

The bigger the faster: non-monotonous translocation time of polymers across pores

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Polymers confined in corrugated channels, i.e. channels of varying amplitude, display **multiple local maxima and minima of the diffusion coefficient upon increasing their degree of polymerization N** . We propose a theoretical effective free energy for linear polymers based on a Fick-Jacobs approach. We validate the predictions against numerical data, obtaining quantitative agreement for **the effective free energy, the diffusion coefficient and the Mean First Passage Time**. Finally, we employ the effective free energy to compute the polymer lengths N_{min} at which the diffusion coefficient presents a minimum: we find a scaling expression that we rationalize with a blob model. Our results could be useful to design porous adsorbers, that separate polymers of different sizes without the action of an external flow.

The transport of polymers across corrugated channels and pores is of capital importance for several biological scenarios and technological applications, such as cell regulation [1], DNA and protein sequencing [2–4] and polymer separation [5]. Further, polymer transport across corrugated channels is still an open challenge [6] since it couples all polymer’s degrees of freedom (from the monomer up to the full chain length) to the channel geometry in a non-trivial manner. Such an interplay can lead to surprising phenomena. Polymers confined within nanoscopic cylindrical pores exhibit an enhanced mobility as compared to polymers in bulk [7] and nano-channel translocation of DNA can be enhanced by tailoring three-dimensional nano-funnels at the channel entrance [8]; similar entropic traps have been used to purify [9] and separate [10–13] DNA and to induce giant enhancement in polymer diffusion [14].

Despite its interest, an overall understanding of polymer transport across channels of varying section is still lacking. On the theoretical side, while much attention has been paid to the case of polymer translocation across a pinhole of the size of the monomers [15] the general problem of translocation across varying-section pores has not yet been fully addressed. The difficulty relies on the fact that, compared to the former case in which the polymer has to cross “head-first”, in the latter case the polymer can cross the pore’s bottleneck in a variety of configurations. The translocation probability will depend on monomer-monomer as well as on the monomer-walls effective interactions. In this regime, some analytical results have been derived for “short” polymers, whose gyration radius is much smaller than the distance L between subsequent bottlenecks [16]; numerical results have been derived for both linear [17] and ring polymers [18].

In this Letter, we show that the translocation time

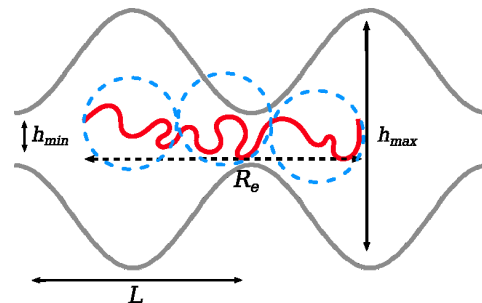


FIG. 1. Sketch of a linear polymer confined in a corrugated channel, whose radius changes from h_{min} at the bottleneck to h_{max} in the widest section. Dashed circles mark correlated blobs of size $h_0 = (h_{min} + h_{max})/2$.

as well as the **effective diffusion coefficient** of a linear polymers across a varying-section channel (see Fig.1) attains a non-monotonous dependence on the polymer size, N . Remarkably, the deviation of the diffusion coefficient from the expected $1/N$ Rouse dependence can be 10 to 100-fold. In order to understand such a behavior we extend the Fick-Jacobs approximation for (short) polymers [16] to the case of arbitrarily long polymers by accounting, in an effective way, for the extension of the polymer inside the corrugated channel. Once validated against the numerical data, we exploit our model to predict the polymer size N_{min} at which the diffusion minima occur and we investigate the scaling properties of such quantities with respect to the geometry of the corrugated channel. These features can be captured by a simple blob model, that yields the scaling of N_{min} as a function of the geometry of the channel. Such a classic approach may provide a useful tool to design channels for polymer sorting.

We perform standard Langevin Dynamics simulations (see Suppl. Mat. 2A)[19] for channels of length $L = 25, 50\sigma$, average width $h_0 = 10, 12\sigma$ and different values of the modulation of the channel; here σ is the monomer size, taken as the unit length. The corrugated channel is characterized by three characteristic length scales: the minimum and maximum widths h_{min} and h_{max} and the corrugation length L along the channel axis (see Fig. 1). One usually recasts h_{min} and h_{max} into the entropic barrier $\Delta S = 2 \ln(h_{max}/h_{min})$ and the average width $h_0 = (h_{min} + h_{max})/2$.

