18.2 Protein Structure and Function: An Overview

► **Protein:** A large biological molecule made of many amino acids linked together through peptide bonds.

► **Alpha-amino acid:** Compound with an amino group bonded to the C atom next to the -COOH group.

► **Peptide bond:** An amide bond linking 2 amino acids.

► A **dipeptide** results from the formation of a peptide bond between 2 amino acids. A **tripeptide** results from linkage of 3 amino acids via 2 peptide bonds. Any number of amino acids can link together to form a linear chainlike polymer—a **polypeptide**.
The alpha carbon is the central carbon in an amino acid to which the amine, carboxyl and side chain R groups attach.

An α-amino acid

\[ \text{Valine} + \text{Cysteine} \rightarrow \text{A dipeptide} \]

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Proteins have four levels of structure, each of which is explored later in this chapter.

- **Primary structure** is the sequence of amino acids in a protein chain (Section 18.7).

- **Secondary structure** is the regular and repeating spatial organization of neighboring segments of single protein chains (Section 18.9).

- **Tertiary structure** is the overall shape of a protein molecule (Section 18.10) produced by regions of secondary structure combined with the overall bending and folding of the protein chain.

- **Quaternary structure** refers to the overall structure of proteins composed of more than one polypeptide chain (Section 18.11).
18.3 Amino Acids

► Nature uses 20 \( \alpha \)-amino acids to build the proteins in all living organisms; 19 of them differ only in the identity of the R group, or side chain, attached to the carbon. The remaining amino acid (proline) is a secondary amine whose nitrogen and carbon atoms are joined in a five-membered ring.

► Each amino acid has a three-letter shorthand code: Ala (alanine), Gly (glycine), Pro (proline), etc.

► The 20 protein amino acids are classified as neutral, acidic, or basic, depending on the nature of their side chains.
The nonpolar side chains are described as **hydrophobic** (water-fearing)—they are not attracted to water molecules.

To avoid aqueous body fluids, they gather into clusters that provide a water-free environment, often a pocket within a large protein molecule.

The polar, acidic, and basic side chains are **hydrophilic** (water-loving)—they are attracted to polar water molecules. They interact with water molecules much as water molecules interact with one another.

Attractions between water molecules and hydrophilic groups on the surface of folded proteins impart water solubility to the proteins.
Amino acids can undergo an intramolecular acid–base reaction. Transfer of the H from the \(-\text{COOH}\) group to the \(-\text{NH}_2\) group forms a neutral dipolar ion, an ion that has one (+) charge and one (-) charge. Neutral dipolar ions are known as zwitterions.

![Threonine—zwitterion](Copyright © 2010 Pearson Prentice Hall, Inc.)
Because they are zwitterions, amino acids have many of the physical properties we associate with salts:
- can form crystals
- have high melting points
- are soluble in water
- not soluble in hydrocarbon solvents

In acidic solution (low pH), amino acid zwitterions accept protons on their basic $-\text{COO}^-$ groups to leave only the positively charged $-\text{NH}_3^+$ groups.

In basic solution (high pH), amino acid zwitterions lose protons from their acidic $-\text{NH}_3^+$ groups to leave only the negatively charged $-\text{COO}^-$ groups.
The charge of an amino acid molecule at any given moment depends on the particular amino acid and the pH of the medium. The pH at which the net positive and negative charges are evenly balanced is the amino acid’s **isoelectric point (pI)**. At this point, the overall charge of all the amino acids in a sample is zero.
Primary protein structure: The sequence in which amino acids are linked by peptide bonds in a protein.
Without interactions between atoms in amino acid side chains or along the backbone, protein chains would twist about randomly in body fluids like spaghetti strands in boiling water.

The essential structure–function relationship for each protein depends on the polypeptide chain being held in its necessary shape by these interactions.

Where there are ionized acidic and basic side chains, the attraction between their positive and negative charges creates what are sometimes known as salt bridges.
Some amino acid side chains can form hydrogen bonds. Side chain hydrogen bonds can connect different parts of a protein molecule, sometimes nearby and sometimes far apart along the chain.

The H in the –NH- groups and the O in the C=O groups along protein backbones hydrogen bond.
Hydrocarbon side chains are attracted to each other by London dispersion forces, these groups cluster together in the same way that oil molecules cluster on water, these are **hydrophobic interactions**.

One type of covalent bond plays a role in protein shape. Cysteine amino acid residues have side chains containing thiol functional groups that can react to form **disulfide, –S–S–, bonds**.

![Chemical Diagram]

Cysteine (Cys) + Cysteine (Cys) → N→O

Oxidizing agent

A disulfide bond

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18.9 Secondary Protein Structure

► The spatial arrangement of the polypeptide backbones of proteins constitutes **secondary protein structure**.

► The secondary structure includes two kinds of repeating patterns known as the \( \alpha \)-helix and the \( \beta \)-sheet.

► In both, hydrogen bonding between backbone atoms holds the polypeptide chain in place.
**Alpha-helix:** (a) The coil is held in place by H bonds. The chain is a right-handed coil and the H bonds lie parallel to the vertical axis. (b) Viewed from the top, the side chains point to the exterior of the helix.
Beta-sheet secondary structure. (a) The protein chains usually lie side by side. (b) The R groups point above and below the sheets.
Fibrous proteins are tough, insoluble proteins in which the chains form long fibers or sheets. Wool, hair, and fingernails are made of fibrous proteins known as α-keratins which are composed almost completely of α-helixes.

