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## ABSTRACT

We propose a general theoretical description of chemical reactions occurring on a catalytic surface with heterogeneous reactivity. The propagator of a diffusion-reaction process with eventual absorption on the heterogeneous partially reactive surface is expressed in terms of a much simpler propagator toward a homogeneous perfectly reactive surface. In other words, the original problem with the general Robin boundary condition that includes, in particular, the mixed Robin-Neumann condition, is reduced to that with the Dirichlet boundary condition. Chemical kinetics on the surface is incorporated as a matrix representation of the surface reactivity in the eigenbasis of the Dirichlet-to-Neumann operator. New spectral representations of important characteristics of diffusion-controlled reactions, such as the survival probability, the distribution of reaction times, and the reaction rate, are deduced. Theoretical and numerical advantages of this spectral approach are illustrated by solving interior and exterior problems for a spherical surface that may describe either an escape from a ball or hitting its surface from outside. The effect of continuously varying or piecewise constant surface reactivity (describing, e.g., many reactive patches) is analyzed.

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## I. INTRODUCTION

Marian von Smoluchowski first emphasized the importance of diffusive dynamics of reactant molecules and thus laid the foundations for the modern theory of diffusion-controlled reactions.<sup>1</sup> In the basic description, the concentration  $c(\mathbf{x}, t)$  of molecules, diffusing toward a static catalytic surface with the diffusivity  $D$ , obeys the diffusion equation in a bulk domain  $\Omega$ ,

$$\frac{\partial}{\partial t} c(\mathbf{x}, t) = D\Delta c(\mathbf{x}, t) \quad (\mathbf{x} \in \Omega) \quad (1)$$

(with  $\Delta$  being the Laplace operator), subject to the Dirichlet boundary condition on the surface  $\partial\Omega$ ,

$$c(\mathbf{x}, t) = 0 \quad (\mathbf{x} \in \partial\Omega). \quad (2)$$

This condition describes a perfect sink, i.e., any molecule hitting the surface reacts with an infinite reaction rate upon the first encounter. Since that seminal paper by Smoluchowski, diffusion-controlled reactions to perfect sinks and the related first-passage phenomena have been thoroughly investigated.<sup>2–8</sup>

The assumption of infinite reaction rate is not realistic for most chemical reactions because a molecule that approached a catalytic surface needs to overcome an activation energy barrier to react that

results in a finite reaction rate.<sup>9,10</sup> This effect was first incorporated by Collins and Kimball<sup>11</sup> who replaced the Dirichlet boundary condition (2) by the Robin boundary condition (also known as Fourier, radiation, or third boundary condition),

$$-D \frac{\partial}{\partial \mathbf{n}} c(\mathbf{x}, t) = \kappa(\mathbf{x}) c(\mathbf{x}, t) \quad (\mathbf{x} \in \partial\Omega), \quad (3)$$

where  $\partial/\partial \mathbf{n}$  is the normal derivative oriented outward the bulk. This condition states that at each boundary point  $\mathbf{s} \in \partial\Omega$ , the diffusive flux density,  $j = (-D\nabla c) \cdot \mathbf{n}_s$ , in the unit direction  $\mathbf{n}_s$  orthogonal to the surface, is proportional to the concentration at this point. The proportionality coefficient,  $\kappa(\mathbf{s})$ , is called the reactivity (with units meter per second) and can in general depend on the point  $\mathbf{s}$ . In this formulation, the Robin boundary condition is essentially a mass conservation law at each point of the boundary: the net influx of molecules diffusing toward the boundary is equal to the amount of reacted molecules. The limit  $\kappa(\mathbf{s}) = 0$  (for all  $\mathbf{s}$ ) describes an inert surface without any reaction (i.e., the net diffusive flux at the surface is zero), whereas the limit  $\kappa(\mathbf{s}) = \kappa \rightarrow \infty$  reduces Eq. (3) to Eq. (2) and describes an immediate reaction upon the first encounter. The reactivity is thus related to the probability of reaction event at the encounter.<sup>12–14</sup> The Robin boundary condition with homogeneous

(constant) reactivity  $\kappa$  was often employed to describe many chemical and biochemical reactions and permeation processes,<sup>15–26</sup> to model stochastic gating,<sup>27–30</sup> or to approximate the effect of microscopic heterogeneities in a random distribution of reactive sites<sup>31–33</sup> (see a recent overview in Ref. 34).

In spite of its practical importance, diffusion-controlled reactions with heterogeneous surface reactivity  $\kappa(\mathbf{s})$  remain much less studied. In fact, when  $\kappa(\mathbf{s})$  is not constant, the eigenfunctions of the Laplace operator with the Robin boundary condition are not known explicitly even for simple domains (e.g., a ball) that prohibit using standard spectral decompositions,<sup>35,36</sup> on which most of the classical solutions are based. One needs therefore to resort to numerical tools such as finite element or finite difference methods for solving the diffusion equation or to Monte Carlo simulations. A notable exception is the case of piecewise constant reactivity that describes a target  $\Gamma$  (or multiple targets  $\Gamma_i$ ) with a constant reactivity  $\kappa$  on the otherwise inert surface. This situation corresponds to the Robin-Neumann (for  $0 < \kappa < \infty$ ) or Dirichlet-Neumann (for  $\kappa = \infty$ ) mixed boundary conditions.<sup>37,38</sup> The Dirichlet-Neumann boundary value problem has been particularly well studied for the Poisson and Laplace equations determining the mean first-passage time to a small target and the reaction rate, respectively (see overviews in Refs. 39–41 and the references therein). On the one hand, matched asymptotic analysis, dual series technique, and conformal mapping were applied to establish the behavior of the mean first-passage time in both two- and three-dimensional domains.<sup>42–50</sup> On the other hand, homogenization techniques were used to substitute piecewise constant reactivity  $\kappa(\mathbf{s})$  by an effective homogeneous reactivity.<sup>31–33,51–58</sup> More recent works investigated how the mean reaction time is affected by a finite lifetime of diffusing particles,<sup>59–61</sup> by partial reactivity and interactions,<sup>62,63</sup> by the target aspect ratio,<sup>64</sup> by reversible target-binding kinetics<sup>65,66</sup> and surface-mediated diffusion,<sup>67–70</sup> by heterogeneous diffusivity,<sup>71</sup> and by rapid rearrangements of the medium.<sup>72–74</sup> Some of the related effects onto the whole distribution of reaction times were analyzed.<sup>75–80</sup> However, the current understanding of diffusion-controlled reactions on catalytic surfaces with continuously varying heterogeneous reactivity remains episodic.

In this paper, we propose a mathematical description of diffusion-controlled reactions on catalytic surfaces, in which chemical kinetics, characterized by heterogeneous surface reactivity  $\kappa(\mathbf{s})$ , is disentangled from the first-passage diffusive steps. In Sec. II, we express the propagator of the sophisticated diffusion-reaction process with multiple reflections on a partially reactive surface in terms of a much simpler Dirichlet propagator toward a homogeneous perfectly reactive surface with the Dirichlet boundary condition. Chemical kinetics is incorporated via a matrix representation of the heterogeneous surface reactivity in the eigenbasis of the Dirichlet-to-Neumann operator, which is also tightly related to the Dirichlet propagator. From the propagator, we deduce other important characteristics of diffusion-controlled reactions such as the survival probability, the distribution of reaction times, and the reaction rate. This formalism provides a general description of such processes and brings conceptually new tools for its investigation. In Sec. III, this spectral approach is applied to an important example of a spherical surface for which the Dirichlet propagator and the Dirichlet-to-Neumann operator are known explicitly. We study both the interior and exterior problems that may describe either an escape from a ball

or hitting its surface from outside. Semianalytical solutions for the probability density of reaction times and for the reaction rate are derived. In Sec. IV, we discuss the advantages and limitations of the spectral approach, its possible extensions, and further applications, in particular, for analytical and numerical studies of mixed boundary value problems. Technical derivations are reported in Appendixes A–E.

## II. GENERAL SPECTRAL DESCRIPTION

We consider a molecule diffusing with the diffusion coefficient  $D$  in a Euclidean domain  $\Omega \subset \mathbb{R}^d$  toward a partially reactive catalytic boundary  $\partial\Omega$  characterized by a prescribed heterogeneous (space-dependent) reactivity  $0 \leq \kappa(\mathbf{s}) < \infty$ . Once the molecule hits the boundary at some point  $\mathbf{s}$ , it may either react or be reflected back to resume its diffusion until the next encounter and so on. The reaction probability at each encounter is characterized by the reactivity  $\kappa(\mathbf{s})$  at the encounter point. In this way, the molecule performs multiple diffusive excursions in the bulk until reaction occurs. The finite reactivity results therefore in a very sophisticated diffusive dynamics near the catalytic surface, which is much more intricate than just the first arrival to a homogeneous perfectly reactive surface. A probabilistic construction of this diffusive process (called partially reflected Brownian motion) was discussed in Refs. 13, 14, and 81–85 (see an overview in Ref. 34).

Without dwelling on the probabilistic aspects of the problem, we aim at characterizing such diffusion-reaction processes via the propagator  $G(\mathbf{x}, t|\mathbf{x}_0)$  (also known as heat kernel or Green's function). This is the probability density for a molecule that has not reacted until time  $t$  on the partially reactive boundary  $\partial\Omega$ , to be in a vicinity of a point  $\mathbf{x}$  at time  $t$ , given that it was started at a point  $\mathbf{x}_0$  at time 0. For any fixed starting point  $\mathbf{x}_0 \in \overline{\Omega} = \Omega \cup \partial\Omega$ , the propagator satisfies the following boundary value problem:

$$\frac{\partial G(\mathbf{x}, t|\mathbf{x}_0)}{\partial t} - D\Delta G(\mathbf{x}, t|\mathbf{x}_0) = 0 \quad (\mathbf{x} \in \Omega), \quad (4a)$$

$$G(\mathbf{x}, t = 0|\mathbf{x}_0) = \delta(\mathbf{x} - \mathbf{x}_0), \quad (4b)$$

$$\left(D\frac{\partial}{\partial \mathbf{n}_x} + \kappa(\mathbf{x})\right)G(\mathbf{x}, t|\mathbf{x}_0) = 0 \quad (\mathbf{x} \in \partial\Omega), \quad (4c)$$

where  $\delta(\mathbf{x} - \mathbf{x}_0)$  is the Dirac distribution, and the Laplace operator  $\Delta$  acts on  $\mathbf{x}$ . If the domain  $\Omega$  is unbounded, these equations are completed by the regularity condition at infinity:  $G(\mathbf{x}, t|\mathbf{x}_0) \rightarrow 0$  as  $|\mathbf{x}| \rightarrow \infty$ . To avoid technicalities, we assume that the boundary  $\partial\Omega$  is smooth. The following discussion extends our former results<sup>14,34,83,86</sup> to heterogeneous reactivity and time-dependent diffusion equation.

We consider the Laplace-transformed propagator,

$$\tilde{G}(\mathbf{x}, p|\mathbf{x}_0) = \int_0^\infty dt e^{-pt} G(\mathbf{x}, t|\mathbf{x}_0), \quad (5)$$

which satisfies the modified Helmholtz equation for each fixed  $\mathbf{x}_0 \in \overline{\Omega}$ ,

$$(p - D\Delta)\tilde{G}(\mathbf{x}, p|\mathbf{x}_0) = \delta(\mathbf{x} - \mathbf{x}_0) \quad (\mathbf{x} \in \Omega), \quad (6a)$$

$$\left(D\frac{\partial}{\partial \mathbf{n}_x} + \kappa(\mathbf{x})\right)\tilde{G}(\mathbf{x}, p|\mathbf{x}_0) = 0 \quad (\mathbf{x} \in \partial\Omega) \quad (6b)$$

(tilde will denote Laplace-transformed quantities).

Our goal is to express the propagator  $\tilde{G}(\mathbf{x}, p|\mathbf{x}_0)$  describing diffusion toward heterogeneous partially reactive surface  $\partial\Omega$  in terms of the much simpler Dirichlet propagator  $\tilde{G}_0(\mathbf{x}, p|\mathbf{x}_0)$  that characterizes diffusion toward the *homogeneous perfectly* reactive surface and satisfies for each fixed  $\mathbf{x}_0 \in \Omega$ ,

$$(p - D\Delta)\tilde{G}_0(\mathbf{x}, p|\mathbf{x}_0) = \delta(\mathbf{x} - \mathbf{x}_0) \quad (\mathbf{x} \in \Omega), \quad (7a)$$

$$\tilde{G}_0(\mathbf{x}, p|\mathbf{x}_0) = 0 \quad (\mathbf{x} \in \partial\Omega). \quad (7b)$$

Due to the linearity of the problem (6), one can search its solution in the form

$$\tilde{G}(\mathbf{x}, p|\mathbf{x}_0) = \tilde{G}_0(\mathbf{x}, p|\mathbf{x}_0) + \tilde{g}(\mathbf{x}, p|\mathbf{x}_0), \quad (8)$$

where the unknown regular part  $\tilde{g}(\mathbf{x}, p|\mathbf{x}_0)$  satisfies

$$(p - D\Delta)\tilde{g}(\mathbf{x}, p|\mathbf{x}_0) = 0 \quad (\mathbf{x} \in \Omega), \quad (9a)$$

$$\left(D\frac{\partial}{\partial \mathbf{n}_x} + \kappa(\mathbf{x})\right)\tilde{g}(\mathbf{x}, p|\mathbf{x}_0) = \tilde{j}_0(\mathbf{x}, p|\mathbf{x}_0) \quad (\mathbf{x} \in \partial\Omega), \quad (9b)$$

where

$$\tilde{j}_0(\mathbf{s}, p|\mathbf{x}_0) = -D\left(\frac{\partial}{\partial \mathbf{n}_x}\tilde{G}_0(\mathbf{x}, p|\mathbf{x}_0)\right)\Big|_{\mathbf{x}=\mathbf{s}} \quad (\mathbf{s} \in \partial\Omega) \quad (10)$$

is the Laplace transform of the diffusive flux density  $j_0(\mathbf{s}, t|\mathbf{x}_0)$  at time  $t$  in a point  $\mathbf{s}$  of the homogeneous perfectly reactive surface (i.e., the probability density of the first arrival in a vicinity of  $\mathbf{s}$  at time  $t$  after starting from  $\mathbf{x}_0$  at time 0).

