

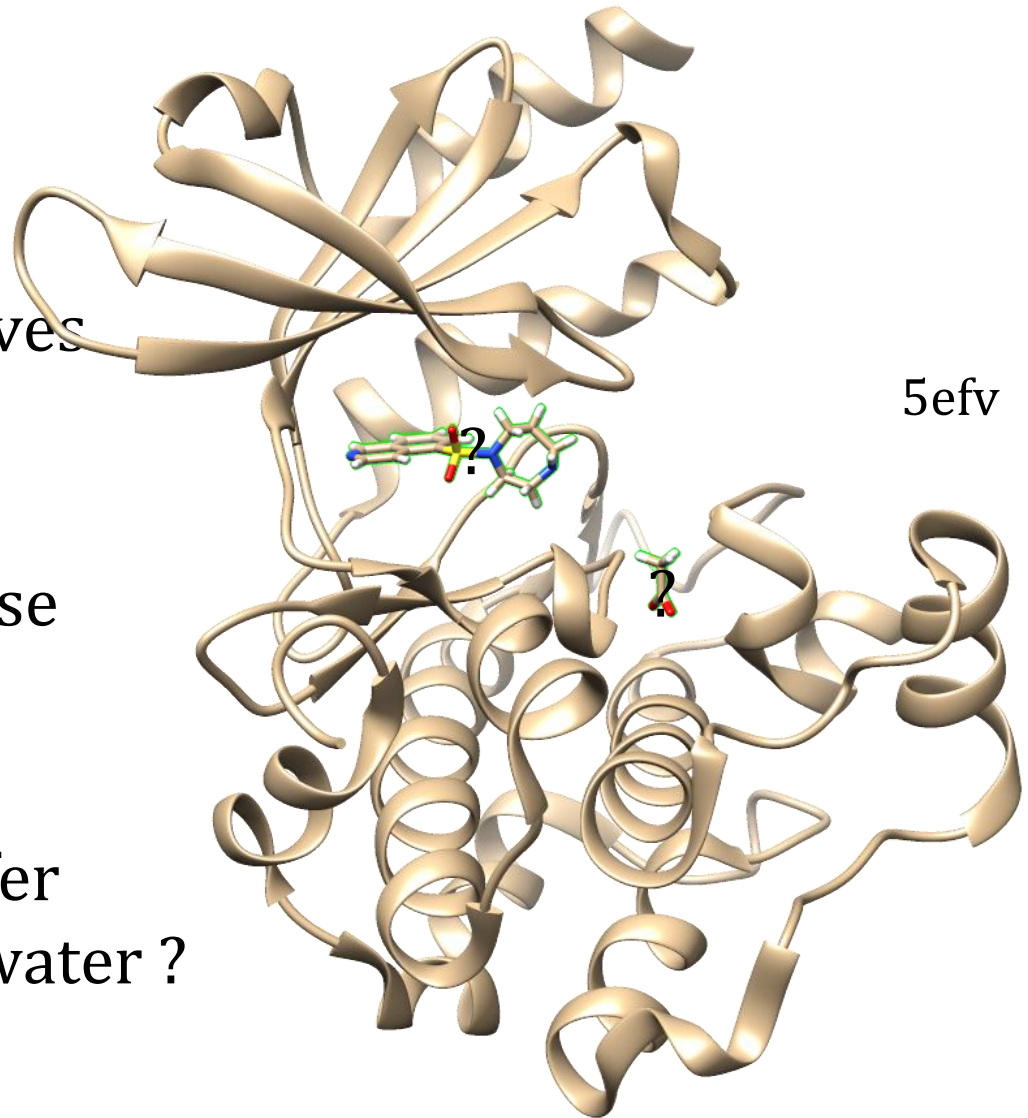
# Energies

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 ?



# more energy questions

Anfinsen's hypothesis

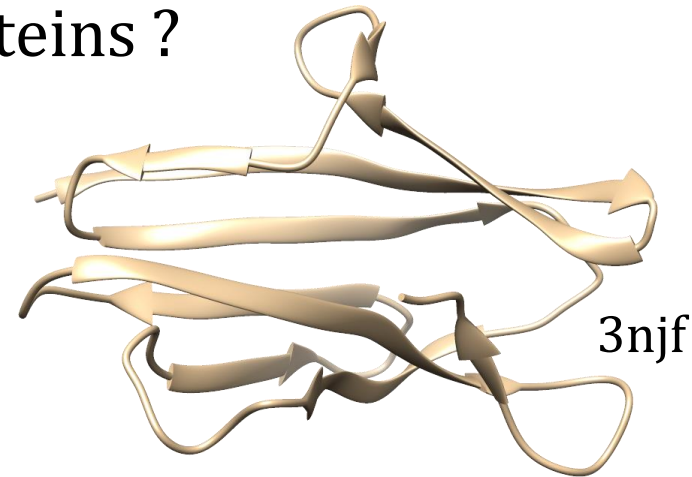
- Proteins fold to lowest (free) energy conformation

If I can predict energies

can I predict the structure of proteins ?

Does it work ?

Later...



# Forces and energies

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 ?

