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Imperfect Diffusion-Controlled Reactions

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Abstract

This chapter aims at emphasizing the crucial role of partial reactivity of a catalytic surface or a target molecule in diffusion-controlled reactions. We discuss various microscopic mechanisms that lead to imperfect reactions, the Robin boundary condition accounting for eventual failed reaction events, and the construction of the underlying stochastic process, the so-called partially reflected Brownian motion. We show that the random path to the reaction event can naturally be separated into the transport step toward the target, and the exploration step near the target surface until reaction. While most studies are focused exclusively on the transport step (describing perfect reactions), the exploration step, consisting is an intricate combination of diffusion-mediated jumps between boundary points, and its consequences for chemical reactions remain poorly understood. We discuss the related mathematical difficulties and recent achievements. In particular, we derive a general representation of the propagator, show its relation to the Dirichlet-to-Neumann operator, and illustrate its properties in the case of a flat surface.

Disclaimer

Apart from the general introduction and motivation, the chapter summarizes former results obtained by the author and his co-workers. For this reason, the chapter presents the author's personal view on the topic, whereas the bibliography is biased.

1 Introduction

Classical reaction kinetics describes the time evolution of spatially homogeneous concentrations of reacting species via a set of coupled nonlinear ordinary differential equations. This description relies on the assumption that the produced species move fast enough to maintain homogeneous concentrations, and the limiting factor is the chemical kinetics itself. Marian von Smoluchowski was the first who emphasized on the importance of the transport step by computing the macroscopic reaction rate of small molecules A diffusing toward a spherical target B of radius R [1]. If the reaction occurs immediately upon the first encounter between the two molecules, the rate is equal to the diffusive flux which is obtained the solving the underlying diffusion equation on the concentration $c(\boldsymbol{x}, t)$ of molecules A:

$$\frac{\partial c(\boldsymbol{x}, t)}{\partial t} = D\Delta c(\boldsymbol{x}, t) \qquad \text{diffusion in the bulk } \Omega, \tag{1a}$$

$$c(\boldsymbol{x}, t = 0) = c_0 \qquad \text{uniform initial condition,} \tag{1b}$$

$$c(\boldsymbol{x}, t)|_{\partial\Omega} = 0 \qquad \text{vanishing on the target surface } \partial\Omega, \tag{1c}$$

$$c(\boldsymbol{x}, t)|_{|\boldsymbol{x}|\to\infty} = c_0 \qquad \text{regularity condition at infinity,} \tag{1d}$$

where D is the diffusion coefficient of molecules A (in units m^2/s), c_0 is their initial concentration (in units $\mathrm{mol}/\mathrm{m}^3$), the confining domain $\Omega = \{\boldsymbol{x} \in \mathbb{R}^3 : |\boldsymbol{x}| > R\}$ is the bulk space outside the target, $\partial\Omega = \{\boldsymbol{x} \in \mathbb{R}^3 : |\boldsymbol{x}| = R\}$ is the reactive surface of the target, and $\Delta = \partial^2/\partial x^2 + \partial^2/\partial y^2 + \partial^2/\partial z^2$ is the Laplace operator governing diffusion. Here and throughout the text, we assume that the target B is immobile while the molecules A can be treated as independent and point-like. Although Smoluchowski considered both molecules to be mobile and of finite size (in which case D and R are respectively the sum of diffusivities and of radii of two molecules), the equivalence between two settings is not valid in general.

The diffusion equation (1a) states that the time evolution of the concentration (the left-hand side) is caused exclusively by diffusive motion (the right-hand side), whereas the Dirichlet boundary condition (1c) ensures that any molecule A arriving at the boundary of the target B immediately reacts, i.e., it is transformed into another molecule A',

$$A + B \longrightarrow A' + B, \tag{2}$$

which diffuses away. This is the basic catalytic reaction, in which the target molecule B is a catalyst, needed to initiate the chemical transformation of A into A'. Since the molecule A, being transformed into A' upon the contact, disappears at the target surface, the concentration $c(\boldsymbol{x}, t)$ vanishes

on $\partial\Omega$. Finally, the regularity condition (1d) claims that the concentration (infinitely) far away from the target remains unaffected and equal to c_0.

Smoluchowski provided the exact solution of the partial differential equation (1) and deduced the diffusive flux of molecules A onto the target:

$$J_{\rm S}(t) = \int\limits_{|\boldsymbol{x}|=R} d\boldsymbol{s} \left(-D\frac{\partial c(\boldsymbol{x},t)}{\partial n}\right)\Big|_{\partial\Omega} = 4\pi c_0 DR\left(1+\frac{R}{\sqrt{\pi Dt}}\right), \qquad (3)$$

where $\partial/\partial n$ is the normal derivative at the boundary, oriented outward the domain (i.e., toward to center of the target in this case). In the long-time limit, the second term vanishes, and one gets the steady-state reaction rate, $J_{\rm S}(\infty) = 4\pi c_0 DR$, which is proportional to the diffusion coefficient D and to the radius R of the target. The seminal work by Smoluchowski focused exclusively onto the transport step as a limiting factor, considering *perfect* immediate reactions upon the first encounter. This setting was later called "diffusion-limited reactions", in contrast to conventional "kinetics-limited reactions" [2]. In numerous following studies, the basic diffusion problem (1) was extended in various directions, in particular, by replacing the exterior of a spherical target by an arbitrary Euclidean domain $\Omega \subset \mathbb{R}^d$ [3, 4], by considering one or multiple targets on the otherwise inert impenetrable boundary [5, 6, 7, 8], by replacing the Laplace operator (ordinary diffusion) by a general second-order elliptic differential operator [9] or a general Fokker-Planck operator [10], by introducing bulk reactivity [11, 12, 13], trapping events [14, 15], or intermittence [16, 17, 18, 19]. However, the focus on the transport step till the first encounter with the target, expressed via Eq. (1c), still remains the dominant paradigm nowadays.

In practice, chemical reactions always combine the transport step until an encounter and the reaction step. While in some situations one of these steps can be much longer than the other, it is important to consider them together, as the impact of a seemingly "irrelevant" step may still be crucial, as we discuss below. Collins and Kimball proposed to describe *imperfect* reactions on the target surface $\partial\Omega$ by replacing the Dirichlet boundary condition (1c) by the Robin boundary condition (also known as Fourier, radiation or third boundary condition):

$$\left(-D\frac{\partial c(\boldsymbol{x},t)}{\partial n}\right)\Big|_{\partial\Omega} = \kappa\, c(\boldsymbol{x},t)|_{\partial\Omega}, \qquad (4)$$

where κ (in units m/s) is called the *reactivity* [20]. Although κ can in general be any nonnegative function of a boundary point, we focus on the practically relevant case of a constant κ (we also discuss below the mixed Robin-Neumann boundary condition when κ is a piecewise constant function).

The relation (4) states that the diffusive flux density of molecules at the target surface (the left-hand side) is proportional to the concentration of the molecules at the target (the right-hand side), κ being the proportionality coefficient. It is important to stress that the diffusive flux density is a macroscopic quantity that describes the average difference between the diffusive flux toward the target and the diffusive flux from the target back to the bulk. In the limit $\kappa = 0$, the diffusive flux density vanishes at the boundary $\partial\Omega$, meaning that, on average, the number of molecules A arriving from the bulk onto the target surface is equal to the number of molecules diffusing from the target back to the bulk. As a consequence, none of these molecules actually react on the target. So the limit $\kappa = 0$ and the corresponding Neumann boundary condition describes a chemically inactive (inert) boundary that just confines the molecules in a prescribed spatial region, with no reaction. When $\kappa > 0$, there is a net difference between the diffusive flux toward the target and that from the target, and this difference is precisely the flux of reacted molecules. In the limit $\kappa \to \infty$, one retrieves the Dirichlet boundary condition (1c) by dividing Eq. (4) by κ and taking the limit. Varying κ from zero to infinity allows one to change the chemical reactivity of the target from inert to perfectly reactive.

