Structure of Proteins

Specific learning objectives

- Structure organization of the Proteins includes:

1) Primary structure (covered in previous lecture)
2) Secondary Structure
3) Tertiary Structure
4) Quaternary Structure

Secondary Structure of Proteins

- Local, regular arrangements of the protein chain are stabilized by hydrogen bonding.

- Polypeptide chains fold into regular structures such as the alpha (α) helix, beta (β) sheet, and turns and loops.

- α-helices, β-strands, and turns are formed by a regular pattern of hydrogen bonds between the peptide N-H and C=O groups of amino acids (aa) that are near one another in the linear sequence. Such folded segments are called secondary structure.

Alpha Helix Is a Coiled Structure Stabilized by Intrachain Hydrogen Bonds

- The α-helix is stabilized by intrachain hydrogen bonding between the NH and CO groups along parallel to the helical turn.
- The R groups of each aminoacyl residue in an α-helix face outward.
- Pitch of the α-helix: length of one complete turn along the helix axis and is equal to the product of the rise (1.5 Å) and the number of amino acid per turn (3.6), or 5.4 Å.

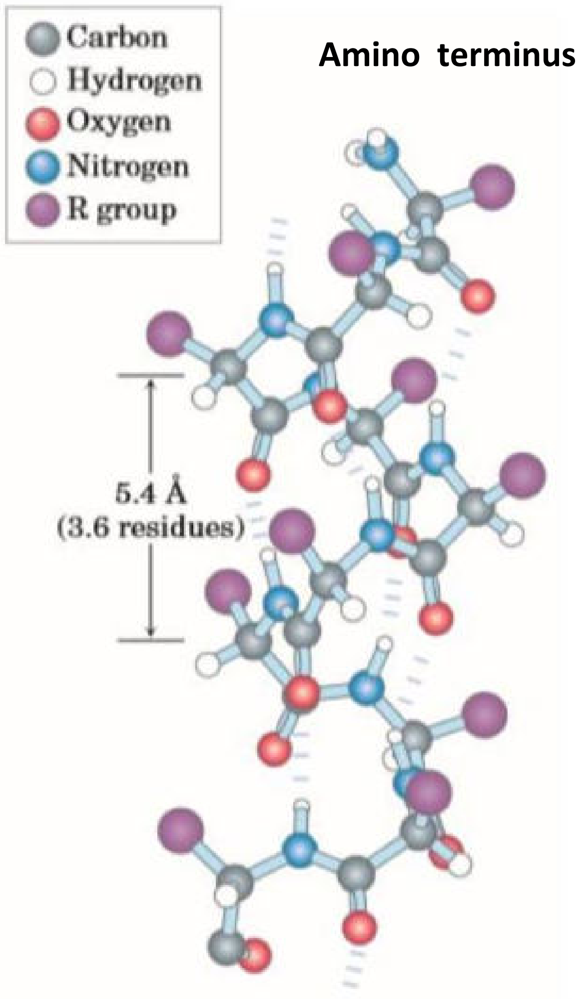

Fig.4.4 b: Ball-and-stick model of a right handed α helix. Lehninger Principles of Biochemistry

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Largely α-helical protein: Ferritin

- ~75% of the residues in ferritin, a protein that helps store iron, are in a helices.
- ~25% of all soluble proteins are composed of a helices connected by loops and turns of the polypeptide chain.
- Many proteins that span biological membranes also contain α-helices.