Remarkably, Fig.2b) shows that for tailored channel geometries, upon growing the polymer length N the diffusion coefficient firstly decreases with N , it attains a minimum and then it grows again. This behavior, differs from the expected $1/N$ Rouse behavior (i.e., upon neglecting hydrodynamic interactions).

In order to clarify the physical origin of such a phenomenon, we derive an analytical model that maps the 3D dynamics of the confined polymers into the dynamics of a point particles moving in an effective 1D potential. In order to do so, we follow the Fick-Jacobs approximation [20–24] that has been validated and used to study the dynamics of diverse confined systems (see Ref.[25] and references therein for a brief Review). A similar model has been derived [16] (see Suppl. Mat. 1A for a brief summary) under the condition that the polymer gyration radius is much smaller than the channel period, L . If so, naming x the position of the centre of mass of the polymer along the channel axis, it is possible to model the effect of the confinement as a local contribution to polymer's free energy [16]. However, upon increasing the degree of polymerization N , such assumption is bound to fail. The polymer is, at some point, large enough to experience multiple channel periods at any location of the center of mass x , as sketched in Fig. 1. Hereby, we propose an approach to construct an effective free energy for arbitrarily long polymers. The free energy should account for the diverse confining scenarios experienced along the chain. Accordingly, we integrate the local free energy from Ref. [16] over an interval equal to the average magnitude of the end-to-end vector (R_e) and centered at the location of the center of mass

$$\beta F(x) = \frac{1}{R_e} \int_{x-R_e/2}^{x+R_e/2} \beta F_0(x') dx' \quad (1)$$

where $\beta F_0(x)$ is the polymer free energy from Ref.[16] and R_e depends on N and on the confinement (see Suppl. Mat. 1B). Finally, using Eq. (1), we compute the long time diffusion coefficient via the Fick-Jacobs formula [20–23, 25]

$$\frac{D}{D_N} = \frac{1}{(1 + \Gamma) \langle e^{-\beta F(x)} \rangle_x \langle e^{\beta F(x)} \rangle_x} \quad (2)$$

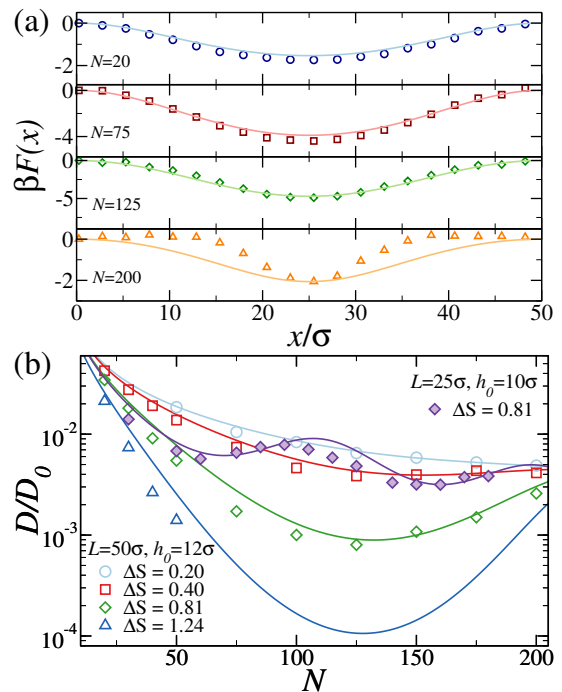


FIG. 2. a) Comparison between theoretical and numerical free energy along the channel axis for $L = 50\sigma$, $h_0 = 12\sigma$ and $\Delta S = 0.81$. Symbols refer to numerical free energies, lines to Eq. (1). We shift the curves so that the free energy at the bottleneck is always zero. b) Long time diffusion coefficient D , normalized by the diffusion coefficient of a single monomer D_0 , as function of N for different values of L , h_0 and ΔS . Symbols refer to numerical data, lines to the theoretical estimation Eqs. (1), (2).

where $\Gamma = 2(h_{max} - h_{min})^2/L^2$ is the so-called Zwanzig coefficient [20]; for most cases considered in this paper Γ is small ($\Gamma \approx 10^{-2}$) and can be rather safely ignored.

First, we compare theoretical and numerical free energies in Fig. 2a as a function of the coordinate x , that again marks the position of the centre of mass of the polymer along the longitudinal axis of the channel, for $L = 50\sigma$, $\Delta S = 0.81$ and $h_0 = 12\sigma$. As shown, the comparison is very favourable up to polymers with $N \approx 125$. Afterwards, it becomes less quantitative, even though the free energy difference $\beta \Delta F$ is quite well captured by the model, even at $N = 200$.

