A Model for Protein Secondary Structure Prediction Meta - Classifiers

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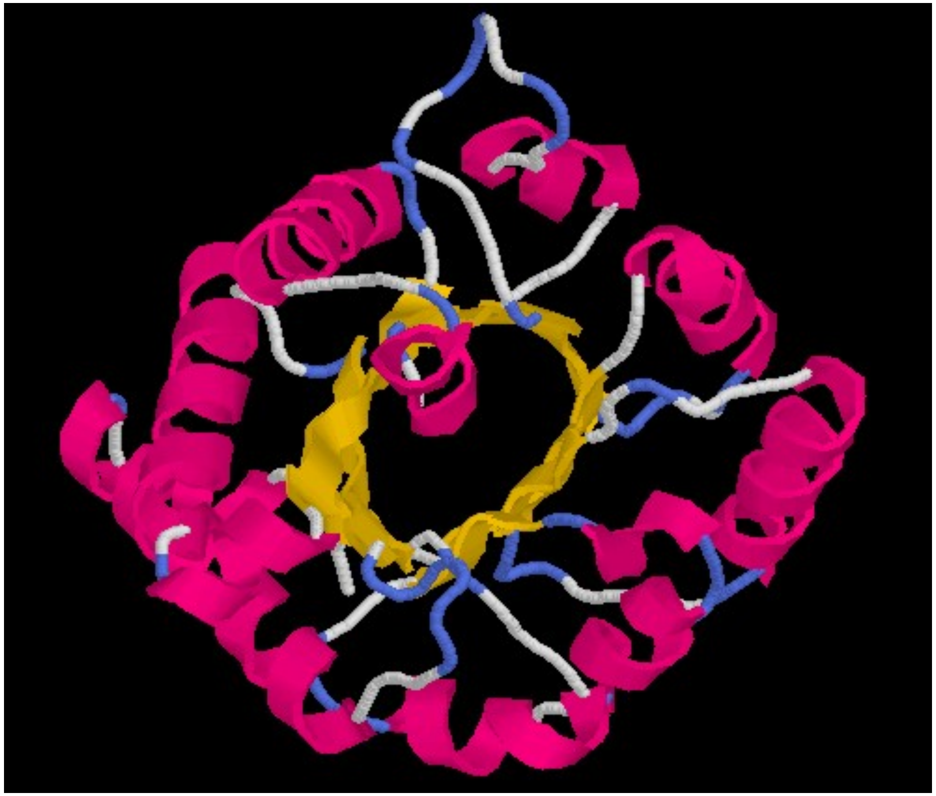
Overview

- Introduction to proteins
- Four levels of protein structure: symbolic model
- Proteomic databases
- PSSP datasets
- Protein Secondary Structure Prediction

  The Window: role and symbolic model

  Use of evolutionary information
- PSSP Metaclassifiers
- Future Research

Introduction to proteins



Proteins

- Protein: from the Greek word PROTEUO which means "to be first (in rank or influence)"

