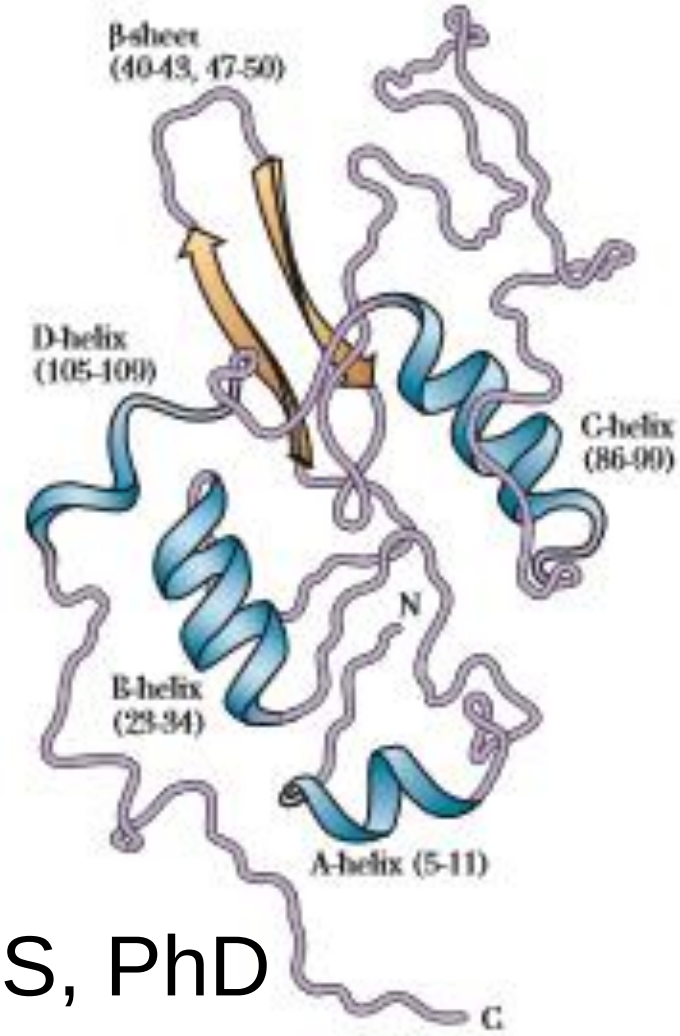
Proteins



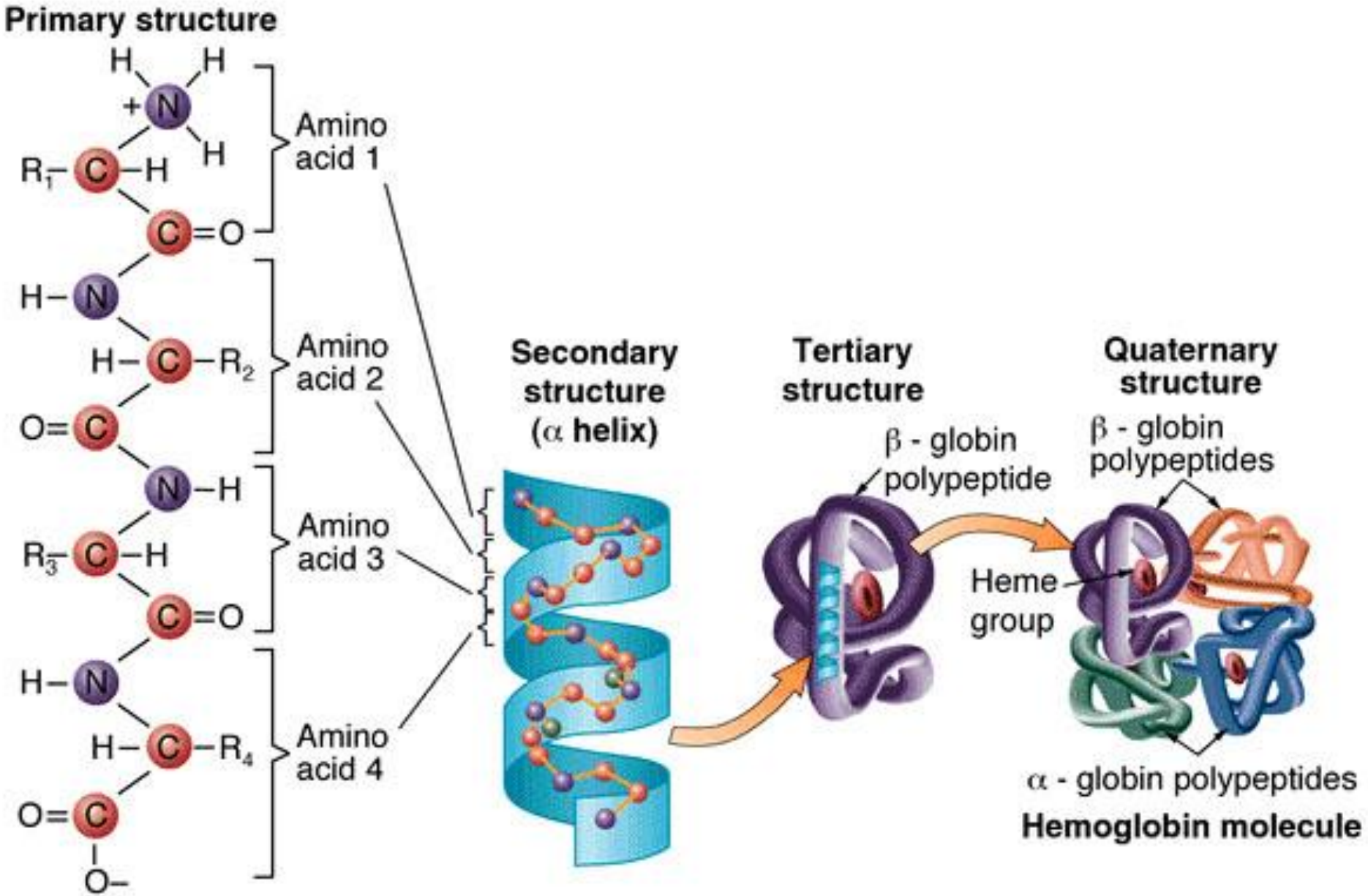
Dr. Diala Abu-Hassan, DDS, PhD

Dr.abuhassand@gmail.com

Protein classification by function

TABLE 18.2 Classification of Proteins by Function

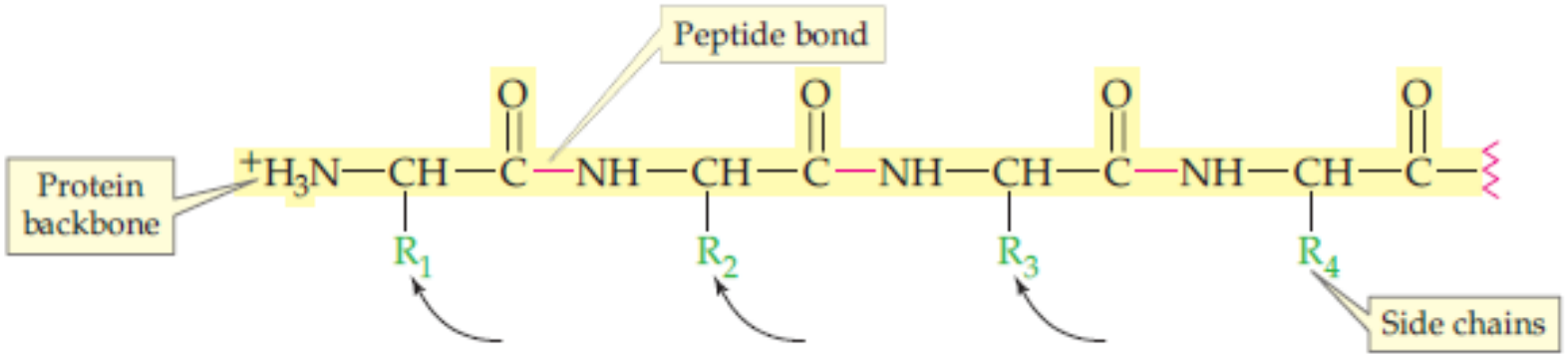
TYPE	FUNCTION	EXAMPLE
Enzymes	Catalysts	*Amylase*—begins digestion of carbohydrates by hydrolysis
Hormones	Regulate body functions by carrying messages to receptors	*Insulin*—facilitates use of glucose for energy generation
Storage proteins	Make essential substances available when needed	*Myoglobin*—stores oxygen in muscles
Transport proteins	Carry substances through body fluids	*Serum albumin*—carries fatty acids in blood
Structural proteins	Provide mechanical shape and support	*Collagen*—provides structure to tendons and cartilage
Protective proteins	Defend the body against foreign matter	*Immunoglobulin*—aids in destruction of invading bacteria
Contractile proteins	Do mechanical work	*Myosin and actin*—govern muscle movement


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

https://www.youtube.com/watch?v=qBRFIMcxZNM

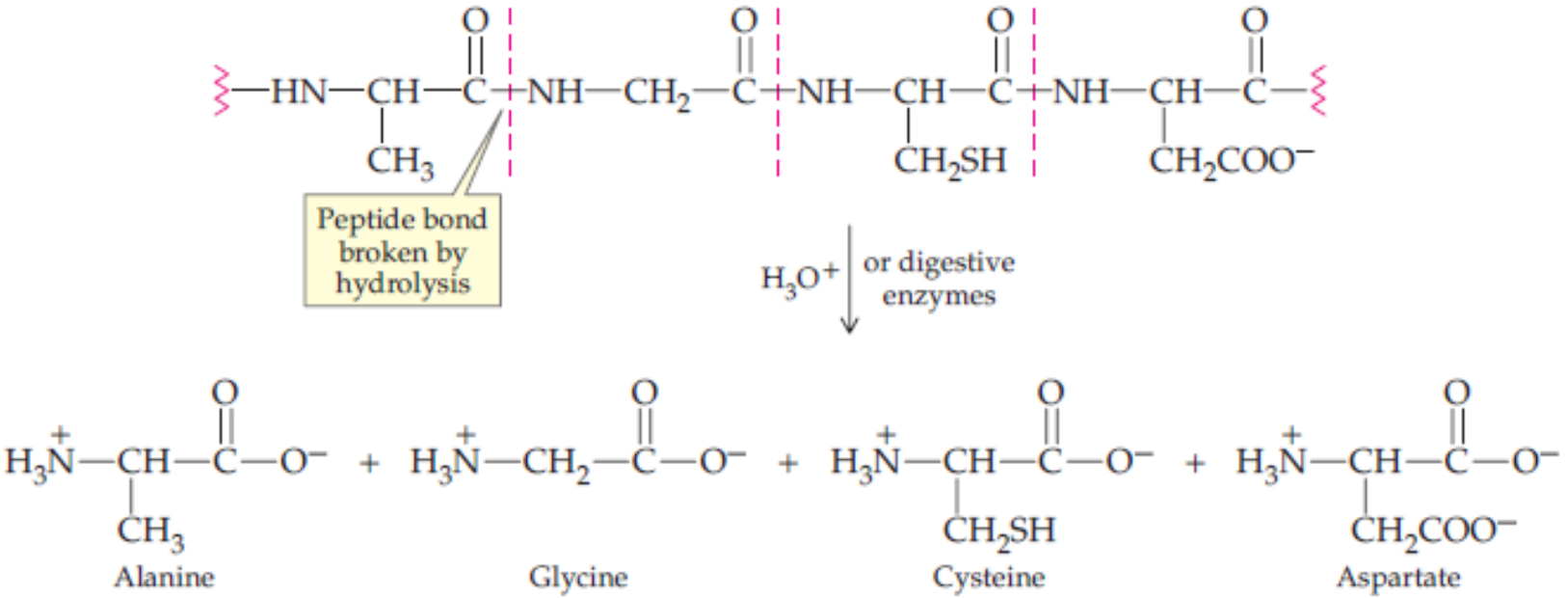
Primary protein structure

- Is the sequence of amino acids connected by peptide bonds in the polypeptide chain
- Primary structure is very essential to function



Chemical Properties of Proteins

Protein Hydrolysis

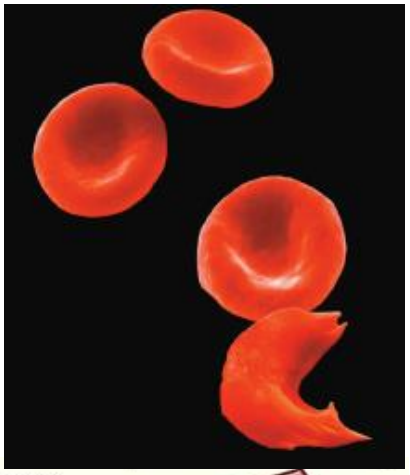


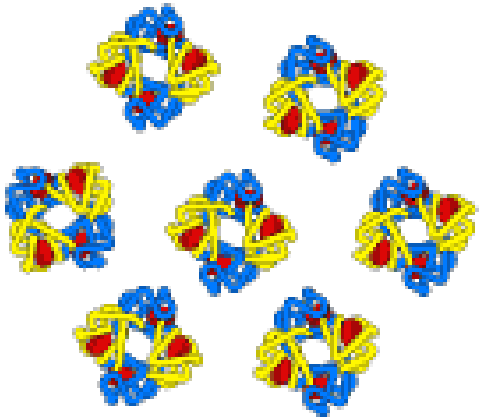
Most digestion of proteins occurs in the stomach and small intestine, where the process is catalyzed by enzyme

Why is it important to know the primary protein structure?

