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Anomalous Dynamics of Unbiased Polymer Translocation through a Narrow Pore

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Abstract

We consider a polymer of length N translocating through a narrow pore in the absence of external fields. Characterization of its purportedly anomalous dynamics has so far remained incomplete. We show that the polymer dynamics is anomalous until the Rouse time $\tau_R \sim N^{1+2\nu}$, with a mean square displacement through the pore consistent with $t^{(1+\nu)/(1+2\nu)}$, with $\nu \approx 0.588$ the Flory exponent. This is shown to be directly related to a decay in time of the excess monomer density near the pore as $t^{-(1+\nu)/(1+2\nu)} \exp(-t/\tau_R)$. Beyond the Rouse time translocation becomes diffusive. In consequence of this, the dwell-time τ_d , the time a translocating polymer typically spends within the pore, scales as $N^{2+\nu}$, in contrast to previous claims.

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Transport of molecules across cell membranes is an essential mechanism for life processes. These molecules are often long and flexible, and the pores in the membranes are too narrow to allow them to pass through as a single

unit. In such circumstances, the passage of a molecule through the pore — i.e. its translocation — proceeds through a random process in which polymer segments sequentially move through the pore. DNA, RNA and proteins are naturally occurring long molecules [1] subject to translocation in a variety of biological processes. Translocation is used in gene therapy [2], in delivery of drug molecules to their activation sites [3], and as an efficient means of single molecule sequencing of DNA and RNA [4]. Understandably, the process of translocation has been an active topic of current research: both because it is an essential ingredient in many biological processes and for its relevance in practical applications.

Translocation is a complicated process in living organisms — its dynamics may be strongly influenced by factors like the presence of chaperon molecules, pH values, chemical potential gradients, assisting molecular motors etc. [5]. In studies of translocation as a *biophysical* process, the polymer is simplified to a sequentially connected string of N monomers. Herein, the quantities of interest are the typical time for the polymer to leave a confining cell or vesicle, the “escape time” [6], and the typical time the polymer spends in the pore or “dwell time” [7], as a function of chain length N and other parameters like membrane thickness, membrane adsorption, electrochemical potential gradient, etc. [8]. These have been measured directly in numerous experiments [9].

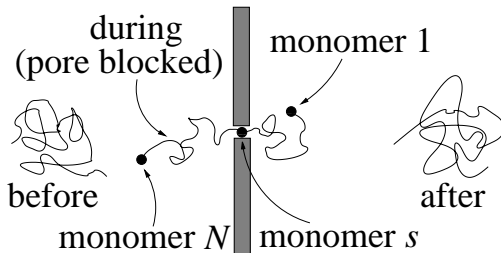


Figure 1: Pictorial representation of a translocation event, with the polymer shown before, during and after translocation. We number the monomers, starting with the end-monomer on the side it moves to. The number of the monomer located in the middle of the pore is s .

Experimentally, the most studied quantity is the dwell time τ_d , i.e., the pore blockade time for a translocation event (see Fig. 1). For theoretical descriptions of τ_d , during the last decade a number of mean-field type the-

ories [6, 7, 8] have been proposed, in which translocation is described by a Fokker-Planck equation for first-passage over an entropic barrier in terms of a single “reaction coordinate” s . Here s is the number of the monomer threaded at the pore ($s = 1, \dots, N$). These theories apply under the assumption that translocation is slower than the equilibration time-scale of the entire polymer, which is likely for high pore friction. In Ref. [10], this assumption was questioned, and the authors found that for a self-avoiding polymer performing Rouse dynamics, $\tau_d \geq \tau_R$, the Rouse time. Using simulation data in 2D, they suggested that the inequality may actually be an equality, i.e., $\tau_d \sim \tau_R \sim N^{1+2\nu}$, which is $N^{2.5}$ in two dimensions. Numerical data in support of this suggestion in 2D appeared in Ref. [11]. However, in a publication due to two of us, τ_d in 3D was numerically found to scale as $\sim N^{2.40 \pm 0.05}$ [13], significantly larger than $N^{1+2\nu}$, which is $N^{2.18}$ in three dimensions. Additionally, in a recent publication [14] τ_d was numerically found to scale as $N^{2.52 \pm 0.04}$ in three dimensions (a discussion on the theory of Ref. [14] appears at the end of this paper). Note that these simulations do not incorporate hydrodynamical interactions, which are certainly important in experiments. Also, these simulations (and all theoretical studies, including this one) ignore interactions with other polymers, i.e., they consider polymers in infinitely dilute solutions, while in cell environments, the solution is not infinitely dilute. In this paper we consider translocation in the absence of hydrodynamical interactions, and at the end we reflect on the results we expect when the hydrodynamical interactions are included. We also note here that simulations with hydrodynamical interactions are non-trivial and costly.