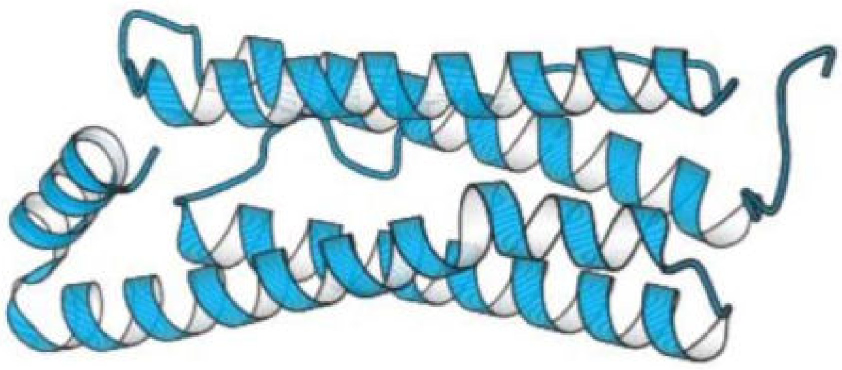

Fig.2.28: Biochemistry 7th edition by Berg, Tymoczko and Stryer

Ramachandran diagram for helices

- Right-handed helices are energetically more favorable because there is less steric clash between the side chains and the backbone.

- **Amino acids favored**: Met, Ala, Leu, Glu, Lys. **Amino acids not-favored:** Bulky aromatics, β-branched, those compete with the backbone of H-bond (Ser, Asp, Asn), and also proline and glycine.

- Polypeptide backbone of an α helix is twisted by an equal amount about each α-carbon with a phi (ϕ) angle of −60° and a psi (ψ) angle of −47°.

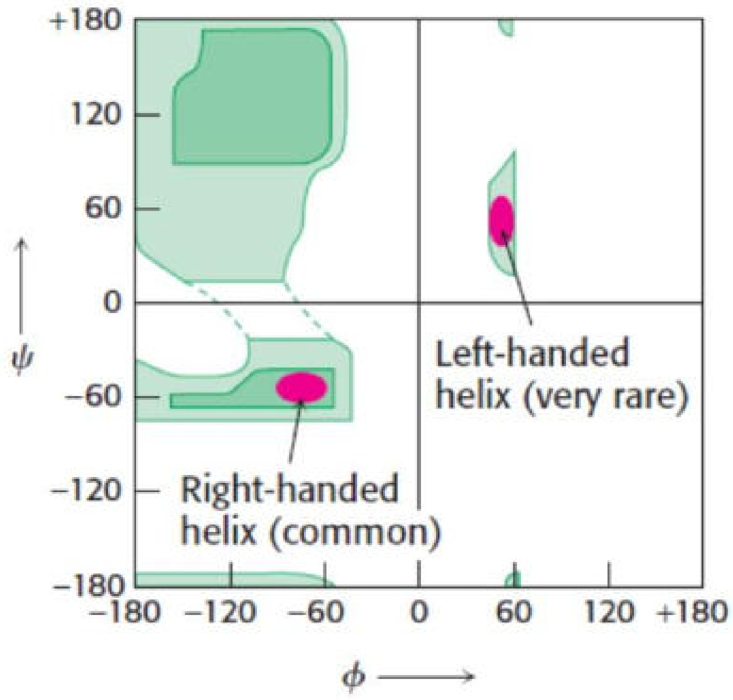

Fig.2.26: Biochemistry 7th edition by Berg, Tymoczko and Stryer

β-Sheets Stabilized by Hydrogen Bonding Between Polypeptide Strands

- Distance between adjacent amino acids along a β strand is approximately 3.5 Å.

- The side chains are above and below the plane of the strands.

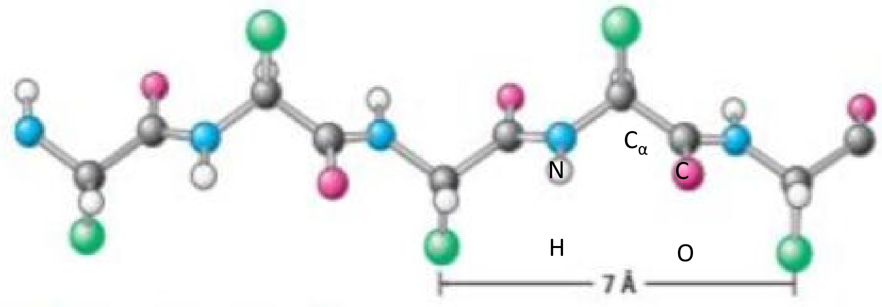

Figure 2.30 Structure of a β strand. The side chains (green) are alternately above and below the plane of the strand.