### A. Dirichlet-to-Neumann operator

The solution of the boundary value problem (9) can be obtained with the help of the *Dirichlet-to-Neumann operator*  $\mathcal{M}_p$  (also known as the Poincaré-Steklov operator).<sup>87–89</sup> This is a pseudodifferential self-adjoint operator that associates to a function  $\tilde{f}$  on the boundary  $\partial\Omega$  another function on that boundary,

$$[\mathcal{M}_p\tilde{f}](\mathbf{s}) = \left(\frac{\partial \tilde{u}(\mathbf{x}, p)}{\partial \mathbf{n}}\right)\Big|_{\mathbf{x}=\mathbf{s}} \quad (\mathbf{s} \in \partial\Omega), \quad (11)$$

where  $\tilde{u}(\mathbf{x}, p)$  is the solution of the Dirichlet boundary value problem,

$$(p - D\Delta)\tilde{u}(\mathbf{x}, p) = 0 \quad (\mathbf{x} \in \Omega), \quad (12a)$$

$$\tilde{u}(\mathbf{x}, p) = \tilde{f}(\mathbf{x}, p) \quad (\mathbf{x} \in \partial\Omega) \quad (12b)$$

(here we skip the usual regularity assumptions on  $\partial\Omega$ , as well as the explicit description of the functional spaces involved in the rigorous definition of  $\mathcal{M}_p$ , see Ref. 87–93 for details). For instance, if  $\tilde{f}$  is understood as a source of molecules on the boundary  $\partial\Omega$  emitted into the reactive bulk, then the operator  $\mathcal{M}_p$  gives their flux density on that boundary. Note that there is a family of operators parameterized by  $p$  (or  $p/D$ ).

As the solution of the Dirichlet boundary value problem (12) can be expressed in terms of the Dirichlet propagator  $\tilde{G}_0(\mathbf{x}, p|\mathbf{x}_0)$  in a standard way,

$$\tilde{u}(\mathbf{x}, p) = \int_{\partial\Omega} ds' \tilde{j}_0(\mathbf{s}', p|\mathbf{x}) \tilde{f}(\mathbf{s}', p),$$

the Dirichlet-to-Neumann propagator acts formally as

$$[\mathcal{M}_p\tilde{f}](\mathbf{s}) = \left(\frac{\partial}{\partial \mathbf{n}} \int_{\partial\Omega} ds' \tilde{j}_0(\mathbf{s}', p|\mathbf{x}) \tilde{f}(\mathbf{s}', p)\right)\Big|_{\mathbf{x}=\mathbf{s}}, \quad (13)$$

and thus, the Dirichlet propagator determines the Dirichlet-to-Neumann operator  $\mathcal{M}_p$ . In Appendix A, it is also shown how the Dirichlet propagator can be constructed from the operator  $\mathcal{M}_p$ . As a consequence, these two important objects are equivalent. As discussed in Ref. 14 for the case  $p = 0$ , the Dirichlet-to-Neumann operator can also be interpreted as the continuous limit of the Brownian self-transport operator  $Q_{ij}$  which was introduced in Refs. 12 and 13 to describe the probability of the first arrival to a site  $j$  of a discretized boundary from another site  $i$  via bulk diffusion.

Let us now return to the boundary value problem (9). Suppose that we have solved this problem and found that the solution  $\tilde{g}(\mathbf{x}, p|\mathbf{x}_0)$  on the boundary  $\partial\Omega$  is equal to some function  $\tilde{f}(\mathbf{x}, p)$ . Applying then the Dirichlet-to-Neumann operator to  $\tilde{f}(\mathbf{x}, p)$ , one can express the normal derivative of  $\tilde{g}(\mathbf{x}, p|\mathbf{x}_0)$ , from which

$$\tilde{g}(\mathbf{s}, p|\mathbf{x}_0) = (\mathcal{M}_p + \mathcal{K})^{-1} \frac{\tilde{j}_0(\mathbf{s}, p|\mathbf{x}_0)}{D} \quad (\mathbf{s} \in \partial\Omega), \quad (14)$$

where  $\mathcal{K}$  is the operator of multiplication by  $\kappa(\mathbf{s})/D$ . Knowing the restriction of  $\tilde{g}(\mathbf{x}, p|\mathbf{x}_0)$  on the boundary  $\partial\Omega$ , one can reconstruct this function in the bulk  $\Omega$  as the solution of the corresponding Dirichlet problem,

$$\tilde{g}(\mathbf{x}, p|\mathbf{x}_0) = \int_{\partial\Omega} ds \tilde{j}_0(\mathbf{s}, p|\mathbf{x}) \tilde{g}(\mathbf{s}, p|\mathbf{x}_0). \quad (15)$$

In this way, we obtain the desired representation of the propagator in the form of a scalar product between two functions on the boundary

$$\tilde{G}(\mathbf{x}, p|\mathbf{x}_0) = \tilde{G}_0(\mathbf{x}, p|\mathbf{x}_0) + \frac{1}{D} (\tilde{j}_0(\cdot, p|\mathbf{x}) \cdot (\mathcal{M}_p + \mathcal{K})^{-1} \tilde{j}_0(\cdot, p|\mathbf{x}_0))_{L_2(\partial\Omega)}, \quad (16)$$

where  $(f \cdot g)_{L_2(\partial\Omega)}$  denotes the standard scalar product between functions  $f$  and  $g$  on the boundary  $\partial\Omega$ ,

$$(f \cdot g)_{L_2(\partial\Omega)} = \int_{\partial\Omega} ds f(\mathbf{s}) g^*(\mathbf{s}),$$

and the asterisk denotes the complex conjugate. Equation (16) is the first main result of the paper. Remarkably, all the “ingredients” of this formula correspond to the Dirichlet condition on a homogeneous perfectly reactive boundary, except for the operator  $\mathcal{K}$  that keeps track of heterogeneous surface reactivity  $\kappa(\mathbf{s})$ . We outline that Eq. (16) does not solve the original problem but reduces it to a much simpler and more thoroughly studied Dirichlet problem.

When  $\mathbf{x}$  and  $\mathbf{x}_0$  are boundary points, the identity  $\tilde{j}_0(\mathbf{s}, p|\mathbf{s}_0) = \delta(\mathbf{s} - \mathbf{s}_0)$  reduces Eq. (16) to

$$D\tilde{G}(\mathbf{s}, p|\mathbf{s}_0) = (\mathcal{M}_p + \mathcal{K})^{-1}\delta(\mathbf{s} - \mathbf{s}_0) \quad (\mathbf{s}_0, \mathbf{s} \in \partial\Omega), \quad (17)$$

i.e.,  $D\tilde{G}(\mathbf{s}, p|\mathbf{s}_0)$  is the kernel of the operator  $\mathcal{M}_p + \mathcal{K}$ . One can therefore rewrite Eq. (16) as

$$\begin{aligned} \tilde{G}(\mathbf{x}, p|\mathbf{x}_0) &= \tilde{G}_0(\mathbf{x}, p|\mathbf{x}_0) + \int_{\partial\Omega} d\mathbf{s}_1 \int_{\partial\Omega} d\mathbf{s}_2 \tilde{j}_0(\mathbf{s}_1, p|\mathbf{x}_0) \\ &\quad \times \tilde{G}(\mathbf{s}_2, p|\mathbf{s}_1) \tilde{j}_0(\mathbf{s}_2, p|\mathbf{x}), \end{aligned} \quad (18)$$

while its inverse Laplace transform reads

$$\begin{aligned} G(\mathbf{x}, t|\mathbf{x}_0) &= G_0(\mathbf{x}, t|\mathbf{x}_0) + \int_{\partial\Omega} d\mathbf{s}_1 \int_{\partial\Omega} d\mathbf{s}_2 \int_0^t dt_1 \int_{t_1}^t dt_2 \\ &\quad \times j_0(\mathbf{s}_1, t_1|\mathbf{x}_0) G(\mathbf{s}_2, t_2 - t_1|\mathbf{s}_1) j_0(\mathbf{s}_2, t - t_2|\mathbf{x}). \end{aligned} \quad (19)$$

This relation expresses the propagator  $G(\mathbf{x}, t|\mathbf{x}_0)$  in the whole domain in terms of the propagator  $G(\mathbf{s}_2, t|\mathbf{s}_1)$  from one boundary point to another boundary point via bulk diffusion. The first term represents the contribution of direct trajectories from  $\mathbf{x}_0$  to  $\mathbf{x}$  that do not touch the boundary  $\partial\Omega$ . The second term also has a simple probabilistic interpretation: a molecule reaches the boundary for the first time at  $t_1$ , performs partially reflected Brownian motion over time  $t_2 - t_1$  (with eventual failed attempts of reaction at each encounter with the surface), and diffuses to the bulk point  $\mathbf{x}$  during time  $t - t_2$  without hitting the reactive surface.

When  $\mathbf{x} = \mathbf{s}$  is a boundary point, one has  $G_0(\mathbf{s}, t|\mathbf{x}_0) = 0$  and  $j_0(\mathbf{s}_2, t - t_2|\mathbf{s}) = \delta(\mathbf{s} - \mathbf{s}_2)\delta(t - t_2)$  so that the integrals over  $\mathbf{s}_2$  and  $t_2$  are removed, reducing Eq. (19) to

$$G(\mathbf{s}, t|\mathbf{x}_0) = \int_{\partial\Omega} d\mathbf{s}_1 \int_0^t dt_1 j_0(\mathbf{s}_1, t_1|\mathbf{x}_0) G(\mathbf{s}, t - t_1|\mathbf{s}_1). \quad (20)$$

This relation justifies the qualitative separation of the diffusion-reaction process into two steps: the first arrival step [described by  $j_0(\mathbf{s}_1, t_1|\mathbf{x}_0)$ ] and the reaction step [described by  $G(\mathbf{s}, t - t_1|\mathbf{s}_1)$ ]. We stress, however, that the reaction step involves the intricate diffusion process near the partially reactive catalytic surface. In addition to the new conceptual view onto partially reflected Brownian motion, the representations (19) and (20) can be helpful for a numerical computation of the propagator because only the boundary-to-boundary transport via  $G(\mathbf{s}_2, t|\mathbf{s}_1)$  needs to be determined. This kernel significantly extends the Brownian self-transport operator introduced in Ref. 12 and 13 (see below).

## B. Other common diffusion characteristics

The propagator  $G(\mathbf{x}, t|\mathbf{x}_0)$  determines many quantities often considered in the context of diffusion-controlled reactions such as the survival probability up to time  $t$ , the reaction time distribution, the distribution of reaction points (at which the reaction occurs), and the reaction rate. For instance, the diffusive flux density at a partially reactive point  $\mathbf{s} \in \partial\Omega$  is

$$j(\mathbf{s}, t|\mathbf{x}_0) = \left(-D \frac{\partial G(\mathbf{x}, t|\mathbf{x}_0)}{\partial \mathbf{n}_x}\right) \Big|_{\mathbf{x}=\mathbf{s}} = \kappa(\mathbf{s})G(\mathbf{s}, t|\mathbf{x}_0), \quad (21)$$

where we used the Robin boundary condition (4c). This is the joint probability density for the reaction time and the reaction point on the catalytic surface. The integral over  $\mathbf{s}$  yields the marginal probability density of reaction times,

$$H(t|\mathbf{x}_0) = \int_{\partial\Omega} d\mathbf{s} j(\mathbf{s}, t|\mathbf{x}_0) = \int_{\partial\Omega} d\mathbf{s} \kappa(\mathbf{s}) G(\mathbf{s}, t|\mathbf{x}_0), \quad (22)$$

whereas the integral over  $t$  gives the marginal probability density of reaction points,

$$\omega(\mathbf{s}|\mathbf{x}_0) = \int_0^\infty dt j(\mathbf{s}, t|\mathbf{x}_0) = \tilde{j}(\mathbf{s}, 0|\mathbf{x}_0) = \kappa(\mathbf{s})\tilde{G}(\mathbf{s}, 0|\mathbf{x}_0). \quad (23)$$

The latter was called the *spread harmonic measure density*.<sup>14,86,94,95</sup>

This is a natural extension of the harmonic measure density  $\tilde{j}_0(\mathbf{s}, 0|\mathbf{x}_0)$  that characterizes the first arrival onto the perfectly reactive surface.<sup>96–98</sup> As the probability density  $H(t|\mathbf{x}_0)$  can be interpreted as the probability flux onto the surface for a molecule started from  $\mathbf{x}_0$ , its integral with the initial concentration of molecules,  $c_0(\mathbf{x}_0)$ , yields the overall diffusive flux onto the surface, i.e., the reaction rate

$$J(t) = \int_{\Omega} d\mathbf{x}_0 c_0(\mathbf{x}_0) H(t|\mathbf{x}_0). \quad (24)$$

In turn, the integral of  $H(t|\mathbf{x}_0)$  gives the survival probability up to time  $t$ ,

$$S(t|\mathbf{x}_0) = 1 - \int_0^t dt' H(t'|\mathbf{x}_0), \quad (25)$$

while  $1 - S(t|\mathbf{x}_0)$  is the probability of reaction up to time  $t$ . All these quantities are expressed in terms of the propagator and thus determined from Eq. (16).