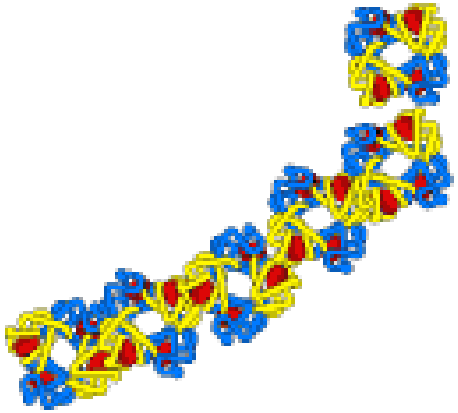
Clinical hint

- Sickle-cell anemia is a result of amino acid substitution.
- A genetic replacement of one Glu in each of two polypeptide chains of the hemoglobin molecule with another Val

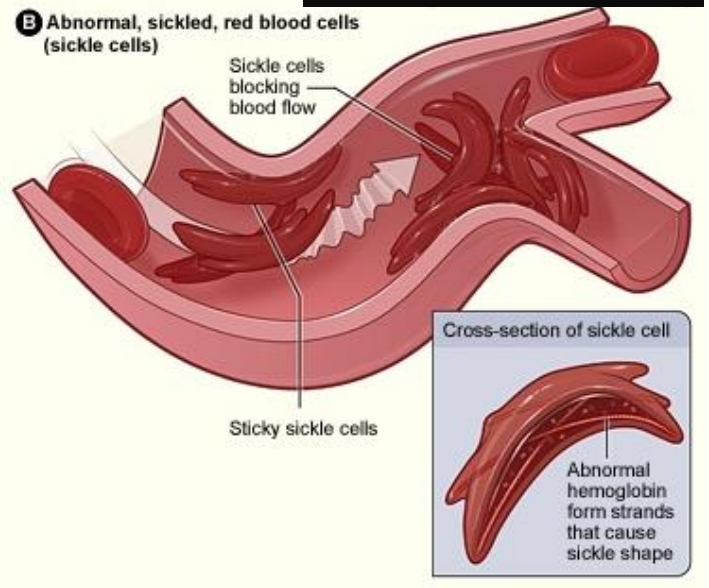




NORMAL HEMOGLOBIN



CLUMPED HEMOGLOBIN

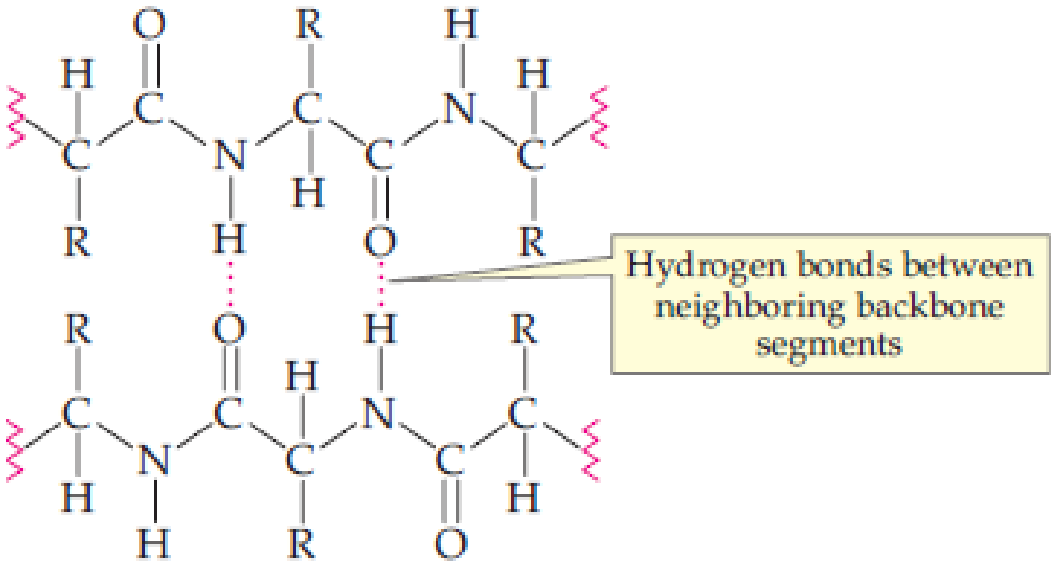


Biochemical application: vegeterians and malnutrition

- A complete protein provides all essential amino acids in appropriate amounts for human survival.
- Essential amino acids cannot be synthesized by humans such as Lys and Met
- Lys and Met are essential amino acids that are found in low amounts in plant proteins.
- Grains such as rice and corn are poor in Lys, and beans are poor in Met
- Complementary proteins concept by eating grains and beans.

Shape-Determining Interactions in Proteins

- Importance of structure-function relationship
- Hydrogen Bonds along the Backbone



Shape-Determining Interactions in Proteins

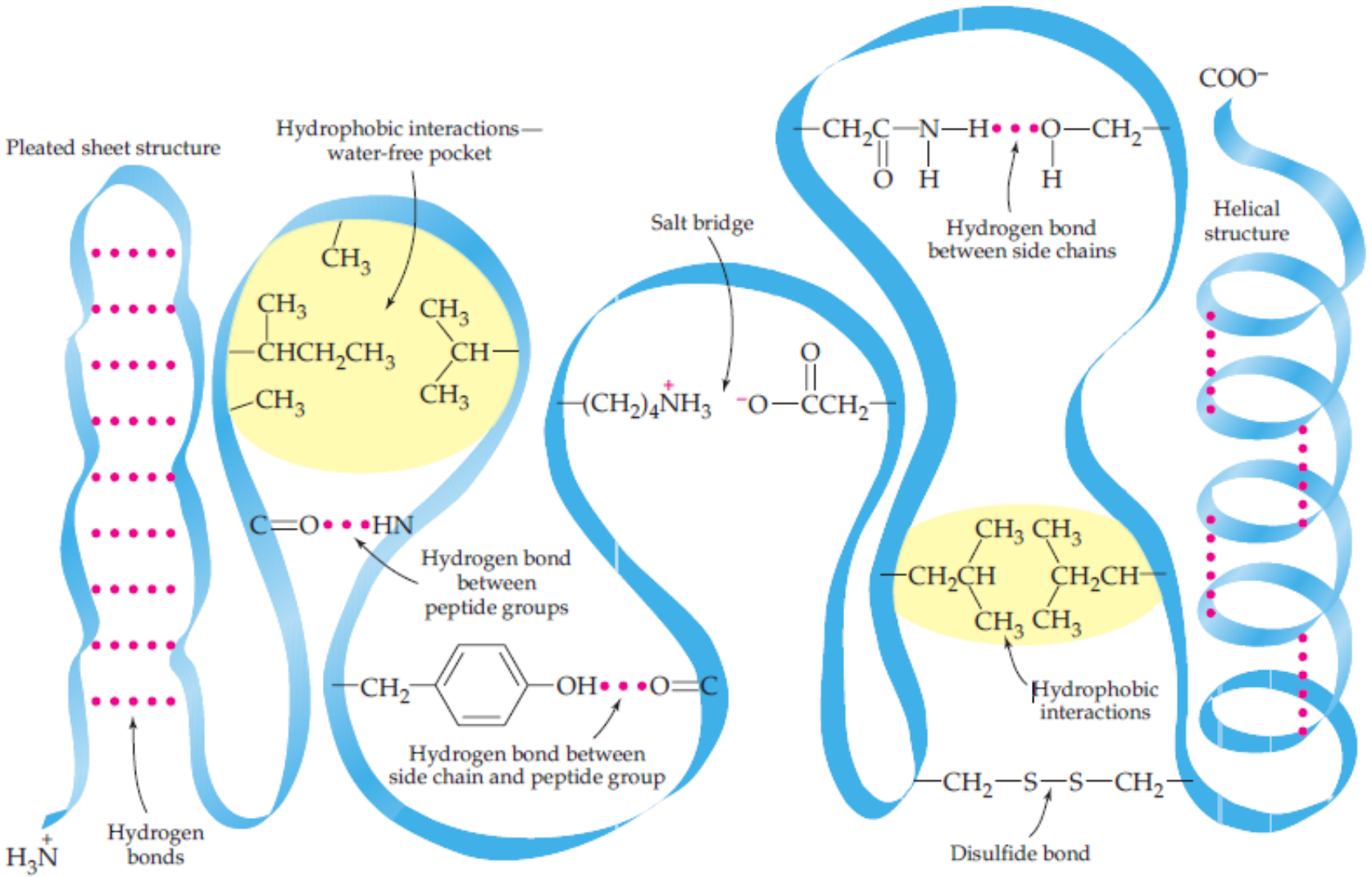
Non-covalent interactions:

- H-bonds of backbone and R groups with each other or with backbone atoms
- Ionic attractions between R groups (Salt bridges)
- Hydrophobic Interactions between R Groups

Covalent bonds:

- Covalent sulfur-sulfur bonds

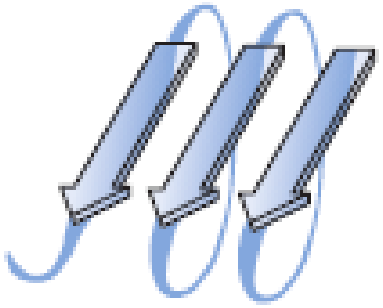
Shape-Determining Interactions in Proteins



Secondary Protein Structure

- The hydrogen-bonded arrangement of the backbone of the protein, the polypeptide chain.
- Is the arrangement in space of the polypeptide chain, which includes regular repeating patterns
- Two kinds of repeating patterns: the **alpha-helix (α-helix), and the beta-sheet (β-sheet)**
- **Also includes turns and loops**

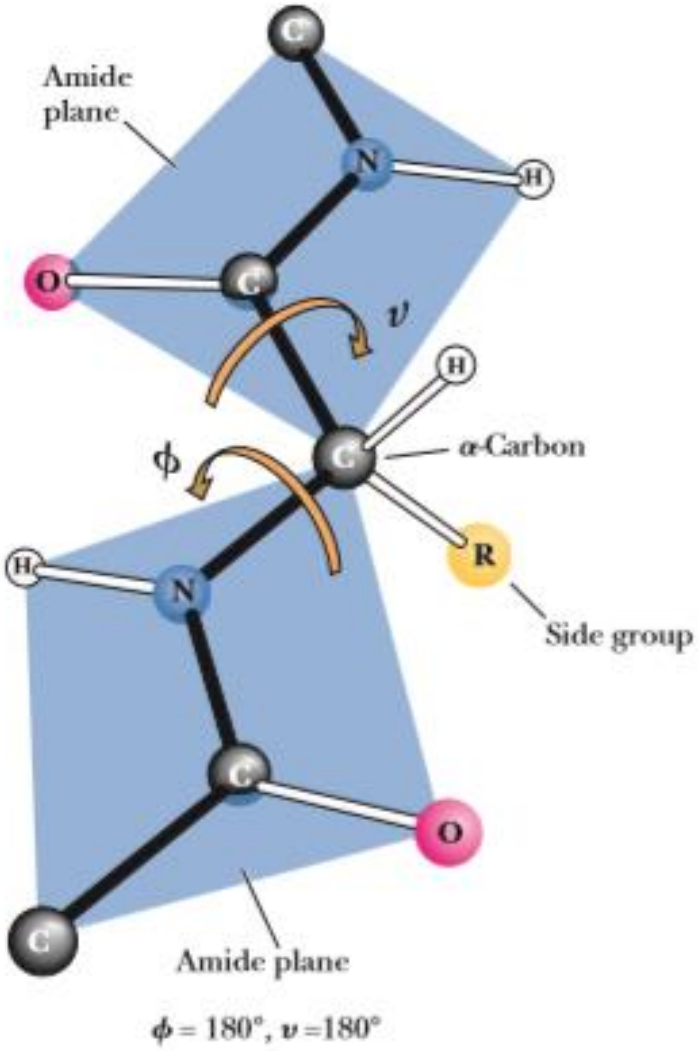
α-helix



β-sheet

- Is The H-bond connects the carbonyl oxygen of one peptide unit with the amide hydrogen of another peptide unit
- The strength of each H-bond is small, but the large number of bonds in the helix or sheet results in a stable secondary structure.

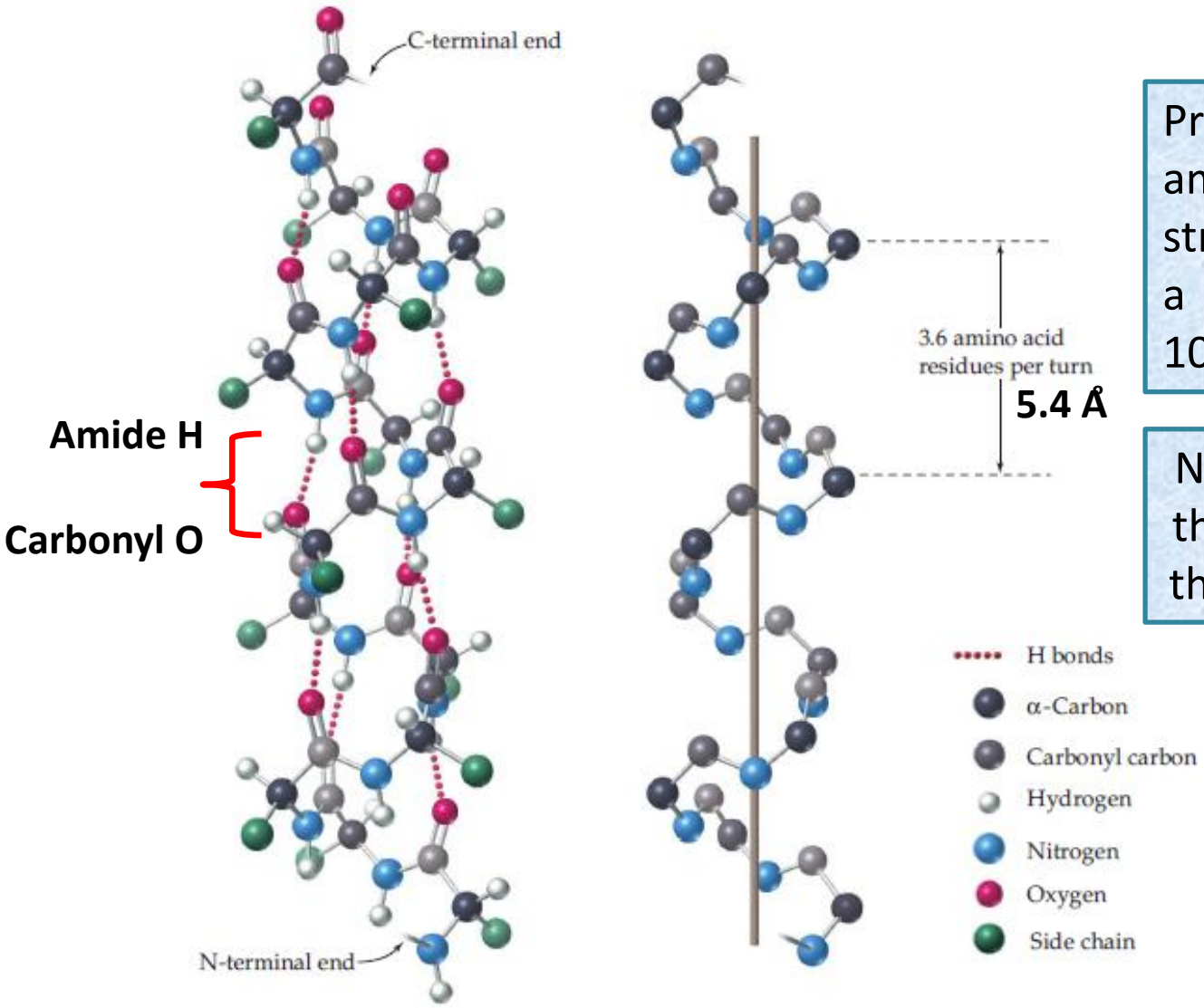
Secondary structure of a protein



- The 3D conformations of peptides and proteins is affected by:

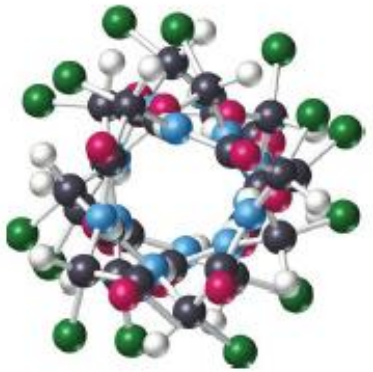
- (1) the bond between the αC and the amino nitrogen of that residue
- (2) the bond between the αC and the carboxyl carbon of that residue.
- (3) the planar peptide group

α-helix



Proteins have varying amounts of α-helical structures, varying from a few percent to nearly 100%

Note: the side chains of the AAs are oriented to the exterior of the helix.