Fig.2.30: Biochemistry 7th edition by Berg, Tymoczko and Stryer

Parallel β-sheet

- In the parallel arrangement, for each aa, the NH group is hydrogen bonded to the CO group of one aa on the adjacent strand.

- 1:2 H-bond pattern: 1 a.a bonds with 2 other a.a in an opposing stand.

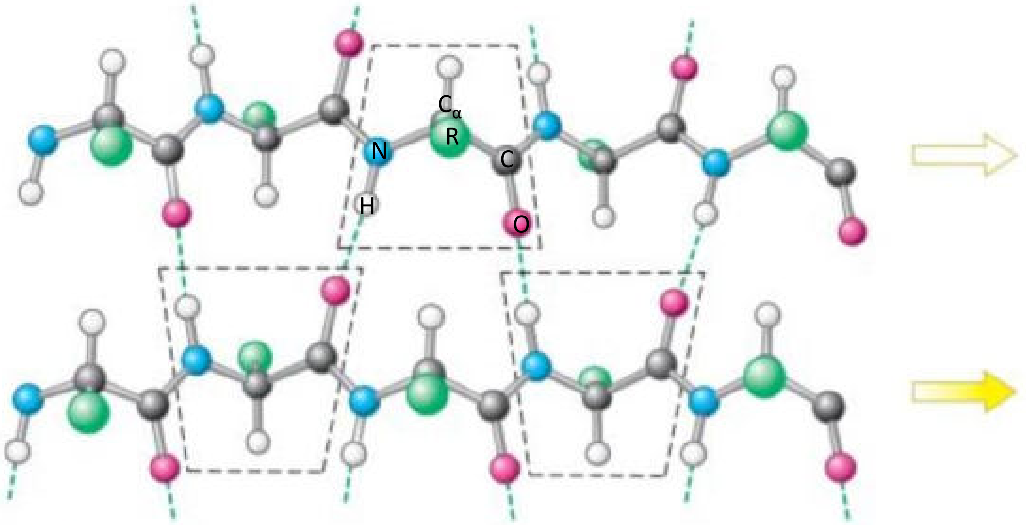

Figure 2.32 A parallel β sheet. Adjacent β strands run in the same direction. Hydrogen bonds connect each amino acid on one strand with two different amino acids on the adjacent strand.

Fig.2.32: Biochemistry 7th edition by Berg, Tymoczko and Stryer

Antiparallel β-sheet

- Adjacent chains in a β sheet can run in opposite directions (antiparallel β sheet) or in the same direction (parallel β sheet).

- Follow 1:1 H-bond pattern.

- In the antiparallel arrangement, the NH group and the CO group of each aa are respectively hydrogen bonded to the CO group and the NH group of a partner on the adjacent chain.

