


## Paradigm Shift in Diffusion-Mediated Surface Phenomena

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 (Received 5 March 2020; accepted 21 July 2020; published 13 August 2020)

Diffusion-mediated surface phenomena are crucial for human life and industry, with examples ranging from oxygen capture by lung alveolar surface to heterogeneous catalysis, gene regulation, membrane permeation, and filtration processes. Their current description via diffusion equations with mixed boundary conditions is limited to simple surface reactions with infinite or constant reactivity. In this Letter, we propose a probabilistic approach based on the concept of boundary local time to investigate the intricate dynamics of diffusing particles near a reactive surface. Reformulating surface-particle interactions in terms of stopping conditions, we obtain in a unified way major diffusion-reaction characteristics such as the propagator, the survival probability, the first-passage time distribution, and the reaction rate. This general formalism allows us to describe new surface reaction mechanisms such as for instance surface reactivity depending on the number of encounters with the diffusing particle that can model the effects of catalyst fooling or membrane degradation. The disentanglement of the geometric structure of the medium from surface reactivity opens far-reaching perspectives for modeling, optimization, and control of diffusion-mediated surface phenomena.

DOI: [10.1103/PhysRevLett.125.078102](https://doi.org/10.1103/PhysRevLett.125.078102)

The dynamics of particles near a reactive surface is critically important for many natural phenomena and industrial processes such as diffusion-mediated heterogeneous catalysis, biochemical reactions on DNA strands, proteins and cell membranes, filtration through porous media, permeation across membranes, surface relaxation in nuclear magnetic resonance, target searching, and animal foraging, to name but a few [1–8]. In a typical setting, a particle (e.g., a molecule, an ion, a protein, a bacterium, an animal) moves inside a confining medium; when the particle comes close to the boundary of the medium, an appropriate surface mechanism can be initiated, e.g., the particle can bind to the boundary, relax its fluorescence, magnetization, or another form of excitation, be chemically transformed into another molecule, be transported through a membrane pore, or be killed or destroyed (all these distinct mechanisms will be generically called “surface reaction” in the following). Whatever the surface mechanism is, its successful realization is not granted and depends on the state of the local environment near the particle. For instance, the boundary can be locally inert for binding, possess no catalytic germ or impurity for chemical transformation or relaxation; the closest membrane pore, channel or gate can be temporarily inactive or already occupied, while a predator can be asleep or not hungry; even if the target molecule or the escape hole is found, the particle may not overcome an energy activation or entropic barrier. In any of such unfavorable circumstances, the particle resumes its bulk motion until the next arrival to the boundary, and so on [9,10]. As a consequence, the successful realization of the surface reaction is typically

preceded by a long sequence of successive bulk explorations, which are started and terminated on the surface [Fig. 1(a)]. Even for ordinary bulk diffusion, partial surface reactivity results in very intricate and still poorly understood dynamics that affects the functioning of chemical reactors, living cells, exchange devices and organs such as lungs and placenta [1–13]. This dynamics becomes even more sophisticated for mortal walkers [14–16] that have a finite random lifetime due to, for instance, bulk relaxation, photobleaching, radioactive decay, bulk reaction, or starving.

The conventional description of these phenomena relies on macroscopic concentrations or, more fundamentally, on a propagator (also known as heat kernel or Green’s function),  $G_q(\mathbf{x}, t|\mathbf{x}_0)$ , that characterizes the likelihood of finding a particle that started from a point  $\mathbf{x}_0$  at time 0 and *survived* (not reacted) up to time  $t$ , in a bulk point  $\mathbf{x}$  at time  $t$ . The propagator obeys the Fokker-Planck equation, in which the bulk dynamics dictates the form of the Fokker-Planck operator, whereas the shape and the reactivity of the surface set boundary conditions [50,51]. For ordinary bulk diffusion, Collins and Kimball [52] put forward the Robin (also known as Fourier, radiation, or third) boundary condition

$$-D\partial_n G_q(\mathbf{x}, t|\mathbf{x}_0) = \kappa G_q(\mathbf{x}, t|\mathbf{x}_0), \quad (1)$$

where  $D$  is the diffusion coefficient and  $\partial_n$  is the normal derivative. At each boundary point, the net diffusive flux density from the bulk (the left-hand side) is equated to the reaction flux density, which is *postulated* to be proportional to  $G_q(\mathbf{x}, t|\mathbf{x}_0)$  on the boundary. The proportionality

