7. Mining Biological Data

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7.1 Introduction

Motivation

Many biological processes are not well-understood

Biological knowledge is

- Highly complex
- Descriptive and experimental
  → Different from physics / chemistry

Wide availability of biological data

- Genome sequencing
- Protein sequencing
- Microarray expression data

Data mining methods to gain biological insights

7.1 Proteins

Function

Structural Proteins
- Building blocks of various tissues

Enzymes
- Catalyze chemical reactions

Transporters
- Carry chemical elements from one part of organism to another

Antibody Proteins
- Part of the immune system

7.1 Proteins

Structure

1D Structure
- Chains of amino-acids: AVFAMLCNFQDMAQSWKKKAVFAAGDE . . .
- 20 different amino-acids (one / three letter codes)
- Typical length of proteins: 3 to 400 amino-acids

Physico-chemical properties
- Hydrophic / hydrophile
- Charged / uncharged
- Polar / non-polar

same properties imply similarity of proteins

Amino-acid	**Three-Letter Code**	**One-Letter Code**	**Physico-chemical Properties**
Alanine	Ala	A	Hydrophobic
Lusine	Lys	K	Charged
Glutamine	Gln	Q	Polar
. . .	. . .	. . .	. . .

7.1 Proteins

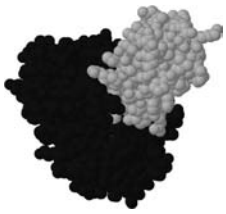
Structure

2D Structure

- Subsequences of the 1D structure form 2D structures such as sheets, strands, . . .

3D Structure

- Coordinates of the atoms in 3D space
- Known only for small subset of all sequenced proteins
- Protein surface important for many biological processes



Protein-Protein Docking

7.1 Proteins

Databases

Swiss-Prot (http://www.ebi.ac.uk/swissprot/)

- Proteins with their 1D structure
- Entries have been checked for sequencing errors
- Entries have a textual description (annotation): organism, function, references to publications, other related information
- Currently, 120‘960 entries

Protein Data Bank (PDB) (http://www.rcsb.org/pdb/)

- Proteins with their 1D, 2D and 3D structure
- Plus annotations
- Currently, 17‘828 protein entries

7.1 DNA (Desoxyribonucleic Acid)

Basics

Function

- Genetic information (genome)
- Codes proteins

Structure

- Chain of nucleotides (bases)
- Four different nucleotides:
  Adenine (A), Guanine (G), Cytosine (C), Thymine (T)
- Two interconnected parallel strands of nucleotides (double helix)
- Second strand is redundant

  DNA can be represented as sequence of nucleotides

7.1 DNA

DNA and Proteins

Structure

- Triplets of nucleotides code one amino-acid
- Genetic code: 64 different nucleotide triplets → 20 different amino-acids

  redundancy
- genome → chromosomes → genes → triplets
  = =
  protein amino-acid

Genes

- Protein coding region (exon / expressed region)
- Delimited by start / stop codons
- Largest part of genome is non-coding (introns)

  95% of human genome is non-coding

7.1 DNA

Mutations

Types

- Substitutions
  one base ←→ another base
- Insertions
  of one or more bases
- Deletions
  of one or more consecutive bases

At gene level or (less frequently) at protein level
Protein mutations may destroy function / create new function

7.1 Sequence Alignment

Goal

- Given two or more input sequences
- Identify similar sequences with long conserved subsequences

Method

- Use substitution matrices (probabilities of substitutions of amino-acids / bases) and probabilities of insertions and deletions
- *Optimal* alignment problem: NP-hard
- Heuristic method to find *good* alignments
- Many algorithms, e.g. BLAST
- Result:
  Alignment of the input sequences
  Similarity measures, score and % sequence identity (for two input sequences)

7.1 Sequence Alignment

Example

Input: ABFGRP, BDFLRP, AFRP

```
AB-FGRTP
-BDFLR-P          - gap
A--F-R-P
```

Output: abdFlR-P (capital letters conserved in all sequences)

