

First-passage statistics of confined colloids

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(Received 6 January 2026; accepted 23 July 2026; published 14 September 2026)

The encounter of diffusing entities underlies a wide range of natural phenomena. The dynamics of these first-passage dynamics are strongly influenced by confining geometries. Confinement modifies microscopic diffusion through conservative and hydrodynamic interactions, making it essential for realistic modeling. In this article, we investigate how confinement affects the first-passage statistics of a diffusing particle. Using *state-of-the-art* holographic microscopy combined with advanced statistical inference, we probe this motion with nanometric precision. Our experimental and numerical results show that confinement can either hinder or enhance first-passage kinetics, depending on the spatial direction. In particular, a wall-normal target finding is accelerated by confinement-induced non-Gaussian displacement statistics—which increases the probability of rare, large displacements—compared to an analogous situation relying on a Gaussian process. The results presented hereafter carry implications for confined chemical reactions and biological *winners-take-all* processes near boundaries.

DOI: [10.1103/6bzx-34wr](https://doi.org/10.1103/6bzx-34wr)

I. INTRODUCTION

The efficiency of stochastic target finding, where noise-driven particles locate specific sites, is fundamental to diverse natural and engineered systems. Examples include chemical and prebiotic reactions [1,2], the transfer of information in neuronal synapses [3–5], DNA-protein interactions [6–9], or even stock-market predictions [10,11]. Specifically, micro- or nanosized entities moving in a viscous liquid typically undergo Brownian motion, a diffusion process driven by thermal fluctuations [12–15]. The dynamics and success of the associated random search processes are profoundly influenced by the complex confining geometries of the local environments, such as blood cells flowing in vessels [16,17], transmitter and receptor proteins in synaptic junctions [3,4], or ions in chemical solutions [2]. Such biological or chemical environments are inherently complex and significantly modulate particle diffusivity and overall behavior.

In recent decades, environment-dependent particle dynamics has fostered extensive research efforts, in both idealized and more realistic scenarios. In the case of purely viscous fluids, confining boundaries are known to hydrodynamically hinder [18] or speed up [19,20] diffusion, depending on the boundaries' wetting and stickiness properties [21]. Such systems exhibit anisotropic spatial variations in diffusivity [22]. In addition, diffusing entities can be subjected to

electrostatic or van der Waals forces [23] originating from confining boundaries or other diffusing entities [9,24]. Interestingly, the combination of confinement-induced static and hydrodynamic interactions often leads to non-Gaussian dynamics [25–28]—in stark contrast with the Gaussian dynamics of unconfined, bulk systems. Consequently, and given the importance and ubiquity in biology and chemistry of target-finding situations near boundaries, it is essential to study how the properties of a confining environment influence the problem of target finding. This problem is fundamentally probabilistic and is analyzed using the statistics of the first-passage time (FPT)—the random time it takes a diffusively searching entity to first reach a specific target [29,30]. Despite extensive studies on FPT statistics in diverse systems [5,30–35], the fundamental case involving classical static and hydrodynamic interactions with a single wall remains unexplored. This work directly addresses this gap.

Experimentally monitoring rare events like colloidal target finding is challenging, as it demands a technique that spans broad spatial and temporal scales. To overcome this obstacle, we employ here holographic microscopy to capture three-dimensional trajectories of isolated colloidal particles diffusing in a viscous liquid near a planar wall. Statistical inference of these trajectories reveals non-Gaussian displacement distributions, indicating a heightened probability of large, rare displacements. These confinement-induced non-Gaussian dynamics appear to accelerate FPT processes, hence offering a perspective on target-reaching scenarios in realistic, bounded environments.

II. METHODS

In this study, the confined diffusion we refer to consists of the Brownian motion of an isolated negatively surface-charged spherical polystyrene colloid, of radius a_p (ranging

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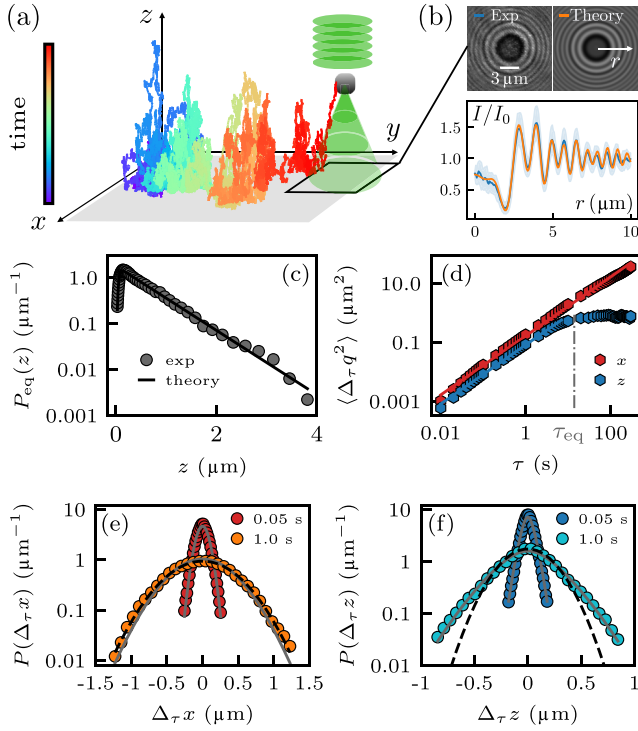


FIG. 1. Monitoring confined diffusion via Mie holography [37]. (a) Three-dimensional trajectory of a spherical polystyrene colloid of radius $a_p = 1.48 \mu\text{m}$ diffusing in a viscous liquid near a rigid glass wall. (b) Raw experimental (Exp) hologram, and corresponding theoretical hologram, with their respective radial intensity profiles. (c) Experimental (exp) equilibrium probability distribution function, P_{eq} , for the altitude z of the colloid (gray circles), with its corresponding fit to Eq. (1) (black line), leading to $B = 6.96$, $l_D = 33 \text{ nm}$, and $l_B = 604 \text{ nm}$. (d) Mean squared displacements $\langle \Delta_\tau q^2 \rangle$ as functions of the time lag τ , in the x direction (red) and the z direction (blue). The corresponding colored solid lines depict the best fits to Eq. (3) in both directions, leading to $D_x = 0.542 D_0$ and $D_z = 0.268 D_0$. The equilibrium time is indicated with the dot-dashed vertical line. (e) Probability distribution function, $P(\Delta_\tau x)$, of the colloid's in-plane displacements $\Delta_\tau x$ over a time τ , for $\tau = 50 \text{ ms}$ (red dots) and 1 s (orange dots). The gray solid lines depict the best fits to the theoretical prediction detailed in Refs. [27,37], with the same parameter values as in panel (c). The black dashed line corresponds to the Gaussian prediction of Eq. (6), with the diffusion coefficient D_x from panel (d). (f) Same as panel (e) but in the z direction.

from 1 to $3 \mu\text{m}$) and density $\rho_p \simeq 1050 \text{ kg/m}^3$, diffusing in a viscous water-ethylene-glycol mixture of density ρ_m and viscosity η_m (ranging from 1000 to 1050 kg/m^3 and from 0.95 to 3.2 mPa s , respectively), and near a negatively surface-charged rigid glass wall, as illustrated in Fig. 1(a).

