Applications – MD / MC

Basic tools

- Force field
- MD / MC

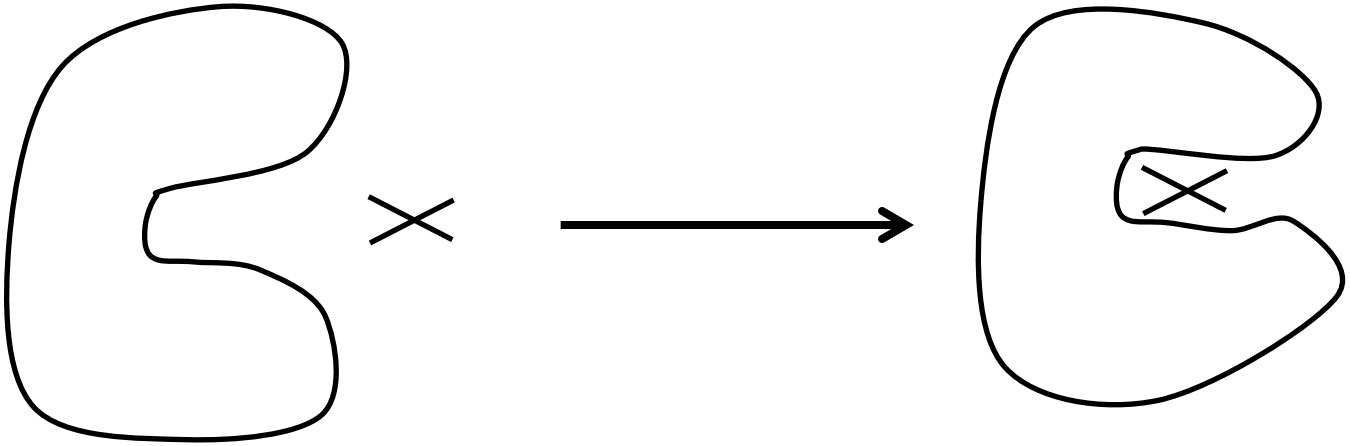
Some application areas

- timescales
- free energy calculations
- simulated annealing
- structure refinement

Simulating dynamics (optimistic / naïve)

Claim

- protein has a hinge which must open to bind ligand



Can one see rates ?

- rates for different ligands ?

Timescales

Most common quantity τ

- time to rotate by 1 rad
- time for decay in $A(\mathrm{t}) = A(0)\, e^{-t/\tau}$
  - relaxation time
  - characteristic time

- times in proteins…

Typical times in proteins

	Amplitude (Å)	$\log_{10} \tau$(s)
bond vibration	0.01 – 0.1	−14 to −13
rotation of surface sidechain	5 – 10	−11 to −10
protein hinge bending	1 – 20	−11 to −7
rotation of sidechain in middle of a protein	5	−4 to 0
local loss of protein structure	5 – 10	−5 to +1

Numbers taken from McCammon, J.A. and Harvey, S.C., Dynamics of proteins and nucleic acids, Cambridge Uni Press, 1987

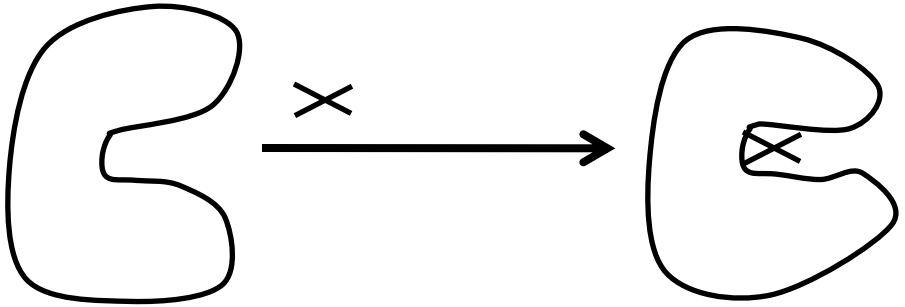
Timescales

- Typical big simulation ≈ 100 ns = 10^{-7}s
- Imagine event with characteristic time 10^{-7}s
  - may or may not be seen
- consider time 10^{-8} s
  - may be seen a few times
- What you would like
  - 100's or 1 000's of observations
- Limits of timescales
  - fast events $\tau \ll t_{simulation}$ OK
  - events $\tau < t_{simulation}$ poor statistics
  - $\tau \approx t_{simulation}$ no statistics
- Previous example (drug binding)
  - it is not enough to observe an event once (or few times)

Free Energy Calculations

- Free energy is most important
- Predicting therapeutic efficacy

$$k_d = \frac{[\text{drug}][\text{protein}]}{[\text{drug}-\text{protein}]} = e^{\frac{-\Delta G}{RT}}$$



Could we just look at energies ? What are contributing terms ?

