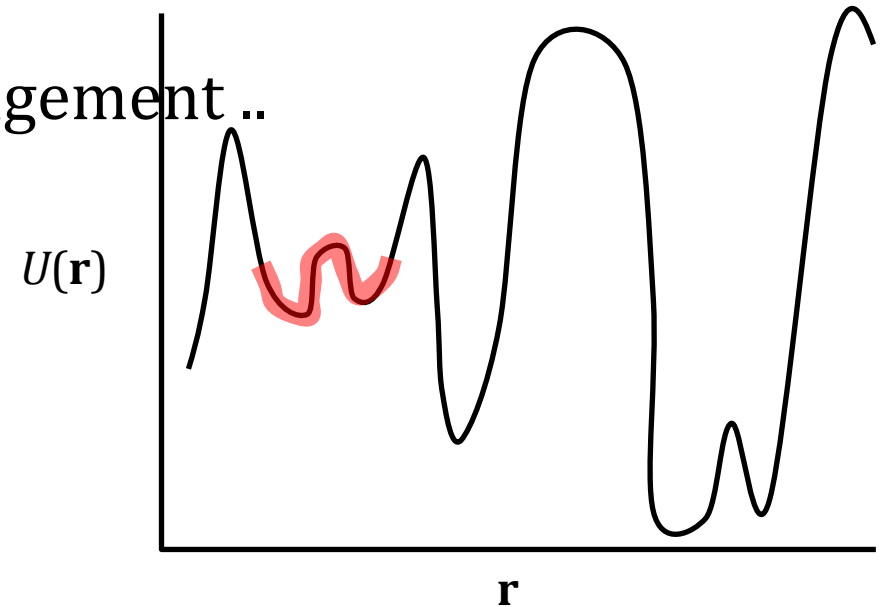


Modern Monte Carlo

Problems

- we are interested in properties at room temperature
- at room temperature, processes are slow
 - phase transitions, protein structure re-arrangement ..
 - system can be trapped
- most large moves are rejected (wasted cpu time)



Goals

Speed simulation

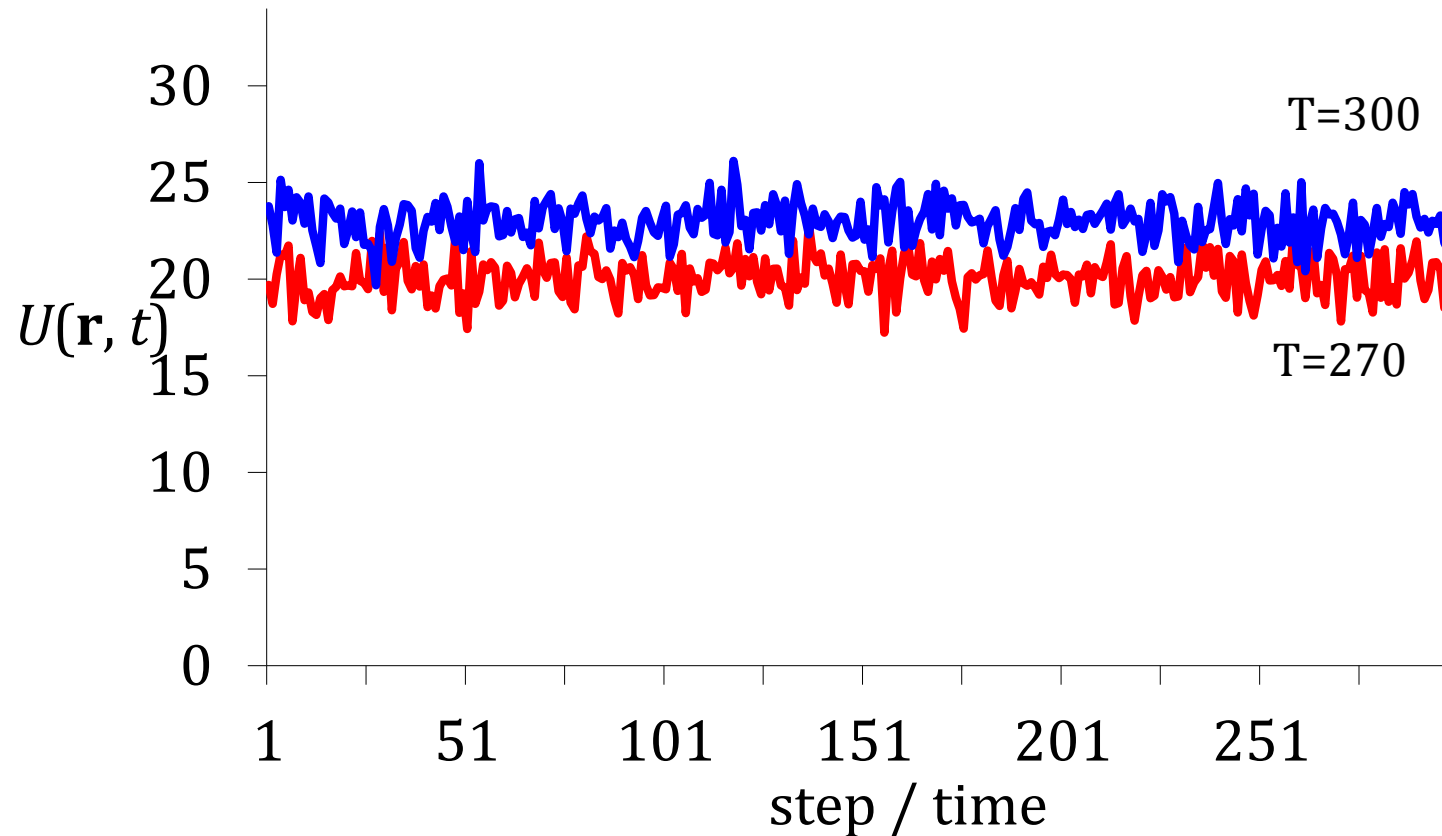
- two approaches
 - make barriers easier to pass
 - waste less time on failed moves

