

Non-physical dynamics

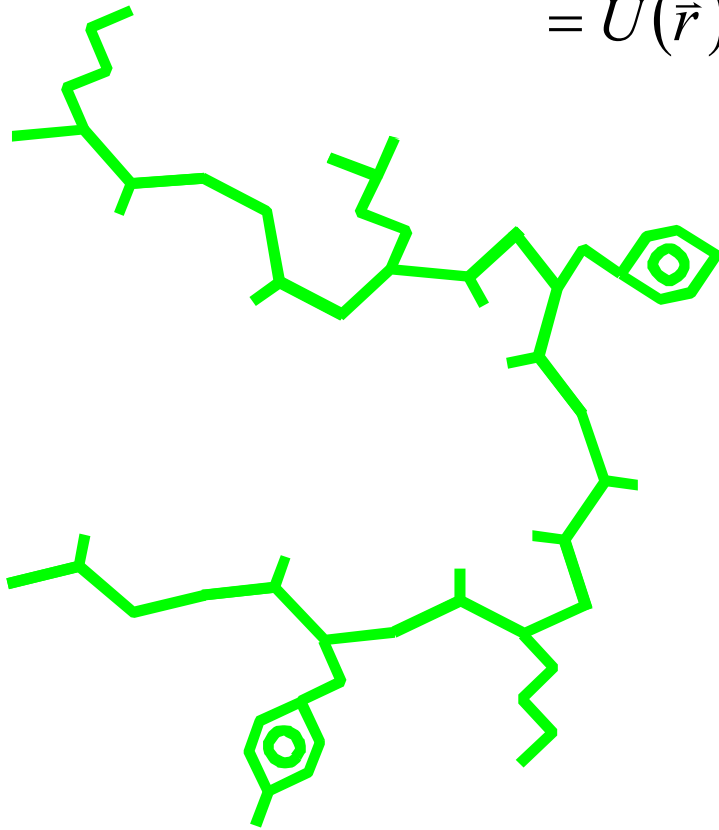
Andrew Torda, Dec 2004

- Why might you want 4 dimensional simulations ?
 - more dimensions
- Completely artificial dynamics

- First, some words about normal MD

Force fields in general

$$\begin{aligned}\text{Energy} &= f(\text{coordinates}, \text{composition}) \\ &= f(\text{coordinates}) \\ &= U(\vec{r})\end{aligned}$$



energy

Why do we need energy ? force fields ?

Applications

- calculating structures
 - distributions of structures
- interactions
- stability
- reaction rates (needs transition states)

Methods

- simulations
 - time
 - molecular dynamics
 - no time
 - Monte Carlo

What do we like in force fields ?

Rules

- no time / path dependence
 - ... if I reach the same coordinates – get same energy
 - energy conservation

Useful

- derivatives
 - (not essential) force $\vec{F} = -\frac{\partial U(\vec{r})}{\partial \vec{r}}$

Dogma

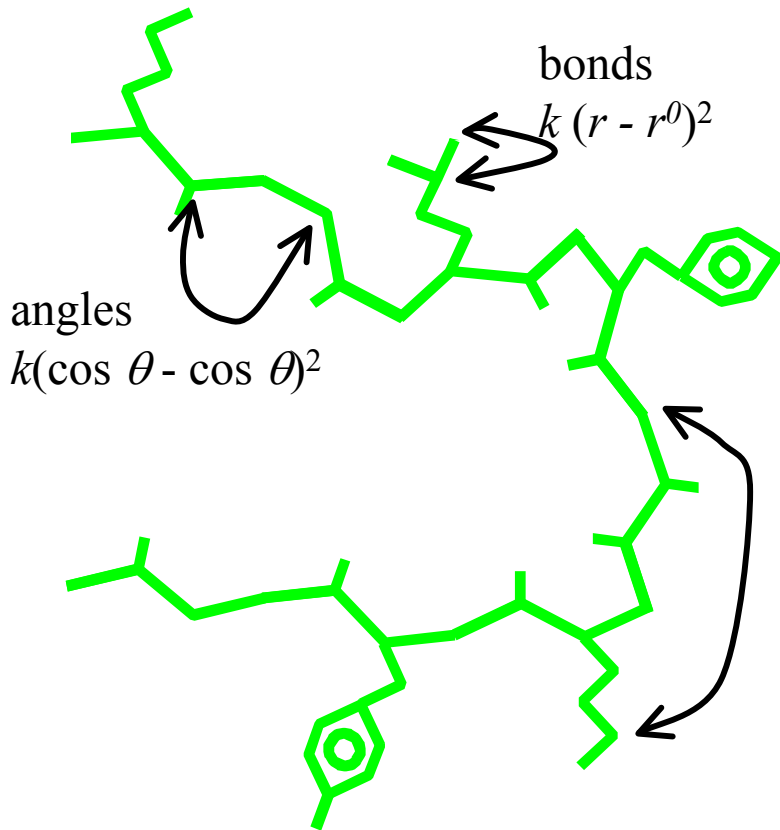
- we care about low energy conformations / configurations

