

Proteins- lecture part 3

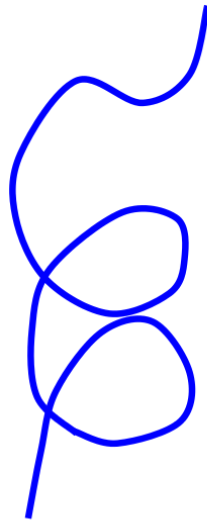
Structural organization of proteins

- Different levels of protein organization



1

Primary



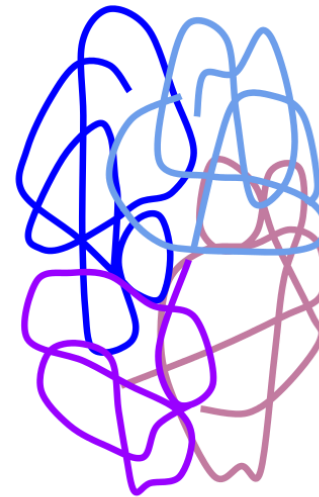
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Secondary



3

Tertiary



4

Quaternary

Levels of structure in proteins

Primary Structure = sequence of amino acids

3-letter code

Lys-Thr-Tyr-Phe-Pro-His-
Phe-Asp-Leu-Ser-His-**Gly** ...

1-letter code

KTYFP~~H~~FDLSH**G**

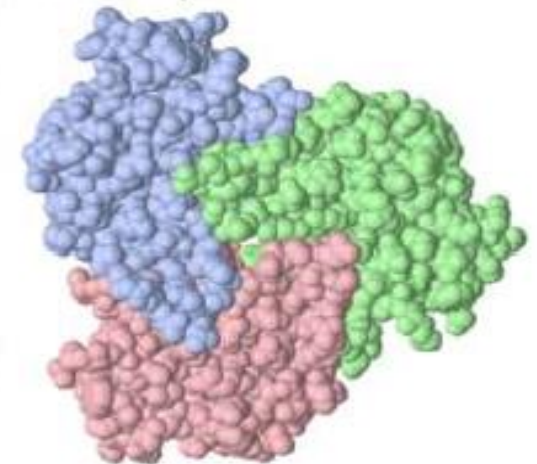
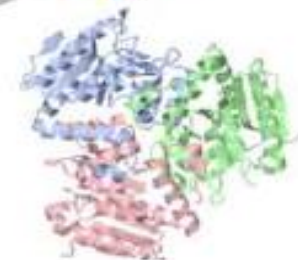
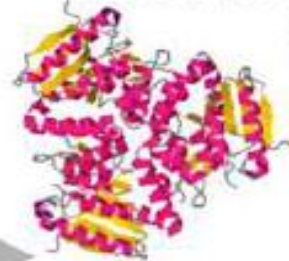
Secondary Structure =
alpha helices, **beta strands**




Tertiary Structure = fold
helices and strands into domains



Quaternary Structure (Biological Units)
= functional assemblies of chains
(subunits)



Structural organization of proteins

- Proteins perform a variety of functions
 - Functions are closely related to the structures of proteins
 - Fundamentally, all proteins are made of amino acids linked to one another by peptide bonds
 - A complex three-dimensional structure is formed by:**
 - Coiling and folding of peptide chains
 - Union of several peptide chains with one another
 - The three-dimensional structure is also known as **conformation of the protein**
 - The conformation is unique to each protein
 - The biological functions of a protein depend upon its conformation
 - Any change in conformation may lead to loss of function
 - The conformation depends upon the sequence of amino acids
- 

Structure of proteins is formed by:

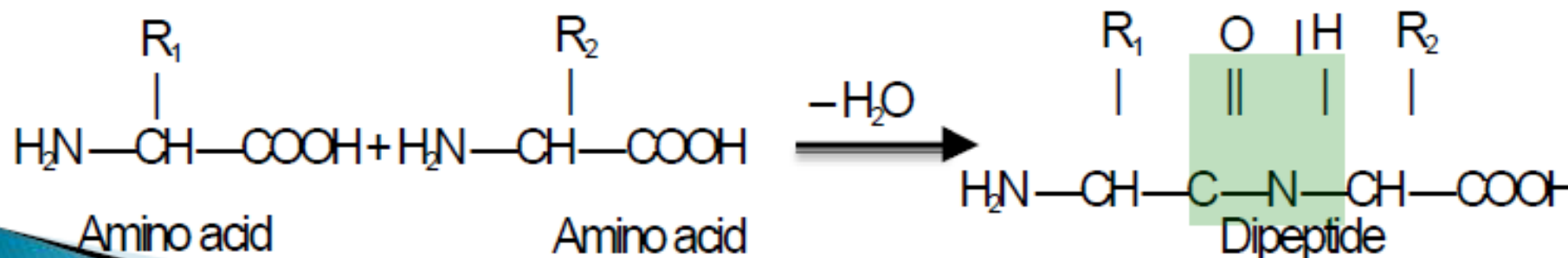
- A) Covalent or strong bonds
- B) Non-covalent or weak bonds

A) Covalent or strong bonds

These bonds are relatively strong

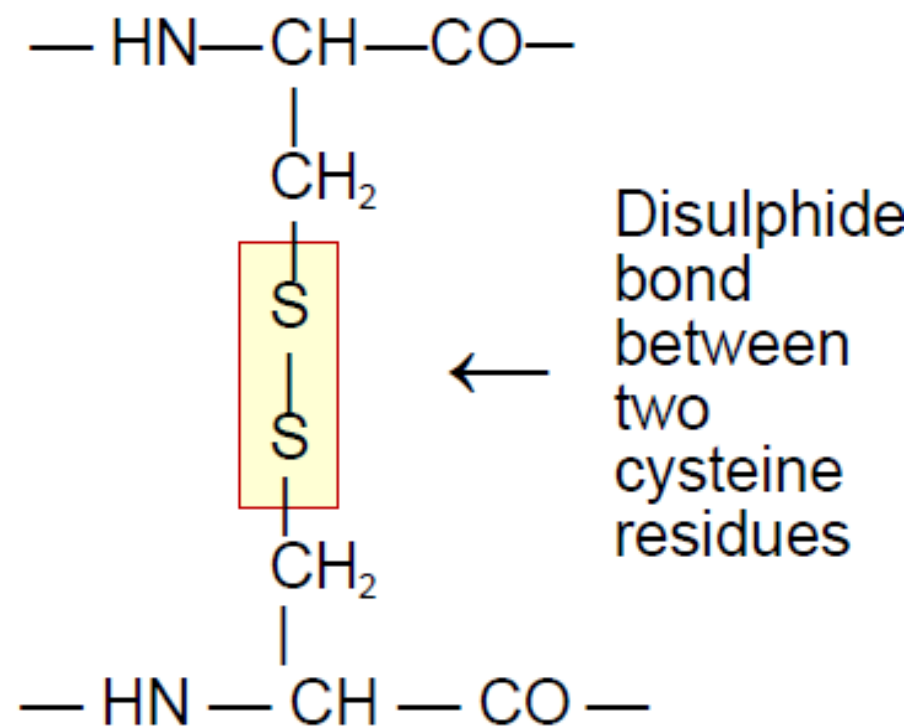
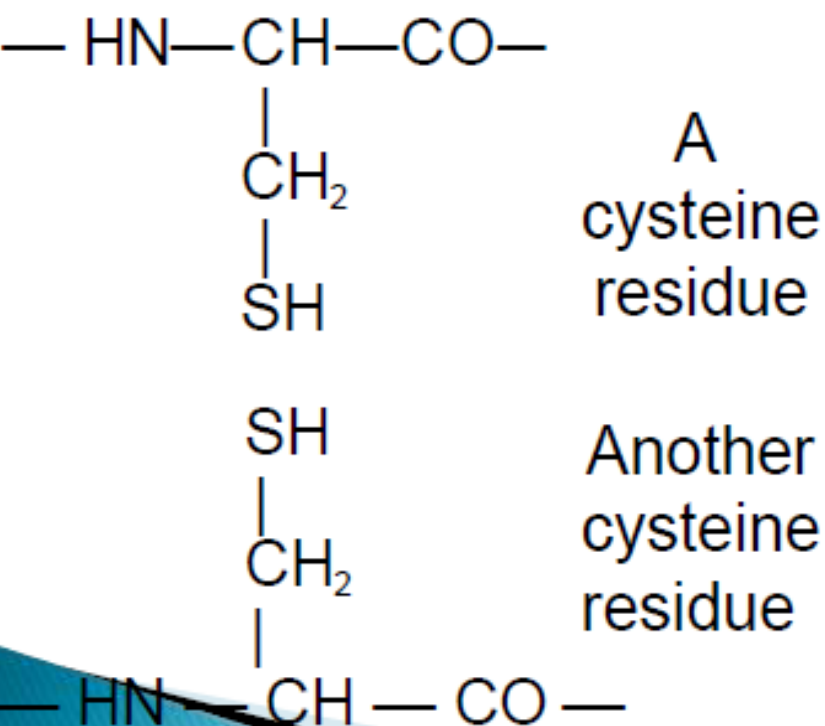
i) Peptide bonds

