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Narrow Escape, Part I

A. Singer,[1] Z. Schuss,[2] D. Holcman,[3] and R. S. Eisenberg[4]

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A Brownian particle with diffusion coefficient D is confined to a bounded domain Ω by a reflecting boundary, except for a small absorbing window $\partial\Omega_a$. The mean time to absorption diverges as the window shrinks, thus rendering the calculation of the mean escape time a singular perturbation problem. In the three-dimensional case, we construct an asymptotic approximation when the window is an ellipse, assuming the large semi axis a is much smaller than $|\Omega|^{1/3}$ ($|\Omega|$ is the volume), and show that the mean escape time is $E\tau \sim \frac{|\Omega|}{2\pi Da}K(e)$, where e is the eccentricity 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 $E\tau \sim \frac{|\Omega|}{4aD}$, which was derived by heuristic considerations. For the special case of a spherical domain, we obtain the asymptotic expansion $E\tau = \frac{|\Omega|}{4aD}[1 + \frac{a}{R}\log\frac{R}{a} + O(\frac{a}{R})]$. This result is important in understanding the flow of ions in and out of narrow valves that control a wide range of biological and technological function. If Ω is a two-dimensional bounded Riemannian manifold with metric g and $\varepsilon = |\partial\Omega_a|_g/|\Omega|_g \ll 1$, we show that $E\tau = \frac{|\Omega|_g}{D\pi}[\log\frac{1}{\varepsilon} + O(1)]$. This result is applicable to diffusion in membrane surfaces.

KEY WORDS: Brownian motion; Exit problem; Singular perturbations.

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 narrow escape

[1] Department of Mathematics, Yale University, 10 Hillhouse Ave. PO Box 208283, New Haven, CT 06520-8283, USA; e-mail: amit.singer@yale.edu
[2] Department of Mathematics, Tel-Aviv University, Tel-Aviv 69978, Israel; e-mail: schuss@post.tau.ac.il
[3] Department of Mathematics, Weizmann Institute of Science, Rehovot 76100 Israel; e-mail holcman@wisdom.weizmann.ac.il
[4] Department of Molecular Biophysics and Physiology, Rush Medical Center, 1750 Harrison St., Chicago, IL 60612, USA; e-mail: beisenbe@rush.edu

problem is to calculate the mean time to absorption. 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.[1] Indeed, one can view an ion channel as the ultimate nanovalve—nearly picovalve—in which macroscopic flows are controlled with atomic resolution. It is particularly important in particle simulations of the permeation process[2–6] that capture much more detail than continuum models. In this context, the narrow escape problem appeared in the calculation of the equilibration time of diffusion between two chambers connected by a capillary.[7] The narrow escape problem comes up, among others, in models of diffusion of proteins in membranes[8] [and references therein], in the diffusion of calcium ions in dendritic spines,[9–11] and in the calculation of forward binding rates in chemical reactions in microdomains.[12]

The narrow escape problem is equivalent to the solution of an inhomogeneous mixed Neumann-Dirichlet boundary value problem for the Poisson equation.[13,14] The 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.[15] He stated[16] (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.[17] Another result was presented in Ref. 8, where a two-dimensional narrow escape problem was considered and whose method is generalized here.

The mixed boundary value problems of classical electrostatics (e.g., the electrified disk problem[18]), 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.[19–23] 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 Ref. 8.

One mathematical aspect of the mixed Neumann-Dirichlet boundary value problem (BVP) for the Poisson equation, also known as the corner problem, is that the solution has singularities at the boundary of the hole.[24–26] Related problems of narrow escape concern absorption in a small component of the boundary, disjoint from the reflecting component were considered in Refs. 27 [and references therein], 28. Kolmogorov, Pontryagin, and Mishchenko calculated the probability distribution of the first passage time of a diffusing particle from a point in $\mathbb{R}^n$ to a given (moving or stationary) small sphere of radius ε in Ref. 28 They obtained an infinite MFPT. These results do not solve the problem considered here. They differ from the narrow escape problem in that there is no singularity at the boundary and there is no boundary layer.

The narrow escape problem does not seem to fall within the theory of large deviations.[29] It is different from Kolmogorov's exit problem[30] 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.,[31,32], 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.

The first main result of this paper 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 $|\Omega|$ to an elliptical hole of large semi axis a that is much smaller than $|\Omega|^{1/3}$,

$$E\tau \sim \frac{|\Omega|}{2\pi Da}K(e), \tag{1.1}$$

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

$$E\tau \sim \frac{|\Omega|}{4aD}. \tag{1.2}$$

Eq. (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,[16] 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[15] and is discussed in Ref. 22, is proportional to $(a^2 - \rho^2)^{-1/2}$ in the circular case, where ρ is the distance from the center of the hole.[18–20] Note that Eqs. (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 Ref. 8 for two-dimensional problems. The leading order term is the solution of Helmholtz's integral equation.[15] The general result for a two-dimensional Riemannian manifold with metric g is

$$E\tau = \frac{|\Omega|_g}{\pi D}\left[\log\frac{1}{\varepsilon} + O(1)\right] \quad \text{for } \varepsilon \ll 1,$$

where $|\Omega|_g$ is the Riemannian area of the domain.

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,

$$E\tau = \frac{|\Omega|}{4aD}\left[1 + \frac{a}{R}\log\frac{R}{a} + O\left(\frac{a}{R}\right)\right]. \tag{1.3}$$

Eq. (1.3) contains both the second term in the asymptotic expansion of the MFPT and an error estimate. We use Collins' method[33,34] 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 Ref. 35 cannot be generalized in a straightforward manner to three dimensions. We postpone the investigation of the three-dimensional problem of the MFPT to windows with singular points in their boundaries to a future paper. In Section 2 we derive a leading order approximation to the MFPT for a general two- and three-dimensional 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 three dimensions. 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. LEADING ORDER ASYMPTOTICS

A Brownian particle diffuses freely in a bounded domain $\Omega \subset \mathbb{R}^n$ $(n = 2, 3)$, whose boundary $\partial\Omega$ is sufficiently smooth (the analysis in higher dimensions is similar to that for $n = 3$). The trajectory of the Brownian particle, denoted $\boldsymbol{x}(t)$, 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 Ω is the first passage time τ of the Brownian particle from any point $\boldsymbol{x} \in \Omega$ to the absorbing boundary $\partial\Omega_a$. The MFPT,

$$v(\boldsymbol{x}) = E[\tau \mid \boldsymbol{x}(0) = \boldsymbol{x}],$$

is finite under quite general conditions.[14] 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,

$$\varepsilon = \left(\frac{|\partial\Omega_a|}{|\partial\Omega|}\right)^{1/(n-1)} \ll 1,$$

