Kernel methods in computational biology: Three examples

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Outline

1. SVM and kernel methods
2. Gene function prediction from phylogenetic profiles
3. Remote protein homology detection
4. Detection of active metabolic pathways from gene expression data
Part 1

SVM and kernel methods
Support vector machines

- Objects to classify $x$ mapped to a feature space
- Largest margin separating hyperplane in the feature space
The kernel trick

- Implicit definition of $x \rightarrow \Phi(x)$ through the kernel:

$$K(x, y) \overset{def}{=} < \Phi(x), \Phi(y)>$$
The kernel trick

- Implicit definition of $x \rightarrow \Phi(x)$ through the kernel:

$$K(x, y) \overset{def}{=} < \Phi(x), \Phi(y) >$$

- Simple kernels can represent complex $\Phi$
The kernel trick

- Implicit definition of \( x \rightarrow \Phi(x) \) through the kernel:

\[
K(x, y) \overset{\text{def}}{=} < \Phi(x), \Phi(y) >
\]

- Simple kernels can represent complex \( \Phi \)

- For a given kernel, not only SVM but also clustering, PCA, ICA... possible in the feature space = kernel methods
Part 2

Gene function prediction from phylogenetic profiles

*(ISMB 02)*
Mini introduction

- **Genes** are small parts of the DNA which encode proteins.
- About 6,000 genes in the baker yeast, 30,000 in human
- The **sequences** of the genes are (almost) known (sequencing projects)
- Next big challenge: understand their **functions**
• The phylogenetic profile of a gene is a vector of bits which indicates the presence (1) or absence (0) of the gene in every fully sequenced genome.

<table>
<thead>
<tr>
<th>Gene</th>
<th>human</th>
<th>yeast</th>
<th>HIV</th>
<th>E. coli</th>
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<tr>
<td>YAL001C</td>
<td>1</td>
<td>1</td>
<td>.</td>
<td>0</td>
</tr>
<tr>
<td>YAB002W</td>
<td>0</td>
<td>0</td>
<td>.</td>
<td>0</td>
</tr>
<tr>
<td>:</td>
<td>:</td>
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<td>:</td>
</tr>
</tbody>
</table>

• Can be estimated *in silico* by sequence similarity search
From profile to function

- Genes are likely to be transmitted together during evolution when they participate:
  - to a common structural complex,
  - to a common pathway.

- Consequently genes with similar phylogenetic profiles are likely to have similar functions

- How to infer the function from the profile?
Naive approach

- Count the number of bits in common:

\[
\begin{array}{cccccccc}
  x & 1 & 1 & 0 & 1 & 0 & 0 & 0 & 1 & 1 & 0 \\
  y & 1 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 1 \\
\end{array}
\]

\[s(x, y) = 5\]

- Cluster or use k-NN for gene function prediction with this similarity measure (Pellegrini et al., 1999)
What is not used in the naive approach

The knowledge of the phylogenetic tree.
A possible **pattern of transmission** during evolution defined by a rooted subtree with nodes labeled 0 or 1.
Evolution patterns and phylogenetic profiles

Is it the true story? We don’t know, but…
Probabilistic model of gene transmission

- The phylogenetic tree as a tree graphical model

- Simplified model:
  - $P(1) = 1 - P(0) = 0.9$, at the root,
  - Along each branch transmission follows the transition matrix:

$$
\begin{pmatrix}
0.9 & 0.1 \\
0.1 & 0.9
\end{pmatrix}
$$
Probabilistic assignment of evolution pattern

For a phylogenetic profile $x$ and an evolution pattern $e$:

- $P(e)$ quantifies how “natural” the pattern is
- $P(x|e)$ quantifies how likely the pattern $e$ is the “true history” of the profile $x$
Representation of a profile in terms of evolution patterns

- Consider all possible evolution patterns \( (e_1, \ldots, e_N) \), and represent each gene \( x \) by the vector:

\[
\Phi(x) = \left( \sqrt{P(e_1)P(x|e_1)}, \ldots, \sqrt{P(e_N)P(x|e_N)} \right)
\]

- Comparing \( \Phi(x) \) and \( \Phi(y) \) gives a precise idea of which evolution patterns are shared or not by \( x \) and \( y \).
Comparing two profiles through evolution patterns
Tree kernel

- Kernel methods (SVM, kernel-PCA, kernel-clustering...) only require the computation of the kernel function:

\[ K(x, y) = \Phi(x) \cdot \Phi(y). \]

- In our case we obtain the tree kernel:

\[ K(x, y) = \sum_e P(e)P(x|e)P(y|e), \]

where the sum is over all possible evolution patterns.
Kernel computation: trick 1

- For any given pattern $e$, the term:

$$\alpha(e) = P(e)P(x|e)P(y|e)$$

can be factorized and computed *recursively* by working up the tree from the leaves.

