Implicit Solvent Models

Wonpil Im
MMTSB/CTBP
2006 Summer Workshop

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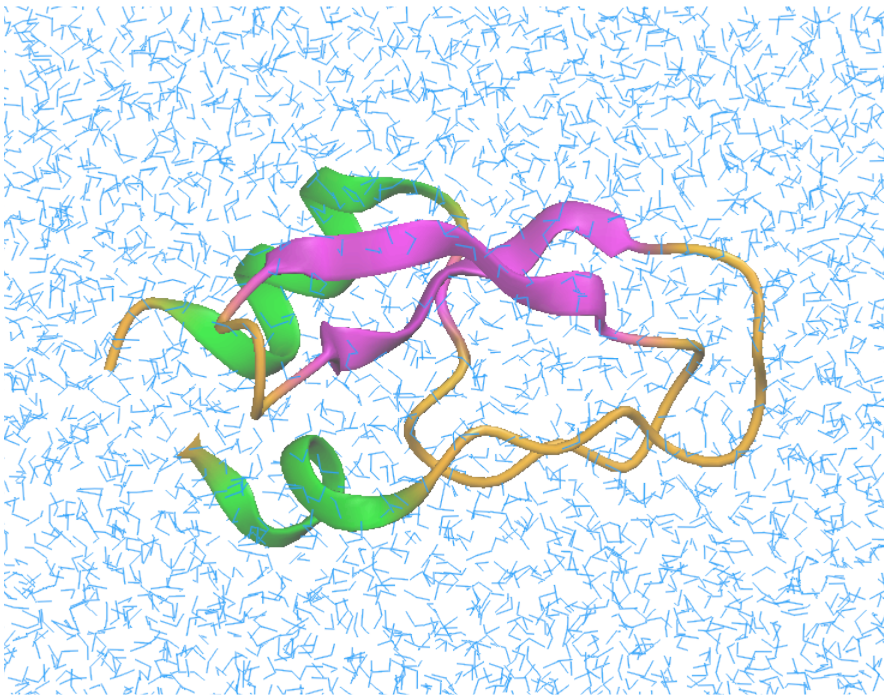
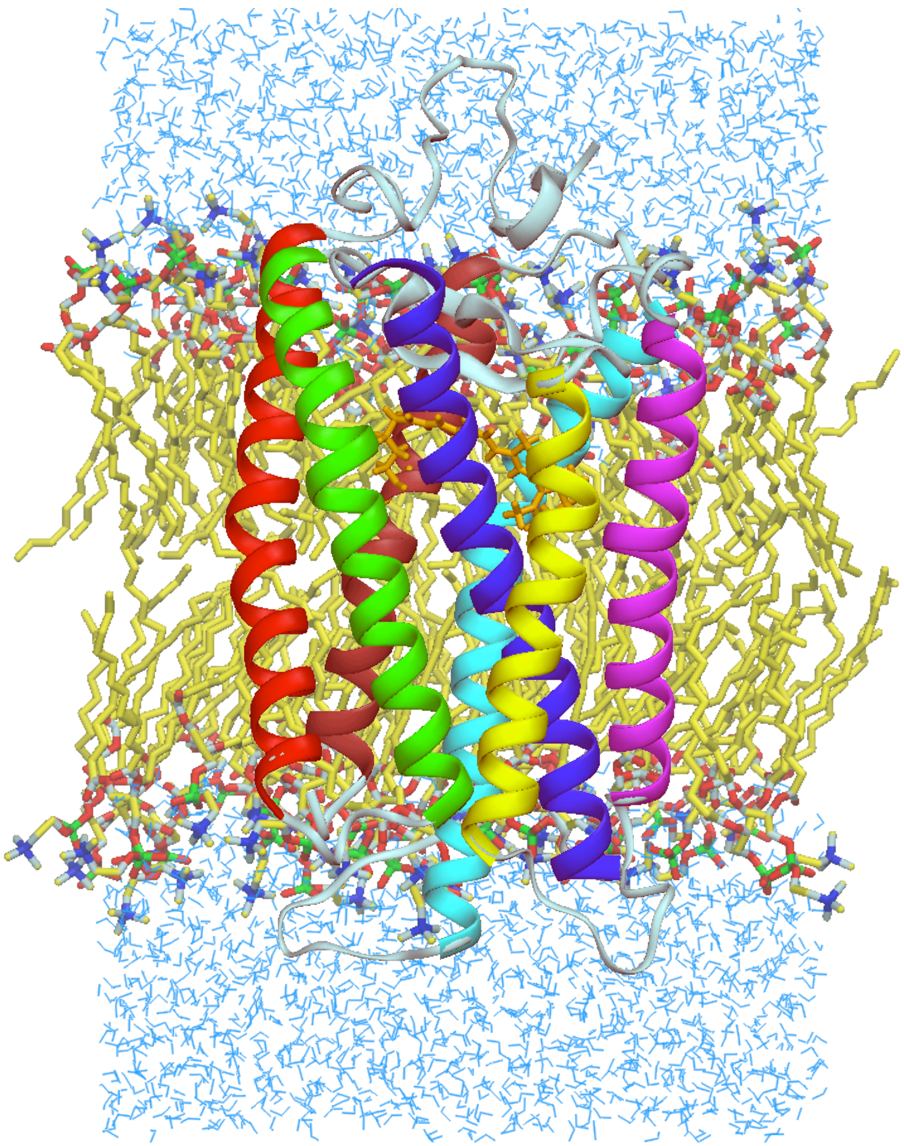
Explicit Solvent





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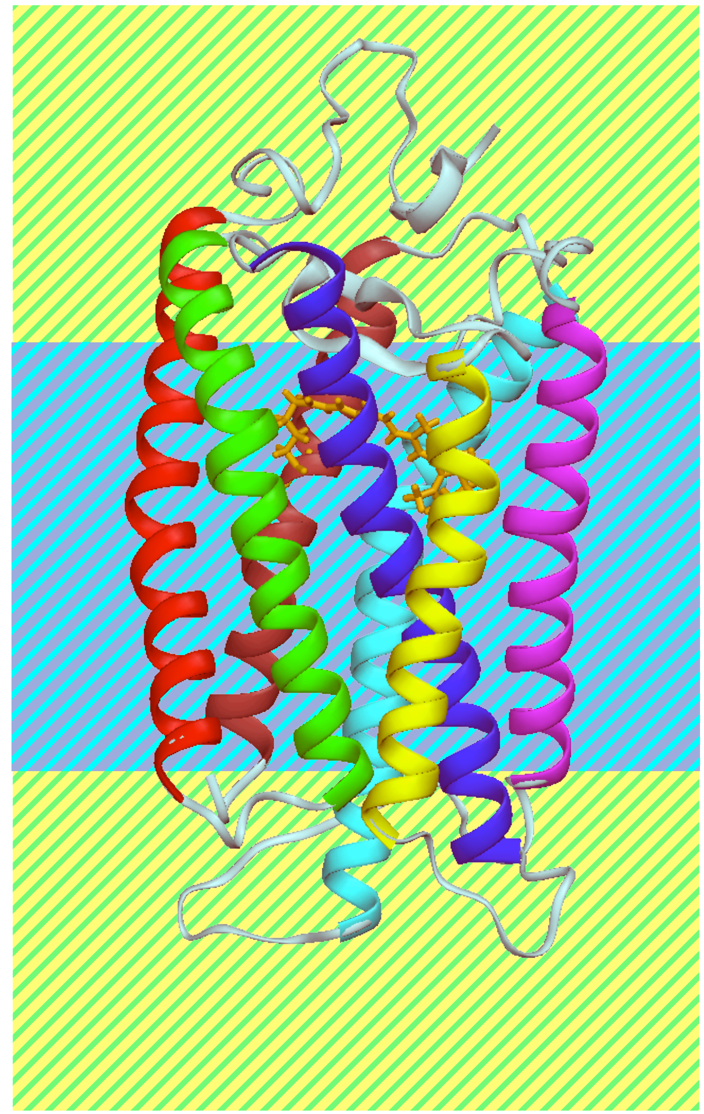
Implicit Solvent



