Active polymer translocation through flickering pores

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Single file translocation of a homopolymer through an active channel under the presence of a driving force is studied using Langevin dynamics simulation. It is shown that a channel with sticky walls and oscillating width could lead to significantly more efficient translocation as compared to a static channel that has a width equal to the mean width of the oscillating pore. The gain in translocation exhibits a strong dependence on the stickiness of the pore, which could allow the polymer translocation process to be highly selective.

Introduction.—The translocation of a polymer through a pore is important in the context of many biological processes such as the transport of RNA through a nuclear membrane pore [1] and the injection of viruses. Its various technological applications such as drug delivery [2], rapid DNA sequencing [2–4] and gene therapy has led to several recent experimental [4–7] and theoretical studies [8–20]. Most theoretical work in this field has focussed on the underlying physics of the translocation process [8, 9, 12] and the effects of the pore-polymer interactions [10, 11, 18], structure of the pore [17], crowding [19] and confinement effects on the dynamics of translocation. Experimental studies on electric field driven translocation of DNA and RNA molecules across α-hemolysin channels [2] prompted the introduction of additional driving forces to aid translocation. In most of these studies the pore is considered static with the polymer always experiencing a constant confinement during its translocation from the cis to the trans side. However, there are a number of biological examples, such as the twin-pore translocase complex in the inner membrane of mitochondria [21] and the nuclear pore complex [22], where it is known that the width of the channel effectively changes during the course of translocation. Inspired by these examples, we set out to study the generic effect of such temporal modulations on the efficiency of polymer translocation, using a simple coarse-grained model.

We find that the translocation of a polymer through a narrow channel with a width that oscillates with a given frequency can be significantly enhanced when compared to a static pore. The time of translocation is sensitive to the initial condition, and the driving force and stickiness of the channel walls significantly affect the translocation at the limit of high frequencies.

Model.—In our simulation, we model the polymer as a bead-spring chain. The polymer beads experience an excluded volume interaction modeled by a repulsive Lennard-Jones (LJ) potential of the form \( U_{\text{mm}}^{\text{LJ}}(r) = 4\epsilon \left[ \left( \frac{\sigma}{r} \right)^{12} - \left( \frac{\sigma}{r} \right)^{6} \right] + \epsilon \) with a cut-off at \( r = 2^{1/6}\sigma \), where \( \sigma \) is the diameter of a bead and \( \epsilon \) gives the strength of the LJ potential. The monomers of the chain experience an additional interaction modeled as a finitely extensible nonlinear elastic (FENE) spring: \( U_{\text{ch}}^{\text{FENE}}(r) = -\frac{1}{2}kR^2 \ln \left( 1 - \frac{r^2}{R^2} \right) \) where \( k \) is the spring constant and \( R \) is the maximum separation between consecutive monomers along the chain. We consider a two-dimensional (2D) geometry where the pore is modeled as being made up of monomers of diameter \( \sigma \) as shown in Fig. 1a (inset). The walls perpendicular to the pore are taken to be long enough to avoid the crossing of the polymer ends. The interaction of the polymer with the wall, \( U_{\text{wm}}^{\text{LJ}} \), is modeled by the same excluded volume interaction that exists between the polymer beads; thus, \( U_{\text{wm}}^{\text{LJ}} = U_{\text{mm}}^{\text{LJ}} \). The interaction of the polymer with the pore is modeled by the Lennard-Jones potential \( U_{\text{ps}}^{\text{LJ}}(r) = 4\epsilon_{\text{ps}} \left[ \left( \frac{\sigma}{r} \right)^{12} - \left( \frac{\sigma}{r} \right)^{6} \right] \) for \( r \leq 2.5\sigma \) and 0 for \( r > 2.5\sigma \). Inside the pore, the polymer experiences an external driving force \( \mathbf{F}_{\text{ext}} = F\hat{x} \) directed along the pore axis. A Langevin dynamics algorithm is used to integrate the equation of motion of the polymer beads m\( \ddot{r}_i = -\nabla U_{\text{f}} - \mathbf{F}_{\text{ext}} - \mathbf{v}_i + \mathbf{\eta}_i \), where \( m \) is the monomer mass, \( \mathbf{U}_{\text{f}} = U_{\text{mm}}^{\text{LJ}} + U_{\text{ch}}^{\text{FENE}} + U_{\text{wm}}^{\text{LJ}} + U_{\text{ps}}^{\text{LJ}} \) is the total potential experienced by a bead, \( \zeta \) is the friction coefficient, \( \mathbf{v}_i \) is the monomer velocity, and \( \mathbf{\eta}_i \) is the random force satisfying the fluctuation–dissipation theorem \( \langle \mathbf{\eta}_i(t) \cdot \mathbf{\eta}_j(t_0) \rangle = 4k_B T\zeta \delta_{ij}(t-t_0) \).

