Non-equilibrium effects in chaperone-assisted translocation of a stiff polymer

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Abstract

Chaperone assisted biopolymer translocation is the main model proposed for translocation in vivo. A dynamical Monte Carlo method is used to simulate the translocation of a stiff homopolymer through a nanopore driven by chaperones. Chaperones are proteins that bind to the polymer near the wall and prevent its backsliding through Cis side. The important parameters include binding energy, size and the local concentration of the chaperones. The profile of these local concentrations, build up the chaperones distribution. Here we investigate the effects of binding energy, size and the exponential distribution of chaperones in their equilibration in each step of the polymer translocation needed for stable translocation time. The simulation results show that in case of chaperones with size of a monomer ($\lambda = 1$) and/or positive effective binding energy and/or uniform distribution, the chaperones binding equilibration rate/frequency is less than 5 times per monomer. However, in some special cases in exponential distribution of chaperones with size $\lambda > 1$ and negative effective binding energy the equilibration rate will diverge to more than 20 times per monomer. We show that this non-equilibrium effect results in supper diffusion, seen before. Moreover, we confirm the equilibration process theoretically.

Keywords: Polymer translocation, First passage time, Chaperone distribution, Binding energy, Nanopore, supper-diffusion

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1. Introduction

Translocation of biomolecules through the nanopores Meller (2003) is one of the most important processes within biological cells. This is a ubiquitous process in cell metabolism. Protein’s translocation through endoplasmic reticulum is an example. The polymer translocation also seen in proteins transport through organelles like mitochondria Alberts et al. (2002); Muthukumar (2007); Rapoport (2007). Translocation of messenger RNA through nuclear pore complexes in gene expression and in transcription through eukaryotic cells are two other biological instances Alberts et al. (2002). Translocation of DNA through protein channels covering the bacterial membrane amid phage infection is another example Bates et al. (2003); Dreiseiklmann (1994). Biotechnological examples also includes gene therapy, drug delivery and cheap rapid sequencing of the biopolymers Marzio and Kasianowicz (2003); Nakane et al. (2003); Branton et al. (2008); Cohen et al. (2012); Fanzio et al. (2012); Carson and Wamuma (2015); Liang and Zhang (2015). The experimental work of Kasianowicz et al. (1996) on ssRNA translocation through an α-hemolysin channel was an influential work. Hereafter, there has been many experimental and theoretical works and simulations in polymer translocation Meller (2003); Panja et al. (2013); Sun and Lu (2014); Palyulin et al. (2014).

There are many different mechanisms to drive translocation of polymers. In vitro, people usually use a strong electric field to drive the translocation of highly charged biopolymers like single stranded DNA or RNA. Moreover, there could be many other parameters affecting the translocation such as crowding Gopinathan and Kim (2007); Pu et al. (2016), pressure and confinement Grayson and Molineux (2007); Panja and Molineux (2010); Molineux and Panja (2013); Palyulin et al. (2014). However, the most important model for the translocation in vivo is chaperone assisted translocation Tomkiewicz et al. (2007). This model with the name of Brownian ratchet mechanism was first proposed by Simon et al. in 1992 Simon et al. (1992). In this model proteins called chaperones are bound to the polymer in the Trans side and actively pull the polymer or just prevent its backsliding through the Cis side Alberts et al. (2002); Tomkiewicz et al. (2007). Later, the experiments of Matlack et al. in 1999 highlights the problem again Liebermeister et al. (2001); Elston (2002); Zandi et al. (2003). Subsequently, many theoretical and simulations struggled to have a better understanding of different aspects of the problem Palyulin et al. (2014); Ambjørnsson and Metzler.
Figure 1: A stiff polymer is translocating from the Cis side (left) to the Trans side (right). Chaperones of size $\lambda\sigma$ are distributed in the Trans side. The total length of the polymer is $L = M\sigma$. $m$ monomers are no translocated to the right.

There are many works on the non-equilibrium aspects of forced polymer translocation: Sakaue (2007); Bhattacharya and Binder (2010); Saito and Sakaue (2013); Vollmer and de Haan (2016). This out of equilibrium property emerges as a result of force pulling the polymer through the Trans side. Here we investigate the chaperone assisted translocation which is used in vivo. Following our recent works we consider the chaperones exponential distribution effects on polymer translocation Abdolvahab (2016, 2017). We will show that even in the case of stiff polymer the distribution may induce the non-equilibrium effects in the translocation process.

In what follows we examine the chaperones binding rate effects on the translocation. Hereafter introducing our dynamical Monte Carlo simulation, we will discuss our simulation results in our main part of article in section 3. Finally we will sum up our findings in the conclusion.