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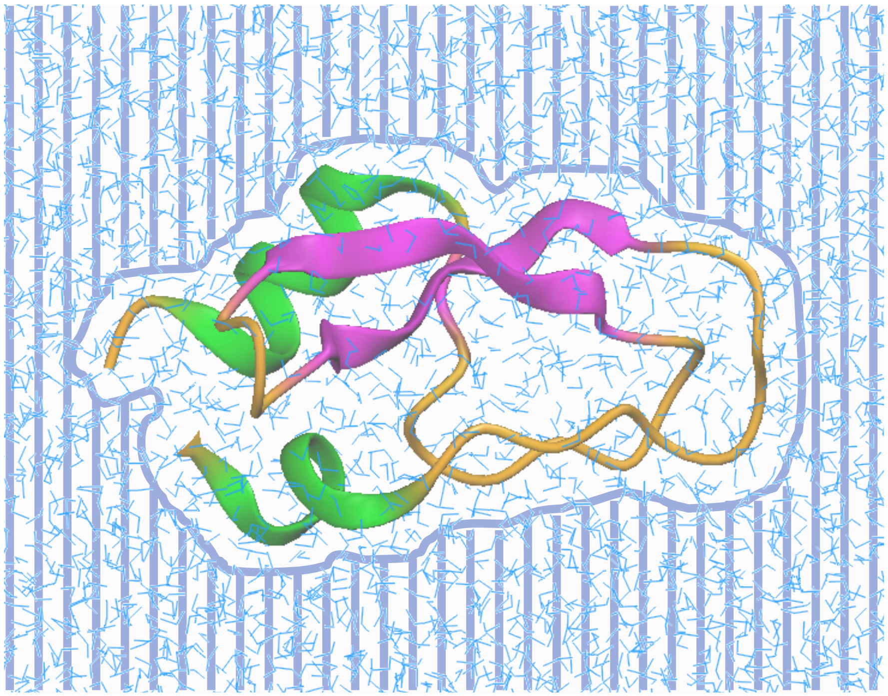
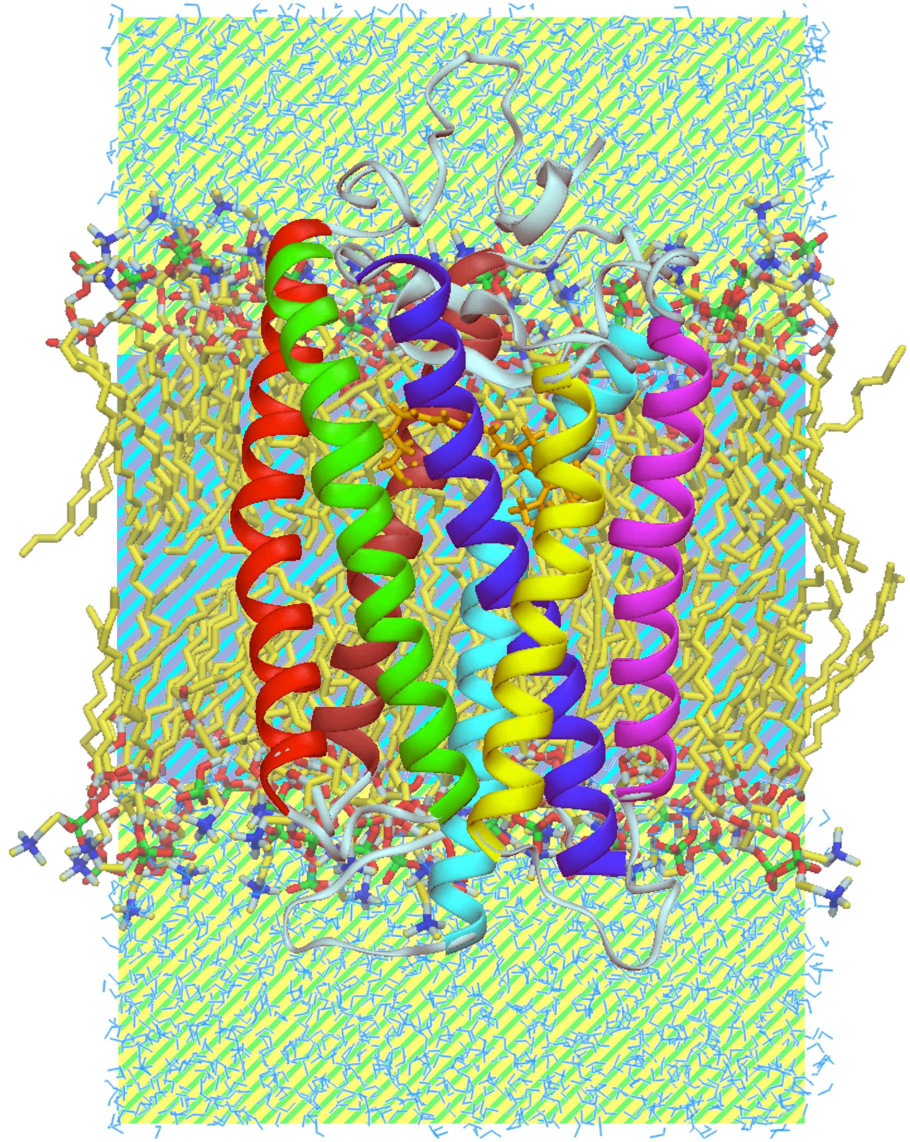
Simple & Efficient





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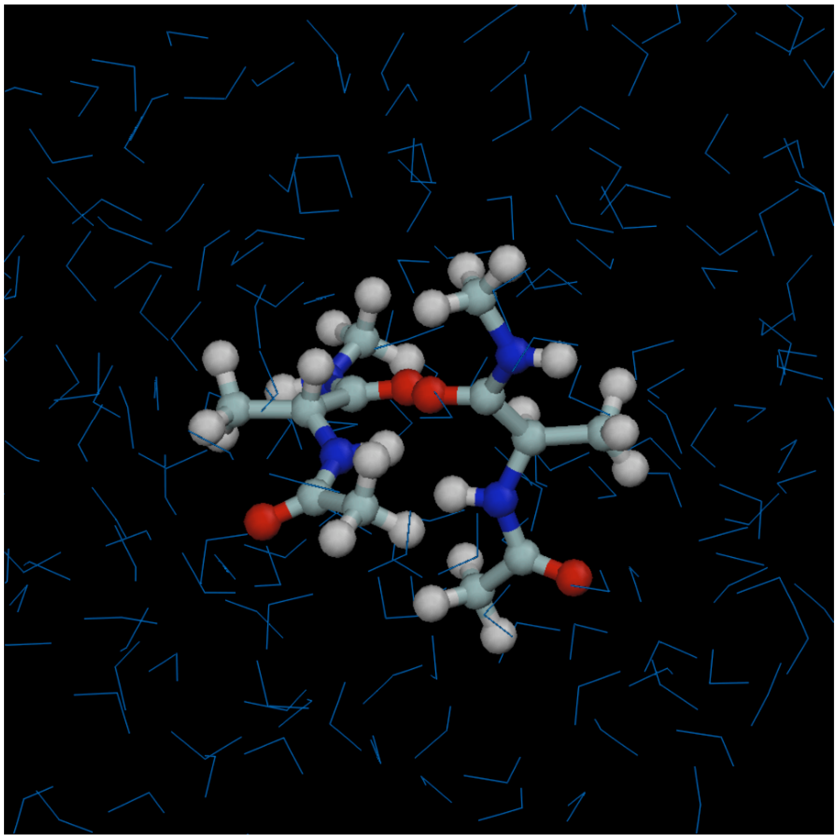
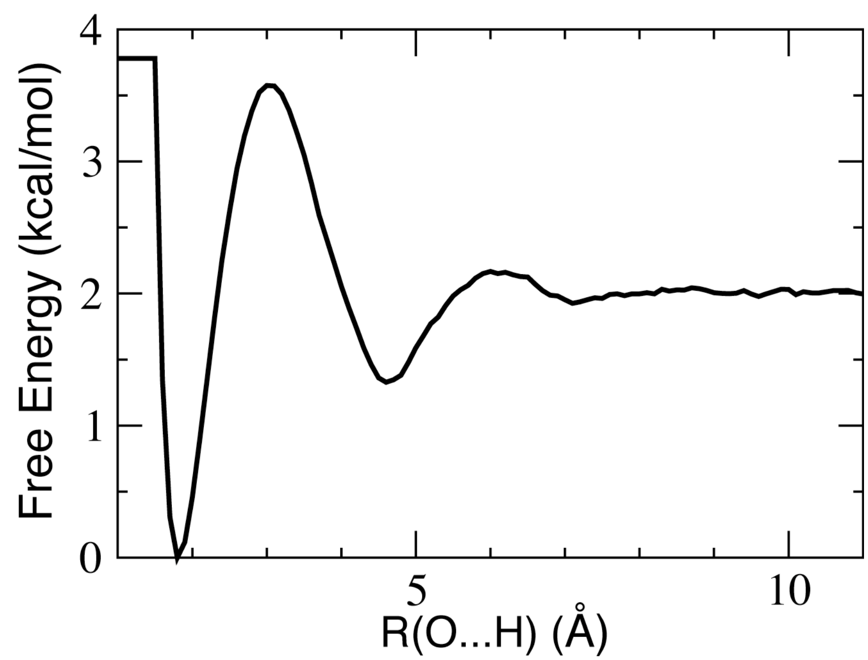
Competition: Not Simple!





Im, Chen, & Brooks (2006) Adv. Protein Chem. 72:173

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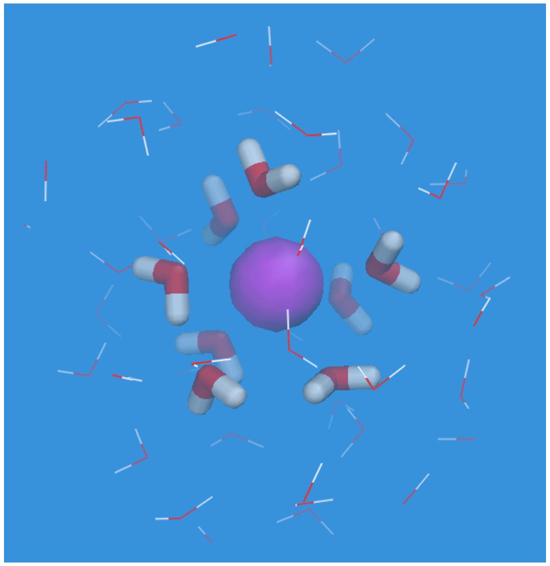
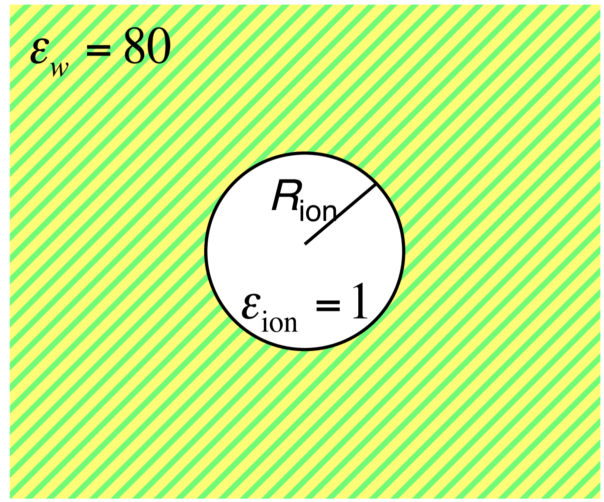
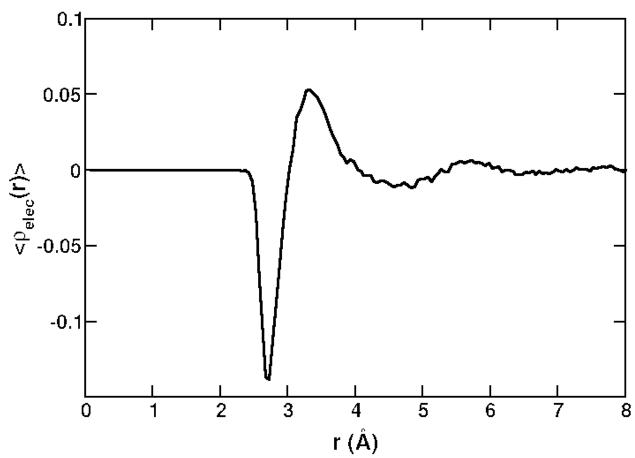
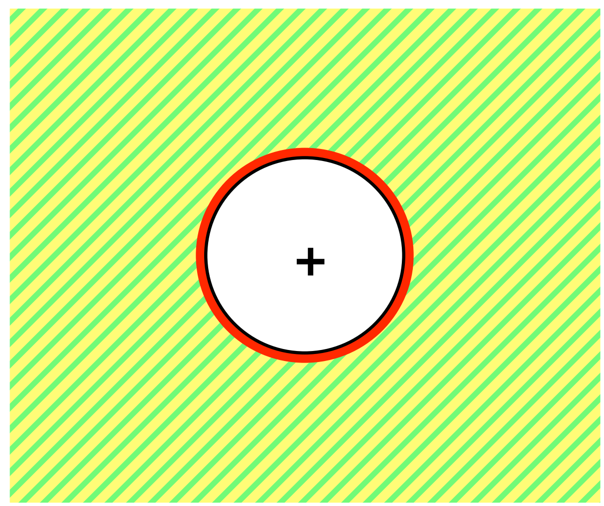
Continuum Electrostatics









