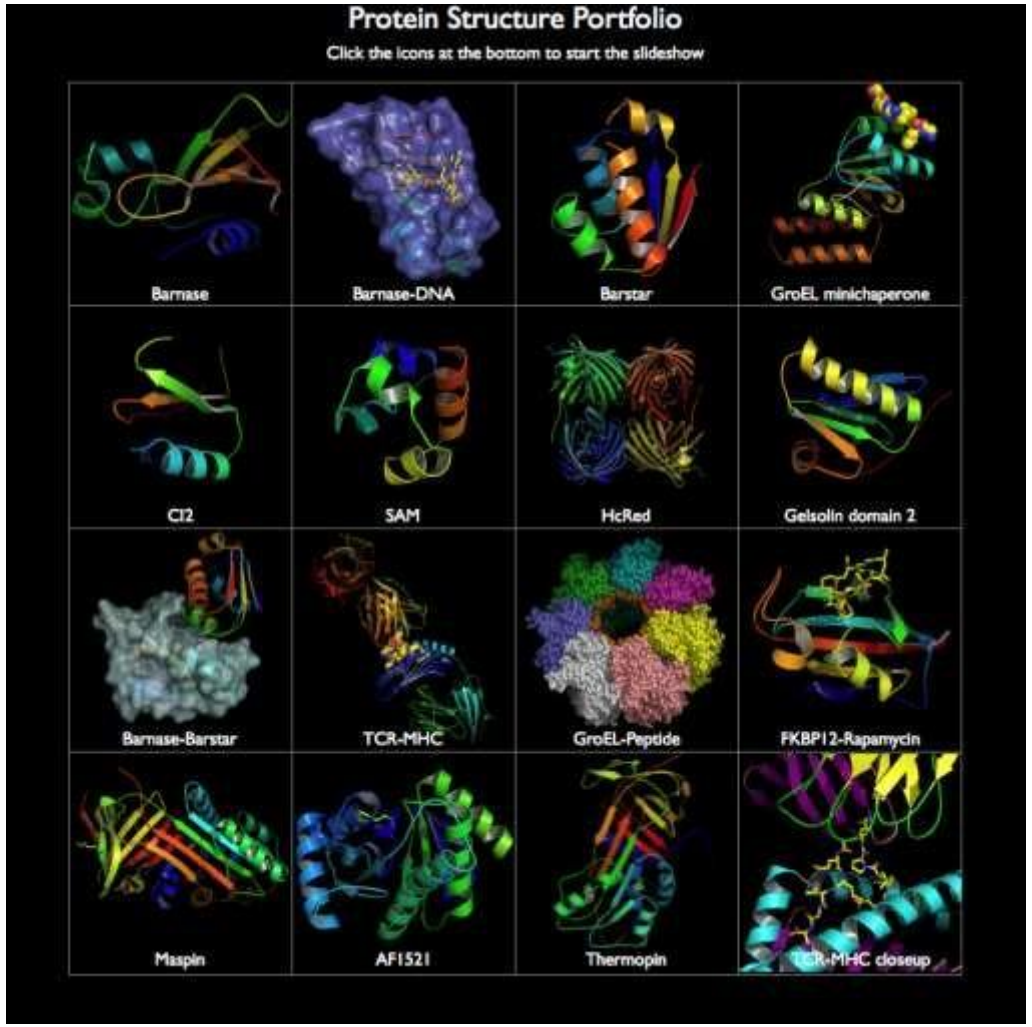
Protein structure

Summer 2023

Overview of proteins

- Proteins have different structures, and some have repeating inner structures, other do not.
- A protein may have *gazillion* possibilities of structures, but a few would be active.
- These active structures are known as native conformations (the 3-dimensioanl structure of a properly folded and functional protein).



Protein shape is depends on its function as example: proteins that has a mechanical function ,usually take a elongated shape . Another example :proteins that have transport function(not membrane proteins) usually have a spherical shape because its esealy to move.

Factors that help in the design of the protein: environment, characteristics and functions of protein and stability of molecule .

When any misfolded or disorder happen there is chaperone control system in the cell give the misfolded protein one chance to rebuilding ,if the protein still misfolded it will be degredated.

Tunyasuvunakool, K., Adler, J., Wu, Z. et al. Highly accurate protein structure prediction for the human proteome. Nature (2021). https://doi.org/10.1038/s41586-021-

When we understand the normal function of protein , we can know the effect of mutations of amino acids on the protein structure

Highly accurate protein structure prediction for the human proteome

Kathryn Tunyasuvunakool, Jonas Adler, [...]Demis Hassabis

Nature (2021) | Cite this article

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New public database of AI-predicted protein structures could transform biology

By Robert F. Service | Jul. 22, 2021 , 11:00 AM

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DeepMind's AlphaFold2 Predicts Protein Structures with Atomic-Level Accuracy

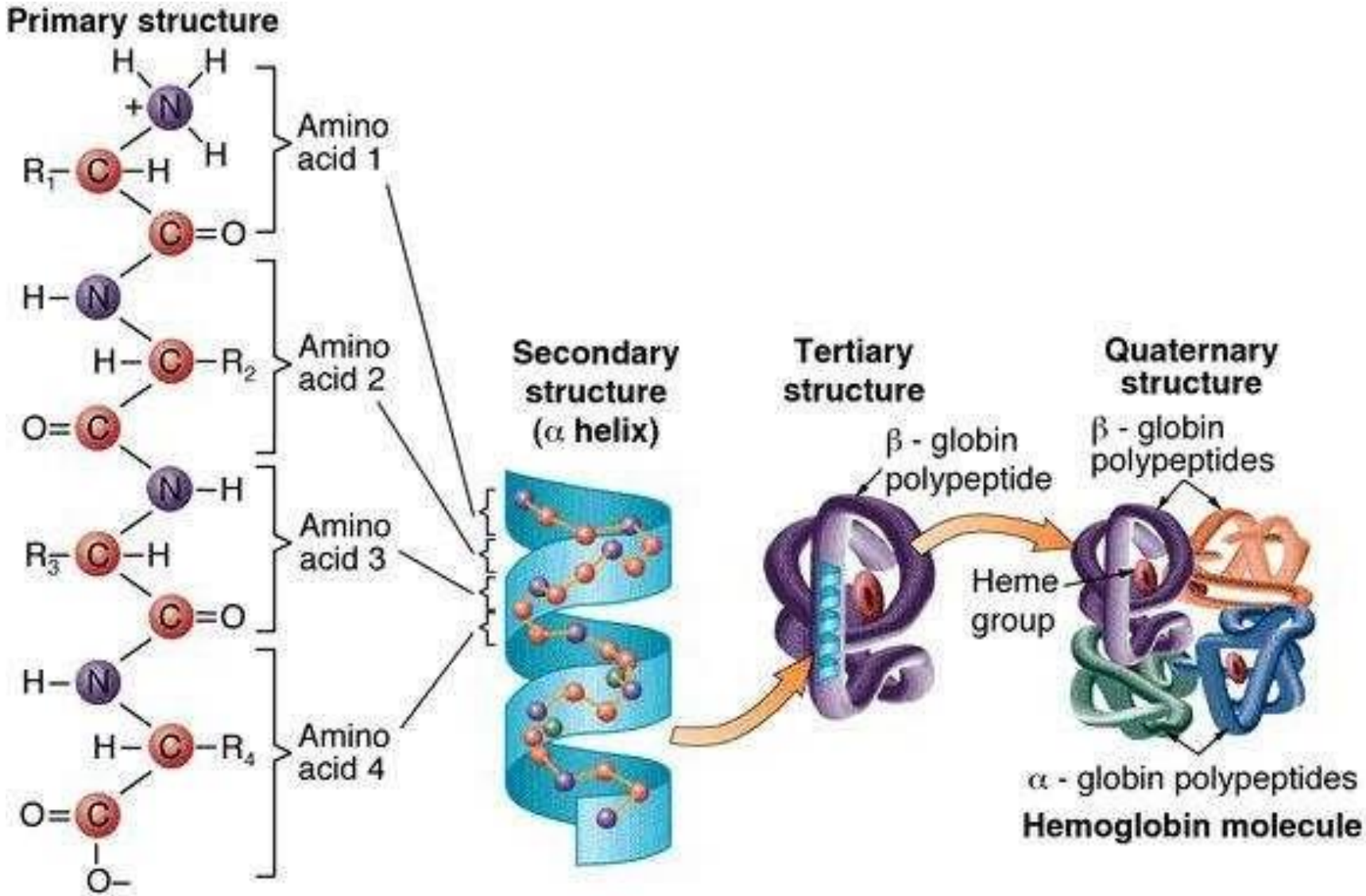
There are a lot of protein that not discovered their structure yet.

Levels of protein structure

- Primary structure: the sequence of amino acid residues
- Secondary structure: the localized organization of parts of a polypeptide chain In this level we don't know the orientation of amino acids .
- Tertiary structure: the three-dimensional structure and/or arrangement of all the amino acids residues of a polypeptide chain We can add a prostatic groups.
- Some proteins are made of multiple polypeptides crosslinked (connected) with each other. These are known as multimeric proteins.
- Quaternary structure describes the number and relative positions of the subunits in a multimeric protein

The proteins that composed of single polypeptide chain will stop at tertiary structure.

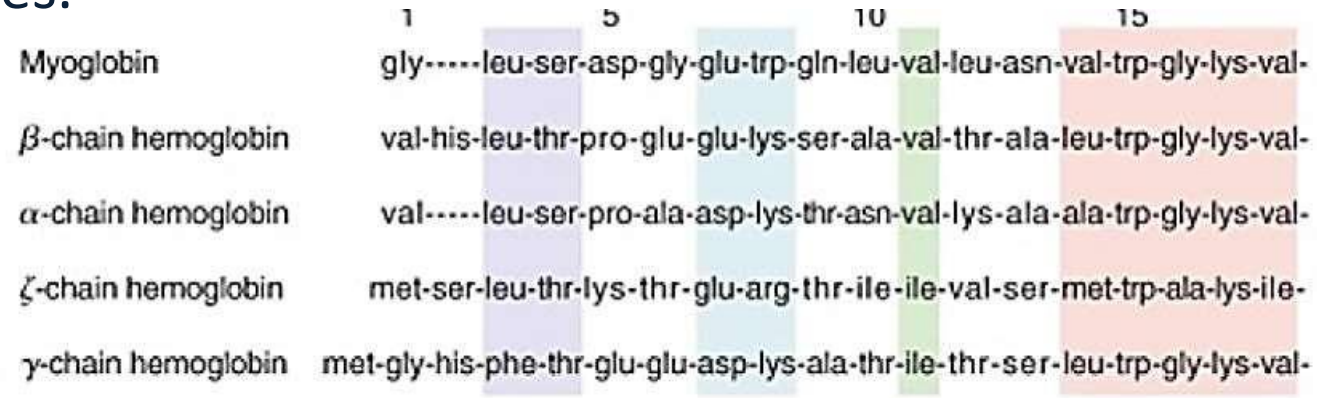
Proteins that composed of multi polypeptide chain will continue into quaternary structure.


Primary structure
Amino acid 1
Amino acid 2
Amino acid 3
Amino acid 4
Secondary structure (α helix)
Tertiary structure
β - globin polypeptide
Quaternary structure
β - globin polypeptides
Heme group
α - globin polypeptides
Hemoglobin molecule

Primary structure

What is primary structure?

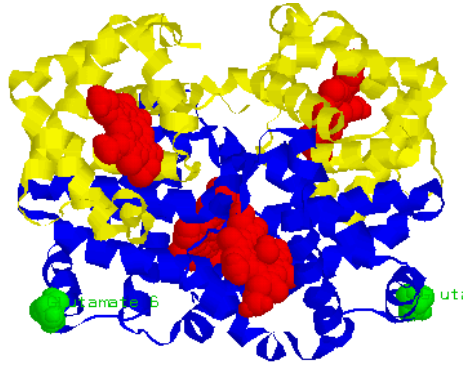
- The order in which the amino acids are covalently linked together.
  - Example: Leu—Gly—Thr—Val—Arg—Asp—His
- The primary structure of a protein determines the other levels of structure.
- Proteins that differ somewhat in primary structure and properties from tissue to tissue, but that retain essentially the same function, are called tissue-specific isoforms or isozymes.

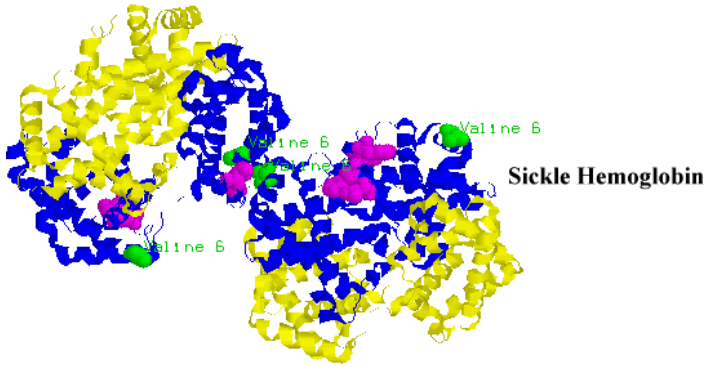


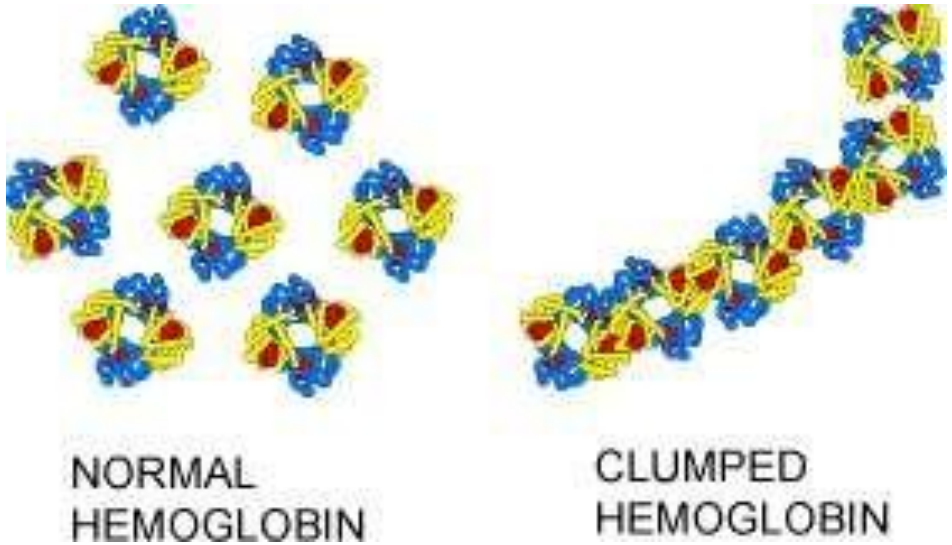
The primary sequence is important to determine the 3D shape not the last shape (the final shape).

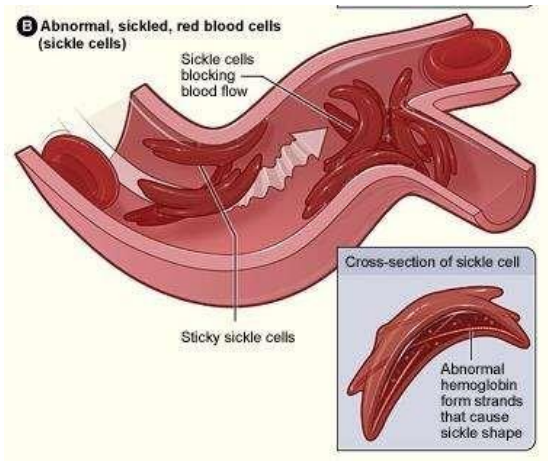
Sickle cell hemoglobin (HbS)

- A single amino acid substitution can give rise to a malfunctioning protein, as is the case with sickle-cell anemia.
- It is caused by a change of amino acids in the 6th position of β globin (Glu to Val).
- The mutation results in: 1) arrays of aggregates of hemoglobin molecules, 2) deformation of the red blood cell, and 3) clotting in blood vessels and tissues.









Sickle cell anemia is a hereditary disease caused by a mutation that affects the gene that codes for hemoglobin, specifically, the beta chains of the hemoglobin protein. One of the nucleotides is causing amino acid number 6 to be changed from glutamate to valine (from polar, charged to nonpolar). In normal hemoglobin, glutamate is present on the surface of the beta chain (from the outside) -- which makes sense because it is charged/polar. When valine (nonpolar) takes glutamate's place the molecule is unstable.

The protein now tries to find a way to hide this hydrophobic side chain. What happens is valine from different hemoglobin molecules interact with each other (hydrophobic interactions) and form aggregates of hemoglobin. Now we have clumped hemoglobin which takes the shape of a sickle قلجنم. The shape of the red blood cell is now affected and has a sickle shape instead of biconcave disc. The problems with this new shape: - The original shape (biconcave disc) was very easy to move because it has little thickness in the center, making it easy to fold. This all helps the cells to move inside small blood vessels. - The sickle cells lose their flexibility due to this shape, so their efficiency in transporting oxygen is greatly decreased. Patients suffering from this disease often get admitted to the hospital for health crisis. Another example like this disease is cystic fibrosis, which is caused by a mutation in a gene called CFTR (linked to fluoride ion transport). It causes the excretions of the exocrine glands to be thick (like mucus), and their movement is harder. This causes many problems in the respiratory system (it becomes a suitable environment for growth of bacteria), digestive system, etc..

Secondary Structure

What is it? How is it caused?

