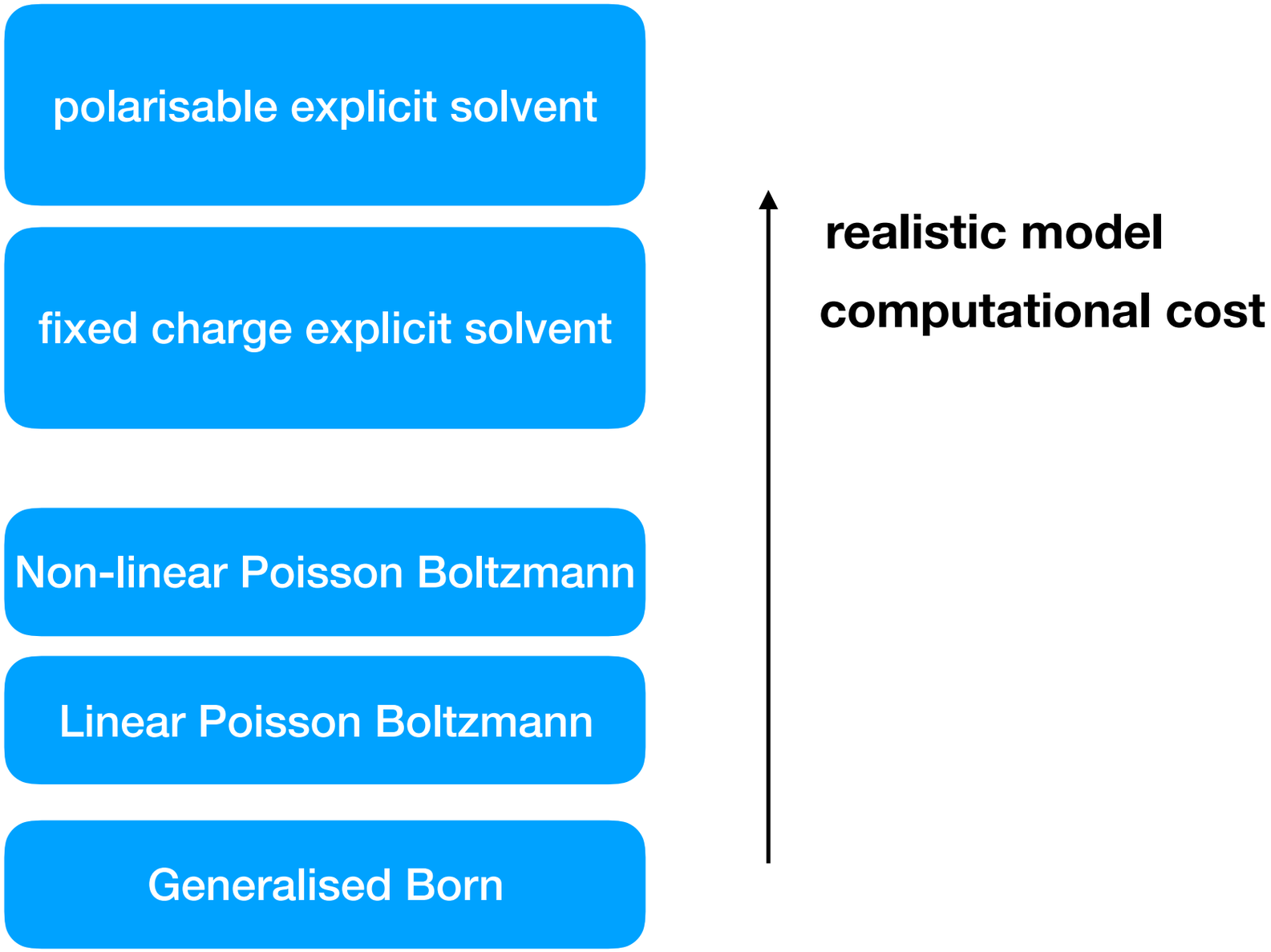
# Lecture 12

CHM695
Feb 13

# Implicit Solvet Models

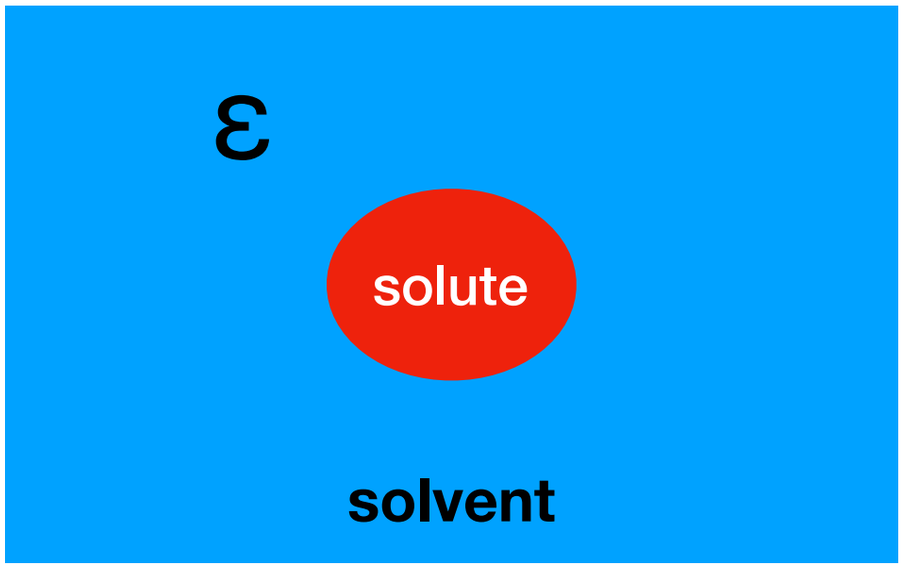
- Hierarchy of solvent models:



# 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:**

dielectric

el. potential

charge density due to solute charges

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

## Debye-Hueckel theory:

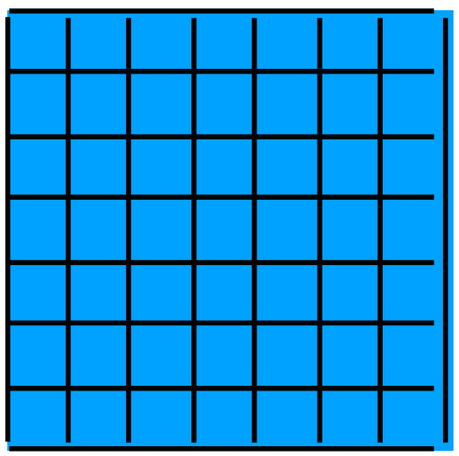
**This is non-linear form of PB equation. Solving this equation is complicated.**