- **Why are proteins important to us:**

  Proteins make up about 15% of the mass of the average person

  Enzyme – acts as a biological catalyst

  Storage and transport – Haemoglobin

  Antibodies

  Hormones – Insulin

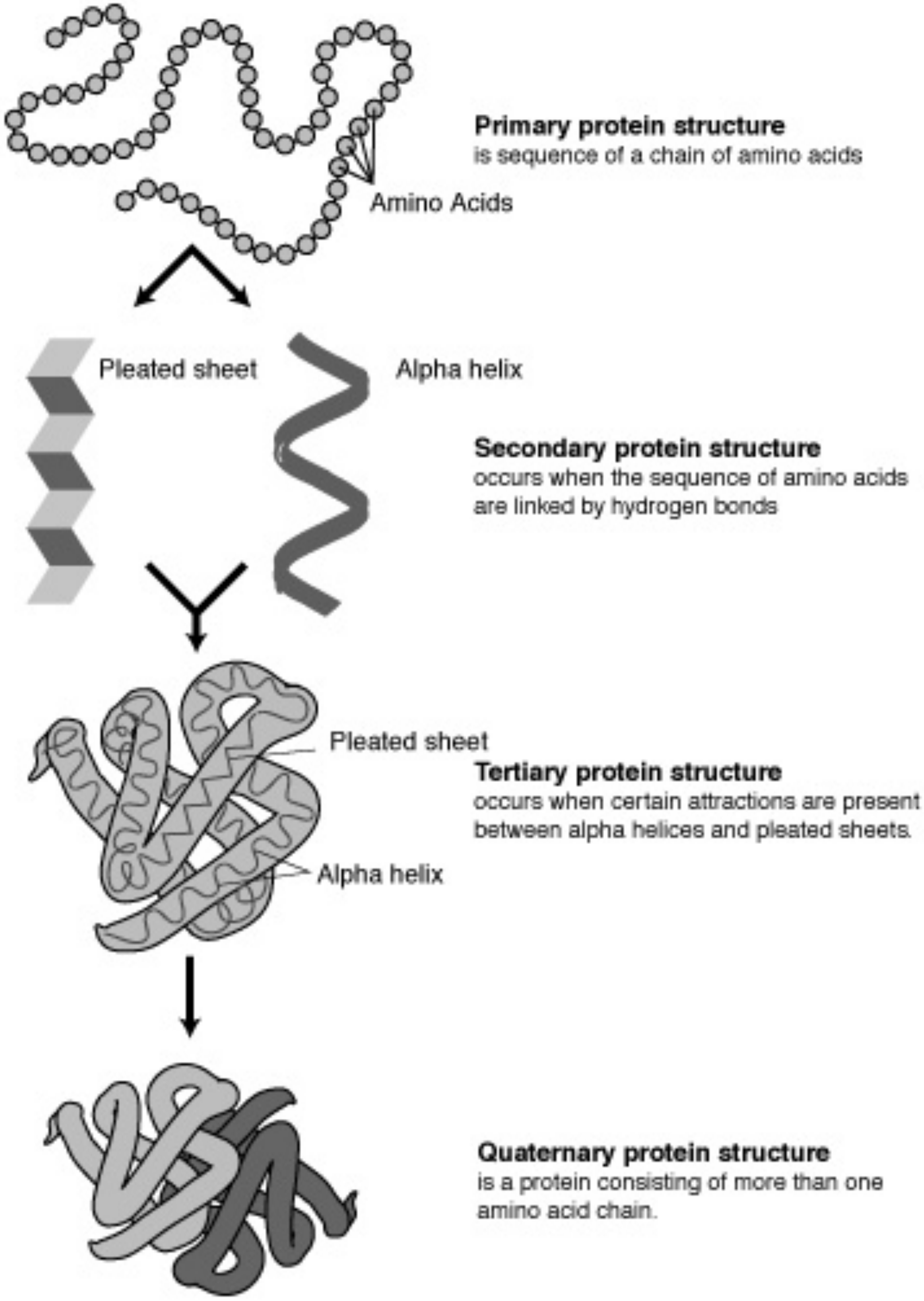
Proteins

- **Why are proteins important to us (c.d.):**
  - Ligaments and arteries (mainly former by elastin protein)
  - Muscle – Proteins in the muscle respond to nerve impulses by changing the packing of their molecules
  - Hair, nails and skins: protein α-keratin as main component
  - And more ……

Proteins Research Benefits

- **Medicine** – design of drugs which inhibit specific enzyme targets for therapeutic purposes (engineering of insulin)
- **Agriculture** – Treat diseases of plants and to modify growth and development of crops
- **Industry** – Synthesis of enzymes to carry out industrial processes on a mass scale

Four levels of protein structure



Primary protein structure
is sequence of a chain of amino acids

Secondary protein structure
occurs when the sequence of amino acids are linked by hydrogen bonds

Tertiary protein structure
occurs when certain attractions are present between alpha helices and pleated sheets.

Quaternary protein structure
is a protein consisting of more than one amino acid chain.

Four Levels of Protein Structure: **AMINOACIDS**

- AMINOACIDS: There are 20 aminoacids:

- Alanine (A), Cysteine (C), Aspartic Acid (D),
- Glutamic Acid (E), Phenylalanine (F), Glicine (G),
- Histidine (H), Isoleucine (I),Lycine (K), Leucine (L),
- Methionine (M), AsparagiNe (N), Proline (P),
- Glutamine (Q), ARginine (R), Serine (S),
- Threonine (T), Valine (V),Tryptophan (W),
- TYrosine (Y)

- AMINOACIDS SYMBOLS: A,C,D,E,F,G,H,I,J,K,L,M,N,P,Q,R,S.T,V,W,Y

Primary Structure
Symbolic Definition

- A = {A,C,D,E,F,G,H,I,J,K,L,M,N,P,Q,R,S.T,V,W,Y } – set of symbols denoting all aminoacids
- A^* - set of all finite sequences formed out of elements of A.
- Elements of A^* are denoted by x, y, z …..i.e. we write $x \in A^*$, $y \in A^*$, $z \in A^*$, … etc
- Any $x \in A^*$ is called a protein sequence or protein sub-unit primary structure
- Any x_1, x_2, ... x_n $\in (A^*)^*$, is called a protein primary structure.