Restrictions

- must retain Boltzmann distribution
- must preserved detailed balance

Parallel Tempering / Replica exchange

Two simulations, two temperatures

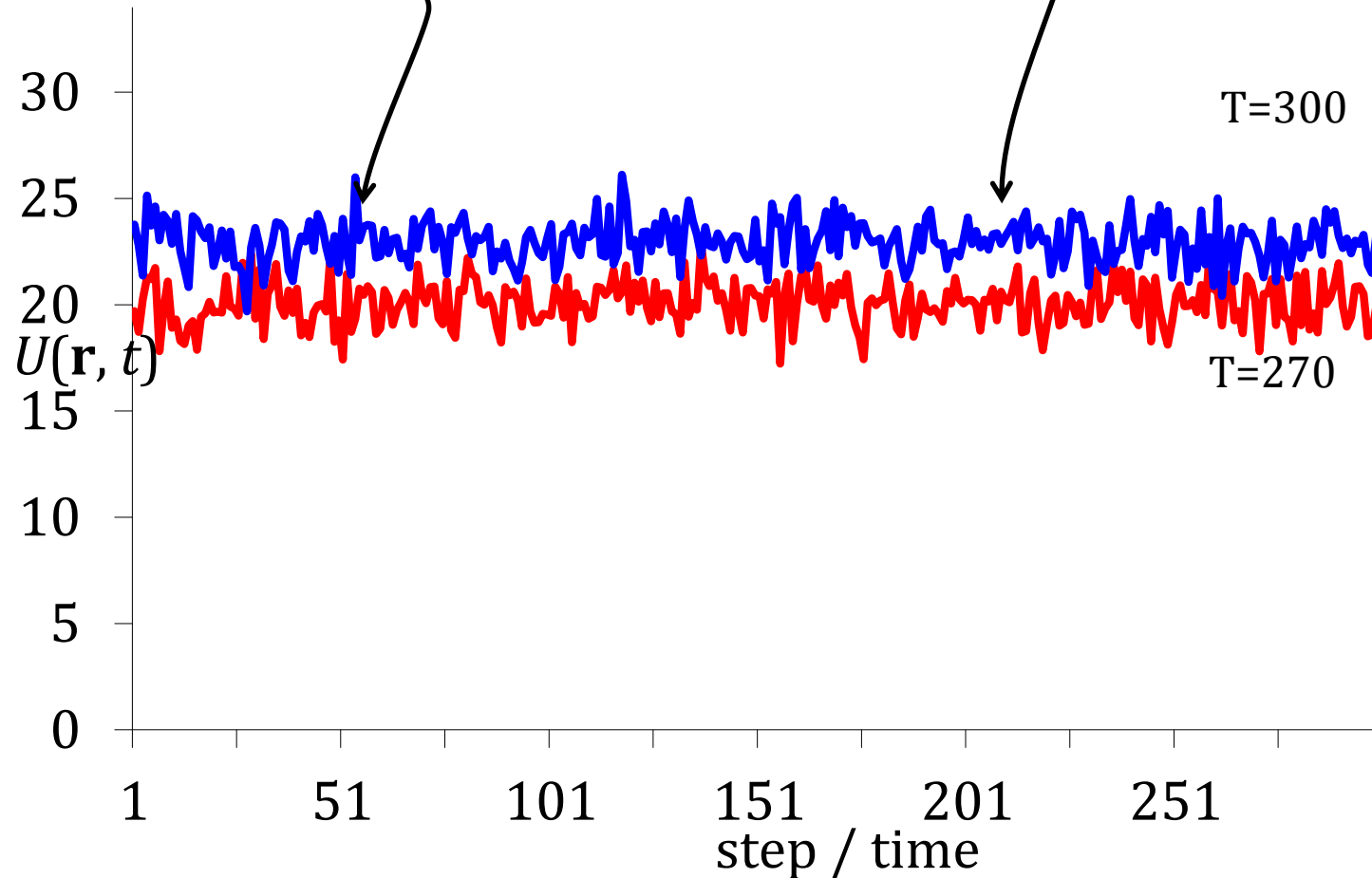


Hotter simulation moves faster, hops over barriers but

- it does not give $\langle \mathcal{A} \rangle$ for desired temperature (270 K)

