Simulations / statistical mechanics / …

Topics

- very simple stat mechanics
- Monte Carlo
- molecular dynamics

Favourite books

- "Understanding Molecular Simulation", Frenkel and Smit, Academic Press, 2002
- "Computer Simulation of Liquids", Allen & Tildesley, Oxford Science Publications, 1990

Concepts

- potential energy
- work
- entropy
- free energy

Goal

- There are models for potential energy
- for free energies we need simulations

Nomenclature

- T temperature
- N all kinds of things, usually number of particles
- k and k_B Boltzmann's constant
- R gas constant = $k\ N_a$
- S entropy
- F Helmholtz (NVT)
- G (Gibbs) free energy (NPT)
- U internal energy
- H enthalpy = $U + pV$
- E energy, E_{kin}, E_{pot}, E_{bond}, …
- Q heat
- W work
- V volume
- Ω (x) number of states of system with property (x)
- $\vec{r}$ or $\vec{r}$ vectors

Potential energy

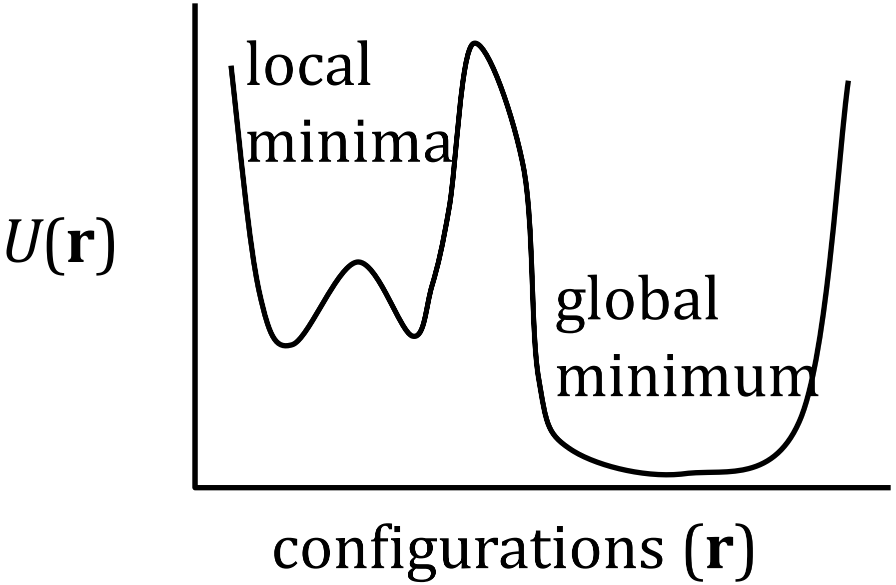
electrostatic $U(r) = \frac{q_1 q_2}{4\pi\epsilon_0 r}$

gravity $U(r) = \frac{G m_1 m_2}{r}$

elastic, …

potential energy of a protein…

- where would the protein like to be ?
- will be more interesting in ten minutes



Conserving energy

For this course:

- first law
- relevant energies
- is it obvious ?
- when do we not conserve energy ?

First law

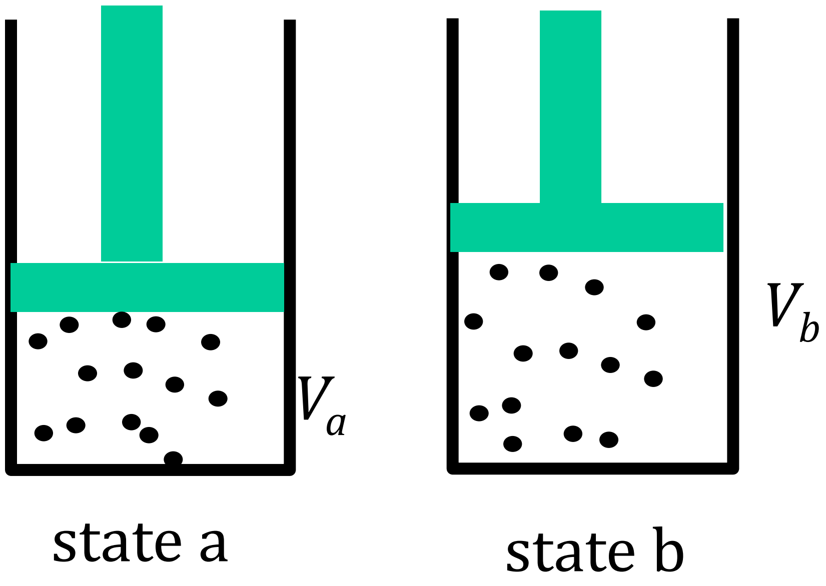
- $dU = \Delta\mathrm{Q} + \Delta W$
- dU change in internal energy
- ΔQ heat given to system
- ΔW work done on system

