This semester

Models – mostly proteins

- from detailed to more abstract models

Some simulation methods

Books

None necessary

- for my group and Prof Rarey
  - “Molecular Modelling: Principles and Applications” Leach, Andrew

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

- atomistiche 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 ?

Organization

Klausurtermine in Stine

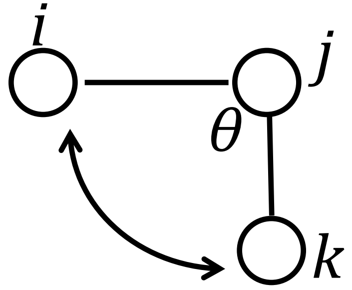
Andrew der Pedant - bei Klausuren

- energie/potenzielle energie/freie energie
- absolute Werte / relative Werte
- grossere / kleinere, mehr positiv / mehr negative
- Vektoren, Skalar
- Vorzeichnungen…

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

Why are we here ?

- observables
- distributions
- two ways to get at distributions
  1. from Boltzmann relation (later)
  2. from dynamics simulations

- dynamics simulations
  - need forces
- forces need energies

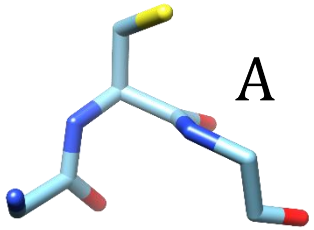
Observables

- $\mathcal{A}$ is density, coordinates, something you can measure
- what you see is $\langle \mathcal{A} \rangle$ the average over time and molecules $\langle \mathcal{A} \rangle = \frac{1}{t}\int_0^t \langle \mathcal{A} \rangle \, dt$

- simulating gives us a sampling over time / molecules

Can we just average over values ?

- 3 rotamers in a protein
- they are not equally likely
    - A is most common, C is high energy and not seen (no contribution)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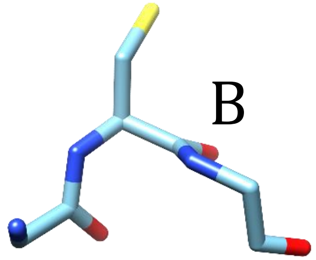
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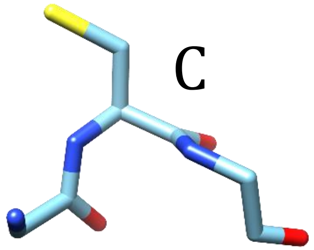
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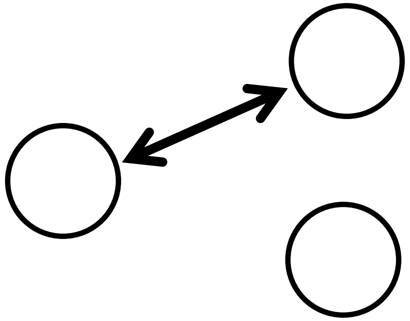
How to get the correct averages ?

- simulate the system and do the averaging over every $\mathcal{A}$ in the simulation
- how would you simulate ?

Simulations need forces and energies



Distributions depend on energies

- dynamics simulations need forces
- forces come from energies $F = \frac{-dU}{\partial r}$
- so we spend weeks discussing energies

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 ?
- are bonds like springs ?

Is energy sufficient ?

Does the world care about potential energy ?

- No. Really cares about free energy

  $G = U - TS$ (usually speak of ΔG)

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 is a force field ?

Set of equations / formulae that tell us about the force acting on a particle

Classic example

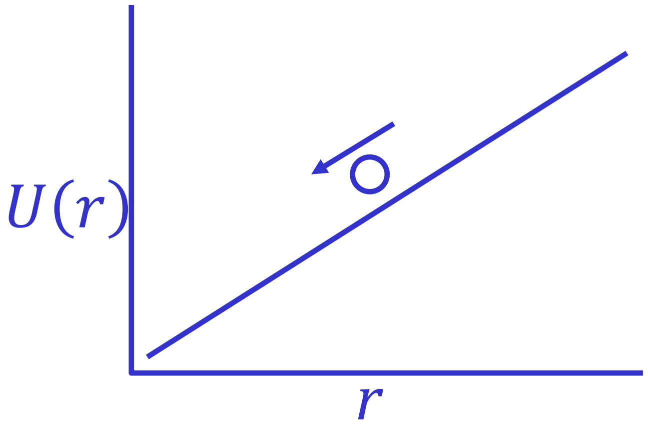
- I have charge
- bring another charge near, it feels a force due to the first
- what is the equation telling me about the energy ?

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

and the force…

Force fields, energies, derivatives

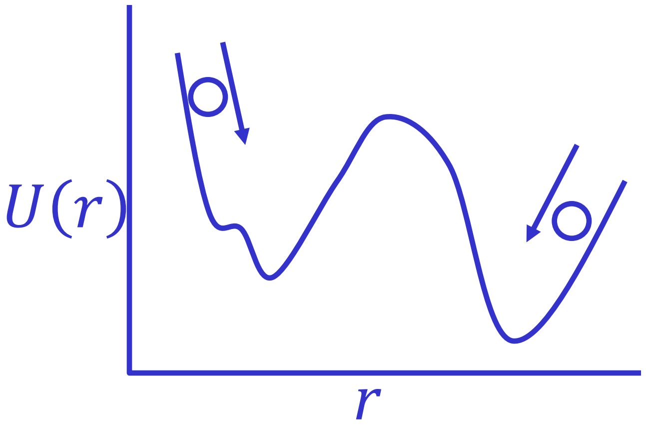
Important rule $\vec{F} = -\frac{dU}{d\vec{r}}$



- a toy example, one dimension $U(\vec{r}) = k\vec{r}$
- force is $\vec{F} = \frac{-dU}{d\vec{F}} = -k$

How do we want force ?

