

# Protein structure

(Foundation Block)

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# Learning outcomes

- What are proteins?
- Structure of proteins:
  - Primary structure.
  - Secondary structure.
  - Tertiary structure.
  - Quaternary structure.
- Denaturation of proteins.
- Protein misfolding.

# What are proteins?

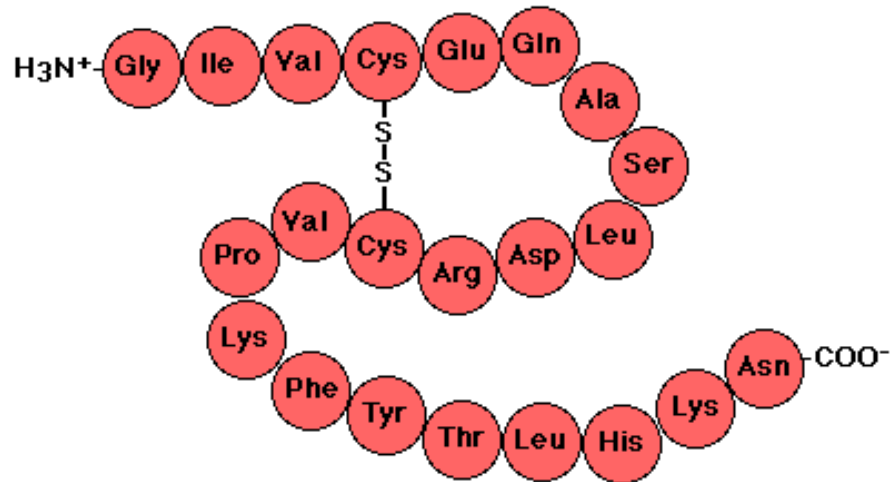
- Proteins are large, complex molecules that play many critical roles in the body.
- They do most of the work in cells and are required for the structure, function, and regulation of the body's tissues and organs.
- Proteins are made up of hundreds or thousands of smaller units called amino acids, which are attached to one another in long chains.

# What are proteins?

- There are mainly 20 different types of amino acids that can be combined to make a protein.
- The sequence of amino acids determines each protein's unique three-dimensional (3D) structure and its specific function.
- Proteins can be described according to their large range of functions in the body e.g. antibody, enzyme, messenger, structural component and transport/storage.

# Primary structure

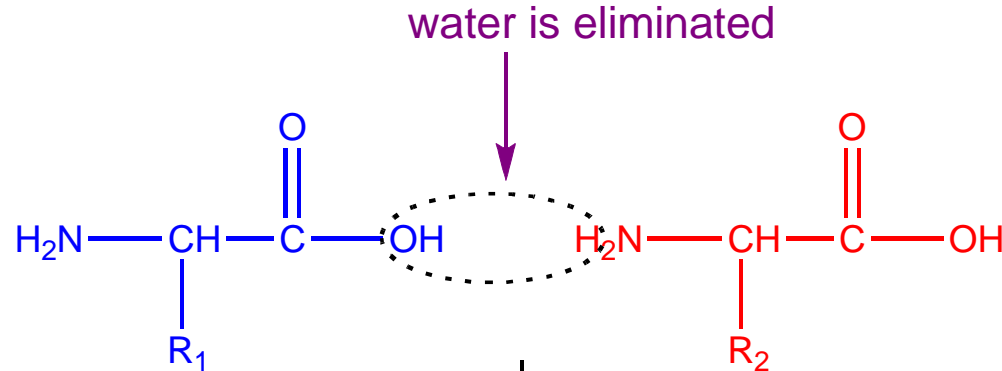
- It is the linear sequence of amino acids.



