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Polymer translocation through a nanopore: A showcase of anomalous diffusion

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The translocation dynamics of a polymer chain through a nanopore in the absence of an external driving force is analyzed by means of scaling arguments, fractional calculus, and computer simulations. The problem at hand is mapped on a one-dimensional anomalous diffusion process in terms of the reaction coordinate s (i.e., the translocated number of segments at time t) and shown to be governed by a universal exponent $\alpha=2/(2\nu+2-\gamma_1)$, where ν is the Flory exponent and γ_1 is the surface exponent. Remarkably, it turns out that the value of α is nearly the same in two and three dimensions. The process is described by a fractional diffusion equation which is solved exactly in the interval $0<s<N$ with appropriate boundary and initial conditions. The solution gives the probability distribution of translocation times as well as the variation with time of the statistical moments $\langle s(t)\rangle$ and $\langle s^2(t)\rangle-\langle s(t)\rangle^2$, which provide a full description of the diffusion process. The comparison of the analytic results with data derived from extensive Monte Carlo simulations reveals very good agreement and proves that the diffusion dynamics of unbiased translocation through a nanopore is anomalous in its nature.

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The dynamics of polymer translocation through a pore has recently received a lot of attention and appears highly relevant in both chemical and biological processes [1]. The theoretical cosideration is usually based on the assumption [2–4] that the problem can be mapped onto a one-dimensional diffusion process. The so-called *translocation coordinate* (i.e., reaction coordinate s) is considered as the only relevant dynamic variable. The whole polymer chain of length N is assumed to be in equilibrium with a corresponding free energy $\mathcal{F}(s)$ of an entropic nature. The one-dimensional (1D) dynamics of the translocation coordinate then follows the conventional Brownian motion, and the one-dimensional Smoluchowski equation [5] can be used with the free energy $\mathcal{F}(s)$ playing the role of an external potential. In the absence of external driving force (unbiased translocation), the corresponding average first-passage time follows the law $\tau(N)\propto a^2N^2/D$, where a is the length of a polymer Kuhn segment and D stands for the proper diffusion coefficient. The question of the choice of the proper diffusion coefficient D, and the nature of the diffusion process, is controversial. Some authors [2,3] adopt $D\propto N^{-1}$, as for Rouse diffusion, which yields $\tau\propto N^3$ as for polymer reptation [8], albeit the short pore constraint is less severe than that for a tube of length N. In Ref. [4] it is assumed that D is not the diffusion coefficient of the whole chain but rather that of the monomer just passing through the pore. The unbiased translocation time is then predicted to vary as $\tau\propto N^2$. The latter assumption has been questioned [6,7] too. Indeed, on the one hand, the mean translocation time scales [4] as $\tau\sim N^2$, but on the other hand the characteristic Rouse time (i.e., the time it takes for a *free* polymer to diffuse a distance of the order of its gyration radius) scales as $\tau_{\text{Rouse}}\propto N^{2\nu+1}$, where the Flory exponent $\nu=0.588$ at $d=3$, and $\nu=0.75$ at $d=2$ [8]. Thus $\tau_{\text{Rouse}}\gg\tau$, against common sense, given that the unimpeded motion should be in any case faster than that of a constrained chain. Moreover, the equilibration of the chain is questionable when the expression for $\mathcal{F}(s)$ is to be used. The characteristic equilibration time scales again as $\tau_{\text{eq}}\propto N^{2\nu+1}$ and is thus always larger than the translocation time, i.e., $\tau_{\text{eq}}\gg\tau$. Again the internal consistency of the whole approach is in doubt. It was found by Monte Carlo (MC) simulation [6,7] that $\tau\propto N^{2.5}$ for translocations in $d=2$. This indicates that the translocation time scales in the same manner as the Rouse time, albeit with a larger prefactor that depends on the size of the nanopore. Kantor and Kardar argued that this finding bears witness to the failure of the Brownian nature of the translocation dynamics and suggested instead that *anomalous diffusion dynamics* [9] should be more adequate. The $\tau\propto N^{2.5}$ scaling law has been corroborated by a further MC study [10], as well as by MC simulations on a 3D lattice [11], and it was shown that $\tau\propto N^{2.46\pm0.03}$. The time variation of the second statistical moment, $\langle s^2\rangle-\langle s\rangle^2\propto t^\alpha$, clearly indicates an anomalous nature [11], since the measured exponent $\alpha=0.81\pm0.01$, while $\tau\propto N^{2/\alpha}$. Still missing is a proper theoretical analysis which could explain the physical origin of the anomalous dynamics, and make it possible to solve the appropriate *fractional diffusion equation* (or, in case of a biased translocation, the fractional Fokker-Planck-Smoluchowski equation) [9,12] governing this dynamics.

