MMTSB/CTBP Workshop

August 4-9, 2009

Implicit Solvent

General Principles & Models in CHARMM

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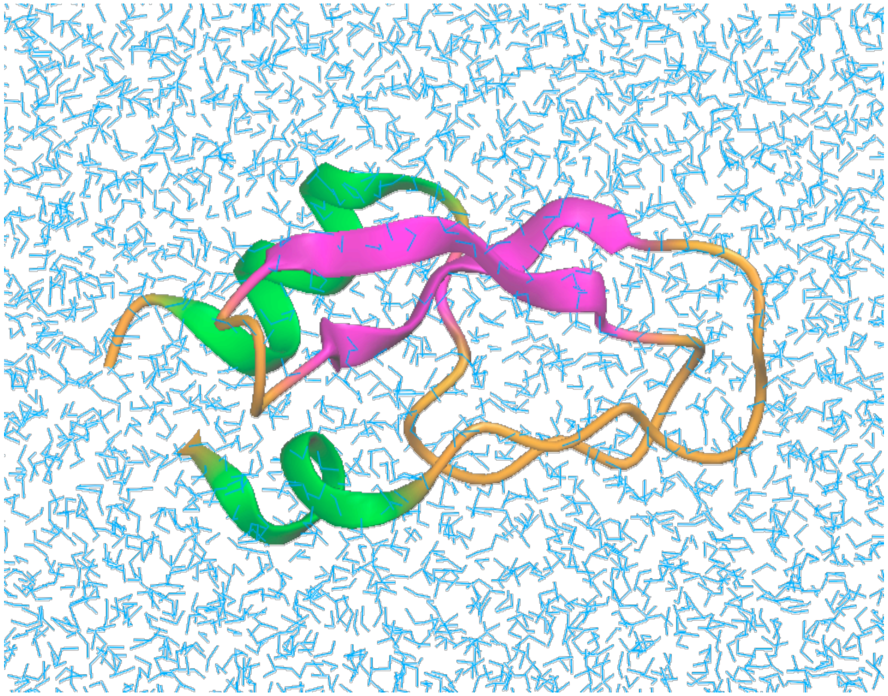
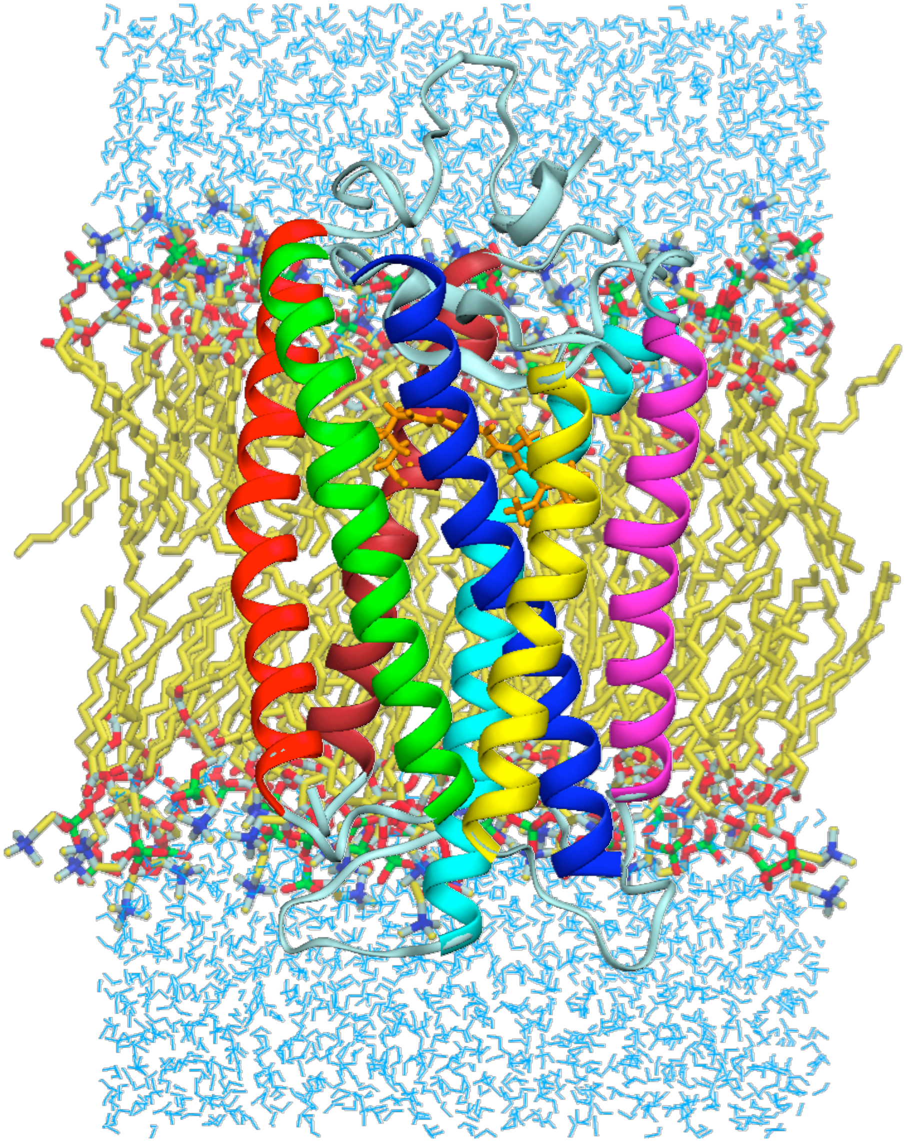
Explicit Solvent





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Solvation Free Energy

- The mean influence of solvent molecules on the solute is captured by the reversible work required to transfer the solute from vacuum to water in a fixed configuration, i.e., the solvation free energy.

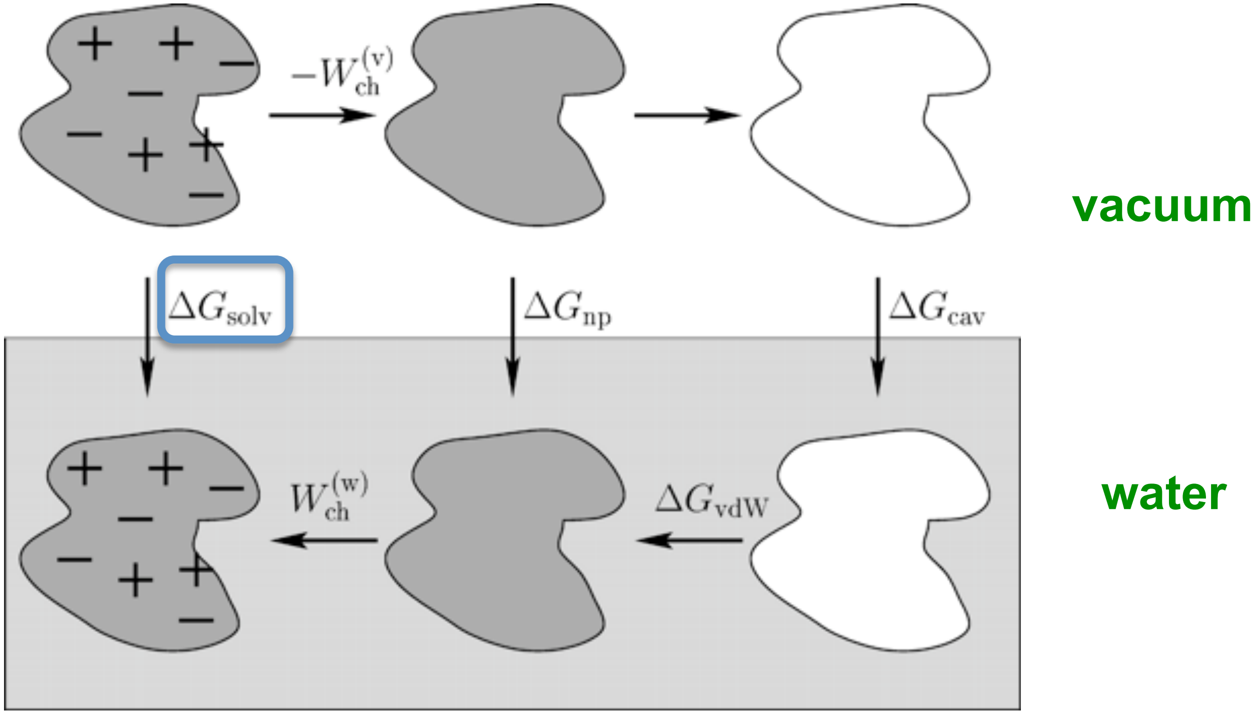
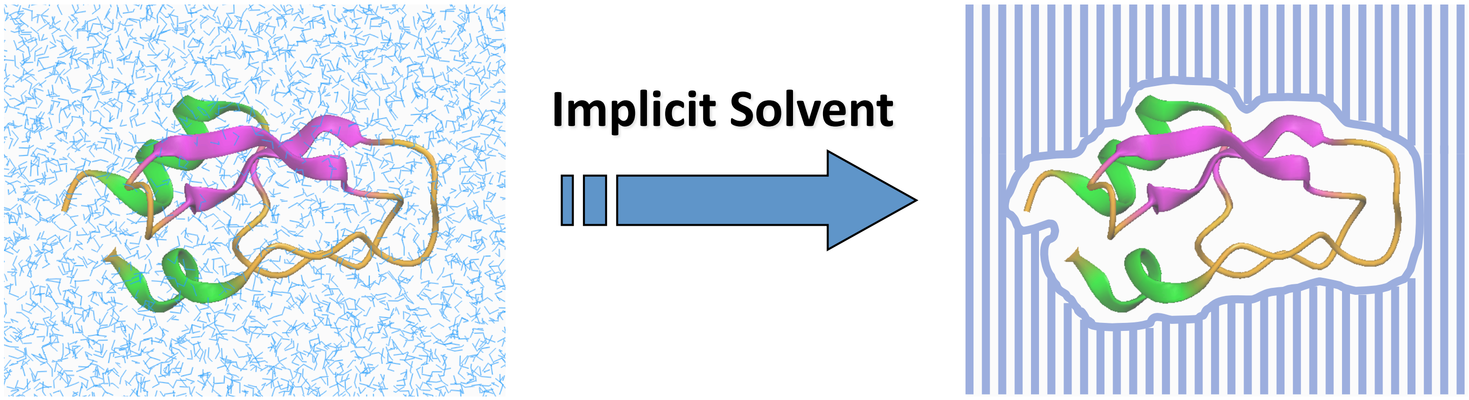