- ligand-water → ligand + water (many interactions, ΔS)
- ligand+protein
- ligand loss of entropy / water entropy change
  - simulate ?

Infinite time – free energy estimate

$$\mathrm{DP} \rightleftharpoons \mathrm{D} + \mathrm{P}$$

$$\Delta G = kT \frac{[\mathrm{D}][\mathrm{P}]}{[\mathrm{DP}]}$$

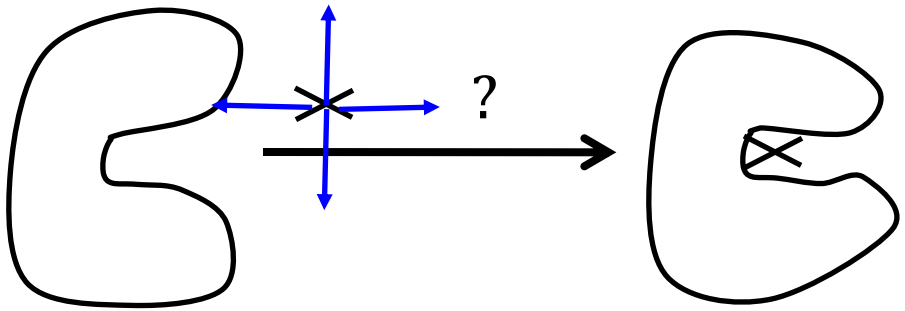
Simulate for long time

- Ligand (drug) goes on and off protein
- Look at [D], [P] and [DP]

- Will not work

Free simulation for binding

If we simulate, where will the ligand go ?



- may take years for ligand to find protein

Short cut ?

- force ligand to protein
  - artificial force + corrections
  - very difficult – still requires rearranging water
  - entropy estimation very difficult

Estimating free energy differences

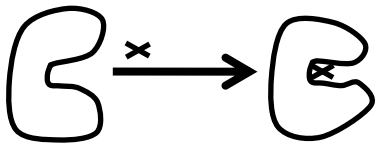
$G = U - TS$

but $S = -k \sum_{i=1}^{N_{state}} p_i \ln p_i$

- so we cannot really get S
- some books write in terms of partition function
- similar problem – especially visiting high energy regions

Forget absolute free energies

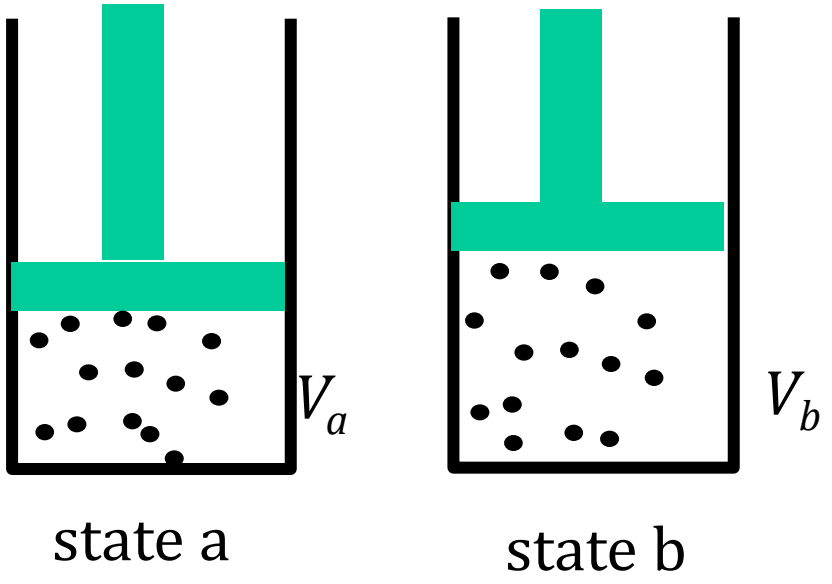
- concentrate on ΔG
- no problem – usually interesting property



