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# Escape of a Sticky Particle

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Adsorption to a surface, reversible-binding, and trapping are all prevalent scenarios where particles exhibit “stickiness”. Escape and first-passage times are known to be drastically affected, but detailed understanding of this phenomenon remains illusive. To tackle this problem, we develop an analytical approach to the escape of a diffusing particle from a domain of arbitrary shape, size, and surface reactivity. This is used to elucidate the effect of stickiness on the escape time from a slab domain: revealing how adsorption and desorption rates affect the mean and variance, thus providing a novel approach to infer these rates from measurements. Moreover, as any smooth boundary is locally flat, slab results are leveraged to devise a numerically efficient scheme for simulating the sticky escape problem in arbitrary domains. This letter thus offers a new starting point for analytical and numerical studies of stickiness and its role in escape, first-passage, and diffusion-controlled reactions.

Stickiness can drastically alter the completion time of random processes. A prominent example is the escape problem, also known as the exit problem, where one considers a particle searching for a hole or another way out of a compartment with otherwise impenetrable boundaries [1–13]. The need to account for stickiness in such scenarios was already recognized for receptors diffusing in and out of the postsynaptic density while reversibly binding to scaffold proteins there [14–16]. Similar issues arise when considering transport through the nuclear pore complex [17, 18], the partially reversible trapping of receptors trafficking in dendrites [19], and the reversible binding of calcium ions to sensors and buffer molecules within nerve terminals [20]. Explicit account of stickiness was also required in order to explain the extremely prolonged survival times of target proteins in a nanostructured on-chip device that was recently fabricated for selective protein separation using antibody–photoacid-modified Si nanopillars [21, 22]. As escape and first-passage times are conceptually equivalent [23–25], stickiness is also expected to affect diffusion-controlled reactions, e.g., the time it takes a sticky ligand to find its receptor on the cell membrane.

Whether the origin of stickiness is physical, chemical or else, it can be described by the adsorption-desorption kinetics framework, which was developed over an entire century of intense research. However, the vast majority of theoretical works in this context were conducted on a macroscopic 1D model of a flat surface immersed in an infinite bulk of adsorbates [26–44]. Recently, a single-particle description of adsorption kinetics was introduced [45], and a relation to reversible binding and association-recombination reactions [20, 46–55] was made. Some authors have also ventured beyond the 1D semi-infinite case considering different geometries and higher dimensions [20, 45, 53–58]. Yet, research and results were always focused on scenarios where all boundaries involved were

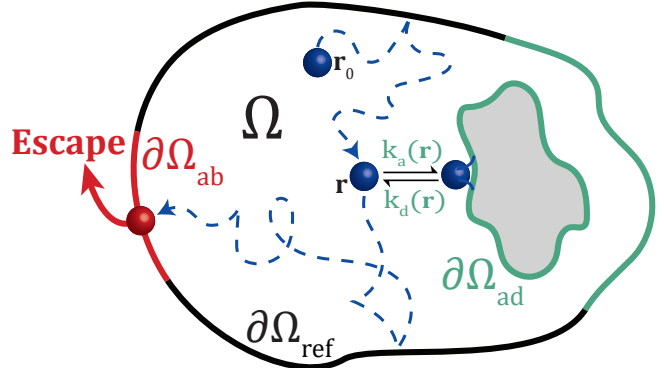


FIG. 1: (a) A schematic illustration of a general domain  $\Omega$  with an adsorbing (sticky) surface  $\partial\Omega_{ad}$  (green), a reflecting surface  $\partial\Omega_{ref}$  (black), and an absorbing surface  $\partial\Omega_{ab}$  (red), through which the particle (blue) can escape the domain.

assumed to be adsorbing, thus completely ignoring the problem of escape via an absorbing boundary. Moreover, in many real-life scenarios, domain boundaries comprise of a mixture of reflecting, absorbing, adsorbing, partially reactive [59–66] and/or gated [67–72] parts, which highlights the need in adequate methods of analysis.

In this Letter, we develop a general formalism to treat the escape problem of a sticky particle diffusing in a domain of arbitrary dimension, geometry, and surface reactivity (Fig. 1). We derive the partial differential equation that governs the escape time distribution for this general problem, and exemplify its solution for a particle confined to a slab with one absorbing wall and one adsorbing wall. In this prototypical example, we show that the mean escape time is only sensitive to the ratio of adsorption and desorption rates, while its variance is sensitive to the actual rates, thus allowing their inference from experimental data of escape time statistics. To

gain physical intuition to the escape problem, we further present a renewal approach to the slab problem, which we then leverage to construct an accurate simulation scheme for the diffusion of a sticky particle in general domains.

*The general case.*—We consider normal diffusion with diffusion coefficient  $D$  in a  $d$ -dimensional domain  $\Omega \subset \mathbb{R}^d$  (Fig. 1), whose boundary  $\partial\Omega = \partial\Omega_{\text{ab}} \cup \partial\Omega_{\text{ad}} \cup \partial\Omega_{\text{ref}}$  is comprised of three disjoint parts: an absorbing part  $\partial\Omega_{\text{ab}}$  through which the particle can escape, a reflecting part  $\partial\Omega_{\text{ref}}$ , and an adsorbing part  $\partial\Omega_{\text{ad}}$ , allowing for reversible trapping of the particle (see below). The propagator  $p(\mathbf{r}, t|\mathbf{r}_0)$ , namely the probability density to find a particle at point  $\mathbf{r} \in \Omega$  at time  $t$  given the initial position  $\mathbf{r}_0$ , satisfies the diffusion equation:

$$\partial_t p(\mathbf{r}, t|\mathbf{r}_0) = D\Delta_{\mathbf{r}} p(\mathbf{r}, t|\mathbf{r}_0), \quad (1)$$

subject to the initial condition  $p(\mathbf{r}, 0|\mathbf{r}_0) = \delta(\mathbf{r} - \mathbf{r}_0)$ , and the Dirichlet boundary conditions  $p(\mathbf{r}, t|\mathbf{r}_0) = 0$  for every  $\mathbf{r} \in \partial\Omega_{\text{ab}}$ . Here,  $\Delta_{\mathbf{r}}$  is the Laplace operator with respect to  $\mathbf{r}$ . The propagator determines the probability flux density  $j_{\text{ab}}(\mathbf{r}, t|\mathbf{r}_0)$  through a point  $\mathbf{r} \in \partial\Omega_{\text{ab}}$  at time  $t$ . This, in turn, yields the probability density function (PDF) of the escape time,  $J_{\text{ab}}(t|\mathbf{r}_0) = \int_{\partial\Omega_{\text{ab}}} j_{\text{ab}}(\mathbf{r}_s, t|\mathbf{r}_0) d\mathbf{r}_s$ , which is also equal to the probability flux from the compartment.

The adsorption condition on  $\partial\Omega_{\text{ad}}$  can be formulated by introducing an auxiliary probability density  $\Pi(\mathbf{r}, t|\mathbf{r}_0)$  of the particle to be adsorbed to point  $\mathbf{r} \in \partial\Omega_{\text{ad}}$  at time  $t$ . We impose the following two equations for every  $\mathbf{r} \in \partial\Omega_{\text{ad}}$  on the adsorbing surface [45, 54]:

$$j_{\text{ad}}(\mathbf{r}, t|\mathbf{r}_0) = k_a(\mathbf{r})p(\mathbf{r}, t|\mathbf{r}_0) - k_d(\mathbf{r})\Pi(\mathbf{r}, t|\mathbf{r}_0), \quad (2a)$$

$$\partial_t \Pi(\mathbf{r}, t|\mathbf{r}_0) = j_{\text{ad}}(\mathbf{r}, t|\mathbf{r}_0), \quad (2b)$$

where  $j_{\text{ad}}(\mathbf{r}, t|\mathbf{r}_0) = -D\partial_n p(\mathbf{r}, t|\mathbf{r}_0)$ . Here,  $\partial_n$  is the normal derivative oriented outwards the domain,  $k_a(\mathbf{r})$  is the reactivity of the surface at the point  $\mathbf{r}$  (characterizing the rate of adsorption from a thin reactive layer near the surface), and  $k_d(\mathbf{r})$  is the desorption rate at that point. Note that the reflecting part of the boundary can be viewed as part of the adsorbing surface with zero reactivity, i.e., we can consistently define  $\partial\Omega_{\text{ref}} \subset \partial\Omega_{\text{ad}}$ , such that  $k_a(\mathbf{r}) = 0$  for every  $\mathbf{r} \in \partial\Omega_{\text{ref}}$ . Equation (S37a) states that the diffusive flux of particles from the bulk at each point  $\mathbf{r} \in \partial\Omega_{\text{ad}}$  is proportional to the reactive flux on the surface,  $k_a(\mathbf{r})p(\mathbf{r}, t|\mathbf{r}_0)$ , minus the flux of particles that desorb from the surface. In turn, Eq. (S37b) is a mass balance equation that simply states that the uptake of adsorbed particles is given by the diffusive flux. Note that  $\Pi(\mathbf{r}, 0|\mathbf{r}_0) = 0$ , since motion starts in the bulk.

The Laplace transform of these two equations allows one to eliminate  $\Pi(\mathbf{r}, t|\mathbf{r}_0)$ , and reduce these equations to a single Robin-like boundary condition. Summarizing,

the original problem reads in the Laplace domain as

$$(s - D\Delta_{\mathbf{r}})\tilde{p}(\mathbf{r}, s|\mathbf{r}_0) = \delta(\mathbf{r} - \mathbf{r}_0), \quad \mathbf{r} \in \Omega, \quad (3a)$$

$$\tilde{p}(\mathbf{r}, s|\mathbf{r}_0) = 0, \quad \mathbf{r} \in \partial\Omega_{\text{ab}}, \quad (3b)$$

$$\partial_n \tilde{p}(\mathbf{r}, s|\mathbf{r}_0) + q_s(\mathbf{r})\tilde{p}(\mathbf{r}, s|\mathbf{r}_0) = 0, \quad \mathbf{r} \in \partial\Omega_{\text{ad}}, \quad (3c)$$

where tilde denotes the Laplace transform,  $\tilde{p}(\mathbf{r}, s|\mathbf{r}_0) = \int_0^\infty dt e^{-ts} p(\mathbf{r}, t|\mathbf{r}_0)$ , and

$$q_s(\mathbf{r}) = \frac{k_a(\mathbf{r})}{D(1 + k_d(\mathbf{r})/s)} \quad (4)$$

is an  $s$ -dependent reactivity parameter.

