

Implicit Solvation methods

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Outline

1. Definition of the Solvation Process
2. Applications of Solvation Free Energy
3. Calculation of Solvation Free Energy
 - Electrostatic Contribution: Poisson(-Boltzmann) equation
 - Dispersion Contribution: surface tension
 - Cavity Formation Contribution: Scaled Particle Theory
4. Commonly Used Solvation Models:
(PBF,PCM,COSMO,DelPhi,GB,SGB,etc)
5. Examples of Solvation Models
 - Fast Solvation Model (FSM)
 - Analytical Volume Generalized Born-Solvent Assessable Surface (AVGB-SAS)
 - Conductor-like Screening Model (COSMO)

Recommended References

- G. Zamanakos, A Fast and Accurate Analytical Method for the Computation of Solvent Effects in Molecular Simulations (PhD thesis) Caltech , 2001 (<http://www.wag.caltech.edu>)

Implicit Solvation Models

Implicit solvation models: Equilibria, structure, spectra, and dynamics, C. J. Cramer, D. G. Truhlar, Chem. Rev., 99, 2161, 1999

Molecular-Interactions in Solution - an Overview of Methods Based on Continuous Distributions of the Solvent. Tomasi, J. and M. Persico, Chemical Reviews, 1994. **94**(7): 2027-2094.

SASA Models

Solvation model based on weighted solvent accessible surface area, J. Wang, W. Wang, S. Huo, M. Lee, and P. A. Kollman, J. Phys. Chem. B, 105, 5055, 2001

Analytic SASA and forces

Exact and efficient analytical calculation of the accessible surface areas and their gradients for macromolecules, J. Comp. Chem., 19, 319, 1998

Recommended References

Implicit Solvation Models

[Solvation free energy of biomacromolecules: Parameters for a modified generalized born model consistent with the AMBER force field](#)

Jayaram B, Sprous D, Beveridge DL, JOURNAL OF PHYSICAL CHEMISTRY B Volume: 102 Issue: 47 Pages: 9571-9576 Published: NOV 19 1998

FREE-ENERGY OF SOLVATION, INTERACTION, AND BINDING OF
ARBITRARY CHARGE-DISTRIBUTIONS IMBEDDED IN A DIELECTRIC
CONTINUUM

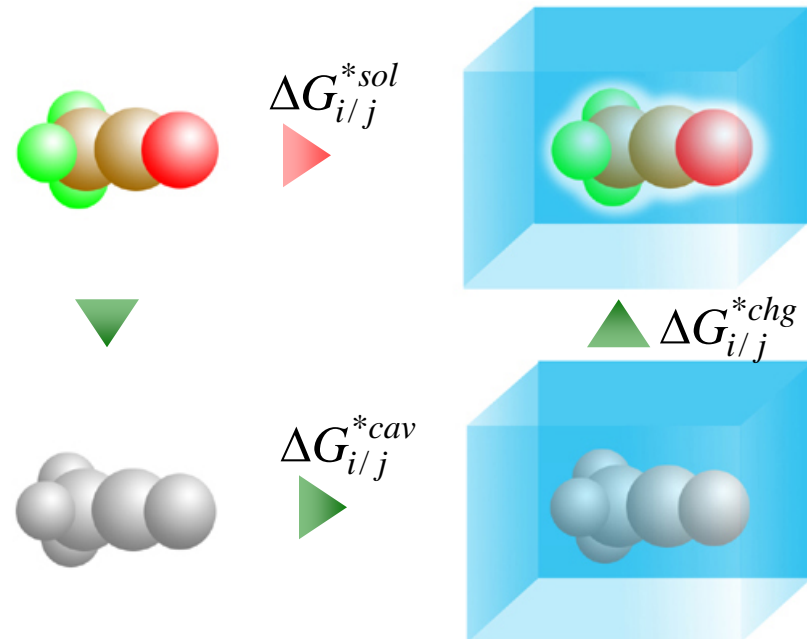
Jayaram B , JOURNAL OF PHYSICAL CHEMISTRY Volume: 98 Issue:
22 Pages: 5773-5777 Published: JUN 2 1994

Definition of Solvation

- Definition of solvation process

Ben-Naim:

The process of transferring one molecule from a fixed position in an ideal gas phase to a fixed position in the fluid phase at constant temperature and pressure.



A. Ben-Naim, Solvation Thermodynamics, Pelunum Press, New York (1987)

Hydration: when water is the solvent

$\Delta G_{i/j}^{*sol}$: solvation free energy

$\Delta G_{i/j}^{*cav}$: cavity formation free energy

$\Delta G_{i/j}^{*chg}$: charging free energy

i/j : solute i in solvent j

c : total molar concentration

Solvation Methods in Molecular Simulations

- Explicit Solvent vs. Implicit Solvent

Explicit: considering the molecular details of each solvent molecules

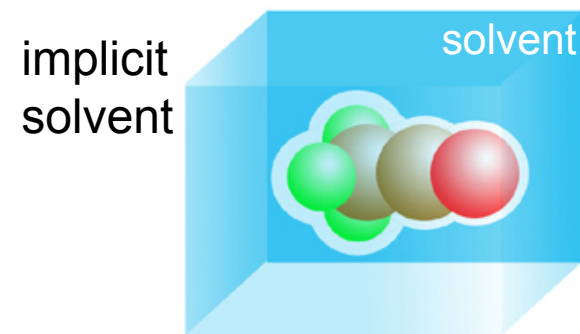
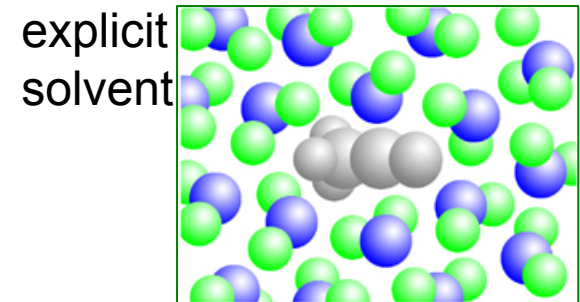
Implicit: treating the solvent as a continuous medium (Reaction Field Method)

note: what are the physical origins of the response of solvent to the existence of solute?

- Rigid Solute vs. Polarizable Solute

Rigid (nonpolarizable): fixed atomic charges (or electron distribution), polarizable solvent [e.g., GB, SGB, AVGB]

Polarizable: considering the mutual polarization between the solute and solvent [e.g. PCM, PBF, COSMO, etc]



Elements in Solvation Free Energy

$$\Delta G^{sol} = \Delta G^{chg} + \Delta G^{cav} = \Delta G_{polar} + \Delta G_{disp} + \Delta G_{cav}$$

Long-Range Effects

- Long range electrostatic interactions ($\sim 1/r$ dependence)
- Also called polarization contributions
- Solute polarization (QM)
- Solvent polarization (ϵ)
- Poisson equation

Mid-Range Effects

- Dispersive interactions ($\sim 1/r^6$ dependence)
- Also called van der Waals contributions
- Usually assumed to be proportional to contact surface area
- Concept of tension parameters σ

Short-Range Effects

- Repulsive interactions ($\sim 1/r^{12}$ dependence)
- Usually assumed to be proportional to the volume of the cavity
- Scaled Particle Theory
- Also has the entropic penalty associated with the reorganization of the solvent molecules around the solute

Why Implicit Solvent?

Method	Explicit Solvent (all-atom description)	Implicit Solvent (Continuum description)
Pros	<ul style="list-style-type: none">• Full details on the molecular structures• Realistic physical picture of the system	<ul style="list-style-type: none">• No explicit solvent atoms• Treatment of solute at highest level possible (QM)
Cons	<ul style="list-style-type: none">• Many atoms--> expensive• Long runs required to equilibrate solvent to solute• Often solvent and solute are not polarizable.• Large fluctuations due to use of small system size	<ul style="list-style-type: none">• Need to define an artificial boundary between the solute and solvent• No “good” model for treating short range effects (dispersion and cavity)

Simple Long-Range Correction

- Approximate distant interactions by assuming uniform distribution beyond cutoff: $g(r) = 1$ $r > r_{\text{cut}}$
- Corrections to thermodynamic properties
 - Internal energy

Expression for Lennard-Jones model

– Virial

$$U_{lrc} = \frac{N}{2} \rho \int_{r_{\text{cut}}}^{\infty} u(r) 4\pi r^2 dr$$

$$U_{lrc}^{LJ} = \frac{8}{9} \pi N \rho \sigma^3 \epsilon \left[\left(\frac{\sigma}{r_c} \right)^9 - 3 \left(\frac{\sigma}{r_c} \right)^3 \right]$$

$$P_{lrc} = \frac{1}{6} \rho^2 \int_{r_{\text{cut}}}^{\infty} r \frac{du}{dr} 4\pi r^2 dr$$

$$P_{lrc}^{LJ} = \frac{32}{9} \pi \rho^2 \sigma^3 \epsilon \left[\left(\frac{\sigma}{r_c} \right)^9 - \frac{3}{2} \left(\frac{\sigma}{r_c} \right)^3 \right]$$

– Chemical potential

$$\mu_{lrc} = \rho \int_{r_{\text{cut}}}^{\infty} u(r) 4\pi r^2 dr = 2 \frac{U_{lrc}}{N}$$

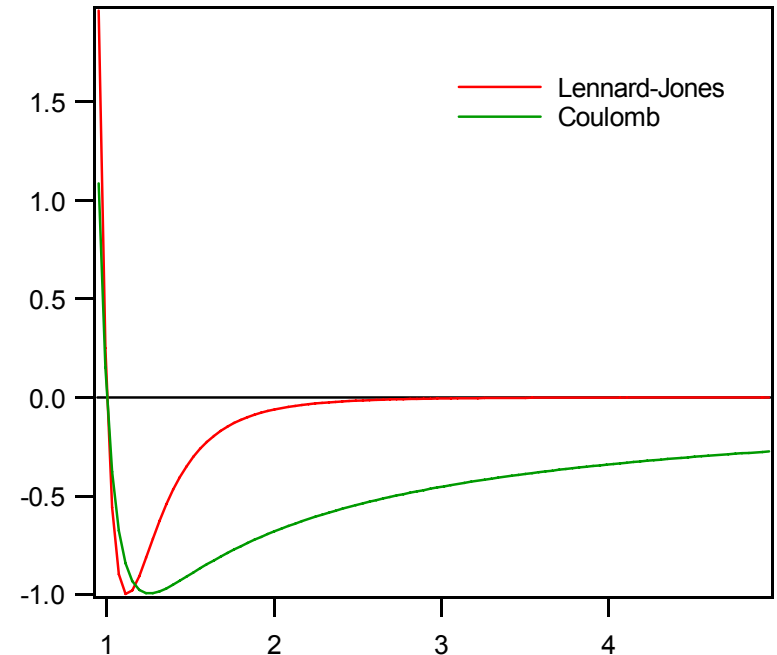
For $r/\sigma = 2.5$, these are about 5-10% of the total values

Coulombic Long-Range Correction

- Coulombic interactions must be treated specially
 - very long range
 - $1/r$ form does not die off as quickly as volume grows

$$u^{tail} = \frac{N\rho}{2} \int_{r_c}^{\infty} dr u(r) 4\pi r^2$$

- Tail correction diverges unless $u(r)$ decays faster than r^{-3}
- So we can not use truncation plus long range correction for Coulombic and dipolar interactions
- Methods
 - Full lattice sum (Ewald summation)
 - Treat surroundings as dielectric continuum



Ewald Sum (Frenkel + Smit, Ch 12)

Consider a system of N positively and negatively charged particles in a volume V ($V=L^3$).

Assume charge neutrality $\sum_i q_i = 0$

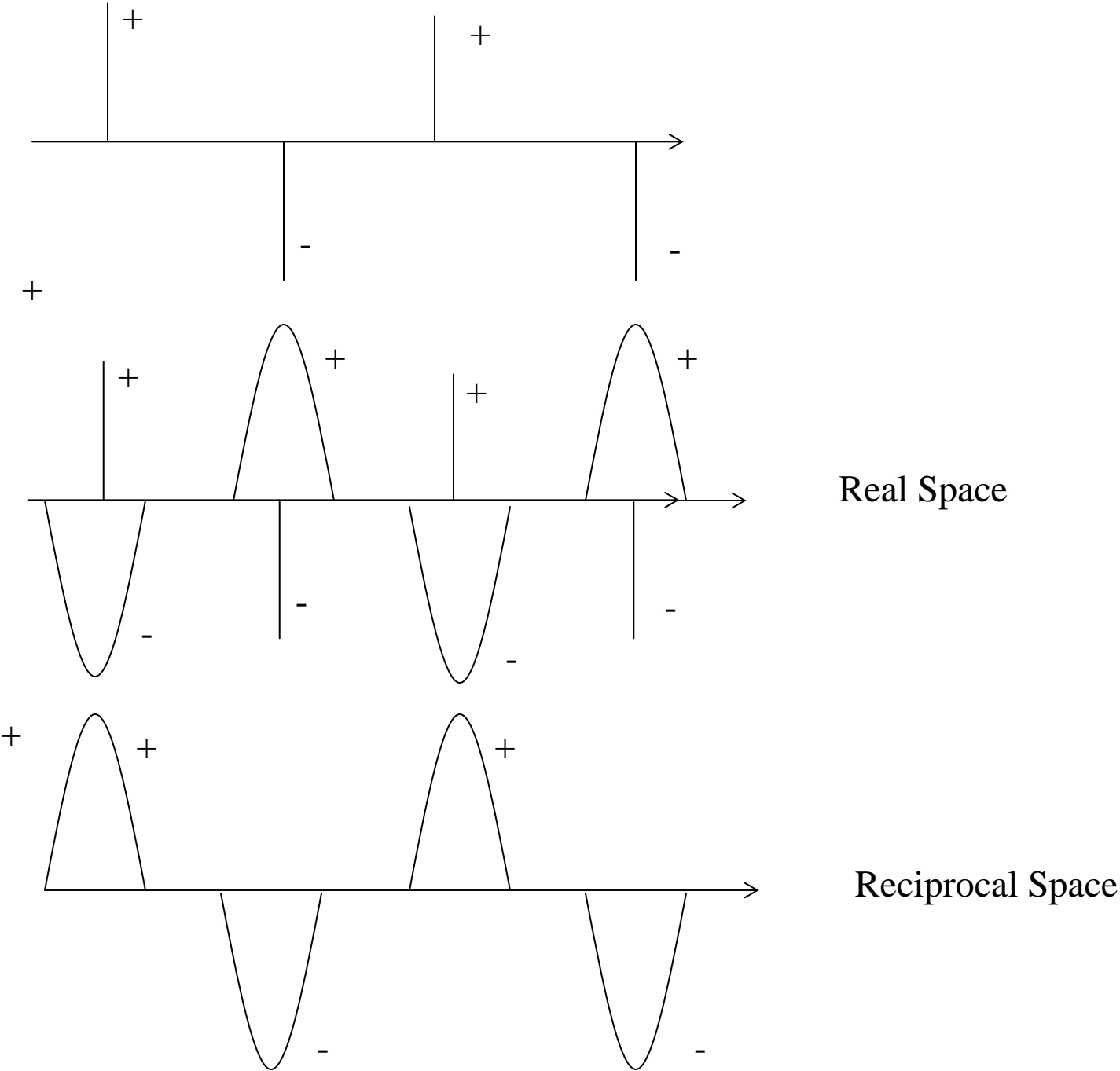
Coulomb energy of this N -particle system is given by

$$u_{Coul} = \frac{1}{2} \sum_{i=1}^N q_i \phi(r_i)$$

$\phi(r_i)$ is the electrostatic potential at the position of ion i

$$\phi(r_i) = \sum_{j,n}^{\prime} \frac{q_j}{|r_{ij} + nL|}$$

The prime on the summation indicates that the sum is over all periodic images n and over all particles j , except $j=i$ if $n=0$. The sum is conditionally convergent. : it contains a mixture of positive and negative terms Separately both the positive and negative terms form a divergent series. The sum of a conditionally convergent series depends on the order in which its terms are considered.