(see, however, a pathological example in Appendix C). The MFPT $v(\boldsymbol{x})$ satisfies the mixed boundary value problem[14]

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

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

$$\frac{\partial v(\boldsymbol{x})}{\partial n(\boldsymbol{x})} = 0, \quad \text{for} \quad \boldsymbol{x} \in \partial\Omega_r, \tag{2.3}$$

where D is the diffusion coefficient. If Ω is a subset of a two-dimensional Riemannian manifold, the Laplace operator is replaced with the Laplace-Beltrami operator. The compatibility condition

$$\int_{\partial\Omega a} \frac{\partial v(\boldsymbol{x}(\boldsymbol{S}))}{\partial n}\, dS = -\frac{|\Omega|}{D}, \tag{2.4}$$

is obtained by integrating (2.1) over Ω and using (2.2) and (2.3).

According to our assumptions $v(\boldsymbol{x}) \to \infty$ as the size of the hole decreases to zero, e.g., as $\varepsilon \to 0$, except in a boundary layer near $\partial\Omega_a$, because the compatibility condition (2.4) fails in the limit. Our purpose is to find an asymptotic approximation to $v(\boldsymbol{x})$ in this limit.

2.1. The Neumann Function and Integral Equations

To calculate the MFPT $v(\boldsymbol{x})$, we use the Neumann function $N(\boldsymbol{x}, \boldsymbol{\xi})$ (see Refs. [8, 27], which is a solution of the boundary value problem

$$\Delta_{\boldsymbol{x}} N(\boldsymbol{x}, \boldsymbol{\xi}) = -\delta(\boldsymbol{x} - \boldsymbol{\xi}), \quad \text{for} \quad \boldsymbol{x}, \boldsymbol{\xi} \in \Omega, \tag{2.5}$$

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

and is defined up to an additive constant. Green's identity gives

$$\begin{aligned}&\int_\Omega [N(\boldsymbol{x},\boldsymbol{\xi})\Delta v(\boldsymbol{x}) - v(\boldsymbol{x})\Delta N(\boldsymbol{x},\boldsymbol{\xi})]\,dx\\&= \int_{\partial\Omega}\left[N(\boldsymbol{x}(\boldsymbol{S}),\boldsymbol{\xi})\frac{\partial v(\boldsymbol{x}(\boldsymbol{S}))}{\partial n} - v(\boldsymbol{x}(\boldsymbol{S}))\frac{\partial N(\boldsymbol{x}(\boldsymbol{S}),\boldsymbol{\xi})}{\partial n}\right]dS\\&= \int_{\partial\Omega} N(\boldsymbol{x}(\boldsymbol{S}),\boldsymbol{\xi})\frac{\partial v(\boldsymbol{x}(\boldsymbol{S}))}{\partial n}\,dS + \frac{1}{|\partial\Omega|}\int_{\partial\Omega} v(\boldsymbol{x}(\boldsymbol{S}))\,dS.\end{aligned}$$

On the other hand, Eqs. (2.1) and (2.5) imply that

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

hence

$$\begin{aligned}&v(\boldsymbol{\xi}) - \frac{1}{D}\int_\Omega N(\boldsymbol{x},\boldsymbol{\xi})\,dx \qquad (2.6)\\&= \int_{\partial\Omega} N(\boldsymbol{x}(\boldsymbol{S}),\boldsymbol{\xi})\frac{\partial v(\boldsymbol{x}(\boldsymbol{S}))}{\partial n}\,dS + \frac{1}{|\partial\Omega|}\int_{\partial\Omega} v(\boldsymbol{x}(\boldsymbol{S}))\,dS.\end{aligned}$$

Note that the second integral on the right hand side of eq. (2.6) is an additive constant. The integral

$$C = \frac{1}{|\partial\Omega|}\int_{\partial\Omega} v(\boldsymbol{x}(\boldsymbol{S}))\,dS, \tag{2.7}$$

is the average of the MFPT on the boundary. Now Eq. (2.6) takes the form

$$v(\boldsymbol{\xi}) = \frac{1}{D}\int_\Omega N(\boldsymbol{x},\boldsymbol{\xi})\,d\boldsymbol{x} + \int_{\partial\Omega_a} N(\boldsymbol{x}(\boldsymbol{S}),\boldsymbol{\xi})\frac{\partial v(\boldsymbol{x}(\boldsymbol{S}))}{\partial n}\,dS + C, \tag{2.8}$$

which is an integral representation of $v(\boldsymbol{\xi})$. We define the boundary flux density

$$g(\boldsymbol{S}) = \frac{\partial v(\boldsymbol{x}(\boldsymbol{S}))}{\partial n}, \tag{2.9}$$

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

$$0 = \frac{1}{D}\int_\Omega N(\boldsymbol{x},\boldsymbol{\xi})\,d\boldsymbol{x} + \int_{\partial\Omega_a} N(\boldsymbol{x}(\boldsymbol{S}),\boldsymbol{\xi})g(\boldsymbol{S})\,dS + C, \tag{2.10}$$

for all $\boldsymbol{\xi} \in \partial\Omega_a$. Eq. (2.10) is an integral equation for $g(\boldsymbol{S})$ and C. To construct an asymptotic approximation to the solution, we note that the first integral in Eq. (2.10) is a regular function of $\boldsymbol{\xi}$ on the boundary. Indeed, due to symmetry of the Neumann function, we have from (2.5)

$$\Delta_{\boldsymbol{\xi}}\int_\Omega N(\boldsymbol{x},\boldsymbol{\xi})\,dx = -1 \quad \text{for} \quad \boldsymbol{\xi} \in \Omega \tag{2.11}$$

and

$$\frac{\partial}{\partial n(\boldsymbol{\xi})}\int_{\Omega} N(\boldsymbol{x},\boldsymbol{\xi})\,d\boldsymbol{x} = -\frac{|\Omega|}{|\partial\Omega|} \quad \text{for} \quad \boldsymbol{\xi}\in\partial\Omega. \tag{2.12}$$

Eq. (2.11) and the boundary condition (2.12) 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 fact that for all $\boldsymbol{x}\in\Omega$, away from $\partial\Omega_a$, the MFPT $v(\boldsymbol{x})$ increases to infinity as the size of the hole decreases and Eq. (2.7) imply that $C\to\infty$ as the size of the hole decreases to zero. This means that for $\boldsymbol{\xi}\in\partial\Omega_a$ the second integral in Eq. (2.10) must also become infinite in this limit, because the first integral is independent of $\partial\Omega_a$. Therefore, the integral equation (2.10) is to leading order

$$\int_{\partial\Omega_a} N(\boldsymbol{x}(\boldsymbol{S}),\boldsymbol{\xi}))g_0(\boldsymbol{S})\,dS = -C_0 \quad \text{for} \quad \boldsymbol{\xi}\in\partial\Omega_a, \tag{2.13}$$

where $g_0(\boldsymbol{S})$ is the first asymptotic approximation to $g(\boldsymbol{S})$ and C_0 is the first approximation to the constant C.