- These are the basic linkages between two consecutive amino acids
- As they are formed between amino groups and carboxyl groups, they are known as peptide bonds
- All amino acids present in a protein take part in the formation of peptide bonds



ii) Disulphide bonds

- A disulphide bond is formed between two cysteine residues
- The sulphydryl groups of residues are linked together



B) Non-covalent or weak bonds

- Non-covalent bonds are much weaker than the covalent bonds
- But they contribute significantly to the stability of protein structure

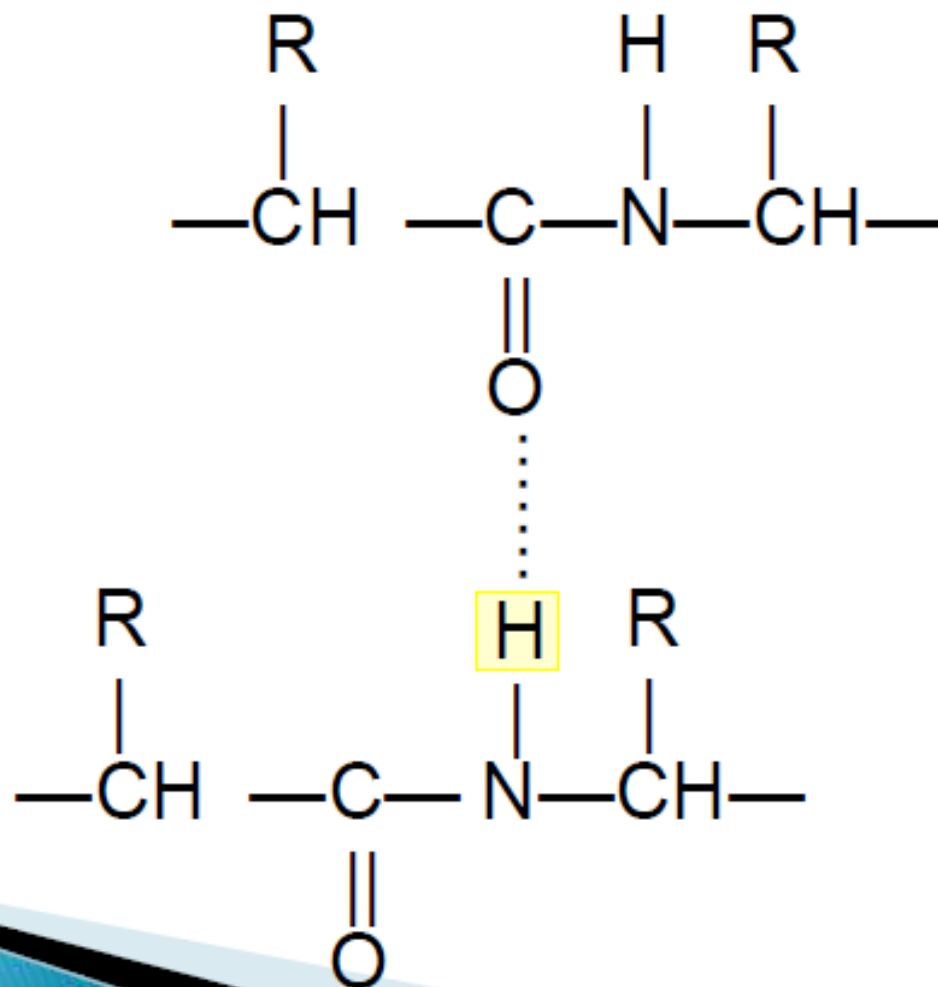
The main non-covalent bonds in proteins are

- (i) Hydrogen bonds
- (ii) Electrostatic bonds
- (iii) Hydrophobic bonds

(i) Hydrogen bonds

- Hydrogen bonds are formed between two peptide linkages
- The peptide linkages may be present in the same polypeptide or in different polypeptide chains
- The hydrogen atom of the N-H group participating in a peptide bond is shared between nitrogen and oxygen atoms

-The nitrogen atom involved in sharing belongs to one peptide bond, and the oxygen atom belongs to another peptide bond



(ii) Electrostatic bonds

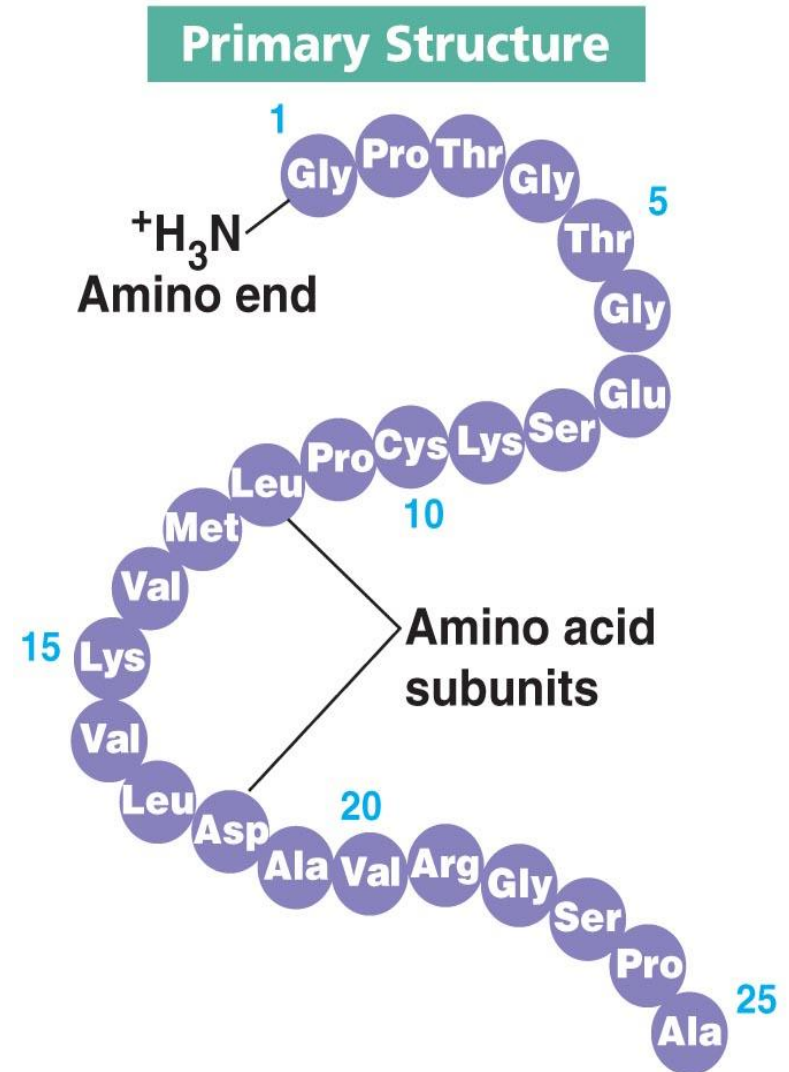
- Electrostatic bonds or salt bonds are formed between two oppositely charged groups
- Side chains of several amino acids contain ionizable groups e.g. amino groups, carboxyl groups, sulphhydryl groups, phenol groups etc
- Such groups may form electrostatic bonds with other groups bearing opposite charges