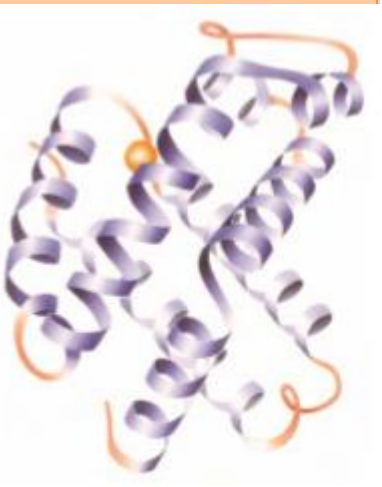


Factors that can disrupt an α-helix

1. **Proline** amino acid because:
(A) rotation around the bond between the N and the α-carbon is severely restricted
(B) α-amino group cannot participate in intrachain hydrogen bonding

2. Amino acids with side chains that have strong **electrostatic repulsion** due to the proximity of several charged groups of the same sign, such as:

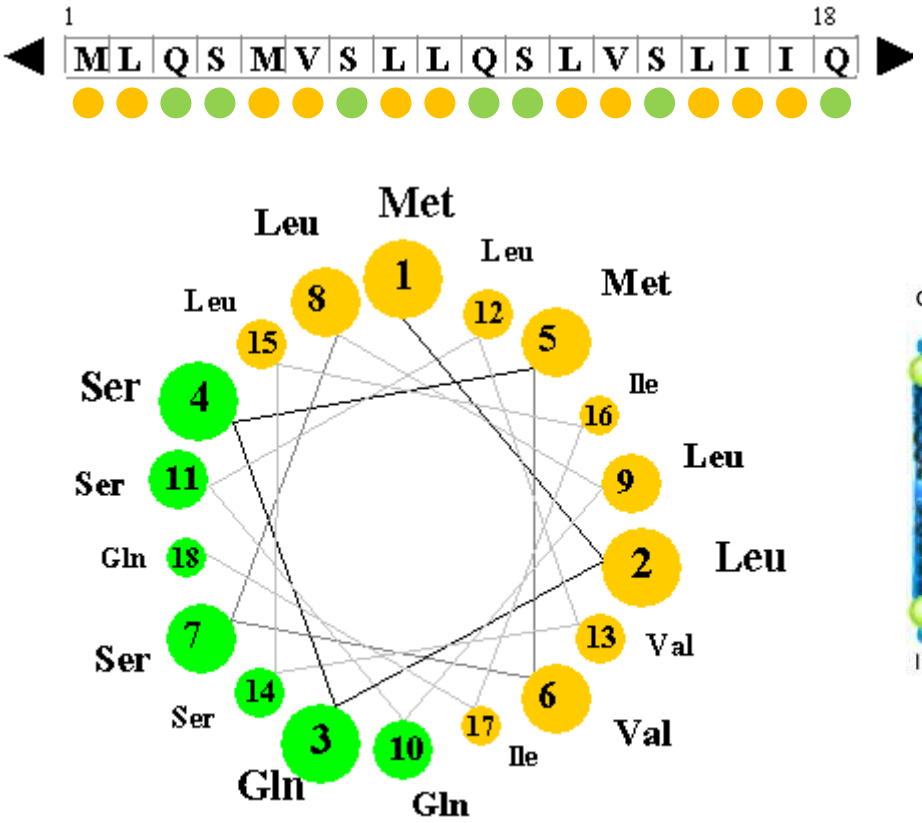
(A) Positively charged groups of Lys and Arg
(B) Negatively charged groups of Glu and Asp

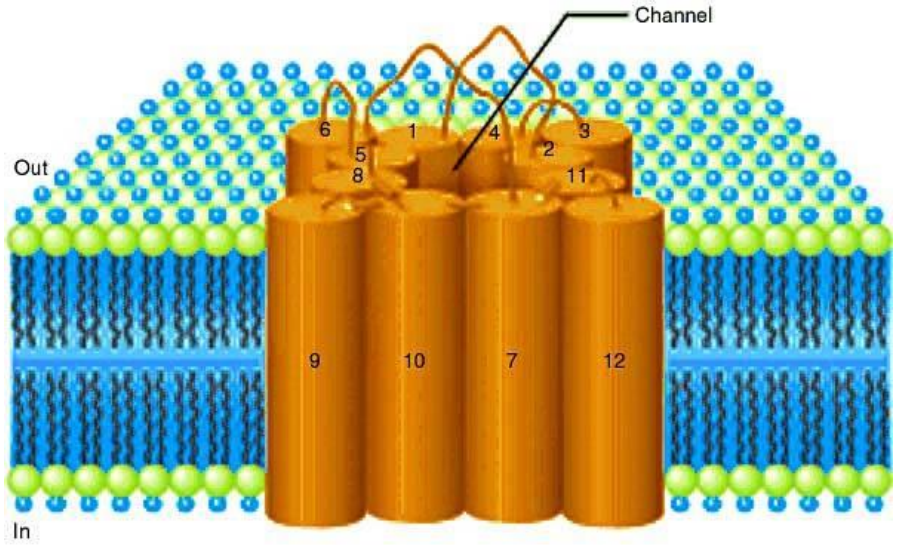


3. Amino acids with **bulky side chains** in close proximity cause crowding (steric repulsion)

4. Amino acids with R chains that are **bonded to two atoms** other than hydrogen, such as Val, Ile and Thr

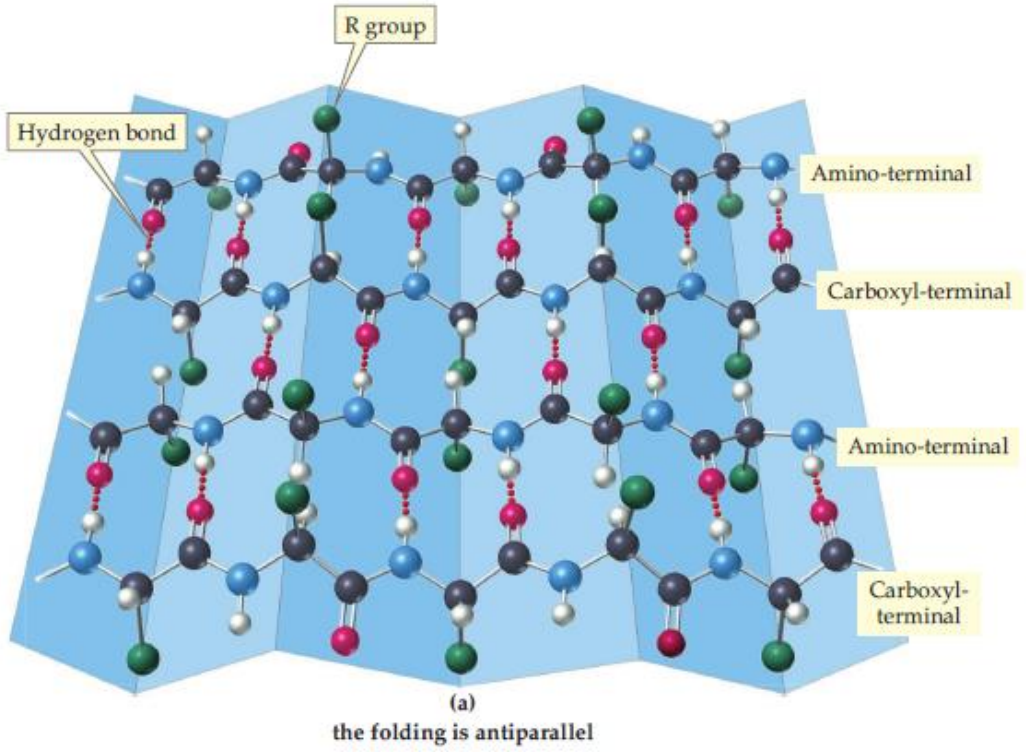
Amphipathic α helices



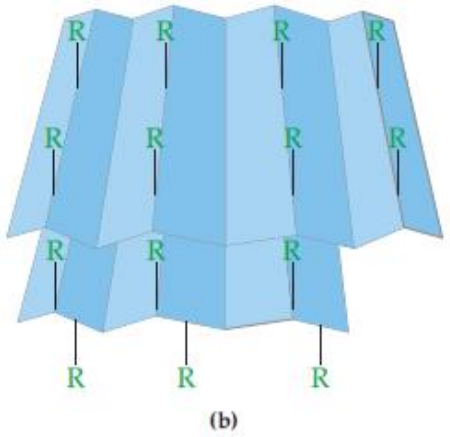


β-sheet

- The peptide backbone in the b-sheet is almost completely extended
- Hydrogen bonds form between different parts of a single chain that is doubled back on itself (intrachain bonds) or between different chains (interchain bonds).
- The protein chains are extended to their full length and bend at each **α**-carbon so that the sheet has a pleated contour

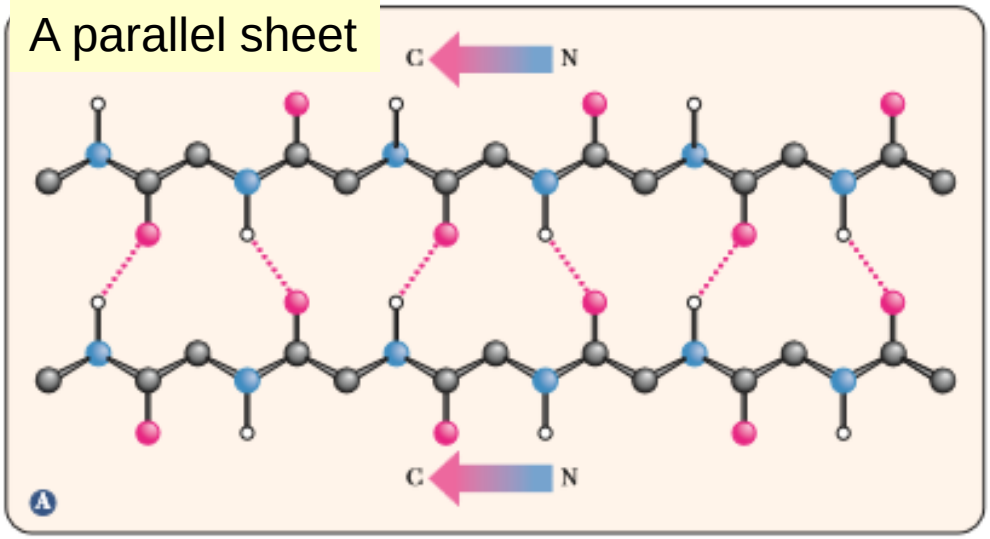


Note: R groups extend above and below the sheet

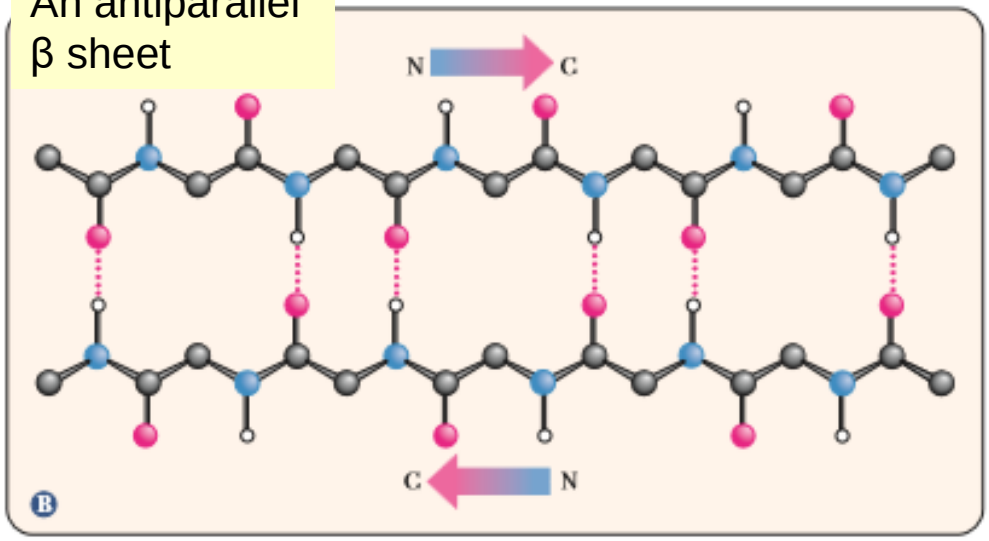


β-sheet

A parallel sheet



An antiparallel β sheet



Parallel pleated sheet is formed if the peptide chains run in the same direction (i.e., if they are all aligned in terms of their N-terminal and C-terminal ends)

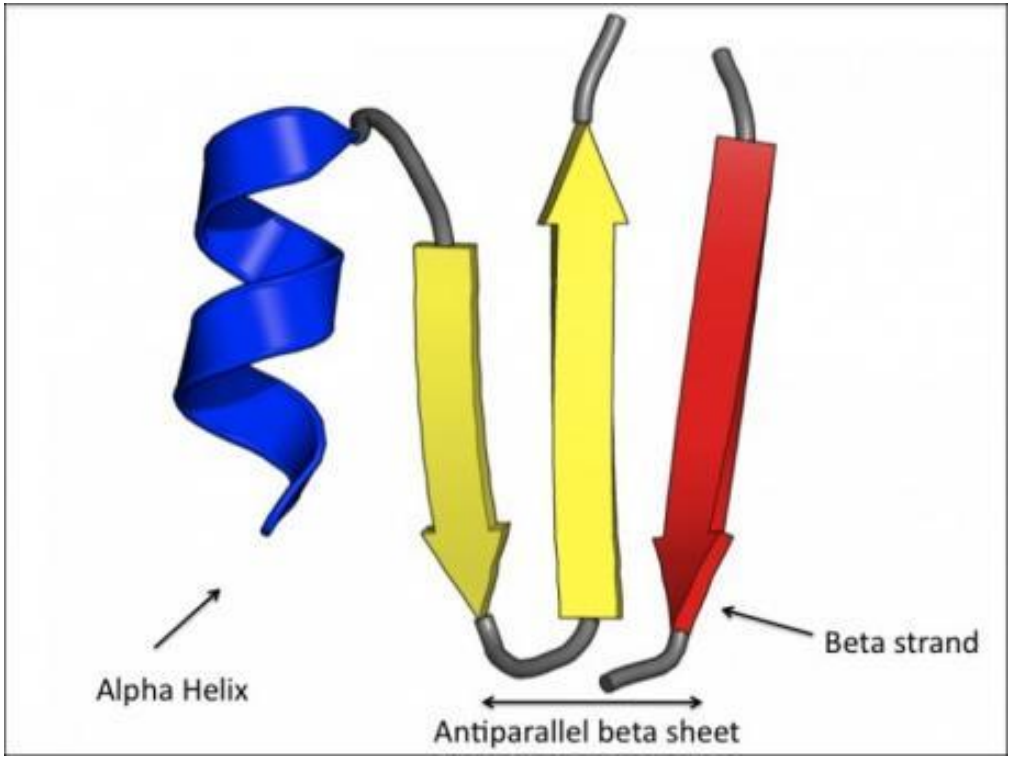
Antiparallel pleated sheet is formed if alternating chains run in opposite directions

H-bonds between backbone atoms create a repeated zigzag structure; hence, the name "pleated sheet"

The H-bonds are perpendicular to the direction of the protein chain, not parallel to it as in the α-helix.