The microscopy method used to monitor the confined diffusion is based on Lorenz-Mie holography [36–38], and is schematized in Fig. 1(a). The sample preparation protocol is detailed in Appendix G. A plane wave (wavelength 532 nm ; output power 4 mW) illuminates the colloid, which scatters part of the incident wave. The interference between the incident and scattered waves produces fringes, which recast in a pattern called a hologram. An experimental hologram is displayed in Fig. 1(b). The experimental hologram is then fitted

to the Lorenz-Mie theory, which leads to the determination of the colloid's radius and refractive index n_p (allowing for *in situ* calibration of each experiment), and of the colloid's three-dimensional position with nanometric precision, as suggested by the agreement between the experimental and theoretical holograms and associated radial intensity profiles represented in Fig. 1(b).

In practice, holograms are recorded via a $100\times$ Olympus immersion-oil objective and a Basler camera, operating at a frame rate of 100 frames per second with an exposure time of 2 ms , over a total recording duration of 1 h . The reconstructed colloid's trajectory $(x(t), y(t), z(t))$ [see Fig. 1(a)] is then analyzed in order to infer characteristic features of confined diffusion, with (x, y, z, t) denoting, respectively, the colloid's in-plane position, the colloid-wall gap distance, and the time. We stress that the specific trajectories used in the current article are original and distinct from the ones used in Refs. [27,37].

The first feature described here stems from the z trajectory and allows for a quantitative description of the confinement considered. By binning the z domain and counting positional occurrences at long times, one gets the equilibrium probability distribution function P_{eq} of presence in the z direction, as displayed in Fig. 1(c). While the electrostatic repulsion between the negatively charged colloid and wall sets the lower boundary of the z domain, an effective upper boundary is set by the colloid's buoyant weight. Specifically, P_{eq} directly depends on the potential U_{eq} governing the process, as

$$P_{\text{eq}}(z) = \mathcal{N} e^{-U_{\text{eq}}(z)/(k_B \Theta)}, \quad (1)$$

where $\mathcal{N}$ is a normalization constant, and k_B and Θ denote the Boltzmann constant and room temperature, respectively. The potential U_{eq} reads

$$\frac{U_{\text{eq}}}{k_B \Theta} = B e^{-z/l_D} + \frac{z}{l_B}. \quad (2)$$

In the above equation, B quantifies the magnitude of surface charges [39], l_D is the Debye length [40], i.e., the ionic screening length of the electrostatic repulsion, and $l_B = \frac{k_B \Theta}{\frac{4}{3} \pi a_p^3 \Delta \rho g}$ (with $\Delta \rho = \rho_p - \rho_m$ the density mismatch and g the local gravity constant) is the Boltzmann length [14], i.e., the typical extent of the reachable z positions. In fact, we scan the confinement strength via the Boltzmann length, by adding ethylene glycol to water solutions and thus tuning the density mismatch (see Appendix B).

We now focus on the confined-diffusion dynamics. The canonical observable related to diffusion, namely, the mean squared displacement (MSD) $\langle \Delta_\tau q^2 \rangle$ (where $q = x, y, z$, $\Delta_\tau q = q(t + \tau) - q(t)$, and $\langle \cdot \rangle$ denotes the average over the time t), is shown in Fig. 1(d). The process is anisotropic and the diffusivity is lower in the normal direction than in the transverse one, as z -data points are systematically lower than x -data points. Nevertheless, at short times, both MSDs are still linear with respect to time, as in bulk configurations, and are ruled by the classical diffusion law:

$$\langle \Delta_\tau q^2 \rangle = 2D_q \tau, \quad (3)$$

where D_q is the diffusion coefficient of the process. In the absence of a wall, this diffusion coefficient would be the bulk

one D_0 , which obeys the Stokes-Einstein relation:

$$D_0 = \frac{k_B \Theta}{\gamma}, \quad (4)$$

where $\gamma = 6\pi\eta_m a_p$ is the bulk Stokes drag coefficient. However, the confining wall, through the associated no-slip boundary condition, amplifies the viscous drag and makes it not only anisotropic but also z dependent [41,42]. Consequently, the colloid's real diffusivity $d_q(z)$ becomes z dependent (see Appendix A), leading to the z -averaged diffusion coefficient D_q , given by [37]

$$D_q = \int_0^{+\infty} dz P_{eq}(z) d_q(z). \quad (5)$$

The average diffusion coefficient D_q is thus reduced compared to D_0 . Besides, we stress here that the z -MSD saturates at longer times, to a value that scale as l_B^2 [37]. This effective trapping directly results from the potential U_{eq} in which the colloid lies. This saturation allows to define the characteristic equilibration time $\tau_{eq} \sim l_B^2/(2D_z)$ of the process, which is the timescale over which the colloid has visited the typically reachable z positions.

Our statistical inference goes further than the simple MSDs, i.e., the variances of the displacement distributions, as one can in fact reconstruct the full distributions $P(\Delta_\tau x)$ and $P(\Delta_\tau z)$ for, respectively, in-plane and normal displacements over a duration τ . For both these observables, which are displayed in Figs. 1(e) and 1(f), we observe a broadening over time, highlighting the diffusive nature of confined Brownian motion. Moreover, for our parameter range, and despite the presence of non-Gaussianities [27,37] due to a multiplicative noise, the in-plane distribution can be fairly approximated by a Gaussian law, P_{Gauss} , that reads

$$P_{Gauss}(\Delta_\tau q) = \frac{1}{\sqrt{4\pi D_q \tau}} e^{-\frac{\Delta_\tau q^2}{4D_q \tau}}. \quad (6)$$

As such, the in-plane process resembles a simple slowed-down ($D_x \leq D_0$) bulklike Gaussian process. In sharp contrast, we observe the emergence of strong non-Gaussian tails in the z -displacement distribution, mostly due to the trapping potential—another clear signature of the confinement-induced symmetry breaking between spatial directions. However, a central question emerges for our purpose here: Do such non-Gaussianities, associated with an increased probability of the rarest events, impact the FPT statistics? Before turning to this open question, we first investigate the target-finding dynamics of a colloid diffusing in the bulk, far from any boundary, in order to recover the classical results as a reference for future comparison.

