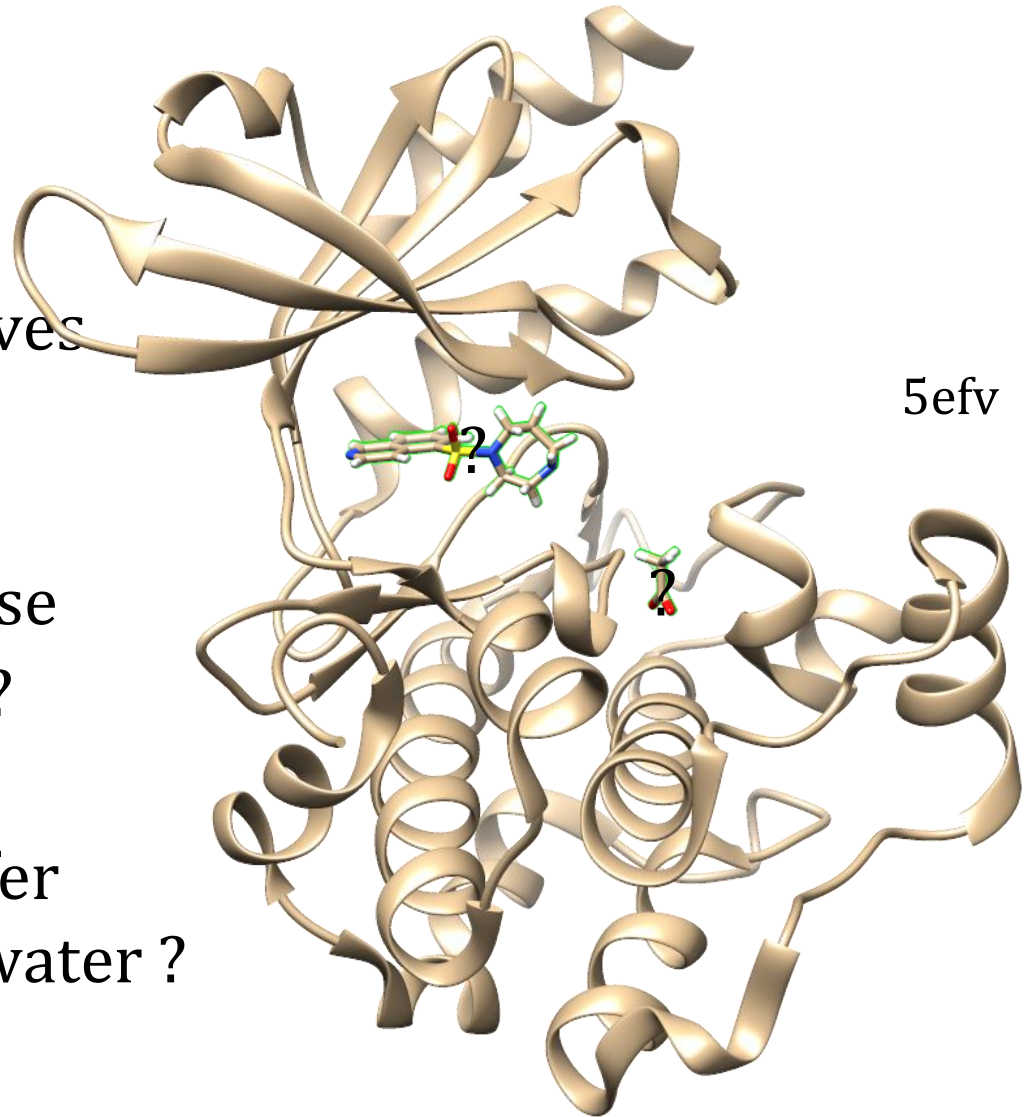# Energies

Where do you think
your drug is binding ?

- necessary if you want
to think about alternatives

If I modify the ligand

- will it bind better ? worse
- will a side chain rotate ?

- Would a side chain prefer
to H-bond to ligand or water ?

5efv
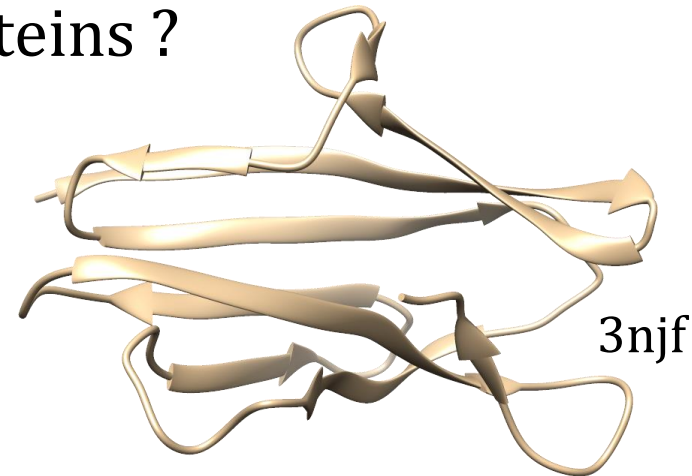
more energy questions

Anfinsen's hypothesis

- Proteins fold to lowest (free) energy conformation

If I can predict energies

can I predict the structure of proteins ?

Does it work ?   Later…

3njf

Things we want to predict
- conformations of proteins, nucleotides
- binding constants (strong / weak binding)
- binding sites

