One way to characterize the compact structures of lattice protein model∗

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Abstract

On the study of protein folding, our understanding about the protein structures is limited. In this paper we find one way to characterize the compact structures of lattice protein model. A quantity called Partnum is given to each compact structure. The Partnum is compared with the concept Designability of protein structures emerged recently. It is shown that the highly designable structures have, on average, an atypical number of local degree of freedom. The statistical property of Partnum and its dependence on sequence length is also studied.

1 Introduction

The study of protein folding is fundamental on both theory and application. In order to tackle protein folding problem physically, it is important to pay much attention to concrete proteins and consider the details of interactions, such as for medical purpose. But there are also “global views” that should be noticed. For example, The possible configurations of folded proteins are enormous, while that can be observed in living form is rather limited. These protein structures generally can be described as belonging to a limit number of families. In each family, ignoring the details, the proteins possess similar overall conformations, and in many cases the structures show regular forms or approximate symmetry.[1, 2, 3, 4, 5, 6] Another example is that single domain proteins was observed only within a certain range of sequence length: the number of amino acid residues in single domain proteins seldom exceeds 200. Larger proteins usually fold into multi-domains native states.[6]

With the accumulation of knowledge about the structures and functions of proteins, it was found that many proteins of similar structures pursue complete different functions, while proteins with different tertiary structures may perform similar functions. These suggested that to

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understand the protein folding problem physically, one should first get to know the properties of protein structures. Based on the concepts from the physics of spin glass, study shows that to fold efficiently, proteins require a specially shaped energy landscape resembling a funnel. A heteropolymer with a completely random sequence generically possess a rugged energy landscape without a funnel. Goldstein et al. have worked on optimizing energy functions for protein structure prediction. They found that some structures are more optimizable than others, i.e., there exist structures for which the funneled energy landscape can be obtained within a wide range of interaction parameters, while for some other structures the parameters for fast folding are much more restricted. The funneled landscape theory argued that the interactions in the folded structure must act in concert more effectively than expected in the most random cases. Accordingly, compared with most other structures, the superiority of highly optimizable structure should be that its geometric arrangement permit more sequences to reach the concert interaction states.

Other studies on the thermodynamic of lattice protein models also support the above idea. In the lattice HP models, a protein is represented by a self avoiding chain of beads placed on a discrete lattice with two types of beads: the Polar (P) and the Hydrophobic (H). A sequence is specified by a choice of monomer type at each position on the chain \{x_i\}. Where \(x_i\) could be either H- or P-type, and \(i\) is a monomer index. A structure is specified by a set of coordinates for all the monomers \(\{r_i\}\). The energy has the form:

\[
H = \sum_{i<j} E_{x_i,x_j} \Delta(r_i - r_j)
\]

where \(\Delta(r_i - r_j) = 1\) when \(r_i\) and \(r_j\) are adjoining lattice sites while they are not adjacent along the sequence, and \(\Delta(r_i - r_j) = 0\) in other cases. Interaction parameter \(E_{x_i,x_j}\) differ according to the contact type HH, HP, or PP. Given the interaction parameters, it is possible to find out the ground state structure(s) of each sequence. Study shows that structures differ markedly in their tendency to be chosen by sequences as their unique ground states. The number of sequences which choice the structure as unique ground state is called the Designability of this structure. It was argued that only highly designable structures are thermodynamically stable and stable against mutation, and thus can be chosen by nature to fulfill the duty of life.

From above discussion we see that it should be essential to investigate the protein folding problem from structural point of view. To see the problem more clearly, we take square lattice HP model as an example. The total number of the most compact structures of 36 beads chain is 57337. Consider 36 beads homopolymer with interaction parameter \(E_{x_i,x_j} = E_0 < 0\). All the 57337 structures give the same energy when one such homopolymer fold onto each of them. Therefore the folded energy can not be used to distinguish the compact structures from each other. The essential here is that of discrimination, or characterization: give ways to tell how and why structures differ from each other. Nature’s way to break the symmetry is to replace homopolymer with heteropolymer. From this point of view, the success of lattice protein model
is that it help to reveal this secret of nature.

Studies focusing on the properties of protein structures is still lack,[17] in spite of some recent elaborations in this direction.[18, 19, 20] In this article we present one way to break the symmetry, to distinguish the compact structures of lattice model without explicitly considering concrete interaction form. However, since only compact structures are considered here, an loose constraint is actually set on interactions: interactions under which compact structures are preferred as ground energy states. The method gives a number called partition number (Partnum) to each compact structure during a simple process. The Partnums of structures differ strongly, so giving one way to distinguish them from each other.

