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# Sucking genes into pores: Insight into driven translocation

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Flexible polymers such as long DNA, RNA molecules, and proteins, can pass through a narrow pore whose size is comparable to their molecular thickness. We highlight the richness and complexity involved in the dynamics of this unique mode of molecular transport, called *translocation*, actively driven by external forces. In particular, the process takes place in the condition far from equilibrium accompanying of large conformational distortion in line with the propagation of the tensile force along the chain backbone. A general framework is proposed, which captures such essential features, whereby can account for reported various experimental data from a unified viewpoint.

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## I. INTRODUCTION

In their pioneering work, Kasianowicz *et al.* demonstrated detection of the passage of single polynucleotide molecules driven by a voltage drop through a nanometer-size ion channel in a lipid bilayer membrane [1]. Since then, the translocation of nucleic acids and other chainlike molecules has been an active research area in the nanobiological sciences [2–5]. Together with rapid progress in the design and fabrication of nanoscale pores, this has opened up a promising pathway for novel macromolecular characterization methods [6]. It has also motivated theoretical studies in which people are seeking to understand the underlying physics of this unique mode of molecular transport [7–14]. Most theories proposed to date have been formulated under the assumption that the translocating polymer essentially remains in an equilibrium shape. However, this naive assumption is questionable in view of the high susceptibility and long relaxation time of polymer molecules [10]. Here we argue that the driven translocation is inherently an out-of-equilibrium process. Following the formalism that explicitly features the propagation of tensile force along the polymer backbone [12], we aim to address various numerical and real experiments from a unified viewpoint. The emergent physical picture may also provide valuable insight into other nonequilibrium phenomena in polymeric systems associated with tension propagation; for example, the dynamics of adsorption [15,16], crystallization and folding [17], responses to mechanical manipulations [18,19], and ultimately the functioning of biopolymers as well as the design of polymer-based nanoscale machines.

Often, the pore is comparable to the monomer in size so that at each moment only one monomer resides at the pore, and there is a driving force $f$ (imposed by a voltage drop for charged polymer or more generally a chemical potential difference across the wall) to achieve the active transport. Given such a set up, a basic question is the following; what is the typical time $\tau(N_0,f)$ for transporting a flexible molecule with the polymerization index $N_0$ under the action of the driving force $f$? Various regimes are expected depending on the magnitude of the driving force [12], as well as characteristics of the pore. Here we shall focus on paradigmatic situations where the pore functions solely as a geometrical constraint, i.e., it has no specific interaction with polymers, and the driving force $f$ is of the order of $k_BT/a$, where $k_BT$ is the thermal energy and $a$ is the monomer size.

Numerous numerical simulations have reported the scaling $\tau \sim N_0^{\alpha}$ with an apparent scatter in the exponent $\alpha$, which may indicate the complexity and subtlety of the problem [11,13–15,20–28]. Interesting theories have been put forward based on either the fractional Fokker-Plank equation [13] or the memory effect arising from monomer exchange across the pore [14], but predictions resulting from either of these approaches do not seem to agree with the latest systematic simulations. An experiment of double-strand DNA translocation through a solid-state nanopore has also been carried out [4,5], but its interpretation, and its relationship with the results of various simulation studies, seem unclear at present [29].

The equilibrium shape assumption in previous studies is based on the fact that the polymer is pulled at only one point inside the pore. However, force applied in such a way can propagate along the polymer backbone; thus it is able to induce large scale shape distortion. In Ref. [12], several predictions were made by pointing out that such a nonequilibrium effect is indispensable for the description of the driven translocation process, but any comparison with experiments was not attempted at that time. In this paper, we generalize the framework proposed in Ref. [12] and provide a unified view by introducing *dynamic* as well as static (Flory) exponents. This leads to the first-ever generic scaling formula for $\tau$ fully consistent with the latest high-accuracy simulations [22] and experiments [4,5]. The theory also resolves (i) a factor entailing the finite-size effect, which may be a source for apparent discrepancies among reported simulations, and (ii) conditions under which different scaling formulas proposed in literatures can be valid.