Figure credit: Levy et al., JACS (2003)

Implicit Treatment of Solvent



Implicit Solvent

$$H = H_{\text{prot}} + H_{\text{prot-wat}} + H_{\text{wat}}$$

$$H = H_{\text{prot}} + \Delta G_{\text{solv}}$$

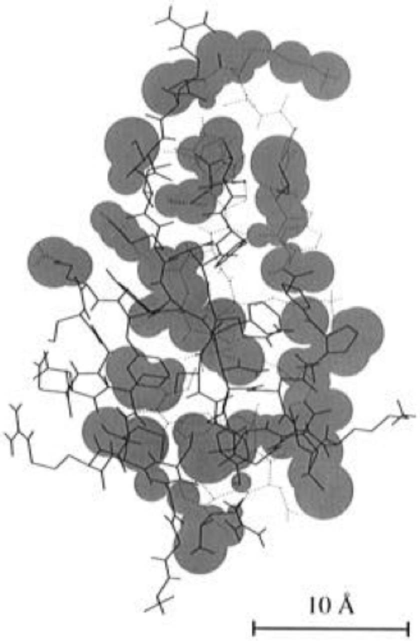
- The solvation free energy in principle contains *all* information of solvent on *equilibrium* properties of solute.
- The goal of implicit solvent models is to calculate ΔG_{solv} with desired computational efficiency and numerical accuracy.
- Important assumptions are required in order to efficiently estimate the solvation free energy without having to extensively sample all water degrees of freedom.

Continuum Water Models

- Water dynamics is typically much faster that that of protein conformational diffusion. Thus water can be described as a continuum medium.
  - This is just one of the possible implicit treatments of water.
- Several "generations" of continuum water models have been explored in biomolecular modeling over the time.
  - Simple dielectric models: constant ε=80, RDIE (distance-dependent dielectric), …
  - Geometric models: based on exposed surface area or solute volume
  - Continuum dielectric: Poisson-Boltzmann (PB), generalized Born (GB)
    - A LOT variations, and with extension to membrane systems!
    - Most of these models are supplement with a SA-based nonpolar term
  - Continuum dielectric + full treatment of nonpolar solvation: the next generation of highly accurate implicit solvent model?

Geometric Models

- Largely based on the observation that waters in the first solvation shell dominates the solvation energetics
- Fully empirical: directly estimating the solvation free energy from certain geometric properties, such as exposed surface area or solvent-exclusion volume.
  - Not very accurate, poor description of conformational dependence
- Models in CHARMM
  - **ASP**: SASA-based (Wesson & Eisenberg, 1986)
    - Documents: aspenr.doc, aspenrmb.doc
  - **RUSH** (rush.doc) (Guvench and Brooks, 2004)
  - **EEF1**: volume-based (Lazaridis & Karplus, 1999)
    - Re-parameterized in 2004
    - Extension to membrane (Lazaridis, 2003)
    - Document: eef1.doc

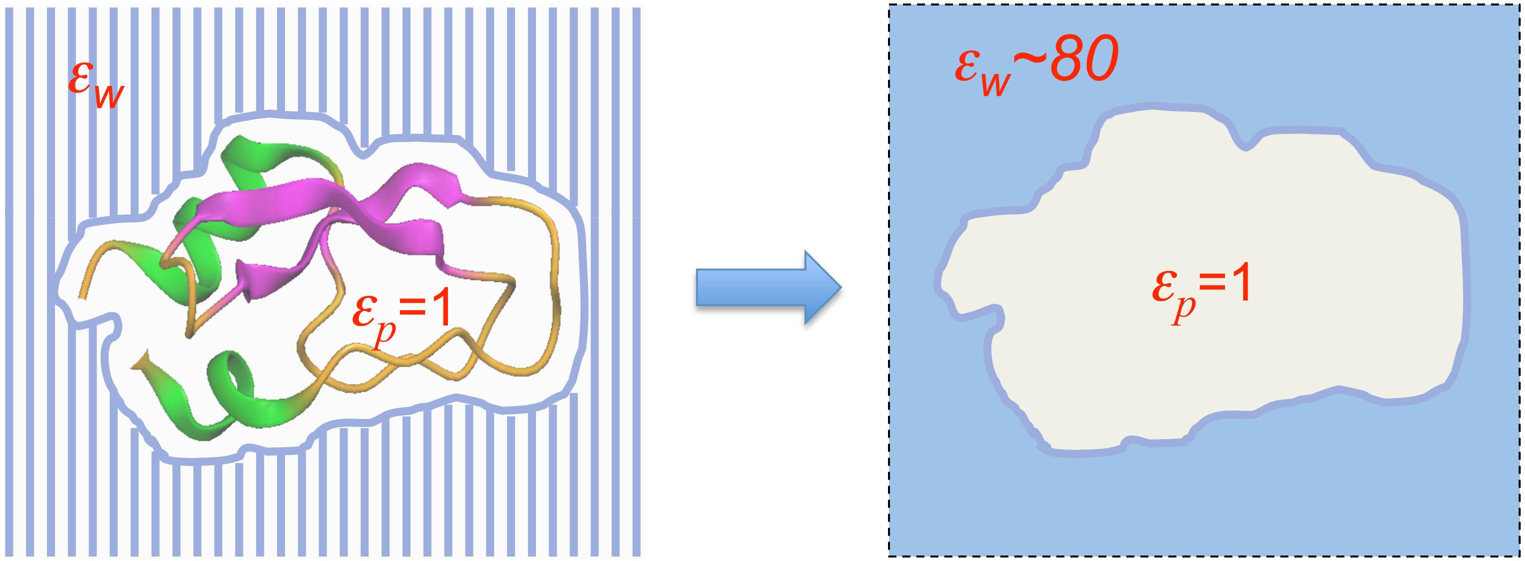


Continuum Electrostatics

- Decompose the total solvation free energy into nonpolar and electrostatic contributions

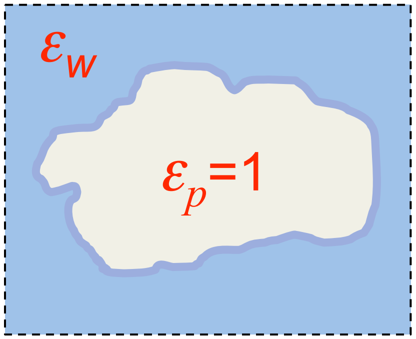
$$\Delta G_{\mathrm{solv}} = \Delta G_{\mathrm{elec}} + \Delta G_{\mathrm{np}}$$

- Electrostatic component: water as a high dielectric medium



- Nonpolar solvation: typically SA-based: $\Delta G_{\mathrm{np}} = \gamma \cdot S$

Poisson-Boltzmann (PB) Theory



- The “standard” of continuum electrostatics
- The Nonlinear PB equation:

$$\nabla \cdot \left[\varepsilon(\mathrm{r})\nabla\phi(\mathrm{r})\right] = -4\pi\left[\rho_{\mathrm{prot}}(\mathrm{r}) + \sum_{\alpha} q_\alpha C_\alpha^{\mathrm{bulk}} \exp\left(-q_\alpha \phi(\mathrm{r})/k_{\mathrm{B}}T\right)\right]$$

- PB equations need to be solved twice, one for vacuum and one for solution, to calculate ΔG_{elec} as:

$$\Delta G_{\mathrm{elec}} = \frac{1}{2}\sum q_i\left[\underline{\phi_s(\mathbf{r}_i)} - \underline{\phi_v(\mathbf{r}_i)}\right]$$

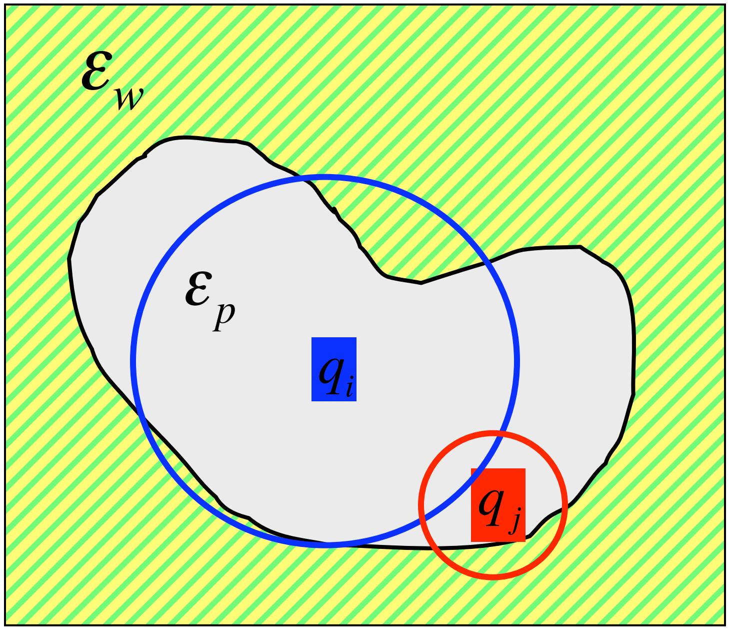
- ϕ(r) is obtained numerically using the finite difference method
  - Very expensive, especially with fine grids for high accuracy
  - Atomic forces are difficult to compute, thus **not suitable for MD**
- CHARMM Implementation: **PBEQ** (see pbeq.doc) (Im et al, 1998)
  - **APBS** also available as a plug-in (apbs.doc) (Baker et al, 2001)

Generalized Born (GB) Theory

- A pair-wise approximation to the PB theory (Still et al., 1990):

$$\Delta G_{\text{elec}} \approx \frac{1}{2}\left(\frac{1}{\varepsilon_{\text{w}}}-\frac{1}{\varepsilon_{\text{p}}}\right)\sum_{ij}\frac{q_i q_j}{\sqrt{r_{ij}^2+\underline{R_i^{\text{GB}}R_j^{\text{GB}}}\exp\left(-r_{ij}^2/4\underline{R_i^{\text{GB}}R_j^{\text{GB}}}\right)}}$$

- The most important quantity in GB is so-called effective Born radius (R^{GB}), which satisfies the Born equation:



$$\Delta G_{\text{elec},i} = \frac{1}{2}\left(\frac{1}{\varepsilon_w}-\frac{1}{\varepsilon_p}\right)\frac{q_i^2}{R_i^{\text{GB}}}$$

$$R_i^{\text{GB}} \rangle R_j^{\text{GB}}$$

“The effective Born radius represents the distance between a particular atom and the effective spherical dielectric boundary.”

