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?

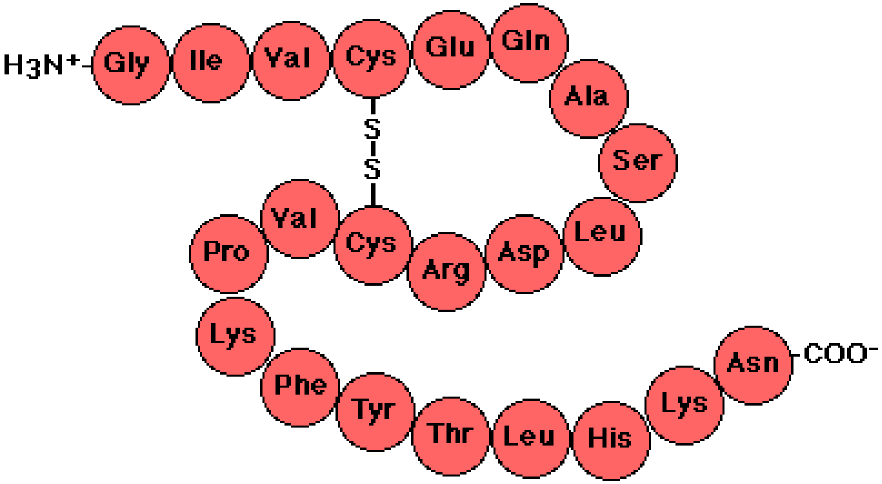
- There are mainly 20 different types of amino acids that can be combined to make a protein.

- 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.