In Fig. 2b we compare theoretical and numerical data for the long-time diffusion coefficient D/D_0 , where D_0 is the diffusion coefficient of a single monomer, as a function of N for different values of L , h_0 and ΔS . Theoretical data are computed using Eq. (1) and (2); numerical data are reported only if the vast majority ($> 90\%$) of the trajectories diffused at least up to one channel corrugation from their initial point x_0 (i.e. up to $x_0 \pm L$). (see Suppl. Mat. 2D).

We find a good agreement between theoretical and numerical data, both showing a clear non-monotonic be-

behaviour. Remarkably, the position of the diffusion minimum N_{min} is always rather well captured by the theory. The non-monotonic nature of the diffusion coefficient can be emphasized looking at D/D_N (see Suppl. Mat. 2B), D_N being the bulk diffusion coefficient of a linear polymer of N monomers. Such a quantity highlights the effect of the confinement, removing the contribution due to the increase in size. However, we highlight in Fig. 2b that the diffusion coefficient may vary by one or even two orders of magnitude, upon changing the polymer size roughly by a factor of two. Thus, the difference in the diffusion time scales for polymers of slightly different size can be substantial: such a difference can easily be measured in experiments or exploited for material design.

In many of biological scenarios, a relevant quantity is the time at which the polymer crosses a bottleneck for the first time i.e. its first passage time. Typically, the mean of the first passage time distribution is taken as representative of the "typical time" taken by the polymer to cross a barrier. However, in several systems [26–29] the distribution of the first passage time is quite broad and skewed, thus its mean may not be so significant. Accordingly, we employ Eq. (1) to compute the Mean First Passage Time (MFPT) T_1 , its variance σ_{T_1} and, the so-called coefficient of variation $\gamma = \sigma_{T_1}/T_1$ [26–29] that quantify the statistical likelihood of a departure from the mean. Following [29], we define the Mean First Passage Time as the time required to the centre of mass of the polymer to displace a distance L in either directions along the channel axis, from its initial point. From Eq. (1), the MFPT can be computed as

$$T_1(x_0) = \frac{1}{D_N} \int_{x_0}^{x_0+L} dx' e^{\beta F(x')} \int_{x_0}^{x'} dx'' e^{-\beta F(x'')} \quad (3)$$

where x_0 is the initial point of the trajectory (see Suppl. Mat. 1E, 2D).

We report, in Fig. 3, the comparison between numerical and analytical results for both T_1 and γ . In particular, we observe in Fig. 3(a) that the comparison for the MFPT is again quantitative; the comparison for γ (Fig. 3 b and c) is instead mostly qualitative. This has to be expected: for $\gamma \approx 1$ the standard deviation is comparable to the mean and a considerable amount of data is required for a precise estimation of σ_{T_1} . Nevertheless, theory and simulations agree on the range of values of γ as well as on the qualitative trends.

Such a remarkable agreement shows that the simple model in Eq. (1) not only provides quantitatively reliable predictions for average quantities such as the diffusion coefficient and the MFPT, but it is also reliable for what concerns higher moments of the first passage time distribution.

This motivated us to examine the predictions of the theory for a broad range of L , h_0 and ΔS values, ex-

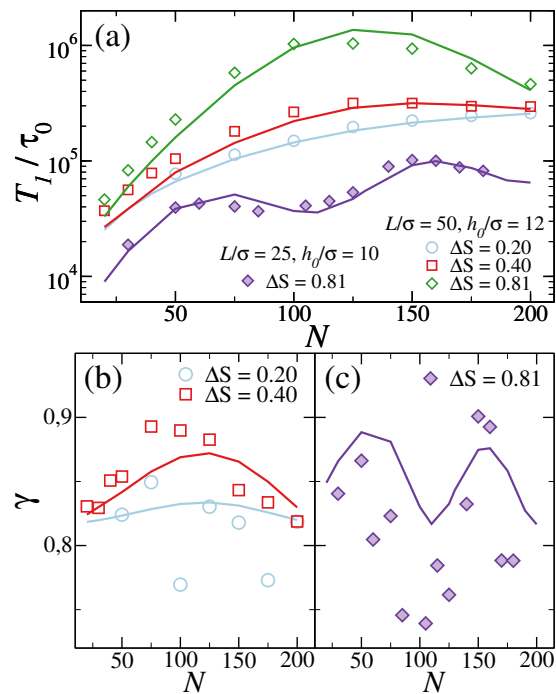


FIG. 3. (a) Mean Passage Time $T_1\tau_0$, normalized over time unit τ_0 , and (b),(c) coefficient of variation γ as a function of N for different values of ΔS , h_0 and L . Symbols refer to results from simulations, lines to theoretical calculations.

