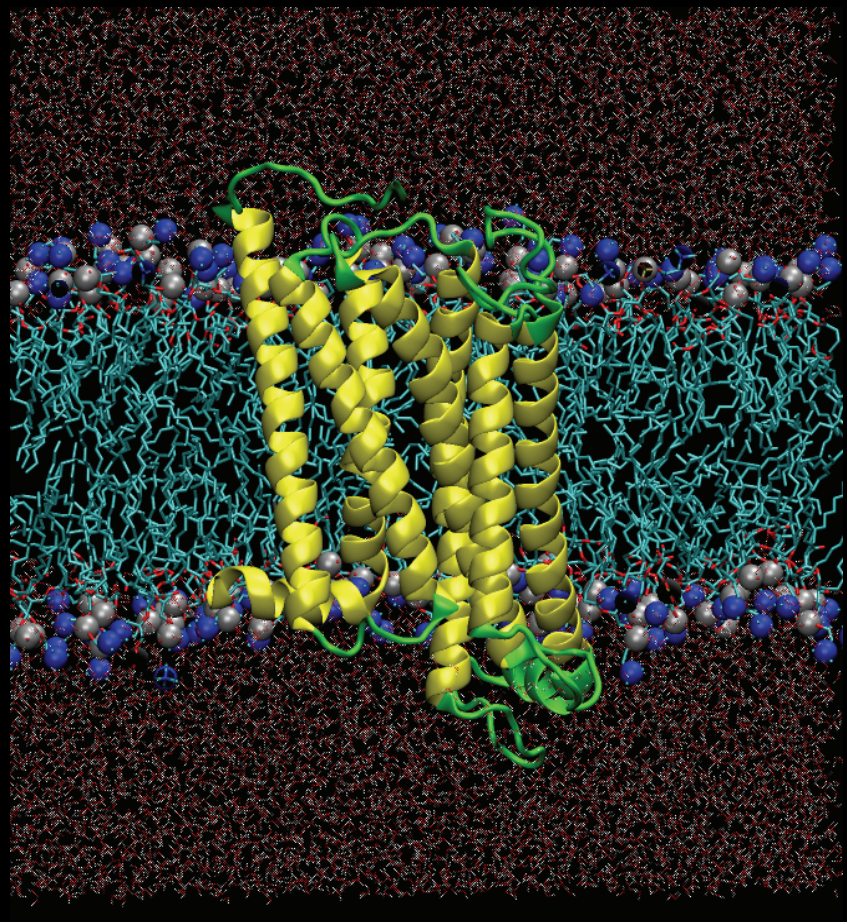
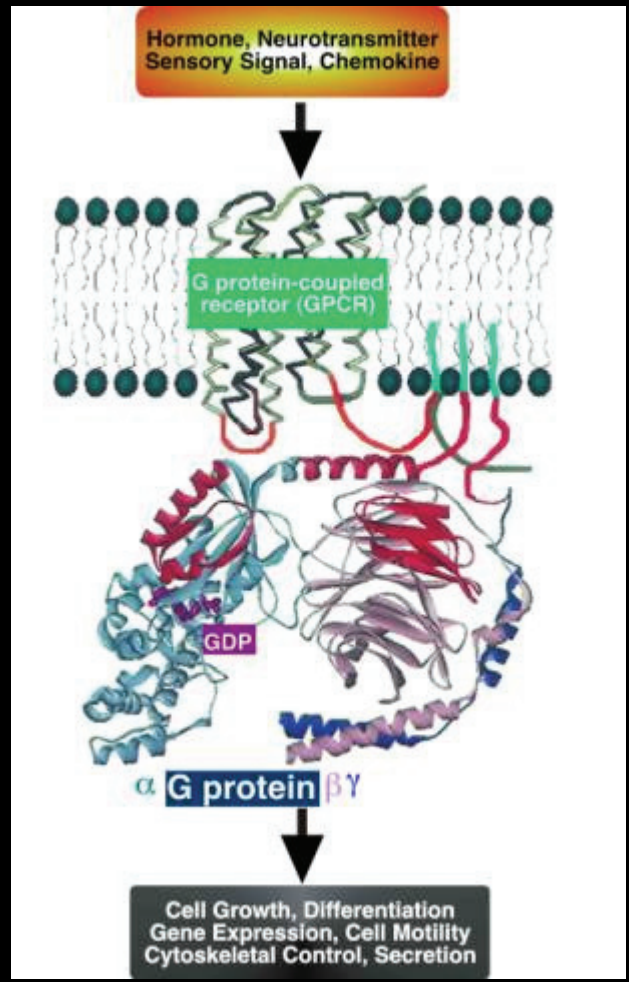
Grand Canonical Monte Carlo … will GPUs help?