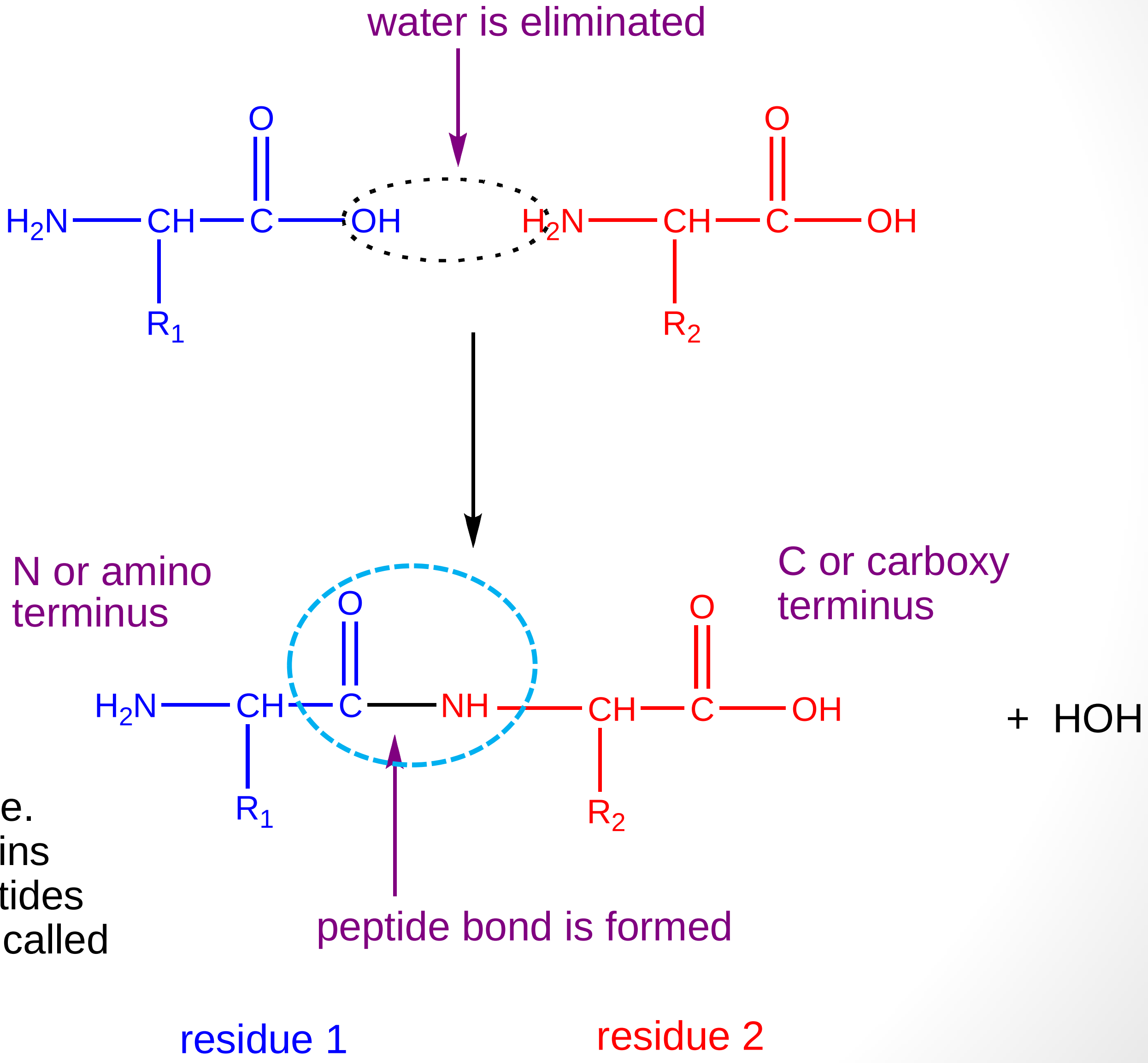


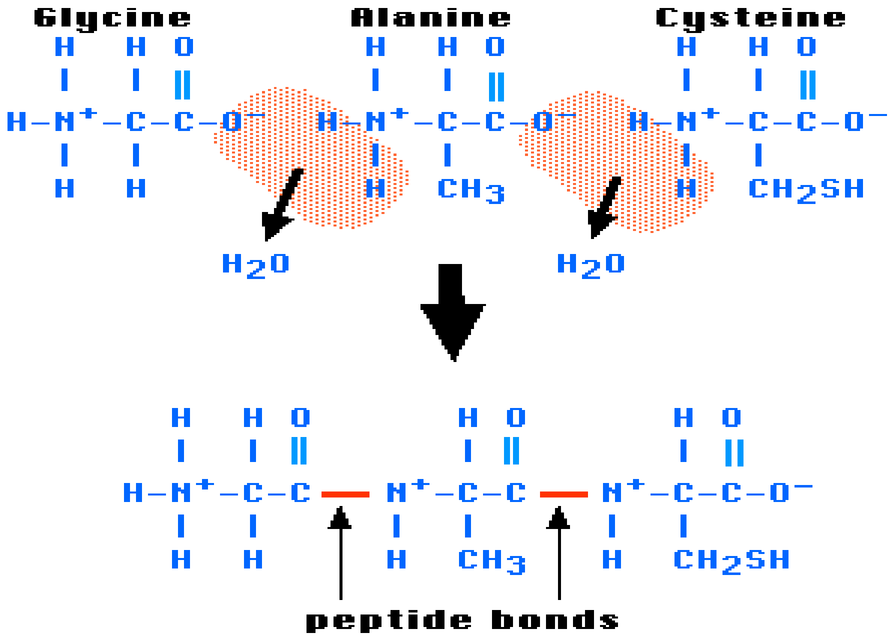
- Covalent bonds in the primary structure of protein:
  - Peptide bond.
  - Disulfide bond (if any).

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_2-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.

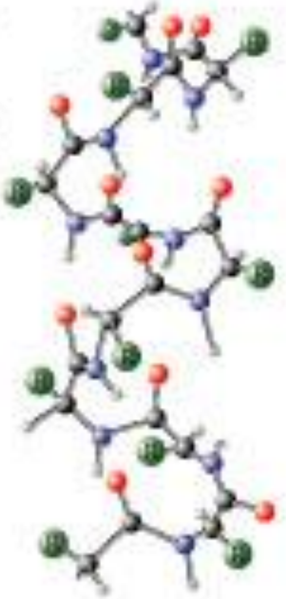
How to determine the primary structure sequence?

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.

