



# Hydrodynamic and entropic effects on colloidal diffusion in corrugated channels

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**In the absence of advection, confined diffusion characterizes transport in many natural and artificial devices, such as ionic channels, zeolites, and nanopores. While extensive theoretical and numerical studies on this subject have produced many important predictions, experimental verifications of the predictions are rare. Here, we experimentally measure colloidal diffusion times in microchannels with periodically varying width and contrast results with predictions from the Fick–Jacobs theory and Brownian dynamics simulation. While the theory and simulation correctly predict the entropic effect of the varying channel width, they fail to account for hydrodynamic effects, which include both an overall decrease and a spatial variation of diffusivity in channels. Neglecting such hydrodynamic effects, the theory and simulation underestimate the mean and standard deviation of first passage times by 40% in channels with a neck width twice the particle diameter. We further show that the validity of the Fick–Jacobs theory can be restored by reformulating it in terms of the experimentally measured diffusivity. Our work thus shows that hydrodynamic effects play a key role in diffusive transport through narrow channels and should be included in theoretical and numerical models.**

diffusion | colloid | confinement | hydrodynamics | entropic effects

**D**iffusive transport occurs prevalently in confined geometries (1, 2). Notable examples include the dispersion of tracers in permeable rocks (3), diffusion of chemicals in ramified matrices (4), and the motion of submicrometer corpuscles in living tissues (5, 6). The subject of confined diffusion is of paramount relevance to technological applications and for this reason, has been generating growing interest in the physics (1, 2), mathematics (7), engineering (3), and biology communities (5, 6, 8).

Spatial confinement can fundamentally change equilibrium and dynamical properties of a system via two different effects: limiting the configuration space accessible to its diffusing components (1) and increasing the hydrodynamic drag (9) on them. The former (entropic effect) has been extensively studied analytically and numerically in the case of quasi-1D structures, such as ionic channels (10), zeolites (4), microfluidic channels (11, 12), and nanopores (13). In these systems, transport takes place along a preferred direction, with the spatial constraints varying along it. Focusing on the transport direction, Jacobs (14) and Zwanzig (15), in the absence of advective effects, assumed that the transverse dfs equilibrate fast and proposed to eliminate them adiabatically by means of an approximate perturbation scheme. In first order, they derived a reduced diffusion equation, known as the Fick–Jacobs (FJ) equation, reminiscent of an ordinary 1D Fokker–Planck equation in vacuo, except for two entropic terms (2, 16–19). Predictions of the FJ equation have been extensively checked against Brownian dynamics (BD) simulations in different types of channels (16, 19–27). Using the FJ theory and BD simulations, researchers have predicted a variety of novel entropy-driven transport mechanisms, such as drive-dependent mobilities (2, 18, 20), stochastic resonance (28, 29), absolute negative mobilities

(30), entropic rectification (31, 32), and particle separation (33). Several of these predictions are presently recognized as being of both fundamental and technological importance.

While these previous studies (2, 14–33) significantly improved our understanding of the entropic effects of confining boundaries, they largely ignored the hydrodynamic effects, which are notoriously difficult to treat analytically and in simulations (9, 34). How will hydrodynamic effects change the established entropic picture? To address this important question, we turn to laboratory experiments (12, 35–39) and measure the diffusive dynamics of micrometric colloidal particles through channels with systematically modulated cross-sections. Contrasting the experimental results with predictions obtained by FJ approximation and from BD simulation, we discover that, as the channel's width shrinks toward the particle's diameter, hydrodynamic effects (9, 34, 40–43) grow in strength and become comparable with the predicted entropic effects, thus indicating an unexpected breakdown of the standard FJ theory and BD simulation in narrow channels. We further show that hydrodynamic effects can be incorporated by using an experimentally measured local diffusivity. With such a phenomenological modification, the FJ theory and BD simulation accurately predict the experimental data.