Work and free energy changes

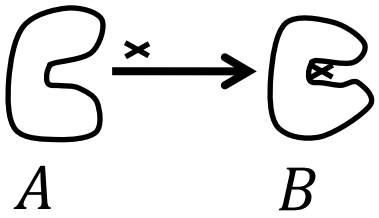
work done A to B

- free energy change
  - look at either state
    - real world automatically includes entropy

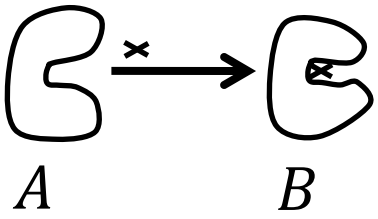


work going from unbound →bound

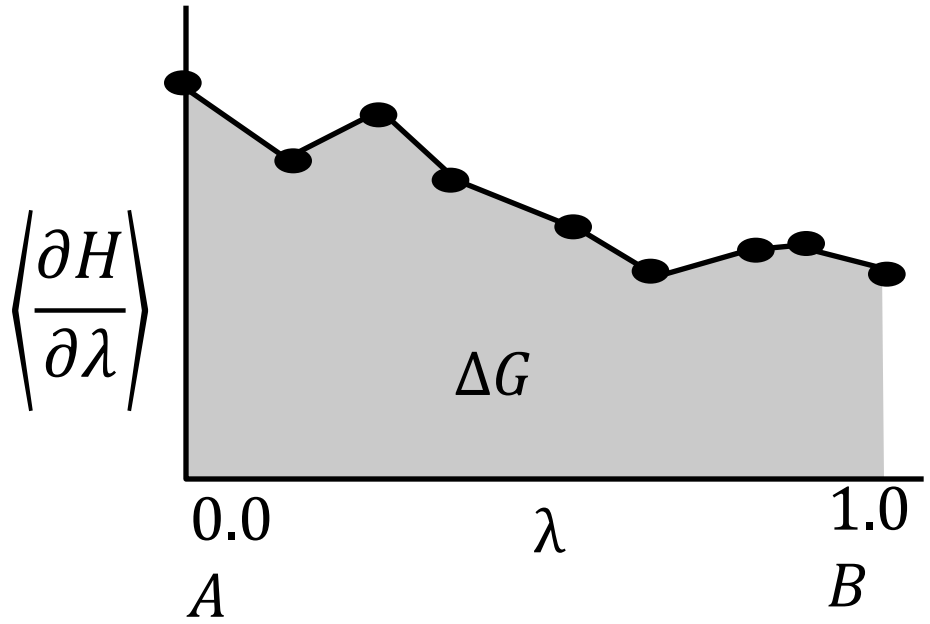
- ΔG_{AB}
- what is B ? what is A ?
  - more later
- measuring work ?



Work and free energy



Measure the work needed to move from A to B



where H is again Hamiltonian (E_{kin} + E_{pot})

$$\Delta G = \int_A^B \left\langle \frac{\partial H(\mathbf{p},\mathbf{r})}{\partial \lambda} \right\rangle_\lambda d\lambda \quad \text{or} \quad \Delta G = \sum_{i=0}^{N_{step}} (H_{i+1} - H_i)$$

Binding energy - feasibility

Would this approach work ?

$\left\langle {}^{\partial H}/_{\partial \lambda} \right\rangle$must be a good average (lots of fluctuations)

must change λ slowly

Chemistry problems: your simulation would

- get averages with all water molecules
- gradually remove water molecules (high energy ?)
- find the correct binding
- get good averaging there

- states A and B are very different they must be well sampled
- intermediate (higher energy states) must also be sampled
- does not work well in practice

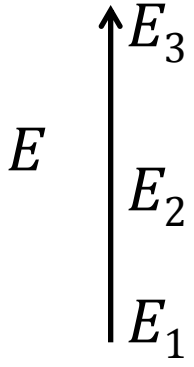
Paths / Energy differences (detour)

Problem – the path is too difficult – changes too big

- Energy differences depend on end states – not paths
- Look at $\Delta E_{1,2} = E_1 - E_2$
  - would it matter if we go $E_1 \rightarrow E_3 \rightarrow E_2$?

Can we take even stranger paths ?

- go through non existent E_4 ?
  - no problem



Same reasoning applies to free energies

Applying different paths

Originally wanted (ligand A or B, protein P)

$A + P \leftrightarrow AP$ $\quad \Delta G_A$

what if I know $B + P \leftrightarrow BP$? $\quad \Delta G_B$

$\Delta\Delta G_{AB}$ is easier

$$\Delta\Delta G_{AB} = \Delta G_A - \Delta G_B$$

$$A + P \xrightarrow{\Delta G_A} AP$$

what would $\Delta\Delta G_{AB}$ mean ?

