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

Biophysics 206

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MMPBSA

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

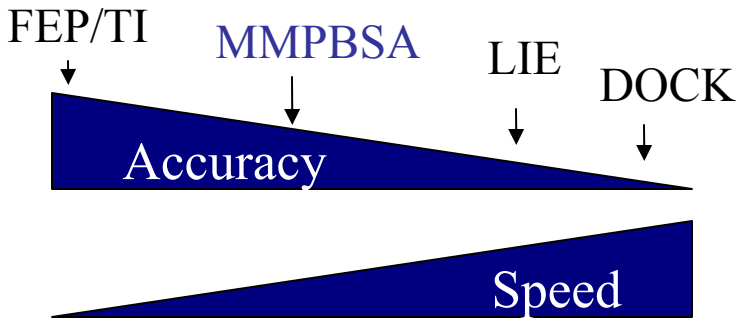
- MM = internal energy of the system (BADH and NB)
- PB = electrostatic contribution to solvation
- SA = nonpolar contribution to solvation

- S = entropic contribution to binding

- Files needed : 1. Topology files for all components (R, L, RL)
  2. Trajectory file (coordinates)

MMPBSA background

- Co-Developed by Dave Case (Scripps) and Peter Kollman (UCSF)
  - First successful implementation Srinivasan (1998) JACS 120(37), 9401-9409.



- Generalizable
- Molecular dynamics used in conjunction with free energy calculation methods can yield energetic determinants to binding.

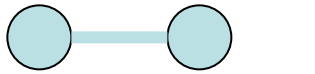
- Advantage over FEP: can take into account large structure changes
  - Calculates G at endpoints, don't sample intermediates
  - But errors larger, still get good agreement with experiment
  - Continuum solvent has integrated out solvent coords

Methodology

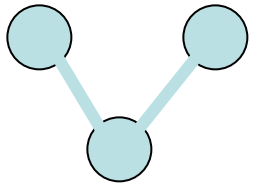
1. Use MD to generate a representative set of structures
2. Representative snapshots taken from the trajectory at fixed intervals (5ps or 10ps intervals)
3. Post-process these structures removing solvent
4. Obtain free energy

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

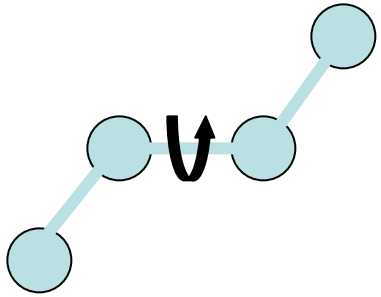
Molecular Mechanics (MM)



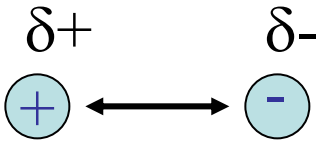
Bond



Angle



Dihedral



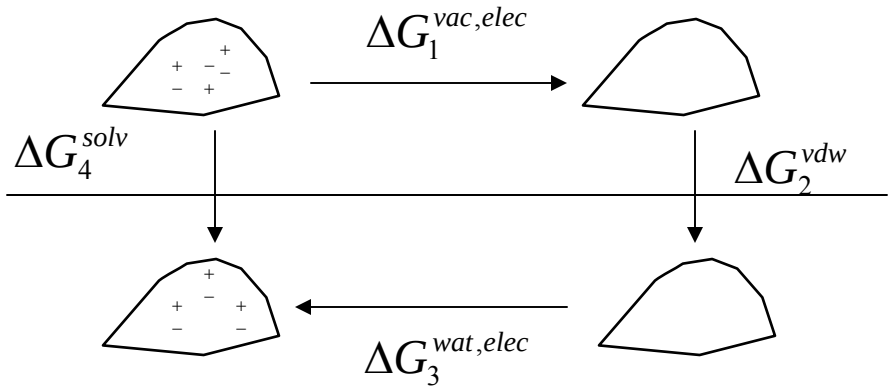
Charge-Charge

Van Der Waals

$$V(r^N) = \sum K_r (l-l_{eq})^2 + \sum K_\theta (\theta-\theta_{eq})^2 + \sum \tfrac{1}{2} V_n (1+\cos(n\omega-\gamma)) +$$