Collins and Kimball solved the diffusion problem (1) with the Robin boundary condition (4) and found the macroscopic reaction rate [20]

$$J_{\mathrm{CK}}(t) = \frac{4\pi c_0 D R}{1 + \frac{D}{\kappa R}} \left(1 + \frac{\kappa R}{D} \operatorname{erfcx}\big((1/R + \kappa/D)\sqrt{Dt}\big) \right), \tag{5}$$

where $\operatorname{erfcx}(z)$ is the scaled complementary error function (see Ref. [21] for an extension to distinct reactivities on two complementary caps of a sphere and Ref. [22] for a perturbative approach for a dilute suspension of multiple partially reactive spheres). In the diffusion-limited case $\kappa \to \infty$, one recovers the Smoluchowski rate $J_{\mathrm{S}}(t)$, whereas the reaction-limited case $\kappa \to 0$ gives the classical limit $J_{\mathrm{reac}} = 4\pi R^2\, c_0 \kappa$, i.e., the rate is proportional to the surface area of the target and to the reactivity κ but is independent of the diffusion coefficient D. One can combine these limiting expressions to rewrite the steady-state limit of Eq. (5) as

$$\frac{1}{J_{\mathrm{CK}}(\infty)} = \frac{1}{J_{\mathrm{S}}(\infty)} + \frac{1}{J_{\mathrm{reac}}}\,. \tag{6}$$

Understanding the inverse of the flux as a "resistance", one gets a simple electric interpretation of the Collins-Kimball rate $J_{\mathrm{CK}}(\infty)$ as the serial connection of two "resistances" characterizing the "difficulty" to access the target (the transport step) and the "difficulty" to react on the target (the reaction

step) [23]. Alternatively, one can think of this relation as the sum of two characteristic times of the underlying steps. Note that a similar additivity law was established for the mean reaction time [24, 25]. Chemical reactions for which both the transport and reaction steps are relevant are sometimes called *diffusion-influenced*, *diffusion-mediated*, or *diffusion-controlled*.

The macroscopic boundary condition (4) can describe various *microscopic* mechanisms of imperfect reactions.

(i) A molecule needs to overcome an energetic activation barrier for reaction to occur [26]; in this setting, the reaction (2) can be written more accurately as

$$A + B \underset{k_{\rm off}}{\overset{k_{\rm on}}{\rightleftarrows}} AB \xrightarrow{k_{\rm reac}} A' + B, \tag{7}$$

where AB is a metastable complex which can either result in the production of A' (if the activation barrier is overpassed, with the rate $k_{\rm reac}$), or be dissociated back to A and B (with the dissociation rate $k_{\rm off}$). The reactivity is thus related to the height of the activation barrier. For instance, the reactivity κ of a spherical target can be directly related to the association rate $k_{\rm on}$ (in units $\mathrm{m}^3/\mathrm{s/mol}$) as $k_{\rm on} = 4\pi R^2\,\kappa\,N_{\rm av}$, where $N_{\rm av} \simeq 6\cdot 10^{23}$ 1/mol is the Avogadro number, and $4\pi R^2$ is the surface area of the target [27, 28]. This description was shown to be important for partial diffusion-controlled recombination [29, 30]. The reversible binding in (7) is also the key element for coupling bulk diffusion to other diffusion-reaction processes on the target. For instance, such a coupling was employed to describe the flux of receptors across the boundary between the dendrite and its spines [31].

(ii) A molecule needs to overcome an entropic barrier [32, 33] if the reaction is understood as an escape from a confining domain through a small opening region on the boundary (e.g., ion channels or aquaporins on the membrane of a living cell). In this case, the reactivity can be related to the geometric shape of the opening region (see Ref. [24] for further discussion).

(iii) There is a stochastic gating when the target can randomly switch between "open" and "closed" states, implying that the diffusing molecule can either go through the open gate, or be stopped at the closed gate and thus reflected back to resume its diffusion [34, 35, 36]; the same stochastic mechanism is relevant for enzymatic reactions when an enzyme can randomly change its conformational state to be active or passive. In both cases, the reactivity is related to the switching rates or to the probability of finding the gate open or the enzyme active.

(iv) When the target is an inert surface covered by small reactive patches, the diffusing molecule can either hit a patch and react immediately, or be reflected on an inert part and resume its diffusion until the next arrival on

the target. Homogenizing such microscopic reactivity heterogeneities by setting an effective finite reactivity κ uniformly on the target is often used to facilitate the analysis (given that the diffusion equation with multiple targets is a much more complicated problem, for both analytical and numerical computations). For instance, for a spherical target covered uniformly by N disks of radius a, Berg and Purcell obtained [37] $\kappa = DNa/(\pi R^2)$ (see further extensions in Refs. [38, 39]).

(v) For larger scale problems (e.g., animal foraging), the finite reactivity can model a "recognition" step when a particle or a species may need to recognize the target [40].

The above (incomplete) list of microscopic mechanisms urges for considering imperfect reactions. We also mention that the Robin boundary condition (4) can describe permeation across a membrane (in which case κ is called permeability) [41, 42, 43], impedance of an electrode [23, 44, 45], surface relaxation in nuclear magnetic resonance [46, 47, 48], etc.

According to Eq. (6), the macroscopic reaction rate results from a balance between the transport and the reaction steps, whereas the diffusion coefficient D and the reactivity κ play the roles of respective weights in the Robin boundary condition (4). The ratio of these quantities naturally defines the *reaction length* [23],

$$\Lambda = D/\kappa, \tag{8}$$

which has to be compared to *geometric length scales* of the problem (e.g., the radius of the target R in our spherical example). In particular, the diffusion-limited and reaction-limited cases correspond to conditions $\Lambda \ll R$ and $\Lambda \gg R$, respectively.

When molecular diffusion occurs in a structurally complex environment (e.g., an overcrowded cytoplasm or a multiscale porous medium), both the transport and reaction steps strongly depend on the geometrical structure of the environment. While the transport step is relatively well understood (see Refs. [49, 50, 51] and references therein), the more sophisticated reaction step was most often just ignored. In the next section, we summarize the main steps of a mathematical construction of the stochastic process allowing one to investigate the reaction step.