Effective Born Radii

- R_i^{GB} (or $\Delta G_{\mathrm{elec,i}}$) can be computed using the PB theory
  - This provide a standard for numerical parameterization of GB
- GB well approximates PB if R_i^{GB} are accurate (Onufriev et al, 2002; Feig et al, 2004)
- The key objective of GB is efficient and accurate evaluation of R_i^{GB}, or equivalently, $\Delta G_{\mathrm{elec,i}}$.
  - This is also where most GB models differ
  - Several "generations" of GB models also exist, depending on the complexity and accuracy of R_i^{GB} evaluation.
  - Direct numerical evaluation of the follow integral appears to be more of the more accurate methods.
  - Coulomb Field Approximation and corrections
- GB allows analytical evaluation of atomic forces and is thus suitable for MD simulations.

The Generalized Born Zoo (as of 2005)

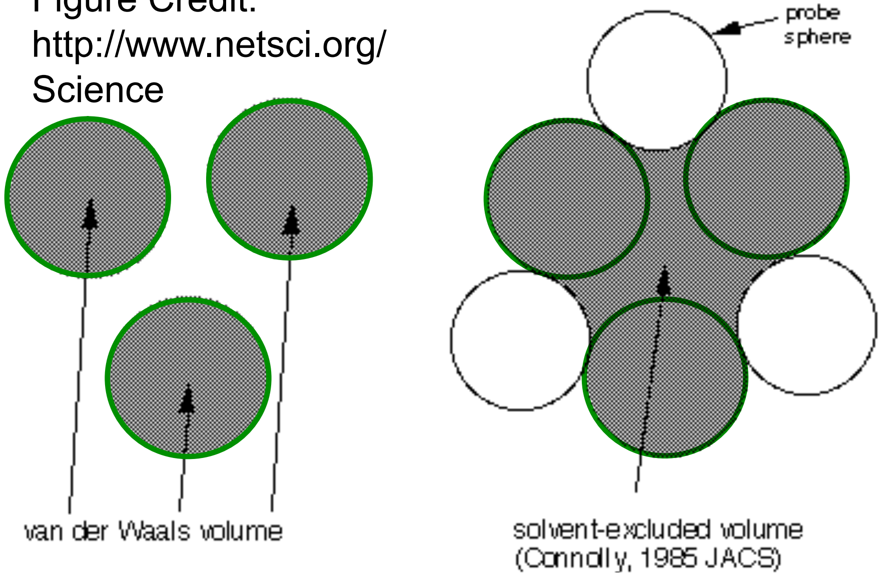
Name	Year	Authors	Program	Calculation of Born radii	CFA Corr.	Dielectric Boundary
GB GB/ SA	1990	Still, Tempczyk, Hawley, Hendrickson	Macromodel	FDPB	Yes	Molecular surface
GB	1995	Hawkins, Cramer, Truhlar	Amber, Tinker	Pairwise descreening	No	Overlapping spheres
ACE	1996/ 2001	Schaefer, Karplus	CHARMM	Pairwise sum of atomic volumes	No	Overlapping Gaussians
GB	1997	Qiu, Shenkin, Hollinger, Still	Macromodel,Tinker	Pairwise sum of atomic volumes	No	Overlapping spheres
S-GB	1998	Ghosh, Rapp, Friesner	Impact	Surface integral formulation	Yes	Overlapping spheres
GenBorn	1999	Dominy, Brooks	CHARMM	Pairwise sum of atomic volumes	No	Overlapping spheres
GBMV	2002/ 2003	Lee, Salsbury, Feig, Brooks	CHARMM	Numerical integration	Yes	Molecular surface
GBSW	2003	Im, Lee, Brooks	CHARMM	Numerical integration	Yes	Overlapping spheres + smooth boundary
AGB	2004	Gallicchio, Levy	Impact	Pairwise descreening	No	Overlapping spheres
GB	2004	Onufriev, Case	Amber	Pairwise descreening, radius rescaling	No	Molecular surface

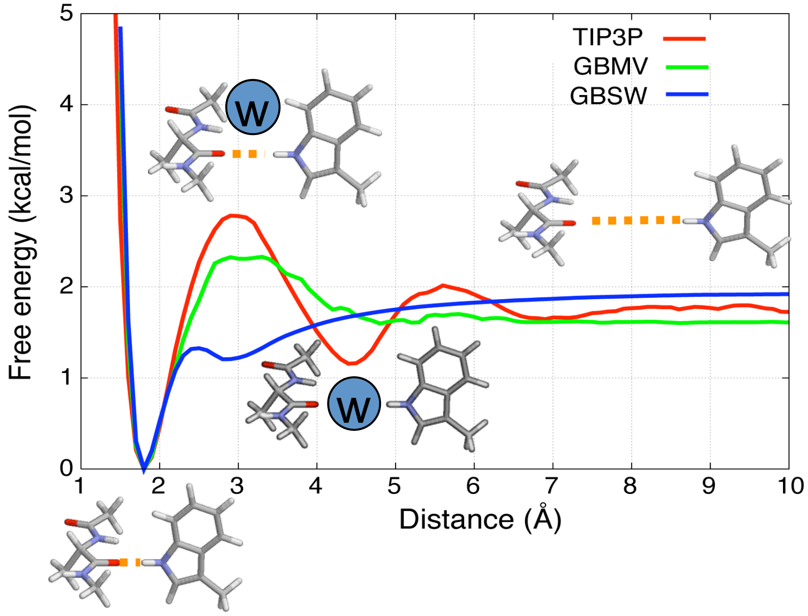
These are just selected examples. There are many more GB models around.

Definition of Solute-Solvent Boundary

- A key property for calculating solvation free energy.
  - Molecular surface (MS) vs. van der Waals (vdW) surface

Figure Credit:
http://www.netsci.org/
Science



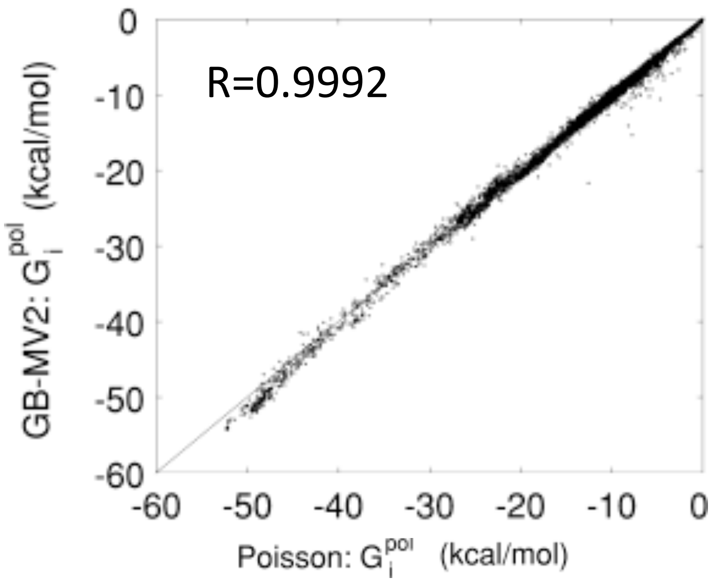


  - MS: physically correct; but more expensive, less stable (**GBMV**)
  - vdW: inexpensive and stable; but with intrinsic limitations such as unphysical interstitial high dielectrics. (**GBSW**)

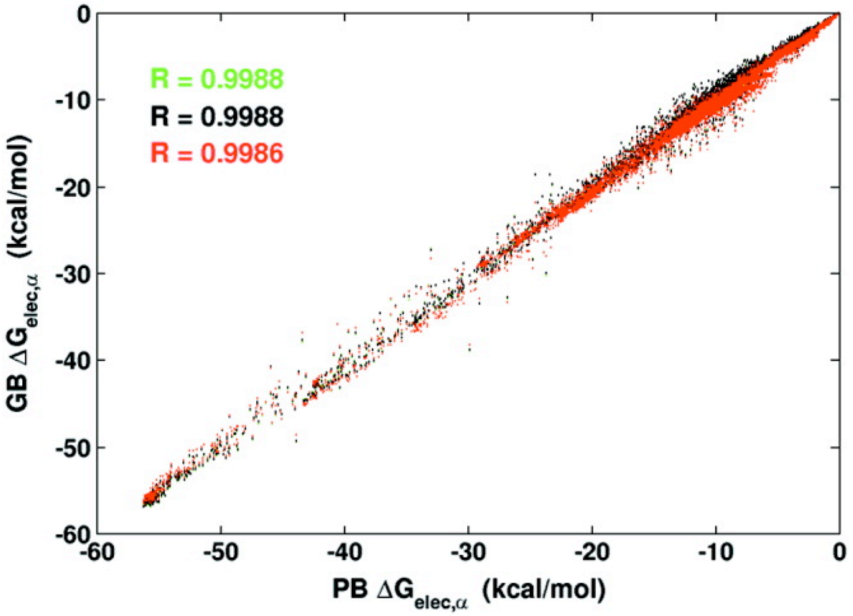
Lee and Olson, JPCB (2005); Swanson et al., JPCB (2005); Zhu et al, JCC (2007);

Numerical Accuracy of GB

- Latest GB models can be much faster, but numerically as accurate, compared to corresponding high-resolution PB calculations (Feig et al, 2004)
  - This is achieved both by advances in formalism and careful parameterization of **numerical parameters**.