What drives the world ?
- energies

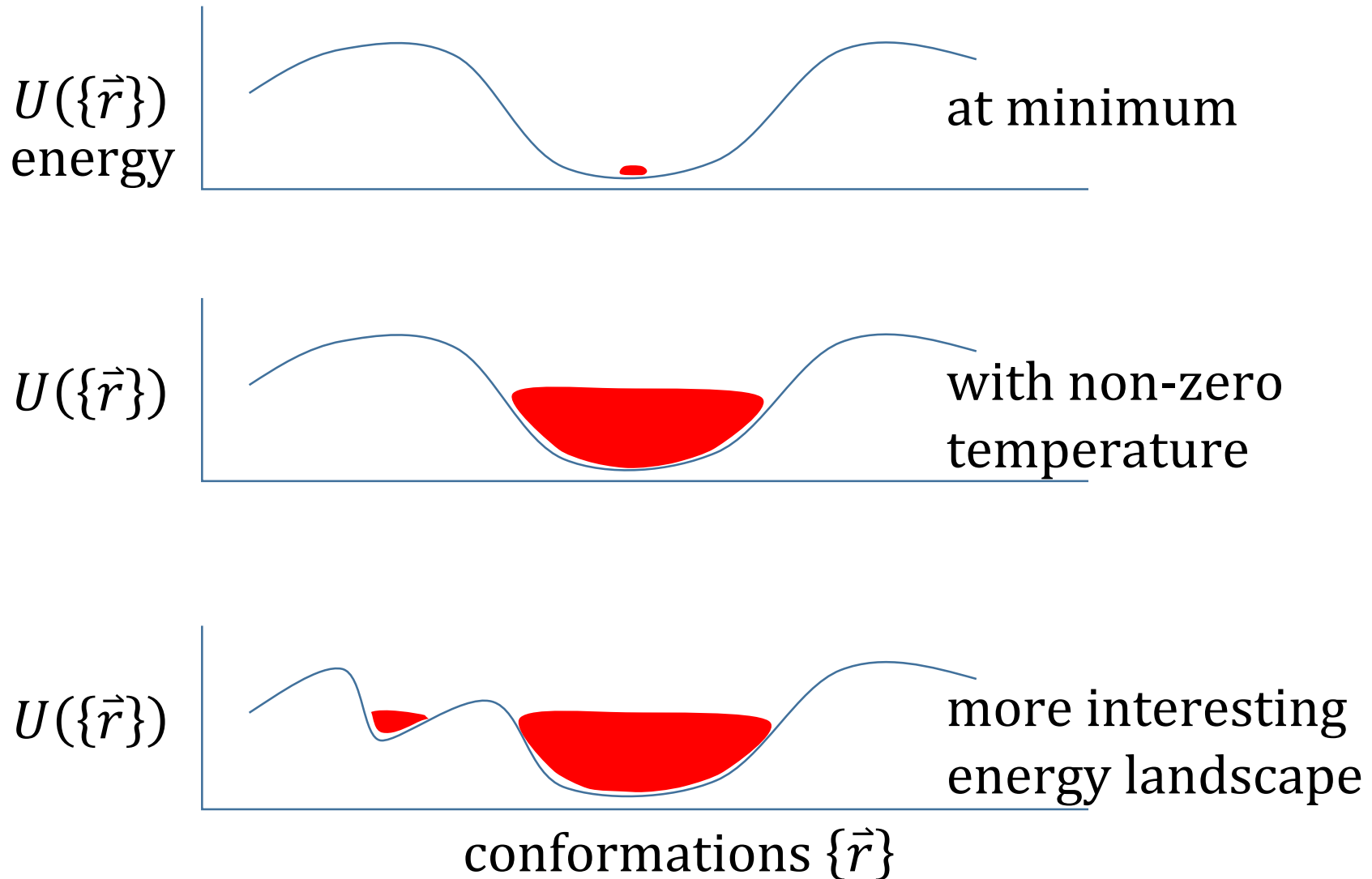What do we learn about energy states ?
- Things tend to go down in energy
- electrons fall down and emit a photon
- high energy states decay via vibrations – gives off heat

Two complications
- equilibria and temperature
- free energy and entropy

Energies and distributions

Do we end up in the lowest energy conformation ?

$U(\{\vec{r}\})$
energy

at minimum

$U(\{\vec{r}\})$

with non-zero
temperature

$U(\{\vec{r}\})$

more interesting
energy landscape

conformations $\{\vec{r}\}$

Energies and distributions
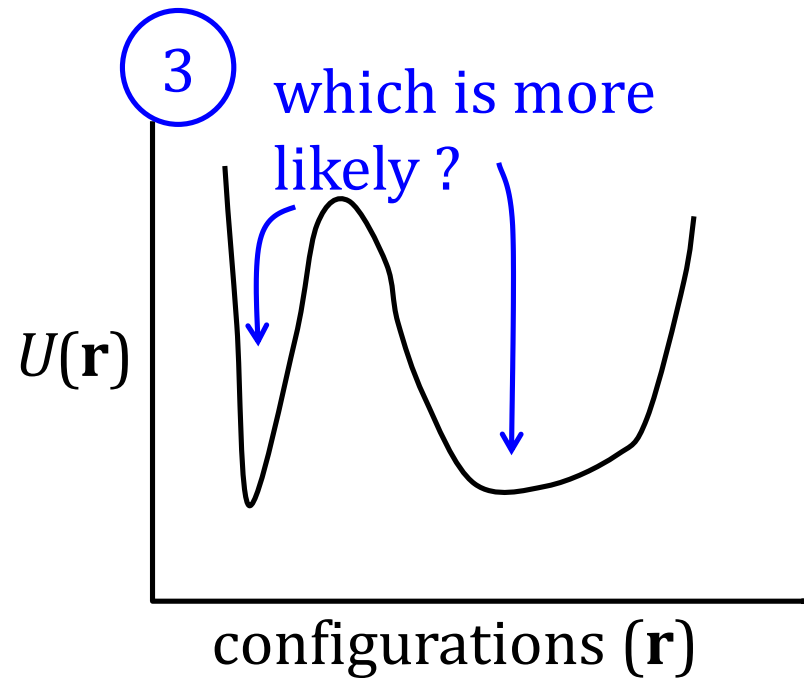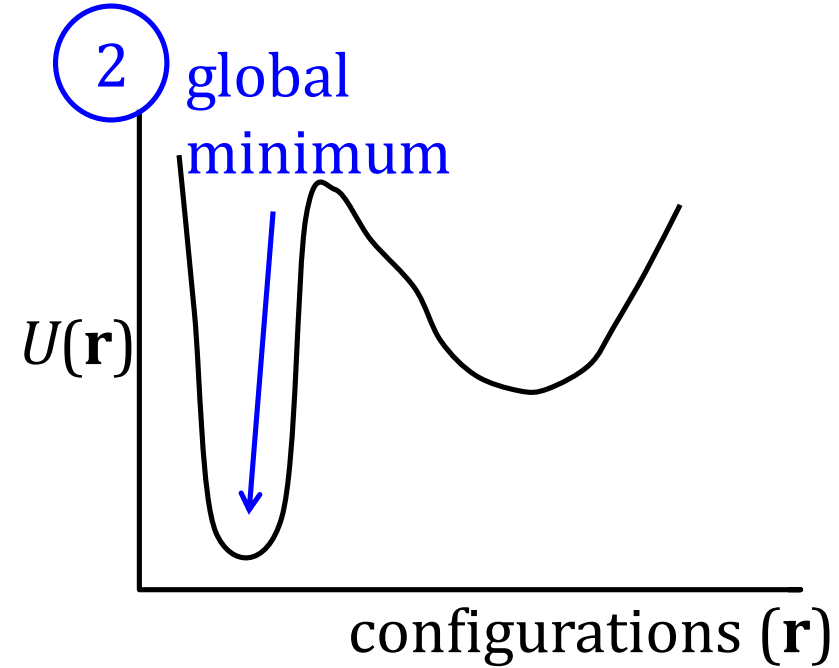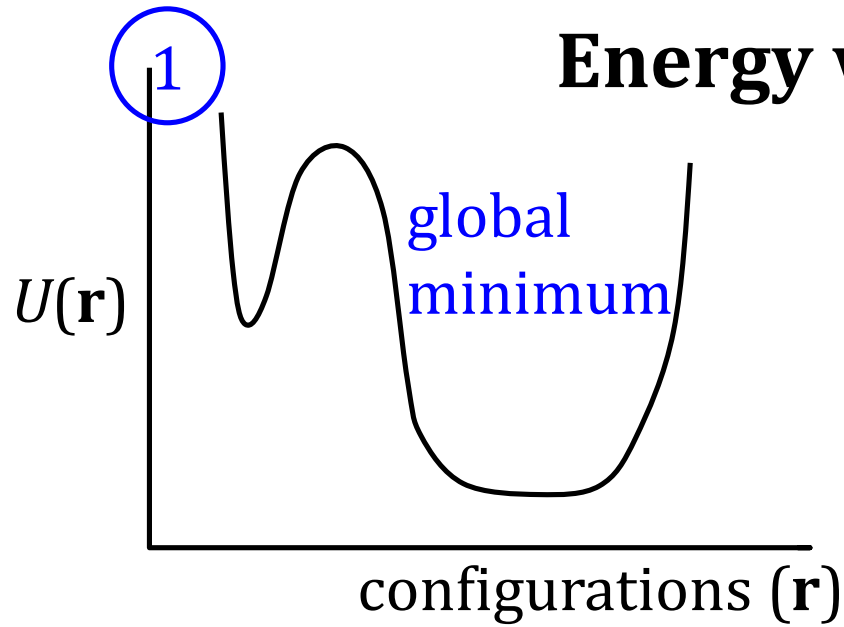
The lowest energy state is not the only relevant one
- but it is the most populated – what we are normally interested in