ploiting the predictive power of Eq. (1). It is instructive to look at the theoretical results as a function of N . In Fig. 4 we plot the theoretical estimates for $\beta\Delta F$ (Fig. 4a) and for D/D_N (Fig. 4b). The theory predicts a periodic dependence for both quantities on the polymer size N , as also observed in our simulation data and in the literature [18]. The period of the oscillations as well as that the ratio between the diffusion coefficient at the extrema, D_{max}/D_{min} , varies with the channel average section h_0 . As expected, the theoretical approach identifies $\beta\Delta F$ as the “driving force” for the non-monotonic diffusion: indeed, the frequency of the oscillation of $\beta\Delta F$ is always half the frequency of the oscillation of D/D_N . As shown in Fig. 4, the extrema of $\beta\Delta F$ correspond to the minima of D/D_N , while the zeros of $\beta\Delta F$, indicating a flat free energy landscape, correspond to the maxima of the diffusion.

Finally, we focus on the theoretical prediction of the position of the diffusion minima. Fig. 5a shows the scaling properties of the first minimum of the diffusion coefficient as function of the channel width. Remarkably, the data obtained at different values of ΔS and L collapse onto a master curve, when reporting N_{min} as a function of $h_0^{2/3}L/\sigma^{5/3}$. Considering all the subsequent minima $N_{min}(\bar{n})$ in Fig. 5b, ranked by their appearance index, for $\Delta S = 0.81$ and different values of L and h_0 , we can clearly observe a linear behaviour. Both results can be understood using a blob model [30] (see Appendix A),

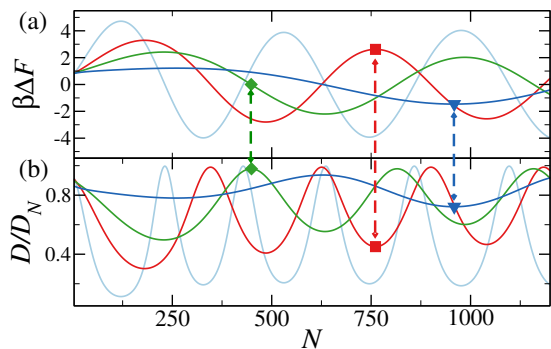


FIG. 4. (a) Theoretical free energy difference $\beta\Delta F$ and (b) theoretical diffusion coefficient D/D_N as a function of the degree of polymerization N for a channel of length $L = 50\sigma$, $\Delta S = 0.81$ and $h_0 = 12\sigma$ (light blue), $h_0 = 20\sigma$ (red), $h_0 = 28\sigma$ (green), $h_0 = 48\sigma$ (blue). Symbols refer to the position of (a) the extrema and the zeros of ΔF (b) maxima and minima of D .

that predicts the scaling reported above; indeed, the blob model properly captures not only the position of the first minimum but also that of all the other minima (Fig. 5b). It also suggests that the position of the minimum (and, actually, of all minima) is independent on ΔS . Such a finding is in agreement with the free energy model (see Appendix B).

The blob model can inspire alternative approaches to an effective free energy. If h_0 is the blob length scale, then one may introduce non-local contributions to the free energy via an effective channel width, averaging the channel profile over the length scale R_e . Albeit less precise, this alternative approach still maintains a very good agreement with numerical data (see Appendix B). This shows that the idea of incorporating contributions by a suitable averaging is robust.

In summary, we have shown that the diffusion coefficient of linear polymers across varying-section channels has a non-monotonous dependence on the polymer length N . In particular, we observe that the deviation from the Rouse behaviour can be significant (10 – 100-fold) and can be exploited to design devices aiming at polymer sorting. In order to understand such a counter-intuitive behavior we have derived (and validated against numerical data) an effective free energy approach which captures the non-monotonic behavior quantitatively. The approach, based on the Fick-Jacobs theory, incorporates non-local effects of the confining channel through the average of the local free energy. Our model shows that the non-monotonous (and oscillating) behavior is due to the (periodic) smearing out of the effective free energy barrier for polymers that occupy an integer number of channels (see Fig. 4). Remarkably, a similar behavior has been observed experimentally, for example in the case of polymer transported across an array of entropic traps [14] as well as for pluronic gels [31]. Moreover, in many circum-