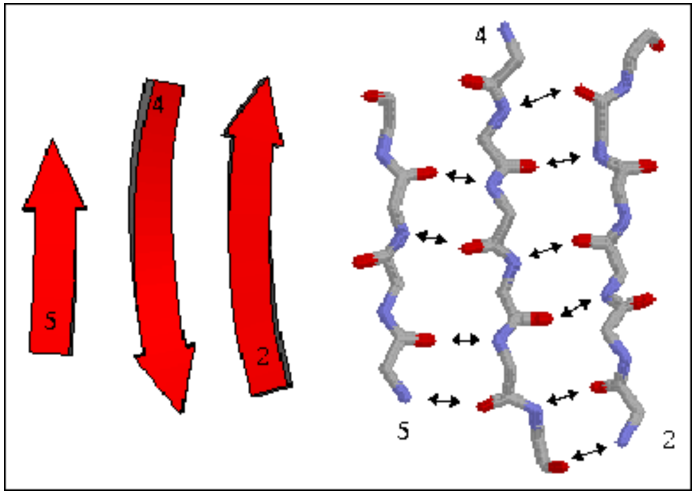
Protein Secondary Structure SS

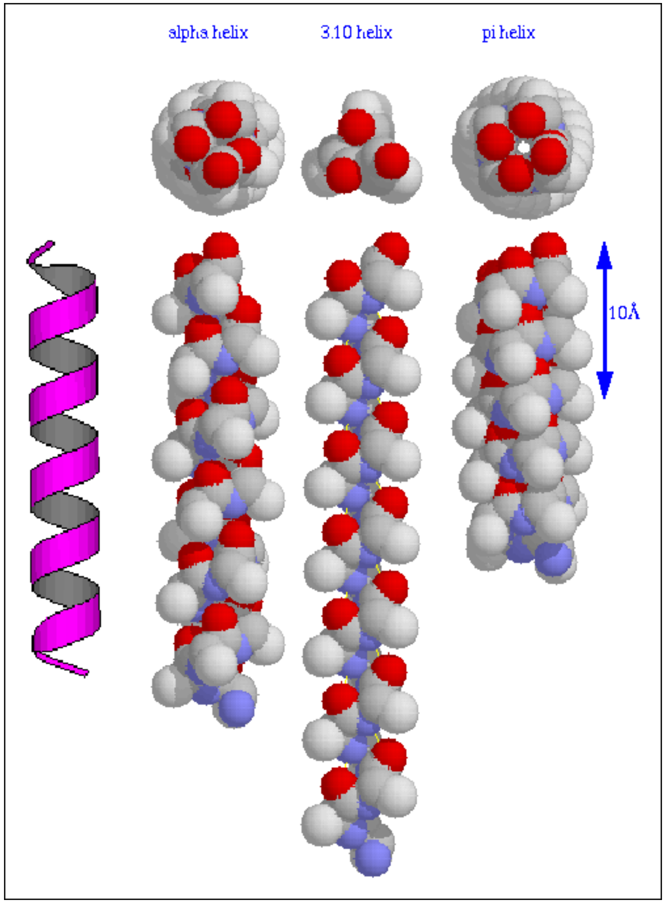
- Secondary structure is the term protein chemist give to the arrangement of the peptide backbone in space. It is produced by hydrogen bondings between aminoacids
- The assignment of the SS categories to the experimentally determined three-dimensional (3D) structure of proteins is a non-trivial process and is typically performed by widely used DSSP program
- PROTEIN SECONDARY STRUCTURE consists of : protein sequence and its hydrogen bonding patterns called SS categories

Secondary Structure

8 different categories (DSSP):

- H: α - helix
- G: 3_{10} – helix
- I: π - helix (extremely rare)
- E: β - strand
- B: β - bridge
- T: β- turn
- S: bend
- L: the rest





Protein Secondary Structure

- Databases for protein sequences are expanding rapidly due to the genome sequencing projects and the gap between the number of determined protein structures (PSS – protein secondary structures) and the number of known protein sequences in public
- Protein data banks (PDB) is growing bigger.

- PSSP (Protein Secondary Structure Prediction) research is trying to breach this gap.

Three secondary structure states

- Prediction methods are normally trained and assessed for only 3 states (residues):
- H (helix), E (strands) and L (coil)
- There are many published 8-to-3 states reduction methods
- **Standard reduction methods are defined by programs** DSSP (Dictionary of SS of Proteins), STRIDE, and DEFINE
- Improvement of predictive accuracy of different SSP (Secondary Structure Prediction) programs depends on the choice of the reduction method

Three SS states: Reduction methods

- **Method 1**, used by DSSP program:
- H(helix) ={ G (3_{10} – helix), H (α- helix)}

  E (strands) = {E (β-strand), B (β-bridge)} , L (coil) – all the rest

  - Shortly: E,B => E; G,H => H; Rest => C
  - **We are using this method that is the most difficult to predict and is used in CASP (International contests for PSSP programs)**

- **Method 2**, used by STRIDE program:
- H(helix) as in Method 1

  E (strands) = {E (β-strand), B (β -bridge)},

  L (coil) – all the rest

Three SS states: Reduction methods

- **Method 3**, used by DEFINE program:
- H(helix) as in Method 1

  E (strands) = {E (β-strand)}, L (coil) – all the rest

- **Some other methods:**

  Method B: E => E; H => H; Rest => L;

  EE and HHHH => L

  Method C: GGGHHHH => HHHHHHH;

  B, GGG => L; H => H; E => E

Example of typical PSS Data

- Protein Data is gathered in a form of protein sub-units (sequences) and assigned to them sequences of SS categories H, E, L as observed empirically in their 3-dimensional structures. The SS categories are assigned by DSSP program

- Example:

  Sequence

  KELVLALYDYQEKSPREVTHKKGDILTLLNSTNKDWWKYEYNDRQGFVP

  Observed SS

  HHHHLLLLEEEHHHLLLEEEEEELLLHHHHHHHHLLLEEEEEELLLHHH

Protein Secondary Structure (PSS): Symbolic Definition

- Given $A = \{A,C,D,E,F,G,H,I,J,K,L,M,N,P,Q,R,S.T,V,W,Y\}$ – set of symbols denoting aminoacids and a protein sequence (sub-unit) $x \in A^*$
- Let $S = \{H, E, L\}$ be the set of symbols of 3 states (residues): H (helix), E (strands) and L (coil) and S^* be the set of all finite sequences of elements of S.
- We denote elements of S^* by e,o, with indices if necessary i.e. we write $e \in S^*$, $e1, e2 \in S^*$, etc…

Protein Secondary Structure (PSS): Symbolic Definition

- **Any PARTIAL, ONE –TO –ONE FUNCTION**

  $f : A^* \longrightarrow S^*$ i.e. $f \subseteq A^* \times S^*$

  is called a protein secondary structure (PSS) sub-unit identification function

- An element $(x, e) \in f$ is a called protein secondary structure (of the protein sub- unit x)

- The element e (of $(x, e) \in \mathbf{f}$) is called secondary structure sequence, or for short a secondary structure of x.

