

Polymer Translocation in Crowded Environments

Ajay Gopinathan¹ and Yong Woon Kim^{2,3}

¹*School of Natural Sciences, University of California, Merced, California 95344, USA*

²*Materials Research Laboratory, University of California, Santa Barbara, California 93106, USA*

³*School of Physics, Korea Institute for Advanced Study, Seoul 130-722, Korea*

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We study the effect of the crowded environments on the translocation of a polymer through a pore in a membrane. By systematically treating the entropic penalty due to crowding, we show that the translocation dynamics are significantly altered, leading to novel scaling behaviors of the translocation time. We also observe new and qualitatively different translocation regimes depending upon the extent of crowding, transmembrane chemical potential asymmetry, and polymer length.

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Transport of a variety of biopolymers across a dividing membrane is a fundamentally important process in biological systems [1]. Examples include transfer of proteins across cellular membranes or endoplasmic reticulum [2], gene swapping through bacterial pili [3], and RNA transport through nuclear pore complexes [4]. Technological applications include gene delivery [5] and DNA sequencing [6]. A considerable amount of theoretical work has focused on both the basic physics [7–11] underlying the translocation process and on how details such as polymer-pore interactions [12], intrinsic polymer structure [13], and confinement [14,15] affect the dynamics of the process. An aspect that has received very little attention is the effect of crowding on the translocation dynamics. For instance, crowding due to macromolecular aggregates and other inclusions in the cellular cytoplasm can be as high as 50% by volume [16] and is known to have considerable influence on reaction rates, protein folding rates, and equilibria *in vivo* [17,18]. A polymer threading its way through such a crowded environment is subject to a large entropic penalty which should dramatically affect the translocation dynamics. In this Letter, we present the first systematic study of polymer translocation in the presence of crowding. The fact that this is a problem that combines aspects of two important issues in polymer science, namely, polymer dynamics in random environments and polymer translocation through a pore, is of significant theoretical and practical interest. We show that the presence of nonlinear terms in the free energy penalty due to crowding leads to qualitatively different translocation dynamics including novel power law scalings of the translocation time with polymer length as well as situations where the translocation time is nearly *independent* of the polymer length over several orders of magnitude.

We consider a Gaussian polymer of length N (in units of the Kuhn length b) threading through a pore in a membrane from *cis* side to *trans* side, as illustrated in Fig. 1. The pore is assumed to be small enough that it allows only one monomer to pass through at a time, with an effective diffusion constant D_p . Crowding is modeled by randomly

distributed spherical obstacles, sterically interacting with the polymer, of radius a and diffusion constant D_o at a volume fraction $\phi_c(\phi_t)$ on the *cis* (*trans*) side. There could also be an excess chemical potential difference for monomers between *cis* and *trans* side, $\Delta\mu$. We now assume that we can treat the process quasistatically with the polymer segments on both sides being in equilibrium at all times. The validity of the assumption depends on the relative magnitudes of the three time scales in the problem: the total translocation time $\tau \sim (b^2/D_p)\tilde{\tau}$, the polymer relaxation time $\tau_R \sim (\eta b^3/k_B T)N^2$ [19], and the time scale set by obstacle motion $\tau_o \sim \phi^{-2/3}/D_o$. Here, $\tilde{\tau}$ is a dimensionless function that characterizes the translocation process and η is the medium's viscosity. Assuming equilibrium statistics for the polymer segments necessarily requires that $\tau_R \ll \tau$ [7]. In the presence of obstacles, this assumption remains valid in two different regimes, $\tau_o \ll \tau_R \ll \tau$ and $\tau_R \ll \tau \ll \tau_o$. The first regime corresponds to the situation where the obstacles diffuse fast enough that the “polymer + obstacles” system can be assumed to be at equilibrium (dynamic obstacles). In the second regime, the obstacles are essentially immobile over τ , and the polymer segment achieves equilibrium statistics in this static ob-