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



$$F_x = \frac{-\partial U}{\partial x}$$

really $$F_y = \frac{-\partial U}{\partial y}$$

$$F_z = \frac{-\partial U}{\partial z}$$

A simple force

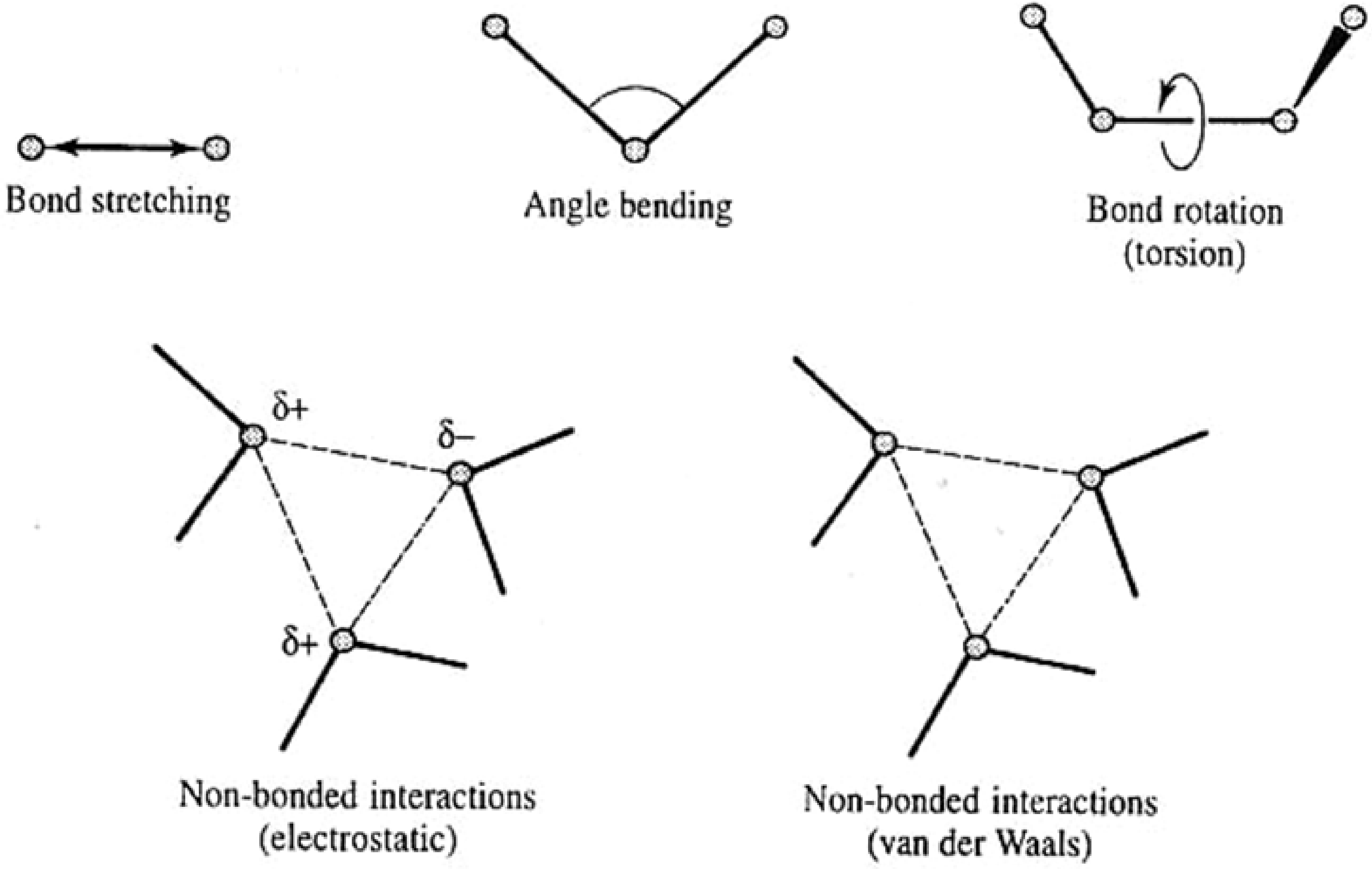
With an energy $U\left(r_{ij}\right) = \frac{1}{4\pi\epsilon_0}\frac{q_i q_j}{r_{ij}}$

force is $\vec{F} = \frac{-dU}{d\vec{r}} = \frac{1}{4\pi\epsilon_0}\frac{q_i q_j}{r_{ij}^2}\ \hat{r}_{ij}$

