Molecular dynamics and advanced scoring

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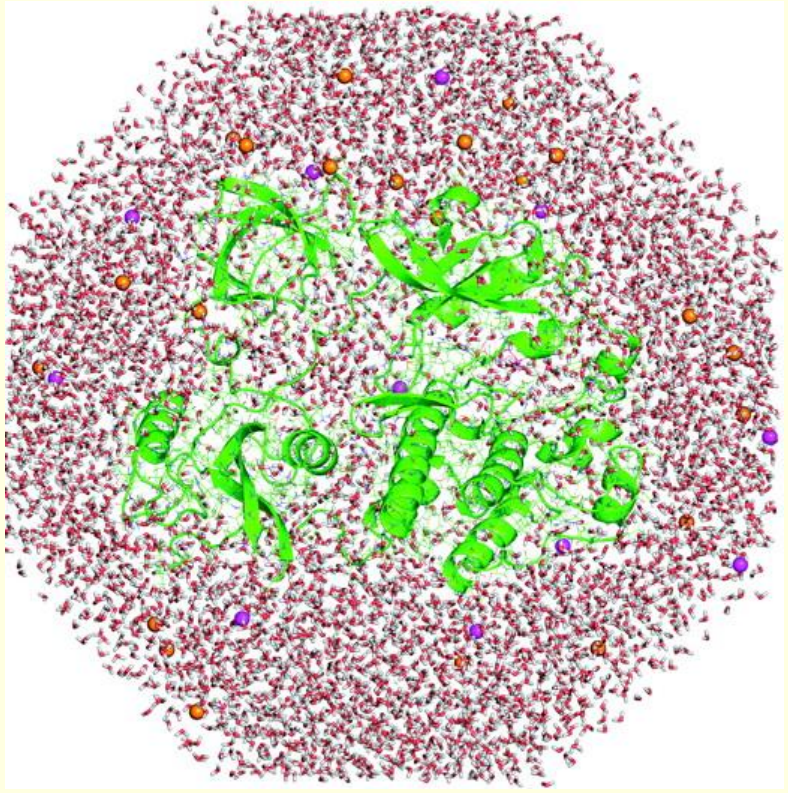
Outline

1. Molecular Dynamics
2. MM-PBSA
3. Free Energy Simulations
4. Bridging Water Thermodynamics
5. QM Scoring

Molecular Dynamics

Simulates molecular motions

- at room temperature
- under physiological pressure
- in solvent (sphere, box, octahedron)
- ionic strength



Thermodynamic Ensembles, Heat, Pressure, Solvent

NVE (microcanonical)
NVT (canonical, isothermal–isochoric)
NPT (Isothermal–isobaric)

Temperature, pressure – coupling to external (heat, pressure) baths

Solvent – implicit (dielectric), explicit (water box)
Ions – implicit (Debye-Huckel), explicit (counterions, physiological)

