Coarse grain models (continuous)

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 ?
- less reasonable
  - given initial coordinates, can I simulate a protein folding ?

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

- 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

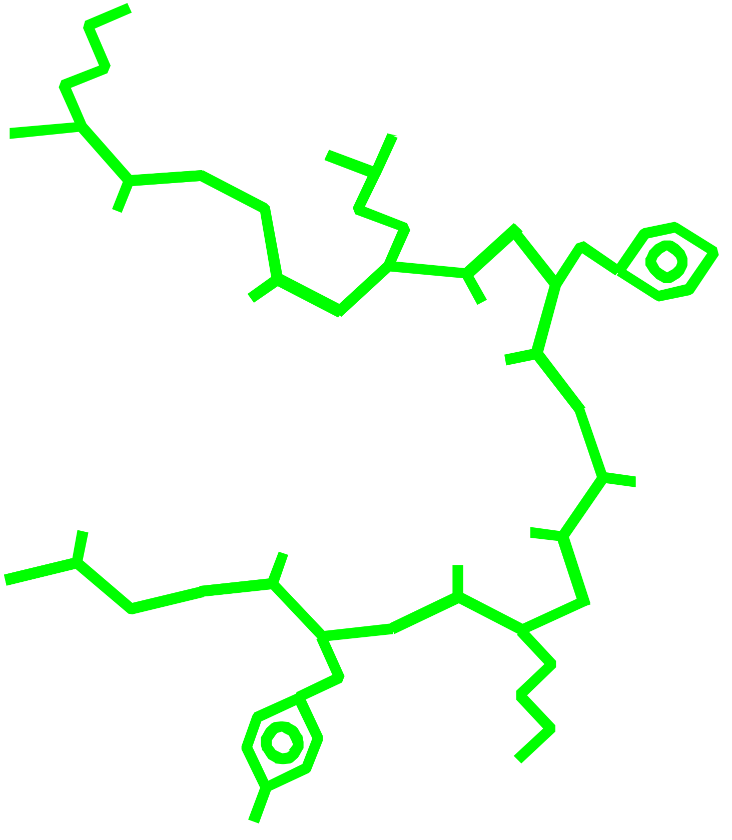
- build something like energy which encapsulates our ideas
- example – define a function which is happiest with
  - hydrophobic residues together
  - charged residues on outside
- would this be enough ?
  - maybe / not for everything

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



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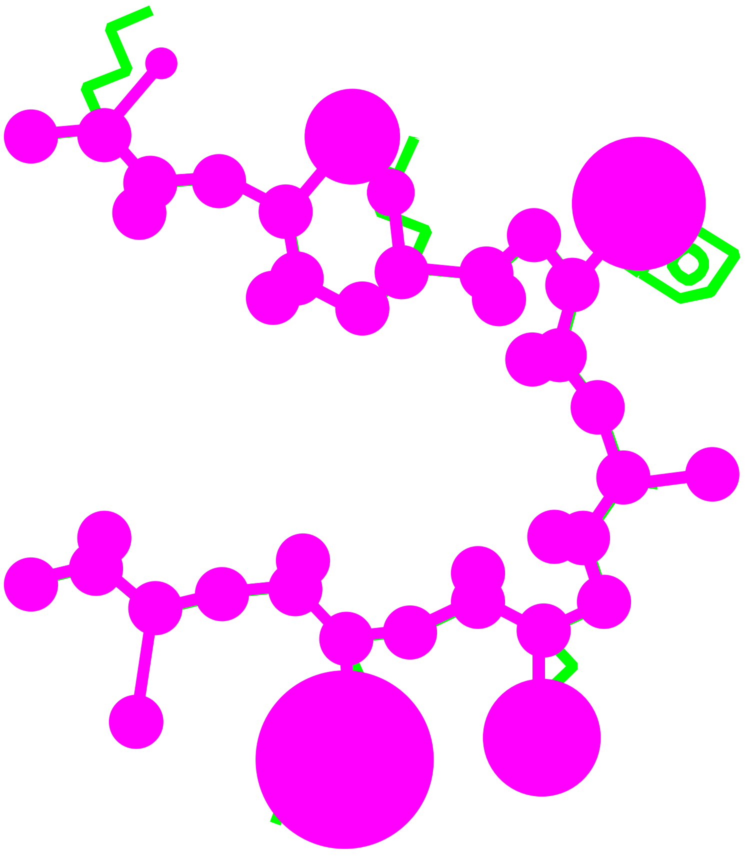

