Proteins' Higher Order Structures

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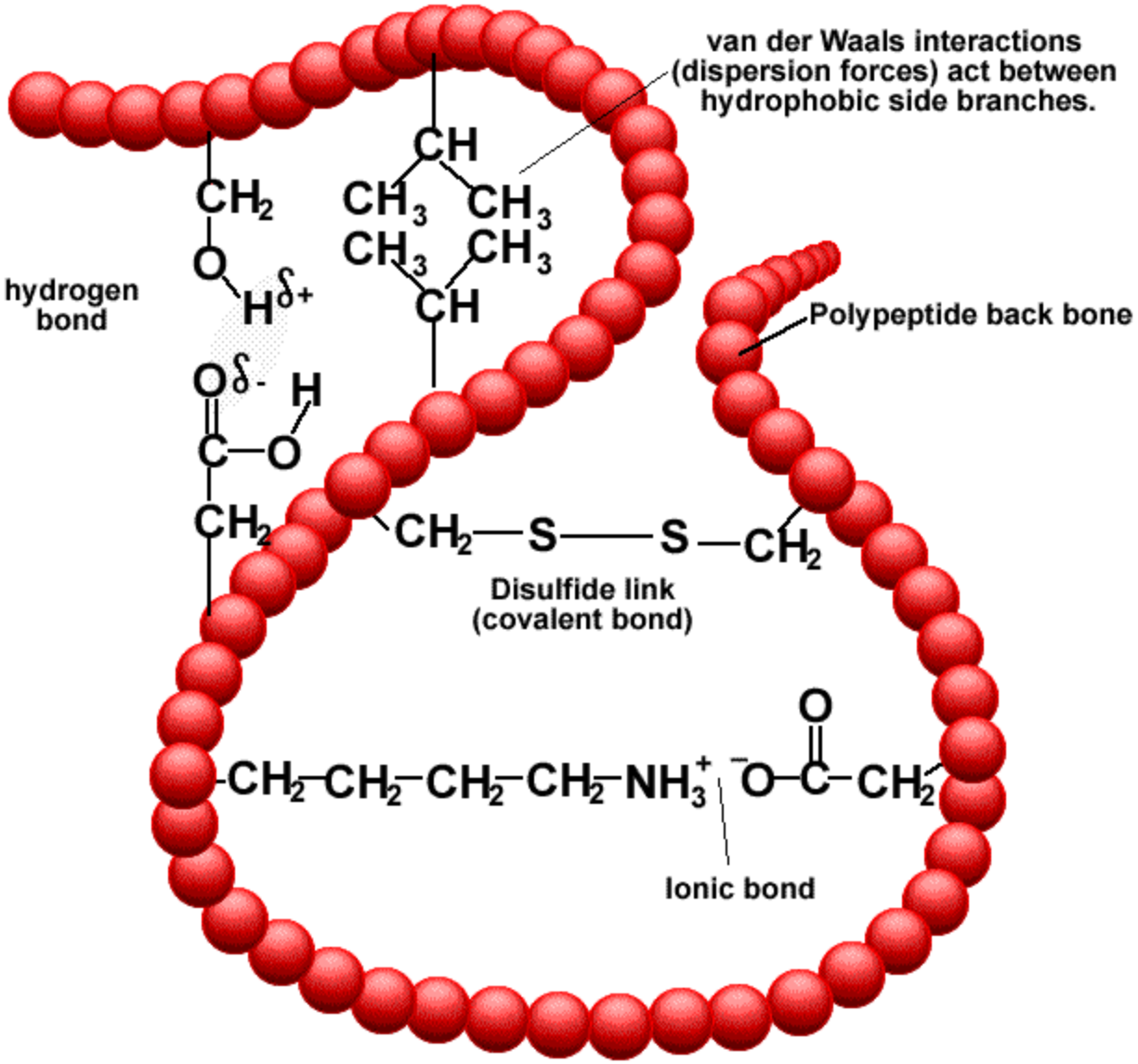
Previously on PHT 426!!



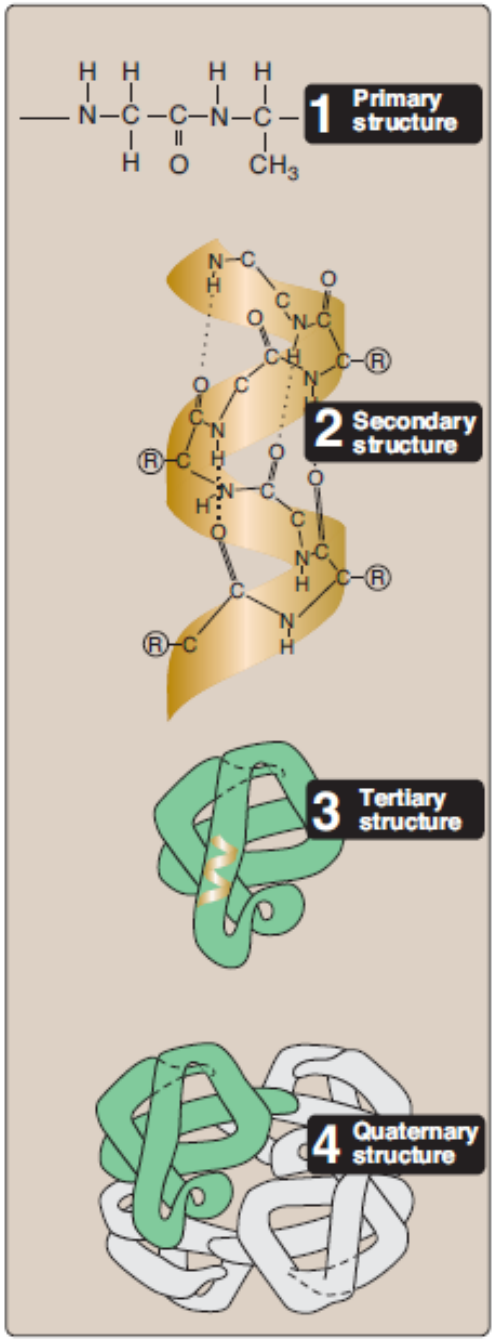
Protein Structures

• **Primary structure:** the amino acid sequence of a protein.

• **Secondary structure:** a specific local structure that is produced by hydrogen bonding within the backbone.

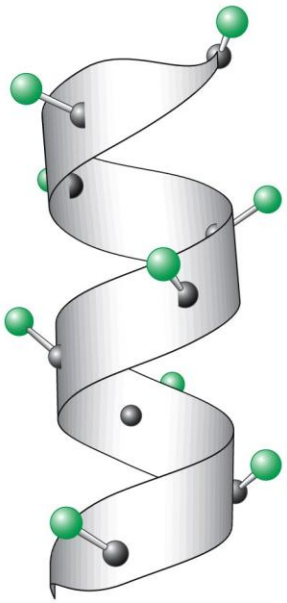
• **Tertiary structure:** the three dimensional structure of a single amino acid chain which is produced by interactions of secondary structures.

