

Translocation of a Confined Polymer through a Hole

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(Received 16 August 2000)

Based on an analogy between polymer translocation across a free energy barrier associated with polymer worming through a hole and classical nucleation and growth process, the escape time τ is predicted asymptotically to be $N(N/\rho)^{1/3\nu}$. N is the polymer length, ρ is the monomer density prior to escape, and ν is the radius of gyration exponent. Monte Carlo simulation data collected in the high salt limit ($\nu \approx 3/5$) are in agreement with the asymptotic law and provide vivid details of the escape.

DOI: 10.1103/PhysRevLett.86.3188

PACS numbers: 87.15.Aa, 47.50.+d, 87.15.He

How a polymer worms through a narrow hole from a confinement is a fundamental time-defining event in various biological processes [1–4]. Examples include passage of *m*-RNA through nuclear pore complexes, injection of DNA from a virus head into the host cell, gene swapping between the guest and host bacteria through pili, translocation of proteins from the *cis* to *trans* side of a membrane through channels, etc. In actuality, the polymer translocation is orchestrated [4] by elaborate and precise chemical specificity. Yet, it is also clear from empirical data [1–4] that the typical length scales of the pores and translocating polymers are of the order of ten nanometers and that the polymer is subjected to significant conformational changes during translocation. It is therefore of interest to apply polymer physics concepts [5] valid at the coarse-grained levels to understand the above-mentioned translocation processes in terms of key variables such as the length and charged nature of the polymer, and size, shape, and solvent quality of the donor compartment. This Letter addresses the question of how an equilibrated polyelectrolyte chain confined inside a spherical cavity escapes when a narrow hole is introduced on the cavity. A formula for the dependence of the translocation time on chain length and size of the sphere is derived and verified using Monte Carlo simulations. The problem addressed here is also of immediate relevance to the recent experiments [6–8] on translocation of DNA and RNA through protein channels under electric fields, gel electrophoresis [9,10], size exclusion chromatography [11], and quantum nucleation [12].

Consider the free energy landscape associated with an escape of a polymer of N monomers from a sphere, as sketched in Fig. 1. The free energy F_1 of a polymer chain in the initial equilibrium state I of confinement within a sphere of radius R is $F_1 = E - k_B T \ln \mathcal{N}$, where \mathcal{N} is the number conformations that can be assumed by the polymer, $k_B T$ is the Boltzmann constant times absolute temperature, and E is the energy of interactions among monomers, molecules, and ions in the solvent medium, and the surrounding cavity. When a hole is introduced on the cavity, the system becomes metastable and the chain escapes. In the final state II, the chain can assume a greater

number of conformations due to the absence of confinement, and consequently the free energy F_2 is lower than F_1 , the value of F_2 being dictated by the size of the reservoir wherein the sphere is placed. Therefore there exists a chemical potential gradient $F_1 - F_2 \equiv N\Delta\mu$ to push the polymer out of the sphere. However, in its trajectory from I to II, the chain must adopt conformations of the type illustrated in the transition state III, as the hole is designed to be small enough to allow only one strand at a time. This constraint reduces the number of allowed chain conformations, and consequently the chain entropy decreases and free energy increases to F_3 , setting up an entropic barrier $F_3 - F_1 \equiv \Delta F$. Although this barrier is termed entropic barrier [9,13], it is indeed a free energy barrier [10], because there can be additional enthalpic contributions to F_3 arising from the interactions of monomers with the hole representing an actual channel. The polymer chain must negotiate the entropic barrier in its successful escape out to the sphere.

