Probabilistic kernels for structured objects

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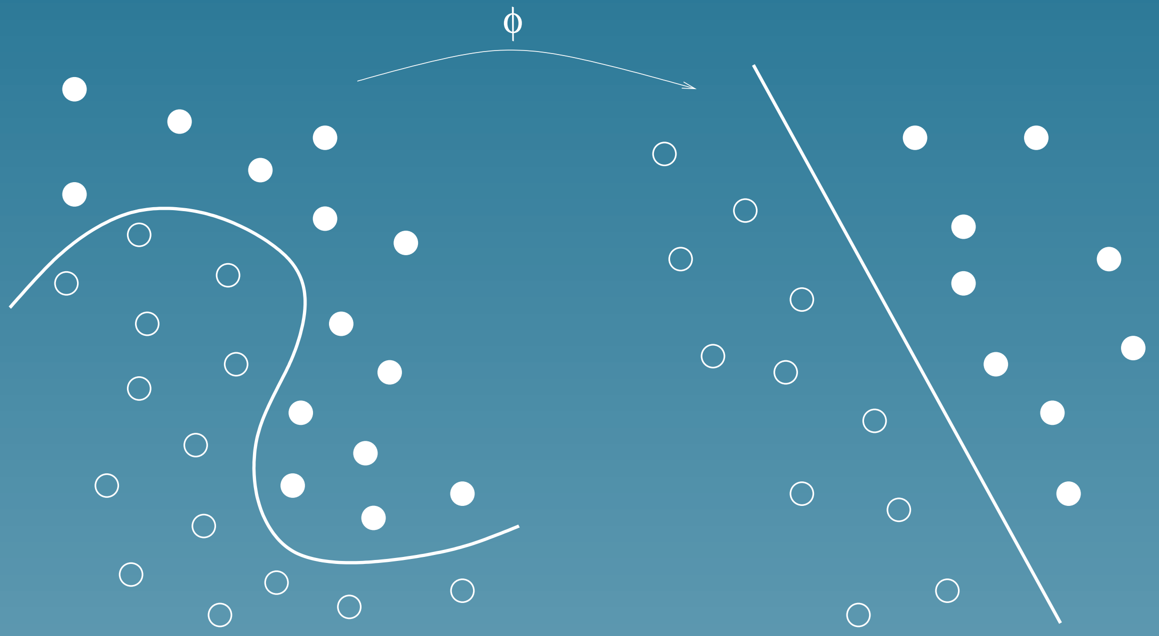
Outline

1. SVM and kernel methods
2. Probabilistic kernels for structured objects
3. Application: gene function prediction from phylogenetic profile

Part 1

SVM and kernel methods

Support vector machines



- Objects to classified x mapped to a feature space
- Largest margin separating hyperplan in the feature space

The kernel trick

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

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- Simple kernels can represent complex Φ
- For a given kernel, not only SVM but also clustering, PCA, ICA... possible in the feature space $=$ kernel methods

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  - ⋆ Spectrum kernel (Leslie et al., PSB 2002)

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- A fonction $K : \mathcal{X}^2 \longrightarrow \mathbb{R}$ is a valid kernel if it is symmetric positive definite.
- Kernel engineering:Use prior knowledge to build the geometry of the feature space through $K(.,.)$

Part 2

Probabilistic kernels for structured objects

The problem

- $\mathcal{X}$ a finite set of (structured) objects

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- $p(x)$ a probability distribution on $\mathcal{X}$

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- How to build $K(x,y)$ from $p(x)$?
- *Remark: up to translation and scaling, we can restrict* K *to be a probability on* $\mathcal{X} \times \mathcal{X}$ *(P-kernel)*

Product kernel

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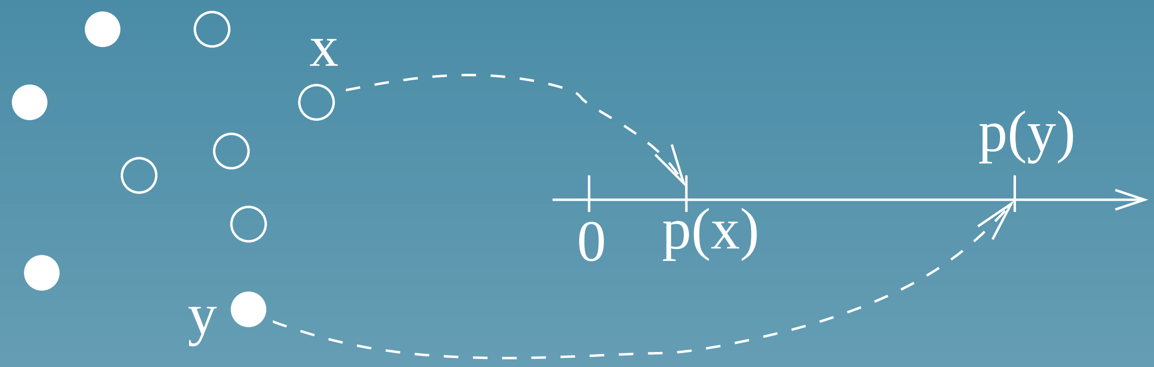

