Geometrically Reduced Number of Protein Ground State Candidates

M.R. Ejtehadi\(^1\)*, N. Hamedani\(^1,2\) and V. Shahrezaei\(^1,2\)

\(^1\) Institute for studies in Theoretical Physics and Mathematics, Tehran P.O. Box 19395-5531, Iran.
\(^2\) Department of Physics, Sharif University of Technology, Tehran P.O. Box: 11365-9161, Iran.

Geometrical properties of protein ground states are studied using an algebraic approach. It is shown that independent from inter-monomer interactions, the collection of ground state candidates for any folded protein is unexpectedly small: For the case of a two-parameter Hydrophobic-Polar lattice model for \(L\)-mers, the number of these candidates grows only as \(L^2\). Moreover, the space of the interaction parameters of the model breaks up into well-defined domains, each corresponding to one ground state candidate, which are separated by sharp boundaries. In addition, by exact enumeration, we show there are some sequences which have one absolute unique native state. These absolute ground states have perfect stability against change of inter-monomer interaction potential.

PACS numbers: 87.10.+e, 87.15.-v, 36.20.Ey, 82.20.Wt

It is well known that the biological functionality of proteins depends on the shape of their native states. This native structure is the unique minimum free energy structure for the protein sequence. Thus, the information about effective inter-monomer interaction energy and coding of the amino acids in the sequence is sufficient to determine the native structure. There are many questions about the folding mechanism, stability, sensitivity to inter-monomer interactions and geometrical properties of these native states. This has motivated extensive studies in the subject of the properties of native states in recent years.

Basically, to determine the native states of a protein one needs to solve the problem with standard quantum mechanical calculations, however the complexity of these macromolecules renders this impossible. A feasible approach to this problem is based on a coarse-grained view to proteins. The most important point in this approach is the choice of effective interactions between the monomers. In this approach, all the necessary information about the protein’s structure is encoded in a binary contact matrix (\(M\)). The non-zero elements of this matrix correspond to non-sequential neighbor monomers in the configuration. However, the shapes of the native states of sequences depend on the inter-monomer interactions, but there are some geometrical properties which distinguish the native state from other configurations.

The number of possible configurations for an \(L\)-mer is equal to the number of self avoiding walks with \(L-1\) steps. Since many of these walks give the same contact matrix, the number of possible contact matrices are much smaller, although it is still very large, and grows exponentially with the length of protein. There have been some attempts to reduce the number of possible protein configurations by considering the compact structure space, or the minimum energy compact structure space. In the present work we look at the geometric constraints of native states in more detail. We show that there are some necessary geometrical properties for a state to be the ground state of a sequence. This leaves only a few candidates for the ground state of any sequence. To find the ground state candidates for any sequence, one need not know anything about inter-monomer interactions, instead these candidates can be found by a simple comparison of the contact matrices. One can then find the ground state from among these candidates by taking the inter-monomer interactions into account. By limiting the number of ground state candidates, this method introduces a stability against the variation of interaction parameters and vastly reduces the computer time needed to find the native state for a particular sequence as one need not search through a huge number of configuration.

Without loss of generality, we use a hydrophobic-polar (HP) lattice model in this paper. The argument can be generalized to any model with any number of monomer types with short range interactions. The general form of interactions between \(H\) and \(P\) monomers in an HP model can be written as follows:\(^7\)\(^12\):

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

These potential energies are only between the non-sequential nearest neighbours. Here \(\gamma\) and \(E_c\) are the mixing and compactness potentials respectively, two free parameters which are determined from experimental data. The compactness of the native states together with some physical arguments about inter-monomer interactions such as\(^13\):

\[
E_{HH} < E_{HP} < E_{PP}, \\
E_{HH} + E_{PP} < 2E_{HP},
\] (2)

restrict \(\gamma\) and \(E_c\) to positive values (\(\gamma, E_c > 0\), however, we need not consider such restrictions in our arguments.

\(^*\)e-mail: reza@theory.ipm.ac.ir
At the first sight it might seem possible to arrive at any native state for a given sequence by changing $\gamma$ and $E_c$, but when we consider the geometrical properties of the ground state, we will find that these parameters are not powerful enough to select any configuration as the native state and native states are stable against the change of interaction parameters, in fact, universal solutions can be found for native states.

