Diffusion-controlled reactions triggered by multiple particles with reversible target-binding kinetics

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We investigate a class of diffusion-controlled reactions that are triggered when a prescribed number $K$ among $N$ independently diffusing particles are simultaneously bound to a target region. If particles that bind to the target stay there forever, the reaction time in this irreversible binding limit is the $K$-th fastest first-passage time to the target, whose distribution is well-known. In turn, reversible binding, which is common for most applications, renders theoretical analysis much more challenging and drastically changes the distribution of reaction times. We develop a renewal-based approach to derive an approximate solution for the probability density of the reaction time. This approximation turns out to be remarkably accurate for a broad range of parameters. We also analyze the dependence of the mean reaction time or, equivalently, the inverse reaction rate, on the main parameters such as $K$, $N$, and binding/unbinding constants. Some biophysical applications and further perspectives are discussed.

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I. INTRODUCTION

Diffusion-controlled reactions play the central role in microbiology, physiology and many industrial processes\textsuperscript{1–9}. In a common setting of bimolecular reactions, two particles (e.g., a ligand and a receptor) need to meet each other to initiate a reaction event. As the encounter results from the stochastic motion of one or both particles, the reaction time is random. Since the seminal works by von Smoluchowski\textsuperscript{10}, such first-encounter or first-passage problems have been thoroughly investigated\textsuperscript{11–43}. However, there exist more sophisticated reaction schemes involving multiple particles. In microbiology, there are many activation mechanisms controlled by a threshold crossing such as signalling in neurons, synaptic plasticity, cell apoptosis caused by double strand DNA breaks, cell differentiation and division\textsuperscript{44–46}. For instance, binding of five calcium ions to a calcium-sensing protein initiates a release of neurotransmitters in the signalling process between two neurons\textsuperscript{47–50}. Similarly, the ryanodine receptor is activated when two calcium ions bind to the receptor binding sites\textsuperscript{51}. In these examples, the reaction is triggered when a fixed number $K$ among $N$ diffusing particles are simultaneously bound to the target region for the first time. If $N(t)$ denotes the number of bound particles at time $t$, the reaction time $T_{K,N} = \inf\{t > 0 : N(t) = K\}$ is the first-crossing time of a fixed threshold $K$ by the stochastic non-Markovian process $N(t)$. In the idealized case of irreversible binding when any particle after its binding to the target stays bound forever, this is the problem of finding the $K$-th fastest first-passage time $T^{(1)}_{K,N}$ to the target\textsuperscript{52–54}. If the particles diffuse independently, the distribution of $T^{(1)}_{K,N}$ can be easily expressed in terms of the survival probability for a single particle (see Appendix A). In most cases, however, binding is reversible so that some particles can unbind and resume their diffusion before the binding of the $K$-th fastest particle that renders the problem of such “impatient” particles\textsuperscript{55–61} much more challenging. Recently, Lawley and Madrid proposed an elegant approximation, in which the first-binding time and the re-binding time $\tau$ after each unbinding event were assumed to obey an exponential law. The process $N(t)$ could thus be approximated by a Markovian birth-death process, for which the distribution of the first-crossing time is known explicitly\textsuperscript{62} (see also\textsuperscript{63}). In the special case $K = N$, we derived the exact solution of the problem of impatient particles and showed both advantages and limitations of the Lawley-Madrid approximation (LMA)\textsuperscript{63}. Despite its crucial role in providing us with analytical insight into the problem of impatient particles and the validity of its approximate treatments, the case when all particles have to bind the target is not so common in applications.

In this paper, we investigate the general problem of impatient particles in a common setting when all particles start from independent uniformly distributed positions. First, we revisit the Lawley-Madrid approximation and discuss its validity range. In particular, we argue that the key assumption of the LMA requires that the target is small and weakly reactive. The condition of weak reactivity, which was not emphasized on in\textsuperscript{62}, limits the applica-
bility of this approximation. To overcome this limitation, we develop an alternative approach to the general problem. Our approximate solution is confronted to Monte Carlo simulations and shown to be remarkably accurate for a broad range of parameters. It allowed us to investigate the short-time and long-time behaviors of the probability density of the reaction time $T_{K,N}$, the dependence of the mean reaction time on the unbinding rate, and the role of $K$ and $N$.

The paper is organized as follows. In Sec. III we formulate the problem of impatient particles and discuss the LMA. Section III presents the main steps of our approach and summarizes the approximate formulas for the probability density of the reaction time $T_{K,N}$, its short-time and long-time behaviors, and the mean reaction time. In Sec. IV we illustrate these results for an emblematic model of restricted diffusion between concentric spheres. We discuss the accuracy of our approximation and its limitations. Section V concludes the paper and suggests further perspectives. As our derivations are technically elaborate, most mathematical details are re-delegated to Appendices in order to facilitate the main text for a wider audience.

II. PROBLEM OF IMPATIENT PARTICLES

We consider $N$ particles that independently diffuse with diffusion coefficient $D$ inside a bounded domain $\Omega \subset \mathbb{R}^d$ with a smooth boundary $\partial \Omega$ that is reflecting everywhere except for a target region $\Gamma$ with a finite reactivity $0 < \nu$. After binding, each particle stays on the target region for a random exponentially distributed waiting time, characterized by the unbinding rate $k_{\text{off}}$, and then resumes its diffusion from a uniformly distributed point on $\Gamma$. The particle diffuses in the bulk until the next binding, and so on (Fig. 1). In other words, each particle alternates between free and bound states. We aim at describing the random reaction time $T_{K,N}$, i.e., the first instance when $K$ particles among $N$ are simultaneously in the bound state on the target region that triggers a reaction event. As binding and unbinding events of all particles are independent from each other and thus asynchronized, finding the probability density $H_{K,N}(t)$ of the $T_{K,N}$ is a challenging open problem. Note that the above problem of impatient particles resembles some stochastic models of multi-channel particulate transport with blockages.\cite{25,29}

The first-binding time $\tau_0$ and the consequent rebinding times $\tau_1, \tau_2, \ldots$ of any particle are random variables, which are characterized by the survival probabilities $S(t|x_0) = \mathbb{P}_{x_0}(\tau_0 > t)$ and $S(t) = \mathbb{P}(\tau_1 > t)$, where $x_0$ is the starting point of the particle, and $\mathbb{P}(\ldots)$ denotes the probability of a random event between braces. Lawley and Madrid proposed a remarkable approximation, which relied on the approximation of these probabilities by an exponential function:

$$S(t|x_0) \approx S(t) \approx e^{-\nu t},$$

(1)

with an appropriate rate $e^{\nu t}$. They argued that this approximation is valid for any small and/or weakly reactive target such that

$$\epsilon = \frac{\kappa |\Gamma| |\Omega|}{D|\partial \Omega|^2} \ll 1,$$

(2)

where $|\Omega|$ is the volume of the confining domain, $|\partial \Omega|$ and $|\Gamma|$ are the surface areas of the boundary and of the target region, respectively (for clarity, we focus here on a three-dimensional setting, $d = 3$, but the arguments are valid in higher dimensions as well). In Appendix III we summarize the explicit formulas of the LMA and discuss the validity of condition (2), which actually combines two distinct properties of the target: its relative size and reactivity. We argue that the LMA is applicable when the target is small and weakly reactive. For instance, when the target is a sphere of radius $\rho$, the following two conditions should be fulfilled:

$$\rho \ll R = \frac{|\partial \Omega|^2}{4\pi|\Gamma|}, \quad \frac{\kappa \rho}{D} \ll 1.$$

(3)

The first condition is purely geometrical (smallness of the target as compared to the confining domain), while the second involves both the reactivity and the size of the target but does not depend on the confining domain. These two conditions evidently imply Eq. (2), but the opposite claim is not true. In particular, if the target is
small but highly reactive, the second condition may not be valid, even if Eq. (2) is fulfilled. This situation will be illustrated in Sec. 14.

III. APPROXIMATE SOLUTION

To overcome the constraint on weak reactivity, we develop an alternative approach, which does not rely on the approximation (1). For this purpose, we extend the derivation in Ref. 23 that was specific to the case $K = N$ and based on a renewal-type equation

$$ P_t(N|0) = \frac{1}{t} \int_0^t dt' H_{N,N}(t') P_{t-t'}(N|N), \quad (4) $$

where $P_t(m|n)$ is the probability of transition from a state with $n$ bound particles to a state with $m$ bound particles. Expressing both $P_t(N|0)$ and $P_{t-t'}(N|N)$ in terms of known occupation probabilities for a single particle and applying the Laplace transform led to the probability density $H_{N,N}(t)$ in the Laplace domain.

A direct extension of this equation to the general case $K < N$ fails. In fact, the probability $P_t(K|0)$ can still be expressed as an integral of $H_{K,N}(t')$ with the probability $P_{t-t'}(K|K)$ of transition from a state with $K$ bound particles to another state with $K$ bound particles. However, this probability also depends on $\text{random positions of the remaining } N-K \text{ free particles at time } t'$ that should be averaged out. Even for independently diffusing particles, an exact computation of this average remains an open problem (see Appendix C for further discussion). Moreover, the resulting probability would be a function of both $t$ and $t'$ so that an extension of Eq. (4) would be no longer a convolution, and thus would not be simplified in the Laplace domain.