- what is relative binding strength ?

$$B + P \xrightarrow{\Delta G_B} BP$$

Alternative routes

$\Delta\ G_A$ and $\Delta\ G_B$ too hard

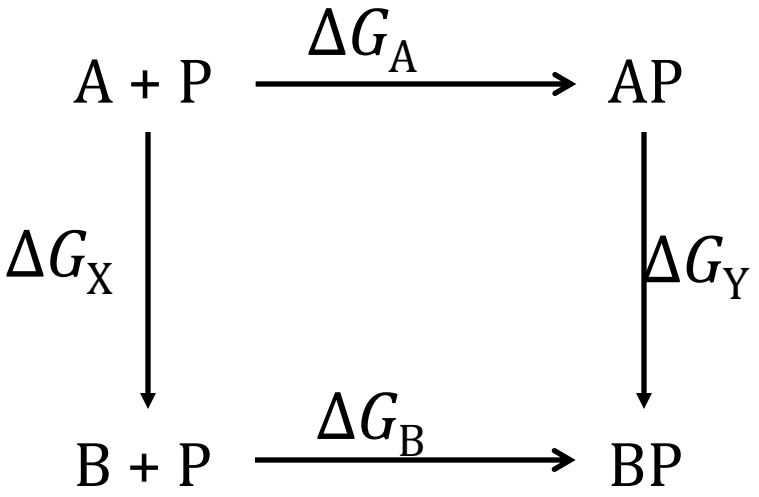
- we would be happy with $\Delta\ \Delta G_{AB}$

$$\Delta G_A + \Delta G_Y = \Delta G_B + \Delta G_X$$

$$\Delta G_A - \Delta G_B = \Delta G_X - \Delta G_Y$$ remember $\Delta\Delta\ G_{AB} = \Delta G_A - \Delta G_B$

So $\Delta\Delta G_{AB} = \Delta\Delta G_{XY}$

- why ΔG_X easier ?
- why ΔG_Y easier ?



Easier free energy changes

if A/B are rather similar

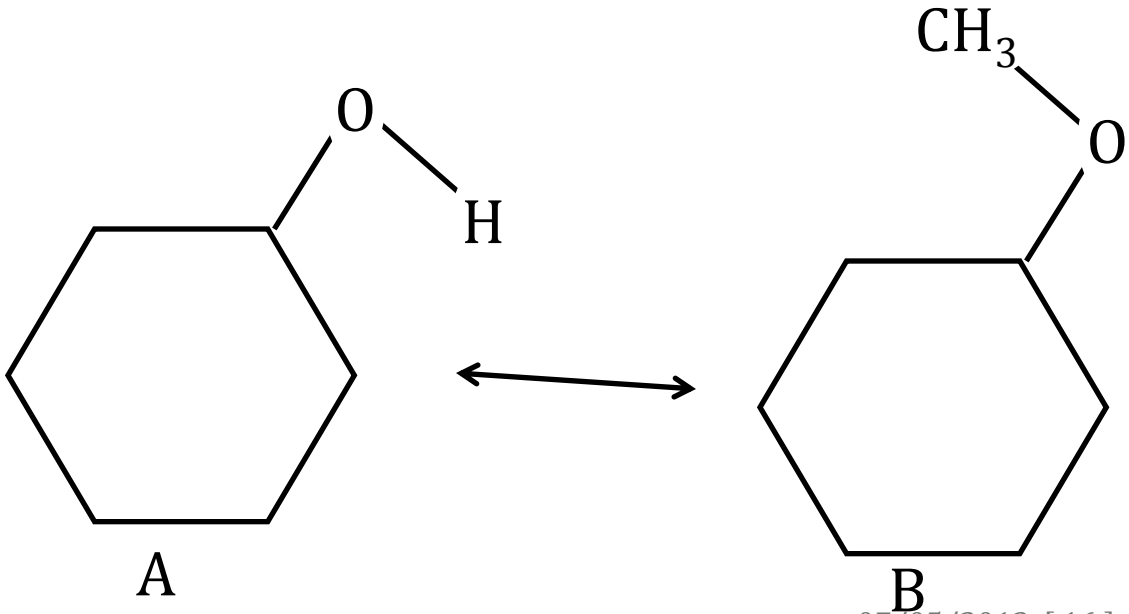
AP ↔ BP or

B + P ↔ A + P (free A ↔ B)