M. Foster, D. L. Lynch, P.H. Reggio,
University of N. Carolina, Greensboro

GPCR Function

- Conduit for signal transduction
- ~50% of drug design targets GPCRs



Locate Fragments for Ligand Design

Location of ligands often unknown

Secondary type of ligand: Allosteric Modulator
- Binds along with ligand
- Effects activation(functional) properties
- Dependent on ligand
- Pharcologically attractive.

Grand Canonical Monte Carlo

Use fragments of particular physico-chemical type
- Hydrophobic
- Hydrophilic
- Aromatic

Produces "hot spots" where binding may occur

Patch full ligand together

Clark et. al. "Grand Canonical Monte Carlo Simulation of Ligand-Protein Binding". J. Chem. Inf. Model. 2006, 46, 231-242.

Grand Canonical Monte Carlo

Reference system to the ideal gas and compute the excess chemical potential.
Convienent to define a parameter

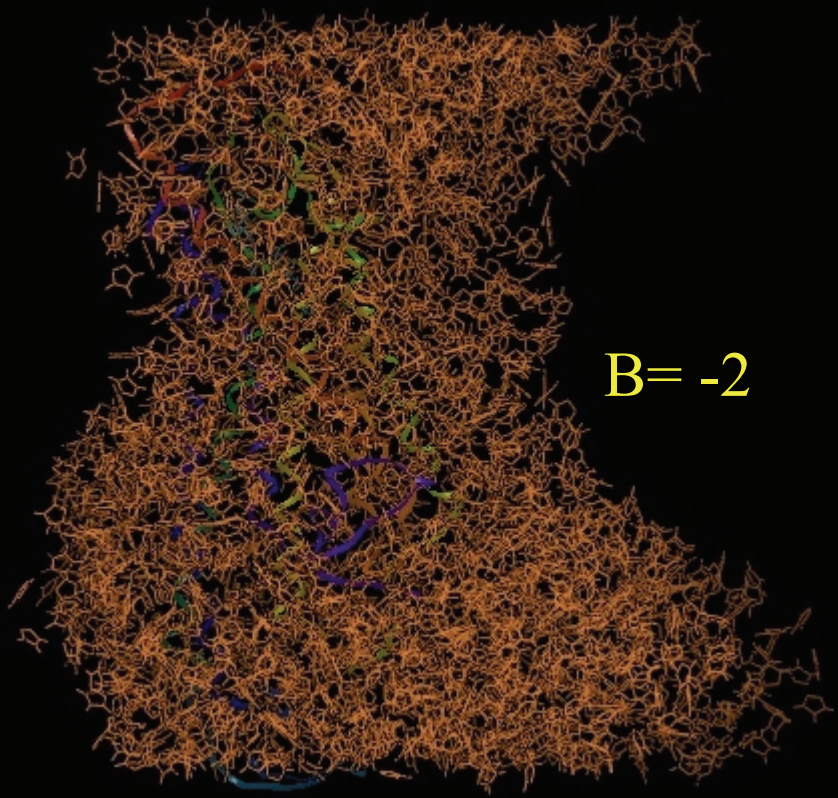
$$B = (\mu - \mu_{id})/kT + \ln\langle N\rangle$$

