Ab Initio Methods for Protein Structure Prediction

Slides modified from Shuai C., Li at University of Waterloo

Motivation

- homology modeling
  - No knowledge about the physical nature of the protein folding and stability.
  - No template available in some cases
- ab-initio methods can
  - augment fold-recognition and homology (refinement, large loops, side chains).
  - it can ease experimental structure determination.
  - It can find new folds

Ab Initio Methods

- Ab initio: “From the beginning”.
- Assumption
  - All the information about the structure of a protein is contained in its sequence of amino acids.
  - The structure that a (globular) protein folds into is the structure with the lowest free energy.
  - The native structure is contained in the search space
- Finding native-like conformations require
  - A scoring function (potential).
  - A search strategy.

ab-initio protein structure prediction

- **Optimization problem**
  - Define some initial model.
  - Define a function mapping structures to numerical values (the lower the better).
  - Solve the computational problem of finding the global minimum.
- **Simulation of the actual folding process**
  - Build an accurate initial model (including energy and forces).
  - Accurately simulate the dynamics of the system.
  - The native structure will emerge.
  - No hope due to large search space

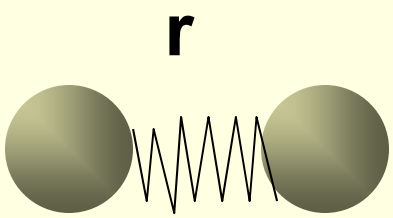
Energy Minimization (Theory)

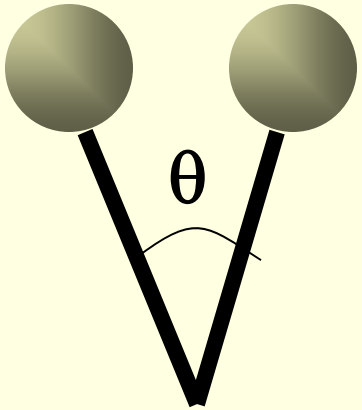
- Treat Protein molecule as a set of balls (with mass) connected by rigid rods and springs
- Rods and springs have empirically determined force constants
- Allows one to treat atomic-scale motions in proteins as classical physics problems

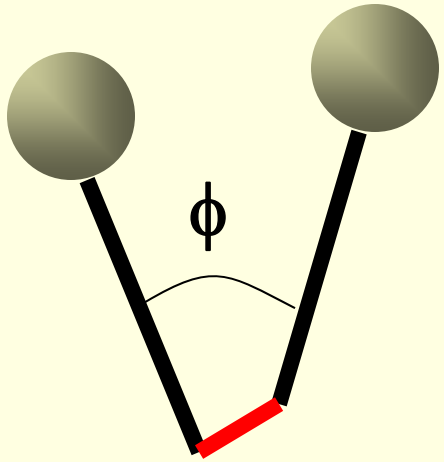
Standard Energy Function

$$
\begin{aligned}
E = \; & K_r(r_i - r_j)^2 + && \text{Bond length} \\
& K_\theta(\theta_i - \theta_j)^2 + && \text{Bond bending} \\
& K_\phi(1-\cos(n\phi_j))^2 + && \text{Bond torsion} \\
& q_i q_j / 4\pi\varepsilon r_{ij} + && \text{Coulomb} \\
& A_{ij}/r^6 - B_{ij}/r^{12} + && \text{van der Waals} \\
& C_{ij}/r^{10} - D_{ij}/r^{12} && \text{H-bond}
\end{aligned}
$$

Energy Terms







$K_r(r_i - r_j)^2$

$K_\theta(\theta_i - \theta_j)^2$

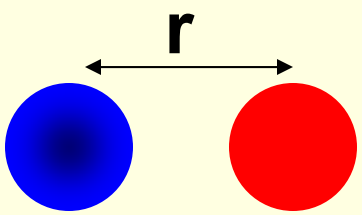
$K_\phi(1-\cos(n\phi_j))^2$

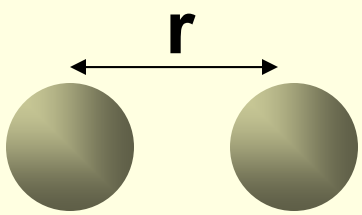
Stretching

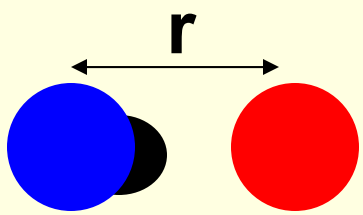
Bending

Torsional

Energy Terms

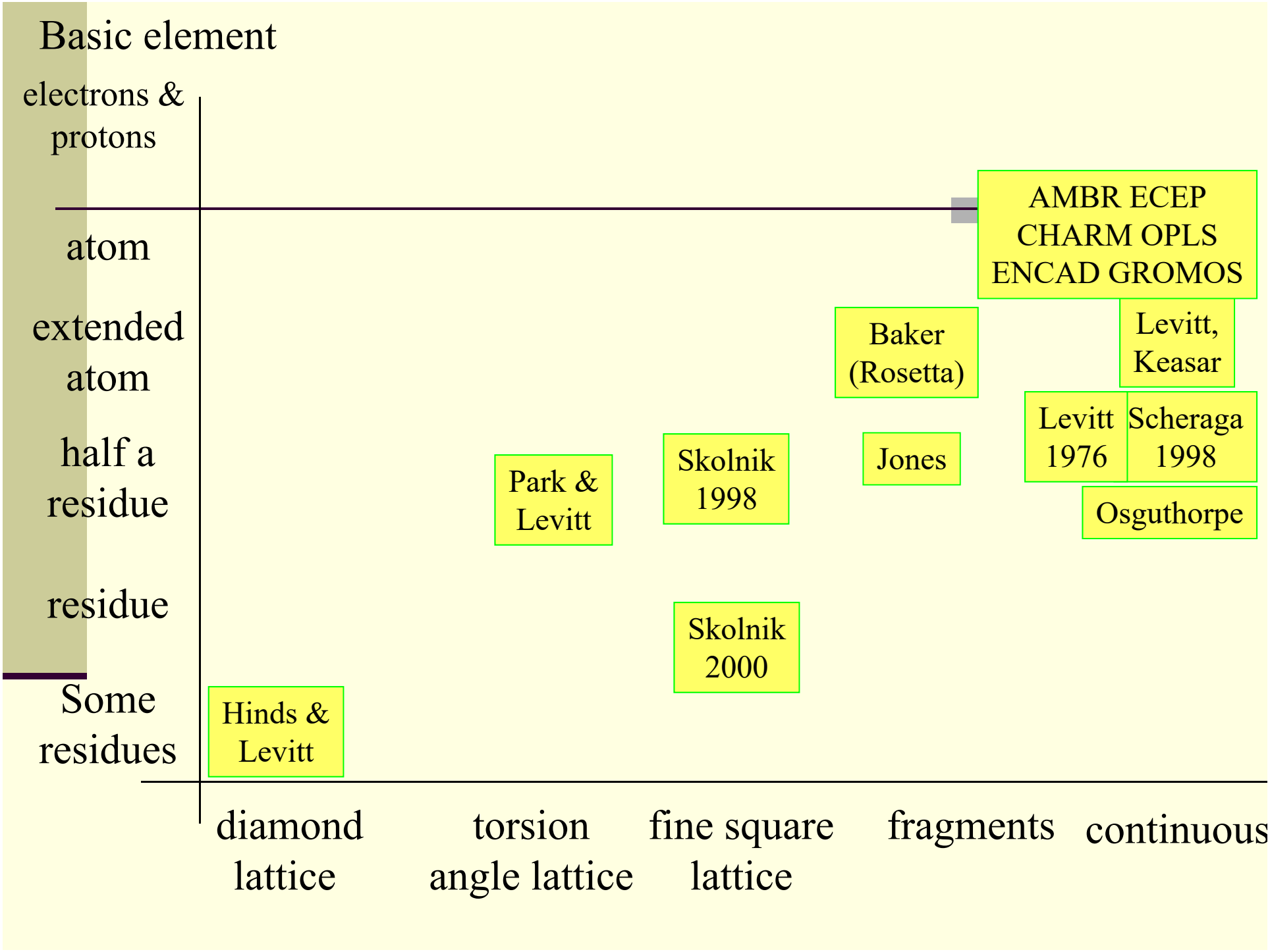






$q_i q_j / 4\pi\varepsilon r_{ij}$ $A_{ij}/r^6 - B_{ij}/r^{12}$ $C_{ij}/r^{10} - D_{ij}/r^{12}$

