Protein Domains: Prediction from Amino Acid Sequence

I619: Structural Bioinformatics

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Introduction

- protein domain identification, given only a sequence, is an important problem
  - gap between sequence and structure data is increasing
- Usual steps given a new sequence
  - if homology can be identified by sequence alignment (to domain databases) the problem is typically easy
  - if homology cannot be reliably identified, the problem is much more difficult
- Databases to look at: Pfam, SMART etc.

Practical Importance

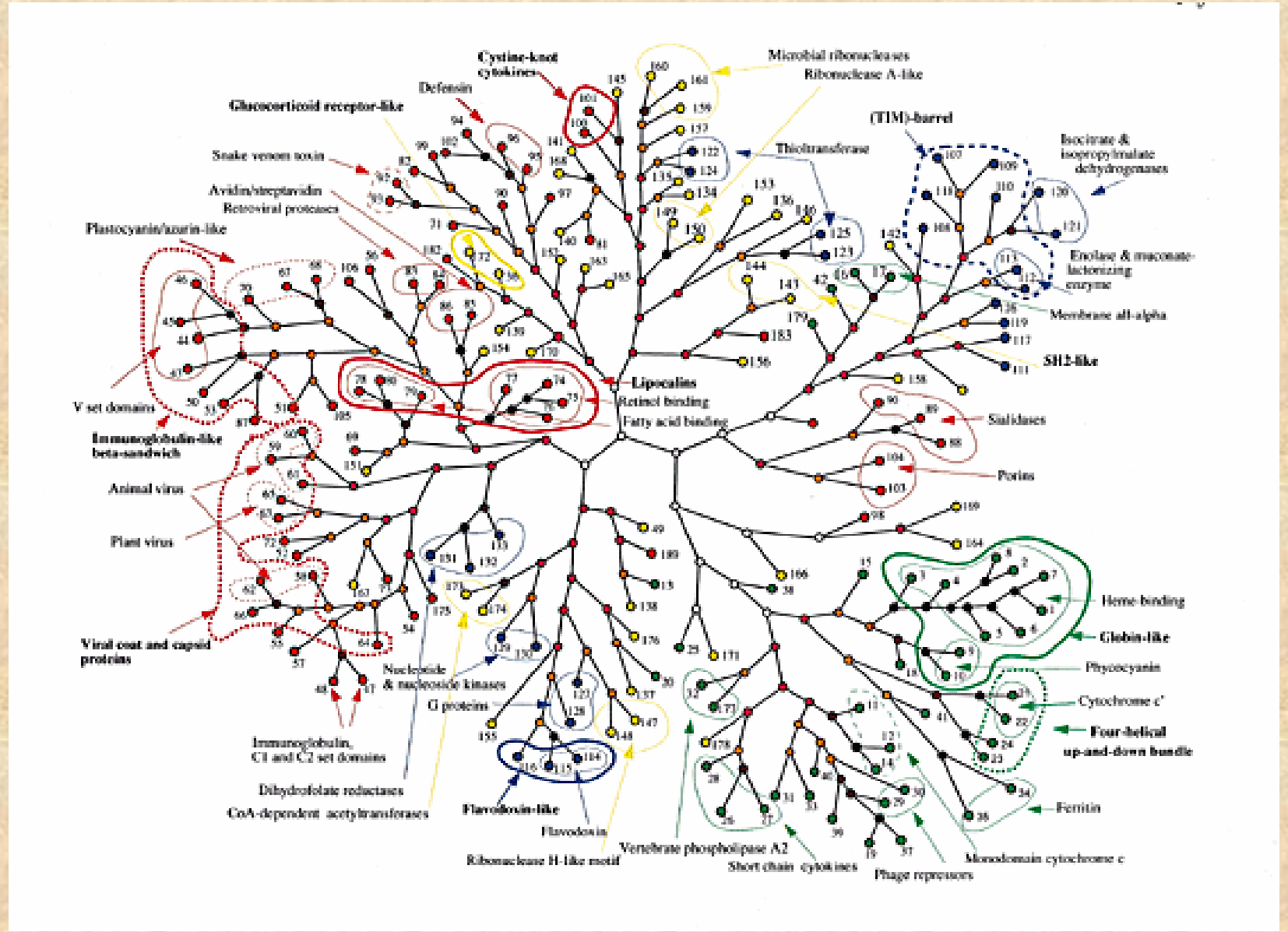
- cost-reduction for experimental methods
  - X-ray crystallography
  - NMR spectroscopy
- to help local multiple sequence alignment
  - difficulties arise when whole sequences with “shuffled” domains need to be aligned
- to help fold recognition methods
  - it is easier to look at a sequence in terms of its constituent domains then as a whole chain