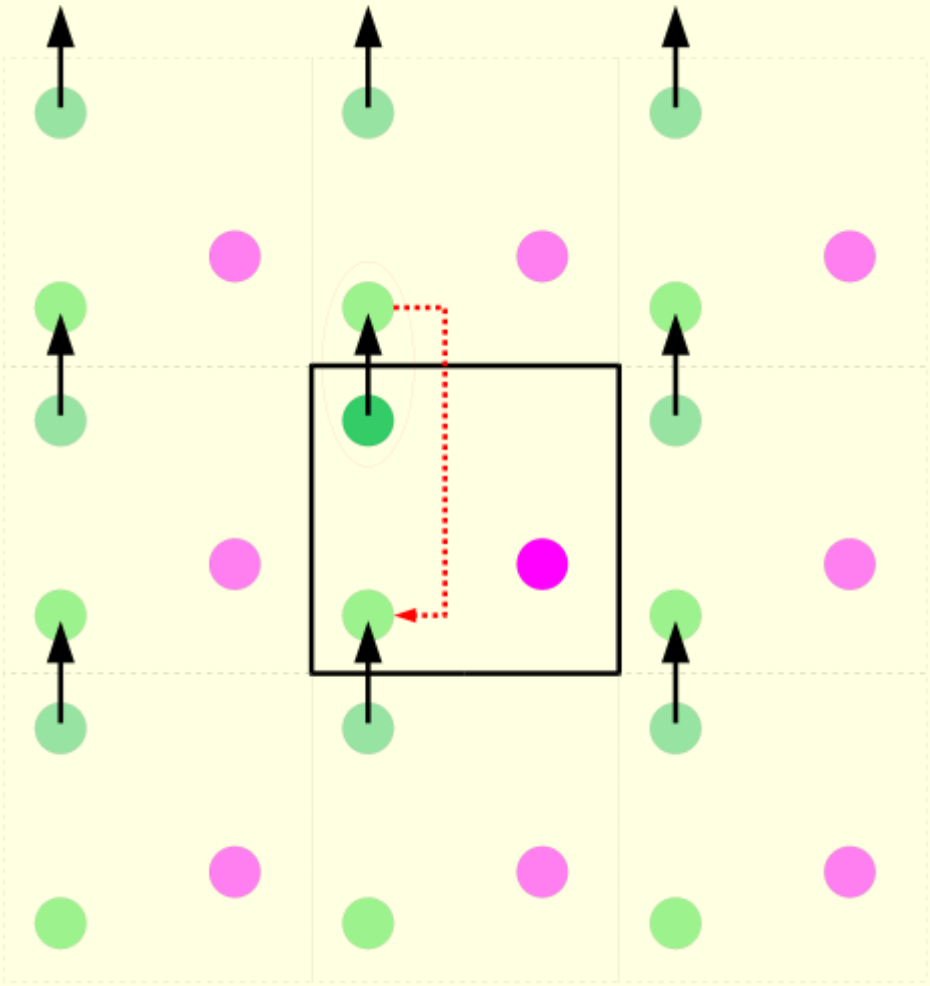
Periodic Boundary Condition

unit cell → infinite system

Boxes

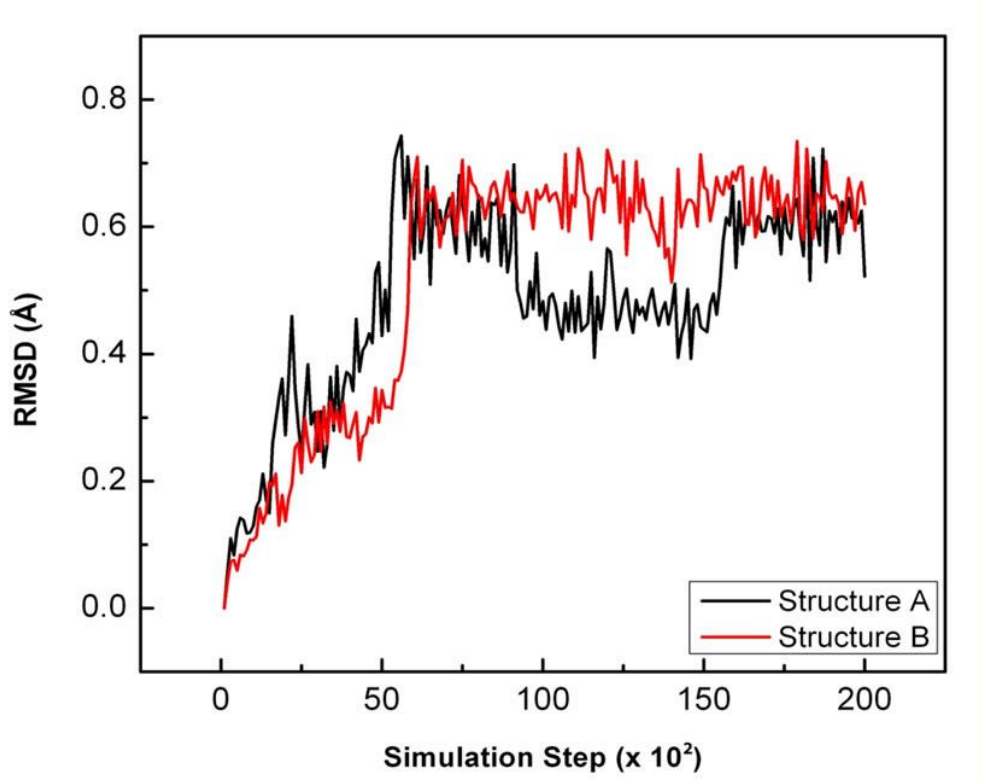
- rectangular,
- truncated octahedron

Long-range electrostatics (particle mesh Ewald)



MD Analyses

Fluctuations of energy, volume, pressure, temperature
Root-mean square deviations (RMSD): protein backbone, ligand
Heating, Equilibration, Production
Atomic fluctuations: B-factors, Order parameters
Atom-atom Distances



