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ACTIVATION THROUGH A NARROW OPENING*

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Abstract. The escape of a Brownian motion through a narrow absorbing window in an otherwise reflecting boundary of a domain is a rare event. In the presence of a deep potential well, there are two long time scales, the mean escape time from the well and the mean time to reach the absorbing window. We derive a generalized Kramers formula for the mean escape time through the narrow window.

Key words. stochastic differential equations, exit problem, narrow escape, mixed boundary value problem

AMS subject classifications. 60H10, 60J60, 35J25

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1. Introduction.

Kramers' theory [12], [6] concerns the thermal activation of a Brownian particle over a high potential barrier. It assumes that the barrier height is much larger than the thermal energy. Its application to the theory of chemical kinetics [20] gives the activation rate of the stochastic dynamics of a reactant molecule over a potential barrier ΔE as the Arrhenius law

$$k = Ae^{-\Delta E/k_B T}, \tag{1.1}$$

where A is a function of temperature, friction, and the potential landscape. A similar, but different situation arises, if the chemical reaction can be described as the diffusion of a Brownian particle through a small opening in the boundary of a domain, whose remaining boundaries are practically reflecting. Such a situation can occur, if the reflecting boundaries are due to a high potential barrier with a small opening, whose energy is not necessarily much higher than the thermal energy. This can happen, for example, if the reflecting boundaries are due to a dielectric barrier, as in biological membranes, and the small opening is a protein channel embedded in an otherwise impenetrable membrane [7]. The small absorbing window setup is also a model for the forward rate of chemical reactions, in which there are small binding sites for the diffusing reacting molecule in the boundary of the domain [9]. The same setup also describes the process of trafficking receptors on biological membranes [8]. The escape of a free Brownian motion (without drift) through a small window was discussed in [17], [18], [19]. Here we consider the narrow escape problem for a Brownian motion in a field of force. The closely related problem of computing the principal eigenvalue of the Laplace operator for mixed boundary conditions on large and small pieces of the boundary was considered in [22], [23], [24], [11] (see section 6 for discussion).

We derive an Arrhenius-like formula (1.1) for the activation rate through narrow openings. Specifically, we consider the diffusion of a Brownian particle in a potential

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field in a bounded domain Ω, where activation occurs if the particle goes through a small opening $\partial\Omega_a$ in the boundary $\partial\Omega$ of the domain. We assume that the remaining boundary $\partial\Omega_r$ reflects the Brownian trajectories. We find the dependence of the rate constant on the potential, specific geometry of the opening and on the volume or surface area of the domain. As in Kramers' theory, we obtain different rate constants for low and high barriers. The activation rates for the different geometries are summarized in (4.6)–(4.13).

2. Formulation. As in classical theories [12], [6], [20], our point of departure is the Langevin dynamics in $\mathbb{R}^n$ $(n = 2, 3)$,

$$m\ddot{\boldsymbol{x}} + \eta\dot{\boldsymbol{x}} + \nabla\Phi(\boldsymbol{x}) = \sqrt{2\eta k_B T}\dot{\boldsymbol{w}}, \tag{2.1}$$

where m is the mass, η is the friction coefficient, $\Phi(x)$ is the potential, T is temperature, k_B is Boltzmann's constant, and $\dot{\boldsymbol{w}}$ is a vector of n independent δ-correlated Gaussian white noises. In the Smoluchowski (Kramers) limit of large friction, the Langevin dynamics (2.1) reduces to the Smoluchowski equation [16], [4], [6]

$$\dot{\boldsymbol{x}} + \frac{1}{\gamma}\nabla\phi(\boldsymbol{x}) = \sqrt{\frac{2k_B T}{m\gamma}}\,\dot{\boldsymbol{w}}, \tag{2.2}$$

where $\gamma = \eta/m$ is the dynamics viscosity and $\phi = \Phi/m$ is the potential per unit mass.

The motion of the Brownian particle is confined to a bounded domain Ω, whose boundary $\partial\Omega$ is reflecting, but for a small absorbing window $\partial\Omega_a$ $(\partial\Omega = \partial\Omega_a \cup \Omega_r)$. The assumption that the window is small means that

$$\delta = \left(\frac{|\partial\Omega_a|}{|\partial\Omega|}\right)^{1/(n-1)} \ll 1 \tag{2.3}$$

(δ is a small parameter).

The probability density function (pdf) $p_\delta(\boldsymbol{x}, t)$ of finding the Brownian particle at location $\boldsymbol{x}$ at time t satisfies the Fokker–Planck equation

$$\gamma\frac{\partial p_\delta}{\partial t} = \varepsilon\Delta p_\delta + \nabla\cdot(p_\delta\nabla\phi) \equiv \mathcal{L}_\delta p_\delta, \tag{2.4}$$

with the initial condition

$$p_\delta(\boldsymbol{x}, 0) = p_0(\boldsymbol{x}), \tag{2.5}$$

and the mixed Dirichlet–Neumann boundary conditions for $t > 0$

$$p_\delta = 0 \quad \text{for} \quad \boldsymbol{x} \in \partial\Omega_a, \tag{2.6}$$

$$\varepsilon\frac{\partial p_\delta}{\partial n} + p_\delta\frac{\partial\phi}{\partial n} = 0 \quad \text{for} \quad \boldsymbol{x} \in \partial\Omega_r, \tag{2.7}$$

where $\varepsilon = k_B T/m$, $\boldsymbol{n}$ is the unit outer normal at the boundary, and $p_0(\boldsymbol{x})$ is the initial pdf (e.g., $p_0(\boldsymbol{x}) = \frac{1}{|\Omega|}$ for a uniform distribution). The function

$$u_\delta(\boldsymbol{x}) = \int_0^\infty p_\delta(\boldsymbol{x}, t)\,dt, \tag{2.8}$$