The Neumann function in three dimensions has the form[36]

$$N(\boldsymbol{x},\boldsymbol{\xi}) = \frac{1}{4\pi|\boldsymbol{x}-\boldsymbol{\xi}|} + v_S(\boldsymbol{x},\boldsymbol{\xi}), \tag{2.14}$$

where $v_S(\boldsymbol{x},\boldsymbol{\xi})$ is a regular harmonic function of $\boldsymbol{x}\in\Omega$ and of $\boldsymbol{\xi}\in\Omega$. It follows that only the singular part of the Neumann function contributes to the leading order, so we obtain the integral equation

$$\frac{1}{2\pi}\int_{\partial\Omega_a}\frac{g_0(\boldsymbol{x})}{|\boldsymbol{x}-\boldsymbol{\xi}|}\,dS_{\boldsymbol{x}} = -C_0, \tag{2.15}$$

where C_0 is a constant, which represents the first approximation to the mean first passage time (MFPT). It is also the electrostatic capacity of the window.[18] 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"). For that reason the factor $\frac{1}{4\pi}$ of Eq. (2.14) was replaced by $\frac{1}{2\pi}$. In general, the integral Eq. (2.15) has no explicit solution, and should be solved numerically.

An important consequence of Eq. (2.8) is that

$$\lim_{\varepsilon\to 0}\frac{v(\boldsymbol{\xi})}{C} = 1 \tag{2.16}$$

uniformly for $\boldsymbol{\xi}$ outside a fixed neighborhood $\mathcal{N}$ of $\partial\Omega_a$. Indeed, for $\boldsymbol{\xi}$ outside $\mathcal{N}$ and $\boldsymbol{x}\in\partial\Omega_a$ the Neumann function $N(\boldsymbol{x},\boldsymbol{\xi})$ is uniformly bounded as $\varepsilon\to 0$. Furthermore, $\frac{\partial v(\boldsymbol{x})}{\partial n} < 0$ for $\boldsymbol{x}\in\partial\Omega_a$, so in view of the compatibility condition (2.4), the integral $\int_{\partial\Omega_a} N(\boldsymbol{x}(\boldsymbol{S}),\boldsymbol{\xi})\frac{\partial v(\boldsymbol{x}(\boldsymbol{S}))}{\partial n}\,dS$ is uniformly bounded for $\boldsymbol{\xi}\notin\mathcal{N}$

and so is the integral $\frac{1}{D}\int_\Omega N(\boldsymbol{x},\boldsymbol{\xi})\,d\boldsymbol{x}$ in (2.8), while $v(\boldsymbol{\xi}), C \to \infty$. Eq. (2.16) means that outside the boundary layer the MFPT $v(\cdot)$ is asymptotically constant.

If Ω is a subset of a two-dimensional Riemannian manifold, the Neumann function exists, as long as the compatibility condition holds. The Neumann function $N(\boldsymbol{x},\boldsymbol{y})$ is constructed by using a parametrix $H(\boldsymbol{x},\boldsymbol{y})$,[37]

$$H(\boldsymbol{x},\boldsymbol{y}) = -\frac{h(d(\boldsymbol{x},\boldsymbol{y}))}{2\pi}\log d(\boldsymbol{x},\boldsymbol{y}), \tag{2.17}$$

where $d(\boldsymbol{x},\boldsymbol{y})$ is the Riemannian distance between $\boldsymbol{x}$ and $\boldsymbol{y}$ and $h(\cdot)$ is a regular function with compact support, equal to 1 in a neighborhood of 0. As a consequence of the construction $N(\boldsymbol{x},\boldsymbol{y}) - H(\boldsymbol{x},\boldsymbol{y})$ is a regular function on Ω. It can be written as

$$N(\boldsymbol{x},\boldsymbol{\xi}) = -\frac{1}{2\pi}\log d(\boldsymbol{x},\boldsymbol{\xi}) + v_N(\boldsymbol{x},\boldsymbol{\xi}), \quad \text{for} \quad \boldsymbol{x}\in B_\delta(\boldsymbol{\xi}), \tag{2.18}$$

where $B_\delta(\boldsymbol{\xi})$ is a geodesic ball of radius δ centered at $\boldsymbol{\xi}$ and $v_N(\boldsymbol{x};\boldsymbol{\xi})$ is a regular function. We consider a normal geodesic coordinate system (x, y) at the origin, such that one of the coordinates coincides with the tangent coordinate to $\partial\Omega_a$. We choose unit vectors $\boldsymbol{e}_1, \boldsymbol{e}_2$ as an orthogonal basis in the tangent plane at 0 so that for any vector field $\boldsymbol{X} = x_1\boldsymbol{e}_1 + x_2\boldsymbol{e}_2$, the metric tensor g can be written as

$$g_{ij} = \delta_{ij} + \varepsilon^2\sum_{kl} a_{ij}^{kl}x_kx_l + o(\varepsilon^2), \tag{2.19}$$

where $|x_k| \le 1$, because ε is small. It follows that for $\boldsymbol{x}, \boldsymbol{y}$ inside the geodesic ball or radius ε, centered at the origin, $d(\boldsymbol{x},\boldsymbol{y}) = d_E(\boldsymbol{x},\boldsymbol{y}) + O(\varepsilon^2)$, where d_E is the Euclidean metric. We can now use the computation given in the Euclidean case in Ref. 8, which gives that for $\boldsymbol{x}$ outside a boundary layer

$$E[\tau \mid \boldsymbol{x}] = u(\boldsymbol{x}) = \frac{|\Omega|_g}{\pi D}\left[\log\frac{1}{\varepsilon} + O(1)\right] \quad \text{for } \varepsilon \ll 1. \tag{2.20}$$