- example of work…

Work on a gas

$$\Delta W = -P\Delta V$$

$$\begin{aligned} dU &= \Delta Q + \Delta W \\ &= \Delta Q - P\Delta V \end{aligned}$$



Others

  - charges in electric fields, surface tension / area, ...

- we do not often do this in this course
- in one lecture: W will be important

Conserving energy

Newtonian dynamics coming soon

- what is the energy of a particle ?

$$E_{tot} = E_{pot} + E_{kin}$$

- energy of a system ? (box of gas, protein in water)

$$E_{tot} = \sum_{i=1}^{N_{particles}} \left(E_{pot_i} + E_{kin_i}\right)$$

- total energy is conserved – potential + kinetic

Do we always have kinetic energy ?

- Monte Carlo – no
- Wirkstoffentwurf-Vorlesungen - no

Conserving energy – always obvious ?

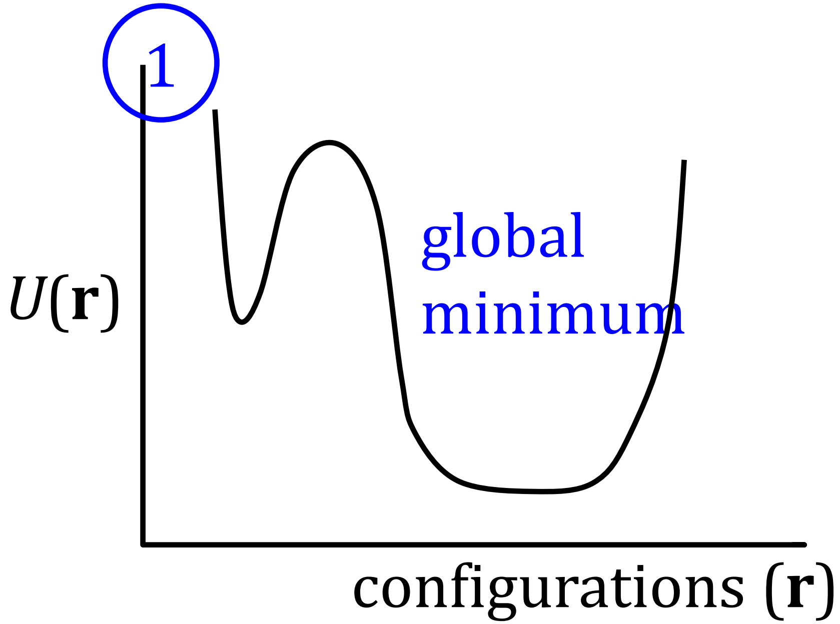
- in the real world ? closed systems ? yes
- almost everything in this course – yes

