Binding free energy theory and MM/PBSA method

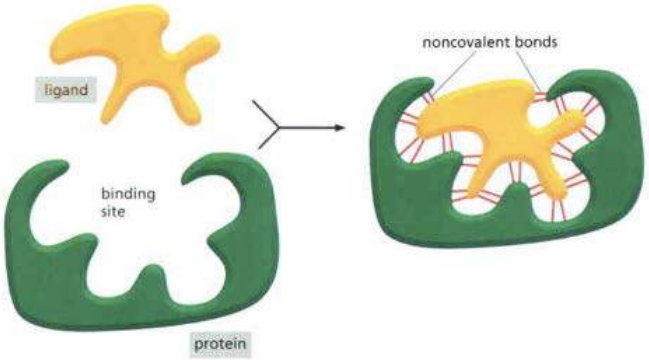
Speaker: Xiaoxiao Zhang

2014.9.24

Overview

Quasi-Chemical Description

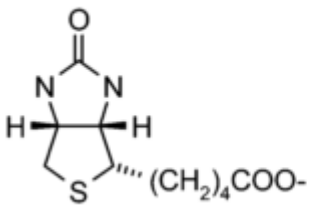
$$A_{(sol)} + B_{(sol)} \rightleftarrows AB_{(sol)}$$



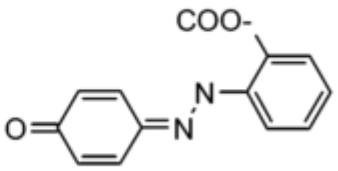
$$\Delta G^{o} = \Delta G^{o}_{tr} + \Delta G^{o}_{rot} + \Delta G^{o}_{int} + \Delta G^{o}_{solvn.}$$

Molecular Mechanic/ Poisson-Boltzmann Surface Area (MM/PBSA)

a)



b)



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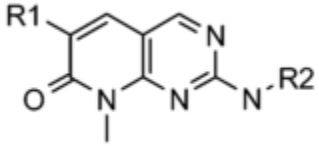

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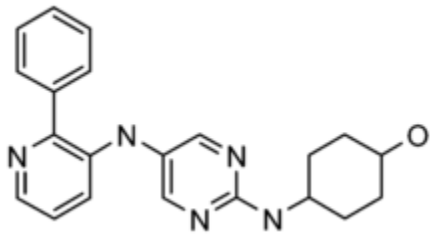
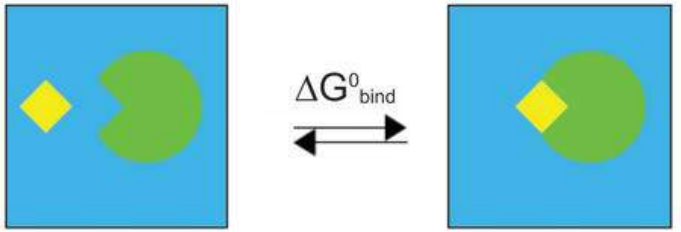


Protein-ligand binding

Quasi-Chemical Description

$$A_{(sol)} + B_{(sol)} \rightleftarrows AB_{(sol)}$$



$$\mu_{sol,i} = \mu^{\circ}_{sol,i} + kT \ln \frac{C_i}{C^{\circ}}$$

$$\Delta G^{\circ}_{AB} = \mu^{\circ}_{AB} - \mu^{\circ}_{A} - \mu^{\circ}_{B} = -kT \ln \frac{C_{AB}/C^{\circ}}{(C_A/C^{\circ})(C_B/C^{\circ})} = -kT \ln K_{AB}$$

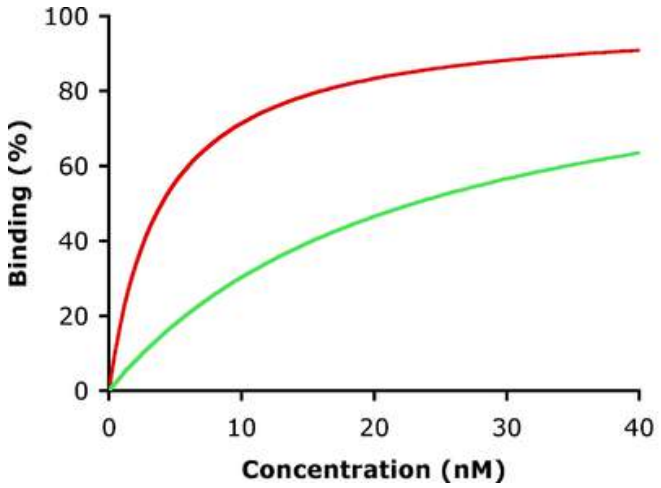
$$K_{AB} = e^{-\beta \Delta G^{\circ}_{AB}} = \frac{e^{-\beta \mu^{\circ}_{AB}}}{e^{-\beta(\mu^{\circ}_{A} + \mu^{\circ}_{B})}} = \frac{C^{\circ}}{8\pi^2} \frac{Z_{AB}}{Z_A Z_B};$$

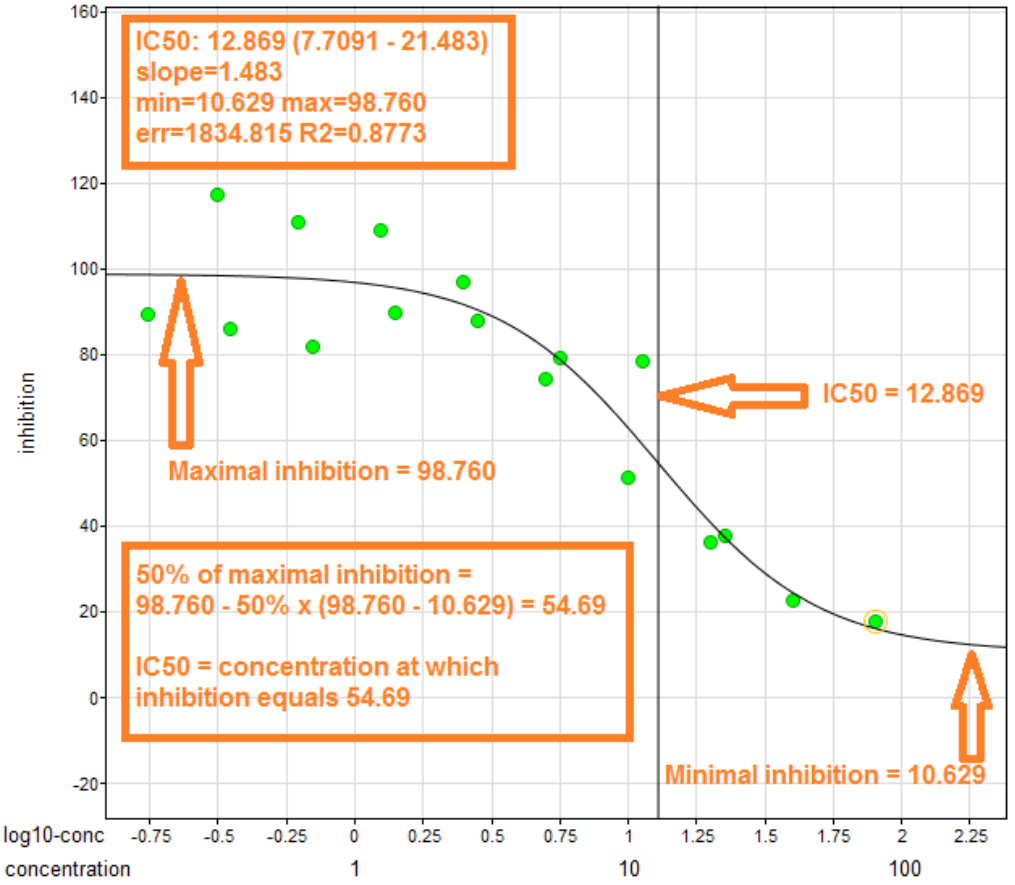
The standart binding free energy:

- Include a definition of the species “AB”.
- Depend on the standard state concentration.