## Results

Our channels were fabricated on a coverslip by means of a two-photon direct laser writing system, which solidifies polymers

### Significance

**When a particle diffuses in a corrugated channel, the channel's boundaries have a twofold effect of limiting the configuration space accessible to the particle and increasing its hydrodynamic drag. Analytical and numerical approaches well-reproduce the former (entropic) effect, while ignoring the latter (hydrodynamic) effect. Here, we experimentally investigate nonadvective colloidal diffusion in channels with periodically varying width. While validating the current theory for channels much wider than the particle radius, we show that, in narrow channels, hydrodynamic and entropic effects can be equally strong and that hydrodynamic effects can be incorporated into existing descriptions by using an experimentally measured diffusivity. These results significantly advance our understanding of diffusive transport in confined geometries, such as in ionic channels and nanopores.**

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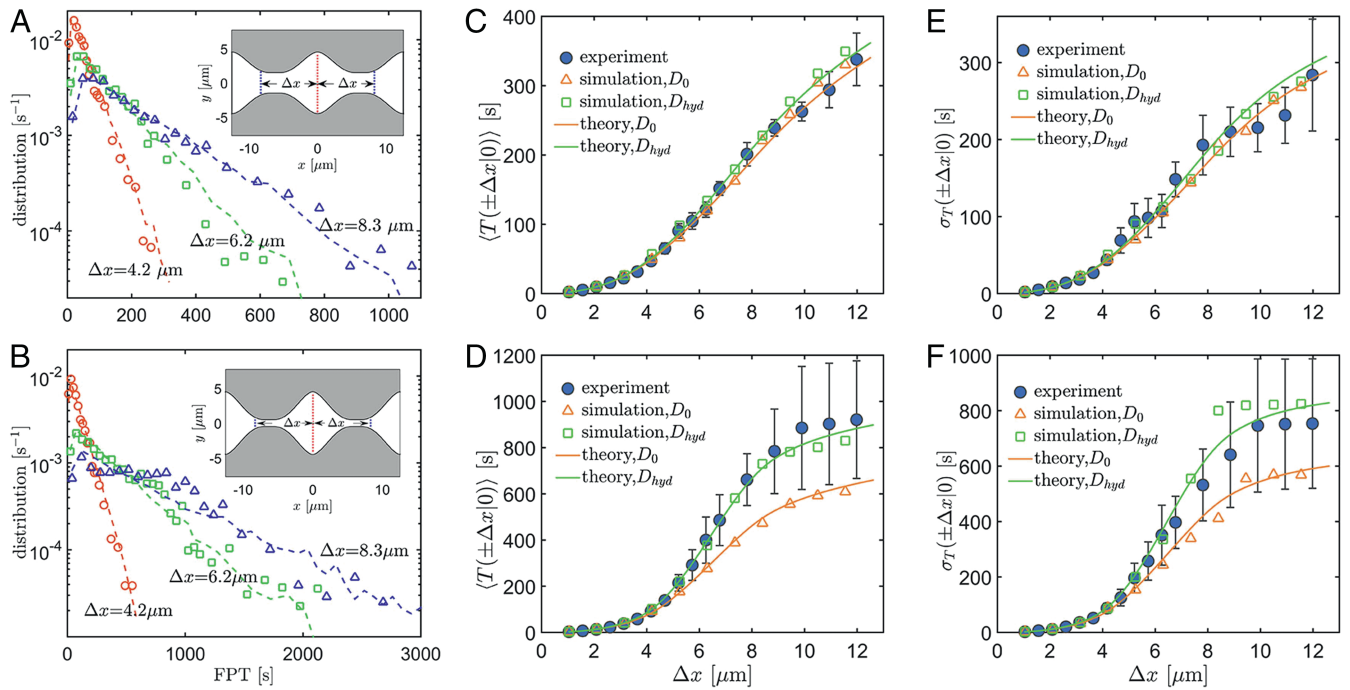
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**Fig. 2.** (A and B) Probability distributions, (C and D) averages, and (E and F) SDs of the FPTs in (A, C, and E) wide ( $g_n = 1.5 \mu\text{m}$ ) and (B, D, and F) narrow ( $g_n = 0.5 \mu\text{m}$ ) channels with the same maximum half-width,  $g_w = 4.5 \mu\text{m}$ . In A and B, experimental data (symbols) are compared with the outcome of BD simulations (curves) for the spatially modulated diffusivity,  $D_{hyd}(x)$ . The relevant channel profiles,  $\pm g(x)$ , are shown in A, *Inset* and B, *Inset*; vertical dashed segments mark the starting (red:  $x = 0$ ) and ending (blue:  $x = \pm\Delta x$ ) positions of the first passage events. In C–F, experimental, numerical, and theoretical results are shown as solid symbols, open symbols, and solid curves, respectively. Numerical and theoretical results with constant  $D_0$  and varying  $D_{hyd}$  diffusivity are color-coded orange and green, respectively.