MM-PBSA

- post-processing of MD trajectory
- estimating ΔG of molecule by averaging over MD trajectory frames (snapshots)

$$\Delta G = \Delta E_{MM} + \Delta G_{solv} - T\Delta S$$

$$\Delta E_{MM} = E_{bond} + E_{angle} + E_{dihedral\ torsion} + E_{electrostatic} + E_{vanderWaals}$$

$$\Delta G_{solv} = \Delta G_{solv\text{-}pol}\ (GB,PB) + \Delta G_{solv\text{-}nonpol}\ (SA)$$

$$T\Delta S = T\Delta S_{trs} + T\Delta S_{rot} + T\Delta S_{vib}$$

$$\Delta G_{bind} = \Delta G_{cplx} - \Delta G_{prot} - \Delta G_{lig}$$

$$\Delta G_{conf} = \Delta G\ (P,L)^{cplx} - \Delta G\ (P,L)^{free}$$

One- or three-trajectory approach
Cancelation of errors

MM-PBSA

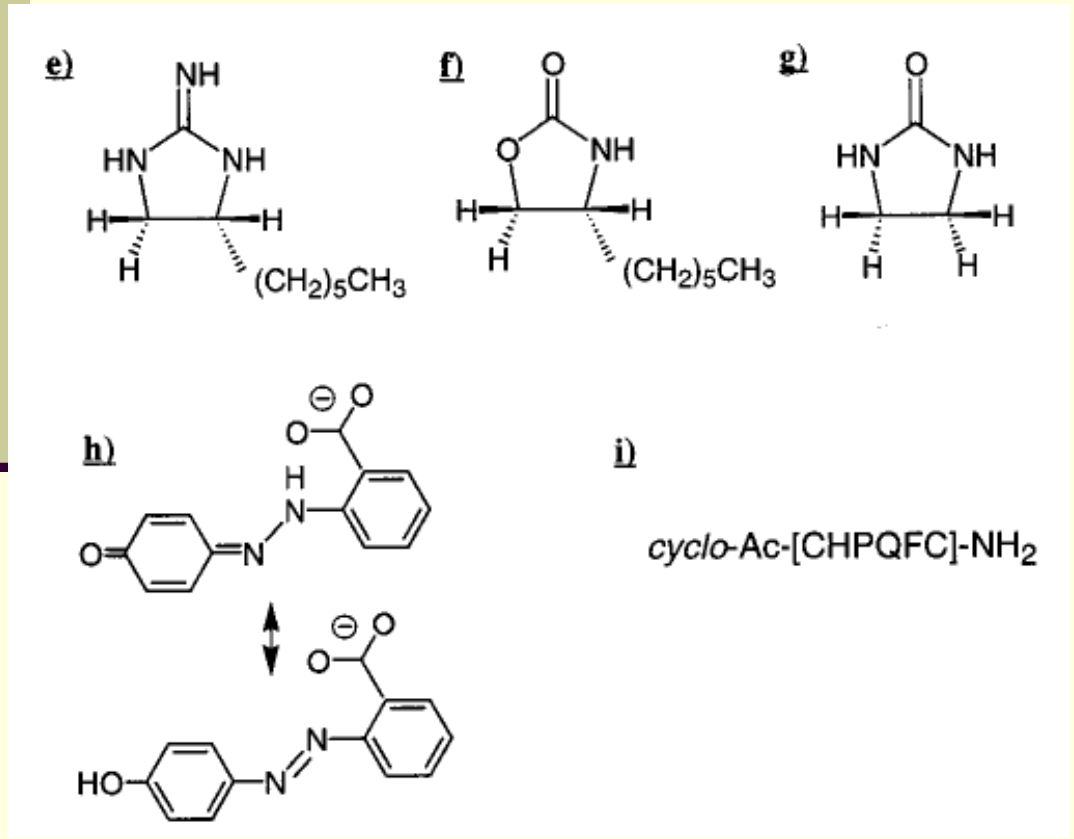
Absolute free energies of solvation, binding – diverse ligands

