Coarse grain models (continuous) … potentials of mean force

So far ?

- very detailed models
  - atomistic, solvation

What are some reasonable aims ?

- given a set of coordinates
  - are these roughly correct for a protein sequence ?
  - is this more likely to be α-helical or β-sheet ?

Should we approach this with a detailed force field ?

- maybe not

Aims

- Why atomistic force fields / score functions are not always best
- Different levels of force fields
- Examples of coarse-grain / low-resolution force fields
- Ways to parameterise force fields
- Score functions directly from structural data

- later…
- extending this idea to lattice models

History

History

- Levitt, M and Warshel, A, Nature, 253, 694-698, Computer simulation of protein folding (1975)
- Kuntz, ID, Crippen, GM, Kollman, PA and Kimelman, D, J. Mol. Biol, 106, 983-994, Calculation of protein tertiary structure (1976)
- Levitt, M, J. Mol. Biol, 104, 59-107, A simplified representation of protein conformations for rapid simulation of protein folding (1976)
- through to today

Problems with detailed force fields

Time

- typical atomistic protein simulations 10^{-9} to 10^{-6} s
- too short for folding

Radius of convergence

- I have coordinates where atoms are perturbed by 1 Å
  - easy to fix – atoms move quickly
- I have completely misfolded, but well packed coordinates
  - may be difficult to fix
  - what dominates ?
    - atomic packing
    - charges
    - solvation ?

Do I care about details ?

Coarse grain / low resolution

Forget atomic details

- build something like energy which encapsulates our ideas
- example – define a function which is happiest with
  - hydrophobic residues together
  - charged residues on outside
- would this be enough ?
  - maybe / not for everything

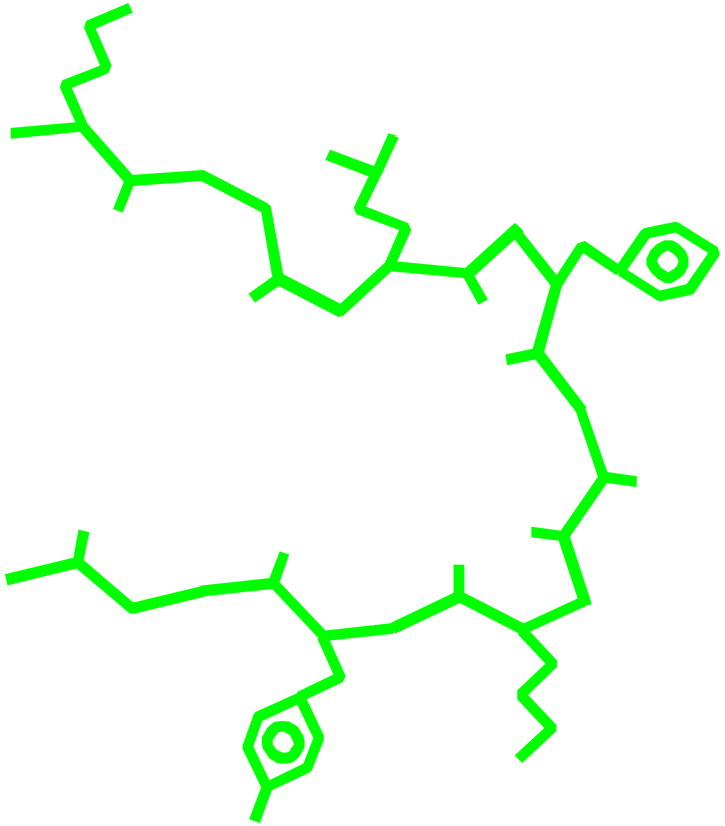
What will I need ?

- some residues like to be near each other (hydrophobic)
- residues are always some constant distance from each other
- only certain backbone angles are allowed

General implementation (easiest)

How do we represent a protein ?

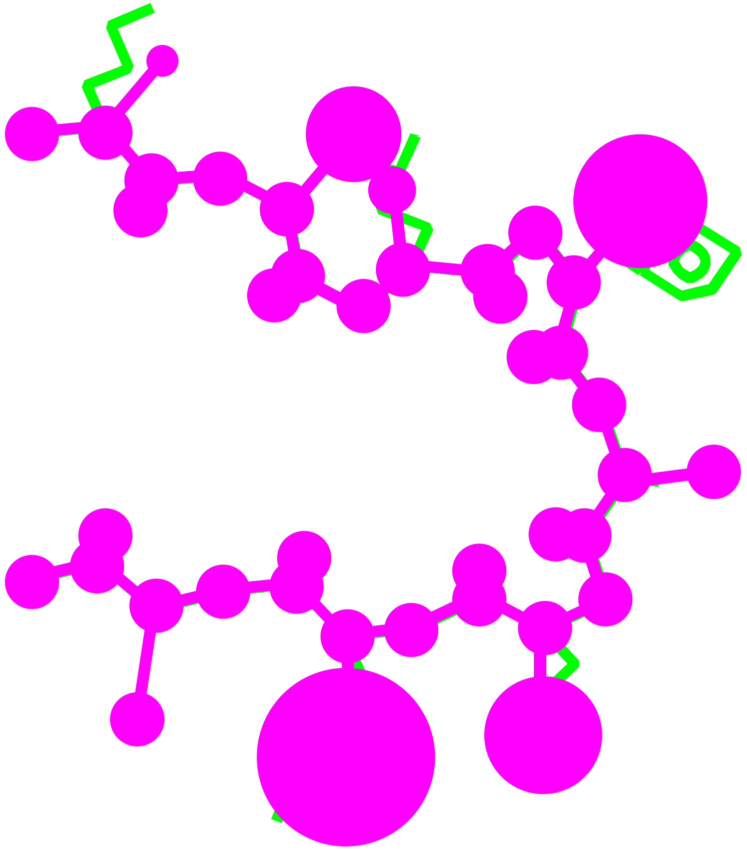
- decide on number of sites per residue



General implementation (easiest)

How do we represent a protein ?

- decide on number of sites per residue



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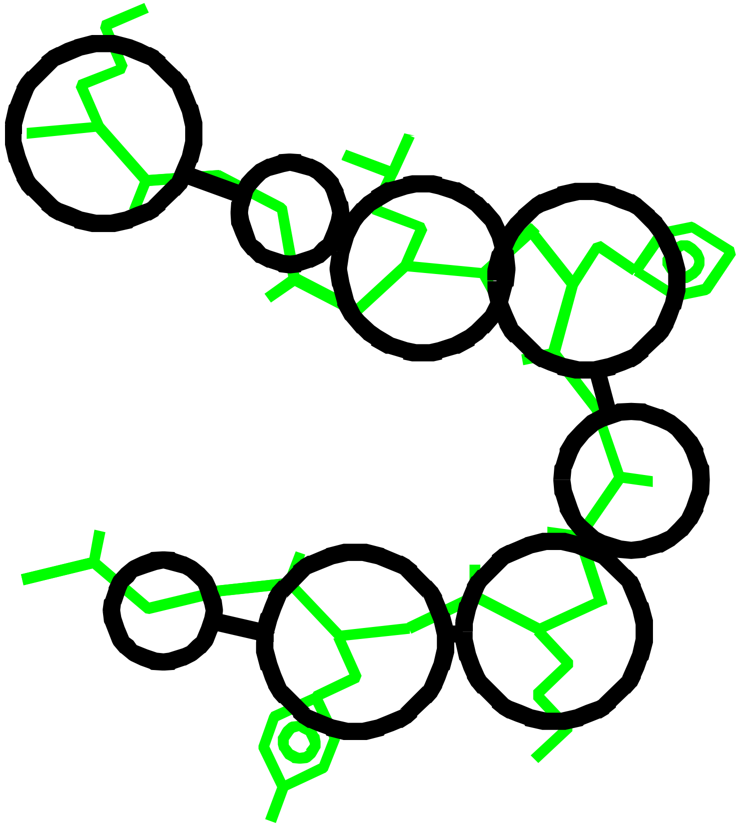


