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ESCAPE FROM SUBCELLULAR DOMAINS WITH RANDOMLY SWITCHING BOUNDARIES*

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Abstract. Motivated by various cellular transport processes, we consider diffusion in a potential and analyze the escape time to boundaries that randomly switch between absorbing and reflecting states. Combining disparate tools from PDEs and probability theory, we study both (a) the escape to the boundary in which the entire boundary switches and (b) the escape to one of N small pieces of the boundary that each randomly switch. For (a), we show how the switching boundary affects the classical rate of escape from a potential well. For (b), we significantly generalize a known result for the gated narrow escape problem and give this result an intuitive probabilistic interpretation. In both cases, our results illustrate the complementary perspectives that PDE and probabilistic methods offer escape problems.

Key words. stochastic hybrid systems, piecewise deterministic Markov process, diffusion, Brownian particles, cell biology

AMS subject classifications. 82C31, 92C37, 35R60, 34F05

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1. Introduction. One of the fundamental transport processes in biological cells is the exchange of ions, proteins, and other macromolecules between subcellular domains, or between the interior and exterior of the cell, via membrane pores and channels [4]. For example, the nucleus of eukaryotes is surrounded by a protective nuclear envelope (NE) within which are embedded nuclear pore complexes (NPCs); see Figure 1(a). The NPCs are the sole mediators of exchange between the nucleus and cytoplasm. In general, small molecules of diameter $\sim 5nm$ can diffuse through the NPCs unhindered, whereas larger molecules up to around $40nm$ in diameter are excluded unless they are bound to a family of soluble protein receptors known as karyopherins (kaps) [21]. Another classical example is the membrane transport of charged particles via voltage-gated or ligand-gated ion channels; see Figure 1(b). In this case, each gate randomly switches between an open and closed state. From a modeling perspective, there are three important characteristics of channel-mediated membrane transport. First, the membrane effectively acts as a *mixed* or *semipermeable* boundary, which is absorbing (open) wherever a channel is located, but is reflecting (closed) in the remainder of the boundary. Second, each channel is typically much smaller than the total membrane surface area, so that one often treats the transport process as a *narrow escape problem* [10, 17, 2, 15, 7, 11]. Finally, the open regions of the boundary do not stay open permanently, but *randomly switch* between open and closed states, either due to intrinsic properties of the channels or due to changes in the conformational state of the diffusing molecules.

In this paper we consider the problem of diffusive transport in a bounded domain, whereby all or parts of the boundary randomly switch between open and closed states. More specifically, let $\Omega \in \mathbb{R}^d$ denote a bounded, open set with smooth boundary $\partial\Omega$.

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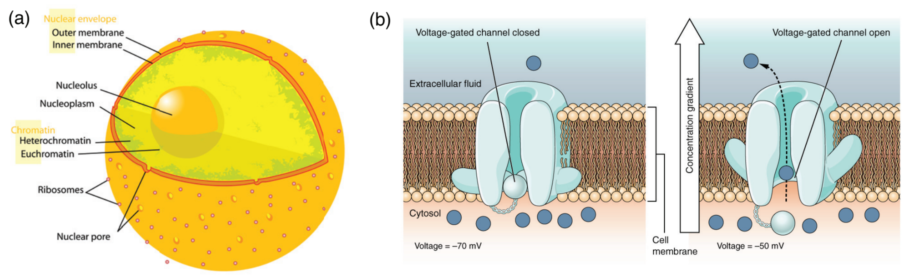

FIG. 1. (a) *Diagram of a cell nucleus surrounded by the nuclear envelope, which is studded with nuclear pore complexes.* (b) *Voltage-gated ion channel. [Public domain figures downloaded from Wikimedia Commons.]*

Let $\Phi : \bar{\Omega} \to \mathbb{R}^d$ be continuously differentiable and suppose $\mathbf{X}(t) \in \Omega$ satisfies

$$d\mathbf{X}(t) = -\nabla\Phi(\mathbf{X}(t))\, dt + \sqrt{2D}\, d\mathbf{W}(t), \tag{1.1}$$

where each component of $\mathbf{W}(t) \in \mathbb{R}^d$ is an independent Wiener process such that

$$\langle dW_i(t)\rangle = 0, \quad \langle dW_i(t) dW_j(t')\rangle = \delta_{i,j}\delta(t-t')dt\, dt', \quad i = 1, \dots, d,$$

and D is a scalar diffusion coefficient. Equation (1.1) represents a Brownian particle moving in an external potential Φ. We will focus on two particular types of escape problem.

(SI) Uniformly switching boundary. The whole boundary randomly switches between absorbing and reflecting. In order to keep track of the boundary state, we introduce the discrete random variable $n(t) \in \{0, 1\}$ such that $n(t) = 0$ if $\partial\Omega$ is absorbing and $n(t) = 1$ if $\partial\Omega$ is reflecting. We assume that transitions between the two states are given by the two-state Markov process

$$0 \underset{\alpha}{\overset{\beta}{\rightleftharpoons}} 1, \tag{1.2}$$

with fixed transition rates α, β. One possible biological interpretation of the switching boundary is that the Brownian particle randomly switches between two conformational states labeled by $n(t)$ such that it can only pass through the membrane when $n(t) = 0$. This is motivated by the example of the nuclear envelope, under the assumption that the nuclear pores are sufficiently dense that one can homogenize the membrane [8, 13]. (It is also possible that the effective potential $\Phi(\mathbf{x})$ and the diffusivity D also switch between the two states, but we will ignore this possibility here.)

(SII) Randomly switching narrow gates. We consider N narrow open gates $\partial\Omega_k^\varepsilon$, $k \in \{1, \dots, N\}$, with the kth gate given by the $\varepsilon > 0$ neighborhood of $\mathbf{x}_k \in \partial\Omega$ defined according to

$$\partial\Omega_k^\varepsilon := \{\mathbf{x} \in \partial\Omega : |\mathbf{x} - \mathbf{x}_k| < \varepsilon\}. \tag{1.3}$$

It is assumed that $|\mathbf{x}_k - \mathbf{x}_l| = O(1)$ for all $k \neq l$, that is, the gates are well separated; see Figure 2. We then partition the boundary $\partial\Omega$ by setting

$$\partial\Omega_a = \cup_{k=1}^N \partial\Omega_k^\varepsilon, \quad \partial\Omega_r = \partial\Omega - \partial\Omega_a.$$

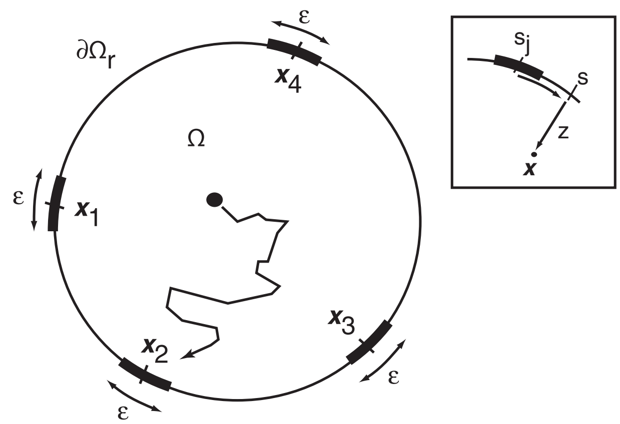

FIG. 2. *Narrow escape problem for a Brownian particle moving in a domain* Ω *with a finite number of small open gates on the boundary. The kth gate is of size* ε *and is centered about a point* $\mathbf{x}_k \in \partial\Omega$. *Inset: a local coordinate system around the* j*th arc.*

Let $\mathbf{n}(t) \in \{0,1\}^N$ be an irreducible Markov process whose kth component, $n_k(t) \in \{0,1\}$, controls the state of the kth gate. We say that gate k is open or closed at time t if $n_k(t)$ is 0 or 1, respectively. We assume $\mathbf{n}(t)$ is independent of $\mathbf{X}(t)$, but we do not necessarily assume that the components of $\mathbf{n}(t)$ are independent of each other. That is, the different gates may be correlated.

The case (SI) is the higher-dimensional analog of the one-dimensional (1D) problem of escape from a bounded interval with a switching boundary at one end (or simultaneously switching boundaries at both ends). We recently analyzed this problem using a combination of PDE methods, e.g., Green's functions, and probabilistic methods based on stopping times [5]. In particular, we determined corrections to the classical 1D escape problem with static boundaries. These corrections involve the statistics of a particle that starts at the switching boundary when the latter is in the reflecting state. The Green's function approach provided explicit expressions for these corrections under a restricted class of potentials, whereas the probabilistic approach allowed us to prove asymptotic formulae for a much more general class of potentials in the small diffusion limit. In particular, we showed that corrections to the mean first passage time (MFPT) depend critically on the gradient of the potential near the switching boundary. The main aim of the current paper is to extend the complementary Green's function and probabilistic approaches to the higher-dimensional escape problems (SI) and (SII). As far as we are aware, the only previous analysis of switching boundaries has been within the context of either a single narrow gate [16] or a set of narrow gates in which only a single gate can be open at any one time [1]; neither consider the effects of a potential nor combine PDE and probabilistic methods.

The structure of the paper is as follows. We first analyze the escape problem for a uniformly switching boundary using Green's functions, illustrating our analysis using a radially symmetric domain and potential (section 2). We then turn to the narrow escape problem for multiple, randomly switching gates in section 3. In particular, we extend the approach of Ward and collaborators for fixed gates [15, 7], which uses a combination of Green's functions and matched asymptotics in the limit $\varepsilon \to 0$, where ε characterizes the size of each gate. For the sake of illustration, we focus on a two-dimensional (2D) domain with zero potential. Finally, in section 4 we turn to the probabilistic approach, and derive asymptotic formulae for the effects of a switching boundary and a nonzero potential on (i) a uniformly switching boundary in the weak diffusion limit and (ii) randomly switching gates in the narrow gate limit $\varepsilon \to 0$.

2. MFPT for a randomly uniformly switching boundary (SI). Let us first consider the case where the whole boundary switches between open and closed, necessitating that we have to keep track of both the continuous stochastic variable $\mathbf{X}(t)$ evolving according to (1.1) and the binary discrete variable $n(t)$ that determines the current boundary condition. We thus have a stochastic hybrid system [4, 5]. If we set $p_n(\mathbf{x},t|\mathbf{y},0) = \mathbb{E}[p(\mathbf{x},t|\mathbf{y},0)1_{n(t)=n}]$, then p_n evolves according to the differential Chapman–Kolmogorov (CK) equation

$$\frac{\partial p_n}{\partial t} = \nabla \cdot (p_n(\mathbf{x},t|\mathbf{y},0)\nabla\Phi(\mathbf{x})) + D\nabla^2 p_n(\mathbf{x},t|\mathbf{y},0) + \sum_{m=0,1} A_{nm}p_m(\mathbf{x},t|\mathbf{y},0), \tag{2.1}$$

with $\mathbf{A}$ the matrix

$$\mathbf{A} = \begin{pmatrix} -\beta & \alpha \\ \beta & -\alpha \end{pmatrix}. \tag{2.2}$$

Equation (2.1) is supplemented by the boundary conditions

$$p_0(\mathbf{x},t|\mathbf{y},0) = 0, \quad \mathbf{J}_1(\mathbf{x},t|\mathbf{y},0) = 0, \quad \mathbf{x} \in \partial\Omega, \tag{2.3}$$

with

$$\mathbf{J}_n(\mathbf{x},t|\mathbf{y},0) = -p_n(\mathbf{x},t|\mathbf{y},0)\nabla\Phi(\mathbf{x}) - D\nabla p_n(\mathbf{x},t|\mathbf{y},0) \tag{2.4}$$

and the initial condition

$$p_n(\mathbf{x},t|\mathbf{y},0) = \delta(\mathbf{x}-\mathbf{y})\rho_n,$$

where ρ_n is the stationary measure of the ergodic two-state Markov process generated by the matrix $\mathbf{A}$,

$$\sum_{m=0,1} A_{nm}\rho_m = 0, \quad \rho_0 = \frac{\alpha}{\alpha+\beta}, \quad \rho_1 = \frac{\beta}{\alpha+\beta}. \tag{2.5}$$

Let $T_m(\mathbf{y})$ denote the MFPT to reach any point on the boundary $\partial\Omega$, given that the particle started in state $(\mathbf{y}, m)$ at $t = 0$. The distribution of first passage times for fixed m is related to the survival probability that the system is still in the domain Ω,

$$\mathcal{P}_m(\mathbf{y},t) \equiv \int_\Omega \sum_{n=0,1} p_n(\mathbf{x},t|\mathbf{y},0)d\mathbf{x}. \tag{2.6}$$

That is, the first passage time density for fixed $(\mathbf{y}, m)$ is

$$f_m(\mathbf{y},t) = -\frac{d\mathcal{P}_m}{dt} = -\int_\Omega \sum_n \frac{\partial p_n(\mathbf{x},t|\mathbf{y},0)}{\partial t}d\mathbf{x}. \tag{2.7}$$