$$(\sum 4e_{ij} [(\sigma/r_{ij})^{12} - (\sigma/r_{ij})^6] + qq/4\pi e r_{ij})$$

Poisson-Boltzmann Surface Area (PBSA)*



- Poisson-Boltzmann for electrostatic solvation energies

$$\Delta G_{electrostatics} = \frac{1}{2}\sum q_i(\phi_i^{80} - \phi_i^{1})$$

- Change in solvent accessible surface area for nonpolar solvation energies

$$\Delta G_{solv}^{nonpolar} = \gamma(SASA) + b$$

y =0.00542 kcal/mol A^2
b = 0.92 kcal/mol

*Sitkoff, JPC 1994, 98(7) 1978-1988

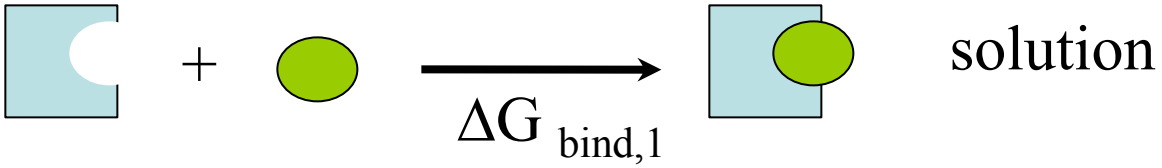
Entropy ($T\Delta S$)

- Many times ignored if ligands all roughly the same size
- Time intensive calculation for very little added information

- Normal Mode (NM)
  - Long minimization time to get tight convergence.

- Quasi-harmonic
  - Need long MD times

One snapshot



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

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

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

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

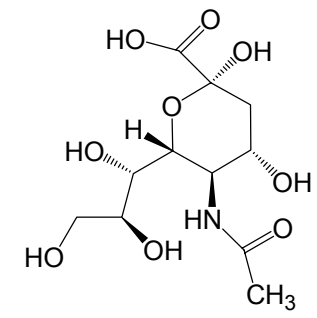
$$\overline{E}_{MM} = \overline{E}_{Bond} + \overline{E}_{Angle} + \overline{E}_{torsion} + \overline{E}_{VDW} + \overline{E}_{Elec}$$

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

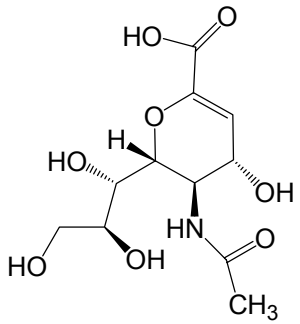
$$\Delta\Delta G_{Bind} = \Delta G_{Bind,1} - \Delta G_{Bind,2} \qquad (2)$$

Neuraminidase study

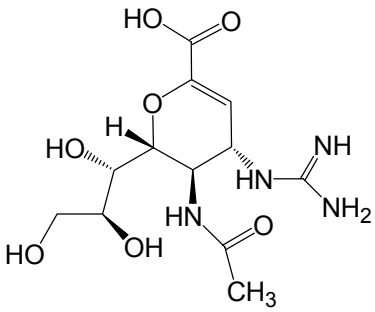
- Structurally similar, but bind with large variation in free energy
- Four co-crystal structures