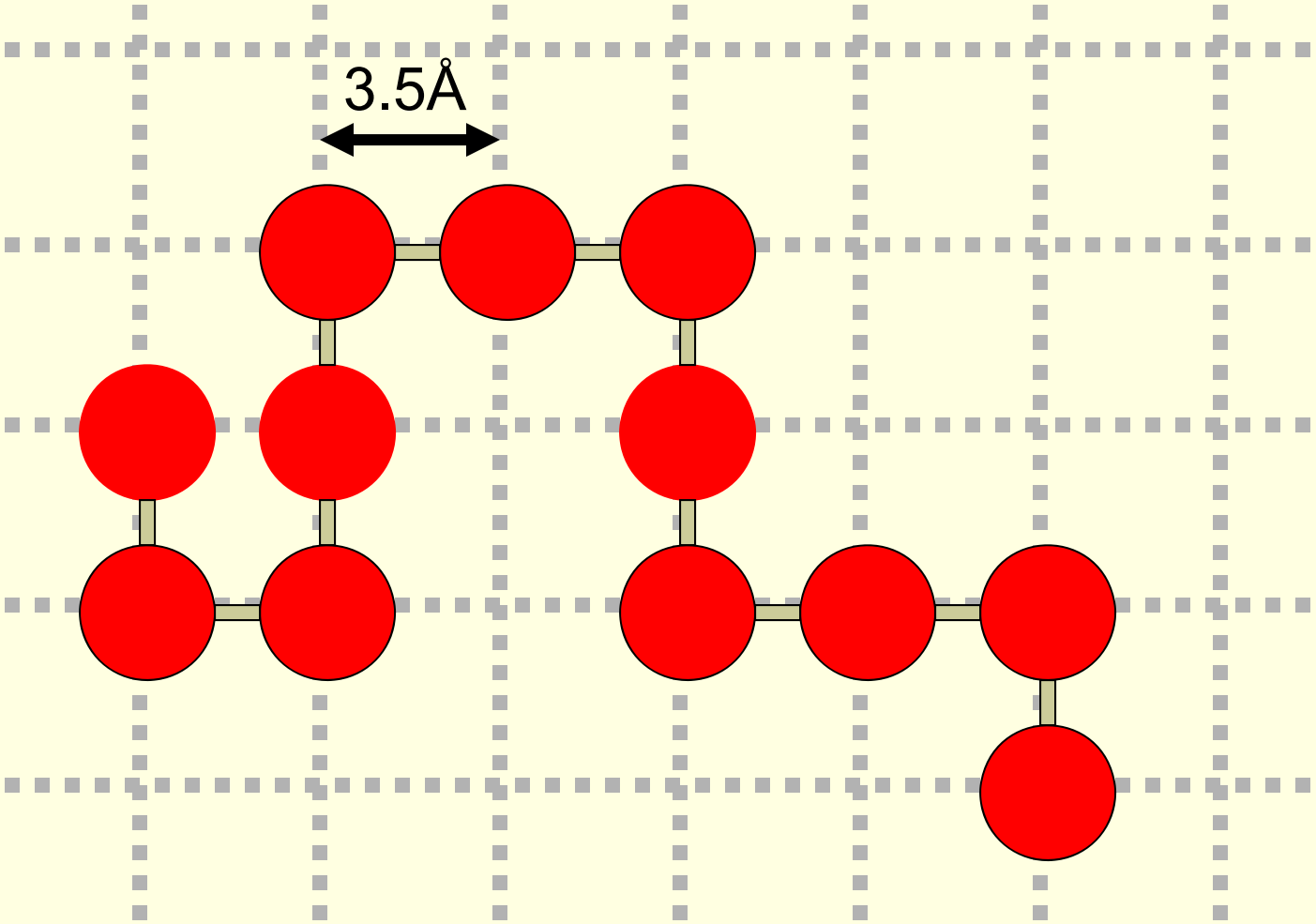
Coulomb **van der Waals** **H-bond**


Basic element
electrons & protons
atom
extended atom
half a residue
residue
Some residues
AMBR ECEP CHARM OPLS ENCAD GROMOS
Baker (Rosetta)
Levitt, Keasar
Levitt 1976
Scheraga 1998
Osguthorpe
Jones
Skolnik 1998
Park & Levitt
Skolnik 2000
Hinds & Levitt
diamond lattice
torsion angle lattice
fine square lattice
fragments
continuous

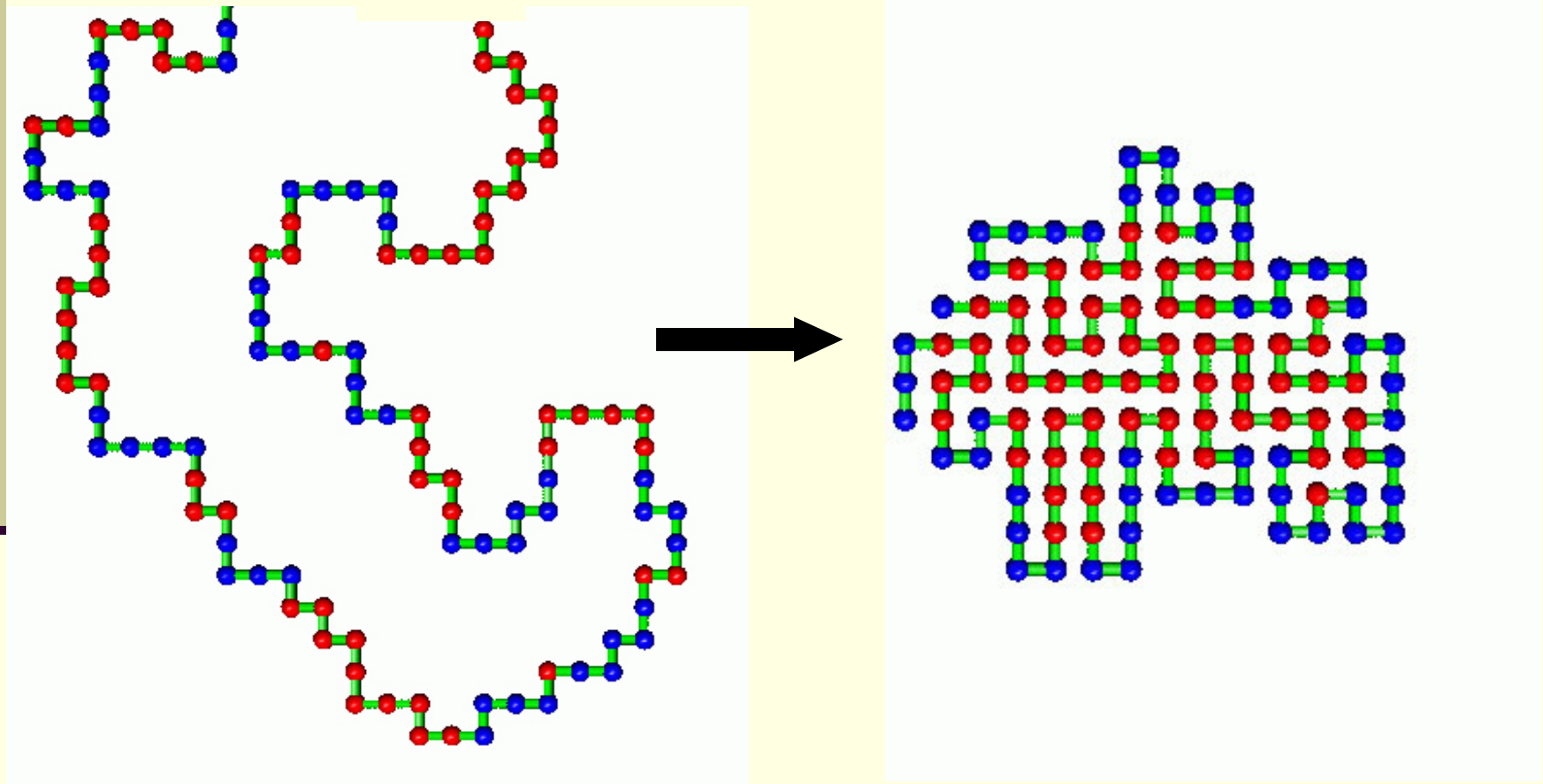
Reduced complexity models

- No side chains
  - sometimes no main chain atoms either
  - Or represent the side chain with C_β
- Reduced degrees of freedom
- On-or off-lattice
- Generally have an environment -based score and a knowledge-based residue-residue interaction term
- Sometimes used as first step to prune the enormous conformational space, then resolution is increased for later fine-tuning

A Simple 2D Lattice



Lattice Folding



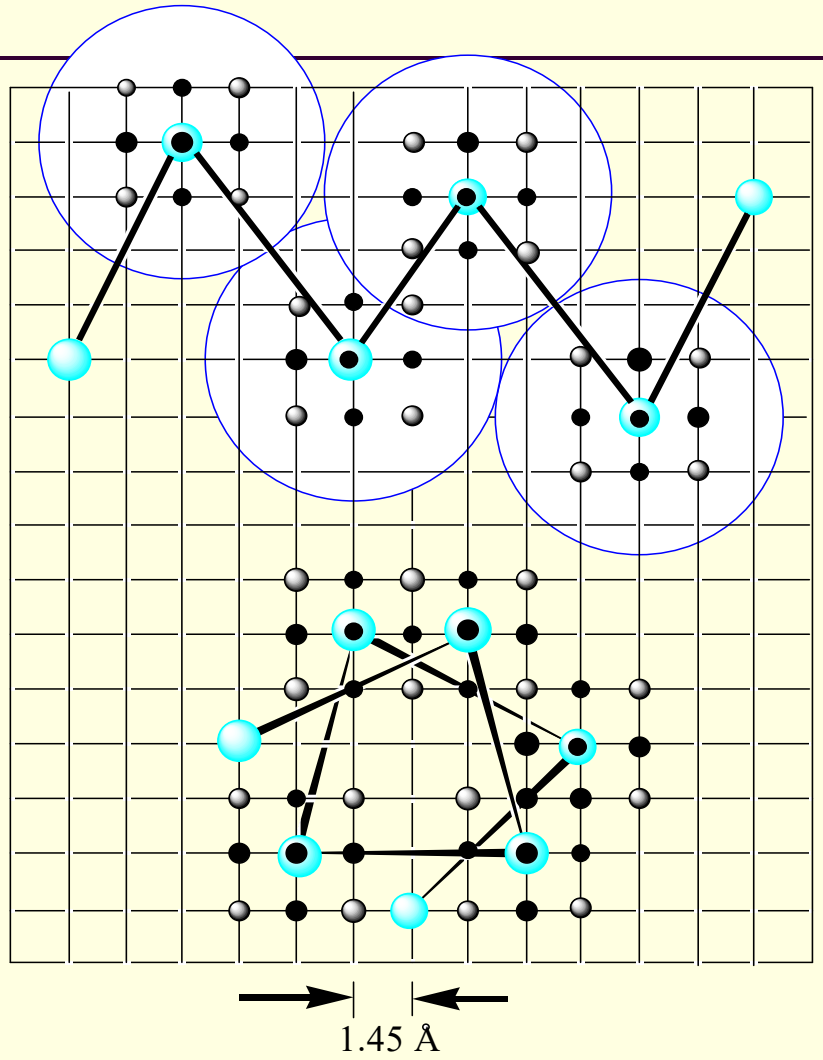
Lattice Algorithm

- *Build a “n x m” matrix (a 2D array)*
- *Choose an arbitrary point as your N terminal residue (start residue)*
- *Add or subtract “1” from the x or y position of the start residue*
- *Check to see if the new point (residue) is off the lattice or is already occupied*
- *Evaluate the energy*
- *Go to step 3) and repeat until done*

