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Direct prediction of HP sequences of compact polymer chains from elastic force

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Abstract

In this paper, a new method is proposed to predict HP sequences of compact polymer chains from elastic force based on the PERM (pruned-enriched-Rosenbluth method) simulation. Two different HP sequences are selected here, and we let them pass through a nanopore after acting of elastic force, which only allow single but not double strands to pass. Some thermodynamics properties of compact polymer chains are investigated during the translocation process, such as average Helmholtz free energy $\langle A \rangle$, average energy per bond $\langle U \rangle$, and average contact energy per bond $\langle U_c \rangle$. We find that the curves of them change non-monotonously with different steps, which inversely can be used to distinguish H and P accurately. The most important parameter of them is elastic force f because it can be measured directly using single-molecule force spectroscopy (SMFS) in experiment. Through recording and comparing force-extension curves, we can determine the HP sequences accurately. This method is also applied to determine DNA sequence directly, and to study the contact interactions in proteins and the protein folding.

Keywords: PERM; Nanopore; HP sequence

1. Introduction

There are a series of recent experiments and theories to study the translocation of DNA, RNA molecules and proteins through narrow pores, which allow single but not double strands to pass [1–10]. Actually, biopolymers translocation across a nanopore or into membranes is ubiquitous in biosystems. Examples include the viral injection of DNA into a host, the invasion of RNA viruses into healthy cell [11], the translocation of RNAs across a nuclear membrane after their synthesis [12], the incorporation of membrane proteins into lipid bilayers [13], and the electric-field-induced migration of DNA through an α-hemolysin protein channel in membrane [7,8]. There are similar macromolecular transport mechanism such as drug delivery and gene therapy [14] in biotechnology where it is fundamental to understand how DNAs can be incorporated into cell. Understanding of the behavior of biopolymers during the translocation process will make us better to explain varieties of biological phenomenon and we can use it in practice to serve us, for example, if we know the whole process of RNA viruses transport into healthy cell, we can try to prevent the translocation process and the advent of the disease.

Recently, experiments are motivated by the possibility to read off the sequence of a DNA or RNA by making it pass through a pore [7–10,15–17]. In the experiment, α-hemolysin and a membrane protein were used as the pore, if the pore is small enough that allows only single but not double strands to pass then it can be used as a single-molecule tool, the significance of which is that single-molecule force spectroscopy (SMFS) [18] based on atomic force microscopy (AFM) [19] is becoming a useful tool to study intermolecular and intra-molecular interactions with its extremely high force sensitivity. In contrast, many theoretical studies have shed light on the dynamics of the translocation process [2–6], until very recently [1], Gerland et al. used the pore to unzip basepaired regions in polynucleotide during the translocation process. Actually, the pore plays a very important role in the translocation of structured polymers, as schematically depicted in Fig. 1. In Fig. 1, two processes of unzipping the contacts in a compact polymer are very different, for example, by pulling on its ends we cannot judge the sequence of contact unzipping, but by passing through a pore the contacts will unfold in a linear order along the sequence.

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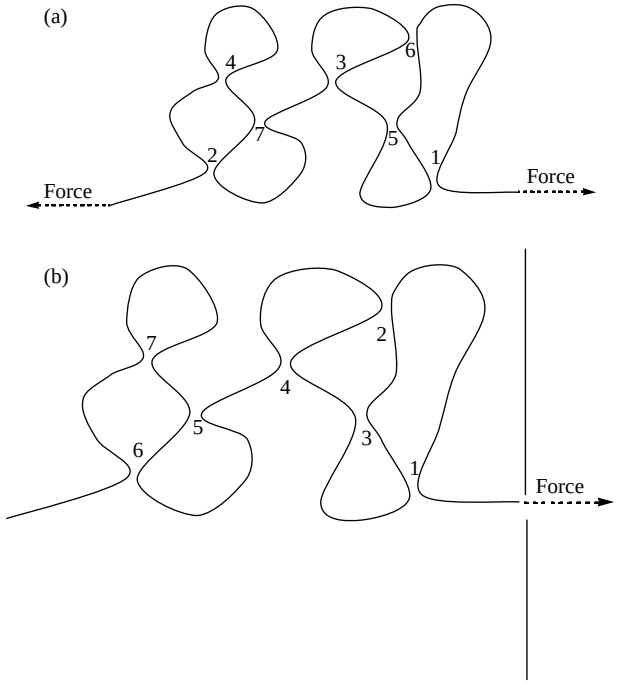

Fig. 1. Two different behaviors of compact polymer chain by pulling on its two ends and by driving it through a nanopore. (a) For pulling on its two ends, the contacts of the chain unzip in an order according to their relative stability and the interior structure, a possible unzipping order 1–7 is indicated. (b) In contrast, the nanopore forces the contacts to unfold along the sequence of the chain, and the order of 1–7 is indicated.