Rule

- if the derivative of an energy is non-zero
    - there is a force (remember for exams)

protein force field (picture)



picture from Leach, A.R., Molecular Modelling Principles and Applications

Protein force fields as equation

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

$$\sum_{i=1}^{N_{bond}} \frac{k_i}{2}\left(r_i - r_{i,0}\right)^2$$ bonds

$$+ \sum_{i=1}^{N_{angles}} \frac{k_i}{2}\left(\cos\theta_i - \cos\theta_{i,0}\right)^2$$ angles

$$+ \sum_{i=1}^{N_{dihedral}} k_i\left(1 + \cos\left(n\varphi_i - \nu_{i,0}\right)\right)$$ dihedrals

$$+ \sum_{i=1}^{N_{atom}} \sum_{i=j+1}^{N_{atom}} 4\epsilon_{ij}\left(\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right) + \frac{q_i q_j}{4\pi\epsilon_0 r_{ij}}$$ non−bonded

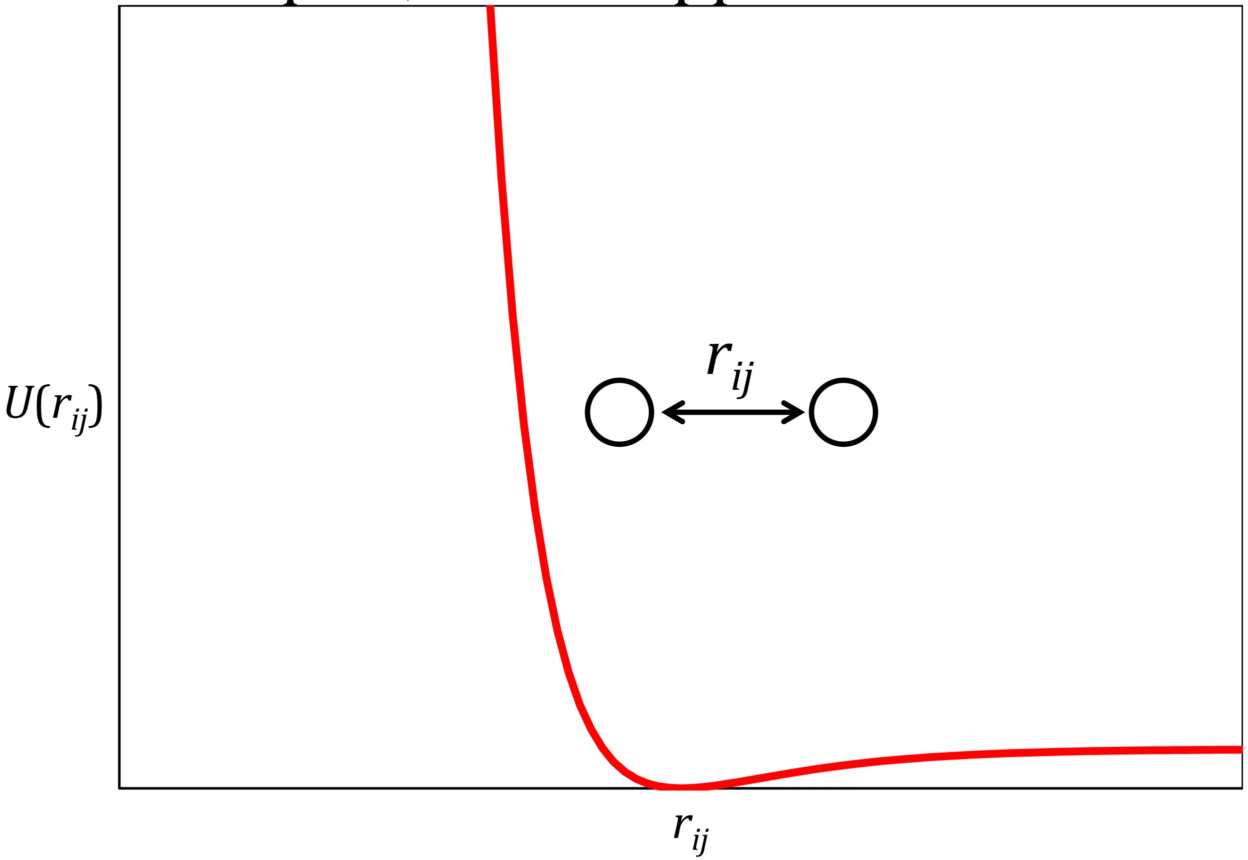
Not a bad approximation

x_i is a value in the coordinates, $x_{i,0}$ is a literature reference value

Bonds

What are bonds really ?