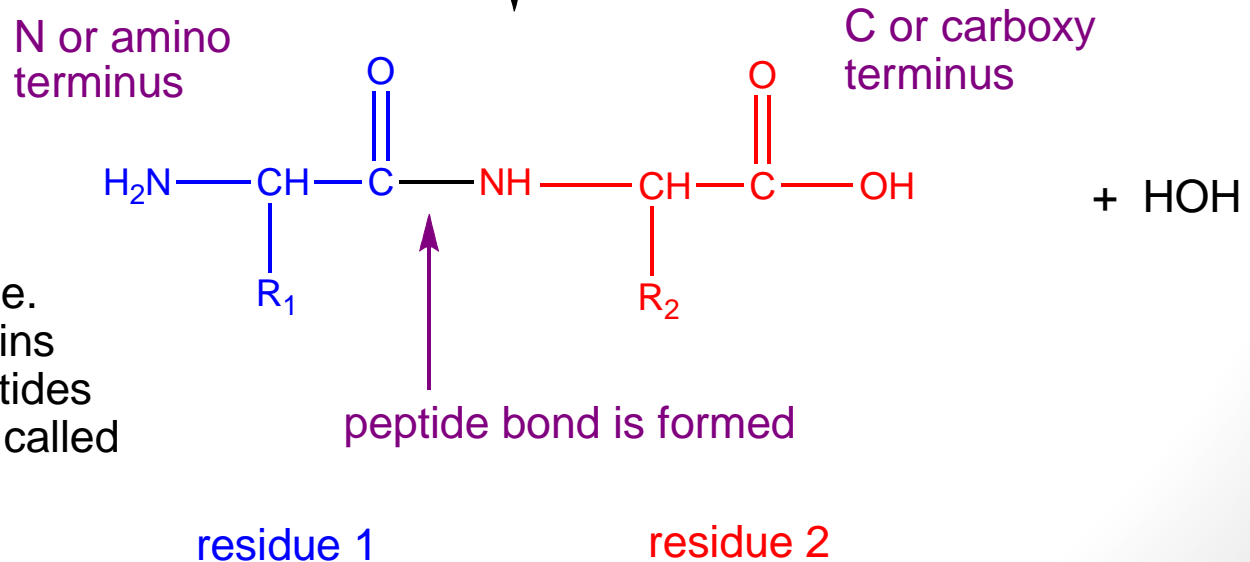
- Covalent bonds in the primary structure of protein:
  - Peptide bond.
  - Disulfide bond (if any).

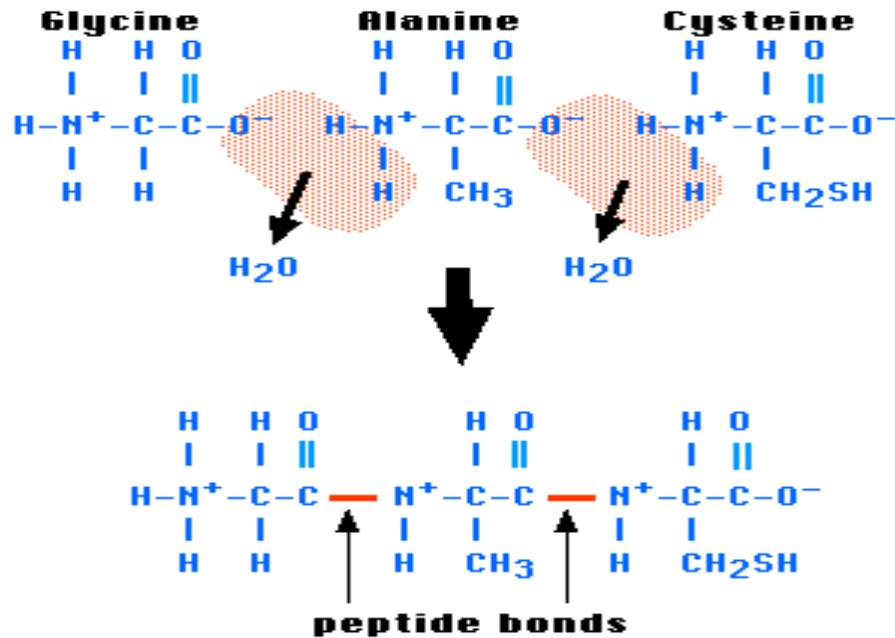
# Peptide Bond (amide bond)

two amino acids  
condense to form...



...a dipeptide. If  
there are more it  
becomes a polypeptide.  
Short polypeptide chains  
are usually called peptides  
while longer ones are called  
proteins.