What is the term used in 1st year chemistry ?
- Energy or free energy (ΔG) ?

What is the practical meaning ? …

Energy vs free energy

① $U(\mathbf{r})$

global minimum

configurations ($\mathbf{r}$)

② global minimum

$U(\mathbf{r})$

configurations ($\mathbf{r}$)

③ which is more likely ?

$U(\mathbf{r})$

configurations ($\mathbf{r}$)

Energy / potential energy / free energy

Potential energy
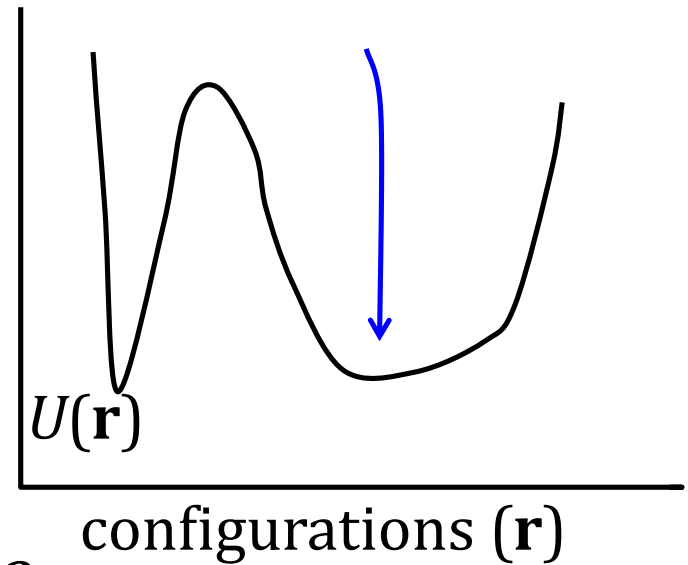- is easy
- important
- not the whole story

Systems
- like to go downhill in potential energy
- likely to go towards bigger (less ordered) regions
- net effect – potential energy and entropy are both important

formalise a bit ..

Entropy contribution

$$\Delta G = \Delta H - T\Delta S$$

- let us say ΔH is potential energy
- T temperature
- ΔS change in entropy

$U(\mathbf{r})$
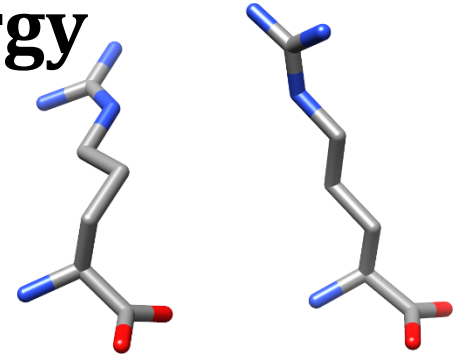
configurations ($\mathbf{r}$)

Why is entropy so difficult to estimate ?

- these two conformations have different potential energies
- they are part of the same set of conformations
- entropy is a property of all states / conformations

- entropy of a conformation has no meaning
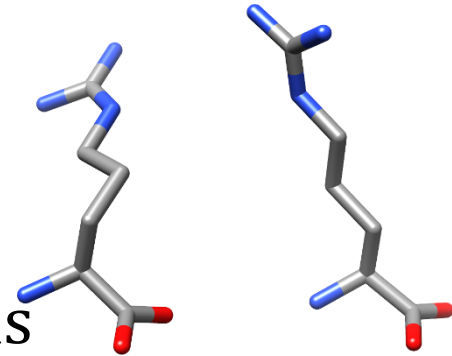
models for potential energy

Why talk about potential energy ?
* we have models for potential energy

Can I model entropic effects ?
* entropic effects ?
  * simulation methods
  * ugly approximations

* today we discuss potential energy

* start with fundamental physics

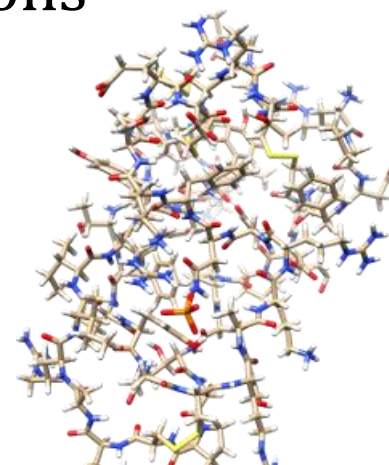# Chemistry is a approximations

Physics is not helpful

strong	particle physicists
weak	
gravity	astronomers
electromagnetic	chemists

True – not helpful – chemists use approximations
- I have coordinates and names of atoms
  - want potential energies
    - electrostatics
    - lennard-jones
    - bonds
    - angles
    - torsion angles