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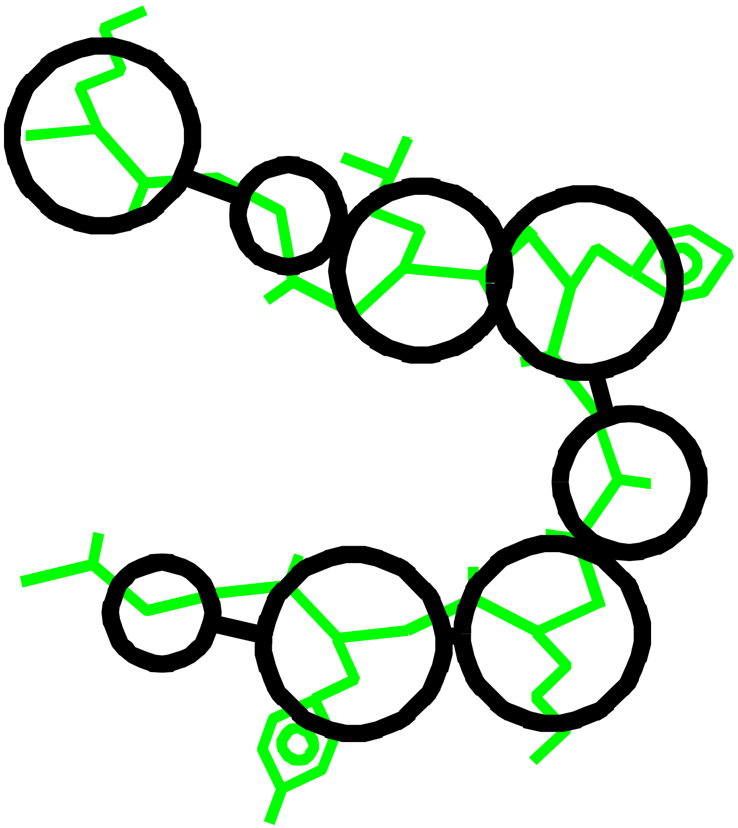


Coarse-graining (steps)

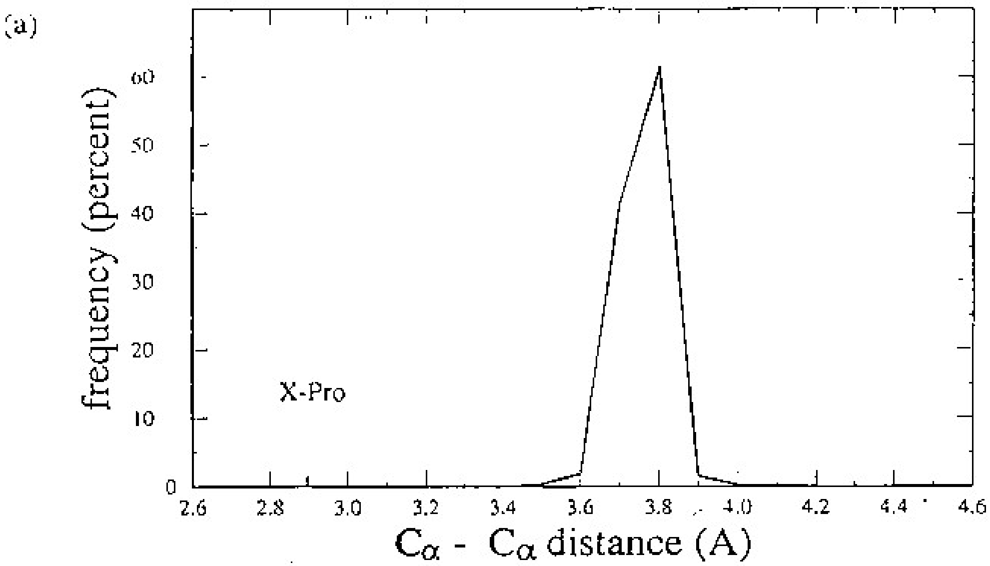
- Decide on representation
- Invent quasi-energy functions
- Our plan
  - step through some examples from literature