2. Simulation

2.1. Theoretical model

As the figure 1 shows, we simulate a stiff homopolymer consisted of $M$ monomer with size of $L = M\sigma$. Chaperones with the same size of $\lambda\sigma$ are distributed only in the Trans side. We suppose the $\lambda$ to be an integer Abdolvahab et al. (2011b); Ambjörnsson and Metzler (2004). They have
local concentration which depends on their distribution. Moreover, there is a binding energy, positive or negative, between the chaperones and the polymer.

They bind (unbind) to (from) the polymer in the Trans side. The polymer always can go to the right. However, for backsliding of the polymer, its near the wall site must be unbound. The wall has no width Abdolvahab (2017). Binding of chaperones bias the translocation through the Trans side. The master equation for this process is written as:

$$\frac{\partial P(m, t)}{\partial t} = W^+(m-1)P(m-1, t-1) + W^-(m+1)P(m+1, t+1) - (W^+(m) + W^-(m))P(m, t)$$ (1)

in which $W^\pm$ are the transfer rates for translocating polymer to the right and left. $P(m, t)$ is the probability of finding polymer in time $t$ at condition in which $m$ monomer of it translocated to the right. Using transfer rates, $W^\pm$, and boundary conditions one could find the translocation time by calculating its mean first passage time Gardiner (2002).

2.2. Describing the Monte-Carlo method

We use a dynamical Monte Carlo method to simulate the translocation of a stiff polymer as follows. The polymer always can go to the right with probability of half. However, backsliding of the polymer is restricted. The polymer may come back through the Cis side only if there is not any chaperone bound to the polymer near the wall. Moreover, we use from the so called transmission boundary condition Redner (2001). It means reflective at first and absorbing at the end. As a result the polymer does not come back to the Cis when the first monomer is near the wall Abdolvahab (2017). Chaperones will try to bind/unbind in each step of the translocation by frequency $f$ per monomer per 40. It means, for example, in the case of a polymer with $m = 40$ and by the frequency $f = 40$, the binding/unbinding process is one time. A monomer in the Trans side is selected randomly. If there is a chaperone bound to it we try to unbind it with its probability and vice versa (it will try to bind a chaperone accordingly). Due to our computational limits, we changed the frequency from 1 to $10^3$. 
Chaperones binding probability: There are three terms in the binding probability. Boltzmann distribution, which depend on the binding energy between chaperones and the polymer. Entropy linked to different patterns in which chaperones may distributed on the polymer and availability of the chaperones related to its local density Ambjörnsson and Metzler (2004); Abdolvahab et al. (2011b). The second term is automatically comes in the simulation. In place of the binding energy, we define effective binding energy (EBE or $E_{eff}$) to combine the first and third term as Abdolvahab et al. (2011b) $E_{eff} \equiv -\frac{1}{\lambda} \log [c_0 v_0 \exp (-\varepsilon/k_B T)]$, where $\varepsilon$ comes for the chaperone binding energy per monomer of the polymer. $c_0$ denotes the chaperone concentration, and $v_0$ stands for their volume Abdolvahab et al. (2011a); Abdolvahab (2017). Thus the binding and unbinding probabilities are written as:

$$P_{bind} = \frac{\exp \left( -\sum_{i=1}^{\lambda} E_{eff}^i \right)}{1 + \exp \left( -\sum_{i=1}^{\lambda} E_{eff}^i \right)}, P_{unbind} = \frac{1}{1 + \exp \left( -\sum_{i=1}^{\lambda} E_{eff}^i \right)}.$$  (2)

The effective binding energy is changed from $-4$ to $4$ and the polymer length is restricted to $M = 50$. In order to reach to an acceptable error, we repeat the translocation process for at least $10^4$ times. Moreover, we use the chaperones of different sizes of $\lambda = 1, 2$ and 6.

Chaperones distributions: For simplicity we restrict the chaperones to distributed only in the right part. We consider the exponential distribution with different rates, $\alpha$, for the chaperones and compare its results with the usual uniform distribution ($\alpha = 0$). In order to change the chaperones distribution in our Monte Carlo simulation it is enough to change the $E_{eff}$ to $E_{eff} + \alpha d$ in which $d$ is the distance (per monomer size) between the wall and the monomer in which we need its near chaperones concentration Abdolvahab (2016, 2017).