2.2. Elliptic Hole in 3D

When the hole $\partial\Omega_a$ is an ellipse, the solution of the integral Eq. (2.15) is known.[16,22] Specifically, assuming the ellipse is given by

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

the solution is

$$g_0(\boldsymbol{x}) = \frac{\tilde{g}_0}{\sqrt{1 - \dfrac{x^2}{a^2} - \dfrac{y^2}{b^2}}}, \tag{2.21}$$

where $\tilde{g}_0$ is a constant (to be determined below). The proof, originally given in Ref. 15, is reproduced in Appendix B. To determine the value of the constant $\tilde{g}_0$, we apply the compatibility condition (2.4). Using the value

$$\int_{\partial\Omega_a} g_0(\boldsymbol{x})\, dS_x = \int_{-a}^{a} dx \int_{-b\sqrt{1-\frac{x^2}{a^2}}}^{b\sqrt{1-\frac{x^2}{a^2}}} \frac{\tilde{g}_0\, dy}{\sqrt{1-\dfrac{x^2}{a^2}-\dfrac{y^2}{b^2}}} = 2\pi ab\tilde{g}_0 \tag{2.22}$$

and the compatibility condition (2.4), we obtain

$$\tilde{g}_0 = -\frac{|\Omega|}{2\pi Dab}. \tag{2.23}$$

Hence, by Eq. (B.5), the leading order approximation to C is

$$C_0 = -\frac{1}{2\pi}\int_{\partial\Omega_a} \frac{g_0(\boldsymbol{x})}{|\boldsymbol{x}-\boldsymbol{y}|}\, dS_x = \frac{|\Omega|}{2\pi Da} K(e), \tag{2.24}$$

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

$$e = \sqrt{1-\frac{b^2}{a^2}}. \tag{2.25}$$

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

$$E\tau(a,b) \sim \frac{|\Omega|}{2\pi Da} K(e). \tag{2.26}$$

For example, in the case of a circular hole, we have $e = 0$ and $K(0) = \frac{\pi}{2}$, so that

$$E\tau(a,a) \sim \frac{|\Omega|}{4Da} = O\left(\frac{1}{\varepsilon}\right), \tag{2.27}$$

provided

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

Eq. (2.27) was used in Refs. [7, 17]. If the mouth of the channel is not circular, the MFPT is different. Equation (2.27) 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.

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 Ω is a ball, the method of Refs. [19–21, 33, 34] 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,[14]

$$\begin{aligned}
\Delta v(r, \theta, \phi) &= -1, \quad \text{for} \quad r < R, \quad 0 \le \theta \le \pi, \quad 0 \le \phi < 2\pi, \\
v(r, \theta, \phi)\Big|_{r=R} &= 0, \quad \text{for} \quad 0 \le \theta < \varepsilon, \quad 0 \le \phi < 2\pi, \\
\frac{\partial v(r, \theta, \phi)}{\partial r}\Big|_{r=R} &= 0, \quad \text{for} \quad \varepsilon \le \theta \le \pi, \quad 0 \le \phi < 2\pi,
\end{aligned} \tag{3.1}$$

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 ϕ, that is, $v(r, \theta, \phi) = v(r, \theta)$, so the system (3.1) can be written as

$$\begin{aligned}
\Delta v(r, \theta) &= -1, \quad \text{for} \quad r < R, \quad 0 \le \theta \le \pi, \\
v(r, \theta)\Big|_{r=R} &= 0, \quad \text{for} \quad 0 \le \theta < \varepsilon, \\
\frac{\partial v(r, \theta)}{\partial r}\Big|_{r=R} &= 0, \quad \text{for} \quad \varepsilon \le \theta \le \pi,
\end{aligned}$$

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

$$\begin{aligned}
\Delta f &= -1, \quad \text{for} \quad r < R, \\
f\Big|_{r=R} &= 0.
\end{aligned}$$

In the decomposition $v = u + f$, the function $u(r, \theta)$ satisfies the mixed Dirichlet-Neumann boundary value problem for the Laplace equation

$$\Delta u(r, \theta) = 0, \quad \text{for} \quad r < R, \quad 0 \le \theta \le \pi,$$

$$u(r,\theta)\Big|_{r=R} = 0, \quad \text{for} \quad 0 \le \theta < \varepsilon, \tag{3.2}$$

$$\frac{\partial u(r,\theta)}{\partial r}\Big|_{r=R} = \frac{R}{3}, \quad \text{for} \quad \varepsilon \le \theta \le \pi.$$

Separation of variables suggests that

$$u(r,\theta) = \sum_{n=0}^{\infty} a_n \left(\frac{r}{R}\right)^n P_n(\cos\theta), \tag{3.3}$$

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

$$u(r,\theta)\Big|_{r=R} = \sum_{n=0}^{\infty} a_n P_n(\cos\theta) = 0, \quad 0 \le \theta < \varepsilon, \tag{3.4}$$

$$\frac{\partial u(r,\theta)}{\partial r}\Big|_{r=R} = \sum_{n=1}^{\infty} n a_n P_n(\cos\theta) = \frac{R^2}{3}, \quad \varepsilon \le \theta \le \pi. \tag{3.5}$$

Obviously, the first coefficient a_0 in the expansion (3.3) is the average of $u(r,\theta)$ with respect to θ. Since $u(r,\theta)$ differs from the MFPT $v(r,\theta)$ by $O(1)$ as $\varepsilon \to 0$, we see that $a_0 \to \infty$ and $v(r,\theta)/a_0 \to 1$ outside a boundary layer around the small window (see (2.16)).