This fundamental difficulty can be partly resolved in the case when the starting positions of $N$ particles are uniformly distributed in the confining domain. The key point is that the distribution of any free particle that started uniformly remains to be almost uniform at all times, except for a boundary layer near the target region. When the target is small and not too highly reactive, this boundary layer is narrow and can be neglected so that all free particles can be approximately treated as uniformly distributed at any time $t'$. As a consequence, the average of $P_{t-t'}(K|K)$ turns out to be only a function of $t-t'$, thus keeping the convolution form of the renewal equation:

$$ P_t(K|0) = \frac{1}{t} \int_0^t dt' H_{K,N}(t') P_{t-t'}(K|K), \quad (5) $$

where overline denotes the average over the uniform positions of $N-K$ free particles. In other words, this integral equation determines an approximation $H_{K,N}(t)$ of the probability density $H_{K,N}(t)$ of the reaction time $T_{K,N}$.

Both transition probabilities in Eq. (5) can be found using combinatorial arguments, namely,

$$ P_t(K|0) = \binom{N}{K} [P(t|0)]^K [1 - P(t|0)]^{N-K} \quad (6) $$

and

$$ P_t(K|K) = \sum_{j=0}^K \binom{K}{j} [Q(t)]^{K-j} [1 - Q(t)]^j \binom{N-K}{j} \times [P(t|0)]^j [1 - P(t|0)]^{N-K-j}, \quad (7) $$

where we use the convention for binomial coefficients that $\binom{n}{k} = 0$ for $n < k$. Here $P(t|0)$ (resp., $Q(t)$) is the probability of finding a particle that was free with uniform initial distribution (resp., bound) at time 0, in the bound state at time $t$. For instance, the term with $j = 0$ in Eq. (7) describes the configuration when all $K$ initially bound particles are found to be bound at time $t$ (note that they can unbind and rebind in the meantime), while $N-K$ initially free particles are found to be free at time $t$ (they can also bind and unbind in the meantime). Similarly, the term with $j = 1$ describes the configuration when $K-1$ initially bound particles are found to be bound at time $t$, one initially bound particle is found to be free at time $t$, $N-K-1$ initially free particles are found to be free at time $t$, while one initially free particle is found to be bound at time $t$ (and all these particles can undertake an arbitrary number of binding/unbinding events in the meantime). In Appendix D we show that

$$ P(t|0) = \frac{1 - Q(t)}{k_{\text{off}}(\tau)}, \quad (8) $$

whereas $Q(t)$ can be expressed in terms of the probability density $H(t)$ of the rebinding time for a single particle, and

$$ \langle \tau \rangle = \frac{[\Omega]}{\kappa[\Gamma]} = \frac{N_A[\Omega]}{k_{\text{on}}} \quad (9) $$

is the mean rebinding time. The latter is expressed in terms of the volume $[\Omega]$ of the confining domain, the surface area $[\Gamma]$ of the target region, and its reactivity $\kappa$ or, equivalently, in terms of the forward reaction constant $k_{\text{on}}$ and the Avogadro number $N_A$. Curiously, the mean rebinding time does not depend on the diffusion coefficient $D$. Solving the convolution equation (5) in the Laplace domain, we obtain the approximate probability density $H_{K,N}(t)$ of the reaction time $T_{K,N}$:

$$ H_{K,N}(t) = \mathcal{L}^{-1} \left\{ \frac{\mathcal{L} \{ P_t(K|0) \}}{\mathcal{L} \{ P_t(K|K) \}} \right\}, \quad (10) $$

where $\mathcal{L}$ and $\mathcal{L}^{-1}$ denote respectively the forward and inverse Laplace transforms. This approximate solution of the general problem of impinging particles constitutes the main result of the paper. For $K = N$, one has $P_t(K|0) = \binom{N}{N} [P(t|0)]^N [1 - P(t|0)]^{N-N}$.
[\{P(t|o)\}^N and \bar{P}_t(K|K) = [Q(t)]^N and thus retrieves an extension of the exact solution from Ref.\[22\] to the case of the uniform initial distribution of the particles.

In addition to a direct numerical way of computing the approximate probability density \(H_{K,N}(t)\) (see Appendix \[E\] for details), Eq. \((10)\) opens a way to access the short-time and long-time asymptotic behaviors of this density (see Appendix \[E\]):

\[
\begin{align*}
H_{K,N}(t) & \approx K \binom{N}{K} \frac{t^{K-1}}{(\tau)^K} (t \to 0), \quad (11) \\
H_{K,N}(t) & \propto \exp(-t/T_{K,N}) (t \to \infty), \quad (12)
\end{align*}
\]

where \(T_{K,N}\) is the decay time whose approximation is given by

\[
T_{K,N} \approx \frac{1}{\bar{P}_\infty(K|K)} \int_0^\infty dt \left( \bar{P}_t(K|K) - \bar{P}_\infty(K|K) \right). \quad (13)
\]

in which \(\bar{P}_\infty(K|K)\) is given by Eq. \((7)\) with \(P(\infty|o) = Q(\infty) = 1/(1 + k_{\text{off}}(\tau))\). In addition, our approximate solution allows us to evaluate the moments of the reaction time \(T_{K,N}\). For instance, we derived the following approximation for the mean reaction time (see Appendix \[E\]):

\[
\langle T_{K,N} \rangle \approx \frac{1}{\bar{P}_\infty(K|0)} \int_0^\infty dt \left( \bar{P}_t(K|0) - \bar{P}_\infty(K|0) \right). \quad (14)
\]

Note that this expression is similar to Eq. \((13)\) for the decay time, and they usually yield very close results.

The dimensionless parameter \(\eta = k_{\text{off}}(\tau) \propto k_{\text{off}}/k_{\text{on}}\) determines whether the reversible binding kinetics is relevant (\(\eta \geq 1\)) or not (\(\eta \ll 1\)). As discussed in Appendix \[E\] Eq. \((14)\) fails as \(\eta \to 0\) but gets more and more accurate as \(\eta\) increases. For \(\eta \gg 1\), the integral in Eq. \((14)\) can be approximately evaluated as

\[
\langle T_{K,N} \rangle \approx \langle \tau \rangle \frac{k_{\text{off}}(\tau) K^{K-1}}{N} (\eta \gg 1). \quad (15)
\]

For \(K = 1\), the approximate mean reaction time \(\langle T_{1,N} \rangle \approx \langle \tau \rangle / N\) does not depend on \(k_{\text{off}}\), as the first-binding event is independent of the unbinding kinetics. This mean value decreases inversely proportional to \(N\), as discussed earlier in Ref.\[22\] in the context of the fastest first-passage time problem.

### IV. DISCUSSION

To illustrate our general results, we consider restricted diffusion inside a confining reflecting sphere of radius \(R\) towards a small partially reactive spherical target of radius \(\rho\) located at the origin. This domain can be considered as an idealized model for the intracellular transport towards the nucleus or a model of the presynaptic

Figure 2: Probability density of the reaction time \(T_{K,N}\) for restricted diffusion between concentric spheres of radii \(\rho\) and \(R = 10\rho\), with \(N = 4\), \(\kappa \rho^2/D = 1\), a timescale \(\delta = \rho^2/D\), three values of \(k_{\text{off}}\) (see legend), and four values of \(K\): \(K = 1\) (a), \(K = 2\) (b), \(K = 3\) (c), and \(K = 4\) (d). Symbols show empirical histograms from Monte Carlo simulations with \(10^6\) particles. Thick solid line presents the exact solution \((A2)\) for irreversible binding; thick dashed lines indicate our approximation \((10)\) evaluated numerically as described in Appendix \[E\]. Thin lines show the Lawley-Madrid approximation \((B3)\); note that the thin line for the case \(k_{\text{off}}\delta = 0.03\) in panel (d) is not visible as it appears below the figure (i.e., \(H_{4,4}(t) < 10^{-6}\)). Thin gray solid line presents the short-time asymptotic behavior \((11)\).
bouthou. Figure 2 illustrates the behavior of the probability density $H_{K,N}(t)$ for $N = 4$ and several values of $K$ in the case of a small ($\rho/R = 0.1$), moderately reactive ($\kappa\rho/D = 1$) target. As the unbinding kinetics can only be initiated after the first binding, the reaction time $T_{K,N}$ is equal to the first-binding time of the fastest particle and thus does not depend on the unbinding rate $k_{\text{off}}$ (see also Appendix A). Expectedly, three curves with different $k_{\text{off}}$ coincide on the panel Fig. 4a. Moreover, the short-time behavior does not depend on $k_{\text{off}}$ for any $K$. In turn, the long-time decay is strongly affected by $k_{\text{off}}$ when $K > 1$: the decay time $T_{K,N}$ increases with $k_{\text{off}}$ and thus the distribution is getting broader for faster unbinding kinetics. In all cases, the approximate solution (10) is in a remarkable agreement with Monte Carlo simulations over a broad range of times. We also stress that our solution is exact for $K = N$. The Lawley-Madrid approximation (see Appendix B) captures correctly the overall behavior but overestimates the decay time. The agreement is better for smaller $k_{\text{off}}$ and smaller $K$. In turn, the disagreement for larger $k_{\text{off}}$ or $K$ is caused by moderate reactivity of the target, for which the second condition in Eq. B is not satisfied. Figure 6 from Appendix C illustrates that the disagreement is getting much bigger for a highly reactive target with $\kappa\rho/D = 10$. In contrast, the LMA is very accurate for weakly reactive targets (see, e.g., Fig. 4 in Ref. 52, which was plotted for the case $\kappa\rho/D = 0.01$ and $k_{\text{off}}\rho^2/D = 0.001$). Finally, we emphasize that the short-time asymptotic relation (11) is not accurate in the considered range of times, requiring many correction terms for amendment (see Appendix D for details). Similar behavior was observed for $N = 2$ and $N = 3$ (see Figs. 4–6 from Appendix E).