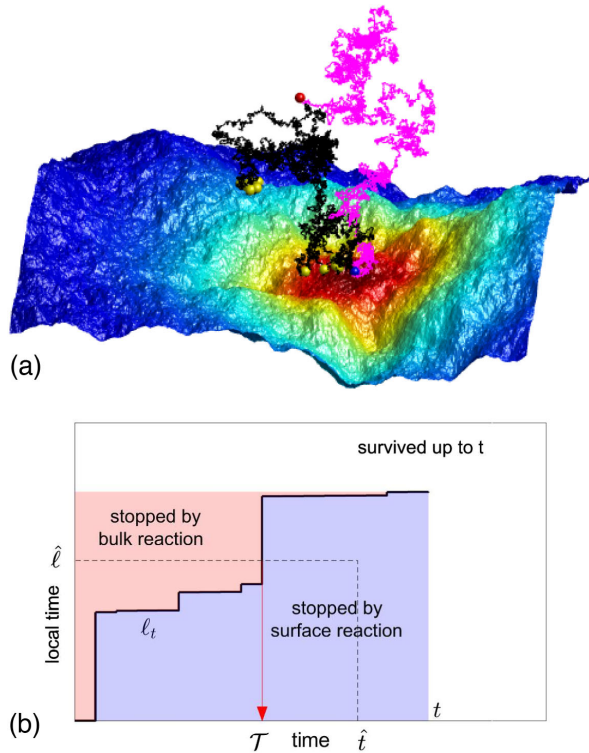


FIG. 1. (a) A simulated trajectory of a particle diffusing over a reactive surface (see the Supplemental Material [17] for details; note that Refs. [18–49] are cited in the SM). Red, blue and yellow balls indicate respectively the starting bulk point  $\mathbf{x}_0$ , the first arrival point  $s_0$  onto the surface, and the consequent boundary points at which the particle encountered the surface. Pink and black colors encode respectively the first segment of the trajectory (from red to blue ball), and the remaining part. (b) The boundary local time  $\ell_t$  of the simulated trajectory (black thick line). The statistics of  $\ell_t$  is determined by reflected Brownian motion, while bulk and surface reaction mechanisms are then incorporated by introducing a stopping time  $\hat{t}$  (vertical dashed line) and a stopping local time  $\hat{\ell}$  (horizontal dashed line), respectively. The surface reaction time  $\mathcal{T} = \inf\{t > 0 : \ell_t > \hat{\ell}\}$  is the random moment (indicated by arrow) when the boundary local time  $\ell_t$  crosses the horizontal line at  $\hat{\ell}$ .

coefficient  $\kappa$  (in units of speed, m/s) bears the names of reactivity, permeability, relaxivity, or inverse surface resistance [53,54], and can be related to the on-rate constant  $k_{\text{on}}$  of chemical reactions [55–57], to the microscopic heterogeneity of catalytic germs [58–61], to the opening dynamics of gates, channels, or pores [62,63], to the energy activation or entropic barrier [64], and to the probability of the reaction event at each encounter [65–67]. The interplay between diffusive transport from the bulk and reaction on the surface is controlled by the ratio  $q = \kappa/D$ , ranging from 0 for an inert boundary, to infinity for a perfectly reactive boundary. The inverse of  $q$ ,  $1/q$ , sets a characteristic reaction length [11,53,54,65,66]. As the surface reaction mechanism is incorporated via the boundary condition (1), the dependence of the propagator  $G_q(\mathbf{x}, t|\mathbf{x}_0)$  on the

reactivity  $\kappa$  (or  $q$ ) is *implicit* that impedes studying these phenomena and optimizing shapes and reactivity patterns of catalysts or clustering of receptors and pores on the cell membrane.

In this Letter, we advocate for an alternative description of diffusion-mediated surface phenomena based on the concept of boundary local time. The main text describes our findings in a general and broadly accessible but still rigorous way (with a limited number of formulas), whereas the Supplemental Material provides all the necessary details for theoreticians [17]. We recall that reflected Brownian motion  $X_t$  in a confining domain  $\Omega \subset \mathbb{R}^d$  with a smooth *inert* boundary  $\partial\Omega$  is mathematically constructed as the solution of the stochastic Skorokhod equation [68–70]:

$$dX_t = \sqrt{2D}dW_t + \mathbf{n}(X_t)d\ell_t, \quad X_0 = \mathbf{x}_0, \quad (2)$$