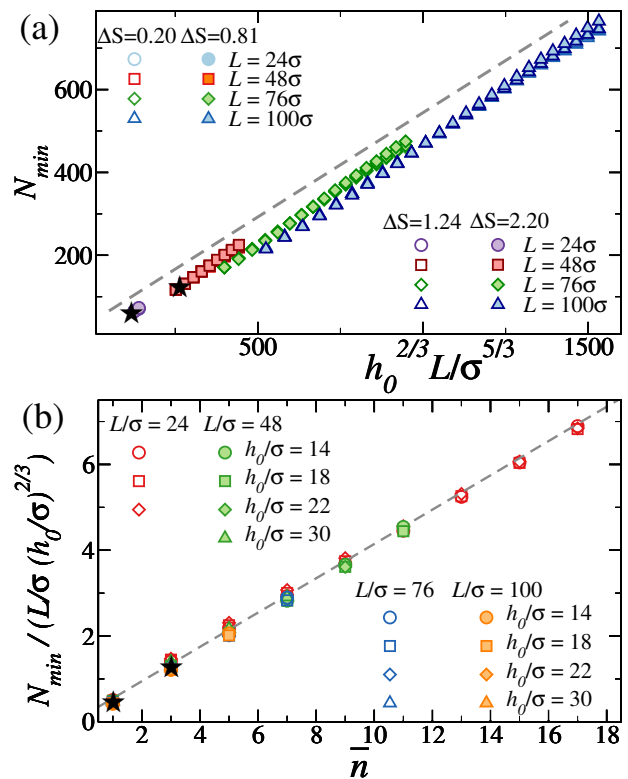


FIG. 5. (a) Scaling of the position of the first minimum of the diffusion coefficient as a function $h_0^{2/3} L / \sigma^{5/3}$ for different values of L and ΔS . (b) Scaling of the positions of the diffusion minima N_{min} as a function of their appearance index n for different values of L and h_0 at $\Delta S = 0.81$. The black star symbols refer to the numerical data, extracted from Fig. 2b.

stances, the dynamics is controlled by the first passage of polymers across a pore. We have used our model to predict both the mean and the variance of the first passage time distribution. As shown in Fig. 3 our model precisely predicts the mean and qualitative captures the dependence of the variance of the first passage distribution on N .

Finally, we exploited the remarkable agreement between theoretical and numerical data to investigate the scaling of the minima of the diffusion coefficient as a function of the channel geometry and we have captured such scaling via blob theory. **Even though our model and numerical results do not account for finite bending rigidity, this can be effectively accounted for by renormalizing the monomer size in the model to the persistence length and the number of monomers to the number of Kuhn segments [32]. Accordingly, we expect our results to hold in presence of a moderate bending rigidity and deviation can be expected when the persistence length becomes comparable with the full contour length of the polymer as well as for rigid rods [33].** Our findings present a significant theoretical improvement in the understanding of the diffusion of polymers in complex landscapes and, further,

provide very useful tools for characterizing the diffusion properties in complex porous materials. One could, for example, envisage a "sponge", designed to have pores of different roughness that can effectively sort different polymers by size in a passive way. Such a device could be useful in situation where it is hard to produce a flow or where the polymers may be degraded by the action of an external force. Finally, from a theoretical perspective, it would be interesting to check if this effective approach works far from equilibrium, for example with active polymers. Work is in progress in that respect, with the aim of unravelling the effect of activity on the polymer dynamics in corrugated channels.

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APPENDIX A: BLOB MODEL

We describe here the blob model, employed to rationalize the scaling of the diffusion minima reported in the main text. We assume that the polymer organizes into blobs of radius $\sim h_0/2$. A polymer made of N monomers has $n_b = N/M$ blobs, where M is the number of monomers in a blob, given by $\alpha M^{\frac{3}{5}} = h_0/(2\sigma)$, α being a dimensionless constant, and σ the monomer size. It follows that