According to this model, here we will discuss something about reading off the HP sequence of compact polymer chain from pulling compact polymer chains through nanopore. By acting a force on compact polymer chain for the translocation and recording force spectrum achieved by AFM, we can determine the HP sequence of compact polymer chains accurately. Of course, this prediction of the HP sequence is now made in theory not in experiments.

2. Model of simulation

In order to simulate the translocation process, we consider a compact polymer chain on cubic lattice, and the chain is adsorbed on the surface near the nanopore and then it is pulled through the nanopore, which is depicted schematically in Fig. 2. Of course, the chains may be away from the surface if the interactions between monomers and attractive surface are weak. In this paper we use the HP lattice model that was proposed by Dill and his cooperators [20,21], and in this model, 20 different amino acids in real proteins are simply divided into two types of amino acids according to the interactions between amino acids and water, i.e. hydrophobic (H) and hydrophilic (P). In the HP model, there is a strong mutual pair-wise attraction between H monomers, and the H monomers can form strong contacts while H–P and P–P monomers can not form any contact, and generally, the values can be employed $\varepsilon_{HP}=\varepsilon_{PP}=0$, $\varepsilon_{HH}=-1$ (in the unit of k_BT) [21–23]. In this paper, we suppose the adsorption surface is hydrophobic, i.e. only the H monomers have adsorption interaction with the surface, which could be done in experiment [24]. With the purpose of discriminating H and P according to the force spectrum we employ the adsorption energy of H and P as $\varepsilon_H=-3$ and $\varepsilon_P=0$, respectively. The Hamiltonian of compact polymer chain system with adsorption interaction can be defined as:

$$E=\sum_{i<j}\varepsilon_{ij}\Delta(r_i-r_j)+V \tag{1}$$

here ε_{ij} is the contact energy between monomers i and j, and $\varepsilon_{HP}=\varepsilon_{PP}=0$, $\varepsilon_{HH}=-1$ [21–23]. $\Delta(r_i-r_j)=1$ if r_i and r_j are adjoining lattice sites with i and j not adjacent along the chain, while $\Delta(r_i-r_j)=0$ otherwise[23]. Compact polymer chain is an important conformation because it is the principal configurations of globular proteins. In the meantime, the additional item V in Eq. (1) represents the adsorption interaction, which is defined as:

$$V=\begin{cases}\varepsilon_H & \text{for H monomers on the surface}\\ 0 & \text{otherwise}\end{cases} \tag{2}$$

In this paper, the pruned-enriched-Rosenbluth method (PERM) [25] is adopted to calculate the thermodynamic properties of compact chains on cubic lattice. Grassberger had used this algorithm to simulate flexible chains and their results can illustrate that this method is the most efficient for three-dimensional polymers on the simple-cubic lattice. In our model, the first monomer of compact chain will start at the continuous lattice position along x-axis, i.e. along the pore direction that is vertical to the surface, as shown in Fig. 2, and the chain is pulled at different position a and a', respectively. If the pulling force is strong enough, the shape of the polymer can be stretched completely [2]. Under this condition, the part of polymer chain that has been pulled through the nanopore is quite stretched, like a directed random walk. According to Kantor's model [2], we suppose the part of compact chain that has been pulled through the nanopore cannot form contacts,

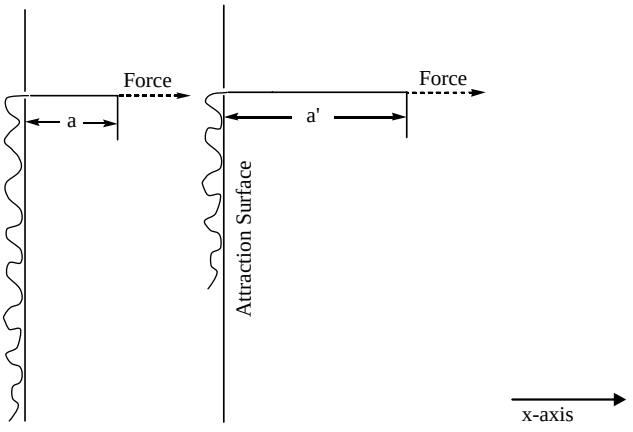

Fig. 2. A HP compact polymer chain adsorbed on the surface is derived through a nanopore by force. Here we suppose that only the H monomers have absorption interaction with the attractive surface, i.e. the surface is hydrophilic, and the adsorption energy of H and P monomers between the monomers and the surface is $\varepsilon_H=\varepsilon_{att}=-3$ and $\varepsilon_P=0$, respectively.

