Molecules in the cell

- Most essential molecules of the cell are known
- Pathways of synthesis and breakdown are known for most
- Chemical energy drives biosynthesis
- Organization of molecules in cells:
  1. Atoms
  2. Small molecules
  3. Macromolecules
  4. Supramolecular aggregates
Atoms

• 95% of a cell’s dry weight is C (50%), O (20%), H (10%), N (10%), P (4%), S (1%)

• Na, K, Cl, Ca, Fe, Zn are each present at less than 1%. 
Small molecules (MW = 100 - 1000)

- Cells are 70% water, nearly 30% carbon compounds

- Molecules are covalently bonded atoms, covalent bonds result from sharing electrons and depend on valence (C: +4, N: -3, O: -2, H:+1)
Covalent bonds

- Covalent bonds form the backbones of molecules.
- Electrons are shared between atoms.
- Single bonds allow rotation, double bonds are rigid.
There are four main classes of small molecules

- **Amino acids**
- **Subunits of proteins**
- 20 major types of amino acids
- Side groups of amino acids dictate protein structure (non-polar, polar, and charged subgroups)
There are four main classes of small molecules

- **Nucleotides**
- Base (adenine, cytosine, thymosine, guanine, Uracil) + sugar + phosphate
- Subunits of DNA and RNA
- ATP - the main energy source
There are four main classes of small molecules

- **Sugars**
- Monosaccharides (i.e. glucose or ribose)
- Sugars are subunits of polysaccharides (cellulose, starch, glycogen)
There are four main classes of small molecules

- **Lipids**
- Fatty acids, triglycerides, steroids, oils, fats, hormones
Macromolecules (MW 1000 - 1,000,000)

Consist of subunits linked by covalent bonds
Macromolecular assemblies

**SUBUNITS**
- e.g., sugars, amino acids, and nucleotides

**MACROMOLECULES**
- e.g., globular proteins and RNA

**MACROMOLECULAR ASSEMBLIES**
- e.g., ribosome

- 30 nm
- 200 nm

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- covalent bonds
- noncovalent bonds

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image of ribosomes
Weak bonds have many important functions in cells

• They determine the shape of macromolecules (i.e. the double stranded helical shape of DNA is determined by many weak hydrogen bonds between complementary base pairs A-T and G-C)

• They produce reversible self-assembly of pre-synthesized subunits into specific structures (i.e. membrane lipid bi-layer, protein "polymers" like microtubules and actin filaments)
Weak bonds have many important functions in cells

- They determine the specificity of most molecular interactions (i.e. enzyme substrate specificity and catalysis)

- Molecules or supramolecular aggregates denature (unfold or fall apart) upon environmental changes which affect the strengths of weak bonds (changes in pH, temperature, or ionic strength)
Weak bonds have many important functions in cells

- Binding of molecules by multiple weak interactions is often highly specific. Tight binding requires multiple complementary weak interactions and complementary surfaces.

  - molecule A randomly encounters other molecules (B, C, and D)
  - the surfaces of molecules A and B, and A and C, are a poor match and are capable of forming only a few weak bonds; thermal motion rapidly breaks them apart
  - the surfaces of molecules A and D match well and therefore can form enough weak bonds to withstand thermal motion; they therefore stay bound to each other
There are 4 major types of weak bonds: (see panel 2-7 in textbook)

1. Hydrogen bonds
2. Hydrophobic interactions
3. Ionic bonds
4. van der Waals interactions
Hydrogen bonds

The interaction of a partially positively charged hydrogen atom in a molecule with unpaired electrons from another atom. May be intermolecular (i.e. water) or intramolecular (i.e. DNA base pairing).
Hydrophobic interactions

Water forces non-polar (uncharged) surfaces out of solution to maximize hydrogen bonding
Ionic bonds

- Strong attractive forces between + and - charged atoms
- Electrons are donated/accepted by atoms rather than shared
- Strong in the absence, weak in the presence of water
• Weak force produced by fluctuations in electron clouds of atoms that are brought in close proximity.