III. RESULTS

In this section, we discuss the reference situation of bulk diffusion. Rationalizing the behavior of a colloid diffusing freely in the bulk [see Fig. 2(a)] starts from the bulk Langevin equation [43]:

$$m\ddot{x}(t) = -\gamma\dot{x}(t) + \sqrt{2k_B\Theta\gamma}\xi(t), \quad (7)$$

where x denotes the coordinate of the particle (the other spatial directions being equivalent in the bulk) and $\xi(t)$ is a Gaussian

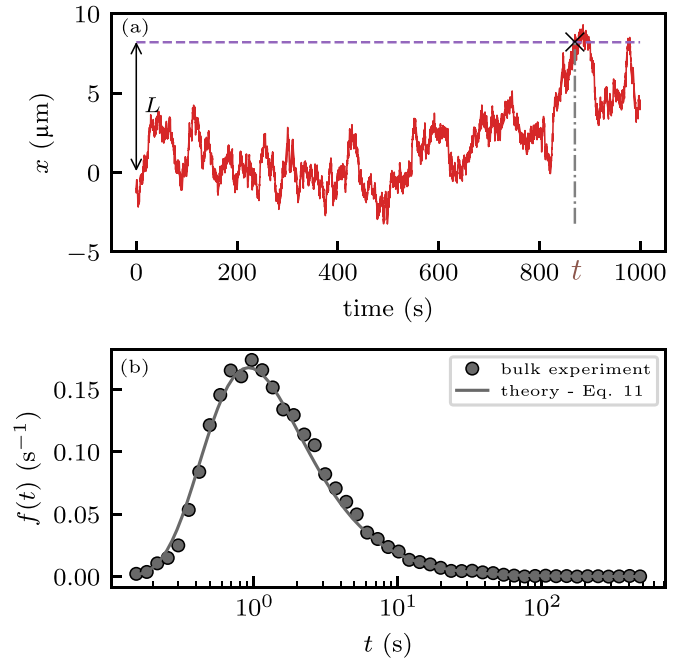


FIG. 2. First-passage statistics of a spherical polystyrene colloid ($a_p = 1.46 \mu\text{m}$) diffusing in the bulk of an ethylene-glycol-water mixture (weight ratio of 42% in ethylene glycol). (a) Trajectory along x . The colloid initially starts at $x = x_0 = 0$ and reaches the target located at $x = x_0 + L = L$, at time t . (b) Distribution $f(t)$ of the first-passage times t , for a target located at a distance $L = 500 \text{ nm}$ from the initial position. Experimental data (gray circles) and theoretical prediction (gray line) of Eq. (11), with the diffusion coefficient $D_0 = 4.53 \times 10^{-2} \mu\text{m}^2/\text{s}$ [see Eq. (4)].

white noise defined by $\langle \xi \rangle = 0$ and $\langle \xi(t)\xi(t') \rangle = \delta_D(t - t')$, with $\delta_D(t)$ the Dirac distribution. Within the overdamped approximation, this Langevin equation leads to the following diffusion equation on the probability distribution function $P(x, t)$ quantifying the probability for the bead to displace by an increment x over a time lag t :

$$\frac{\partial P(x, t)}{\partial t} = D_0 \frac{\partial^2 P(x, t)}{\partial x^2}. \quad (8)$$

The target-finding process suggests an absorbing boundary condition at the target coordinate, i.e., $P(x = x_0 + L, t) = 0$, and a point-source-like initial condition $P(x, t = 0) = \delta(x - x_0)$, where x_0 denotes the initial position of the particle and L is the distance between the initial position and the target, which is assumed to be positive without loss of generality. The Green's function and the image method are used to solve this problem, leading to

$$P(x, t) = \frac{1}{\sqrt{4D_0\pi t}} \left\{ e^{-\frac{(x-x_0)^2}{4D_0 t}} - e^{-\frac{[x-(2L+x_0)]^2}{4D_0 t}} \right\}. \quad (9)$$

Then, the probability that the colloid has not found the target after a time t , aptly named the survival probability $S(t)$, is expressed as the integral of $P(x, t)$ over the free domain $]-\infty; x_0 + L]$, as

$$S(t) = \int_{-\infty}^{x_0+L} dx P(x, t) = \text{erf}\left(\frac{L}{\sqrt{4D_0 t}}\right), \quad (10)$$

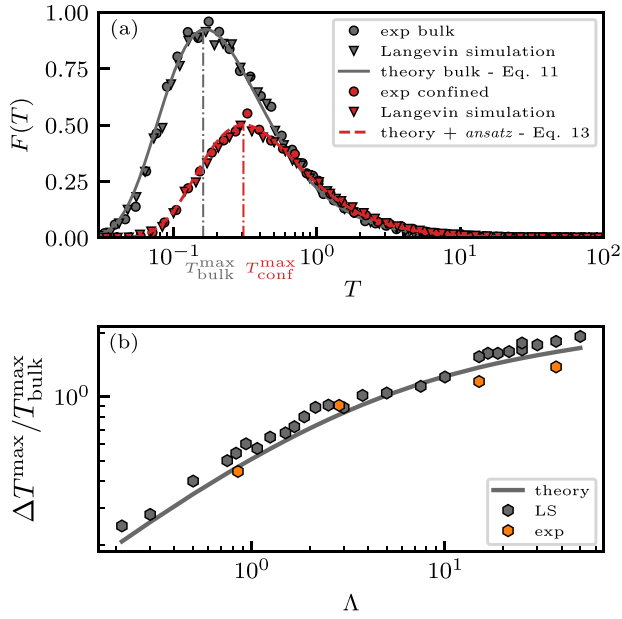


FIG. 3. First-passage-time statistics in confinement for a wall-parallel search with a target located at a distance $L = 500$ nm from the initial position. (a) Dimensionless distributions $F(T)$ of the dimensionless first-passage times T of a colloid diffusing, either in the bulk (gray) or near a wall (red). Circles correspond to experimental (exp) data, upside-down triangles to Langevin simulation (LS) data [see Eq. (12a)], and the solid lines to the theoretical predictions of Eq. (11) (bulk, $D_0 = 4.53 \times 10^{-2} \mu\text{m}^2/\text{s}$) and Eq. (13) (confined, $D_0 = 15.1 \times 10^{-2} \mu\text{m}^2/\text{s}$, $D_x = 8.18 \times 10^{-2} \mu\text{m}^2/\text{s}$). (b) Relative delay $\Delta T^{\max}/T^{\max}_{\text{bulk}}$ [see Eq. (14)] of the most likely dimensionless first-passage time as a function of the confinement parameter $\Lambda = a_p/l_B$. Orange hexagons correspond to experiments, gray hexagons to simulations, and the gray line to the associated theoretical prediction (see Appendix E), with no adjustable parameter.

where erf denotes the Gauss error function. Finally, we derive the first-passage-time distribution (FPTD), $f(t)$, i.e., the normalized distribution of the first time t at which the colloid reaches a given target placed at position $x = x_0 + L$. The FPTD is a Lévy distribution [29], given by

$$f(t) = -\frac{dS(t)}{dt} = \frac{L}{\sqrt{4\pi D_0 t^3}} e^{-\frac{L^2}{4D_0 t}}. \quad (11)$$

For clarity and simplicity sake, only one type of bulk experiment (detailed in Table II of Appendix B) has been performed and shown in Figs. 2(b), 3(a), and 4(a).