Protein MD/molecular mechanics example

- classic literature application
- example force field

$$U(\vec{r}) = \frac{1}{2} \sum_{bonds} k_b (b - b_0)^2 + \frac{1}{2} \sum_{\substack{bond \\ angles}} k_{angles} (\theta - \theta_0)^2 + \sum_{dihedrals} k_\phi (1 + \cos(n\phi - \delta))$$
$$+ \sum_{i < j} (ar^{-12} + br^{-6}) + \sum_{i < j} \frac{q_i q_j}{Dr}$$

- friendly version...



More on applications

Distributions

- move atoms
 - molecular dynamics (MD), monte carlo
 - explore allowed configurations

Low energy configurations

- cool system

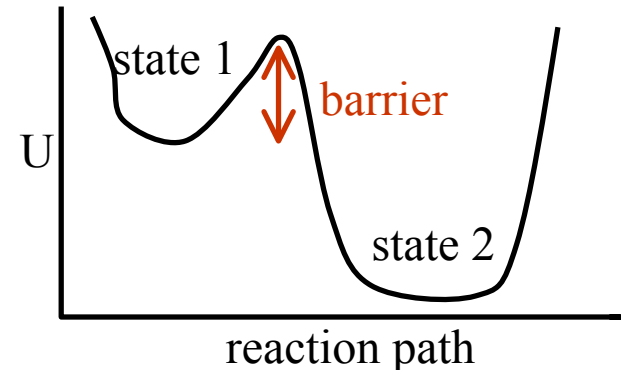
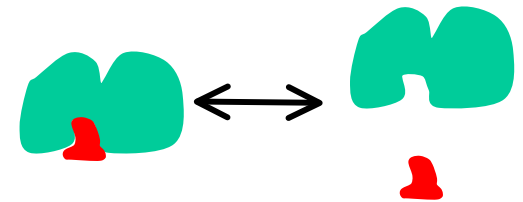
Binding ?

- what is energy difference between states ?

Kinetics ?

- not likely – assumes pathway

...Back to low energy configurations



Low energy configurations proteins ?

Protein chemists / calculators

- 100s cpu years ...
- take protein
- simulate
- wait (months)
- look at configurations

Can one do something more imaginative ?

- methodology nice
 - uses gradients
 - suitable for annealing (cooling)
- entertaining applications

Imaginary degrees of freedom

How many degrees of freedom do you have ?

- atoms $3n / 3n - 6$?

How many would you like ?

- more

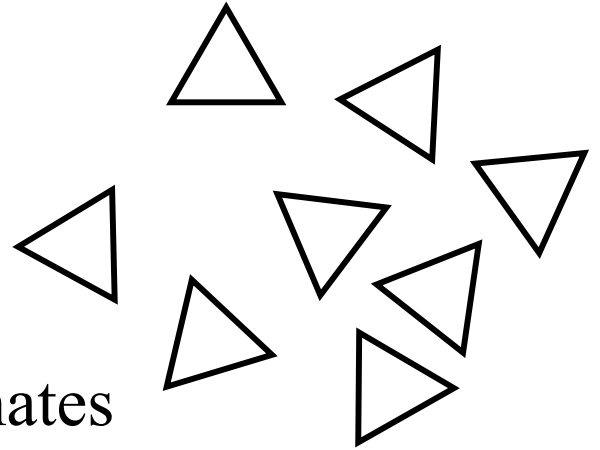
Reasons

- 4d dynamics
- distance geometry
- energy embedding
- thermostats
- orbitals
- charges