## C. Spectral decompositions

When the boundary  $\partial\Omega$  is bounded, the Dirichlet-to-Neumann operator  $\mathcal{M}_p$  has a discrete spectrum, with a set of non-negative eigenvalues  $\mu_n^{(p)}$  and  $L_2(\partial\Omega)$ -normalized eigenfunctions  $v_n^{(p)}$  forming a complete orthogonal basis in  $L_2(\partial\Omega)$ ,

$$\mathcal{M}_p v_n^{(p)}(\mathbf{s}) = \mu_n^{(p)} v_n^{(p)}(\mathbf{s}) \quad (n = 0, 1, \dots). \quad (26)$$

We emphasize that both  $\mu_n^{(p)}$  and  $v_n^{(p)}$  depend in general on  $p$  as a parameter. Expanding the scalar product in Eq. (16) over this basis, one gets

$$\begin{aligned} \tilde{G}(\mathbf{x}, p|\mathbf{x}_0) &= \tilde{G}_0(\mathbf{x}, p|\mathbf{x}_0) + \frac{1}{D} \sum_{n, n'=0}^\infty V_n^{(p)}(\mathbf{x}_0) \\ &\quad \times [(\mathbf{M} + \mathbf{K})^{-1}]_{n, n'} [V_{n'}^{(p)}(\mathbf{x})]^*, \end{aligned} \quad (27)$$

where

$$V_n^{(p)}(\mathbf{x}_0) = \int_{\partial\Omega} d\mathbf{s} \tilde{j}_0(\mathbf{s}, p|\mathbf{x}_0) v_n^{(p)}(\mathbf{s}) \quad (28)$$

is the projection of the Laplace-transformed flux density  $\tilde{j}_0(\mathbf{s}, p|\mathbf{x}_0)$  onto the eigenfunction  $v_n^{(p)}(\mathbf{s})$ , and

$$\mathbf{M}_{n,n'} = \delta_{nn'} \mu_n^{(p)}, \quad (29a)$$

$$\mathbf{K}_{n,n'} = \int_{\partial\Omega} d\mathbf{s} [v_n^{(p)}(\mathbf{s})]^* \frac{\kappa(\mathbf{s})}{D} v_{n'}^{(p)}(\mathbf{s}) \quad (29b)$$

are infinite-dimensional matrices that represent the Dirichlet-to-Neumann operator  $\mathcal{M}_p$  and the reactivity multiplication operator  $\mathcal{K}$  in the basis of eigenfunctions  $v_n^{(p)}(\mathbf{s})$ .

From the spectral representation (27) and Eq. (21), we deduce

$$\tilde{j}(\mathbf{s}, p|\mathbf{x}_0) = \sum_{n,n'=0}^{\infty} V_n^{(p)}(\mathbf{x}_0) [(\mathbf{M} + \mathbf{K})^{-1} \mathbf{K}]_{n,n'} [v_{n'}^{(p)}(\mathbf{s})]^*, \quad (30)$$

where we used the completeness of eigenfunctions  $v_n^{(p)}$  to represent  $\kappa(\mathbf{s})/D$  as multiplication by the matrix  $\mathbf{K}$ . According to Eqs. (22) and (23), the spectral decomposition (30) yields immediately

$$\omega(\mathbf{s}|\mathbf{x}_0) = \sum_{n,n'=0}^{\infty} V_n^{(0)}(\mathbf{x}_0) [(\mathbf{M} + \mathbf{K})^{-1} \mathbf{K}]_{n,n'}^{(p=0)} [v_{n'}^{(0)}(\mathbf{s})]^* \quad (31)$$

and

$$\tilde{H}(p|\mathbf{x}_0) = |\partial\Omega|^{1/2} \sum_{n=0}^{\infty} h_n^{(p)} V_n^{(p)}(\mathbf{x}_0), \quad (32)$$

where

$$h_n^{(p)} = |\partial\Omega|^{-1/2} \sum_{n'=0}^{\infty} [(\mathbf{M} + \mathbf{K})^{-1} \mathbf{K}]_{n,n'} \int_{\partial\Omega} d\mathbf{s} [v_{n'}^{(p)}(\mathbf{s})]^* \quad (33)$$

are dimensionless coefficients. In particular,  $\tilde{H}(0|\mathbf{x}_0)$  is the reaction probability (in Appendix B 1, we prove the expected identity  $\tilde{H}(0|\mathbf{x}_0) = 1$  for any bounded domain). According to Eq. (24), the Laplace-transformed reaction rate is then

$$\tilde{j}(p) = |\partial\Omega|^{1/2} \sum_{n,n'=0}^{\infty} h_n^{(p)} \int_{\Omega} d\mathbf{x}_0 V_n^{(p)}(\mathbf{x}_0) c_0(\mathbf{x}_0). \quad (34)$$

In Appendix B 2, we show how this expression can be further simplified in the case of the uniform initial concentration.

While we mainly focus on Laplace-transformed quantities, their representations in time domain can be obtained via Laplace transform inversion either analytically or numerically. For instance, the inversion in the case of bounded domains can be performed via the residue theorem by computing the poles  $\{p_n\} \subset \mathbb{C}$  of functions in Eqs. (27), (32), and (34), which are determined by the condition

$$\det(\mathbf{M} + \mathbf{K}) = 0. \quad (35)$$

In general, the spectral representation (27) is not simpler than Eq. (16) because all  $V_n^{(p)}$ ,  $\mathbf{M}$ , and  $\mathbf{K}$  depend on  $p$  as a parameter. However, in some domains, these “ingredients” can be

evaluated explicitly, providing a semianalytical form of the Laplace-transformed propagator and related quantities. We will illustrate this point in Sec. III for a spherical boundary.

#### D. Homogeneous partial reactivity

In the particular case of homogeneous reactivity,  $\kappa(\mathbf{s}) = \kappa$ , the operator  $\mathcal{K}$  is proportional to the identity operator, and Eq. (17) implies that  $D\tilde{G}(\mathbf{s}, p|\mathbf{s}_0)$  is the resolvent of the Dirichlet-to-Neumann operator  $\mathcal{M}_p$ . Moreover, as

$$\mathbf{K}_{n,n'} = \delta_{n,n'} \frac{\kappa}{D}, \quad (36)$$

Eq. (27) is reduced to

$$\tilde{G}_{\text{hom}}(\mathbf{x}, p|\mathbf{x}_0) = \tilde{G}_0(\mathbf{x}, p|\mathbf{x}_0) + \sum_{n=0}^{\infty} \frac{V_n^{(p)}(\mathbf{x}_0) [V_n^{(p)}(\mathbf{x})]^*}{D\mu_n^{(p)} + \kappa}. \quad (37)$$

In turn, the condition (35) on the poles is reduced to a set of decoupled equations

$$\mu_n^{(p)} + \frac{\kappa}{D} = 0, \quad (38)$$

showing how the eigenvalues  $\mu_n^{(p)}$  of the Dirichlet-to-Neumann operator determine the eigenvalues of the associated Laplace operator with the Robin boundary condition.

The other spectral decompositions are also simplified,

$$\omega_{\text{hom}}(\mathbf{s}|\mathbf{x}_0) = \sum_{n=0}^{\infty} \frac{V_n^{(0)}(\mathbf{x}_0) [v_n^{(0)}(\mathbf{s})]^*}{\frac{D}{\kappa} \mu_n^{(0)} + 1}, \quad (39)$$

$$\tilde{H}_{\text{hom}}(p|\mathbf{x}_0) = \sum_{n=0}^{\infty} \frac{V_n^{(p)}(\mathbf{x}_0) \int_{\partial\Omega} d\mathbf{s} [v_n^{(p)}(\mathbf{s})]^*}{\frac{D}{\kappa} \mu_n^{(p)} + 1}, \quad (40)$$

and

$$\tilde{j}_{\text{hom}}(p) = \frac{c_0 D}{p} \sum_{n=0}^{\infty} \frac{\mu_n^{(p)}}{\frac{D}{\kappa} \mu_n^{(p)} + 1} \left| \int_{\partial\Omega} d\mathbf{s} v_n^{(p)}(\mathbf{s}) \right|^2, \quad (41)$$

where we used Eq. (B8) for the uniform initial concentration  $c_0$ . In the limit  $p \rightarrow 0$ , one recovers the formula for the total steady-state flux derived in Ref. 86; Eq. (41) is therefore its extension to time-dependent diffusion. To our knowledge, Eqs. (37) and (39)–(41) that are fully explicit in terms of the eigenvalues and eigenfunctions of the Dirichlet-to-Neumann operator have not been earlier reported. While alternative spectral decompositions on the Laplace operator eigenfunctions are known for bounded domains, there is no such expansion for unbounded domains, for which the spectrum of the Laplace operator is continuous. The spectral formulation in terms of the eigenfunctions of the Dirichlet-to-Neumann operator opens therefore new perspectives for studying diffusion-reaction processes even for homogeneous reactivity. From the numerical point of view, the computation of the eigenfunctions of the Dirichlet-to-Neumann operator could in general be simpler due to the reduced dimensionality:  $v_n^{(p)}$  need to be found on the boundary  $\partial\Omega$ , whereas the Laplace operator eigenfunctions have to be computed in the whole domain  $\Omega$ .

### III. SPHERICAL BOUNDARY

In this section, we apply our general spectral decompositions to the case of a spherical boundary for which the eigenbasis of the Dirichlet-to-Neumann operator is known explicitly. We first discuss in Sec. III A the interior problem that may describe, for instance, an escape from a ball, and then in Sec. III B, we dwell on the exterior problem and related chemical kinetics. In both cases, we provide semianalytical solutions for an arbitrary heterogeneous surface reactivity and then discuss some particular cases, e.g., a piecewise constant reactivity that describes single or multiple reactive targets on the otherwise inert boundary. Technical details of calculations are reported in [Appendices C–E](#).

#### A. Diffusion inside a ball

We consider a diffusion-reaction process inside a ball of radius  $R$ ,  $\Omega = \{\mathbf{x} \in \mathbb{R}^3 : |\mathbf{x}| < R\}$ , with a prescribed heterogeneous surface reactivity  $\kappa(\mathbf{s})$ . For this domain, the eigenvalues and eigenfunctions of the Dirichlet-to-Neumann operator are known explicitly ([Appendix C](#)),

$$\mu_{nm}^{(p)} = \sqrt{p/D} \frac{i'_n(R\sqrt{p/D})}{i_n(R\sqrt{p/D})}, \quad (42a)$$

$$v_{nm}(\theta, \phi) = \frac{1}{R} Y_{nm}(\theta, \phi), \quad (42b)$$

where  $i_n(z)$  are the modified spherical Bessel functions of the first kind,  $Y_{nm}(\theta, \phi)$  are the  $L_2(\partial\Omega)$ -normalized spherical harmonics, the prime denotes the derivative with respect to the argument, and we used spherical coordinates  $(r, \theta, \phi)$ . Here, we employ the double index  $nm$  to enumerate the eigenfunctions as well as the elements of the matrices  $\mathbf{M}$  and  $\mathbf{K}$ . Note that the eigenvalues do not depend on the index  $m$  and thus are of multiplicity  $2n + 1$ , whereas the eigenfunctions  $v_{nm}$  do not depend on the parameter  $p$ . The eigenvalues determine the matrix  $\mathbf{M}$  via Eq. (29a), while Eq. (29b) for the matrix  $\mathbf{K}$  reads

$$\mathbf{K}_{nm,n'm'} = \int_0^\pi d\theta \sin\theta \int_0^{2\pi} d\phi \frac{\kappa(\theta, \phi)}{D} Y_{nm}^*(\theta, \phi) Y_{n'm'}(\theta, \phi). \quad (43)$$

The calculation of the matrix  $\mathbf{K}$  in Eq. (43) involves integrals with spherical harmonics that can often be evaluated explicitly. In [Appendix D](#), we discuss several common situations such as a single target, multiple nonoverlapping targets of circular shape or multiple latitudinal stripes, axisymmetric reactivity  $\kappa(\theta, \phi) = \kappa(\theta)$ , and an expansion of  $\kappa(\theta, \phi)$  into a finite sum over spherical harmonics. Although cumbersome, resulting expressions for the matrix  $\mathbf{K}$  are exact and do not involve numerical quadrature, providing a powerful computational tool. These cases can further be extended by adding another concentric surface with reflecting or absorbing boundary condition. This modification does not change the matrix  $\mathbf{K}$  but affects the eigenvalues of the Dirichlet-to-Neumann operator and thus the matrix  $\mathbf{M}$ .

As the Dirichlet propagator is also known, we deduce in [Appendix C](#)

$$V_{nm}^{(p)}(\mathbf{x}_0) = R^{-1} \frac{i_n(r_0\sqrt{p/D})}{i_n(R\sqrt{p/D})} Y_{nm}(\theta_0, \phi_0), \quad (44)$$

so that the Laplace-transformed propagator  $\tilde{G}(\mathbf{x}, p|\mathbf{x}_0)$  is determined in the semianalytical form (27), in which the dependence on points  $\mathbf{x}_0$  and  $\mathbf{x}$  is fully explicit, whereas the computation of the coefficients involves a numerical inversion of the matrix  $\mathbf{M} + \mathbf{K}$ . Similarly, one gets semianalytical expressions for the Laplace-transformed probability density of reaction times and the spread harmonic measure (see [Appendix C](#)), e.g.,

$$\tilde{H}(p|\mathbf{x}_0) = \sqrt{4\pi} \sum_{n=0}^{\infty} \sum_{m=-n}^n h_{nm}^{(p)} \frac{i_n(r_0\sqrt{p/D})}{i_n(R\sqrt{p/D})} Y_{nm}(\theta_0, \phi_0), \quad (45)$$

with

$$h_{nm}^{(p)} = [(\mathbf{M} + \mathbf{K})^{-1}\mathbf{K}]_{nm,00}. \quad (46)$$

The Laplace-transformed survival probability is related to  $\tilde{H}(p|\mathbf{x}_0)$  as

$$\tilde{S}(p|\mathbf{x}_0) = \frac{1 - \tilde{H}(p|\mathbf{x}_0)}{p}, \quad (47)$$

whereas the mean reaction time is simply  $\tilde{S}(0|\mathbf{x}_0)$ .

[Figures 1\(b\)](#) and [1\(c\)](#) illustrate how the mean reaction time depends on the starting point  $\mathbf{x}_0$  for a particular choice of a continuously varying heterogeneous surface reactivity  $\kappa(\theta, \phi)$  shown in [Fig. 1\(a\)](#). When the mean reactivity is weak [ $\kappa R/D = 1$ , [Fig. 1\(b\)](#)],  $\tilde{S}(0|\mathbf{x}_0)$  is close to the mean reaction time  $\tilde{S}_{\text{hom}}(0|\mathbf{x}_0) = R/(3\kappa)$  corresponding to homogeneous reactivity  $\kappa$ . Here, multiple failed reaction attempts homogenize the mean reaction time, even though the starting point  $\mathbf{x}_0$  lies on the catalytic boundary. In turn, significant deviations from  $R/(3\kappa)$  are observed at a larger mean reactivity  $\kappa R/D = 10$ . In this case, the mean reactivity is not representative and heterogeneities start to be more and more important.

