**BINF 731**

# Protein Structure Analysis

http://binf.gmu.edu/vaisman/binf731/

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2015

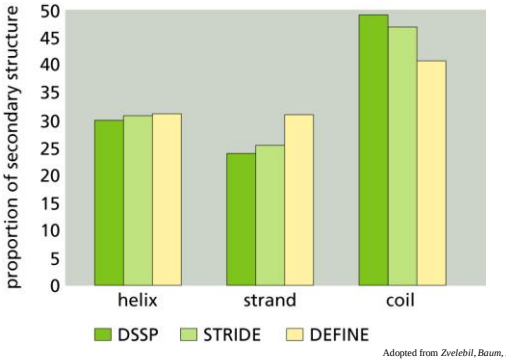
## Secondary Structure: Computational Problems

Secondary structure characterization
Secondary structure assignment
Secondary structure prediction
Protein structure classification

## Secondary Structure Conformations

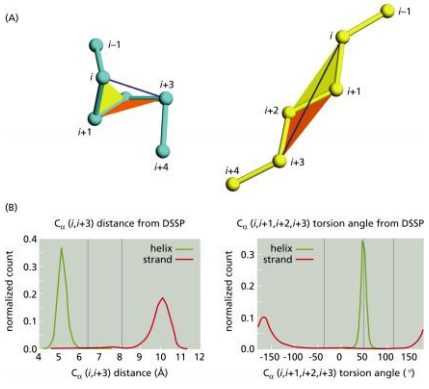
| | ϕ | ψ |
|---|---|---|
| alpha helix | -57 | -47 |
| alpha-L | 57 | 47 |
| 3-10 helix | -49 | -26 |
| π helix | -57 | -80 |
| type II helix | -79 | 150 |
| β-sheet parallel | -119 | 113 |
| β-sheet antiparallel | -139 | 135 |

## Secondary Structure Assignment




Adopted from *Zvelebil, Baum, 2008*

## Secondary Structure Assignment

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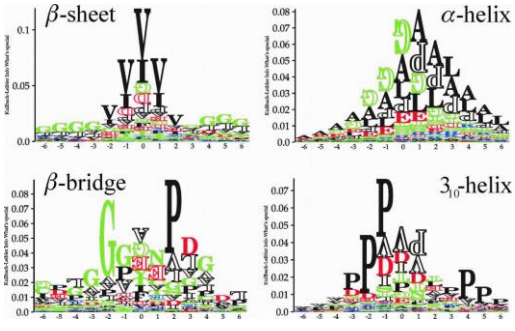



Sequence distributions for secondary structure

The number of aligned segments are: (A) 41803, (B) 4952, (C) 27320, (D) 1851 (707 non-homologous protein chains using DSSP).

C. Andersen & B. Rost, 2003

## Secondary Structure Assignment

```
....;....1....;....2....;....3....;....4....;....5....;....6....;....7..
    .-- sequential resnumber, including chain breaks as extra residues
    |    .-- original PDB resname, not nec. sequential, may contain letters
    |    |   .-- amino acid sequence in one letter code
    |    |   |  .-- secondary structure summary based on columns 19-38
    |    |   |  | xxxxxxxxxxxxxxxxxxxx recommend columns for secstruc details
    |    |   |  | .-- 3-turns/helix
    |    |   |  | |.-- 4-turns/helix
    |    |   |  | ||.-- 5-turns/helix
    |    |   |  | |||.-- geometrical bend
    |    |   |  | ||||.-- chirality
    |    |   |  | |||||.-- beta bridge label
    |    |   |  | ||||||.-- beta bridge label
    |    |   |  | |||||||   .-- beta bridge partner resnum
    |    |   |  | |||||||   |   .-- beta bridge partner resnum
    |    |   |  | |||||||   |   |.-- beta sheet label
    |    |   |  | |||||||   |   ||    .-- solvent accessibility
    |    |   |  | |||||||   |   ||    |
#  RESIDUE AA STRUCTURE BP1 BP2  ACC
    |    |   |  | |||||||   |   ||    |
35   47   I  E     +     0   0    2
36   48   R  E >  S- K   0  39C  97
37   49   Q  T 3  S+      0   0   86    (example from 1EST)
38   50   N  T 3  S+      0   0   34
39   51   W  E <    -KL   36  98C   6
```