- Each amino acid in a chain makes two peptide bonds.
- The amino acids at the two ends of a chain make only one peptide bond.
- The amino acid with a free amino group is called amino terminus or NH<sub>2</sub>-terminus.
- The amino acid with a free carboxylic group is called carboxyl terminus or COOH-terminus.

# Peptides

- **Amino acids can be polymerized to form chains:**
  - Two amino acids → dipeptide → one peptide bond.
  - Three amino acids → tripeptide → two peptide bonds.
  - Four amino acids → tetrapeptide → three peptide bonds.
  - Few (2-20 amino acids) → oligopeptide.
  - More (>20 amino acids) → polypeptide.



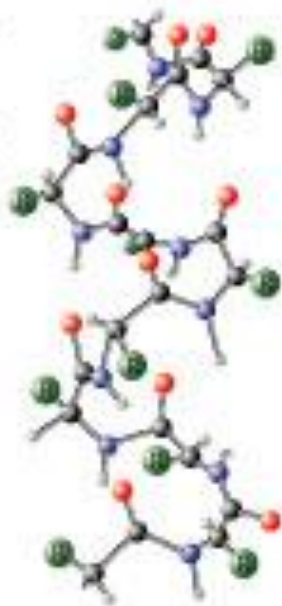
- DNA sequencing.
- Direct amino acids sequencing.

**How to determine the primary structure  
sequence?**

# Secondary structure

- It is regular arrangements of amino acids that are located near to each other in the linear sequence.
- Excluding the conformations (3D arrangements) of its side chains.
- $\alpha$ -helix,  $\beta$ -sheet and  $\beta$ -bend are examples of secondary structures frequently found in proteins.

Ball-and-stick model of a portion of the  $\alpha$ -helical secondary structure of a protein molecule



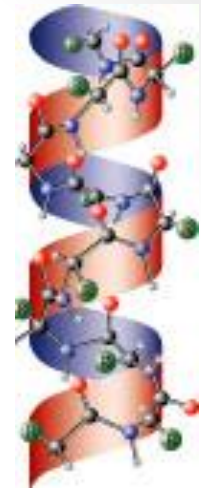
This ribbon model shows the general arrangement of atoms in a portion of the  $\alpha$ -helical secondary structure of a protein molecule.