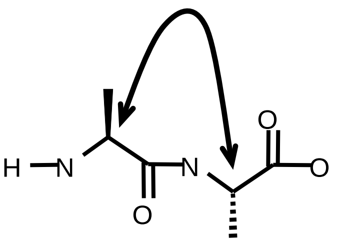
Common features

- 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 C^{α} to C^{α} distances

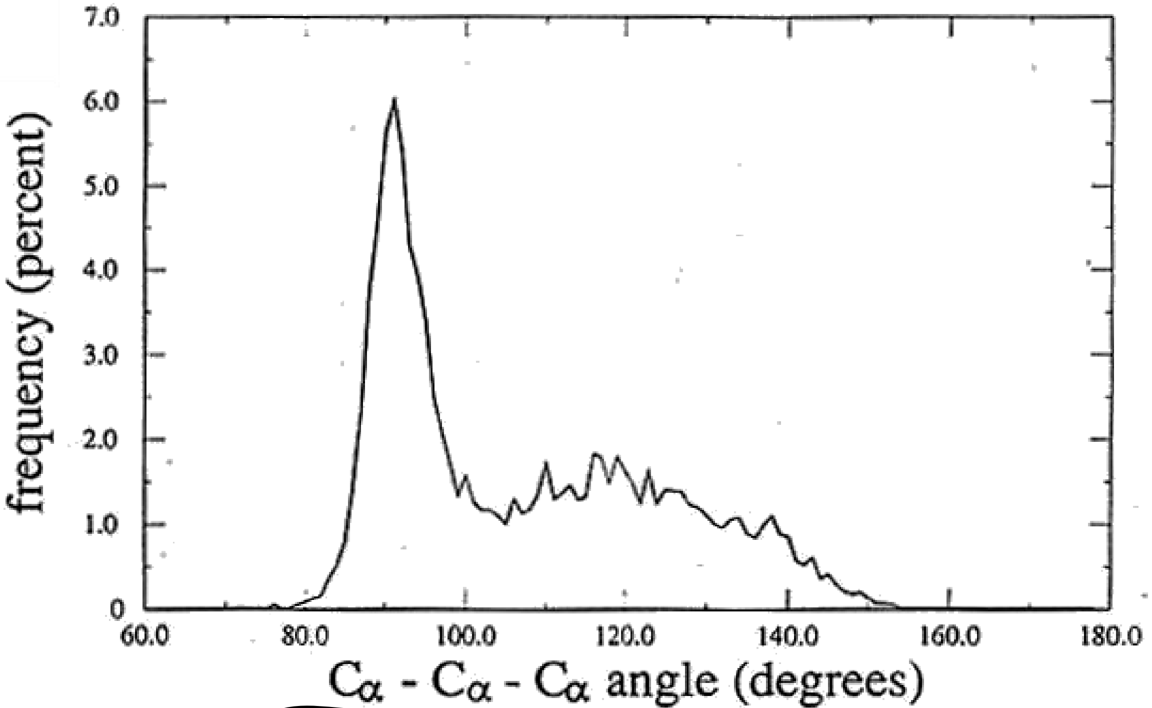


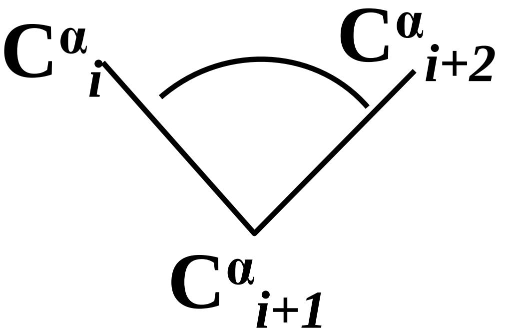


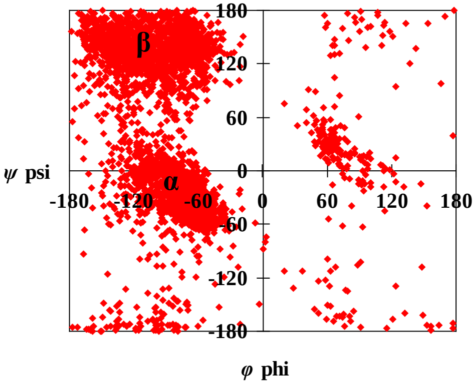
- Conclusion is easy
  - any model should fix $C^{\alpha}_{i,i+1}$ distances at 3.8 Å
- what other properties do we know ?

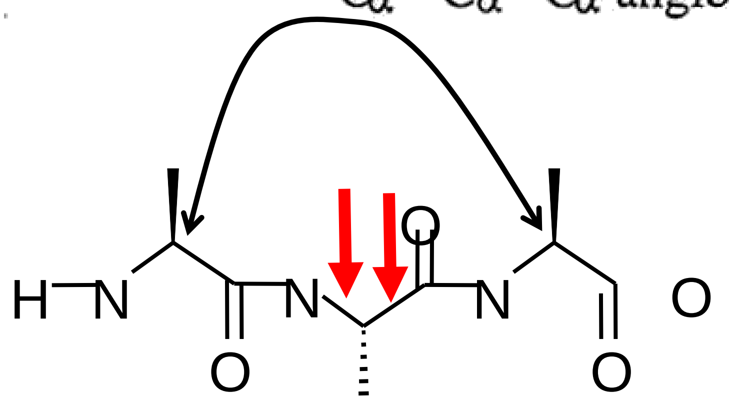
from Godzik, A., Kolinski, A, Skolnick, J. 1993, J. Comput. Chem. 14, 1194-1202

$C^{\alpha}_{i,i+2}$ 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
- $U(r_{ij})=(\mathrm{radius}_i + \mathrm{radius}_j)^2 - r_{ij}^2$

force hydrophilic residues to surface, for these residues

- $U^*(r_{ij})= (100 – d_i^2)$ where d_i is distance to centre, 100 is arbitrary

disulfide bonds

- very strong

residue specific interactions

- $U^{long}(r_i)=c_{ij}\ (r_{ij}^2-R^2)$ 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

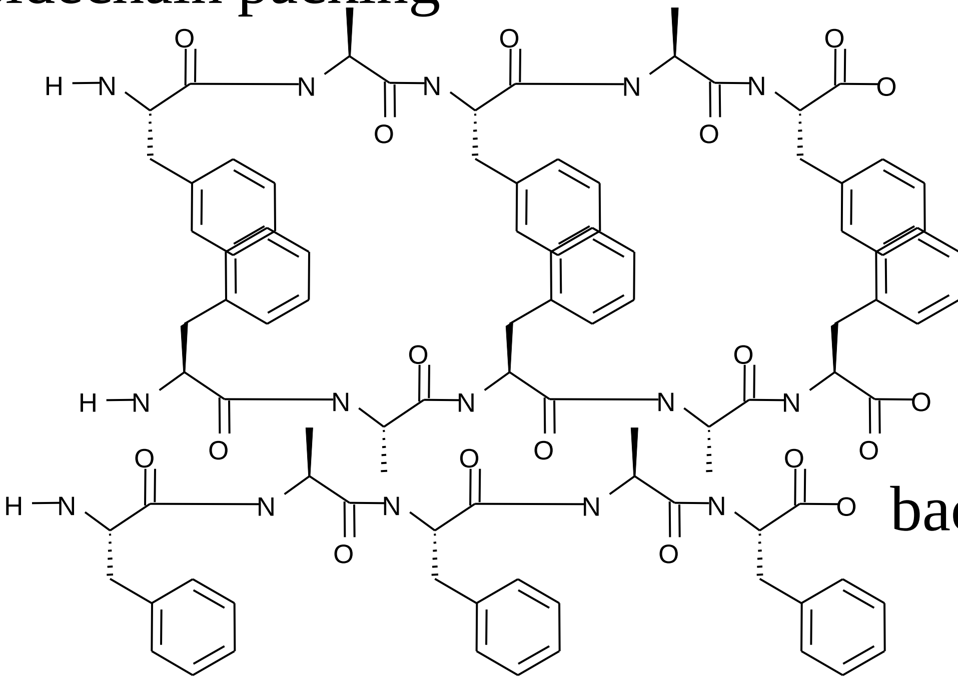
- try to "optimise" protein structure
- for 50 residues, maybe about 5 Å rms
  - maybe not important
- model does..
  - make a hydrophobic core
  - put charged and polar residues at surface
  - differentiate between possible and impossible structures
- model does not
  - reproduce any geometry to Å accuracy
  - details of secondary structure types
    - not the intention
  - predict physical pathways
  - depend on subtle sequence features (simplicity of c_{ij} matrix)

