

# Lecture 3: Differential Geometry-based Models for Electrostatics and Solvation

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NSF-CBMS Conference on Mathematical Molecular Bioscience and  
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University of Alabama

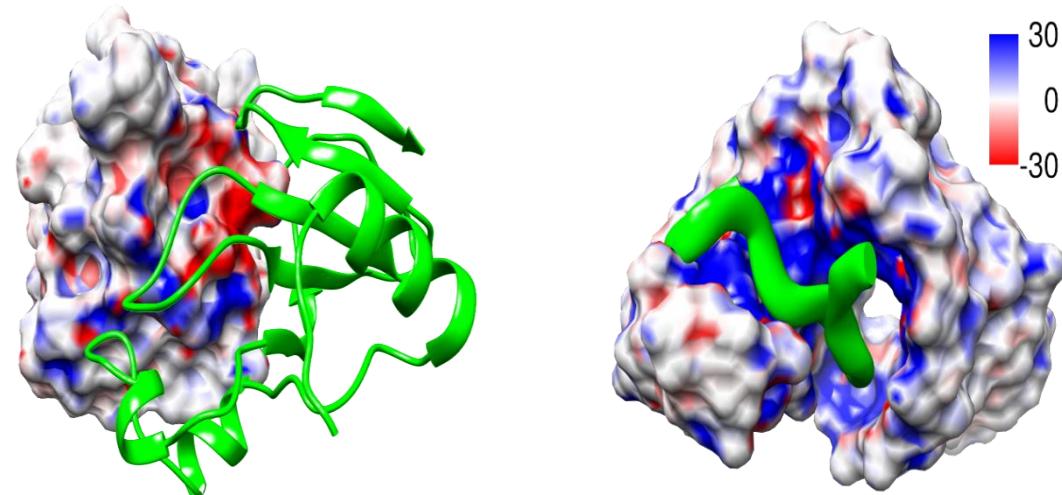
Tuscaloosa, May, 13-17, 2019

**Grant support: NSF, NIH, MSU, BMS, and Pfizer**

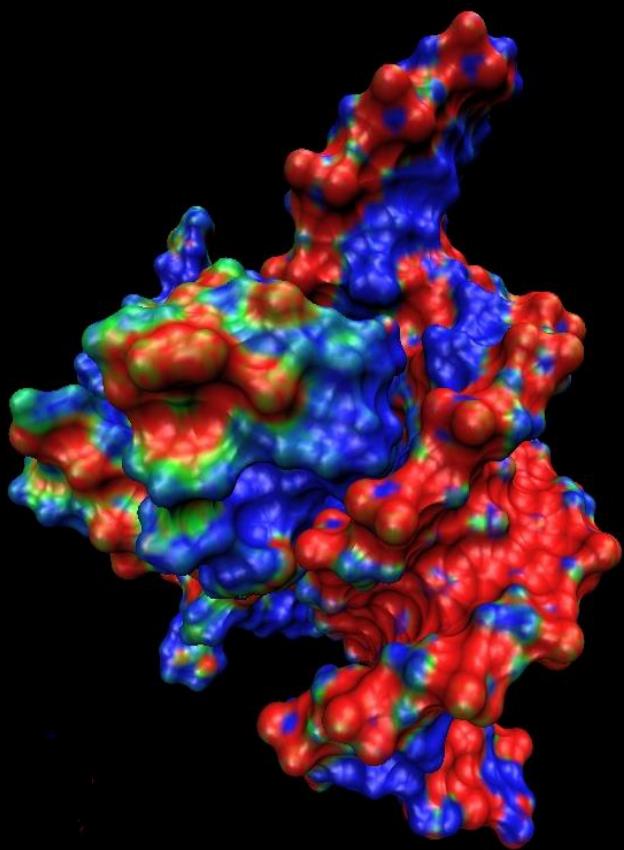


# Effects of electrostatics

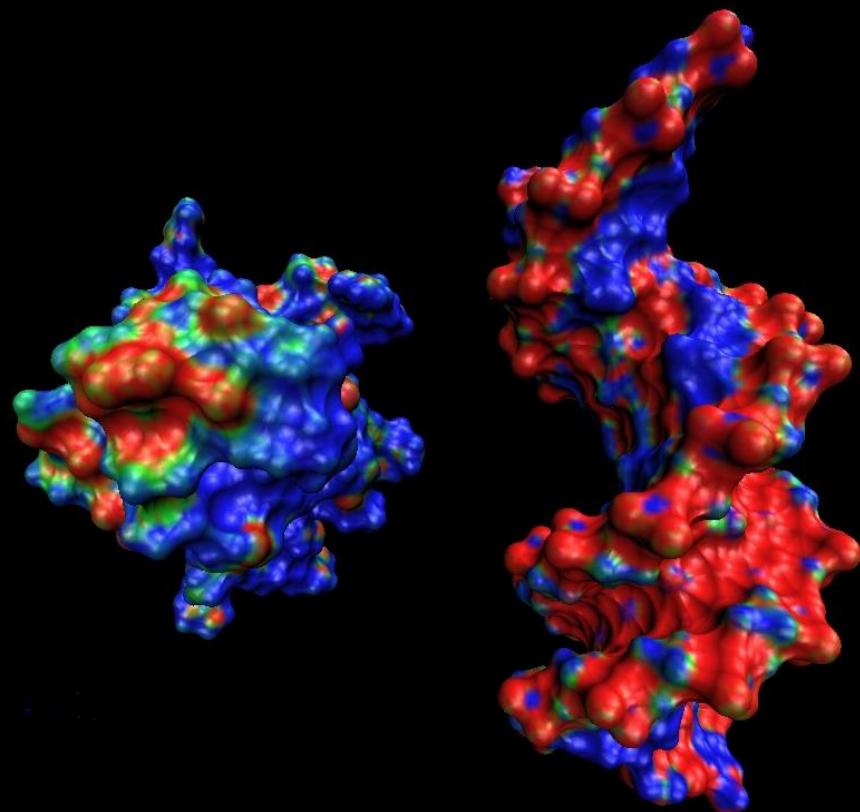
- Electrostatic steering, binding and solvation
- Electrostatic forces, ionic distributions, ion permeation
- Stability of protein folding, **molecular recognition**
- pKa, pH values
- Molecular Mechanism, Brownian dynamics, Monte Claro
- A tool for rational drug design (**interactions of receptor-inhibitor, protein-ligand, protein-protein, signal, enzyme, regulator, etc.**)



# Electrostatic maps of protein-DNA binding



(PDB Id: 9ant)

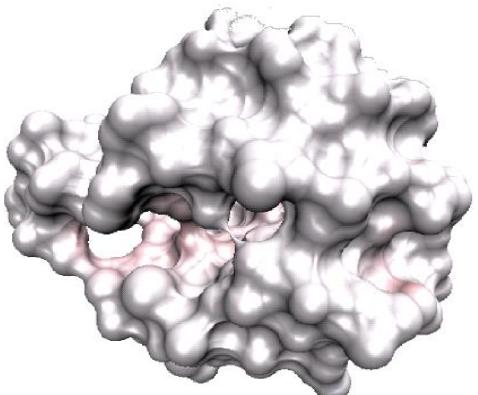


Protein-DNA complex.  
At the interface, protein is  
positively charged while the  
DNA is negatively charged.

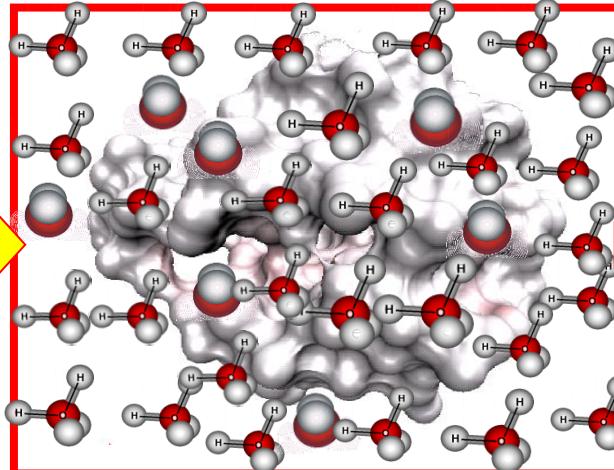
# Implicit solvent models

- About 65-90% of human body mass is water.
- Implicit solvent models enable to deal with electrostatic interactions of very large macromolecules with solvent.
- Implicit solvent models are promising means for the investigation of biomolecular structures and dynamics.
- Implicit solvent models are tools for rational drug design (interactions of receptor-inhibitor, protein-ligand, and protein-protein, signal, enzyme, regulator, etc.)

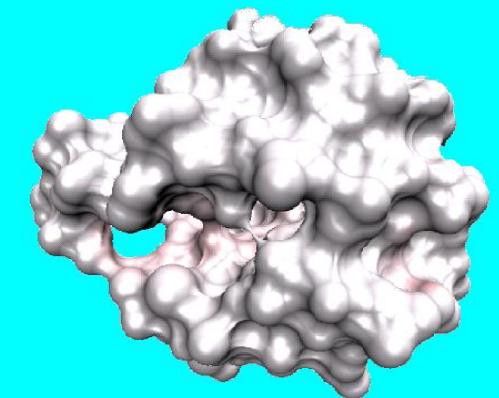
**Protein in Vacuum**



**Protein in water**



**Implicit solvent model**



# Implicit Solvent Models

## Explicit solvent models:

Water and other solvent molecules are represented by atomistic models. Polarized force fields and QM/MM approaches are often used to further improve the accuracy.

## Implicit solvent model:

Water and other solvent molecules are represented by continuum models. Solvation free energy is often modeled as

$$\Delta G = \Delta G_{\text{nonpolar}} + \Delta G_{\text{polar}}$$

$$\Delta G_{\text{nonpolar}} = \gamma A$$

where  $\gamma$  is the surface tension and  $A$  the surface area.

$\Delta G_{\text{polar}}$  is often modeled by

- Generalized Born,
- Poisson-Boltzmann model, and/or
- Polarizable continuum model, etc.
- Integral equation (classic DFT, RISM)

# Implicit Solvent Models— Generalized Born

Generalized Born (Forouzesh, Izadi and Onufriev, 2017):

$$\Delta G^{\text{GB}} \approx \sum_{ij} \Delta G_{ij}^{\text{GB}} = -\frac{1}{2} \left( \frac{1}{\varepsilon_m} - \frac{1}{\varepsilon_s} \right) \frac{1}{1 + \alpha\beta} \sum_{ij} q_i q_j \left( \frac{1}{f_{ij}} + \frac{\alpha\beta}{A} \right)$$

where  $\beta = \varepsilon_m / \varepsilon_s$ ,  $\alpha = 0.571412$ ,  $A$  is the electrostatic size of the molecule, and

$$f_{ij} = \sqrt{r_{ij} + R_i R_j \exp\left(-\frac{r_{ij}^2}{4R_i R_j}\right)}$$

$r_{ij}$  is the distance between atoms  $i$  and  $j$ , and  $R$  the effective Born radii:

$$R_i^{-1} = \left( -\frac{1}{4} \oint_{\Gamma} \frac{\mathbf{r} - \mathbf{r}_i}{|\mathbf{r} - \mathbf{r}_i|^6} \cdot d\mathbf{s} \right)^{1/3}$$

This model can be very accurate when it is parametrized with highly accurate PB solver.

(Still, Tempczyk, Hawley and Hendrickson, 1990; Bashford and Case, 2000, Tjong and Zhou, 161; Feig and Brooks, 2003; Zhu, Alexov and Honig, 2008,.....)

# Interface and boundary conditions of the Poisson-Boltzmann equation

(Warwicker and Watson, 1982;  
Sharp and Honig, 1990; Holst, 1993)

The Poisson-Boltzmann equation

$$-\nabla \cdot (\varepsilon(\mathbf{r}) \nabla \phi) - \sum_j q_j c_j e^{-\frac{q_j \phi}{kT}} = \sum_j Q_j \delta(\mathbf{r} - \mathbf{r}_j), \quad \forall \mathbf{r} \in \Omega = \Omega_s \cup \Omega_m$$

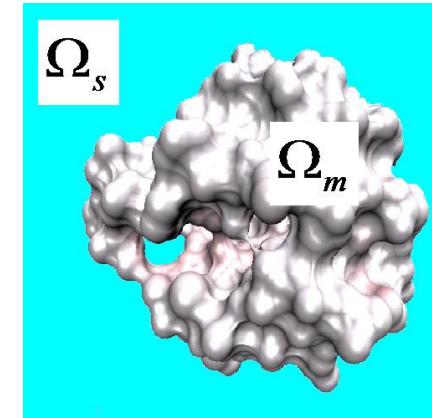
For  $\phi$  and  $\varepsilon(\mathbf{r}) \nabla \phi$  to be differentiable at the interface

$$\begin{cases} \phi^- = \phi^+, & \forall \mathbf{r} \in \partial \Omega_m \\ \varepsilon_m \frac{\partial \phi^-}{\partial n} = \varepsilon_s \frac{\partial \phi^+}{\partial n}, & \forall \mathbf{r} \in \partial \Omega_m \end{cases}$$

where  $\phi^-$  and  $\phi^+$  are the limiting values at the interface.

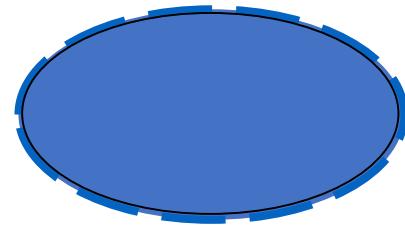
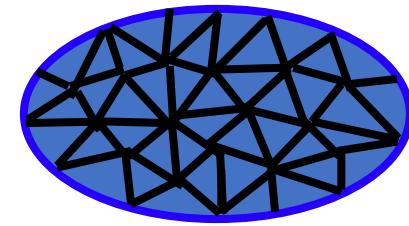
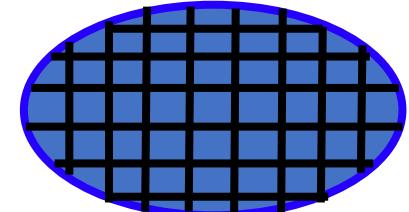
The Dirichlet boundary condition can be used:

$$\phi(\mathbf{r}) = \phi_0(\mathbf{r}), \quad \forall \mathbf{r} \in \partial \Omega$$



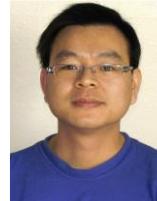
# Major discretization methods for the Poisson-Boltzmann equation

- Finite Difference Method: Klapper (1986); Honig (1987, 1991); Im et al (1989)...  
Software: DelPhi (Honig, Alexov, Rocchia...); PBEQ(CHARMM, Im, Roux); FDPB(AMBER, Luo); MEAD; APBS (Baker, Holst, ...); MIBPB.
- Finite Element Method: Holst (1994); Baker et al (APBS 2001); Xie (2017),...
- Boundary Element Method/Fast multipole: Zauhar (1985); HX Zhou (1993); Boschitsch (2002); McCammon (2005); Lu et al (2010); Treecode: Geng & Krasny (2013);...
- Monte Carlo PBE: Hwang, Mascagni, Fenley (2001,2007,2010), ...



# Implicit Solvent Models – Nonpolar Solvation Model

(Wei, BMB, 2010;  
Chen, Zhao, Baker, Bates, Wei, JMB, 2011)



Nonpolar energy functional  $G = \int [\text{Nonpolar}] d\mathbf{r}$

Nonpolar=area, volume and solvent-solute interaction.

Geometric measure theory: area  $\sim |\nabla S|$

$$G = \int [\gamma |\nabla S| + Sp + (1 - S)U] d\mathbf{r}$$

where  $p$  is the hydrodynamic pressure and  $U$  the van der Waals potential.

