Implicit Models of Solvation

- Goal: Reasonable treatment of water (solvation free energies) without explicit solvent.
- Can dramatically improve speed of simulations; in explicit solvent simulations, most computational power goes towards treating water, most of which is not near protein.
- Focus will be on models of solvation based on continuum electrostatics.
Hierarchy of Solvent Models

Quantum Mechanics

Polarizable explicit solvent

Fixed charge explicit solvent

Nonlinear Poisson-Boltzmann

Linear Poisson-Boltzmann

Generalized Born

Distance-dependent dielectric

Surface area based models
Introduction to PB

• Basic idea: Treat solvent as a dielectric continuum. Essentially exact within the constraints of this approximation.
• The continuum approximation simply cannot account for a number of important “first-shell” solvation effects related to the size of a water molecule. There is no information about the size of a water molecule with PB treatments.
• Numerical solution of the continuum electrostatics introduces additional approximations.
• Barry Honig was one of the first people to recognize the usefulness of PB for macromolecules, and developed the most important program, Delphi.
• There are other methods that are formally similar, e.g., the Langevin dipole method of Warshel. But PB has had the largest impact by far.
The Poisson Part of PB

\[ \nabla \cdot \varepsilon(\vec{r}) \nabla \varphi(\vec{r}) = -4\pi \rho(\vec{r}) \]

\[ \varphi(\vec{r}) = \text{electrostatic potential} \]
\[ \varepsilon(\vec{r}) = \text{dielectric constant (small inside protein; 80 outside)} \]
\[ \rho(\vec{r}) = \text{charge density (partial charges inside; ions outside)} \]

This is one of the fundamental equations of classical electrostatics. In fact, Coulomb's law can be derived as a special case where the dielectric is constant.

The treatment of charge density due to ions in solution needs special consideration. Can build a model based on the assumptions of Debye-Huckel theory; that's how we get the Boltzmann part ...
Ionic Contributions to Charge Density

Debye-Huckel theory gives the density of ions as

\[ \rho_i(\vec{r}) = \rho_i^0 e^{-q_i \phi(\vec{r})/kT} \]

Ionic density in bulk solution

This just gives a model for the enrichment of, e.g., negative ions in places where the potential is positive. So, for a 1:1 salt solution, we have

\[ \rho_{ionic}(\vec{r}) = \rho_+(\vec{r}) + \rho_-(\vec{r}) = \rho^0 e^{-\phi(\vec{r})/kT} - \rho^0 e^{+\phi(\vec{r})/kT} = 2\rho^0 \sinh\left(\frac{\phi(\vec{r})}{kT}\right) \]

The general result is written as ...
The Boltzmann Part of PB

\[ \nabla \cdot \varepsilon(\vec{r}) \nabla \varphi(\vec{r}) - \kappa \sinh[\varphi(\vec{r})] = -4\pi \rho(\vec{r}) \]

This is the nonlinear PB equation. Note that the charge density on the right side is now just the partial charges in the cavity. In many applications, the ionic strength term is “linearized”, by expanding it in a Taylor series and taking the first term:

\[ \sinh[\varphi(\vec{r})] = \varphi(\vec{r}) + \frac{\varphi(\vec{r})^3}{6} + \cdots \approx \varphi(\vec{r}) \]

\[ \nabla \cdot \varepsilon(\vec{r}) \nabla \varphi(\vec{r}) - \kappa \varphi(\vec{r}) = -4\pi \rho(\vec{r}) \]

This is reasonable when the ionic strength of the solution is not too high. The linear PB equation is computationally simpler to solve, but the nonlinear PB equation is probably safer for things like DNA/RNA where ionic strength effects are known to be important.
**Finite Difference Solutions for PB**

• Delphi uses this method.
• Lay down a 3D grid around the protein. The PB equation must be satisfied at every grid point. Derivatives in the PB equation replaced by finite differences over this cube.
• Partial charges of protein must be distributed onto grid (similar to PME). Dielectric constant simple to assign.
• The value of the potential at each grid point depends on the neighboring grid points. Thus you need an iterative solution.
• The accuracy of this method depends critically on the fineness of the grid. Can perform a series of calculations with increasing grid size ("focusing").