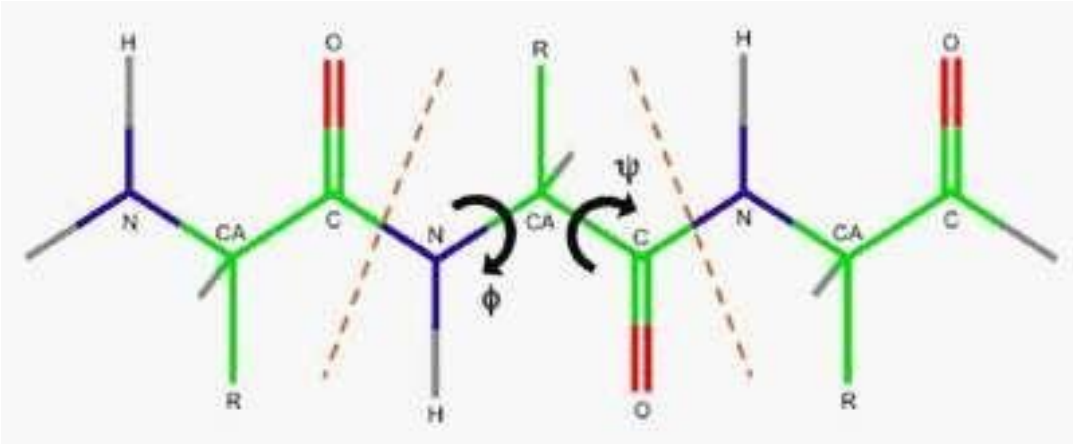
- The two bonds within each amino acid residue freely rotate.
  - the bond between the α-carbon and the amino nitrogen
  - the bond between the α-carbon and the carboxyl carbon

- A hydrogen-bonded, local arrangement of the backbone of a polypeptide chain.
- Polypeptide chains can fold into regular structures such as:
  - Alpha helix
  - Beta-pleated sheet

  } Regular secondary structures

  - Turns
  - Loops
  - Bends
  - Coils

  } Nonregular secondary structures

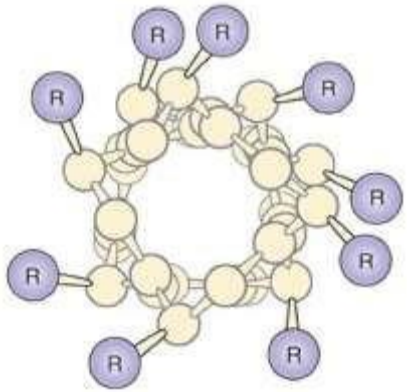


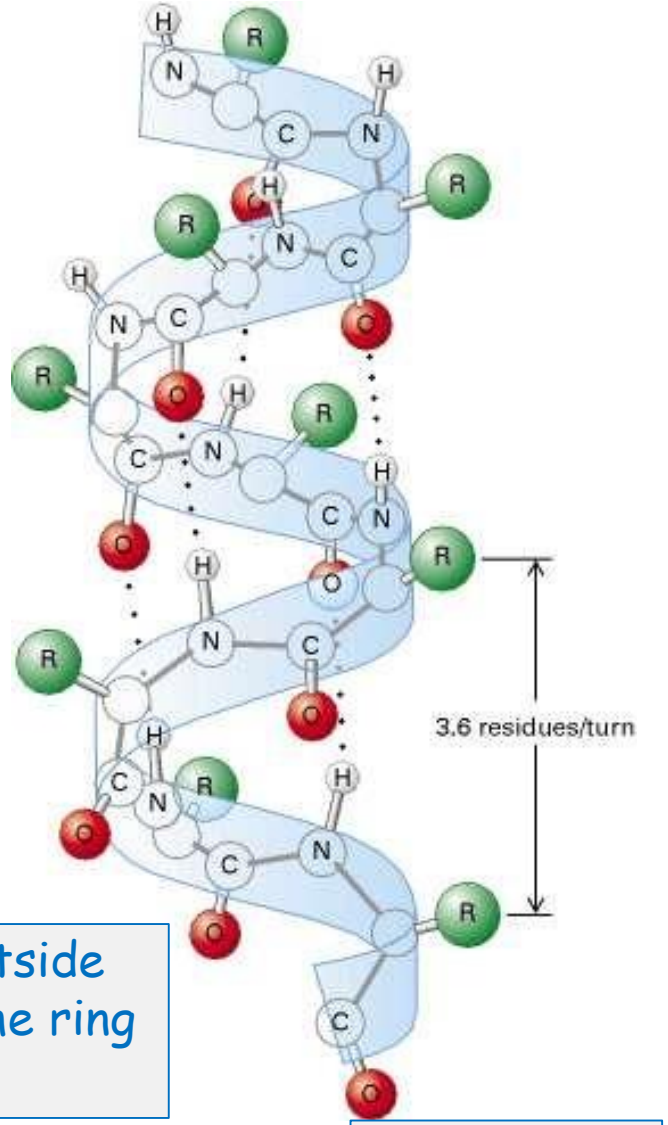
The α helix

Each amino acid composed of amine group,alpha carbon, carboxylic carbon and each 3.6 amino acid complete one helix

- It looks like a helical rod.
- The helix has an average of 3.6 amino acids per turn.
- The pitch of the helix (the linear distance between corresponding points on successive turns) is 5.4 Å.
  - 1 Å = 10^{-10} m
- It is very stable because of the linear hydrogen bondings.

- The trans side chains of the amino acids project outward from the helix, thereby avoiding steric hindrance with the polypeptide backbone and with each other.





The H-bonds between (O) of carbonyl carbon and (H) of amine group involve in the stabilization of the protein shape in the back bone

The R group of the amino acids are outside cause of the very little space inside the ring forming

Turns and loops have the ability to move and rotate. Proteins can differ in the loops and turns they have. These give them a variety of different movements compared to other proteins. The helix and sheets are the same in different proteins but what gives them different movement abilities is the difference in turns and loops. Ex: The difference between the active state and the inactive state of the protein is the turns and loops they have.

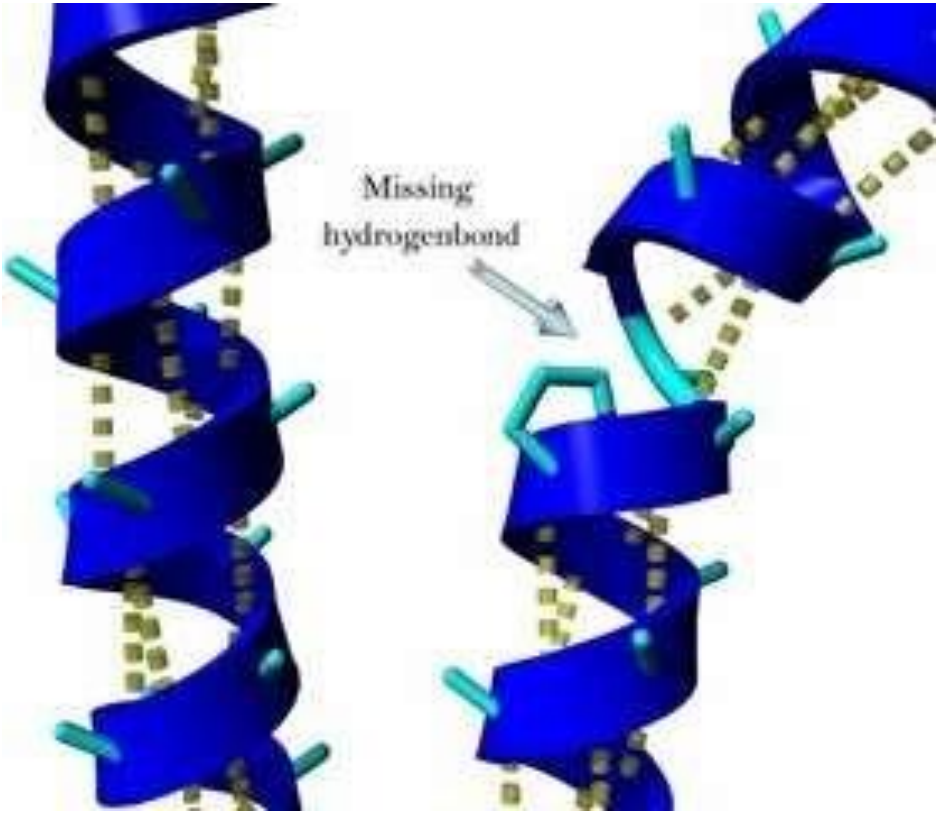
- Alpha helix
- Beta-pleated sheet
- Turns
- Loops
- Bends
- Coils

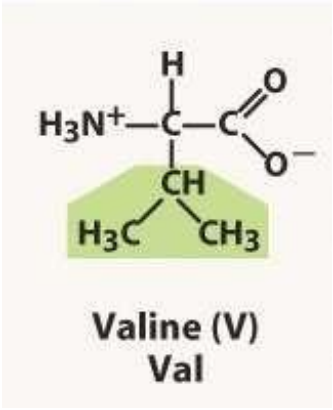
These are the four major components in the secondary structure of a polypeptide. Loops are long, turns are short.

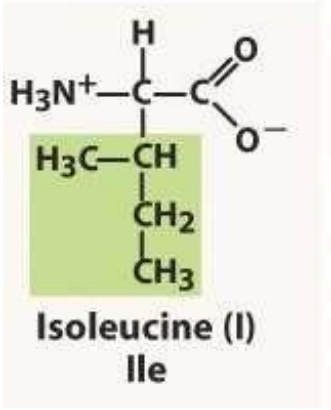
Each protein reading from N terminus to C terminus

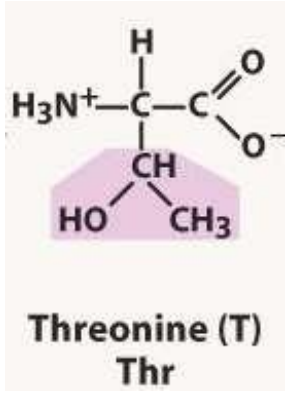
Amino acids NOT found in α-helix

- Glycine: too small
- Proline
  - No rotation around N-Cα bond
  - No hydrogen bonding of α-amino group
- Close proximity of a pair of charged amino acids with similar charges
- Amino acids with branches at the β-carbon atom (valine, threonine, and isoleucine)







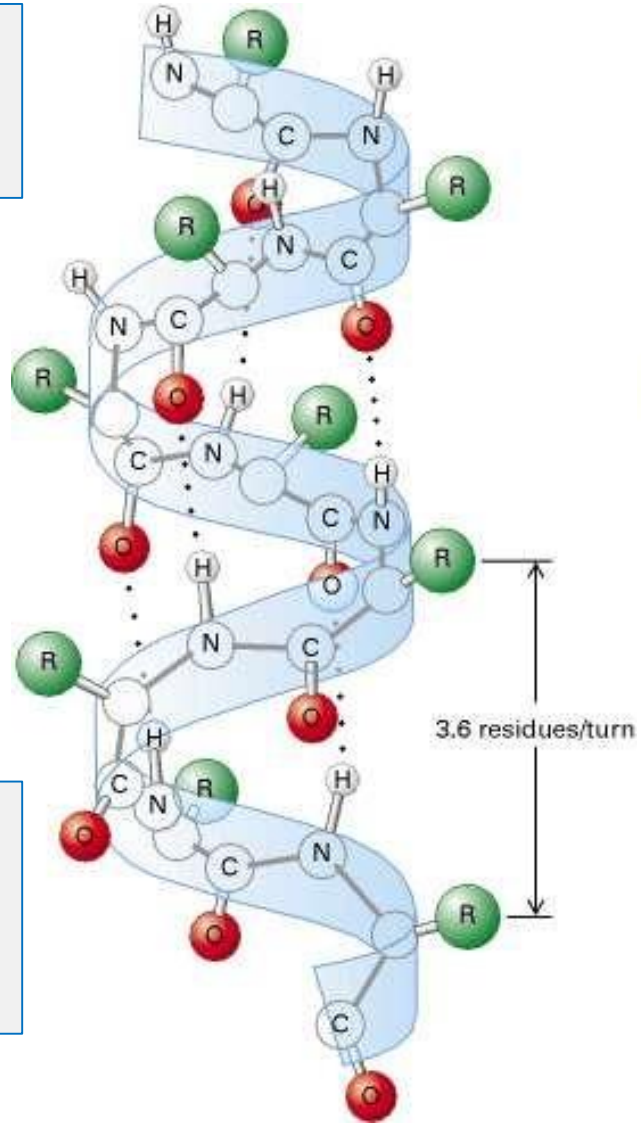


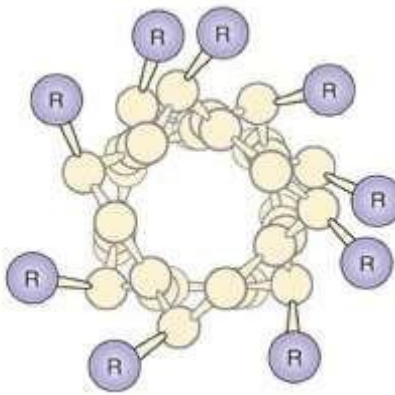
Sometime the R chain contribute in protein forming for example : 2 amino acid with bulky side chain (tryptophan with another tryptophan) so the protein can't be formed.

Another example: lysine with arginine both positively charged,so stop the process of forming protein

Bulky with bulky, positive with positive or negative with negative amino acids can involve in protein synthesis unless they aren't close together to avoid the repulsion from each other's

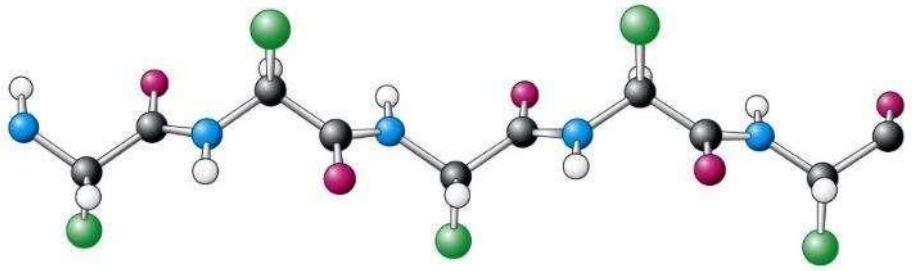
Also the proline and glycine aren't present in alpha helixes (proline cant make H-bonds)
(Glycine very small so it moves a lot) so both are considered unstable amino acid (irregular structure)





β pleated sheet (β sheet)

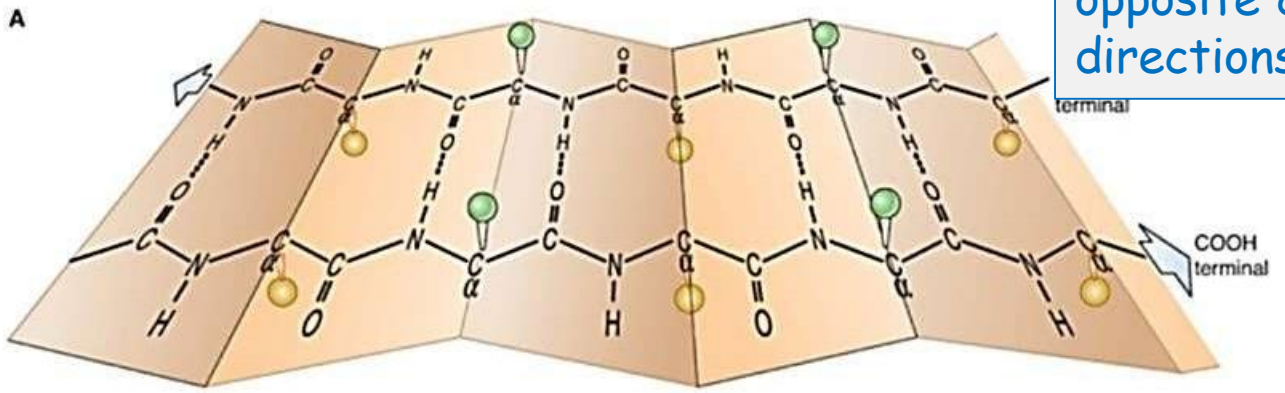
- They are composed of two or more straight chains (β strands) that are hydrogen bonded side by side.



β strand

- Optimal hydrogen bonding occurs when the sheet is bent (pleated) to form β-pleated sheets.

Each sheet composed of strands (in opposite called antiparallel or in same directions called parallel)

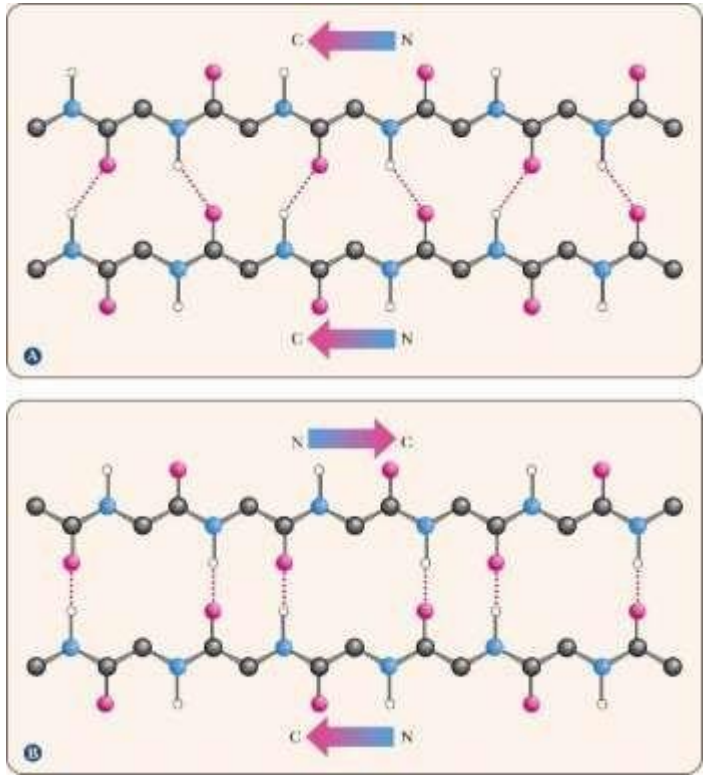


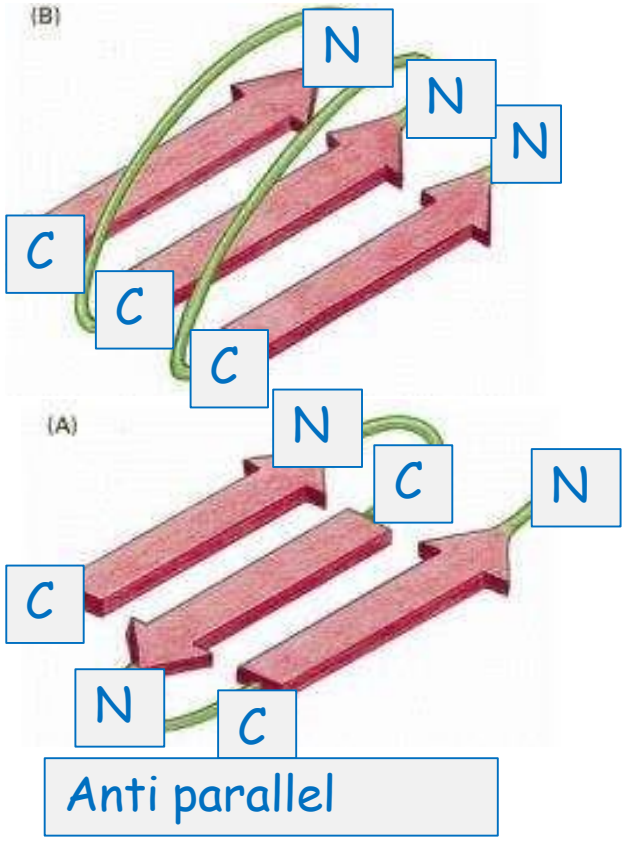
More on β-sheets

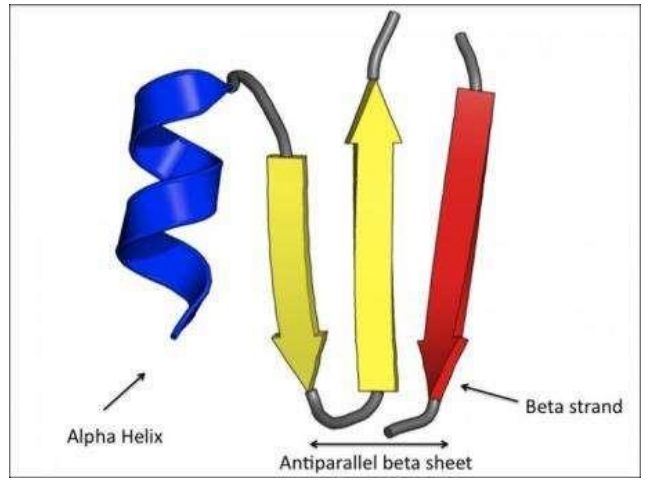
- β sheets can form between many strands, typically 4 or 5 but as many as 10 or more.
- Such β sheets can be purely antiparallel, purely parallel, or mixed.

