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Activation through a narrow opening

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The escape of 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.

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Many situations in molecular biophysics can be described as chemical reactions that consist in the diffusion of a Brownian particle through a small opening in the boundary of a domain whose remaining boundaries are essentially reflecting. This can happen, for example, if the reflecting boundaries are due to a dielectric barrier, as in biological membranes, and the small opening may be a protein channel embedded in an otherwise impenetrable membrane [1]. In this case 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. 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 a domain [2]. The same setup describes also the process of trafficking receptors on biological membranes [3]. The escape of free Brownian motion (without drift) through a small window was discussed in [3]. Here we consider the narrow escape problem for Brownian motion in a field of force. Our result is a generalized multidimensional Kramers formula for the activation rate constant, which depends on the potential, the specific geometry of the opening, and the volume or surface area of the domain [see Eqs. (27)–(31)].

Consider a bounded domain $\Omega \subset \mathbb{R}^n$, with a small absorbing part $\partial\Omega_a$ of the boundary $\partial\Omega$ and the remaining boundary $\partial\Omega_r$ reflecting Brownian trajectories, and assume that

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

The diffusion is described by the probability density function $p_\delta(\boldsymbol{x},t)$, which solves the Fokker-Planck equation

$$\gamma \frac{\partial p_\delta}{\partial t} = \varepsilon \Delta p_\delta + \nabla \cdot (p_\delta \nabla \phi) \equiv \mathcal{L}_\delta p_\delta, \tag{1}$$

with the initial condition $p_\delta(\boldsymbol{x},0)=p_0(\boldsymbol{x})$, and Dirichlet-Neumann boundary conditions for $t>0$,

$$p_\delta = 0 \quad \text{for } \boldsymbol{x} \in \partial\Omega_a, \tag{2}$$

$$\varepsilon \frac{\partial p_\delta}{\partial n} + p_\delta \frac{\partial \phi}{\partial n} = 0 \quad \text{for } \boldsymbol{x} \in \partial\Omega_r, \tag{3}$$

where $\varepsilon = k_B T/m$. The function

$$u_\delta(\boldsymbol{x}) = \int_0^\infty p_\delta(\boldsymbol{x},t)dt, \tag{4}$$

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

$$\mathcal{L}_\delta u_\delta = -\gamma p_0 \quad \text{for } \boldsymbol{x} \in \Omega, \tag{5}$$

$$u_\delta = 0 \quad \text{for } \boldsymbol{x} \in \partial\Omega_a, \tag{6}$$

$$\varepsilon \frac{\partial u_\delta}{\partial n} + u_\delta \frac{\partial \phi}{\partial n} = 0 \quad \text{for } \boldsymbol{x} \in \partial\Omega_r. \tag{7}$$

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

$$\mathcal{L}_\delta^* g_\delta = -\gamma p_0 e^{\phi/\varepsilon} \quad \text{for } \boldsymbol{x} \in \Omega, \tag{8}$$

$$\begin{aligned} \frac{\partial g_\delta(\boldsymbol{x})}{\partial n} &= 0 \qquad \text{for } \boldsymbol{x} \in \partial\Omega_r, \\ g_\delta(\boldsymbol{x}) &= 0 \qquad \text{for } \boldsymbol{x} \in \partial\Omega_a. \end{aligned} \tag{9}$$

Equation (8) can be written in the divergence form

$$\nabla\left(e^{-\phi/\varepsilon}\nabla g_\delta\right) = -\frac{\gamma p_0}{\varepsilon}. \tag{10}$$

The adjoint operators $\mathcal{L}_\delta$ and $\mathcal{L}_\delta^*$, defined by Eqs. (1) and (5)–(9), 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

$$p_\delta(\boldsymbol{x},t) = \sum_{i=0}^{\infty} a_i(\delta)\psi_i(\boldsymbol{x},\delta)e^{-\lambda_i(\delta)t/\gamma}, \tag{11}$$

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), is dropped, so that $\lambda_0(\delta) \to 0$ [the first eigenvalue of the prob-

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lem (1) and (3) with $\partial\Omega_r=\partial\Omega$], with the normalized eigenfunction

$$\psi_0(\boldsymbol{x},0)=\frac{\exp\{-\phi(\boldsymbol{x})/\varepsilon\}}{\int_\Omega \exp\{-\phi(\boldsymbol{x})/\varepsilon\}d\boldsymbol{x}}, \tag{12}$$

and $a_0(\delta)\to 1$. It follows from Eqs. (4) and (11) that for all $\boldsymbol{x}\in\Omega$

$$u_\delta(\boldsymbol{x})=\gamma\sum_{i=0}^{\infty}\frac{a_i(\delta)\psi_i(\boldsymbol{x},\delta)}{\lambda_i(\delta)}\to\infty \quad \text{as } \delta\to 0. \tag{13}$$

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

$$\langle\tau_\delta\rangle=\int_\Omega u_\delta(\boldsymbol{x})d\boldsymbol{x}=\gamma\sum_{i=0}^{\infty}\frac{a_i(\delta)}{\lambda_i(\delta)} \tag{14}$$

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.