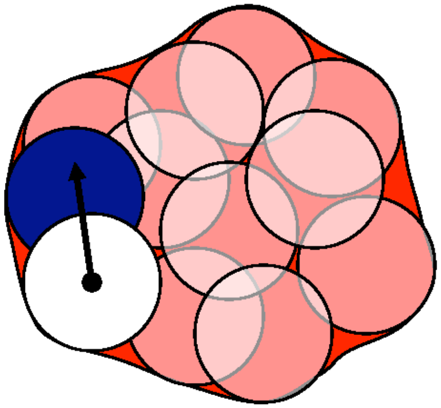
GBMV Lee et al., JCC (2003).



GBSW Im et al., JCC (2003).

Physical Parameters of GB (or PB)

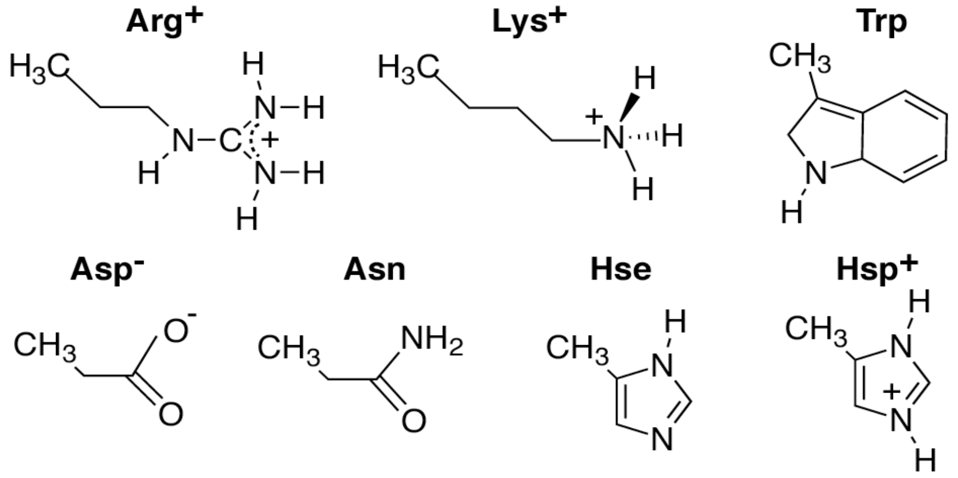
- Underlying biomolecular force field: partial charges, Lennard-Jones parameters, **torsion potentials**
- Continuum electrostatics (PB or GB)
  - Solvent boundary definition: MS vs. vdW surface
  - **Atomic (input) radii**
  - Dielectric constants (ε_w=80, ε_p=1)
  - Probe radius (for MS; fixed in analytical MS)
- Non-polar solvation models
  - Surface definition: MS, SASA or vdW
  - Atomic (input) radii
  - (Effective) surface tension coefficient



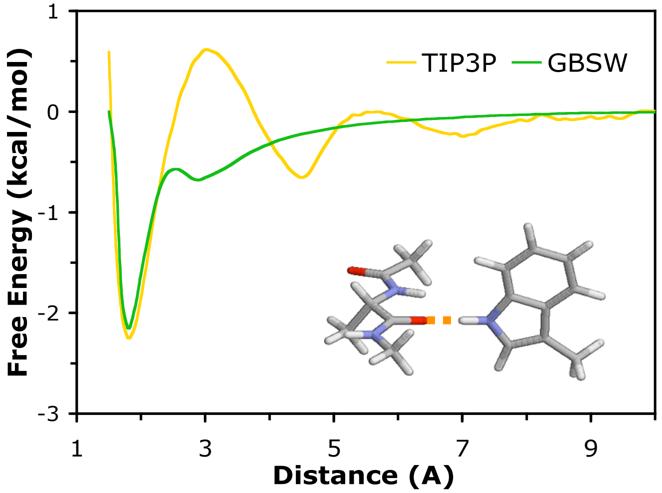
While numerical accuracy dedicates the "precision",
the physical parameters determine the accuracy of GB.

GBSW Can Be Optimized to Balance Electrostatic Solvation and Intramolecular Interactions

I. Model Compounds



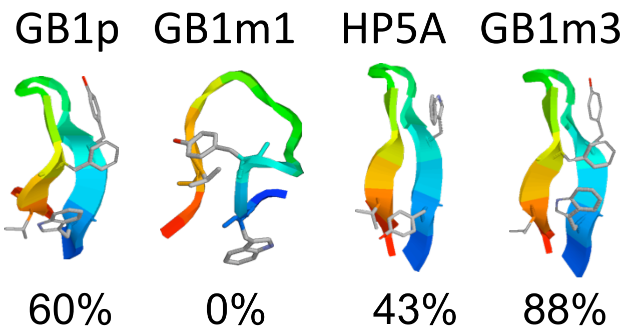
Potentials of Mean Force



II. Model Peptides

name	sequence	expr. fold	
$(AAQAA)_3$	AAQAAAAQAAAAQAA	α	~50%
GB1p	GEWTYDDATKTFTVTE	β	30~80%
GB1m1	GEWTYDDATKTATVTE	β	6 ± 6%
HP5A	KKYTWNPATGKATVQE	β	21±10%
GB1m3	KKWTYNPATGKFTVQE	β	86 ± 3%

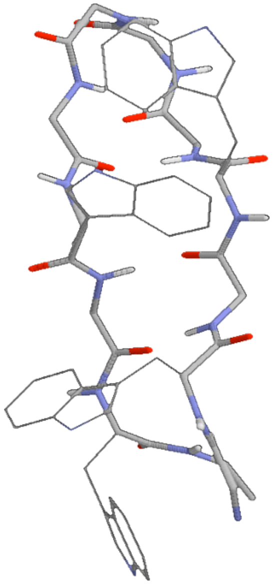
Simulated Folded Populations



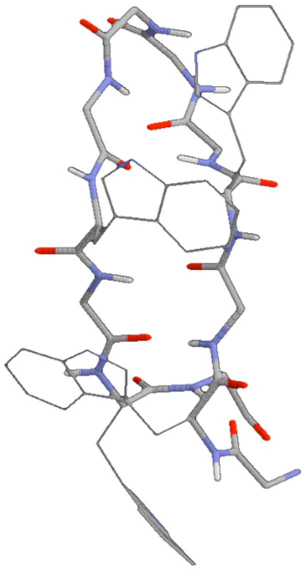
Chen, et al., JACS (2006).

Trpzip2 and Trp-Cage

SWTWE NGKWT WK

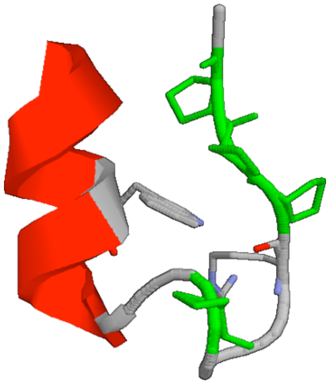


PDB: 1le1

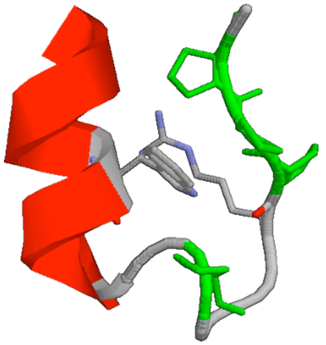


54%, 1.0 Å

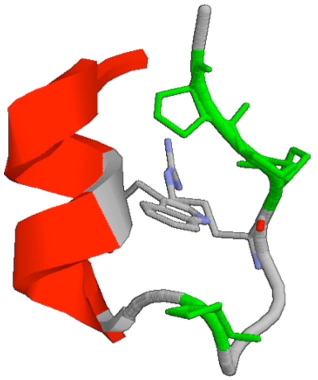
NLYIQ WLKDG GPSSG RPPPS



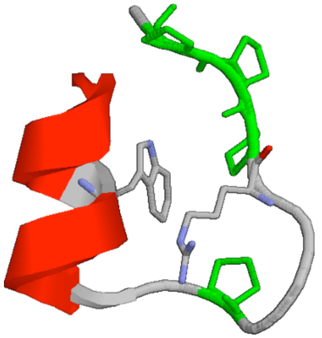
NMR (1l2y)