Protein Secondary Structure (PSS)
Symbolic Definition

- Following the standard way we write in PSS research the pairs sequence-structure, we represent the pair (x,e) i.e. the protein secondary structure in a vertical form: $\left(\boxed{\begin{matrix}x\\ e\end{matrix}}\right)$ and hence the PSS identification function f is viewed as the set of all secondary structures it identifies i.e.
- $f = \left\{ \left(\boxed{\begin{matrix}x\\ e\end{matrix}}\right) : \quad x \in A^{*} \ \cap \ x \in \mathrm{Dom}\,\mathbf{f} \ \cap \ e = \mathbf{f}(x) \right\}$

PSS Identification Function Examples

- Any Data Set (DS) used in PSS Prediction defines its own identification function f_{DS} empirically and by DSSP program and we identify DS with f_{DS} and write

$$DS = \left\{ \left(\boxed{\begin{matrix} x \\ e \end{matrix}} \right) : \quad f_{DS}(x) = e \right\}$$

- For example: if DS is such that a protein sequence

ARNVSTVVLA has the observed SS sequence HHHEEECCCHH

we put :

$$f_{DS}(\text{ARNVSTVVLA}) = \text{HHHEEECCCHH}$$ and write

$$\left(\boxed{\begin{matrix} \text{ARNVSTVVLA} \\ \text{HHHEEECCCHH} \end{matrix}} \right) \in DS$$

Tertiary Structure

- The tertiary structure of a protein is the arrangement in space of all its atoms
- The overall 3D shape of a protein molecule is a compromise, where the structure has the best balance of attractive and repulsive forces between different regions of the molecule
- For a given protein we can experimentally determine its tertiary structure by X-rays or NMR
- **Given the tertiary structure of a protein we can know its secondary structure with the DSSP program**

Protein Sequence Tertiary Structure **Symbolic Definition**

- Let $s \in (\mathcal{A}^*)^*$ denote a protein sequence,
- $\mathbf{P} = (s, e) \in \mathcal{F}$ be secondary structure of s, the element

$$\varphi_x = (\mathbf{P}, t_s)$$

is a tertiary structure of s

where t_s is the sequence' s s tertiary folding function

Quaternary Structure

- Many globular proteins are made up of several polypeptide chains called **sub-units**, stuck to each other by a variety of attractive forces but rarely by covalent bonds. Protein chemists describe this as **quaternary structure**.

Protein Quaternary Structure

- **Quaternary structure is a pair**

$$(\mathbf{Q}, f_Q)$$

- where **Q** **is a multiset of tertiary structures,**

(for example $Q=[\alpha , \alpha , \beta , \beta]$ in a haemoglobin) and

- f_Q **is the quaternary folding function**

Protein Symbolic Definition

PROTEIN **P** = { protein P primary structure, protein **P** sub-units, their secondary structures, their tertiary structure, their quaternary structure}

PROTEIN **P** = $\{x_1 \ldots x_n\,,\ (x_1,e_1)(x_2,e_2)..(x_n,e_n),$

$\alpha_{x1}=((x_1,e_1),\ t_{x1}) \ldots \quad \alpha_{xn}=((x_n,e_n),\ t_{xn}),$

$(\ [\alpha_{x1},\ldots\ \alpha_{xn}]\ ,\ f_{\alpha x1,\ldots\ \alpha xn})\ \}$

where x_i is protein **P** ith sub-unit, t_{xi} is x_i's tertiary folding function and $f_{\alpha x1,\ldots\ \alpha xn}$ is protein **P** quaternary folding function

Protein: Symbolic Definition

- In PSSP research we deal with protein sub-units (sequences) X_i, not with the whole sequence of sub-units $X1, X2, \ldots Xn$
- We write $\mathbf{P}_{Xk}$ when we refer only to the sub-unit X_k of the protein $\mathbf{P}$
- We write $\mathbf{P}_{(xi,\ ei)}$ when we refer to the sub-unit x_i of the protein $\mathbf{P}$ and its secondary structure
- We write $\mathbf{P}\ \alpha_{xi}$ when we refer to the sub-unit x_i of the protein $\mathbf{P}$ and its secondary structure

  and its tertiary structure

Protein sub-units

Given a protein **P** = $\{x_1 \ldots x_n,\ (x_1,e_1)(x_2,e_2)..(x_n,e_n),$

$\alpha_{x1}=((x_1,e_1),\ t_{x1}) \ldots \quad \alpha_{xn}= ((x_n,e_n),\ t_{xn}),\ (\ [\alpha_{x1},\ldots\ \alpha_{xn}]\ ,$
$f_{\alpha x1,\ldots\ \alpha xn})\ \}$

- **P**$_{xi} = \{\ xi\ \}$
- **P**$(xi,\ ei) = \{\ xi,\ (xi,\ ei)\ \}$
- **P**$_{\alpha xi} = \{\ xi,\ (xi,\ ei),\ \alpha_{xi} = ((x_i,e_i),\ t_{xi})\ \}$

Example: Haemoglobin

- Haemoglobin = $\{ x,y , (x,e_x), (y, e_y), \alpha = ((x,e_x), t_x) , \beta = ((y, e_y), t_y), ([\alpha , \alpha , \beta , \beta] , f_{\alpha , \beta}) \}$

Where $x,y \in A^*$, are called haemoglobin sub-units

Proteomic Databases

- The most important proteomic databases are:

  Swiss-Prot + TrEMBL

  PIR-PSD

  PIR-NREF

  PDB

Swiss-Prot + TrEMBL

Web site: *http://us.expasy.org/sprot/*

- Swiss-Prot is a protein sequence database with high level of annotations, a minimal level of redundancy and high level of integration with other databases. 124464 entries
- **TrEMBL** is a computer-annotated supplement of Swiss-Prot that contains all sequence entries not yet integrated in Swiss-Prot. 828210 entries

PIR-PSD

- Web site: *http://pir.georgetown.edu/*
- PIR-PSD: Protein Information Resource - Protein Sequence Database
- Founded in 1960 by Margaret Dayhoff
- Comprehensive and annotated protein sequence database in the public domain. 283308 entries