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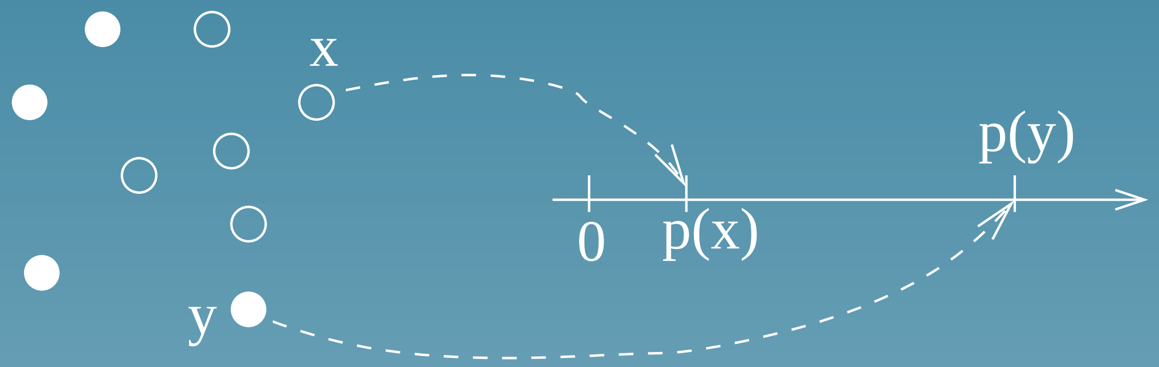

SVM $=$ probability threshold classifier

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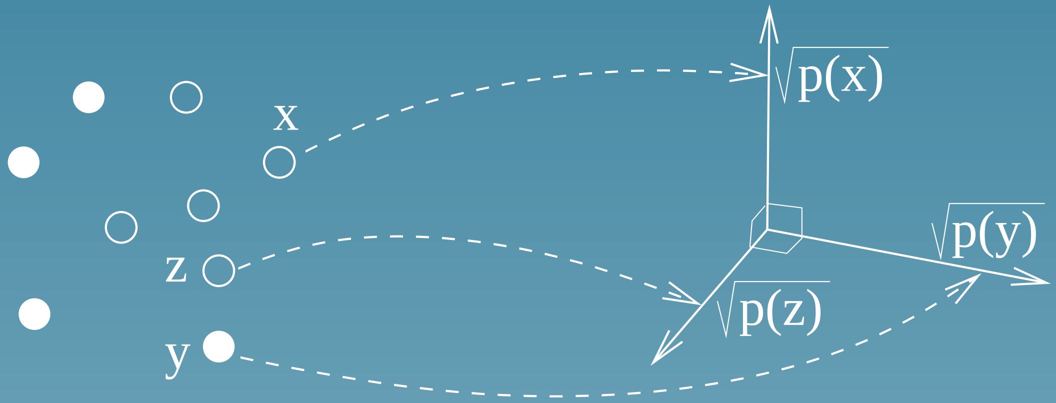

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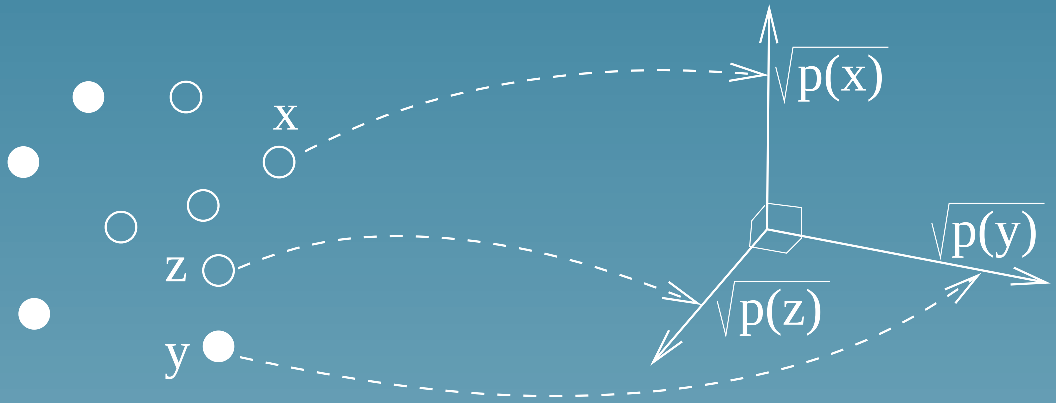