In the following section we will give the detail of the method, and compare the Partnum with designability. The statistical properties of Partnums are discussed in section II. The last section is for some remarks.

2 The definition and interpretation of Partnum

It is easy to find out all the compact structures of certain chain length with computer.[21] Take 9 beads chain as an example. The search is self avoiding and restricted to the 3×3 square lattice shown in Fig.1(A), and the resulting structures should not be related by rotation or reflection symmetry. As a result, there are only three starting points, (0,0), (0,1) and (1,1), for the search of structures. To find the structures start at (0,0), the first step is to go to (1,0). This is the only choice, because (0,1) is a symmetric point of (1,0). We give all the structures following this step a number $p_1 = \ln(1)$. Now go to the next site. There are two possible choices: (2,0) or (1,1). Since the walk is self avoiding and restricted to the 3×3 lattices, the walk following certain choice may fail to extend to 9 beads length. The choice that will reach to 9 beads length is called acceptable. Suppose that both (2,0) and (1,1) are acceptable. Then each compact structure which will be generated following (0,0) → (1,0) → (2,0) or (0,0) → (1,0) → (1,1) is given a number $ln(1/2)$. Generally speaking, restricting to 3×3 lattice and beginning at a starting point, there are totally 8 steps to finish a self avoiding walk. Each step is given one number according to the following rule: if the $i$-th step has totally $C$ acceptable choices not being symmetrically related, then the step is given a number called partnum of $i$-th step $p_i = \ln(1/C)$. For 2D square lattice, the largest possible choice $C_0$ is 3.

Adding all the 8 numbers and then dividing the sum by 8, we get the Partnum $P_1$. Here the structure is actually oriented. The consideration of oriented walk is reasonable in the case of protein structures, because the native protein structure would become unstable if the sequence is reversed, and also protein in life are produced successively from one end to another. However, if one consider the start and end reversal of the walk as a symmetric operation, then one oriented walk and its reverse together correspond to a structure that is not related with the direction. In the follows, oriented walk and non-oriented structures are used to distinguish the two different ways of viewing structure, and the Partnums corresponding to them are denoted as $P_1$ and $P_2$, respectively. However, when it is no need to distinguish them, simply structure is used and the Partnum is denoted as $P$. For the non-oriented structure, the Partnum can be define as:
\( P_2 = P_1(1) + P_1(2) \), where \( P_1(1) \) is the Partnum of one of two oriented walks and \( P_1(2) \) is that of its reverse.

The Partnums of structures of other chain length can be obtained similarly.

Since the original motivation of developing the Partnums of structures is to account for the difference of Designability of structures, in Fig.2 we give the plot of Designability against Partnum of oriented structures on \( 5 \times 5 \) lattice (the interaction parameters for calculating Designability is the same as used in Ref. [13]). There is not strict correspondence between Designability and Partnum. However the linear fit of the data revealed that Designability tends to increase with the increase of Partnum (see Fig.2). The same thing happens for other sequence length. In the case of \( 6 \times 6 \) lattice, the structure with highest Designability[13, 15] possess the second largest Partnum (\( P_2 \)).

According to Fig.1(B), an oriented walk corresponds to one path from the root to the top leave of the hierarchical tree. The value of Partnum of the structure is determined by the frequency of the path being disturbed by branches. If the path of a walk meet with fewer branches, the Partnum would be larger. This can be compared with the conclusion in Ref. [16]. In Ref. [16] a simple version of HP model of protein is employed. A walk is reduced to a string of 0s and 1s, which represent the surface and core site respectively, as the backbone is traced. Each walk is therefore associated with a point in a high dimensional space. Sequences are represented by strings of their hydrophobicity and thus can be mapped into the same space. It was found that walks far away from other walks in the high dimensional space are highly designable and thermodynamically stable. For this reason, highly designable structures are called *atypical* in Ref. [16]. Here the structures with large Partnum can also be called *atypical* (atypical average local freedom) since these structures correspond to paths on the hierarchical tree with fewer branches.

In an analog to the suggestion that nature selected out only highly designable structures, we assume that there exists a random process which selects out only the structures with the largest Partnum. It is interesting to see what this assumption will result in.