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Poisson-Boltzmann (PB) Equation

Poisson Equation : $\nabla \cdot [\varepsilon(\mathbf{r}) \nabla \phi(\mathbf{r})] = -4\pi \left[\rho_{\text{prot}}(\mathbf{r}) + \sum_{\alpha} q_{\alpha} C_{\alpha}(\mathbf{r}) \right]$

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

$\exp(-x) \approx 1 - x$

linearized PB Equation : $\nabla \cdot [\varepsilon(\mathbf{r}) \nabla \phi(\mathbf{r})] - \bar{\kappa}^2(\mathbf{r}) \phi(\mathbf{r}) = -4\pi \rho_{\text{prot}}(\mathbf{r})$

$$\bar{\kappa}^2(\mathbf{r}) = \frac{8\pi q_{\alpha}^2 C^{\text{bulk}}}{k_{\text{B}} T}$$

$$G_{\text{elec}} = \frac{1}{2} \sum q_i \phi(\mathbf{r}_i)$$

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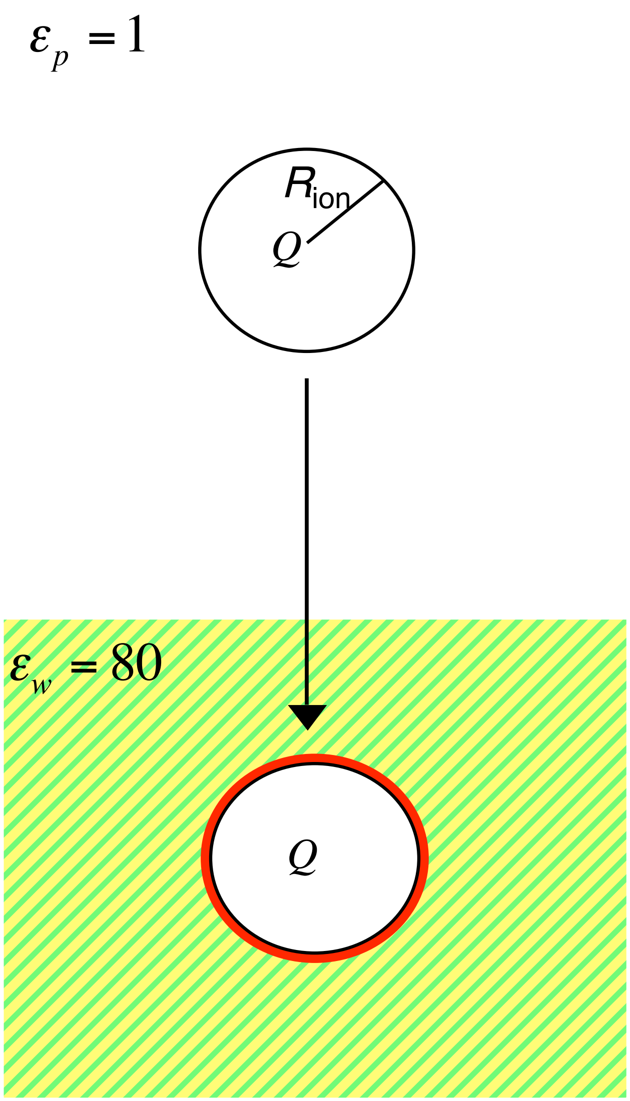
Born Equation: Solvation Energy of Ion



Reaction Field (Potential)

$$\Delta G_{\text{elec}} = \frac{1}{2} Q\left[\phi_s(\mathbf{r}_Q) - \phi_v(\mathbf{r}_Q)\right]$$

$$= \frac{1}{2}\frac{Q^2}{R_{\text{ion}}}\left(\frac{1}{\varepsilon_w} - \frac{1}{\varepsilon_p}\right)$$

$$R_{\text{ion}} \uparrow \;\Rightarrow\; \Delta G_{\text{elec}} \uparrow$$

Born (1920) *Z. Phys.* 1: 45
Roux et. al. (2000) *Biochemistry* 39: 13295

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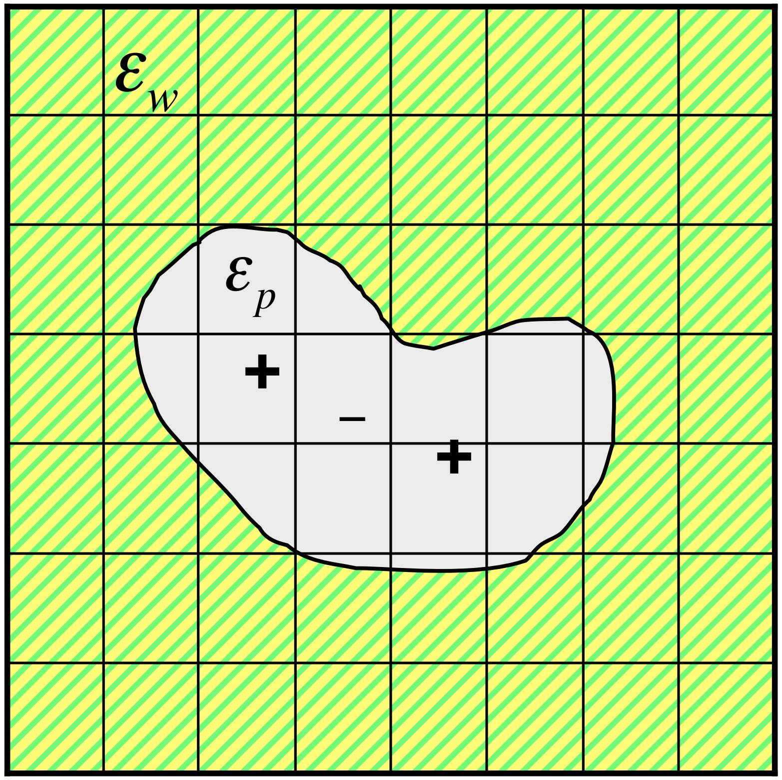
Finite-Difference PB Calculations



$$\nabla \cdot [\varepsilon(\mathbf{r})\nabla\phi(\mathbf{r})] - \bar{\kappa}^2(\mathbf{r})\phi(\mathbf{r}) = -4\pi\rho_{\text{prot}}(\mathbf{r})$$

on 3d-grid

$$\begin{aligned}
&\varepsilon_x(i,j,k)[\phi(i+1,j,k)-\phi(i,j,k)]+\\
&\varepsilon_x(i-1,j,k)[\phi(i-1,j,k)-\phi(i,j,k)]+\\
&\varepsilon_y(i,j,k)[\phi(i,j+1,k)-\phi(i,j,k)]+\\
&\varepsilon_y(i,j-1,k)[\phi(i,j-1,k)-\phi(i,j,k)]+\\
&\varepsilon_z(i,j,k)[\phi(i,j,k+1)-\phi(i,j,k)]+\\
&\varepsilon_z(i,j,k-1)[\phi(i,j,k-1)-\phi(i,j,k)]-\\
&\bar{\kappa}^2(i,j,k)\phi(i,j,k)h^2 = -4\pi\frac{q(i,j,k)}{h}
\end{aligned}$$

PB radii are very important
Self-energy should be removed

Klapper et. al (1986) *Proteins* 1: 47
Im et. al. (1998) *Comp. Phys. Comm.* 111: 59

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Applications of PB Calculations

- Visualization of electrostatic potential of macromolecules
- Solvation free energy
- Protein-protein interactions in solution
- pKa shifts in specific residues in proteins
- Incorporation of transmembrane potential
- Electrostatic solvation forces

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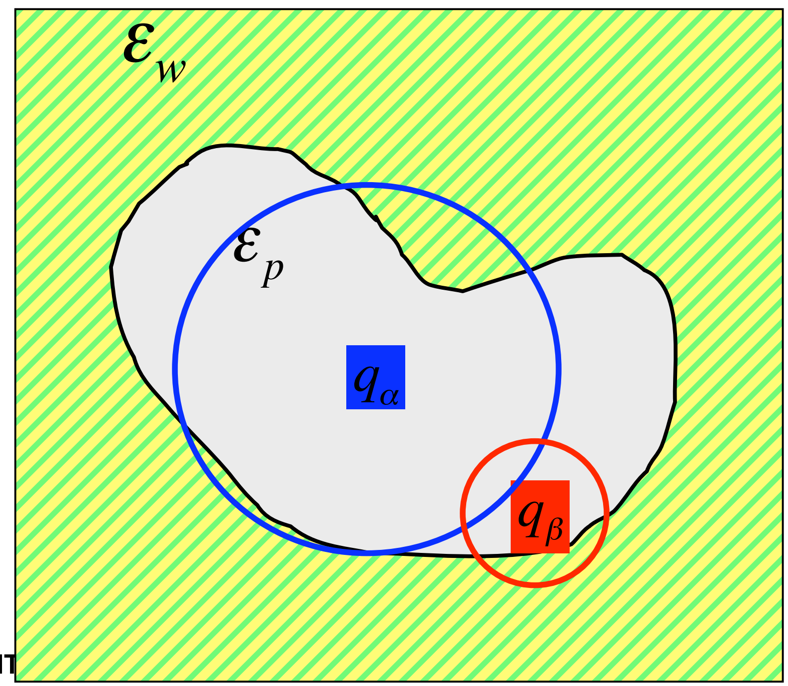
Generalized Born (GB) Equation

$$\Delta G_{\mathrm{elec}} \approx \frac{1}{2}\left(\frac{1}{\varepsilon_{\mathrm{w}}}-\frac{1}{\varepsilon_{\mathrm{p}}}\right)\sum_{\alpha\beta}\frac{q_\alpha q_\beta}{\sqrt{r_{\alpha\beta}^2 + R_\alpha^{\mathrm{GB}}R_\beta^{\mathrm{GB}}\exp\left(-r_{\alpha\beta}^2/4R_\alpha^{\mathrm{GB}}R_\beta^{\mathrm{GB}}\right)}}$$