- α-helix, β-sheet and β-bend are examples of secondary structures frequently found in proteins.



Ball-and-stick model of a portion of the α-helical secondary structure of a protein molecule

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

The two models superimposed

Secondary structure

- **α-helix:**
  - It is a right-handed spiral, in which side chains of amino acids extended outward.
  - Hydrogen bonds: Stabilize the α-helix.

  form between the peptide bond carbonyl oxygen and amide hydrogen.

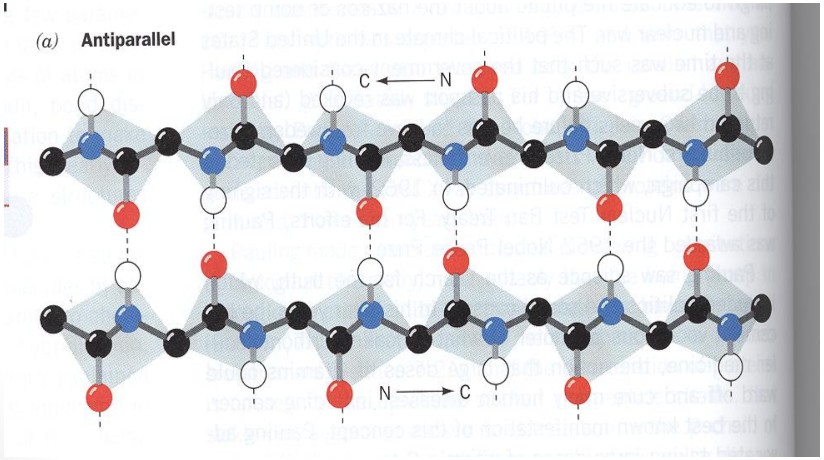
  - Amino acids per turn: Each turn contains 3.6 amino acids.
  - Amino acids that disrupt an α-helix:
    - Proline ➔ imino group, interferes with the smooth helical structure.
    - Glutamate, aspartate, histidine, lysine or arginine ➔ form ionic bonds.
    - Bulky side chain, such as tryptophan.
    - Branched amino acids at the β-carbon, such as valine or isoleucine.

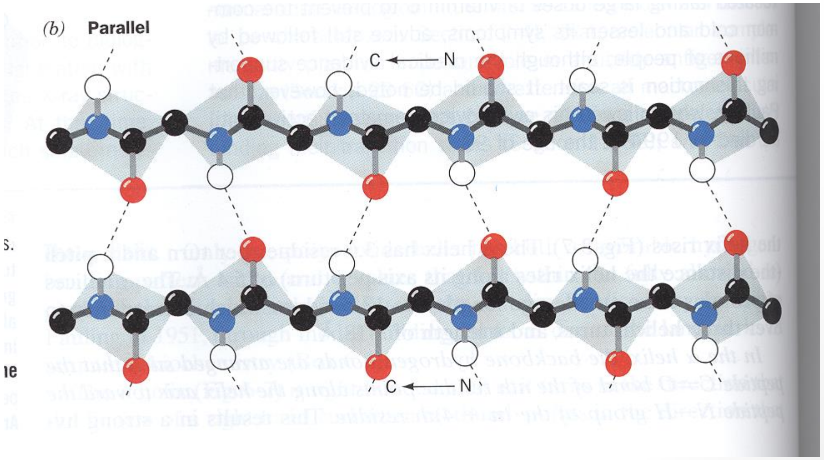
Secondary structure

- **β-sheet** (Composition of a β-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

- **β-sheet** (Antiparallel and parallel sheets)





