Kernels for strings and applications in bioinformatics

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Outline

1. Kernels and kernel methods

2. Kernels for biological sequences
   - Explicit vector space embedding
   - Mutual information kernels
   - Alignment kernels
   - Application: remote homology detection

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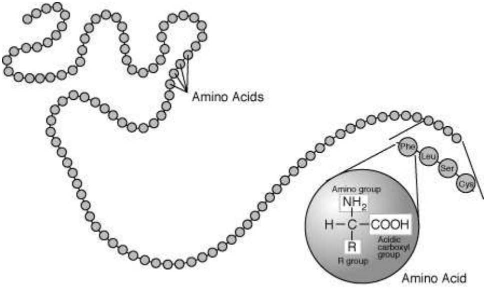
Kernels and Kernel Methods

Proteins



A : Alanine	V : Valine	L : Leucine
F : Phenylalanine	P : Proline	M : Méthionine
E : Acide glutamique	K : Lysine	R : Arginine
T : Threonine	C : Cysteine	N : Asparagine
H : Histidine	V : Thyrosine	W : Tryptophane
I : Isoleucine	S : Sérine	Q : Glutamine
D : Acide aspartique	G : Glycine	

Challenges with protein sequences

- A protein sequences can be seen as a variable-length sequence over the 20-letter alphabet of amino-acids, e.g., insuline: FVNQHLCGSHLVEALYLVCGERGFFYTPKA
- These sequences are produced at a fast rate (result of the sequencing programs)
- Need for algorithms to compare, classify, analyze these sequences
- Applications: classification into functional or structural classes, prediction of cellular localization and interactions, ...

Example: supervised sequence classification

Data (training)

- Secreted proteins:

  MASKATLLLAFTLLFATCIARHQQRQQQQNQCQLQNIEA...
  MARSSLFTFLCLAVFINGCLSQIEQQSPWEFQGSEVW...
  MALHTVLIMLSLLPMLEAQNPEHANITIGEPITNETLGWL...
  ...

- Non-secreted proteins:

  MAPPSVFAEVPQAQPVLVFKLIADFREDPDPRKVNLGVG...
  MAHTLGLTQPNSTEPHKISFTAKEIDVIEWKGDILVVG...
  MSISESYAKEIKTAFRQFTDFPIEGEQFEDFLPIIGNP..
  ...

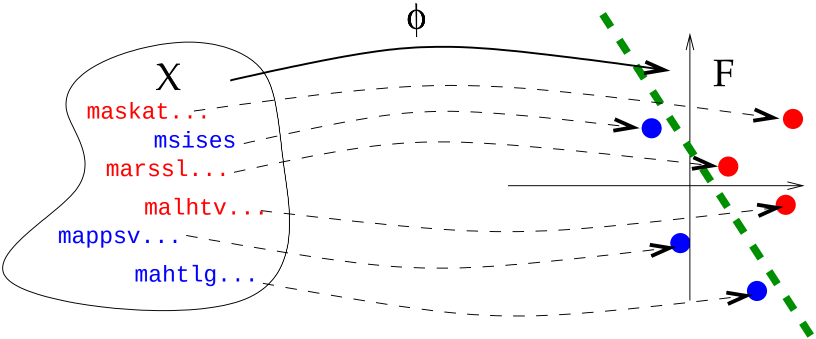
Goal

- Build a classifier to predict whether new proteins are secreted or not.

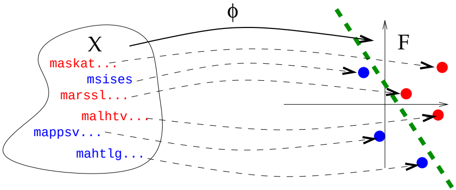
Supervised classification with vector embedding

The idea

- Map each string $x \in \mathcal{X}$ to a vector $\Phi(x) \in \mathbb{R}^p$.
- Train a classifier for vectors on the images $\Phi(x_1), \ldots, \Phi(x_n)$ of the training set (nearest neighbor, linear perceptron, logistic regression, support vector machine...)