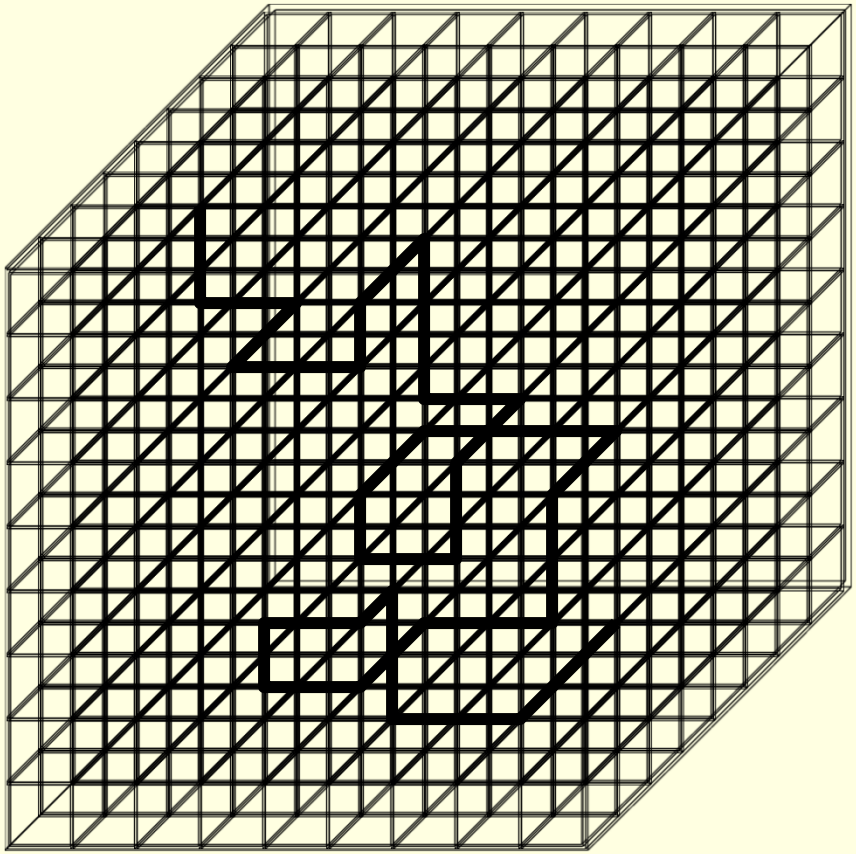
Lattice Energy Algorithm

- *Red = hydrophobic, Blue = hydrophilic*
- *If Red is near empty space E = E+1*
- *If Blue is near empty space E = E-1*
- *If Red is near another Red E = E-1*
- *If Blue is near another Blue E = E+0*
- *If Blue is near Red E = E+0*

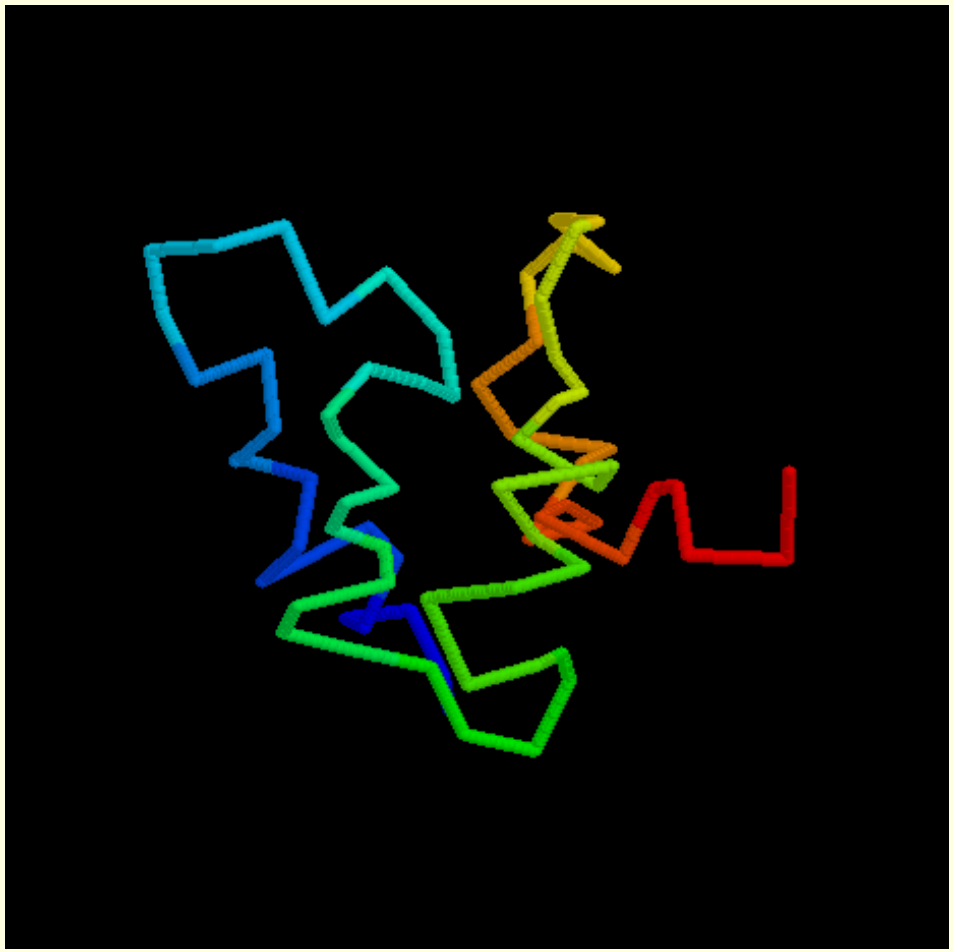
More Complex Lattices



3D Lattices



Really Complex 3D Lattices



J. Skolnick

Lattice Methods

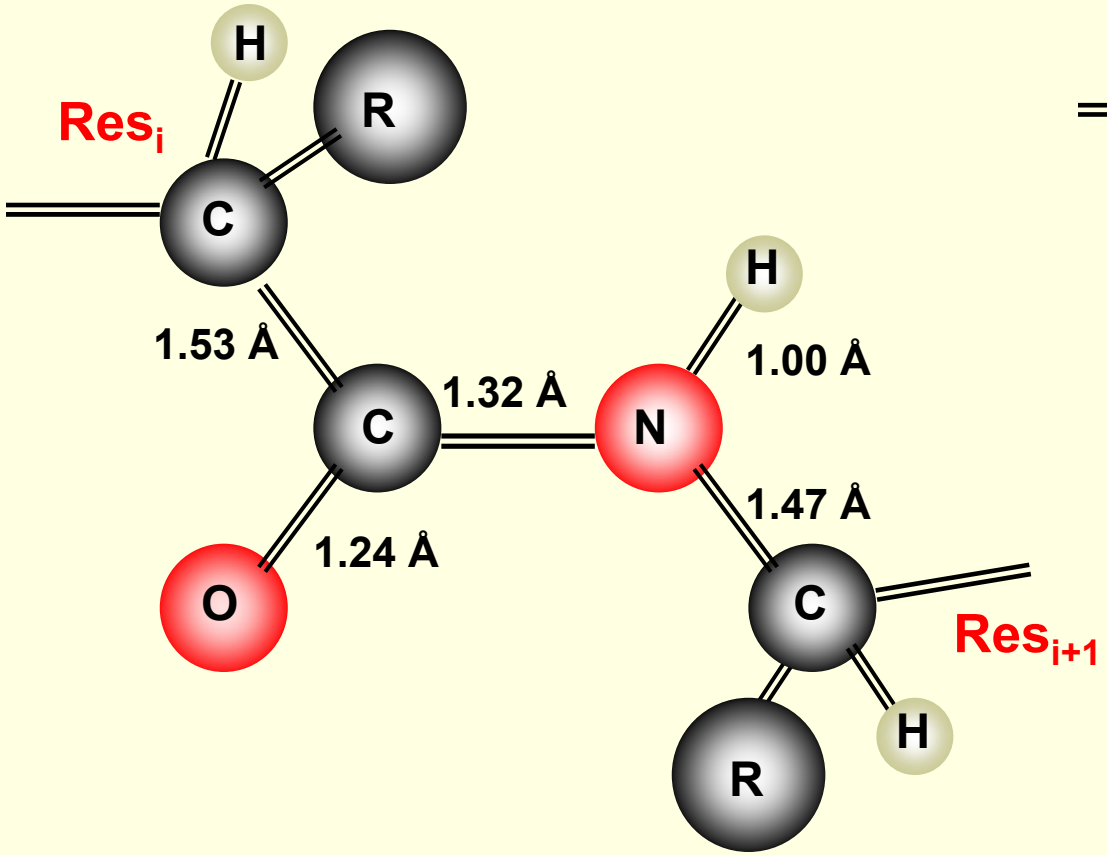
Advantages

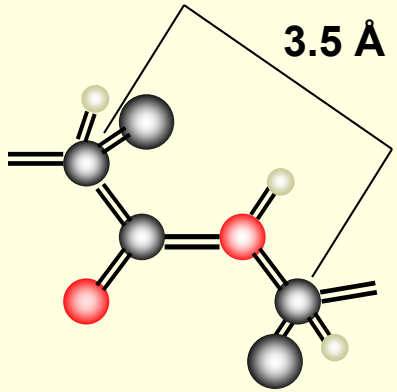
- Easiest and quickest way to build a polypeptide
- More complex lattices allow reasonably accurate representation