where  $g'(x)$  is the slope of the channel's profile  $g(x)$ , and  $D_0$  is the particle's diffusivity away from side walls. We also calculated the second FPT moment,

$$\langle T_{FJ}^2(\pm\Delta x|0) \rangle = \int_0^{\Delta x} \frac{2d\eta}{g(\eta)\mathbb{D}(\eta)} \int_0^{\eta} g(\xi) \langle T_{FJ}(\pm\Delta x|\xi) \rangle d\xi, \quad [4]$$

where  $\langle T_{FJ}(\pm\Delta x|\xi) \rangle$  reads like in Eq. 2, except that the outer integral runs here from  $\xi$  to  $\Delta x$ . The derivation of Eqs. 2 and 4 can be found in *SI Appendix*.

To use Eqs. 2 to 4, one needs to know the diffusivity  $D_0$ . In an unbounded space, the diffusivity of a sphere coincides with the Stokes–Einstein value,  $D_{SE}$ . However, a general expression for the diffusivity of a colloidal particle in a confined geometry is not available. Hence, we experimentally measured  $D_0$  by monitoring the diffusion of the particle about the center of a channel's cell, where the entropic effects are minimal, and for displacements smaller than one particle radius. Eqs. 2 and 4 were then computed explicitly for the measured value of  $D_0$  and the actual channel geometry (namely, the parameters  $g_n$ ,  $g_w$ , and  $L$ ). For the sake of a comparison, 2D BD simulations were also performed for the same model parameters. Theoretical and numerical results (orange symbols and curves in Fig. 2 C–F) agree closely with each other for both the wide and narrow channels. The comparison with the experimental data, instead, is satisfactory only in the case of the wide channel (Fig. 2 C and E). For the narrow channel in Fig. 2 D and F, the experimental data with  $\Delta x > 6 \mu\text{m}$  are as much as 40% larger than the predicted values. To further investigate this discrepancy, we carried out experiments in channels with different width parameters,  $g_w$  and  $g_n$ ; the discrepancy is quantified in Fig. 3 by the relative mean–FPT difference at  $\Delta x = L/2$  (bottleneck midpoints),

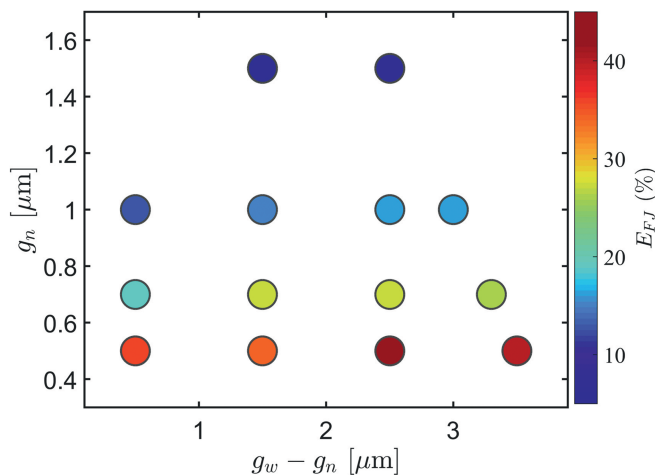
$E_{FJ} = [\langle T(\pm L/2|0) \rangle - \langle T_{FJ}(\pm L/2|0) \rangle] / \langle T_{FJ}(\pm L/2|0) \rangle$ . For narrow channels, the experimental values are consistently larger than the corresponding theoretical and numerical predictions. The discrepancy depends weakly on the amplitude of the channel modulation,  $g_w - g_n$ , but increases significantly with decreasing bottleneck half-width,  $g_n$ .

