Stochastically gated diffusion-limited reactions for a small target in a bounded domain

Paul C. Bressloff* and Sean D. Lawley†

Department of Mathematics, University of Utah, 155 South 1400 East, Salt Lake City, Utah 84112, USA

We calculate the reaction rate for stochastically gated ligands diffusing in a two-dimensional and a three-dimensional bounded domain with a single small target. Each ligand independently switches between an open and a closed state according to a two-state Markov process; a reaction between ligand and target can only occur when the former is an open state. In the large-time limit the reaction-rate is an exponentially decaying function of time, whose rate of decay is given by the principal eigenvalue of the Laplacian. We calculate the principal eigenvalue using matched asymptotics and determine the leading-order reduction in the reaction rate due to stochastic gating. We also develop a probabilistic interpretation of the reaction rate in terms of the first-passage time density to the target.

I. INTRODUCTION

An important problem in cell biology is determining the reaction rate of diffusing molecules binding to some target substrate. One example is the arrival of a receptor at a localized reaction site on the surface of an immune cell, which is a key step in the signaling cascade responsible for activating the cell [1,2]. The classical theory of diffusion-limited reaction rates is based on the Smoluchowski formulation [3–7]. One of the simplest versions is to consider a spherical target Ω of radius a at the origin of the infinite domain $\mathbb{R}^d$ and to solve the diffusion equation for the concentration $c(r,t)$ of molecules exterior to the target. This takes the form $\partial_t c = D\nabla^2 c$ subject to the boundary conditions $c(a,t) = 0$ and $\lim_{r\to\infty} c(r,t) = \bar{c}$. Here D is the diffusivity and $\bar{c}$ is the initial concentration, which is taken to be fixed at spatial infinity. The reaction rate is then defined according to

$$k(t) = D \int_{\partial\Omega} \nabla c \Big|_{r=a} \cdot \mathbf{n} d\sigma, \qquad (1.1)$$

where $\mathbf{n}$ is the outward normal to the surface of the target. The formula for the reaction rate depends on the dimension d. In three-dimensional space one finds that

$$k(t) = 4\pi Da\bar{c}\left(1 + \frac{a}{\sqrt{\pi Dt}}\right) \underset{t\to\infty}{\to} 4\pi Da\bar{c}, \qquad (1.2)$$

whereas in two-dimensional space the reaction rate is independent of the target radius and has the leading order form

$$k(t) \sim \frac{4\pi D\bar{c}}{\ln t} \underset{t\to\infty}{\to} 0. \qquad (1.3)$$

These differences reflect the fact that a two-dimensional random walker starting at some distance $r > a$ has a unit probability of eventually being captured by the target (recurrent random walk), whereas a three-dimensional random walker has a finite probability of escaping to infinity (transient random walk).

The classical theory assumes that the domain exterior to the target is unbounded. Recently, Straube *et al.* [1] have calculated the diffusion-limited reaction rate in the case of a two-dimensional bounded domain, under the assumption that the target is much smaller than the domain size L. Using an eigenfunction expansion of the solution to the diffusion equation, they showed that the long-time behavior of the reaction rate is characterized by a single exponential $k(t) = Ae^{-\lambda_0 t}$. The authors then calculated the principle eigenvalue λ_0 using an asymptotic expansion in powers of the small parameter $\nu = 1/\ln(L/a)$.

In this paper we extend the analysis of Straube *et al.* [1] to the case of *stochastically gated* reactions with a small target in a two-dimensional bounded domain. For unbounded domains, this problem was first studied by Szabo *et al.* [8], who considered a target protein randomly switching between an open and a closed state according to a two-state Markov process; diffusing ligand molecules only react with the target when it is open. This work assumed that it is irrelevant whether it is the target protein or the diffusing ligands that switch between conformational states. Although this symmetry holds for a pair of reacting particles, it breaks down when a single protein is surrounded by many ligands [9–14]. For one of the basic simplifying assumptions of Smoluchowski theory is that one can ignore many-particle effects, namely, correlations in the dynamics of the ligands. However, correlations arise when the protein switches between reactive states, since this is simultaneously experienced by all of the ligands. In other words, all of the ligands diffuse in the same randomly switching environment. (A similar issue arises in the case of proteins escaping through a randomly switching membrane [15,16]). On the other hand, such correlations don't arise if the ligands are assumed to independently switch between conformational states, and it is this so-called particle interpretation that we consider in the paper.

II. DIFFUSION-LIMITED REACTION RATE WITHOUT SWITCHING

Consider a small target disk Ω_ε of radius a and center $\mathbf{x}_0$ that is located in the interior of a two-dimensional bounded domain Ω of size $O(L)$; see Fig. 1. We introduce the small parameter $\varepsilon = a/L$ with $\varepsilon \ll 1$ and nondimensionalize the

---

*bressloff@math.utah.edu
†lawley@math.utah.edu
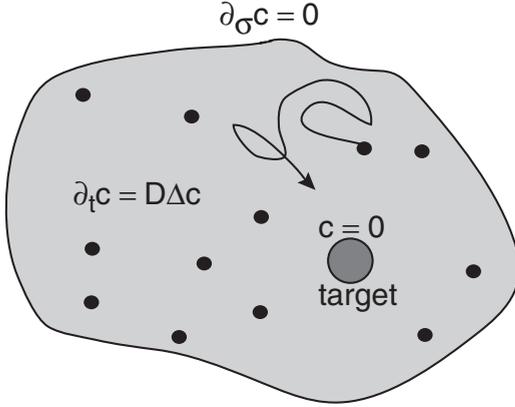
FIG. 1. Diffusion-limited reaction rate for a small target in a bounded domain.

FIG. 2. Construction of the matched asymptotic solution for the small target problem. (a) Inner solution φ in $\mathbb{R}\backslash S^1$ with Dirichlet boundary condition S^1. (b) Outer solution Φ with a reflecting boundary condition on $\partial\Omega$.

problem and set $L = 1$. The calculation of the reaction rate can be formulated in terms of the solution to the following diffusion equation:

$$\frac{\partial c(\boldsymbol{x},t)}{\partial t} = D\nabla^2 c(\boldsymbol{x},t), \quad \boldsymbol{x} \in \Omega\backslash\Omega_\varepsilon, \tag{2.1}$$

with $\partial_\sigma c = 0$ on the exterior boundary $\partial\Omega$ and $c = 0$ on the interior boundary $\partial\Omega_\varepsilon$. (Here ∂_σ denotes normal derivative.) The initial condition is taken to be $c(\boldsymbol{x},0) = \bar{c}$. Following Straube *et al.* [1], we seek a solution in the form of an eigenfunction expansion,

$$c(\boldsymbol{x},t) = \sum_{j=0}^{\infty} C_j \phi^{(j)}(\boldsymbol{x})e^{-\lambda_j Dt}, \tag{2.2}$$

where the eigenfunctions $\phi_j(\boldsymbol{x})$ satisfy the Helmholtz equation,

$$0 = \nabla^2\phi^{(j)} + \lambda_j\phi^{(j)}, \quad \boldsymbol{x} \in \Omega\backslash\Omega_\varepsilon, \tag{2.3}$$

subject to the same boundary conditions as $c(\boldsymbol{x},t)$. The eigenfunctions are orthogonalized as

$$\int_{\Omega\backslash\Omega_\varepsilon} \phi^{(i)}(\boldsymbol{x})\phi^{(j)}(\boldsymbol{x})d\boldsymbol{x} = \delta_{i,j}. \tag{2.4}$$

The initial condition then implies that

$$C_j = \bar{c}\int_{\Omega\backslash\Omega_\varepsilon} \phi^{(j)}(\boldsymbol{x})d\boldsymbol{x}. \tag{2.5}$$

Taking the limit $\varepsilon \to 0$ results in an eigenvalue problem for the bounded domain without a hole. It is well known that the eigenvalues are ordered as $\lambda_0 = 0 < \lambda_1 \leqslant \lambda_2 \leqslant \dots$. This ordering will persist when $0 < \varepsilon \ll 1$ so that in the long-time limit, the solution will be dominated by the eigenmode $\phi^{(0)} \equiv \Phi$ with the smallest eigenvalue:

$$c(\boldsymbol{x},t) \sim C_0\Phi(\boldsymbol{x})e^{-\lambda_0 Dt}, \tag{2.6}$$

with

$$0 = \nabla^2\Phi + \lambda_0\Phi, \tag{2.7}$$

and normalization

$$\int_{\Omega\backslash\Omega_\varepsilon} \Phi^2(\boldsymbol{x})d\boldsymbol{x} = 1. \tag{2.8}$$

The initial condition implies that

$$C_0 = \bar{c}\int_{\Omega\backslash\Omega_\varepsilon} \Phi(\boldsymbol{x})\,d\boldsymbol{x}. \tag{2.9}$$

Finally, the time-dependent flux is

$$J(t) = DC_0 e^{-\lambda_0 Dt}\int_0^{2\pi} \left(r\frac{\partial\Phi}{\partial r}\right)\bigg|_{r=\varepsilon} d\theta. \tag{2.10}$$

