Introduction to Protein Structure Prediction

BMI/CS 776
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Spring 2011

The Protein Folding Problem

- we know that the function of a protein is determined in large part by its 3D shape (*fold*, *conformation*)
- can we predict the 3D shape of a protein given only its amino-acid sequence?

Protein Architecture

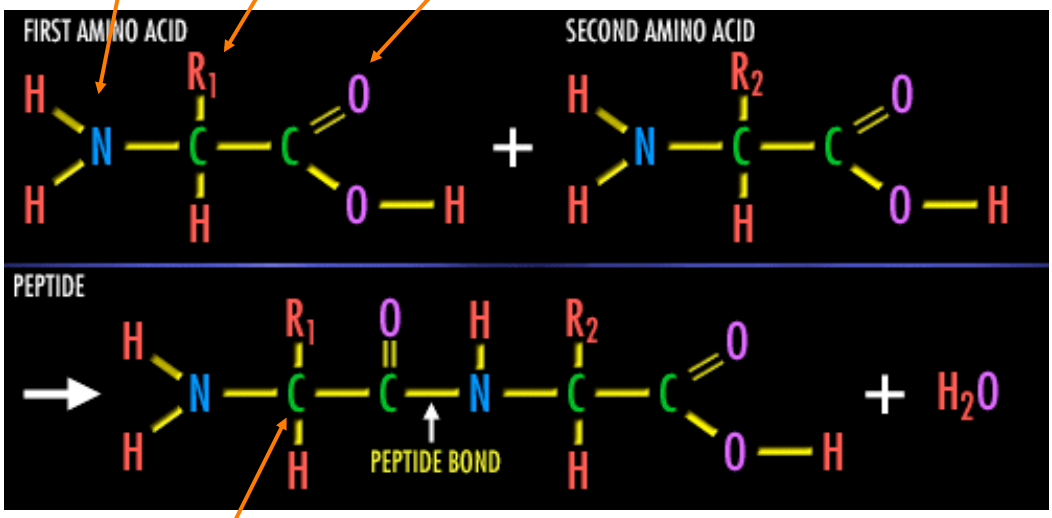
- proteins are polymers consisting of amino acids linked by *peptide* bonds
- each amino acid consists of
  - a central carbon atom
  - an amino group, NH_2
  - a carboxyl group, COOH
  - a side chain
- differences in side chains distinguish different amino acids

