Molecular Modeling -- Lecture 15
Surfaces and electrostatics

Molecular surfaces
The Hydrophobic Effect
Electrostatics
Poisson-Boltzmann Equation
Electrostatic maps
Electrostatic surfaces in MOE
• 15.1 The hydrophobic effect
Molecular surface

Water that sits on the surface behaves differently than water that is surrounded by water. So, surfaces can be used to model solvation.
How does water interact with a polar versus a non-polar surface?

- Water has a partial charge separation along the O-H bonds -- a dipole.

- On a **polar** surface it loses entropy and gains enthalpy through Coulombic interactions (charge-charge).

- On a **non-polar** surface it loses entropy and does not gain enthalpy.
Shape dependence.

- Water loses entropy in proportion to degrees of freedom lost. A water on a convex surface loses less entropy than a water in a concave surface.
Hydrophobic collapse releases high energy waters in proportion to the buried surface area.

Purple waters have reduced entropy. Only the waters associated with the blue group are shown. The green group also has its low-entropy waters.
Nature abhors a vacuum

There is only one way to make space empty, but many ways to fill it.

The entropy is larger if the number of different states available to the system is larger.

Lower entropy implies higher free energy (unfavorable).
Better fit, less wasted space, lower energy.

If we compare two surface-surface interactions, all else being equal, the one with more void spaces has a higher free energy, and is therefore less favorable. The one that fills space has a lower energy.
The Hydrophobic Effect

What happens to the **surface** as two hydrophobic spheres come together??

closest positions of probe centers
The Hydrophobic Effect

White area is excluded volume. Water can't go closer than one radius (1.4 Å).
The Hydrophobic Effect

First, SAS (green) is increased by new "toroidal" surface (brown).
The Hydrophobic Effect

Toroidal surface (brown) grows faster than atom surface is lost. SAS goes up.
The Hydrophobic Effect

At short distance, toroidal surface stops growing, atom surface shrinks faster.
Is there an energy barrier to hydrophobic collapse? (yes)

Solvation energy $\Delta G$ parallels SES, not SAS or excluded volume. Thus hydrophobic surface area is related to solvation energy.

$\Delta G^{**}$

Distance between pairs of hydrophobic spheres of radius 1.5Å

**(Rank & Baker, Czaplewski & Sheraga)**
Summary

• The **hydrophobic effect** is related to water -- specifically to the solvation of the hydrophobic surface.

• The **solvation energy** is composed of enthalpy (Coulombs law) and entropy. Loss of entropy depends on the surface **shape**.

• There is a **barrier** to hydrophobic collapse, caused by transient shape changes.
• 15.2 Electrostatics
**Partial charges**

*Quantum mechanical* calculations can tell us the electron distributions around atom nuclei. If there are more or less electrons that belong to a given atom nucleus, it has a non-zero charge.

- **Formal charge** is the net charge of an ion or ionized group.
- **Partial charge** is the charge introduced by polarization of electron clouds.

E.g. the backbone amide group N-H. Which atoms has partial positive charge and which has partial negative charge? What about the carbonyl group C=O?

Critical for calculating the electrostatic potential map and surface!
Coulomb's Law: Energy of a charge-charge interaction

\[ E = \frac{q_i q_j}{\varepsilon r_{ij}} \]

where \( q_i \) is the charge on particle \( i \), \( q_j \) is the charge on particle \( j \), \( r_{ij} \) is the distance between them, and \( \varepsilon \) is the dielectric constant.

This is the energy required to bring two charges from infinite distance to the distance \( r_{ij} \) in a medium with dielectric constant \( \varepsilon \).
Dielectric (dielectric?)

The dielectric $\varepsilon$ is the degree to which a medium disperses charge, or the ability to reduce electrostatic interaction. Charge dispersion can happen by rotating dipoles (like water) or by induced polarization (aromatics).

In a higher dielectric, the charges feel less force. The energy to pull two like charges together is less, and the energy to push two opposite charges apart is less.

Water has $\varepsilon$ of $\sim 80$, while inside the hydrophobic core of a protein $\varepsilon$ is 2-4.

$$E = \frac{q_i q_j}{\varepsilon r_{ij}}$$

$(\varepsilon \text{ must be } \geq 1.000 \text{ (vacuum)})$
Assuming a dielectric constant $\varepsilon$, the energy for putting a charge $q$ at any position $r$ is summed using Coulomb's Law. Then, we define the electrostatic potential as $\Phi=E/q$. In this space we can draw contours where $\Phi$ is constant (isopotential surfaces). Isopotential surfaces are useful for considering the docking of charged or polar ligands to a protein.
Electrostatic potential map of a non-homogeneous medium

An electrostatic potential map $\Phi(x)$ is the energy landscape for a point charge brought from infinite distance to point $x$.

