I. INTRODUCTION

Reaction kinetics in confined systems where a small number of reactants are involved, such as porous catalysts and living cells, can be limited by the time needed for molecules to meet and react \[^2\,^3\]. This time is known in random walk theory as a first-passage time (FPT) \([4,\,5]\). For the specific case of biochemical reactions in living cells, these general considerations have to incorporate two important features. First, while passive diffusion is the dominant mode of transport in chemical systems, active transport has been shown to play a prominent role in living cells \([8]\). As a matter of fact, various motor proteins such as kinesin and myosin are able to convert the chemical fuel provided by ATP into mechanical work by interacting with the filaments of the cytoskeleton. Many macromolecules or larger cellular organelles such as vesicles, lysosomes or mitochondria, can randomly bind and unbind to these motors \([9,\,11]\).

As a result, the overall transport of such tracers in the cell can be described in a first approximation as diffusion in a force field \([12]\). Second, reactions in confined domains like cells generally involve surface-mediated diffusion that combines bulk transport and surface diffusion due to non-specific interactions with the domain boundary (e.g., cell membrane) \([13,\,18]\). Such two-state paths and the corresponding first-passage properties have been studied in the broader context of intermittent search strategies \([19,\,22]\) under the hypothesis that the times spent in each state (surface and bulk) are controlled by an internal clock independent of any geometrical parameter. In most cases, the sojourn times in each state have been assumed to be exponentially distributed \([21]\), with the notable exception of Lévy \([23]\) and deterministic laws \([24,\,25]\). However, in the case of interfacial reactions, for which molecules react on target sites located on the surface of the confining domain, the time spent in a bulk excursion is controlled by the statistics of return to the surface and therefore by the geometry of the confining domain \([26,\,30]\). Hence this return time is not an external parameter but is generated by the very dynamics of the diffusing molecule in confinement.

Recently, such coupling of the intermittent dynamics to the geometry of the confinement has been explicitly taken into account \([1,\,31,\,35]\). Exact calculations of the mean FPT to a target on the surface of a 2D or 3D spherical domain, for a molecule performing surface-mediated diffusion, have been proposed \([1,\,33]\). However, these works have been limited to passive transport alone. The present article develops a general theoretical framework which in particular allows one to incorporate the effect of active transport on surface-mediated diffusion.

More precisely, we extend the results of \([1,\,33]\) in four directions: (i) we consider the general case of an imperfect adsorption step, so that the molecule can bounce several times before being adsorbed to the confining surface \([36,\,44]\); (ii) the geometry adopted is a general annulus, whose either interior, or exterior boundary is purely reflecting; (iii) we take into account the effect of an exterior radial force field which, for instance, can schematically mimic the effect of active transport; (iv) we consider the possibility of having an arbitrary number of regularly spaced targets on the surface. Relying on an integral equation approach, we provide an exact solution for the mean FPT, both for 2D and 3D spherical domains, and for any spherical target size. We also develop approximation schemes, numerically validated, that provide more tractable expressions of the mean first passage time (MFPT).

The article is organized as follows. In Sec. II, we define the model under study; in Sec. III, we show that the MFPT can be determined by solving coupled partial differential equations that can actually be converted into a single integral equation. We then provide an exact solution of this integral equation, as well as an approximate, more tractable,
solution. In Sec. IV, we give fully explicit expressions of the MFPT by applying this general formalism to particular
cases, representative of the four aforementioned extensions.

II. THE MODEL

The surface-mediated process under study is illustrated in Fig. 1. We consider a molecule diffusing in the volume
$S$ between two concentric spheres of radii $R$ and $R_c$. The molecule alternates phases of bulk diffusion (with diffusion
coefficient $D_2$) and phases of surface diffusion on the boundary of the sphere of radius $R$ (with diffusion coefficient
$D_1$) which contains a target. The target is defined in 2D by the arc $\theta \in [-\epsilon, \epsilon]$, and in 3D by the region of the sphere
such that $\theta \in [0, \epsilon]$ where $\theta$ is in this case the elevation angle in spherical coordinates. Note that as soon as $\epsilon \neq 0$, the
target can be reached both by surface and bulk diffusion.

In the following, the case $R > R_c$ will be called an exit problem and the case $R_c > R$ an entrance problem (Fig. 1).
In 3D, the entrance problem can account for the time needed for a virus initially in the cell (the sphere of radius $R_c$)
to get into the nucleus (the sphere of radius $R$) through a single nuclear pore (the target) in the presence of diffusion
on the nuclear membrane. In turn, the exit problem in 3D may describe macromolecules searching an exit from the
cell through a channel (or channels) in the cellular membrane. In that case, the surface of the nucleus is considered
as purely reflecting. The 2D geometry could correspond to cells that are confined, as realized in vitro for example in
[48].

In this model, a molecule hitting the sphere of radius $R_c$ is immediately reflected. In contrast, when the molecule
reaches the sphere of radius $R$, which contains the target, it is imperfectly adsorbed: the molecule hitting the boundary
at $r = (R, \theta)$, $\theta \in [0, \pi]$ is at random either adsorbed to the sphere of radius $R$ or reflected back in the bulk. The
quantity $k$ which describes the rate of adsorption is more precisely defined through the radiative boundary condition
Eq. (4) (see also Eq. (A4) of the discrete lattice approach discussed in Appendix A). In particular, $k = \infty$ corresponds
to a perfectly adsorbing boundary and $k = 0$ to a perfectly reflecting boundary. Notice that for finite $k$, molecules
hitting the target from the bulk can be reflected.

The time spent during each surface exploration on the sphere of radius $R$ is assumed to follow an exponential
law with desorption rate $\lambda$. At each desorption event, the molecule is assumed to be ejected from the surface point
$r = (R, \theta)$ to the bulk point $r = (R - a, \theta)$. In what follows, $a$ can be positive or negative: $a > 0$ for the exit problem
$(R > R_c)$, and $a < 0$ for the entrance problem $(R < R_c)$. Although formulated for any value of the parameter $a$ such
that $|a| \leq |R - R_c|$ (to ensure that the particle remains inside the domain after reflection), in most physical situations
of interest $|a|$ is much smaller than $R$. Note finally that a non zero ejection distance $a$ is required in the limit of
perfect adsorption $k = \infty$, otherwise the diffusing molecule would be instantaneously re-adsorbed on the surface.

FIG. 1: Model - Left: Static picture of the entrance problem in 3D - Right: Dynamic picture of the exit problem in 2D. The
green sphere stands for the diffusing molecule and the red sector stands for the target.
III. GENERAL SOLUTION

A. Basic equations

For the process defined above, the mean first-passage time (MFPT) satisfies the following backward equations

\[ \frac{D_1}{R^2} \Delta_{\theta} t_1(\theta) + \lambda (t_2(R-a, \theta) - t_1(\theta)) = -1 \quad (\epsilon < \theta < \pi), \]

\[ D_2 \left( \Delta_r + \frac{v(r)}{D_2} \partial_r + \frac{\Delta_{\theta}}{r^2} \right) t_2(r, \theta) = -1 \quad ((r, \theta) \in S), \]

where: (i) \( t_1(\theta) \) stands for the MFPT for a molecule initially on the sphere of radius \( R \) at angle \( \theta \), and \( t_2(r, \theta) \) stands for the MFPT for a molecule initially at a bulk point \((r, \theta)\) within the annulus \( S = (R_c, R) \times [0, \pi] \); note that, due to the symmetry \( t_i(\theta) = t_i(-\theta) \), in 2D \( \theta \) can be restricted to \([0, \pi]\); (ii) the radial and angular Laplace operators are respectively

\[ \Delta_r = \frac{\partial^2}{\partial r^2} + \frac{d-1}{r} \frac{\partial}{\partial r}, \quad \Delta_{\theta} = (\sin \theta)^{2-d} \partial_{\theta} (\sin \theta)^{d-2} \partial_{\theta}, \]

and \( d \) stands for the space dimension (in practice, \( d \) will be taken equal to 2 or 3); (iii) \( v(r) \) is the radial velocity of the molecule resulting from an external force.

In Eqs. (1, 2), the first terms of the left hand side account for diffusion respectively on the surface and in the bulk, while the second term of Eq. (1) describes desorption events. These equations have to be completed by boundary conditions:

(i) reflecting boundary condition on the sphere of radius \( R_c \geq 0 \)

\[ \frac{\partial t_2}{\partial r} \bigg|_{r=(R_c, \theta)} = 0 \quad (0 \leq \theta \leq \pi) \]

(note that this condition holds even in the presence of the velocity field \( v(r) \), see e.g. [45]);

(ii) radiative boundary condition

\[ \frac{\partial t_2}{\partial r} \bigg|_{r=(R, \theta)} = k \{ t_1(\theta) - t_2(R, \theta) \} \quad (0 \leq \theta \leq \pi), \]

which describes the partial adsorption events on the sphere of radius \( R \) (see Appendix A for justification of this boundary condition). For the exit problem \((R > R_c)\), the radial axis points towards the surface and \( k > 0 \), while for the entrance problem \((R < R_c)\), the radial axis points outwards the surface and \( k < 0 \). Finally, the limit \( k = \pm \infty \) describes the perfect adsorption for which the above condition reads as \( t_1(\theta) = t_2(R, \theta) \).

(iii) Dirichlet boundary condition

\[ t_1(\theta) = 0 \quad (0 \leq \theta \leq \epsilon), \]

which expresses that the target is an absorbing zone (the search process is stopped on the target).

