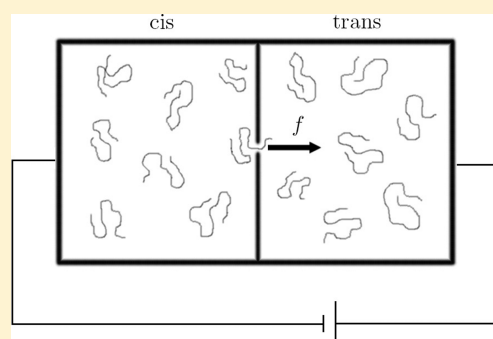


Force-Driven Polymer Translocation through a Nanopore: An Old Problem Revisited

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ABSTRACT: We consider DNA translocation through a pore in a planar membrane. The pore is so narrow that only one DNA segment can fit in. Assuming that the biasing force f acts inside the pore only, and that the DNA monomer number N is asymptotically large, we modify the previously developed treatment of the stretched part of the pre-translocated polymer by introducing the concept of “iso-flux trumpet”. We show that friction of a moving chain in the trumpet, although it determines the speed of the process, provides only a marginal fraction of overall dissipation in the process. The dominant dissipation turns out to be due to irreversible entropic squeezing of the chain into the small pore. We also discover that because of the role of the membrane a much larger amount of heat of order $k_B T$ per monomer gets transferred from the heat bath on the post-translocation side to that on the pre-translocation side.



1. INTRODUCTION

Motivated both by natural phenomena such as virus genome ejection¹ or macromolecular transport through nuclear pores² and by the prospect of a robust sequencing technique,^{3–6} voltage-driven translocation of DNA through a nanopore (Figure 1) has been the subject of extensive experimental, theoretical, and computational work. The pore is too narrow for the polymer chain to pass through while keeping its coiled conformation, so the polymer has to partially unwind while it passes from the cis to trans side of the membrane.

Various aspects of the process such as screening effects inside the pore,^{7,8} the effect of pore geometry and symmetry of monomers on the passage dynamics,^{9–12} and polymer capture into the pore^{13–16} have been studied. Both solid-state pores,^{17–24} which are tunable in size and geometry, and protein-based^{13,25–34} pores have been employed. There is also no shortage of theoretical studies, but surprisingly, there is no convergence of opinion on the passage dynamics even for the most dramatically simplified model. In such studies, the stage of DNA capture into the pore is put aside, and the question addressed is the scaling of translocation time τ_{tr} with chain length N and applied force f , which given all the simplifications is expected to be universal. Despite the seeming simplicity of this problem, it remains incompletely understood.

The model consists of a polymer with no topological constraints and no polyelectrolyte effects passing through a pore narrow enough to only allow single-fold passage. Two assumptions further simplify the model. First, the polymer chain is assumed to be very long and flexible. The chemical length of the polymer not only is much larger than its persistence length but also is much longer than any length scale associated with the pore. For sufficiently large N , the friction felt by the coil outside

the pore dominates over the friction caused by the pore; therefore, the geometry of the pore is unimportant, and the scaling of translocation time is pore-independent. Second, the force is assumed to only be significant inside the pore. This assumption is equivalent to the statement that voltage drop mostly takes place inside the pore and is justified for properly narrow pores.³⁵

Different approaches have been used to address the passage of the polymer. The earliest works by Sung and Park³⁶ and Muthukumar³⁷ treated it as a near-equilibrium escape process over an entropic barrier created by the membrane. This partial equilibrium assumption was later questioned by Chuang et al.,³⁸ by showing unbiased Brownian translocation time to be counter-intuitively smaller than the polymer relaxation time. In agreement with their simulation results, they hypothesized that the unbiased translocation time must instead have the same scaling behavior as the relaxation time with a larger numerical prefactor. They thus concluded that the process could not be reduced to a simple diffusion of the translocation coordinate and has to be anomalous. Driven translocation was then shown by Kantor and Kardar³⁹ to be a biased subdiffusion.

The result obtained for the driven translocation time in ref 20 by balancing the external force with friction between the polymer and solvent follows the same subdiffusive scaling form as suggested in ref 39. Also, using the trumpet model for a polymer being pulled from one end,⁴⁰ Sakaue has obtained the similar subdiffusive behavior by improving the force balance method and

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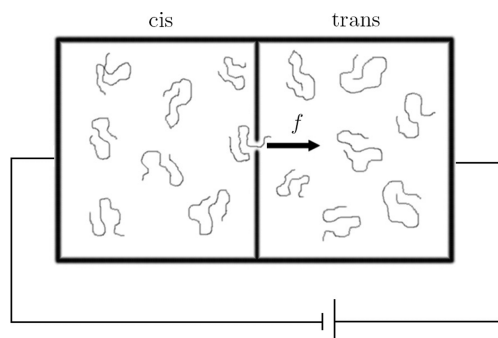


Figure 1. DNA molecules driven through the pore by an external voltage. Field lines are squeezed through the pore, so the field is very strong inside the pore and negligible elsewhere.

explicitly considering the deformation of polymer caused by the external force during translocation.^{41,42}

The anomalous diffusive behavior of the translocation coordinate has been studied from a different point of view by considering the memory effects which cause the subdiffusive behavior of monomers.^{43–45} More recently, Panja⁴⁶ has categorized translocation as one form of anomalous diffusive process described by a Generalized Fluctuation–Dissipation Theorem and characterized by a specific memory kernel. Dubbeldam et al.^{47,48} have also attempted to approach the escape problem for both unbiased and driven translocation using a fractional calculus description of anomalous diffusion.

Despite using the same model and general agreement regarding far from equilibrium and subdiffusive character of the process, there is a considerable disagreement between the results obtained by different groups, particularly upon driven translocation. A similar diversity is found in the results obtained using computer simulations. Mostly done in the absence of hydrodynamic interactions, simulations do not conclusively confirm one or another theoretical predictions. More recent works to some extent relate seemingly contradicting results by identifying them as crossovers from short to long polymers^{49,50} and from slow to fast translocation;^{51,52} however, a clear understanding of the crossover force and polymer length and their scaling behavior is still to be presented. In addition, one group has simulated the hydrodynamic interactions by lattice Boltzmann treatment.⁵³ The obtained results⁵⁴ were declared to be in agreement with models presented in refs 20 and 42; however, the agreement becomes less clear by noting that the two models make completely different assumptions about the force strength and polymer deformation during translocation.