Conventionally the survival probability for the escape of a particle from a compartment is defined to be the spatial integral of the propagator over the entire compartment,  $S_b(t|\mathbf{r}_0) = \int_\Omega p(\mathbf{r}, t|\mathbf{r}_0) d\mathbf{r}$ . Here we added the subscript ‘ $b$ ’, standing for bulk, since survival must also include the probability to be adsorbed (thus being neither in the bulk nor escaped). The survival probability is thus given by

$$S_{\text{ab}}(t|\mathbf{r}_0) := S_b(t|\mathbf{r}_0) + \Pi(t|\mathbf{r}_0), \quad (5)$$

where the subscript ‘ab’ stands for the fact that the escape is through  $\partial\Omega_{\text{ab}}$ , and  $\Pi(t|\mathbf{r}_0) = \int_{\partial\Omega_{\text{ad}}} \Pi(\mathbf{r}, t|\mathbf{r}_0) d\mathbf{r}$  is the overall probability to be adsorbed at  $t$ . Taking the time derivative of Eq. (5), one can rewrite it in terms of conservation of the probability fluxes:  $J_b := -\partial_t S_b = J_{\text{ab}} + J_{\text{ad}}$ , where we used Eq. (S37b). Note that this relation could also be obtained by integrating the diffusion equation (1). In the supplemental material (SM) we derive the partial differential equations governing the Laplace-transformed probability fluxes  $\tilde{J}_{\text{ad}}(s|\mathbf{r}_0)$  and  $\tilde{J}_{\text{ab}}(s|\mathbf{r}_0)$  [73]. The latter is given by:

$$(s - D\Delta_{\mathbf{r}_0})\tilde{J}_{\text{ab}}(s|\mathbf{r}_0) = 0, \quad \mathbf{r}_0 \in \Omega, \quad (6a)$$

$$\tilde{J}_{\text{ab}}(s|\mathbf{r}_0) = 1, \quad \mathbf{r}_0 \in \partial\Omega_{\text{ab}}, \quad (6b)$$

$$\partial_{n_0} \tilde{J}_{\text{ab}}(s|\mathbf{r}_0) + q_s(\mathbf{r}_0)\tilde{J}_{\text{ab}}(s|\mathbf{r}_0) = 0, \quad \mathbf{r}_0 \in \partial\Omega_{\text{ad}}. \quad (6c)$$

Solving this boundary value problem for a given compartment  $\Omega$  and reactivity parameter  $q_s(\mathbf{r})$  yields the Laplace transform of the escape time  $\mathcal{T}$ :  $\tilde{J}_{\text{ab}}(s|\mathbf{r}_0) = \langle e^{-s\mathcal{T}} \rangle$ . Its derivatives give the positive-order moments,  $\langle \mathcal{T}^n \rangle = (-1)^n (\partial_s^n \tilde{J}_{\text{ab}}(s|\mathbf{r}_0))_{s=0}$ , while an inverse Laplace transform yields the PDF of the escape time,  $J_{\text{ab}}(t|\mathbf{r}_0)$ . Hence, we provided a general framework for studying the statistics of the escape time.

*Escape from a slab.*—We now exemplify the application of the general formalism to the case of a particle diffusing in a slab domain between two parallel planes separated by distance  $H$  (Fig. 2). The boundary at  $z = H$  is absorbing, while the boundary at  $z = 0$  is adsorbing with  $k_a$  and  $k_d$ . For the slab domain, Eq. (4) simplifies to  $q_s = k_a/[D(1 + k_d/s)]$ . This setting is equivalent to diffusion on the interval  $(0, H)$  with adsorbing and absorbing

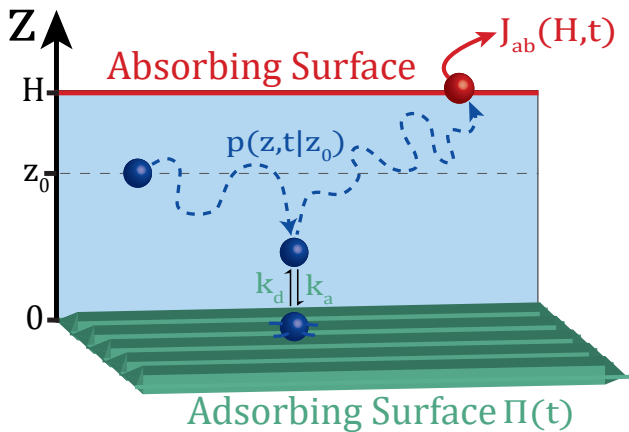


FIG. 2: A schematic illustration of a slab domain  $\Omega = \mathbb{R}^2 \times (0, H) \subset \mathbb{R}^3$  with absorbing wall at  $z = H$  and adsorbing wall at  $z = 0$ . The particle starts its motions at  $z = z_0$ .

endpoints at 0 and  $H$ , and we are interested in getting the PDF  $J_{\text{ab}}(t|z_0)$  of the escape time from the slab, i.e., the first-passage time to  $H$ .

In this case, equations (3a)-(3c) for the propagator simplify as  $\mathbf{r} = z$ ,  $q_s(\mathbf{r}) = q_s$  and  $\partial_n = -\partial_z$  at  $z = 0$ . One divides the solution into two restrictions  $z > z_0$  and  $z < z_0$  and further imposes continuity of the densities and the fluxes at  $z = z_0$ . This yields:

$$\tilde{p}(z, t|z_0) = \begin{cases} \frac{g(z_0, s) \sinh(\alpha(H-z))}{g(H, s) D\alpha}, & z > z_0, \\ \frac{\sinh(\alpha(H-z_0))}{D\alpha} \frac{g(z, s)}{g(H, s)}, & z < z_0, \end{cases} \quad (7)$$

where  $g(x, s) := \alpha \cosh(\alpha x) + q_s \sinh(\alpha x)$  and  $\alpha = \sqrt{s/D}$ . Since in the one-dimensional case  $\tilde{J}_{\text{ab}}(s|z_0) = D\partial_z \tilde{p}(z, s|z_0)_{z=H}$ , we have

$$\tilde{J}_{\text{ab}}(s|z_0) = \frac{g(z_0, s)}{g(H, s)}, \quad (8)$$

for the escape time probability density in the Laplace domain. Note that  $\tilde{J}_{\text{ab}}(s|z_0)$  is a solution of Eq. (S5a) under the boundary conditions in Eqs. (S5b)-(6c), and we could have bypassed the calculation of the propagator.

The escape time PDF is obtained by inverse Laplace transforming Eq. (8) (see details in the SM [73]):

$$J_{\text{ab}}(t|z_0) = \sum_{n=0}^{\infty} e^{-\beta_n^2 D t / H^2} \times \quad (9)$$

$$\frac{2D\beta_n}{H^2} \left[ \beta_n \cos(\beta_n z_0 / H) + \frac{\kappa_a \beta_n^2}{\beta_n^2 - \kappa_d} \sin(\beta_n z_0 / H) \right] \times \left[ \left( 1 + \frac{2\kappa_a \kappa_d}{(\beta_n^2 - \kappa_d)^2} \right) \beta_n \sin \beta_n - \left( 1 + \frac{\kappa_a \beta_n^2}{\beta_n^2 - \kappa_d} \right) \cos \beta_n \right]^{-1},$$

where  $\beta_n$  are the positive solutions of the transcendental equation  $\beta \tan(\beta) = (\kappa_d - \beta^2) / \kappa_a$ , with  $\kappa_a = k_a H / D$  and  $\kappa_d = k_d H^2 / D$  standing for the dimensionless adsorption and desorption rate constants.

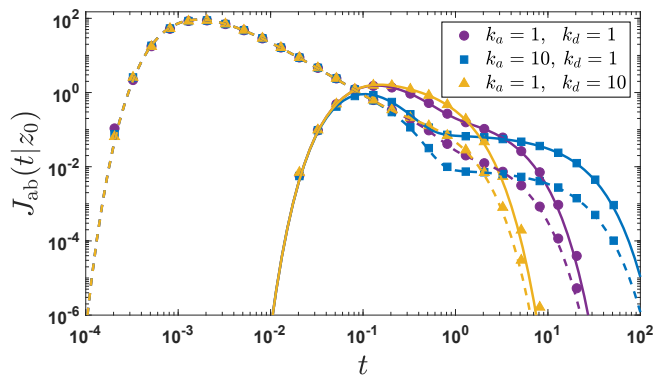


FIG. 3: PDF  $J_{\text{ab}}(t|z_0)$  of the escape time from the slab domain illustrated in Fig. 2. Here, we set  $H = 1$ ,  $D = 1$ , and values for  $k_a$  and  $k_d$  are given in the legend. Solid lines (resp., dashed lines) are the PDFs for  $z_0 = 0.1$  (resp.,  $z_0 = 0.9$ ). Symbols come from Monte Carlo simulations with  $10^6$  particles (see SM for details [73]).

Figure 3 shows the behavior of  $J_{\text{ab}}(t|z_0)$  for different values of  $k_a$ ,  $k_d$  and  $z_0$ . Markedly, the rates change the shape of the PDF at intermediate timescales. The short-time behavior is determined by “direct trajectories” going to the absorbing wall (the escape region). One gets the typical Lévy-Smirnov short-time asymptotics  $J_{\text{ab}}(t|z_0) \simeq (H - z_0) e^{-(H-z_0)^2 / (4Dt)} / \sqrt{4\pi Dt^3}$ , that does not depend on the adsorption/desorption rates. Conversely, the long-time decay is exponential and controlled by the smallest eigenvalue  $D\beta_0^2 / H^2$ . To see that this strongly depends on adsorption kinetics, consider the asymptotic behavior of the transcendental equation as  $\beta \rightarrow 0$ , from which one gets  $\beta_0^2 \approx \kappa_d / (1 + \kappa_a)$ . This approximation is valid whenever  $\beta_0$  is small, i.e., when  $\kappa_d$  is small or/and  $\kappa_a$  is large. Indeed, the adsorbing wall plays the role of a temporal trap for the particle: when the particle reaches this wall, it can be easily trapped but requires long time for release. As a consequence, the survival probability decays exponentially, with the decay time  $T = H^2 / (D\beta_0^2)$ , which can be very large. In the SM [73], the dependence of  $\beta_0$  on the adsorption-desorption rates is discussed further.

As the Laplace transform  $\tilde{J}_{\text{ab}}(s|z_0)$  is the moment generating function of the escape time, we deduce its mean

$$\langle \mathcal{T} \rangle = \frac{H^2 - z_0^2}{2D} + \frac{K(H - z_0)}{D}, \quad (10)$$

where  $K := k_a / k_d$  is the equilibrium constant. The first term in Eq. (S44) corresponds to the mean escape time from an interval  $(0, H)$  with reflecting endpoint 0 and absorbing endpoint  $H$ . In turn, the second term accounts for adsorption-desorption kinetics.

*Renewal Approach.*—To gain a deeper understanding of the above relation, we stress that the escape time  $\mathcal{T}$  is the sum of the (random) diffusion time  $\mathcal{T}_d$  on the interval  $(0, H)$  with reflecting endpoint 0, and the total waiting

time in the adsorbed state. Denoting the random number of adsorption events  $\mathcal{N}$  and their independent, identically distributed random durations as  $\mathcal{T}_w^1, \dots, \mathcal{T}_w^{\mathcal{N}}$ , we write

$$\mathcal{T} = \mathcal{T}_d + \sum_{i=1}^{\mathcal{N}} \mathcal{T}_w^i. \quad (11)$$

Taking mean of both sides we have  $\langle \mathcal{T} \rangle = \langle \mathcal{T}_d \rangle + \langle \mathcal{N} \rangle \langle \mathcal{T}_w \rangle$ , where  $\langle \mathcal{T}_w \rangle$  denotes the mean of  $\mathcal{T}_w^i$ . Comparing this result with Eq. (S44), we can identify  $\langle \mathcal{T}_d \rangle = (H^2 - z_0^2)/2D$  and  $\langle \mathcal{T}_w \rangle = k_d^{-1}$ , which gives  $\langle \mathcal{N} \rangle = k_a(H - z_0)/D$ .