For concise we assume a critical Partnum \( P_c \), so that only a small portion of oriented walks for which \( P_1 > P_c \) can be selected out. Two oriented walks are called \( n \)-level similar if their first \( n - 1 \) steps are along the same path, and they branched at the \( n \)-th steps. Suppose \( s_1 \) is among the structures with the most highest Partnum satisfying \( P_1(s_1) > P_c \). This means that there are few branches along the path of \( s_1 \). As a result, it is difficult to find walks which show high level similarity to \( s_1 \). But if there do exist such walks, these walks should have high possibility to be selected out. For example, if \( s_2 \) is \( N - 1 \) level similar with \( s_1 \), \( N \) being the chain length, then \( P_1(s_2) = P_1(s_1) > P_c \). More generally, let \( n_{12} \) being the similarity level between \( s_2 \) and \( s_1 \). We know that \( P_1(s_2) = P_1(s_1) - (1 - \frac{n_{12}}{N} \ln(C_0)), C_0 = 3 \) being the maximal possible choices per step during the search of structures. According to this expression, the more similar \( s_2 \) is to \( s_1 \), the more possible it is to be selected out.

Assuming that \( s_3 \) is another walks with \( P_1(s_3) > P_c \), but it is dissimilar to \( s_1 \). From above discussion we know that there are two families, all the members of which are selected out. Within each family, the similarity level of two walks is much higher than \( n_{13} \), while any two walks from
different families are dissimilar from each other, and the similarity level is $n_{13}$. We thus come to the conclusion that the selected walks belong to separate families. Walks within each family are similar, while walks belonging to different families are dissimilar.

For the non-oriented structures, there is no the convenience of the hierarchical tree to discuss their properties. But it is believable that the above result be kept once similarity between structures is properly defined. This is the case for the classification of real protein structures, where more or less arbitrary criteria[1, 2, 3, 22, 23, 24, 25] are used to define the similarity between protein structures and to classify structure into families, superfamilies, folds, and so on.

3 The statistical properties of Partnums

Natural single domain proteins exist only within a limit range of sequence length. By both theoretical and numerical studies it is showed in Ref. [26] that the stability of folded sequences against mutation decrease with the increase of chain length. In that follows the dependence of the statistical properties of Partnum on chain length will be discussed. We will show how some structural properties are determined by general statistical principle.

The density distribution of $P_2$ are shown in Fig.4. Things are similar for $P_1$. In both cases, visually the distribution becomes more and more normal. Actually it will be shown that the distribution is Gauss distribution in the long chain limit. As the first step, however, let’s much generally, assume that the Partnums of chain length $N$ can be described by a density distribution function, $F(P, v_1, v_2...)$, $v_i$ being the moment of $i$-th orders. It is easy to get the average $v_1 = \langle P \rangle$ and variance $v_2 = \Delta P$. The results of both oriented walk and non-oriented structures are shown in Fig.3.

Fig.3 shows that $\langle P \rangle$ (both $\langle P_1 \rangle$ and $\langle P_2 \rangle$) decrease with the increase of chain length. However, from the definition of Partnum we know that $\langle P_1 \rangle$ ($\langle P_2 \rangle$) can not be smaller than $-ln3$ $(-2ln3)$. So, for either oriented walks or non-oriented structures, there must exist $\delta$, so that

$$\lim_{N \to \infty} \langle P \rangle = \delta.$$

A similar argument applies to $\Delta P$, where

$$\lim_{N \to \infty} \Delta P = \epsilon, \epsilon \geq 0.$$

It is known that the total number of compact structures $M$ increase exponentially with the increase of chain length $N$: $M(N) \sim (C_{av})^N$, $C_{av} < C_0 = 3$ being the average number possible choices per step for the walks. This gives one way to estimate the value of $C_{av}$ using the knowledge of $M(N)$. Fig.5 show the fit of the data $M(N)$ to $f(N) = (lnC_{av})N + b$. The result is $C_{av} = 1.397$. Viewing this value of $C_{av}$ as the value in long chain limit, we get that $\delta = ln(1/C_{av}) = -0.3343$ for oriented walks, a reasonable estimation (see Fig.3). It should be noticed that $C_{av}$ get this way is much larger that given by mean field consideration,[21, 27] where $C_{av} = C_0/\epsilon = 1.1$. According to this $C_{av}$, $\delta = -0.099$ for non-oriented walks. From Fig.3
we know that this is a value too large to be the long chain limit of $<P_1>$. So it seems that the mean field treatment does not apply to the two dimensional protein model.