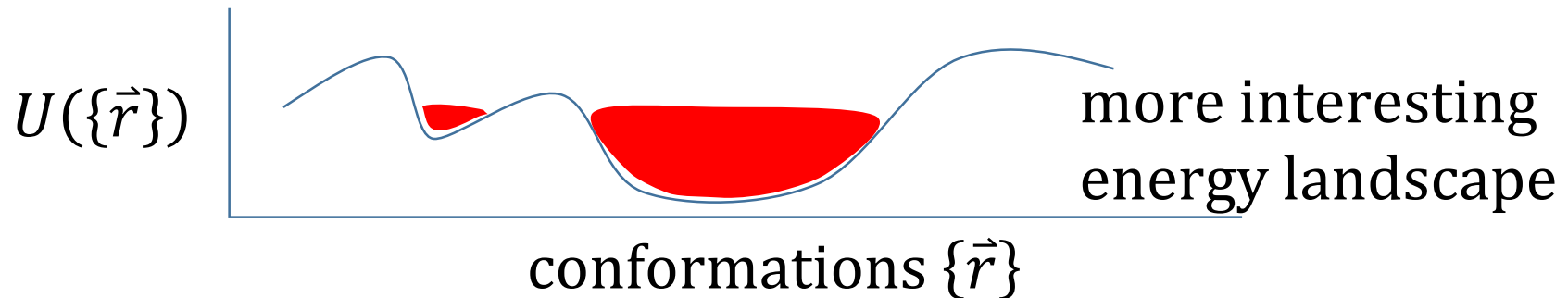
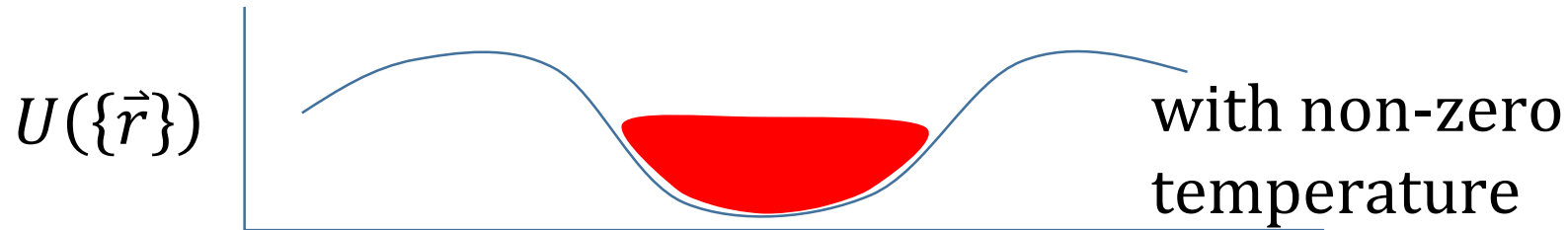
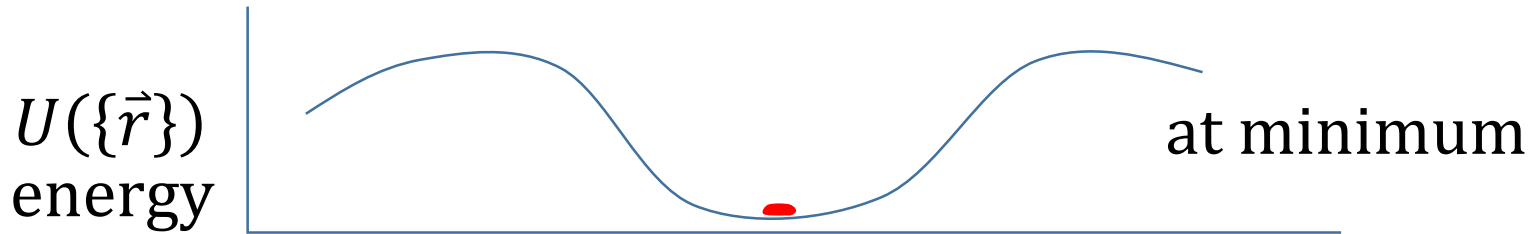
- Things tend to go down in energy
- electrons fall down and emit a photon
- high energy states decay via vibrations – gives off heat

Two complications

- equilibria and temperature
- free energy and entropy

# Energies and distributions

Do we end up in the lowest energy conformation ?



# Energies and distributions

The lowest energy state is not the only relevant one

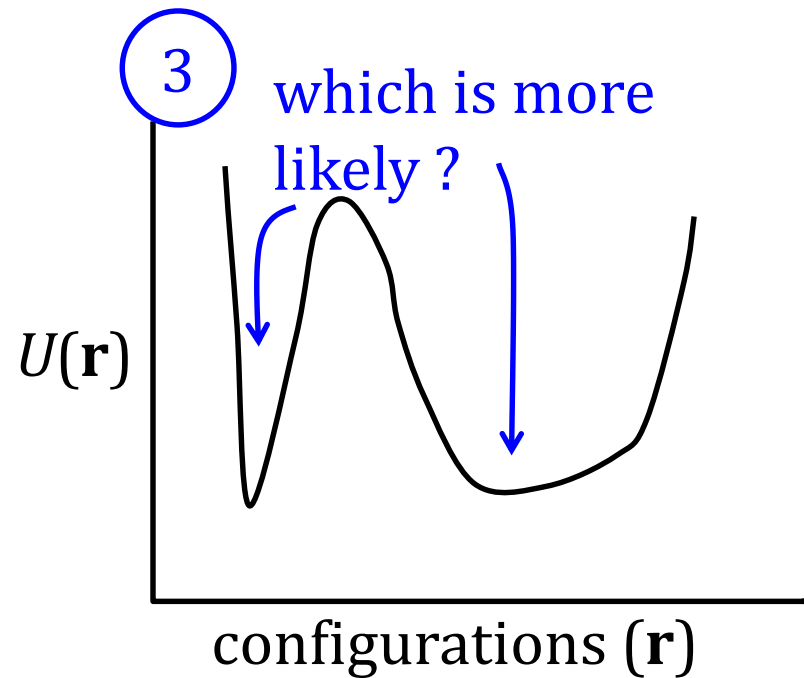
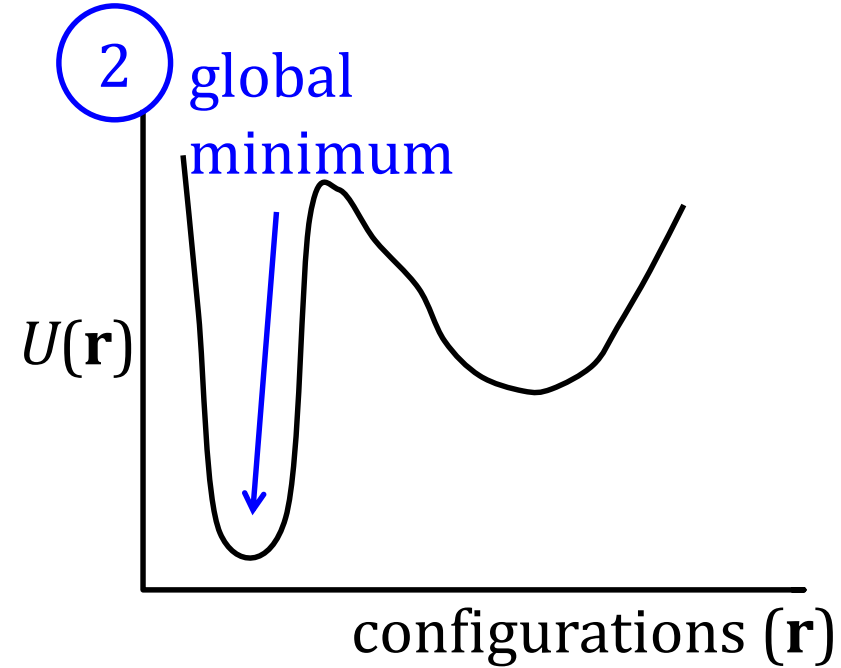
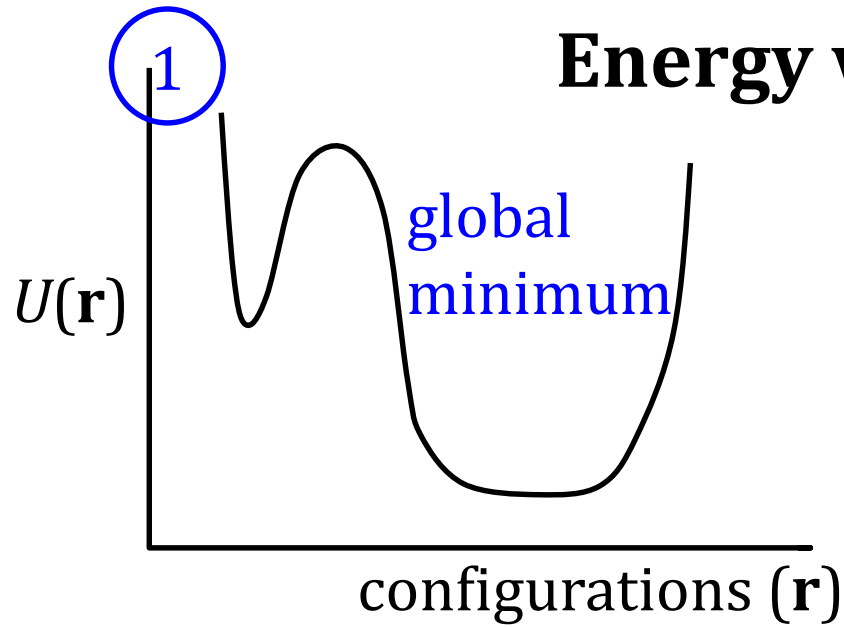
- but it is the most populated – what we are normally interested in