The discrepancies described above are deepened by problems with two important issues, namely, conservation of energy and mass. First, as pointed out by Vocks et al.,⁴⁵ in the case of voltage-driven translocation, the energy given to the polymer by the electric field has to be dissipated during the process. Some of the known theories can be shown to violate this energy conservation condition. In general, where and how energy is dissipated is an open question. Second, as a process in which mass is being transferred from one place to another, translocation has to satisfy a continuity relation. More specifically, in cases where the deformation of the polymer during the process is explicitly taken into account, an even more detailed estimation of the flux and its consistency with the translocation speed is necessary. Once again there appears to be a lack of such a detailed investigation in previous works.

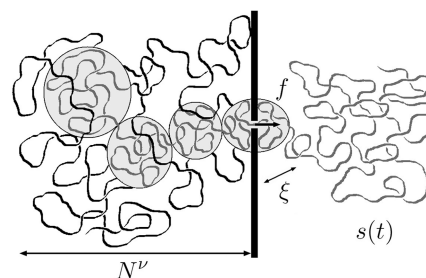


Figure 2. Polymer getting deformed and sucked into the pore. Part of the polymer involved in the forced motion adopts a trumpet-like shape, a sequence of blobs increasing in size. The trumpet slowly grows but mostly acts like a tunnel for the polymer. The two blobs at the pore are related to the role of the membrane, explained in Section 2.2.

The plan of this work is to shed more light on translocation as a far from equilibrium process by explicitly addressing these two issues. The article is divided into two parts. In part one, we describe our model by introducing the concept of iso-flux trumpet and show how this special kind of trumpet could be used to address the mass conservation. In part two, we illustrate how dissipative mechanisms are closely related to the strong tensions created in the polymer by the membrane. We also discover that such strong tensions cause a net heat transfer from the heat bath on the trans to the cis side during translocation.

2. MODEL AND RESULTS

Consider a very long polymer containing N monomers with one end captured inside the pore, which for simplicity is assumed to have the same dimensions a as a monomer. At $t = 0$, we switch on the driving force f inside the pore. As monomers get sucked into the pore, the polymer gets stretched by the force, and the deforming effect of the force propagates along the chain. Therefore, at each moment of time, apart from $s(t)$ monomers that have passed through the pore, $\ell(t)$ monomers exist on the untranslocated side that feel the effect of force and move under its influence. Considering the $\ell(t)$ trailing monomers as a trumpet shape,⁴⁰ Sakaue^{41,42} has formulated the problem by balancing the driving force with the friction force between the trailing monomers and solvent.

Modifying Sakaue's consideration and keeping the mass conservation in mind, in Section 2.1, we build our model by arguing that the trailing part could be well described by an “iso-flux” trumpet. Unlike a steady trumpet characterized by a velocity scale, an iso-flux trumpet is characterized by a flux scale, which allows the mass conservation to be explicitly imposed.

The trumpet model however leaves the conservation of energy unanswered. We show that the friction between the trumpet and solvent is too small to account for all the dissipation. Moreover, the trumpet model does not clarify how the moderate driving force can squeeze the monomers inside a monomer-size pore. Both of these seemingly unrelated issues, as will be shown in Section 2.2, are resolved by explicitly considering the role of the membrane. Mostly overlooked in previous works, a polymer with one end captured inside the pore, just like a polymer grafted from one end to a surface, experiences a very strong tension in the vicinity of the pore/grafting point. Thus, during the process both translocated and untranslocated sections of the polymer are strongly stretched. While these strong tensions are the result of squeezing the chain into the pore, the role of the driving force is

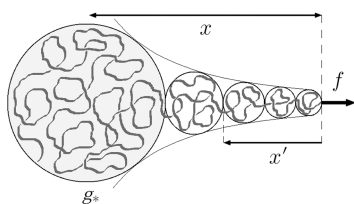


Figure 3. Every blob in the trumpet experiences the action of three forces which balance each other: polymer tension force on the front and back ends and friction. By contrast, the largest blob moves under a force comparable to the tension it feels; this condition determines the size of this blob, g^* .

only to bias the process in one direction by slightly unbalancing the tensions on the two sides of the pore. The relaxation of monomers as they pass through the pore turns out to be the major source of dissipation.

For brevity of writing, we will use everywhere the dimensionless distance $x \rightarrow (x/a)$, force $f \rightarrow [(fa)/T]$, and time $t \rightarrow (t/\tau_{\text{mon}})$, where a is a microscopic length scale associated with both monomer and pore sizes; $\tau_{\text{mon}} = [(\eta a^3)/T]$ is a monomer time scale; η is solvent viscosity; and T is absolute temperature in energy units.

2.1. Iso-Flux Trumpet Model. The general scenario of the driven translocation process is illustrated in Figure 2. Its idea is the same as in the work of Sakaue.^{41,42} A translocating polymer gets stretched, and $\ell(t)$ trailing monomers affected by the force form a trumpet⁴⁰ of length $x(t)$ in front of the pore. Such a trumpet can form for a range of “moderate” force f by which we mean

$$N^{-\nu} \ll f \ll 1 \quad (1)$$

The trumpet grows as the force propagates along the chain, and at some time τ when $x(\tau) \sim N^\nu$ the effect of force reaches the far end of the coil. Since the trumpet is a directed object (at scales larger than a blob size), its size is much larger than the size of an unperturbed coil of the same chemical length. Therefore, $\ell(\tau) \ll N$ is much smaller than the number of translocated monomers $s(\tau) \sim N$, and translocation time τ_{tr} is the same as τ to the leading order.