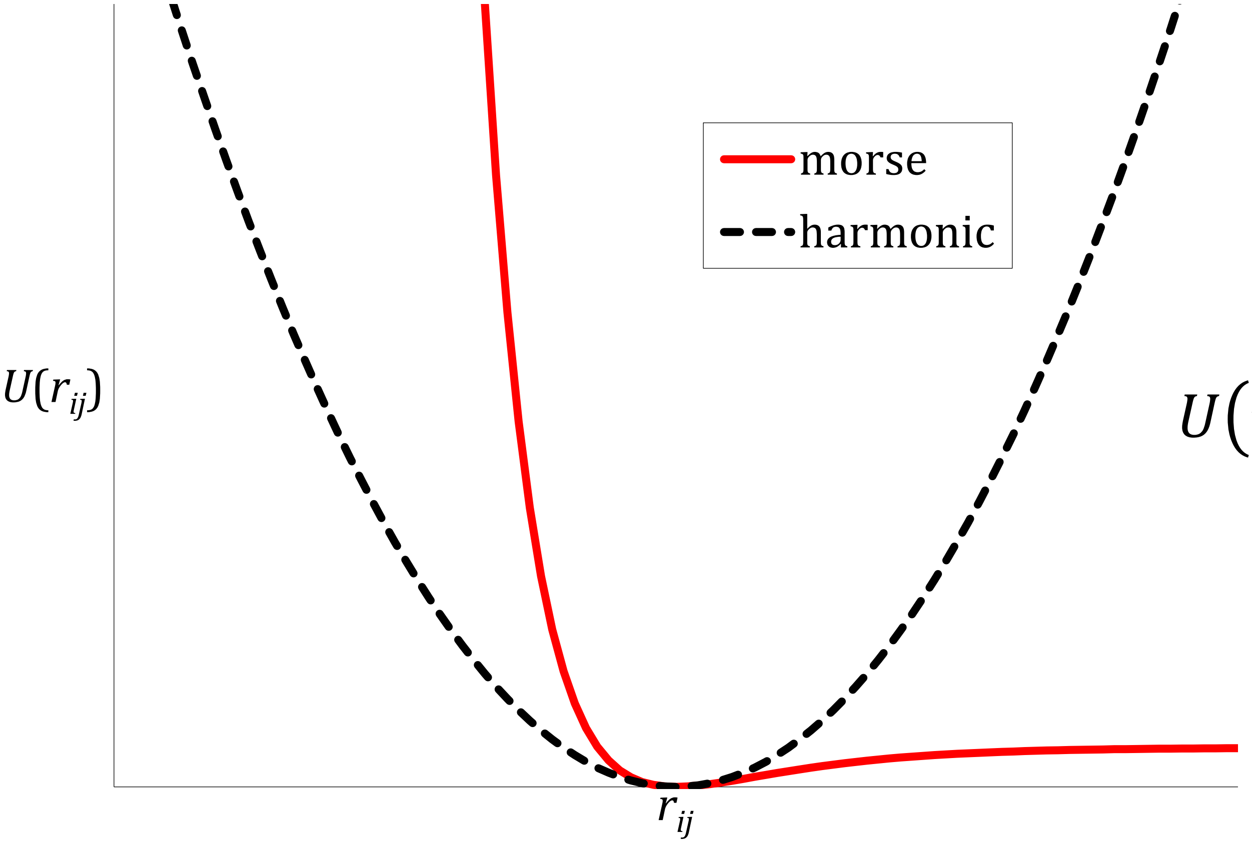
- as we pull two particles apart, what happens ?



- can we approximate ?

Bonds - approximate

Is the black line a good approximation ?

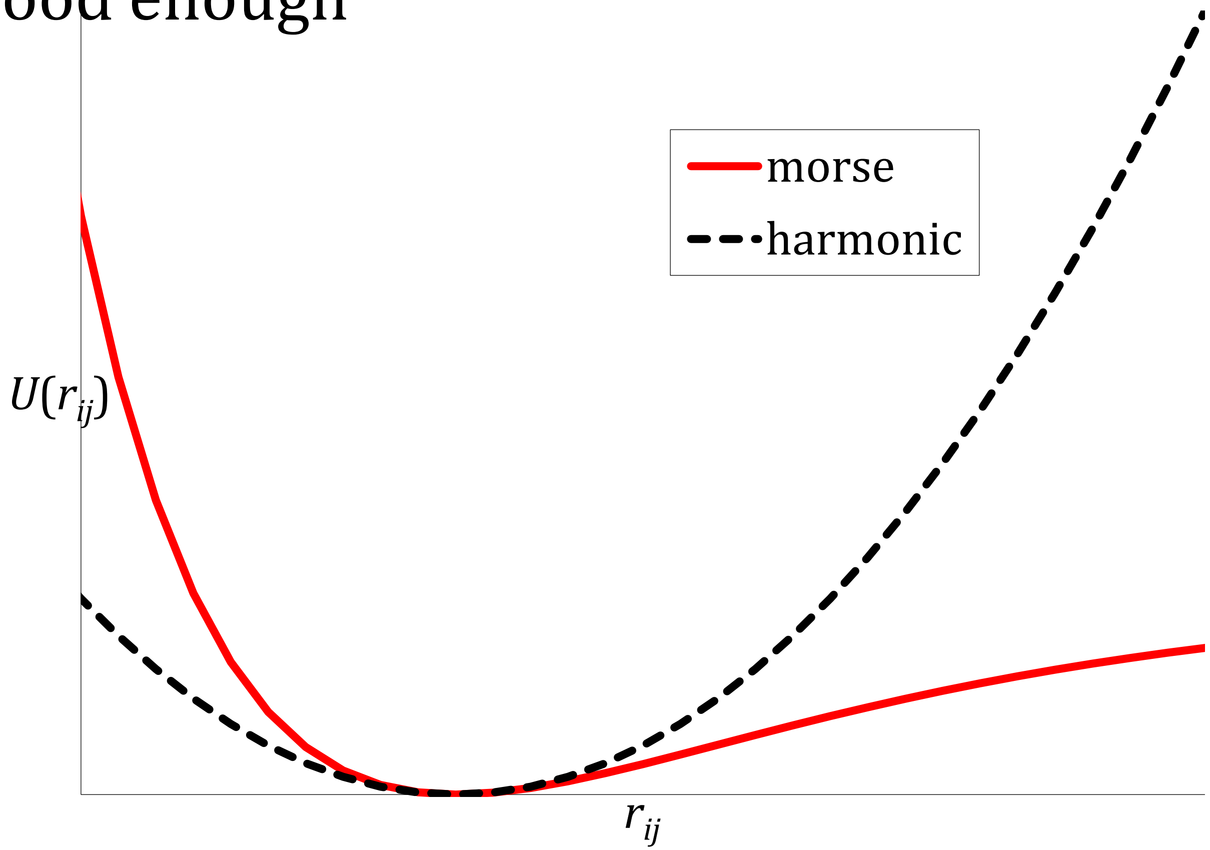


$$U(r_{ij}) = \frac{k}{2}(r_{ij} - r_0)^2$$

Bonds – good enough

Bonds don't stretch much

- harmonic is often good enough



Why do we write $\frac{k}{2}\left(r_{ij} - r_0\right)^2$ (not just k) ?