More dimensions are useful

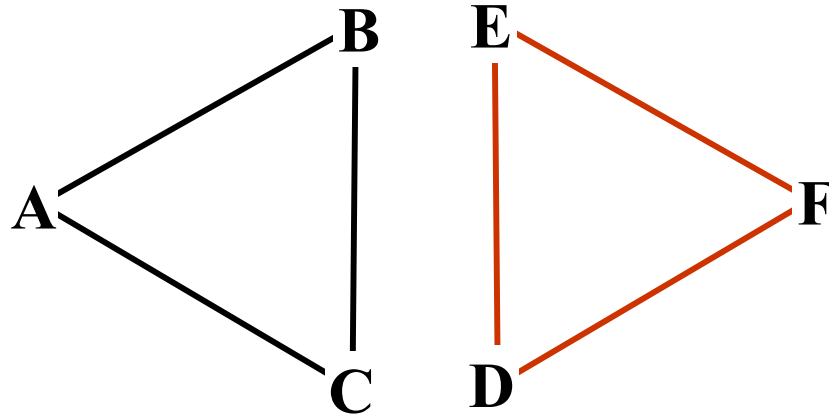
Simple world

- 2D chemistry
- optimisation of geometry
- we work with two dimensional coordinates



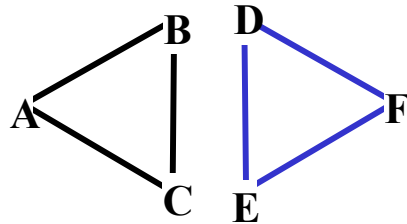
Mission

- optimise geometry

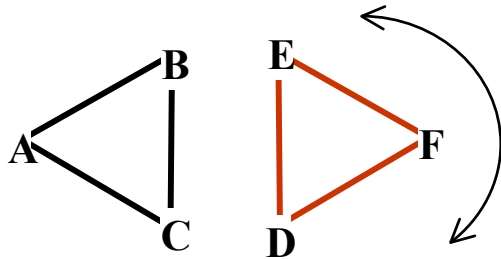


More than 3 D

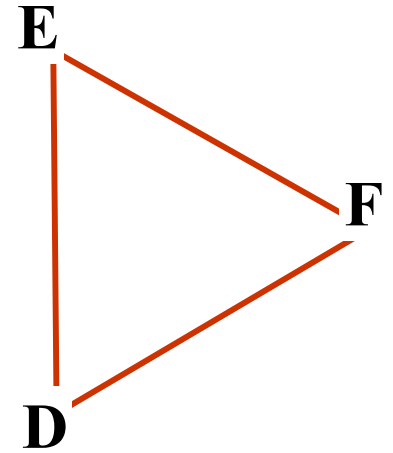
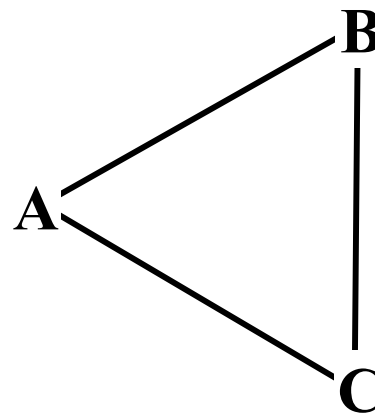
- 6 atoms / 2 molecules
- measured
 - $BD=1$
 - $CE=1$
 - $BE=4$
- solution ?