In our model, \( \epsilon, \sigma, \) and \( m \) set the units of energy, length, and mass, respectively, which result in a unit of time as \((m\sigma^2/\epsilon)^{1/2}\). Using these units, the dimensionless parameters of \( R = 2, k = 7, k_B T = 1.2, \) and \( \zeta = 0.7 \) have been chosen for the simulations, in accordance with earlier simulation studies of polymer translocation dynamics [14, 15]. The length of the pore is fixed at \( L = 5 \), and the length of the polymer is \( N = 32 \) unless otherwise specified.

We consider the case where the width of the pore, \( W(t) \), is allowed to oscillate harmonically, with frequency \( \omega = 2\pi/T \) and amplitude \( W_A \), about an average width \( W_0 = \langle W(t) \rangle_T \), namely \( W(t) = W_0 + W_A \sin(\omega t + \phi) \), where \( \phi \) is an initial phase. Note that \( W_{\text{min}} = W_0 - W_A \) and \( W_{\text{max}} = W_0 + W_A \) are the minimal and maximal
This gives the translocation time of the polymer through the pore, which elapses between the entrance of this monomer into the pore and the exit of the last monomer when the width of the pore is always greater than the average width, $W_0$, which is the width of the static pore. Therefore, we observe a second peak at $\tilde{\omega} \sim 0.5$ and 1.5, with the translocation time at $\tilde{\omega} \sim 0.5$ almost half of that for the static pore. This behavior can be understood by noting that during the first half period of oscillation of the pore (between $t = 0$ and $t = T/2$), the width of the pore is always greater than the average width, $W_0$, which is the width of the static pore. When the oscillation frequency is sufficiently small, then the polymer only experiences this half of the cycle before the completion of the translocation process. The average translocation time therefore increases steadily for small frequencies. Beyond the critical oscillation frequency corresponding to $\tilde{\omega} \sim 0.5$, the polymer experiences the effect of the second half of the cycle where the pore width is always smaller than the static pore width, $W_0$. The average translocation time increases, thus lowering the gain substantially, until it reaches a minimum corresponding to $\tilde{\omega} \sim 1$. For higher oscillation frequencies, the polymer starts experiencing the next half of the cycle between $t = T$ and $t = 3T/2$, when the pore width is again larger than the static pore. Therefore, we observe a second peak in the gain corresponding to $\tau_{\text{osc}} \sim 3T/2$. This peak is much smaller in magnitude because at higher frequencies a substantial amount of time is spent by the polymer in a trapped state. As the frequency is increased further, the gain becomes insensitive to the frequency and develops a plateau [23]. Note that as the frequency tends to zero,
the pore is essentially static and the polymer translocation time reduces to the translocation time for the static pore and the gain approaches unity. We have observed that the behavior of the system is robust as the length of the polymer is changed. For example, Fig. 1a shows that the behavior of the system is robust as the length of the pore and the gain approaches unity. We have observed that two distinct behaviors, namely, a very sharp decrease for \(W < L_y\), leaving the part of length \(y\) empty, and a part that has gone outside. The entropic penalty for the partial confinement of the polymer inside the channel is \(\sim k_B T (L - y)/W\). The monomers that are inside the channel will experience an external force \(F\). Therefore, displacing the polymer by a length \(y\) inside the channel will result in a gain of \(-F(L^2 - y^2 + 2Ly)/2W\) in mechanical energy. The interaction between the monomers and the sticky walls of the pore should also be taken into account. Since the LJ attraction is short ranged, we can estimate this contribution by assigning an energy gain of \(-\epsilon_{pm}\) to every monomer that is in the vicinity of the channel walls. Counting these monomers, we find this “adsorption energy” as \(-2\epsilon_{pm}[(L - y)/W]|W^{4/3}/(1/W)|\). Therefore, the total free energy for escape (up to a constant) is given as \(\mathcal{F}(y) = \left[ -c_1 k_B T \frac{F}{W} + \frac{2c_2 \epsilon_{pm} y - F L}{W} \right] + \frac{F y^2}{2W^2},\) where \(c_1\) and \(c_2\) are constants of order unity. We can now treat the escape problem as diffusion across a one-dimensional effective potential barrier, and calculate the mean first passage time \(\tau\). The resulting escape time would lead to a similar trend as in Fig. 1c.