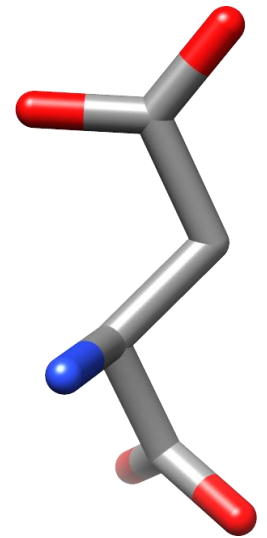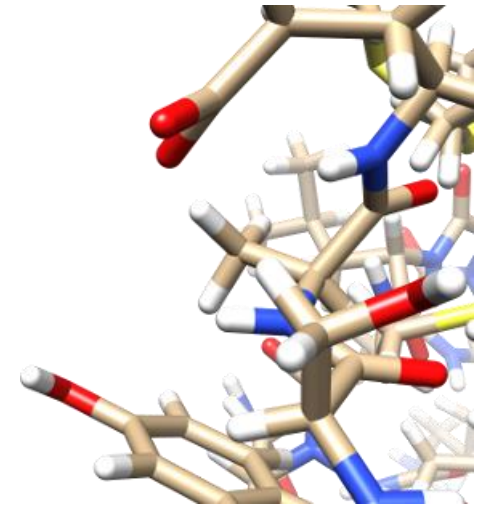# electrostatics

Can we just use Coulombs Law ?

$$U(\vec{r}_i, \vec{r}_j) = \frac{q_i q_j}{4\pi\epsilon_0 r_{ij}}$$

- charges q_i, q_j
- distance r_{ij}
- constants $4\pi\epsilon_0$

Yes, but what are the charges ?

Look at asp
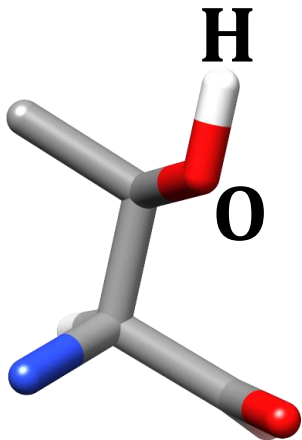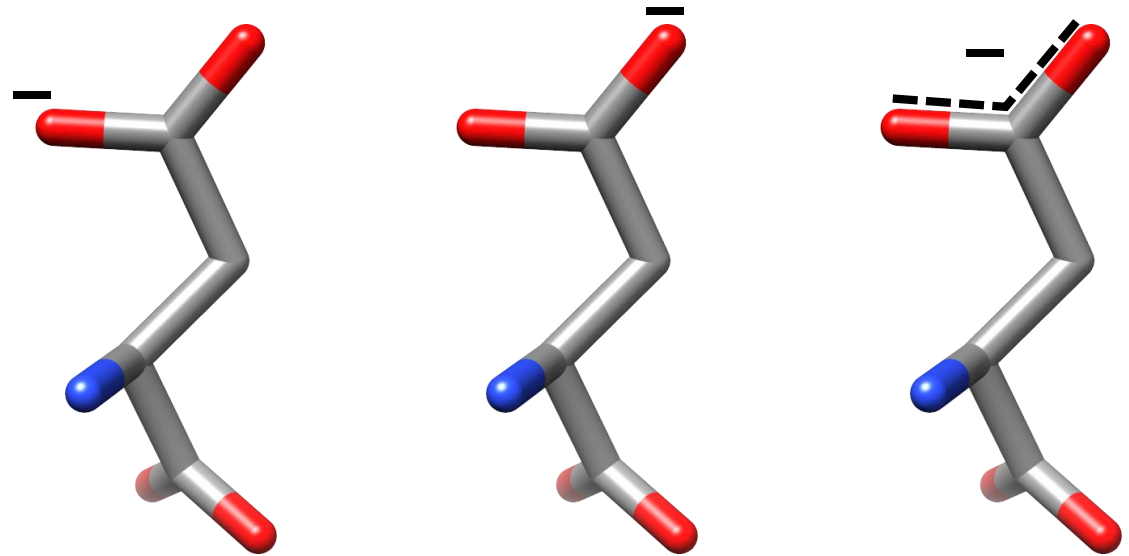- I know it has a charge of −1, but where ?

charges

where is the charge ?

- spread around
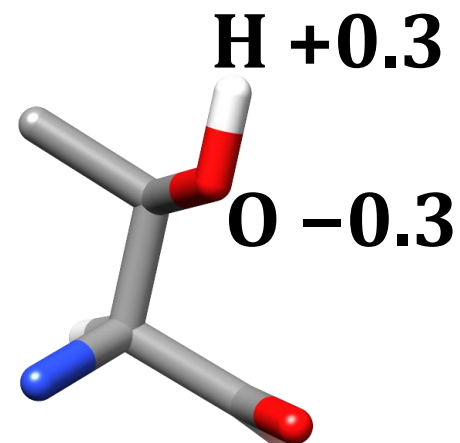
A neutral
but polar sidechain

an OH group

- is neutral
- likes water

H

O

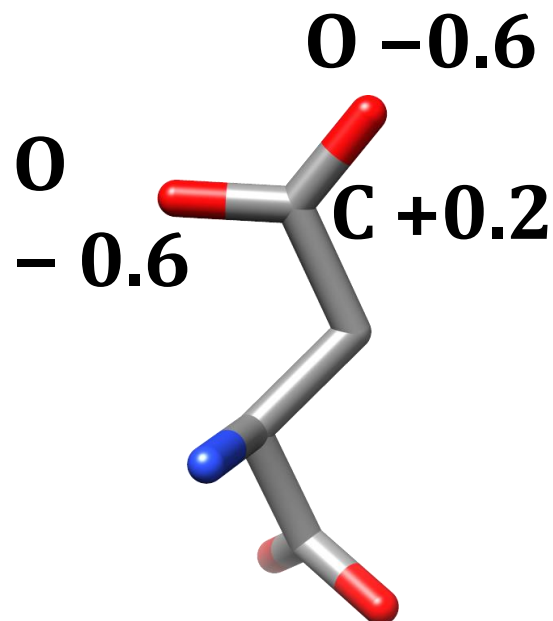how does one model these properties ?