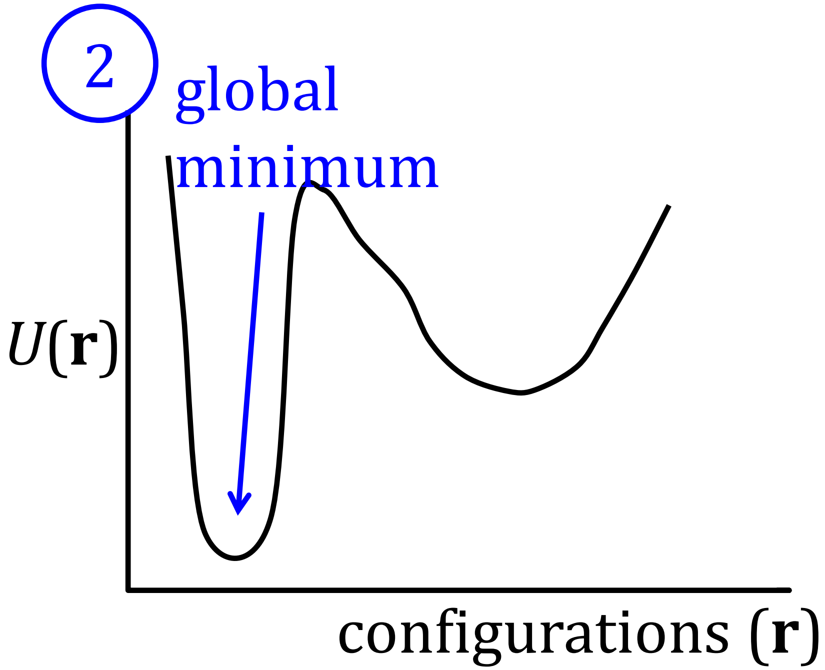
Simulations

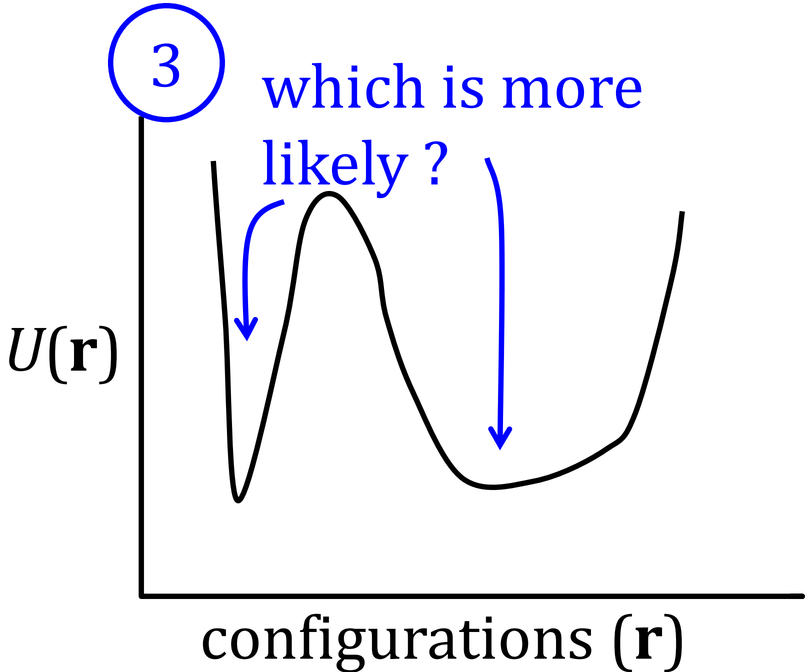
- if I want to use statistical mechanics, standard theory
  - no heating
  - no changing the force field – obvious ?
    - I want to simulate protein (un)folding
      - pull on the C-terminus – illegal – does work on system
      - heat system – illegal
  - push a drug (Medikament) into binding pocket – illegal

There is more than kinetic and potential energy..

