Molecular Forces in Biological Systems

- Electrostatic Interactions;

- Shielding of charged objects in solution
Electrostatic self-energy, effects of size and dielectric constant

\[ \delta U_{el} = \frac{q \delta q}{4\pi\varepsilon_0 \varepsilon r} \]

\( \delta q \) brought from infinity

\[ U_{el} = \frac{1}{4\pi\varepsilon\varepsilon_0} \int_0^q q \, dq = \frac{q^2}{8\pi\varepsilon_0 \varepsilon r} \]

\[ \Delta U = \Delta W_{\text{Born}} = \frac{q^2}{4\pi\varepsilon_0} \frac{1}{2r} \left( \frac{1}{\varepsilon_2} - \frac{1}{\varepsilon_1} \right) = \frac{cz^2}{2r} \left( \frac{1}{\varepsilon_2} - \frac{1}{\varepsilon_1} \right) \]

where \( c = e^2/4\pi\varepsilon_0 = 14.4 \text{ eV} \cdot \text{Å} = 2.3 \times 10^{-28} \text{ J} \cdot \text{m} \)

For a typical small ion \((r = 2 - 4\text{Å})\) the energy of transfer between water \((\varepsilon = 80)\) and interior of cellular membrane \((\varepsilon = 2)\) is about 30 – 60 kcal/mol.

The larger the ion, the easier is to transfer it to low dielectric medium.
Biological macromolecules are stabilized by physical interactions:

<table>
<thead>
<tr>
<th>Strong</th>
<th>Weak</th>
</tr>
</thead>
<tbody>
<tr>
<td>Covalent bonds</td>
<td>Ionic interactions</td>
</tr>
<tr>
<td>-200 - -800 kJ/mol</td>
<td>-40 - -400 kJ/mol</td>
</tr>
<tr>
<td>(-50 - -200 kcal/mol)</td>
<td>(-10 - -100 kcal/mol)</td>
</tr>
<tr>
<td>Ion-dipole interactions</td>
<td>Hydrogen bonds</td>
</tr>
<tr>
<td>Van der Waals interactions</td>
<td>Hydrophobic effect</td>
</tr>
</tbody>
</table>
Why care about electrostatics?

- Longest-range biologically relevant interactions.
- A lot of biological molecules are charged. Amino acids: Asp\(^-\), Glu\(^-\), Lys\(^+\) Arg\(^+\), His\(^+\); DNA: phosphates\(^-\) in backbone, lipids, salt ions, etc.
Electrostatic field

\[ V(r) = \frac{q_A}{4\pi\varepsilon\varepsilon_0 r} \]

\[ \vec{E}(r) = \frac{q_A}{4\pi\varepsilon\varepsilon_0 r^2} \left| \frac{\vec{r}}{r} \right| \]

\[ \vec{E} = -\nabla V(r) = -\left( \frac{\partial V(r)}{\partial x} \vec{i} + \frac{\partial V(r)}{\partial y} \vec{j} + \frac{\partial V(r)}{\partial z} \vec{k} \right) \]

Energy = \[ q_B V(r) \]

\[ \vec{F}(r) = q_B \vec{E} \]

Assumptions:

– homogeneous dielectric medium
– point charges
– no mobile ions
– infinite boundaries
**Electrostatic force**

\[ \vec{F}(r) = \frac{q_A q_B}{4\pi\epsilon\epsilon_0 r^2} \frac{\vec{r}}{|r|} \]

*Force on charge B due to charge A.*

---

**Superposition**

\[ U = \frac{q_{\text{ref}}}{4\pi\epsilon_0 \epsilon} \sum_i \frac{q_i}{|x_i - x_{\text{ref}}|} \]

\[ \mathbf{F} = \frac{q_{\text{ref}}}{4\pi\epsilon_0 \epsilon} \sum_i \frac{q_i}{|x_i - x_{\text{ref}}|^2} \frac{x_i - x_{\text{ref}}}{|x_i - x_{\text{ref}}|} \]
A mean field theory replaces the interaction between elements in the system by the interaction of a single element with an effective field, which is the sum of the external field and the internal field.
Bjerrum length.