## II. EQUILIBRIUM SHAPE ASSUMPTION

Let us first disregard the out-of-equilibrium effect and assume that a polymer takes an equilibrium conformation in the presence of a wall all the way along the translocation

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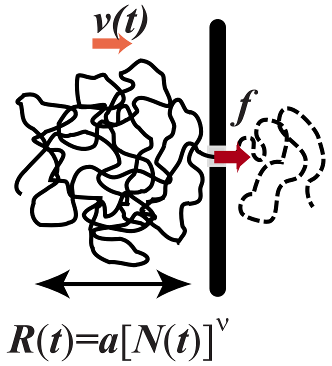

FIG. 1. (Color online) Equilibrium shape assumption for the driven translocation process. The translocated part of the chain is represented by the dotted curve.

(Fig. 1). This may be a reasonable approximation when the driving force is sufficiently weak $\tilde{f}_a \lesssim N_0^{-\nu} \ll 1$. Hereinafter, we adopt the notation $\tilde{f}_x \equiv fx/(k_BT)$ for the dimensionless force, with the quantity $x$ possessing the dimension of length. The dynamics is regulated by the balance between the driving force $f$ and the dissipative force $\sim \gamma v$. Under the equilibrium shape assumption, the friction coefficient $\gamma$ can be expressed as

$$\gamma = \gamma_0 R^{z-2} = \gamma_0 N^{(z-2)\nu}, \tag{1}$$

where $R \simeq aN^{\nu}$ is the equilibrium size of a polymer of length $N$, $\gamma_0 \simeq \eta a$ is the monomeric friction coefficient with solvent viscosity $\eta$, $\nu$ is the Flory exponent and $z$ is a so-called dynamic exponent associated with the dissipation mechanism [30]. Therefore, if we drag a polymer by pulling it at one end with a constant force $f$, the steady-state relation between the velocity $v$ and the force can be expressed as

$$\tilde{f}_a \simeq \tilde{v} N^{(z-2)\nu} \simeq \tilde{v} \tilde{R}^{z-2}. \tag{2}$$

Here the velocity and the chain size are also made dimensionless; $\tilde{v} \equiv \tau_0 v/a$ and $\tilde{R} = R/a$, respectively, where $\tau_0 \simeq \eta a^3/(k_BT)$ is the microscopic time scale. In our problem, the number of "relevant" monomers changes with time as $N(t) = N_0 - m(t)$, where $m(t)$ is the number of monomers already transferred at time $t$ (Fig. 1).

Hence, the translocating velocity $v$ and the friction coefficient $\gamma$ are, respectively, given by $v(t)/a \simeq -dN(t)^{\nu}/dt$ and $\gamma(t)/\gamma_0 \simeq N(t)^{(z-2)\nu}$. Equation (2) is then a differential equation with respect to $N(t)$, the solution of which is

$$N(\tilde{t}) \simeq N_0 (1 - \tilde{t}/\tilde{\tau})^{1/[(z-1)\nu]}, \tag{3}$$

where $\tilde{t} = t/\tau_0$ is the dimensionless time. The translocation time is found to be

$$\tilde{\tau} = \frac{\tilde{R}_0^z}{\tilde{f}_{R_0}} = \frac{N_0^{(z-1)\nu}}{\tilde{f}_a}. \tag{4}$$

Two cases deserve further elaboration. In the first case, we assume that the friction is a local event, i.e., free draining. Then, $z = (1+2\nu)/\nu$ and Eq. (4) lead to $\tilde{\tau} = N_0^{1+\nu}/\tilde{f}_a$. In the second case, we allow for the collective effect of hydrodynamic interactions and adopt a nondraining approximation [30]. Then, we have $z = 3$, thus, $\tilde{\tau} = N_0^{2\nu}/\tilde{f}_a$. We see that the first is a paradigmatic formula initially proposed by Kantor and Kardar, and often seen in the literature [11] and the second corresponds to the result proposed by Storm *et al.* to interpret their experiment of DNA translocation across a solid-state nanopore [4,29]. We also note that these two formulas with or without hydrodynamic interactions accord with the recent results from a Monte Carlo algorithm [25].