Gilson et al., Biophys. J.(1997)

Binding affinity measurements



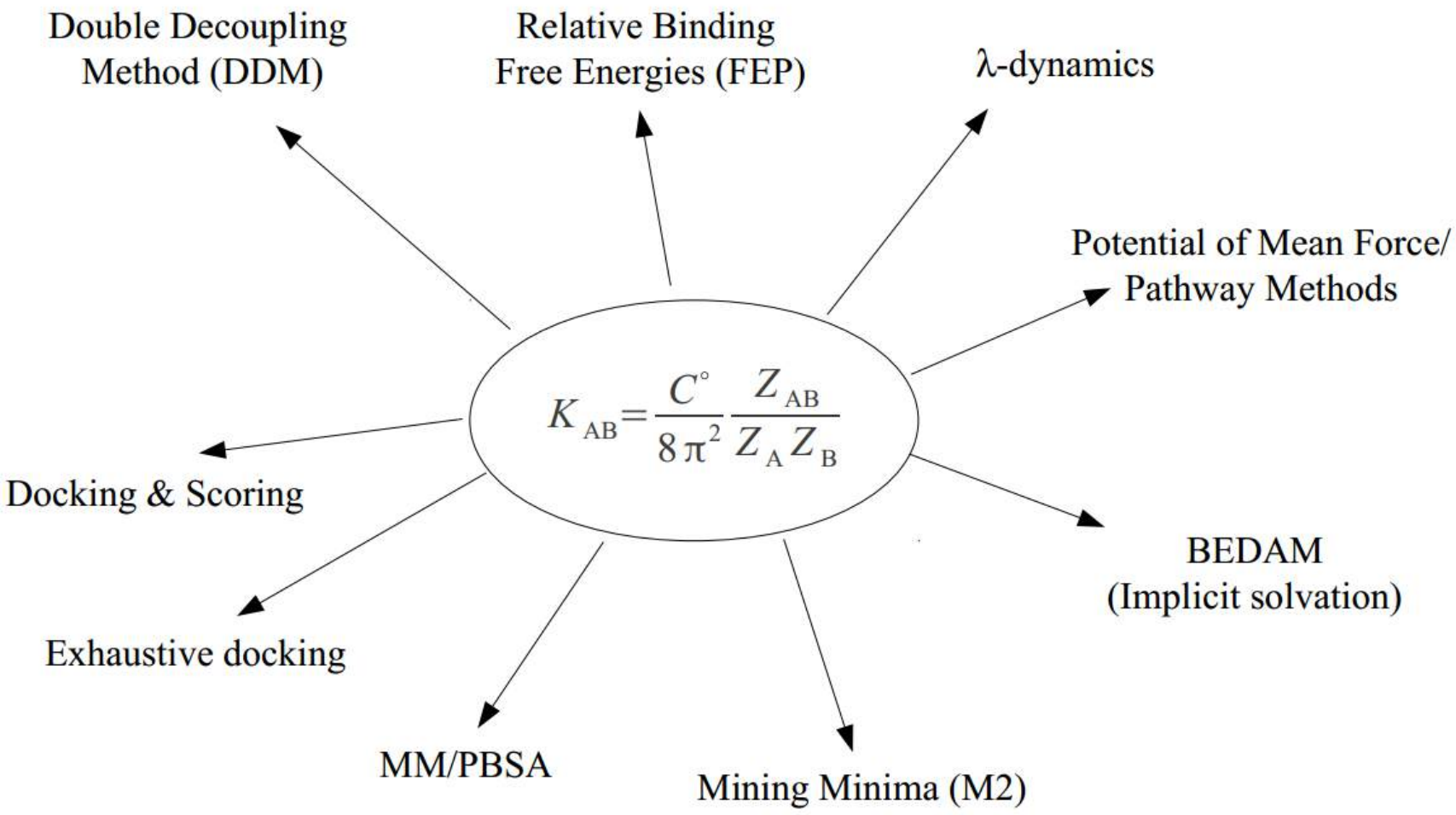


Cheng-Prusoff Equation:

$$K_i = IC_{50}/(1 + [L]/K_d)$$

- The affinity (equilibrium inhibition constant K_i) of a drug for a receptor is a measure of how strongly that drug binds to the receptor.
- The **IC_{50}** stands for the half maximal inhibitory concentration.
- The lower K_i, the higher binding affinity.

Free Energy Computational Methods

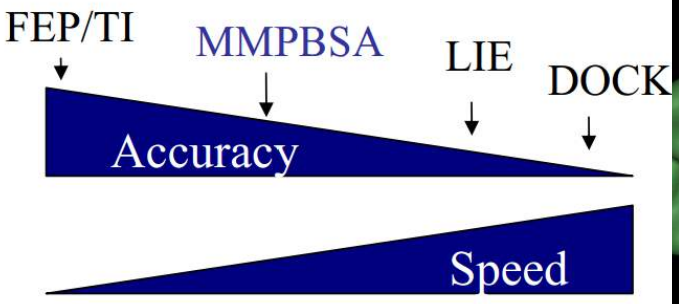


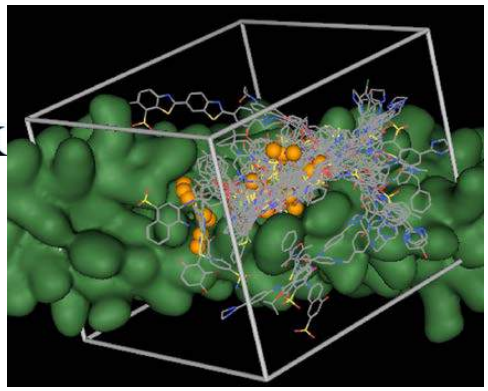
Free Energy Computational Methods

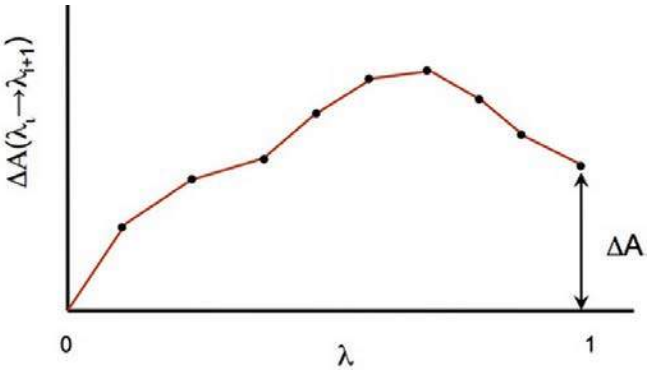
The theoretical basis for the additivity assumed in free energy computation:

$$\Delta G^{o} = \Delta G^{o}_{tr} + \Delta G^{o}_{rot} + \Delta G^{o}_{int} + \Delta G^{o}_{solvn.}$$

Docking & Scoring	Screening & Enrichment	1000's of compounds
MM-PB/SA Linear Interaction Energy	Ranking	100's of compounds
Absolute/Relative Binding Free Energy Methods	Ranking, Optimization, Specificity, Resistance	10's of compounds