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

Secondary structure

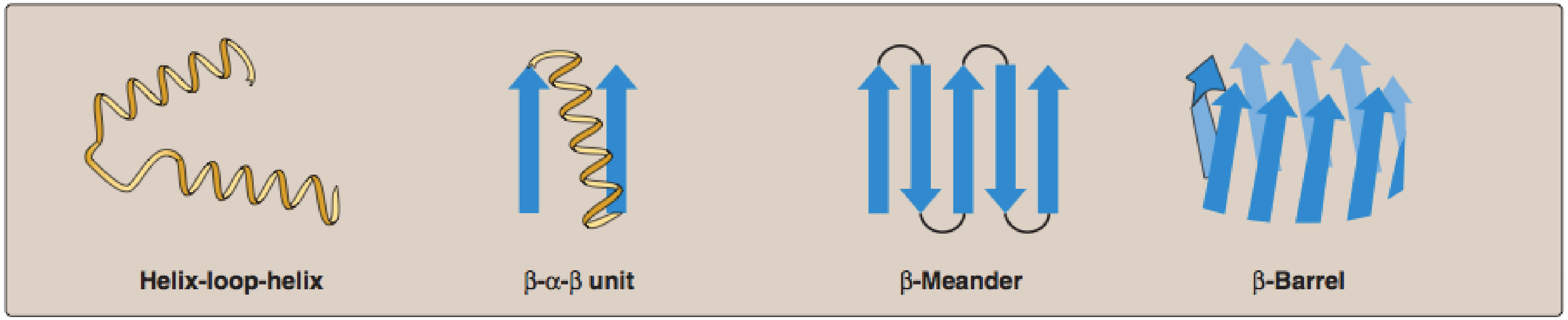
- **Other secondary structure examples:**
  - β-bends (reverse turns):
    - Reverse the direction of a polypeptide chain.
    - Usually found on the surface of the molecule and often include charged residues.
    - The name comes because they often connect successive strands of antiparallel β-sheets.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



α α motif: two α helices together

β α β motif: a helix connects two β sheets

β hairpin: reverse turns connect antiparallel β sheets

β barrels: rolls of β 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.

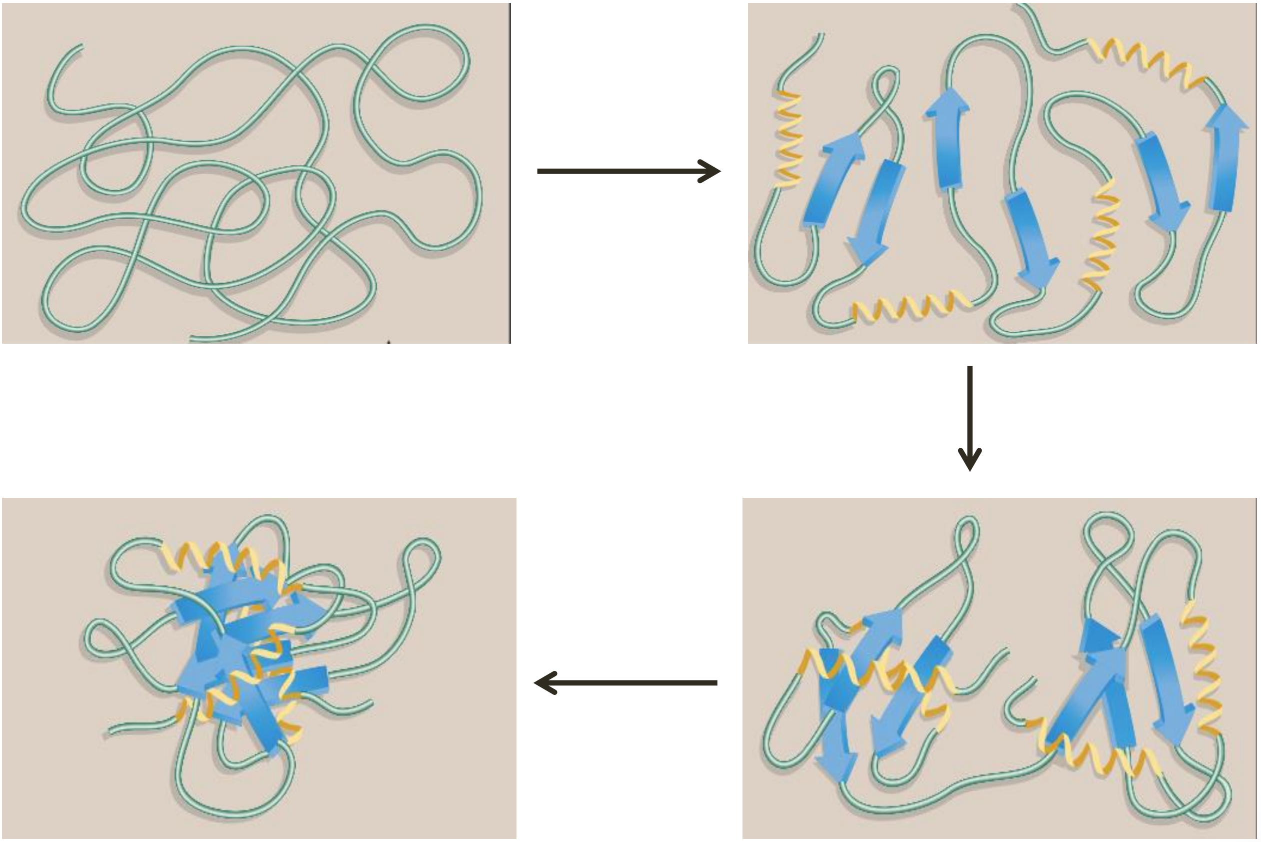
- Domains can be combined to form tertiary structure.