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

$$\Delta_y N(\boldsymbol{x},\boldsymbol{y})=-\delta(\boldsymbol{x}-\boldsymbol{y}) \quad \text{for } \boldsymbol{x},\boldsymbol{y}\in\Omega,$$

$$\frac{\partial N(\boldsymbol{x},\boldsymbol{y})}{\partial n_y}=-\frac{1}{|\partial\Omega|} \quad \text{for } \boldsymbol{x}\in\Omega,\ \boldsymbol{y}\in\partial\Omega. \tag{15}$$

Using Green's identity, the boundary conditions (5)–(7) and (15) give (see [4] for detailed calculations)

$$\int_{\partial\Omega_a}N(\boldsymbol{x},\boldsymbol{y})\frac{\partial u_\delta(\boldsymbol{y})}{\partial n_y}dS_y-u_\delta(\boldsymbol{x})$$
$$=\left(\frac{-1}{|\partial\Omega|}\int_{\partial\Omega_r}u_\delta(\boldsymbol{y})dS_y+\frac{1}{\varepsilon}\int_\Omega u_\delta(\boldsymbol{y})\nabla_y\phi(\boldsymbol{y})\cdot\nabla_y N(\boldsymbol{x},\boldsymbol{y})d\boldsymbol{y}\right)$$
$$\times[1+o(1)]. \tag{16}$$

In view of (13), 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 p_0 as $\delta\to 0$, while all other terms in (16) are unbounded. For $\boldsymbol{x}\in\Omega$, at a distance $O(1)$ away from the absorbing window $\partial\Omega_a$, the Neumann function is uniformly bounded.

Note that integrating (10) and using the boundary conditions (9), we obtain the compatibility condition

$$\int_{\partial\Omega_a}\frac{\partial u_\delta}{\partial n}dS=-\frac{\gamma}{\varepsilon}. \tag{17}$$

Due to the fact that the normal derivative $\partial u_\delta(\boldsymbol{y})/\partial n_y$ is negative on $\partial\Omega_a$, Eq. (17) implies that $\int_{\partial\Omega_a}N(\boldsymbol{x},\boldsymbol{y})\times[\partial u_\delta(\boldsymbol{y})/\partial n_y]dS_y$ is uniformly bounded for $\boldsymbol{x}$ outside the neighborhood of $\partial\Omega_a$. It follows that for $\boldsymbol{x}\in\Omega$, at a distance $O(1)$ (with respect to δ) away from the window, the integral equation (16) is to leading order

$$u_\delta(\boldsymbol{x})\sim\frac{1}{|\partial\Omega|}\int_{\partial\Omega}u_\delta(\boldsymbol{y})dS_y$$
$$-\frac{1}{\varepsilon}\int_\Omega u_\delta(\boldsymbol{y})\nabla_y\phi(\boldsymbol{y})\cdot\nabla_y N(\boldsymbol{x},\boldsymbol{y})d\boldsymbol{y}, \tag{18}$$

which is the integral representation of the boundary value problem $\mathcal{L}_\delta u_\delta=0$ with the no-flux boundary condition (7) on the entire boundary (i.e., with $\partial\Omega_r=\partial\Omega$), whose solution is the Boltzmann distribution

$$u_\delta(\boldsymbol{x})\sim C_\delta e^{-\phi(\boldsymbol{x})/\varepsilon}. \tag{19}$$

Equation (19) represents the averaged time the particle spent at a point $\boldsymbol{x}$ at a distance $O(1)$ away from the absorbing window prior to absorbtion.

Substituting (19) in (16) yields an integral equation for the flux $\partial u_\delta/\partial n$ into the absorbing window,

$$\int_{\partial\Omega_a}N(\boldsymbol{x},\boldsymbol{y})\frac{\partial u_\delta(\boldsymbol{y})}{\partial n_y}dS_y=-C_\delta e^{-\phi(\boldsymbol{x})/\varepsilon}[1+o(1)] \quad \text{for } \delta\ll 1. \tag{20}$$

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

$$N(\boldsymbol{x},\boldsymbol{y})=\frac{1}{4\pi|\boldsymbol{x}-\boldsymbol{y}|}+v_S(\boldsymbol{x},\boldsymbol{y}), \tag{21}$$

where v_S is a regular harmonic function [5], so the leading order contribution to (20) is due to the singular part of the Neumann function. Thus the leading order approximation $\partial u_0/\partial n$ to the absorption flux is the solution of

$$\frac{1}{2\pi}\int_{\partial\Omega_a}\frac{\partial u_0(\boldsymbol{y})}{\partial n_y}\frac{dS_y}{|\boldsymbol{x}-\boldsymbol{y}|}=-C_\delta e^{-\phi_0/\varepsilon}. \tag{22}$$

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 $1/4\pi$ in Eq. (21) was replaced by $1/2\pi$.