The variation leads to the generalized Laplace-Beltrami equation:

$$\frac{\partial S}{\partial t} = |\nabla S| \left[ \nabla \cdot \left( \frac{\gamma \nabla S}{|\nabla S|} \right) - p + U \right]$$

# Examine the coarea formula from geometric measure theory

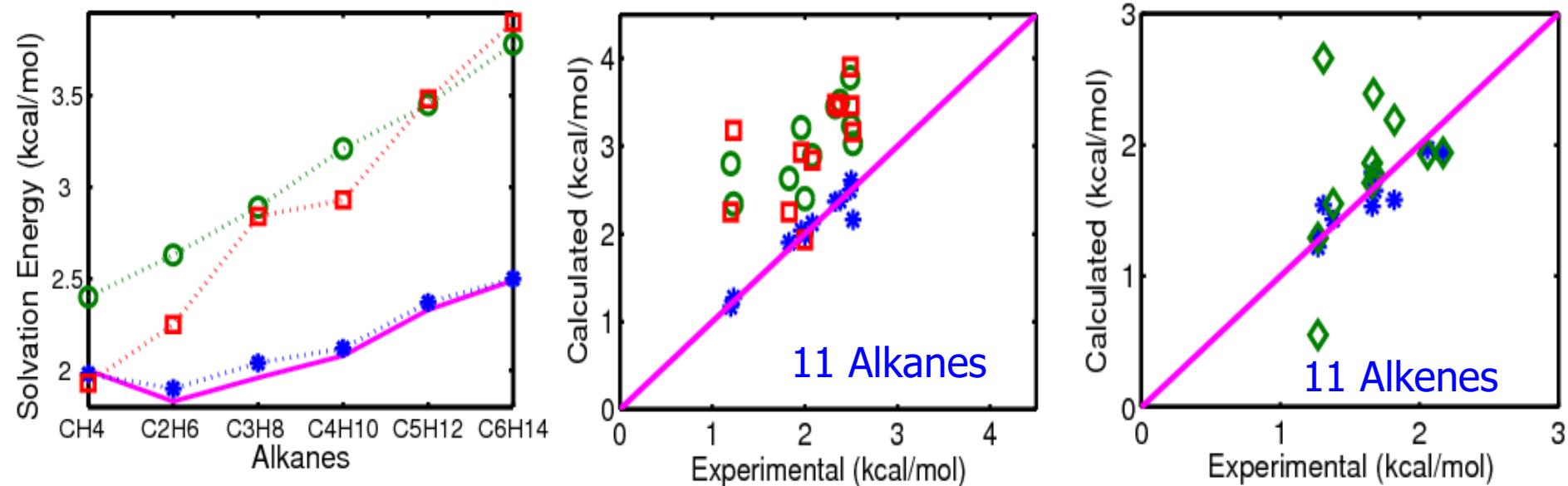
$$\text{Area} = \iint \sqrt{g} du_1 du_2 = \int_{\Omega} |\nabla S| dr$$

Areas computed from the coarea formula for bounded open sets.

Case	Grid spacing					Exact value
	0.5	0.25	0.1	0.05	0.025	
Sphere	4.00	4.00	4.15	4.17	4.18	4.189
Cylinder	22.50	23.25	24.49	24.84	25.01	25.133
Ellipsoid	37.75	37.97	38.10	38.17	38.16	38.163

(Chen, Baker, Wei, JCP, 2010)

# Comparison of nonpolar solvation free energies



◆ Our model (Chen, Zhao, Baker, Bates, Wei, JCP, 2012)  
◻ Wagoner and Baker. PNAS, 103, 8331, 2006.

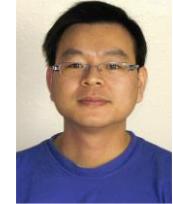
○ Gallicchio, Kubo, Levy, J. Phys. Chem. B, 104, 6271, 2000  
◇ Ratkova et al, (integral eqn theory) J. Phys. Chem. B, 114, 12068, 2010.

# Implicit Solvent Models— Full Solvation Model

Full energy functional  $G$

$$G = \int [\text{Nonpolar} + \text{Polar}] d\mathbf{r}$$

(Sharp & Honig, 1990;  
Dzubiella, Swanson, McCammon,  
PRL, 2006; Cheng et al, 2007;  
Wei, BMB, 2010;  
Chen, Baker, Wei, JCP, 2010)



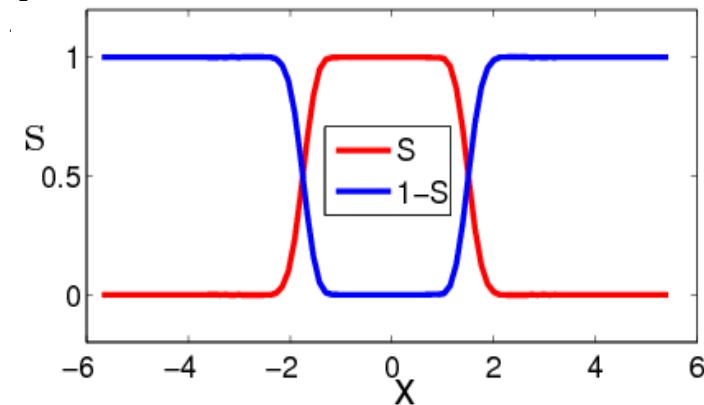
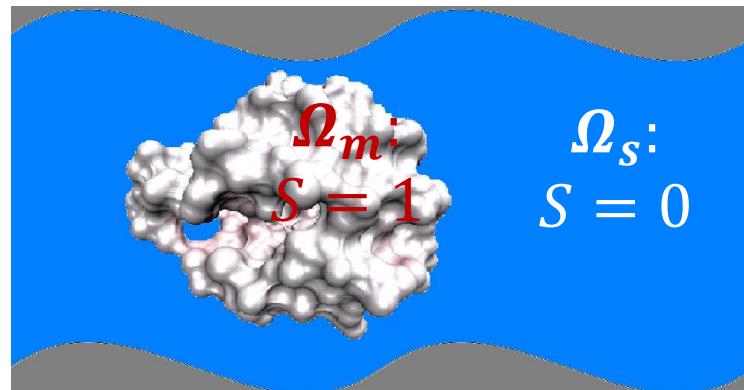
Nonpolar=area, volume and solvent-solute interaction:

$$\text{Nonpolar} = \gamma |\nabla S| + Sp + (1 - S)U$$

Polar = electric field + solute charges + solevent charges:

$$\text{Polar} = S \left( \phi n - \frac{\varepsilon_m}{2} |\nabla \phi|^2 \right) + (1 - S) \left[ -\frac{\varepsilon_s}{2} |\nabla \phi|^2 - kT \sum_j c_j \left( e^{-\frac{q_j \phi}{kT}} - 1 \right) \right]$$

where charge density in the solute:  $n = \sum_j Q_j \delta(\mathbf{r} - \mathbf{r}_j)$



# Implicit Solvent Models— Full Solvation Model

Generalized Laplace-Beltrami equation:

$$\frac{\partial S}{\partial t} = |\nabla S| \left[ \nabla \cdot \left( \frac{\gamma \nabla S}{|\nabla S|} \right) + V_{\text{full}} \right]$$

$V_{\text{full}}$

$$= -p + U + \left( \frac{\varepsilon_m}{2} |\nabla \phi|^2 - \phi n \right)$$
$$- \left[ \frac{\varepsilon_s}{2} |\nabla \phi|^2 + kT \sum_j c_j \left( e^{-\frac{q_j \phi}{kT}} - 1 \right) \right]$$

Generalized Poisson Boltzmann equation:

$$-\nabla \cdot (\varepsilon(S) \nabla \phi) = (1 - S) \sum_j q_j c_j e^{-\frac{q_j \phi}{kT}} + S n,$$

$$\text{where } \varepsilon(S) = S \varepsilon_m + (1 - S) \varepsilon_s$$

# ADI method for the geometric flow equation

$$\frac{\partial S}{\partial t} = \|\nabla S\| \left[ \nabla \cdot \left( \gamma \frac{\nabla S}{\|\nabla S\|} \right) + V \right] \Rightarrow$$

$$\left(1 - \frac{A_x}{2}\right) S_{ijk}^{n+\frac{1}{3}} = \left(1 + \frac{A_x}{2} + A_y + A_z\right) S_{ijk}^n + \mathcal{F}_{ijk}^n$$

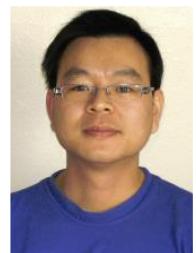
$$\left(1 - \frac{A_y}{2}\right) S_{ijk}^{n+\frac{2}{3}} = S_{ijk}^{n+\frac{1}{3}} - \frac{A_y}{2} S_{ijk}^n$$

$$\left(1 - \frac{A_z}{2}\right) S_{ijk}^{n+1} = S_{ijk}^{n+\frac{2}{3}} - \frac{A_z}{2} S_{ijk}^n$$

where  $f_{ijk}^n = \left\{ -2 \frac{\sum_{\beta,\alpha} S_\alpha S_\beta S_{\alpha\beta}}{\sum_\beta S_\beta^2} + \sqrt{\sum_\beta S_\beta^2} V / \gamma \right\}_{ijk}^n$

$$A_\alpha = \tau \left\{ \frac{\sum_{\beta \neq \alpha} S_\beta^2}{\sum_\beta S_\beta^2} \right\}_{ijk}^n \partial_\alpha^2$$

$$\partial_x^2 S_{ijk}^n = (S_{(i-1)jk}^n - 2S_{ijk}^n + S_{(i+1)jk}^n) / h^2 \quad \text{and} \quad \{S_x\}_{ijk}^n = (S_{(i+1)jk}^n - S_{(i-1)jk}^n) / 2h$$



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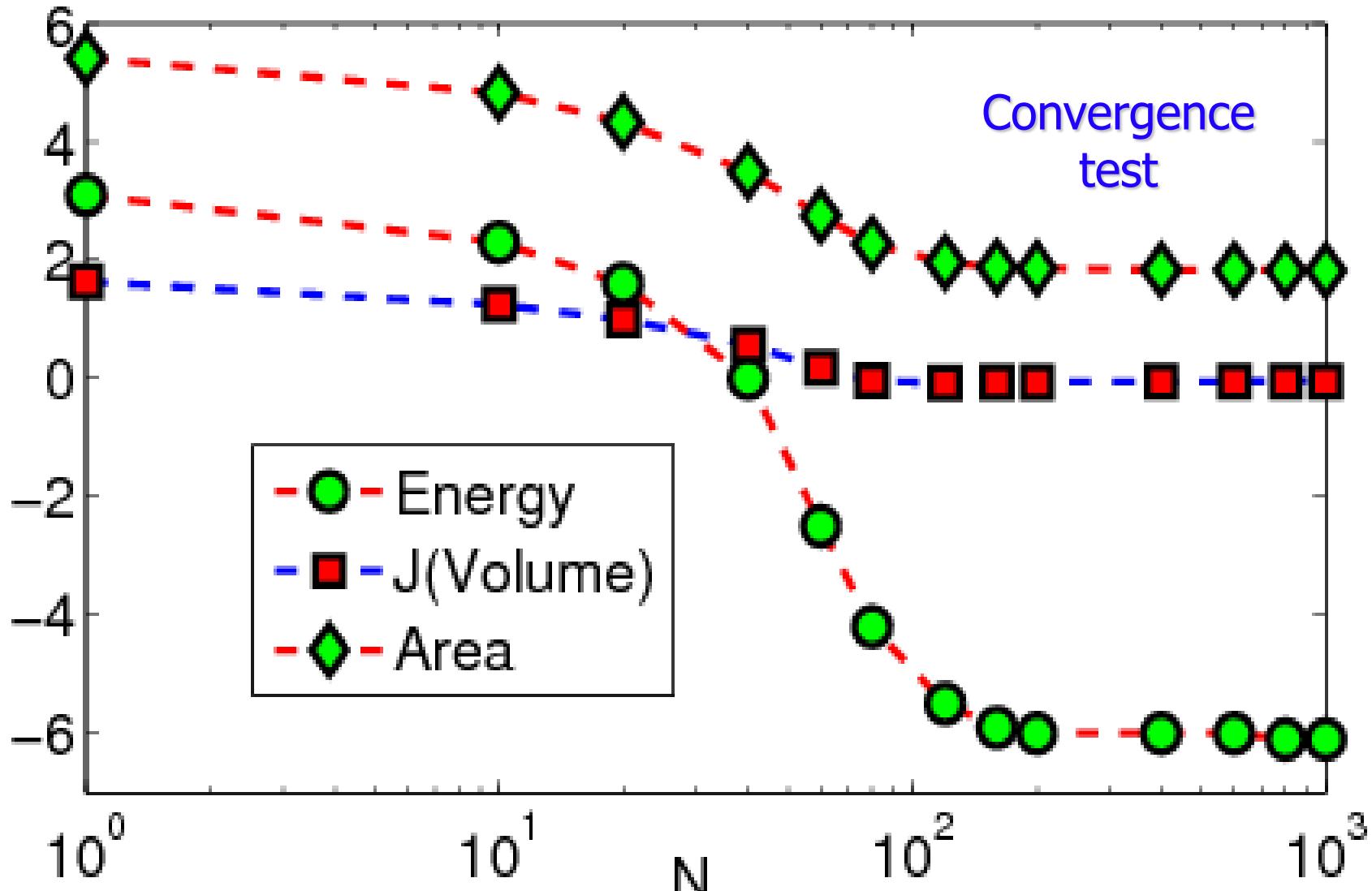
(Bates, Chen, Sun, Wei & Zhao, J. Math. Biol. 2008; Zhao, 2011, 2014)

# Second order discretization of the generalized Poisson-Boltzmann equation

$$\begin{aligned} -\nabla \bullet \varepsilon(S) \nabla u + (1-S) \kappa^2 u = S \rho_m \Rightarrow \\ \varepsilon_{(i+\frac{1}{2})jk} [u_{(i+1)jk} - u_{ijk}] + \varepsilon_{(i-\frac{1}{2})jk} [u_{(i-1)jk} - u_{ijk}] + \\ \varepsilon_{i(j+\frac{1}{2})k} [u_{i(j+1)k} - u_{ijk}] + \varepsilon_{i(j-\frac{1}{2})k} [u_{i(j-1)k} - u_{ijk}] + \\ \varepsilon_{ij(k+\frac{1}{2})} [u_{ij(k+1)} - u_{ijk}] + \varepsilon_{ij(k-\frac{1}{2})} [u_{ij(k-1)} - u_{ijk}] - \\ 4(1 - S_{ijk}) \kappa^2 u_{ijk} = -4S_{ijk} q_{ijk} / h \end{aligned}$$

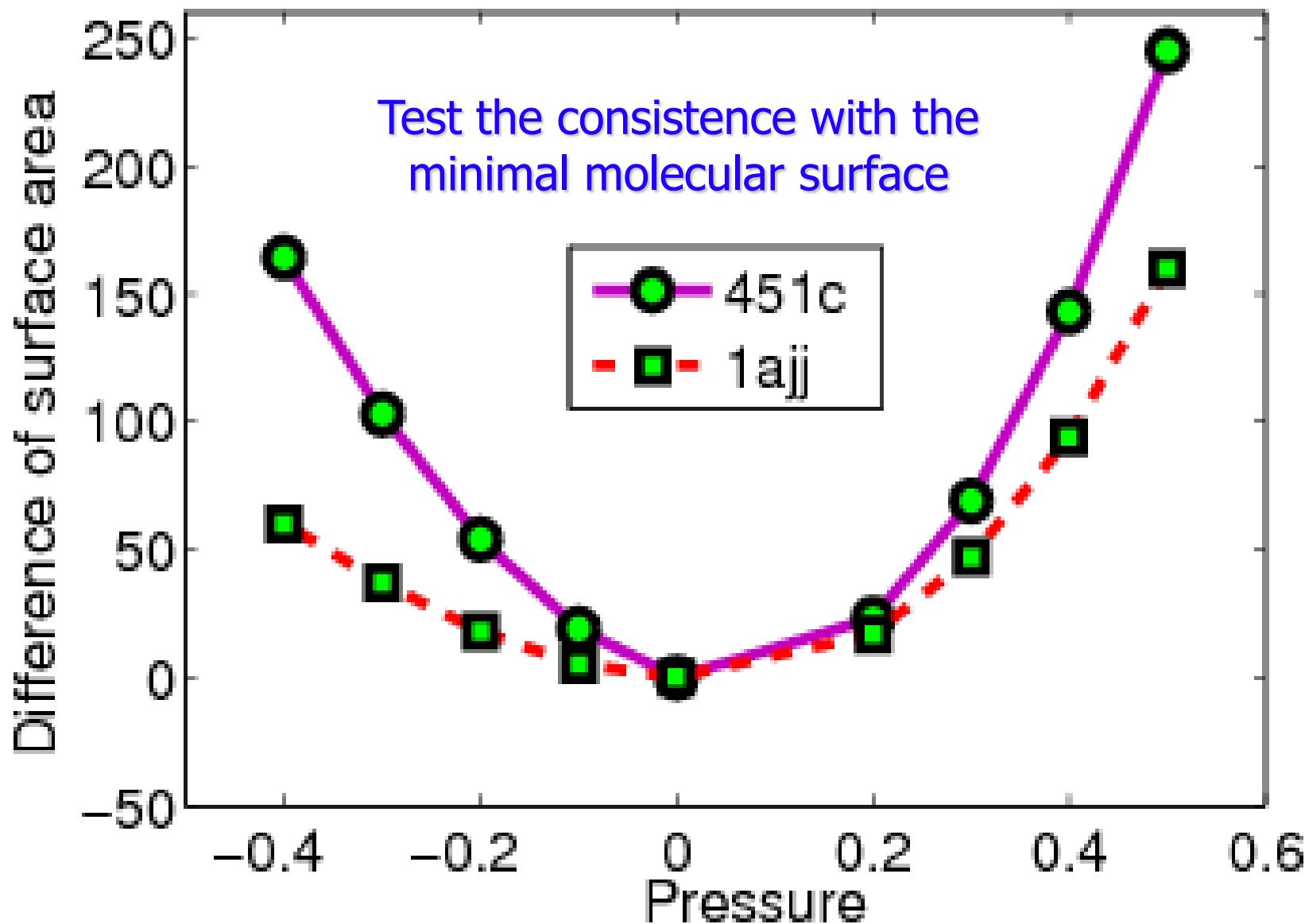
where  $q_{ijk}$  is resulted from the interpolation of the chargedensity  $\rho_m$