The two models superimposed



# Secondary structure



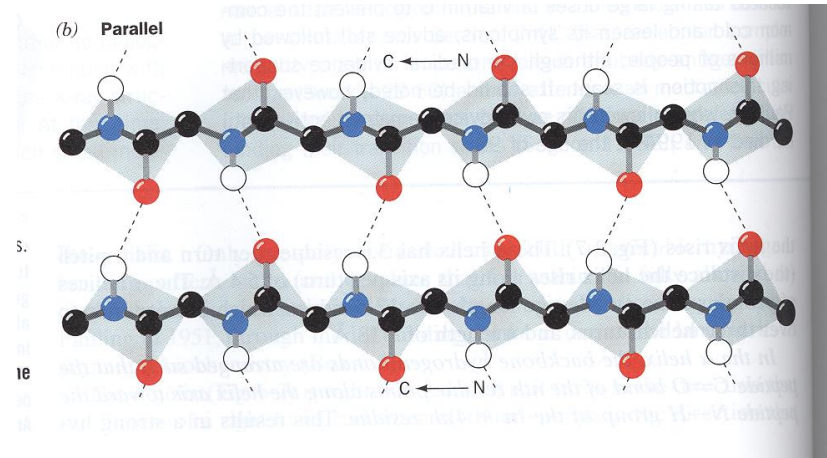
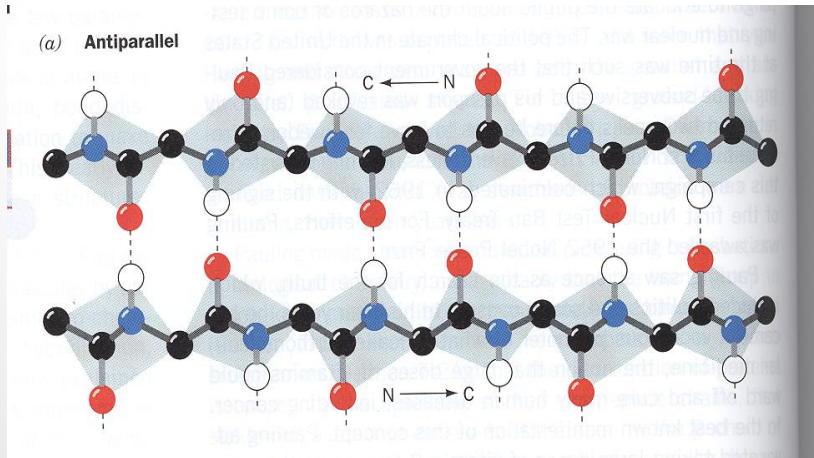
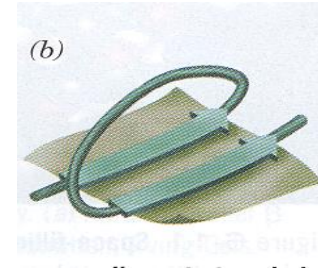
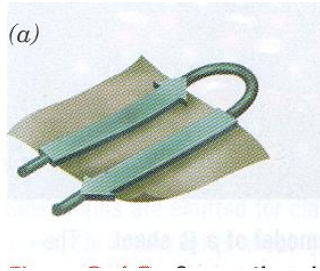
- **$\alpha$ -helix:**
  - It is a right-handed spiral, in which side chains of amino acids extended outward.
  - Hydrogen bonds: Stabilize the  $\alpha$ -helix.  
form between the peptide bond carbonyl oxygen and amide hydrogen.
  - Amino acids per turn: Each turn contains 3.6 amino acids.
  - Amino acids that disrupt an  $\alpha$ -helix:
    - Proline  $\rightarrow$  imino group, interferes with the smooth helical structure.
    - Glutamate, aspartate, histidine, lysine or arginine  $\rightarrow$  form ionic bonds.
    - Bulky side chain, such as tryptophan.
    - Branched amino acids at the  $\beta$ -carbon, such as valine or isoleucine.

# Secondary structure

- **$\beta$ -sheet** (Composition of a  $\beta$ -sheet)
  - Two or more polypeptide chains make hydrogen bonding with each other.
  - Also called pleated sheets because they appear as folded structures with edges.

# Secondary structure

- **$\beta$ -sheet** (Antiparallel and parallel sheets)



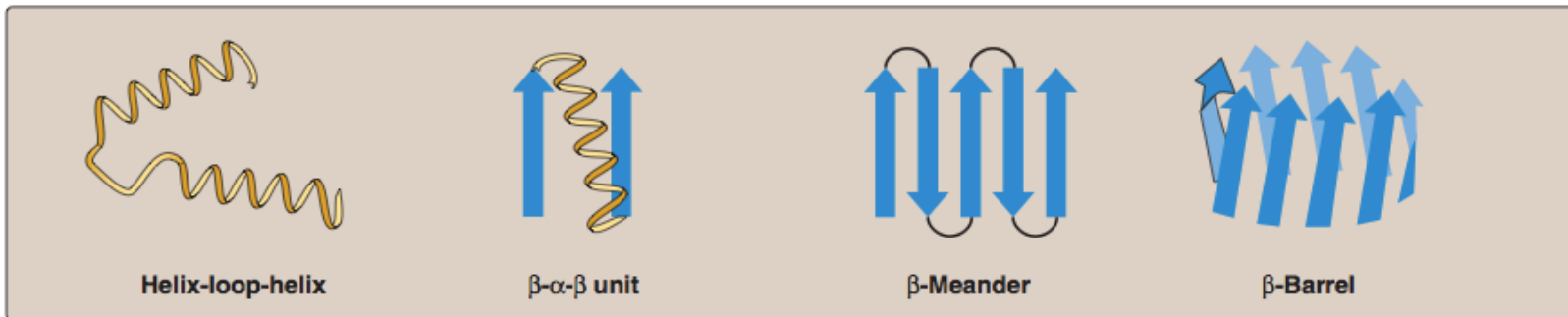
Hydrogen bonds in parallel direction is less stable than in antiparallel direction