The calculation of the free energy landscape for the general situation of a polyelectrolyte captured inside a cavity under varying levels of added salt is nontrivial, and explicit expressions for F_1 , F_2 , and F_3 are unknown, despite some recent attempts [14]. However, simpler situations of a chain in transit through a hole in a planar membrane [15–17] and a Gaussian chain [18] released from a sphere

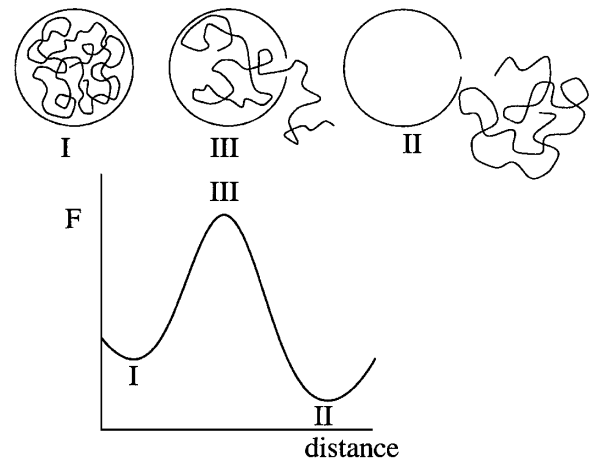


FIG. 1. Genesis of entropic barrier for polymer escape.

have recently been addressed theoretically with divergent predictions [16,17]. In view of the unavailability of explicit free energy expressions, we have performed Monte Carlo simulations of chain escape from a sphere to obtain some insight into the process and assumptions of theoretical models [15–18].

Consider a spherical cavity of inner radius R and wall thickness λ . A pearl-necklace chain of N beads of hard diameter h freely jointed together by $N - 1$ rigid links of length ℓ is grown inside the sphere. The potential interaction between any two beads is taken to be Debye-Hückel, and in this paper we consider only the limit of short Debye lengths where the polyelectrolyte obeys the self-avoiding walk statistics [19] in an unconfined medium. The interaction between the cavity and beads is hard, with the shell of thickness $h/2$ from the inner surface of the sphere totally inaccessible to the beads. The initially grown chain is equilibrated for typically $10^3 N^2$ Monte Carlo steps using the kink-jump dynamics and Metropolis algorithm as described in Refs. [13,19]. After the equilibration step, a hole of diameter 2ℓ (and thickness λ) is introduced at one location on the wall of the sphere. From this point of time onwards, the coordinates of the beads are monitored and the statistics on the process of chain escape are compiled, as the chain evolves with kink-jump dynamics. In the simulations reported here, $\ell = 1$, $\lambda/\ell = 0.15$, $h/\ell = 0.87$, $2.0 \leq R/\ell \leq 6.59$, and $9 \leq N \leq 232$. Statistics were compiled based on at least 300 simulations for each pair of N and R .

The typical course of polymer escape as observed in these simulations is as follows (Figs. 2a–2f). Immediately after the hole is created, the chain continues to undergo its conformational changes inside the sphere (Fig. 2a). After a certain time, one end arrives at the hole (Fig. 2b) and the front end of the chain pushes outward (Fig. 2c) by back and forth motion into and outside the sphere. This step does not necessarily lead to the spontaneous spillage of the chain in spite of the fact that the monomer density is high inside the sphere and essentially zero outside. The entropic force arising from chain connectivity inside the sphere dominates at this stage so that the chain end is pulled back into the sphere (Fig. 2d) as time progresses. Next the chain rattles around and one of the chain ends attempts again to carry out the chain escape. After hundreds of such attempts, a successful escape occurs eventually. In each of the failed attempts, the number of monomers which have managed to get outside is smaller than a critical number (which in turn depends on R and N). In the event of successful escape, enough (Fig. 2e) monomers above the critical number are pushed outside by a sequence of random events which then allows the full escape (Fig. 2f).