In fact, Eq. (11) suggests that the slab case can be readily analyzed using a renewal approach, where the distribution of  $\mathcal{N}$  is given in terms of the splitting probability  $\mathcal{E}_H(z_0)$ , namely the probability of escaping the compartment *without any adsorption event*, given the starting position  $z_0$ . It is thus enough to solve the corresponding problem of diffusion in the slab, but without desorption. For example, we can generally write  $\langle \mathcal{N} \rangle = (1 - \mathcal{E}_H(z_0))/\mathcal{E}_H(0)$ , which admits the following interpretation: Starting from  $z_0$ , there is a probability  $1 - \mathcal{E}_H(z_0)$  that the particle was adsorbed before escaping such that  $\mathcal{N} > 0$ . If so, the particle will desorb to position  $z = 0$ , from which the probability of escaping before re-adsorbing is given by  $\mathcal{E}_H(0)$ . Essentially, adsorption at the lower boundary is a renewal moment that will repeat again and again until the particle finally escapes. We thus have a sequence of trails geometrically distributed with success probability  $\mathcal{E}_H(0)$ , and so the mean number of trials, each corresponding to a re-adsorption event, is simply  $1/\mathcal{E}_H(0)$ . Indeed, by plugging  $\mathcal{E}_H(z_0) = (D + k_a z_0)/(D + k_a H)$ , which is the splitting probability of the problem considered above, we retrieve  $\langle \mathcal{N} \rangle = k_a(H - z_0)/D$ .

For a more detailed discussion of the renewal approach see the SM [73]; therein, we generalize the model by allowing for an arbitrary waiting time distribution  $\psi(t)$  in the adsorbed state, and different spatial dynamics with general  $\mathcal{T}_d$  and  $\mathcal{E}_H(z_0)$ . We derive generalized formulas for the PDF, the mean and the variance of the escape time, and the correlation between the diffusion time and the total waiting time.

*Inference of the adsorption-desorption rates.*—While the mean escape time in Eq. (11) is only sensitive to the equilibrium constant  $K$ , we find that the variance also carries information on the adsorption-desorption rates themselves:

$$\text{Var}\{\mathcal{T}\} = \frac{H^4 - z_0^4}{6D^2} + \frac{2K(H^3 - z_0^3)}{3D^2} + \frac{K^2(H^2 - z_0^2)}{D^2} + \underbrace{\frac{2K(H - z_0)}{k_d D}}_{k_d \text{ sensitive}}. \quad (12)$$

As a consequence, one can infer  $K = k_a/k_d$  by measuring the mean in Eq. (S44), and then extract  $k_a$  and  $k_d$

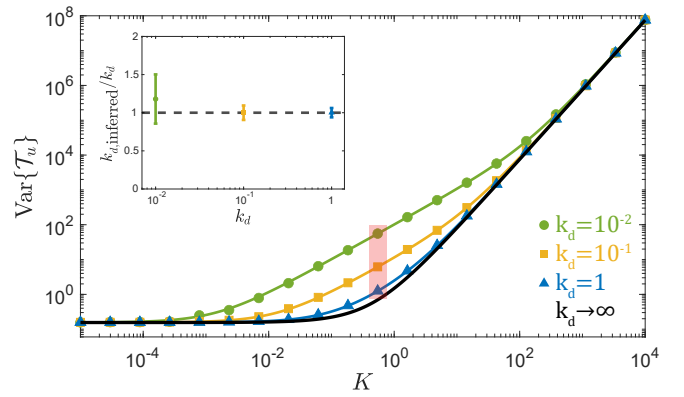


FIG. 4: Variance of the escape time vs. the equilibrium constant  $K = k_a/k_d$  for different values of  $k_d$ , with  $H$  and  $D$  set to 1. Here, we mimic common experimental conditions by taking the initial distribution to be uniform. Averaging over the initial position in Eq. (8), and calculating moments yields:  $\langle \mathcal{T}_u \rangle = H^2/(3D) + KH/(2D)$  and  $\text{Var}\{\mathcal{T}_u\} = 7H^4/(45D^2) + 7KH^3/(12D^2) + 3H^2K^2/(4D^2) + HK/(k_d D)$  (solid lines). Symbols come from Monte Carlo simulations with  $10^7$  particles. The black curve represents the fast desorption limit ( $k_d \rightarrow \infty$ ), for which the fourth term in  $\text{Var}\{\mathcal{T}_u\}$  vanishes. The inset shows a successful implementation of the suggested inference scheme. To come closer to experimental conditions, we only simulated  $10^4$  particles. The relative error of the inferred  $k_d$  values is plotted vs. the true  $k_d$ s that were fed into the simulations. All  $k_d$  values share the same  $K = 0.43$ , marked by the red strip. Error bars were calculated by repeating this procedure  $10^2$  times. A detailed analysis of the statistical error can be found in the SM [73].

from the measured variance. In Fig. 4, we plot  $\text{Var}\{\mathcal{T}_u\}$  vs  $K$  for three different values of  $k_d$ . The subscript ‘ $u$ ’ denotes re-derivation of Eqs. (S44) and (12) according to a uniform distribution of the initial position. It can be appreciated that, for a wide range of  $K$  values, the variance varies considerably with different values of  $k_d$ , thus allowing its inference. The inset demonstrates an application of this inference scheme on simulated data.

*Simulating an adsorbing boundary.*—When thinking of an adsorbing boundary, one usually imagines a surface layer of width  $\epsilon \ll 1$ , from which the particle is adsorbed with rate  $k_a/\epsilon$ . A standard Monte Carlo simulation would thus implement such an adsorption event, wait for a random time, and then re-inject the particle into a distanced point in the bulk to resume diffusion. However, this basic scheme misses multiple adsorption events that may occur between the first desorption moment and the escape from the layer of width  $\epsilon$ . Indeed, the fractal self-similar character of Brownian motion implies that a Brownian path released on a smooth boundary bounces on this boundary infinitely many times before escaping, and accurate modeling of this dynamics would require extremely small simulation time steps. If the waiting time in the adsorbed state was comparable to the time step, such missed multiple adsorptions would not mat-



ter. However, in many applications, these waiting times are macroscopically large, and omission of even a single adsorption event can result in considerable errors.

For this reason, an accurate modeling of the diffusive dynamics in the presence of an adsorbing boundary is a challenging problem. We solve it by applying our result for the escape time from an adsorbing slab where we set  $H = \epsilon$ . In other words, as any smooth boundary is locally flat, the escape time from a thin layer of width  $\epsilon$  can be accurately approximated by the escape time from a slab of the same width. We can thus account for multiple adsorption events by drawing random times according to the distribution in Eq. (9), with  $H = \epsilon$ . In the SM we exploit insight from the renewal approach to show how this can be done efficiently via a simpler algorithm that is approximate yet highly accurate [73]. This opens the door for accurate simulations of diffusion with adsorbing boundaries in general domains and arbitrary smoothly varying adsorption-desorption rates.

*Outlook.*—When coming to solve the escape problem for a sticky particle, researchers have so far resorted to simplifying assumptions [15–17, 21]. Here, we tackled this problem rigorously, providing a general framework, and demonstrating its applicability using the paradigmatic problem of escape from a sticky slab domain. From an analytical perspective, this is clearly just the tip of the iceberg. In the SM, we solve a related problem of escape from a sticky spherical shell [73], and other cases of interest will be analyzed elsewhere.

Our analysis revealed that adsorption and desorption rates, which may be very hard to measure directly, can instead be inferred from the mean and variance of the escape time. This opens the door for the design of experimental setups for this purpose. For example, in a spin-off on fluorescence recovery after photobleaching, one can imagine fluorescent particles in a virtual slab, where a strong laser photobleaches fluorescence above height  $H$ . The normalized signal from the remaining particles amounts to the survival probability and can thus be used to extract the mean and variance of the escape time. Similarly, one can think of nuclear magnetic resonance experiments, in which a surface at height  $H$  causes strong relaxation that kills the transverse magnetization of the nuclei. These and other methods, e.g., single-particle tracking, can now be coupled with the results reported herein to offer new and promising ways for probing molecular interactions.

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- [73] See Supplemental Material for: (i) Derivation of the partial differential equation and boundary conditions governing  $\tilde{J}_{ab}(s|\mathbf{r}_0)$ ; (ii) Inverse Laplace transformation of Eq. (8) of the main text. The dependence of  $\beta_0^2$  on the adsorption-desorption rates; (iii) Renewal approach. Mean and variance of the escape time. Correlations between the diffusion time and the total waiting time. Splitting probabilities in terms of the Laplace transforms of the fluxes from the bulk; (iv) Simulating an adsorbing boundary condition: Explanation and an example Matlab code; (v) Estimation of the statistical error in the inference of the desorption rate; (vi) Diffusion in a shell with an adsorbing inner sphere and an absorbing outer sphere.



## Supplemental Material for “Escape of a Sticky Particle”

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**DERIVATION OF THE PARTIAL DIFFERENTIAL EQUATION AND BOUNDARY CONDITIONS  
GOVERNING  $\tilde{J}_{ab}(s|\mathbf{r}_0)$**

We can write the backward diffusion equation corresponding to Eq. (3a) of the main text, and further note that it implies a time reversal symmetry that allows us to rewrite the boundary conditions accordingly:

$$(s - D\Delta_{\mathbf{r}_0})\tilde{p}(\mathbf{r}, s|\mathbf{r}_0) = \delta(\mathbf{r} - \mathbf{r}_0), \quad \mathbf{r}_0 \in \Omega, \quad (\text{S1a})$$

$$\tilde{p}(\mathbf{r}, s|\mathbf{r}_0) = 0, \quad \mathbf{r}_0 \in \Omega_{ab}, \quad (\text{S1b})$$

$$\partial_{n_0}\tilde{p}(\mathbf{r}, s|\mathbf{r}_0) + q_s(\mathbf{r}_0)\tilde{p}(\mathbf{r}, s|\mathbf{r}_0) = 0, \quad \mathbf{r}_0 \in \Omega_{ad}, \quad (\text{S1c})$$

where  $\partial_{n_0}$  is the normal derivative with respect to the starting point  $\mathbf{r}_0$ . Integrating over  $\mathbf{r} \in \Omega$  we obtain

$$(s - D\Delta_{\mathbf{r}_0})\tilde{S}_b(s|\mathbf{r}_0) = 1, \quad \mathbf{r}_0 \in \Omega, \quad (\text{S2a})$$

$$\tilde{S}_b(s|\mathbf{r}_0) = 0, \quad \mathbf{r}_0 \in \Omega_{ab}, \quad (\text{S2b})$$

$$\partial_{n_0}\tilde{S}_b(s|\mathbf{r}_0) + q_s(\mathbf{r}_0)\tilde{S}_b(s|\mathbf{r}_0) = 0, \quad \mathbf{r}_0 \in \Omega_{ad}. \quad (\text{S2c})$$