43%, 1.0 Å



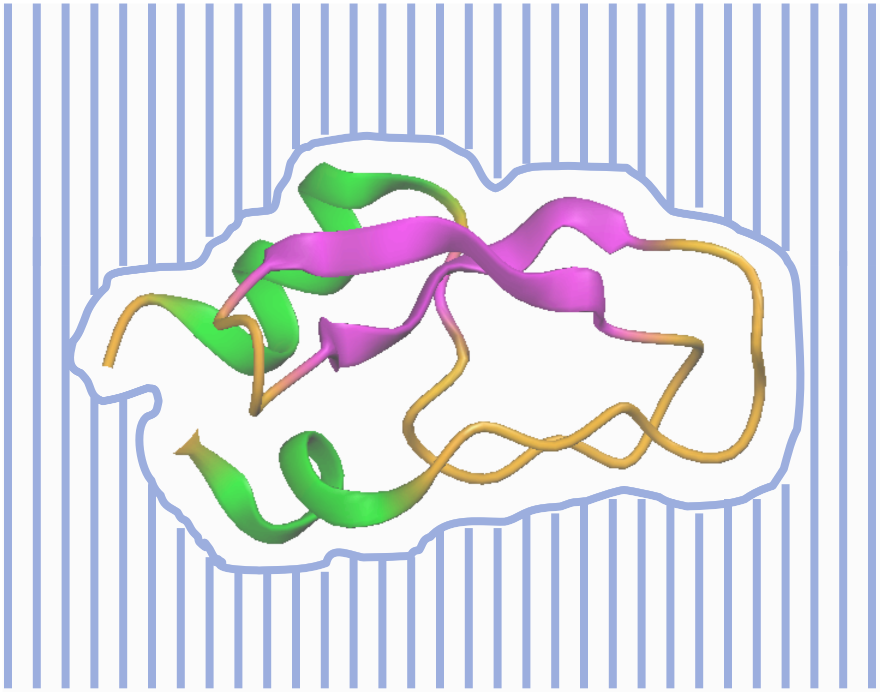
26%, 2.1 Å

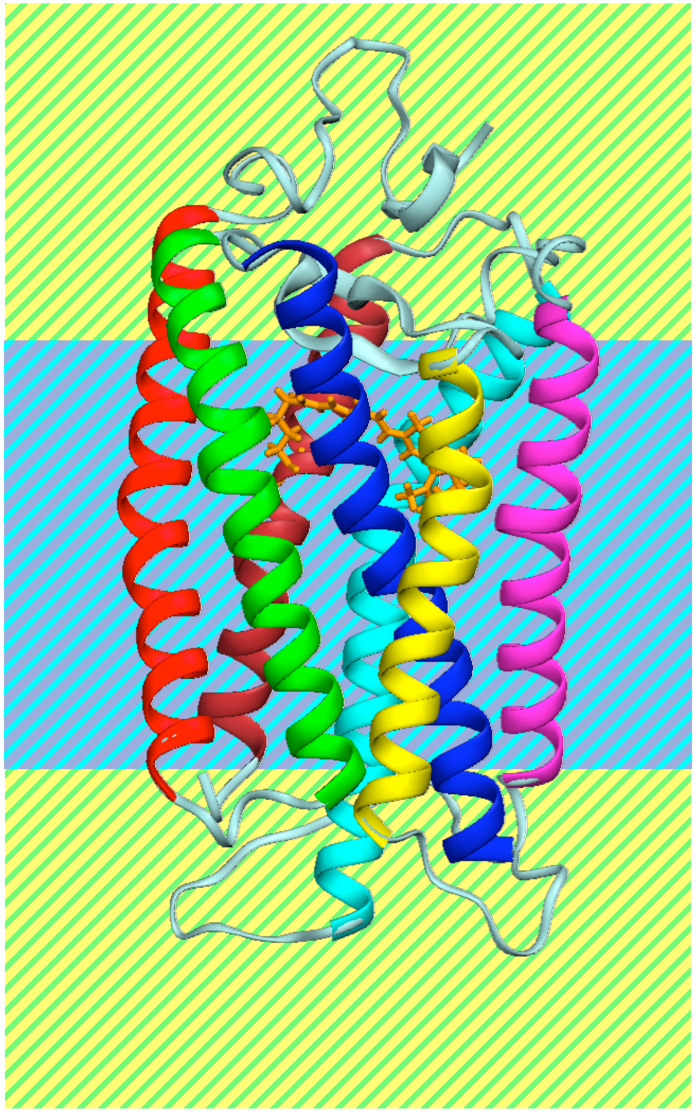


14%, 3.2 Å

Chen, et al., JACS (2006).

Implicit Solvent and Membrane





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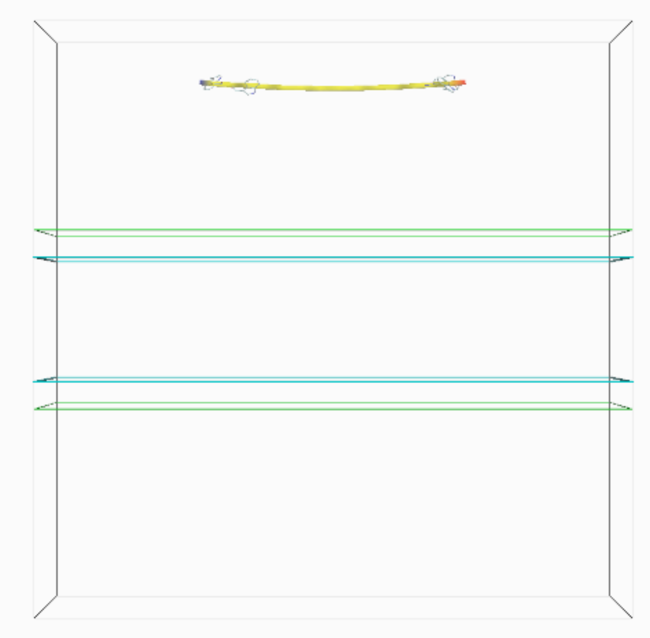
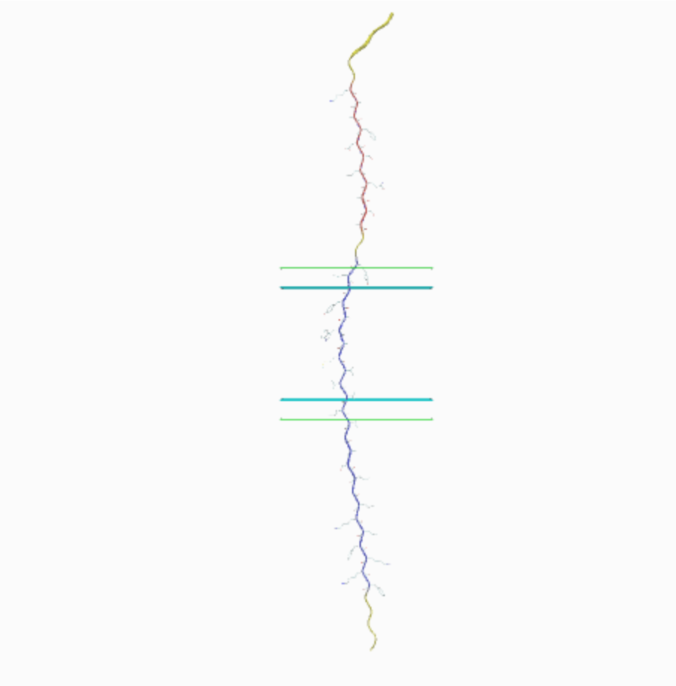
GBSW Implicit Membrane

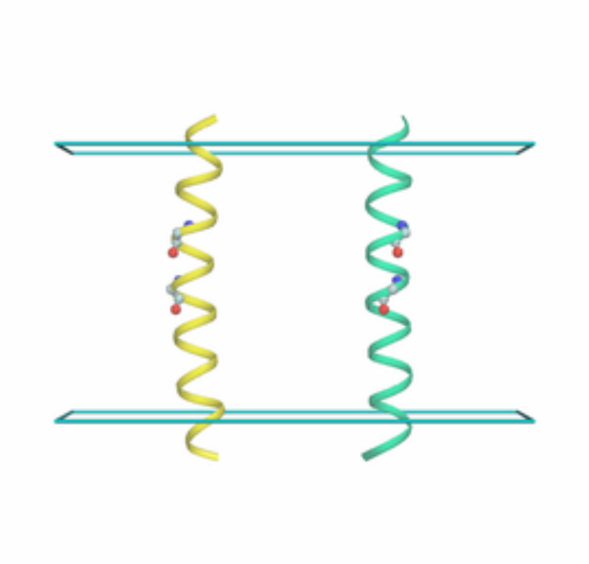
- Membrane as a low-dielectric slab with $\varepsilon=1$.
- Model insertion, folding and assembly of membrane proteins