To optimize statistical reliability, we use an algorithmic procedure (see Appendix C) that enables the construction of a well-converged normalized histogram of FPTs from a single trajectory. The resulting FPTD is shown in Fig. 2(b). The close agreement observed between the experimental and theoretical [Eq. (11)] FPTDs for free diffusion in the bulk validates our approach and motivates the exploration of more complex, confined scenarios.

Having assessed the reference bulk case, we turn to a detailed examination of how confinement influences the first-passage statistics, through the FPTD $f(t)$.

As mentioned previously, the confinement-induced hydrodynamic interactions alter the colloid's mobility, both

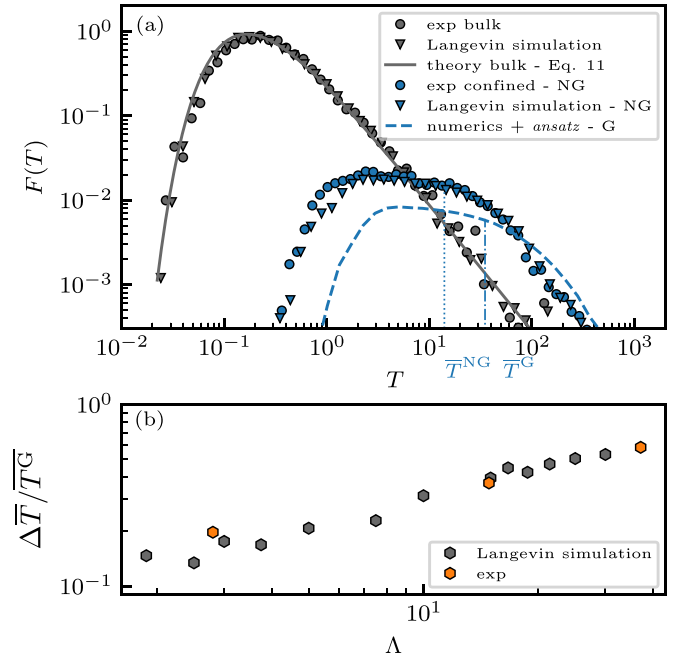


FIG. 4. First-passage-time statistics in confinement for a target located along z at a distance $L = 300$ nm from the initial position. Note that the latter is randomly selected from $P_{\text{eq}}(z)$ for prethermalized samples. (a) Dimensionless distribution $F(T)$ of the dimensionless first-passage times T for a colloid diffusing either in the bulk (gray) with $D_0 = 4.53 \times 10^{-2} \mu\text{m}^2/\text{s}$ or near a wall (blue) with $D_0 = 7.14 \times 10^{-2} \mu\text{m}^2/\text{s}$ and $D_z = 4.3 \times 10^{-3} \mu\text{m}^2/\text{s}$. Circles correspond to experimental data (non-Gaussian), upside-down triangles to simulation data (non-Gaussian) [see Eq. (12b)], the gray solid line to the bulk theoretical prediction of Eq. (11), and the blue dashed line to simulation data when replacing the z -dependent diffusivity $d_z(z) = k_B \Theta / \gamma_z(z)$ by D_z within Eq. (12b) (Gaussian). (b) Relative reduction $\Delta T/T^{\text{G}}$ [see Eq. (15)] of the dimensionless mean first-passage time as a function of the confinement parameter $\Lambda = a_p/l_B$. Langevin simulations are indicated with gray hexagons, while experiments (exp) are indicated with orange hexagons.

perpendicular [42] and parallel [41] to the wall. Hence, the stochastic processes are treated starting from the following set of coupled Langevin equations:

$$m\ddot{x}(t) = -\gamma_x(z)\dot{x}(t) + \sqrt{2k_B\Theta\gamma_x(z)}\xi_x(t), \quad (12a)$$

$$m\ddot{z}(t) = -\gamma_z(z)\dot{z}(t) - U'_{\text{eq}}(z) + \sqrt{2k_B\Theta\gamma_z(z)}\xi_z(t), \quad (12b)$$

where $\gamma_x(z)$ and $\gamma_z(z)$ are the z -dependent viscous drag coefficients along x [41] and z [42], respectively, $\xi_x(t)$ and $\xi_z(t)$ are independent Gaussian white noises, satisfying $\langle \xi_q \rangle = 0$ and $\langle \xi_q(t)\xi_q(t') \rangle = \delta(t - t')$, and U'_{eq} denotes the z derivative of the potential $U_{\text{eq}}(z)$ [see Eq. (2)].

In contrast with the aforementioned bulk scenario, given the wall-induced anisotropy in the problem, we distinguish between two target-finding processes, namely, a parallel search along the x axis (the same process can be discussed along y) or a normal search along the z axis. The aim of the two following subsections is to characterize the FPTD of the confined colloid in these two situations.

In the in-plane dynamics described by Eq. (12a), hydrodynamic interactions with the wall constitute the only

deviation from the bulk behavior described by Eq. (11). The in-plane motion exhibits an MSD that increases linearly with time [Fig. 1(d)], as well as a nearly Gaussian displacement distribution [Fig. 1(e)] for our current range of parameters [27,37], both fully characterized by the average diffusion coefficient D_x . Accordingly, the confined in-plane dynamics—characterized by a z -dependent diffusivity $d_x(z) = k_B \Theta / \gamma_x(z)$ —can be fairly approximated by a bulklike Gaussian process but with a lower, effective diffusivity D_x . As a consequence, we substitute D_x into the Lévy distribution of Eq. (11) originally derived for the bulk case, which then takes the following form:

$$f(t) = \frac{L}{\sqrt{4\pi D_x t^3}} e^{-\frac{L^2}{4D_x t}} \quad (13)$$

and stands as a theoretical ansatz for the in-plane target-finding process. As shown in Fig. 3(a), Eq. (13) correctly captures the experimental FPTDs. This agreement is further confirmed by numerical Langevin simulations mimicking the experimental confined diffusion, following the method of Ref. [44] (see Appendix D for details on the simulations). Variables are rescaled here in order to account for the different viscous liquids considered, through $T = D_0 t / L^2$ and $F(T) = f(t) \frac{L^2}{D_0}$.

