Some contributions of machine learning to bioinformatics

Jean-Philippe Vert

Jean-Philippe.Vert@ensmp.fr

Mines ParisTech / Institut Curie / Inserm

Université de Provence, Marseille, France, March 10, 2009.

Where I come from

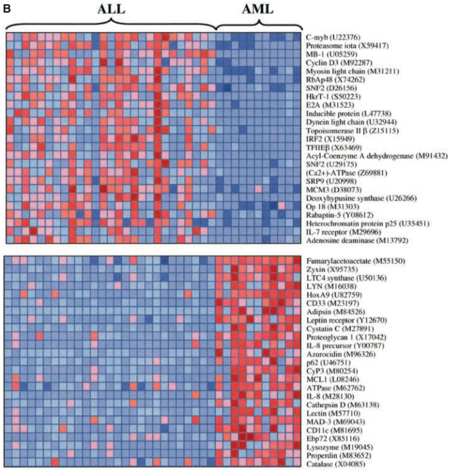
- A joint lab about “Cancer computational genomics, bioinformatics, biostatistics and epidemiology”
- Located in th Institut Curie, a major hospital and cancer research institute in Europe

”Statistical machine learning for cancer informatics” team

Main topics

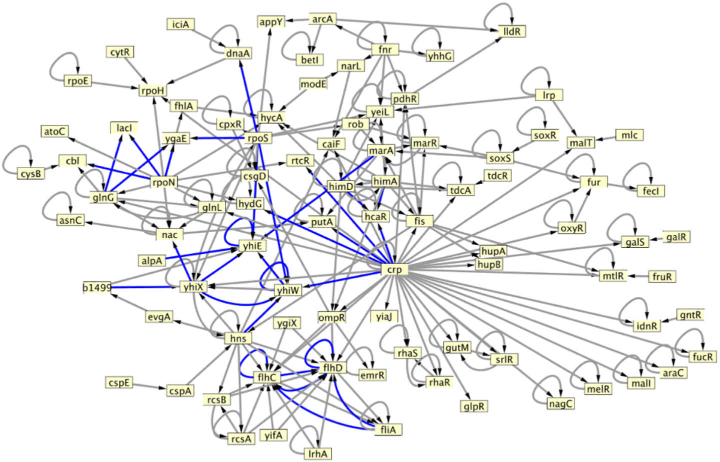
- Towards better diagnosis, prognosis, and personalized medicine
  - Supervised classification of genomic, transcriptomic, proteomic data; heterogeneous data integration
- Towards new drug targets
  - Systems biology, reconstruction of gene networks, pathway enrichment analysis, multidimensional phenotyping of cell populations.
- Towards new drugs
  - Ligand-based virtual screening, *in silico* chemogenomics.

Towards personalized medicine: Diagnosis/prognosis from genome/transcriptome



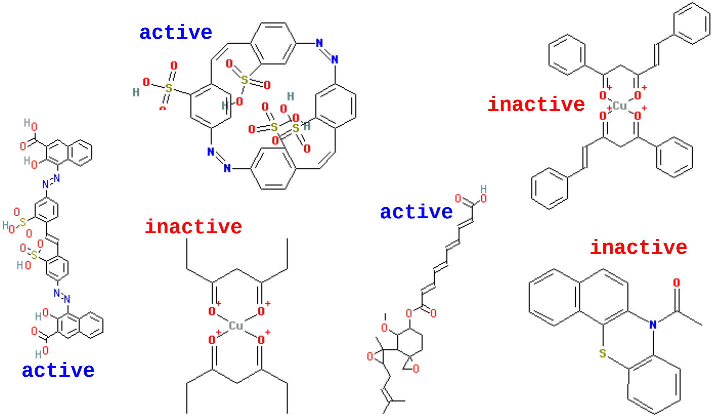
From Golub et al., Science, 1999.