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

dielectric properties of solute & solvent

solute charge distribution

accessibility of ions to solute interior

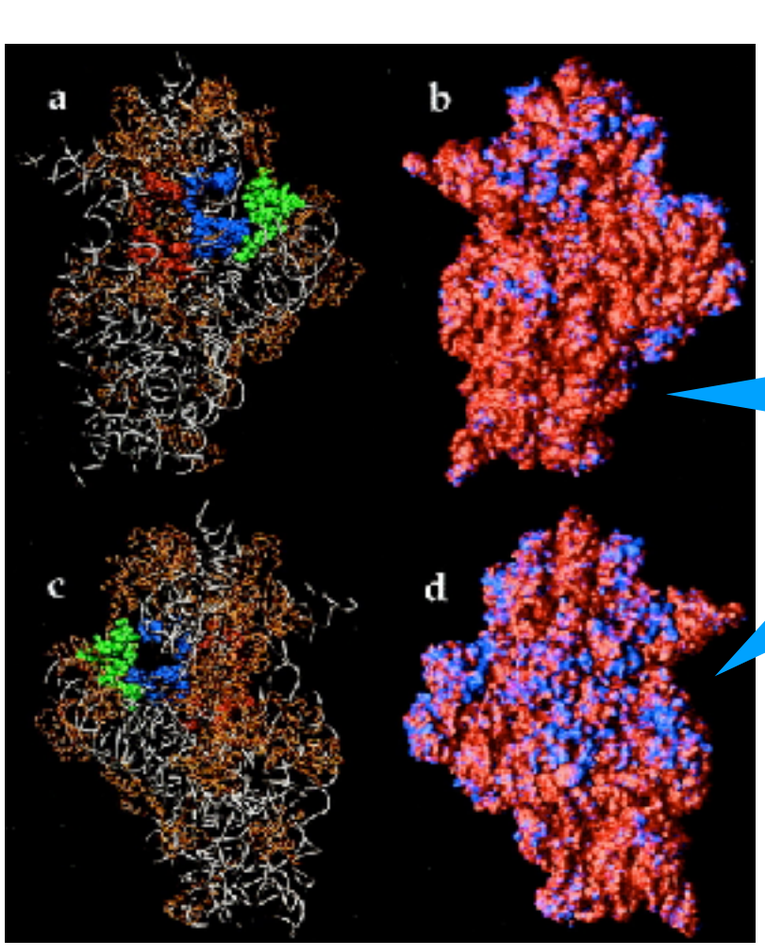


**Solved by finite difference methods (on grids)**

**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.

$\phi(r)$

PNAS | August 28, 2001 | vol. 98 | no. 18 | 10037–10041

## Electrostatics of nanosystems: Application to microtubules and the ribosome

Nathan A. Baker*†‡, David Sept§, Simpson Joseph*, Michael J. Holst¶, and J. Andrew McCammon*†‖

Departments of *Chemistry and Biochemistry, ¶Mathematics, and ‖Pharmacology, and †Howard Hughes Medical Institute, University of Califo at San Diego, 9500 Gilman Drive, La Jolla, CA 92093; and §Department of Biomedical Engineering, Washington University, One Brookings Dri St. Louis, MO 63130-4899

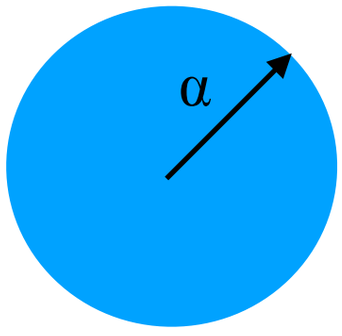
# Generalized Born Model (GBM)

- 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 $\alpha$ 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

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

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

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.

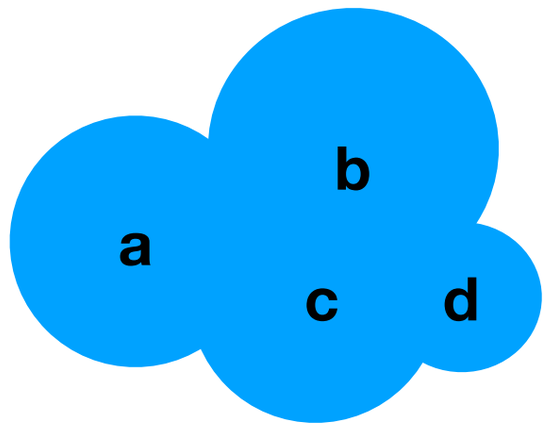
# LCPO method (Linear combination of pairwise overlaps)

- 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

$$SA_i = P_{1,i} 4\pi R_i^2 + P_{2,i} \sum_{j \in N(i)} A_{ij} + P_{3,i} \sum_{j \in N(i)} A_{ij} \sum_{k \in N(i) \cap N(j)} A_{jk} + P_{4,i} \sum_{j \in N(i)} \left[ A_{ij} \sum_{j \in N(i)} \sum_{k \in N(i) \cap N(j)} A_{jk} \right]$$

parameters

force due to SA area on atom *I*

$$\vec{F}_l^{SA} = -T_S \sum_{i \in N(l)} (dSA_i / dr_l)$$

- **<u>Applications:</u>**

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