

This semester

Andrew Torda, April 2011

- Models – mostly proteins
 - from detailed to more abstract models

Books

- None necessary
 - for my group and Prof Rarey
 - “Molecular Modelling: Principles and Applications”
Leach, Andrew
 - some later material (Monte Carlo) from
 - "Understanding Molecular Simulation", Frenkel and Smit

Grand Plan

- Models for proteins (mostly)
 - from detailed to less details
- Energies
- Dynamics
- Basis of them
- How to work with them
 - simulations, calculations
 - protein folding, evolution
- What kind of model is appropriate for different problems ?

Themes

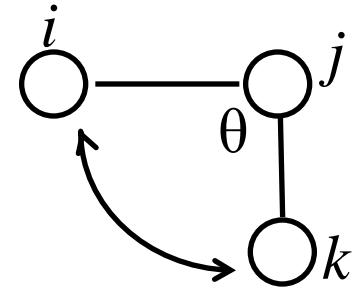
- atomistische Energie-Modelle
- Energie / Freie Energie
- Monte Carlo (MC)
- Molecular Dynamics Simulations (MD)
- Applications and Extensions of MC and MD
- Advanced Monte Carlo
- Water
- Coarse Grain / Mesoscopic / low resolution methods
- Lattice Methods
- Evolution
- Protein Folding

Organization

- In prinzip
 - 2 × Vorlesung
 - 1 × Vorlesung
 - 1 × Übung
- In Praxis
 - 2 × Vorlesung + 2 × Vorlesung or
 - 2 × Vorlesung + 2 × Übung
- People
 - Marco Matthies
- Sprache
 - Sind wir mit Englisch wirklich glücklich ?

Some questions

- 3 bonded atoms – push atom k left
 - which atoms will feel a force ?
- I have a multiple sequence alignment
 - the conserved sites are most important
 - is this true ?
- Can you compare the free energy of two conformations of
 - a drug
 - a protein ?
- to be answered during the semester



Do I have to memorise all the formula ?

- Very few
 - Coulombs law
 - example form of energy for bonds and angles
 - Boltzmann distribution
 - definition of entropy
 - relationship of free and potential energy
- Most other examples will be derived

Atomistic Energy Models

- Why do we need models ?
- Previous lectures – need for low energy configurations
 - really needs definition of energy
- Can we define energy ?
 - for very simple systems yes
 - for more complex systems
 - only approximations
- Need to know when approximations are small and when bad
 - are charges on atoms like fixed charges ?
 - not for chemical reactions
 - are bonds like springs ?

Is energy sufficient ?

Does the world care about potential energy ?

- no. Really cares about free energy

$$G = U - TS \quad (\text{usually speak of } \Delta G)$$

Approach to free energy

- calculate potential energy " U " with a model
- get entropy " S " from some sampling method (often implicit)

Need good models for energy

Definitions

- This topic is classical / atomistic
- Often referred to as “molecular mechanics”
- quantum effects are not reproduced

Different levels of models

	ab initio	very detailed
QM		
	semi-empirical	
atomistic		
coarse grain		
continuous		
lattice		
big molecule as single point		very coarse (colloids, diffusion)

Why we like atomistic models

- intuitive
 - how do we draw structures ? store coordinates ?
- atoms sometimes correspond to measurable properties
 - x-ray crystallography, NMR
- predicting some dynamics
- interactions between proteins, proteins + ligands

What do we want to be able to do ?

- Often to simulate a system
 - Monte Carlo, molecular dynamics (MD)
 - details later, for MD we need
 - $F = ma$ (Newton), $a = F/m$ gives us acceleration and
 - $F = -dU / dr$ or better $\vec{F} = -dU / d\vec{r}$
 - important.. friendly energies have proper derivatives

Force fields in general

- What is a force field ?
 - the set of equations / formulae that tell us about the force acting on a particle
 - classic example
 - I have charge
 - if I bring another charge near, it feels a force due to the first
 - what is the equation telling me about the energy ?

$$U(r_{ij}) = \left(\frac{1}{4\pi\epsilon_0} \right) \frac{q_i q_j}{r_{ij}}$$

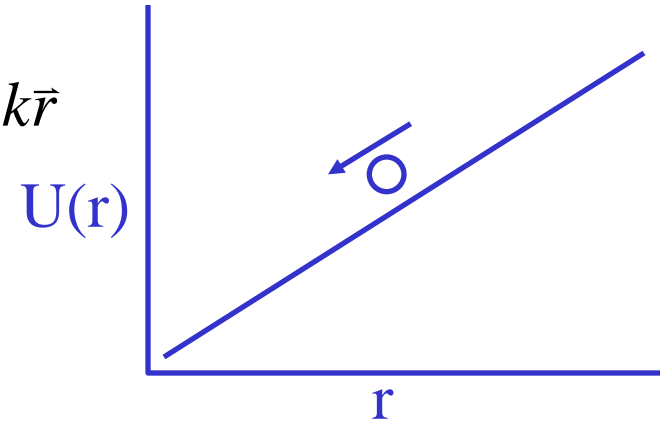
- and the force...

Force fields, energies, derivatives

- Important rule $\vec{F} = -dU/d\vec{r}$

- a toy example, one dimension $U(\vec{r}) = k\vec{r}$

- force is
$$\vec{F} = -dU/d\vec{r}$$
$$= -k$$



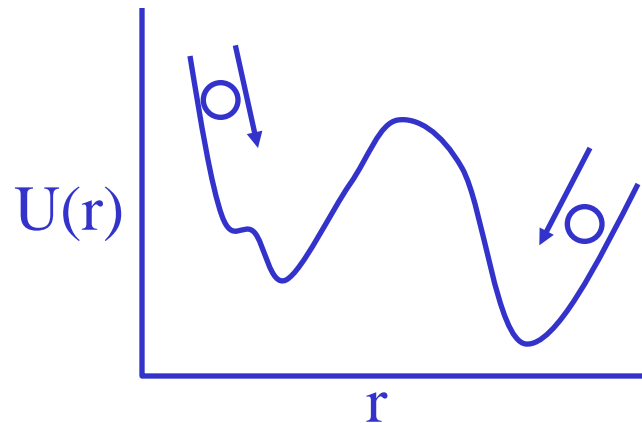
- how do we want force ?