The distance at which two unit charges interact with \( kT \) of energy.

\[
\begin{align*}
R T &= \ell_B \\
u(\ell) &= 2002
\end{align*}
\]

Approximately 7 Å for water \(( \varepsilon = 80) \) at 298 °K.

Electrostatic interactions are much stronger than most other non-bonded interactions; e.g., gravitational.

\[
\begin{align*}
k_B T &= \frac{e^2}{4\pi D \varepsilon_0 l_B} \\
\ell_B &= \frac{e^2}{4\pi D \varepsilon_0 k_B T}
\end{align*}
\]

\[
\begin{align*}
U_{\text{grav}} &= -\frac{G m_p^2}{r} \approx \frac{1.87 \times 10^{-64}}{r} \text{ J m} \\
U_{\text{elec}} &= \frac{e_c^2}{4\pi \varepsilon_0 r} \approx \frac{2.30 \times 10^{-28}}{r} \text{ J m}
\end{align*}
\]

\[
\frac{U_{\text{elec}}}{U_{\text{grav}}} \approx 1.23 \times 10^{36}
\]
**Flux of an electric field**

Fluxes arise from
- Sources: positive charges
- Sinks: negative charges

Electric field flux: integral of electric displacement over a surface.

\[
\Phi = \int_{\partial \Omega} \varepsilon \mathbf{E}(s) \cdot d\mathbf{s}
\]

- **Boundary surface of volume \( \Omega \)**
- **Electric displacement**
- **Jacobian; points in surface normal direction**
**Gauss’ law**

The integral of field flux through a closed, simple surface is equal to the total charge inside the surface

This is true for both homogeneous and inhomogeneous dielectric media

**Point charge in a sphere**

- Point charge has spherically-symmetric field
- Field is constant on sphere surface
- Flux is independent of sphere diameter

\[
\Phi = \varepsilon E(r) 4\pi r^2 = \varepsilon \frac{q}{4\pi\varepsilon_0 \varepsilon r^2} 4\pi r^2 = \frac{q}{\varepsilon_0}
\]
Field from a line charge

Assumptions:
- Homogeneous medium
- Line of length $L$, where $L$ is “very big” (radial symmetry)
- Linear charge density of $\lambda$

\[ \Phi = \oint_{\partial(\text{cylinder})} \varepsilon \mathbf{E}(\mathbf{s}) \cdot d\mathbf{s} \]
\[ = \int_0^{2\pi} \int_0^L \varepsilon E(r) r \, dz \, d\theta \]
\[ = 2\pi r L \varepsilon E(r) \]

\[ \Phi = \int_{\text{cylinder}} \rho(x) \, dx = \frac{q}{\varepsilon_0} = \frac{\lambda L}{\varepsilon_0} \]

\[ 2\pi r L \varepsilon E(r) = \frac{\lambda L}{\varepsilon_0} \]

\[ E(r) = \frac{\lambda}{2\pi \varepsilon \varepsilon_0 r} \]
Field around DNA

B-DNA shape:
• 2 phosphates every 3.4 Å
• water dielectric constant of 80

What is the field 40 Å away from a “very long” B-DNA molecule?

\[
E(r) = \frac{\lambda}{2\pi\varepsilon_0\varepsilon_r r} \\
\frac{(1.60 \times 10^{-19} \text{ C})}{(1.7 \times 10^{-10} \text{ m})} \div \frac{2\pi(8.854 \times 10^{-12} \text{ C}^2 \text{ J}^{-1} \text{ m}^{-1})(80)(4 \times 10^{-9} \text{ m})}{2\pi(8.854 \times 10^{-12} \text{ C}^2 \text{ J}^{-1} \text{ m}^{-1})(80)(4 \times 10^{-9} \text{ m})} = 5.29 \times 10^7 \text{ V m}^{-1}
\]
Field from a charged plane

Assumptions:

- Homogeneous medium
- Surface of area $A$
- Surface charge density of $\sigma$

\[
\Phi = \oint_{\partial\text{ (pillbox)}} \varepsilon \mathbf{E}(\mathbf{s}) \cdot d\mathbf{s}
\]

\[
= 2 \int_0^{2\pi} \int_0^{2\pi} \varepsilon E(r) r d\theta d\phi
\]

\[
= 4\pi R^2 \varepsilon E(r) = 2A \varepsilon E(r)
\]

\[
\Phi = \int_{\text{pillbox}} \rho(x) dx = \frac{q}{\varepsilon_0} = \frac{\sigma A}{\varepsilon_0}
\]

\[
2A \varepsilon E(r) = \frac{\sigma A}{\varepsilon_0}
\]

\[
E(r) = \frac{\sigma}{2\varepsilon \varepsilon_0}
\]

What is the field at distance $r$ from the source?
**Field around a membrane**

POPS membrane
- -1 e charge per lipid
- 1 lipid per 55 Å²

\[
\sigma = \left( \frac{1 \text{ e}}{55 \text{ Å}^2} \right) \left( \frac{1.60 \times 10^{-19} \text{ C}}{\text{e}} \right) \left( \frac{\text{Å}^2}{10^{-20} \text{ m}} \right) = 0.29 \text{ C m}^{-2}
\]

\[
E(z) = \frac{\sigma}{2\varepsilon_0\varepsilon} = \frac{0.29 \text{ C m}^{-2}}{2 \left( 8.854 \times 10^{-12} \text{ C}^2 \text{ J}^{-1} \text{ m}^{-1} \right)} = 8.19 \times 10^9 \text{ V m}^{-1}
\]

What is the field 20 Å away from the membrane (in water)?

Bigger than DNA!

Electric dipole moment

\[ \vec{p} = q \vec{r} \]

\[ \vec{p} = \sum_i q_i \vec{r}_i \]

Interaction energy of a dipole with a field

\[ U = -\vec{p} \cdot \vec{E} \]

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Dipole moment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>1.9</td>
</tr>
<tr>
<td>Ethanol</td>
<td>1.7</td>
</tr>
<tr>
<td>Acetic acid (neutral)</td>
<td>1.7</td>
</tr>
<tr>
<td>Acetone</td>
<td>2.88</td>
</tr>
<tr>
<td>Acetamide</td>
<td>3.8</td>
</tr>
</tbody>
</table>

1 Debye = 0.2 electron-Angstroms = 3.3x10^{-23} Cm
Charge-Dipole and Dipole-Dipole interactions

**Charge - Dipole**

\[ U = -\frac{qd \cos \theta}{4\pi\varepsilon_0 \varepsilon r^2} \]

with Brownian tumbling

\[ U = -\frac{q^2 d^2}{(4\pi\varepsilon_0 \varepsilon)^2 3kT r^4} \]

**Dipole-Dipole**

**static**

\[ U = \frac{d_1 d_2 K}{4\pi\varepsilon_0 \varepsilon r^3} \quad K – orientation factor dependent on angles \]

with Brownian motion

\[ U = -2 \frac{d_1^2 d_2^2}{3kT (4\pi\varepsilon_0 \varepsilon)^2 r^6} \]
Partial Charges

N-Acetyl-N’-Methylserinyl amide
Electrostatics of macromolecules

With point charges and a constant dielectric constant, $\varepsilon$, Coulomb's law allows calculation of a potential at any point.

$\text{Electrostatic potential} = V_{e_i} = \sum_{i} \frac{-Q_i}{\varepsilon |R_i|}$

$R_i =$ distance from probe to atom $i$

$Q_i =$ charge of atom $i$

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Electrostatically Accelerated Protein-Protein Association

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Potential gradients around the Glu-Arg dipeptide

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A continuum dielectric medium

- Reduces the strength of electrostatic interactions relative to a vacuum.
- It has no atomic detail.