Eqs. (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

$$\sum_{n=0}^{\infty} a_n P_n(\cos\theta) = 0, \quad \text{for} \quad 0 \le \theta < \varepsilon, \tag{3.6}$$

$$\sum_{n=0}^{\infty} (2n+1) a_n P_n(\cos\theta) = G(\theta), \quad \text{for} \quad \varepsilon \le \theta \le \pi \tag{3.7}$$

are solved in [Ref. 19, Eqs.(5.5.12)–(5.5.14), (5.6.12)]. However, the dual series Eqs. (3.6)–(3.7) are different from Eqs. (3.4)–(3.5). The factor $2n + 1$ that appears in Eq. (3.7) is replaced by n in Eq. (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 Eqs. ((3.4)–(3.5)) (see Ref. 19 (5.6.19)–(5.6.20)) is discussed in Refs. 33, 34. Specifically, assume that for given functions $G(\theta)$ and $F(\theta)$ we have the representation

$$\sum_{n=0}^{\infty}(1+H_n)b_n T_{m+n}^{-m}(\cos\theta) = F(\theta), \quad \text{for} \quad 0 \le \theta < \varepsilon,$$

$$\sum_{n=0}^{\infty}(2n+2m+1)b_n T_{m+n}^{-m}(\cos\theta) = G(\theta), \quad \text{for} \quad \varepsilon < \theta \le \pi,$$

where T_{m+n}^{-m} are Ferrer's associated Legendre polynomials[39,40] and $\{H_n\}$ is a given series that is $O(n^{-1})$ as $n \to \infty$. Then for $m = 0$, we have

$$\sum_{n=0}^{\infty}(1+H_n)b_n P_n(\cos\theta) = F(\theta), \quad \text{for} \quad 0 \le \theta < \varepsilon, \tag{3.8}$$

$$\sum_{n=0}^{\infty}(2n+1)b_n P_n(\cos\theta) = G(\theta), \quad \text{for} \quad \varepsilon < \theta \le \pi. \tag{3.9}$$

Setting $a_0 = b_0,\ a_n = \dfrac{2n+1}{2n} b_n,\ n \ge 1$ in Eqs. (3.4)–(3.5) results in

$$\sum_{n=0}^{\infty}(1+H_n)b_n P_n(\cos\theta) = 0, \quad \text{for} \quad 0 \le \theta < \varepsilon, \tag{3.10}$$

$$\sum_{n=0}^{\infty}(2n+1)b_n P_n(\cos\theta) = \frac{2R^2}{3} + b_0, \quad \text{for} \quad \varepsilon \le \theta \le \pi. \tag{3.11}$$

Eqs. (3.10)–(3.11) are equivalent to (3.8)–(3.9) with $H_0 = 0,\ H_n = \dfrac{1}{2n},\ n \ge 1$, $F(\theta) = 0$, and $G(\theta) = \dfrac{2R^2}{3} + b_0$. Collins' method of solution consists in finding an integral equation for the function

$$h(\theta) = \sum_{n=0}^{\infty}(2n+1)b_n P_n(\cos\theta), \quad \text{for} \quad 0 \le \theta < \varepsilon,$$

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 Eq. (3.8), with $F(\theta) \equiv 0$, we find for $0 \leq \theta < \varepsilon$ that

$$0 = \frac{1}{2}\int_0^{\varepsilon} h(\alpha)\sum_{n=0}^{\infty}(1 + H_n)P_n(\cos\alpha)P_n(\cos\theta)\sin\alpha\, d\alpha$$
$$+\frac{1}{2}\int_{\varepsilon}^{\pi} G(\alpha)\sum_{n=0}^{\infty}(1 + H_n)P_n(\cos\alpha)P_n(\cos\theta)\sin\alpha\, d\alpha. \qquad (3.12)$$

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 of 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,[38,41]

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

and the identity[19]

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

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

$$\frac{1}{2}\int_{\varepsilon}^{\pi} G(\alpha)\sum_{n=0}^{\infty} P_n(\cos\alpha)P_n(\cos\theta)\sin\alpha\, d\alpha$$
$$= \frac{1}{2}\int_{\varepsilon}^{\pi} G(\alpha)\sum_{n=0}^{\infty} P_n(\cos\alpha)\frac{\sqrt{2}}{\pi}\int_0^{\theta} \frac{\cos(n + \frac{1}{2})u\, du}{\sqrt{\cos u - \cos\theta}}\sin\alpha\, d\alpha$$
$$= \frac{1}{2\pi}\int_0^{\theta} \frac{du}{\sqrt{\cos u - \cos\theta}}\int_{\varepsilon}^{\pi} \frac{G(\alpha)\sin\alpha\, d\alpha}{\sqrt{\cos u - \cos\alpha}}. \qquad (3.15)$$

Similarly,

$$\frac{1}{2}\int_0^{\varepsilon} h(\alpha)\sum_{n=0}^{\infty} P_n(\cos\alpha)P_n(\cos\theta)\sin\alpha\, d\alpha$$

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

Hence,

$$\int_0^\theta \frac{du}{\sqrt{\cos u - \cos\theta}} \int_u^\varepsilon \frac{h(\alpha)\sin\alpha\, d\alpha}{\sqrt{\cos u - \cos\alpha}} = - \int_0^\theta \frac{du}{\sqrt{\cos u - \cos\theta}} \int_\varepsilon^\pi \frac{G(\alpha)\sin\alpha\, d\alpha}{\sqrt{\cos u - \cos\alpha}}. \tag{3.17}$$

Eq. (3.17) means that the Abel transforms[42] of two functions are the same, so that

$$\int_u^\varepsilon \frac{h(\alpha)\sin\alpha\, d\alpha}{\sqrt{\cos u - \cos\alpha}} = - \int_\varepsilon^\pi \frac{G(\alpha)\sin\alpha\, d\alpha}{\sqrt{\cos u - \cos\alpha}}, \tag{3.18}$$

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

$$h(\theta)\sin\theta = \frac{1}{\pi}\frac{d}{d\theta} \int_\theta^\varepsilon \frac{\sin u\, du}{\sqrt{\cos\theta - \cos u}} \int_\varepsilon^\pi \frac{G(\alpha)\sin\alpha\, d\alpha}{\sqrt{\cos u - \cos\alpha}}, \tag{3.19}$$

or

$$h(\theta) = -\frac{2}{\sin\theta}\frac{d}{d\theta} \int_\theta^\varepsilon \frac{H(u)\sin u\, du}{\sqrt{\cos\theta - \cos u}}, \tag{3.20}$$

where

$$H(u) = -G(u, \varepsilon), \tag{3.21}$$

and

$$G(u, \varepsilon) = \frac{1}{2\pi} \int_\varepsilon^\pi \frac{G(\theta)\sin\theta\, d\theta}{\sqrt{\cos u - \cos\theta}}. \tag{3.22}$$

The dual integral Eqs. (3.10)–(3.11) define $G(\theta) = \dfrac{2R^2}{3} + b_0$, so that

$$\begin{aligned} G(\psi, \phi) &= \frac{1}{2\pi} \int_\phi^\pi \left(\frac{2R^2}{3} + b_0\right) \frac{\sin\theta\, d\theta}{\sqrt{\cos\psi - \cos\theta}} \\ &= \left(\frac{2R^2}{3} + b_0\right) \frac{1}{\pi} \sqrt{\cos\psi - \cos\theta}\,\Big|_{\theta=\phi}^{\pi} \\ &= \left(\frac{2R^2}{3} + b_0\right) \frac{1}{\pi} \left(\sqrt{2}\cos\frac{\psi}{2} - \sqrt{\cos\psi - \cos\phi}\right), \quad \text{for} \quad \psi < \phi. \end{aligned} \tag{3.23}$$