Substituting for $\partial p_n/\partial t$ using the CK equation (2.1), applying the divergence theorem and the identity $\sum_n A_{nm} = 0$ yields

$$f_m(\mathbf{y},t) = -\int_{\partial\Omega} \mathbf{J}_m(\mathbf{x},t|\mathbf{y},0)\cdot d\sigma.$$

Given this density, the MFPT $T_m(\mathbf{y})$ is determined by

$$T_m(\mathbf{y}) \equiv \int_0^\infty f_m(\mathbf{y},t)t dt = -\int_0^\infty t\frac{\partial \mathcal{P}_m(\mathbf{y},t)}{\partial t}dt = \int_0^\infty \mathcal{P}_m(\mathbf{y},t)dt.$$

In order to derive a differential equation for the MFPT, consider the backward CK equation for $q_m(\mathbf{x},t|\mathbf{y},0) = \mathbb{E}[p(\mathbf{x},t|\mathbf{y},0)1_{n(0)=m}]$ with $\mathbf{x}$ fixed:

$$\partial_t q_m(\mathbf{x},t|\mathbf{y},0) = \text{Ł}_{\text{FP}} q_m(\mathbf{x},t|\mathbf{y},0) + \sum_{n=0,1} A_{mn}^\top q_n(\mathbf{x},t|\mathbf{y},0), \tag{2.8}$$

with linear operator

$$\text{Ł}_{\text{FP}} = -\nabla\Phi(\mathbf{y})\cdot\nabla + D\nabla^2 \tag{2.9}$$

and boundary conditions

$$q_0(\mathbf{x},t|\mathbf{y},0) = 0, \quad \nabla q_1(\mathbf{x},t|\mathbf{y},0)\cdot\boldsymbol{\sigma}(\mathbf{y}) = 0, \quad \mathbf{y}\in\partial\Omega. \tag{2.10}$$

Note that Ł_{FP} is non-Hermitian with respect to the inner product

$$\langle f, v\rangle = \int_\Omega f(\mathbf{x})g(\mathbf{x})dx,$$

with f and g satisfying the same Neumann or Dirichlet boundary conditions on $\partial\Omega$. Integrating (2.8) with respect to $\mathbf{x}\in\Omega$ shows that $\mathcal{P}_m(\mathbf{y},t)$, and hence $f_m(\mathbf{y},t)$, also satisfies a backward CK equation. It follows that

$$\text{Ł}_{\text{FP}} T_m(\mathbf{y}) + \sum_{n=0,1} A_{mn}^\top T_n(\mathbf{y}) = -1, \tag{2.11}$$

with boundary conditions

$$T_0(\mathbf{y}) = 0, \quad \nabla T_1(\mathbf{y})\cdot\boldsymbol{\sigma}(\mathbf{y}) = 0, \quad \mathbf{y}\in\partial\Omega.$$

Performing the change of variables

$$w_n(\mathbf{y}) = \rho_n T_n(\mathbf{y}),$$

(2.11) becomes the pair of equations

$$\text{Ł}_{\text{FP}} w_0(\mathbf{y}) - \beta w_0(\mathbf{y}) + \alpha w_1(\mathbf{y}) = -\rho_0, \tag{2.12a}$$

$$\text{Ł}_{\text{FP}} w_1(\mathbf{y}) + \beta w_0(\mathbf{y}) - \alpha w_1(\mathbf{y}) = -\rho_1, \tag{2.12b}$$

with $w_m(\mathbf{y})$ satisfying the same boundary conditions as $T_m(\mathbf{y})$. Adding (2.12a), (2.12b), and setting $w(\mathbf{y}) = w_0(\mathbf{y}) + w_1(\mathbf{y})$ gives

$$\text{Ł}_{\text{FP}} w(\mathbf{y}) = -1, \quad \mathbf{y}\in\Omega, \quad w(\mathbf{y}) = w_1(\mathbf{y}), \quad \mathbf{y}\in\partial\Omega. \tag{2.13}$$

It follows that

$$w(\mathbf{y}) = \tau(\mathbf{y}) + \phi(\mathbf{y}), \tag{2.14}$$

where $\tau(\mathbf{y})$ is the MFPT for a nonswitching boundary and $\phi(\mathbf{y})$ satisfies the equation

$$\text{Ł}_{\text{FP}}\phi(\mathbf{y}) = 0, \quad \phi(\mathbf{y}) = w_1(\mathbf{y}), \quad \mathbf{y}\in\partial\Omega. \tag{2.15}$$

We can solve (2.15) using Green's functions. That is, let $G_0(\mathbf{x},\mathbf{y})$ satisfy the adjoint equation

$$\mathbb{L}^{\dagger}_{\mathrm{FP},\mathrm{y}} G_0(\mathbf{x},\mathbf{y}) = -\delta(\mathbf{x}-\mathbf{y}), \tag{2.16}$$

with

$$G_0(\mathbf{x},\mathbf{y}) = 0, \quad \mathbf{x} \in \partial\Omega.$$

Then

$$\phi(\mathbf{y}) = \int_{\partial\Omega} w_1(\mathbf{y}') \left[\nabla_{\mathbf{y}} G_0(\mathbf{y},\mathbf{y}') \cdot \boldsymbol{\sigma}(\mathbf{y}')\right] d\mathbf{y}'. \tag{2.17}$$

We thus have

$$w(\mathbf{y}) = \tau(\mathbf{y}) + \int_{\partial\Omega} w_1(\mathbf{y}') Q(\mathbf{y}'|\mathbf{y}) d\mathbf{y}', \tag{2.18}$$

with

$$Q(\mathbf{y}'|\mathbf{y}) = \nabla_{\mathbf{y}} G_0(\mathbf{y},\mathbf{y}') \cdot \boldsymbol{\sigma}(\mathbf{y}'). \tag{2.19}$$

Equation (2.18) has a direct probabilistic interpretation: $\tau(\mathbf{y})$ is the time expected to reach the switching boundary for the first time starting from $\mathbf{y}$, but there is now the possibility that the boundary is closed on arrival. Thus, there is an additional contribution whereby $Q(\mathbf{y}'|\mathbf{y})$ is the conditional probability density that the particle will first hit the boundary at $\mathbf{y}' \in \partial\Omega$ and $w_1(\mathbf{y}')$ is the MFPT that the particle starts at position $\mathbf{y}' \in \partial\Omega$ when the boundary is closed.

Now substituting (2.18) into (2.12b) and using $w_0 = w - w_1$, we obtain the following inhomogeneous equation for w_1:

$$\mathbb{L}_{\mathrm{FP}} w_1(\mathbf{y}) - (\alpha+\beta) w_1(\mathbf{y}) = -\beta w(\mathbf{y}) - \rho_1. \tag{2.20}$$

Introduce the modified Helmholtz Green's function $G(\mathbf{x},\mathbf{y})$ with

$$\left[\mathbb{L}^{\dagger}_{\mathrm{FP},\mathrm{y}} - (\alpha+\beta)\right] G(\mathbf{x},\mathbf{y}) = -\delta(\mathbf{x}-\mathbf{y}) \tag{2.21}$$

and

$$\nabla\Phi(\mathbf{y}) G(\mathbf{x},\mathbf{y}) + D\nabla_{\mathbf{y}} G(\mathbf{x},\mathbf{y}) \cdot \boldsymbol{\sigma}(\mathbf{y}) = 0, \quad \mathbf{x} \in \partial\Omega.$$

Then

$$w_1(\mathbf{y}) = \int_{\Omega} G(\mathbf{y},\mathbf{y}')[\beta w(\mathbf{y}') + \rho_1] d\mathbf{y}'. \tag{2.22}$$

Finally, since $w(\mathbf{y}) = \tau(\mathbf{y}) + \phi(\mathbf{y})$, and taking $\mathbf{y} \in \partial\Omega$, we obtain the self-consistency condition

$$w_1(\mathbf{y}) = \int_{\Omega} G(\mathbf{y},\mathbf{y}')[\beta\tau(\mathbf{y}') + \rho_1] d\mathbf{y}' + \int_{\partial\Omega} \mathcal{H}(\mathbf{y},\mathbf{y}') w_1(\mathbf{y}') d\mathbf{y}', \quad \mathbf{y} \in \partial\Omega, \tag{2.23}$$

with

$$\mathcal{H}(\mathbf{y},\mathbf{y}') = \int_{\Omega} G(\mathbf{y},\mathbf{y}'') Q(\mathbf{y}'|\mathbf{y}'') d\mathbf{y}''. \tag{2.24}$$

2.1. Example: Radially symmetric potential. In the special case of a radially symmetric potential, $\Phi(\mathbf{x}) = \Phi(r)$, and $\Omega = S^d$ for $d \geq 2$, our analysis reduces to an effective 1D problem, which is an extension of our previous work on the escape from a finite interval with a switching boundary at one of the ends [5, 12]. The basic observation is that the MFPT will only depend on the radial distance r of the starting position from the origin. The radially symmetric form of the differential operator $\mathbb{L}_{\mathrm{FP}}$ is

$$\mathbb{L}_r = -\Phi'(r)\frac{d}{dr} + D\left[\frac{d-1}{r}\frac{d}{dr} + \frac{d^2}{dr^2}\right], \quad 0 < r < R, \tag{2.25}$$

with R the radius of the hypersphere. In the case of a fixed boundary, we have the MFPT $\tau(r)$ satisfying the equation

$$-\widehat{\Phi}'(r)\frac{d\tau}{dr} + D\frac{d^2\tau}{dr^2} = -1, \quad 0 < r < R, \quad \tau(R) = 0, \tag{2.26}$$

where

$$\widehat{\Phi}(r) = \Phi(r) - D(d-1)\ln(r). \tag{2.27}$$

This is equivalent to the FPT problem of a 1D particle moving in an effective potential $\widehat{\Phi}(r)$ on the interval $[0, R]$, with a reflecting boundary at $r = 0$ and an absorbing boundary at $r = R$. (It is not necessary to impose a reflecting boundary condition at $r = 0$, since the effective potential has a logarithmic term that blows up at $r = 0$.) From a physical perspective, we see that the logarithmic term reduces the slope of the potential at the boundary, $\widehat{\Phi}'(R) < \Phi'(R)$, which means that there is an additional effective force that tends to push the particle towards the boundary, thus reducing the MFPT.

In the case of a zero potential, $\Phi(r) = 0$, the classical MFPT $\tau(r)$ satisfies $\tau'(r) = u(r)$, with

$$\frac{d}{dr}(ur^{d-1}) = -\frac{r^{d-1}}{D}.$$

It follows that

$$u(r) = \frac{A}{r^{d-1}} - \frac{r}{(d-1)D}.$$

In the case $\Phi(r) = 0$, the MFPT $\tau(r)$ satisfying $\tau(R) = 0$ is

$$\tau(r) = \frac{R^2 - r^2}{2(d-1)D}. \tag{2.28}$$

For an r-dependent potential, (2.26) has the classical solution [9]

$$\tau(r) = \frac{1}{D}\int_r^R \int_0^z \mathrm{e}^{[\widehat{\Phi}(z) - \widehat{\Phi}(r')]/D} dr'\, dz. \tag{2.29}$$

Suppose that the effective potential $\widehat{\Phi}$ is twice differentiable with a unique minimum at $r_{\min} \in (0, R)$. If the particle starts in a neighborhood of $r_{\min}$, then we can

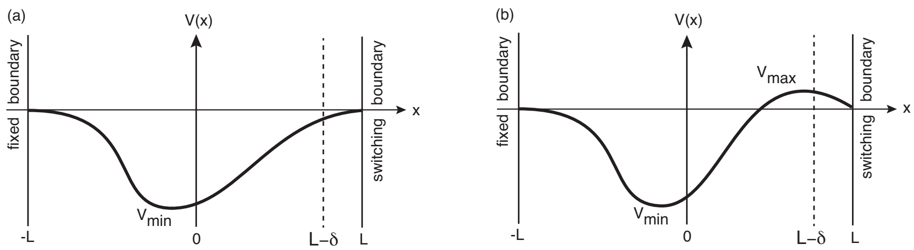

FIG. 3. *Radially symmetric effective potential well* $\widehat{\Phi}(r)$ *with* (a) $\widehat{\Phi}'(r) > 0$ *and* (b) $\widehat{\Phi}'(r) < 0$ *on* $[R-\delta, R]$.

use Laplace's method for small D to give

$$\begin{aligned}\tau(r) &= \frac{1}{D}\int_{r_{\min}}^{R}\int_0^z \mathrm{e}^{[\widehat{\Phi}(z)-\widehat{\Phi}(r)]/D} dr\, dz \\ &\sim \frac{1}{D}\left[\int_0^R \mathrm{e}^{-\widehat{\Phi}(r)/D} dr\right]\left[\int_{r_{\min}}^R \mathrm{e}^{\widehat{\Phi}(z)/D} dz\right] \\ &\sim \sqrt{\frac{2\pi}{\widehat{\Phi}''(r_{\min})}}\mathrm{e}^{-\widehat{\Phi}(r_{\min})/D}\left[\int_{r_{\min}}^R \mathrm{e}^{\widehat{\Phi}(z)/D} dz\right] \quad \text{as } D\to 0.\end{aligned}$$