Disadvantages

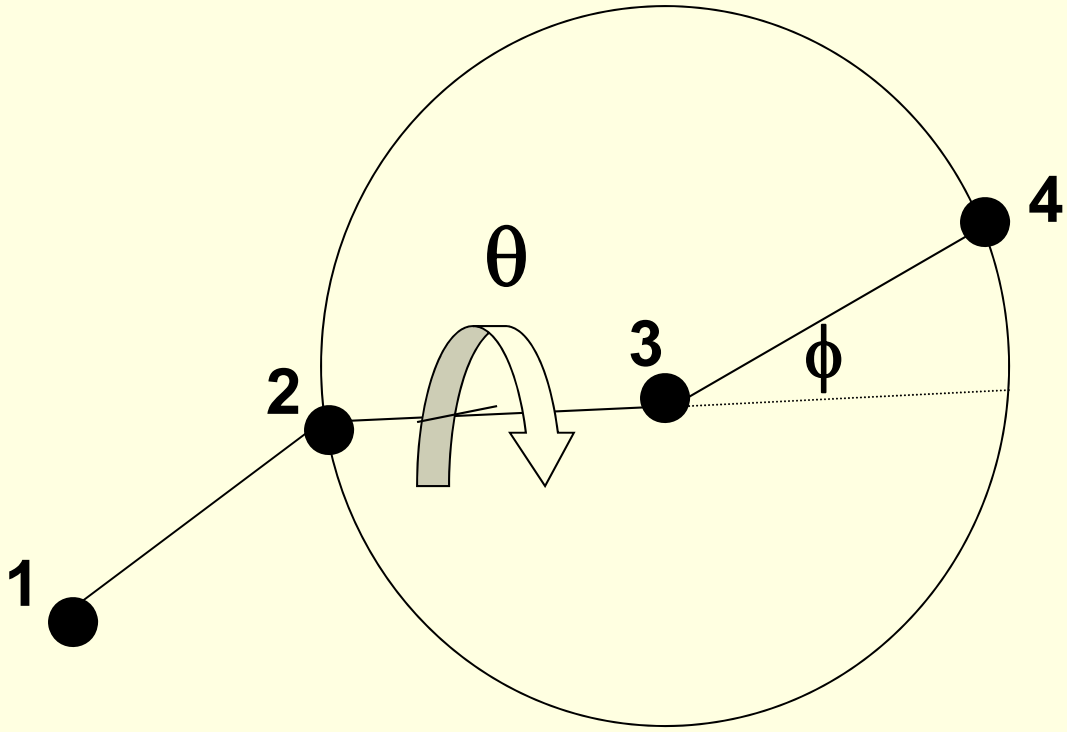
- At best, only an approximation to the real thing
- Does not allow accurate constructs
- Complex lattices are as “costly” as the real thing