Example: support vector machine



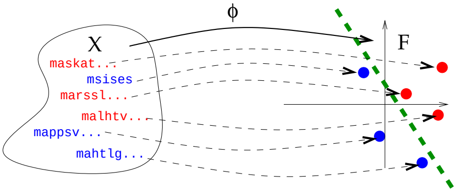
SVM algorithm

$$f(x) = \text{sign}\left(\sum_{i=1}^{n} \alpha_i y_i \Phi(x_i)^\top \Phi(x)\right) \; ,$$

where $\alpha_1, \ldots, \alpha_n$ solve, under the constraints $0 \leq \alpha_i \leq C$:

$$\min_{\alpha}\left(\frac{1}{2}\sum_{i=1}^{n}\sum_{i=1}^{n} \alpha_i \alpha_j y_i y_j \Phi(x_i)^\top \Phi(x_j) - \sum_{i=1}^{n} \alpha_i\right) \; .$$

Explicit vector embedding



Difficulties

- How to define the mapping $\Phi : \mathcal{X} \to \mathbb{R}^p$?
- No obvious vector embedding for strings in general.
- How to include prior knowledge about the strings (grammar, probabilistic model...)?

Implicit vector embedding with kernels

The kernel trick

- Many algorithms just require inner products of the embeddings
- We call it a kernel between strings:

$$K(x, x') \triangleq \Phi(x)^\top \Phi(x')$$

Examples

- SVM
- Nearest neighbor:

$$d(x, x')^2 = \| \Phi(x) - \Phi(x') \|^2 = K(x, x) + K(x', x') - 2K(x, x') .$$

- Many other kernel methods (perceptron, regression...)

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Positive Definite Kernels

Definition

A positive definite (p.d.) kernel on the set $\mathcal{X}$ is a function $K : \mathcal{X} \times \mathcal{X} \to \mathbb{R}$ symmetric:

$$\forall \left(\mathbf{x}, \mathbf{x}'\right) \in \mathcal{X}^2, \quad K\left(\mathbf{x}, \mathbf{x}'\right) = K\left(\mathbf{x}', \mathbf{x}\right),$$

and which satisfies, for all $N \in \mathbb{N}$, $(\mathbf{x}_1, \mathbf{x}_2, \ldots, \mathbf{x}_N) \in \mathcal{X}^N$ et $(a_1, a_2, \ldots, a_N) \in \mathbb{R}^N$:

$$\sum_{i=1}^{N} \sum_{j=1}^{N} a_i a_j K\left(\mathbf{x}_i, \mathbf{x}_j\right) \geq 0.$$

Kernels as Inner Products

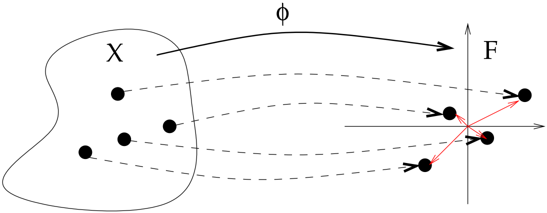
Theorem (Aronszajn, 1950)

K is a p.d. kernel on the set $\mathcal{X}$ if and only if there exists a Hilbert space $\mathcal{H}$ and a mapping

$$\Phi : \mathcal{X} \mapsto \mathcal{H} \, ,$$

such that, for any $\mathbf{x}, \mathbf{x}'$ in $\mathcal{X}$:

$$K\left(\mathbf{x}, \mathbf{x}'\right) = \left\langle \Phi\left(\mathbf{x}\right), \Phi\left(\mathbf{x}'\right) \right\rangle_{\mathcal{H}} \, .$$



Examples

Kernels for vectors

Classical kernels for vectors ($\mathcal{X} = \mathbb{R}^p$) include:

- The linear kernel

$$K_{lin}\left(\mathbf{x}, \mathbf{x}'\right) = \mathbf{x}^\top \mathbf{x}' .$$

- The polynomial kernel

$$K_{poly}\left(\mathbf{x}, \mathbf{x}'\right) = \left(\mathbf{x}^\top \mathbf{x}' + a\right)^d .$$

- The Gaussian RBF kernel:

$$K_{Gaussian}\left(\mathbf{x}, \mathbf{x}'\right) = \exp\left(-\frac{\parallel \mathbf{x} - \mathbf{x}' \parallel^2}{2\sigma^2}\right) .$$

Kernel for strings?

- A kernel defines an implicit geometry on the space of data, although data do not need to have any prior geometric/algebric structure
- Kernel engineering is the problem of designing specific kernel for specific data and specific tasks. Good place to put prior knowledge!
- We will now see on a practical examples different technical tricks to design kernels.

Kernels for Biological Sequences

Outline

Vector embedding for strings

The idea

Represent each sequence $\mathbf{x}$ by a fixed-length numerical vector $\Phi(\mathbf{x}) \in \mathbb{R}^p$. How to perform this embedding?

Physico-chemical kernel

Extract relevant features, such as:

- length of the sequence
- time series analysis of numerical physico-chemical properties of amino-acids along the sequence (e.g., polarity, hydrophobicity), using for example:
  - Fourier transforms (Wang et al., 2004)
  - Autocorrelation functions (Zhang et al., 2003)

$$r_j = \frac{1}{n-j} \sum_{i=1}^{n-j} h_i h_{i+j}$$

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Substring indexation

The approach

Alternatively, index the feature space by fixed-length strings, i.e.,

$$\Phi(\mathbf{x}) = (\Phi_u(\mathbf{x}))_{u \in \mathcal{A}^k}$$

where $\Phi_u(\mathbf{x})$ can be:

- the number of occurrences of u in $\mathbf{x}$ (without gaps) : spectrum kernel (Leslie et al., 2002)
- the number of occurrences of u in $\mathbf{x}$ up to m mismatches (without gaps) : mismatch kernel (Leslie et al., 2004)
- the number of occurrences of u in $\mathbf{x}$ allowing gaps, with a weight decaying exponentially with the number of gaps : substring kernel (Lohdi et al., 2002)

Example: spectrum kernel

- The 3-spectrum of

$$\mathbf{x} = \texttt{CGGSLIAMMWFGV}$$

  is:

$$(\texttt{CGG,GGS,GSL,SLI,LIA,IAM,AMM,MMW,MWF,WFG,FGV})\ .$$

- Let $\Phi_u(\mathbf{x})$ denote the number of occurrences of u in $\mathbf{x}$. The k-spectrum kernel is:

$$K(\mathbf{x}, \mathbf{x}') := \sum_{u \in \mathcal{A}^k} \Phi_u(\mathbf{x}) \Phi_u(\mathbf{x}')\ .$$

- This is formally a sum over $|\mathcal{A}|^k$ terms, but at most $|\mathbf{x}| - k + 1$ terms are non-zero in $\Phi(\mathbf{x})$

Substring indexation in practice

- Implementation in $O(|\mathbf{x}| + |\mathbf{x}'|)$ in memory and time for the spectrum and mismatch kernels (with suffix trees)
- Implementation in $O(|\mathbf{x}| \times |\mathbf{x}'|)$ in memory and time for the substring kernels
- The feature space has high dimension ($|\mathcal{A}|^k$), so learning requires regularized methods (such as SVM)

Dictionary-based indexation

The approach

- Chose a dictionary of sequences $\mathcal{D} = (\mathbf{x}_1, \mathbf{x}_2, \ldots, \mathbf{x}_n)$
- Chose a measure of similarity $s(\mathbf{x}, \mathbf{x}')$
- Define the mapping $\Phi_{\mathcal{D}}(\mathbf{x}) = (s(\mathbf{x}, \mathbf{x}_i))_{\mathbf{x}_i \in \mathcal{D}}$

Examples

This includes:

- Motif kernels (Logan et al., 2001): the dictionary is a library of motifs, the similarity function is a matching function
- Pairwise kernel (Liao & Noble, 2003): the dictionary is the training set, the similarity is a classical measure of similarity between sequences.