# Convergence analysis of the multiscale model

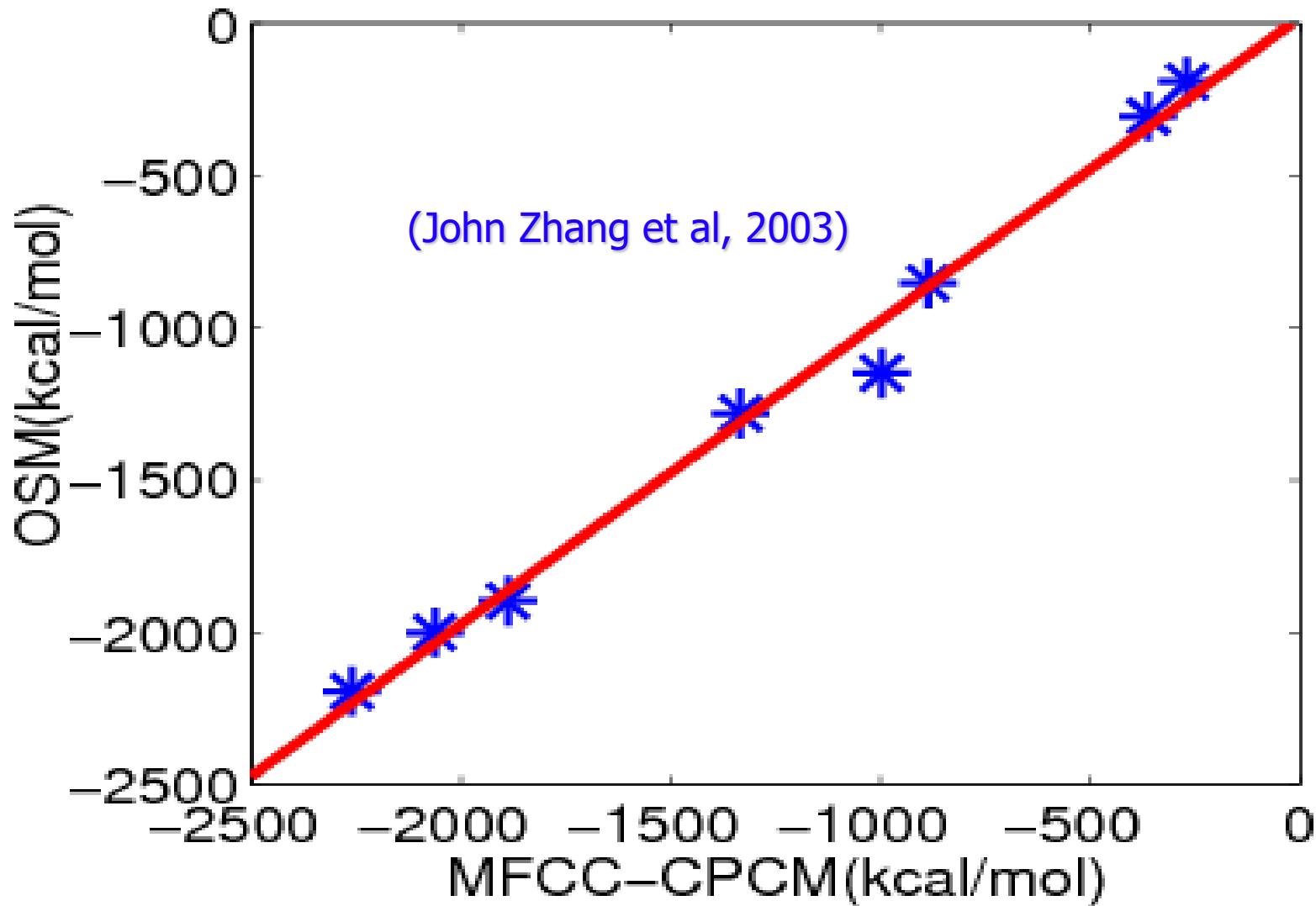


(Chen, Baker & Wei, JCP, 2010)

# Convergence analysis of the multiscale model

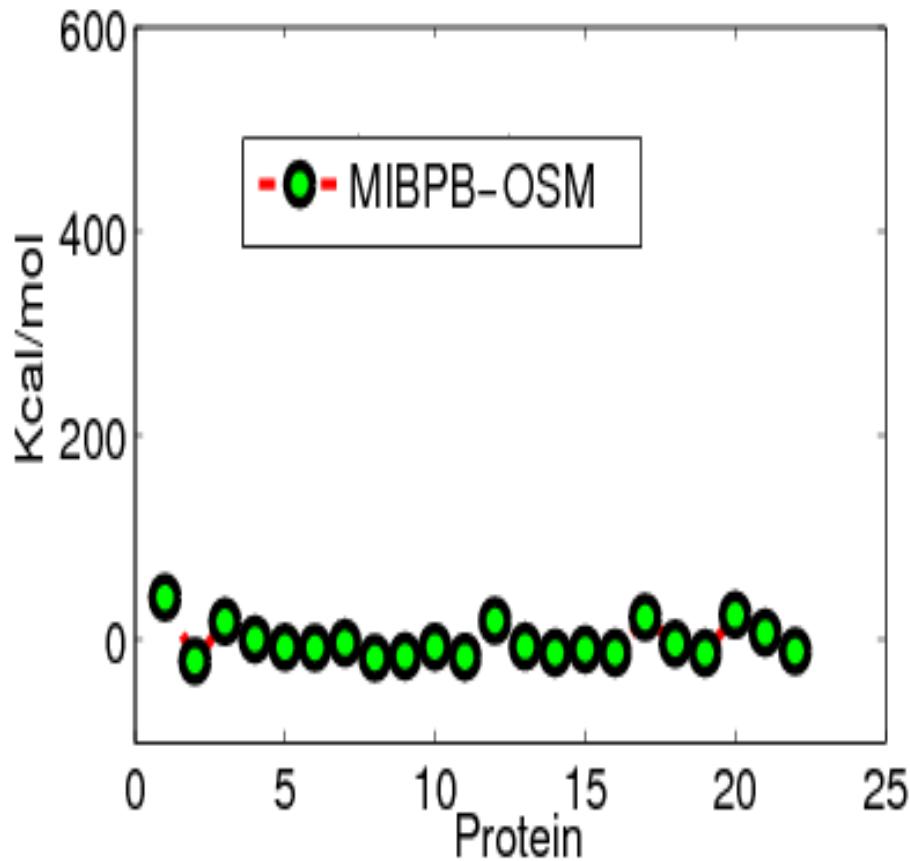
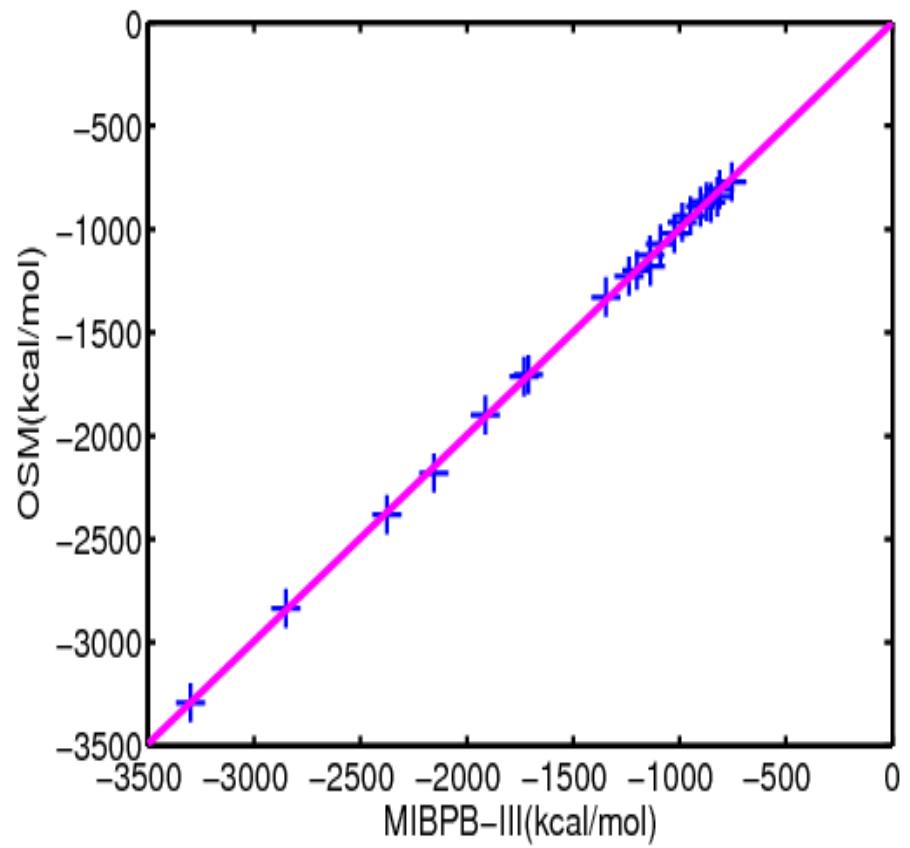


# Energy comparison with the quantum mechanical continuum model



(Chen, Baker & Wei, JCP, 2010)

# Comparison of electrostatic energies of 23 proteins



# Blind test of 17 compounds: No parameter fitting!

(Chen, Baker & Wei, JCP, 2010)

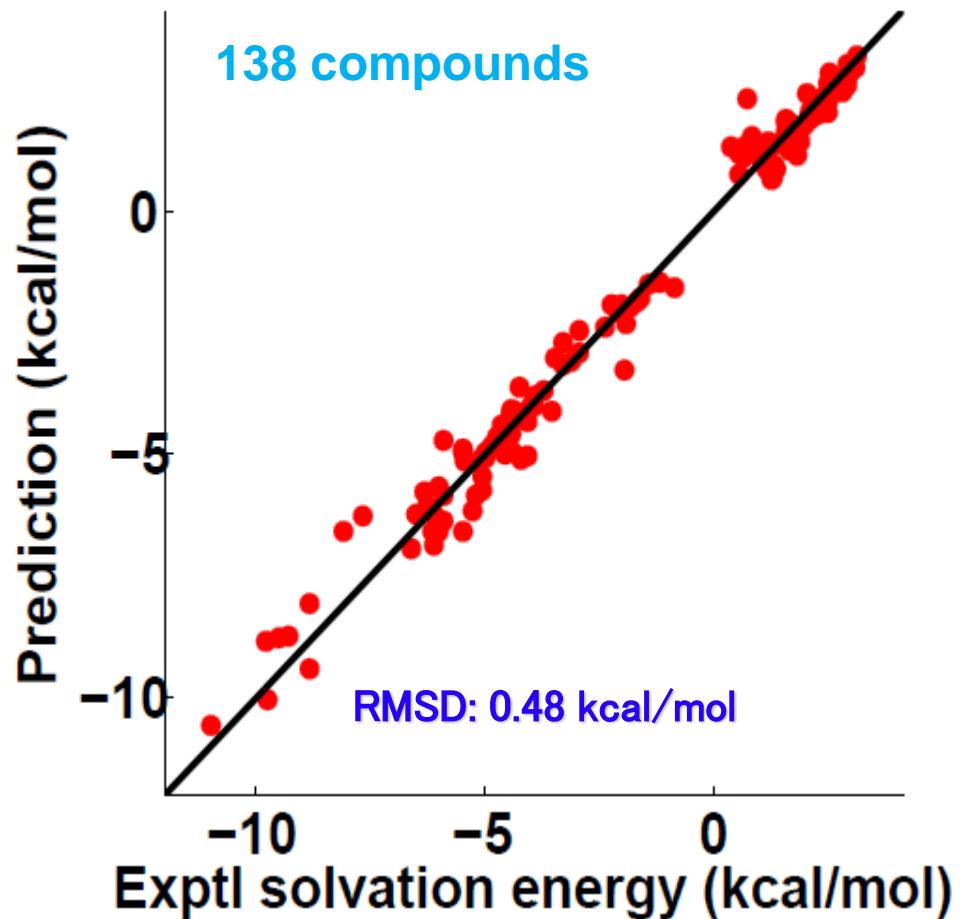
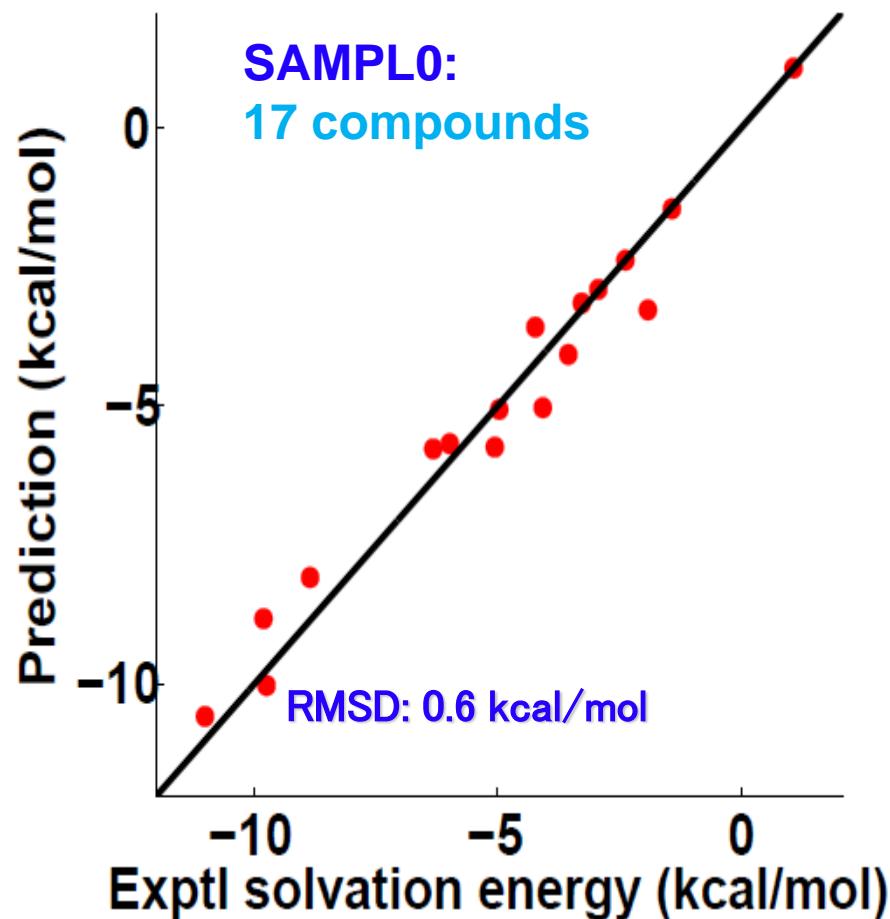
Compound	Area	Volume	$G_{ap}$	$\Delta G_p$	$\Delta G$	Exptl	Error
glycerol triacetate	241.34	234.11	2.33	-12.36	-10.03	-8.84	-1.19
benzyl bromide	150.66	136.36	1.39	-4.87	-3.47	-2.38	-1.09
benzyl chloride	148.14	133.84	1.36	-5.06	-3.70	-1.93	-1.77
m-bis(trifluoromethyl)benzene	266.67	306.86	2.22	-3.30	-1.07	1.07	-2.14
N,N-dimethyl-p-methoxybenzamide	209.31	202.02	1.99	-9.22	-7.22	-11.01	3.79
N,N,4-trimethylbenzamide	200.27	193.25	1.91	-7.84	-5.93	-9.76	3.83
bis-2-chloroethyl ether	155.71	130.90	1.44	-4.16	-2.71	-4.23	1.52
1,1-diacetoxymethane	177.82	160.48	1.67	-8.21	-6.53	-4.97	-1.56
1,1-diethoxymethane	163.66	143.73	1.55	-4.63	-3.08	-3.28	0.20
1,4-dioxane	109.56	143.73	1.01	-5.64	-4.62	-5.05	0.43
diethyl propanedioate	195.06	182.22	1.87	-7.75	-5.88	-6.00	0.12
dimethoxymethane	109.17	88.36	1.02	-4.64	-3.62	-2.93	-0.69
ethylene glycol diacetate	168.19	160.95	1.62	-8.40	-6.78	-6.34	0.44
1,2-diethoxymethane	169.25	141.92	1.57	-4.40	-2.83	-3.54	0.71
diethyl sulfide	133.81	116.84	1.22	-2.40	-1.17	-1.43	0.26
phenyl formate	148.14	134.84	1.37	-7.82	-6.45	-4.08	-2.37
imidazole	89.05	68.59	0.80	-11.56	-10.76	-9.81	-0.95

