DNA

Central Dogma: DNA → RNA → Protein

B-DNA right handed double helix:

\[
5' - ATGGTTCTGTCTGAAGGTGAATGG - 3' \\
3' - TACCAAGACAGACCTCCTTACCTAC - 5'
\]

(Courier font gives equal character spacing)
DNA Bases and major/minor groove:

- **Adenine (A)** (a purine)
- **Thymidine (T)** (a pyrimidine)
- **Guanine (G)** (a purine)
- **Cytosine (C)** (a pyrimidine)

DNA components:

DNA base pairs:

- Thymine
- Adenine
- Cytosine
- Guanine
Forms of DNA:

![DNA structures: B-DNA, A-DNA, Z-DNA](image)

Codon Chart:

<table>
<thead>
<tr>
<th>First Base in Codon</th>
<th>Second Base in Codon</th>
<th>Third Base in Codon</th>
</tr>
</thead>
<tbody>
<tr>
<td>U</td>
<td>C</td>
<td>A</td>
</tr>
<tr>
<td>UUU</td>
<td>UCU</td>
<td>UAU</td>
</tr>
<tr>
<td>UUC</td>
<td>UCC</td>
<td>UAC</td>
</tr>
<tr>
<td>UUA</td>
<td>UCA</td>
<td>UAA</td>
</tr>
<tr>
<td>UUG</td>
<td>UCG</td>
<td>UAG</td>
</tr>
<tr>
<td>Leu</td>
<td>Ser</td>
<td>Tyr</td>
</tr>
<tr>
<td>Leu</td>
<td>Pro</td>
<td>His</td>
</tr>
<tr>
<td>Leu</td>
<td>Thr</td>
<td>Asn</td>
</tr>
<tr>
<td>Met or Start</td>
<td>Ala</td>
<td>Asp</td>
</tr>
<tr>
<td>Val</td>
<td>Gln</td>
<td>Gly</td>
</tr>
<tr>
<td>G</td>
<td>U</td>
<td>C</td>
</tr>
<tr>
<td>GUU</td>
<td>GCU</td>
<td>GAU</td>
</tr>
<tr>
<td>GUC</td>
<td>GCC</td>
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<td>Arg</td>
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<tr>
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<tr>
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<td>GCU</td>
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<td>Ala</td>
<td>Asp</td>
</tr>
<tr>
<td>Ser</td>
<td>Arg</td>
<td>Arg</td>
</tr>
</tbody>
</table>
Amino acid side chains:

*note: selenocysteine is not one of the 20 natural amino acids
Protein Structure:

(a) Primary structure

(b) Secondary structure

Hydrogen bonds between amino acids at different locations in polypeptide chain

α helix

Pleated sheet

(c) Tertiary structure

(d) Quaternary structure

β polypeptide

Heme group

Heme
Protein Secondary Structure:

![Diagram of secondary structures](image)

**Phi and Psi Angles:**

\[ \phi = \psi = 180^\circ \]  
\[ \phi = -120^\circ, \psi = 120^\circ \]

"fully extended"  \[ \leftrightarrow \]  \[ \beta\text{-strand structures} \]

Ramachandran Plot:

![Ramachandran plot diagram](image)
Thermodynamics of protein folding:

\[ \Delta G_0 = \Delta H_0 - T \Delta S \]

\[ \Delta G_0 = -RT \cdot \ln K \]

Protein folding landscape:
Chaperonin Case Study: GroEL/GroES

GroEL provides a chamber for unfolded proteins to reach their correct state. In the absence of GroES (the lid), GroEL will have exposed hydrophobic residues in its chamber which can interact with exposed hydrophobics in unfolded proteins. When the lid GroES binds GroEL, it undergoes a conformational change that buries the hydrophobic residues that were exposed. The unfolded protein is then isolated in a chamber where the only hydrophobic residues it can interact with is within itself. This protein will then undergo hydrophobic collapse to fold and will be released into solution when the ATP hydrolysis cycle releases GroES. The chamber volume of GroEL has been carefully evolved such that only one protein can enter the chamber at a time.

GroEL/GroES does NOT actively fold or disaggregate protein and it also does NOT degrade misfolded protein. Other cellular machineries (such as chaperones and proteasomes) exist to perform these functions.
Protein X-ray Crystallography:

1. Protein purification
2. Protein crystallization
3. Diffraction data collection
4. Structure determination
5. Model building

Diagram:
- Protein 2μl + reservoir 2μl
- Coverslip & grease
- H₂O
- Reservoir ~1m l
Protein misfolding diseases:
Prions

Prp\textsuperscript{C}  Prp\textsuperscript{Sc}

Amyloid-beta

Addition of Seeds

Nucleation phase
Monomer Misfolded monomer Dimer Oligomers Protofibrils Mature fibrils

Elongation phase

Time

Aggregation
1. DNA Practice Problem

DNA is read 5’→3’
Protein is translated N→C

What protein is encoded by the following DNA strand?

DNA: 5’ CTACTCTTTAGCCAT 3’

Solution:
DNA: 5’ CTACTCTTTAGCCAT 3’
Complementary RNA: 5’ AUGGCUAAAGAGUAG 3’
Protein: MAKE

2. Denaturation Practice Problem

Identify the dominant interactions involved in cold denaturation of proteins.

Solution:
Water has a defined crystal lattice at low temperatures, and exposure of internal hydrophobics decreases protein-water bonding and increases the water-water lattice structure, which is exothermic (same direction as ice formation). The predominant force is the hydrophobic effect as hydrogen bonding and ion-ion networks broken during denaturation can be reformed with water.

3. pH/pKa

Useful equations:
\[ \text{pH} = -\log_{10}[H^+] \]
\[ AH \rightleftharpoons A^- + H^+ \]
\[ K_a = \frac{[A^-][H^+]}{[AH]} \]
\[ pK_a = -\log_{10} K_a \]
\[ pH = pK_a + \log_{10} \frac{[A^-]}{[AH]} \]

What is the protonation state of lysine at pH 2? pH 7? pH 12?
Solution:

- pKa of side chain: 10.53
- pKa carboxylic acid: 2.18
- pKa amino group: 8.95

If pKa > pH: protonated
If pKa < pH: deprotonated

pH 2: lysine protonated, carboxylic acid protonated, amino protonated
pH 7: lysine protonated, carboxylic acid deprotonated, amino protonated
pH 12: lysine deprotonated, carboxylic acid deprotonated, amino deprotonated

pH 7 (physiological pH)