→ Consensus sequence

7.1 Sequence Alignment

Example

Input: AAAAABBBBB, BBBBBAAAAA

Solution 1:

```
-----AAAAABBBBB
BBBBBAAAAA-----
```

Output: AAAAA

Solution 2:

```
-----BBBBBAAAAA
AAAAABBBBB-----
```

Output: BBBBB

→ One of the two domains (AAAAA, BBBBB) will always be missed

7.1 Mining Biological Data

Data Mining Tasks

Tissue classification from micro-array data

- Input: micro-array data for a small number of tissues from two classes (e.g., cancer and normal)
- Goals: (1) accurate classification and (2) discovery of responsible genes

Protein subcellular localization prediction

- Input: protein sequences with their subcellular localization types (e.g., cytoplasmic, periplasmic and extracellular)
- Goals: (1) accurate classification and (2) insight into the determining factors

7.1 Mining Biological Data

Data Mining Tasks

Protein secondary structure prediction

- Input: set of proteins with sequences and 3D structures
- Goal: accurate prediction of the (unknown) 3D structure based on the (known) sequence
  → Structure is a strong indicator of function

Detection of protein families

- Input: set of protein sequences
- Goal: hierarchical structure of protein superfamilies, families, . . .
  → Clustering problem

7.1 Mining Biological Data

Challenges

- Ambiguity of genetic and protein sequences
  Same sequence can have different functions, different sequences same function
- High percentage of noise
  Large portions of genetic data seem to carry no information
- Representation of sequence and 3D data
  No straightforward mapping to a feature space
- Integration of different datatypes
  Sequence, 3D, textual, micro-arrays, . . .
- High precision
  Required for biological applications
- Understandability of discovered knowledge (biological insights!)

7.2 Mining Frequent Sequential Patterns

Motivation

- Similar sequences have the same or similar function with a high probability
- Typically large portions of DNA or protein sequences are considered to be noise
- Sequential patterns determining the function are expected to be relatively short and to occur much more frequently than (random) noise patterns

Find *frequent* (sub)sequences / patterns

- Many frequent sequences
- Find only interesting frequent sequences

E.g., find *maximal* frequent patterns,
(all of its superpatterns are infrequent)

7.2 Mining Frequent Sequential Patterns

Approaches

Bottom-Up Enumeration

- Begin with empty pattern
- Extend in all possible ways
- If extension has minimum support, then continue extending it, else discard the extended pattern

A	B	D	K
AA	AD	DA	DD
	AAD		ADD

Top-Down Alignment

- Align all pairs of sequences
- Continue aligning the alignments until their support reaches minimum support

ABDDKA BADDKDFF BBADD

ADDK BADD

ADD

7.2 Frequent Sequential Patterns in Transactional Data

Overview

Data

- *Sequences* of transactions
- Transaction: *set* of items or attribute-value pairs (with timestamp)

Patterns

time t1 Later time t2

((T = 90F) → (H=60%, P=1.1atm))

attribute value item item item

item

itemset

- k-sequence: sequence /pattern with k items

  Examples: T1→H2P1T3→P2 and P1T2→H4P2T5 are 5-sequences

- S1 is subsequence of S2 (S1 ≤ S2)

  T1→P1T2 ≤ H1T1→P2→H2P1T2 (T1 ⊆ H1T1 , P1T2 ⊆ H2P1T2)

7.2 Frequent Sequential Patterns in Transactional Data

DATABASE

Lid	Time	Event	Lid	Time	Event	Lid	Time	Event	Lid	Time	Event
0	0	H2	4	0	H2	8	0	P1H2	12	0	T1
0	1	T2	4	1	T2	8	1	T2	12	1	H3P1
0	2	P3T3	4	2	P3T3	8	2	P3T3	12	2	P2
1	0	H2T3	5	0	T1	9	0	H2T3	13	0	T1
1	1	T2	5	1	H3P1	9	1	T2	13	1	H3P1
1	2	T3	5	2	P2	9	2	H1T3	13	2	P2
2	0	P1H2	6	0	T1	10	0	T1	14	0	H2
2	1	T2	6	1	H3P1	10	1	H3P1	14	1	T2
2	2	H1T3	6	2	P2	10	2	P2	14	2	T3
3	0	H2	7	0	T1	11	0	T1	15	0	T1
3	1	T2	7	1	H3P1	11	1	H3P1	15	1	H3P1
3	2	H1T3	7	2	P2	11	2	P2	15	2	P2