Improvements to simple model

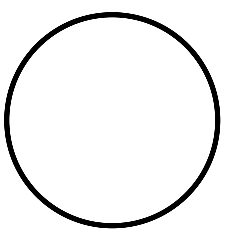
- aim
  - biggest improvement for least complication
- possibilities
  - more points per residue
  - more complicated c_{ij} matrix...
  - an example weakness
- important structural features of proteins
  - all proteins have hydrogen bonds at backbone
  - proteins differ in their sidechain interactions..

more complicated interactions

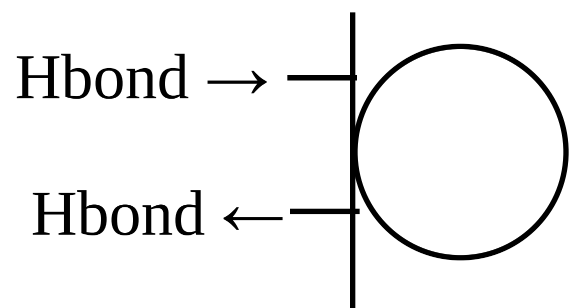
sidechain packing



backbone Hbonds



one point residue

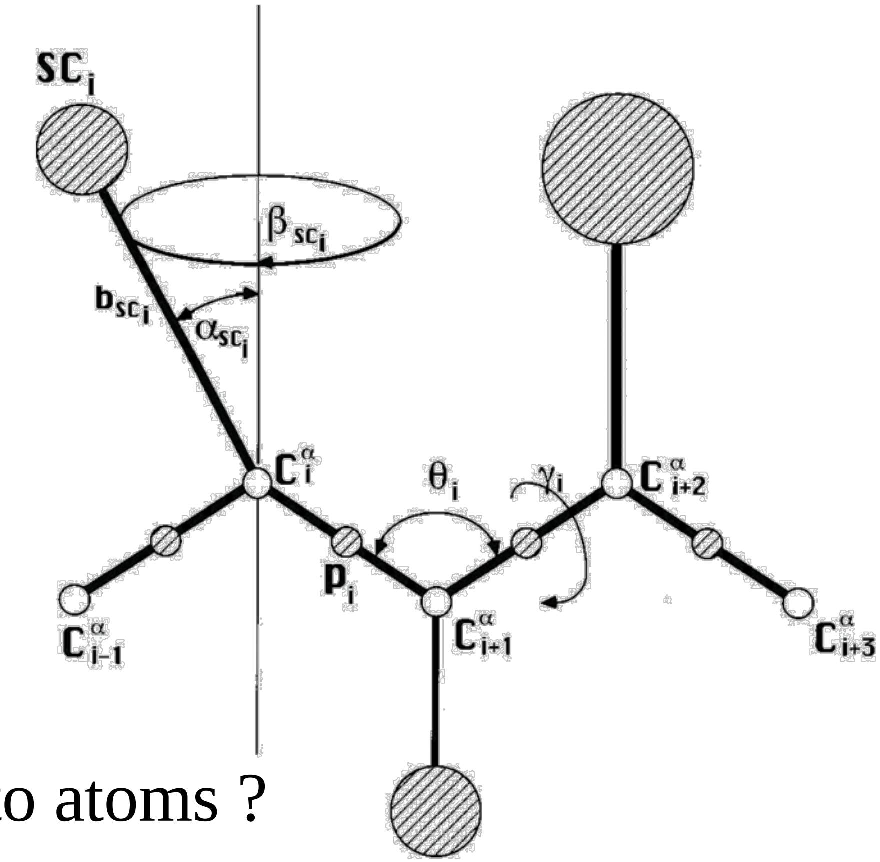


3 points per residue

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

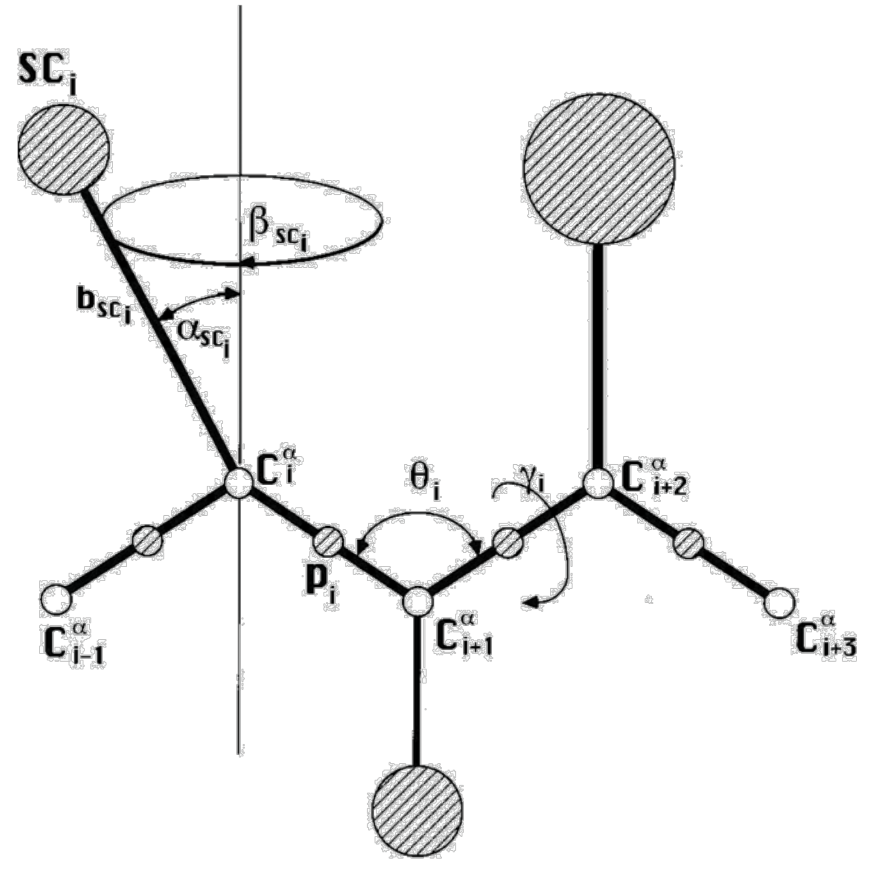


- do interaction sites correspond to atoms ?

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}

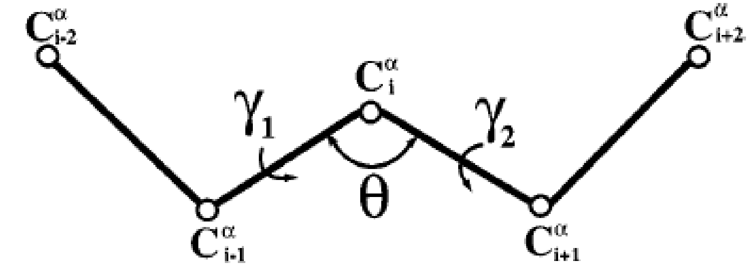


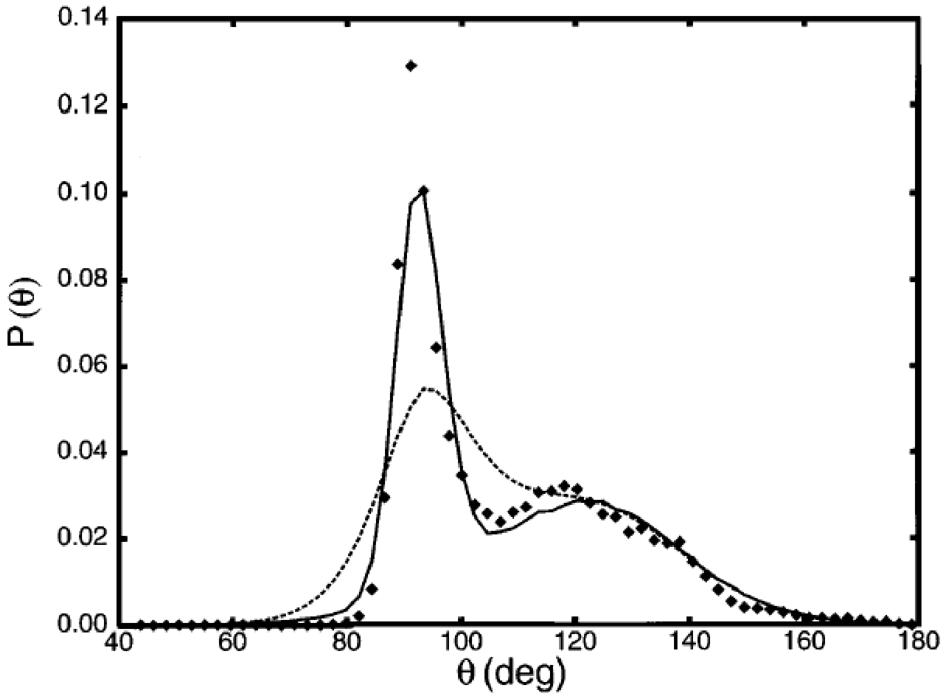
angle between C^{α} sites

- cunning approach
  - look at θ distribution
  - model with Gaussians
- then say