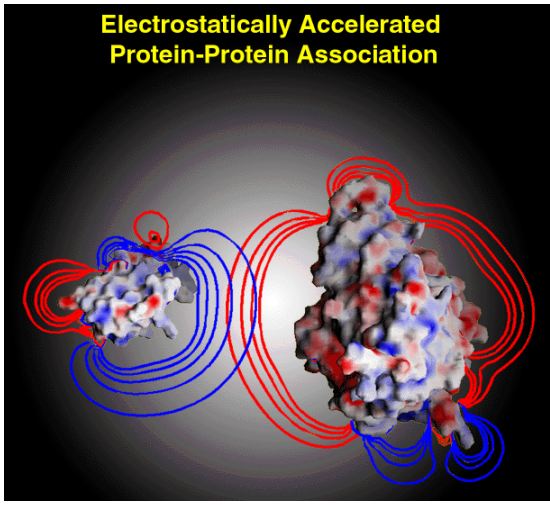






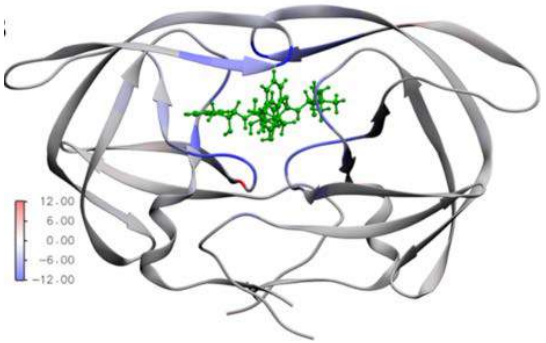
MM/PBSA & MM/GBSA

- Molecular Mechanic/ Poisson-Boltzmann Surface Area (MM/PBSA)
- MM = internal energy of the system (bonded & non-bonded)
- PB = electrostatic contribution to solvation
- SA = nonpolar contribution to solvation
- S = entropic contribution to binding

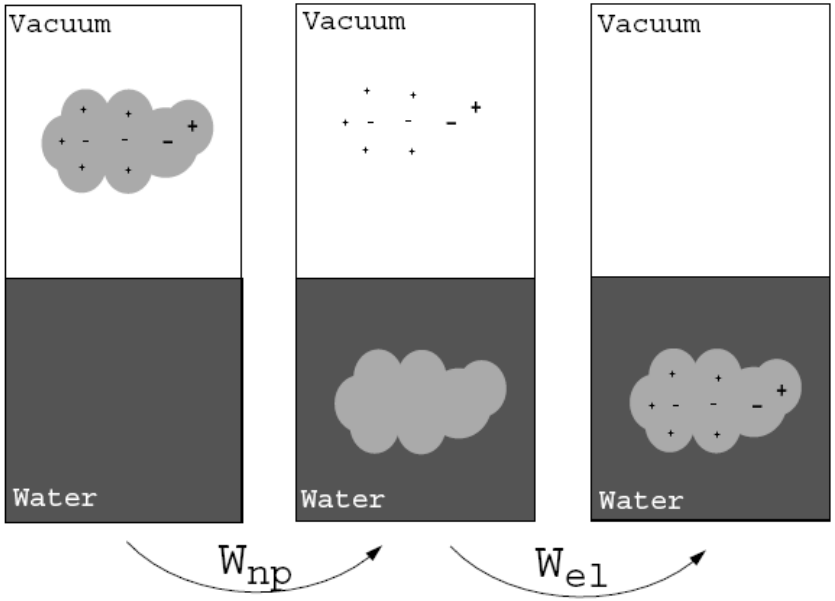


Advantage over FEP:

- Generalizable.
- Can take into account large structure changes.
- Calculates G at endpoints, don't sample intermediates.
- With errors larger, still get good agreement with experiment.
- Continuum solvent has integrated out solvent coordinates.



Solvation Model



$$\Delta G_{sol} = \Delta G_{np} + \Delta G_{el}$$

$$\Delta G_{np} = \Delta G_{vdW} + \Delta G_{cav}$$

- Net electrostatics.
- Van der Waals interactions.
- Cavitation effects.

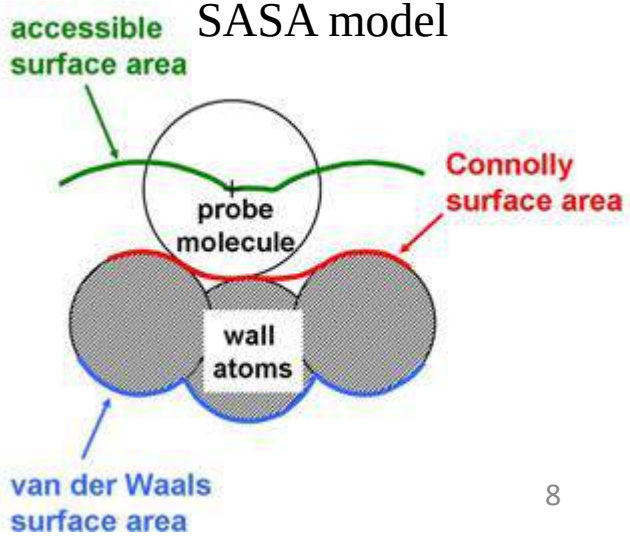
Generalized Born Equation

$$G_{pol} = -166\left(1-\frac{1}{\varepsilon}\right)\sum_{i=1}^{n}\sum_{\substack{j=1\\ j\neq i}}^{n}\frac{q_i q_j}{f_{GB}} - 166\left(1-\frac{1}{\varepsilon}\right)\sum_{i=1}^{n}\frac{q_i^2}{\alpha_i}$$

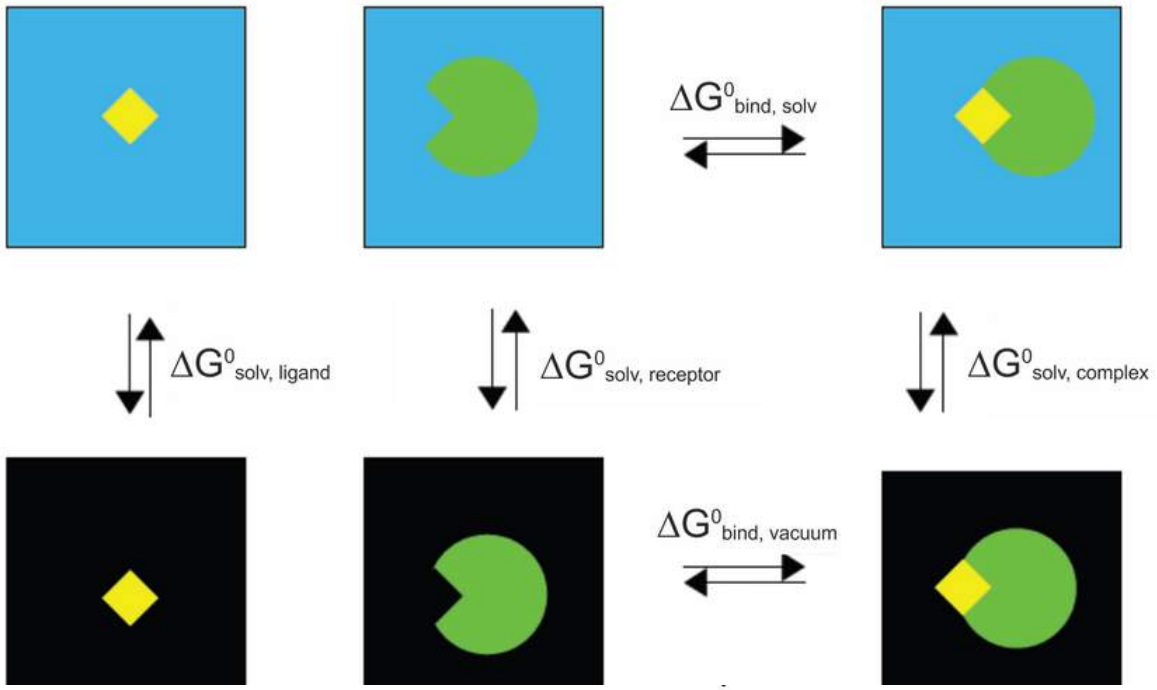
Poisson-Boltzmann Equation

$$\nabla\left[\varepsilon(r)\nabla\phi(r)\right] = -4\pi\left(\rho_{solute}(r) + \sum_{i=1}^{N} q_i c_i^{bulk}\exp\left(-q_i\phi(r)/RT\right)\right)$$