A. Matched asymptotics

For small ε, the principal eigenvalue λ_0 of the Helmholtz operator has an infinite logarithmic expansion [1,17]:

$$\lambda_0 = \nu\Lambda_1 + \nu^2\Lambda_2 + \cdots, \quad \nu = -\frac{1}{\ln\varepsilon}. \tag{2.11}$$

Moreover, the eigenfunction $\Phi(\boldsymbol{x})$ develops a boundary layer in a neighborhood of the target, where it changes rapidly from zero on the boundary $\partial\Omega_\varepsilon$ to a value of $O(1)$ away from the target. This suggests dividing the domain into inner and outer regions, see Fig. 2, and using matched asymptotics. The logarithmic expansion of λ_0 implies that the right-hand side of the rescaled eigenvalue equation is of $O(\varepsilon^2\nu^2) = o(\nu^k)$ for all $k \geqslant 0$. Thus, to logarithmic accuracy it follows that the inner problem $\Phi = \varphi$ with stretched coordinates $\boldsymbol{y} = (\boldsymbol{x} - \boldsymbol{x}_0)/\varepsilon$ is

$$\nabla^2\varphi(\boldsymbol{y}) = 0, \quad \boldsymbol{y} \in \mathbb{R}^2\backslash S^1,$$

where S^1 is the unit circle centered about the origin, and $\varphi = 0$ on $|\boldsymbol{y}| = 1$. Hence, $\varphi(\boldsymbol{y}) = A\ln|\boldsymbol{y}|$ and the inner solution has the far-field behavior

$$\varphi \sim A\ln(|\boldsymbol{x} - \boldsymbol{x}_0|/\varepsilon). \tag{2.12}$$

The outer solution satisfies the equation

$$\nabla^2\Phi + \lambda_0\Phi = 0, \quad \boldsymbol{x} \in \Omega\backslash\{\boldsymbol{x}_0\},$$

$$\Phi \sim A\ln(|\boldsymbol{x} - \boldsymbol{x}_0|/\varepsilon), \quad \boldsymbol{x} \to \boldsymbol{x}_0,$$

$$\int_\Omega \Phi^2(\boldsymbol{x})d\boldsymbol{x} = 1.$$

The outer problem can be solved in terms of the Neumann Green's function for the Helmholtz

equation:

$$\nabla^2 G(\boldsymbol{x},\boldsymbol{x}_0;\lambda_0) + \lambda_0 G(\boldsymbol{x},\boldsymbol{x}_0;\lambda_0) = -\delta(\boldsymbol{x} - \boldsymbol{x}_0), \quad x \in \Omega,$$
(2.13a)

$$\partial_\sigma G(\boldsymbol{x},\boldsymbol{x}_0;\lambda_0) = 0, \quad \boldsymbol{x} \in \partial\Omega, \qquad (2.13b)$$

$$G(\boldsymbol{x},\boldsymbol{x}_0;\lambda_0) \sim -\frac{1}{2\pi}\ln|\boldsymbol{x} - \boldsymbol{x}_0|$$
$$+ R(\boldsymbol{x},\boldsymbol{x}_0;\lambda_0), \ \boldsymbol{x} \to \boldsymbol{x}_0,$$
(2.13c)

with $R(\boldsymbol{x},\boldsymbol{x}_0;\lambda_0)$ the regular part of the Green's function. That is,

$$\Phi(\boldsymbol{x}) = -2\pi A G(\boldsymbol{x},\boldsymbol{x}_0;\lambda_0). \qquad (2.14)$$

Matching the near-field behavior of the outer solution with the far-field behavior of the inner solution then yields a transcendental equation for the principal eigenvalue:

$$R(\boldsymbol{x}_0,\boldsymbol{x}_0;\lambda_0) = -\frac{1}{2\pi\nu}. \qquad (2.15)$$

Finally, the normalization condition for Φ determines the amplitude A according to

$$4\pi^2 A^2 \int_\Omega G(\boldsymbol{x},\boldsymbol{x}_0;\lambda_0)^2 d\boldsymbol{x} = 1. \qquad (2.16)$$

Since $0 < \lambda_0 \ll 1$ for a small target, the Green's function has the expansion

$$G(\boldsymbol{x},\boldsymbol{x}_0;\lambda_0) = -\frac{1}{\lambda_0|\Omega|} + G_1(\boldsymbol{x},\boldsymbol{x}_0) + \lambda_0 G_2(\boldsymbol{x},\boldsymbol{x}_0) + O(\lambda_0^2),$$

with $\int_\Omega G_j(\boldsymbol{x},\boldsymbol{x}_0)d\boldsymbol{x} = 0$. Substituting this expansion into Eq. (2.16) shows that to leading order in λ_0,

$$A \approx \frac{\sqrt{|\Omega|}\lambda_0}{2\pi}. \qquad (2.17)$$

Similarly, Eqs. (2.5) and (2.14) imply that

$$C_0 = -2\pi A\bar{c} \int_\Omega G(\boldsymbol{x},\boldsymbol{x}_0;\lambda_0)d\boldsymbol{x} \approx \bar{c}\frac{2\pi A}{\lambda_0} \approx \bar{c}\sqrt{|\Omega|}.$$
(2.18)

The regular part $R(\boldsymbol{x},\boldsymbol{x}_0;\lambda_0)$ can also be expanded in terms of λ_0. Hence, neglecting terms of $O(\lambda_0)$ and higher, substitute $R(\boldsymbol{x},\boldsymbol{x}_0;\lambda_0) \approx -(\lambda_0|\Omega|)^{-1} + R_1(\boldsymbol{x},\boldsymbol{x}_0)$ into Eq. (2.15). This yields a linear equation for λ_0 such that

$$\lambda_0 \approx \frac{2\pi\nu}{|\Omega|}\frac{1}{1 + 2\pi\nu R_1(\boldsymbol{x}_0,\boldsymbol{x}_0)}. \qquad (2.19)$$

We now have all the components necessary to determine the time-dependent reaction rate. That is, substituting the inner solution $\varphi(\boldsymbol{x}) = A\ln(r/\varepsilon)$, $r = |\boldsymbol{x} - \boldsymbol{x}_0|$, into Eq. (2.10), and using Eqs. (2.17) and (2.18), yields the result

$$J(t) \approx D|\Omega|\bar{c}\lambda_0 e^{-\lambda_0 Dt}, \quad \lambda_0 = \frac{2\pi\nu}{|\Omega|} + O(\nu^2). \qquad (2.20)$$

B. Reaction rate at small times

Comparison of Eq. (2.20) for a bounded domain with (1.3) for an unbounded domain shows that the two cases have very
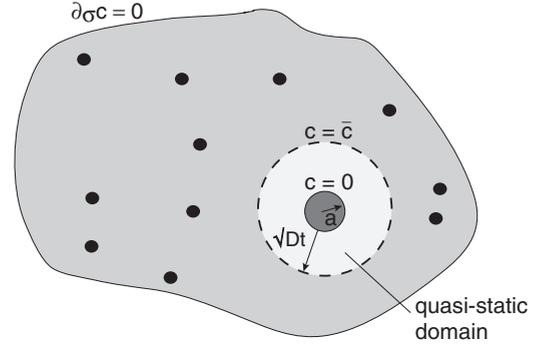
FIG. 3. Quasistatic approximation for calculating the reaction rate at intermediate times.

different time-dependent reaction rates. This suggests that as the size of the domain increases, there is a crossover from the $1/\ln(t)$ behavior at intermediate times to the exponential decay at large times, with the crossover point going to infinity as $|\Omega| \to \infty$. One way to understand this idea is to extend the quasistatic approximation considered by Redner [7]. Let $R_0 = \min\{|\boldsymbol{x} - \boldsymbol{x}_0|, \boldsymbol{x} \in \partial\Omega\}$. If $\sqrt{Dt} \ll R_0$ then we can divide the region exterior to the disk into a *near zone* that extends a distance $\sqrt{Dt}$ from the target and a complementary *far zone*; see Fig. 3. In the near zone, it is assumed that diffusing particles have sufficient time to explore the domain before being absorbed by the target so that the concentration in the near zone can be treated as almost steady or quasistatic. Conversely, it is assumed that the probability of a particle being absorbed by the target is negligible in the far zone, since a particle is unlikely to diffuse more than a distance $\sqrt{Dt}$ over a time interval of length t. Thus, $c(r) \approx \bar{c}$ for $r > \sqrt{Dt} + \varepsilon$. The near-zone concentration is taken to be a radially symmetric solution of Laplace's equation, since it is sufficiently far from the boundary $\partial\Omega$, which for $d = 2$ is $c(r) = A + B\ln r$. Matching the solution to the boundary conditions $c(\varepsilon) = 0$ and $c(\varepsilon + \sqrt{Dt}) = \bar{c}$ then gives (for $R_0 \gg \sqrt{Dt} \gg \varepsilon$)

$$c(r,t) \approx \frac{\bar{c}\ln(r/\varepsilon)}{\ln(\sqrt{Dt}/\varepsilon)}, \qquad (2.21)$$

so that the corresponding time-dependent flux is of the form of Eq. (1.3). On the other hand, when $\sqrt{Dt} \sim R_0$ then boundary effects are going to be important such that in the large-t limit we have the exponential decay given by Eq. (2.20). Finally, in the limit $|\Omega| \to \infty$, we have $R_0 \to \infty$ and the quasistatic approximation holds for large times.