Since the mean FPT is infinite in the unbounded wall-parallel domain, we focus on the most likely FPT, denoted as $T^{\max}$. The latter increases due to confinement, as qualitatively highlighted in Fig. 3(a). Intuitively and as discussed above, the colloid is essentially slowed down by wall-induced friction as it moves near and parallel to the wall, thus postponing the typical moment in time at which it can reach a given target. In order to quantitatively evaluate the magnitude of such an effect, we define a relative time delay with respect to the bulk reference, as

$$\frac{\Delta T^{\max}}{T_{\text{bulk}}^{\max}} = \frac{T_{\text{conf}}^{\max} - T_{\text{bulk}}^{\max}}{T_{\text{bulk}}^{\max}}, \quad (14)$$

in which $T_{\text{bulk}}^{\max}$ and $T_{\text{conf}}^{\max}$ denote the most likely FPT in bulk and confined situations, respectively. As shown in Fig. 3(b), the relative time shift between the bulk and wall-parallel search processes—deduced from FPTDs of both the experiments and Langevin simulations—increases with the confinement parameter $\Lambda = \frac{a_p}{l_B}$. The experimental and simulated data are consistent with the theoretical prediction (see details in Appendix E). We stress that, in normalized units, the value of the distance L to the target location does not affect this result (see Appendix F). In summary, the confined wall-parallel target-finding process is bulk like, but with wall-induced friction slowing down the clock.

We now turn to the wall-normal search dynamics, along the z axis. The z process exhibits a markedly richer dynamics [see Eq. (12b)] that strongly affects the FPTD, as discussed hereafter. First, as evidenced above via the overall time shift between the bulk and confined FPTDs, the FPT dynamics is essentially slowed down as compared to the corresponding bulk FPT dynamics, which echoes the “slowed-clock” effect observed along x . However, in the confined scenario, the z -FPTD exhibits a noticeable flattening, which stems from the combined influence of gravity and electrostatic repulsion,

through the equilibrium potential U_{eq} [see Eq. (2)]. Such a static origin of the FPTD flattening can be demonstrated by coarsely replacing the z -dependent diffusivity $d_z(z) = k_B \Theta / \gamma_z(z)$ by the constant, average one D_z within Eq. (12b), and then numerically solving the latter. Then, by constructing the FPTD from the simulated trajectories, one indeed sees a functional form that is flattened [see dashed line in Fig. 4(a)], as compared to the bulk FPTD.

Furthermore, and more strikingly, the aforementioned coarse numerical simulations (blue dashed line, with D_z replacing $d_z(z)$ making the process Gaussian: “-G”), while properly capturing the flattening of the FPTD, fail to quantitatively capture the experimental and full numerical simulations (blue circles and triangles, respectively, with $d_z(z)$ triggering non-Gaussianities: “-NG”). Such a discrepancy is rooted in the confinement-induced hydrodynamic interactions with the wall, which are more pronounced along z than along x . Indeed, while $\gamma_x(z)$ scales as $\ln(a/z)$ [45] and is nearly a plateau in the accessed z range [37,41], $\gamma_z(z)$ scales as a/z [37,42]. The latter space-dependent drag coefficient along z , coupled to the potential $U_{\text{eq}}(z)$, leads to large non-Gaussianities of the z -displacement probability [see Fig. 1(f)]. Consequently, the probability of large displacements is increased, as compared to a Gaussian reference case (such as the one in the coarse simulations), and the search process gets comparatively faster.

Since the mean FPT (MFPT) $\bar{T}$ (denoting the average weighted by $F(T)$) is finite in the wall-normal z domain, due to the confining potential $U_{\text{eq}}(z)$, one can use it as a relevant measure of the typical search time in this direction. We compare the experimental or numerical MFPT $\bar{T}^{\text{NG}}$, which includes non-Gaussian effects, with the MFPT $\bar{T}^{\text{G}}$ obtained from the coarse simulations described above in which such non-Gaussian effects are suppressed by construction. To do so, we introduce a relative time reduction, expressed as

$$\frac{\Delta \bar{T}}{\bar{T}^{\text{G}}} = \frac{\bar{T}^{\text{G}} - \bar{T}^{\text{NG}}}{\bar{T}^{\text{G}}}. \quad (15)$$

As shown in Fig. 4(b), this relative time reduction is positive and increases with confinement. In summary, confinement-induced non-Gaussianities act as a boost for the target-finding process in the wall-normal direction, making it faster than if the displacement distribution was Gaussian.

IV. DISCUSSIONS

To conclude, we have investigated first-passage processes in the presence of confinement effects, such as surface forces, hydrodynamic interactions with a wall, and resulting non-Gaussian displacements. By the use of holographic microscopy and statistical inference, usual observables related to Brownian motion, such as displacement distributions, mean squared displacements, and equilibrium distributions in position, were measured with state-of-the-art precisions allowing for a quantitative analysis of first-passage stochastic dynamics in confinement. Our main findings, backed up by theoretical and numerical models, are listed hereafter. First, if the colloid randomly moves transversely to the wall, the process remains almost Gaussian and bulklike, but the clock is slowed down as compared to the bulk case due to the wall-induced

friction. Hence, target finding is slowed down as well. Second, if the colloid moves in the direction normal to the wall, the process is strongly non-Gaussian due to the intricate combination of wall-normal forces and space-dependent mobility. Strikingly, target finding is then typically reaccelerated by such non-Gaussianities, compared to a Gaussian process under the same potential with a hindered mobility. This key result can be understood by recalling that the probability of observing large displacements is enhanced in this case through the presence of the non-Gaussian tails in the displacement distribution. Such a non-Gaussianity-induced enhanced target-finding dynamics of confined colloids opens promising paths for confined chemistry [46] and biophysics [47], and might have drastic consequences in winners-take-all processes near boundaries, such as fecundation, where one single rare event can entirely dominate the dynamics [48]. Investigating further the influence of curved surfaces—where the hydrodynamic interactions are more intricate—or soft boundaries in such problems, through Brownian elastohydrodynamic couplings [49–52], would be a relevant task for the future.

ACKNOWLEDGMENTS

The authors thank E. Millan and M. Lavaud for useful insights into materials, as well as J. Lacherez, L. Anderson, J. McGraw, and D. Dean for enlightening discussions. They also thank J. Parzych and V. Thouard for financial project management, as well as T. Guillaume, R. Houques, and A. Tempel for laboratory-space installation. Moreover, they acknowledge financial support from the European Union through the European Research Council under EMetBrown (ERC-CoG-101039103) grant. The authors also acknowledge financial support from the Agence Nationale de la Recherche under EMetBrown (ANR-21-ERCC-0010-01), Softer (ANR21-CE06-0029), and Fricolas (ANR-21-CE06-0039) grants, as well as from the Interdisciplinary and Exploratory Research program at Univ. Bordeaux under MISTIC grant, France. Besides, they acknowledge the support from the LIGHT Sciences and Technologies Graduate Program (PIA3 Investment for the Future Program, ANR-17EURE-0027) and the Réseau de Recherche Impulsion (RRI) “Frontiers of Life,” which received financial support from the French government in the framework of Univ. Bordeaux’s France 2030 program. Finally, they thank the Soft Matter Collaborative Research Unit, Frontier Research Center for Advanced Material and Life Science, Faculty of Advanced Life Science at Hokkaido University, Sapporo, Japan, and the CNRS International Research Network between France and India on “Hydrodynamics at small scales: from soft matter to bioengineering.”