and it has not contribution to the partition function of the whole system. The partition function of the system is

$$Z = \sum_i \exp\left(\frac{-E_i}{k_B T}\right) \tag{3}$$

here $\sum_i$ is the sum of all conformations with first monomer fixed at the position a, and E_i is the total energy of the compact polymer chain of i-th conformation, which is given according to Eq. (1). It is well known that the partition function is widely used to study the thermodynamic properties. Since the number of conformations is very large for long compact polymer chains, it is very difficult to calculate the partition function by the enumeration calculation method. Therefore, the pruned-enriched-Rosenbluth method (PERM) [25] is adopted here instead of the enumeration calculation method, and we can investigate some statistical properties of compact polymer chains in more detail.

The average free energy of the system can be derived from the partition function:

$$\langle A \rangle = -k_B T \ln Z \tag{4}$$

This parameter is discussed in more detail in our previous work [26–29] and it can supply important thermodynamic information for compact chains. Meanwhile, elastic force f can be obtained from the dependence of $\langle A \rangle$ on the elongated distance along the force direction [26–29], i.e.

$$f = \frac{\partial \langle A \rangle}{\partial a} \tag{5}$$

At the same time, energy contribution to the elastic force f_u is defined as:

$$f_u = \frac{\partial \langle U \rangle}{\partial a} \tag{6}$$

In fact, elastic behaviors of general polymer chains have been investigated for a long time [30,31], and elastic behavior of adsorbed polymer chains may be different from general chains [32]. However, here we focus on reading off the HP sequence of compact polymer chains by elastic force. As we know that the elastic force of polymer chains can be measured by single-molecule force spectroscopy (SMFS) based on atomic force microscope (AFM), so we can use SMFS to record the force spectrum of compact polymer chains in experiment. If we can find the relationship between elastic force and the HP sequence, we therefore can determine HP sequence accurately. In fact, in this paper, we find that there does exist this relationship between force spectrum and HP sequence.

3. Results and discussion

3.1. HP sequence prediction from force spectrum

The Helmholtz free energy of compact polymer chains is investigated during the translocation process. When the chain is pulled through a nanopore, the conformations change, and this leads the Helmholtz free energy to change. In Fig. 3, we plot average Helmholtz free energy as a function of a for compact chains with two different HP sequences during the translocation process. The two HP compact chains both contain 64 HP monomers with different sequences, and they all contain 22 P monomers and 42 H monomers, respectively. In fact, these 2 HP sequences are selected at random and they are HHHHHHHHHHHHPHPHPPHHPPHHPPHPPHHPPHHPP-HPPHHPPHHPPHPHPHHHHHHHHHHHH and HHPPHH HHHPHHHHPHHPHHPHHPHPHHHPHPHPHHHHPHHHP-HHHPPHHHHPHPHPPHPHPPH. At the beginning of the translocation process, the chains are adsorbed on the surface near the nanopore, and the average Helmholtz free energy are −157.4 and −157.9, respectively, then the chain is pulled slowly along x-axis, after pulling 50 monomers through the pore, the average Helmholtz free energy become −41.8 and −28.9, respectively. During the translocation process we find that the average Helmholtz free energy increases non-monotonously, and the curves contain some steps, i.e. when there is a P monomer or some continuous P monomers passing through the nanopore, a step is formed, which means that the average Helmholtz free energy changes a little temporarily. The reason is that P monomers have no adsorption interaction with the surface and cannot form any contact, so when P monomers leave from the surface and pass through the nanopore, the average Helmholtz free energy will change a little. If the chains only contain H monomers, the curves would change monotonously in a straight line, while the curves are semi-parallel with x-axis for P monomer chains. From Fig. 3 we know the steps are semi-parallel with x-axis and the length of them are proportional to the number of P monomers, and we can get a conclusion from the curves that along x-axis for each step the first monomer is P monomer and the last one is H, while the monomers between them are all P monomers. Actually, the important one hidden in the curves is that we can use the curves to read off the HP sequence of compact chains accurately, i.e. if we want to predict the sequence of an