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which is the mean time the particle spends at $\boldsymbol{x}$ before it escapes through the narrow window, is the solution of the boundary value problem

$$\mathcal{L}_\delta u_\delta = -\gamma p_0 \quad \text{for} \quad \boldsymbol{x} \in \Omega, \tag{2.9}$$

$$u_\delta = 0 \quad \text{for} \quad \boldsymbol{x} \in \partial\Omega_a, \tag{2.10}$$

$$\varepsilon \frac{\partial u_\delta}{\partial n} + u_\delta \frac{\partial \phi}{\partial n} = 0 \quad \text{for} \quad \boldsymbol{x} \in \partial\Omega_r. \tag{2.11}$$

The function $g_\delta = u_\delta e^{\phi/\varepsilon}$ is the solution of the adjoint problem

$$\mathcal{L}_\delta^* g_\delta = -\gamma p_0 e^{\phi/\varepsilon} \quad \text{for} \quad \boldsymbol{x} \in \Omega, \tag{2.12}$$

$$\begin{aligned} \frac{\partial g_\delta(\boldsymbol{x})}{\partial n} &= 0 \quad \text{for} \quad \boldsymbol{x} \in \partial\Omega_r, \\ g_\delta(\boldsymbol{x}) &= 0 \quad \text{for} \quad \boldsymbol{x} \in \partial\Omega_a. \end{aligned} \tag{2.13}$$

Equation (2.12) can be written in the divergence form

$$\nabla \left(e^{-\phi/\varepsilon} \nabla g_\delta \right) = -\frac{\gamma p_0}{\varepsilon}. \tag{2.14}$$

The adjoint operators $\mathcal{L}_\delta$ and $\mathcal{L}_\delta^*$, defined by (2.4), (2.9), (2.10), (2.11), and (2.12), (2.13), respectively, have biorthogonal systems of normalized eigenfunctions, $\{\psi_i(\boldsymbol{x}, \delta)\}$ and $\{\varphi_i(\boldsymbol{x}, \delta)\}$ $(i = 0, 1, \ldots)$, and we can expand

$$p_\delta(\boldsymbol{x}, t) = \sum_{i=0}^{\infty} a_i(\delta) \psi_i(\boldsymbol{x}, \delta) e^{-\lambda_i(\delta) t/\gamma}, \tag{2.15}$$

where $\lambda_i(\delta)$ are the eigenvalues of $\mathcal{L}_\delta$. The $a_i(\delta)$ are the Fourier coefficients of the initial function $p_0(\boldsymbol{x})$. In the limit $\delta \to 0$ the Dirichlet part of the boundary conditions, (2.6), is dropped, so that $\lambda_0(\delta) \to 0$ (the first eigenvalue of the problem (2.4), (2.7) with $\partial\Omega_r = \partial\Omega$), with the normalized eigenfunction

$$\psi_0(\boldsymbol{x}, 0) = \frac{\exp\{-\phi(\boldsymbol{x})/\varepsilon\}}{\displaystyle\int_\Omega \exp\{-\phi(\boldsymbol{x})/\varepsilon\}\, d\boldsymbol{x}}, \tag{2.16}$$

and $a_0(\delta) \to 1$. It follows from (2.8) and (2.15) that for all $\boldsymbol{x} \in \Omega$

$$u_\delta(\boldsymbol{x}) = \gamma \sum_{i=0}^{\infty} \frac{a_i(\delta) \psi_i(\boldsymbol{x}, \delta)}{\lambda_i(\delta)} \to \infty \quad \text{as} \quad \delta \to 0. \tag{2.17}$$

In particular, the first passage time $\tau_\delta = \inf\{t > 0 \mid \boldsymbol{x}(t) \in \partial\Omega_a\}$ diverges. That is, $\lim_{\delta \to 0} \tau_\delta = \infty$ on almost every trajectory $\boldsymbol{x}(t)$. Obviously, the mean first passage time,

$$\langle \tau_\delta \rangle = \int_\Omega u_\delta(\boldsymbol{x})\, d\boldsymbol{x} = \gamma \sum_{i=0}^{\infty} \frac{a_i(\delta)}{\lambda_i(\delta)}, \tag{2.18}$$

also diverges as $\delta \to 0$. It is the purpose of this paper to find the orders of magnitude of $u_\delta(\boldsymbol{x})$ and $\langle \tau_\delta \rangle$ for small δ.