RMS=1.75 compared with RMS=1.87 by Nicholls et al (2008)

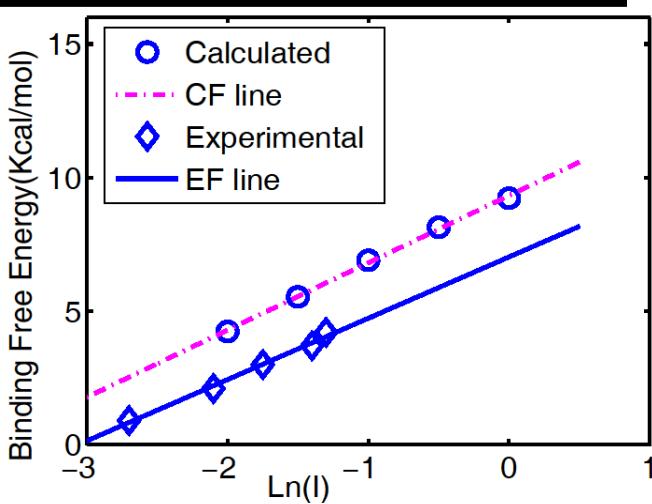
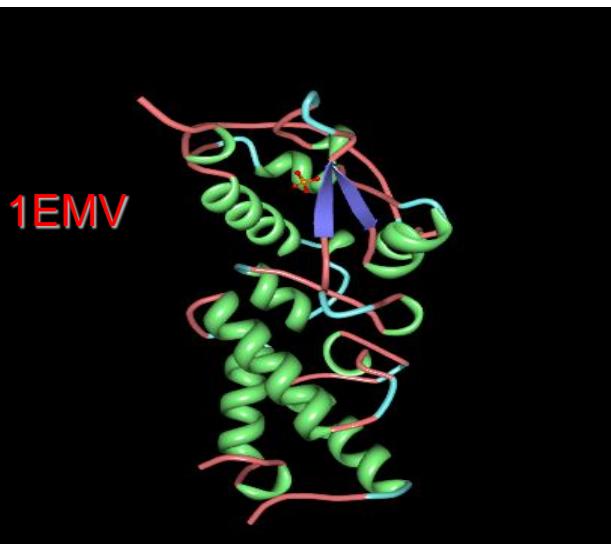
# Test of solvation energies



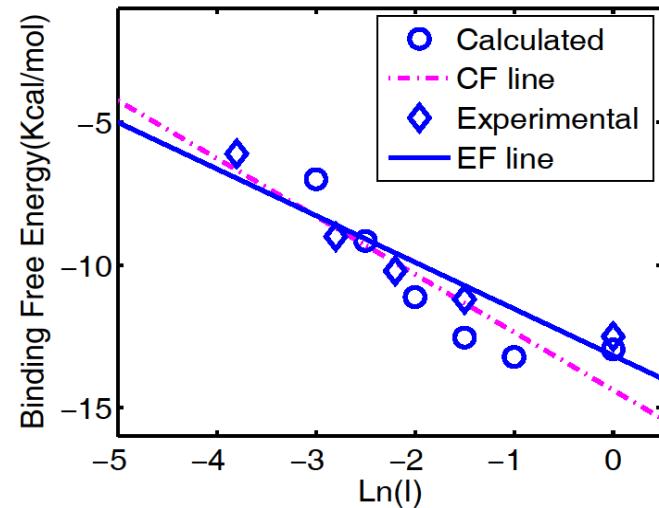
Wang & Wei, JCP, 2015



# Binding free energies of protein-protein interactions



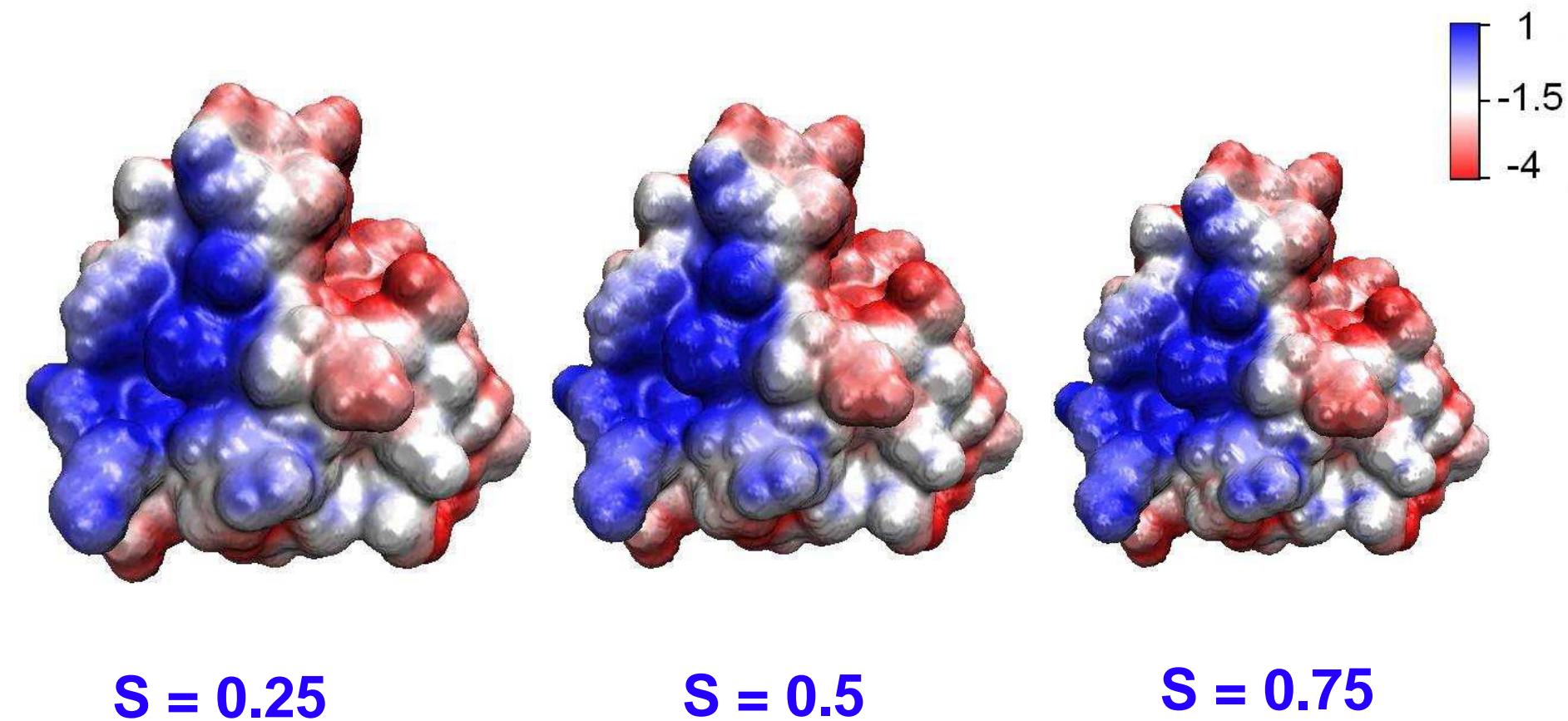
(Approach established by Barry Honig et al. 2005; Chen, Baker & Wei, JMB, 2011)



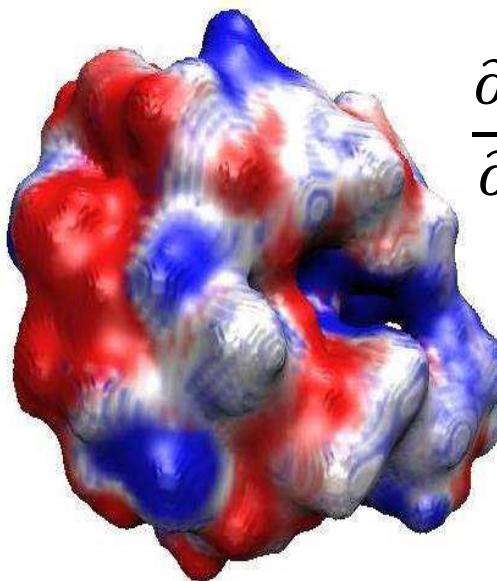
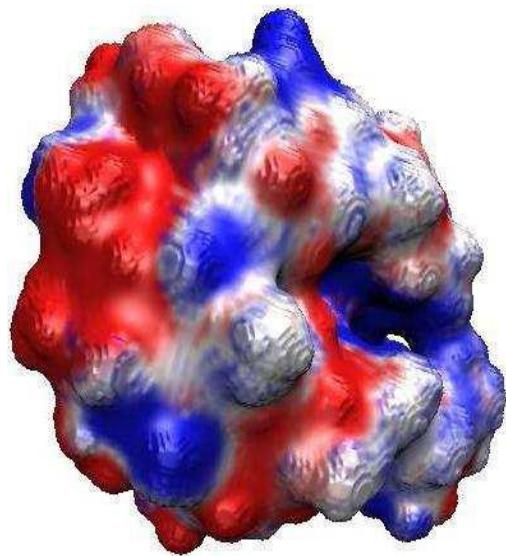
Complex	PDB code	Complex charge	Surface Area ( $\text{\AA}^2$ )	Charge of the free monomers	Experimental data	Calculated
E9Dnase-lm9 (10)	1emv	-3	1465	B=+5; A=-8	2.17	2.52
Lactoglobulin Dimer (57) (A-B)	1beb	+26	1167	A=B=+13	-1.62	-2.02

# Surface electrostatic potentials at different $S$ values

$$\frac{\partial S}{\partial t} = |\nabla S| \left[ \nabla \cdot \left( \frac{\gamma \nabla S}{|\nabla S|} \right) + V \right]$$



# Effect of interaction potentials

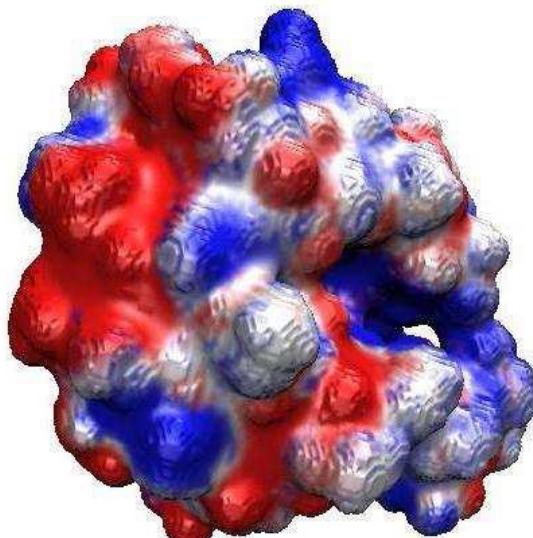


$$\frac{\partial S}{\partial t} = |\nabla S| \left[ \nabla \cdot \left( \frac{\gamma \nabla S}{|\nabla S|} \right) + v \right]$$

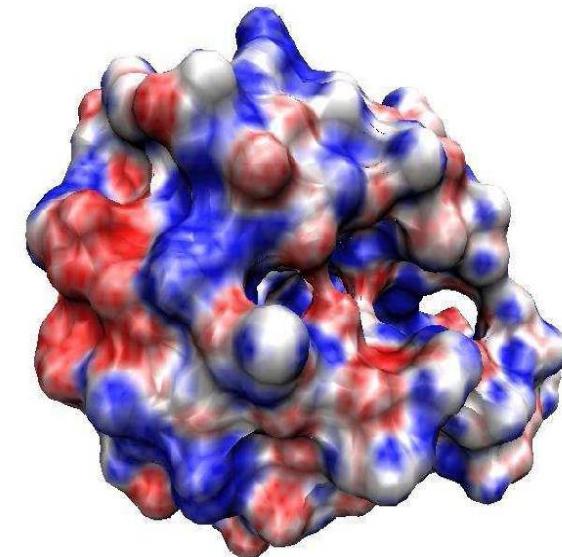
Minimal molecular surface

Repulsive surface

Protein 451c

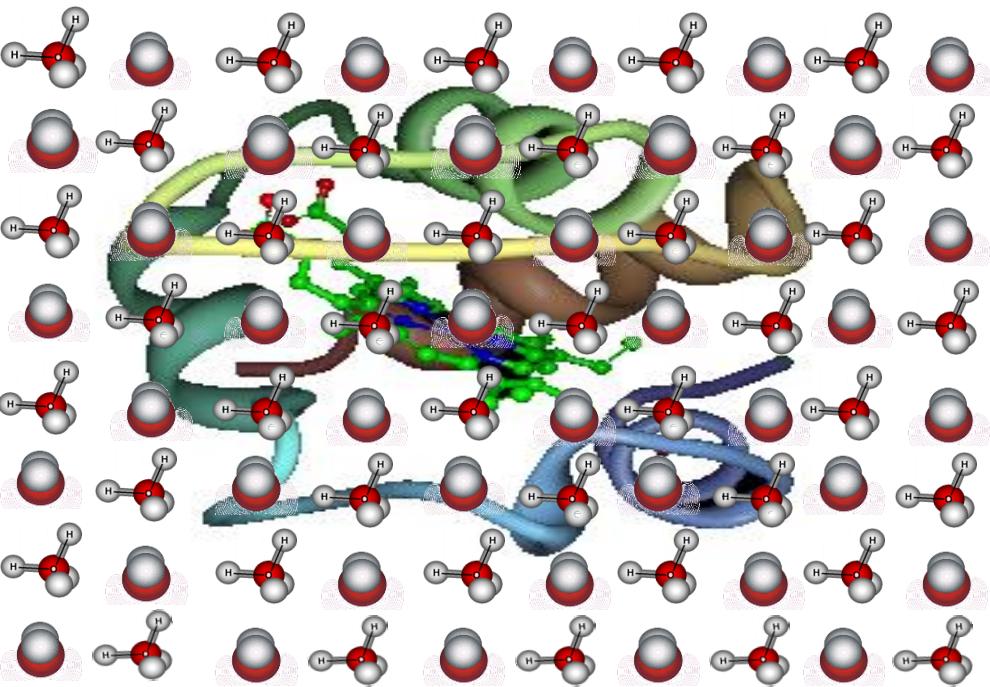


Attractive surface



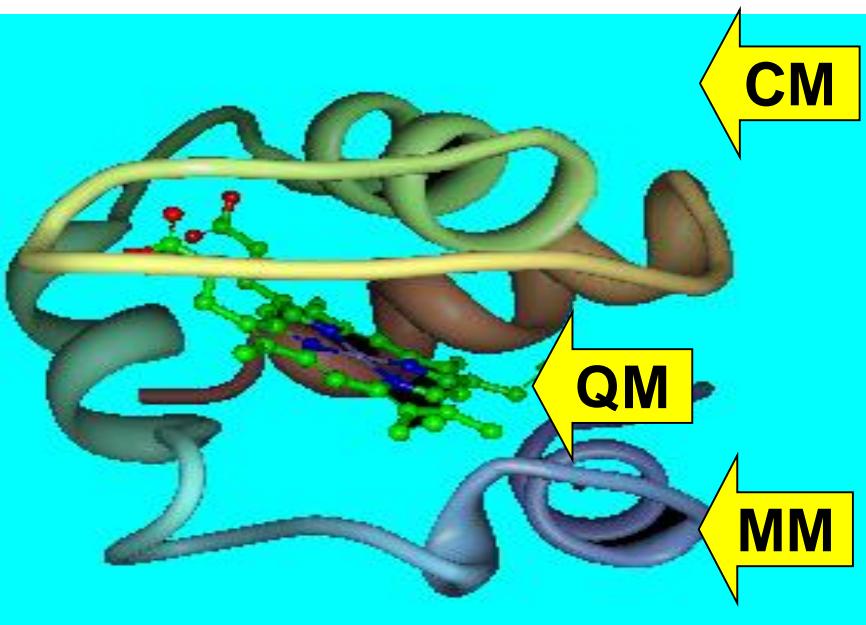
Connolly surface

(Chen, Baker & Wei, JCP, 2010)



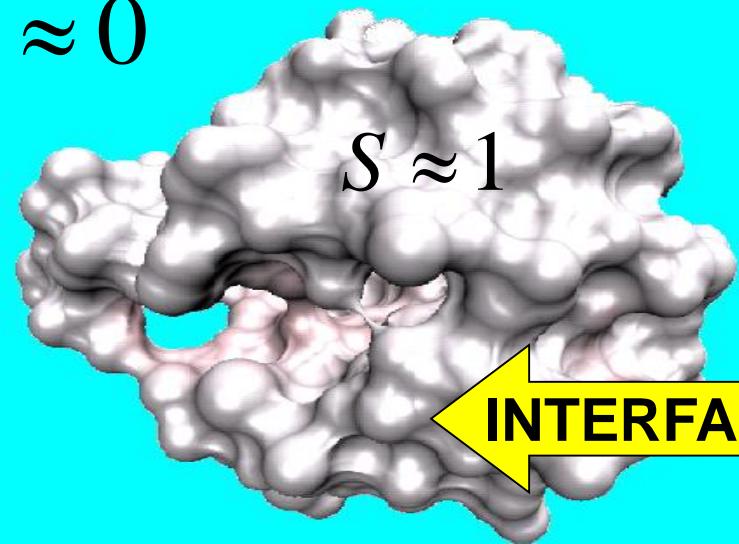
## Quantum PB models

(Bashford & coworkers, 1994;  
Honig & coworkers, 1994;  
Wang & Wong, 2006)