#### B. Diffusion outside a ball

For diffusion in the unbounded domain  $\Omega = \{\mathbf{x} \in \mathbb{R}^3 : |\mathbf{x}| > R\}$  outside the spherical surface of radius  $R$ , the eigenfunctions of the Dirichlet-to-Neumann operator are still given by Eq. (42b) so that the matrix  $\mathbf{K}$  remains unchanged. In turn, the matrix  $\mathbf{M}$  is now determined by the eigenvalues

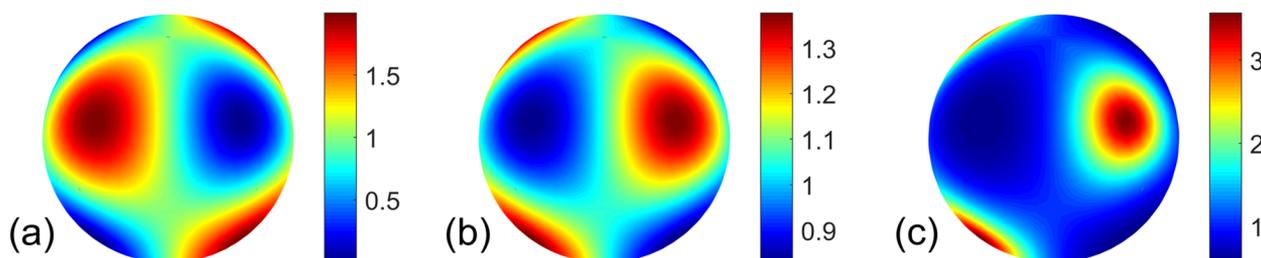
$$\mu_{nm}^{(p)} = -\sqrt{p/D} \frac{k'_n(R\sqrt{p/D})}{k_n(R\sqrt{p/D})}, \quad (48)$$

where  $k_n(z)$  are the modified spherical Bessel function of the second kind. From the known Dirichlet propagator, we compute in [Appendix E](#)

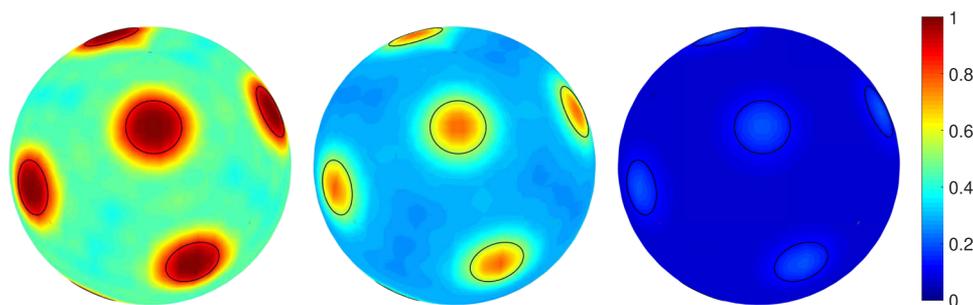
$$V_{nm}^{(p)}(\mathbf{x}_0) = R^{-1} \frac{k_n(r_0\sqrt{p/D})}{k_n(R\sqrt{p/D})} Y_{nm}(\theta_0, \phi_0). \quad (49)$$

As a consequence, our spectral decomposition (27) fully determines the Laplace-transformed propagator  $\tilde{G}(\mathbf{x}, p|\mathbf{x}_0)$ . The Laplace-transformed probability density of reaction times is again obtained from Eq. (32),

$$\tilde{H}(p|\mathbf{x}_0) = \sqrt{4\pi} \sum_{n=0}^{\infty} \sum_{m=-n}^n h_{nm}^{(p)} \frac{k_n(r_0\sqrt{p/D})}{k_n(R\sqrt{p/D})} Y_{nm}(\theta_0, \phi_0), \quad (50)$$



**FIG. 1.** Diffusion inside a ball of radius  $R$ . (a) Heterogeneous surface reactivity  $\kappa(\theta, \phi) = \kappa(1 + cY_{2,3}(\theta, \phi) + cY_{-2,3}(\theta, \phi))$ , with  $\kappa R/D = 1$  and  $c = 1.2728$  [this value ensures the positivity of  $\kappa(\theta, \phi)$ ]. [(b) and (c)] Mean reaction time  $\bar{S}(0|\mathbf{x}_0)$ , rescaled by  $\bar{S}_{\text{hom}}(0|\mathbf{x}_0) = R/(3\kappa)$ , as a function of the starting point  $\mathbf{x}_0 = (r_0, \theta_0, \phi_0)$  with  $r_0 = R$ , for such a reactivity  $\kappa(\theta, \phi)$ , with  $\kappa R/D = 1$  (b) and  $\kappa R/D = 10$  (c). The matrix  $\mathbf{K}$  was computed with the truncation order  $n_{\text{max}} = 20$  as described in Appendix D 1.



**FIG. 2.** Diffusion outside a ball of radius  $R$ . The reaction probability  $\bar{H}(0|\mathbf{x}_0)$  on the spherical surface of radius  $R$  as a function of the starting point  $\mathbf{x}_0 = (r_0, \theta_0, \phi_0)$  with  $r_0 = R$ . Ten circular targets of angular size  $\varepsilon = 0.2$  (shown by thin black circles) are evenly distributed on the surface, with three values of reactivity:  $\kappa R/D = 100$  (left),  $\kappa R/D = 10$  (middle), and  $\kappa R/D = 1$  (right). The matrix  $\mathbf{K}$  was computed with the truncation order  $n_{\text{max}} = 20$  as described in Appendix D 4.

with  $h_{nm}^{(p)}$  given by Eq. (46), in which the matrices  $\mathbf{K}$  and  $\mathbf{M}$  are determined by Eqs. (43) and (48). The Laplace-transformed survival probability is still given by Eq. (47), while the mean reaction time is infinite.

According to Eq. (34), the Laplace-transformed reaction rate can be obtained by integrating  $\bar{H}(p|\mathbf{x}_0)$  with the initial concentration of molecules, which for the uniform concentration,  $c_0(\mathbf{x}_0) = c_0$ , yields

$$\bar{J}(p) = 4\pi DRc_0 \frac{R\mu_{00}^{(p)} h_{00}^{(p)}}{p} \quad (51)$$

(note that the same formula with the appropriate matrix  $\mathbf{M}$  holds for diffusion inside the ball). The prefactor  $4\pi DRc_0$  is the Smoluchowski rate to a homogeneous perfectly reactive ball of radius  $R$ , whereas the second factor describes the effect of heterogeneous surface reactivity. In the limit  $p \rightarrow 0$ , this expression yields the steady-state reaction rate

$$J(\infty) = 4\pi DRc_0 h_{00}^{(0)}. \quad (52)$$

For the homogeneous reactivity, our formulas are reduced to that of Collins and Kimball,<sup>11</sup> see Appendix E, with

$$h_{00}^{(0)} = \frac{1}{1 + D/(\kappa R)}. \quad (53)$$

Figure 2 shows the reaction probability  $\bar{H}(0|\mathbf{x}_0)$  from Eq. (50) [see also Eq. (E8)] on the inert spherical surface covered by ten evenly distributed circular partially reactive targets of angular size  $\varepsilon = 0.2$ . Even though the starting point  $\mathbf{x}_0$  lies on the surface ( $r_0 = R$ ),

the reaction probability is not equal to 1 due to the partial reactivity and eventual failed attempts to react. When the reactivity is large ( $\kappa R/D = 100$ , left panel), the reaction probability is close to 1 when the molecule starts at any target and drops to 0.4 in between two targets. At intermediate reactivity ( $\kappa R/D = 10$ , middle panel), the reaction probability is expectedly reduced, as more frequent failed reaction attempts give more chances for the molecule to escape to infinity. This effect is further enhanced at even smaller reactivity  $\kappa R/D = 1$  (right panel). In this regime, there is almost no distinction between weakly reactive targets and the remaining inert surface.

#### IV. DISCUSSION

We developed a general mathematical description of diffusion-controlled reactions on catalytic surfaces with heterogeneous reactivity  $\kappa(\mathbf{s})$ . We showed how the propagator of the diffusion equation with the Robin boundary condition can be expressed in terms of the Dirichlet propagator for a homogeneous perfectly reactive surface. The latter involves a much simpler and more studied Dirichlet boundary condition and thus describes exclusively the first-passage events to the boundary that are independent of the surface reactivity. In other words, the diffusive exploration of the bulk is disentangled from the chemical kinetics on the boundary. As a consequence, the Dirichlet propagator needs to be computed only once for a given geometric configuration, offering a powerful theoretical and numerical tool for investigating the effects of heterogeneous surface reactivity.

Numerical or eventually analytical inversion of the Laplace transform allows one to recover the propagator in time domain. Moreover, the Laplace-transformed propagator itself is important as it describes the steady-state diffusion of molecules which may spontaneously disappear in the bulk with the rate  $p$ .<sup>59–61</sup> Such “mortal walkers” may represent radioactive nuclei, photobleaching fluorophores, molecules in an excited state, metastable complexes, spermatozoa, and other particles subject to spontaneous decay, disintegration, ground state recovery, or death.

When the boundary of the domain is bounded, our general representation yields the spectral decompositions of the propagator and of other important quantities such as the survival probability, the probability density of reaction times, the spread harmonic measure, and the reaction rate. These decompositions involve the eigenvalues and eigenfunctions of the Dirichlet-to-Neumann operator, as well as the associated basis elements of the surface reactivity  $\kappa(\mathbf{s})$ . This spectral description brings new insights onto imperfect diffusion-controlled reactions and creates a mathematical basis for formulating and solving optimization and inverse problems on surface reactivity  $\kappa(\mathbf{s})$  (see, e.g., Refs. 99 and 100).

We highlight a similarity between the representation of surface reactivity in the eigenbasis of the Dirichlet-to-Neumann operator and the representation of the bulk reactivity in the Laplace operator eigenbasis studied in Refs. 99. Such matrix representations have proved to be efficient for solving numerically the Bloch-Torrey equation that describes diffusion magnetic resonance imaging (see Refs. 102–104 and the references therein). Note that the surface reactivity could also be incorporated via the Laplacian eigenbasis by introducing an infinitely thin reactive boundary layer as discussed in Refs. 83 and 85. However, the eigenbasis of the Dirichlet-to-Neumann operator acting on the boundary seems to be more natural for dealing with surface reactivity. Most importantly, our spectral description is also valid for exterior problems, for which the spectrum of the Laplace operator is continuous and thus not suitable for such representations; in turn, the spectrum of the Dirichlet-to-Neumann operator on a bounded boundary remains discrete.

We applied the spectral approach to an important example of a spherical surface, for which both the Dirichlet propagator and the eigenbasis of the Dirichlet-to-Neumann operator are known explicitly. In this case, the Robin propagator and the related quantities (such as the probability density of reaction times) are obtained in a semianalytical form, in which the dependence on the starting and arrival points is fully explicit, whereas the coefficients need to be computed by truncating and inverting an explicitly known matrix. However, the proposed approach is not limited to the spherical boundary. For instance, the case of a hyperplane was partly studied in Refs. 34 and 101; apart from straightforward extensions to disks and cylinders, one can consider more complicated catalytic surfaces formed by multiple nonoverlapping spheres, for which the Dirichlet propagator in the steady-state regime was recently investigated in Ref. 26. In general, the eigenbasis of the Dirichlet-to-Neumann operator  $\mathcal{M}_p$  can be constructed numerically; since  $\mathcal{M}_p$  is independent of the surface reactivity, this construction has to be performed only once for a given catalytic surface.

As mentioned earlier, most former studies focused on the mixed Dirichlet-Neumann boundary value problem describing perfectly reactive targets on an otherwise inert boundary. In spite of its oversimplified character from the chemical point of view, this

problem may look simpler from the mathematical point of view. For instance, as both Dirichlet and Neumann boundary conditions are conformally invariant, conformal mapping results in a universal integral representation of the mean first-passage time for planar domains.<sup>50</sup> In addition, the technique of dual series is more developed for this case.<sup>37,38</sup> At the same time, the mixed Dirichlet-Neumann condition is the most problematic from the perspective of the present work. Even though the Dirichlet boundary condition can be formally implemented by setting  $\kappa(\mathbf{s}) = \kappa$  on the target and then letting  $\kappa$  go to infinity, an infinitely large jump of reactivity at the border of the target requires elaborate asymptotic analysis. In fact, this limit is in general highly nontrivial because the unbounded Dirichlet-to-Neumann operator  $\mathcal{M}_p$  cannot be neglected as compared to the bounded operator  $\mathcal{K}$  (representing the reactivity) even as  $\kappa \rightarrow \infty$ . This situation resembles the asymptotic analysis of the Schrödinger operator  $-\hbar^2\Delta + V$  in the semiclassical limit  $\hbar \rightarrow 0$ , where  $V$  is a bounded potential. While the application of asymptotic techniques from spectral theory and quantum mechanics to our setting presents an interesting mathematical perspective for future research, our spectral approach is not well suited for studying mixed Dirichlet-Neumann boundary value problems.

Similarly, in the narrow escape limit (when targets are very small), a large number of eigenfunctions of the Dirichlet-to-Neumann operator are needed to accurately represent the multiplication operator  $\mathcal{K}$  by a truncated matrix  $\mathbf{K}$ , making numerical computations time-consuming. More generally, when the shape of the boundary is rather complex or not smooth enough (e.g., containing corners or cusps), the computation of the Dirichlet-to-Neumann eigenfunctions becomes difficult, whereas a large number of eigenfunctions may be needed to project even a smooth surface reactivity. In other words, when the surface reactivity has a substantial projection on a large number of eigenfunctions, the “effective” dimensionality of the matrix  $\mathbf{K}$  can be large, making the proposed spectral approach less efficient from the numerical point of view. Nevertheless, the present approach can still be advantageous for exterior problems, which are particularly difficult to deal with by other numerical techniques. In this light, the present approach does not substitute conventional techniques but aims to complement them by addressing imperfect diffusion-controlled reactions on catalytic surfaces with finite continuously varying heterogeneous reactivity.

