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Collaborative effects in polymer translocation and the appearance of fictitious free-energy barriers

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The translocation time of a polymer through a pore under the influence of an external field depends on a number of parameters, the most important of which are the field strength, the interaction with the pore, and the confinement entropy. Experimentally, the translocation is dominated either by the driving force (electrophoretic regime) or by the entropy of confinement or pore interaction (barrier dominated regime). In this Rapid Communication we study a simple model for polymer translocation, loosely based on the asymmetric exclusion process, which shows that it is possible to have what experimentally would be interpreted as barrier dominated, even where there is no barrier to translocation. This effective barrier is interpreted as being due to collaborative effects between the monomers forming the polymer chain.

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The translocation of polymers through a nanopore is ubiquitous in the behavior of biological systems. Nanopores are used by the biological cell to exchange proteins [1] and used by toxins to destroy the cell [2]. Nanopores, both biological and synthetic, are used by experimentalists to study the conformational behavior of polymers and proteins [3,4] and their use provides a promising avenue for the fast sequencing of DNA molecules [5]. One of the most commonly used pores for these experiments is the α-hemolysin pore [6], corresponding to a self-inserting heptomer pore used by staphylococcus aureus to attack biological cells. In experiments the presence of the polymer in the pore is detected by measuring the current of charged ions through the pore between electrodes. The presence of the polymer in the pore corresponds to a drop in the detected current [7].

While at first sight the problem of polymer translocation seems simple, there are many factors that need to be taken into account. Other than the loss of entropy of the polymer confined in the pore [8,9], there will in general also be an interaction between the monomers and the pore walls [10,11], as well as the driving effect of the electric field. The electric field acts either directly on the polymer (if charged [12–14]) or via an electro-osmotic pressure [15,16].

Experimental results due to Meller and Branton [11] for the translocation of ssDNA through an α-hemolysin pore are shown in Fig. 1 as an example of the translocation time dependence on polymer length. The length of the pore was about the same length as twelve bases and the passage of the monomers is believed to be single file. It can be seen that there are two regimes: For short chains there is a rapid increase in translocation time τ with chain length N, while for longer chains the time is essentially linear.

The rapid increase of τ with N is usually interpreted as indicating the presence of a free-energy barrier to translocation [8,9,17,18]. For short polymers it is expected that the crossing of this barrier will be the dominant factor in determining the translocation time, which then behaves as

$$\tau \sim \exp\left(\frac{\Delta F}{kT}\right), \tag{1}$$

where $\Delta F \propto N$ is the height of the free-energy barrier [9,17,19].

In this Rapid Communication we present a simple model for the driven translocation of a polymer through a pore. This model reproduces the same qualitative behavior as seen in Fig. 1. Surprisingly, the qualitative agreement arises even when the confinement entropy and pore interaction balance, i.e., when there is no free-energy barrier for the polymer at any stage of the translocation process. In this case, the behavior is interpreted as being a result of the collaborative effects in the driven diffusion of the monomers in the pore. This possibility is explicitly ignored in the translocation literature, which tends to model polymer translocation by reaction coordinate methods such as the Fokker-Planck method [8,9]. Our simple model also has the advantage of being several orders of magnitude faster than direct molecular dynamics simulation. This is particularly true in the weak driving force limit. This limit is of interest for the fast decoding of DNA sequences [5].

The idea is to model the translocating polymer as a stream of monomers moving through the pore. This is shown schematically in Fig. 2. The polymer chain is split into N_l monomers to the left of the pore (waiting to enter the pore), N_p monomers in the pore, and N_r monomers to the right of the pore (having exited the pore). The monomers outside the pore (to the left or right) are represented by two free-energy reservoirs of free energy $\mathcal{F}_{\text{left}}(N_l)$ and $\mathcal{F}_{\text{right}}(N_r)$ for the left and right reservoirs, respectively. We have $N_l + N_r + N_p = N$, the number of monomers making up the polymer.