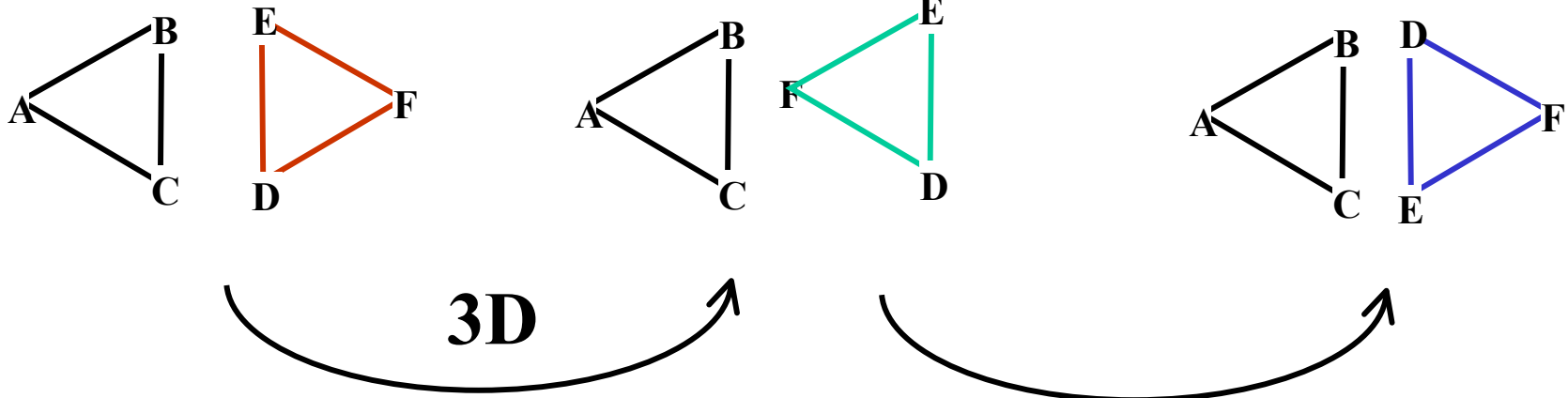
- path ?



- not a problem in 3D



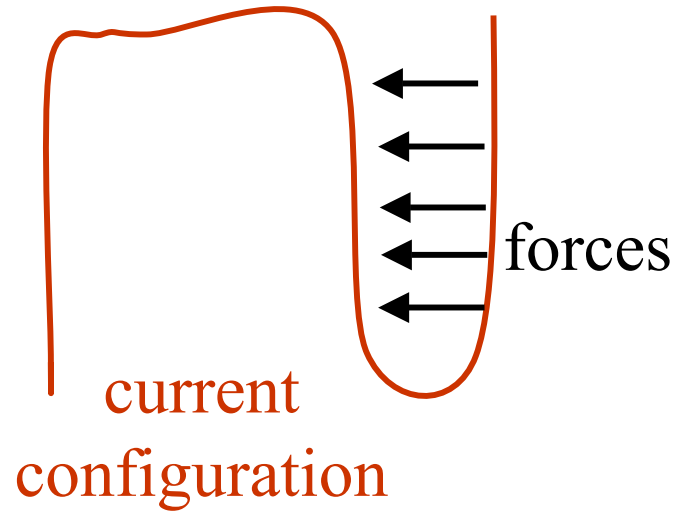
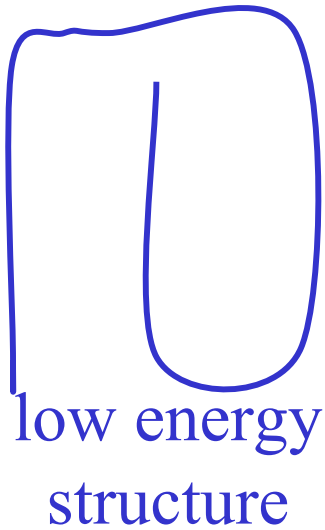
Adding a third dimension



- Is this only an issue in toy systems ?

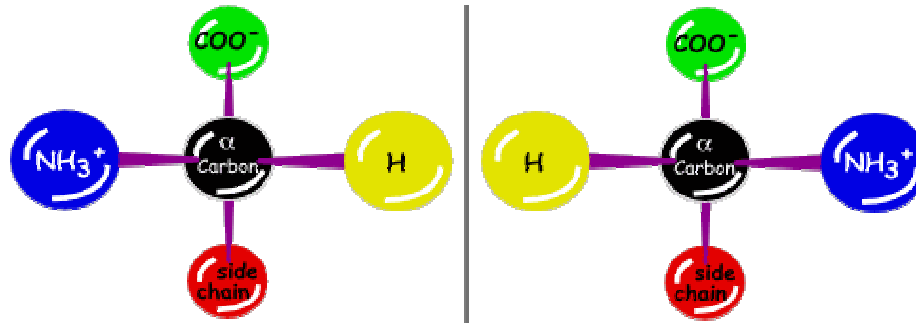
Why 4D ?