Coarse-graining (steps)

- Decide on representation
- Invent quasi-energy functions

Our plan

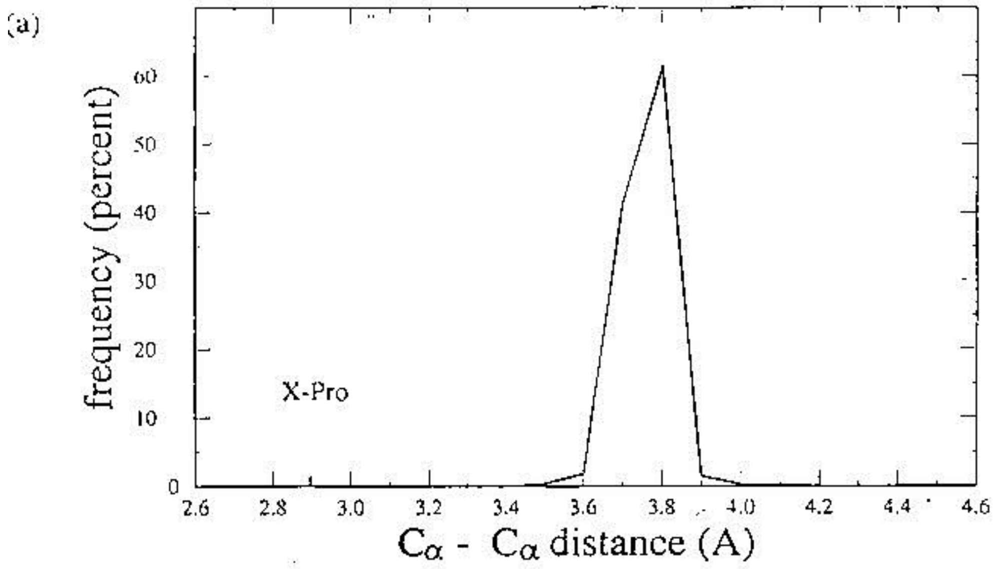
- step through some examples from literature

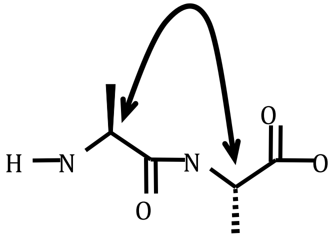
Common features

- some way to maintain basic geometry
- size
- hydrophobicity ? which residues interact with each other/solvent

Basic geometry

Survey protein data bank files and look at Cα to Cα distances





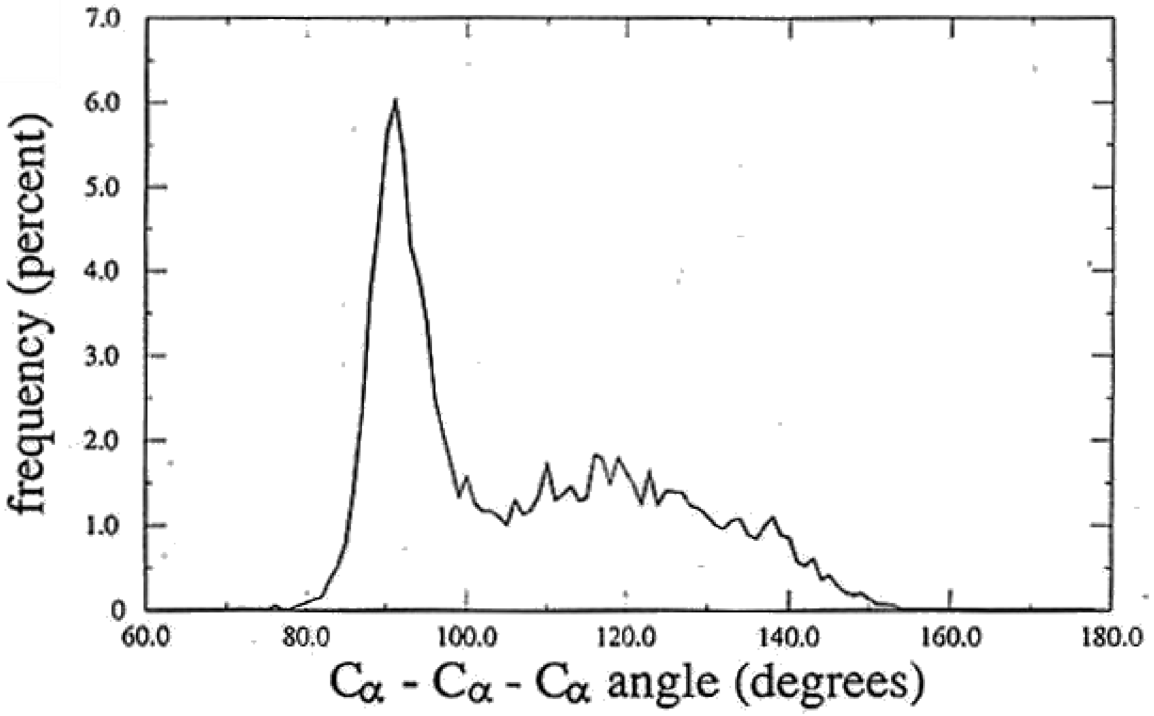
Conclusion is easy

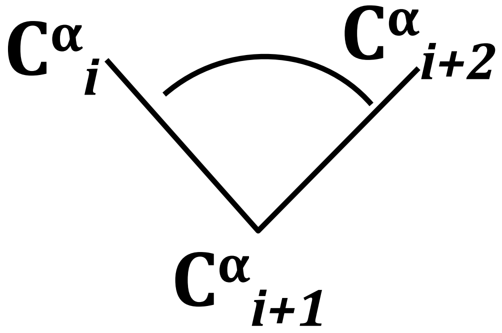
- any model should fix Cαi,i+1 distances at 3.8 Å

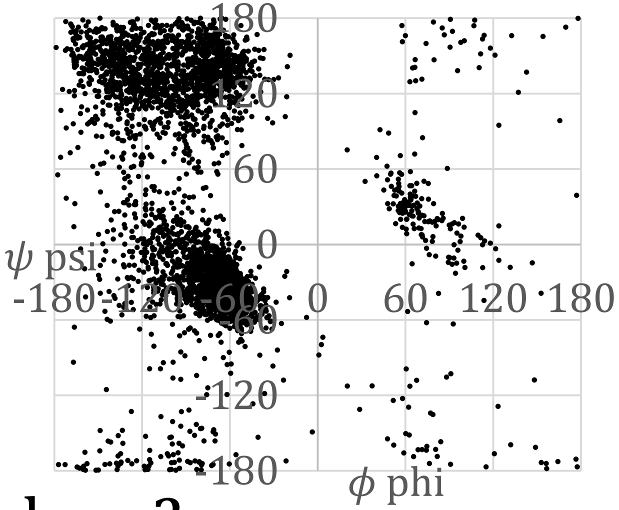
- what other properties do we know ?