- are small changes – smaller than
  - removing water order, removing water energy, finding protein…

Example

- small change

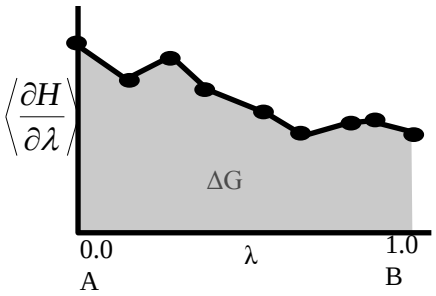


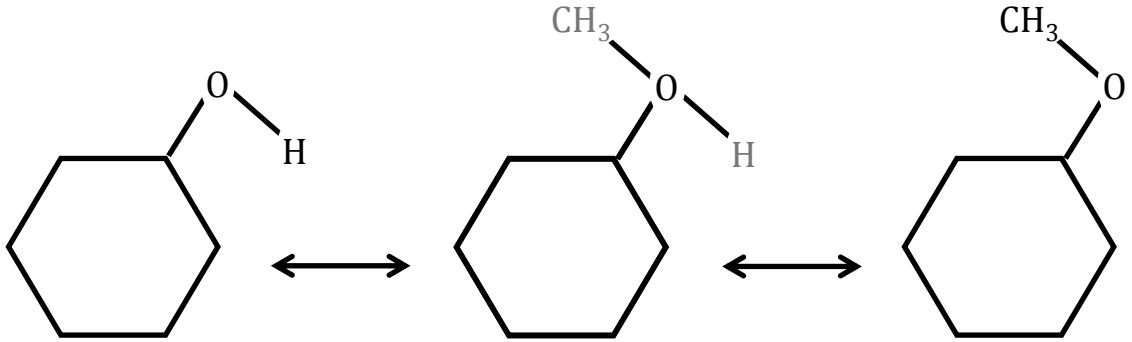
Fictitious states

remember formula $\Delta G = \int_A^B \left\langle \frac{\partial H(\mathbf{p},\mathbf{r})}{\partial \lambda} \right\rangle_\lambda d\lambda$

or $\Delta G = \sum_{i=0}^{N_{step}} (H_{i+1} - H_i)$

we need to make chemistry a function of λ





A
λ=0

A/B
λ=0.5

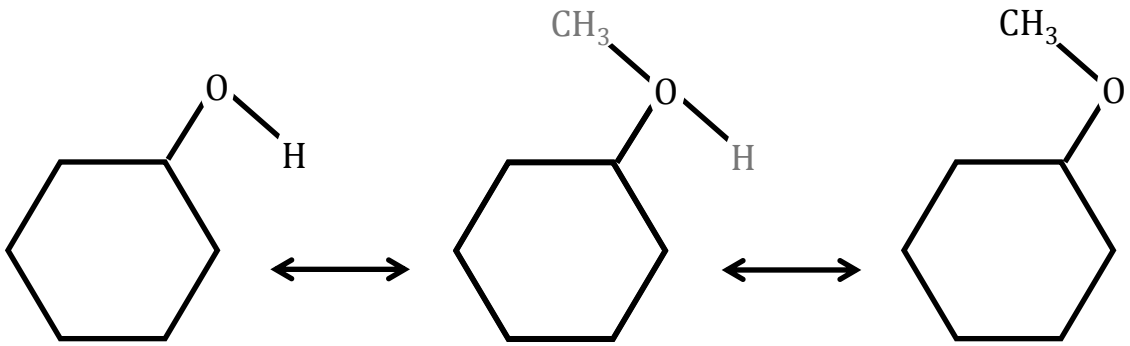
B
λ=1

Fictitious states

- remember formulae

$$\Delta G = \int_A^B \left\langle \frac{\partial H(\mathbf{p},\mathbf{r})}{\partial \lambda} \right\rangle_\lambda d\lambda \quad \text{and} \quad \Delta G = \sum_{i=0}^{N_{step}} (H_{i+1} - H_i)$$