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

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



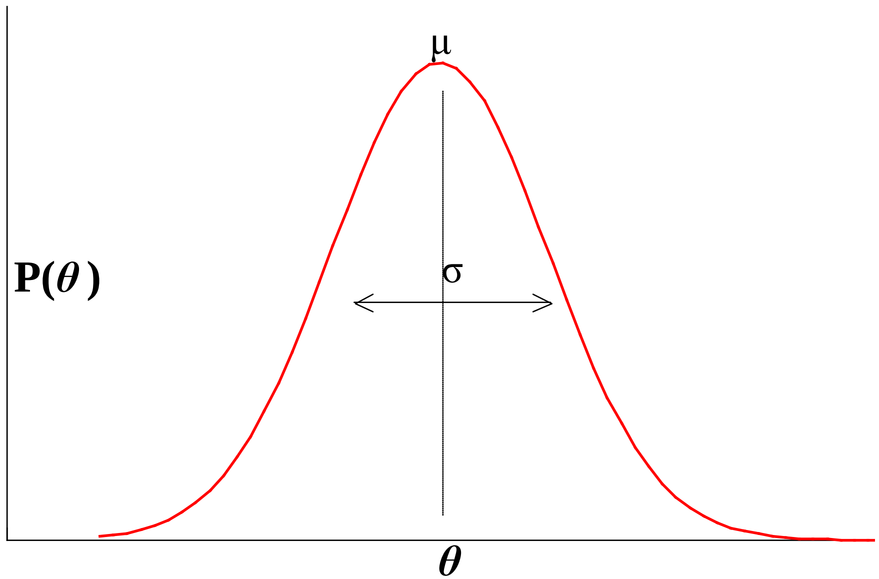


Gaussian reminder

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

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

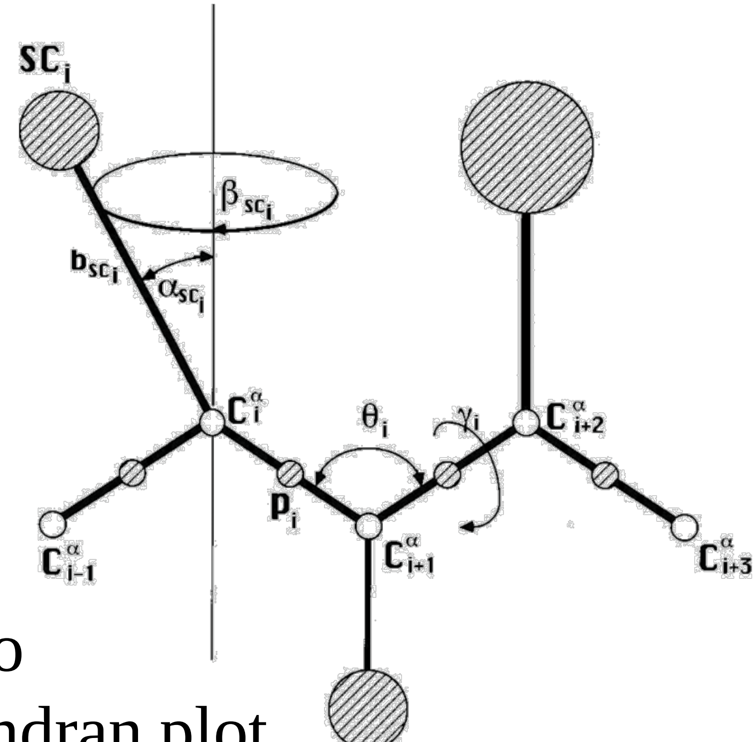
- how would forces work ?
- express θ in terms of *r*'s



- use $U(\theta)^{bend} = -RT \log P(\theta)$
- take $\dfrac{dU}{d\theta}\dfrac{\partial\theta}{\partial\vec{r}}$

pseudo torsion term

- like an 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, j
  - three kinds of i,j 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

- maybe not so important
  - mostly repulsive

$$U^{sc-peptide}(r_{scp}) = k r_{scp}^{-6}$$

  - *k* is positive, so energy goes up as particles approach

side chain interactions

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

- 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

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 modellingÜbung ?

- 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 has represent 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)

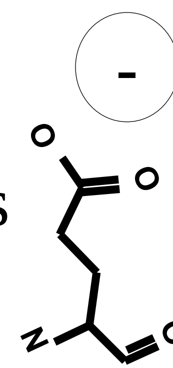
From detailed to coarse grain

Assume detailed model is best

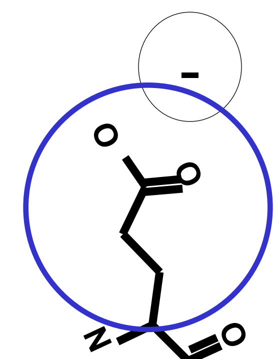
- Can we derive coarse grain properties from detailed ?

Examples – consider one or two sites per residue

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



glu



- charge ? not easy
  - is charge important ? sometimes
  - size of charge obvious
  - location of charge may not be the same as a single site
  - does this let us include polarity ? No.
- is this the right way to think about it ?...

Averaging over details is not easy

If we have electrostatics

- perhaps we can have coarse electrostatics
- maybe better to forget serious physics / strict electrostatics

Earlier example (Kuntz et al)

- pairwise interactions like (r_0^2-r_{ij}^2) + term for sending residues / to from centre of molecule
- you can not easily get parameters from a more detailed force field here

General interaction between two residues

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

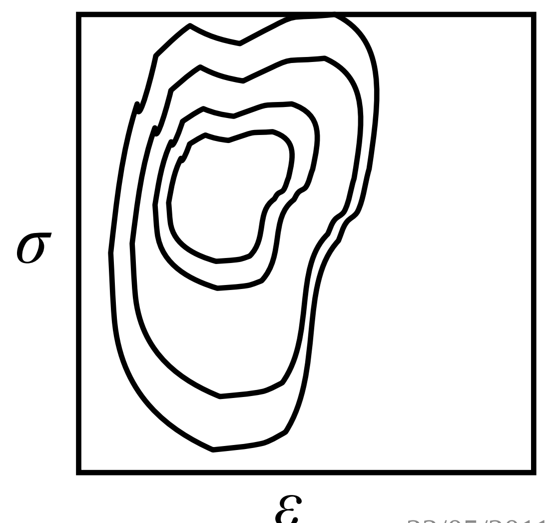
Parameterising by adjustment

Basic idea

- build some representation (like examples above)
- adjust parameters to give desired result
- An example method
- define a simple force field like

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

  - run a calculation and measure a property
    - density ? how near to correct structure ?
    - repeat for many values of ε and σ
    - build a cost / merit map



mapping parameter space

What does this tell us ?