The confined monomers progress on the central axis of the pore along discrete sites labeled $i \in [1,L]$. Each site can be either occupied or empty, representing the presence or absence of a monomer. We take the distance between lattice sites to be d. Unlike the standard asymmetric simple exclusion process (ASEP) model, we must model the fact that the monomers are chemically linked to their neighbors along the polymer chain. This is modeled by constraining the distance between monomers to be between a minimum distance $\delta x_{\min} = d$ and some maximum distance $\delta x_{\max}$, taken here to be $2d$. Once the monomers are in the pore they feel the applied electric field

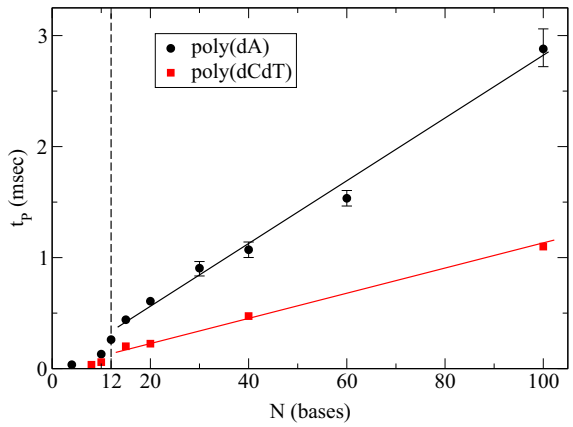

FIG. 1. (Color online) Experimental results for the translocation of single-stranded DNA molecules made up of either adenine [poly(dA)] or alternating cytosine and thymine [poly(dCdT)] taken from Meller and Branton [11]. The most probable translocation time t_p is plotted against chain length.

and hop preferentially to the right. To model the monomers entering or leaving the pore two additional sites are included ($i = 0$ and $i = L + 1$), representing the monomers about to enter or the space for the polymer to leave the pore as required. The state of these sites is not *a priori* determined, unlike the sites within the pore. The dynamics used for the simulation is detailed below.

Initially, all the monomers are contained in the left-hand-side reservoir. The translocation time is defined as the time it takes for all the monomers to cross the system and enter the right-hand-side reservoir. In order to implement the dynamics of the monomer hopping, a site $i \in [0, L + 1]$ is chosen at random and updated according to the following rules.

(i) If the site is empty nothing is done.

(ii) If the site is occupied with a monomer, a direction (left or right) is chosen at random with equal probability and the monomer is moved in the chosen direction if possible (i.e., if the neighboring site is empty and if the resulting maximal distance to its neighboring monomers is less than $\delta x_{\max}$). If the move is possible, the difference in the free energy $\delta\mathcal{F}$ of the system is calculated.

(a) If $\delta\mathcal{F} < 0$ the move is accepted.

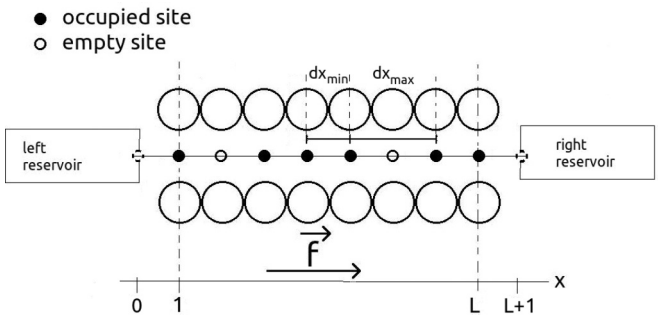

FIG. 2. Schematic diagram showing the pore modeled as a one-dimensional lattice. The external portions of the polymer are modeled as particle reservoirs at equilibrium. The particles hop preferentially to the right under the influence of the external force field $\vec{f}$.

(b) If $\delta\mathcal{F} > 0$ the move is accepted with a probability $\exp(-\frac{\delta\mathcal{F}}{kT})$, where T is the system temperature.

(iii) If the chosen direction results in a monomer jumping on sites $i = 0$ or $i = L + 1$ then the monomer is removed from the pore and the corresponding reservoir free-energy difference is $\delta\mathcal{F}_{l/r} = \mathcal{F}_{l/r}(N_{l/r} + 1) - \mathcal{F}_{l/r}(N_{l/r})$.