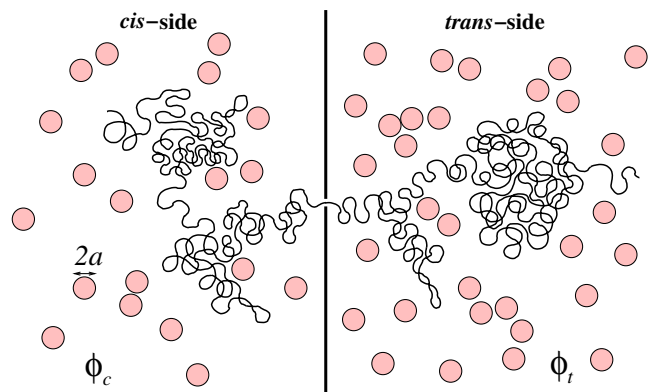


FIG. 1 (color online). Schematic illustration of the translocation process of a polymer in the presence of crowding.

stacle environment. It should be noted that if the pore friction is not high enough (i.e., $\tau_R \approx \tau$) [9] or if $\tau_R \leq \tau_o \leq \tau$, the quasistatic assumption breaks down leading to anomalous dynamics. In the regimes where the assumption remains valid, we have a well-defined free energy barrier whose form is governed by the polymer statistics, presence of the membrane, chemical potential gradient, and the presence of crowding. Since the contributions to the free energy from factors other than crowding have been worked out before [7,8], we focus on the entropic penalty that arises from crowding.

Polymer configurations in the presence of static obstacles correspond to Brownian walk trajectories with a diffusion constant $b^2/6$ that have survived to a time $t = n$ with the obstacles playing the role of traps. The fraction of allowed polymer configurations is therefore identical to the survival probability of such a Brownian walker, leading to the free energy expression for the entropic penalty in units of $k_B T$ as

$$F_{\text{cr}}^s(n) = -\log S(n), \quad (1)$$

where $S(t)$ is the survival probability of an appropriate Brownian walker at time t [18,20]. For short times, $S(t)$ is given by the Smoluchowski solution $S(t) \sim \exp(-\kappa t)$ [21,22], while for long times, it is dominated by walkers trapped in large void regions leading to the stretched exponential Donsker-Varadhan (DV) solution $S(t) \sim \exp(-\lambda t^{3/5})$ [23,24], where κ and λ are constants that depend on trap radius, trap density, and geometry. Using the exact solutions for $S(t)$ [21,23], we can explicitly compute the free energy penalty for a chain of length n due to static obstacles at volume fraction ϕ , yielding

$$\begin{aligned} F_{\text{cr}}^s(\phi, n) &= \frac{1}{2} \left(\frac{b}{a}\right)^2 \phi \left(n + \sqrt{\frac{24a^2 n}{\pi b^2}} \right) \quad \text{for } n \ll N_\times \\ &= 2.6 \left(\frac{b}{a}\right)^{6/5} \phi^{2/5} n^{3/5} \quad \text{for } n \gg N_\times, \end{aligned} \quad (2)$$

where $N_\times \sim (a/b)^2 \phi^{-3/2}$ represents the crossover polymer length from the Smoluchowski regime to the DV regime [25]. For the dynamic obstacle case, the ‘‘polymer + obstacles’’ system comes to equilibrium. The presence of the obstacles gives rise to a depletion induced attraction between monomers that can lead to a collapsed polymer phase similar to that induced by poor solvents [26]. Simulations [27] and analytical work [28] have shown that hard spheres can cause polymers to collapse if the sphere density is high enough. For the range of ϕ ($0.1 < \phi < 0.5$) that we are interested in, the collapse occurs whenever $a \geq 2b$. For our purposes, it is then safe to assume that our Gaussian polymer is in a collapsed ‘‘dense globule’’ state with a volume Nb^3 . The free energy penalty is then given by the sum of the confinement entropic penalty ($= \pi^2 R_G^2 / 6R^2$ where $R \sim N^{1/3}b$ is the confining radius) and the work done to create a cavity of

volume Nb^3 that is devoid of obstacles, which is known exactly from scaled particle theory [29]. The resulting free energy penalty for the chain due to dynamic obstacles reads as

$$\begin{aligned} F_{\text{cr}}^d(\phi, n) &\sim \frac{3b^3(1 + \phi + \phi^2)\phi n}{4\pi a^3(1 - \phi)^3} \\ &\quad - \frac{9}{2} \left(\frac{3}{4\pi}\right)^{2/3} \frac{b^2 \phi^2 (1 + \phi) n^{2/3}}{a^2 (1 - \phi)^3} \\ &\quad + \left(\frac{\pi^2}{6} + 9\left(\frac{3}{4\pi}\right)^{1/3} \frac{b \phi^3}{a(1 - \phi)^3}\right) n^{1/3}. \end{aligned} \quad (3)$$