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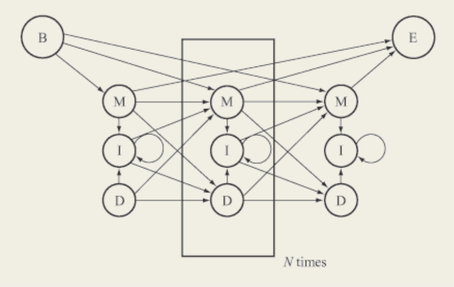
Probabilistic models for sequences

Probabilistic modeling of biological sequences is older than kernel designs. Important models include HMM for protein sequences, SCFG for RNA sequences.



Parametric model

A model is a family of distribution

$$\{P_\theta, \theta \in \Theta \subset \mathbb{R}^m\} \subset \mathcal{M}_1^+(\mathcal{X})$$

Mutual information kernels

Definition

- Chose a prior $w(d\theta)$ on the measurable set Θ
- Form the kernel (Seeger, 2002):

$$K(\mathbf{x}, \mathbf{x}') = \int_{\theta \in \Theta} P_\theta(\mathbf{x}) P_\theta(\mathbf{x}') w(d\theta) \, .$$

- No explicit computation of a finite-dimensional feature vector
- $K(\mathbf{x}, \mathbf{x}') = < \phi(\mathbf{x}), \phi(\mathbf{x}') >_{L_2(w)}$ with

$$\phi(\mathbf{x}) = (P_\theta(\mathbf{x}))_{\theta \in \Theta} \, .$$

Example: coin toss

- Let $P_\theta(X = 1) = \theta$ and $P_\theta(X = 0) = 1 - \theta$ a model for random coin toss, with $\theta \in [0, 1]$.
- Let $d\theta$ be the Lebesgue measure on $[0, 1]$
- The mutual information kernel between $\mathbf{x} = 001$ and $\mathbf{x}' = 1010$ is:

$$\begin{cases} P_\theta(\mathbf{x}) & = \theta (1 - \theta)^2 \ , \\ P_\theta(\mathbf{x}') & = \theta^2 (1 - \theta)^2 \ , \end{cases}$$

$$K(\mathbf{x}, \mathbf{x}') = \int_0^1 \theta^3 (1 - \theta)^4 \, d\theta = \frac{3!4!}{8!} = \frac{1}{280} \ .$$

Context-tree model

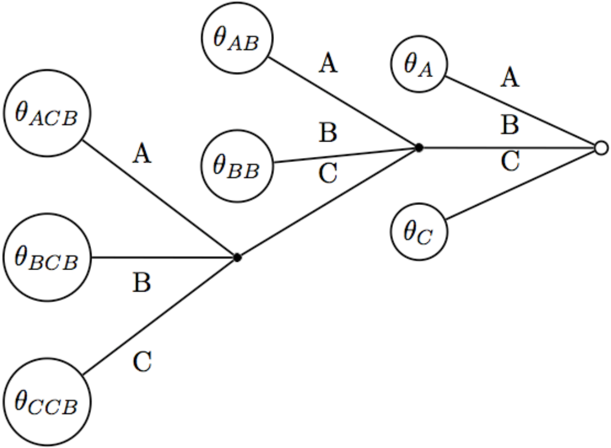
Definition

A context-tree model is a variable-memory Markov chain:

$$P_{\mathcal{D},\theta}(\mathbf{x}) = P_{\mathcal{D},\theta}\left(x_1 \dots x_D\right) \prod_{i=D+1}^{n} P_{\mathcal{D},\theta}\left(x_i \mid x_{i-D} \dots x_{i-1}\right)$$