• Individually very weak, but may become important when two macromolecular surfaces are brought close together.
Protein structure: proteins are identified by their amino acid sequences

- Methionine (Met)
- Aspartic acid (Asp)
- Leucine (Leu)
- Tyrosine (Tyr)

Polypeptide backbone

Amino, or N-, terminus

Peptide bonds

Carboxyl, or C-, terminus

Side chains
The 20 amino acids may be categorized into 4 groups based on their side chains:

<table>
<thead>
<tr>
<th>AMINO ACID</th>
<th>SIDE CHAIN</th>
<th>AMINO ACID</th>
<th>SIDE CHAIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspartic acid</td>
<td>Asp D</td>
<td>Alanine</td>
<td>Ala A</td>
</tr>
<tr>
<td>Glutamic acid</td>
<td>Glu E</td>
<td>Glycine</td>
<td>Gly G</td>
</tr>
<tr>
<td>Arginine</td>
<td>Arg R</td>
<td>Valine</td>
<td>Val V</td>
</tr>
<tr>
<td>Lysine</td>
<td>Lys K</td>
<td>Leucine</td>
<td>Leu L</td>
</tr>
<tr>
<td>Histidine</td>
<td>His H</td>
<td>Isoleucine</td>
<td>Ile I</td>
</tr>
<tr>
<td>Asparagine</td>
<td>Asn N</td>
<td>Proline</td>
<td>Pro P</td>
</tr>
<tr>
<td>Glutamine</td>
<td>Gln Q</td>
<td>Phenylalanine</td>
<td>Phe F</td>
</tr>
<tr>
<td>Serine</td>
<td>Ser S</td>
<td>Methionine</td>
<td>Met M</td>
</tr>
<tr>
<td>Threonine</td>
<td>Thr T</td>
<td>Tryptophan</td>
<td>Trp W</td>
</tr>
<tr>
<td>Tyrosine</td>
<td>Tyr Y</td>
<td>Cysteine</td>
<td>Cys C</td>
</tr>
</tbody>
</table>

Polar Amino Acids  Nonpolar Amino Acids

- D: Negative
- E: Negative
- R: Positive
- K: Positive
- H: Positive
- N: Uncharged polar
- Q: Uncharged polar
- S: Uncharged polar
- T: Uncharged polar
- Y: Uncharged polar
The conformation (shape) of a protein is determined by its AA sequence

- All 3 types of noncovalent bonds help a protein fold properly
- Together, multiple weak bonds cooperate to produce a strong bonding arrangement
The conformation (shape) of a protein is determined by its AA sequence

- The polypeptide chain folds in 3-D to maximize weak interactions
- Hydrogen bonds play a major role in holding different regions together
The conformation (shape) of a protein is determined by its AA sequence

- Covalent di-sulphide bonds help stabilize favored protein conformations
- Occur on proteins in oxidizing environments (lumen of the secretory pathway, outside the cell)
Proteins exhibit a wide variety of shapes.
Proteins exhibit multiple layers of structural complexity

Primary => secondary => tertiary => quaternary structures

(sequence) => (local folding) => (long-range) => (large assemblies)
The primary structure of a protein is its linear arrangement of amino acids

- Ala - Glu - Val - Thr - Asp - Pro - Gly -
Secondary structures are the core elements of protein architecture.
Secondary structures are the core elements of protein architecture.
Overall folding of a polypeptide chain yields its tertiary structure

Example: green fluorescent protein
Interactions between multiple polypeptide chains produce quaternary structure

Hemoglobin Molecule

- α chain
- β chain
- iron
- heme group

red blood cell
helical shape of the polypeptide molecule
Protein domains are modular units from which larger proteins are built.
Protein activity may be regulated by multiple mechanisms

1. Phosphorylation
2. Binding to GTP
3. Allosteric regulation
4. Feedback inhibition
Protein phosphorylation

(A) ATP → ADP

serine side chain

PROTEIN KINASE

PROTEIN PHOSPHATASE

P_i

OFF kinase phosphatase ON

(B) kinase phosphatase

ON OFF

P P
GTP binding

Active

Inactive

Inactive

Active
Allosteric regulation

(A) Inactive

(B) 10% active

(C) 100% active

ADP positive feedback
Degradation by ubiquitination