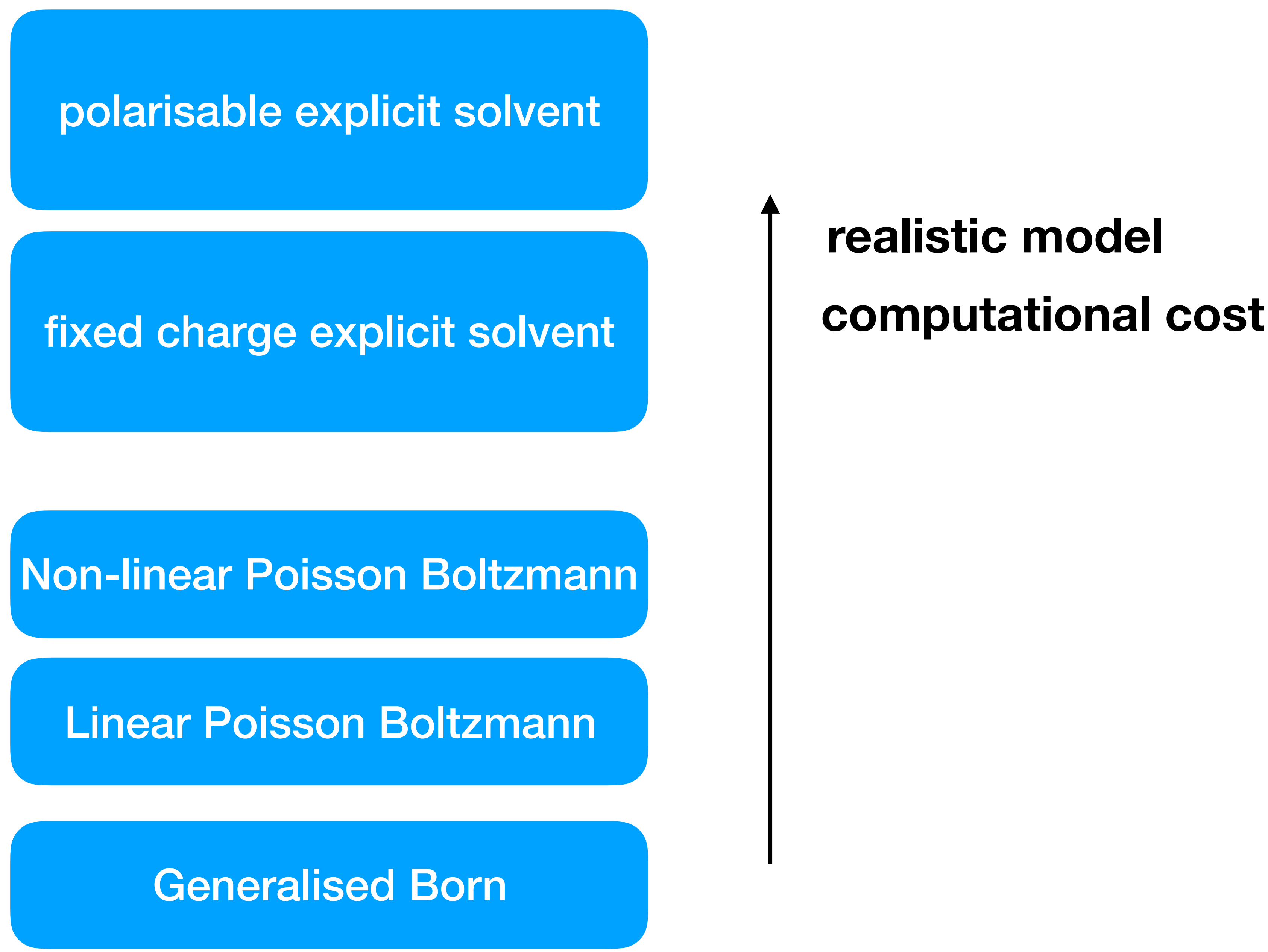
Lecture 12

CHM695
Feb 13

Implicit Solvet Models

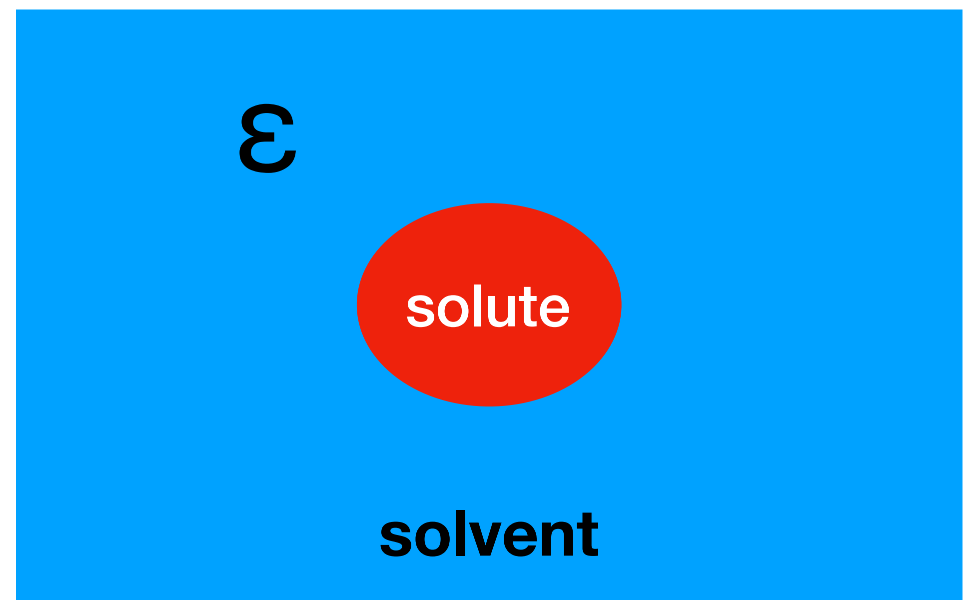
- Hierarchy of solvent models:



Poisson Boltzmann Techniques

- Solvent is treated as dielectric continuum

No explicit solvents - thus no direct interactions with first shell solvation can be treated



Classical electrostatics:

$$\nabla \cdot [\epsilon(\mathbf{r})\,\nabla\phi(\mathbf{r})] = -4\pi\rho(\mathbf{r})$$

dielectric

el. potential

charge density due to solute charges

Now we need to include charge density due to ions in solutions

Debye-Hueckel theory:

$$\rho_I(\mathbf{r}) = \rho_I^0 \exp\left(-\frac{q_I \phi(\mathbf{r})}{kT}\right)$$

$$\nabla \cdot [\epsilon(\mathbf{r})\, \nabla\phi(\mathbf{r})] = -4\pi\rho(\mathbf{r}) - 4\pi \sum_I \rho_I^0(\mathbf{r}) \exp\left(-\frac{q_I \phi(\mathbf{r})}{kT}\right)$$

This is non-linear form of PB equation. Solving this equation is complicated.

If solvent ionic strength is not very large, then we can linearise the Boltzmann part.

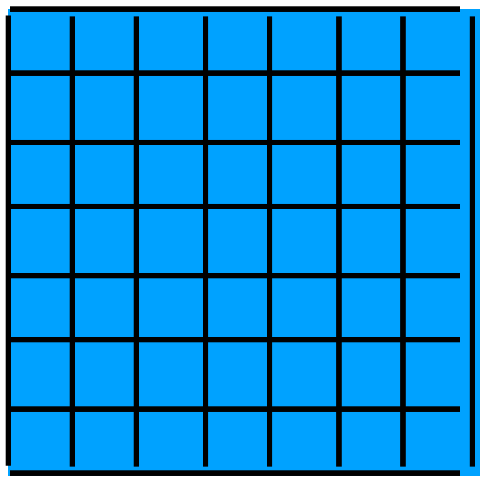
$$\nabla \cdot [\epsilon(\mathbf{r})\, \nabla\phi(\mathbf{r})] = -4\pi\rho(\mathbf{r}) - \sum_I \kappa_I \phi(\mathbf{r})$$