Cost of Ewald summation

Real space part of the energy involves evaluating (consider $\alpha^{1/2} = \alpha$)

$$\begin{aligned}\Delta U &= \frac{1}{2} \sum_{\mathbf{n}} \sum_{i \neq j} q_i \Delta \phi_j(r_{ij}) \\ &= \frac{1}{2} \sum_{\mathbf{n}} \sum_{i \neq j} \frac{q_i q_j}{r_{ij}} \operatorname{erfc}(\sqrt{\alpha} r_{ij})\end{aligned}$$

To ensure convergence of the real space part we need to choose α such that erfc is small at the real-space cutoff R . Suppose we specify small to be $\exp(-p)$. So p controls the accuracy. For large values of argument erfc behaves as $\exp(-\alpha^2 r^2)$. SO we demand

$$\begin{aligned}\alpha^2 r^2 &= p \\ \text{or } \alpha &= p^{1/2}/R\end{aligned}\quad (1)$$

Fincham, Mol. Simulation, 13,1-9 (1994)

For reciprocal space we need to compute the following

$$\begin{aligned}
 U_q &= \frac{1}{2} \sum_i q_i \phi(\mathbf{r}_i) \\
 &= \frac{1}{2} \sum_{\mathbf{k} \neq 0} \frac{4\pi V}{k^2} e^{-k^2/4\alpha} \sum_{i,j} \frac{q_i q_j}{V^2} e^{i\mathbf{k} \cdot (\mathbf{r}_i - \mathbf{r}_j)} \\
 &= \frac{1}{2} \sum_{\mathbf{k} \neq 0} \frac{4\pi V}{k^2} e^{-k^2/4\alpha} |\rho(\mathbf{k})|^2
 \end{aligned}$$

The rate of convergence is controlled by the factor $\exp(-k^2/4\alpha^2)$. Like before if we require the terms to have the value $\exp(-p)$ at the reciprocal cutoff K , then we have

$$\begin{aligned}
 p &= K^2/4\alpha^2 \\
 \text{or } K &= 2\alpha p^{1/2} = 2p/R \quad (2)
 \end{aligned}$$

Equ. 1 and 2 specify the choice of parameters α and reciprocal cutoff K once the accuracy parameter p and real space cutoff R have been chosen

Time estimate for Ewald summation

The number of ions within the cutoff sphere is

$$4\pi/3R^3n, \text{ n is the number density}$$

Each of the N ions interacts with the other ions in the surrounding cutoff sphere, but each pair interactions needs to be considered only once. Thus

$$T_R = 1/2 N 4\pi/3R^3nt_R$$

The value of reciprocal space within a cutoff K is

$$\frac{4\pi}{3} K^3 = \frac{4\pi}{3} \frac{8p^3}{R^3}$$

The reciprocal-space points are given by $k=2\pi/L(l,m,n)$, where l, m, n are integers. The volume of each reciprocal point is $(2\pi/L)^3$. The number of reciprocal points with the cutoff K is given by

$$\frac{4\pi}{3} \frac{8p^3}{R^3} \frac{L^3}{8\pi^3} = \frac{4\pi}{3} \left(\frac{p}{\pi}\right)^3 \frac{N}{nR^3} \quad \text{Where } n = N/L^3$$

This grows as N as the density of points in k-space increases with system

For each k-points a sum over over N ions needs to be performed and the execution time is

$$T_F = \frac{1}{2} \frac{4\pi}{3} \left(\frac{p}{\pi}\right)^3 \frac{N}{nR^3} t_F$$

So the total execution time for real space and k-space summation is given by

$$T = \frac{1}{2} \frac{4\pi}{3} \left[N n R^3 t_R + \left(\frac{p}{\pi}\right)^3 \frac{N}{nR^3} t_F \right]$$

For fixed p and R , T_R varies as N and T_F varies as N^2

To find the optimal value of R which minimizes the total execution time T we have $dT/dR=0$, which gives

$$R_{OPT} = \left(\frac{p}{\pi}\right)^{1/2} \left[\frac{t_F}{t_R}\right]^{1/6} \frac{N^{1/6}}{N^{1/3}}$$

This choice of optimal real-space cutoff gives the following optimal time

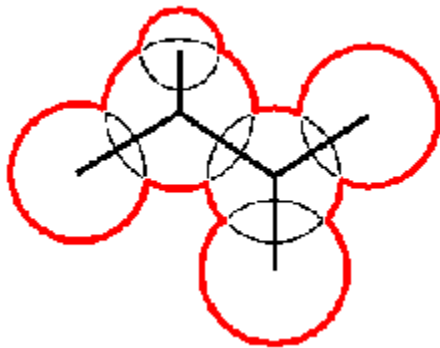
$$T_{OPT} = 2T_R = 2T_F = \frac{4\pi}{3} N^{3/2} \left(\frac{p}{\pi}\right)^{3/2} \left(t_R t_F\right)^{1/2}$$

When optimized it is equally divided between real and reciprocal space parts calculation and it grows as $N^{3/2}$

Different Ways of Defining the Solvation Cavity

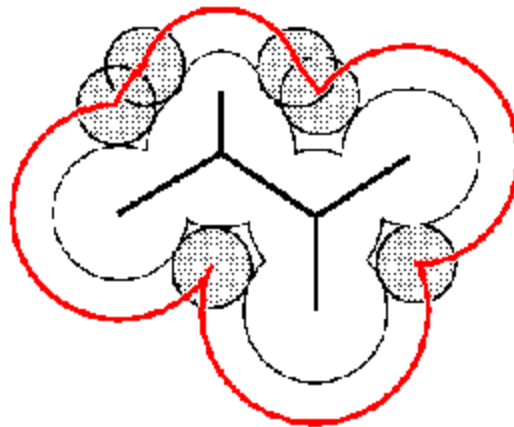
- Three Commonly Used Surfaces in Implicit Solvation

van der Waals surface
(vdWS)



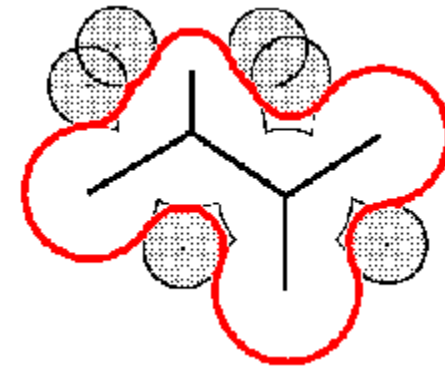
Molecular surface
Sometimes used in
electrostatic and/or
dispersion contribution
calculations

Solvent Accessible Surface
(SAS)



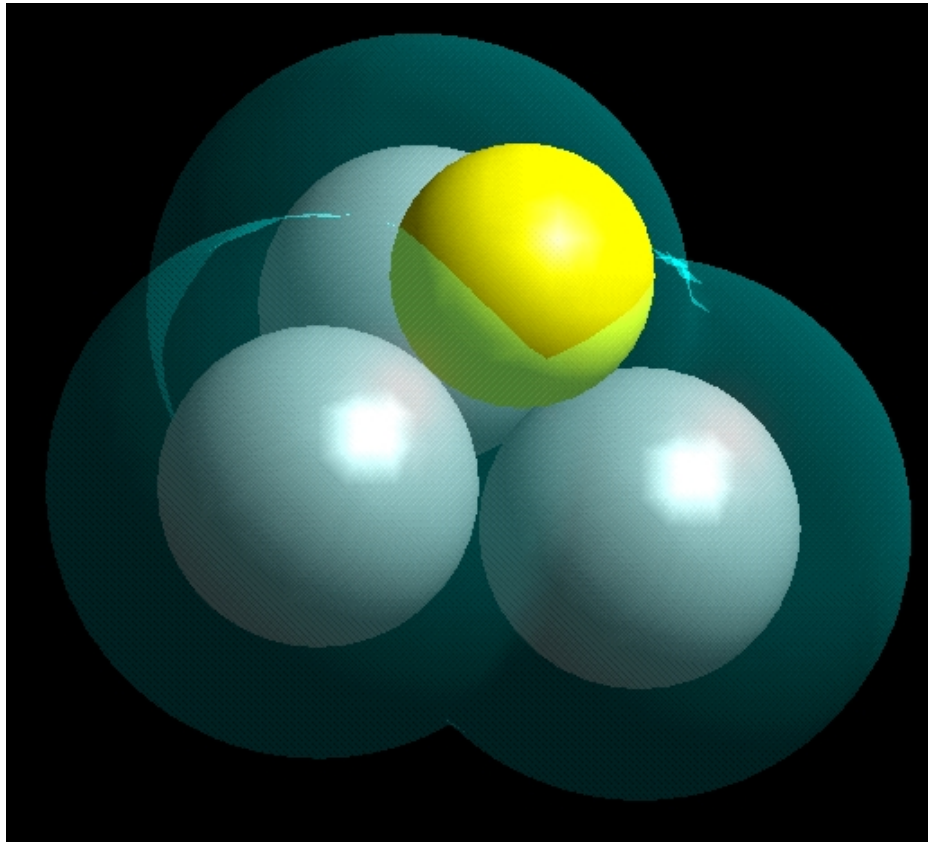
Commonly used in
electrostatic and/or
dispersion contribution
calculations

Solvent Excluded Surface
(SES)



Also used in
dispersion and cavity
contribution
calculations

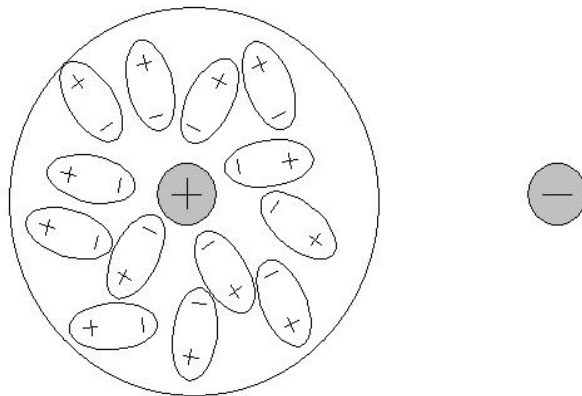
SASA



The Solvent Accessible Surface (transparent) of 3 carbon atoms with radius 1.7 Å (gray), as is traced by a probe of radius 1.4 Å (yellow.)

Electrostatic Interactions

The charge distributions of the solute and solvent play a fundamental role in the solvation process. The polar contribution to the solvation energy, ΔG_{polar} includes the work necessary to create the solute's gas-phase charge distribution in solution and the work required to polarize the solute charge distribution.



Reorganization of the solvent around a solute charge and dielectric screening of intra-molecular interactions.

Electrostatic Interactions: Poisson Equation

- Poisson Eq.: Interaction between Solute and Continuum Solvent

$\varepsilon(\vec{r})$: dielectric constant at position \vec{r}

$\phi(\vec{r})$: electrostatic potential at \vec{r}

$\rho(\vec{r})$: charge density at \vec{r}

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

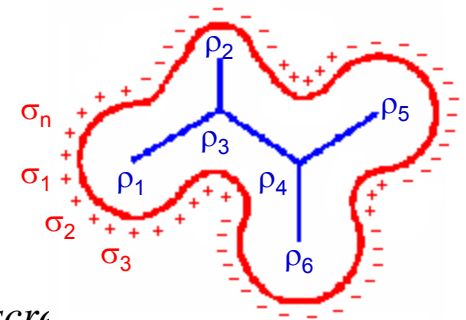
- Apparent Surface Charges

if $\varepsilon = 1 \Rightarrow \phi(r) = \int dr' \frac{\rho(r')}{|r-r'|}$ Coulomb's law

$$\sigma = \frac{\varepsilon - 1}{4\pi\varepsilon} \nabla \phi_{in} \cdot \vec{n}$$

- Energy of Interaction

$$\Delta E_{polar} = \int_V d^3\vec{r} \phi_{solvent}(\vec{r}) \rho_{solute}(\vec{r}) = \int_S d^2\vec{r} \phi_{solute}(\vec{r}) \sigma_{screened}$$



- Electrostatic Solvation Free Energy

$$\Delta G_{i/S}^{*ele} = \int_{\lambda=0}^{\lambda=1} d\lambda \Delta E_{i/S}^{*ele}(\lambda) = \frac{1}{2} \Delta E_{i/S}^{*ele}(\lambda=1) = \frac{1}{2} \int_V d^3\vec{r} \phi(\vec{r}) \rho(\vec{r})$$

Electrolyte Solutions: Poisson-Boltzmann Equation

- Poisson Equation

$$-\nabla \cdot [\varepsilon(\vec{r}) \nabla \phi(\vec{r})] = 4\pi\rho(\vec{r}) \quad \rho(\vec{r}) = \rho_{solute}(\vec{r}) + \rho_{ions}(\vec{r})$$

we assume that the ratio of the concentration of ion type i around the solute to its concentration far away from the solute is given by the Boltzmann distribution

$$\exp(-W_i(\vec{r}) / k_B T)$$

$W_i(\vec{r})$ is the work required to move the ion of type i from from infinity (where $\Phi(\infty) = 0$) to point r .