In what follows we will use two dimensionless quantities

\[ x \equiv 1 - a/R, \]

\[ \omega \equiv R \sqrt{\lambda/D_1}, \]

and the operator \( L \) acting on a function \( f \) as

\[ (L f)(r) \equiv f(r-a) - f(r) - \frac{1}{k} \partial_r f(r). \]

B. General integral equation

We generalize the approach presented in [1] and show that the coupled Eqs. (1, 2) with the boundary conditions (3-5) lead to the integral equation (22) for \( t_1 \) only.
The starting point is a Fourier decomposition of $t_2$. Eq. (2) is easily shown to be satisfied by

$$t_2(r, \theta) = \alpha_0 + \frac{1}{D_2} \hat{f}(r) + \beta_0 f_0(r) + \sum_{n=1}^{\infty} \alpha_n f_n(r) V_n(\theta) + \sum_{n=1}^{\infty} \alpha_{-n} f_{-n}(r) V_n(\theta),$$

(9)

with coefficients $\alpha_n$ to be determined, and

(i) $\hat{f}(r)$ is a rotation-invariant solution of Eq. (2) regular at $r = 0$, i.e.

$$\left( \Delta_r + \frac{v(r)}{D_2} \frac{\partial}{\partial r} \right) \hat{f}(r) = -1,$$

(10)

the choice of $\hat{f}(r)$ being up to an additive constant;

(ii) $f_0(r)$ is a non-constant solution of the homogeneous equation

$$\left( \Delta_r + \frac{v(r)}{D_2} \frac{\partial}{\partial r} \right) f_0(r) = 0,$$

(11)

the choice of $f_0(r)$ being up to an additive constant and a multiplicative prefactor. It can be shown that $f_0(r)$ necessarily diverges at $r = 0$ in our cases of interest;

(iii) the set of functions $\{f_n(r), V_n(\theta)\}_{n \in \mathbb{Z}}$ is an eigenbasis of the homogeneous equation associated to Eq. (2):

$$-\Delta_\theta V_n(\theta) = \rho_n V_n(\theta) \quad (n \geq 0),$$

(12)

$$r^2 \left( \Delta_r + \frac{v(r)}{D_2} \frac{\partial}{\partial r} \right) f_n(r) = \rho_{|n|} f_n(r) \quad (n \in \mathbb{Z}),$$

(13)

with $V_{-n}(\theta) = V_n(\theta)$ due to the reflection symmetry, and

$$\rho_n = \begin{cases} n^2 & (d = 2), \\ n(n+1) & (d = 3). \end{cases}$$

(14)

We set

$$V_n(\theta) = \begin{cases} 1 & (n = 0) \\ \sqrt{2} \cos(n\theta) & (n > 0) \\ \sqrt{2n + 1} P_n(\cos \theta) & (n \geq 0) \end{cases} \quad (d = 3),$$

(15)

where $P_n(z)$ are Legendre polynomials. In turn, the functions $f_n(r)$ which depend on the velocity field $v(r)$, will be determined individually case by case (see Sec. IV).

In the following, we will use two inner products:

$$(f, g) \rightarrow \langle f | g \rangle \equiv \int_0^\pi f(\theta) g(\theta) d\mu_d(\theta),$$

$$(f, g) \rightarrow \langle f | g \rangle_r \equiv \int_0^\pi f(\theta) g(\theta) d\mu_d(\theta),$$

where $d\mu_d(\theta)$ are the measures in polar $(d = 2)$ and spherical coordinates $(d = 3)$:

$$d\mu_2(\theta) = \frac{d\theta}{\pi}, \quad d\mu_3(\theta) = \frac{\sin \theta}{2} d\theta.$$  

(16)

With these definitions, the eigenvectors $V_n(\theta)$ are orthonormal

$$(V_n | V_m) = \delta_{nm}.$$  

(17)

We now use the boundary conditions (3)(5) to determine the coefficients $\{\alpha_n\}_n$ defining $t_2(r, \theta)$ in Eq. (9).

(i) The reflecting boundary condition (3) reads

$$\beta_0 \frac{\partial_r f_0(r)}{|R_e |} + \frac{1}{D_2} \frac{\partial_r \hat{f}(r)}{|R_e |} + \sum_{n=1}^{\infty} (\alpha_n \partial_r f_n + \alpha_{-n} \partial_r f_{-n}) |_{R_e} V_n(\theta) = 0,$$

(18)
which, using the orthogonality in Eq. (17), leads to the following relations

\[ \beta_0 = -\frac{1}{D_2} \left( \frac{\partial_r \hat{f}(r)}{\partial_r f_0(r)} \right) \bigg|_{r=R_c}, \quad \alpha_n \partial_r f_n(r)\big|_{r=R_c} = -\alpha_n \partial_r f_{-n}(r)\big|_{r=R_c}. \]  

(19)

Note that, in the case \( R_c = 0 \), the first condition reads \( \beta_0 = 0 \). Indeed, if \( \beta_0 \) were non zero, the MFPT of a molecule initially at the origin would diverge (by definition of the function \( f_0 \)).

(ii) Substituting Eq. (9) into the radiative boundary condition Eq. (4), projecting it onto the basis \( V_n(\theta) \) and using Eq. (19), we obtain two supplementary conditions:

\[ \alpha_0 - \frac{1}{D_2} \left( \frac{\partial_r f(r)}{\partial_r f_0(r)} \right) \bigg|_{r=R_c} \left( f_0(R) + \frac{1}{k} \partial_r f_0(R) \right) + \frac{1}{D_2} \left( \hat{f}(R) + \frac{1}{k} \partial_r \hat{f}(R) \right) = \langle t_1 | 1 \rangle, \]  

(20)

\[ \alpha_n \left[ f_n(R) + \frac{1}{k} \partial_r f_n(R) - \left( \frac{\partial_r f_n(r)}{\partial_r f_{-n}(r)} \right) \bigg|_{r=R_c} \right] \left( f_{-n}(R) + \frac{1}{k} \partial_r f_{-n}(R) \right) = \langle t_1 | V_n \rangle \quad (n > 0). \]  

(21)

On the other hand, the radiative boundary condition in Eq. (4) and the operator \( L \) defined in Eq. (8) allow one to rewrite Eq. (1) as

\[ -\Delta_\theta t_1(\theta) = \frac{\omega^2}{\lambda} + \omega^2 (Lt_2)(R) \quad (\epsilon < \theta < \pi), \]  

which becomes, using Eqs. (9) [19] [20] [21],

\[ -\Delta_\theta t_1(\theta) = \omega^2 T + \omega^2 \sum_{n=1}^{\infty} X_n \langle t_1 | V_n \rangle V_n(\theta) \quad (\epsilon < \theta < \pi), \]  

(22)

where

\[ T \equiv \frac{1}{\lambda} + \frac{\eta_d}{D_2}, \]  

(23)

\[ \eta_d \equiv -\left( \frac{\partial_r \hat{f}(r)}{\partial_r f_0(r)} \right) \bigg|_{r=R_c} Lf_0(R) + L\hat{f}(R), \]  

(24)

\[ X_n \equiv \frac{L f_n(R) - \left( \frac{\partial_r f_n(r)}{\partial_r f_{-n}(r)} \right) \bigg|_{r=R_c} L f_{-n}(R)}{f_n(R) + \frac{1}{k} \partial_r f_n(R) - \left( \frac{\partial_r f_n(r)}{\partial_r f_{-n}(r)} \right) \bigg|_{r=R_c} f_{-n}(R) + \frac{1}{k} \partial_r f_{-n}(R)} \quad (n \geq 1). \]  

(25)

In Appendix B we identify the quantity \( \eta_d/D_2 \) as the mean first passage time on the sphere of radius \( R \) for a molecule initially at \( r = R - a \). Thus the time \( T \) is the sum of a mean exploration time \( \eta_d/D_2 \) and a mean “exploitation” time \( 1/\lambda \).

(iii) The absorbing boundary condition (5) and the relation \( t'_1(\pi) = 0 \) which comes from the invariance of \( t_1 \) under the symmetry \( \theta \rightarrow 2\pi - \theta \), lead after integration of Eq. (22) to

\[ t_1(\theta) = \begin{cases} 
\omega^2 T \ g_\epsilon(\theta) + \omega^2 \sum_{n=1}^{\infty} \frac{\Delta_\rho_n}{\rho_n} \langle V_n | t_1 \rangle \epsilon \{ V_n(\theta) - V_n(\epsilon) \} & (\epsilon < \theta < \pi), \\
0 & (0 \leq \theta \leq \epsilon),
\end{cases} \]  

(26)

where \( \rho_n \) is defined in Eq. (14) and \( g_\epsilon(\theta) \) is the solution of the problem:

\[ \Delta_\theta g_\epsilon(\theta) = -1, \quad \text{with} \quad g_\epsilon(\epsilon) = 0 \quad \text{and} \quad g_\epsilon(\pi) = 0. \]  

(27)

Note that \( R^2 g_\epsilon(\theta)/D_1 \) represents the MFPT to the target when \( \lambda = 0 \), i.e. in absence of desorption events, hence \( g_\epsilon(\theta) \) is well known:

\[ g_\epsilon(\theta) = \begin{cases} 
\frac{1}{2} (\theta - \epsilon)(2\pi - \epsilon - \theta) & (d = 2), \\
\ln \left( \frac{1 - \cos(\theta)}{1 - \cos(\epsilon)} \right) & (d = 3).
\end{cases} \]  

(28)
Equivalently, Eq. (26) reads
\[
\psi(\theta) = \begin{cases} 
g_r(\theta) + \omega^2 \sum_{n=1}^{\infty} \frac{X_n}{\rho_n} \langle \psi \rangle \{ V_n(\theta) - V_n(\epsilon) \} & (\epsilon < \theta < \pi), \\
0 & (0 \leq \theta \leq \epsilon),
\end{cases}
\]  
(29)
where \( \psi(\theta) \equiv t_1(\theta)/(\omega^2 T) \) is a dimensionless function.