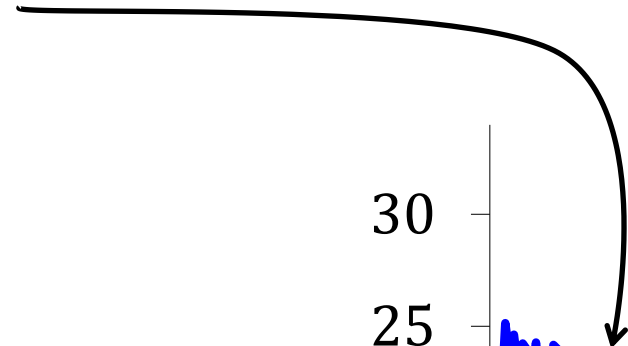
Closer temperatures

- copies of system different
- sometimes similar



swaps of copies

Try swapping here

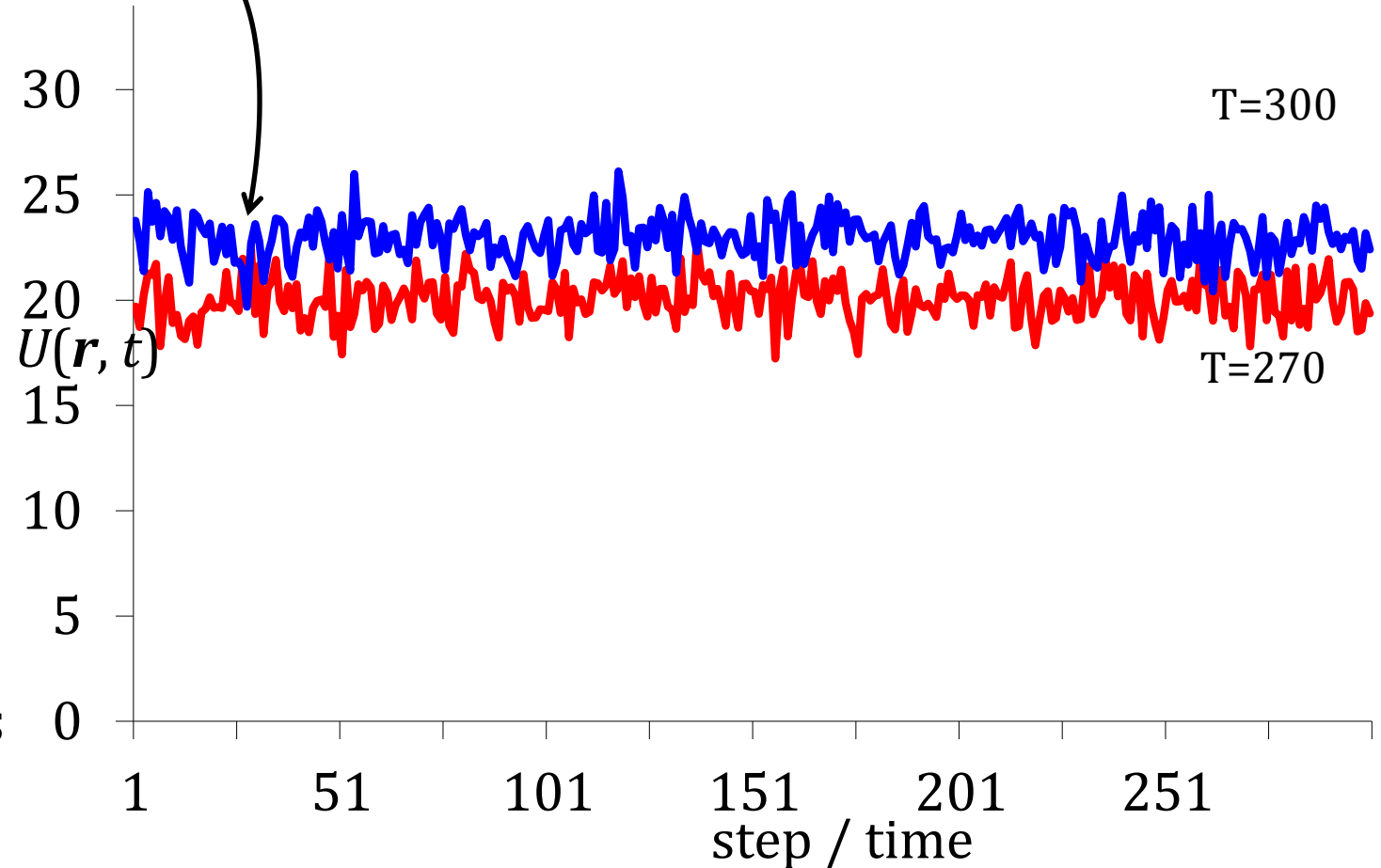


Energy

- no problem

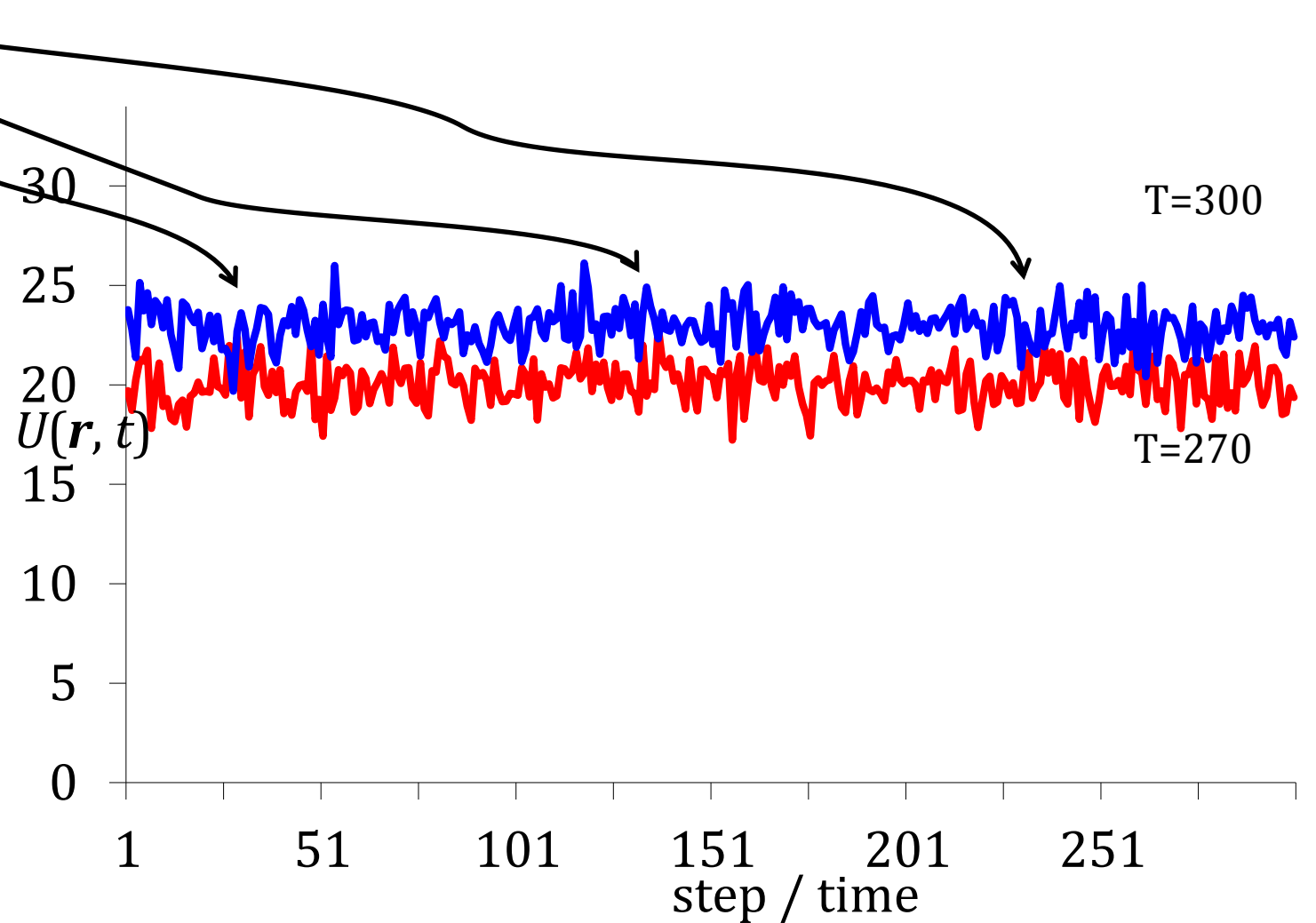
Effect ?