where  $W_t$  is the standard Brownian motion,  $\mathbf{n}(\mathbf{x})$  is the unit normal vector, and  $\ell_t$  (with  $\ell_0 = 0$ ) is a nondecreasing process, which increases only when  $X_t \in \partial\Omega$ , known as the boundary local time (see Sec. I of [17] for a discussion of this concept). Qualitatively, Eq. (2) can be understood as a Langevin equation with a very strong short-range repulsive force localized on the boundary. Indeed, the second term in Eq. (2) is nonzero only for  $X_t \in \partial\Omega$  and ensures that the particle is reflected in the perpendicular direction  $\mathbf{n}(\mathbf{x})$  from the boundary at each encounter. The peculiar feature of this construction is that the single Skorokhod equation determines simultaneously two tightly related stochastic processes:  $X_t$  and  $\ell_t$ . The conventional propagator  $G_0(\mathbf{x}, t|\mathbf{x}_0)$  (with  $q = 0$ ) characterizes the position  $X_t$  of the diffusing particle but ignores its boundary local time  $\ell_t$ . But it is precisely the local time that bears information on particle’s encounters with the boundary and is thus the key ingredient to account for surface reactions. We therefore build an alternative description on the full propagator  $P(\mathbf{x}, \ell, t|\mathbf{x}_0)$ , i.e., the joint probability density of both  $X_t$  and  $\ell_t$  at time  $t$ . Due to the jumplike character of the boundary local time [see Fig. 1(b)], finding the full propagator was the most challenging and mathematically involved part of this work (see Sec. II of [17]).

As the full propagator characterizes the diffusive dynamics alone (without reactions), it is the most natural theoretical ground, to which both bulk and surface reactions can be added *explicitly* via stopping conditions. Indeed, if the diffusing particle can spontaneously die, relax its excitation, be chemically transformed, killed, or destroyed in the bulk, its finite lifetime can be modeled by a random stopping time  $\hat{t}$ . In a common Poissonian setting, such a bulk reaction can occur at any time instance with equal chances (characterized by rate  $p$ ), so that the lifetime of the particle obeys the exponential distribution:  $\mathbb{P}\{\hat{t} > t\} = e^{-pt}$ . If this bulk reaction mechanism is independent of the diffusive dynamics, averaging the full propagator  $P(\mathbf{x}, \ell, \hat{t}|\mathbf{x}_0)$  over random realizations of  $\hat{t}$  yields the joint distribution of  $X_{\hat{t}}$  and  $\ell_{\hat{t}}$

at the moment  $\hat{t}$  of bulk reaction (or the particle's death). More generally, one can introduce elaborate stopping times to incorporate eventual delays in the bulk diffusion due to reversible binding to immobile centers or mobile buffer molecules (like waiting time distribution in continuous-time random walks), time-dependent or switching diffusivity, the effects of rapidly rearranging dynamic medium, and other subordination mechanisms (see [71–73] and references therein).

Remarkably, we argue that surface reaction mechanisms can be implemented in essentially the same way. At each encounter with the partially reactive surface, the particle either reacts with the probability  $\Pi = 1/[1 + D/(\kappa a)] \simeq aq \ll 1$ , or resumes its bulk diffusion with the probability  $1 - \Pi$ , where  $a$  is the width of a thin reactive boundary layer (i.e., the interaction range) [65,66]. If all reaction attempts are independent from each other, the number  $\hat{n}$  of failed attempts until the successful reaction follows the geometric law,  $\mathbb{P}\{\hat{n} > n\} = (1 - \Pi)^n \approx \exp(-qna)$ . The rescaled number of failed reaction attempts,  $\hat{\ell} = a\hat{n}$ , obeys thus the exponential law:  $\mathbb{P}\{\hat{\ell} > \ell\} = e^{-q\ell}$ , with  $\ell = an$ . As the boundary local time  $\ell_t$  is related to the number  $\mathcal{N}_t^a$  of encounters of the particle with the surface up to time  $t$ ,  $\ell_t = \lim_{a \rightarrow 0} a\mathcal{N}_t^a$  [68,69] (see also Sec. I of [17]), the reaction time  $\mathcal{T}$  can be defined as the moment, at which  $\ell_t$  exceeds an independent random stopping local time  $\hat{\ell}$ :  $\mathcal{T} = \inf\{t > 0: \ell_t > \hat{\ell}\}$  [67,74,75]. Multiplication of the full propagator  $P(\mathbf{x}, \ell, t|\mathbf{x}_0)$  by the probability  $\mathbb{P}\{\hat{\ell} > \ell\} = e^{-q\ell}$  of no surface reaction up to  $\ell$  and integration over  $\ell$  yield the marginal propagator of the position  $\mathbf{X}_t$  at time  $t$  of a particle, conditioned to survive up to time  $t$  (i.e., with the condition  $\mathcal{T} > t$ , which is equivalent to  $\hat{\ell} > \ell_t$ ). By construction, this average is precisely the conventional propagator:

$$G_q(\mathbf{x}, t|\mathbf{x}_0) = \int_0^\infty d\ell e^{-q\ell} P(\mathbf{x}, \ell, t|\mathbf{x}_0). \quad (3)$$

To our knowledge, this fundamental relation was not reported earlier, in spite of mathematical advances in probabilistic approaches to solving diffusion equations [26,27].

Moreover, changing the distribution of the stopping local time  $\hat{\ell}$ , one can now easily implement new surface reaction mechanisms. In fact, the average of the full propagator  $P(\mathbf{x}, \ell, t|\mathbf{x}_0)$  with the probability of no surface reaction up to  $\ell$ , now determined by a desired distribution  $\Psi(\ell) = \mathbb{P}\{\hat{\ell} > \ell\}$  of  $\hat{\ell}$ , yields a generalized propagator

$$G_\Psi(\mathbf{x}, t|\mathbf{x}_0) = \int_0^\infty d\ell \Psi(\ell) P(\mathbf{x}, \ell, t|\mathbf{x}_0). \quad (4)$$

This relation couples explicitly the surface reaction mechanism [represented by  $\Psi(\ell)$ ] and the dynamics of the particle diffusing in a domain with reflecting boundary [represented by  $P(\mathbf{x}, \ell, t|\mathbf{x}_0)$ ]. The striking similarity of our

implementations of bulk and surface reactions is not surprising: while time  $t$  mimics the number of bulk steps (and thus exposure of the particle to bulk reaction), the local time  $\ell$  counts the number of encounters with the boundary (and its exposure to surface reaction). It is crucial that both bulk and surface reaction mechanisms, introduced via two independent random variables  $\hat{t}$  and  $\hat{\ell}$  [Fig. 1(b)], are disentangled from the dynamics. In other words, one can first investigate the dynamics in the case of reflecting boundary and then couple it explicitly to reaction mechanisms.

The alternative description allows one to go far beyond the constant reactivity based on the Robin boundary condition (1). Indeed, the former exponential law  $\Psi(\ell) = e^{-q\ell}$  described a Poissonian-like mechanism when the particle could react at each encounter with the boundary with equal probabilities. To incorporate variable reaction probabilities, we introduce the reactivity  $\kappa(\ell)$  that changes with the local time  $\ell$  (i.e., with the rescaled number of encounters), alike time-dependent diffusivity  $D(t)$  for bulk diffusion. Extending our previous arguments (see Sec. III of [17]), we derive the probability distribution for the corresponding stopping local time  $\hat{\ell}$ :

$$\Psi(\ell) = \exp\left(-\frac{1}{D} \int_0^\ell d\ell' \kappa(\ell')\right). \quad (5)$$

This is a new feature brought by our probabilistic description, which allows us to investigate within the unique theoretical framework many important diffusion-mediated surface phenomena such as catalyst's fooling or membrane degradation [76,77]. In fact, choosing an appropriate  $\kappa(\ell)$  [or  $\Psi(\ell)$ ], one can control the reaction dynamics of the boundary. For instance, the reactivity  $\kappa(\ell)$ , which is small at  $\ell \approx 0$  and then reaches a constant level, can model situations when the surface needs to be progressively activated by repeated encounters with the diffusing particle. In contrast, when  $\kappa(\ell)$  is large at small  $\ell$  and then reaches a constant (or vanishes), one models a progressive passivation of initially highly reactive surfaces.