Parallel

Antiparallel







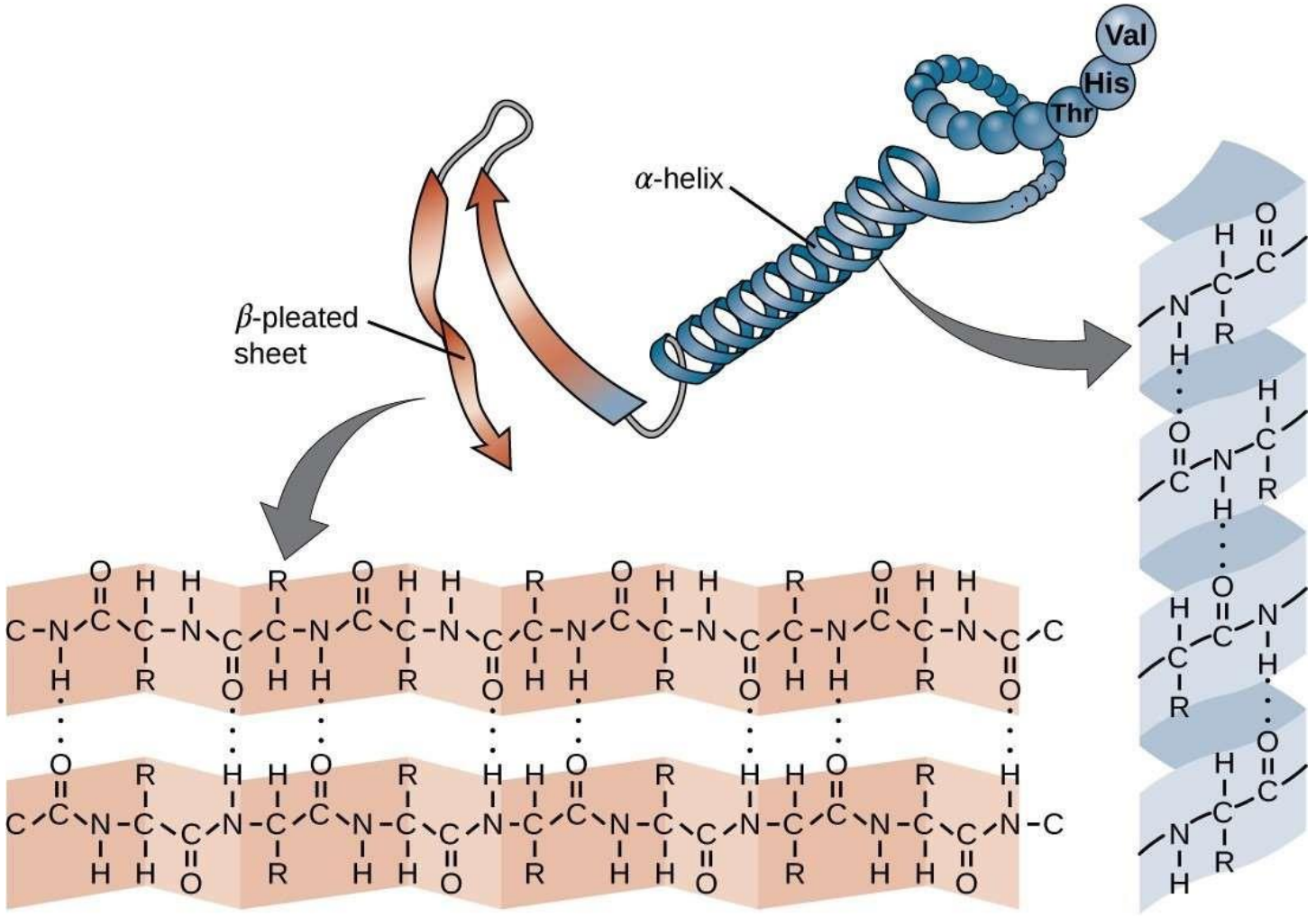
Based on hydrogen bonding pattern, which do you think is more stable: parallel or anti-parallel sheets?

Effect of amino acids

- Valine, threonine and Isoleucine with branched R groups at β-carbon and the large aromatic amino acids (phenylalanine, tryptophan, and tyrosine) tend to be present in β-sheets.

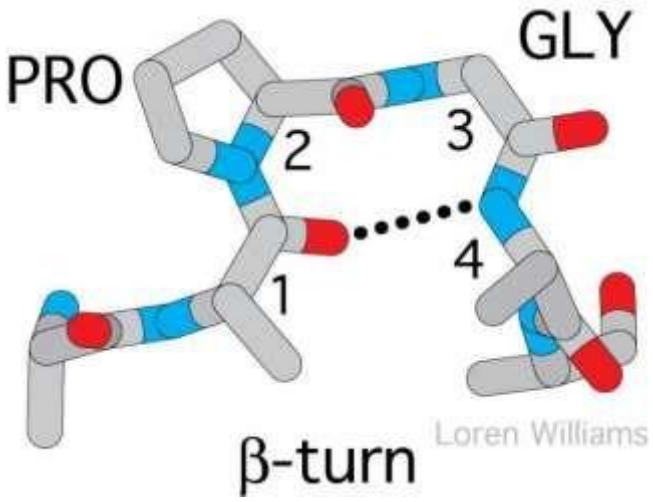
- Proline tends to disrupt β strands

How are they illustrated/drawn?



β-turns

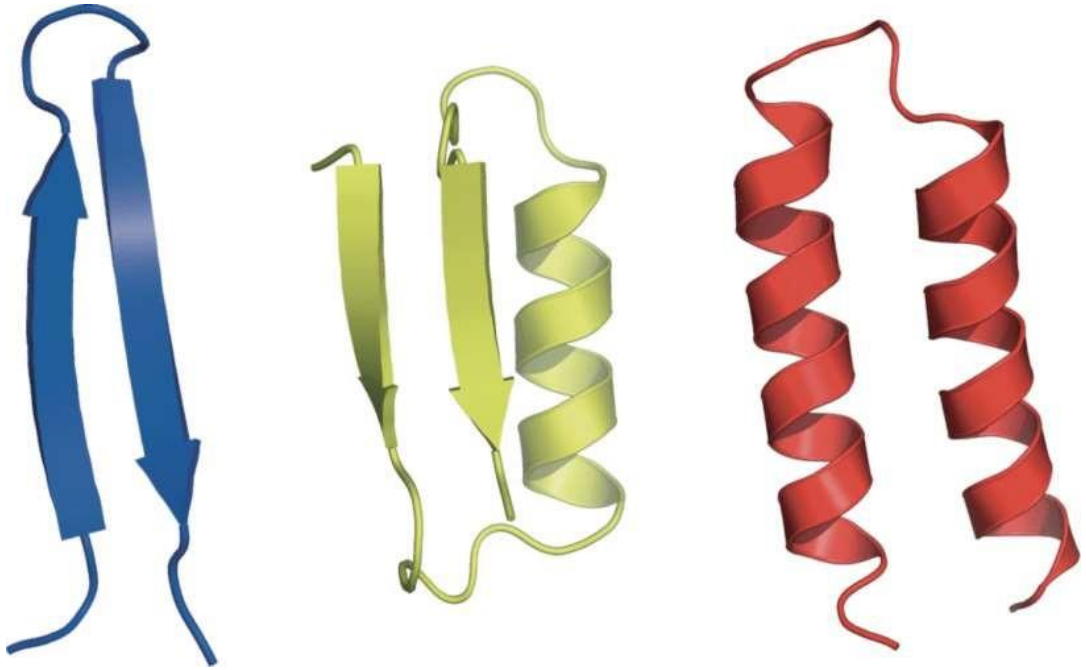
- Turns are compact, U-shaped secondary structures.
- They are also known as β turn or hairpin bend.
- What are they used for? How are they stabilized?
- Glycine and proline are commonly present in turns.
- Why?



U shaped structure, shorter than loops , rich in glycine (small amino can move freely) and proline(bent structure because of the covalent bond between side chain and back bone) so that's help in formation of beta turns

Loops and coils

- Loops are a diverse class of secondary structures in proteins with irregular geometry and that connect the main secondary structures.
- They are found on surface of molecule (and contain polar residues) and provide flexibility to proteins.
- Amino acids in loops are often not conserved.



Super-secondary structures

- They are regions in proteins that contain an ordered organization of secondary structures.
- There are at least types:
  - Motifs
  - Domains

- Super-secondary structures is a collection of multiple secondary structures .
- Super-secondary structures are a combination of secondary structural elements that are arranged in a certain way and repeated, it may be within one protein or between 2 different proteins, they are called motifs they may be simple or complicated (larger) .
- motifs are more than secondary and less than tertiary

Important

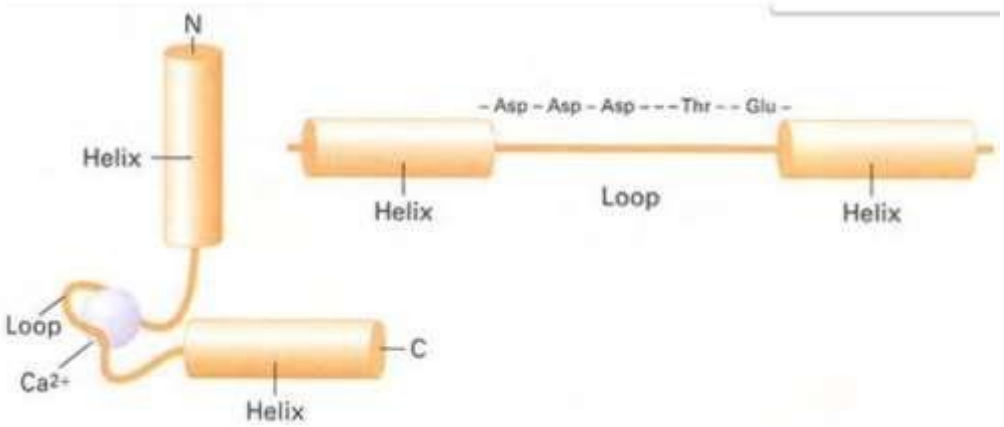
- Domains are related to function like DNA binding domain

- Domains Give me information about the structure whether Transcription factor or ligand binding domain for hormone or growth factor or an enzyme (catalytic domain (has a specific function))

A motif (a module)

- It isn't considered as a functional unit

- •A motif is a repetitive super secondary structure, which can often be repeated and organized into larger motifs and they can be part of domains.
- •It usually constitutes a small portion of a protein (typically less than 20 amino acids).
- •In general, motifs may provide us with information about the folding of proteins, but not the biological function of the protein.

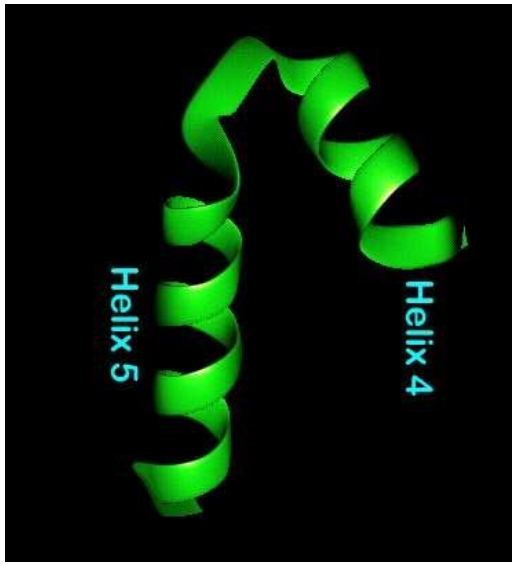


Helix-loop-helix is found in many proteins that bind DNA. It is characterized by two α-helices connected by a loop.

- two α-helices separated by a loop

Helix-turn-helix is a structural motif capable of binding DNA. It is composed of two α helices joined by a short strand of amino acids

- an α-helical region is followed by a sharp β-turn and then another α-helical region.
- They are very common in protein that bounded with DNA



- Extra information
- The key difference between helix-loop-helix and helix-turn-helix is that helix-loop-helix mediates protein dimerization, whereas helix-turn-helix regulates gene expression through DNA binding.

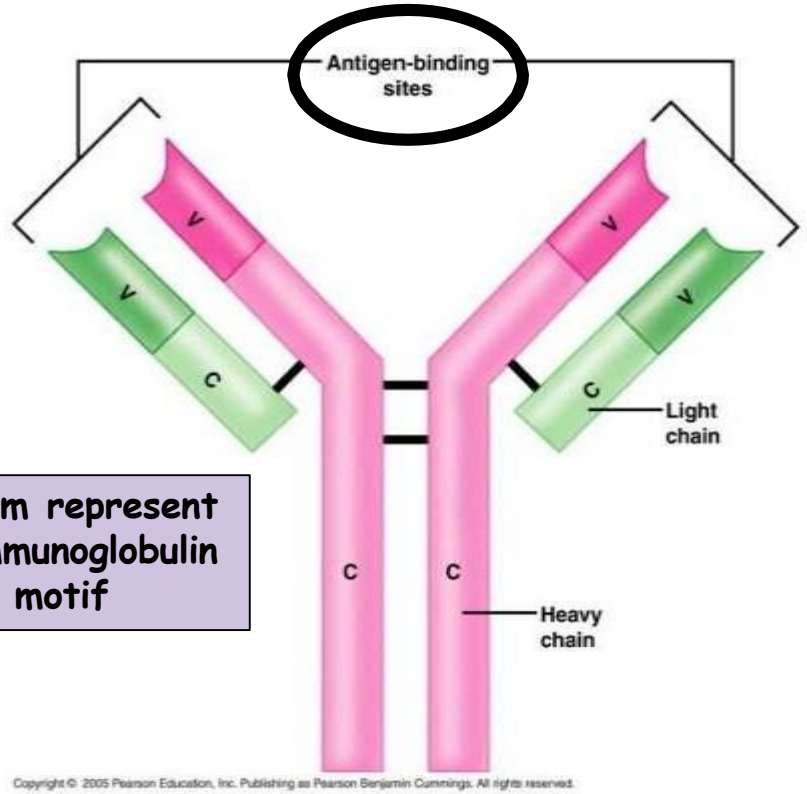
A more complex motif is…

- The immunoglobulin fold or module that enables interaction with molecules of various structures and sizes.

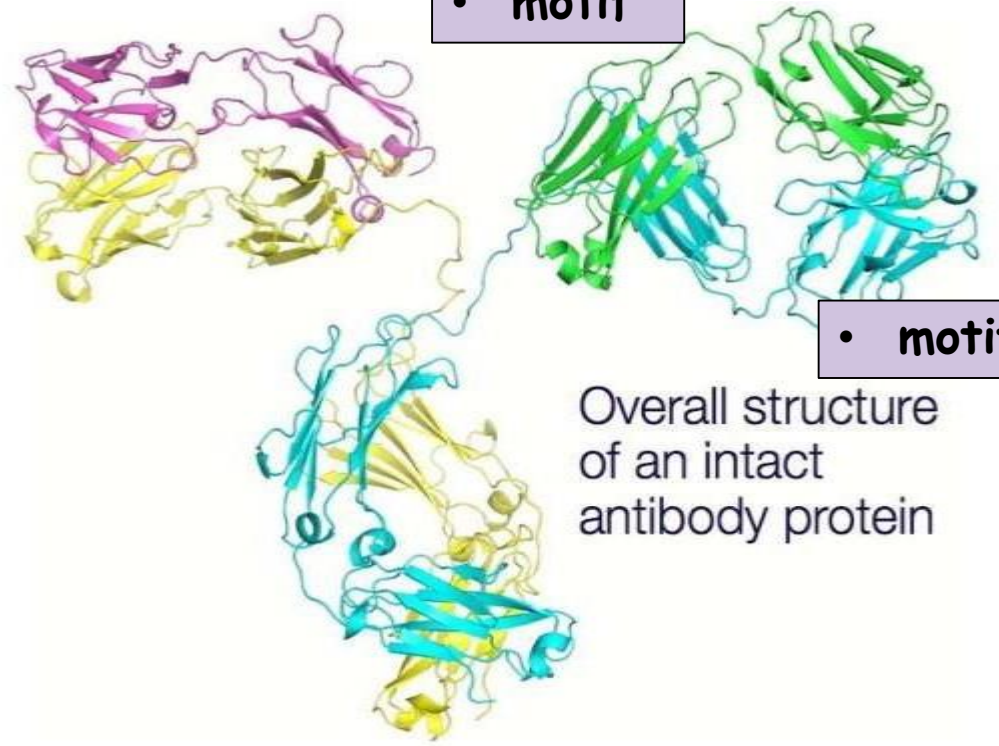
- **Antigen binding site for foreign Bodys binding**

- **Motif (not considered as a tertiary structure**

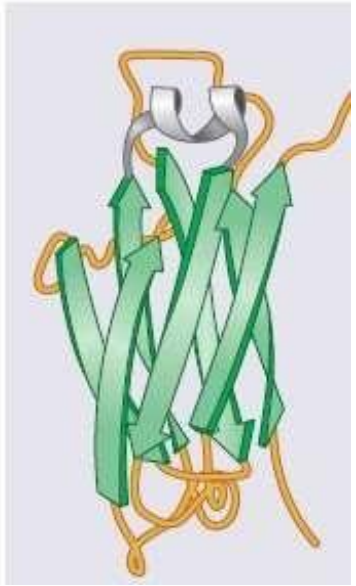
- **motif**



One arm represent an Immunoglobulin fold or motif



- **motif**



- **Anti parallel beta sheets**
- **Loop connected**

Immunoglobulin structure

- **Antibody is produced from an antigen**

Tertiary structure

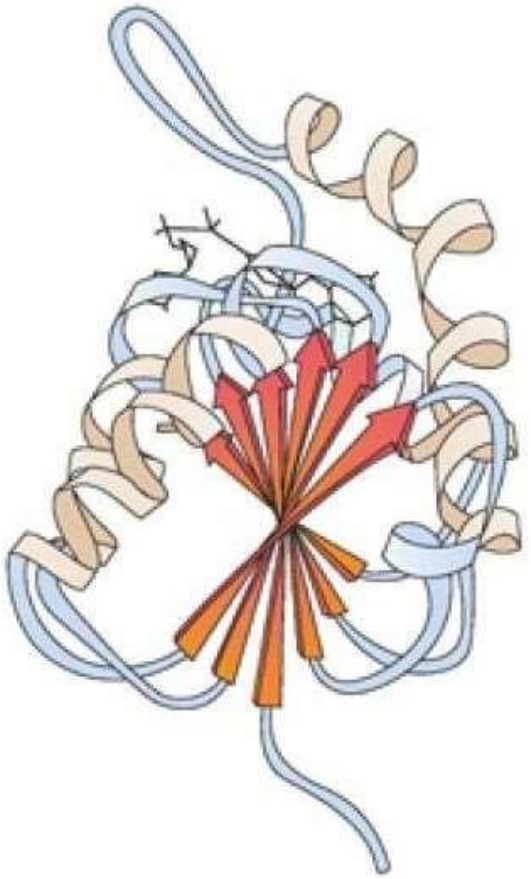
- The tertiary structure of a protein refers to the overall three-dimensional arrangement 3D of its polypeptide chain in space

What is tertiary structure?