- in x, y, z terms \vec{r}

- really $F_x = -\partial U/\partial x$

$$F_y = -\partial U/\partial y$$

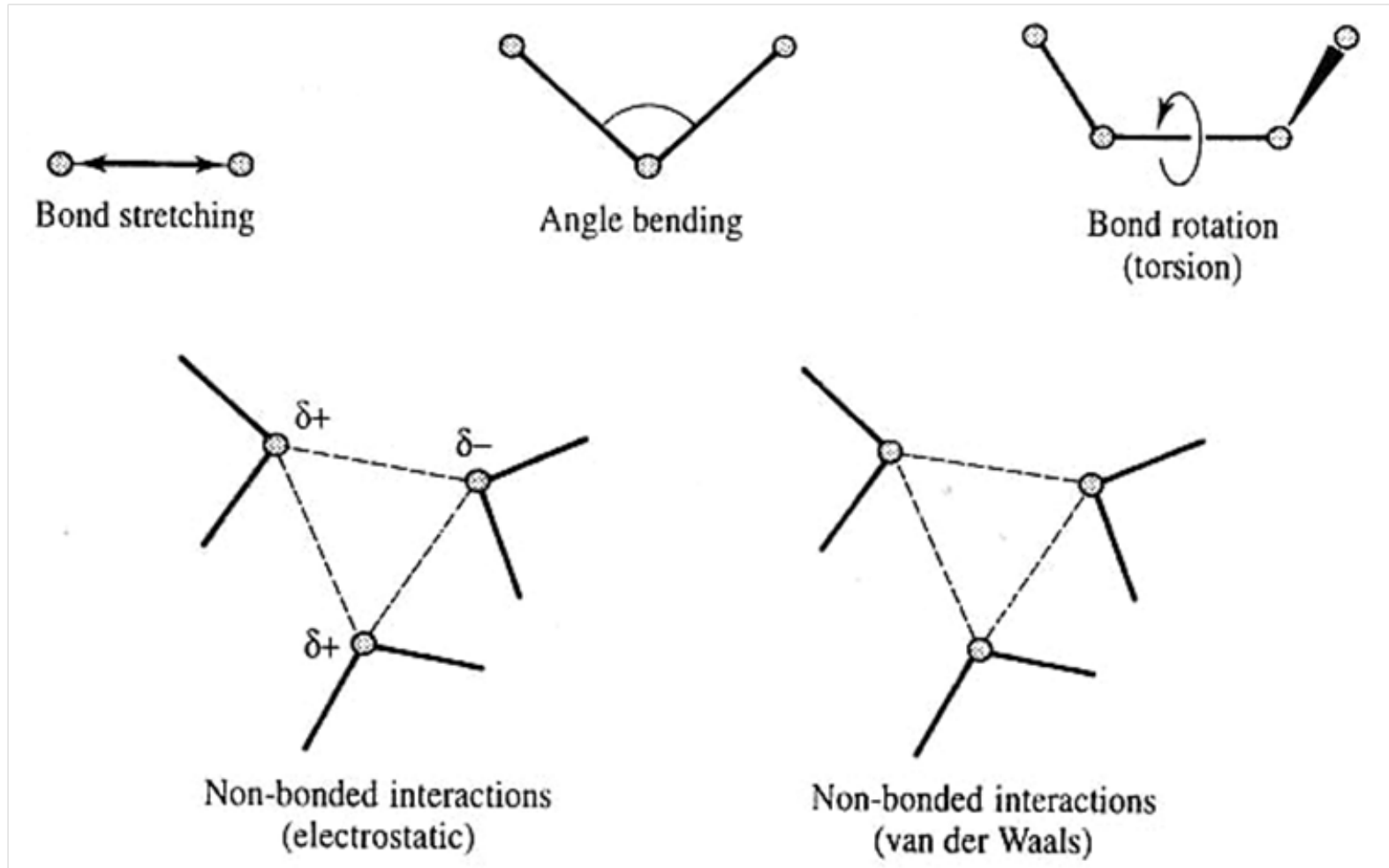
$$F_z = -\partial U/\partial z$$



A simple force

- With an energy $U(r_{ij}) = \left(\frac{1}{4\pi\epsilon_0} \right) \frac{q_i q_j}{r_{ij}}$
- force is $\vec{F} = -dU/d\vec{r} = \left(\frac{1}{4\pi\epsilon_0} \right) \frac{q_i q_j}{r_{ij}^2} \hat{r}_{ij}$
- Rule
 - if the derivative of energy is non-zero
 - there is a force
 - exam questions about bond angles, dihedrals, ...

protein force field (picture)



Protein force fields scary equation

$$\begin{aligned}
 U(\mathbf{r}) = & \sum_{i=1}^{N_{bond}} \frac{k_i}{2} (r_i - r_{i,0})^2 && \text{bonds} \\
 + & \sum_{i=1}^{N_{angle}} \frac{k_i}{2} (\theta_i - \theta_{i,0})^2 && \text{angles} \\
 + & \sum_{i=1}^{N_{dihedral}} k_i (1 + \cos(n\varphi_i - v_0)) && \text{dihedrals} \\
 + & \sum_{i=1}^{N_{atom}} \sum_{j=i+1}^{N_{atom}} 4\epsilon_{ij} \left(\left(\frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}} \right)^6 \right) + \frac{q_i q_j}{4\pi\epsilon_0 r_{ij}} && \text{non - bonded}
 \end{aligned}$$