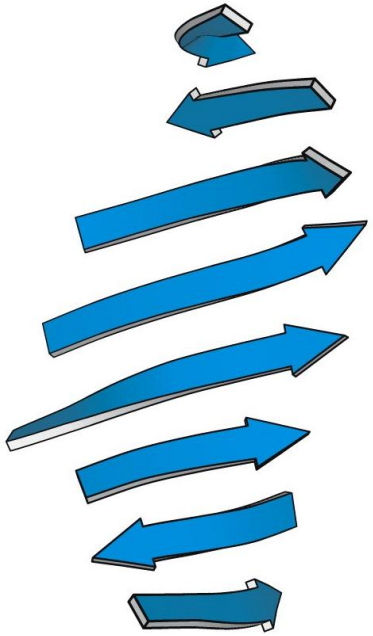
• **Quaternary structure:** the three dimensional structure of protein that is resulted from intermolecular interaction within two or more protein units.

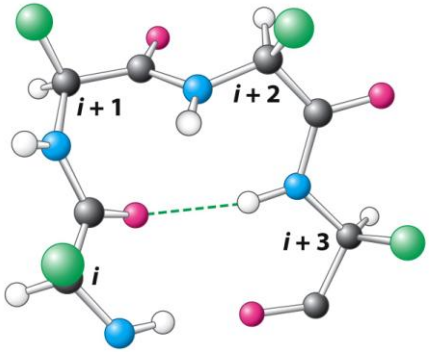


Secondary Structure

- Helices
- β- Sheets
- Turns





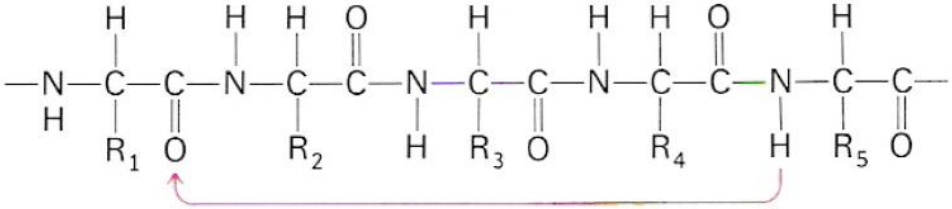


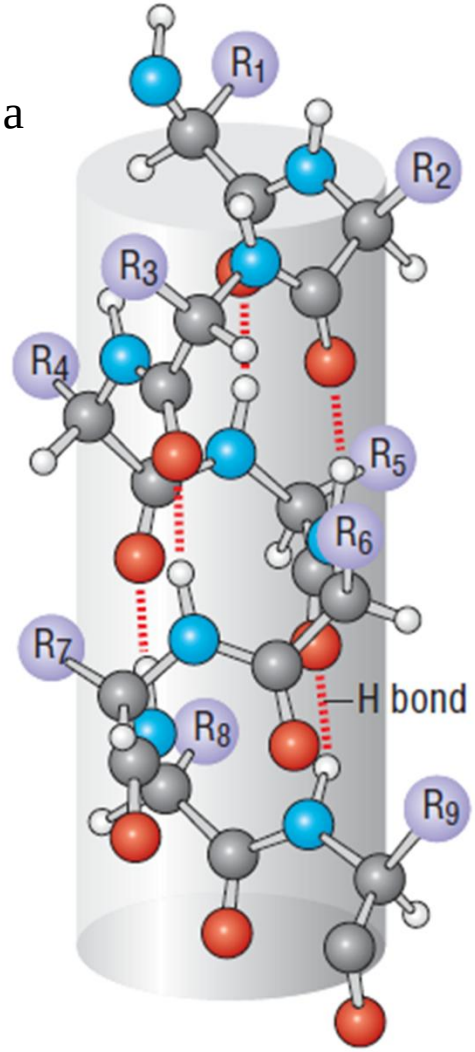
α- Helices

• Alpha helices are versatile cylindrical structures stabilized by a network of backbone hydrogen bonds between C=O and N–H groups close together in the sequence.

• In an alpha helix, the carbonyl oxygen atom of each residue (n) accepts a hydrogen bond from the amide nitrogen four residues further along (n+4) in the sequence, so that all of the polar amide groups in the helix are hydrogen bonded to one another.

• At the start of an α-helix, four amide groups are always free, and at the end of an α-helix, four carbonyl groups are also free. As a result, both ends of an α-helix are highly polar.



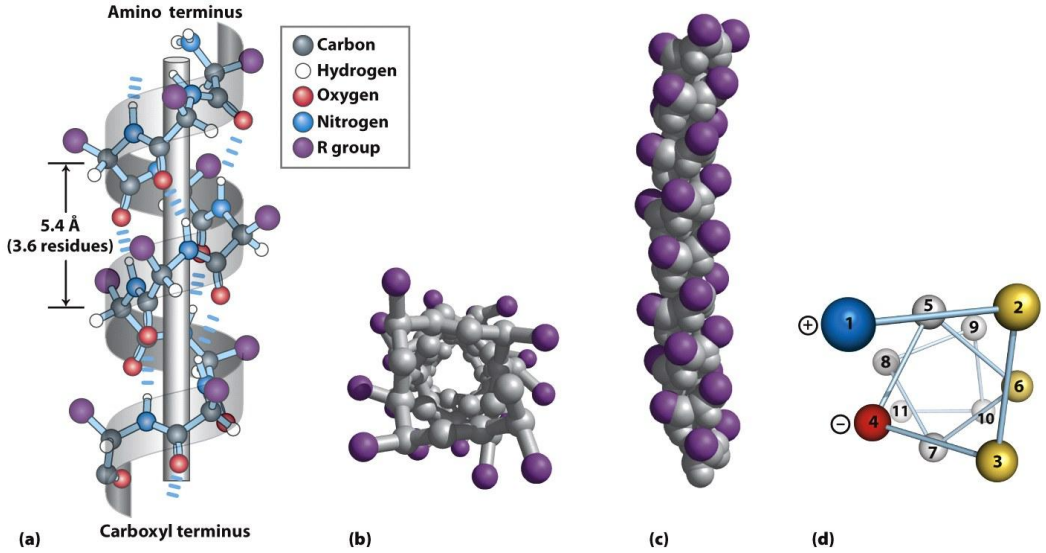


α- Helices

• The result is a cylindrical structure where the wall of the cylinder is formed by the hydrogen-bonded backbone, and the outside is studded with side chains. The protruding side chains determine the interactions of the alpha helix both with other parts of a folded protein chain and with other protein molecules.

• Often an α-helix serves as a building block for the three-dimensional structure of globular proteins by bringing hydrophobic side chains to one side of a helix and hydrophilic side chains to the opposite side of the same helix.