- we have correct energy of red system, but it has been hotter
 - more likely to cross barriers



easy swaps

Try swapping here



if $E_{hot} < E_{cold}$

- no problem to swap copies

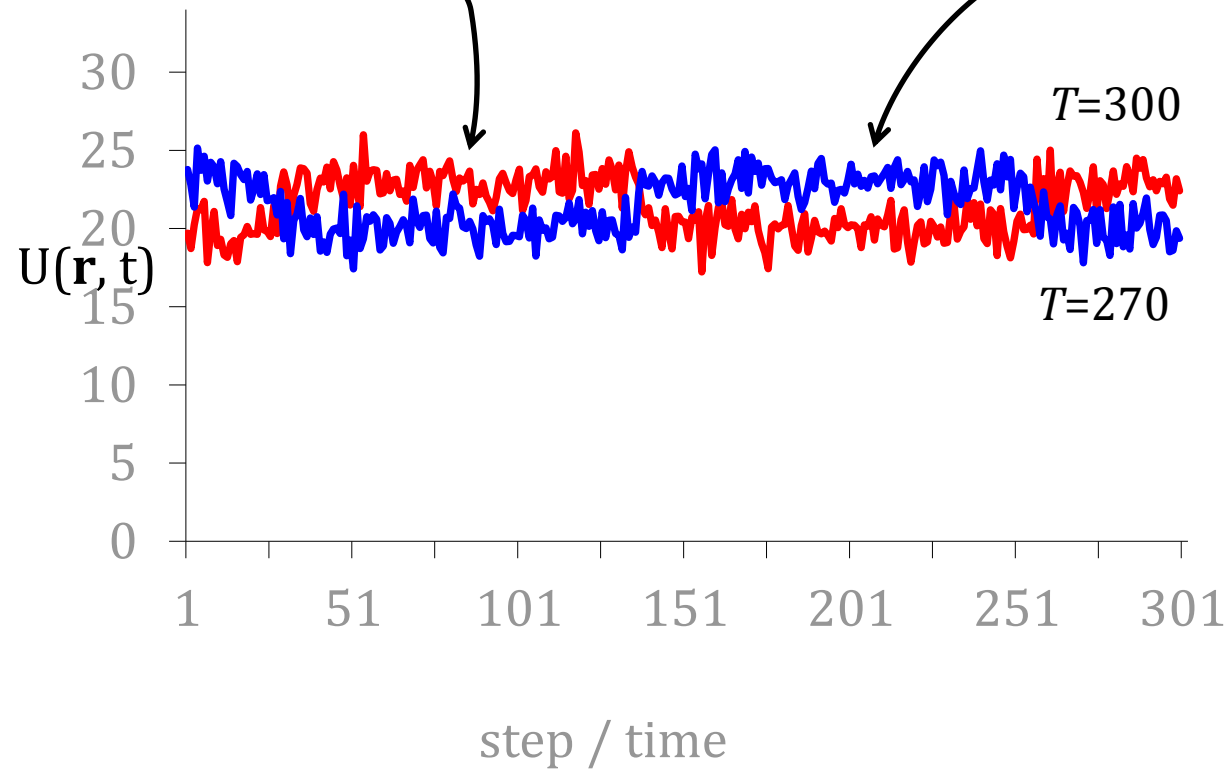
possible swaps

$E_{blue} < E_{red}$ but not by much

- swapping possible

$E_{blue} \gg E_{red}$

- swapping not likely



so if $\Delta E < 0$

- no problem

if $\Delta E > 0$

- small ? possible
- big ? less likely

Probability of a total system

- probability of one system i $p_i = \frac{e^{-E_i/kT_i}}{Z_i}$

- probability of whole system

$$\begin{aligned} p_{old} = p_i p_j &= \frac{e^{-E_i/kT_i}}{Z_i} \frac{e^{-E_j/kT_j}}{Z_j} \\ &= \frac{e^{\left(\frac{-E_i}{kT_i} + \frac{-E_j}{kT_j}\right)}}{Z_i Z_j} \end{aligned}$$

- probability of system before and after swap ? $\frac{p_{new}}{p_{old}}$
- Z 's will cancel

Exchange Probability

Question

- could the blue be part of the red ensemble ?
- could the red be part of the blue ensemble ?

Depends on temperatures, ΔE

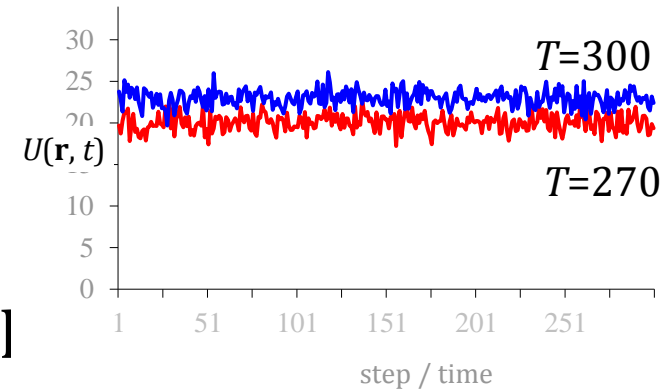
$$p_{\text{swap}} = \exp\left(\frac{E_j - E_i}{k(T_i - T_j)}\right)$$

if $p_{\text{swap}} > 1$

- accept

else use random number $[0..1]$ and compare with

- consider $E_j \approx E_i$
- blue bit higher than red (moves likely)
- blue much higher than red (moves very unlikely)