SASA model



Methodology



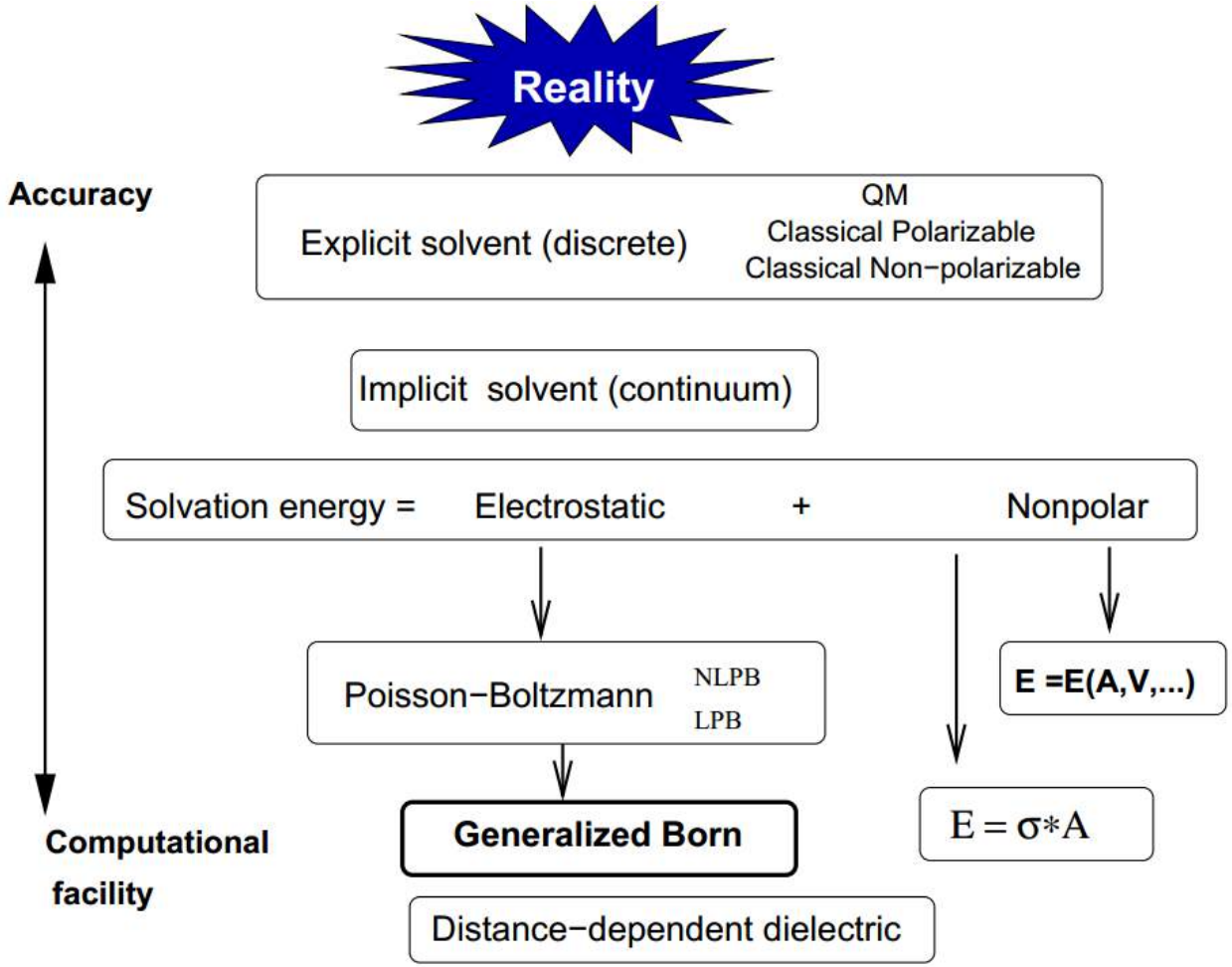
$$\Delta G^0_{bind,\,solv} = \Delta G^0_{bind,\,vacuum} + \Delta G^0_{solv,\,complex} - (\Delta G^0_{solv,\,ligand} + \Delta G^0_{solv,\,receptor})$$

$$\Delta G^0_{solv} = G^0_{electrostatic,\,\epsilon=80} - G^0_{electrostatic,\,\epsilon=1} + \Delta G^0_{hydrophobic}$$

$$\Delta G^0_{vacuum} = \Delta E^0_{molecular\ mechanics} - T \cdot \Delta S^0_{normal\ mode\ analysis}$$

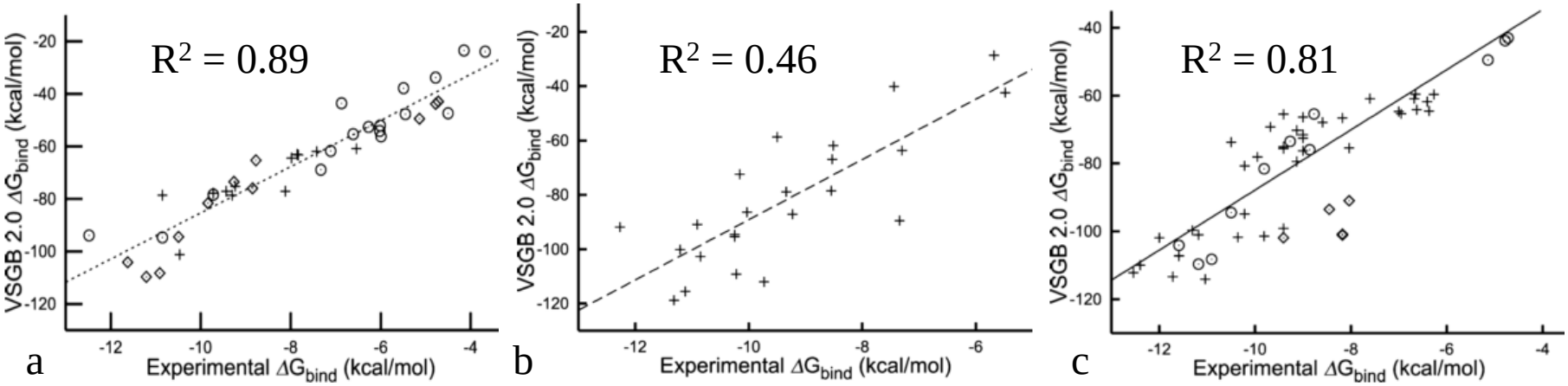
Takes advantage of multiple snapshots from a trajectory to get an average of energies.

Accuracy



The hierarchy of representations of solvent effects in molecular modeling. The GB model is separated from reality by several layers of approximation.

Accurate enough to correlate with binding affinity?



a. the most accurate data-set.
b. human aldose reductase with high variability in the affinity data.
c. PDPK1 family with affinity data but no crystal structures.

- Demonstrate the importance of affinity data variability and errors in the modeled complexes used for computing binding free energies.
- MM/PBSA could be approaching the accuracy required for evaluating relative binding free energies.

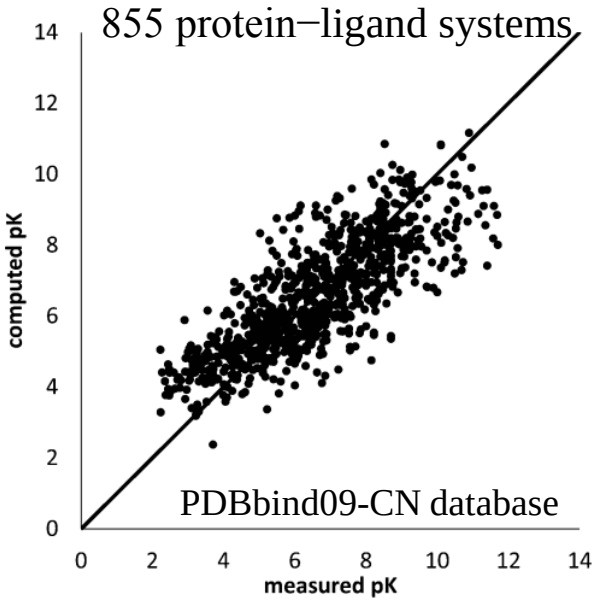
Mulakala, C., & Viswanadhan, V. N. (2013). *Journal of Molecular Graphics & Modelling*, *46*, 41–51.