- $\mathcal{D}$ is a suffix tree
- $\theta \in \Sigma^{\mathcal{D}}$ is a set of conditional probabilities (multinomials)

Context-tree model: example



$$P(AABACBACC) = P(AAB)\theta_{AB}(A)\theta_A(C)\theta_C(B)\theta_{ACB}(A)\theta_A(C)\theta_C(A) .$$

The context-tree kernel

Theorem (Cuturi et al., 2004)

- *For particular choices of priors, the context-tree kernel:*

$$K\left(\mathbf{x},\mathbf{x}'\right)=\sum_{\mathcal{D}}\int_{\theta\in\Sigma^{\mathcal{D}}}P_{\mathcal{D},\theta}(\mathbf{x})P_{\mathcal{D},\theta}(\mathbf{x}')w(d\theta|\mathcal{D})\pi(\mathcal{D})$$

  can be computed in $O(|\mathbf{x}|+|\mathbf{x}'|)$ with a variant of the Context-Tree Weighting algorithm.
- *This is a valid mutual information kernel.*
- *The similarity is related to information-theoretical measure of mutual information between strings.*

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Sequence alignment

Motivation

How to compare 2 sequences?

$$\mathbf{x}_1 = \texttt{CGGSLIAMMWFGV}$$
$$\mathbf{x}_2 = \texttt{CLIVMMNRLMWFGV}$$

Find a good alignment:

```
CGGSLIAMM----WFGV
|...|||||....||||
C---LIVMMNRLMWFGV
```

Alignment score

In order to quantify the relevance of an alignment π, define:

- a substitution matrix $S \in \mathbb{R}^{\mathcal{A}\times\mathcal{A}}$
- a gap penalty function $g : \mathbb{N} \rightarrow \mathbb{R}$

Any alignment is then scored as follows

```
CGGSLIAMM----WFGV
|...|||||....||||
C---LIVMMNRLMWFGV
```

$$s_{S,g}(\pi) = S(C,C) + S(L,L) + S(I,I) + S(A,V) + 2S(M,M) + S(W,W) + S(F,F) + S(G,G) + S(V,V) - g(3) - g(4)$$

Local alignment kernel

Smith-Waterman score

- The widely-used Smith-Waterman local alignment score is defined by:

$$SW_{S,g}(\mathbf{x},\mathbf{y}) := \max_{\pi\in\Pi(\mathbf{x},\mathbf{y})} s_{S,g}(\pi).$$

- It is symmetric, but not positive definite...

LA kernel

The local alignment kernel:

$$K_{LA}^{(\beta)}(\mathbf{x},\mathbf{y}) = \sum_{\pi\in\Pi(\mathbf{x},\mathbf{y})} \exp\left(\beta s_{S,g}(\mathbf{x},\mathbf{y},\pi)\right),$$

is symmetric positive definite (Vert et al., 2004).

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is symmetric positive definite (Vert et al., 2004).

LA kernel is p.d.: proof

- If K_1 and K_2 are p.d. kernels for strings, then their convolution defined by:

$$K_1 \star K_2(\mathbf{x}, \mathbf{y}) := \sum_{\mathbf{x}_1\mathbf{x}_2 = \mathbf{x}, \mathbf{y}_1\mathbf{y}_2 = \mathbf{y}} K_1(\mathbf{x}_1, \mathbf{y}_1) K_2(\mathbf{x}_2, \mathbf{y}_2)$$

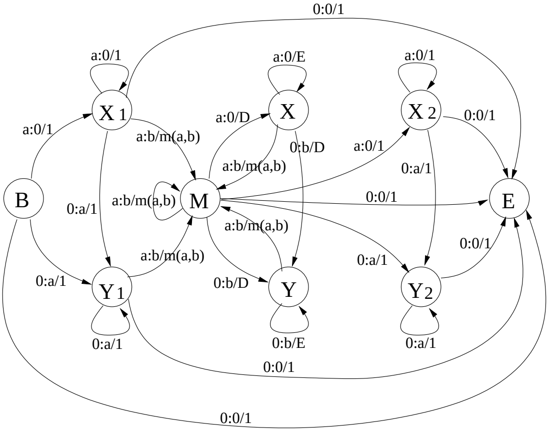
  is also p.d. (Haussler, 1999).