- Large scale problem
 - protein fold rearrangement



- how nasty ?
- another major problem

Chirality



who makes mess of chirality ?

- simulators ? No

distance geometry

- left and right pictures are indistinguishable in DG
- worse – DG structures have a mix of correct /incorrect chirality
- real algorithms...

DG and 4D

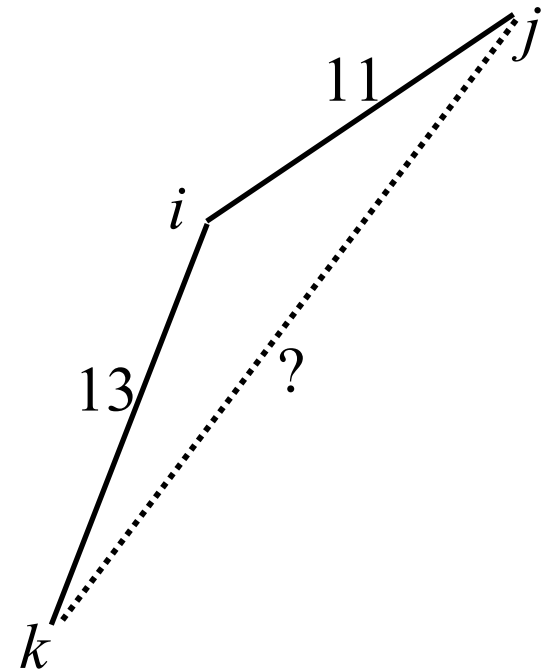
- Distance matrix \rightarrow metric matrix \rightarrow 3D coordinates
- Take mirror image
- calculate overall chirality error of left and right
- pick best overall
- refine

OR (Hare approach ?)

- Distance matrix \rightarrow metric matrix \rightarrow **4D** coordinates
- turn on 3D chirality term
- penalty function
 - 3D chirality, 4D penalty
- dynamics
 - squash to 3D

Distances and dimensions

- molecular dynamics in 4D*
 - pure refinement trick / barrier crossing
 - demonstrated on small peptides
- general problem
 - distance information
 - $d_{ij}=11$ $d_{ik}=13$ $d_{jk}=25$
- sneak into higher dimensions
- what if I have lots of atoms.. ?



energy embedding

- 3 dimensions is good for 4 points
 - 4 D for 5 points
- N-1 dimensions are good for N points
- high dimensions
 - easy to place atoms
 - can accommodate distances +
 - can minimise functions like $E = k (r-r_0)^2$
- method

```
embed  $N$  points in  $N_d=N-1$  dimensions
while ( $N_d > 3$ ) {
     $N_d := N_d - 1$       (how ?)
    optimise            (local optimiser)
}
```

Reducing dimensions

General idea

- find the dimension where system is smallest
- get rid of it

Example

- find moments of inertia + rotations + projections

Other ways

- cunning methods to do local rotations /maintain chemistry*
- 4 to 3 D
 - rotation + abfall bin
 - penalty function
 - first order coupling (3 to 4 to 3)

Why we do not like 4D (and more)

Problems

- 100 to 99 easy, 4 to 3 no fun
- a 4D configuration may not be so close to correct answer
- the projection/compression may distort 3D structure
- do N D optima correspond to 3D ones ?
- path dependence of dimensional reduction
- memory (N^2)

Peculiarities

Properties and Peculiarities

Comparison with annealing ?

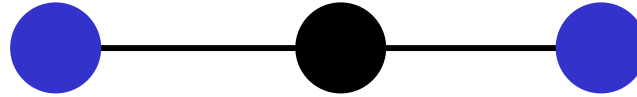
- annealing gives you a continuous variable (good)
- annealing takes forever / non-deterministic (bad)

Quirks

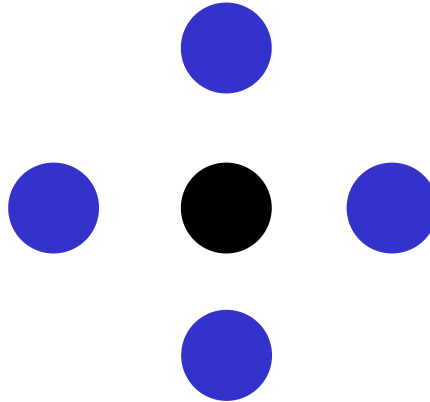
- distance terms are easy in ND
- trig terms are not
 - dihedrals / torsions
- speed / neighbours / memory ...