We here suggest a slight modification of this idea. Namely, we have to realize that the trumpet itself in the translocation problem—unlike the original steady trumpet⁴⁰—does not move anywhere, but the polymer gets “pumped” through it. Knowing that $s(\tau_{\text{tr}}) \sim N \gg \ell(\tau_{\text{tr}})$, the growth rate of the trumpet $\dot{\ell}(t)$ has to be much smaller than the translocation rate $\dot{s}(t)$. Since the latter is the flux passing through the narrow end of the trumpet and the former is the difference between the fluxes at the narrow and the wide ends, the flux along the trumpet is almost constant. Therefore, the defining property of this trumpet is the fact that the flux of monomers, ϕ , is the same through every cross-section of the trumpet. Here we briefly describe the trumpet theory modified to take into account the iso-flux constraint.

Assuming the speed of monomers some distance x' from the pore (or from the trumpet narrow tip) is $v(x')$ while polymer tension force is $f(x')$ (Figure 3), we can write the flux conservation as

$$f^{[(\nu-1)/\nu]}(x')v(x') = \phi \quad (2)$$

This is because the linear density in the trumpet (the number of monomers per unit length along the trumpet) is estimated as

$g(x')/\xi(x') = f^{[(\nu-1)/\nu]}(x')$, where $g(x')$ is the number of monomers in one Pincus (stretching) blob at force $f(x')$, while $\xi(x') \sim g^\nu(x') \sim 1/f(x')$ is the size of that blob. We assume here that $x' < x$, with x being the length of the trumpet.

As in a regular trumpet, the difference between tension forces in points x' and $x' + dx'$ is compensated by the viscous friction experienced by the moving piece of polymer between x' and $x' + dx'$. Given that flux (eq 2) is the same everywhere along the trumpet, this condition is written as

$$\text{Rouse} \rightarrow \frac{df(x')}{dx'} = -\phi \quad (3a)$$

$$\text{Zimm} \rightarrow \frac{df(x')}{dx'} = -\phi f^{[(1-\nu)/\nu]}(x') \quad (3b)$$

where the friction coefficient per monomer is 1 for the Rouse chain and $\xi(x')/g(x') \sim f^{[(1-\nu)/\nu]}(x')$ for Zimm dynamics. Since the tension at the trumpet tip is the known force, $f(x')|_{x'=0} = f$, the above equations are integrated to yield

$$\text{Rouse} \rightarrow f(x') = f - \phi x' \quad (4a)$$

$$\text{Zimm} \rightarrow f(x') = (f^{[(2\nu-1)/\nu]} - \phi x'^{[(\nu/(2\nu-1))]} \quad (4b)$$

Here and below we drop for simplicity the coefficient $2\nu - 1$ assuming $\nu > 1/2$; in fact, for the Gaussian polymer ($\nu = 1/2$) this coefficient regularizes the expressions like $[\nu/(2\nu - 1)](f^{[(2\nu-1)/\nu]} - 1)|_{\nu=1/2} = \ln f$; for brevity we omit this case, as it can be easily reconstructed at every step.

The delicate step is to establish the boundary condition at the wide part of the trumpet, which eventually determines its overall size. Since the tension force appears to vanish at some finite x' , one might be tempted to identify this place as the end of the trumpet. In fact, the tension blob size becomes infinite in this place, which is meaningless. We argue that the trumpet is meaningfully described as such only up to about the middle of the last blob, as illustrated in Figure 3. Denoting the location of this last blob as x , its size and monomer number as $\xi_* = 1/f(x)$, and $g_* = \xi_*^{1/\nu}$, we arrive at the conditions which are similar to eq 3a and eq 3b, except the last blob experiences only two forces, tension from the leading end balanced by friction

$$\text{Rouse} \rightarrow f(x) = v(x)g_* \quad (5a)$$

$$\text{Zimm} \rightarrow f(x) = v(x)\xi_* \quad (5b)$$

A few lines of simple algebra then yield

$$\text{Rouse} \rightarrow f(x) = \phi^{1/2}, \quad g_* = \phi^{[-1/(2\nu)]} \quad (6a)$$

$$\text{Zimm} \rightarrow f(x) = \phi^{[\nu/(3\nu-1)]}, \quad g_* = \phi^{[-1/(3\nu-1)]} \quad (6b)$$

Since we know $f(x')$, we can also find from here the trumpet length

$$\text{Rouse} \rightarrow x = \frac{f}{\phi} - \phi^{-1/2} \simeq \frac{f}{\phi} \quad (7a)$$

$$\text{Zimm} \rightarrow x = \frac{f^{[(2\nu-1)/\nu]}}{\phi} - \phi^{[-\nu/(3\nu-1)]} \simeq \frac{f^{[(2\nu-1)/\nu]}}{\phi} \quad (7b)$$

By integrating the linear density $\int_0^x f^{[(\nu-1)/\nu]}(x')dx'$, we can find the number of monomers involved in the trumpet. Interestingly,

this integration for Zimm dynamics is controlled by the upper limit, which means a large fraction of all monomers in the trumpet is located in the last few blobs. The result reads

$$\text{Rouse} \rightarrow \ell = \frac{\nu}{2\nu - 1} \left[\frac{f^{[(2\nu - 1)/\nu]}}{\phi} - \phi^{-[1/(2\nu)]} \right] \sim \frac{f^{[(2\nu - 1)/\nu]}}{\phi} \quad (8a)$$

$$\begin{aligned} \text{Zimm} \rightarrow \ell &= \frac{2\nu - 1}{2 - 3\nu} \left[\phi^{[-1/(3\nu - 1)]} - \frac{f^{[(3\nu - 2)/\nu]}}{\phi} \right] \sim \phi^{[-1/(3\nu - 1)]} \end{aligned} \quad (8b)$$

Finally, the relation between the number of monomers in the trumpet and the trumpet length is

$$\text{Rouse} \rightarrow x \sim f^{[(1 - \nu)/\nu]} \ell \quad (9a)$$

$$\text{Zimm} \rightarrow x \sim f^{[(2\nu - 1)/\nu]} \ell^{3\nu - 1} \quad (9b)$$