Non-Lattice Models



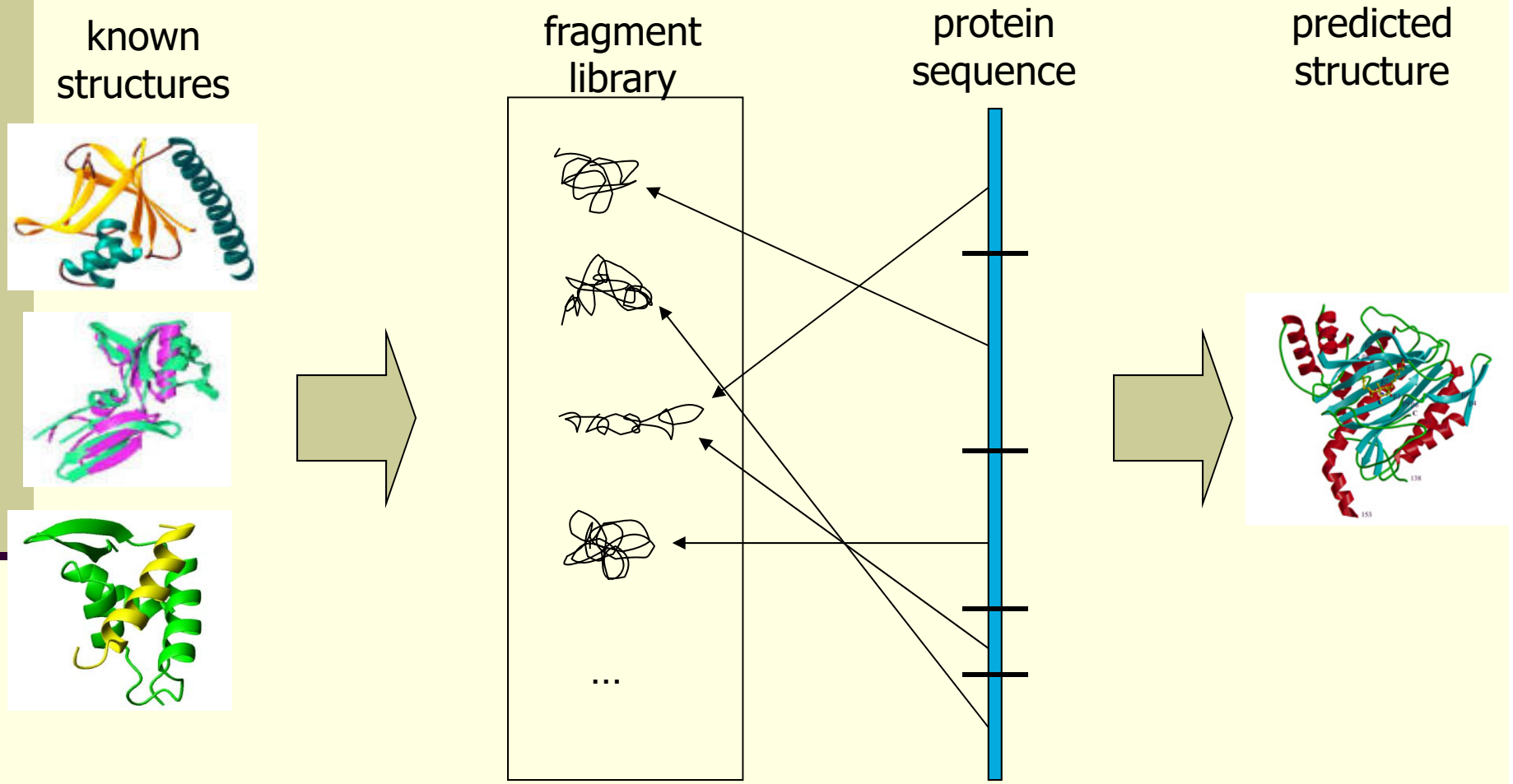


Simplified Chain Representation

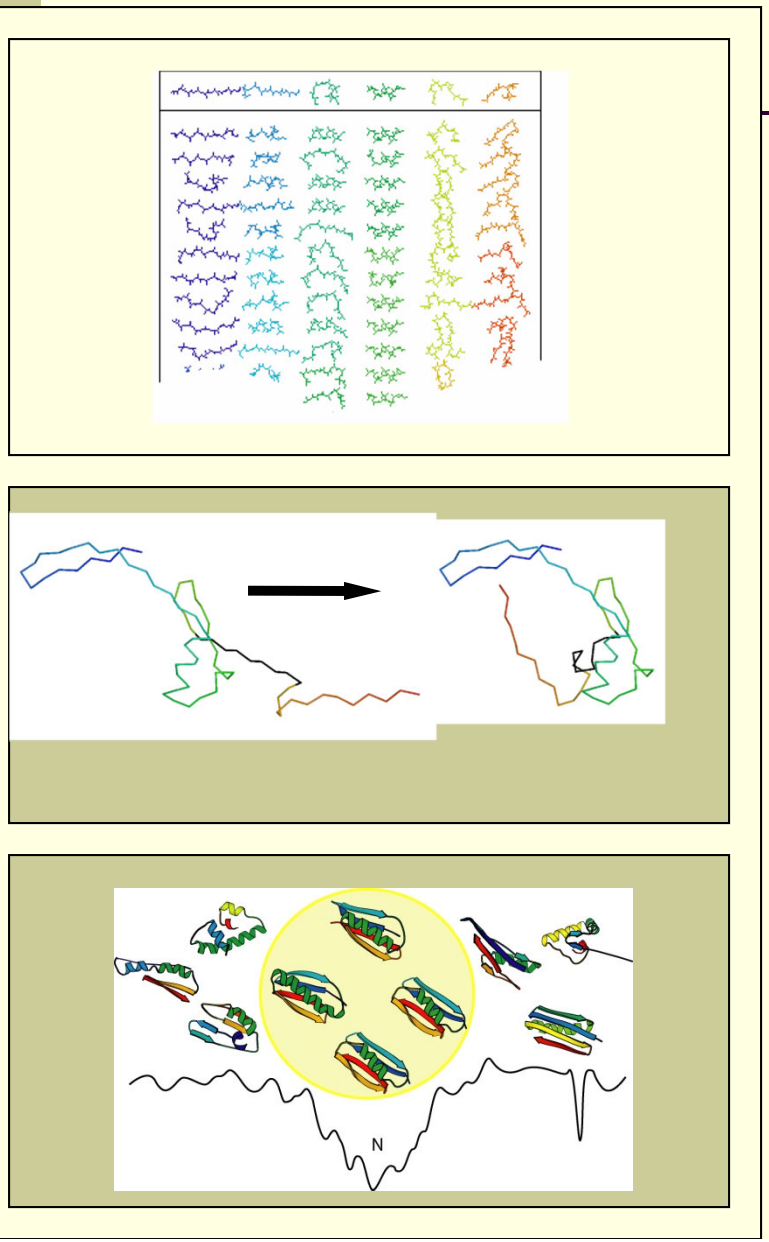


Spherical Coordinates

Assembly of sub-structural units

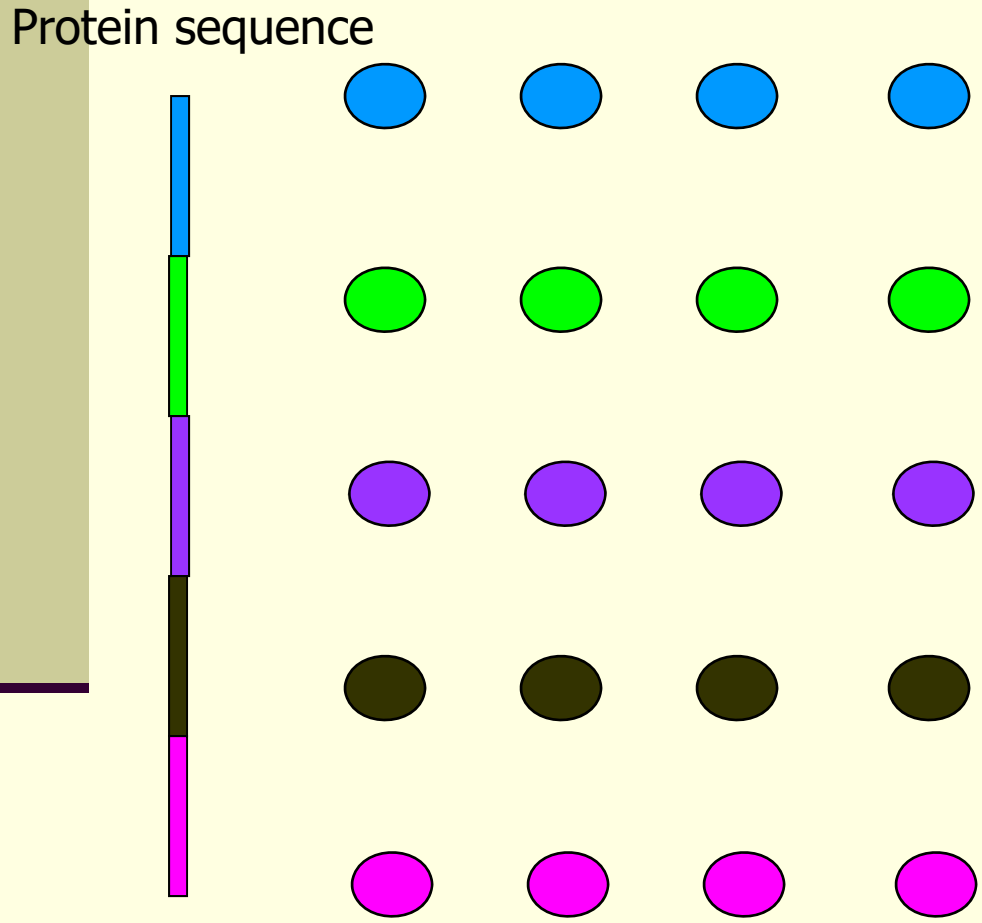


Structure Prediction with Rosetta



- Select fragments consistent with local sequence preferences
- Assemble fragments into models with native-like global properties
- Identify the best model from the population of decoys