## Secondary Structure Assignment

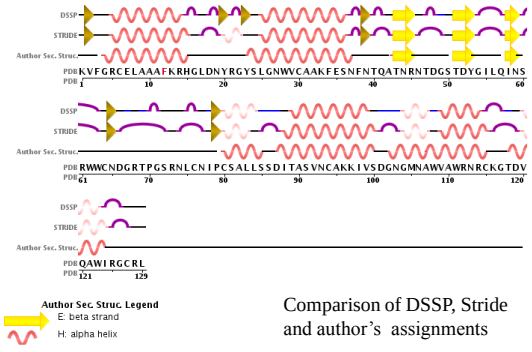
| # | RESIDUE | AA | STRUCTURE | BP1 | BP2 | ACC |
|---|---|---|---|---|---|---|
| 1 | 2 | A | T | | 0 | 0 | 77 |
| 2 | 3 | A | T | E | -A 34 | 0A | 21 |
| 3 | 4 | A | a | E | -A 33 | 0A | 0 |
| 4 | 5 | A | b | | - 0 | 0 | 0 |
| 5 | 6 | A | P | S | S+ 0 | 0 | 52 |
| 6 | 7 | A | S | S | > S- 0 | 0 | 48 |
| 7 | 8 | A | I | H | > S+ 0 | 0 | 123 |
| 8 | 9 | A | V | H | > S+ 0 | 0 | 98 |
| 9 | 10 | A | A | H | > S+ 0 | 0 | 6 |
| 10 | 11 | A | R | H | X S+ 0 | 0 | 55 |

B = residue in isolated β-bridge
E = extended strand, in β-ladder
G = 3-helix (3/10 helix)
H = α-helix
I = 5-helix (π helix)
T = hydrogen bonded turn
S = bend

**Figure 1.** Essentials of the DSSP file. Left: a small part of a secondary structure description. From left to right the columns contain the sequential number of the amino acid, its PDB number, the chain identifier, the amino acid sequence (with paired cysteines replaced by pairs of lower case characters), the actual secondary structure assignment (in red), a description of the type of turn encountered, in case of β-sheets the partner β-strand(s) and the sequential strand identifier, the solvent accessibility of the residue in square Ångströms. The lines further contain information (data not shown) about the geometry of the hydrogen bond(s) that were used to assign the secondary structure, local backbone angles and torsion angles and the coordinates of the Cα. Right: the meaning of the most used (red) column from DSSP files: the secondary structure assignments. Most people convert B, S and T simply into loop (which is a blank in DSSP), sometimes the G is converted into a H, and the I (π helix) is so rare that people tend to just forget about it.