## APPENDIX A: ALTERNATIVE REPRESENTATION BASED ON THE FUNDAMENTAL SOLUTION

In this Appendix, we describe an alternative scheme for representing the propagator in terms of the fundamental solution of the modified Helmholtz equation.

### 1. Dirichlet propagator and the Dirichlet-to-Neumann operator

The Laplace-transformed Dirichlet propagator  $\tilde{G}_0(\mathbf{x}, p|\mathbf{x}_0)$  and the Dirichlet-to-Neumann operator  $\mathcal{M}_p$  are closely related. On the one hand, the action of  $\mathcal{M}_p$  onto a given function can be expressed via Eq. (13) in terms of the propagator  $\tilde{G}_0(\mathbf{x}, p|\mathbf{x}_0)$  by solving the corresponding Dirichlet boundary value problem. On the other

hand, the Dirichlet propagator can be constructed explicitly from the Dirichlet-to-Neumann operator. For this purpose, one can first represent the propagator as

$$\tilde{G}_0(\mathbf{x}, p|\mathbf{x}_0) = \hat{G}_f(\mathbf{x}, p|\mathbf{x}_0) + \hat{g}_0(\mathbf{x}, p|\mathbf{x}_0), \quad (\text{A1})$$

where

$$\hat{G}_f(\mathbf{x}, p|\mathbf{x}_0) = \frac{K_{1-d/2}(|\mathbf{x} - \mathbf{x}_0| \sqrt{p/D})}{(2\pi)^{d/2} D} \left( \frac{|\mathbf{x} - \mathbf{x}_0|}{\sqrt{p/D}} \right)^{1-d/2} \quad (\text{A2})$$

is the fundamental solution of the modified Helmholtz equation,

$$(p - D\Delta)\hat{G}_f(\mathbf{x}, p|\mathbf{x}_0) = \delta(\mathbf{x} - \mathbf{x}_0), \quad (\text{A3})$$

whereas  $\hat{g}_0(\mathbf{x}, p|\mathbf{x}_0)$  is the regular part of the propagator satisfying, for any fixed  $\mathbf{x}_0 \in \bar{\Omega}$ ,

$$(p - D\Delta)\hat{g}_0(\mathbf{x}, p|\mathbf{x}_0) = 0 \quad (\mathbf{x} \in \Omega), \quad (\text{A4a})$$

$$\hat{g}_0(\mathbf{x}, p|\mathbf{x}_0) + \hat{G}_f(\mathbf{x}, p|\mathbf{x}_0) = 0 \quad (\mathbf{x} \in \partial\Omega). \quad (\text{A4b})$$

Here, we use a hat symbol instead of a tilde in order to distinguish the involved quantities from those in Sec. II C.

The above problem can be solved in a standard way by using the Dirichlet propagator  $\tilde{G}_0(\mathbf{x}, p|\mathbf{x}_0)$ ,

$$\hat{g}_0(\mathbf{x}, p|\mathbf{x}_0) = \int_{\partial\Omega} ds \hat{g}_0(\mathbf{s}, p|\mathbf{x}_0) \left( -D \frac{\partial \tilde{G}_0(\mathbf{x}', p|\mathbf{x})}{\partial \mathbf{n}_{\mathbf{x}'}} \right)_{\mathbf{x}'=\mathbf{x}}.$$

Using the boundary condition (A4b) and substituting the representation (A1), one gets

$$\hat{g}_0(\mathbf{x}, p|\mathbf{x}_0) = \int_{\partial\Omega} ds (-\hat{G}_f(\mathbf{s}, p|\mathbf{x}_0)) (\hat{j}_f(\mathbf{s}, p|\mathbf{x}) + [D\mathcal{M}_p \hat{G}_f(\cdot, p|\mathbf{x})](\mathbf{s})), \quad (\text{A5})$$

where

$$\hat{j}_f(\mathbf{s}, p|\mathbf{x}_0) = -D \left( \frac{\partial \hat{G}_f(\mathbf{x}, p|\mathbf{x}_0)}{\partial \mathbf{n}_{\mathbf{x}}} \right) \Big|_{\mathbf{x}=\mathbf{s}} \quad (\mathbf{s} \in \partial\Omega) \quad (\text{A6})$$

is also a fully explicit function, and we used the Dirichlet-to-Neumann operator  $\mathcal{M}_p$ , acting on  $\hat{G}_f(\mathbf{s}', p|\mathbf{x})$  as a function of a boundary point  $\mathbf{s}'$ , to represent the normal derivative of  $\hat{g}_0(\mathbf{x}', p|\mathbf{x})$ . Combining Eqs. (A1) and (A5), we get the representation of the Dirichlet propagator in terms of the Dirichlet-to-Neumann operator  $\mathcal{M}_p$  and fully explicit functions  $\hat{G}_f$  and  $\hat{j}_f$ .

## 2. General Robin boundary value problem

Similarly, for a given function  $\tilde{f}(\mathbf{s}, p)$  on the boundary  $\partial\Omega$ , the solution  $\tilde{u}(\mathbf{x}, p)$  of a general Robin boundary value problem

$$(p - D\Delta)\tilde{u} = 0 \quad (\mathbf{x} \in \Omega), \quad (\text{A7a})$$

$$\left( D \frac{\partial}{\partial \mathbf{n}} + \kappa(\mathbf{x}) \right) \tilde{u} = \tilde{f} \quad (\mathbf{x} \in \partial\Omega) \quad (\text{A7b})$$

can be obtained by multiplying Eqs. (A3) and (A7a) by  $\tilde{u}(\mathbf{x}, p)$  and  $\hat{G}_f(\mathbf{x}, p|\mathbf{x}_0)$ , respectively, subtracting them, integrating over  $\mathbf{x} \in \Omega$ , and applying Green's formula,

$$\tilde{u}(\mathbf{x}_0, p) = \int_{\partial\Omega} ds \left( D \hat{G}_f(\mathbf{s}, p|\mathbf{x}_0) \frac{\partial \tilde{u}(\mathbf{x}, p)}{\partial \mathbf{n}_{\mathbf{x}}} \Big|_{\mathbf{x}=\mathbf{s}} + \tilde{u}(\mathbf{s}, p) \hat{j}_f(\mathbf{s}, p|\mathbf{x}_0) \right). \quad (\text{A8})$$

This is a standard representation of a solution of the modified Helmholtz equation in terms of the surface integral with the potential  $\hat{G}_f(\mathbf{x}, p|\mathbf{x}_0)$  and its normal derivative  $\hat{j}_f(\mathbf{s}, p|\mathbf{x}_0)$ . Here,  $\tilde{u}(\mathbf{x}_0, p)$  in a bulk point  $\mathbf{x}_0 \in \Omega$  is determined by its values and its normal derivative on the boundary. In turn, the Robin boundary condition (A7b) can be expressed in terms of the Dirichlet-to-Neumann operator  $\mathcal{M}_p$  and the operator  $\mathcal{K}$  of multiplication by  $\kappa(\mathbf{x})/D$  as  $\tilde{u}(\mathbf{s}, p) = \frac{1}{D} [(\mathcal{M}_p + \mathcal{K})^{-1} \tilde{f}](\mathbf{s})$ , from which Eq. (A8) yields

$$\tilde{u}(\mathbf{x}_0, p) = \int_{\partial\Omega} ds \left( \hat{G}_f(\mathbf{s}, p|\mathbf{x}_0) [\mathcal{M}_p (\mathcal{M}_p + \mathcal{K})^{-1} \tilde{f}](\mathbf{s}) + \frac{1}{D} [(\mathcal{M}_p + \mathcal{K})^{-1} \tilde{f}](\mathbf{s}) \hat{j}_f(\mathbf{s}, p|\mathbf{x}_0) \right). \quad (\text{A9})$$

Since the operator  $\mathcal{M}_p$  is self-adjoint, this solution can also be written as

$$\tilde{u}(\mathbf{x}_0, p) = \frac{1}{D} \int_{\partial\Omega} ds (\hat{j}_f(\mathbf{s}, p|\mathbf{x}_0) + [D\mathcal{M}_p \hat{G}_f(\cdot, p|\mathbf{x}_0)](\mathbf{s})) \times [(\mathcal{M}_p + \mathcal{K})^{-1} \tilde{f}](\mathbf{s}). \quad (\text{A10})$$

If the boundary  $\partial\Omega$  is bounded, the spectrum of  $\mathcal{M}_p$  is discrete, and this solution can be written as a spectral decomposition,

$$\tilde{u}(\mathbf{x}_0, p) = \frac{1}{D} \sum_{n, n'=0}^{\infty} \hat{V}_n^{(p)}(\mathbf{x}_0) [(\mathbf{M} + \mathbf{K})^{-1}]_{n, n'} \int_{\partial\Omega} ds [v_{n'}^{(p)}(\mathbf{s})]^* \tilde{f}(\mathbf{s}, p), \quad (\text{A11})$$

where

$$\hat{V}_n^{(p)}(\mathbf{x}_0) = \int_{\partial\Omega} ds v_n^{(p)}(\mathbf{s}) (\hat{j}_f(\mathbf{s}, p|\mathbf{x}_0) + D\mu_n^{(p)} \hat{G}_f(\mathbf{s}, p|\mathbf{x}_0)), \quad (\text{A12})$$

and the matrices  $\mathbf{M}$  and  $\mathbf{K}$  are defined in Eq. (29). In particular, the Laplace-transformed propagator  $\tilde{G}(\mathbf{x}, p|\mathbf{x}_0)$  for the Robin boundary value problem (6) can be written as

$$\tilde{G}(\mathbf{x}, p|\mathbf{x}_0) = \hat{G}_f(\mathbf{x}, p|\mathbf{x}_0) + \frac{1}{D} \sum_{n, n'=0}^{\infty} \hat{V}_n^{(p)}(\mathbf{x}_0) \times [(\mathbf{M} + \mathbf{K})^{-1}]_{n, n'} [\hat{U}_{n'}^{(p)}(\mathbf{x})]^*, \quad (\text{A13})$$

where

$$\hat{U}_n^{(p)}(\mathbf{x}) = \int_{\partial\Omega} ds v_n^{(p)}(\mathbf{s}) (\hat{j}_f(\mathbf{s}, p|\mathbf{x}) - \kappa(\mathbf{s}) \hat{G}_f(\mathbf{s}, p|\mathbf{x})). \quad (\text{A14})$$

In contrast to Eq. (27), this representation is based on the explicitly known fundamental solution  $\hat{G}_f(\mathbf{x}, p|\mathbf{x}_0)$  and does not involve the Dirichlet propagator  $\tilde{G}_0(\mathbf{x}, p|\mathbf{x}_0)$ . As a consequence, all the deduced spectral decompositions rely uniquely on the eigenbasis of the Dirichlet-to-Neumann operator. While the representations (27) and (A13) are equivalent and complementary to each other, we keep using the former one due to its simpler form and clearer probabilistic interpretation.

## APPENDIX B: TECHNICAL DERIVATIONS

### 1. Reaction probability

The reaction probability can be obtained by integrating the probability density  $H(t|\mathbf{x}_0)$  of reaction times over  $t$  from 0 to infinity, giving  $\tilde{H}(0|\mathbf{x}_0)$ . For any bounded domain, a diffusing molecule cannot avoid the reaction event so that  $\tilde{H}(0|\mathbf{x}_0) = 1$ , ensuring the correct normalization of the probability density  $H(t|\mathbf{x}_0)$ . This property can be checked directly from our spectral representation (32). Setting  $p = 0$  yields the reaction probability

$$\tilde{H}(0|\mathbf{x}_0) = \sum_{n,n'=0}^{\infty} V_n^{(0)}(\mathbf{x}_0) [(\mathbf{M} + \mathbf{K})^{-1} \mathbf{K}]_{n,n'}^{(p=0)} \int_{\partial\Omega} ds [v_{n'}^{(0)}(\mathbf{s})]^*. \quad (\text{B1})$$

For any bounded domain, the Laplace equation  $\Delta u = 0$  with  $u|_{\partial\Omega} = 1$  on the boundary has the constant solution,  $u \equiv 1$ , so that a constant function 1 on the boundary is an eigenfunction of the Dirichlet-to-Neumann operator,  $v_0^{(0)}(\mathbf{s}) = |\partial\Omega|^{-1/2}$ , corresponding to  $\mu_0^{(0)} = 0$ . As a consequence, the second sum over  $n'$  in Eq. (B1) vanishes due to the orthogonality of eigenfunctions, yielding

$$\tilde{H}(0|\mathbf{x}_0) = \sum_{n=0}^{\infty} V_n^{(0)}(\mathbf{x}_0) [(\mathbf{M} + \mathbf{K})^{-1} \mathbf{K}]_{n,0}^{(p=0)} |\partial\Omega|^{1/2}. \quad (\text{B2})$$

Rewriting  $(\mathbf{M} + \mathbf{K})^{-1} \mathbf{K}$  as  $\mathbf{I} - (\mathbf{M} + \mathbf{K})^{-1} \mathbf{M}$  and using the diagonal structure of  $\mathbf{M}$ , one gets

$$\begin{aligned} \tilde{H}(0|\mathbf{x}_0) &= V_0^{(0)}(\mathbf{x}_0) |\partial\Omega|^{1/2} - |\partial\Omega|^{1/2} \\ &\quad \times \sum_{n=0}^{\infty} V_n^{(0)}(\mathbf{x}_0) [(\mathbf{M} + \mathbf{K})^{-1} \mathbf{K}]_{n,0}^{(p=0)} \underbrace{\mu_0^{(0)}}_{=0} \\ &= \int_{\partial\Omega} ds \tilde{j}_0(\mathbf{s}, 0|\mathbf{x}_0) = 1, \end{aligned} \quad (\text{B3})$$

where the last integral reflects the normalization of the harmonic measure density  $\tilde{j}_0(\mathbf{s}, 0|\mathbf{x}_0)$  for a bounded domain.