As explained in our previous works, if we consider $H = -1$ for hydrophobic monomers and $P = 0$ for polar monomers, a given sequence can then be represented by a binary vector ($\sigma$). The energy of this sequence in a configuration characterized by a contact matrix $M$, can be written as:

$$E = -m - a\gamma - bE_c,$$  

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

$$m = -1^T \cdot M \cdot 1,$$
$$a = \frac{1}{2}1^T \cdot M \cdot \sigma,$$
$$b = \frac{1}{2}1^T \cdot M \cdot 1.$$  

Therefore, $m$ is equal to the number of all non-sequential neighbors of H monomers in the configuration, $a$ is the number of H-H contacts and $b$ is the number of all contacts. It can be seen easily that the following inequalities hold:

$$m - b \leq a \leq \frac{m}{2} \leq b.$$  

Equation suggests that the energy levels of a given sequence can be described by three integer numbers $(m, a, b)$. It is highly probable that these states are degenerate. There are three kinds of degeneracy: (Type 1) $M = M'$ in which case two or more configurations with different shapes have the same matrix. These configurations will remain degenerate for any sequence, and any choice of $\gamma$ and $E_c$. This type of degeneracy is more probable for configurations with low compactness. Note that the configurations which are related to each other by spatial symmetries i.e. rotation, reflection, etc., are the same and are not considered as separate. (Type 2) $(m, a, b) = (m', a', b')$ but $M \neq M'$; in this case one particular sequence has the same $m$, $a$ and $b$ values in two or more configurations. This degeneracy persist for any value of $\gamma$ and $E_c$, but may disappear for another sequence. Although this degeneracy depends on sequence coding, but the $b = b'$ condition is purely geometrical, and is a necessary condition for this degeneracy. (Type 3) $E = E'$, but $(m, a, b) \neq (m', a', b')$; one sequence has the same energy in two different states $(m, a, b)$ and $(m', a', b')$, provided $\gamma$ and $E_c$ obey the following relation:

$$(m - m') + (a - a')\gamma + (b - b')E_c = 0.$$  

This degeneracy is related to both sequence coding $\sigma$ and inter-monomer interactions.

The first type of these degeneracies is completely geometric. The second one depends on both geometry and sequence arrangement. These two types don’t depend on the values of the interaction energies. Thus, in the energy spectrum of any sequence there are some states which, independent of the potential, are degenerate. If the ground state of one sequence is one of these degenerate states, it means that this sequence has not a unique native structure. The third type is not actually a degeneracy at all. Equation corresponds to a line in the parameter space of $E_c$ and $\gamma$. This line is a level crossing line. Degeneracy occurs only on the line, and it needs highly accurate fine tuning. For the two sets of interaction energy parameters on the two sides of this line, the energy ordering of states is different. For any pair of states there is such an ordering line. By drawing all ordering lines in the space of $E_c$ and $\gamma$, this space is divided into many ordering zones. We are only interested in the ground state, which means that many of these ordering lines are not relevant. Some of them only govern the ordering of excited states. By removing the irrelevant lines, one gets a diagram which shows the ground state cells (Fig. 1). As mentioned before changing the inter-monomer interaction parameters inside any of these cells does not change the ground state. Mourik et al. introduced this picture to show stability of native states against the interaction parameters. They only looked at one of these cells in the neighbourhood of selected interaction values. But by looking at the whole energy space, one can find all possible ground states and their corresponding cells. Any such cell in the space of energy parameters associates with one ground state candidate. The number of cells is the number of candidates ($G_c(\sigma)$) for ground state. By drawing such diagram, one can easily find the ground state for any choice of $E_c$ and $\gamma$. Fig. 1 shows this diagram for an 18-mer, which is the result of an exact enumeration of a two dimensional folding problem. The interesting point is that the number of ground state candidates is very small. In this example there are only five possible ground states. The cells marked with the numbers “1” and “2” correspond to type 1 and 2 degenerate states respectively, therefore there is no unique native structure for these cells. The sequence in this example has two nondegenerate states. These structures are shown in the figure. It is possible that all the ground state candidates of a given sequence are degenerate. These sequences constitute universally bad sequences for any value of interaction parameters. It means that they do not have a native structure.

In Fig. 2 the histogram of $G_c(\sigma)$ for all $2^{18}$ sequences is shown. The narrow line in this figure shows the result for all $2^{18}$ sequences, and the thick line shows the remaining sequences after removing the bad ones. The interesting point in this diagram is the smallness of the mean value of $G_c(\sigma)$, (1.49 for all sequences and 1.7 for good sequences). The maximum of $G_c(\sigma)$ for 18-mers is 6.
...and only 2 sequences with length 18 have this maximum. Comparison of $G_c(\sigma)$ for these sequences with the number of all configurations ($\sim 10^7$), shows that the geometric constraints play an important role in choosing a state as the ground state. As this diagram shows, there are some sequences which regardless of the values for energy parameters, have only one unique ground state. Fig. 3 shows one of these sequences and its unique native structure. Indeed the native state of these sequences have perfect stability with respect to energy parameters. This enumeration shows that nearly 17.8% of the $2^{18}$ possible sequences have perfect stability and absolute unique native states. Interestingly, our enumeration shows that these absolute native structures are between the most compact structures. Although the ratio of the perfectly stable proteins to all possible proteins decreases with increasing $L$, their actual number increases \[16\]. This suggests that for the proteins with typical length near natural proteins there are a small but non-zero fraction of perfectly stable sequences. The existence of these sequences may answer some questions about protein folding. Their perfect stability with respect to energy parameters, have only one unique ground state. From this picture it is obvious that the possible number of configurations, $E_c$ is an irrelevant parameter. In this special case the space of energy parameters is one dimensional (only $\gamma$), and the space of states is two dimensional ($a$ and $m$) \[8\]. This argument can be generalized to models with more than two kinds of monomers, and also to off-lattice models. For off-lattice models, it is necessary for the energy function between monomers to be in the form of a step potential. For this form, a contact matrix can give the configuration energy by a relation similar to equation \[8\]. If the inter-monomer interaction has $t$ free parameters, the energy levels can be described by $t + 1$ integer. The introduction of $n$-body interaction ($n > 2$) only increases this difference the dimensionality of state space and the space of energy parameters \[8\]. Threfore, quite generally, the ground state candidates of any given sequence are between the corner states of a hyper polyhedron in a hyper space which is very smaller than the number of all possible structures.