$$\nabla \cdot [\epsilon(\mathbf{r}) \nabla\phi(\mathbf{r})] = -4\pi\rho(\mathbf{r}) - \sum_I \kappa_I \phi(\mathbf{r})$$

dielectric properties of solute & solvent

solute charge distribution

accessibility of ions to solute interior

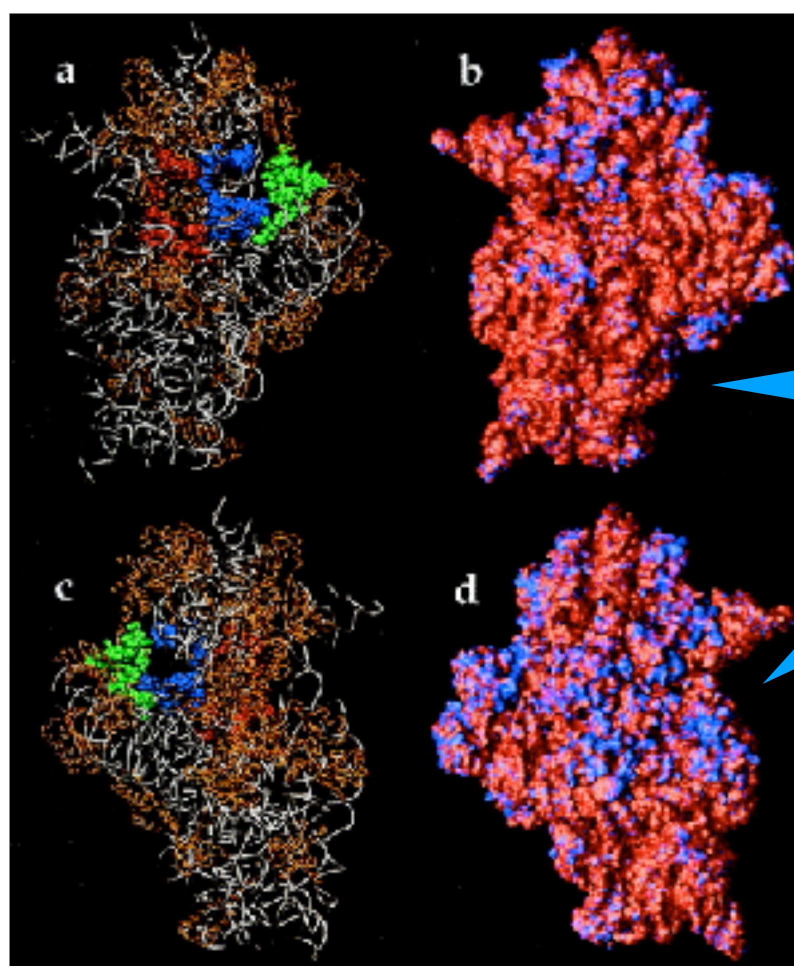


Solved by finite difference methods (on grids)

http://honig.c2b2.columbia.edu/delphi

Solvent dielectric: ~80

Solute dielectric: 2-20



Electrostatic properties of the 30S ribosomal subunit. Potential obtained by solution of the LPBE at 150 mM ionic strength with a solute dielectric of 2 and a solvent dielectric of 78.5 by using the 30S structure from the 1FJG Protein Data Bank entry.

$\phi(r)$

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Electrostatics of nanosystems: Application to microtubules and the ribosome

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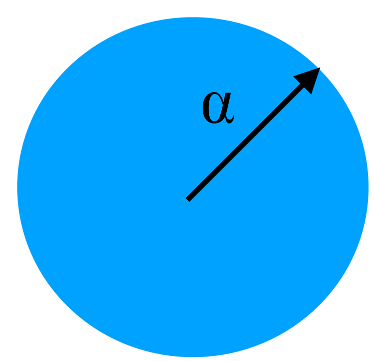
Generalized Born Model (GBM)

- Considering solute molecules as spheres (or within cavities)
- Single charge in the centre of a sphere has the following solution for GB equation:

$$\Delta G_{\mathrm{solv}} = -\frac{1}{2}\left(1 - \frac{1}{\epsilon_{\mathrm{ext}}}\right)\frac{q^2}{R}$$

Born radii

We will use α for Born radii hereafter



If an atom is solvent exposed, R is close to atomic radius (but larger).