Still et. al. (1990) *J. Am. Chem. Soc.*

$$\Delta G_{\mathrm{elec},\alpha} = \frac{1}{2}\left(\frac{1}{\varepsilon_w}-\frac{1}{\varepsilon_p}\right)\frac{q_\alpha^{\;2}}{R_\alpha^{\mathrm{GB}}}\ , \quad R_\alpha^{\mathrm{GB}}\uparrow \;\Rightarrow\; \Delta G_{\mathrm{elec},\alpha}\uparrow$$



$$\Delta G_{\mathrm{elec},\alpha} \rangle \Delta G_{\mathrm{elec},\beta}$$

$$R_\alpha^{\mathrm{GB}} \rangle R_\beta^{\mathrm{GB}}$$

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

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Calculation of Effective Born Radii

- Continuum electrostatics

$$\Delta G_{\text{elec},\alpha} = \frac{1}{8\pi}\int \frac{D^2(\mathbf{r})}{\varepsilon(\mathbf{r})}d\mathbf{r} = \frac{1}{8\pi\varepsilon_{\text{w}}}\int D^2(\mathbf{r})d\mathbf{r} + \frac{1}{8\pi}\left(\frac{1}{\varepsilon_{\text{p}}} - \frac{1}{\varepsilon_{\text{w}}}\right)\int_{\text{solute}} D^2(\mathbf{r})d\mathbf{r}$$

- Coulomb Field Approximation (CFA)

volume function

$$\Delta G_{\text{elec},\alpha} \approx \Delta G^0_{\text{elec},\alpha} = -\frac{q_\alpha^2}{2}\left(\frac{1}{\varepsilon_{\text{p}}} - \frac{1}{\varepsilon_{\text{w}}}\right)\left(\frac{1}{\eta_\alpha} - \frac{1}{4\pi}\int_{r>\eta_\alpha} d\mathbf{r}\,\frac{\upsilon(\mathbf{r};\{\mathbf{r}_\alpha\})}{|\mathbf{r}-\mathbf{r}_\alpha|^4}\right)$$

Pairwise Summation
GenBorn

Volume Integration
GBMV and GBSW

$$\frac{1}{R_\alpha^{\text{GB}}} = \frac{1}{R_\alpha + P_1} + \sum_{bonds}\frac{P_2 V_\beta}{r_{\alpha\beta}^4} + \sum_{angles}\frac{P_3 V_\beta}{r_{\alpha\beta}^4} + \sum_{non-bonded}\frac{P_4 V_\beta CCF}{r_{\alpha\beta}^4}$$

Dominy and Brooks (1999) *J. Phys. Chem. B* 103:3765
Lee et. al. (2002) *J. Chem. Phys.* 116:10606
Im et. al. (2003) *J. Comput. Chem.* 24:1691

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The Generalized Born Zoo

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

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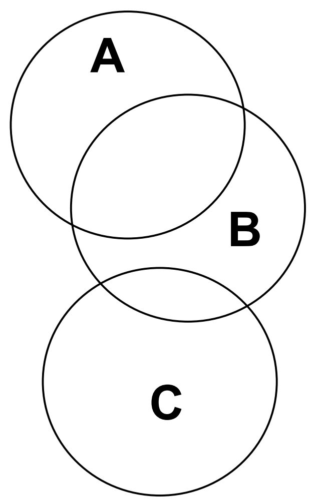
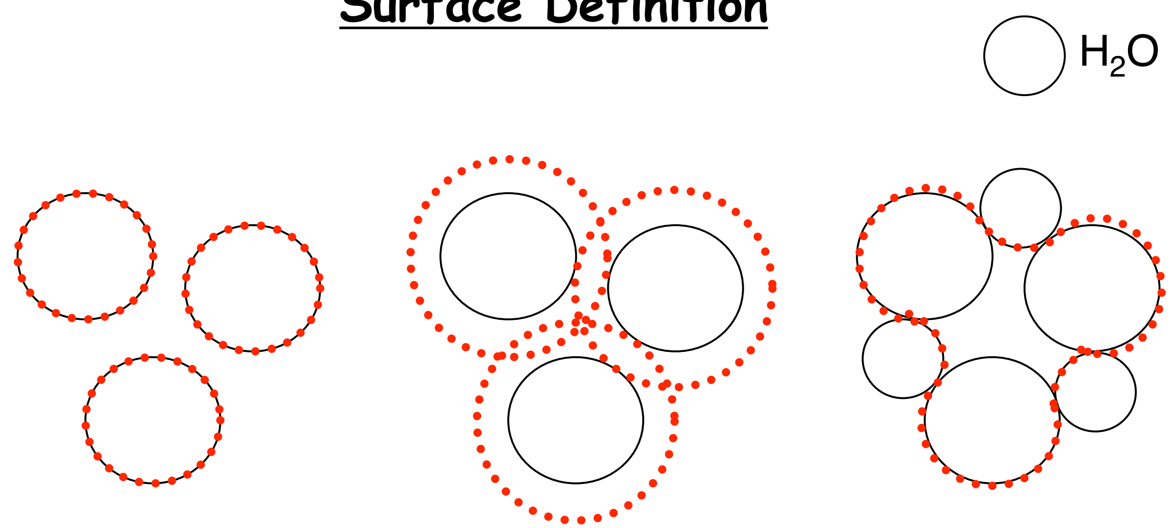
Dielectric Boundary: A Key Concept

In continuum dielectric solvent models, the extent of solvent-exposure of each atom at the dielectric boundary dictates all of the electrostatic and most of nonpolar solvation energetics.



$$\Delta G^{\mathrm{C}}_{\mathrm{elec}} < \Delta G^{\mathrm{A}}_{\mathrm{elec}} < \Delta G^{\mathrm{B}}_{\mathrm{elec}}$$

Surface Definition



van der Waals surface | **solvent-accessible surface** | **molecular surface**

Input radii are very important.

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GBMV vs. GBSW

- Correction term

$$\Delta G_{\mathrm{elec},\alpha} \approx -a_0 \Delta G^0_{\mathrm{elec},\alpha} + a_1 \Delta G^1_{\mathrm{elec},\alpha}$$

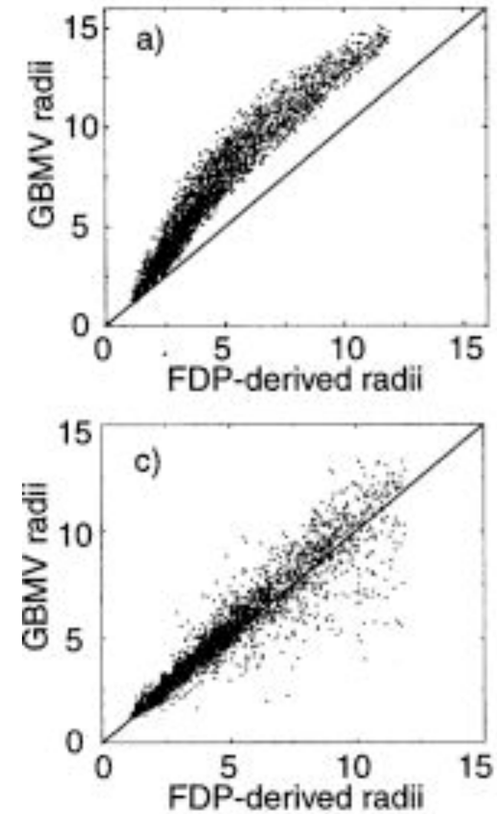
$$\Delta G^0_{\mathrm{elec},\alpha} = -\frac{q_\alpha^2}{2}\left(\frac{1}{\varepsilon_\mathrm{p}} - \frac{1}{\varepsilon_\mathrm{w}}\right)\left(\frac{1}{\eta_\alpha} - \frac{1}{4\pi}\int_{r>\eta_\alpha} d\mathbf{r}\frac{\upsilon(\mathbf{r};\{\mathbf{r}_\alpha\})}{|\mathbf{r}-\mathbf{r}_\alpha|^4}\right)$$

$$\Delta G^1_{\mathrm{elec},\alpha} = -\frac{q_\alpha^2}{2}\left(\frac{1}{\varepsilon_\mathrm{p}} - \frac{1}{\varepsilon_\mathrm{w}}\right)\sqrt{\frac{1}{2\eta_\alpha^2} - \frac{1}{4\pi}\int_{r>\eta_\alpha} d\mathbf{r}\frac{\upsilon(\mathbf{r};\{\mathbf{r}_\alpha\})}{|\mathbf{r}-\mathbf{r}_\alpha|^5}}$$

- Target Surface

GBSW: van der Waals smoothed surface

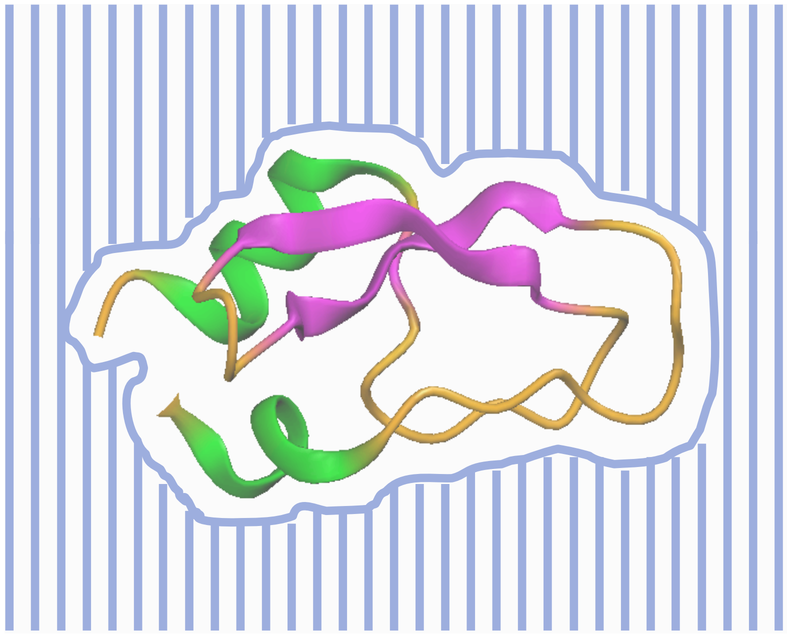
GBMV: molecular surface



Lee,Salsbury, and Brooks (2002) *J. Chem. Phys.* 116:10606
Lee, Feig, Salsbury, and Brooks (2003) *J. Comput. Chem.* 24:1348
Im, Lee, and Brooks (2003) *J. Comput. Chem.* 24:1691

© Wonpil Im , 2006.