• Not all polypeptide sequences adopt α-helical structures. Small hydrophobic residues such as Ala and Leu are strong helix formers. Pro acts as a helix breaker because the rotation around the N-Cα bond is impossible. Gly acts as a helix breaker because the tiny R-group supports other conformations.

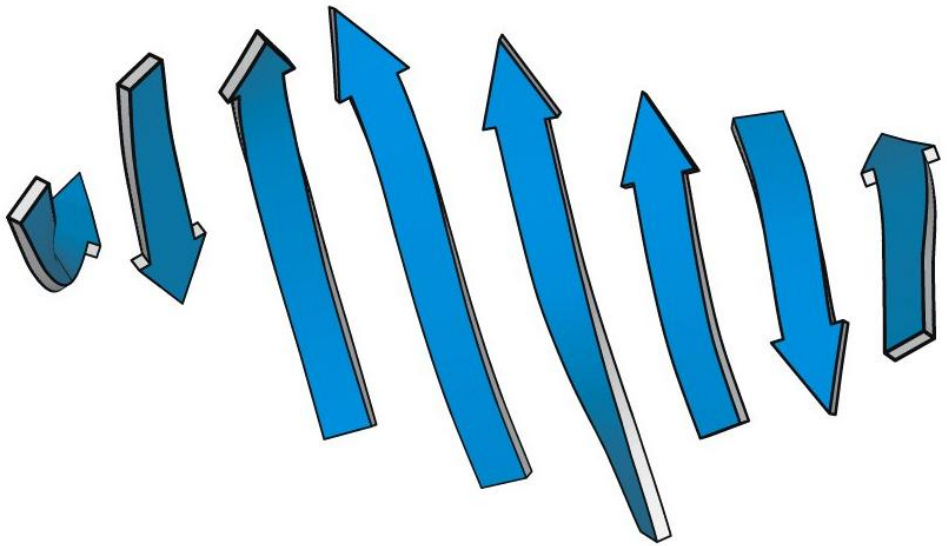


β- Sheets

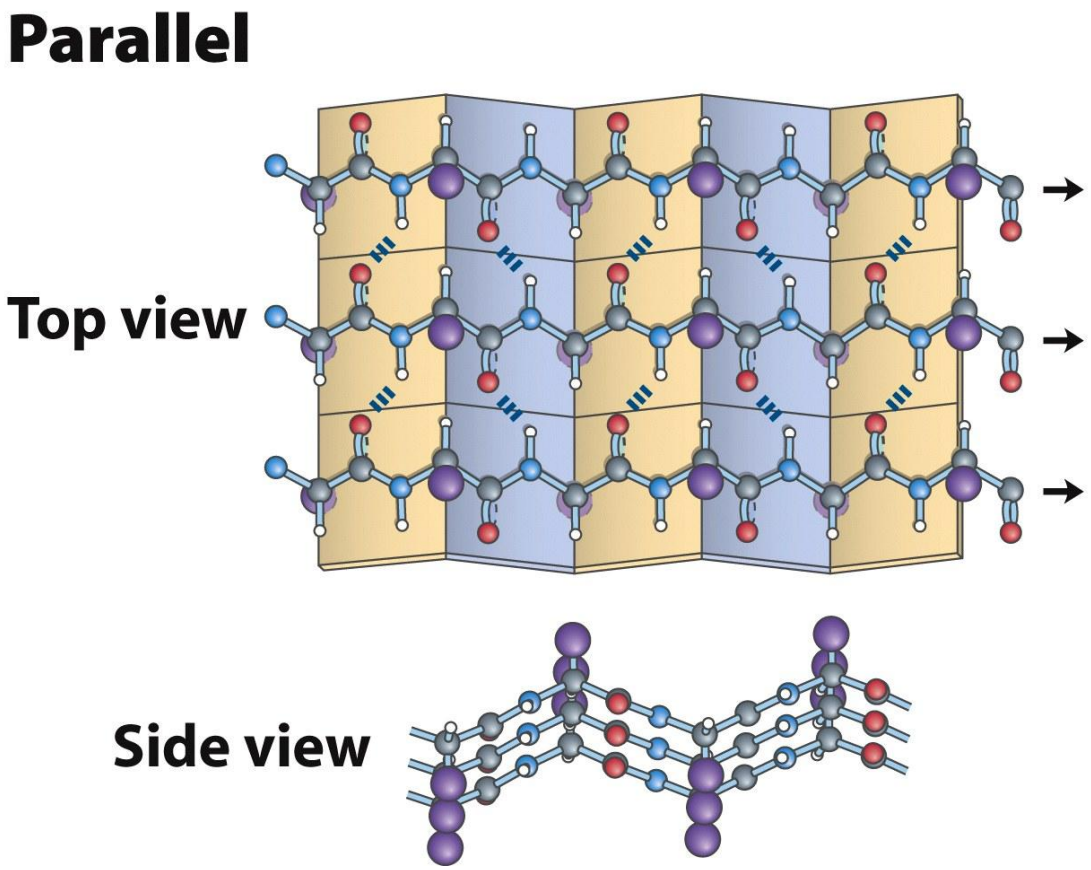
• In contrast to the α-helix, which is built up from a continuous region with a peptide hydrogen bond linking every fourth amino acid, the β-sheet is comprised of peptide hydrogen bonds between different regions of the polypeptide that may be far apart in sequence.

• β-sheets can interact with each other in two ways, either parallel or antiparallel. Mixed sheets with both parallel and antiparallel strands are also possible.

• Because the polypeptide chain in a beta sheet is extended, amino-acid side chains such as those of valine and isoleucine, which branch at the beta carbon, can be accommodated more easily in a beta structure than in a tightly coiled alpha helix where side chains are crowded more closely together. Although unbranched side chains can fit in beta structures as well, branched side chains appear to provide closer packing so they are found more frequently in sheets than other residues.