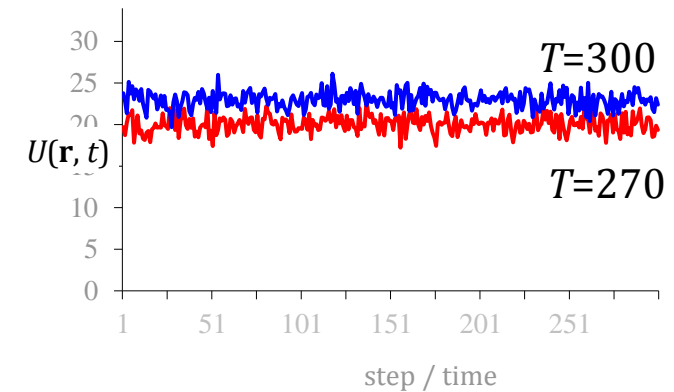
Implementing

Example

- try 100 moves normal MC of each system
- try 1 exchange / swap of systems
- swap means:
 - in MC steps ($e^{-\Delta E/kT}$) change T_1 and T_2

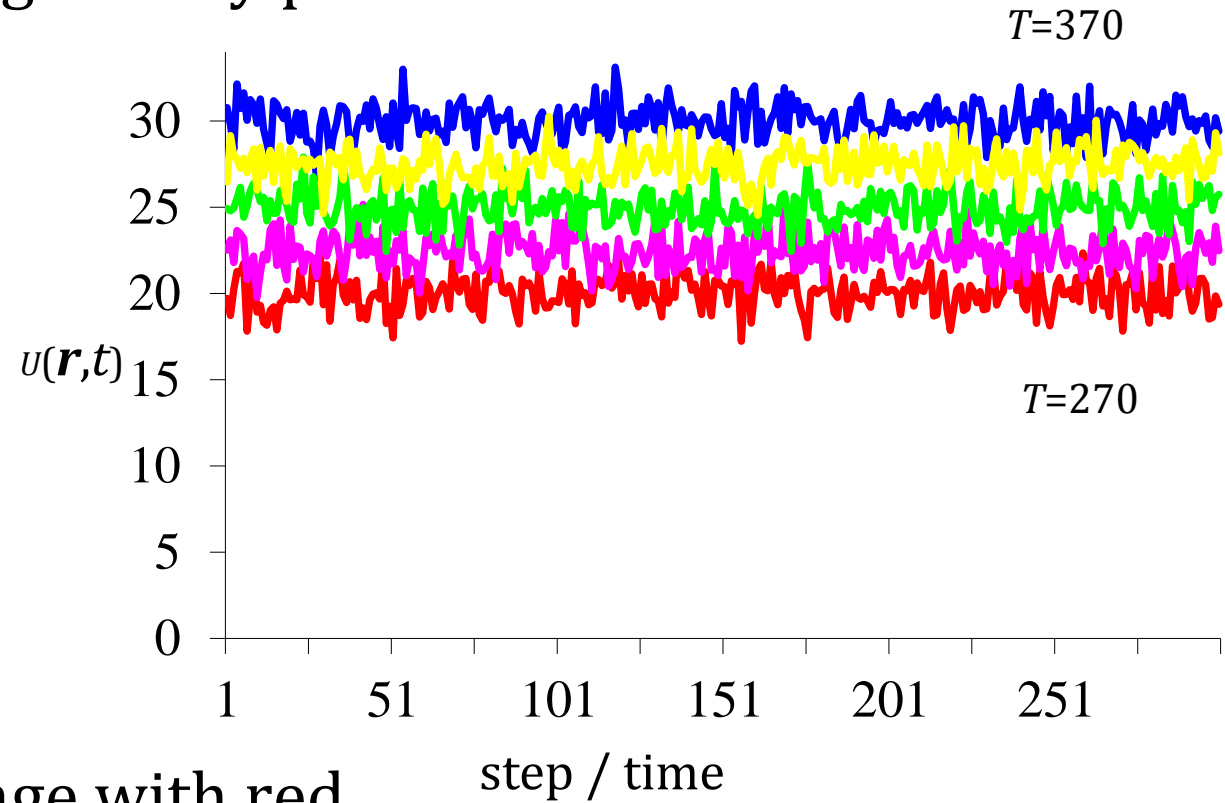
Result

- two simulations
- each has Boltzmann distribution at right temperature
- cooler system has visited high temperatures / moved faster
- generalising
 - ...



Many replicas

- run many copies, similar temperatures
- every N moves, attempt an exchange of any pair



- normally blue would never exchange with red
- now possible in several steps
- red simulation is a valid ensemble at T_{red}

Implementation

Any set of exchange attempts OK

- may not be efficient

Detail balance preserved

Easy to implement

- set up N simulations at different temperatures
- whenever a swap is successful, set T_i to T_j and T_j to T_i

Alternative perspective

- like simulated annealing but
 - annealing schedule (cooling) is automatic

Configurational Bias Monte Carlo

Rosenbluth sampling

Many Monte Carlo methods

- do not take random step
- find a low energy direction
- trial move more likely in that direction
- make acceptance probability less likely

Result

- less time spent generating unlikely moves + energy calculation

Rule

- must maintain detailed balance
- must finish with a Boltzmann distribution

Example – discrete system

Discrete Models / Chain growth moves

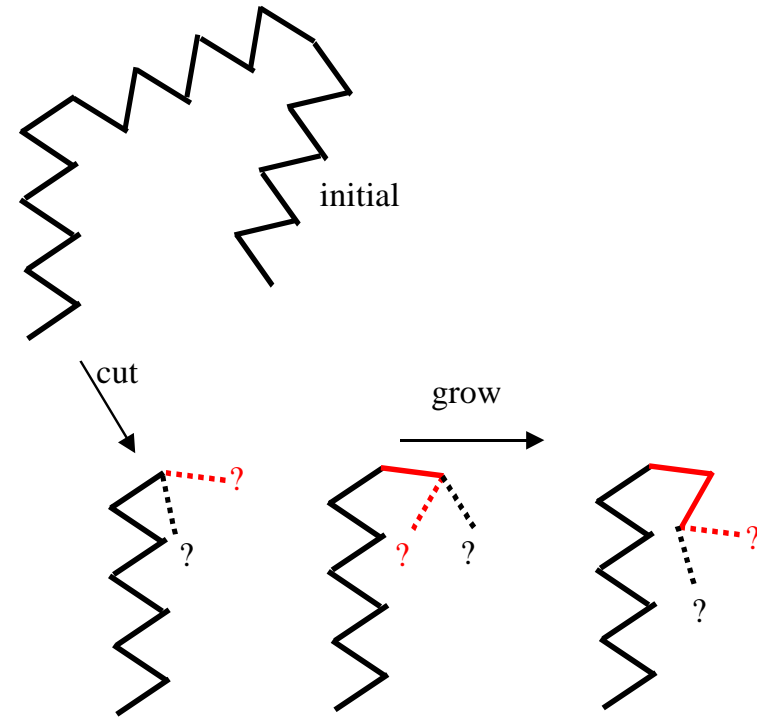
Lattice / off-lattice often easier to deal with