(iii) Hydrophobic bonds

- The side chains of non-polar amino acids attract each other because of their hydrophobic nature
- However, this is only a physical attraction and no chemical bonds are really formed

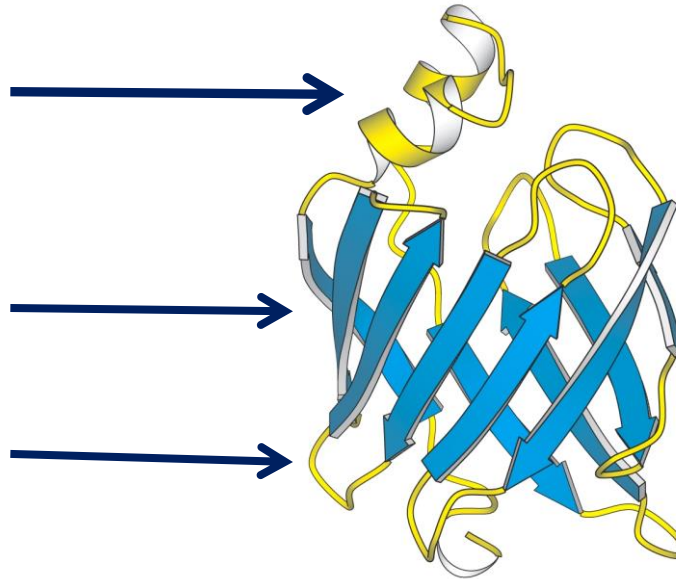
Primary structure

- **Linear sequence of amino acids** joined by peptide bonds in a polypeptide chain refers to the primary structure.
- The **peptide bonds** form the **backbone**.
- Amino end in the primary structure is the beginning residue of a polypeptide and known as **amino terminus**. The other end is a **carboxyl terminus**.
- The free -NH_2 group of the terminal amino acid is called as **N-terminal end** and the free -COOH end is called **C-terminal end**.
- Potential to form **hydrogen bonds** between oxygen of carboxyl group of one amino acid and hydrogen of amino group of another amino acid.



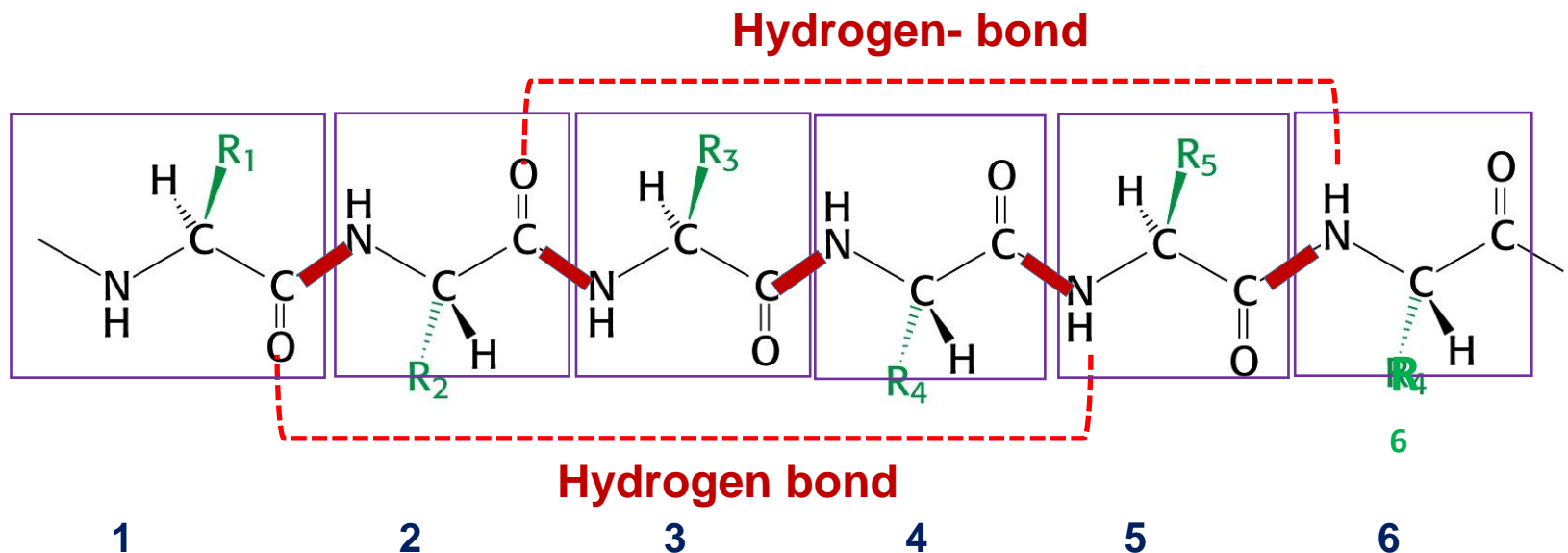
Secondary structure

- Amino acids in primary structure interact with one another to form the secondary structure.
- Interaction occurs through **hydrogen bonds**.
- The common secondary structures found in proteins are:
 - alpha (α)-helix
 - Beta (β)-strand/sheets
 - β -turns or reverse turns