Example

FREQUENT SEQUENCES

Frequent 1-sequences		Frequent 2-sequences		Frequent 3-sequences	
H2	8	H2→T2	8	H2→T2→T3	8
H3	8	H2→T3	8	T1→H3P1	8
P1	8	T2→T3	8	T1→H3→P2	8
P2	8	T1→H3	8	T1→P1→P2	8
T1	8	T1→P1	8	H3P1→P2	8
T2	8	T1→P2	8		
T3	8	H3P1	8		
		H3→P2	8		
		P1→P2	8		

Frequent 4-sequences	
T1→H3P1→P2	8

7.2 Frequent Sequential Patterns in Transactional Data

GSP [Srikant & Agrawal 1996]

Problem Specification

- Sliding window model with maximum gap / minimum gap
- Item taxonomy / graph

Bottom-Up Enumeration

- Candidate generation

  Generate (join) *k*-candidates from two *k*-1 frequent patterns

  (a) (b) (c) and (b) (c) (d) → (a) (b) (c) (d)

- Support counting

  Hash-tree for storing candidates

  Transform data sequences using item taxonomy

7.2 Frequent Sequential Patterns in Transactional Data

Discussion

Breadth-first search

- Generate all *k*-1-patterns before starting with the *k*-candidates
- Number of patterns may become very large
  - → Not all candidates fit into memory

Support counting

- Requires one DB scan for each level / length of patterns
- Very expensive operation
  - → Need more efficient method

7.2 Frequent Sequential Patterns in Transactional Data

SPADE [Zaki 2001]

Depth-first search

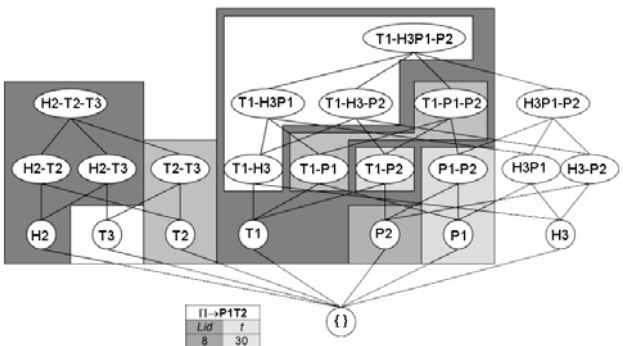
- Extend a frequent *k*-sequence until it becomes infrequent before considering another *k*-sequence
- Need only the path from the root of the lattice (of all patterns) to the current sequence in main memory

Less pruning possible

Vertical representation

- For a candidate sequence, store list of occurrences (sequence, position) or (lid, time) resp.
- Initially, representation of the database:
  For each 1-sequence, store its occurrences
- Support counting: merge of two lists → no DB access

7.2 Frequent Sequential Patterns in Transactional Data



Example

T1→H3P1→P2	
Lid	t
5	2
6	2
7	2
10	2
11	2
12	2
13	2
15	2

T1→H3P1	
Lid	t
5	1
6	1
7	1
10	1
11	1
12	1
13	1
15	1

T1→H3→P2	
Lid	t
5	2
6	2
7	2
10	2
11	2
12	2
13	2
15	2

T1→H3	
Lid	t
5	1
6	1
7	1
10	1
11	1
12	1
13	1
15	1

T1→P1	
Lid	t
5	1
6	1
7	1
10	1
11	1
12	1
13	1
15	1

T1	
Lid	t
5	0
6	0
7	0
10	0
11	0
12	0
13	0
15	0

H3	
Lid	t
5	1
6	1
7	1
10	1
11	1
12	1
13	1
15	1

P1	
Lid	t
2	0
5	1
6	1
7	1
8	0
10	1
11	1
12	1
13	1
15	1

P2	
Lid	T
5	2
6	2
7	2
10	2
11	2
12	2
13	2
15	2

Π→P1T2	
Lid	t
8	30
8	50
8	80

Π→P1	
Lid	t
1	20
1	30
1	40
4	60
7	40
8	10
8	30
8	50
8	80
13	50
13	70
15	60
17	20
20	10

