Geometry Selects Highly Designable Structures

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By enumerating all sequences of length 20, we study the designability of structures in a two-dimensional Hydrophobic-Polar (HP) lattice model in a wide range of inter-monomer interaction parameters. We find that although the histogram of designability depends on interaction parameters, the set of highly designable structures is invariant. So in the HP lattice model the High Designability should be a purely geometrical feature. Our results suggest two geometrical properties for highly designable structures, they have maximum number of contacts and unique neighborhood vector representation. Also we show that contribution of perfectly stable sequences in designability of structures plays a major role to make them highly designable.

Proteins are bio-macromolecules, which consist of linear sequences of monomers, the 20 naturally occurring amino acids. Each protein folds to a unique spatial structure as its native state, which is its global minimum of the free energy. This structure specifies the functionality of the protein sequence in the nature.

It has been noted that certain structures are more commonly observed among proteins than others. There are efforts to explain this phenomenon by considering protein structure designability, defined as the number of sequences that would successfully fold in one structure. By definition, highly designable structures (HDSs) have more chance to be found as native, and also they have good stability against sequence mutations. A recent numerical analysis on experimental data revealed that the distribution of observed protein families over different folds can be modeled with a highly stretched exponential. This observation is quite consistent with designability explanation. Highly designable structures might also represent attractive targets for protein design.

In study of designability of native structures like many other features in the field of protein folding, the complexity of the problem forces to use more simplified models. Coarse grained view point to proteins introduce effective inter-monomer interactions as a relevant factor in designability of structures. Analyzing the interaction between the 20 amino acids suggests that amino asides can be separated to Hydrophobic (H) and Polar (P) groups. This introduces a very simple but highly popular two monomer types model, HP model. Although the chains in this simple model are too far from realistic protein and surly could not explain many features of real proteins, but this model had good success in clarifying the concept of designability. The simplicity of this model allows one to study the ground state properties of model proteins by enumerating chains and configurations for short length chains.

Enumerations on two and three dimensional lattice models have shown the existence of a few highly designable structures among many lowly designable ones. Some studies on dynamical properties of those model chains, which fold in the highly designable lattice structures, show that they are more protein-like. Such sequences are thermodynamically more stable and they fold to native state faster than random sequences.

There have been many efforts to find the factors determining the high designability of a structure using simple models. One element is the set of inter-monomer interactions. Some evidences suggest that the set of highly designable structures depends on the number of monomer types in the model. However in lattice models with short chains, it is too difficult to talk about helixes and sheets, it is claimed that HDSs possess secondary structure in two and three dimensional HP model. By the use of a clever algebraic approach in the framework of a simple solvation model it is shown that HDSs should be rare and atypical in structure space. A recent argument shows that this result remains valid for more general models.

In this paper we study the designability of lattice structures in a wide range of interaction parameters between H and P monomers by using of a recently developed method. Results confirm that designability of structures depends on inter-monomer interactions but interestingly we find that the set of HDSs is invariant. Therefore in this simple model the geometry should have the essential role in the selection of some structures as most HDSs. Also the correlation with some other geometrical properties will be shown.

We use of a two dimensional Hydrophobic-Polar (HP) lattice Model for sequences with length 20. It is obvious that two dimensional structures have significant differences with real three dimensional ones, but to get considerable results in three dimension it needs to go to the too longer chains which is not computationally accessible. Short chains in three dimension do not possess natural ratio of core sites. The method of this paper is based on contact matrix. Thus it can be easily generalized to any pair contact model.

In Pair Contact Models the energy of a given sequence $\sigma$ in a given structure can be written as

$$E = \sum_{i,j} c_{i,j} n_{\sigma_i \sigma_j},$$

(1)
Where $c_{ij}$ and $m_{\sigma_i\sigma_j}$ are respectively the elements of the contact matrix ($C$) and the interaction matrix ($M$). $c_{ij}$ is 1 if the monomers $i$ and $j$ are non-sequential neighbor and is 0 otherwise. $\sigma_i$ is $i$th component of sequence vector $\sigma$. In our HP model, it is equal to 0 ($-1$) if $i$th monomer in sequence is a polar (hydrophobic) residue. The $m_{\sigma_i\sigma_j}$ is the interaction energy between monomer type $\sigma_i$ and $\sigma_j$.