Evaluation of the final integral depends on whether or not $\widehat{\Phi}(r)$ has a local maximum in the domain $[r_{\min}, R]$ such that $\widehat{\Phi}_{\max} > \widehat{\Phi}(R)$; see Figure 3. If this is the case, then we can apply Laplace's method to obtain the classical Kramers' formula

$$\tau(r) = 2\pi\sqrt{\frac{1}{\widehat{\Phi}''(r_{\min})|\widehat{\Phi}''(r_{\max})|}}\mathrm{e}^{[\widehat{\Phi}(r_{\max})-\widehat{\Phi}(r_{\min})]/D}. \tag{2.30}$$

In the case of a switching boundary, we find that (2.14) becomes $w(r) = \tau(r) + w_1(R)$ and (2.20) reduces to the 1D form

$$-\widehat{\Phi}'(r)\frac{dw_1}{dr} + D\frac{d^2w_1}{dr^2} - (\alpha+\beta)w_1 = -\beta w(r) - \rho_1, \quad 0 < r < R, \quad \partial w_1(R) = 0. \tag{2.31}$$

This has the solution

$$w_1(z) = \int_0^R G(z,r)[\beta w(r) + \rho_1]dr,$$

where G is the 1D Green's function defined according to

$$\frac{1}{r^{d-1}}\frac{d}{dr}(r^{d-1}G(z,r)\Phi'(r)) + D\left[\frac{d-1}{r}\frac{d}{dr} + \frac{d^2}{dr^2}\right]G(z,r) - (\alpha+\beta)G(z,r) = -\delta(z-r),$$

with $\Phi'(r)G(z,r) + D\partial_r G(z,r) = 0$ at $r = R$. Finally, since $w(r) = \tau(r) + w_1(R)$, we obtain the self-consistency condition

$$w_1(R) = [\rho_1 + \beta w_1(R)]\int_0^R G(R,r)dr + \beta\int_0^R G(R,r)\tau(r)dr,$$

that is,

$$w_1(R) = \frac{\rho_1 \Lambda_R + \beta \Gamma_R}{1 - \beta \Lambda_R}, \tag{2.32}$$

with

$$\Lambda_R = \int_0^R G(R,r)dr, \quad \Gamma_R = \int_0^R G(R,r)\tau(r)dr. \tag{2.33}$$

In the case of an r-dependent potential well $\Phi(r)$, one typically has to carry out out an eigenfunction expansion of the associated Green's function $G(z,r)$. However, as we previously showed in the 1D case [5], there is only a restricted class of potentials for which the eigenfunctions can be calculated exactly. In principle, we could also carry out eigenfunction expansions of the multidimensional Green's functions $G_0(\mathbf{x},\mathbf{y})$ and $G(\mathbf{x},\mathbf{y})$ for a nonradially symmetric potential $\Phi(\mathbf{x})$. However, the resulting calculations rapidly become unwieldy. Therefore, in section 4.1, we will consider an alternative, probabilistic approach based on stopping times, which is valid in the small diffusion limit. In particular, we will show that the effect of a switching boundary on the rate of escape from a potential well depends on the sign of the gradient of the potential in a neighborhood of the boundary.

3. MFPT for randomly switching narrow gates (SII). Suppose that the boundary $\partial\Omega$ is now closed except for a set of small open gates of size εl_k located at a set of boundary points $\mathbf{x}_j \in \partial\Omega$. This narrow escape problem has been studied extensively by a number of groups [10, 17, 2, 15, 7, 11]. All of these studies assume that the gate is always open and that the potential is flat. The example of escape through a narrow open gate in the presence of a potential has been studied by Singer and Schuss [18], whereas the narrow escape problem for a stochastically gated Brownian particle in the absence of a potential has been studied by Riengruber and Holcman [16]. In the latter case, the gate is fixed but the particle is assumed to switch between two conformational states with different diffusivities and such that the particle can only pass through the gate in one of the states. This is equivalent to a single particle trying to escape through a stochastically switching gate when the diffusivity of the two conformational states is the same. However, it is important to emphasize that when there are multiple particles, the two scenarios are not equivalent, since in the case of switching gates there are additional correlations due to the fact that all particles experience the same switching environment [6]. In this section, we will show how to modify the Green's function analysis of section 2 in order to handle the case of multiple switching gates. For the sake of illustration, we will develop the analysis for a two-dimensional (2D) domain in the absence of a potential, and use matched asymptotics along the lines of Ward et al. [15] and Cheviakov, Ward, and Straube [7] to determine the effects of switching on the MFPT in the narrow gate limit $\varepsilon \to 0$. The effects of a potential in this limit will be investigated in section 4 using an alternative probabilistic approach.

3.1. Narrow escape problem for a 2D domain with switching gates on the boundary and a zero potential. In order to develop the basic theory, we will take $d = 2$ and Ω to be the unit disc. As a further simplification, let us focus on the case of a zero potential, $\Phi = 0$, and assume that the gates open and close independently, with the kth gate having the transition rates α_k, β_k; see (1.2). Since there are N switching gates, we now have to introduce N discrete variables $n_k(t)$,

$k = 1, \ldots, N$, with $n_k(t) = 0$ if the kth gate is open and $n_k(t) = 1$ if it is closed. Defining $p_{\mathbf{n}}(\mathbf{x}, t|\mathbf{y}, 0) = \mathbb{E}[p(\mathbf{x}, t|\mathbf{y}, 0) 1_{\mathbf{n}(t)=\mathbf{n}}]$ with $\mathbf{n} = (n_1, \ldots, n_N)$, the CK equation (2.1) becomes

$$\frac{\partial p_{\mathbf{n}}}{\partial t} = D\nabla^2 p_{\mathbf{n}}(\mathbf{x}, t|\mathbf{y}, 0) + \sum_{\mathbf{m}} \mathcal{A}_{\mathbf{nm}} p_{\mathbf{m}}(\mathbf{x}, t|\mathbf{y}, 0), \tag{3.1}$$

with $\mathcal{A}$ the $2^N \times 2^N$ matrix with elements

$$\mathcal{A}_{\mathbf{nm}} = \sum_{k=1}^{N} A^{(k)}_{n_k m_k} \prod_{l \neq k} \delta_{n_l, m_l} \tag{3.2}$$

and $\mathbf{A}^{(k)}$ given by (2.2) for $\alpha, \beta \to \alpha_k, \beta_k$. The boundary conditions are

$$p_{\mathbf{n}}(\mathbf{x}, t|\mathbf{y}, 0) = 0, \quad \mathbf{x} \in \sum_{k=1}^{N} (1 - n_k) \partial\Omega_k^{\varepsilon}, \tag{3.3a}$$

$$\nabla p_{\mathbf{n}}(\mathbf{x}, t|\mathbf{y}, 0) = 0 \quad \mathbf{x} \in \partial\Omega - \sum_{k=1}^{N} (1 - n_k) \partial\Omega_k^{\varepsilon}. \tag{3.3b}$$

Proceeding along similar lines as in section 2, we find that the MFPT $T_{\mathbf{m}}(\mathbf{y})$ for the particle exiting one of the gates when it is open, starting at position $\mathbf{y}$ and with $\mathbf{n}(0) = \mathbf{m}$, satisfies the corresponding backwards CK equation

$$D\nabla^2 T_{\mathbf{m}}(\mathbf{y}) + \sum_{\mathbf{n}} \mathcal{A}^{\top}_{\mathbf{mn}} T_{\mathbf{n}}(\mathbf{y}) = -1, \tag{3.4}$$

with the boundary conditions

$$T_{\mathbf{m}}(\mathbf{y}) = 0, \quad \mathbf{y} \in \sum_{k=1}^{N} (1 - m_k) \partial\Omega_k^{\varepsilon}, \tag{3.5a}$$

$$\nabla T_{\mathbf{m}}(\mathbf{y}) \cdot \boldsymbol{\sigma}(\mathbf{y}) = 0, \quad \mathbf{y} \in \partial\Omega - \sum_{k=1}^{N} (1 - m_k) \partial\Omega_k^{\varepsilon}. \tag{3.5b}$$

The matrix $\mathcal{A}$ satisfies detailed balance, that is,

$$\mathcal{A}_{\mathbf{nm}} \mathcal{P}_{\mathbf{m}} = \mathcal{A}_{\mathbf{mn}} \mathcal{P}_{\mathbf{n}},$$

where $\mathcal{P}$ is the unique stationary distribution of the discrete Markov process:

$$\mathcal{P}_{\mathbf{n}} = \prod_{k=1}^{N} \rho^{(k)}_{n_k}, \quad \rho^{(k)}_0 = \frac{\alpha_k}{\alpha_k + \beta_k}, \quad \rho^{(k)}_1 = \frac{\beta_k}{\alpha_k + \beta_k}. \tag{3.6}$$

Hence, setting $w_{\mathbf{n}}(\mathbf{y}) = \mathcal{P}_{\mathbf{n}} T_{\mathbf{n}}(\mathbf{y})$, we find that

$$D\nabla^2 w_{\mathbf{m}}(\mathbf{y}) + \sum_{\mathbf{n}} \mathcal{A}_{\mathbf{mn}} w_{\mathbf{n}}(\mathbf{y}) = -\mathcal{P}_{\mathbf{m}}, \tag{3.7}$$

with $w_{\mathbf{n}}$ satisfying the same boundary conditions as $T_{\mathbf{m}}$. Setting $w(\mathbf{y}) = \sum_{\mathbf{n}} w_{\mathbf{n}}(\mathbf{y})$, we finally obtain the analog of (2.13):

$$D\nabla^2 w(\mathbf{y}) = -1, \tag{3.8}$$

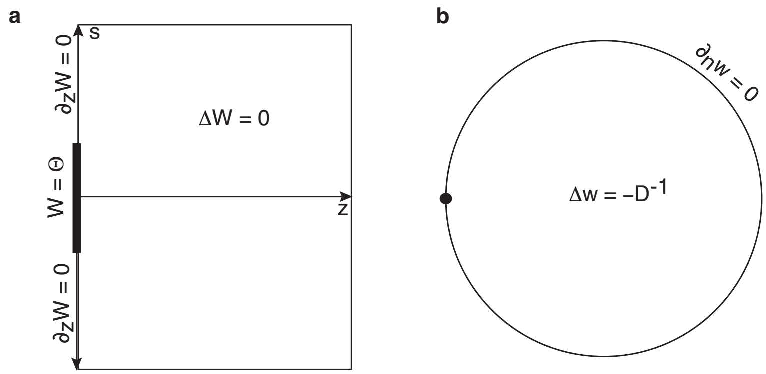

Fig. 4. *Construction of the matched asymptotic solution for the narrow escape problem for a disc with a single gate.* (a) *Inner solution W in the half-plane $s \in \mathbb{R}, z \in \mathbb{R}^+$ with mixed boundary conditions on $z = 0$.* (b) *Outer solution w in the disc with a reflecting boundary condition and the gate treated as a point.*

with boundary conditions

$$w(\mathbf{y}) = \Theta_k, \quad \mathbf{y} \in \partial\Omega_k^\varepsilon, \quad \nabla w(\mathbf{y}) \cdot \boldsymbol{\sigma}(\mathbf{y}) = 0, \quad \mathbf{y} \in \partial\Omega - \sum_{k=1}^N \partial\Omega_k^\varepsilon. \tag{3.9}$$

Here Θ_k denotes the MFPT to escape through any of the gates, given that the particle started at the kth gate with the latter closed. If $\Theta_k \equiv 0$ for all k, then we would have the classical narrow escape problem through a set of N narrow open gates. Here we show how to modify the analysis when $\Theta_k \neq 0$, following the particular approach of Ward and collaborators [15, 7]. For a complementary Green's function approach, see the work of Holcman and Schuss reviewed in [11].