Neighbour counting ND

- 1D 2 neighbours



- 2D 4 neighbours



- 3 D 6 neighbours

- ND ?

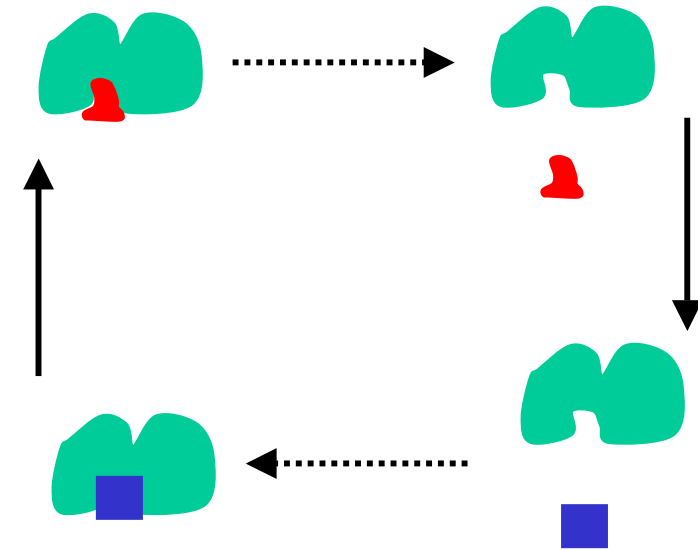
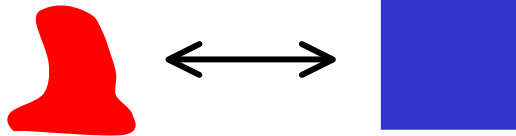
- more in 4D...

Free energy

Who binds best ?

- red  or blue ? 

How to go ?



- $\Delta \Delta G$ is path independent
- bonds, atoms, charges in any order

Real problem

- sampling

$$G = -kT \ln \left(\frac{1}{h^{3N} N!} \int e^{-H(\mathbf{p}^N, \mathbf{r}^N) / kT} d\mathbf{p}^N d\mathbf{r}^N \right)$$

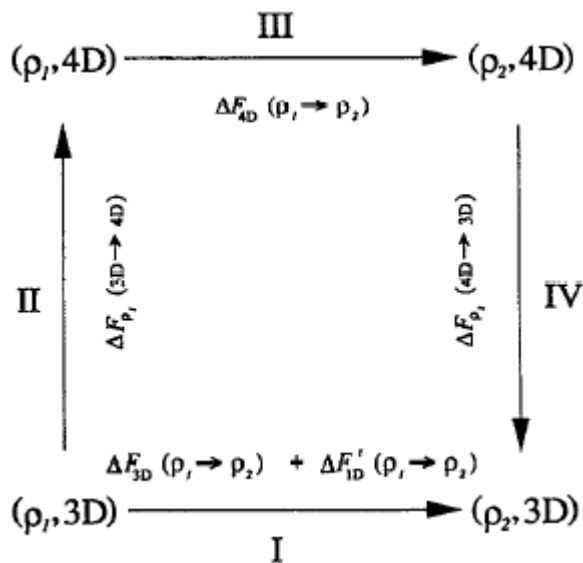
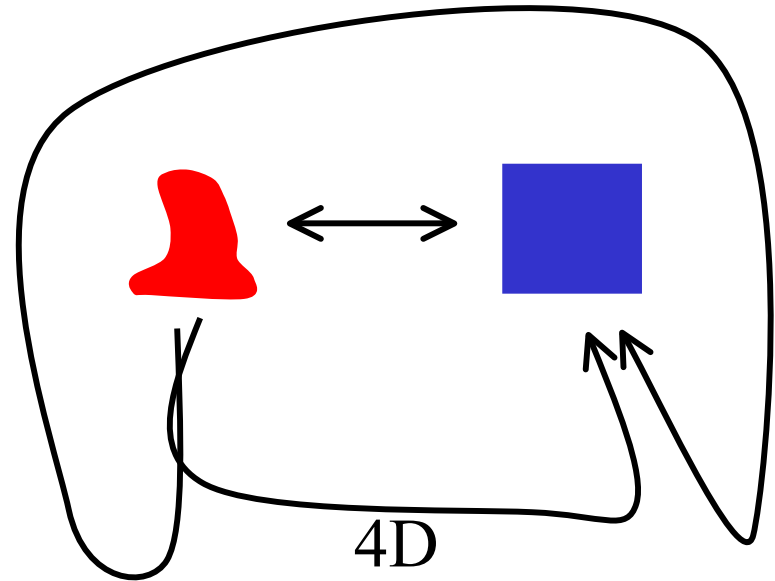
More entertaining paths