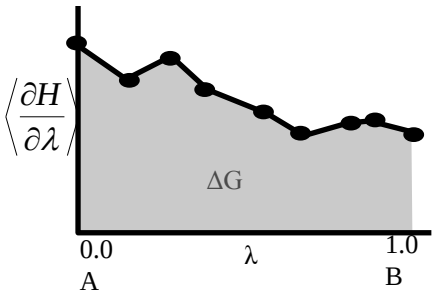
- make chemistry a function of λ



A
λ=0

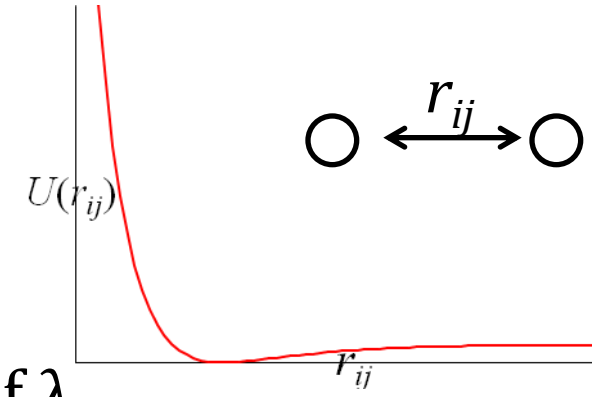
A/B
λ=0.5

B
λ=1

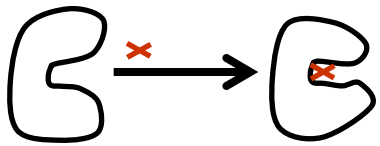


λ dependence

- λ = 0 an OH group
- λ = 1 an OCH_3 group
- λ = 0.5
  - charge of H – half of original charge
  - radius / size (σ, ε) half of real value and so on
  - atoms gradually
    - appear in one direction
    - disappear in other
- description of system is now function of λ

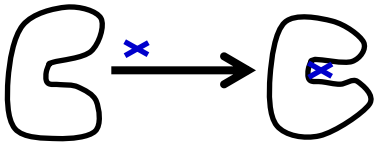


λ dependent simulations



Two simulations necessary

- λ from 0.0 ↔ 1.0 in protein
- λ from 0.0 ↔ 1.0 in water
- both from red ↔ blue



As λ slowly moves from 0.0

- water gradually feels more/less influence of some atoms
- system should not have to rearrange itself too much

When does method work best ?

- when changes are small
  - comparison of similar ligands in a protein

Summary of free energy calculations

From first principles: free energy differences, equilibria

- easy to calculate
- in practice impossible (sampling not possible)

Forget absolute free energies

- ΔG determine most phenomena in the world

Processes like binding still too difficult to simulate

- slow, too many conformations / states to visit

Most calculations use $\Delta\Delta G$

- aim to get relative binding strengths

Simulated Annealing

Classic reference – in stine

Basic tools

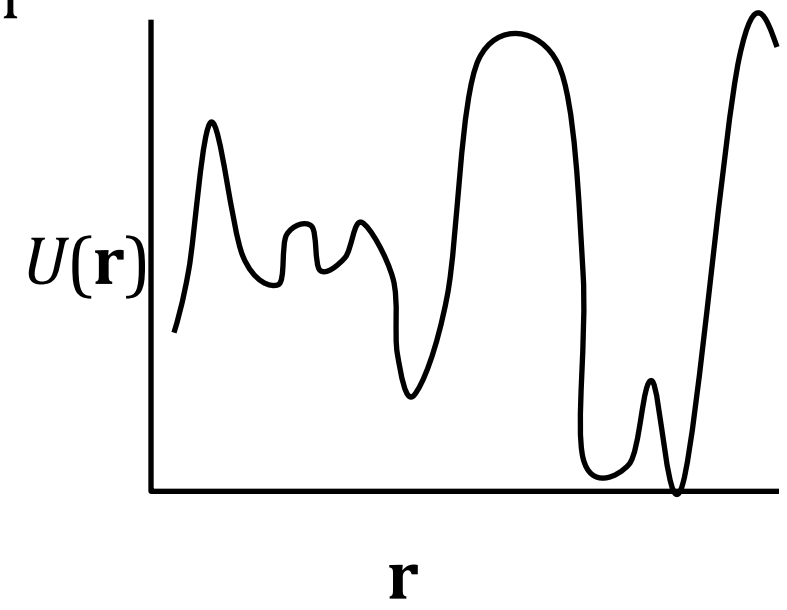
- MC or MD
  - with control of temperature (temperature bath)

Use : difficult optimisation problem

- chip layout
- travelling salesman problem
- protein structure

Optimisation problem

- several dimensional (2 to 2 000)
- many local minima



Kirkpatrick, Gelatt and Vecchi, Science, 220, 671-680, "Optimization by Simulated Annealing" (1983)