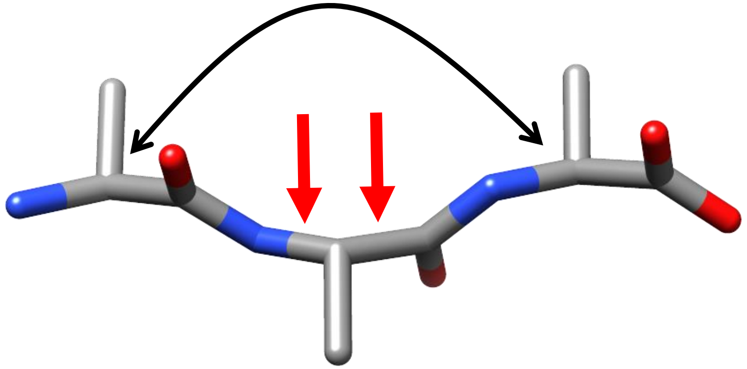
from Godzik, A., Kolinski, A, Skolnick, J. 1993, J. Comput. Chem. 14, 1194-1202

$C^{\alpha}_{i,i+2}$ distance / angle









- why is distance less clear ?
- think of ramachandran plot

from Godzik, A., Kolinski, A, Skolnick, J. 1993, J. Comput. Chem. 14, 1194-1202

First simple model

n residues, *n* interaction sites i, i+1 restrained (C^β formulation)

Overlap penalty / radii

- lys 4.3 Å, gly 2.0 Å, ... trp 5.0 Å
- $U(r_{ij})=(\text{radius}_i + \text{radius}_j)^2 - r_{ij}^2$

force hydrophilic residues to surface, for these residues

- $U^*\left(r_{ij}\right) = (100 - d_i^2)$ where

  d_i is distance to centre, 100 is arbitrary

disulfide bonds

- very strong

residue specific interactions

- $U^{long}(r_i) = c_{ij}\left(r_{ij}^2 - R^2\right)$where c_{ij} is residue specific
- R is 10 Å for attraction, 15 Å for repulsion

Kuntz, ID, Crippen, GM, Kollman, PA, Kimelman, D 1976, J Mol Biol, 106, 983-994, Calculation of protein structure

residue specific part of interaction

- c_{ij} table
- features
  - hydrophobic
  - + -
  - nothing much

	lys	glu	...	gly	pro	val
lys	25	-10		0	0	10
glu	-10	25		0	0	10
...						
gly	0	0		0	0	0
pro	0	0		0	0	0
val	10	10		0	0	-8

summary

- *i*,*i*+1 residue-residue
- overlap
- long range
- solvation

where is physics ?

- solvation ?
  - term pushes some residues away from centre
- electrostatics
- hydrophobic attraction
  - by pair specific c_{ij} terms

other properties

- smooth / continuous function
- derivative with respect to coordinates
  - (good for minimisation)

does it work ? what can one do ?

results from first model

- try to "optimise" protein structure
- for 50 residues, maybe about 5 Å rms
    - maybe not important

Model does..

- make a hydrophobic core
- put charged and polar residues at surface
- differentiate between possible and impossible structures

Model does not reproduce

- any geometry to Å accuracy
- details of secondary structure types (not intented)
- physical pathways
- subtleties of sequence features (simplicity of c_{ij} matrix)

Improvements to simple model

Aim

- biggest improvement for least complication

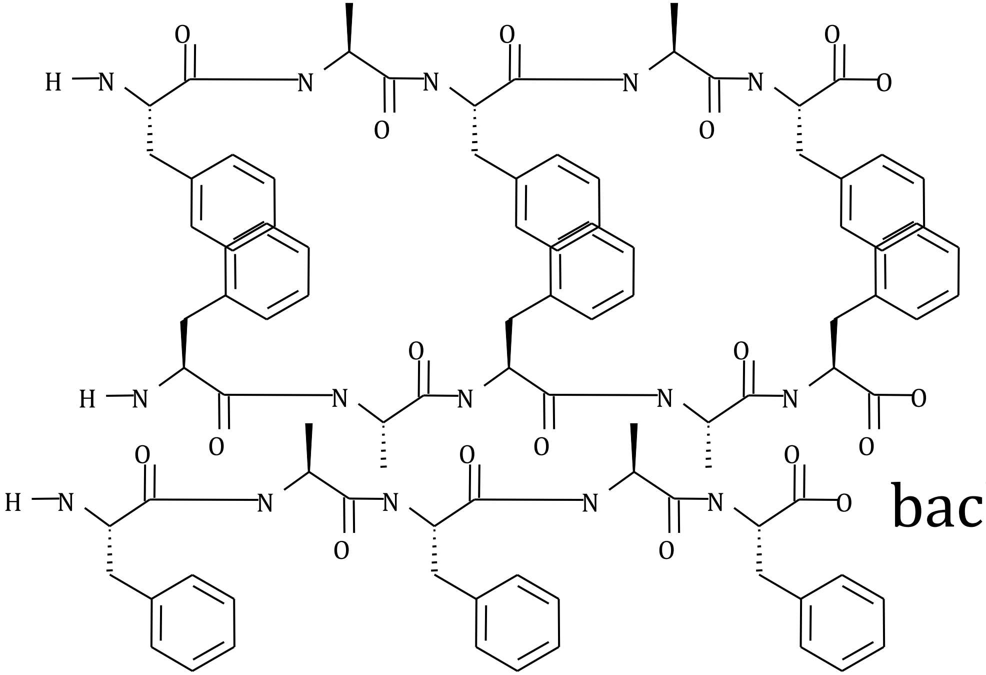
Possibilities

- more points per residue
- more complicated c_{ij} matrix...
- an example weakness

Important structural features of proteins

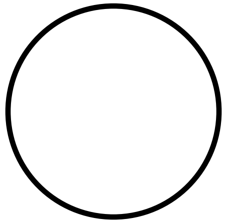
- all proteins have hydrogen bonds at backbone
- proteins differ in their sidechain interactions..

more complicated interactions



sidechain packing

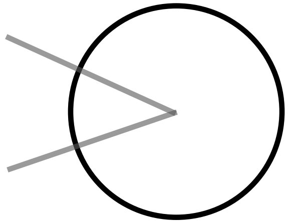
backbone Hbonds



one point residue

Hbond →

Hbond ←

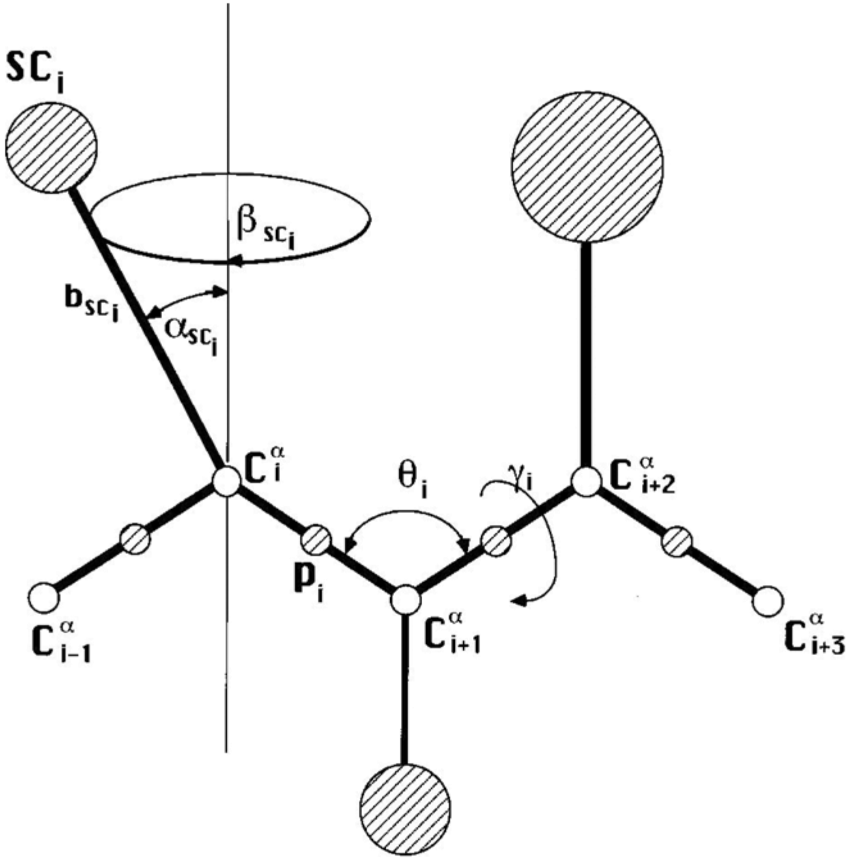


3 points per residue

Scheraga model

3 points per residue

- 2 for interactions
  - p_i is peptide bond centre
  - SC_i is sidechain
- 1 for geometry
  - C^α
- $C^{\alpha} - C^{\alpha}$ fixed at 3.8 Å