We have a sampling problem ?

- use a better sampling method

problem ?

- change density of a LJ fluid



4D paths not quite so simple

- obscure coupling of 3 and 4D energy components
- separate 4D temperature / energy / dynamics
- some energy terms difficult
 - anytime you cannot remove cross products
 - torsions, ring planarity, chirality
- work done on system 3D \rightarrow 4D \rightarrow 3D
 - use a harmonic penalty function
 - can be calculated analytically
- justification ?
 - more homogenous sampling of phase space
- more fictitious degrees of freedom

fictitious degrees of freedom / particles

Problem class

- serious physical model (atoms, bonds, ...) +
- interacting component, we do not want details

Car-Parinello method

- we think about heavy atoms
- they know where their electrons are
- model electrons in some arbitrary manner
- electrons adapt to motion of nuclei
- attach fictitious masses to orbitals – let them do MD in their own space

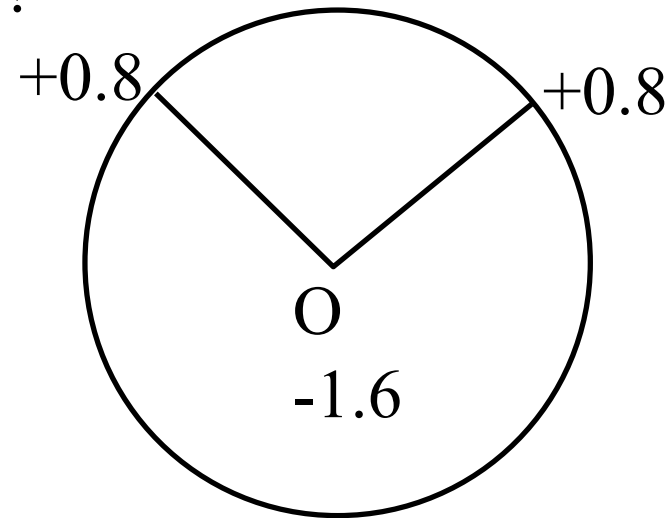
more classical application...

Classic water models

What does an MD simulator think of water ?

- one radius for L-J
- 3 charges
- one mass point
- fixed geometry

- occasionally reparameterised



Water model properties

Good parts

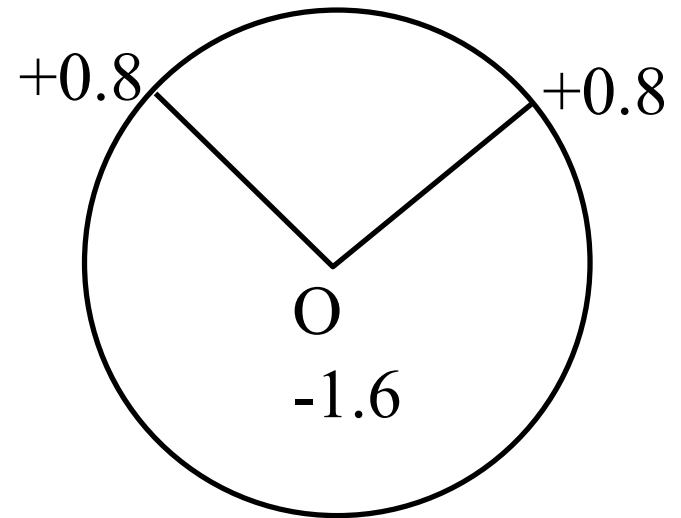
- radial distribution function
- energies
- maintaining protein / solute structure

more difficult

- dielectric constant
- diffusion, translation, rotation

why ?

- permanently polarised



How to fix

Water molecules talk to each other + solutes

- charges move

Quantum mechanical approach ?