Im & Brooks (2005)
Proc. Natl. Acad. Sci. 102:6771



Im & Brooks (2004)
J. Mol. Biol. 337:515

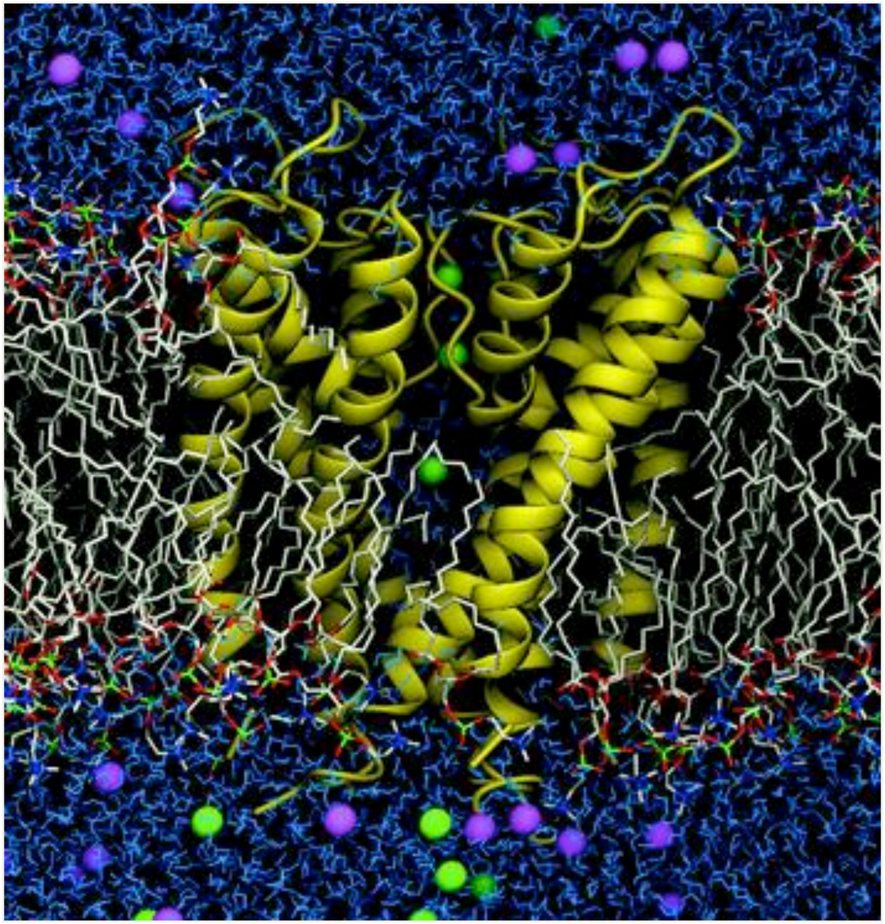


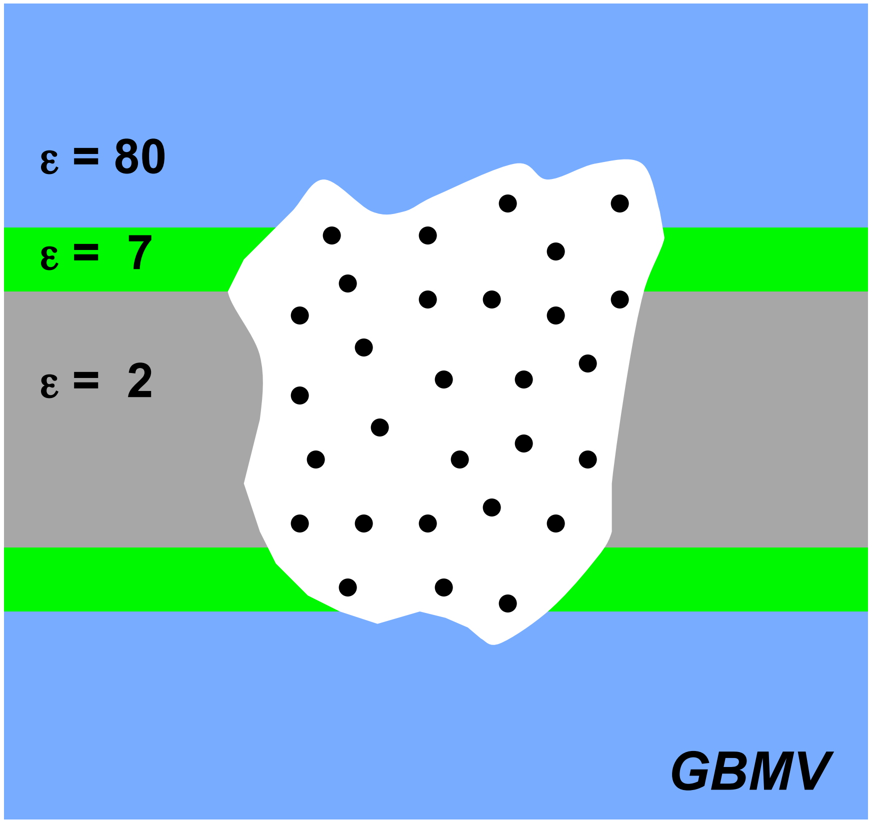
Im, Feig, and Brooks (2003)
Biophys. J. 85:2900

http://www.charmm-gui.org/?doc=gallery&sort=snapshot&pi=CharlesLBrooksIII

All movies created by Wonpil Im

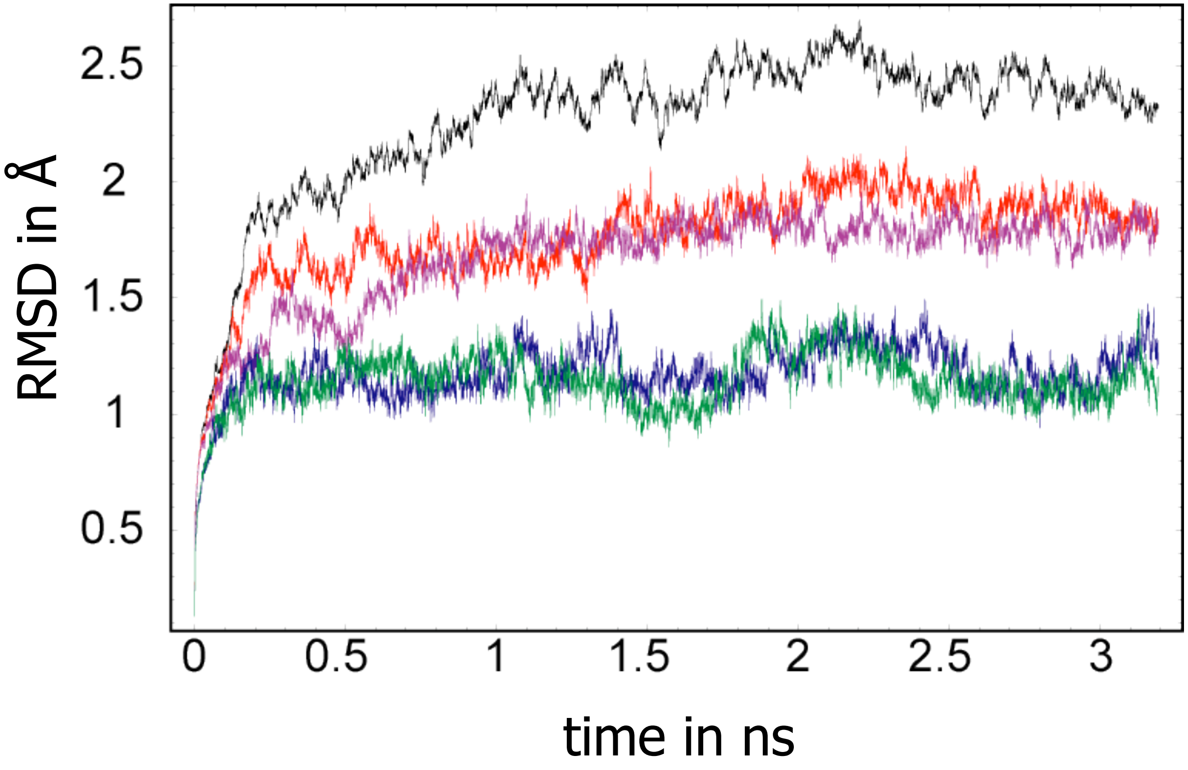
GBMV Membrane

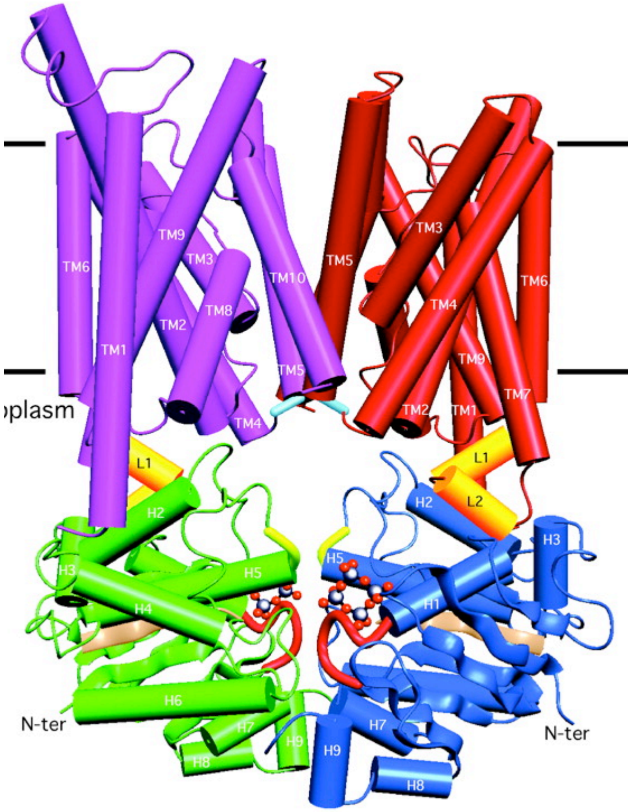




Tanizaki & Feig (2005) *J. Chem. Phys.* 122:124706

Simulations of Membrane Proteins: B_{12} Transporter ButCD





Tanizaki & Feig (2005) *J. Chem. Phys.* 122:124706

Variable Dielectric Environments

- Most GB models are designed and parameterized for the typical situation of ε_p=1 and ε_w~80.
  - The effective Born radii do not dependent on internal dielectric constant
  - Not suitable for modeling variable dielectric environments
- HDGB: extended GBMV model (Feig et al, 2004)

$$\alpha_i(\varepsilon_w,\varepsilon_p) = \frac{1}{C_0 A_4 + C_1\left(\frac{3\varepsilon_w}{3\varepsilon_w + 2\varepsilon_p}\right)A_7} + D + \frac{E}{\varepsilon_w + 1}$$

- ALPB: GB-like models Sigalov et al, 2005, 2006) (in Amber)