Surface function  $S$

$$S \approx 0$$



# Implicit Solvent Models– Quantum formulation

Quantum mechanic energy functional  $G$

$$G = \int [\text{Nonpolar} + \text{Polar} + \text{QM}] d\mathbf{r}$$

Nonpolar=area, volume and solvent-solute interaction:

$$\text{Nonpolar} = \gamma |\nabla S| + Sp + (1 - S)U$$

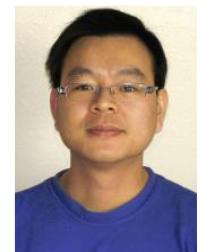
Polar = electric field + solute charges + solevent charges:

$$\text{Polar} = S \left( \phi n - \frac{\varepsilon_m}{2} |\nabla \phi|^2 \right) - (1 - S) \left[ \frac{\varepsilon_s}{2} |\nabla \phi|^2 + kT \sum_j c_j \left( e^{-\frac{q_j \phi}{kT}} - 1 \right) \right]$$

QM = Kinetic + Potential + Lagrange multiplier

$$\text{QM} = S \left( - \sum_j \frac{\hbar^2}{2m} |\nabla \psi_j|^2 - E_{XC}[n] + \sum_j E_i |\psi_j|^2 \right)$$

$$\text{Electron density: } n = \sum_j |\psi_j|^2$$



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# Implicit Solvent Models– Quantum formulation

Generalized Poisson-Boltzmann equation

$$-\nabla \cdot (\varepsilon(S) \nabla \phi) = (1 - S) \sum_j q_j c_j e^{-\frac{q_j \phi}{kT}} + Sn$$

Kohn-Sham equation for electron

$$-\frac{\hbar^2}{2m} \nabla^2 \psi_j + (U_{XC}[n] - \phi) \psi_j = E_j \psi_j$$

where exchange correlation energy:  $U_{XC}[n] = \frac{\delta E_{XC}[n]}{\delta n}$

Generalized Laplace Beltrami equation

$$\frac{\partial S}{\partial t} = |\nabla S| \left[ \nabla \cdot \left( \frac{\gamma \nabla S}{|\nabla S|} \right) + V \right]$$

where

$$\begin{aligned} V = & -p + U + \left( \frac{\varepsilon_m}{2} |\nabla \phi|^2 - \phi n \right) - \left[ \frac{\varepsilon_s}{2} |\nabla \phi|^2 + kT \sum_j c_j \left( e^{-\frac{q_j \phi}{kT}} - 1 \right) \right] \\ & + \sum_j \frac{\hbar^2}{2m} |\nabla \psi_j|^2 - E_{XC}[n] + \sum_j E_i |\psi_j|^2 \end{aligned}$$

# The proof of the total free energy decay

$$G = \int [\text{Nonpolar} + \text{Polar} + \text{QM}] dr = \int G_f dr$$

Consider coupled geometric and potential flows obtained via the steepest decent

Time-dependent Poisson-Boltzmann equation

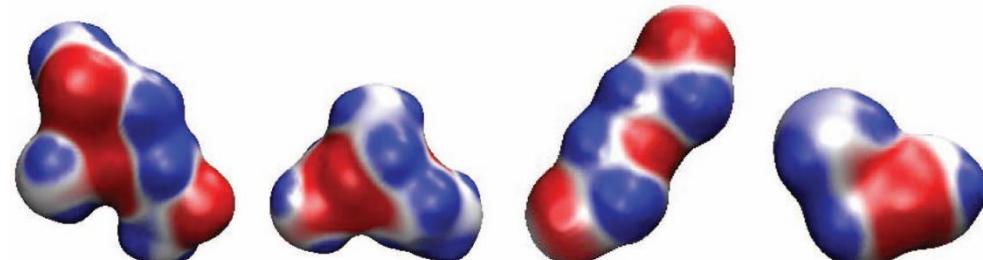
$$\frac{\partial \phi}{\partial t} = \nabla \cdot (\varepsilon(S) \nabla \phi) + (1 - S) \sum_j q_j c_j e^{-\frac{q_j \phi}{kT}} + Sn$$

Time-dependent Kohn-Sham equation

$$i\hbar \frac{\partial \psi_j}{\partial t} = -\frac{\hbar^2}{2m} \nabla^2 \psi_j + (U_{XC}[n] - \phi - E_j) \psi_j$$

Generalized Laplace Beltrami equation

$$\frac{\partial S}{\partial t} = |\nabla S| \left[ \nabla \cdot \left( \frac{\gamma \nabla S}{|\nabla S|} \right) + V \right]$$



# The proof of the total free energy decay

(Wei, 2012)

The time dependence of the total free energy

$$\begin{aligned}\frac{dG}{dt} &= \int \left[ \frac{\delta G_f}{\delta S} \frac{\delta S}{\delta t} + \frac{\delta G_f}{\delta \phi} \frac{\delta \phi}{\delta t} + \sum_j \left( \frac{\delta G_f}{\delta \psi_j} \frac{\delta \psi_j}{\delta t} + \frac{\delta G_f}{\delta \psi_j^*} \frac{\delta \psi_j^*}{\delta t} \right) \right] dr \\ &= - \int \left[ |\nabla S| \left( \frac{\delta G_f}{\delta S} \right)^2 + \left( \frac{\delta G_f}{\delta \phi} \right)^2 \right] dr \leq 0,\end{aligned}$$

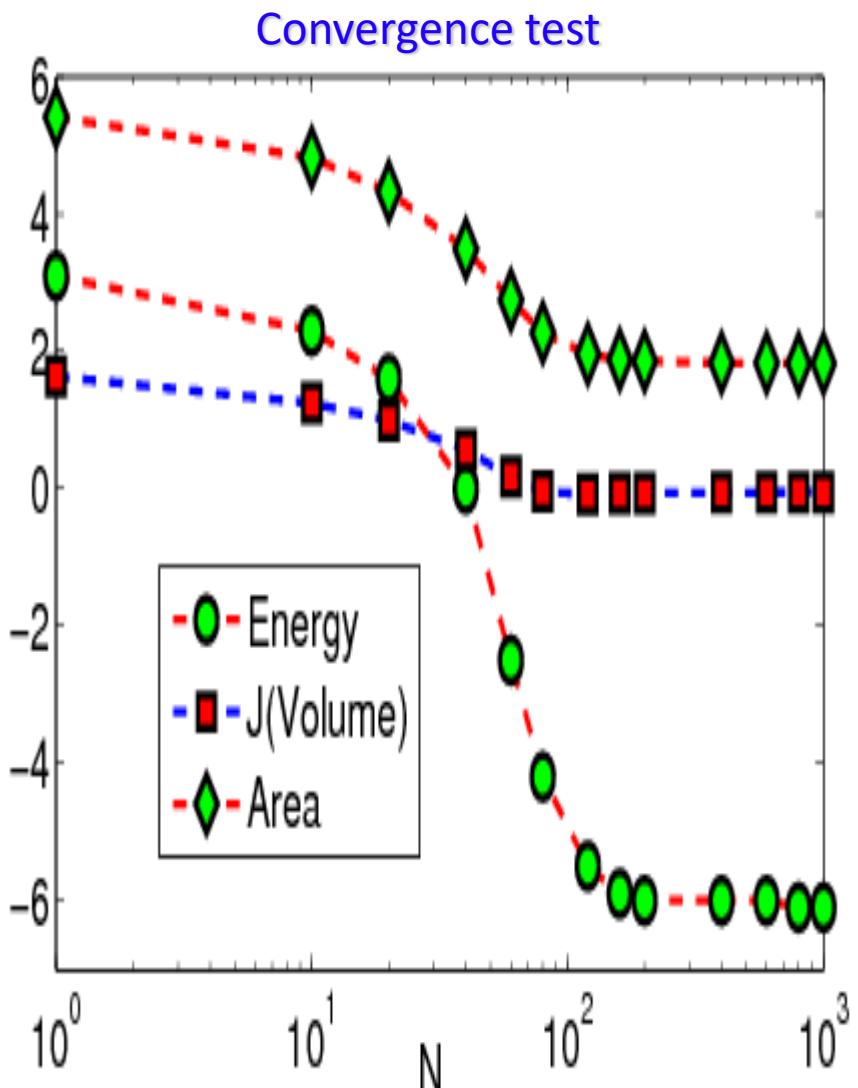
where  $\frac{\delta S}{\delta t} = -|\nabla S| \frac{\delta G_f}{\delta S}$ ,

$$\frac{\delta \phi}{\delta t} = -\frac{\delta G_f}{\delta \phi} \quad \text{and}$$

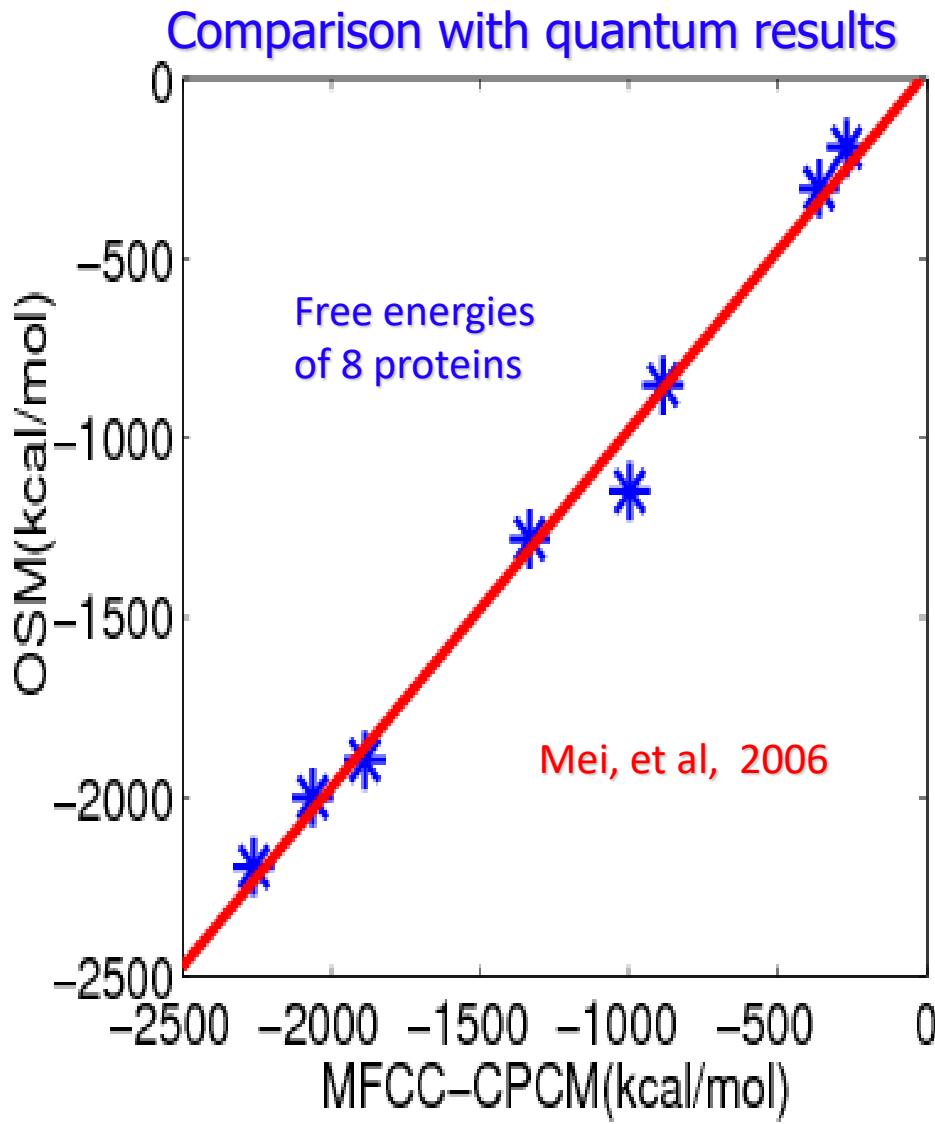
$$\sum_j \left( \frac{\delta G_f}{\delta \psi_j} \frac{\delta \psi_j}{\delta t} + \frac{\delta G_f}{\delta \psi_j^*} \frac{\delta \psi_j^*}{\delta t} \right) = 0$$

(similar to Bo Li's analysis)

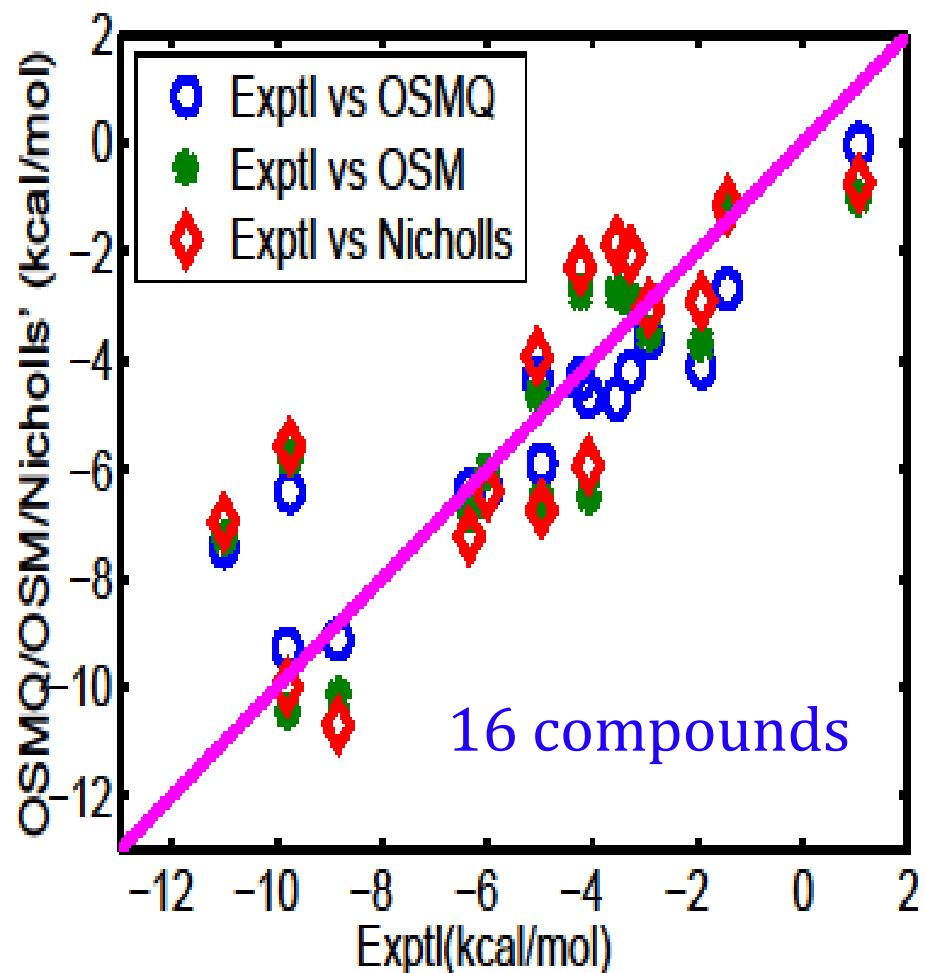
# Validation of the multiscale solvation model



(Chen, Baker & Wei, JMB, 2011)