To continue with the translocation model, we note that the characteristic flux of the trumpet determines the translocation rate

$$\frac{ds(t)}{dt} \sim \phi(t) \quad (10)$$

One last consideration closes this set of equations. At each time t , there are $N - [\ell(t) + s(t)]$ monomers behind the trumpet that have not yet been affected by the force. Therefore, where the end of the trumpet lies at time t is where initially an unperturbed coil containing $\ell(t) + s(t)$ monomers had extended to; i.e., the trumpet size is equal to the size of a coil with $\ell(t) + s(t)$ monomers

$$x(t) \sim [\ell(t) + s(t)]^\nu \quad (11)$$

Putting eqs 7a, 7b, 9a, 9b, 10, and 11 together, we find

$$\text{Rouse} \rightarrow [x^{1/\nu}(t) - f^{[(\nu - 1)/\nu]} x(t)] \dot{x}(t) \sim f \quad (12a)$$

$$\begin{aligned} \text{Zimm} \rightarrow & [x^{1/\nu}(t) - f^{[(1 - 2\nu)/\nu(3\nu - 1)]} x^{[1/(3\nu - 1)]}(t)] \dot{x}(t) \sim f^{[(2\nu - 1)/\nu]} \end{aligned} \quad (12b)$$

which can be integrated to yield

$$\text{Rouse} \rightarrow x^{[(1 + \nu)/\nu]}(t) - f^{[(\nu - 1)/\nu]} x^2(t) \sim ft \quad (13a)$$

$$\begin{aligned} \text{Zimm} \rightarrow & x^{[(1 + \nu)/\nu]}(t) - f^{[(1 - 2\nu)/\nu(3\nu - 1)]} x^{[3\nu/(3\nu - 1)]}(t) \sim f^{[(2\nu - 1)/\nu]} t \end{aligned} \quad (13b)$$

where all the numerical coefficients have been dropped. Measured in units of monomer size, $x(t)$ is a large quantity, and as a result, for times larger than a critical time τ_c the first terms on the left-hand sides of eqs 13a and 13b dominate over the second. Interestingly, for both Rouse and Zimm dynamics, $x(\tau_c) \sim (1/f) \sim \xi$, which is exactly the size of a blob created under the tension f . Equations 13a and 13b have no solution for $t < \tau_c$ meaning at early times the force-affected trailing part is too small to form a

trumpet of several blobs, and as a result its dynamics could not be described by the equations above. We will study this regime separately later to demonstrate a crossover from “blob regime” to “trumpet regime” at time τ_c and show that for moderate forces the process is dominated by the trumpet regime.

Neglecting the second term on the left-hand side, we can write the quantities of interest

$$\begin{aligned} \text{Rouse} \rightarrow x(t) &\sim f^{[\nu/(1 + \nu)]} t^{[\nu/(1 + \nu)]}, \\ s(t) &\sim f^{[1/(1 + \nu)]} t^{[1/(1 + \nu)]} \end{aligned} \quad (14a)$$

$$\begin{aligned} \text{Zimm} \rightarrow x(t) &\sim f^{[(2\nu - 1)/(1 + \nu)]} t^{[\nu/(1 + \nu)]}, \\ s(t) &\sim f^{[(2\nu - 1)/(\nu(1 + \nu))]} t^{[1/(1 + \nu)]} \end{aligned} \quad (14b)$$

Note that $x(t) \sim s^\nu(t)$, so two different criteria $x(\tau_{tr}) \sim N^\nu$ and $s(\tau_{tr}) \sim N$ consistently determine translocation time to be

$$\text{Rouse} \rightarrow \tau_{tr} \sim f^{-1} N^{1 + \nu} \quad (15a)$$

$$\text{Zimm} \rightarrow \tau_{tr} \sim f^{[(1 - 2\nu)/\nu]} N^{1 + \nu} \quad (15b)$$

The force dependence of translocation time is the only place where Rouse and Zimm dynamics are different. This is because the dynamic part, trumpet, is a rodlike object that has a friction coefficient proportional to its size but with different force dependence for Rouse and Zimm dynamics.

As already mentioned, the trumpet solution is meaningful only when trumpet length $x(t)$ exceeds at least the smallest blob size. As eqs 14a and 14b indicate, this is true at $t > \tau_c$ where τ_c is $f^{[-(1 + 2\nu)/\nu]}$ for Rouse and f^{-3} for Zimm. For $t < \tau_c$ the trailing part is a blob too small to be perturbed by the force f , so eqs 7a, 7b, 9a, 9b, and 10 must be changed to describe the dynamics of the trailing blob. For this blob, $x_b(t) \sim \ell_b^\nu(t)$, with subscripts denoting the blob regime. The linear density of this blob now depends on $\ell_b(t)$, and the translocation rate and flux are related through the relation $(ds_b(t))/dt \sim v_b(t) \ell_b^{\nu - 1}(t) \sim \phi_b$, where $v_b(t)$ is the velocity of the blob (strictly speaking, this velocity scale has to be determined by considering an iso-flux blob, which is a simple calculation in agreement with the latter relation). The force balance is $f \sim \phi_b(t) \ell_b^\nu(t)$ for Rouse dynamics and $f \sim \phi_b(t) \ell_b^{2\nu - 1}(t)$ for Zimm. Together with eq 11, which is still valid, we get

$$\begin{aligned} \text{Rouse} \rightarrow x_b(t) &\sim f^{[\nu/(1 + \nu)]} t^{[\nu/(1 + \nu)]}, \\ s_b(t) &\sim f^{[1/(1 + \nu)]} t^{[1/(1 + \nu)]} \end{aligned} \quad (16a)$$

$$\text{Zimm} \rightarrow x_b(t) \sim f^{1/2} t^{1/2}, \quad s_b(t) \sim f^{1/(2\nu)} t^{1/(2\nu)} \quad (16b)$$

For either Rouse or Zimm cases, both $x(t)$ and $s(t)$ exhibit smooth crossover at $t = \tau_c$ from the blob regime (eqs 16a and 16b) to the trumpet regime (eqs 14a and 14b). At forces $f \gg N^{-\nu}$ when the trumpet model applies, translocation time is dominated by the trumpet regime, i.e., $\tau_c \ll \tau_{tr}$. Furthermore, for forces as weak as $f \sim N^{-\nu}$, both τ_c and τ_{tr} become comparable to the relaxation time of the polymer, which is $N^{1 + 2\nu}$ for Rouse and $N^{3\nu}$ for Zimm. Thus, our results are consistent with the earlier suggestion³⁸ that the unbiased translocation time scales the same way as the polymer relaxation time and that the process crosses over from driven to diffusion-dominated translocation at a force about $f \sim N^{-\nu}$. In fact, the blob regime is hidden under the diffusion-dominated regime because the onset of both regimes happens simultaneously at the same force scale. Finally, this is