C. Exact solution

The function \( \psi(\theta) \) can be developed on the basis of functions \( \{ V_n(\theta) - V_n(\epsilon) \} \),
\[
\psi(\theta) = g_r(\theta) + \sum_{n=1}^{\infty} d_n \{ V_n(\theta) - V_n(\epsilon) \} \quad (\epsilon < \theta < \pi),
\]
with coefficients \( \{ d_n \}_{n \geq 1} \) to be determined. Due to Eq. (26), the vector \( \mathbf{d} = \{ d_n \}_{n \geq 1} \) is a solution of the equation
\[
\sum_{n=1}^{\infty} d_n \{ V_n(\theta) - V_n(\epsilon) \} = \omega^2 \sum_{n=1}^{\infty} \left( U_n + \sum_{m=1}^{\infty} Q_n,m d_m \right) \{ V_n(\theta) - V_n(\epsilon) \},
\]  
(30)
where we have defined the vectors \( U \) and \( \xi \) by their \( n \)-th coordinates:
\[
U_n \equiv \frac{X_n}{\rho_n^2} \xi_n, \quad \xi_n \equiv \rho_n \langle g_r(\theta) | V_n(\theta) \rangle_\epsilon \quad (n \geq 1),
\]  
(31)
and the matrices \( Q \) and \( I \) by their elements:
\[
Q_n,m \equiv \frac{X_n}{\rho_n^2} I_c(n, m), \quad I_c(n, m) \equiv \langle V_n(\theta) | V_m(\theta) - V_m(\epsilon) \rangle_\epsilon \quad (m \geq 1, \ n \geq 1).
\]  
(32)
As Eq. (30) is satisfied for all \( \theta \in (\epsilon, \pi) \), the coefficients \( d_n \) can be found by inverting the underlying matrix equation as
\[
d_n = \left[ \omega^2 (I - \omega^2 Q)^{-1} U \right]_n.
\]  
(33)

The MFPT \( t_1(\theta) \) can be explicitly rewritten as
\[
t_1(\theta) = \begin{cases} 
\omega^2 T \left[ g_r(\theta) + \sum_{n=1}^{\infty} d_n \{ V_n(\theta) - V_n(\epsilon) \} \right] & (\epsilon < \theta < \pi), \\
0 & (0 \leq \theta \leq \epsilon).
\end{cases}
\]  
(34)

The averaged MFPT \( \langle t_1 \rangle \) which is defined by averaging over a uniform distribution of the starting point, is then easily obtained as
\[
\langle t_1 \rangle \equiv \int_0^\pi t_1(\theta) d\mu_\epsilon(\theta) = \omega^2 T \left( \langle g_r | 1 \rangle_\epsilon + \sum_{n=1}^{\infty} d_n \xi_n \right),
\]  
(35)
where we have used the following relation
\[
\langle V_n(\theta) - V_n(\epsilon) | 1 \rangle_\epsilon = -(V_n(\theta) - V_n(\epsilon) | \Delta \theta g_r(\theta) \rangle_\epsilon = \rho_n \langle V_n(\theta) | g_r(\theta) \rangle_\epsilon = \xi_n.
\]

Finally, the MFPT \( t_2(r, \theta) \) is given by Eq. (9), in which the coefficients \( \beta_0 \) and \( \alpha_n \) are obtained from Eqs. (19) (20) (21):
\[
t_2(r, \theta) = \langle t_1 \rangle + \frac{\eta d}{D_2} + \frac{1}{D_2} \left( \hat{f}(r) - \hat{f}(R - a) \right) - \frac{1}{D_2} \left( \frac{\partial f}{\partial f_0} \right)_{r=R_c} \left( f_0(r) - f_0(R - a) \right)
\]
\[
+ \sum_{n=1}^{\infty} \alpha_n V_n(\theta) \left\{ f_n(r) - \left( \frac{\partial f_n}{\partial f_{-n}} \right)_{r=R_c} f_{-n}(r) \right\},
\]  
(36)
If the derivative is negative at the point of interest, we address the important issue of determining the coefficients $d_n$ according to Eq. (33). Table I summarizes the quantities which are involved in Eqs. (34), (35), (36) and independent of the detail of the radial bulk dynamics. In turn, the quantities $T$, $\eta_d$ and $X_n$ are expressed by Eqs. (24), (25) through the functions $\tilde{f}$, $f_0$ and $f_n$ and thus depend on the specific dynamics in the bulk phase and will be discussed in Sec. IV for several particular examples.

A numerical implementation of the exact solutions in Eqs. (34), (35), (36) requires a truncation of the infinite-dimensional matrix $Q$ to a finite size $N \times N$. After a direct numerical inversion of the truncated matrix $(I - \omega^2 Q)$ in Eq. (34), the MFPTs from Eqs. (34), (35), (36) are approximated by truncated series (with $N$ terms). We checked numerically that the truncation errors decay very rapidly with $N$. In a typical case of moderate $\omega < 100$, the results with $N = 100$ and $N = 200$ are barely distinguishable. In turn, larger values of $\omega$ (or $\lambda$) may require larger truncation sizes. In the following examples, we used $N = 200$. In spite of the truncation, we will refer to the results obtained by this numerical procedure as exact solutions, as their accuracy can be arbitrarily improved by increasing the truncation size $N$. These exact solutions will be confronted to approximate and perturbative solutions described in the next subsections.

### D. Are bulk excursions beneficial?

Before considering these perturbative and approximate solutions, we address the important issue of determining whether bulk excursions are beneficial for the search. This question can be answered by studying the sign of the derivative of $t_1$ with respect to $\lambda$ at $\lambda = 0$. In terms of $\bar{Q} = -QR^2/D_1$, the MFPT from Eq. (35) reads

$$
\langle t_1 \rangle = \frac{R^2}{D_1^2} (1 + \lambda \eta_d/D_2) \left[ \frac{D_1}{R^2} \langle g_1 | 1 \rangle_\epsilon + \left( \xi \lambda (I + \lambda \bar{Q})^{-1} U \right) \right].
$$

The derivative of $\langle t_1 \rangle$ with respect to $\lambda$ is

$$
\frac{\partial \langle t_1 \rangle}{\partial \lambda} = \frac{R^4 \eta_d}{D_1^2} \left[ \frac{D_1}{D_2 R^2} \langle g_1 | 1 \rangle_\epsilon + \left( \xi \frac{(\eta_d^{-1} + 2\lambda)}{(I + \lambda \bar{Q})^2} U \right) \right].
$$

If the derivative is negative at $\lambda = 0$, i.e.

$$
\frac{D_1}{D_2} \leq - \frac{R^2}{\langle g_1 | 1 \rangle_\epsilon} \frac{\xi U}{\eta_d},
$$

Table I: Summary of formulas for computing the vector $\xi$ and the matrix $Q$ in Eqs. (31), (32) that determine the coefficients $d_n$ according to Eq. (33).
bulk excursions are beneficial for the search. Explicitly, the critical ratio of the bulk-to-surface diffusion coefficients, below which bulk excursions are beneficial, is

\[
\frac{D_{2\epsilon}}{D_1} = -\frac{\eta_d(g_{c1})\epsilon}{R^2} \left[ \sum_{n=1}^{\infty} X_n \langle g_{c1} | V_n \rangle^2 \right]^{-1}.
\] (40)

E. Perturbative solution (small \(\epsilon\) expansion)

While Eq. (34) for \(t_1\) is exact, it is not fully explicit since it requires either the inversion of the (infinite-dimensional) matrix \(I - \omega^2Q\), or the calculation of all the powers of \(Q\). In this section, we give the first terms of a small \(\epsilon\) expansion of the MFPT, while in the next one we provide an approximate solution that improves in practice the range of validity of this perturbative solution. Both solutions rely on the orthogonality of functions \(V_n\) in the small target size limit \(\epsilon \to 0\), which implies that the matrix \(Q\) is diagonal in this limit.

More precisely, as \(V_n(\theta) = V_n(-\theta)\), necessarily \(\partial_\theta V_n(0) = 0\), so that for \(\epsilon\) close to zero and for all \(\theta \in [0,\epsilon]\), one has: 

\[V_n(\theta) = V_n(0) + O(\theta^2)\].

As a consequence, the function \(I_{nm}\) introduced in Eq. (32), reads for all \(m,n \geq 1\) (see also Appendix C)

\[I_{(n,m)} \equiv \langle V_n(\theta)|V_m(\theta) - V_m(\epsilon)\rangle = \langle V_n(\theta)|V_m(\theta)\rangle - \langle V_n(\theta)|V_m(\theta)|1\rangle + O(\epsilon^3) = \delta_{nm} + O(\epsilon^3).
\] (41)

The first terms of a small \(\epsilon\) expansion of the MFPT can then be exactly calculated. Relying on the expansion Eq. (41), one can replace \(I_{(n,n)}\) by 1 to get in 2D

\[
\langle t_1 \rangle = \frac{\pi^2}{3} + 2\omega^2 \sum_{n=1}^{\infty} \frac{X_n}{n^2 n^2 - \omega^2 X_n^2} - \pi\epsilon + \left(1 - 2\omega^2 \sum_{n=1}^{\infty} \frac{X_n}{n^2 n^2 - \omega^2 X_n^2}\right) \epsilon^2 + O(\epsilon^3),
\] (42)

and in 3D

\[
\langle t_1 \rangle = -2 \ln(\epsilon/2) - \left(1 +\omega^2 \sum_{n=1}^{\infty} \frac{(2n+1)X_n}{n (n+1) (\omega^2 X_n - n(n+1))}\right) + O(\epsilon^2).
\] (43)

The comparison of the perturbative solutions to the exact and approximate ones is presented in Figs. 2 3 5 7 and it is discussed below.

F. Approximate solution

As mentioned above, we now provide an approximate solution that improves in practice the range of validity of the perturbative solution. This approximation relies on the fact that, due to Eq. (41), the matrix \(Q\) defined in Eq. (32) reads

\[Q_{nm} = \delta_{nm} Q_{nn} + O(\epsilon^3).
\] (44)

Keeping only the leading term of this expansion, one gets

\[d_n \approx \frac{\omega^2 U_n}{1 - \omega^2 Q_{nn}} \quad (n \geq 1).
\] (45)

From Eqs. (41) 33 45 we then obtain the following approximation for the search time:

\[
\langle t_1 \rangle \approx \omega^2 T \left[ \langle g_{c1} |1\rangle + \omega^2 \sum_{n=1}^{\infty} \frac{X_n \langle g_{c1} | V_n \rangle^2}{1 - \omega^2 Q_{nn}} I_{(n,n)} \right].
\] (46)

Note that this expression is fully explicit as soon as the functions \(\tilde{f}, f_0\) and \(f_n\) defined in Eqs. (10) 11 13 are determined. In Section IV, we will consider particular examples and write these functions explicitly. As we will show numerically, this approximation of \(t_1\), which was derived for small \(\epsilon\), is in an excellent quantitative agreement with the exact expression for a wide range of parameters and even for large targets (see Figs. 2 3 5 7).
TABLE II: Functions $\hat{f}$, $f_0$ and $f_n$ for several particular cases in 2D and 3D (see also Appendix D).