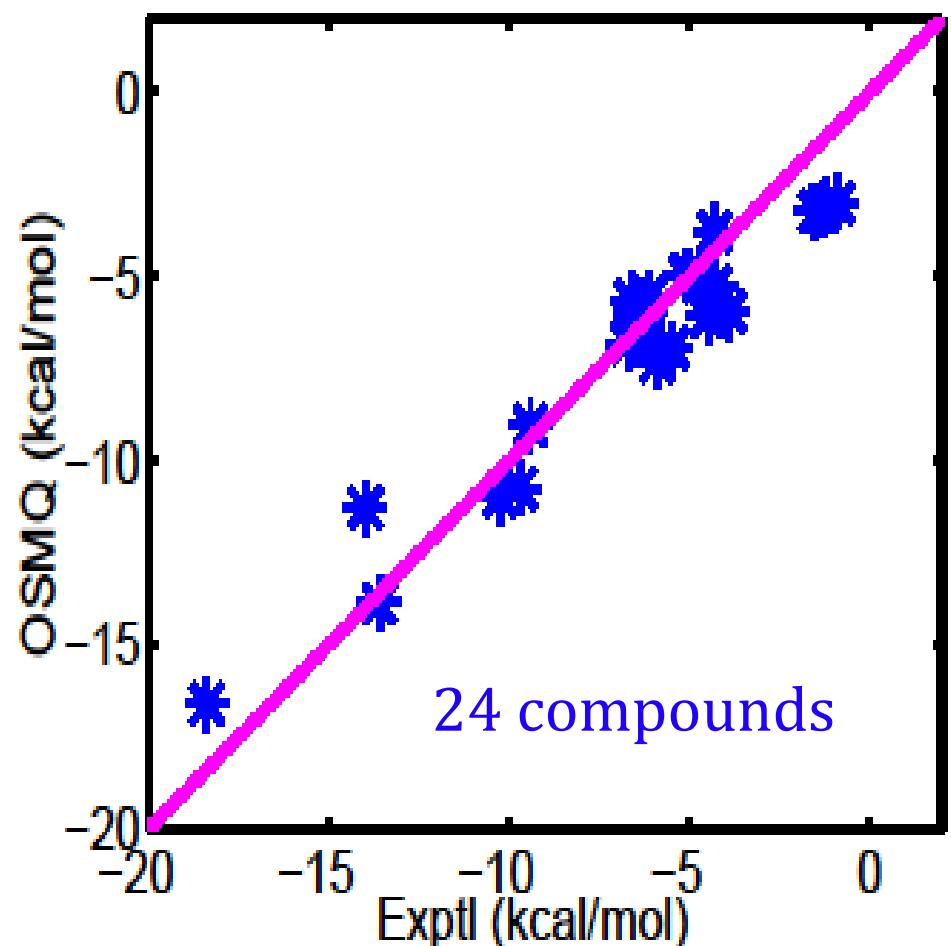
# Validation of the multiscale solvation model



RMSD: OSMQ = 1.50

OSM = 1.76

Nicholls = 1.71 (MD), 1.87(PB)



RMS: OSMQ=1.31

(Chen & Wei, JCP, 2011)

# Implicit Solvent Models— Atomic surface tension

(Wang, Wang, Huo, Les and Kollman, JPCB, 2001;  
Wang, Zhao, Wei, JCP, 2016)

Solvation free energy:

$$\Delta G = \Delta G^p + \Delta G^{np}$$

Nonpolar=area, volume and solvent-solute interaction:

$$\Delta G - \Delta G^p = \Delta G^{np} = \sum_{\alpha} \gamma_{\alpha} \text{Area}_{\alpha} + pV$$

where  $\gamma_{\alpha}$  and  $\text{Area}_{\alpha}$  are the surface tension and surface area of  $\alpha$ th – type of atoms.

$$\Delta G^{\text{Exp}} - \Delta G^p = \Delta G^{np}(\theta)$$

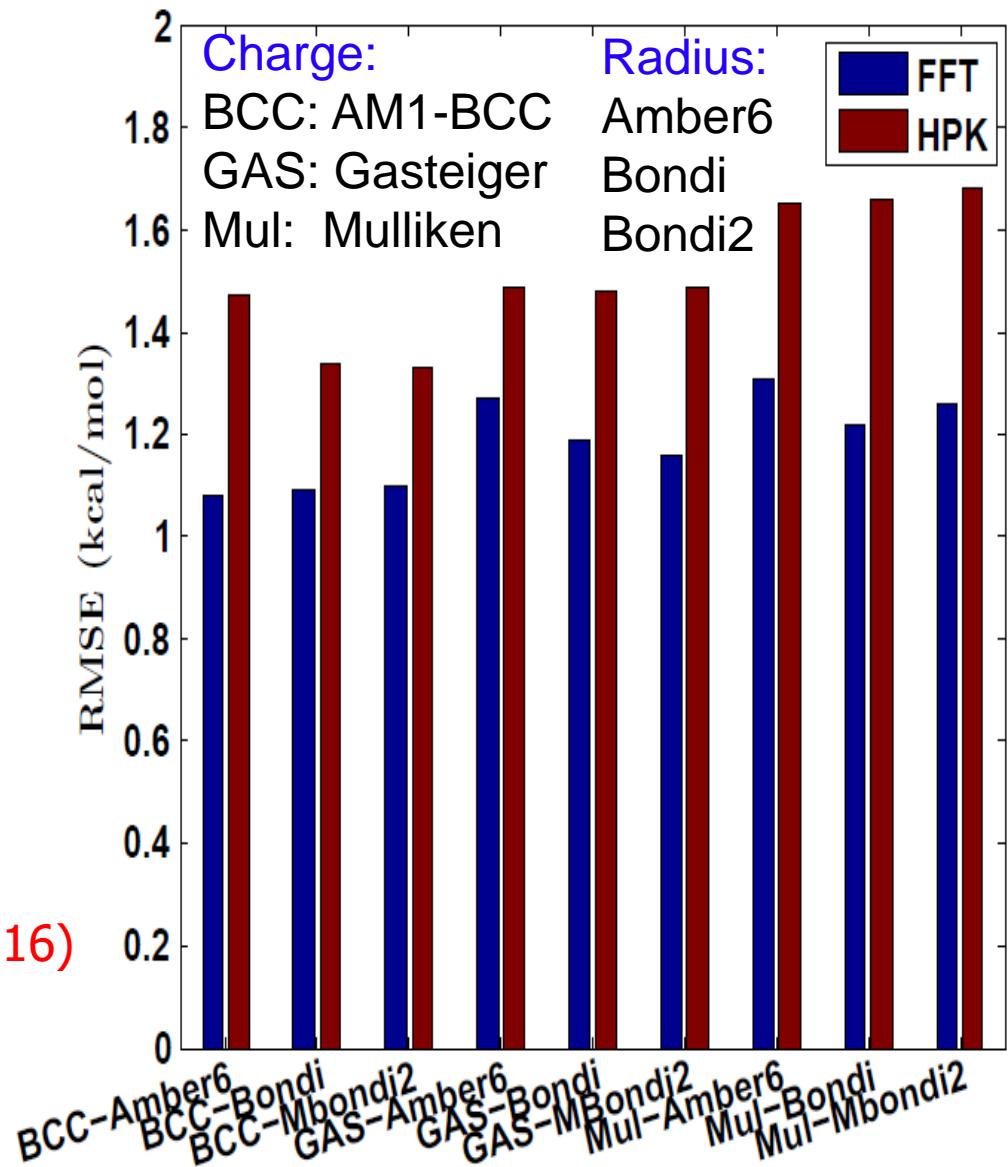
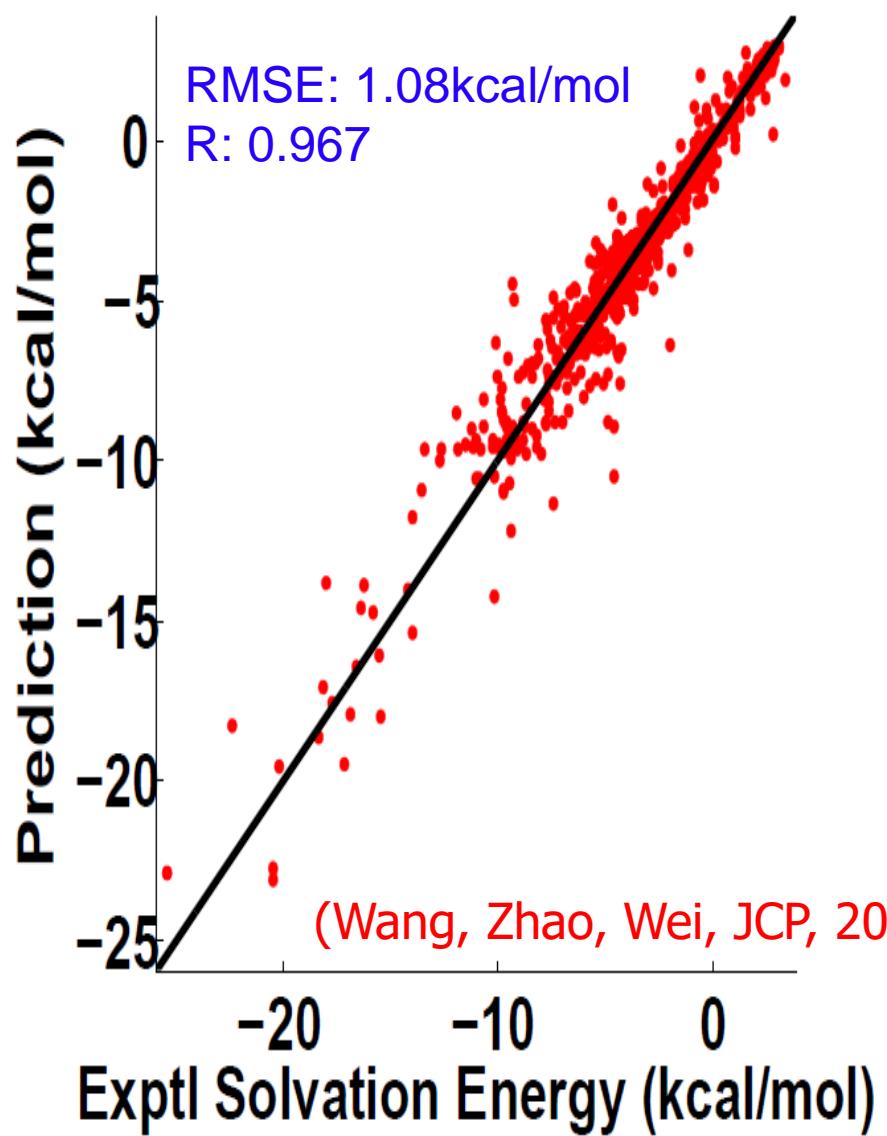
$\theta$ — hyperparameters, i.e.,  $\{\gamma_1, \gamma_2, \dots, p\}$  to be determined by the Tikhonov optimization over  $N$  samples:

$$\operatorname{argmin}_{\theta} \sum_j^N \left( \Delta G_j^{\text{Exp}} - \Delta G_j^p \right)^2 + \lambda \|\theta\|_2$$



