Basic Biophysical Chemistry

- Electrostatic Interactions
- Van der Waals Interactions
- Hydrogen-bonded Interactions
- Hydrophobic Interactions

\[ \Delta G_{ab} = \Delta H - T \Delta S \]
\[ \Delta G_{ab} = -RT \ln K_{ab} \]
Defining Content:

**Potential Energy**

**(Spontaneous events make U smaller -- move negative)**

\[ AU < 0 \]

1. **Electrostatic Interaction**

\[ F = k \frac{q_1 q_2}{r^2} \]

\[ k = \frac{1}{4\pi \epsilon_0} \]

\[ U = -\nabla \cdot U \]

\[ U = -\int F \, dr \]

\[ U = k \frac{q_1 q_2}{r} + C \]

Choose \( C \) so that \( U = 0 \) at \( r = \infty \)

\[ U = k \frac{q_1 q_2}{r} \]

\[ \text{sgn}(q_1) \text{sgn}(q_2) > 0 \Rightarrow U > 0 \]

\[ \text{repulsive} \]

\[ \text{sgn}(q_1) \text{sgn}(q_2) < 0 \Rightarrow U < 0 \]

\[ \text{attractive} \]

\[ \text{nb} \] \[ \sum_{i} e r = \frac{-q}{r} \]
2. Van der Waals Interactions.

\[ F_A = -\frac{KL}{r^q} \]

\[ K_L = \frac{4 I_A I_B d_A d_B}{(I_A + I_B)} \]

London Dispersion Force. \( d \) - polarizabilities. \( I \) - ionizability.

\[ F_R = + \frac{L}{r^m} \]

Lennard-Jones. Shown \( m = 12 - 15 \). Usually choose \( m = 13 \).

\[ F_{\text{vdW}} = \frac{1}{r^6} - \frac{K_L}{r^q} \]

\[ U = \int_{-\infty}^{\infty} F_{\text{vdW}} \, dr = \frac{1}{12} \frac{1}{r^{12}} - \frac{1}{6} \frac{K_L}{r^q} \]

\[ U(\infty) = 0 \]

\[ U = \frac{a}{r^{12}} - \frac{b}{r^6} \]

Lennard-Jones \( 12 - 6 \) Potential.
Biological Chemistry

Explain Potential Energy. (Smaller -- more negative)

1. Electrostatic Interactions.

Consider charges \( q_1, q_2 \).

\[ F = \frac{k q_1 q_2}{r^2} \quad F \text{ is attractive or repulsive.} \]

\[ k = \frac{1}{4\pi\varepsilon_0} \quad \text{Coulomb's constant.} \]

\[ U = \frac{k q_1 q_2}{r} \quad \text{Potential energy.} \]

\[ \oint_{\text{closed loop}} F \cdot dr = 0 \]

Choose \( C \) so \( U = 0 \) at \( r = \infty \).

\[ U = \frac{k q_1 q_2}{r} \]

Electrostatic Potential.

\( \text{Sign}(q_1) \cdot \text{Sign}(q_2) > 0 \quad U > 0 \quad \text{repulsive} \)

\( \text{Sign}(q_1) \cdot \text{Sign}(q_2) < 0 \quad U < 0 \quad \text{attractive} \)
Potential energy function:
\[ V(r) = \begin{cases} \frac{a}{r^2} & \text{repulsive} \\ \frac{b}{r^6} & \text{attractive} \end{cases} \]

Parameters:
- \( R_0 \): position of minimum energy
- \( R \): distance of closest approach (van der Waals radius)

Typical van der Waals radii:
- H: 1.3 Å
- C: 1.5 Å
- N: 1.7 Å
- O: 1.5 Å
- S: 1.8 Å

\( \text{Å} = 10^{-10} \text{ m} \)
\( \text{nm} = 10^{-9} \text{ m} \)

\[
X - H \cdots Y \quad X, Y = O, N, S
\]

\[
\uparrow \quad \uparrow
\]

2.8 - 3.5 Å

<table>
<thead>
<tr>
<th>Donor</th>
<th>Acceptor</th>
</tr>
</thead>
</table>

- OH --- O\(^-\)  
- NH --- O\(^-\)

- OH --- O = C  
- NH --- O = C

\[\text{\textit{O}} = \text{C}\]

\[\text{\textit{O}} ^{\text{H}} \text{ sp}^2 \text{ hybridized}\]

\[R\]

\[V = \frac{C}{r^{10}} - \frac{d}{r^6}\]

| Modified Leonard-Jones potential. |
Figure 2.10
Structure of ice. The structure of ice can be considered an indefinite repetition of the tetrahedral hydrogen-bonding pattern shown for a single water molecule in Figure 2.9. Because of the length of the hydrogen bonds, the structure is a relatively open one, which accounts for the low density of ice.
Figure 2.11
Structure of liquid water. When ice melts to water, the regular tetrahedral lattice is broken. However, substantial remnants of it remain, especially at low temperatures. The structure of liquid water can be best thought of as flickering clusters of molecules held together by hydrogen bonds that are continually breaking and reforming. In this schematic "motion picture," successive frames represent changes occurring in picoseconds ($10^{-12}$ s).