Amid all the above results on τ_d mutually differing by $\sim O(N^{0.2})$, the only consensus that survives is that $\tau_d \geq \tau_R$ [10, 13]. Simulation results alone cannot determine the scaling of τ_d : different groups use different polymer models with widely different criteria for convergence for scaling results, and as a consequence, settling differences of $\sim O(N^{0.2})$ in $O(\tau_R)$, is extremely delicate.

An alternative approach that can potentially settle the issue of τ_d scaling with N is to analyze the dynamics of translocation at a microscopic level. Indeed, the lower limit τ_R for τ_d implies that the dynamics of translocation is anomalous [10]. We know of only two published studies on the anomalous dynamics of translocation, both using a fractional Fokker-Planck equation (FFPE) [12, 14]. However, whether the assumptions underlying a FFPE apply for polymer translocation are not clear. Additionally, none of the

studies used FFPE for the purpose of determining the scaling of τ_d . In view of the above, such a potential clearly has not been thoroughly exploited.

The purpose of this paper is to report the characteristics of the anomalous dynamics of translocation, *derived from the microscopic dynamics of the polymer*, and the scaling of τ_d obtained therefrom. Translocation proceeds via the exchange of monomers through the pore: imagine a situation when a monomer from the left of the membrane translocates to the right. This process increases the monomer density in the right neighbourhood of the pore, and simultaneously reduces the monomer density in the left neighbourhood of the pore. The local enhancement in the monomer density on the right of the pore *takes a finite time to dissipate away from the membrane along the backbone of the polymer* (similarly for replenishing monomer density on the left neighbourhood of the pore). The imbalance in the monomer densities between the two local neighbourhoods of the pore during this time implies that there is an enhanced chance of the translocated monomer to return to the left of the membrane, thereby giving rise to *memory effects*, and consequently, rendering the translocation dynamics subdiffusive. More quantitatively, the excess monomer density (or the lack of it) in the vicinity of the pore manifests itself in reduced (or increased) chain tension around the pore, creating an imbalance of chain tension across the pore (we note here that the chain tension at the pore acts as monomeric chemical potential, and from now on we use both terms interchangeably). We use well-known laws of polymer physics to show that in time the imbalance in the chain tension across the pore relaxes as $t^{-(1+\nu)/(1+2\nu)} \exp(-t/\tau_R)$. (Strictly speaking, τ_R in this expression should be replaced by the characteristic equilibration time of a tethered polymer with length of $O(N)$; since both scale as $N^{1+2\nu}$, we use τ_R here, favouring notational simplicity). This results in translocation dynamics being subdiffusive for $t < \tau_R$, with the mean-square displacement $\langle \Delta s^2(t) \rangle$ of the reaction coordinate $s(t)$ increasing as $t^{(1+\nu)/(1+2\nu)}$; and diffusive for $t > \tau_R$. With $\sqrt{\langle \Delta s^2(\tau_d) \rangle} \sim N$, this leads to $\tau_d \sim N^{2+\nu}$.

We substantiate our theoretical derivations with extensive Monte Carlo simulations, in which the polymer performs single-monomer moves. The definition of time is such that single-monomer moves along the polymer's contour are attempted at a fixed rate of unity, while moves that change the polymer's contour are attempted ten times less often. Details of our self-avoiding polymer model in 3D can be found in Refs. [15, 16].

The key step in quantitatively formulating the anomalous dynamics of translocation is the following observation: a translocating polymer com-

prises of *two polymer segments tethered at opposite ends of the pore* that are able to exchange monomers between them through the pore; so *each acts as a reservoir of monomers for the other*. The velocity of translocation $v(t) = \dot{s}(t)$, representing monomer current, responds to $\phi(t)$, the imbalance in the monomeric chemical potential across the pore acting as “voltage”. Simultaneously, $\phi(t)$ also adjusts in response to $v(t)$. In the presence of memory effects, they are related to each other by $\phi(t) = \int_0^t dt' \mu(t-t')v(t')$ via the memory kernel $\mu(t)$, which can be thought of as the (time-dependent) ‘impedance’ of the system. Supposing a zero-current equilibrium condition at time 0, this relation can be inverted to obtain $v(t) = \int_0^t dt' a(t-t')\phi(t')$, where $a(t)$ can be thought of as the ‘admittance’. In the Laplace transform language, $\tilde{\mu}(k) = \tilde{a}^{-1}(k)$, where k is the Laplace variable representing inverse time. Via the fluctuation-dissipation theorem, they are related to the respective autocorrelation functions as $\mu(t-t') = \langle \phi(t)\phi(t') \rangle_{v=0}$ and $a(t-t') = \langle v(t)v(t') \rangle_{\phi=0}$.