partial charges

- assign a value like $q_H = 0.3$ or $q_O = -0.3$
- overall correct charge
- locally we have correct properties
  - imagine two OH groups come together
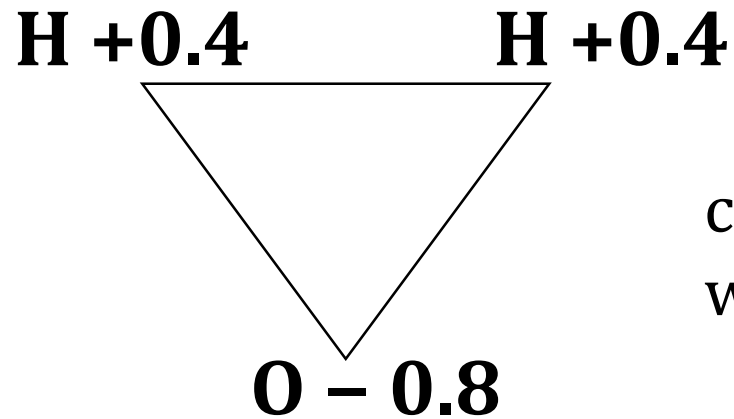 - only sensible geometries are preferred
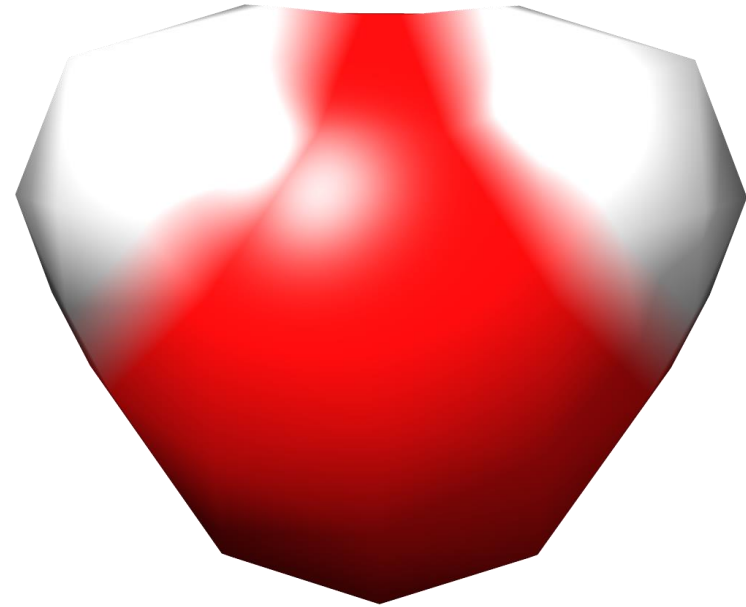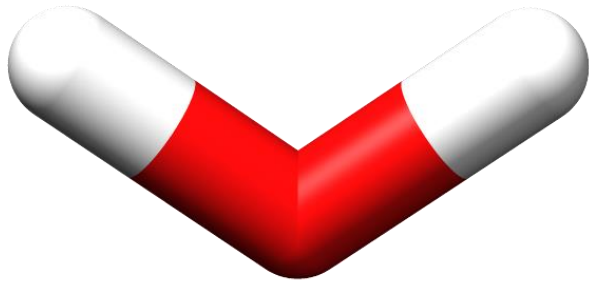
H +0.3

O −0.3

- similar rules for all atoms in polar and charged environments

O −0.6

O − 0.6

C +0.2

- famous example

a water model

water

H +0.4   H +0.4

O − 0.8

common model for
water electrostatics

partial charges

Weak physical basis
* there is no such thing as 0.4 of an electron
* they are a good approximation

Distances
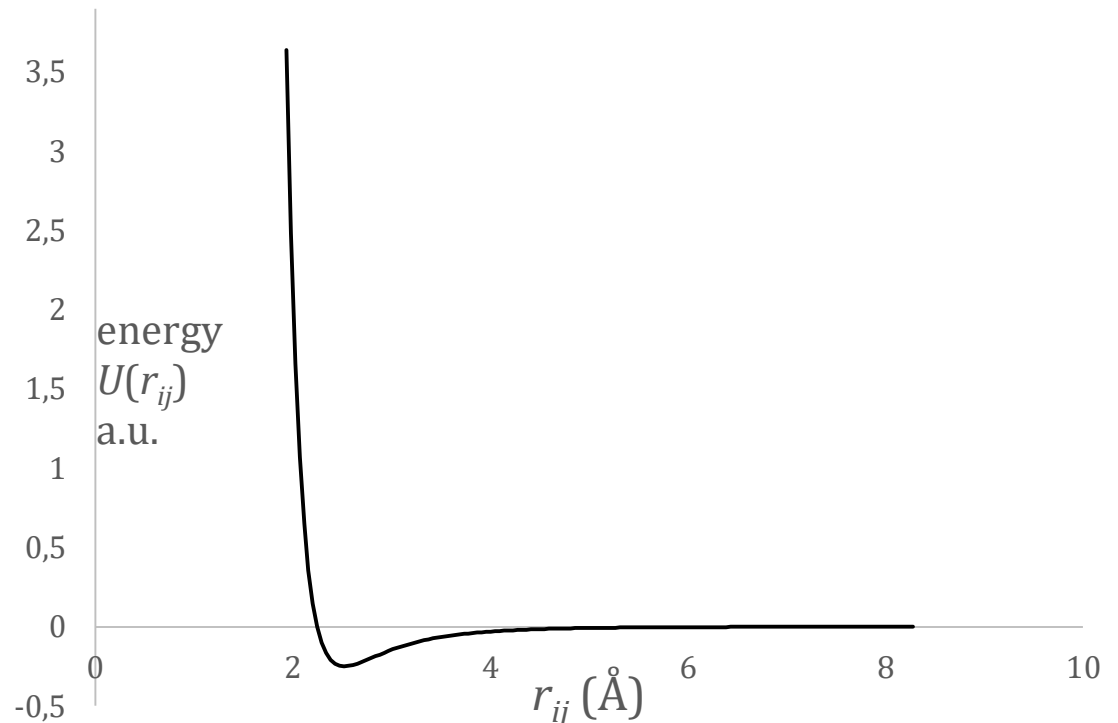* electrostatic interactions are very small after about 15 Å

What next ?
* why does argon form a liquid ?

Lennard-Jones / van der Waals

argon / methane / benzene / N_2
- completely neutral / non-polar
- do form liquids

- electrostatic effect, but complicated

Lennard-Jones

- weak
- between all atoms not connected by bonds or bond angles
- all atoms like to be near each other
- atoms do not want to be on top of each other
- at long distance atoms do not know about each other
- short range (disappears $r_{ij} > 8$ Å)
- only important energy term in middle of proteins