Bonds – the end

We normally write $U\left(r_{ij}\right) = \frac{k}{2}\left(r_{ij} - r_0\right)^2$

as scalar.. $F = \frac{-dU}{dr} = -k(r - r_0)$

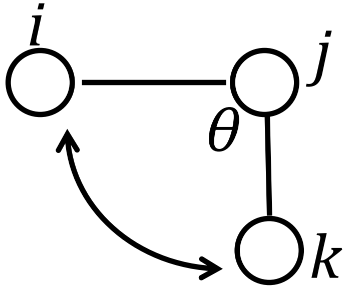
- so first form looks like Hookes law

Do bonds matter ?

- fluctuations very small at room temp (< 0.1 Å)
- 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



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

or

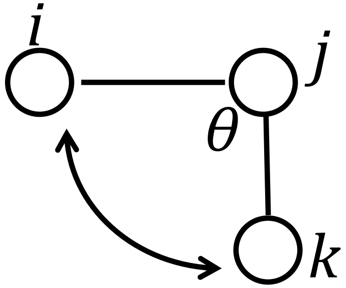
$$U_{angle(\vec{r}_i,\vec{r}_j,\vec{r}_k)} = \frac{k}{2}\left(\theta_{ijk} - \theta_0\right)^2$$

but to get forces is messy (use chain rule) … why

Why are forces difficult ?

We use physical models like

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



Force is obvious

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

$$\vec{F}_{angle}(\vec{r}_i\ ) = \frac{-\partial U(\vec{r}_i)}{\partial(\vec{r}_i)}$$

$$= \frac{-\partial U(\vec{r}_i)}{\partial\cos\theta}\frac{\partial\cos\theta}{\partial(\vec{r}_i)}$$

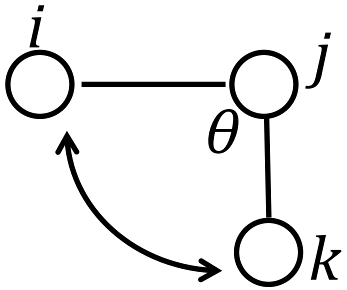
$$= \frac{-\partial U(\vec{r}_i)}{\partial\cos\theta}\frac{\partial\cos\theta}{\partial\theta}\frac{\partial\theta}{\partial(\vec{r}_i)}$$

Angle forces

$$F_{angle_i} = \frac{-\partial U_{angle}(\vec{r}_i)}{\partial \vec{r}_i}$$

$$= \frac{-\partial U_{angle}(\vec{r}_i)}{\partial \cos\theta_{ijk}} \frac{\partial \cos\theta_{ijk}}{\partial \vec{r}_i}$$

$$= k\left(\cos\theta_{ijk} - \cos\theta_0\right)\left(\frac{\vec{r}_{kj}}{r_{jk}} - \frac{\vec{r}_{ij}}{r_{ij}}\cos\theta_{ijk}\right)\frac{1}{r_{ij}}$$



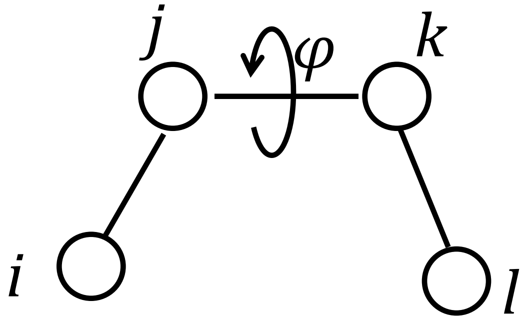
The other atoms ?

