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
• Nils Petersen

Zeitplan
• Di 12:15
• Mi 9:00

Sprache?
Organization

Klausurtermine in Stine (21 Juli, 22 Sep)

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 $\langle \mathcal{A} \rangle = \frac{1}{\tau} \int_0^\tau \mathcal{A}_t \, dt$

- 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)

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

• we need energies

Dynamics simulations need forces

• forces come from energies \( F = \frac{-dU}{dr} \)

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 \( \Delta G \))

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

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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?

\[ U(r_{ij}) = \left( \frac{1}{4\pi\varepsilon_0} \right) \frac{q_i q_j}{r_{ij}} \]

and the force...
Force fields, energies, derivatives

Important rule $\mathbf{F} = -\frac{dU}{dr}$

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

How do we want force?
- in $x, y, z$ terms $\mathbf{r}$

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

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

$F_z = \frac{-\partial U}{\partial z}$
A simple force

With an energy $U(r_{ij}) = \frac{1}{4\pi \varepsilon_0} \frac{q_i q_j}{r_{ij}}$

force is $\vec{F} = \frac{-dU}{d\vec{r}} = \frac{1}{4\pi \varepsilon_0} \frac{q_i q_j}{r_{ij}^2} \hat{r}_{ij}$

Rule
• if the derivative of an energy is non-zero
  • there is a force (remember for exams)
protein force field (pictures)

- 3 types of bonded energies
- 2 types of non-bonded energies

- bonds
- angles
- dihedrals

- electrostatic
- van der Waals
Protein force fields as equation

\[ U(\{\vec{r}\}) = \]

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

\[ \sum_{i=1}^{N_{\text{angle}}} k_i \left( \frac{1}{2} (\cos \theta_i - \cos \theta_{i,0})^2 \right) \quad \text{angles} \]

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

\[ \sum_{i=1}^{N_{\text{atom}}} \sum_{i=j+1}^{N_{\text{atom}}} 4\varepsilon_{ij} \left( \left( \frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left( \frac{\sigma_{ij}}{r_{ij}} \right)^6 \right) + \frac{q_i q_j}{4\pi \varepsilon_0 r_{ij}} \quad \text{non-bonded} \]

Not a bad approximation

\(x_i\) is a value in the coordinates, \(x_{i,0}\) is a literature reference value.
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 do not stretch much
• harmonic is often good enough

Why do we write $\frac{k}{2} (r_{ij} - r_0)^2$? (not just $k$)
We normally write $U(r_{ij}) = \frac{k}{2} (r_{ij} - r_0)^2$

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

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

or

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

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

Andrew Torda
05.04.2016
Why are forces 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 \( \theta \) ?
- 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

\[ \mathbf{F}_{angle_i} = \frac{-\partial U_{angle}(\mathbf{r}_i)}{\partial \mathbf{r}_i} \frac{\partial \cos \theta_{ijk}}{\partial \mathbf{r}_i} \]

\[ \mathbf{F}_{angle_i} = k \left( \cos \theta_{ijk} - \cos \theta_0 \right) \left( \frac{\mathbf{r}_{kj}}{r_{kj}} - \frac{\mathbf{r}_{ij}}{r_{ij}} \cos \theta_{ijk} \right) \frac{1}{r_{ij}} \]

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

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

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
• $\varepsilon$, $\sigma$ = “well depth” and size
• $\varepsilon$, $\sigma$ specific for atom pairs
  • $\sigma$ for H is tiny, for C is much bigger
Electrostatics

Coulomb's law

Sounds easy

\[ U(r_{ij}) = \frac{q_i q_j}{4\pi \varepsilon_0 r_{ij}} \quad \text{or} \quad U(r_{ij}) = \frac{q_i q_j}{D r_{ij}} \]

\( D \) 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 $\approx 90\%$ 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, CH₂, CH₃
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

\[ U_{ij} = 4\varepsilon_{ij} \left( \frac{(\sigma_{ij})^{12}}{r_{ij}} - \frac{(\sigma_{ij})^{6}}{r_{ij}^{6}} \right) \]

• \( r^{-6} \) and \( r^{-12} \) become small quickly

• if \( r_{ij} > 6 \) to \( 8 \) 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)

In practice
- use one cutoff for all non-bonded calculations

Problems
- subtle – look at derivative

$$U(r_{ij}) = \frac{q_i q_j}{4\pi \varepsilon_0 r_{ij}}$$
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, $\varepsilon, \sigma$
- 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 $\sigma$ to increase density
    - decrease $\varepsilon$ 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