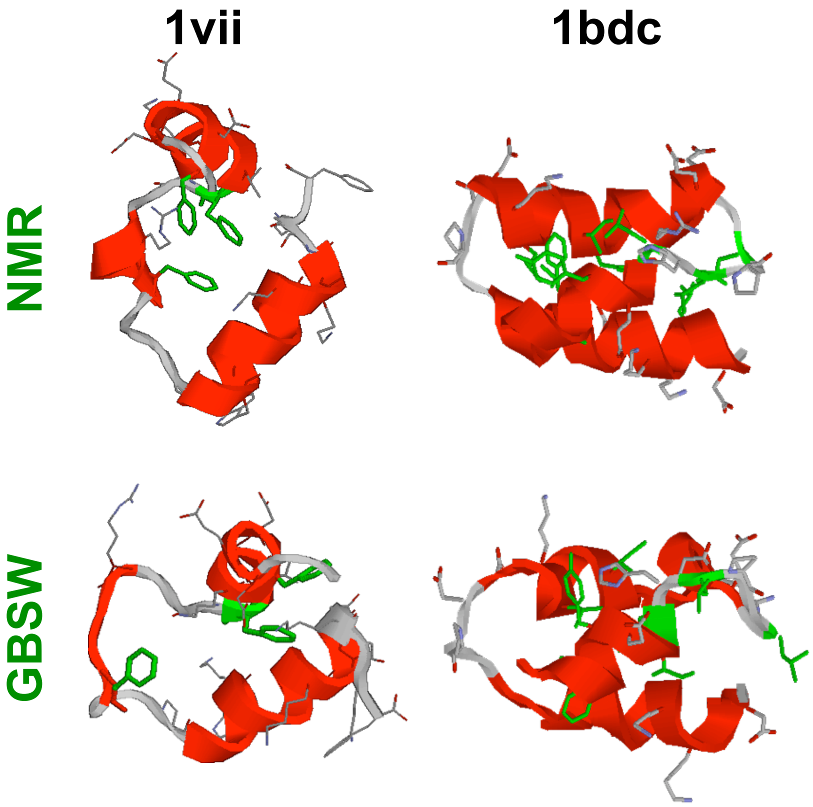
$$\Delta G_{\text{el}} \approx -\frac{1}{2}\left(\frac{1}{\epsilon_{\text{in}}} - \frac{1}{\epsilon_{\text{out}}}\right)\frac{1}{1+\alpha\beta}\sum_{ij} q_i q_j\left(\frac{1}{f_{ij}} + \frac{\alpha\beta}{A}\right)$$

$\beta = \varepsilon_{in} / \varepsilon_{out}$

electrostatic size

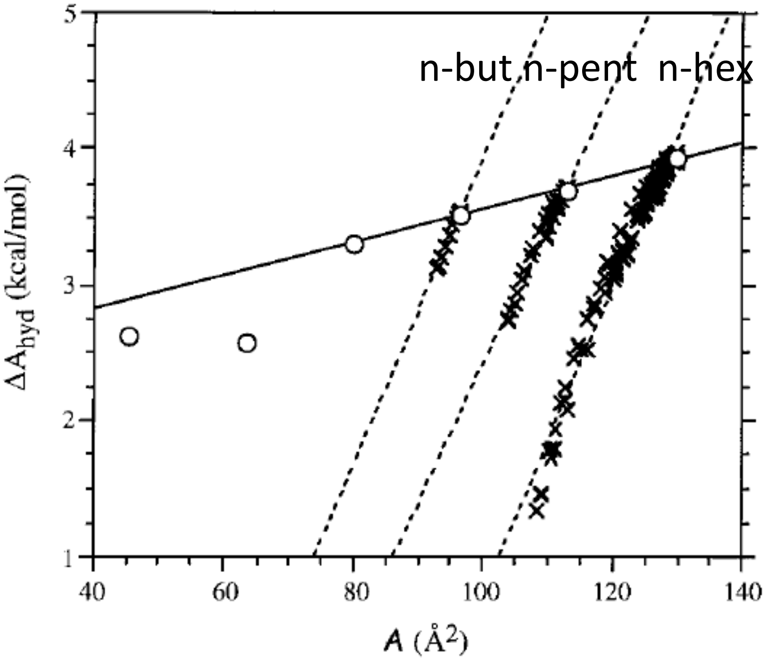
Treatment of Nonpolar Solvation

- The SA-based model is insufficient in describing the conformational dependence of nonpolar solvation



Alkane solvation free energy

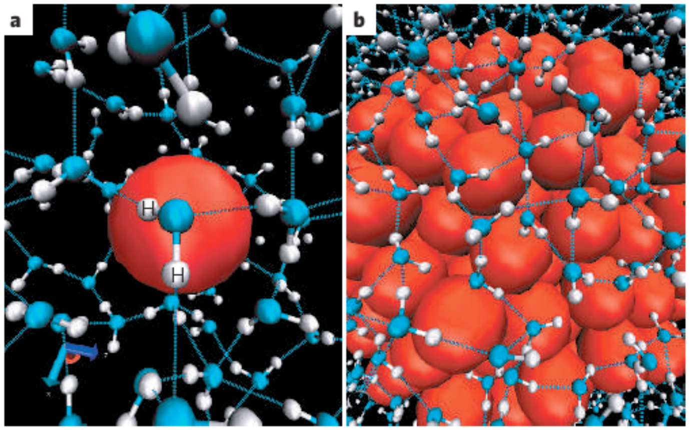
Ashbaugh et al., JACS (1999).

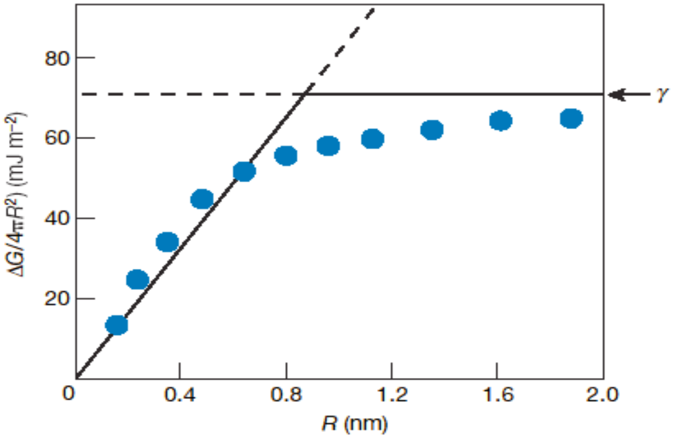


Chen and Brooks PCCP (2008); Chen et al COSB (2008)

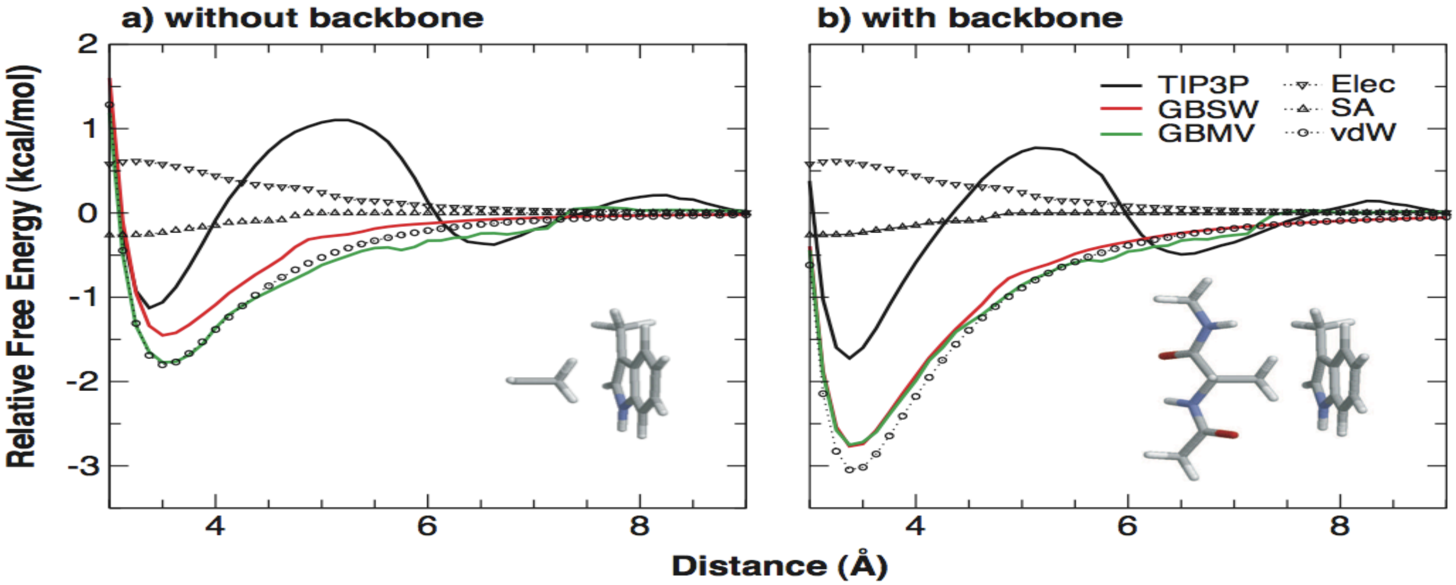
Two Key Properties of Nonpolar Solvation

- Length-scale dependence of hydrophobic solvation (Chandler, 2005)