# Secondary structure

- **Other secondary structure examples:**
  - $\beta$ -bends (reverse turns):
    - Reverse the direction of a polypeptide chain.
    - Usually found on the surface of the molecule and often include charged residues.
    - The name comes because they often connect successive strands of antiparallel  $\beta$ -sheets.
    - $\beta$ -bends are generally composed of four amino acid residues, proline or glycine are frequently found in  $\beta$ -bends.
  - Nonrepetitive secondary structure:
    - e.g. loop or coil conformation.

# Secondary structure

- **Other secondary structure examples:**
  - Supersecondary structures (motifs):  
A combination of secondary structural elements.



$\alpha$   $\alpha$  motif: two  $\alpha$  helices together

$\beta$   $\alpha$   $\beta$  motif: a helix connects two  $\beta$  sheets

$\beta$  hairpin: reverse turns connect antiparallel  $\beta$  sheets

$\beta$  barrels: rolls of  $\beta$  sheets



# Tertiary structure

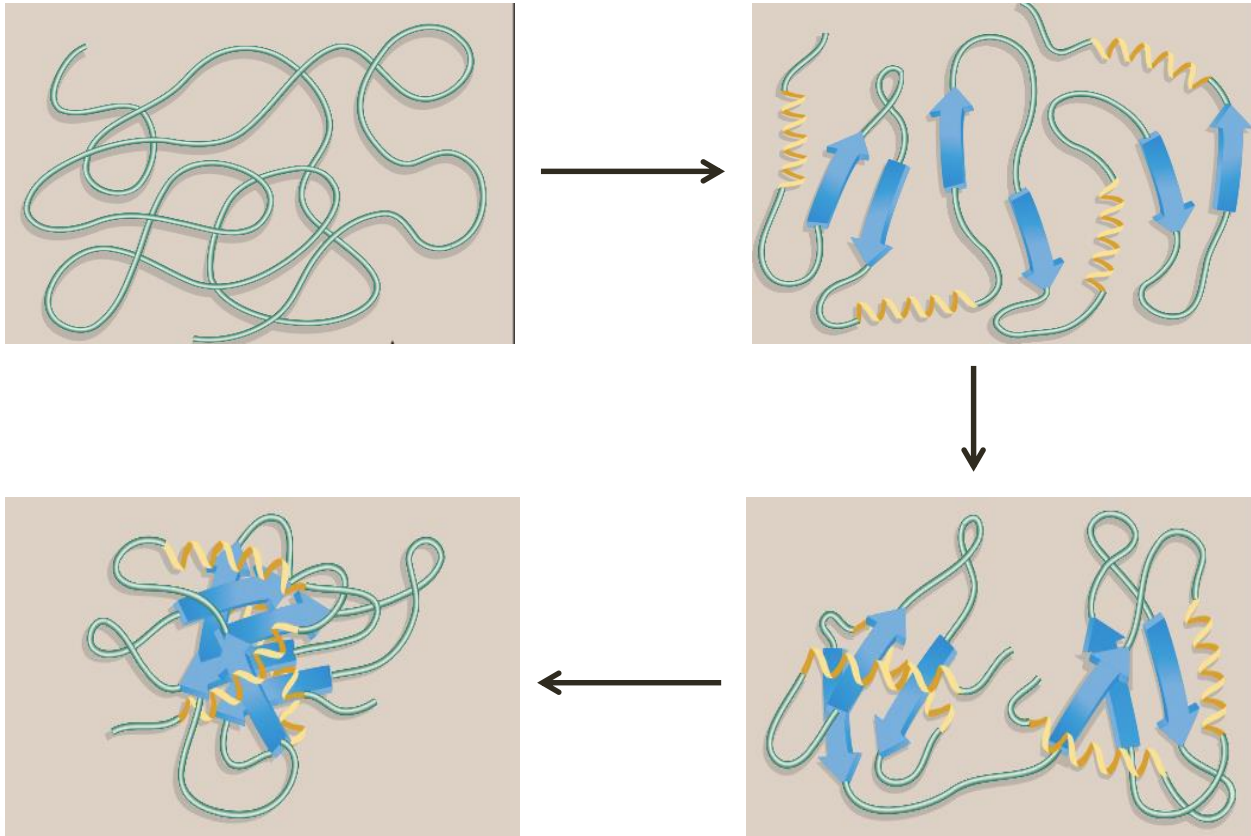
- It is the three-dimensional (3D) structure of an entire polypeptide chain including side chains.
- The fundamental functional and 3D structural units of a polypeptide known as domains, >200 amino acids fold into two or more clusters.
- The core of a domain is built from combinations of supersecondary structural elements (motifs) and their side chains.
- Domains can be combined to form tertiary structure.