These observations are fully consistent with the free energy landscape of Fig. 1. Since a free energy barrier separates states I and II, the metastable state of polymer confined inside a sphere with a hole evolves into the final state by nucleation. If a nucleus of monomers less than

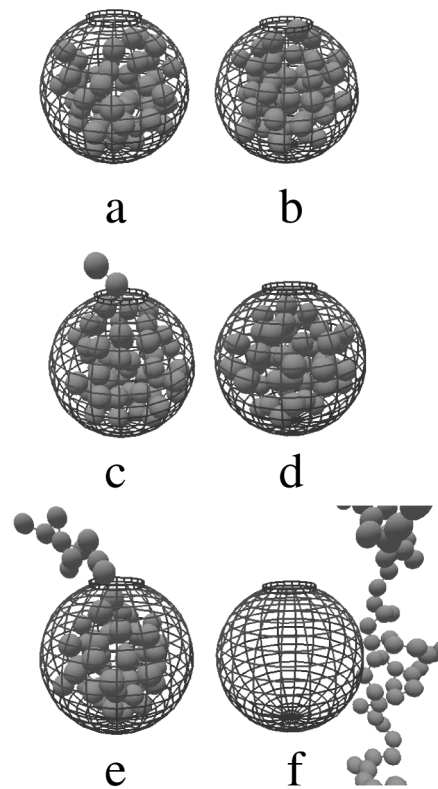


FIG. 2. Polymer escape for $N = 60$, $R/\ell = 3.0$. The Monte Carlo time is (a) 50, (b) 350, (c) 450, (d) 1000, (e) 4850, and (f) 25 000.

a critical number (determined by the free energy barrier) is made outside the sphere, it will dissolve back; i.e., the chain will go back into the sphere. If a sufficiently large nucleus containing more monomers than the critical number is made outside the sphere by the initial random process, then this nucleus will grow until the whole chain is outside.

The typical results for the N dependence of average escape time τ (duration of escape after the arrival of one end at the hole for the case of successful escape) are given in Fig. 3 for $R/\ell = 2.5, 3.5$, and 4.0 . Data for other values of R are not included in this figure for the sake of clarity. The (average) arrival time τ_a , required by one chain end to eventually arrive at the hole, resulting in successful chain escape is also included in Fig. 3 for $R/\ell = 3.5$. As expected τ increases with N because it takes longer time to thread a longer chain through a hole. Furthermore, as N increases, the pressure from excluded volume builds up, and it takes shorter time for the chain end to be placed at the hole. It is to be noted that the chains under study are not too long to allow additional complicating factors such as entanglements [5]. Although these qualitative trends are borne out in Fig. 3, the N dependence of τ and τ_a are not simple power laws, the sigmoidal shape of the curves indicating a crossover behavior discussed below.

We now attempt to interpret these data using the analogy with the nucleation and growth. Following the usual arguments [20] of the nucleation theory, the probability

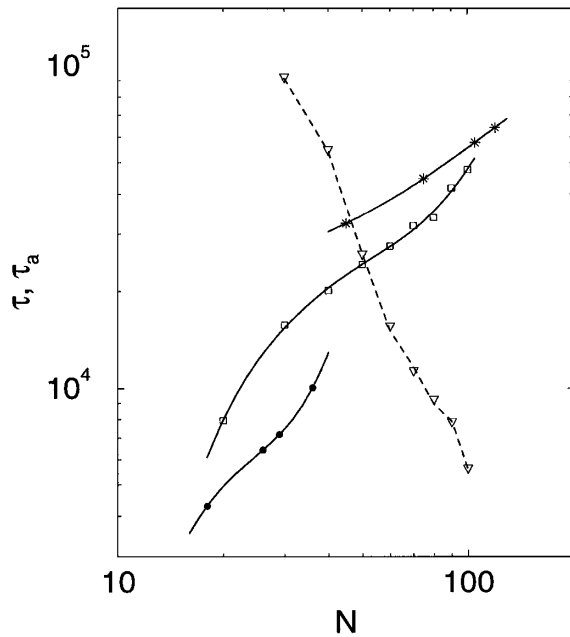


FIG. 3. N dependence of escape time τ in Monte Carlo step units. \bullet , $R = 2.5$; \square , $R = 3.5$; $*$, $R = 4.0$; ∇ , arrival time τ_a for $R = 3.5$. Curves are guides to the eye.