What is the term used in 1<sup>st</sup> year chemistry ?

- Energy or free energy ( $\Delta G$ ) ?

What is the practical meaning ? ...

# Energy vs free energy



# Energy / potential energy / free energy

## Potential energy

- is easy
- important
- not the whole story

## Systems

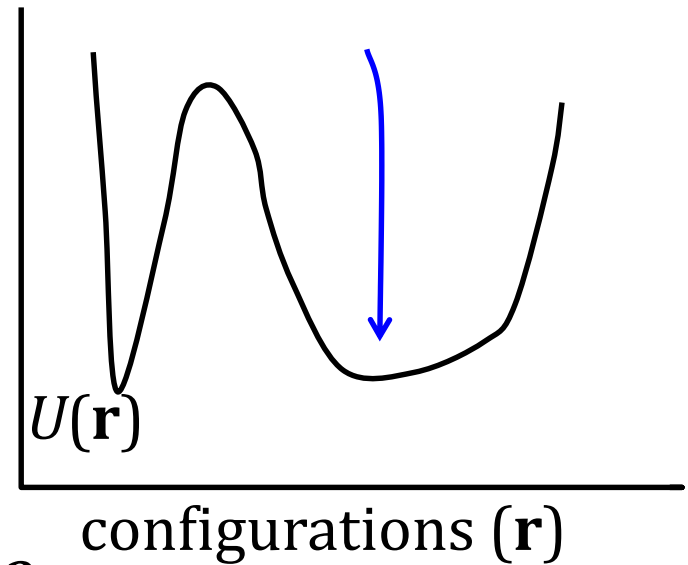
- like to go downhill in potential energy
- likely to go towards bigger (less ordered) regions
- net effect – potential energy and entropy are both important

formalise a bit ..

# Entropy contribution

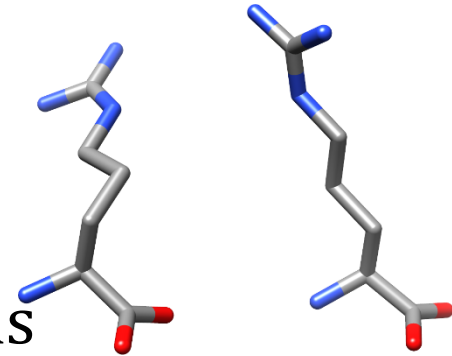
$$\Delta G = \Delta H - T\Delta S$$

- let us say  $\Delta H$  is potential energy
- $T$  temperature
- $\Delta S$  change in entropy



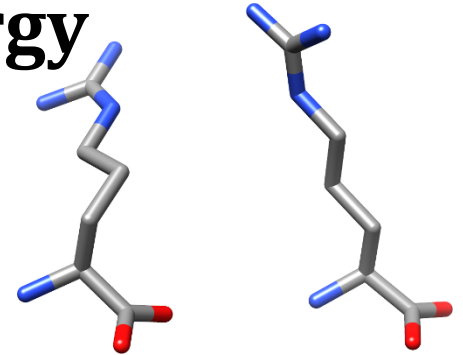
Why is entropy so difficult to estimate ?