An isotropic dielectric continuum exhibits the same response in all directions

- the dielectric tensor can be reduced to a scalar
- for a homogeneous isotropic Coulomb’s law takes a very simple, scaled form

\[-\nabla \cdot [\varepsilon(r) \nabla \varphi(r)] = \frac{\rho(r)}{\varepsilon_0}\]

\[-\nabla \cdot \nabla V(r) = \frac{\rho(r)}{\varepsilon_0 \varepsilon}\]

\[u(r) = \frac{q_1 q_2}{4\pi \varepsilon \varepsilon_0 r}\]
**Dielectric Boundaries**

- Boundary can be modeled as a step–function change in dielectric constant.
- The relevant form of the Poisson equation is:
  \[-\nabla \cdot [\varepsilon(r)\nabla \varphi(r)] = \frac{\rho(r)}{\varepsilon_0}\]
- The dielectric discontinuity can serve as a source of E-field lines even if there are no source charges there ($\rho = 0$).
When a charge approaches a dielectric discontinuity:

\[ q_{image} = -\left(\frac{\varepsilon_2 - \varepsilon_1}{\varepsilon_2 + \varepsilon_1}\right)Q = kQ \]

(charge is in medium with \( \varepsilon_1 \))

Force = \( kQ^2/(4\pi\varepsilon_0\varepsilon_1(2d)^2) \)

k < 0 when \( \varepsilon_1 < \varepsilon_2 \) (charge in low dielectric) → image charge of opposite sign, **force is attractive**.

k > 0 when \( \varepsilon_1 > \varepsilon_2 \) (charge in high dielectric) → image charge of same sign, **force is repulsive**.
**Induced dipole**

\[ \vec{p} = \alpha \varepsilon_0 \vec{E}_A \]

\( \alpha \) – polarizability of the molecule

Interaction energy between the induced dipole and the inducing field

\[ U = -\int \vec{p} \cdot d\vec{E} = -\int \alpha \varepsilon_0 \vec{E} d\vec{E} = -\frac{1}{2} \alpha \varepsilon_0 E^2 \]

Induced dipoles: dependent upon polarizability of molecule, how easily electrons can shuffle around to react to a charge
Induced dipoles and Van der Waals (dispersion) forces

\[ d = \alpha E \]
\[ d - \text{dipole moment} \]
\[ \alpha - \text{polarizability} \]

\[ U = -\frac{\alpha d^2}{(4\pi)^2 \varepsilon \varepsilon_0 r^6} \]

\[ U = -\frac{I_1 I_2 \alpha_1 \alpha_2}{(I_1 + I_2)3n^4 r^6} \]
\[ I_{1,2} - \text{ionization energies} \]
\[ \alpha_{1,2} - \text{polarizabilities} \]
\[ n - \text{refractive index of the medium} \]

Large planar assemblies of dipoles are capable of generating long-range interactions.
van der Waals interactions

This is a general term for the favorable interactions that occur between uncharged atoms.

Van der Waals forces include:
- permanent dipole-permanent dipole interactions
- permanent dipole-induced dipole interactions
- dispersion interactions

All have energies that depend on $1/\text{distance}^6$

We consider London dispersion interactions here:
- these are common to all atoms
- even atoms that have no permanent dipoles (e.g. Ar)
London dispersion interactions

also known as ‘temporary dipole-induced dipole’ interactions

consider an argon atom

on average, its electron distribution will be spherically symmetrical:

but at any instant, it will not be perfectly symmetric, e.g.:

when the distribution is like this, there will be an electronic dipole:

δ+ δ−
London dispersion interactions

- now consider a second atom adjacent to the first:

- it will be polarized by the first atom:

- this will lead to a favorable dipole-dipole interaction between the two atoms

- the interaction occurs because the electron distributions become correlated
London dispersion interactions

London J Chem Soc 33, 8-26 (1937)

The magnitude of this effect depends on the distance between the two atoms:

\[ E_{\text{dispersion}} \propto -1 / r^6 \]

It also depends on the atoms’ polarizabilities \( a \):

\[ E_{\text{dispersion}} \propto a_{\text{atom1}} \times a_{\text{atom2}} \]

\( a \) describes how much an electron distribution can fluctuate or respond to an applied electric field.
London dispersion interactions