Views and opinions expressed are, however, those of the authors only and do not necessarily reflect those of the European Union or the European Research Council. Neither the European Union nor the granting authority can be held responsible for them.

DATA AVAILABILITY

Experimental data and analysis codes are accessible in Ref. [53].

APPENDIX A: LOCAL DIFFUSIVITIES

1. z dependency

Target finding is narrowly linked to the diffusivity of the system, which is characterized by a diffusion coefficient D_q (with $q = x, z$). The latter is expressed through

$$\langle \Delta_\tau q^2 \rangle = 2D_q \tau, \quad \text{with} \quad D_q = \frac{k_B \Theta}{\gamma_q}, \quad (\text{A1})$$

where τ is the lag time, k_B is the Boltzmann constant, Θ is the room temperature, and γ_q is the drag term. In the absence of a wall, the bulk drag coefficient γ reads $\gamma = 6\pi\eta_m a_p$, leading to the bulk diffusion coefficient $D_0 = k_B \Theta / \gamma$ (Stokes-Einstein relation). The relation in Eq. (A1) is used to compare the experimental and theoretical mean squared displacements shown in Fig. 1(d). The latter observable provides an estimation of the reduced diffusion coefficient D_q , deduced when $\tau < \tau_{\text{eq}}$ (the equilibrium time is defined in Sec. II). More precisely, the no-slip boundary condition at the substrate ($z = 0$) reduces the colloid’s diffusivity. Besides, the anisotropy of the colloid’s motion recasts into a smaller average diffusion coefficient in the vertical direction as compared to the horizontal one ($D_z < D_x$). Furthermore, the aforementioned diffusion and drag coefficients are actually averaged over all colloid-wall gap distances z . However, the hydrodynamic drag felt by the colloid is in fact z dependent. This hydrodynamic drag increases as the colloid approaches the surface, as accurately described within the theoretical frameworks developed by Faxen [41] and Brenner [42], which, respectively, account for the in-plane and perpendicular drags acting on the colloid. This leads to altitude-dependent local diffusion coefficients d_q . The altitude dependency of the parallel diffusion coefficient d_x reads

$$d_x = D_0 \left(1 - \frac{9}{16}Z + \frac{1}{8}Z^3 + \frac{45}{256}Z^4 + \frac{1}{16}Z^5 \right), \quad (\text{A2})$$

with $Z = (\frac{a_p}{a_p + z})$. The one of the perpendicular diffusion coefficient d_z , within the Padé approximation (leading to a 1% accuracy), reads

$$d_z = D_0 \left(\frac{6z^2 + 2a_p z}{6z^2 + 9a_p z + 2a_p^2} \right). \quad (\text{A3})$$

The theoretical and experimental z dependencies of these local diffusion coefficients d_q are shown in Fig. 5.

2. Inference of local diffusion coefficients

The determination of the local diffusion coefficients d_q with nanometric spatial precision requires going beyond simple spatial binning. Indeed, conventional binning approaches, which are suitable for static observables, fail to capture the subtle variations of dynamic quantities such as local diffusion. To overcome this limitation, the experimental profiles of the local diffusion coefficients presented in Fig. 5 are obtained using a stochastic force inference algorithm [54]. This method combines statistical inference with trajectory analysis to extract diffusion properties even in the presence of measurement noise.

An unbiased estimator $\hat{\delta}$ of the local diffusion coefficient in the x direction (which can be straightforwardly extended to

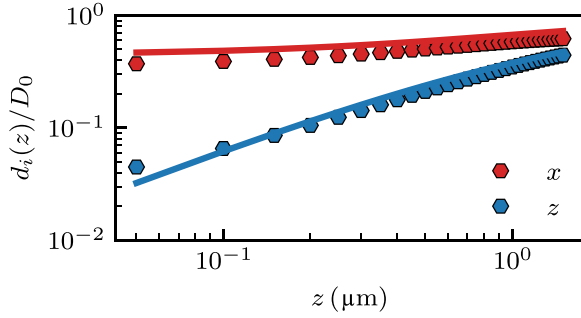


FIG. 5. Local diffusion coefficients in both the perpendicular (blue hexagons) and in-plane (red hexagons) directions, as a function of the wall-colloid gap distance z , for a spherical polystyrene colloid of radius $a_p = 1.48 \mu\text{m}$ diffusing in water, of viscosity $\eta_m = 0.95 \text{ mPa s}$, near a rigid glass wall. Theoretical predictions from Eq. (A3) (blue line) for the perpendicular diffusion coefficient and Eq. (A2) (red line) for the parallel diffusion coefficient are also shown.

the z direction) is defined as

$$\hat{\delta} = \frac{(\Delta_\tau x(t_{j-1}) + \Delta_\tau x(t_j))^2}{4\tau} + \frac{\Delta_\tau x(t_{j-1}) \Delta_\tau x(t_j)}{2\tau}, \quad (\text{A4})$$

where τ represents an integer multiple of the sampling acquisition rate ($dt = 1/\text{fps}$) and $\Delta_\tau x(t_j)$ denotes the colloid displacement over a time interval τ starting at time t_j . Each estimator value $\hat{\delta}$ corresponds to a specific height z , and its spatial distribution is reconstructed on a regular grid $\hat{z}$ through polynomial interpolation of the form $\sum a_k(\hat{z})z^k$, where a_k are real coefficients. In this work, polynomial bases of third or fourth order are employed, while truncating at $k = 0$ corresponds to the conventional binning approach.

The two terms in Eq. (A4) serve distinct purposes. The first corresponds to the classical definition of the diffusion coefficient in the two-dimensional (2D) case [see Eq. (A1)], while the second acts as a corrective term compensating for noise-induced correlations in experimental data. In an ideal Brownian process, successive displacements $\Delta_\tau x$ are delta correlated. However, measurement errors violate this assumption, introducing spurious correlations. Incorporating the autocorrelation term [second term in Eq. (A4)] therefore isolates the true diffusive behavior from noise artifacts, yielding an unbiased estimator. Under the present experimental conditions, this correction is essential for obtaining accurate local diffusion coefficients near the substrate ($z \leq 100 \text{ nm}$), where data are limited due to electrostatic repulsion and statistical fluctuations are most pronounced due to the increased dissipation therein.