- particles only exist in certain places
- can only occupy certain states

Off-lattice discrete protein

Typical moves set

- pick random site in chain
 - discard one half
 - re-grow each site
-
- look at new configuration, accept/reject
 - big reorganisation possible

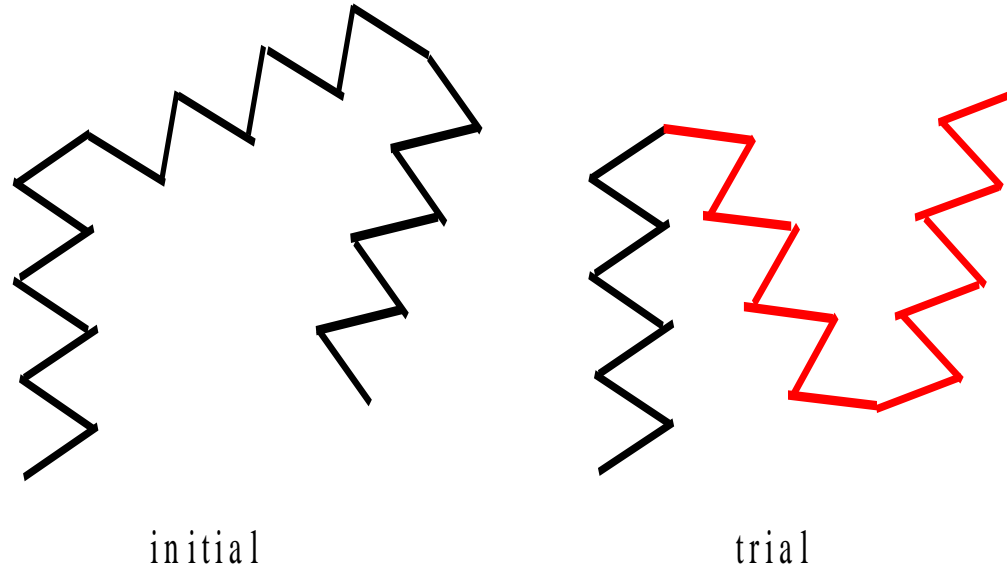


Chain regrowth methods

Moves are big, but

- in a dense system, most will be rejected

We have big moves, but consider each step



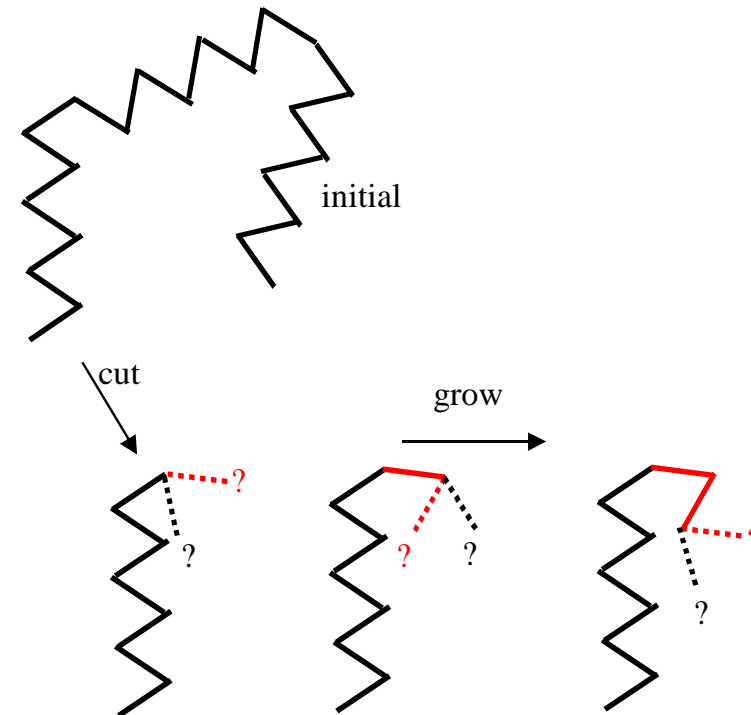
Looking at sub-moves

at first step

- one possible direction is more likely

what if we move in the more likely region ?

- we will tend to move downhill energetically
 - no Boltzmann distribution
- move $N_i \pi(i \rightarrow j) \neq N_j \pi(j \rightarrow i)$
 - detailed balance not preserved



Bias

Make downhill moves more likely

- make them more difficult to accept

Sometimes try uphill moves

- gain
 - fewer attempts at uphill moves
 - keep detailed balance + Boltzmann distribution

Next step

- do several biased moves
 - set of (probably) downhill moves

One step

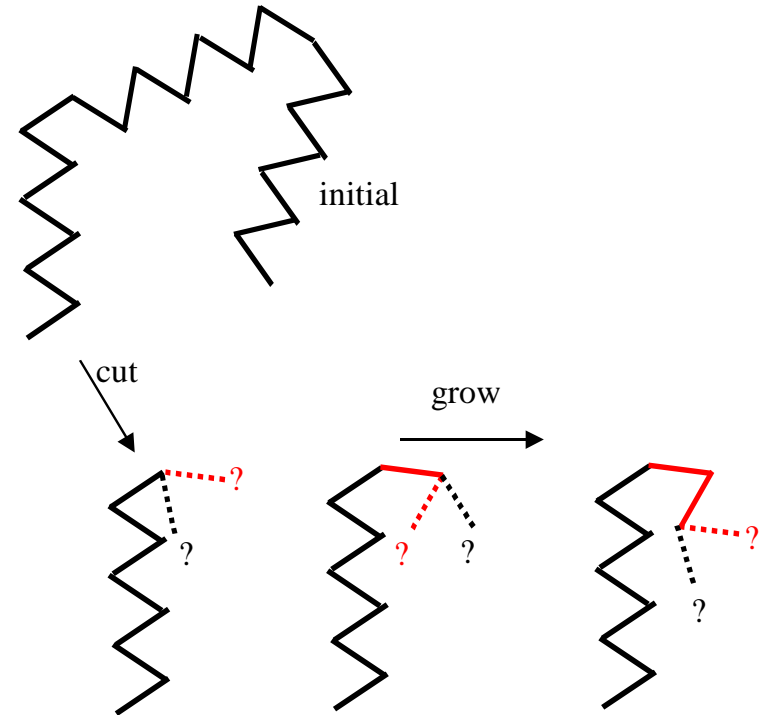
Look at red and black choices

- calculate E_{black} , E_{red} and probabilities

$$p_{black} = \frac{e^{\frac{-E_{black}}{kT}}}{\sum_i^{red, black, \dots} e^{\frac{-E_i}{kT}}}$$