How many β strands can a β sheet have?

- 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



Effect of amino acids

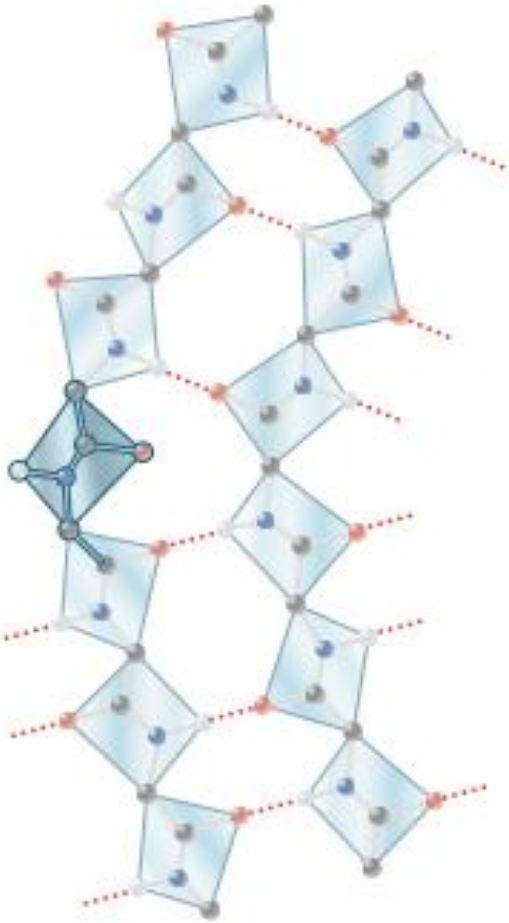
- Valine, threonine and Isoleucine tend to be present in β-sheets
- Proline tends to disrupt β strands

Irregularities in regular structures

1. the 3_{10} helix (3 residues per turn and 10 atoms in the ring formed by making the hydrogen bond

2. The 2_7 and 4.4_{16} helices

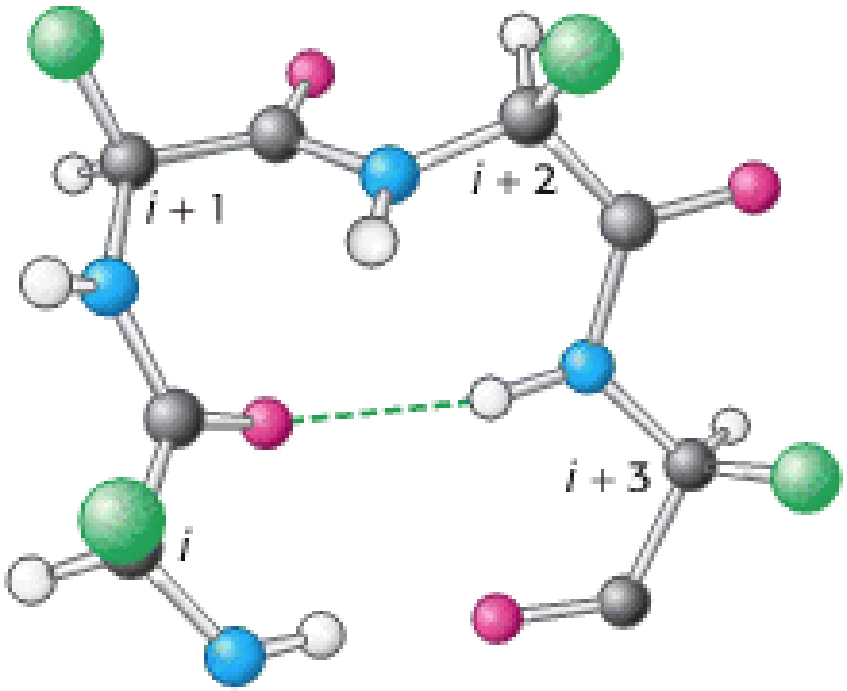
1. A β-bulge is a common nonrepetitive irregularity found in antiparallel β-sheets.



Classic bulge

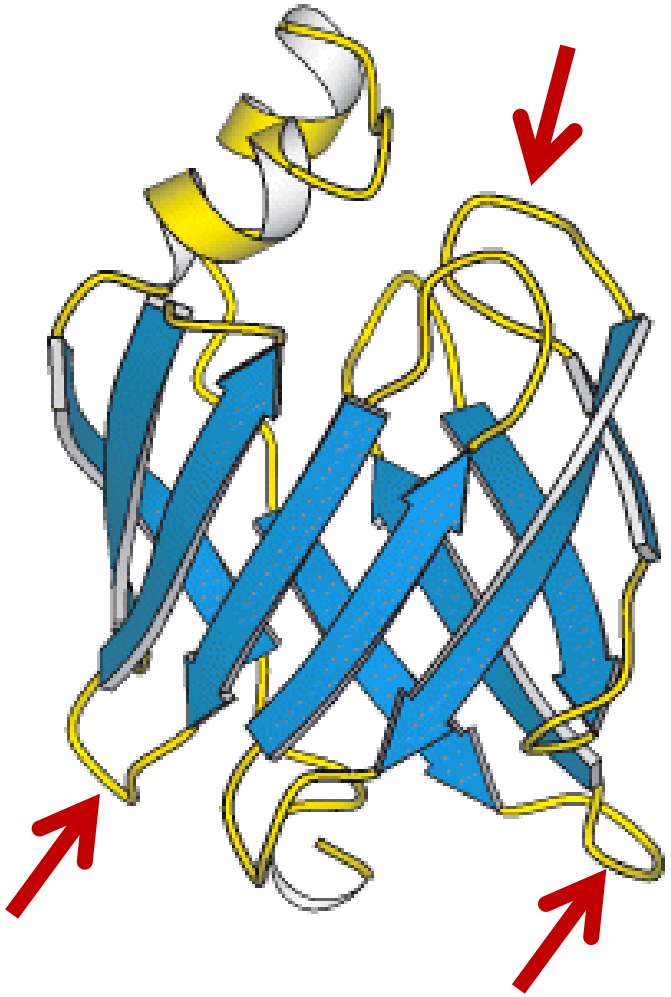
Turns

- 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?



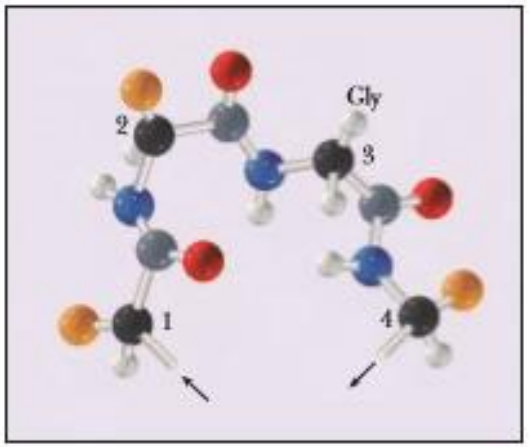
Loops

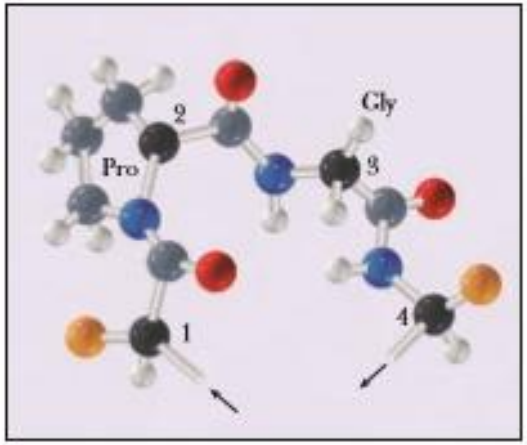
- Loops do not have regular structures.

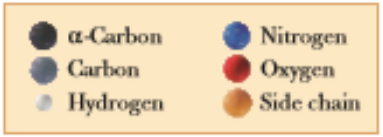


Reverse turns in secondary structures

1. Gly is frequently found in reverse turns, where the polypeptide chain changes direction
2. Pro is frequently found in reverse turns because its cyclic structure has the correct geometry for a reverse turn







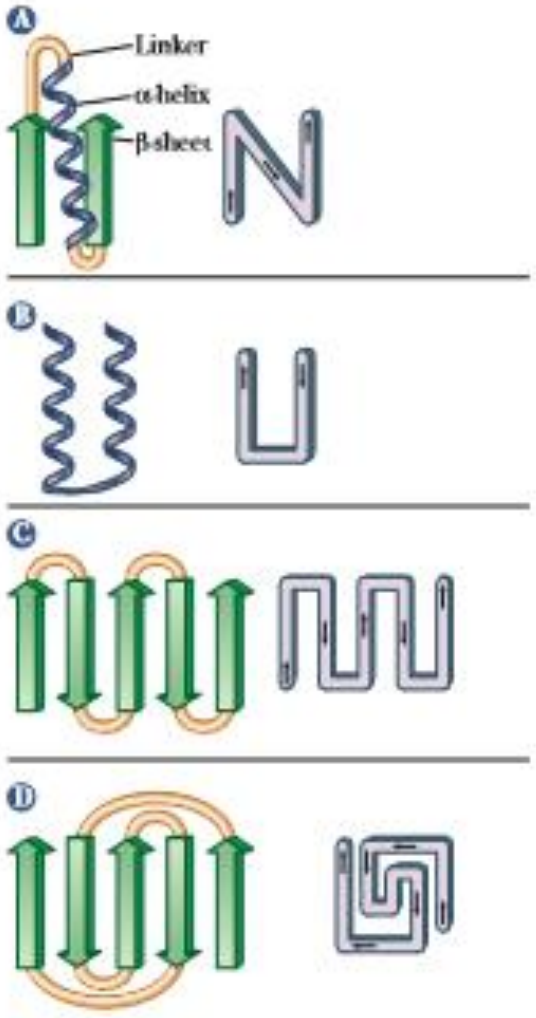
Supersecondary structures
Motifs and Domains

βαβ unit

αα unit

β-meander

The Greek key



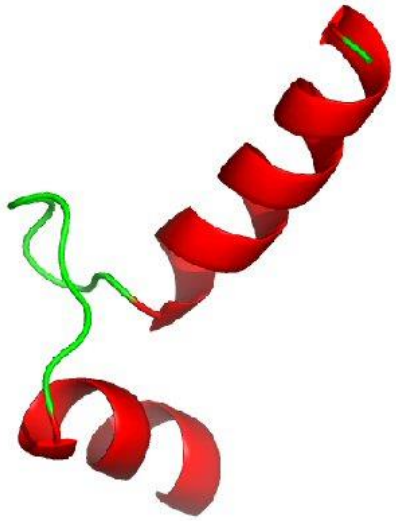
- They are regions in proteins that contain an ordered organization of secondary structures.
- The combination of α-helices and β-strands produces various kinds of supersecondary structures in protein

A motif (a module)

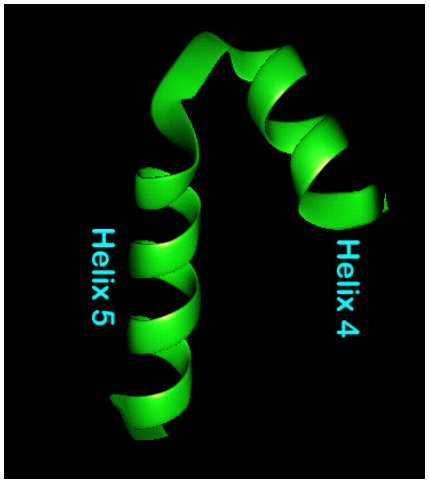
- A motif is a repetitive supersecondary structure, which can often be repeated and organized into larger motifs.
- A small portion of a protein (typically less than 20 amino acids)
- In general, motifs may provide us with information about the folding of proteins, but not the biological function of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

Examples of motifs

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

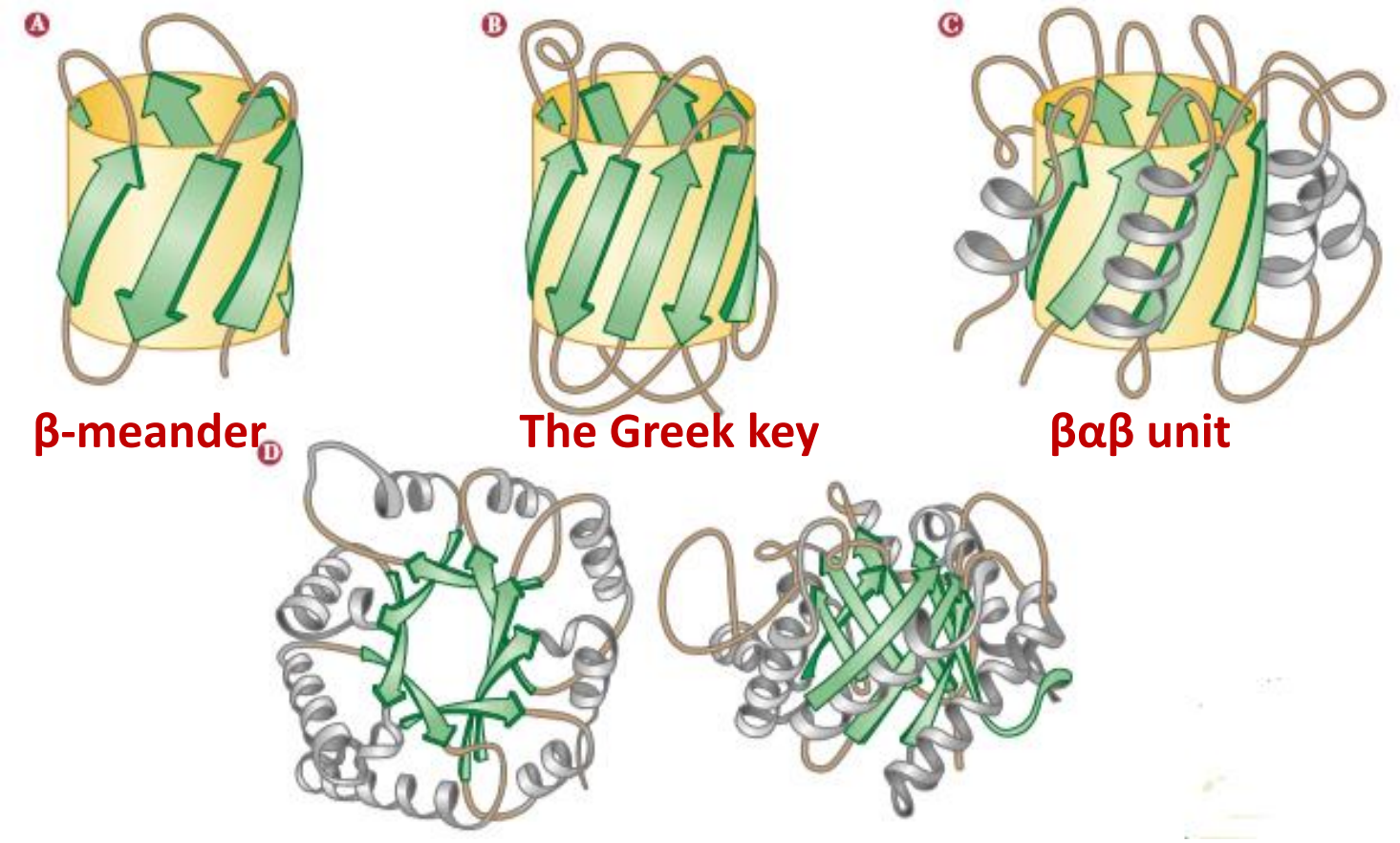


Helix-turn-helix is a structural motif capable of binding DNA. It is composed of two α helices joined by a short strand of amino acids