Assume we have only two types of ions, negative and positive (such that the total system is electrically neutral). So for each ionic species we have

$$W_1(\vec{r}) = +e_c \Phi(\vec{r}) \quad W_2(\vec{r}) = -e_c \Phi(\vec{r})$$

Electrolyte Solutions: Poisson-Boltzmann Equation

The concentration of each species is given by

$$M_+ = M \exp(-e_c \Phi(\vec{r}) / k_B T) \quad M_- = M \exp(+e_c \Phi(\vec{r}) / k_B T)$$

The charge density of ions around the solute should be

$$\rho_{ion}(\vec{r}) = e_c (M_+ - M_-) = -2M e_c \sinh\left(\frac{e_c \Phi(\vec{r})}{k_B T}\right)$$

Define ionic strength I in terms of salt concentration M

$$I = 0.5 \sum_{i=1}^N c_i z_i^2 = 1000M / N_A$$

Electrolyte Solutions: Poisson-Boltzmann Equation

The Poisson equation is written as

$$-\nabla \cdot (\epsilon(\vec{r}) \nabla \Phi(\vec{r})) + \kappa(\vec{r})^2 \sinh\left(\frac{e_c \Phi(\vec{r})}{k_B T}\right) = 4\pi\rho(\vec{r})$$

κ is the Debye-Huckel parameter and is given by

$$\kappa(\vec{r}) = \sqrt{\frac{8\pi N_A e_c^2 I}{1000 \epsilon(\vec{r}) k_B T}}$$

Expanding the hyperbolic sine function as Taylor series and keeping only the first term we have linearised Poisson-Boltzmann equation

$$-\nabla \cdot (\epsilon(\vec{r}) \nabla \Phi(\vec{r})) + \kappa(\vec{r})^2 \Phi(\vec{r}) = 4\pi\rho(\vec{r})$$

Solution of PB equation : a computational challenge

The most common assumption for solving the PB equation is that the dielectric permittivity takes two values,

ϵ_{in} in the solute cavity ϵ_{out} for outside

electrostatic free energy of solvation can be obtained by solving this equation twice, once with the solute inside the solvent dielectric and once with the solute in vacuum and can be written as

$$\Delta G_{polar} = \frac{1}{2} \sum_{i=1}^N q_i \left(\Phi^{solv}(\vec{r}_i) - \Phi^{vac}(\vec{r}_i) \right)$$

Exact analytical solutions of the PB or in the absence of salt, the Poisson equation, are not possible except for very few simple cases with simple solute shape like proteins treated as spherical cavities or DNA is modeled as a charged cylinder..

Theory of Protein Titration Curves. I. General Equations for Impenetrable Spheres

BY CHARLES TANFORD¹ AND JOHN G. KIRKWOOD

RECEIVED MAY 8, 1957

JACS, 1957

For many years the theory of titration curves of impenetrable proteins has been based on a model which represents the protein molecule as a sphere with a continuous and uniform distribution of charge on its surface. In this paper this model is replaced by a more realistic one in which the charges are taken to be discrete unit charges located at fixed positions. General equations are obtained which express the titration curve as a function of the locations of ionizable sites and of their intrinsic properties. It is concluded that the intrinsic properties may themselves be quite sensitive to the location of the dissociable site with respect to the surface of the protein molecule.

J. Phys. Chem. **1994**, *98*, 5773–5777

5773

Free Energy of Solvation, Interaction, and Binding of Arbitrary Charge Distributions Imbedded in a Dielectric Continuum

B. Jayaram

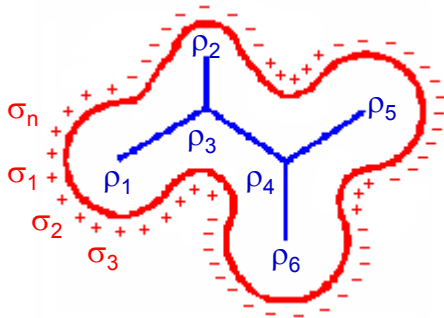
Department of Chemistry, Indian Institute of Technology, Hauz Khas, New Delhi-110016, India

*Received: September 28, 1993; In Final Form: February 17, 1994**

A theoretical treatment of solvation and interaction of two arbitrary charge distributions imbedded in a dielectric continuum solvent is presented. The electrostatic component of the total free energy of such a charge assembly contains contributions from the solvation energies of each charge distribution, and modified Coulomb interaction energies between the two charge distributions. The theory developed is illustrated for special cases along with an application to the interaction between two ions in a continuum solvent.

Not very useful! simplifications needed in the shape of the solute limit severely the applicability of the model to realistic systems. Numerical solution is developed.

Solution to the Poisson Equation for Real Molecules

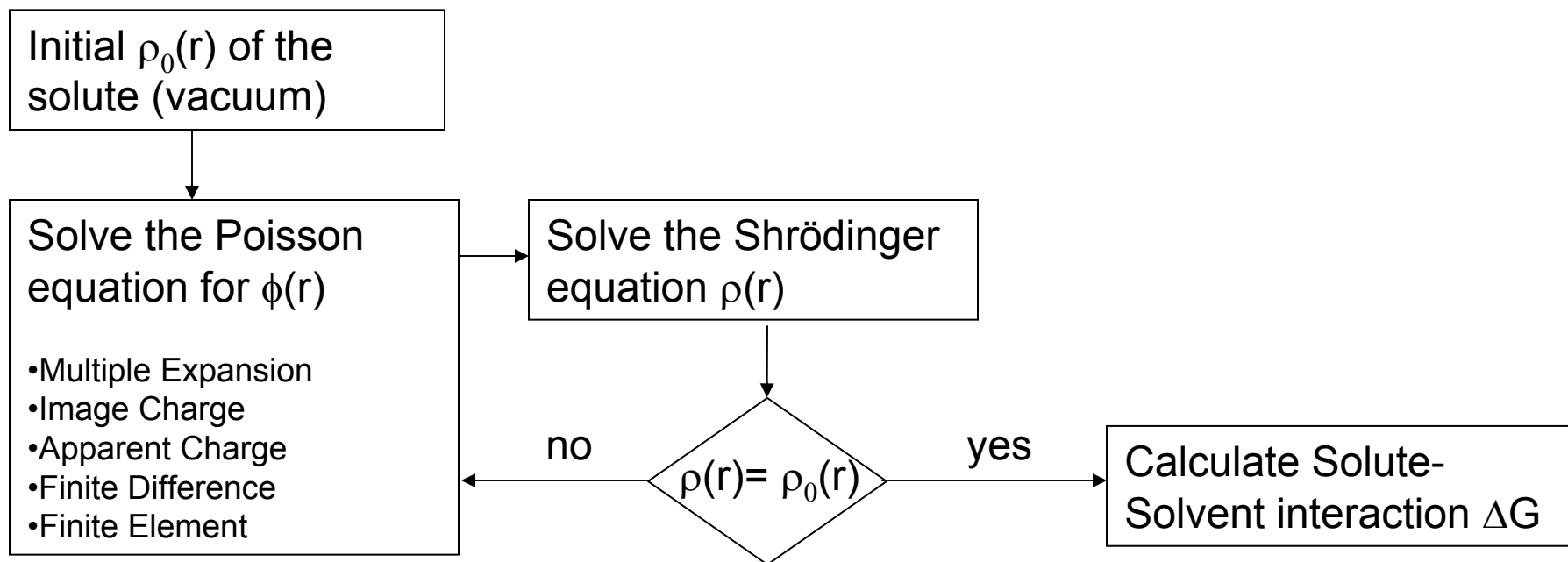


Solvent Polarization: Poisson Equation

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

Solute Polarization: Schrödinger Equation

$$H(\rho, \sigma) = H^{(0)}(\rho) + V_{\text{int}}(\rho, \sigma)$$



-
- Numerical solution, CPU intensive, scales as $O(N^3)$
 - Lack of gradients (atomic forces)
 - Accuracy depends on grid resolution.
 - Not parallelizable, QM implementations available
 - Applications show successful predictions.

Approximate Solutions for the Continuum Dielectric Model

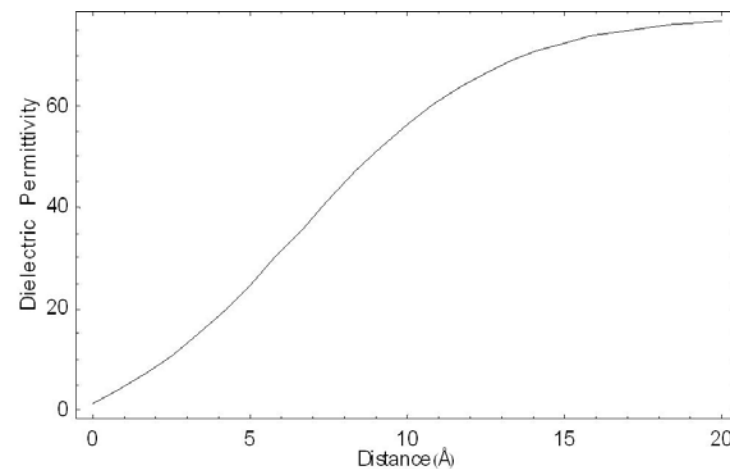
Multipole Expansions:

Electrostatic potential is determined by assuming very simple shapes for the solute cavity and using limited multipole expansions to represent the solute charge distribution. The electrostatic potential can be written as a series of spherical harmonic terms.

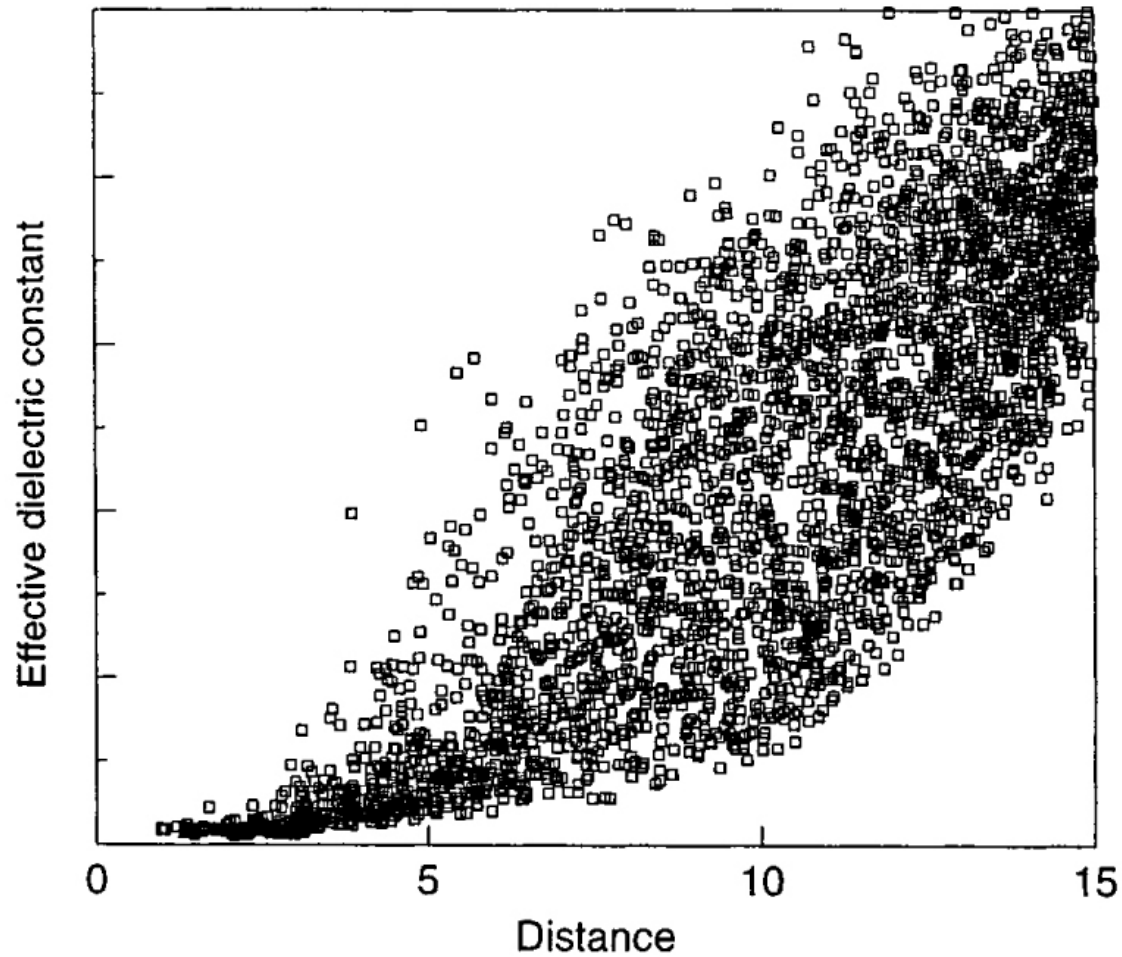
Distance Dependent Dielectric (DDD) methods

the solvent molecules surrounding the solute are polarized due to the solute charge distribution. This generates a reaction field, which in turn polarizes the solute. The intramolecular coulombic interactions are screened because of the surrounding solvent molecules. Dielectric permittivity taken to be distance dependent and given by a sigmoid profiles

$$\varepsilon(r_{ij}) = A + \frac{B}{1 + k \exp(-\lambda B r_{ij})}$$



Distance Dependent Dielectric (DDD) methods



Srinivasan J., Trevathan M. W., Beroza P., Case D. A., *Theor. Chem. Acc.*, **101**, 426 (1999)

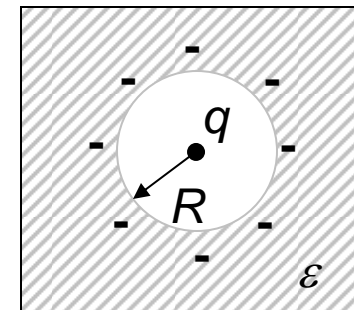
Analytical Solutions to the Poisson Equation

- Born Model: point charge in a spherical cavity

The electrostatic energy G_{pol} of a charged dielectric sphere of radius R and charge q , embedded in a dielectric of permittivity ϵ can be calculated by

$$\int \vec{E} \cdot d\vec{s} = 4\pi q$$

$$G_{pol} = \frac{1}{4\pi} \int E^2 dv = \frac{q^2}{2\epsilon R}$$



Assume that the sphere has interior dielectric of 1, and it is reversibly transferred from the vacuum to a medium of dielectric permittivity ϵ , the change in the electrostatic free energy is given by

$$\Delta G_{pol} = -\frac{1}{2} \left(1 - \frac{1}{\epsilon} \right) \frac{q^2}{R}$$