- The overall conformation of a polypeptide chain
- The three-dimensional arrangement of all the amino acids residues
- The spatial arrangement of amino acid residues that are far apart in the sequence

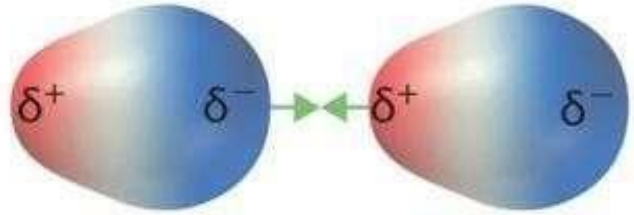
The tertiary structure usually depends on the interaction between R groups

- **Each polypeptide it has a special shape**



van der Waals attractions

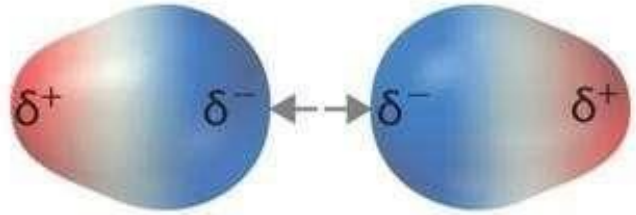
- There are both attractive and repulsive van der Waals forces that control protein folding.
- Although van der Waals forces are extremely weak, they are significant because there are so many of them in large protein molecules.



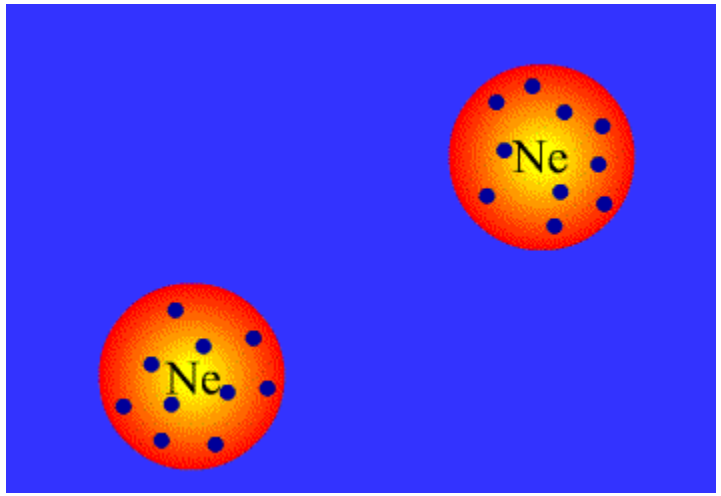
(b) Attraction

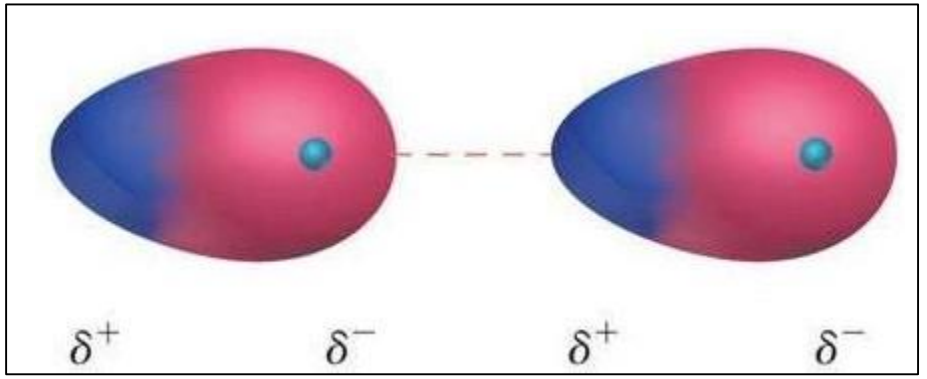
- **van der Waals attractions:**

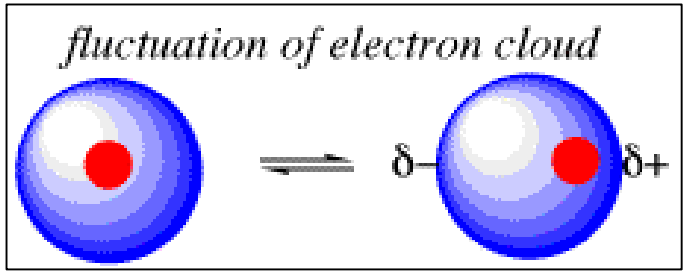
the relatively weak attractive forces that act on neutral atoms and molecules but a lot of them act as a strong bond



(d) Repulsion

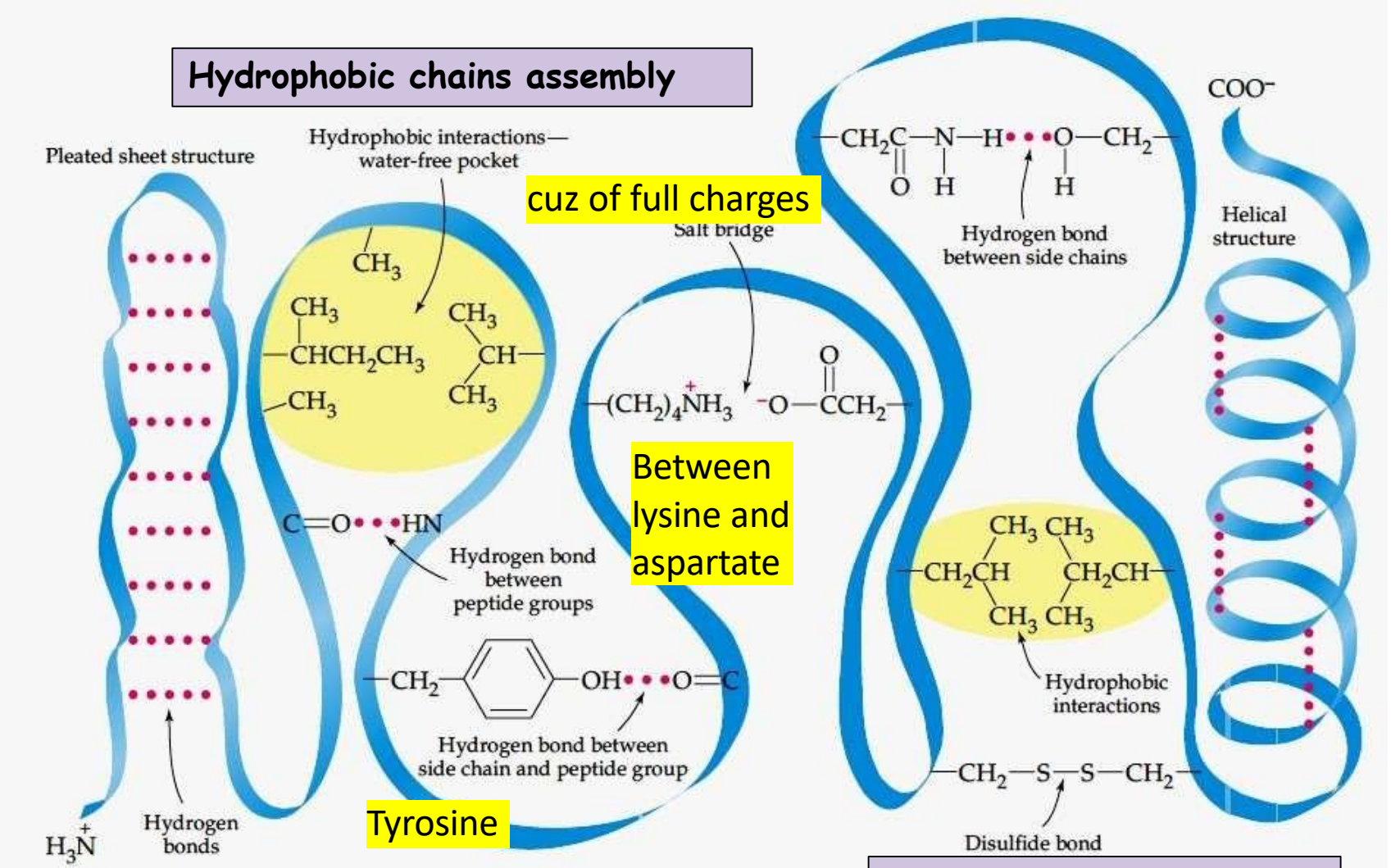






Shape-determining forces

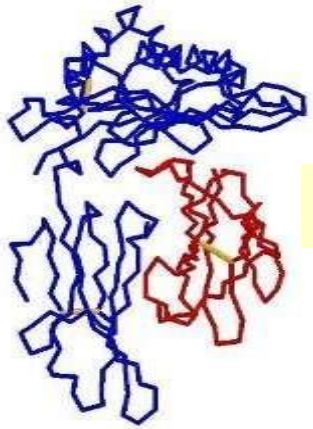
Between asparagine and serine



The only covalent bond between two cysteine

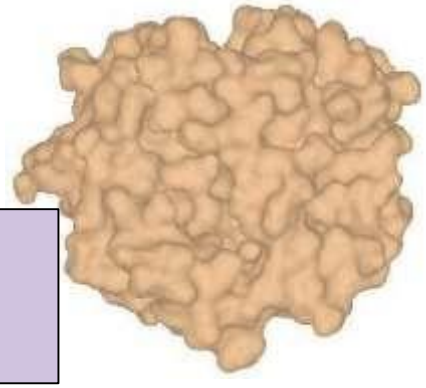
How to look at proteins…

The most two common :
(Ribbon)and (Ball and stick structure)



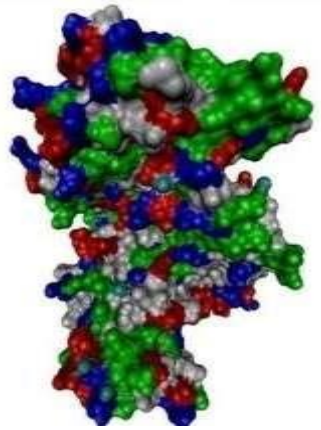
Trace structure

Protein surface map



Know the topography of protein

Space-filling structure



- This structure has a color coding depends on the atom.
- And we can know the topography ,and the relative position and the distribution of atoms

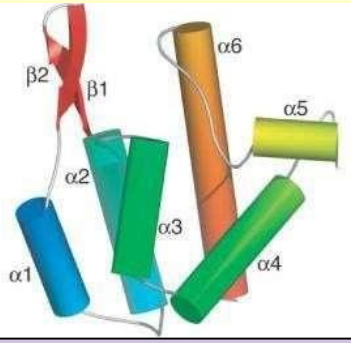
Ribbon structure

Sheet

Helix

The two colors represent the active and the inactive form

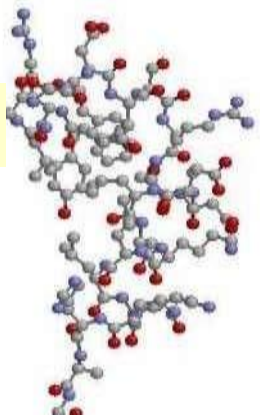
Cylinder structure



This structure helps to know the general structure and the relative relation function

Ball for the atoms and the sticks for the bonds

Ball and stick structure

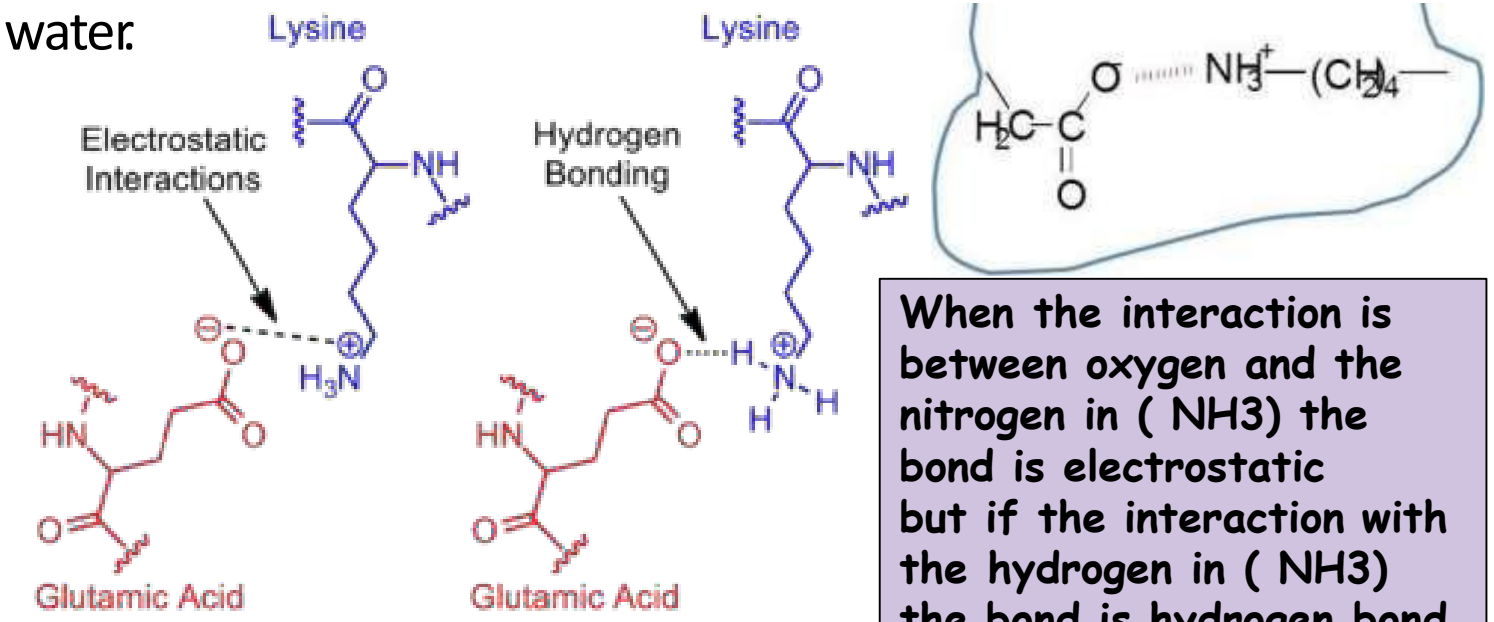


Usually, We have a color coding to give the information of the general shape and orientation

Non-covalent interactions

- Hydrogen bonds occur not only within and between polypeptide chains but with the surrounding aqueous medium.
- Charge-charge interactions (salt bridges) occur between oppositely charged R-groups of amino acids.
  - Charge-dipole interactions form between charged R groups with the partial charges of water.

The same charged group can form either hydrogen bonding or electrostatic interactions



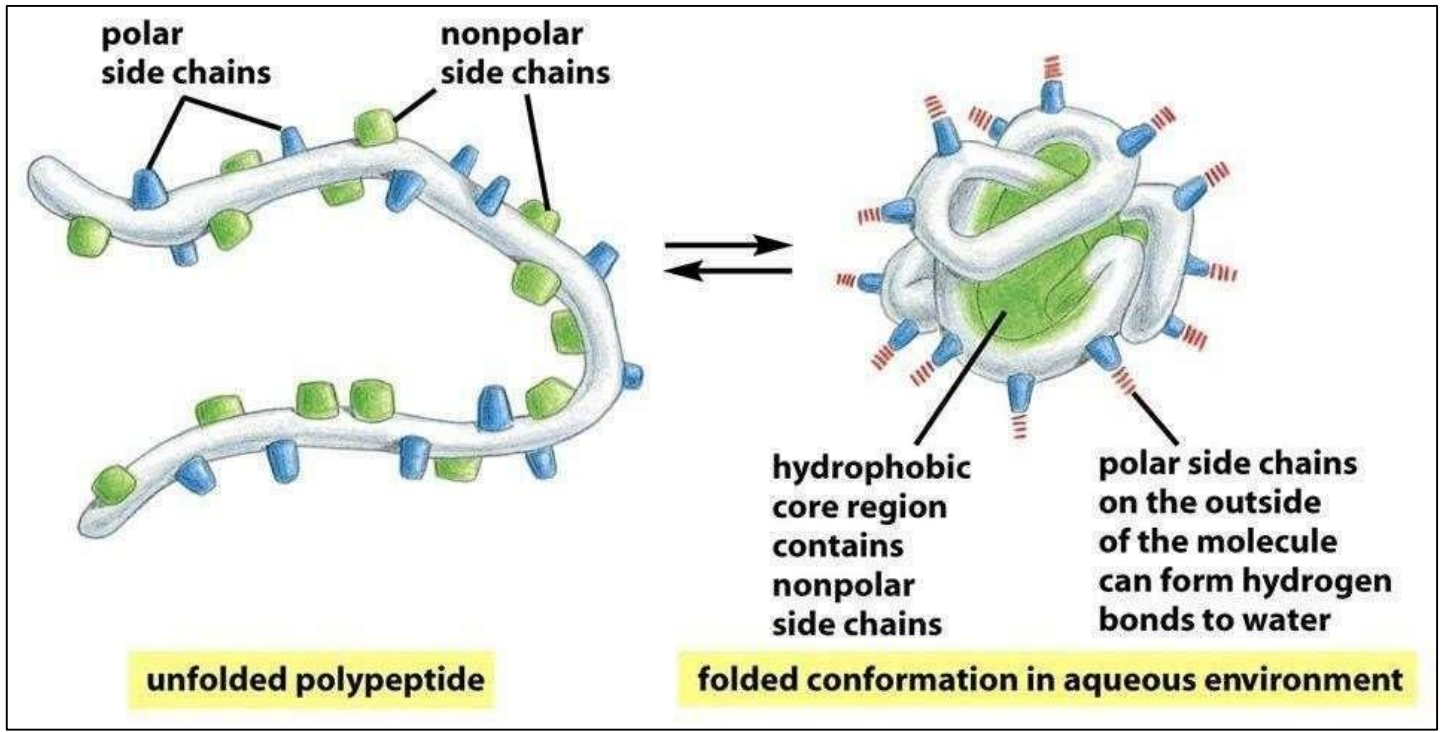
When the interaction is between oxygen and the nitrogen in (NH3) the bond is electrostatic
but if the interaction with the hydrogen in (NH3) the bond is hydrogen bond