$$\sum_{i=1}^{N_{choices}} p_i = 1$$

- pick a direction according to p_i
- example...



direction picking

We have three possible directions

- $p_1 = 0.2, p_2 = 0.5, p_3 = 0.3$ from Boltzmann weights

```
pick random number  $0 \leq x \leq 1$   
if  $0 \leq x < 0.2$       choose (1)  
    elseif  $x < 0.7$     choose (2)  
    else                choose (3)
```

- what have we got now ? not much yet
- usually choose single steps and preserve Boltzmann distribution

formalism

Where we have N_{choice} possible directions

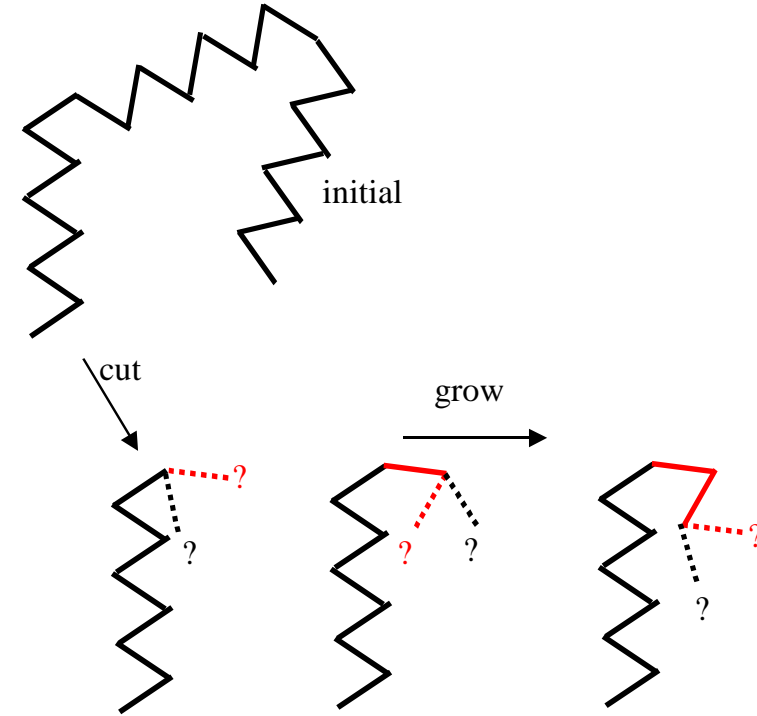
$$p_i = \frac{e^{\frac{-E_i}{kT}}}{w}$$

$$w = \sum_{j=1}^{N_{choice}} e^{\frac{-E_j}{kT}}$$

w will come back in a moment

Several Bias steps

- break chain
- pick first step with bias
- second step with bias
- ...
- chain complete
- heavily biased
 - series of N_{step} steps – usually favourable
 - without accept / reject along the way
- how to correct ?
 - introduce "Rosenbluth factor"
 - W_o (old), W_n (new / trial)



Rosenbluth factor

Rosenbluth factor W_n

$$W = \prod_{m=1}^{N_{step}} w_m$$

$$p_i = \frac{e^{\frac{-E_i}{kT}}}{w}$$

$$w = \sum_{j=1}^{N_{choice}} e^{\frac{-E_j}{kT}}$$

Rosenbluth factor W_o

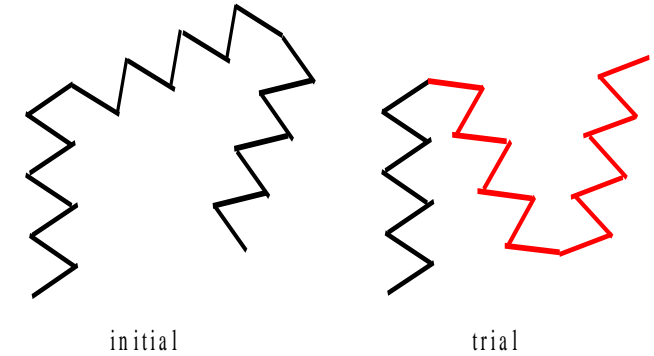
- pretend that the chain was chopped and calculate w_m for each step

Accept reject

- if $W_n/W_o > 1$ accept
- else accept with $p = W_n/W_o$

Net result ?

- take N_{step} biased moves
- fix up distribution via acceptance criterion



Practical explanation (dense protein)

- each step we put atoms in a likely place (not on top of other atoms)
- after N_{steps} we have a chain which is probably physically likely (unlikely to waste time on crazy moves)

Compare with normal Monte Carlo

- to go from black to red would have required a very specific set of random moves (unlikely to be found)

Who uses configurational biased MC ?

