Protein Structure Prediction: Secondary Structure

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Protein Folding vs Structure Prediction

- Protein folding is concerned with the process of the protein taking its three dimensional shape.
- Protein structure prediction is solely concerned with the 3D structure of the protein.

Levinthal's Paradox

Consider this greatly simplified view of protein folding for a protein of 100 amino acids:

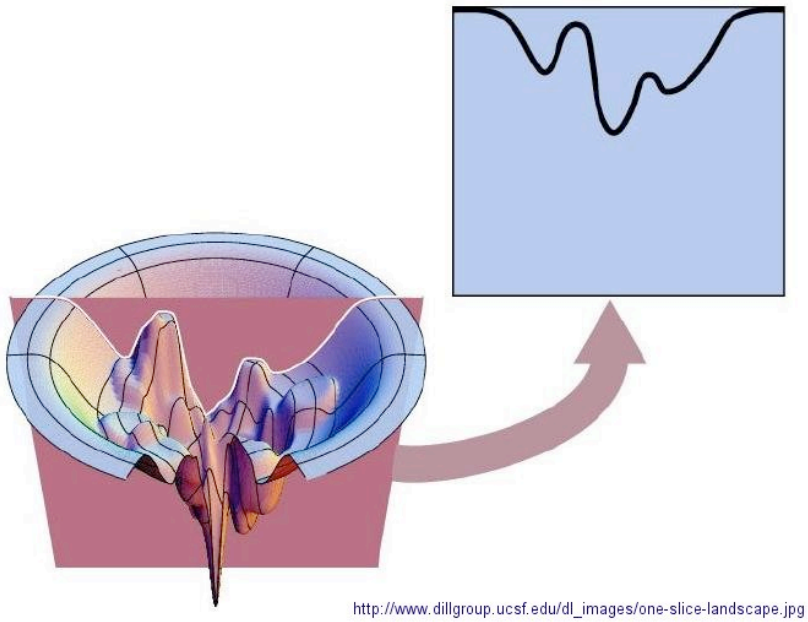
- If each amino acid can adopt only 3 possible conformations, the total number of conformations is $3^{100} = 5 \times 10^{47}$.
- Assuming it would take 10^{-13} seconds to change each conformation, the time required to test all conformations would be 5×10^{34} seconds, or 10^{27} years (the age of the universe is thought to be about 10^{10} years).
- Proteins usually fold in seconds or fractions thereof.

The Central Dogma

"The three-dimensional structure of a protein is determined by its sequence and its environment without the obligatory role of extrinsic factors".

Anfinsen (1973) Renaturation of ribonuclease.