similar expression for F_k

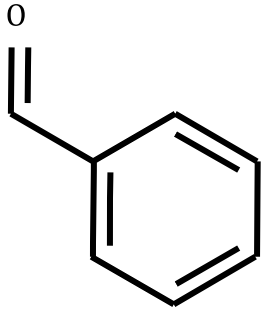
$F_j = -(F_i + F_k)$

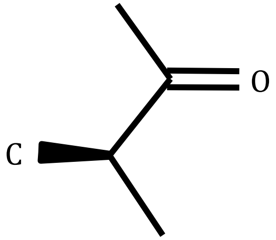
dihedral / torsion angles

basically…



but details will vary

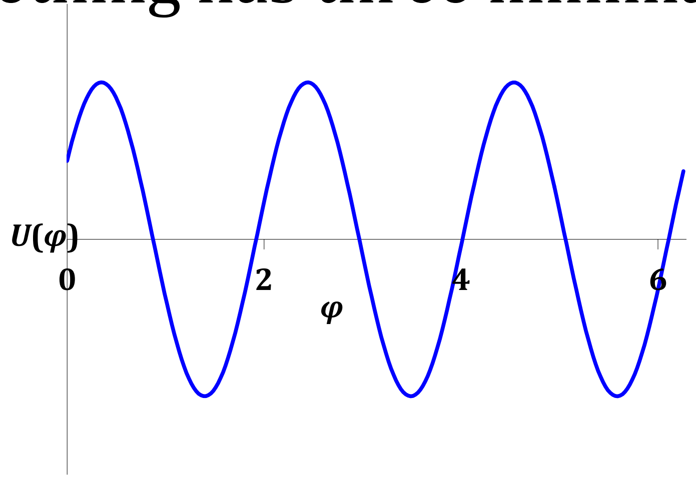


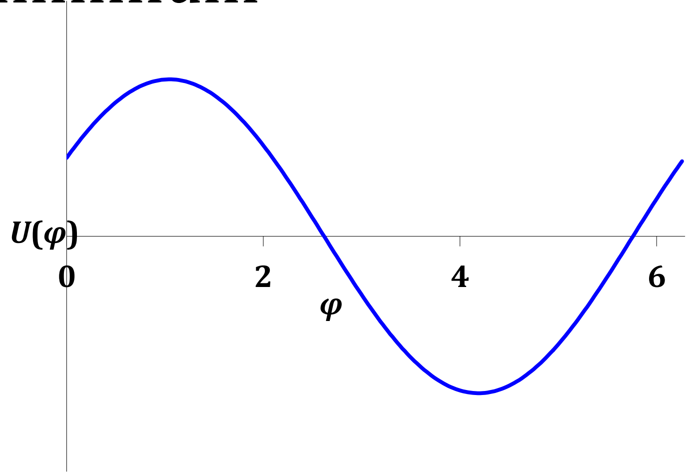


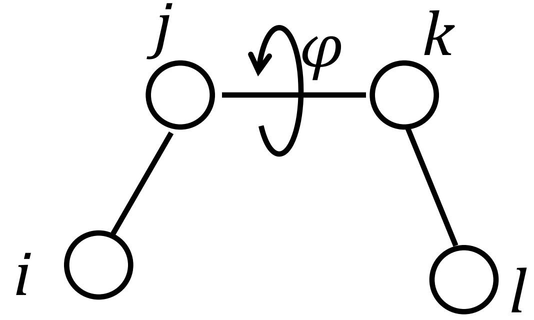
- how large are energy barriers ?
- how many minima are there ?

Form of dihedral term

Maybe something has three minima or one minimum



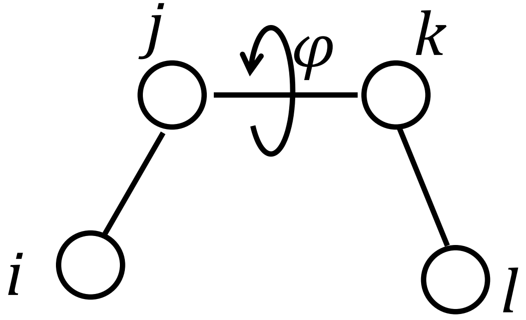




What are the causes ?

- 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



$U(\vec{r}) = k_i(1 + \cos(n\varphi_i - \nu_0))$

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 ? Not perfect

- 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

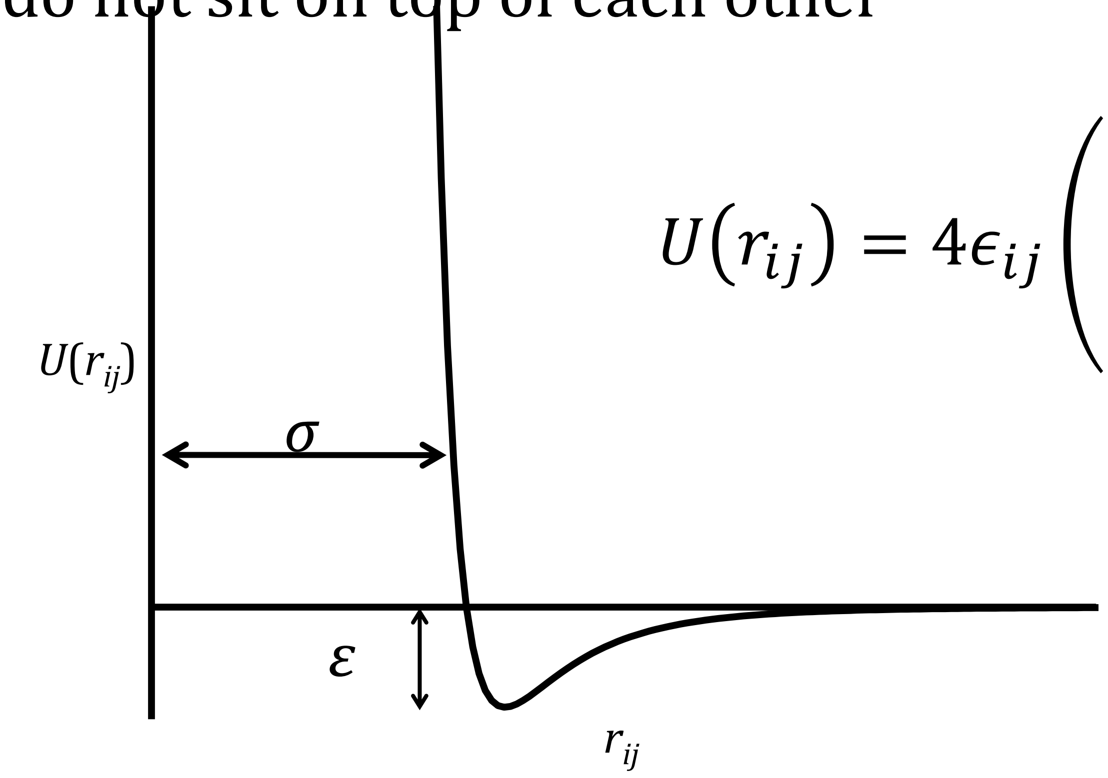
Why are they separated from others ?