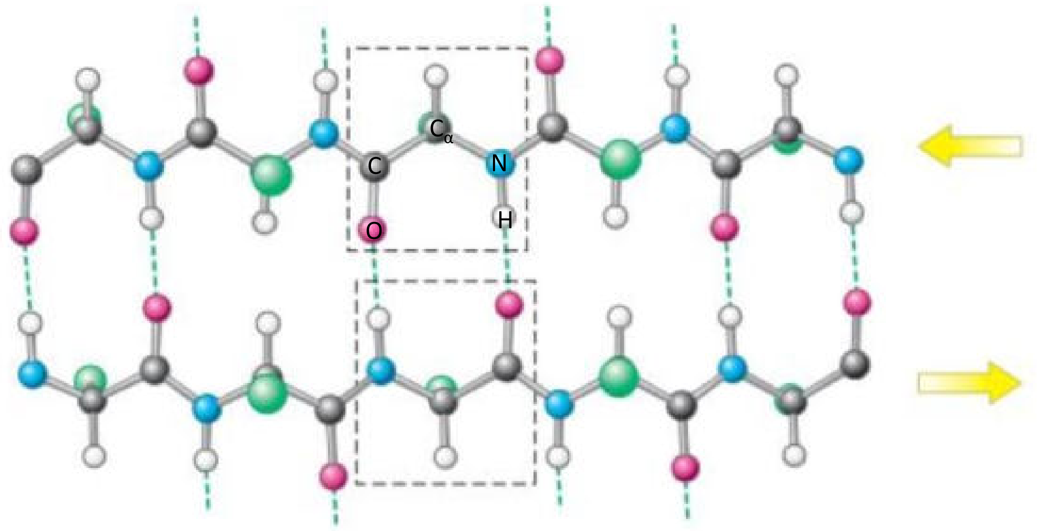

Figure 2.31 An antiparallel β sheet. Adjacent β strands run in opposite directions. Hydrogen bonds between NH and CO groups connect each amino acid to a single amino acid on an adjacent strand, stabilizing the structure.

Fig.2.31: Biochemistry 7th edition by Berg, Tymoczko and Stryer

Ramachandran diagram for Beta strands

- Ramachandran angles occupy the upper quadrant (ϕ=-135° and ψ=+135°).
- The pink area shows the sterically allowed conformations of extended, β-strand like structures.
- β-strand is extended rather than being tightly coiled as in the α-helix.

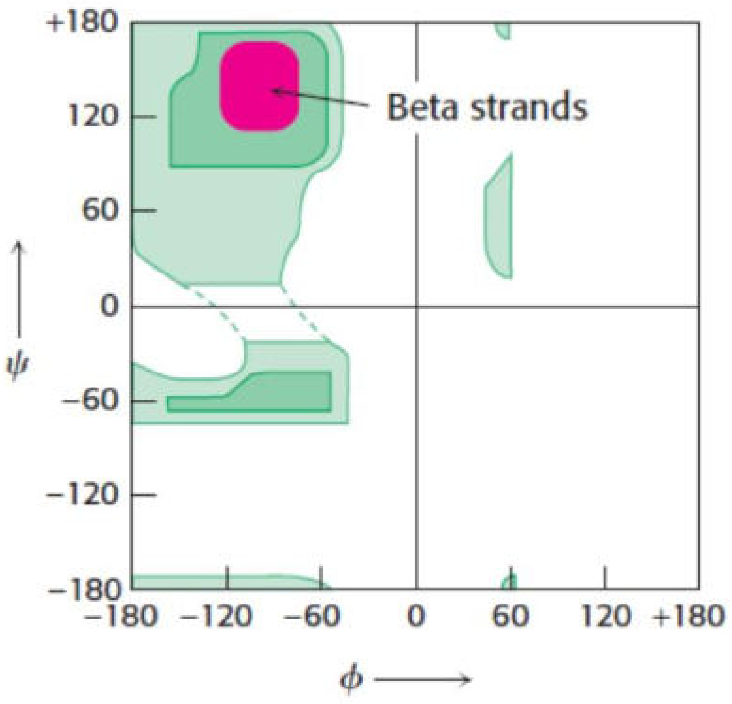

Fig.2.29: Biochemistry 7th edition by Berg, Tymoczko and Stryer

Protein rich in β-sheet

- Fatty acid-binding proteins (FABP), important for lipid metabolism, are built almost entirely from β-sheets.

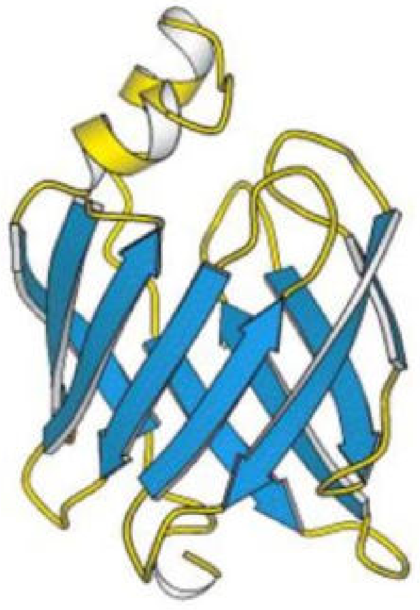

Fig.2.35: Biochemistry 7th edition by Berg, Tymoczko and Stryer

Reverse Turns

- In compact globular proteins, a polypeptide often makes a sharp turn.
- They cause packing and make it possible for the molecule to become globular.
- Turns connect helical twists and sheets.
- The structure is a 180° turn involving four aa residues, with the CO of the residue i forming a hydrogen bond with the NH of the residue i+3.