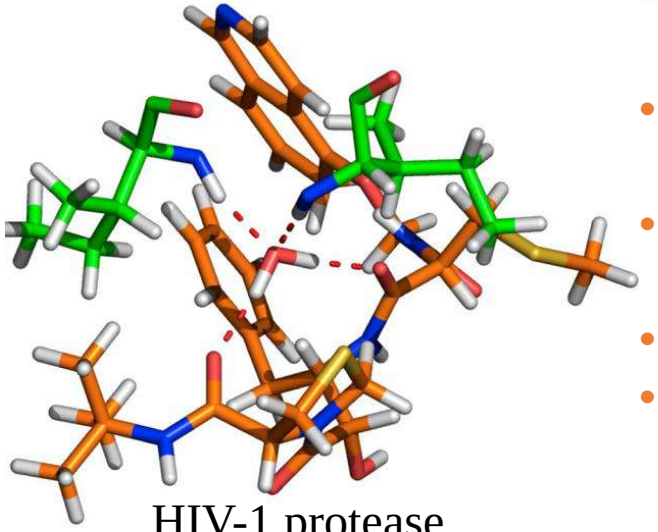
Accurate enough to correlate with binding affinity?

$$computed\ pK = -0.0456 * MM\text{-}GBSA\ Energy + 2.564$$

Table 1. Summary of R^2, RSE, and MUE Values for MM/GBSA Calculations with Different Conditions

conditions	R^2	RSE	MUE
ligand strain/water	0.58	1.29	1.03
ligand strain/no water	**0.63**	**1.20**	**0.96**
no ligand strain/no water	0.61	**1.20**	0.98
no ligand strain/water	0.56	1.32	1.06



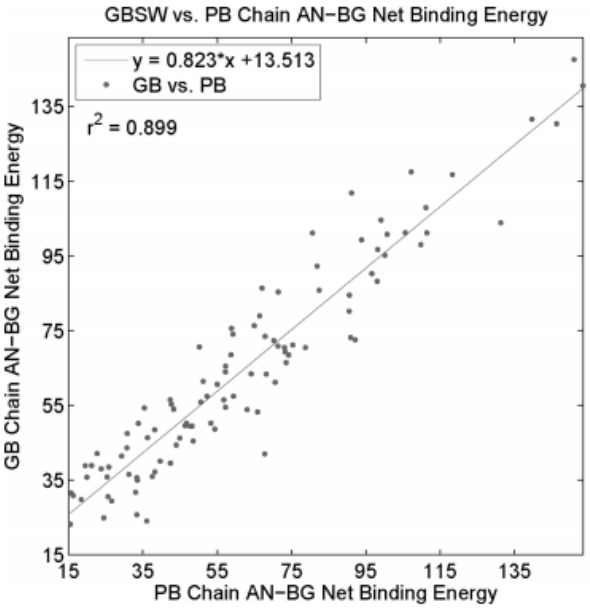


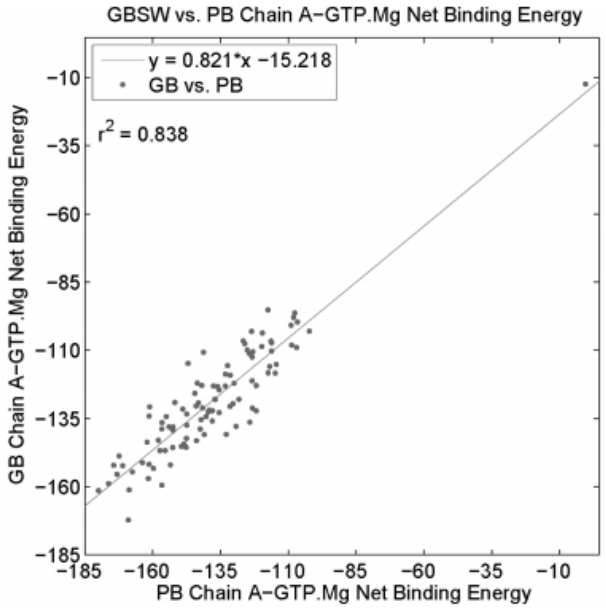
HIV-1 protease

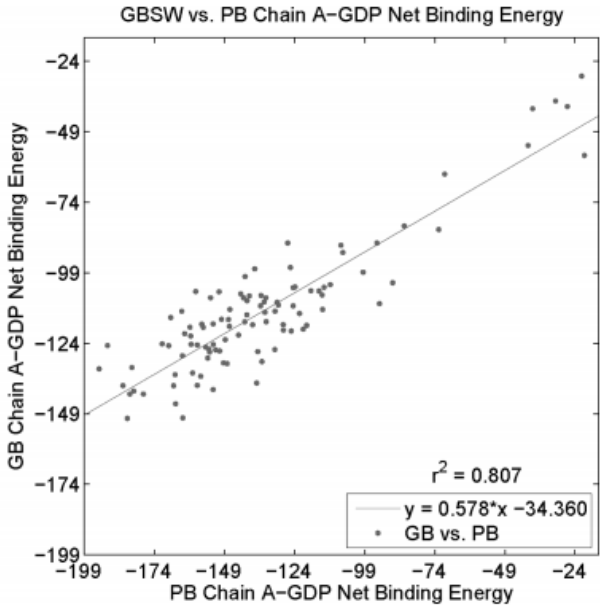
- A significant correlation between MM/GBSA energies and experimental Ki.
- MM/GBSA approach can yield values that are comparable even among different targets.
- The inclusion of water deteriorates the predictive quality.
- The inclusion of ligand strain slightly improves the overall accuracy.

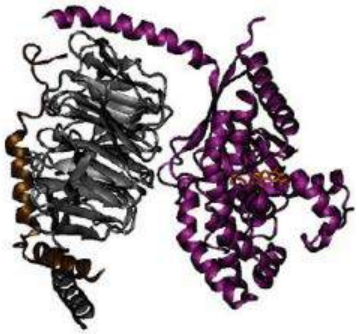
Greenidge, P. a, Wolf, R. M. (2013). *Journal of Chemical Information and Modeling*, *53*(1), 201–9.

Performance of MM/PBSA vs. MM/GBSA









$G_{\alpha}^{GDP}/G_{\beta\gamma}$

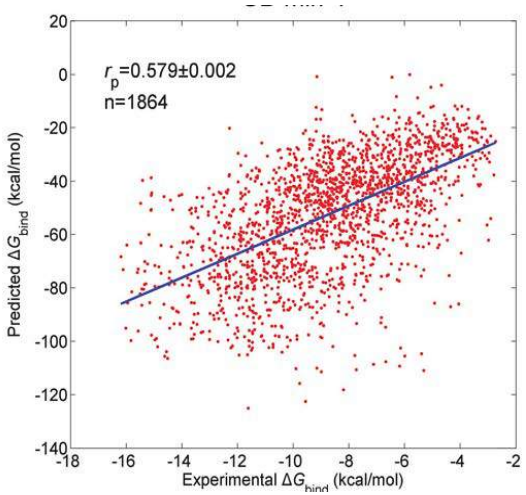
$G_{\alpha}/GTP{\cdot}Mg$

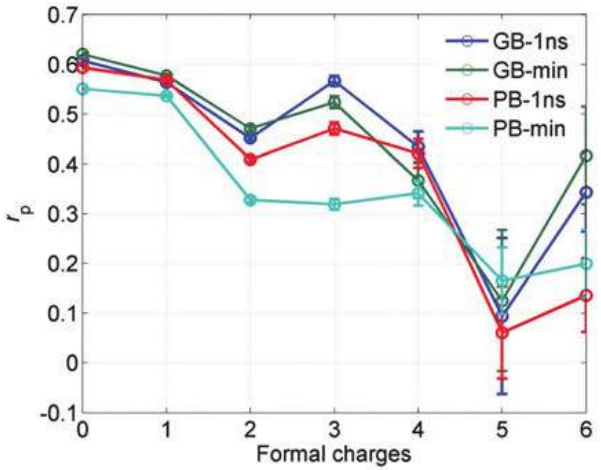
G_{α}/GDP

Performance of MM/PBSA vs. MM/GBSA

Dielectric constant: 4

MM/GBSA		MM/PBSA	
Classification[a]	r_p[b]	Classification	r_p[b]
GB-1ns-1	0.353 ± 0.002[d]	PB-1ns-1	0.071 ± 0.002
GB-1ns-2	0.521 ± 0.002	PB-1ns-2	0.306 ± 0.004
GB-1ns-4	0.564 ± 0.002	PB-1ns-4	0.491 ± 0.003
GB-min-1	0.352 ± 0.002	PB-min-1	−0.043 ± 0.002
GB-min-2	0.535 ± 0.002	PB-min-2	0.152 ± 0.002
GB-min-4	0.579 ± 0.002	PB-min-4	0.412 ± 0.003