III. EFFECTS OF LIGAND SWITCHING

Now suppose that each diffusing ligand has two conformational states $n(t) = 0, 1$ and it can only bind to the target when $n(t) = 0$, otherwise it is reflected. We assume that ligands independently switch between the two states according to the two-state Markov process,

$$0 \underset{\alpha}{\overset{\beta}{\rightleftharpoons}} 1, \qquad (3.1)$$

with fixed transition rates α, β. Let $c_n(\boldsymbol{x},t)$ with $n = 0, 1$ denote the concentration of ligands that are at position $\boldsymbol{x}$ and

in state n at time t. The pair (c_0, c_1) then satisfy the differential Chapman-Kolmogorov (CK) equation:

$$\frac{\partial c_0}{\partial t} = D\nabla^2 c_0 - \beta c_0 + \alpha c_1, \qquad (3.2a)$$

$$\frac{\partial c_1}{\partial t} = D\nabla^2 c_1 + \beta c_0 - \alpha c_1. \qquad (3.2b)$$

The boundary conditions are

$$c_0(\boldsymbol{x},t) = 0, \quad \partial_\sigma c_1(\boldsymbol{x},t) = 0, \quad \forall \boldsymbol{x} \in \partial\Omega_\varepsilon, \qquad (3.3a)$$

$$\partial_\sigma c_0(\boldsymbol{x},t) = 0, \quad \partial_\sigma c_1(\boldsymbol{x},t) = 0, \quad \forall \boldsymbol{x} \in \partial\Omega, \qquad (3.3b)$$

and the initial conditions are

$$c_0(\boldsymbol{x},0) = \rho_0\bar{c} \equiv \frac{\alpha}{\alpha+\beta}\bar{c}, \quad c_1(\boldsymbol{x},0) = \rho_1\bar{c} \equiv \frac{\beta}{\alpha+\beta}\bar{c}. \qquad (3.4)$$

Equation (3.2) can be written in the form

$$\frac{\partial \mathbf{c}}{\partial t} = D\nabla^2 \mathbf{c} + \mathbf{A}\mathbf{c}, \quad \mathbf{A} = \begin{pmatrix} -\beta & \alpha \\ \beta & -\alpha \end{pmatrix}, \quad \mathbf{c} = \begin{pmatrix} c_0 \\ c_1 \end{pmatrix}. \qquad (3.5)$$

Carrying out an eigenfunction expansion along the lines of Sec. II and keeping only the dominant mode gives

$$c_n(\boldsymbol{x},t) \sim C_0\Phi_n(\boldsymbol{x})e^{-\lambda_0 Dt}, \quad n = 0,1, \qquad (3.6)$$

with $D\nabla^2\boldsymbol{\Phi} + \lambda_0\boldsymbol{\Phi} + \mathbf{A}\boldsymbol{\Phi} = 0$, that is,

$$0 = D[\nabla^2\Phi_0 + \lambda_0\Phi_0] - \beta\Phi_0 + \alpha\Phi_1, \qquad (3.7a)$$

$$0 = D[\nabla^2\Phi_1 + \lambda_0\Phi_1] + \beta\Phi_0 - \alpha\Phi_1, \qquad (3.7b)$$

and boundary conditions

$$\Phi_0(\boldsymbol{x}) = 0, \quad \partial_\sigma\Phi_1(\boldsymbol{x}) = 0, \quad \forall \boldsymbol{x} \in \partial\Omega_\varepsilon, \qquad (3.8a)$$

$$\partial_\sigma\Phi_0(\boldsymbol{x}) = 0, \quad \partial_\sigma\Phi_1(\boldsymbol{x}) = 0, \quad \forall \boldsymbol{x} \in \partial\Omega. \qquad (3.8b)$$

Let $\boldsymbol{\Psi}$ be the eigenfunction of the adjoint equation $D\nabla^2\boldsymbol{\Psi} + \lambda_0\boldsymbol{\Psi} + \mathbf{A}^\top\boldsymbol{\Psi} = 0$, that is,

$$0 = D[\nabla^2\Psi_0 + \lambda_0\Psi_0] - \beta\Psi_0 + \beta\Psi_1, \qquad (3.9a)$$

$$0 = D[\nabla^2\Psi_1 + \lambda_0\Psi_1] + \alpha\Psi_0 - \alpha\Psi_1, \qquad (3.9b)$$

with the same boundary conditions as $\boldsymbol{\Phi}$ and normalization

$$\int_\Omega [\Psi_0(\boldsymbol{x})\Phi_0(\boldsymbol{x}) + \Psi_1(\boldsymbol{x})\Phi_1(\boldsymbol{x})]d\boldsymbol{x} = 1.$$

Comparison of Eqs. (3.7) and (3.9) shows that $\Phi_n = \rho_n\Psi_n, n = 0, 1$, and hence we have

$$\int_\Omega \left[\rho_0^{-1}\Phi_0(\boldsymbol{x})^2 + \rho_1^{-1}\Phi_1(\boldsymbol{x})^2\right]d\boldsymbol{x} = 1. \qquad (3.10)$$

The initial conditions then imply

$$C_0 = \bar{c}\int_\Omega \Phi(\boldsymbol{x})d\boldsymbol{x}, \qquad (3.11)$$

where $\Phi(\boldsymbol{x}) = \Phi_0(\boldsymbol{x}) + \Phi_1(\boldsymbol{x})$.

Adding Eqs. (3.7a) and (3.7b) gives

$$0 = \nabla^2\Phi + \lambda_0\Phi, \qquad (3.12)$$

with boundary conditions

$$\Phi(\boldsymbol{x}) = \Phi_1(\boldsymbol{x}), \quad \forall \boldsymbol{x} \in \partial\Omega_\varepsilon, \quad \partial_\sigma\Phi(\boldsymbol{x}) = 0 \,\forall \boldsymbol{x} \in \partial\Omega. \qquad (3.13)$$

Setting $\Phi_0 = \Phi - \Phi_1$ in Eq. (3.7b) then yields

$$D\nabla^2\Phi_1 - (\alpha + \beta - D\lambda_0)\Phi_1 = -\beta\Phi, \qquad (3.14)$$

with boundary conditions

$$\partial_\sigma\Phi_1(\boldsymbol{x}) = 0 \,\forall \boldsymbol{x} \in \partial\Omega_\varepsilon, \quad \partial_\sigma\Phi_1(\boldsymbol{x}) = 0 \,\forall \boldsymbol{x} \in \partial\Omega. \qquad (3.15)$$

We will proceed by first solving the Helmholtz Eq. (3.12) for Φ, which will depend on Φ_1 due to the boundary condition on $\partial\Omega_\varepsilon$, and then solving Eq. (3.14) for Φ_1; since $\lambda_0 \approx 0$, it follows that Eq. (3.14) is a modified Helmholtz equation.

A. Matched asymptotics

The analysis of Eq. (3.12) proceeds along almost identical lines to Sec. II, except that we now have the inhomogeneous boundary condition $\Phi(\boldsymbol{x}) = \Phi_1(\boldsymbol{x})$ for all $\boldsymbol{x} \in \partial\Omega_\varepsilon$. This means that the inner solution, Eq. (2.12), becomes

$$\varphi \sim \Theta + A\ln(|\boldsymbol{x} - \boldsymbol{x}_0|/\varepsilon). \qquad (3.16)$$

with the constant $\Theta = \Phi_1(\boldsymbol{x}_0)$ to be determined. It follows that the outer solution, Eq. (2.14), becomes

$$\Phi(\boldsymbol{x}) = \Theta - 2\pi A G(\boldsymbol{x},\boldsymbol{x}_0;\lambda_0). \qquad (3.17)$$

Matching the near-field behavior of the outer solution with the far-field behavior of the inner solution then yields the same transcendental Eq. (2.15) for the principal eigenvalue λ_0. In order to determine the unknown constants A and Θ we need to solve for Φ_1. Since we now have a Neumann boundary condition on the target, it follows that the inner solution is simply Θ and we can solve the inhomogeneous equation for the outer solution using the Green's function of the modified Helmholtz equation.