3. Results and discussion

3.1. Mean translocation time

We simulate 1 dimensional stiff homopolymer translocation through a nanopore using a dynamic Monte Carlo method in presence of the chaperones with different sizes and different spatial distributions. There are chaperones with distinct spatial distributions and various EBEs by monomers in the
Figure 2: Translocation time of polymers, constructed of 50 monomers, versus try number. Chaperones size are \( \lambda = 2 \) and exponential rates are \( \alpha = 0, 5 \). The dash-dotted lines are for \( \alpha = 5 \) while the solid lines stand for \( \alpha = 0 \). The right figure is a zoom on the left one.
Trans side (There is not any chaperone in the Cis side.). Try number, or chaperones rate of binding (its frequency denotes by \( f \)), is an important parameter in calculating the translocation time of the polymer. In spite of this importance, there are few works on investigating its effects on the polymer translocation \( D’Orsogna \) et al. (2007). People suppose that due to interaction of the polymer with the pore and its size, the chaperones will reach to equilibrium in each step of the polymer translocation Ambjörnsson and Metzler (2004).

In what follows we will show that although this is true for the case of uniform distribution of chaperones, in exponential distribution, the equilibration frequency will become large and the assumption is violated.

We translocate polymers in presence of chaperones of sizes \( \lambda = 1, 2, 6 \) and spatial distributions of \( \alpha = 0, 1, 5, 10 \) and \( EBE = -4 : +4 \). The figure 2 shows mean translocation time versus frequency or rate of the chaperones for different exponential chaperone distributions of \( \alpha = 0, 5 \) and different EBEs for chaperones of size \( \lambda = 2 \). Different curves stand for different chaperones spatial distribution and/or different EBEs. The right figure is a zoom of the left one for faster polymers. Note that \( \alpha = 0 \) means uniform spatial distribution of the chaperones.

The simulation results show that there are different regimes based on convexity and/or equilibrium rate:

- In large enough and positive EBEs the time versus rate curves are strictly ascending. They soon will reach to their equilibrium rates.

- In large enough and negative EBEs the time versus rate curves are strictly descending. They quickly will reach to their equilibrium rates usually but in some special cases the equilibrium rate will become quite large.

- In some intermediate energies, we will see a maximum in time versus rate curves.

In large positive EBEs, the chaperones do not prefer to bind to the polymer. Hence, the probability density function of finding the monomers bound are well asymmetric to the left (see the figure 3). In asymmetric density functions of this kind, mean is always in right and close to the most probable. We will show that in this situation increasing the fluctuation, will increase the \( P_{bind} \) (near the wall binding probability). Consequently, by increasing the rate and decreasing the fluctuation, the translocation time will
be increased (see the Appendix A.1). In contrast in large negative EBEs, 
increasing the frequency will cause the translocation time to be decreased 
(see the Appendix A.2).

3.2. Equilibrium rate

As discussed in the previous section, an important parameter in describ-
ing the polymer translocation is the equilibrium rate (the rate from which 
the translocation time does not change). In this regard, the polymers have 
two different behaviours. All the polymers with positive $E_{\text{eff}}$, which means 
the chaperones prefer not to bind to the polymer, have the small equilibrium 
rates. In contrast in the case of negative $E_{\text{eff}}$, the equilibrium rate could be 
relatively large. Indeed, our simulation results show that this non-equlibrium 
properties comes from the chaperones exponential distribution. We did not 
see any divergence in the uniform distribution of the chaperones (compare 
the plots in figure [4]). The equilibrium rate of the polymers translocation in 
vicinity of the chaperones with different sizes of $\lambda = 1, 2, 6$ and with chaper-
one spatial distribution with different exponential rates of $\alpha = 0, 1, 5, 10$ are 
plotted against $E_{\text{eff}}$ in figure [4]. As it shows there is not any important di-
vergence in the cases of uniform distribution, $\alpha = 0$, and/or chaperones with 
the size of a monomer, $\lambda = 1$. To better understand this results one should 
find a more detailed description of the chaperones exponential distributions 
effects on the polymer translocation (see Abdolvahab (2017)).
Effective binding energy

Equilibrium rate

\[ \lambda = 1, \alpha = 0 \]
\[ \lambda = 2, \alpha = 0 \]
\[ \lambda = 2, \alpha = 1 \]
\[ \lambda = 2, \alpha = 5 \]
\[ \lambda = 2, \alpha = 10 \]
\[ \lambda = 6, \alpha = 0 \]
\[ \lambda = 6, \alpha = 1 \]
\[ \lambda = 6, \alpha = 5 \]
\[ \lambda = 6, \alpha = 10 \]

Figure 4: Equilibrium rates are plotted against EBEs for different binding sizes \( \lambda = 1, 2, 6 \) and different chaperones distributions of \( \alpha = 0, 1, 5, 10 \). The dashed line shows the maximum rate in the simulation. The points over the black dashed line are not real data and just estimated (based on figure 2).