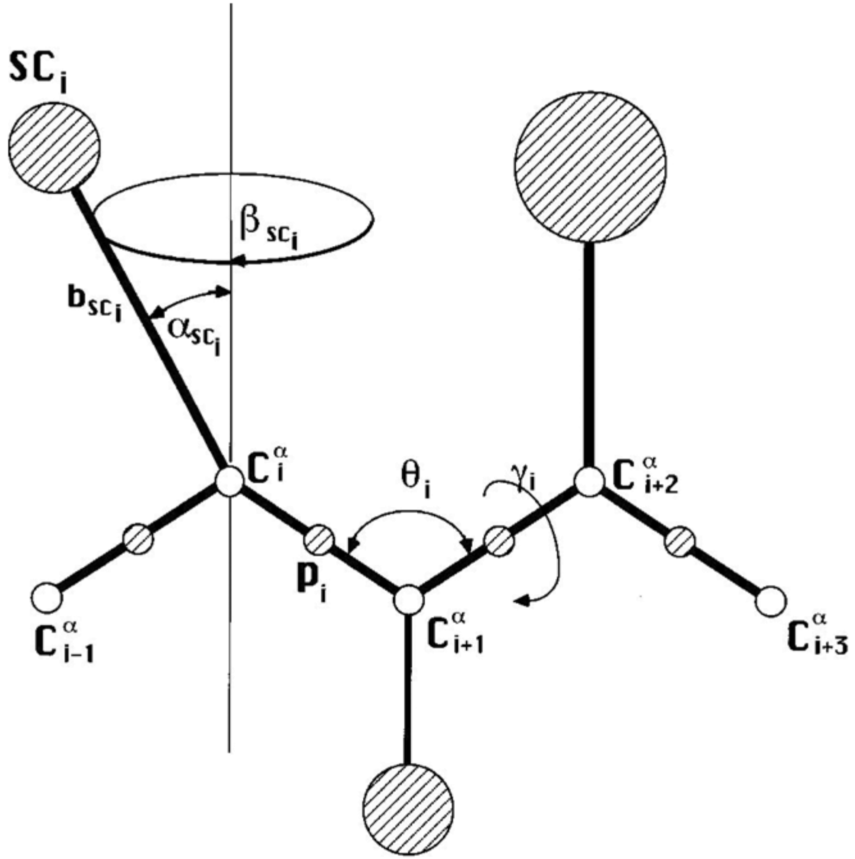
Do interaction sites correspond to atoms ?

Liwo, A., Oldziej, S, Pincus, MR, Wawak, RJ, Rackovsky, S, Scheraga, HA, 1997, J Comput Chem 18, 849-873, "A united-residue force field for off-lattice protein-structure simulations"

Terms in Scheraga model

Total quasi energy =

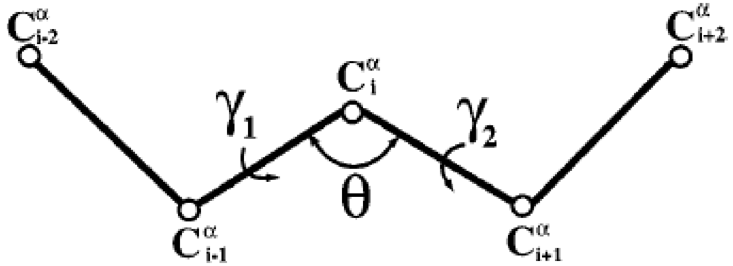
- side-chain to side-chain
- side-chain to peptide
- peptide to peptide
- torsion angle γ
- bending of θ
- …
  - bending α_{sc}



angle between C^{α} sites

Cunning approach

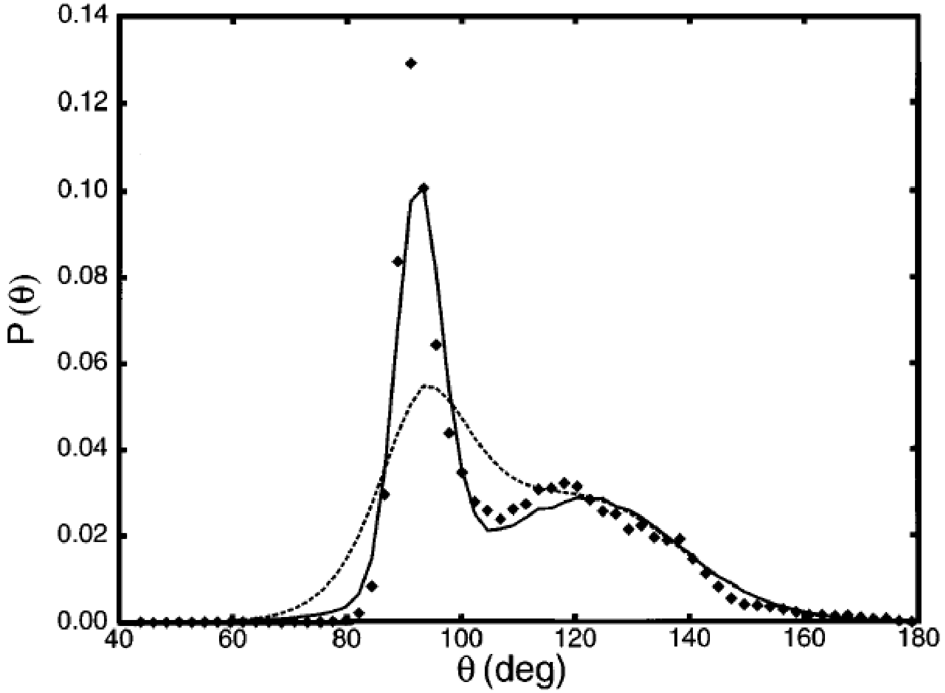
- look at θ distribution
- model with Gaussians



then say

$$U(\theta)^{bend} = -RT \ln P(\theta)$$

where $P(x)$ is the probability of finding a certain x



Liwo, A., Oldziej, S, Pincus, MR, Wawak, RJ, Rackovsky, S, Scheraga, HA, J Comput Chem, 18, 874-887 (1998)

Gaussian reminder

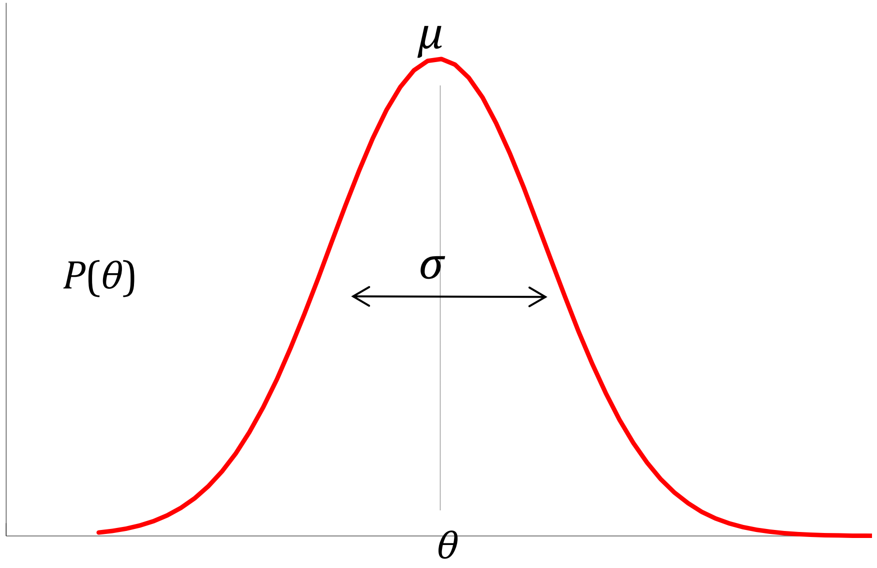
- get μ and σ from fitting
- angle θ depends on structure

$$P(\theta) = \frac{1}{\sigma\sqrt{2\pi}} \exp\left(\frac{-(\theta-\mu)^2}{2\sigma^2}\right)$$