2 Partially reflected Brownian motion

The macroscopic formulation of diffusion-reaction processes in terms of partial differential equations such as Eq. (1) admits an equivalent microscopic probabilistic interpretation in terms of random trajectories of appropriate stochastic processes [52, 53, 9, 54]. From the mathematical point of view,

the Dirichlet boundary condition (1c) is the easiest to deal with. In fact, for a given continuous stochastic process X_t, it is sufficient to define the first passage time τ_0 to the target surface $\partial\Omega$,

$$\tau_0 = \inf\{t > 0 \ : \ X_t \in \partial\Omega\}, \tag{9}$$

and then to stop the process at this time. For instance, the solution of the steady-state diffusion equation, $\Delta u(\boldsymbol{x}) = 0$, subject to the Dirichlet boundary condition, $u(\boldsymbol{x})|_{\partial\Omega} = \psi(\boldsymbol{x})$, is $u(\boldsymbol{x}) = \mathbb{E}\{\psi(X_{\tau_0})|X_0 = x\}$, where $\mathbb{E}$ denotes the (conditional) expectation and $\psi(\boldsymbol{x})$ is a prescribed function on the boundary. In other words, one can think of the solution $u(\boldsymbol{x})$ as the average of the function $\psi(\boldsymbol{x})$ evaluated at random boundary points X_{τ_0} at which the stochastic process X_t (started from x) has arrived onto the boundary $\partial\Omega$ for the first time. In this way, the presence of a perfectly absorbing boundary can be accounted for via the first passage time τ_0, *with no modification to the stochastic process itself.*

In contrast, accounting for an inert or partially reactive boundary requires to modify the stochastic process. In fact, when a molecule arrives onto an inert boundary, its motion across this boundary should be prohibited. Physically, one can think of applying a very strong potential, localized in an infinitesimal vicinity of the boundary, to force the molecule moving back into the bulk. In mathematical terms, the so-called *reflected Brownian motion* can be defined as the solution of the stochastic Skorokhod equation [52]. This is a standard probabilistic way of implementing the Neumann boundary condition for an inert boundary. Once the reflected Brownian motion is constructed, one can implement eventual reactions to treat the Robin boundary condition [55, 56, 57, 58, 59]. While the related mathematical theory is well developed, its details are beyond the scope of this chapter.

The easier and physically more appealing approach consists in modeling the diffusion process as a discrete-time random walk on a lattice $\mathbb{Z}^d$ with the inter-site distance a. In a bulk site, the molecule jumps with the probability $1/(2d)$ to one of the neighboring sites. When the molecule sits at a boundary site, it can either react with the probability

$$q_a = (1 + \Lambda/a)^{-1}, \tag{10}$$

or move back to a neighboring bulk site with the probability $1 - q_a$ and continue the random walk until the next arrival onto the boundary [44, 60]. The trajectory of a molecule near a partially reactive boundary can thus be seen as a sequence of independent diffusion-mediated jumps between boundary points, each jump being a random walk in the bulk that starts from the closest bulk neighbor of a boundary site and terminates at another boundary site

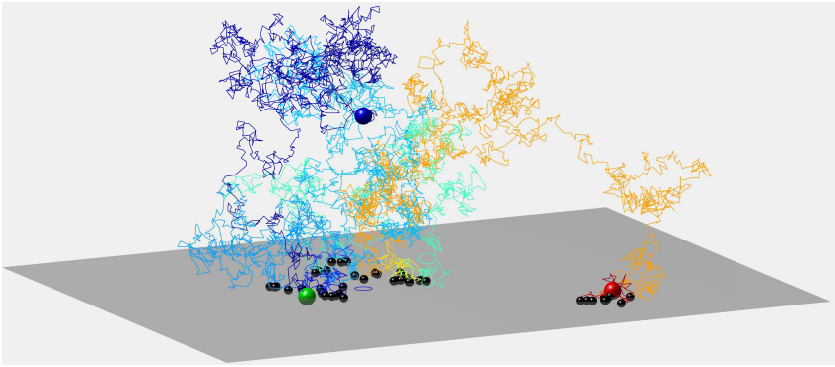


Figure 1: A simulated trajectory of partially reflected Brownian motion with $\Lambda = 10$ and $a = 0.05$. Blue, green and red balls show respectively the starting point $(0, 0, 2)$, the first arrival point, and the reaction point, whereas small black balls indicate reflection events. Diffusion-mediated jumps are drawn by different colors. Length units are arbitrary. We chose this continuous-space simulation instead of a lattice random walk for a better visualization.

upon the first arrival onto the boundary (Fig. 1). This process is called *partially reflected random walk*, whereas the statistical properties of the jumps are described by the so-called Brownian self-transport operator [44, 60]. One naturally recovers the two limiting cases: certain reaction ($q_a = 1$) for a perfectly reactive surface ($\Lambda = 0$ or $\kappa = \infty$) and certain reflection ($q_a = 0$) for an inert surface ($\Lambda = \infty$ or $\kappa = 0$).

Since the reaction event and jumps are independent, the random number η of jumps until reaction follows a geometric distribution: $\mathbb{P}\{\eta = n\} = q_a(1 - q_a)^n$ $(n = 0, 1, 2, \ldots)$. In particular, the mean number of jumps, $\mathbb{E}\{\eta\} = (1 - q_a)/q_a = \Lambda/a$, is proportional to the reaction length Λ and inversely proportional to the lattice mesh size a. When a is small, it is thus convenient to consider a rescaled variable $\chi = \eta a$ which follows an exponential distribution:

$$\mathbb{P}\{\chi \geq x\} = \mathbb{P}\{\eta \geq x/a\} = (1 - q_a)^{x/a} = (1 + a/\Lambda)^{-x/a} \approx e^{-x/\Lambda}. \qquad (11)$$

From the probabilistic point of view, consecutive individual trials after each jump with probability q_a are fully equivalent to saying that the trajectory is stopped when the number of realized jumps, multiplied by a, exceeds an independent exponentially distributed random variable χ.

Each jump started at the distance a from the boundary has high chances to return to the boundary within the distance a to the starting point. In other words, each jump explores the boundary at a typical distance of the

order of a (we emphasize that the *mean* exploration distance can be infinite, see Sec. 4). As a consequence, the whole trajectory from the first arrival onto the boundary until reaction, being a sequence of Λ/a jumps on average, explores the surface up to a typical distance Λ. These qualitative arguments provide the geometric meaning of the reaction length Λ as a typical size of the surface region around the first arrival point explored until reaction (see Sec. 4 for precise statements).

The above lattice-based construction of partially reflected random walks employs the mesh distance a. In the limit $a \to 0$, each jump starts closer to the boundary and thus explores shorter distances, but the number of jumps increases (given that $q_a \to 0$) so that these effects compensate each other. One can thus expect that such partially reflected trajectories on a lattice converge to a well-defined continuous limit as $a \to 0$ (in the same way as ordinary random walks converge to Brownian motion). This limit that we call *partially reflected Brownian motion* (PRBM) [61], is defined as reflected Brownian motion stopped at the random time

$$\tau_\Lambda = \inf\{t > 0 \ : \ \ell_t > \chi\}, \tag{12}$$

where ℓ_t is the local time process of the reflected Brownian motion on the boundary, which is a continuous analog of the rescaled number of jumps on the boundary (ηa) up to time t, and an independent random variable χ was defined by Eq. (11). The reaction length Λ appears in the exponential law (11) and thus parameterizes the family of PRBMs. In the limit $\Lambda = 0$, the exponential distribution for χ degenerates to the Dirac distribution at 0, so that Eq. (12) is reduced to $\tau_0 = \inf\{t > 0 \ : \ \ell_t > 0\}$, i.e., τ_0 is the first moment when the local time process becomes strictly positive that occurs on the first arrival onto the boundary, and one retrieves Eq. (9).

In spite of apparent similarities between discrete-space and continuous-space partially reflected diffusions, there is a peculiar difference in their construction. In the discrete-space approach, one considers a sequence of diffusion-mediated jumps, in which each jump terminates upon the first arrival on the boundary. In other words, the boundary is treated as perfectly absorbing for each jump, whereas the partial reactivity is controlled by the number of jumps. In contrast, in the continuous-space approach, the underlying process is the reflected Brownian motion so that the boundary is treated as fully reflecting, whereas the partial reactivity is again controlled by the (rescaled) number of jump (i.e., the local time process).