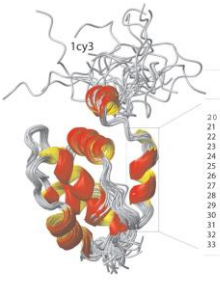
Joosten et al., 2010

## Secondary Structure Assignment




Comparison of DSSP, Stride and author's assignments

## Secondary Structure Assignment




(a) DSSP assignment for models 1-23 | (b) DSSPcont assignment for model 1

| | | 1 5 10 15 20 23 | G | H | I | T | E | B | S | L |
|---|---|---|---|---|---|---|---|---|---|---|
| 20 | Val | LLLLLLLLLLLLLLLLLLLLL | 0 | 0 | 0 | 32 | 0 | 0 | 0 | 68 |
| 21 | Ser | TLLHTLLTLLLLHLLLHLLTLLT | 0 | 0 | 0 | 100 | 0 | 0 | 0 | 0 |
| 22 | Glu | TTTHTTTHTSHTSHTSTSSTLTT | 0 | 0 | 0 | 100 | 0 | 0 | 0 | 0 |
| 23 | Glu | STTHTTHTTHTSHTHTTHSSHTH | 0 | 32 | 0 | 21 | 0 | 0 | 47 | 0 |
| 24 | Ser | HHHHHHHHHHHHHHHHHHHHH | 0 | 99 | 0 | 1 | 0 | 0 | 0 | 0 |
| 25 | Leu | HHHHHHHHHHHHHHHHHHHHH | 0 | 99 | 0 | 1 | 0 | 0 | 0 | 0 |
| 26 | Asn | HHHHHHHHHHHHHHHHHHHHH | 0 | 99 | 0 | 1 | 0 | 0 | 0 | 0 |
| 27 | Lys | HHHHHHHHHHHHHHHHHHHHH | 1 | 99 | 0 | 0 | 0 | 0 | 0 | 0 |
| 28 | Val | HTHTHHTHHTHHTHHHHTHHH | 1 | 87 | 0 | 12 | 0 | 0 | 0 | 0 |
| 29 | Arg | TTTTTTTHTTTTTTTTTTTTT | 1 | 53 | 0 | 46 | 0 | 0 | 0 | 0 |
| 30 | Asn | SSTSSSSSTSSSSTSTTSSTS | 0 | 0 | 0 | 10 | 0 | 0 | 90 | 0 |
| 31 | Arg | SSTTTSSSTTSTTTTTTSTS | 0 | 0 | 0 | 32 | 0 | 0 | 68 | 0 |
| 32 | Glu | SSTTTLLLTTSTTTTTTLLL | 0 | 0 | 0 | 32 | 0 | 0 | 68 | 0 |
| 33 | Glu | LLLLLLLLLLLLLLLLLLLLL | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 100 |

1cy3 structure from: Rothemund et al. & Sonnichesen, 1999, Structure, 7, 1325

DSSPcont assignment for 1c3y fragment. The variations between the secondary structure assignments for different NMR models of the same protein illustrate the impact of fluctuations on structure

P. Carter et al., 2003

## Secondary Structure: Computational Problems

Secondary structure characterization
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Protein structure classification

## Secondary Structure Prediction

Three-state model: helix, strand, coil

Given a protein sequence:
- NWVLSTAADMQGVVTDGMASGLDKD...

Predict a secondary structure sequence:
- LLEEEELLLLHHHHHHHHHHLHHHL...

Methods:
- statistical
- stereochemical

Accuracy: 50-85%

## Statistical Methods

Residue conformational preferences:

Glu, Ala, Leu, Met, Gln, Lys, Arg - helix
Val, Ile, Tyr, Cys, Trp, Phe, Thr - strand
Gly, Asn, Pro, Ser, Asp - turn

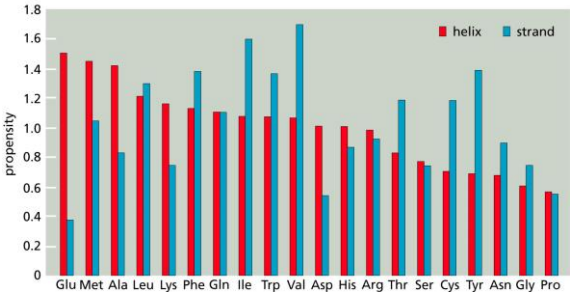
Chou-Fasman algorithm:

Identification of helix and sheet "nuclei"
Propagation until termination criteria met

## Chou-Fasman Parameters

| Name | P(a) | P(b) | P(turn) | f(i) | f(i+1) | f(i+2) | f(i+3) |
|---|---|---|---|---|---|---|---|
| Alanine | 142 | 83 | 66 | 0.06 | 0.076 | 0.035 | 0.058 |
| Arginine | 98 | 93 | 95 | 0.070 | 0.106 | 0.099 | 0.085 |
| Aspartic Acid | 101 | 54 | 146 | 0.147 | 0.110 | 0.179 | 0.081 |
| Asparagine | 67 | 89 | 156 | 0.161 | 0.083 | 0.191 | 0.091 |
| Cysteine | 70 | 119 | 119 | 0.149 | 0.050 | 0.117 | 0.128 |
| Glutamic Acid | 151 | 37 | 74 | 0.056 | 0.060 | 0.077 | 0.064 |
| Glutamine | 111 | 110 | 98 | 0.074 | 0.098 | 0.037 | 0.098 |
| Glycine | 57 | 75 | 156 | 0.102 | 0.085 | 0.190 | 0.152 |
| Histidine | 100 | 87 | 95 | 0.140 | 0.047 | 0.093 | 0.054 |
| Isoleucine | 108 | 160 | 47 | 0.043 | 0.034 | 0.013 | 0.056 |
| Leucine | 121 | 130 | 59 | 0.061 | 0.025 | 0.036 | 0.070 |
| Lysine | 114 | 74 | 101 | 0.055 | 0.115 | 0.072 | 0.095 |
| Methionine | 145 | 105 | 60 | 0.068 | 0.082 | 0.014 | 0.055 |
| Phenylalanine | 113 | 138 | 60 | 0.059 | 0.041 | 0.065 | 0.065 |
| Proline | 57 | 55 | 152 | 0.102 | 0.301 | 0.034 | 0.068 |
| Serine | 77 | 75 | 143 | 0.120 | 0.139 | 0.125 | 0.106 |
| Threonine | 83 | 119 | 96 | 0.086 | 0.108 | 0.065 | 0.079 |
| Tryptophan | 108 | 137 | 96 | 0.077 | 0.013 | 0.064 | 0.167 |
| Tyrosine | 69 | 147 | 114 | 0.082 | 0.065 | 0.114 | 0.125 |
| Valine | 106 | 170 | 50 | 0.062 | 0.048 | 0.028 | 0.053 |