- 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

weak

gravity

electromagnetic

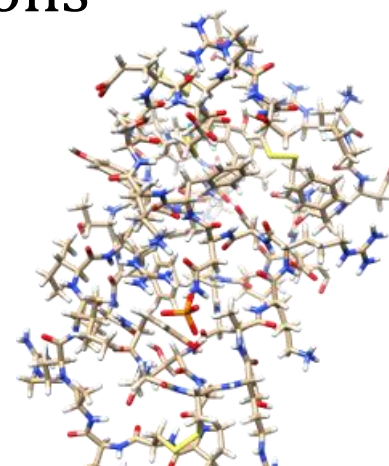
particle physicists

astronomers

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 ?

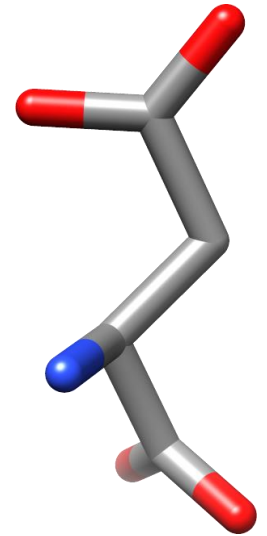
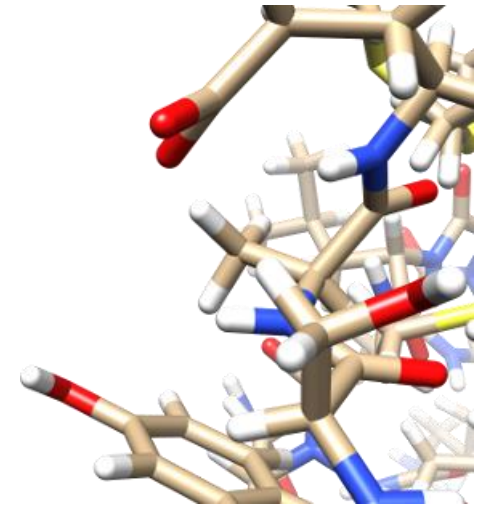
$$U(\vec{r}_i, \vec{r}_j) = \frac{q_i q_j}{4\pi\epsilon_0 r_{ij}}$$

- 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 ?

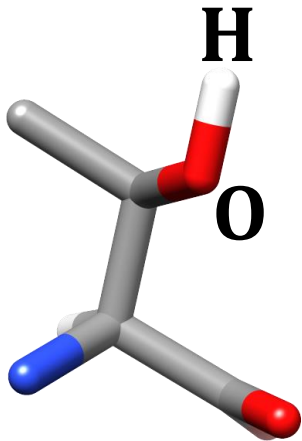
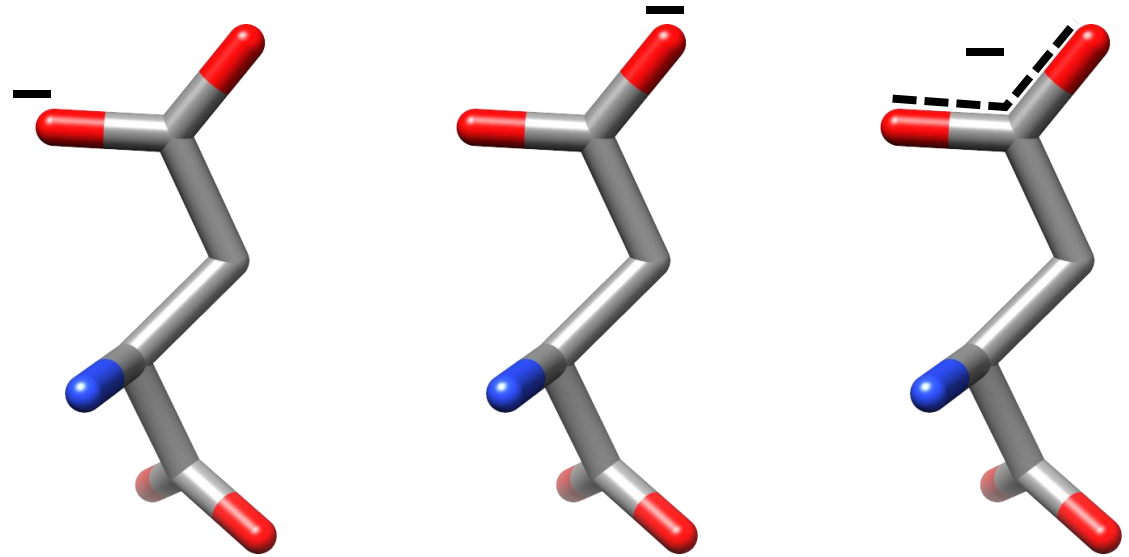


# charges

where is the charge ?

- spread around

A neutral  
but polar sidechain



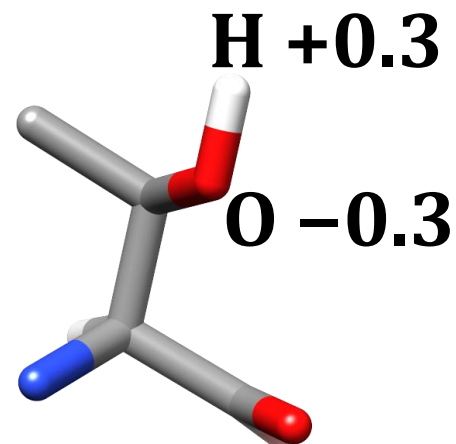
an OH group

- is neutral
- likes water

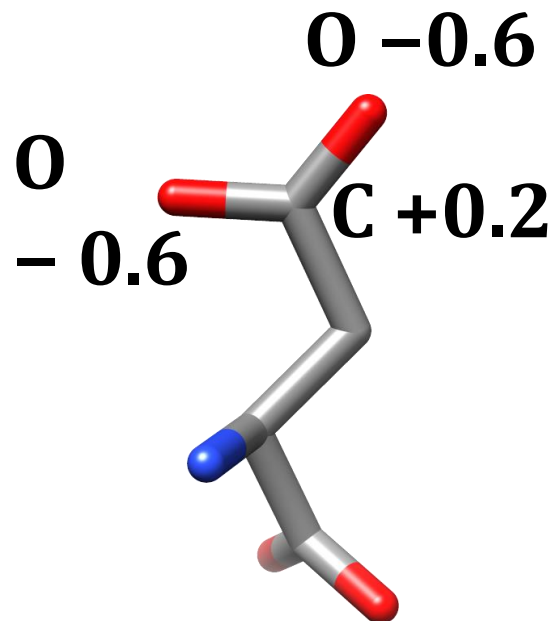
how does one model these properties ?