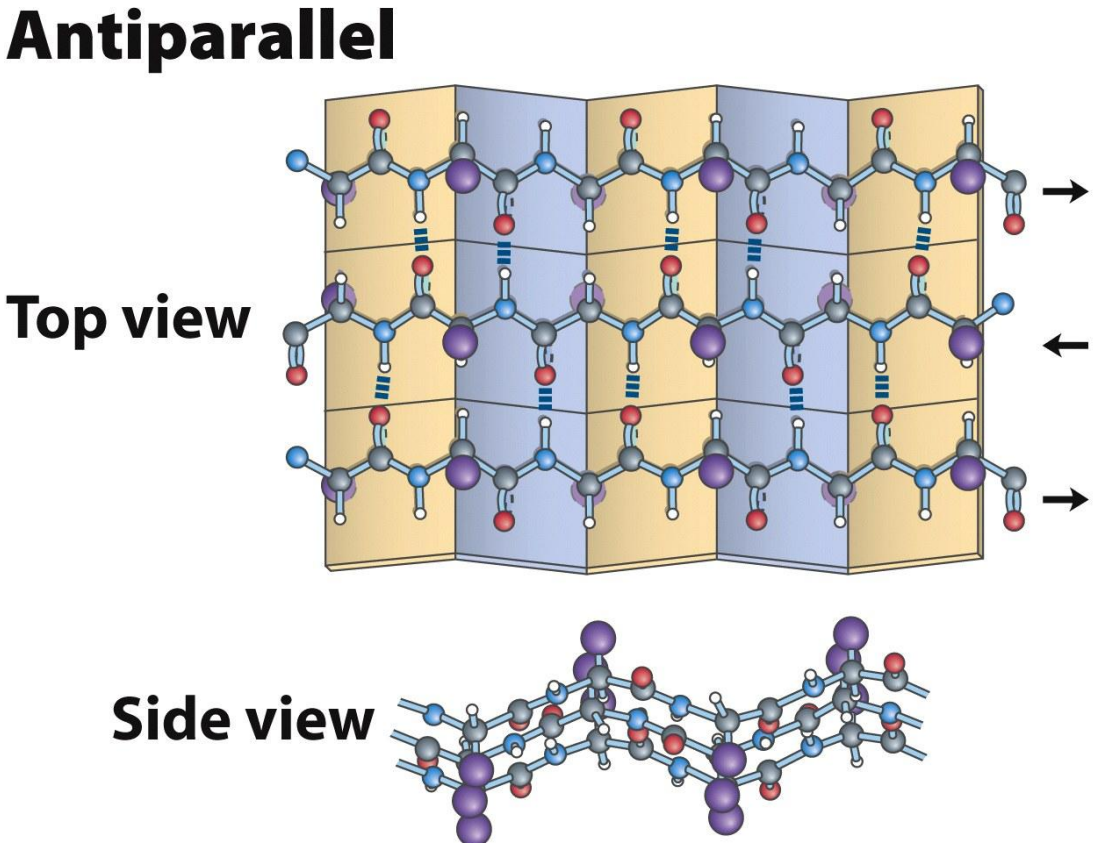


β- Sheets



- In parallel β-sheets, each strand is oriented in the same direction with peptide hydrogen bonds formed between the strands.
- Side chains protrude from the sheet alternating in up and down direction projecting perpendicularly to the plane.

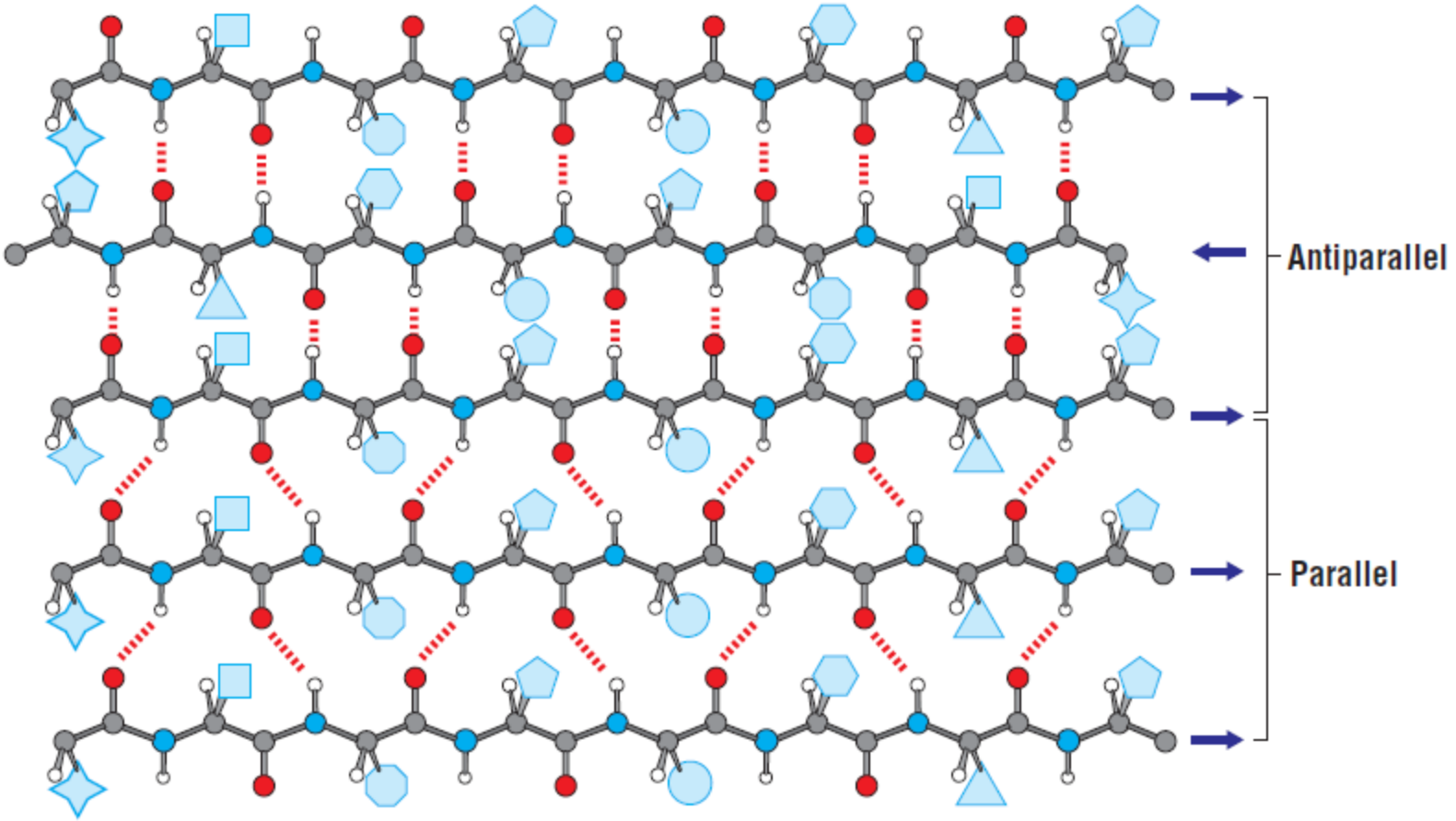
β- Sheets



- In Antiparallel β-sheets, the polypeptide sequence is oriented in the opposite direction.
- Antiparallel sheets are more stable, which is consistent with their hydrogen bonds being more linear.
- Side chains protrude from the sheet alternating in up and down direction projecting perpendicularly to the plane.