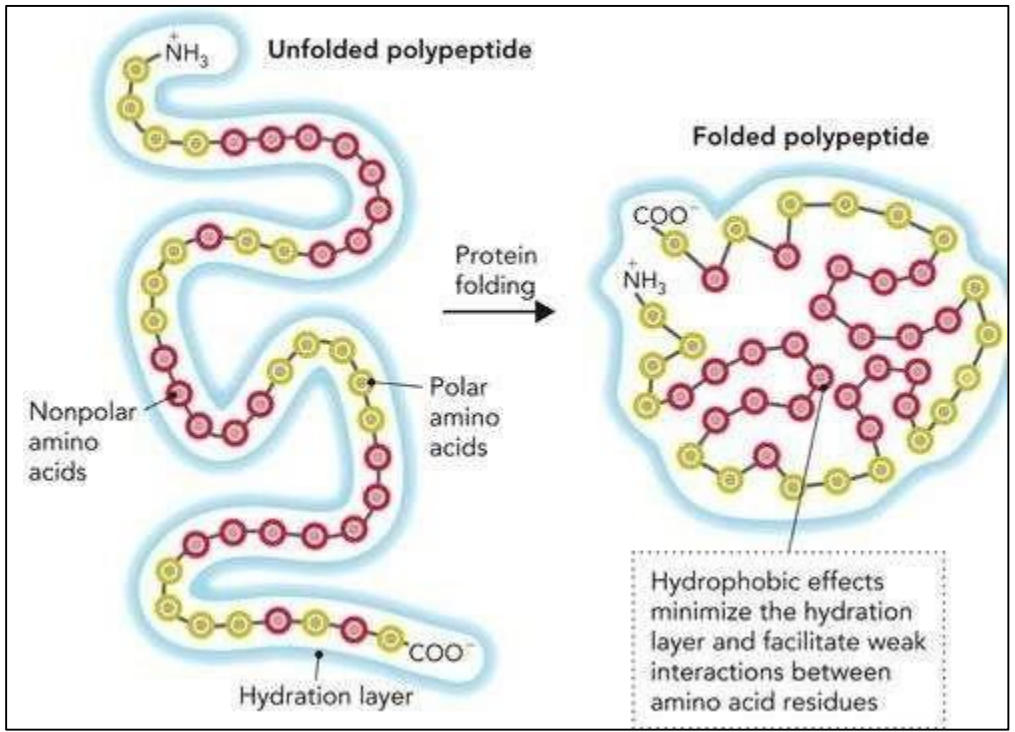
Hydrophobic interactions

- A system is more thermodynamically (energetically) stable when hydrophobic groups are clustered together rather than extended into the aqueous surroundings.

- **The hydrophobic chains isolated inside away from the surrounding aquatic environment**

- **We found the hydrophobic chain outward and the hydrophilic chain inward , but have some exceptions**
- **Some hydrophilic (polar) inside to help in catalyzation In the integral membrane protein the hydrophobic (non-polar) found in the trans domain**

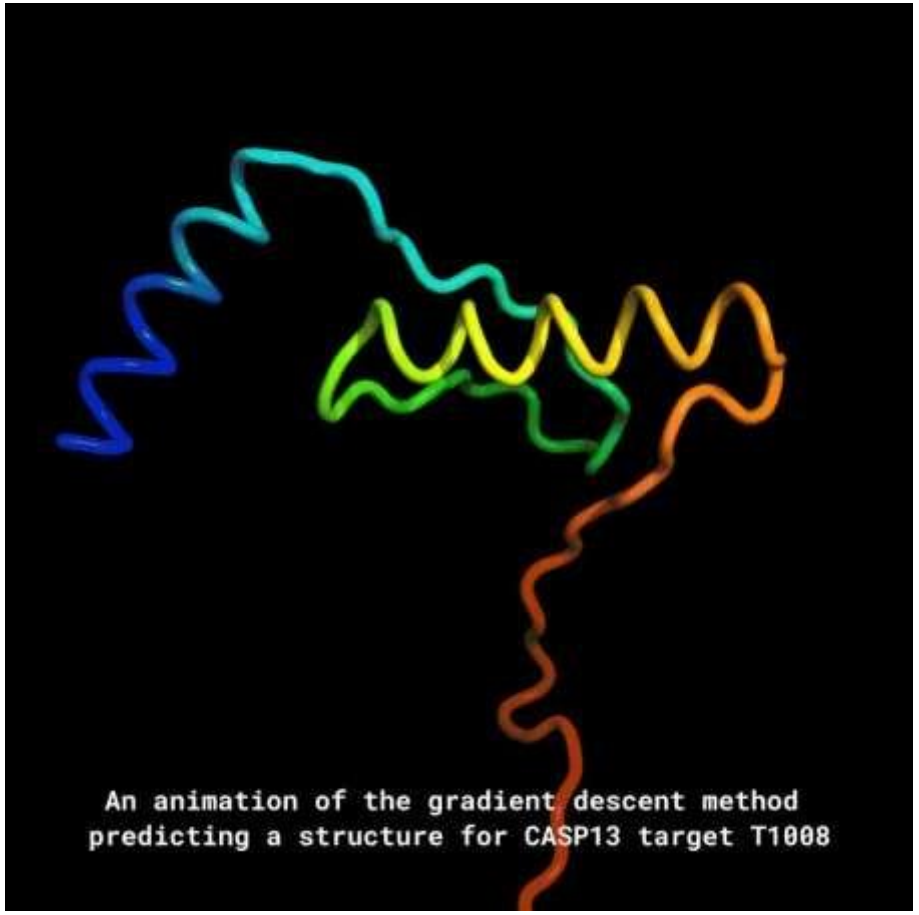




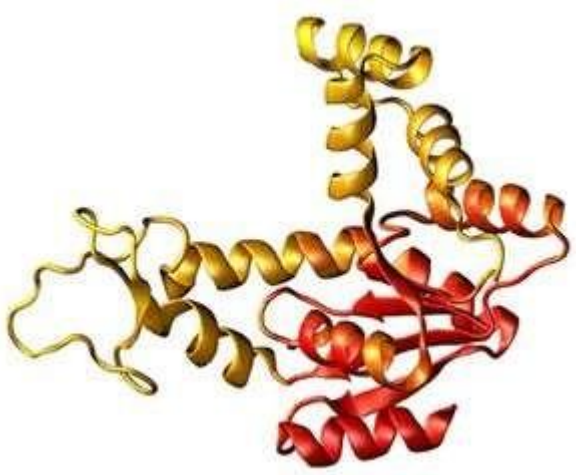
Can polar amino acids be found in the interior?...YES

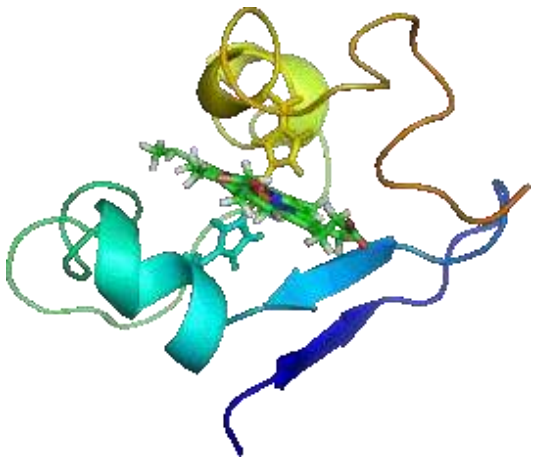
- Polar amino acids can be found in the interior of proteins
- In this case, they form hydrogen bonds to other amino acids or to the polypeptide backbone
- They play important roles in the function of the protein

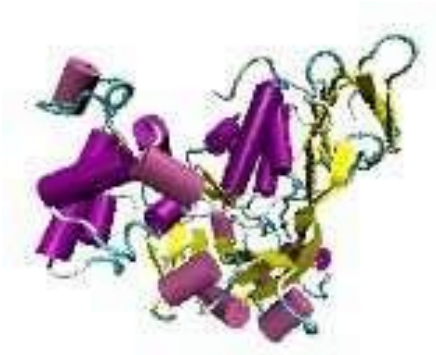
A hypothetical look at protein folding

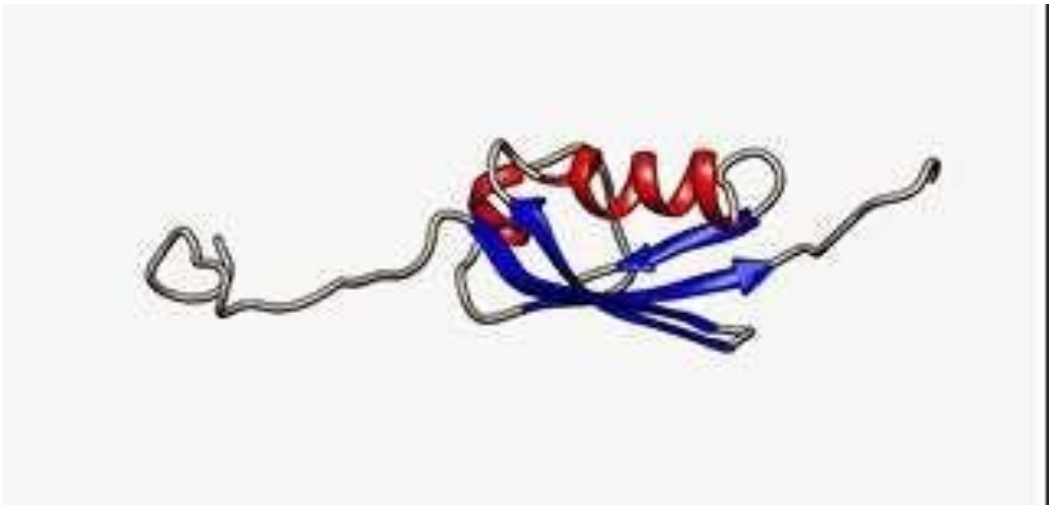


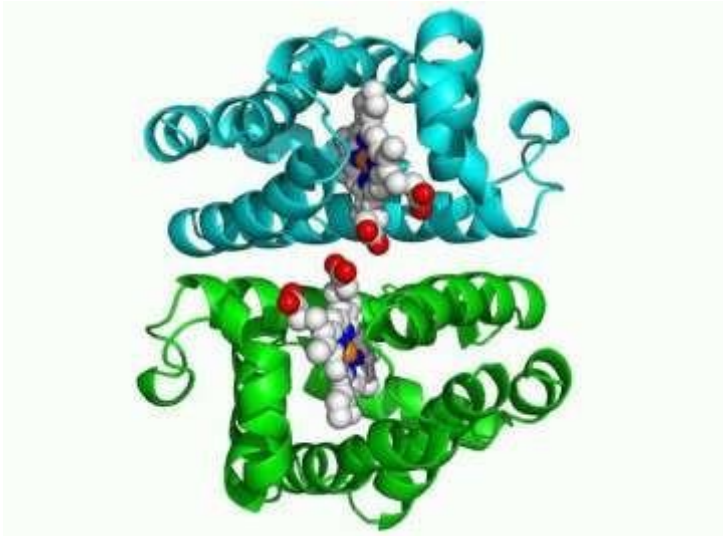
Protein are NOT static











Stabilizing factors

- There are two forces that do not determine the three-dimensional structure of proteins, but stabilize these structures:
  - Disulfide bonds
  - Metal ions

Disulfide bonds

- The side chain of cysteine contains a reactive sulfhydryl group (—SH), which can oxidize to form a disulfide bond (—S—S—) to a second cysteine.
- The crosslinking of two cysteines to form a new amino acid, called cystine.

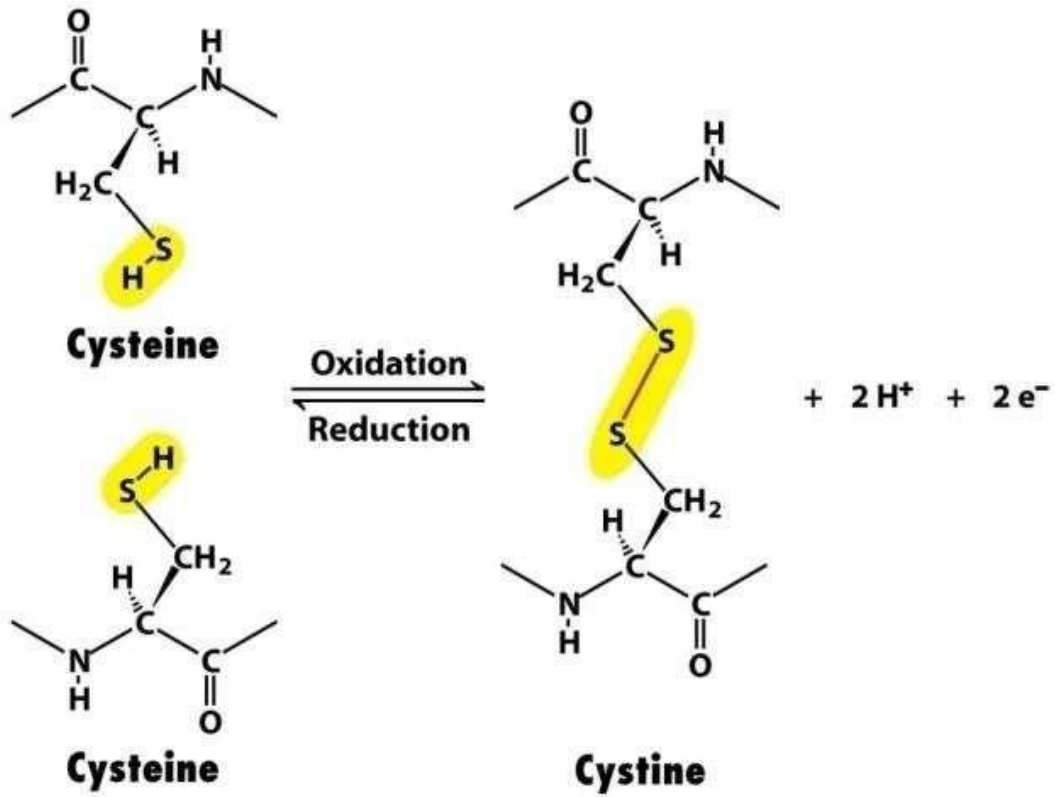


Figure 2-21
Biochemistry, Sixth Edition
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Two cystine connected with disulfide bridge

Important

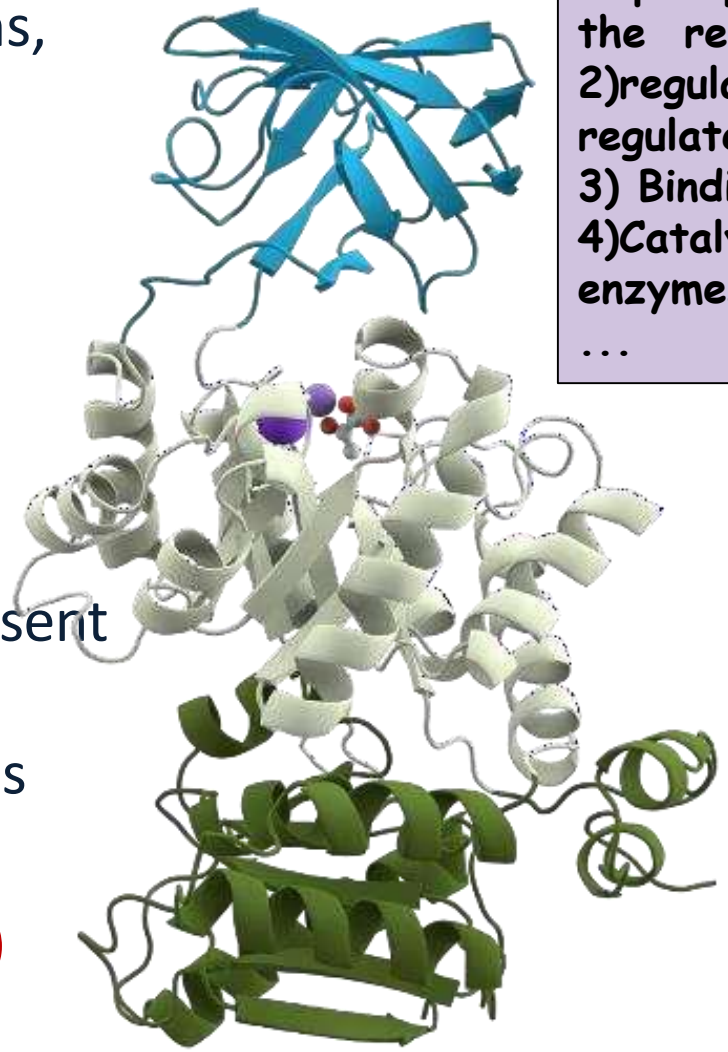
- **The protein continues to oxidize and reduce until it reaches the correct shape**

Domains

- The protein composed of more than one structural units depends on the function

There are a lot of units with different functions as:
1) works as kinase helps in phosphorylation into the reactions
2)regulation one to regulate the protein work
3) Binding domain
4)Catalytic domain for enzymes
...