The introduction of a small distance a to restart each jump was crucial to avoid an immediate return to the boundary. In contrast, discrete space and time random walks on a lattice can be easily replaced by continuous trajectories of Brownian motion [61, 62]. While we focused on partially reflected

Brownian motion governed by the Laplace operator, one can construct much more general partially reflected diffusions governed by elliptic second-order differential operators [59]. In particular, one can consider Markovian jump processes generated by the Euler discretization scheme of a more general stochastic process in the bulk [63]. Once the generated trajectory crosses the boundary, it can be either terminated with probability q_a, or reflected back. In our notations, the probability q_a obtained by Singer *et al.* reads

$$q_a = \sqrt{\pi}\kappa\sqrt{\Delta t}/\sqrt{2D} = (\sqrt{\pi}/2)\kappa a/D = (\sqrt{\pi}/2)a/\Lambda, \tag{13}$$

with $a = \sqrt{2D\Delta t}$, where Δt is the time step. This expression is close to the formula (10), which for small a/Λ yield $q_a \approx a/\Lambda$. The extra factor $\sqrt{\pi}/2 \approx 0.89$ is related to the use of Gaussian jumps in the Euler scheme instead of discrete-space random walks. In contrast to Eq. (13), the formula (10) is applicable for any reactivity, i.e. a/Λ does not need to be a small parameter.

In the next section, we discuss the propagator of PRBM and show the impact of the reactivity onto various statistics relevant to diffusion-controlled reactions.

3 General representation of the propagator

In this section, we derive a general representation of the propagator $G_\Lambda(\boldsymbol{x}_0, \boldsymbol{x}; t)$ of partially reflected Brownian motion, i.e., the probability density of finding a molecule started at a point $\boldsymbol{x}_0$ at time 0 in a vicinity of a point $\boldsymbol{x}$ at time t in the presence of a partially reactive boundary $\partial\Omega$ characterized by the reaction length Λ. The propagator satisfies the following equations

$$\frac{\partial G_\Lambda(\boldsymbol{x}_0, \boldsymbol{x}; t)}{\partial t} - D\Delta G_\Lambda(\boldsymbol{x}_0, \boldsymbol{x}; t) = 0 \qquad (\boldsymbol{x} \in \Omega), \tag{14a}$$

$$G_\Lambda(\boldsymbol{x}_0, \boldsymbol{x}; t = 0) = \delta(\boldsymbol{x} - \boldsymbol{x}_0), \tag{14b}$$

$$\left(\Lambda\frac{\partial}{\partial n} + 1\right) G_\Lambda(\boldsymbol{x}_0, \boldsymbol{x}; t) = 0 \qquad (\boldsymbol{x} \in \partial\Omega), \tag{14c}$$

where $\delta(\boldsymbol{x} - \boldsymbol{x}_0)$ is the Dirac distribution (if the domain Ω is unbounded, these equations should be completed by the regularity condition at infinity: $G_\Lambda(\boldsymbol{x}_0, \boldsymbol{x}; t) \to 0$ as $|\boldsymbol{x}| \to \infty$). To avoid technical details, we assume that the boundary $\partial\Omega$ is smooth.

The propagator can be decomposed into two parts: the contribution of direct trajectories from $\boldsymbol{x}_0$ to $\boldsymbol{x}$ without touching the reactive surface,

$G_0(\boldsymbol{x}_0, \boldsymbol{x}; t)$, and the contribution of trajectories that hit this surface at a point $\boldsymbol{s}_1 \in \partial\Omega$ at an intermediate time $0 < t_1 < t$:

$$G_\Lambda(\boldsymbol{x}_0, \boldsymbol{x}; t) = G_0(\boldsymbol{x}_0, \boldsymbol{x}; t) + \int\limits_{\partial\Omega} d\boldsymbol{s}_1 \int\limits_0^t dt_1\, j_0(\boldsymbol{x}_0, \boldsymbol{s}_1; t_1)\, G_\Lambda(\boldsymbol{s}_1, \boldsymbol{x}; t - t_1), \quad (15)$$

where

$$j_0(\boldsymbol{x}_0, \boldsymbol{s}_1; t_1) = \left(-D \frac{\partial}{\partial n} G_0(\boldsymbol{x}_0, \boldsymbol{x}; t_1) \right)_{\boldsymbol{x}=\boldsymbol{s}_1} \quad (16)$$

is the diffusive flux density at time t_1 at a point $\boldsymbol{s}_1$ of the *perfectly* reactive surface (i.e., the probability density of the first arrival in a vicinity of $\boldsymbol{s}_1$ at time t_1). This density describes the transport step and is independent of Λ. Next, employing the reversal symmetry of the propagator, $G_\Lambda(\boldsymbol{x}_0, \boldsymbol{x}; t) = G_\Lambda(\boldsymbol{x}, \boldsymbol{x}_0; t)$, which is also valid when $\boldsymbol{x}_0$ is a boundary point for $\Lambda > 0$, one can represent $G_\Lambda(\boldsymbol{s}_1, \boldsymbol{x}; t)$ in Eq. (15) using again Eq. (15) to obtain

$$\begin{aligned} G_\Lambda(\boldsymbol{x}_0, \boldsymbol{x}; t) \;=\; & G_0(\boldsymbol{x}_0, \boldsymbol{x}; t) + \int\limits_{\partial\Omega} d\boldsymbol{s}_1 \int\limits_{\partial\Omega} d\boldsymbol{s}_2 \int\limits_0^t dt_1 \int\limits_{t_1}^t dt_2\, j_0(\boldsymbol{x}_0, \boldsymbol{s}_1; t_1) \\ & \times G_\Lambda(\boldsymbol{s}_1, \boldsymbol{s}_2; t_2 - t_1)\, j_0(\boldsymbol{x}, \boldsymbol{s}_2; t - t_2). \end{aligned} \quad (17)$$

This relation expresses the propagator $G_\Lambda(\boldsymbol{x}_0, \boldsymbol{x}; t)$ in the whole domain in terms of the propagator $G_\Lambda(\boldsymbol{s}_1, \boldsymbol{s}_2; t)$ from one boundary point to another via bulk diffusion. The second term in Eq. (17) has a simple probabilistic interpretation: a molecule reaches the boundary for the first time at t_1, performs partially reflected Brownian motion (with eventual reaction) over time $t_2 - t_1$ and, if not reacted during this time, diffuses to the bulk point $\boldsymbol{x}$ during time $t - t_2$ without hitting the reactive surface. We emphasize that the last step would not be possible in the perfectly reactive case because the propagator $G_0(\boldsymbol{x}_0, \boldsymbol{x}; t)$ is zero when $\boldsymbol{x}$ is a boundary point. We also stress that Eq. (17) is valid if $\boldsymbol{x} = \boldsymbol{s} \in \partial\Omega$ is a boundary point. In this case, $G_0(\boldsymbol{x}_0, \boldsymbol{s}; t) = 0$, while $j_0(\boldsymbol{s}, \boldsymbol{s}_2; t - t_2) = \delta(\boldsymbol{s} - \boldsymbol{s}_2)\delta(t - t_2)$, so that the integrals over $\boldsymbol{s}_2$ and t_2 are removed, reducing Eq. (17) to

$$G_\Lambda(\boldsymbol{x}_0, \boldsymbol{s}; t) = \int\limits_{\partial\Omega} d\boldsymbol{s}_1 \int\limits_0^t dt_1\, j_0(\boldsymbol{x}_0, \boldsymbol{s}_1; t_1)\, G_\Lambda(\boldsymbol{s}_1, \boldsymbol{s}; t - t_1). \quad (18)$$

This relation justifies the qualitative separation of the diffusion-reaction process into two steps: the transport step (described by $j_0(\boldsymbol{x}_0, \boldsymbol{s}_1; t_1)$) and the reaction step (described by $G_\Lambda(\boldsymbol{s}_1, \boldsymbol{s}; t - t_1)$ or related quantities, see below).

