Adsorption vs. folding of a Hydrophobic Chain Protein Model near an Attractive Surface

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Abstract

The folding vs. adsorption behaviour of a coarse-grained off-lattice protein model near an attractive surface is presented within the frame of a Multicanonical Monte Carlo simulations. In the polymer-surface model, the Lennard-Jones potential is assumed as an interaction potential between the effective monomers and the attractive surface. Thermodynamic properties and some structural parameters for the minimum energy conformations are calculated for comparison of the folding and adsorption cases.

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I. INTRODUCTION

Adsorption of polymers on flat surfaces and geometries is a longstanding challenge that draw attention of researcher from different areas and has many applications varying from adhesion [1], pattern recognition [2, 3], biomedical implant modification to protein ligand binding and docking [4–7]. The arrangement of polymers on the surface attracts attention because of it is an onset of electronic circuits in nanotechnological device invention [2, 8, 9]. Therefore, too much theoretical and experimental study focus on how the binding affinity of proteins and polymers affect the adsorption phenomena. In these content, there are many interesting and important problems, which are concerned with the general aspects of the questions how the proteins fold or adsorb on the surface [10]. If we understand the folding vs. adsorption mechanism of a polymer or protein on a flat surface, then it would be possible to engineer desirable biologically active surfaces with specific properties [11].

Surprisingly, the self-assembly of proteins and polymers near a surface is not studied in detail because the length and time scale of relevance largely conflict with experimental techniques and full atom computer simulations. Therefore, the theoretical treatment of the adsorption of polymers and proteins in the framework of a minimalistic coarse-grained protein models in statistical mechanism is a fascinating field that still attract interest [12–14]. Coarse-grained models for polymers or proteins include two monomer types which stand for at the primitive order the amino acids [15–17]. These monomers classified either hydrophobic and polar types which these models are known as hydrophobic-polar (HP) or AB models. The presence of an flat surface strongly affects the polymers or proteins conformational behaviour in the near of the interface [18]. Because in their own right the monomer-monomer attraction is responsible for the collapse and the explicit surface, that is surface-monomer attraction will compete with each other. This competition will results in folding vs. adsorption for polymers near an attractive surface.

In this letter, a minimal theoretical model that presents some base trends of polymer adsorption is studied. In order to analyze thermodynamic properties and some structural parameters of the adsorption of polymer chains near an unstructured, attractive flat surface Multicanonical Monte Carlo simulations are performed. Firstly, the representation proceed by replacing the explicit attractive surface with an implicit potential, Lennard-Jones potential between the monomers and the surface. The objective of this work is to show that with
a simple, minimal model, it is prospective to capture folding vs. adsorption mechanism for the polymer-surface system.

This paper is organized as follows. In Sec.II the minimalistic coarse-grained polymer-surface model and the multicanonical simulation method are given. In Sec.III, the results are presented and the paper is concluded in Sec. IV.

II. THE MODEL

The polymer chain are described by a coarse-grained hydrophobic-polar model. A manifest off-lattice generalisation of the hydrophobic-polar (HP) model \[19\] is the AB model \[20\], where the hydrophobic monomers are labelled by \( A \) and the polar or hydrophilic ones by \( B \). The contact interaction is replaced by a distance-dependent Lennard-Jones type of potential accounting for short-range excluded volume repulsion and long-range interaction, the latter being attractive for \( AA \) and \( BB \) pairs and repulsive for \( AB \) pairs of monomers. An additional interaction accounts for the bending energy of any pair of successive bonds. This model was first applied in two dimensions \[20\] and generalized to three-dimensional AB proteins \[21, 22\], partially with modifications taking implicitly into account additional torsional energy contributions of each bond.

AB model as proposed in Ref. \[20\] with the energy function

\[
E_{AB} = \frac{1}{4} \sum_{k=1}^{N-2} (1 - \cos \vartheta_k) + \\
\frac{4}{4} \sum_{i=1}^{N-2} \sum_{j=i+2}^{N} \left( \frac{1}{r_{ij}^6} - \frac{C_{AB}(\sigma_i, \sigma_j)}{r_{ij}^8} \right),
\]

where the first sum runs over the \((N-2)\) angles \(0 \leq \vartheta_k \leq \pi\) of successive bond vectors. This term is the bending energy and the coupling is “ferromagnetic”, i.e., it costs energy to bend the chain. The second term partially competes with the bending barrier by a potential of Lennard-Jones type depending on the distance between monomers being non-adjacent along the chain. It also accounts for the influence of the AB sequence (\(\sigma_i = A\) for hydrophobic and \(\sigma_i = B\) for hydrophilic monomers) on the energy of a conformation as its long-range
behavior is attractive for pairs of like monomers and repulsive for $AB$ pairs of monomers:

\[
C_{AB}(\sigma_i, \sigma_j) = \begin{cases} 
+1, & \sigma_i, \sigma_j = A, \\
+1/2, & \sigma_i, \sigma_j = B, \\
-1/2, & \sigma_i \neq \sigma_j.
\end{cases}
\]  

(2)

The adsorption of a hydrophobic polymer chain near an attractive surface is simulated using off-lattice AB model. It is considered that a polymer chain is over the surface enough to not to cause reducing the entropic freedom of the polymer. The surface is composed of purely same type of sites that hydrophobic monomers in the polymer chain has an attractive interaction with the surface and additionally with a surface attraction strength parameter ($\epsilon$) the dosage of the attraction is varied. A start configuration to the simulation is presented in Figure 1.