The impact of unbinding kinetics and the consequent rebinding events can be characterized by the dimensionless parameter $\eta = k_{\text{off}}/k_{\text{on}}$, which is proportional to the ratio $k_{\text{off}}/k_{\text{on}}$ (or $k_{\text{off}}/\kappa$, see Eq. 9). In particular, this parameter fully determines the steady-state probability $P_{\text{ss}} = 1/(1 + \eta)$ for a particle to be in the bound state. Intuitively, one might expect that $\eta$ mainly controls the statistics of the reaction times $T_{K,N}$. To emphasize on the respective roles of binding and unbinding effects, we fix $\eta = 1$ and compare the probability densities for three combinations of $\kappa$ and $k_{\text{off}}$. Figure 3 shows that two curves with larger unbinding rates $k_{\text{off}}(\rho^2/D) = 0.03$ and $k_{\text{off}}(\rho^2/D) = 0.3$ (and, accordingly, larger reactivities) almost coincide. This effect can be attributed to a sort of statistical averaging due to multiple rebinding events. In contrast, the curve with the lowest $k_{\text{off}}$ and $\kappa$ differs from the others, due to a limited number of rebinding events. We conclude that the parameter $\eta$ plays an important role but does not fully determine the statistics of the reaction time. Expectedly, the Lawley-Madrid approximation gets less and less accurate as the reactivity increases.

We complete this section by looking at the mean reaction time $\langle T_{K,N} \rangle$. Figure 4 shows the dependence of $\langle T_{K,N} \rangle$ on the unbinding rate $k_{\text{off}}$ (rescaled by $\langle \tau \rangle$) for a...
the mean reaction time is almost constant and close to the exact probability density and our approximation \((\delta)\). When the target is reactive, binding events lead to a formation of a depletion boundary layer near the target, in which the probability density of finding a diffusing particle is lower, and thus not uniform. In contrast, unbinding events tend to homogenize the probability density and thus render our assumption more accurate. As a consequence, our approximation is applicable whenever the binding/unbinding kinetics ensure a nearly uniform distribution of free particles. A systematic study of quantitative conditions for the validity of our approximation presents an important perspective of this work in the future. Meanwhile, Monte Carlo simulations that we realized in this paper indicate that the approximation is remarkably accurate when \(\eta = k_{\text{off}}(\tau)\) is not too small. As the limit \(\eta = 0\) corresponds to irreversible binding (with either \(k_{\text{off}} = 0\), or \(\kappa = \infty\)), our approximation complements this well-studied setting and thus provides the overall insight onto diffusion-controlled reactions with multiple particles.

We also emphasize on the conceptual difference between our approach and the Lawley-Madrid approximation. The latter relied on the exponential approximation for the survival probability of a single particle, which is valid only for small and weakly reactive targets. This restriction concerns only binding events and does not involve unbinding kinetics. In turn, our approximation deals with the exact form of the survival probability, while the underlying assumption depends on binding/unbinding kinetics. As a consequence, it yields accurate results even for highly reactive targets, if the unbinding rate is large enough. In summary, the validity range of our approximation is different from that of the Lawley-Madrid approximation, and it is actually broader. At the same time, we outline that the LMA is much more explicit and easier to implement and to analyze. Moreover, the LMA provides bounds to the true first-crossing times for impatient particles. These two approximations present valuable and complementary theoretical tools for studying sophisticated diffusion-controlled reactions.

**V. CONCLUSION**

In this paper, we investigated diffusion-controlled reactions triggered on a target region by binding a prescribed number \(K\) among \(N\) independently diffusing particles. The reversible target-binding kinetics, which is so common for most applications, presented the major mathematical difficulty. We developed a powerful theoretical approach to derive a new approximation for the probability density of the reaction time \(T_{K,N}\) in the case when the particles were initially released uniformly. Under the assumption that the random positions of free particles at time \(T_{K,N}\) remain to be uniform, we derived a renewal equation that determines the approximation \(H_{K,N}(t)\). This convolution-type equation was then solved in the Laplace domain to relate the probability density via Eq. \(10\) to two occupancy probabilities, which were in turn expressed in terms of the survival probability for a single particle. In this way, we managed to describe the collective effect of multiple diffusing particles in terms of the diffusive dynamics of a single particle and thus to extend the well-known extreme statistics for the \(K\)-th fastest first-passage time to a more general and much more challenging setting with reversible binding.

The assumption of uniform positions was the crucial step and the only source of eventual deviations between the exact probability density and our approximation \(10\). Strictly speaking, this assumption is fulfilled exactly only for an inert non-reactive boundary \((\kappa = 0)\). When the target is reactive, binding events lead to a formation of a depletion boundary layer near the target, in which the probability density of finding a diffusing particle is lower, and thus not uniform. In contrast, unbinding events tend to homogenize the probability density and thus render our assumption more accurate. As a consequence, our approximation is applicable whenever the binding/unbinding kinetics ensure a nearly uniform distribution of free particles. A systematic study of quantitative conditions for the validity of our approximation presents an important perspective of this work in the future. Meanwhile, Monte Carlo simulations that we realized in this paper indicate that the approximation is remarkably accurate when \(\eta = k_{\text{off}}(\tau)\) is not too small. As the limit \(\eta = 0\) corresponds to irreversible binding (with either \(k_{\text{off}} = 0\), or \(\kappa = \infty\)), our approximation complements this well-studied setting and thus provides the overall insight onto diffusion-controlled reactions with multiple particles.

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**Conflicts of interest**

There are no conflicts to declare.
Appendix A: Irreversible binding

For irreversible binding ($k_{\text{off}} = 0$), the first-crossing time $T_{K,N}$ is identical to the $K$-th fastest first-passage time $T_{K,N}^0$ whose distribution is well known:

$$P\{T_{K,N}^0 > t\} = \sum_{j=0}^{K-1} \binom{N}{j} [S(t|\omega)]^{N-j}[1 - S(t|\omega)]^j$$  \hspace{1cm} (A1)

and

$$H_{K,N}^0(t) = -\frac{dP\{T_{K,N}^0 > t\}}{dt} = K \binom{N}{K} [S(t|\omega)]^{N-K}[1 - S(t|\omega)]^{K-1}H(t|\omega).$$  \hspace{1cm} (A2)

In the short-time limit, one can use the asymptotic relation \( \text{(D11)} \) for $H(t|\omega)$ to get

$$H_{K,N}^0(t) \approx \frac{K \binom{N}{K}}{(\tau)^K} t^{K-1} \quad (t \to 0).$$  \hspace{1cm} (A3)

In the case $K = 1$, the first-crossing time $T_{1,N}$ for any $k_{\text{off}}$ is equal to the first-passage time of the fastest particle, $T_{1,N}^0$, because unbinding kinetics does not matter here. As a consequence, one has the exact form:

$$H_{1,N}(t) = -\partial_t [S(t|\omega)]^N = N[S(t|\omega)]^{N-1}H(t|\omega).$$  \hspace{1cm} (A4)

Appendix B: Lawley-Madrid approximation

Lawley and Madrid developed an elegant approximate solution to the general problem of impatant particles\(^2\). In the limit of small and/or weakly reactive target such that Eq. 2 is fulfilled, the probability density $H(t|x_0)$ of the first-binding time was approximated by an exponential density, $H(t|x_0) \approx \nu e^{-\nu t}$, with the rate $\nu$ determined by the smallest eigenvalue of the Laplace operator. Under this approximation, the number of bound particles $N(t)$ can be modeled by a Markovian birth-death process $\dot{N}(t)$ between $N + 1$ states of $0, 1, 2, \ldots, N$ bound particles:

$$0 \underbrace{\frac{N \nu}{k_{\text{off}}} \frac{1}{2k_{\text{off}}} \frac{2}{3k_{\text{off}}} \cdots} _{N - 1} \underbrace{\frac{\nu}{Nk_{\text{off}}}} _{N}$$  \hspace{1cm} (B1)

(bar denotes the quantities corresponding to the LMA). Let $W$ be an $(N + 1) \times (N + 1)$-dimensional matrix with zero elements except for $W_{i+1} = ik_{\text{off}}, \quad W_{i+1,i} = (N+1-i)\nu \quad (i = 1, 2, \ldots, N),$ and $W_{i,i}$ are chosen so that $W$ has zero column sums. The distribution of the first-crossing time $T_{K,N} = \inf\{t > 0 : N(t) = K\}$ can be written as\(^2\)

$$P\{T_{K,N} > t\} = \sum_{j=1}^{K} [\exp(W^{(K)}t)]_{j,1},$$  \hspace{1cm} (B2)

where $W^{(K)}$ is the $K \times K$ matrix obtained by retaining the first $K$ columns and $K$ rows from $W$ and discarding everything else, and the initial state was assumed to be 0 (no bound particles). The probability density is

$$H_{K,N}(t) = \nu(N - K + 1)[\exp(W^{(K)}t)]_{K,1},$$  \hspace{1cm} (B3)

while the mean time is fully explicit:

$$(\bar{T}_{K,N}) = \frac{1}{\nu} \sum_{m=1}^{K} \left( \frac{1}{b_m} + \sum_{j=m+1}^{K} \frac{(k_{\text{off}}/\nu)^{j-m}}{b_j} \prod_{i=m}^{j-1} \frac{d_i}{b_i} \right),$$  \hspace{1cm} (B4)

with $b_m = N - K + m$ and $d_m = K - m$.