Furthermore, the inspection of Eq. (3) indicates the faster translocation velocity in later time (the nondraining case with $\nu = 1/2$ is marginal). This acceleration is a consequence of the time dependent frictional force which decreases with the process advanced under the constant driving force.

## III. OUT-OF-EQUILIBRIUM DYNAMICS

### A. Qualitative picture

In reality, however, the translocating polymer no longer retains an equilibrium conformation under the action of moderate driving forces $\tilde{f}_a \simeq 1$. To get a feeling for this, it is instructive to recall a macroscopic thought experiment of pulling a rope randomly dropped on a desk, described in Ref. [15]. If one suddenly pulls the rope by one end from the desk edge, it is obvious that the rope does not move all at once, and instead, exhibits a sequential dynamical response. Returning to the microscopic world of polymers, this dynamical response is again governed by the balance between driving and dissipative forces, but now with proper consideration of the chain deformation dynamics associated with propagation of the tensile force along the chain (Fig. 2).

At the beginning of the translocation, i.e., at time $t = 0$, only part of the chain of size $\xi_{pore} \simeq a\tilde{f}_a^{-1}$, comprised of $g_{pore} \simeq \tilde{f}_a^{-1/\nu}$ monomers in the immediate vicinity of the pore, is tensed and able to react to the driving force with speed $v(0) = f/\gamma(0)$, while the remaining rear part is essentially unaffected as yet. It should be noted that it is $g_{pore}$ monomers only that contribute to the friction coefficient $\gamma(0)$ at this moment. The driving force which constantly pulls the polymer at the pore necessitates the formation of a tensed blob of size $\xi_{pore}$ in the immediate vicinity of the pore, down through the translocation process. This is local regulation occurring at fast time scales, thus, it is realized irrespective of the entire chain conformation. At the next moment, as initially $g_{pore}$ monomers have already been transported across the pore, some monomer in the rear part has to be pulled and reloaded to recreate the $\xi_{pore}$ blob at the pore. Here again, only parts of polymers adjacent to the initial $\xi_{pore}$ blob can respond, i.e., the tensile force is transmitted to the rear section over a finite range by the moment. Along with such a tension propagation process, the friction coefficient grows, by which the conformation of the tensed part and its average velocity are self-adjusted. In this way, the polymer sequentially responds to the driving force by progressively transforming its larger scale conformations. To proceed with the quantitative argument, we need to know the conformational property of the dragged chain which shall be briefly sketched in Appendix.