3.2. Calculation of $w(\mathbf{y})$ using matched asymptotics. The basic idea is to construct the asymptotic solution for $w(\mathbf{y})$ in the limit $\varepsilon \to 0$ using the method of matched asymptotic expansions. That is, an inner or local solution valid in a $\mathcal{O}(\varepsilon)$ neighborhood of each gate is constructed and then these are matched to an outer or global solution that is valid away from these neighborhoods; see Figure 4. In the case of a disc, each gate is represented by an arc of length εl_j with $l_j = O(1)$. In order to construct the inner solution, (3.8) is rewritten in terms of a local orthogonal coordinate system (z, s), in which s denotes the arc length along $\partial\Omega$ and z is the minimal distance from $\partial\Omega$ to an interior point $\mathbf{y} \in \Omega$, as shown in the inset of Figure 2. Now we introduce stretched coordinates $\widehat{z} = z/\varepsilon$ and $\widehat{s} = (s - s_k)/\varepsilon$, and write the solution to the inner problem as $W(\mathbf{y}) = w(\widehat{z}, \widehat{s})$. Neglecting terms of $\mathcal{O}(\varepsilon)$, it can be shown that W satisfies the homogeneous equation [15]

$$\frac{\partial^2 W}{\partial^2 \widehat{z}} + \frac{\partial^2 W}{\partial^2 \widehat{s}} = 0, \quad 0 < \widehat{z} < \infty, \quad -\infty < \widehat{s} < \infty, \tag{3.10}$$

with the following boundary conditions on $\widehat{z} = 0$:

$$\frac{\partial W}{\partial \widehat{z}} = 0 \text{ for } |\widehat{s}| > l_k/2, \quad W = \theta_k \text{ for } |\widehat{s}| < l_k/2. \tag{3.11}$$

The resulting boundary value problem can be solved by introducing elliptic cylinder coordinates. However, in order to match the outer solution we need only specify the far-field behavior of the inner solution, which takes the form

$$W(\mathbf{y}) \sim \Theta_k + B_k \left[\log\left(|\mathbf{y}-\mathbf{x}_k|/\varepsilon\right) - \log(l_k/4) + o(1)\right] \text{ as } |\mathbf{y}-\mathbf{x}_k|/\varepsilon \to \infty, \tag{3.12}$$

where the B_k are unknown constants, which are determined by matching with the outer solution.

As far as the outer solution is concerned, each absorbing arc shrinks to a point $\mathbf{x}_k \in \partial\Omega$ as $\varepsilon \to 0$; see Figure 4(b). Each point $\mathbf{x}_j$ effectively acts as a point source that generates a logarithmic singularity resulting from the asymptotic matching of the outer solution to the far–field behavior of the inner solution. Thus the outer solution satisfies

$$\nabla^2 w(\mathbf{y}) = -\frac{1}{D}, \quad \mathbf{y} \in \Omega, \tag{3.13}$$

with reflecting boundary condition

$$\nabla w(\mathbf{y}) \cdot \boldsymbol{\sigma}(\mathbf{y}) = 0 \quad \text{for } \mathbf{y} \in \partial\Omega \backslash \{\mathbf{x}_1, \ldots, \mathbf{x}_N\} \tag{3.14}$$

and

$$w(\mathbf{y}) \sim \Theta_k + \frac{B_k}{\nu_k} + B_k \log|\mathbf{y}-\mathbf{x}_k| \text{ as } \mathbf{y} \to \mathbf{x}_k,\ k = 1, \ldots, N, \tag{3.15}$$

where

$$\nu_k \equiv -\frac{1}{\log(\varepsilon l_k/4)}. \tag{3.16}$$

This can be solved in terms of the Neumann Green's function G, defined as the unique solution of

$$\nabla^2 G(\mathbf{x},\mathbf{x}') = \frac{1}{|\Omega|} - \delta(\mathbf{x}-\mathbf{x}'), \quad x \in \Omega, \tag{3.17a}$$

$$G(\mathbf{x},\mathbf{x}_k) \sim -\frac{1}{\pi}\log|\mathbf{x}-\mathbf{x}_k| + R(\mathbf{x}_k,\mathbf{x}_k) \text{ as } \mathbf{x} \to \mathbf{x}_k \in \partial\Omega, \tag{3.17b}$$

$$\partial_n G(\mathbf{x},\mathbf{x}') = 0,\ \mathbf{x} \in \partial\Omega, \quad \int_\Omega G(\mathbf{x},\mathbf{x}_k) d\mathbf{x} = 0, \tag{3.17c}$$

where $R(\mathbf{x},\mathbf{x}')$ is the regular part of $G(\mathbf{x},\mathbf{x}')$. It follows that the outer solution can be expressed as

$$w(\mathbf{y}) = -\pi \sum_{k=1}^N B_k G(\mathbf{y},\mathbf{x}_k) + \chi, \tag{3.18}$$

where χ is an unknown constant. Integrating both sides of (3.18) shows that

$$\chi = \overline{w} \equiv \frac{1}{|\Omega|}\int_\Omega w(\mathbf{y}) d\mathbf{y}. \tag{3.19}$$

The problem has now reduced to solving $N+1$ linear equations for $N+1$ unknowns B_k, χ. The first N equations are obtained by matching the near-field behavior of the outer solution as $\mathbf{x} \to \mathbf{x}_k$, with the far–field behavior of the corresponding inner solution (3.12). After cancellation of the logarithmic terms, we have

$$-\pi B_k R_k - \pi \sum_{j \neq k} B_j G_{kj} + \chi - \Theta_k = \frac{B_k}{\nu_k}, \tag{3.20}$$

for $j = 1, \dots, N$, where $G_{kj} \equiv G(\mathbf{x}_k, \mathbf{x}_j)$ and $R_k \equiv R(\mathbf{x}_k, \mathbf{x}_k)$. The remaining equation is obtained by noting that $\nabla^2 w(\mathbf{y}) = -\pi \sum_{k=1}^N B_k \nabla^2 G(\mathbf{y}, \mathbf{x}_k)$ and, hence,

$$\pi|\Omega|^{-1} \sum_{j=1}^N B_j = \frac{1}{D}. \tag{3.21}$$

The regular part of the Neumann Green's function $R(\mathbf{x}, \mathbf{x}_j)$ will depend on the geometry of the domain Ω. For example, in the case of a unit disk when the source $\mathbf{x}_k$ is on the unit circle, G has the well-known formula

$$G(\mathbf{x}, \mathbf{x}_k) = -\frac{1}{\pi} \log|\mathbf{x} - \mathbf{x}_k| + \frac{|\mathbf{x}|^2}{4\pi} - \frac{1}{8\pi}.$$

For a single gate of arc length 2ε ($l_1 = 2$), (3.20) and (3.21) are easily solved to give $B_1 = |\Omega|/\pi D$ and

$$\chi = \Theta_1 + (\pi R_1 + 1/\nu_1) B_1,$$

so that

$$w(\mathbf{y}) \sim \Theta_1 + \frac{|\Omega|}{D}\left[-\frac{1}{\pi}\log(\varepsilon/2) + R(\mathbf{x}_1, \mathbf{x}_1) - G(\mathbf{y}, \mathbf{x}_1)\right]. \tag{3.22}$$

It is straightforward to interpret the solution (3.22), namely, $w(\mathbf{y}) = \tau(\mathbf{y}) + \Theta_1$, where $\tau(\mathbf{y})$ is the solution to the classical narrow escape problem when the gate is always open, that is, it determines the MFPT to reach the gate, and the correction term Θ_1 is the MFPT to eventually escape through the gate given that the particle starts at $\mathbf{y} = \mathbf{x}_1$ and the gate is closed.

For multiple gates, (3.20) and (3.21) can be solved by Taylor expanding in powers of ν_j [15]. This gives

(3.23a)

$$B_k \sim \frac{\nu_k}{N\bar{\nu}}\left[\frac{|\Omega|}{D\pi} + \sum_{j=1}^N \nu_j(\Theta_j - \Theta_k)\right] + O(|\nu|),$$

$$\chi \sim \frac{1}{N\bar{\nu}}\left[1 + \frac{\pi}{N\bar{\nu}}\sum_{i=1}^N\sum_{j=1}^N \nu_i\nu_j\widehat{G}_{ij}\right]\left[\frac{|\Omega|}{D\pi} + \sum_{j=1}^N \nu_j\Theta_j - \pi\sum_{i=1}^N\sum_{j=1}^N \nu_i\nu_j\widehat{G}_{ij}\Theta_j\right]$$

$$+ O(|\nu|), \tag{3.23b}$$

where $\widehat{G}_{ij} = G_{ij}$ for all $i \neq j$ and $\widehat{G}_{ii} = R_i$, and $\bar{\nu} = N^{-1}\sum_{j=1}^N \nu_j$. We have also used the fact that $\Theta_k = O(|\nu|^{-1})$.

Substituting (3.23) into (3.18) shows that we can decompose the MFPT as $w(\mathbf{y}) = \tau(\mathbf{y}) + \Psi(\mathbf{y})$, where

$$\Psi(\mathbf{y}) \sim -\pi\sum_{k=1}^N \frac{\nu_k}{N\bar{\nu}}\left[\sum_{j=1}^N \nu_j(\Theta_j - \Theta_k)\right] G(\mathbf{y}, \mathbf{x}_k) + \frac{1}{N\bar{\nu}}\sum_{j=1}^N \nu_j\Theta_j + O(|\nu|). \tag{3.24}$$

We can decompose $\Psi(\mathbf{y})$ as

$$\Psi(\mathbf{y}) = \sum_{k=1}^N \pi_k(\mathbf{y})\Theta_k, \tag{3.25}$$

where $\pi_k(\mathbf{y})$ is the probability that the particle first hits the kth gate starting at position $\mathbf{y}$, and assuming that the initial state of the gates is $\mathbf{n}(0) = \mathbf{m}$ with probability $\mathcal{P}_{\mathbf{m}}$. Comparison with (3.24) implies that

$$\pi_k(\mathbf{y}) \sim \frac{\nu_k}{N\bar{\nu}} \left[1 - \pi \sum_j [G(\mathbf{y}, \mathbf{x}_j) - G(\mathbf{y}, \mathbf{x}_k)]\nu_j \right] + O(|\nu|^2). \tag{3.26}$$

3.3. Self-consistency condition for $\boldsymbol{\Theta_k}$. Having solved $w(\mathbf{y})$ in terms of Θ_k, $k = 1, \ldots, N$, we now need to derive self-consistency conditions for the Θ_k. Again, let us first consider a single gate with $\alpha_1 = \alpha$ and $\beta_1 = \beta$. Equation (3.7) implies that $w_1(\mathbf{y})$ satisfies

$$D\nabla^2 w_1(\mathbf{y}) - (\alpha + \beta)w_1(\mathbf{y}) = -\beta w(\mathbf{y}) - \rho_1, \tag{3.27}$$

with boundary condition $\nabla w_1(\mathbf{y}) \cdot \boldsymbol{\sigma} = 0$ for all $\mathbf{y} \in \partial\Omega$. The solution of equation (3.27) can be solved in terms of the Green's function $\mathcal{G}(\mathbf{x}, \mathbf{y})$ of the modified Helmholtz equation:

$$\nabla^2_{\mathbf{y}} \mathcal{G}(\mathbf{x}, \mathbf{y}) - (\alpha + \beta)\mathcal{G}(\mathbf{x}, \mathbf{y}) = -\delta(\mathbf{x} - \mathbf{y}), \quad \mathbf{y} \in \Omega. \tag{3.28a}$$

$$\mathcal{G}(\mathbf{x}, \mathbf{x}_k) \sim -\frac{1}{\pi} \log|\mathbf{x} - \mathbf{x}_k| + \mathcal{R}(\mathbf{x}_k, \mathbf{x}_k) \text{ as } \mathbf{x} \to \mathbf{x}_k \in \partial\Omega, \tag{3.28b}$$

$$\nabla \mathcal{G}(\mathbf{x}, \mathbf{y}) \cdot \sigma(\mathbf{y}) = 0, \quad \mathbf{y} \in \partial\Omega, \tag{3.28c}$$

where $\mathcal{R}(\mathbf{x}, \mathbf{y})$ is the regular part of $\mathcal{G}(\mathbf{x}, \mathbf{x}')$, and the Neumann boundary conditions imply that

$$\int_\Omega \mathcal{G}(\mathbf{x}, \mathbf{y}) d\mathbf{y} = (\alpha + \beta)^{-1}.$$

Using Green's theorem, we find that

$$w_1(\mathbf{y}) = \int_\Omega \mathcal{G}(\mathbf{y}, \mathbf{x})[\beta w(\mathbf{x}) + \rho_1] d\mathbf{x}. \tag{3.29}$$

Finally, setting $\mathbf{y} = \mathbf{x}_1$, we obtain the self-consistency condition

$$\Theta_1 = \int_\Omega \mathcal{G}(\mathbf{x}_1, \mathbf{x})[\beta w(\mathbf{x}) + \rho_1] d\mathbf{x}. \tag{3.30}$$

Substituting for $w(\mathbf{x})$, using the asymptotic expansion (3.22) gives

$$\Theta_1 = \frac{1}{\alpha + \beta}(\beta\Theta_1 + \rho_1) + \int_\Omega \mathcal{G}(\mathbf{x}_1, \mathbf{x})\beta\tau(\mathbf{x}) d\mathbf{x},$$

which shows that

$$\Theta_1 = \frac{\beta}{\alpha(\alpha + \beta)} + \frac{\beta}{\alpha}(\alpha + \beta) \int_\Omega \mathcal{G}(\mathbf{x}_1, \mathbf{x})\tau(\mathbf{x}) d\mathbf{x}. \tag{3.31}$$

Equations (3.22) and (3.31) yield the solution to the narrow escape problem for a single switching gate. To leading order, we have

$$\tau(\mathbf{y}) \sim \bar{\tau} \equiv -\frac{|\Omega|}{\pi D} \log(\varepsilon/2),$$

which is independent of the starting position $\mathbf{y}$ so that $\Theta_1 \sim (\beta/\alpha)\bar{\tau}$ and thus

$$w(\mathbf{y}) \sim \frac{\alpha+\beta}{\alpha}\bar{\tau}. \tag{3.32}$$

This result was also derived in [16]. Note that one could calculate higher-order terms in the asymptotic expansion of $\tau(\mathbf{y})$, and hence $w(\mathbf{y})$, as a power series in $\nu = -1/\ln\varepsilon$. However, in this paper we are mainly interested in comparing the leading order results of matched asymptotics with those from the probabilistic approach presented in section 4.

