}{b^2} = L(y) - 2\phi_1 \rho - \phi_2 \rho^2, \tag{B.2}
\]

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where $\phi_1 = \frac{x \cos \theta}{a^2} + \frac{y \sin \theta}{b^2}$ and $\phi_2 = \frac{\cos^2 \theta}{a^2} + \frac{\sin^2 \theta}{b^2}$. Solving the quadratic equation (B.2) for $\rho$, taking the positive root, we obtain

$$\rho(x) = \frac{1}{\phi_2} \left\{ -\phi_1 + \left[ \phi_1^2 + \phi_2 (L(y) - L(x)) \right]^{1/2} \right\}, \quad \text{(B.3)}$$

therefore, for fixed $y$ and $\theta$,

$$d\rho(x) = -\frac{1}{2} \frac{dL(x)}{[\phi_1^2 + \phi_2 (L(y) - L(x))]^{1/2}}, \quad \text{(B.4)}$$

and the integral takes the form

$$\int_{\partial \Omega_a} g_0(\mathbf{x}) \left\{ \frac{dL(x)}{|x-y|} \right\} dS_x = \int_0^{2\pi} d\theta \int_0^1 \frac{dL(y)}{2 \sqrt{\phi_1^2 + \phi_2 (L(y) - L(x))}^{1/2}} \frac{\bar{g}_0}{\sqrt{L(x)}}$$

Substituting $s = \frac{z}{L(y)}$ and setting $\psi = \frac{\phi_1^2}{\phi_2 L(y)}$, we find that

$$\int_{\partial \Omega_a} \frac{g_0(\mathbf{x})}{|x-y|} dS_x = \int_0^{2\pi} d\theta \int_0^1 \frac{dL(y)}{2 \sqrt{\phi_1^2 + \phi_2 (L(y) - L(x))}^{1/2}} \frac{\bar{g}_0}{\sqrt{\psi + s}}$$

$$= \int_0^{2\pi} d\theta \frac{\bar{g}_0}{2 \sqrt{\phi_2}} \frac{\arctan}{1 - s} \left( \sqrt{\psi + s} \right)$$

$$= \int_0^{2\pi} d\theta \frac{\bar{g}_0}{2 \sqrt{\phi_2}} \left( \frac{\arctan}{1 - s} \sqrt{\psi} \right)$$

The arctan term changes sign when $\theta$ is replaced by $\theta + \pi$, therefore its integral vanishes, and we remain with

$$\int_{\partial \Omega_a} \frac{g_0(\mathbf{x})}{|x-y|} dS_x = \frac{\pi \bar{g}_0}{2} \int_0^{2\pi} \frac{d\theta}{\sqrt{\cos^2 \theta + \sin^2 \theta}}$$

$$= 2\pi b \bar{g}_0 \int_0^{\pi/2} \frac{d\theta}{\sqrt{1 - \frac{a^2 - b^2}{b^2} \sin^2 \theta}}$$

$$= 2\pi b \bar{g}_0 K(e), \quad \text{(B.5)}$$
where $K(\cdot)$ is the complete elliptic integral of the first kind, and $e$ is the eccentricity of the ellipse

$$e = \sqrt{1 - \frac{b^2}{a^2}}, \quad (a > b). \quad (B.6)$$

We note that the integral (B.5) is independent of $y$, so we conclude that (2.14) is the solution of the integral equation (2.13).

C  A pathological example

We have derived an integral equation for the leading order terms of the flux and the MFPT in the case where the MFPT increases indefinitely as the relative area of the hole decreases to zero. However, the MFPT does not necessarily increase to infinity as the relative area of the hole decreases to zero. This is illustrated by the following example. Consider a cylinder of length $L$ and radius $a$. The boundary of the cylinder is reflecting, except for one of its bases (at $z = 0$, say), which is absorbing. The MFPT problem becomes one dimensional and its solution is

$$v(z) = Lz - \frac{z^2}{2}. \quad (C.1)$$

Here there is neither a boundary layer nor a constant outer solution; the MFPT grows gradually with $z$. The MFPT, averaged against a uniform initial distribution in the cylinder, is $E\tau = \frac{L^2}{3}$ and is independent of $a$, that is, the assumption that the MFPT becomes infinite is violated.

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References

[1] M. Dauge, *Elliptic Boundary Value Problems on Corner Domains: Smoothness and Asymptotics of Solutions*, Lecture Notes in Mathematics, 1341, Springer-Verlag, NY (1988).

[2] V.A. Kozlov, V.G. Mazya and J. Rossmann, *Elliptic Boundary Value Problems in Domains with Point Singularities*, American Mathematical Society, Mathematical Surveys and Monographs, vol. 52, 1997.
[3] V.A. Kozlov, J. Rossmann, V.G. Mazya, *Spectral Problems Associated With Corner Singularities of Solutions of Elliptic Equations*, Mathematical Surveys and Monographs, vol. 85, American Mathematical Society 2001.

[4] P. Hännig, P. Talkner, and M. Borkovec, “50 year after Kramers”, *Rev. Mod. Phys.* 62, p.251 (1990).

[5] M. Freidlin, *Markov Processes And Differential Equations*, Birkhauser Boston 2002

[6] H.L.F. von Helmholtz, *Crelle, Bd. 7* (1860).

[7] J.W.S. Baron Rayleigh, *The Theory of Sound*, Vol. 2, 2nd Ed., Dover, New York, 1945.

[8] I. V. Grigoriev, Y. A. Makhnovskii, A. M. Berezhkovskii, V. Y. Zitserman, “Kinetics of escape through a small hole”, *J. Chem. Phys.*, 116 (22), pp.9574-9577 (2002).