In\(^2\), we showed that in the case $K = N$, the LMA captures qualitatively the behavior of the probability density $H_{N,N}(t)$. However, it overestimates the mean reaction time and the decay time, and totally fails at short times. This is expected because the LMA ignores the starting positions of the particles.

When the starting points of all particles are uniformly distributed, the LMA turns out to be more accurate even at short times. In fact, the Taylor expansion of the exponential matrix in Eq. \( \text{(B3)} \) yields the correct power-law short-time behavior:

$$H_{K,N}(t) \approx \nu(N - K + 1)[(W^{(K)})^{K-1}]_{K,1} t^{K-1} + O(t^K),$$  \hspace{1cm} (B5)

in which the lower-order terms were canceled due to the tridiagonal structure of the matrix $W^{(K)}$. If $\nu$ is set to be $1/(\tau)$, the prefactor of this power law differs from the exact asymptotic relation \( \text{(D11)} \) only by a factor $\frac{1}{(K-1)!}$. Moreover, the long-time behavior remains qualitatively correct, even though the decay time is still overestimated (see Figs. 2 \( \text{(B3)} \)).

Validity of the LMA

Lawley and Madrid required the smallness of the parameter $\epsilon$ from Eq. 2 for approximating the smallest eigenvalue $\lambda_1$ of the Laplace operator in the confining domain $\Omega$ with mixed Robin-Neumann boundary condition on the boundary $\partial \Omega$ for the associated eigenfunction $u_1(x)$,

$$\begin{cases} \quad D\partial_n u_1(x) + \kappa u_1(x) = 0 \quad (&x \in \Gamma), \\ \quad D\partial_n u_1(x) = 0 \quad (&x \in \partial \Omega \setminus \Gamma), \end{cases}$$

where $\partial_n$ is the normal derivative oriented outwards the domain. Their approximation

$$\lambda_1 \approx \frac{\kappa |\Gamma|}{D|\Omega|},$$  \hspace{1cm} (B6)

can be easily obtained by integrating the eigenvalue equation $-\Delta u_1(x) = \lambda_1 u_1(x)$ over $x \in \Omega$ and using the above
boundary condition:
\[
\lambda_1 = -\frac{\int_{\Omega} d\mathbf{x} \,(\partial_{\mathbf{n}} u_1(\mathbf{x}))}{\int_{\Omega} d\mathbf{x} \, u_1(\mathbf{x})} = \kappa \frac{\int_{\Omega} d\mathbf{x} \, u_1(\mathbf{x})}{D \int_{\Omega} d\mathbf{x} \, u_1(\mathbf{x})}.
\]  
(B7)

The approximation \((B9)\) follows immediately if \(u_1(\mathbf{x})\) is replaced by a constant. This relation implies
\[
\nu = D\lambda_1 \approx \frac{\kappa|\Gamma|}{|\Omega|} = \frac{1}{\langle \tau \rangle},
\]  
(B8)

that is quite natural given that if the rebinding time \(\tau\) is assumed to obey an exponential law, its rate should be the inverse of the mean rebinding time.

However, the condition \((2)\) is not sufficient for getting the approximation \((B6)\). For instance, in the case of diffusion between concentric spheres with \(\rho = 1\), \(R = 10\), \(D = 1\), and \(\kappa = 1\), one has \(\epsilon \approx 0.033\) and \(1/\langle \tau \rangle \approx 0.0030\), whereas the numerical solution of Eq. \((B5)\) yields \(D\lambda_1 \approx 0.0016\). In other words, if one employs the approximate relation \((B8)\) in this example, the twofold error in the rate \(\nu\) will be drastically amplified in the computation of the mean reaction time \((\mathcal{T}_{K,N})\) or the decay time \(T_{K,N}\). For this reason, Lawley and Madrid used the numerically computed smallest eigenvalue for plotting their figures.

To further clarify this issue, it is instructive to analyze the smallest eigenvalue \(\lambda_1\). For diffusion between concentric spheres, the solution is summarized in Appendix C. In particular, \(\lambda_1\) is determined by the smallest strictly positive solution of Eq. \((B5)\), whose asymptotic behavior was given by Eq. (28) of Ref.\(^{24}\). When \(\rho \ll R\), a first-order approximation reads
\[
\lambda_1 \approx \frac{\kappa|\Gamma|}{D|\Omega|(1 + \kappa\rho/D)}.
\]  
(B9)

In the case \(\kappa\rho/D \ll 1\), we retrieve the approximate relation \((B6)\). However, the smallness of the parameter \(\epsilon = \frac{\kappa\rho}{D}(\rho/R)\) from Eq. \((2)\) does not necessarily imply that \(\kappa\rho/D\) is small. Actually, in the above example, we had \(\kappa\rho/D = 1\) that yielded the twofold smaller value of \(\nu = D\lambda_1\), as compared to \(1/\langle \tau \rangle\).

Let us provide some heuristic arguments for extending Eq. \((B9)\) to a general setting in three dimensions. In the first step, we consider a small partially reactive spherical target of radius \(\rho\) inside a bounded domain \(\Omega\) of a characteristic size \(R = |\partial\Omega|^2/(4\pi|\Omega|)\). This particular definition of \(R\) ensures that for a spherical domain, \(R\) is its radius. For “regularly-shaped” domains, \(R\) can still be interpreted as their “size”, whereas irregular domains with rough boundaries, for which \(|\partial\Omega|\) can be extremely large, require a separate analysis and are not considered here. We assume that the target is disjoined and well separated from the remaining inert boundary \(\partial\Omega_0 = \partial\Omega\setminus\Gamma\), i.e., \(|\Gamma - \partial\Omega_0| \gg \rho\). As the target is small, Eq. \((B7)\) implies that \(\lambda_1\) is small as well, while \(u_1\) is nearly uniform, except for a boundary layer near the target. When \(\kappa\) is small enough, this boundary layer can be neglected, and one retrieves the approximate relation \((B6)\) in turn, deviations from this formula result from the boundary layer. As \(u_1\) is uniform far from the target, the actual form of the outer boundary \(\partial\Omega_0\) does not matter and can thus be replaced by an equivalent sphere (of volume \(|\Omega|\)) that is concentric with the target. One can therefore apply Eq. \((B9)\). In the second step, one can replace the spherical target by an arbitrary compact target. To ensure that the asymptotic formula reaches to the correct limit \(C/|\Omega|\) as \(\kappa \to \infty\), one can define the effective size of the target as \(\rho = |\Gamma|/C\), where \(C\) is the harmonic capacity (or capacitance) of the target (e.g., \(C = 4\pi\rho\) for a sphere of radius \(\rho\)).

In fact, for a perfectly reactive target \((\kappa = \infty)\), one can use the first equality in \((B7)\) to estimate \(\lambda_1\). For a small target, \(\lambda_1\) is small and \(u_1\) is close to a constant function \(u_1(\mathbf{x}) \approx u_0\), except for a boundary layer near the target; in particular, the Neumann boundary condition at the outer reflecting boundary can be replaced by the Dirichlet condition \(u_1(\mathbf{x}) = u_0\). In turn, the function \(u_1(\mathbf{x})\) vanishes on the target. One can thus approximate \(u_1(\mathbf{x})\) near the target by setting \(u_1(\mathbf{x}) \approx u_0(1 - v(\mathbf{x}))\), where \(v(\mathbf{x})\) is the solution of the boundary value problem:
\[
\Delta v = 0, \quad v|_{\partial\Omega_0} = 0, \quad v|_{\Gamma} = 1, \quad (B10)
\]
from which (see also Ref.\(^{23}\))
\[
\lambda_1 \approx \frac{1}{u_0|\Omega|} \int_{\Gamma} d\mathbf{x} \, u_0(\partial_{\mathbf{n}} v) = \frac{C}{|\Omega|}. \quad (B11)
\]

If the outer boundary \(\partial\Omega_0\) is far away from the target \(\Gamma\), its location does not affect much the harmonic capacity so that it can be moved to infinity. This is equivalent to replacing the boundary condition \(v|_{\partial\Omega_0} = 0\) by the regularity condition \(v(\mathbf{x}) \to 0\) as \(|\mathbf{x}| \to \infty\).

In summary, we conjecture the following approximation in three dimensions:
\[
\lambda_1 \approx \frac{\kappa|\Gamma|}{D|\Omega|(1 + \kappa|\Gamma|/(DC))}. \quad (B12)
\]

The condition
\[
\kappa|\Gamma|/(DC) \ll 1 \quad (B13)
\]
ensures that \(\nu = D\lambda_1 \approx 1/\langle \tau \rangle\) that makes the exponential approximation of the survival probability self-consistent. We conjecture that this condition is necessary for the Lawley-Madrid approximation to be accurate. In other words, the target should be small and weakly reactive. A rigorous derivation of Eq. \((B12)\) and further analysis of the condition \((B13)\) for the LMA present important perspectives for future mathematical studies.