For an unbounded domain, a nonzero constant cannot be a solution of the Laplace equation  $\Delta u = 0$  with  $u|_{\partial\Omega} = 1$  due to the regularity condition  $u(\mathbf{x}) \rightarrow 0$  as  $|\mathbf{x}| \rightarrow \infty$ . The function  $\mathcal{M}_0 1$  is thus not zero, and the smallest eigenvalue  $\mu_0^{(0)}$  is strictly positive. As a consequence, the second term in Eq. (B3) does not vanish, while the first term is not equal to 1. In other words, the reaction probability  $\tilde{H}(0|\mathbf{x}_0)$  is in general less than 1 due to the possibility for a molecule to escape at infinity. In this case,  $H(t|\mathbf{x}_0)$  can be renormalized by  $\tilde{H}(0|\mathbf{x}_0)$  to get the conditional probability density of reaction times.

### 2. Laplace-transformed reaction rate

We briefly discuss how Eq. (34) for the Laplace-transformed reaction rate  $\tilde{j}(p)$  can be further simplified when the initial concentration is uniform:  $c_0(\mathbf{x}_0) = c_0$ .

Integrating Eq. (6a) for the propagator  $\tilde{G}_0(\mathbf{x}, p|\mathbf{x}_0)$  over  $\mathbf{x} \in \Omega$  yields

$$p \int_{\Omega} d\mathbf{x}_0 \tilde{G}_0(\mathbf{x}, p|\mathbf{x}_0) = 1 + D \int_{\partial\Omega} d\mathbf{x}_0 \frac{\partial \tilde{G}_0(\mathbf{x}, p|\mathbf{x}_0)}{\partial \mathbf{n}_{\mathbf{x}_0}}, \quad (\text{B4})$$

where we exchanged  $\mathbf{x}$  and  $\mathbf{x}_0$  due to the symmetry of the propagator. Applying the normal derivative at a boundary point  $\mathbf{x} = \mathbf{s} \in \partial\Omega$  and multiplying by  $-D$ , we get

$$\int_{\Omega} d\mathbf{x}_0 \tilde{j}_0(\mathbf{s}, p|\mathbf{x}_0) = \frac{D}{p} \int_{\partial\Omega} ds_0 \left( \frac{\partial \tilde{j}_0(\mathbf{s}, p|\mathbf{x}_0)}{\partial \mathbf{n}_{\mathbf{x}_0}} \right) \Big|_{\mathbf{x}_0=\mathbf{s}_0}. \quad (\text{B5})$$

Multiplying this relation by a function  $f(\mathbf{s})$  and integrating over  $\mathbf{s} \in \partial\Omega$ , we have

$$\begin{aligned} &\int_{\Omega} d\mathbf{x}_0 \int_{\partial\Omega} ds \tilde{j}_0(\mathbf{s}, p|\mathbf{x}_0) f(\mathbf{s}) \\ &= \frac{D}{p} \int_{\partial\Omega} ds_0 \left( \frac{\partial}{\partial \mathbf{n}_{\mathbf{x}_0}} \int_{\partial\Omega} ds \tilde{j}_0(\mathbf{s}, p|\mathbf{x}_0) f(\mathbf{s}) \right) \Big|_{\mathbf{x}_0=\mathbf{s}_0} \\ &= \frac{D}{p} \int_{\partial\Omega} ds_0 [\mathcal{M}_p f](\mathbf{s}_0), \end{aligned}$$

where the order of integrals was exchanged. As it is satisfied for any  $f(\mathbf{s})$ , we conclude that

$$[\mathcal{M}_p 1](\mathbf{s}) = \frac{p}{D} \int_{\Omega} d\mathbf{x}_0 \tilde{j}_0(\mathbf{s}, p|\mathbf{x}_0). \quad (\text{B6})$$

Setting  $f(\mathbf{s}) = v_n^{(p)}(\mathbf{s})$ , we also deduce

$$\int_{\Omega} d\mathbf{x}_0 V_n^{(p)}(\mathbf{x}_0) = \frac{D}{p} \mu_n^{(p)} \int_{\partial\Omega} ds v_n^{(p)}(\mathbf{s}). \quad (\text{B7})$$

This expression allows us to compute the integral in Eq. (34), yielding

$$\begin{aligned} \tilde{j}(p) &= \frac{c_0 D}{p} \sum_{n,n'=0}^{\infty} \left( \int_{\partial\Omega} ds v_n^{(p)}(\mathbf{s}) \right) \\ &\quad \times [\mathbf{M}(\mathbf{M} + \mathbf{K})^{-1} \mathbf{K}]_{n,n'} \left( \int_{\partial\Omega} ds [v_{n'}^{(p)}(\mathbf{s})]^* \right). \end{aligned} \quad (\text{B8})$$

## APPENDIX C: DIFFUSION INSIDE A BALL

Solutions of Dirichlet boundary value problems for the modified Helmholtz equation in a ball and the related operators are well known. For the sake of clarity and completeness, we summarize the main “ingredients” involved in our spectral decompositions.

To determine the eigenbasis of the Dirichlet-to-Neumann operator in a ball of radius  $R$ ,  $\Omega = \{\mathbf{x} \in \mathbb{R}^3 : |\mathbf{x}| < R\}$ , one simply notes that a general solution of the modified Helmholtz equation  $(p - D\Delta)\tilde{u} = 0$  can be written in spherical coordinates  $(r, \theta, \phi)$  as

$$\tilde{u}(\mathbf{x}, p) = \sum_{n=0}^{\infty} \sum_{m=-n}^m a_{mn} i_n(r\sqrt{p/D}) Y_{mn}(\theta, \phi), \quad (\text{C1})$$

where  $a_{mn}$  are unknown coefficients,

$$i_n(z) = \sqrt{\pi/2} \frac{I_{n+1/2}(z)}{\sqrt{z}} \quad (\text{C2})$$

are the modified spherical Bessel functions of the first kind, and

$$Y_{mn}(\theta, \phi) = c_{nm} P_n^m(\cos \theta) e^{im\phi} \quad (\text{C3})$$

are the spherical harmonics, with  $P_n^m(x)$  being the associated Legendre functions and  $c_{nm}$  being the normalization coefficients,

$$c_{nm} = \sqrt{\frac{2n+1}{4\pi} \frac{(n-m)!}{(n+m)!}} \quad (\text{C4})$$

As the normal derivative of  $\tilde{u}$  on the boundary involves only the radial coordinate and does not affect  $Y_{mn}(\theta, \phi)$ , the eigenvalues and eigenfunctions of the Dirichlet-to-Neumann operator are

$$\mu_{nm}^{(p)} = \sqrt{p/D} \frac{i_n'(R\sqrt{p/D})}{i_n(R\sqrt{p/D})}, \quad (\text{C5a})$$

$$v_{nm}(\theta, \phi) = \frac{1}{R} Y_{mn}(\theta, \phi), \quad (\text{C5b})$$

where the prime denotes the derivative with respect to the argument. As stated in the main text, the double index  $nm$  is employed to enumerate the eigenfunctions as well as the elements of the matrices  $\mathbf{M}$  and  $\mathbf{K}$ . Note that the eigenvalues that determine the matrix  $\mathbf{M}$  in Eq. (29a) do not depend on the index  $m$  and thus are of multiplicity  $2n+1$ . In turn, the eigenfunctions  $v_{nm}$  do not depend on the parameter  $p$  that will simplify further expressions. The explicit computation of the matrix  $\mathbf{K}$  from Eq. (43) is discussed in Appendix D.

For a ball, the Dirichlet propagator is known explicitly

$$G_0(\mathbf{x}, t|\mathbf{x}_0) = \frac{1}{2\pi R^3} \sum_{n=0}^{\infty} (2n+1) P_n \left( \frac{(\mathbf{x} \cdot \mathbf{x}_0)}{|\mathbf{x}| |\mathbf{x}_0|} \right) \times \sum_{k=0}^{\infty} \frac{e^{-Dt\alpha_{nk}^2/R^2}}{[j_n'(\alpha_{nk})]^2} j_n(\alpha_{nk}r/R) j_n(\alpha_{nk}r_0/R), \quad (\text{C6})$$

where  $\alpha_{nk}$  are the positive zeros (enumerated by the index  $k = 0, 1, 2, \dots$ ) of the spherical Bessel functions  $j_n(z)$  of the first kind, and we used the addition theorem for spherical harmonics to evaluate the sum over the index  $m$ ,

$$P_n \left( \frac{(\mathbf{x} \cdot \mathbf{x}_0)}{|\mathbf{x}| |\mathbf{x}_0|} \right) = 4\pi \sum_{m=-n}^n \frac{Y_{mn}(\theta_0, \phi_0) Y_{mn}^*(\theta, \phi)}{2n+1} = \frac{4\pi R^2}{2n+1} \sum_{m=-n}^n v_{nm}(\theta_0, \phi_0) v_{nm}^*(\theta, \phi), \quad (\text{C7})$$

where  $P_n(z)$  are the Legendre polynomials. The Laplace transform of Eq. (C6) reads

$$\tilde{G}_0(\mathbf{x}, p|\mathbf{x}_0) = \frac{1}{2\pi R^3} \sum_{n=0}^{\infty} (2n+1) P_n \left( \frac{(\mathbf{x} \cdot \mathbf{x}_0)}{|\mathbf{x}| |\mathbf{x}_0|} \right) \times \sum_{k=0}^{\infty} \frac{j_n(\alpha_{nk}r/R) j_n(\alpha_{nk}r_0/R)}{(D\alpha_{nk}^2/R^2 + p) [j_n'(\alpha_{nk})]^2}. \quad (\text{C8})$$

As  $\frac{(\mathbf{x} \cdot \mathbf{x}_0)}{|\mathbf{x}| |\mathbf{x}_0|}$  is the cosine of the angle between the vectors  $\mathbf{x}$  and  $\mathbf{x}_0$ , it does not depend on the radial coordinates  $r$  and  $r_0$ . We get thus

$$\tilde{j}_0(\mathbf{s}, p|\mathbf{x}_0) = -\frac{1}{2\pi R^2} \sum_{n=0}^{\infty} (2n+1) P_n \left( \frac{(\mathbf{s} \cdot \mathbf{x}_0)}{|\mathbf{s}| |\mathbf{x}_0|} \right) \times \sum_{k=0}^{\infty} \frac{\alpha_{nk} j_n(\alpha_{nk}r_0/R)}{(\alpha_{nk}^2 + pR^2/D) j_n'(\alpha_{nk})}, \quad (\text{C9})$$

from which

$$V_{nm}^{(p)}(\mathbf{x}_0) = -2v_{nm}(\theta_0, \phi_0) \sum_{k=0}^{\infty} \frac{\alpha_{nk} j_n(\alpha_{nk}r_0/R)}{(\alpha_{nk}^2 + pR^2/D) j_n'(\alpha_{nk})} = v_{nm}(\theta_0, \phi_0) \frac{i_n(r_0\sqrt{p/D})}{i_n(R\sqrt{p/D})}, \quad (\text{C10})$$

where we used the summation formula over zeros  $\alpha_{nk}$  [see Eq. (S9) from Table 3 of Ref. 105]. Expressions (C8)–(C10) determine the Laplace-transformed propagator  $\tilde{G}(\mathbf{x}, p|\mathbf{x}_0)$  of the Robin boundary value problem in the semianalytical form (27), in which the dependence on points  $\mathbf{x}_0$  and  $\mathbf{x}$  is fully explicit, whereas the computation of the coefficients involves a numerical inversion of the matrix  $\mathbf{M} + \mathbf{K}$ . Similarly, we deduce semianalytical expressions for the Laplace-transformed probability density of reaction times and the spread harmonic measure presented in the main text. For instance, as the eigenfunctions  $v_{nm}$  are orthogonal to  $v_{00}(\theta, \phi) = 1/(\sqrt{4\pi}R)$ , the sum in Eq. (33) is reduced to a single term, yielding Eq. (46).

We also compute the mean reaction time  $\tilde{S}(0|\mathbf{x}_0)$  by evaluating the limit  $p \rightarrow 0$  of the Laplace-transformed survival probability from Eq. (47). In this limit, one gets

$$\mu_{nm}^{(0)} = n/R, \quad V_{nm}^{(0)}(\mathbf{x}_0) = v_{nm}(\theta_0, \phi_0) (r_0/R)^n \quad (\text{C11})$$

so that

$$\tilde{S}(0|\mathbf{x}_0) = \sqrt{4\pi} \sum_{n=0}^{\infty} \sum_{m=-n}^n Y_{mn}(\theta_0, \phi_0) (r_0/R)^n \times \left( \frac{R^2 - r_0^2}{4D(n+3/2)} h_{mn}^{(0)} - \left( \frac{h_{mn}^{(p)}}{dp} \right)_{p=0} \right). \quad (\text{C12})$$

The last term can be evaluated explicitly as

$$\left( \frac{h_{mn}^{(p)}}{dp} \right)_{p=0} = -[(\mathbf{M}_0 + \mathbf{K})^{-1} \mathbf{M}_1 (\mathbf{M}_0 + \mathbf{K})^{-1} \mathbf{K}]_{nm,00}, \quad (\text{C13})$$

where  $\mathbf{M}_0$  and  $\mathbf{M}_1$  are diagonal matrices obtained by expanding the elements of  $\mathbf{M}$  into powers  $p$ :  $[\mathbf{M}_0]_{nm,n'm'} = \delta_{n,n'} \delta_{m,m'} n/R$  and  $[\mathbf{M}_1]_{nm,n'm'} = \delta_{n,n'} \delta_{m,m'} \frac{R/D}{2n+3}$ .