### IV. PARTICULAR CASES

We now show how the above theoretical approach can be applied to various important examples. The only quantities needed to obtain fully explicit expressions of Eqs. (35, 46, 42, 43) are the functions $\hat{T}$, $T_0$ and $T_n$ which are involved in the definitions of the quantities $T$ and $X_n$ according to Eqs. (23, 25). These quantities are listed in Table II for the representative cases discussed in this section. Throughout in this section, all the quantities ($R$, $R_c$, $a$, $\lambda$, $D_1$, $D_2$, $k$, $(t_1)$) are written in dimensionless units. The physical units can be easily retrieved from the definitions of these quantities.

#### A. Zero bias ($V = 0$)

1. Exit problem for a perfect adsorption

In the case of the exit problem with $R_c = 0$, perfect adsorption ($k = \infty$) and no bias, the formula (46) reproduces the results of [1]. The coefficient $\eta_d/D_2$ is the mean first passage time to the sphere of radius $R$, starting from $r = R - a$,

$$\frac{\eta_d}{D_2} = \frac{a(2R - a)}{2d}.$$ (47)

From the expressions for the quantities $T$ and $X_n$,

$$T = \frac{1}{\lambda} + \frac{R^2}{2dD_2}(1 - x^2), \quad X_n = x^n - 1,$$

we retrieve the approximate expressions for the MFPT in 2D

$$\langle t_1 \rangle \approx \frac{\omega^2 T}{\pi} \left[ \frac{1}{3}(\pi - \epsilon)^3 + \frac{2\omega^2}{\pi} \sum_{n=1}^{\infty} \frac{x^n - 1}{n^4} \left( \frac{\pi n}{n^2} \right)^2 \right],$$

and in 3D:

$$\langle t_1 \rangle \approx \frac{\omega^2 T}{2} \left[ \ln \left( \frac{2}{1 - \cos \epsilon} \right) + \frac{1 + \cos \epsilon}{2} + \frac{\omega^2}{4} \sum_{n=1}^{\infty} \frac{(n^2 - 1)(2n + 1)}{n^2(n + 1)} \left( \frac{1}{2} + \frac{\cos \epsilon}{n^2} \right) \right].$$
We emphasize that bulk excursions can be beneficial for the MFPT even for the bulk diffusion coefficient $D_2$ smaller than the surface diffusion coefficient $D_1$. This can be understood qualitatively by the fact that bulk diffusion induces flights towards remote and unvisited regions of the sphere $r = R$. These long-range hops can diminish the time for target encounter (provided that the time spent in the bulk phase is not too large).

2. Exit time for a partial adsorption

We now give an explicit expression of the results (46) and (40) for a 2D exit problem with $R_c = 0$ and with an imperfect adsorption on the sphere of radius $R$. Using the expressions from Table I the coefficients $\eta_d$ and $X_n$ are

$$\eta_d = \frac{R^2}{2d} \left( 1 - x^2 + \frac{2}{kR} \right), \quad X_n = \frac{x^n - \frac{n}{kR}}{1 + \frac{n}{kR}}. \quad (48)$$

Thus the approximate MFPT in 2D reads

$$\langle t_1 \rangle \approx \frac{\omega^2}{\pi} \left[ \frac{1}{3} (\pi - \epsilon)^3 - \frac{2 \omega^2}{\pi} \sum_{n=1}^{\infty} \frac{1}{n^4 (1 + \frac{n}{kR})} \left( (\pi - \epsilon) \cos(n\epsilon) + \sin(n\epsilon)/n \right)^2 \right], \quad (49)$$

and the critical ratio of the bulk-to-surface diffusion coefficients in Eq. (40), below which bulk excursions are beneficial, takes the form

$$\frac{D_{2c}}{D_1} = \left( 1 - x^2 + \frac{2}{kR} \right) \frac{\pi (\pi - \epsilon)^3}{24} \sum_{n=1}^{\infty} \frac{1}{n^4 (1 + \frac{n}{kR})} \left( (\pi - \epsilon) \cos(n\epsilon) + \sin(n\epsilon)/n \right)^2. \quad (50)$$

Similarly, one can write explicit formulas in 3D.

The MFPT as a function of the desorption rate $\lambda$ is shown on Fig. 2 for different values of the bulk diffusion coefficient $D_2$ and the target sizes $\epsilon = 0.01$ and $\epsilon = 0.1$, both in two and three dimensions. One can see that the approximate solution (49) (shown by circles) accurately follows the exact solution (shown by lines) for a wide range of parameters. In turn, the perturbative solutions in Eqs. (42), (43) (shown by pluses) are accurate for small $\epsilon = 0.01$ but they deviate from the exact ones for larger $\epsilon = 0.1$.

The quality of the approximate and perturbative solutions can also be analyzed on Fig. 3 which shows the MFPT as a function of the target size $\epsilon$ (with a moderate value $\lambda = 10$). Once again, the approximate solution is very accurate for the whole range of $\epsilon$, with a notable deviation only at $\epsilon$ close to 1. The perturbative solution starts to deviate for $\epsilon \geq 0.1$ (as the desorption rate $\lambda$ appears in the coefficients of the perturbative series, the validity range would of course depend on $\lambda$ used).

The situation of quasi-perfect adsorption ($kR \gg 1$) can be shown to be asymptotically equivalent with the case of short ejection distance ($a/R \ll 1$), as illustrated on Fig. 4.

3. Reflecting boundary and entrance time

Now we provide an explicit form for Eqs. (46), (40) in the presence of a perfectly reflecting sphere of radius $R_c$. We recall that the case $R_c > R$ (resp. $R_c < R$) is called an entrance (resp. exit) problem.

Using the expressions from Table I the coefficients $\eta_d$ and $X_n$ can be written as

$$\eta_2 = \frac{R^2}{4} \left( 1 - x^2 + \frac{2}{kR} \right) + \frac{R^2}{2} \left( \ln(x) - \frac{1}{kR} \right), \quad (51)$$

$$\eta_3 = \frac{R^2}{6} \left( 1 - x^2 + \frac{2}{kR} \right) + \frac{R^2}{3R} \left( 1 - \frac{x}{kR} \right), \quad (52)$$

and

$$X_n = \frac{x^n - \frac{n}{kR} + \left( R_c/R \right)^{2n} [x^{-n} - 1 + \frac{n}{kR}]}{1 + \frac{n}{kR} + \left( R_c/R \right)^{2n} [1 - \frac{n}{kR}]} \quad (d = 2), \quad (53)$$

$$X_n = \frac{x^n - \frac{n}{kR} + \frac{n}{n+1} \left( R_c/R \right)^{2n+1} [x^{-n} - 1 + \frac{n+1}{kR}]}{1 + \frac{n}{kR} + \frac{n}{n+1} \left( R_c/R \right)^{2n+1} [1 - \frac{n+1}{kR}]} \quad (d = 3). \quad (54)$$
FIG. 2: MFPT $\langle t_1 \rangle$ as a function of the desorption rate $\lambda$ for domains with partial adsorption $k = 1$: comparison between the exact solution (lines), approximate solution (circles) and perturbative solution (pluses) for 2D (left) and 3D (right), with $\epsilon = 0.01$ (top) and $\epsilon = 0.1$ (bottom). The other parameters are: $R = 1, D_1 = 1, a = 0.01$, no bias ($V = 0$), and $D_2$ takes three values 0.5, 1 and 5 (the truncation size is $N = 200$).

FIG. 3: MFPT $\langle t_1 \rangle$ as a function of the target size $\epsilon$ for domains with partial adsorption $k = 1$: Comparison between the exact solution (lines), approximate solution (circles) and perturbative solution (pluses) for 2D (left) and 3D (right). The other parameters are: $R = 1, D_1 = 1, a = 0.01, \lambda = 10$, no bias ($V = 0$), and $D_2$ takes three values 0.5, 1 and 5 (the truncation size is $N = 200$).

It is worth noting an interesting dependence of $\langle t_1 \rangle$ on the radius $R_c$ when $R_c$ and $a$ are both small. One finds in 2D

$$\frac{\partial \langle t_1 \rangle}{\partial R_c |_{R_c=0}} = 0, \quad \frac{\partial^2 \langle t_1 \rangle}{\partial R_c^2 |_{R_c=0}} = \left(\frac{D_2}{D_1} - \frac{\pi^2}{24}\right) \frac{4\lambda a R}{D_1 D_2},$$

(55)
Substituting the functions $\hat{\eta}$ and $\hat{\gamma}$, we have reduced the search time only if they are not too time costly, hence the condition on $1/k$ to be considered separately because $\hat{\eta}$ and $\hat{\gamma}$ are close to zero, the MFPT (green line) tends to be a constant which is equal to the MFPT on a segment of length $2\pi$. Here $d = 2$, $R = 1$, $D_1 = 1$, $D_2 = 5$, $\epsilon = 0$, no bias ($V = 0$) (the truncation size is $N = 200$).

and in 3D,

$$\frac{\partial(t_1)}{\partial R_c |_{R_c=0}} = \frac{\partial^2 (t_1)}{\partial R_c^2 |_{R_c=0}} = 0, \quad \frac{\partial^2 (t_1)}{\partial R_c^2 |_{R_c=0}} = \left( \frac{D_2}{D_1} - \frac{8}{27} [2 \ln (2/\epsilon) - 1] \right) \frac{9 \lambda a R}{8 D_1 D_2}. \quad (56)$$

In 2D, as long as $D_2/D_1 > \pi^2/24 \approx 0.411$ introducing a reflecting sphere of small radius $R_c$ increases the search time. This can be understood as follows: increasing $R_c < R$ increases the duration of flights between remote and unvisited regions of the sphere $r = R$, as these flights have to circumvent an obstacle at $r = R_c$. These long-range flights can reduce the search time only if they are not too time costly, hence the condition on $D_2 > D_2c$. The critical diffusion coefficient $D_{2c}$ increases with $R_c < R$ (Fig. 3).