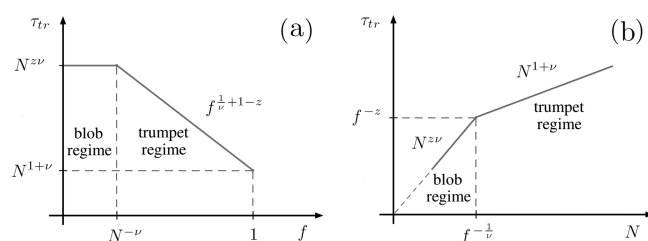


Figure 4. Different regimes of translocation time as a function of (a) force and (b) polymer length. For brevity, we have used the “dynamic exponent” z which is $2 + 1/\nu$ for Rouse and 3 for Zimm dynamics. Trumpet and single blob regimes are shown.

indeed true as long as our results allow us to verify the main assumption behind the iso-flux trumpet model, namely, $\dot{s}(t) \gg \dot{z}(t)$. Figure 4 summarizes our results.

2.2. Energy Dissipation and the Role of the Membrane.

The force acting only inside the pore corresponds to a peculiar potential energy landscape for every monomer—it is flat in the bulk on either side of the membrane and contains a ramp of gradient f inside the pore. Given that the pore length is of order unity (or a), this means the driving force performs a work about f on every monomer translocated or fN on the entire chain, and that amount of energy must be dissipated during translocation. As it was emphasized by Vocks et al.,⁴⁵ this fact imposes an unavoidable constraint on the possible scenarios of translocation. It turns out that satisfying this requirement is not trivial.

First, we consider how it is violated in the simplest possible theory.²⁰ In that theory, translocation time is estimated based on the idea that driving force f is balanced by the friction of the entire trailing coil ($f \sim N\nu$ for Rouse and $f \sim N^\nu\nu$ for Zimm) and that translocation involves moving the coil a distance about the coil size ($\nu \sim N^\nu/\tau_{tr}$). This simple argument yields an estimate of translocation time which is good enough for both experimenters²⁰ and simulators⁵⁴ to claim agreement, but the argument fails as far as dissipation is concerned. Indeed, the dissipation in this scenario seems to be the work of the friction force, which is equal to f by assumption, over the distance about the coil size, which is N^ν . Thus, viscous dissipation in this case scales as fN^ν ; i.e., it does not dissipate nearly as much energy as expected because $fN^\nu \ll fN$.

A similar problem appears to exist also in the trumpet solution of Sakaue⁴² and even in our own solution above. Similar to eqs 3a and 3b determining friction force acting on a dx' part of the trumpet, we can also write down the dissipated power: the number of monomers is $f^{[(\nu-1)/\nu]}(x')dx'$, the friction coefficient per monomer is also known to us for both models, while velocity squared $v^2(x')$ can be expressed in terms of the flux according to eq 2. Together with the force profile of the iso-flux trumpet (eq 4a, eq 4b), the overall dissipated power evaluates to

$$\text{Rouse} \rightarrow w(t) = \int_0^{x(t)} v^2(x') f^{[(\nu-1)/\nu]}(x') dx' \approx \phi(t) f^{1/\nu} \quad (17a)$$

$$\text{Zimm} \rightarrow w(t) = \int_0^{x(t)} v^2(x') dx' \approx \phi(t) f^{1/\nu} \quad (17b)$$

Further integration of this power over the entire translocation time obviously yields the total amount of $f^{(1/\nu)}N$ dissipated energy in both cases, which is again far too small, because $f^{(1/\nu)}N \ll fN$. Thus, the viscous friction in the trumpet does

not dissipate all the energy, and the dominant dissipation must occur elsewhere.

We found the key to understanding this paradox in the fact that even the first blob at the very tip of the trumpet is far too big to fit into the pore: $\xi = (1/f) \gg 1$. To get squeezed into the pore of size unity (or a), the chain must be stretched with a force of order unity (of order T/a in regular units). Where does this large stretching force come from? At the very beginning of translocation, when one of the chain terminals should enter the pore, this must happen because of fluctuation. This fluctuation does involve a large free energy barrier and occurs very infrequently. However, as soon as the polymer is already in the pore, its further motion does not involve overcoming a large barrier at every step because some part of the chain remains strongly stretched during the whole translocation time and it only moves along the chain—not unlike a soliton (except it undergoes a (biased) subdiffusion instead of directed motion for a regular soliton). We will show now that this strongly stretched part of the chain provides the main mechanism of energy dissipation.

To understand this, it is necessary to realize that the chain is strongly stretched not only inside the pore but also over a large distance outside the pore, on both sides. Indeed, if we forget for a moment about chain motion through the pore, then the coil on either side of the pore looks like it is grafted by one end to a planar impermeable surface. As such, it exerts a pulling force of order unity (or T/a) on its grafting bond and experiences also a tension along the chain which decays relatively slowly with the distance from the grafting point (which is the pore mouth in our case). The existence of this force of entropic nature is a very general and elementary property of any grafted polymer. To distinguish it from the applied force f , we call this much larger force F . Although various manifestations of it are scattered in the literature (see ref 55 for instance), to our surprise, we did not find anywhere an explicit general formulation. This is why we present a brief discussion in Appendix A.

The grafted polymer pulls itself off the grafting point pretty much like Baron Munchausen was pulling himself from the swamp by his own hair⁵⁶—except it does not violate the third Newton’s law because it pulls off at the expense of exerting a compensating pressure on the membrane around the grafting point. This is important because it means tension force F is not compensated by the viscous friction force and thus in itself does not cause any motion of the chain.