For a homogeneous reactivity,  $\kappa(\theta, \phi) = \kappa$ , Eqs. (36) and (45) imply

$$\tilde{H}_{\text{hom}}(p|\mathbf{x}_0) = \frac{\kappa i_0(r_0\sqrt{p/D})}{\sqrt{pD} i_0'(R\sqrt{p/D}) + \kappa i_0(R\sqrt{p/D})} \quad (\text{C14})$$

[since  $i_0(z) = \sinh(z)/z$ , one can further simplify this expression]. In turn, Eq. (51) gives

$$\tilde{J}_{\text{hom}}(p) = 4\pi DRc_0 \left( \frac{i_0(R\sqrt{p/D})}{R\sqrt{p/D} i_1(R\sqrt{p/D})} + \frac{D}{\kappa R} \right)^{-1}, \quad (\text{C15})$$

and its inverse Laplace transform yields an infinite sum of exponentially decaying functions with the rates determined by the poles of this expression (see Refs. 3, 35, and 36). Finally, Eq. (C12) yields the classical result

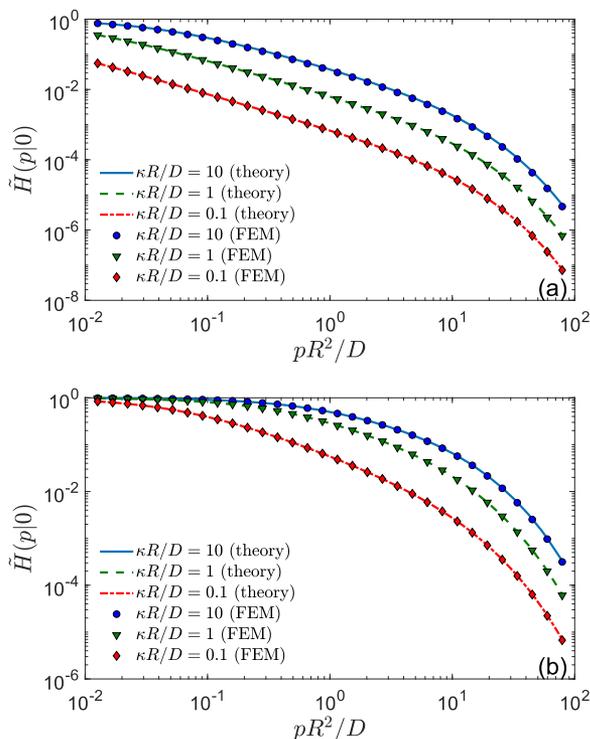
$$\tilde{S}_{\text{hom}}(0|\mathbf{x}_0) = \frac{R^2 - r_0^2}{6D} + \frac{R}{3\kappa}. \quad (\text{C16})$$

## 1. Numerical Validation

To illustrate the quality of our semianalytical solution, we look at the Laplace-transformed probability density  $\tilde{H}(p|\mathbf{x}_0)$  that satisfies the boundary value problem

$$\begin{aligned} (p - D\Delta_{\mathbf{x}_0})\tilde{H}(p|\mathbf{x}_0) &= 0 \quad (\mathbf{x}_0 \in \Omega), \\ \left( D\frac{\partial}{\partial \mathbf{n}_{\mathbf{x}_0}} + \kappa(\mathbf{x}_0) \right)\tilde{H}(p|\mathbf{x}_0) &= \kappa(\mathbf{x}_0) \quad (\mathbf{x}_0 \in \partial\Omega), \end{aligned}$$

with  $\Delta_{\mathbf{x}_0}$  acting on  $\mathbf{x}_0$ . We set  $\kappa(\theta, \phi) = \kappa \Theta(\varepsilon - \theta)$  to describe a single partially reactive circular target of angular size  $\varepsilon$  and reactivity  $\kappa$ , located at the North pole [here  $\Theta(z)$  is the Heaviside function].



**FIG. 3.** Laplace-transformed probability density  $\tilde{H}(p|0)$  of reaction times on a partially reactive circular target of reactivity  $\kappa$  and angular size  $\varepsilon$ , located on the inert spherical surface of radius  $R$ , for a molecule started from the origin, with  $\varepsilon = 0.1$  (a) and  $\varepsilon = 1$  (b). Lines show the semianalytical solution (C17), in which  $h_{00}^{(p)}$  was found from Eq. (46) with the matrices  $\mathbf{M}$  and  $\mathbf{K}$  truncated at  $n_{\text{max}} = 20$ . Symbols present a FEM numerical solution with the maximal mesh size of 0.01.

The axial symmetry of this geometric setting allows one to reduce the original three-dimensional problem to a two-dimensional one on the rectangle  $[0, R] \times [0, \pi]$  in the coordinates  $(r, \theta)$ . We solve this problem by using a finite element method implemented in the Matlab Partial Differential Equation (PDE) toolbox. The computational domain was meshed with the constraint on the largest mesh size to be 0.01. For the sake of simplicity, we fix the starting point at the origin, in which case Eq. (45) is reduced to

$$\tilde{H}(p|0) = h_{00}^{(p)} \frac{R\sqrt{p/D}}{\sinh(R\sqrt{p/D})}, \quad (\text{C17})$$

where  $h_{00}^{(p)}$  is given by Eq. (46) and computed with the matrices  $\mathbf{K}$  and  $\mathbf{M}$  truncated to the size  $n_{\text{max}} = 20$  and constructed from Eqs. (D12) and (29a). Figure 3 shows an excellent agreement between this semianalytical form and the FEM solution for both a small target of angular size  $\varepsilon = 0.1$  [with the surface fraction  $\sigma = (1 - \cos \varepsilon)/2 \approx 0.0025$ ] and a large target of angular size  $\varepsilon = 1$  (with  $\sigma \approx 0.23$ ) and different reactivities.

## APPENDIX D: COMPUTATION OF THE MATRIX $\mathbf{K}$

The key element of the spectral approach is the possibility to disentangle first-passage diffusive steps from the heterogeneous reactivity which is incorporated via the matrix  $\mathbf{K}$ . In this Appendix, we compute this matrix for several most common settings on the spherical boundary.

### 1. General setting

In general, the reactivity  $\kappa(\theta, \phi)$  can be expanded over the complete basis of spherical harmonics,

$$\kappa(\theta, \phi) = \sum_{n=0}^{\infty} \sum_{m=-n}^n \kappa_{nm} Y_{nm}(\theta, \phi), \quad (\text{D1})$$

with coefficients  $\kappa_{nm}$ . When this expansion can be truncated at a low order  $n^*$ , one can compute the elements of the matrix  $\mathbf{K}$  explicitly, without numerical quadrature in Eq. (43), by using the following identity:

$$\begin{aligned} \int_0^\pi d\theta \sin \theta \int_0^{2\pi} d\phi Y_{m_1 n_1}(\theta, \phi) Y_{m_2 n_2}(\theta, \phi) Y_{m_3 n_3}(\theta, \phi) \\ = \sqrt{\frac{(2n_1 + 1)(2n_2 + 1)(2n_3 + 1)}{4\pi}} \begin{pmatrix} n_1 & n_2 & n_3 \\ m_1 & m_2 & m_3 \end{pmatrix} \begin{pmatrix} n_1 & n_2 & n_3 \\ 0 & 0 & 0 \end{pmatrix}, \end{aligned} \quad (\text{D2})$$

where  $\begin{pmatrix} n_1 & n_2 & n_3 \\ m_1 & m_2 & m_3 \end{pmatrix}$  is the Wigner 3j symbol. We note that the truncation order  $n_{\text{max}}$  should significantly exceed  $n^*$  to ensure accurate computations.

### 2. Axially symmetric problems

When the reactivity is axially symmetric,  $\kappa(\theta, \phi) = \kappa(\theta)$ , the integral over  $\phi$  in Eq. (43) yields  $2\pi\delta_{m, m'}$ , and the matrix  $\mathbf{K}$  has a block structure. If in addition one is interested in axially symmetric quantities [e.g.,  $\tilde{H}(p|\mathbf{x}_0)$  which does not depend on  $\phi_0$  due to the

axial symmetry], it is sufficient to construct a reduced version of the matrix  $\mathbf{K}$  by eliminating repeated lines and rows and keeping only the elements with  $m = m' = 0$ ,

$$\mathbf{K}_{n0,n'0} = \sqrt{(n+1/2)(n'+1/2)} \times \int_0^\pi d\theta \sin\theta \frac{\kappa(\theta)}{D} P_n(\cos\theta) P_{n'}(\cos\theta). \quad (\text{D3})$$

From the numerical point of view, this drastically speeds up computations because the size of the matrix  $\mathbf{K}$ , truncated to the order  $n_{\max}$ , becomes  $(n_{\max} + 1) \times (n_{\max} + 1)$  instead of  $(n_{\max} + 1)^2 \times (n_{\max} + 1)^2$  in the general setting. Semianalytical expressions also become simpler, e.g., Eqs. (45) and (50) read, respectively,

$$\hat{H}(p|\mathbf{x}_0) = \sum_{n=0}^{\infty} \sqrt{2n+1} h_{n0}^{(p)} \frac{i_n(r_0\sqrt{p/D})}{i_n(R\sqrt{p/D})} P_n(\cos\theta_0) \quad (\text{D4})$$

and

$$\hat{H}(p|\mathbf{x}_0) = \sum_{n=0}^{\infty} \sqrt{2n+1} h_{n0}^{(p)} \frac{k_n(r_0\sqrt{p/D})}{k_n(R\sqrt{p/D})} P_n(\cos\theta_0), \quad (\text{D5})$$

with  $h_{n0}^{(p)}$  given by Eq. (46).

If an expansion of the reactivity  $\kappa(\theta)$  over the complete basis of Legendre polynomials is known,

$$\kappa(\theta) = \sum_{n=0}^{\infty} \kappa_n P_n(\cos\theta), \quad (\text{D6})$$

then the elements of the matrix  $\mathbf{K}$  can be computed by using the identity

$$\int_{-1}^1 dx P_{n_1}(x) P_{n_2}(x) P_n(x) = 2 \begin{pmatrix} n_1 & n_2 & n \\ 0 & 0 & 0 \end{pmatrix}^2, \quad (\text{D7})$$

which follows from Eq. (D2). As the selection rule for Wigner 3j-symbols requires that  $|n_1 - n_2| \leq n \leq n_1 + n_2$ , the truncation of the expansion (D6) at the order  $n^*$  implies that the matrix  $\mathbf{K}$  has at most  $n^*$  subdiagonals above and below the main diagonal that simplifies the construction of this matrix. One advantage of the representation (D6) is that the average reactivity is equal to  $\kappa_0$  and is independent of  $\kappa_n$  with  $n \geq 1$  due to the orthogonality of Legendre polynomials.

We emphasize however that the above simplified construction is not sufficient for computing the Laplace-transformed propagator  $\hat{G}(\mathbf{x}, p|\mathbf{x}_0)$  which is not axially symmetric. In fact, Eq. (27) involves the coefficients  $[(\mathbf{M} + \mathbf{K})^{-1}]_{nm,n'm'}$ , whose computation requires all the elements  $\mathbf{K}_{nm,n'm'}$  even for axially symmetric reactivity, and it is not reducible to that with the elements  $\mathbf{K}_{n0,n'0}$ . In this case, the general scheme from Appendix D 1 should be used.

### 3. Single circular target

To model a single circular partially reactive target of angular size  $\varepsilon$  at the North pole (with the remaining inert boundary), one sets

$$\kappa(\theta, \phi) = \kappa \Theta(\varepsilon - \theta) \quad (\text{D8})$$

so that Eq. (D3) yields

$$\mathbf{K}_{n0,n'0} = \frac{\kappa}{D} \sqrt{(n+1/2)(n'+1/2)} \int_{\cos\varepsilon}^1 dx P_n(x) P_{n'}(x). \quad (\text{D9})$$

To compute explicitly the matrix  $\mathbf{K}$ , one can use Adams-Neumann's product formula (see Ref. 106),

$$P_n(x)P_{n'}(x) = \sum_{k=0}^{\min\{n,n'\}} B_{nn'}^k P_{n+n'-2k}(x), \quad (\text{D10})$$

where

$$B_{nn'}^k = \frac{A_k A_{n-k} A_{n'-k}}{A_{n+n'-k}} \frac{2n+2n'-4k+1}{2n+2n'-2k+1}, \quad (\text{D11})$$

with  $A_k = \frac{\Gamma(k+1/2)}{\sqrt{\pi}\Gamma(k+1)}$  (with  $A_0 = 1$ ). We get thus

$$\mathbf{K}_{n0,n'0} = \frac{\kappa}{D} \sqrt{(n+1/2)(n'+1/2)} \sum_{k=0}^{\min\{n,n'\}} B_{nn'}^k \times \frac{P_{n+n'-2k-1}(\cos\varepsilon) - P_{n+n'-2k+1}(\cos\varepsilon)}{2(n+n'-2k)+1}, \quad (\text{D12})$$

where we used the identity for  $n \geq 0$

$$\int_a^b dx P_n(x) = \frac{P_{n+1}(b) - P_{n-1}(b) - P_{n+1}(a) + P_{n-1}(a)}{2n+1} \quad (\text{D13})$$

[with the convention  $P_{-1}(x) = 1$ ].

An explicit formula for  $\mathbf{K}$  is also easily deducible for multiple latitudinal stripes. The domain is still axially symmetric, and one just needs to sum up contributions from each stripe, relying on the explicit integral of  $P_n(x)$  in Eq. (D13).