In this Rapid Communication, we suggest a unique physical picture that justifies the mapping of the 3D problem on a 1D reaction cooordinate s, and we show that the latter obeys anomalous diffusion dynamics, described by a fractional diffusion equation. We solve this equation exactly, subject to the proper boundary conditions, and find a perfect agreement with our scaling prediction. Eventually, we demonstrate that the results of our 3D off-lattice MC simulations are in accord with our analytical findings.

Mapping onto 1D dynamics. As indicated above, the assumption that the whole polymer chain is in equilibrium and the diffusion is governed by conventional Brownian dynamics leads to contradictions. Instead, we assume now that only a *part* of the whole chain may equilibrate between two successive threadings. This part of the chain which adjoins the membrane on the *cis* or *trans* side will be denoted as *fold*, and we assume that it is much shorter than the whole chain length N but is still long enough so that one can use the

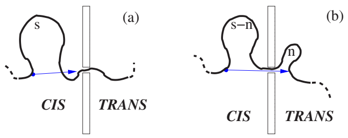

FIG. 1. (Color online) Schematic representation of a chain fold of length s moving through a nanopore. The transition rate is slowed down by an entropic barrier: (a) initially the fold is on the *cis* side of the wall; (b) the fold entropy decreases during threading because of the fold fragmentation.

principles of statistical physics. We also assume that the excluded volume interaction of a fold with the rest of the chain is relatively weak, so that it could be treated as a subsystem with a well-defined free energy. This latter assumption is based on the observation that the chain on either of the two sides may be seen as a polymeric "mushroom" whereby the monomer density close to the membrane (or wall) is much smaller than the density inside a single coil [see Fig. 4 and Eq. (II.4) in Ref. [13]]. Thus one can claim that there is a depletion area near the membrane [14].

Figure 1 illustrates how a fold squeezes from the *cis* to the *trans* side through a short nanopore (of length $\approx a$), which is slightly wider than the chain itself. It is self-evident that, in the absence of the external force, with the equal probability folds from the *trans* side could go to the *cis* side. If the *trans* part of the fold in Fig. 1 has length n then the corresponding free energy function $F^t(n)/T=-n\ln\kappa-(\gamma_1-1)\ln n$, where κ is the connective constant and γ_1 is the surface entropic exponent [15]. For the *cis* part of the fold, one has $F^c(n)/T=-(s-n)\ln\kappa-(\gamma_1-1)\ln(s-n)$ so that the total free energy is $\mathcal{F}(n)/T=-s\ln\kappa-(\gamma_1-1)\ln[n(s-n)]$. One can, therefore, ascribe to the fold *cis-trans* transition a pretty broad barrier given by $\mathcal{F}(n)$. The corresponding activation energy of the fold can be calculated as $\Delta E(s)=\mathcal{F}(s/2)-\mathcal{F}(1)=(1-\gamma_1)T\ln s$.