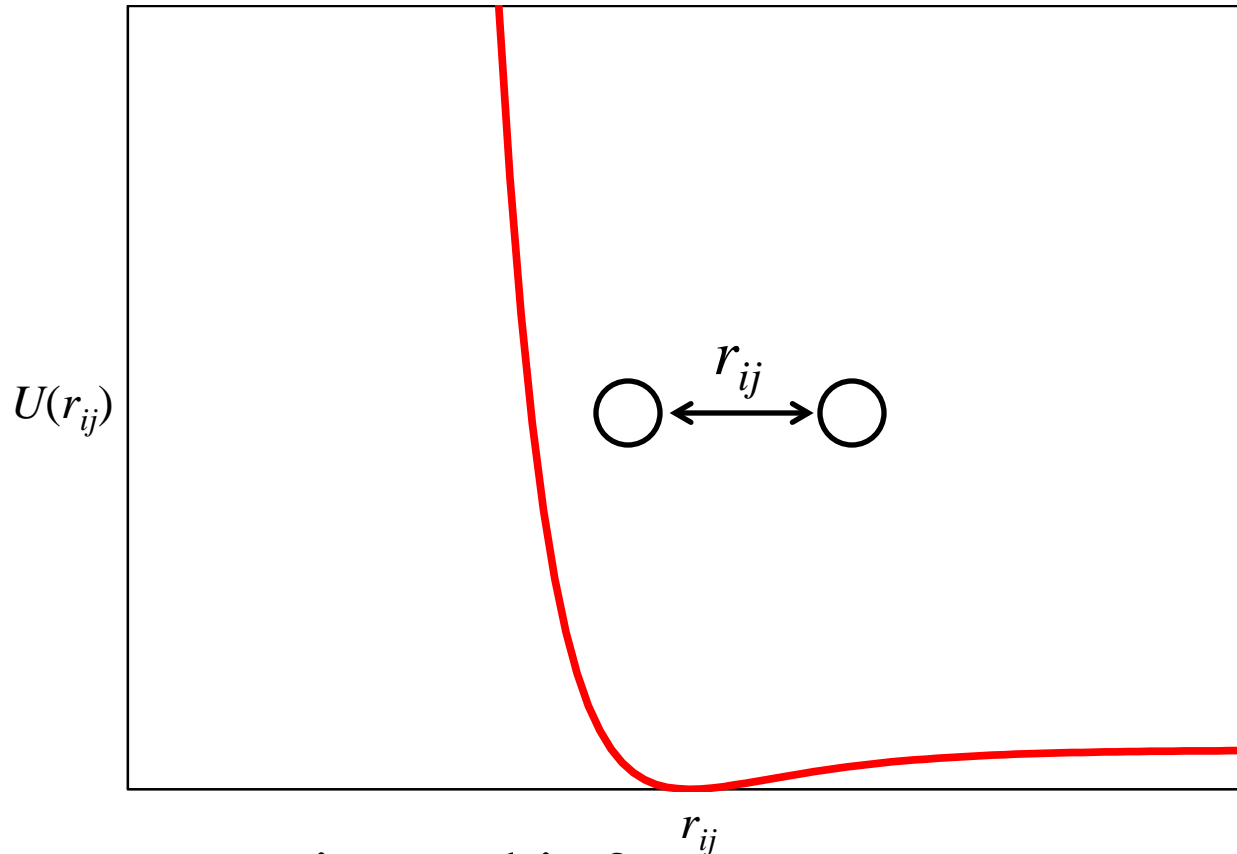
Is this the truth ?

- not a bad model

Bonds

What are bonds really ?

- as we pull two particles apart, what happens ?

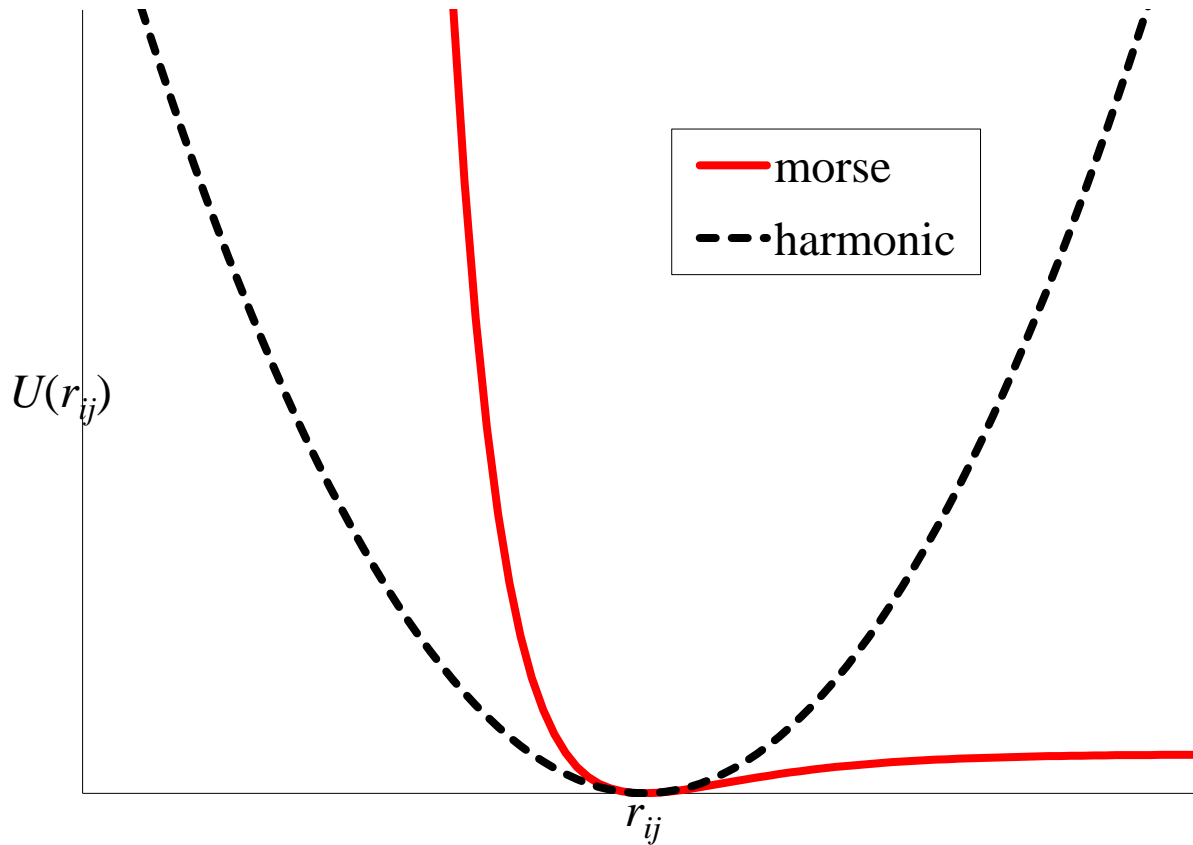


Can we approximate this ?