DomSSEA: idea

- alignment of (predicted) secondary structures can be used for sequence alignment when identity is low
- prediction of secondary structure is sufficiently accurate to be useful (77% or higher; 3-state)

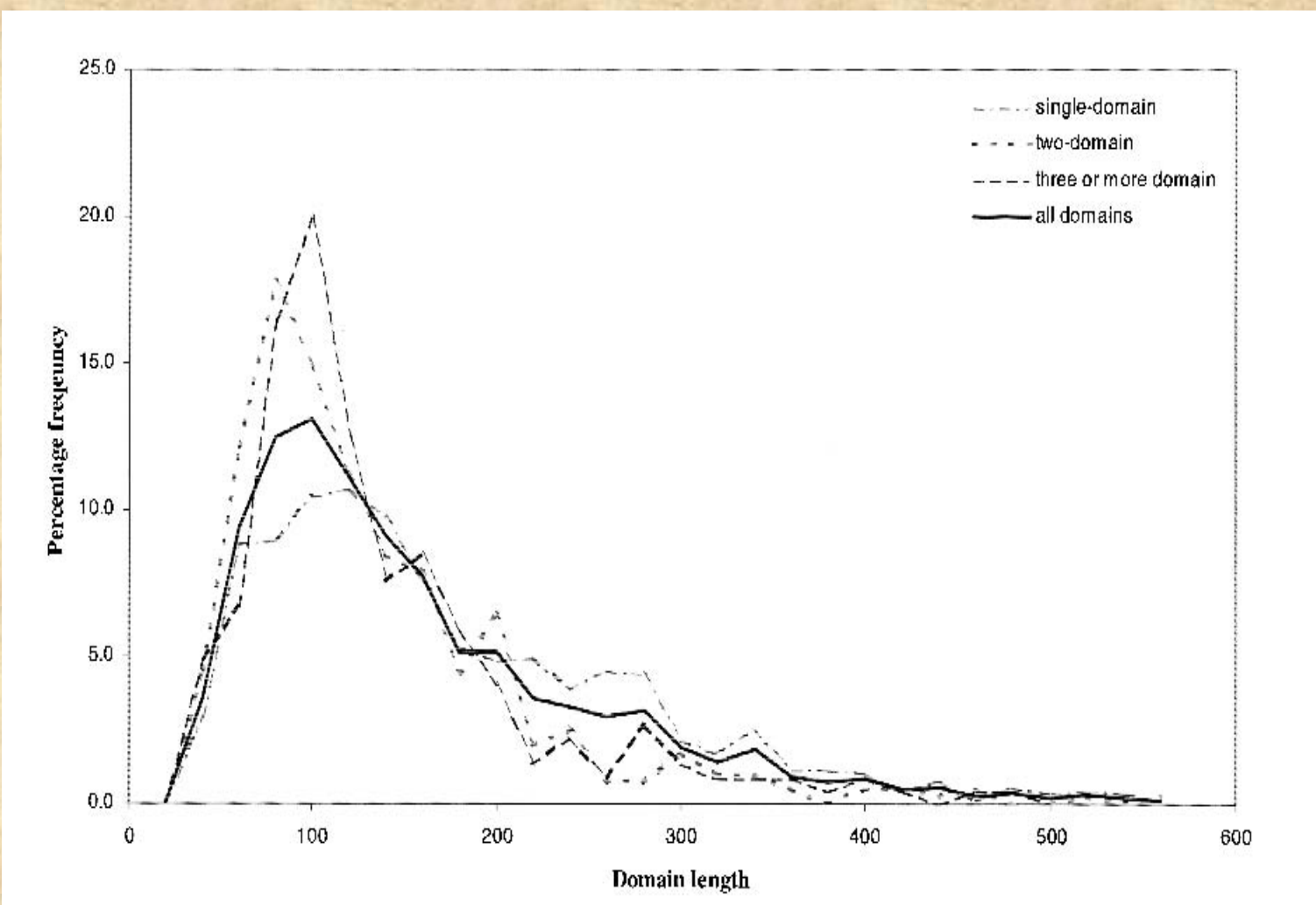
- Idea:
  - use Secondary Structure Element Alignment (SSEA)
  - it has been used for fold recognition when no detectable homology existed (using standard sequence alignments)
- Goal:
  - to have a fast method capable of predicting on whole genomes
  - result: DomSSEA