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 shock**” proteins.
  - They 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**.

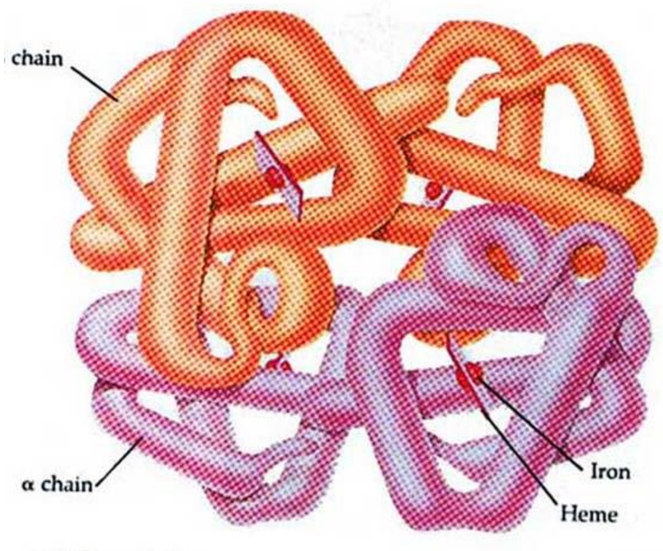
- Each chain forms a 3D structure called subunit.

- 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.