Towards new drug targets: Inference of biological networks



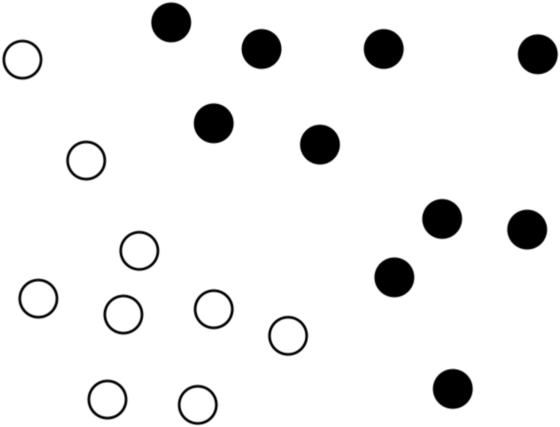
From Mordelet and Vert, Bioinformatics, 2008.

Towards new drugs: Ligand-Based Virtual Screening and QSAR



NCI AIDS screen results (from http://cactus.nci.nih.gov).

Pattern recognition, *aka* supervised classification



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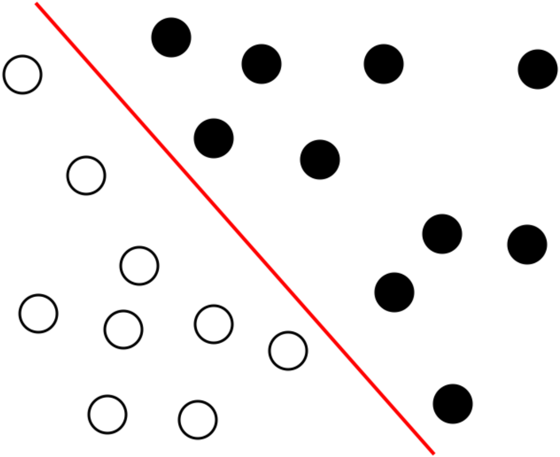

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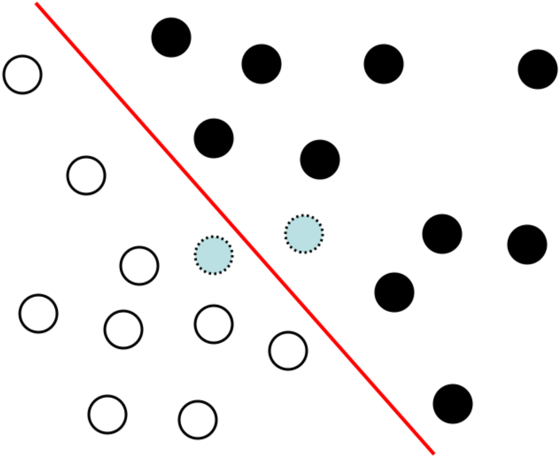

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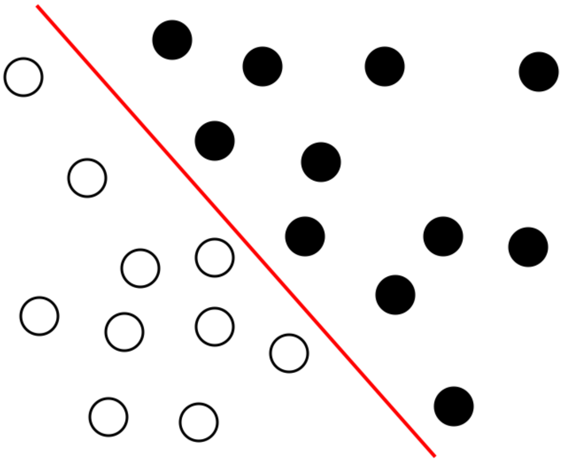

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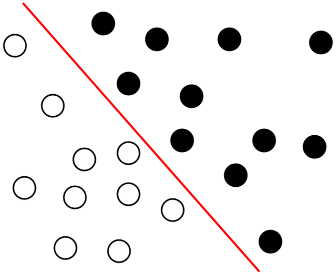

Challenges

- High dimension
- Few samples
- Structured data
- Prior knowledge
- Fast and scalable implementations

Outline

1. Supervised classification of genomic data
2. Inference of biological networks
3. Virtual screening and chemogenomics
4. Conclusion