- 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

- quite different

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

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 just 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

Electrostatics

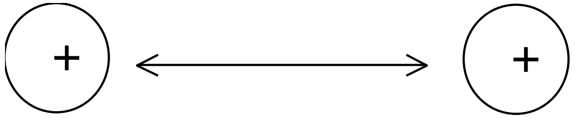
Coulombs law

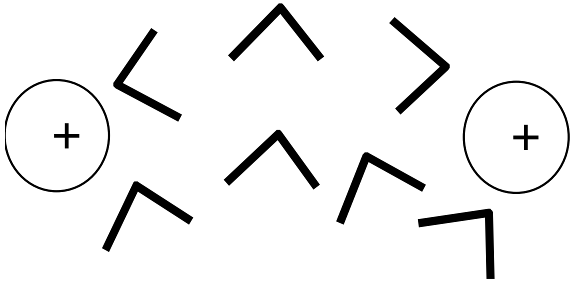
Sounds easy $$U(r_{ij}) = \frac{q_i q_j}{4\pi\epsilon_0 r_{ij}} \quad \text{or} \quad U(r_{ij}) = \frac{q_i q_j}{D\, r_{ij}}$$

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
- cpu intensive

Conflicting goals

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

Cost of model

Cost of model ?

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

Many simplifications

- some are popular and important

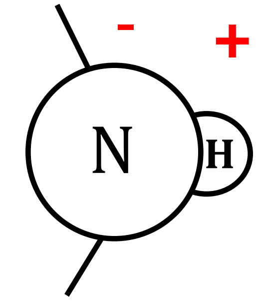
Cheaper models - United atoms / heavy atoms

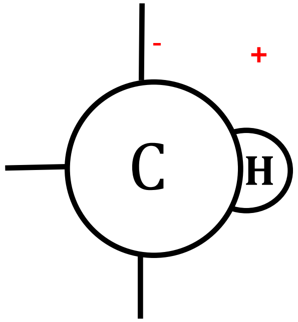
When does a proton matter ?
- charge interactions, H bonds

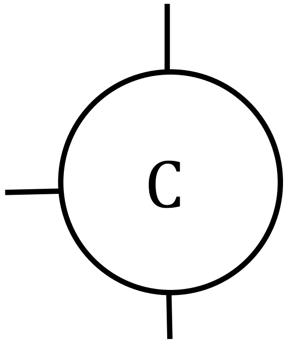
When is a proton not interesting ?
- most aliphatic and aromatic
- hardly a charge / tiny radius

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, CH_2, CH_3







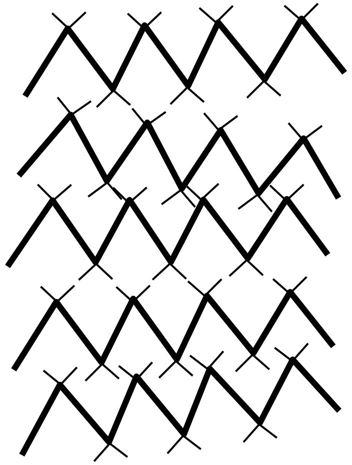
United atoms how bad ?

Gain of united atoms ?

- roughly halve number of atoms
- Costs ?
  - dynamics ? no problem
  - structure ? not too bad

Problems ?

- some small effects can be seen in certain systems
  - lipids
- maybe some effects in proteins



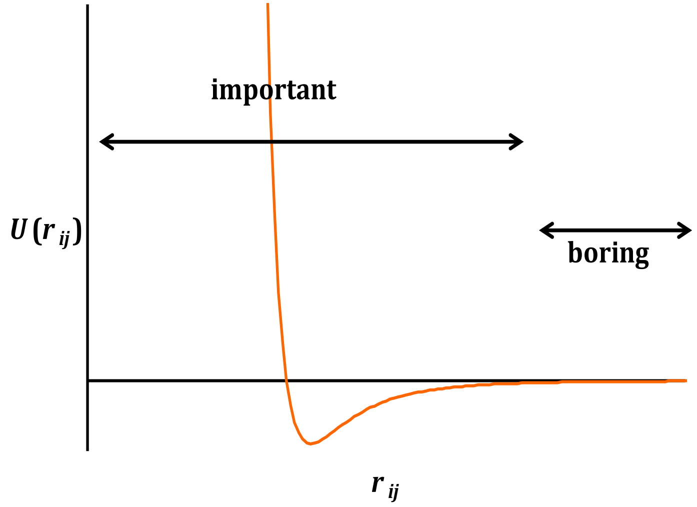
Cutoffs (cheaper models)

How important is an interaction ?