### 4. Multiple targets of circular shape

The matrix  $\mathbf{K}$  can also be computed explicitly for multiple partially reactive nonoverlapping targets of circular shape. In fact, the additivity of the integral in Eq. (43) implies that contributions for all targets are just summed up. We consider thus the contribution of the  $i$ th target  $\Gamma_i$  of angle  $\varepsilon_i$ , reactivity  $\kappa_i$ , and the angular coordinates  $(\theta_i, \phi_i)$  for its center. It is convenient to apply the rotational addition theorem for spherical harmonics to rotate the coordinate system,<sup>107</sup>

$$Y_{mn}(\theta', \phi') = \sum_{m'=-n}^n [D_{mm'}^n(\phi_i, \theta_i, \phi_i)]^* Y_{m'n}(\theta, \phi), \quad (\text{D14})$$

where  $D_{mm'}^n(\alpha, \beta, \gamma)$  is the Wigner D-matrix describing the rotation by Euler angles  $(\alpha, \beta, \gamma)$ . As a consequence, the  $i$ th contribution to the matrix  $\mathbf{K}$  reads

$$\begin{aligned} \mathbf{K}_{n_1 m_1, n_2 m_2}^{(i)} &= \frac{\kappa_i}{DR^2} \int_{\Gamma_i} ds' Y_{m_1 n_1}^*(\theta', \phi') Y_{m_2 n_2}(\theta', \phi') \\ &= \frac{\kappa_i}{DR^2} \sum_{m'_1=-n_1}^{n_1} D_{m'_1 m_1}^{n_1}(\phi_i, \theta_i, \phi_i) \sum_{m'_2=-n_2}^{n_2} [D_{m'_2 m'_2}^{n_2}(\phi_i, \theta_i, \phi_i)]^* \\ &\quad \times \int_{\Gamma_0} ds Y_{m'_1 n_1}^*(\theta, \phi) Y_{m'_2 n_2}(\theta, \phi), \end{aligned}$$

where  $\Gamma_0$  is the  $i$ th target rotated to be centered around the North pole. To proceed, one can express the product of two spherical harmonics as

$$Y_{m'_1 n_1}(\theta, \phi) Y_{m'_2 n_2}(\theta, \phi) = \sum_{n=|n_1-n_2|}^{n_1+n_2} B_{m'_1 n_1 m'_2 n_2}^n Y_{(m'_1+m'_2)n}(\theta, \phi) \quad (\text{D15})$$

[which follows from Eq. (D2)], where

$$B_{m'_1 n_1 m'_2 n_2}^n = \sqrt{\frac{(2n+1)(2n_1+1)(2n_2+1)}{4\pi}} \times (-1)^{m'_1+m'_2} \begin{pmatrix} n_1 & n_2 & n \\ m'_1 & m'_2 & -m'_1-m'_2 \end{pmatrix} \begin{pmatrix} n_1 & n_2 & n \\ 0 & 0 & 0 \end{pmatrix}, \quad (\text{D16})$$

with  $\begin{pmatrix} n_1 & n_2 & n \\ m_1 & m_2 & m \end{pmatrix}$  being again the Wigner 3-j symbols,<sup>108</sup> and we employ the convention that  $Y_{mn}(\theta, \phi) \equiv 0$  if  $|m| > n$ . Using the identity

$$Y_{mn}^*(\theta, \phi) = (-1)^m Y_{(-m)n}(\theta, \phi),$$

the above formula yields

$$Y_{m'_1 n_1}^*(\theta, \phi) Y_{m'_2 n_2}(\theta, \phi) = (-1)^{m'_2} \sum_{n=|n_1-n_2|}^{n_1+n_2} B_{(-m'_1)n_1 m'_2 n_2}^n Y_{(m'_2-m'_1)n}(\theta, \phi), \quad (\text{D17})$$

from which

$$\mathbf{K}_{m'_1 n_1 m'_2 n_2}^{(i)} = \sqrt{\pi} \frac{\kappa_i}{D} \sum_{n=|n_1-n_2|}^{n_1+n_2} \frac{P_{n-1}(\cos \varepsilon_i) - P_{n+1}(\cos \varepsilon_i)}{\sqrt{2n+1}} \times \sum_{m=-\min\{n_1, n_2\}}^{\min\{n_1, n_2\}} (-1)^m D_{m_1 m}^{n_1}(\phi_i, \theta_i, \phi_i) \times [D_{m_2 m}^{n_2}(\phi_i, \theta_i, \phi_i)]^* B_{(-m)n_1 m_2}^n, \quad (\text{D18})$$

where the integral over  $\phi$  yielded  $2\pi\delta_{m'_1, m'_2}$  that removed one sum, while the integral of  $P_n(x)$  was evaluated from Eq. (D13). We get therefore a fully explicit expression for the contribution of the  $i$ th target to the matrix  $\mathbf{K}$ . One can thus compute the Laplace-transformed propagator in the semianalytical form, as for a single target.

## APPENDIX E: DIFFUSION OUTSIDE A BALL

For diffusion in the unbounded domain  $\Omega = \{\mathbf{x} \in \mathbb{R}^3 : |\mathbf{x}| > R\}$  outside a ball of radius  $R$ , the eigenfunctions of the Dirichlet-to-Neumann operator are still given by Eq. (42b), whereas the eigenvalues are

$$\mu_{nm}^{(p)} = -\sqrt{p/D} \frac{k'_n(R\sqrt{p/D})}{k_n(R\sqrt{p/D})}, \quad (\text{E1})$$

where  $k_n(z)$  are the modified spherical Bessel functions of the second kind,

$$k_n(z) = \sqrt{2/\pi} \frac{K_{n+1/2}(z)}{\sqrt{z}}. \quad (\text{E2})$$

As for the interior problem, the eigenvalue  $\mu_{nm}^{(p)}$  does not depend on  $m$  and has thus the multiplicity  $2n+1$ . Note that  $\mu_{nm}^{(p)}$  are just polynomials of  $R\sqrt{p/D}$ , e.g.,  $\mu_{00}^{(p)} = (1 + R\sqrt{p/D})/R$ .

The Laplace-transformed Dirichlet propagator is known,

$$\tilde{G}_0(\mathbf{x}, p|\mathbf{x}_0) = \frac{e^{-\sqrt{p/D}|\mathbf{x}-\mathbf{x}_0|}}{4\pi D|\mathbf{x}-\mathbf{x}_0|} - \frac{\sqrt{p/D}}{4\pi D} \sum_{n=0}^{\infty} (2n+1) \times P_n\left(\frac{\mathbf{x} \cdot \mathbf{x}_0}{|\mathbf{x}||\mathbf{x}_0|}\right) \frac{i_n(R\sqrt{p/D})}{k_n(R\sqrt{p/D})} k_n(r\sqrt{p/D}) k_n(r_0\sqrt{p/D}).$$

Note that the fundamental solution (the first term) also admits the decomposition,

$$\frac{e^{-\sqrt{p/D}|\mathbf{x}-\mathbf{x}_0|}}{4\pi|\mathbf{x}-\mathbf{x}_0|} = \frac{\sqrt{p/D}}{4\pi} \sum_{n=0}^{\infty} (2n+1) P_n\left(\frac{\mathbf{x} \cdot \mathbf{x}_0}{|\mathbf{x}||\mathbf{x}_0|}\right) \times k_n(r_0\sqrt{p/D}) i_n(r\sqrt{p/D}) \quad (\text{E3})$$

for  $r < r_0$  (and  $r_0$  is exchanged with  $r$  for  $r > r_0$ ), where we applied the addition theorem (C7) for spherical harmonics. One gets then

$$\tilde{G}_0(\mathbf{x}, p|\mathbf{x}_0) = \frac{\sqrt{p/D}}{4\pi D} \sum_{n=0}^{\infty} (2n+1) P_n\left(\frac{\mathbf{x} \cdot \mathbf{x}_0}{|\mathbf{x}||\mathbf{x}_0|}\right) k_n(r_0\sqrt{p/D}) \times \left( i_n(r\sqrt{p/D}) - k_n(r\sqrt{p/D}) \frac{i_n(R\sqrt{p/D})}{k_n(R\sqrt{p/D})} \right) \quad (\text{E4})$$

for  $r < r_0$ . In particular, one deduces

$$\tilde{j}_0(\mathbf{s}, p|\mathbf{x}_0) = \sum_{n=0}^{\infty} \frac{2n+1}{4\pi R^2} P_n\left(\frac{\mathbf{s} \cdot \mathbf{x}_0}{|\mathbf{s}||\mathbf{x}_0|}\right) \frac{k_n(r_0\sqrt{p/D})}{k_n(R\sqrt{p/D})}, \quad (\text{E5})$$

where we used the Wronskian  $i'_n(z)k_n(z) - k'_n(z)i_n(z) = 1/z^2$ . We compute then

$$V_{nm}^{(p)} = v_{nm}(\theta_0, \phi_0) \frac{k_n(r_0\sqrt{p/D})}{k_n(R\sqrt{p/D})}. \quad (\text{E6})$$

According to our spectral decomposition (27), Eqs. (E4) and (E6), together with the matrices  $\mathbf{M}$  and  $\mathbf{K}$ , fully determine the Laplace-transformed propagator  $\tilde{G}(\mathbf{x}, p|\mathbf{x}_0)$ . Similarly, we deduce the Laplace-transformed probability density of reaction times and the reaction time presented in the main text.

In the limit  $p \rightarrow 0$ , one has

$$\mu_{nm}^{(0)} = (n+1)/R, \quad V_{nm}^{(0)}(\mathbf{x}_0) = v_{nm}(\theta_0, \phi_0)(R/r_0)^{n+1}, \quad (\text{E7})$$

from which

$$\tilde{H}(0|\mathbf{x}_0) = \sqrt{4\pi} \sum_{n=0}^{\infty} \sum_{m=-n}^n h_{nm}^{(0)}(R/r_0)^{n+1} Y_{nm}(\theta_0, \phi_0) \quad (\text{E8})$$

is the probability of reaction on the ball, and  $h_{nm}^{(p)}$  are defined by Eq. (46). In contrast to bounded domains, for which this probability was equal to 1 [see Eq. (B3)], the transient character of Brownian motion in three dimensions makes this probability less than 1. Rewriting Eq. (46) as

$$h_{nm}^{(0)} = \delta_{n,0}\delta_{m,0} - \frac{1}{R}[(\mathbf{M}_{p=0} + \mathbf{K})^{-1}]_{nm,00}, \quad (\text{E9})$$

one can split  $\tilde{H}(0|\mathbf{x}_0)$  into two terms, in which the first term  $R/r_0$  is the hitting probability to a perfectly reactive ball, while the second term accounts for partial heterogeneous reactivity. The limit  $p \rightarrow 0$  also determines the long-time behavior of Eq. (51) that yields Eq. (52) for the steady-state reaction rate  $J(\infty)$ .

For homogeneous reactivity,  $\kappa(s) = \kappa$ ,  $\mathbf{M} + \mathbf{K}$  is a diagonal matrix and thus only the term with  $m = n = 0$  survives in Eq. (E8), yielding the classical result for the hitting probability of a homogeneous partially reactive ball,

$$\tilde{H}_{\text{hom}}(0|\mathbf{x}_0) = \frac{R}{r_0} \frac{1}{1 + D/(\kappa R)}. \quad (\text{E10})$$

More generally, Eq. (50) yields

$$\tilde{H}_{\text{hom}}(p|\mathbf{x}_0) = \frac{R}{r_0(1 + \frac{D}{\kappa R})} \frac{e^{-(r_0-R)\sqrt{p/D}}}{1 + \frac{R\sqrt{p/D}}{1 + \kappa R/D}}, \quad (\text{E11})$$

where we used  $k_0(z) = e^{-z}/z$ . The Laplace inversion recovers the result by Collins and Kimball,<sup>11</sup>

$$H_{\text{hom}}(t|\mathbf{x}_0) = \frac{\kappa}{r_0} \exp\left(-\frac{(r_0-R)^2}{4Dt}\right) \left\{ \frac{R}{\sqrt{\pi Dt}} - \left(1 + \frac{\kappa R}{D}\right) \times \text{erfcx}\left(\frac{r_0-R}{\sqrt{4Dt}} + \left(1 + \frac{\kappa R}{D}\right) \frac{\sqrt{Dt}}{R}\right) \right\}, \quad (\text{E12})$$

where  $\text{erfcx}(x) = e^{x^2} \text{erfc}(x)$  is the scaled complementary error function (see also the discussion in Ref. 79). In the limit  $\kappa \rightarrow \infty$ , this expression reduces to

$$H_{\text{hom}}(t|\mathbf{x}_0) = \frac{R}{r_0} \frac{r_0-R}{\sqrt{4\pi Dt^3}} \exp\left(-\frac{(r_0-R)^2}{4Dt}\right). \quad (\text{E13})$$

Finally, Eq. (51) gives after simplifications

$$\tilde{J}_{\text{hom}}(p) = \frac{4\pi DRc_0}{1 + \frac{D}{\kappa R}} \left( \frac{1}{p} + \frac{\kappa R/D}{p + (1 + \frac{\kappa R}{D})\sqrt{pD}/R} \right), \quad (\text{E14})$$

from which one retrieves in time domain the reaction rate derived by Collins and Kimball,<sup>11</sup>

$$\frac{J_{\text{hom}}(t)}{J_{\text{hom}}(\infty)} = 1 + \frac{\kappa R}{D} \text{erfcx}\left(\left(1 + \frac{\kappa R}{D}\right) \frac{\sqrt{Dt}}{R}\right), \quad (\text{E15a})$$

$$J_{\text{hom}}(\infty) = \frac{4\pi DRc_0}{1 + \frac{D}{\kappa R}}. \quad (\text{E15b})$$

In the short-time limit  $t \rightarrow 0$ , the reaction rate approaches a constant,  $J_{\text{hom}}(0) = 4\pi\kappa R^2 c_0$ , which corresponds to reaction-limited kinetics [note that  $J_{\text{hom}}(0) > J_{\text{hom}}(\infty)$ ]. In the limit  $\kappa \rightarrow \infty$ , one retrieves the Smoluchowski result,

$$J_{\text{hom}}(t) = 4\pi DRc_0 \left( 1 + \frac{\sqrt{R}}{\sqrt{\pi Dt}} \right). \quad (\text{E16})$$

We note that the above analysis can be easily extended to the case when the spherical target of radius  $R$  is surrounded by an outer reflecting concentric sphere of radius  $R_0$ . The eigenfunctions of the Dirichlet-to-Neumann operator remain unchanged, whereas the eigenvalues become

$$\mu_n^{(p)} = -\sqrt{p/D} \frac{k'_n(R_0\sqrt{p/D}) i'_n(R\sqrt{p/D}) - i'_n(R_0\sqrt{p/D}) k'_n(R\sqrt{p/D})}{k'_n(R_0\sqrt{p/D}) i_n(R\sqrt{p/D}) - i'_n(R_0\sqrt{p/D}) k_n(R\sqrt{p/D})}. \quad (\text{E17})$$

In the limit  $R_0 \rightarrow \infty$ , one retrieves Eq. (E1) for the exterior of a ball. As  $p \rightarrow 0$ , one also gets

$$\mu_n^{(0)} = \frac{n+1}{R} \frac{1 - (R/R_0)^{2n+1}}{1 + (1+1/n)(R/R_0)^{2n+1}}. \quad (\text{E18})$$

As a consequence, one can easily extend the former results to this setting.

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