# partial charges

- assign a value like  $q_{\text{H}} = 0.3$  or  $q_{\text{O}} = -0.3$
- overall correct charge
- locally we have correct properties
  - imagine two OH groups come together
  - only sensible geometries are preferred



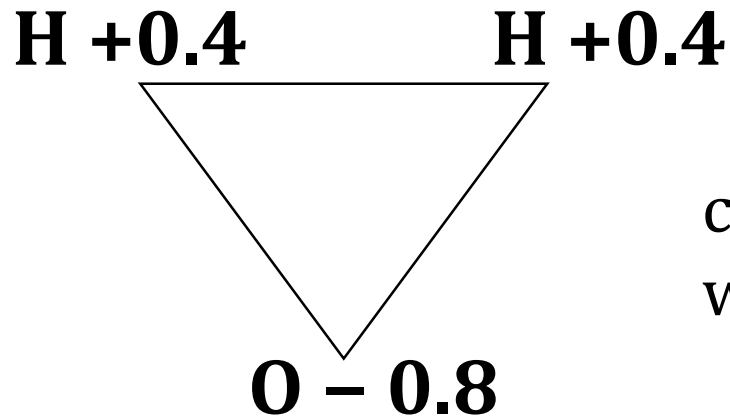
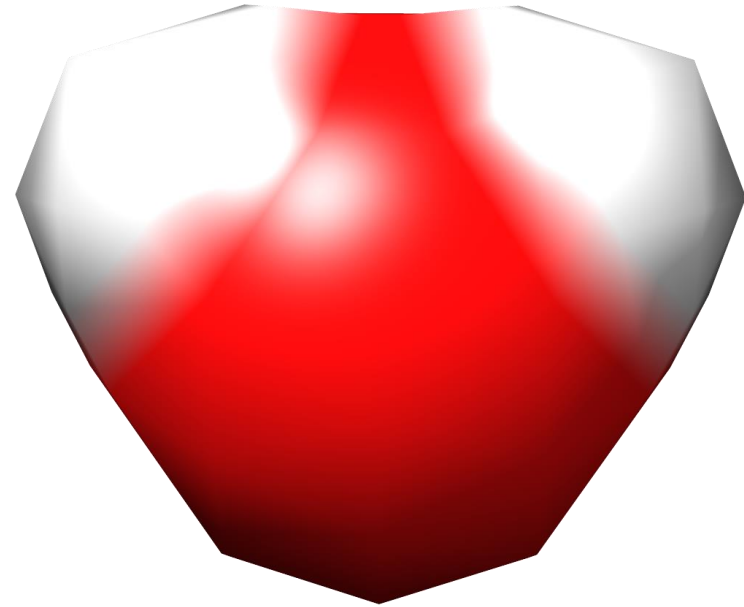
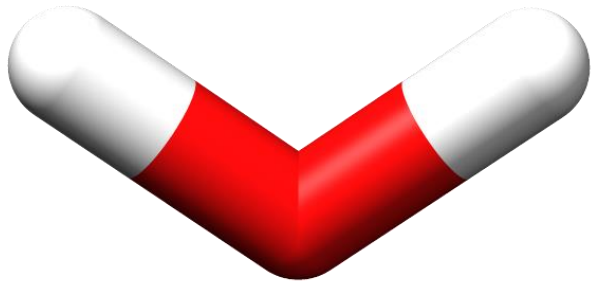
- similar rules for all atoms in polar and charged environments



- famous example

# a water model

water



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

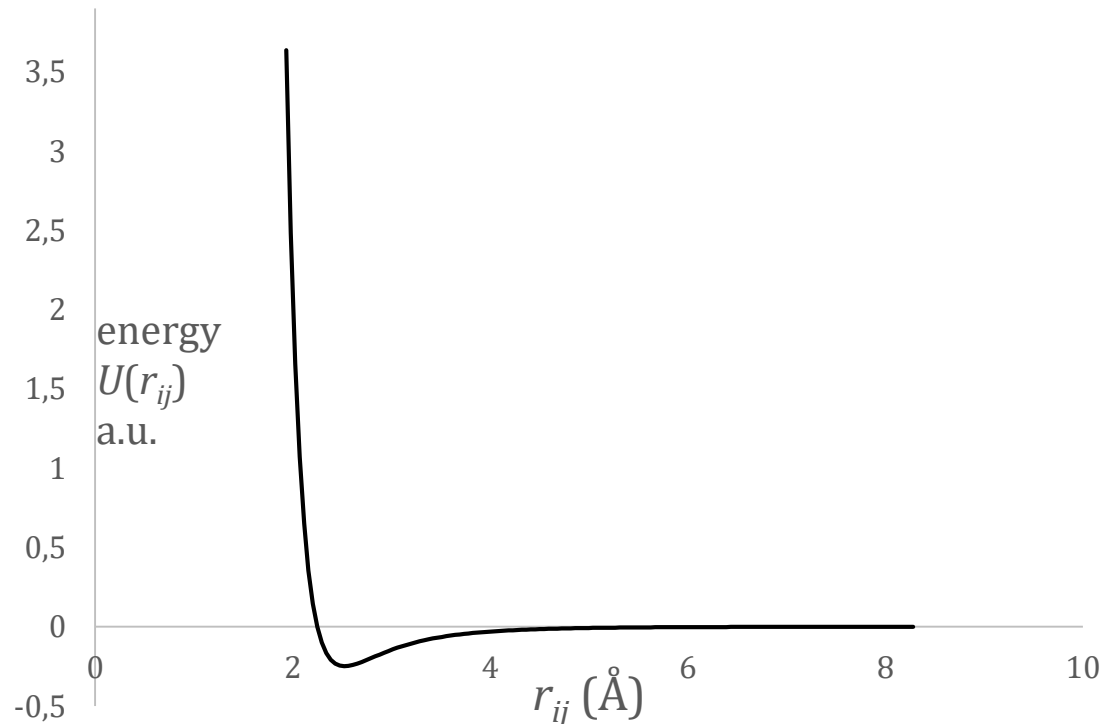
## What next ?