How can we estimate the characteristic time for the fold *cis-trans* translocation? In the absence of a separating membrane this would be the pure Rouse time $t_R\propto s^{2\nu+1}$ [8]. The membrane with a nanopore imposes an additional entropic activation barrier $\Delta E(s)$, which slows down the transition rate. The characteristic time, therefore, scales as $t(s)=t_R(s)\exp[\Delta E(s)]\propto s^{2\nu+2-\gamma_1}$. This makes it possible to estimate the mean-squared displacement of the s coordinate:

$$\langle s^2\rangle \propto t^{2/(2\nu+2-\gamma_1)}. \tag{1}$$

Hence, the mapping onto the s coordinate leads to an *anomalous diffusion* law $\langle s^2\rangle\propto t^\alpha$, where $\alpha=2/(2\nu+2-\gamma_1)$. Taking into account the most accurate values of the exponents for $d=3$, $\nu=0.588$, and $\gamma_1=0.680$ [16], we obtain $\alpha=0.801$. In turn, the average translocation time $\tau\propto N^{2/\alpha}\propto N^{2.496}$. Remarkably, in 2D, where $\nu_{2D}=0.75$ and $\gamma_1\approx 0.945$ [17], one finds $\alpha\approx 0.783$ (i.e., α is almost unchanged). This explains why the measured exponents in both 2D [6] and 3D [11] are so close. The derivation of α is our central scaling prediction. It also agrees well (see below) with our own MC data on the translocation exponent.

Fractional diffusion equation. We now turn to the fractional diffusion equation (FDE) that furnishes a natural framework for the study of anomalous diffusion [9,12]. Here we make use of this method in a systematic way. Our FDE reads

$$\frac{\partial}{\partial t}W(s,t)={}_0D_t^{1-\alpha}K_\alpha\frac{\partial^2}{\partial s^2}W(s,t), \tag{2}$$

where $W(s,t)$ is the probability distribution function (PDF) for having a segment s at time t in the pore, and the fractional Riemann-Liouville operator ${}_0D_t^{1-\alpha}W(s,t)=[1/\Gamma(\alpha)](\partial/\partial t)\int_0^t dt'\,W(s,t')/(t-t')^{1-\alpha}$. In Eq. (2) $\Gamma(\alpha)$ is the Gamma function, and K_α is the so-called generalized diffusion constant. This constant could be defined as $K_\alpha=\Gamma(1+\alpha)l^2/(2\tau_w^\alpha)$ in terms of the fold length l and the waiting time scale τ_w (see Chapter 3.4 in [9]). It should be mentioned that the constant K_α is the only adjustable parameter of our theory, and will be fixed below through the comparison with our MC data.

Recently the method of the generalized Langevin equation (GLE) has been used to describe anomalous conformational dynamics within single-molecule proteins [18]. In contrast to the FDE approach, which deals with the total distribution function at particular boundary conditions (see below), the GLE method treats only the first two moments (or time-correlation functions, memory kernel, etc.). To the best of our knowledge, at the present time it is not clear how one can derive in a closed form a non-Markovian Fokker-Planck equation for the distribution function [19] starting from the GLE. On the other hand, the translocation time distribution function (see below) is an entity of great importance because it could be directly measured in experiment [1]. Therefore, we prefer to use the FDE approach for the translocation problem.

Consider the boundary value problem for the FDE in the interval $0\leqslant s\leqslant N$. This problem has been discussed before in the context of the even more general fractional Fokker-Planck equation [20]. The boundary conditions correspond to the *reflecting-adsorbing* case, i.e., $(\partial/\partial s)W(s,t)|_{s=0}=0$ and $W(s=N,t)=0$. The initial distribution is concentrated in s_0, i.e., $W(s,t=0)=\delta(s-s_0)$. The full solution can be represented as a sum over all eigenfunctions $\varphi_n(s)$, i.e., $W(s,t)=\sum_{n=0}^\infty T_n(t)\varphi_n(s)$, where $\varphi_n(s)$ obey the equations $K_\alpha(d^2/ds^2)\varphi_n(s)+\lambda_{n,\alpha}\varphi_n(s)=0$, and the eigenvalues $\lambda_{n,\alpha}$ can be readily found from the foregoing boundary conditions; as a result $\lambda_{n,\alpha}=(2n+1)^2\pi^2K_\alpha/(4N^2)$. The temporal part $T_n(t)$ obeys the equation $(d/dt)T_n(t)=-\lambda_{n,\alpha}\,{}_0D_t^{1-\alpha}T_n(t)$. The solution of this equation is given by $T_n(t)=T_n(t=0)E_\alpha(-\lambda_{n,\alpha}t^\alpha)$ [9], where the Mittag-Leffler function $E_\alpha(x)$ is defined by the series expansion $E_\alpha(x)=\sum_{n=0}^\infty x^k/\Gamma(1+\alpha k)$. At $\alpha=1$ it turns back into a standard exponential function (normal diffusion). Thus we arrive at the complete solution of Eq. (2):