Π→T2	
Lid	t
1	70
1	80
3	10
5	70
8	30
8	40
8	50
8	80
11	30
13	10
16	80
20	20

Π→T2→P1	
Lid	t
8	50
8	80
13	50
13	70

Π→P1→T2	
Lid	T
1	70
1	80
8	30
8	40
8	50
8	80

7.2 Frequent Sequential Patterns in Transactional Data

Comparison with Mining Biological Data

- Data is sequences of *sets* of items instead of sequences of single symbols.
- Sequential order represents *temporal*, not spatial relationship.
- *Many short* data sequences, instead of few long ones.
- *No explicit gaps* in patterns (gaps do not matter).
- Typically, these methods discover *all* frequent patterns.

7.2 Frequent Sequential Patterns in Biological Data

Pattern Types

Concrete patterns

- Strings from the alphabet Σ (nucleotides or amino-acids)

  ABDAWWF

With rigid gaps

- Introduce "." (matches *one* arbitrary symbol from Σ)

  A. . .BDA..W.WF

With unrestricted gaps

- Introduce "*" (matches *zero or more* arbitrary symbols from Σ)

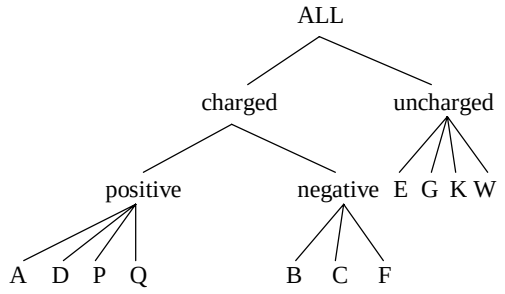
  ABD*AWW*F

7.2 Frequent Sequential Patterns in Biological Data

Pattern Types

With concepts

- Introduce concepts (subsets of Σ), e.g. "unchargedBLLApositivenegative"
- With a tree structure or even a graph structure



7.2 Frequent Sequential Patterns in Biological Data

TEIRESIAS [Rigoutsos & Floratos 1998]

- Pattern class: Σ (Σ U {'.'})* Σ

  e.g. A.CH..E or SA.CH..E

- Restricted to <l,w> patterns with l <= w: every subpattern of length w or more contains at least l symbols from Σ

  patterns must be "dense enough"

- Finds all *maximal* <l,w> patterns with support of at least *min-supp*

7.2 Frequent Sequential Patterns in Biological Data

Method

Scanning phase

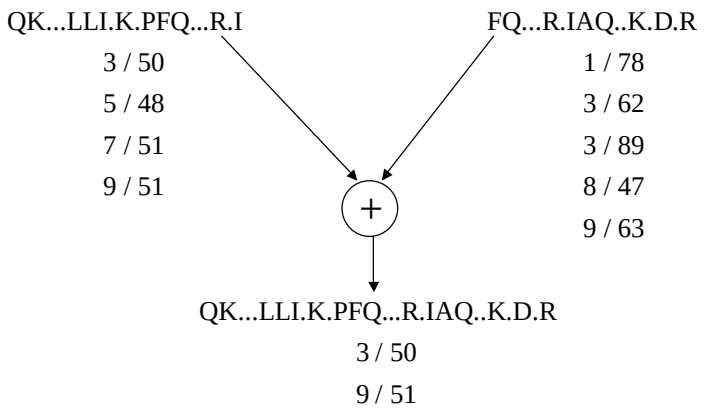
- Determine all elementary patterns: frequent <l,w> patterns with exactly l symbols from Σ
- Ex.: <3,4> patterns F.AS, AST, AS.S, STS, A.TS