[9] D. Holcman, Z. Schuss, “Diffusion through narrow openings: the dynamics of AMPA receptors on a postsynaptic membrane”, *J. Stat. Phys.* (in print).

[10] D. Holcman, Z. Schuss, “Stochastic chemical reactions in microdomains”, *submitted* (in print).

[11] R. G. Pinsky, “Asymptotics of the principal eigenvalue and expected hitting time for positive recurrent elliptic operators in a domain with a small puncture”, *Journal of Functional Analysis* 200, 1, pp. 177-197, 2003.

[12] J. D. Jackson, *Classical Electrodynamics*, 2nd Ed., Wiley, NY, 1975.

[13] I. N. Sneddon, *Mixed Boundary Value Problems in Potential Theory*, Wiley, NY, 1966.

[14] V. I. Fabrikant, *Applications of Potential Theory in Mechanics*, Kluwer, 1989.

[15] V. I. Fabrikant, *Mixed Boundary Value Problems of Potential Theory and Their Applications in Engineering*, Kluwer, 1991.

[16] A. I. Lur’e, *Three-Dimensional Problems of the Theory of Elasticity*, Interscience publishers, NY 1964.

[17] S. S. Vinogradov, P. D. Smith, E. D. Vinogradova, *Canonical Problems in Scattering and Potential Theory, Parts I and II*, Chapman & Hall/CRC, 2002.

25
[18] A. Dembo and O. Zeitouni, *Large Deviations Techniques and Applications*, Jones and Bartlett, Boston 1992.

[19] B. Matkowsky and Z. Schuss, “The exit problem for randomly perturbed dynamical systems”, *SIAM J. Appl. Math.* 33 (12), pp.365-382 (1977).

[20] W. D. Collins, “On some dual series equations and their application to electrostatic problems for spheroidal caps”, *Proc. Cambridge Phil. Soc.* 57, pp. 367-384, 1961.

[21] W. D. Collins, “Note on an electrified circular disk situated inside an earthed coaxial infinite hollow cylinder”, *Proc. Cambridge Phil. Soc.* 57, pp. 623-627, 1961.

[22] A. Singer, Z. Schuss, D. Holcman, “Narrow Escape, Part III: Riemann surfaces and non-smooth domains”, (preprint)

[23] L. Dagdug, A. M. Berezhkovskii, S. Y. Shvartsman, G. H. Weiss, “Equilibration in two chambers connected by a capillary”, *J. Chem. Phys.* 119 (23), pp.12473-12478 (2003).

[24] Z. Schuss, *Theory and Applications of Stochastic Differential Equations*, Wiley Series in Probability and Statistics, Wiley, NY 1980.

[25] P. R. Garabedian, *Partial Differential Equations*, Wiley, NY 1964.

[26] M. Abramowitz, I. A. Stegun, *Handbook of Mathematical Functions*, Dover Publications, NY, 1972.

[27] A. Erdélyi, W. Magnus, F. Oberhettinger, F.G. Tricomi, *Tables of Integral Transforms*, Volume 1, McGraw-Hill, NY, 1954.

[28] G.E. Andrews, R. Askey, R. Roy, *Special Functions*, Cambridge University Press, 2000.

[29] W. Magnus, F. Oberhettinger, *Formulas and Theorems for the Special Functions of Mathematical Physics*, Chelsea Publishing Company, NY, 1949.

[30] E. T. Whittaker, G. N. Watson, *A Course of Modern Analysis*, Cambridge University Press, NY, 1973.

[31] B. Hille, *Ionic Channels of Excitable Membranes*, 2nd ed., Sinauer, Mass., 1992.

[32] R. B. Kelman, “Steady-State Diffusion Through a Finite Pore Into an Infinite Reservoir: an Exact Solution”, *Bulletin of Mathematical Biophysics* 27, pp.57-65 (1965).
[33] W. Im and B. Roux, “Ion permeation and selectivity of ompf porin: a theoretical study based on molecular dynamics, brownian dynamics, and continuum electrodiffusion theory,” J. Mol. Bio. 322 (4), pp. 851–869 (2002).

[34] W. Im and B. Roux, “Ions and counterions in a biological channel: a molecular dynamics simulation of ompf porin from escherichia coli in an explicit membrane with 1 m kcl aqueous salt solution,” J. Mol. Bio. 319 (5), pp. 1177–1197, (2002).

[35] B. Corry, M. Hoyles, T. W. Allen, M. Walker, S. Kuyucak, and S. H. Chung, “Reservoir boundaries in brownian dynamics simulations of ion channels,” Biophys. J. 82, pp. 1975–1984 (2002).

[36] S. Wigger-Aboud, M. Saraniti, and R. S. Eisenberg, “Self-consistent particle based simulations of three dimensional ionic solutions,” Nanotech 3, p. 443 (2003).

[37] T. A. van der Straaten, J. Tang, R. S. Eisenberg, U. Ravaioli, and N. R. Aluru, “Three-dimensional continuum simulations of ion transport through biological ion channels: effects of charge distribution in the constriction region of porin,” J. Computational Electronics 1, pp. 335–340 (2002).

[38] R.S. Eisenberg, M.M. Klosek, and Z. Schuss, “Diffusion as a chemical reaction: Stochastic trajectories between fixed concentrations”, J. Chem. Phys. 102, pp.1767-1780 (1995).

[39] D. Holcman, Z. Schuss, E. Korkotian, “Calcium dynamics in denritic spines and spine motility”, Biophysical Journal 87, pp.81-91 (2004)

[40] R.C. Malenka, J.A. Kauer, D.J. Perkel, R.A. Nicoll, “The impact of postsynaptic calcium on synaptic transmission–its role in long-term potentiation”, Trends Neurosci. 12 (11), pp.444-50 (1989).