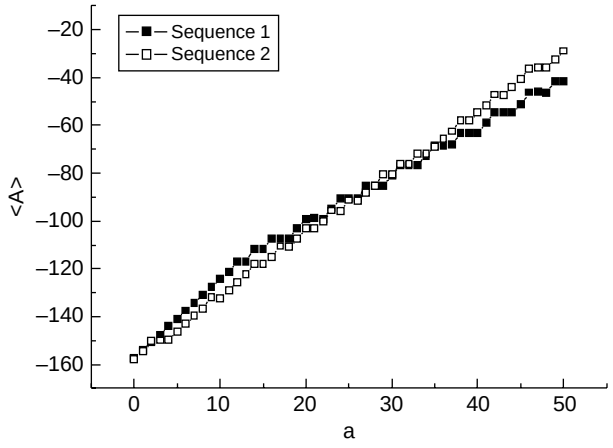

Fig. 3. Average Helmholtz free energy $\langle A \rangle$ as a function of a during the translocation process. Sequence 1: HHHHHHHHHHHHPHPHPPHHPP HHPPHPPHHPPHHPPHPPHHPPHHPPHPHPHHHHHHHHHHHH; and sequence 2: HHPPHHHHHPHHHHPHHPHHPHHPHPHHHPHPHPHHHH PHHHPHHHPPHHHHPHPHPPHPHPPH.

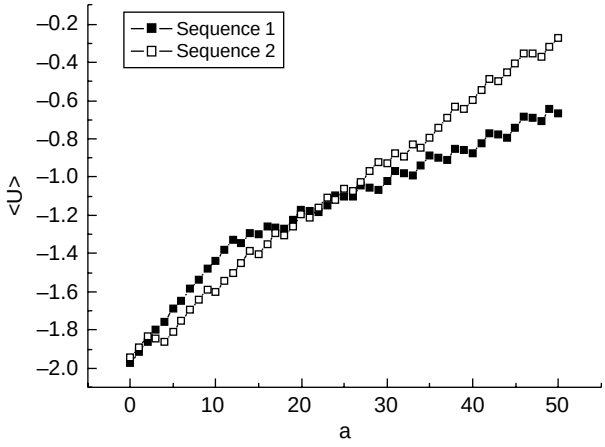

Fig. 4. Average energy per bond $\langle U \rangle$ as a function of a during the translocation process. Sequence 1: HHHHHHHHHHHHPHPHPPHHPPHHPPHPPHHPPHHPPHPPHHPPHPHPHHHHHHHHHHHH; and sequence 2: HHPPHHHHHPHHHHPHHPHHPHHPHPHHHPHPHPHHHHPHHHPHHHPPHHHHPHPHPPHPHPPH.

unknown HP compact chain, we can use this method to calculate the average Helmholtz free energy during the translocation process and then obtain the sequence directly from the corresponding figures. Of course, the average Helmholtz free energy cannot be measured directly in experiment. However, in fact, HP sequence of compact polymer chains cannot be determined directly through comparing the average Helmholtz free energy because we can determine them directly in experiments. This problem will be discussed in more detail through calculating elastic force of compact polymer chains.

Average total energy per bond $\langle U \rangle$ of compact polymer chain is also investigated, and the results are shown in Fig. 4, which change similarly to average Helmholtz free energy in Fig. 3. Average total energy per bond is defined as $\langle U \rangle = \langle E \rangle / (N-1)$, here $\langle E \rangle$ is given in Eq. (1), and N is the total number of monomers ($N=64$ in this paper). At the beginning of the translocation process, the chains are adsorbed on the surface and the average energy per bond of compact polymer chains with two HP sequences are -1.97 and -1.95, respectively. When the chains are pulled through the nanopore, the average energy per bond both increases non-monotonously with a increasing, and after pulling 50 monomers through the nanopore, the values become -0.67 and -0.27, respectively. During the pulling process, P monomers also produce steps which are different from the steps in Fig. 3, i.e. the steps are not parallel with x-axis anymore and all of them are tilted, which means when P monomers pass through the nanopore, the average energy per bond changes a little more and it comes from the change of the structure of compact chains, while the Helmholtz free energy belongs to the whole chain system and the values are much larger than the average energy per bond so the difference in Fig. 3 is not obvious. After the H monomers passing through the nanopore, the contacts between H monomers are unzipped, meanwhile, the adsorption interaction of H monomers disappears when they leave the surface, and the average energy per bond increases. The part of chains passed through the nanopore is in a straight line along x-axis and cannot form contacts anymore. Therefore, we can also read off the chain sequence from Fig. 4.