It is convenient to search the solution in the form  $\tilde{J}_b(s|\mathbf{r}_0) = 1 - s\tilde{S}_b(s|\mathbf{r}_0)$ , where the new function satisfies the homogeneous modified Helmholtz equation:

$$(s - D\Delta_{\mathbf{r}_0})\tilde{J}_b(s|\mathbf{r}_0) = 0, \quad \mathbf{r}_0 \in \Omega, \quad (\text{S3a})$$

$$\tilde{J}_b(s|\mathbf{r}_0) = 1, \quad \mathbf{r}_0 \in \Omega_{ab}, \quad (\text{S3b})$$

$$\partial_{n_0}\tilde{J}_b(s|\mathbf{r}_0) + q_s(\mathbf{r}_0)\tilde{J}_b(s|\mathbf{r}_0) = q_s(\mathbf{r}_0), \quad \mathbf{r}_0 \in \Omega_{ad}. \quad (\text{S3c})$$

Note that by defining  $\tilde{J}_{ab}(s|\mathbf{r}_0) = 1 - s\tilde{S}_{ab}(s|\mathbf{r}_0)$  and using the definition in Eq. (5) of the main text we obtain  $\tilde{J}_b = \tilde{J}_{ab} + s\tilde{\Pi} = \tilde{J}_{ab} + \tilde{J}_{ad}$ . This relation simply asserts that the overall probability flux in the compartment is the sum of the probability flux to the adsorbing boundary  $\Omega_{ad}$  and the probability flux the absorbing boundary  $\Omega_{ab}$ . From the linearity of Eq. (S3a) it is clear that  $\tilde{J}_b$  can be written as a sum of two functions, each obeying the same system of equations, but with one of the boundary conditions replaced with an homogeneous boundary condition. It turns out that these functions are exactly  $\tilde{J}_{ad}$  and  $\tilde{J}_{ab}$ :

$$(s - D\Delta_{\mathbf{r}_0})\tilde{J}_{ad}(s|\mathbf{r}_0) = 0, \quad \mathbf{r}_0 \in \Omega, \quad (\text{S4a})$$

$$\tilde{J}_{ad}(s|\mathbf{r}_0) = 0, \quad \mathbf{r}_0 \in \Omega_{ab}, \quad (\text{S4b})$$

$$\partial_{n_0}\tilde{J}_{ad}(s|\mathbf{r}_0) + q_s(\mathbf{r}_0)\tilde{J}_{ad}(s|\mathbf{r}_0) = q_s(\mathbf{r}_0), \quad \mathbf{r}_0 \in \Omega_{ad}. \quad (\text{S4c})$$

and

$$(s - D\Delta_{\mathbf{r}_0})\tilde{J}_{ab}(s|\mathbf{r}_0) = 0, \quad \mathbf{r}_0 \in \Omega, \quad (\text{S5a})$$

$$\tilde{J}_{ab}(s|\mathbf{r}_0) = 1, \quad \mathbf{r}_0 \in \Omega_{ab}, \quad (\text{S5b})$$

$$\partial_{n_0}\tilde{J}_{ab}(s|\mathbf{r}_0) + q_s(\mathbf{r}_0)\tilde{J}_{ab}(s|\mathbf{r}_0) = 0, \quad \mathbf{r}_0 \in \Omega_{ad}, \quad (\text{S5c})$$

Let us now supply a more rigorous proof that  $\tilde{J}_{ab}(s|\mathbf{r}_0)$  is governed by Eqs. (S5a)-(S5c). Note that the propagator also satisfies the backward diffusion equation of Eq. (S1c)

$$(s - D\Delta_{\mathbf{r}_0})\tilde{p}(\mathbf{r}, s|\mathbf{r}_0) = \delta(\mathbf{r} - \mathbf{r}_0) \quad (\mathbf{r}_0 \in \Omega), \quad (\text{S6a})$$

$$\tilde{p}(\mathbf{r}, s|\mathbf{r}_0) = 0 \quad (\mathbf{r}_0 \in \Omega_{ab}), \quad (\text{S6b})$$

$$\mathcal{B}\tilde{p}(\mathbf{r}, s|\mathbf{r}_0) = 0 \quad (\mathbf{r}_0 \in \Omega_{ad}), \quad (\text{S6c})$$

where the operator  $\mathcal{B} = \partial_{n_0} + q_s$  represents the Robin-like boundary condition. The probability density function of the escape time is obtained by integrating the probability flux density over the absorbing part:

$$\tilde{J}_{ab}(s|\mathbf{r}_0) = \int_{\Omega_{ab}} d\mathbf{r} \underbrace{(-D\partial_n\tilde{p})}_{=\tilde{J}_{ab}(\mathbf{r}, s|\mathbf{r}_0)}. \quad (\text{S7})$$

The backward equation (S6a) implies that

$$(s - D\Delta_{\mathbf{r}_0})\tilde{J}_{\text{ab}}(s|\mathbf{r}_0) = 0 \quad (\mathbf{r}_0 \in \Omega), \quad (\text{S8})$$

because the arrival point  $\mathbf{r}$  belongs to the absorbing boundary (and thus  $\delta(\mathbf{r} - \mathbf{r}_0) = 0$ ). In addition, one immediately gets  $\mathcal{B}\tilde{J}_{\text{ab}}(s|\mathbf{r}_0) = 0$  from Eq. (S6c). Finally, one can prove the following boundary condition on the absorbing part:

$$\tilde{J}_{\text{ab}}(s|\mathbf{r}_0) = 1 \quad (\mathbf{r}_0 \in \Omega_{\text{ab}}). \quad (\text{S9})$$

In probabilistic terms, this relation simply states that any particle that starts from the escape region immediately escapes the domain so that the escape time  $\mathcal{T}$  is zero, and thus  $\tilde{J}_{\text{ab}}(s|\mathbf{r}_0) = \langle e^{-s\mathcal{T}} \rangle = 1$ .

One can also give a formal but rather technical proof. For this purpose, one can multiply Eq. (S8) by  $\tilde{p}(\mathbf{r}, s|\mathbf{r}_0)$ , multiply Eq. (S6a) by  $\tilde{J}_{\text{ab}}(s|\mathbf{r}_0)$ , subtract them and integrate over  $\mathbf{r}_0 \in \Omega$ :

$$\begin{aligned} \tilde{J}_{\text{ab}}(s|\mathbf{r}) &= \int_{\Omega} d\mathbf{r}_0 \delta(\mathbf{r} - \mathbf{r}_0) \tilde{J}_{\text{ab}}(s|\mathbf{r}_0) = \int_{\Omega} d\mathbf{r}_0 \left[ \tilde{J}_{\text{ab}}(s|\mathbf{r}_0)(s - D\Delta_{\mathbf{r}_0})\tilde{p}(\mathbf{r}, s|\mathbf{r}_0) - \tilde{p}(\mathbf{r}, s|\mathbf{r}_0)(s - D\Delta_{\mathbf{r}_0})\tilde{J}_{\text{ab}}(s|\mathbf{r}_0) \right] \\ &= \int_{\partial\Omega} d\mathbf{r}_0 \left[ \tilde{p}(\mathbf{r}, s|\mathbf{r}_0) D\partial_{n_0} \tilde{J}_{\text{ab}}(s|\mathbf{r}_0) - \tilde{J}_{\text{ab}}(s|\mathbf{r}_0) D\partial_{n_0} \tilde{p}(\mathbf{r}, s|\mathbf{r}_0) \right] \\ &= \int_{\Omega_{\text{ab}}} d\mathbf{r}_0 \left[ \underbrace{\tilde{p}(\mathbf{r}, s|\mathbf{r}_0)}_{=0} D\partial_{n_0} \tilde{J}_{\text{ab}}(s|\mathbf{r}_0) - \tilde{J}_{\text{ab}}(s|\mathbf{r}_0) D\partial_{n_0} \tilde{p}(\mathbf{r}, s|\mathbf{r}_0) \right], \end{aligned}$$

where we used the Green's second identity and boundary conditions. As a consequence, we get

$$\tilde{J}_{\text{ab}}(s|\mathbf{r}) = \int_{\Omega_{\text{ab}}} d\mathbf{r}_0 \tilde{J}_{\text{ab}}(s|\mathbf{r}_0) \underbrace{(-D\partial_{n_0} \tilde{p}(\mathbf{r}, s|\mathbf{r}_0))}_{=\tilde{j}_{\text{ab}}(\mathbf{r}_0, s|\mathbf{r})}. \quad (\text{S10})$$

The time reversal symmetry of ordinary diffusion implies that the expression in parentheses is the probability flux density  $\tilde{j}_{\text{ab}}(\mathbf{r}_0, s|\mathbf{r})$ . Exchanging notations  $\mathbf{r} \leftrightarrow \mathbf{r}_0$ , one gets

$$\tilde{J}_{\text{ab}}(s|\mathbf{r}_0) = \int_{\Omega_{\text{ab}}} d\mathbf{r} \tilde{J}_{\text{ab}}(s|\mathbf{r}) \tilde{j}_{\text{ab}}(\mathbf{r}, s|\mathbf{r}_0). \quad (\text{S11})$$

Comparing this expression with Eq. (S7), one sees that  $\tilde{J}_{\text{ab}}(s|\mathbf{r})$  must be 1 for all  $\mathbf{r} \in \Omega_{\text{ab}}$  (more rigorously, it follows from the uniqueness of the solution of the modified Helmholtz equation).

## INVERSE LAPLACE TRANSFORMATION OF EQ. (8) IN THE MAIN TEXT

We now proceed to invert the Laplace transform of the escape time PDF of Eq. (8) in the main text. The poles of this function are determined by zeros of the denominator. Setting  $\beta = i\alpha H$ , such that  $s = -\beta^2 D/H^2$ , we get the following equation for  $\beta$  (and thus for the poles):

$$\beta \tan(\beta) = \frac{\kappa_d - \beta^2}{\kappa_a}, \quad (\text{S12})$$

where we introduced dimensionless adsorption and desorption constants  $\kappa_a = k_a H/D$  and  $\kappa_d = k_d H^2/D$ .

The left-hand side is a piecewise monotonously increasing function on the intervals  $(0, \pi/2)$ ,  $(\pi/2, 3\pi/2)$ , etc, whereas the right-hand side is monotonously decreasing. There is an infinite set of solutions of this equation that we denote as  $\beta_n$ . The first solution  $\beta_0$  lies on the interval  $(0, \pi/2)$ , while the others lie on  $(\pi/2 + \pi(n-1), \pi/2 + \pi n)$ . In the limit  $\kappa_a = 0$  (no adsorption), the first solution is  $\beta_0 = \pi/2$ , while the other solutions are  $\beta_n = \pi/2 + \pi n$ ; they correspond to an interval  $(0, H)$  with reflecting endpoint 0 and absorbing endpoint  $H$ . Clearly, the adsorption mechanism yields  $\beta_0$  lying between 0 and  $\pi/2$ . One sees that both the adsorption and desorption rates affect  $\beta_0$  and thus the decay rate in a non-trivial way. In turn, in the limit  $\kappa_d = 0$  (no desorption) and  $\kappa_a \rightarrow \infty$ , the first solution  $\beta_0 = 0$  should be excluded, while the others have a simple form  $\beta_n = \pi n$ ; they correspond to an interval  $(0, H)$  with two absorbing

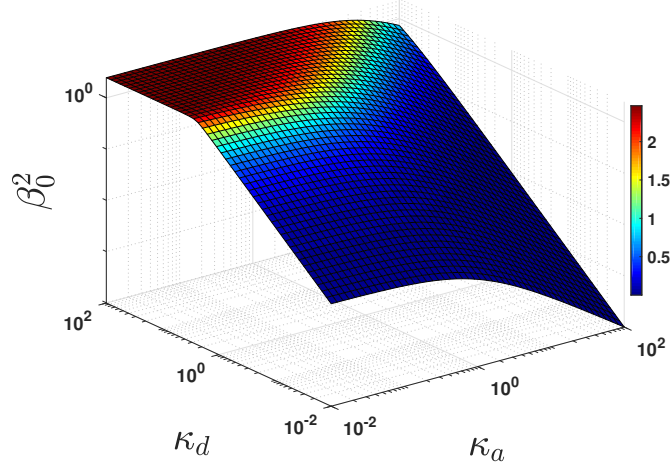


FIG. S1: The first solution  $\beta_0$  of Eq. (S12) that determines the smallest eigenvalue  $\beta_0^2/H^2$  of the Laplace operator on the interval  $(0, H)$ .

endpoints. If we keep  $k_d = 0$  but now set a finite  $0 < k_a < \infty$ , the solution corresponds to the case of one partially absorbing endpoint (Robin boundary condition) and one absorbing endpoint.