Applying this idea to the translocation case is justified because the tension F is governed by a small piece of the chain which has plenty of time to equilibrate at every stage of translocation so that application of equilibrium estimate for F is justified. Equilibrium consideration, outlined in Appendix A, indicates that tension force F drops as $F \sim 1/r$ (or T/r in regular units) at distance r from the pore. That means, at a distance larger than the first tension blob size $\xi \sim 1/f$, the force F is negligible compared to the viscosity-balanced force $f(x)$ analyzed above. In this range, the iso-flux trumpet consideration remains valid. At smaller distances, within the first blob, the force F dominates and is balanced by the membrane. This is all illustrated in Figure 2.

How does this help us understand the puzzle of dissipated energy? Consider a short segment of the chain and imagine its travel in the course of translocation. It starts far away on the cis side and slowly gets more and more stretched until it becomes stretched by a force of order F when it enters the pore mouth. In the subsequent motion on the trans side, the chain fragment stretch slowly reduces and eventually disappears. In this process,

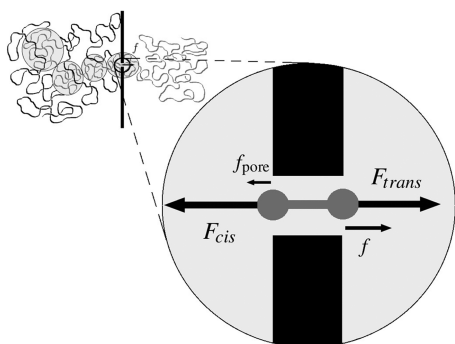


Figure 5. Force balance of the chain segment inside the pore involves four forces: the biasing force f , friction of monomers inside the pore f_{pore} (which includes friction against the pore walls and the solvent), and two tension forces created by the entropic elasticity of the coils on both sides, F_{cis} and F_{trans} . Given that the pore is very narrow, forces F_{cis} and F_{trans} are large and almost completely compensate each other. Their small difference is balanced by $\tilde{f} = f - f_{\text{pore}}$, such that $F_{\text{cis}} = F + \alpha\tilde{f}$ and $F_{\text{trans}} = F - (1 - \alpha)\tilde{f}$, where the coefficient α is unknown and may depend on model details but does not affect our results either.

entropy of the chain piece first reduces because transverse fluctuations of the chain get increasingly suppressed as it approaches the pore, and then entropy increases on the other side of the membrane. The initial entropy reduction is driven by the tension force pulling on the fragment's leading end, and the work of this force goes into the heat bath surrounding the chain on the cis side. Similarly, entropy increase on the post-translocation (trans) side provides the force which pulls on the trailing end of the given fragment and helps the subsequent fragment; the work of this force is provided by taking energy from the heat bath on the trans side.

It is useful to imagine an idealized case when the membrane itself does not conduct heat. In this case, what happens is that some heat—about $k_{\text{B}}T$ per monomer—gets absorbed on the trans side of the membrane, and a similar amount gets released on the cis side. As a useful corollary to this result, one can think hypothetically about what happens if the temperatures on two sides of the membrane are different, in which case the entropic elasticity will be stronger on the hotter side, providing a bias in translocation.

Yet another interesting thought experiment would be to imagine an enzyme (such as a restriction enzyme) chopping off the translocated pieces of polymer; in this case the tension force F_{cis} will be uncompensated, and polymer would retract from the pore.

A more accurate analysis now shows that the amount of heat released on the cis side is slightly larger than the amount absorbed on the trans side, and this difference is exactly f (or fa in regular units) per monomer or fN per chain. To see this, let us consider a piece of polymer which is presently inside the pore (Figure 5). The forces acting on this piece must be balanced, and since there is a force $\tilde{f} = f - f_{\text{pore}}$ acting inside the pore (with f_{pore} being the friction due to the pore), the tension must be $F + \alpha\tilde{f}$ at the pore entrance and $F - (1 - \alpha)\tilde{f}$ at the pore exit, where α is a nonuniversal coefficient of order unity which depends on the local details of chain structure (e.g., wormlike chain versus other flexibility mechanisms, etc.). Therefore, the free energy of this segment before it entered the pore was $\phi(F + \alpha\tilde{f})$, which was the amount dissipated into the heat bath on the cis side, and the free energy of the segment after exiting will be $\phi(F - (1 - \alpha)\tilde{f})$.

Here, ϕ is a force-dependent thermodynamic potential (similar to a Gibbs free energy in regular thermodynamics) per monomer of the given chain, which just like α does not have to be universal and may depend on the chain flexibility mechanism, etc. Because of the tension drop across the pore, the amount of heat dissipated on the cis side exceeds that absorbed on the trans side by the amount $\phi(F + \alpha\tilde{f}) - \phi(F - (1 - \alpha)\tilde{f})$. Since $\tilde{f} < f \ll F$ (see eq 1), we can Taylor expand ϕ around F and obtain $\phi'(F)\tilde{f} = a\tilde{f}$ independently of α because the quantity $\phi'(F) \sim a$ is of course the length of one fully stretched monomer. Finally, to obtain the total dissipation, we should also add the work of friction inside the pore which is $a\tilde{f}_{\text{pore}}$, yielding the expected answer for total dissipation to be $a\tilde{f} + a\tilde{f}_{\text{pore}} = a\tilde{f}$ per monomer.

It is worth emphasizing that although dissipation occurs mostly within the strongly stretched region of the first blob it is not determined by the friction due to the motion of monomers inside the pore. This point becomes clear by noting that the friction inside the pore may be arbitrarily small or even vanishing—and still there is dissipation of $a\tilde{f}$ per monomer. It is important to note that the dissipative mechanism described above is not frictionless. It is based on the coupling between polymer conformations and the heat bath which in reality is realized through solvent viscosity. What we mean is that dissipation is not determined by the forced directed motion of the polymer through the liquid; instead, dissipation mostly results from the forced directed flow of heat from polymer to the solvent on the cis side and from the solvent to polymer on the trans side.