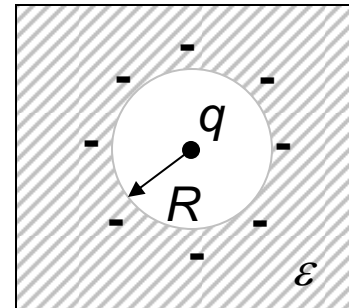
More general expression

$$\Delta G_{pol} = -\frac{1}{2} \left(\frac{1}{\epsilon_{in}} - \frac{1}{\epsilon_{out}} \right) \frac{q^2}{R}$$

Analytical Solutions to the Poisson Equation

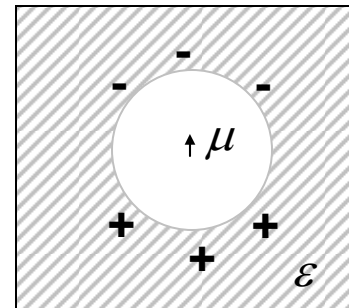
- Born Model: point charge in a spherical cavity

$$\Delta G_{i/S}^{*ele} = -\frac{\varepsilon - 1}{2\varepsilon} \frac{q^2}{R} \quad (\text{energies in electrostatic unit})$$



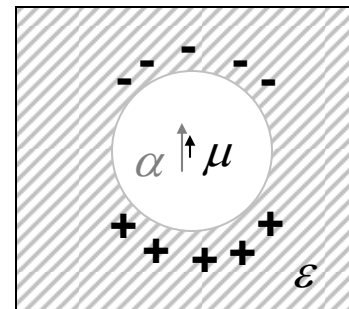
- Bell Model: rigid dipole in a spherical cavity

$$\Delta G_{i/S}^{*ele} = -\frac{\varepsilon - 1}{2\varepsilon + 1} \frac{\mu^2}{R^3}$$



- Onsager: polarizable dipole in a spherical cavity

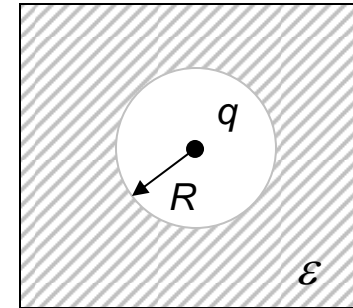
$$\Delta G_{i/S}^{*ele} = -\frac{\varepsilon - 1}{2\varepsilon + 1} \frac{\mu^2}{R^3} \left[1 - \frac{\varepsilon - 1}{2\varepsilon + 1} \frac{\alpha}{R^3} \right]^{-1}$$



Simplifications: 1. Generalized Born Approximation

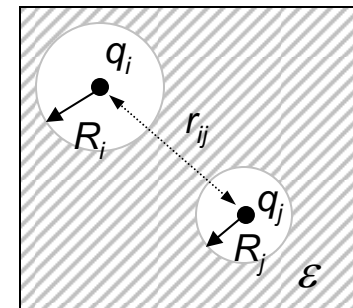
- Polar Solvation Energy of a charged centered at spherical cavity of radius R in dielectric medium ϵ (Born):

$$\Delta G_{pol} = -\frac{1}{2} \left(\frac{1}{\epsilon_{in}} - \frac{1}{\epsilon_{out}} \right) \frac{q^2}{R}$$



- System of N spheres of radii α_i , far away from each other:

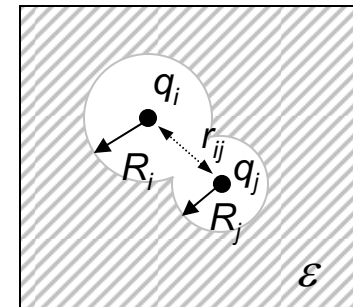
$$\Delta G_{pol} = -\frac{1}{2} \left(\frac{1}{\epsilon_{in}} - \frac{1}{\epsilon_{out}} \right) \left[\sum_{i=1}^N \frac{q_i^2}{\alpha_i} + \sum_{i \neq j=1}^N \sum_{j=1}^N \frac{q_i q_j}{r_{ij}} \right]$$



- Generalized Born (Still et al., 1990):

$$\Delta G_{pol} = -\frac{1}{2} \left(\frac{1}{\epsilon_{in}} - \frac{1}{\epsilon_{out}} \right) \sum_{i=1}^N \sum_{j=1}^N \frac{q_i q_j}{f_{ij}} \quad f_{ij} = \left(r_{ij}^2 + \alpha_{ij}^2 e^{-\frac{r_{ij}^2}{4\alpha_{ij}^2}} \right)^{1/2}$$

$\alpha_{ij} = \sqrt{\alpha_i \alpha_j}$ α_i : Born radius for atom i



The Generalized Born Model

- Interpolation formula:

$$f_{ij} = \sqrt{r_{ij}^2 + \alpha_i \alpha_j \exp(-r_{ij}^2 / 4\alpha_i \alpha_j)}$$

- Limit $r_{ij} = 0 \Rightarrow f_{ij} = \alpha_i$

$$\Delta G_{pol} = -\frac{1}{2} \left(\frac{1}{\epsilon_{in}} - \frac{1}{\epsilon_{out}} \right) \frac{q_i^2}{\alpha_i} \quad (\text{Born Formula})$$

- Limit $r_{ij} \rightarrow \infty \Rightarrow f_{ij} \rightarrow r_{ij}$

$$\Delta G_{pol}^{ij} \rightarrow -\frac{1}{2} \left(\frac{1}{\epsilon_{in}} - \frac{1}{\epsilon_{out}} \right) \frac{q_i q_j}{r_{ij}} \quad (\text{Coulomb Limit})$$

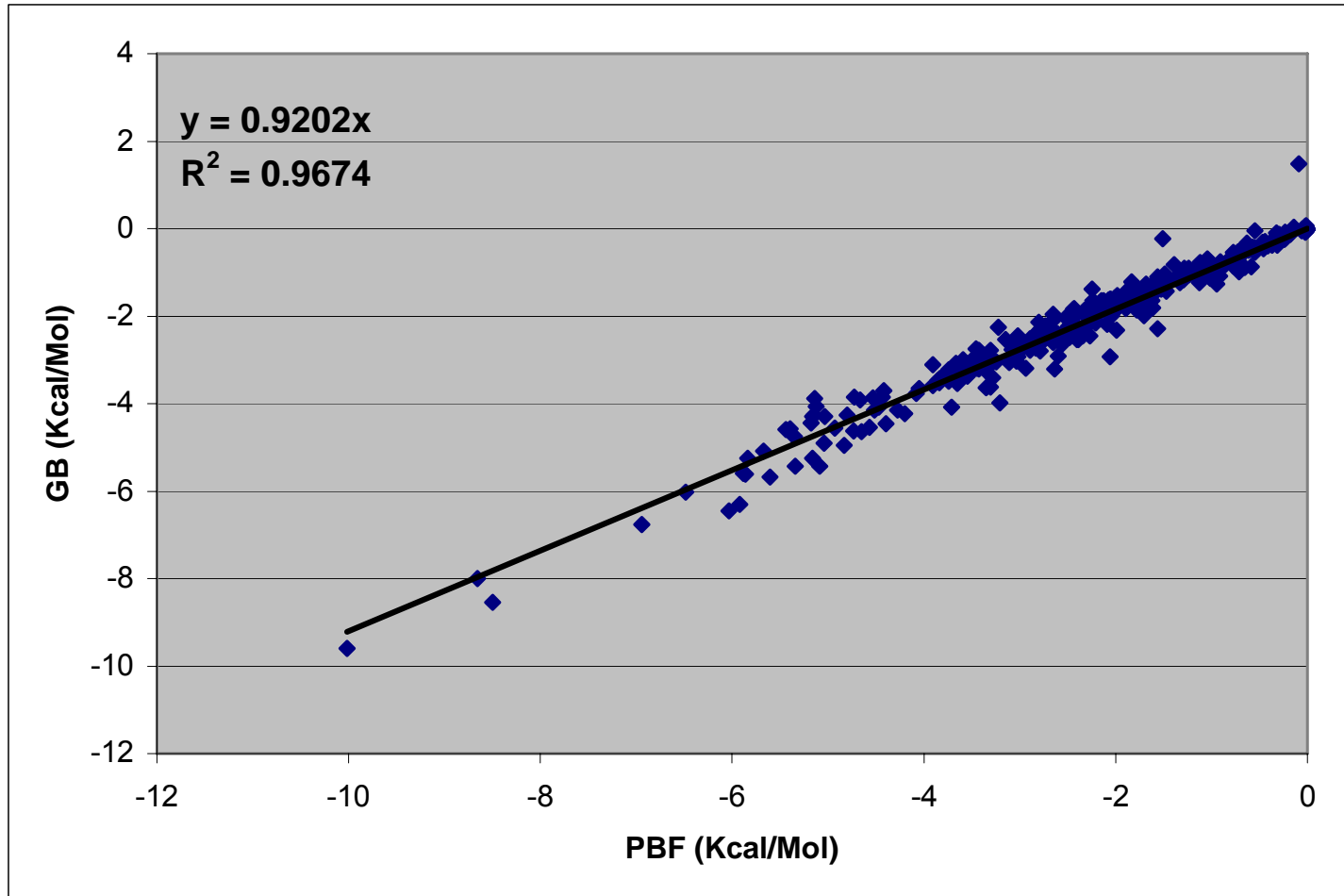
Physical meaning of Born radii

- If we set all charges to zero except q_k , we get:

$$\Delta G_{pol} = -\frac{1}{2} \left(\frac{1}{\epsilon_{in}} - \frac{1}{\epsilon_{out}} \right) \frac{q_k^2}{\alpha_k}$$

- Parameters α_k are the Born Radii.
- Physical Meaning: the effective radius of an ion of charge q_k , whose solvation energy is equal to the self-energy of polarization of atom in the molecule.
- Difficult to calculate.

Accuracy of Interpolation Formula



How to compute Born Radii

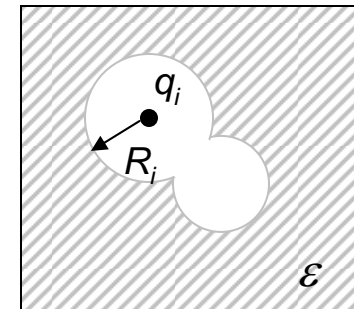
Still W. C., Tempczyk A., Hawley R. C., Hendrickson T., *J. Am. Chem. Soc.*, **112**, 6127 (1990)

Ghosh A., Rapp C. S., Friesner R. A., *J. Phys. Chem. B*, **102**, 10983 (1998)

Zhang L. Y., Gallichio E., Friesner R. A., Levy R. M., *J. Comp. Chem.*, **22**, 591 (2001)

Simplifications: 1. Generalized Born: Born Radii

- **The Born radius of an atom corresponds to the radius that would return the electrostatic energy of the system according to the Born equation if all of the other molecules in the system were uncharged.**



$$\Delta G_{pol} = -\frac{1}{2} \left(\frac{\epsilon - 1}{\epsilon} \right) \frac{q_i^2}{\alpha_i}$$

- It can be proven that (Still et al., 1990):

$$\frac{1}{\alpha_k} = \frac{1}{R_k} - \frac{1}{4\pi} \int_V \frac{1}{|\vec{r} - \vec{r}_k|^4} d^3r$$

Require volume integral

- S-GB (Surface area based GB, Ghosh et al., 1998):

$$\frac{1}{\alpha_k} = \frac{1}{R_k} - \frac{1}{4\pi} \int_S \frac{(\vec{r} - \vec{r}_k) \cdot \vec{n}}{|\vec{r} - \vec{r}_k|^4} d^2r$$

Require surface integral

Born Radii

The electrostatic self-energy of solvation of an atom is due to the interaction of the solute charge distribution $\rho(r)$ with the induced dipoles of the solvent. This is called the reaction field $\Phi(r)$ and is responsible for polarizing the solute atoms. The polarization is described by the induced surface charge $\sigma_{pol}(r)$ on the surface of the solute atoms

$$\Phi_{react}(\vec{r}) = \oint_S \frac{\sigma_{pol}(\vec{R})}{|\vec{r} - \vec{R}|} d^2 R$$

S is the solvent accessible surface of the solute. So the solvation free energy is given by

$$\Delta G_{pol} = \frac{1}{2} \int \rho(\vec{r}) \Phi_{react}(\vec{r}) d^3 r$$

Assuming that the solute charge distribution is a set of N point charges q_k located at points r_k

$$\rho(\vec{r}) = \sum_{k=1}^N q_k \delta(\vec{r} - \vec{r}_k)$$

$$\Delta G_{pol} = \frac{1}{2} \sum_{k=1}^N q_k \oint_S \frac{\sigma_{pol}(\vec{r})}{|\vec{r} - \vec{r}_k|} d^2 r$$

Born Radii

Now apply Gauss law on the boundary surface that separates the two dielectrics ϵ_{in} and ϵ_{out}

$$\oint_S \vec{E} \cdot d\vec{s} = 4\pi q$$

or,

$$\left(\vec{E}_{out} - \vec{E}_{in} \right) \cdot \hat{n} = 4\pi\sigma_{pol}\Delta S$$

\hat{n} is the normal to the boundary surface

\vec{E} is the electric field due to the local polarization charge density

$$\sigma_{pol}(\vec{r}) = \frac{1}{4\pi} \left(\frac{\epsilon_{in}}{\epsilon_{out}} - 1 \right) \vec{E}_{in}(\vec{r}) \cdot \hat{n}$$

Born Radii

If we set all charges to zero except q_k , we get:

$$\Delta G_{pol,k} = \frac{1}{8\pi} q_k \left(\frac{\epsilon_{in}}{\epsilon_{out}} - 1 \right) \oint_S \frac{\vec{E}_{in}(\vec{r}) \cdot \hat{n}}{|\vec{r} - \vec{r}_k|} d^2 r$$

Note that for point charge q_k , located at \vec{r}_k in a spherical cavity we have

$$\vec{E}_{in}(\vec{r}) = \frac{1}{\epsilon_{in}} q_k \frac{\vec{r} - \vec{r}_k}{|\vec{r} - \vec{r}_k|^3}$$

So we have expression for the self-energy in terms of the geometry of the system

$$\Delta G_{pol,k} = -\frac{1}{8\pi} \left(\frac{1}{\epsilon_{in}} - \frac{1}{\epsilon_{out}} \right) q_k^2 \oint_S \frac{(\vec{r} - \vec{r}_k) \cdot \hat{n}}{|\vec{r} - \vec{r}_k|^4} d^2 r$$

Born Radii

The use of Coulomb's law for the electric field is exact only in the case of a single charge q_k in the center of a spherically symmetric cavity. We can expect that this approximation for the local electrostatic field will be valid for cases that the molecule's surface is locally convex. This approximation is known as the “**Coulombic approximation**”

Coulombic approximation works very well for a diverse set of molecules.