Examples of motifs

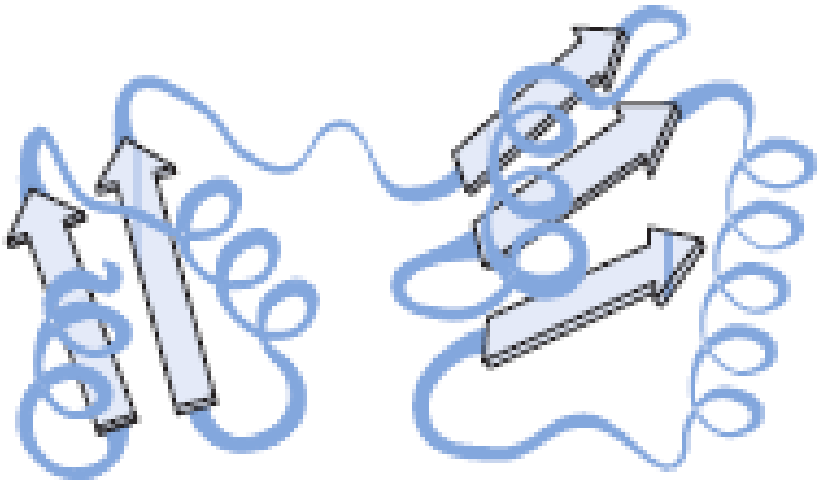
A motif is a repetitive supersecondary structure



Tertiary Protein Structure

- The overall 3D arrangement of all the atoms in the molecule.
- Tertiary structure involves:

1. The conformations and arrangements of the side chains
2. The positions of any prosthetic groups

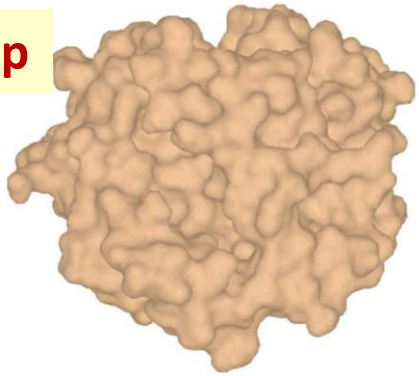


3. The arrangement of helical and pleated-sheet sections with respect to one another

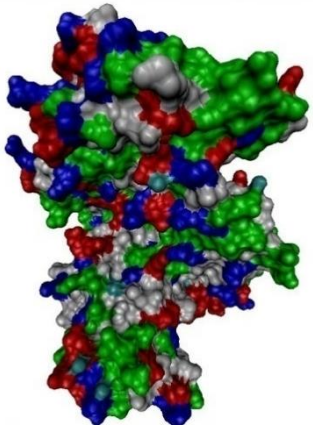
- Depends on noncovalent interactions and S-S covalent bonds of AA side chains that are far apart along the same backbone

How to look at proteins…

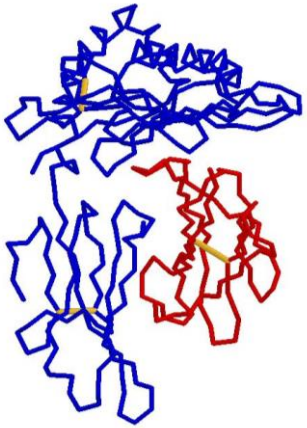
Protein surface map



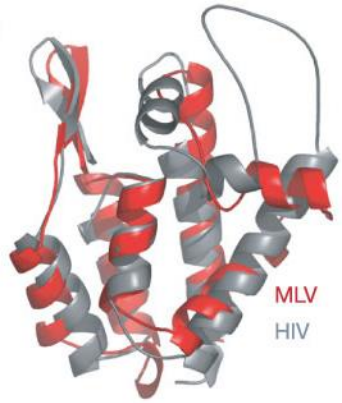
Space filling structure



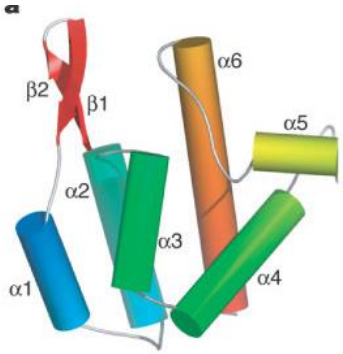
Trace structure



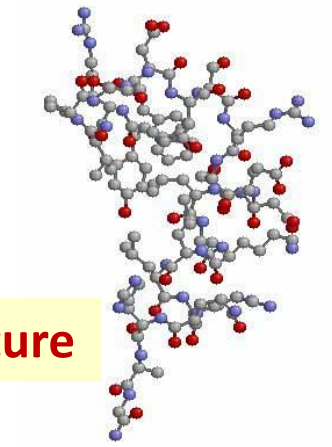
Ribbon structure



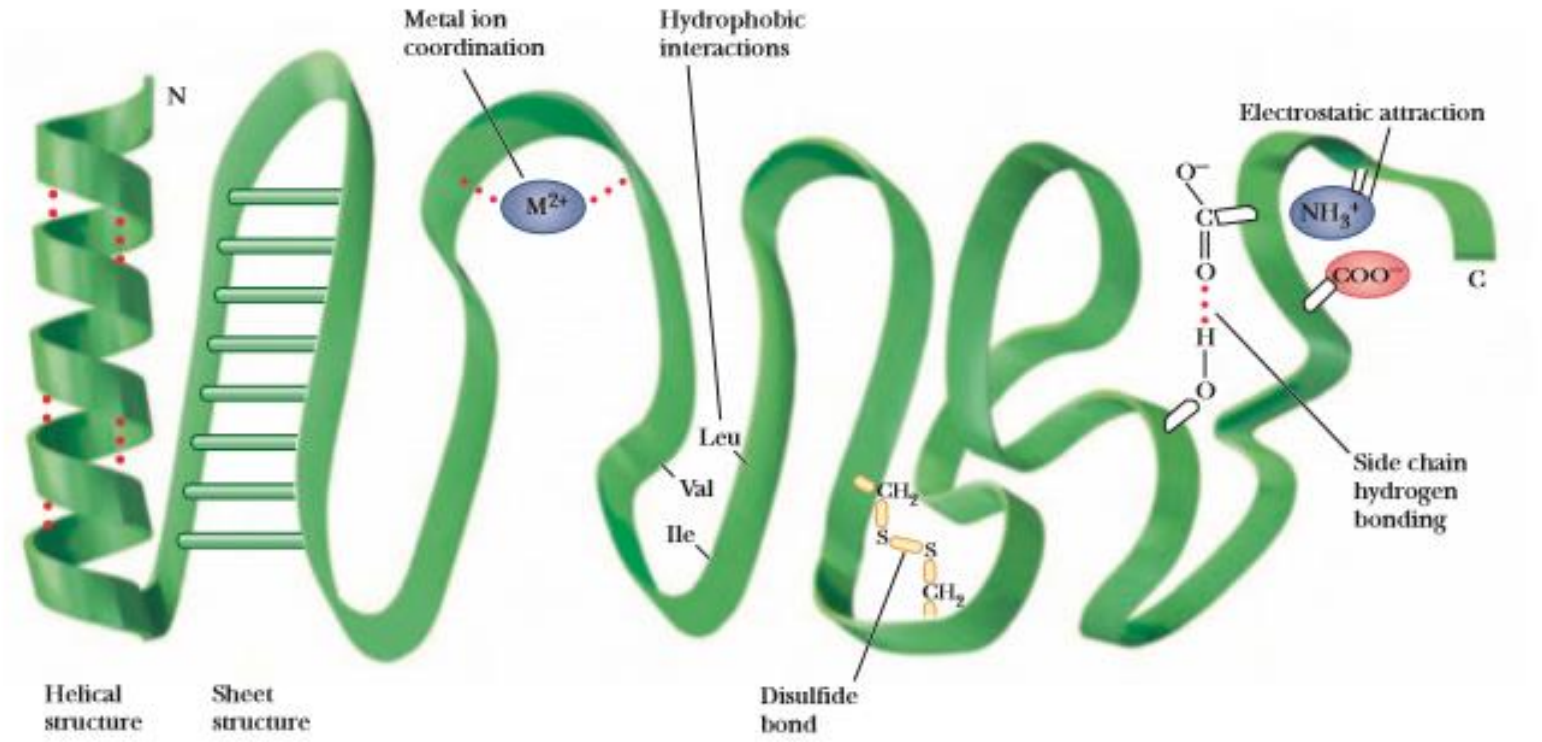
Cylinder structure



Ball and stick structure



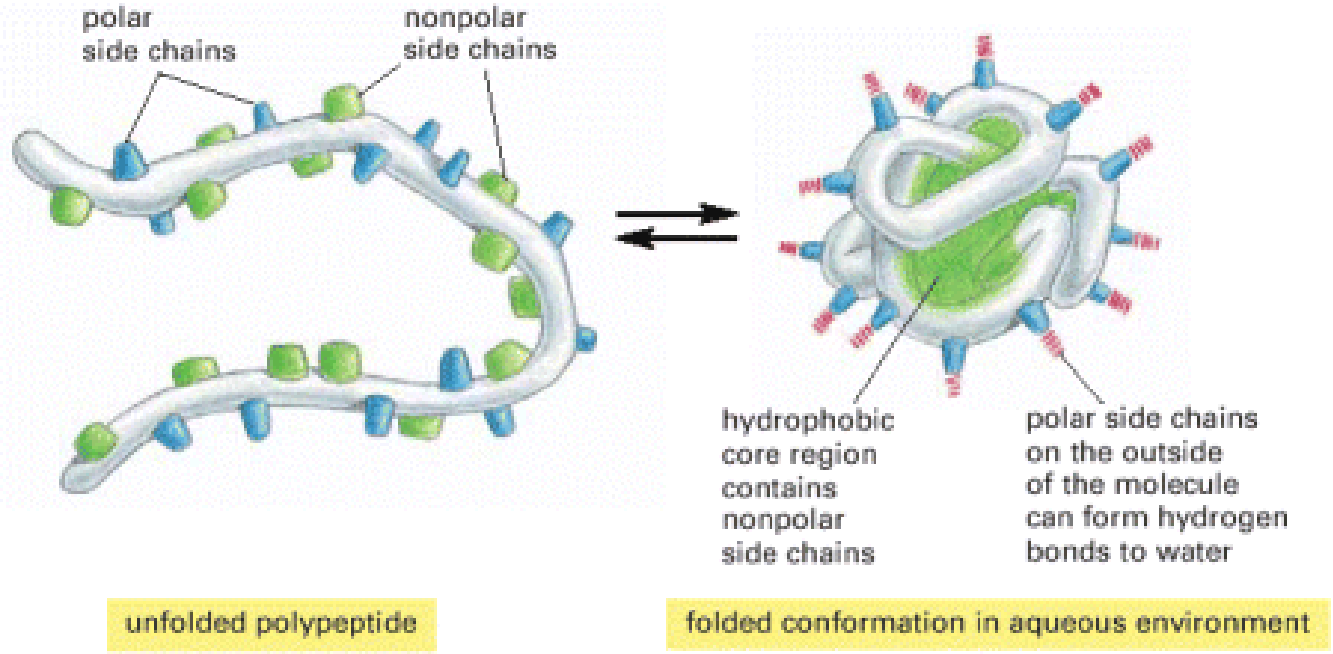
Forces that determine the tertiary structure of proteins



- **Native protein is a** protein with the shape in which it functions in living systems
- There are two forces that do not determine the 3D structure of proteins, but stabilize these structures:
  - Disulfide bonds
  - Metal ions

Hydrophobic interactions

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

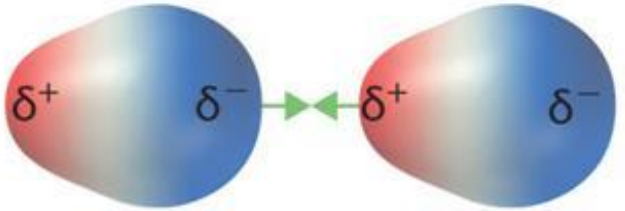


Can polar amino acids be found in the interior?

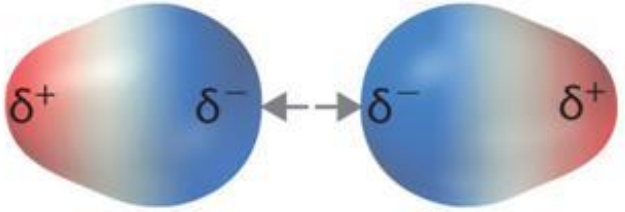
- Polar amino acids can be found in the interior of proteins
- In this situation, they form H-bonds to other amino acids or to the polypeptide backbone
- They play important roles in the function of the protein

van der Waals attractions

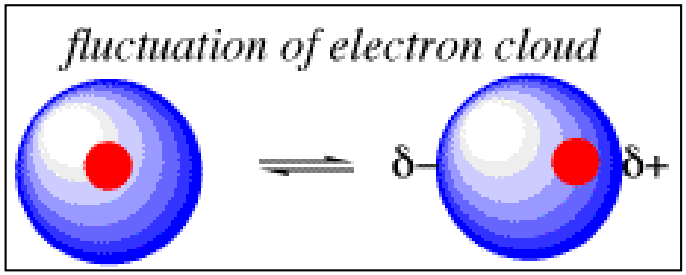
- There are both attractive and repulsive van der Waals forces that control protein folding.
- Although van der Waals forces are extremely weak, they are significant because there are so many of them in large protein molecules.