Let $D\Lambda_0 = \alpha + \beta - D\lambda_0$ and introduce the linear operator $\mathbb{L} = \nabla^2 - \Lambda_0\mathbb{I}$, where $\mathbb{I}$ is the identity operator. It follows that

$$\mathbb{L}G(\boldsymbol{x},\boldsymbol{y};-\Lambda_0) = -\delta(\boldsymbol{x} - \boldsymbol{y}),$$

with G defined according to Eqs. (2.13) with $\lambda_0 \to -\Lambda_0$ (yielding the Green's function of the modified Helmholtz equation). From Green's theorem, the outer solution to the inhomogeneous Eq. (3.14) satisfies

$$\int_\Omega [\Phi_1(\boldsymbol{x})\mathbb{L}G(\boldsymbol{x},\boldsymbol{y};-\Lambda_0) - G(\boldsymbol{x},\boldsymbol{y};-\Lambda_0)\mathbb{L}\Phi_1(\boldsymbol{x})]d\boldsymbol{x}$$

$$= \int_{\partial\Omega} [\Phi_1(\boldsymbol{x})\nabla G(\boldsymbol{x},\boldsymbol{y};-\Lambda_0)$$

$$- G(\boldsymbol{x},\boldsymbol{y};-\Lambda_0)\nabla\Phi_1(\boldsymbol{x})] \cdot \mathbf{n}d\sigma.$$

Using the boundary conditions for G and Φ_1, we obtain the solution

$$\Phi_1(\boldsymbol{x}) = \frac{\beta}{D}\int_\Omega G(\boldsymbol{y},\boldsymbol{x};-\Lambda_0)\Phi(\boldsymbol{y})d\boldsymbol{y}, \qquad (3.18)$$

with $\Phi(\mathbf{x}) \to \Theta$ as $\mathbf{x} \to \mathbf{x}_0$. It follows that

$$\Theta = \frac{\beta}{D} \int_\Omega G(\mathbf{x},\mathbf{x}_0;-\Lambda_0)\Phi(\mathbf{x})d\mathbf{x}. \qquad (3.19)$$

Substituting for $\Phi(\mathbf{x})$ using the outer solution, Eq. (3.17), gives

$$\Theta = \frac{\beta\Theta}{[\alpha + \beta - D\lambda_0]}$$
$$- \frac{2\pi A\beta}{D} \int_\Omega G(\mathbf{x},\mathbf{x}_0;-\Lambda_0)G(\mathbf{x},\mathbf{x}_0;\lambda_0)d\mathbf{x},$$

that is,

$$\frac{\Theta}{A} = -\frac{2\pi\beta}{D}\Gamma(\lambda_0) \int_\Omega G(\mathbf{x},\mathbf{x}_0;-\Lambda_0)G(\mathbf{x},\mathbf{x}_0;\lambda_0)d\mathbf{x}, \quad (3.20)$$

where

$$\Gamma^{-1}(\lambda_0) = 1 - \frac{\beta}{\alpha + \beta - D\lambda_0}. \qquad (3.21)$$

The final step is to determine A using the normalization condition Eq. (3.10), rewritten as

$$\int_\Omega \left[\rho_0^{-1}[\Phi(\mathbf{x}) - \Phi_1(\mathbf{x})]^2 + \rho_1^{-1}\Phi_1(\mathbf{x})^2\right]d\mathbf{x} = 1. \quad (3.22)$$

B. Perturbation expansion

As in the nonswitching case, we now perform a perturbation expansion in λ_0. First, we have

$$G(\mathbf{x},\mathbf{x}_0;\lambda_0) = -\frac{1}{\lambda_0|\Omega|} + G_1(\mathbf{x},\mathbf{x}_0) + \lambda_0 G_2(\mathbf{x},\mathbf{x}_0) + O(\lambda_0^2)$$

$$G(\mathbf{x},\mathbf{x}_0;-\Lambda_0) = \frac{D}{(\alpha + \beta)|\Omega|} + H_1(\mathbf{x},\mathbf{x}_0)$$
$$+ \lambda_0\left[\frac{D^2}{(\alpha + \beta)^2|\Omega|} + H_2(\mathbf{x},\mathbf{x}_0)\right] + O(\lambda_0^2), \tag{3.23}$$

with

$$\int_\Omega G_j(\mathbf{x},\mathbf{x}_0)d\mathbf{x} = \int_\Omega H_j(\mathbf{x},\mathbf{x}_0)d\mathbf{x} = 0.$$

Substituting this expansion into Eq. (3.20) shows that to leading order in λ_0,

$$\frac{\Theta}{A} = \frac{2\pi\chi_0}{\lambda_0|\Omega|} + \chi_1 + O(\lambda_0), \quad \chi_0 = \frac{\beta\Gamma(0)}{(\alpha + \beta)} = \frac{\beta}{\alpha}, \quad (3.24)$$

and

$$\chi_1 = \frac{2\pi\chi_0}{|\Omega|}\left[\frac{\Gamma'(0)}{\Gamma(0)} + \frac{D}{\alpha + \beta}\right]$$
$$- \frac{2\pi\beta\Gamma(0)}{D} \int_\Omega G_1(\mathbf{x},\mathbf{x}_0)H_1(\mathbf{x},\mathbf{x}_0)d\mathbf{x}. \qquad (3.25)$$

Similarly, Eqs. (3.17) and (3.18) have the leading-order approximations

$$\Phi(\mathbf{x}) \sim A\left[\frac{2\pi(\alpha + \beta)}{\lambda_0|\Omega|\alpha} + \chi_1 - 2\pi G_1(\mathbf{x},\mathbf{x}_0)\right],$$
$$\equiv \frac{2\pi A}{\lambda_0|\Omega|}\left[\frac{\alpha + \beta}{\alpha} + \overline{\Phi}(\mathbf{x})\lambda_0\right], \qquad (3.26)$$

and

$$\Phi_1(\mathbf{x}) \sim A\left[\frac{2\pi\beta}{\lambda_0|\Omega|\alpha} + \frac{\beta}{\alpha + \beta}\chi_1 + \frac{\beta}{\alpha + \beta}\frac{2\pi D}{|\Omega|\alpha}\right.$$
$$\left. - \frac{2\pi\beta}{D} \int H_1(\mathbf{y},\mathbf{x})G_1(\mathbf{y},\mathbf{x}_0)d\mathbf{y}\right]$$
$$\equiv \frac{2\pi A}{\lambda_0|\Omega|}\left[\frac{\beta}{\alpha} + \overline{\Phi}_1(\mathbf{x})\lambda_0\right]. \qquad (3.27)$$

The normalization condition Eq. (3.22) then gives

$$1 = \left(\frac{2\pi A}{\lambda_0|\Omega|}\right)^2 \int_\Omega \left[\rho_0^{-1}(1 + \lambda_0(\overline{\Phi}(\mathbf{x}) - \overline{\Phi}_1(\mathbf{x}))^2\right.$$
$$\left. + \rho_1^{-1}(\beta/\alpha + \lambda_0\overline{\Phi}_1(\mathbf{x}))^2\right]d\mathbf{x}$$
$$= \left(\frac{2\pi A}{\lambda_0|\Omega|}\right)^2\left[|\Omega|\left(\frac{\alpha + \beta}{\alpha}\right)^2 + 2\lambda_0\frac{\alpha + \beta}{\alpha}\int_\Omega \overline{\Phi}(\mathbf{x})d\mathbf{x}\right]$$
$$+ O(\lambda_0^2). \qquad (3.28)$$

It follows that

$$A = \frac{\lambda_0\sqrt{|\Omega|}}{2\pi}\frac{\alpha}{\alpha + \beta}\left[1 - \frac{\lambda_0}{|\Omega|}\frac{\alpha}{\alpha + \beta}\int_\Omega \overline{\Phi}(\mathbf{x})d\mathbf{x}\right] + O(\lambda_0^3), \qquad (3.29)$$

and Eq. (3.11) becomes

$$C_0 = \frac{2\pi A\bar{c}}{\lambda_0|\Omega|}\left[\frac{\alpha + \beta}{\alpha}|\Omega| + \lambda_0\int_\Omega \overline{\Phi}(\mathbf{x})d\mathbf{x}\right]$$
$$= \bar{c}\sqrt{|\Omega|} + O(\lambda_0^2). \qquad (3.30)$$

Combining all our approximations, we can now determine the time-dependent reaction rate for a stochastically gated target in the particle perspective (ligands switch conformational states). That is, substituting the inner solution $\varphi(\mathbf{x}) = \Theta + A\ln(r/\varepsilon)$, $r = |\mathbf{x} - \mathbf{x}_0|$, into Eq. (2.10), and using Eqs. (3.29) and (3.30), yields the result

$$J(t) \approx \frac{\alpha}{\alpha + \beta}\left[1 - \frac{\lambda_0}{|\Omega|}\frac{\alpha}{\alpha + \beta}\int_\Omega \overline{\Phi}(\mathbf{x})d\mathbf{x}\right]D|\Omega|\bar{c}\lambda_0 e^{-\lambda_0 Dt}. \qquad (3.31)$$

We conclude that in terms of the asymptotic expansion in ν, the principal eigenvalue λ_0 is not changed when the ligands can switch conformational state, but the reaction rate or flux is reduced by a factor $\Gamma_0 = \alpha/(\alpha + \beta)[1 + O(\lambda_0)]$ such that $\Gamma_0 \to 1$ in the limit $\beta \to 0$ (ligands always active) and $\Gamma_0 \to 0$ in the limit $\alpha \to 0$ (ligands always inactive).