It is pertinent to mention that our results paved the way for understanding the supper diffusion reported in our previous work [Abdolvahab, 2017]. In that article we show that in some special case the scaling exponent of time vs polymer length, \( \beta (T \sim M^\beta ) \), becomes less than 1 (\( \beta < 1 \)). It can be explained as follows. Increasing the polymer length will increase the time for chaperones to equilibrate. Consequently, the equilibration rate will be decreased. Hence, trying to calculate the scaling exponent \( \beta \) before equilibrium will cause the translocation time increase less than the expected amount and the exponents could even become less than 1.

3.3. Mean waiting time

Details of the translocation can be seen from its waiting times. Mean Waiting Time (MWT) of the translocation for chaperones of size \( \lambda = 2 \) and \( \varepsilon_{eff} = -4, 4 \) for uniform chaperone’s distribution and 3 different rates of \( f = 10, 300, 900 \) is shown in figure 5a. As it shows MWT for \( \varepsilon_{eff} = 4 \) and for rates of \( f \geq 300 \) are decreasing linearly. However, for the same \( \varepsilon_{eff} \) but for smaller rate of \( f = 10 \), it starts from smaller amounts and it makes its translocation velocity faster. In contrast, in case of \( \varepsilon_{eff} = -4 \), the translocation velocity increase by increasing the rate from \( f = 10 \) to \( f = 300, 900 \). As a result of the large binding probability the MWT for the rates \( f = 300, 900 \) becomes completely sawtooth shape.

As we saw in figure 2b, the translocation time for two different case of
Figure 5: Mean waiting times of polymer translocation in different conditions are compared. In above figure, the chaperones have uniform distribution and different EBEs of $\mathcal{E}_{\text{eff}} = -4, 4$ and rate frequencies of $f = 10, 300, 900$ are compared (note that the chaperones with $\mathcal{E}_{\text{eff}} = -4$ and rate frequencies of $f = 300, 900$ are exactly the same.). In the figure (b), we compare the uniform and exponential distribution of chaperones.
uniform distribution and exponential distribution with $\alpha = 5$, both with 
chaperones of size $\lambda = 2$ and $\mathcal{E}_{\text{eff}} = -4$ in rates of $f = 300$ equalize to 
each other. MWT for these two case is plotted in figure 5b. Because of the 
large negative $\mathcal{E}_{\text{eff}}$, the chaperones bind to the polymer as right as it find 
a free place near the wall. In the case of uniform distribution availability 
of the chaperones are the same through the whole polymer which cause the 
sawtooth shape. However, in the case of exponential distribution, the chap-
erones may unbind from the polymer in further sites away from the wall. 
Consequently, the sawtooth shape becomes smooth or disappeared. On the 
other hand, in this case it takes time for the system to find its equilibrium 
and thus we see the translocation time is decreased by rate frequency and in 
f = 300 it coincide with its uniform counterparts.

4. Conclusions

We simulate the translocation of stiff homopolymer through a nanopore 
driven by chaperones. We investigate specially the chaperones binding fre-
quency and spatial distribution on the translocation time. Our results show 
that there are different patterns of equilibration in terms of chaperones size, 
effective binding energy and spatial distribution. In most cases the equilib-
rium is reaching soon (less than 10 try per monomer). However, an increase 
in equilibration frequency (more than 20 try per monomer) is seen in the cases 
of $\lambda > 1$, $\mathcal{E}_{\text{eff}} < 0$ and $\alpha > 0$ roughly in the interval of $-6 < \lambda \mathcal{E}_{\text{eff}} + \alpha < -1$. 
In larger amounts the chaperones do not prefer to bind and in less amounts 
the chaperones could not unbound from further sites. This result pave the 
way for understanding the supper diffusion reported in Abdolvahab (2017). 
We also strengthen our simulation results by theoretical discussion about the 
effect of chaperones binding rate on translocation time.