Figure S1 illustrates the behavior of  $\beta_0^2$  as a function of the rescaled adsorption and desorption rates  $\kappa_a$  and  $\kappa_d$ . When  $\kappa_a \rightarrow 0$  and/or  $\kappa_d \rightarrow \infty$ , the left endpoint becomes reflecting, such that  $\beta_0^2 \approx \pi^2/4$ , as discussed earlier. In the limit  $\kappa_d \rightarrow 0$ , the left endpoint becomes partially reactive, with the reactivity given by  $\kappa_a$ . In this case,  $\beta_0^2 \rightarrow 0$ , but 0 is not the pole of  $\tilde{J}_{\text{ab}}(s|z_0)$ , so that the limiting value should be excluded, and the smallest eigenvalue is actually given by  $\beta_1^2$ , which is equal to  $\pi^2$  in the limit  $\kappa_a \rightarrow \infty$ , as expected.

To get the inverse Laplace transform of  $\tilde{J}_{\text{ab}}(s|z_0)$  we proceed to compute its residues at the poles. For this purpose, we first evaluate

$$g'(H, s) = \frac{\partial g(H, s)}{\partial s} = \frac{\partial g}{\partial \alpha} \frac{d\alpha}{ds} = \frac{H}{2iD\beta} \left[ \cos \beta \left( 1 + \frac{\kappa_a \beta^2}{\beta^2 - \kappa_d} \right) - \beta \sin \beta \left( 1 + \frac{2\kappa_a \kappa_d}{(\beta^2 - \kappa_d)^2} \right) \right]. \quad (\text{S13})$$

Then, the residues are given by  $2\pi i \cdot g(z_0, s_n)/g'(H, s_n)$ , where  $s_n = -\beta_n^2 D/H^2$ . Hence, applying the residue theorem, we get

$$\begin{aligned} J_{\text{ab}}(t|z_0) &= \frac{1}{2\pi i} \int_{\gamma} e^{st} \tilde{J}_{\text{ab}}(s|z_0) ds = \sum_n e^{s_n t} \text{Res}_{s_n} \{ \tilde{J}_{\text{ab}}(s|z_0) \} \\ &= \sum_{n=0}^{\infty} e^{-\beta_n^2 D t/H^2} \frac{i}{H g'(H, s_n)} \left( \beta_n \cos(\beta_n z_0/H) + \frac{\kappa_a \beta_n^2}{\beta_n^2 - \kappa_d} \sin(\beta_n z_0/H) \right), \end{aligned} \quad (\text{S14})$$

which is equivalent to Eq. (9) in the main text.

## RENEWAL APPROACH

For an interval, one can implement a renewal approach. In fact, the PDF of the escape time can be written as

$$\begin{aligned} J_{\text{ab}}(t|z_0) &= j_H(t|z_0) + \int_0^t dt_1 j_0(t_1|z_0) \int_{t_1}^t dt'_1 \psi(t'_1 - t_1) j_H(t - t'_1|0) \\ &+ \int_0^t dt_1 j_0(t_1|z_0) \int_{t_1}^t dt'_1 \psi(t'_1 - t_1) \int_{t'_1}^t dt_2 j_0(t_2 - t'_1|0) \int_{t_2}^t dt'_2 \psi(t'_2 - t_2) j_H(t - t'_2|0) + \dots \end{aligned} \quad (\text{S15})$$

where  $j_H(t|z_0)$  and  $j_0(t|z_0)$  are the probability fluxes from the bulk at  $z = H$  and  $z = 0$ , and  $\psi(t)$  is the probability density of the waiting time in the adsorbed state. We emphasize that these are the fluxes from the bulk, i.e.,  $j_0(t|z_0)$  here does not contain the contribution from desorption (unlike  $j_{\text{ad}}(t|z_0)$  defined in the main text) – this contribution is taken care of by  $\psi(t)$ . Thus, the fluxes from the bulk can be equivalently defined as the fluxes out of an interval  $(0, H)$  with absorbing endpoint at  $H$  and partially reactive ( $k_a > 0, k_d = 0$ ) endpoint at 0. The first term in Eq. (S15) represents trajectories that escaped the domain without any adsorption, the second term accounts for a single adsorption, the third term for two adsorptions, and so on. In Laplace domain, one gets

$$\tilde{J}_{\text{ab}}(s|z_0) = \tilde{j}_H(s|z_0) + \tilde{j}_0(s|z_0)\tilde{\psi}(s)\tilde{j}_H(s|0) + \dots = \tilde{j}_H(s|z_0) + \frac{\tilde{j}_0(s|z_0)\tilde{\psi}(s)\tilde{j}_H(s|0)}{1 - \tilde{j}_H(s|0)\tilde{\psi}(s)}, \quad (\text{S16})$$

where we summed the geometric series.

For the interval  $(0, H)$  with absorbing endpoint at  $H$  and a partially reactive (note again, no desorption) endpoint at 0, one has

$$\tilde{j}_H(s|z_0) = \frac{\alpha \cosh(\alpha z_0) + q \sinh(\alpha z_0)}{\alpha \cosh(\alpha H) + q \sinh(\alpha H)}, \quad (\text{S17})$$

$$\tilde{j}_0(s|z_0) = \frac{q \sinh(\alpha(H - z_0))}{\alpha \cosh(\alpha H) + q \sinh(\alpha H)}, \quad (\text{S18})$$

where  $\alpha = \sqrt{s/D}$  and  $q = k_a/D$ .

Let us now consider an adsorbing boundary at 0 with exponentially distributed waiting time,  $\psi(t) = k_d e^{-k_d t}$  so that  $\tilde{\psi}(s) = 1/(1 + s/k_d)$ . Substituting these expressions in Eq. (S16), we retrieve Eq. (8) of the main text.

### Mean and variance of the escape time

In the limit  $s \rightarrow 0$ , we get

$$\tilde{j}_H(s|z_0) \approx \mathcal{E}_H(z_0)[1 - s\langle\mathcal{T}_H(z_0)\rangle + O(s^2)], \quad (\text{S19})$$

$$\tilde{j}_0(s|z_0) \approx \mathcal{E}_0(z_0)[1 - s\langle\mathcal{T}_0(z_0)\rangle + O(s^2)], \quad (\text{S20})$$

where

$$\mathcal{E}_H(z_0) = \frac{1 + qz_0}{1 + qH}, \quad \mathcal{E}_0(z_0) = \frac{q(H - z_0)}{1 + qH} \quad (\text{S21})$$

are the splitting probabilities on the endpoints  $H$  and 0 (e.g.,  $\mathcal{E}_H(z_0)$  is the probability of absorption on the endpoint  $H$ ; evidently,  $\mathcal{E}_H(z_0) + \mathcal{E}_0(z_0) = 1$ ), and where

$$\langle\mathcal{T}_H(z_0)\rangle = \frac{H - z_0}{6D(1 + qH)(1 + qz_0)} \left[ 3(H + z_0) + q(H + z_0)^2 + 2qHz_0 + q^2Hz_0(H + z_0) \right], \quad (\text{S22})$$

$$\langle\mathcal{T}_0(z_0)\rangle = \frac{2H^2 + 2Hz_0 + 2H^2qz_0 - z_0^2 - z_0^2qH}{6D(1 + qH)} \quad (\text{S23})$$

are the *conditional* mean absorption times to the endpoints 0 and  $H$ , respectively (e.g.,  $\langle\mathcal{T}_H(z_0)\rangle$  is the MFPT to the endpoint  $H$ , which is conditioned by the arrival onto this endpoint). Note that the conditional form is necessary here because  $j_H(t|z_0)$  is not normalized to 1 since the particle may be absorbed on the endpoint 0. Substituting these expansions into Eq. (S16), we get

$$\tilde{J}_{\text{ab}}(s|z_0) \approx \mathcal{E}_H(z_0)(1 - \langle\mathcal{T}_H(z_0)\rangle s) + \frac{\mathcal{E}_0(z_0)(1 - \langle\mathcal{T}_0(z_0)\rangle s)\mathcal{E}_H(0)(1 - \langle\mathcal{T}_H(0)\rangle s)}{(1 + \langle\mathcal{T}_w\rangle s) - \mathcal{E}_0(0)(1 - \langle\mathcal{T}_0(0)\rangle s)}, \quad (\text{S24})$$

where we used  $\tilde{\psi}(s) = 1 - s\langle\mathcal{T}_w\rangle + O(s^2)$ , and  $\langle\mathcal{T}_w\rangle$  is the mean waiting time in the adsorbed state. Using  $1 - \mathcal{E}_0(0) = \mathcal{E}_H(0)$ , we then get  $\tilde{J}_{\text{ab}}(s|z_0) = 1 - \langle\mathcal{T}(z_0)\rangle s + O(s^2)$ , with

$$\langle\mathcal{T}(z_0)\rangle = \left( \mathcal{E}_H(z_0)\langle\mathcal{T}_H(z_0)\rangle + \mathcal{E}_0(z_0)\langle\mathcal{T}_0(z_0)\rangle \right) + \mathcal{E}_0(z_0) \left[ \langle\mathcal{T}_H(0)\rangle + \frac{\langle\mathcal{T}_w\rangle + \mathcal{E}_0(0)\langle\mathcal{T}_0(0)\rangle}{\mathcal{E}_H(0)} \right]. \quad (\text{S25})$$



