Noise driven translocation of short polymers in crowded solutions

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Abstract. In this work we study the noise induced effects on the dynamics of short polymers crossing a potential barrier, in the presence of a metastable state. An improved version of the Rouse model for a flexible polymer has been adopted to mimic the molecular dynamics by both taking into account the interactions between adjacent monomers and introducing a Lennard-Jones potential between all beads. A bending recoil torque has also been included in our model. The polymer dynamics is simulated in a two-dimensional domain by numerically solving the Langevin equations of motion with a Gaussian uncorrelated noise. We find a non-monotonic behavior of the mean first-passage time and the most probable translocation time of the polymer center of inertia as a function of the polymer length at low noise intensity. We show how thermal fluctuations influence the motion of short polymers, by inducing two different regimes of translocation in the molecule transport dynamics. In this context, the role played by the length of the molecule in the translocation time is investigated.

Keywords: dynamics (theory), mechanical properties (DNA, RNA, membranes, bio-polymers) (theory)
1. Introduction

The knowledge of the translocation dynamics of a molecule moving across a membrane or surmounting a barrier is a fundamental step towards the full comprehension of the functioning of many biological systems. In the cell environment, DNA and RNA translocate across nuclear pores and many proteins work on the bases of their ability to go beyond a potential barrier. Reciprocal translocation between portions of chromosomes causes the genetic mutations which characterize several tumors [1, 2]. The cancer target therapy is based on a drug delivery mechanism that crucially depends on the translocation time of the chemotherapeutic molecules [3]–[5]. Polymer translocation has been found to play a key role in the acquisition of multi-drug resistance to cancer therapy [6]. The study of the transport of macromolecules across a nanopore is also important for technological applications. For example, the development of chemomechanical actuators [7], the separation of molecules by liquid chromatography [8, 9] and fast DNA sequencing techniques [10] are performed by forcing the molecule to move inside nanochannel devices.

Many experimental studies on polymer translocation have been carried out in the wake of the pioneering work of Kasianowicz and collaborators (1996). In these experiments, single-stranded DNA (ssDNA) molecules are forced by a voltage bias to pass through an α-hemolysin (α-HL) pore embedded into a membrane. The passage of the molecule inside the protein channel causes a reduction of the electrolyte ion current and the duration time of any current blockade is recorded. In this way, a linear relationship of the most probable crossing time \( \tau_p \) with the molecule length and an inverse proportionality law between \( \tau_p \) and the applied voltage were established [11]. The α-HL channel device has been extensively used for probing the transport dynamics of several types of polynucleotide (DNA or RNA) molecules having same length but different adenine and cytosine contents [12]–[14]. A different nucleotide composition of the DNA brings about a significant change in the distributions of the duration times of the corresponding current drops. These findings confirm that the dynamics of biopolymer translocation across an α-HL channel is governed by pore–molecule interactions, which are dependent on the details...
of DNA sequences [15], the orientation and the driving voltage [16]. Moreover, \( \tau_p \) scales as the inverse square of the temperature and the differences in crossing time due to different nucleotide compositions are progressively reduced when the temperature increases [13].

Recent advances in semiconductor technology have enabled the construction of synthetic nanopores for DNA translocation experiments [17,18]. By using a silicon oxide nanopore, there was found a power law relationship between \( \tau_p \) and the polymer length, with an exponent of 1.27 [19,20]. However, a retarding effect on the crossing time has been observed as an effect of the voltage dragging itself, which could be strong enough to disturb the biopolymer on finding the best orientation for the translocation [21]. In fact, other experiments show that the DNA molecule's translocation speed in a solid-state nanopore is strongly dependent on the electrolyte temperature, salt concentration, viscosity and applied voltage bias [22,23].

In contrast to the proportionality law between the translocation time and the polymer length, experiments on the transport dynamics of DNA molecules driven inside an entropic trap array have shown longer crossing times for shorter molecules, suggesting the existence of a quasi-equilibrium state of the polymer during the passage [24,25].