In two-dimensional square lattice there are 41,889,578 distinct structures (non-related by rotation or reflection symmetries) for a sequence with length 20. There is a contact matrix corresponding to each structure. It is possible that some structures have the same contact matrix. Such contact matrices which point to more than one structure are called degenerate contact matrices. The number of non-degenerate distinct contact matrices are about 1 million which is much less than the number of all possible structures. The maximum number of possible contacts for the sequences with length 20 is 12, and the number of maximally compact structures i.e. with maximum contacts, are 503.

In HP model the monomers are divided to two Hydrophobic (H) and Polar (P) groups. The interaction matrix $M$ is thus a $2 \times 2$ matrix and its elements are $E_{HH}$ and $E_{HP}$ and $E_{PP}$. By choosing an arbitrary energy scale, we can parameterize these three elements of the interaction matrix in terms if two positive parameters, $\gamma$ and $E_c$.

\[
E_{HH} = -2 - \gamma - E_c, \\
E_{HP} = -1 - E_c, \\
E_{PP} = -E_c, 
\]

(2)

Substituting these elements of interaction matrix in equation (1) gives following simple expression for configuration energy.

\[
E = -m - E_c \cdot b - \gamma \cdot a 
\]

(3)

where $m$, $b$ and $a$ are three positive integers, related to $\sigma$ and $C$ as follows:

\[
m = -\sigma^t \cdot C \cdot 1, \\
a = \frac{1}{2} \sigma^t \cdot C \cdot \sigma, \\
b = \frac{1}{2} 1^t \cdot C \cdot 1. 
\]

(4)

Using the set of possible ground states of sequences, enables us to find the ground state of any sequence for any given values of energy parameters $E_c$ and $\gamma$. In this way the designability of all structures in a wide range of energy parameters $E_c$ and $\gamma$ is obtained by enumerating the all $2^{20}$ sequences. Fig 1 shows the average designability of structures in a 10 by 10 square region with the mesh 0.1 in the space of $E_c$ and $\gamma$. In this average the structures with zero designability are excluded. 19,132 structures (about 0.05% of all structures) have non-zero designability at least for some given values of $E_c$ and $\gamma$. As one can see in this figure, the average designability shows two different regimes in space of energy parameters. In a wide area of energy parameters it has a value in order of 10, but for large $E_c$ and small $\gamma$ it rapidly jumps to several hundreds. This can be explained by the fact that for $E_c \gg \gamma$ the contribution of $b$ in the configuration energy (eq. 3) is more essential. Therefore, all native structures are between the most compact ones. We can call this area of interaction parameters, compact regime. In this regime reduction in the number of native structures, increases the average designability. Alternatively when $\gamma$ is greater than $E_c$ or comparable with it, some non-compact configuration can compete with compact ones. We call this area swollen regime.

Fig. 2 shows the histogram of designability for two pairs of values of $E_c$ and $\gamma$. Fig 2.a is for the pair $E_c = 3$, $\gamma = 8$ which is a point in the swollen regime and fig 2.b is for the pair $E_c = 9$, $\gamma = 0.5$ which is a point in the compact regime. In the swollen regime where native structures are not restricted to only highly compact structures, there are many lowly designable structures and a few HDSs. Alternatively in the compact regime there are many intermediary designable structures and again a few HDSs. Similar results are reported when one compares histograms of designability for a fixed given set of energy parameters using the search space of all structures and compact structures. Therefore, the interaction parameters just choose the search space and inside each regime (compact or swollen), the statistics of designability does not change qualitatively.

The relevant question is, if the set of HDSs depend on the interaction parameters. To study this, we sort the structures by their designabilities at any set of energy parameters. In this manner, the place of any structure in competition for designability is recognized with its rank. The rank one is the most HDS for those given energy parameters. Averaging the rank of one structure in all space of energy parameters gives a good perspective about its global attitude toward high designability.