- A domain is a combination of α helices and/or β sheets that are connected to each other via turns, loops, and coils and are organized in a specific three-dimensional structure.
  - A domain may consist of 100–200 residues.
- Domains fold independently of the rest of the protein or of other domains within the same protein.
- Similar domains can be found in proteins with similar function and/or structure and can be present in different proteins
- Domains may also be defined in functional terms
  - Enzymatic activity
  - Binding ability (e.g., a DNA-binding domain)



metal ions

ions

- Several proteins can be complexed to a single metal ion that can stabilize protein structure by forming:
  - Covalent interaction (myoglobin)
  - Salt bridges (carbonic anhydrase)

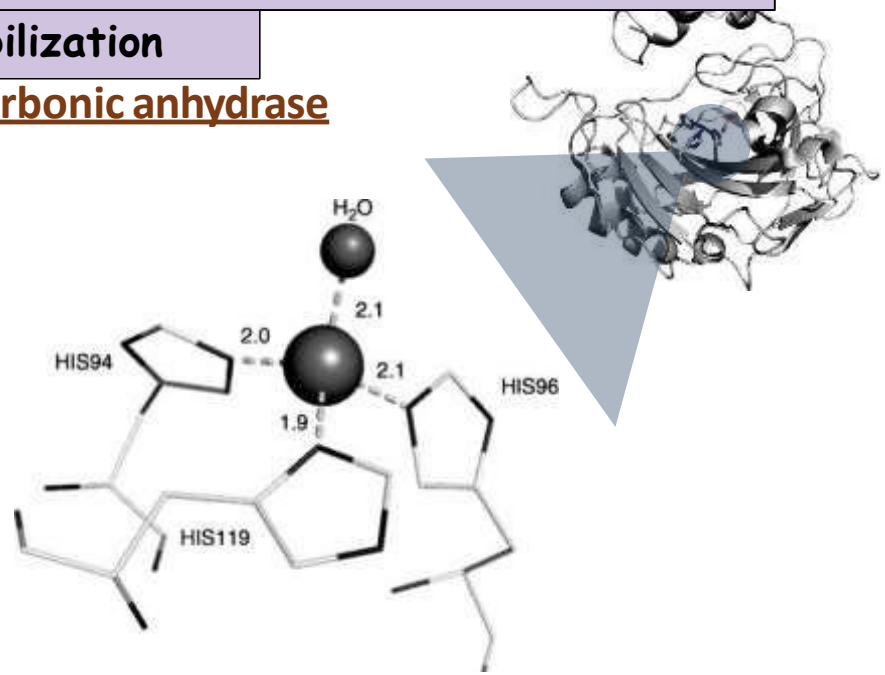
The myoglobin doesn't have the quaternary structure due to it's a single peptide chain

(for stabilization)

Make (H2CO2) in preparation of buffers

Make stabilization

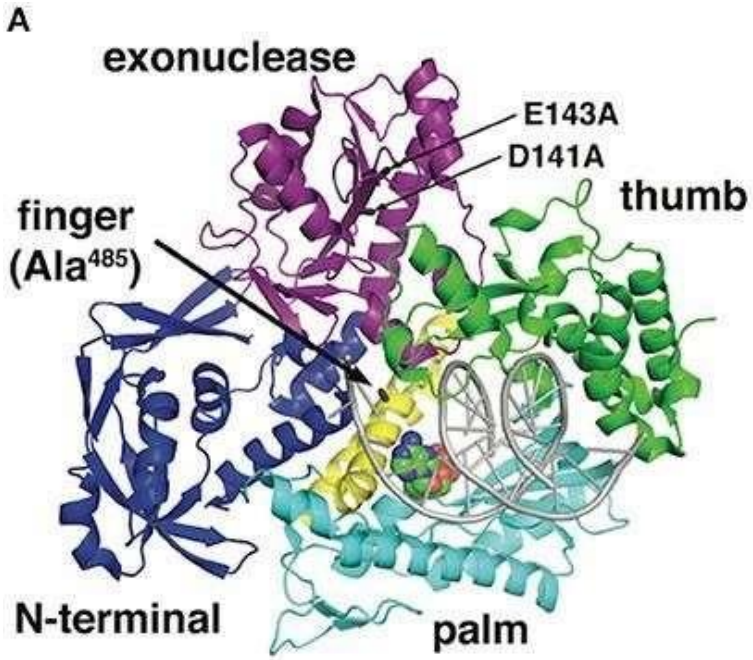
Carbonic anhydrase

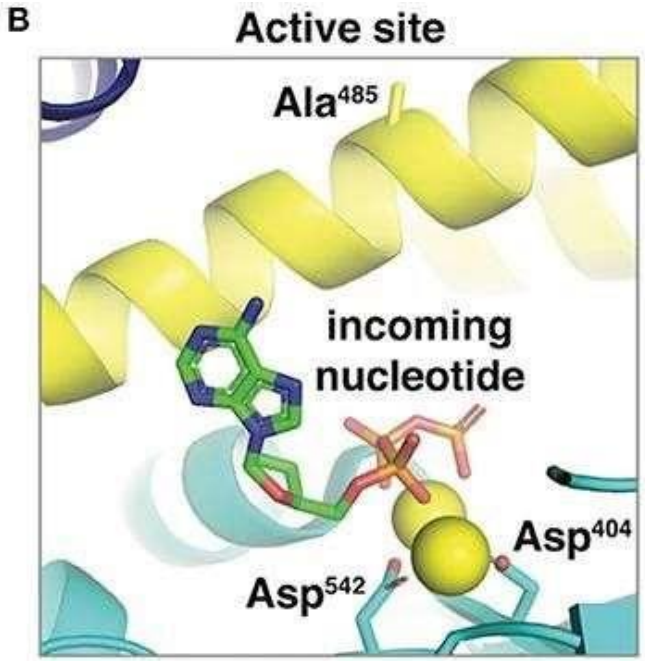


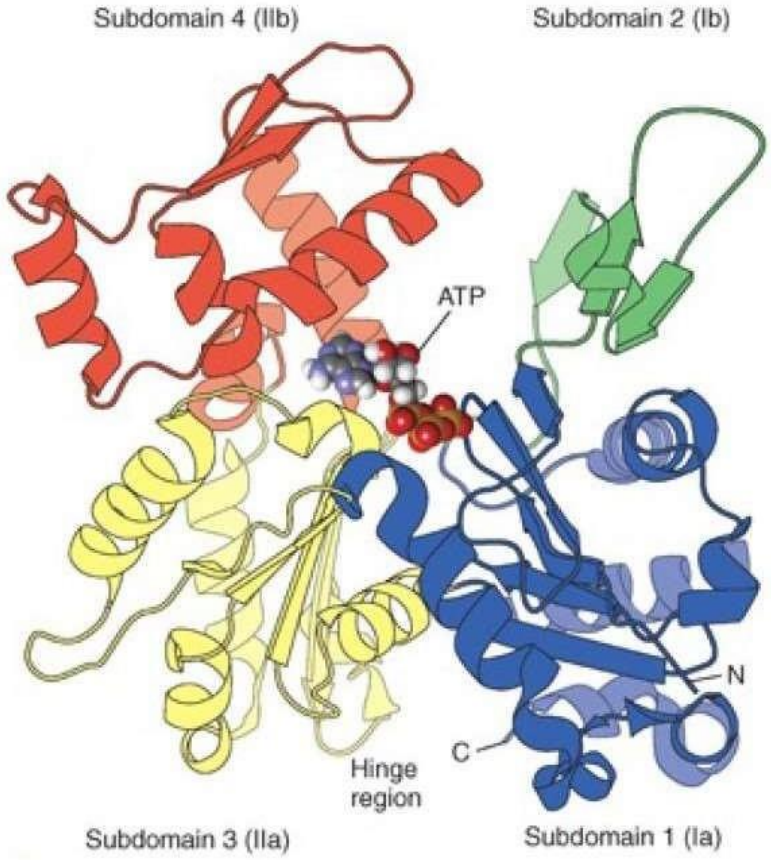
Myoglobin

Folds

- When large patterns of secondary structures or multiple domains within a protein possess specific functions, they are known as **Folds**.
  - The actin fold **Especially in actin**
  - The nucleotide-binding fold

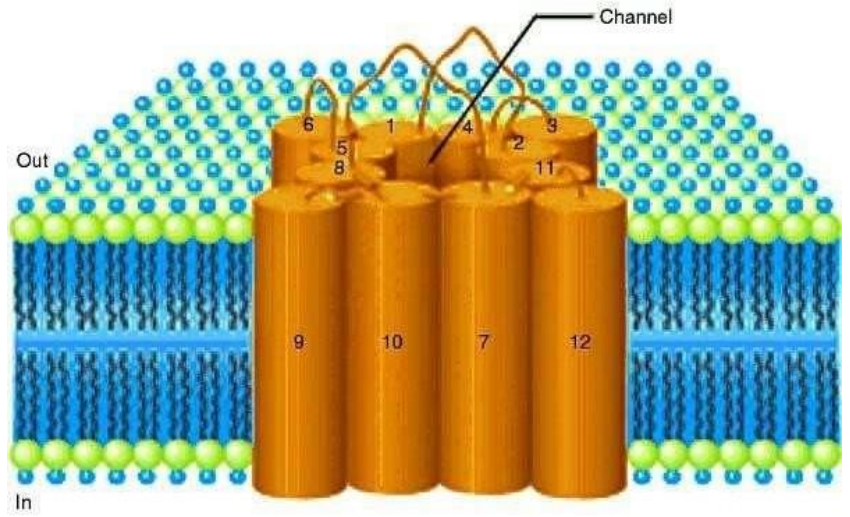


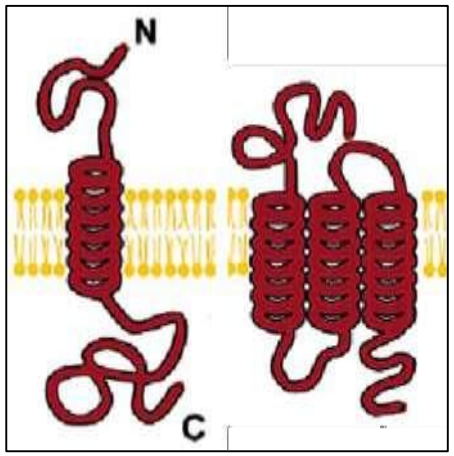


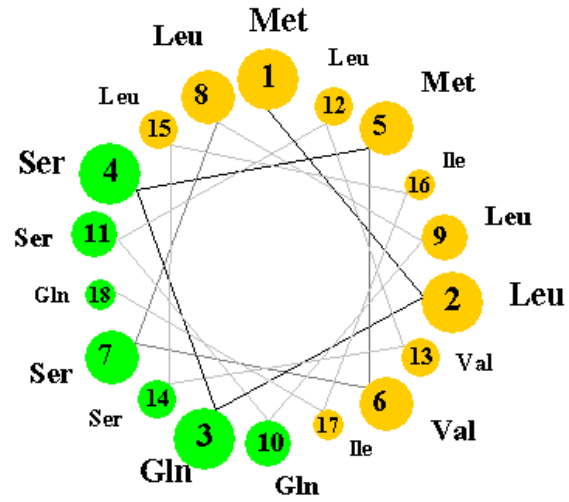


α-helices as transmembrane domains

- Membrane-spanning proteins contain a transmembrane domain that is an α–helix made of hydrophobic amino acids.
- Some membrane proteins contain several transmembrane domains that are also α-helices.
- For receptors, the helices are connected by loops containing hydrophilic amino acid side chains that extend into outside of both sides of the membrane.
- Membrane ion channels contain amphipathic α–helices.

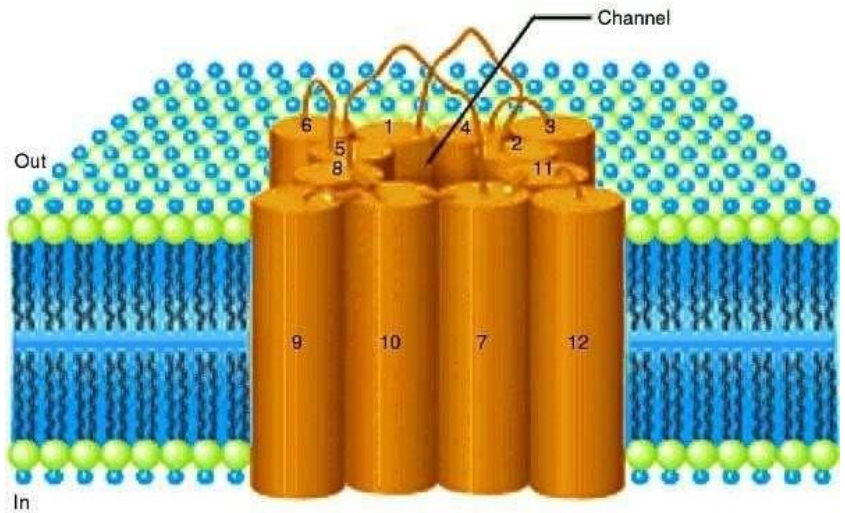






The integral protein mostly composed from helix

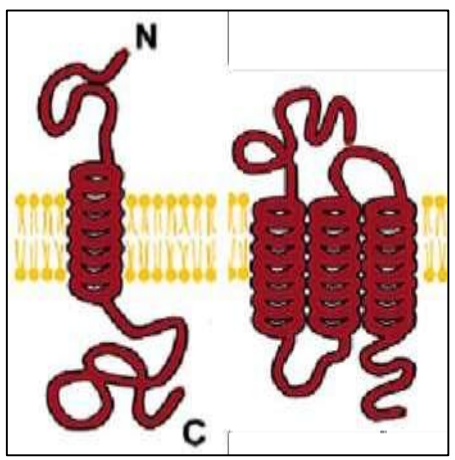
The side that interacts with the lipids and cholesterol is hydrophobic

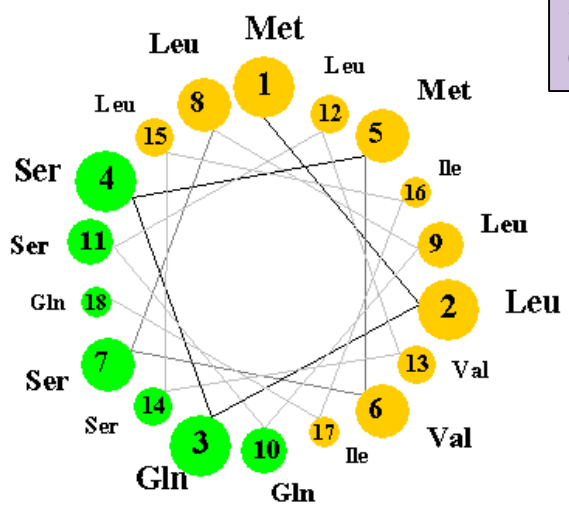


The side that interacts with the adjacent proteins or the polar lumen is hydrophilic
** it is the line between 2 integral proteins (the green line)

In the figure We can see the layers of a helix composed of amino acids

The left one is a single protein so it's only has a helix (only hydrophobic)





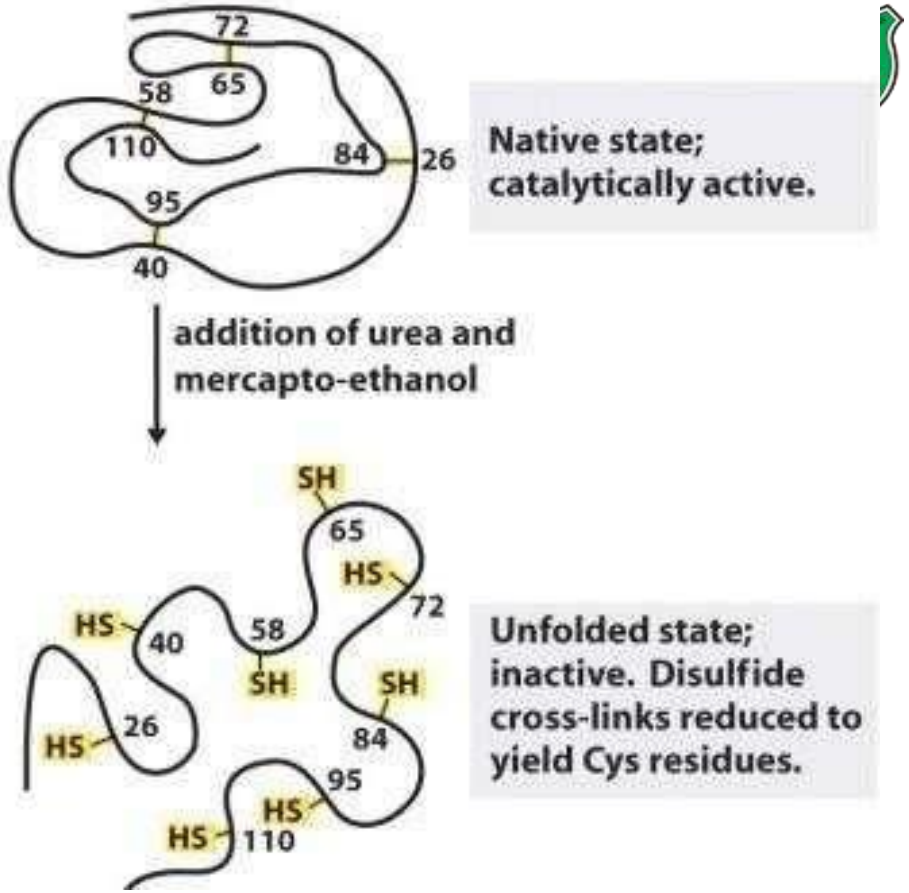
Important

Every turn in the helix composed of approximately four amino acids
Two non-polar then two polar

Properties of Proteins:
Denaturation and Renaturation

Denaturation

- Denaturation is the disruption of the native conformation of a protein via breaking the noncovalent bonds that determine the structure of a protein
- Complete disruption of tertiary structure is achieved by reduction of the disulfide bonds in a protein
- The denatured protein loses its properties such as activity and become insoluble.



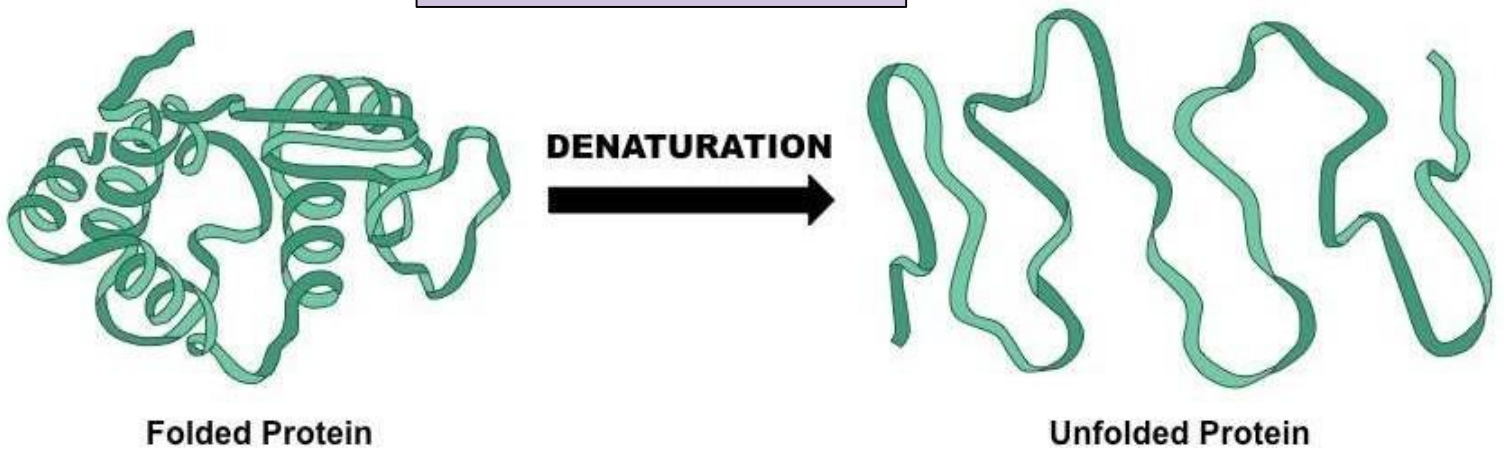
Further explanation regarding the previous slide:

- Denaturation : it is the losing of protein structure (secondary , tertiary and quaternary structures) , primary structure isn't affected at all because peptide bond will remain .
- The overall shape (structure) will be damaged not digested .
- Denaturation can be happened by physical or chemical factors temperature ,ph value changes , reducing conditions which disrupt disulfide bridges)
- Example:

--> when you eat proteins after they reach the stomach how they are digested? If the protein structure was too large , compact the stomach enzyme which has a ph =2.3 will cut these large molecules into small parts after that they will be desaturated and losing the structure of protein and become nonfunctional protein .