C. Reaction rate at small times

We now approximate the reaction rate at small times. Let $R_0 = \min\{|\mathbf{x} - \mathbf{x}_0|, \mathbf{x} \in \partial\Omega\}$ and assume $\sqrt{Dt} \ll R_0$. As in Sec. II B, we divide the domain into a near zone that extends a distance $\sqrt{Dt}$ from the target and a complementary far zone. In the far zone, the probability of a particle being absorbed by the target is small and so we suppose that $c_n(\mathbf{x},t) = \rho_n\bar{c}$. In the near zone, we suppose that the particles have enough time to explore the domain before being absorbed by the target so that the concentrations in the near zone are quasistatic. Thus, the

near zone concentrations are radially symmetric and satisfy

$$D\partial_{rr}c_0 + (D/r)\partial_r c_0 - \beta c_0 + \alpha c_1 = 0, \qquad (3.32a)$$

$$D\partial_{rr}c_1 + (D/r)\partial_r c_1 + \beta c_0 - \alpha c_1 = 0, \qquad (3.32b)$$

with boundary conditions at the target,

$$c_0(\varepsilon) = 0, \quad \partial_r c_1(\varepsilon) = 0,$$

and boundary conditions that match the near zone and far zone solutions, $c_n(\varepsilon + \sqrt{Dt}) = \rho_n \bar{c}$. Adding the pair of Eqs. (3.32) shows that

$$D\partial_{rr}c + (D/r)\partial_r c = 0,$$

with boundary condition at the target $c(\varepsilon) = c_1(\varepsilon) = \Phi$, with Φ to be determined. We thus obtain the near zone solution for c similar to the case without switching found in Eq. (2.21), namely,

$$c(r,t) \approx c_1(\varepsilon) + \frac{[\bar{c} - \Phi]\ln(r/\varepsilon)}{\ln(\sqrt{Dt}/\varepsilon)}.$$

It remains to determine $c_1(r)$ from the inhomogeneous equation

$$D\partial_{rr}c_1 + (D/r)\partial_r c_1 - (\alpha + \beta)c_1 = -\beta c.$$

This has a solution of the form

$$c_1(r) = \frac{\beta}{\alpha + \beta}c(r) + AK_0(r\sqrt{(\alpha + \beta)/D}),$$

where K_0 is the modified Bessel function of zeroth order. Note that this solution automatically satisfies the far-field condition $c_1(r) \to \rho_1 \bar{c}$ as $r \to \infty$. The constant A is determined by the boundary condition $c_1(\varepsilon) = \Phi$:

$$A = \frac{\alpha}{\alpha + \beta}\frac{\Phi}{K_0(\varepsilon\sqrt{(\alpha + \beta)/D})}.$$

Finally, we can determine Φ by imposing the no-flux boundary condition $\partial_r c_1(\varepsilon) = 0$. Using the explicit solution for $c(r)$ and the identity $K_0'(r) = -K_1(r)$, we have

$$\partial c_1(r) = \frac{\beta}{\alpha + \beta}\frac{[\bar{c} - \Phi]}{r\ln(\sqrt{Dt}/\varepsilon)}$$
$$+ \frac{\alpha\Phi}{\alpha + \beta}\sqrt{\frac{\alpha + \beta}{D}}\frac{K_1(\varepsilon\sqrt{(\alpha + \beta)/D})}{K_0(\varepsilon\sqrt{(\alpha + \beta)/D})}.$$

Setting $r = \varepsilon$, using the approximations $K_0(\varepsilon) \sim -\ln\varepsilon$, $K_1(\varepsilon) \sim \varepsilon^{-1}$, and dropping the term $\varepsilon\ln(\sqrt{Dt})$ in the limit $\varepsilon \to 0$, we find that $\Phi \approx \beta\bar{c}/(\alpha + \beta)$, and thus

$$c(r,t) \approx c_1(\varepsilon) + \frac{\alpha}{\alpha + \beta}\frac{\bar{c}\ln(r/\varepsilon)}{\ln(\sqrt{Dt}/\varepsilon)}.$$

Hence,

$$\partial_r[c_0(\varepsilon,t) + c_1(\varepsilon,t)] \sim \frac{\alpha}{\alpha + \beta}\partial_r c(\varepsilon,t) \quad \text{as } \varepsilon \to 0,$$

where $c(r,t)$ is the near zone solution without switching.

IV. 3D REACTION RATES

We now consider the three-dimensional analogs to Secs. II and III.

A. 3D reaction rate without switching

Let Ω_ε be a small target sphere of radius ε and center $\boldsymbol{x}_0$ that is located in the interior of a three-dimensional bounded domain Ω of size $O(L)$. The calculation of the reaction rate can be formulated in terms of the solution to the diffusion equation:

$$\frac{\partial c(\boldsymbol{x},t)}{\partial t} = D\nabla^2 c(\boldsymbol{x},t), \quad \boldsymbol{x} \in \Omega\backslash\Omega_\varepsilon,$$

with $\partial_\sigma c = 0$ on the exterior boundary $\partial\Omega$ and $c = 0$ on the interior boundary $\partial\Omega_\varepsilon$. We take $c(\boldsymbol{x},0) = \bar{c}$. As in the 2D case, the solution is dominated at large times by the principal eigenvalue according to Eqs. (2.6)–(2.9). However, the time-dependent flux at large times is now given by

$$J(t) = DC_0 e^{-\lambda_0 Dt}\int_0^{2\pi}\int_0^{\pi}\left(r\frac{\partial\Phi}{\partial r}\right)\bigg|_{r=\varepsilon}\sin(\phi)\,d\phi\,d\theta. \qquad (4.1)$$

Following Cheviakov *et al.* [18], we first expand the principal eigenvalue λ_0:

$$\lambda_0 = \varepsilon\Lambda_1 + \varepsilon^2\Lambda_2 + \dots.$$

Next, since the eigenfunction $\Phi(\boldsymbol{x})$ develops a boundary layer near the target, we divide the domain into inner and outer regions and use matched asymptotics. The expansion of λ_0 implies that the right-hand side of the rescaled eigenvalue Eq. (3.12) is $O(\varepsilon^3)$. Thus, to third-order accuracy, the inner problem $\Phi = \varphi$ with stretched coordinates $\boldsymbol{y} = (\boldsymbol{x} - \boldsymbol{x}_0)/\varepsilon$ is

$$\nabla^2\varphi(\boldsymbol{y}) = 0, \quad \boldsymbol{y} \in \mathbb{R}^3\backslash S^2,$$

where S^2 is the unit sphere centered about the origin, and $\varphi = 0$ on $|\boldsymbol{y}| = 1$. Thus, $\varphi(\boldsymbol{y}) = A(1 - 1/|\boldsymbol{y}|)$ with far-field behavior:

$$\varphi \sim A(1 - \varepsilon/|\boldsymbol{x} - \boldsymbol{x}_0|).$$

The outer solution satisfies

$$\nabla^2\Phi + \lambda_0\Phi = 0, \quad \boldsymbol{x} \in \Omega\backslash\{\boldsymbol{x}_0\},$$
$$\Phi \sim A(1 - \varepsilon/|\boldsymbol{x} - \boldsymbol{x}_0|), \quad \boldsymbol{x} \to \boldsymbol{x}_0,$$
$$\int_\Omega \Phi^2(\boldsymbol{x})\,dx = 1.$$

As before, we employ the Neumann Green's function to solve the outer problem:

$$\nabla^2 G(\boldsymbol{x},\boldsymbol{x}_0;\lambda_0) + \lambda_0 G(\boldsymbol{x},\boldsymbol{x}_0;\lambda_0) = -\delta(\boldsymbol{x} - \boldsymbol{x}_0), \quad \boldsymbol{x} \in \Omega,$$
$$\partial_\sigma G(\boldsymbol{x},\boldsymbol{x}_0;\lambda_0) = 0, \quad \boldsymbol{x} \in \partial\Omega,$$
$$G(\boldsymbol{x},\boldsymbol{x}_0;\lambda_0) \sim \frac{1}{4\pi|\boldsymbol{x} - \boldsymbol{x}_0|} + R(\boldsymbol{x},\boldsymbol{x}_0;\lambda_0), \quad \boldsymbol{x} \to \boldsymbol{x}_0, \qquad (4.2)$$

with $R(\boldsymbol{x},\boldsymbol{x}_0;\lambda_0)$ the regular part of the Green's function. In particular,

$$\Phi(\boldsymbol{x}) = A(1 - 4\pi G(\boldsymbol{x},\boldsymbol{x}_0;\lambda_0)). \qquad (4.3)$$

Matching the near-field behavior of the outer solution with the far-field behavior of the inner solution then yields a transcendental equation for the principal eigenvalue:

$$R(\boldsymbol{x}_0,\boldsymbol{x}_0;\lambda_0) = \frac{1}{4\pi}\left(1 - \frac{1}{\varepsilon}\right). \tag{4.4}$$

Finally, the normalization Eq. (2.8) for Φ determines the amplitude A according to

$$A^2 \int_\Omega (1 - 4\pi\, G(\boldsymbol{x},\boldsymbol{x}_0;\lambda_0))^2\, d\boldsymbol{x} = 1. \tag{4.5}$$

Since $0 < \lambda_0 \ll 1$ for a small target, the Green's function has the expansion

$$G(\boldsymbol{x},\boldsymbol{x}_0;\lambda_0) = \frac{-1}{\lambda_0|\Omega|} + G_1(\boldsymbol{x},\boldsymbol{x}_0) + \lambda_0 G_2(\boldsymbol{x},\boldsymbol{x}_0) + O(\lambda_0^2),$$

with $\int_\Omega G_j(\boldsymbol{x},\boldsymbol{x}_0)d\boldsymbol{x} = 0$. Substituting this expansion into Eq. (4.5) shows that to leading order in λ_0,

$$A \approx \frac{\sqrt{|\Omega|\lambda_0}}{4\pi}.$$

Similarly, Eqs. (2.9) and (4.3) imply that

$$C_0 = \bar{c}A \int_\Omega (1 - 4\pi\, G(\boldsymbol{x},\boldsymbol{x}_0;\lambda_0))\, d\boldsymbol{x} \approx \bar{c}\frac{4\pi A}{\lambda_0} \approx \bar{c}\sqrt{|\Omega|}.$$