The contact energy of compact polymer chains for two HP sequences is different at the beginning of the translocation process, and the values are -0.204 and -0.180, respectively. Fig. 5 describes the average contact energy per bond $\langle U_c \rangle$ as a function of a during the translocation process for compact polymer chains. In this paper, contacts only exist between H monomers, therefore, when H monomers pass through the nanopore, the corresponding contacts will be unzipped, and this leads average contact energy to decrease. For example, the average contact energy per bond with $a=12$ is greater than that with $a=13$ for sequence 1 because there is P monomer for 13-th monomer and H for 14-th monomer in sequence 1. In Fig. 5, the average contact energy per bond increases with a increasing as a whole but locally decreases at some HP orders because when H monomers passed through the nanopore, the corresponding contacts are unzipped, and the decrease of contacts number results in the increase of contact energy. In fact, if the chain only contains H monomers, the average number of contact per monomer can be expressed as $C \sim ((N-1)/2)b$ [33], here b is the average number of contact between i monomer and j monomer and N is the number of monomers, so the average number of contact per bond will decrease monotonously with the decrease of a. Meanwhile, the average contact energy per bond will increase monotonously, this can be seen clearly in Fig. 5 for sequence 1 from $a=0$ to 10. Since there are many P monomers in sequence 1 from $a=$ 10 to 50, the average contact energy per bond does not increase monotonously anymore, and there some local decrease for some HP orders. We can also read off the HP sequence of compact chains according to $\langle U_c \rangle$. However, $\langle U_c \rangle$ cannot be determined directly in experiments, thus we cannot also obtain HP sequence directly by comparing $\langle U_c \rangle$. The average attractive energy per bond $\langle U_a \rangle$ is very similar to the average contact energy per bond and the results are given in Fig. 6.

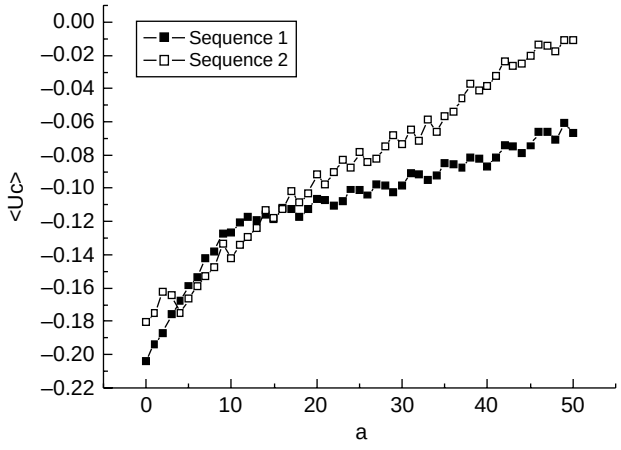

Fig. 5. Average contact energy per bond $\langle U_c \rangle$ as a function of a during the translocation process. Sequence 1: HHHHHHHHHHHHPHPHPPHHPPHHPPHPPHHPPHHPPHPPHHPPHPHPHHHHHHHHHHHH; and sequence 2: HHPPHHHHHPHHHHPHHPHHPHHPHPHHHPHPHPHHHHPHHHPHHHPPHHHHPHPHPPHPHPPH.

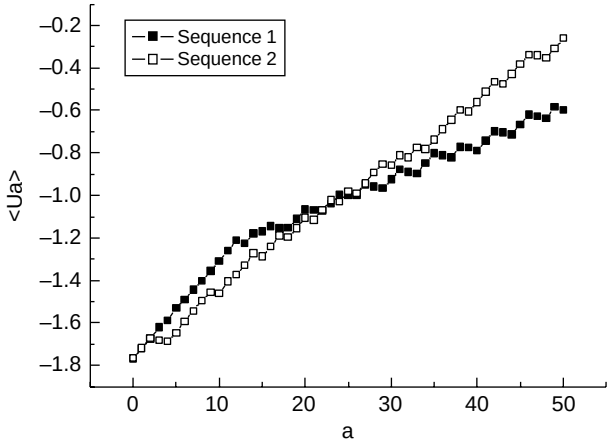

Fig. 6. Average attractive energy per bond $\langle U_a \rangle$ as a function of a during the translocation process. Sequence 1: HHHHHHHHHHHHHPHPHPPHHPPHHPPHPPHHPPHHPPHPPHHPPHHPPHPHPHHHHHHHHHHHH; and sequence 2: HHPPHHHHHPHHHHPHHPHHPHHPHPHHHPHPHPHHHHPHHHPHHHPPHHHHPHPHPPHPHPPH.