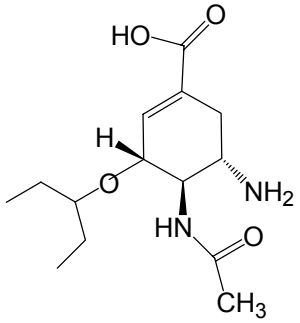
Sialic Acid



DANA



Relenza



Tamiflu

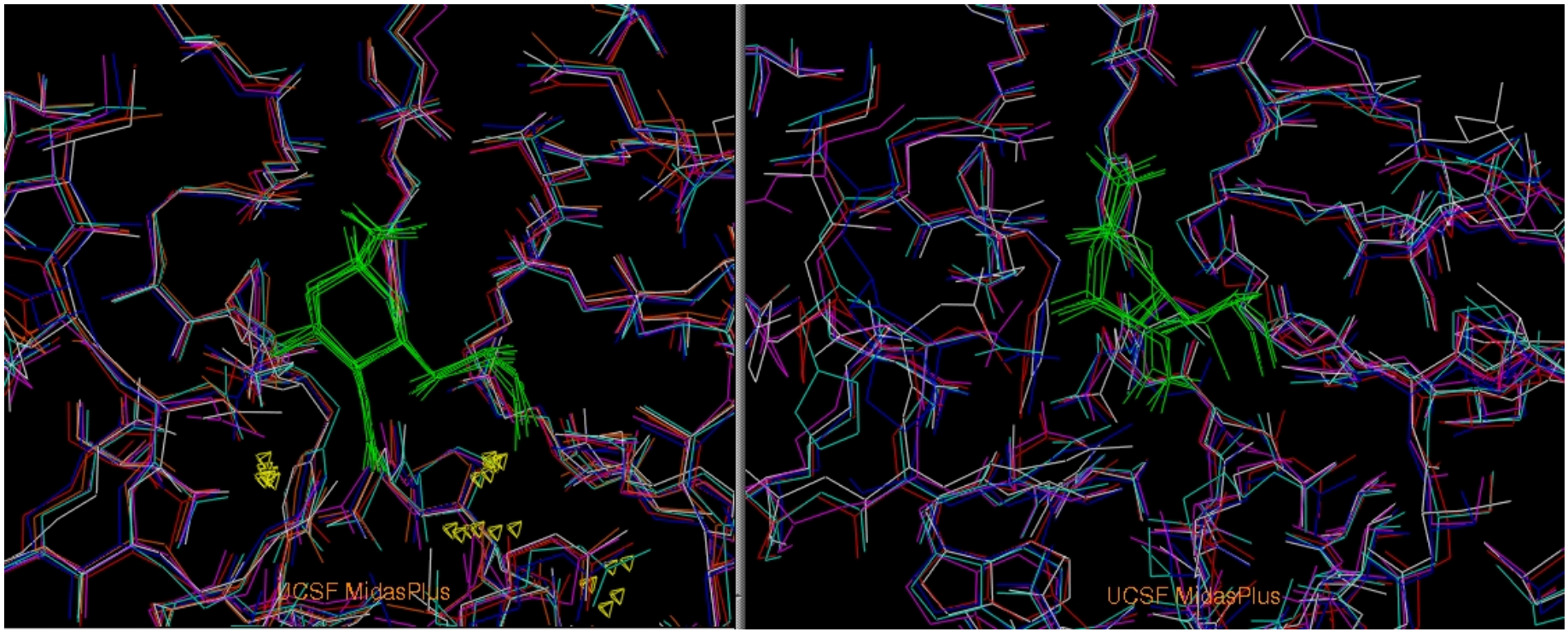
Sialic Acid	-2.76 kcal/mol
DANA	-6.91 kcal/mol
Relenza	-13.2 kcal/mol
Tamiflu	-15.2 kcal/mol

Interaction Energies

Contribution	Tamiflu	Relenza	DANA	Sialic Acid
ΔE internal[1]	-6.07 (0.51)	1.90 (0.68)	-5.36 (0.53)	5.16 (0.48)
ΔE VDW[2]	-29.16 (0.48)	-29.99 (0.51)	-23.13 (0.56)	-23.32 (0.47)
ΔE elect, internal[3]	-44.49 (0.52)	-58.49 (0.39)	-35.15 (0.53)	-44.91(0.28)
ΔG elect,solv[4]	46.81 (0.42)	58.22 (0.27)	38.46 (0.39)	45.4(0.21)
ΔG nonpolar, solv[5]	-4.46 (0.01)	-4.65 (0.01)	-4.12 (0.01)	-4.13 (0.01)
ΔE Elec, int+solv[6]	2.31 (0.17)	-0.26 (0.22)	3.31 (0.24)	0.49 (0.21)
-TΔS[7]	21.6 (1.35)	19.6 (1.56)	22.4 (1.64)	20.11 (1.47)
ΔG bind[8]	-15.78 (1.49)	-13.4 (1.63)	-6.90 (1.70)	-1.69 (1.58)

[1] Internal contributions from bond, angle, and dihedral terms
[2] Non-bonded van der Waals
[3] Non-bonded electrostatics
[4] Non-polar and electrostatic components to solvation
[5] Electrostatic components to solvation
[6] Total electrostatic change upon binding
[7] Entropic contributions to binding
[8] Total change of free energy in binding

