

Molecular Chaperone-Dependent Polymer Translocation through Nanopores: The Effects of Chaperone Concentration and Chaperone-Polymer Interaction

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Abstract The polymer translocation through a nanopore from a donor space (or named *cis* side) to a receiver space (*trans* side) in the chaperone-induced crowded environment has attracted increasing attention in recent years due to its significance in biological systems and technological applications. In this work, we mainly focus on the effects of chaperone concentration and chaperone-polymer interaction on the polymer translocation. By assuming the polymer translocation to be a quasi-equilibrium process, the free energy F of the polymer can be estimated by Rosenbluth-Rosenbluth method and then the translocation time τ can be calculated by Fokker-Plank equation based on the obtained free energy landscape. Our calculation results show that the translocation time can be controlled by independently tuning the chaperone concentration and chaperone-polymer interaction at the *cis* side or the *trans* side. There exists a critical chaperone-polymer attraction $\varepsilon^* = -0.2$ at which the volume exclusion and interaction effects of the chaperone can balance each other. Additionally, we also find that at large chaperone-polymer attraction, the translocation time is mainly governed by the diffusion coefficient of the polymer.

Keywords Polymer translocation; Rosenbluth-Rosenbluth method; Fokker-Plank equation; Free energy landscapes

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INTRODUCTION

The translocation of a polymer through a nanopore plays a crucial role in many biological processes,^[1–4] such as mRNA molecules passing across nuclear pores,^[5] proteins transporting through membrane channels,^[6] and DNA or RNA molecules transferring from virus to host cell and genes transferring between bacteria.^[7] Moreover, the nanopore-based polymer translocation has shown potentially biotechnological applications, such as rapid DNA sequencing,^[8] gene therapy,^[9] controlled drug delivery,^[10] gel electrophoresis,^[11] biological sensors,^[12] and size exclusion chromatography.^[13] Therefore, the study of polymer translocation process can advance the understanding of biological process and improve the nanotechnological applications.

The translocation dynamics of polymer through the nanopores is highly dependent on the translocation environment, which is composed of multiple factors, such as the structure of pore,^[14,15] polymer-pore interaction,^[16–19] driving force,^[20–23] and solvent property.^[24,25] In addition, the translo-

cation process is also governed by molecular chaperones (such as small ligands) in the environment. In general, the molecular chaperones can change the entropy and enthalpy of the polymer chain during the translocation. The number of all possible polymer chain configurations decreases due to the existence of molecular chaperones outside of the nanopore, giving rise to a different entropy change for the polymer chain moving into the nanopore from outside. In addition, there may exist an interaction between the polymer chain and molecular chaperones, which can offer the polymer chain an additional pushing or pulling force for the translocation process.

Due to the significance in biology and applications, the chaperone-accompanied polymer translocation has been extensively studied, especially by the computational simulations.^[26–30] It was found that the effects of chaperones on the translocation are mainly determined by the chaperone locations. When the chaperones are at the donor space (or named *cis* side), where the polymer chain starts the translocation, the chaperones decrease the entropic barrier of the polymer chain at the pore entry, favoring the translocation; meanwhile the polymer-chaperone attraction results in a retarding force to slow down the translocation speed. Whereas, the chaperones would generate opposite effects on the translocation if they are placed at the receiver space (or named *trans*

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side). Under the circumstances, the volume exclusion and attraction of the chaperones provide the negative and positive effects for the translocation process respectively. Furthermore, the crowded environment can largely change the diffusion property of the polymer chain, which impacts on the translocation dynamics consequently. As a result, for the polymer translocation accompanied by the binding chaperones at the *trans* side, there is a minimum translocation time as a function of the binding affinity.^[30] This is due to the competition between the reduced polymer chain diffusivity and the increased drag force with the increase of binding interactions.

In order to have a deeper understanding of the chaperone effects on the translocation, besides the simulations, the theoretical studies are also necessary as more easy-to-understand physical pictures (such as free-energy landscapes) can be presented. A crucial premise of the free-energy-based analysis is the assumption that the polymer translocation is an equilibrium (or quasi-equilibrium) process. Previous studies reported that for a short single-stranded nucleic acid (<1000 nucleotides), its relaxation time is longer than translocation time during the translocation, demonstrating that the quasi-equilibrium treatment is reasonable.^[31–34] Based on the theoretical calculations, the quantitative relationships between the entropic penalty and the crowded environment (at the *cis* side, *trans* side, and both sides) have been obtained, providing clear explanations for the aforementioned simulation results. Furthermore, the translocation time can be estimated by Fokker-Plank equation combined with the obtained free energy landscapes.^[35–38] The calculation results suggested that the scaling relationship between the translocation time and the polymer chain length is dependent on the accompanied chaperones.