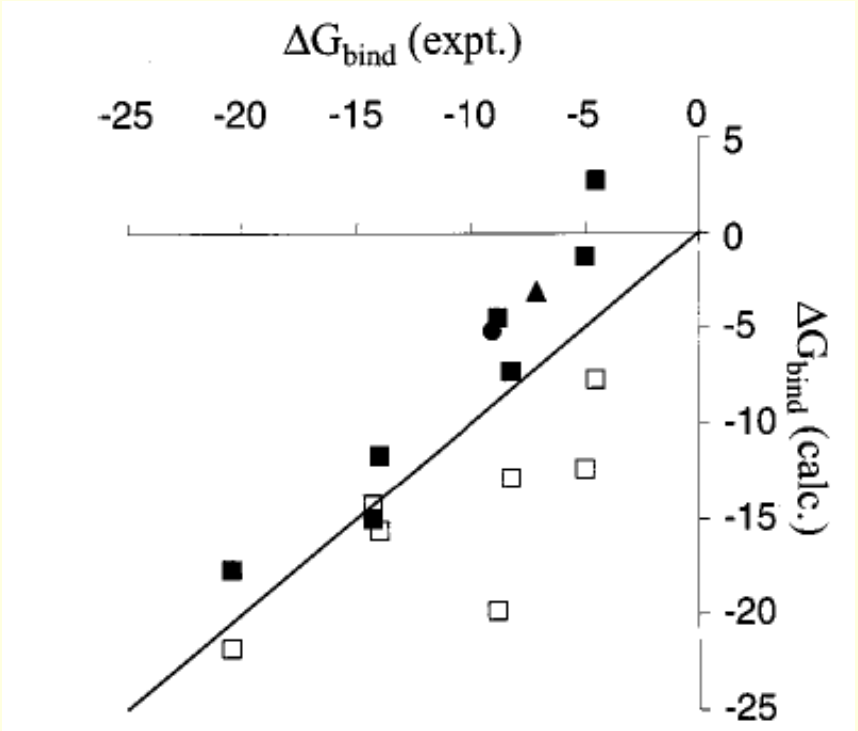
Protein many amino acid mutations

Nucleic acids

Per-residue decomposition

Varied accuracy





Alchemical Free Energy Simulations

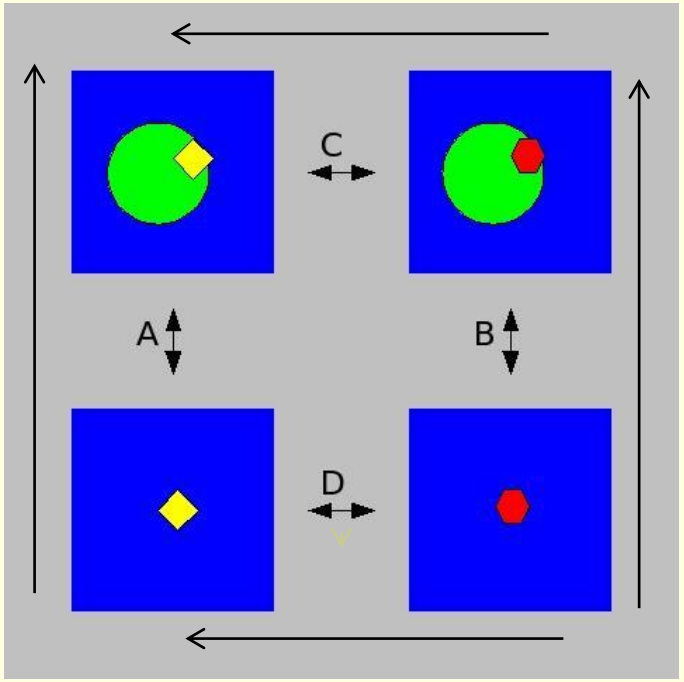
Relative free energies of solvation, binding - only small changes

Thermodynamic Cycle
ΔG – state function

ΔG(D+A) = ΔG(B+C)

ΔG(A-B) = ΔG(C-D)