Continuum Electrostatics



$$W = U_{\mathrm{MM}} + \Delta G_{\mathrm{solv}}$$
$$= U_{\mathrm{MM}} + \Delta G_{\mathrm{elec}} + \Delta G_{\mathrm{np}}$$
$$\Delta G_{\mathrm{np}} = \gamma \cdot S$$

Continuum Electrostatics :

Protein/solvent system is divided into an interior **low dielectric** (ε_p) and an exterior **high dielectric** (ε_w) region

- Poisson-Boltzmann (PB): $\nabla \cdot [\varepsilon(\mathrm{r})\nabla\phi(\mathrm{r})] - \bar{\kappa}^2(\mathrm{r})\phi(\mathrm{r}) = -4\pi\rho_{\mathrm{prot}}(\mathrm{r})$

$$\Delta G_{\mathrm{elec}} = \frac{1}{2}\sum q_i \phi(\mathbf{r}_i)$$

- Generalized Born (GB)

$$\Delta G_{\mathrm{elec}} \approx \frac{1}{2}\left(\frac{1}{\varepsilon_{\mathrm{w}}} - \frac{1}{\varepsilon_{\mathrm{p}}}\right)\sum_{\alpha\beta} \frac{q_\alpha q_\beta}{\sqrt{r_{\alpha\beta}^2 + R_\alpha^{\mathrm{GB}} R_\beta^{\mathrm{GB}} \exp\left(-r_{\alpha\beta}^2 / 4R_\alpha^{\mathrm{GB}} R_\beta^{\mathrm{GB}}\right)}}$$

♥ **Please, be careful with nonbond options**

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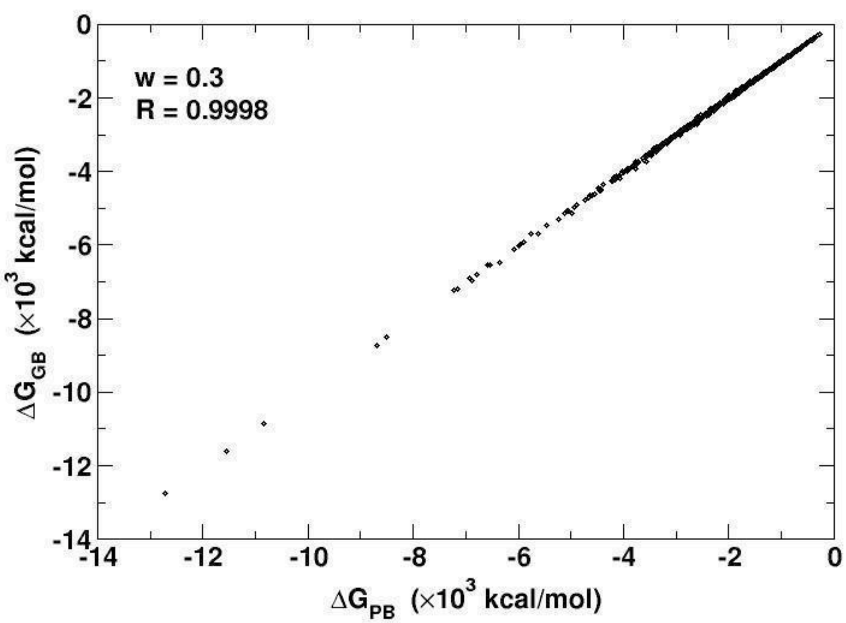
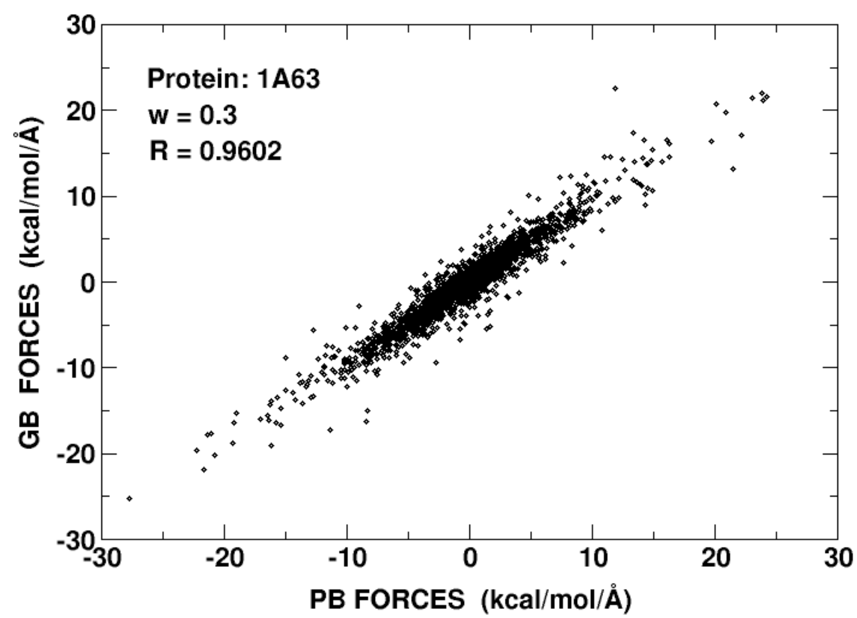
PB Forces vs. GB Forces





Im et. al. (2003) *J. Comput. Chem.* 24:1691

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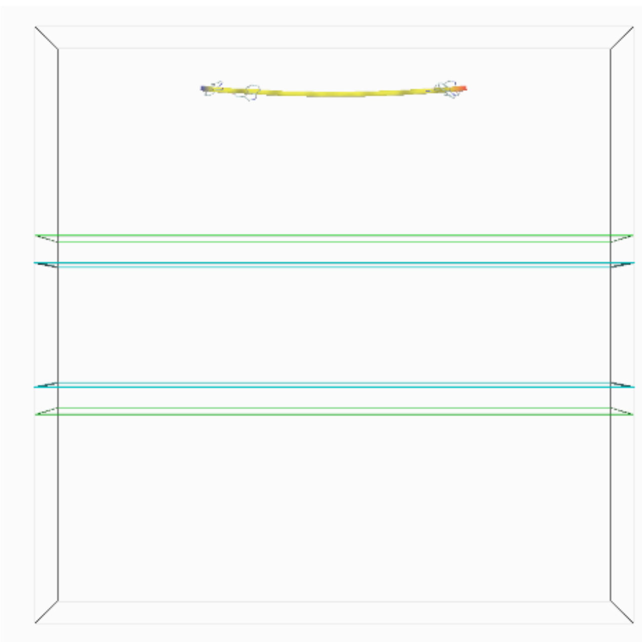
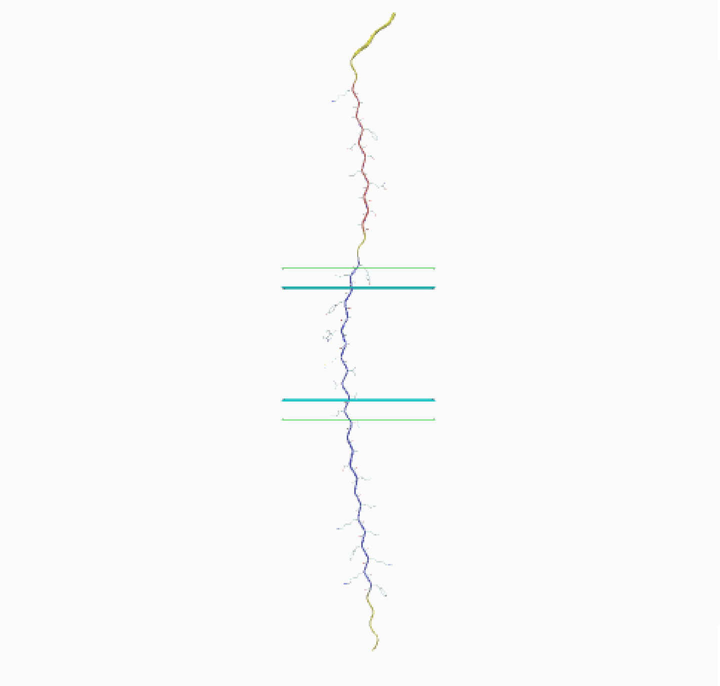
Membrane GB models : GBSWmemb

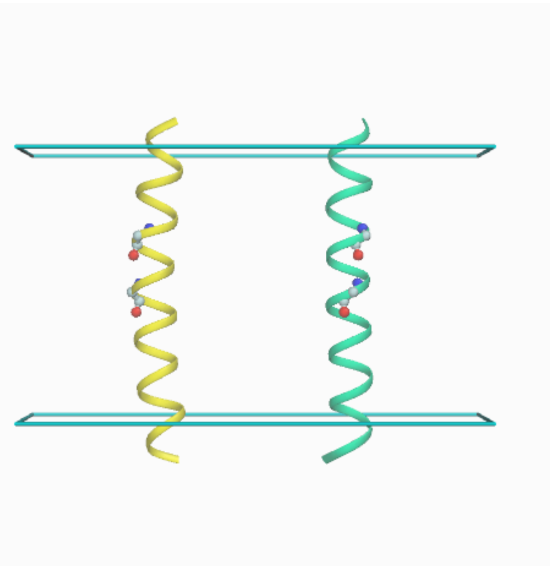
Insertion, Folding, and Assembly
of
Membrane Proteins/Peptides