The complex scenario of the translocation dynamics coming from experiments has been enriched by several theoretical and simulation studies [26]–[29], [21], [30]–[32], [15]. A power law relationship between the translocation time of a long \( N \)-segment chain molecule and the polymer length has been found, with an exponent of 2 in the presence of a free energy bias between the two sides of the membrane or 3 in the absence of adsorption [33]. The relationship between the crossing time and \( N \) becomes linear in the presence of strong interactions between the polymer and the pore walls [28] or in the case of a hairpin crossing mechanism of translocation [34].

In spite of the above contributions, the complicated biological environments and boundary conditions make the problem of polymer translocation still far from a common understanding and, in this framework, a detailed description of the transport dynamics of short chain molecules is missing. The motion of a polymer passing through a pore takes place in solutions where thermal fluctuations always affect the translocation dynamics. In this paper we present the results of our studies on the noise induced effects on the transport dynamics of short polymers surmounting a potential barrier, in the presence of a metastable state. Molecular dynamics simulations are performed by modeling the polymer as a flexible chain molecule with harmonic interactions between adjacent monomers and a Lennard-Jones (LJ) potential between all beads. A bending recoil torque has also been included in our model. The polymer dynamics is simulated in a two-dimensional domain by numerically solving the Langevin equations of motion with a Gaussian uncorrelated noise. The dependence of the mean first-passage time (MFPT) of the polymer center of inertia on the length \( L \) of the chain molecule critically changes with the noise intensity [35]. In this paper we focus our research on short polymers, which usually show two different regimes of translocation depending on the ratio of \( L \) over the length of the channel [36]. We find a non-monotonic behavior of both MFPT and \( \tau_p \) as a function of polymer length at low noise intensity. In this context, the role played by the stiffness of the molecule in the translocation dynamics is also investigated. In section 2 we present our polymer chain model and give the details of the molecular dynamics simulations. The final results are described in section 3 and discussed in section 4.

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2. Model and method

2.1. The polymer chain model

In our simulations, the polymer is modeled by a semi-flexible chain of \( N \) beads connected by harmonic springs [37]. The contour length is defined as \( L_0 = N d \), where \( d \) is the equilibrium distance between adjacent monomers. Both excluded volume effects and van der Waals interactions between all beads are taken into account by introducing a Lennard-Jones potential. In this work, we investigate the dynamics of a linear chain molecule. In order to confer a suitable stiffness to the chain, a bending recoil torque is included in the model, with a rest angle \( \theta_0 = 0 \) between two consecutive bonds. The polymer motion in the liquid solvent induces a velocity field which is felt by all the beads. To first order, we neglect this hydrodynamic effect. Such approximation implies that our model cannot be used to mimic the molecule behavior in dilute polymeric solutions, but it appears to be much more appropriate for polymeric melts [38]. The potential energy of the modeled chain molecule is

\[
U = U_{\text{Har}} + U_{\text{Bend}} + U_{\text{LJ}} \tag{1}
\]

where \( U_{\text{Har}} \) represents the energy required to extend the bond between two consecutive beads, \( U_{\text{Bend}} \) the work required to bend the chain, and \( U_{\text{LJ}} \) the Lennard-Jones potential. Respectively, we have

\[
U_{\text{Har}} = \sum_{i=1}^{N-1} K_r (r_{i,i+1} - d)^2 \tag{2}
\]

\[
U_{\text{Bend}} = \sum_{i=2}^{N-1} K_\theta (\theta_{i-1,i+1} - \theta_0)^2 \tag{3}
\]

\[
U_{\text{LJ}} = 4\epsilon_{\text{LJ}} \sum_{i,j(i\neq j)} \left[ \left( \frac{\sigma}{r_{ij}} \right)^{12} - \left( \frac{\sigma}{r_{ij}} \right)^{6} \right] \tag{4}
\]

where \( K_r \) is the elastic constant, \( r_{ij} \) the distance between particles \( i \) and \( j \), \( K_\theta \) the bending modulus, \( \epsilon_{\text{LJ}} \) the LJ energy depth and \( \sigma \) the monomer diameter.

