Applications – MD / MC

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Basic tools

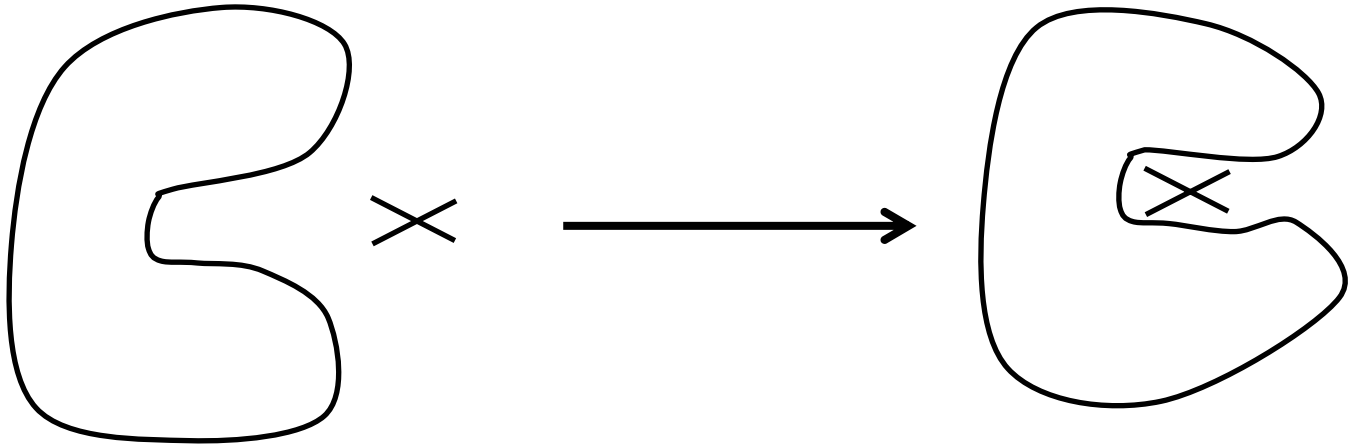
- Force field
- MD / MC

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 $A(t) = A(0)\, e^{-t/\tau}$
    - relaxation time
    - characteristic time
- times in proteins…

Some 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 – 5	-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

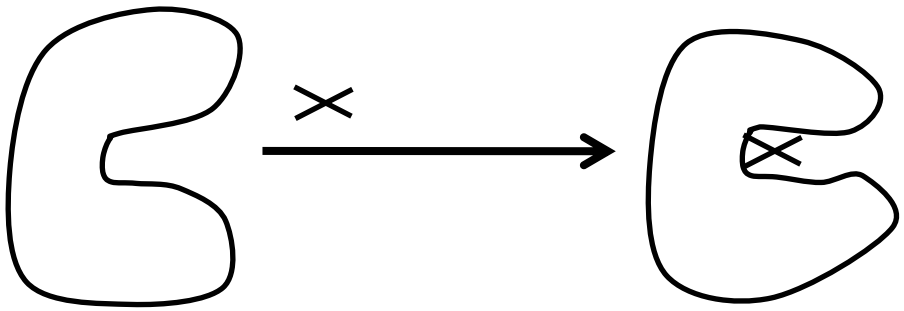
- Typical big simulation ≈ 1ns = 10^{-9}s
- Imagine event with characteristic time 10^{-9}s
  - may or may not be seen
- consider time 10^{-10} s
  - may be seen a few times
- What you would like
  - 100's or 1000's of observations
- Limits of timescales
  - fast events $\tau \ll t_{simulation}$ OK
  - 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 drug efficacy

$$k_d = \frac{[\text{drug}][\text{protein}]}{[\text{drug - protein}]}$$

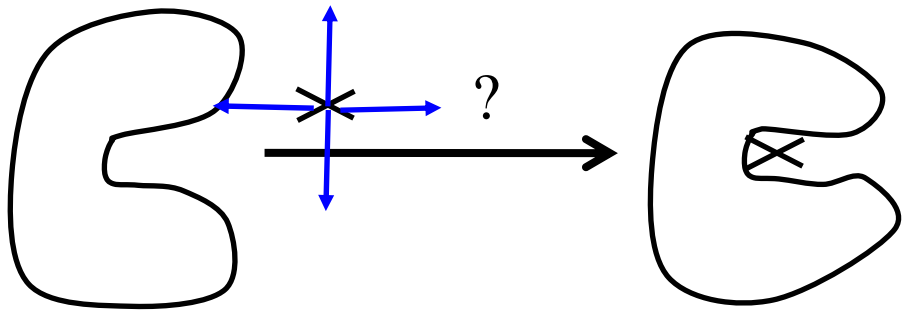
$$= RT \ln \Delta G$$



- 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 ?