We stress, however, that the reaction step involves intricate diffusion process near the partially reactive surface. In addition to the new conceptual view onto partially reflected Brownian motion, the representations (17, 18) can be helpful for a numerical computation of the propagator because only the boundary-to-boundary transport $G_\Lambda(\boldsymbol{s}_1, \boldsymbol{s}_2; t)$ needs to be evaluated. Note also that the time convolution can be removed by passing to the Laplace domain, in which Eq. (17) becomes

$$\begin{aligned} \tilde{G}_\Lambda(\boldsymbol{x}_0, \boldsymbol{x}; p) &= \tilde{G}_0(\boldsymbol{x}_0, \boldsymbol{x}; p) \\ &+ \int\limits_{\partial\Omega} d\boldsymbol{s}_1 \int\limits_{\partial\Omega} d\boldsymbol{s}_2\, \tilde{j}_0(\boldsymbol{x}_0, \boldsymbol{s}_1; p)\, \tilde{G}_\Lambda(\boldsymbol{s}_1, \boldsymbol{s}_2; p)\, \tilde{j}_0(\boldsymbol{x}, \boldsymbol{s}_2; p), \end{aligned} \tag{19}$$

where tilde denotes the Laplace transform: $\tilde{f}(p) = \int_0^\infty dt\, e^{-pt} f(t)$.

Relation to the Dirichlet-to-Neumann operator

The Laplace-transformed propagator $\tilde{G}_\Lambda(\boldsymbol{s}_1, \boldsymbol{s}_2; p)$ turns out to be the resolvent of the *Dirichlet-to-Neumann operator* $\mathcal{M}_p$ for the modified Helmholtz equation: to a given function f on the boundary $\partial\Omega$ of a confining domain $\Omega \subset \mathbb{R}^d$, the operator $\mathcal{M}_p$ associates another function on the boundary,

$$\mathcal{M}_p f = \left(\frac{\partial u(\boldsymbol{x}; p)}{\partial n} \right)_{|\boldsymbol{x} \in \partial\Omega}, \tag{20}$$

where $u(\boldsymbol{x}; p)$ is the solution of the Dirichlet boundary value problem:

$$(p - D\Delta) u(\boldsymbol{x}; p) = 0 \qquad (\boldsymbol{x} \in \Omega), \tag{21a}$$

$$u(\boldsymbol{x}; p)_{|\partial\Omega} = f(\boldsymbol{x}; p) \quad (\boldsymbol{x} \in \partial\Omega). \tag{21b}$$

For instance, if $f(\boldsymbol{x}; p)$ 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). While the Dirichlet-to-Neumann operator was conventionally studied for the Laplace equation (i.e., $p = 0$), the above extension to the modified Helmholtz equation is straightforward.

One can use the Dirichlet-to-Neumann operator to represent the Laplace-transformed propagator $\tilde{G}_\Lambda(\boldsymbol{x}_0, \boldsymbol{x}; p)$ which satisfies for each fixed $\boldsymbol{x}_0 \in \Omega$ the modified Helmholtz equation:

$$(p - D\Delta) \tilde{G}_\Lambda(\boldsymbol{x}_0, \boldsymbol{x}; p) = \delta(\boldsymbol{x} - \boldsymbol{x}_0) \quad (\boldsymbol{x} \in \Omega), \tag{22a}$$

$$\left(\Lambda \frac{\partial}{\partial n} + 1 \right) \tilde{G}_\Lambda(\boldsymbol{x}_0, \boldsymbol{x}; p) = 0 \quad (\boldsymbol{x} \in \partial\Omega). \tag{22b}$$

To get rid off $\delta(\boldsymbol{x}-\boldsymbol{x}_0)$, one can search the solution in the form

$$\tilde{G}_\Lambda(\boldsymbol{x}_0,\boldsymbol{x};p)=\tilde{G}_0(\boldsymbol{x}_0,\boldsymbol{x};p)+\tilde{g}_\Lambda(\boldsymbol{x}_0,\boldsymbol{x};p), \tag{23}$$

where the unknown regular part $\tilde{g}_\Lambda(\boldsymbol{x}_0,\boldsymbol{x};p)$ satisfies

$$\begin{aligned}(p-D\Delta)\tilde{g}_\Lambda(\boldsymbol{x}_0,\boldsymbol{x};p) &= 0 \quad (\boldsymbol{x}\in\Omega), &\text{(24a)}\\ \left(\Lambda\frac{\partial}{\partial n}+1\right)\tilde{g}_\Lambda(\boldsymbol{x}_0,\boldsymbol{x};p) &= \underbrace{-\Lambda\left(\frac{\partial}{\partial n}\tilde{G}_0(\boldsymbol{x}_0,\boldsymbol{x};p)\right)}_{=(\Lambda/D)\tilde{j}_0(\boldsymbol{x}_0,\boldsymbol{x};p)} \quad (\boldsymbol{x}\in\partial\Omega). &\text{(24b)}\end{aligned}$$

Suppose that we have solved this problem and found that the solution $\tilde{g}_\Lambda(\boldsymbol{x}_0,\boldsymbol{x};p)$ on the boundary $\partial\Omega$ is equal to some function $f(\boldsymbol{x};p)$. Once we know $f(\boldsymbol{x};p)$, we can simply reconstruct $\tilde{g}_\Lambda(\boldsymbol{x}_0,\boldsymbol{x};p)$ as the solution of the corresponding Dirichlet problem. Applying then the Dirichlet-to-Neumann operator to $f(\boldsymbol{x};p)$, we can express the normal derivative of $\tilde{g}_\Lambda(\boldsymbol{x}_0,\boldsymbol{x};p)$. Summarizing these steps, one can express the restriction of the solution $\tilde{g}_\Lambda(\boldsymbol{x}_0,\boldsymbol{x};p)$ onto the boundary as

$$\tilde{g}_\Lambda(\boldsymbol{x}_0,\boldsymbol{s};p)=\left(\Lambda\mathcal{M}_p+I\right)^{-1}\frac{\Lambda}{D}\tilde{j}_0(\boldsymbol{x}_0,\boldsymbol{s};p) \qquad (\boldsymbol{s}\in\partial\Omega), \tag{25}$$

where I is the identity operator. Finally, if the starting point $\boldsymbol{x}_0=\boldsymbol{s}_0$ lies on the boundary, one has $\tilde{j}_0(\boldsymbol{s}_0,\boldsymbol{s};p)=\delta(\boldsymbol{s}-\boldsymbol{s}_0)$, the Dirichlet propagator $\tilde{G}_0(\boldsymbol{s}_0,\boldsymbol{x};p)$ vanishes in Eq. (23), and we get

$$D\tilde{G}_\Lambda(\boldsymbol{s}_0,\boldsymbol{s};p)=\left(\mathcal{M}_p+I/\Lambda\right)^{-1}\delta(\boldsymbol{s}-\boldsymbol{s}_0) \qquad (\boldsymbol{s}_0,\boldsymbol{s}\in\partial\Omega). \tag{26}$$