- how would forces work ?
- express θ in terms of r's

- use $U(\theta)^{bend} = -RT \ln P(\theta)$

- take $\frac{dU}{d\theta}\frac{\partial\theta}{\partial\vec{r}}$



pseudo torsion term

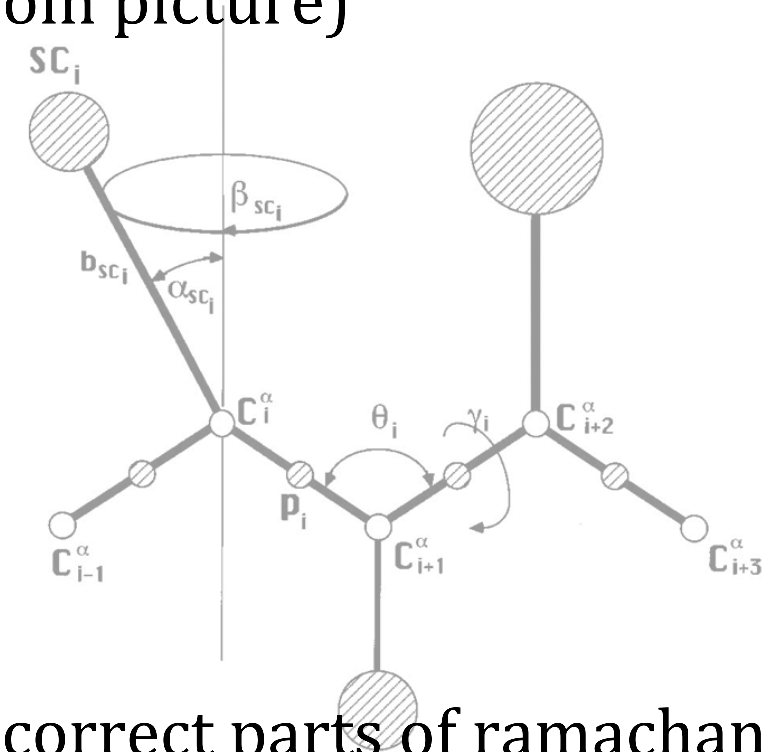
Like atomic torsion $U(\gamma_i) = a_i \cos n\gamma_i + 1 + b_i \sin n\gamma_i + 1$

- n varies from 3 to 6 depending on types $i + 1, i + 2$

(numbering from picture)

Three kinds of pair

- gly
- pro
- others



Net result ?

- residues will be positioned so as to populate correct parts of ramachandran plot
- this model will reproduce α-helix and β-sheets

side-chain peptide

Not so important

- mostly repulsive $U^{sc-p}(r_{sc-p}) = kr_{sc-p}^{-6}$
- k is positive, so energy goes up as particles approach

side chain interactions

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

- but, consider all the σ and ε
- main result
  - some side chains like each other (big ε)
  - some pairs can be entirely repulsive (small ε big σ)
  - some not important (small ε small σ)

more complications

Real work used

- different forms for long range interactions
- cross terms in pseudo angles

nicht für Klausur

What can one do ?

Typical application

Background

- protein comparison lectures..
- different sequences have similar structure
    - can we test some structure for a sequence

Remember sequence + structure testing in modelling Übung ?

- here
    - given some possible structures for a sequence
        - can be tested with this simple force field

What can we not do ?

- physical simulations
    - think of energy barriers (not real)
    - time scale

summary of philosophy

- Is any model better than others ?
- Each model represents something of interest
  - hydrophobic / hydrophilic separation
  - reasonably good quality structure with
    - real secondary structure
    - accurate geometry

Main aims

- pick the simplest model which reproduces quantity of interest

Are there bad models ?

- complicated, but not effective
- interaction sites at wrong places
  - not efficient
  - not effective

Parameterisation..

Problem example

- charge of an atom ?
    - can be guessed, measured ? - calculated from QM
- ε and σ in atomistic systems
    - can be taken from experiment (maybe)
    - adjust to reproduce something like density

What if a particle is a whole amino acid or sidechain ?

- is there such a thing as
- charge ?
- ε and σ ?

Approaches to parameterisation

General methods

- average over more detailed force field (brief)
- optimise / adjust for properties (brief)
- potentials of mean force / knowledge based (detailed)

From detailed to coarse grain

Assume detailed model is best

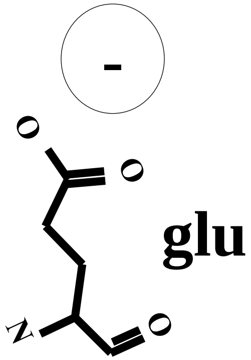
- Can we derive coarse grain properties from detailed ?

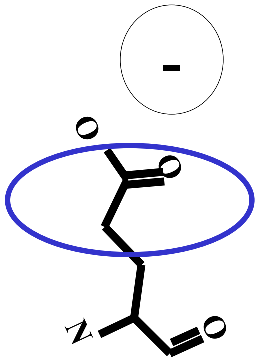
Examples – consider one or two sites per residue

- mass ? easy – add up the mass of atoms (also boring)

Charge ? not easy

- size of charge - obvious
- location ?
  - not easy
  - does this let us include polarity ? No.
- is this the right way to think about it ?...





Averaging over details is not easy

General interaction between two residues

- will depend on orientation, distance, other neighbours
- not all orientations occur equally likely
- sensible averaging not obvious
- better approach ...

Parameterising by adjustment / optimisation

```
while not happy
        move a parameter up or down
        measure happiness
```

```
for (parameter = small; parameter < big ; parameter++)
        measure happiness
```

Define happiness - what do you want ?

- density at equilibrium
- free energy change of some process
- distance of average protein structure from X-ray
- ….

cost function

For your definition of happiness

- some measured observable $\mathcal{A}_{obs}$
  - density, dielectric constant, diffusion constant, ..

From simulation with parameter p

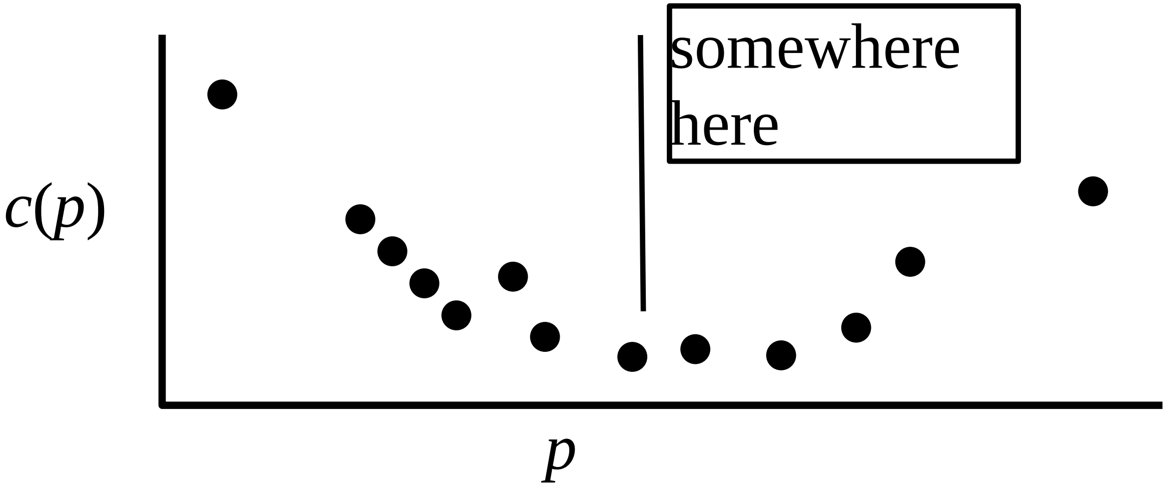
- simulate and get $\mathcal{A}_p$

- unhappiness (cost) is a function of p, so we have $c(p)$

$$c(p) = \left|\mathcal{A}_{obs} - \mathcal{A}_p\right|$$

or maybe $c(p) = \left(\mathcal{A}_{obs} - \mathcal{A}_p\right)^2$

- very concrete



- each point is result from a simulation
- noise / inaccuracy, not symmetric / linear

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

we would be adjusting the size of particles

parameters optimisation – boring ? easy ?