Free simulation for binding

- if we simulate, where will the ligand go ?

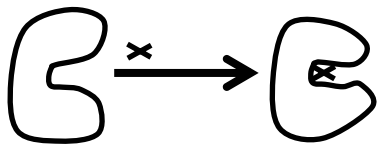


- may take years for ligand to find protein
- short cut ?
  - force ligand to protein
    - artificial force + corrections
    - very difficult – still requires rearranging water
    - entropy estimation very difficult

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

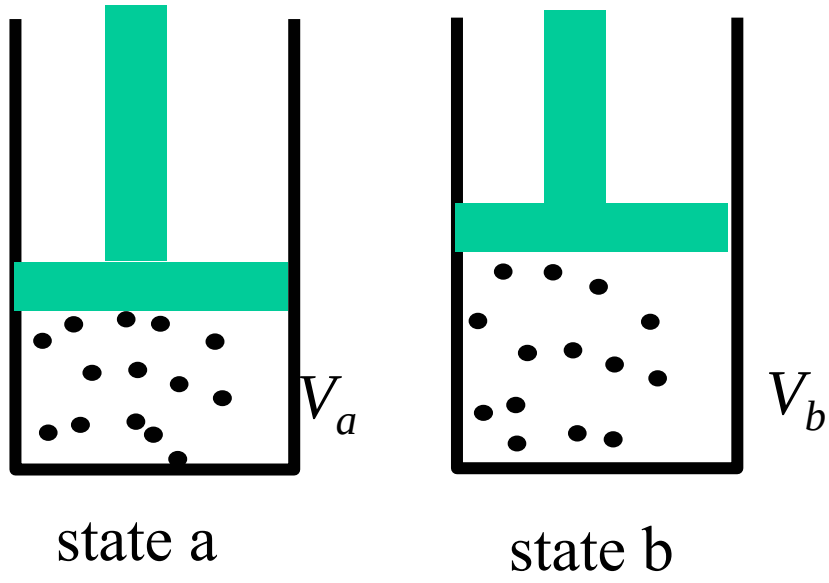
- forget absolute free energies
  - concentrate on ΔG
  - no problem – usually interesting property



Work and free energy changes

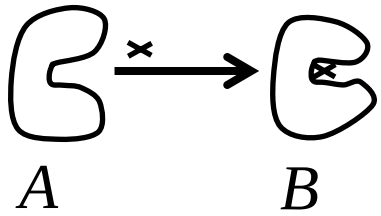
work done A to B

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

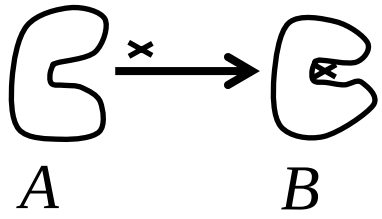


work going from unbound →bound

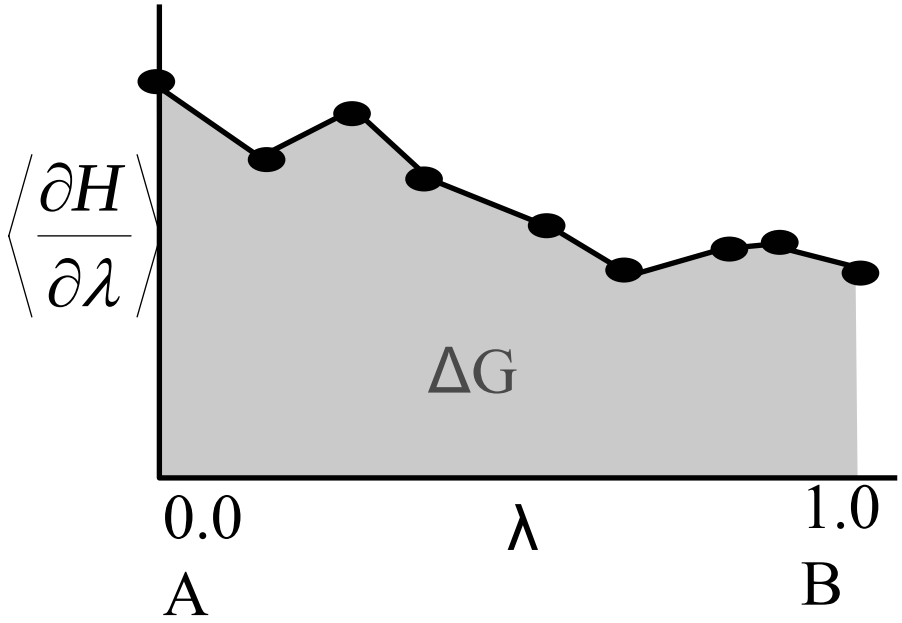
- ΔG_{AB}
- what is B ? what is A ?
  - more later
- measuring work ?