## Chou-Fasman Parameters




Adopted from *Zvelebil, Baum, 2008*

## Chou-Fasman Algorithm

Identification of helix and sheet "nuclei"
- helix - 4 out of 6 residues with high helix propensity (P > 100)
- sheet - 3 out of 5 residues with high sheet propensity (P > 100)

Propagation until termination criteria met

Turn prediction

1) `p(t) > 0.000075`
2) `P(turn) > 1.00`
3) `P(a) < P(turn) > P(b)`

where `p(t) = f(j)f(j+1)f(j+2)f(j+3)`

P.Y. Chou, G.D. Fasman, *Biochemistry*, 1974, **13**, 211-222

## Garnier - Osguthorpe - Robson (GOR) Algorithm

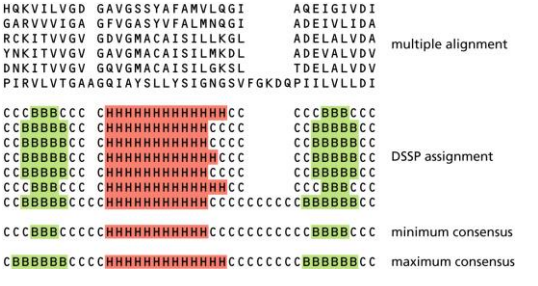
Likelihood of a secondary structure state depends on the neighboring residues:

$$L(S_j) = \Sigma\ (S_j;R_{j+m})$$

Window size - [j-8; j+8] residues

Accuracy for a single sequence - 60%
Accuracy for an alignment - 65%

## Evolutionary Information




Adopted from *Zvelebil, Baum, 2008*

## Evolutionary Methods

Taking into account related sequences helps in identification of “structurally important” residues.

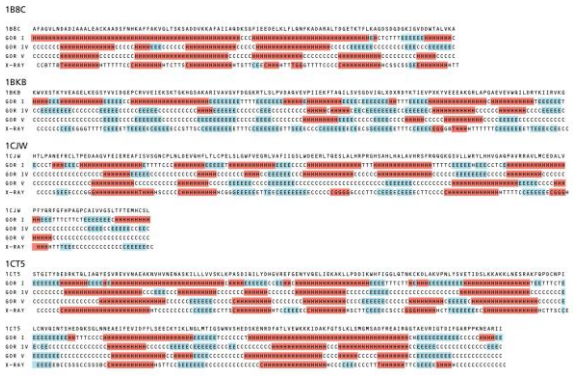
Algorithm:

- find similar sequences
- construct multiple alignment
- use alignment profile for secondary structure prediction

Additional information used for prediction

- mutation statistics
- residue position in sequence
- sequence length

## Evolutionary Methods

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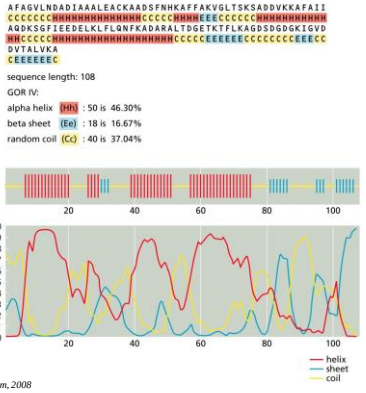
## Evolutionary Methods