The PB equation can also be solved by a boundary element method. The two approaches are formally equivalent. My understanding is that FD is more efficient for nonlinear PB, but BE may be more efficient for linear PB.
What is the internal dielectric constant of a protein/membrane?

• Nonpolar organic molecules have dielectric constant of ~2-4. This is due primarily to electronic polarizability. This is a reasonable estimate for the internal dielectric of a protein.

• Some computational work, e.g., predicting the pKa’s of groups inside proteins, has shown better agreement with experiment using larger values of the internal dielectric, such as 20. Some experiments have also suggested large internal dielectrics.

• However, these large values may reflect effects that should not be considered as part of the dielectric constant, specifically
  1) Conformational relaxation. When the charge state of a group changes, the rest of the macromolecule can respond to help stabilize it. However, most PB calculations are done with a fixed structure; using a high dielectric introduces an artificial screening that can crudely mimic the effects of relaxation.
  2) Protonation state changes. Changing the charge state of a group can induce other protonation states to change. If this is not explicitly taken into account, the effective dielectric again appears to be bigger.
Grasp

This is a general program for visualizing various properties on the surface of a macromolecule (developed by Nicholls and Honig), but the most important application is visualizing the electrostatic field (i.e., as the field lines intersect the surface).

Red = negative
Blue = positive
Electrostatic forces speed the binding of the positively-charged substrate to acetylcholinesterase by a factor of more than 100.

AChE and Fasciculin 2 bind with electrostatically-steered, diffusion-controlled kinetics.

Honig group, Columbia U.
Applications of PB. 2. Role of electrostatics in ion channels

Continuum electrostatics calculations based on the finite-difference Poisson-Boltzmann equation are used to show that the cavity and the pore helices of the KcsA channel are "tuned" to be preferably occupied by a monovalent cation. Note that the role of helix dipole in other proteins is controversial, but in membranes (low dielectric), seems to be fairly strong.

Applications of PB. 3. pKa calculations

The effective pKa of a group (e.g., carboxylate) can be strongly perturbed by its environment in a macromolecule. For example, a carboxylate that forms a salt bridge with Arg or Lys is more likely to be negatively charged, while a carboxylate buried in a hydrophobic cavity is more likely to be neutral (desolvation of a unit charge costs about 60 kcal/mol!).

PB calculations can quantify this effect, and predict how the effective pKa (i.e., the pH at which the group is 50% protonated) shifts from the nominal value.

\[
pK_{d}^{macro} = pK_{d}^{model} - \frac{(\Delta G_{i}^{macro} - \Delta G_{i}^{model})}{2.303RT}
\]

The tricky part is that the pKa of the group will depend on protonation states of all other titratable side chains; need some sort of optimization strategy.
Implicit Solvent vs. Explicit Solvent

• Implicit solvent generally cannot be used when trying to learn about dynamics or kinetics, which are obviously influenced by the granularity of water. Dynamics are generally much faster in implicit solvent.

• Keep in mind that the key issue is not the cost of calculating an energy of interaction between the protein and explicit solvent, but getting a solvation free energy (i.e., ensemble averaging over solvent configurations).

• Explicit solvent models, and periodic boundary conditions, of course are not free from artifacts.

• From my research and others, it is clear that implicit solvent models can have a tough time with charged systems. Water in confined spaces is another tricky issue.
Breakdown of implicit solvent

solid line: explicit solvent (+ charge in surface)
dashed line: explicit solvent (- charge in surface)
dotted line: PB

Note the massive errors of PB in the convex surface case. Also, note the asymmetry of the explicit solvent results due to interchanging charges.