- why does argon form a liquid ?

# Lennard-Jones / van der Waals

argon / methane / benzene / N<sub>2</sub>

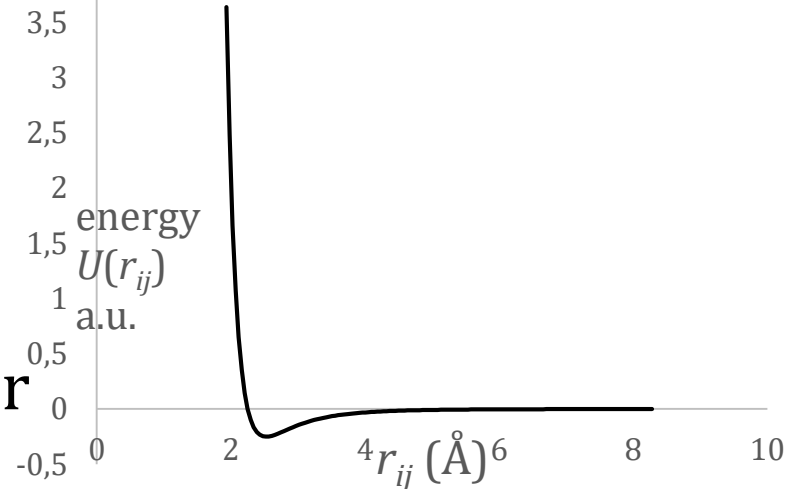
- completely neutral / non-polar
- do form liquids
- electrostatic effect, but complicated





# 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 before 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 ?

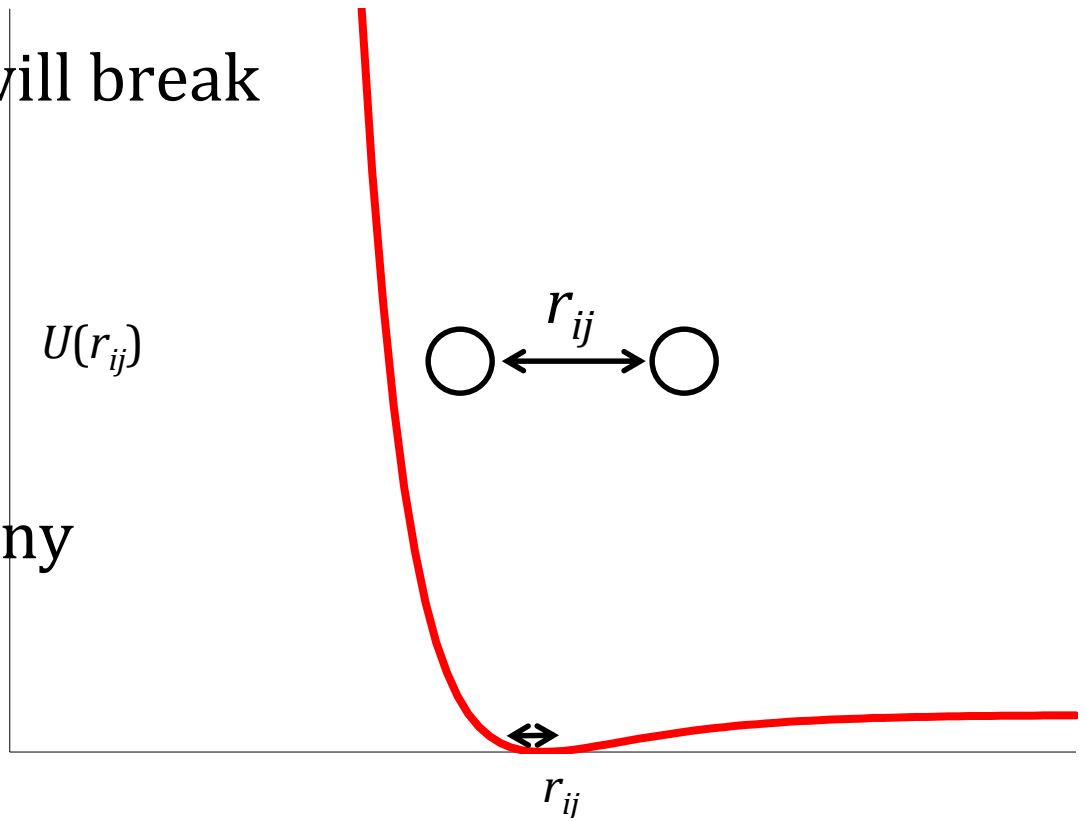
- the Lennard-Jones term would go up

Pull them apart

- eventually the bond will break

Will you meet this ?

- hopefully no
- bond vibrations are tiny



# 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 ?

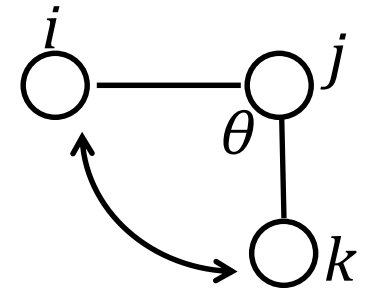
- maybe people simulating chemical reactions

What about angles ?

# Angles

Are they interesting ?