Anneal B

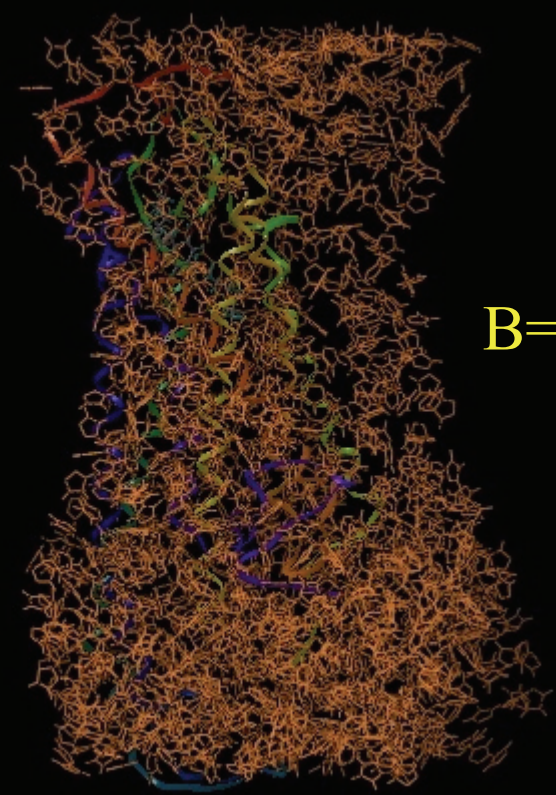
Constant μ, V, T ensemble

Adams, "Grand Canonical Ensemble Monte Carlo for a Lennard Jones Fluid", J. Mol. Phys. 1975, 29, 307
Mezei, M. Grand-Canonical Ensemble Monte Carlo Simulation of Dense Fluids:
Lennard-Jones, Soft Spheres and Water.
Mol. Phys. **1987**, *61*, 565−582.
Mezei, M. Monte Carlo Method for the Computer Simulation of Fluids. *Mol. Phys.* **1980**, *40*, 901.