The behaviour of $\mu(t)$ may be obtained by considering the polymer segment on one side of the membrane only, say the right, with a sudden introduction of p extra monomers at the pore, corresponding to impulse current $v(t) = p\delta(t)$. We then ask for the time-evolution of the mean response $\langle \delta\Phi^{(r)}(t) \rangle$, where $\delta\Phi^{(r)}(t)$ is the shift in chemical potential for the right segment of the polymer at the pore. This means that for the translocation problem (with both right and left segments), we would have $\phi(t) = \delta\Phi^{(r)}(t) - \delta\Phi^{(l)}(t)$, where $\delta\Phi^{(l)}(t)$ is the shift in chemical potential for the left segment at the pore due to an opposite input current to it.

We now argue that this mean response, and hence $\mu(t)$, takes the form $\mu(t) \sim t^{-\alpha} \exp(-t/\tau_R)$. The terminal exponential decay $\exp(-t/\tau_R)$ is expected from the relaxation dynamics of the entire right segment of the polymer with one end tethered at the pore [16]. To understand the physics behind the exponent α , we use the well-established result for the relaxation time t_n for n self-avoiding Rouse monomers scaling as $t_n \sim n^{1+2\nu}$. Based on the expression of t_n , we anticipate that by time t the extra monomers will be well equilibrated across the inner part of the chain up to $n_t \sim t^{1/(1+2\nu)}$ monomers from the pore, but not significantly further. This internally equilibrated section of $n_t + p$ monomers extends only $r(n_t) \sim n_t^\nu$, less than its equilibrated value $(n_t + p)^\nu$, because the larger scale conformation has yet to adjust: the corresponding compressive force from these $n_t + p$ monomers is expected by standard polymer scaling [18] to follow $f/(k_B T) \sim \delta r(n_t)/r^2(n_t) \sim \nu p/[n_t r(n_t)] \sim t^{-(1+\nu)/(1+2\nu)}$, for $p \ll n_t$. This