- ask me why I do not write a formula
- summarise ...
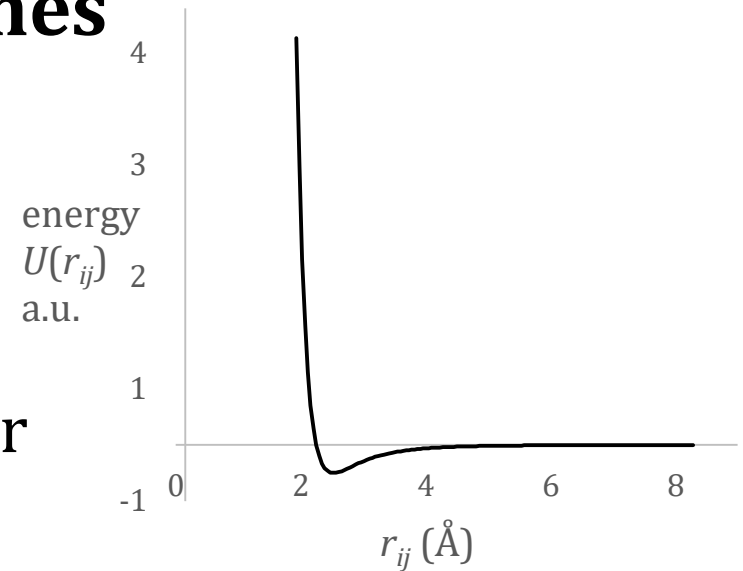
non-bonded energies

so far - two contributions to energies
1. electrostatics (energy= $q_i q_j / Dr$)
2. lennard-jones

Call them "non-bonded" energies

Distances – after about 10 or 15 Å nearly zero

- medium size protein – lots of atoms do not directly interact

What else is there ?

- bonded contributions
  - bonds
  - angles
  - torsion angles

Bond energies ?

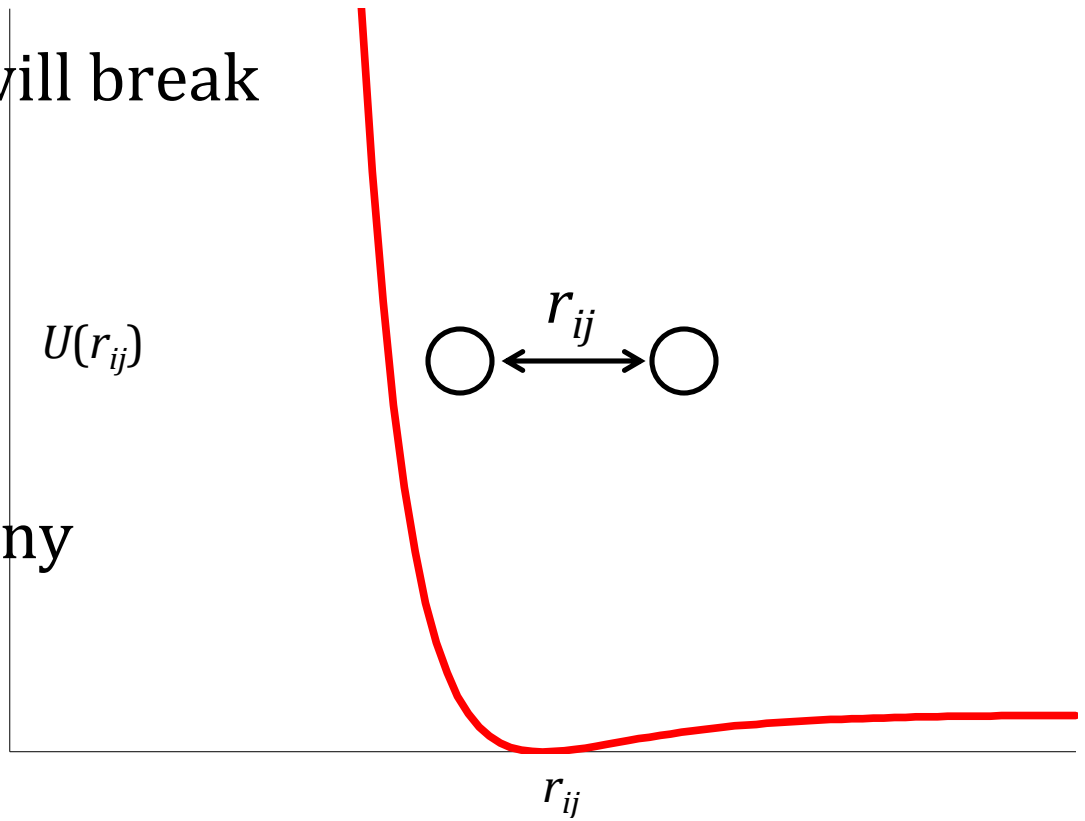Push two bonded atoms together ?
- the Lennard-Jones term would go up

Pull them apart
- eventually the bond will break

Will you meet this ?
- hopefully no

- bond vibrations are tiny

$U(r_{ij})$

r_{ij}

r_{ij}

Bonds

- at room temperature we can treat them as fixed
- if you have a model with bad bonds, energy is not so helpful
  - you have a very bad model
    - very bad or very very bad is usually not important

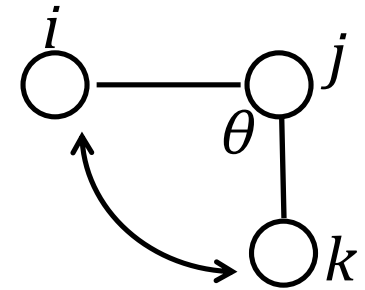Who cares about bond energies ?

- maybe people simulating chemical reactions

What about angles ?

Angles

Are they interesting ?
- not very
- a bit more flexible than bonds
- might fluctuate a bit at room temperature
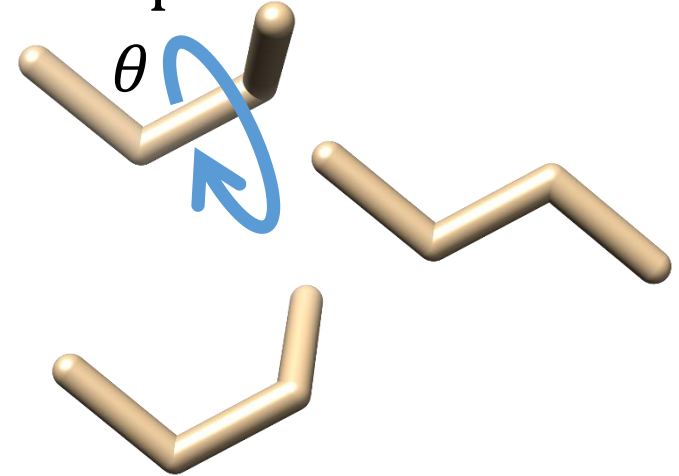
If you have a tetrahedral carbon
- an angle is 115° instead of 109.5° it is not just high energy
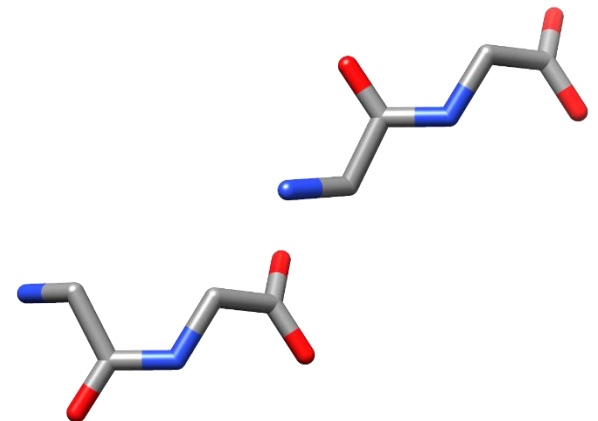 It is broken

What is more interesting ?

torsion angles

More interesting

- most single bonds can rotate at room temperature
- there are preferred conformations

- number of minima varies
- butane 3
- peptide bond 2 (*cis / trans*)

θ

What would the form look like ?