The general expression for total free energy, taking into account the presence of the dividing wall and chemical potential difference, of a chain with n monomers on the *trans* side and $N - n$ on the *cis* side is then given by

$$\begin{aligned} F_{\text{tot}}^s(n) &= F_{\text{cr}}^s(\phi_c, N - n) + F_{\text{cr}}^s(\phi_t, n) \\ &\quad + \frac{1}{2} \ln[n(N - n)] + n\Delta\mu \end{aligned} \quad (4)$$

for the static obstacles and

$$F_{\text{tot}}^d(n) = F_{\text{cr}}^d(\phi_c, N - n) + F_{\text{cr}}^d(\phi_t, n) + n\Delta\mu \quad (5)$$

for the dynamic obstacles. It is to be noted that the logarithmic term in Eq. (4), resulting from reduced chain configurations confined in a half-space, does not appear in Eq. (5) because F_{cr}^d already includes the entropic penalty associated with confining the chain to a dense globule. The translocation process can now be described by diffusion along the translocation coordinate n under a well-defined $F_{\text{tot}}^{d(s)}(n)$. The dynamics of this process is governed by a Fokker-Planck equation which then allows one to compute the translocation time (mean first passage time for the chain to diffuse across the pore [7]) as

$$\tau_{d(s)} = \frac{b^2}{D_P} \int_1^{N-1} dn e^{F_{\text{tot}}^{d(s)}(n)} \int_1^n dn' e^{-F_{\text{tot}}^{d(s)}(n')}. \quad (6)$$

Since we have nonlinear terms in the free energy, we first consider the behavior of τ for a general free energy functional with a power law scaling, e.g., $F(n) \sim n^\alpha$. Equation (6) and saddle point approximations (in the large N limit) to do the integrals yield

$$\begin{aligned} \tau &\sim N^{2-\alpha} \quad \text{for } F(n) \sim (N - n)^\alpha \\ \tau &\sim \exp(N^\alpha) \quad \text{for } F(n) \sim n^\alpha \end{aligned} \quad (7)$$

for translocation out of and into a crowded half-space, respectively. Thus, we anticipate new exponents characterizing the scaling properties of the mean passage time with the number of monomers in the crowded medium.

We now consider the impact of crowding on translocation dynamics in some physically interesting situations. The first example is that of a polymer escaping from a crowded environment, i.e., where the *cis* side is crowded

and the *trans* side is not ($\phi_t = 0$). In the static case, the dominant contribution to the free energy has the form $\phi_c^{2/5}(N - n)^{3/5}$ for a long chain and $\phi_c(N - n)$ for a short chain [see Eq. (2)]. Saddle point approximation shows τ scales as $\phi_c^{-2/5}N^{7/5}$ and $\phi_c^{-1}N$, respectively. Exact numerical evaluations of Eq. (6) confirm the predicted power law scalings with both N (Fig. 2) and ϕ_c (inset in Fig. 2). In contrast to the dynamic case where the leading order behavior simply corresponds to having an effective “osmotic pressure” from obstacles, the driving force for translocation in randomly distributed immobile obstacles is weakened by the existence of rare, large voids on the *cis* side that sufficiently long polymers can explore. This is the physical origin for the novel exponents describing the scaling of τ with respect to both N and ϕ_c for a long enough chain in the static case.