Average attractive energy per bond is defined as $\langle U_a \rangle = \langle V \rangle / (N-1)$, here $\langle V \rangle$ is given in Eq. (1), and N is the total number of monomers ($N=64$ in this paper). As the adsorption interaction ($\varepsilon_H = -3$) is stronger than the contact attraction ($\varepsilon_C = -1$), the adsorption interaction is the dominate contribution to the whole energy. The average attractive energies per bond are -1.768 and -1.766 at the beginning, and become -0.599 and -0.260, respectively, for sequences 1 and 2 after 50 monomers passing through the nanopore.

We calculate the elastic force f according to Eq. (5) and plot as a function of a during the translocation process in Fig. 7. Actually, this parameter is very important because it can be measured directly by atomic force microscope in experiment. In the meantime, because there exist H–H contact interactions between H monomers and strong adsorption interactions between H monomers and the surface, it needs much larger elastic force to pull H monomers through the nanopore than to pull P monomers. In Fig. 7, the average elastic force per bond for the two chains is close to zero when P monomers passing through the nanopore while the value is greater than 0.044 when H monomers passing through the nanopore. For example, from the average elastic force for the two chains with $a=0$–14, we can obtain the part of sequence is HHHHHHHHHHHHPHP in Fig. 7(a) and HHPPHHHHHPHHHHP in Fig. 7(b), respectively, which is in good agreement with the given HP sequence. As the force spectrum can be recorded by atomic force microscope (AFM) in experiments, we can read off the HP sequence of compact polymer chains easily and accurately. Our method can be applied to determine DNA sequence or RNA sequence. On the other hand, the elastic force may have some relationships with some conformational properties, so we can also investigate the conformational properties directly by studying the force spectrum recorded by AFM in experiments. The energy contribution to elastic force per bond is also calculated according to Eq. (6) and the results are also shown in Fig. 8. The value of f_u is similar to f in Fig. 7, and it is close to -0.05 when H monomer passing through the nanopore and close to 0.01 when P monomer passing through the nanopore. We can also determine which is H monomer or P monomer easily according to the value of f_u in theory although the energy contribution to force per bond f_u cannot be measured directly in experiment.

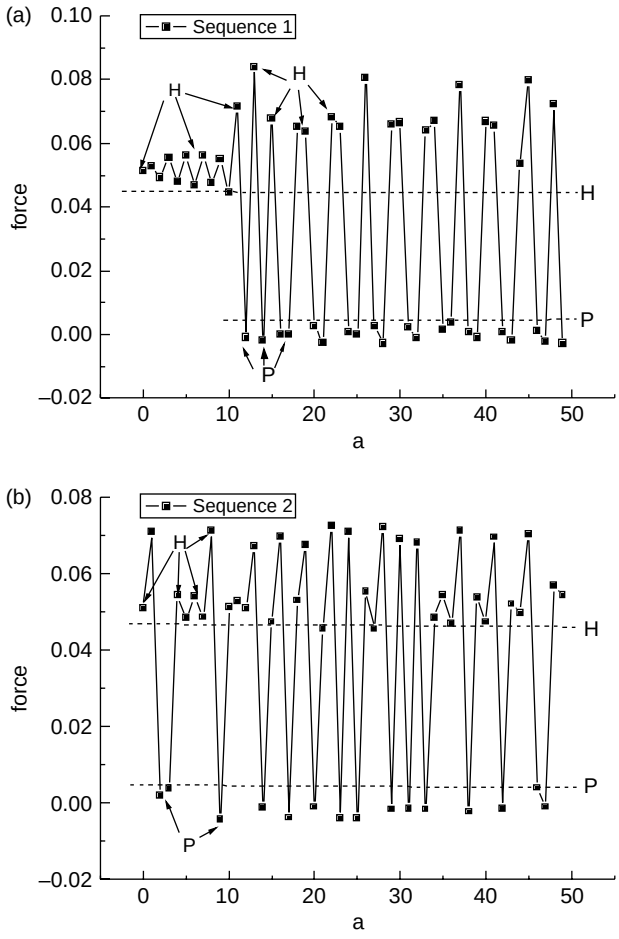

Fig. 7. Elastic force per bond f as a function of a during the translocation process. (a): sequence 1: HHHHHHHHHHHHHPHPHPPHHPPHHPPHPPHHPPHHPPHPPHHPPHHPPHPHPHHHHHHHHHHHH; and (b): sequence 2: HHPPHHHHHPHHHHPHHPHHPHHPHPHHHPHPHPHHHHPHHHPHHHPPHHHHPHPHPPHPHPPH.