However, there is still lack of a systematically free-energy-based analysis of the chaperone-accompanied polymer translocation, since it is difficult to count the number of polymer chain conformations efficiently and accurately in crowded environment. In fact, for the polymer chain in an empty space (in the absence of chaperone), its conformation number can be estimated by functional descriptions (such as scaling estimation^[39] and blob approximation^[40,41]) and computationally counting methods (such as exact enumeration^[16] and scanning algorithm^[42,43]). Whereas, these methods might be not suitable to calculate the conformation number of polymer chain in crowded environment. For example, there is no precise function to estimate the reduction of conformation number for the functional descriptions due to the presence of the chaperones, and the explicit distributions of the chaperones drastically increase the computer time for the computational method methods.

In this work, we use the Rosenbluth-Rosenbluth method^[44] to calculate the conformation number of the polymer chain in the presence of chaperones, which is implicitly treated. The effect of the chaperones on the polymer chain conformation number is considered as a probability term in our calculations. As a result, the calculation of the free energy for the chaperone-accompanied polymer chain are equally efficient as that for free polymer chain. Based on our calculations, we will theoretically analyse the chaperone concentration and interaction-dependent polymer translocation. Moreover, we

also consider the diffusivity change of the polymer chain induced by the chaperones during the translocation.

MODEL AND METHODS

Lattice Model of the Translocation Region

In order to conveniently calculate the free energy landscape of the polymer translocation, we use a simple cubic lattice with a grid (lattice) size l in the translocation system (box), as shown in Fig. 1. Here we set $l=1$. The boundaries of the box are $(-L_x/2, L_x/2)$, $(-L_y/2, L_y/2)$, and $(-L_z/2, L_z/2)$ at x , y , and z directions, respectively. A y - z planar wall located at $x=0$ divides the entire box into a donor space (or named *cis* side) and a receptor space (or named *trans* side), where the polymer stays before and after the translocation, respectively. As the only passageway for the polymer translocation from the *cis* side to the *trans* side, a site-large nanopore (i.e., an empty site) is embedded at the center of the planar wall. The position of pore locates at $(x, y, z)=(0, 0, 0)$. The size of the nanopore can avoid the hairpin conformations of the polymer during the translocation. In fact, it is difficult to produce a nanopore with the same size as the monomer in nanopore fabrication. However, a sub-2 nm wide nanopore^[45] can allow the monomers of the polymer to move through one by one. Therefore, the pore size used in this paper is reasonable.

The self-avoiding walking (SAW) polymer model is considered. The polymer chain of length N is formed by N SAW monomers. Each monomer occupies a lattice site, and the bond length between two bond-connected monomers is equal to the lattice size l ($=1$). In addition, the chaperones are arbitrarily distributed inside the box. Here, the size of chaperone is the same as the monomer. The concentrations of the chaperones at the *cis* side $c_c = M_c/V_c$ and at the *trans* side $c_t = M_t/V_t$, where M and V denote the number of chaperones in a space (*cis* or *trans* side) and the volume of this space.

Due to the volume exclusion effects, each site in the box can be occupied by at most a monomer (or a chaperone). The interactions between monomers and chaperones (denoted by ϵ_c at the *cis* side and ϵ_t at the *trans* side) are taken into account when they are at nearest neighboring (NN) sites, as shown in Fig. 1. However, as the chaperones distribute in the box at random, due to the fluctuation and chaperone-monomer coupling effects, explicit treatment of the chaper-

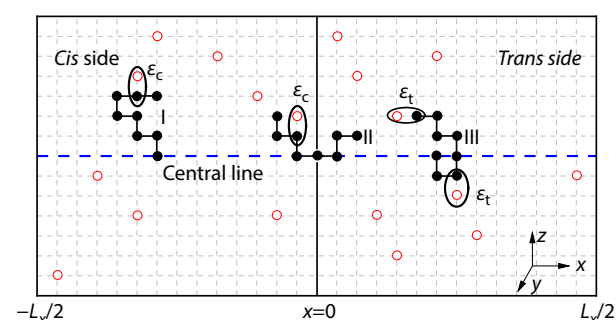


Fig. 1 A two-dimensional graph of the cubic lattice model. The red dots represent the chaperones, the interconnecting black dots represent the monomers of the polymer, while the red open circles denote the chaperones within the box. If the monomer is located at the nearest neighboring (NN) site of a chaperone, the polymer will gain an energy (namely ϵ_c at the *cis* side and ϵ_t at the *trans* side).

ones requires an exceedingly long computing time in estimation of the polymer conformations. As a result, we will implicitly treat the chaperones and use a probability term to consider the volume exclusion and interaction of the chaperones.

Free Energy Calculation

Before or after the translocation process (the polymer is outside the nanopore), the first monomer is placed on the central line (see the blue dashed line in Fig. 1) and other monomers will be added one by one until the whole polymer chain is generated. During the polymer translocation, as a monomer is already inside the nanopore, we separately grow the two parts of the polymer at the *cis* and *trans* side, respectively.