More than potential energy

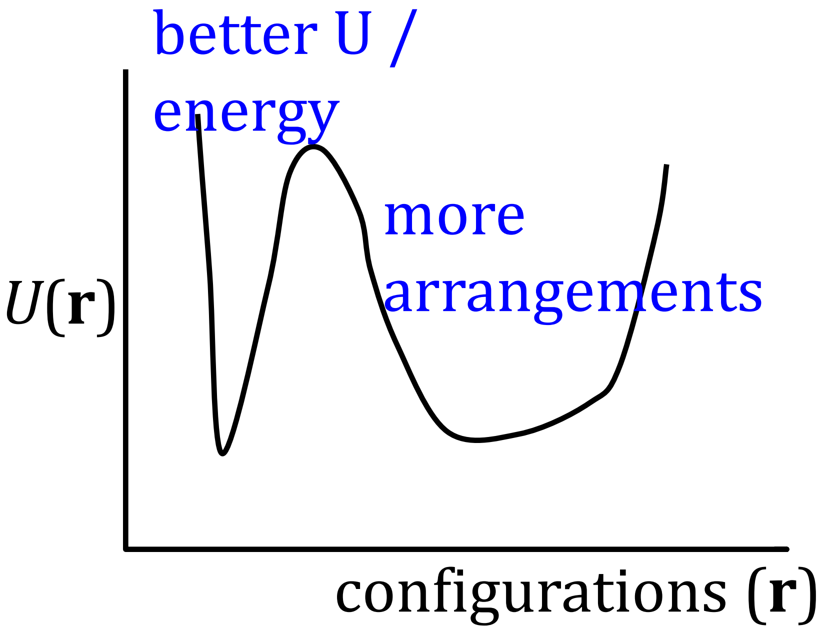






- in more detail …

Simulation and formal statistical mechanics



Quantified ?

- entropy and free energy

Dumb simulation, preferring to go downhill

- should show how probabilities (entropy) are balanced against energy

History

Statistical mechanics

- derived by summing up properties of individual particles

Thermodynamics

- less emphasis on individual particles

Lots of formulae which cannot be completely applied to proteins

- sums over infinite volumes, numbers of particles, time

Rules and Limitations

Always at equilibrium

Entropy

- you tend to become disordered (2nd law)
- role in free energy
- formula for simple systems

Disorder, how many ways can the system arrange itself..
- depends on energy (and volume and number of particles)
- two formulae coming… simple, more useful

How many states can the system have (specified E) ? $\Omega(E)$

Entropy

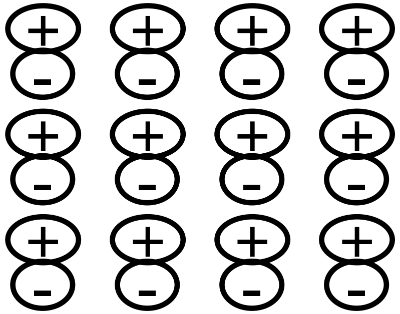
$S = k \ln \Omega(E)$ (very simple form)

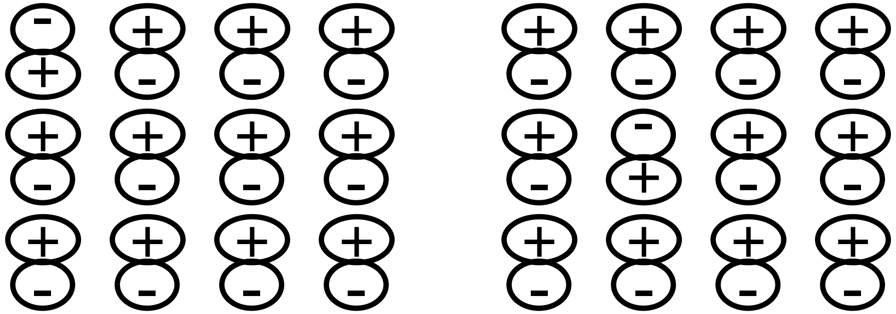
Number of states $\Omega(X)$

$T = 0$

$\Omega(E) = 1$

$S = k \ln 1 = 0$





$T > 0$ small

$\Omega(E) = n_{mol}$

$S = k \ln n_{mol}$

A bit more energy ? more states

- more.. solid →liquid .. many many more

Gibbs

What if states are not equally likely ?

