

Biomolecular Structures Assignment 1 Question 3

Helical Order Parameter

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We can define order parameters to quantify the order of the alpha helices in proteins. Can we define a similar order parameter for beta sheets? Do literature survey and make a written report on this.

1 Introduction

Helices are the most commonly occurring secondary structures in proteins. This makes it essential to understand the structural details of them in order to get a complete understanding of the properties of proteins in general. The Zimm–Bragg model is a famous model to describe secondary structures of proteins in the following format: each molecule is assumed to be either in coil state or helix state and two parameters are used to describe the interactions between each state. The first parameter is Δf_s (free-energy gain in the molecule when in helical state and during the transition to the helical state, this parameter goes to 0). The second parameter is Δf_σ (free-energy loss due to reduction in entropy from the nucleation of a new helical segment indicating increase in stability). These parameters are used as the statistical weights of the various states while calculating relevant quantities about the structure and so on. The transition from coil to helix has been extensively studied and this has led us to the understanding that the system can be treated as a single first-order-like transition of a coil to a helix and since the problem is one dimensional, the transition is not a true phase transition in the thermodynamic limit.

Recent studies have led to interesting conclusions about helices like the one done by Kumar and Manju which says that the characteristics of α -helices in globular proteins can be characterised as kinked, rigid or curved.

Nowadays, it has become more popular to study these structures with the use of computer simulations in order to obtain a more direct physical picture of the system. To study helix formation via computer simulations, first we need to create a model that has a helical ground state at low temperatures. This is done by trying to copy the way proteins interact and then choosing a sequence

which is known to be a good helix former.

The problem with using computer software which runs using the above methodology is that the potential energy function of a protein is extremely complicated as it depends on the type of solvent environment in addition to the amino acids present in the sequence. To solve this problem, it would be best to attempt understanding helix formation on a fundamental level and to understand the necessary interactions required to create these structures.

This is why minimal models and off-lattice models have become popular in recent years to decipher complex systems like protein potential energy functions.

2 Minimal Model

Before talking about the simulation technique, let's try to understand what is needed to produce the desired helical ground state that we talked about earlier. This is also known as the minimal model of a helix, hence the name.

If we examine the type of interactions in real protein systems, we see that one of the most dominant interactions between the constituent amino acids during the process of protein folding is the **hydrophobic interaction** between them. However, this is not responsible for generating the helical secondary structures in proteins. This has been confirmed experimentally by running a simulation of all atomic models of a protein called polyanine to show that helical states can be formed in vacuum. Thus, hydrophobic interactions can be removed from the picture.

The other kinds of interactions to stabilise the helix can be either **local interactions** or **non local interactions**.

Local interactions are between the nearest amino acids neighbors like torsional / dihedral interactions. When we plot these interactions to get the Ramachandran plot, we understand that there is typically not one unique energy minimum meaning several protein conformations are available to the residue. It has been shown that one can create a minimal model of a helix using these interactions but these are not the dominant interactions in the stabilisation of helical structures. Thus, we exclude local interactions too.

Non local interactions could create bonds with any molecule along the chain. This includes electrostatic forces, dipole interactions and hydrogen bonds out of which the most prominent is hydrogen bonding interactions. These forces interact over short distances and due to the planar structure of an amino acid, the non local interactions also contain an element of anisotropy (different properties in different directions) in the overall nature of interaction. This directional

property leads to the stable formation of unique α helix or β sheet in proteins.

Therefore, we can create a helical ground state using an inosotropic potential. The technique used to create the minimal model is the Monte Carlo pivot (non local) algorithm.

Now we talk about the simulation results obtained. The most common measured quantity is the specific heat per monomer C_v because it provides direct information about the free energy of the system. Any structural changes are reflected by anomalous behaviour of C_v . To assess the arrangement of the monomers, the radius of gyration squared is used. This measure of the size of the polymer can be measured directly through light-scattering experiments and any major structural change in the polymer will be reflected in the measurement of the radius of gyration squared. It is also worth dissecting the radius of gyration further to examine the structural changes in the helix regime. We can define an overall helical axis for the entire polymer as the vector which is the sum of all the bond direction vectors. We can break the radius of gyration into components parallel and perpendicular to the vector. During helix formation, the two parameters (perpendicular component and parallel component) would be expected to diverge from each other as the parallel component increases and the perpendicular component decreases to approach the square diameter of the helix.

We describe the orientation fluctuations of the bond directional vector using quantitative methods.

H_1 : Configuration of a group of atoms is examined using a predetermined criterion. We check if a cluster is in a helical configuration using the distance between the i^{th} and the $(i + 3)^{th}$ monomer. If the distance falls within the length criterion for a helix, the unit is considered to be helical. This relies on an arbitrary definition of a helical unit and thus is probably not the best. For this reason, it is worth defining other order parameters that do not use predetermined criteria for defining helicity. Thus, we define H_2 , H_3 and H_4 .

$$H_2 = \frac{1}{(N-3)} \sum_{i=2}^{N-2} u_i \cdot u_{i+1}$$

$$H_3 = \frac{1}{(N-2)} \sum_{i=2}^{N-1} u_i \cdot u_{mid} \text{ where } u_{mid} \text{ is the bond vector of the } floor((\frac{N}{2})^{th}) \text{ monomer.}$$

$$H_4 = (\frac{1}{(N-2)} \sum_{i=2}^{N-1} u_i)^2$$

Although any of the four parameters could be used to calculate the average helicity, parameter H_1 is most suitable for calculating average segment length.

3 Order Parameters for Beta Sheets

If we look at β sheets in terms of a piece of a helical surface, we can define two parameters for it: the twist (turn of the helical surface per residue) and the coiling (curvature along the strands or in a direction perpendicular to the strands of the sheet). We shall look at more details of this now.

The main chains of β sheets form a two dimensional curved surface whose shape is defined by the interactions between the strands. As stated earlier, the geometry of a β sheet is defined by two parameters determining the twist and the coiling.

The meaning of a twist is as follows: the average twist of the strands derived from the backbone atoms dihedral angles ϕ and ψ . An alternative definition uses the four α carbons of the two terminal residues from each of the two most external strands of a sheet. A right handed twist is an intrinsic property of a β sheet. The definition of coiling has been stated earlier.

β sheet coiling depends on the nature of residues and the interactions of the residues in the protein. This is expected. Smaller β sheets usually have close to zero bending factor and thus, coiling can safely be ignored for them. For longer sheets / barrels, coiling is considered.

As per the paper I have done this literature survey on, we first define an ideal β sheet using helical parameters. The ideal β sheet had the following variables: $x = \cos \theta$ (θ is the angle of rotation of a strand around the z-axis.), $y = r \sin \theta$ (r is the distance between a strand and the z-axis) and $z = H\theta$ (such that $2\pi H$ is the step of the helical surface). We choose parameters to try and minimise the root mean distance of the α carbons of the ideal sheet and the real sheet.

This was done on one sheet of a piece of helical surface (due to easier computation) and can be shown to model three-strand models and four-strand sheets.

Thus, we can conclude that for smaller β sheets, the twist parameter (with units $^\circ/\text{\AA}$) is an order parameter and for larger β sheets / barrels, an additional parameter, the coiling factor, is also an order parameter.