- this formula has $\exp()$ terms - cpu expensive

Bonds - approximate

- Is the black line a good approximation ?

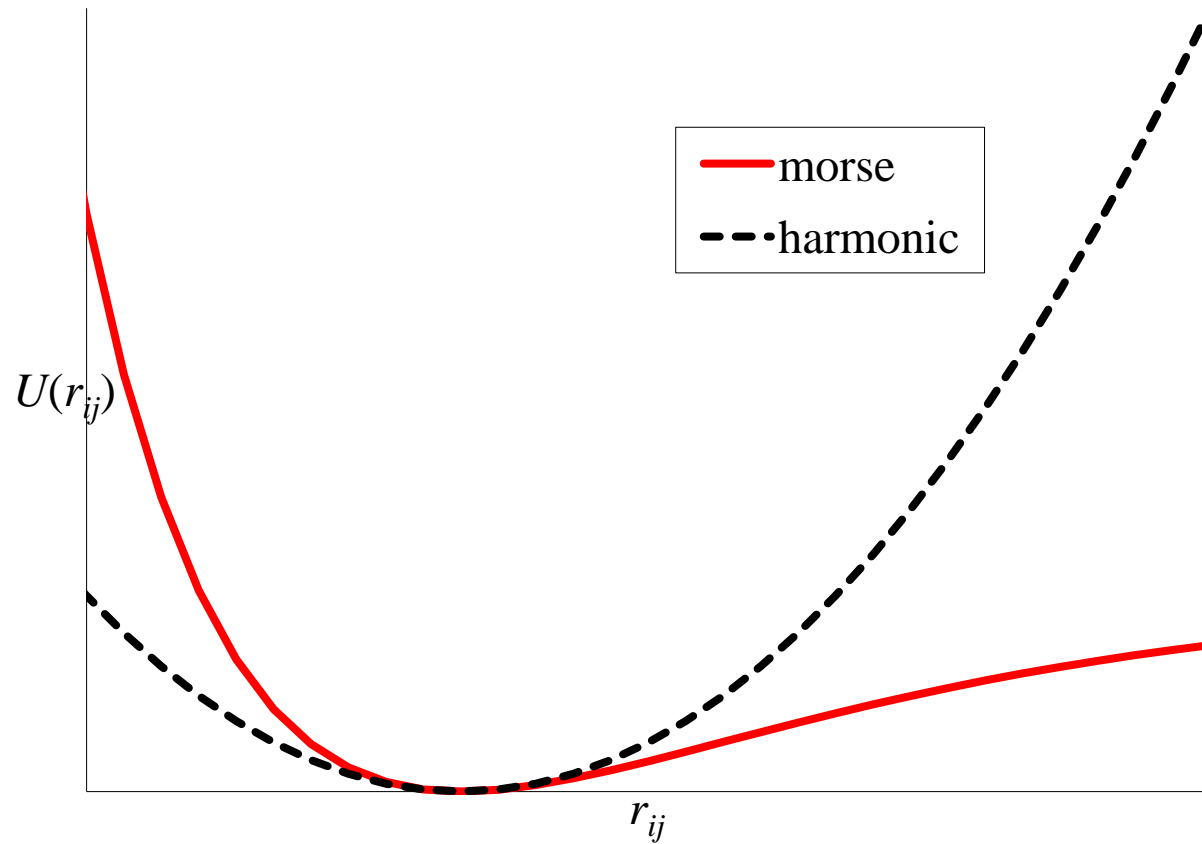


$$U(r_{ij}) = \frac{k}{2} (r_{ij} - r_0)^2$$

Bonds – good enough

Bonds don't stretch much

- harmonic is often good enough



Why do we write $k/2(r_{ij}-r_0)^2$?

Bonds – the end

- We normally write $U(r_{ij}) = k/2 (r_{ij} - r_0)^2$

$$\begin{aligned}\vec{F}_i &= -\frac{k_{ij}}{2} \frac{dU\left(|\vec{r}_{ij}| - r_{ij,0}\right)^2}{d\vec{r}_{ij}} \\ &= -k_{ij} \left(|\vec{r}_{ij}| - r_{ij,0}\right) \vec{r}_{ij}\end{aligned}$$

- so first form looks like Hookes law

Do bonds matter ?

- fluctuations very small at room temp ($< 0.1 \text{ \AA}$)
- our structures are not so accurate / we simulate to look at coarse features
- often treated as rigid joints (maybe more in MD lectures)

Angles

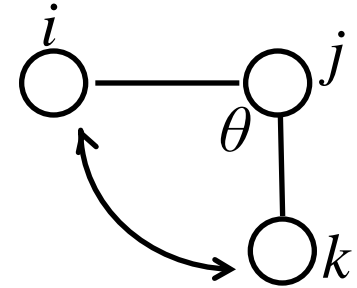
- Angles are not as boring as bonds

$$U_{angle}(\vec{r}_i, \vec{r}_j, \vec{r}_k) = \frac{k}{2} (\theta_{ijk} - \theta_0)^2$$

or

$$U_{angle}(\vec{r}_i, \vec{r}_j, \vec{r}_k) = \frac{k}{2} (\cos \theta_{ijk} - \cos \theta_0)^2$$

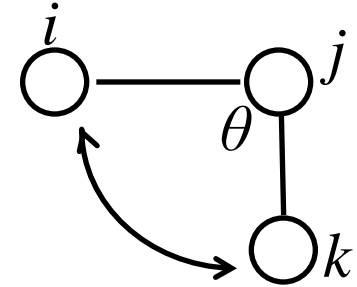
but to get forces is messy
(use chain rule)



Why is this difficult ?

