### Distribution of the amino acids in Nature

<table>
<thead>
<tr>
<th>Amino Acid</th>
<th>Frequency in proteins (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leucine</td>
<td>9.0</td>
</tr>
<tr>
<td>Alanine</td>
<td>8.3</td>
</tr>
<tr>
<td>Glycine</td>
<td>7.2</td>
</tr>
<tr>
<td>Serine</td>
<td>6.9</td>
</tr>
<tr>
<td>Valine</td>
<td>6.6</td>
</tr>
<tr>
<td>Glutamic acid</td>
<td>6.2</td>
</tr>
<tr>
<td>Threonine</td>
<td>5.8</td>
</tr>
<tr>
<td>Arginine</td>
<td>5.7</td>
</tr>
<tr>
<td>Lysine</td>
<td>5.7</td>
</tr>
<tr>
<td>Aspartic acid</td>
<td>5.3</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>5.2</td>
</tr>
<tr>
<td>Proline</td>
<td>5.1</td>
</tr>
<tr>
<td>Asparagine</td>
<td>4.4</td>
</tr>
<tr>
<td>Glutamine</td>
<td>4.0</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>3.9</td>
</tr>
<tr>
<td>Tyrosine</td>
<td>3.2</td>
</tr>
<tr>
<td>Methionine</td>
<td>2.4</td>
</tr>
<tr>
<td>Histidine</td>
<td>2.2</td>
</tr>
<tr>
<td>Cysteine</td>
<td>1.7</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>1.3</td>
</tr>
</tbody>
</table>

### Four special amino acids

- **Glycine**
- **Proline**
- **Cysteine**
- **Histidine**
Glycine: The Smallest Amino Acid

- First amino acid discovered in 1820 from gelatin.
- “R” = hydrogen
- Reduced steric hindrance: can adopt a wider range of peptide conformations compared to other amino acids.

Proline

In proline, the trans isomer is only slightly favored over the cis isomer. Thus, proline can readily adopt the *cis* conformation.
Cysteine and Cystine

- Disulfide bonds constrain protein conformation

Disulfide Bonds and “Perms”
What is $pK_a$?

$K_a = \frac{[H_3^+][H^+]}{[H_2N^\cdot]}$

$pK_a = -\log K_a$

$pK_a = -\log [H^+] = \text{pH}$

Histidine can shuffle between forms

slight increase in physiological pH (more basic)

slight decrease in physiological pH (more acidic)
Hydrolysis of a peptide bond

Enzymes make the rate of reactions go faster.

Amino acids cooperate in catalysis

The catalytic triad: serine, histidine, and aspartic acid work together to cleave amide bonds

The aspartate H-bonds to the histidine side chain, perturbing its pKa and making it more basic. This makes it easier for histidine to remove a proton from serine during the reaction.
Take home messages

- Proteins are polymers of amino acids.
- Amino acids are connected through peptide bonds.
- The nature of the peptide bond constrains the shape of the polymer.
- Nonbonded interactions between side chains also constrain the shape of the peptide backbone.
- There are twenty amino acids, each containing unique side chains.
- Amino acids can work in concert in a polypeptide chain to generate new functions.

**Question:** How does a straight chain polymer of amino acids fold??

Protein Structure and Folding

HUMPTY DUMPTY SAT ON A WALL. HUMPTY DUMPTY HAD A GREAT FALL. ALL THE KING'S HORSES AND ALL THE KING'S MEN, COULDN'T PUT HUMPTY TOGETHER AGAIN.

Life Sciences 1a
Lecture Notes Set 5
Fall 2006
Prof. Daniel Kahne
Lectures 7-8: The Molecular Basis of Translation:

Proteins: The Workhorses of Biology

a. A chemical look at proteins
   i. Introduction to proteins and amino acids
   ii. Conformational peculiarities of peptide bonds
   iii. Structures and properties of the twenty natural amino acids
   iv. A closer look at four special amino acids -- Gly, Pro, Cys, and His.
   v. Collaborations between amino acids in proteins

b. Protein structure
   i. The four levels of structure
   ii. A closer look at secondary structure

c. Protein folding:
   i. Anfinsen's experiment
   ii. Thermodynamic forces involved in protein structures.
   iii. Thermodynamics of protein folding
   iv. The Levinthal paradox (the kinetics of protein folding)
   v. Molecular chaperones

Lecture Readings
Alberts pp. 119-128;
McMurry: pp. 182-192,
233-238

Four Levels of Protein Structure

[Diagram of primary, secondary, tertiary, and quaternary protein structures]
Different Proteins Contain Different Secondary Structural Elements

Cytochrome b$_{562}$  LDH  Antibody

Hierarchical Organization of Protein Structure

Protein Molecule  Single Polypeptide Domain  Secondary Structure
Only some peptide backbone conformations are sterically allowed. A Ramachandran plot shows the allowed combinations of the dihedral angles.

Secondary Structure: \( \alpha \)-helices

Details about $\alpha$-helices

Secondary Structure: $\beta$-sheets
Christian Anfinsen, Nobel Prize in Chemistry 1972

Thermodynamic Hypothesis: The information contained in the primary amino acid sequence leads to the correct protein fold. (or in other words . . . Could you put Humpty Dumpty back together again?)

Test: Will a denatured protein (RibonucleaseA) refold to its native conformation?

Anfinsen’s protein folding experiment

The Control:
- Native
- Denatured
- "Scrambled" (1-2% active)

The Observation:
- Native (100% active)
- Denatured (inactive)
- Native (100% active)

Conclusion: The information required to fold a protein is contained within its sequence.