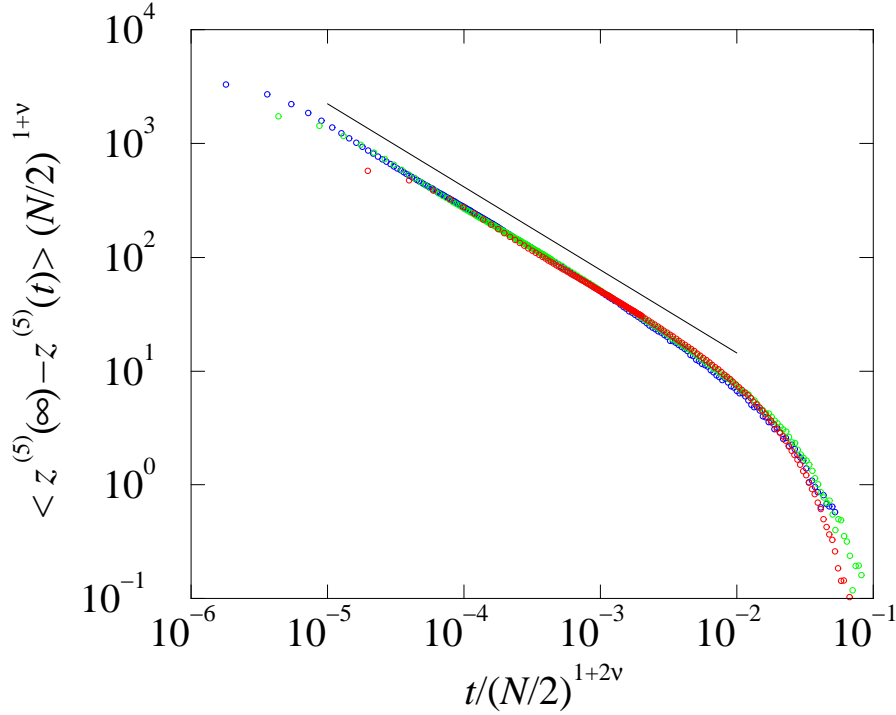


Figure 2: Simulation results for the average chain tension component perpendicular to the membrane proxied by $\langle z^{(5)}(\infty) - z^{(5)}(t) \rangle$ following monomer injection at the pore corresponding to $v(t) = p\delta(t)$, with $p = 10$. See text for details. Red circles: $N/2 = 50$, green circles: $N/2 = 100$, blue circles: $N/2 = 150$, solid black line: $t^{-(1+\nu)/(1+2\nu)}$ with $\nu = 0.588$ for self-avoiding polymers. To obtain a data collapse, the horizontal and vertical axes are scaled by $(N/2)^{1+2\nu}$ and $(N/2)^{1+\nu}$, respectively. The steeper drop at large times correspond to the exponential decay $\exp(-t/\tau_R)$.

force f must be transmitted to the membrane, through a combination of decreased tension at the pore and increased incidence of other membrane contacts. The fraction borne by reducing chain tension at the pore leads us to the inequality $\alpha \geq (1 + \nu)/(1 + 2\nu)$, which is significantly different from (but compatible with) the value $\alpha_1 = 2/(1 + 2\nu)$ required to obtain $\tau_d \sim \tau_R$. It seems unlikely that the adjustment at the membrane should be disproportionately distributed between the chain tension at the pore and other membrane contacts, leading to the expectation that the inequality above is actually an equality.

We have confirmed this picture by measuring the impedance response through simulations. In Ref. [17], two of us have shown that the centre-of-mass of the first few monomers is an excellent proxy for chain tension at the pore and we assume here that this further serves as a proxy for $\delta\Phi$. Based on this idea, we track $\langle\delta\Phi^{(r)}(t)\rangle$ by measuring the distance of the average centre-of-mass of the first 5 monomers from the membrane, $\langle z^{(5)}(t)\rangle$, in response to the injection of extra monomers near the pore at time 0. Specifically we consider the equilibrated right segment of the polymer, of length $N/2 - 10$ (with one end tethered at the pore), adding 10 extra monomers at the tethered end of the right segment at time 0, corresponding to $p = 10$, bringing its length up to $N/2$. Using the proxy $\langle z^{(5)}(t)\rangle$ we then track $\langle\delta\Phi^{(r)}(t)\rangle$. The clear agreement between the exponent obtained from the simulation results with the theoretical prediction of $\alpha = (1 + \nu)/(1 + 2\nu)$ can be seen in Fig. 2. Note that the sharp deviation of the data from the power law $t^{-(1+\nu)/(1+2\nu)}$ at long times is due to the asymptotic exponential decay as $\exp(-t/\tau_R)$, as the data collapse shows.

Having thus shown that $\mu(t) \sim t^{-\frac{1+\nu}{1+2\nu}} \exp(-t/\tau_R)$, we can expect that the translocation dynamics is anomalous for $t < \tau_R$, in the sense that the mean-square displacement of the monomers through the pore, $\langle\Delta s^2(t)\rangle \sim t^\beta$ for some $\beta < 1$ and time $t < \tau_R$, whilst beyond the Rouse time it becomes simply diffusive. The value $\beta = \alpha = \frac{1+\nu}{1+2\nu}$ follows trivially by expressing $\langle\Delta s^2(t)\rangle$ in terms of (translocative) velocity correlations $\langle v(t)v(t')\rangle$, which (by the Fluctuation Dissipation theorem) are given in terms of the time dependent admittance $a(t - t')$, and hence inversely in terms of the corresponding impedance.

Indeed, as shown in Fig. 3, a double-logarithmic plot of $\langle\Delta s^2(t)\rangle$ vs. t is consistent with $\langle\Delta s^2(t)\rangle \sim t^{(1+\nu)/(1+2\nu)}$. The behaviour of $\langle\Delta s^2(t)\rangle$ at short times is an artifact of our model: at short times reptation moves dominate, leading to a transport mechanism for “stored lengths” [19] along the polymer’s contour in which individual units of stored length cannot pass each other. As a result, the dynamics of $s(t)$, governed by the movement of stored length units across the pore, is equivalent to a process known as “single-file diffusion” on a line, characterized by the scaling $\langle\Delta s^2(t)\rangle \sim t^{1/2}$ (not shown here). At long times the polymer tails will relax, leading to $\langle\Delta s^2(t)\rangle \sim t$ for $t > \tau_R$. The presence of two crossovers, the first one from $\langle\Delta s^2(t)\rangle \sim t^{1/2}$ to $\langle\Delta s^2(t)\rangle \sim t^{(1+\nu)/(1+2\nu)}$ and the second one from $\langle\Delta s^2(t)\rangle \sim t^{(1+\nu)/(1+2\nu)}$ to $\langle\Delta s^2(t)\rangle \sim t$ at $t \approx \tau_R$, complicates the precise numerical verification of the exponent