- We use physical models like

$$U_{angle}(\vec{r}_i, \vec{r}_j, \vec{r}_k) = \frac{k}{2} (\cos \theta_{ijk} - \cos \theta_0)^2$$



- force is obvious
 - looking at picture
 - in terms of $\cos \theta$
 - in terms of θ ?
 - we want x, y, z

$$\begin{aligned} F_{angle}(\vec{r}_i) &= -\frac{\partial U(\vec{r}_i)}{\partial(\vec{r}_i)} \\ &= \frac{-\partial U(\vec{r}_i)}{\partial \cos \theta} \frac{\partial \cos \theta}{\partial(\vec{r}_i)} \\ &= \frac{-\partial U(\vec{r}_i)}{\partial \cos \theta} \frac{\partial \cos \theta}{\partial \theta} \frac{\partial \theta}{\partial(\vec{r}_i)} \end{aligned}$$

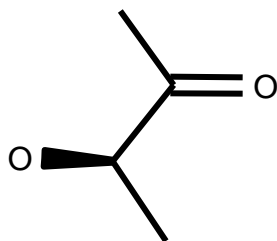
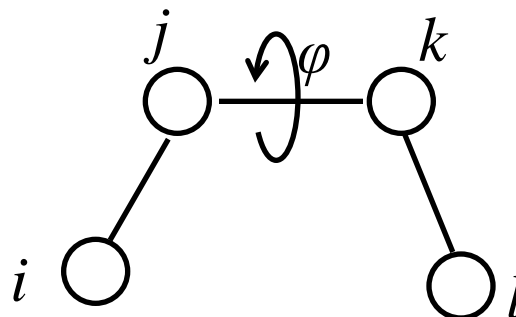
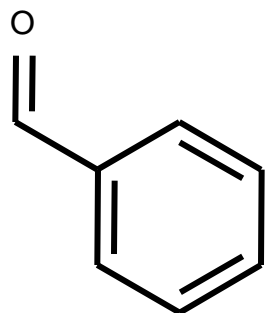
Angle forces

$$\begin{aligned} F_{angle_i} &= \frac{-\partial U_{angle}(\vec{r}_i)}{\partial \vec{r}_i} \\ &= \frac{-\partial U_{angle}(\vec{r}_i)}{\partial \cos \theta_{ijk}} \frac{\partial \cos \theta_{ijk}}{\partial \vec{r}_i} \\ &= -k(\cos \theta_{ijk} - \cos \theta_0) \left(\frac{\vec{r}_{kj}}{r_{kj}} - \frac{\vec{r}_{ij}}{r_{ij}} \cos \theta_{ijk} \right) \frac{1}{r_{ij}} \end{aligned}$$

- the other atoms ?
 - similar expression for F_k
 - $F_j = -(F_i + F_k)$

dihedral / torsion angles

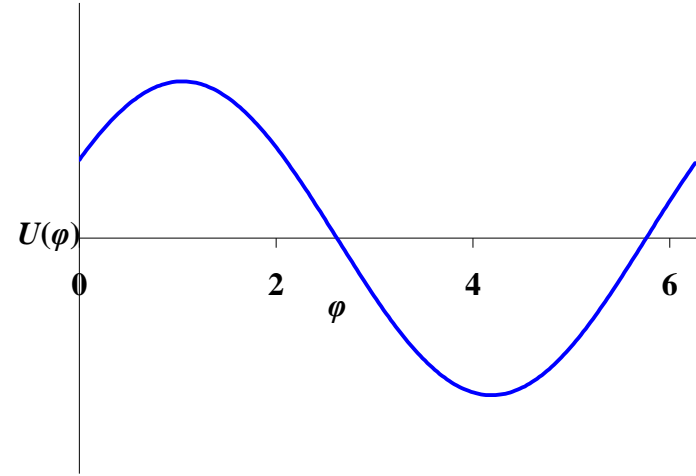
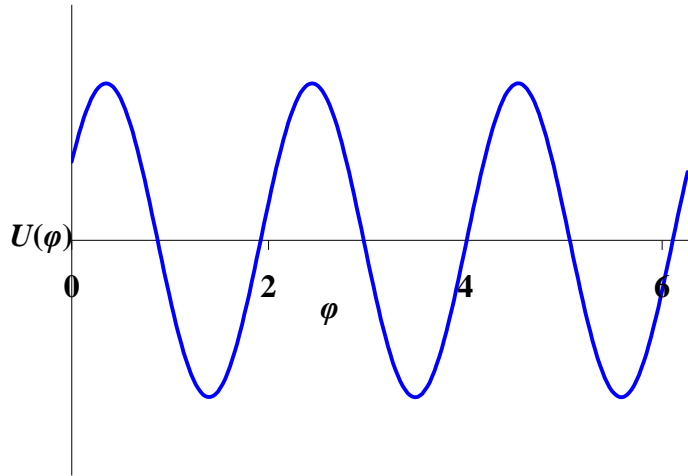
- basically...
- but details will vary



- how large are energy barriers ?
- how many minima are there ?

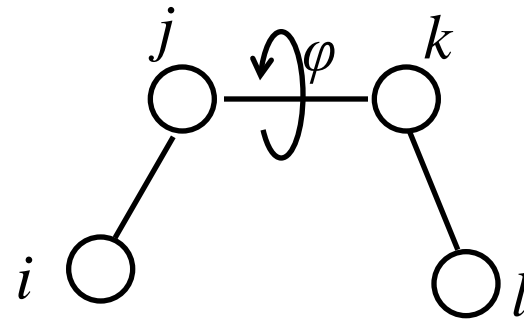
Form of dihedral term

Maybe something has three minima or one minimum



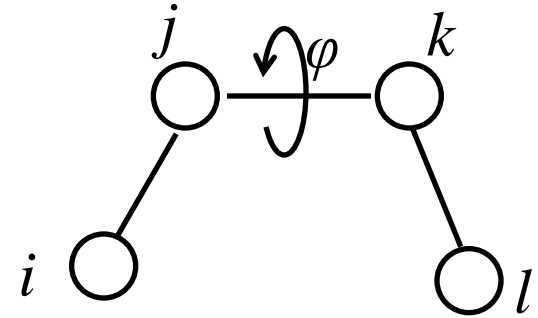
What are the causes ?