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3. The Neumann function. The Neumann function for Ω is the solution of the boundary value problem

$$\begin{aligned} &\Delta_{\boldsymbol{y}} N(\boldsymbol{x},\boldsymbol{y}) = -\delta(\boldsymbol{x}-\boldsymbol{y}) \quad \text{for} \quad \boldsymbol{x},\boldsymbol{y}\in\Omega, \\ &\frac{\partial N(\boldsymbol{x},\boldsymbol{y})}{\partial n_{\boldsymbol{y}}} = -\frac{1}{|\partial\Omega|} \quad \text{for} \quad \boldsymbol{x}\in\Omega,\ \boldsymbol{y}\in\partial\Omega, \end{aligned} \tag{3.1}$$

with $N(\boldsymbol{x},\boldsymbol{y})$ fixed at a given point, to ensure uniqueness. Using Green's identity and the boundary conditions (2.10)–(2.11) and (3.1) gives

$$\begin{aligned} &\int_\Omega N(\boldsymbol{x},\boldsymbol{y})\Delta_{\boldsymbol{y}} u_\delta(\boldsymbol{y})\,d\boldsymbol{y} \\ &= \int_\Omega u_\delta(\boldsymbol{y})\Delta_{\boldsymbol{y}} N(\boldsymbol{x},\boldsymbol{y})\,d\boldsymbol{y} + \int_{\partial\Omega}\left(N(\boldsymbol{x},\boldsymbol{y})\frac{\partial u_\delta(\boldsymbol{y})}{\partial n_{\boldsymbol{y}}} - u_\delta(\boldsymbol{y})\frac{\partial N(\boldsymbol{x},\boldsymbol{y})}{\partial n_{\boldsymbol{y}}}\right) dS_{\boldsymbol{y}} \\ &= -u_\delta(\boldsymbol{x}) + \int_{\partial\Omega_a} N(\boldsymbol{x},\boldsymbol{y})\frac{\partial u_\delta(\boldsymbol{y})}{\partial n_{\boldsymbol{y}}}\,dS_{\boldsymbol{y}} - \frac{1}{\varepsilon}\int_{\partial\Omega_r} N(\boldsymbol{x},\boldsymbol{y})u_\delta(\boldsymbol{y})\frac{\partial\phi(\boldsymbol{y})}{\partial n_{\boldsymbol{y}}}\,dS_{\boldsymbol{y}} \\ &\quad + \frac{1}{|\partial\Omega|}\int_{\partial\Omega_r} u_\delta(\boldsymbol{y})\,dS_{\boldsymbol{y}}. \end{aligned} \tag{3.2}$$

On the other hand, (2.9) gives

$$\begin{aligned} &\int_\Omega N(\boldsymbol{x},\boldsymbol{y})\Delta_{\boldsymbol{y}} u_\delta(\boldsymbol{y})\,d\boldsymbol{y} \\ &\quad = \int_\Omega N(\boldsymbol{x},\boldsymbol{y})\left[-\frac{\gamma p_0}{\varepsilon} - \frac{1}{\varepsilon}\nabla\cdot(u_\delta\nabla\phi)\right] d\boldsymbol{y} \\ &\quad = -\frac{\gamma}{\varepsilon}\int_\Omega N(\boldsymbol{x},\boldsymbol{y})p_0(\boldsymbol{y})\,d\boldsymbol{y} - \frac{1}{\varepsilon}\int_\Omega \nabla_{\boldsymbol{y}}\cdot[N(\boldsymbol{x},\boldsymbol{y})u_\delta(\boldsymbol{y})\nabla_{\boldsymbol{y}}\phi(\boldsymbol{y})]\,d\boldsymbol{y} \\ &\qquad + \frac{1}{\varepsilon}\int_\Omega u_\delta(\boldsymbol{y})\nabla_{\boldsymbol{y}}\phi(\boldsymbol{y})\cdot\nabla_{\boldsymbol{y}} N(\boldsymbol{x},\boldsymbol{y})\,d\boldsymbol{y} \\ &\quad = -\frac{\gamma}{\varepsilon}\int_\Omega N(\boldsymbol{x},\boldsymbol{y})p_0(\boldsymbol{y})\,d\boldsymbol{y} - \frac{1}{\varepsilon}\int_{\partial\Omega_r} N(\boldsymbol{x},\boldsymbol{y})u_\delta(\boldsymbol{y})\frac{\partial\phi(\boldsymbol{y})}{\partial n}\,dS_{\boldsymbol{y}} \\ &\qquad + \frac{1}{\varepsilon}\int_\Omega u_\delta(\boldsymbol{y})\nabla_{\boldsymbol{y}}\phi(\boldsymbol{y})\cdot\nabla_{\boldsymbol{y}} N(\boldsymbol{x},\boldsymbol{y})\,d\boldsymbol{y}. \end{aligned} \tag{3.3}$$

Combining (3.2) and (3.3) yields

$$\begin{aligned} &-u_\delta(\boldsymbol{x}) + \frac{1}{|\partial\Omega|}\int_{\partial\Omega_r} u_\delta(\boldsymbol{y})\,dS_{\boldsymbol{y}} + \int_{\partial\Omega_a} N(\boldsymbol{x},\boldsymbol{y})\frac{\partial u_\delta(\boldsymbol{y})}{\partial n_{\boldsymbol{y}}}\,dS_{\boldsymbol{y}} \\ &\quad = -\frac{\gamma}{\varepsilon}\int_\Omega N(\boldsymbol{x},\boldsymbol{y})p_0(\boldsymbol{y})\,d\boldsymbol{y} + \frac{1}{\varepsilon}\int_\Omega u_\delta(\boldsymbol{y})\nabla_{\boldsymbol{y}}\phi(\boldsymbol{y})\cdot\nabla_{\boldsymbol{y}} N(\boldsymbol{x},\boldsymbol{y})\,d\boldsymbol{y}. \end{aligned} \tag{3.4}$$

In view of (2.17), the integral $\int_\Omega N(\boldsymbol{x},\boldsymbol{y})p_0(\boldsymbol{y})\,d\boldsymbol{y}$ can be neglected to leading order, because it is uniformly bounded for smooth initial distributions[1] p_0 as $\delta\to 0$, while all other terms in (3.4) are unbounded. For $\boldsymbol{x}\in\Omega$, at a distance $O(1)$ away from the window, the Neumann function is uniformly bounded.