- Denaturating 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

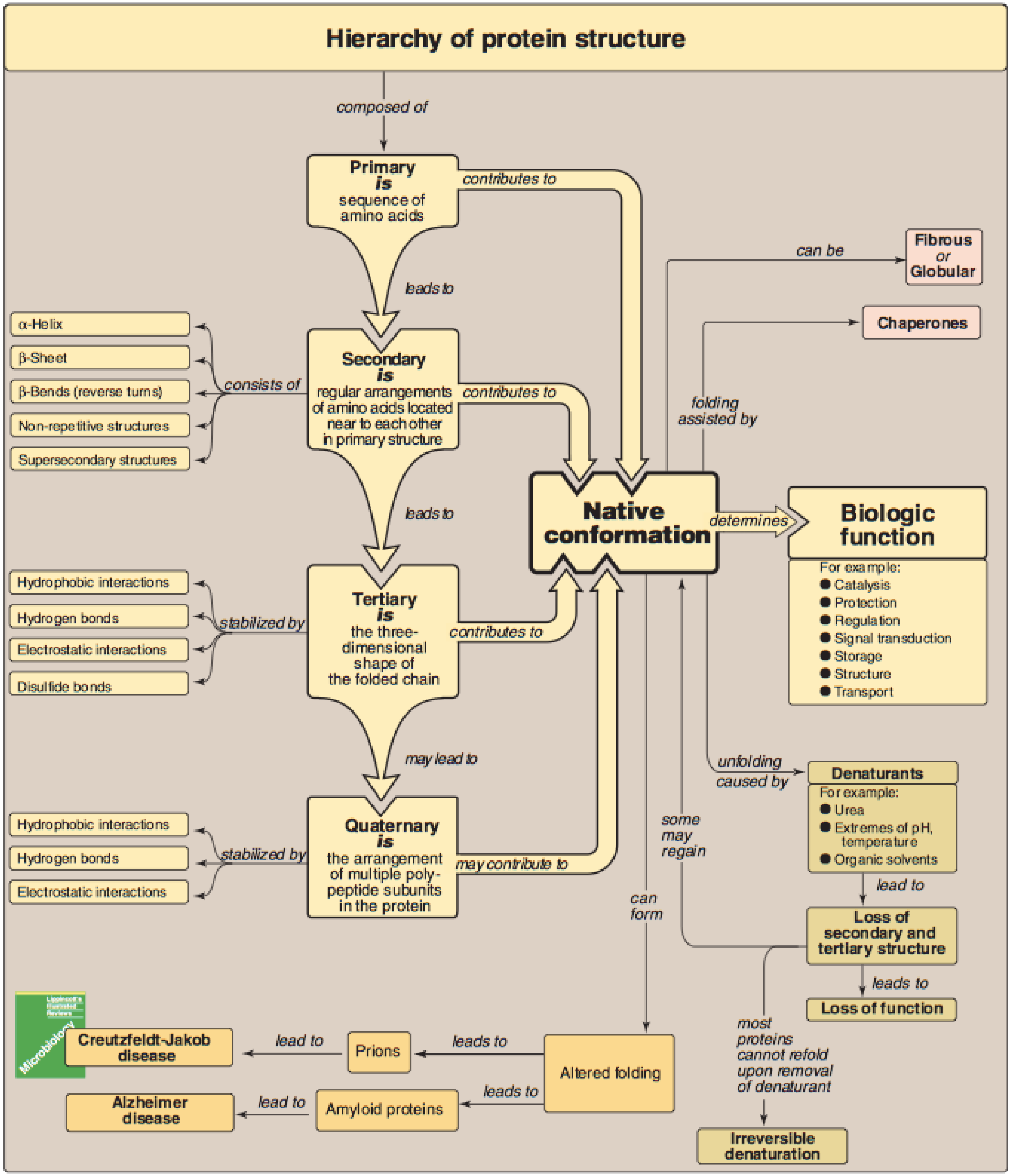
- Every protein must fold to achieve its normal conformation and function.

- Abnormal folding of proteins leads to a number of diseases in humans.

Protein misfolding

- **Alzheimer’s disease:**
  - β 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

composed of

Primary ***is*** sequence of amino acids

contributes to

leads to

Secondary ***is*** regular arrangements of amino acids located near to each other in primary structure

consists of

- α-Helix
- β-Sheet
- β-Bends (reverse turns)
- Non-repetitive structures
- Supersecondary structures

contributes to

leads to

Tertiary ***is*** the three-dimensional shape of the folded chain

stabilized by

- Hydrophobic interactions
- Hydrogen bonds
- Electrostatic interactions
- Disulfide bonds

contributes to

may lead to

Quaternary ***is*** the arrangement of multiple polypeptide subunits in the protein

stabilized by

- Hydrophobic interactions
- Hydrogen bonds
- Electrostatic interactions

may contribute to

Native conformation

can be **Fibrous** *or* **Globular**

folding assisted by **Chaperones**

determines **Biologic function**

For example:
- Catalysis
- Protection
- Regulation
- Signal transduction
- Storage
- Structure
- Transport

unfolding caused by **Denaturants**

For example:
- Urea
- Extremes of pH, temperature
- Organic solvents

lead to **Loss of secondary and tertiary structure**

leads to **Loss of function**

some may regain

most proteins cannot refold upon removal of denaturant

Irreversible denaturation

can form

Altered folding

leads to Prions

lead to **Creutzfeldt-Jakob disease**

leads to Amyloid proteins

lead to **Alzheimer disease**

Lippincott's Illustrated Reviews Microbiology

Reference

- Lippincott's Illustrated reviews: Biochemistry 4th edition – unit 2.