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

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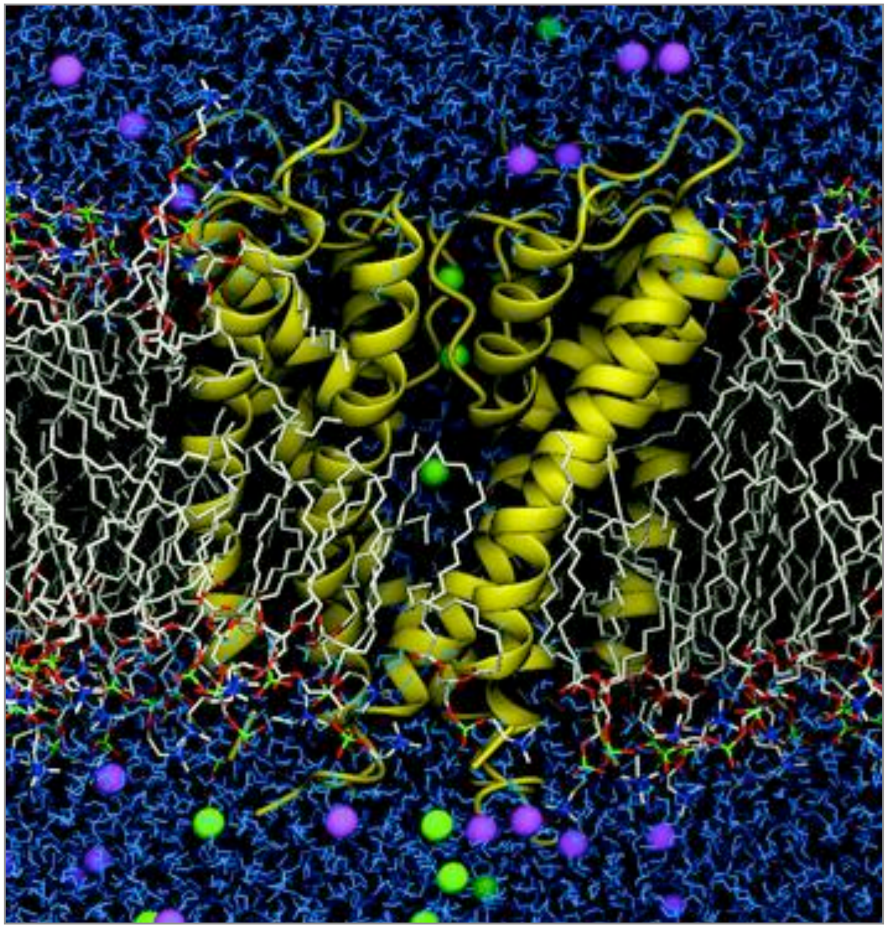
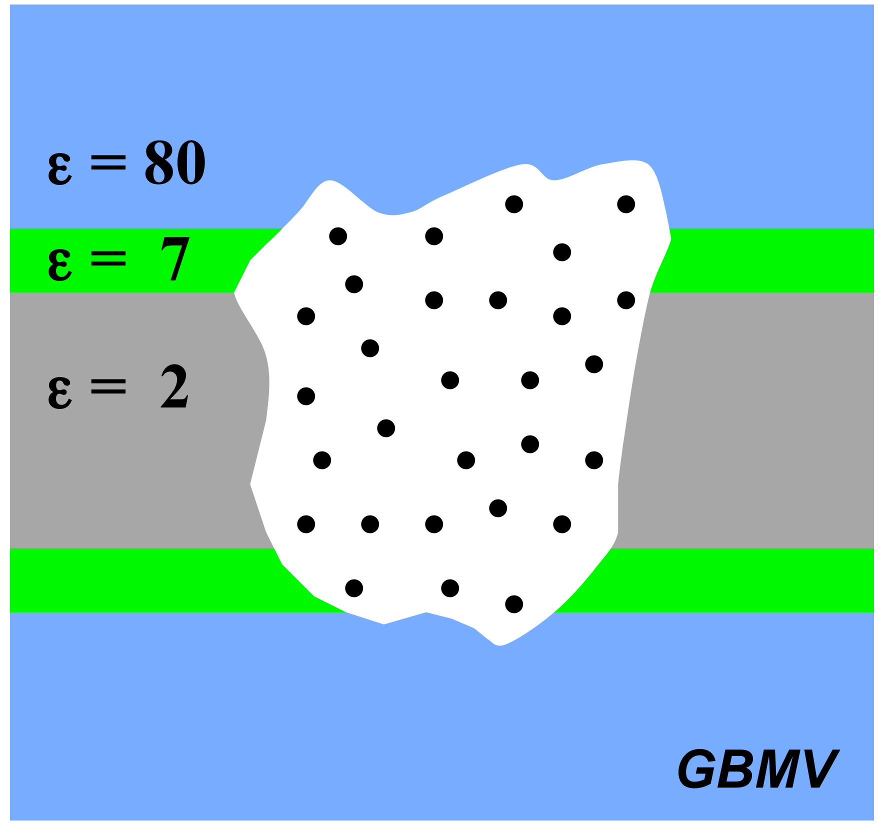
GBMV Membrane





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

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GB for Heterogeneous Environments

$$\Delta G_{elst} = -166\left(1-\frac{1}{\varepsilon}\right)\sum_i\sum_j \frac{q_i q_j}{\sqrt{r_{ij} + \alpha_i\alpha_j \exp(-r_{ij}^2/F\alpha_i\alpha_j)}}$$

$$\Downarrow$$

$$\Delta G_{elst} = -166\sum_i\sum_j \left(1-\frac{1}{\varepsilon_{ij}}\right)\frac{q_i q_j}{\sqrt{r_{ij} + \alpha_i(\varepsilon_i)\alpha_j(\varepsilon_j)\exp(-r_{ij}^2/F\alpha_i(\varepsilon_i)\alpha_j(\varepsilon_j))}}$$

$$\varepsilon_{ij} = \frac{\varepsilon_i + \varepsilon_j}{2} \qquad \varepsilon_i = \varepsilon_{eff}(z_i)$$

Feig, Im, and Brooks (2004) *J. Chem. Phys.* 120:903

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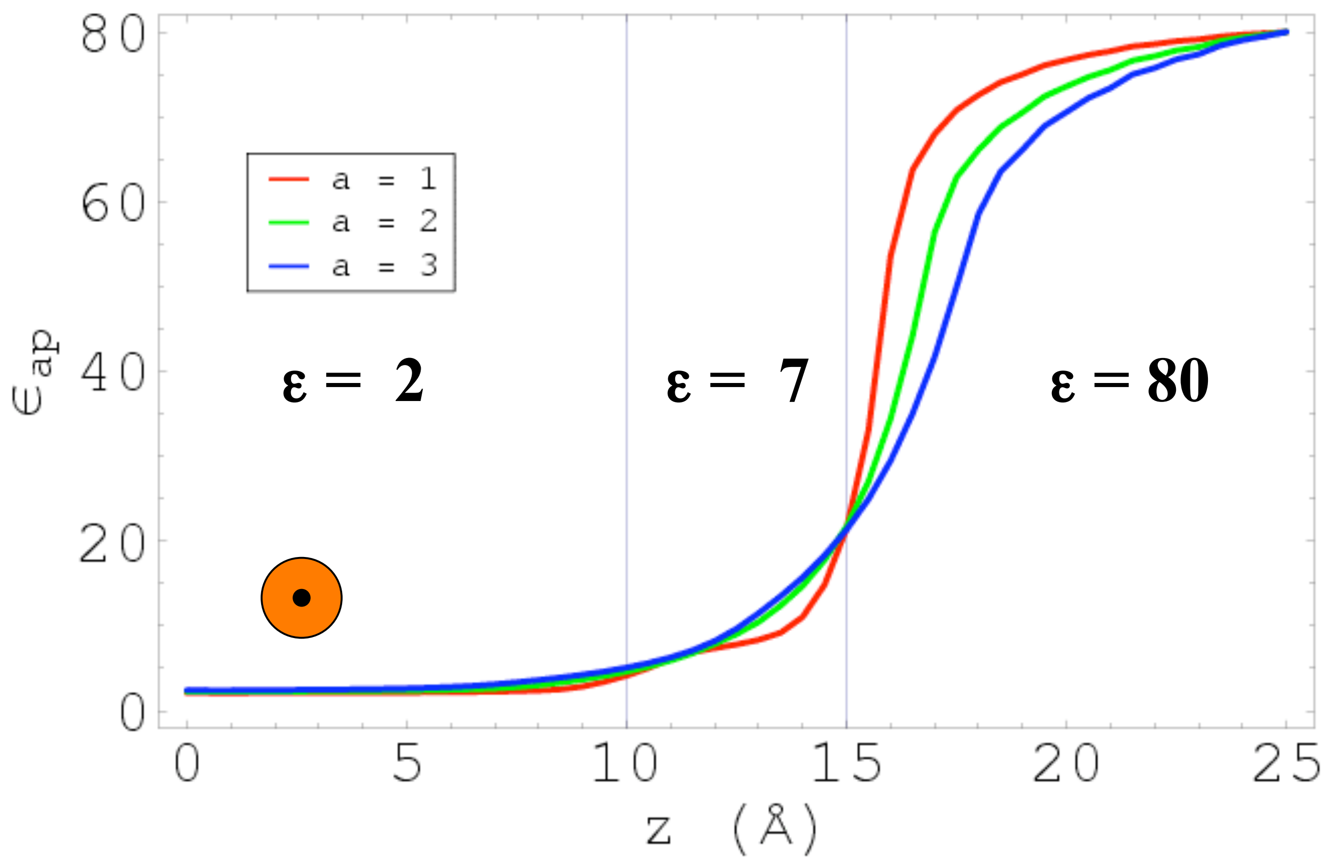
Effective Dielectric Constant



$$\Delta G_{elst}(PB) = -166\left(1 - \frac{1}{\varepsilon_{eff}(z)}\right)\frac{q^2}{a}$$