$$M = \left(\frac{h_0}{2\alpha\sigma} \right)^{\frac{5}{3}} \quad (4)$$

In blob theory, the length of a polymer ℓ scales linearly with the number of blobs; in our case $\ell = n_b h_0$. We argue that, when ℓ exactly matches an integer multiple of L $\ell = \bar{n}L$ ($\bar{n} = 1, 2, 3, \dots$) we expect $\beta\Delta F$ to be null, i.e. $\beta F(x)$ to be constant. In fact, for such a case, the polymer experiences the "same confinement" (in the sense of the effective free energy) irrespective of the position of the center of mass, as a consequence of the **periodicity** of the corrugation profile. Since this is true only for the set of values $\ell = \bar{n}L$ ($\bar{n} = 1, 2, 3, \dots$), this also entails that $\beta\Delta F$ as a function of N is oscillating; the extremal point will be then placed at $\ell = \bar{n}L/2$. As seen in the main text, the extrema in the free energy difference correspond to minima in the diffusion: thus

$$\frac{\bar{n}}{2}L = n_b^{\min} h_0 = \frac{N_{\min}}{M} h_0 \quad (5)$$

sets the condition for N_{\min} . Accordingly, we get

$$N_{\min} = \frac{\bar{n}}{2} \frac{L}{h_0} \left(\frac{h_0}{2\alpha\sigma} \right)^{\frac{5}{3}} = \frac{\bar{n}}{2} \frac{1}{\alpha^{\frac{5}{3}}} \frac{L}{\sigma} \left(\frac{h_0}{2\sigma} \right)^{\frac{2}{3}} \quad (6)$$

As noticed in the main text, this relation can be recast as

$$\frac{N_{\min}^{3/2}}{(L/\sigma)^{5/2}} \propto h_0/L \quad (7)$$

which highlights the two length scales of the system h_0 and L . As noticed in the main text, this relation is unaware of ΔS , which is also reflected by the numerical data (see Suppl. Mat. Section 1.E). Finally, it is interesting to notice that, via our model, a similar scaling is expected also for the maxima of the diffusion coefficient.

APPENDIX B: EFFECTIVE FREE ENERGY APPROACHES

We consider three different approaches to construct an effective free energy; each one is characterized by a different approximation. While all of them qualitatively explain the non-monotonicity of the diffusion coefficient as a function of N , the agreement with numerical data varies quantitatively.

We start recalling the definition of the free energy in the case of a polymer whose gyration radius is much shorter than the channel length

$$\beta F_0(x) = - (d-1) \left\{ \ln \left[\frac{16h(x)}{h_0\pi^2} \right] + \ln \left[\sum_{p=1,3,\dots}^{\infty} \frac{1}{p^2} \exp \left(-\pi^2 p^2 \left(\frac{R_g}{2h(x)} \right)^{1/\nu} \right) \right] \right\} \quad (8)$$

where the values of ν and R_g depend on the polymer chain considered (Gaussian or self-avoiding). For our purposes, we used the following functional form for the bulk gyration radius $R_g^b = 0.58735 \cdot N^{0.588} \cdot (1 - 0.435588 \cdot N^{-0.2228})$, with thus $\nu = 0.588$.

The *first approach* is the one reported in the main text: we average the free energy Eq.(8) over the characteristic length scale given by the magnitude of the (average) end-to-end vector. This approach provides the best comparison with the numerical data. The main idea is to include non-local contributions to the free energy. These contributions come from the fact that a sufficiently large polymer is, at any given time, extended along the channel and experiences different degrees of confinement. The resulting free energy reads

$$\beta F(x) = \frac{1}{R_e} \int_{x-R_e/2}^{x+R_e/2} \beta F_0(x') dx' \quad (9)$$

where $\beta F_0(x')$ is the polymer free energy from Ref.[16] and R_e depends on N and on the confinement.

The *second approach* aims at incorporating the hypothesis of the blob model (see Appendix A) into the calculation of the free energy. The blob model assumes that the polymer organizes into sections with correlation length (blob radius) h_0 ; thus h_0 is the relevant length scale of the confinement. Yet, for a single blob picture, such as the one proposed here, an effective confinement length h_0^* is necessary; it has to include the contributions of non-locality and of the channel geometry. We thus define $h_0^*(x)$ as

$$h_0^*(x) = \frac{1}{R_e} \int_{x-R_e/2}^{x+R_e/2} h(x') dx' \quad (10)$$

The free energy is given by Eq. (8) where $h(x)$ is replaced with $h_0^*(x)$.