The energy function of the polymer chain is introduced above and the interaction of polymer chain monomers ($m$) and surface ($s$) is given with Lennard-Jones type potential:

\[
E_{ms} = 4 \epsilon \sum_{i=1}^{N_m} \sum_{j=1}^{N_s} \left( \frac{1}{r_{ij}^{12}} - \frac{C_{ms}(\sigma_i, \sigma_j)}{r_{ij}^{6}} \right),
\]  

(3)

where the $N_m$ is the number of monomers and $N_s$ is the number of interaction sites in the surface. The $C_{ms}$ parameter is settled for one between the $AA$ contacts and $\epsilon$ is the surface attraction strength which is varied in the simulation. Then the total energy ($E_T$) of the system will contain pure AB model polymer chain energy and the polymer chain surface interaction energy ($E_T = E_{AB} + E_{ms}$). The initial configuration of the polymer chain is randomly generated where the ends have no contact with the surface. In some theoretical and computational studies the polymer is attached at the surface with one of its ends but this reduces the entropic freedom of the system [9]. However, in many recent experiments of the peptide-metal or peptide semiconductor interfaces the setup is considered by a freely moving polymer in a surface. This enables to polymer conformations to choose folding vs. adsorption behaviours without constraint.

Simulations of this model were performed with Multicanonical Algorithm [23], which the details are given below. The update mechanism for a polymer chain is spherical update which is described in Ref. [24] in detail. The surface position is fixed in the whole simulation. The atomistic detailed plot of the surface is only chosen for better visualization.
III. SIMULATION METHOD

The multicanonical ensemble is based on a probability function in which the different energies are equally probable. However, implementation of the multicanonical algorithm (MUCA) is not straightforward because the density of states $n(E)$ is \textit{a priori} unknown. In practice, one only needs to know the weights $\omega$, 

$$w(E) \sim 1/n(E) = \exp[(E - F_{T(E)})/k_B T(E)],$$

and these weights are calculated in the first stage of simulation process by an iterative procedure in which the temperatures $T(E)$ are built recursively together with the micro-canonical free energies $F_{T(E)}/k_B T(E)$ up to an additive constant. The iterative procedure is followed by a long production run based on the fixed $w$’s where equilibrium configurations are sampled. Re-weighting techniques [25] enable one to obtain Boltzmann averages of various physical variables over a wide range of temperatures.

As pointed out above, calculation of the \textit{a priori} unknown MUCA weights is not trivial, requiring an experienced intervention. For lattice models, this problem was addressed in a sketchy way by Berg and Çelik [23] and later by Berg [26]. An alternative way is to establish an automatic process by incorporating the statistical errors within the recursion procedure.

IV. RESULTS AND DISCUSSIONS

For each $\epsilon$ values ($\epsilon = 0.01, 0.5, 1.0$), after calculating the multicanonical weights $5 \times 10^7$ iteration were performed in production run. In literature, many recent papers [27–31] give only the minimum energy values for different sequences in the frame of this model, but no other aspects of physics are investigated for this effective protein models. The main aim of this study is that by employing a simple coarse-grained hydrophobic-polar model and adding an interaction term to the energy which describes the interaction with the environment, it is indeed possible to identify fundamental characteristics of the physics of protein adsorption. This work can be extend or give the basis of the adsorption process of real proteins.

In Fig 2 a chart of folding vs. adsorption mechanisms are presented visually for the three $\epsilon$ values. At the top of the chart, there is the start conformation of the all different simulations. Afterward the chart goes to three different paths which corresponds to different
surface attraction strengths $\epsilon$. $\epsilon$ parameter and temperature increases from right to left and from bottom to top, respectively. The right column corresponds to $\epsilon = 0.01$, the middle corresponds to $\epsilon = 0.5$ and the left one corresponds to $\epsilon = 1.0$. Beginning with the right column, it is easily verified that when the temperature is decreasing the polymers goes from random coil conformation to collapse one and at the end it is folded to its native structure. There is no contact with the surface in other words no adsorbed conformations can be found. In the middle column, the chain is going very close to the surface but at the same time it is also going to collapse. The existence of a surface strongly affects the polymers conformational behaviour in the interface. Because in their own right the monomer-monomer attraction is responsible for the collapse and the explicit surface, that is surface-monomer attraction will compete with each other. This competition gives rise to different conformational phases. At somewhat high temperatures, two way can be seen in dependence of the competition between monomer-monomer and monomer-surface interactions. In first case, desorbed globule conformation will adsorbed to the surface, in the other case absorbed but random coil state will rearranged and get its adsorbed compact conformation. Finally, if the $\epsilon$ is sufficiently greater (the left column) then the polymer first adsorb to the surface with an expanded conformation and finally to getting a flat two-dimensional conformation.