$$W(s,t)=\frac{2}{N}\sum_{n=0}^{\infty}\cos\left(\frac{(2n+1)\pi s_0}{2N}\right)\cos\left(\frac{(2n+1)\pi s}{2N}\right)\times E_\alpha\left(-\frac{(2n+1)^2\pi^2}{4N^2}K_\alpha t^\alpha\right). \tag{3}$$

First-passage time distribution. The distribution of translocation times (which could, in principle, be measured in experiment) is nothing but the *first-passage time distribution* (FPTD) $Q(s_0,t)$, where s_0 stands for the initial value of the s coordinate. Knowing the probability distribution function $W(s,t)$, we can calculate the FPTD $Q(s_0,t)$. The relation between the two functions is given as $Q(s_0,t) = -(d/dt)\int_0^t W(s,t)ds$ [5]. This yields the FPTD as follows:

$$Q(s_0,t) = \frac{\pi K_\alpha t^{\alpha-1}}{N^2}\sum_{n=0}^{\infty}(-1)^n(2n+1)\cos\left(\frac{(2n+1)\pi s_0}{2N}\right) \times E_{\alpha,\alpha}\left(-\frac{(2n+1)^2\pi^2}{4N^2}K_\alpha t^\alpha\right), \tag{4}$$

where the generalized Mittag-Leffler function $E_{\alpha,\alpha}(x) = \sum_{k=0}^{\infty} x^k/\Gamma(\alpha+k\alpha)$. The long time limits of Mittag-Leffler functions in Eqs. (3) and (4) follow an inverse power law behavior, $E_\alpha(-\lambda_{n,\alpha}t^\alpha) \propto 1/\Gamma(1-\alpha)\lambda_{n,\alpha}t^\alpha$ and $E_{\alpha,\alpha}(-\lambda_{n,\alpha}t^\alpha) \propto \alpha/\Gamma(1-\alpha)\lambda_{n,\alpha}^2 t^{2\alpha}$. By making use of this in Eq. (4), the long time tail of the FPTD then reads $Q(t) \propto \alpha N^2/2\Gamma(1-\alpha)K_\alpha t^{1+\alpha}$. This behavior is checked below in our MC investigation. It can be seen that the mean first-passage time, defined simply as $\tau = \int_0^\infty tQ(t)dt$, does not exist [21,22]. On the other hand, in a laboratory experiment there always exists some upper time limit t^*. Taking this into account, one can show that an "experimental" first-passage time scales as $\tau \sim N^{2/\alpha}$ [21], which we observe in our MC simulation.

Statistical moments $\langle s\rangle$ *and* $\langle s^2\rangle$ *vs time*. The subdiffusive behavior of the second moment $\langle s^2\rangle - \langle s\rangle^2 \propto t^\alpha$ is a hallmark of anomalous diffusion. Starting from Eq. (3) we can immediately calculate them. The calculation of the first moment $\langle s\rangle = \int_0^N sW(s,t)ds/\int_0^N W(s,t)ds$ yields

$$\frac{\langle s\rangle(t)}{N} = 1 - \frac{2\sum_{n=0}^{\infty}\frac{1}{(2n+1)^2}E_\alpha\left(-\frac{(2n+1)^2\pi^2}{4N^2}K_\alpha t^\alpha\right)}{\pi\sum_{n=0}^{\infty}\frac{(-1)^n}{(2n+1)}E_\alpha\left(-\frac{(2n+1)^2\pi^2}{4N^2}K_\alpha t^\alpha\right)}. \tag{5}$$