- how many orbitals to treat ?
- which phenomena to treat (correlation / exchange / ...)
- who cares ? we want macroscopic properties

Special dipole term ?

- what level ?
- r^{-3} interactions
- usually expensive matrix inversions

Aim

- some way to model the effect of charges feeling each other
- Rick.. Berne water model

Fluctuating charges

Electrons are a gas

- not a wave or anything fancy
- this gas moves faster than atoms

How to code this ?

model

- charges interact with each other
- charges interact with their home atom

$$U(\mathbf{Q}, \mathbf{r}) = \sum_A Q_A + \frac{1}{2} \sum_{AA} J_{AA}^0 Q_A^2 \quad \text{charge on atom}$$
$$+ \sum_{iA < jB} J_{AB}^0(r_{iAjB}) Q_{iA} Q_{jB} \quad \text{Coulomb}$$
$$+ V(r_{iAjB}) \quad \text{miscellany}$$

- does this help us ?

Fictitious dynamics

Normal MD $\vec{F} = m\vec{a}$ $\vec{F} = \frac{\partial U}{\partial \vec{r}}$ $a = m^{-1} \frac{\partial U}{\partial \vec{r}}$

swap notation $\ddot{x} = m^{-1} \frac{\partial U}{\partial x}$

for normal systems we use
$$U(\vec{r}) = \frac{1}{2} \sum_{bonds} k_b (b - b_0)^2 + \frac{1}{2} \sum_{bond\ angles} k_{angles} (\theta - \theta_0)^2 + \sum_{dihedrals} k_\phi (1 + \cos(n\phi - \delta))$$
$$+ \sum_{i < j} (ar^{-12} + br^{-6}) + \sum_{i < j} \frac{q_i q_j}{Dr}$$

The trick – we have $U(\mathbf{Q}, \mathbf{r}) = \dots$

$$\ddot{Q} = m^{-1} \frac{\partial U}{\partial Q}$$

the meaning

Using this acceleration

$$\ddot{Q} = m^{-1} \frac{\partial U}{\partial Q}$$

- use numerical integration
- partial charges run around like particles

Fictitious charge dynamics

- temperature
- temperature bath
- extra constraints possible
 - overall charge conservation
- coupling ?
 - as atoms move they talk through r_{iAjB} terms
 - no real thermal coupling
- how real ?

How real are the dynamics ?

Mass

- arbitrary
- too small – too hard to integrate
- too big – responds slowly

Implementation

- keep charges cool
- near lowest energy
 - they simply follow movement of heavy particles

More tricks

- can apply hard restraints
 - overall neutrality

What else can one do ?

Car-Parrinello

- use DFT methods to optimise orbitals
- fictitious masses / dynamics

Small approximation (compared to matrix methods)

- system is not absolutely optimised

Useful property

- $U(\mathbf{r})$ or $U(\mathbf{q})$..
- no time – conserve energy

Last example

Some examples

- 4D weakly coupled to 3D
- thermal coupling depends on frequencies of motions
- 4D dynamics coupling via some scalar energy terms
- fluctuating charges

Deliberately couple a system to something non-existent ?

- add (some) fictitious degrees of freedom which interact
- they can add or remove energy
 - regulate energy

Why we need heat baths

Simulations make /consume energy

- errors, rounding
 - NOT wanted

Artificially control energy

- annealing
- gradients

Problems are usually artificial

- solutions (heat baths) artificial

A thermostat

- invent a degree of freedom (like a particle in a 1D space)
- interacts according to temperature of real system
- normal Newtonian dynamics $m\vec{a} = \vec{F}$
- different notation $\dot{p}_i = \vec{F}$
- heat bath ? $\dot{p}_i = \vec{F} - \zeta \dot{p}_i$
- coupling $\zeta = M_{fake}^{-1} \sum_{i=1}^N \frac{p_i^2}{m} - k$
- as in other schemes, M_{fake} determines coupling
 - maintains ensemble, need not interfere with dynamics (much)

The end

- most boring packages work in 3D
- most statistical mechanics generalises readily to ND
- extra degrees of freedom
 - searching methods
 - models to optimise parts of a system
 - act as a reservoir for real system

- next week
 - history and mistakes in protein structure prediction