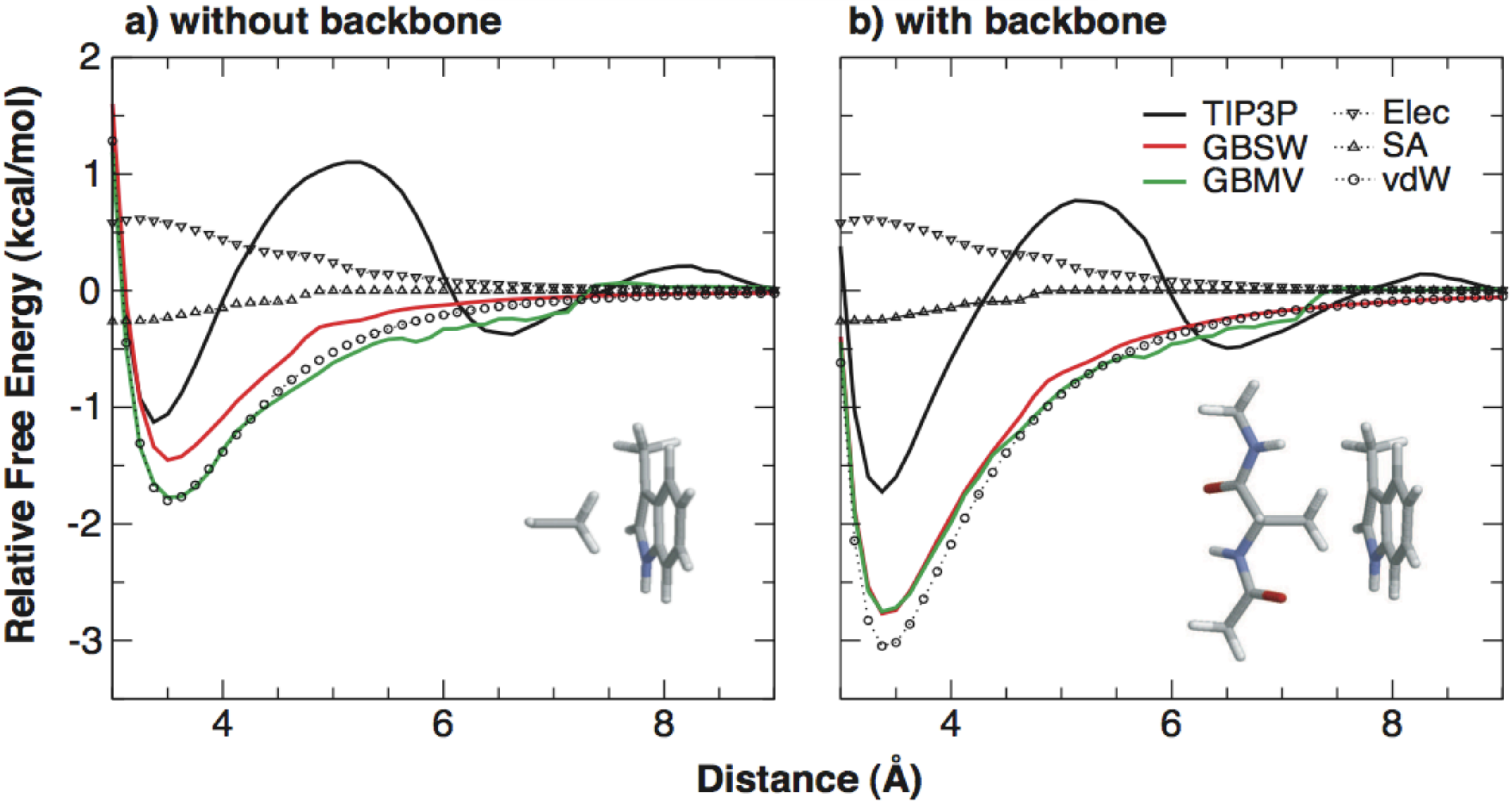




- Solvent screening of solute-solute dispersion interaction



	w/o	bb	diff
TIP3P	-1.13	-1.73	-0.60
GBSW	-1.45	-2.77	-1.32
Elec	0.58	0.53	-0.05
SA	-0.23	-0.25	-0.02
vdW	-1.80	-3.05	-1.25



Solvation Free Energy

$$\Delta G_{\mathbf{solv}} = \Delta G_{\mathbf{elec}} + \Delta G_{\mathbf{np}} = \underline{\Delta G_{\mathbf{elec}} + \Delta G_{\mathbf{vdW}} + \Delta G_{\mathbf{cav}}}$$

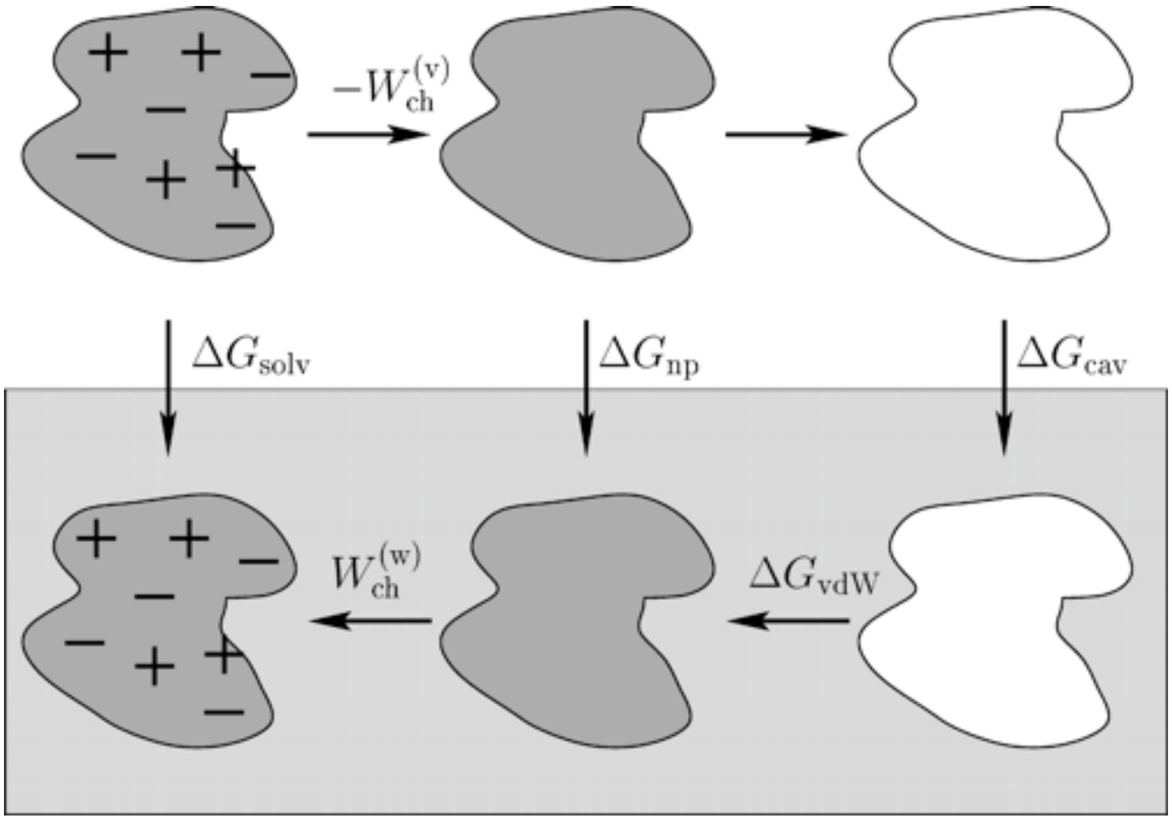
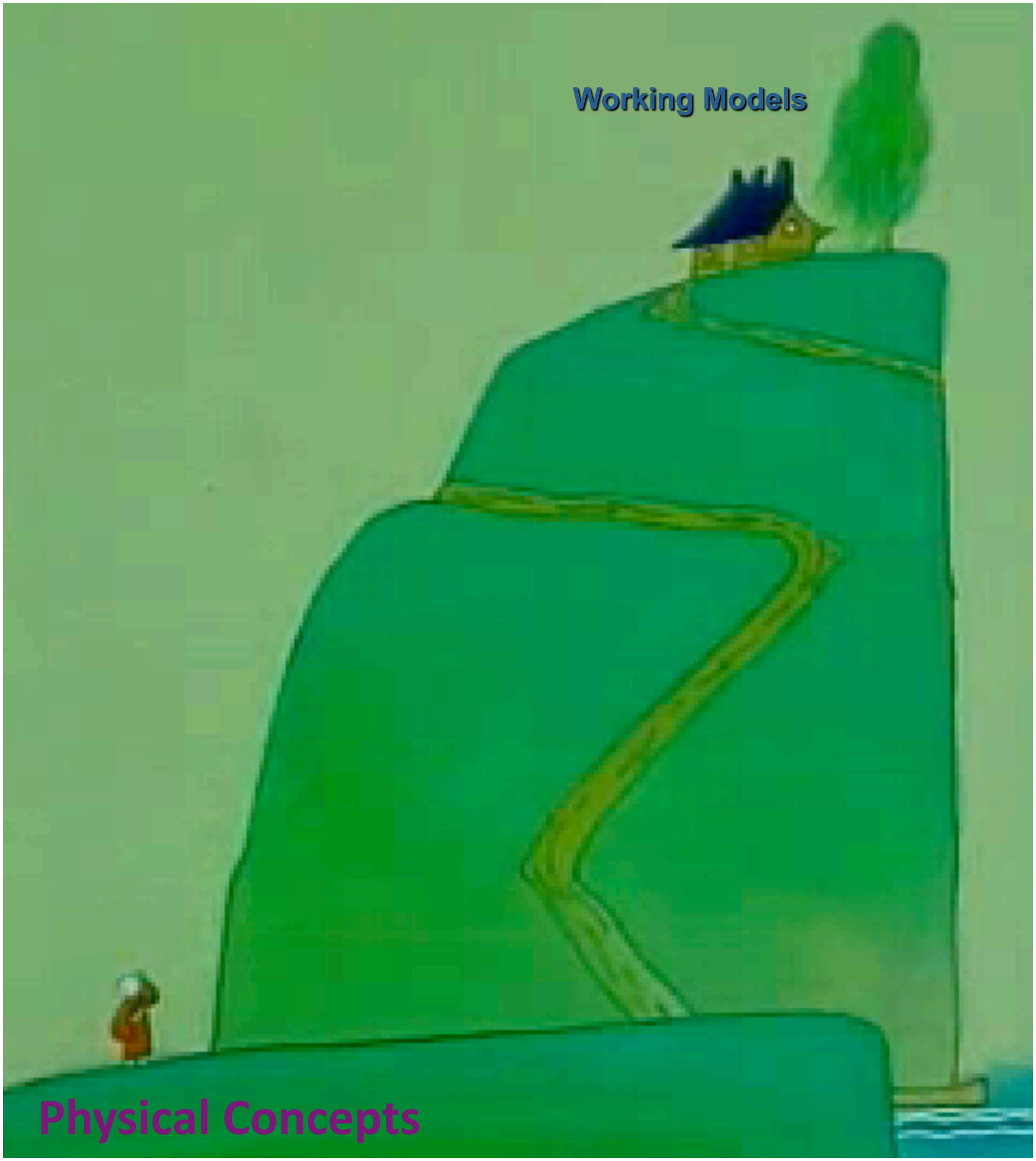


Figure credit: Levy et al., JACS (2003)


Working Models
Physical Concepts