For atoms buried inside, R can be quite large.

- Pair form of GB equation

$$\Delta G_{\text{solv}} = \sum_I \Delta G_I^{\text{self}} + 2 \sum_I \sum_{J>I} \Delta G_{IJ}^{\text{pair}}$$

$$\Delta G_{IJ}^{\text{pair}} = -\frac{1}{2}\left(1 - \frac{1}{\epsilon_{\text{ext}}}\right) \frac{q_I q_J}{\sqrt{R_{IJ}^2 + \alpha_I \alpha_J \exp\left(-\frac{R_{IJ}}{4\alpha_I \alpha_J}\right)}}$$

Born radii

Onufriev A, Case DA, Bashford D (Nov 2002). "Effective Born radii in the generalized Born approximation: the importance of being perfect". Journal of Computational Chemistry. ***23*** *(14): 1297–304. doi:10.1002/jcc.10126. PMID 12214312.*

Solvent Accessible Surface Area

- The generalized Born model only describes the polar, i.e., hydrophilic, energy of solvation.

- It is desirable to account also for the nonpolar, i.e., hydrophobic, energy of solvation through a solvent-accessible surface area (SA) calculation, as it is known that the hydrophobic solvation energy is approximately proportional to SA.

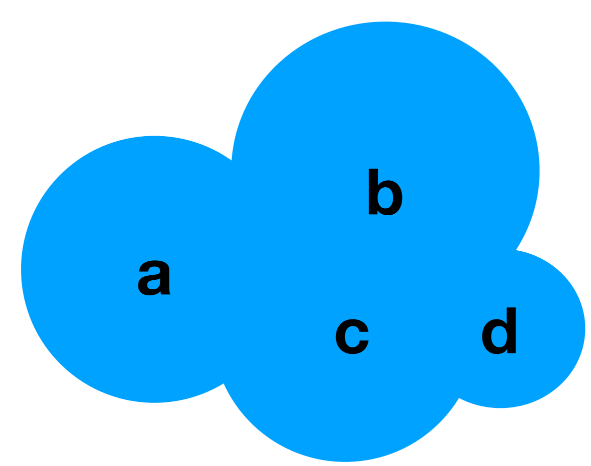
LCPO method (Linear combination of pairwise overlaps)

- The LCPO method, which considers only non-hydrogen atoms, is founded on calculating the surface area overlap between two spheres representing atoms

$$A_{IJ} = 2\pi R_I \left[R_I - \frac{R_{IJ}}{2} - \left(R_I^2 - R_J^2 \right) / \left(2R_{IJ} \right) \right]$$

area of I overlapped with J

vdW radii + 1.4 Ang.



total surface area of an atom i

$$
\begin{aligned}
\mathrm{SA}_i = {} & P_{1,i} 4\pi R_i^2 + P_{2,i} \sum_{j \in N(i)} A_{ij} \\
& + P_{3,i} \sum_{j \in N(i)} A_{ij} \sum_{k \in N(i) \cap N(j)} A_{jk} \\
& + P_{4,i} \sum_{j \in N(i)} [A_{ij} \sum_{j \in N(i)} \sum_{k \in N(i) \cap N(j)} A_{jk}]
\end{aligned}
$$

parameters

force due to SA area on atom *l*

$$
\vec{F}_l^{\,\mathrm{SA}} = -T_S \sum_{i \in N(l)} (d\mathrm{SA}_i / d r_l)
$$

- **Applications:**

a) MM-PBSA: a popular method for ligand binding
b) pKa computation of ligands in proteins
c) protein folding
d) protein aggregation

Advantages:
(a) computationally cheap;
(b) energy minimisations of structure & potential energy based predictions

D**isadvantages**:
(a) GB is very crude and empirical - but PB is more reliable, however, expensive
(b) derivatives are computationally expensive or not accurate (due to numerical issues using GB models)

- Read the link: http://ambermd.org/tutorials/basic/tutorial1/section4.htm

- Workout the tutorial: http://ambermd.org/tutorials/basic/tutorial3/index.htm