- do i and l interact ?
- electron clouds from j and k ?
- model $k_i (1 + \cos(n\varphi_i - \nu_0))$



model for dihedral angles

$$U(\vec{r}) = k_i (1 + \cos(n\varphi_i - v_0))$$



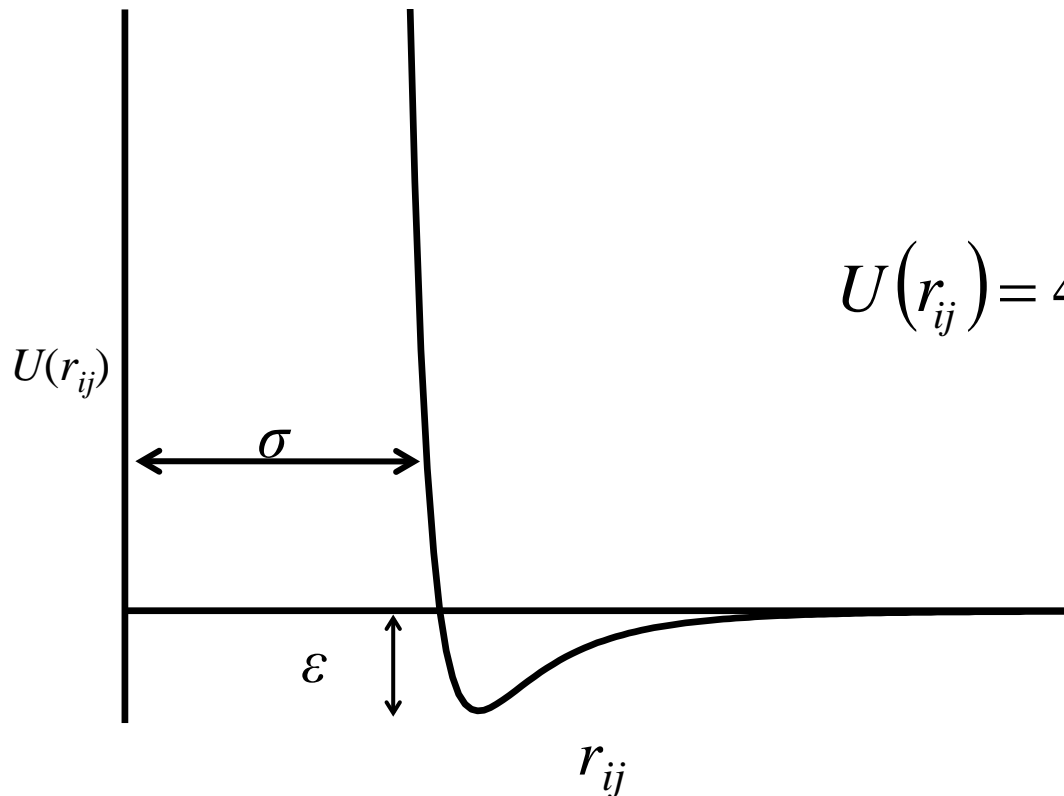
- Properties ?
 - n controls multiplicity
 - $n = 3$ butane
 - $n = 2$ peptide bond
- at room temperature, barriers are similar to kT so
 - atoms do rotate, but there are preferences (from spectroscopy)
- how good is the model ?
 - some rotamers are preferred (need other terms)
- What do forces look like ? scary (much trigonometry)
 - intuitively easy, maths messy- think of j and k

Non bonded forces

- van der Waals / Lennard-Jones / dispersion + attraction
- electrostatic
- why are they separated from others ?
 - bonds, angles and dihedrals
 - you know the participants in advance
 - non-bonded
 - atoms can move to and from each other

van der Waals

- what do we know in advance ?
 - “inert” gases do form liquids (atoms like each other)
 - atoms do not sit on top of each other



$$U(r_{ij}) = 4\epsilon_{ij} \left(\left(\frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}} \right)^6 \right)$$

distance of minimum energy = $2^{1/6} \sigma$

van der Waals – how good is it ?

- repulsive and attractive look similar

$$U(r_{ij}) = 4\varepsilon_{ij} \left(\left(\frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}} \right)^6 \right)$$

- quite different
- attractive part ?
 - electrons wobble and talk to neighbours – induce charges
 - r^{-6} pretty good
- repulsive part ?
 - what do atoms look like ?
 - really exponential, r^{-12} is very convenient

Lennard-Jones terms – how real

- how real is it ?
 - good for liquid argon
 - diffusion, transport...
- Lennard-Jones fluids
- nice features
 - ϵ , σ = “well depth” and size
 - ϵ , σ specific for atom pairs
 - σ for H is tiny, for C is much bigger
- typical exam question
 - dimensions of energy are ML^2T^{-2}
 - if the units of σ are Angstrom \AA (dimension L)
 - what are the units (or dimensions) of ϵ ?

Electrostatics

- Coulombs law

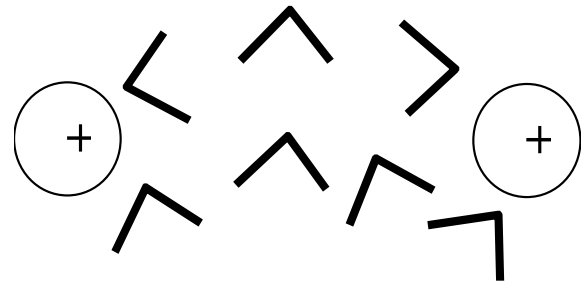
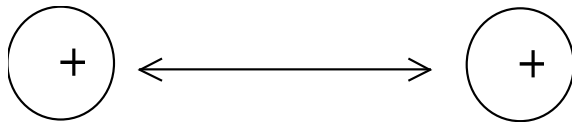
- Sounds easy

$$U(r_{ij}) = \frac{q_i q_j}{4\pi\epsilon_0 r_{ij}}$$

sometimes

$$U(r_{ij}) = \frac{q_i q_j}{D r_{ij}}$$

- where D is dielectric constant
- why is it difficult ?
 - what is D ?
 - with and without water ?
 - intervening protein ?