You would not choose p values randomly

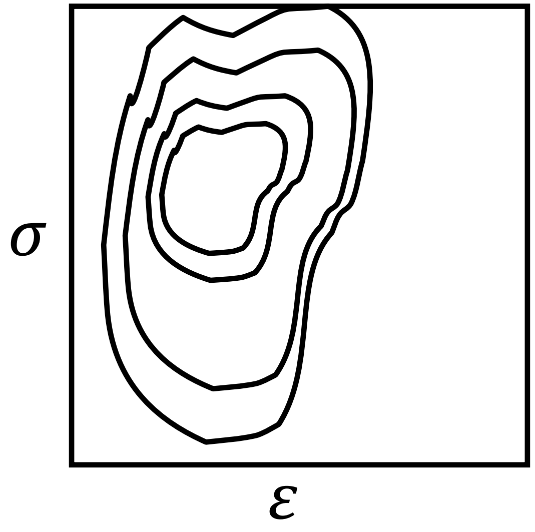
- (use a classic optimisation method)

Is this too easy and dull ?

- what you probably have is several parameters $c(p_1, p_2)$

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

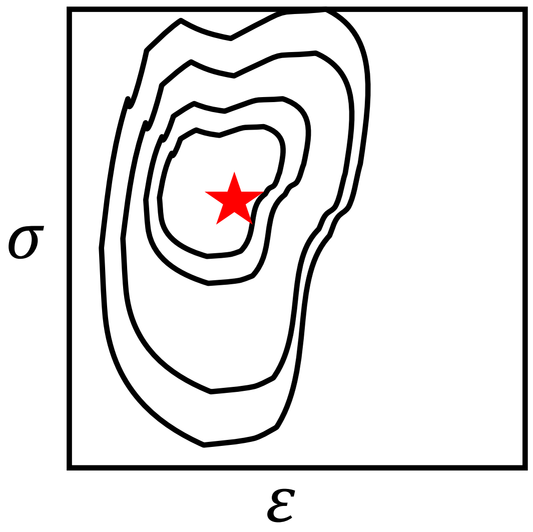
- measure the error/cost in 2D space



mapping parameter space

What does this tell us ?

- find best ε and σ
- see that ε is critical, σ less so



Practical implementation

- systematic search ? Inefficient
- automate the optimisation

- Problems…

Problems with parameterisation

- scheme requires a believable measure of quality
- easy for two parameters
- possible for 3, 4 parameters
- very difficult for 100 parameters

- you optimize for density
  - diffusion, free energy changes ….
    - all broken
  - you optimise based on 10 proteins
    - test of 11th - bad results (too small training set)

Different kind of score function

Change of style…

- questions on coarse-graining ?
- why is entropy an issue ?   (numbers of particles / states)

- from nice ideas to dumb empiricism

Potentials of mean force

Potential of mean force ... knowledge based score functions

- very general
- history from atomistic simulations

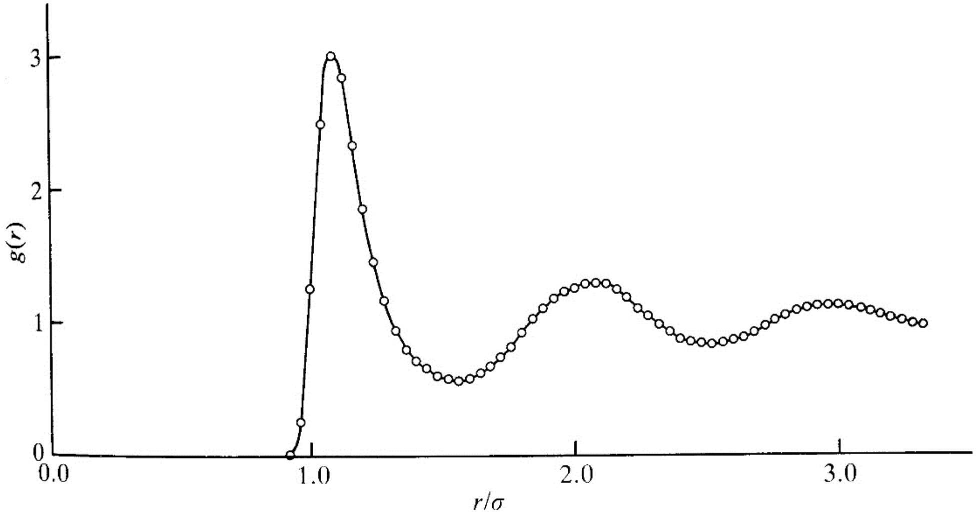
Basic idea .. easy

- from radial distribution function, to something like energy..

Intuitive version of potential of mean force

Radial distribution function $g(r)$

- probability of finding a neighbour at a certain distance



What does this suggest about energy ?

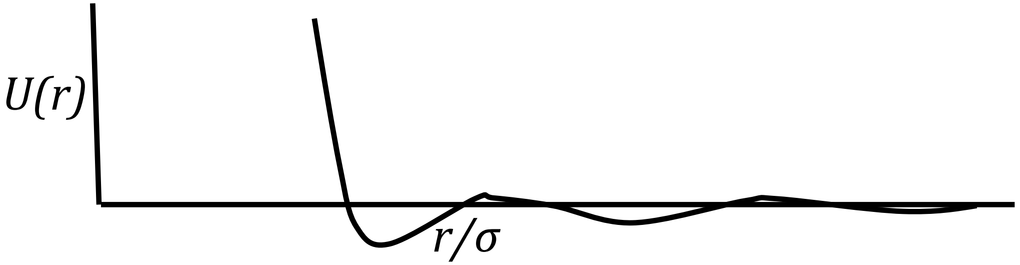
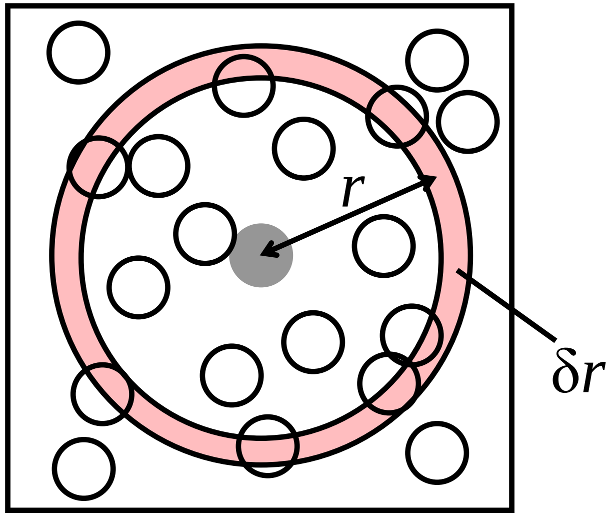


diagram from Allen, MP, Tildesley, DJ, Computer simulation of liquids, Oxford University Press, 1990