### Appendix C: Distribution of a free particle

In this Appendix, we compute the probability density \(P(\mathbf{x}, t|\mathbf{x}_0)\) of finding a free particle that started from a
point $\mathbf{x}_0$ at time 0, in the vicinity of a point $\mathbf{x}$ at time $t$. For this purpose, we extend the computation from Ref. 52,63 that consists in adding up contributions according to the number of binding events:

$$
P(\mathbf{x}, t|\mathbf{x}_0) = G(\mathbf{x}, t|\mathbf{x}_0) + \int_0^t dt_1 \int_{t_1}^t dt_1' H(t_1|\mathbf{x}_0) \psi(t_1' - t_1) g(\mathbf{x}, t - t_1') + \int_0^t dt_1 \int_{t_1}^t dt_1' \int_{t_1'}^t dt_2 H(t_1|\mathbf{x}_0) \psi(t_1' - t_1)$$

$$
\times H(t_2 - t_1') \psi(t_2' - t_2) g(\mathbf{x}, t - t_2') + \ldots,$$

where $\psi(t) = k_{\text{off}} e^{-k_{\text{off}} t}$ is the probability density of the waiting time on the target, and $H(t|\mathbf{x}_0)$ is the probability density of the first-binding time for a particle started from $\mathbf{x}_0$. The first term represents the contribution without binding, with $G(\mathbf{x}, t|\mathbf{x}_0)$ being the propagator for a single particle in the presence of a partially reactive target. The second term includes the contribution with a single binding at time $t_1$, staying on the target up to time $t_1'$, at which the particle unbinds and resumes its diffusion to $\mathbf{x}$, where

$$
g(\mathbf{x}, t) = \frac{1}{|\Omega|} \int_\Omega d\mathbf{x}_0 G(\mathbf{x}, t|\mathbf{x}_0)$$

is the propagator for a particle that started from a uniformly distributed point on the target $\Gamma$. The third term counts two bindings events: binding at $t_1$, unbinding at $t_1'$, binding at $t_2$, unbinding at $t_2'$, and arrival in $\mathbf{x}$ at $t$, where

$$
H(t) = \frac{1}{|\Omega|} \int_\Omega d\mathbf{x}_0 H(t|\mathbf{x}_0)
$$

is the probability density of the rebinding time (given that the unbound particle is released from a uniformly distributed point on the target). The fourth, fifth and next terms correspond to 3, 4, \ldots binding events. In the Laplace domain, one gets

$$
\tilde{P}(\mathbf{x}, p|\mathbf{x}_0) = \tilde{G}(\mathbf{x}, p|\mathbf{x}_0) + \tilde{H}(p|\mathbf{x}_0) \frac{k_{\text{off}}}{p + k_{\text{off}}} \tilde{g}(\mathbf{x}, p)$$

$$
+ \tilde{H}(p|\mathbf{x}_0) \frac{k_{\text{off}}}{p + k_{\text{off}}} \tilde{H}(p) \frac{k_{\text{off}}}{p + k_{\text{off}}} \tilde{g}(\mathbf{x}, p) + \ldots
$$

$$
= \tilde{G}(\mathbf{x}, p|\mathbf{x}_0) + \tilde{H}(p|\mathbf{x}_0) \frac{k_{\text{off}}}{p + k_{\text{off}}(1 - \tilde{H}(p))} \tilde{g}(\mathbf{x}, p),
$$

where all terms were summed up as a geometric series, and tilde denotes Laplace transformed quantities, e.g.,

$$
\tilde{f}(p) = \mathcal{L}\{f(t)\}(p) = \int_0^\infty dt e^{-pt} f(t).
$$

Since the probability density $H(t|\mathbf{x}_0)$ can be understood as the integral of the probability flux density over the target region, one gets

$$
H(t|\mathbf{x}_0) = \int_\Gamma dx (-D \partial_n G(\mathbf{x}, t|\mathbf{x}_0))
$$

$$
= \int_\Gamma dx (\kappa G(\mathbf{x}, t|\mathbf{x}_0)) = \kappa |\Gamma| g(\mathbf{x}_0, t),
$$

i.e.,

$$
\tilde{g}(\mathbf{x}, p) = \frac{\langle \tau \rangle}{|\Omega|} \tilde{H}(p|\mathbf{x}),
$$

where we used Eq. 9 for the mean rebinding time $\langle \tau \rangle$, and the Robin boundary condition on the target region. We conclude that

$$
\tilde{P}(\mathbf{x}, p|\mathbf{x}_0) = \tilde{G}(\mathbf{x}, p|\mathbf{x}_0) + \tilde{H}(p|\mathbf{x}_0) k_{\text{off}} \langle \tau \rangle \tilde{H}(p|\mathbf{x}) |\Omega|(p + k_{\text{off}}(1 - \tilde{H}(p))).
$$

Similarly, if $P_0(\mathbf{x}, t)$ denotes the probability density for a particle that was initially bound to the target, to be in the vicinity of a point $\mathbf{x}$ at time $t$, one gets in the Laplace domain:

$$
\tilde{P}_0(\mathbf{x}, p) = \tilde{G}(\mathbf{x}, p|\mathbf{x}_0) + \tilde{H}(p|\mathbf{x}_0) \frac{k_{\text{off}}}{p + k_{\text{off}}} \tilde{g}(\mathbf{x}, p) + \ldots = \frac{\tilde{g}(\mathbf{x}, p)}{1 - \tilde{H}(p) \tilde{g}(\mathbf{x}, p)},
$$

that yields

$$
P_0(\mathbf{x}, t) = \frac{k_{\text{off}} \langle \tau \rangle}{|\Omega|} P(t|\mathbf{x}),
$$

where $P(t|\mathbf{x})$ is the occupancy probability of the target (see also Appendix D).

**Normalization**

It is instructive to check that the probability density $P(\mathbf{x}, t|\mathbf{x}_0)$ is correctly normalized. For this purpose, we recall that the Green’s function $\tilde{G}(\mathbf{x}, p|\mathbf{x}_0)$ satisfies the boundary value problem

$$
\begin{cases}
(p - D\Delta_x)\tilde{G}(\mathbf{x}, p|\mathbf{x}_0) = \delta(\mathbf{x} - \mathbf{x}_0) \\
(D\partial_n + \kappa \Gamma(\mathbf{x}))\tilde{G}(\mathbf{x}, p|\mathbf{x}_0) = 0
\end{cases}
$$

where $\Delta_x$ is the Laplace operator acting on $\mathbf{x}$, $\delta(\mathbf{x} - \mathbf{x}_0)$ is the Dirac distribution, and $\Gamma(\mathbf{x})$ is the indicator function of $\Gamma$: $\Gamma(\mathbf{x}) = 1$ for $\mathbf{x} \in \Gamma$, and 0 otherwise. The second relation is the mixed Robin-Neumann boundary condition representing reflections on the inert boundary $\partial \Omega \setminus \Gamma$, and partial reactivity on the target region $\Gamma$. The integral of the first relation over $\mathbf{x} \in \Omega$ yields

$$
\int_\Omega d\mathbf{x} \tilde{G}(\mathbf{x}, p|\mathbf{x}_0) = \tilde{S}(p|\mathbf{x}_0) = \frac{1 - \tilde{H}(p|\mathbf{x}_0)}{p},
$$

where $\tilde{S}(p|\mathbf{x}_0)$ is the Laplace transform of the steady-state probability that a particle on the target region is released at $\mathbf{x}_0$.
where $\tilde{S}(p|x_0)$ is the Laplace-transformed survival probability. Similarly, as $\tilde{H}(p|x_0)$ satisfies

$$
\begin{cases}
(p - D\Delta x_0)\tilde{H}(p|x_0) = 0 \\
(D\partial_n + \kappa\mathbf{1}_{\Gamma}(x_0))\tilde{H}(p|x_0) = \kappa\mathbf{1}_{\Gamma}(x_0)
\end{cases}
$$

(C8)

the integral of the first relation over $x_0 \in \Omega$ yields

$$
\tilde{H}(p|o) \equiv \frac{1}{|\Omega|} \int_{\Omega} dx \tilde{H}(p|x) = \frac{1 - \tilde{H}(p)}{p\langle \tau \rangle} = \frac{\tilde{S}(p)}{\langle \tau \rangle},
$$

(C9)

where we used Eq. (4) for the mean rebinding time $\langle \tau \rangle$. Here $o$ denotes the average over uniformly distributed starting point. This relation implies that

$$
H(t,o) = \frac{S(t)}{\langle \tau \rangle}
$$

is a monotonously decreasing function of time. Note also that the Taylor expansion of Eq. (C9) allows one to express the moments of the first-binding time $\tau_o$, e.g.,

$$
\langle \tau^2 \rangle = \int_0^\infty dt \; t \; H(t,o) = \frac{\langle \tau^2 \rangle}{\langle \tau \rangle}.
$$

(C11)

We outline that $\tau_o$ is the first-binding time for a particle that started uniformly in the bulk $\Omega$, whereas $\tau$ is the re-binding time (i.e., the first-binding time for a particle that started uniformly on the target). Combining Eqs. (C7) and (C9), the integral of Eq. (C4) over $x \in \Omega$ reads

$$
\int_{\Omega} dx \; \tilde{P}(x,p|x_0) = \frac{1}{\tilde{H}(p|x_0)} \frac{\tilde{H}(p|x)}{p + k_{\text{off}}(1 - \tilde{H}(p))},
$$

(C12)

where the last term is the Laplace transform of the occupancy probability $P(t|x_0)$ of the target for a particle that started from $x_0$, see also Eq. (D2). Moving the last term to the left-hand side, one sees that the normalization is indeed satisfied:

$$
P(t|x_0) + \int_{\Omega} dx \; P(x,t|x_0) = 1.
$$

(C13)

Similarly, the integral of Eq. (C5) reads in the Laplace domain:

$$
\int_{\Omega} dx \; \tilde{P}_0(x,p) = k_{\text{off}}(\tau) \tilde{P}(p|o) = k_{\text{off}}\tilde{Q}(p)\tilde{S}(p)
$$

$$
= \tilde{Q}(p)(k_{\text{off}}\tilde{S}(p) + 1) - \tilde{Q}(p) = \frac{1}{p} - \tilde{Q}(p),
$$

where $\tilde{Q}(p)$ is the Laplace transform of the occupancy probability $Q(t)$ of the target for a particle that was initially bound, see also Eq. (D1). The above relation implies the normalization of $P_0(x,t)$:

$$
Q(t) + \int_{\Omega} dx \; P_0(x,t) = 1.
$$

(C14)

Long-time behavior

In the long-time limit, $G(x,t|x_0)$ vanishes exponentially fast and does not contribute. In turn, the second term in Eq. (C4) yields as $p \to 0$:

$$
\frac{\tilde{H}(p|x_0) k_{\text{off}}(\tau) \tilde{H}(p|x)}{|\Omega|(p + k_{\text{off}}(1 - \tilde{H}(p)))} \approx \frac{k_{\text{off}}(\tau)}{|\Omega|p(1 + k_{\text{off}}(\tau))},
$$

(C15)

so that

$$
\lim_{t \to \infty} P(x,t|x_0) = \frac{1}{1 - P_\infty}|\Omega|.
$$

(C16)

In other word, unbinding events ensure that the position of a free particle in the long-time limit is distributed uniformly inside the domain, as expected.