The above analysis can be extended to multiple gates. Defining

$$\mathbf{m}_k = (m_1, \ldots, m_{k-1}, m_{k+1}, \ldots, m_N),$$

let

$$w^m_{\mathbf{m}_k}(\mathbf{y}) = w_{\mathbf{m}}|_{m_k=m}, \quad \mathcal{A}^{mn}_{\mathbf{m}_k\mathbf{n}_k} = \mathcal{A}_{\mathbf{mn}}|_{m_k=m, n_k=n},$$

and

$$\theta_k(\mathbf{y}) = \sum_{\mathbf{m}_k} w^1_{\mathbf{m}_k}(\mathbf{y}) = \sum_{\mathbf{m}} m_k w_{\mathbf{m}}.$$

Fixing $m_k = 1$ in (3.27) and summing over $\mathbf{m}_k$ gives

$$D\nabla^2\theta_k(\mathbf{y}) + \sum_{\mathbf{m}_k,\mathbf{n}_k}\left[\mathcal{A}^{10}_{\mathbf{m}_k\mathbf{n}_k} w^0_{\mathbf{n}_k}(\mathbf{y}) + \mathcal{A}^{11}_{\mathbf{m}_k\mathbf{n}_k} w^1_{\mathbf{n}_k}(\mathbf{y})\right] = -\sum_{\mathbf{m}} \mathcal{P}_{\mathbf{m}} m_k.$$

Now use the identities

$$\sum_{\mathbf{m}_k} \mathcal{A}^{1n}_{\mathbf{m}_k\mathbf{n}_k} = -\sum_{\mathbf{m}_k} \mathcal{A}^{0n}_{\mathbf{m}_k\mathbf{n}_k}, \quad \mathcal{A}^{10}_{\mathbf{m}_k\mathbf{n}_k} = \alpha_k \delta_{\mathbf{m}_k,\mathbf{n}_k}, \quad \mathcal{A}^{01}_{\mathbf{m}_k\mathbf{n}_k} = \beta_k \delta_{\mathbf{m}_k,\mathbf{n}_k},$$

to give

$$D\nabla^2\theta_k(\mathbf{y}) + \beta_k \sum_{\mathbf{m}_k} w^0_{\mathbf{m}_k}(\mathbf{y}) - \alpha_k\theta_k(\mathbf{y}) = -\sum_{\mathbf{m}} \mathcal{P}_{\mathbf{m}} m_k = -\rho_1^{(k)}.$$

Finally, using the identity

$$\sum_{\mathbf{n}_k} w^0_{\mathbf{n}_k}(\mathbf{y}) + \sum_{\mathbf{n}_k} w^1_{\mathbf{n}_k}(\mathbf{y}) = w(\mathbf{y})$$

gives

$$D\nabla^2\theta_k(\mathbf{y}) - (\alpha_k+\beta_k)\theta_k(\mathbf{y}) = -\beta w(\mathbf{y}) - \rho_1^{(k)}. \tag{3.33}$$

Note that $\theta_k(\mathbf{y})$ satisfies the boundary conditions

$$\nabla\theta_k(\mathbf{y})\cdot\boldsymbol{\sigma} = 0,\ \mathbf{y} \in \partial\Omega - \sum_{j\neq k}\partial\Omega_j^\varepsilon, \quad \theta_k(\mathbf{y}) = \Theta_j,\ \mathbf{y} \in \partial\Omega_j^\varepsilon. \tag{3.34}$$

Equation (3.33) can be solved along lines analogous to (3.8) using matched asymptotics and the modified Helmholtz Green's function $\mathcal{G}^{(k)}$ defined by (3.28), with

$\alpha, \beta \to \alpha_k, \beta_k$. After introducing stretched variables, one finds that the inner solution is identical in form to (3.12),

$$\theta_k(\mathbf{y}) \sim \Theta_j + B_{kj}\left[\log\left(|\mathbf{y}-\mathbf{x}_j|/\varepsilon\right) - \log(l_j/4) + o(1)\right] \text{ as } |\mathbf{y}-\mathbf{x}_j|/\varepsilon \to \infty. \tag{3.35}$$

The outer solution now satisfies

$$D\nabla^2\theta_k(\mathbf{y}) - (\alpha_k+\beta_k)\theta_k(\mathbf{y}) = -\beta_k w(\mathbf{y}) - \rho_1^{(k)}, \quad k=1,\ldots,N, \tag{3.36}$$

with reflecting boundary condition

$$\nabla\theta_k(\mathbf{y})\cdot\boldsymbol{\sigma}(\mathbf{y}) = 0 \quad \text{for } \mathbf{y} \in \partial\Omega\backslash\{\mathbf{x}_1,\ldots,\mathbf{x}_N\} \tag{3.37}$$

and

$$\theta_k(\mathbf{y}) \sim \Theta_j + \frac{B_{kj}}{\nu_j} + B_{kj}\log|\mathbf{y}-\mathbf{x}_j| \text{ as } \mathbf{y}\to\mathbf{x}_j,\ j=1,\ldots,N. \tag{3.38}$$

It follows that the outer solution can be expressed as

$$\theta_k(\mathbf{y}) = -\pi\sum_{j\neq k} B_{kj}\mathcal{G}^{(k)}(\mathbf{y},\mathbf{x}_j) + \int_\Omega \mathcal{G}^{(k)}(\mathbf{y},\mathbf{x})[\beta_k w(\mathbf{x}) + \rho_1^{(k)}]d\mathbf{x}. \tag{3.39}$$

For each k, the problem has reduced to solving N linear equations for N unknowns B_{kj}, which are obtained by matching the near-field behavior of the outer solution as $\mathbf{x}\to\mathbf{x}_j$, with the far–field behavior of the corresponding inner solution (3.12). After cancellation of the logarithmic terms, we find that

$$\int_\Omega \mathcal{G}^{(k)}(\mathbf{x}_j,\mathbf{x})[\beta w(\mathbf{x}) + \rho_1]d\mathbf{x} - \pi B_{kj}\mathcal{R}_j^{(k)} - \pi\sum_{j'\neq k,j} B_{kj'}\mathcal{G}_{jj'}^{(k)} - \Theta_j = \frac{B_{kj}}{\nu_j} \tag{3.40}$$

for $j \neq k$, where $\mathcal{G}_{jl}^{(k)} \equiv \mathcal{G}^{(k)}(\mathbf{x}_j,\mathbf{x}_l)$ and $\mathcal{R}_j^{(k)} \equiv \mathcal{R}^{(k)}(\mathbf{x}_j,\mathbf{x}_j)$. Comparing equations (3.39) and (3.40), we see that the first term on the right-hand side of (3.39) is $O(\nu)$ smaller than the second term, where $\nu = -1/\ln(\varepsilon)$. Hence, to leading order,

$$\theta_k(\mathbf{y}) \sim \int_\Omega \mathcal{G}^{(k)}(\mathbf{y},\mathbf{x})[\beta_k w(\mathbf{x}) + \rho_1^{(k)}]d\mathbf{x}. \tag{3.41}$$

Setting $\mathbf{y}=\mathbf{x}_k$, we obtain the self-consistency condition

$$\Theta_k \sim \int_\Omega \mathcal{G}^{(k)}(\mathbf{x}_k,\mathbf{x})[\beta_k w(\mathbf{x}) + \rho_1^{(k)}]d\mathbf{x}, \tag{3.42}$$

with $w(\mathbf{y}) = \tau(\mathbf{y}) + \sum_k \pi_k(\mathbf{y})\Theta_k$. As in the example of a single gate, we now exploit the fact that the dominant (singular) terms of $\tau(\mathbf{y})$ and $\pi_k(\mathbf{y})$ are independent of $\mathbf{y}$; see also section 4. (The intuitive explanation for this is that as the size of each gate shrinks to zero, the expected time to reach any gate starting from a point $\mathbf{y}\in\Omega$ is significantly longer than the time to reach some neighborhood of any other point $\mathbf{y}'\in\Omega$.) Then

$$\Theta_k \sim \frac{\beta_k}{\alpha_k+\beta_k}\left(\bar{\tau} + \sum_l \bar{\pi}_l\Theta_l\right),$$

where $\bar{\pi}_k \sim \nu_k/(N\bar{\nu})$; see (3.26). Multiplying both sides by $\bar{\pi}_k$, summing over k, and setting $\overline{\Psi} = \sum_l \bar{\pi}_l \Theta_l$ then gives

$$\overline{\Psi} \sim (\bar{\tau} + \overline{\Psi}) \sum_k \bar{\pi}_k \rho_1^{(k)}.$$

Hence, solving for $\overline{\Psi}$ finally yields the result

$$w(\mathbf{y}) \sim \frac{\bar{\tau}}{1 - \sum_k \bar{\pi}_k \rho_1^{(k)}}. \tag{3.43}$$

Some remarks.

1. Although we have developed the analysis of switching gates by considering a 2D domain, similar results can be obtained in higher dimensions by using the appropriate singularity structure of the Green's functions. For example, in three dimensions the logarithmic fundamental solution $-(1/2\pi)\log|\mathbf{x}|$ is replaced by $1/(4\pi|\mathbf{x}|)$. Additionally, if the gates are located on the boundary of the domain, then there is a weak logarithmic term $\log|\mathbf{x}-\mathbf{x}_0|$ that appears after this fundamental singularity. Further terms again require determining the regular part of the Green's function.
2. The asymptotic result (3.43) for the leading order correction to the MFPT due to switching gates holds in higher dimensions. It relies on the observation that in the small gate limit $\varepsilon \to 0$, the leading order contributions to the MFPT and splitting probabilities are independent on the starting position $\mathbf{y} \in \Omega$.
3. In Figure 5, we compare (3.43) with Monte Carlo simulations. One could also use a numerical PDE solver to examine the convergence of (3.43) as $\varepsilon \to 0$.
4. One could now generalize the analysis to take into account a nonzero potential $\Phi(\mathbf{x})$. In particular, suppose that $\Phi(\mathbf{x})$ has a unique minimum at $\mathbf{x} = \mathbf{x}_0$. This escape problem has been considered elsewhere for a single, nonswitching gate in the weak diffusion limit [18]. There are then two small parameters in the problem, the diffusivity D and gate size ε, such that in an appropriate asymptotic limit, one can obtain a generalization of Kramers escape rate formula. In section 4, we use a probabilistic approach to show that the asymptotic formula (3.43) for switching gates still holds in the presence of a potential well, provided that the slowest time-scale of the system is the time to escape through a gate. In particular, the latter is much larger than the expected time needed to escape from the potential well—this will hold if $\varepsilon \to 0$ with D fixed.

4. Probabilistic approach.

In this section, we use probabilistic tools to analyze escape problems with either a uniformly switching boundary (SI) or switching narrow gates (SII). For (SI), we determine how the switching boundary affects the rate of escape from a radially symmetric potential well in the small diffusion limit. For (SII), we give a simple probabilistic interpretation of (3.43) and show that it holds under more general conditions.