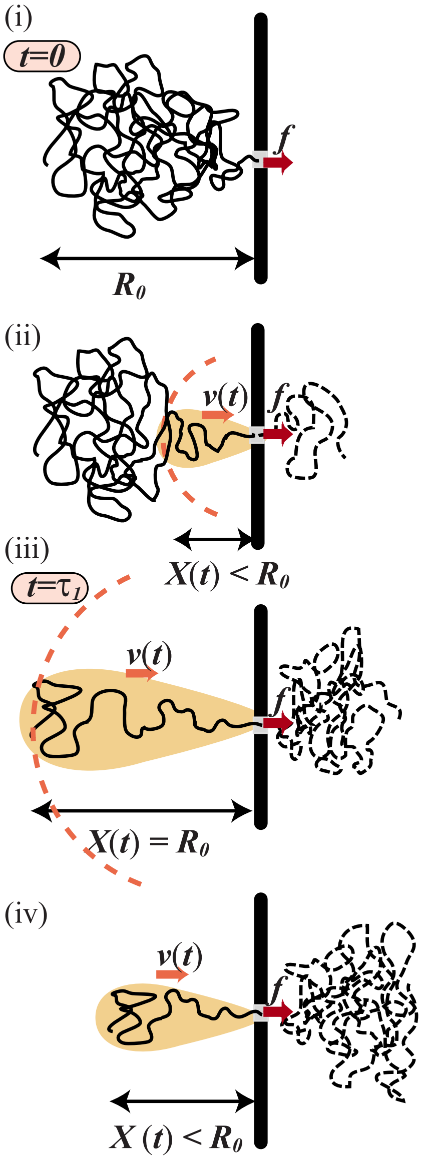

FIG. 2. (Color online) Schematics of the translocation process driven by the action of a moderate force $\tilde{f}_a \simeq 1$. The front (represented by a dashed curve) separates the steady-state region under tension (designated by the colored area) and the rear part as yet at rest.

### B. Quantitative formulation

At time $t$, the tension is transmitted as far as the $M(t)$-th monomer (counting from the head). One can define an associated front whose location is characterized by its distance $X(t)$ from the pore (Fig. 2). Inside the front, the polymer is under tension and sucked into the pore at an average velocity $v(t)=f/\gamma[X(t)]$, while outside the front, the polymer is essentially at rest. To quantify the dynamical response, let us relate the evolution of the front to the monomer flux across it;

$$[\rho S]_{front}\left\{\frac{dX(t)}{dt}+v(t)\right\}=\frac{dM(t)}{dt}, \tag{5}$$

where $\rho$ and $S$ are the monomer number density and the cross sectional area of the conformation of the tensed part, respectively. Along with this continuity equation, we have to identify the relations among the dynamical variables $v(t)$, $X(t)$, $M(t)$, and $[\rho S]_{front} \simeq g_{free}/\xi_{free}$ (see Appendix). An additional key relation emerges from the fact that the $M(t)$-th monomer has not been affected by the driving force by this time, so its average position $X(t)$ is given by the equilibrium conformation at $t=0$; thus, the following Flory relation holds

$$M(t)^{\nu} \simeq \tilde{X}(t). \tag{6}$$

Combining Eqs. (A2), (A3), and (6) with Eq. (5), one arrives at the tension propagation law

$$\tilde{f}_a^{\omega+2-z}\tilde{X}(t)^{\omega+2}\Phi(\tilde{f}_{X(t)})=\tilde{t}, \tag{7}$$

where we define $\omega=(1-\nu)(z-2)/[\nu(z-1)]$ and the function $\Phi(x)\equiv 1-cx^{-\omega}$, with $c$ being a numerical coefficient of order unity. This is the generalization of the result of Ref. [12] with the dynamic exponent. By setting $\tilde{X}(\tau_1)=\tilde{R}_0=N_0^{\nu}$ in Eq. (7), one finds the characteristic time

$$\tilde{\tau}_1 \simeq (\tilde{R}_0)^z(\tilde{f}_{R_0})^{\omega+2-z}[1-c(\tilde{f}_{R_0})^{-\omega}], \tag{8}$$

at which the tensile force reaches the chain end.

*Remarks*. (i) Under the condition of interest $\tilde{f}_{R_0} \gg \tilde{f}_a \simeq 1$, Eq. (8) reduces to