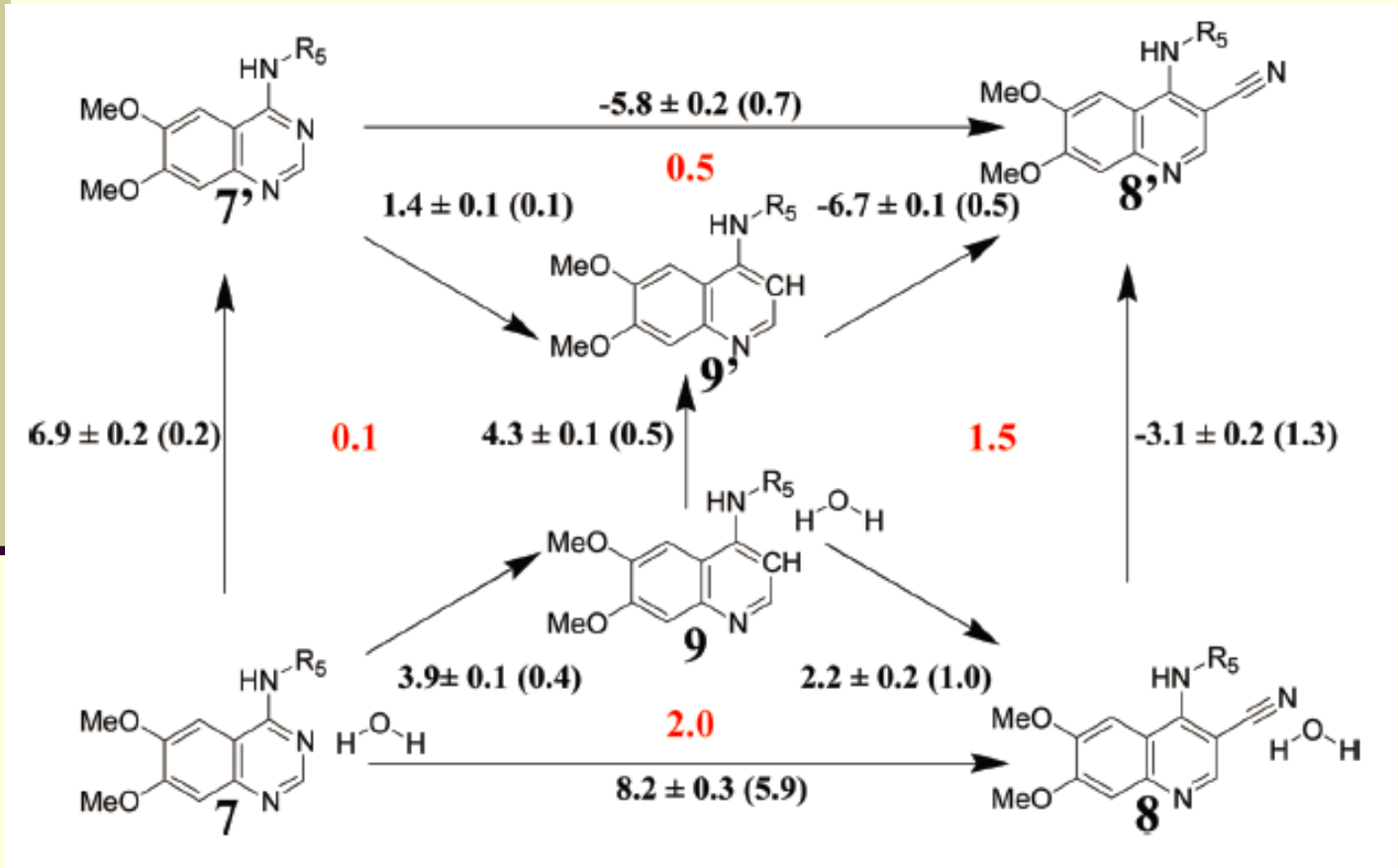
Experimental binding



Alchemical Simulation
Chemical accuracy (+/- 1 kcal/mol)
Forward-reverse hysteresis, sampling, convergence, force-field limitations