β- Sheets

Mixed Sheets



Turns

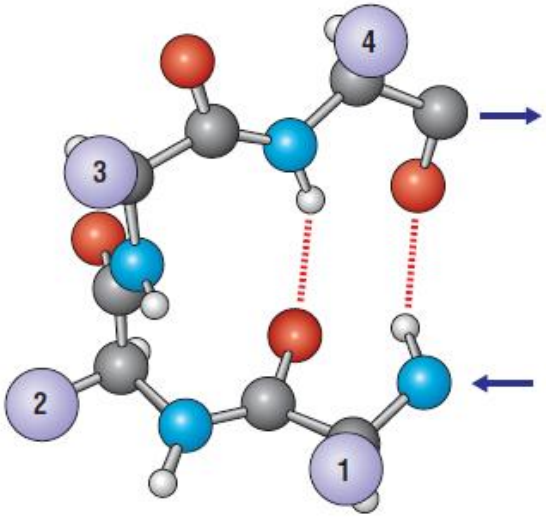
• The simplest secondary structure element.

• Usually involves four residues but sometimes requires only three. It consists of a hydrogen bond between the carbonyl oxygen of one residue (n) and the amide N–H of residue n+3, reversing the direction of the chain.

• They are comprised of an amino acid sequence which is usually hydrophilic and exposed to the solvent.

• It usually consists of Pro at the second position of the turn and a Gly at the third/fourth position.

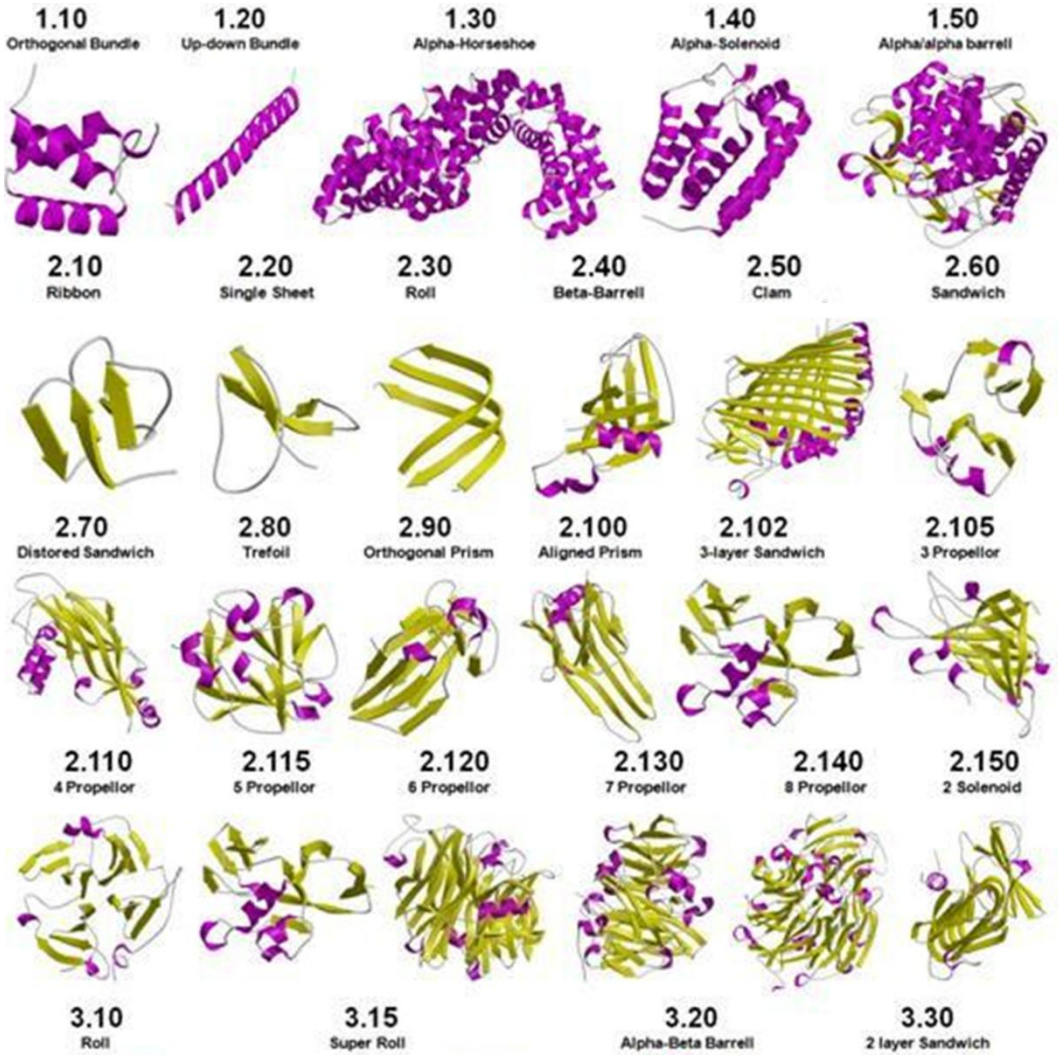
• Turns occur frequently whenever strands in β-sheets change direction.



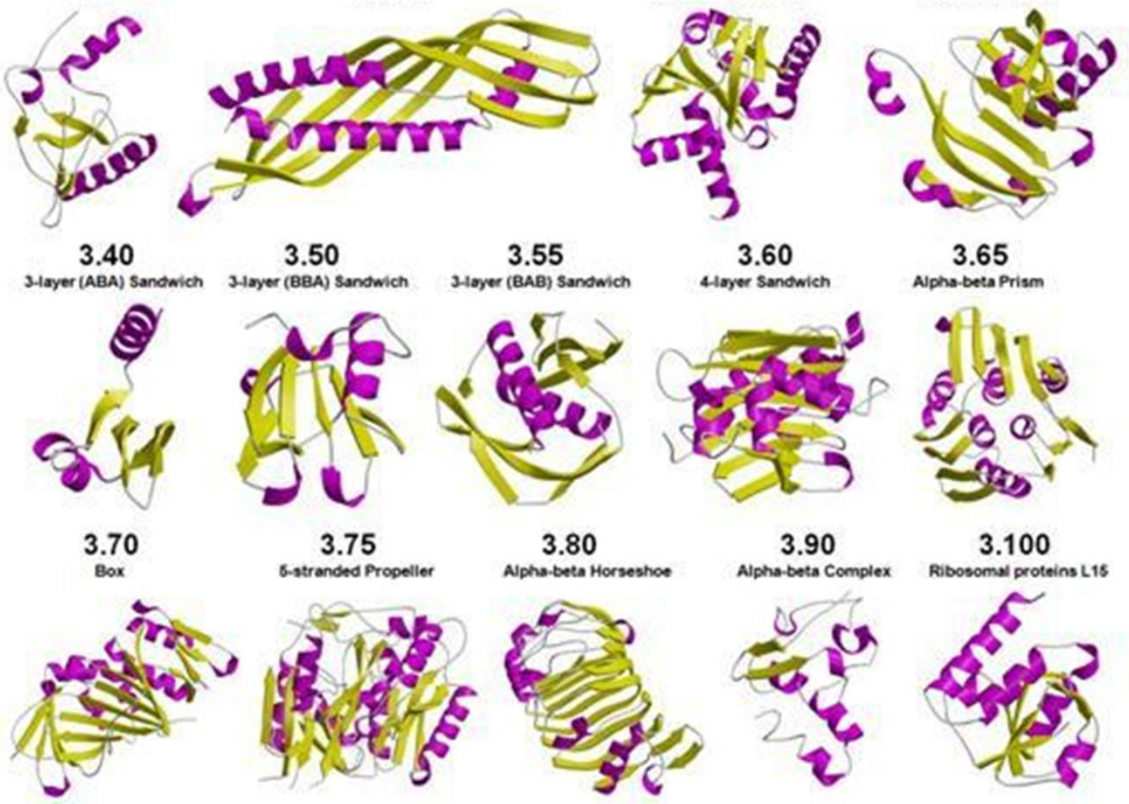
Tertiary Structure

• Combination of various secondary structures in a protein results in its three-dimensional structure.