APPENDIX B: TUNING THE CONFINEMENT

In order to choose a given confinement strength for the colloid, we use the following procedure. The upper boundary of the confinement is set by the Boltzmann length l_B , as shown in Fig. 1(f). Indeed, the typical altitude at which the colloid

starts to feel the confinement due to gravity is expressed as

$$l_B = \frac{k_B \Theta}{\Delta m g}, \quad \text{with} \quad \Delta m = \frac{4}{3} \pi a_p^3 \Delta \rho = \frac{4}{3} \pi a_p^3 (\rho_p - \rho_m), \quad (\text{B1})$$

where a_p is the radius of the colloid, and ρ_p and ρ_m , respectively, are the density of the colloid and the density of the medium. Consequently, tuning the density of the mixture ρ_m , through the addition of one fluid element, would lead to a different Boltzmann length l_B , i.e., a different confinement. Two side effects of this experimental method are to be noticed:

(1) It affects the optical index of the medium n_m , which is involved in our monitoring method.

(2) It changes as well the viscosity of the medium η_m , inducing a modification of the bulk diffusion coefficient.

A detailed explanation on how one can overpass these two subtleties is detailed hereafter.

(1) Since the holography method we use partly relies on the optical-index difference between the monitored object and its environment, a modification in these optical indices would lead to a misinterpretation of the observables. In order to avoid any confusion between the different experiments, optical indices are precalibrated using a refractometer (DR-M2/1550 from ATAGO). A table listing optical indices, as a function of the ethylene-glycol weight ratio W_{EG} , is shown in Table I.

(2) The Boltzmann length l_B as a function of the density difference $\Delta \rho$ is straightforwardly expressed in Eq. (B1). Subsequently, we aim to cover a couple of decades in l_B to have a thorough understanding of the influence of confinement on the FPTD, ranging from few tens of nanometers to the bulk case ($l_B \rightarrow \infty$).

First, the good agreement, detailed in Table II, between the theoretical [Eq. (B1)] and experimental [deduced from the best fit of the experimental $P_{\text{eq}}(z)$ to Eq. (1)] Boltzmann lengths serves as a validation of our method. Second, one can notice that as the ethylene-glycol weight ratio W_{EG} in the mixture increases, the mixture's dynamic viscosity η_m increases as well. This would lead to different bulk diffusion coefficients D_0 [see Eq. (A1)], hence a different effective diffusion coefficient D_x [see Eq. (A2)], for each experiment, preventing any possible comparison between bulk and confined FPTDs. This hurdle, and the will to generalize the results to any distance L to the target, suggests the use of rescaled and dimensionless variables accounting for the change of diffusion coefficient, as

$$T = \frac{D_0 t}{L^2}, \quad F(T) = f(T) \frac{L^2}{D_0}. \quad (\text{B2})$$

Remark. For bulk and quasibulk experiments ($l_B \rightarrow +\infty$ and $l_B = 1802 \text{ nm}$, respectively), some of the observables

TABLE I. Optical indices of the solution that contains the diffusing colloid, as functions of the ethylene-glycol-water solution's weight ratio W_{EG} in ethylene glycol.

$W_{\text{EG}} \%$	42	30	0
$n(\lambda = 500 \text{ nm})$	1.3769	1.3690	1.3350
$n(\lambda = 600 \text{ nm})$	1.3735	1.3663	1.3323
$n(\lambda_{\text{laser}} = 532 \text{ nm})$	1.3705	1.3681	1.3341

TABLE II. List of the Boltzmann lengths $l_B = [79 \text{ nm}, 204 \text{ nm}, 604 \text{ nm}, 1802 \text{ nm}, +\infty]$ obtained from different ethylene-glycol-water mixtures of ethylene-glycol weight ratios W_{EG} , for two radii a_p of the colloid.

W_{EG} (%)	η_m (mPa s)	ρ_m (kg/m ³)	ρ_p (kg/m ³)	$\Delta\rho$ (kg/m ³)	a (μm)	l_B^{th} (nm)	l_B^{exp} (nm)	Λ	D_0 (μm ² /s)	D_x (μm ² /s)	D_z (μm ² /s)
42	3.2	1050	1050	0	1.48	$+\infty$	$+\infty$	0	0.045	0.041	0.045
30	2.10	1033	1050	17	1.47	1787	1802	0.82	0.085	0.054	0.034
0	0.95	1000	1050	50	1.48	596	604	2.45	0.151	0.082	0.042
30	2.10	1033	1050	17	2.98	215	204	14.61	0.034	0.013	0.0035
0	0.95	1000	1050	50	2.98	73	79	37.72	0.071	0.031	0.0043

struggled to converge, for instance, $P_{\text{eq}}(z)$, since the equilibrium time τ_{eq} gets greater as l_B increases. In these cases, the MSD was the most suitable observable to deduce information on confinement.

APPENDIX C: STATISTICAL OPTIMIZATION ALGORITHM

In order to optimize the statistical reliability of our experimental and numerical data, an optimization has been performed in agreement with the theory. Indeed, we use an experiment that contains an entire trajectory as a group of many trajectories, as follows: One FPT is extracted when a colloid starting at $q = q(t = 0) = q_0$ (where $q = x, z$) reaches $q = q_0 + L$. The work-around resides in considering successively every position as an initial position q_0 : The first initial position $q_0 = q(t = 0)$ leads to the first FPT, the second initial position $q_0 = q(t = \tau)$ leads to the second FPT, and so on until the FPT of the n th initial position $q_0 = q[t = (n - 1)\tau]$ is never reached because of the end of the recording. By applying this algorithm, one can infer from a single trajectory a well-converged distribution as shown in Figs. 2(b), 3(a), and 4(a). We stress that, in the case of a wall-normal target search along z , the initial positions z_0 are selected from the equilibrium distribution $P_{\text{eq}}(z)$ [see Fig. 1(c)]. The validity of this algorithm relies on the fact that the total trajectory duration is much greater than the FPT timescale, so that one can obtain many independent realizations of the noise.

APPENDIX D: LANGEVIN SIMULATIONS

Numerical simulations are conducted based on the over-damped version of the Langevin equations presented in the main text [see Eq. (12)], which are discretized using a numerical integration time step of 10 ms. This time step is selected to match the experimental acquisition frame rate.

In order of appearance, the input variables of the function `compute_one_traj`, shown in Fig. 6, are defined as follows: an integer index (used when the function is executed within a loop), the numerical integration time step, the total number of simulated points N_{tot} , the subsampling factor, the colloid radius a_p , half-length H of the interwall separation $2H$ within the confining chamber, the Debye length l_D , the Boltzmann length l_B , the dimensionless amplitude B of the electrostatic repulsion (expressed in units of $k_B\Theta$), the dynamic viscosity of the medium η_m , the temperature Θ , and the initial position ($x_0 = x(t = 0)$, $z_0 = z(t = 0)$) of the colloid. Further details concerning the simulation procedure are provided in Ref. [44] and codes can be found in Ref. [55].