When $i-1$ monomers have been generated, there are m_i available NN sites for the i^{th} monomer to choose. In the absence of the chaperones, the individual weight $w(i)$ of the monomer can be expressed as $w(i) = m_i$, indicating that there are m_i possible selections of the i^{th} monomer. However, due to the volume exclusion effect, the chaperones can reduce the possible selection number of the i^{th} monomer. For the box with the chaperones of concentration c_{ob} (which is c_c at the *cis* side or c_t at the *trans* side), each site has a possibility c_{ob} to be occupied by the chaperones because of the random distribution of the chaperones. As a result, the individual weight $\omega(i)$ of the i^{th} monomer with m_i empty NN sites can be given as:

$$\omega(i) = m_i(1 - c_{\text{ob}}) \quad (1)$$

Here we should note that the above equation indicates that the volume exclusion of the chaperone has been taken into account. If $m_i=0$, the polymer chain should be reconstructed from the first monomer. If $m_i>0$, we select a NN site j according to the probability of the i^{th} monomer placed at site j :

$$p_j = \frac{1 - c_{\text{ob}}}{\omega(i)} = \frac{1}{m_i} \quad (2)$$

where $j = 1, 2, \dots, m_i$ indicating that the i^{th} monomer has the same probability to occupy each possible site. Afterwards, a random number $r \in (0, 1]$ is generated to be used to select site j .

Once the N^{th} monomer is added, the entire polymer has been generated. The total weight W_N of the entire polymer of length N can be written as:

$$W_N = \prod_{i=1}^{N-1} \omega(i) \quad (3)$$

In this calculation, we need to grow the polymer chain by M samples and calculate the average total weight $\overline{W_N}$. Finally, the free energy of the polymer can be represented as:

$$F = -k_B T \ln(\overline{W_N}) \quad (4)$$

where k_B is Boltzmann constant and T is thermodynamic temperature.

The free energy calculation described above does not involve the interaction of polymer with chaperone. But in the biological function of cell, the translocation behavior of macromolecules is often accompanied by interactive force between polymer and chaperones. These forces profoundly influence the polymer translocation process. Here, in the model, monomer-chaperone interaction is considered when the polymer grows.

As mentioned above, there are m_i available sites for the i^{th}

monomer after $(i-1)$ monomers have been placed. The i^{th} monomer chooses its target location from the sites with the same probability (see Eq. 2) without the consideration of monomer-chaperone interaction. However, if such an interaction is taken into account, the probabilities of the i^{th} monomer to choose the sites are different as the chaperones around can affect the polymer conformations. At site j , the new added monomer gets an energy $n_j \epsilon$ with n_j as the chaperone number at the NN sites of the site j and ϵ as the monomer-chaperone interaction. The chaperone number near site j can be calculated as $n_j = m_j c_{\text{ob}}$ with m_j as the available near site j (expect the NN sites occupied by monomers). As a result, the individual weight $\omega(i)$ of the i^{th} monomer can be written as:

$$\omega(i) = \sum_{j=1}^{m_i} \omega_j(i) = \sum_{j=1}^{m_i} (1 - c_{\text{ob}}) \exp(-m_j c_{\text{ob}} \epsilon) \quad (5)$$

where $\omega_j(i)$ present the weight of i^{th} monomer located at site j . In selection of the new site of the monomer, the probability of site j is revised as:

$$p_j = \frac{\omega_j(i)}{\omega(i)} \quad (6)$$

By combining Eqs. (3)–(6), we can obtain the free energy of the polymer under the effects of monomer-chaperone interactions. In calculations, we set $k_B T$ as the unit of energy.

Translocation Coordinate of the Free Energy Landscape

When the polymer chain walks into the pore (see stage II of Fig. 1), the conformation number will decrease fast for an instant, which will lead to a huge entropy change. In order to clearly present the entropy change, we intend to introduce a new coordinate system that is called translocation coordinate to discuss translocation process. The whole translocation process is comprised of three stages. The three stages I, II, and III of the polymer chain during the translocation from *cis* side to *trans* side are presented in Fig. 1. (1) $x_t = x$ with $x < 0$ for the whole chain is located at the *cis* side ($x_t = -1$ indicates that the head monomer is at the pore entry to try enter the pore); (2) $x_t = n$ during the translocation when n monomers are located at the *trans* side, here $0 \leq n < N$ ($x_t = 0$ means the head monomer is in the pore and the rest ones are located at the *cis* side); and (3) $x_t = x + N - 1$ with $x > 0$ for the whole chain is located at the *trans* side ($x_t = N$ means that the tail monomer is at the pore exit when the whole chain is located at the *trans* side). In fact, the polymer can diffuse anywhere at the *cis* side and *trans* side in the stages I and III, respectively. To conveniently understand the translocation process from the free energy landscape, we thus assume that the first monomer is placed on the central line before and after the translocation.