Helmholtz [6] (see also Rayleigh [7] and others, e.g., [8]) solved the integral equation (22) analytically for the case of an elliptical absorbing window $\partial\Omega_a$,

$$\frac{\partial u_0(y_1,y_2)}{\partial n}=-\frac{C_\delta e^{-\phi_0/\varepsilon}}{\sqrt{1-\frac{y_1^2}{a^2}-\frac{y_2^2}{b^2}}}, \tag{23}$$

where a and b are the semiaxes of the ellipse, 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 (17) to be

$$C_\delta = \frac{\gamma K(e)}{2\pi\varepsilon a} e^{\phi_0/\varepsilon}, \tag{24}$$

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 Eq. (19)]

$$u_\delta(\boldsymbol{x}) \approx \frac{\gamma K(e)}{2\pi\varepsilon a} \exp\left(\frac{\phi_0 - \phi(\boldsymbol{x})}{\varepsilon}\right). \tag{25}$$

Equations (14) and (25) give now the mean escape time as

$$\langle \tau_\delta \rangle = \frac{\gamma K(e) e^{\phi_0/\varepsilon}}{2\pi\varepsilon a} \int_\Omega \exp\left(-\frac{\phi(\boldsymbol{x})}{\varepsilon}\right) d\boldsymbol{x}. \tag{26}$$

If the barrier is sufficiently high, we evaluate the integral in (26) by the Laplace method, assuming that ϕ has a single global minimum ϕ_m at $\boldsymbol{x}_m$,

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

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

$$\kappa_\delta = \frac{1}{\langle \tau_\delta \rangle} \sim \frac{a\omega_1\omega_2\omega_3}{\sqrt{2\pi\varepsilon}\,\gamma K(e)} e^{-\Delta E/\varepsilon}, \tag{27}$$

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

$$\kappa_\delta \sim \frac{4a\omega_1\omega_2\omega_3}{(2\pi)^{3/2}\gamma\sqrt{\varepsilon}} e^{-\Delta E/\varepsilon}, \tag{28}$$

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 the geometry of the absorbing window alone. Unlike the free diffusion case [3], geometrical properties of the domain, such as its volume, are not included in the leading order asymptotics of the reaction rate.

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

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

in (26) gives

$$k \sim \frac{2\pi\varepsilon a}{\gamma K(e)|\Omega|} \left(1 - \frac{\langle\phi\rangle - \phi_0}{\varepsilon} + O(\varepsilon^{-2})\right)^{-1}, \tag{29}$$

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

$$k \sim \frac{2\pi\varepsilon a}{\gamma K(e)|\Omega|} e^{-\langle\Delta E\rangle/\varepsilon}, \tag{30}$$

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 spatially averaged potential has only an $O(\varepsilon^{-1})$ effect.

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

$$k \sim \begin{cases} \dfrac{\pi\varepsilon}{\gamma|\Omega|} \dfrac{e^{-\langle\Delta E\rangle/\varepsilon}}{\left[\ln\dfrac{1}{\delta} + O(1)\right]} & \text{for } \varepsilon \gg \Delta E, \\ \dfrac{\varepsilon\sqrt{\omega_1\omega_2}}{2\gamma} \dfrac{e^{-\Delta E/\varepsilon}}{\left[\ln\dfrac{1}{\delta} + O(1)\right]} & \text{for } \varepsilon \ll \Delta E \end{cases} \tag{31}$$

The remainder $O(1)$ is important, because in real life applications even if δ is small, $\ln(1/\delta)$ is not necessarily large. In [3] 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).

The modified Kramers formulas (27) or (31) can be explained by coarse-graining the diffusive motion into a simplified three-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, where the trajectory is trapped in the deep well; (ii) state D, where the trajectory diffuses in the domain $\Omega_D = \Omega - \Omega_W$, outside the well; (iii) state A, where the trajectory is absorbed in the small hole. Once the trajectory is absorbed in the small hole, its motion is terminated, 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, so not all mean transition times are finite. The particle leaves the well for the outer domain in finite mean time, that is,

$$\Pr\{\tau_{W\to D} < \infty\} = 1 \quad \mathbb{E}\tau_{W\to D} < \infty. \tag{32}$$

For small ε, the mean time spent in the well, $\mathbb{E}\tau_{W\to D}$, is exponentially large and is given by the multidimensional Kramers formula [9].