The generalized propagator  $G_\Psi(\mathbf{x}, t|\mathbf{x}_0)$  determines other common characteristics of diffusion-reaction processes such as, e.g., the survival probability or the reaction rate (see Fig. S2 and Sec. IV of [17]). For instance, we show in the Supplemental Material that the probability density of the first-passage (or reaction) time  $\mathcal{T}$  can be written as

$$H_\Psi(t|\mathbf{x}_0) = \int_0^\infty d\ell \psi(\ell) U(\ell, t|\mathbf{x}_0), \quad (6)$$

where  $\psi(\ell) = -d\Psi(\ell)/d\ell$  is the probability density of the stopping local time  $\hat{\ell}$ , and  $U(\ell, t|\mathbf{x}_0) = D \int_{\partial\Omega} ds P(\mathbf{s}, \ell, t|\mathbf{x}_0)$  is the probability density of the first-crossing time of a level  $\ell$  by the boundary local time  $\ell_t$  (see Sec. II. F of [17]). This relation expresses the idea



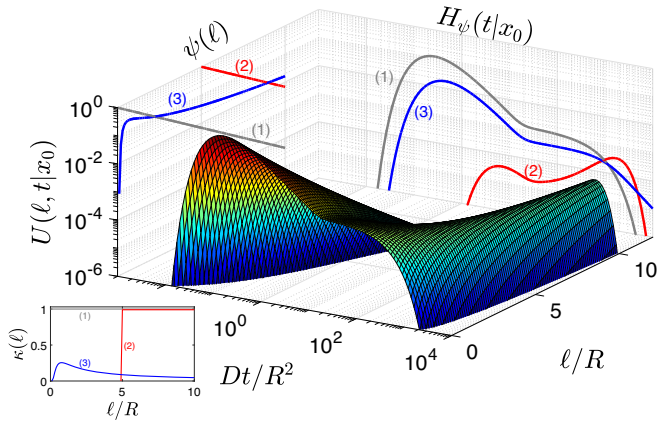


FIG. 2. The probability density  $U(\ell, t|x_0)$  (rescaled by  $R^2/D$ ) of the first-crossing time of a level  $\ell$  by the boundary local time  $\ell_t$  for a spherical target of radius  $R$ , surrounded by an outer reflecting concentric sphere of radius  $L$ , with  $|x_0|/R = 2$  and  $L/R = 10$ . Three curves on the left projection illustrate three probability densities  $\psi(\ell)$  of the stopping local time  $\hat{\ell}$  (with  $qR = 1$ ): (1)  $\psi(\ell) = qe^{-q\ell}$  (gray line, conventional setting), (2)  $\psi(\ell) = qe^{-q\ell}\Theta(\ell - \ell_0)$  with  $\ell_0/R = 5$  (red line), and (3)  $\psi(\ell) = qe^{-1/(q\ell)}/[\sqrt{\pi}(q\ell)^{3/2}]$  (blue line). These densities correspond, respectively, to three reactivity profiles shown on the inset:  $\kappa(\ell) = qD$ ,  $\kappa(\ell) = qD\Theta(\ell - \ell_0)$ , and  $\kappa(\ell) = qDe^{-1/(q\ell)}/[\sqrt{\pi}(q\ell)^{3/2}\text{erf}(1/\sqrt{q\ell})]$ . Three curves on the right projection show the corresponding probability densities  $H_\psi(t|x_0)$  from Eq. (6).

illustrated in Fig. 1(b): the surface reaction occurs when the boundary local time  $\ell_t$  exceeds a random level  $\hat{\ell}$  determined by  $\psi(\ell)$ . For a perfectly reactive boundary, the reaction occurs at the first encounter with the boundary, i.e., at the first moment when the boundary local time exceeds 0. This is precisely the first-crossing time of the level 0, i.e.,  $\psi(\ell) = \delta(\ell)$ , and thus  $U(0, t|x_0)$  is the probability density of the common first-passage time to a perfect target [78]. In turn,  $U(\ell, t|x_0)$  for any  $\ell > 0$  describes the reaction time in the case when the reaction occurs at the boundary local time  $\ell_t = \ell$  (i.e., after a prescribed number of failed reaction attempts). According to Eq. (6), other surface reaction mechanisms can be described by setting the level  $\ell$  randomly, i.e., by introducing the stopping local time  $\hat{\ell}$ .