To summarize, we have found that the main mechanism of dissipation is the one in which the chain gets strongly stretched before it enters the pore and gets slightly relaxed as it exits. An interesting aspect of this result is that a much larger amount of energy, about $k_{\text{B}}T$ per monomer, is taken away from the heat bath on the post-translocation (trans) side and given to the heat bath on the pre-translocation (cis) side. This is entirely due to the strong stretch of the chain created not only by the pore but also by the impermeable membrane. Indeed, the strong tension F on each side is not balanced by friction but rather by the pressure of the chain on the membrane. In this sense, we in this work return to the original ideas of Sung and Park³⁶ and Muthukumar,³⁷ suggesting the important role of chain restriction by the membrane, except we now view the role of the membrane to be the creation of the strong tension force rather than only a logarithmic free energy barrier.

3. CONCLUSION

To conclude, we have developed the iso-flux trumpet model which accounts correctly for the amount of dissipated energy. We show that energy is mostly dissipated not by the viscous friction in the trumpet but rather through the process of stretching and then relaxing the chain in the first blob vicinity of the pore itself. This stretching is supported by the membrane and, unexpectedly, is also accompanied by the pumping of a significant amount of heat from the post-translocation to the pre-translocation side of the membrane.

For the translocation time, our model predicts in the long-chain length limit $\tau_{\text{tr}} \sim f^{-1}N^{1+\nu}$ for the Rouse (immobile solvent) dynamics and $\tau_{\text{tr}} \sim f^{[(1-2\nu)/\nu]}N^{1+\nu}$ for the Zimm (solvent involvement) dynamics (see also above about logarithmic regularization for the $\nu = 1/2$ case). This is in agreement with some of the earlier studies^{39,49} as well as the most recent one,⁵² where the $N^{1+\nu}$ scaling was reported for the regime of slow

translocation. Furthermore, at $f \sim N^{-\nu}$, our results do cross over to the unbiased translocation time of order coil relaxation time, as hypothesized by Chuang et al.³⁸ Therefore, our theory presented in this work lends additional credibility to this hypothesis and places greater doubt on the alternative claims. Regarding the force dependence, the f^{-1} scaling should be expected for Rouse dynamics with moderate forces on very general grounds, and indeed it was recently observed⁵⁷ for sufficiently narrow pores and moderate forces. In this context, we interpret the force-independent regime for weak forces reported in ref 57 as a crossover to the diffusion controlled (unbiased) translocation regime.

Our results do of course obey the lower bound of translocation time, $\tau_{tr} \geq N^{2\nu}$, formulated by Vocks et al.,⁴⁵ but our time estimate is significantly longer because the lower bound derivation incorrectly associates all the dissipation with trumpet friction.

The most ambitious claim in the translocation theory literature so far is that the simple theoretical argument put forward in ref 20 (outlined above in Section 2.2), yielding translocation time $\sim N^{2\nu}$ for Zimm dynamics, explains both the real experiment²⁰ and the simulation with hydrodynamic interactions.⁵⁴ The agreement is however not so obvious because, first, both experiment and simulation claim to observe $\tau_{tr} \sim N^{1.27}$, while $2\nu \approx 1.18$. Second, it may seem surprising that such a successful agreement is achieved for the more complex Zimm case, while different simulations are in disagreement for the much simpler Rouse dynamics. Third, both Luo et al.⁵⁰ and Luo⁵² report the existence of two separate N -dependence regimes for translocation time in the Rouse model; assuming two similar regimes also exist in Zimm dynamics, which is consistent with our observation that the difference between Rouse and Zimm exists only in the force dependence, we can speculate that the observed $N^{1.27}$ scaling²⁰ is in fact an intermediate regime for a limited range of N .

Reference 42 also claims agreement with the same experiment²⁰ and simulation.⁵⁴

Trying to look deeper into the differences between our prediction and those of refs 20 and 42 for the most realistic Zimm dynamics case, it is useful to present all three in a similar form

$$\begin{aligned}\tau_{tr} &\sim N^{1+\nu} f^{-(2\nu-1)/\nu} \\ &= N^{3\nu} (fN^\nu)^{-(2\nu-1)/\nu} && \text{this work} \\ \tau_{tr} &\sim N^{2\nu} f^{-1} = N^{3\nu} (fN^\nu)^{-1} && \text{work 20} \\ \tau_{tr} &\sim N^{[(1+3\nu)/2]} f^{-(3\nu-1)/2\nu} \\ &= N^{3\nu} (fN^\nu)^{-(3\nu-1)/2\nu} && \text{work 42}\end{aligned}\quad (18)$$

As this representation emphasizes, all three theories claim applicability at $fN^\nu \gg 1$, and all imply smooth crossover to Zimm time ($N^{3\nu}$) at $fN^\nu \sim 1$. It is also true that all three are based on the same assumption that the applied force is balanced by the drag of the untranslocated part of the chain: symbolically, they all operate with equation (friction coefficient) $\times v = f$ (v being the velocity scale), and as it turns out, their estimates of friction coefficient have the same scaling ($\sim N^\nu$). Thus, the differences arise from the estimate of velocity.

- We argue that the fundamental speed scale is set by the flux which must be $\phi \sim N/\tau_{tr}$ to translocate N monomers during time τ_{tr} . Then, $v \sim \phi/\rho$, where ρ is the linear density of monomers in the trumpet. Given the tension blob scale $\xi \sim f^{-1}$, the linear density in such a blob should be

$\rho \sim (\xi^{1/\nu})/(\xi)$, which implies velocity $\sim (\phi/\rho) \sim f^{[(1-\nu)/\nu]} \phi$ and yields our result for τ_{tr} .

- Reference 20 does not consider the flux but estimates the velocity by assuming that the coil as a whole moves a distance of order its own size: $v \sim N^\nu/\tau_{tr}$. In our opinion, this leads to underestimated time because in reality not all monomers move simultaneously, and the sequential motion of polymer pieces, each of which has a friction comparable to that of the whole coil, slows the process down. (We note parenthetically that a similar comparative analysis can be easily done for the Rouse case, where our smaller friction coefficient balances our larger travel distance, such that our results do match those of the work 20.)
- For the purpose of comparison, it is useful to recast the calculations of the work 42 by writing $\tau_{tr} = N/\phi = N/\nu\rho$. Since this work assumed the entire trumpet to be characterized by a single velocity scale (rather than a flux scale), to obtain the flux, it considered the density ρ at the wide end of the trumpet where tension is very weak and ρ is very large. In our opinion, this resulted in an underestimated time because the large ρ at the wide end of the trumpet is in fact compensated by the slow velocity there. Another way to put it is to say that the integration of flux over translocation time using the results of reference 42 yields a quantity smaller than N .