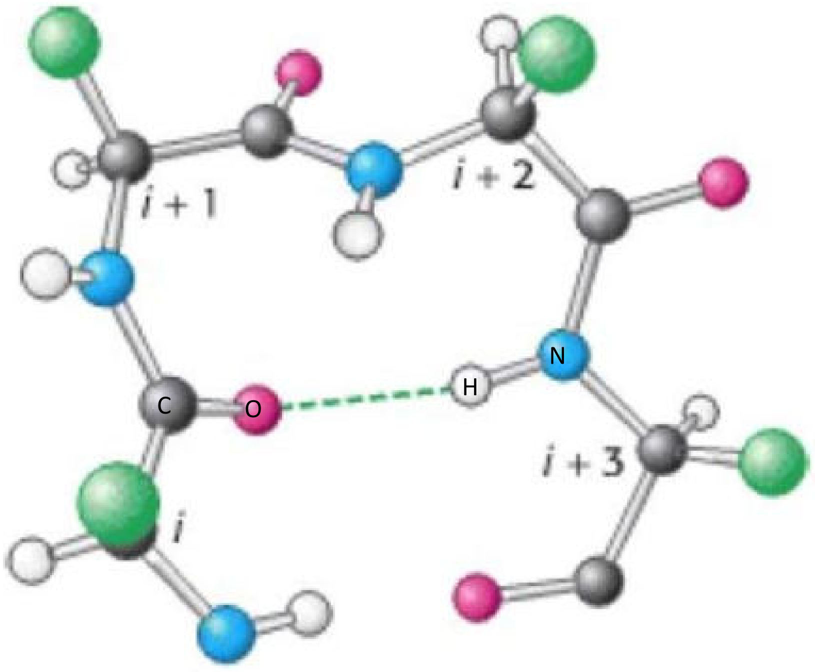

Fig.3.42: Biochemistry 7th edition by Berg, Tymoczko and Stryer

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- Loops are responsible for chain reversals and overall shape.
- Turns and loops invariably lie on the surfaces of proteins and participate in the recognition role of proteins, such as the recognition of specific antigens by antibodies.
- Ex. part of antibody molecule has surface loops (shown in red) that mediate interactions with other molecules.

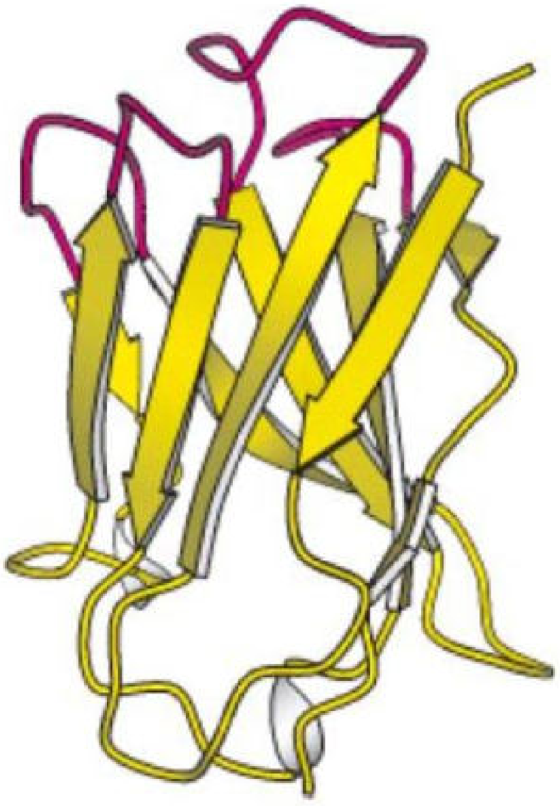

Fig.3.43: Biochemistry 7th edition by Berg, Tymoczko and Stryer

Special types of helices are present in the two proteins

1. **α-keratin** is an elongated *α*-helix. Pairs of these helices are interwound in a left-handed sense to form two-chain coiled coils.