[1]For nonsmooth p_0 the integral is not uniformly bounded. For example, for $p_0 = \delta(\boldsymbol{x}-\boldsymbol{x}_0)$ we have $\int_\Omega N(\boldsymbol{x},\boldsymbol{y})p_0(\boldsymbol{y})\,d\boldsymbol{y} = N(\boldsymbol{x},\boldsymbol{x}_0)$, which becomes singular as $\boldsymbol{x}\to\boldsymbol{x}_0$. However, this is an integrable singularity, and as such it does not affect the leading order asymptotics in δ.

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Note that integrating (2.14) and using the boundary conditions (2.13), we obtain the compatibility condition

$$\int_{\partial\Omega_a} \frac{\partial u_\delta}{\partial n}\, dS = -\frac{\gamma}{\varepsilon}. \tag{3.5}$$

Because of the fact that the normal derivative $\frac{\partial u_\delta(\boldsymbol{y})}{\partial n_{\boldsymbol{y}}}$ is negative on $\partial\Omega_a$, (3.5) implies that $\int_{\partial\Omega_a} N(\boldsymbol{x},\boldsymbol{y})\frac{\partial u_\delta(\boldsymbol{y})}{\partial n_{\boldsymbol{y}}}\, dS_{\boldsymbol{y}}$ is uniformly bounded. It follows that for $\boldsymbol{x}\in\Omega$, at a distance $O(1)$ (with respect to δ) away from the window, the integral equation (3.4) is to leading order

$$u_\delta(\boldsymbol{x}) \sim \frac{1}{|\partial\Omega|}\int_{\partial\Omega} u_\delta(\boldsymbol{y})\, dS_{\boldsymbol{y}} - \frac{1}{\varepsilon}\int_\Omega u_\delta(\boldsymbol{y})\nabla_{\boldsymbol{y}}\phi(\boldsymbol{y})\cdot\nabla N(\boldsymbol{x},\boldsymbol{y})\, d\boldsymbol{y}, \tag{3.6}$$

which is the integral representation of the boundary value problem $\mathcal{L}_\delta u_\delta = 0$ with the no flux boundary condition (2.11) on the entire boundary (i.e., with $\partial\Omega_r = \partial\Omega$), whose solution is the Boltzmann distribution

$$u_\delta(\boldsymbol{x}) \sim C_\delta e^{-\phi(\boldsymbol{x})/\varepsilon}. \tag{3.7}$$

Equation (3.7) represents the averaged time the particle spent at a point $\boldsymbol{x}$ at a distance $O(1)$ away from the absorbing window prior to absorption.

Due to the absorbing boundary condition (2.10), (3.4) reduces to

$$\begin{aligned}&\int_{\partial\Omega_a} N(\boldsymbol{x},\boldsymbol{y})\frac{\partial u_\delta(\boldsymbol{y})}{\partial n_{\boldsymbol{y}}}\, dS_{\boldsymbol{y}}\\ &\quad= \left\{\frac{-1}{|\partial\Omega|}\int_{\partial\Omega_r} u_\delta(\boldsymbol{y})\, dS_{\boldsymbol{y}} + \frac{1}{\varepsilon}\int_\Omega u_\delta(\boldsymbol{y})\nabla_{\boldsymbol{y}}\phi(\boldsymbol{y})\cdot\nabla_{\boldsymbol{y}} N(\boldsymbol{x},\boldsymbol{y})\, d\boldsymbol{y}\right\}(1+o(1))\end{aligned} \tag{3.8}$$

for all $\boldsymbol{x}\in\partial\Omega_a$. Substituting (3.7) into (3.8) yields an integral equation for the flux $\frac{\partial u_\delta}{\partial n}$ into the absorbing window,

$$\int_{\partial\Omega_a} N(\boldsymbol{x},\boldsymbol{y})\frac{\partial u_\delta(\boldsymbol{y})}{\partial n_{\boldsymbol{y}}}\, dS_{\boldsymbol{y}} = -C_\delta e^{-\phi(\boldsymbol{x})/\varepsilon}(1+o(1)) \quad \text{for} \quad \delta \ll 1. \tag{3.9}$$

If $\phi(\boldsymbol{x})$ does not change much in the window, we can use the constant approximation $\phi(\boldsymbol{x}) \approx \phi(\text{window}) = \phi_0$.