Work and free energy



- measure the work needed to move from A to B



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

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

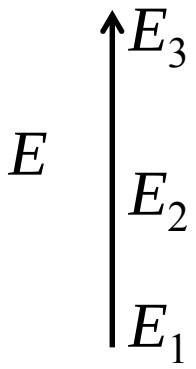
Binding energy - feasibility

- Would this approach work ?
  - $\langle \partial H/\partial \lambda \rangle$ 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)
  - $A + P \leftrightarrow AP$ ΔG_A
- what if I know $B + P \leftrightarrow BP$? ΔG_B
- maybe $\Delta\Delta G_{AB}$ would be easier
  - $\Delta\Delta G_{AB} = \Delta G_A - \Delta G_B$

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

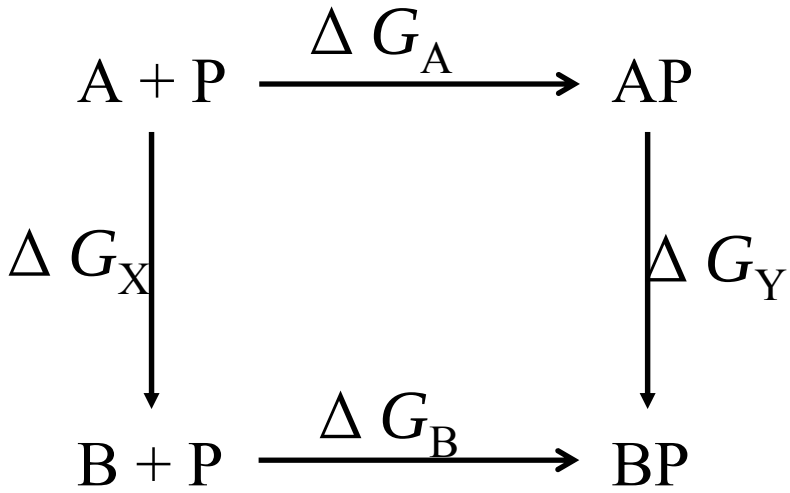
- what would $\Delta\Delta G_{AB}$ mean ?
  - what is relative binding strength ?

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

Alternative routes

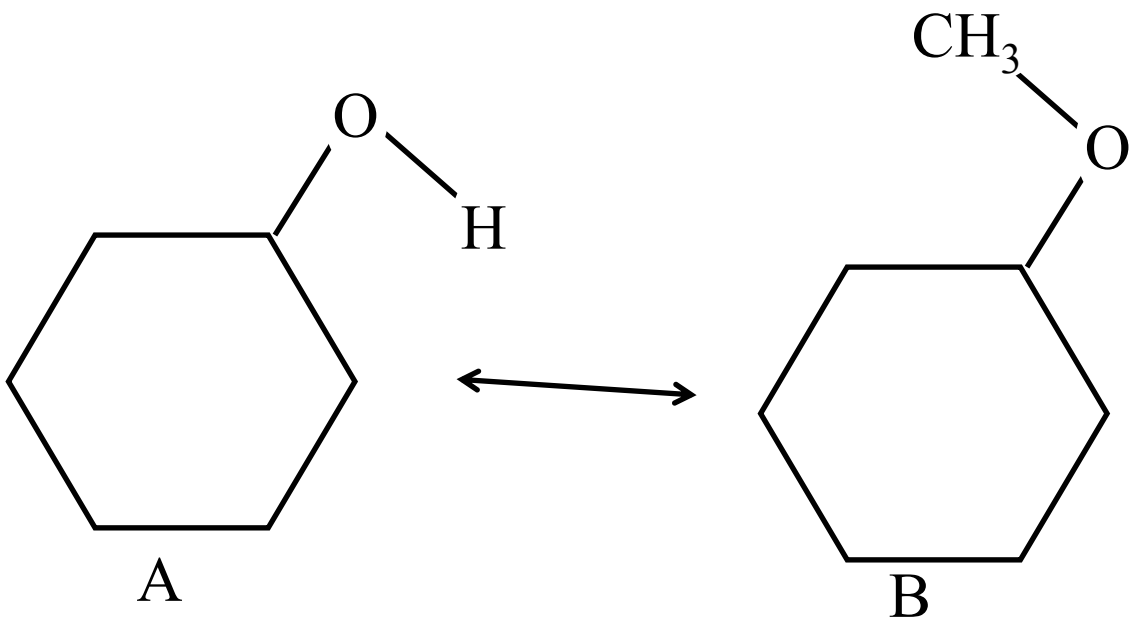
- $\Delta\, G_A$ and $\Delta\, G_B$ too hard
- we would be happy with $\Delta\, \Delta G_{AB}$
- $\Delta G_A + \Delta G_Y = \Delta G_B + \Delta G_X$
- $\Delta G_A - \Delta G_B = \Delta G_X - \Delta G_Y$ remember $\Delta\, \Delta\, G_{AB} = \Delta G_A - \Delta G_B$