Now use Green's theorem to convert the surface integral to a volume integral

$$\oint_{\partial V=S} \vec{A} \cdot d\vec{s} = \int_V \nabla \cdot \vec{A} d^3r$$

Born Radii

$$\vec{A} = \frac{\vec{r} - \vec{r}_k}{|\vec{r} - \vec{r}_k|^4}$$

break the integration over the solute volume into two regions: the volume of a sphere of radius R_k and the volume of the solute excluding the sphere of radius R_k

$$\begin{aligned} \oint_{\partial V=S} \frac{\vec{r} - \vec{r}_k}{|\vec{r} - \vec{r}_k|^4} \cdot d\vec{s} &= \int_V \nabla \cdot \frac{\vec{r} - \vec{r}_k}{|\vec{r} - \vec{r}_k|^4} d^3 r \\ &= \int_{\Omega_k} \nabla \cdot \frac{\vec{r} - \vec{r}_k}{|\vec{r} - \vec{r}_k|^4} d^3 r + \int_{|\vec{r} - \vec{r}_k| \leq R_k} \nabla \cdot \frac{\vec{r} - \vec{r}_k}{|\vec{r} - \vec{r}_k|^4} d^3 r \end{aligned}$$

Born Radii

$$\begin{aligned}
 \int_{|\vec{r}-\vec{r}_k|\leq R_k} \nabla \cdot \frac{\vec{r}-\vec{r}_k}{|\vec{r}-\vec{r}_k|^4} d^3 r &= \oint_{|\vec{r}-\vec{r}_k|=R_k} \frac{\vec{r}-\vec{r}_k}{|\vec{r}-\vec{r}_k|^4} \cdot d\vec{s} \\
 &= \frac{R_k}{R_k^4} 4\pi R_k^2 \\
 &= \frac{4\pi}{R_k}
 \end{aligned}$$

Also

$$\nabla \cdot \left(\frac{\vec{r}-\vec{r}_k}{|\vec{r}-\vec{r}_k|^4} \right) = -\frac{1}{|\vec{r}-\vec{r}_k|^4} \quad \nabla \cdot (\vec{r}-\vec{r}_k) = 3$$

Identity

Finally we get

$$\oint_{\partial V=S} \frac{\vec{r}-\vec{r}_k}{|\vec{r}-\vec{r}_k|^4} \cdot d\vec{s} = \frac{4\pi}{R} - \frac{1}{4\pi} \int_{\Omega_k} \frac{1}{|\vec{r}-\vec{r}_k|^4} d^3 r$$

Born Radii

Finally we have

$$\frac{1}{\alpha_k} = \frac{1}{R} - \frac{1}{4\pi} \int_{\Omega_k} \frac{1}{|\vec{r} - \vec{r}_k|^4} d^3r$$

Volume integral is very difficult to be calculated analytically for cases of arbitrary molecular geometry.

- Numerical integration
- The asymptotic model: ad-hoc analytical model for Born radii
- The pairwise descreening approximation (PDA)
- The surface generalized Born model (SGB)
- The overlapping spheres approximation and the analytical volume model

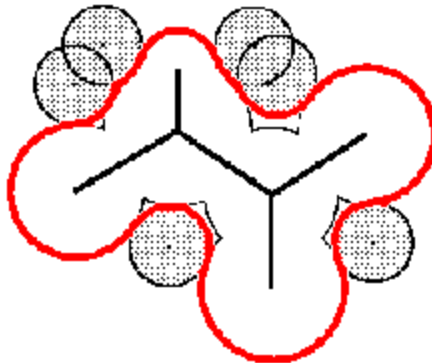
Dispersion Free Energy

sum over atom types

$$\Delta G_{dips} = \sum_{i=1}^N \sigma_i A_i$$

“surface tension” for atom type i
 σ is solvent dependent!

exposed surface area of atom type i
SES usually chosen for A_i
 A_i depends on atomic radius and probe radius



AVGB Solvation Energy

Zamanakos, Phd thesis (Caltech), 2002

- Long-Range Effects:

$$\Delta G_{pol} = -\frac{1}{2} \left(\frac{1}{\epsilon_{in}} - \frac{1}{\epsilon_{out}} \right) \sum_{i=1}^N \sum_{j=1}^N \frac{q_i q_j}{\sqrt{r_{ij}^2 + \alpha_i \alpha_j \exp(-r_{ij}^2 / 4\alpha_i \alpha_j)}}$$

$$\frac{1}{\alpha_k} = \frac{1}{R_k} - \frac{1}{4\pi} \sum_{k' \neq k} \int_{V_{k'}} \frac{1}{|\vec{r} - \vec{r}_k|^4} d^3 r$$

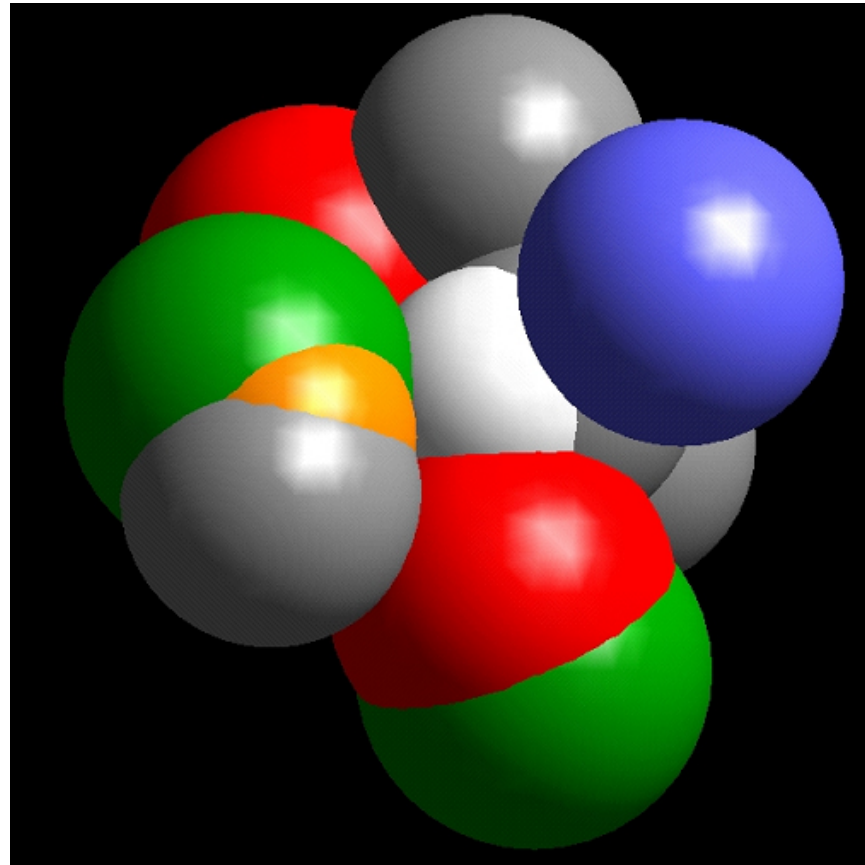
- Short-Range Effects:

$$\Delta G_{vdW} + \Delta G_{cav} = \sum_{i=1}^N \sigma_i A_i$$

Solvent accessible surface areas and solvent excluded volumes must be calculated fast and accurately

The Fused-Sphere Model

- Analytical calculation of volumes and areas, with gradients
- Complicated topologies
- Robust algorithms



An example of the fused-sphere model: The central atom (white) is surrounded by a number of neighbors that define its exposed surface area and volume

Area Calculation

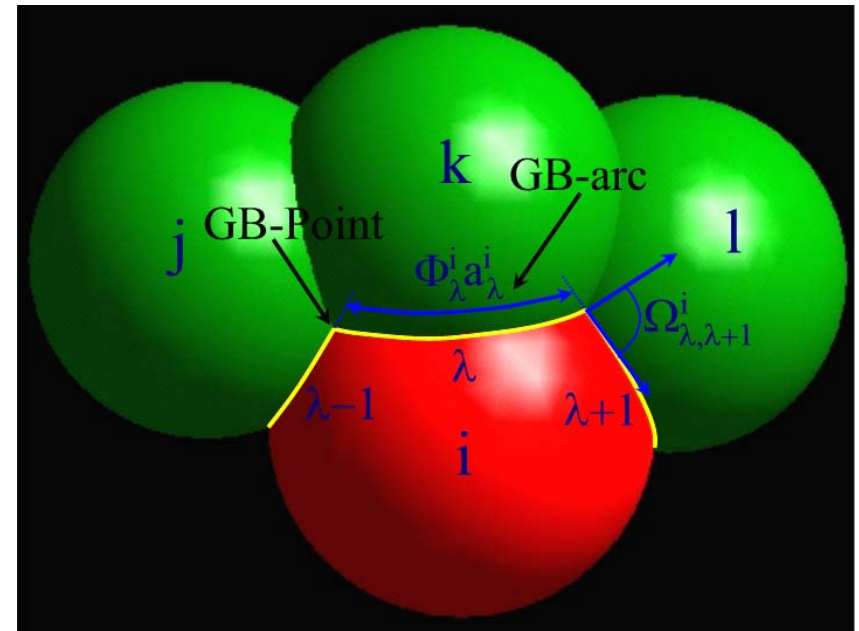
Zamanakos, Phd thesis (Caltech), 2002

Gauss-Bonnet Theorem

$$\sum_{i=1}^n \int_{C_i} k_g(l) dl + \iint_R K(s) ds + \sum_{i=1}^m \Omega_i = 2\pi\chi(R)$$

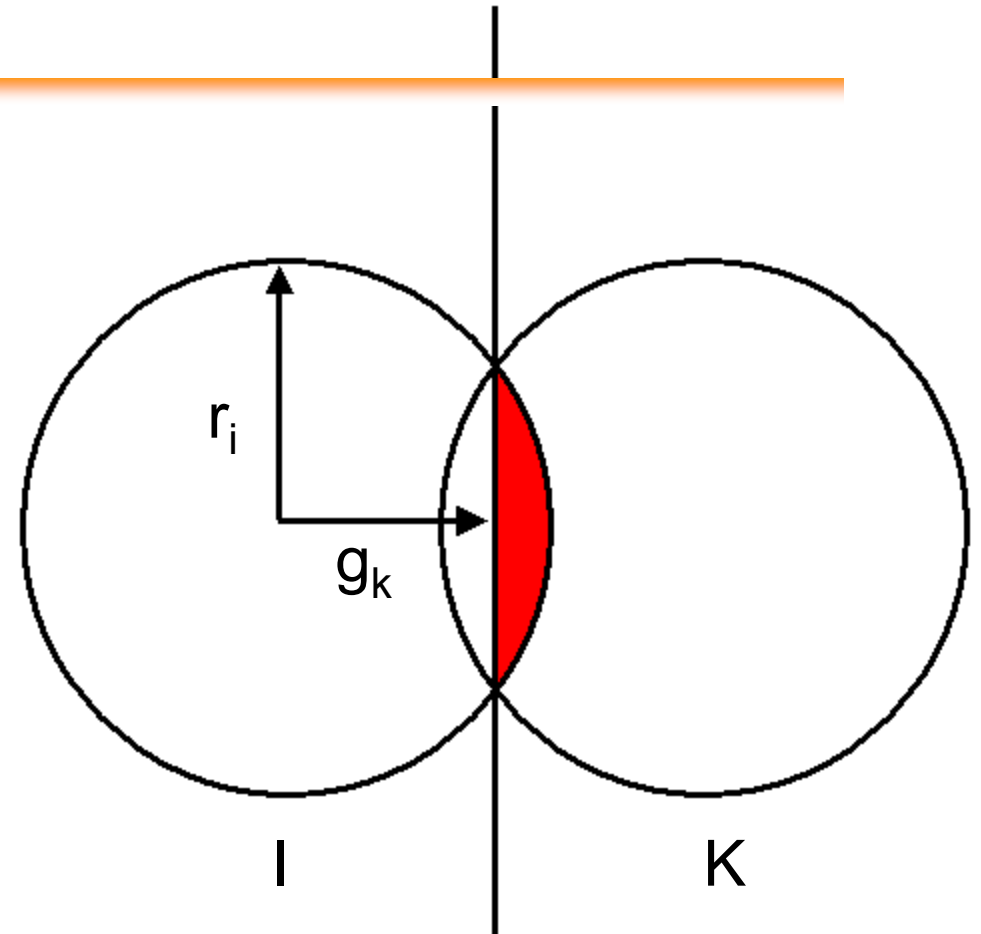
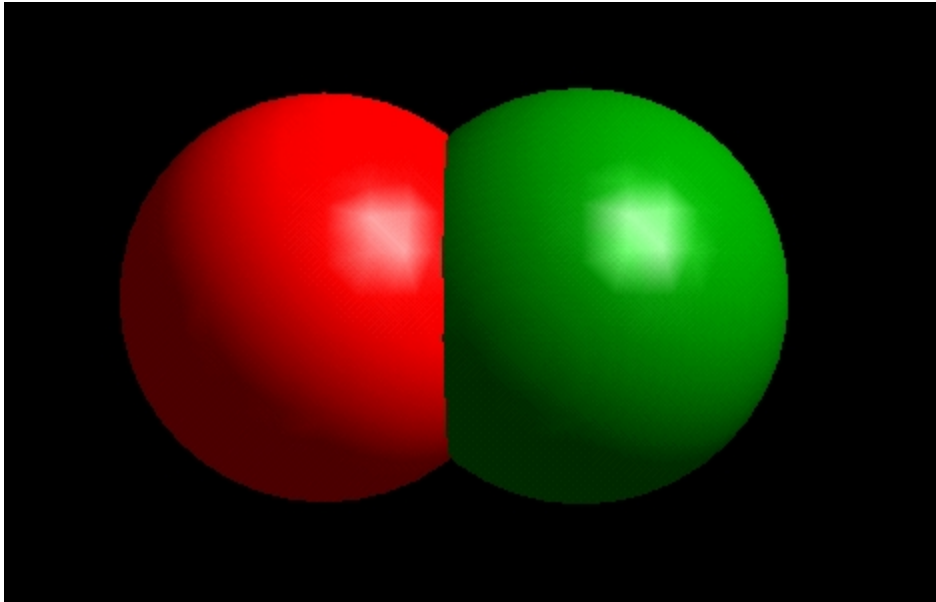
External angles of surface