- proteins, polymers
- easiest when system is discrete
 - difficult to code in continuous systems
- typical of many methods (introduce bias and correct afterwards)
- putting techniques together

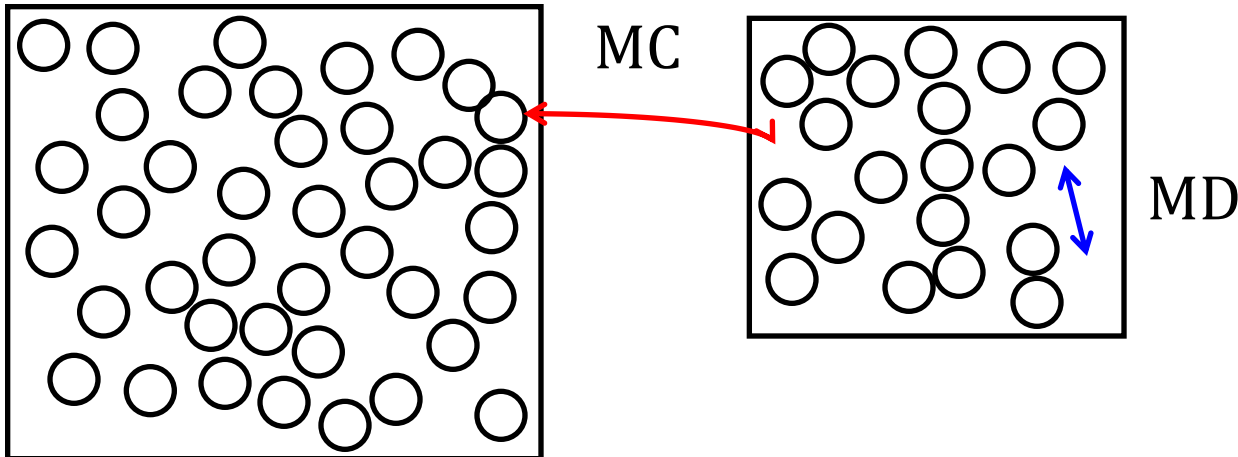
Combinations of techniques

Goal

- finish with a Boltzmann distribution
- dynamics ? maybe

Combinations

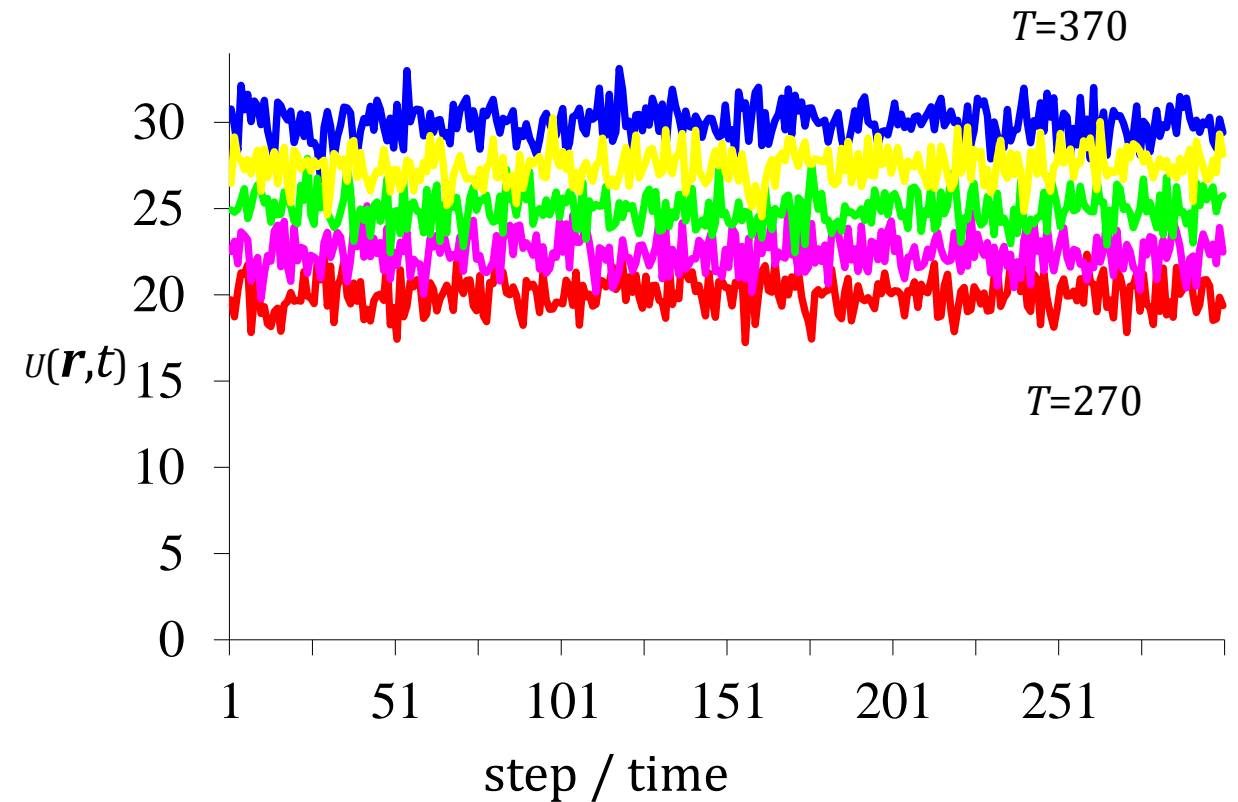
- Molecular dynamics and Monte Carlo ?
- Monte Carlo good for non-physical systems



More combinations

Replica Exchange method

- MC or MD
- both will give ensemble / distribution at desired temperature



Imagine

- MC is good for complete re-arrangement of chain
- MD explores local (nearby) configurations
- could combine biased MC with MD

Comparison with other methods

- classic minimisation method – genetic algorithm
- basic idea
 - 100 or 1000 copies of system (protein, travelling salesman routes)
- make 100 copies of system
while (not happy)
 - find 50 worst copies (highest energy) throw away
 - copy 50 best
 - for ($i = 0; i < 50; i++$)
 - apply random changes, combine copies
- system will gradually improve – fittest copies are kept

Comparing to MC

- Methods like genetic algorithm work with unknown distribution
- no theory to fall back on
 - no defined temperature
 - no defined probabilities

Summary of everything

Methods like molecular dynamics /Monte Carlo

- infinite number of variations possible / legal
- best may be system dependent
- not restricted to molecular / atomic systems

Arbitrary decisions

- temperature, move types

Questions

- how happy are we with replica exchange ?
 - I simulate with four replicas – $4 \times$ the time
 - Could I just simulate 4 times ?
- some questions
 - could we use Monte Carlo for sequence optimisation ?
 - could we use Monte Carlo for sequence alignments ?
 - why would you want to ?
 - what might be the problems ?
- why I hate genetic algorithms