Another situation of interest is translocation into a crowded environment driven by a chemical potential gradient. Here, we take $\phi_c = 0$ and $\Delta\mu = -\mu$ where μ is a positive value representing a chemical potential gradient that favors translocation into the crowded *trans* side. For the static obstacle case in the large N limit, the linear chemical potential term always dominates for any nonzero value of μ . Thus $\tau \sim N$ in this limit, while for $\mu = 0$, $\tau \sim \exp(N^{3/5})$ [from Eq. (7)]. The situation is similar for the dynamic case but only if μ exceeds a critical threshold μ^* that is sufficient to overcome the osmotic pressure term (μ^* is here defined by the value of the prefactor of the n -linear osmotic pressure term in F_{cr}). For $\mu < \mu^*$, $\tau \sim$

$\exp(N)$ for a long chain when obstacles are mobile. Figures 3(a) and 3(c) clearly show these distinct limiting behaviors. The plots also reveal a striking phenomenon that seems to occur at intermediate N . Depending on the parameter values, there appear to be regimes spanning several orders of magnitude in polymer length, where τ is nearly independent of N . The reason for this can be understood by considering the form of the relevant free energy profile as a function of the translocation coordinate n . For the static obstacle case, there is a competition between a linear term ($\sim n$) due to the chemical potential and a sublinear term ($\sim n^{3/5}$) that comes from the crowding for a long chain. This gives rise to a free energy barrier whose height and position are nearly independent of N followed by a “downward slope” all the way to $n = N$. The time taken to surmount this barrier, which is independent of N , is rate-limiting and hence effectively the total translocation time for polymer lengths shorter than the value of N at which the time taken to traverse the downward slope becomes comparable. At this point, the scaling crosses over to being linear in N . Similar behavior was discussed in the context of polymer barrier crossing in a biased double well potential [30]. The situation for the dynamic obstacle case is similar except that the presence of two sublinear terms “softens” the plateau because barrier height and position are no longer independent of N . Figures 3(b) and 3(d) show the different translocation time scaling regimes in the (ϕ_t, μ) phase space at a fixed N . The disappearance of the plateau regime for the dynamic obstacles at high concen-

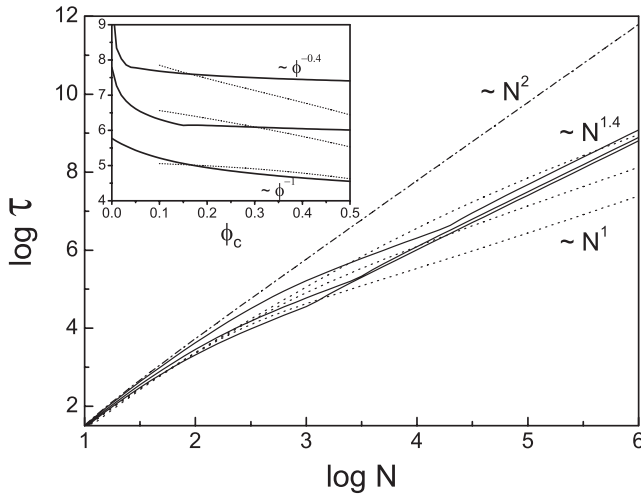


FIG. 2. Translocation time τ (in units of b^2/D_P) of a polymer of length N releasing out of the crowded *cis* side with static obstacles (solid lines: $\phi_c = 0.1, 0.3, 0.5$ in descending order), dynamic obstacles (dotted lines: for the same values of ϕ_c), and no crowding (dashed-dotted line: $\phi_c = 0$). Inset: τ vs obstacle volume concentration ϕ_c for static (solid lines: $N = 10^5, 10^4, 10^3$ in descending order) and dynamic obstacles (dotted lines: for the same values of N). Note $\phi_t = \Delta\mu = 0$ here and the value of $b/a = 0.3$ is used throughout the Letter.