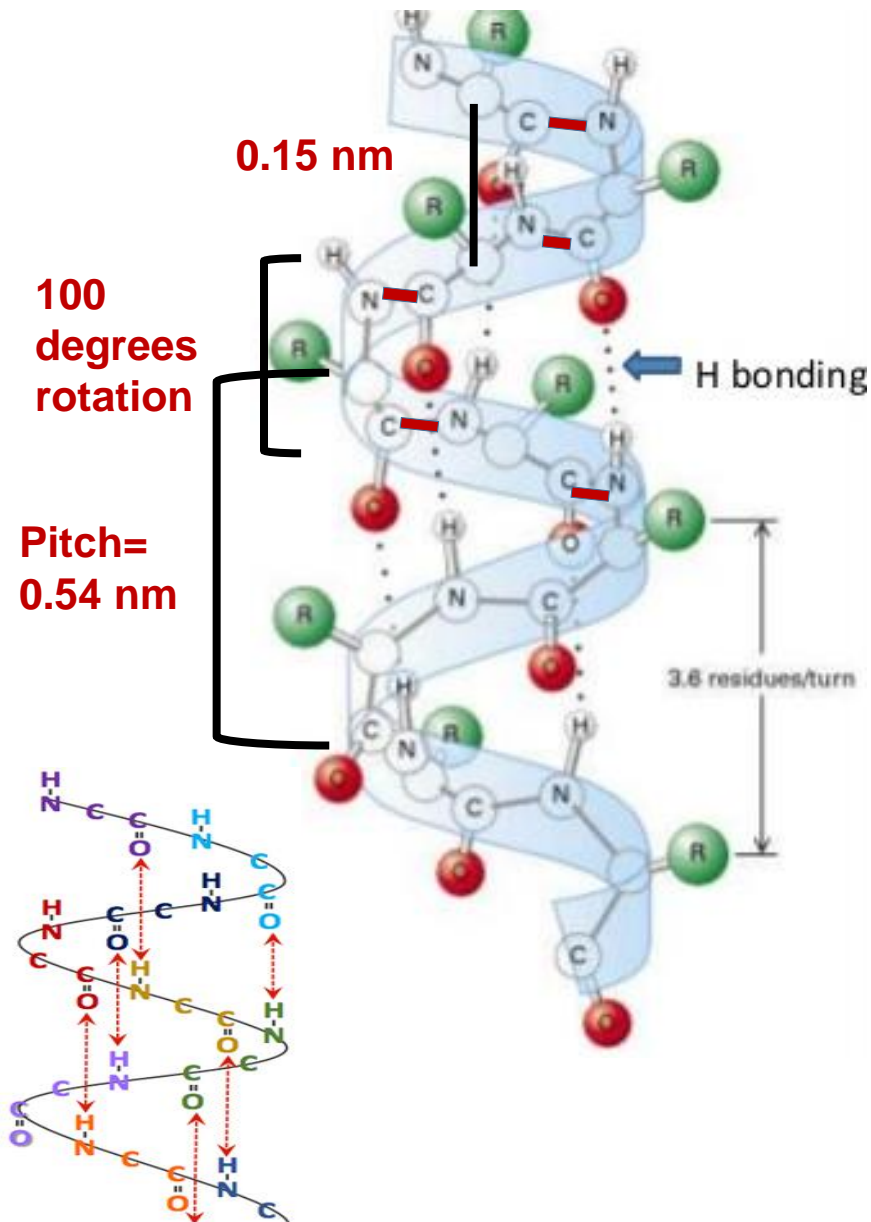
Alpha (α)-helix

- Rod-like structure, the polypeptide chain forms a spiral or a coiling with the backbone forming inner part of the coil and the side chains extend outward in helical array.
- Stabilized by **the intrachain hydrogen bonds** formed between the oxygen atom of carboxyl group of one amino acid and hydrogen atom of amino group of other amino acid.
- Hydrogen bond between every i (Residue 1) and $i+4$ (Residue 5) residue of polypeptide chain. “ i ” refers to any number of amino acid. If it “ i ” is first aa, “ $i+4$ ” is the fifth amino acid.



α -helical structure

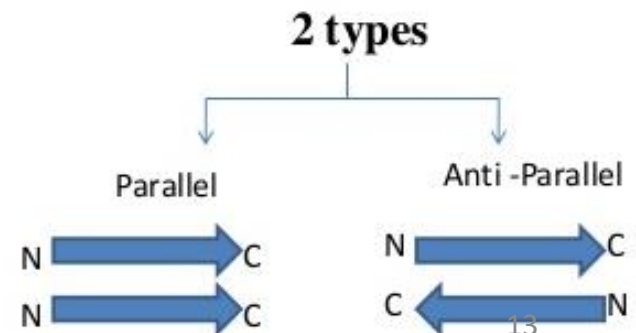
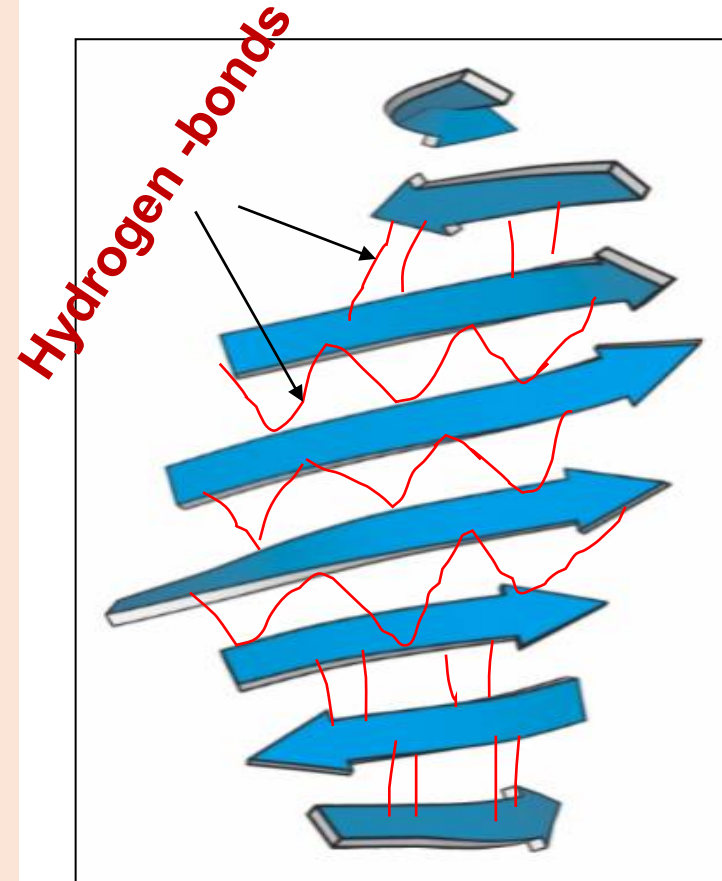
X-ray crystallography (XRC)- determines molecular and atomic positions



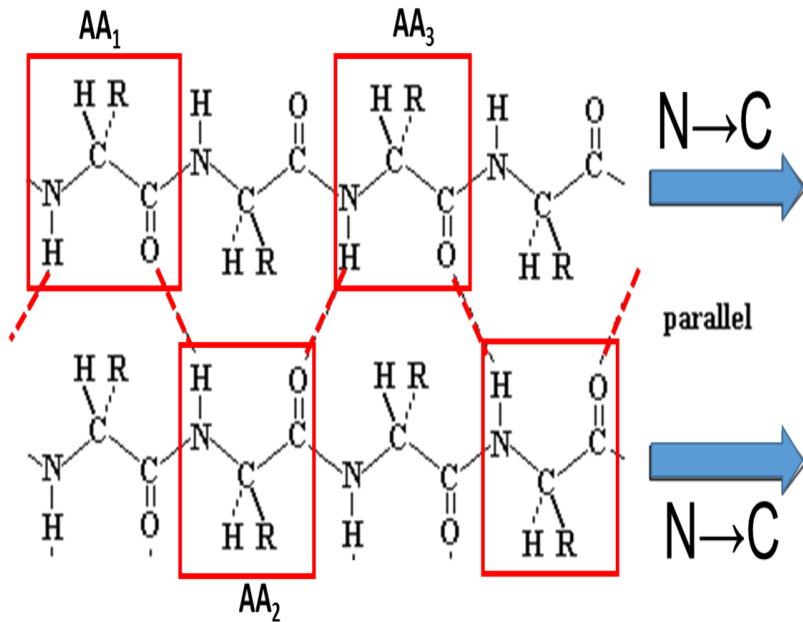
- Amino acids per turn=3.6 residues
- Amino acid distance from one another along the helix axis= 0.15 nm
- Pitch of the helix = 0.54 nm
- (Vertical distance between consecutive turns)
- Screw sense of the helix-describes the direction in which a helical structure rotates with respect to its axis.
- Right-handed helix: chain turns in a clockwise direction
- Left-handed helix: chain turns in an anticlockwise direction

Beta (β)-strand/beta pleated sheet

- ❖ β -strand is a linear strand of amino acid.
- ❖ β -strands line up as side by side and form hydrogen bonds with one another. This structure is **called β -pleated sheet**.
- ❖ The β -pleated sheet is stabilized by **Hydrogen bonds** between -NH and -CO groups of adjacent chains.
- ❖ The amino acids in one β -strand can also form hydrogen bonds with **the amino acid in α -helix**.
- ❖ Adjacent beta strands can run either in opposite directions (**antiparallel**) or in the same directions (**parallel**) giving rise to **antiparallel beta sheet** and **parallel beta sheet**, respectively.