4.1. MFPT for a randomly uniformly switching boundary (SI).

We now use probabilistic methods to analyze the problem, described in subsection 2.1, of finding the MFPT to a randomly switching uniform boundary in the special case of a radially symmetric potential, $\Phi(\mathbf{x}) = \Phi(r)$, in a hypersphere $\Omega = S^d$ for $d \geq 2$. As shown in subsection 2.1, this reduces to the 1D problem of a particle diffusing in an interval $[0, R]$ with effective potential, $\widehat{\Phi}$, given by (2.27). Furthermore, it was shown

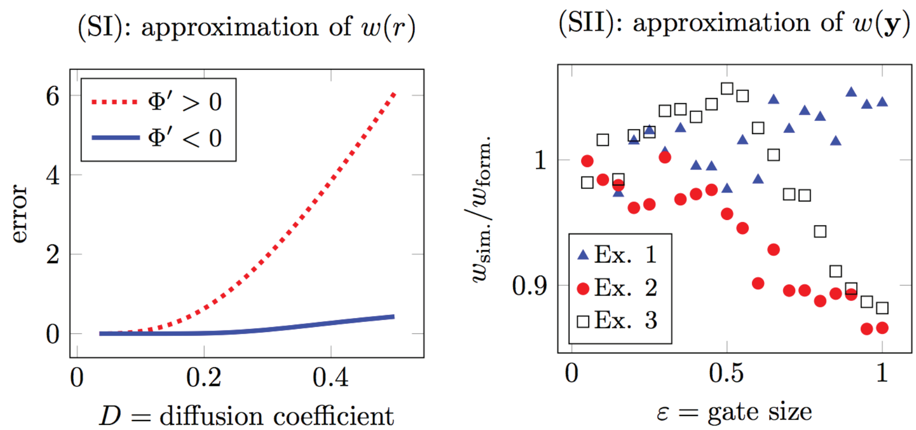

FIG. 5. Left: *Comparison of the probabilistic results of section* 4.1 *to numerical solutions of the corresponding PDEs derived in section* 2. *The* $\Phi' > 0$ *curve verifies Proposition* 4.1 *by plotting* $|w_1(R)/(\frac{\beta}{\alpha}\tau(R-\delta)) - 1|$ *as a function of the diffusion coefficient in the case when the potential is* $\Phi(r) = r^{20}$. *The* $\Phi' < 0$ *curve verifies Proposition* 4.2 *by plotting* $|w_1(R)/\tau(0) - 1|$ *as a function of the diffusion coefficient in the case when* $\Phi(r) = r^6 - 10r^4 + 10r^2$. *In both cases,* w_1 *is the numerical solution to* (2.12b), τ *is given by* (2.29), *and* $\alpha = \beta = R = 1$. Right: *Comparison of Theorem* 1 *to Monte Carlo simulations. The vertical axis is the ratio of* $w_{sim.}$ *to* $w_{form.}$, *where* $w_{sim.}$ *is the empirical MFPT to an open gate of* 10^4 *simulated trajectories, and* $w_{form.}$ *is the formula in Theorem* 1. *In order to compute* $w_{form.}$, *the value of* τ *is the empirical MFPT to a (closed or open) gate of* 10^4 *simulated trajectories, and the invariant distributions of each gate are chosen to be identical so that* $\bar{\pi}$ *is irrelevant. The horizontal axis is the size of each gate. Example* 1 *corresponds to domain* $\Omega = [-1,1]^2$, *potential* $\Phi = x^2 - y^2$, *diffusion coefficient* $D = 1/4$, *initial condition* $(0,0)$, *independent gates with rates* $\alpha = .1$, $\beta = .2$, *and two gates centered at* $(\pm 1, 0)$. *Example* 2 *corresponds to domain* $\Omega = [-1,1]^2$, *no potential, diffusion coefficient* $D = 1/4$, *initial condition* $(0,0)$, *independent gates with rates* $\alpha = \beta = 2/3$, *and four gates centered at* $(\pm 1, 0)$ *and* $(0, \pm 1)$. *Example* 3 *corresponds to domain* $\Omega = [-1,1]^2$, *potential* $\Phi = -y^2$, *diffusion coefficient* $D = 1/4$, *initial condition* $(0,0)$, *independent gates with rates* $\alpha = \beta = 3/4$, *and four gates centered at* $(\pm 1, 0)$ *and* $(0, \pm 1)$.

there that the MFPT to a switching boundary at R starting from $r \in [0, R]$ is given by $\tau(r) + w_1(R)$, where $\tau(r)$ is the classical MFPT to a nonswitching boundary (see (2.29)) and $w_1(R)$ is the MFPT to the switching boundary starting from R. Hence, the problem reduces to finding $w_1(R)$.

We considered a similar class of problems in [6], where we showed that corrections to the classical MFPT in the small diffusion limit depend on the gradient of the potential in a neighborhood of the boundary. These results carry over to the case of a radially symmetric potential well $\Phi(r)$, provided that Φ is either strictly increasing or strictly decreasing in a neighborhood of R; see Figure 3. For in the limit $D \to 0$, both the potential $\Phi'(r)$ and the effective potential $\widehat{\Phi}'(r)$ have the same sign close to the boundary. We give these results in two propositions at the end of this section. While we omit the detailed proofs since they are analogous to those in [6], we briefly sketch the argument. A similar argument will also be employed in section 4.2 for narrow gates.

Suppose $X(t) \in [0, R]$ satisfies (1.1) with the potential given by (2.27), and let $n(t) \in \{0, 1\}$ be an independent Markov process with transition rates given by (1.2).

Define the following two stopping times:[1]

$$\mathcal{S}_t := \inf\{s \geq t : X(s) = R\} \quad \text{and} \quad \mathcal{T}_t := \inf\big\{s \geq t : \{X(s) = R\} \cap \{n(s) = 0\}\big\},$$

which are the first passage times to the boundary, and to the boundary in its open state, respectively, starting at time t. We will use $\mathcal{S}$ and $\mathcal{T}$ to denote $\mathcal{S}_0$ and $\mathcal{T}_0$, and $\mathbb{E}_r$ to denote expectation conditioned on $X(0) = r$. Uniting notation from previous sections,

$$\mathbb{E}_r[\mathcal{S}] = \tau(r) \quad \text{and} \quad \mathbb{E}_r[\mathcal{T}] = w(r).$$

Let $0 < \delta < R$, and define the stopping time

$$\sigma := \inf\{s \geq 0 : |X(s) - X(0)| \geq \delta\}.$$

If $\Phi' > 0$ on $[R-\delta, R]$, D is small, and the boundary is initially reflecting, then the potential term will dominate and thus with high probability the particle will hit $R-\delta$ before exiting. Further, once the particle hits $R-\delta$, by the time it reaches R again the state of the boundary will be roughly independent of the particle's last visit to R. Thus, we can think of the time required to exit as a series of independent Bernoulli trials with probability of success equal to ρ_0, where we must wait a time $\mathbb{E}_R[\mathcal{S}_\sigma]$ between trials. Hence for small D,

$$w_1(R) \approx \rho_0 \mathbb{E}_R[\mathcal{S}_\sigma] \sum_{k=1}^{\infty} k \rho_1^k = \rho_0 \mathbb{E}_R[\mathcal{S}_\sigma] \frac{\rho_1}{(\rho_0)^2} = \frac{\beta}{\alpha} \mathbb{E}_R[\mathcal{S}_\sigma].$$

Using the fact that $\mathbb{E}_R[\mathcal{S}_\sigma] = \mathbb{E}_{R-\sigma}[\mathcal{S}] = \tau(R-\delta)$ gives the following correction to the escape time in the presence of a switching boundary:

Proposition 4.1. *If $\delta > 0$ is such that $\Phi' > 0$ on $[R-\delta, R]$, then for $r \in [0, R]$*

$$w(r) \sim \tau(r) + (\beta/\alpha)\tau(R-\delta) \quad \text{as } D \to 0.$$

In Proposition 4.1, visits to the boundary are rare events and thus a correction to the usual MFPT is needed. On the other hand, if $\Phi'(r) < 0$ on $[R-\delta, R]$, then visits to the boundary occur frequently once the particle is in a small neighborhood of the boundary. Thus, the contribution of the switching boundary is negligible compared to the escape time from a well.

Proposition 4.2. *Assume $r_{\min} \in (0, R)$ is a unique minimum of Φ. If there exists a $\delta > 0$ such that $\Phi' < 0$ on $[R-\delta, R]$, then*

$$w(r_{\min}) \sim \tau(r_{\min}) \quad \text{as } D \to 0.$$

In Figure 5, we compare the predictions of Propositions 4.1 and 4.2 with numerical solutions of the corresponding PDEs derived in section 2.

4.2. MFPT for randomly switching gates (SII). Suppose $\mathbf{X}(t) \in \Omega \subset \mathbb{R}^d$ satisfies (1.1) with reflecting boundary conditions. We suppose that the boundary contains N distinguished points $\{\mathbf{x}_1, \ldots, \mathbf{x}_N\}$, and we denote the $\varepsilon > 0$ neighborhood about each point by $\partial\Omega_k^\varepsilon$, which we refer to as a "gate" (see (1.3)). Let $\mathbf{n}(t) \in \{0,1\}^N$

[1] A stopping time $\mathcal{T}$ is a random variable whose value is interpreted as the time (finite or infinite) at which a given stochastic process is terminated according to some stopping rule that depends on current and past states. A classical example of a stopping time is a first passage time.

be an irreducible Markov process whose kth component, $n_k(t) \in \{0, 1\}$, controls the state of the kth gate. We say that gate k is open or closed at time t if $n_k(t)$ is 0 or 1, respectively. We assume $\mathbf{n}(t)$ is independent of $\mathbf{X}(t)$, but we do not assume that the components of $\mathbf{n}(t)$ are independent of each other. It follows that $(\mathbf{X}(t), \mathbf{n}(t))_{t\geq 0}$ is a strong Markov process.

Define the following stopping times:

$$\mathcal{S}_t := \inf_{1\leq k\leq N} \big\{ \inf\{s \geq 0 : \mathbf{X}(t+s) \in \partial\Omega_k^\varepsilon\}\big\},$$
$$\mathcal{T}_t := \inf_{1\leq k\leq N} \big\{ \inf \big\{s \geq 0 : \{\mathbf{X}(t+s) \in \partial\Omega_k^\varepsilon\} \cap \{n_k(t+s) = 0\}\big\}\big\},$$

which are the first passage times after time t to a gate and an open gate, respectively. Let $\mathcal{T}$ and $\mathcal{S}$ denote $\mathcal{T}_0$ and $\mathcal{S}_0$, respectively. For $\mathbf{x} \in \bar{\Omega}$, let $\mathbb{P}_\mathbf{x}$ denote the probability measure conditioned on $\mathbf{X}(0) = \mathbf{x}$ and the process $\mathbf{n}(t)$ starting in its invariant distribution, and let $\mathbb{E}_\mathbf{x}$ denote expectation with respect to this probability measure. Uniting notation from previous sections,

$$\mathbb{E}_\mathbf{y}[\mathcal{S}] = \tau(\mathbf{y}) \quad \text{and} \quad \mathbb{E}_\mathbf{y}[\mathcal{T}] = w(\mathbf{y}).$$

In this section, we use probabilistic tools to show that the relationship between $\mathbb{E}[\mathcal{T}]$ and $\mathbb{E}[\mathcal{S}]$ given in (3.43) holds in the presence of a potential.

Before proving this relationship in Theorem 1, we first give a simple probabilistic argument for deriving it (see also section 4.1). For the sake of illustration, suppose there is only one gate. We can approximate $\mathbb{E}[\mathcal{T}]$ by conditioning on the number of visits to the gate before exiting. Supposing that the gate is small, visits to the gate by the particle are rare events separated in time by approximately $\mathbb{E}[\mathcal{S}]$. Since $\mathbb{E}[\mathcal{S}]$ is large, the states of the gate upon successive visits by the particle are approximately independent. If the gate is open the first time the particle visits the gate, then $\mathbb{E}[\mathcal{T}] \approx \mathbb{E}[\mathcal{S}]$, and the probability of this event is just the probability that the gate is open, say $1 - p$. If the particle makes two visits to the gate before exiting, then $\mathbb{E}[\mathcal{T}] \approx 2\mathbb{E}[\mathcal{S}]$, and this event has probability $p(1 - p)$. Continuing in this manner, we see that the exit time can be thought of as a series of independent Bernoulli trials with probability of success equal to the probability that the gate is open, where we must wait time $\mathbb{E}[\mathcal{S}]$ between trials. Hence,

$$\mathbb{E}[\mathcal{T}] \approx \mathbb{E}[\mathcal{S}](1-p)\sum_{k=1}^{\infty} kp^{k-1} = \frac{1}{1-p}\mathbb{E}[\mathcal{S}].$$

The remainder of this section formalizes this argument and generalizes it to N gates.

For each $\mathbf{x} \in \tilde{\Omega} := \bar{\Omega} - \{\mathbf{x}_1, \ldots, \mathbf{x}_N\}$, let $\pi(\mathbf{x}) \in \mathbb{R}^N$ be the vector whose kth component is the probability that a particle starting at $\mathbf{x}$ hits gate k before any other gate. That is, define $H \in \{1, \ldots, N\}$ to be the random variable such that $\mathbf{X}(\mathcal{S}) \in \partial\Omega_H^\varepsilon$ and define $\pi_k(\mathbf{x}) := \mathbb{P}_\mathbf{x}(H = k)$.

We prove the simple relationship between $\mathbb{E}[\mathcal{T}]$ and $\mathbb{E}[\mathcal{S}]$ in the small gate limit under the following assumptions. Some of the assumptions can be relaxed, but for the sake of simplicity we do not give the most general hypotheses.

Assumptions.