- so $\Delta\, \Delta\, G_{AB} = \Delta\, \Delta\, G_{XY}$
- why $\Delta\, G_X$ easier ?
- why $\Delta\, G_Y$ 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

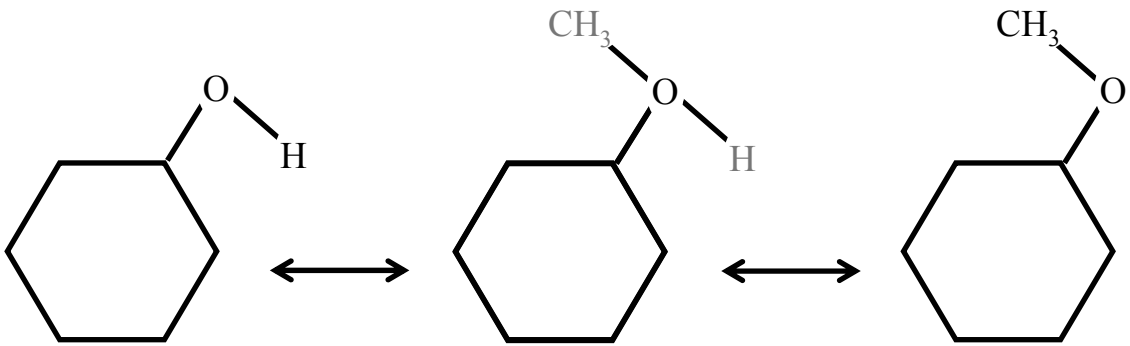


Fictitious states

- remember formulae
- we need to make chemistry a function of λ

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

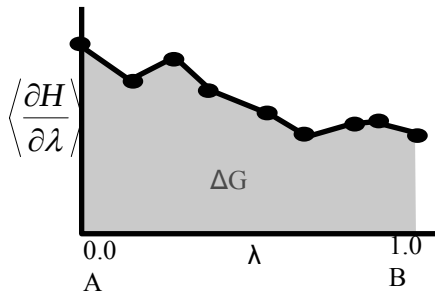
$$\Delta G = \sum_{i=0}^{N_{step}} \left(H_{i+1} - H_i \right)$$



A
λ=0

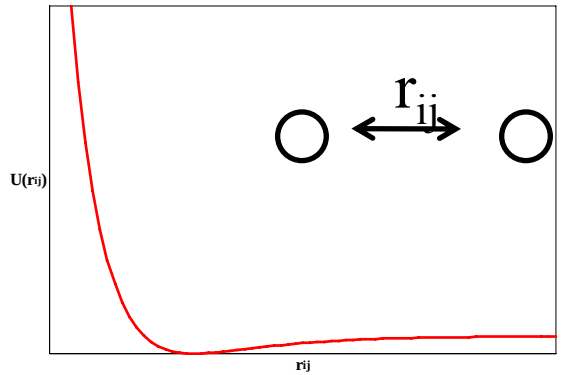
A/B
λ=0.5

B
λ=1

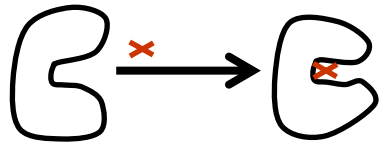


λ dependence

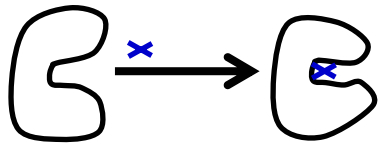
- λ = 0 an OH group
- λ = 1 an OCH_3 group
- λ = 0.5
  - charge of H – half of original charge
  - radius / size (σ, ε) half of real value and so on
  - atoms gradually
    - appear in one direction
    - disappear in other
- description of system is now function of λ