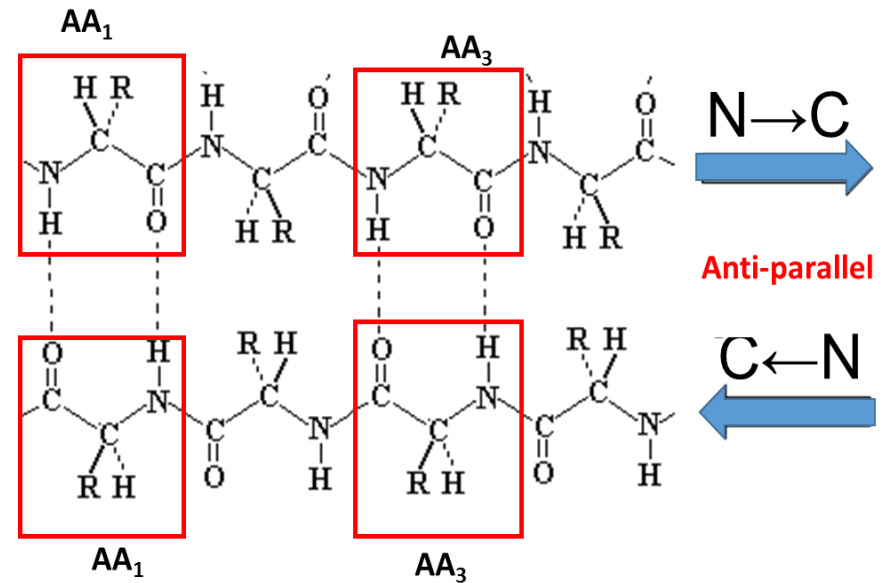


Parallel beta sheet



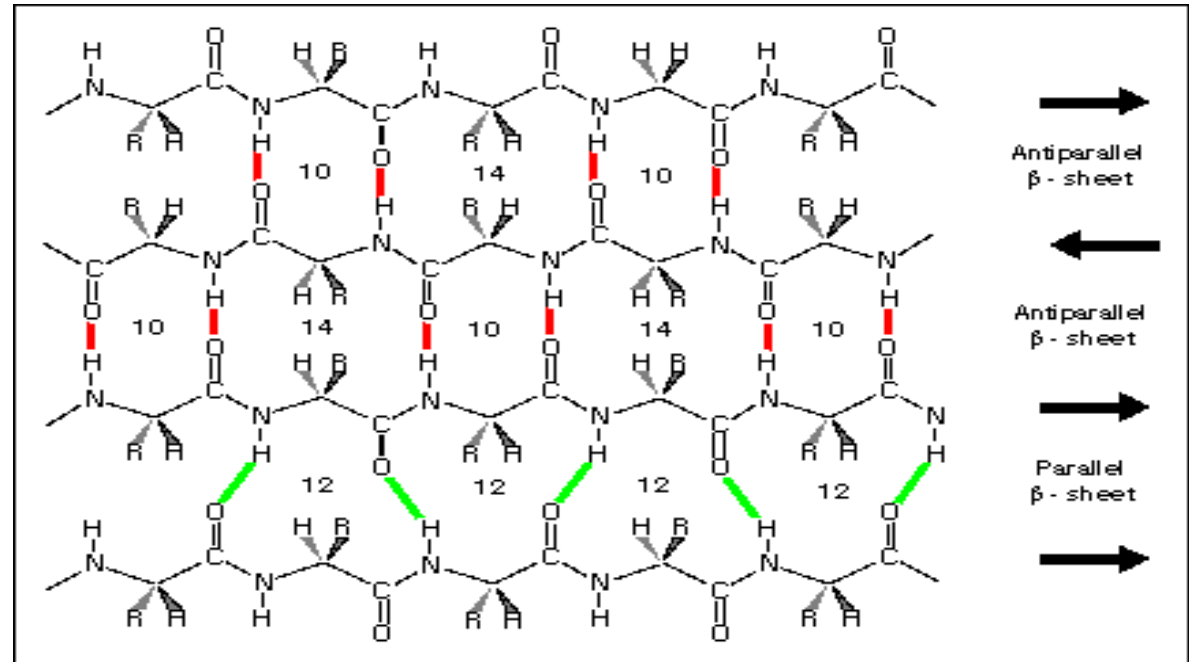
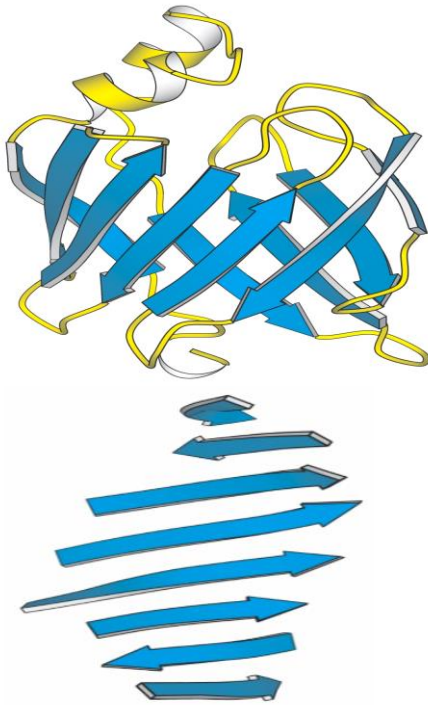
- **Parallel arrangement:** two beta strands run in same directions.
- **Hydrogen bonds:** H-bonds connect each amino acid on one strand with two different amino acids on the adjacent strand, in a **zig zag manner**, stabilizing the structure. **Amino acid 1 and 3** of one strand **interact with the amino acid 2** on the adjacent strand..

Antiparallel beta sheet

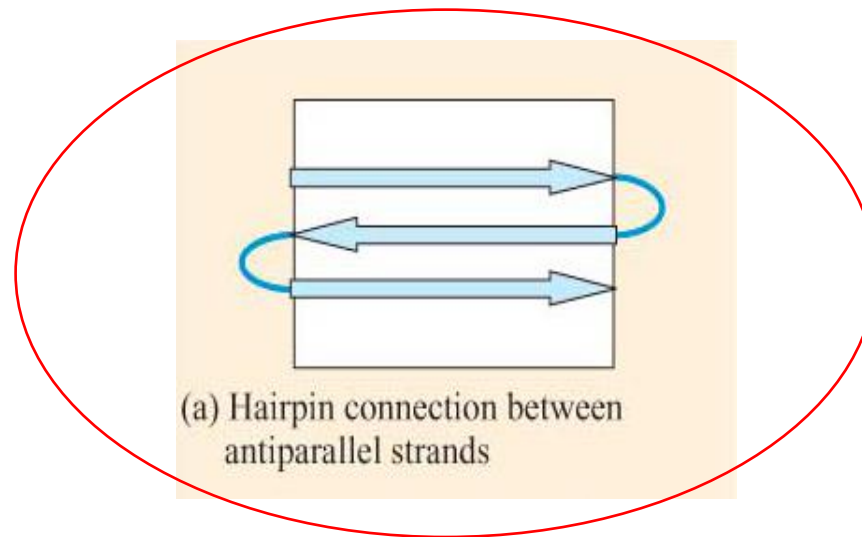


- **Antiparallel arrangement:** two beta strands run in opposite directions.
- **Hydrogen bonds:** The -NH group and the -CO group of each amino acid are hydrogen bonded to the -CO group and the -NH group of a partner on the adjacent beta strand. The hydrogen bonding pattern in **Antiparallel beta sheet** is “ **i of one strand and i of adjacent strand, i+2 of one strand and i+2 of adjacent strand, i+4 of one strand and i+4 of adjacent strand.**”