Lower B



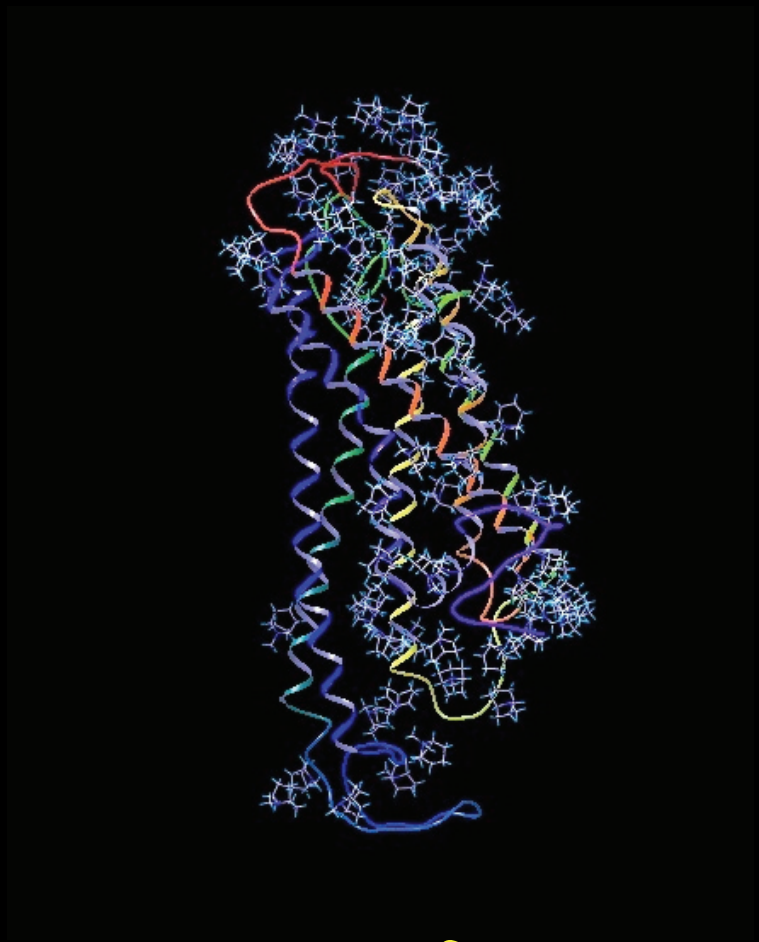
B= -2

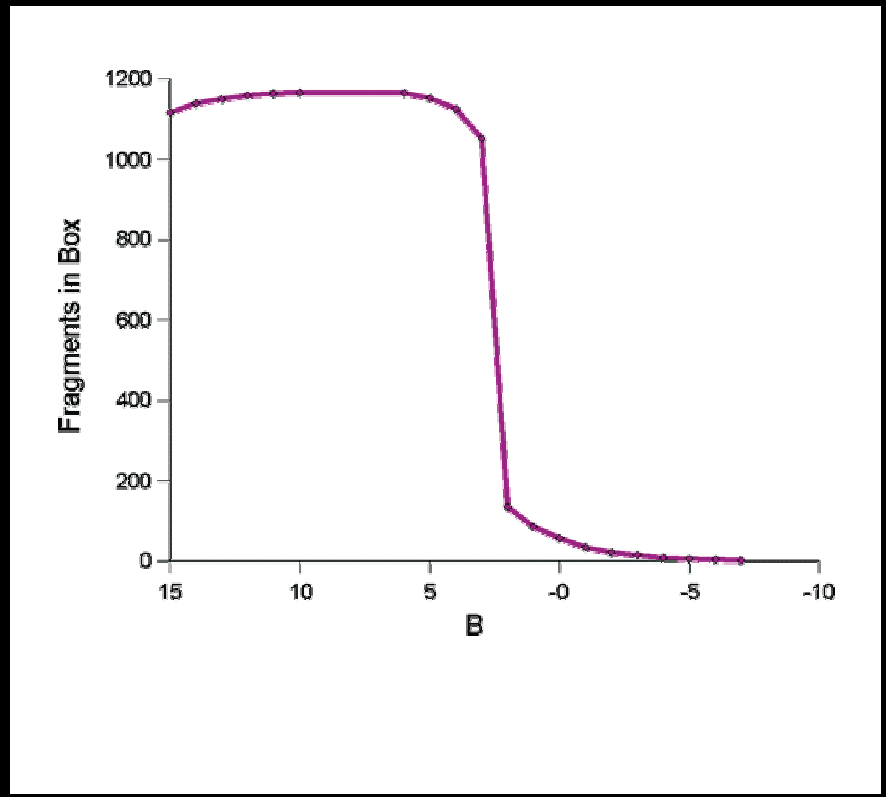


B= -3

Anneal the B value, strips away low affinity fragments

Lower B





Get regions of low free energy.

Grand Canonical Monte Carlo

Protein fixed, fragments rigid

Number of molecules varied, attempt insertions and deletions along with translations/rotations

For insertion accept with probablility (go from state i to state j)

$$\frac{p_{ij}}{p_{ji}} = \frac{V \exp\left[B-(Ej-Ei)/kT \right]}{N} = \frac{V \exp(B) \exp-(\Delta E/kT)}{N}$$