(iv) If the site chosen is $i = 0$ or $i = L + 1$ then the sites are assumed to be occupied (assuming there are still monomers in the corresponding reservoir). If the direction chosen corresponds to the monomer entering the pore then the reservoir free-energy difference is $\delta\mathcal{F}_{l/r} = \mathcal{F}_{l/r}(N_{l/r} - 1) - \mathcal{F}_{l/r}(N_{l/r})$.

A time step corresponds to choosing on average each site once, i.e., one step corresponds to $L + 2$ single-site choices. A time step does not depend on the number of monomers in the pore or the number of monomers making up the polymer, as expected for a correctly defined time step.

The total change in free energy for one update is given by

$$\delta\mathcal{F} = \delta\mathcal{F}_l + \delta\mathcal{F}_r - qE\delta x - \varepsilon\delta N_p, \tag{2}$$

where q is the charge on the monomer, E is the uniform applied field in the pore, ε is the interaction energy with the pore (here $\varepsilon < 0$), $\delta x = 0, \pm d$ is the distance moved by the monomer (if present), and $\delta N_p = 0, \pm 1$ is the change in number of monomers in the pore. The free energy of the polymer segment in the reservoirs may be taken as

$$\mathcal{F}_{l/r} = -N_{l/r} kT \ln \tilde{z}, \tag{3}$$

where $\tilde{z}$ is the effective coordination number (or connective constant). The value of $\tilde{z}$ depends on the solvent quality. One could include the $(1 - \gamma_1) \ln N$ correction term, where γ_1 is the connective exponent for a self-avoiding walk with one end attached or close to a surface. This correction term is small compared to the leading term and is dropped. The chemical potential is essentially given by $kT \ln \tilde{z}$.

In what follows, we simplify the model further, taking $\varepsilon = kT \ln \mu$. This removes any possibility of a free-energy barrier to either polymer insertion or polymer exit from the pore. The behavior of the translocation time is then entirely determined by the dynamics of the monomers within the pore and the strength of the driving force qE.

In order to compare, at least qualitatively, with the results of Meller and Branton [11], presented in Fig. 1, we choose to study a pore of length $L = 12d$. The polymer was driven using a force $qE = 0.05kT/d$ in the pore. This value was chosen small enough for the translocation not to be electrophoretic, but to allow a competition between the collaborative effects within the chain and the driving force. The results presented here correspond to actual translocation events. There are translocation attempts that do not succeed, where the polymer retreats back into its original reservoir. For the parameters presented here, successful translocations corresponded to about 1/6 of events, largely independently of the polymer length. The translocation time as a function of length is shown in Fig. 3. Qualitatively, the figure is very similar to the experimental curve in Fig. 1.

The curve clearly shows the characteristic signal usually associated with a free-energy barrier, even though, by construction, there is no free-energy barrier. In the inset of Fig. 3 we fit the short-chain behavior by the exponential law given in

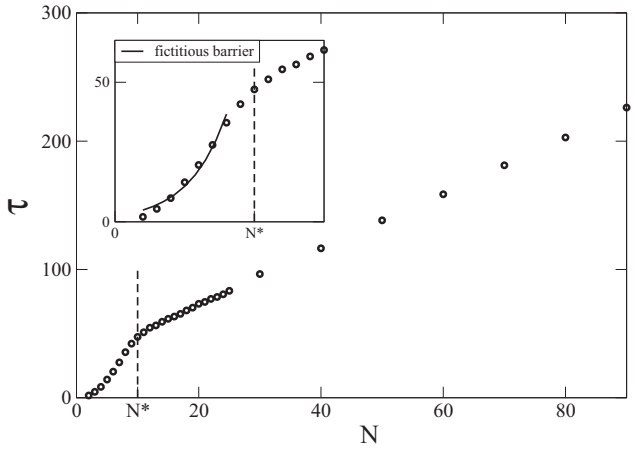

FIG. 3. Total translocation time as a function of the chain length for a pore of length $12d$. The inset shows a possible fit of the short-chain portion with a barrier model (1).