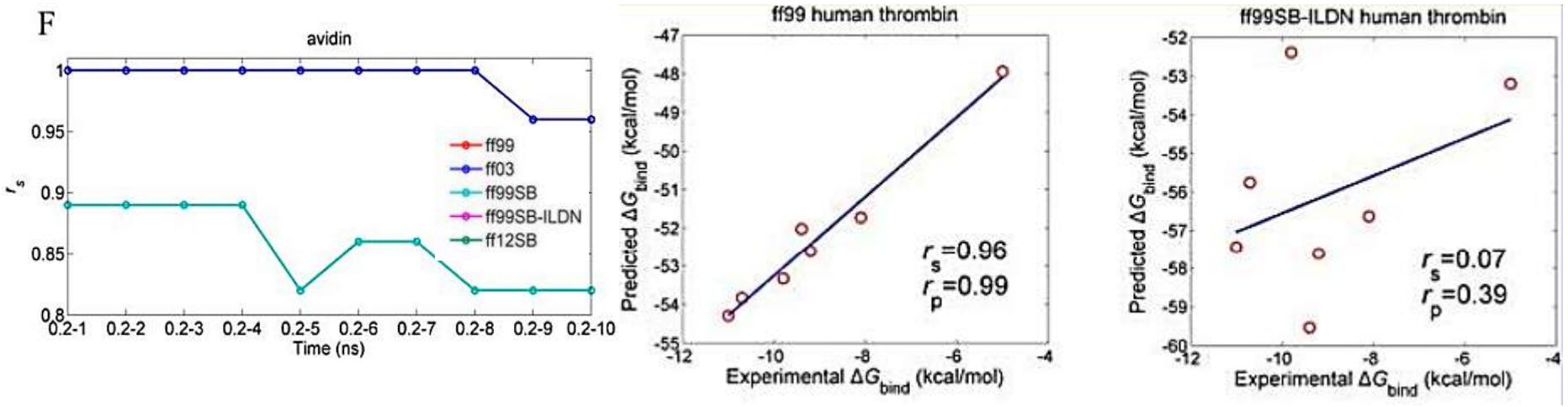




- The predicted binding affinities by MM/GB(PB)SA are unrealistically large.
- Accuracy decreases with the increase of the ligand formal charge.
- MM/PBSA is more sensitive to the investigated systems, more suitable for the individual target prediction.

Sun, H., Li, Y., & Hou, T. (2014). *Physical Chemistry Chemical Physics*, *16*(31), 16719–29.