No learning

Interpolated kernel

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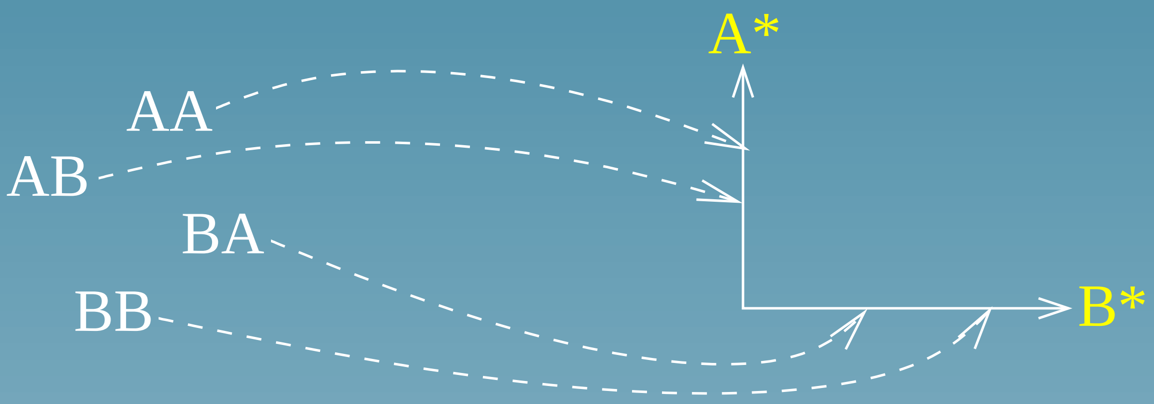
$$\begin{aligned} K(x,y) &= K_{diag}(x_1, y_1) K_{prod}(x_2, y_2) \\ &= p(x_1)\delta(x_1, y_1) \times p(x_2|x_1)p(y_2|y_1) \end{aligned}$$



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- A list of index subsets: $\mathcal{V} = \{I_1, \ldots, I_v\}$ where $I_i \subset \{1, \ldots, n\}$ for $i = 1, \ldots, v$.
- Interpolated kernel:

$$K_{\mathcal{V}}(x, y) = \frac{1}{|\mathcal{V}|} \sum_{I \in \mathcal{V}} K_{diag}(x_I, y_I) K_{prod}(x_{I^c}, y_{I^c})$$

Examples

- If $\mathcal{V} = \{\emptyset\}$, then:

$$K_{\mathcal{V}}(x,y) = K_{prod}(x,y).$$

- If $\mathcal{V} = \{[1,n]\}$, then:

$$K_{\mathcal{V}}(x,y) = K_{diag}(x,y).$$

Rare common subparts

For a given $p(x)$ and $p(y)$, we have:

$$K_{\mathcal{V}}(x, y) = K_{prod}(x, y) \times \frac{1}{|\mathcal{V}|} \sum_{I \in \mathcal{V}} \frac{\delta(x_I, y_I)}{p(x_I)}$$

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x and y get closer in the feature space when they share rare common subparts

Implementation

- For many applications, computation time of the kernel is a limiting factor
- The sum in the interpolated might involve up to 2^n terms...
- Good news: factorization possible for particular choices of $p(.)$ and $\mathcal{V}$

Example 1: Weight matrix kernel

$$p(x) = \prod_{i=1}^{n} p_i(x_i)$$

$$\mathcal{V} = \mathcal{P}([1, n])$$

then:

$$K_{\mathcal{V}}(x, y) = \frac{1}{2^n} \prod_{i=1}^{n} \phi_i(x_i, y_i),$$

with:

$$\phi_i(x_i, y_i) = \begin{cases} p_i(x_i) + p_i(x_i)^2 & \text{if } x_i = y_i \\ p_i(x_i)p_i(y_i) & \text{if } x_i \neq y_i \end{cases}$$

Weight matrix kernel: Proof

$$
\begin{aligned}
K(x,y) &= \frac{1}{2^n} \sum_{\mathcal{V}\subset[1,n]} \left[\prod_{i\in\mathcal{V}} p(x_i)\delta(x_i,y_i) \times \prod_{i\notin\mathcal{V}} p(x_i)p(y_i) \right] \\
&= \frac{1}{2^n} \prod_{i=1}^{n} \left[p(x_i)\delta(x_i,y_i) + p(x_i)p(y_i) \right].
\end{aligned}
$$

Example 2: Markov block kernel

$$p(x) = p_1(x_1) \prod_{i=2}^{n} p_i(x_i | x_{i-1})$$

$$\mathcal{V} = \{[k, l] : 1 \leq k \leq l \leq n\} \cap \{\emptyset\}$$

then:

$$K_{\mathcal{V}}(x, y) = \phi_0(n) + \phi_1(n) + \phi_2(n),$$

with:

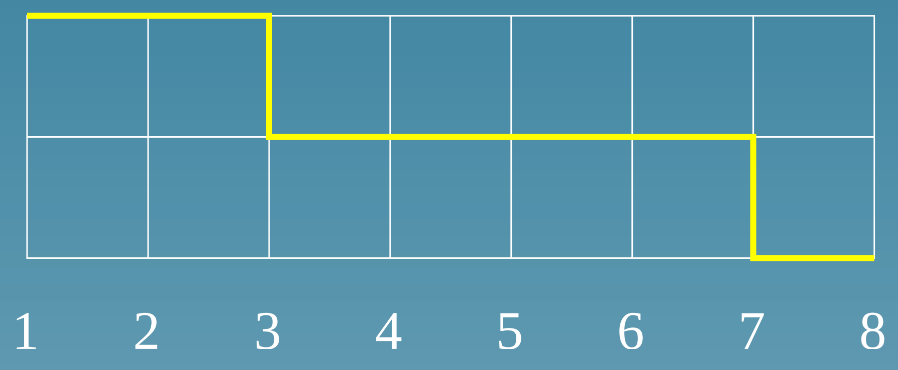
$$\begin{cases} \phi_0(1) = p_1(x_1)p_1(y_1) \\ \phi_1(1) = p_1(x_1)\delta(x_1, y_1) \\ \phi_2(1) = 0 \end{cases}$$

and for $i = 2, \ldots, n$:

$$\begin{cases} \phi_0(i) = p_i(x_i|x_{i-1})p_i(y_i|y_{i-1}) \times \phi_0(i-1) \\ \phi_1(i) = p_i(x_i|x_{i-1})\delta(x_i, y_i) \\ \qquad\qquad \times \left[\phi_1(i-1) + \frac{p_i(y_i|y_{i-1})}{p_i(x_i)}\phi_0(i-1)\right] \\ \phi_2(i) = p_i(x_i|x_{i-1})p_i(y_i|y_{i-1}) \times [\phi_1(i-1) + \phi_2(i-1)] \end{cases}$$

Weight matrix kernel: Proof

- Bijection between the set of intervals and the set of paths



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- Factorization along each path
- Classical dynamic programming for the summation

Example 3: common subtree kernel

- Let T be a rooted tree
- λ the root, $f(s)$ the father node of any node $s \in T$
- Graphical model and common subtrees:

$$p(x) = p_\lambda(x_\lambda) \prod_{s \in T \setminus \{\lambda\}} p_s(x_s | x_{f(s)})$$

$$\mathcal{V} = \{S \text{ rooted subtree of T}\}$$

Then:

$$K(x,y) = \sum_{S \in \mathcal{V}} \Big[\prod_{s \in S} p(x_s | x_{f(s)}) \delta(x_s, y_s) \times \prod_{s \notin S} p(x_s | x_{f(s)} p(y_s | y_{f(s)}) \Big]$$

Can be computed in linear time by one post-order traversal of the tree (similar to the CTW algorithm by Willems et al.)

Example 4: common subtree kernel with latent variables

- Same as example 3 but some variables are not observed:

$$K(x_{obs}, y_{obs}) = \sum_{S \in \mathcal{V}} \sum_{z_S \in \mathcal{A}^S} p(z_S) p(x_{obs}|z_S) p(y_{obs}|z_S)$$

- A bit longer to write, but still possible
- Linear time computation

Part 3

Application: Gene functional prediction from phylogenetic profiles

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 sequence of the genes are (almost) known (sequencing projets)
- Next big challenge: understand the function of the genes

Definition

- 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.

Gene	aero	aful	...	tpal	worm
YAL001C	1	1	...	0	0
YAB002W	0	0	...	0	1
⋮	⋮	⋮	⋮	⋮	⋮

- 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 measure the similarity between profiles?

Naive approach

- Count the number of bits in common:

x	1	1	0	1	0	0	0	1	1	0
y	1	0	1	0	0	0	0	1	0	1

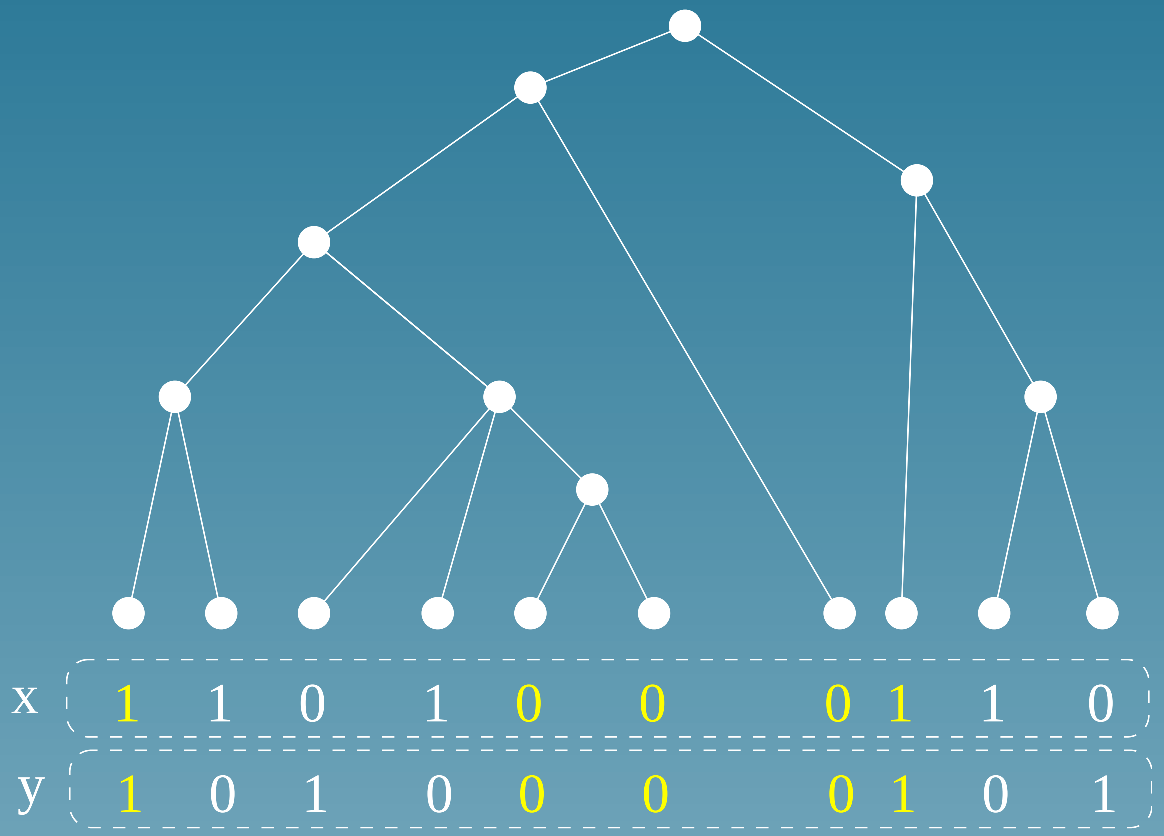
$$s(x, y) = 5$$

- Cluster or use k-NN for gene function prediction with this similarity measure (Pellegrini et al., 1999)

Limitations of the naive approach

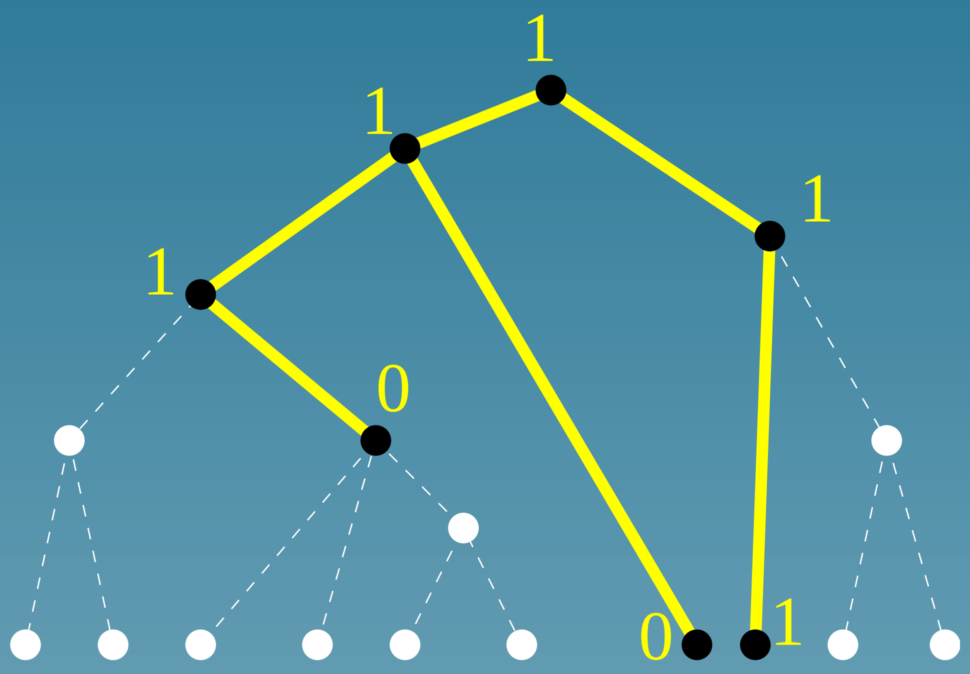
- The set of sequenced organisms has a strong influence on the similarity score (e.g., eukaryotes are under-represented)
- A more detailed understanding of when two proteins were transmitted together or not during evolution could be useful