Finally, the *third approach* aims at introducing a minimal perspective. Indeed, we compute the free energy difference using the first approach but we drastically simplify the functional form by considering a piece-wise linear function

$$\beta F(x) = \begin{cases} -\frac{2|\beta\Delta F|x}{L} & x < L/2 \\ -2|\beta\Delta F| + \frac{2|\beta\Delta F|x}{L} & x \geq L/2 \end{cases} \quad (11)$$

In Fig. 6, we report the comparison between the first and second approach. The first approach incorporates non-local effect averaging the free energy, the second approach averaging of the corrugation profile. In Fig. 6(a) we compare the theoretical free energies for different values of N for the same systems considered in the main text, i.e. for $\Delta S = 0.81$, $L = 50\sigma$, $h_0 = 12\sigma$. The comparison is favourable and, upon increasing N the two approaches produce the same free energy difference. Indeed, as reported in Fig. 6(b), the diffusion coefficient predicted by the two approaches are very similar (here for $\Delta S = 0.81$, $L = 25\sigma$, $h_0 = 10\sigma$). Albeit the second approach is slightly less precise, it is able to reproduce very well the important features of the numerical data, such as the position of the two diffusion minima. It also remains predictive even when the polymer size is larger than the corrugation length (see Suppl. Mat. 2.C). Further, in the inset of Fig. 6(b) we plot the difference between the free energy difference for the two approaches in a large span of values of N . Notably, the absolute difference never exceeds $0.6 k_B T$ ($0.1 k_B T$ if $N > 200$).

Finally, we compare the second and third approaches with numerical data. In Fig. 7(a) we compare the diffusion coefficient while in Fig. 7(b) we compare the Mean Passage Times. In both cases we observe that the alternative approaches are less precise than the free energy average but retain the salient features, such as the position of the minimum, and provide a decent comparison with numerical data, considering there are no free parameters and no input from the simulations.

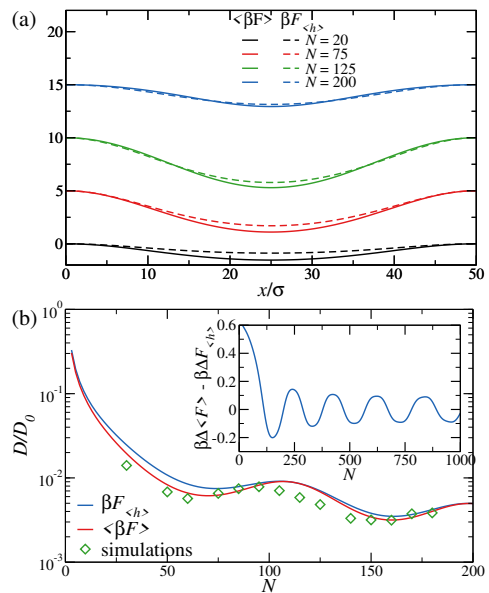


FIG. 6. (a) Comparison between the free energy from the first approach Eq. (9) (solid lines) and the second approach Eqs. (8) and (10) (dashed lines), as a function of the channel coordinate. Curves have been shifted arbitrarily. (b) Comparison between the prediction of the first two theoretical approaches and numerical data as a function of N . Inset: Difference between the free energy differences obtained through the first and second theoretical approaches as a function of N . In all panels $\Delta S = 0.81$ while panel (a): $L = 50\sigma$, $h_0 = 12\sigma$; panel (b) $L = 25\sigma$, $h_0 = 10\sigma$

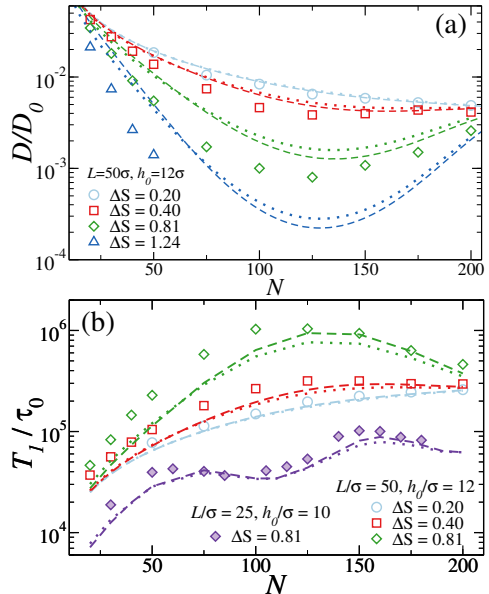


FIG. 7. Comparison between the alternative theoretical approaches and the numerical data for (a) the diffusion coefficient and (b) the Mean Passage Time, for different values of ΔS , L and h_0 .