Since we have obtained free energy landscape $F(x_t)$, the first-passage time of polymer moving from $x_t = b_0$ to $x_t = b_1$ can be estimated by Fokker-Plank equation:

$$\tau_{\text{FP}}(b_0, b_1) = \frac{l^2}{D(x_t)} \sum_{x_t=b_0}^{b_1} \left[e^{F(x_t)} \Delta x_t \sum_{x'_t=b_0}^{b'_1} e^{-F(x'_t)} \Delta x'_t \right] \quad (7)$$

In our calculations, the diffusion coefficient $D(x_t)$ is assumed as a constant $D_0=1$, unless otherwise mentioned. l is the lattice size of the translocation model, as $l=1$. Δx_t and $\Delta x'_t$ represent the moving step of the polymer, which are equal to the lattice size as $\Delta x_t = \Delta x'_t = 1$. $b'_1 \in [b_0, b_1]$ represents the posi-

tion of the polymer along the translocation coordinate.

RESULTS AND DISCUSSION

In this study, the polymer length is fixed as $N = 60$ and the sizes of the box are set as $L_x = 120$, $L_y = 60$, and $L_z = 60$. Using such a large box, we can avoid the boundary effects in the estimations of the polymer conformation number.

Free Energy Landscape and Translocation Time without Chaperone-polymer Interaction

When a polymer chain translocates through a nanopore from *cis* side to *trans* side, the free energy landscape will be affected by chaperone concentrations c_c at the *cis* side and c_t at the *trans* side. Fig. 2 shows the free energy landscape for polymer translocation with same chaperone concentration at both sides ($c_c = c_t$). When the polymer chain gradually approaches to the pore ($-20 \leq x_t < 0$), the conformation number of polymer chain will gradually decrease due to the wall effect. Thus, the free energy landscape will gradually increase in this process. When the first monomer of the polymer chain enters into the pore ($x_t = 0$), the conformation number of the polymer chain will suddenly decrease, and the free energy will increase sharply. After the translocation ($x_t \geq 60$), the free energy at the *trans* side decreases when the polymer is farther from the pore as the possible conformations increase. Due to the condition of $c_c = c_t$, we find that the free energy landscape is symmetrical against $x_t = 30$, indicating that there is no free energy difference between the polymer at the *cis* side and at the *trans* side. As chaperone concentration increases, the conformation number will decrease in the whole translocation process, leading to the increase of the free energy landscape. In addition, due to the conformation loss of the polymer inside the nanopore, there is an energy barrier $F_b (= F_{\max} - F_{\min})$ with $F_{\max}$ and $F_{\min}$ as the maximum and minimum in the free energy landscape, which hinders the polymer translocation. Our calculation results show that the free energy barrier F_b decreases gradually as chaperone concentration increases (see the inset of Fig. 2), which agrees with the previous theoretical analyses.^[16,46,47]

We also calculate the free energy landscapes of the poly-

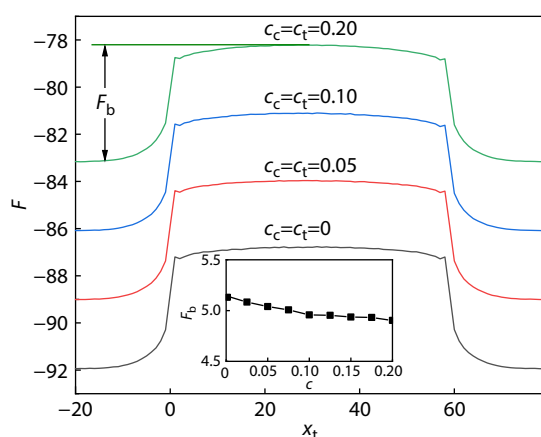


Fig. 2 Free energy landscape with same chaperone concentration at *cis* side and *trans* side ($c_c = c_t$), chaperone-polymer interaction is not considered here.

mer translocation in asymmetrical crowded environment between the *cis* and *trans* sides ($c_c \neq c_t$), as shown in Fig. 3. In the absence of the chaperone at the *cis* side ($c_c = 0$), we find that the free energy landscape (see Fig. 3a) becomes more and more asymmetrical with the increase of chaperone concentration c_t at the *trans* side. Due to the chaperones at the *trans* side, the polymer conformation number decreases sharply during the translocation process, leading to that the polymer chain needs to overcome more higher free energy barrier F_b for larger c_t in order to translocate through the small pore. A high chaperone concentration at the *trans* side will prevent polymer from translocating through the pore due to the high free energy barrier, giving rise to a long duration of the polymer in the translocation process.^[27]

Fig. 3(b) shows the free energy landscapes with different chaperone concentrations c_c at the *cis* side under $c_t = 0$. We find that at $x_t \approx 60$, the free energy becomes larger with the increase of c_c . Before the polymer chain enters the pore, the heights of free energy barriers with different c_c are almost the same. However, the free energy decreases sharply with the increase of concentration of chaperones c_c . At $x_t = 60$, since the entire polymer chain is at the *trans* side, at which the chaperone is absent, all the free energy landscapes remain the same value on *trans* side.