In three dimensions

$$N(\boldsymbol{x},\boldsymbol{y}) = \frac{1}{4\pi|\boldsymbol{x}-\boldsymbol{y}|} + v_S(\boldsymbol{x},\boldsymbol{y}), \tag{3.10}$$

where v_S is a regular harmonic function [10], and so the leading order contribution to (3.9) is due to the singular part of the Neumann function. Thus the leading order approximation $\frac{\partial u_0}{\partial n}$ to the absorption flux is the solution of

$$\frac{1}{2\pi}\int_{\partial\Omega_a} \frac{\partial u_0(\boldsymbol{y})}{\partial n_{\boldsymbol{y}}}\frac{dS_{\boldsymbol{y}}}{|\boldsymbol{x}-\boldsymbol{y}|} = -C_\delta e^{-\phi_0/\varepsilon}. \tag{3.11}$$

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 $\frac{1}{4\pi}$ in (3.10) was replaced by $\frac{1}{2\pi}$.

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4. Narrow escape. von Helmholtz [21] (see also Rayleigh [1] and others, e.g., [13]) solved the integral equation (3.11) analytically for the case of an elliptical absorbing window $\partial\Omega_a$,

$$\frac{\partial u_0(y_1,y_2)}{\partial n} = -\frac{C_\delta e^{-\phi_0/\varepsilon}}{\sqrt{1-\dfrac{y_1^2}{a^2}-\dfrac{y_2^2}{b^2}}}, \tag{4.1}$$

where a and b are the ellipse semiaxes, and $\boldsymbol{y} = (y_1, y_2)$ are local Cartesian coordinates in the ellipse. The value of the constant C_δ is calculated using the compatibility condition (3.5) to be

$$C_\delta = \frac{\gamma K(e)}{2\pi\varepsilon a} e^{\phi_0/\varepsilon}, \tag{4.2}$$

where e is the eccentricity of the ellipse and $K(\cdot)$ is the complete elliptic integral of the first kind. In a three-dimensional domain, the averaged time spent at point $\boldsymbol{x}$ before escape through an elliptical absorbing window is given by (see (3.7))

$$u_\delta(\boldsymbol{x}) \approx \frac{\gamma K(e)}{2\pi\varepsilon a} \exp\left\{\frac{\phi_0 - \phi(\boldsymbol{x})}{\varepsilon}\right\}. \tag{4.3}$$

Equations (2.18) and (4.3) now give the mean escape time as

$$\langle \tau_\delta \rangle = \frac{\gamma K(e) e^{\phi_0/\varepsilon}}{2\pi\varepsilon a} \int_\Omega \exp\left\{-\frac{\phi(\boldsymbol{x})}{\varepsilon}\right\} d\boldsymbol{x}. \tag{4.4}$$

If the barrier is sufficiently high, we evaluate the integral in (4.4) by the Laplace method, assuming that ϕ has a single global minimum ϕ_m at $\boldsymbol{x}_m$,

$$\int_\Omega \exp\left\{-\frac{\phi(\boldsymbol{x})}{\varepsilon}\right\} d\boldsymbol{x} \approx \frac{(2\pi\varepsilon)^{n/2}}{\prod_{i=1}^{n} \omega_i} \exp\left\{-\frac{\phi_m}{\varepsilon}\right\}, \tag{4.5}$$

where ω_i are the frequencies at the minimum $\boldsymbol{x}_m$. For reactions that consist in passing through a small elliptical window (assuming no returns are possible), the reaction rate is the modified Kramers formula

$$\kappa_\delta = \frac{1}{\langle \tau_\delta \rangle} \sim \frac{a\omega_1\omega_2\omega_3}{\sqrt{2\pi\varepsilon}\,\gamma K(e)}\, e^{-\Delta E/\varepsilon}, \tag{4.6}$$

where $\Delta E = \phi_0 - \phi_m$. In the special case of a circular window, we obtain

$$\kappa_\delta \sim \frac{4a\omega_1\omega_2\omega_3}{(2\pi)^{3/2}\gamma\sqrt{\varepsilon}}\, e^{-\Delta E/\varepsilon}, \tag{4.7}$$

where a is the radius of the window. Note that ΔE is not the barrier height. We conclude that the activation rate is of Arrhenius form and has two contributions. The first is due to the potential, while the second is due to geometry of the absorbing window alone. Unlike the free diffusion case [17], [18], [19], geometrical properties of the domain, such as its volume, are not included in the leading order asymptotics of the reaction rate.

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Second, in the limit of large ε, the power series approximation

$$e^{-(\phi(\boldsymbol{x})-\phi_0)/\varepsilon} = 1 - \frac{\phi(\boldsymbol{x})-\phi_0}{\varepsilon} + \frac{(\phi(\boldsymbol{x})-\phi_0)^2}{2\varepsilon^2}\cdots$$

in (4.4) gives

$$k \sim \frac{2\pi\varepsilon a}{\gamma K(e)|\Omega|}\left(1 - \frac{\langle\phi\rangle-\phi_0}{\varepsilon} + O\left(\varepsilon^{-2}\right)\right)^{-1}, \tag{4.8}$$

where $\langle\phi\rangle = \frac{1}{|\Omega|}\int_\Omega \phi(\boldsymbol{x})\,d\boldsymbol{x}$ is the spatial average of the potential. The rate can also be rewritten into an Arrhenius form as

$$k \sim \frac{2\pi\varepsilon a}{\gamma K(e)|\Omega|}\, e^{-\langle\Delta E\rangle/\varepsilon}, \tag{4.9}$$

where $\langle\Delta E\rangle = \phi_0 - \langle\phi\rangle$. In the case of large ε the reaction rate depends not merely on the geometry of the window but also on the geometry of the domain itself through its volume. Large ε means that the motion is diffusion limited; therefore, fine details of the potential are less important and the spatial averaged potential has only an $O(\varepsilon^{-1})$ effect.