- not very
- a bit more flexible than bonds
- might fluctuate a bit at room temperature



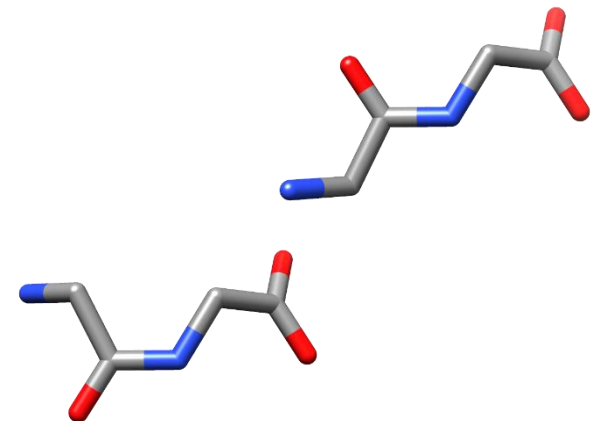
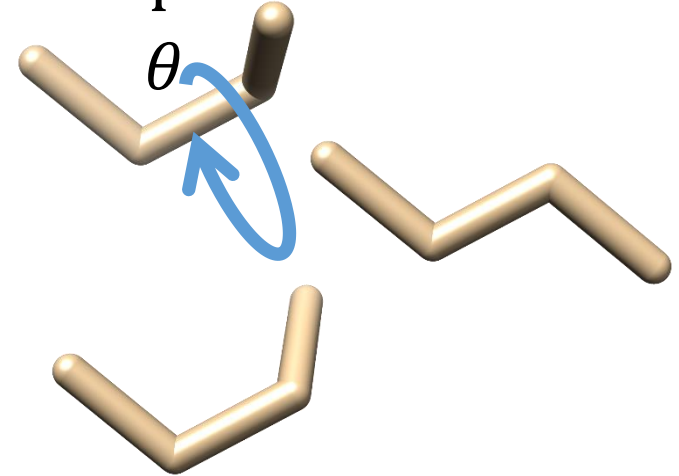
If you have a tetrahedral carbon

- an angle is  $115^\circ$  instead of  $109.5^\circ$  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*)
- what would the form look like ?



# Form of torsion terms

a periodic function

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

with a shift of  $\nu$

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

with periodicity  $n$

$$U(\theta) = \sin(n(\theta - \nu))$$

how high are the barriers ?

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

no physics – just created

# summarise energies

A classic force field has..

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

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torsions	important	
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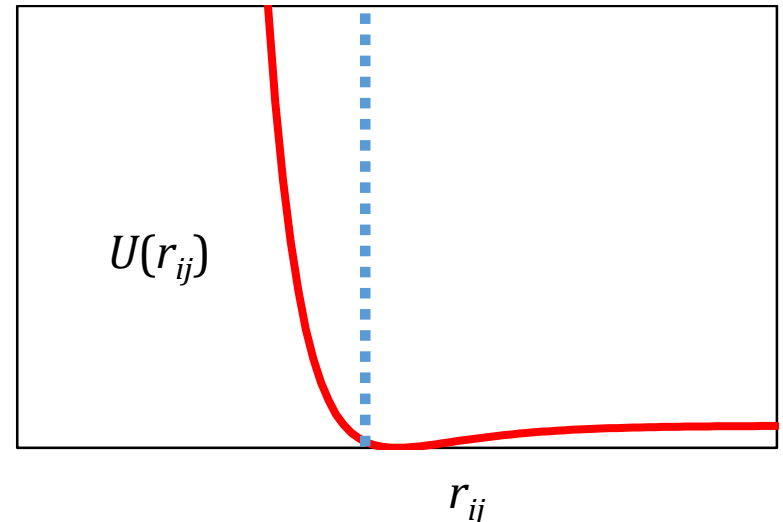


# Not all force fields are the same

Parameters differ (partial charges, barriers)

Forms differ

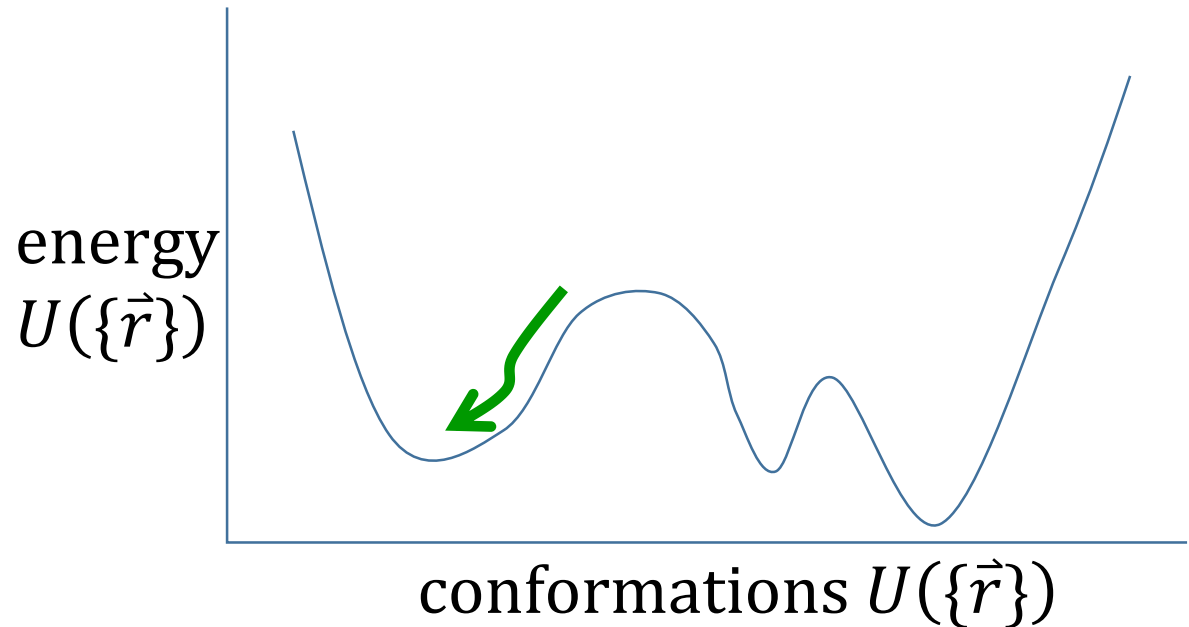
- one often does not care about details
- drop terms that are not interesting
  - treat bonds and angles as rigid