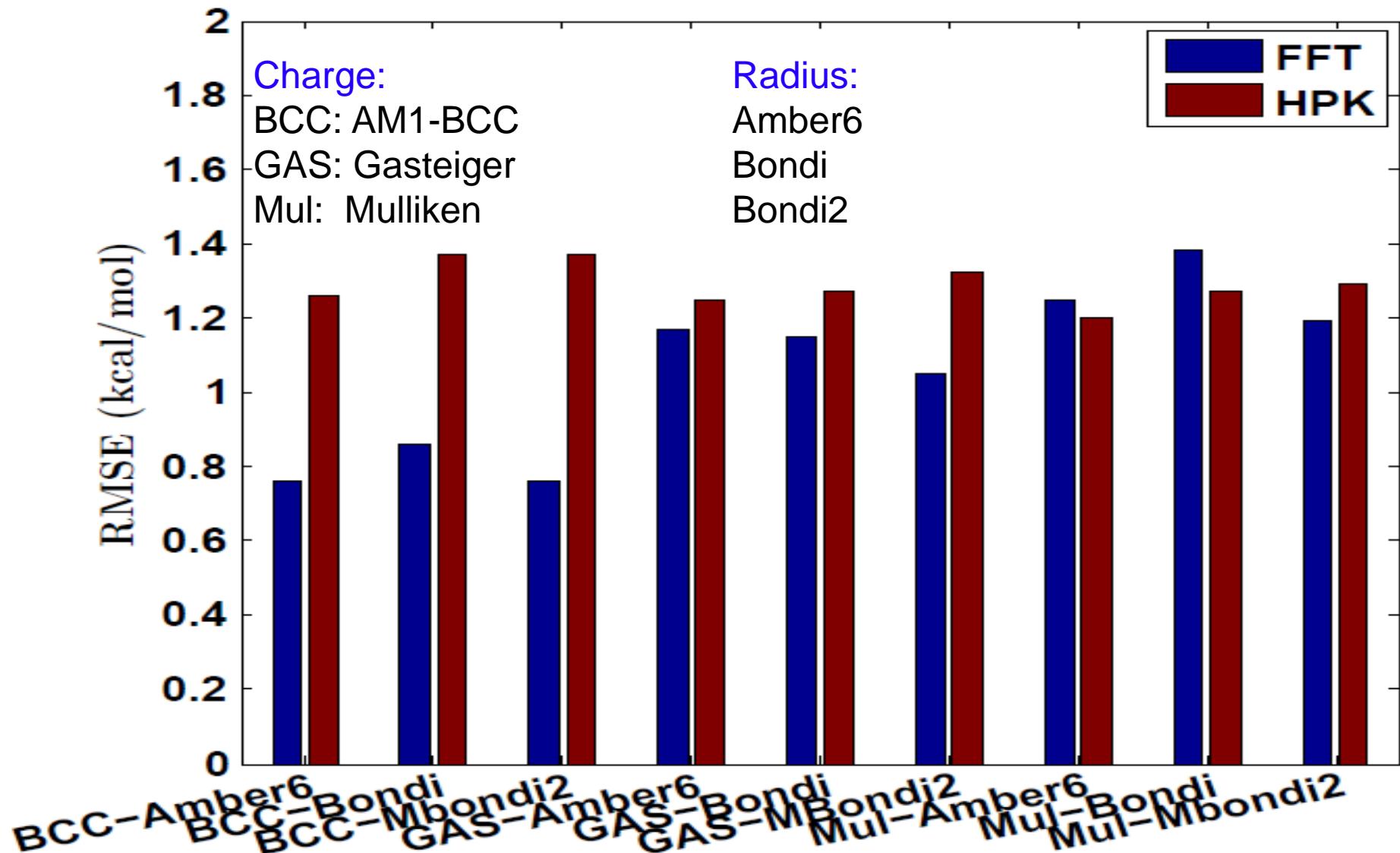
B Wang      ZX Zhao

# Leave-one-out prediction for solvation free energies of 668 molecules

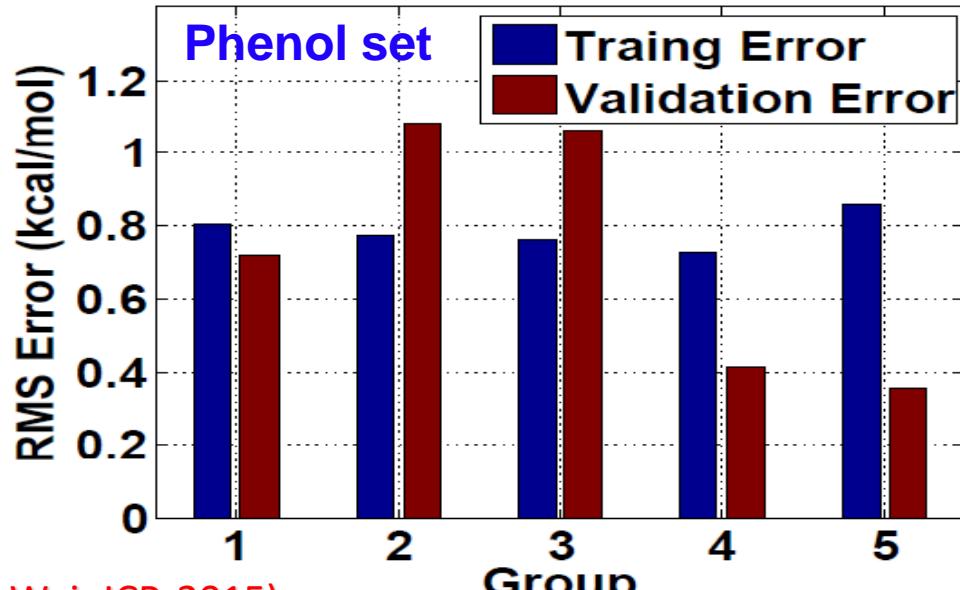
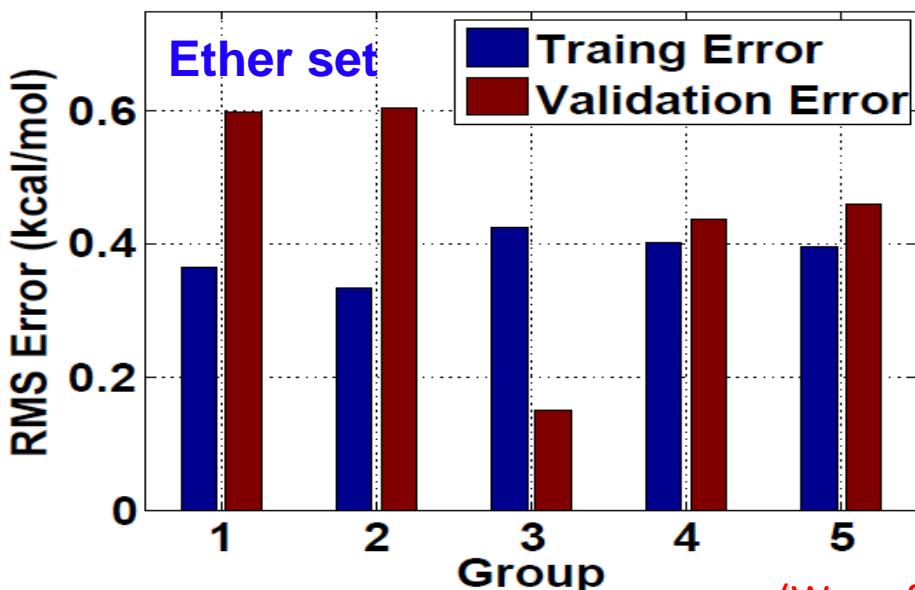
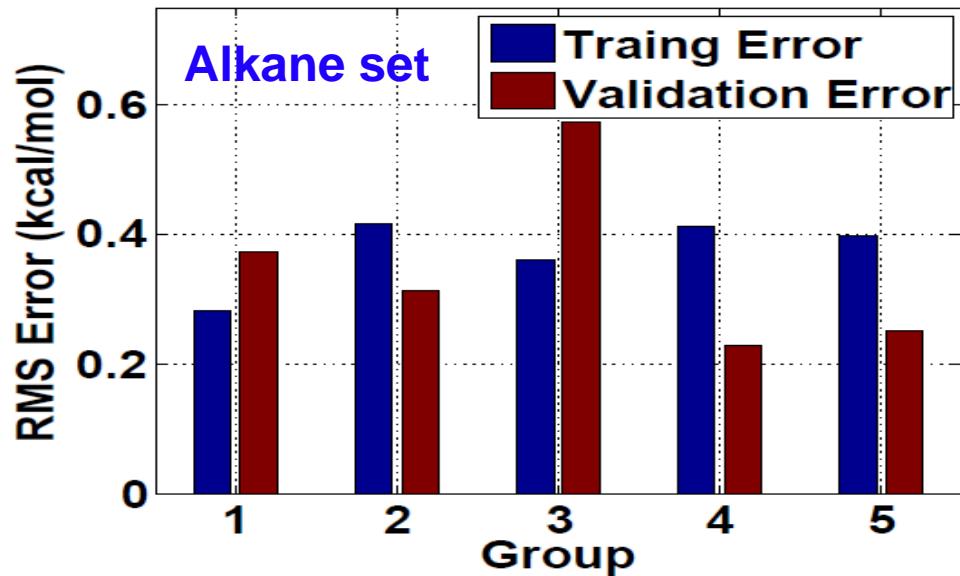
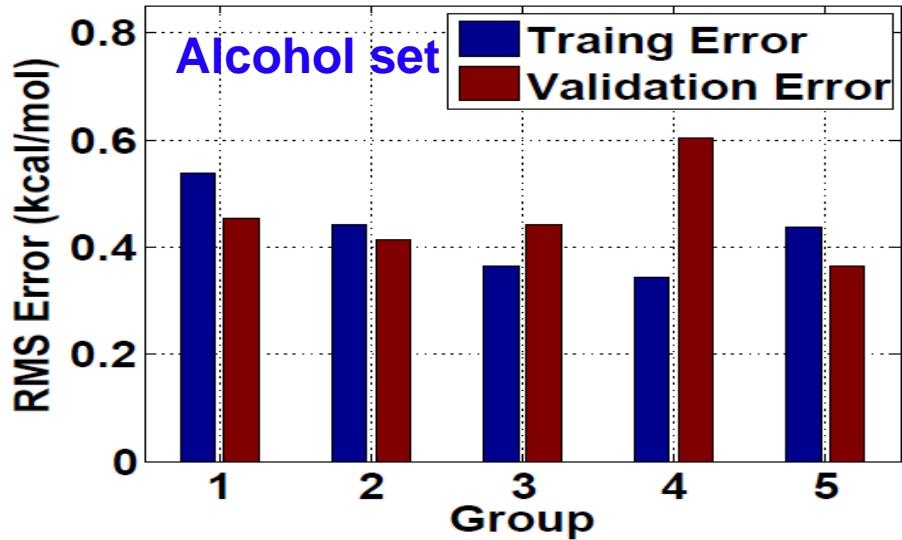


# Blind predictions of SAMPL0 challenge set

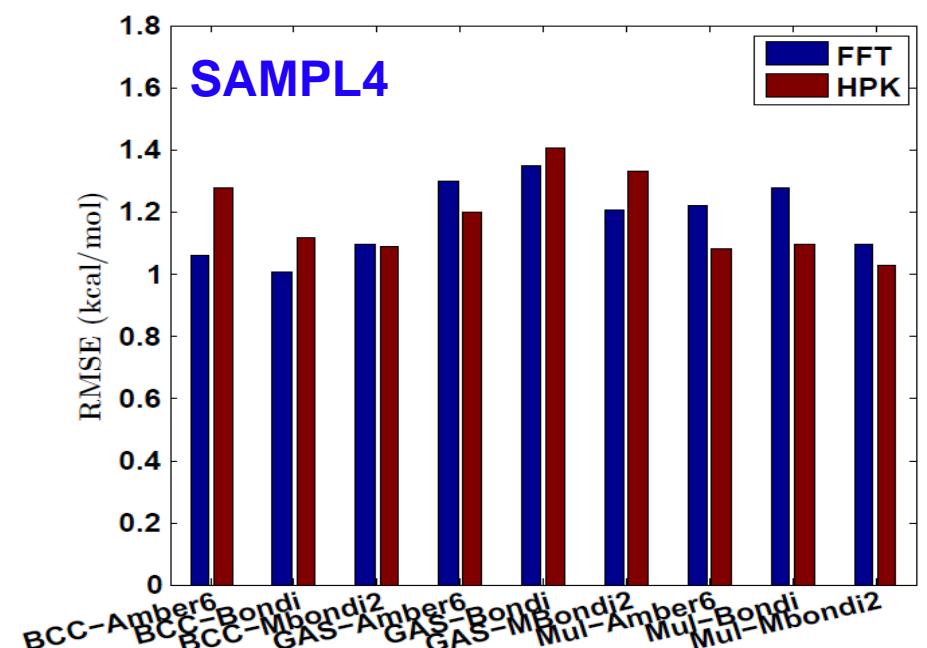
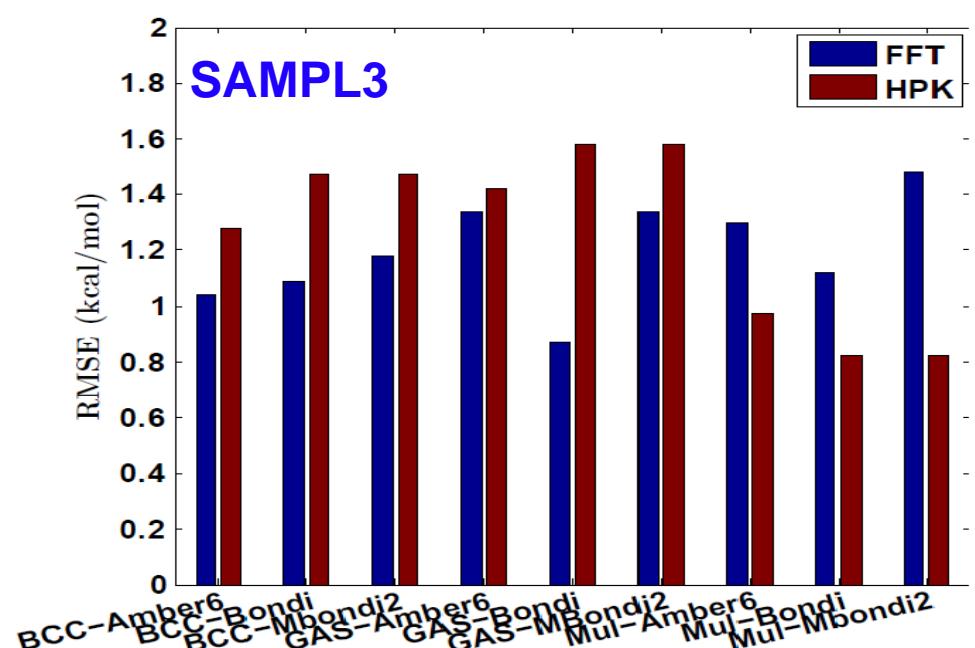
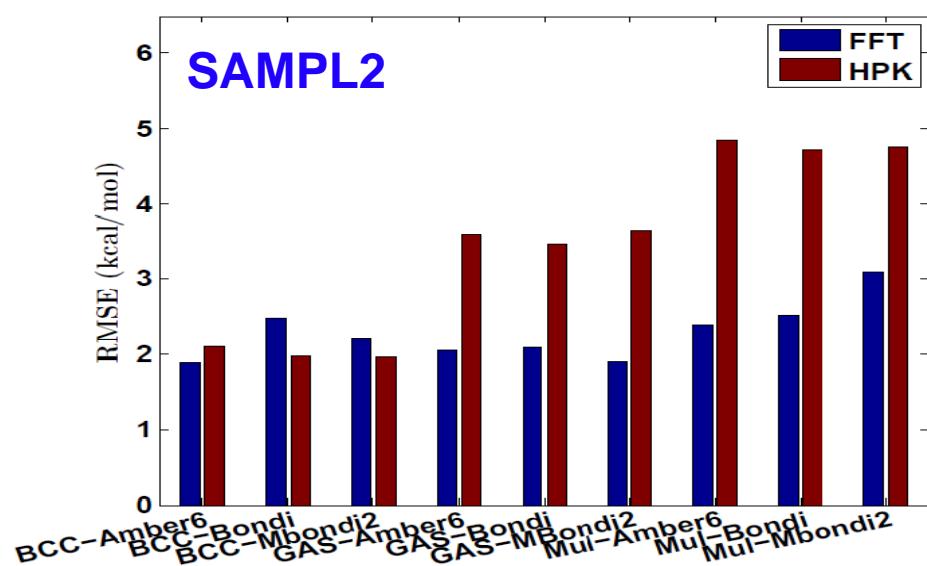
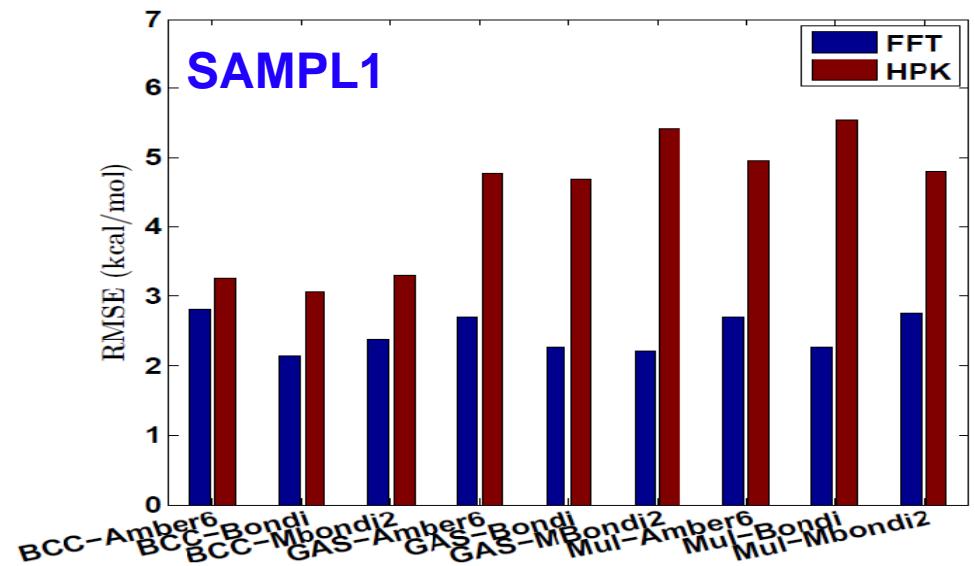
{Wang, Zhao, Wei, JCP, 2016}



# Five-fold validation of solvation free energy prediction

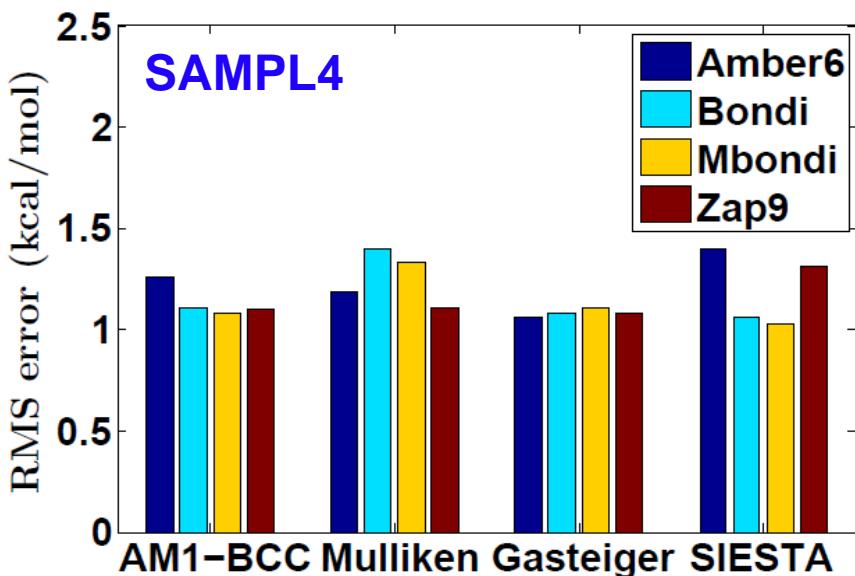
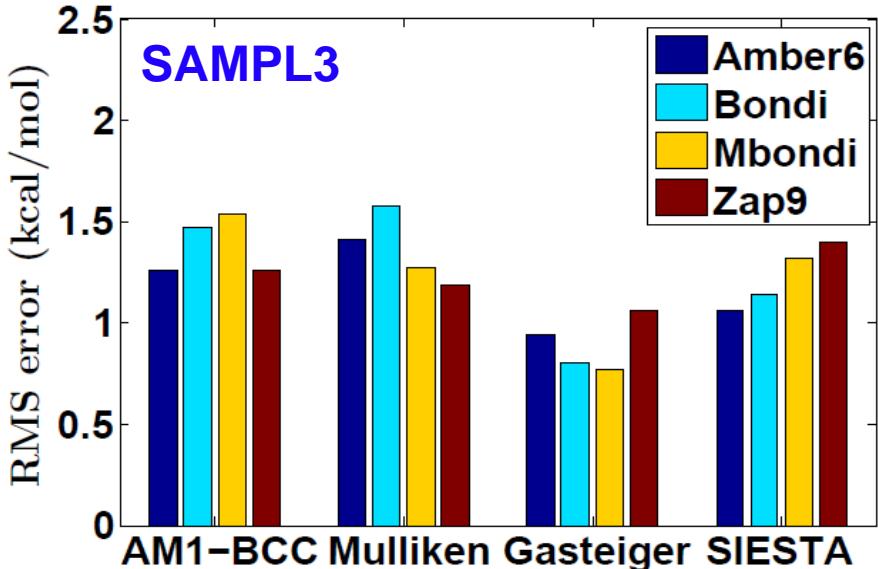
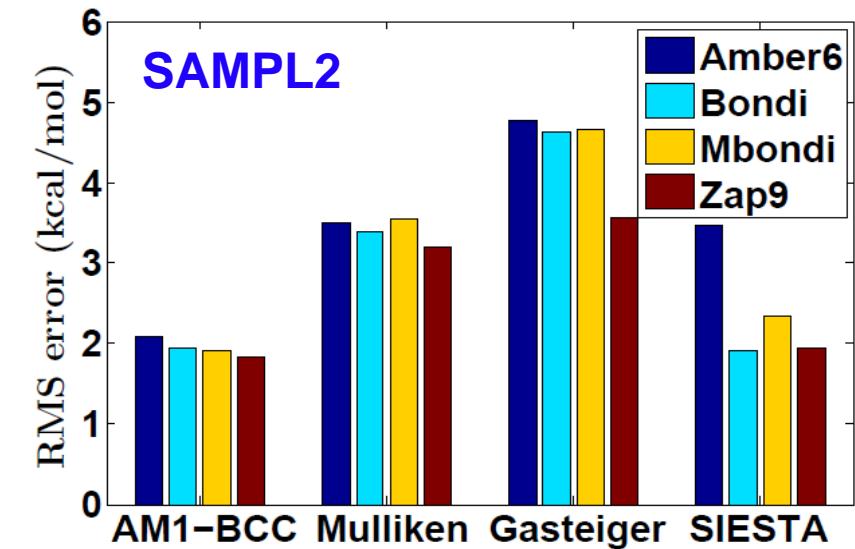
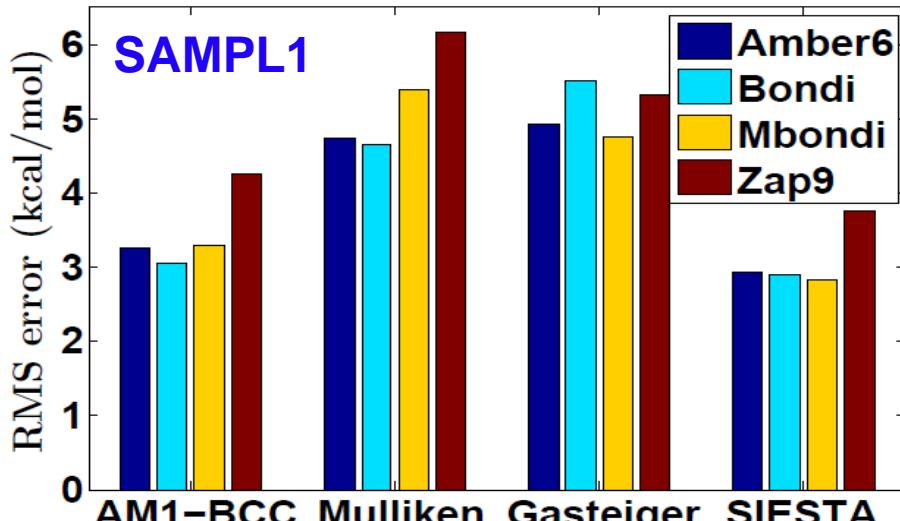