- These combine in higher-order structures called protofilaments and protofibrils.

- About four protofibrils—32 strands of α-keratin altogether—combine to form an intermediate filament.

- Contribute to the cell cytoskeleton (internal scaffolding in a cell), and the muscle proteins myosin and tropomyosin.

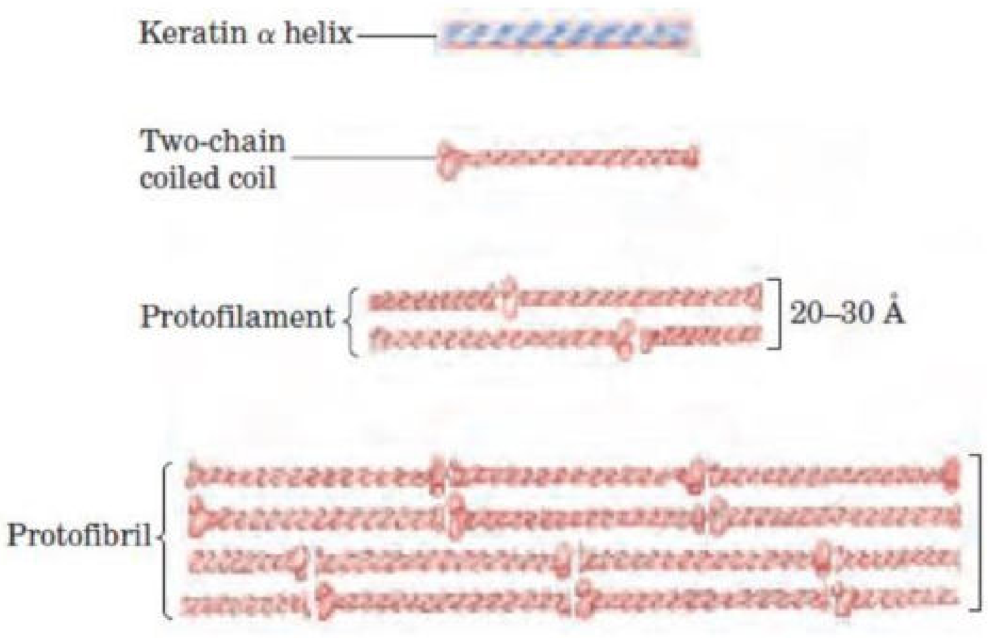

Fig.4.11: Biochemistry 7th edition by Berg, Tymoczko and Stryer

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2. Collagen is the main fibrous component of skin, bone, tendon, cartilage, and teeth.

- Glycine appears at every third residue in the amino acid sequence.

- Hydrogen bonds within a strand are absent. Helix is stabilized by steric repulsion of the pyrrolidine rings of the proline and hydroxyproline residues.

Fig.2.40: Biochemistry 7th edition by Berg, Tymoczko and Stryer

Cont--

- Importance of the positioning of glycine inside the triple helix is illustrated in osteogenesis imperfecta. In this condition, other amino acids replace the internal glycine residue.

- The -OH groups of hydroxyproline residues participate in hydrogen bonding, and the absence of the -OH groups results in the disease scurvy.

Tertiary Structure of Proteins

Tertiary Structure: Water-Soluble Proteins Fold Into Compact Structures with Nonpolar Cores

- The tertiary structure of a protein is its 3-D arrangement; that is, the folding of its 2°structural elements, together with the spatial dispositions of its side chains.

- Ex. myoglobin carried out by John Kendrew and his colleagues in the 1950s.

- Myoglobin, the oxygen carrier in muscle. It functions both to store oxygen and to facilitate oxygen diffusion in rapidly contracting muscle tissue.