Uniformly distributed starting points

When all particles start initially from uniformly distributed points, one defines

$$
\tilde{P}(x,p|o) \equiv \frac{1}{|\Omega|} \int_{\Omega} dx \; \tilde{P}(x,p|x_0)
$$

$$
= \frac{1}{|\Omega|} \frac{\tilde{H}(p|x)}{|\Omega|(p + k_{\text{off}}(1 - \tilde{H}(p)))},
$$

(C18)

where we used Eq. (C12) and the symmetry $P(x,t|x_0) = P(x_0,t|x)$. In the time domain, we get thus

$$
P(x,t|o) = \frac{1 - P(t|x)}{|\Omega|}.
$$

(C19)

Why $P(x,t|o)$ is not uniform? At short times, the main contribution to the probability density of arriving at $x$ comes from the trajectories started close to that point. If $x$ is far from the target, the probability of binding the target $P(t|x)$ is very small, and thus $P(x,t|o)$ is almost constant. In turn, if $x$ is close to the target, the particles started from its neighborhood have higher chances to bind to the target and thus be in the bound state at time $t$. As a consequence, $P(x,t|o)$ is smaller near the target; this is similar to the formation of a depletion zone near a reactive target. The difference is that, as time goes on, all particles, irrespective of their starting points, start to experience the same effect of reversible binding, and $P(x,t|o)$ is getting uniform (in contrast to the case of a reactive target with irreversible binding when the depletion zone would grow and finally exhaust all particles).
Appendix D: Occupancy probabilities

In Ref.\textsuperscript{63}, the focus was on the case when the particles start from a fixed point \(x_0\) and search for a partially reactive target \(\Gamma\) with reactivity \(\kappa\), from which they can unbind at rate \(k_{\text{off}}\). The statistics of the first-crossing time \(T_{K,N}\) was determined by two occupancy probabilities: the probability \(Q(t)\) of finding the particle in the bound state at time \(t\) given that it was bound at time 0, and the probability \(P(t|x_0)\) of finding the particle in the bound state at time \(t\) given that it was initially released from a point \(x_0\). Both probabilities were found explicitly in the Laplace domain in the same way as presented in Appendix C.

\[
\hat{Q}(p) = \frac{1}{p + k_{\text{off}}(1 - \hat{H}(p))}
\]

and

\[
\hat{P}(p|x_0) = \hat{H}(p|x_0) \hat{Q}(p),
\]

where \(\hat{H}(p)\) is the Laplace transform of the probability density of the rebinding time \(\tau\), see Eq. \textsuperscript{(C2)}. If the starting point \(x_0\) is uniformly distributed, \(P(t|x_0)\) should be replaced by

\[
P(t|\circ) = \frac{1}{|\Omega|} \int d\Omega x_0 P(t|x_0),
\]

where \(\circ\) indicates the uniform starting point. According to Eqs. \textsuperscript{(C5)-(C14)}, one gets Eq. \textsuperscript{(C8)}. One sees that \(\hat{Q}(p)\) and thus \(\hat{P}(p|\circ)\) are expressed in terms of \(\hat{H}(p)\). Note also that Eqs. \textsuperscript{(C9)-(C12)-(C13)} yield

\[
\hat{P}(p|\circ) = \hat{Q}(p) \hat{H}(p|\circ),
\]

which in the time domain reads

\[
P(t|\circ) = \int \frac{dt}{\langle \tau \rangle} Q(t'\circ) H(t - t'|\circ).
\]

Alternatively, if \(\{p_n\}\) are the poles of \(\hat{P}(p|x_0)\), the residue theorem allows one to invert the Laplace transform to get (if all poles are simples):

\[
P(t|x_0) = P_\infty + \sum_{n=1}^{\infty} v_n(x_0) e^{p_n t},
\]

where \(v_n(x_0)\) is the residue of \(\hat{P}(p|x_0)\) at the pole \(p_n\), and \(P_\infty\) is the residue at pole \(p_0 = 0\) (that we treat separately, see\textsuperscript{63} for details). As a consequence,

\[
P(t|\circ) = P_\infty + \sum_{n=1}^{\infty} \hat{v}_n e^{p_n t},
\]

where

\[
\hat{v}_n = \frac{1}{|\Omega|} \int d\Omega x_0 v_n(x),
\]

from which

\[
Q(t) = P_\infty - \eta \sum_{n=1}^{\infty} \hat{v}_n e^{p_n t}.
\]

Short-time asymptotic behavior

In the short-time limit, the target region can be considered as locally flat so that \(\hat{H}(p|x_0)\) can be approximated by

\[
\hat{H}_{\text{hl}}(p|\delta) = e^{-\delta \sqrt{D/\pi}} (1 + \sqrt{D/\pi})/\kappa
\]

for the half-line, where \(\delta\) is the distance to the boundary. As a consequence, \(\hat{H}(p) \approx 1/(1 + \sqrt{D/\kappa})\) and thus

\[
\hat{H}(p|\circ) \approx \frac{1}{p(\tau)(1 + \kappa/\sqrt{Dp})} \approx \frac{1}{\kappa/\sqrt{Dp}} + O(p^{-2}),
\]

from which

\[
H(t|\circ) \approx \frac{1}{\langle \tau \rangle} \left(1 - \frac{2\kappa\sqrt{Dt}}{3\sqrt{\pi D}} + O(t)\right) \quad (t \to 0),
\]

and thus

\[
1 - S(t|\circ) \approx \frac{t}{\langle \tau \rangle} \left(1 - \frac{4\kappa\sqrt{Dt}}{3\sqrt{\pi D}} + O(t)\right)
\]

and

\[
P(t|\circ) \approx \frac{t}{\langle \tau \rangle} + O(t^{3/2}) \quad (t \to 0).
\]

Note also that Eq. \textsuperscript{(C8)} implies a monotonous decrease of \(P(t|\circ)\) with time: \(dP(t|\circ)/dt \geq 0\).

Appendix E: Numerical computation

Probability density

Following\textsuperscript{22,63}, we integrate by parts the convolution \textsuperscript{(10)} to transform it into an integral equation

\[
P_1(K|K) - P_1(K|0) = S_{K,N}(t) - \int_0^t dt S_{K,N}(t-t')\left(-\partial_t \overline{P_1(K|K)}\right),
\]

where \(S_{K,N}(t) = P\{T_{K,N} > t\}\) is the approximate survival probability, and we used that \(\tilde{S}_{K,N}(0) = \tilde{P}_0(K|K) = 1\). Here \(P_1(K|0)\) and \(P_1(K|K)\) are expressed via Eqs. \textsuperscript{(B7)-(B9)} in terms of \(P(t|\circ)\) and \(Q(t)\), which in turn are given by Eqs. \textsuperscript{(D7)-(D9)}. For diffusion between concentric spheres, the poles \(\{p_n\}\) and the related residues were determined in Ref.\textsuperscript{22,63}. Note that the integral of the function \(v_n(x)\) in Eq. \textsuperscript{(D8)} can be found explicitly. After discretization of the integral in Eq. \textsuperscript{(E1)} over a linear grid, we evaluate \(S_{K,N}(t)\) and then \(\tilde{H}_{K,N}(t)\) by applying the fast Fourier transform to resolve the convolution problem (see details in Ref.\textsuperscript{63}).
Monte Carlo simulations

For Monte Carlo simulations, we use a standard event-driven scheme described in detail in Ref. 63. The only difference concerns the generation of the first-binding times that are governed by the probability density $H(t|\phi)$ instead of $H(t|x_0)$. This probability density and the related survival probability $S(t|\phi)$ can be found from their spectral expansions:

$$S(t|\phi) = \sum_{n=1}^{\infty} a_n e^{-D t \lambda_n}, \quad (E2)$$
$$H(t|\phi) = D \sum_{n=1}^{\infty} \lambda_n a_n e^{-D t \lambda_n}, \quad (E3)$$

where $\lambda_n$ are the eigenvalues of the Laplace operator in $\Omega$, and

$$a_n = \frac{1}{|\Omega|} \left( \int_{\Omega} dx \ u_n(x) \right)^2 \quad (E4)$$

are the coefficients obtained from the $L_2$-normalized eigenfunctions $u_n(x)$. As their computation is detailed in Ref. 63, we only recall that the eigenvalues are determined as $\lambda_n = \alpha_n^2 / R^2$, where $\{\alpha_n\}$ are strictly positive solutions of the trigonometric equation [52]:

$$- \frac{\alpha_n^2 + 1}{1 - \alpha_n \cot((1 - \rho / R^2) \alpha_n)} - \frac{R}{\rho} + 1 = \frac{\kappa |\Omega|}{D |\Omega|}, \quad (E5)$$

which is equivalent to Eq. (B9) from Ref. 63. In turn, the coefficients $a_n$ are

$$a_n = 6 \rho^4 \mu \left( (R - \rho) \alpha_n \cos(\alpha_n \beta) - (\rho + R \alpha_n^2) \sin(\alpha_n \beta) \right)$$
$$\times \left( (\mu \rho^2 - R (R - \rho) \alpha_n^2) \cos(\alpha_n \beta) - (R (R - \rho) + (R^2 + \rho^2)) \alpha_n \sin(\alpha_n \beta) \right)^{-1},$$

where $\mu = \rho \kappa / D$ and $\beta = R / \rho - 1$.