The first term is the (unconditional) mean escape time from an interval  $(0, H)$  with absorbing endpoint at  $H$  and partially reactive ( $k_a > 0, k_d = 0$ ) endpoint at  $0$ . This is equal to

$$\mathcal{E}_H(z_0)\langle\mathcal{T}_H(z_0)\rangle + \mathcal{E}_0(z_0)\langle\mathcal{T}_0(z_0)\rangle = \frac{(H + z_0(1 + qH))(H - z_0)}{2D(1 + qH)} = \frac{H^2 - z_0^2}{2D} - \mathcal{E}_0(z_0)\frac{H^2}{2D}, \quad (\text{S26})$$

and note that one recovers the results for a fully reflecting and fully absorbing boundaries at  $z = 0$  by setting  $\mathcal{E}_0(z_0) = 0$  and  $\mathcal{E}_0(z_0) = \frac{H - z_0}{H}$ , respectively. As a consequence, we have

$$\begin{aligned} \langle\mathcal{T}(z_0)\rangle &= \frac{H^2 - z_0^2}{2D} + \mathcal{E}_0(z_0) \left[ T_H(0) - \frac{H^2}{2D} + \frac{\langle\mathcal{T}_w\rangle + \mathcal{E}_0(0)T_0(0)}{\mathcal{E}_H(0)} \right] \\ &= \frac{H^2 - z_0^2}{2D} + \mathcal{E}_0(z_0) \left[ \frac{\langle\mathcal{T}_w\rangle}{\mathcal{E}_H(0)} + \underbrace{\frac{\mathcal{E}_H(0)T_H(0) + \mathcal{E}_0(0)T_0(0)}{\mathcal{E}_H(0)} - \frac{H^2}{2D}}_{=0} \right] \\ &= \frac{H^2 - z_0^2}{2D} + \underbrace{\mathcal{E}_0(z_0)\frac{\langle\mathcal{T}_w\rangle}{\mathcal{E}_H(0)}}_{=q(H-z_0)\langle\mathcal{T}_w\rangle}, \end{aligned} \quad (\text{S27})$$

where in going from the first to second line we used Eq. (S26). Thus, despite the complexity of the general relation (S25), most contributions compensate each other, yielding a remarkably simple expression:

$$\langle\mathcal{T}\rangle := \langle\mathcal{T}(z_0)\rangle = \frac{H^2 - z_0^2}{2D} + q(H - z_0)\langle\mathcal{T}_w\rangle, \quad (\text{S28})$$

where  $q = k_a/D$ . The first term is the MFPT from an interval  $(0, H)$  with absorbing endpoint at  $H$  and reflecting endpoint at  $0$ . In turn, the second term incorporates all contributions from the adsorption/desorption events. The proportionality of this term to  $\langle\mathcal{T}_w\rangle$  suggests it can be interpreted as the mean cumulative waiting time in the adsorbed state, whereas the first term is the mean cumulative diffusion time in the bulk.

To justify this interpretation, let us examine a random trajectory of a particle that started from  $z_0$  and arrived onto the endpoint  $H$ . As previously, one can distinguish two cases by whether the diffusing particle has or has not been adsorbed on the endpoint  $0$  before the escape. In the second case, there is no waiting time, and the only contribution comes from the diffusion time. We therefore focus on the first case where the particle has been adsorbed (at least once) on  $0$  before escaping the interval. Between the first adsorption on  $0$  and the escape from the interval through the endpoint  $H$ , the particle experienced multiple reflections from the endpoint  $0$ . After a number of reflections, it may be re-adsorbed, spend some time on  $0$ , be desorbed, and so on. However, if we cut off all the waiting periods in the adsorbed state (we treat them below), the adsorption/desorption mechanism does not affect the diffusive dynamics of the particle, as if the endpoint  $0$  was *purely reflecting*. In other words, if  $\langle\mathcal{T}_w\rangle = 0$  (or, in the Markovian setting, for  $k_d = \infty$ ), there is no effect coming from adsorption/desorption, and one retrieves the results for a reflecting boundary. As a consequence, the diffusion time in the free state is given by the first term in Eq. (S28).

For  $\langle\mathcal{T}_w\rangle \neq 0$ , the diffusion time should be complemented by the total waiting time that the particle has spent in the adsorbed state. According to our derivation, the mean total waiting time is  $\mathcal{E}_0(z_0)\langle\mathcal{T}_w\rangle/\mathcal{E}_H(0)$ . How can one interpret this relation? First of all, if the particle has escaped without any adsorption, there is no such contribution. This explains the presence of the splitting probability  $\mathcal{E}_0(z_0)$ , i.e., the probability that at least one adsorption occurred before escaping. After each desorption, the particle starts from  $0$  and can escape the interval with the probability  $\mathcal{E}_H(0)$ . Let  $\chi_i$  denote a Bernoulli random variable, which takes the value  $0$  (re-adsorption at  $i$ -th trial, i.e., failure to escape) with probability  $1 - \mathcal{E}_H(0)$  and the value  $1$  (successful escape) with probability  $\mathcal{E}_H(0)$ . As all escape trials are independent, the number of Bernoulli trials before escape has a geometric distribution, with the mean  $1/\mathcal{E}_H(0)$ . As the particle spends in each adsorbed state on average  $\langle\mathcal{T}_w\rangle$  units of time, the total mean waiting time is  $\mathcal{E}_0(z)\langle\mathcal{T}_w\rangle/\mathcal{E}_H(0)$ , in agreement with the second term in Eq. (S28).

Let us extend the above rationale to represent the escape time  $\mathcal{T}$  as the sum of the (random) diffusion time  $\mathcal{T}_d$  on the interval  $(0, H)$  with reflecting endpoint  $0$ , and the (random) total waiting time  $\mathcal{T}_{ad}$  in the adsorbed state:

$\mathcal{T} = \mathcal{T}_d + \mathcal{T}_{\text{ad}}$ . The latter can be formally defined as

$$\mathcal{T}_{\text{ad}} = \begin{cases} 0, & \text{with probability } \mathcal{E}_H(z_0), \\ \tau_1, & \text{with probability } \mathcal{E}_0(z_0)\mathcal{E}_H(0)\psi(t), \\ \tau_2, & \text{with probability } \mathcal{E}_0(z_0)(1 - \mathcal{E}_H(0))\mathcal{E}_H(0)\psi_2(t), \\ \dots & \\ \tau_k, & \text{with probability } \mathcal{E}_0(z_0)(1 - \mathcal{E}_H(0))^{k-1}\mathcal{E}_H(0)\psi_k(t), \\ \dots & \end{cases} \quad (\text{S29})$$

where  $\psi_k(t) = (\psi \circ \psi \circ \dots \circ \psi)(t)$  is the probability density function of  $\tau_k$ , which is defined as a sum of  $k$  independent waiting times (note that  $\tau_1 = \mathcal{T}_w$ ). This time is obtained as the  $k$ -order convolution of PDF  $\psi(t)$ . In other words, if  $\mathcal{N}$  is the (random) number of trials before escape, governed by the geometric law with  $\mathcal{E}_H(0)$ ,  $\mathcal{T}_{\text{ad}}$  is equal to  $\tau_{\mathcal{N}}$  (apart from the value 0, which corresponds to no adsorption with probability  $\mathcal{E}_H(z)$ ).

It is important to emphasize that the random variables  $\mathcal{T}_d$  and  $\mathcal{N}$  (and thus  $\mathcal{T}_{\text{ad}}$ ) are not independent. In fact, one can intuitively expect that large values of  $\mathcal{N}$  would correspond to large values of  $\mathcal{T}_d$  (i.e., more escape trials imply longer diffusion times). The mean values  $\langle \mathcal{T}_d \rangle$  and  $\langle \mathcal{T}_{\text{ad}} \rangle$ , whose sum yields the mean escape time, can be computed independently, despite correlations between  $\mathcal{T}_d$  and  $\mathcal{T}_{\text{ad}}$ , as we did above. In contrast, correlations affect higher-order moments and the whole distribution. In particular, the variance of the escape time has three contributions:

$$\text{Var}\{\mathcal{T}\} = \text{Var}\{\mathcal{T}_d\} + \text{Var}\{\mathcal{T}_{\text{ad}}\} + 2\left(\langle \mathcal{T}_d \mathcal{T}_{\text{ad}} \rangle - \langle \mathcal{T}_d \rangle \langle \mathcal{T}_{\text{ad}} \rangle\right). \quad (\text{S30})$$

The first term is well-known:

$$\text{Var}\{\mathcal{T}_d\} = \frac{H^4 - z_0^4}{6D^2}. \quad (\text{S31})$$

We compute the mean by direct computation

$$\langle \mathcal{T}_{\text{ad}} \rangle = \int_0^\infty dt t \text{pdf}(t) = \mathcal{E}_0(z_0)\mathcal{E}_H(0) \sum_{n=1}^\infty (1 - \mathcal{E}_H(0))^{n-1} \underbrace{\int_0^\infty dt t \psi_n(t)}_{=n\langle \mathcal{T}_w \rangle} = \langle \mathcal{T}_w \rangle \mathcal{E}_0(z_0) / \mathcal{E}_H(0). \quad (\text{S32})$$

To compute variance we use the law of total variance and obtain

$$\begin{aligned} \text{Var}\{\mathcal{T}_{\text{ad}}\} &= \langle \mathcal{N} \rangle \text{Var}\{\mathcal{T}_w\} + \text{Var}\{\mathcal{N}\} \langle \mathcal{T}_w \rangle^2 \\ &= q(H - z_0) \text{Var}\{\mathcal{T}_w\} + q(H - z_0)[1 + q(H + z_0)] \langle \mathcal{T}_w \rangle^2 = \\ &= q(H - z_0) \langle \mathcal{T}_w^2 \rangle + q^2(H^2 - z_0^2) \langle \mathcal{T}_w \rangle^2, \end{aligned} \quad (\text{S33})$$

where in moving to the second line we have plugged in the first two moments of  $\mathcal{N}$ , which are derived in detail in Sec. (see Eq. (S42)).

Comparing Eqs. (S30, S31, S33) with the variance of  $\mathcal{T}$ , that we obtain directly from the small- $s$  expansion of  $\tilde{\mathcal{J}}_{\text{ab}}(s|z_0)$ ,

$$\text{Var}\{\mathcal{T}\} = \frac{H^4 - z_0^4}{6D^2} + \frac{2q(H^3 - z_0^3)}{3D} \langle \mathcal{T}_w \rangle + q^2(H^2 - z_0^2) \langle \mathcal{T}_w \rangle^2 + q(H - z_0) \langle \mathcal{T}_w^2 \rangle, \quad (\text{S34})$$

we conclude that

$$\langle \mathcal{T}_d \mathcal{T}_{\text{ad}} \rangle - \langle \mathcal{T}_d \rangle \langle \mathcal{T}_{\text{ad}} \rangle = \frac{2q(H^3 - z_0^3)}{3D} \langle \mathcal{T}_w \rangle. \quad (\text{S35})$$

In this way, we managed to characterize correlations between the diffusion time  $\mathcal{T}_d$  and the total waiting time  $\mathcal{T}_{\text{ad}}$ .

While the mean escape time in Eq. (S28) depends only on  $q\langle \mathcal{T}_w \rangle$ , the variance of the escape time in Eq. (S34) depends on both  $q\langle \mathcal{T}_w \rangle$  and  $q\langle \mathcal{T}_w^2 \rangle$ . For the Markovian case (an exponential distribution of the adsorption time), one has  $\langle \mathcal{T}_w \rangle = 1/k_d$  and  $\langle \mathcal{T}_w^2 \rangle = 2/k_d^2$ , that implies separate dependence on  $k_a$  and  $k_d$  in the variance:

$$\text{Var}\{\mathcal{T}\} = \frac{H^4 - z_0^4}{6D^2} + \frac{K^2(H^2 - z_0^2)}{D^2} + \frac{2K(H^3 - z_0^3)}{3D^2} + \frac{2K(H - z_0)}{k_d D}, \quad (\text{S36})$$

where  $K = k_a/k_d$ .