We conclude that $D\tilde{G}_\Lambda(\boldsymbol{s}_0,\boldsymbol{s};p)$ is the resolvent of the Dirichlet-to-Neumann operator $\mathcal{M}_p$. In particular, one can rewrite Eq. (19) in the form of a scalar product between two functions on the boundary

$$\tilde{G}_\Lambda(\boldsymbol{x}_0,\boldsymbol{x};p)=\tilde{G}_0(\boldsymbol{x}_0,\boldsymbol{x};p)+\frac{\Lambda}{D}\left(\tilde{j}_0(\boldsymbol{x}_0,\cdot;p)\,\cdot\,(I+\Lambda\mathcal{M}_p)^{-1}\tilde{j}_0(\boldsymbol{x},\cdot;p)\right)_{L_2(\partial\Omega)}. \tag{27}$$

Remarkably, all the "ingredients" of this formula correspond to the Dirichlet condition on a perfectly reactive boundary, and only the reaction length Λ keeps track of partial reactivity. Note that this is a significant extension of the formula for the total steady-state flux derived in Ref. [45]. This profound connection (that was earlier established for the conventional setting of the Laplace equation [61, 45]) allows one to express many probabilistic quantities through the spectral properties of the Dirichlet-to-Neumann operator.

Reaction time distribution and spread harmonic measure

The propagator determines many quantities often considered in the context of diffusion-controlled reactions: the survival probability up to time t, the reaction time distribution, the distribution of the reaction point (at which reaction occurs), etc. For instance, the diffusive flux density at a partially reactive point $\boldsymbol{s} \in \partial\Omega$ is

$$j_\Lambda(\boldsymbol{x}_0, \boldsymbol{s}; t) = \left(-D\frac{\partial}{\partial n} G_\Lambda(\boldsymbol{x}_0, \boldsymbol{x}; t)\right)_{\boldsymbol{x}=\boldsymbol{s}} = \frac{D}{\Lambda} G_\Lambda(\boldsymbol{x}_0, \boldsymbol{s}; t), \tag{28}$$

where we used the Robin boundary condition (14c). This is the joint probability density for the reaction time and reaction point on the boundary (from the starting point $\boldsymbol{x}_0$). The integral over $\boldsymbol{s}$ yields the marginal probability density of reaction times,

$$\rho_\Lambda(t; \boldsymbol{x}_0) = \int\limits_{\partial\Omega} d\boldsymbol{s}\, j_\Lambda(\boldsymbol{x}_0, \boldsymbol{s}; t) = \frac{D}{\Lambda} \int\limits_{\partial\Omega} d\boldsymbol{s}\, G_\Lambda(\boldsymbol{x}_0, \boldsymbol{s}; t), \tag{29}$$

whereas the integral over time t yields the marginal probability density of reaction points:

$$\omega_\Lambda(\boldsymbol{s}; \boldsymbol{x}_0) = \int\limits_0^\infty dt\, j_\Lambda(\boldsymbol{x}_0, \boldsymbol{s}; t) = \frac{D}{\Lambda} \tilde{G}_\Lambda(\boldsymbol{x}_0, \boldsymbol{s}; p = 0). \tag{30}$$

The latter was called the *spread harmonic measure* [61, 45, 64, 65]. This is a natural extension of the harmonic measure [66] that characterizes the first arrival onto the perfectly reactive boundary [67, 68].

In general, the reactive surface does not need to be the whole boundary of the confining domain Ω. The above analysis remains applicable when only a part of the boundary is partially reactive, whereas the remaining part is inert. In this case, the Neumann boundary condition is imposed on the inert part so that one faces the mixed Robin-Neumann boundary condition. In this setting, the propagator $G_0(\boldsymbol{x}_0, \boldsymbol{x}; t)$ corresponds to the respective Dirichlet-Neumann problem, with a perfectly reactive part. In other words, the presence of the inert part does not change the above arguments, once the involved quantities are treated accordingly.

4 An example: the half-space

As a basic example, we consider the partially reflected Brownian motion in an upper half-space, $\Omega = \{\boldsymbol{x} = (\boldsymbol{y}, z) \in \mathbb{R}^d \ : \ z > 0\}$, with partially re-

active hyperplane $\partial\Omega = \mathbb{R}^{d-1}$. For convenience, we represent each point $\boldsymbol{x}$ as $(\boldsymbol{y}, z)$, where $\boldsymbol{y} \in \mathbb{R}^{d-1}$ are lateral coordinates, and $z \geq 0$ is the transverse coordinate. In this example, the transverse and lateral motions are independent, and the propagator $G_\Lambda(\boldsymbol{x}_0, \boldsymbol{x}; t)$ is the product of the Gaussian propagator in lateral directions and the propagator on the transverse positive semi-axis with the Robin boundary condition at the zero endpoint. The latter propagator is well known (see, e.g., the book [69]), and we get

$$G_\Lambda(\boldsymbol{x}_0, \boldsymbol{x}; t) = \frac{\exp\left(-\frac{|\boldsymbol{y}-\boldsymbol{y}_0|^2}{4Dt}\right)}{(4\pi Dt)^{(d-1)/2}} \left\{ \frac{\exp\left(-\frac{(z-z_0)^2}{4Dt}\right) + \exp\left(-\frac{(z+z_0)^2}{4Dt}\right)}{\sqrt{4\pi Dt}} - \frac{1}{\Lambda} \exp\left(\frac{z+z_0}{\Lambda} + \frac{Dt}{\Lambda^2}\right) \operatorname{erfc}\left(\frac{z+z_0}{\sqrt{4Dt}} + \frac{\sqrt{Dt}}{\Lambda}\right) \right\}, \quad (31)$$

where $\operatorname{erfc}(z)$ is the complementary error function. This is a rare example when the propagator can be obtained in a fully explicit form. In the limit $\Lambda = 0$, Eq. (31) is reduced to the Dirichlet propagator in the upper half-space:

$$G_0(\boldsymbol{x}_0, \boldsymbol{x}; t) = \underbrace{\frac{\exp\left(-\frac{|\boldsymbol{y}-\boldsymbol{y}_0|^2}{4Dt}\right)}{(4\pi Dt)^{(d-1)/2}}}_{\text{lateral}} \underbrace{\frac{\exp\left(-\frac{(z-z_0)^2}{4Dt}\right) - \exp\left(-\frac{(z+z_0)^2}{4Dt}\right)}{\sqrt{4\pi Dt}}}_{\text{transverse}}, \quad (32)$$

from which

$$j_0(\boldsymbol{x}_0, \boldsymbol{s}; t) = \frac{\exp\left(-\frac{|\boldsymbol{s}-\boldsymbol{y}_0|^2}{4Dt}\right)}{(4\pi Dt)^{(d-1)/2}} \frac{z_0 \exp\left(-\frac{z_0^2}{4Dt}\right)}{\sqrt{4\pi Dt^3}}. \quad (33)$$

The above formulas help to compute other quantities of interest. For instance, the probability density of the reaction time follows from Eqs. (29)

$$\rho_\Lambda(t; z_0) = \frac{D \exp\left(-\frac{z_0^2}{4Dt}\right)}{\Lambda} \left\{ \frac{1}{\sqrt{\pi Dt}} - \frac{1}{\Lambda} \operatorname{erfcx}\left(\frac{z_0}{\sqrt{4Dt}} + \frac{\sqrt{Dt}}{\Lambda}\right) \right] \right\} \quad (34)$$

(note that the density depends only on the height z_0 of the starting point $\boldsymbol{x}_0 = (\boldsymbol{y}_0, z_0)$ above the boundary). In the limit $\Lambda = 0$, one retrieves the classical expression $\rho_0(t; z_0) = \frac{z_0}{\sqrt{4\pi Dt^3}} e^{-z_0^2/(4Dt)}$. In the long-time limit, one gets $\rho_\Lambda(t; z_0) \simeq \frac{z_0+\Lambda}{\sqrt{4\pi Dt^3}}$, as though the height of the starting point is increased by the reaction length Λ. In the short-time limit, one gets either a very fast vanishing as $t \to 0$ for $z_0 > 0$, or a power law divergence $\rho_\Lambda(t; z_0) \simeq \frac{D/\Lambda}{\sqrt{\pi Dt}}$ for $z_0 = 0$. This behavior is illustrated in Fig. 2.