### B. Case of a 1/\(r\) velocity field

We now examine the case of a radial $1/r$ velocity field $\vec{v}(r)$ characterized by a dimensionless parameter $\mu$:

$$\vec{v}(r) = -\frac{\mu D_2}{r^2} \hat{\vec{r}}. \quad (57)$$

Substituting the functions $\hat{f}$, $f_0$ and $f_n$ from Table II into Eq. (23), we can write the coefficients $\eta_d$ and $X_n$ as

$$\eta_2 = \frac{R^2}{2(2-\mu)} \left[ \left( 1 - x^2 + \frac{2}{kR} \right) + \frac{2R_c}{\mu} \left( R_c/R \right)^{2-\mu} \left( x^\mu - 1 - \frac{\mu}{kR} \right) \right], \quad (58)$$

$$\eta_3 = \frac{R^2}{2(3-\mu)} \left[ \left( 1 - x^2 + \frac{2}{kR} \right) + \frac{2R_c}{\mu} \left( R_c/R \right)^{3-\mu} \left( x^{\mu-1} - 1 - \frac{\mu-1}{kR} \right) \right], \quad (59)$$

$$X_n = \frac{x^{\gamma_0 + \gamma_n} - 1 - \gamma_n + \gamma_0 + \gamma_n + \gamma_0 \left( R_c/R \right)^{2\gamma_n} \left[ x^{\gamma_0 - \gamma_n} - 1 + \gamma_n - \gamma_0 \right]}{1 + \gamma_n + \gamma_0 + \gamma_n + \gamma_0 \left( R_c/R \right)^{2\gamma_n} \left[ 1 - \gamma_n - \gamma_0 \right]}, \quad (60)$$

where

$$\gamma_n = \begin{cases} \sqrt{n^2 + \mu^2/4} & (d = 2) \\ \sqrt{n(n+1) + (\mu -1)^2/4} & (d = 3) \end{cases} \quad (n \geq 1), \quad (61)$$

and $\gamma_0 = \mu/2$ in 2D and $\gamma_0 = (\mu -1)/2$ in 3D. Note that in the limit $\mu = 0$, one gets $\gamma_n = n \ (n \geq 0)$ in 2D, and $\gamma_0 = -1/2$ and $\gamma_n = n + 1/2$ in 3D, so that the above results are reduced to the previous case. The case $\mu = d$ has to be considered separately because $\hat{f}(r) = \frac{r^2}{4}(1 - 2 \ln r)$ in both 2D and 3D.
FIG. 5: MFPT $\langle t_1 \rangle$ as a function of the desorption rate $\lambda$ for an annulus with the inner radius $R_c = 0.5$ and the outer radius $R = 1$: comparison between the exact solution (lines), approximate solution (circles) and perturbative solution (pluses) for 2D (left) and 3D (right), with $\epsilon = 0.01$ (top) and $\epsilon = 0.1$ (bottom). The other parameters are: $D_1 = 1$, $a = 0.01$, $k = \infty$, no bias ($V = 0$), and $D_2$ takes three values $0.5$, $1$, and $5$ (the truncation size is $N = 200$).

FIG. 6: Critical ratio of the bulk-to-surface diffusion coefficients $D_{2c}/D_1$ in 2D, with perfect adsorption and no bias ($k = \infty$, $V = 0$) computed through Eq. (40) as a function of the target size $\epsilon$ for different values of $a$ and $R_c$: the exit problem ($R_c < 1$) on the left and the entrance problem ($R_c > 1$) on the right (the truncation size is $N = 200$).

The same expression for $\eta_d$ stands in the cases $\mu = 0$ in 2D and $\mu = 1$ in 3D:

$$\eta_d = \frac{R^2}{4} \left( 1 - x^2 + \frac{2}{kR} \right) + \frac{R^2}{2} \left( \ln x - \frac{1}{kR} \right).$$

When $R_c = 0$ and $\mu \geq d$, the MFPT to the sphere $\eta_d/D_2$ diverges, which causes the critical bulk diffusion coefficient $D_{2c}$ to diverge.

Figure 7 shows the MFPT $\langle t_1 \rangle$ as a function of the desorption rate $\lambda$ in the presence of a $1/r$ velocity field. As earlier, the exact, approximate and perturbative solutions are in an excellent agreement for a wide range of parameters. Figure 8 shows a similar dependence for different field intensities $\mu$ (if $\mu > 0$, the velocity field points towards the
origin, while $\mu < 0$ means that the velocity field points towards the exterior). For $R_c < R$ (resp. $R_c > R$), for a fixed $\lambda$ the search is on average faster as $\mu$ is more negative (resp. positive). Finally, in Fig. 9 the critical ratio of the bulk-to-surface diffusion coefficients is shown as a function of the target size, both in two and three dimensions. The dependence on the field intensity $\mu$ is stronger in 2D than in 3D.

For $R < R_c$, large absolute values of the drift coefficient increase $\langle t_1 \rangle$ and $D_2^c$ as (i) a strong outward drift ($|\mu| \gg |\mu_c|$) diminishes the probability for fast relocation through the central region; (ii) a strong inward drift ($\mu \gg |\mu_c|$) traps the diffusing molecule in the central region and increases $\eta_d/D_2$, the MFPT to the surface $r = R$ after ejection.

Although we derived the formulas for both 2D and 3D cases, the $1/r$ velocity field is mainly relevant in two dimensions as being a potential field. In three dimensions, the potential field exhibits $1/r^2$ dependence. This case, as well as many others, can be treated by our theoretical approach after solving Eqs. (10, 11, 13) for the functions $f_0(r)$, $\hat{f}(r)$ and $f_n(r)$. This is a classical problem in mathematical physics. For instance, the aforementioned velocity field $1/r^2$ in three dimensions involves hypergeometric functions, as shown in Appendix D.

C. Circular and spherical sectors

The above approach can also be applied for investigating the MFPTs in circular and spherical sectors of a given angle $\phi$ (Fig. 10). In most biological situation such as viral trafficking, $\phi \ll \pi$ but the arguments presented here stand for arbitrary $\phi$. For this purpose, the angular basis functions $V_n(\theta)$ can be rescaled by the factor $\phi/\pi$:

$$V_n(\theta) = \begin{cases} 1 & (n = 0), \\ \sqrt{2} \cos(n\pi/\phi) & (n > 0) \\ \sqrt{2n + 1} P_n(\cos(\theta\pi/\phi)) & (n \geq 0) \end{cases} \quad (d = 3),$$

FIG. 7: MFPT $\langle t_1 \rangle$ as a function of the desorption rate $\lambda$ in the presence of a $1/r$ velocity field: comparison between the exact solution (lines), approximate solution (circles) and perturbative solution (pluses) for 2D with $\mu = 1$ (left) and 3D with $\mu = 2$ (right), with $\epsilon = 0.01$ (top) and $\epsilon = 0.1$ (bottom). The other parameters are: $D_1 = 1$, $a = 0.01$, $k = \infty$, and $D_2$ takes three values $0.5$, $1$ and $5$ (the truncation size is $N = 200$).
FIG. 8: MFPT $\langle t_1 \rangle$ computed through Eq. (46) as a function of the desorption rate $\lambda$ for several values of the drift coefficient for $R_c = 0$ (left) and $R_c = \sqrt{2} > R = 1$ (right), in 2D. When $\mu > 0$, the velocity field points towards the origin, while $\mu < 0$ means that the velocity field points towards the exterior. For $R_c < R$ (resp. $R_c > R$), for a fixed $\lambda$ the search is on average faster as $\mu$ is more negative (resp. positive). Here $d = 2$, $R = 1$, $D_1 = 1$, $D_2 = 5$, $\epsilon = 0$, $k = \infty$ and $a = 0.05$ for $R_c = 0$ and $a = -0.05$ for $R_c = \sqrt{2}$ (the truncation size is $N = 200$).

FIG. 9: The critical ratio $D_{2c}/D_1$ as a function of the target size $\epsilon$ in 2D (left) and 3D (right) in the presence of a $1/r$ velocity field with three force intensities: $\mu = 0$ (solid line), $\mu = 1$ (dashed line) and $\mu = 1.5$ (dash-dotted line). The other parameters are: $R = 1$, $a = 0.01$, $R_c = 0$ and $k = \infty$ (the truncation size is $N = 200$).

and $V_{-n}(\theta) = V_n(\theta)$. These basis functions satisfy

$$-\Delta V_n(\theta) = \frac{\pi}{\phi^2} \rho_n V_n(\theta) \quad (0 \leq \theta \leq \phi, \ n \geq 0),$$

$$r^2 \left( \Delta_r + \frac{v(r)}{D_2} \partial_r \right) f_n(r) = \frac{\pi}{\phi^2} \rho_n f_n(r) \quad (n \in \mathbb{Z}).$$

As previously, we define two scalar products

$$(f, g) \rightarrow \langle f | g \rangle = \int_0^\phi f(\theta) g(\theta) d\mu_d(\theta),$$

$$(f, g) \rightarrow \langle f | g \rangle_\epsilon = \int_\epsilon^\phi f(\theta) g(\theta) d\mu_d(\theta),$$

where $d\mu_d(\theta)$ is the measure in polar ($d = 2$) or spherical ($d = 3$) coordinates for all $\theta \in [0, \phi]$:

$$d\mu_2(\theta) = \frac{d\theta}{\phi} \quad \text{and} \quad d\mu_3(\theta) = \frac{\pi \sin \theta}{\phi} d\theta.$$
1. Circular sector

One can easily extend the function $g_{\epsilon}(\theta)$ for a sector of angle $\phi$:

$$g_{\epsilon}(\theta) = \frac{1}{2}(\theta - \epsilon)(2\phi - \epsilon - \theta). \quad (65)$$

The direct computation yields

$$\langle g_{\epsilon}|1\rangle = \frac{(\phi - \epsilon)^3}{3\phi},$$

$$\langle g_{\epsilon}|V_n\rangle = -\frac{2\sqrt{\pi}}{\pi^2n^2}\left((\phi - \epsilon)\cos(\pi n\epsilon/\phi) + \phi \sin(\pi n\epsilon/\phi) \right),$$

and

$$I_{nn} = \frac{2m^2}{\pi(m^2 - n^2)} \left(\cos(\pi n\epsilon/\phi) \sin(\pi n\epsilon/\phi) \right) \left(\cos(\pi n\epsilon/\phi) \sin(\pi n\epsilon/\phi) \right) \left(\cos(\pi n\epsilon/\phi) \sin(\pi n\epsilon/\phi) \right)$$

that generalize formulas from Table I.