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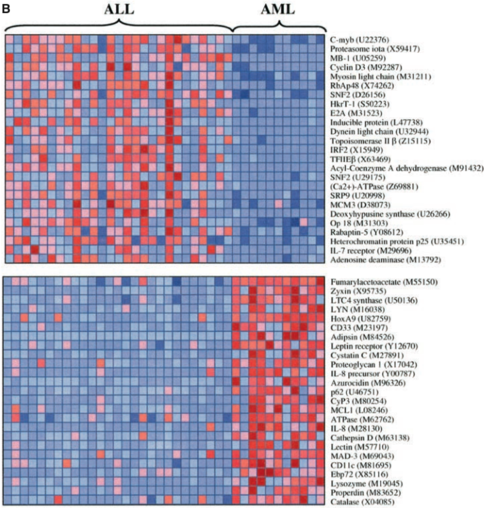
Motivation



Goal

- Design a classifier to automatically assign a class to future samples from their expression profile
- Interpret biologically the differences between the classes

Difficulty

- Large dimension
- Few samples

Linear classifiers

The model

- Each sample is represented by a vector $x = (x_1, \ldots, x_p)$
- Goal: estimate a linear function:

$$f_\beta(x) = \sum_{i=1}^{p} \beta_i x_i + \beta_0 \ .$$

- Interpretability: the weight β_i quantifies the influence of feature i (but...)

Linear classifiers

Training the model

$$f_\beta(x) = \sum_{i=1}^{p} \beta_i x_i + \beta_0 \; .$$

- Minimize an empirical risk on the training samples:

$$\min_{\beta \in \mathbb{R}^{p+1}} R_{emp}(\beta) = \frac{1}{n} \sum_{i=1}^{n} l(f_\beta(x_i), y_i) \, ,$$

- ... subject to some constraint on β, e.g.:

$$\Omega(\beta) \leq C \, .$$

Example : Norm Constraints

The approach

A common method in statistics to learn with few samples in high dimension is to constrain the Euclidean norm of β

$$\Omega_{ridge}(\beta) = \parallel \beta \parallel_2^2 = \sum_{i=1}^{p} \beta_i^2 ,$$

(ridge regression, support vector machines...)

Pros

- Good performance in classification

Cons

- Limited interpretation (small weights)
- No prior biological knowledge

Example : Feature Selection

The approach

Constrain most weights to be 0, i.e., select a few genes (< 100) whose expression are sufficient for classification.

- Greedy feature selection (T-tests, ...)
- Contrain the norm of β: LASSO penalty ($\| \beta \|_1 = \sum_{i=1}^{p} | \beta_i |$), elastic net penalty ($\| \beta \|_1 + \| \beta \|_2$), ...)

Pros

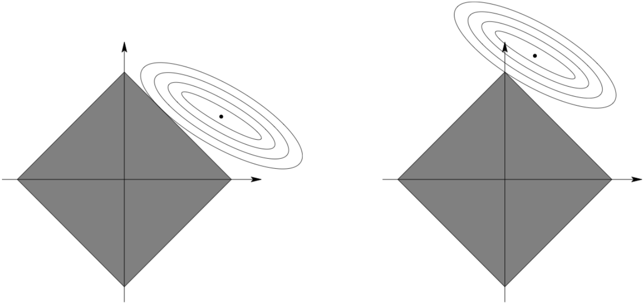
- Good performance in classification
- Biomarker selection
- Interpretability

Cons

- The gene selection process is usually not robust
- No use of prior biological knowledge

Why LASSO leads to sparse solutions

Geometric interpretation with $p = 2$



Incorporating prior knowledge

The idea

- If we have a specific prior knowledge about the “correct” weights, it can be included in Ω in the contraint:

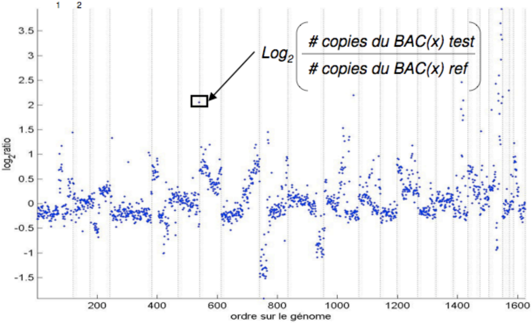
$$\text{Minimize } R_{emp}(\beta) \text{ subject to } \Omega(\beta) \leq C \,.$$

- If we design a convex function Ω, then the algorithm boils down to a convex optimization problem (usually easy to solve).
- Similar to priors in Bayesian statistics