Figure 2 exemplifies the impact of surface reaction mechanisms onto the distribution of the reaction time. Here the family of the probability densities  $U(\ell, t|x_0)$  (parametrized by  $\ell$ ) is presented for a spherical target, surrounded by an outer reflecting sphere. Three probability densities  $\psi(\ell)$  determining surface reaction mechanisms [with  $\kappa(\ell)$  in the inset] are plotted on the left projection, while the resulting reaction time densities  $H_\psi(t|x_0)$  are shown on the right projection. For a constant reactivity, the average of  $U(\ell, t|x_0)$  with the exponential density  $qe^{-q\ell}$  (gray line) results in the conventional reaction time distribution [79]. Here, a single ‘‘hump’’ region around the

most probable reaction time is followed by a flat part and ultimate exponential decay, as it should be for a bounded domain. If the target is passive at the beginning (red line), first arrivals of the particle onto the target do not produce reaction up to some local time  $\ell_0$ , thus shifting the probability density of the reaction time to longer times. Curiously, an unusual second ‘‘hump’’ region emerges due to the particles that moved away from the target, explored the confining domain and then returned to the target (see also Sec. VI of [17]). In the third example (blue line), the reactivity is negligible at the beginning, reaches a maximum around  $\ell/R \approx 0.7$ , and then slowly decreases as  $1/(2q\ell)$  at large  $\ell$ . The overall shape of the reaction time density  $H_\psi(t|x_0)$  resembles that of the conventional setting, but exhibits anomalous power law decay at long times:  $H_\psi(t|x_0) \propto t^{-3/2}$ . Here, as the encounter-dependent reactivity offers an optimal range of local times for surface reaction, a particle that failed to react during this range, has lower and lower chances to react after more or more returns to the target.

More generally, the asymptotic large- $\ell$  decay  $\kappa(\ell) \propto 1/\ell$  turns out to be the critical regime that distinguished three scenarios for arbitrary bounded domains (see Sec. VI of [17]): (i) if  $\kappa(\ell)$  decays slower than  $1/\ell$  (or increases with  $\ell$ ),  $H_\psi(t|x_0)$  exhibits the long-time exponential decay, as in the conventional setting; (ii) if  $\kappa(\ell)$  decreases as  $\nu D/\ell$  with some constant  $0 < \nu < 1$ , then  $H_\psi(t|x_0) \propto t^{1-\nu}$ , which is a new unexpected feature for bounded domains; (iii) if  $\kappa(\ell)$  decays faster than  $1/\ell$ , the reaction time can be infinite with a finite probability:

$$\mathbb{P}\{T = \infty\} = \Psi(\infty) = \exp\left(-\int_0^\infty d\ell \frac{\kappa(\ell)}{D}\right) > 0. \quad (7)$$

In other words, this is the probability of no surface reaction in a bounded domain: even though the exploration is compact, the reactivity decays too fast so that the particle may fail to react even after an infinite number of returns to the target. Several surface reaction models and the behavior of the underlying reaction time distributions and reaction rates are discussed in Sec. VI of [17].

In summary, we developed a powerful probabilistic description of diffusion-mediated surface phenomena based on the concept of boundary local time. By introducing the full propagator to describe confined diffusion with reflections on the boundary, we succeeded to incorporate surface reactivity *explicitly* via a stopping condition. The disentanglement of the surface reactivity from the dynamics allowed us to introduce encounter-dependent reactivity  $\kappa(\ell)$  and to describe a variety of new surface reaction mechanisms. We discussed how different forms of  $\kappa(\ell)$  affect the reaction times and revealed some intriguing anomalous features in their distribution.

The developed formalism opens a vast area for future research. On the theoretical side, one can study how the

diffusive dynamics in domains with complex geometric structures (such as the interior of an eukaryotic cell, a chemical reactor, or a human acinus) is coupled to different surface reaction mechanisms. One can further extend this approach to investigate (i) the (anti)cooperativity effects of multiple diffusing particles whose individual encounters with the boundary change its reactivity; (ii) the competition between multiple targets, each described by its own boundary local time; (iii) the combined impact of bulk and surface reaction mechanisms; (iv) the effects of correlations between successive encounters, and (v) the presence of long-range interactions with and reversible binding to the boundary. In particular, our probabilistic description of the bulk exploration step until reversible binding to the boundary can bring complementary insights to former theoretical approaches based on coupled diffusion-reaction equations [80–84] (see Sec. VII of [17]). On the application side, appropriate surface reaction models should be identified to describe industrial examples of catalyst fooling, membrane aging and many other diffusion-mediated surface phenomena, in which the surface properties depend on the number of encounters. One can also address a new class of optimization problems targeting optimal reaction rates or prescribed distributions of reaction times or positions, either by adapting the surface reaction mechanisms for a given geometric structure of the medium, or by optimizing its structure for a given surface reaction mechanism, or both. The disentanglement of the geometric structure from the surface reaction mechanism is the key that has now opened the door to such applications.

The author acknowledges a partial financial support from the Alexander von Humboldt Foundation through a Bessel Research Award.

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