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

Good result ?

- parameters from one or several proteins should work on all

Refinement ?

- optimisation can be automated

Problems

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

parameterising from potential of mean force

Potential of mean force ... knowledge based score functions

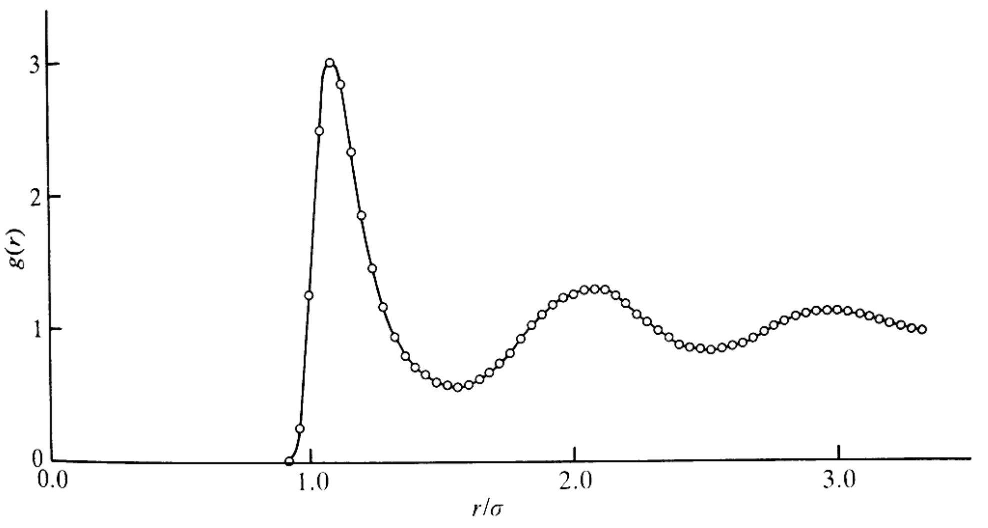
- very general
- history from atomistic simulations

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 ?

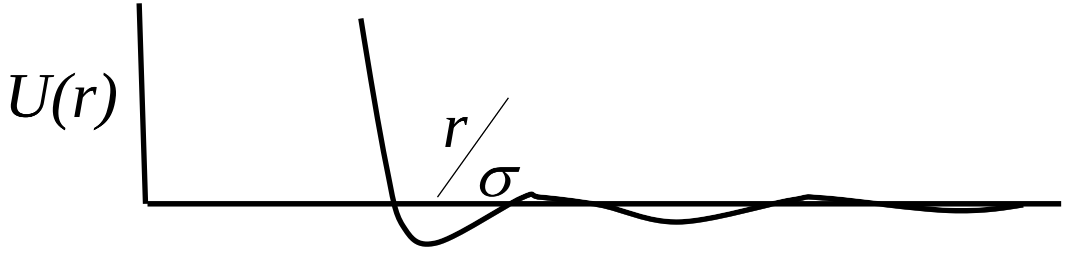


diagram from Allen, MP, Tildesley, DJ, Computer simulation of liquids, Oxford University Press, 1990