Geodesic curvature, gaussian curvature of surface, Euler-Poincare characteristic of surface R



Simple Example Single Neighbor

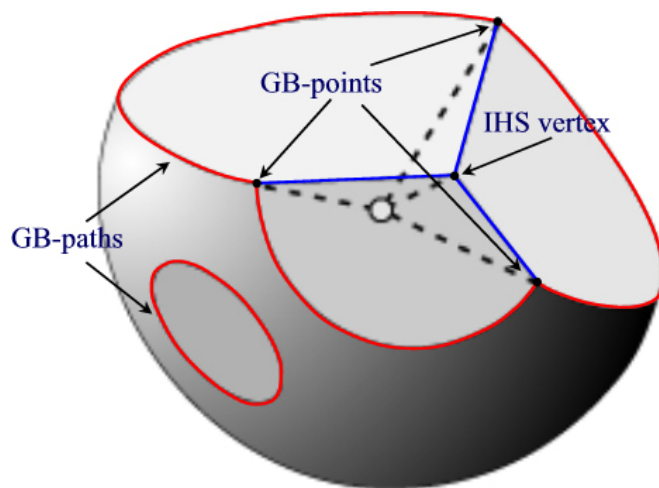
50



$$A_B = 2\pi r_i (r_i - g_k)$$

$$A_{SAS} = 4\pi r_i^2 - A_B$$

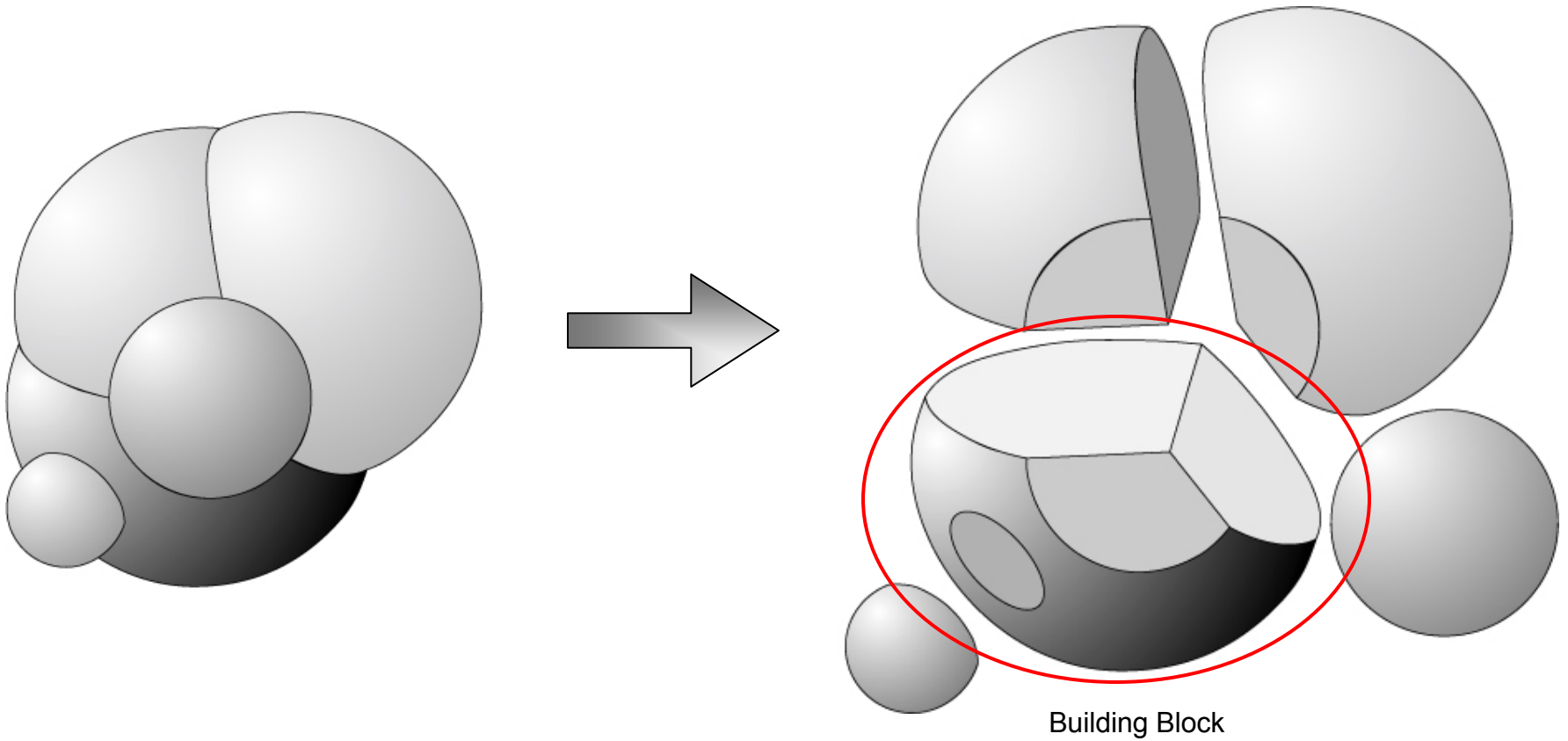
Determine GB-paths



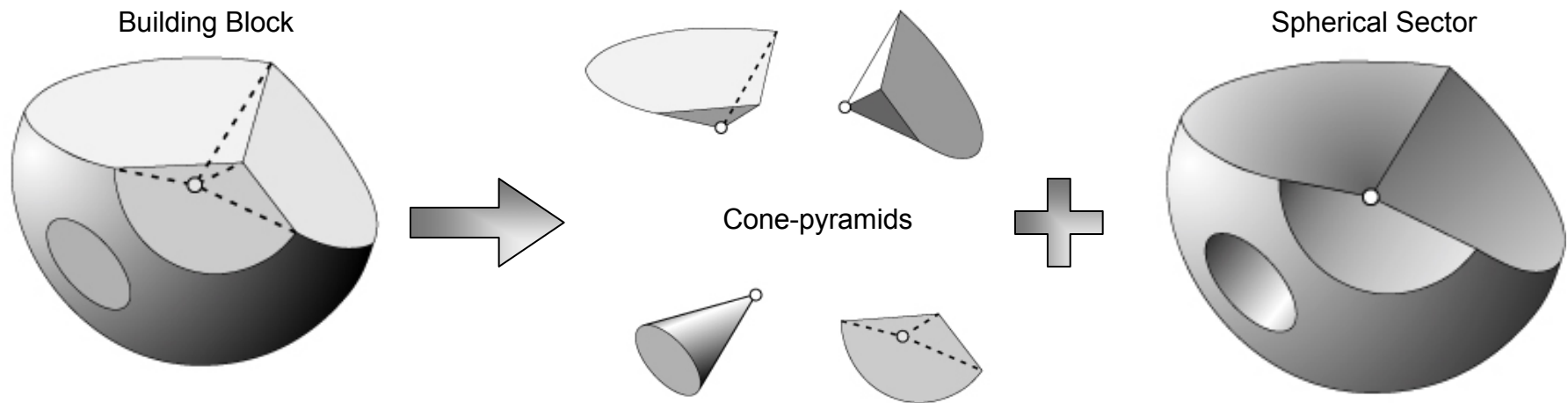
- Identify GB-points (intersection of two neighbors on surface of atom)
- Group GB-points that belong to the same GB-path
- Order GB-points in a CCW fashion to identify GB-paths

Key property: edges of IHS pierce atom at the GB-points

Decomposition into Building Blocks

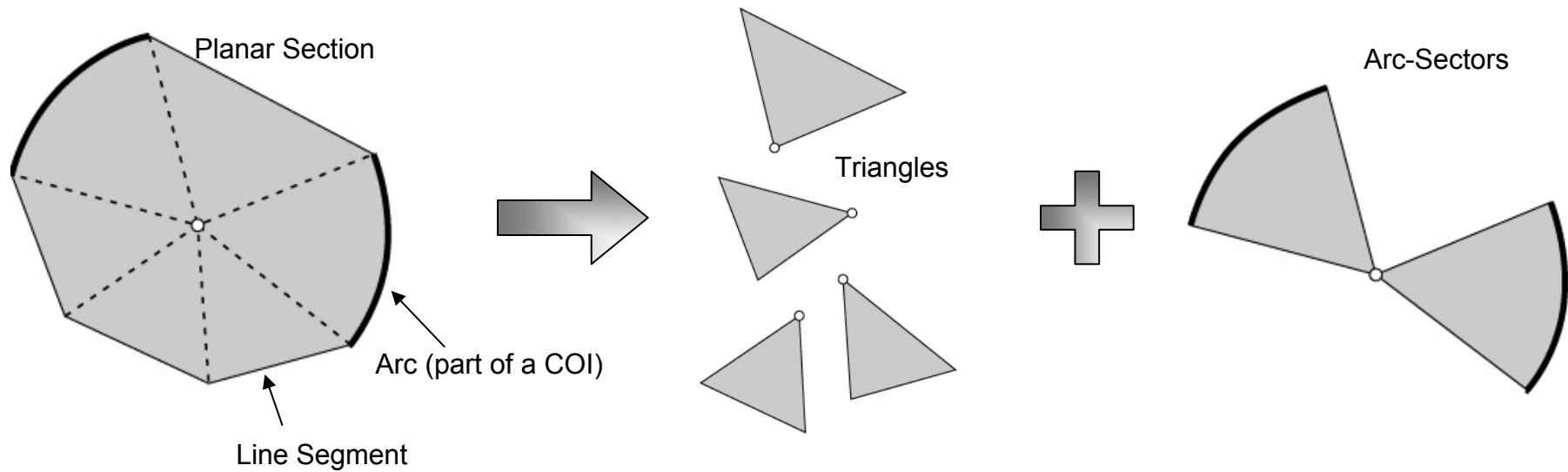


Volume Calculation



$$V_i = \sum_{j=1}^M \frac{1}{3} g_{ij} A_{ij} + \frac{1}{3} r_i S_i^{\text{exp}}$$

Volume Calculation



$$A_{ij} = \sum_{\mu=1}^{M_{ij}^{seg}} \frac{1}{2} h_{\mu} t_{\mu} + \sum_{\lambda=1}^{M_{ij}^{arcs}} \frac{1}{2} a_{ij} S_{\lambda}$$

COSMO solvation

- CONductor-like Screening MOdel (COSMO)
 - Consider the solvent being a conductor
 - Net potential at solute-solvent boundary is zero
 - Screening charge $\sigma(r_b)$ can be obtained in a single step

$$\phi(\vec{r}_b) = \phi_{solute}(\vec{r}_b) + \phi_{solvent}(\vec{r}_b) = 0 \quad \text{for all } \vec{r}_b \text{ at boundary}$$

$$\phi_{solute}(\vec{r}_b) = \int d^2\vec{r} \frac{\rho(\vec{r})}{|\vec{r} - \vec{r}_b|}$$

$$\phi_{solvent}(\vec{r}_b) = \int d^2\vec{r}_v \frac{\sigma(\vec{r}_v)}{|\vec{r}_v - \vec{r}_b|} = \sum_{v \neq b} \frac{\sigma(\vec{r}_v)}{|\vec{r}_v - \vec{r}_b|} + a\sigma(\vec{r}_b)$$

- Solvation free energy from the screening charges

$$\Delta G_{i/S}^{*ele} = \frac{1}{2} \Delta E_{i/S}^{*ele} = \frac{1}{2} \sum_b \sigma(\vec{r}_b) \phi(\vec{r}_b)$$

Cavity Formation Free Energy: Scaled Particle Theory

- Cavity Formation Free Energy:

Work to create a cavity of size V in solution

Related to the probability of finding a void of size V in solution

$$\Delta G_{i/S}^{*cav}(v) = -kT \ln p_0(v)$$

- The Scaled Particle Theory: (Reiss et al. 1959)

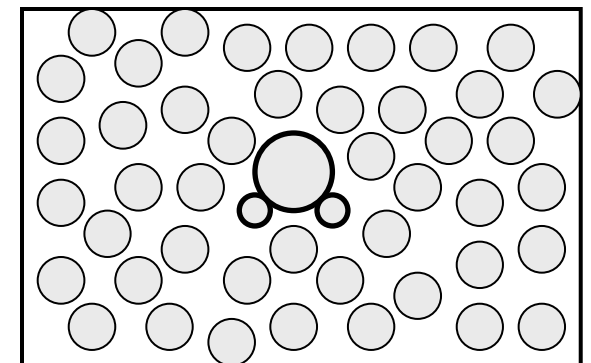
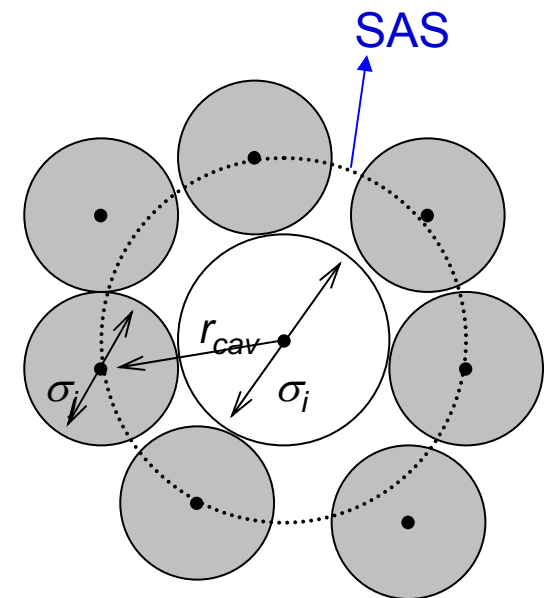
Hard sphere solute (σ_i) in hard sphere solvent (σ_j)

$$\Delta G^{SPT}(r) = K_0 + K_1 r + K_2 r^2 + K_3 r^3 \quad r = \frac{\sigma_i + \sigma_j}{2}$$

- Modified Scaled Particle Theory:

Molecular shape solute (σ_i) in hard sphere solvent (σ_j)

$$\Delta G_{i/S}^{*cav} = \sum_i^{spheres} \frac{A_i}{4\pi r_i} \Delta G_i^{SPT}(r_i)$$