Example: CGH array classification

Motivation

- Comparative genomic hybridization (CGH) data measure the DNA copy number along the genome
- Very useful, in particular in cancer research
- Can we classify CGH arrays for diagnosis or prognosis purpose?



$$\mathrm{Log}_2\left(\frac{\text{\# copies du BAC(x) test}}{\text{\# copies du BAC(x) ref}}\right)$$

Jain et al. Genome research 2002 12:325-332

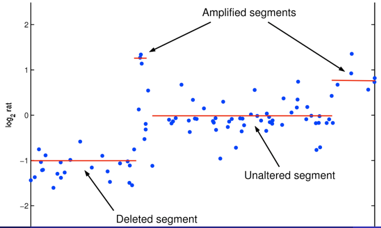
Example: CGH array classification

Prior knowledge

- Let **x** be a CGH profile
- We focus on linear classifiers, i.e., the sign of :

$$f(\mathbf{x}) = \mathbf{x}^\top \beta \,.$$

- We expect β to be
  - sparse : only a few positions should be discriminative
  - piecewise constant : within a region, all probes should contribute equally

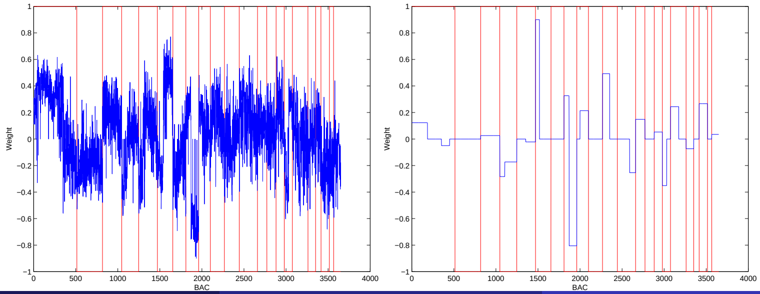


Example: CGH array classification

A solution (Rapaport et al., 2008)

$$\Omega_{fusedlasso}(\beta) = \sum_{i} |\beta_i| + \sum_{i \sim j} |\beta_i - \beta_j| \,.$$

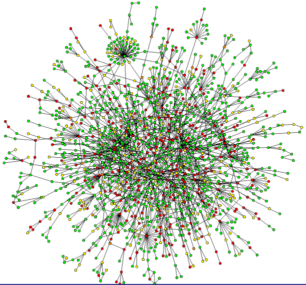
- Good performance on diagnosis for bladder cancer, and prognosis for melanoma.
- More interpretable classifiers



Example: finding discriminant modules in gene networks

The problem

- Classification of gene expression: too many genes
- A gene network is given (PPI, metabolic, regulatory, signaling, co-expression...)
- We expect that "clusters of genes" (modules) in the network contribute similarly to the classification



Example: finding discriminant modules in gene networks

Prior hypothesis

Genes near each other on the graph should have similar weigths.

Two solutions (Rapaport et al., 2007, 2008)

$$\Omega_{spectral}(\beta) = \sum_{i \sim j} (\beta_i - \beta_j)^2 \,,$$

$$\Omega_{graphfusion}(\beta) = \sum_{i \sim j} |\beta_i - \beta_j| + \sum_i |\beta_i| \,.$$

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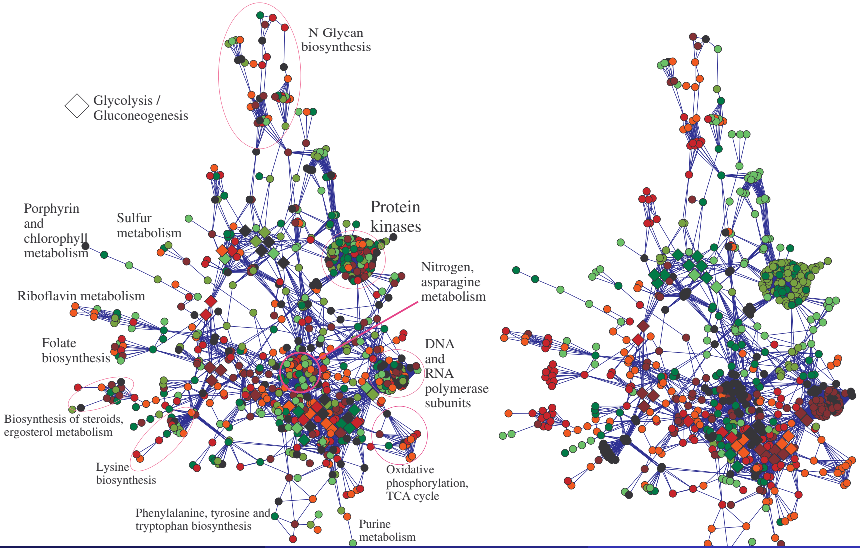
N Glycan biosynthesis
◇ Glycolysis / Gluconeogenesis
Porphyrin and chlorophyll metabolism
Sulfur metabolism
Protein kinases
Nitrogen, asparagine metabolism
Riboflavin metabolism
Folate biosynthesis
DNA and RNA polymerase subunits
Biosynthesis of steroids, ergosterol metabolism
Lysine biosynthesis
Oxidative phosphorylation, TCA cycle
Phenylalanine, tyrosine and tryptophan biosynthesis
Purine metabolism