The spread harmonic measure density is obtained from Eq. (30):

$$\omega_\Lambda(\boldsymbol{s}; \boldsymbol{x}_0) = \int\limits_{\mathbb{R}^{d-1}} \frac{d\boldsymbol{q}}{(2\pi)^{d-1}} \frac{e^{-i(\boldsymbol{q}(\boldsymbol{s}-\boldsymbol{y}_0))}}{1+\Lambda|\boldsymbol{q}|} = \int\limits_0^\infty dz \frac{e^{-z/\Lambda}}{\Lambda} \omega_0(\boldsymbol{s}; (\boldsymbol{y}, z_0 + z)), \quad (35)$$

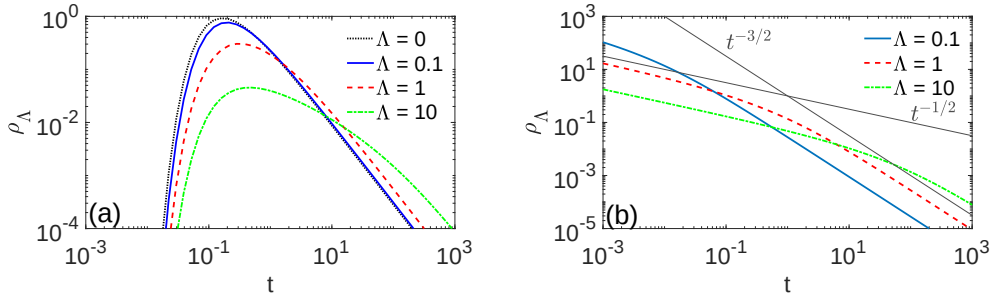


Figure 2: The probability density $\rho_\Lambda(t; z_0)$ of the reaction time for a molecule started at height z_0 above a flat surface, with $z_0 = 1$ **(a)** and $z_0 = 0$ **(b)**, and four values of the reaction length Λ (arbitrary units are used, with $D = 1$). In the second plot, the density $\rho_0(t; z_0 = 0) = \delta(t)$ for $\Lambda = 0$ is not shown. Gray lines indicate power law asymptotics $t^{-1/2}$ and $t^{-3/2}$.

where

$$\omega_0(\boldsymbol{s}; (\boldsymbol{y}_0, z_0)) = \frac{\Gamma(d/2)}{\pi^{d/2}} \frac{z_0}{[z_0^2 + |\boldsymbol{s} - \boldsymbol{y}_0|^2]^{d/2}} \tag{36}$$

is the harmonic measure density (see Ref. [65] for the derivation of the last equality in Eq. (35)). In other words, the effect of partial reflections on the boundary can be seen as an effective increase the height z_0 of the starting point above the boundary. This increase is randomly distributed with an exponential law determined by the reaction length Λ. As expected, the density ω_Λ is radially symmetric with respect to the line which is perpendicular to the reactive surface and passes through the starting point $\boldsymbol{x}_0$. In other words, it depends only on the height z_0 and the radial distance $r = |\boldsymbol{s} - \boldsymbol{y}_0|$. The behavior of the spread harmonic measure is illustrated in Fig. 3. One can easily check that the *mean* exploration distance, defined as the standard deviation of explored distance from the first arrival point to the reaction point, is infinite (see also Ref. [70]). This is related to the fact that each jump can go unlimitedly far away from the reactive boundary, and such rare but anomalously long trajectories dominate in the second moment, due to the power-law asymptotic decay of the harmonic measure density in Eq. (36). In this way, the successive arrival points of partially reflected Brownian motion onto the reactive surface can be seen as Lévy flights on that surface [71, 72, 73, 74, 75].

Integrating the spread harmonic measure over $\boldsymbol{s}$ with $|\boldsymbol{s} - \boldsymbol{y}_0| > R$, one gets the probability of the reaction event at boundary points whose distance

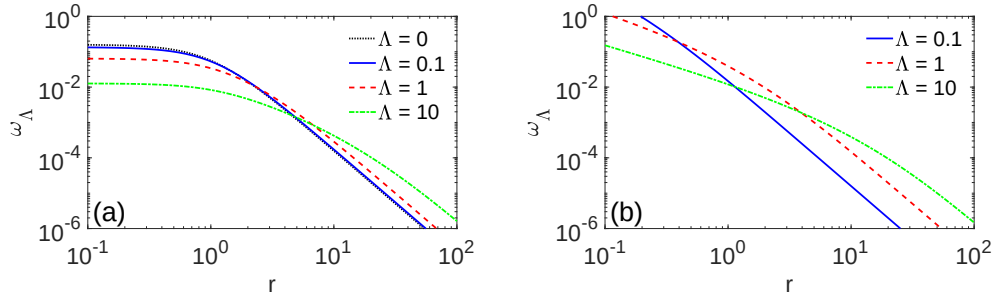


Figure 3: The spread harmonic measure density $\omega_\Lambda(\boldsymbol{s};(\boldsymbol{y}_0,z_0))$ of the reaction point $\boldsymbol{s}$ as a function of the radial distance $r=|\boldsymbol{s}-\boldsymbol{y}_0|$ for a molecule started at height z_0 above the plane in the three-dimensional space ($d=3$), with $z_0=1$ **(a)** and $z_0=0$ **(b)**, and four values of the reaction length Λ (arbitrary units are used, with $D=1$). In the second plot, the harmonic measure density $\omega_0(\boldsymbol{s};(\boldsymbol{y}_0,0))=\delta(\boldsymbol{s}-\boldsymbol{y}_0)$ for $\Lambda=0$ is not shown.

to the first arrival point is greater than R:

$$P_\Lambda(R)=\int\limits_{|\boldsymbol{s}-\boldsymbol{y}_0|>R} d\boldsymbol{s}\,\omega_\Lambda(\boldsymbol{s};(\boldsymbol{y}_0,0))=\frac{2\Gamma(d/2)}{\sqrt{\pi}\,\Gamma((d-1)/2)}\int\limits_0^\infty dx\,\frac{e^{-xR/\Lambda}}{(1+x^2)^{d/2}} \tag{37}$$

(the last equality was derived in Ref. [65]). This probability characterizes the exploration of a flat partially reactive surface after the first arrival and till the reaction. This is a function of R/Λ, which monotonously decreases from 1 to 0. The condition $P_\Lambda(R_m)=0.5$ defines the median radius R_m of the spherical domain around the first arrival point, at which half of molecules react. In three dimensions, one gets $R_m\approx 1.17\,\Lambda$, providing a geometric interpretation of the reaction length Λ. The behavior of the probability $P_\Lambda(R)$ is illustrated in Fig. 4.