**Diffusivity Measurements.** The theoretical and numerical predictions discussed so far assume a constant particle diffusivity,  $D_0$ , throughout the channel, which is a reasonable approximation for particle diameters much smaller than the channel width. However, this assumption is doomed to fail for small bottleneck widths (when the FJ approach is supposed to work best), because the proximity of no slip side walls in the neck regions is known to increase the hydrodynamic drag on a finite-sized particle and therefore, suppress its local diffusivity (40–43, 47, 48).

To show such a hydrodynamic effect in our device, we measured the particle diffusivity inside the channel. At any given location,  $(x, y)$ , we recorded the particle mean-squared displacement in the  $x$  direction,  $\langle \delta x^2(x, y) \rangle$ , for a time interval  $\delta t = 0.2$  s and estimated the local diffusivity through Einstein's law,  $D(x, y) = \langle \delta x^2(x, y) \rangle / (2\delta t)$ . As shown in *SI Appendix*, the value chosen for  $\delta t$  is long enough to ensure good statistics for our measurements of  $D(x, y)$ ; during  $\delta t$ , particle displacements are smaller than  $0.5 \mu\text{m}$ , so that channel corrugation does not affect diffusivity measurements (46). Measurements of  $D(x, y)$  in the wide and narrow channels are shown in Fig. 4 A and B. In both,  $D(x, y)$  is largest in the open regions at the center of the unit cells and strongly suppressed in the bottlenecks. In the spirit of the FJ theory, we average  $D(x, y)$  along the transverse direction

$$D_{hyd}(x) := \frac{1}{2g(x)} \int_{-g(x)}^{g(x)} D(x, y) dy \quad [5]$$





**Fig. 3.** Deviation of theoretical predictions from experimental results,  $E_{FJ}$  (definition in the text), increases with decreasing the bottleneck half-width,  $g_n$ , and weakly depends on the modulation amplitude,  $g_w - g_n$ , of the channel.

and plot  $D_{hyd}(x)/D_0$  as a function of  $x$  in Fig. 4C. The spatial variabilities of  $D_{hyd}(x)$  are about 10 and 40% for the wide and narrow channels, respectively.

We corroborate the local diffusivity measurements with full hydrodynamic computations. The hydrodynamic friction coefficient in the  $x$  direction  $\gamma(x, y)$  was computed by means of a finite element package (COMSOL); the local diffusivity was calculated via the fluctuation–dissipation theorem,  $D(x, y) = k_B T / \gamma(x, y)$ , and the result is averaged over the  $y$  coordinate to obtain  $D_{hyd}(x)$ . Results from finite element calculations are shown in Fig. 4C as curves and are in excellent agreement with the experimental data.