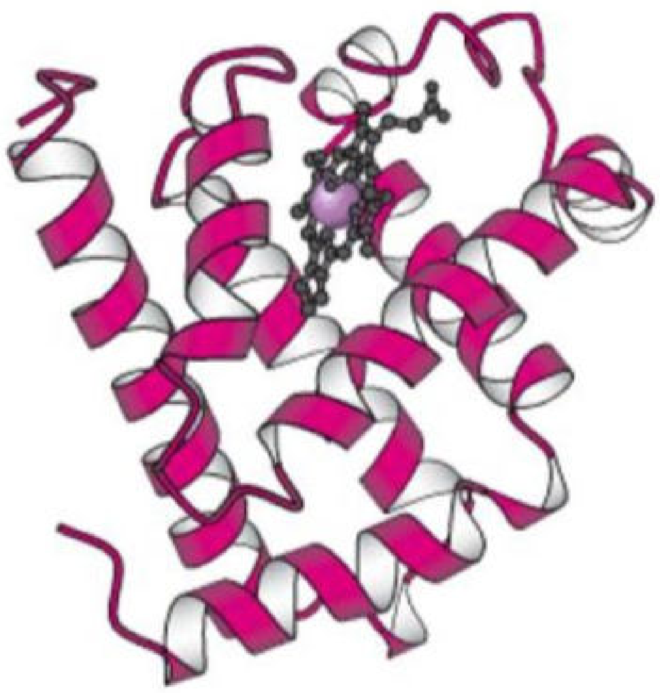


Fig.3.44 b: Biochemistry 7th edition by Berg, Tymoczko and Stryer

- Capacity of myoglobin to bind oxygen depends on the presence of heme, a non-polypeptide prosthetic group consisting of protoporphyrin IX and a central iron atom.

- The interior consists of nonpolar residues such as leucine, valine, methionine, and phenylalanine.

- The only polar residues inside are two histidine residues, play critical roles in binding iron and oxygen. The outside of myoglobin, consists of both polar and nonpolar residues.

- **Principles of the Protein structure**:

1. Hydrophobic amino acid side chains located interior of the protein and hydrophilic side chains are located on the exterior of the protein.

2. Structure: Devoid of symmetry (globular).

3. Tightly packed.

4. Tertiary structure also include disulfide bonds.

Cont---

5. Polypeptide chains folded into a spherical or globular shape. Globular proteins are stabilized by all weak interactions:

a) Hydrogen bonds
b) Hydrophobic interactions
c) Ionic interactions: Negatively charged groups, such as the carboxylate group (–COO–) in the side chain of aspartate or glutamate, can interact with positively charged groups such as the amino group (– NH3+) in the side chain of lysine.
d) Vander wall’s forces: Contribute to both the packing of atoms in proteins as well as the space between atoms.

Cont---

6. **Tertiary structure can be sub-divided into domains:**

- Part of protein sequence and structure that can evolve, function, and exist independently of the rest of the protein chain. , ex. ligand binding domain, membrane spanning domain.

- Protein domain is a conserved part of a given protein sequence and tertiary structure that can evolve, function and exist independently of the rest of the protein chain.

- Independently folded portion of the protein linked by helical hinges.

- Evolutionary conserved structure common in many proteins.

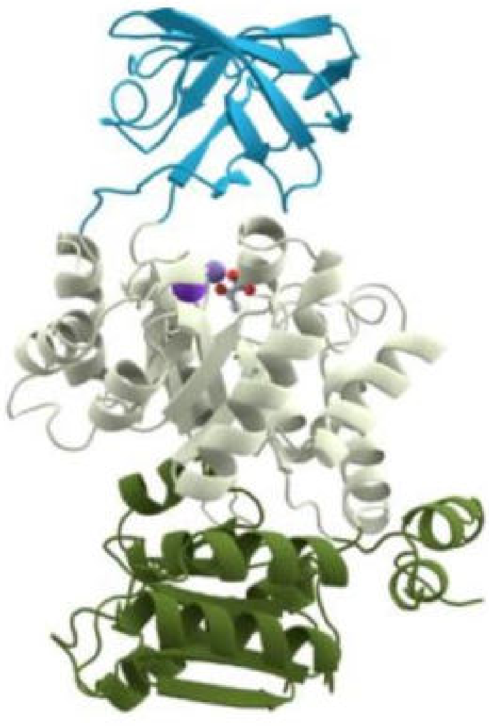
Cont--

- Many proteins consist of several structural domain. Ex. Protein pyruvate kinase show three domains:

a) It contains an all-β nucleotide binding domain (in blue).

b) α/β-substrate binding domain (in grey).

c) α/β-regulatory domain (in green) connected by several polypeptide linkers.