With the help of central limit theorem, we can argue that the density distribution is Gaussian distribution in long chain limit, and $\epsilon = 0$. See follows.

In the space of compact structures, the Partnum $P$ of certain structure is the average of the partnums $p_i$ of all the $T$ steps. For oriented walks $T$ equals to the chain length subtracted by 1, and for non-oriented structures this value should be doubled further. Now divide the $T$ partnums into $(T)/n$ groups (suppose $T/n$ is an integer). In each group the $n$ members are chosen randomly within the total $T$ numbers. For each group we define a new random variable $q_k = \sum_i p_i/n$, $k$ being the group index. Since the members in each group are chosen randomly form the total $T$ numbers, the $T/n$ newly defined random variable should have the same average and variance when $n \rightarrow \infty$. At the same time, since $P = \frac{\sum_k q_k}{(T-1)/n}$, applying the central limit theorem,\cite{28} we know that $P$ is a Gaussian random variable, and $\delta P \rightarrow 0$ when $T/n \rightarrow \infty$.

From the above discussion we know that, according to Partnums, statistically all the compact structures become indistinguishable in long chain limit. Recalling the selection rule assumed above, we know that it becomes increasingly difficult to select out atypical structures when chain length increases. These results show some connection to the work of Ejtihadi et al.\cite{20} With a purely geometrical approach, they were able to reduce largely the candidates of structures that can be chosen as the ground states of sequences. They found that for the case of HP protein model the number of ground state candidates grows only as $N^2$, $N$ being the sequence length. While, as pointed out above, the total number of compact structures increase exponentially with the increase of $N$. So it becomes increasingly difficult to find the ground state candidates. This is in accordance with the statistical property of Partnum.

For fulfilling biology functions, proteins should possess some properties, for example fast folding, thermodynamically stable and stable against mutation.\cite{12, 13, 26, 29, 30} It was postulated that with the increase of sequence length, the folded structures become more and more difficult to possess these properties.\cite{26} Based on the study of Partnum, we propose that this property of proteins is determined by the statistical properties of protein structures, the detail of interaction having weak influence.

4 Conclusion Remarks

Protein structures seem to be a very special class among all the possible folded configurations of polypeptide chain. We now know something about how special it is, but little on why it be so. Ways of characterizing folded structures, from whatever point of view, will help to deepen our understanding about protein structures. In this paper, the study on Partnum itself is interesting, and more interesting when compared with the dynamic and thermodynamic study of proteins. The concept of Partnum is simple and can only be applied to lattice model. But the study on it reveals that it is possible to investigate protein structures with no consideration of interaction detail.
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Figure 1: (A): The 3×3 square lattices used to find out all the compact structures of 9 beads chain. The bold curve is an oriented walk start at (0,0) and end at (0,2). The arrows show that instead of walking along the bold curve, one can find other structures in the direction of the arrows. (B): The oriented walks and their branching pattern during the search of them. Note that only some points show branching on the tree. Others are truncated because they can not extend to 9 beads length due to the restriction of lattice size and self avoiding. The number at the right of the figure show the steps of the search.

Figure 2: Points: Designability against Partnum of non-oriented compact structures of chain length 25. Line: the curve of $f(x) = ax + b$ with $a = 488809$ and $b = 300344$. The correlation coefficient is $r = 0.447$, with totally 621 data points.
Figure 3: (A): The dependence of the average of Partnums $< P >$ on chain length. The upper line-points curve is for the oriented walks, and the lower line-points curve is for the non-oriented structures. The upper and lower dotted straight lines $< P > = -0.3343$ and $< P > = -0.6686$ are the estimated long chain limit of $< P1 >$ and $< P2 >$, respectively (see text). (B): The dependence of the variance of Partnums on chain length.
Figure 4: The density distributions of Partnums of non-oriented structures under various chain length. The number “49” in “P2-49”, for example, is the chain length. The distribution curves are shown in step curve style.

Figure 5: Logarithm of the total number of oriented walks versus the chain length. The line is the fit using $\ln M = \ln(C_{av}) \times N + b$, with $C_{av} = 1.3969$ and $b = -0.9489$. The correlation coefficient is $r = 0.99$. 

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