PIR-NREF

- Web site: *http://pir.georgetown.edu/*
- **PIR-NREF**: **PIR Non-Redundant Reference Protein Database**
- It contains all sequences in PIR-PSD, SwissProt, TrEMBL, RefSeq, GenPept, and PDB.
- **1,186,271 entries**
- The most used for finding protein profiles with PSI-BLAST program.
- **A mandatory in Protein Secondary Structure Prediction (PSSP) research**

PDB: Protein Data Bank

- Web site: *http://www.rcsb.org/pdb/*
- PDB contains 3-D biological macromolecular structure data
- 22-April-2003 => 20747 Structures
- How do we use PDB?
- All PSSP datasets start with some PDB sequences with known secondary structures. Then, with DSSP program we get the secondary structure and its reduction to three categories and use it as learning data for our algorithms

Protein Secondary Structure Prediction

- Techniques for the prediction of protein secondary structure provide information that is useful both in
- ab initio structure prediction and
- as an additional constraint for fold-recognition algorithms.
- Knowledge of secondary structure alone can help the design of site-directed or deletion mutants that will not destroy the native protein structure.
- For all these applications it is essential that the secondary structure prediction be accurate, or at least that, the reliability for each residue can be assessed.

Protein Secondary Structure Prediction

- If a protein sequence shows clear similarity to a protein of known three dimensional structure, then the most accurate method of predicting the secondary structure is to align the sequences by standard dynamic programming algorithms, as the homology modelling is much more accurate than secondary structure prediction for high levels of sequence identity.
- Secondary structure prediction methods are of most use when sequence similarity to a protein of known structure is undetectable.
- It is important that there is no detectable sequence similarity between sequences used to train and test secondary structure prediction methods.

PSSP Datasets

- Historic **RS126** dataset. Contains126 sub-units with known secondary structure selected by Rost and Sander. Today is not used anymore
- **CB513** dataset. Contains 513 sub-units with known secondary structure selected by Cuff and Barton in 1999. Very much used in PSSP research
- **HS17771** dataset. Created by Hobohm and Scharf. In March-2002 it contained 1771 sub-units
- This family of datasets are non redundant **PDB** (Protein Data Bank) subsets. Sub-units in the dataset never have an identity bigger than 25%.
- Lots of authors has their own and "*secret*" datasets

PSSP Algorithms

- There are three generations in PSSP algorithms
  - **First Generation**: based on statistical information of single aminoacids
  - **Second Generation**: based on windows (segments) of aminoacids. Typically a window containes 11-21 aminoacids
  - **Third Generation**: based on the use of windows on evolutionary information

PSSP: First Generation

- First generation PSSP systems are based on statistical information on a single aminoacid
- The most relevant algorithms:

  Chow-Fasman, 1974

  GOR, 1978
- Both algorithms claimed 74-78% of predictive accuracy, but tested with better constructed datasets were proved to have the predictive accuracy ~50% (Nishikawa, 1983)

PSSP: Second Generation

- Based on the information contained in a window of aminoacids (11-21 aa.)
- The most systems use algorithms based on:
  - Statistical information
  - Physico-chemical properties
  - Sequence patterns
  - Multi-layered neural networks
  - Graph-theory
  - Multivariante statistics
  - Expert rules
  - Nearest-neighbour algorithms
  - No Bayesian networks

PSSP: Second Generation

- **Main problems:**

  Prediction accuracy <70%

  Prediction accuracy for β-strand 28-48%

  Predicted chains are usually too short what leads do the difficult use of predictions

PSSP: Third Generation

- **PHD:** First algorithm in this generation (1994)
- Evolutionary information improves the prediction accuracy to 72%
- **Use of evolutionary information:**

1. Scan a database with known sequences with alignment methods for finding similar sequences
2. Filter the previous list with a threshold to identify the most significant sequences
3. Build aminoacid exchange profiles based on the probable **homologs** (most significant sequences)
4. The **profiles** are used in the prediction

PSSP: Third Generation

- Many of the second generation algorithms have been **updated to third** generation
- **The most important algorithms of today**

  Predator: Nearest-neighbour

  PSI-Pred: Neural networks

  SSPro: Neural networks

  SAM-T02: Homologs (Hidden Markov Models)

  PHD: Neural networks
- Due to the improvement of protein information in databases i.e. better evolutionary information, today's predictive accuracy is ~80%
- It is believed that maximum reachable accuracy is 88%

PSSP Data Preparation

- Public Protein Data Sets used in PSSP research contain protein secondary structure sequences. In order to use classification algorithms we must transform secondary structure sequences into classification data tables.
- Records in the classification data tables are called, in PSSP literature (learning) instances.
- **The mechanism used in this transformation process is called window.**
- **A window algorithm** has a secondary structure as input and returns a classification table: set of instances for the classification algorithm.

Window

- Consider a secondary structure (x, e).
- (x,e)= $(x_1x_2 ..x_n, e_1e_2…e_n)$
- **Window** of the length k chooses a **subsequence of length k** of $x_1x_2 ..x_n$, and **an element** $\mathbf{e_i}$ from $e_1e_2…e_n$, corresponding to a special position in the window, usually the middle
- **Window moves** along the sequences

  x = $x_1x_2 ..x_n$ and e= $e_1e_2…e_n$ simultaneously, starting at the beginning moving to the right one letter at the time at each step of the process.

Window: Sequence to Structure

- Such window is called **sequence to structure window.** We will call is for short **a window.**
- The process terminates when the window or its middle position reaches the end of the sequence x.