- Classical trick for computing likelihood with tree graphical models, cf. Felsenstein’s algorithm.
Kernel computation: trick 2

- The sum

\[ \sum_{e} \alpha(e) \]

over all subtrees can also be factorized and computed recursively by working up the tree from the leaves.

- Similar in spirit to the Context Tree Weighting algorithm (Willems et al., 1995).
Combining tricks

- Both tricks can be combined
- $K(x, y)$ can be computed by two post-order traversals of the tree
- The complexity is linear with the length of the profile.
Gene function prediction with SVM

- Profiles for 2465 genes of *S. Cerevisiae* were computed by BLAST search (cf Pavlidis et al. 2001), using 24 genomes.

- Consensus phylogenetic tree (cf. Liberles et al. 2002) with simplified probabilistic model of gene transmission

- SVM trained to predict all functional classes of the MIPS catalog with at least 10 genes (cross-validation)

- Comparison of the tree kernel with the naive kernel
## Results (ROC 50)

<table>
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<tr>
<th>Functional class</th>
<th>Naive kernel</th>
<th>Tree kernel</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amino-acid transporters</td>
<td>0.74</td>
<td>0.81</td>
<td>+ 9%</td>
</tr>
<tr>
<td>Fermentation</td>
<td>0.68</td>
<td>0.73</td>
<td>+ 7%</td>
</tr>
<tr>
<td>ABC transporters</td>
<td>0.64</td>
<td>0.87</td>
<td>+ 36%</td>
</tr>
<tr>
<td>C-compound transport</td>
<td>0.59</td>
<td>0.68</td>
<td>+ 15%</td>
</tr>
<tr>
<td>Amino-acid biosynthesis</td>
<td>0.37</td>
<td>0.46</td>
<td>+ 24%</td>
</tr>
<tr>
<td>Amino-acid metabolism</td>
<td>0.35</td>
<td>0.32</td>
<td>- 9%</td>
</tr>
<tr>
<td>Tricarboxylic-acid pathway</td>
<td>0.33</td>
<td>0.48</td>
<td>+ 45%</td>
</tr>
<tr>
<td>Transport Facilitation</td>
<td>0.33</td>
<td>0.28</td>
<td>- 15%</td>
</tr>
</tbody>
</table>
A insight into the feature space

- PCA can be performed implicitly in the feature space with a kernel function: kernel-PCA (Scholkopf et al. 1999)
- Projecting the genes on the first principal components gives an idea of the shape of the features space
Naive kernel PCA

- Amino-acid transporters
- Fermentation
- ABC transporters
- C-compound, carbohydrate transport
Tree kernel PCA

- Amino-acid transporters
- Fermentation
- ABC transporters
- C–compound, carbohydrate transport
Extensions

- $X_1, \ldots, X_n$ discrete r.v.
- $I_1, \ldots, I_v \subset \{1, \ldots, n\}$ a family of subsets
- Interpolated kernel:

$$K(x, y) = \frac{1}{v} \sum_{i=1}^{v} p(x_{I_i}) p(y_{I_i}) \times p(x_{I_i^c}) \delta(x_{I_i^c}, x_{I_i^c})$$
Property 1

This kernel interpolates between the diagonal kernel:

\[ K_{\text{diag}}(x, y) = p(x)\delta(x, y) \]

and the product kernel:

\[ K_{\text{prod}}(x, y) = p(x)p(y). \]
Property 2

Two objects $x$ and $y$ get closer in the feature space when they share rare common subparts:

$$K(x, y) = K_{\text{prod}}(x, y) \times \frac{1}{v} \sum_{i=1}^{v} \frac{\delta(x_{I_i}, y_{I_i})}{p(x_{I_i})}$$
Linear-time implementations

- iid r.v., all possible subsets ($PSB \ 02$):

  \[ X_1 \ \ X_2 \ \ X_3 \ \ X_4 \ \ X_5 \]
Linear-time implementations

- iid r.v., all possible subsets \((PSB 02)\):

- Markov model, common blocks
Linear-time implementations

- Tree graphical model, common rooted subtrees
Linear-time implementations

- Tree graphical model, common subtrees
Remote protein homology detection

(with S. Hiroto, N. Ueda, T. Akutsu, preprint 2003)
Motivations

- Develop a **kernel for strings** adapted to protein / DNA sequences
- Several methods have been adopted in bioinformatics to measure the similarity between sequences... but are not valid kernels
- How to mimic them?
Local alignment

- For two strings $x$ and $y$, a local alignment $\pi$ with gaps is:

```
ABCD  EF----G--HI  JKL
  |    |    |    |
MNO  EFPORGSI  TUVWX
```