An Example of Solvation Energy Calculation

1056 *J. Phys. Chem. B, Vol. 101, No. 6, 1997*

Amovilli and Mennucci

TABLE 2: Computed Solvation Free Energies, and Their Components, of Different Solutes in Water at 298 K

solute	W_1^a	W_2^a	ΔG_{sol} components (kcal/mol)						exp ^b	err
			iec	pol	rep	disp	cav	tot		
H ₂ O	DZP+s,p,d		1.0	-8.2	1.7	-4.6	4.2	-6.0	-6.3	0.3
NH ₃	DZP+s,p,d		0.8	-6.1	2.3	-5.7	4.6	-4.2	-4.3	0.1
H ₂ O ₂	DZP+s,p,d		1.2	-10.2	1.9	-6.7	5.6	-8.3	-8.7	0.4
N ₂	DZP+s,p,d		0.0	-0.2	0.7	-3.9	5.4	2.0	2.3	-0.3
CH ₄	DZP+s,p,d		0.0	-0.2	2.0	-5.5	6.0	2.3	2.0	0.3
CH ₄	DZP	s,p,d	0.0	-0.2	2.0	-6.0	6.0	1.8	2.0	-0.2
CH ₄	MINI	2s,2p,2d	0.0	-0.4	2.0	-6.6	6.0	2.0	2.0	0.0
CO	DZP+s,p,d		0.1	-0.9	0.7	-4.0	5.5	1.4	2.2	-0.8
HCHO	DZP+s,p,d		1.3	-7.2	1.4	-5.6	6.2	-3.9	-1.7	-2.2
HCN	DZP+s,p,d		1.2	-6.9	1.6	-4.7	6.0	-2.8	-3.2	0.4
N ₂ H ₄	DZP+s,p,d		1.7	-10.0	2.2	-8.2	6.5	-7.8	-9.3	1.5
CH ₃ OH	DZP+s,p,d		0.9	-6.8	2.2	-7.5	7.2	-4.0	-5.1	1.1
C ₂ H ₂	DZP+s,p,d		0.2	-3.2	1.5	-5.1	6.6	0.0	0.0	0.0
C ₂ H ₄	DZP+s,p,d		0.1	-1.3	2.8	-7.1	7.5	1.9	1.3	0.6
CH ₃ NH ₂	DZP	s,p,d	0.6	-5.3	2.2	-8.4	7.7	-3.2	-4.6	1.4
C ₂ H ₆	DZP	s,p,d	0.0	-0.2	2.5	-8.8	8.8	2.2	1.8	0.4
CH ₃ CHO	DZP	s,p,d	1.5	-7.9	2.0	-8.6	8.8	-4.2	-3.5	-0.7
C ₂ H ₅ OH	DZP	s,p,d	0.8	-6.8	2.6	-10.0	9.9	-3.5	-5.0	1.5
C ₃ H ₈	MINI	2s,2p,2d	0.0	-0.5	4.3	-12.9	11.5	2.4	2.0	0.4
CH ₃ COCH ₃	MINI	2s,2p,2d	0.8	-4.8	3.0	-13.1	11.6	-2.5	-3.8	1.3
C ₆ H ₆	MINI	2s,2p,2d	0.2	-2.7	4.7	-15.8	12.7	-0.9	-0.9	0.0
n-C ₈ H ₁₈	MINI	2s,2p,2d	0.0	-1.3	8.6	-28.3	27.0	5.9	3.0	2.9

 ΔG^{ele}  ΔG^{disp}  ΔG^{cav}

Commonly Used Solvation Models

Model Name	ΔG^{*ele} solute polarization/solvent pol.	ΔG^{*disp}	ΔG^{*cav}
PBF (Jaguar)	QM/Finite Difference	surface tension	
PCM (Gaussian)	QM/Apparent Charge	surface tension	SPT
COSMO-RS	QM/Conductor	surface tension	
DelPhi	Point Charge/Finite Difference	surface tension	
GB/SA	Point Charge/GB	surface tension	
SGB-SAS	Point Charge/SGB	surface tension	
FSM	none	surface tension	

Continuum Methods Accuracy

•Jaguar (QM) with PBF (finite element PB solver):

- Self-Consistent Reaction Field method to converge wavefunction
- Solvation energies are calculated within 0.2 kcal/mol of experiment
- pKa calculations are calculated within 1 unit for organics.
- Forces are calculated : get optimum geometry for solvated molecule

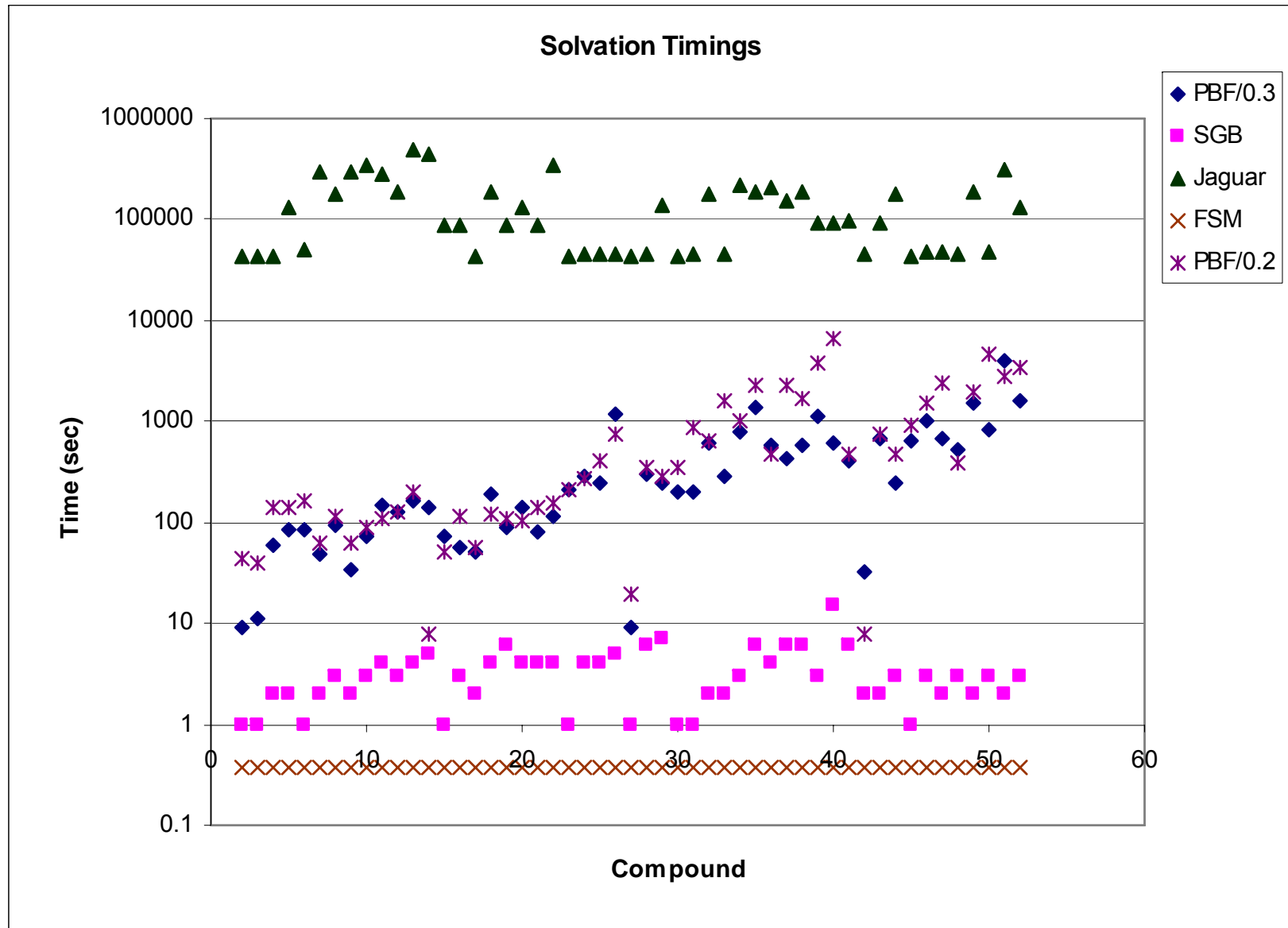
•SGB: Surface Generalized Born Algorithm

- Parameterized against dense mesh PBF results for organics
- Absolute Energies: within ~ 2 kcal/mol for polypeptides (400 atoms)
- Relative Energies: Accurate ranking of polypeptide conformations
- Performance: depends on surface area (not volume) leads to better scaling with system size. Roughly 10x faster than PBF.
- Parallelizable: atomic terms can be done independently: excellent distribution of work allows for very large simulations.

Comparison of Solvation Models

Name	Exp. RMS	PBF (1) 1.49	SGB 2.93	Jaguar 0.81	FSM 0.96
methane	2.00	1.92	1.34	1.16	0.31
ethane	1.83	2.16	1.60	1.76	0.44
propane	1.95	2.31	1.44	1.74	0.53
butane	2.08	2.47	1.51	1.74	0.61
2-methylpropane	2.32	2.39	1.29	1.40	1.62
pentane	2.33	2.63	1.76	2.00	0.73
2-methylbutane	2.38	2.57	1.46	1.17	1.38
2,2-dimethylpropane	2.50	2.44	1.24	1.67	0.88
hexane	2.48	2.81	1.74	2.12	0.79
2,2-dimethylbutane	2.59	2.67	1.29	1.96	0.89
heptane	2.62	2.97	1.79	2.61	0.89
2,2-dimethylpentane	2.88	2.80	1.51	1.86	0.98
octane	2.89	3.14	2.06	2.38	1.00
cyclopropane	0.75	1.62	1.19	0.04	0.23
cyclopentane	1.20	2.47	1.83	2.09	0.48
cyclohexane	1.23	2.61	1.95	1.73	0.58
methylcyclopentane	1.60	2.56	1.49	1.46	1.56
cycloheptane	0.80	2.72	2.04	1.30	0.65
methylcyclohexane	1.71	2.67	1.72	1.12	1.37
cyclooctane	0.86	2.85	2.16	0.95	0.75
1,2-dimethylcyclohexane	1.58	2.82	1.70	0.58	1.45
cyclopentene	0.56	1.81	1.18	0.42	0.28
cyclohexene	0.37	1.74	1.28	0.78	0.43
1-methylcyclohexene	0.67	2.16	1.53	0.96	0.28
1,3,5-cycloheptatriene	-0.99	0.09	0.21	-1.66	-0.16
benzene	-0.86	-0.44	0.17	-2.09	-1.29
methylbenzene	-0.89	-0.04	0.32	-2.17	-1.26
1,4-dimethylbenzene	-0.80	0.48	0.66	-2.12	-1.27

Efficiency



Examples: 1. Fast Solvation Model (FSM)

- Fast Solvation Model

- Developed by Dr. Mario Blanco

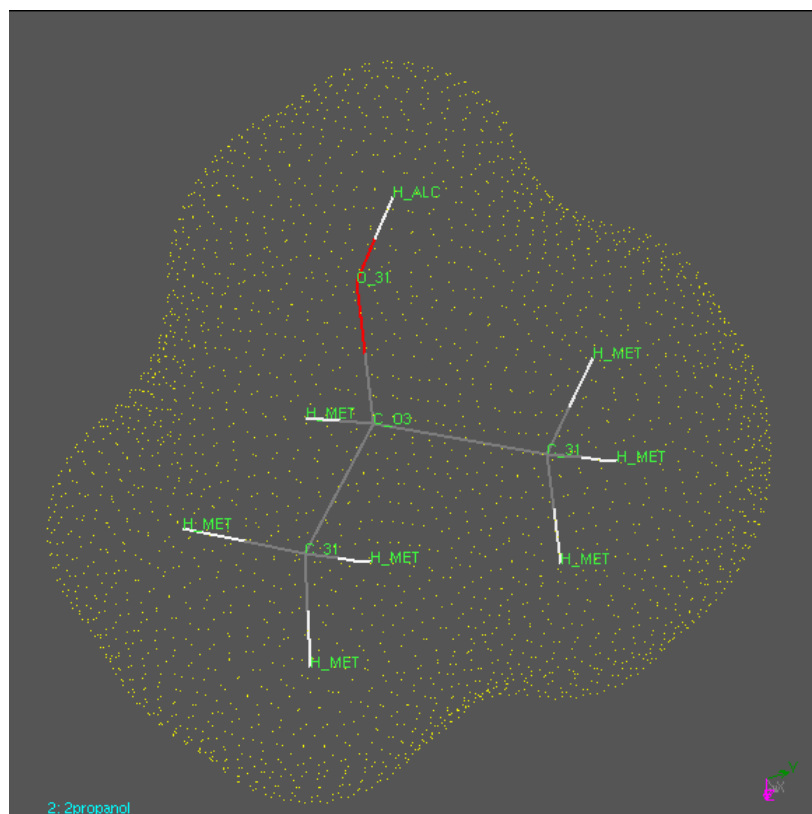
- Available in Cerius2

$$\Delta G_{i/S}^{*sol} = \cancel{\Delta G_{i/S}^{*ele}} + \Delta G_{i/S}^{*disp} + \Delta G_{i/S}^{*cav} = \sum_{i=1}^N \sigma_i A_i$$

- Parameters: 78 surface tension coefficients (103 atomic radii)
- Parameters fitted to 376 small molecules in water (Cabani Set)
- SES used
- Good for nonpolar solutes, worse for polar solutes
 - RMS (kcal/mol): 0.26 (HC), 0.78 (O), 1.21 (N), 1.99 (F), 1.52 (Cl, Br, I), 0.16 (S,P)

Examples: 1. Fast Solvation Model: Example

Hydration free energy of 2-propanol



Atom Type	Surf. Tension	Area (A^2)	Solvation
H_MET	0.0132	39.7501	0.5247
H_ALC	-0.1381	6.5777	-0.9084
C_31	0.0054	33.3833	0.1803
C_O3	-0.0391	5.3865	-0.2106
O_31	-0.2988	13.8971	-4.1525
Total Area =99.0 (A^2)			
Solvation Free Energy = -4.57 Kcal/mol			