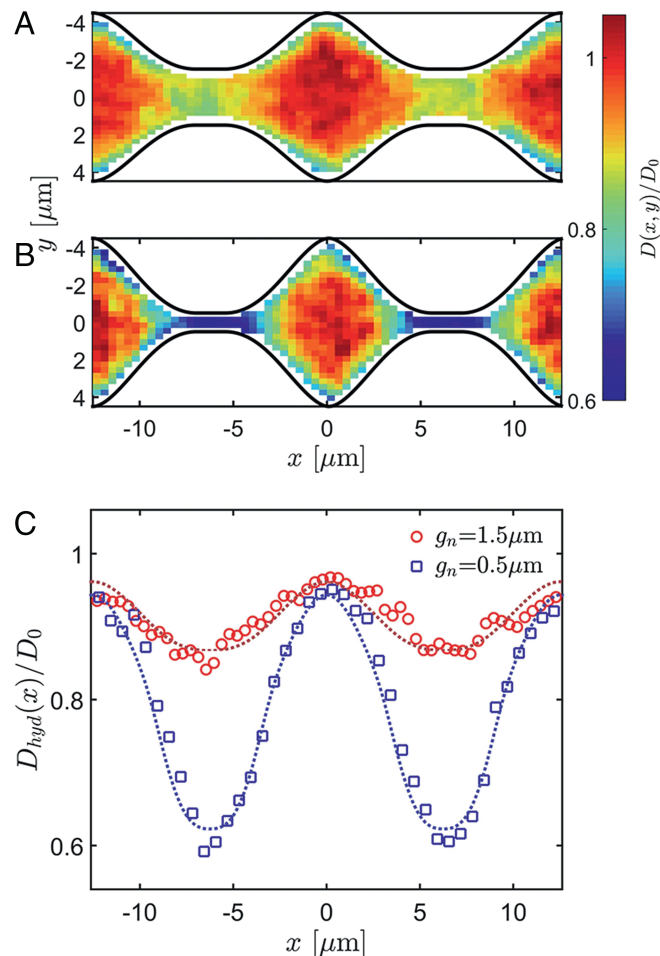
**Hydrodynamic Correction.** Fig. 4 depicts that particle diffusion through narrow bottlenecks can be significantly slower than in the wide region; moreover, the spatial modulation of the local particle diffusivity increases with decrease in the bottleneck width, which explains the results in Fig. 3. This spatial modulation is in clear contrast with the assumption of constant diffusivity that we adopted above when implementing the FJ formalism and the BD simulation code. To appreciate the effect of the spatial dependence of the local diffusivity, we replace the constant diffusivity,  $D_0$ , with the experimental measurement,  $D_{hyd}(x)$ , reported in Fig. 4C, both in the theoretical treatment and in the numerical code. The analytical and numerical predictions are plotted in Fig. 2 C–F as green curves and symbols, respectively. Their agreement with the experimental data is excellent. Furthermore, we used the improved BD code to also compute, other than the first two FPT moments, the FPT distributions displayed in Fig. 2 A and B. Again, the close comparison obtained with the experimental data confirms the validity of our phenomenological approach.

## Discussion

The coincidence of approximate analytical predictions and simulation results occurs for any choice of the local diffusivity [i.e.,  $D_0$  or  $D_{hyd}(x)$ ] as illustrated in Fig. 2. This means that the FJ theory well-describes the entropic effects of particle transport in weakly corrugated channels with  $|g'(x)| < 1$  (21). However, assuming constant particle diffusivity, as is common practice in the current literature, can lead to large discrepancies between theoretical predictions and experimental observations. Indeed, to correctly analyze the diffusion of finite-sized parti-

cles in narrow channels, one needs to account for the hydrodynamic effects as well. Because there is no general analytical solution for particle diffusivity in a corrugated confinement, we substituted the constant diffusivity,  $D_0$ , with an empirical function from experimental measurements,  $D_{hyd}(x)$ . The substitution  $D_0 \rightarrow D_{hyd}(x)$  in Eq. 3 suggests a phenomenological factorization of entropic and hydrodynamic effects, with validity that is justified a posteriori by the reported close comparison with the experimental data. In conclusion, we have shown that, by making use of the measured diffusivity  $D_{hyd}(x)$  in Fig. 4C, the FJ theory can be improved to accurately predict the FPT statistics of Fig. 2; the FJ approach thus remains a powerful analytical tool to investigate diffusion in complex channels.

As shown in Fig. 4 A and B, the local diffusivity,  $D(x, y)$ , displays a rich 2D structure, which cannot be analytically predicted. The comparison with a more tractable geometry helps illustrate the phenomenon of the hydrodynamic diffusivity suppression advocated above. For a spherical particle of a radius  $r$  diffusing along the axis of a relatively long cylinder (34, 49), the particle diffusivity is approximated by



**Fig. 4.** (A and B) Normalized local diffusivity from experiments,  $D(x, y)/D_0$ , measured in the wide and narrow channels of Fig. 2. (C) Normalized diffusivity,  $D_{hyd}(x)/D_0$ , vs.  $x$ . Experimental data and results from finite element calculations are represented by symbols and curves, respectively. Experimentally measured  $D_0$  values are 0.29 and 0.27  $\mu\text{m}^2/\text{s}$  for wide and narrow channels, respectively; the Stokes–Einstein equation predicts a sphere diffusivity of  $D_{SE} = 0.5 \mu\text{m}^2/\text{s}$  in an unbounded space.