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



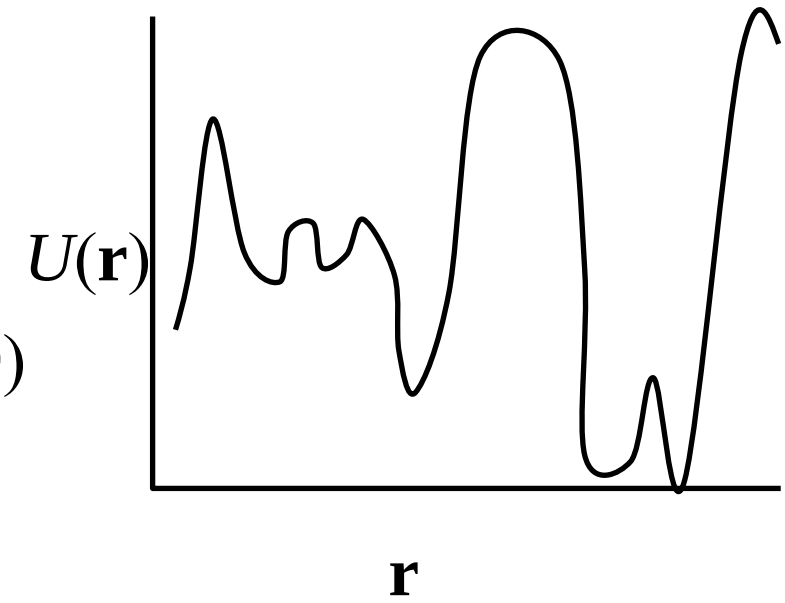
- As λ slowly moves from 0.0
  - water gradually feels more/less influence of some atoms
  - system should not have to rearrange itself too much
- when does method work best ?
  - when changes are small
    - comparison of similar ligands in a protein

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 these days use $\Delta\Delta G$
  - aim to get relative binding strengths

Simulated Annealing

- Classic reference – separate handout / not on web (naughty)
- Basic tools
  - MC or MD with control of temperature
- 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)

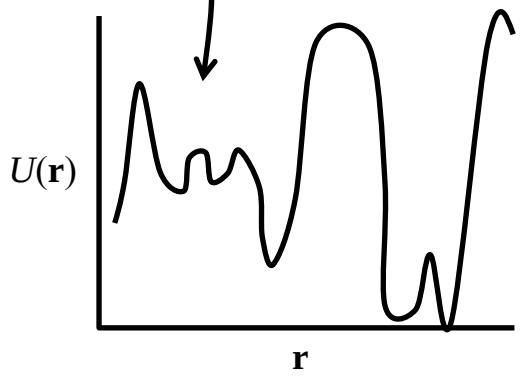
Procedure

```
while (T > T_end)
   T(t) = T_0 e^(-ct)
   move system (Monte Carlo)
```

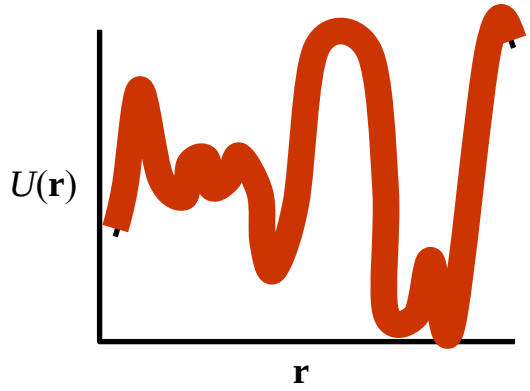
- T_0 initial temperature is hot
- c is decay rate (rate of decrease)
- cost function is
  - E_{pot} in chemistry
  - path length in travelling salesman
  - board cost in chip layout problem …
- why may this work ?