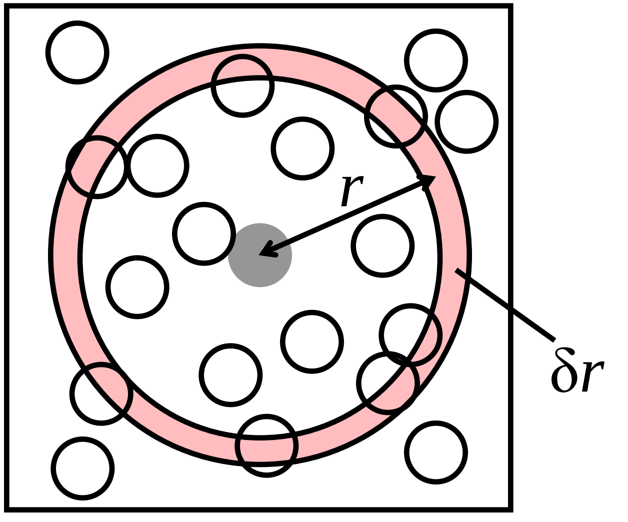
Radial distribution function

- Formal idea

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

- N particles
- V volume

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



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

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

Rationale for potentials of mean force

- For state i compared to some reference x

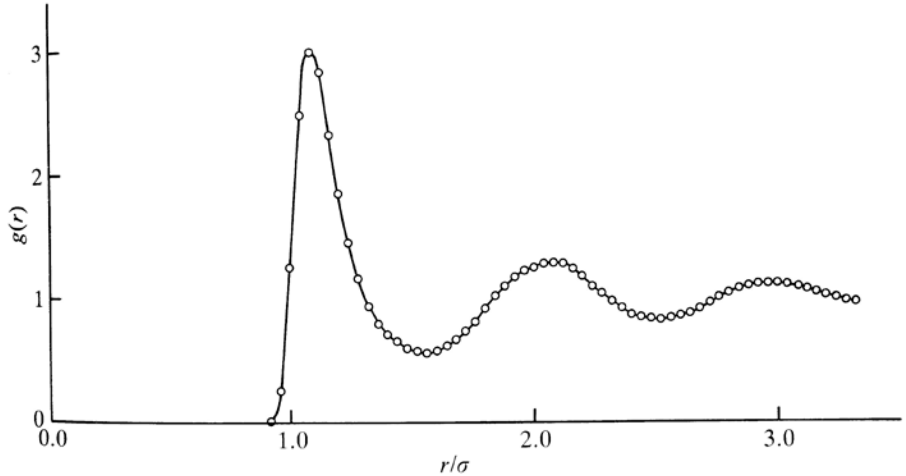
$$\frac{p_i}{p_x} = \frac{e^{-E_i/kT}}{e^{-E_x/kT}}$$

$$= e^{E_x - E_i/kT}$$

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

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

Information in distribution function



Intuitive properties ?

- how likely is it that atoms get ne
- what would a crystal look like ?
- 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 $g(r) = e^{-w(r)/kT}$

- 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 (or simulation) – free energy
- how would we get $g(r)$?
  - experiment ? sometimes
  - simulation – easy
- assumptions
  - our system is at equilibrium
  - it is some kind of ensemble

Generalising ideas of potential of mean force

What else can we do ?

- think of more interesting system ($H_2 0$)

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

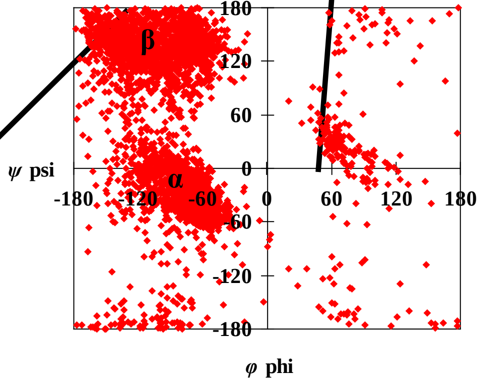
- both valid
- could look at the work done to bring an O to O, O to H, H to H

More general..

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

low probability / high energy

high probability / low energy



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

Define

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

- 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
    - $N_{NaCl}{}^{exp} = N_{all} X_{\mathrm{Na}} X_{\mathrm{Cl}}$ (use mole fractions)
- use this idea to build a protein force field / score function

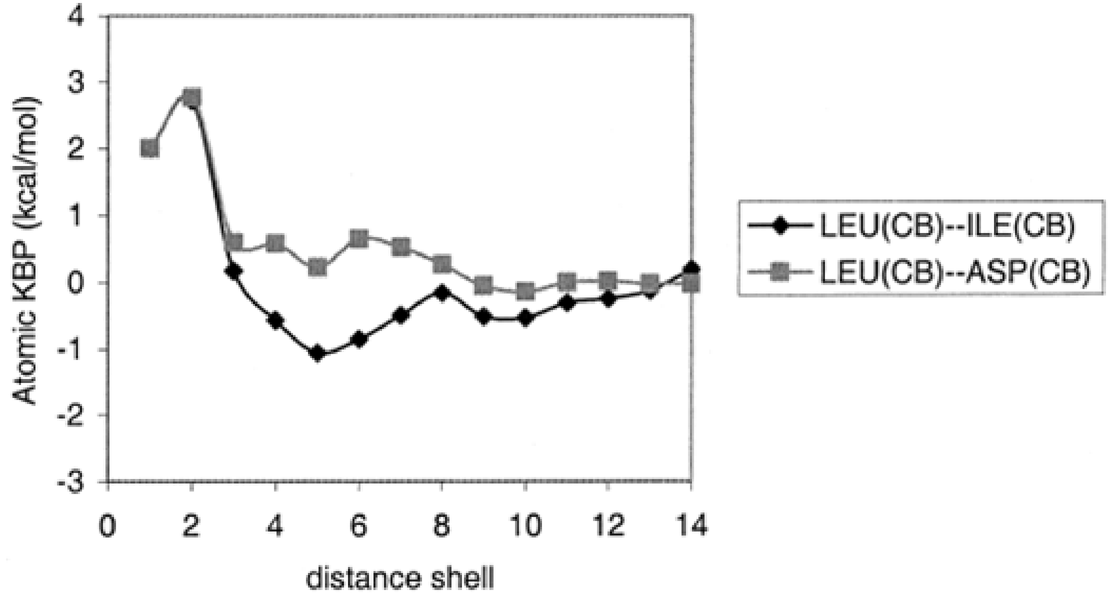
Protein score function

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 x 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 (dU / dr)
  - it is not necessarily defined for all coordinates

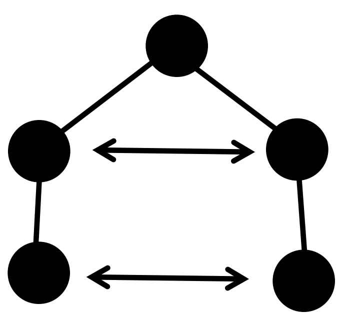
Practical Problems Boltzmann score functions

Practical

- 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

Problems of Principle

- Boltzmann statistics
  - is the protein data bank any ensemble ?
- 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

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

Next

- even less physical