# Blind predictions of SAMPLx challenge sets



# Blind solvation free energy prediction using HPK model

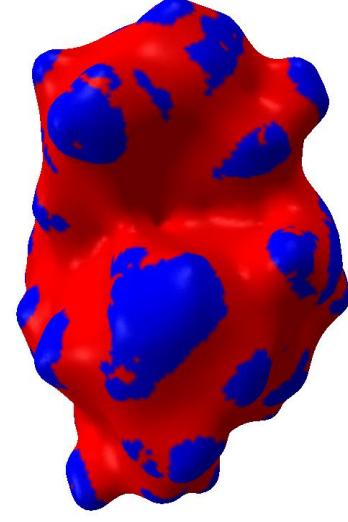
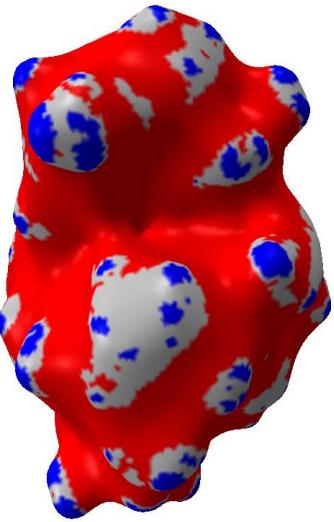
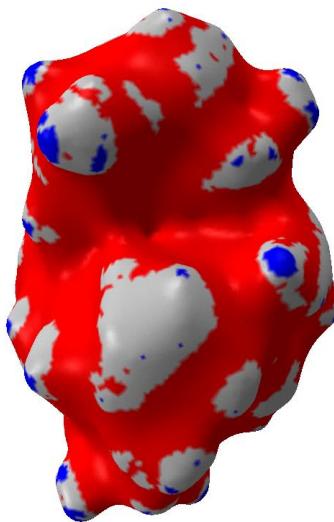
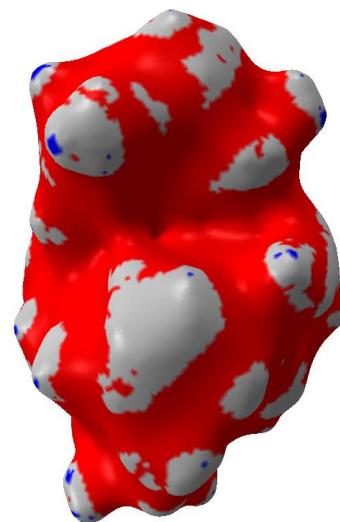
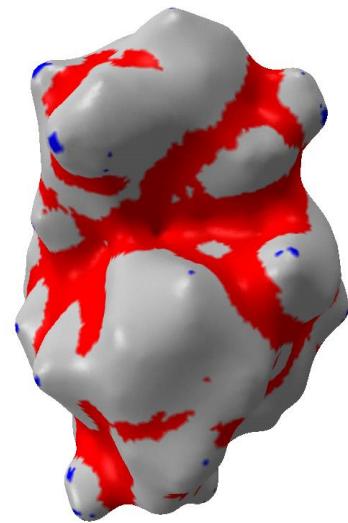
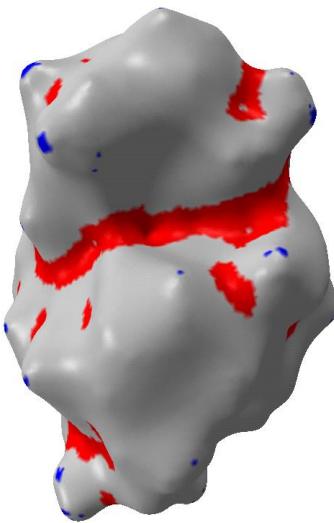
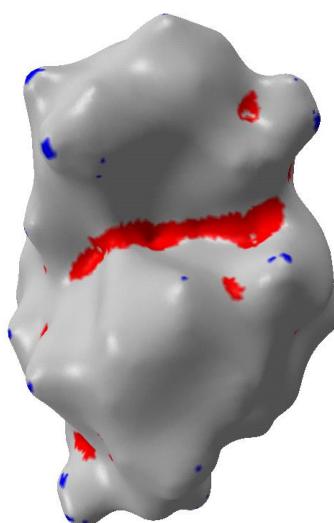
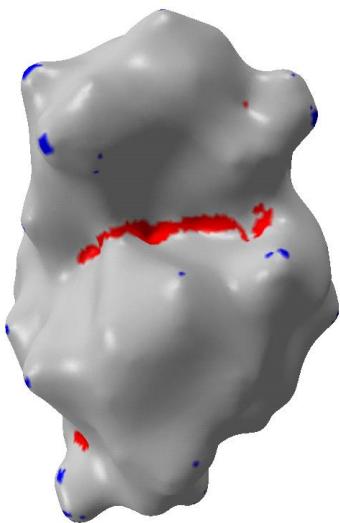
Good news: best results; Bad news: parameterization sensitive.



# Coupled surface and electrostatic modeling

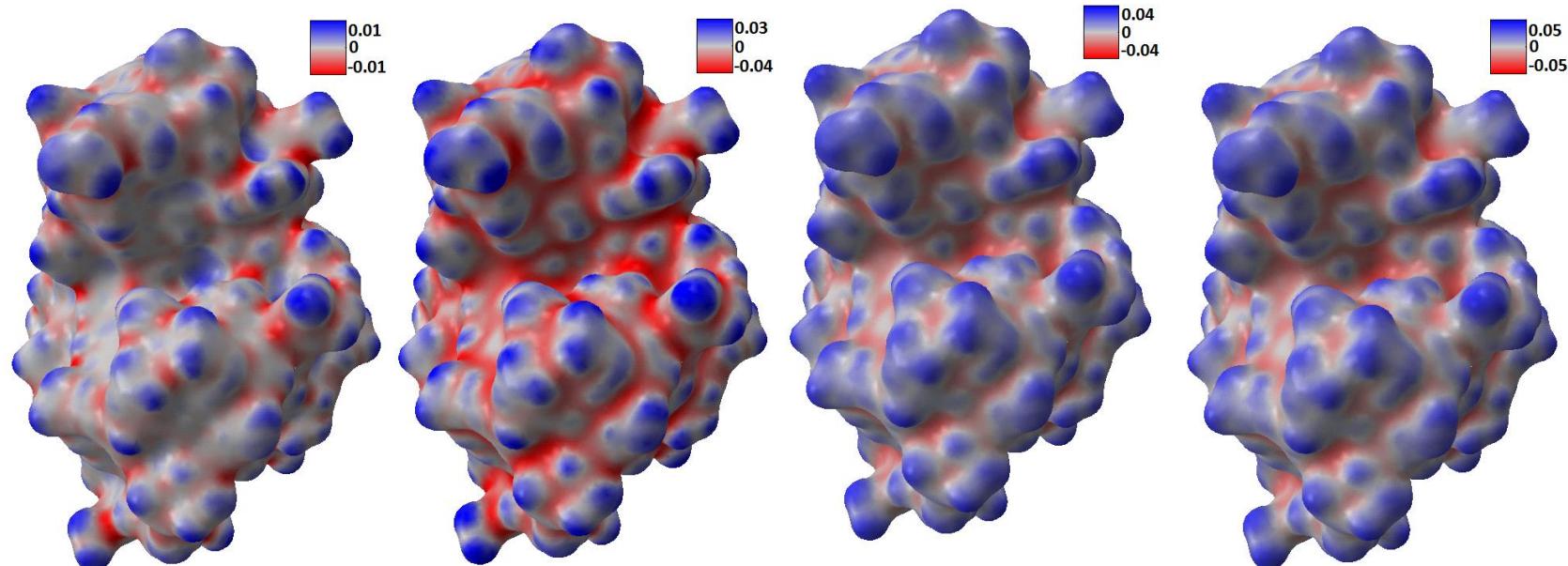
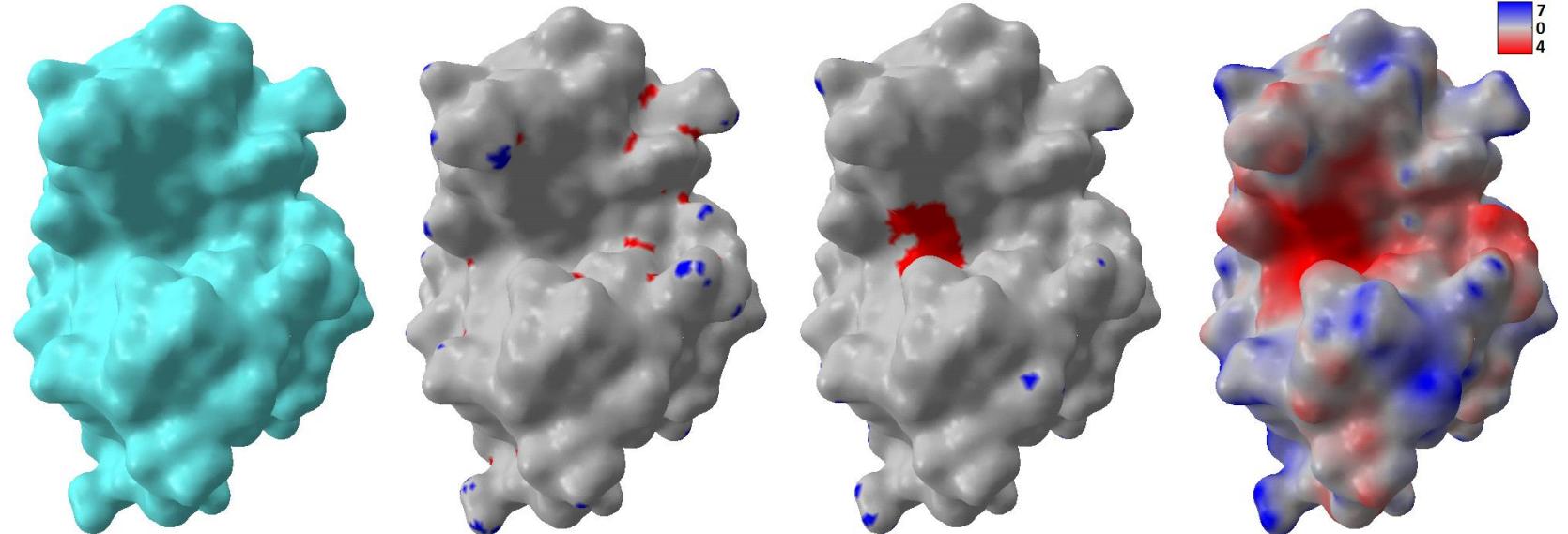
Curvature maps of a protein:

(Xia, Feng, Tong & Wei, JCP 2013)



# Coupled surface and electrostatic modeling

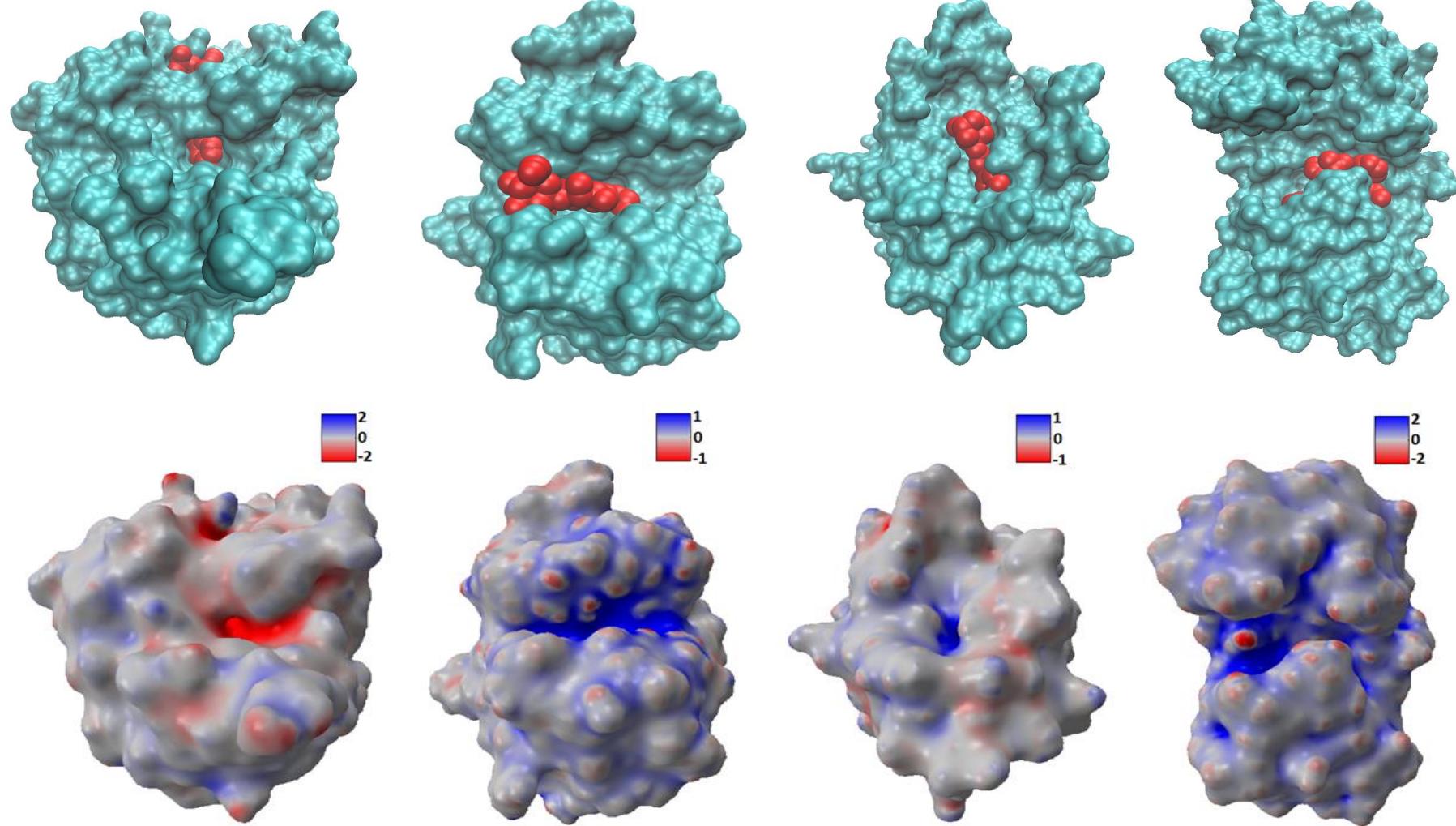
Electrostatic maps of a protein: (Xia, Feng, Tong & Wei, JCP 2013)



# Protein-ligand binding site prediction by the product of curvature and electrostatics



Lin Mu



(Xia, Feng, Tong & Wei, JCP 2013; Mu, Xia & Wei, JCAM, 2017)

## **Further topics and future directions**

- Electrostatic analysis of chromosomes and DNA packaging (DNA wrapped histone, nucleosomes and chromatins).
- Nonlocal Poisson-Boltzmann model.
- Image charge method.
- Dynamics coupled pKa.
- Element specific electrostatic analysis.
- Helmholtz-Hodge decomposition of molecular electric fields.
- Differential geometry based analysis of biomolecular polarizations and interactions.
- Differential geometry based high-order force fields.
- Molecular shape adaption to polarization and interaction.
- Coupling of solvation and ion transport.
- Coupling of solvation and electron transport.
- The interconnections between solvation, solubility, permeability, and partition coefficient.
- Proton-coupled electron translocation in biomolecular enzymes.
- Electrostatic steering effects in phosphorylation and signal transduction pathways.



thank you