Hyrophilic: Water Loving
- Form H-Bonds with $H_2O$.
- Polar (OH, SH, NH)

Hyrophobic: Water Fearing
- No H-Bonds with $H_2O$.
- Non-polar (CH$_3$, O)
- Form "Clathrate Cage"

Ordered structure of $H_2O$ - entropically unfavorable.

Less "Clathrate Cage". More entropically favored.
Basic Biophysical Chemistry

• Electrostatic Interactions
• Van der Waals Interactions
• Hydrogen-bonded Interactions
• Hydrophobic Interactions

\[ \Delta G_{ab} = \Delta H - T \Delta S \]

\[ \Delta G_{ab} = -RT \ln K_{ab} \]
Dihedral Angles in Polypeptides
Planarity of Peptide Bond.

\[ \text{CO} \quad \text{C} = \text{N} \quad \text{H} \quad \text{Ca} \quad \xleftrightarrow{\text{trans}} \quad \text{C} = \text{N}^+ \quad \text{H} \quad \text{Ca} \]

\[ \text{trans} \quad \text{cis} \]

Free Energy

\[ \Delta G \approx 5 \text{ kcal/mol} \]
X-Pro Peptide Bonds.

\[ \begin{align*}
\text{Trans} & \quad \text{Cis} \\
\text{O} & \quad \text{O} \\
\text{C} & \quad \text{C} \\
\text{N} & \quad \text{N} \\
\text{C} & \quad \text{C} \\
\text{C} & \quad \text{C} \\
\Delta \theta & \quad \text{NO} 
\end{align*} \]
Amide plane

$\phi = 180^\circ, \psi = 180^\circ$

$\alpha$-Carbon

Side group

Amide plane
Figure 2.5. The planar characteristics of the peptide bond, and rotation of the peptide backbone about the $C_\alpha$ atom. Note the two planar peptide bonds about a central alpha carbon, shown here as a ball-and-stick model. Rotation is only possible about the $\Phi (C_\alpha-N)$ and $\Psi (C_\alpha-C)$ angles. Arrows about the two angles show the direction that is considered positive rotation. In this figure, both angles are approximately 180°. From R.E. Dickerson and I. Geis. The Structure and Action of Proteins. New York: Harper & Row, 1969. Used with permission from Geis Archives.
Ramachandran Plot of Polypeptide Conformation

\[ n = \# \text{ residues} / \text{ turn} \]
FIG. 7. Plot of main chain dihedral angles $\phi$ and $\psi$ (see Fig. 2 for definitions) experimentally determined for approximately 1000 anglycine residues in 78 proteins whose structures have been refined at high resolution (chosen to be representative of all categories of tertiary structure).

Ac-L-Ala-NHMe

Ac-Gly-NHMe

FIG. 8. Plot of main chain dihedral angles $\phi$ and $\psi$ experimentally determined for the glycines in 20 high-resolution protein structures.
\[ p = \frac{\text{pitch}}{\text{turn}} = \frac{\Delta Z}{\text{turn}} \]

\[ \text{Rise (h)} = \frac{\Delta Z}{\text{rise \ residue}} \]

\[ \text{Run (R)} = \frac{\Delta Z}{\text{run \ residue}} \]
The hydrogen bonding patterns of different helical secondary structures. The peptide backbone is shown in an extended conformation, noting the hydrogen bonding pairings that would occur in each type of helix. The common \( \alpha \) helix, depicted in Figure 2.7, forms hydrogen bonds between the carbonyl oxygen of each residue and the amide proton of the residue 4 residues ahead in the helix. The \( 3_{10} \) helix forms hydrogen bonds between the carbonyl oxygen of each residue and the amide proton of the residue 3 residues ahead, forming a more narrow and elongated helix. The \( \pi \) helix bonds between the carbonyl oxygen of each residue and the amide proton of the residue five residues ahead, forming a wider helix. A regular secondary structure, but is shown here to demonstrate all possible hydrogen bond pairings. From R. E. Dickerson and I. Geis. The Proteins. New York: Harper & Row, 1969. Used with permission from Geis Archives.
The Right-Handed 
Alpha Helix

(3.6_{13} Helix)

Alpha helix
3.6 residues / turn
5.4 Ang / turn
13 atoms / H-bond loop
Right-handed alpha helix