In order to get an insight about conformational transitions, the specific heats $C_V(T) = \langle E^2 \rangle - \langle E \rangle^2/k_B T^2$ with $\langle E^k \rangle = \sum_E g(E) E^k \exp(-E/k_B T)/\sum_E g(E) \exp(-E/k_B T)$ are calculated by reweighting the multicanonical energy distribution obtained with multicanonical sampling to the canonical distribution. Details are given in Ref. [24]. In Fig 3 the specific heats for the three $\epsilon = 0.01, 0.5, 1.0$ values are given. Firstly interpreting the curves for the specific heats in Fig 3 in terms of conformational transitions, it can be concluded that the specific heat curve for the $\epsilon = 0.01$ exhibits a pronounced peak at $T = 0.25$ which interpreted as the folding temperature. The polymer chain tend to form more compact conformations in this temperature region. It is widely believed and experimentally consolidated that realistic short single domain proteins are usually two-state folders [32]. This means, there is only one folding transition and the protein is either in the folded or an unfolded (or denatured) state. This results is consistent with our previous work [24]. But the specific heat curves for $\epsilon = 0.5, 1.0$ exhibits one pronounced peak at even higher temperature values and one shoulder indicating two transitions in the profile of the specific heat. First one is the adsorption transition separating the desorbed and adsorbed conformations at high tem-
peratures and the second one is same kind of freezing transition which the conformations rearranged and get its compact conformations \[18, 33\]. An explicit demonstration that the polymer is freely moving and going self-folding or is very close to the surface can be elucidate with the distance of the center of mass of the polymer to the flat surface. The average of the center of mass distance to the surface ( \( R_{\text{dis}} \) ) are calculated and presented for the three \( \epsilon \) values in Fig 4. This parameter detects nicely the distinction between adsorption transition and self-folding of the polymer chain near the flat surfaces. As can be seen in Fig 4 for small value of \( \epsilon \), the polymer chain moves freely above the surface and will go to self-folding. Therefore the average value of the \( R_{\text{dis}} \) is approximately constant at all temperature range. On the other hand, at higher \( \epsilon \) values the \( R_{\text{dis}} \) parameter presents a prominent turning points. For \( \epsilon = 0.5 \) this turning point occurs at \( T = 0.85 \) and for \( \epsilon = 1.0 \) at \( T = 1.56 \) which can also detectable from the specific heat peaks in Fig 3.

Finally, in order to check the structural compactness of conformations for the folded case or to identify the possible dispersion of conformations because of adsorption, the radius of gyration and the end-to-end distance parameters of the global-minimum conformations for different \( \epsilon \) values are calculated and given in Table I. For the folded conformation which is the \( \epsilon = 0.01 \) case the radius of gyration and the end-to-end distance parameters are smallest. For higher values of \( \epsilon \) parameters, the end-to-end distances and radius of gyrations are increased because of adsorption to the flat surface.

V. CONCLUSION

In this paper, the adsorption of proteins and peptides within the framework of minimalist effective coarse-grained polymer model is presented. As the adsorption potential, Lennard-Jones type potential, between the effective monomers and the flat surface is assumed. By changing the attraction strength of the flat surface folding vs. adsorption transition are detected and the typical conformations are presented. Despite the simplicity of the model, it is possible to see some basic characteristics of the protein adsorption. The work considered in this paper will promote practical implications for a wide sort of problems ranging from
protein-ligand binding to designing smart sensors.

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FIG. 1: The starting configuration of the simulation. The polymer chain is an randomly start configuration and the surface is fixed in the whole simulation.

TABLE I: The radius of gyration, the end-to-end distance and the average of the center of mass distance parameters for different surface attraction strength values for the global minimum energy conformations.

| $\varepsilon$ | $R_{gy}$ | $D_{ee}$ | $R_{dis}$ |
|--------------|---------|---------|---------|
| 0.01         | 1.23    | 1.55    | 6.61    |
| 0.5          | 1.37    | 2.50    | 1.21    |
| 1.0          | 2.02    | 2.66    | 1.02    |
FIG. 2: The chart of typical conformations for different regions of temperature and surface attraction strength.
FIG. 3: The specific heat as a function of temperature for different values of $\epsilon$ parameter.
FIG. 4: The average of the center of mass distance to the surface as a function of temperature for different values of \( \epsilon \) parameter.