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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 the 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 the 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.

1. Introduction

Translocation of biomolecules through the nanopores [25] 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 is seen in proteins transport through organelles like mitochondria [6,27,34]. Translocation of messenger RNA through nuclear pore complexes in gene expression and in transcription through eukaryotic cells are two other biological instances [6]. Translocation of DNA through protein channels covering the bacterial membrane amid phage infection is another example [8,14]. Biotechnological examples also include gene therapy, drug delivery and cheap rapid sequencing of the biopolymers [24,28,10,12,16,11,22]. The experimental work of Kasianowicz et al. [21] 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 [25,31,41,30].

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 [19,33], pressure and confinement [20,32,26,30]. However, the most important model for the translocation *in vivo* is chaperone-assisted translocation [42]. This model with the name of Brownian ratchet mechanism was first proposed by Simon et al. in 1992 [38]. 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 [6,42]. Later, the experiments of Matlack et al. in 1999 highlights the problem again [23,15,47]. Subsequently, many theoretical and simulations struggled to have a better understanding of different aspects of the problem [30,7,5,4,3,45,46,44,40,1].

There are many works on the non-equilibrium aspects of forced polymer translocation [37,9,36,43]. 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 [1,2]. We will show that even in the case of the 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

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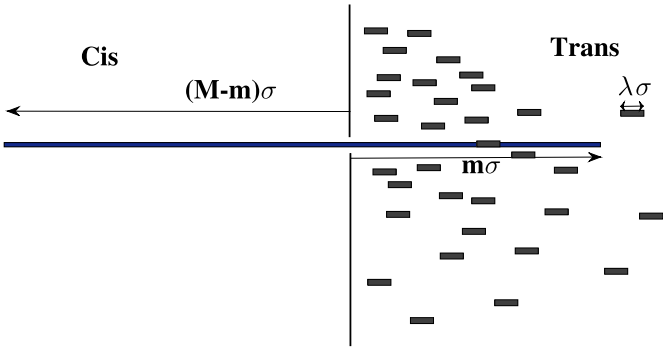

Fig. 1. A stiff polymer is translocating from the Cis side (left) to the Trans side (right). Chaperones of size $\lambda\sigma$ are distributed in the Trans side. The total length of the polymer is $L = M\sigma$. m monomers are no translocated to the right.

main part of the article in section 3. Finally, we will sum up our findings in the conclusion.

2. Simulation

2.1. Theoretical model

As the Fig. 1 shows, we simulate a stiff homopolymer consisted of M monomer with the size of $L = M\sigma$. σ is the size of a single monomer. Chaperones with the same size of $\lambda\sigma$ are distributed only in the Trans side. We suppose the λ to be an integer [4,7]. 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 [2]. Binding of chaperones biases the translocation through the Trans side. The master equation for this process is written as:

$$\begin{aligned}\frac{\partial P(m,t)}{\partial t} &= \mathcal{W}^{+}(m-1)P(m-1,t-1)\\ &+ \mathcal{W}^{-}(m+1)P(m+1,t+1)\\ &- (\mathcal{W}^{+}(m)+\mathcal{W}^{-}(m))P(m,t)\end{aligned} \tag{1}$$

in which $\mathcal{W}^{\pm}(m)$ are the transfer rates for translocating polymer to the right and left when m monomers passed the wall. $P(m,t)$ is the probability of finding polymer in time t at the condition in which m monomer of it translocated to the right. Using transfer rates, $\mathcal{W}^{\pm}$, and boundary conditions one could find the translocation time by calculating its mean first passage time [18].

It is also interesting to note here that this approach is useful in so-called *Rubber band revisited model* in calculating the entropy of the polydisperse chains ([39,17,29]).

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 a 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 the so called transmission boundary condition [35]. 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 [2]. 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 depends on the binding energy between chaperones and the polymer. Entropy linked to different patterns in which chaperones may distribute on the polymer and availability of the chaperones related to its local density [7,4]. The second term is automatically comes in the simulation. In place of the binding energy, we define effective binding energy (EBE or $\mathscr{E}_{eff}$) to combine the first and third term as [4] $\mathscr{E}_{eff} \equiv -\frac{1}{\lambda}\log[c_0 v_0 \exp(-\varepsilon/k_B T)]$, where ε comes for the chaperone binding energy per monomer of the polymer. c_0 denotes the chaperone concentration, and v_0 stands for their volume [3,2]. Thus, the binding and unbinding probabilities are written as:

$$\begin{aligned}P_{bind} &= \frac{\exp\left(-\sum_{i=1}^{\lambda}\mathscr{E}_{eff}^{i}\right)}{1+\exp\left(-\sum_{i=1}^{\lambda}\mathscr{E}_{eff}^{i}\right)},\\ P_{unbind} &= \frac{1}{1+\exp\left(-\sum_{i=1}^{\lambda}\mathscr{E}_{eff}^{i}\right)}.\end{aligned} \tag{2}$$

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, α, 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 $\mathscr{E}_{eff}$ to $\mathscr{E}_{eff} + \alpha d$ in which d is the distance (per monomer size) between the wall and the monomer in which we need its near chaperones concentration [1,2].

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 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 [13]. People suppose that due to the interaction of the polymer with the pore and its size, the chaperones will reach to equilibrium in each step of the polymer translocation [7]. 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 Fig. 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