Since $E_\alpha(t=0)=1$, the initial value $\langle s\rangle(t=0)=0$ (we put $s_0=0$), as it should be. In the opposite limit, $t\to\infty$, we can use the asymptotic behavior $E_\alpha[-\lambda_{n,\alpha}t^\alpha] \simeq 1/\Gamma(1-\alpha)\lambda_{n,\alpha}t^\alpha$ as well as the sum values $\sum_{n=0}^{\infty}1/(2n+1)^4 = \pi^4/96$ and $\sum_{n=0}^{\infty}(-1)^n/(2n+1)^3 = \pi^3/32$ in the numerator and denominator, respectively. After that $\langle s\rangle(t\to\infty) = N/3$, i.e., the function goes to a *plateau*.

The result for the second moment $\langle s^2\rangle = \int_0^N s^2 W(s,t)ds/\int_0^N W(s,t)ds$ can be cast in the following form:

$$\frac{\langle s^2\rangle(t)}{N^2} = 1 - \frac{8\sum_{n=0}^{\infty}\frac{(-1)^n}{(2n+1)^3}E_\alpha\left(-\frac{(2n+1)^2\pi^2}{4N^2}K_\alpha t^\alpha\right)}{\pi^2\sum_{n=0}^{\infty}\frac{(-1)^n}{(2n+1)}E_\alpha\left(-\frac{(2n+1)^2\pi^2}{4N^2}K_\alpha t^\alpha\right)}. \tag{6}$$

Again, it can be readily shown that $\langle s^2\rangle(0) - \langle s\rangle^2(0) = 0$. In the long time limit, in the same way as before and taking into account that $\sum_{n=0}^{\infty}(-1)^n/(2n+1)^5 = 5\pi^5/1536$, we find $\langle s^2\rangle(t\to\infty) - \langle s\rangle^2(t\to\infty) = N^2/9$ [23].

Monte Carlo data vs theory. We have carried out extensive MC simulations in order to check the main predictions of the foregoing analytical theory. We use a dynamic bead-spring model which has been described before [24]; therefore we mention only the salient features here. Each chain contains N effective monomers (beads), connected by anharmonic finitely extensible nonlinear elastic springs, and the nonbonded segments interact by a Morse potential. An elementary MC move is performed by picking an effective monomer at random and trying to displace it from its position to a new one chosen at random. These trial moves are accepted as new configurations if they pass the standard Metropolis acceptance test. It is well established that such a MC algorithm, based on local moves, realizes Rouse model dynamics for the polymer chain. In the course of the simulation we perform successive run for chain lengths $N = 16, 32, 64, 128, 256$, whereby a run starts with a configuration with only a few segmens on the *trans* side. Each run is stopped, once the entire chain moves to the *trans* side. Complete retracting of the chain back to the *cis* side is prohibited. During each run we record the translocation time τ and the translocation coordinate $s(t)$. Then we average all data over typically 10^4 runs. In principle, the pore may apply a drag force on the threading chain due to a chemical potential gradient; however, in the present work we consider only unbiased diffusion. In Fig. 2(a) we show a master plot of the translocation time distribution $Q(t)$ derived from Eq. (4) for different chain lengths $N = 16, 32, 64, 128, 256$. For the calculation of data we have used MATHEMATICA with a special package for computation of Mittag-Leffler functions [25]. Evidently, all curves collapse on a single one when time is