(b) Attraction

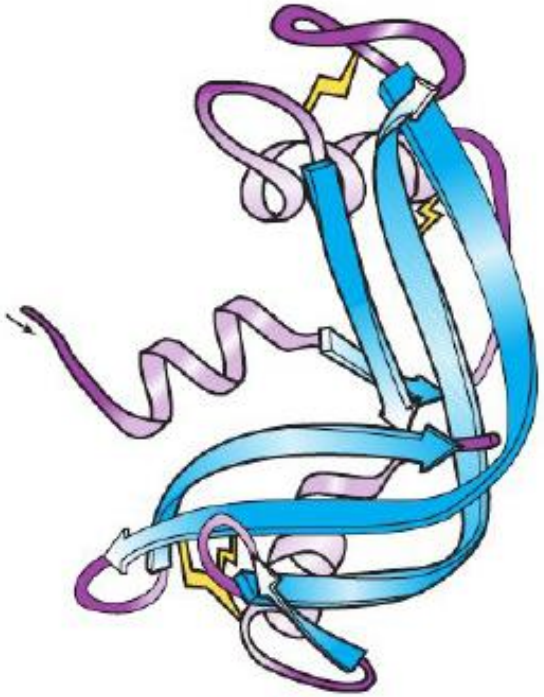


(d) Repulsion

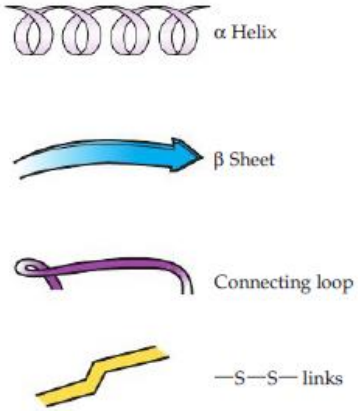


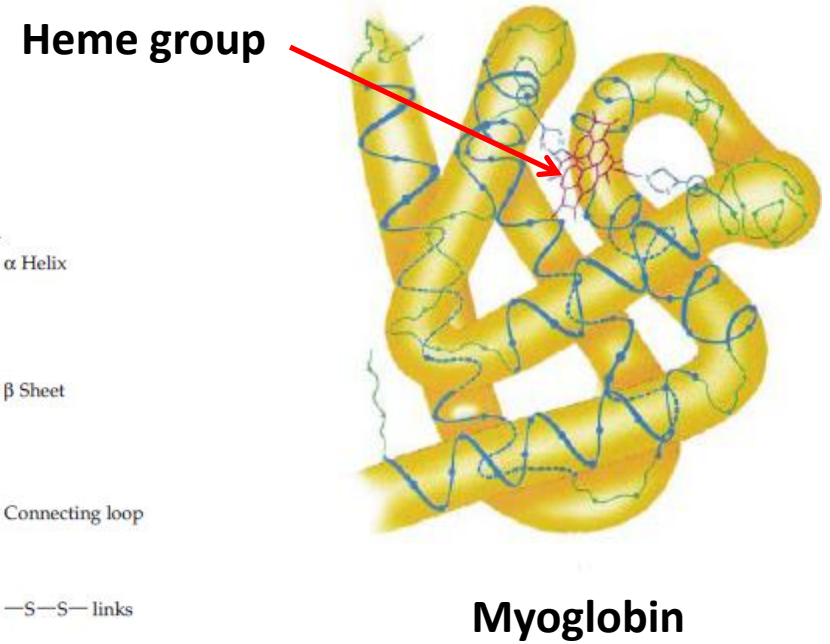
Simple and conjugated proteins

- **Simple protein is composed** of only AA residues
- **Conjugated protein** incorporates one or more non amino acid units in its structure



Ribonuclease





Myoglobin

Conjugated proteins

TABLE 18.5 Some Examples of Conjugated Proteins

CLASS OF PROTEIN	NONPROTEIN PART	EXAMPLES
Glycoproteins	Carbohydrates	Glycoproteins in cell membranes (Section 24.7)
Lipoproteins	Lipids	High- and low-density lipoproteins that transport cholesterol and other lipids through the body (Section 25.2)
Metalloproteins	Metal ions	The enzyme cytochrome oxidase, necessary for biological energy production, and many other enzymes
Phosphoproteins	Phosphate groups	Milk casein, which provides essential nutrients to infants
Hemoproteins	Heme	Hemoglobin (transplants oxygen) and myoglobin (stores oxygen)
Nucleoproteins	RNA (ribonucleic acid)	Found in cell ribosomes, where they take part in protein synthesis

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.

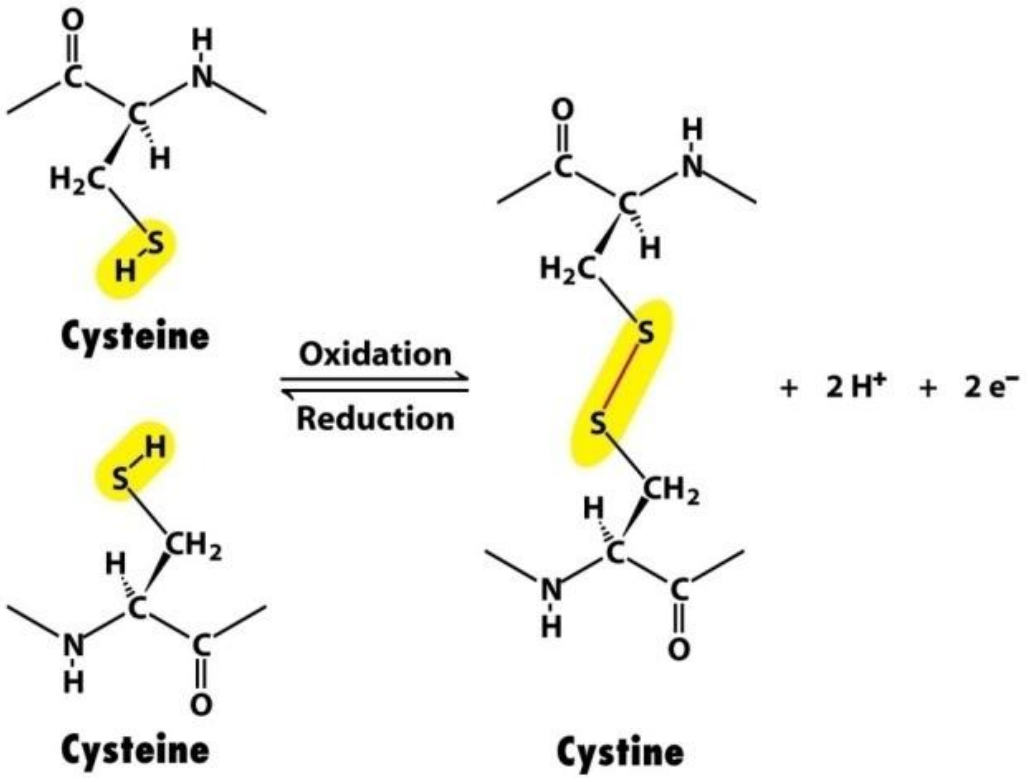
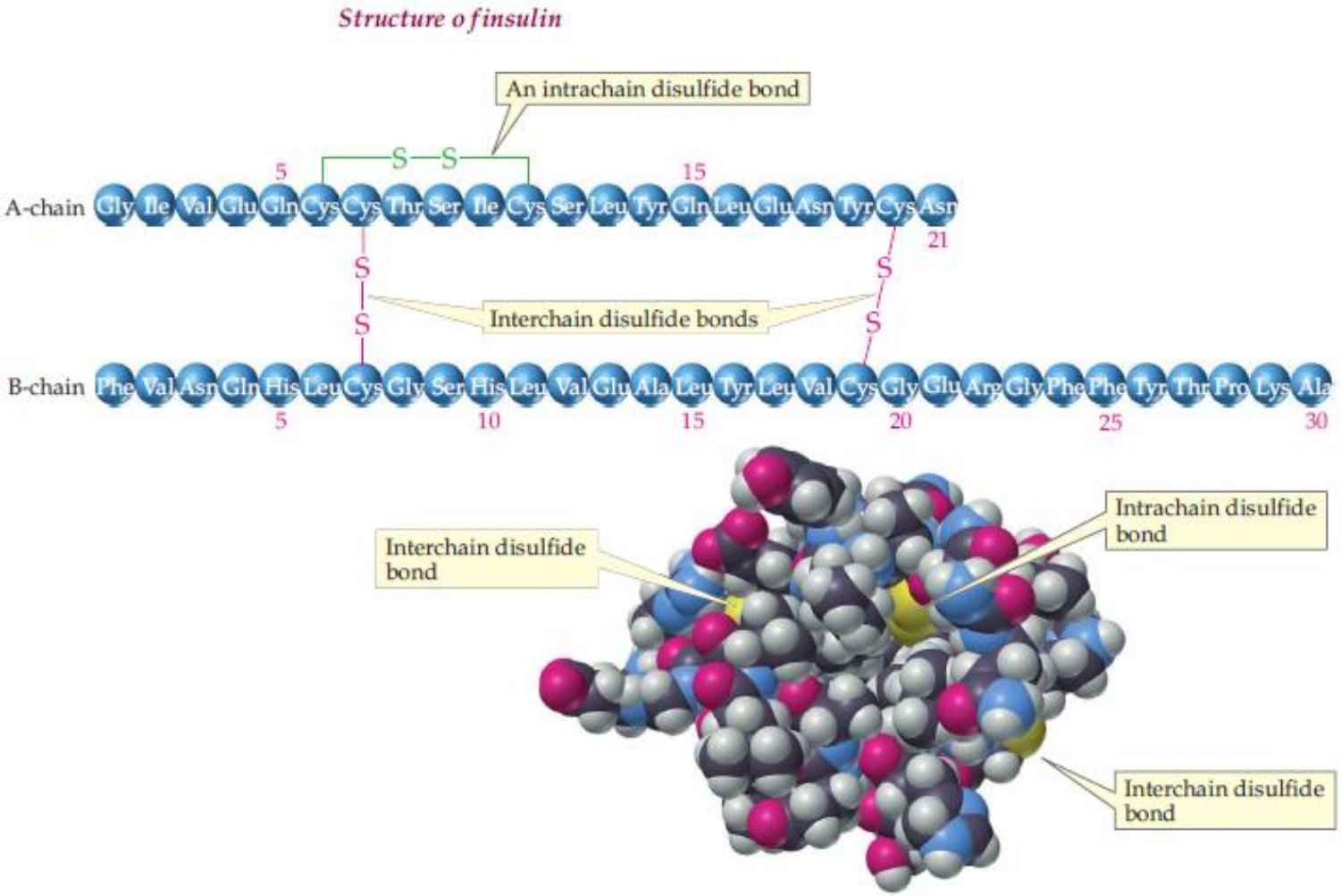


Figure 2-21
Biochemistry, Sixth Edition

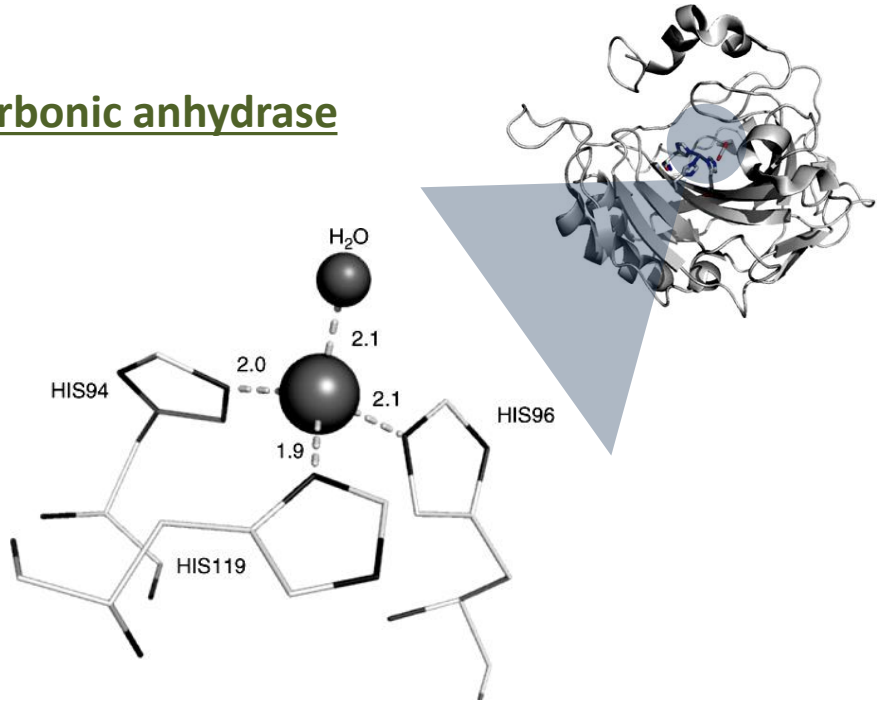
Insulin structure and disulfide bonds



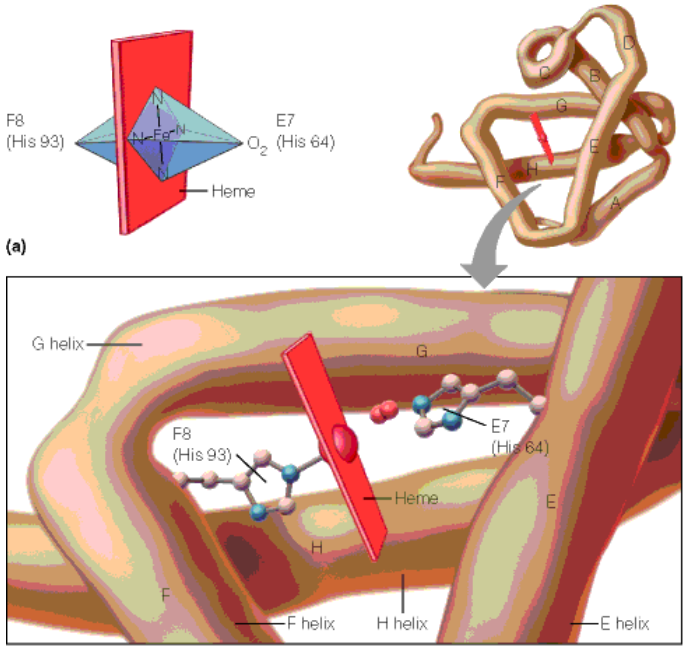
Metal ions

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

Carbonic anhydrase

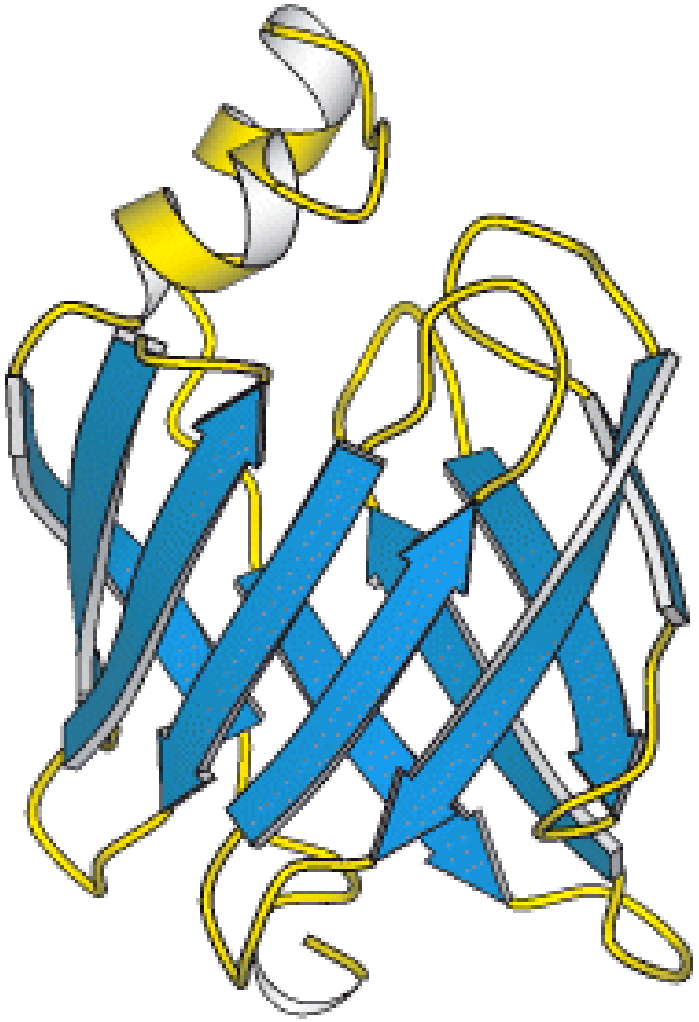


Myoglobin



Domains

- A domain is a compactly folded region of polypeptide found in proteins with similar function and/or structure.
- Domains with similar conformations are associated with the particular function.
- A structural domain may consist of 100–200 residues in various combinations of α helices, β sheets, turns, and random coils.
- They fold independently of the rest of the protein.
- Domains may also be defined in functional terms
  - enzymatic activity
  - binding ability (e.g., a DNA-binding domain)