- more on solvent models later

Model can be made better / worse

Is this model good or bad ? fast or slow ?

What will it be used for ?

- molecular dynamics simulations, energy minimising, rarely a simple energy evaluation
- very cpu intensive

Two conflicting goals

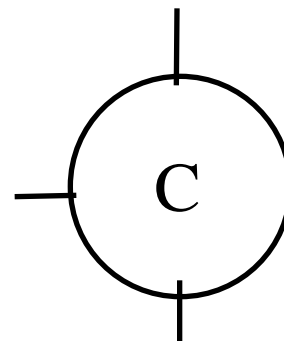
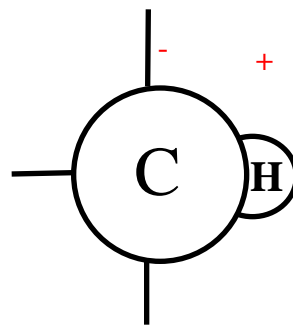
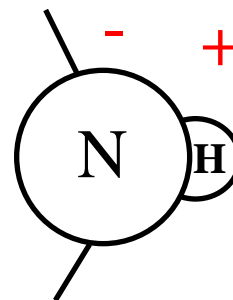
- make model cheaper, but maintain quality
- add details to make model better

Cost of model ?

- bonds, angles, dihedrals $O(n)$
- non-bonded n particles interact with n particles $O(n^2)$
- probably $\approx 90\%$ of time spent on non-bonded interactions

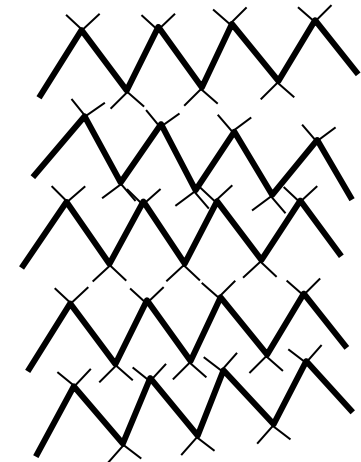
Cheaper models - United atoms / heavy atoms

- When does a proton matter ?
 - charge interactions, H bonds
- When is a proton not interesting ?
 - most aliphatic and aromatic
 - hardly a charge / tiny radius
- Do we even need the hydrogen ?
 - Use a "united atom"
 - mass – easy 12 + 1
 - charge ? nothing
 - radius slightly larger
- Rule
 - Use explicit H in polar groups
 - absorb everywhere else
 - CH, CH₂, CH₃



United atoms how bad ?

- Gain of united atoms ?
 - roughly halve number of atoms
 - Costs ?
 - dynamics ? no problem
 - structure ? no real problem
- Problems ?
 - some small effects can be seen in certain systems
 - lipids
 - maybe some effects in proteins



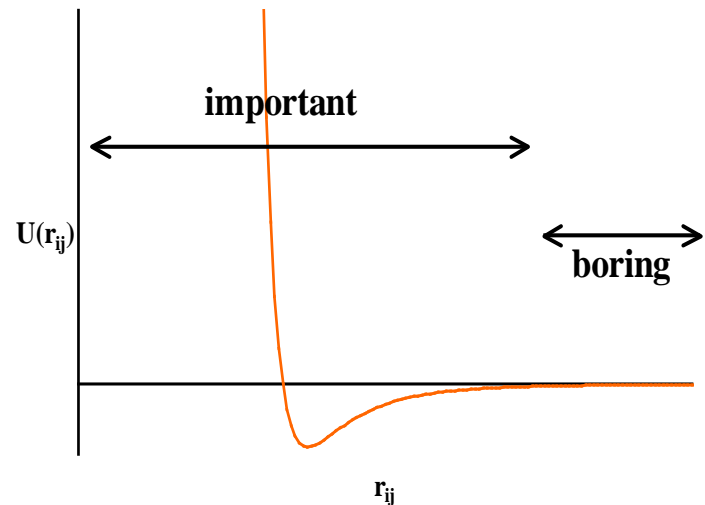
Cutoffs (cheaper models)

How important is an interaction ?

- some are not interesting (bonds)
- some depend where you are

$$U(r_{ij}) = 4\epsilon_{ij} \left(\left(\frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}} \right)^6 \right)$$

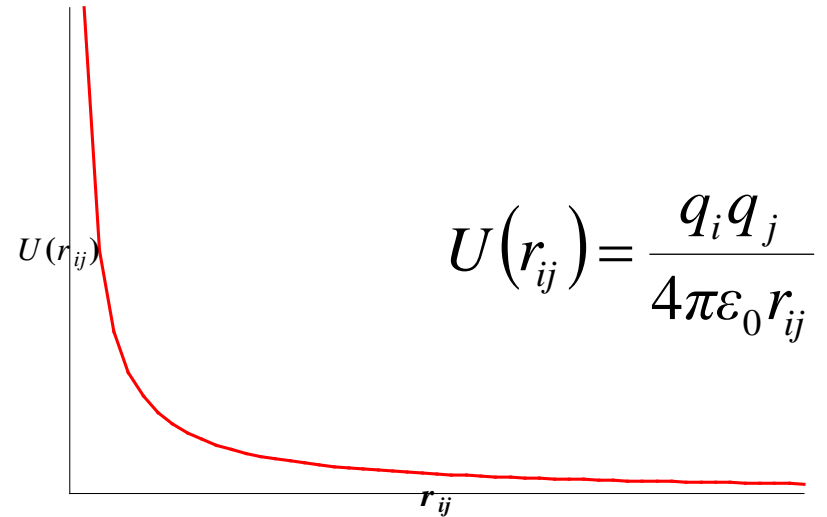
- r^{-6} and r^{-12} become small quickly
- if $r_{ij} > 6 - 8 \text{ \AA}$, $U_{LJ}(r_{ij}) = 0$
 - not a problem



- more difficult.. for other terms

cutoffs - problems

- electrostatics
- r^{-1} shrinks slowly
- but eventually, we should be able to ignore
- bigger cutoff (10 – 15 Å)



- in practice
 - use one cutoff for all non-bonded calculations
- problems
 - subtle – look at derivative

Possible improvements

Better bonds ?