Radial distribution function

Formal idea $g(r) = \frac{N_{neighbours\,seen(r)}}{N_{neighbours\,expected(r)}}$



$$N_{expected} = \frac{V_{shell}}{V} N$$

- N particles
- V volume
- Calculating it ?
  - define a shell thickness (δr)
  - around each particle
    - at each distance, count neighbours within shell

$$g(r) = \frac{V}{NV_{shell}} N_{shell}(r)$$

Rationale for potentials of mean force

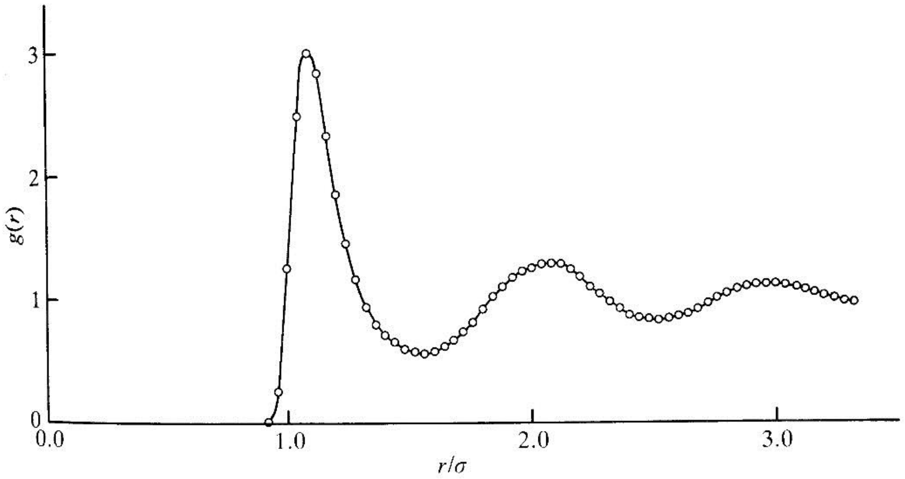
For state i compared to some reference x

$$\frac{p_i}{p_x} = \frac{e^{\frac{-E_i}{kT}}}{e^{\frac{-E_x}{kT}}} = e^{\frac{E_x - E_i}{kT}}$$

$$\ln \frac{p_i}{p_x} = \frac{E_x - E_i}{kT}$$

$$\Delta E = kT \ln \frac{p_i}{p_x}$$

Information in distribution function



Intuitive properties ?

- how likely is it that atoms get near to each other ($< \sigma$) ?
- what would a crystal look like ? (very ordered)
- what if interactions are
  - very strong (compared to temperature)
  - very weak
- Seems to reflect
  - strength of interactions / order

Relate this back to energy

Energy from *g(r)*

From statistical mechanics $g(r) = e^{\frac{-w(r)}{kT}}$

- use work $w(r)$ for a picture moving particle by r

so strictly $w(r) = -kT \ln g(r)$

- already useful for looking at liquid systems

Properties

- are we looking at potential energy U or free energy G ?
  - if our results from nature / simulation – free energy

How would we get $g(r)$?

- experiment ? sometimes
- simulation – easy – simulate at high resolution

Assumptions

- our system is at equilibrium

Generalising ideas of potential of mean force

What else can we do ?

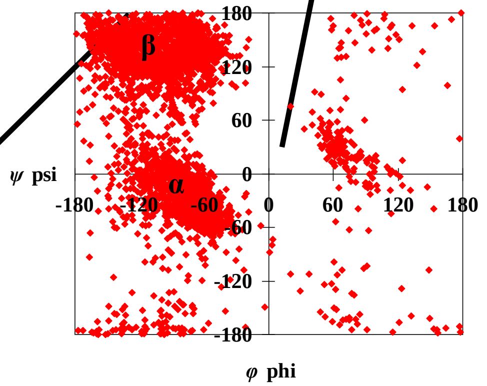
- think of more interesting system (H_20)

Would we express our function in terms of O ? H ?

- both valid
- could consider work done bringing an O to O, O to H, H to H
  - for fun on next page

More general..

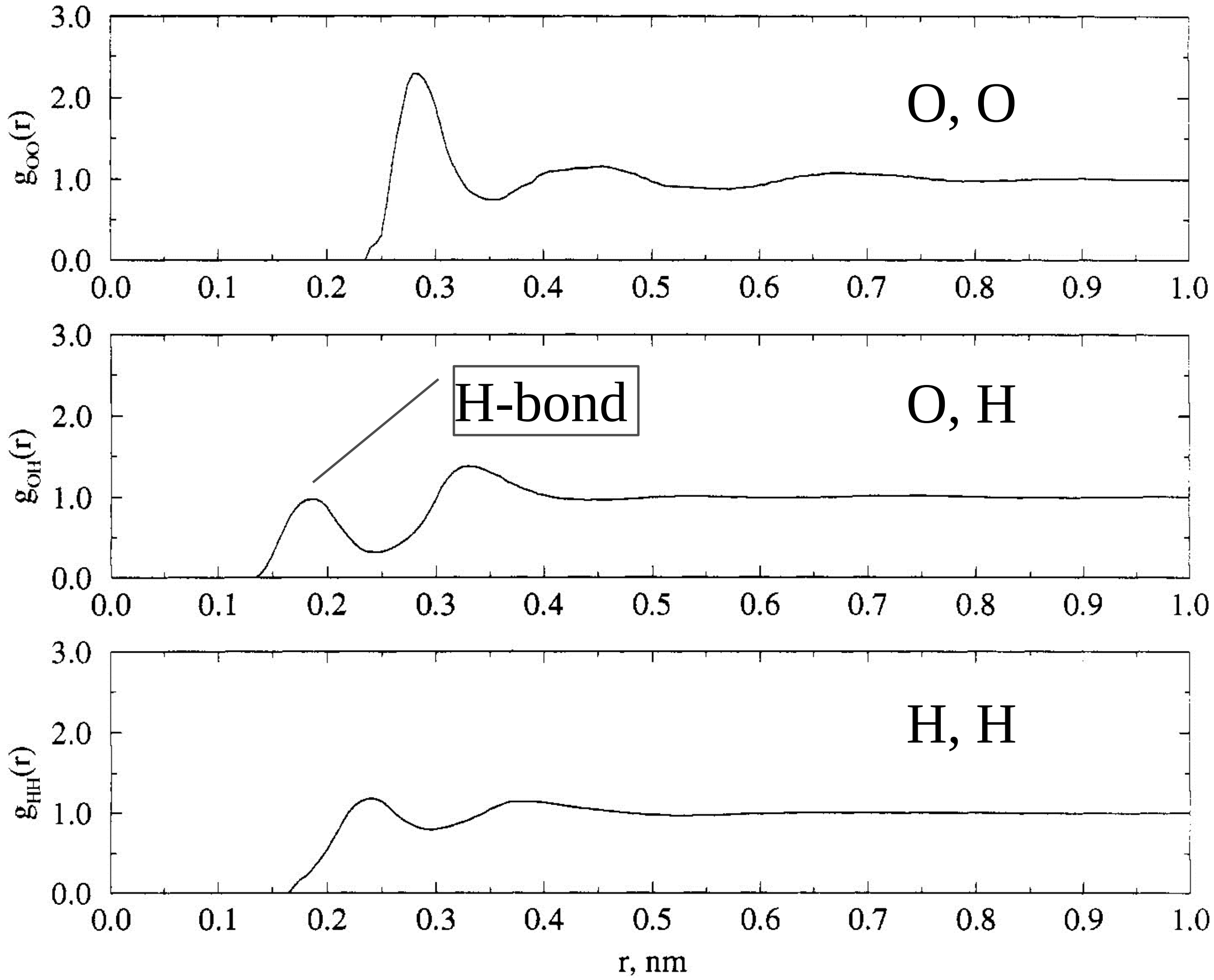
- are we limited to distances ? No
- example – ramachandran plot



low probability / high energy

high probability / low energy

radial distribution function (water)



Wallqvist, A. & Mountain, R.D., "Molecular Models of Water" in Reviews in Computational Chemistry Vol 13, ed. Lipkowitz, K.B. and Boyd, D.B., Wiley, New York, 1999

Reformulating for our purposes

Can one use these ideas for proteins ?

Our goal ?

- a force field / score function for deciding if a protein is happy
- work with particles / interaction sites
- slightly different formulation
    - if I see a pair of particles close to each other,
        - is this more or less likely than random chance ?
    - treat pieces of protein like a gas
    - care about types of particles (unlike simple liquid)

Let us define...

Score energy formulation

$$W_{AB}(r) = -RT \ln\left(\frac{N_{AB}^{obs}(r \pm \delta r)}{N_{AB}^{exp}(r \pm \delta r)}\right)$$

N_{AB}^{obs} how many times do we see

- particles of types A and B
- distance *r* given some range δr

N_{AB}^{exp} how often would you expect to see AB pair at *r* ?

- remember Boltzmann statistics

This is not yet an energy / score function !