Figure 2.7. Diagram of an $\alpha$ helix using a ball-and-stick model. The bonds forming the backbone of the polypeptide are darkly shaded. The $\alpha$ helix is stabilized by internal hydrogen bonds formed between the carbonyl oxygen of each residue and the amide proton of the residue 4 residues ahead in the helix, shown here as dashed lines. Note that the polypeptide backbone curves towards the right, and as such the $\alpha$ helix is a right-handed helix. From R.E. Dickerson and I. Geis. The Structure and Action of Proteins. New York: Harper & Row, 1969. Used with permission from Geis Archives.
Alpha Helix
3.6 residues / turn
13 atoms / H-bonded loop
Figure 2.6. The hydrogen bonding patterns of different helical secondary structures. The peptide backbone is shown in an extended conformation, with an arrow denoting the hydrogen bonding pairs that would occur in each type of helix. The common α-helix, depicted in Figure 2.7, forms hydrogen bonds between the carbonyl oxygen of each residue and the amide proton of the residue two residues ahead in the helix. The 3_10-helix forms hydrogen bonds between the carbonyl oxygen of each residue and the amide proton of the residue five residues ahead, forming a more compact and elongated helix. The ß-helix forms hydrogen bonds between the carbonyl oxygen of each residue and the amide proton of the residue four residues ahead, forming a wider helix. The ß: ribbon is not a regular secondary structure, but is shown here to demonstrate all possible hydrogen bond pairings. From K. E. Laursen and J. Orci. The structure and function of proteins. New York: Harper & Row, 1965. Used with permission from Cold Spring Harbor Laboratory Press.
Helix Dipole
Helical Wheels

Amphipathic Helices - every 3-4 residues is hydrophobic
Four Helical Bundle With Antiparallel Helices

Amphipathic Helices forming a Hydrophobic Core
Beta-Sheets
Top - antiparallel
Bottom - parallel
Ramachandran
Plot of Polypeptide Conformation

n = # residues / turn
Beta-Turns
(tight turns)

antigen binding sites from a known antibody sequence is thus essentially a problem of modeling the three-dimensional structures of loop regions since the core structures of all antibodies are very similar. Such model building has been
Beta-Turns
(tight turns)
Principal Classes of Proteins

- Globular
- Membrane
- Fiberous
Representations of Protein Structures

a - full atom

b, c - strands / helices

d - Topology diagrams
Storing Protein Structure Information

**Cartesian Coordinates**
- x, y, z coordinate for each atom
- 3 per atom / 30 - 100 per residue

**Dihedral Angles**
- assumes fixed bond lengths and fixed bond angles
- 3 - 8 per residue

```
ATOM  1  C   ACE     0       9.401  30.166  60.595  1.00
      0           1GKY 67
ATOM  2  O   ACE     0      10.432  30.832  60.722  1.00
      50.35                 1GKY 68
ATOM  3  CH3 ACE     0       8.876  29.767  59.226  1.00
      50.04                 1GKY 69
ATOM  4  N   SER     1       8.753  29.755  61.685  1.00
      49.13                 1GKY 70
ATOM  5  CA  SER     1       9.242  30.200  62.974  1.00
      46.62                 1GKY 71
ATOM  6  C   SER     1      10.453  29.500  63.579  1.00
      41.99                 1GKY 72
ATOM  7  O   SER     1      10.593  29.607  64.814  1.00
      43.24                 1GKY 73
ATOM  8  CB  SER     1      10.593  29.607  64.814  1.00
      43.24                 1GKY 74
ATOM  9  CG  SER     1      10.593  29.607  64.814  1.00
      43.24                 1GKY 75
ATOM 10  O   ARG     2     11.360  28.819  62.827  1.00
      62.94                 1GKY1515
```
Principal Protein Fold Classes

All alpha

All beta

alpha + beta

alpha / beta
Classification of Protein Folds
- SCOP
- CATH
- DALI / FSSP
Protein Domains

“Independent Folding Units”

50 - 350 residues
Mean size - 125 residues

Alpha folds; Beta Folds;
Alpha+Beta Folds; Alpha/Beta Folds
Cadherins

**Cadherin Proteins in Caenorhabditis elegans**

- CDH-4
- CDH-5
- CDH-12
- HMR-1a
- HMR-1b
- CDH-1
- CDH-6
- CDH-10
- CDH-8
- CDH-7
- CDH-11
- CDH-9
- T01D3.1
- Y37E11A.94.a

**Cadherin Proteins in Drosophila melanogaster**

- Fat
- CG7740
- Staum
- Ds
- CadN
- CG14900
- CG3389
- CG4655/CG4509
- CG15511/CG7885
- CG6445
- CG7527
- Slk
- CG66977
- Ret
- CG11059
- CG10244/HD-14
- CG10421

![Signal peptide](signal_peptide.png)
- Cytoskeleton domain
- Transmembrane Helix
- 7 Pass Transmembrane Domain
- EGF
- EGF_CA
- Laminin G
- Merge Position

**Cadherins**

courtesy of C. Chothia
Most proteins in biology have been produced by the duplication, divergence and recombination of the members of a small number of protein domain families.

courtesy of C. Chothia
Domain Combinations in Genome Sequences

In bacteria close to
  1/3 of proteins consist of one domain and
  2/3 consist of two or more domains.

In eukaryotes close to
  1/4 of proteins consist of one domain and
  3/4 consist of two or more domains.