Plugging the expansion $R(\boldsymbol{x},\boldsymbol{x}_0;\lambda_0) \approx -(\lambda_0|\Omega|)^{-1} + R_1(\boldsymbol{x},\boldsymbol{x}_0)$ into Eq. (4.4) gives the following approximation of λ_0:

$$\lambda_0 \approx \frac{4\pi\varepsilon}{|\Omega|}\frac{1}{1 + 4\pi\varepsilon R_1(\boldsymbol{x}_0,\boldsymbol{x}_0) - 1}.$$

Putting this together, we approximate the time-dependent reaction rate Eq. (4.1) at large times by

$$J(t) \approx D|\Omega|\bar{c}\lambda_0 e^{-\lambda_0 D t}, \quad \lambda_0 = \frac{4\pi\varepsilon}{|\Omega|} + O(\varepsilon^2). \tag{4.6}$$

As in Sec. II B, we can use the quasistatic approximation to estimate the flux at small times. Proceeding as before, we seek a radially symmetric near-zone solution $c(r,t)$ valid for (r,t) such that $\varepsilon < r < \sqrt{Dt} \ll \min\{|\boldsymbol{x} - \boldsymbol{x}_0|, \boldsymbol{x} \in \partial\Omega\}$, which satisfies Laplace's equation with boundary conditions $c(\varepsilon) = 0$ and $c(\varepsilon + \sqrt{Dt}) = \bar{c}$. This near-zone solution is then given by

$$c(r,t) = \bar{c}\frac{(r - \varepsilon)(\sqrt{Dt} + \varepsilon)}{r\sqrt{Dt}}. \tag{4.7}$$

From this, we see that the corresponding time-dependent flux is of the form of Eq. (1.2).

B. 3D reaction rate with switching

As in Sec. III, we now suppose that each diffusing ligand has two conformational states, $n(t) = 0, 1$, and it can only bind to the target when $n(t) = 0$, otherwise it is reflected. We assume that ligands independently switch between the two states according to the two-state Markov process Eq. (3.1). We thus obtain Eqs. (3.12)–(3.15) for $\Phi(\boldsymbol{x}) = \Phi_0(\boldsymbol{x}) + \Phi_1(\boldsymbol{x})$ and $\Phi_1(\boldsymbol{x})$, together with the normalization condition Eq. (3.22). We approximate Φ by an inner solution,

$$\varphi \sim \Theta + A(1 - \varepsilon/|\boldsymbol{x} - \boldsymbol{x}_0|),$$

and an outer solution,

$$\Phi(\boldsymbol{x}) = \Theta + A(1 - 4\pi\, G(\boldsymbol{x},\boldsymbol{x}_0;\lambda_0)), \tag{4.8}$$

with the constant $\Theta = \Phi_1(\boldsymbol{x}_0)$ to be determined. Matching the near-field behavior of the outer solution with the far-field behavior of the inner solution gives the same transcendental Eq. (4.4) for the principal eigenvalue. In order to determine the unknown constants A and Θ we need to solve for Φ_1 in terms of the Green's function of the 3D modified Helmholtz, which yields Eq. (3.18). When this is combined with Eq. (4.8), we obtain the result

$$\frac{\Theta}{A} = \Gamma(\lambda_0)\left[\frac{\beta}{\alpha + \beta - D\lambda_0}\right.$$
$$\left. - \frac{4\pi\beta}{D}\int_\Omega G(\boldsymbol{x},\boldsymbol{x}_0;-\Lambda_0)G(\boldsymbol{x},\boldsymbol{x}_0;\lambda_0)\,d\boldsymbol{x}\right], \tag{4.9}$$

where Γ is defined in Eq. (3.21).

Expanding the Green's functions as in Eq. (3.23) and substituting into Eq. (4.9) gives

$$\frac{\Theta}{A} = \frac{4\pi\alpha}{\beta\lambda_0|\Omega|} + \chi_{1,3D} + O(\lambda_0),$$

with

$$\chi_{1,3D} = \frac{4\pi\chi_0}{|\Omega|}\left[\frac{\Gamma'(0)}{\Gamma(0)} + \frac{D}{\alpha+\beta}\right] + \frac{\beta}{\alpha}$$
$$- \frac{4\pi\beta}{D}\Gamma(0)\int_\Omega G_1(\boldsymbol{x},\boldsymbol{x}_0)H_1(\boldsymbol{x},\boldsymbol{x}_0)\,d\boldsymbol{x}.$$

Similarly, we find

$$\Phi(\boldsymbol{x}) \sim \frac{4\pi A}{\lambda_0|\Omega|}\left\{\frac{\alpha+\beta}{\alpha}\right.$$
$$\left. + \lambda_0\left[\frac{|\Omega|}{4\pi}(\chi_{1,3D} + 1) - |\Omega|G_1(\boldsymbol{x},\boldsymbol{x}_0)\right]\right\}$$
$$\equiv \frac{4\pi A}{\lambda_0|\Omega|}\left[\frac{\alpha+\beta}{\alpha} + \lambda_0\overline{\Phi}_{3D}(\boldsymbol{x})\right], \tag{4.10}$$

and

$$\Phi_1(\boldsymbol{x}) \sim \frac{4\pi A}{\lambda_0|\Omega|}\left\{\frac{\beta}{\alpha} + \lambda_0\left[\frac{|\Omega|}{4\pi}(\chi_{1,3D} + 1)\right.\right.$$
$$\left.\left. - \frac{\beta|\Omega|}{D}\int_\Omega H_1(\boldsymbol{x},\boldsymbol{x}_0)G_1(\boldsymbol{x},\boldsymbol{x}_0)\,d\boldsymbol{x} + \frac{\beta}{\alpha+\beta}\frac{D}{\alpha}\right]\right\}$$
$$\equiv \frac{4\pi A}{\lambda_0|\Omega|}\left[\frac{\beta}{\alpha} + \lambda_0\overline{\Phi}_{1,3D}(\boldsymbol{x})\right]. \tag{4.11}$$

Equations (3.22) and (3.11) then give

$$A = \frac{\lambda_0\sqrt{|\Omega|}}{4\pi}\frac{\alpha}{\alpha+\beta}\left[1 - \frac{\lambda_0}{|\Omega|}\frac{\alpha}{\alpha+\beta}\int_\Omega \overline{\Phi}_{3D}(\boldsymbol{x})\,d\boldsymbol{x}\right] + O(\lambda_0^3),$$
$$C_0 = \bar{c}\sqrt{|\Omega|} + O(\lambda_0^2).$$

Putting this together, we approximate the time-dependent reaction rate, Eq. (4.1), at large times by

$$J(t) \approx \frac{\alpha}{\alpha+\beta}\left[1 - \frac{\lambda_0}{|\Omega|}\frac{\alpha}{\alpha+\beta}\int_\Omega \overline{\Phi}_{3D}(\boldsymbol{x})\,d\boldsymbol{x}\right]$$
$$\times D|\Omega|\bar{c}\lambda_0 e^{-\lambda_0 D t},$$

where λ_0 and $\overline{\Phi}_{3D}(\boldsymbol{x})$ are given in Eqs. (4.6) and (4.10), respectively. Finally, proceeding as in Sec. III C, we can use the quasistatic approximation to estimate the flux at small times. Again, we find that

$$\partial_r [c_0(\varepsilon,t) + c_1(\varepsilon,t)] \sim \frac{\alpha}{\alpha + \beta} \partial_r c(\varepsilon,t) \quad \text{as } \varepsilon \to 0,$$

where $c(r,t)$ is the near-zone solution without switching found above in Eq. (4.7).

V. PROBABILISTIC APPROACH

In a number of different scenarios in the previous sections, we have used asymptotic analysis of partial differential equations (PDEs) to show that (in the small target limit) the flux to a stochastically gated target (from the perspective of a particle that switches states) is equal to the proportion of time the target is open multiplied by the flux to the corresponding nongated target. In this section, we use a general probabilistic argument to extend our result to the case of a Brownian particle moving in a bounded domain with multiple small targets and an external force. In Sec. V A we show that the probability density of the particle's first passage time (FPT) to a gated target is equal to the probability of an open target multiplied by the probability density of the FPT to a nongated target. Then in Sec. V B, we show that the probability density of the FPT to a gated (nongated) target is equal to the flux of a PDE solution to a gated (nongated) target. Combining Secs. V A and V B gives the desired result. Note, however, that if one wants to calculate higher-order corrections to the flux then one needs to use PDE methods and matched asymptotics as in previous sections.