In the case of $c_c \neq c_t$, the free energy landscape is asymmetrical which will result in a free energy difference $\Delta F = F_{cis} - F_{trans}$ between the *cis* and *trans* sides (Fig. 3b). F_{cis} and F_{trans} are the minimum free energies at the *cis* and *trans* side, respectively. Since we do not consider chaperone-polymer interaction here, the value of ΔF is only dependent on the difference of chaperone concentrations Δc ($\Delta c = c_c - c_t$) at two sides. when c_c is large than c_t , ΔF is positive, indicating that ΔF can drive polymer chain to translocate through the pore. In contrast, when c_c is small than c_t , the negative ΔF will prevent the polymer from the translocation. We find that the chemical potential is proportional to the concentration difference as $\Delta F \sim \Delta c$ as shown in the inset of Fig. 4.

By combining the free energy landscapes with Eq. (7), we can estimate the translocation time $\tau = \tau_{FP}$ ($x_t = -1$, $x_t = 60$) between the moment of the head monomer at the pore entry

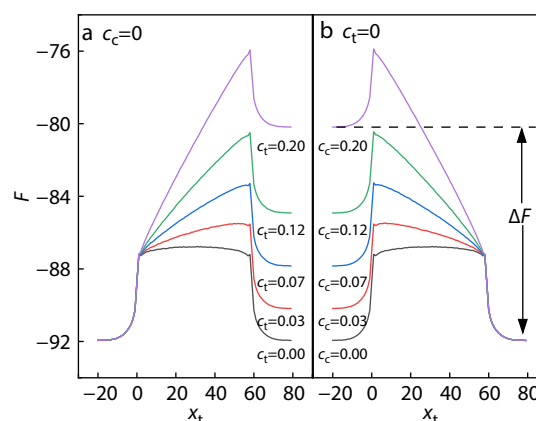


Fig. 3 Free energy landscapes for polymer chain at $c_c = 0$ with $c_t = 0.00, 0.03, 0.07, 0.12, 0.20$ for (a) and $c_t = 0$ with $c_c = 0.00, 0.03, 0.007, 0.12, 0.20$ for (b), chaperone-polymer interaction is not considered here.

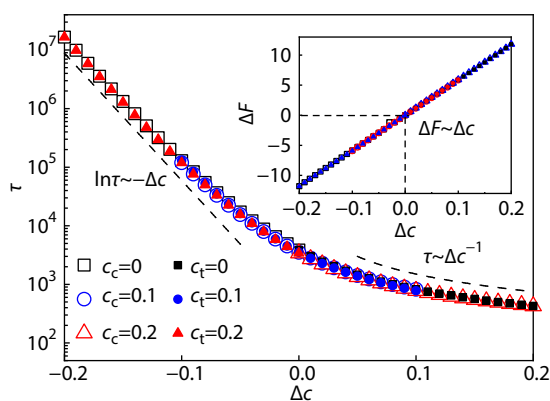


Fig. 4 The dependence of translocation time on chaperone concentration difference Δc , the inset shows the relationship between chemical potential ΔF and the chaperone concentration difference Δc .

($x_t = -1$) and the moment of the tail monomer at the pore exit ($x_t = 60$). Fig. 4 shows the relationship between the translocation time τ and the chaperone concentration difference Δc with various c_c or c_t . As the chemical potential ΔF increases linearly with the increase of Δc , the translocation time decreases with the increase of Δc , which agrees with the previous simulation results.^[27] In addition, we find that, at small value of the concentration difference $\Delta c < -0.05$, there is a powerful relationship between the translocation time and the chaperone concentration difference as $\ln(\tau) \sim -\Delta c$, while at large value $\Delta c > 0.05$, the translocation time τ is inversely proportional to Δc as $\tau \sim \Delta c^{-1}$.

Free Energy Landscape and Translocation Time with Chaperone-polymer Interaction

Besides chaperone concentration, chaperone-polymer interaction also influences the free energy landscapes. Fig. 5 shows the free energy landscape under different chaperone-polymer interactions and chaperone concentrations at *trans* side with the fixed $c_c = 0.1$ and $\varepsilon_c = 0$ at the *cis* side. We find that the free energy is strongly dependent on the chaperone-

polymer interactions. Even if $c_c > c_t$, the chaperone-polymer repulsion at the *trans* side still can create a free energy barrier (see green line) to prevent the polymer from passing through the pore. In addition, we find that the free energy at the *trans* side decreases with ε_t , changing the energy difference ΔF from a negative value (that hinders the translocation) to a positive one (that facilitates the translocation). Therefore, the attractive chaperones at the *trans* side can generate an additional effective driving force to help the polymer translocation.^[27] The combination in the changes of the chaperone-polymer interaction and the chaperone concentration can effectively control the polymer translocation time.