- LA kernel is p.d. because it is a convolution kernel (Haussler, 1999):

$$K_{LA}^{(\beta)} = \sum_{n=0}^{\infty} K_0 \star \left(K_a^{(\beta)} \star K_g^{(\beta)} \right)^{(n-1)} \star K_a^{(\beta)} \star K_0 .$$

  where K_0, K_a and K_g are three basic p.d. kernels (Vert et al., 2004).

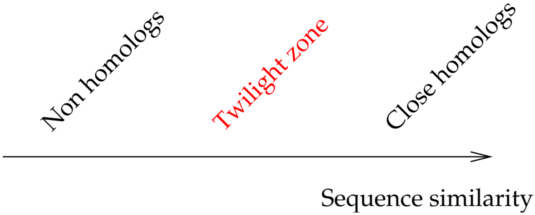
- Implementation by dynamic programming in $O(|\mathbf{x}| \times |\mathbf{x}'|)$



- In practice, values are too large (exponential scale) so taking its logarithm is a safer choice (but not p.d. anymore!)

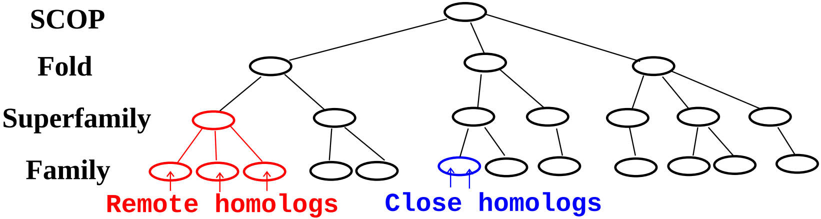
Outline

Remote homology



- Homologs have common ancestors
- Structures and functions are more conserved than sequences
- Remote homologs can not be detected by direct sequence comparison

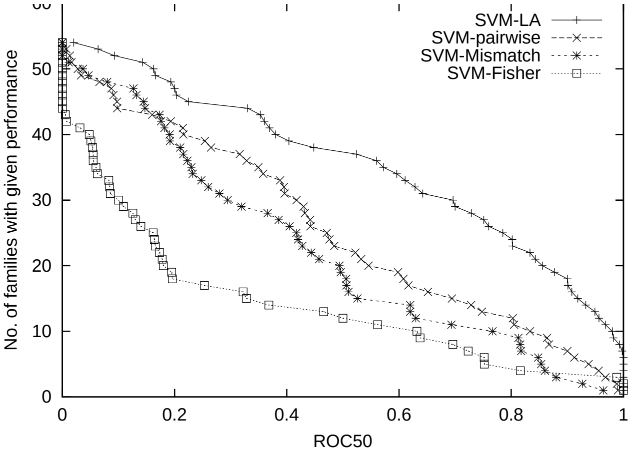
SCOP database



A benchmark experiment

- Goal: recognize directly the superfamily
- Training: for a sequence of interest, positive examples come from the same superfamily, but different families. Negative from other superfamilies.
- Test: predict the superfamily.

Difference in performance



Performance on the SCOP superfamily recognition benchmark (from Vert et al., 2004).

Conclusion

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- Many multivariate statistical methods can be used with strings when a string kernel is defined.
- We saw several principles for string kernel design
  - explicit vector embedding
  - mutual information kernels
  - alignment kernels
- We omitted many other examples (marginalized kernels, Fisher kernels, ...)
- The choice of the kernel does matter in the final performance.
- Many open questions: which principles to choose / select good kernels?