What is not used in the naive approach



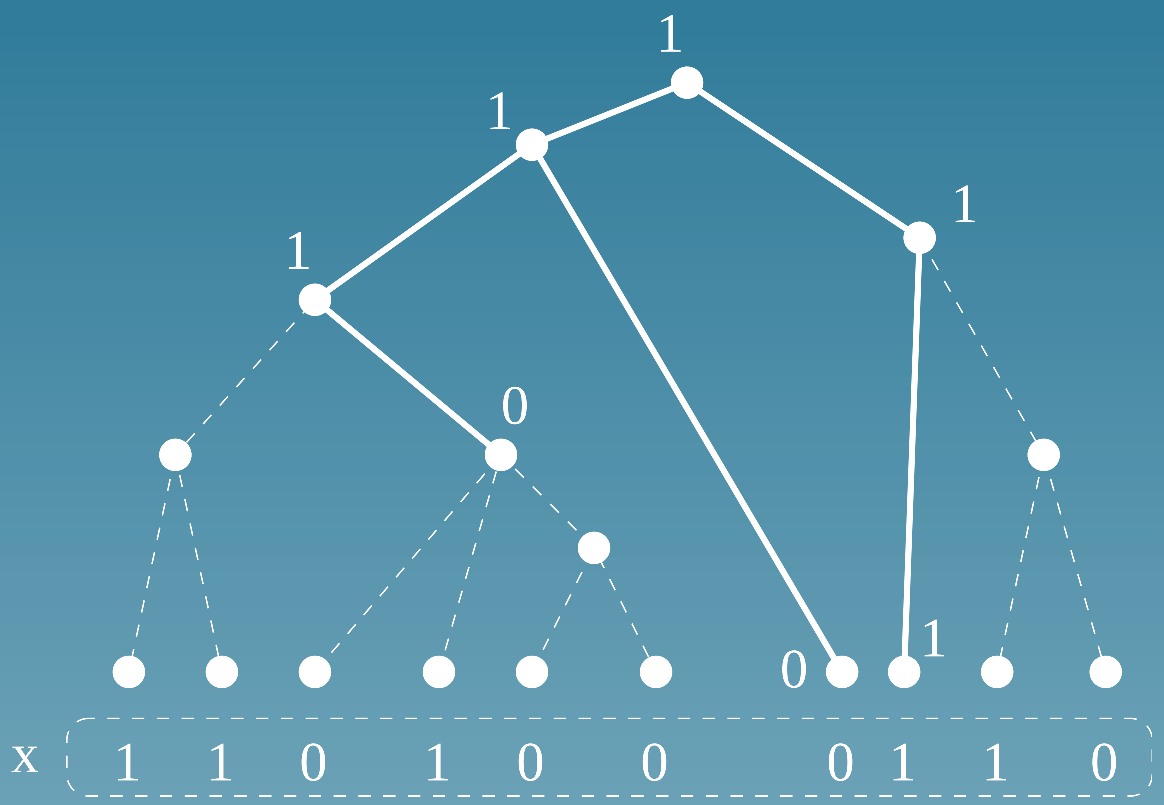
The knowledge of the phylogenetic tree.

Evolution pattern



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

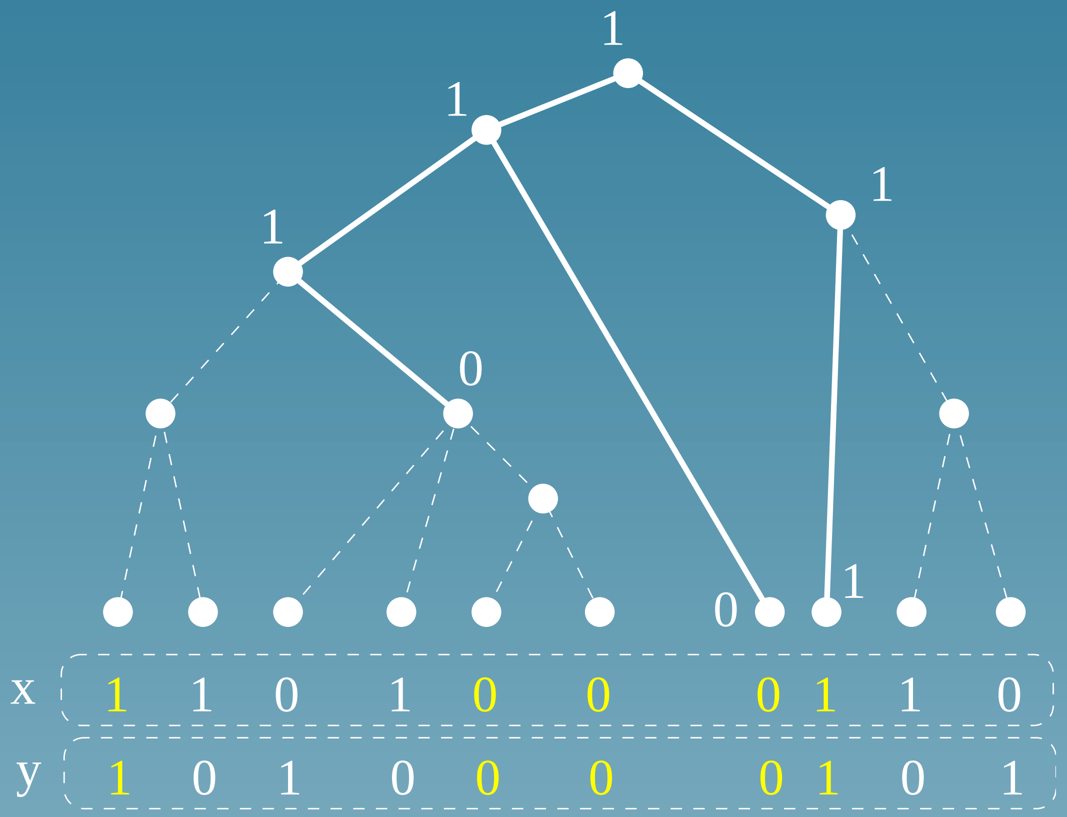
Representation of a profile in terms of evolution patterns