• The folding of a protein molecule into a distinct three-dimensional structure determines its function.



Tertiary Structure



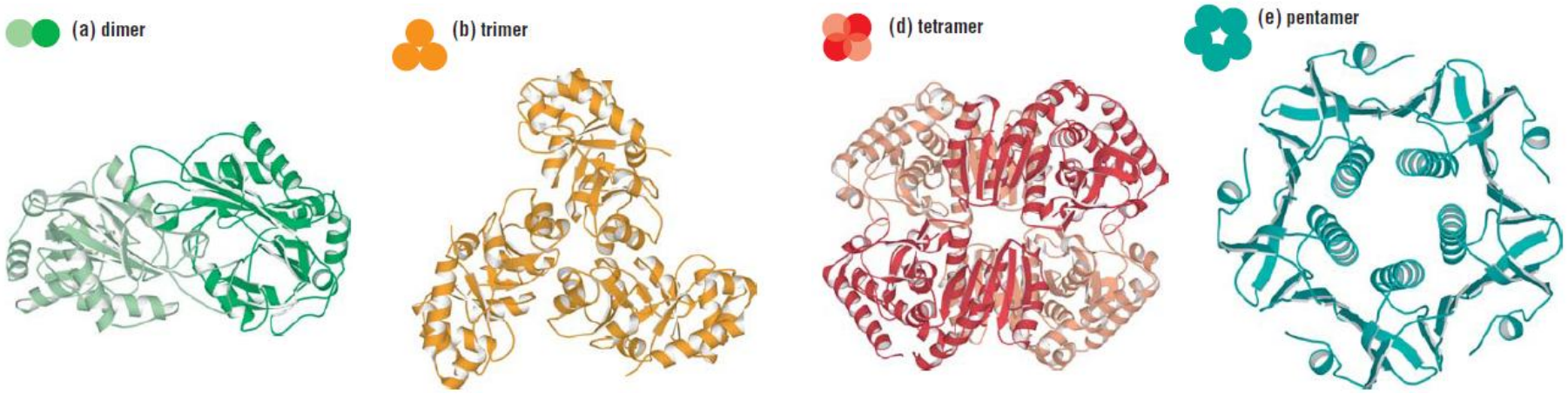
Quaternary Structure

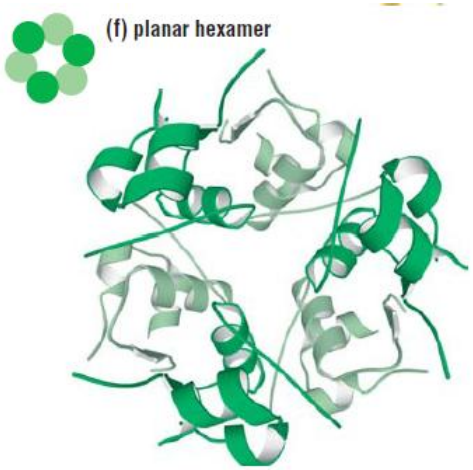
• A unique tertiary structure of a protein can often result in the assembly of the protein into a distinct quaternary structure consisting of a fixed stoichiometry of protein chains within the complex.

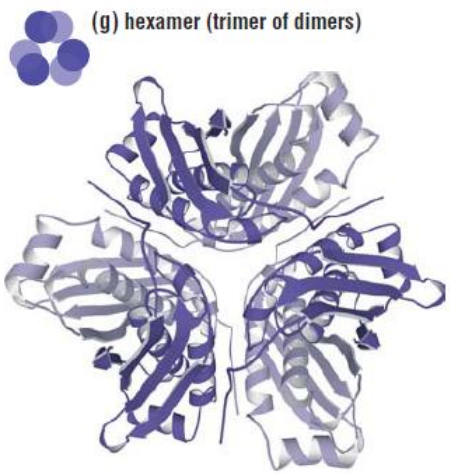
• Assembly can occur between the same proteins or between different polypeptide chains.

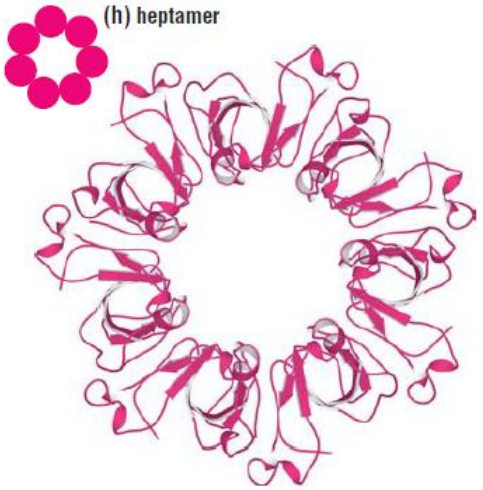
• Each molecule in the complex is called a subunit.

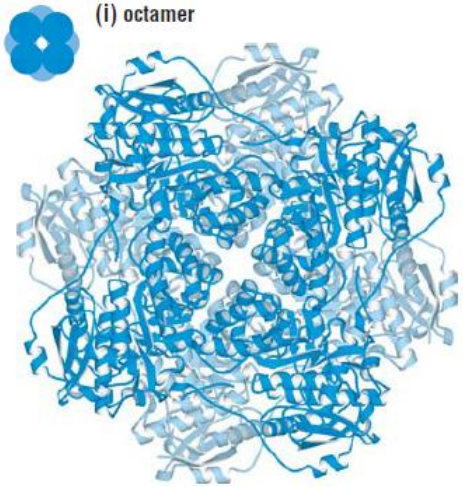
• The formation of quaternary structure occurs via non-covalent interactions or through disulfide bonds between the subunits.