$W_m(t)$ of finding a nucleus with m monomers in region II at time t is given by [17]

$$\frac{\partial}{\partial t} W_m(t) = \frac{\partial}{\partial m} \left[\frac{k_0}{k_B T} \frac{\partial F_m}{\partial m} W_m(t) + k_0 \frac{\partial}{\partial m} W_m(t) \right], \quad (1)$$

where F_m is the free energy of a chain with m monomers outside the sphere and k_0 (independent of N) is the rate constant associated with the local friction in the transfer of one monomer through the hole so that a nucleus of m monomers grows into that of $m + 1$ monomers. When the drift (first) term in Eq. (1) dominates the problem, τ is given by the mean first passage time to be [17]

$$\tau = \frac{k_B T}{k_0 \Delta \mu} N \sim \frac{N}{\Delta \mu}, \quad N \Delta \mu > 1, \quad (2)$$

and $\tau \sim N^2$ for $N \Delta \mu < 1$, where $\Delta \mu$ is the chemical potential gradient per monomer. These results are in excellent agreement with experimental data [6,7] on the blockade of α -hemolysin channel by single stranded DNA and RNA.

Since explicit expressions for $\Delta \mu$ are currently unavailable for a self-avoiding walk inside a sphere, we apply well known scaling results [5] for the confinement free energy of a polymer chain. The free energy per chain of confinement inside a sphere of radius R is $F_1 \sim k_B T N / R^{1/\nu}$, where ν is the exponent defining the N dependence of the radius of gyration R_g ($R_g \sim N^\nu$) of the chain in the absence of any confinement. In state II, the confining radius is essentially ∞ so that $F_2 = 0$. Therefore, $\Delta \mu \sim (F_1 - F_2)/N \sim R^{-1/\nu}$. Substituting this result in Eq. (2), we get

$$\tau \sim N R^{1/\nu} \sim N(N/\rho)^{1/3\nu}, \quad (3)$$

where ρ ($\sim N/R^3$) is the monomer density inside the sphere in the initial state. For self-avoiding polymers ($\nu \approx 3/5$), Eq. (3) gives the asymptotic law, $\tau \sim N(N/\rho)^{5/9}$ for $N \Delta \mu > 1$. All of our Monte Carlo data for τ including the samples given in Fig. 3 are presented in Fig. 4 where τ is plotted against $N(N/\rho)^{5/9}$ and the agreement with scaling prediction is remarkable. Equation (3) is valid only in the drift-dominated regime and in this limit, $\tau \sim N$ for a fixed R . The data in Fig. 3 are in the crossover region between diffusion-dominated and drift-dominated behaviors and constitute only the lower part of Fig. 4. Therefore, for small N values, where $\tau \sim N^2$, systematic deviations from the asymptotic result should occur as seen in Fig. 4.

An estimate of τ_a is made as follows. Based on classical nucleation theory [20], the homogeneous nucleation rate J ($\sim \tau_a^{-1}$) for the present situation is given by

$$J \sim n k_0 \exp[-(F_3 - F_1)/k_B T], \quad (4)$$

where n is the number density of ends ($\sim 2/R^3$). The free energy F_3 associated with placing one end at the hole and the rest of the chain inside the sphere (i.e., a tail configuration inside the sphere) is $k_B T(1 - \gamma') \ln(N - 1) + (N - 1)\mu$ and free energy F_1 is $N\mu$, where μ is proportional to $R^{-1/\nu}$ as discussed above, and γ' is the critical exponent associated with the impenetrability of monomers of a tail across a wall [14,17]. Therefore, the barrier is estimated to be $(1 - \gamma') \ln(N)$, for large N values. For self-avoiding polymer chains, the universal critical exponent γ' is ≈ 0.69 , independent of the radius of the sphere (whose effect appears only through the chemical potential). Substituting this result into Eq. (4) we get $\tau_a \sim \rho^{-1} N^{2-\gamma'} \sim N^{1.31}$.