Procedure

while ($T > T_{end}$)

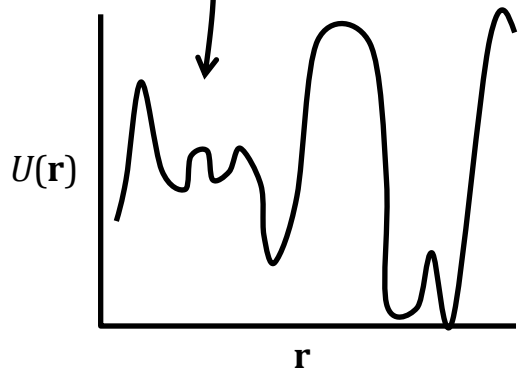
$T(t) = T_0 \, e^{-ct}$

move system (Monte Carlo)

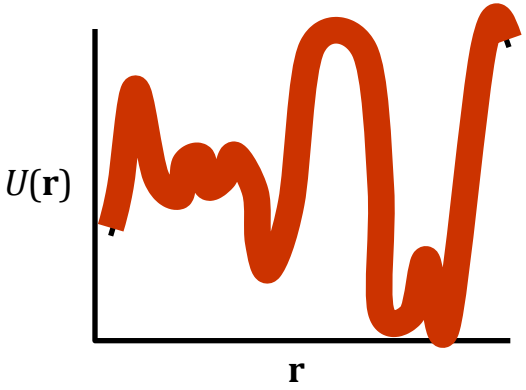
- T_0 initial temperature is hot
- c is decay rate (rate of decrease)
- cost function is
  - E_{pot} in chemistry
  - path length in travelling salesman
  - board cost in chip layout problem …
- why may this work ?

Simulated Annealing concept

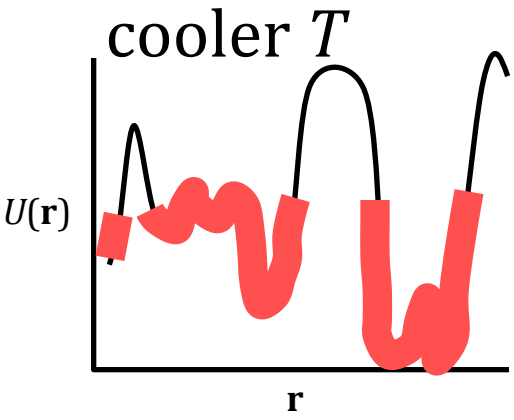
initial (poor) guess



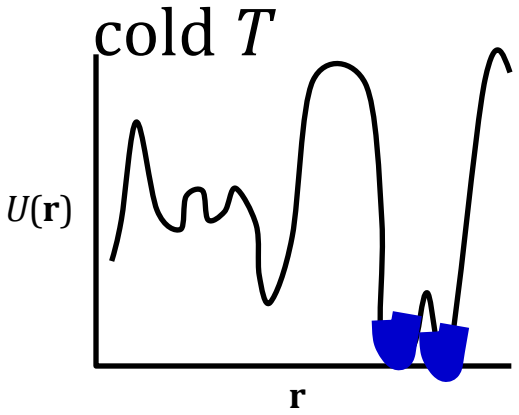
initial high T distribution



cooler T



cold T

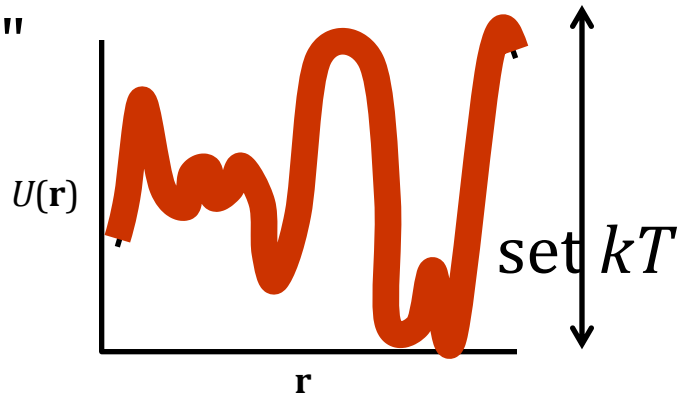


Properties, practical issues

Admit that there may not be a best solution

- not worth spending effort between many very good solutions

Some problems have "phase transitions"



How hot should T_0 be ?