Analysis: Domain Lengths

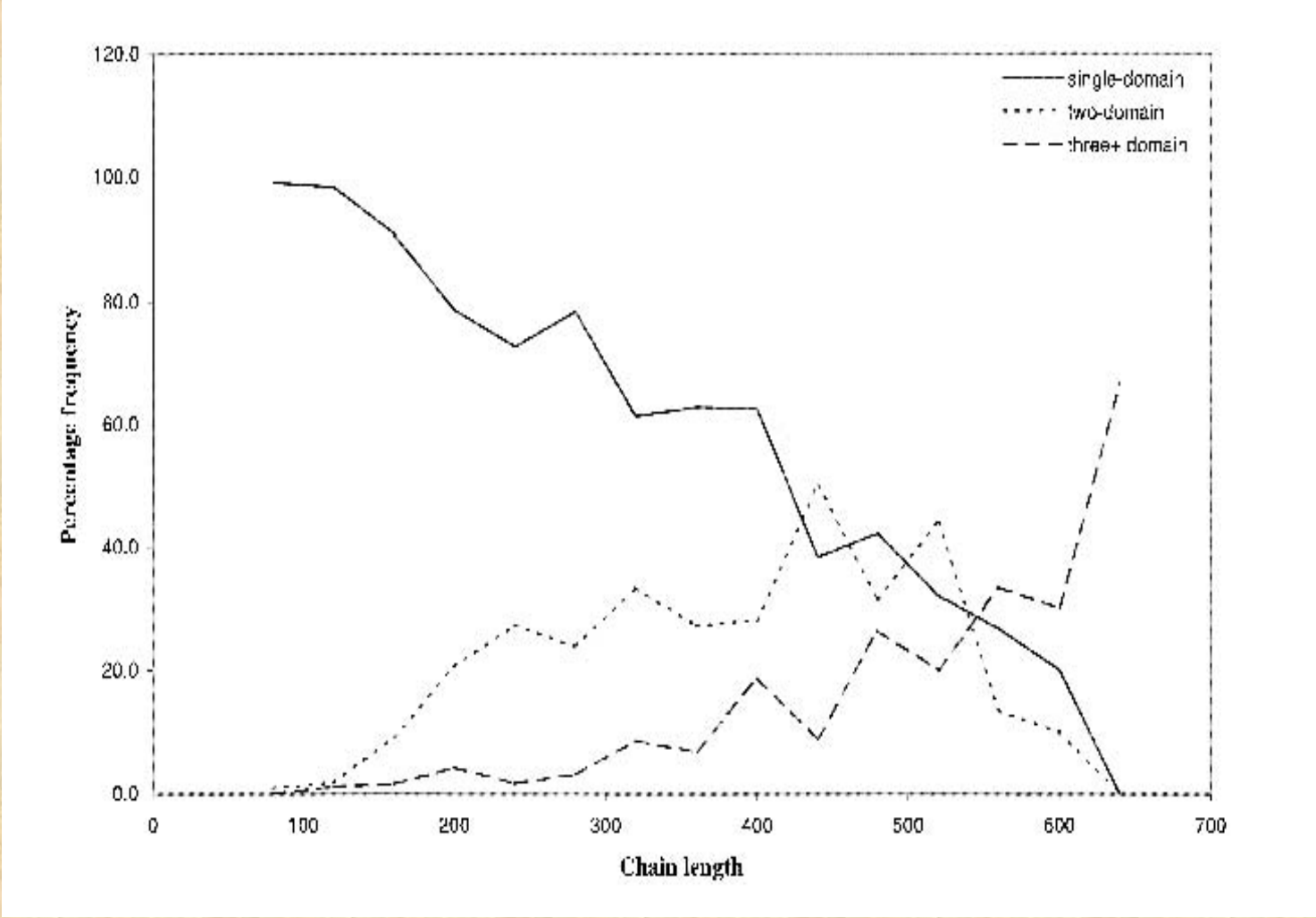


=> Przytycka et al, 1999

Analysis: Domain Lengths



Analysis: Domain Lengths



=> Domains can be predicted using the size of proteins

DomSSEA: algorithm

- predict secondary structure on a new (query) protein
  - PSIPRED (Jones, 1999)
- align query sequence of predicted secondary structures to all sequences in the database (of domains)
  - dynamic programming (McGuffin et al, 2001)
  - adjusted scoring scheme (Przytycka et al, 1999)
- collect top hit from the pair with the highest score
  - use PSI-BLAST to find homologs of the best hit
- make a cut within a coil region

Przytycka et al, 1999

Alignment between	Score
Identical elements	$\min(l_i, l_j)$
Helix/strand and loop	$0.5\min(l_i, l_j)$
Helix and strand	0

As a clarifying example, consider two secondary sequences: S_1 = h7, l3, h7 and S_2 = h5, l6, h6. For optimal alignment, l6 in the second sequence is split into l2, l3, l1. Then, h7 is aligned with h5 + l2, l3 with l3, and the second h7 is aligned with l1 + h6. The total score is: 5 + 0.5*2 + 3 + 0.5*1 + 6 = 15.5, and the normalized score is 0.91.

Accuracy

Standard measures

- accuracy in domain number prediction
- accuracy of domain boundary prediction
  - ±20 residues from the CATH assignment ⇒ correct

Table 1. *Prediction of one, two, or three or more domain chains*

	% Correctly assigned			
Prediction of number of domains	All	1 domain	2 domains	3 or more domains
PUU	79.0	81.0	66.0	65.0