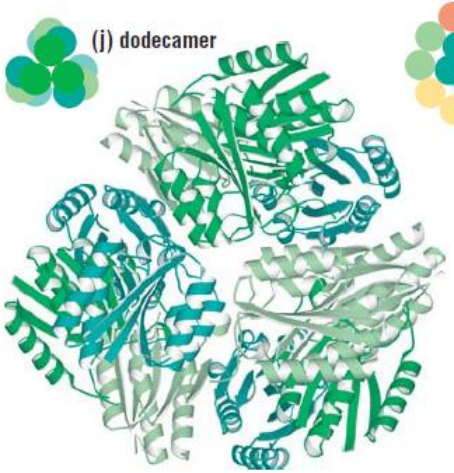


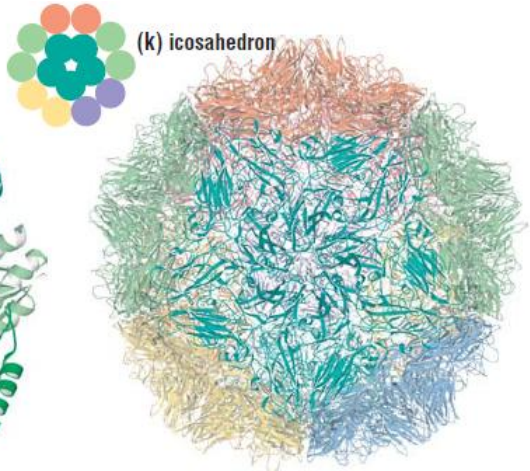

(f) planar hexamer


(g) hexamer (trimer of dimers)