$$\tilde{\tau}_1 \simeq \tilde{f}_a^{\omega+2-z} N_0^{(\omega+2)\nu}. \tag{9}$$

In the limit of long chains, this corresponds to a translocation time $\tau=\tau_1$. (ii) Contrary to the predictions of other theories $\tau \sim f^{-1}$ (linear response), Eq. (9) predicts a highly nonlinear response behavior. This point has been addressed in a recent simulation [24] and deserves further careful examinations. (iii) Strictly speaking, the entire discussion applies to the translocation process driven by a moderate force $N_0^{-\nu}<\tilde{f}_a<1$. For stronger forces, the results need to be modified to encompass the crossover to the regime of very strong forcing, in which the precise dynamics depends on the flexibility mechanism. In the limit of the very strong forcing, we expect $\tilde{\tau} \simeq N_0^{1+\nu}/\tilde{f}_a$, the same scaling structure as the translocation time in the weak driving regime [Eq. (4) with the free draining] [12]. (iv) The result is consistent with crossover to the unbiased limit $\tilde{\tau} \simeq (\tilde{R}_0)^z$ at $\tilde{f}_{R_0} \rightarrow 1$, in accordance with the natural scaling hypothesis (see also the discussion in Sec. V). (v) Because of the piling up of the translocated monomers [dotted curve in Fig. 2], the transient monomer density at the *trans*-side is slightly higher than that expected from the equilibrium conformation [20,24]. The resultant imbalance in the osmotic pressure acts as a retarding force, but does not alter the scaling limit as it is much smaller than the driving force. (vi) In contrast to Eq. (3) in the weak driving regime, the inspection of Eq. (7) indicates the *deceleration* of the translocation process. Physically, this is a consequence of the tension propagation which results in the increasing number of monomers set in motion, thus, higher friction.

## IV. COMPARISON WITH EXPERIMENTS

Most simulation studies adopt a flexible polymer model in a good solvent ($\nu=0.5876$) with a free-draining dynamics

$[z=(1+2\nu)/\nu=3.70]$. We then find the translocation exponent $\alpha=1.43$, which agrees remarkably with recent high-accuracy numerical simulations using Langevin dynamics with the bead-spring model for which $\alpha=1.41\pm0.01$ and atomistic molecular dynamic simulations for which $\alpha=1.42\pm0.01$ [22]. We note, however, a slightly lower value of $\alpha\simeq1.36\sim1.37$ is also reported in the literature [23,24]. The reason for such a discrepancy among simulation results is not clear, but the effects associated with various crossovers and/or finite chain length effect may play some role (see the comment in Sec. V). Turning to the experiment in Refs. [4,5], we set $z=3$ (hydrodynamic interactions) and $\nu=0.5$, as the DNA chain is practically ideal for the length range investigated because of the stiffness of double-strand DNA [29,30]. We then find $\alpha=1.25$ which again is in very good agreement with the experimental data for which $\alpha=1.27\pm0.03$. In addition, overall trends found in the multiscale modeling simulation focusing on the effect of hydrodynamic interactions [26–28] are similar and consistent with the prediction.

Simulations with a two-dimensional (2D) model reported a crossover from $\alpha\simeq1.5$ for short chains ($N_0\lesssim70$) to $\alpha\simeq1.65$ for long chains ($N_0\gtrsim300$) [20–22]. Substituting $\nu=0.75$ for 2D polymers and $z=(1+2\nu)/\nu=3.33$, our version of the formula that is valid in the long chain limit predicts $\alpha=1.64$ which, as expected, corresponds well with the latter value. To address a different exponent for shorter chains, consider the moment $t=\tau_1$ at which the tensile force has just reached the chain end [Fig. 2 (iii)]. $N_0-M(\tau_1)$ monomers are still on the *cis*-side and yet to be transported. These remaining monomers are under the influence of the tension, hence the process at $t>\tau_1$ is similar to that based on the equilibrium shape assumption. The only distinction lies in the fact that the overall conformation of these monomers is in a steady-state and not in an undistorted equilibrium state; consequently the dynamic equation is given by Eq. (A2) instead of Eq. (2). Then, the characteristic time for this second stage is calculated to be $\tilde{\tau}_2\simeq\tilde{R}_0^z(\tilde{f}_{R_0})^{2-z}$ [36]. The total translocation time $\tilde{\tau}=\tilde{\tau}_1+\tilde{\tau}_2$ is then given by