Mixed beta sheet

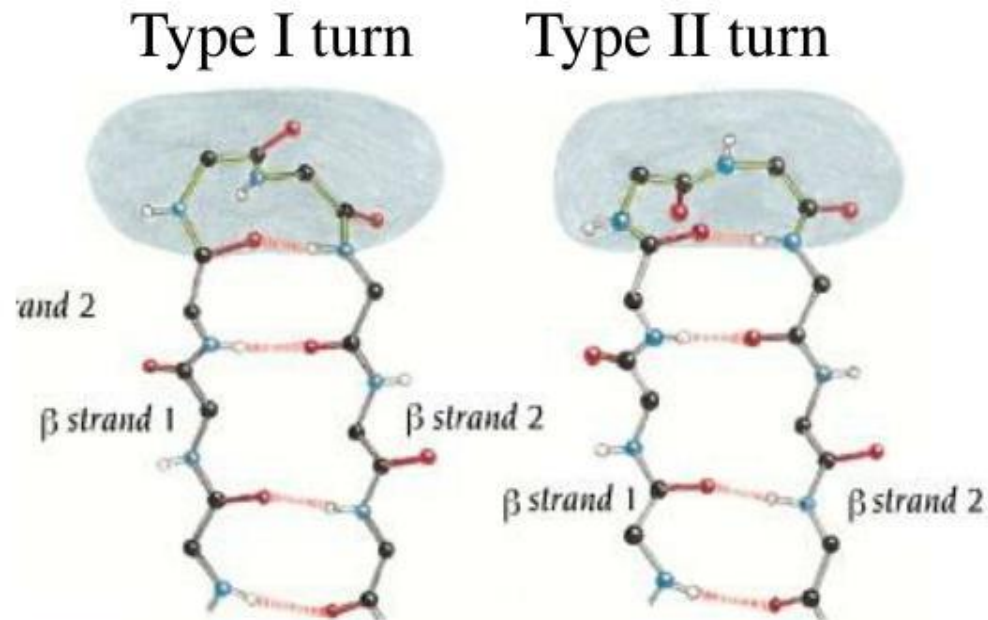
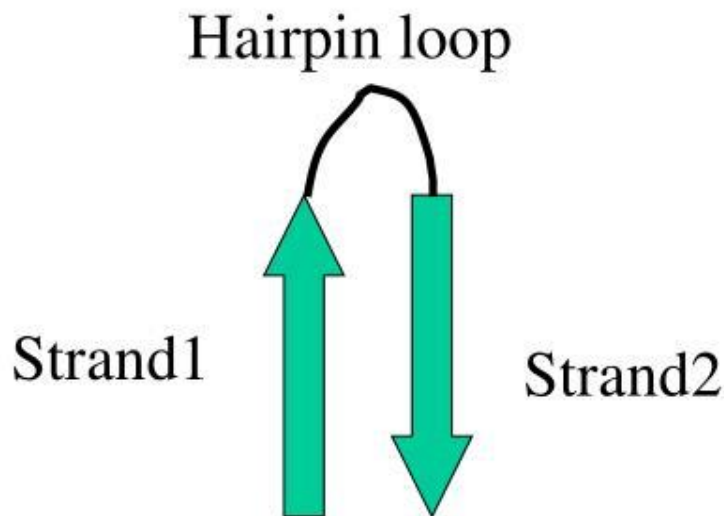


How are beta strands joined to one another in mixed beta sheet?

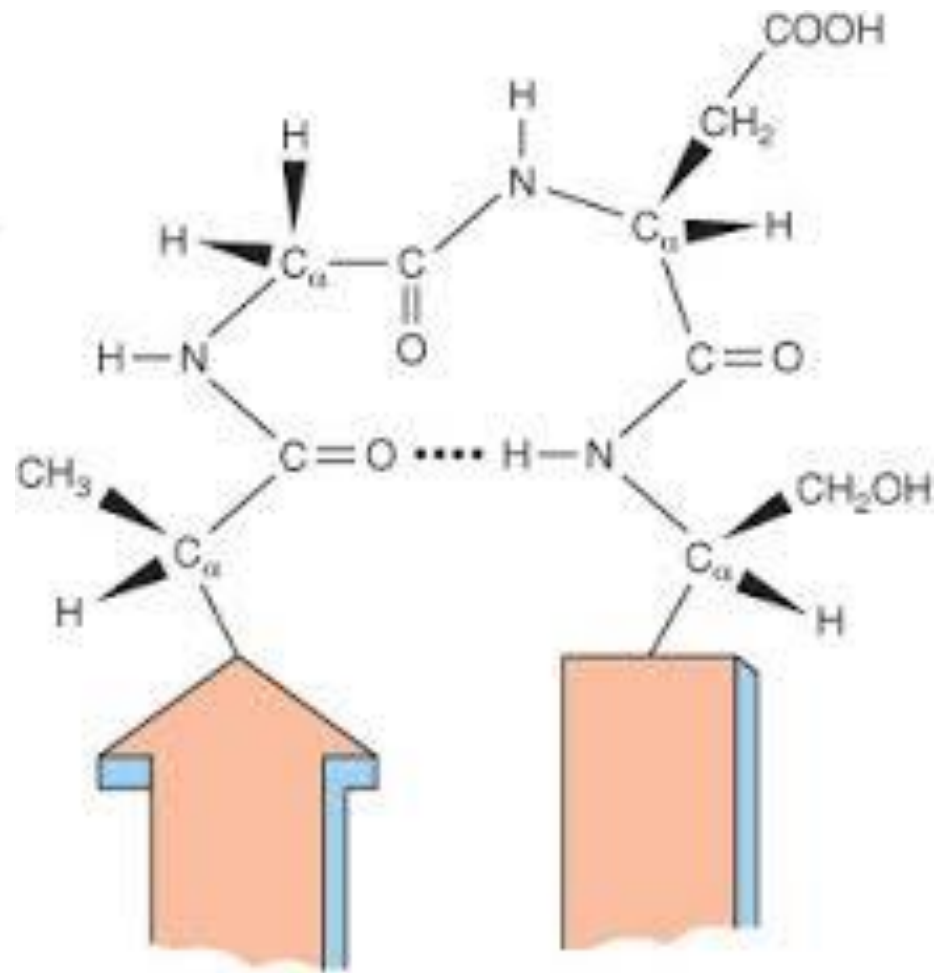


Hairpin loops and reverse turns

- Loops, which connect two adjacent antiparallel beta strands are called hairpin loops
- 2 residues long hairpin loops are often called reverse turns, beta turns or simply turns



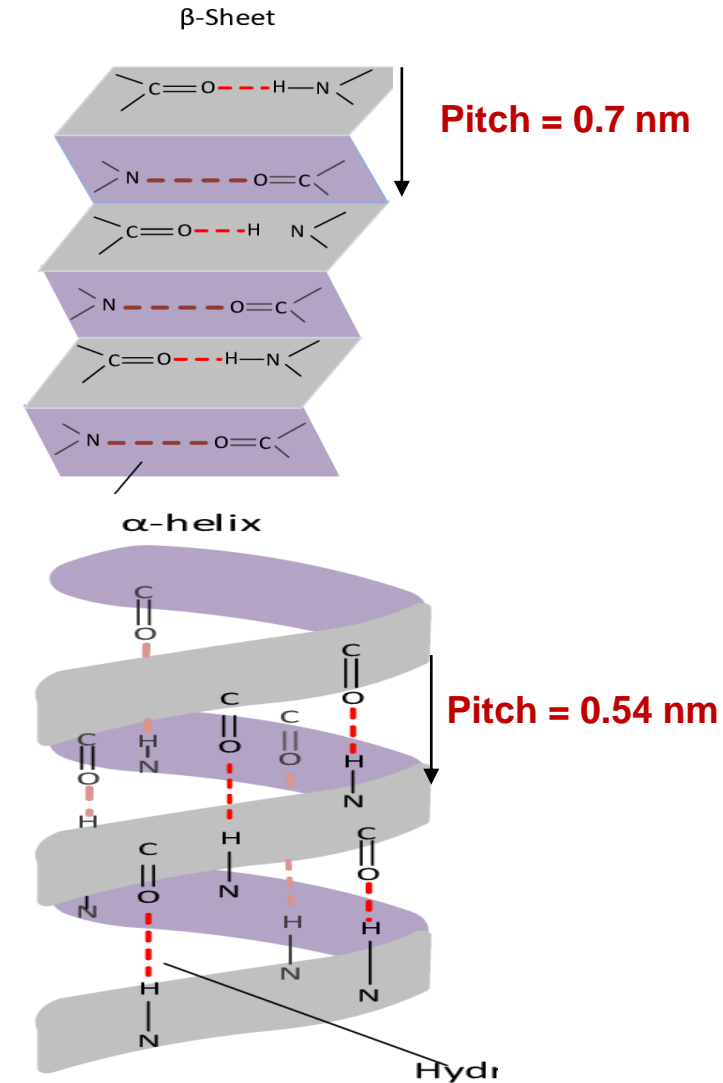
- Permits the change of direction of the peptide chain to get a folded structure.
- It gives a protein globularity rather than linearity.
- H bond stabilizes the beta bend structure.
- Proline and Glycine are frequently found in beta turns.
- Beta turns often promote the formation of antiparallel beta sheets.
- Occur at protein surfaces.
- Involve four successive amino acid residues