In order to complete the formulas for search times, one needs to compute the coefficient $\eta_d$ in Eq. (24) and the coefficients $X_n$ in Eq. (25) that incorporate the radial dependences (e.g., the velocity field $v(r)$ or the partial adsorption on the boundary). Since the functions $\hat{f}(r)$ and $f_0(r)$ remain unchanged (see Table II), the coefficient $\eta_d$ is given by previous explicit formulas: Eqs. (51, 52) with no bias ($V = 0$) and Eqs. (58, 59) for the velocity field $1/r$.

In turn, the functions $f_n(r)$ are modified for the sector because of the prefactor ($\pi/\phi$) in Eq. (64). For instance, if there is no bias, $f_n(r) = r^{n\pi/\phi}$, from which

$$X_n = \left( x^{n\pi/\phi} - 1 - \frac{n\pi\phi}{kr} \right) + \left( R_c/r \right)^{2n\pi/\phi} \left( x^{-n\pi/\phi} - 1 + \frac{n\pi\phi}{kr} \right)$$

that extends Eq. (53) in 2D. The case of the velocity field $1/r$ can be studied in a similar way.

Note that the small $\epsilon$ expansion (42) is modified as

$$\langle g_{\epsilon}|1\rangle = \left(1 - \cos\phi\right) \frac{2}{3} \ln\left(\sin\phi\sin\epsilon\right) + \left(1 - 2\cos(\phi/\pi)^2 \right) \sum_{n=1}^{\infty} \frac{X_n}{n^2 - \omega^2 X_n} \epsilon^2 + O(\epsilon^3). \quad (66)$$

2. Spherical sector

One can also compute the MFPT for a spherical sector of angle $\phi$. The angular basis functions $V_n(\theta)$ were given in Eq. (62), while the function $g_{\epsilon}(\theta)$ satisfying Eq. (27) with $g'_{\epsilon}(\phi) = 0$ is

$$g_{\epsilon}(\theta) = \frac{1 - \cos\phi}{2} \ln\left(\frac{1 - \cos\theta}{1 - \cos\epsilon}\right) + \frac{1 + \cos\phi}{2} \ln\left(\frac{1 + \cos\theta}{1 + \cos\epsilon}\right). \quad (67)$$

The integration yields

$$\langle g_{\epsilon}|1\rangle = \frac{(1 - \cos\phi)^2}{2} \ln\left(\frac{\sin\phi}{\sin\epsilon}\right) + \frac{1 + \cos(\phi)}{2} \ln\left(\frac{1 + \cos\epsilon}{1 + \cos\phi}\right) + \frac{\cos\phi - \cos\epsilon}{2}. \quad (68)$$

One also needs to compute the projections

$$\langle g_{\epsilon}|V_n\rangle = \sqrt{2n + 1} \frac{\pi}{2\phi} \int_0^\phi d\theta \sin\theta \ g_{\epsilon}(\theta) P_n(\cos(\theta\pi/\phi)). \quad (69)$$
When \( m = \pi / \phi \) is an integer, \( \cos(m \theta) \) can be expressed in powers of \( \cos \theta \),

\[
\cos(m \theta) = 2^{m-1} \cos^m \theta + m \sum_{j=1}^{[m/2]} (-1)^j \binom{m-2-j}{j} \cos^{m-2j} \theta,
\]

(here \([m/2]\) is the integer part of \( m/2 \), and we used the convention for binomial coefficients that \( \binom{n}{0} = 1 \) for any \( n \)) so that the computation is reduced to the integrals

\[
J_k = 2k \int_\epsilon^\phi d\theta \sin \theta \ g_n(\theta) [\cos(\theta)]^{k-1}
\]

\[
= (1 - \cos \phi) \left( [\cos \phi]^k - 1 \right) \ln \left( \frac{1 - \cos \epsilon}{1 - \cos \phi} \right) - (1 - \cos \phi) \sum_{j=1}^{k} \frac{[\cos \epsilon]^j - [\cos \phi]^j}{j}
\]

\[
+ (1 + \cos \phi) \left( [\cos \phi]^k + (-1)^k \right) \ln \left( \frac{1 + \cos \epsilon}{1 + \cos \phi} \right) - (1 + \cos \phi) \sum_{j=1}^{k} (-1)^j \frac{[\cos \epsilon]^j - [\cos \phi]^j}{j}.
\]

Using this formula, the projections \( \langle g_n | V_n \rangle \) can be easily and rapidly computed. Similarly, one can proceed with the computation of the matrix elements \( I_n(n', n') \),

\[
I_n(n', n') = \sqrt{2n + 1} \sqrt{2n' + 1} \frac{\pi}{2\phi} \int_\epsilon^\phi d\theta \sin \theta \ P_n(\cos(m \theta)) \left[ P_{n'}(\cos(m \theta)) - P_{n'}(\cos(m \epsilon)) \right],
\]

which are reduced to integrals of polynomials. When \( \pi / \phi \) is not integer, the above integrals can be computed numerically.

The radial functions \( f(r) \) and \( f_0(r) \) remain unchanged, while \( f_n(r) \) are given in Table II for the case with no bias. The coefficient \( \eta_d \) remains unchanged (cf. Eq. (52)), while the coefficients \( X_n \) are given by Eq. (60) with \( \gamma_0 = -1/2 \) and \( \gamma_n = \sqrt{n(n+1)(\pi/\phi)^2 + 1}/4 \). The case of the velocity field \( 1/r \) can be studied in a similar way.

3. Multiple targets on the circle

The MFPT to reach a target of angular extension \( 2 \epsilon \) in a circular sector of half aperture \( \phi = \pi / N_t > \epsilon \) (with integer \( m \)) (see Fig. 10) can actually be rephrased as the unconditional mean search time of \( N_t \) equally spaced targets of the same size \( 2 \epsilon \) on the circle of radius \( R \). Indeed in 2D, due to the reflection principle for random walks, the time spent to reach any of the \( m \) equally spaced targets on the circle is equal to the time required to reach a single target within a wedge with reflecting edges at \( \theta = \pm \pi / N_t \).

Figure 10 shows the MFPT \( \langle t_1 \rangle \) in 2D as a function of the number of targets \( N_t \), with a fixed total target length \( \epsilon_{\text{total}} = 0.01 \). This time decreases as \( 1/N_t^2 \), as one can expect from the limiting case \( \lambda = 0 \).

The same procedure in 3D would be to match the time spent to reach any of \( m \) equally spaced target caps of size \( 2 \epsilon < 2 \pi / N_t \) on a sphere with the time required to reach the target cap \( \theta \in [-\epsilon, \epsilon] \) of a cone with reflecting edges at \( \theta = \pm \pi / N_t > \epsilon \) (for all \( \phi \in [0, 2\pi] \)). Although not exact because the volume of a sphere cannot be filled by cones, this procedure is expected to provide an accurate approximation for the unconditional MFPT as soon as the number of targets is sufficiently high. For instance, in the case of 60 equally spaced targets on the sphere, the total excluded volume (i.e. the volume between cones) represents less than 1% of the total sphere volume. Knowing that the number of membranes or nuclear pores in a cell usually exceeds 100 \( \text{[12]} \), the results of Sec. IV C should to be relevant for cell trafficking studies.

V. CONCLUSION

We have developed a general theoretical approach to investigate searching of targets on the boundary of a confining medium by surface-mediated diffusion when the phases of bulk and surface diffusion are alternating. This is a significant extension of the previous results from \( \text{[13]} \) in order to take into account imperfect adsorption, the presence of an exterior radial force, multiple regularly spaced targets and general annulus shapes. The coupled PDEs
for the MFPTs $t_1(\theta)$ and $t_2(r, \theta)$ are reduced to an integral equation for $t_1(\theta)$ alone whose solution is then found in a form of Fourier series. Linear relations for the Fourier coefficients involve an infinite-dimensional matrix whose inversion yields an exact but formal solution for the MFPTs. A finite-size truncation of this matrix yields a very accurate and rapid numerical solution of the original problem. In addition, we propose a fully explicit approximate solution as well as a perturbative one. Although both solutions are derived under the assumption of small targets, the approximate solution turned out to be remarkably accurate even for large targets. We illustrate the practical uses of the theoretical approach and the properties of the MFPTs by considering in detail several important examples, for instance diffusion in a velocity $1/r$ field.

The developed approach forms the theoretical ground for a systematic study of surface-mediated processes which are relevant for chemical and biochemical reactions in porous catalysts and living cells. From the mathematical point of view, the remarkable accuracy of the approximate solution even beyond the expected range of validity remains striking and requires further clarifications.

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Appendix A: Boundary condition for the MFPT

We check that Eq. (4) giving the discontinuity relation of the MFPT between the semi-reflecting surface and the bulk can be derived either from a discrete lattice model or from a standard forward equation on conditional probabilities [4, 46].