- N_{state} states with distribution

  Say $p_1 = 0.999, p_2 = 0.00001, p_3 = 0.00001$, ….
- just as if the system had one state - low entropy

  Say $p_1 = 0.5, p_2 = 0.1, p_3 = 0.1$, ….
- a bit more entropy, but still very much dominated by p_1

  Say $p_1 = 0.01, p_2 = 0.01, p_3 = 0.01$, ….
- lots of states, all equally likely
  - lots of entropy

In general

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

Gibbs entropy !!

Applicability

Can one really estimate ? $S = -k \sum_{i=1}^{N_{state}} p_i \ln p_i$

- liquid.. no
- protein ..no

With a simulation ?

- too many states
- approximations to ΔS later

Simple system (grid / lattice)

- yes .. later in semester

Units

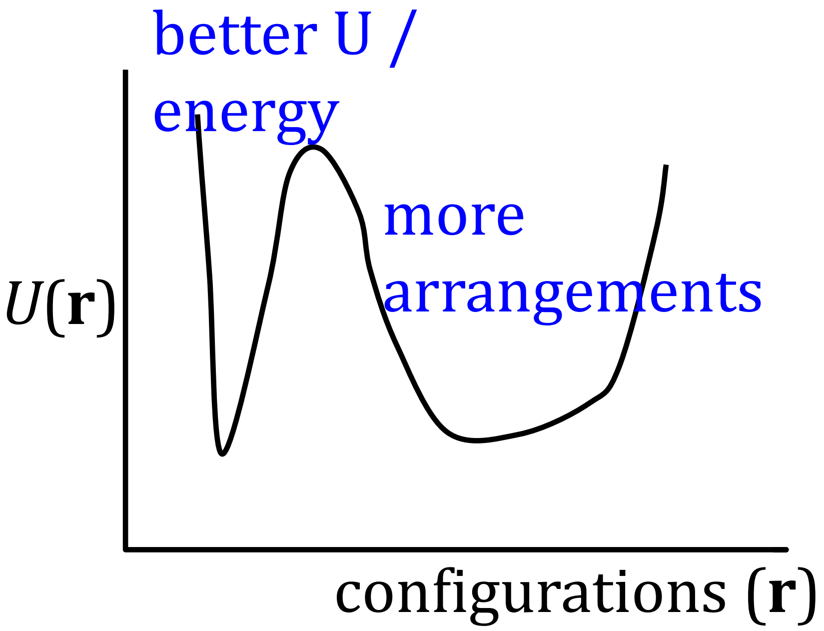
More arrangements = more entropy

Connected to energy

- balance of energy and entropy

Entropy units

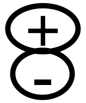
- energy / temp (JK^{-1})



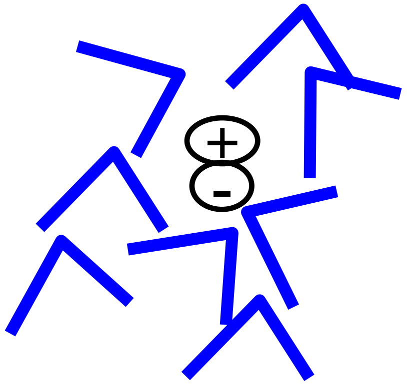
Where can we use this ?

What is the entropy of a molecule ?

- sounds easy
- really…



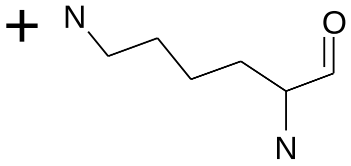
Entropy depends on solvent (system)



Entropy of a conformation ?

- has no meaning

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



Is it additive ? Only rarely – not for interesting systems

Adding entropy

Ω_A Ω_B $\Omega_{AB} = \Omega_A \Omega_B$

Entropy is "extensive"

$$S_{AB} = -\,k\ \ln(\Omega_A\,\Omega_B)\ = -\,(k\ \ln(\Omega_A) + k\ \ln(\Omega_B)) = SA\ + SB$$

Assumption

- for my new system A and B do not interact

What if they interact ?