Amino Acids and Peptide Bonds

amino group

side chain

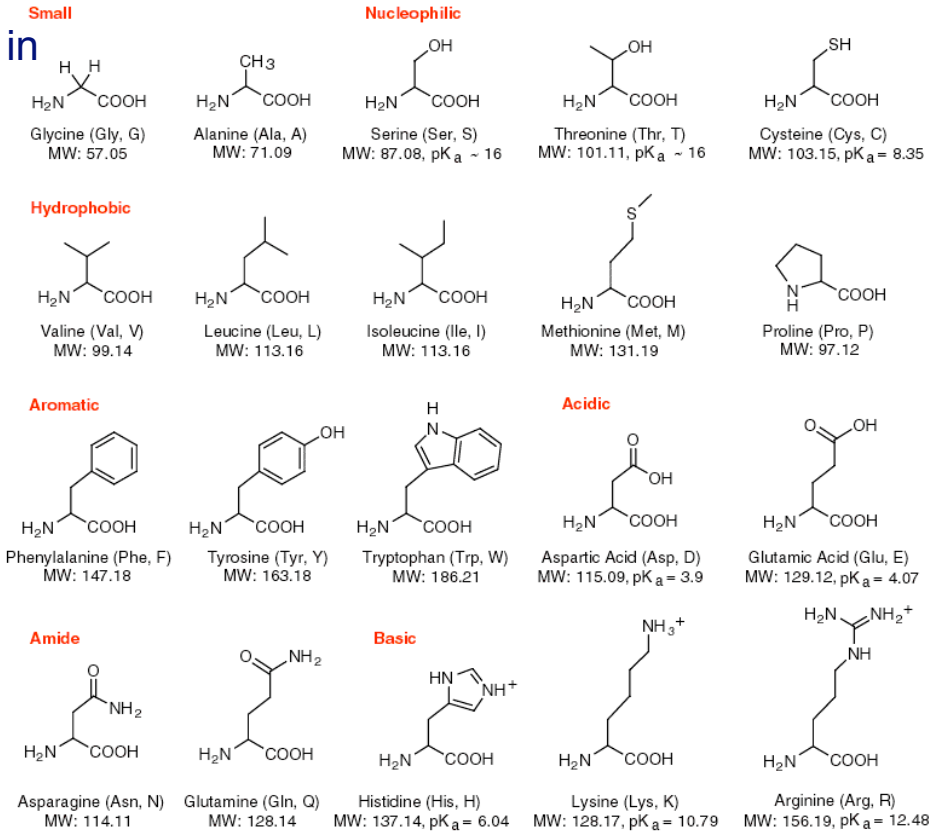
carboxyl group



α carbon (common reference point for coordinates of a structure)

Amino Acid Side Chains

side chains vary in
- shape
- size
- charge
- polarity



What Determines Conformation?

- in general, the amino-acid sequence of a protein determines the 3D shape of a protein [Anfinsen et al., 1950s]

- but some qualifications
  - all proteins can be denatured
  - some proteins are inherently *disordered* (i.e. lack a regular structure)
  - some proteins get folding help from *chaperones*
  - there are various mechanisms through which the conformation of a protein can be changed in vivo
    - post-translational modifications such as *phosphorylation*
    - *prions*
    - etc.

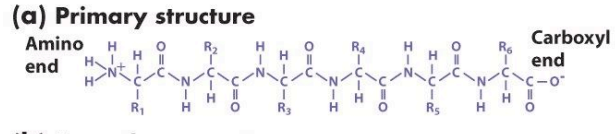
What Determines Conformation?

- Which physical properties of the protein determine its fold?
  - rigidity of the protein backbone
  - interactions among amino acids, including
    - electrostatic interactions
    - van der Waals forces
    - volume constraints
    - hydrogen, disulfide bonds
  - interactions of amino acids with water

Levels of Description

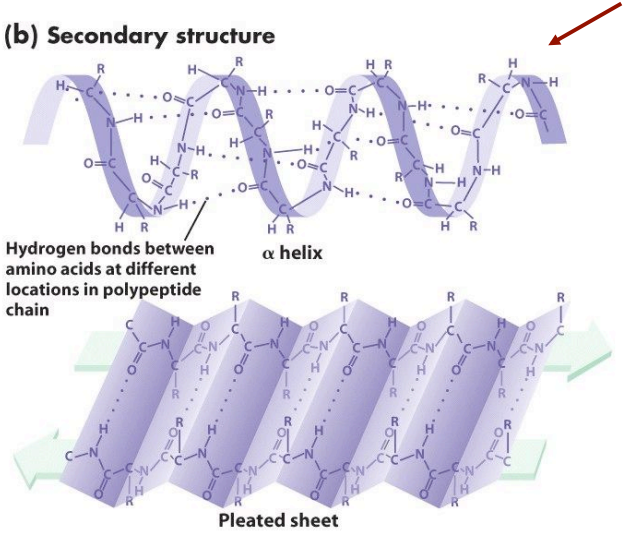
- protein structure is often described at four different scales
  - primary structure
  - secondary structure
  - tertiary structure
  - quaternary structure