Simulated Annealing concept

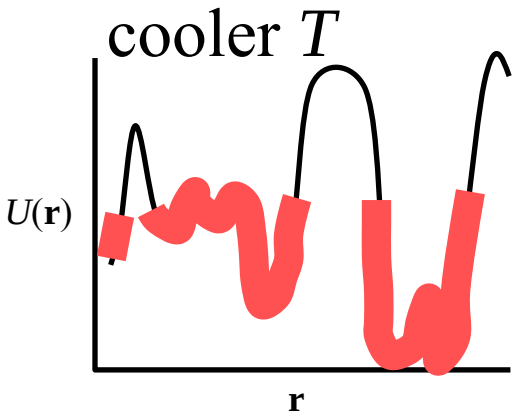
initial (poor) guess



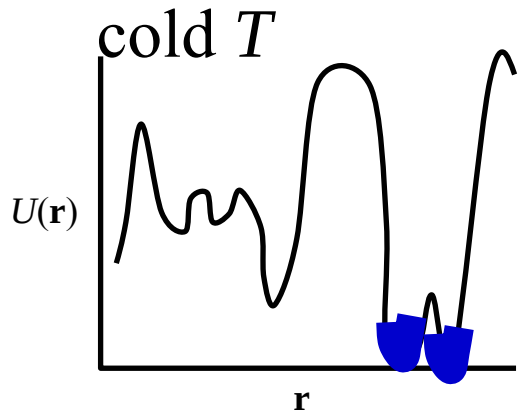
initial high T distribution



cooler T



cold T

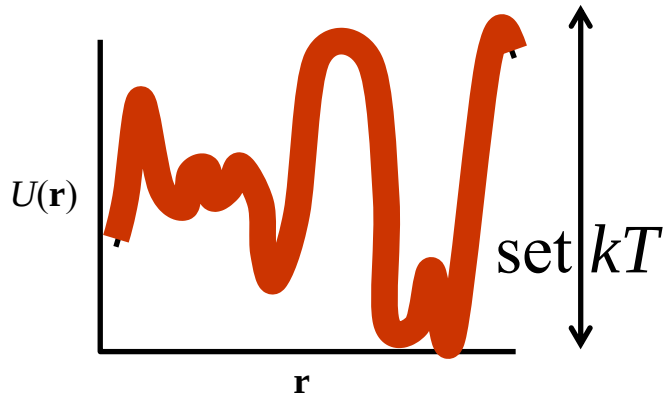


Properties, practical issues

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)

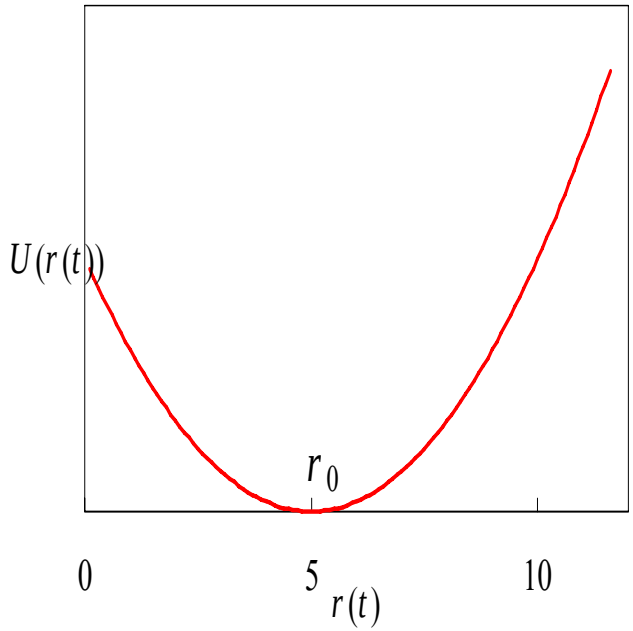
- Story from first semester
- Problem : generate protein coordinates from NMR information (or X-ray)
  - distance geometry gives an initial guess, but
    - distance geometry methods spread error across all distances
    - errors are spread across bonds, measured distances
    - chirality may be broken (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

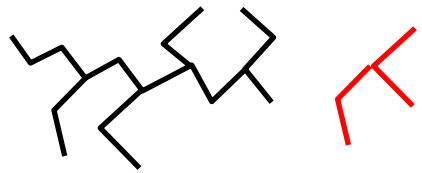
- Practical issues
- $U_i(r) = c_i\,(r(t) - r_0)^2$
  - big c very artificial
  - small c system will be slightly biased to agree with experimental data

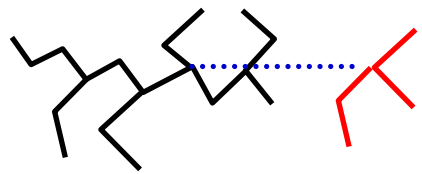
$$U_{tot}(\mathbf{r}) = U_{physical}(\mathbf{r}) + \sum_{i=1}^{N_{restraints}} U_i(\mathbf{r})$$

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, …)