$$D_{\text{cyl}} \approx D_{\text{SE}} \left[ 1 - 2.104 \left( \frac{r}{R} \right) + 2.089 \left( \frac{r}{R} \right)^3 \right], \quad [6]$$

where  $R$  denotes the cylinder radius. According to Eq. 6, particle diffusivity in confined geometries is generally smaller than in an unbounded space. In our channels, the maximum diffusivity  $D_0$  is about 60% of the Stokes–Einstein predicted value,  $D_{\text{SE}}$  (Fig. 4). Diffusivity also tends to decrease as the confinement grows tighter (i.e., for larger  $r/R$ ); this qualitatively explains why diffusivity is smaller in the necking regions of our channel. In certain applications, such as the entropic splitters (33), one has recourse to tight confinement to generate high entropic barriers; we expect hydrodynamically suppressed diffusion to play an important role in these situations and possibly boost the separation efficiency.

In this work, we focused on the nonadvective diffusion of a single particle, although technological applications often involve many suspended particles driven by external fields (12, 35–38). Particle transport is certainly complicated by excluded volume and hydrodynamic interactions between nearby particles in dense suspensions. Moreover, external driving may prevent the system from equilibrating in the transverse directions and produce even more complex transport patterns (20); it can also cause additional hydrodynamic effects (36, 37, 50). The experimental setup and the data analysis methods presented here provide a promising framework for future systematic investigations of these important and challenging problems.

## Materials and Methods

**Channel Fabrication and Imaging Procedure.** Microchannels were fabricated with a two-photon direct laser writing system ( $\mu\text{FAB3D}$  from Teem Photonics). This system uses a microscope objective lens (Zeiss Fluor 100 $\times$ , N.A. 1.3) to focus pulsed laser (Nd:YAG microchip laser with 532-nm wavelength, 750-ps pulse width, and 40-kHz repetition rate) into a droplet of photorealist resin that is mounted on a piezo-nanopositioning stage (Physik Instrumente model P-563.3CL). We used a polymer resin ORMOCOMP (Micro Resist Technology GmbH) with a photoinitiator [1,3,5-Tris(2-(9-ethylcabazyl-

3)ethylene)benzene]. Photopolymerization occurs and solidifies the resin at the focal point; the piezo stage scans the resin relative to the focal point along a preassigned trajectory [ $f(x)$  in Fig. 1A, *Inset*] to fabricate the desired structure. After the scanning is finished, the remaining liquid resin was removed by washing the structure with 4-methyl-2-pentanone and then acetone for 5 min. Then, channels were thoroughly cleaned with distilled water to prevent particles from sticking to the channel boundaries.

Fluorescently labeled Polystyrene particles were purchased from Invitrogen (catalog no. F13080). Particle motion was recorded through a 60 $\times$  oil objective (N.A. 1.3) in an inverted fluorescent microscope (Nikon Ti-E). With the help of an autofocus function (Nikon Perfect Focus), we imaged the diffusion of a colloidal particle in the channel for up to 20 h at room temperature (27  $^{\circ}\text{C}$ ).

**BD Simulation.** The motion of a colloid particle is governed by a 2D overdamped Langevin equation in simulations. The particle diffusivity varies spatially when the diffusivity function  $D_{\text{hyd}}(x)$  is used; for thermodynamic consistency, we adopted the transport (also known as kinetic or isothermal) convention (51–54) to compute the stochastic integral (51, 55). The channel boundary was represented by a string of fixed particles, which interact with the colloidal particle via a short-range repulsive force. Particle trajectories from simulation were analyzed in the same way as their experimental counterpart to extract the effective volume of the channel's unit cell and the FPTs. *SI Appendix* has more details.

**Finite Element Calculation.** We solved the Stokes equations in a typical setup shown in *SI Appendix*, Fig. S2A. No slip boundary conditions were imposed on the side walls, floor, and ceiling, and open boundary conditions were imposed at the channel openings. The geometry of the side wall was set to reproduce the inner channel boundary measured in the experiments (Fig. 1A, *Inset*). A sphere was driven with a constant speed,  $v_x$ , in the  $x$  direction; at different points,  $(x, y)$  is on a horizontal plane. We measured the drag force,  $f_x$ , and computed the hydrodynamic drag coefficient,  $\gamma(x, y) = f_x/v_x$ . *SI Appendix* has more details.

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