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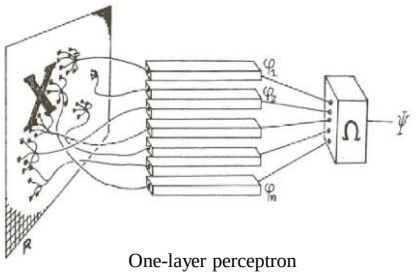
## Neural Networks

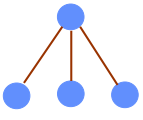


One-layer perceptron

M. L. Minsky & S. Papert, 1969

## Neural Networks

Perceptron



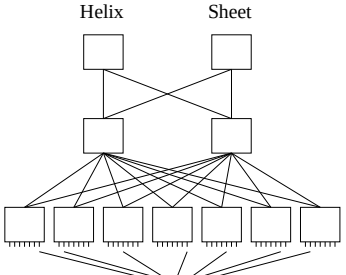
Output layer

Input layer

$$Y = \begin{cases} 1 \text{ if } \Sigma w_i i_i > \Theta \\ 0 \text{ otherwise} \end{cases}$$

Learning process: $\Delta w_i = (T_p - Y_p) i_{pi}$

## Neural Networks Methods




MKFGNFLLTYQP [ PELSQTE ] VMKRLVNLGKASEGC...

## Stereochemical Methods

Patterns of hydrophobic and hydrophilic residues in secondary structure elements:

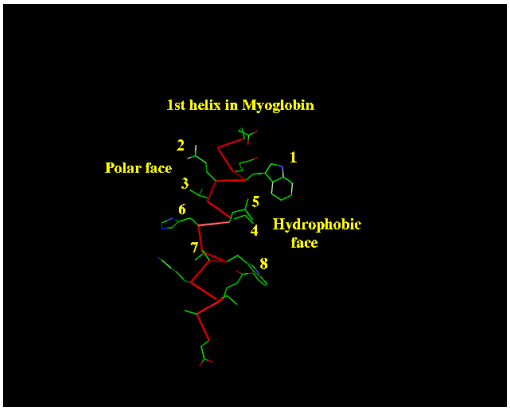
- segregation of hydrophobic and hydrophilic residues
- hydrophobic residues in the positions 1-2-5 and 1-4-5
- oppositely charged polar residues in the positions 1-5 and 1-4 (e.g. Glu (i), Lys (i+4))

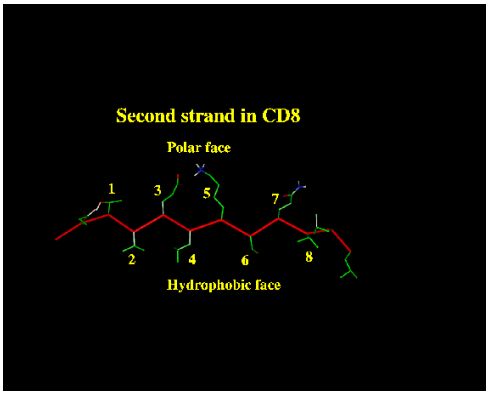
Definitions of hydrophobic and hydrophilic residues (hydrophobicity scales) are ambiguous