DomSSEA observed secondary structure	75.4	83.9	47.5	38.1
DomSSEA predicted secondary structure	73.3	82.3	46.0	36.5
DGS-M	76.7	99.8	1.0	0.0
DGS-W	76.7	100.0	0.0	0.0
Absolute difference in length	66.2	78.4	22.3	38.1
Fasta	60.9	74.9	17.3	7.9
Random (weighted)	61.4	75.8	16.8	6.3
Random (basic)	37.9	45.0	16.8	7.9
Sum of squares	62.0	76.0	17.0	7.0

The percentage of chains given a correctly assigned domain number (top prediction), for single, two, and three or more domain chains, as well as for all chains in the representative set.

Accuracy

Table 3. *Prediction of domain boundaries, given a representative set of two domain protein chains (±20 residues)*

Methods	% Correctly assigned boundaries
PUU	81.8
Consensus	52.5
L/(N-1)	49.5
DomSSEA observed secondary structure	49.5
DomSSEA predicted secondary structure	49.0
DGS-M	46.0
Absolute difference in length	44.6
DGS-W	37.1
FASTA	30.0
Random (weighted)	26.8

Other Methods

- **SnapDRAGON**
  - George and Heringa, 2002
  - *ab initio* protein folding method: DRAGON
    - predicts secondary structure, makes sequence alignment, then folds each chain based on conserved hydrophobicity
    - each folded chain is evaluated for domain boundaries
    - large number of structures are evaluated for domain consistency
  - 72% accuracy for # of domains; 51% overall cut prediction
- **CHOPnet**
  - Liu and Rost, 2004
  - uses aa composition, many predicted features, sequence alignments and combines them using neural networks
  - 69% accuracy for # of domains; 50% cut prediction (for 2 domain) chains