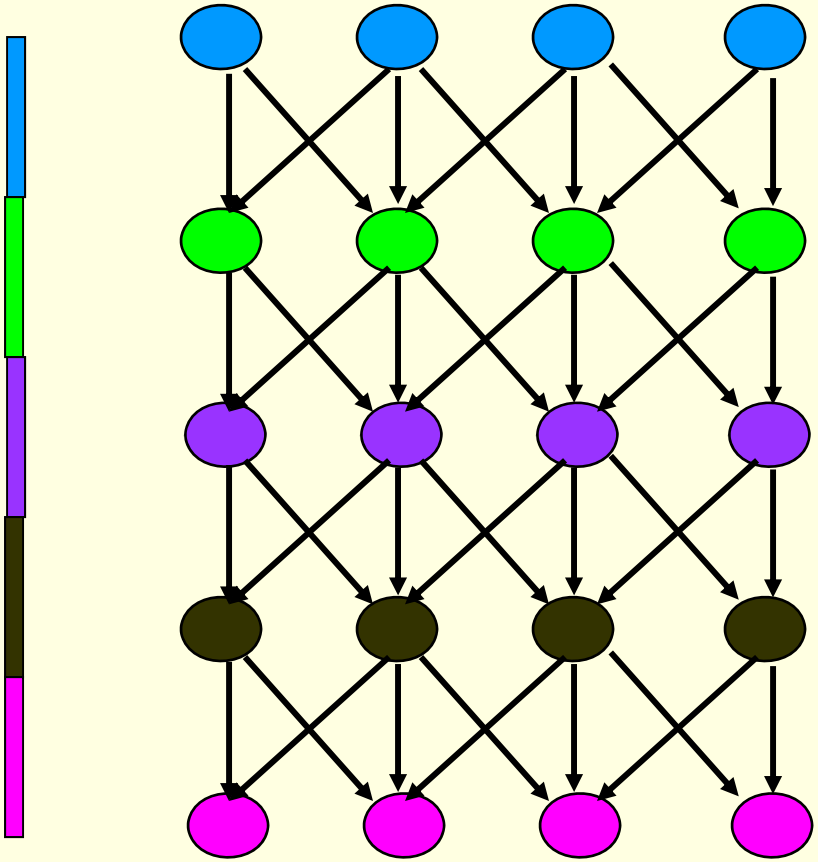
Modelling



- Model each candidate local structure as a node

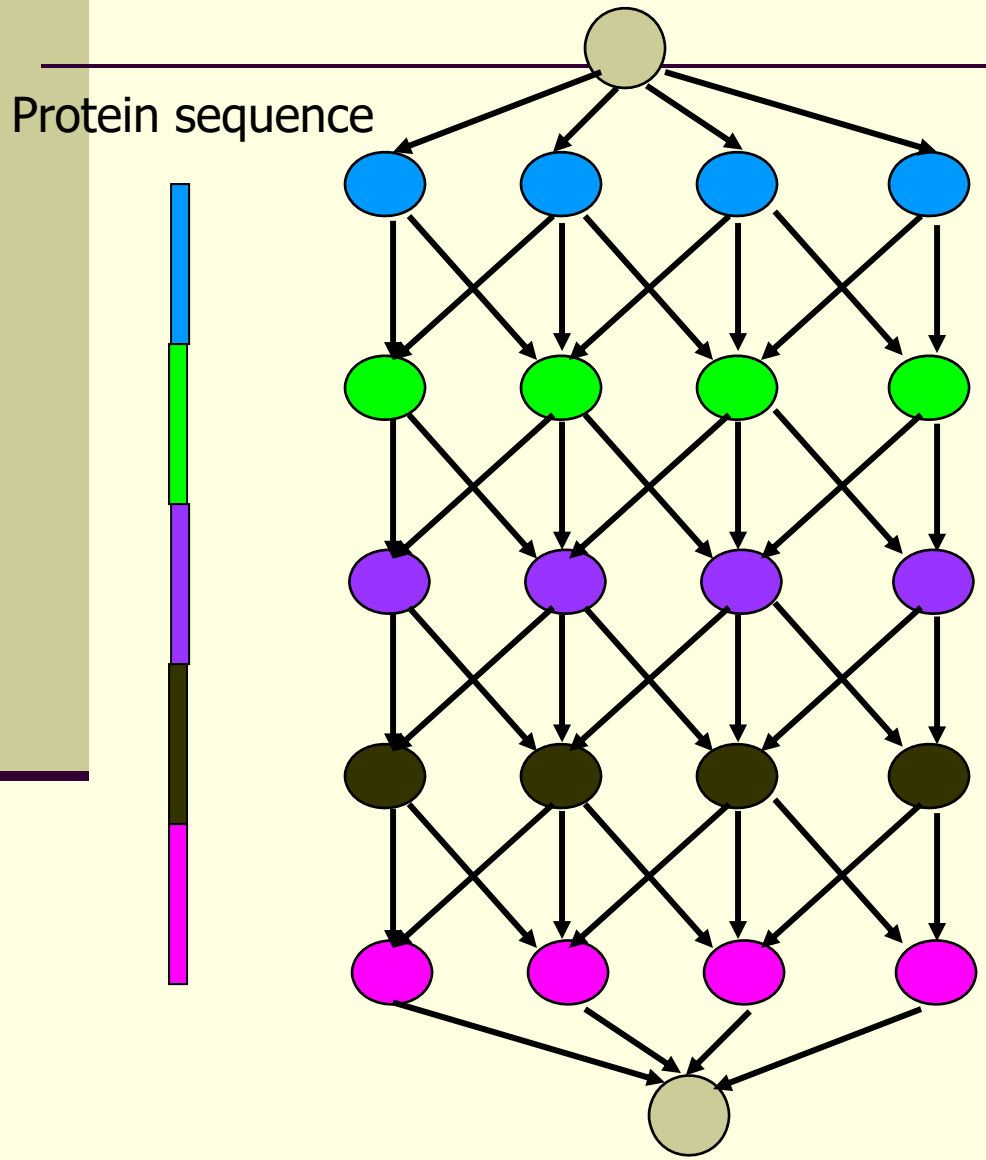
Modelling

Protein sequence



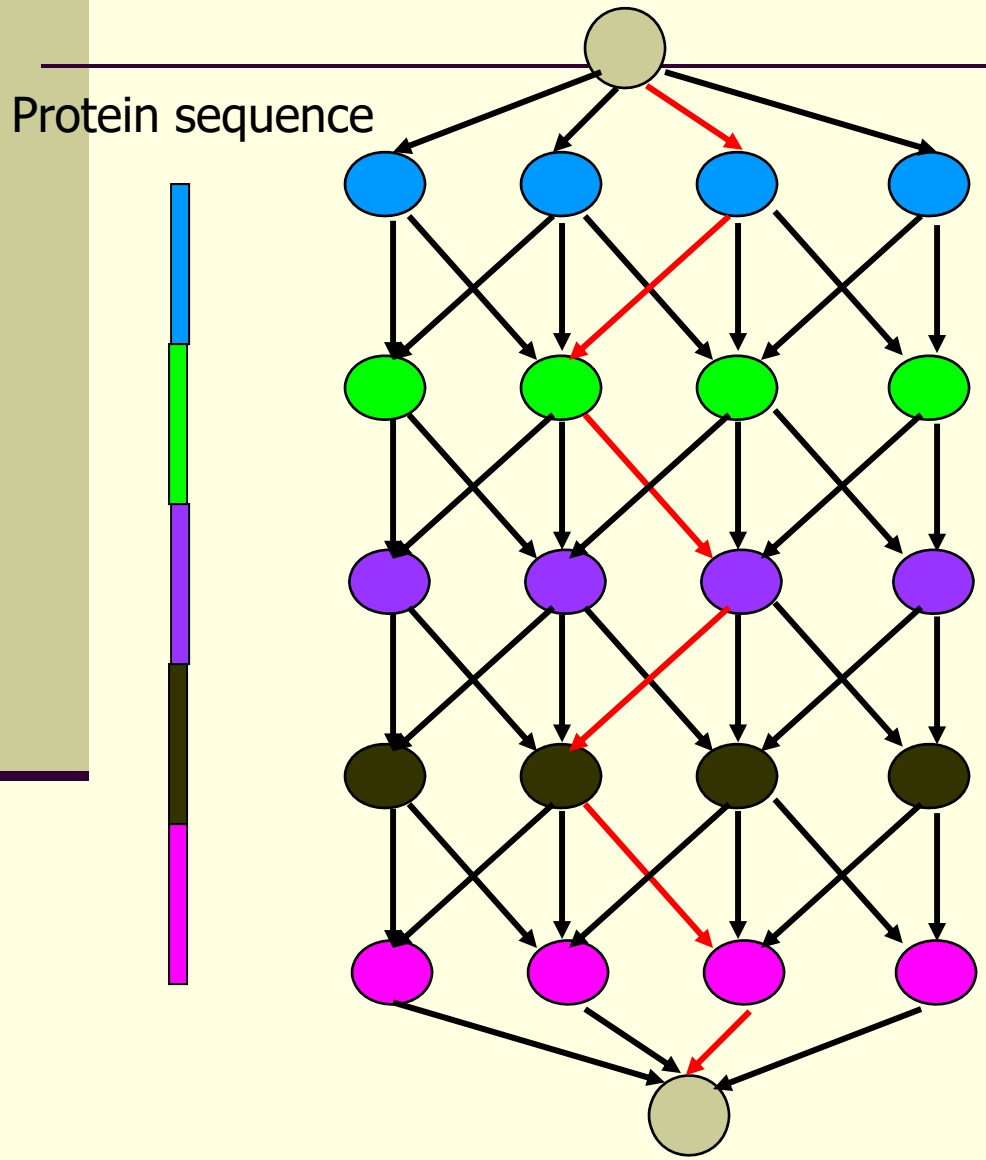
- Model each candidate local structure as a node
- If two consecutive local structure are compatible, an edge joins them

Modelling



- Model each candidate local structure as a node
- If two consecutive local structure are compatible, an edge joins them
- Add a source s and sink t to the graph

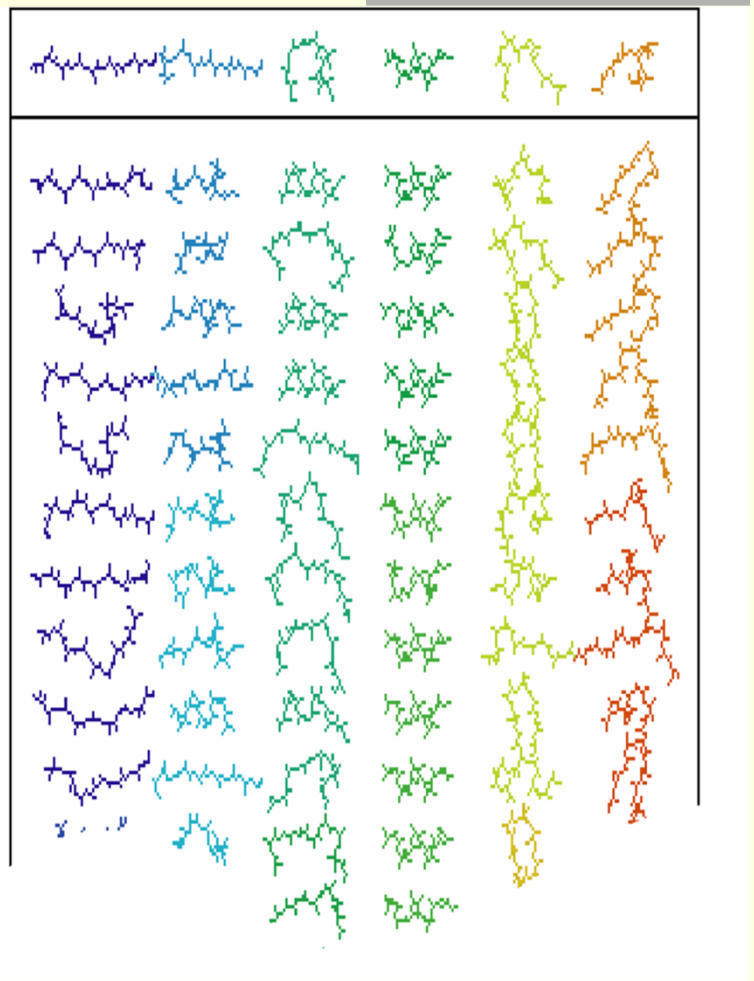
Modelling



- Each path from s to t forms a candidate structure
  - At least one of the s-t paths is native-like structure
  - A good search strategy should pick up this path with less time consuming
  - A good model should reduce the search space