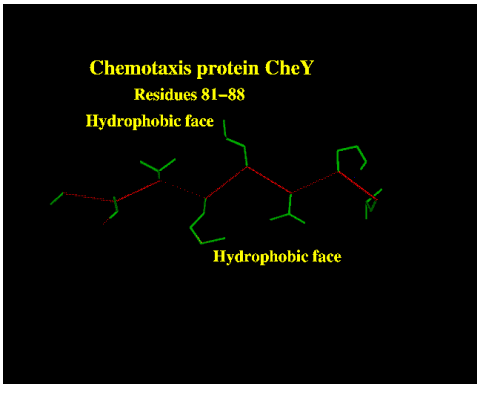
## Stereochemical Methods

Hydropathic correlations in helices and sheets

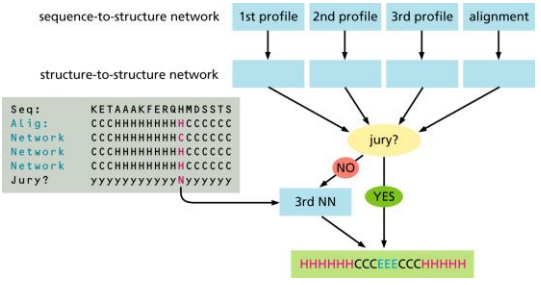
| | | F-F | F-L | L-F | L-L |
|---|---|---|---|---|---|
| $\alpha$ | *i, i+2* | - | + | + | - |
| | *i, i+3* | + | - | - | + |
| | *i, i+4* | + | - | - | + |
| | *i, i+5* | - | + | + | - |
| $\beta$ | *i, i+1* | - | + | + | - |
| | *i, i+2* | + | - | - | + |
| | *i, i+3* | - | + | + | - |



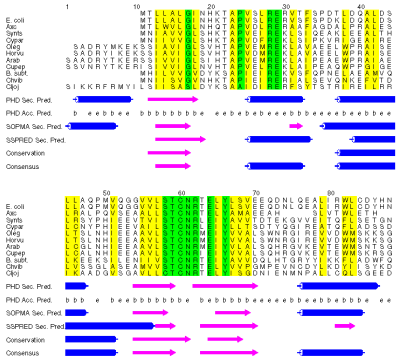




## Jnet Algorithm

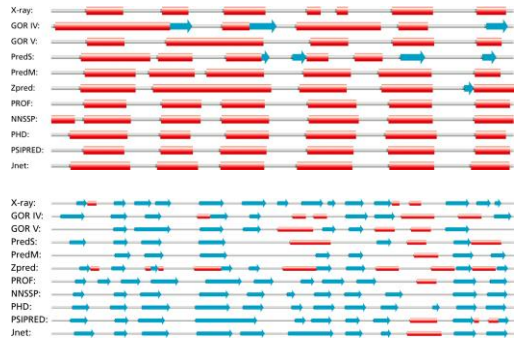



Adopted from *Zvelebil, Baum, 2008*

## Jnet Algorithm




## Accuracy of prediction

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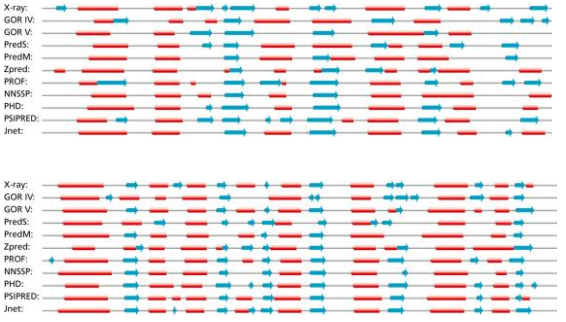



Adopted from *Zvelebil, Baum, 2008*

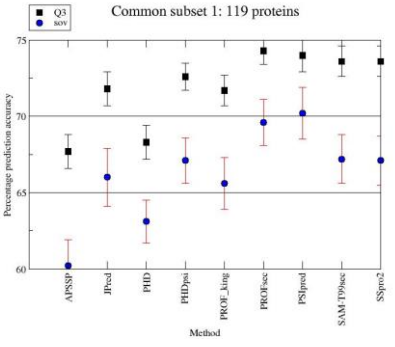
## Accuracy of Prediction

$$Q_3 = \frac{PH + PE + PC}{N}$$

$$W = \log \frac{TP \times TN}{FP \times FN}$$

Range: 50-85%

## Accuracy of prediction




EVA (http://cubic.bioc.columbia.edu/eva/)

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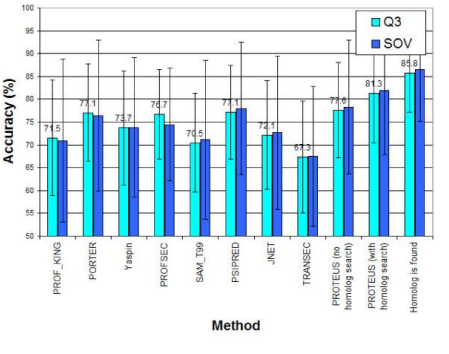


S. Montgomerie et al., 2006