### Splitting probabilities in terms of the Laplace transforms of the fluxes from the bulk

The splitting probability  $\mathcal{E}_H(z_0)$  is the probability that a diffusing particle, initially at  $z_0$ , is absorbed at  $H$ , without adsorbing to the surface at 0 beforehand. The complementary splitting probability  $\mathcal{E}_0(z_0)$  is the probability that the particle is adsorbed at 0 before it manages to escape. Note that  $\mathcal{E}_0(z_0)$  accounts for at least one adsorption. Thus, for the purpose of the calculation of the splitting probabilities, the adsorbing boundary can be safely replaced with a partially absorbing boundary with reactivity  $k_a$  (and no desorption). In other words, one only needs the fluxes from the bulk to get  $\mathcal{E}_H(z_0) = \int_0^\infty J_H(t|z_0)dt = \tilde{J}_H(s=0|z_0)$  and  $\mathcal{E}_0(z_0) = \int_0^\infty J_0(t|z_0)dt = \tilde{J}_0(s=0|z_0)$ . Note that this result was already used in Eqs. (S19)-(S20). We thus see that all the previously derived expressions that contained splitting probabilities can be written in terms of the Laplace transform  $\tilde{J}_0(s=0|z_0)$  and/or  $\tilde{J}_H(s=0|z_0)$ . In fact, the renewal approach allows one to express the solution for the problem in a compartment with an adsorbing boundary in terms of the solution for the simpler problem where the adsorbing boundaries are replaced with partially reactive boundaries of reactivity  $k_a$  and a waiting time distribution,  $\psi(t)$ , in the adsorbed state.

### SIMULATING AN ADSORBING BOUNDARY CONDITION

#### Explanation

Recall the general adsorbing boundary condition given in Eqs. (2a)-(2b) of the main text. For the one-dimensional case, we have

$$j_{\text{ad}}(0, t|z_0) = k_a p(0, t|z_0) - k_a \Pi(t|z_0), \quad (\text{S37a})$$

$$\partial_t \Pi(t|z_0) = j_{\text{ad}}(0, t|z_0). \quad (\text{S37b})$$

We show here how a numerical simulation of such a boundary condition can be performed efficiently using insights from the renewal technique presented in Sec. .

As discussed in Sec. , the splitting probability  $\mathcal{E}_H(z_0)$  is the probability that a diffusing particle, initially at  $z_0$ , will be absorbed at  $H$ , without adsorbing to the surface at 0 beforehand. The complementary splitting probability  $\mathcal{E}_0(z_0)$  is the probability that the particle is adsorbed at least once before it manages to escape. Let  $\mathcal{N}$  denote the number of adsorption events before escape. We thus have:

$$\mathbb{P}\{\mathcal{N} = 0 \mid z_0\} = \mathcal{E}_H(z_0) = \frac{1 + qz_0}{1 + qH}, \quad (\text{S38})$$

and

$$\mathbb{P}\{\mathcal{N} > 0 \mid z_0\} = 1 - \mathbb{P}\{\mathcal{N} = 0 \mid z_0\} = \mathcal{E}_0(z_0) = \frac{q(H - z_0)}{1 + qH}. \quad (\text{S39})$$

Markedly, when starting from the adsorbing surface we have

$$\mathbb{P}\{\mathcal{N} = 0 \mid z_0 = 0\} = \mathcal{E}_H(0) = \frac{1}{1 + qH}. \quad (\text{S40})$$

We now aim to compute  $\mathbb{P}\{\mathcal{N} = n \mid z_0\}$ , namely the probability of  $n > 0$  adsorptions events prior to the escape, given the initial position  $z_0$ . First, the particle has to be adsorbed once, the probability of which is given by  $\mathcal{E}_0(z_0)$ . Immediately after that adsorption event, the particle starts diffusing again, from  $z_0 = 0$ , and has the probability  $\mathbb{P}\{\mathcal{N} = 0 \mid z_0 = 0\}$  to escape without adsorbing for the second time. With the complementary probability the particle will adsorb again before escape and from this point onward the process is renewed. We thus have a geometrically distributed process with “success” probability  $\mathbb{P}\{\mathcal{N} = 0 \mid z_0 = 0\}$ . Overall we obtain

$$\mathbb{P}\{\mathcal{N} = n \mid z_0 = 0\} = \mathcal{E}_0(z_0) \mathcal{E}_0(0)^{n-1} \mathcal{E}_H(0). \quad (\text{S41})$$

In particular we have

$$\langle \mathcal{N} \rangle = q(H - z_0), \quad \langle \mathcal{N}^2 \rangle = q(H - z_0)(1 + 2qH). \quad (\text{S42})$$

Let us now describe the simulation procedure of an adsorbing boundary located at  $z = 0$ . We introduce a thin boundary layer of width  $\epsilon$  near the endpoint 0. The width should be larger than a typical one-step displacement  $\sigma$

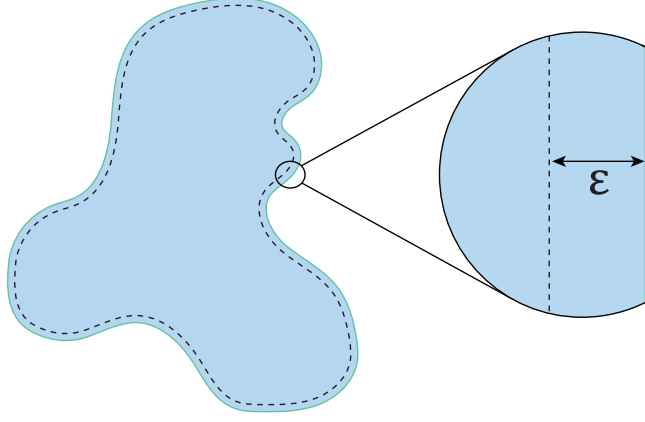


FIG. S2: Simulation of an adsorbing surface of higher-dimensional domain and of complex morphology: As any smooth boundary is locally flat, the escape time from a thin layer of width  $\epsilon$  can be accurately approximated by the escape time from a slab of the same width.

(say,  $\epsilon = 5\sigma$ ). When the particle position  $z$  is at a distance smaller than  $\epsilon/2$  from the boundary, we consider that they start to “interact”. As a result of this interaction, the particle may be adsorbed a number of times, before it escapes the layer of width  $\epsilon$  (we thus consider the escape problem with  $H = \epsilon$ ).

The escape time distribution is given exactly in Eq. (9) of the main text, but drawing random times from this bulky expression can prove numerically taxing. Instead, we suggest an alternative algorithm that reproduces the results with excellent precision and can be easily generalized. This alternative algorithm is based on the realization that in the limit  $\epsilon \ll 1$  fluctuations in the escape time from the boundary layer are mostly due to fluctuations in the time spent in the adsorbed state. Thus, it is enough to retain only the effect of fluctuations in the waiting times  $\mathcal{T}_w^1, \dots, \mathcal{T}_w^{\mathcal{N}}$ . Indeed, by setting  $H = \epsilon$  in Eq. (S34) and taking this limit we are left only with the last two terms, which are equal to  $\text{Var}\{\mathcal{T}_{\text{ad}}\}$ .

First, one performs a Bernoulli trial to decide whether  $\mathcal{N} = 0$  (with probability  $\mathcal{E}_\epsilon(z) = (1 + qz)/(1 + q\epsilon)$ ) or  $\mathcal{N} > 0$ . In the former case, the particle is relocated to a new position  $z = \epsilon$ , while the time counter is incremented by  $(\epsilon^2 - z^2)/(2D)$ , i.e., the mean time needed to escape the interval  $(0, \epsilon)$  with reflecting endpoint 0 and absorbing endpoint  $\epsilon$ . In turn, in the latter case, we generate the random number  $\mathcal{N} = n$  of adsorptions from the geometric distribution  $\mathcal{E}_0(0)^{n-1}\mathcal{E}_\epsilon(0)$  for  $n = 1, 2, \dots$ . The particle is again relocated at  $z = \epsilon$ , while the time counter is incremented by

$$\frac{\epsilon^2 - z^2}{2D} + \sum_{i=1}^{\mathcal{N}} \mathcal{T}_w^i, \quad (\text{S43})$$

where  $\mathcal{T}_w^1, \dots, \mathcal{T}_w^{\mathcal{N}}$  are independent waiting times generated from the exponential law with the rate  $k_d$  in accordance with the first-order desorption kinetics described by the last term in Eq. (S37a). Note that Eq. (S43) captures the mean escape time from the boundary layer exactly. It also captures the variance of the escape time to second order in the layer’s width  $\epsilon$ , with errors being  $O(\epsilon^3)$ . A generalization for non-exponential waiting times is trivial: one has to generate  $\mathcal{T}_w^i$  according to the given probability density  $\psi(t)$ .

As any smooth boundary is locally flat, we can use the above procedure when simulating higher-dimensional domains. All we have to do is make sure that the simulation step size is small enough such that the surface can be locally approximated as a flat surface. Then, a thin subsurface layer of width  $\epsilon$  can be approximated by a slab of length  $\epsilon$ . This is illustrated in Fig. (S2).

### An example Matlab code

Below we supply an example Matlab code for simulating the escape of a diffusing particle from an interval with an adsorbing boundary at 0, and an absorbing boundary at  $H$  (see Fig. 2 of the main text). The simulation output is the escape time. In fact, we have used this code to simulate data shown in Fig. 3 and Fig. 4 of the main text. Green text denotes commentary, as we supply a short explanation of each simulation step. Note that we do not claim that the following code is of optimal performance.

```

function escape = ExampleFunction(ka, kd, H, D, z0,epsilon, dt,tmax)

escape=0; counter=0; %Define escape time and counter.

z=z0; %The location is set to the initial location.

while 1 %Endless loop unless break command is performed.

    dz=sqrt(2*D*dt)*randn(); z=z+dz; %Random step of a free diffusing particle.

    if z < epsilon/2 %When the particle position z is closer to the boundary than  $\epsilon/2$ .

        B1=rand(); %Generate a random number between 0 and 1.

        pesc = (1 + ka*z/D)/(1 + ka*epsilon/D); %The splitting probability  $\mathcal{E}_\epsilon(z)$ .

        B=(B1 < pesc); %Boolean: 1 if the particle first cross  $\epsilon$  and 0 if the particle first adsorb.

        teps = (epsilon^2 - z^2)/(2*D); %Time that is added to the counter later in both cases.

        z=epsilon; %The particle is relocated to  $\epsilon$ .

        if B==0 %If the particle adsorbed before crossing  $\epsilon$ .

            Nads = 1 + geornd(1/(1+ka*epsilon/D),1); %Number of adsorption events.

            counter = counter + teps + sum(exprnd(1/kd,1,Nads)); %Update the time counter by the adsorbed
                %time+time needed to diffuse a distance  $\epsilon$ .

        else %If crossed  $\epsilon$  without first adsorbing.

            counter = counter + teps; %Update the time counter by the time needed to diffuse a distance  $\epsilon$ .

        end

    end

end

if counter>tmax

    escape=tmax; %In case simulation power is limited. It is best to set tmax=inf.

    break;

elseif z>H

    escape=counter; %Save escape time and break.

    break;

end

counter=counter+dt; %Move time step forward.

end
end

```



## ESTIMATION OF THE STATISTICAL ERROR IN THE INFERENCE OF THE DESORPTION RATE

We can write our expressions for the mean and variance of the escape time  $\mathcal{T}$  as

$$\mu := \langle \mathcal{T} \rangle = A + BK, \quad (\text{S44})$$

$$\sigma^2 := \text{Var}\{\mathcal{T}\} = a + bK + cK^2 + dK/k_d, \quad (\text{S45})$$

where  $A, B, a, b, c, d$  are explicitly known constants, see Eqs. (10) and (12) of the main text for the delta-function initial condition, and the expressions given in the caption of Fig. 4 for the uniform initial condition. For completeness, let us cite the latter here again:  $\langle \mathcal{T}_u \rangle = H^2/(3D) + KH/(2D)$  and  $\text{Var}\{\mathcal{T}_u\} = 7H^4/(45D^2) + 7KH^3/(12D^2) + 3H^2K^2/(4D^2) + HK/(k_dD)$ , where the subscript ‘ $u$ ’ denotes re-derivation of Eqs. (10) and (12) of the main text according to a uniform initial distribution. Importantly, for both the delta-function and the uniform initial conditions the mean and variance follow the general form in Eqs. (S44) and (S45).