- Lysosomes , which are a membrane-bound cell organelle that contains digestive enzymes , do degradation of different molecules like bacteria or viruses include proteins .

Extra picture :-



Denaturing agents

- Heat disrupts low-energy van der Waals forces in proteins
- Extremes of pH: change in the charge of the protein's amino acid side chains (electrostatic and hydrogen bonds).
- Detergents: Triton X-100 (nonionic, uncharged) and sodium dodecyl sulfate (SDS, anionic, charged) disrupt the hydrophobic forces.
  - SDS also disrupt electrostatic interactions.
- Urea and guanidine hydrochloride disrupt hydrogen bonding and hydrophobic interactions.
- Reducing agents: β-mercaptoethanol (β-ME) and dithiothreitol (DTT)
  - Both reduce disulfide bonds.

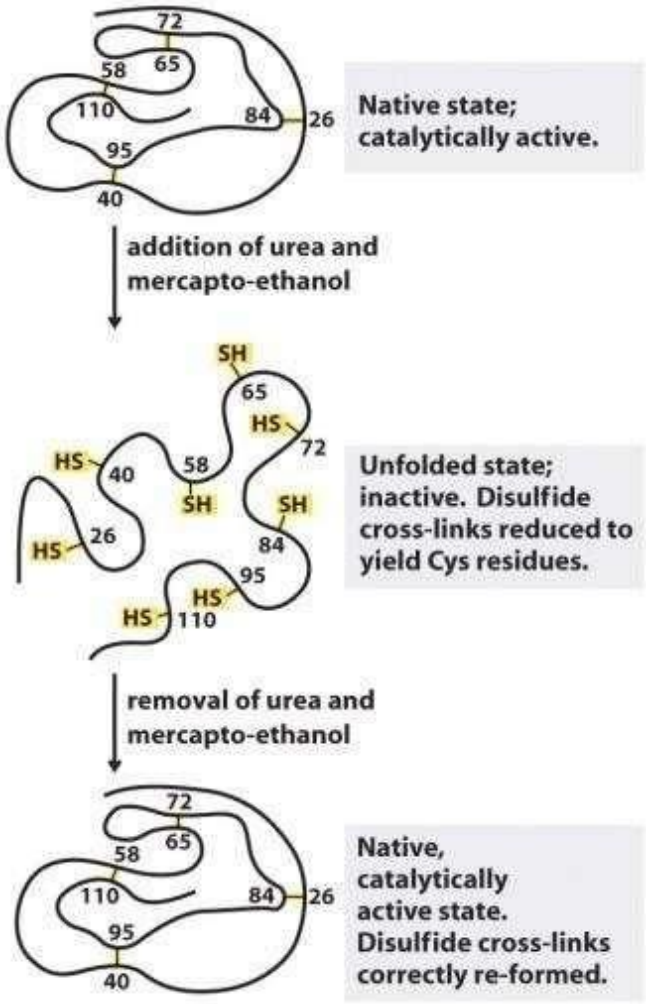
High or low PH values

Detergents
فيظلا داوم

Renaturatio

n

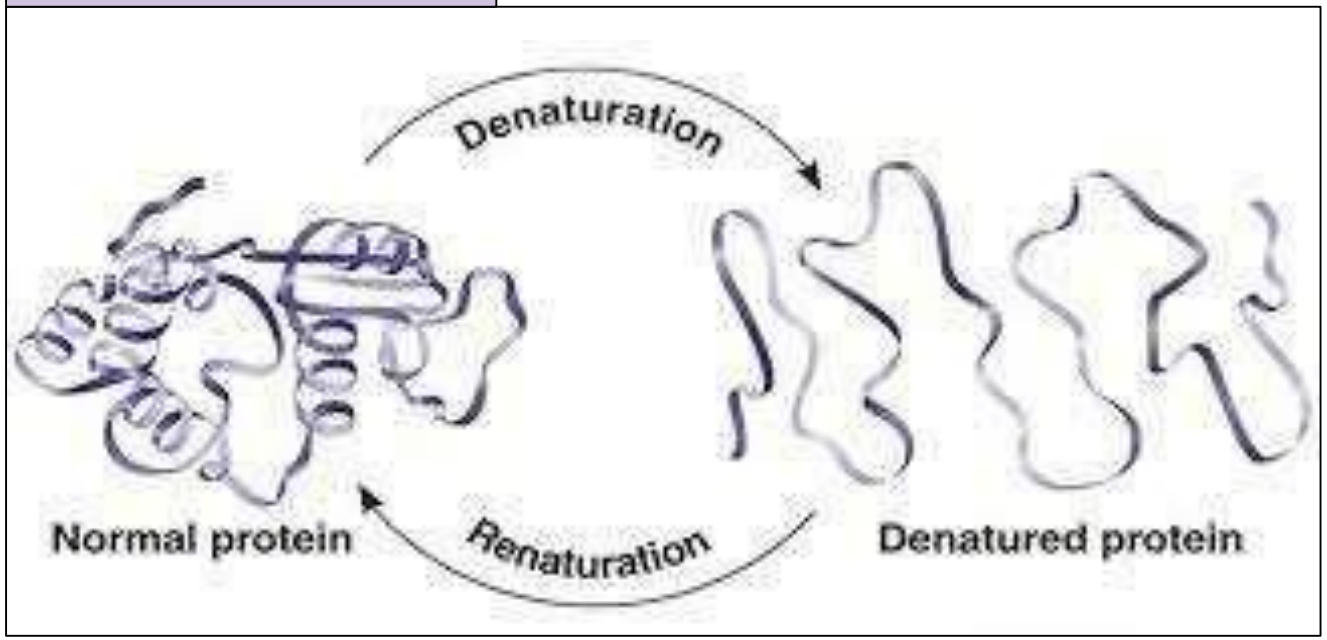
- Renaturation is the process in which the native conformation of a protein is re-acquired.
- Renaturation can occur quickly and spontaneously, and disulfide bonds are formed correctly.
- If a protein is unfolded, it can refold to its correct structure placing the S-S bonds in the right orientation (adjacent to each other prior to formation), then the correct S-S bonds are reformed.
- This is particularly true for small proteins.



Further explanation regarding the previous slide:

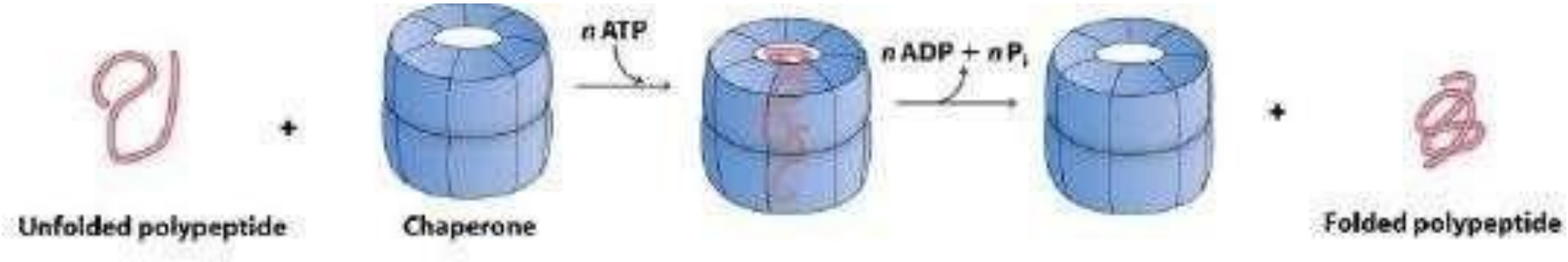
- Renaturation of a protein is the conversion of a denatured protein back into its native 3D structure
- Not all denatured proteins will be renatured In many cases, denaturation is reversible. Since the primary structure of protein is intact, once the denaturing influence is removed, proteins can regain their native state by folding back to the original conformation.
- Renaturation in some cases need an oxidizing agent to happen renature of disulfide bridges need an oxidizing agent .

Extra picture :-



Problem solvers: chaperones

- •These proteins bind to polypeptide chains and help them fold with the most energetically favorable folding pathway.
- •Chaperones also prevent the hydrophobic regions in newly synthesized protein chains from associating with each other to form protein aggregates .



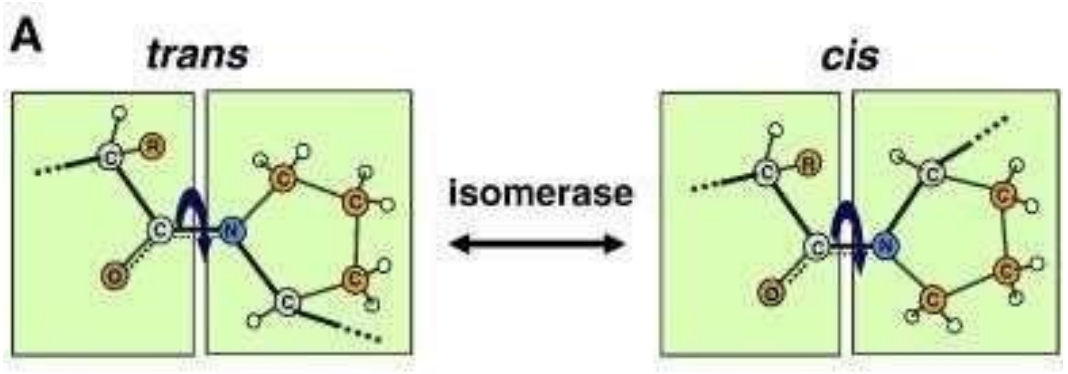
Many diseases are the result of defects in protein folding.

- Chaperones(the general name) are a family of proteins that helps in folding of proteins .
- They guide proteins along the proper pathways for folding and protect proteins when they are in the process of folding.
- One of them helps in protein folding , one check it , one revise it if the protein has a mistake chaperones back the protein to its primary structure and give it a chance to refold again, if it still have a mistake chaperons will denature it :)

Other players

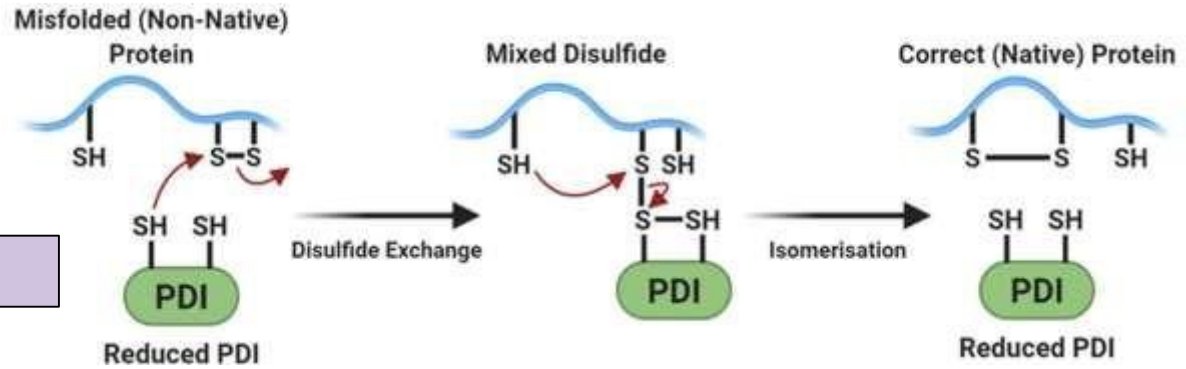
- A cis–trans isomerase converts a trans peptide bond preceding a proline into the cis conformation, which is well-suited for making hairpin turns.

catalyzing the correct folding of many prokaryotic and eukaryotic proteins



- A protein disulfide isomerase, after the protein has folded, breaks and reforms disulfide bonds between the –SH groups of two cysteine residues.

PDI breaks S-S bond



a chaperone, a binding partner of other proteins, and a hormone reservoir as well as a disulfide isomerase in the formation of disulfide bonds.

Factors that determine protein structure

- The least amount of energy needed to stabilize the protein. This is determined by:
  - The amino acid sequence (the primary structure), mainly the internal residues.
  - The proper angles between the amino acids
  - The different sets of weak noncovalent bonds that form between the mainly the R groups.
  - Non-protein molecules.

noncovalent bonds can be between :
1- backbone-backbone
2- Backbone- R groups
3- R group – R group

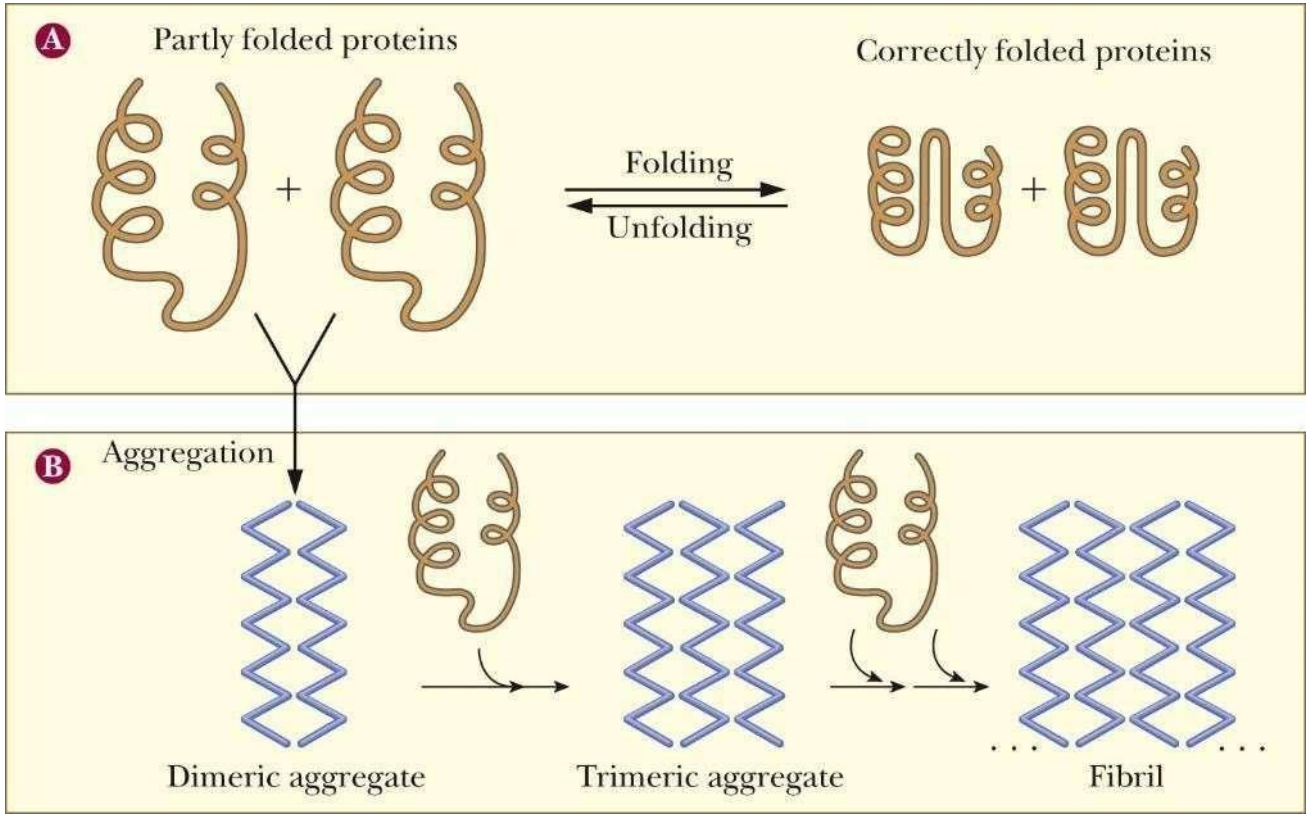
The planner shape of peptide bond and its environment

Non protein molecules can be :
1 sugars
2 lipids
3 ions
4 hem groups

Important :-
- The whole information that is very important for protein folding are exist in the primary structure which is the sequence of amino acids groups.

The problem of misfolding

- When proteins do not fold correctly, their internal hydrophobic regions become exposed and interact with other hydrophobic regions on other molecules, and form aggregates.



Nonpolar amino acid (large amounts)aren't completely folded so they will be exposed which will make protein aggregation (by a hydrophobic interactions) these structures will affect on cell's function --> low movement for organelles and the cell itself --> low response for the changes that happened in environment

Outcome of protein misfolding

- Partly folded or misfolded polypeptides or fragments may sometimes associate with similar chains to form aggregates.

- Aggregates vary in size from soluble dimers and trimers up to insoluble fibrillar structures (amyloid).

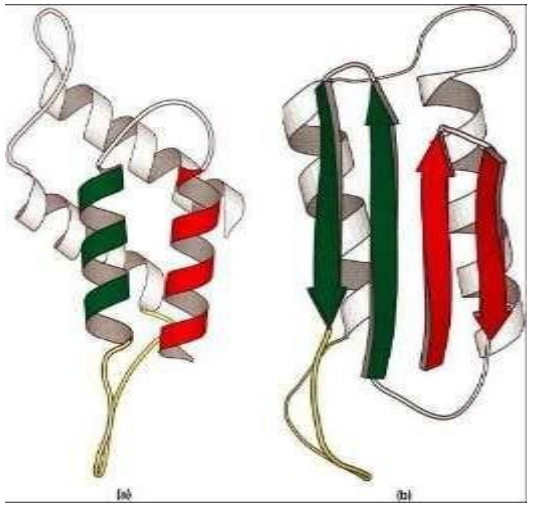
- Both soluble and insoluble aggregates can be toxic to cells.