In particular, setting $n = 0$ in Eq. (3.12) and using Eq. (3.20), gives

$$b_0 = \frac{1}{2}\int_0^{\varepsilon} h(\alpha)\sin\alpha\, d\alpha + \frac{1}{2}\int_{\varepsilon}^{\pi}\left(\frac{2R^2}{3} + b_0\right)\sin\alpha\, d\alpha$$
$$= \sqrt{2}\int_0^{\varepsilon} H(\psi)\cos\frac{\psi}{2}\, d\psi + \left(\frac{2R^2}{3} + b_0\right)\cos^2\frac{\varepsilon}{2}. \tag{3.24}$$

Integrating Eq. (3.23), we obtain

$$\sqrt{2}\int_0^{\varepsilon} G(\psi,\varepsilon)\cos\frac{\psi}{2}\, d\psi$$
$$= \left(\frac{2R^2}{3} + b_0\right)\frac{\sqrt{2}}{\pi}\int_0^{\varepsilon}\left(\sqrt{2}\cos\frac{\psi}{2} - \sqrt{\cos\psi - \cos\varepsilon}\right)\cos\frac{\psi}{2}\, d\psi$$
$$= \frac{\frac{2R^2}{3} + b_0}{\pi}(\varepsilon + \sin\varepsilon) - \left(\frac{2R^2}{3} + b_0\right)\frac{4}{\pi}\int_0^{\sin\frac{\varepsilon}{2}}\frac{s^2\, ds}{\sqrt{\sin^2\frac{\varepsilon}{2} - s^2}}$$
$$= \frac{\frac{2R^2}{3} + b_0}{\pi}(\varepsilon + \sin\varepsilon) - \left(\frac{2R^2}{3} + b_0\right)\sin^2\frac{\varepsilon}{2}. \tag{3.25}$$

Combining Eqs. (3.24) and (3.25) gives

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

where $|\Omega| = \dfrac{4\pi R^3}{3}$ 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

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

$$= \frac{1}{2\pi}\int_0^{\varepsilon} h(\alpha)\sin\alpha\, d\alpha \int_0^{\alpha} \frac{dv}{\sqrt{\cos v - \cos\alpha}} \int_0^{\theta} \frac{K(u,v)\, du}{\sqrt{\cos u - \cos\theta}}$$

$$= \frac{1}{2\pi}\int_0^{\theta} \frac{du}{\sqrt{\cos u - \cos\theta}} \int_0^{\varepsilon} K(u,v)\, dv \int_v^{\varepsilon} \frac{h(\alpha)\, \sin\alpha\, d\alpha}{\sqrt{\cos v - \cos\alpha}}, \tag{3.27}$$

where

$$\begin{aligned} K(u,v) &= \frac{2}{\pi}\sum_{n=0}^{\infty} H_n \cos\left(n+\frac{1}{2}\right) u \cos\left(n+\frac{1}{2}\right) v \\ &= -\frac{\cos\frac{1}{2}(v+u)}{2\pi}\log 2\left|\sin\frac{1}{2}(v+u)\right| \\ &\quad -\frac{\cos\frac{1}{2}(v-u)}{2\pi}\log 2\left|\sin\frac{1}{2}(v-u)\right| \\ &\quad +\frac{v+u-\pi}{4\pi}\sin\frac{1}{2}(v+u) + \frac{v-u-\pi}{4\pi}\sin\frac{1}{2}(v-u). \end{aligned} \tag{3.28}$$

Similarly,

$$\begin{aligned} &\frac{1}{2}\int_{\varepsilon}^{\pi} G(\alpha)\sum_{n=0}^{\infty} H_n P_n(\cos\alpha)P_n(\cos\theta)\sin\alpha\, d\alpha \\ &\quad = \frac{1}{2\pi}\int_{\varepsilon}^{\pi} G(\alpha)\sin\alpha\, d\alpha \int_0^{\alpha} \frac{dv}{\sqrt{\cos v - \cos\alpha}} \int_0^{\theta} \frac{K(u,v)\, du}{\sqrt{\cos u - \cos\theta}} \\ &\quad = \frac{1}{2\pi}\int_0^{\theta} \frac{du}{\sqrt{\cos u - \cos\theta}} \int_{\varepsilon}^{\pi} G(\alpha)\sin\alpha\, d\alpha \int_0^{\alpha} \frac{K(u,v)\, dv}{\sqrt{\cos v - \cos\alpha}}. \end{aligned} \tag{3.29}$$

Substituting Eqs. (3.15), (3.16), (3.27), and (3.29) into Eq. (3.12) yields

$$\begin{aligned} 0 &= \frac{1}{2\pi}\int_0^{\theta} \frac{du}{\sqrt{\cos u - \cos\theta}} \int_u^{\varepsilon} \frac{h(\alpha)\sin\alpha\, d\alpha}{\sqrt{\cos u - \cos\alpha}} \\ &\quad + \frac{1}{2\pi}\int_0^{\theta} \frac{du}{\sqrt{\cos u - \cos\theta}} \int_0^{\varepsilon} K(u,v)\, dv \int_v^{\varepsilon} \frac{h(\alpha)\, \sin\alpha\, d\alpha}{\sqrt{\cos v - \cos\alpha}} \\ &\quad + \frac{1}{2\pi}\int_0^{\theta} \frac{du}{\sqrt{\cos u - \cos\theta}} \int_{\varepsilon}^{\pi} \frac{G(\alpha)\sin\alpha\, d\alpha}{\sqrt{\cos u - \cos\alpha}} \\ &\quad + \frac{1}{2\pi}\int_0^{\theta} \frac{du}{\sqrt{\cos u - \cos\theta}} \int_{\varepsilon}^{\pi} G(\alpha)\sin\alpha\, d\alpha \int_0^{\alpha} \frac{K(u,v)\, dv}{\sqrt{\cos v - \cos\alpha}}, \end{aligned}$$

which is again an Abel-type integral equation. Inverting the Abel transform,[42] we obtain

$$0 = \frac{1}{2\pi}\int_u^{\varepsilon} \frac{h(\alpha)\sin\alpha\, d\alpha}{\sqrt{\cos u - \cos\alpha}} + \frac{1}{2\pi}\int_0^{\varepsilon} K(u,v)\,dv \int_v^{\varepsilon} \frac{h(\alpha)\,\sin\alpha\, d\alpha}{\sqrt{\cos v - \cos\alpha}} \tag{3.30}$$

$$+\frac{1}{2\pi}\int_{\varepsilon}^{\pi} \frac{G(\alpha)\sin\alpha\, d\alpha}{\sqrt{\cos u - \cos\alpha}} + \frac{1}{2\pi}\int_{\varepsilon}^{\pi} G(\alpha)\sin\alpha\, d\alpha \int_0^{\alpha} \frac{K(u,v)\,dv}{\sqrt{\cos v - \cos\alpha}}.$$