Form of torsion terms

a periodic function

$$U(\theta) = \sin(\theta)$$

with a shift of v

$$U(\theta) = \sin(\theta - v)$$

with periodicity n

$$U(\theta) = \sin\big(n(\theta - v)\big)$$

how high are the barriers ?

$$U(\theta) = k_{torsion}\sin\big(n(\theta - v)\big)$$

no physics – just created

summarise energies

A classic force field has..

| electrostatics	important	varies as atom move
lennard-jones	important	real meaning of steric effects / collisions
bonds		do not change much
angles		
torsions	important	

Not all force fields are the same

Parameters differ (partial charges, barriers)

Forms differ
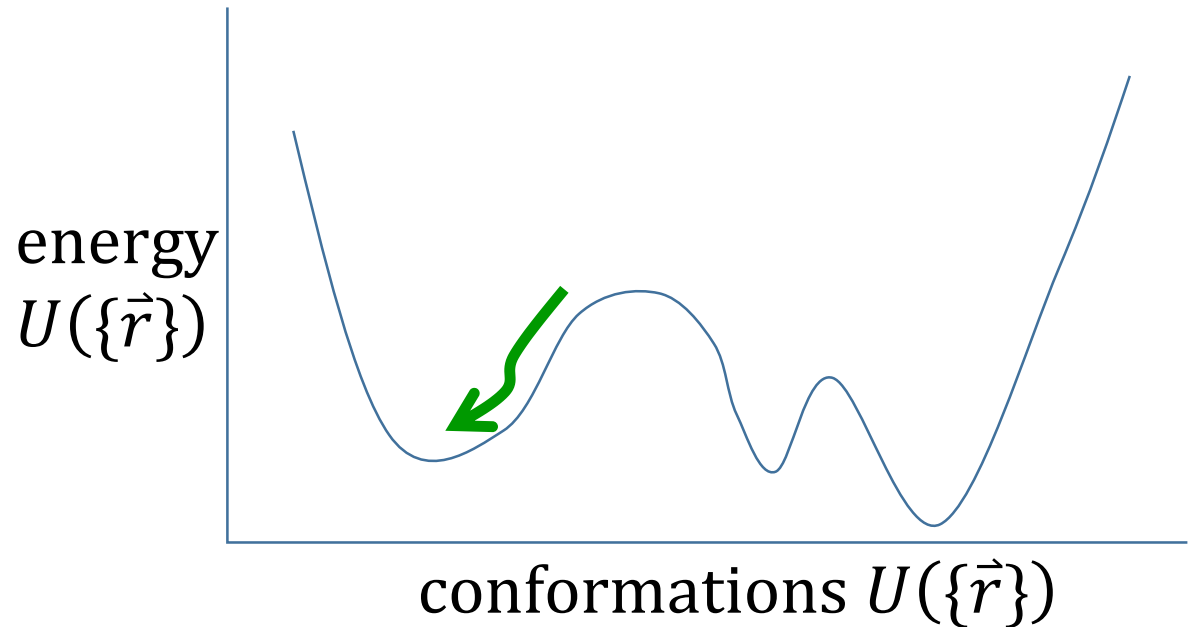- one often does not care about details
- drop terms that are not interesting
  - treat bonds and angles as rigid

$U(r_{ij})$

r_{ij}
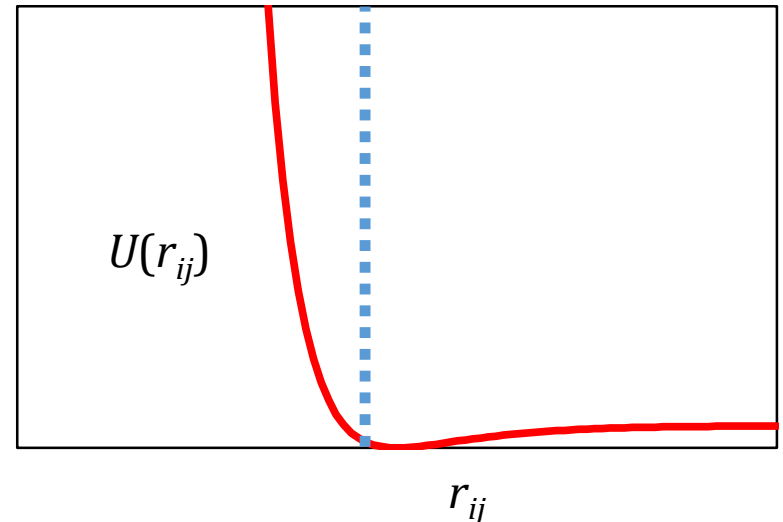
How do you use them ? (1)

3 or 4 ways

I have coordinates
and just want
to remove
clashes and small
problems

energy $U(\{\vec{r}\})$

conformations $U(\{\vec{r}\})$

1. energy minimisation / gradient descent

How do you use them ? (2)