- putting A in state 1 changes probability of B in state 1

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

$$\Omega_{AB} \neq \ \Omega_A\,\Omega_B$$

Adding entropy

I cannot usually add the entropy of two systems to get the entropy of new total system

Two systems

- could be boxes (previous slide)
- could be parts of a molecule (coming)

Do not add entropy terms ! Exam questions (promise)

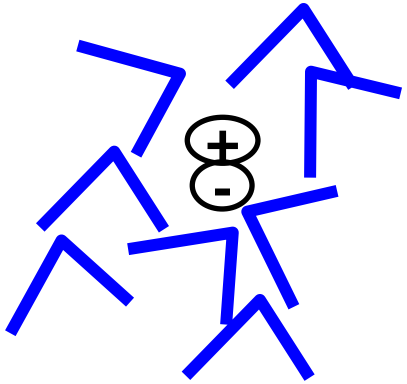
Can I decompose entropy ?

May we decompose entropy ?

Remember energy in proteins

$$E_{tot} = E_{bonds} + E_{vdw} + E_{...}$$

$$S_{tot} = S_{bonds} + S_{vdw} + \ldots ?$$



No.

- Makes no sense unless bonds are decoupled from atoms and angles…

$$S_{ligand} + S_{solvent} + \ldots$$

- obviously do interact

Free energies

G_{solv}, $G_{protein}$, G_{ligand}, G_{bonds} not really legal

- imagine bonds are system A, angles are system B, ..

Decomposing Free Energy

Would you see this in the literature ?

Example
- in protein asp → asn mutation (COO⁻ to CON)
- protein becomes more stable

Claim:
- the protein is more stable due to a change in electrostatic free energy

What has been implicitly assumed ?
There is no such thing as ΔG_{el}

More examples – particle interactions

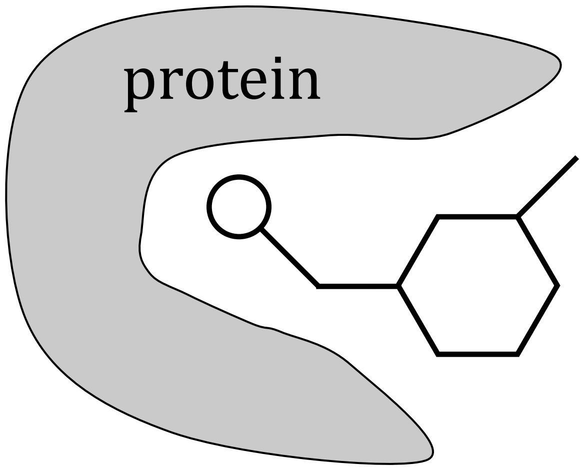
- You have a scoring function for interactions
- usually called ΔG

$\Delta G_{tot} =$ $\Delta G_{HB} +$ H-bonds

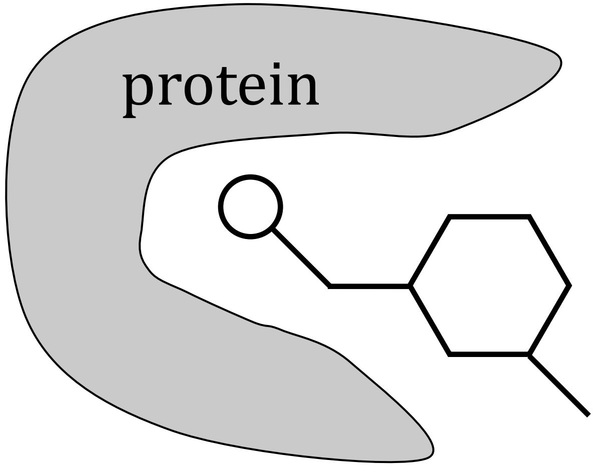
$\Delta G_{ionic} + \ldots.$ ionic

- is this legal ?

Entropy of a conformation ?



binding 1



binding 2

Can I talk about ΔG_1 vs ΔG_2 ?