Levels of Description



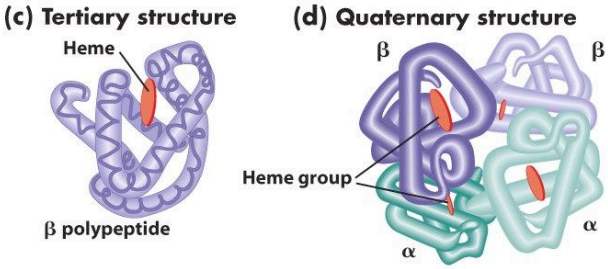
the amino acid sequence itself

"local" description of structure: desribes it in terms of certain common repeating elements



3D conformation of a polypeptide

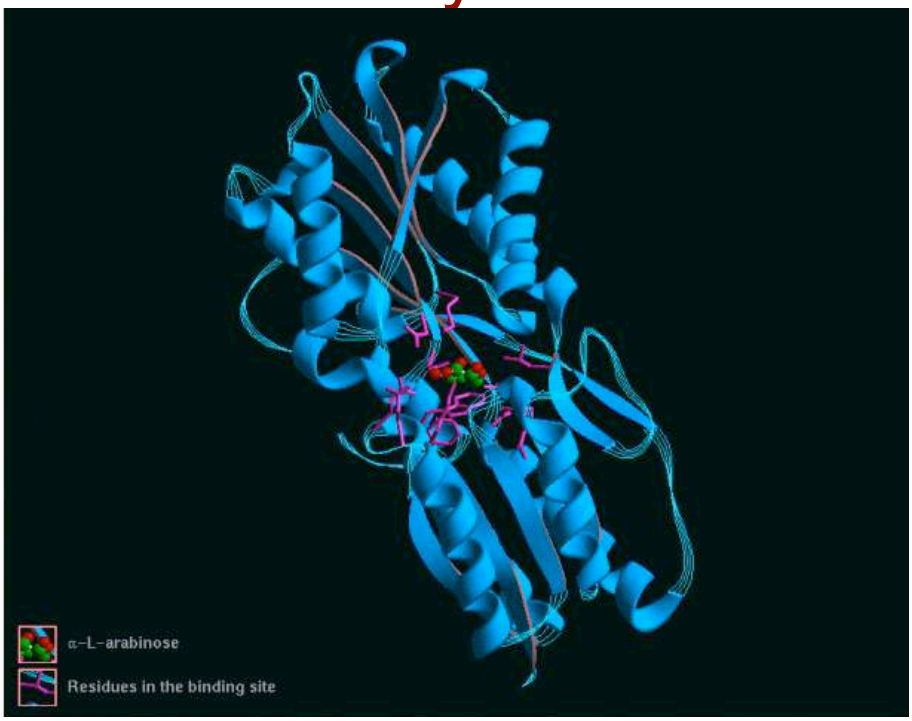
3D conformation of a complex of polypeptides



Secondary Structure

- secondary structure refers to certain common repeating structures
- it is a "local" description of structure
- two common secondary structures
  - α helices
  - β strands/sheets
- a third category, called *coil* or *loop*, refers to everything else

Ribbon Diagram Showing Secondary Structures



Determining Protein Structures

- protein structures can be determined experimentally (in most cases) by
  - x-ray crystallography
  - nuclear magnetic resonance (NMR)
- but this is very expensive and time-consuming
- there is a large sequence-structure gap
  ≈ 500K protein sequences in SwissProt database
  < 67K protein structures in PDB database

- key question: can we predict structures by computational means instead?

Types of Protein Structure Predictions

- prediction in 1D
  - secondary structure
  - solvent accessibility (which residues are exposed to water, which are buried)
  - transmembrane helices (which residues span membranes)
- prediction in 2D
  - inter-residue/strand contacts
- prediction in 3D
  - homology modeling
  - fold recognition (e.g. via threading)
  - *ab initio* prediction (e.g. via molecular dynamics)