Quaternary Protein Structure

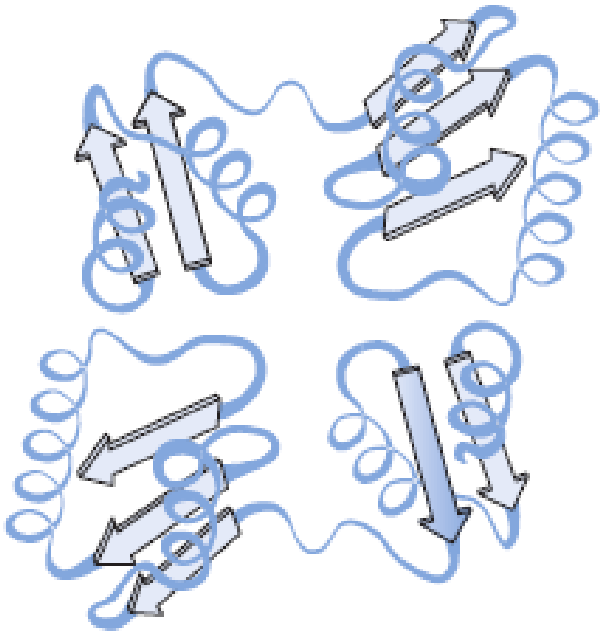
- Two or more polypeptide subunits associate to form a single 3D protein unit (oligomers suchas dimers, trimers, and tetramers)
- Each chain is called a subunit.
- Noncovalent interactions between chains hold them together

(electrostatic attractions,

hydrogen bonds, and

hydrophobic interactions)

- Examples: Hemoglobin and collagen



What is it?

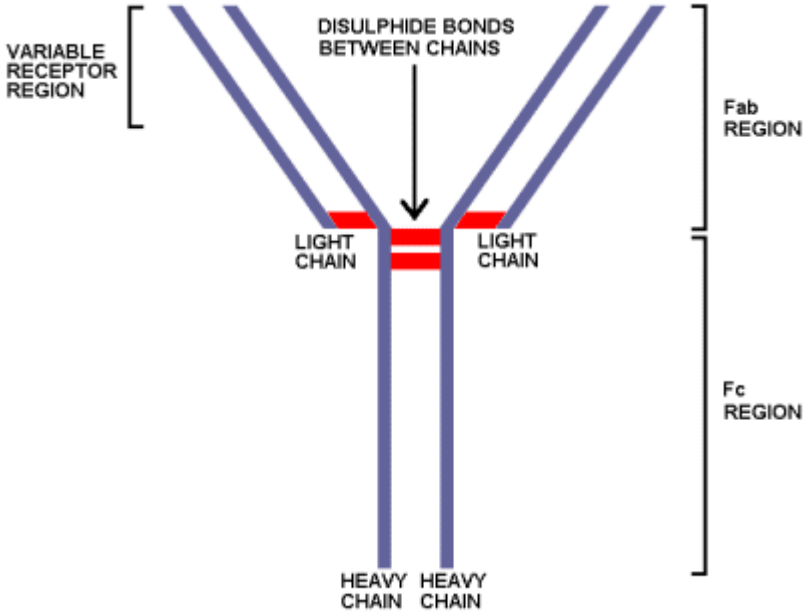
- Proteins are composed of more than one polypeptide chain.
  - They are oligomeric proteins (oligo = a few or small or short; mer = part or unit)
- The spatial arrangement of subunits and the nature of their interactions.
- Proteins made of
  - One subunit = monomer
  - Two subunits: dimer
  - Three subunts: trimer
  - Four subunit: tetramer
  - …etc

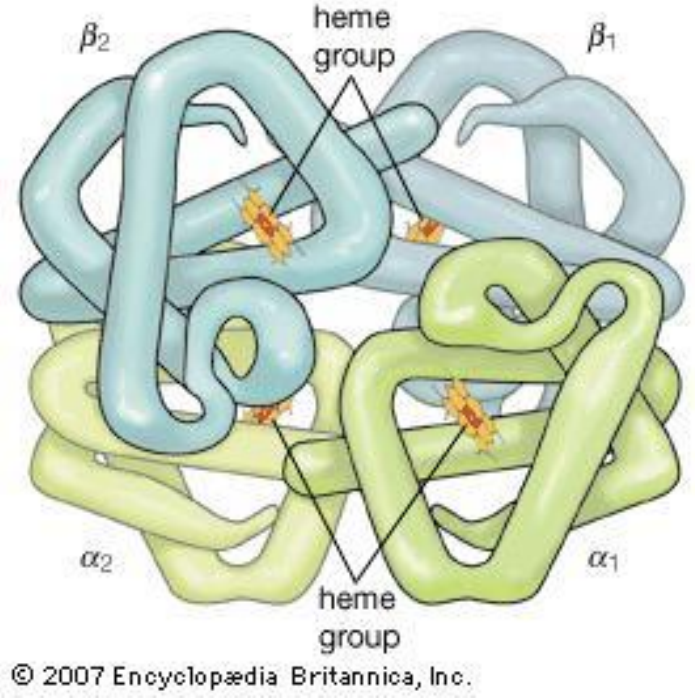
Naming of structures

- Each polypeptide chain in such a protein is called a subunit.
- Oligomeric proteins can be made of multiple polypeptides that are
  - identical $\rightarrow$ homooligomers (homo = same), or
  - different $\rightarrow$ heterooligomers (hetero = different)
- The simplest: a homodimer

How are the subunits connected?

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





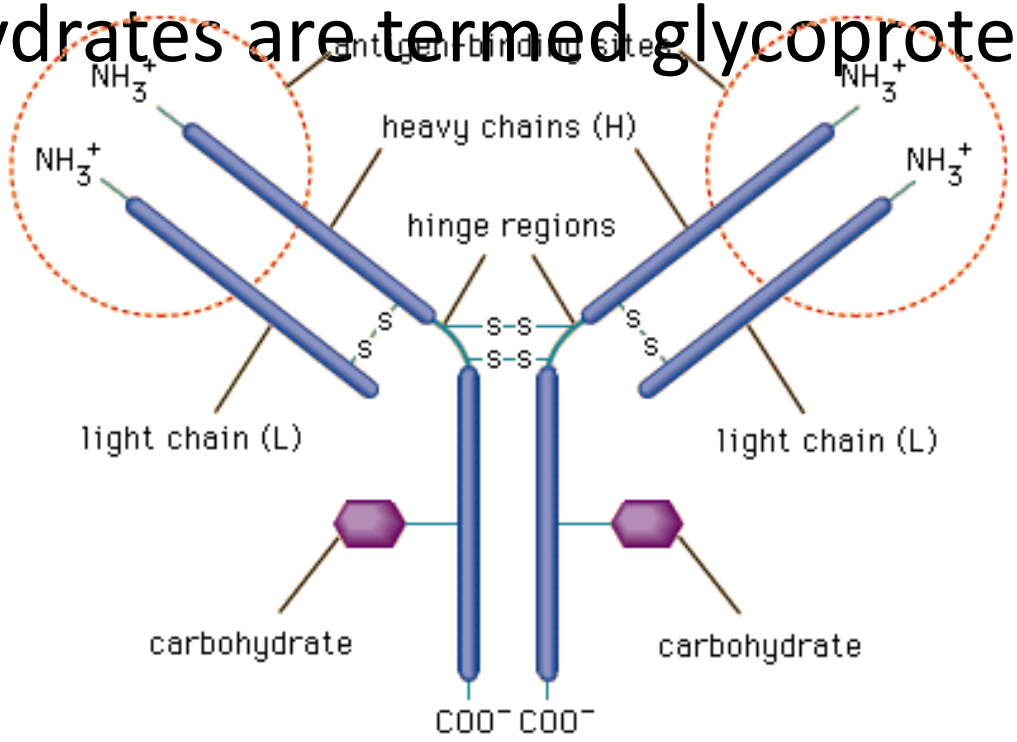
Complex protein structures

Holo- and apo-proteins

- Sometimes, proteins are linked (conjugated) to non-protein molecules. Proteins are known as holoproteins.
- If the non-protein component is removed, the protein is known as an apoprotein.

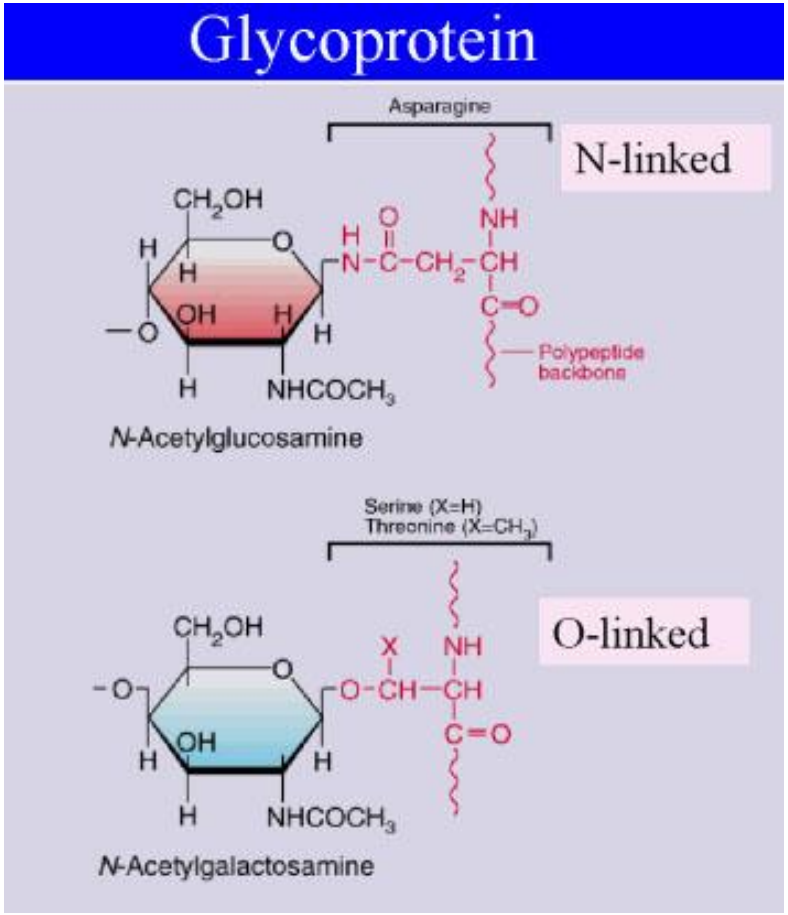
Glycoproteins

- Proteins also are found to be covalently conjugated with carbohydrates.
- Proteins covalently associated with carbohydrates are termed glycoproteins.



Classes of glycoproteins

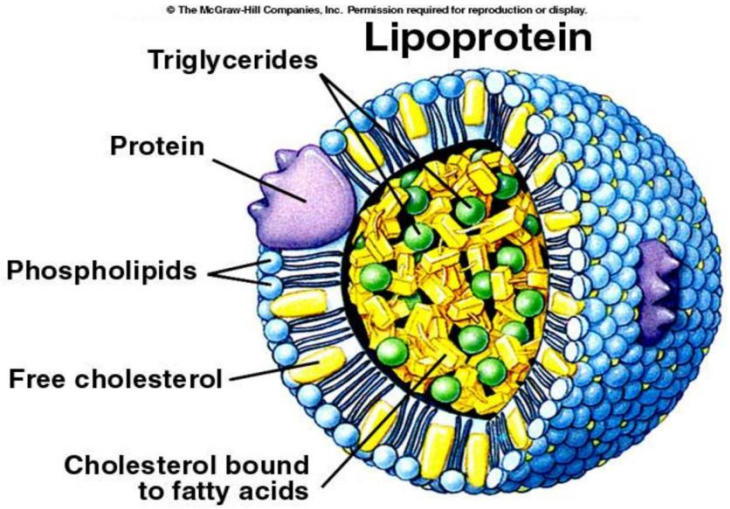
- N-linked sugars
  - The amide nitrogen of the R-group of asparagine
- O-linked sugars
  - The hydroxyl groups of either serine or threonine
  - Occasionally to hydroxylysine

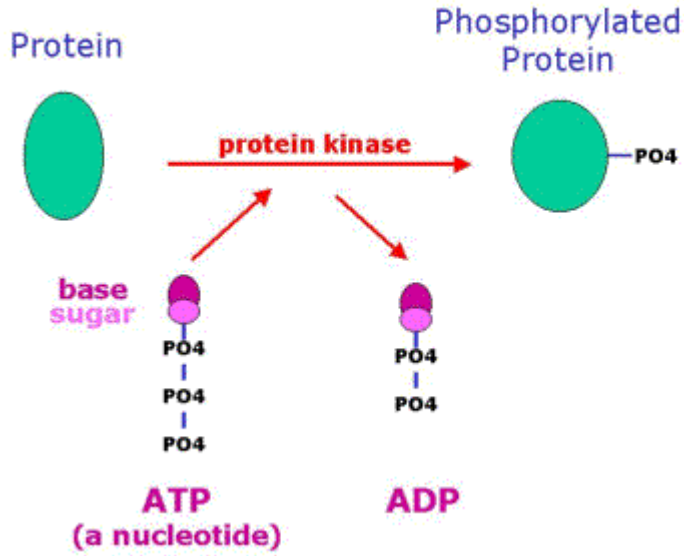


Others

- Proteins can also be associated with lipid and are termed lipoproteins.