# How do you use them ? (1)

3 or 4 ways

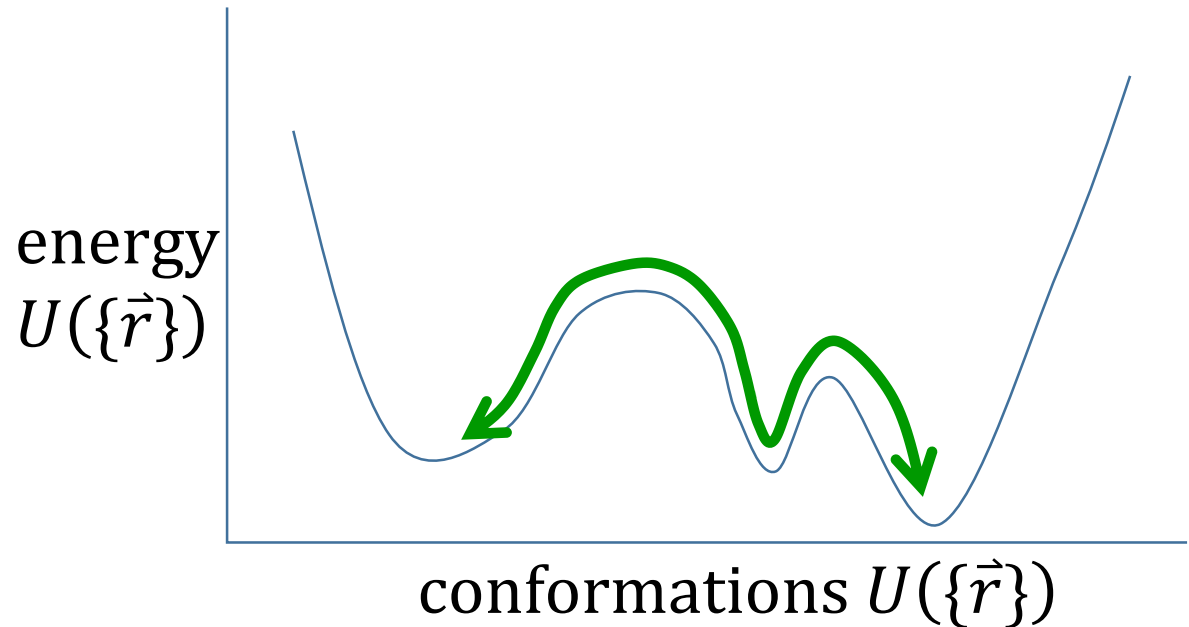
I have coordinates  
and just want  
to remove  
clashes and small  
problems



1. energy minimisation / gradient descent

# How do you use them ? (2)

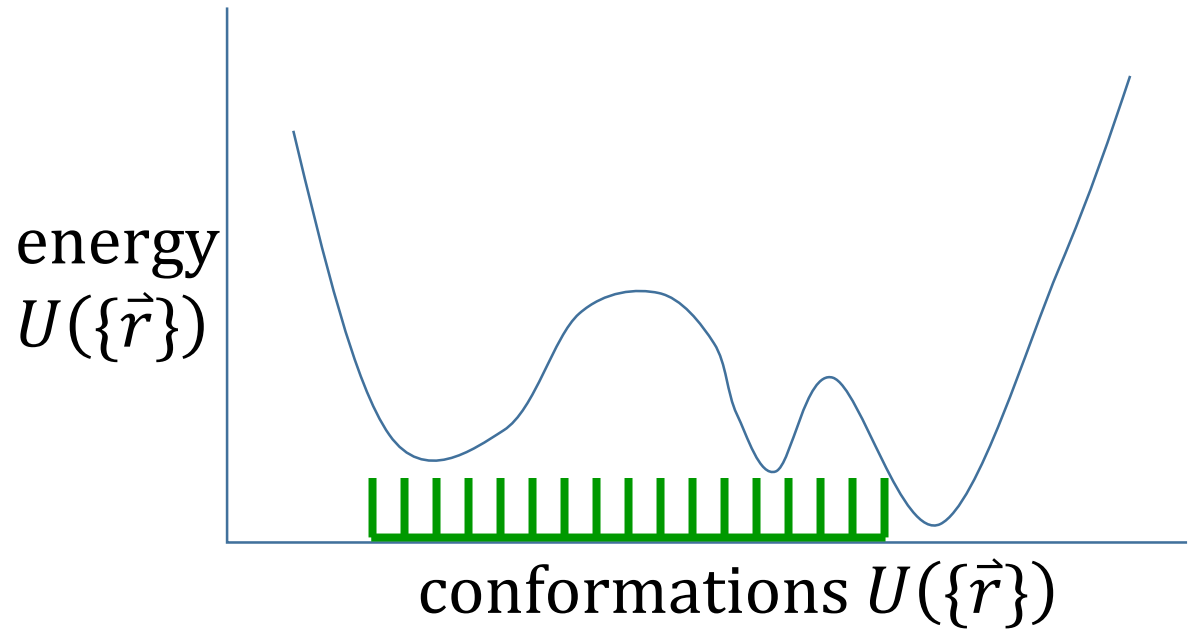
I want to search a big space or simulate dynamics



2. molecular dynamics (or Monte Carlo)  
computationally expensive

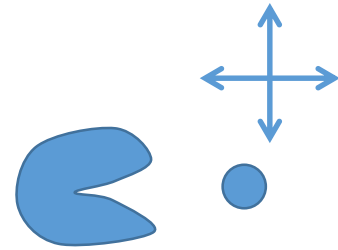
# How do you use them ? (3)

small set of possibilities



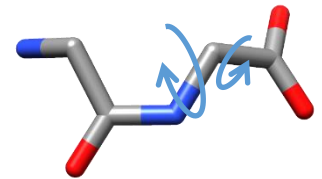
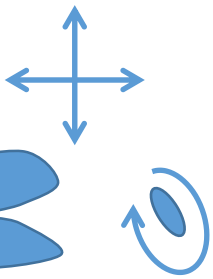
3. grid / gitter search

# 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 rotamers then  $3^m$  search space
- for a protein with  $n$  residues we have  $\phi$  and  $\psi$  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 ?

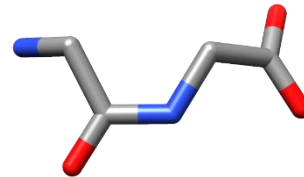
# Entropy

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 ?