(h) heptamer


(i) octamer

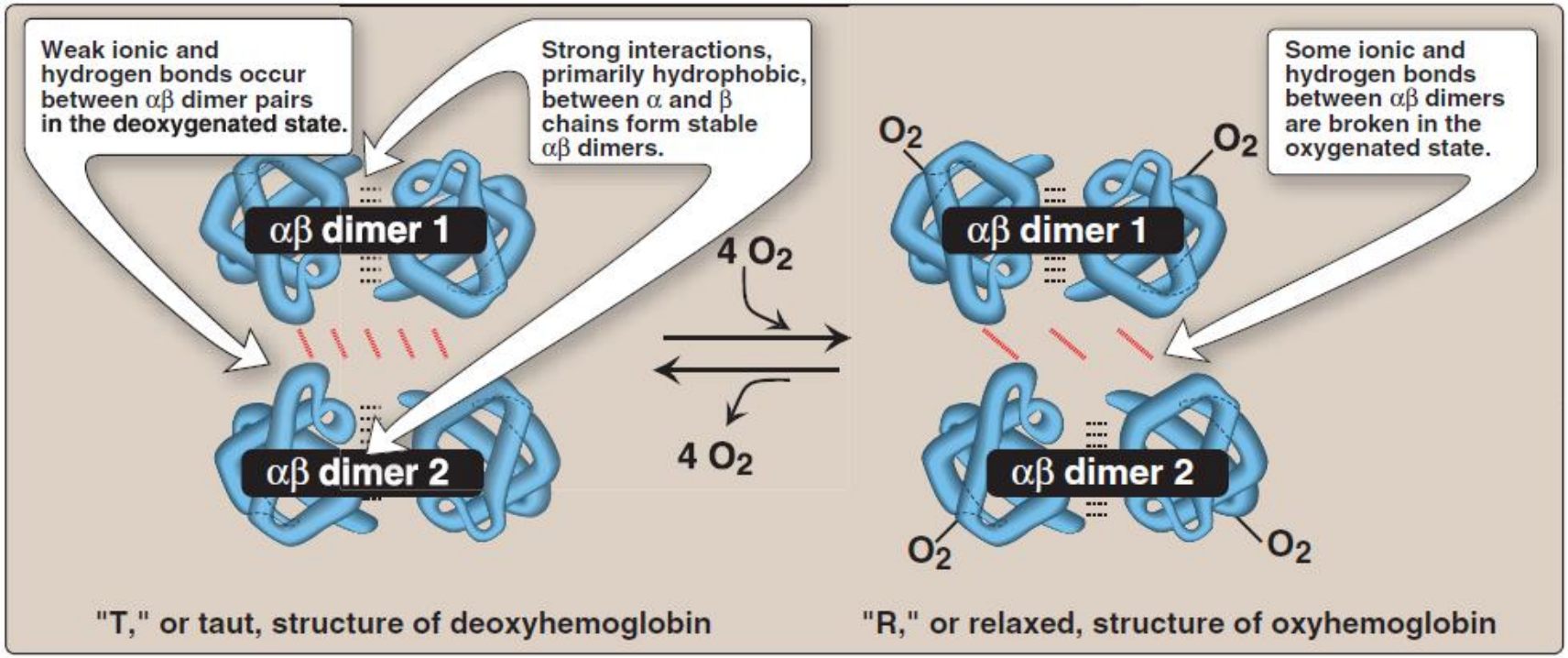

(j) dodecamer


(k) icosahedron

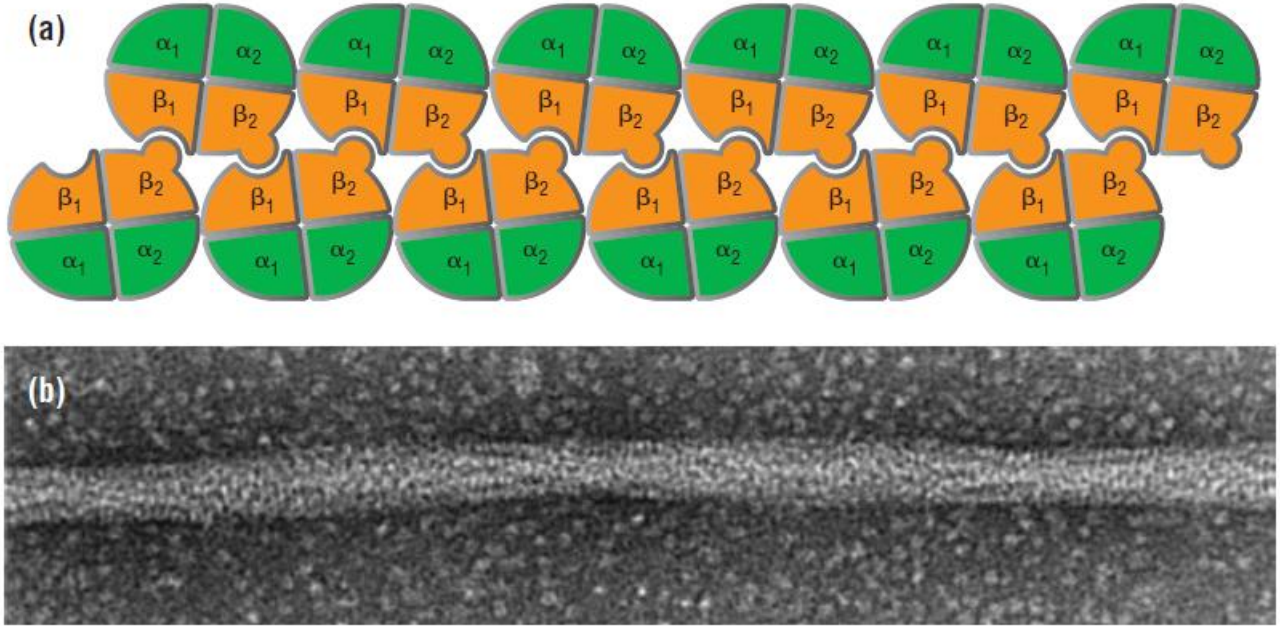
Quaternary structure of some proteins

Hemoglobin

Tetramer, consisting of two α and two β subunits



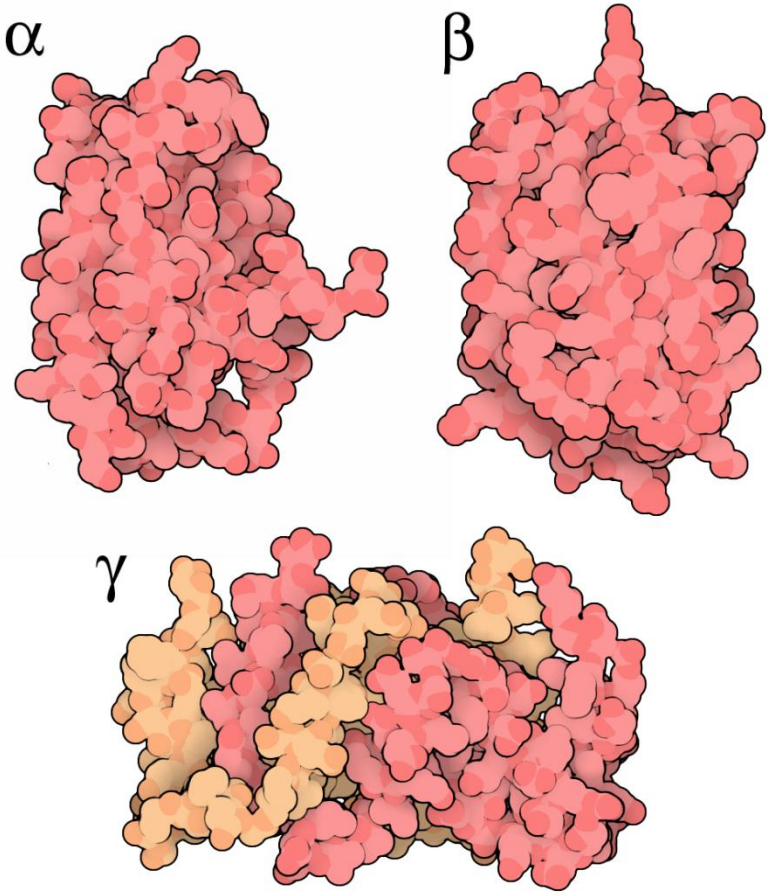
Inappropriate quaternary interactions can have dramatic functional consequences!!



Sickle-cell hemoglobin: Hemoglobin molecules form long polymers when they carry the sickle-cell mutation, in which a hydrophobic patch is created on the surface of the tetramer by the substitution of a hydrophobic valine for a hydrophilic glutamine in the beta subunit. (a) The hydrophobic patch created by the mutant valine is represented by a bump in the beta2 subunit, which binds in a hydrophobic pocket in the beta1 subunit of another hemoglobin molecule. Because the hydrophobic pocket into which the mutant valine binds is present only in the deoxy form of hemoglobin, the formation of the fibers, which constrains the molecule in the deoxy state, also functionally disables it. (b) Polymers of sickle-cell hemoglobin aggregate to form thicker fibers. These rigid fibers distort the hemoglobin-carrying red blood cells, causing them to rupture or to block blood vessels, with painful and sometimes fatal consequences. Severe anemia is thus not the only pathological consequence of the sickle-cell mutation.

Quaternary structure of some proteins

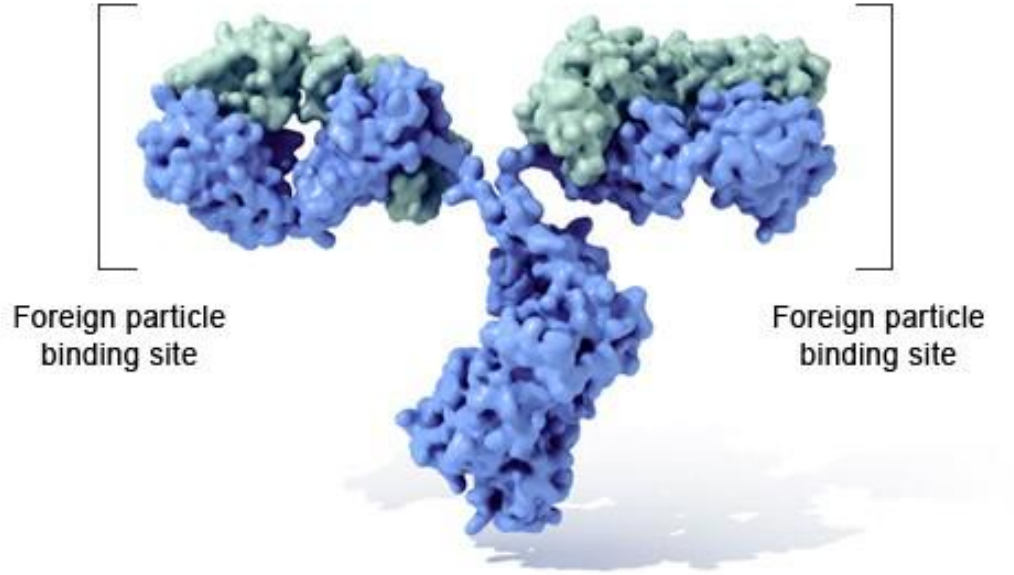
Interferon-γ is a homodimer

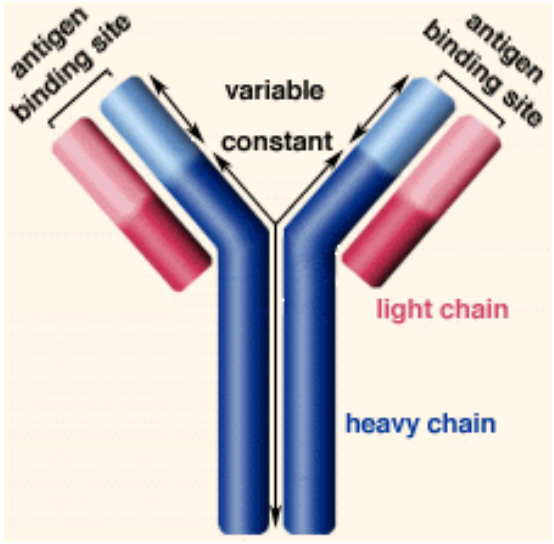


Quaternary structure of some proteins

IgG's are homodimers

Immunoglobulin G (IgG)





Quaternary structure of some proteins

Insulin in the presence of Zinc forms a hexameric complex