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

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

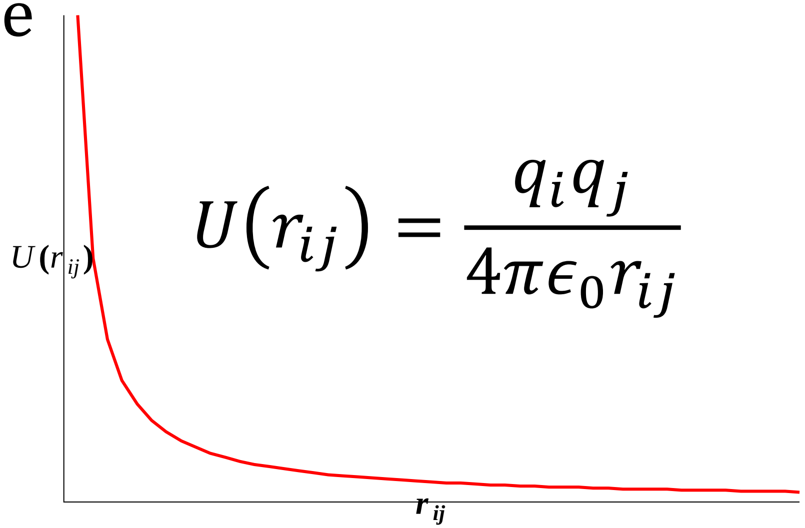
- r^{-6} and r^{-12} become small quickly
- if $r_{ij} > 6 - 8$ Å, $U_{LJ}(r_{ij}) = 0$
  - not a problem



- 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)



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

In practice

- use one cutoff for all non-bonded calculations

Problems

  - subtle – look at derivative

Possible improvements

Better bonds ?

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

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

- can do - not worth worrying about

Electrostatics

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

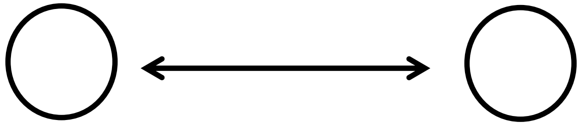
Water

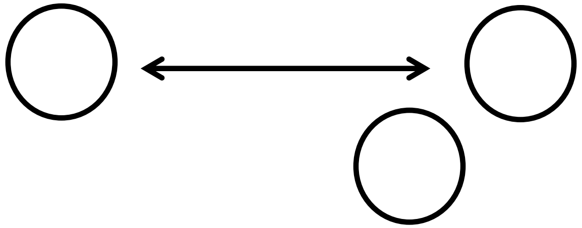
- model so far is *in vacuo* ... more later

Problems and fixes in model

Model is fundamentally wrong

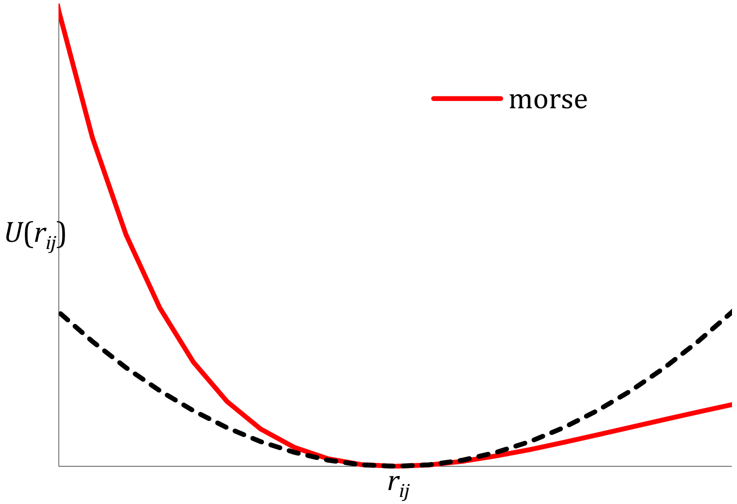
- think about forms of functions
- all two-body based, compare...





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 ?

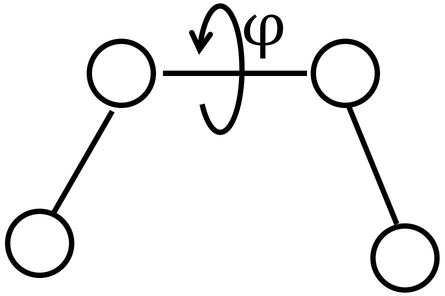
- lots of parameters, not independent

Simple example

- what controls density of a polar fluid
  - charges ?
  - Lennard-Jones terms ?
  - both

Complicated example

- rate of rotation..
  - torsional term (*k* in torsion term)
  - size of atoms and barriers (ε, σ) (less important)
  - angles ? (less important)



Errors in one part of force field compensated elsewhere

Testing force fields

What should a force field do ?

- structure
  - simulate a protein
    - it should not blow up (necessary / not sufficient)
  - density
  - anything you can measure and calculate (distances, chemical shifts..)
- reproduce energy changes (free energies)
- global minimum (free) energy should agree with experiment
- dynamics properties
  - which torsion angles rotate at room temperature ?
  - order parameters from NMR

Transferability

Perfect model of physics would work in all cases

- 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 (crystallography)
  - bond lengths, geometry
- trial and error (example)
  - simulate a liquid
    - 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

Model for potential energy

- proteins, organic molecules ..

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

more summary

- main model
- speed-ups – cutoffs, united atoms
- where do parameters come from ?
- what should parameters do ?
- why may you not see errors in parameters ?

Where next ?

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

- Simulation
- first some rules from statistical mechanics