Setting

$$H(u) = \frac{1}{2\pi}\int_u^{\varepsilon} \frac{h(\alpha)\sin\alpha\, d\alpha}{\sqrt{\cos u - \cos\alpha}}, \tag{3.31}$$

we invert the Abel transform (3.31) to obtain

$$h(\theta) = -\frac{2}{\sin\theta}\frac{d}{d\theta}\int_{\theta}^{\varepsilon} \frac{\sin u H(u)\,du}{\sqrt{\cos\theta - \cos u}}. \tag{3.32}$$

Writing

$$J(u) = H(u) + G(u,\varepsilon), \tag{3.33}$$

Eq. (3.30) becomes

$$J(u) + \int_0^{\varepsilon} K(u,v)J(v)\,dv = M(u), \tag{3.34}$$

where the free term $M(u)$ is given by

$$M(u) = -\int_{\varepsilon}^{\pi} K(u,v)G(v,v)\,dv. \tag{3.35}$$

Eq. (3.34) is a Fredholm integral equation for J.

3.2.3. The Second Term and the Remaining Error: L^2 Estimates

Eqs. (3.24), (3.25), and (3.33) give that

$$b_0 + \frac{2R^2}{3} = \frac{2R^2}{3}\frac{\pi}{\varepsilon + \sin\varepsilon} + \frac{\sqrt{2}\pi}{\varepsilon + \sin\varepsilon}\int_0^{\varepsilon} J(u)\cos\frac{u}{2}\,du, \tag{3.36}$$

where J is the solution of the Fredholm Eq. (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 $\frac{R^2}{3}\frac{\pi}{\varepsilon}$, obtained in Section 3.2.2 This confirms the intuitive results of, Refs. [7, 17], 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

$$Kf(u) = \int_0^\varepsilon K(u, v) f(v)\, dv, \tag{3.37}$$

maps $L^2[0, \varepsilon]$ into $L^2[0, \varepsilon]$. In Appendix A we derive the estimate

$$\|K\|_2 \le \frac{\sqrt{30}}{2\pi}\, \varepsilon \log \frac{1}{\varepsilon}, \tag{3.38}$$

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, Eq. (3.34) can be written as

$$J = M - KJ. \tag{3.39}$$

The triangle inequality yields

$$\|J\|_2 \le \|M\|_2 + \|KJ\|_2 \le \|M\|_2 + \|K\|_2 \|J\|_2, \tag{3.40}$$

which together with the estimate (3.38) gives

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

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

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

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

$$\begin{aligned}
\int_0^\pi K(u, v) \cos \frac{v}{2}\, dv &= \frac{1}{\pi} \sum_{n=1}^\infty \frac{\cos\left(\frac{n+1}{2}\right) u}{n} \int_0^\pi \cos\left(n + \frac{1}{2}\right) v \cos \frac{v}{2}\, dv \\
&= \frac{1}{2\pi} \sum_{n=1}^\infty \frac{\cos\left(\frac{n+1}{2}\right) u}{n} \int_0^\pi (\cos(n+1)v + \cos nv)\, dv \\
&= 0.
\end{aligned} \tag{3.43}$$

Eqs. (3.23), (3.35), and (3.42) imply that

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

The estimate (3.38) gives

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

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

$$\|J\|_2 \le \frac{4}{\pi^2}\left(\frac{2R^2}{3} + b_0\right)\varepsilon^{3/2}\log\frac{1}{\varepsilon} = \left(\frac{2R^2}{3} + b_0\right)O(\varepsilon^{3/2}\log\varepsilon). \tag{3.46}$$

3.2.6. The Second Term and Error Estimate

The Cauchy-Schwartz inequality implies that

$$\frac{\sqrt{2}\pi}{\varepsilon + \sin\varepsilon}\left|\int_0^{\varepsilon} J(u)\cos\frac{u}{2}\,du\right| \le \left(\frac{2R^2}{3} + b_0\right)\varepsilon\log\frac{1}{\varepsilon}, \tag{3.47}$$

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

$$b_0 = \frac{\pi R^2}{3\varepsilon}\left(1 + O(\varepsilon\log\varepsilon)\right) = \frac{|\Omega|}{4a}\left(1 + O(\varepsilon\log\varepsilon)\right). \tag{3.48}$$

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

$$(I + K)J = M. \tag{3.49}$$

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

$$J = M + O\left(\|K\|_2\|M\|_2\right). \tag{3.50}$$

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

$$\begin{aligned}\int_0^{\varepsilon} J(u)\cos\frac{u}{2}\,du &= \int_0^{\varepsilon} M(u)\cos\frac{u}{2}\,du + O\left(\varepsilon\|K\|_2\|M\|_2\right)\\ &= \frac{\sqrt{2}}{\pi}\left(b_0 + \frac{2R^2}{3}\right)\left[\int_0^{\varepsilon}\int_0^{\varepsilon} K(u, v)\cos\frac{u}{2}\cos\frac{v}{2}\,du\,dv + O\left(\varepsilon^3\log^2\varepsilon\right)\right].\end{aligned} \tag{3.51}$$

Eq. (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 Eq. (3.36) that

$$b_0=\frac{|\Omega|}{4a}\left[1+\varepsilon\log\frac{1}{\varepsilon}+O(\varepsilon)\right]. \tag{3.52}$$

3.3. The MFPT

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

$$v\bigg|_{r=0}=u\bigg|_{r=0}+\frac{R^2}{6}=b_0+\frac{R^2}{6}=\frac{|\Omega|}{4a}\left[1+\varepsilon\log\frac{1}{\varepsilon}+O(\varepsilon)\right]. \tag{3.53}$$

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 ε^{-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, such as at corners, cusps, and so on is postponed to a future paper.