$$\tilde{\tau}=c_1\tilde{f}_a^{\omega+2-z}N_0^{(\omega+2)\nu}+c_2(\tilde{f}_a)^{2-z}N_0^{2\nu}, \qquad (10)$$

where the numerical coefficients $c_1$, $c_2$ are undetermined and may possibly depend on the model details. The first term dominates under the condition $\tilde{f}_aN_0^{\nu}\gg(c_2/c_1)^{\omega^{-1}}$. This is readily satisfied for long enough chains, but if $c_2>c_1$ holds, there appears a regime dominated by the second term in Eq. (10) before the weak driving or unbiased regime $\tilde{f}_aN_0^{\nu}\lesssim1$ is entered. This predicts a value of $\alpha=1.5$ for short chains in 2D, again in perfect agreement with the reported data [20,22]. It is noteworthy that the relevant exponent in 2D ($\omega^{-1}=5.26$) is much higher than that in three-dimensional (3D) ($\omega^{-1}=2.27$), which takes account of the appreciable crossover effect in 2D [11,20–22]. As both $c_1$ and $c_2$ are of order unity, the value $c_2/c_1$ would be, say, at most five or less (it can be estimated from the analysis of numerical simulations as the translocation dynamics changes qualitatively after $t=\tau_1$, see the discussion in Sec. V). Then, the crossover point $N_0\simeq100$ found in 2D simulations seems to be reasonable. In 3D, recent simulations have detected no crossover [22] in agreement with the present analysis.

## V. DISCUSSION AND PERSPECTIVES

First of all, some comments on the generic description presented are noted. The theory is based on the blob picture, so it works for the situation under which the magnitude of the tensile force is on the order of $\tilde{f}_a\simeq1$ or less. For stronger driving force, the blob description is no longer valid, and the precise dynamics then depend on the flexibility mechanics (freely joined, or wormlike chain, etc.). The force range in typical DNA experiments seems to be higher than the above threshold force [31], thus, dynamics of the DNA translocation during the initial period should be different from what predicted from the present theory. In fact, the fast time/short length scale behaviors should be governed by the bonding mode [18,19]. In later time [for example, imagine the situation between (ii) and (iii) in Fig. 2], however, the tensile force acting the chain becomes weaker along the chain, thus, the blob picture becomes again feasible for the large scale behaviors at later time. The translocation time is thus a sum of the initial period (dictated by the bending mode) and the later stage described by the present theory. Under the action of the driving force which is not too strong, the asymptotic scaling for the translocation time is controlled by the latter contribution [12]. We believe that this is the primal reason why the present theory is able to account for the asymptotic scaling for the DNA experiments.

Simple and heuristic scaling types of arguments have been shown to be very powerful in understanding the complex physical properties of polymer systems. We have to keep it in mind, however, that there are cases in which a great care has to be taken to properly take the underlying physics into account. A polymer confined in a small closed cavity (a situation called the strong confinement regime in Refs. [32,33]) would be one of such examples, in which a length scale (mesh size) other the geometrical size of the confinement emerges upon the confinement. In the present problem, the main complexity originates from the out-of-equilibrium, transient nature of the process. We described the process as the progressive response of the chain along with the tension propagation, and demonstrated very good agreements with various measurements as long as the asymptotic scaling of the translocation time is concerned. However, the presence of various crossovers and/or finite-size effects [see the remark (iii) after Eq. (8) and the discussion around Eq. (10)] must not be forgotten. This generally complicates the identification of the scaling exponent through the data analysis.

The effect of the transient piling-up of monomers at the *trans*-side [the remark (v) after Eq. (8)] should be incorporated in a more refined treatment. The idea in Ref. [14] would be useful for it.