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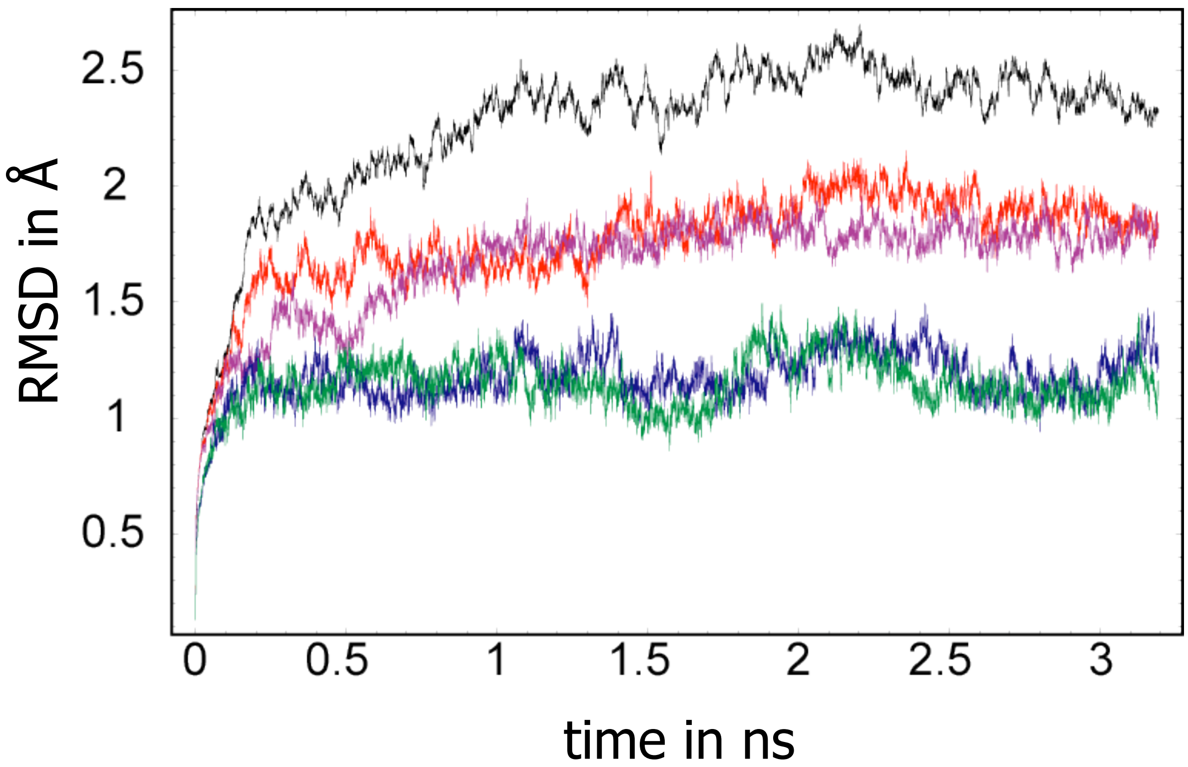
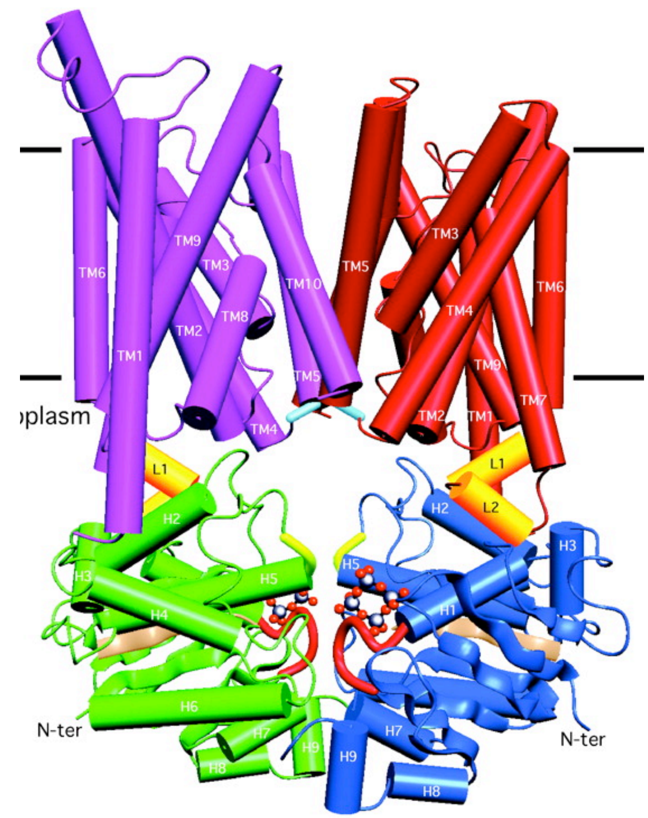
Simulations of Membrane Proteins: B_{12} Transporter ButCD





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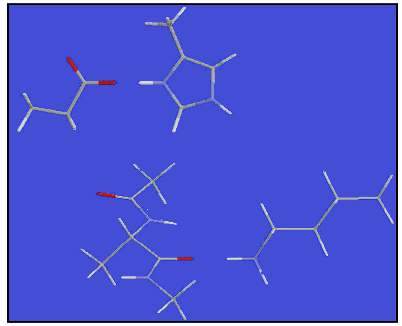
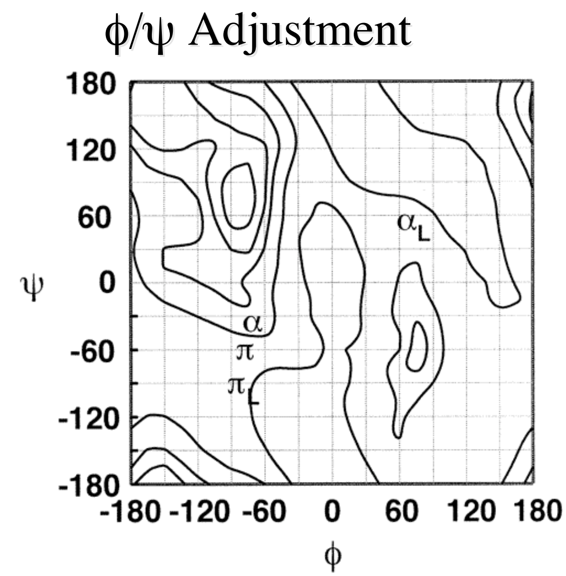
Recent Optimization for GBSW

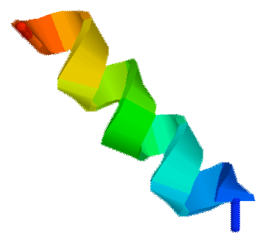
QM ϕ/ψ Surface; PMF optimized radii



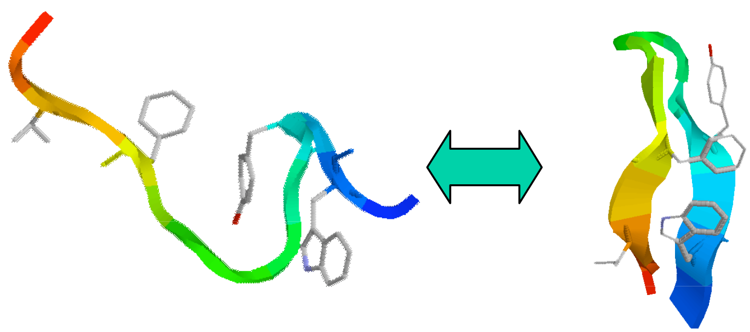
adjust ϕ/ψ



recalibrate backbone to obtain correct helicity for $(AAQAA)_3$



conformational equilibria of GB1p series beta-hairpins

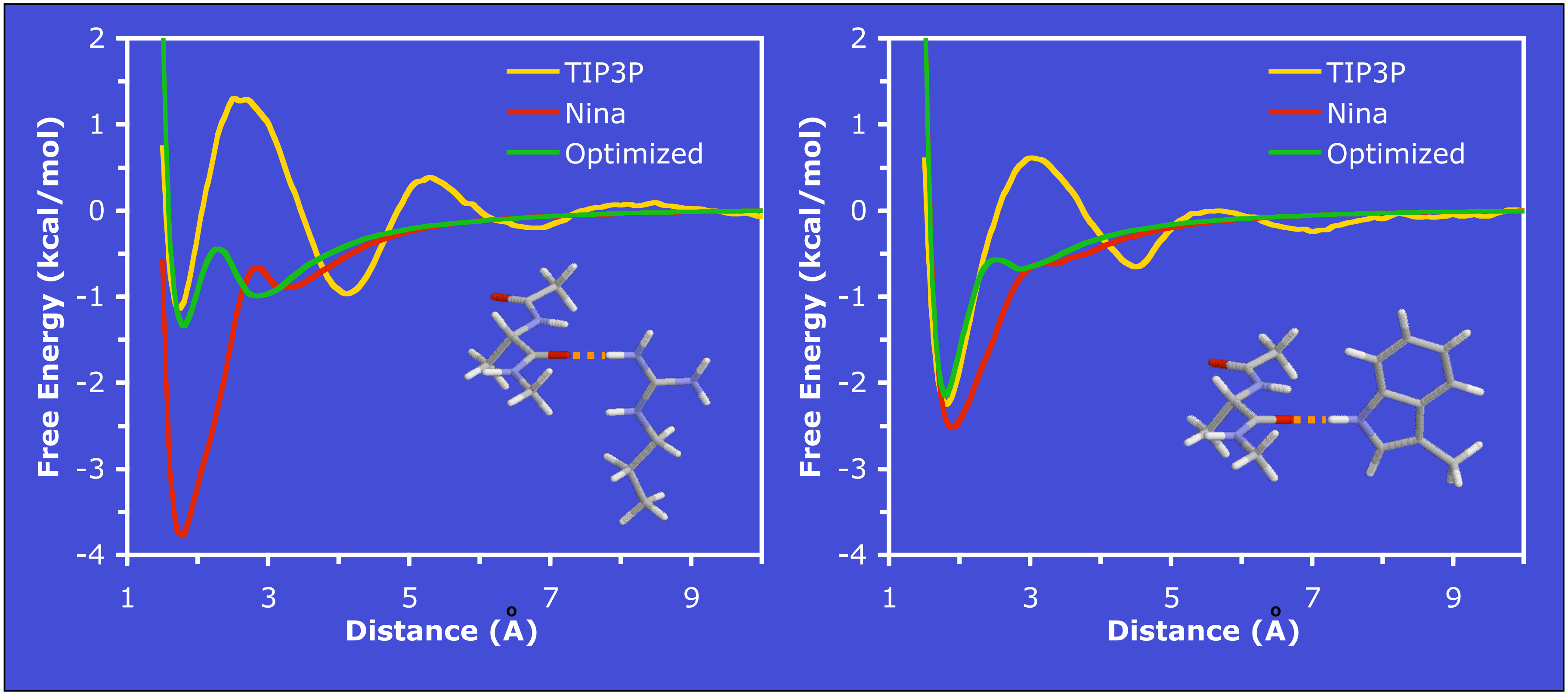


NO

YES

Chen, Im, and Brooks (2006) *J. Am. Chem. Soc.* 128:3728.

Pair-wise Interactions



- Hydrogen bonding is often over-stabilized with the original Nina radii;
- Agreement with explicit solvent is significantly improved after direct optimization of the pair-wise interactions.