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 Ref. 7 that the flux profile in the connecting hole was uniform. The structure of the flux profile, which is proportional to $(a^2 - \rho^2)^{-1/2}$, was observed by Rayleigh in 1877.[16] 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 Ref. 43 by solving the same problem, and gave a result that differs from that of Ref. 16, 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 Ref. 21. Another application of the narrow escape problem concerns ionic channels,[1] and particularly particle simulations of the permeation process[2–6] 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 0.1 Molar, channel radius $a = 20\,\text{Å}$, diffusion coefficient $D = 1.5 \times 10^{-9}\,\text{m}^2/\text{sec}$ is $\bar{\tau} \approx 1n$ sec. 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.[44]

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 $|\Omega|$, the approximate expression for the MFPT is

$$E\tau \approx \frac{|\Omega|}{4\varepsilon D} + \frac{L^2}{2D}. \tag{4.2}$$

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 $|\Omega| = \frac{4\pi R^3}{3}$, with a small opening of size ε 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.(9,10) This coupling is involved in the induction of processes such as synaptic plasticity.(11) 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.(12) 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).

Finally, we note that the results can be generalized to higher dimensions in a straightforward manner.

APPENDIX A: Estimate of $\|K\|_2$

A.1. Estimate of the Kernel

A rough estimate of the kernel, for $0 \le u, v \le \varepsilon$, is obtained from Eq. (3.28) as

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

Furthermore,

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

$$\le 2\left(\sin\frac{1}{2}(v+\varepsilon)-\sin\frac{1}{2}v\right)\left(\log 2\left|\sin\frac{1}{2}v\right|\right)^2 \le \varepsilon\cos\frac{1}{2}v\left(\log 2\left|\sin\frac{1}{2}v\right|\right)^2$$

and

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

Similarly,

$$\int_0^\varepsilon \cos\frac{1}{2}(v-u)\left(\log\left|2\sin\frac{1}{2}(v-u)\right|\right)^2 dv$$

$$= \int_0^{2\sin\frac{1}{2}u} (\log x)^2\, dx + \int_0^{2\sin\frac{1}{2}(\varepsilon-u)} (\log x)^2\, dx$$

$$\le 2u\log^2 u + 2(\varepsilon-u)\log^2(\varepsilon-u).$$

It follows that

$$\int_0^\varepsilon \left(2u\log^2 u + 2(\varepsilon-u)\log^2(\varepsilon-u)\right) du \le 4\varepsilon^2\log^2\varepsilon,$$

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

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

which is (3.38).

APPENDIX B: Elliptic Hole

We present here, for completeness, Lure's[22] solution to the integral Eq. (2.15) in the elliptic hole case. We define for $\boldsymbol{y}=(x,y)$

$$L(\boldsymbol{y}) = 1-\frac{x^2}{a^2}-\frac{y^2}{b^2}\quad (b\le a)$$

and introduce polar coordinates in the ellipse $\partial\Omega_a$

$$\boldsymbol{x} = \boldsymbol{y} + (\rho\cos\theta,\, \rho\sin\theta),$$

with origin at the point $\boldsymbol{y}$. The integral in Eq. (2.15) takes the form

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

where $\rho_0(\theta)$ denotes the distance between $\boldsymbol{y}$ and the boundary of the ellipse in the direction θ. Expanding $L(\boldsymbol{x})$ in powers of ρ, we find that

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

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 Eq. (B.2) for ρ, taking the positive root, we obtain

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

therefore, for fixed $\boldsymbol{y}$ and θ,

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

and the integral takes the form

$$\begin{aligned}\int_{\partial\Omega_a} \frac{g_0(\boldsymbol{x})}{|\boldsymbol{x}-\boldsymbol{y}|}\, dS_x &= \int_0^{2\pi} d\theta \int_0^{L(\boldsymbol{y})} \frac{1}{2}\frac{dL(\boldsymbol{x})}{\left[\phi_1^2 + \phi_2\left(L(\boldsymbol{y}) - L(\boldsymbol{x})\right)\right]^{1/2}}\frac{\tilde{g}_0}{\sqrt{L(\boldsymbol{x})}}\\ &= \int_0^{2\pi} d\theta \int_0^{L(\boldsymbol{y})} \frac{1}{2}\frac{\tilde{g}_0\, dz}{\sqrt{\phi_1^2 + \phi_2 z}\sqrt{L(\boldsymbol{y}) - z}}.\end{aligned}$$

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

$$\begin{aligned}\int_{\partial\Omega_a} \frac{g_0(\boldsymbol{x})}{|\boldsymbol{x}-\boldsymbol{y}|}\, dS_x &= \int_0^{2\pi} d\theta \frac{\tilde{g}_0}{2\sqrt{\phi_2}} \int_0^1 \frac{d\boldsymbol{s}}{\sqrt{\psi + \boldsymbol{s}}\sqrt{1-\boldsymbol{s}}}\\ &= \int_0^{2\pi} d\theta \frac{\tilde{g}_0}{2\sqrt{\phi_2}} 2\arctan\sqrt{\frac{\psi+s}{1-s}}\,\Bigg|_0^1\\ &= \int_0^{2\pi} \frac{\tilde{g}_0}{2\sqrt{\phi_2}}\left(\pi - 2\arctan\sqrt{\psi}\right) d\theta\\ &= \int_0^{2\pi} \frac{\tilde{g}_0\, d\theta}{2\sqrt{\frac{\cos^2\theta}{a^2} + \frac{\sin^2\theta}{b^2}}}\left(\pi - 2\arctan\frac{\frac{x\cos\theta}{a^2} + \frac{y\sin\theta}{b^2}}{\sqrt{\frac{\cos^2\theta}{a^2} + \frac{\sin^2\theta}{b^2}L(\boldsymbol{y})}}\right).\end{aligned}$$

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

$$\int_{\partial\Omega_a} \frac{g_0(\boldsymbol{x})}{|\boldsymbol{x} - \boldsymbol{y}|}\, dS_x = \frac{\pi \tilde{g}_0}{2} \int_0^{2\pi} \frac{d\theta}{\sqrt{\dfrac{\cos^2\theta}{a^2} + \dfrac{\sin^2\theta}{b^2}}}$$

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

$$= 2\pi b \tilde{g}_0 K(e), \tag{B.5}$$

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

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

We note that the integral (B.5) is independent of $\boldsymbol{y}$, so we conclude that (2.21) is the solution of the integral Eq. (2.15).

APPENDIX 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

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

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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