A generated array of independent random realizations of the reaction times $T_{K,N}$ is used to compute the mean value, $\langle T_{K,N} \rangle$, and the empirical probability density of $T_{K,N}$. As the probability density $H_{K,N}(t)$ typically spans several orders of magnitude in time, we produce a renormalized histogram $h(z)$ of $\zeta = \ln T_{K,N}$ and then draw $h(z)/e^z$ versus $t = e^z$; see Figs. 2, 4.

Appendix F: Asymptotic behavior

Short-time limit

In the short-time limit, unbinding kinetics does not matter so that $H_{K,N}(t) \approx H_{K,N}^0(t)$, where $H_{K,N}^0(t)$ is given by Eq. (A2) and its short-time asymptotic behavior (A3) implies Eq. (11). However, Fig. 2 shows a considerable deviation from this behavior because it is achieved only at very short times, at which the probability density is too small and thus not relevant.

In order to clarify this point, we focus on diffusion between concentric spheres and compute next-order terms of the probability density $H(t|\phi)$ as $t \to 0$. For this purpose, we analyze the large-$p$ behavior of its Laplace transform,

$$\tilde{H}(p|\phi) = \frac{3 p D}{p^2 \rho^2 D^2 + 2 p \kappa D} \left( \left( \rho - \rho \alpha_n^2 \right) \tanh \left( \frac{\lambda_n t}{\rho} \right) \right), \quad (F1)$$

where $\alpha = \sqrt{p / D}$ and $\xi = \alpha (R - \rho)$. In the limit $p \to \infty$, $\tanh(\xi)$ can be replaced by 1, with exponentially small corrections:

$$\tilde{H}(p|\phi) \approx \frac{1}{p \tau} - \frac{\kappa \rho}{D \tau^2} \left( \frac{1}{(1 + \mu) \alpha^2} - \frac{\rho}{(1 + \mu)^2 \alpha} \right) + \frac{\rho^2}{(1 + \mu)^2 (\alpha \rho + 1 + \mu)};$$

This expression can be decomposed into partial fractions as

$$\tilde{H}(p|\phi) \approx \frac{1}{p \tau} - \frac{\kappa \rho}{D \tau^2} \left( \frac{1}{(1 + \mu) \alpha^2} - \frac{\rho}{(1 + \mu)^2 \alpha} \right) + \frac{\rho^2}{(1 + \mu)^2 (\alpha \rho + 1 + \mu)};$$

where $\mu = \rho \kappa / D$. The inverse Laplace transform yields

$$H(t|\phi) \approx \frac{1}{\tau} \left( 1 + \kappa \rho / D \right) \frac{\kappa \rho^2}{\sqrt{\pi} D \tau (1 + \mu)^2} \frac{1 - \sqrt{\tau} E_{\alpha,\beta}(\tau - (1 + \mu) \sqrt{Dt / \rho})}{\sqrt{Dt / \rho}} \tag{F2};$$

where $E_{\alpha,\beta}(z)$ is the Mittag-Leffler function:

$$E_{\alpha,\beta}(z) = \sum_{n=0}^{\infty} \frac{z^n}{\Gamma(\alpha n + \beta)}. \tag{F2}$$

Using the identity $E_{\alpha,\beta}(z) = z E_{\alpha + \beta}(z) + 1 / \Gamma(\beta)$, we get

$$H(t|\phi) \approx \frac{1}{\tau} \left( 1 + \kappa \rho / D \right) \frac{1 - \sqrt{\tau} E_{\alpha,\beta}(\tau - (1 + \mu) \sqrt{Dt / \rho})}{\sqrt{Dt / \rho}} \tag{F3};$$

The short-time expansion reads then

$$H(t|\phi) \approx \frac{1}{\tau} \left( 1 + \mu \sum_{n=1}^{\infty} \frac{(-1 + \mu) \sqrt{Dt / \rho}^n}{\Gamma(\frac{1}{2} n + 1)} \right). \tag{F4}$$

This expansion can be truncated to few terms when $(1 + \mu) \sqrt{Dt / \rho} \ll 1$. However, when this condition is not satisfied, one needs many terms to get an accurate result.
This is precisely what happens in Fig. 2 in which the short-time behavior is established for $t/\delta = Dt/\rho^2 \sim 10$, at which the above condition is not fulfilled. In this case, it is more convenient to keep the Mittag-Leffler function (note also that $E_{\frac{1}{2},1}(-z) = \text{erfc}(z) = e^{z^2} \text{erfc}(z)$ is the scaled complementary error function). However, Eq. (23) is specific to the case of concentric spheres and is not applicable for general domains.

From Eq. (23), we can also obtain the short-time behavior of the survival probability:

$$
1 - S(t|\circ) = \int_0^t dt' H(t'|\circ) \approx \frac{1}{(\tau)(1+\mu)} \times \left\{ t + \mu t E_{\frac{1}{2},2}(-t) \right\},
$$

where we used the identity:

$$
\int_0^z dz' E_{\alpha,1}(z') = z E_{\alpha,2}(z).
$$

(F5)

Using the identity,

$$
E_{\frac{1}{2},2}(-c\sqrt{t}) = 1 - \frac{4c\sqrt{t}}{3\sqrt{\pi}} + c^2 E_{\frac{1}{2},1}(-c\sqrt{t}),
$$

one also gets

$$
1 - S(t|\circ) \approx \frac{t}{(\tau)} \left\{ 1 - \frac{4\mu\sqrt{Dt}}{3\sqrt{\pi}\rho} + \frac{\mu(1+\mu)Dt}{\rho^2} E_{\frac{1}{2},1}(-t) \right\}. \tag{F6}
$$

**Long-time limit**

At long times, the probability density $H_{K,N}(t)$ decays exponentially according to Eq. (12), with the decay time $T_{K,N}$ determined by the largest (negative) pole $p_c$ of $H_{K,N}(p)$, which is given by the largest (negative) zero of $\mathcal{L}\{\mathcal{P}_1(K|K)\}(p)$. Following the approach from $^{53}$, we get

$$
p_c \approx \mathcal{P}_\infty(K|K) \left( \int_0^\infty dt (\mathcal{P}_1(K|K) - \mathcal{P}_\infty(K|K)) \right)^{-1}, \tag{F7}
$$

from which the decay time $T_{K,N}$ can be approximated by Eq. (13).

**Appendix G: Mean reaction time**

**Derivation**

In this Appendix, we derive and analyze an approximation for the mean reaction time:

$$
\langle T_{K,N} \rangle = - \lim_{p \to 0} \frac{\partial \tilde{H}_{K,N}(p|\circ)}{\partial p} \approx - \lim_{p \to 0} \frac{\partial \tilde{H}_{K,N}(p|\circ)}{\partial p} = \lim_{p \to 0} \left( \frac{\mathcal{L}\{\mathcal{P}_1(K|0)\} - (\mathcal{L}\{\mathcal{P}_1(K|K)\})^2}{(\mathcal{L}\{\mathcal{P}_1(K|K)\})^2} \right),
$$

where we used our approximation (10). Setting

$$
a_k = \int_0^\infty dt \ t^k (\mathcal{P}_1(K|0) - \mathcal{P}_\infty(K|0)), \tag{G1}
$$

$$
b_k = \int_0^\infty dt \ t^k (\mathcal{P}_1(K|K) - \mathcal{P}_\infty(K|K)), \tag{G2}
$$

one can employ Taylor expansions of the above Laplace transforms to get

$$
\langle T_{K,N} \rangle \approx \frac{\mathcal{P}_\infty(K|0)a_0}{|\mathcal{P}_\infty(K|K)|^2} - \frac{a_0}{\mathcal{P}_\infty(K|K)}. \tag{G3}
$$

Using the identity

$$
\sum_{j=0}^K \binom{K}{j} \binom{N-K}{j} = \binom{N}{K}, \tag{G4}
$$

one can check that

$$
\mathcal{P}_\infty(K|0) = (\mathcal{P}_\infty(K|K))^{N-K} = \binom{N}{K} P^K (1 - P)_{N-K}, \tag{G5}
$$

so that

$$
\langle T_{K,N} \rangle \approx \frac{b_0 - a_0}{\mathcal{P}_\infty(K|0)}, \tag{G6}
$$

which can be rewritten in a more explicit form as Eq. (13). The same technique can be used to get higher-order moments. We emphasize that this relation is not applicable for irreversible binding because $k_{\text{off}} = 0$ implies $P_\infty = 1$ and thus $P_\infty(K|0) = 0$ for any $K < N$. In turn, for $K = N$, Eq. (13) remains valid even for $k_{\text{off}} = 0$ and coincides with the exact relation derived in Ref. $^{53}$.