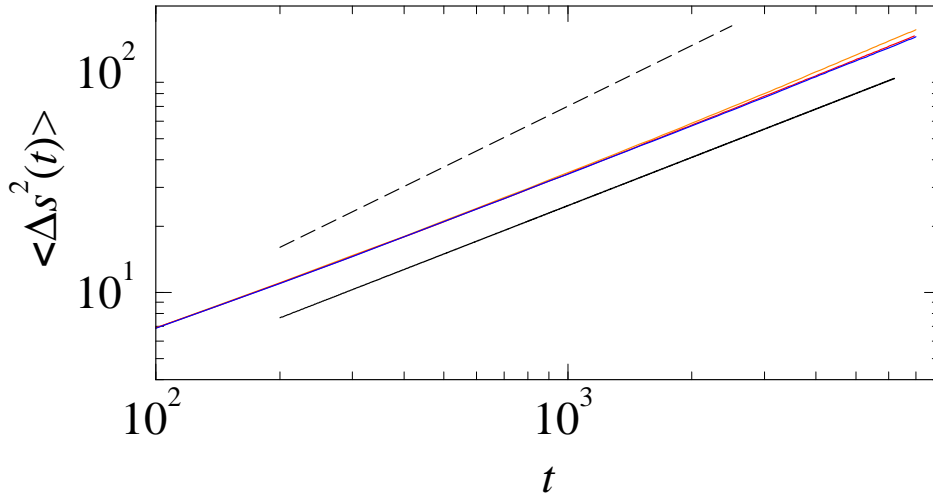


Figure 3: Double-logarithmic plot of the mean squared displacement of the reaction coordinate $\langle \Delta s^2(t) \rangle$ as a function of time t , for $N = 100$ (orange), 200 (red) and 500 (blue). The thick black line indicates the theoretically expected slope corresponding to $\langle \Delta s^2(t) \rangle \sim t^{(1+\nu)/(1+2\nu)}$. The dashed black line corresponds to $\langle \Delta s^2(t) \rangle \sim t^{2/(1+2\nu)}$, which would have been the slope of the $\langle \Delta s^2(t) \rangle$ vs. t curve in a double-logarithmic plot, if τ_d were to scale as $\tau_R \sim N^{1+2\nu}$.

$(1 + \nu)/(1 + 2\nu)$. However, as shown in Fig. 3, there is an extended regime in time at which the quantity $t^{-(1+\nu)/(1+2\nu)} \langle \Delta s^2(t) \rangle$ is nearly constant.

The subdiffusive behaviour $\langle \Delta s^2(t) \rangle \sim t^{\frac{1+\nu}{1+2\nu}}$ for $t < \tau_R$, combined with the diffusive behaviour for $t \geq \tau_R$ leads to the dwell time scaling as $\tau_d \sim N^{2+\nu}$, based on the criterion that $\sqrt{\langle \Delta s^2(\tau_d) \rangle} \sim N$. The dwell time exponent $2 + \nu \simeq 2.59$ is in acceptable agreement with the two numerical results on τ_d in 3D as mentioned in the introduction of this paper, and in Table I below we present new high-precision simulation data in support of $\tau_d \sim N^{2+\nu}$, in terms of the median unthreading time. The unthreading time τ_u is defined as the time for the polymer to leave the pore with $s(t=0) = N/2$ and the two polymer segments equilibrated at $t=0$. Both τ_u and τ_d scale the same way, since $\tau_u < \tau_d < 2\tau_u$ [16].

N	τ_u	$\tau_u/N^{2+\nu}$
100	65136	0.434
150	183423	0.428
200	393245	0.436
250	714619	0.445
300	1133948	0.440
400	2369379	0.437
500	4160669	0.431

Table I: Median unthreading time over 1,024 runs for each N .

We now reflect on the theory presented in Ref. [14].