2.2. Molecular dynamics simulations

The effect of temperature fluctuations on the dynamics of a chain polymer escaping from a metastable state is studied in a two-dimensional domain. The polymer motion is modeled as a stochastic process of diffusion in the presence of a potential barrier having the form

\[
U_{\text{Ext}}(x) = ax^2 - bx^3 \tag{5}
\]

with parameters \( a = 3 \times 10^{-3} \) and \( b = 2 \times 10^{-4} \). A three-dimensional view of \( U_{\text{Ext}} \) is plotted in figure 1. The drift of the \( i \)th monomer of the chain molecule is described by
the following overdamped Langevin equations:

\[ \gamma \frac{dx}{dt} = -\frac{\partial U}{\partial x} - \frac{\partial U_{\text{Ext}}(x)}{\partial x} + \sqrt{D} \xi_x(t) \]  

\[ \gamma \frac{dy}{dt} = -\frac{\partial U}{\partial y} + \sqrt{D} \xi_y(t) \]  

where \( U \) is the interaction potential, defined by equation (1), \( \xi_x(t) \) and \( \xi_y(t) \) are white Gaussian noises modeling the temperature fluctuations, with the usual statistical properties, namely \( \langle \xi_k(t) \rangle = 0 \) and \( \langle \xi_k(t)\xi_l(t+\tau) \rangle = D\delta_{k,l}\delta(\tau) \) for \( (k,l=x,y) \) and \( \gamma \) is the friction coefficient. In this work we set the \( \gamma \) parameter equal to 1. The standard Lennard-Jones timescale is \( \tau_{\text{LJ}} = (m\sigma^2/\epsilon_{\text{LJ}})^{1/2} \), where \( m \) is the mass of the monomer. A bead of single-stranded DNA is formed approximately by three nucleotide bases and then \( \sigma \sim 1.5 \text{ nm} \) and \( m \approx 936 \text{ amu} \) [15]. Orders of magnitude of the quantities here involved are nanometers for the characteristic lengths of the system (polymer and barrier extension) and microseconds for the time domain. Moreover, our simulation time \( t_s \) is scaled with the friction parameter as \( t_s = t/\gamma \); therefore we use arbitrary units for all computed translocation times. We set both \( K_t \) and \( K_\theta \) equal to 10, \( \epsilon_{LJ} \) equal to 0.1 and \( \sigma \) equal to 3, in arbitrary units. The inter-bead rest length \( d \) is chosen equal to 5, while the number of monomers \( N \) ranges from 4 to 40 units.
A sequence of $10^5$ numerical simulations has been performed for each of the seven different values of the noise intensity $D$ and eleven different polymer lengths. The starting condition for all molecular dynamics simulations performed provides that the initial distance between two adjacent monomers of the chain is equal to the rest length $d$ of the ideal spring connecting them. We have carried out our study by selecting an initial spatial distribution of the polymer with all monomers at the same $x$ coordinate equal to $x_0 = 0$, which corresponds to the local minimum (metastable state) of the potential energy of the barrier. Every simulation stops when the $x$ coordinate of the center of mass of the chain reaches the final position at $x_f = 15$. This value has been chosen after performing a set of simulations by assuming $x_f = 30$ and the noise intensities $D = 0.3, 1.0, 4.0$ and 10.0, respectively. We have found that the polymer center of mass takes a very short time to travel from $x = 15$ to $x_f = 30$ in comparison with the average escape time from $x_i = 0$ to $x_f = 15$. Therefore, by assuming $x_f = 15$, we are confident that the probability for the polymer to be trapped back into the potential well is extremely low. The distribution of the translocation times is analyzed and the MFPT, $\tau_p$, and the median of the distribution (hereafter ‘the median’) are calculated.