- more sophisticated than harmonic $(r - r_0)^2$
- not very interesting

L-Jones better than r^{-12} ?

- not worth worrying about

Electrostatics

- polarisation ?
 - completely lacking from model so far (fixed partial charges)
 - we know it is important
 - popular, difficult

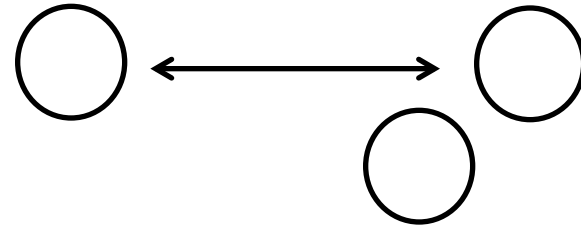
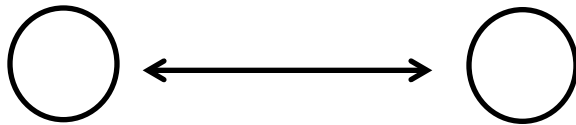
Water

- model so far is *in vacuo* ... more later

Problems and fixes in model

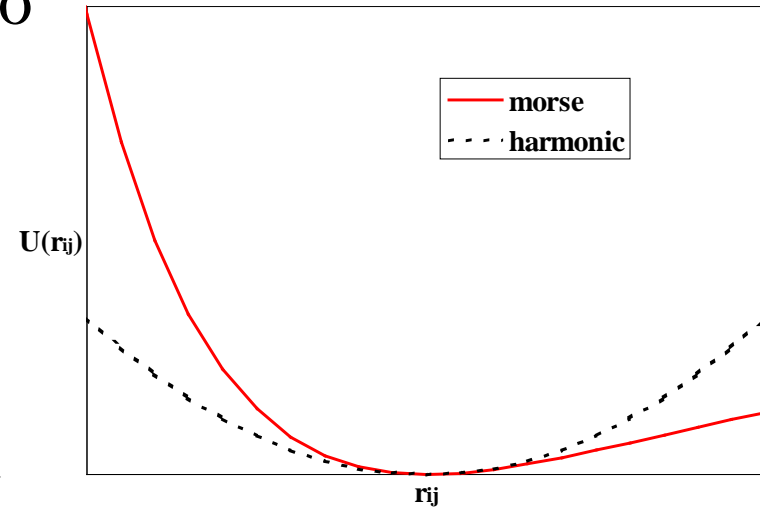
Model is fundamentally wrong

- think about forms of functions
- all two-body based, compare...



• can we represent interactions with two body form ?

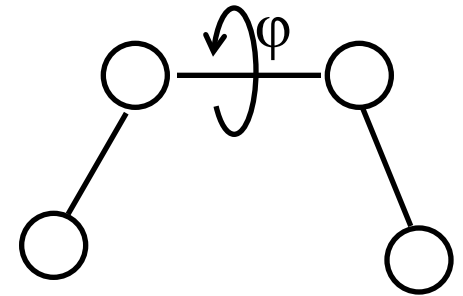
- can be good for a small range
- remember earlier picture...
- what works well at 300K may not work at 600K



Why problems may not be seen

Model is not perfect, why do simulations work ?

- lots of parameters, not independent
- example
 - what controls density of a polar fluid
 - charges ?
 - Lennard-Jones terms ?
 - both
- complicated example
 - rate of rotation..
 - torsional term ***
 - size of atoms and barriers (ϵ , σ) **
 - angles ? a bit
 - errors in one part of force field compensated elsewhere



Testing force fields

What should a force field do ?

- if I simulate a protein
 - it should not blow up
 - necessary / not sufficient
- reproduce energy changes
- global minimum (free) energy should agree with experiment

Dream properties

Perfect model of physics would work in all cases

Transferability

- atomic parameters same from protein to protein
- from protein to organic molecule
- across temperature ranges ?

Disappointments /difficulties

Special systems / special problems

- highly charged systems
 - DNA
 - solvent and charges
- lipids
 - repetitive nature emphasises some problems

Meaning of disappointment

- simulate a protein and it falls apart
- it implodes
- density of a system is wrong
- energetic predictions are wrong
- dynamic predictions are wrong
- smaller structural predictions are wrong

Parameters

Force field / model has lots of parameters

- charge, mass, ϵ , σ ,
- bondlengths, angles, ... for each type of bond / angle /dihedral

Sources

- literature
 - mass
- partial charges ?
 - high level calculations
- measurements on small molecules
 - bond lengths, geometry
- trial and error (example)
 - simulate a liquid and
 - reduce σ to increase density
 - decrease ϵ to make it boil more easily

Parameters are a compromise

Model is not perfect

- internal compensation
- compromise example
 - partial charges are not really fixed
 - depend on environment + geometry
- make a decision and adjust others to work in important area

Atomistic force field summary

- very good model for much
 - protein dynamics
 - interactions
 - structure
- main model
 - ignore water
 - 3 kinds of bonded interactions
 - 2 non-bonded
- conservative force field
 - $U(r_{ij})$ energy depends on coordinates only
 - no time component
- energy continuous
 - useful
 - derivative always defined
 - very useful

Where next ?

- Better models (not much)
- Fixing worst aspects
- Simpler models

- Simulation
- first some rules from statistical mechanics