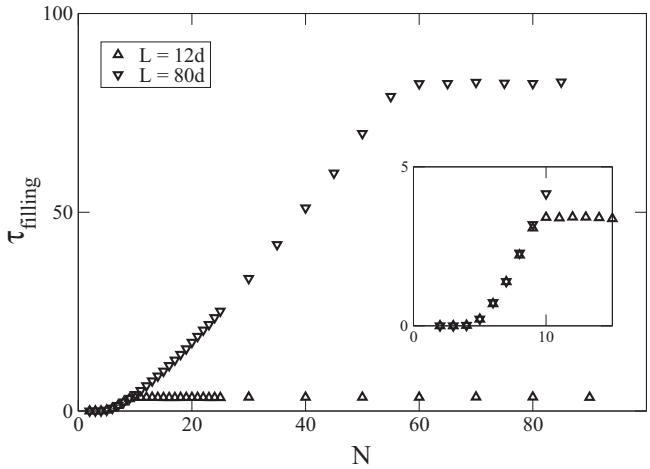

FIG. 4. Filling time as a function of chain length compared for two different pores, one of length $12d$ and one of length $80d$. The filling time is the time required to either fill the pore or fully enter the pore (depending on the length of the chain).

Eq. (1) with $\Delta F = \chi N$; a reasonable fit would give a value

$$\frac{\chi}{kT} = 0.37. \tag{4}$$

The system within the pore is not at equilibrium and the movement of the monomers is hindered by two effects: They cannot move forward until the site ahead is empty and they cannot move more than two lattice spaces from the previous monomer. This leads to a correlated movement that is slower than a simple driven diffusion of the center of mass. The translocation time is divided into three parts: the time to fill the pore (or for the polymer to completely enter the pore for short chains), the time for the polymer to transfer through the pore, and finally the time to empty the pore. Once the average linear dimension of the polymer exceeds the length of the pore, the filling and emptying times saturate and the length dependence is dictated by the transfer stage. In this regime the transfer velocity is constant and the translocation time becomes linear with the chain length [11,13,20]. The average distance between monomers $\sigma \in [d, 2d]$ and from Fig. 3 we see that $\sigma \approx 4d/3$.

The interesting portions of the translocation process for the discussion here are the filling and emptying times, shown in Figs. 4 and 5 for two pores of lengths $12d$ and $80d$. In both phases, the filling and emptying times vary rapidly for short chains. For a monomer to enter or leave the pore the other monomers must arrange themselves appropriately: For filling they must leave the first site empty and for emptying they must be close enough to the exiting monomer to enable its exit. This means that the monomers are correlated, defining a boundary correlation length. If the polymer length within the pore is smaller than this correlation length, the rate of adding a new monomer is sensitive to the number of monomers already in the pore. Beyond this correlation length, the correlation effects will saturate and no further change in the insertion rate is expected; the filling time then becomes linear with length. It is interesting that the emptying phase is not symmetric with respect to the filling phase because there is not the hole-particle symmetry present in the standard ASEP model (the monomers are linked and the holes are not). The influence of the exit is clearly visible in Fig. 5, where there is an inflection at $N \approx 20$.

In the filling stage the curve seems to saturate to become linear, but does not show, at least at the pore lengths studied, an inflection. The reason for this difference in behavior remains an open question. Of course, in the absence of field, there is no difference between the filling and the emptying phases and the two curves are superimposed.

In Fig. 6 the different times are shown for the longer pore ($L = 80d$), as well as the resulting translocation time. While the filling and emptying times still show the exponential behavior (as discussed above), the effect of the transfer time is greater, which makes the total curve more difficult to interpret. This pore would correspond to a pore that is longer than the biological pores used in Meller and Branton [11] as a multiple of the monomer length. It would be interesting to know if in