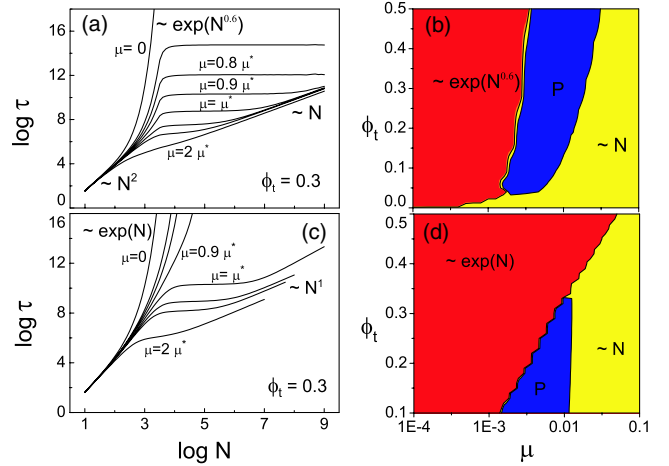


FIG. 3 (color online). Translocation time τ (in units of b^2/D_P) vs N for (a) static and (c) dynamic obstacles on the *trans* side ($\phi_t = 0.3, \phi_c = 0$) for different values of chemical potential gradient, showing the asymptotic power law scalings as well as the plateau regime at intermediate length scales. Note μ^* denotes the value of the prefactor of the n -linear term of F_{cr} in Eqs. (2) and (3), respectively. Different scaling behaviors (exponential, plateau, power law) of τ in the (ϕ_t, μ) phase space for (b) static and (d) dynamic obstacles at a fixed $N = 10^5$.

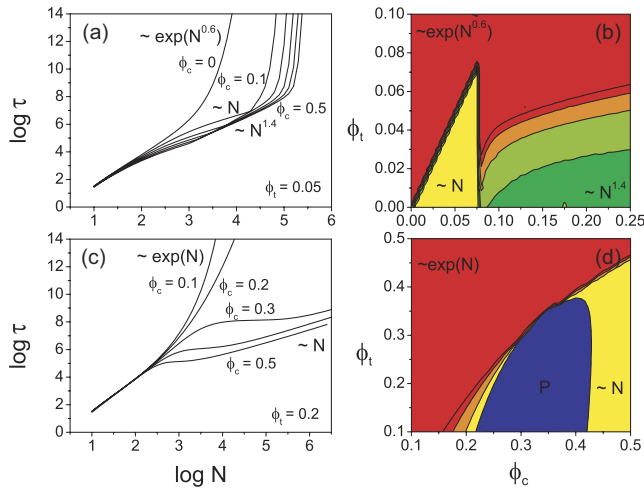


FIG. 4 (color online). τ (in units of b^2/D_p) vs N for (a) static ($\phi_t = 0.05$) and (c) dynamic obstacles ($\phi_t = 0.2$) for different values of ϕ_c . Different scaling behaviors (exponential, plateau, power law) of τ in the (ϕ_t, ϕ_c) phase space for (b) static and (d) dynamic obstacles at a fixed $N = 3 \times 10^4$. Note that $\Delta\mu = 0$ here.

trations is because the presence of two sublinear terms becomes more apparent at higher ϕ_t .

As a final example, we consider the polymer translocation when both sides are crowded and $\Delta\mu = 0$. For dynamic obstacles, the qualitative picture is similar to that with *trans* side crowding and a chemical potential gradient [compare Figs. 3(c) and 3(d) with Figs. 4(c) and 4(d)]. It is to be noted that the presence of sublinear free energy contributions from both sides of the membrane smears out the plateau even more. In the static case, however, the absence of a linear term in the large N limit gives rise to qualitatively different results. As seen in Fig. 4(a), even a minute amount of ϕ_t leads to $\tau \sim \exp(N^{3/5})$ at large polymer lengths despite substantial crowding on the *cis* side. This counter-intuitive behavior arises because the free energy profile in this situation always has a barrier whose height scales to leading order as $N^{3/5}$, which in turn implies exponential barrier crossing times.

The existence of regimes where the translocation time depends very weakly on polymer length, apart from being of theoretical significance, suggests the possibility of designing filters for a tunable range of polymer lengths and also has implications for “synchronized” transport of proteins or nucleic acids from a wide range of sizes in the cellular context. Our predictions can be tested by combining suspensions of uncharged colloids with a conventional setup for DNA translocation experiments. The plateau regimes of Fig. 3, for example, should be observed for double-stranded DNA by crowding the *trans* side with neutral colloids of radii 300 nm up to a volume fraction $\phi \sim 0.3$ and applying an electric field of 0.1 V/cm across a 100 nm thick dividing membrane.

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