Appendix A. Fluctuation in binding probability and translocation 
time

Based on a master equation approach and using mean first passage time 
theory, we provide translocation time as follows [Abolvahab et al] (2011b):

$$T = \frac{2 \tau_0}{P_{\text{bind}}} \left( N + 1 - \frac{1 - P_{\text{bind}}}{P_{\text{bind}}} \left[ 1 - (1 - P_{\text{bind}})^{N+1} \right] \right), \quad (A.1)$$

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where $\tau_0$ is the time takes for a bare polymer to translocate over distance of a monomer, $N$ is the total number of the monomers and $P_{\text{bind}}$ is the probability of the polymer to be bound near the wall. In the small and large amount of $P_{\text{bind}}$ one may approximate the equation $\text{A.1}$ as follows:

Appendix A.1. Large binding probability

In large enough binding probability $P_{\text{bind}} \simeq 1$ which occurs in large negative EBE, expansion of the equation $\text{A.1}$ leads to:

\[
T \simeq \frac{2\tau_0}{P_{\text{bind}}} (N + 1).
\]  

(A.2)

Fluctuation of $P_{\text{bind}}$ which shows itself in translocation time can be investigated as follows. Admit the change in $P_{\text{bind}}$ to be of order $\delta$; $P_{\text{bind}} \to P_{\text{bind}} \pm \delta$. We then average over this range by integration:

\[
\bar{T}_{\text{large}} \simeq \frac{1}{2\delta} \left( \int_{P_{\text{bind}} - \delta}^{P_{\text{bind}} + \delta} \frac{2\tau_0}{P} (N + 1) dP \right) \simeq \frac{2\tau_0 (N + 1)}{P_{\text{bind}} - \delta},
\]  

(A.3)

where $\bar{T}_{\text{large}}$ is average of $T$ over fluctuations of $P_{\text{bind}}$ for large binding probabilities. As expected from our simulation results, it shows that increasing the chaperones binding rate which decreases the fluctuation $\delta$, will reduce the mean translocation time.

Appendix A.2. Small binding probability

In contrast to the previous section, in small binding probability, expansion of equation $\text{A.1}$ results in:

\[
T(P_{\text{bind}}) = 2\tau_0 (N + 1) \times \left( C_0(N) - C_1(N) P_{\text{bind}} + C_2(N) P_{\text{bind}}^2 - \cdots \right),
\]  

(A.4)

\[
C_0(N) = 1 + \frac{N}{2}, C_1(N) = \frac{N}{2} \left( 1 + \frac{N - 1}{3} \right), C_2(N) = \frac{N(N - 1)}{3!} \left( 1 + \frac{N - 2}{4} \right).
\]

Note that this approximation is true when $NP_{\text{bind}} \ll 1$ and the important parameter here is the Péclet number not $P_{\text{bind}}$ itself (see Abdolvahab et al. (2011a) for more detail). As the figure 3 shows, the binding probability distribution is exponential. Let assume its exponential determines by parameter $a$; $P(P_{\text{bind}}) \propto \exp(-aP_{\text{bind}})$. Averaging of the translocation time over fluctuations of $P_{\text{bind}}$ leads to:
\[ Z \equiv \left( \int_{P_{\text{bind}}-\delta}^{P_{\text{bind}}+\delta} \exp(-aP)dP \right) \]

\[ \Rightarrow P_{\text{bind}} = -\frac{\partial \ln(Z)}{\partial a} \approx \frac{\partial \ln\left(2\delta \exp(-aP_{\text{bind}})(1-(a\delta)^2)\right)}{\partial a} \approx P_{\text{bind}} + 2a\delta^2 \]

\[ T_{\text{small}} - T = \frac{1}{2\delta} \left( \int_{P_{\text{bind}}-\delta}^{P_{\text{bind}}+\delta} T(P) \exp(-aP)dP \right) - T(P_{\text{bind}}) \]

\[ \Rightarrow T_{\text{small}} - T \approx -C_1(N)2a\delta^2. \] (A.6)

Increasing the chaperones binding rate will decrease the fluctuation over \(P_{\text{bind}}, \delta\), and as a result the mean translocation time, \(T_{\text{small}}\), will be increased.

It is in place to note here that the EBE in which the regimes changed, say \(EBE_0\), may be obtained by comparison of second and third term in equation A.4.

\[ C_1(N)P_{\text{bind}} > C_2(N)P_{\text{bind}}^2 \Rightarrow \frac{N}{3}P_{\text{bind}} < 1. \] (A.7)

Presume the binding probability to be proportional to its Boltzmann distribution \((P_{\text{bind}} \propto \exp(-\lambda EBE))\) leads us to \(EBE_0 \approx \frac{1}{\lambda} \ln\left(\frac{N}{3}\right)\). As an example in case of \(\lambda = 2\) and \(N = 50\), \(EBE_0 \approx 1.4\) which is compatible with the simulation results (see e.g. figure 2a).

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