*Relative polarizability generally increases with more electrons:

<table>
<thead>
<tr>
<th></th>
<th>Relative polarizability</th>
<th>Boiling point</th>
</tr>
</thead>
<tbody>
<tr>
<td>He</td>
<td>0.20</td>
<td>4</td>
</tr>
<tr>
<td>Ne</td>
<td>0.39</td>
<td>27</td>
</tr>
<tr>
<td>Ar</td>
<td>1.63</td>
<td>87</td>
</tr>
<tr>
<td>Kr</td>
<td>2.46</td>
<td>120</td>
</tr>
<tr>
<td>Xe</td>
<td>4.00</td>
<td>165</td>
</tr>
</tbody>
</table>

So more energy required to do this:

\[ \Delta H_{vaporization} \]
London dispersion interactions

```
the dispersion interaction between many atoms is usually approximated as a sum of London terms:

\[ E_{\text{dispersion}} = \sum E_{\text{London}}(r_{ij}) \]

for \( N \) atoms, the total energy will be a sum of \( N(N-1)/2 \) terms

this is the pairwise additivity assumption
```
**London dispersion + sterics**

- We can now consider the sum of the two types of interactions that we’ve seen so far.
- Consider approach of two uncharged atoms (e.g., Ar).

![Graph](image)

**Graph Description**
- The graph shows the energy (in kcal/mol) as a function of the distance between atoms (in Å).
- There are two terms: 
  - $\frac{1}{r^{12}}$ term
  - $\frac{1}{r^6}$ term
- The total energy is the sum of these two terms.

- Unfavorable electron overlap dominates at short distance.
- Favorable dispersion interaction dominates at ‘long’ distance.
so favorable interactions with close-packed atoms in the folded state are partly balanced by:

favorable interactions with water molecules in the unfolded state

the density of atoms is higher in a protein’s folded state than in water (proteins are very tightly packed) so dispersion interactions will stabilize proteins
Dispersion interactions in nature

Geckos get a grip using Van-der-Waals-forces

The Gecko toe has 500,000 microhairs (setae)

The seta has 1,000 nanohairs

Nanostructure of the Gecko toe
Technical surface 1
Contact area
Technical surface 2

If all of a gecko’s setae were stuck to a surface at the same time it would be able to support 140 kg!

Small contact area 
Large adhesion force

Adhesion effect through Van-der-Waals-forces

Nanohairs!

Microhair
Small insects: Compliant pads (to shape themselves to rough surfaces) + sweat

Medium insects: Multiple pads per leg + sweat

Spiders and lizards: Lots of pads (hair) per foot - but dry / no secretions

("From micro to nano contacts in biological attachment devices," Arzt et al., PNAS 100(19) 2003)
### Electrostatic Steering

<table>
<thead>
<tr>
<th>System</th>
<th>Potential dependence on distance</th>
<th>Energy [kJ/mol]</th>
</tr>
</thead>
<tbody>
<tr>
<td>ion-ion</td>
<td>$r^{-1}$</td>
<td>250</td>
</tr>
<tr>
<td>ion-dipole</td>
<td>$r^{-2}$</td>
<td>15</td>
</tr>
<tr>
<td>dipol – dipol</td>
<td>$r^{-3}$</td>
<td>2</td>
</tr>
<tr>
<td>London</td>
<td>$r^{-6}$</td>
<td>1</td>
</tr>
</tbody>
</table>

**Legend:**
- **Dipole - dipole interactions**
- **Dipole - induced dipole interactions**
- **Induced dipole - induced dipole interactions**
Interaction between ions and macromolecules

**Non-specific screening effects**
- Depends only on ionic strength (not species)
- Results of damped electrostatic potential
- Described by Debye-Hückel and Poisson-Boltzmann theory for low concentration

**Site-specific binding**
- Ionic specific (concentration of specific ion, not necessarily ionic strength)
- Site geometry, electrostatics, coordination, etc. enables favorable binding
- Influences
  - Co-factors
  - Allosteric activation
  - Folding (RNA)
Polar solvation: Poisson equation