Energy Landscape

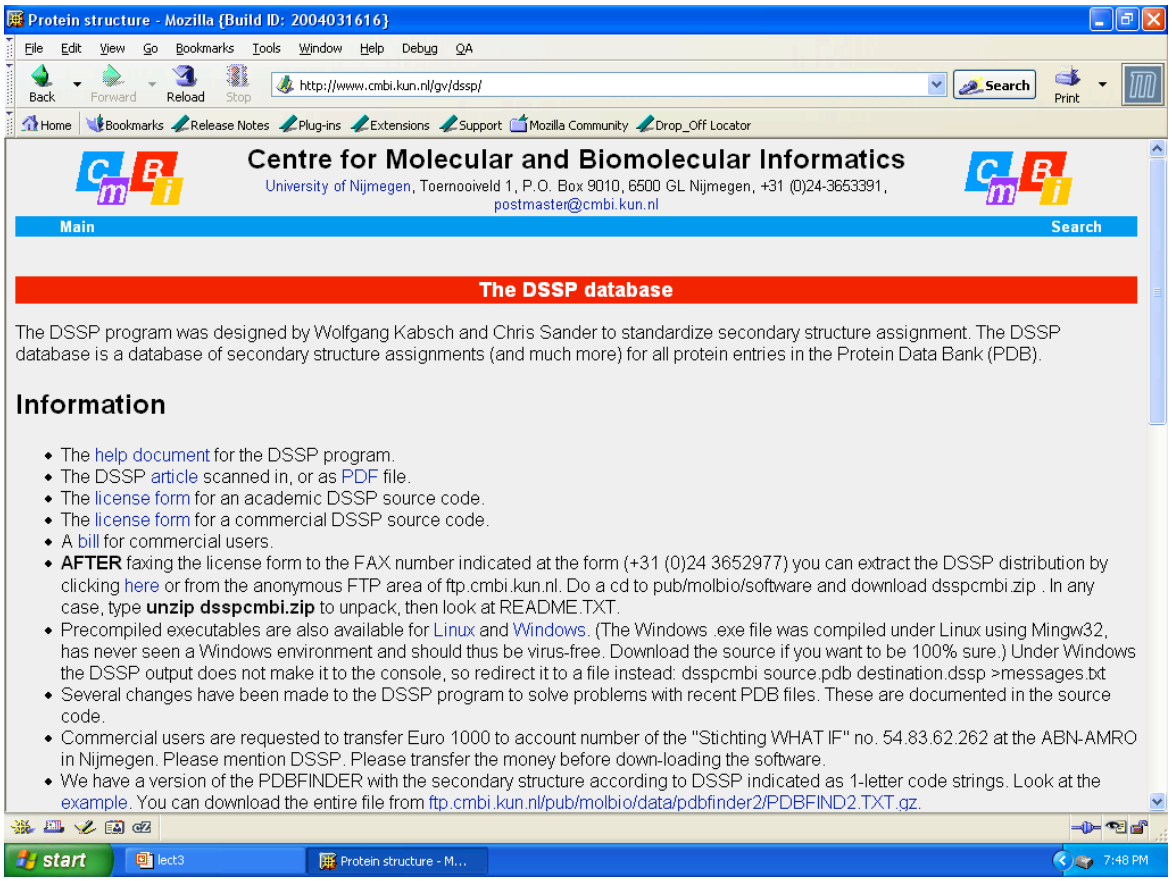


http://www.dillgroup.ucsf.edu/dl_images/one-slice-landscape.jpg

Flavors of Structure Prediction

- Homology modeling.
- Fold recognition (also called ‘inverse folding’, ‘threading’, or ‘sequence-structure threading’).
- Ab initio (also called ‘de novo’ or ‘new folds methods’).

Predicting protein interaction (for example docking) also has to do with structure prediction, but is not considered in this lecture.



Secondary Structure Assignment

Eight states from DSSP:

- H: α–helix
- G: 3_{10} helix
- I: π-helix
- E: β–strand
- B: bridge
- T: β–turn
- S: bend
- C: coil

CASP standard:

H = (H, G, I), E = (E, B), C = (C, T, S).

Secondary Structure Prediction

Given the sequence of amino acids of a protein, what is its secondary structure?

Primary structure: GHWIATRGQLIREAYEDYRHFSSECPFIP

Secondary structure: CEEEEECHHHHHHHHHHHHCCCHHCCCCCC

Notation: H: Helix E: Strand C: Coil

Secondary Structure Prediction

Helix

Edge strand

Buried strand

By eye!

A Little Bit of History…

The early methods for secondary structure prediction suffered from lack of data, and were usually performed on single sequences.

1974: Chou and Fasman.
Propensities of formation based upon frequency of occurrence, rule based.

1974: Lim.
Theory based on chemical side-chain properties, very complex rules.

1978: Garnier, Osguthorpe, Robson.
Sliding window, consensus approach.

The prediction accuracy for all of those methods were roughly 50-55%.

Measures for Prediction Accuracy

The standard measure for prediction accuracy is (still) the Q3 measure. It is simply the proportion (in percent) of all amino acids that have correct matches for the three states C, E, H.

In recent years, the segment overlap measure (SOV) has been used more extensively. It aims for measuring how well secondary structure elements have been predicted rather than individual residues.

Rost et al (1994), JMB 235, pp 13-26.

Automated Methods

The availability of large families of homologous sequences together with advances in computing techniques has pushed the prediction accuracy well above 70%. Most methods are available as web servers. They include:

PHD

`http://www.embl-heidelberg.de/predictprotein/predictprotein.html`

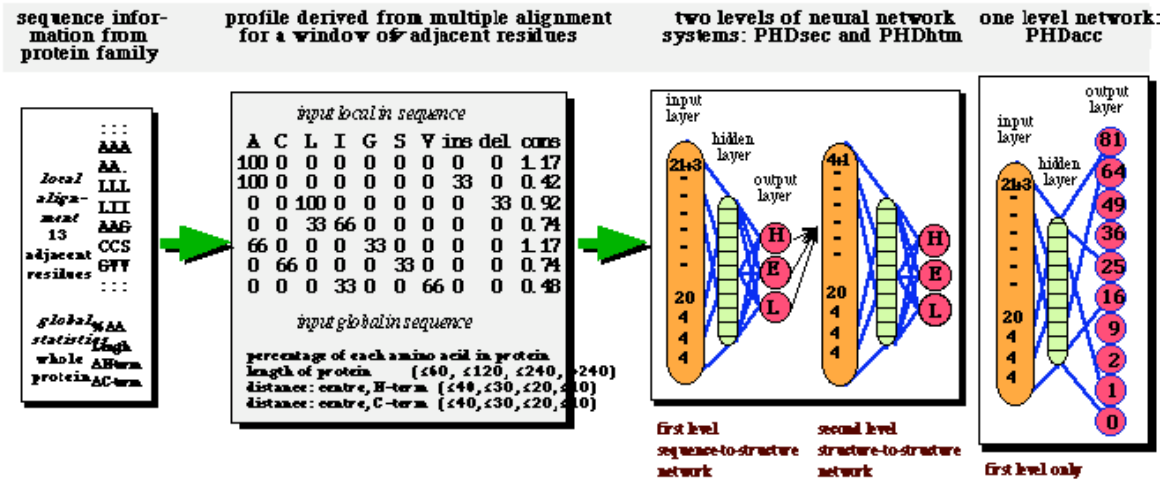
PSI-PRED

`http://bioinf.cs.ucl.ac.uk/psipred/`

JPRED

`http://www.compbio.dundee.ac.uk/~www-jpred/`

PHD



Other References

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Consensus