Wikipedia

Quaternary Structure of Proteins

Quaternary Structure: Polypeptide Chains Can Assemble Into Multi-subunit Structures

- This level of protein structure applies only to those proteins that consist of more than one polypeptide chain, termed subunits.

- Quaternary structure implies the non-covalent interaction that stabilise the folded polypeptides leads to multisubunit proteins.

Cont--

- Multisubunit proteins can have a number of identical (homomeric) or non-identical (heteromeric) subunits.
- The simplest multisubunit proteins are homodimers – two identical polypeptide chains that are independently folded but held together by non-covalent interactions.

Cont--

- Example. Hemoglobin (Hb), oxygen carrying protein in blood contains four polypeptide chains and four heme prosthetic groups, in which the iron atoms are in the ferrous (Fe2+) state.
- The protein portion, called globin, consists of two α-chains and two β-chains.

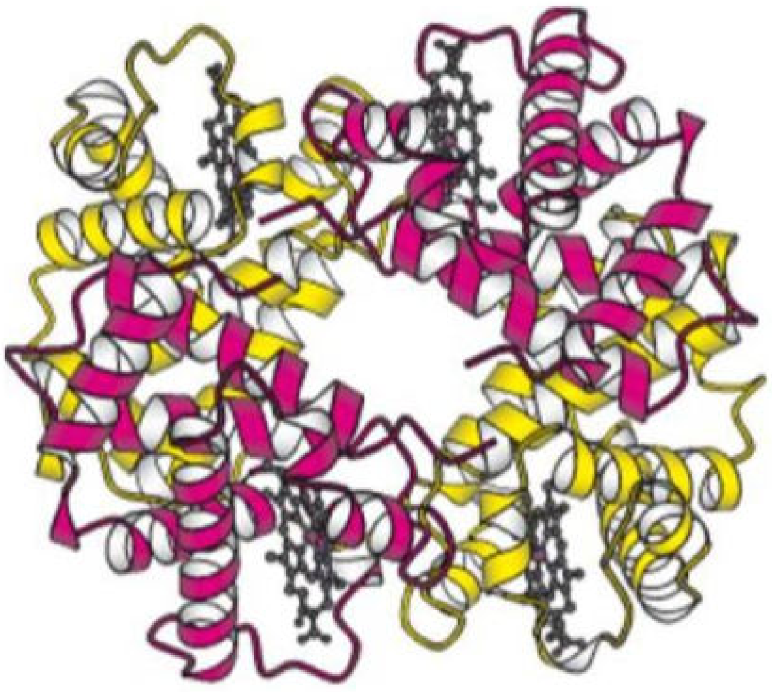


Fig.3.49: Biochemistry 7th edition by Berg, Tymoczko and Stryer

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- Subunits of Hb are arranged in symmetric pairs, each pair having one α and one β subunit.

- Hb exists as an $\alpha_2\beta_2$ tetramer. Subtle changes in the arrangement of subunits within the Hb molecule allow it to carry oxygen from the lungs to tissues with great efficiency.

Summary

- The gene-encoded primary structure of a polypeptide is the sequence of its amino acids.

- Secondary structure refers to stable arrangements of amino acid residues giving rise to recurring structural patterns.

- Folding of polypeptides into hydrogen-bonded motifs such as the α helix, the β-pleated sheet, β bends, and loops.

- Tertiary structure is the complete three-dimensional structure of a polypeptide chain.

- When a protein has two or more polypeptide subunits, their arrangement in space is referred to as quaternary structure

Interaction with students

- Distributed subtopics of class to students for participate in group discussion in next class.

Reference Books

1) Harper's Illustrated Biochemistry-30th edition
2) Biochemistry. 4th edition. Donald Voet and Judith G. Voet.
3) Biochemistry 7th edition by Jeremy M. Berg, John L. Tymoczko and Lubert Stryer
4) Lehninger Principles of Biochemistry

Thank you