- it is how to build one

Intuitive version

- Cl^- and Na^+ in water like to interact (distance r^0)
- N_{AB}^{obs} is higher than random particles
- $W_{\mathrm{ClNa}}(r)$ is more negative at r^0

Details of formulation

$$W_{AB}(r) = -RT \ln\left(\frac{N_{AB}^{obs}(r \pm \delta r)}{N_{AB}^{exp}(r \pm \delta r)}\right)$$

- looks easy, but what is N^{exp} ?

Maybe fraction of particles is a good approximation

$$N_{AB}^{exp} = N_{all} X_{\mathrm{Na}} X_{\mathrm{Cl}} \quad \text{(use mole fractions)}$$

- use this idea to build a protein force field / score function

Protein score function

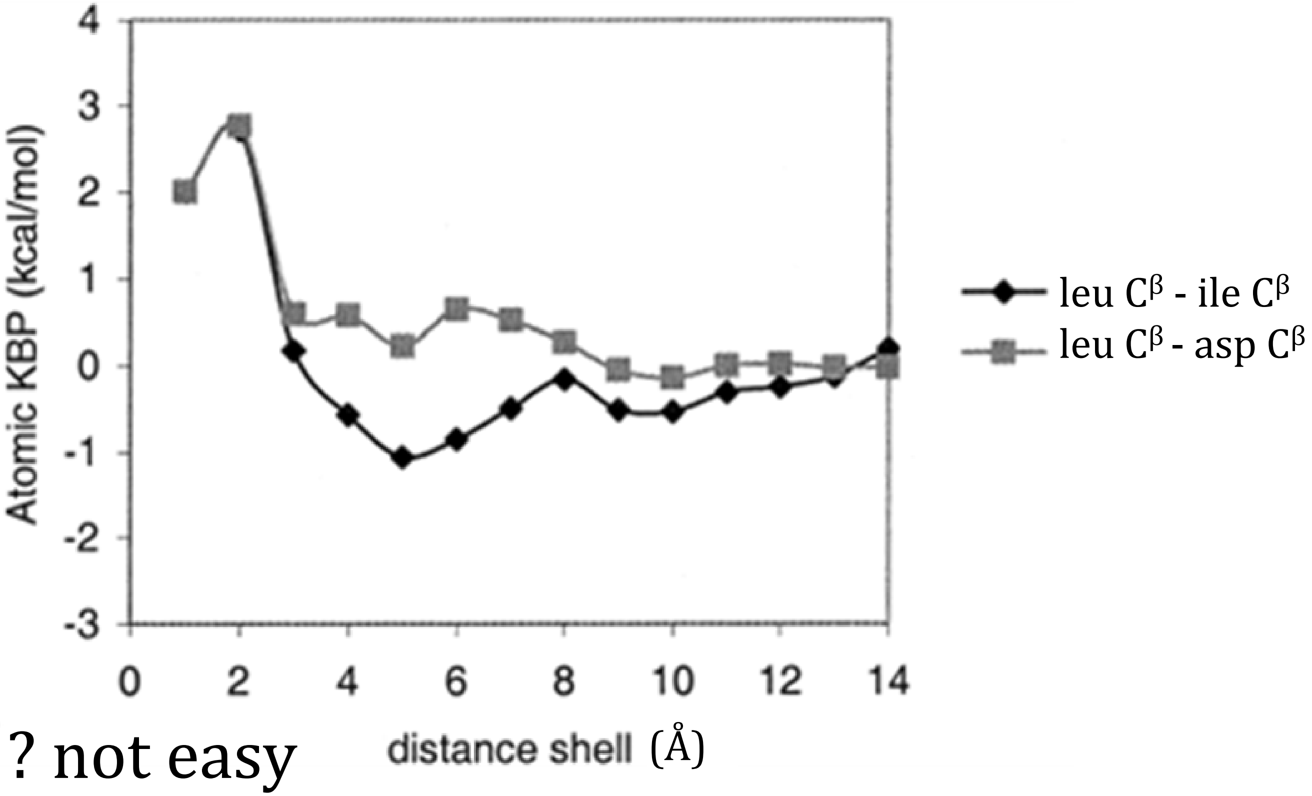
Arbitrarily

- define interaction sites as one per residue
  - maybe at C^{α} or C^{β}
- collect set of structures from protein data bank
- define a distance (4 Å) and range (± 0.5 Å)
- count how often do I see
  - gly-gly at this range, gly-ala, gly-X, X-Y ...
    - gives me N^{obs}
  - how many pairs of type gly-gly, gly-ala, gly-X, X-Y... are there ?
    - gives me N^{exp}
  - repeat for 5 Å, 6 Å, ...
- resulting score function...

final score function

For every type of interaction AB (20 × 21 /2)

- set of $W_{AB}(r)$



All ingredients in place

- can we use this for simulations ? not easy
- can we use to score a protein ? yes

Names

- Boltzmann-based, knowledge based

Lu, H and Skolnick, J (2001) Proteins 44, 223-232, A distance dependent knowledge-based potential for improved protein structure selection

Applying knowledge-based score function

Take your protein

- for every pair of residues
  - calculate C^{β} C^{β} distance (for example)
  - look up type of residues (ala-ala, trp-ala, ...)
  - look up distance range
  - add in value from table
- what is intuitive result from a
  - a sensible protein / a misfolded protein ?
- is this a real force field ? yes
- is this like the atomistic ones ? no
  - there are no derivatives $\left(\frac{dU}{dr}\right)$
  - it is not necessarily defined for all coordinates

Practical Problems Boltzmann score functions

Do we have enough data ?

- how common are Asp-Asp pairs at short distance ?

How should we pick distance ranges ?

- small bins (δr) give a lot of detail, but there is less data

What are my interaction sites ?

- C^{α} ? C^{β} ? both ?

Data bias

- Can I ever find a representative set of proteins ?
  - PDB is a set of proteins which have been crystallised

Reminder

- we want low-resolution score functions
- if we work in a Boltzmann framework, we work with real energies
- everything ends up as $\frac{p_i}{p_j} = e^{-\frac{\Delta E}{RT}}$ or here $\Delta E = -RT \ln \frac{p_i}{p_j}$ or $\Delta E = -RT \ln \frac{N_{obs}}{N_{exp}}$
- we are comparing against what you expect from random events without interactions p_j
- work with kJ mol^{-1}, we can
  - make real energetic predictions (kinetics, equilibria)
  - combine with other energy terms

Problems of Principle

Boltzmann statistics

- is the protein data bank a set of structures at equilibrium ?

Is this a potential of mean force ? Think of Na, Cl example

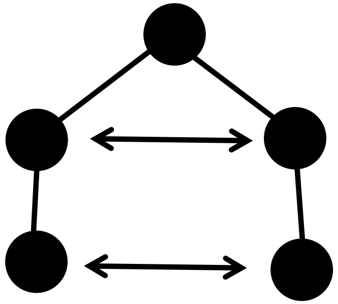
- that is a valid PMF since we can average over the system

Energy / Free energy

  - how real ?

N^{exp} ? how should it be calculated ?

- is the fraction of amino acid a good estimate ? No.
- there are well known effects.. Examples



i,*i*+2

i,*i*+4 very different statistics

Boltzmann based scores: improvements / applications

- collect data separately for (*i*, *i*+2), (*i*, *i*+3), ...
  - problems with sparse (missing) data
- collect data on angles
- collect data from different atoms
- collect protein – small molecule data

Are these functions useful ?

- not perfect, not much good for simulation
- we can take any coordinates and calculate a score
  - directly reflects how likely the coordinates are
- threading / fold recognition

Parameterising summary

- Inventing a score function / force field needs parameters
- totally invented (Crippen, Kuntz, …)
- optimisation / systematic search
- statistics + Boltzmann distribution

Summary of low-resolution force fields

Properties

- do we always need a physical basis ?
- do we need physical score (energy) ?

Questions

- pick interaction sites
- pick interaction functions / tables

What is your application ?

- simulation
  - reproducing a physical phenomenon (folding, binding)
- scoring coordinates

Parameterisation

- Averaging, optimisation, potentials of mean force

Next – less physical