APPENDIX E: RELATIVE TIME DELAY

In order to quantify the time shift between the bulk and confined FPTDs, as the colloid searches for a target in the direction parallel to the wall, we build a dimensionless rescaled time shift, detailed hereafter. In the case of a colloid searching a target placed along x (or along y), its most likely first-passage time can be deduced from the time derivative of its FPTD, as

$$\frac{dF(T)}{dT} = 0 \quad \text{for} \quad T = T^{\text{max}}. \quad (\text{E1})$$

This general consideration leads to

$$T^{\text{max}} = \frac{L^2}{6D}, \quad (\text{E2})$$

with D the coefficient of the colloid in its environment. In the case of confined diffusion, this diffusion coefficient exhibits a z dependency, as mentioned at the beginning of this Appendix. The quantity we aim to characterize is the dimensionless rescaled time shift $\frac{\Delta T^{\text{max}}}{T^{\text{max}}_{\text{bulk}}}$ and is expressed as

$$\frac{\Delta T^{\text{max}}}{T^{\text{max}}_{\text{bulk}}}(z, a_p) = \frac{D_0}{d_x(z, a_p)} - 1. \quad (\text{E3})$$

Since we showed that a Levy distribution containing an ansatz that sets the local diffusion coefficient d_x to its average value D_x [see Eqs. (5) and (13)] is a valid approximation [see Fig. 3(a)], one has

$$\frac{\Delta T^{\text{max}}}{T^{\text{max}}_{\text{bulk}}}\left(\frac{a_p}{l_B}\right) = \int_0^{+\infty} dz P_{\text{eq}}(z, B, l_D, l_B) \left[\frac{D_0}{d_x(z, a_p)} - 1 \right]. \quad (\text{E4})$$

From this integral, one can deduce using, e.g., Mathematica, $\frac{\Delta T^{\text{max}}}{T^{\text{max}}_{\text{bulk}}}$ as a function of the confinement parameter $\Lambda = \frac{a_p}{l_B}$.

```

1 from simulations.langevin.DoubleWalls_Overdamped_Langevin import DoubleWallsLangevin
2 def compute_one_traj(i, dt, Nt, Nt_sub, a, H, lD, lB, B, etam, T, R0=None):
3     brown = DoubleWallsLangevin(
4         dt=dt, Nt=Nt, Nt_sub=Nt_sub,
5         a=a, H=H, lD=lD, lB=lB, B=B, etam=etam, T=T,
6         R0=R0,
7     )
8     brown.trajectory()
9     x = brown.Xn
10    z = brown.Zn + H
11    return x, z
12 x, z = compute_one_traj(i, dt, Nt, Nt_sub, a, H, lD, lB, B, etam, T, R0=None)

```

FIG. 6. Code snippet to generate confined Brownian trajectories.

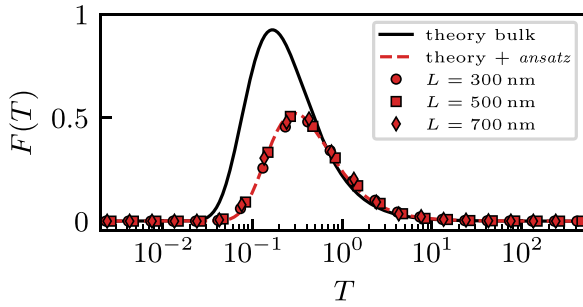


FIG. 7. First-passage-time distribution for a confined polystyrene colloid with a radius $a_p = 1.5 \mu\text{m}$ in water ($D_0 = 15.1 \times 10^{-2} \mu\text{m}^2/\text{s}$), for a target placed at a distance $L = [300 \text{ nm}, 500 \text{ nm}, 700 \text{ nm}]$ (along x) from the initial position $x = x_0$.

APPENDIX F: INFLUENCE OF THE DISTANCE TO THE TARGET

Here, we discuss the influence of the distance L between the initial position q_0 and the target placed at $q_0 + L$. One can notice the fair agreement between the rescaled FPTDs, obtained for different distances $L = [300 \text{ nm}, 500 \text{ nm}, 700 \text{ nm}]$ and $[300 \text{ nm}, 400 \text{ nm}, 500 \text{ nm}]$, for search processes, respectively, along x as shown in Fig. 7, and along z as shown in Fig. 8. Hence, the proposed variable rescaling captures the L dependency.

APPENDIX G: SAMPLE PREPARATION

In this Appendix, we provide useful information concerning the sample preparation. The experiment consists of monitoring confined Brownian motion for about 1 h (in most cases). To do so, one needs a sample that is stable (in time and space) and highly reproducible.

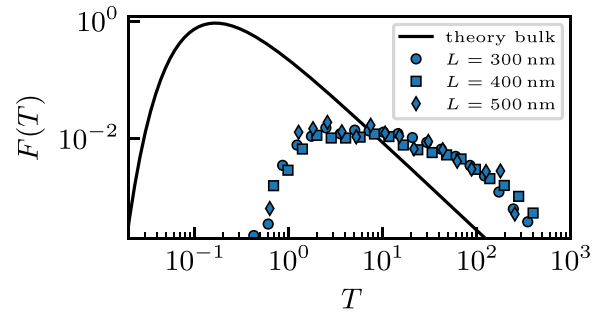


FIG. 8. First-passage-time distribution for a confined polystyrene colloid with a radius $a_p = 3 \mu\text{m}$ in water ($D_0 = 7.53 \times 10^{-2} \mu\text{m}^2/\text{s}$), for a target placed at a distance $L = [300 \text{ nm}, 400 \text{ nm}, 500 \text{ nm}]$ (along z) from the initial position z_0 , where the latter is randomly selected from the equilibrium distribution P_{eq} .

The sample is composed of a glass slide (1 mm thick) on which two small paraffin bands are placed (thickness $e = 250 \mu\text{m}$). This support can be placed on a warming plate so that the paraffin slightly melts and becomes sticky. After a few seconds on the warming plate, a coverslip (180 μm thick) is deposited onto the sticky paraffin bands. The glass slides and cover slip composing the sample are cleaned with ethanol and dried with an air gun before making the sample. The reference of the glass slide is “Marienfeld 0704008, $76 \times 26 \times 1 \text{ mm}$ ” and the one of the cover slip is “Scientec 1015291, $40 \times 24 \times (0.13\text{--}0.17) \text{ mm}$ ”.

The solution, containing polystyrene particles diffusing in the mixture (water and possibly ethylene glycol), is then injected between the glass slide and the coverslip. Both sides of the sample are sealed with hydrophobic grease. Such a sample is fully hermetic and prevents any evaporation, which could lead to convection currents and introduce drift into the Brownian diffusion.

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