PROTEINS
An Introduction to Structure and Functions of Proteins

Proteins play key roles in living systems

• Examples of protein functions
  – Catalysis: Almost all chemical reactions in a living cell are catalyzed by protein enzymes.
  – Transport: Some proteins transport various substances, such as oxygen, ions, and so on.
  – Information transfer: For example, hormones.
  – Control of genetic expression: Transcription factors

Function of a Protein Depends mainly on:

• Structure (folding)
• Chemical nature of the side chains of amino acids (the building blocks of proteins)
• Fold depends on amino acid type and sequence
• Conditions of medium (temperature, pH, ionic strength, etc.)
• Two major Types of protein:
  – Fibrous: elongated and tensile
  – Globular: soluble in water
Hierarchical nature of Protein Structure

- **Primary structure**
  (Amino acid sequence)

- **Secondary structure**
  (α-helix, β-sheet)

- **Tertiary structure**
  (Three-dimensional structure formed by assembly of secondary structures)

- **Quaternary structure**
  (Structure formed by more than one polypeptide chains)

Organization within a Protein

Amino Acid: Basic Unit of Protein

- **Amino group**
- **Carboxylic acid group**

Different side chains*, R, determine the properties of 20 amino acids.

An amino acid

Main Chain (backbone) Atoms(Cα,C=N)
Exceptions: glycine and cysteine (R)

Hydrophobic amino acids

- Stabilize tertiary and quaternary structure of proteins
- Create an organic solvent-like environment in the interior

Charged amino acids

- Acid-base chemistry
- Salt bridges builders
- Lewis bases (ligands for metal ions)
Hydrogen bonds
Other dipole-dipole interactions
Lewis bases (Coordination Chemistry)
Redox chemistry (cysteine)

20 Amino acids

Primary Structure

Biosynthesis proceeds for the N-terminal to the C terminal of the protein.
The peptide bond has partial double bond character

Rotations are allowed around the $\text{C}_\alpha$-C=carbonyl $\rightarrow$ psi ($\Psi$) angle
Rotations are allowed around the $\text{C}_\alpha$-N bond $\rightarrow$ phi ($\Phi$)

Peptide torsion angles.

Only certain combinations of $\Psi$ and $\Phi$ angles are energetically favorable; those that can accommodate side chains in given secondary structures
Basic 3D structural units of proteins: Secondary structure

- α-helix
  - Hydrogen bonding between C=O of n residues and N-H of n+4 residue
  - Right handed
  - Phi angles -50° to -80°
  - Psi angles -20° to -60°
  - Rise per residue: 1.5 Å along the helical axis
  - 3.6 residues per turn
  - Average length: 10 residues, 3 turns
  - Good alpha helix formers: Glu(E), Leu(L), Met(M)
  - Poor alpha helix formers: Pro (P), Gly (G), Tyr(Y), Ser(S)
  - The alpha helix has a dipole moment

- β-sheet
  - Parallel or Antiparallel
  - Regular hydrogen-bonding patterns
**Beta Strands and Beta sheets**

- Symbol arrows
- Hydrogen bonds formed between C=O and NH on adjacent beta strands
- Antiparallel
  - One beta strand runs from amino to carboxyl terminal and the other runs from carboxyl terminal to amino terminal
  - H-bonds formed between the amino and carbonyl groups of one residue and the carbonyl and amino groups of another single residue
- Parallel
  - Both strands run from amino to carboxyl terminal
  - H-bonds formed between the amino and carbonyl groups of one residue on one strand, and the carbonyl and amino groups of residues number n and n+2 respectively, on the other strand.

**Antiparallel Beta Sheet**

![Antiparallel Beta Sheet](image-url)
Other secondary structural elements

- Loops: connect beta strands and alpha helices
- Hairpin loop: connects two adjacent antiparallel beta strands

Three-dimensional structure of proteins
Motifs

- Motifs are super secondary structures that have been identified in several proteins.
- Some motifs are associated with specific functions.

Geek key

Beta hair pin

EF hand motif/ alpha-loop-alpha

Calmodulin (CaM) is a Ca$^{2+}$-binding protein that is a key component of the Ca$^{2+}$ second-messenger system and is involved in controlling many of the biochemical processes of cells.

Helix-Turn-Helix motif

- Found in many proteins that regulate gene expression

$\lambda$ repressor of bacteriophage Lambda
Role of Metal Ions

- Stabilize particular conformation by coordinating to atoms of residues that are sequentially distant (tertiary) (Zinc fingers)
- Drive formation of quaternary structure by coordinating atoms of residues on different subunits (pancreatic insulin)
- Serve as acid catalysts
- Serve as electron transfer centers (Ribonucleotide reductase)

Protein Domain

- Motifs combine to form domains, which are compact globular structures within a proteins
- Stable subassemblies
- Domains are often functional units
- Usually, a domain separated from the rest of the protein can fold independently
- Example: lactoferrin (alpha-beta protein) (MW ~ 80,000)
  - the iron binding protein in milk
  - folds in two domains
  - Each domain binds one atom of Fe(III)
  - When separated, each domain maintains its fold and binds iron

Protein Domain

Zinc finger of Zif268
A domain that binds to DNA
- **Zif268** is a mammalian transcription factor
• A **transcription factor** is a protein that regulates the binding of RNA polymerase and the initiation of transcription. A transcription factor binds to either enhance or repress transcription of a gene by assisting or blocking RNA polymerase binding.

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**Zwitterion character, pKₐ and pI**

• Amino acids are amphoteric
• Under physiological conditions they exist as zwitterion with the carboxyl group deprotonated and the amino group protonated
• There exists a pH at which the amino acid carries no net charge, the isoelectric point (pI).
• The pI depends on the pKₐ of the amino and carboxylic groups
• The pI of amino acids with no ionizable side chains can be estimated according to:

  \[ pI = \frac{1}{2}(pK_a + pK_c) \]

  • For amino acids with more than two ionizable groups, such as lysine for example, the same formula is used, but the two pKₐ's used are those of the two groups that lose and gain a charge from the neutral form of the amino acid.
  
  *p.5 and p.7 in textbook*

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**Applications relying the pI**

• Separation of proteins by Isoelectric Focusing
• Separation of proteins by precipitation
• Crystallization of proteins