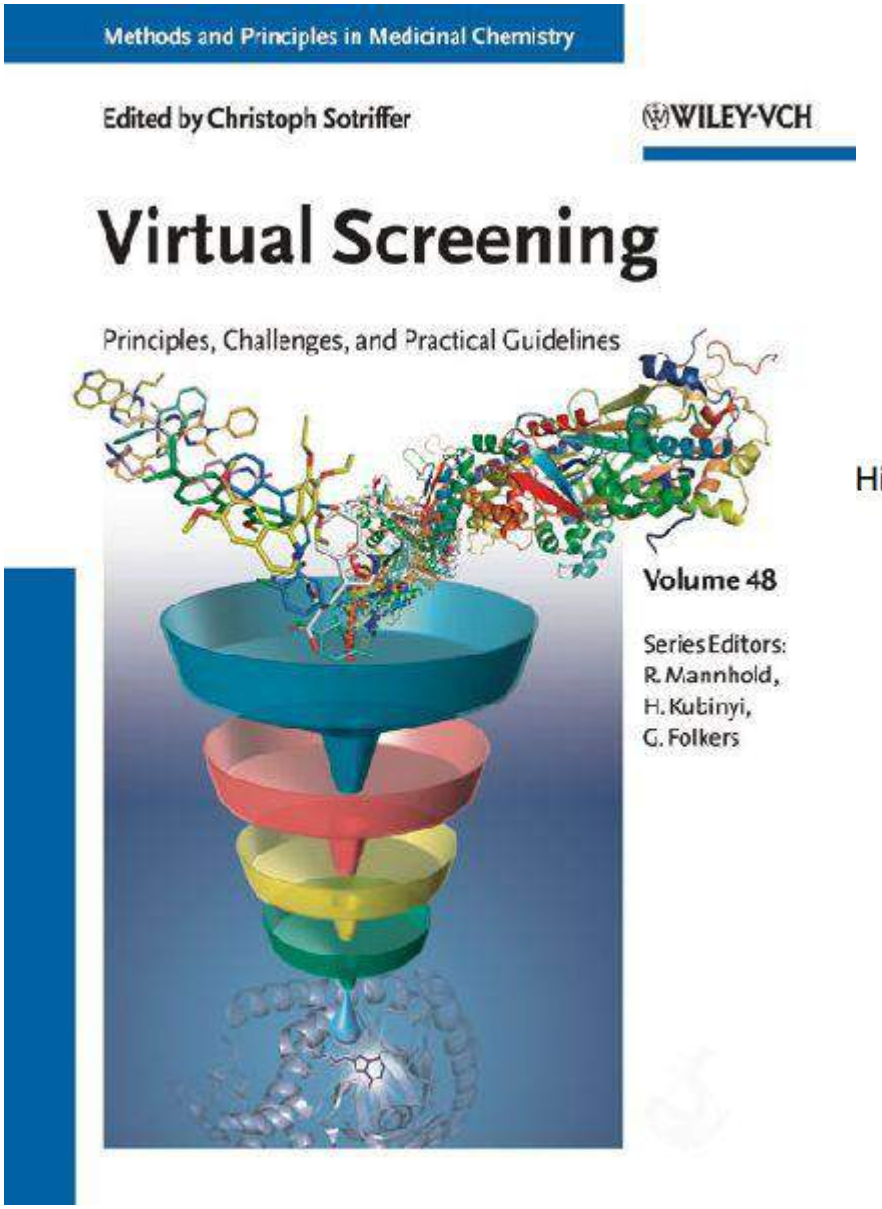
Influence of the MM methods



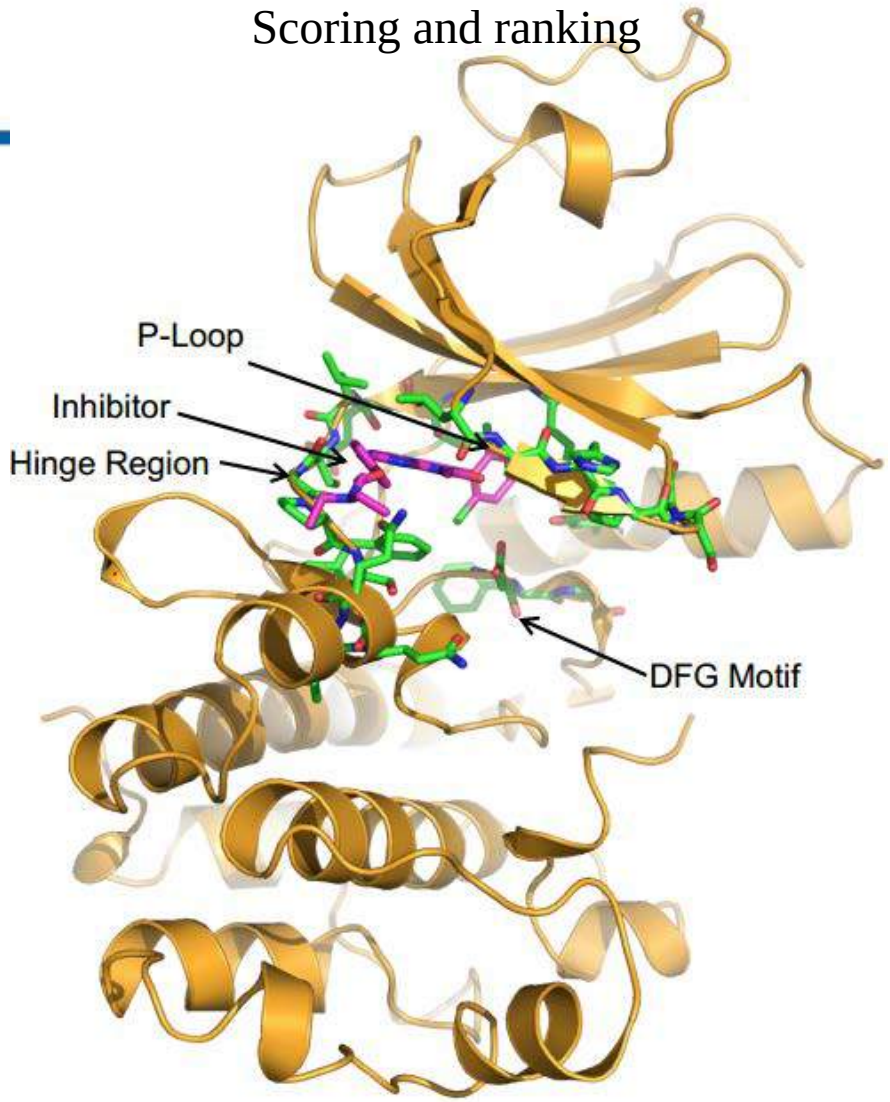
- The ff99 yields better correlation with experimental ΔG values than ff99SB-ILDN.
- For 2−4 ns MD simulations, MM/GBSA based on the ff99 force field yields the best predictions, while MM/PBSA based on the ff99SB force field does the best.
- 5 ns MD simulations may not be quite necessary.
- the RESP charges show the best performance for both MM/PBSA and MM/GBSA.

Sun, H., Li, Y., & Hou, T. (2013). *J. Phys. Chem. B.*, *16*(117), 8408−8421.

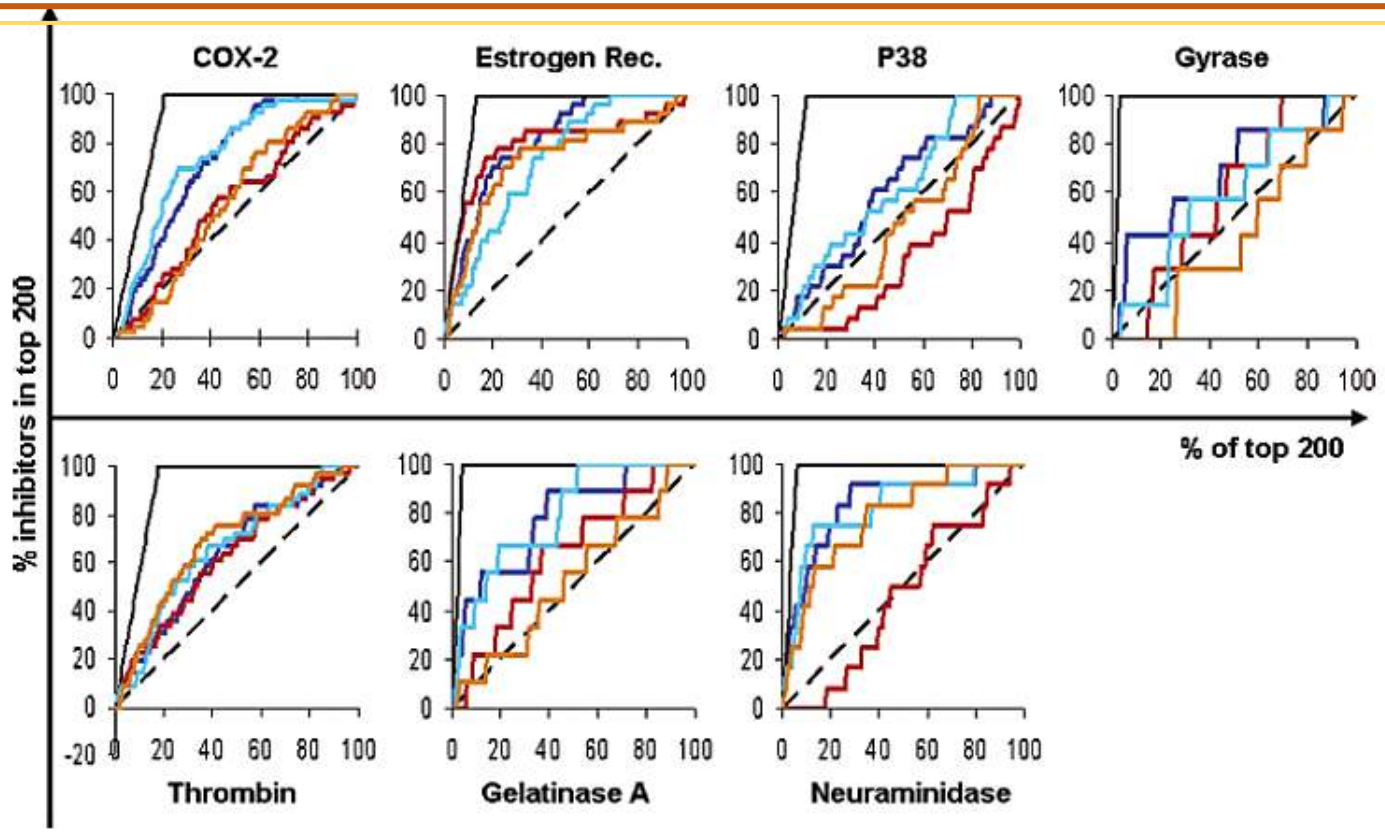
MM/PBSA Approach for Drug Discovery



Scoring and ranking



Performance of MM/PBSA in VS

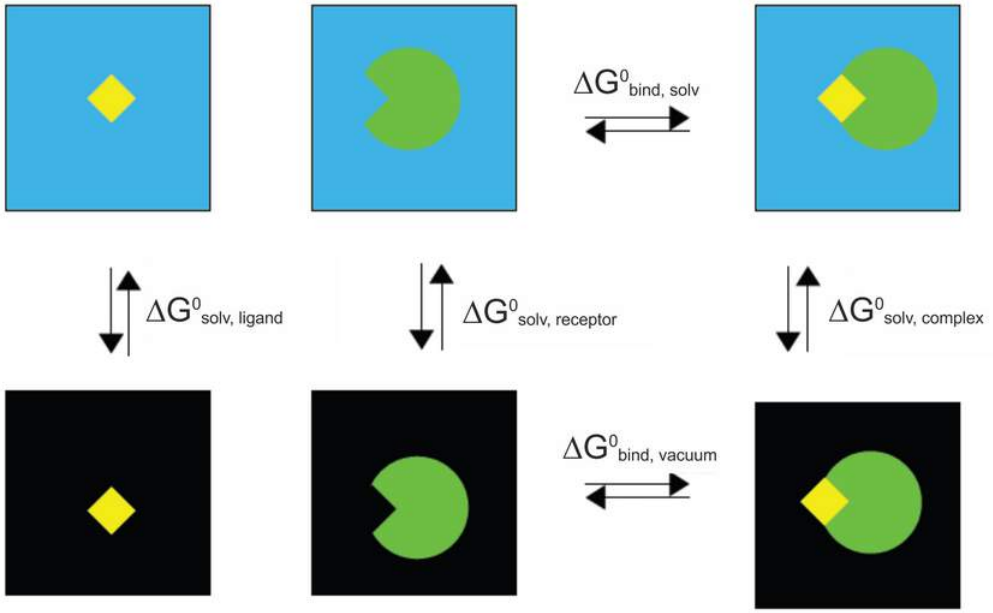


- Comparison of virtual screening performance for seven different proteins.
- Random selection (black, dashed), ideal performance (black, solid), FRED/ChemScore ranking (red), MM-RDIEL ranking with MAB* force field (orange), MM-PBSA ranking with MAB* force field (blue), and MM-PBSA ranking with GAFF force field (cyan).