Fig. 6 shows the translocation time as a function of the chaperone-polymer interaction for the conditions of $c_t = 0.1$ (see panel (a)) and $c_c = 0.1$ (panel b). Here we consider that the chaperones at the *cis* side and *trans* side provide the same interaction energy for the polymer, as $\varepsilon_c = \varepsilon_t = \varepsilon$. There exists a competitive effect between the chaperones at the *cis* side and *trans* side on the polymer translocation. If $c_c < c_t$, the chaperones at the *trans* side will win the competition. Therefore,

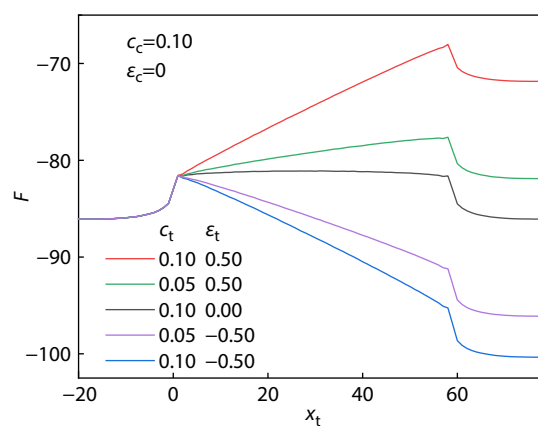


Fig. 5 Free energy landscape for polymer chain at $c_c = 0.10$ and $\varepsilon_c = 0.00$, the chaperone concentrations c_t are 0.10, 0.05, 0.10, 0.05, 0.10 and the interactions ε_t are 0.50, 0.50, 0.00, -0.50, -0.50 from top to bottom.

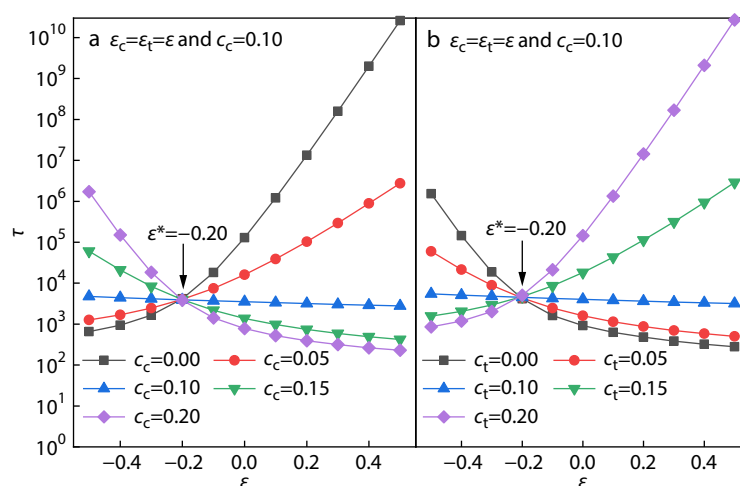


Fig. 6 (a) The relationship between translocation time and the chaperone-polymer interaction under fixed chaperone concentrations at *trans* side and different chaperone concentrations at *cis* side; (b) The relationship between translocation time and chaperone-polymer interaction under fixed chaperone concentrations at *cis* side and different chaperone concentrations at *trans* sides.

the strong attraction (such as $\varepsilon = -0.4$) from the *trans* side facilitates the polymer translocation, while the strong repulsion (such as $\varepsilon = 0.4$) slows down the translocation speed, resulting that the translocation time τ increases with ε . In contrast, if $c_c > c_t$, the more pronounced interactions of the chaperones at the *cis* side lead to the decrease of the translocation time with the increase in ε . When $c_c = c_t$, as the chaperone-induced interactions from the two sides are the same, the translocation time nearly keeps constant.

In fact, a bound chaperone impacts on the polymer translocation by two effects: the volume exclusion and the chaperone-polymer interaction. The former effect leads to the increase of the polymer free energy. However, the effect of the chaperone-polymer interaction depends on the value of ε . If $\varepsilon < 0$, the free energy can be reduced, as shown in Fig. 5. Therefore, there is a critical value $\varepsilon^* (< 0)$, at which the chaperone-induced attraction and volume exclusion can balance each other; consequently, the translocation time is independent of the chaperone concentrations. Our simulation results presented in Fig. 6 reveal this critical attraction $\varepsilon^* = -0.2$, which agrees with the previous simulation results.^[30]

The free energy difference $\Delta F (= F_{cis} - F_{trans}) = 0$ at $\varepsilon = \varepsilon^*$ since the chaperone attraction offsets the volume exclusion. In addition to relationship $\Delta F \sim \Delta c \times (\varepsilon - \varepsilon^*)$ found in the inset of Fig. 3, we observe that $\Delta F \sim \Delta c \times (\varepsilon - \varepsilon^*)$ as depicted in the inset of Fig. 7(a). As a result, similar to the relationship between the translocation time and the chaperone concentration, as shown in Fig. 3, we find a powerful relationship as $\ln(\tau) \sim -\Delta c \times (\varepsilon - \varepsilon^*)$ at small value of $\Delta c \times (\varepsilon - \varepsilon^*)$ and an inverse proportion relationship as $\tau \sim [\Delta c \times (\varepsilon - \varepsilon^*)]^{-1}$ at large $\Delta c \times (\varepsilon - \varepsilon^*)$, which are shown in Fig. 7(a).