Expt value: -4.76 Kcal/mo

Examples: 2. AVGB-SAS

•Analytical Volume Generalized Born- Solvent Accessible Surface

-Developed by Dr. Georgios Zamanakos

-Available in MPSim

$$\Delta G_{i/S}^{*sol} = \Delta G_{i/S}^{*ele} + \Delta G_{i/S}^{*disp} + \Delta G_{i/S}^{*cav}$$

same as FSM

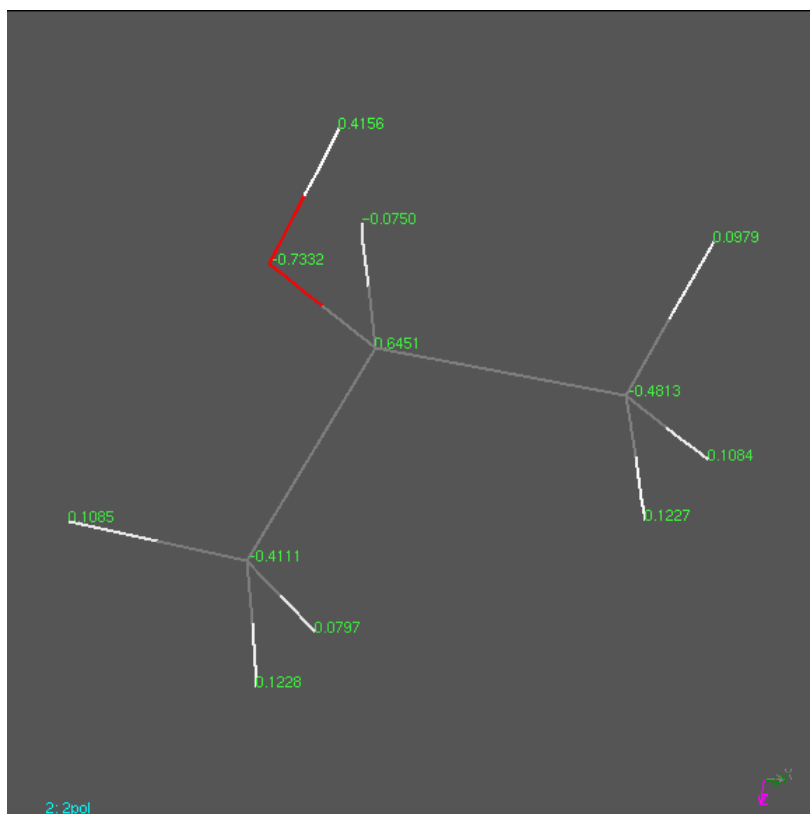
$$\Delta G_{i/S}^{*disp} + \Delta G_{i/S}^{*cav} = \sum_{i=1}^N \sigma_i A_i$$

$$\Delta G_{i/S}^{*ele} = -\frac{1}{2} \left(\frac{\epsilon - 1}{\epsilon} \right) \sum_{i=1}^N \sum_{j=1}^N \frac{q_i q_j}{\sqrt{r_{ij}^2 + \alpha_i \alpha_j \exp(-r_{ij}^2 / 4\alpha_i \alpha_j)}}$$

$$\frac{1}{\alpha_k} = \frac{1}{R_k} - \frac{1}{4\pi} \sum_{k' \neq k} \int_{V_{k'}} \frac{1}{|\vec{r} - \vec{r}_k|^4} d^3 r$$

Solvent accessible surface areas and solvent excluded volumes must be calculated fast and accurately

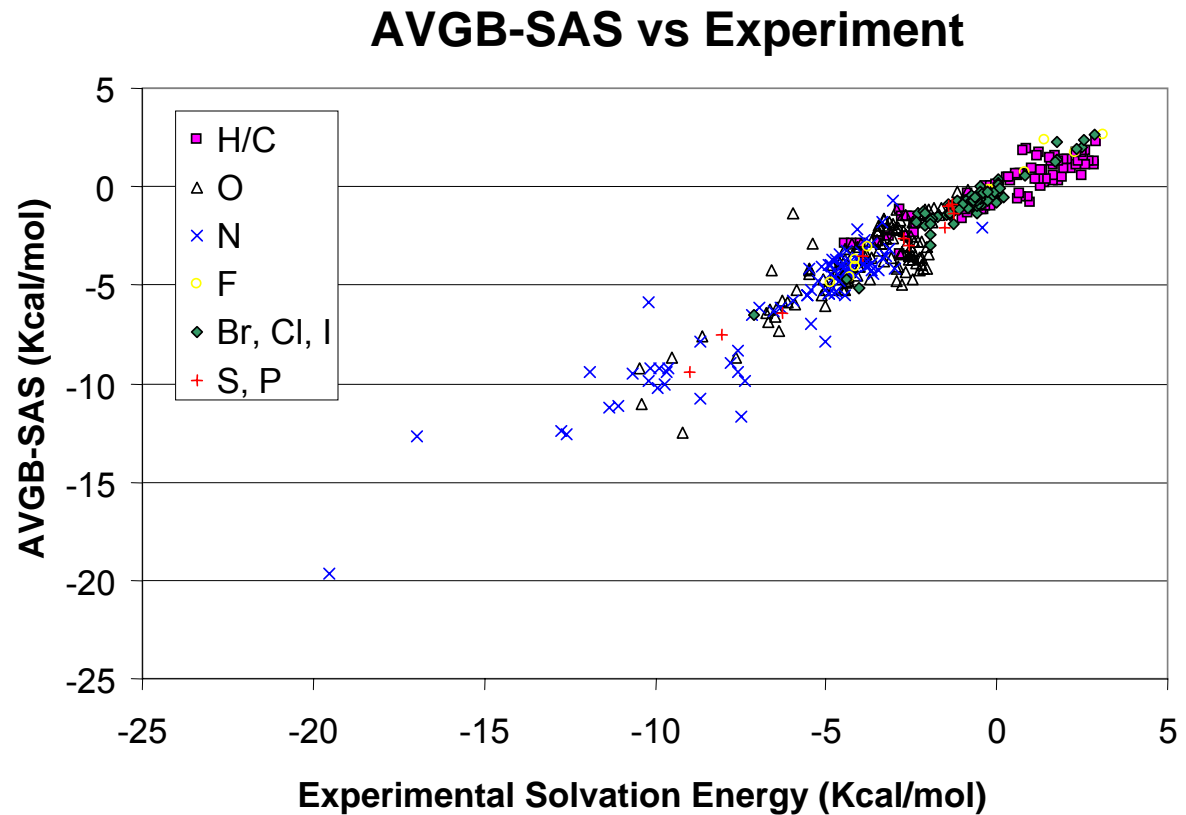
Examples: 2. AVGB-SAS: Example



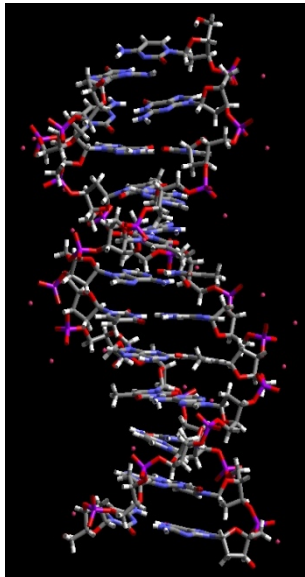
Valence	
Bonds :	0.62474
Angles :	0.96765
Torsion :	0.00697
Inversions :	0
Nonbond	
Nonbond :	-101.03811
Coulomb :	-103.55434
VDW :	2.51624
Hbonds :	0
Solvation	
FSM - Cavity :	-0.33879
FSM - Polar :	-5.27538
Total Solvation	-5.61417

Examples: 2. AVGB-SAS: Hydration Free Energy

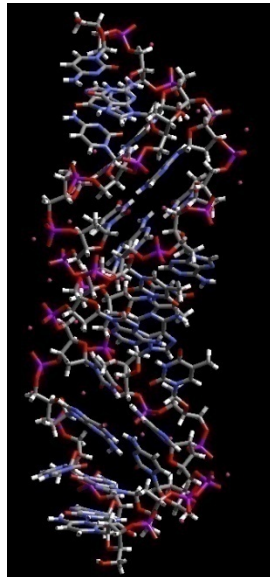
- Parameters: 78 surface tension coefficients (103 atomic radii)
- Parameters fitted to 376 small molecules in water (Cabani Set)
- Overall RMS: 0.74 kcal/mol



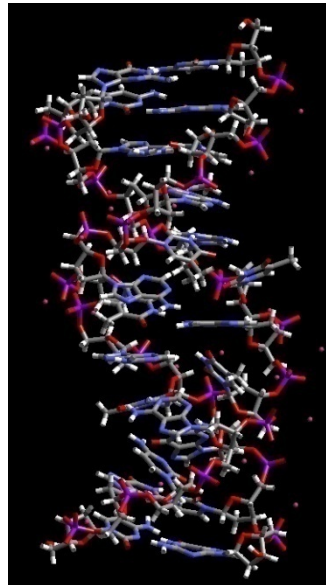
Examples: 2. AVGB-SAS: B-DNA Dynamics



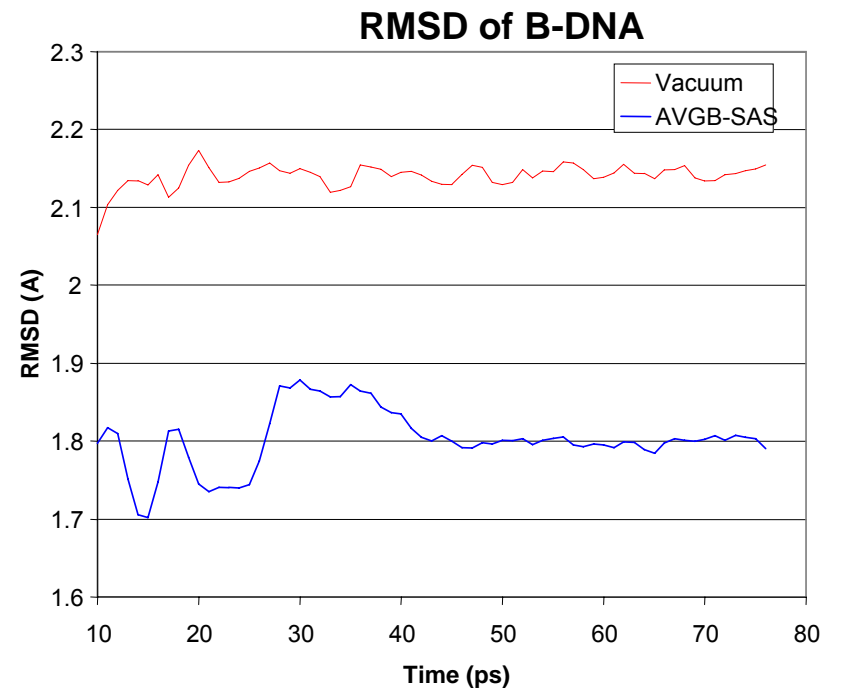
Canonical



Vacuum



AVGB-SAS

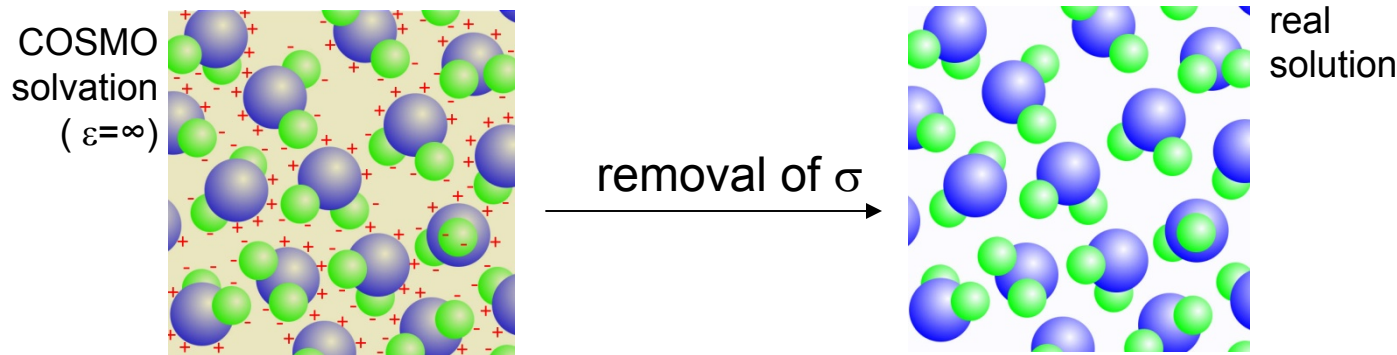


Examples: 3. COSMO-RS/COSMO-SAC

- COSMO-for realistic solvent (RS)/segment activity coefficient (SAC)

- Developed by Klamt and coworkers/ST Lin and coworkers

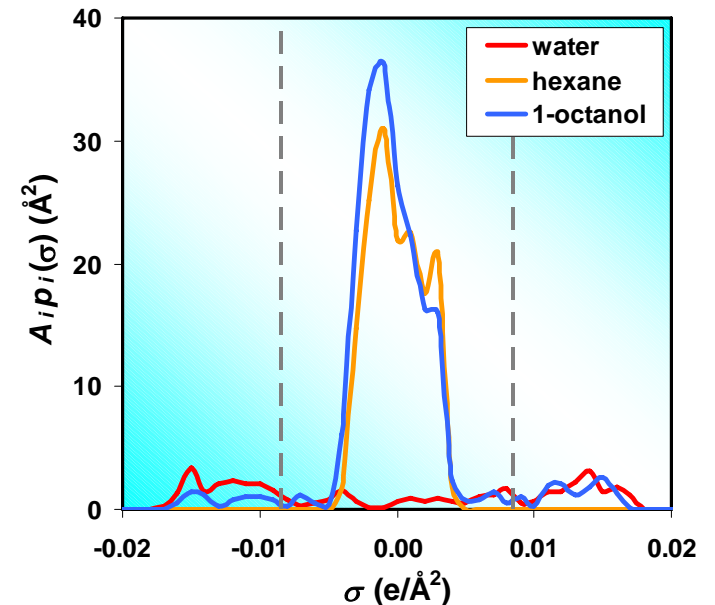
- Available in Cerius²/DMol³



- Use the screening charges σ
- Histogram of σ – the σ -profile, $p(\sigma)$
- Solvation Free Energy from the σ -profile

$$\Delta G_{i/S}^{*ele} = \Delta G_{i/conductor}^{COSMO} + \frac{A_i}{a_{eff}} \sum_{\sigma_m} p_S(\sigma_n) \ln \Gamma_S(\sigma_m)$$

$$\ln \Gamma_S(\sigma_m) = -\ln \left\{ \sum_{\sigma_n} p_S(\sigma_n) \Gamma_S(\sigma_n) \exp \left[\frac{-\Delta W(\sigma_m, \sigma_n)}{kT} \right] \right\}$$



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