Acknowledgements: We would like to thank H. Seyed-Allaei, S. E. Faez, R. Gerami for useful discussions, R. Golestanian for helpful comments on the style of presentation and N. Heydari for carefully reading the manuscript.

[1] C.B. Anfinsen, Science 181, 223 (1973).
[2] S. Miyazawa and A. Jernigan, Macromolecules 18, 534 (1985).
[3] S. Lilson and C. Sander, Nature 282, 109 (1979).
[4] V.S. Pande, A.Yu. Grosberg and T. Tanaka, J. Chem. Phys. 103, 9482 (1995).
[5] H. Li, R. Helling, C. Tang and N. Wingreen, Science 273, 666 (1996).
[6] M. Vendruscolo, B. Subramanian, J. Kanter, E. Domany and J. Lebowitz, Preprint [cond-mat/9810283].
[7] M.R. Ejtehadi, N. Hamedani, H. Seyed-Allaei, V. Shahrezaei and M. Yahyanejad, Phys. Rev. E 57, 3298 (1998).
[8] M.R. Ejtehadi, N. Hamedani, H. Seyed-Allaei, V. Shahrezaei and M. Yahyanejad, J. Phys. A 31, 6141 (1998).
[9] K.A. Dill, Biochemistry 24, 1510 (1985); K.A. Dill, S. Bromberg, K. Yue, K.M. Fiebig, D.P. Yee, P.D. Thomas...
and H.S. Chan, Protein Science 4, 561 (1995).
[10] C.J. Camacho and D. Thirumalai, Phys. Rev. Lett. 71, 2505 (1993).
[11] H.S. Chan, K.A. Dill, J. Chem. Phys. 90, 492 (1989);
H.S. Chan, K.A. Dill, D. Shottle, “Statistical Mechanics
and Protein Folding”, Princeton Lectures on Biophysics,
W. Bialek ed., (World Scientific, 1992).
[12] R. Melin, H. Li, N. S. Wingreen and C. Tang, Preprint
cond-mat/9806197.
[13] H. Li, C. Tang and N. Wingreen, Phys. Rev. Lett. 79,
765 (1997).
[14] J. Mourik, C. Clementi, A. Maritan, F. Seno and J. R.
Banavar, Preprint cond-mat/9801137.
[15] In their work they parametrize the energy space by $E_{HP}$
and $E_{PP}$ instead of $\gamma$ and $E_c$.
[16] V. Shahrezaei, N. Hamedani and M.R. Ejtehadi, In
Preparation.
[17] M.E. Fisher and B.J. Hiley, J. Chem. Phys. 44, 616
(1961).
[18] N. Hamedani, V. Shahrezaei and M.R. Ejtehadi, In
Preparation.
Figure Captions

Figure 1. The space of energy parameters for one particular sequence which is shown in the top of the picture is divided to five cells. The integer numbers \((m, a, b)\), inside any cell indicate the ground state corresponding to the cells. Three of these states are degenerate. The types of degeneracies for degenerate states and shape of structures for non-degenerates are indicated in the cells.

Figure 2. The histogram of the number of ground state candidates for 18-mers with positive values of \(\gamma\) and \(E_c\). The narrow and thick lines show the results for all sequences and good sequences respectively. There are some “good sequences” with only one ground state candidate.

Figure 3. One perfectly stable sequence and its absolute native structure. For any positive value of \(\gamma\) and \(E_c\) this sequence is folded uniquely in the shown structure.

Figure 4. State space of the particular sequence which is shown in figure 1. All states are inside a diamond like polygon inside a pyramid. Top viewed corner points of this polygon are the ground state candidates.
$E_c$ vs $\gamma$

- Point 1: (13,6,8)
- Point 2: (12,6,9)
- Point 3: (11,5,10)
- Point 4: (12,4,10)
- Point 5: (12,6,9)

Legend:
- PPHPHPHPHPHPHPHPHPHPHHP

Graphical representation of the data points in a 2D coordinate system.
Graph showing frequency distribution of sequences as a function of $G_c(\sigma)$.