A. FPT distributions

Let $d \geqslant 2$ be an integer and let $\Omega \subset \mathbb{R}^d$ be a bounded open set. For $k = 0, \ldots, N - 1$, let $\boldsymbol{x}_k \in \overline{\Omega}$ be N points in the closure of Ω, denoted by $\overline{\Omega}$. For $\varepsilon > 0$ and $k = 0, \ldots, N - 1$, let Ω_ε^k be the open ball of radius ε centered at $\boldsymbol{x}_k$ and define

$$\Omega_\varepsilon := \cup_{k=0}^{N-1} \Omega_\varepsilon^k.$$

Suppose that the $\overline{\Omega \backslash \Omega_\varepsilon}$-valued process $\{\mathbf{X}(t)\}_{t \geqslant 0}$ satisfies the stochastic differential equation

$$d\mathbf{X}(t) = \mathbf{F}(\mathbf{X}) \, dt + \sqrt{2D} \, d\mathbf{W}(t),$$

with reflecting boundary conditions on $\partial \Omega \cup \partial \Omega_\varepsilon$, where $\mathbf{F} : \mathbb{R}^d \to \mathbb{R}^d$ is some given function and $\mathbf{W}(t)$ is an $\mathbb{R}^d$-valued standard Brownian motion.

Let $\mathbf{n}(t) \in \{0,1\}^N$ be an irreducible Markov process. We say that target k is (from the perspective of a particle that switches states) open or closed at time t if the k-th component $n_k(t)$ of $\mathbf{n}(t)$ is 0 or 1, respectively. We assume $\mathbf{n}(t)$ is independent of $\mathbf{W}(t)$, but we do not assume that the components of $\mathbf{n}(t)$ are independent of each other. It follows that $\{(\mathbf{X}(t), \mathbf{n}(t))\}_{t \geqslant 0}$ is a strong Markov process.

Define the following stopping times

$$\mathcal{S} := \inf_{1 \leqslant k \leqslant N} \big\{ \inf \big\{ t \geqslant 0 : \mathbf{X}(t) \in \partial \Omega_k^\varepsilon \big\} \big\},$$

$$\mathcal{T} := \inf_{1 \leqslant k \leqslant N} \big\{ \inf \big\{ t \geqslant 0 : \big\{ \mathbf{X}(t) \in \partial \Omega_k^\varepsilon \big\} \cap \{ n_k(t) = 0 \} \big\} \big\},$$

which are the FPTs to a target and an open target, respectively. Let H be the first target that $\mathbf{X}$ hits. That is, define $H \in \{1, \ldots, N\}$ to be the random variable such that $\mathbf{X}(\mathcal{S}) \in \partial \Omega_\varepsilon^H$.

Let $\mathbb{P}$ and $\mathbb{E}$ denote the probability measure conditioned on $\mathbf{X}(0)$ being uniformly distributed in $\Omega \backslash \Omega_\varepsilon$ and $\mathbf{n}(0)$ being distributed according to its unique invariant measure. Fix a $t \geqslant 0$ and observe that

$$\begin{aligned} \mathbb{P}(\mathcal{T} \leqslant t) &= \mathbb{P}(\{\mathcal{T} \leqslant t\} \cap \{n_H(\mathcal{S}) = 0\}) \\ &\quad + \mathbb{P}(\{\mathcal{T} \leqslant t\} \cap \{n_H(\mathcal{S}) = 1\}) \\ &= \mathbb{P}(n_H(\mathcal{S}) = 0)\mathbb{P}(\mathcal{S} \leqslant t) \\ &\quad + \mathbb{P}(\{\mathcal{T} \leqslant t\} \cap \{n_H(\mathcal{S}) = 1\}). \end{aligned} \quad (5.1)$$

Now since $\mathcal{S} \leqslant \mathcal{T}$ with probability one, we have that

$$\begin{aligned} &\mathbb{P}(\{\mathcal{T} \leqslant t\} \cap \{n_H(\mathcal{S}) = 1\}) \\ &= \mathbb{P}(\{\mathcal{T} \leqslant t\} \cap \{n_H(\mathcal{S}) = 1\}|\mathcal{S} \leqslant t)\mathbb{P}(\mathcal{S} \leqslant t) \\ &= \mathbb{P}(\mathcal{T} \leqslant t|\{n_H(\mathcal{S}) = 1\} \cap \{\mathcal{S} \leqslant t\}) \\ &\quad \times \mathbb{P}(n_H(\mathcal{S}) = 1)\mathbb{P}(\mathcal{S} \leqslant t). \end{aligned} \quad (5.2)$$

If we assume that $\mathbb{P}(n_k(0) = 0) = \alpha/(\alpha + \beta)$ for each k, it follows from Eqs. (5.1) and (5.2) that

$$\frac{\mathbb{P}(\mathcal{T} \leqslant t)}{\frac{\alpha}{\alpha+\beta}\mathbb{P}(\mathcal{S} \leqslant t)} = 1 + \frac{\beta}{\alpha} \mathbb{P}(\mathcal{T} \leqslant t|\{n_H(\mathcal{S}) = 1\} \cap \{\mathcal{S} \leqslant t\}).$$

If we assume that

$$\mathbb{P}(\mathcal{T} \leqslant t|\{n_H(\mathcal{S}) = 1\} \cap \{\mathcal{S} \leqslant t\}) \quad (5.3)$$

goes to 0 as $\varepsilon \to 0$, then we have that the cumulative distribution functions of $\mathcal{T}$ and $\mathcal{S}$ satisfy

$$\mathbb{P}(\mathcal{T} \leqslant t) \sim \frac{\alpha}{\alpha + \beta}\mathbb{P}(\mathcal{S} \leqslant t) \quad \text{as } \varepsilon \to 0. \quad (5.4)$$

If we further assume that $\mathcal{T}$ and $\mathcal{S}$ have probability densities, $f_{\mathcal{T}}$ and $f_{\mathcal{S}}$, and that the time derivative of Eq. (5.3) converges to 0 as $\varepsilon \to 0$, then Eq. (5.4) becomes

$$f_{\mathcal{T}}(t) \sim \frac{\alpha}{\alpha + \beta} f_{\mathcal{S}}(t) \quad \text{as } \varepsilon \to 0. \quad (5.5)$$

That is, the probability density of the FPT with gating is equal to the probability density of the FPT without gating multiplied by the probability of an open target.

In Sec. V B, we relate Eq. (5.5) to the flux of a PDE to a target, but first we justify the assumption that Eq. (5.3) goes to 0 as $\varepsilon \to 0$. By the strong Markov property we have that

$$\begin{aligned} &\mathbb{P}(\mathcal{T} \leqslant t|\{n_H(\mathcal{S}) = 1\} \cap \{\mathcal{S} \leqslant t\}) \\ &\leqslant \mathbb{P}(\mathcal{T} \leqslant t + \mathcal{S}|\{n_H(\mathcal{S}) = 1\} \cap \{\mathcal{S} \leqslant t\}) \\ &\leqslant \sup_k \sup_{\boldsymbol{x} \in \partial \Omega_\varepsilon^k} \mathbb{P}(\mathcal{T} \leqslant t|\{\mathbf{X}(0) = \boldsymbol{x}\} \cap \{n_k(0) = 1\}). \end{aligned} \quad (5.6)$$

Now, we certainly expect the FPT to a target to diverge in probability in the small target limit for any initial particle position, as long as the particle does not start exactly on a target (see Ref. [19] for the case $d = 2$ or 3). Assuming that the bound in Eq. (5.6) goes to 0 as $\varepsilon \to 0$ means that the FPT to an open target diverges in probability in the small target limit even if the particle starts at a target, as long as the target is initially closed. The basic reason this holds is that although

the particle starts at a target, if the target is initially closed, then the particle will wander away, and once it wanders away it takes a long time to find a target again.

To make this argument more precise, let $\eta > 0$ be arbitrary and choose $\delta > 0$ so that the probability that the target opens before the particle leaves a δ neighborhood of the target is less than η. That is, if $\boldsymbol{x} \in \partial \Omega_\varepsilon^k$, then

$$\mathbb{P}(\tau_{\text{open}} < \tau_{\text{leave}} | \{\mathbf{X}(0) = \boldsymbol{x}\} \cap \{n_k(0) = 1\}) < \eta,$$

where

$$\tau_{\text{open}} := \inf\{s \geqslant 0 : n_k(s) = 0\},$$
$$\tau_{\text{leave}} := \inf\{s \geqslant 0 : |\mathbf{X}(s) - \boldsymbol{x}_k| \geqslant \delta\}.$$

The existence of such a δ follows from standard SDE results and the fact that τ_{open} is exponentially distributed. Thus, if $\boldsymbol{x} \in \partial \Omega_\varepsilon^k$, then by the strong Markov property and the fact that $\mathcal{S} \leqslant \mathcal{T}$, we have

$$\mathbb{P}(\mathcal{T} \leqslant t | \{\mathbf{X}(0) = \boldsymbol{x}\} \cap \{n_k(0) = 1\})$$
$$\leqslant \eta + \sup_{\{\boldsymbol{y} : |\boldsymbol{y} - \boldsymbol{x}_k| = \delta\}} \mathbb{P}(\mathcal{S} \leqslant t | \mathbf{X}(0) = \boldsymbol{y}).$$

We can then make the second term in the bound above arbitrarily small by taking ε small since the FPT to a target diverges in probability if the particle does not start exactly on a target.