3. Results

The polymer center of mass crosses the line at $x_f$ with translocation times having a distribution that crucially depends on the noise intensity $D$. The mean crossing time, the median and $\tau_p$ are analyzed as a function of $D$ for different values of the polymer length. In particular, figure 2(a) shows a decreasing trend of the MFPT with increasing the intensity of the fluctuations affecting the monomer motion. This result is expected from the standard theory of the transport dynamics of a particle escaping from a metastable state [39]. However, when the noise intensity goes down $D \simeq 1$, the polymer dynamics appears to be very sensitive to the molecule length, with shorter chains ($N \lesssim 12$) translocating more slowly (higher MFPTs) compared to longer molecules. In particular, the dynamics of polymers with $N \lesssim 10$ and $D \lesssim 1$ shows interesting details inside the
common behavior, while the dependence of the MFPT on \( D \) converges to an almost unique path for greater values of \( N \). The crossing dynamics of chains with \( N = 4 \) (blue line in figure 2(a)) resembles that of a single particle (see figure 2 in [40] and figure 1 in [41]), by showing a marked power law relationship between the MFPT and the noise intensity (straight line in a log–log plot). The comparison of the polymer behavior with that of a single particle started outside the potential minimum, as studied in [40] and [41], is possible because the exact initial point becomes irrelevant at strong noise intensities, where the power law behavior is observed.

Many experimental works report their results in terms of the most probable translocation time instead of the MFPT. For this reason, we have also investigated how the median and \( \tau_p \) depend on the noise intensity. The dependence of the median on \( D \) is very similar to that of MFPT, with a little exception at \( D = 10 \). On the contrary, the diagram of \( \tau_p \) versus \( D \) in figure 2(b) shows some diversities. The single-particle-like behavior is still observed for \( N = 4 \). However, when the polymer length increases, the index of the power law between \( \tau_p \) and \( D \) (the slope of the curve) progressively drops. For \( N \geq 12 \) the translocation dynamics changes with respect to shorter chains and the dependence of \( \tau_p \) from the noise intensity becomes almost equal to that observed for the MFPT. In figure 2(c) the ratio \( \tau_p / \text{MFPT} \) is plotted as a function of \( D \). We can see that the two characteristic crossing times are not related to each other by a simple proportionality law for different polymer lengths and noise intensities. However, a common non-monotonic behavior of this ratio as a function of the noise intensity is observed.

The different dynamics of translocation of short and long polymers is investigated as a function of the noise intensity. Figure 3 shows the dependence of the MFPT, the median and \( \tau_p \) on the polymer length (the number \( N \) of chain beads) for four different values of noise intensity. In the diagram with \( D = 0.3 \) (figure 3(a)) two different regimes of translocation are clearly present: for \( N \lesssim 15 \) all characteristic times show a maximum at \( N \approx 7 \), while for \( N \gtrsim 15 \) a common plateau is observed. This maximum is more evident in the MFPT than in \( \tau_p \), but the heights of both peaks are rapidly reduced when the noise intensity increases. This maximum occurs at a polymer length corresponding to the persistence length of the chain \( L_p \), which represents the length over which the correlations in the direction of the tangent to the polymer are lost. For our discrete chain model, we have calculated the directional correlation:

\[
\langle \cos(\theta(s_j)) \rangle = \frac{\sum_{k=0}^{N-j-1} (x_k - \bar{x})(x_{k+j} - \bar{x})}{\sum_{k=0}^{N-1} (x_k - \bar{x})^2}
\]

as a function of the contour length \( s_j \) corresponding to the \( j \)th segment of the polymer chain, where \( x_k \) represents \( \cos(\theta(s_k)) \), \( \theta(s_k) \) is the angle between the tangent vector at one end of the chain molecule and the tangent vector at the contour length corresponding to the \( k \)th segment of the polymer chain, \( \bar{x} \) the mean of \( x \). We have computed an ensemble average over \( 5 \times 10^5 \) different steric configurations of the polymer fluctuating in a flat potential domain at the noise intensity \( D = 0.3 \) (the value for which the maximum of translocation time is observed in figure 3(a)). The directional correlation presents damped oscillations as a function of the polymer contour length, following an overall exponentially decreasing trend. By best fitting this calculated correlation function with the expression \( \langle \cos(\theta(s)) \rangle = \exp(-s/L_p) \), which is valid for the continuous worm-like chain model, we have obtained \( L_p = 29.8 \). This value of \( L_p \) corresponds to \( N \approx 6 \).