$S = -k \ln \Omega$

- but Ω depends on all accessible states

If binding 1 can change to binding 2, they are both part of Ω

- I do believe we can talk about U_1 and U_2

Meaning of labelled free energies

If we have "free energy contributions"

- we have entropy contributions

ΔG_{HB} implies H_{HB} + Δ TS_{HB}

ΔG_{ionic} implies H_{ionic} + Δ TS_{ionic}

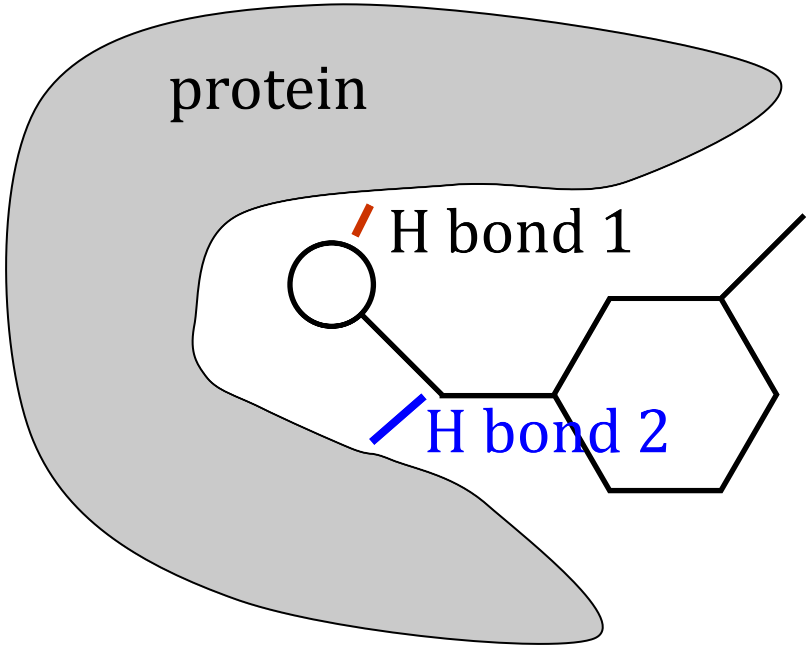
what is S_{ionic}? $\mathrm{S} = - k \ln \Omega_{\mathrm{ionic}}$

- no meaning

One cannot have "free energy contributions"

independence of terms

Even without labelled entropies



- can we add free energy due to Hbond 1 and 2 ?
- implies $\Delta S = \Delta S_1 + \Delta S_2$
- $-k \ln \Omega = -\ (k \ln \Omega_1 +\ k \ln \Omega_2)$
- $-k \ln \Omega = -\ k \ln(\Omega_1 \Omega_2)$

- only possible if there is no interaction between 1 and 2

- additivity of free energies is widely used (usually wrong)

Stop and summarise

- Internal energy U – things like springs
- Enthalpy H – includes pressure
- Gibbs free energy G what we usually use
  - no discussion of different ensembles in this course
- Free energy lets us incorporate the concept of what is most likely
- Entropy is not additive between systems (parts of systems) that interact

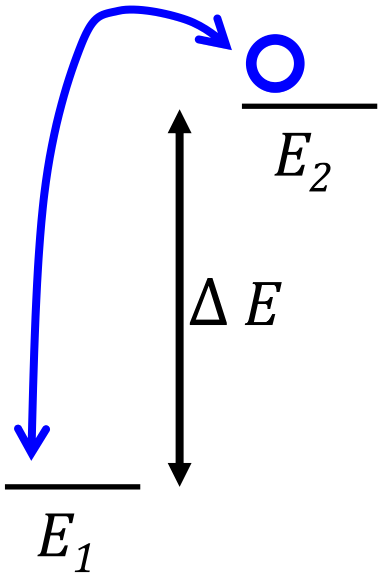
Boltzmann distribution – two states

System with two energy levels

- I know the temperature and energy difference
- How likely is system to sit in E_1 ? E_2 ?
    - System is very cold,
        - ΔE seems big
    - System is very very hot T→∞
        - ΔE does not matter, seems small
- Relative populations (probabilities) p_1, p_2
- $\Delta E = E_2 - E_1$

$$\frac{p_1}{p_2} = e^{-\Delta E / kT}$$

- sometimes $\frac{p_1}{p_2} = e^{-\beta \Delta E}$



Sign conventions

$\Delta E = E_1 - E_2$ or $\Delta E = E_2 - E_1$?