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

$$\Phi(x) = \begin{pmatrix} \sqrt{P(e_1)}P(x|e_1) \\ \vdots \\ \sqrt{P(e_N)}P(x|e_N) \end{pmatrix}$$

- This leads to the probabilistic kernel described before

Comparing two profiles through evolution patterns



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

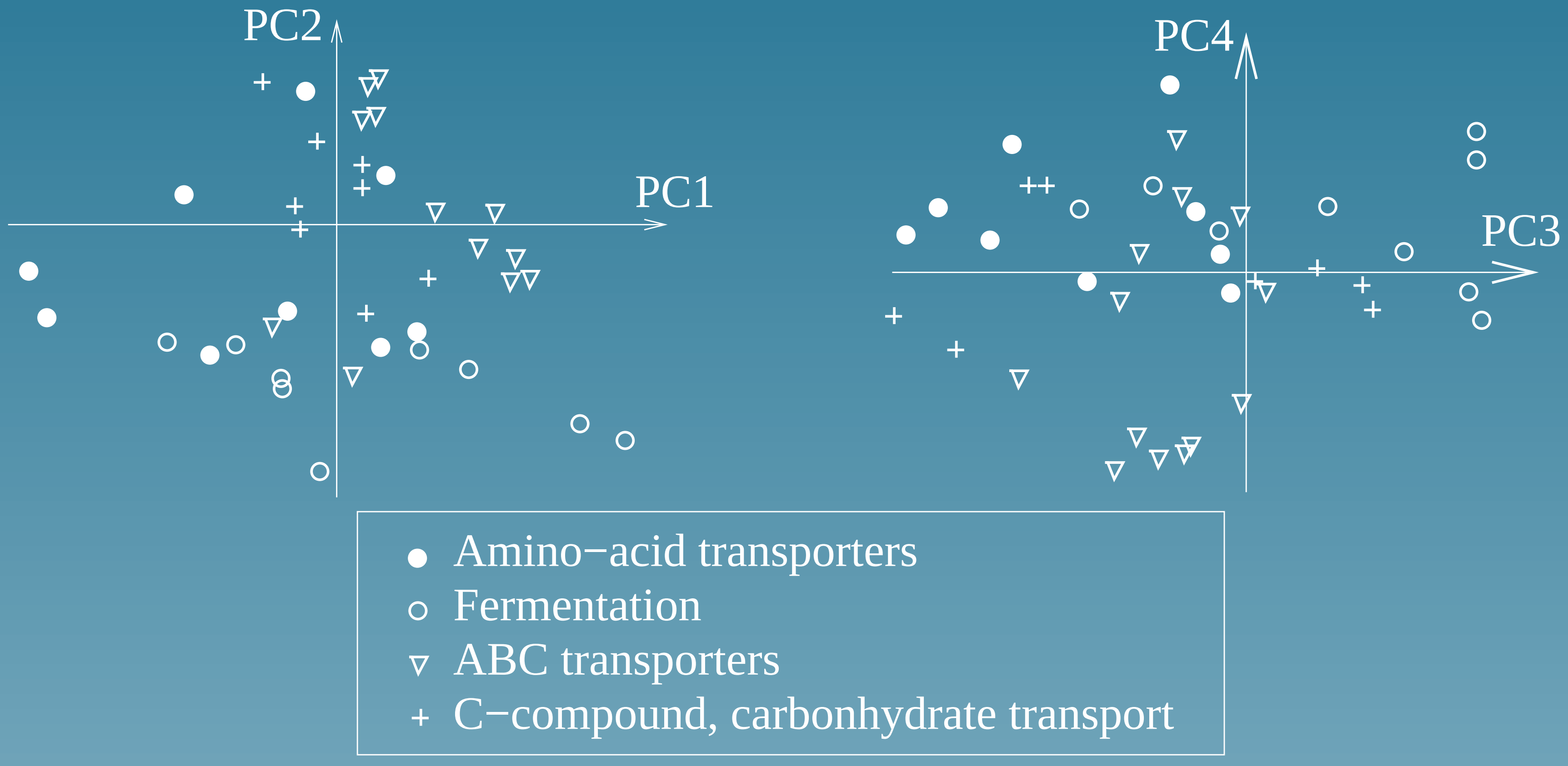
Results (ROC 50)