Finally, we give rate functions for small and large ε for several geometries. For the case of diffusion in a ball of radius R, the results of [17] show that

$$\begin{aligned} k &\sim \frac{4\varepsilon a}{\gamma|\Omega|}\left[1 + \frac{a}{R}\ln\frac{R}{a} + O\left(\frac{a}{R}\right)\right]^{-1} e^{-\langle\Delta E\rangle/\varepsilon} \quad \text{for} \quad \varepsilon \gg \Delta E, \\ k &\sim \frac{4\varepsilon a\omega_1\omega_2\omega_3}{\gamma(2\pi)^{3/2}}\left[1 + \frac{a}{R}\ln\frac{R}{a} + O\left(\frac{a}{R}\right)\right]^{-1} e^{-\Delta E/\varepsilon} \quad \text{for} \quad \varepsilon \ll \Delta E. \end{aligned} \tag{4.10}$$

We conjecture that the second order term is $O(\delta\ln\delta)$ also for a general three-dimensional domain, though we were unable to prove it so far.

In two dimensions the singularity of the Neumann function is logarithmic, and so the leading order approximation to the activation rate is

$$\begin{aligned} k &\sim \frac{\pi\varepsilon}{\gamma|\Omega|}\frac{e^{-\langle\Delta E\rangle/\varepsilon}}{\left[\ln\dfrac{1}{\delta} + O(1)\right]} \quad \text{for} \quad \varepsilon \gg \Delta E, \\ k &\sim \frac{\varepsilon\sqrt{\omega_1\omega_2}}{2\gamma}\frac{e^{-\Delta E/\varepsilon}}{\left[\ln\dfrac{1}{\delta} + O(1)\right]} \quad \text{for} \quad \varepsilon \ll \Delta E. \end{aligned} \tag{4.11}$$

The remainder $O(1)$ is important, because in real life applications even if δ is small, $\ln\frac{1}{\delta}$ is not necessarily large. In [18], [19] we have calculated the $O(1)$ term for diffusion in a circular disk, in a circular annulus, and on a sphere. These results extend in a straightforward way to domains that can be mapped conformally onto these shapes (e.g., all simply connected planar domains).

If the boundary of the absorbing window contains a singular point of $\partial\Omega$, such as a corner or a cusp, the order of magnitude of the activation rate may change. Thus, if the window is at a corner of angle α, then the rate is [19]

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$$
\begin{aligned}
k &\sim \frac{\alpha\varepsilon}{\gamma|\Omega|}\,\frac{e^{-\langle\Delta E\rangle/\varepsilon}}{\left[\ln\dfrac{1}{\delta}+O(1)\right]} \quad \text{for} \quad \varepsilon \gg \Delta E,\\
k &\sim \frac{\alpha\varepsilon\sqrt{\omega_1\omega_2}}{2\pi\gamma}\,\frac{e^{-\Delta E/\varepsilon}}{\left[\ln\dfrac{1}{\delta}+O(1)\right]} \quad \text{for} \quad \varepsilon \ll \Delta E.
\end{aligned}
\tag{4.12}
$$

If the absorbing window is near a cusp, then $\langle\tau_\delta\rangle$ grows algebraically rather than logarithmically. For example, in the domain bounded between two tangent circles, the activation rate is

$$
\begin{aligned}
k &\sim \frac{(d^{-1}-1)\varepsilon}{\gamma|\Omega|}\left[\delta+O(\delta^2)\right]e^{-\langle\Delta E\rangle/\varepsilon} \quad \text{for} \quad \varepsilon \gg \Delta E,\\
k &\sim \frac{(d^{-1}-1)\varepsilon\sqrt{\omega_1\omega_2}}{2\pi\gamma}\left[\delta+O(\delta^2)\right]e^{-\Delta E/\varepsilon} \quad \text{for} \quad \varepsilon \ll \Delta E,
\end{aligned}
\tag{4.13}
$$

where $d<1$ is the ratio of the radii.

5. Deep well—a Markov chain model. The modified Kramers formulas (4.6) or (4.11) can be explained by coarse-graining the diffusive motion into a simplified 3-state Markov model, when the domain contains a deep well $\Omega_W \subset \Omega$. The three states of the Markov process are (i) state W—the trajectory is trapped in the deep well; (ii) state D—the trajectory diffuses in the domain $\Omega_D = \Omega - \Omega_W$, outside the well; (iii) state A—the trajectory is absorbed into the small hole. Once the trajectory is absorbed into the small hole, its motion is terminated, and so A is a terminal state of the Markov chain. For simplicity, we assume $\Omega \subset \mathbb{R}^2$.