For exams

- the lower energy state is always more populated

- there are always questions about probabilities / energies
- state with most negative energy is most populated

Boltzmann distribution

What is the probability of a certain energy level ?

- depends on all available levels

$$p_i = \frac{e^{-\beta E_i}}{\sum_j e^{-\beta E_j}}$$

- name of bottom … partition function, $Z = \sum_i e^{-E_i/kT}$

- does this agree with previous slide ?

Consequences of Boltzmann distribution

At absolute zero

- only lowest energy state is populated

At low temperatures

- low energy states favoured

High temperature

- system can visit high energy regions

Infinite temperature

- all states equally likely

For two states (bound / unbound)

- exponential term means populations quickly become big/small $\frac{p_1}{p_2} = e^{-\Delta E/_{kT}}$

How big are energy differences ?

Simplest case, equal populations $\frac{p_1}{p_2} = e^{\frac{\Delta E}{kT}}$

$p_1 = p_2$

$$1 = e^{\Delta E / kT}$$
$$\ln 1 = {\Delta E}/{kT}$$
$$\Delta E = 0$$

k =1.38×10^{-23} J K^{-1}, but use

$$R = k\, N_A$$
$$= k \;\; 6.02 \times 10^{23} \text{ J K}^{-1}\text{mol}^{-1}$$
$$= 8.314 \text{ J K}^{-1} \text{ mol}^{-1}$$

Examples of populations

$$\frac{p_1}{p_2} = e^{\frac{\Delta E}{kT}}$$

$$\ln \frac{p_1}{p_2} = \frac{\Delta E}{kT}$$

$$\Delta E = kT \ln \frac{p_1}{p_2}$$

For 99:1 at 300 K

- ΔE = 11 kJ mol^{-1}

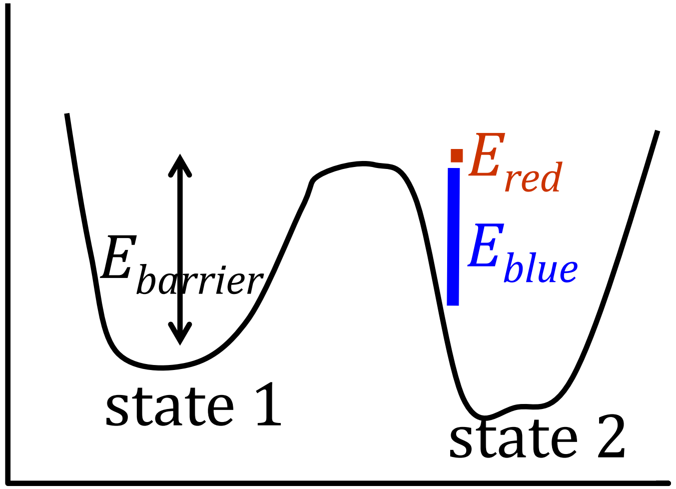
Drugs

- Dissociation constant k_d of drug D to protein P $k_d = \frac{[D][P]}{[DP]}$
- nanomolar drugs are 10^{-9},
- difference between 1 and 10 nm binding drug
  - 46 vs 52 kJ mol^{-1}
- topic will return later

Barrier crossing

How likely are you to cross a barrier ?

- p_{red} vs p_{blue}



- all the blue copies of system will not make it over $E_{barrier}$
- red population is small, even for $E_{barrier} \sim kT$
- but explains why $\ln(rate) \propto T$

where next ?

- how to see some of these properties by simulating
- how simulating depends on these properties