1. For each $\mathbf{x} \in \tilde{\Omega}$ and $t \geq 0$, we have that $\mathbb{P}_{\mathbf{x}}(\mathcal{S} < t) \to 0$ as $\varepsilon \to 0$.
2. For each $k \in \{1, \ldots, N\}$, we have that $\mathbb{E}_{\mathbf{x}_k}[\mathcal{T}] \to \infty$ as $\varepsilon \to 0$.
3. For each $\mathbf{x} \in \tilde{\Omega}$ and $\eta > 0$, there exists a $\gamma(\mathbf{x}, \eta) > 0$ such that if $|\mathbf{x} - \mathbf{y}| < \gamma(\mathbf{x}, \eta)$, then for all $k \in \{1, \ldots, N\}$ and ε sufficiently small, we have that
$$|\pi_k(\mathbf{x}) - \pi_k(\mathbf{y})| < \eta.$$
4. For each $\eta > 0$ and $\kappa > 0$, there exists an $\varepsilon_0(\eta, \kappa) > 0$ such that if $|\mathbf{x} - \mathbf{x}_k| \geq \kappa$ and $|\mathbf{y} - \mathbf{x}_k| \geq \kappa$ for all $k \in \{1, \ldots, N\}$ and $\varepsilon < \varepsilon_0(\eta, \kappa)$, then
$$|\mathbb{E}_{\mathbf{y}}[\mathcal{S}]/\mathbb{E}_{\mathbf{x}}[\mathcal{S}] - 1| < \eta.$$
5. For each $\eta > 0$, there exists an $\varepsilon_0(\eta) > 0$ and $B > 0$ such that if $\varepsilon < \varepsilon_0(\eta)$, $k \in \{1, \ldots, N\}$, and $\mathbf{y} \in \partial\Omega_k^\varepsilon$, then for $\bar{\pi}$ as in Lemma 4.3 we have
$$\frac{\mathbb{E}_{\mathbf{y}}[\mathcal{T}]}{\sum_{j=1}^N \bar{\pi}_j \mathbb{E}_{\mathbf{x}_j}[\mathcal{T}]} < B \quad \text{and} \quad \left| \frac{\mathbb{E}_{\mathbf{y}}[\mathcal{T}] - \mathbb{E}_{\mathbf{x}_k}[\mathcal{T}]}{\sum_{j=1}^N \bar{\pi}_j \mathbb{E}_{\mathbf{x}_j}[\mathcal{T}]} \right| < \eta.$$

Assumption 1 ensures that the first passage time to a gate diverges in probability in the small gate limit. This assumption was shown to hold in [18] in dimensions 2 and 3. Assumption 2 states that the MFPT to an open gate diverges in the small gate limit when the initial condition is in the center of a gate. Though the particle starts at a gate, if the gate is initially closed, then the particle will wander away, and once it wanders away it takes a long time to find a gate again. Assumption 3 assumes a certain continuity of the splitting probability. Assumption 4 states that the leading order term of the MFPT to a gate is independent of the initial condition. The reasoning for this assumption is that the amount of time that it takes a particle starting at $\mathbf{x} \in \tilde{\Omega}$ to reach a neighborhood of $\mathbf{y} \in \tilde{\Omega}$ is independent of ε, whereas the time it takes the particle to reach a gate diverges as $\varepsilon \to 0$. Hence, the particle explores the whole domain before it finds a small gate. It is known that in two dimensions and in the absence of a potential, the leading order term of the MFPT to a gate is independent of the initial condition in the small gate limit (see section 3.3 and [15]). Finally, Assumption 5 asserts that the MFPTs to an open gate starting from points on a gate should be close to each other.

The following lemma shows that Assumption 3 is enough to guarantee that the splitting probability is independent of the initial position in the small gate limit.

LEMMA 4.3. *There exists an* $\mathbf{x}$ *independent vector* $\bar{\pi} \in \mathbb{R}^N$ *such that*
$$\pi(\mathbf{x}) \to \bar{\pi} \quad \text{as } \varepsilon \to 0 \qquad \text{for each } \mathbf{x} \in \tilde{\Omega}.$$

Proof. Let $\mathbf{x}, \mathbf{y} \in \tilde{\Omega}$, and $\eta > 0$. Let $\gamma(\mathbf{x}, \eta)$ be as in Assumption 3 above. Define the first time that the particle is within $\gamma(\mathbf{x}, \eta)$ of $\mathbf{x}$:
$$s_{\mathbf{x}} := \inf\{t \geq 0 : |\mathbf{X}(t) - \mathbf{x}| < \gamma(\mathbf{x}, \eta)\}.$$
For $j \in \{1, \ldots, N\}$, define the first time the particle hits $\partial\Omega_j^\varepsilon$ when it is open:
$$t_j := \inf\{t \geq 0 : \{\mathbf{X}(t) \in \partial\Omega_j^\varepsilon\} \cap \{n_j(t) = 0\}\}.$$
Now, for $k \in \{1, \ldots, N\}$, it is immediate that
$$|\pi_k(\mathbf{y}) - \pi_k(\mathbf{x})| \leq \mathbb{P}_{\mathbf{y}}(t_j < s_{\mathbf{x}}\ \forall j) + |\mathbb{P}_{\mathbf{y}}(\{t_k \leq t_j\ \forall j\} \cap \{t_j \geq s_{\mathbf{x}}\ \forall j\}) - \pi_k(\mathbf{x})|.$$

For each $j \in \{1, \ldots, N\}$, define the stopping time

$$\hat{t}_j := \inf\{t \geq 0 : \{\mathbf{X}(s_{\mathbf{x}} + t) \in \partial\Omega_j^\varepsilon\} \cap \{n_j(s_{\mathbf{x}} + t) = 0\}\}.$$

Now, observe that

$$\mathbb{P}_{\mathbf{y}}(\{t_k \leq t_j \ \forall j\} \cap \{t_j \geq s_{\mathbf{x}} \ \forall j\}) = \mathbb{P}_{\mathbf{y}}(\{\hat{t}_k \leq \hat{t}_j \ \forall j\} \cap \{t_j \geq s_{\mathbf{x}} \ \forall j\}).$$

Hence,

$$|\mathbb{P}_{\mathbf{y}}(t_k \leq t_j \ \forall j \cap t_j \geq s_{\mathbf{x}} \ \forall j) - \pi_k(\mathbf{x})| \leq |\mathbb{P}_{\mathbf{y}}(\hat{t}_k \leq \hat{t}_j \ \forall j) - \pi_k(\mathbf{x})| + \sum_j \mathbb{P}_{\mathbf{y}}(t_j < s_{\mathbf{x}}).$$

By the strong Markov property[2] and the choice of $\gamma(\mathbf{x}, \eta)$, we have that

$$|\mathbb{P}_{\mathbf{y}}(\hat{t}_k \leq \hat{t}_j \ \forall j) - \pi_k(\mathbf{x})| \leq \sup\{|\pi_k(\mathbf{z}) - \pi_k(\mathbf{x})| : |\mathbf{z} - \mathbf{x}| \leq \gamma(\mathbf{x}, \eta)\} < \eta$$

for ε sufficiently small. Hence,

$$|\pi_k(\mathbf{y}) - \pi_k(\mathbf{x})| \leq \eta + 2\sum_j \mathbb{P}_{\mathbf{y}}(t_j < s_{\mathbf{x}})$$

for ε sufficiently small. Next, observe that for $t \geq 0$ and $j \in \{1, \ldots, N\}$ we have

$$\mathbb{P}_{\mathbf{y}}(t_j < s_{\mathbf{x}}) \leq \mathbb{P}_{\mathbf{y}}(t_j \leq t) + \mathbb{P}_{\mathbf{y}}(s_{\mathbf{x}} > t).$$

Take t sufficiently large to make $\mathbb{P}_{\mathbf{y}}(s_{\mathbf{x}} > t) < \eta$. Then, for this fixed large t, observe that $\mathbb{P}_{\mathbf{y}}(t_j \leq t) \leq \mathbb{P}_{\mathbf{y}}(\mathcal{S} \leq t)$. By Assumption 1, we can take ε small to make $\mathbb{P}_{\mathbf{y}}(\mathcal{S} \leq t) < \eta$. Since $\mathbf{x}, \mathbf{y} \in \tilde{\Omega}$ and $\eta > 0$ were arbitrary, the proof is complete. ∎

The following theorem uses probabilistic tools to obtain (3.43) in a general domain $\Omega \subset \mathbb{R}^d$ in dimension $d \geq 2$, with a potential, and gates that may be correlated.

THEOREM 1. *Let $\bar{\pi} \in \mathbb{R}^N$ be as in Lemma 4.3, and let p_k be the stationary probability that $n_k(t) = 1$. If $\mathbf{x} \in \tilde{\Omega}$, then*

$$w(\mathbf{x}) \sim \frac{\tau(\mathbf{x})}{1 - \sum_k \bar{\pi}_k p_k} \quad \text{as } \varepsilon \to 0.$$

In Figure 5, we compare the conclusion of this theorem with Monte Carlo simulations.

Proof. For $\delta \geq \varepsilon > 0$, define the stopping time $\sigma := \inf\{t \geq 0 : |\mathbf{X}(t) - \mathbf{X}(0)| \geq \delta\}$ and the event $A := \{\sigma < \mathcal{T}\}$. We then have that

$$\mathbb{E}_{\mathbf{x}_k}[\mathcal{T}] = \mathbb{E}_{\mathbf{x}_k}[\mathcal{T}1_{A^c}] + \mathbb{E}_{\mathbf{x}_k}[\sigma 1_A] + \mathbb{E}_{\mathbf{x}_k}[\mathcal{S}_\sigma 1_A] + \mathbb{E}_{\mathbf{x}_k}[\mathcal{T}_{\sigma+\mathcal{S}_\sigma} 1_A]. \quad (4.1)$$

Further, by Assumption 2, we have that

$$\big(\mathbb{E}_{\mathbf{x}_k}[\mathcal{T}1_{A^c}] + \mathbb{E}_{\mathbf{x}_k}[\sigma 1_A]\big)/\mathbb{E}_{\mathbf{x}_k}[\mathcal{T}] \to 0 \quad \text{as } \varepsilon \to 0,$$

[2]Recall that a stochastic process has the Markov property if the conditional probability distribution of future states of the process (conditional on both past and present states) depends only upon the present state, not on the sequence of events that preceded it. The term *strong Markov property* is similar to the Markov property, except that "present" is defined in terms of a stopping time.

since $\mathbb{E}_{\mathbf{x}_k}[\mathcal{T}1_{A^c}] + \mathbb{E}_{\mathbf{x}_k}[\sigma 1_A] \le \mathbb{E}_{\mathbf{x}_k}[\sigma]$ is bounded in ε. Thus, applying Lemmas A.1, A.2, and A.3 to (4.1), we obtain, for $\mathbf{x} \in \tilde{\Omega}$, that

$$\mathbb{E}_{\mathbf{x}_k}[\mathcal{T}] \sim p_k \mathbb{E}_{\mathbf{x}}[\mathcal{S}] + p_k \sum_j \bar{\pi}_j \mathbb{E}_{\mathbf{x}_j}[\mathcal{T}] \quad \text{as } \varepsilon \to 0. \tag{4.2}$$

If we let $\mathbb{T} \in \mathbb{R}^N$ denote the vector with kth component equal to $\mathbb{E}_{\mathbf{x}_k}[\mathcal{T}]$, then writing (4.2) in vector notation, we have that $\mathbb{T} \sim (\mathbb{E}_{\mathbf{x}}[\mathcal{S}] + \bar{\pi}^T \mathbb{T}) p$ as $\varepsilon \to 0$, where superscript T denotes the transpose. It is straightforward to check that the norm of $p\bar{\pi}^T$ is strictly less than 1, and thus

$$\mathbb{T} \sim (I - p\bar{\pi}^T)^{-1} p \mathbb{E}_{\mathbf{x}}[\mathcal{S}] = \left(\sum_{m=0}^{\infty} (p\bar{\pi}^T)^m \right) p \mathbb{E}_{\mathbf{x}}[\mathcal{S}]. \tag{4.3}$$

Now, it's immediate that for each $\mathbf{x} \in \tilde{\Omega}$, we have that

$$\mathbb{E}_{\mathbf{x}}[\mathcal{T}] = \mathbb{E}_{\mathbf{x}}[\mathcal{S}] + \mathbb{E}_{\mathbf{x}}[\mathcal{T}_{\mathcal{S}}]. \tag{4.4}$$

A similar argument to the one used in Lemma A.2 yields

$$\mathbb{E}_{\mathbf{x}}[\mathcal{T}_{\mathcal{S}}] \sim \sum_j \bar{\pi}_j \mathbb{E}_{\mathbf{x}_j}[\mathcal{T}] = \bar{\pi}^T \mathbb{T} \quad \text{as } \varepsilon \to 0. \tag{4.5}$$

Hence, by combining (4.3), (4.4), (4.5), we have that

$$\mathbb{E}_{\mathbf{x}}[\mathcal{T}] \sim \left(1 + \bar{\pi}^T \sum_{m=0}^{\infty} (p\bar{\pi}^T)^m p \right) \mathbb{E}_{\mathbf{x}}[\mathcal{S}] \quad \text{as } \varepsilon \to 0.$$

Recalling the formula for the sum of a geometric series completes the proof. ◻

5. Discussion.

Motivated by a number of transport mechanisms in biological cells, in this paper we studied diffusion in a potential with boundaries that randomly switch between absorbing and reflecting states. We analyzed the escape time to the boundary in the case that the entire boundary switches state (SI), and the escape time to one of N small pieces of the boundary that each switch state (SII). For (SI), we assumed a radially symmetric domain and potential and derived corrections to the classical escape time to a static boundary. This extended our previous work on exit statistics for a particle diffusing with a potential in a finite interval with randomly switching boundaries [6]. For (SII), we significantly generalized a result appearing in [1] and [16]. Under mild assumptions on certain asymptotic statistics, we used probabilistic methods to prove that this result holds in the presence of a potential, and we generalized it to the case of N gates that are arbitrarily correlated in their opening and closing. Further, we gave an intuitive probabilistic interpretation to this result. Notably, for both (SI) and (SII), we arrived at our results by combining tools from PDEs and probability theory. Such an approach is uncommon in the study of escape problems. Coupling these disparate methods provided a unique perspective, and we believe that our two-pronged approach can serve as a prototype for future studies.

