6.0 The Three-Dimensional Structure of Proteins

Objectives

1. Know the 4 levels of structural complexity of proteins
2. Understand the properties of a peptide bond
3. Know the a helix and b sheet structures
4. Know the structures of a keratin, b silk fibroin, and collagen
5. Be familiar with coils, bulges, turns, loops, and cross-overs
6. Read about X-ray crystallography and NMR
7. Be familiar with common supersecondary motifs
8. Understand the forces holding 3D & 4D structures
9. Understand protein folding

6.1 Secondary Structure

Proteins have four levels of structural complexity:

- **Primary (1°)** structure is the amino acid sequence
- **Secondary (2°)** structure is local areas of protein chain structure
- **Tertiary (3°)** structure is the arrangement of secondary structural elements
- **Quaternary (4°)** structure is the arrangement of polypeptides to form multisubunit complexes

Common secondary protein structures:

- α helices
- β sheets
- Reverse turns
- β bulges
- Coils
- Ω loops

Both α helices and β sheets are important structural units that together form more complex arrangements of proteins. In fact, these arrangements are the most commonly observed secondary structures in proteins.

Reverse turns are regions where a polypeptide makes a sharp turn, and are common at the surface of globular proteins. β bulges are areas of dense Hydrogen bonding of β sheets.

Coils are secondary structures where polypeptides wrap around themselves or other polypeptides. Ω loops are strands of amino acid sequences that loop back on themselves, forming a shape similar to the Greek letter Omega (Ω). These structures may then go on to form supersecondary structures called motifs.

6.2 Fibrous Proteins

Some proteins, known as "fibrous" proteins, are remarkable for their filamentous forms. These proteins form many of the hard, elastic, and connective tissues in animals and other organisms.

Keratins

Keratins are classes of proteins with long peptide sequences that make up many animal tissues. α keratins in particular are common in hair, horns, nails, and feathers, and are distinguished by a 3.6 residue/turn α-helix, which tends to create coiled-coil structures where the inside of the coils form a hydrophobic interface.

Fibroin

The β sheet structure can be arranged in stacked, antiparallel forms that yield both flexibility and strength. The strong Van der Waals interactions of β sheets are what give spider silk its impressive tensile strength, in a structure called β silk fibroin.

Collagen

Collagen is another fibrous protein, a triple helix structure found in skin, tendons, cartilage, bone, and teeth. Like keratin, collagen's multiple-helix structure gives it ample flexibility and strength.

6.3 Globular Proteins

Groups of folded α-helices and β-sheets can form higher-level structures known as globular proteins. These proteins form when secondary structures pack closely together to create more stable structures.

6.4 Factors Determining Secondary and Tertiary Structure

The final structure of a protein is determined by a complex set of variables ranging from temperature, pH, and influence from other molecules. Primary thermodynamic factors can be grouped into three categories:

1. Intramolecular Interactions (charge-charge, H-bonds, Van der Waals)
2. Conformational Entropy
3. Solvent Entropy

Chaperones are molecules that promote folding of proteins in a specific way that increases the likelihood of a particular final product. By using chaperones, the time and difficulty of folding proteins can be greatly reduced.

6.5 Dynamics of Globular Protein Structure

When proteins condense,they go through a process known as "folding," where the molecule twists and turns itself as it descends down an energy gradient towards a local energy minimum.

Simulating protein folding is difficult due to the sheer number of possible conformations for a given protein. Each conformation represents a potential combinatorial state and, assuming even a modest simulation rate, one of millions of potential states that may take years to simulate.

Due to the sensitive, stochastic nature of protein folding, it's sometimes possible for proteins to misfold. In animals, protein misfolding can lead to life-threatening diseases. Alzheimer's, Parkinson's, and ALS are a few of many diseases thought to be caused by or related to protein misfolding.

6.6 Prediction of Protein Secondary and Tertiary Structure

As one might expect, predicting higher-level structures in proteins is difficult due to the large number of complex interactions involved. Some properties of amino acid sequences provide hints about the secondary structure of proteins. Computational simulation is the current best method for predicting tertiary protein structures, and is unfortunately only about 60% accurate.

6.7 Quaternary Structure of Proteins

When tertiary protein structures interact, they may form quaternary structures, the highest protein structure level. These structures are created and repaired piece-by-piece due to their size. Quaternary structures have some advantages over tertiary structures, such as increased genetic efficiency and stability. Quaternary structures are said to have varying degrees of α-helix or β-sheet character.