Build the Fragment Library-Rosetta

- Extract possible local structures from PDB



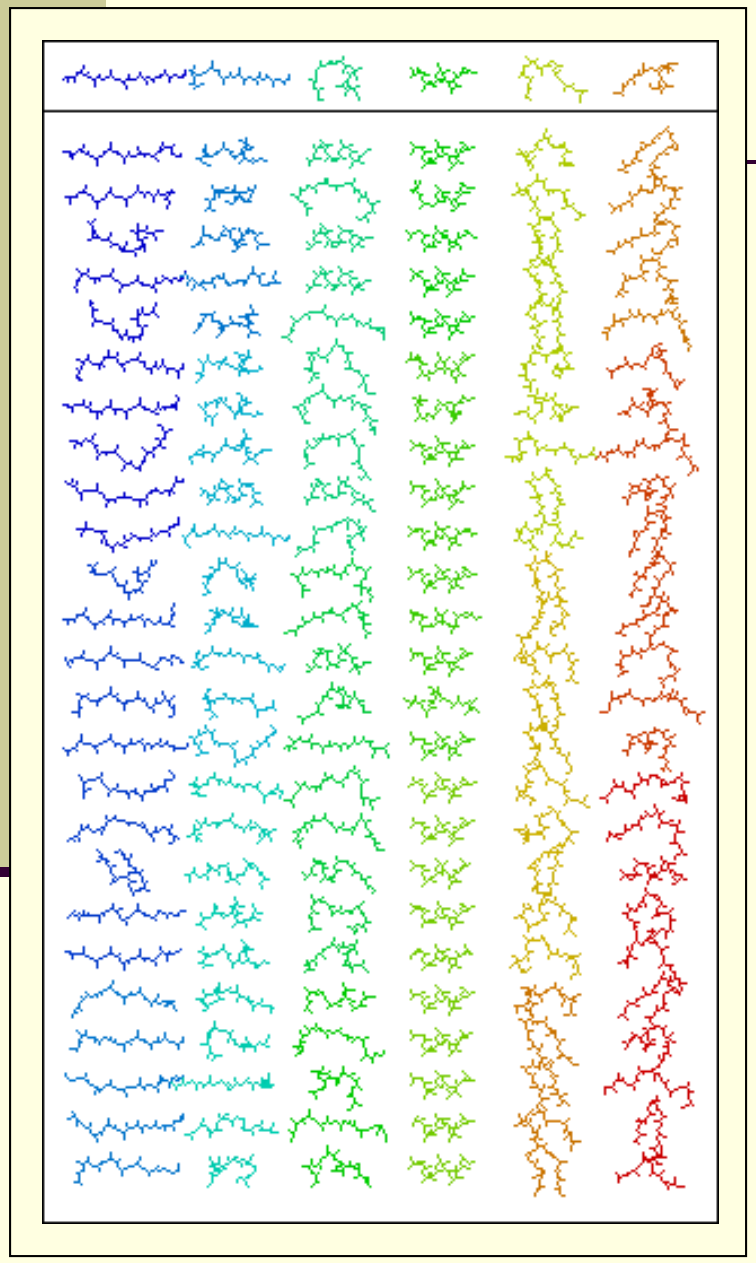
Generate the Fragment Library

- Select PDB template
  - Select Sequence Families
  - Each Family has a single known structure (family)
  - Has no more than 25% sequence identity between any two sequence
- Clustering the fragments
  - Generate all the fragments from the selected families

Find Local Structures

- Given a subsequence, a local structure to be identified
  - Represent each subsequence with a vector
    - $V=\{v_1, v_2, \ldots, v_k\}$
    - eg: V as a 20*l matrix, with the (i, j)-th entry represent the frequency of amino acid i occurs at position j
  - Represent each substructure with a vector
    - $V'=\{v_1', v_2', \ldots, v_k'\}$
    - eg: V as a 20*l matrix, with the (i, j)-th entry represent the frequency of amino acid i occurs at position j
  - Rank the structure according to:
    - $\sum_i |v_i - v_i'|$
    - This implies that the entries of the vectors are independent.

Rosetta Fragment Libraries



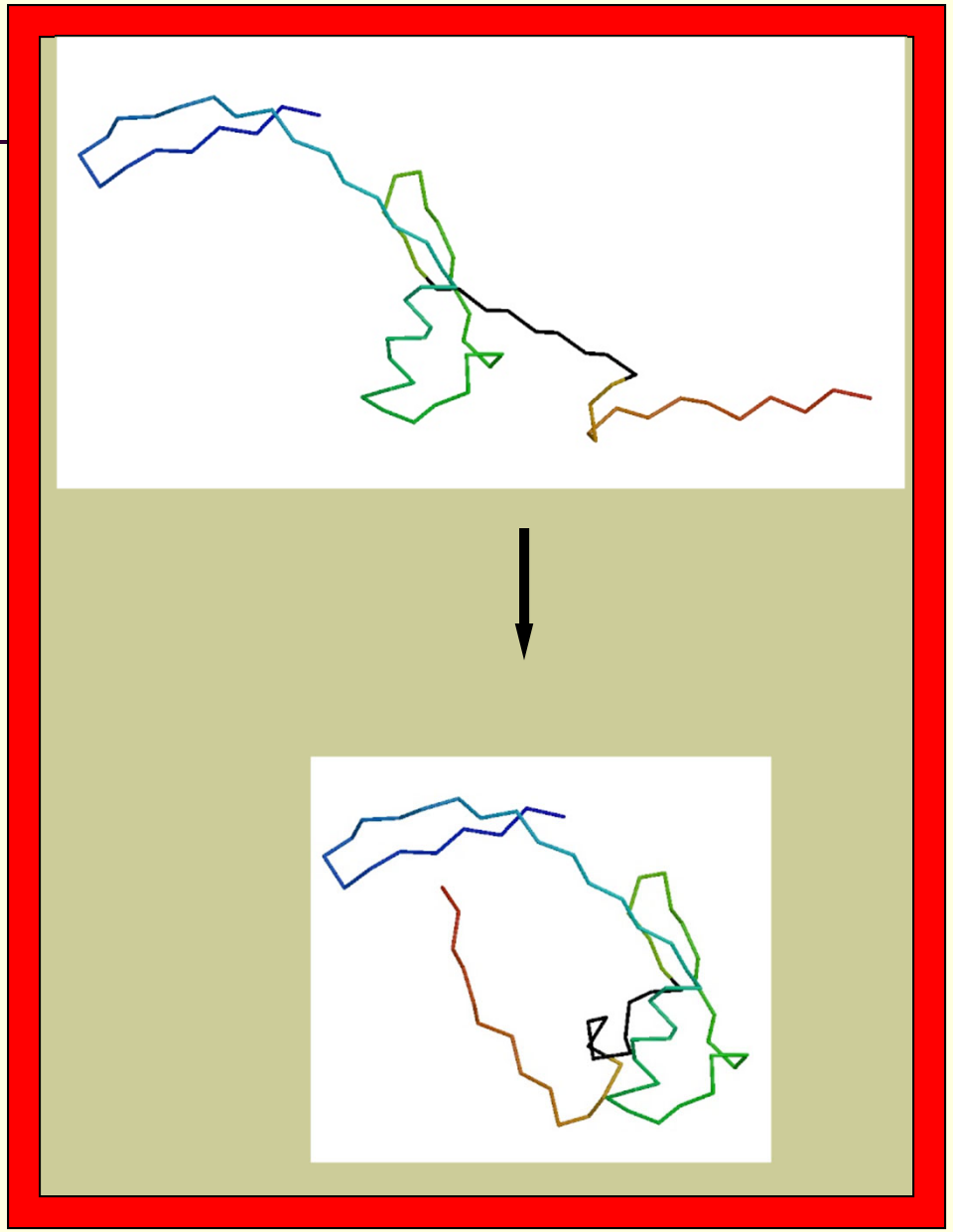
- 25-200 fragments for each 3 and 9 residue sequence window
- Selected from database of known structures
  - > 2.5Å resolution
  - < 50% sequence identity
- Ranked by sequence similarity and similarity of predicted and known secondary structure

Scoring Function

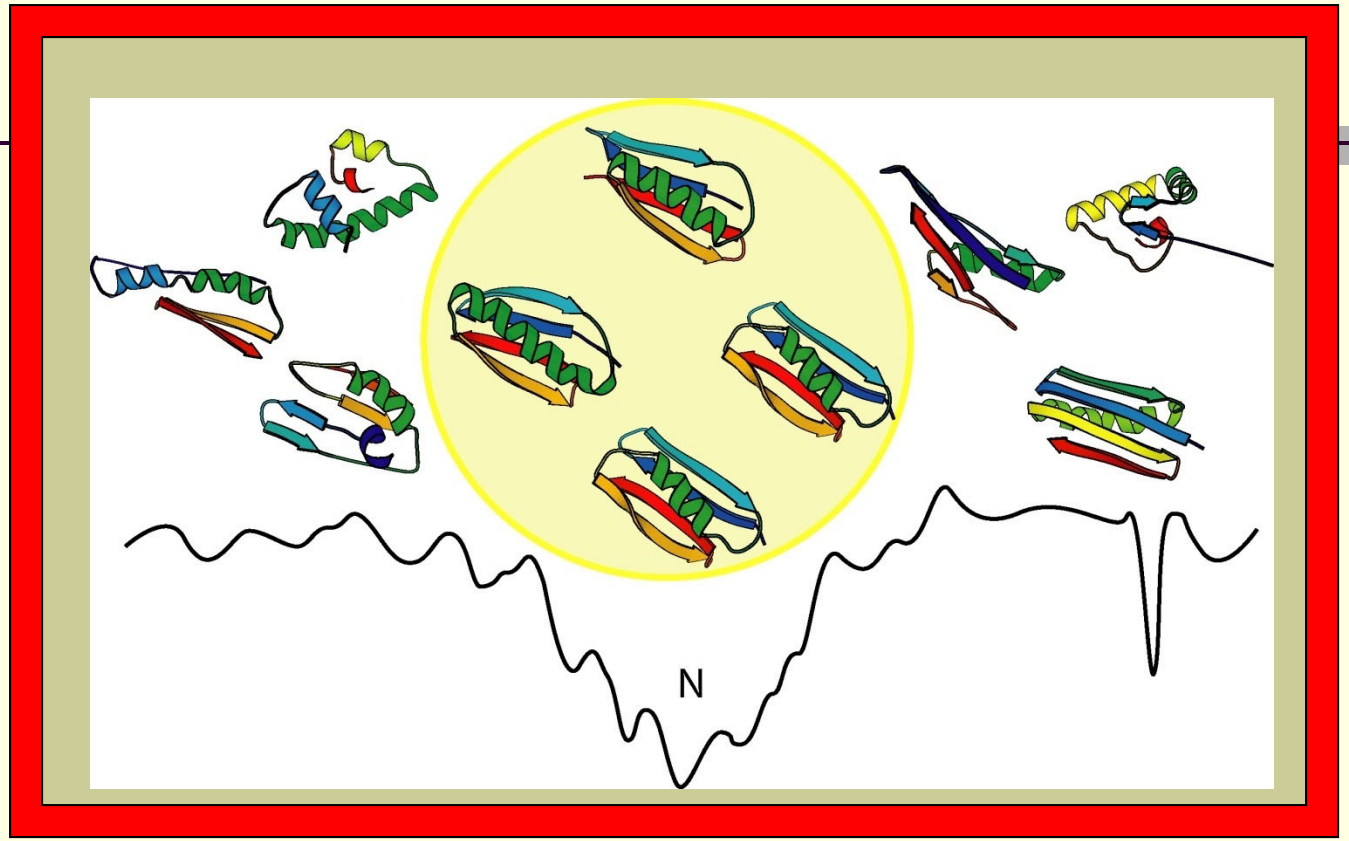
- Ideal energy function
  - Has a clear minimum in the native structure.
  - Has a clear path towards the minimum.
  - Global optimization algorithm should find the native structure.