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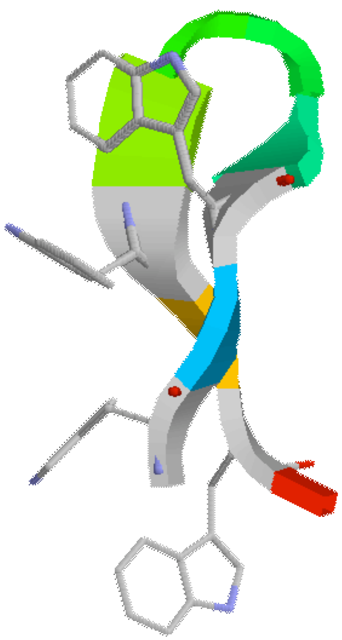
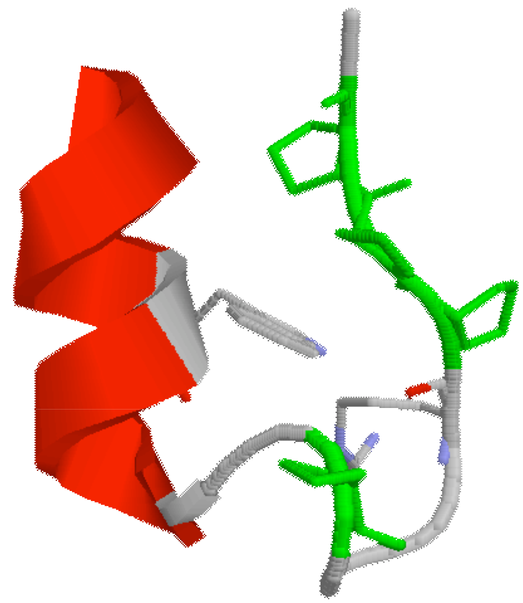
Trpzip2 and Trp-Cage

SWTWE NGKWT WK

NLYIQ WLKDG GPSSG RPPPS



PDB:1LE1



PDB:1L2Y

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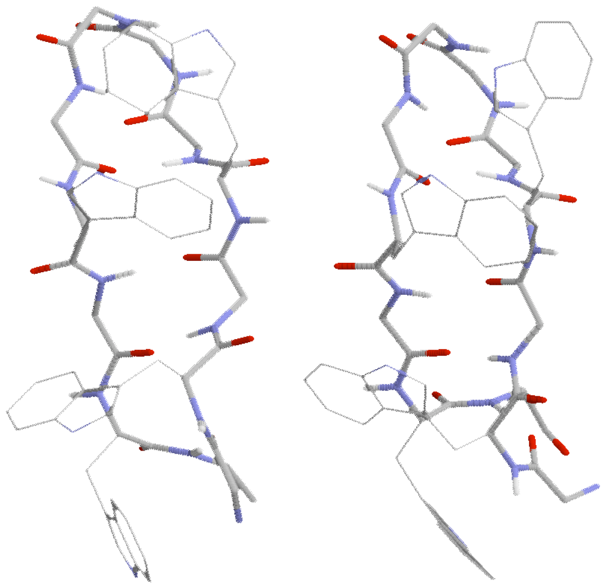
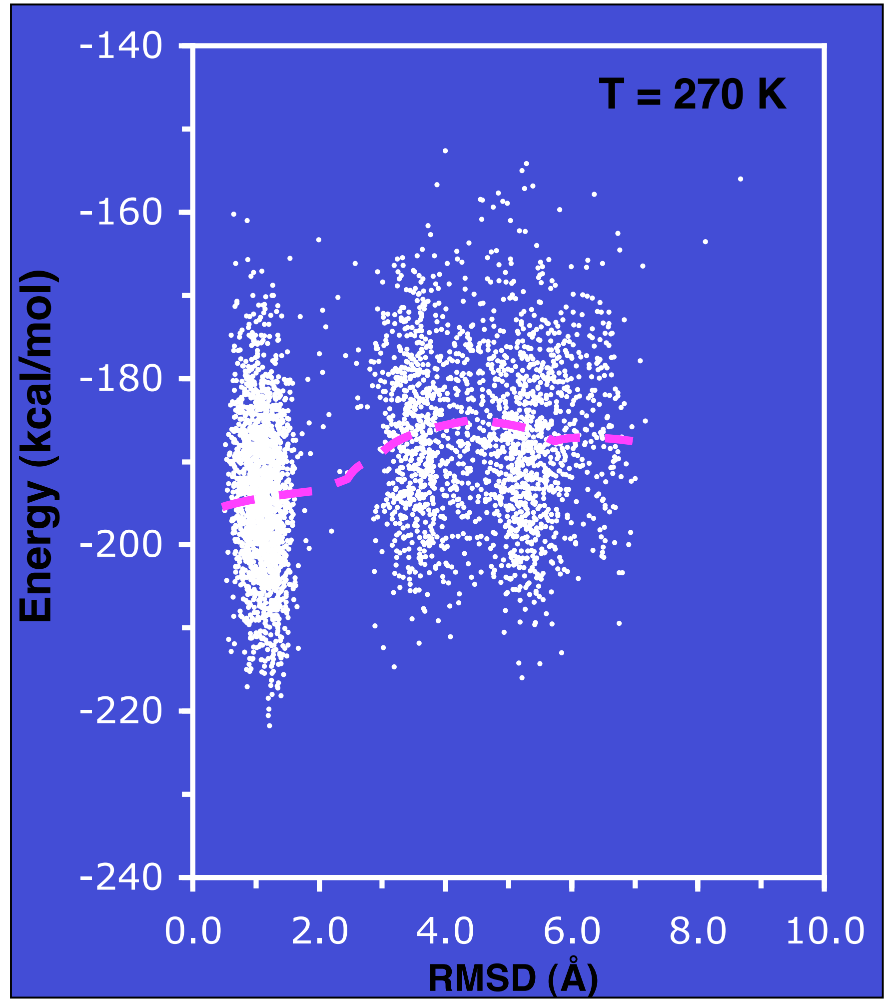
Folding of Trpzip2



PDB: 1le1 **54%, 1.0 Å**



Simulation details:
40 ns REX-MD with 16 replicas @ 270-550K;
CHARMM22/CMAP^{GBSW}/GBSW;
The population shown is computed from clustering the last 10 ns of the lowest temperature ensemble.

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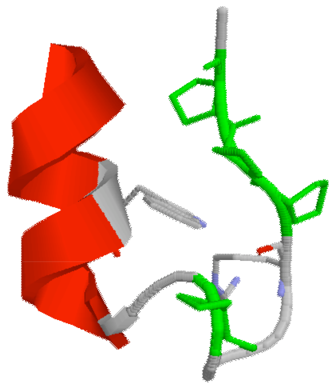
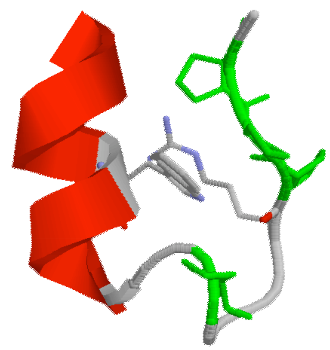
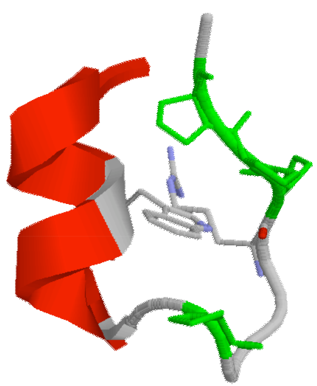
Folding of Trp-Cage



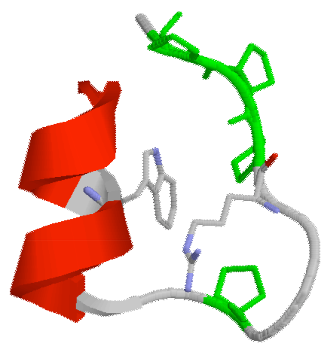
NMR (1l2y)



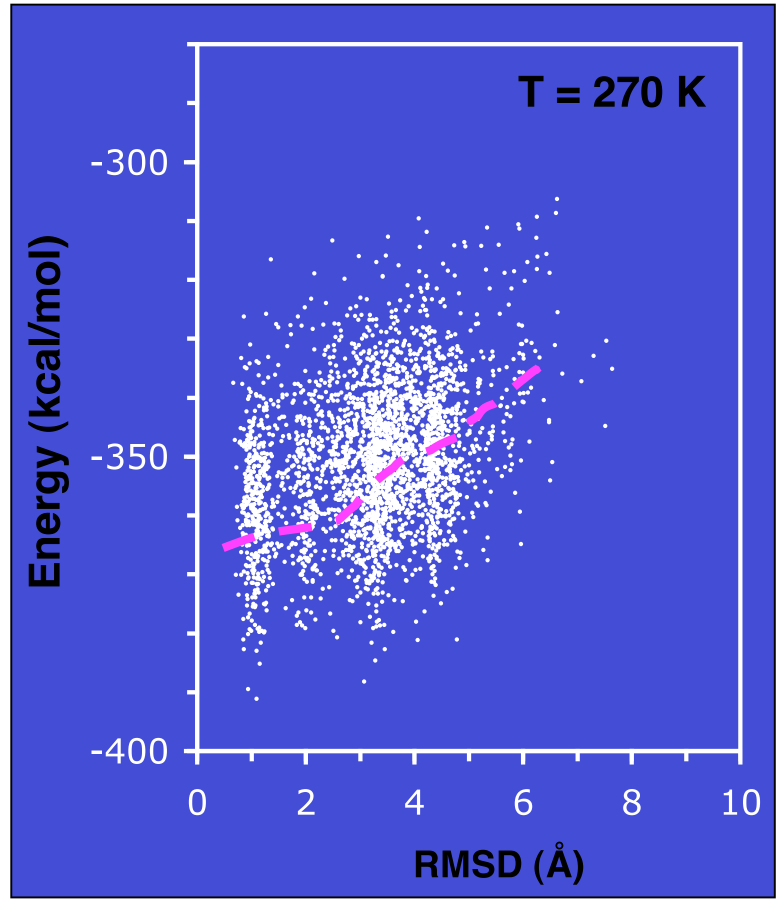
43%, 1.0 Å



26%, 2.1 Å



14%, 3.2 Å



Simulation details:
30 ns REX-MD with16 replicas @ 270-550K;
CHARMM22/CMAP^{GBSW}/GBSW;
The population shown are computed from clustering the last 10 ns of the lowest temperature ensemble.

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