Choose move/insert/delete

Randomly choose

Accept/Reject with probability α to ΔE

Ulberg and Gubbins, Mol. Sim. 13, 205 1994

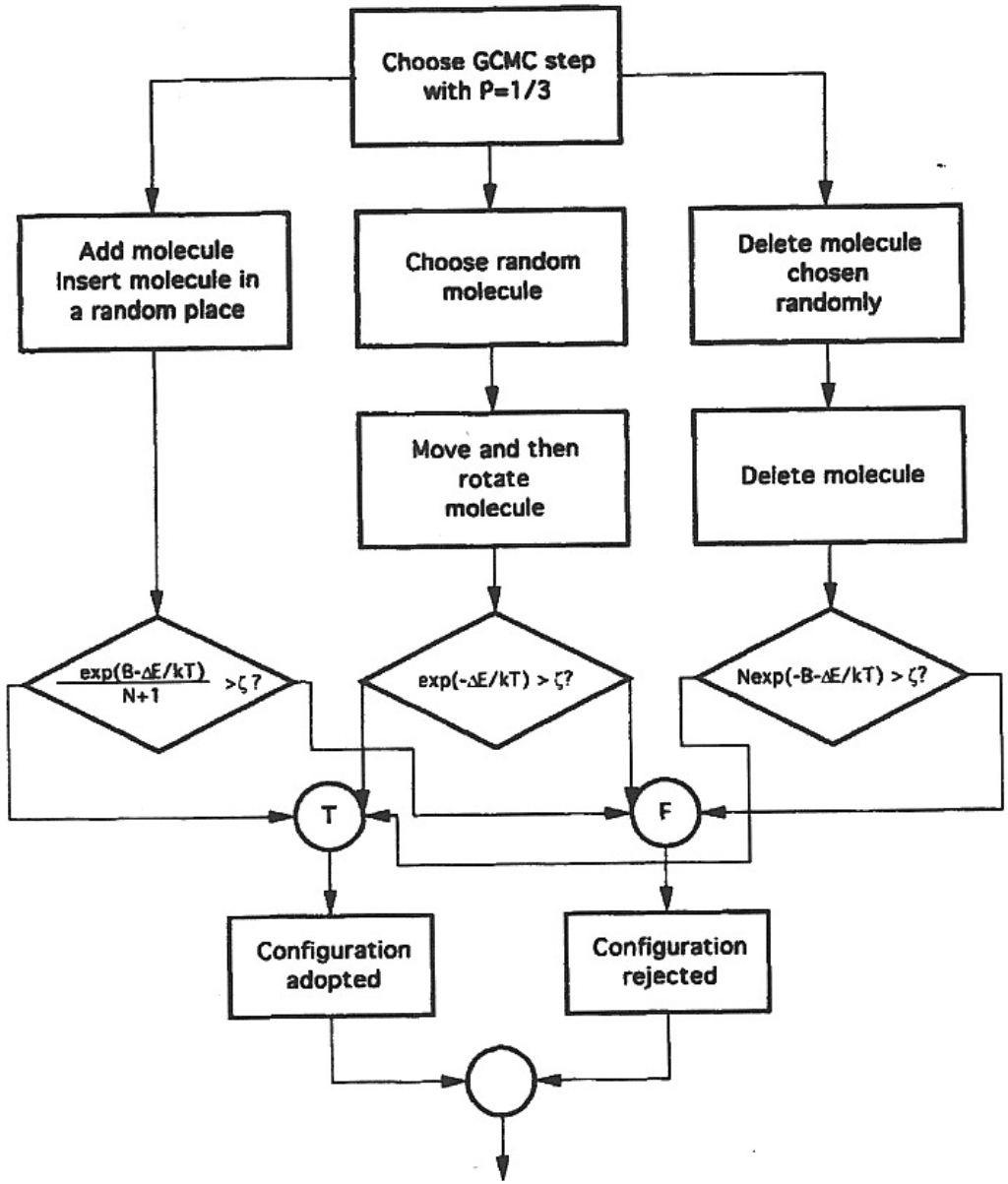


Figure 3 Block scheme of the Grand Canonical Monte Carlo algorithm.

Grand Canonical Monte Carlo

Currently very slow.

- B hard to equilibrate.
- Millions of steps per B value.
- Get one result for one B value then compute next

GPU's?

- Legacy fortran code

Parallelize?

Time spent in calculating ΔE

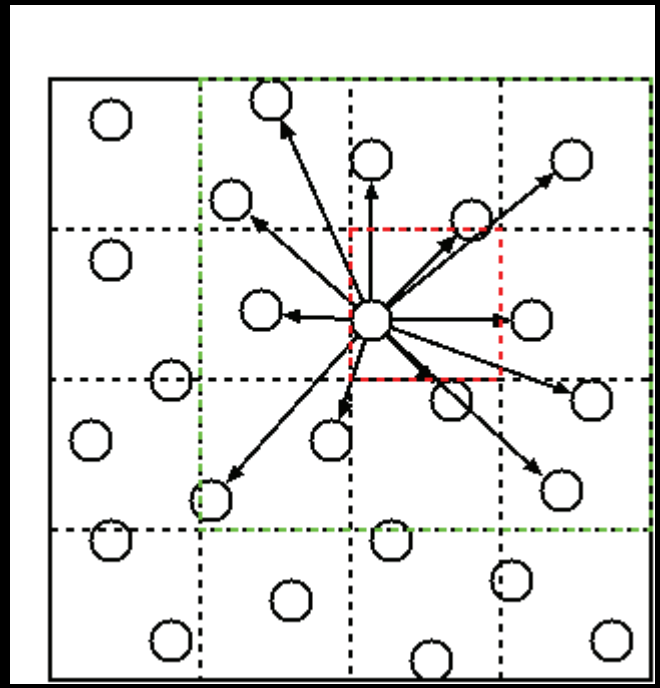
$$V = \sum q_i q_j / r_{ij} + \varepsilon[(\sigma/r_{ij})^{12} - (\sigma/r_{ij})^{6}]$$

Similar to Ion Placement with addition of LJ term.

Except....

- Moving one molecule at a time.
- Large fraction of other molecules aren't moving
- Inherently serial

Domain Decomp. know which molecules are close/far.

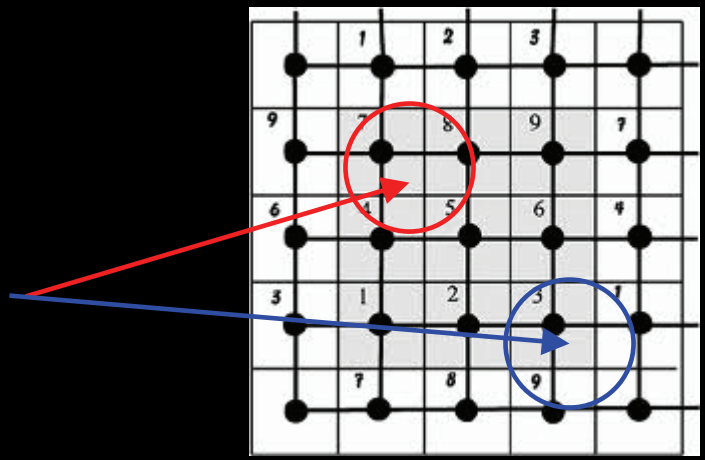


Farm out the "changed" interactions to threads?

Spacial Decomp?

Since have cutoffs do multiparticle moves

Move particles simulataneously when outside the cutoffs



Parallelize?

Hybrid Monte Carlo.

Modified markov chain.
move atoms biased in direction of force.

Molecular Dynamics

Expectations?

Looking for modest improvements due to nature of algorithm.