I want to search a big space or simulate dynamics

energy
$U(\{\vec{r}\})$

conformations $U(\{\vec{r}\})$
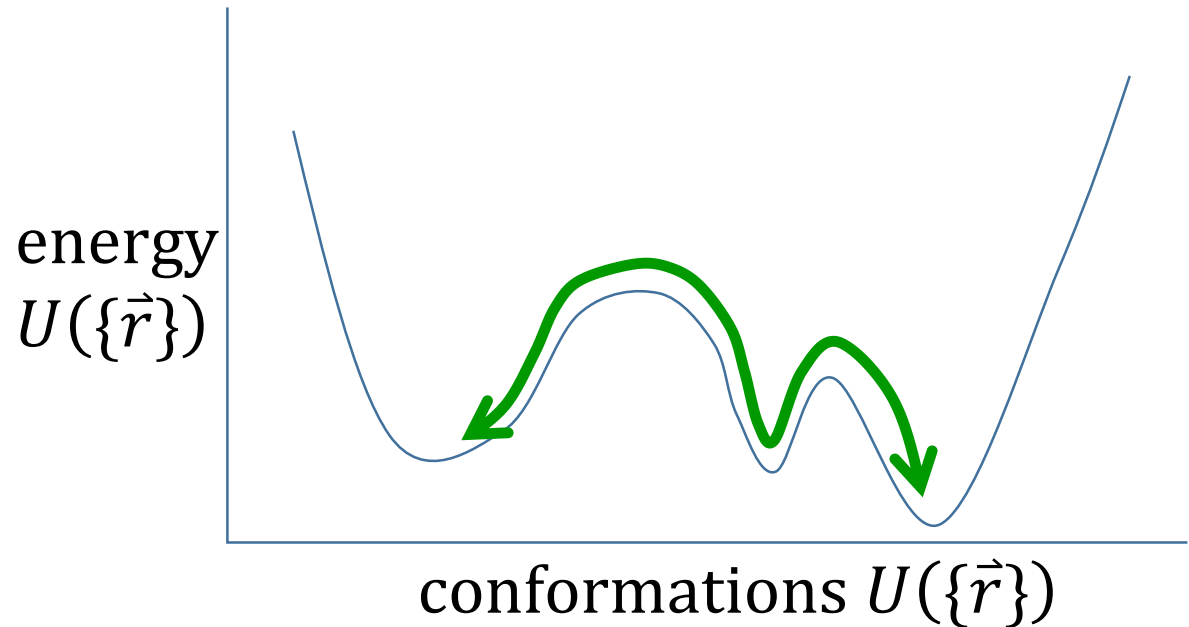
2. molecular dynamics (or Monte Carlo)
        computationally expensive

How do you use them ? (3)

small set of possibilities

energy
$U(\{\vec{r}\})$

conformations $U(\{\vec{r}\})$
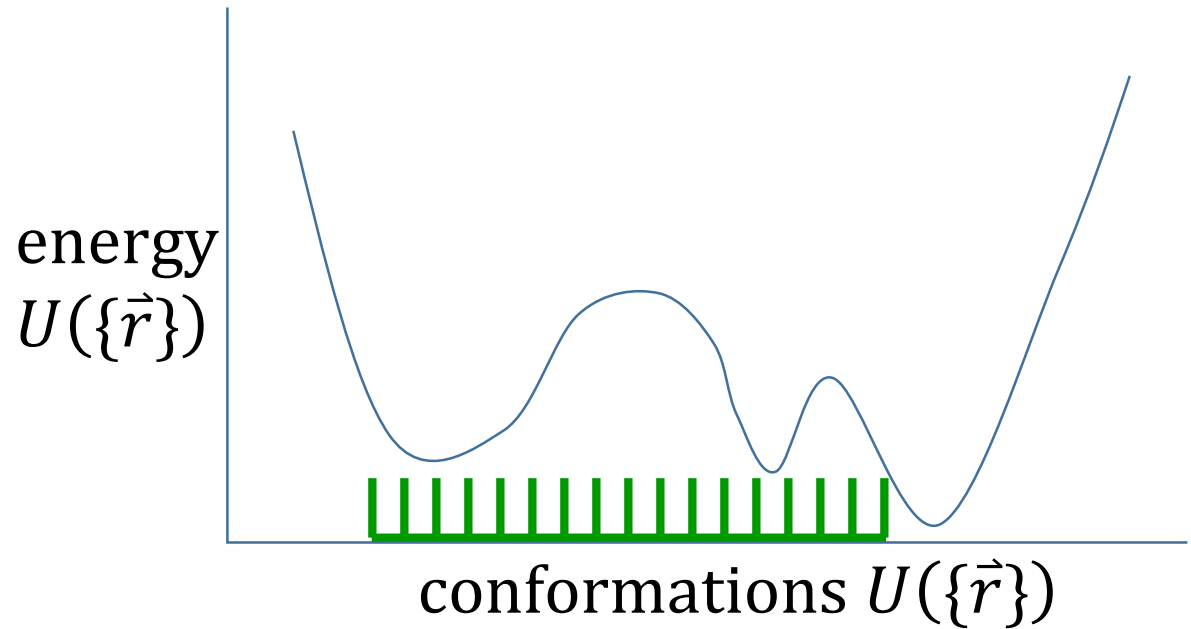
3. grid (gitter) search

How big is the search space ?
protein + ligand
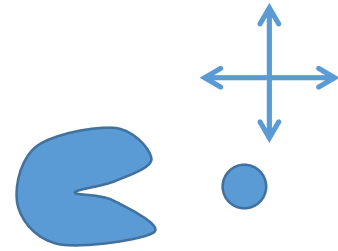
Imagine

- rigid ligand and spherical
- n possibilities in each dimension
- n^3 is search space size (3 degrees of freedom)

- if ligand is not round – rotation about x, y, z
  - extra n^3 rotations
  - total search space is $n^3 n^3 = n^6$ (6 degrees of freedom)

- what if there are internal torsion rotations ?
  - we have m angles each with n possibilities $= n^m$
  - space is now $n^6 n^m$ let us say n^{6+m}
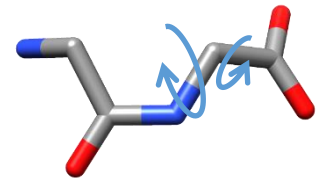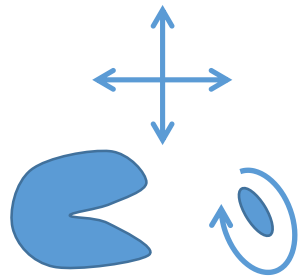
conformational space for protein

Previous slide assumed protein was rigid

How big is the space for a protein ?

- say bonds and angles are fixed

- we have m torsion angles

- if each has n possibilities, we have n^m search space

- chemistry simplification

  - -there are 3 sidechain conformations then 3^m search space

- for a protein with n residues we have ϕ and ψ angles

- total space is $(2 \cdot 3)^m$

- for a protein of 100 residues $= 6^{100}$ possibilities

- cannot visit them all

the set of conformations is very big

Answer to question at start

- if I can calculate energies – can I predict protein structure ?

Entropy

Everything I have said was focussed on potential energy, but
$$\Delta G = H - T\Delta S$$

How important is entropy ?

- protein folding – HUGE – there are many unfolded states higher entropy – preferred
  - you need a lot of favourable potential energy
- ligand binding
  - free ligand can
    1. rotate freely
    2. visit much of space (drift around in solution)
  - many of these states (entropy) are lost when a ligand binds
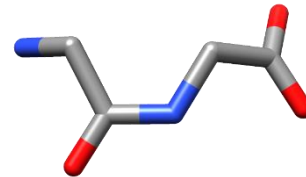
summary of energies

- remember components of potential energy and which are important

- why potential energy is not sufficient to predict behaviour

- even if you could predict energies, could you predict structure ?