Comparative measurements of alpha helix and beta strands



	Alpha helix	Beta strands
The distance between two adjacent amino acids / axial distance	0.15 nm	0.35 nm
Amino acids covering one turn/sheet	3.6 amino acids	2 amino acids
Pitch (extended length along the helix axis)	0.54 nm (5.4 Å) which is 0.15 nm x 3.6 amino acids	0.7 nm, which is 0.35 x 2




- Polypeptides in the **beta-conformation** are **far more extended** than those in the **alpha-helical conformation**.

Tertiary structure

- The polypeptide chain is folded in complex ways
- Folding produces different types of secondary structures in different regions of the chain
- Some supersecondary motifs are also formed

The folding occurs due to formation of: Disulphide bonds, Hydrogen bonds, Electrostatic bonds, Hydrophobic bonds

- Some amino acid residues which are distant from each other in the polypeptide chain are brought closer
 - Some residues are buried into the interior of the molecule
 - Some are exposed on the surface of the molecule
- 

1. Water soluble proteins exists as globular protein and have common features:

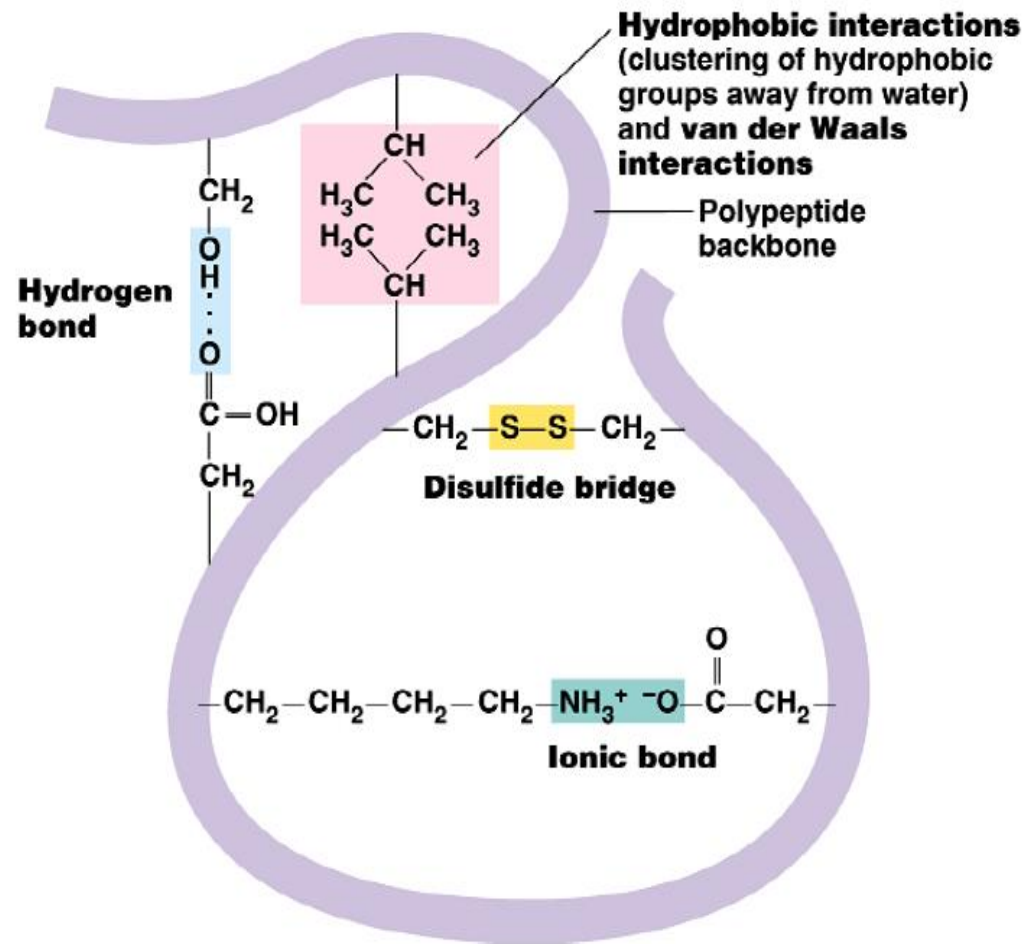
- Interior of the protein are formed of hydrophobic side chains
- Surface of the protein are formed largely of hydrophilic amino acids that interact with the aqueous environment

Example: Myoglobin, albumin

2. Membrane proteins exists as fibrous proteins

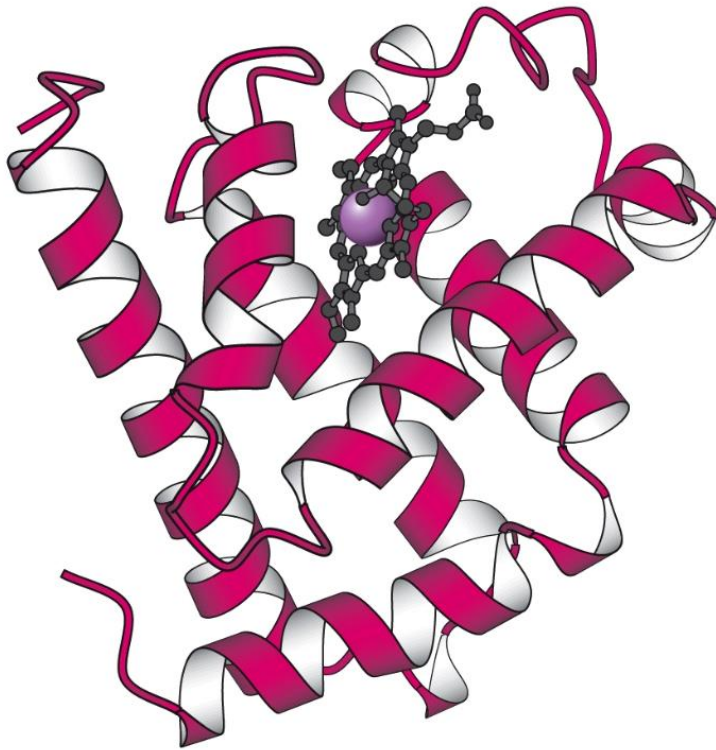
- Hydrophobic amino acids are on the surface to interact with the lipid bilayer of the membrane
- Hydrophilic groups are shielded from the environment in the interior of the protein

Example: Aquaporin, keratin, collagen



Myoglobin -an example of a Globular protein

- Myoglobin (oxygen carrier protein in muscle) in its tertiary structure



- **Globular proteins** fold up into compact, **spherical shapes**.
 - Their functions include biosynthesis, transport and metabolism.
 - For example, **myoglobin is a globular protein** that stores oxygen in the muscles.
- myoglobin is a single peptide chain that is mostly α -helix
 - the O₂ binding pocket is formed by a heme group and specific amino acid side-chains that are brought into position by the tertiary structure

Fibrous Proteins

▣ **Fibrous proteins** consist of long fibers and are mainly structural proteins.