# Tertiary structure

- **Interactions stabilizing tertiary structure:**
  - Disulfide bonds.
  - Hydrophobic interactions.
  - Hydrogen bonds.
  - Ionic interactions.

# Tertiary structure

- **Protein folding:**



# Tertiary structure

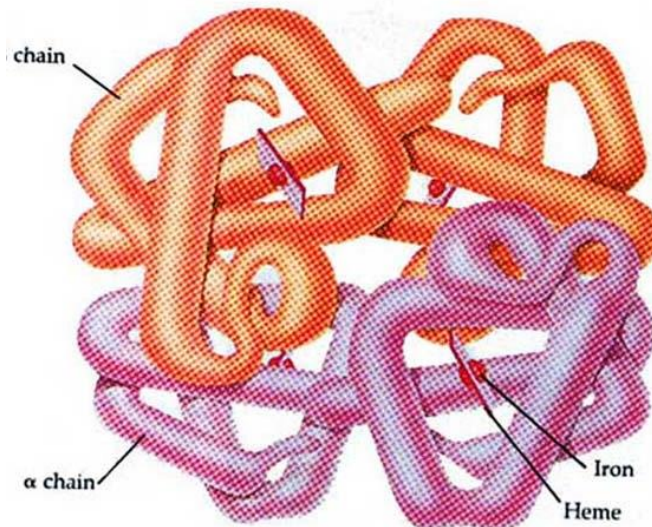
- **Role of chaperons in protein folding:**
  - Chaperons are a specialized group of proteins, required for the proper folding of many species of proteins.
  - They also known as “**heat chock**” proteins.
  - The interact with polypeptide at various stages during the folding process.

# Quaternary structure

- Some proteins contain two or more polypeptide chains that may be structurally **identical** or totally **unrelated**.
- Each chain forms a 3D structure called subunit.
- According to the number of subunits: dimeric, trimeric, ... or multimeric.
- Subunits may either function independently of each other, or work cooperatively, e.g. **hemoglobin**.

# Hemoglobin

- Hemoglobin is a globular protein.
- A multisubunit protein is called oligomer.
- Composed of  $\alpha_2 \beta_2$  subunits (4 subunits).
- Two same subunits are called protomers.



(b) Hemoglobin

# Denaturation of proteins

- It results in the unfolding and disorganization of the protein's secondary and tertiary structures.
- Denaturing agents include:
  - Heat.
  - Organic solvents.
  - Mechanical mixing.
  - Strong acids or bases.
  - Detergents.
  - Ions of heavy metals (e.g. lead and mercury).
- Most proteins, once denatured, remain permanently disordered.
- Denatured proteins are often insoluble and, therefore, precipitate from solution.