Rosetta Potential Function

- Derived from Bayesian treatment of residue distributions in known protein structures
- Reduced representation of protein used; one centroid per sidechain
- Potential Terms:
  - environment (solvation)
  - pairwise interactions (electostatics)
  - strand pairing
  - radius of gyration
  - Cβ density
  - steric overlap



Decoy Discrimination: Identifying the Best Structure



- 1000-100,000 short simulations to generate a population of 'decoys'
- Filter population to correct systematic biases
- Full atom potential functions to select the deepest energy minimum
- Cluster analysis to select the broadest minimum
- Structure-structure matches to database of known structures

The Rosetta Scoring Function

$$P(\text{structure}|\text{sequence}) \propto P(\text{sequence}|\text{structure}) \times P(\text{structure})$$

Sequence dependent:

- hydrophobic burial
- residue pair interaction

Sequence independent:

- helix-strand packing
- strand-strand packing
- sheet configurations
- vdW interactions

The Sequence Dependent Term

$$P(aa_1, \ldots, aa_n|X) =$$

$$\prod_i P(aa_i|X) \times$$

$$\prod_{i<j} \frac{P(aa_i, aa_j|X)}{P(aa_i|X)P(aa_j|X)} \times$$

$$\prod_{i<j<k} \frac{P(aa_i, aa_j, aa_k|X)P(aa_i|X)P(aa_j|X)P(aa_k|X)}{P(aa_i, aa_j|X)P(aa_i, aa_k|X)P(aa_j, aa_k|X)} \times$$

$$\ldots$$

The Sequence Dependent Term

$$P(\text{sequence}|\text{structure}) \approx P_{env} \times P_{pair}$$

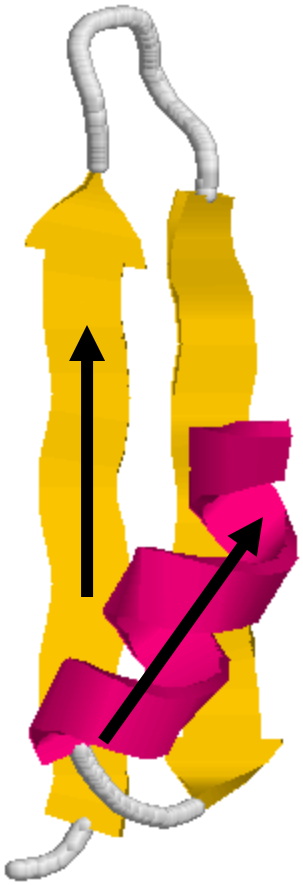
$$P_{env} = \prod_i P(aa_i|E_i)$$

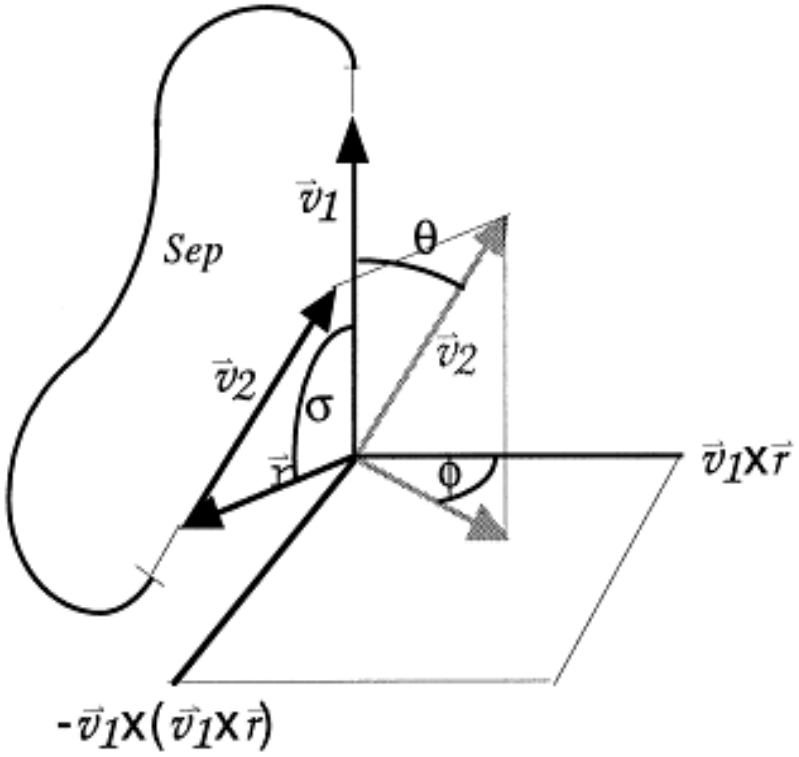
$$P_{pair} = \prod_{i<j} \frac{P(aa_i, aa_j|E_i, E_j, r_{ij})}{P(aa_i|E_i, r_{ij})P(aa_j|E_j, r_{ij})}$$

The Sequence Independent Term

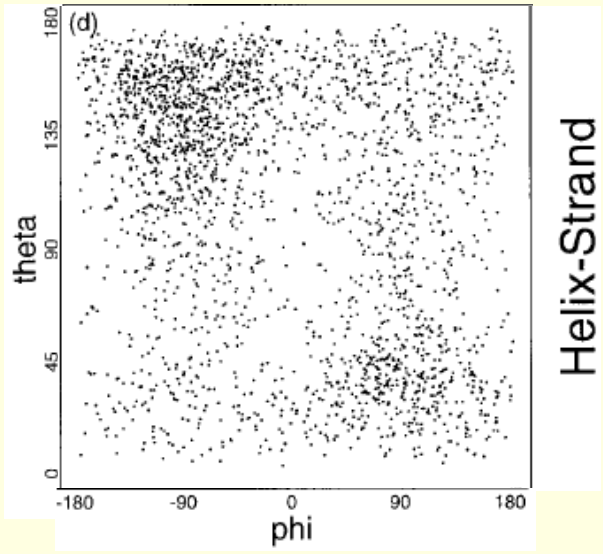
$$P(r, \phi, \theta, \sigma, hb|sep) \approx$$

$$P(\phi, \theta|r,sep) \times P(hb|r,sep) \times P(\sigma|r,sep) \times P(r|sep)$$





vector representation



The Model

$$\mathrm{P(structure)} = \mathrm{P_A^{w_A} P_B^{w_B} P_C^{w_C}}, \quad w_X > 0.$$

$$-\log \mathrm{P(structure|sequence)} \propto$$
$$-\log \mathrm{P(sequence|structure)} - \log \mathrm{P(structure)}$$

$$\mathrm{g(rmsd)} = w_{\mathrm{protein}} + w_{\mathrm{HS}} \log \mathrm{P_{HS}} + w_{\mathrm{SS}} \log \mathrm{P_{SS}} + w_{\mathrm{VdW}} \mathrm{VdW} +$$
$$w_{\mathrm{sheet}} \log \mathrm{P_{sheet}} + w_{\mathrm{seq}} \left(\log \mathrm{P_{env}} + \log \mathrm{P_{pair}}\right)$$

Search Strategy

- Reduce the Search Space
- Design Better Search Strategies

Search Strategy

- Requirement
  - Identify the native structure easily
    - Filter out those non-native ones
  - Eliminate the non-native candidates as early as possible
  - Jumping out from the local minimum
  - No repetitions
  - …
- Search Strategies
  - Taboo search, simulated annealing, genetic algorithms, multi-agent, …
  -

ROSETTA search algorithm
Monte Carlo/Simulated Annealing

- Structures are assembled from fragments by:
  - Begin with a fully extended chain
  - Randomly replace the conformation of one 9 residue segment with the conformation of one of its neighbors in the library
  - Evaluate the move: Accept or reject based on an energy function
  - Make another random move, tabu list is built to forbidden some local minimums
  - After a prescribed number of cycles, switch to 3-residue fragment moves

A Filter for Bad β-Sheets

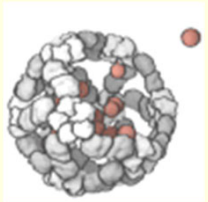
Many decoys do not have proper sheets. Filtering those out seems to enhance the rmsd distribution in the decoy set. Bad features we see in decoys include:

- No strands,
- Single strands,
- Too many neighbors,
- Single strand in sheets,
- Bad dot-product,
- False sheet type (barrel),

ROSETTA Obstacles & Enhancements

- generate lots of unrealistic decoys
  - Filter based on contact order
  - quality of β-sheets
  - poor packing
- large search space
  - Bias fragment picking by predicted secondary structure, faster computational algorithms
- low confidence in the result
  - – Fold many homologs of the target, cluster the answers, report the cluster with highest occupancy

The future of protein structure



http://www.sciencemag.org/news/2016/07/protein-designer-aims-revolutionize-medicines-and-materials

https://elifesciences.org/articles/10606

http://science.sciencemag.org/content/353/6297/389