- infinite ? No : look at barriers

How slow should cooling be (c) ?

- system should be at equilibrium
- very slow

Cool exponentially ?

- best first guess
- should certainly cool more slowly at transition points

Anneal with MC or MD ?

Historic use of Monte Carlo

- easiest to apply to many problems

Use MD ?

- provides expected advantages (efficiency)
- uses available gradient / derivative information

Implementation

  - Couple to temperature bath, make *T* time dependent

Use in practice ?

- simulated annealing in
  - most MD codes, refinement packages, …

Refinement of Structures (NMR / X-ray)

- Story from first semester

Problem : generate protein coordinates from NMR information (or X-ray)

- distance geometry gives an initial guess, but
  - distance geometry methods spread error across all distances
  - errors are spread across bonds, measured distances
  - chirality may be broken (causes distance problems)

Belief

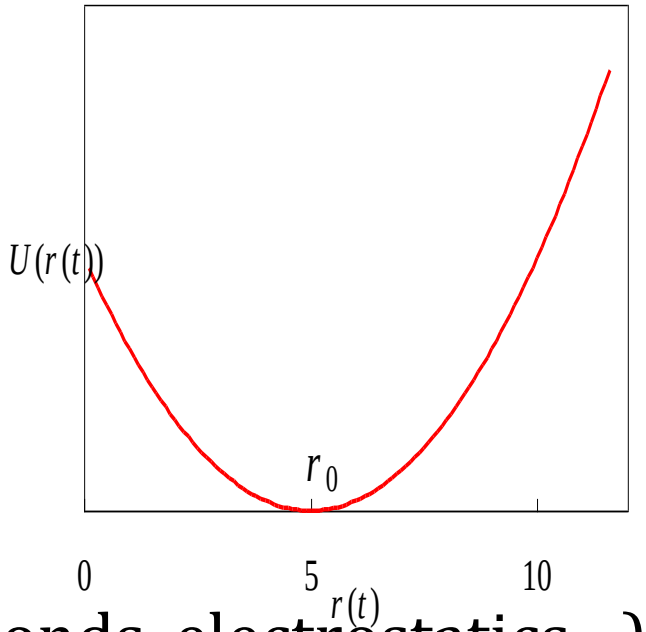
- coordinates are not bad, but could be improved

Pseudo – energy terms

For some distance measurement *i* between some pair of atoms

- r_0 measured distance
- $r(t)$ distance between particles at time (t)
- say $U_i(r) = c_i\,(r(t) - r_0)^2$
- add this to normal force field

$$U_{tot}(\mathbf{r}) = U_{phys}(\mathbf{r}) + \sum_{i=1}^{N_{restraints}} U_i(\mathbf{r})$$



$U_{phys}(\mathbf{r})$ normal force field - atomistic (bonds, electrostatics…)

result ?

System moves to low energy + low fake energy

- gradually moves to agree with experimental data

Practical issues $U_{tot}(\mathbf{r}) = U_{phys}(\mathbf{r}) + \sum_{i=1}^{N restraints} U_i(\mathbf{r})$

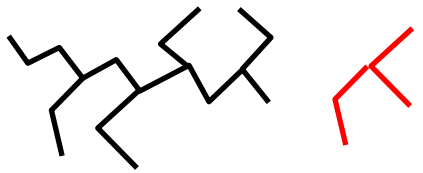
$U_i(r) = c_i\,(r(t) - r_0)^2$

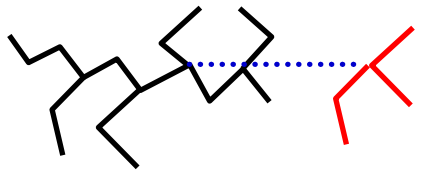
- big c very artificial
- small c system will be slightly biased to agree with experimental data

Fake Energies

Fake energies for many purposes

- Refinement of
  - X-ray structures (common)
  - NMR (often)
  - others: microwave spectroscopy, …
- Modelling problems
- you want to put a bond in a model
  - putting it in directly
    - high energy bond
    - system stuck in minimum
  - introduce a distance restraint
    - gradually increase associated constant *c*





Summary

What one can do with related methods

- look at timescales of motions (very superficial)
- free energy calculations – important for problems such as binding of ligands
- simulated annealing – methods used as minimizers, not necessarily to get an ensemble
- pseudo-(potential) energies (X-ray, NMR, …)