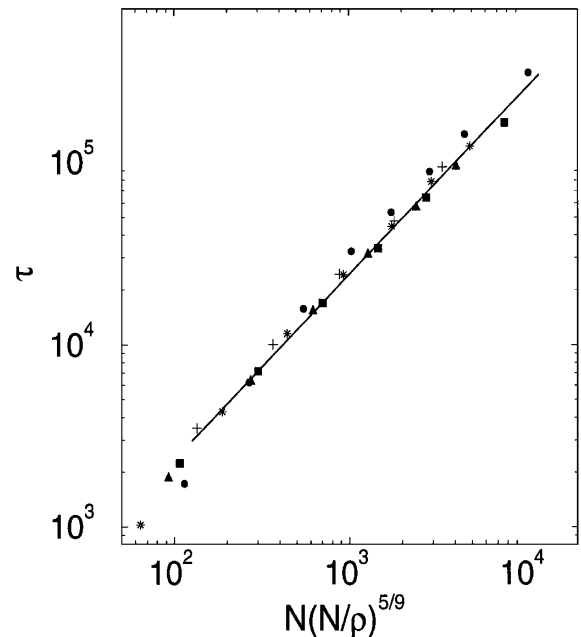


FIG. 4. Comparison with scaling prediction. ρ is 0.168, \bullet ; 0.27, $*$; 0.387, \blacktriangle ; 0.443, \blacksquare ; and 0.57, $+$. Solid line, a guide to the eye, has a slope of 1.

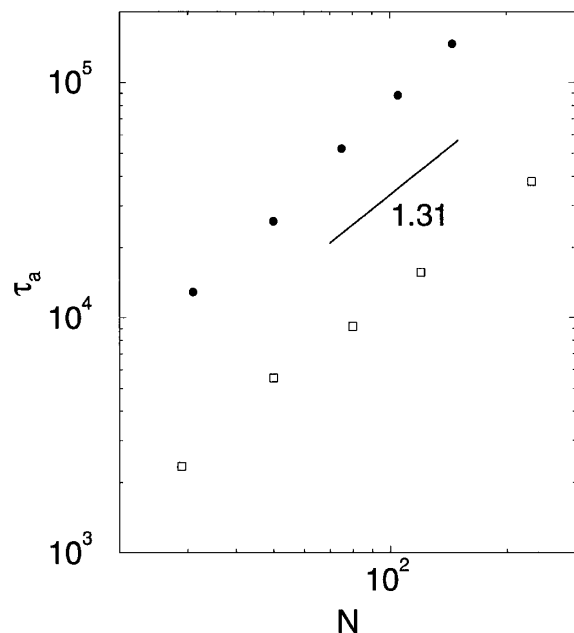


FIG. 5. N dependence of nucleation time τ_a . ρ is 0.27 for • and 0.443 for □. Predicted slope of 1.31 is shown as a guide.

This estimate is in reasonable agreement with the simulation data as shown in Fig. 5.

In summary, the fundamental problem of how a polymer escapes through a hole can be understood by mapping to the nucleation phenomenon and combining with scaling laws of polymer physics. We hope that this approach will provide useful strategies to facilitate selective translocation of polymers of different sequences across specific biological and synthetic pores and an understanding of signal transduction by manipulating the corresponding free energy barriers. Furthermore, we hope that further investigations will clarify and append the adequacy of the formalism employed here. The osmotic and entanglement contributions when multiple chains are confined, and specific interactions between the polymer and the pore, are of particular interest.

This research was supported by the NSF Grant No. DMR 9970718 and the MRSEC at the University of Massachusetts. I am grateful to C. Y. Kong, R. Mondescu,

J. Kasianowicz, and D. Branton for stimulating discussions and to C. Y. Kong and J. Zissu for technical assistance.

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