- The score is:

$$s(x, y, \pi) = s(E, E) + s(F, F) + s(G, G) + s(I, I) - s(gaps)$$
Smith-Waterman (SW) score

\[ SW(x, y) = \max_{\pi \in \Pi(x, y)} s(x, y, \pi) \]

- Computed by dynamic programming
- Not a kernel in general
Convolution kernels (Haussler 99)

- Let $K_1$ and $K_2$ be two kernels for strings.
- Their convolution is the following valid kernel:

$$K_1 * K_2(x, y) = \sum_{x_1x_2 = x, y_1y_2 = y} K_1(x_1, y_1)K_2(x_2, y_2)$$
3 basic kernels

- For the unaligned parts: $K_0(x, y) = 1$. 
3 basic kernels

- For the unaligned parts: $K_0(x, y) = 1$.
- For aligned residues:

$$K_\alpha^{(\beta)}(x, y) = \begin{cases} 
0 & \text{if } |x| \neq 1 \text{ or } |y| \neq 1, \\
\exp(\beta s(x, y)) & \text{otherwise}
\end{cases}$$
3 basic kernels

- For the unaligned parts: \( K_0(x, y) = 1 \).

- For aligned residues:

\[
K^{(\beta)}_a(x, y) = \begin{cases} 
0 & \text{if } |x| \neq 1 \text{ or } |y| \neq 1, \\
\exp(\beta s(x, y)) & \text{otherwise}
\end{cases}
\]

- For gaps:

\[
K^{(\beta)}_g(x, y) = \exp[\beta (g(|x|) + g(|y|))]
\]
Combining the kernels

- Detecting local alignments of exactly \( n \) residues:

\[
K^{(\beta)}_{(n)}(x, y) = K_0 \star \left( K^{(\beta)}_a \star K^{(\beta)}_g \right)^{(n-1)} \star K^{(\beta)}_a \star K_0.
\]
Combining the kernels

- Detecting local alignments of exactly $n$ residues:
  \[
  K^{(\beta)}_{(n)}(x, y) = K_0 \ast \left( K_a^{(\beta)} \ast K_g^{(\beta)} \right)^{(n-1)} \ast K_a^{(\beta)} \ast K_0.
  \]

- Considering all possible local alignments:
  \[
  K_{LA}^{(\beta)} = \sum_{i=0}^{\infty} K_{(i)}^{(\beta)}.
  \]
Properties

\[ K^{(\beta)}_{LA}(x, y) = \sum_{\pi \in \Pi(x, y)} \exp(\beta s(x, y, \pi)), \]
Properties

\[ K^{(\beta)}_{LA}(x, y) = \sum_{\pi \in \Pi(x, y)} \exp (\beta s(x, y, \pi)), \]

\[ \lim_{\beta \to +\infty} \frac{1}{\beta} \ln K^{(\beta)}_{LA}(x, y) = SW(x, y). \]
Kernel computation
SCOP superfamily recognition benchmark
Part 3

Detection of active metabolic pathways from gene expression data

(NIPS 02)
Genes encode proteins which can catalyse chemical reactions

Nicotinamide Mononucleotide Adenylyltransferase With Bound Nad+
Chemical reactions are often parts of pathways

From http://www.genome.ad.jp/kegg/pathway
Microarray technology monitors RNA quantity

(From Spellman et al., 1998)
Comparing gene expression and protein network

Gene network

Expression profiles

Are there “correlations”?
Pattern of expression

- In yellow: a candidate pattern, and the correlation coefficient with each gene profile.
Pattern smoothness

-0.8
+0.1
+0.2
+0.4
+0.5
-0.4
-0.7
-0.8
+0.8
+0.2
+0.4
+0.5
+0.8

- The correlation function with interesting patterns should vary smoothly on the graph
Pattern relevance

- Interesting patterns involve many genes
- The projection of profiles onto an interesting pattern should capture a lot of variations among profiles
- Relevant patterns can be found by PCA
Problem

Find patterns of expression which are \textit{simultaneously}

- smooth
- relevant
From kernels to RKHS

- To each kernel $K$ is associated a reproducing kernel Hilbert space (RKHS), subset of $\mathbb{R}^\mathcal{X}$, defined as the completion of:

$$\text{span}\{K(x, .), x \in \mathcal{X}\}.$$

- The norm of a function $f = \sum_i a_i K(x_i, .)$ in the RKHS is:

$$\|f\|_\mathcal{H} = \sum_{i,j} a_i a_j K(x_i, x_j).$$
Pattern relevance

• Let $e(x)$ the profile of gene $x$

• Let $K_1(x, y) = e(x).e(y)$ be the linear kernel, with RKHS $H_1$.

• The norm $||.||_{H_1}$ is a relevance functional: the relevance of $f \in H_1$ increases when the following decreases:

\[
\frac{||f||_{H_1}}{||f||_{L_2}}
\]
Pattern smoothness

- Let $K_2(x, y)$ be the diffusion kernel obtained from the gene network, with RKHS $H_2$.