- The pair: (subsequence, element of e) is often written in a form **subsequence → H, E or C** is called **an instance**, or **a rule**.

Example: Window

- Consider a secondary structure (x, e) and the window of length 5 with the special position in the middle (bold letters)
- Fist position of the window is:

- x = A R **N** S T V V S T A A ….
- e = H H **H** H C C C E E E

- Window returns instance:
- A R **N** S T → **H**

Example: Window

- Second position of the window is:

- x = A R N **S** T V V S T A A ….
- e = H H H **H** C C C E E E

- Windows returns instance:
- R N **S** T V → **H**
- Next instances are:
- N S T V V → **C**
- S T V V S → **C**
- T V V S T → **C**

Symbolic Notation

- Let **f** be a protein secondary structure (PSS) identification function:
- $f : A^* \rightarrow S^*$ i.e. $f \subseteq A^* \mathrm{x}\ S^*$
- Let x= x1 x2 … xn, e= e1 e2 … en and
- f(x)= e, we define
- f(x1 x2 … xn)|{xi}= ei, i.e.
- **f(x)|{xi}= ei**

Example:Semantics of Instances

Let

- x = A R **N** S T V V S T A A ….
- e = H H **H** H C C C E E E

And assume that the windows returns an instance:

A R **N** S T → **H**

- Semantics of the instance is:

$$f(x)|\{N\}=H,$$

where f is the identification function and N is preceded by A R and followed by S T and the window has the length 5

Classification Data Base (Table)

- **We build the classification table** with attributes being the positions p1, p2, p3, p4, p5 .. pn in the window, where n is length of the window. The corresponding values of attributes are elements of of the subsequent on the given position.
- Classification attribute is **S** with values in the set {H, E, C} assigned by the window operation (instance, rule).
- The classification table for our example (fist few records) is the following.

Classification Table (Example)

- x = A R **N** S T V V S T A A ….
- e = H H **H** H C C C E E E

p1	p2	p3	p4	p5	**S**
A	R	N	S	T	**H**
R	N	S	T	V	**H**
N	S	T	V	V	**C**
S	T	V	V	S	**C**

Semantics of record r= r(p1, p2, p3,p4,p5, S) is :

$$f(x)|\{V_{p3}\} = V_{s}$$

where V_a denotes a value of the attribute a.

Missing Values

- **Missing values**: if we want to "cover" assignment of elements of S corresponding to all of the elements of the sequence x, we have to position the window with its middle position at the first element of x.
- In this case our classification table is (for our x and e)

  - x = A R **N** S T V V S T A A
  - e = H H **H** H C C C E E E

p1	p2	p3	p4	p5	S
		A	R	N	H
	A	R	N	S	H
A	R	N	S	T	H
R	N	S	T	V	H

Size of classification datasets (tables)

- The window mechanism produces very large datasets
- For example window of size 13 applied to the CB513 dataset of 513 protein subunits produces about

  70,000 records (instances)

Window

- **Window has the following parameters:**
- **PARAMETER 1** : $i \in N+$ (Natural numbers >0) , the starting point of the window as it moves along the sequence x= x1 x2 …. xn. The value i=1 means that window starts at x1, i=5 means that window starts at x5, etc.
- **PARAMETER 2**: $k \in N+$ denotes the size (length) of the window.
- For example:
- the PHD system of Rost and Sander (1994) uses two window sizes: 13 and 17.
- The BRNN (Bidirectional Recurrent Neural Networks) of Pollastri, Rost, Baldi and Przybylski (2002) use variable sizes of windows: 7,9,5 with additional windows (located on the "wheels") of sizes 3 , 4 or 2

Window

- **PARAMETER 3**: $p \in \{1, 2, \ldots, k\}$

- where p is a special position of the window that returns the classification attribute values from S ={H, E, C} and
- k is the size (length) of the window

- **PSSP PROBLEM:**

find optimal size k, optimal special position p for the best prediction accuracy

Window: Symbolic Definition

- WINDOW ARGUMENTS: window parameters and secondary structure (x,e)
- WINDOW VALUE: (subsequence of x, element of e)

- OPERATION (sequence – to –structure window)

W is a partial function

$$\mathbf{W}: \mathbf{N+} \times \mathbf{N+} \times \{\mathbf{1,\dots,\ k}\} \times (\mathbf{A}^{*} \times \mathbf{S}^{*}) \rightarrow \mathbf{A}^{*} \times \mathbf{S}$$

$$\mathbf{W}(\mathbf{i,\ k,\ p,\ (x,e)}) = (\mathbf{xi\ x(i+1)\dots.\ x(i+k-1),\ f(x)|\{x(i+p)\}})$$

where $(x,e) = (x_1 x_2 \, ..x_n, \, e_1 e_2 \dots e_n)$

Sequence Alignment

- We perform sequence alignment to know if two sequences are **homologs**
- **Homologs: sequences with the same 3D structure and function**
- Main aspects:
  1. **Alignment classes**: Gapped vs. ungapped, global vs. partial
  2. **Punctuation systems**: Substitution matrices
  3. **Alignment Algorithms**:
     1. Dynamic programming: Needleman-Wunsch, Smith-Waterman
     2. Heuristics: **BLAST, FASTA**

Example (ungrapped alignment)