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Figure 3. Mean first-passage time (blue line), median of the crossing time distribution (red line) and most probable translocation time (green line) versus polymer length (number of beads) for four different noise intensities $D = 0.3, 1.0, 4.0, 10.0$. The inset on each diagram shows an enlarged, on the $y$-scale, view of the region with $N > 20$.

In the short-length domain, the most probable translocation time shows an inversion of the dependence from the polymer length at higher values of $D$ with respect to that observed at lower noise intensities. For $D \gtrsim 2$, the most probable translocation time increases monotonically with the chain length and, for $N \gtrsim 15$, it reaches almost the same level as the MFPT. The inset of each diagram in figure 3 shows the flat region of the corresponding plot in the range $20 \leq N \leq 40$ with an enlarged $y$-scaling. For any values of $D$, we observe a slightly increasing trend of the characteristic crossing times for longer molecules.

4. Conclusions

In this paper we focus our study on the noise influence on the translocation dynamics of short polymers. We model the molecule as a chain of spatially extended interacting beads. The transport dynamics is simulated in a noisy environment and in the presence of a potential barrier by solving the Langevin equation of motion for every single monomer.

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We find a maximum of the MFPT and $\tau_p$ as a function of the number of beads of the chain at low noise intensity. This maximum occurs at a polymer length corresponding to the persistence length of the chain $L_p$. This characteristic length represents a transition point between two different dynamical behaviors of the polymer approaching the barrier. The chain molecule having length lower than $L_p$ moves like a flexible elastic rod and the addition of a monomer to the chain causes longer crossing times. For lengths greater than $L_p$ the polymer can fold, assuming a snake-like shape. This configuration helps the molecule into the translocation process, reducing the crossing times. For short molecules in a low noise environment, the relationship between $\tau_p$ and the chain length is similar to that of MFPT. In contrast, when the thermal fluctuations are stronger, the MFPT and $\tau_p$ show different dependences on $N$.

In order to compare our results with available experimental findings, we restrict the following discussion to the behavior of the most probable time. For a low noise environment, we confirm that short polymers can travel more slowly than longer ones, as firstly observed by Han and collaborators [24]. For greater values of polymer length ($N \gtrsim 25$), our findings are in agreement with an almost linear relationship between the most probable translocation time and the polymer length [11]. At higher temperatures, the fluctuations dominate the transport dynamics of short polymers, canceling any dependence of the translocation time on the stiffness of the molecule. In this regime, longer molecules take longer times to cross the barrier.

For polymer chains having length in a range close to $L_p$ the noise acts as a trigger of the translocation dynamics. Low intensities of thermal fluctuations bring the molecule to cross the barrier by a transport mechanism that is completely different from that observed at higher temperatures. The measured crossing times are a direct consequence of the noise influence on the molecule dynamical regime of translocation. Further work is required to include in our description a polymer–pore interaction term and to explore the noise induced modifications of the polymer dynamics in a sub-persistence length confinement.

The saturation of all the times represents an effect still not completely understood. A possible explanation could be related to the intrinsic stochastic behavior of the polymer dynamics: large number of monomers gives an average contribution to the motion of the polymer center of mass. When the number $N$ increases, the fluctuations of the single monomer affect less and less the overall motion of the polymer. This could be considered as a ‘coarse-grained’ one-particle description in the limit $N \to \infty$. Moreover, the three characteristic translocation times saturate to almost the same value, indicating that the escaping time probability distributions tend to become more symmetric on increasing the number of monomers. A detailed investigation of these features will be the subject of a future work.

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