Further explanation regarding the previous point :

- **Sometimes protein misfolding exposes hydrophobic regions and they clump together Then the protein aggregate is formed The protein aggregate, when it accumulates in the cell and tissue, becomes toxic and kills the cells**

Prion disease

- •Striking examples of protein folding-related diseases are prion diseases, such as Creutzfeldt-Jacob disease (in humans), and mad cow disease (in cows), and scrapie (in sheep).
- •Pathological conditions can result if a brain protein known to as prion protein (PrP) is misfolded into an incorrect form called PrPsc.
- • PrPC has a lot of α-helical conformation, but PrPsc has more β strands
  - forming aggregates.



The prion protein

- The disease is caused by a transmissible
- agent Abnormal protein can be acquired by
  - Infection
  - Inheritance
  - Spontaneously

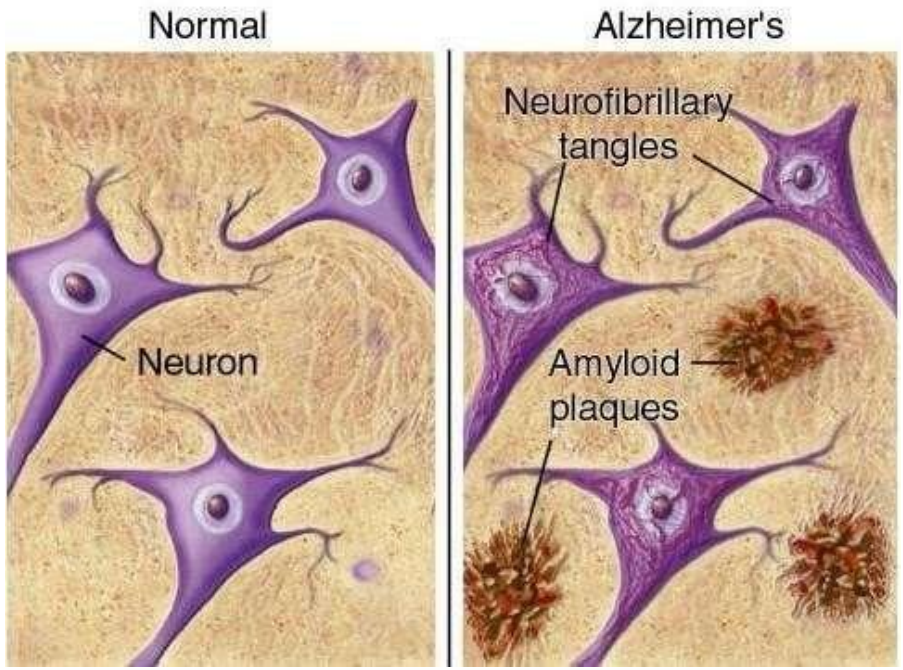
Further explanation regarding the previous point :

- **Prion disease: Scientists have discovered that it is a protein, and the reason is that this protein is misfolding, so it makes all proteins the same and becomes protein aggregate**
- **The prion protein: It has the Alpha Helix, then it turns into the Beta Strand When it turns into a beta-strand, it binds to other proteins, changes shape and misfolds, so protein aggregate works, especially in the brain, and this thing will kill neurons.**

Alzheimer’s Disease

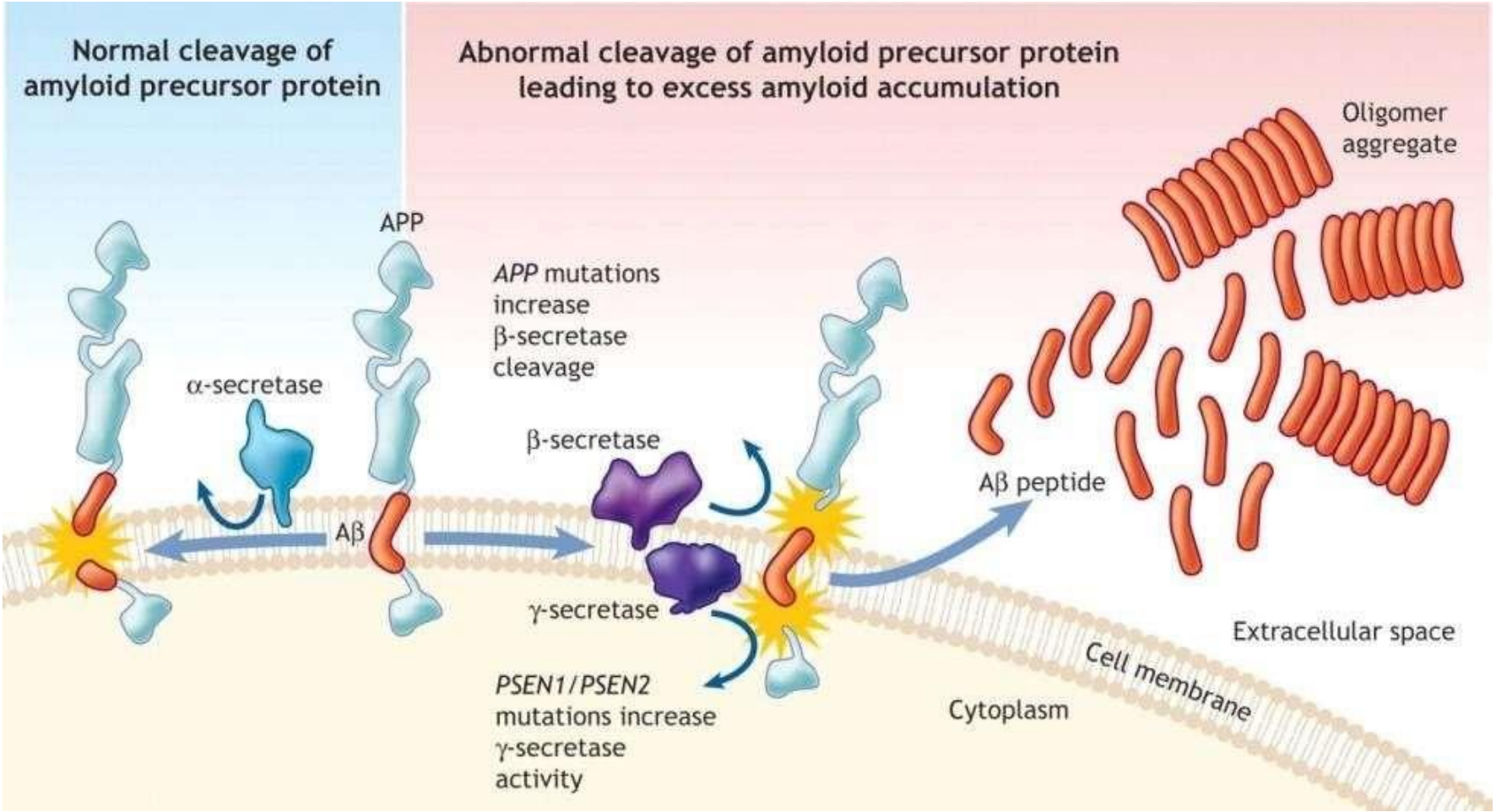
- Not transmissible between individuals

- Extracellular plaques of protein aggregates of a protein called tau and another known as amyloid peptides (Aβ
- damage neurons.



- **Scientists noticed black dots like accumulations in the brain They saw its protein aggregate for amyloid peptides This is what causes Alzheimer's**

Formation of plaques



Further explanation regarding the previous slide:

- The cell removes the proteins on the surface of the cell and puts in their place newer proteins so that it performs protein shedding (The protease enzyme that works to cleavage the protein removes it and replaces it with a new one) Hydrophobic peptides accumulate on each other and act as an aggregate protein that damages the surround cell, such as the nerve cell

Quaternary

- All proteins have a tertiary structure But not all of them have quaternary structure
- The quaternary structure has a protein that is made of more than one polypeptide The polypeptide can be different gene or same

What is it?

Proteins are composed of more than one polypeptide chain.

They are oligomeric proteins (oligo = a few or small or short; mer = part or unit)

The spatial arrangement of subunits and the nature of their interactions.

Proteins made of

One subunit = monomer

Two subunits: dimer

The simplest: a homodimer

Three subunits: trimer

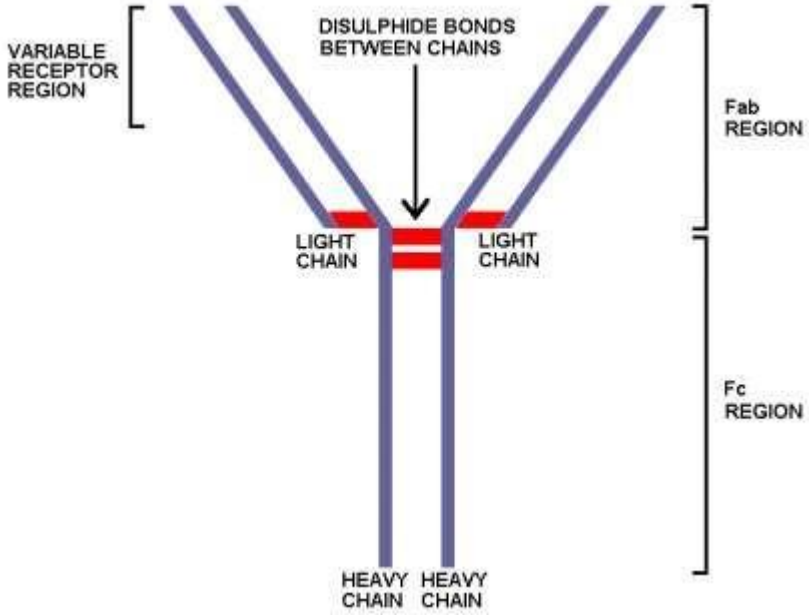
Four subunit: tetramer

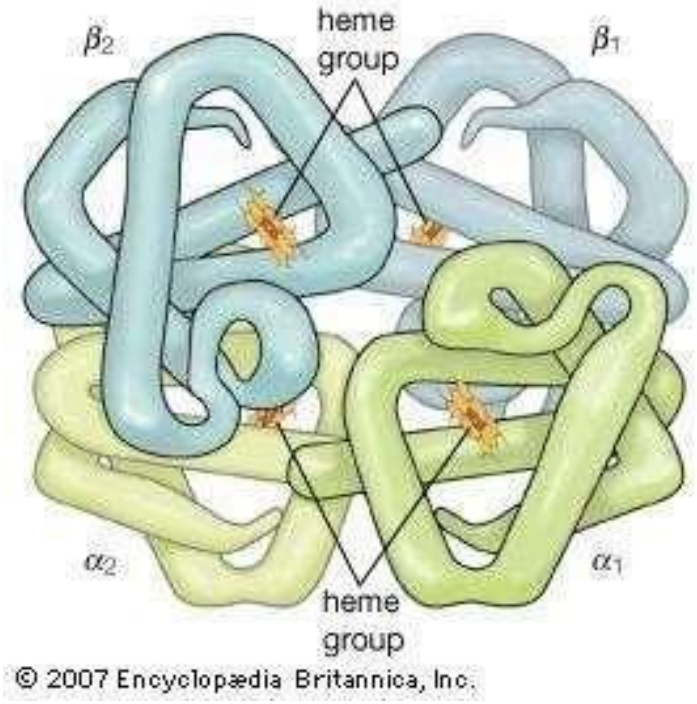
…etc

- Each polypeptide chain is called a subunit.
- Oligomeric proteins are made of multiple polypeptides that are
  - identical → homooligomers (homo = same), or
  - different → heterooligomers (hetero = different)
- Oligomer sometimes refers to a multisubunit protein composed of identical subunits, whereas a multimer (or protomer) describes a protein made of many subunits of more than one type.

How are the subunits connected?

- Sometimes subunits are disulfide-bonded together, other times, noncovalent bonds stabilize interactions between subunits



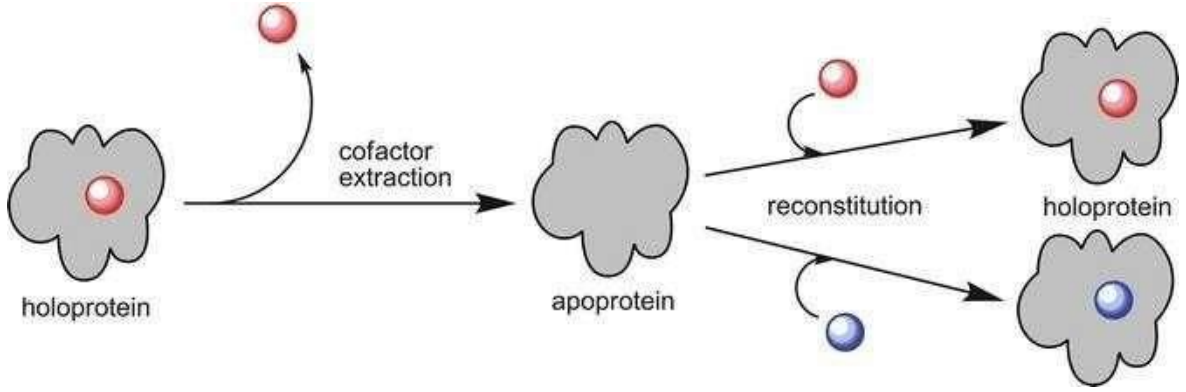


- **The two chain polypeptides bind to each other depending on the protein**
- **Example :**
- **hemoglobin: 4 polypeptide chains non-covalently (hydrophobic interaction), tetramer, 2 alpha & 2 beta**
- **Immunoglobulin: 4 chain polypeptides linked to some covalently (disulfide bond), tetramer, 2 heavy chains &2 light chains**

Complex protein structures

Holo- and apo-proteins

- When a protein is conjugated to any associated non-protein components, such as prosthetic groups or metal ions, the protein is known as a **holoprotein** (AKA a conjugated protein).
- If the non-protein component is removed, the protein is known as an **apoprotein**.
  - In other words, it is the protein portion of a conjugated protein without the attached non-protein group.

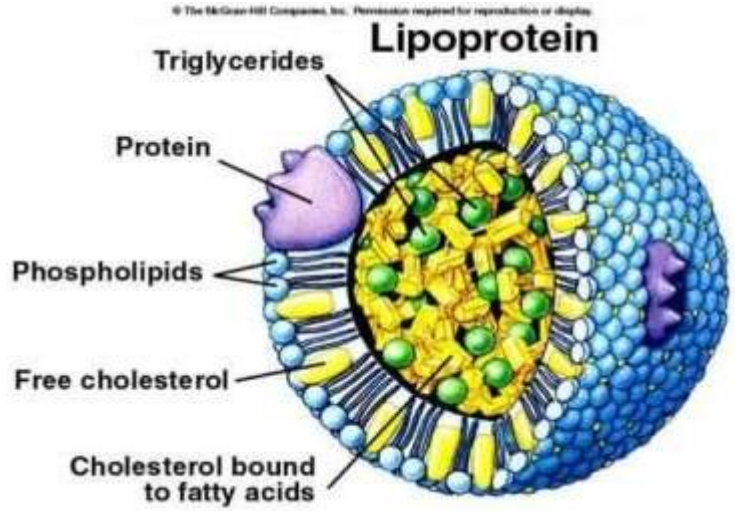


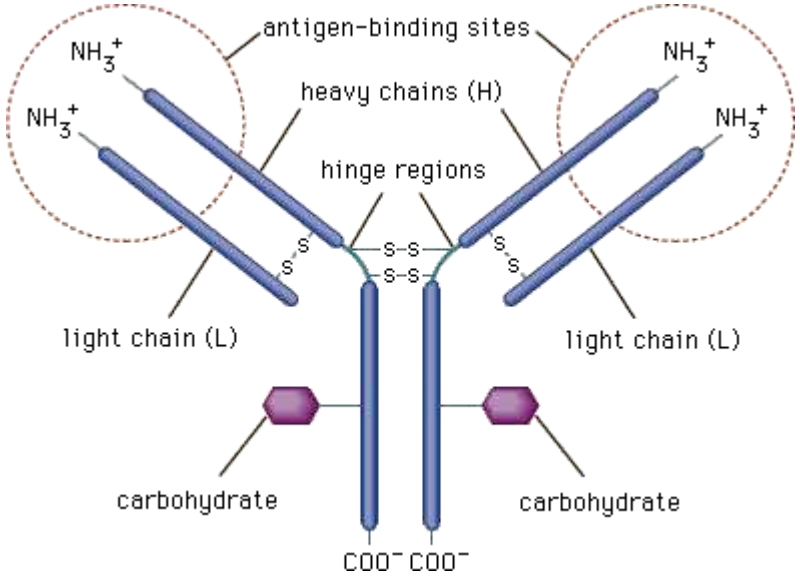
Coenzymes: complex organic molecules that assist enzymes in catalyzing biochemical reactions
Prosthetic groups: Coenzymes or metals that are tightly (covalently) bound to proteins

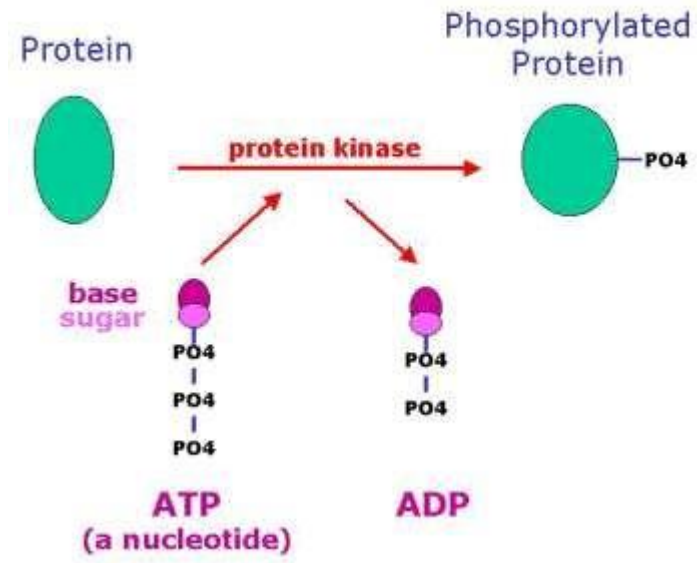
- Protein times have non-protein groups, we call them conjugated or holo protein such as:
- Hemoglobin is made up of globulin (a protein) And heme (Organic Molecules)
- Lipoprotein works as a transport for lipids Composed of Lipids & Protein
- If we remove the non-protein groups, we call them apo protein

Other names of conjugated proteins

- Lipoproteins: Proteins associated with lipids
- Phosphoproteins: proteins that are phosphorylated
- Hemoproteins: proteins with heme
- Nucleoproteins: proteins with a nucleic acid
- Glycoproteins: proteins with carbohydrate groups







Classes of glycoproteins

- N-linked sugars
  - The amide nitrogen of the R-group of asparagine
- O-linked sugars
  - The hydroxyl groups of either serine or threonine
  - Occasionally to hydroxylysine such as in collagen

- **How do sugars bind to protein?**
- **They work in attachment with the amino acid via**
- **N-linked sugars**
- **O-linked sugars**