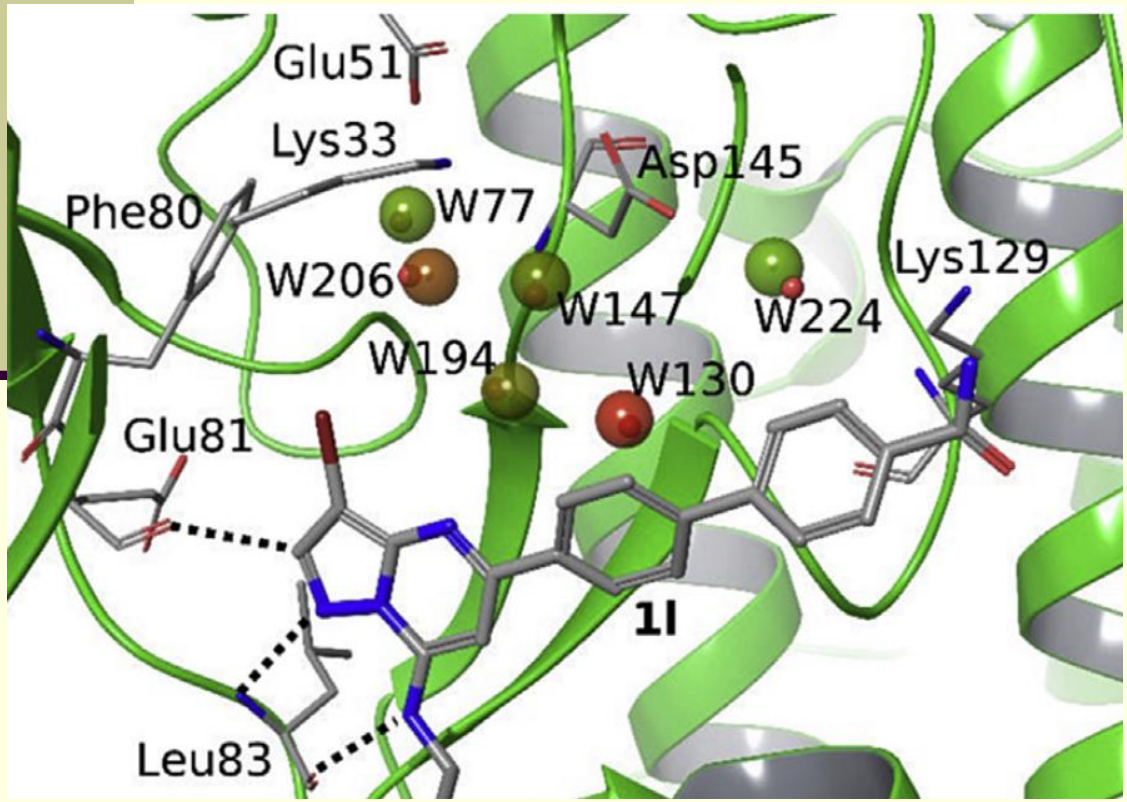
Alchemical Free Energy Simulations

Thermodynamic Cycle Closure – ideal 0 (deviations in red)



Bridging Water Thermodynamics

Monte Carlo, MD, water site clustering
Thermodynamics - Inhomogeneous solvation theory (IST)
ΔG, ΔH, TΔS of bridging waters with respect to bulk solvent
Firmly bound/displaceable waters



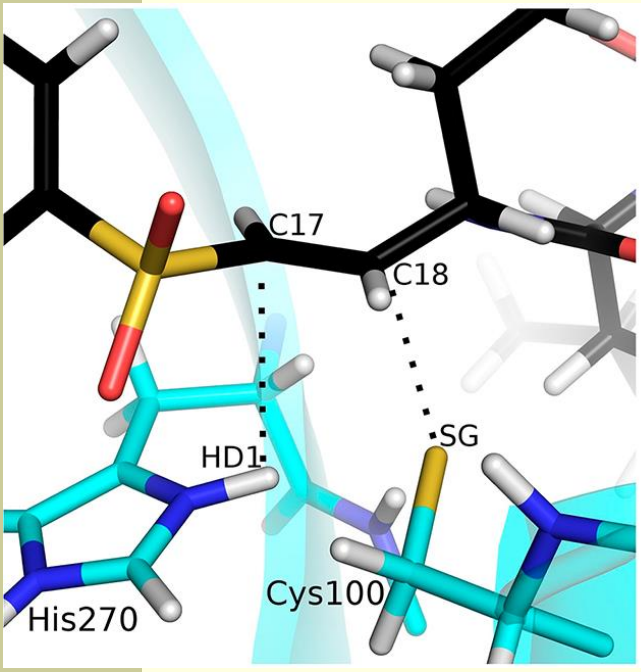
Water	ΔG	ΔH	-TΔS
W77	1.2	−3.2	4.4
W206	4.4	0.5	3.9
W194	2.4	−1.6	4.0
W147	2.4	−2.0	4.5
W224	0.8	−4.4	5.1
W130	6.2	2.1	4.1