We can now calculate the translocation velocity, defined as \(V = N/\tau_{stat}\), for a static pore as a function of the width, and use the time dependence of the width to extract the translocation velocity as a function of time over a full period. These are shown as insets in Fig. 1b. Integrating the velocity over a time range that is just long enough to allow for the translocation of the entire polymer, we get the translocation time for an oscillating pore within this approximate scheme. The solid lines in Fig. 1b show the result of this calculation for the high frequency saturation value of the gain for different values of \(F\) and \(\epsilon_{pm}\). The instantaneous static pore picture thus seems to provide a reasonable account of the phenomenon, although it systematically underestimates the gain due to the absence of noise. The asymmetry observed in the two half cycles of the translocation velocity is a direct consequence of choosing the average width \(W_0\) to be the crossover point between two different regimes in the translocation time versus width plot in Fig. 1b.

It is instructive to examine the distribution of the translocation times in the high frequency regime. As shown in Fig. 2 we find that the distribution consists of a series of peaks separated by distinct minima. These minima correspond to the points in the oscillation cycle when the width of the pore is at its minimum, \(W_{min}\). We can further explore the detailed dynamics of polymer translocation by looking at the number of translocated monomers, \(N_{trans}\), i.e. the number of monomers that have left the pore as a function of time. The plot shown
in Fig. 2 is calculated by averaging over all successful translocation events. \( N_{\text{trans}} \) as a function of time alternates between flat and linearly increasing regions. The flat regions correspond to the time periods in the oscillation cycle when the pore width varies between \( W_{\text{min}} \) and \( W_0 \), when the polymer has very little space to manoeuvre itself and is essentially trapped. Therefore, the monomers are not able to leave the pore, and hence, \( N_{\text{trans}} \) does not change. During the periods in the oscillation cycle when the width varies between \( W_0 \) and \( W_{\text{max}} \), the polymer is no longer trapped and the monomers can escape the pore resulting in an increase in \( N_{\text{trans}} \). Note that an increase in the frequency of oscillation \( \dot{\omega} \) causes an increase in the number of peaks in the translocation time distribution.

In our analysis so far we have assumed that the pore width at the beginning of the translocation process is the mean width of the oscillation cycle. Figure 3 shows the effect of the initial phase \( \phi \) on the gain as a function of the oscillation frequency. We observe that at low frequencies the initial phase strongly affects the translocation gain by controlling the effective width during the translocation period, in agreement with the picture described above. However, as the initial phase only affects the first couple of cycles, we expect that at sufficiently high frequencies the translocation process becomes insensitive to it. This is confirmed by the observation that the saturation value of the gain at high frequencies is independent of the initial phase, as Fig. 3 demonstrates. The robust high frequency behavior of the system has remarkable implications. It suggest that even stochastic flickering of the pore will result in a steady average translocation with a gain that can be tuned via \( F \) and \( \epsilon_{\text{pm}} \), as long as \( T \ll \tau_{\text{stat}} \), where \( T \) is the characteristic period of the random opening and closing of the pore. Moreover, we can infer from Fig. 1b that the translocation rate for such random flickering pores is extremely sensitive to the stickiness of the pore, which could bring about the possibility of a high degree of robust selectivity in the translocation process.

It will be interesting to probe whether such potential for selectivity is already exploited in biological active pores. Other interesting factors could be the flexibility of the polymer and the strength of the noise, which could potentially lead to stochastic resonance of the polymer [20]. The design rules that can be obtained from our study could also be used in fabricating highly selective synthetic active pores, which might be able to perform tasks such as sequencing.

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\[ \eta = \frac{\tau_{\text{stat}}}{\tau_0} \]

\[ \phi = 0 \]

\[ \phi = \frac{\pi}{2} \]

\[ \phi = \pi \]

\[ \phi = \frac{3\pi}{2} \]

\[ \omega = \frac{T_{\text{stat}}}{T} \]

\[ W_{\text{min}} \]

\[ W_0 \]

\[ W_{\text{max}} \]

\[ \omega_{\text{stat}} = \frac{T_{\text{stat}}}{T} \]

\[ \tau_{\text{stat}}/T \]

\[ \text{FIG. 3: Gain as a function of the scaled frequency for different values of } \phi. \text{ The plots correspond to } F = 1.0 \text{ and } \epsilon_{\text{pm}} = 1.0. \text{ Inset shows the corresponding width oscillation cycles.} \]

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