Functional class	Naive kernel	Tree kernel	Difference
Amino-acid transporters	0.74	0.81	**+ 9%**
Fermentation	0.68	0.73	**+ 7%**
ABC transporters	0.64	0.87	**+ 36%**
C-compound transport	0.59	0.68	**+ 15%**
Amino-acid biosynthesis	0.37	0.46	**+ 24%**
Amino-acid metabolism	0.35	0.32	- *9%*
Tricarboxylic-acid pathway	0.33	0.48	**+ 45%**
Transport Facilitation	0.33	0.28	- *15%*

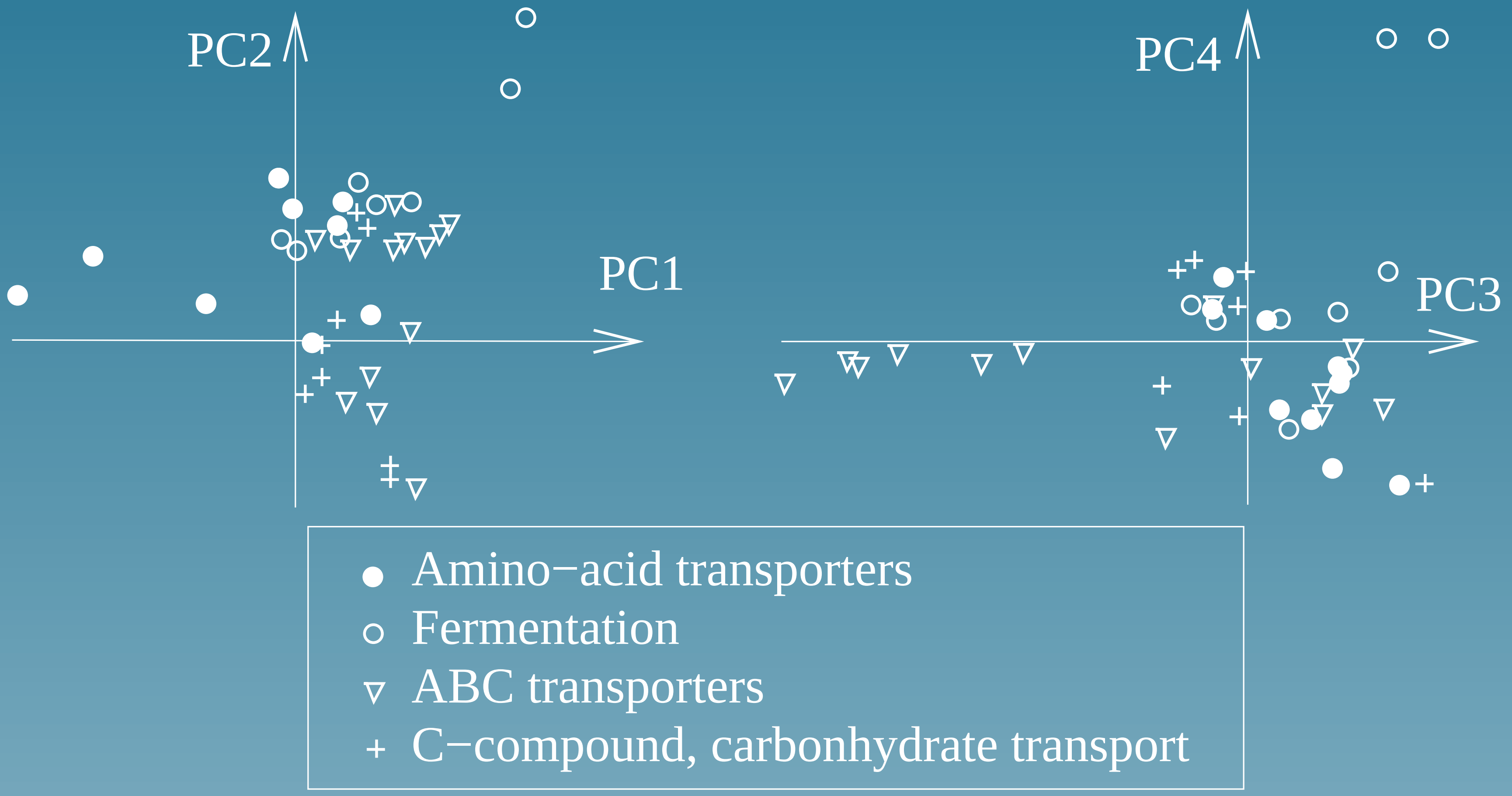
A insight into the feature space

- 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



Tree kernel PCA



Conclusion

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- A general method to derive a kernel from a probability distribution
- Encouraging results
- Some problems and questions: diagonal dominance? Role of the prior distribution?
- Contributes to a general approach: encode genomic information into kernel functions.