We have defined τ_d as the pore-blockade time in experiments; i.e., if we define a state of the polymer with $s(t) = 0$ as ‘0’ (polymer just detached from the pore on one side), and with $s(t) = N$ as ‘N’, then τ_d is the first passage time required to travel from state 0 to state N *without* possible reoccurrences of state 0. In Ref. [14], the authors attach a bead at the $s = 0$ end of the polymer, preventing it from leaving the pore, creating a situation where the polymer returns to state 0 multiple number of times before it eventually reaches state N. The repeated returns to state 0 implies that by construction of the problem, the polymer encounters a free energy barrier on its way from state 0 to $s = N/2$, where the polymer’s configurational entropy is the lowest. The authors then proceed to express their translocation time (τ_t hereafter), defined as the first passage time required to travel from state 0 to state N *with* reoccurrences of state 0, in terms of this free energy barrier. Below we settle the differences between τ_t of Ref. [14] and our τ_d .

Consider the case where we attach a bead at $s = 0$ and another at $s = N$, preventing it from leaving the pore. We then characterize the state of the polymer as follows. At state x and x' the polymer can have all values of s except $0, N/2$ and N ; and at states m and m' , $s = N/2$. The notational distinction between primed and unprimed states is that a primed state can occur only between two consecutive states 0, or between two consecutive states N, while an unprimed state occurs only between state 0 and state N. Its dynamics is then given by the sequence of states, e.g.,

$$\dots N x m x \overbrace{0 x' 0 x' m' x' m' x' 0 x' 0 x m x m x m x N}^{\tau_t} x' N \dots$$

τ_d

where the corresponding times taken (τ_t and τ_d) are indicated. Note in the above definitions that $\tau_t > \tau_d$: since, due to the presence of the entropic barrier as described above, τ_t includes the extra time spent in between the first and the last occurrence of state 0 before the polymer eventually proceeds to state N. In other words, τ_t *includes the effect of the entropic barrier, while τ_d does not*. A probability argument then leads us to

$$\frac{\tau_t}{\tau_d} = \frac{1}{p_x + p_m} = \frac{f_x(1 + f_m)}{(p_m + p_{m'})f_m(1 + f_x)}, \quad (1)$$

where p_m , $p_{m'}$ and p_x are the probabilities of the corresponding states, $f_m = p_m/p_{m'}$ and $f_x = p_m/p_x$. The partition sum of a polymer of length n with one end tethered on a membrane is given by $Z_n \sim \lambda^n n^{\gamma_1-1}$ with λ a non-universal constant and $\gamma_1 = 0.68$ [20], and therefore we have $p_m + p_{m'} = Z_{N/2}^2 / \left[\sum_{s=0}^N Z_s Z_{N-s} \right] \sim 1/N$. Similarly, $f_x \sim 1/N$ [13]. Finally, $f_m \approx 1$ [21] yields $\tau_t \sim \tau_d$.

In Ref. [14] the authors include a factor $N^{1-\gamma_1}$ in τ_t to account for the effect of the entropic barrier. However, we have shown above that $\tau_t \sim \tau_d$, i.e., the free energy barrier does not play a role for the scaling behaviour of τ_t with N . This implies, since τ_t includes the effect of the entropic barrier and τ_d does not, that the theoretical expression for τ_t in Ref. [14] cannot be correct. The numerical result $\tau_t \sim N^{2.52 \pm 0.04}$ in Ref. [14], however, confirms our theoretical expression $\tau_d \sim N^{2+\nu}$.

To conclude, in this paper we have characterized the anomalous dynamics of unbiased translocation and obtained the scaling of the dwell time in terms of the polymer length. In future work, we will study the role of hydrodynamics. Rouse friction may be an appropriate model for the dynamics of long biopolymers in the environment within living cells, if it is sufficiently gel-like to support screened hydrodynamics on the timescale of their configurational relaxation. However, we should also ask what is expected in the other extreme of unscreened (Zimm) hydrodynamics. For our theoretical discussion the key difference is that, instead of the Rouse time τ_R , in the Zimm case the configurational relaxation times scale with N according to $\tau_{\text{Zimm}} \sim N^{3\nu}$ in 3D, which upon substitution into our earlier argument would give the lower bound value $\alpha = (1 + \nu)/(3\nu)$ for the time exponent of the impedance, leading to $\tau_d \sim N^{1+2\nu}$ (whose resemblance to the Rouse time is a coincidence — note that with hydrodynamics Rouse time loses all relevance). These results, however, do need to be verified by simulations incorporating hydrodynamics.

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- [21] f_m is a number slightly smaller than 1: if the polymer reaches $s = N/2$ from state 0, due to the memory effects, it will have slightly higher chance to go back to state 0 rather than to proceed to state N [13].