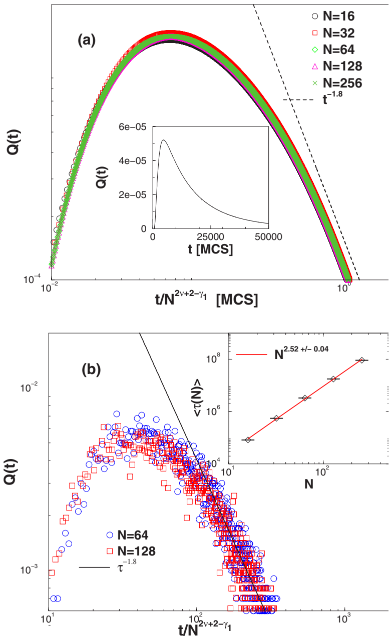

FIG. 2. (Color online) Translocation time distribution function $Q(t)$. (a) Scaling plot of the theoretical predictions calculated from Eq. (4) for different chain lengths N. Dashed line denotes the long time asymptotic tail with slope -1.8. The inset shows $Q(t)$ for $N = 256$ in normal coordinates. (b) The FPDT $Q(t)$ from the MC simulation for $N = 64, 128$. The inset shows the expected $\langle\tau\rangle$ vs chain length N dependence, and the straight line is a best fit with slope $\approx 2.52 \pm 0.04$.

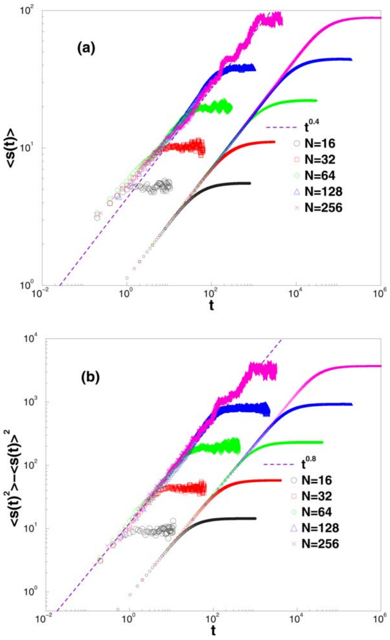

FIG. 3. (Color online) Variation of the first and second moments of the PDF $W(s,t)$ with time for chain lengths $N=16,32,64,128,256$. (a) Log-log plot of the first moment $\langle s\rangle$ vs time t from a MC simulation (big symbols) and from Eq. (5) (small symbols). The dashed line denotes $t^{\alpha/2}$ with a slope of 0.4. (b) The same as in (a) but for $\langle s^2\rangle-\langle s\rangle^2$. Analytical data are obtained from Eq. (6). The dashed line has a slope of 0.8.

scaled as $t\propto N^{2/\alpha}$ with the predicted $\alpha=0.8$. The long time tail for this value of α should exhibit a slope of -1.8. The inset in Fig. 2(a) reveals the long tail of $Q(t)$ for large times. A comparison with Fig. 2(b) demonstrates good agreement with the simulation data despite some scatter in the FPDF even after averaging over 10 000 runs. As shown in the inset, the mean translocation time scales as $\langle\tau\rangle\propto N^{2.5}$ in good agreement with the predicted $\alpha=0.8$. An inspection of Fig. 3, where the time variations of the PDF $W(s,t)$ moments are compared, demonstrates again that data from the numeric experiment and the analytic theory agree well within the limits of statistical accuracy (which is worse for $N=256$). Not surprisingly, the time scale of the MC results does not coincide with that of Eqs. (5) and (6) since in the latter we have set K_α, which fixes the time scale, equal to unity. Closer examination of Fig. 3 shows that the resetting of the generalized diffusion coefficient as $K_\alpha\simeq(80)^{0.8}\simeq33.3$ enables to superimpose the results of theoretical calculation and MC data.

In summary, we have shown unambiguously that the translocation dynamics of a polymer chain threading through a nanopore is anomalous in its nature. We have succeeded in calculating the anomalous exponent $\alpha=2/(2\nu+2-\gamma_1)$ from simple scaling arguments, and embedded it in the fractional diffusion formalism. We derived exact analytic expressions for the translocation time probability distribution as well as for the moments of the translocation coordinates, which are shown to agree well with our MC simulation data. The present treatment can be readily generalized to account for a drag force on the chain, and results for this case will be reported in a separate presentation.

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