We further investigate the effects of the chaperone-polymer interaction difference between at the *cis* side and the *trans* side, $\Delta\varepsilon = \varepsilon_c - \varepsilon_t$, on the polymer translocation. To emphasize the $\Delta\varepsilon$ -induced effects, we set the chaperone concentrations at the two sides to be the same, as $c_c = c_t$. If $\Delta\varepsilon < 0$, as the free energy of the polymer at the *cis* side is smaller than that at the *trans* side ($\Delta F < 0$), the polymer translocation is hindered; while if $\Delta\varepsilon > 0$, the positive value of the free energy difference can facilitate the translocation. Therefore, the

translocation time τ decreases as $\Delta\varepsilon$ increases (see Fig. 7b). Additionally, we find that there is a proportional relationship between the free energy difference ΔF and the interaction difference $\Delta\varepsilon$, as shown in the inset of the Fig. 7(a). As a result, for the translocation time τ , a powerful relationship $\ln(\tau) \sim -\Delta\varepsilon$ and an inversely proportional relationship $\tau \sim \Delta\varepsilon^{-1}$ can be observed at small and large $\Delta\varepsilon$, respectively.

Effects of Diffusion Coefficient on the Translocation Time

According to the analyses based on the free energy landscapes (Fig. 5), it seems that the attractive chaperones at the *trans* side can effectively accelerate the polymer translocation, even at strong chaperone-polymer attraction ($\varepsilon_t < 0$). However, two independent simulation studies^[27,30] suggested different results. Specifically, the simulation results showed that the translocation time decreases at first and then increases with the increase of chaperone-polymer attraction (*i.e.*, decrease in ε_t at $\varepsilon_t < 0$). This non-monotonic behavior of the translocation time cannot be observed in our calculation results (Fig. 7) as the aforementioned calculations are based on an assumption of the diffusion coefficient fixed as a constant as $D_0 = 1$ (Eq. 7). In fact, the diffusion coefficient should be dependent on the chaperone concentration and interaction.^[48] In order to achieve a clearer view of the polymer translocation, we will take the chaperone-dependent diffusion coefficient D_0 into account when we calculate the translocation time. The data of diffusion coefficient at different conditions are obtained from the reference.^[48]

In order to make the translocation environment comparable with the diffusion environment, here we set $c_c = c_t$ and $\varepsilon_c = \varepsilon_t$. Under the circumstances, if the change in D_0 is ignored, the translocation time almost keeps constant as depicted in Fig. 6. This phenomenon can still be observed at weak chaperone-polymer attraction when the chaperone-dependent D_0 is taken into account (Fig. 8), as the diffusion coefficient is nearly unchanged. However, with the increase of the attraction, the polymer can be easily trapped by the chaperones, leading to a small D_0 . Consequently, the translocation time increases rapidly with the increase of the attraction, which agrees with the simulation results.^[27,30] Moreover, we also

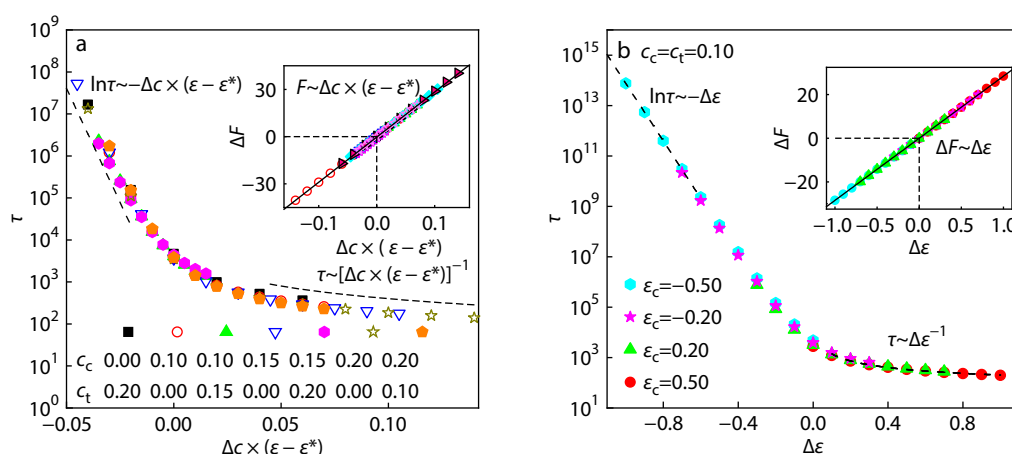


Fig. 7 (a) The dependence of translocation time on interaction difference $\Delta\varepsilon$ ($\Delta\varepsilon = \varepsilon_c - \varepsilon_t$), the inset shows the relationship between chemical potential ΔF and interaction difference $\Delta\varepsilon$; (b) The dependence of translocation time on $\Delta c \times (\varepsilon - \varepsilon^*)$, the inset shows the relationship between chemical potential ΔF and $\Delta c \times (\varepsilon - \varepsilon^*)$.