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 $\mathbb{E}[\tau_{D\to W} | \tau_{D\to W} < \tau_{D\to A}]$ are finite. For small ε, δ, the conditional mean time $\mathbb{E}[\tau_{D\to W} | \tau_{D\to W} < \tau_{D\to A}]$ 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, so the effect on the conditional mean time is small, regardless of whether this mean time is long or short. The conditional

mean transition time $\mathbb{E}[\tau_{D\to W}|\tau_{D\to W}<\tau_{D\to A}]$ from Ω_D to Ω_W is also given by an appropriate multidimensional Kramers formula. The mean transition time $\mathbb{E}[\tau_{D\to A}|\tau_{D\to A}<\tau_{D\to W}]$ from Ω_D to the absorbing window is given by (31). If we assume that the effect of the small window on the mean escape time, $\ln\delta^{-1}$ (or $1/\delta$ in three dimensional), 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, $\mathbb{E}[\tau_{D\to W}\mid\tau_{D\to W}<\tau_{D\to A}]\ll\mathbb{E}[\tau_{D\to A}\mid\tau_{D\to A}<\tau_{D\to W}]$, so

$$\Pr\{\tau_{D\to A}<\tau_{D\to W}\}\sim\frac{\mathbb{E}[\tau_{D\to W}|\tau_{D\to W}<\tau_{D\to A}]}{\mathbb{E}[\tau_{D\to A}|\tau_{D\to A}<\tau_{D\to W}]}. \tag{33}$$

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

$$\mathbb{E}\tau_{D\to A}=\Pr\{\tau_{D\to A}<\tau_{D\to W}\}\mathbb{E}[\tau_{D\to A}|\tau_{D\to A}<\tau_{D\to W}]+\Pr\{\tau_{D\to W}<\tau_{D\to A}\}\mathbb{E}\tau_{W\to A}, \tag{34}$$

$$\mathbb{E}\tau_{W\to A}=\mathbb{E}\tau_{W\to D}+\mathbb{E}\tau_{D\to A} \tag{35}$$

(see [10]). Adding Eqs. (34) and (35), and dividing by $\Pr\{\tau_{D\to A}<\tau_{D\to W}\}=1-\Pr\{\tau_{D\to W}<\tau_{D\to A}\}$, we obtain

$$\mathbb{E}\tau_{W\to A}=\mathbb{E}\big[\tau_{D\to A}|\tau_{D\to A}<\tau_{D\to W}\big]+\frac{\mathbb{E}\tau_{W\to D}}{\Pr\{\tau_{D\to A}<\tau_{D\to W}\}}. \tag{36}$$

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

$$\mathbb{E}\tau_{W\to A}\sim\frac{\mathbb{E}\tau_{W\to D}}{\Pr\{\tau_{D\to A}<\tau_{D\to W}\}}. \tag{37}$$

Now, by Eq. (35), we have

$$\mathbb{E}\tau_{D\to A}\sim\mathbb{E}\tau_{W\to D}\left(\frac{1}{\Pr\{\tau_{D\to A}<\tau_{D\to W}\}}-1\right)\sim\frac{\mathbb{E}\tau_{W\to D}}{\Pr\{\tau_{D\to A}<\tau_{D\to W}\}}, \tag{38}$$

because $\Pr\{\tau_{D\to A}<\tau_{D\to W}\}\to 0$ as $\delta\to 0$. The meaning of Eqs. (37) and (38) is that for each realization of the Markov chain, e.g., *DW DW DW DW DW DW DW DA*, the number of visits to state D is larger by 1, or equal to the number of visits to 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 to state D times the average time of a single visit to the deep well. The average number of visits to state D prior to absorbtion is $1/\Pr\{\tau_{D\to A}<\tau_{D\to W}\}$, as in a geometric distribution, and (37) follows. We conclude that

$$\mathbb{E}\tau_{D\to A}\sim\mathbb{E}\tau_{W\to A}, \tag{39}$$

i.e., the initial state (or location) of the particle has no (leading order) significance for the mean absorbtion time $\langle\tau_\delta\rangle$, which by Eqs. (33) and (37) is

$$\langle\tau_\delta\rangle\sim\mathbb{E}\tau_{W\to A}\sim\frac{\mathbb{E}\tau_{W\to D}}{\Pr\{\tau_{D\to W}<\tau_{D\to A}\}}. \tag{40}$$

Using the multidimensional Kramers formulas and (33) in (40) yields (31).

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