Convolution phase

- Join pairs of elementary patterns P1 and P2 where the suffix of P1 is identical to the prefix of P2 (convolution)
- Ex.: F.AS and AST → F.AST and AST
  F.AST and STS → F.ASTS

7.2 Frequent Sequential Patterns in Biological Data

Example



7.2 Frequent Sequential Patterns in Biological Data

Discussion

Properties

- Can extend patterns by more than one symbol at a time
- Maximal patterns generated before non-maximal subpatterns
- Compare new frequent pattern with all frequent patterns already discovered
  - → Use hash table to efficiently locate superpatterns
- Returns only maximal patterns
- Generates all such patterns
- Can also handle concept trees / graphs

7.2 Frequent Sequential Patterns in Biological Data

Top-Down Alignment Method [Martinez 1988]

- Align all pairs of input sequences
- Pairwise alignments have (at least) a support of two
- Score all pairwise alignments and order them according to decreasing score

  place similar alignments close together
- Iteratively, keep aligning the alignments

  until their support reaches minimum support

7.2 Frequent Sequential Patterns in Biological Data

Other Alignment Methods

- Use pairwise alignments to create dendrogram
  and apply hierarchical clustering algorithm
- Perform multiple sequence alignment
  and create consensus sequence directly

Generates only one pattern (consensus pattern)

7.3 Sequence Classification

Overview

Feature Selection

Support Vector Machines (SVM)

- Application for sequence classification

Markov Models

- Markov chains
- Hidden Markov models

7.3 Sequence Classification

Types of Features

Amino-acid / Nucleotide Composition

- 20 dim. / 4 dim. vectors

Physico-chemical properties

- Hydrophobicity, charge, polarity, size, . . .

Subsequences

- All possible subsequences of length *k*
- All frequent subsequences

7.3 Sequence Classification

Feature Selection

Method

- Measure the *relevance* of features w.r.t. classification:

  T-test for continuous attributes $t = \frac{\mu_1 - \mu_2}{\sigma}$

  Mutual information for categorical attributes

- Consider the *redundancy* of features

  Minimize correlation among selected features

  → Weighted combination of relevance and redundancy

- Greedily, select top *k* features

7.3 Sequence Classification

SVM for Protein Classification [Leslie et al 2002]

- Two sequences are similar when they share many common substrings (subsequences)
- $K(x, x') = \sum_{s \text{ common substring}} \lambda^{|s|}$ where λ is a parameter

  and |s| denotes the length of string s

- Very high classification accuracy for protein sequences
- Variation of the kernel (when allowing gaps)

$$K(x, x') = \sum_{s \text{ common substring}} \lambda^{length(s,x)+length(s,x')}$$

length(s,x): length of the subsequence of x matching s

7.3 Sequence Classification

SVM for Prediction of Translation Initiation Sites [Zien et al 2000]

- Translation initiation site (TIS): starting position of a protein coding region in DNA

  all TIS start with the triplet "ATG"
- Problem: given an "ATG" triplet, does it belong to a TIS?
- Representation of DNA

  window of 200 nucleotides around candidate "ATG"

  encode each nucleotide with a 5 bit word (00001, 00010, . . ., 10000) for

  A, C, G, T and unknown

  → Vectors of 1000 bits

7.3 Sequence Classification

SVM for Prediction of Translation Initiation Sites

- Kernels

  $K(x, x') = (\mathrm{x.x'})^d$ d = 1: number of common bits

  d = 2: number of common pairs of bits

  . . .

  locally improved kernel: compare only small window around "ATG"
- Experimental results

  long range correlations do not improve performance

  locally improved kernel performs best

  outperforms state-of-the-art methods

7.3 Sequence Classification

Markov models

- Markov chains (Markov models)

  Symbol in a sequence depends only on its preceding symbol(s)