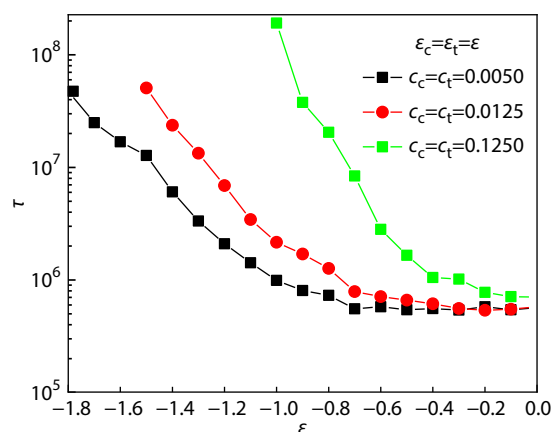


Fig. 8 Dependence of translocation time τ on the attractive chaperone-polymer interaction ε by taking the change of diffusion coefficient D_0 into account. The data of D_0 are obtained from the Fig. 1 in reference.^[48]

find that the chaperone concentration will affect the translocation time. For a given chaperone-polymer attraction, the more chaperones are in the translocation environment, the higher probability of the polymer can be trapped, leading to a larger translocation time.

CONCLUSIONS

In this work, the translocation of polymer chain worming through a nanopore in crowded environment has been discussed. Rosenbluth-Rosenbluth method has been applied to calculate the conformation number of polymer chain. The free energy landscapes for the polymer chain from *cis* side to *trans* side are discussed under different chaperone concentrations and chaperone-polymer interaction. Based on the obtained free energy landscapes, the translocation time can be estimated from the Fokker-Plank equation.

The effects of the chaperones on the polymer translocation can be classified into three types, the negative effect which hinders the translocation, the positive effect which accelerates the translocation, and the neutral effect between the negative and positive effects. The effect types of the chaperones are decided by the free energy difference $\Delta F (= F_{cis} - F_{trans})$,^[49] which can be controlled by the chaperone concentration difference $\Delta c (= c_c - c_t)$ and the chaperone-polymer interaction difference $\Delta \varepsilon (= \varepsilon_c - \varepsilon_t)$. Specially, when $\Delta F < 0$, which can be induced by $\Delta c < 0$ at $\Delta \varepsilon = 0$ or $\Delta \varepsilon < 0$ at $\Delta c = 0$, the higher free energy for the polymer at the *trans* side can hinder the translocation process, leading to a long translocation time; while $\Delta F > 0$, the higher free energy at the *cis* side can speed up the translocation time. In addition, we also find a critical attraction $\varepsilon^* (= -0.2)$ at which the effects of the attraction and volume exclusion from the chaperones can balance each other. As a result, if $\varepsilon_c = \varepsilon_t = \varepsilon^*$, the free energy difference disappears ($\Delta F = 0$) no matter what the chaperone concentration difference is, leading to the neutral effect of the chaperones.

Based on the previous theoretical analyses,^[49] there are two scaling relationships between the translocation time τ and the free energy difference ΔF , as $\ln(\tau) \sim -\Delta F$ if $\Delta F < 0$ and

$\tau \sim \Delta F^{-1}$ if $\Delta F > 0$. In this work, our calculation results show that ΔF is proportional to Δc (without the chaperone-polymer interaction), $\Delta c \times (\varepsilon - \varepsilon^*)$ (with the same chaperone-polymer interaction at the *cis* and *trans* sides), and $\Delta \varepsilon$ (with the same chaperone concentration at the *cis* and *trans* sides). Therefore, we can observe the scaling relationships as $\ln(\tau) \sim -\Delta c$, $-\Delta c \times (\varepsilon - \varepsilon^*)$, and $-\Delta \varepsilon$ at strong negative effect of the chaperones, and $\tau \sim \Delta c^{-1}$, $[\Delta c \times (\varepsilon - \varepsilon^*)]^{-1}$, and $\Delta \varepsilon^{-1}$ at strong positive effect of the chaperones.

Furthermore, our calculation results suggest that a more accurate relationship between the translocation time and the crowded environment should account for the effects of the chaperones on the diffusion coefficient of the polymer. However, to our best knowledge, achieving a precise description of the diffusion coefficient is still challenging. In our future study, we will add the change of diffusion coefficient into the relationships found in this study.

Conflict of Interests

The authors declare no interest conflict.

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