In α-keratins pairs of α-helixes are twisted together into small fibrils that are in turn twisted into larger and larger bundles. The hardness, flexibility, and stretchiness of the material varies with the number of disulfide bonds. In fingernails, for example, large numbers of disulfide bonds hold the bundles in place.
Globular proteins are water-soluble proteins whose chains are folded into compact, globe-like shapes. Their structures, which vary widely with their functions, are not regular like those of fibrous proteins. Where the protein chain folds back on itself, sections of $\alpha$-helix and $\beta$-sheet are usually present.

The presence of hydrophilic side chains on the outer surfaces of globular proteins accounts for their water solubility, allowing them to travel through the blood and other body fluids to sites where their activity is needed.
<table>
<thead>
<tr>
<th>NAME</th>
<th>OCCURRENCE AND FUNCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fibrous proteins (insoluble)</strong></td>
<td></td>
</tr>
<tr>
<td>Keratins</td>
<td>Found in skin, wool, feathers, hooves, silk, fingernails</td>
</tr>
<tr>
<td>Collagens</td>
<td>Found in animal hide, tendons, bone, eye cornea, and other connective tissue</td>
</tr>
<tr>
<td>Elastins</td>
<td>Found in blood vessels and ligaments, where ability of the tissue to stretch is important</td>
</tr>
<tr>
<td>Myosins</td>
<td>Found in muscle tissue</td>
</tr>
<tr>
<td>Fibrin</td>
<td>Found in blood clots</td>
</tr>
<tr>
<td><strong>Globular proteins (soluble)</strong></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>Regulatory hormone for controlling glucose metabolism</td>
</tr>
<tr>
<td>Ribonuclease</td>
<td>Enzyme that catalyzes RNA hydrolysis</td>
</tr>
<tr>
<td>Immunoglobulins</td>
<td>Proteins involved in immune response</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Protein involved in oxygen transport</td>
</tr>
<tr>
<td>Albumins</td>
<td>Proteins that perform many transport functions in blood; protein in egg white</td>
</tr>
</tbody>
</table>
18.10 Tertiary Protein Structure

► The overall three-dimensional shape that results from the folding of a protein chain is the protein’s tertiary structure.

► In contrast to secondary structure, which depends mainly on attraction between backbone atoms, tertiary structure depends mainly on interactions of amino acid side chains that are far apart along the same backbone.
α Helix

β Sheet

Connecting loop

S—S— links

Ribonuclease
Myoglobin, drawn four ways. (a) tube representing the helical portions. (b) ribbon model shows the helical portions. (c) A ball-and-stick molecular model. (d) A space-filling model, with hydrophobic residues (blue) and hydrophilic residues (purple).
18.11 Quaternary Protein Structure

- The fourth and final level of protein structure, and the most complex, is **quaternary protein structure**—the way in which two or more polypeptide subunits associate to form a single three-dimensional protein unit.

- The individual polypeptides are held together by the same noncovalent forces responsible for tertiary structure. In some cases, there are also covalent bonds and the protein may incorporate a non–amino acid portion.
(a) Heme units shown in red, each polypeptide resembles myoglobin. (b) A heme unit is present in each of the four polypeptides in hemoglobin.
In protein hydrolysis, the reverse of protein formation, peptide bonds are hydrolyzed to yield amino acids.

\[
\begin{align*}
\text{Protein} &: \text{H}_3\text{N} & \text{C} & \text{O} & \text{O}^- \\
\text{Alanine} & : \text{H}_3\text{N} & \text{CH} & \text{C} & \text{CH}_3 \\
\text{Glycine} & : \text{H}_3\text{N} & \text{CH}_2 & \text{C} & \text{O}^- \\
\text{Cysteine} & : \text{H}_3\text{N} & \text{CH}_2\text{SH} & \text{C} & \text{O}^- \\
\text{Aspartate} & : \text{H}_3\text{N} & \text{CH}_2\text{COO}^- \\
\end{align*}
\]
**Denaturation:** The loss of secondary, tertiary, or quaternary protein structure due to disruption of noncovalent interactions and/or disulfide bonds that leaves peptide bonds and primary structure intact.
Agents that cause denaturation include heat, mechanical agitation, detergents, organic solvents, extremely acidic or basic pH, and inorganic salts.

**Heat:** The weak side-chain attractions in globular proteins are easily disrupted by heating, in many cases only to temperatures above 50°C.

**Mechanical agitation:** The most familiar example of denaturation by agitation is the foam produced by beating egg whites. Denaturation of proteins at the surface of the air bubbles stiffens the protein and causes the bubbles to be held in place.

**Detergents:** Even very low concentrations of detergents can cause denaturation by disrupting the association of hydrophobic side chains.
Organic compounds: Organic solvents can interfere with hydrogen bonding or hydrophobic interactions. The disinfectant action of ethanol results from its ability to denature bacterial protein.

pH change: Excess $\text{H}^+$ or $\text{OH}^-$ ions react with the basic or acidic side chains in amino acid residues and disrupt salt bridges. An example of denaturation by pH change is the protein coagulation that occurs when milk turns sour because it has become acidic.

Inorganic salts: Sufficiently high concentrations of ions can disturb salt bridges.

Most denaturation is irreversible. Hard-boiled eggs do not soften when their temperature is lowered.