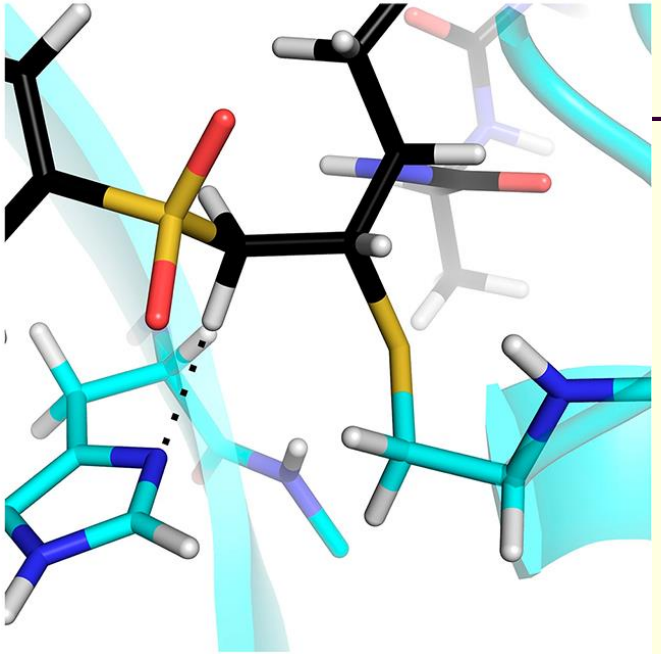
QM scoring

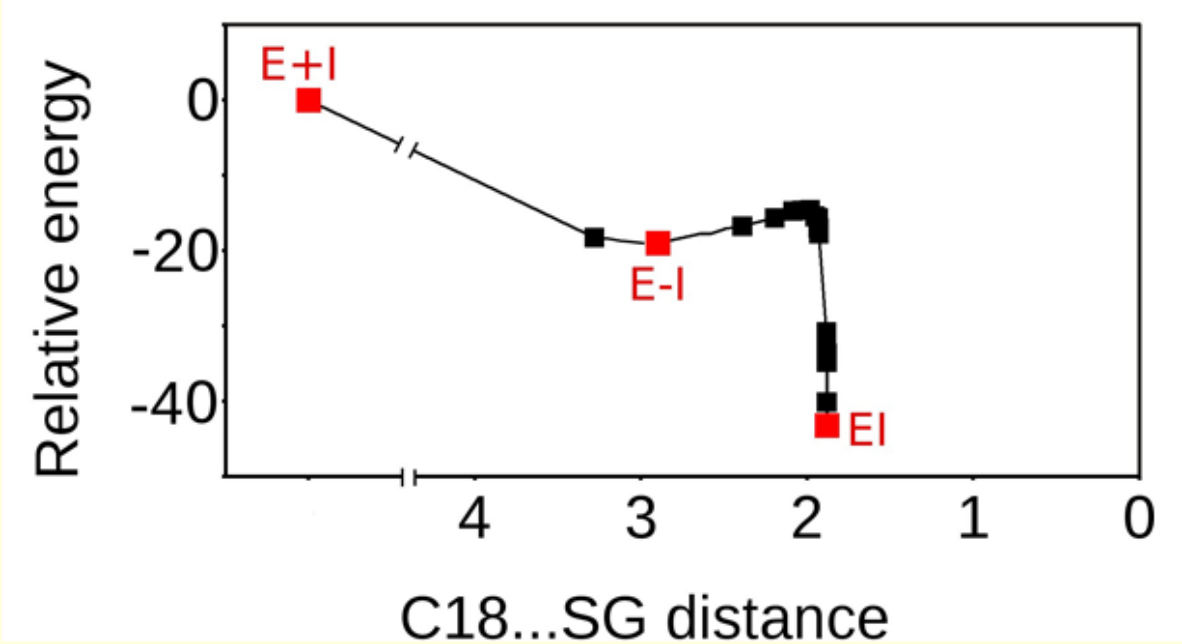
- when QM phenomena occur
- charge transfer (metalloproteins), halogen bonding, inorganic ligands, covalent binding, etc.

Fast:
- semiempirical QM (SQM)
- fragmentation QM/MM or MFCC
- no dynamics
- implicit solvent