  Can be used for classification

  [Deshpande & Karypis 2002]

- Hidden Markov Models

  Symbol in a sequence depends on a hidden state

  State depends on preceding state

7.3 Sequence Classification

1-order Markov Chains

- For each class, determine the conditional probabilities $P(s_i|s_j)$

  → For each pair of symbols s_i and s_j

- For each class c_i, calculate the probability $P(s|\ c_i)$

  of observing the given sequence $s = s_1 s_2 \cdots s_L$

$$P(s \mid c_i) = P(s_L \mid s_{L-1}, c_i) \cdot \cdots \cdot P(s_2 \mid s_1, c_i) \cdot P(s_1 \mid c_i)$$

- Choose the class with the highest likelihood
- Decision function for two classes (+ and -)

$$f(s) = \sum_{i=1}^{L} \log \frac{P(s_i \mid s_{i-1}, +)}{P(s_i \mid s_{i-1}, -)}$$

7.3 Sequence Classification

Higher-order Markov Chains

Idea

- Symbol in a sequence depends on all its *k* preceding symbols

Discussion

- In general: higher classification accuracy than 1-order Markov chains
- But

Exponential number of transition probabilities

Hard to accurately estimate these probabilities

7.3 Sequence Classification

Hidden Markov Models

- Goal: distinguish patterns (motifs) from background in a sequence

  motif: relatively short highly conserved region in a biological sequence
- Hidden Markov Model (HMM)

  Generative process for motifs/patterns of length L with

  consensus pattern (motif)

  noise level ε

  frequency F
- Hidden states: one for each position of the motif, one for the background

  Determines the next symbol to be generated (multinomial distribution)

  Determines the next state (transition probabilities)

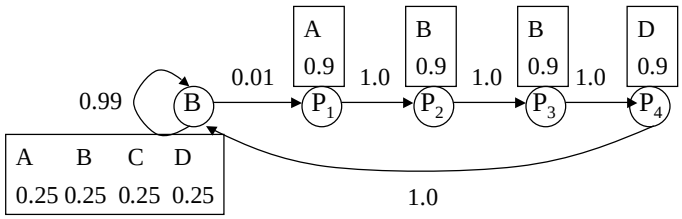
7.3 Sequence Classification

Basics

- Background state: probability of symbols = frequency in background
- Pattern states $P_i, 1 \le i \le L$

  Symbol at position *i* in consensus pattern: probability $1-\varepsilon$

  Other symbols: probability ε
- Example (consensus pattern ABBD, uniform background)



7.4 Sequence Clustering

Overview

Alignment-Based Methods

- Pairwise alignment allows to define similarity / distance
- Hierarchical agglomerative clustering
- Connected components of graph

Frequent-Sequence-Based Methods

- No alignment, but mining of frequent subsequences
- Use vector space model and any applicable algorithm

7.4 Sequence Clustering

Alignment-Based Methods

Hierarchical agglomerative clustering [Barton & Sternberg 1987]

- Perform all pairwise alignments
- Define appropriate similarity measure:

  percentage identity, normalised alignment score (raw score divided by the length of the alignment), etc.
- Apply agglomerative hierarchical clustering

Runtime complexity > $O(n^2)$

7.4 Sequence Clustering

Alignment-Based Methods

Connected components of graph [Bolten et al 2000]

- Homologue proteins: share an ancestor
- Many homologue proteins do not have a significant sequence similarity
- Need to consider transitivity of homology
- Construct a graph: nodes = sequences, edges = significant sequence similarity
- Clusters: connected components of this graph

→ Runtime for clustering SwissProt: 600 CPU days

7.4 Sequence Clustering

Frequent-Sequence-Based Methods

Method [Guralnik & Karypis 2001]

- Determine all frequent subsequences
- Efficiently select relevant subset of these sequences (features)
- Count occurrences of features (vector space model)
- Apply any clustering algorithm for vector spaces

  e.g. *k*-means

  Very efficient

  But feature selection is difficult

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