(a) the electrostatic potential map for a single charge in low dielectric (membrane). (b) High dielectric (water). (c) point charge on the surface of a membrane.
Charge density

Like mass density, charge density is the sum over all point sources of charge, divided by the volume. In this case, however, the value summed is signed. The charge density at \( r \), \( \rho(r) \), can be expressed as,

\[
\rho(r) = \sum_{i=1}^{N} q_i \delta(r - r_i)
\]

Where \( q_i \) is the charge (which may be a partial charge).

\( \delta(r-r_i) \) is the delta function, which is 1 if \( r = r_i \) and zero otherwise.
An electric field $\mathbf{E}(r)$ is the amplitude and direction of force on a particle of unit (+) charge, sitting at location $r$, which depends on the charge density distribution $\rho(r)$.

$$\mathbf{E}(r) = \frac{1}{4\pi\varepsilon_0} \iiint \frac{\mathbf{r} - \mathbf{r}'}{||\mathbf{r} - \mathbf{r}'||^3} \rho(r') \, d^3r'.$$

The electric field is the gradient of the electrostatic potential map.
Poisson's equation

If charges are movable in the space r, then charge density \( \rho(r) \) can move to find the lowest energy. The condition for this equilibrium is that the charge density \( \rho(r) \) is everywhere inversely proportional to the curvature of the electrostatic potential.

\[
\nabla^2 \phi(r) = -\frac{\rho(r)}{\varepsilon}
\]

The Laplacian of \( \phi \).

\( \nabla \) "del" means the gradient, or 3-dimensional 1st derivative \((d/dx)i+(d/dy)j+(d/dz)k\)

\( \nabla^2 \) means \( \nabla \cdot \nabla \), the "divergence" of the gradient.

\( \nabla^2 \phi \) is the 3-dimensional 2nd derivative. It expresses the degree to which a point in space is a "sink" or a "source". Think mountain or valley.

So... if we know \( \rho \), we can get \( \phi \), by solving Poisson’s equation.

**DelPhi** is a program that calculates the electrostatic potential map, developed by Barry Honig at Columbia University.
Two problems when calculating electrostatics...

(1) Mobile charges redistribute themselves in the electric field.

When an ion moves to a position of opposite electrostatic potential, it changes the charge distribution \( \rho(r) \), which in turn changes the electrostatic potential. E.g. \( \text{Na}^+ \) and \( \text{Cl}^- \) in a protein solution or in our body.

(2) We can't assume that the dielectric is a constant throughout our system.

The dielectric is the ability of the medium to disperse the charge. Solid or semisolid objects have a much lower dielectric than liquids, especially polar liquids like water.
Boltzmann distribution of charges

Boltzmann states that the number density of ions in an electric field or map is related to the electrostatic potential as follows:

\[ \rho(r) = Ie^{-\frac{-\phi(r)}{k_bT}} \]

number density of ions (charges) \[\rho(r)\]

bulk number density \[\approx\] ionic strength \[Ie\]

energy to bring a charge to point \(r\) from infinity \[-\phi(r)\]

Boltzmann constant \[k_bT\]

So.... if we know \(\phi\), we can get \(\rho\) by solving the Boltzmann equation.

NOTE: take the log of both sides, change variable names and you get Gibbs Free Energy: \[\Delta G = -RT\log(K_{eq})\]
Poisson-Boltzmann equation

\[ \nabla \cdot \varepsilon(r) \nabla \phi(r) - \kappa \phi(r) = -4\pi \rho(r) \]

Features of the P-B equation:

• It expresses the relationship between the electrostatic potential and the charge distribution.

• It has a position specific dielectric \( \varepsilon(r) \).

• It has a position specific charge density \( \rho(r) \).

• It has a position specific electrostatic potential \( \phi(r) \).

• It has a Boltzmann correction \( \kappa \) to account for redistributed charges.

• The P-B equation must hold for any two functions \( \rho \) and \( \phi \).

• \( \rho \) and \( \phi \) are solved numerically, over the space \( r \).
Variable dielectric

Generally, we assume there is a $\varepsilon$ for inside the protein (green, $\varepsilon=2$ or 4), and a $\varepsilon$ for outside in the solvent ($\varepsilon=80$).
P-B algorithm

Until converged {
    For each grid point,
        Calculate the 2nd derivative of the electrostatic potential \( \phi \) given the charge density \( \rho \), in each direction.

    For each grid point,
        Calculate the new charge density \( \rho \) given the 2nd derivative of the electrostatic potential \( \phi \).

}
Projecting the electrostatic potential onto the surface

For each point on the molecular surface {
    Find the 8 bordering gridpoints.
    Find the electrostatic potential $\phi$
    by 3-way linear interpolation.
    Convert to a color.
}
Projecting the electrostatic potential onto the surface

Active sites and binding surfaces can be found by coloring the surface by the electrostatic potential. Here we ignore all grid points except the ones closest to the surface.

A ligand should have a complementary electrostatic surface AND a complementary shape!
Exercise/Demo:
Use MOE to view the electrostatics on the molecular surface

- Display the Connolly surface of the protein.
- Calculate the electrostatic potential.
- Limit the surface by selected atoms.
- Show complementary surfaces. (1bgs chains A and E)
- Slice through the surface.