Not all transition times between the different states are finite with probability 1, and so not all mean transition times are finite. The particle leaves the well to the outer in finite mean time, that is,

$$
\Pr\{\tau_{W\to D}<\infty\}=1, \quad \mathbb{E}\tau_{W\to D}<\infty. \tag{5.1}
$$

For small ε, the mean time spent in the well, $\mathbb{E}\tau_{W\to D}$, is exponentially large and is given by [14]

$$
\mathbb{E}\tau_{W\to D} \sim \frac{2\pi\sqrt{\dfrac{\partial^2\phi(x_S)}{\partial s^2}}}{\sqrt{-\dfrac{\partial^2\phi(x_S)}{\partial\nu^2}}\sqrt{H(x_W)}}\exp\left\{\frac{\phi(x_S)-\phi(x_W)}{\varepsilon}\right\}, \tag{5.2}
$$

where ν and s are the distance to and arclength on $\partial\Omega_W$, respectively, x_W is the deepest point of the well, x_S is the point on $\partial\Omega_W$, where ϕ achieves its minimum, and H is the Hessian of ϕ.

The time $\tau_{D\to W}$, however, is not finite with probability 1, because there is a finite probability $\Pr\{\tau_{D\to A}<\tau_{D\to W}\}$ of termination at A without returning to W, and there is no return from A to W. Consequently, $\mathbb{E}\tau_{D\to W}=\infty$. However, $\mathbb{E}\tau_{D\to A}$ and $\mathbb{E}[\tau_{D\to W} \mid \tau_{D\to W}<\tau_{D\to A}]$ are finite. For small ε,δ, the conditional mean time $\mathbb{E}[\tau_{D\to W} \mid \tau_{D\to W}<\tau_{D\to A}]$ is asymptotically the same as $\mathbb{E}\tau_{D\to W}$ for a problem without the small absorbing window, because the conditioning changes the drift only near A, to repel the trajectory from the window, and so the effect on the conditional mean time is small, regardless of whether this mean time is long or short. The

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transition probabilities from the outer domain to the absorbing window and to the well are

$$\Pr\{\tau_{D\to A}<\tau_{D\to W}\}\sim\frac{\mathbb{E}[\tau_{D\to W}\mid\tau_{D\to W}<\tau_{D\to A}]}{\mathbb{E}[\tau_{D\to W}\mid\tau_{D\to W}<\tau_{D\to A}]+\mathbb{E}[\tau_{D\to A}\mid\tau_{D\to A}<\tau_{D\to W}]},$$

(5.3)

$$\Pr\{\tau_{D\to W}<\tau_{D\to A}\}\sim\frac{\mathbb{E}[\tau_{D\to A}\mid\tau_{D\to A}<\tau_{D\to W}]}{\mathbb{E}[\tau_{D\to W}\mid\tau_{D\to W}<\tau_{D\to A}]+\mathbb{E}[\tau_{D\to A}\mid\tau_{D\to A}<\tau_{D\to W}]},$$

respectively. The conditional mean transition time $\mathbb{E}[\tau_{D\to W}\mid\tau_{D\to W}<\tau_{D\to A}]$ from Ω_D to Ω_W is similar to (5.2),

$$\mathbb{E}[\tau_{D\to W}\mid\tau_{D\to W}<\tau_{D\to A}]\sim\frac{2\pi\sqrt{\dfrac{\partial^2\phi(x_S)}{\partial s^2}}}{\sqrt{-\dfrac{\partial^2\phi(x_S)}{\partial\nu^2}}\sqrt{H(x_D)}}\exp\left\{\frac{\phi(x_S)-\phi(x_D)}{\varepsilon}\right\},\tag{5.4}$$

where x_D is the deepest point of the potential in the outer domain, $\phi(x_W)<\phi(x_D)<\phi(x_S)$. The mean transition time $\mathbb{E}[\tau_{D\to A}\mid\tau_{D\to A}<\tau_{D\to W}]$ from Ω_D to the absorbing window is given by (4.11)

$$\mathbb{E}[\tau_{D\to A}\mid\tau_{D\to A}<\tau_{D\to W}]\sim\frac{2\gamma\ln\delta^{-1}}{\varepsilon\sqrt{H(x_D)}}\exp\left\{\frac{\phi_0-\phi(x_D)}{\varepsilon}\right\}.\tag{5.5}$$

If we assume that the effect of the small window on the mean escape time, $\ln\delta^{-1}$ (or $1/\delta$ in three dimensions), is larger than that of the energy barrier, $\exp\{[\phi_0-\phi(x_S)]/\varepsilon\}$, then, according to our assumption that the potential is relatively flat outside the deep well, $\mathbb{E}[\tau_{D\to W}\mid\tau_{D\to W}<\tau_{D\to A}]\ll\mathbb{E}[\tau_{D\to A}\mid\tau_{D\to A}<\tau_{D\to W}]$, and so (5.3) implies

$$\Pr\{\tau_{D\to A}<\tau_{D\to W}\}\sim\frac{\mathbb{E}[\tau_{D\to W}\mid\tau_{D\to W}<\tau_{D\to A}]}{\mathbb{E}[\tau_{D\to A}\mid\tau_{D\to A}<\tau_{D\to W}]}.\tag{5.6}$$