Figure 3 shows the histogram of this average rank for all structures in the studied square region of energy parameters. The interesting point in this diagram is that there are a few structures with very small average rank. For example there are 8 structure with average rank less than 10 and lowest average rank value is equal to 1.48. It must be noted that since the rank of a structure is a positive quantity, the smallness of its average shows that the structure has small rank in all space of energy parameters. Thus structures with very low rank always are inside the hit-list of HDSs. We compared the behavior of average rank of structures with two asymptotic limits. If the rank of structures were invariant against the change of energy parameters, the histogram would show a completely flat behavior (solid line in figure 3). In the other side, if the structures rank were changed uncorrelatively by the changing the inter-monomer interactions, it would result a very sharp Gaussian distribution as a consequence of central limit theorem (dashed line in figure 3).
3). As one can see in figure 3 it seems that the average rank behaves more similar to the case of quenched rank, than the random case. Especially, for the low ranks the histogram lies on the solid line very well. This shows that the ranks of HDSs are more rigid than the ranks of lowly designable structures. So, the set of HDSs does not depend on the interaction parameters, although the designability of structures does. The fact that the role of the interaction parameters is not important for choosing a structure as HDS, demonstrates the importance of geometry. This leads to the question which purely geometrical properties or symmetries select some structures as HDS. Furthermore it justifies the restriction of the search for HDS to highly compact structures.

Recently we have shown in HP lattice model that there are some sequences which have only one non-degenerate possible ground state in all space of energy parameter. Because the native structures of these sequences have perfect stability against the changing of inter-monomer interaction, we call them perfectly stable sequences (PSSs). PSSs give constant contribution to the designability of structures. For any given interaction parameters, each set of sequences which have a common ground state structure contains an invariant subset, constituted by PSSs. The designability of any structure has a constant part equal to the number of the members of its invariant subset of sequences. In our model, about 7% of the sequences of length 20 are PSS. These PSSs select 489 structures as their absolute native state out of the 503 most compact structures i.e. only 489 structures have a non-zero constant part of designability. (It is not possible that PSSs select non-compact structures as ground state because with a large enough $E_c$ the compact structures will gain lower energies.)

There is a strong correlation between the designability and its constant part. In figure 4 we have plotted the constant part of designability against the designability, for two sets of interaction parameters used in figure 2. This figure shows that designability is nearly proportional to its constant part, but the slope is a function of interaction parameters.

Indeed, in the swollen regime the slope is of order unity (fig 4.a). This means that the invariant subsets of sequences dominate the designability of structure. But in the compact regime, where the constant part of designability has a small contribution to designability, these quantities remain nearly proportional yet, and the most HDSs have the bigger constant parts (fig 4.b). This correlation is considerable because by definition the source of designability is different from its constant part. The former shows stability against monomer mutations in the sequence, and the later shows ability of structure to be an interaction independent native state. The strong correlation between these quantities suggests that they may have the same geometrical origin. It has been reported that designability has a good correlation with Energy gap. So it can be claimed that the existence of a large constant part in designability of a structure is a sign of large average energy gap. In fact, when a PSS exist, changing interaction parameters does not change the native structure of sequence. So the exited states of the sequence should be far enough and separated by a large energy gap.

As mentioned above the compactness is a necessary condition of HDSs because all interaction parameters are negative. We have found an additional geometrical symmetry for HDSs which is related to the solvation nature of proteins. In a HP solvation model for proteins a H monomer decrease the energy proportional to the number of non-sequential contacts in the structure and the position of P monomers does not change the energy. In a simpler version of the solvation model all non-core monomers behave the same (it takes both corner and edge monomers as surface). In contrast the solvation model is a pair contact model. Our pair contact model in the special case $\gamma = 0$ becomes a simple solvation model. (We may call it alternatively additive.) This special case has some theoretical advantages because the energy has a simpler form. In this case to calculate the configuration energy (eq. 9) a is an irrelevant parameter, and one can re-write $m$ and $b$ (equation 4) as follows.