1. A discrete lattice approach

Let us first consider a 2D geometry in which the bulk and surface states are two lattices with radial and angular steps $\Delta r$ and $\Delta \theta$. The circular geometry imposes the relation on the radial and angular steps in the bulk at the radius $r$: $\Delta r(r) = r \Delta \theta$. At each time step $\Delta t$, the molecule moves to one of its closest neighboring sites. The value of the time step is adjusted according to the position of the molecule:

$$\Delta t(i, r) = \sqrt{r \Delta \theta / D_i},$$

where $i = 1$ for the molecule on the adsorbing surface and $i = 2$ for the molecule in the bulk. This choice maintains in the continuous limit a spatially constant value for the diffusion coefficient $D_2$. At $r = R$, a molecule may either (i) get
reflected to \( r = R - \Delta r \) with probability \( q/2 \), (ii) get adsorbed onto the surface with probability \((1 - q)/2 \), (iii) move along the angular direction, with probability \(1/2 \) (see Fig. 11). Let the random variable \( \tau_2(r, \theta) \) (resp. \( \tau_1(\theta) \)) denote the first passage time (FPT) for a molecule initially in the bulk at \((r, \theta)\) (resp., on the surface at \( \theta \)). The probability for \( \tau_2(r, \theta) \) to be \( t = m\Delta t \) \((m \in \mathbb{N})\), is equal to an average of the probabilities of the FPT from neighboring sites to be \((m - 1)\Delta t\):

\[
P\left\{ \tau_2(R, \theta) = m\Delta t \right\} = \frac{q}{2} P\left\{ \tau_2(R - \Delta r, \theta) = (m - 1)\Delta t \right\} + \frac{1 - q}{2} P\left\{ \tau_1(\theta) = (m - 1)\Delta t \right\}
+ \frac{1}{4} P\left\{ \tau_2(R, \theta + \Delta \theta) = (m - 1)\Delta t \right\} + \frac{1}{4} P\left\{ \tau_1(R, \theta - \Delta \theta) = (m - 1)\Delta t \right\}.
\] (A1)

The mean FPT in the discrete lattice model is defined as

\[
t_2(r, \theta) \equiv \sum_{m=1}^{\infty} m \Delta t \ P\{ \tau_2(r, \theta) = m\Delta t \}.
\] (A2)

Combining this definition with Eq. (A1) leads to

\[
t_2(R, \theta) = \frac{q}{2} t_2(R - \Delta r, \theta) + \frac{1 - q}{2} t_1(\theta) + \frac{1}{4} (t_2(R, \theta + \Delta \theta) + t_2(R, \theta - \Delta \theta)) + \Delta t.
\]

The Taylor expansion of \( t_2(R, \theta) \) gives

\[
q\Delta r \frac{\partial t_2}{\partial r} \bigg|_{r=(R,\theta)} + \frac{\Delta \theta^2}{\Delta \theta} \frac{\partial^2 t_2}{\partial \theta^2} \bigg|_{r=(R,\theta)} = (1 - q) (t_1(\theta) - t_2(R, \theta)) + O(\Delta r^2, \Delta \theta^3, \Delta t).
\] (A3)

Following [44, 47], the adsorption coefficient is defined as

\[
k = \frac{1 - q}{q} \frac{1}{R \Delta \theta}.
\] (A4)

In the continuous limit, when all \( \Delta r, \Delta \theta, \Delta t \) tend to 0 with \( \Delta r/\Delta \theta = r \) and \( D_2 \equiv \Delta r^2/(2\Delta t) \) constant, Eq. (A3) turns out to be expressed in terms of \( k \) only:

\[
\frac{\partial t_2}{\partial r} \bigg|_{r=(R,\theta)} = k (t_1(\theta) - t_2(R, \theta)) + o(1).
\] (A5)

Indeed \( \Delta t/\Delta r = o(1) \) and \( \Delta \theta^2/\Delta r = o(1) \) in this limit. For a perfectly adsorbing boundary we have \( q = 0 \), \( k \to \infty \), which is indeed compatible with the continuity relation \( t_2(R, \theta) = t_1(\theta) \) used in Ref [4]. For a perfectly reflecting boundary \( q = 1 \), \( k \to 0 \) and \( \partial_r t_2(r, \theta) = 0 \) at \( r = R \) [4]. This is indeed the condition that we imposed on the boundary \( r = R_c \) in Sec. III.

![FIG. 11: A discrete lattice model. Regular \( \Delta \theta \) slicing imposes \( \Delta t \) and \( \Delta r \) to vary over the domain \( S \) in order to maintain an isotropic diffusion constant \( D_2 \). Only one quadrant is presented.](image-url)
2. Equivalence with a forward boundary condition

We now check that the MFPT condition of Eq. (4) is also compatible with the following boundary condition on the conditional probability [4]

\[
\frac{\partial p(r, \theta, t|x, t')}{\partial r} \bigg|_{r=R} = -k \ p((r, \theta)|x, t') \bigg|_{r=R}, \quad (A6)
\]

where \( p(x, t|x', t') \) is the probability for a molecule to be at \( x \) at time \( t \) provided that the molecule was at \( x' \) at an earlier time \( t' < t \). We denote the spatial coordinate \( x = (r, \theta) \) if the molecule is in the bulk and \( x = \theta \) if it is adsorbed on the surface.

We follow the standard method presented in [46]. The stochastic process under study is Markovian hence the conditional probabilities satisfy the Chapman-Kolmogorov equation, with \( t > s > t' \),

\[
p(x, t|x', t') = \int_S d\nu(y) \ p(x, t|y, s) p(y, s|x', t') + \int_0^\pi Rd^{-1} d\nu(\theta) \ p(x, t|\theta, s) p(\theta, s|x', t'),
\]

where \( S = (R, R_c) \times [0, \pi] \) and the measure \( d\nu \) is

\[
d\nu_2(\theta) = 2 \ drd\theta, \quad d\nu_2(\theta) = 2 \ d\theta, \quad d\nu_3(\theta) = 2\pi r \ sin \theta \ drd\theta, \quad d\nu_3(\theta) = 2\pi \ sin \theta d\theta.
\]

Taking the derivative with respect to the intermediate time \( s \) leads to the expression

\[
0 = \frac{\partial}{\partial s} p(x, t|x', t') = \int_S d\nu(y) \ \frac{\partial p(x, t|y, s)}{\partial s} p(y, s|x', t') + \int_S d\nu(y) \ p(x, t|y, s) \frac{\partial p(y, s|x', t')}{\partial s} + \int_0^\pi d\nu(\theta) \ \frac{\partial p(x, t|\theta, s)}{\partial s} p(\theta, s|x', t') + \int_0^\pi d\nu(\theta) \ p(x, t|\theta, s) \frac{\partial p(\theta, s|x', t')}{\partial s}.
\]

The backward Chapman-Kolmogorov equations read

\[
\frac{\partial p(x, t|\theta, s)}{\partial s} = -\frac{D_1}{R^2} \Delta_{\theta} p(x, t|\theta, s) + \lambda \bigg\{ p(x, t|\theta, s) - p(x, t|R - a, \theta, s) \bigg\}, \quad (A8)
\]

\[
\frac{\partial p(x, t|\theta, s)}{\partial s} = -D_2 \Delta_{(r,\theta)} p(x, t|\theta, s) - v(r) \ \nabla p(x, t|(r, \theta), s).
\]

The forward Chapman-Kolmogorov equations are

\[
\frac{\partial p(\theta, s|x', t')}{\partial s} = +\frac{D_1}{R^2} \Delta_{\theta} p(\theta, s|x', t') - \lambda \ p(\theta, s|x', t') - D_2 \frac{\partial p((r, \theta), s|x', t')}{\partial r} \bigg|_{r=R}
\]

\[
+ v(R) \ p((R, \theta), s|x', t'), \quad (A10)
\]

\[
\frac{\partial p(y, s|x', t')}{\partial s} = D_2 \Delta_y \ p(y, s|x', t') - \nabla (v(r)p(y, s|x', t'))
\]

\[
+ \lambda \ \left( \frac{R}{R - a} \right)^{-d-1} \delta^d(\mathbf{r} - (R - a, \theta)) \ p(\theta, s|x', t'). \quad (A11)
\]

The terms in Eqs. (A10) and (A11) are justified as follows: (i) \(-\lambda \ p(\theta, s|x', t')\) corresponds to a constant rate of desorption from the surface to the bulk; (ii) \(-D_2\partial_{\theta} p((r, \theta), s|x', t')\) is the flux into the surface due to diffusion; (iii) \(v(R) \ p((R, \theta), s|x', t')\) is the flux into the surface due to the drift (by convention, \(v(R) > 0\) for a velocity drift field oriented towards the exterior); (iv) \(\lambda \ [R/(R - a)]^{-d-1} \delta^d(\mathbf{r} - (R - a, \theta)) \ p(\theta, s|x', t')\) corresponds to the flux into the bulk due to the desorption from the surface and the ejection at a distance \(a\) (\(\delta\) being the Dirac delta function).

For convenience, we will use the shorthand notations \( \bar{p}(y, s|x', t') \equiv p(y) \), \( \bar{p}(x, t|y, s) \equiv \bar{p}(y) \) and \( p(\theta, s|x', t') \equiv \bar{p}(\theta) \). Substituting the Chapman-Kolmogorov Eqs. (A8 - A11) into Eq. (A7) leads to the following equation

\[
0 = \int_S d\nu(y) \ [-D_2 \Delta_{\theta} \bar{p}(y)] p(y)
\]

\[
+ \int_S d\nu(y) \bar{p}(y) \left[ D_2 \Delta_{\theta} \bar{p}(y) + \lambda \left( \frac{R}{R - a} \right)^{-d-1} \delta^d(\mathbf{r} - (R - a, \theta)) \ p(\theta) \right]
\]

\[
+ \int_0^\pi Rd^{-1} d\nu(\theta) \left[ -\frac{D_1}{R^2} \Delta_{\theta} \bar{p}(\theta) + \lambda \bar{p}(\theta) - \bar{p}(R - a, \theta) \right] \ p(\theta, s)
\]

\[
+ \int_0^\pi Rd^{-1} d\nu(\theta) \bar{p}(\theta) \left[ \frac{D_1}{R^2} \Delta_{\theta} \bar{p}(\theta) - \lambda \ p(\theta) - D_2 \frac{\partial p((r, \theta), s|x', t')}{\partial r} \bigg|_{r=R} \right].
\]
Integrating over the space and time variables \( x \), one notices that

\[
\int_S d\nu(y) \left( \frac{R}{R-a} \right)^{d-1} \delta^d(x - (R-a, \theta)) \bar{p}(r, \theta) p(\theta) + \int_0^\pi R^{d-1} d\nu(\theta) \bar{p}(R-a, \theta)p(\theta) = 0,
\]

and that the four terms proportional to \( \lambda \) vanish. Two terms with angular Laplacians also cancel each other due to the hermiticity of the angular diffusion operator:

\[
\int_0^\pi d\nu(\theta) \Delta_\theta \bar{p}(\theta)p(y) = \int_0^\pi d\nu(\theta) \Delta_\theta \bar{p}(\theta)\bar{p}(y) = 0.
\]