(a)

```
HBA_HUMAN   GSAQVKGHGKKVADALV    Homologs
            G+ +VK+ HGKKV A+
HBB_HUMAN   GNPKVKAHGKKVLGAF
```

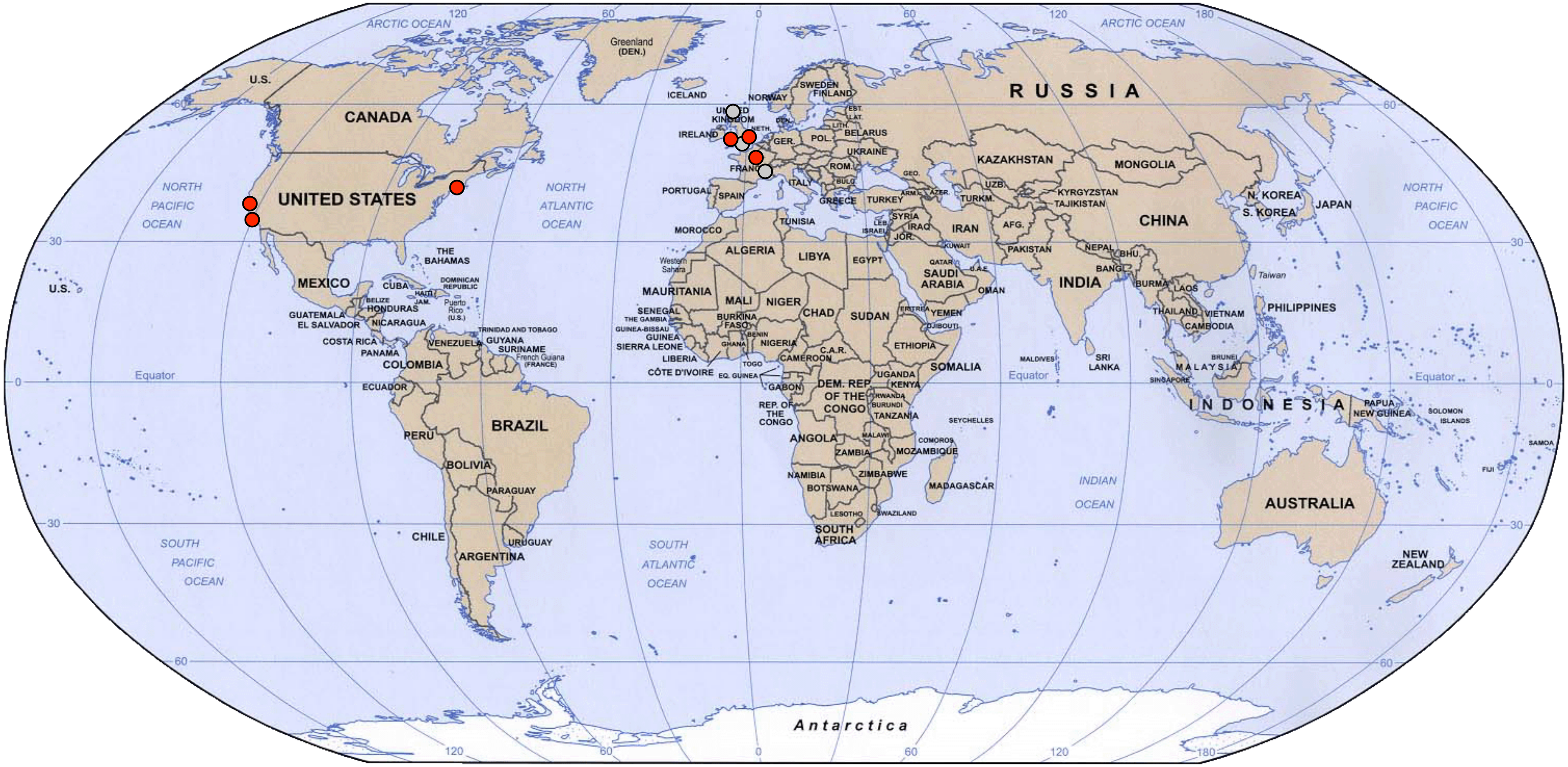
(b)

```
HBA_HUMAN   GSAQVKGHGKKVADAL     Homologs
            ++ ++++H+ KV    +
LGB2_LUPLU  NNPELQAHAGKVFKLV
```

(c)