Example: finding discriminant modules in gene networks

Prior hypothesis

Genes near each other on the graph should have non-zero weigths (i.e., the support of β should be made of a few connected components).

Two solutions?

$$\Omega_{intersection}(\beta) = \sum_{i \sim j} \sqrt{\beta_i^2 + \beta_j^2} \,,$$

$$\Omega_{union}(\beta) = \sup_{\alpha \in \mathbb{R}^p : \forall i \sim j, \| \alpha_i^2 + \alpha_j^2 \| \leq 1} \alpha^\top \beta \,.$$

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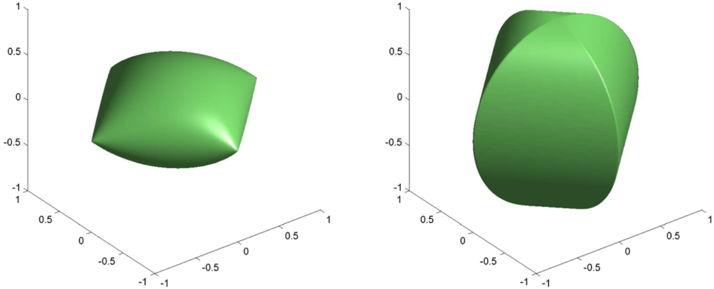
Example: finding discriminant modules in gene networks



Groups $(1,2)$ *and* $(2,3)$*. Left:* $\Omega_{intersection}(\beta)$*. Right:* $\Omega_{union}(\beta)$*. Vertical axis is* β_2*.*

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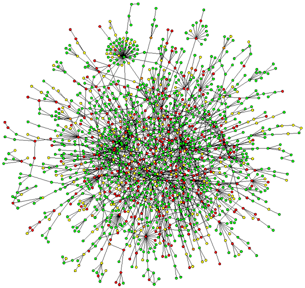
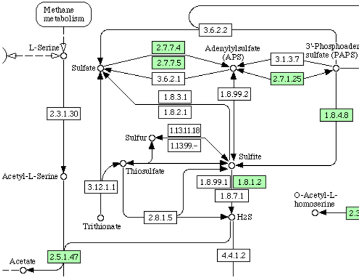
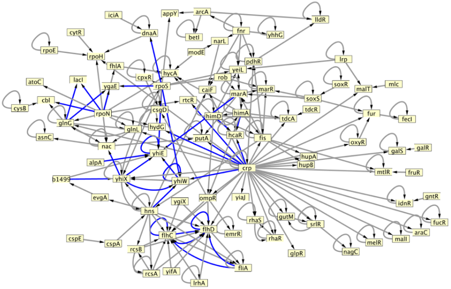
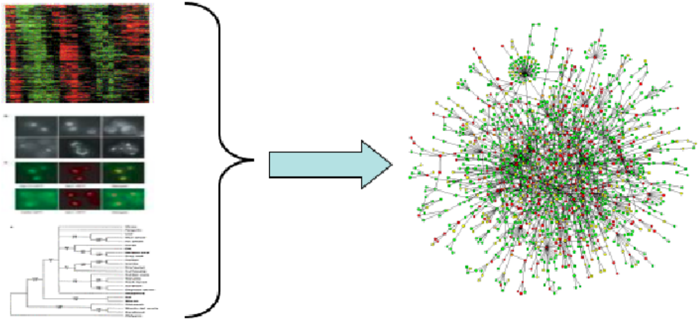
Biological networks







Our goal



Data

- Gene expression,
- Gene sequence,
- Protein localization, ...