- Poisson equation
  - Classic equation for continuum electrostatics
  - Can be derived from hard sphere dipolar solvent
- Assumptions
  - No dielectric saturation (linear response)
  - No solvent-solvent correlation (local response)

\[-\nabla \cdot \varepsilon(x) \nabla u(x) = 4\pi \rho(x) \quad \text{for } x \in \Omega\]

\[u(x) = u_0(x) \quad \text{for } x \in \partial \Omega\]
**Polar solvation: Boltzmann equation**

- Mean field model
  - Include “mobile” charges
  - Boltzmann distribution
  - Ignore charge-charge correlations
    - Finite ion size
    - Weak ion-ion electrostatics
    - Low ion correlations
- Missing ion “chemistry”
  - No detailed ion-solvent interactions
  - No ion coordination, etc.

\[
\rho(x) = \rho_f(x) + \rho_m(x) \\
= \rho_f(x) + \sum_i q_i c_i e^{-q_i u(x) - V_i(x)}
\]
**Poisson-Boltzmann equation**

The space – dielectric properties

**Mobile charge distribution**

\[ 4\pi \rho(x) \]

\[ -\nabla \cdot \varepsilon(x) \nabla \phi(x) = 4\pi \sum_i q_i \delta(x - x_i) + 4\pi \rho(x) \]

\[ \phi(\infty) = 0 \]
**Mobile ion charge distribution form:**

- Boltzmann distribution – no explicit ion-ion interaction
- No detailed structure for atom (de)solvation

\[
\rho(x) = \sum_{m} Q_m \bar{n}_m e^{-\beta Q_m \phi(x) + V_m(x)}
\]

- \( \rho(x) \) is the charge density
- \( Q_m \) are the ion charges
- \( \bar{n}_m \) are the ion bulk densities
- \( \phi(x) \) is the electrostatic potential
- \( V_m(x) \) are the ion-protein steric interactions

**Result:** Nonlinear partial differential equation

\[
-\nabla \cdot \varepsilon(x) \nabla \phi(x) - 4\pi \sum_{m} Q_m \bar{n}_m e^{-\beta Q_m \phi(x) + V_m(x)} = 4\pi \sum_{i} q_i \delta(x - x_i)
\]

\[
\phi(\infty) = 0
\]
For not very high ion concentrations $\kappa a << 1$

$$V(r) = \frac{z_+e}{4\pi\varepsilon\varepsilon_0 r} e^{-\kappa r}$$

- Viewed from beyond the counterion cloud, the macroion appears neutral.

- Macroions will not feel each other until they’re nearby.

- Once they are nearby, the detailed surface pattern of charges can be felt by its neighbor, not just overall charge-streospecificity.
Hydrogen bonds

The covalent bond between H and O in water is about 492 kJ mol\(^{-1}\).

The hydrogen bonds is in the range of 3 - 40 kcal mol\(^{-1}\).

The van der Waals interaction is about 5.5 kJ mol\(^{-1}\).
A hydrogen bond consists of a hydrogen atom lying between two small, strongly electronegative atoms with lone pairs of electrons (N, O, F).

The hydrogen bond is stronger than typical electrostatic interactions between partial charges, but it is easily disassociated by heat or by interaction with other atoms.
Distance

Van der Waals radius of

H: 1.1Å, O 1.5 Å.

The closest approach should be 2.6 Å.

Separation is about 1 Å less! It is 1.76 Å.

Intermediate between VdW distance and typical O-H covalent bond of 0.96Å.

The shorter the distance between D & A the stronger the interaction.
Hydrogen bond is directional

Hydrogen bond potential energy

\[ U = \left( \frac{A}{r^{12}} - \frac{B}{r^6} \right) \cos \theta + \left( \frac{A'}{r'^{12}} - \frac{B'}{r'^6} \right) (1 - \cos \theta) \]
The hydrogen bonds define secondary structure of proteins. They are formed between the backbone oxygens.

Hydrogen bonds define protein binding specificity.