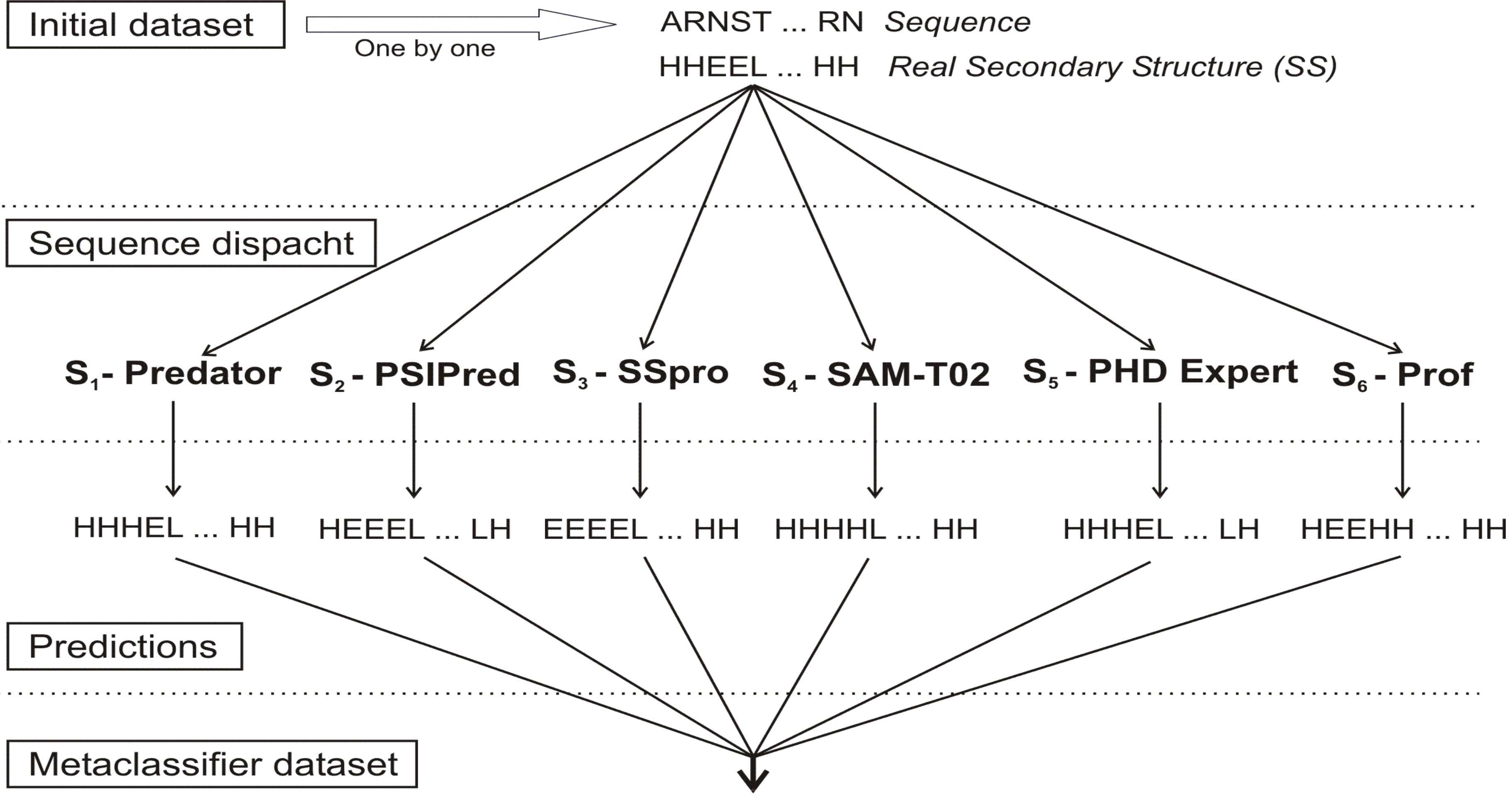
```
HBA_HUMAN   GSAQVKGHGKKVADAL     No homologs
            GS+ + G +   +D L
F11G11.2    GSGYLVGDSLTFVDLL
```

Metaclassifier: Many Servers



Metaclassifier: Some servers

NAME	LOCATION	PREDICTION METHOD	Q3 CB513	RESULTS
Predator	Institut Pasteur - Paris	Nearest neighbour	**80.0**	e-mail
PSIpred	Univ College London	Neural network	**79.9**	e-mail
Sspro	Univ California Irvine	Neural network	**79.1**	e-mail
SAM-T02	Univ California, Santa Cruz	Homologs	**78.1**	e-mail
PHD Exp	Columbia Univ, New York	Neural network	**77.6**	e-mail
Prof	Univ Wales	Neural network	**77.1**	e-mail
Jpred	Univ Dundee, Scotland	Consensum	73.4	e-mail
SOPM	Institute of Biology, Lyon	Homologs	66.8	web
GOR	Univ Southampton. UK	Information Theory	55.4	web



Initial dataset

One by one

ARNST ... RN *Sequence*

HHEEL ... HH *Real Secondary Structure (SS)*

Sequence dispacht

S_1- Predator **S_2 - PSIPred** **S_3 - SSpro** **S_4 - SAM-T02** **S_5 - PHD Expert** **S_6 - Prof**

Predictions

HHHEL ... HH HEEEL ... LH EEEEL ... HH HHHHL ... HH HHHEL ... LH HEEHH ... HH

Metaclassifier dataset

Creating the metaclassifier dataset

S_1	**S_2**	**S_3**	**S_4**	**S_5**	**S_6**	**SS**
H	H	E	H	H	H	*H*
H	E	E	H	H	E	*H*
E	E	E	H	H	E	*E*
E	E	E	H	E	H	*E*
L	L	L	L	L	H	*L*
...						...
H	L	H	H	L	H	*H*
H	H	H	H	H	H	*H*

Past Results

- The choice of servers is essential to the final results obtained by trained and tested meta classifiers.
- The experiments presented in *Bayesian Network Multi-classifiers for Protein Secondary Structure Prediction Artificial Intelligence in Medicine,2004; 31, pp. 117 – 136* *(Victor Robles, Pedro Larranaga, Jose M. Pena, Ernestina Menasalvas, Maria S. Perez, Vanessa Herves, Anita*
- *Wasilewska)*
- involved 4, 5, and 6 "hand selected" servers.
- It gave a 2-3% improvement in accuracy over the best single method and 15-20% over the worst.

Future Research

- Observe that we deal with a large amount of data.

- The 9 datasets available for training and testing provide a really (about 1,000,000 records) large, already well prepared, standardized, and publicly available set of data to experiment with.

- The meta classifiers data do not contain missing values, and other then the statistical methods (Bayes) can be used, unlike in the case of PSSP classifiers.

Future Research

- It is hence natural to explore also the non-statistical, descriptive methods.

- Additionally, these experiments could form a basis for a well founded research into comparison of statistical and non-statistical approaches.

- We refer interested readers to *Bayesian Network Multi-classifiers for Protein Secondary Structure Prediction Artificial Intelligence in Medicine,2004; 31, pp. 117 – 136* for detailed methods of evaluating obtained results.