5 Conclusion: Is the finite reactivity important?

As discussed in Sec. 1, there are various microscopic mechanisms that naturally lead to a finite reactivity of the target surface. However, the mathematical description of imperfect reactions involves more sophisticated Robin boundary condition and partially reflected Brownian motion. While most of the results known for perfect reactions can be generalized to imperfect ones,

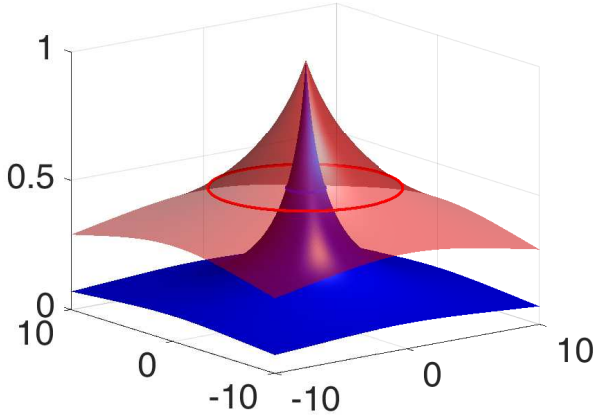


Figure 4: The probability $P_\Lambda(R)$ of the reaction event at a boundary point $\boldsymbol{s}$ at distance greater than R to the first arrival point (here, the origin) on the plane in the three-dimensional space ($d = 3$), for two values of the reaction length: $\Lambda = 1$ (blue narrower surface) and $\Lambda = 5$ (red broader surface). Two circles show the median reaction radius $R_m \approx 1.17\,\Lambda$ at which this probability is equal to 0.5. Arbitrary length units are used.

mathematical derivations are usually much more involved. It is probably for this reason that the majority of theoretical studies remains focused on perfect reactions. It is therefore natural to ask whether the finite reactivity is indeed important?

The reactivity of the target introduces the reaction length $\Lambda = D/\kappa$ which controls the balance between the transport step toward the target and the reaction step on the target. The latter step involves the intricate exploration of the partially reactive surface until the reaction occurs. This process mixes bulk diffusion from surface to surface points and eventual reaction trials. Since the process is strongly coupled to the geometry of the environment, the dependence of diffusion characteristics (such as the total flux) on Λ can reveal geometric structure of the target surface [76].

When the reaction length is the smallest length scale of the problem, the effects of finite reactivity can be neglected. In practice, however, there is a conceptual difference between setting $\Lambda = 0$ (the idealized case of perfect reactions with Dirichlet boundary condition, $\kappa = \infty$), and $\Lambda > 0$, even if Λ remains small. For instance, in the analysis of the short-time asymptotic behavior of a diffusion problem, the diffusion length $\sqrt{Dt}$ can become smaller than the reaction length $\Lambda > 0$ as $t \to 0$. As a consequence, the short-time asymptotic behavior for perfect and imperfect reactions is different [40, 77].

For example, the probability density of the reaction time on a spherical target of radius R reads [40]

$$\rho_\Lambda(t;\boldsymbol{x}_0) \simeq \frac{R}{|\boldsymbol{x}_0|}\,\frac{\exp\bigl(-\frac{(|\boldsymbol{x}_0|-R)^2}{4Dt}\bigr)}{t\sqrt{\pi}} \times \begin{cases} \dfrac{|\boldsymbol{x}_0|-R}{\sqrt{4Dt}} & (\Lambda=0), \\ \dfrac{\sqrt{Dt}}{\Lambda} & (\Lambda>0) \end{cases} \tag{38}$$

(with the starting point $\boldsymbol{x}_0$ outside the target: $|\boldsymbol{x}_0| > R$). One can see that the power law prefactor is different in two cases. Moreover, when Λ is small, one can also expect the transition from the short-time regime at $\sqrt{Dt} \ll \Lambda \ll |\boldsymbol{x}_0| - R$ (given by the second expression) to an intermediate regime at $\Lambda \ll \sqrt{Dt} \ll |\boldsymbol{x}_0| - R$ (given by the first expression).

Another important example is the so-called narrow escape problem from an Euclidean domain Ω through a small hole Γ on the boundary $\partial\Omega$ (see the review [6] and references therein). In this setting, the escape through a hole Γ can be understood as reaction on the target Γ upon the first arrival. When the (nondimensional) size ε of the escape region goes to zero, the mean exit time diverges as $\log(1/\varepsilon)$ in two dimensions and as ε^{-1} in three dimensions [78, 6]. However, an escape through a small opening requires overpassing either an entropic or an energetic barrier, or both. Once the escape region is considered as partially reactive ($\Lambda > 0$), the asymptotic behavior of the mean exit time changes drastically [24]. In the narrow escape limit $\varepsilon \to 0$, the dominant contribution to the mean exit time comes from the finite reactivity and scales as ε^{-1}/κ in two dimensions and ε^{-2}/κ in three dimensions. This contribution does not exist for idealized perfect escape ($\kappa = \infty$) but becomes dominant for a finite reactivity κ. Once again, in the narrow escape limit, the size of the hole becomes the smallest length scale, and thus the finite reactivity cannot be ignored. The impact of κ on the whole distribution of the reaction time was recently investigated [79].

These two examples illustrate how an idealized assumption of perfect reactions can be misleading. Even though the analysis of imperfect reactions is mathematically more involved, the related technical difficulties are generally not insurmountable. As a matter of fact, the finite reactivity often "regularizes" solutions and helps to resolve some apparent "paradoxical" properties of Brownian motion. For instance, the Smoluchowski flux (3) toward a perfectly reactive spherical target diverges as $t \to 0$, meaning that too many molecules in a close vicinity of the target react at first time instances. This unrealistic divergence does not appear in the Collins-Kimball flux (5) toward a partially reactive target. Moreover, partially reflected Brownian motion can be started right at the partially reactive boundary whereas ordinary Brownian motion started on an absorbing boundary would immediately

react. As a consequence, the Robin boundary condition is necessary for a natural implementation of reversible association of a diffusing molecule with the target. In fact, when the formed metastable complex AB in (7) dissociates (with some rate $k_{\rm off}$), the just dissociated molecule is released *on* the target surface. If the latter was perfectly reactive, the molecule would *immediately* react again, making such a dissociation process impossible [80, 81]. A standard trick to overcome this problem consists in ejecting the just dissociated molecule to a finite distance a from the target, from which its diffusion is released [44, 60, 16, 17, 18, 19]. While the introduction of such an ejection distance can be rationalized from the physical point of view (e.g., a finite size of molecules, the presence of a specific surface layer, a finite range binding interaction, etc.), this is precisely an intermediate step of the construction of partially reflected Brownian motion as described in Sec. 2. In other words, even when one tries to avoid using partial reactivity and the associated PRBM, one often uses it implicitly via a "regularization" by a finite ejection distance a.

The mathematical theory of partially reflected diffusions is rather well developed [55, 56, 57, 58, 59]. In particular, the fundamental interconnection between the stochastic process, the diffusion equation with Robin boundary condition, and the spectral properties of the underlying diffusion operator and the Dirichlet-to-Neumann operator provides the solid mathematical foundation for investigating imperfect diffusion-controlled reactions. In turn, the intricate exploration of the partially reactive surface via diffusion-mediated jumps in complicated structures such as multiscale porous media or domains with irregular or fractal boundaries, remains poorly understood. In this light, efficient numerical techniques such as fast Monte Carlo methods [82, 67, 68, 83] or semi-analytical solutions [84, 85] become particularly important.

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