In relation with the remark (iv) after Eq. (8), we notice that both translocation times born of the equilibrium shape assumption [Eq. (4)] and of the analysis of the out-of-equilibrium process [Eq. (9)] show the crossover to $\tilde{\tau}\simeq(\tilde{R}_0)^z$ at $\tilde{f}_{R_0}\to1$. Thus, from the scaling argument alone,

one cannot draw the definite conclusion on the presence of the regime described by the equilibrium shape assumption (weak driving regime). However, a recent simulation in 3D with the weak driving force has reported $\alpha = 1+\nu$, which is consistent with our prediction Eq. (4) under the equilibrium shape assumption [24].

It is certainly interesting to go beyond the discussion of the asymptotic scaling. This is a natural direction toward the better understanding, and at the same time would find a practical importance given the rapid experimental progress, in which the detailed characterization of the translocation process is becoming feasible [31]. One of the appealing dynamical features predicted is the deceleration of the process during the driven translocation [remark (vi) after Eq. (8)]. As already discussed in Sec. IV, however, the deceleration process is to be ceased at $t=\tau_1$, when the tension reaches at the chain end. The following dynamical stage at $t>\tau_1$ is qualitatively different, in which the process is accelerated [12]. A physical reason for it is the same as that causes the acceleration in the weak driving regime as this later stage is the generalization of the weak driving regime discussed in Sec. II.

Another interesting direction is to leave the set up with a passive pore and take into account the complex (and specific) interactions between the pore and the passing polymer [8]. Such a study would have intimate links with many of realistic situations in biological sciences.

Aside from the translocation, there would be a barrel of situation in which polymers show unique dynamic response inherent in themselves. Clarifying underlying physics there is certainly a boon, for which the present formalism would play a vital role by furnishing lucid molecular pictures.

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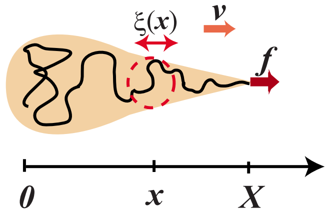

FIG. 3. (Color online) Steady-state conformation of a chain dragged by a constant force $f$ with velocity $v$ and longitudinal length $X$. The length scale $\xi(x)$ corresponds to the size of the lateral chain excursion at the position $x$.

## APPENDIX: STEADY-STATE OF A DRAGGED CHAIN

For a dragged chain, there is a length scale $\xi(x)$ below which the effect of pulling is insignificant (Fig. 3), and thus one can expect that a near-equilibrium formula for the dragging coefficient can be applied [Eq. (1) with $N$ replaced by $g(x) \simeq (\xi(x)/a)^{1/\nu}$] [34]. The overall deformed conformation can be pictured as a sequence of blobs of size $\xi(x)$ which are hydrodynamically decoupled, hence the dragging force acting at the position $x$ is

$$f_{drag}(x) \simeq \tilde{v}\int_0^{\tilde{x}} d\tilde{x}\frac{\tilde{\xi}(x)^{z-2}}{\tilde{\xi}(x)}. \tag{A1}$$

Utilizing the Pincus blob prescription $\xi(x) \simeq k_BT/f_{drag}(x)$ [35], the above consideration can be mathematically expressed as $\tilde{\xi}(x) \simeq [\tilde{v}\tilde{x}]^{1/(2-z)}$. Now let us look at both chain ends. One end is pulled by the force $f$, thus, its balance with the total dragging force $f \simeq k_BT/\xi(X)$ leads to a steady-state dynamical relation among the global variables $f$, $v$, and $X$:

$$\tilde{f}_a \simeq [\tilde{v}\tilde{X}]^{1/(z-2)}. \tag{A2}$$

The other end is free; thus, the largest blob of size $\xi_{free}$ there experiences the dragging force acting on itself only. The Pincus relation leads to $\tilde{\xi}_{free}^{-1} \simeq \tilde{v}\tilde{\xi}_{free}^{z-2}$, yielding

$$\tilde{\xi}_{free} \simeq \tilde{v}^{-1/(z-1)}. \tag{A3}$$

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