While we cannot claim unequivocal agreement with all data in the literature, even the expectation of such agreement would be premature in our opinion, given the lack of unity in the data themselves. Rather, we think that the diversity of the data indicates some underappreciated complexity. To this end, we think that our realization of significant heat transfer across the membrane—transfer of heat which is much larger than the work of the translocation force—might be an important factor explaining the underlying difficulties in the simulations. Further simulations and experiments as well as further theoretical efforts will be needed to clarify the finite N corrections to scaling as well as other aspects among which we think the unavoidable presence of the unscreened Coulomb field outside the pore (proportional to the access resistance) is one of the most important.

A. WHY THE GRAFTED COIL PULLS ITSELF OFF

We show here that any polymer grafted to a solid impermeable membrane pulls itself off the grafting point with a force of entropic nature which is of the order T/a , where a is the effective segment length scale. For a flexible polymer, this force can well be as large as a few picoNewtons.

This force could have been described in any polymer physics textbook, including old ones. To our surprise, we have not found it explicitly mentioned in any such common sources. Not that it was completely unknown; some manifestations of it are discussed in various rather complex contexts, e.g., in refs 55, 58, and 59, but a simple and general statement—as simple and general as the idea itself—appears to be missing. Accordingly, we put it here.

Since we are talking here about a very elementary property of any polymer chain, it is useful to start with the simplest exactly solvable model. Consider a Gaussian coil with one end kept fixed at a distance h from an impermeable plane, as shown in Figure 6. The probability that the other end is at some point z satisfies a diffusion equation with absorbing boundary condition on the plane. It can be solved by the standard image

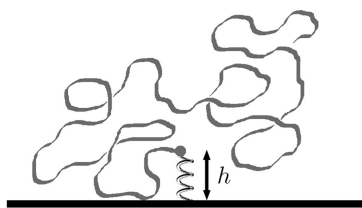


Figure 6. Sketch of a grafted coil. One end is fixed at a distance h from the plane, while the other is free to do whatever it wants. The fixed end exerts a force on the grafting bond.

method, yielding

$$G = \frac{1}{\sqrt{\pi}R} \left\{ \exp \left[-\frac{(z-h)^2}{R^2} \right] - \exp \left[-\frac{(z+h)^2}{R^2} \right] \right\} \quad (19)$$

where $R \sim a\sqrt{N}$ is the coil size. We did not write down here the x and y dependence part of G (along the plane), as it is independent of h and cancels out in final results. A full partition function normalized by the partition function of a free coil away from the membrane is obtained from here by integration over the end coordinate z

$$Z(h) = \int_0^\infty G dz = \text{Erf} \left(\frac{h}{R} \right) \quad (20)$$

Accordingly, there is a free energy cost for bringing the chain end to within a distance h of the impermeable membrane, $\Phi(h) = -T \ln \text{Erf}(h/R)$, and if the chain terminal is kept at distance h by some bond, then this bond experiences tension

$$F(h) = -\frac{\partial \Phi(h)}{\partial h} = \frac{2T}{\sqrt{\pi}R} \frac{e^{-h^2/R^2}}{\text{Erf} \left(\frac{h}{R} \right)} \quad (21)$$

At first glance, this seems to scale as T/R , which is a very small force. However, the h -dependent factor diverges at $h \ll R$. Indeed, free energy in this limit is

$$\Phi(h)|_{h \ll R} \approx -T \ln \left(\frac{2}{\sqrt{\pi}} \frac{h}{R} \right) = \frac{T}{2} \ln N - T \ln \frac{h}{a} + \text{const} \quad (22)$$

which corresponds to the force

$$F(h)|_{h \ll R} \approx \frac{T}{h} \quad (23)$$

Thus, free energy is dominated by the $\sim T \ln N$ term, but it also has an N -independent but h -dependent correction term which produces a large N -independent tension force. As h increases and reaches to about the full coil size, the force drops to about T/R —the same force scale as would have been obtained if the coil were to be confined in a slit of the width of order coil size.

One way to understand this force is to realize that even a straight single segment of length l , if bonded by one end at a distance $h < l$ from the membrane, will exert a pulling force on the bond for entropic reasons. Another way to think about it is by saying that fixation of the chain terminal at a distance $h \ll R$ not only confines the entire coil within a distance R from the membrane but also confines every monomer indexed g to within a distance $a\sqrt{g}$ from the membrane, as long as $g \geq (h/a)^2$.

The result (eq 23) remains valid without any modifications also for the coil with excluded volume. This can be understood by noting that the partition sum (normalized by the partition sum of a free coil away from the membrane) in this case should be written as $Z(h) = \zeta(h/R)$ because there is no other length scale apart from coil size $R \sim aN^\nu$, and then scaling function $\zeta(x)$ at small x is a power law, $\zeta(x) \sim x^\beta$. Independently of the specific value of β , this returns free energy dominated by the $T \ln N$ term and the force $\sim T/h$ (eq 23).

These considerations allow us also to estimate the tension force at a distance r away from the grafting point because the blob of $g \sim (r/a)^{1/\nu}$ monomers acts like an effective grafting bond for the other $N - g$ monomers which can be considered effectively as “grafted” at a distance $h \sim ag^\nu \sim r$ from the membrane. As long as $g \ll N$, this corresponds to a tension force decaying as $\sim T/r$ at $r \ll R$. At larger r , it drops exponentially and seems to cause no noticeable consequences.

To conclude, conventional wisdom posits that bringing the chain to the impermeable membrane costs about $T \ln N$ of free energy; this is of course true. However, free energy also has a term which is small but much more sharply changing with the distance between the polymer end and membrane, which is why there is a large force. Grafted polymer pulls itself off the grafting bond pretty much like Baron Munchausen was pulling himself from the swamp by his own hair.⁵⁶

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