B. Relationship to fluxes

We now relate Eq. (5.5) to the flux of a solution to a PDE. The Chapman-Kolmogorov equation for the probability density of $\mathbf{X}(t)$ is

$$\partial_t \mathbf{p}(\boldsymbol{x}, t) = (L + Q^T) \mathbf{p}(\boldsymbol{x}, t), \qquad (5.7)$$

where L is the differential operator with kth component

$$(L\mathbf{p}(\boldsymbol{x}, t))_k = -\nabla \cdot [\mathbf{F}(\boldsymbol{x}) p_k(\boldsymbol{x}, t)] + D \nabla^2 p_k(\boldsymbol{x}, t),$$

$Q^T \in \mathbb{R}^{2^N \times 2^N}$ is the infinitesimal generator of $\mathbf{n}(t)$, and the kth component $p_k(\boldsymbol{x}, t)$ of $\mathbf{p}(\boldsymbol{x}, t) \in \mathbb{R}^{2^N}$ is the probability density of $\mathbf{X}(t) = \boldsymbol{x}$ and $\mathbf{n}(t)$ equal state k given that $\mathbf{X}(0)$ is uniformly distributed on $\Omega \backslash \Omega_\varepsilon$ and $\mathbf{n}(0)$ is distributed according to its unique invariant measure. The boundary conditions are $\partial_\sigma p_k(\boldsymbol{x}, t) = 0$ if $\boldsymbol{x} \in \partial \Omega$ for all k and either

$$p_k(\boldsymbol{x}, t) = 0 \quad \text{or} \quad \partial_\sigma p_k(\boldsymbol{x}, t) = 0, \qquad (5.8)$$

for $\boldsymbol{x} \in \partial \Omega_\varepsilon^j$ depending on if state k corresponds to target j being open or closed.

Thus, the cumulative distribution function of $\mathcal{T}$ is

$$\mathbb{P}(\mathcal{T} \leqslant t) = 1 - \int_{\Omega \backslash \Omega_\varepsilon} \mathbf{1}^T \mathbf{p}(\boldsymbol{x}, t) \, d\boldsymbol{x},$$

where $\mathbf{1}^T \mathbf{p}$ denotes the sum of the components of $\mathbf{p}$. Taking the time derivative then gives the following equation for the probability density of $\mathcal{T}$,

$$f_{\mathcal{T}}(t) = -\int_{\Omega \backslash \Omega_\varepsilon} L \mathbf{1}^T \mathbf{p}(\boldsymbol{x}, t) \, d\boldsymbol{x}, \qquad (5.9)$$

since Q^T has zero column sums. Applying the divergence theorem to Eq. (5.9) shows that $f_{\mathcal{T}}(t)$ is the flux of $\mathbf{p}$ through $\partial \Omega_\varepsilon$.
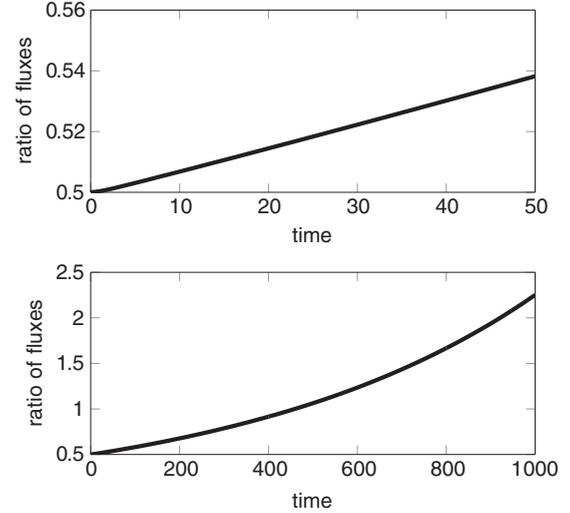
FIG. 4. Ratio of gated to nongated flux as a function of time. We take $D = \alpha = \beta = 1$ and Ω and Ω_ε to be spheres with respective radii 1 and 10^{-3}, with Ω_ε located in the center of Ω. As our theory predicts, in the top plot the ratio of gated flux to nongated flux is approximately $\alpha/(\alpha + \beta)$ for times $t \ll 1/\varepsilon$, whereas in the bottom plot the gated flux exceeds the nongated flux for large times, $t = O(1/\varepsilon)$.

Finally, we note that Eqs. (5.7) and (5.8) are identical in form to Eqs. (3.2) and (3.3). A similar calculation shows that $f_{\mathcal{S}}(t)$ is the flux through $\partial \Omega_\varepsilon$ of a solution to a PDE identical in form to Eq. (2.1).

VI. DISCUSSION

In this paper we extended previous work on the Smoluchowski theory of diffusion-limited reactions to the case of the stochastically gated flux to a small target in a bounded domain. We have found that stochastic gating reduces the flux to a small target by a factor equal to the proportion of time the target is open.

This approximation holds in the small target limit for any fixed time t. We remark that if we instead fix the target size and then take time to be sufficiently large, then this relation no longer holds. Indeed, the flux to a gated target must be greater than the flux to a nongated target at very large times (see Fig. 4). Intuitively, this holds because at large times most of the mass in the nonswitching system has already exited, while the switching system has comparatively more remaining mass to exit. In probabilistic terms, both FPT densities must integrate to one, so if the switching density is less than the nonswitching density at intermediate times, then it must be greater at very large times. In terms of our asymptotic analysis, we have neglected $O(\varepsilon)$ corrections to the principal eigenvalue (with $\varepsilon \ll \nu$), and these corrections become relevant at large times. We note that these corrections are smaller in three dimensions compared to two. Thus, the approximation holds over a larger time range in three dimensions compared to two. This is also reflected in our probabilistic approach, as the analysis there relies on the fact that finding a small target is a rare event, and it is much rarer to find a small target in three dimensions compared to two.

One of the novel features of our analysis is that we combine tools from PDEs and probability theory. In the case of Smoluchowski theory, this connection can be established by noting that the flux through a boundary is related to the probability density function of the FPT to a target. Coupling these disparate methods provides a unique perspective, which we believe can serve as a prototype for future studies. We have also carried out a similar approach to a variety of escape problems from domains with partially switching boundaries [15,16].

In future work, 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. This subtlety has been studied before [9,10,13],

and we hope that coupling PDE and probability techniques can give further insights into this problem.

One potential application of our theoretical work is to modeling the exchange of macromolecules between the cytoplasm and nucleus via the nuclear pore complex. The nucleus of eukaryotes is surrounded by a protective nuclear envelope (NE) within which are embedded nuclear pore complexes (NPCs). The NPCs are the sole mediators of exchange between the nucleus and cytoplasm. In general small molecules of diameter $\sim$5 nm can diffuse through the NPCs unhindered, whereas larger molecules up to around 40 nm in diameter are excluded unless they are bound to a family of soluble protein receptors known as karyopherins (kaps) [20]. The kaps thus provide a substrate for stochastically gating flux through the nuclear pore complex.

[1] R. Straube, M. J. Ward, and M. Falcke, J. Stat. Phys. **129**, 377 (2007).

[2] D. Coombs, R. Straube, and M. J. Ward, SIAM J. Appl. Math. **70**, 302 (2009).

[3] M. V. Z. Smoluchowski, Phys. Chem. **92**, 129 (1917).

[4] F. C. Collins and G. E. Kimball, J. Colloid Sci. **4**, 425 (1949).

[5] J. Keizer, J. Phys. Chem. **86**, 5052 (1982).

[6] S. A. Rice, *Diffusion-limited Reactions* (Elsevier, Amsterdam, 1985).

[7] S. Redner, *A Guide to First-passage Processes* (Cambridge University Press, Cambridge, UK, 2001).

[8] A. Szabo, D. Shoup, S. H. Northrup, and J. A. McCammon, J. Chem. Phys. **77**, 4484 (1982).

[9] H.-X. Zhou and A. Szabo, J. Phys. Chem. **100**, 2597 (1996).

[10] A. M. Berezhkovskii, D.-Y. Yang, S.-Y. Sheu, and S. H. Lin, Phys. Rev. E **54**, 4462 (1996).

[11] J. L. Spouge, A. Szabo, and G. H. Weiss, Phys. Rev. E **54**, 2248 (1996).

[12] A. M. Berezhkovskii, D.-Y. Yang, S. H. Lin, Yu. A. Makhnovskii, and S.-Y. Sheu, J. Chem. Phys. **106**, 6985 (1997).

[13] Yu. A. Makhnovskii, A. M. Berezhkovskii, S.-Y. Sheu, D.-Y. Yang, J. Kuo, and S. H. Lin, J. Chem. Phys. **108**, 971 (1998).

[14] O. Benichou, M. Moreau, and G. Oshanin, Phys. Rev. E **61**, 3388 (2000).

[15] P. C. Bressloff and S. D. Lawley, J. Phys. A **48**, 225001 (2015).

[16] P. C. Bressloff and S. D. Lawley (unpublished).

[17] M. J. Ward, W. D. Henshaw, and J. B. Keller, SIAM J. Appl. Math. **53**, 799 (1993).

[18] A. F. Cheviakov and M. J. Ward, Math. Comput. Model. **53**, 1394 (2011).

[19] A. Singer and Z. Schuss, SIAM J. Appl. Math. **68**, 98 (2007).

[20] E. J. Tran and S. R. Wente, Cell **125**, 1041 (2006).