Prediction in 1D, 2D and 3D

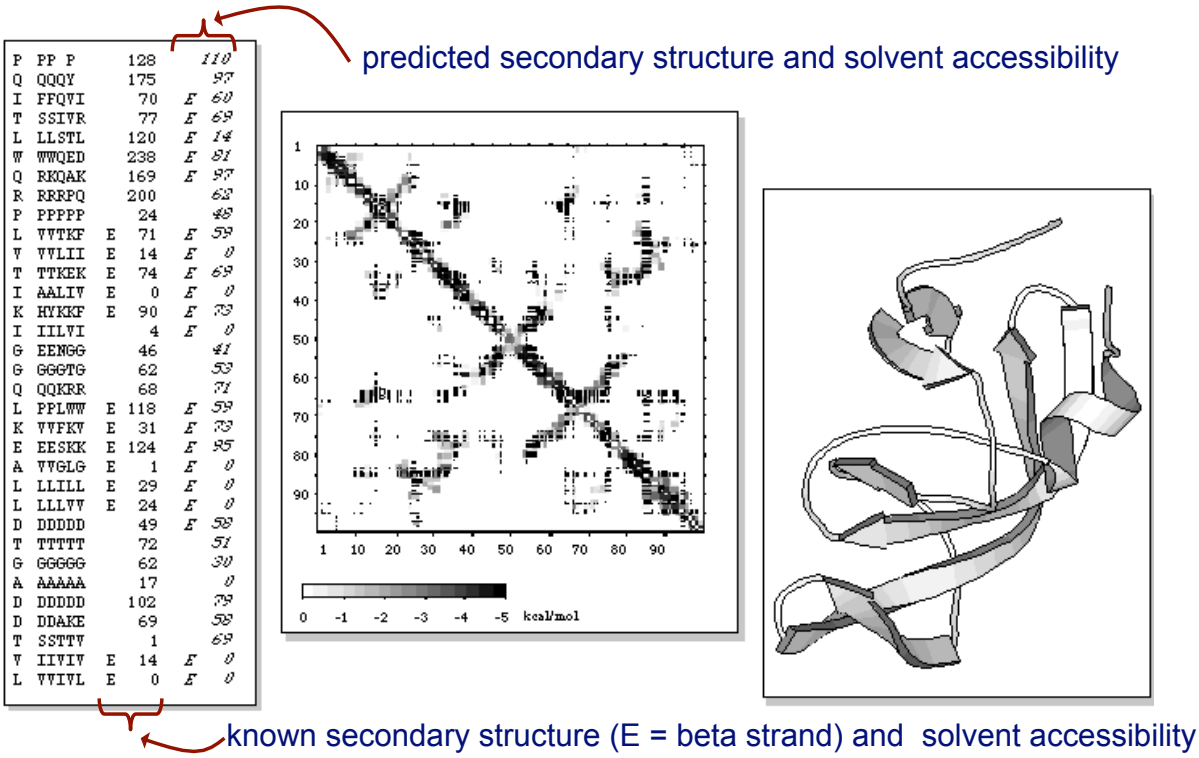


Figure from B. Rost, "Protein Structure in 1D, 2D, and 3D", *The Encyclopaedia of Computational Chemistry,* 1998

Prediction in 3D

- ***homology modeling***
  given: a query sequence *Q*, a database of protein structures
  do:
    - find protein *P* such that
      - structure of *P* is known
      - *P* has high sequence similarity to *Q*
    - return P's structure as an approximation to *Q*'s structure

- ***fold recognition*** (threading)
  given: a query sequence *Q*, a database of known folds
  do:
    - find fold *F* such that *Q* can be aligned with *F* in a highly compatible manner
    - return *F* as an approximation to *Q*'s structure

Prediction in 3D

- ***"fragment assembly"*** (Rosetta)
  given: a query sequence *Q*, a database of structure fragments
  do:
    - find a set of fragments that *Q* can be aligned with in a highly compatible manner
    - return fragment assembly as an approximation to *Q*'s structure

- ***molecular dynamics***
  given: a query sequence *Q*
  do: use laws of Physics to simulate folding of *Q*

Prediction in 3D