For the inference procedure, we replace the exact mean and variance by its empirical estimates from  $N$  measured escape times  $\mathcal{T}_1, \dots, \mathcal{T}_N$ :

$$T_1 = \frac{1}{N} \sum_{n=1}^N \mathcal{T}_n, \quad T_2 = \frac{1}{N} \sum_{n=1}^N (\mathcal{T}_n - T_1)^2. \quad (\text{S46})$$

In other words, we express:

$$K = \frac{T_1 - A}{B}, \quad k_d = \frac{dT_2}{T_2 - a - bK - cK^2}, \quad (\text{S47})$$

which are now random variables due to fluctuations (statistical noise) in the empirical estimates  $T_1$  and  $T_2$ . Since the fluctuations of the empirical mean  $T_1$  are given by standard deviation,  $\Delta T_1 = \sigma/\sqrt{N}$ , one has

$$\Delta K = \frac{\Delta T_1}{B} = \frac{\sigma}{B\sqrt{N}}. \quad (\text{S48})$$

The fluctuations of  $T_2$  are given by the standard formula from statistics,

$$\Delta T_2 = \sqrt{\frac{\mu_4}{N} - \frac{\sigma^4(N-3)}{N(N-1)}} \approx \frac{\sqrt{\mu_4 - \sigma^4}}{\sqrt{N}}, \quad (\text{S49})$$

where  $\mu_4 = \langle (\mathcal{T} - \mu)^4 \rangle$  is the fourth central moment of the escape time  $\mathcal{T}$ .

Using the standard formulas for estimating the errors of measured quantities, we have

$$\Delta k_d = \frac{d\Delta K}{T_2 - a - bK - cK^2} + \frac{dK(\Delta T_2 + b\Delta K + 2cK\Delta K)}{(T_2 - a - bK - cK^2)^2}, \quad (\text{S50})$$

from which

$$\begin{aligned} \frac{\Delta k_d}{k_d} &= \frac{\Delta K}{K} + \frac{\Delta T_2 + (b + 2cK)\Delta K}{dK} k_d \\ &= \frac{1}{\sqrt{N}} \left( \frac{\sigma}{KB} + \frac{\sqrt{\mu_4 - \sigma^4} + (b + 2cK)\sigma/B}{dK} k_d \right). \end{aligned} \quad (\text{S51})$$

First, we note that the relative error in the estimation of the desorption rate  $k_d$  decreases as  $1/\sqrt{N}$ , as expected. Let us now inspect the coefficient in front of this factor. For fixed  $K$ , in the limit  $k_d \rightarrow 0$  the first term diverges according to Eq. (S45) as  $\sigma \propto 1/\sqrt{k_d}$ , yielding large relative error in the estimation of  $k_d$  (note that the absolute error  $\Delta k_d$  vanishes as  $\sqrt{k_d}$  in the limit  $k_d \rightarrow 0$ ). Finding the behavior of the second term in Eq. (S51) requires the computation of  $\mu_4$  to know its dependence on  $K$  and  $k_d$ . This computation is feasible but rather tedious and is actually unnecessary. In fact, this term can only degrade the quality of the estimation and thus it does not alter the above conclusion: the relative error of  $k_d$  increases in the limit  $k_d \rightarrow 0$ .

Away from this limit, the relative error exhibits non-monotonous behavior. To show this we present a contour plot of the relative error as function of  $K$  and  $k_d$ , see Fig. S3. For instance, if  $K$  is fixed, the ratio  $\Delta k_d/k_d$  increases in both limits  $k_d \rightarrow 0$  and  $k_d \rightarrow \infty$  but reaches a minimum at an intermediate value of  $k_d$ . Figure S3 can thus be used as a guide for designing inference techniques, as it gives a theoretical estimation for the accuracy of the results in different regimes of the parameters space. Note that in making this figure we have assumed a uniform initial distribution and set  $H$  and  $D$  to 1. It can be thus seen as complementary to Fig. 4 of the main text.

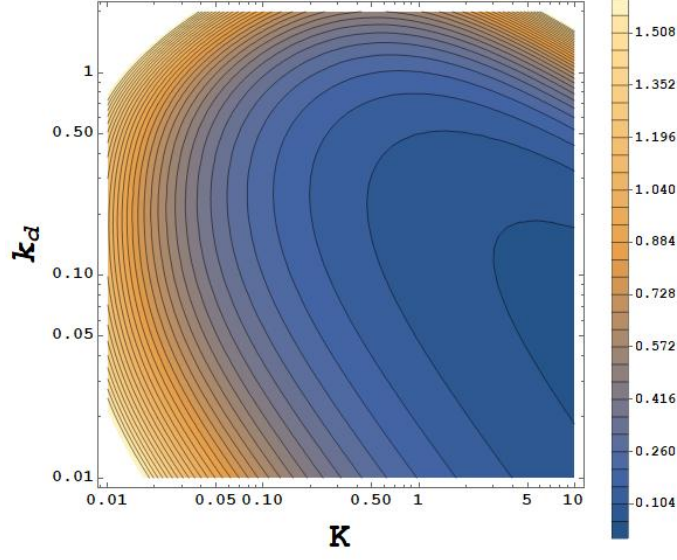


FIG. S3: A contour plot of the estimated relative statistical error in the inference of  $k_d$  vs. the imposed values of  $K$  and  $k_d$ , according to Eq. (S51).  $H$  and  $D$  were set to 1 and a uniform initial distribution was assumed. This plot presents the case where the mean and variance are calculated from a sample of  $10^4$  escape times. The fourth central moment  $\mu_d$  of the escape time was found for the parameters at hand, using the fact that the Laplace transform in Eq. (8) of the main text is the moment generating function. A general expression is computable, but it is very cumbersome and is thus not given here explicitly (it is numerically advantageous to plug the values of  $D$  and  $H$  in Eq. (8) of the main text before computing the moments, to avoid extremely long expressions).

### DIFFUSION IN A SHELL WITH AN ADSORBING INNER SPHERE AND AN ABSORBING OUTER SPHERE

To give another example of an explicit computation of the probability density of the escape time, we also consider diffusion between concentric circles or spheres of radii  $R_1 < R_2$ , such that one of them is absorbing and the other is adsorbing. The spherical symmetry renders this problem effectively one-dimensional, and it can thus be solved in a very similar way to the escape problem from the interval, i.e., by solving the corresponding version of Eqs. (6a)-(6c) in the main text. For instance, let us consider a three-dimensional setting and assume that the inner boundary is adsorbing and the outer is absorbing. In this case, one still has  $\tilde{J}_{ab}(s|r_0) = g(r_0, s)/g(R_2, s)$ , where

$$g(r, s) = \frac{\sqrt{s/D} \cosh\left[\sqrt{s/D}(r - R_1)\right]}{r} + \frac{(q_s + 1/R_1) \sinh\left[\sqrt{s/D}(r - R_1)\right]}{r}.$$

The poles are determined by the condition  $g(R_2, s) = 0$ . Setting  $s = -D\beta^2/(R_2 - R_1)^2$ , the equation  $g(R_2, s) = 0$  reads

$$0 = \frac{(R_2 - R_1)R_2}{i} g(R_2, s) = \beta \cos(\beta) + \left( \frac{\kappa_a}{1 - \kappa_d/\beta^2} + \frac{R_2 - R_1}{R_1} \right) \sin(\beta),$$

with  $\kappa_a = k_a(R_2 - R_1)/D$  and  $\kappa_d = k_d(R_2 - R_1)^2/D$ . This can also be written as

$$\frac{\beta}{\tan(\beta)} = - \left( \frac{\kappa_a}{1 - \kappa_d/\beta^2} + \frac{R_2 - R_1}{R_1} \right). \quad (\text{S52})$$

The left-hand side decreases piecewise monotonously on the intervals  $(0, \pi)$ ,  $(\pi, 2\pi)$ , etc., whereas the right-hand side increases piecewise monotonously on  $(0, \sqrt{\kappa_d})$  and  $(\sqrt{\kappa_d}, +\infty)$ . One can therefore check that there is a single solution on each interval  $(\pi n, \pi(n+1))$  denoted as  $\beta_n$ . In turn, there are two solutions on the interval that contains  $\sqrt{\kappa_d}$ , except if  $\sqrt{\kappa_d} = \pi k$ . These solutions determine the poles  $s_n = -D\beta_n^2/(R_2 - R_1)^2$ . For evaluating the residues, one finds

$$\frac{dg(R_2, s)}{ds} \Big|_{s=s_n} = \frac{R_2 - R_1}{2DR_2i\beta_n} \left\{ \left( 1 + \frac{R_2 - R_1}{R_1} + \frac{\kappa_a}{1 - \kappa_d/\beta_n^2} \right) \cos \beta_n - \left( 1 + \frac{2\kappa_a\kappa_d}{(\kappa_d - \beta_n^2)^2} \right) \beta_n \sin \beta_n \right\}.$$

As a consequence, one gets

$$J(t|r) = \sum_{n=0}^{\infty} \frac{g(r, -D\beta_n^2/(R_2 - R_1)^2)}{\left. \frac{dg(R_2, s)}{ds} \right|_{s=s_n}} e^{-Dt\beta_n^2/(R_2 - R_1)^2}, \quad (\text{S53})$$

where

$$\begin{aligned} g(r, -D\beta_n^2/(R_2 - R_1)^2) &= \frac{i\beta_n \cos[\beta_n(r - R_1)/(R_2 - R_1)]}{r(R_2 - R_1)} \\ &+ \frac{[\kappa_a/(1 - \kappa_d/\beta_n^2) + (R_2 - R_1)/R_1] i \sin[\beta_n(r - R_1)/(R_2 - R_1)]}{r(R_2 - R_1)}. \end{aligned} \quad (\text{S54})$$

In two dimensions, one has

$$\begin{aligned} g(r, s) &= \left[ q_s K_0(R_1 \sqrt{s/D}) + \sqrt{s/D} K_1(R_1 \sqrt{s/D}) \right] I_0(r \sqrt{s/D}) \\ &- \left[ q_s I_0(R_1 \sqrt{s/D}) - \sqrt{s/D} I_1(R_1 \sqrt{s/D}) \right] K_0(r \sqrt{s/D}), \end{aligned} \quad (\text{S55})$$

where  $I_0(\cdot)$  and  $K_0(\cdot)$  are the modified Bessel functions of the first and second kind of order 0. Similar computations can be performed.