Here some thermodynamic properties of compact polymer chains are investigated during the translocation process with the purpose of prediction the HP sequence according to these parameters. The average Helmholtz free energy increases non-monotonously during this process. Here the most important parameter is the elastic force f because it can be measured directly in experiment. Through comparing different force spectrum, we can predict the HP sequence accurately.

3.2. The shape of compact polymer chains

The radius of gyration tensor S can be defined as:

$$S = \frac{1}{N+1}\sum_{i=0}^{N} S_i S_i^T = \begin{pmatrix} S_{xx} & S_{xy} & S_{xz} \\ S_{yx} & S_{yy} & S_{yz} \\ S_{zx} & S_{zy} & S_{zz} \end{pmatrix} \quad (7)$$

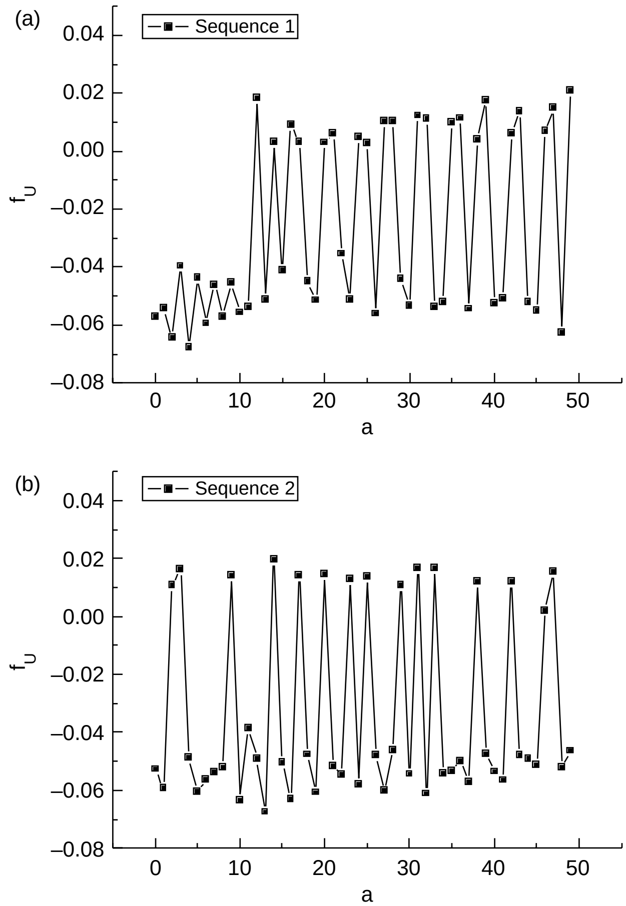

Fig. 8. Energy contribution to force per bond f_u as a function of a during the translocation process.(a) sequence 1: HHHHHHHHHHHHPHPHPPHHP PHHPPHPPHHPPHHPPHPPHHPPHHPPHPHPHHHHHHHHHHHHH; and (b): sequence 2: HHPPHHHHHPHHHHPHHPHHPHHPHPHHHHPHPHP HHHHPHHHPHHHPPHHHHHPHPHPPHPHPPH.

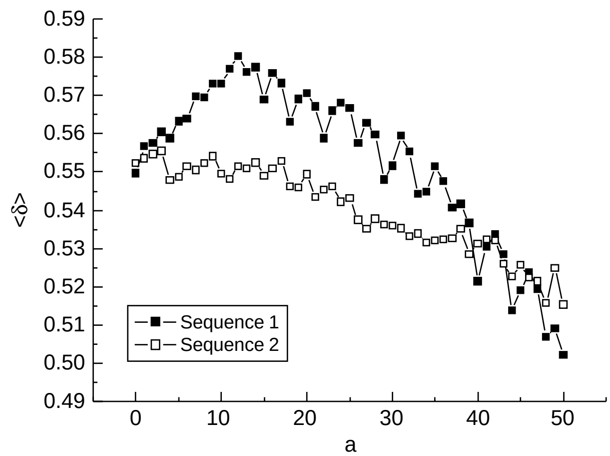

Fig. 9. $\langle\delta\rangle$ as a function of a during the translocation process. Sequence 1: HHHHHHHHHHHHPHPHPPHHPPHHPPHPPHHPPHHPPHPPHHPPHPPHHPPHHPP-HPHPHHHHHHHHHHHHH; and sequence 2: HHPPHHHHHPHHHHPHHP HHPHHPHPHHHHPHPHPHHHHPHHHPHHHPPHHHHPHPHPPHPHPPH.