\[
m = -\sigma^t \cdot V, \\
b = \frac{1}{2} t^t \cdot V, \\
\]

where $V$ is neighborhood vector (NV). Its $i$th component shows the number of non sequential neighbors of the $i$th monomer and is related to the contact matrix.

\[
V_i = C \cdot 1 = \sum_j c_{ij}. \\
\]

In this case the information needed to calculate the configuration energy can be coded in a vector instead of a matrix. Obviously this is a source of an additional degeneracy in energy spectrum. This degeneracy is equal to the number of spatial structures which have the same NV and we label it by $N_d$. In our enumeration for native configurations of length 20 the biggest $N_d$ for NVs is 4.

We found that all HDSs are between those structures with unique NVs ($N_d = 1$). Thus this additional geometric symmetry is another common property of HDSs.

Table 1. The average designability of structures

| $N_d$ | Number of contacts |
|-------|-------------------|
| 1 | 0.85 2.07 14.17 692.78 |
| 2 | 1.09 4.97 155.71 |
| 3 | 1.87 2.65 101.17 |
| 4 | 2.69 40.04 |

Table 1 shows the average designability of structures with specific compactness and degeneracy of NVs. It can be inferred that the average designability of structures
increase with the growth of compactness and with the decreasing of $N_d$. Thus those structures which have the highest compactness and unique NVs are good candidates for being highly designable. These are only necessary conditions for high designability and as some lowly designable structures also fulfill these criteria. In fact recently it was shown that these atypical structures possess α helices which are another character of real proteins. Also the uniqueness of NV representation of structures can give an explanation for the ratio of surface to core monomers in real proteins. 

In summary we have studied the designability of structures in a two-dimensional HP pair contact lattice model in a wide range of inter-monomer interaction parameters by considering HP constraints. We find the designability of all structures by enumerating all sequences of length 20. Our results confirm that changing the inter-monomer interactions affects the structure designability and also chooses the search space of native state but the set of HDSs is invariant. Therefore geometry should have the essential role in the selection of some structures as most HDSs.

In some regions of inter-monomer interaction parameter space, the constant contribution of PSSs to designability of structures is dominant in selection of HDSs. Even in those regions where the designability is much larger than constant part, there is still a strong correlation between designability and its constant part. Thus those structures, which are attractive for PSSs, are in the set of HDSs. This suggests a close relation between average energy gap of a structure and its constant part of designability.

We find two geometrical necessary conditions for a structure to be HD. The first one is compactness. This is because the PSSs select only highly compact structures as absolute native states. Also we find that all HDSs have a non-degenerate NV representation. In average the designability of structures decreases by increasing the degeneracy of neighborhood vector and decreasing of compactness. This result shows that two monomer type pair contact models have the common result for designability of HDSs with the solvation model which is consistent with the recent study. The relevant question remains what will happen in models with more than two monomer types.

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Figure Captions

Figure 1.
The Average Designability of all native structures against interaction parameters $E_c$ and $\gamma$ in a 10 by 10 square region with mesh 0.1. The compact and swollen regime correspond to areas of interaction space with large and small average designability respectively.

Figure 2.
Histogram of Designability for two pairs of interaction parameters. a) $E_c = 3$ and $\gamma = 8$ (swollen regime), b) $E_c = 9$ and $\gamma = 0.5$ (compact regime).

Figure 3.
The histogram of the number of structure with average ranks inside the intervals with width 50 is compared with the uncorrelated (dash line) and fixed (solid line) cases.

Figure 4.
The Designability of structures vs. the number of PSSs which choose the structure as unique ground state (the constant part of designability) for two pairs of interaction parameters. a) $E_c = 3$ and $\gamma = 8$ (swollen regime), b) $E_c = 9$ and $\gamma = 0.5$ (compact regime).
This figure "fig1.jpg" is available in "jpg" format from:

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Number of sequences vs Designability