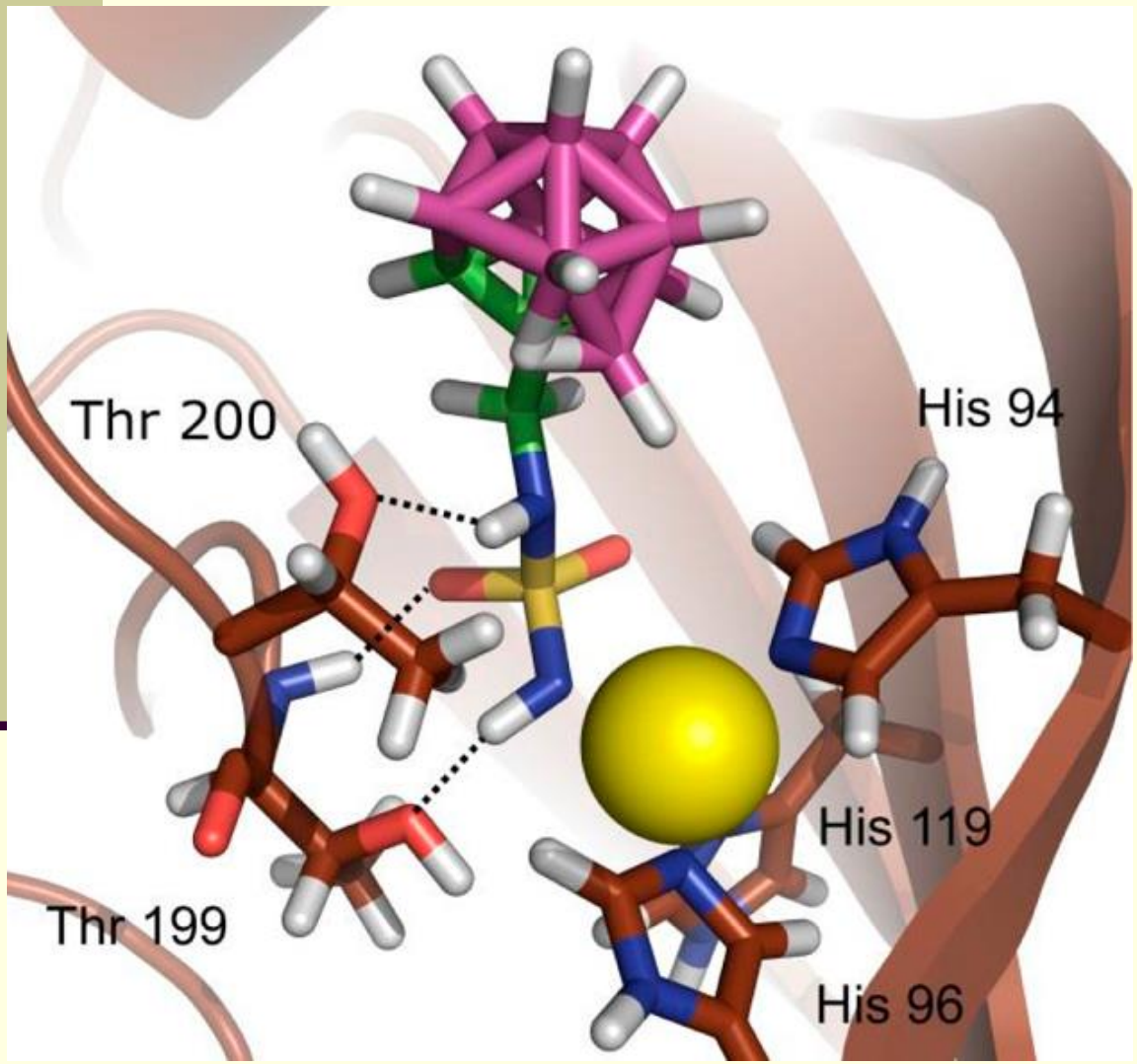
QM scoring: Covalent Binding



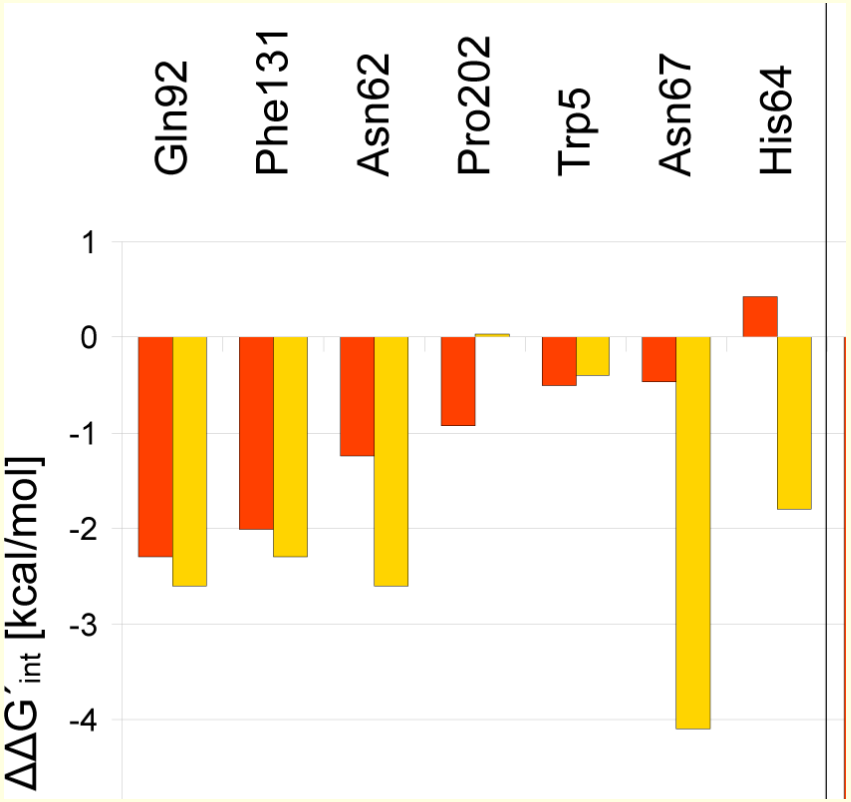




QM scoring: Halogen Bonding



- Zn^{2+} metalloprotein
- Boron hydride cluster
- Dihydrogen bonding



Conclusions

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