Kuhn, B., Gerber, P., Stahl, M. (2005). *Journal of Medicinal Chemistry*, *48*(12), 4040–8.

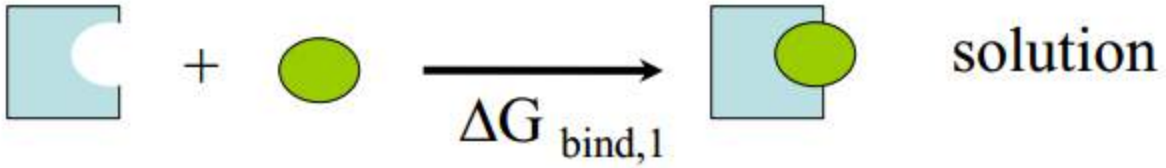
Summary

- The MM/PBSA method is a reasonable approximated free-energy calculation method, which considered the solvation energy in terms of Poisson-Boltzmann model and SASA.
- The accuracy of MM/PBSA is sensitive to the dielectric constant, the ligand formal charge, the initial protein structure and MD sampling.
- The MM/PBSA method is widely used in virtual screening, performs much better than docking and empirical scoring methods.



Thank You !!!

One snapshot



$$\Delta\overline{G}_{bind,1} = \Delta\overline{E}_{MM} + \Delta\overline{G}_{Solv}^{PBSA} - T\Delta\overline{S} \quad (1)$$

$$\Delta E_{MM} = (E_{MM}^{complex} - E_{MM}^{Receptor} - E_{MM}^{Ligand})$$

$$\Delta G_{solvation} = (\Delta G_{solv}^{complex} - \Delta G_{solv}^{Receptor} - \Delta G_{solv}^{Ligand})$$

$$\Delta S = (S^{complex} - S^{Receptor} - S^{Ligand})$$

$$\overline{E}_{MM} = \overline{E}_{Bond} + \overline{E}_{Angle} + \overline{E}_{torsion} + \overline{E}_{VDW} + \overline{E}_{Elec}$$

$$\Delta G_{solv}^{PBSA} = \Delta G_{solv}^{nonpolar} + \Delta G_{solv}^{electrostatic}$$

$$\Delta\Delta G_{Bind} = \Delta G_{Bind,1} - \Delta G_{Bind,2} \quad (2)$$

$$\Delta G^0_{vacuum} = \Delta E^0_{molecular\ mechanics} - T \cdot \Delta S^0_{normal\ mode\ analysis}$$

$$\mathrm{A}_x\mathrm{B}_y \rightleftharpoons x\mathrm{A} + y\mathrm{B}$$

$$K_d = \frac{[A]^x \cdot [B]^y}{[A_x B_y]}$$

For a general reaction:

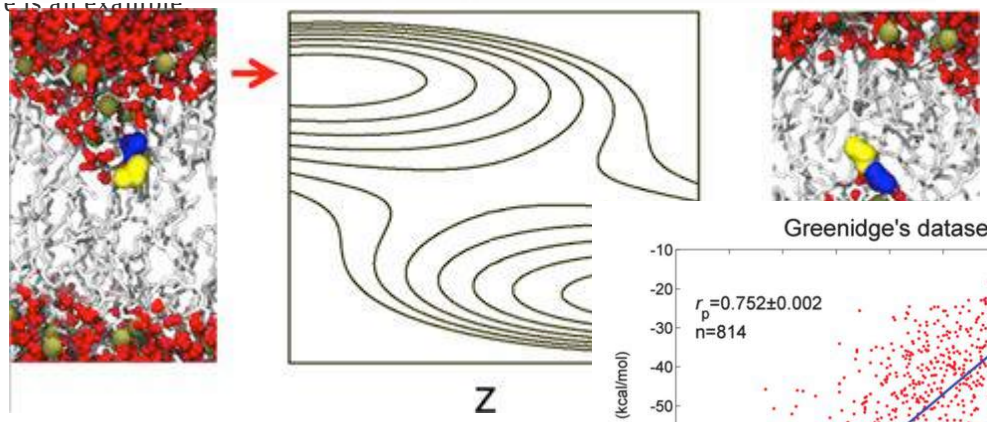
in which a complex $\mathrm{A}_x\mathrm{B}_y$ breaks down into *x* A subunits and *y* B subunits, the dissociation constant is defined

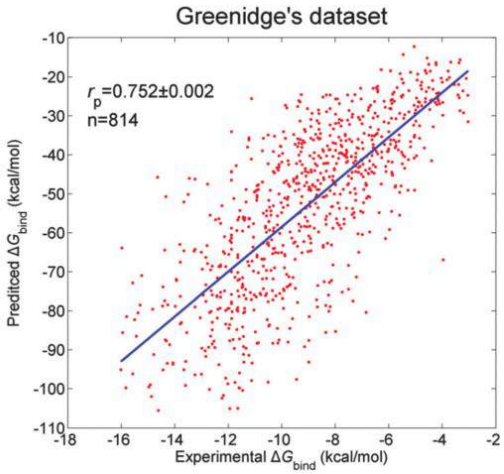
Affinity is not potency, EC50

In the MM-PBSA approach the different contributions to the binding free energy a
Solvation free energies are calculated by either solving the linearised Poisson Bo

delta-G_{vacuum} is obtained by calculating the average interaction energy between receptor and ligand and taking the entrop

The entropy contribution can be found by performing normal mode analysis on the three species but in practice entropy
The average interaction energies of receptor and ligand are usually obtained by performing calculations on an ensemble
In this tutorial we will demonstrate the use of the MM/PB(GB)SA scripts included with Amber and AmberTools to automat





The above figure depicts a drug(yellow and blue) movi epresenting hydrophobic core and red is water and brown, the int

How do we improve sampling?
FEP is one such method used to improve sampling,by l). It is nothing but a step wise thermodynamic integration,by bre

Change between initial and final states are controlled
L=0, could represent state X
L=1, will represent state Y
0<L<1 will represent a series of intermediate states

And every potential term will be defined as a function of L:

- Bonds: $k(\lambda) = \lambda k(Y) + (1-\lambda)k(X)$
  $l_o(\lambda) = \lambda l_o(Y) + (1-\lambda)l_o(X)$
- Angles: $k_\theta(\lambda) = \lambda k_\theta(Y) + (1-\lambda)k_\theta(X)$
  $\theta_o(\lambda) = \lambda \theta_o(Y) + (1-\lambda)\theta_o(X)$
- Charges: $q(\lambda) = \lambda q(Y) + (1-\lambda)q(X)$
- VDW: $\varepsilon(\lambda) = \lambda \varepsilon(Y) + (1-\lambda)\varepsilon(X)$
  $\sigma(\lambda) = \lambda \sigma(Y) + (1-\lambda)\sigma(X)$
- etc.