**Validity**

We stress that the above derivation is based on the approximate relation (10) so that Eq. (13) is an approximation of the mean reaction time. We recall that our approximation relied on the assumption that the $N-K$ free particles are uniformly distributed at the time when
the threshold crossing event happens. According to Eq. (48), this assumption is better fulfilled when
\[ P(t|\circ) \leq P_\infty = \frac{1}{1 + \eta} < 1, \quad (G7) \]
i.e., \( \eta = k_{\text{off}}(\tau) \) is large. In contrast, when \( k_{\text{off}} \to 0 \), unbinding events are rare and thus do not allow to spread away the depletion zone near the target. As a consequence, our assumption is not applicable, and the derived approximate formulas may fail. Note that in the limit \( k_{\text{off}} = 0 \), the mean reaction time is given by
\[ \langle T_{K,N} \rangle = \int_0^\infty dt \, t \, H_{K,N}^0(t), \quad (G8) \]
with \( H_{K,N}^0(t) \) being determined by the exact relation (A.2).

The failure of our approximation can be illustrated by taking the limit \( k_{\text{off}} \to 0 \), for which the numerator of Eq. (14) should vanish, yielding an identity
\[ \int_0^\infty dt \, [S(t|\circ)]^{N-K} \left( 1 - \left( \binom{N}{K} [1 - S(t|\circ)]^K \right) \right) = 0 \quad (G9) \]
for any \( K < N \). This identity is satisfied for \( S(t|\circ) = e^{-\nu t} \), i.e., if the first-binding time obeys an exponential distribution with a rate \( \nu \). We note that this is also related to the assumption of the Lawley-Madrid approximation, see further discussion in Appendix H. We emphasize that the identity (G9) does not hold in general, thus invalidating Eq. (14) in the limit \( k_{\text{off}} \to 0 \).

Figure 5 illustrates the validity range of the approximate relation (14). Here we plot the ratio between the approximate value of \( \langle T_{1,N} \rangle \) from Eq. (14), and the exact value \( \langle T_{1,N}^0 \rangle \) from Eq. (G8). As binding of the first particle does not depend on the unbinding kinetics, this ratio should be equal to 1 for any \( k_{\text{off}} \). In turn, deviations from 1 highlight limitations of the approximate relation (14). For \( N = 2 \), the ratio remains close to 1 for the considered range of \( \eta = k_{\text{off}}(\tau) \). As \( N \) increases, one observes deviations from 1 for \( \eta \lesssim 1 \). A more systematic study is needed for establishing quantitative criteria of the validity range of the developed approximation.

Asymptotic behavior

When \( \eta \) is large enough, the inequality (G7) implies \( \mathcal{P}_\infty(K|0) \approx \binom{N}{K} P^K_{\text{K}} \) and \( \mathcal{P}_\infty(K|K) \approx \langle Q(t) \rangle^K \), from which
\[ \langle T_{K,N} \rangle \approx \frac{1}{\binom{N}{K} P^K_{\text{K}}} \int_0^\infty dt \langle [Q(t)]^K - P^K_{\text{K}} \rangle. \quad (G10) \]

In this regime, the mean reaction time \( \langle T_{K,N} \rangle \) is close to the mean reaction time \( \langle T_{K,K} \rangle \) divided by the combinatorial factor \( \binom{N}{K} \). The latter was investigated in Ref. (58), and it was shown to behave as \( (1 + \eta)^K / (k_{\text{off}} K) \) for large \( K \). Neglecting 1 in comparison to \( \eta K \), one deduces Eq. (15). Strictly speaking, this relation is valid for \( N \geq K \gg 1 \) but Fig. 4 suggests that this asymptotic relation can be used for any \( K > 1 \) if \( \eta \) is large enough.

Note that in the case \( K = 1 \), one can compute the integral exactly by using the small-\( p \) asymptotic behavior of \( Q(p) \):
\[ \langle T_{1,1} \rangle \approx \frac{1}{P_\infty} \int_0^\infty dt \langle Q(t) - P_\infty \rangle = \frac{k_{\text{off}}(\tau^2)}{2(1 + k_{\text{off}}(\tau))}. \quad (G11) \]

As \( k_{\text{off}} \to 0 \), this expression vanishes, indicating again the failure of our approximation. In turn, as \( k_{\text{off}} \to \infty \), one gets the limit \( \langle \tau^2 \rangle / (2 \langle \tau \rangle) = \tau_0 \) according to Eq. (C11). In other words, we retrieve the exact value of the mean first-passage time \( \langle T_{1,1} \rangle = \langle T_{1,1}^{0} \rangle = \tau_0 \) for \( N = 1 \).

Appendix H: Further discussion on the validity of two approximations

The Lawley-Madrid approximation relied on the assumption that both the first-binding time and the rebinding time obey an exponential law with some rate \( \nu \), i.e., \( S(t|\circ) \approx S(t) \approx e^{-\nu t} \). In Appendix G we emphasized that the validity of our approximation at small \( k_{\text{off}} \) requires that \( S(t|\circ) \approx e^{-\nu t} \). In this Appendix, we further discuss these points.

The spectral expansion (E.2) indicates that its coefficients \( a_n \geq 0 \), defined by Eq. (E.4), can be understood as the relative weights of different Laplacian eigenmodes, given that \( 1 = S(0|\circ) = \sum_{n=1}^\infty a_n \). When the target is small and/or weakly reactive, the ground eigenfunction \( u_1(x) \) is almost constant so that \( a_1 \approx 1 \), whereas...
the other eigenfunctions are orthogonal to it, implying \( a_n \approx 0 \) for \( n > 1 \) (see \( 59,62 \)). In other words, one has \( S(t|\varnothing) \approx e^{-\nu t} \), with \( \nu = D\lambda_1 \). For instance, when the target is a sphere of radius \( \rho = 1 \) surrounded by a larger reflecting sphere of radius \( R = 10 \), we got numerically \( a_1 \approx 0.9989 \) for \( \kappa\rho/D = 1 \) and \( a_1 \approx 0.9946 \) for \( \kappa\rho/D = 100 \), i.e., even for a highly reactive target, the exponential law approximation is applicable for \( S(t|\varnothing) \).

Even for a large highly reactive target with \( \rho/R = 0.5 \) and \( \kappa\rho/D = 100 \), one has \( a_1 \approx 0.92 \), i.e., the ground eigenmode still yields the dominant contribution. This observation justifies the high accuracy of our approximation even for highly reactive targets.

While the first-binding time can indeed be considered as exponentially distributed, the situation is more subtle for the rebinding time \( \tau \) that is governed by the survival probability

\[
S(t|\varnothing) = \langle \tau \rangle H(t|\varnothing) = \sum_{n=1}^{\infty} a_n D\lambda_n \langle \tau \rangle e^{-D\lambda_n t}, \tag{H1}
\]

where we used Eq. \( \text{(C10)} \). The new coefficients \( a'_n = \)
\(a_\tau D\lambda_n(\tau)\) are as well the relative weights of the eigenmodes. Since the coefficient \(a_1 \approx 1\) is multiplied by a small eigenvalue \(\lambda_1\), the resulting coefficient \(a'_1\) is not necessarily dominant. For the above example with \(\rho/R = 0.1\), we get \(a'_1 \approx 0.5474\) for a moderately reactive target \((\kappa \rho/D = 1)\), i.e., the contribution of the ground mode is still dominant (55%) but not exclusive. In turn, for a highly reactive target \((\kappa \rho/D = 100)\), one has \(a'_1 \approx 0.0119\), i.e., the contribution of the ground mode is only 1%. In both cases, the approximation of the re-binding time distribution by an exponential distribution is not valid, and one needs much smaller or less reactive targets to apply this approximation. In summary, modeling the re-binding time distribution by an exponential law imposes strong restrictions onto the target size and reactivity. As our approximation employs the exact form of the probability density \(H(t)\) of the rebinding time, it does not suffer from these limitations and yields more accurate results than the Lawley-Madrid approximation. In turn, the latter has a great advantage of being much simpler and more explicit.

### Appendix I: Other Illustrations

Figure 6 illustrates the behavior of the probability density \(H_{K,N}(t)\) for \(N = 4\) and several values of \(K\) when the target is highly reactive \((\kappa \rho/D = 10)\). One sees that our approximation remains to be very accurate whereas the LMA fails in this case.

Figures 7 and 8 show the probability density \(H_{K,N}(t)\) for \(N = 2\) and \(N = 3\), respectively. Its behavior is similar to that discussed in the main text for Fig. 2 with \(N = 4\).

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Figure 8: Probability density of the reaction time $T_{K,N}$ for restricted diffusion between concentric spheres of radii $\rho$ and $R = 10\rho$, with $N = 3$, $k_D/D = 1$, a timescale $\delta = \rho^2/D$, three values of $k_{\text{off}}$ (see legend), and three values of $K$: $K = 1$ (a), $K = 2$ (b), and $K = 3$ (c). Symbols show empirical histograms from Monte Carlo simulations with $10^6$ particles. Thick lines indicate our approximation (10) evaluated numerically as described in Appendix E, whereas thin lines show the Lawley-Madrid approximation (B3). Thin gray solid line presents the short-time asymptotic behavior (11).