The divergence theorem yields the integral over the frontier \( \partial S \) of the annulus \( S \):

\[
0 = D_2 \int_{\partial S} d\nu(\theta) \left[ \frac{\partial p(r, \theta)}{\partial r} \bigg|_{r=R} \bar{p}(r, \theta) - \frac{\partial \bar{p}(r, \theta)}{\partial r} \bigg|_{r=R} p(r, \theta) - \frac{\partial p(r, \theta)}{\partial r} \bigg|_{r=R} \bar{p}(\theta, s) \right].
\]

This equality can be satisfied only if:

\[
\frac{\partial \bar{p}(r, \theta, s)}{\partial r} \bigg|_{r=R} = \frac{\partial p(r, \theta, s)}{\partial r} \bigg|_{r=R} \left[ \bar{p}(r, \theta, s) - \bar{p}(\theta, s) \right]. \tag{A12}
\]

Inserting the forward boundary condition \( (A6) \) into Eq. \( (A12) \) gives the boundary condition on the backward probability distribution

\[
\frac{\partial p(x, t|r, \theta, s)}{\partial r} \bigg|_{r=R} = k \left\{ p(x, t|\theta, s) - p(x, t|r, \theta, s) \right\} \bigg|_{r=R}.
\]

Integrating over the space and time variables \( x \) and \( t \), we obtain the boundary condition for the MFPT:

\[
\frac{\partial t_2}{\partial r} \bigg|_{r=R} = k \{ t_1(\theta) - t_2(R, \theta) \} \quad (0 \leq \theta \leq \pi),
\]

which identifies with Eq. \( (\ref{eq:t_2}) \).

**Appendix B: Interpretation of \( \eta_d/D_2 \) as a mean first passage time**

We consider the probability density \( \Pi(\tilde{\theta}|\theta) \) for a molecule initially at the bulk point \( (R-a, \theta) \) to first reach the surface \( r=R \) at the angle \( \theta \). The mean duration of this Brownian path is denoted \( t_c(\tilde{\theta}|\theta) \).

The MFPT \( t_2(R-a, \theta) \) to reach the target can be expressed as the averaged sum of the MFPT to reach a point \( (R, \bar{\theta}) \) on the surface and the MFPT to reach the target from this point of the surface, the probability density for the first hitting point \( (R, \bar{\theta}) \) being the harmonic measure \( \Pi(\tilde{\theta}|\theta) \):

\[
t_2(R-a, \theta) = \int_0^\pi \left( t_c(\tilde{\theta}|\theta) + t_1(\tilde{\theta}) \right) \Pi(\tilde{\theta}|\theta) d\mu_d(\tilde{\theta}). \tag{B1}
\]

In 2D and in the general case considered in Sec. \( \Pi \) the probability density \( \Pi(\tilde{\theta}|\theta) \) is

\[
\Pi(\tilde{\theta}|\theta) = 1 + 2 \sum_{n=1}^\infty (X_n + 1) \cos(n(\tilde{\theta} - \theta)), \tag{B2}
\]

where \( X_n \) is given by Eq. \( (\ref{eq:X_n}) \). Substitution of this expression in Eq. \( (B1) \) leads to

\[
t_2(R-a, \theta) = \langle t_1 \rangle + \frac{1}{\pi} \int_0^\pi t_c(\tilde{\theta}|\theta) \Pi(\tilde{\theta}|\theta) d\tilde{\theta} + \frac{2}{\pi} \sum_{n=1}^\infty (X_n + 1) \int_0^\pi \cos(n(\tilde{\theta} - \theta)) t_1(\tilde{\theta}) d\tilde{\theta}. \tag{B3}
\]

Identification with Eq. \( (\ref{eq:t_3}) \) gives

\[
\frac{\eta_d}{D_2} = \frac{1}{\pi} \int_0^\pi t_c(\tilde{\theta}|\theta) \Pi(\tilde{\theta}|\theta) d\tilde{\theta} = \frac{1}{\pi} \int_0^\pi t_c(\tilde{\theta}|0) \Pi(\tilde{\theta}|0) d\tilde{\theta}, \tag{B4}
\]
which identifies $\eta_4/D_2$ as the MFPT to the circle of radius $R$. In particular, it can be shown that in the 2D case of Sec. IV A 1

$$\Pi(\tilde{\theta}|\theta) t_c(\tilde{\theta}|\theta) = \frac{R^2}{4D_2} \left( 1 - (r/R)^2 \right) \left( 1 + \sum_{n=1}^{\infty} \frac{(r/R)^n}{2(1+n)} \cos(n(\theta - \tilde{\theta})) \right).$$

(B5)

One can verify that the substitution of this expression into Eq. (B4) leads to the well known result of Eq. (47), $\eta_2 = R^2(1 - x^2)/4$.

The argument leading to Eq. (B4) can be extended to the 3D case with the following expression for the probability density:

$$\Pi(\tilde{\theta}|\theta) = 1 + \sum_{n=1}^{\infty} (2n + 1)(X_n + 1)P_n(\cos \theta)P_n(\cos \tilde{\theta}).$$

(B6)

Appendix C: Matrix elements $I_c(n,m)$ in 3D

The matrix elements $I_c(n,m)$ in 3D were computed in [1]. An explicit formula for non-diagonal elements $(m \neq n)$ is given in Table I. In turn, the diagonal elements $I_c(n,n)$ can be expressed as

$$I_c(n,n) = -P_n(u) \frac{n P_n(u) - P_{n-1}(u)}{n+1} + \frac{F_n(u) + 1}{2n+1}, \quad u = \cos \epsilon,$n

through the function $F_n(u)$, for which the explicit representation was derived in [1]

$$F_n(u) = u[P_n^2(u) + 2P_{n-1}^2(u) + \ldots + 2P_0^2(u) + P_0(u)] - 2P_n(u)P_{n-1}(u) - 2P_{n-1}(u)P_{n-2}(u) - \ldots - 2P_1(u)P_0(u) + u

= \sum_{k=1}^{n} [2(u - 1)P_k^2(u) + [P_k(u) - P_{k-1}(u)]^2] - (u - 1)P_n^2(u) + (u - 1)P_0^2(u) + u. \quad \text{(C1)}$$

One can also check that this function satisfies the recurrence relations

$$F_n(u) = F_{n-1}(u) + u[P_n^2(u) + P_{n-1}^2(u)] - 2P_n(u)P_{n-1}(u), \quad F_0(u) = u. \quad \text{(C2)}$$

that simplifies its numerical computation. Note that $F_n(\pm 1) = F_{n-1}(\pm 1) = \ldots = \pm 1$.

Appendix D: Case of a $1/r^2$ velocity field

We now examine the 3D case of a radial $1/r^2$ velocity field $\vec{v}(r)$, which is characterized by the dimensionless parameter $\mu$:

$$\vec{v}(r) = -\frac{\mu D_2 R}{r^3} \hat{r}. \quad \text{(D1)}$$

The function $\hat{f}$ is expressed as

$$\hat{f}(r) = -\frac{r^2}{6} - \frac{rR\mu}{6} + \frac{R^2 \mu^2}{6} e^{-\mu R/r} \text{Ei}(\mu R/r), \quad \text{(D2)}$$

where $\text{Ei}(z)$ is the exponential integral:

$$\text{Ei}(z) = \int_{-\infty}^{z} \frac{e^x}{x} \, dx.$$

The function $f_0$ is

$$f_0(r) = \frac{1 - e^{-\mu R/r}}{\mu} \quad \text{(D3)}$$
Radial functions $f_n(r)$ are found as products of powers and confluent hypergeometric functions $1F_1$ of $r$:

$$f_n(r) = r^n \left(-n, -2n, -\mu R/r\right) \quad (n > 0),$$
$$f_{-n}(r) = r^{-n-1} \left(n+1, 2n+2, -\mu R/r\right) \quad (n > 0).$$

For $n = 0$, this expression is reduced to $e^{-\mu R/r}$. In the limit $\mu \to 0$, the above functions reduce to $r^n$ and $r^{-n-1}$ from the earlier case $\mu = 0$. On the one hand we have

$$\partial_r f_n(r) = n r^{n-1} \left(-n+1, -2n, -\mu R/r\right) \quad (n > 0),$$
$$\partial_r f_{-n}(r) = -(n+1) r^{-n-2} \left(n+2, 2n+2, -\mu R/r\right) \quad (n > 0),$$
from which

$$\frac{\partial_r f_n(r)}{\partial_r f_{-n}(r)} = -\frac{n}{n+1} r^{2n+1} \left(-n+1, -2n, -\mu R/r\right) \frac{1}{1F_1(n+2, 2n+2, -\mu R/r)}.$$ (D6)

On the other hand we have

$$\partial_r \tilde{f}(r) = \frac{1}{6} \left[ (\mu R)^3 \frac{1}{r^2} e^{-\mu R/r} \text{Ei}(\mu R/r) - \frac{(\mu R)^2}{r} - (\mu R) - 2 \right],$$
$$\partial_r f_0(r) = -\frac{R}{r^2} e^{-\mu R/r},$$
from which

$$\frac{\partial_r \tilde{f}(r)}{\partial_r f_0(r)} = -\frac{\mu}{6} \left[ (\mu R)^2 \text{Ei}(\mu R/r) - e^{-\mu R/r} \left[ \mu R r + r^2 - 2r^3/(\mu R) \right] \right].$$ (D7)

This last expression is needed to compute the quantities $\eta_d$ and $X_n$.

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