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- [1] B. Alberts, A. Johnson, J. Lewis, M. Raff, K. Roberts, and P. Walter, *Molecular Biology of the Cell* (Garland Science, Oxford, 2007).
- [2] W. Reisner, J. N. Pedersen, and R. H. Austin, Reports on Progress in Physics **75**, 106601 (2012).
- [3] C. Rathnayaka, C. A. Amarasekara, K. Akabirov, M. C. Murphy, S. Park, M. A. Witek, and S. A. Soper, Journal of Chromatography A **1683**, 463539 (2022).
- [4] B. M. Floyd and E. M. Marcotte, Annual Review of Biophysics **51**, 181 (2022).
- [5] M. Sonker, D. Kim, A. Egatz-Gomez, and A. Ros, Annual Review of Analytical Chemistry **12**, 475 (2019).
- [6] M. Ding and L. Li, Macromolecules **54**, 9773 (2021).
- [7] K. Shin, S. Obukhov, J.-T. Chen, J. Huh, Y. Hwang, S. Mok, P. Dobriyal, P. Thiagarajan, and T. P. Russell, Nature Materials **6**, 961 (2007).
- [8] J. Zhou, Y. Wang, L. D. Menard, S. Panyukov, M. Rubinstein, and J. M. Ramsey, Nat Commun **8**, 807 (2017), number: 1 Publisher: Nature Publishing Group.
- [9] P. Agrawal, Z. Bognár, and K. D. Dorfman, Lab Chip **18**, 955 (2018), publisher: The Royal Society of Chemistry.
- [10] J. Han, S. W. Turner, and H. G. Craighead, Phys. Rev. Lett. **83**, 1688 (1999).
- [11] L. Liu, P. Li, and S. Asher, Nature **397**, 41 (1999).
- [12] J. Han and H. G. Craighead, Science **288**, 1026 (2000).
- [13] Y. M. Lee and Y. L. Joo, The Journal of Chemical Physics **127**, 124902 (2007).
- [14] D. Kim, C. Bowman, J. T. Del Bonis-O'Donnell, A. Matzavinos, and D. Stein, Phys. Rev. Lett. **118**, 048002 (2017), publisher: American Physical Society.
- [15] M. Muthukumar, *Polymer translocation* (CRC Press, Boca Raton, 2011).
- [16] V. Bianco and P. Malgaretti, The Journal of Chemical Physics **145**, 114904 (2016).
- [17] D. Mondal and M. Muthukumar, The Journal of Chemical Physics **145**, 084906 (2016).
- [18] M. Marenza, E. Orlandini, and C. Micheletti, Soft Matter **13**, 795 (2017).
- [19] See Supplemental Materials at [URL will be inserted by publisher] for additional definitions and theoretical details, model and simulation details, and additional numerical data, including Refs.[68-73].
- [20] R. Zwanzig, J. Phys. Chem. **96**, 3926 (1992).
- [21] D. Reguera, G. Schmid, P. S. Burada, J. M. Rubi, P. Reimann, and P. Hänggi, Phys. Rev. Lett. **96**, 130603 (2006).
- [22] I. Pineda, J. Alvarez-Ramirez, and L. Dagdug, J. Chem. Phys. **137**, 174103 (2012).
- [23] A. M. Berezhkovskii, L. Dagdug, and S. M. Bezrukov, J. Chem. Phys. **143**, 164102 (2015).
- [24] I. Malgaretti, P. Pagonabarraga and M. Rubi, Frontiers in Physics **1**, 21 (2013).
- [25] P. Malgaretti and J. Harting, Entropy **25**, 470 (2023).
- [26] T. Mattos, C. Mejía-Monasterio, R. Metzler, and G. Oshanin, Phys. Rev. E **86**, 031143 (2012).
- [27] T. Mattos, C. Mejía-Monasterio, R. Metzler, G. Oshanin, and G. Schehr, in *First-Passage Phenomena and Their Applications*, edited by R. Metzler, G. Oshanin, and S. Redner (2014).
- [28] D. S. Grebenkov, R. Metzler, and G. Oshanin, Communications Chemistry **1**, 96 (2018).
- [29] P. Malgaretti and G. Oshanin, Polymers **11**, 251 (2019).
- [30] P. deGennes, *Scaling concepts in polymer physics* (Cornell University Press, Ithaca, 1979).
- [31] S. You, L. Wei, S. Shanbhag, and D. H. Van Winkle, Phys. Rev. E **95**, 042602 (2017), publisher: American Physical Society.
- [32] M. Doi and S. Edwards, *The theory of polymer dynamics* (Clarendon Press, 1986).
- [33] P. Malgaretti and J. Harting, Soft Matter **17**, 2062 (2021).