- It can be considered as a discretized version of a Gaussian kernel (solving the heat equation with the graph Laplacian)

- The norm $\| \cdot \|_{H_2}$ is a smoothness functional: the smoother a function $f : \mathcal{X} \to \mathbb{R}$, the larger the function:

\[
\frac{\| f \|_{H_1}}{\| f \|_{L_2}}
\]
Problem reformulation

Find a linear function $f_1$ and a function $f_2$ such that:

- $f_1$ be relevant: $\frac{||f_1||_{L^2}}{||f_1||_{H_1}}$ be large
- $f_2$ be smooth: $\frac{||f_2||_{L^2}}{||f_2||_{H_2}}$ be large
- $f_1$ and $f_2$ be correlated:

$$\frac{f_1 \cdot f_2}{||f_1||_{L^2} ||f_2||_{L^2}}$$

be large
Problem reformulation (2)

The three goals can be combined in the following problem:

\[
\max_{f_1, f_2} \frac{f_1 \cdot f_2}{\left( \|f_1\|_{L_2}^2 + \delta \|f_1\|_{H_1}^2 \right)^{\frac{1}{2}} \left( \|f_2\|_{L_2}^2 + \delta \|f_2\|_{H_2}^2 \right)^{\frac{1}{2}}}
\]

where the parameter \( \delta \) controls the trade-off between relevance/smoothness on the one hand, correlation on the other hand.
Solving the problem

This formulation is equivalent to a generalized form of CCA (Kernel-CCA, Bach and Jordan, 2002), which is equivalent to the following generalized eigenvector problem

\[
\begin{pmatrix}
0 & K_1 K_2 \\
K_2 K_1 & 0
\end{pmatrix}
\begin{pmatrix}
\alpha \\
\beta
\end{pmatrix}
= \rho
\begin{pmatrix}
K_1^2 + \delta K_1 & 0 \\
0 & K_2^2 + \delta K_2
\end{pmatrix}
\begin{pmatrix}
\alpha \\
\beta
\end{pmatrix}
\]
Summary

Diffusion kernel

Kernel CCA

Linear kernel
Data

- **Gene network**: two genes are linked if the catalyze successive reactions in the KEGG database

- **Expression profiles**: 18 time series measures for the 6,000 genes of yeast, during two cell cycles
First pattern of expression
Related metabolic pathways

50 genes with highest $s_2 - s_1$ belong to:

- Oxidative phosphorylation (10 genes)
- Citrate cycle (7)
- Purine metabolism (6)
- Glycerolipid metabolism (6)
- Sulfur metabolism (5)
- Selenoaminoacid metabolism (4), etc...
Related genes
Related genes

Sulfur metabolism: reduction and fixation

- Sulfate
- Adenylylsulfate (APS)
- 3'-Phosphoadenylylsulfate (PAPS)
- Sulfite
- Thiosulfate
- Trithionate
- H2S
Related genes
Opposite pattern
Related genes

- RNA polymerase (11 genes)
- Pyrimidine metabolism (10)
- Aminoacyl-tRNA biosynthesis (7)
- Urea cycle and metabolism of amino groups (3)
- Oxidative phosphorylation (3)
- ATP synthesis(3), etc...
Related genes

RNA polymerase II (Saccharomyces cerevisiae)

Eukaryotic Pol II

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<th>B3</th>
<th>B4</th>
<th>B5</th>
<th>B6</th>
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Eukaryotic Pol III

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Eukaryotic Pol I

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<th>A49</th>
</tr>
</thead>
</table>
Related genes
Related genes

UREA CYCLE AND METABOLISM OF AMINO GROUPS

Amino acid metabolism

Purine metabolism

Glutamate metabolism

N-acetylimidazole

N-acetylglutamate

N-acetylglutamate semialdehyde

N-Acetylglutamate semialdehyde

L-Glutamate 5-semiaaldehyde

L-Glutamyl-P

Glutamate

1.4.1.3

2.3.1.1

2.7.2.11

2.6.1.13

3.5.1.16

3.5.1.14

2.3.1.35

2.6.1.69

2.6.1.11

1.2.1.38

1.2.1.41

6.3.4.16
Extensions

- Can be used to **extract features** from expression profiles (preprint 2002)

- Can be generalized to **more than 2 datasets** and other kernels

- Can be used to extract **clusters of genes** (e.g., operon detection, *ISMB 03* with Y. Yamanishi, A. Nakaya and M. Kanehisa)
Conclusion
Conclusion

- Kernels offer a versatile framework to represent biological data
- Increasing library of kernels and kernel methods
- Encouraging results on real-world applications
- Candidate to play an important role in learning from heterogeneous data