In particular, one future goal related to the present work is to extend the classical Smoluchowski theory of diffusion-limited reaction rates to the case of a stochastically-gated target. While this stochastically-gated problem was first studied by Szabo et al. [20] for unbounded domains, the case of bounded domains remains unexplored. Recently, Straube, Ward, and Falcke [19] calculated the diffusion-limited reaction rate in a bounded domain with a static target. One would like to see how their results are altered in the case of a stochastically-gated target. This is a natural extension of the present work for two reasons. First, while reaction rates are sometimes defined as inverse MFPTs, the Smoluchowski theory that defines reaction rates via flux through a boundary is an alternative and perhaps more common formulation. Second, the flux through a boundary is related to the probability density function of the FPT to a target. Thus, this future project would extend the present work on *means* of FPTs to *distributions* of FPTs.

Another possible extension of our work is to consider multiple diffusing particles. It would be interesting to analyze the difference between having the particles switch states and having the boundaries switch states. In the latter case, even though the particles are diffusing independently, they are correlated because they are all diffusing in the same random environment [5]. This subtlety has been studied before [3, 14, 22], and we hope that coupling PDE and probability techniques can give further insight into this problem.

Appendix. Under the assumptions of section 4.2, we now prove the lemmas used in the proof of Theorem 1.

LEMMA A.1. *For each* $k \in \{1, \ldots, N\}$ *we have that*

$$\mathbb{P}_{\mathbf{x}_k}(A) \to p_k := \mathbb{P}(n_k(0) = 1) \quad \text{as } \varepsilon \to 0.$$

Proof. Define the stopping time $s_k := \inf\{t \geq 0 : n_k(t) = 0\}$. For $t > 0$, we have

$$\mathbb{P}_{\mathbf{x}_k}(A^c \,|\, n_k(0) = 1) \leq \mathbb{P}_{\mathbf{x}_k}(s_k < \sigma |\, n_k(0) = 1) \leq \mathbb{P}_{\mathbf{x}_k}(t \leq \sigma) + \mathbb{P}(s_k < t |\, n_k(0) = 1).$$

We can make the second term arbitrarily small by taking t small, and then take $\delta > \varepsilon$ small to make the first term arbitrarily small. ∎

LEMMA A.2. *For each* $k \in \{1, \ldots, N\}$ *we have that*

$$\mathbb{E}_{\mathbf{x}_k}[\mathcal{T}_{\sigma + \mathcal{S}_\sigma} 1_A] \sim p_k \sum_{j=1}^{N} \bar{\pi}_j \mathbb{E}_{\mathbf{x}_j}[\mathcal{T}] \quad \text{as } \varepsilon \to 0.$$

Proof. Let $\{\mathcal{F}_t\}_{t \geq 0}$ be the filtration generated by the strong Markov process $\{(\mathbf{X}(t), \mathbf{n}(t))\}_{t \geq 0}$. For $\mathbf{x} \in \bar{\Omega}$ and $\mathbf{m} \in \{0,1\}^N$, let $\mathbb{P}_{\mathbf{x},\mathbf{m}}$ denote the probability measure conditioned on $\mathbf{X}(0) = \mathbf{x}$ and $\mathbf{n}(t) = \mathbf{m}$, and let $\mathbb{E}_{\mathbf{x},\mathbf{m}}$ denote expectation with respect to this probability measure. Observe that by the tower property of conditional expectation and the strong Markov property, we have that

$$\left|\mathbb{E}_{\mathbf{x}_k}[\mathcal{T}_{\sigma + \mathcal{S}_\sigma} 1_A] - \mathbb{P}_{\mathbf{x}_k}(A) \sum_j \bar{\pi}_j \mathbb{E}_{\mathbf{x}_j}[\mathcal{T}]\right| \leq \mathbb{E}_{\mathbf{x}_k}\left|\mathbb{E}_{\mathbf{X}(\sigma),\mathbf{n}(\sigma)}[\mathcal{T}_\mathcal{S}] - \sum_j \bar{\pi}_j \mathbb{E}_{\mathbf{x}_j}[\mathcal{T}]\right|.$$

Let $\mathbf{z} \in \tilde{\Omega}$ and $\mathbf{m} \in \{0,1\}^N$ be arbitrary. Then

$$\left|\mathbb{E}_{\mathbf{z},\mathbf{m}}[\mathcal{T}_\mathcal{S}] - \sum_j \bar{\pi}_j \mathbb{E}_{\mathbf{x}_j}[\mathcal{T}]\right| \leq \sum_j \left|\mathbb{E}_{\mathbf{z},\mathbf{m}}[1_{H=j}(\mathbb{E}_{\mathbf{z},\mathbf{m}}[\mathcal{T}_\mathcal{S} | \mathcal{F}_\mathcal{S}] - \mathbb{E}_{\mathbf{x}_j}[\mathcal{T}])]\right|$$
$$+ \sum_j \left|(\mathbb{P}_{\mathbf{z},\mathbf{m}}(H = j) - \bar{\pi}_j)\mathbb{E}_{\mathbf{x}_j}[\mathcal{T}]]\right|.$$

Let Σ_1 and Σ_2 denote, respectively, the two sums on the right-hand side of the above equation. Since $\mathbf{X}(\sigma) \in \tilde{\Omega}$ almost surely if $\mathbf{X}(0) = \mathbf{x}_k$, and since $\mathbb{P}_{\mathbf{x}_k}(A) \to p_k > 0$ by Lemma A.1, by the bounded convergence theorem it is enough to show that

$$(\Sigma_1 + \Sigma_2)\bigg(\sum_j \bar{\pi}_j \mathbb{E}_{\mathbf{x}_j}[\mathcal{T}]\bigg)^{-1}$$

converges to 0 almost surely as $\varepsilon \to 0$, and is bounded independent of $\mathbf{z}$ and $\mathbf{m}$ for ε sufficiently small. This bound and convergence for the Σ_2 term follow from Lemma 4.3 and Assumption 5.

To bound Σ_1, observe that by the strong Markov property

(A.1)
$$\begin{aligned}&\big|\mathbb{E}_{\mathbf{z},\mathbf{m}}[1_{H=j}(\mathbb{E}_{\mathbf{z},\mathbf{m}}[\mathcal{T}_{\mathcal{S}}|\mathcal{F}_{\mathcal{S}}] - \mathbb{E}_{\mathbf{x}_j}[\mathcal{T}])]\big| = \big|\mathbb{E}_{\mathbf{z},\mathbf{m}}[1_{H=j}(\mathbb{E}_{\mathbf{X}(\mathcal{S}),\mathbf{n}(\mathcal{S})}[\mathcal{T}] - \mathbb{E}_{\mathbf{x}_j}[\mathcal{T}])]\big|\\ &\quad\le \big|\mathbb{E}_{\mathbf{z},\mathbf{m}}[1_{H=j}(\mathbb{E}_{\mathbf{X}(\mathcal{S}),\mathbf{n}(\mathcal{S})}[\mathcal{T}] - \mathbb{E}_{\mathbf{X}(\mathcal{S})}[\mathcal{T}])]\big| + \big|\mathbb{E}_{\mathbf{z},\mathbf{m}}[1_{H=j}(\mathbb{E}_{\mathbf{X}(\mathcal{S})}[\mathcal{T}] - \mathbb{E}_{\mathbf{x}_j}[\mathcal{T}])]\big|.\end{aligned}$$

It follows immediately from Assumption 5 that

$$\big|\mathbb{E}_{\mathbf{z},\mathbf{m}}[1_{H=j}(\mathbb{E}_{\mathbf{X}(\mathcal{S})}[\mathcal{T}] - \mathbb{E}_{\mathbf{x}_j}[\mathcal{T}])]\big|\bigg(\sum_m \bar{\pi}_m \mathbb{E}_{\mathbf{x}_m}[\mathcal{T}]\bigg)^{-1}$$

converges to 0 almost surely as $\varepsilon \to 0$, and is bounded independent of $\mathbf{z}$ and $\mathbf{m}$ for ε sufficiently small.

Next, to bound the first term on the bound in (A.1), let us enumerate the elements of the state space of $\mathbf{n}(t)$ by $\{a_i\}_{i\in I}$ for some finite index set I. Then, if $\nu \in \bigcup_i \{a_i\}$ is distributed according to the invariant measure of $\mathbf{n}(t)$, then

$$\begin{aligned}&\big|\mathbb{E}_{\mathbf{z},\mathbf{m}}[1_{H=j}(\mathbb{E}_{\mathbf{X}(\mathcal{S}),\mathbf{n}(\mathcal{S})}[\mathcal{T}] - \mathbb{E}_{\mathbf{X}(\mathcal{S})}[\mathcal{T}])]\big|\\ &\quad= \bigg|\mathbb{E}_{\mathbf{z},\mathbf{m}}\bigg[1_{H=j}\sum_{i\in I}\big(\mathbb{P}_{\mathbf{z},\mathbf{m}}(\mathbf{n}(\mathcal{S}) = a_i) - \mathbb{P}(\nu = a_i)\big)\mathbb{E}_{\mathbf{X}(\mathcal{S}),a_i}[\mathcal{T}]\bigg]\bigg|.\end{aligned}$$

Since $\mathbf{n}(t)$ is irreducible, $\mathcal{S} \to \infty$ in probability as $\varepsilon \to 0$ by Assumption 1, and since $\mathcal{S}$ is independent of $\mathbf{n}(t)$, we have that $\mathbb{P}_{\mathbf{z},\mathbf{m}}(\mathbf{n}(\mathcal{S}) = a_i) \to \mathbb{P}(\nu = a_i)$ as $\varepsilon \to 0$ for each $i \in I$. Further, it follows from Assumption 5 that there exists a B such that if $j \in \{1, \ldots, N\}$, then for all $\mathbf{y} \in \partial\Omega_j^\varepsilon$, $i \in I$, and ε sufficiently small, we have that

$$\mathbb{E}_{\mathbf{y},a_i}[\mathcal{T}]\bigg(\sum_j \bar{\pi}_j \mathbb{E}_{\mathbf{x}_j}[\mathcal{T}]\bigg)^{-1} \le B. \tag{A.2}$$

The desired bound and convergence of Σ_1 follows. ∎

LEMMA A.3. *If* $\mathbf{x} \in \tilde{\Omega}$, *then* $\mathbb{E}_{\mathbf{x}_k}[\mathcal{S}_\sigma 1_A] \sim p_k \mathbb{E}_{\mathbf{x}}[\mathcal{S}]$ *as* $\varepsilon \to 0$.

Proof. By the tower property of conditional expectation, the strong Markov property, and the fact that the distribution of $\mathcal{S}$ does not depend on $n(t)$, we have that

$$\mathbb{E}_{\mathbf{x}_k}[\mathcal{S}_\sigma 1_A] = \mathbb{E}_{\mathbf{x}_k}[1_A \mathbb{E}_{\mathbf{x}_k}[\mathcal{S}_\sigma|\mathcal{F}_\sigma]] = \mathbb{E}_{\mathbf{x}_k}[1_A \mathbb{E}_{\mathbf{X}(\sigma)}[\mathcal{S}]].$$

Hence,

$$\frac{\big|\mathbb{E}_{\mathbf{x}_k}[\mathcal{S}_\sigma 1_A] - \mathbb{P}_{\mathbf{x}_k}(A)\mathbb{E}_{\mathbf{x}}[\mathcal{S}]\big|}{p_k \mathbb{E}_{\mathbf{x}}[\mathcal{S}]} \le \frac{1}{p_k}\mathbb{E}_{\mathbf{x}_k}\Big|\frac{\mathbb{E}_{\mathbf{X}(\sigma)}[\mathcal{S}]}{\mathbb{E}_{\mathbf{x}}[\mathcal{S}]} - 1\Big|. \tag{A.3}$$

Since $\mathbb{P}_{\mathbf{x}_k}(A) \to p_k > 0$ by Lemma A.1, it is enough to show that the bound in (A.3) goes to 0 as $\varepsilon \to 0$. Define $\kappa := \inf_{k\in\{1,\ldots,N\}} |\mathbf{x} - \mathbf{x}_k|$. Choosing $\delta > \varepsilon$ sufficiently small ensures that $|\mathbf{X}(\sigma) - \mathbf{x}_k| > \kappa$ almost surely for all $k \in \{1, \ldots, N\}$. The desired convergence follows from Assumption 4 and the bounded convergence theorem. ∎

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