Here $S_i = \mathrm{col}(x_i, y_i, z_i)$ is the position of monomer i in a frame of reference with its origin at the center of a chain. The tensor S can be diagonalized to be a diagonal matrix with three eigenvalues L_1^2, L_2^2 and L_3^2 ($L_1^2 \le L_2^2 \le L_3^2$). Actually, Solc and Stockmayer had used these parameters to measure the shape of flexible polymer chains [34,35], and they estimated the ratio $\langle L_1^2\rangle : \langle L_2^2\rangle : \langle L_3^2\rangle$ to be 1:2.7:11.7 based on a random walk of 100 bonds on a simple cubic lattice using Monte Carlo (MC) technique. According to the three eigenvalues from Eq. (7), another important parameter [36,37] of the shape of compact polymer chains can be obtained by combining the reduced components to a single quantity that varies between 0 (sphere) and 1 (rod), and it is defined as:

$$\langle\delta\rangle = 1 - 3\left\langle \frac{L_1^2L_2^2 + L_2^2L_3^2 + L_1^2L_3^2}{(L_1^2 + L_2^2 + L_3^2)^2} \right\rangle \tag{8}$$

In general, mean-square end-to-end distance $\langle R^2\rangle$ and mean-square radius of gyration $\langle R^2\rangle$ are important parameters to illuminate the dimensions of compact polymer chains, but in this paper as the part of chains pulled through the nanopore are in a straight line and cannot form contacts anymore, therefore $\langle R^2\rangle$ and $\langle S^2\rangle$ become meaningless, as well as, our major purpose is to predict the HP sequence of the chains according to the force spectrum. So here we only consider the shape factor $\langle\delta\rangle$ and it as a function of a during the translocation process is shown in Fig. 9. As we all know, the value of $\langle\delta\rangle$ for general compact polymer should be zero because it is a completely sphere and generally, the $\langle\delta\rangle$ will be asphericity [38]. For example, when compact polymer chains are adsorbed on the attractive surface, they will be compressed by the surface and their shapes are not sphere anymore, and at the beginning of the translocation process, the chains are adsorbed on the surface near the nanopore and the values of $\langle\delta\rangle$ are 0.549 and 0.552 ($a=0$). As the chains are pulled through the nanopore, the value of $\langle\delta\rangle$ decreases gradually, and it becomes 0.502 and 0.515, respectively, after 50-monomer passing through the nanopore. However, we can see from Fig. 9, for sequence 1 the values of $\langle\delta\rangle$ increase monotonously from $a=0$ to 10, and then the values decrease as a whole but locally increase just as the whole change of sequence 2. From $a=0$ to 10 there are all H monomers for sequence 1, so the values of $\langle\delta\rangle$ will change steadily, while there some P monomers in sequence 2 from $a=0$ to 10, so the values will change wavily. In fact, after 50-monomer pulling through the nanopore, it is in a straight line and the rest parts of the chains are also adsorbed on the surface near the pore.

In this paper we perform the pruned-enriched-Rosenbluth method (PERM), to study the translocation process of three-dimensional adsorbed compact polymer chains. The pore here is used as a tool to unzip the contacts in the chains, and we mainly investigate some thermodynamic properties of compact polymer chains in order to predict the sequence of unknown HP chains using these thermodynamic parameters. The most important parameter is the elastic force because this parameter can be measured directly by atomic force microscope (AFM) in experiment. If we can find the relationship between the sequence of unknown HP chain and elastic force in theory,

we therefore can determine the sequence accurately through investigating the force spectrum of the chains recorded by AFM. In a word, our method is also a useful tool to study protein folding both in theory and in experiment. On the other hand, we may use this method to predict unknown DNA sequence. The HP lattice model used in our simulation is very rough. In this model, 20 amino acid residues of proteins are divided into two types, i.e. hydrophobic and hydrophilic, which omits the other differences between these amino acids, and so far in real experiment we can not use this model. However, it is an important model for studying protein conformations and protein folding [21–23,39–44]. Here we propose a feasible idea to predict the sequence of HP chains with the hope of doing it in experiment someday, and it is also expected that this model can be used to predict the sequence of DNA and make it into practice in the future.

Acknowledgements

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