▣ For example,

α -keratins are fibrous proteins that make **hair, fur, nails and skin**.

- hair is made of twined fibrils, which are braids of three α -helices (similar to the triple helix structure of collagen)
- the α -helices are held together by disulfide bonds

β -keratins are fibrous proteins found in **feathers and scales** that are made up mostly of β -pleated sheets



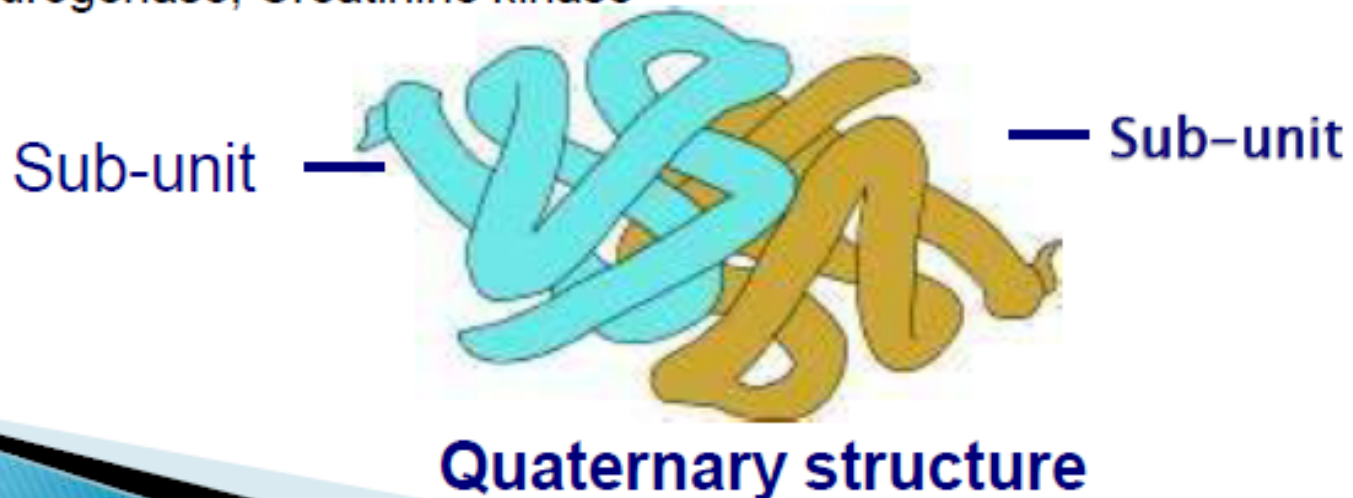
DETERMINATION OF TERTIARY STRUCTURE

- The known protein structures have come to light through:
- **X-ray crystallographic studies**
- **Nuclear Magnetic Resonance studies**
- The atomic coordinates of most of these structures are deposited in a database known as the Protein Data Bank (PDB).
- It allows the tertiary structures of a variety of proteins to be analyzed and compared.

Quaternary structure

- Many proteins are made up of two or more polypeptide chains
- Each chain is known as a protomer or a sub-unit
- The sub-units may be similar or dissimilar
- The sub-units are joined to each other by non-covalent bonds
- Joining of sub-units produces the quaternary structure of the protein

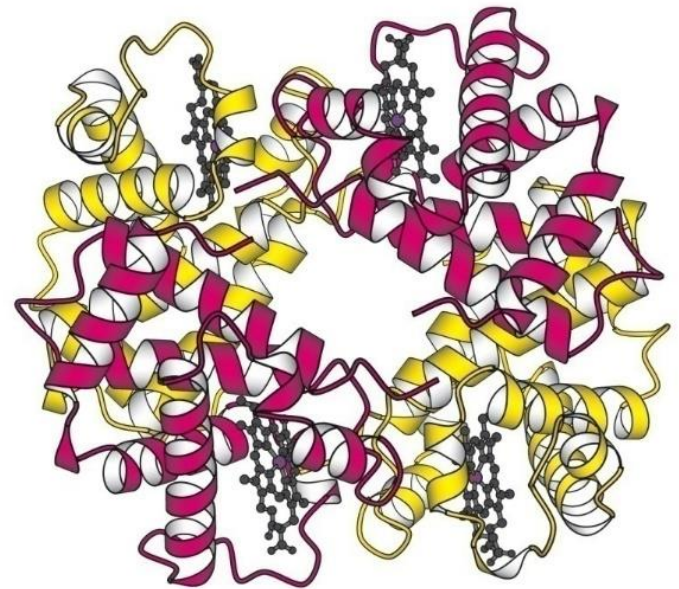
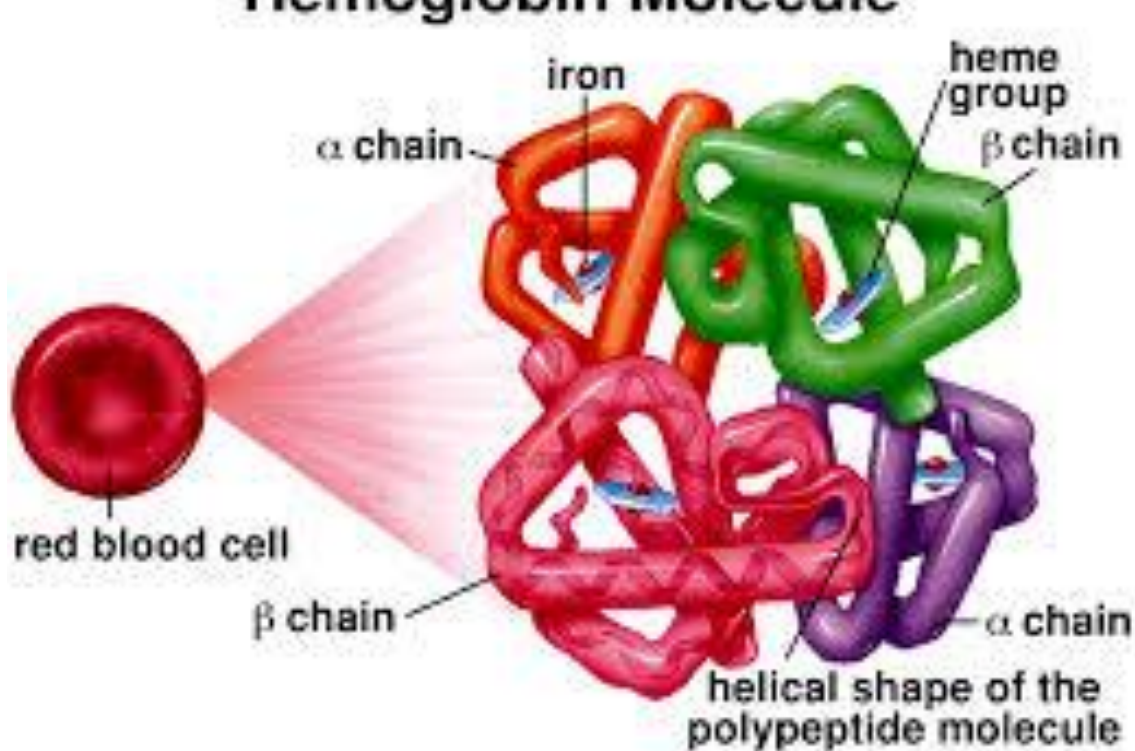
Examples of proteins having quaternary structure are: Haemoglobin, Lactate dehydrogenase, Creatinine kinase



Quaternary Structure

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Hemoglobin Molecule



Quaternary Structure

- Subunits are held together by many **weak, noncovalent interactions**