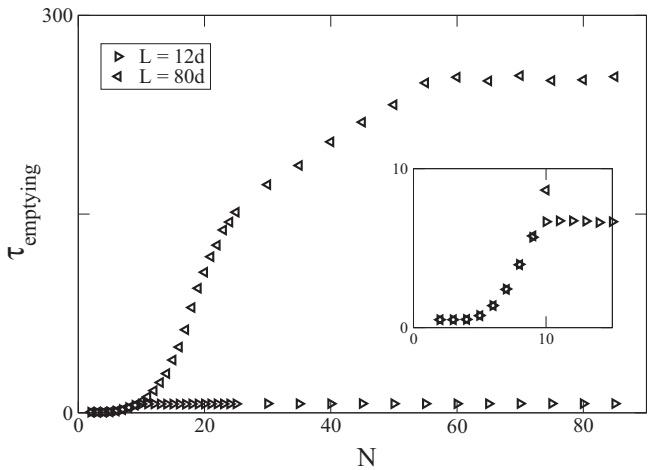

FIG. 5. Time to empty the pore as a function of chain length. The emptying time is defined as the time for the polymer to leave the pore measured from when the first monomer permanently leaves the pore, i.e., at no stage during the emptying process is the polymer totally within the pore.

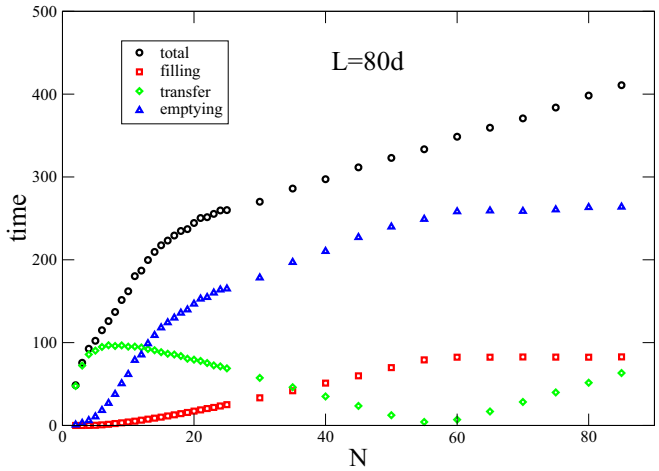

FIG. 6. (Color online) Different times are shown (filling, transfer, and emptying times) as well as the resulting translocation time for a pore of length 80d.

longer pores a similar behavior would be observed in a real experiment.

The systematic interpretation of a rapidly varying translocation time with polymer length as a free-energy barrier is consistent with a vision of the dynamics of the polymer in terms of the diffusion of the center of mass. This interpretation is helped by comparing the experimental results with Fokker-Planck-type calculations, which explicitly reduce the polymer to a diffusion of the reaction coordinate. In this Rapid Communication we show that a simple model system where the collaborative dynamics of the monomers is explicitly allowed gives rise to the same behavior without an explicit free-energy barrier. This is an important factor to take into account when interpreting or designing translocation experiments. One may imagine that the ssDNA molecule is rigid and thus the model adopted here is not realistic; however, experiments [21] show that the bond length may easily fluctuate 20% under the experimental conditions used by Meller and Branton [11]. We have looked at a modified model in which both $\delta x_{\min}$ and $\delta x_{\max}$ were modified and a Hookes law force was added to the bonds, but the qualitative behavior was not affected. We also studied the situation where the chemical potential was not the same on each side of the pore. If the chemical potential difference was favorable to translocation, a fictitious barrier remained for a range of chemical potential differences, disappearing once the chemical potential difference reached a certain threshold.

It is often assumed that during the translocation process the portions of the polymer outside the pore have time to equilibrate [8,9]. While it is not obvious that this is always true, it is not an unreasonable assumption in the weak-field case studied here. This assumption is the basis of the main simplification of the translocation model used in this Rapid Communication. It enables us to calculate each point of Fig. 3 in a few seconds of CPU time rather than of the order of a month of CPU time for a model using Langevin dynamics on the full chain [20]. In any case, the assumption of equilibration outside the pore is consistent with what is used in Fokker-Planck calculations. The restriction of the dynamics to one dimension inside the pore is consistent with the translocation results presented by Meller and Branton [11], but even for looser polymers, such as polyethyl glycol, one might expect the translocation to be one dimensional but with the monomers being replaced by statistical blobs (in the manner of de Gennes [22]).

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