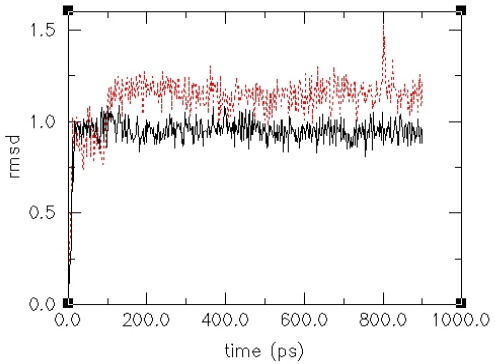
SIA structure overlay



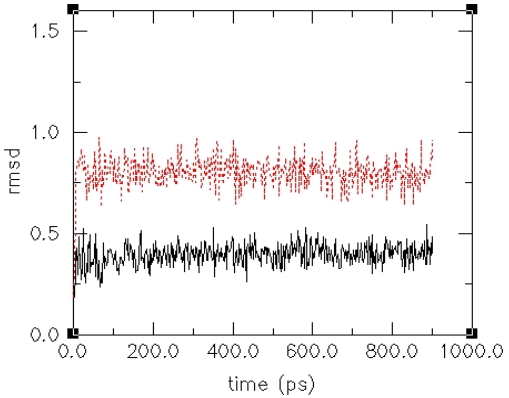
Simulation w/ crystal waters

Simulation without

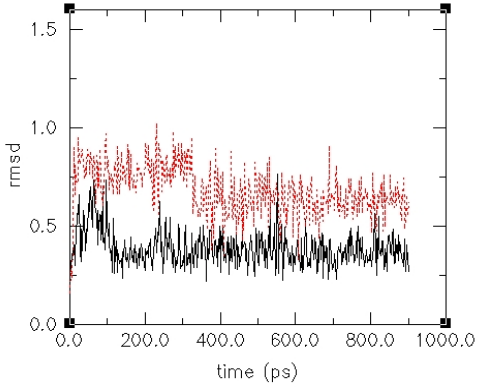
Ligand RMSD During Simulations



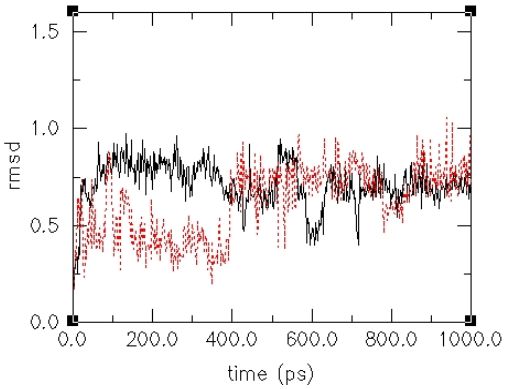
Sialic Acid



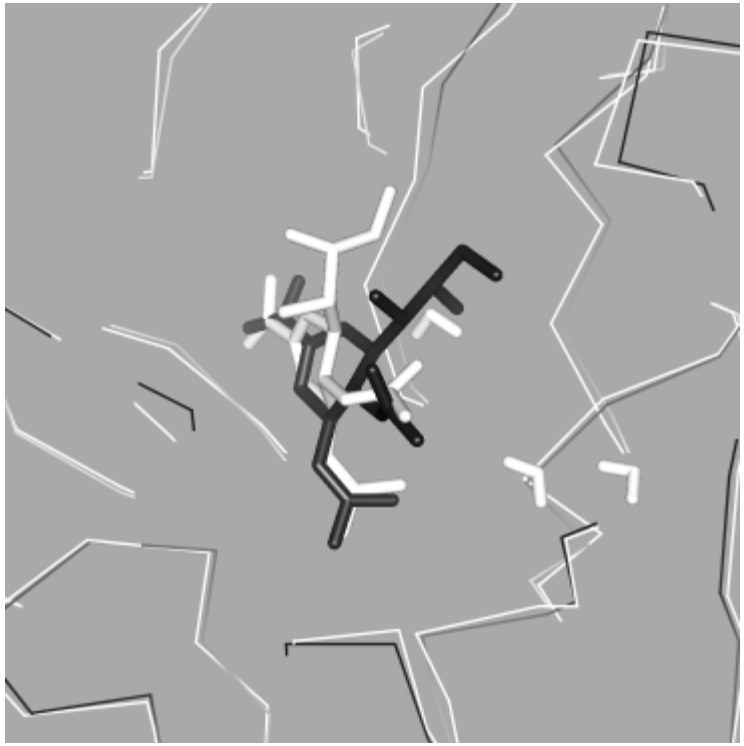
Relenza

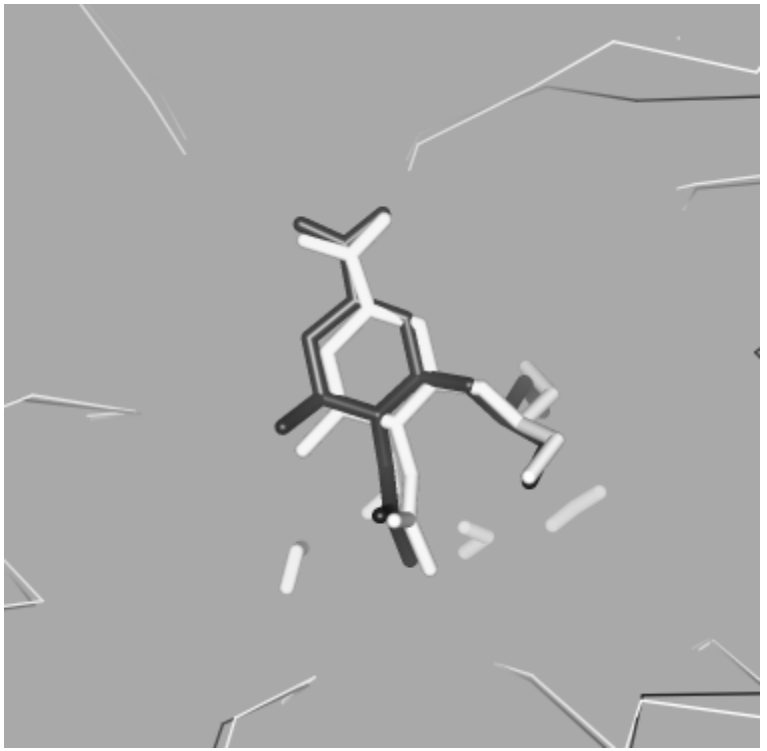


DANA



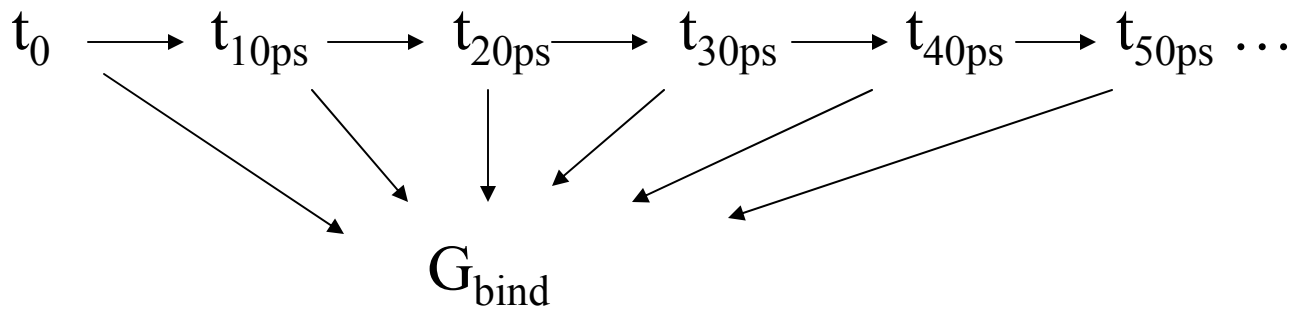
Tamiflu





MM/PBSA overview

- Combines molecular dynamics and a free energy scoring scheme to get free energies of binding
  - Free energy of binding determined via Molecular Mechanic/ Poisson-Boltzmann Surface Area scoring function (MM/PBSA)

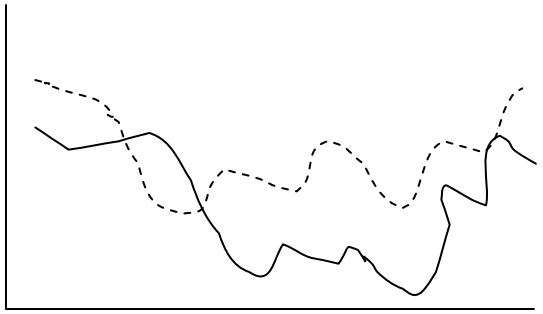


$$\Delta G_{bind} = \bar{G}_{complex} - (\bar{G}_{rec} + \bar{G}_{ligand})$$

$$\bar{G} = \bar{E}_{mm} + \bar{G}_{solv} - \bar{TS}$$

Caveats

- Errors (2-4 kcal/mol)
- Entropy
- Sampling landscape vs. MMPBSA landscape



- Sampling and Scoring

Some References

- MMPBSA overview
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