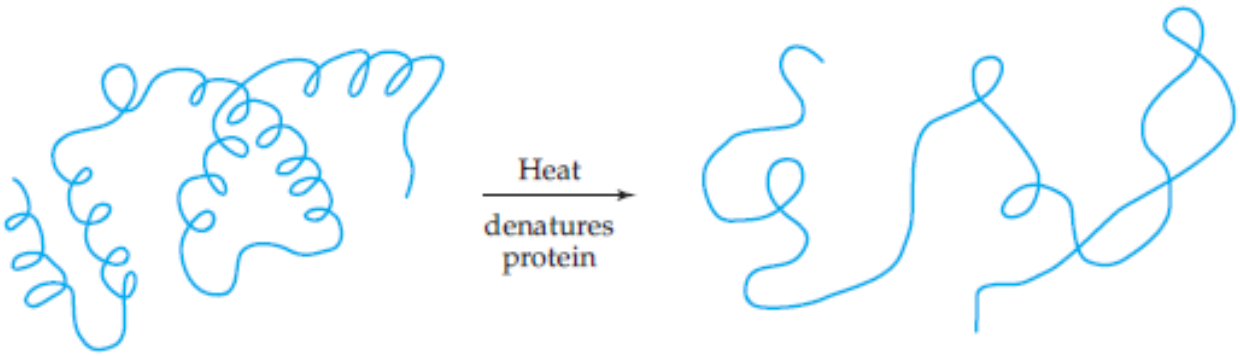
- Other proteins are phsophorylated and these are known as phosphoproteins





Chemical Properties of Proteins

Protein Denaturation: unfolding of a protein that causes disruption in protein shape (native conformation) but does not affect its primary structure

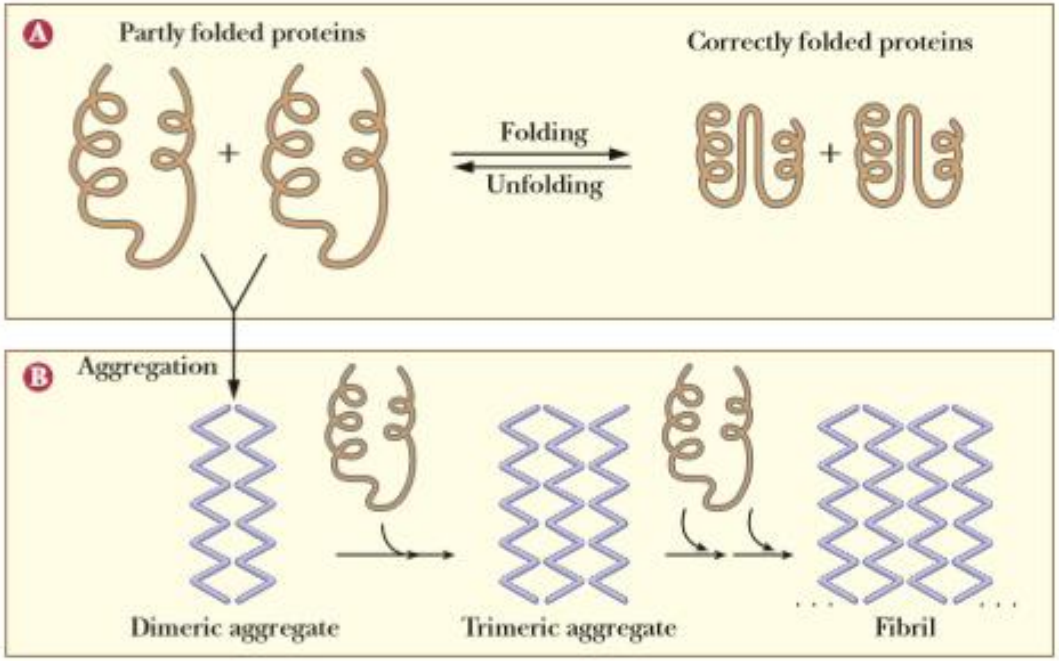


- Affects the noncovalent interactions
- Solubility is often decreased
- Functionality is lost
- Changes in physical, chemical, and biological properties.

Protein Denaturation

- Denaturation agents include heat, mechanical agitation, detergents, organic solvents, extremely acidic or basic pH, and inorganic salts.
- **Most** denaturation is irreversible but renaturation (refolding) is possible
- For reversible denaturation, the primary structure determines the tertiary structure.

The Importance of Correct Folding



When proteins do not fold correctly, they may interact with other proteins and form aggregates. This occurs because hydrophobic regions that should be buried inside the protein remain exposed and interact with other hydrophobic regions on other molecules.
Examples: Alzheimer's, Parkinson's diseases

- The primary structure conveys all the information necessary to produce the correct tertiary structure
- Inside a cell, proteins may begin to fold incorrectly as they are produced, or they may begin to associate with other proteins before completing their folding process.
- Chaperons assist proteins to fold correctly

Factors that determine protein structure

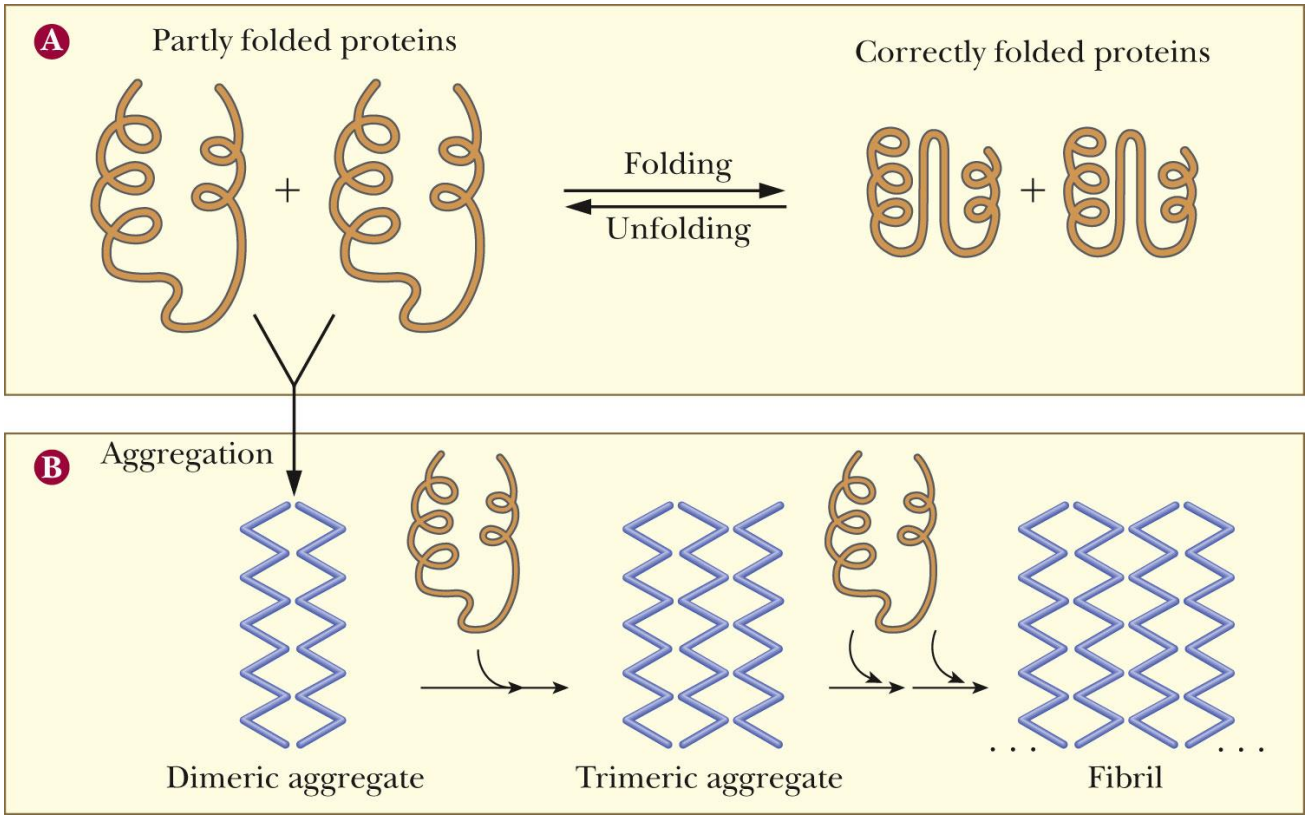
- The least amount of energy needed to stabilize the protein. This is determined by:
  - The amino acid sequence (the primary structure), mainly the internal residues.
  - The proper angles between the amino acids
    - The different sets of weak noncovalent bonds that form between the mainly the R groups.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

Can an unfolded protein re-fold?

- 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.

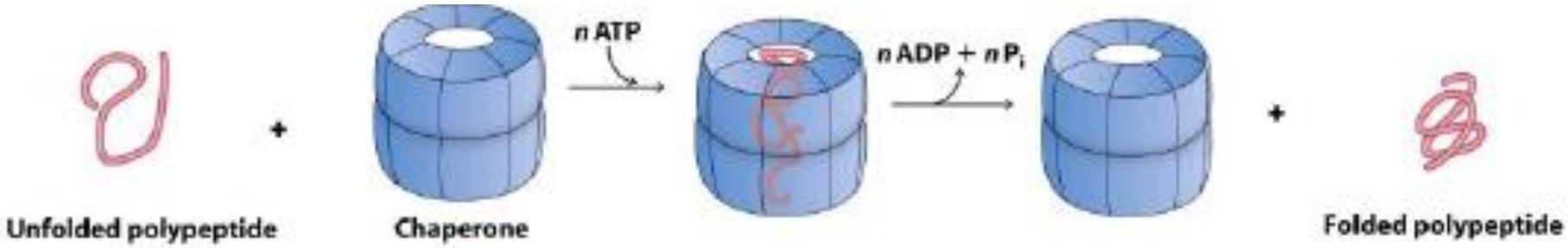
The problem of misfolding

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



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

Outcome of protein misfolding

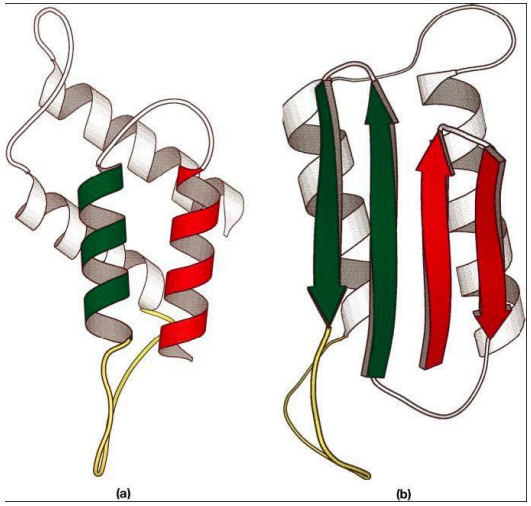
- Partly folded or misfolded polypeptides or fragments may sometimes associate with similar chains to form aggregates.

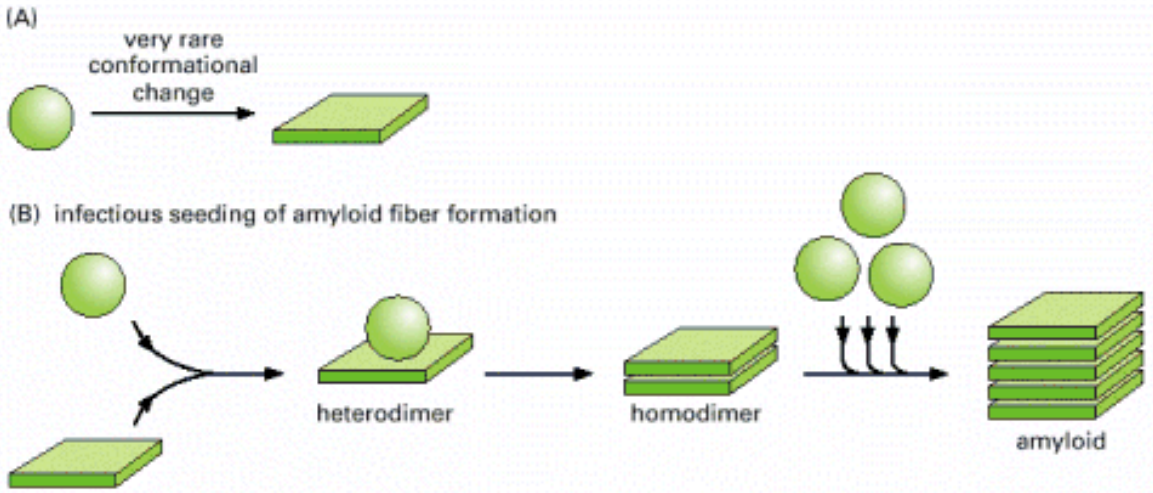
- Aggregates vary in size from soluble dimers and trimers up to insoluble fibrillar structures (amyloid).

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

Prion disease

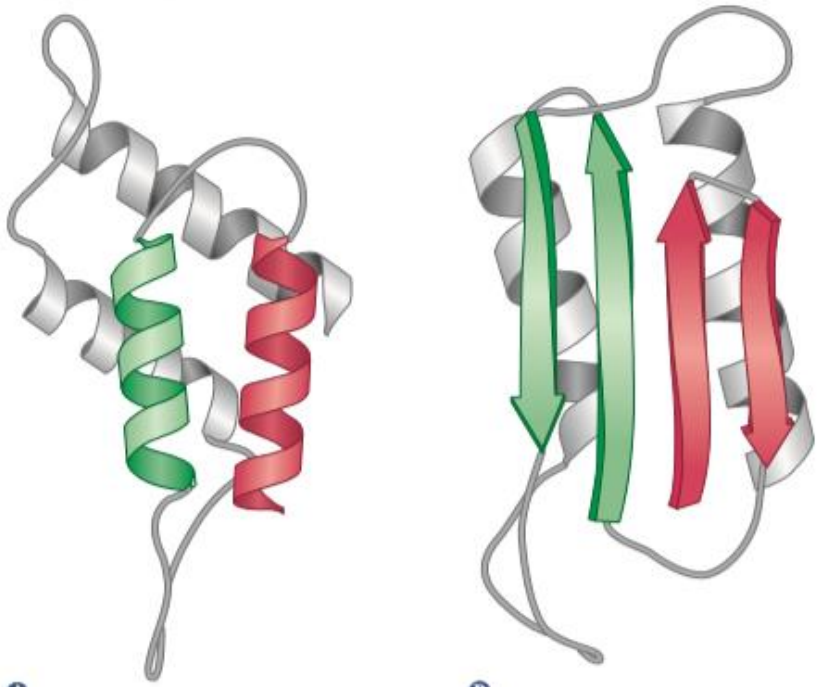
- Striking examples are prion diseases, such as Creutzfeldt-Jacob disease (in humans), and mad cow disease (in cows), and scrapie (in sheep)
- Pathological conditions can result if a brain protein known to as prion protein (PrP) is misfolded into an incorrect form called PrP^{sc}.
- PrP^{C} has a lot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





Prions: proteinaceous infectious particles

- Proteins that Cause Disease
- Creutzfeldt Jakob disease (CJD) or mad cow disease (bovine spongiform encephalopathy)
- Prions are natural glycoproteins found in the cell membranes of nerve tissue
- The abnormal form of the prion protein is able to convert other, normal forms into abnormal forms.
- The β-pleated sheets in the abnormal prions interact between protein molecules and form insoluble plaques, as seen in Alzheimer's disease



(a) Normal prion structure (PrP).
(b) Abnormal prion (PrP^{sc}).

Formation of plaques