The mean absorption times $\mathbb{E}\tau_{i\to A}$ are finite for $i=D,W$. They satisfy the renewal equations

$$\begin{aligned}\mathbb{E}\tau_{D\to A}&=\Pr\{\tau_{D\to A}<\tau_{D\to W}\}\mathbb{E}\left[\tau_{D\to A}\mid\tau_{D\to A}<\tau_{D\to W}\right]\\&\quad+\Pr\{\tau_{D\to W}<\tau_{D\to A}\}\mathbb{E}\tau_{W\to A},\end{aligned}\tag{5.7}$$

$$\mathbb{E}\tau_{W\to A}=\mathbb{E}\tau_{W\to D}+\mathbb{E}\tau_{D\to A}\tag{5.8}$$

(see [15]). Adding (5.7) and (5.8), and dividing by $\Pr\{\tau_{D\to A}<\tau_{D\to W}\}=1-\Pr\{\tau_{D\to W}<\tau_{D\to A}\}$, we obtain

$$\mathbb{E}\tau_{W\to A}=\mathbb{E}\left[\tau_{D\to A}\mid\tau_{D\to A}<\tau_{D\to W}\right]+\frac{\mathbb{E}\tau_{W\to D}}{\Pr\{\tau_{D\to A}<\tau_{D\to W}\}}.\tag{5.9}$$

Both $\mathbb{E}[\tau_{D\to A}\mid\tau_{D\to A}<\tau_{D\to W}]$ and $1/\Pr\{\tau_{D\to A}<\tau_{D\to W}\}$ have the same order of magnitude as functions of δ; however, $\mathbb{E}\tau_{W\to D}$ is exponentially large. Therefore,

$$\mathbb{E}\tau_{W\to A}\sim\frac{\mathbb{E}\tau_{W\to D}}{\Pr\{\tau_{D\to A}<\tau_{D\to W}\}}.\tag{5.10}$$

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Now, by (5.8), we have

$$\mathbb{E}\tau_{D\to A} \sim \mathbb{E}\tau_{W\to D}\left(\frac{1}{\Pr\{\tau_{D\to A} < \tau_{D\to W}\}} - 1\right) \sim \frac{\mathbb{E}\tau_{W\to D}}{\Pr\{\tau_{D\to A} < \tau_{D\to W}\}}, \tag{5.11}$$

because $\Pr\{\tau_{D\to A} < \tau_{D\to W}\} \to 0$ as $\delta \to 0$. The meaning of (5.10) and (5.11) is that for each realization of the Markov chain, e.g., $DWDWDWDWDWDWDWDA$, the number of visits in state D is larger by 1, or equal to the number of visits at state W. The mean time that the particle spends at state W is exponentially larger than the mean time spent at state D. Therefore, the mean time to absorption is approximately the average number of visits at state D times the average time of a single visit in the deep well. The average number of visits in state D prior to absorption is $1/\Pr\{\tau_{D\to A} < \tau_{D\to W}\}$, as in a geometric distribution, and (5.10) follows. We conclude that

$$\mathbb{E}\tau_{D\to A} \sim \mathbb{E}\tau_{W\to A}; \tag{5.12}$$

i.e., the initial state (or location) of the particle has no (leading order) significance for the mean absorption time $\langle\tau_\delta\rangle$, which by (5.6) and (5.10) is

$$\langle\tau_\delta\rangle \sim \mathbb{E}\tau_{W\to A} \sim \frac{\mathbb{E}\tau_{W\to D}}{\Pr\{\tau_{D\to W} < \tau_{D\to A}\}}. \tag{5.13}$$

Substituting (5.2), (5.4)–(5.6) into (5.13) yields

$$\langle\tau_\delta\rangle = \frac{2\gamma \ln\dfrac{1}{\delta}}{\varepsilon\sqrt{H(x_W)}} \exp\left\{\frac{\phi_0 - \phi(x_W)}{\varepsilon}\right\}, \tag{5.14}$$

in agreement with (4.11).

6. Summary and discussion. The narrow escape problem of a Brownian particle through a small absorbing window in an otherwise reflecting boundary was discussed in [8], [17], [18], and [19]. Here we solve the narrow escape problem for a Brownian particle in a force field. In cases where there is a deep potential well inside the domain, there are two time scales in the problem, the mean time to escape the well and the mean time to reach the small window. We give explicit asymptotic expressions for the mean escape time when the time scales are comparable and in the case where one is much longer than the other.

Matched asymptotics of two- and three-dimensional problems [22], [23], [24], [11] yield the leading term in the expansion of the principal eigenvalue in three dimensions and a full expansion in two dimensions. For the special case of the mixed Neumann problem with a small Dirichlet window in the boundary, the leading term obtained in [17], [18], [19] can be obtained by the application of the matched asymptotics expansion to this problem. In this paper we generalize the method of [17], [18], [19] to obtain the leading term for the corresponding boundary value problem for the Fokker–Planck operator, though matched asymptotics can be applied to this problem as well. The advantage of our method, as demonstrated in [17], is that it reveals the order of magnitude of the second term in three dimensions, while the matched asymptotics method does not indicate this in a simple way. In the particular case of a ball with a small Dirichlet cap, the application of the special functions method of Collins [2], [3] gave in [17] the unexpected estimate on the remainder term $O(\delta^2 \log\delta)$

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to the expected leading term $O(\delta)$. Another advantage of the present method is the Helmholtz integral equation (3.11) for the flux and capacity of the small window. This equation is easier to solve numerically than the mixed Neumann–Dirichlet problem for a half space, as required in the boundary layer equation of the matched asymptotics expansion.

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