# Protein misfolding

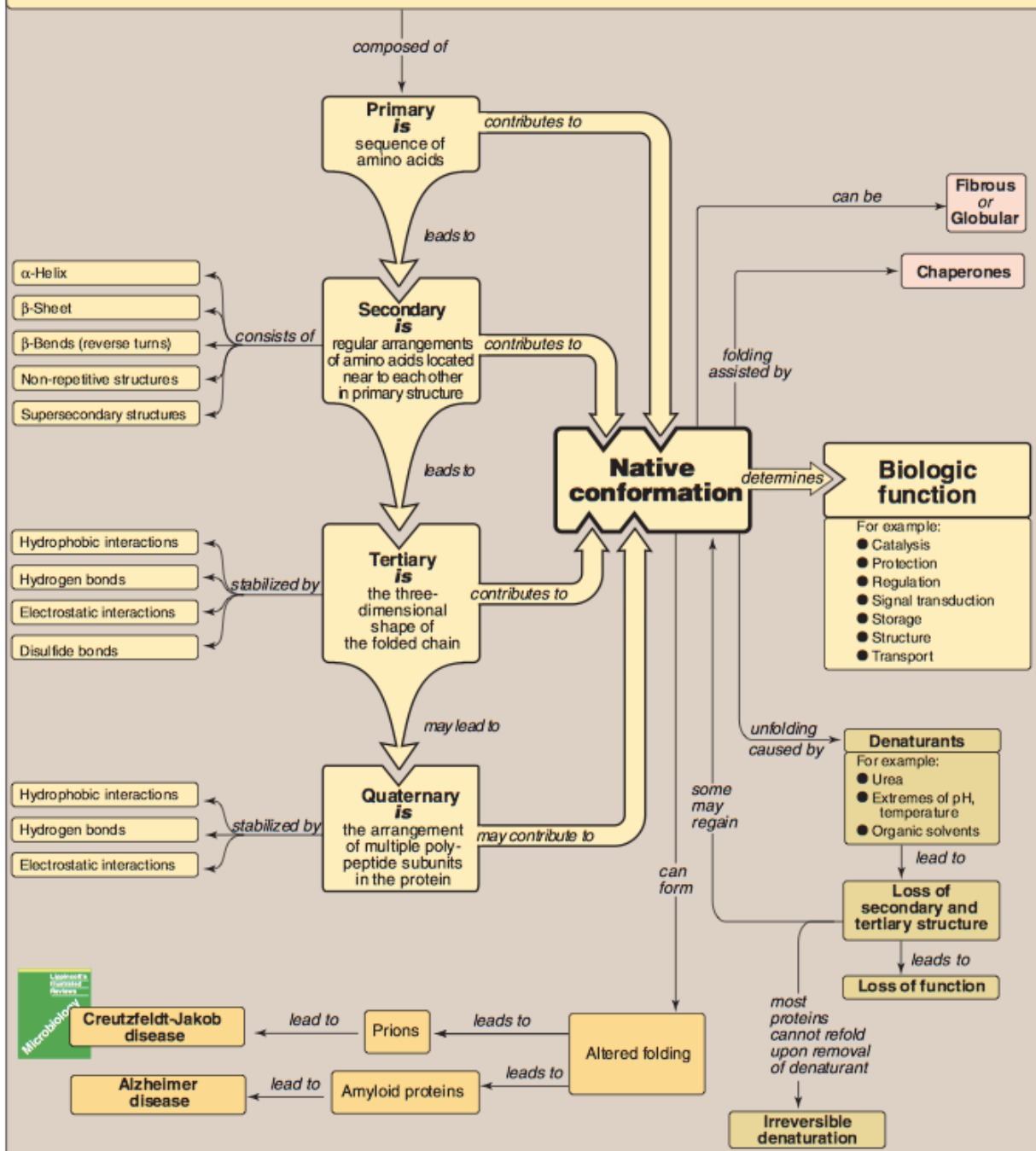
- Every protein must fold to achieve its normal conformation and function.
- Abnormal folding of proteins leads to a number of diseases in humans.



# Protein misfolding

- **Alzheimer's disease:**
  - $\beta$  amyloid protein is a misfolded protein.
  - It forms fibrous deposits or plaques in the brains of Alzheimer's patients.
- **Creutzfeldt-Jacob or prion disease:**
  - Prion protein is present in normal brain tissue.
  - In diseased brains, the same protein is misfolded.
  - It, therefore, forms insoluble fibrous aggregates that damage brain cells.

# Hierarchy of protein structure



# Reference

- Lippincott's Illustrated reviews: Biochemistry 4<sup>th</sup> edition – unit 2.