Graph

- Protein-protein interactions,
- Metabolic pathways,
- Signaling pathways, ...

More precisely

“De novo” inference

- Given data about individual genes and proteins
- Infer the edges between genes and proteins

“Supervised” inference

- Given data about individual genes and proteins
- and given some known interactions
- infer unknown interactions

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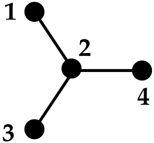
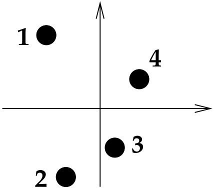
Supervised inference by pattern recognition

Formulation and basic issue

- A pair can be connected (1) or not connected (-1)
- From the known subgraph we can extract examples of connected and non-connected pairs
- However the genomic data characterize individual proteins; we need to work with pairs of proteins instead!



Known graph



Genomic data

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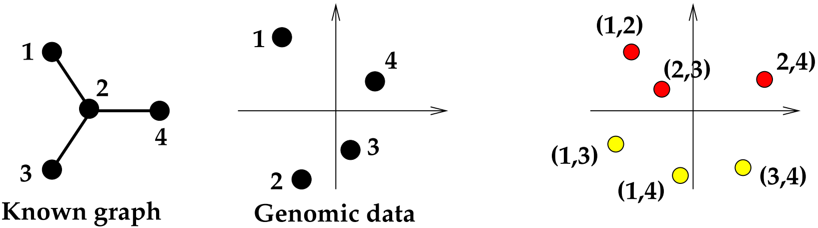

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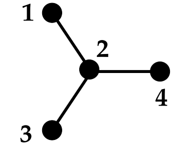

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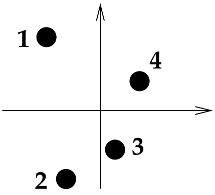

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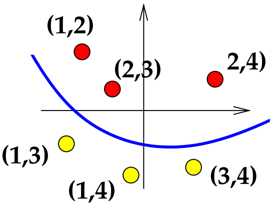

Tensor product SVM (Ben-Hur and Noble, 2006)

- Intuition: a pair (A, B) is similar to a pair (C, D) if:
  - A is similar to C and B is similar to D, or...
  - A is similar to D and B is similar to C
- Formally, define a similarity between pairs from a similarity between individuals by

$$K_{TPPK}\left((a,b),(c,d)\right) = K(a,c)K(b,d) + K(a,d)K(b,c) \,.$$

- If K is a positive definite kernel for individuals then K_{TPPK} is a p.d. kernel for pairs which can be used by SVM
- This amounts to representing a pair (a, b) by the symmetrized tensor product:

$$(a,b) \to (a \otimes b) \oplus (b \otimes a) \,.$$

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Metric learning pairwise SVM (V. et al, 2007)

- Intuition: a pair (A, B) is similar to a pair (C, D) if:
  - $A - B$ is similar to $C - D$, or...
  - $A - B$ is similar to $D - C$.
- Formally, define a similarity between pairs from a similarity between individuals by

$$K_{MLPK}((a,b),(c,d)) = (K(a,c) + K(b,d) - K(a,c) - K(b,d))^2 \ .$$

- If K is a positive definite kernel for individuals then K_{MLPK} is a p.d. kernel for pairs which can be used by SVM
- This amounts to representing a pair (a, b) by the symmetrized difference:

$$(a,b) \to (a-b)^{\otimes 2} \ .$$

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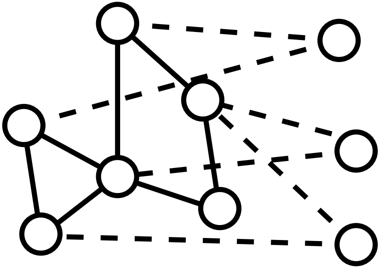
Supervised inference with local models

The idea (Bleakley et al., 2007)

- Motivation: define specific models for each target node to discriminate between its neighbors and the others
- Treat each node independently from the other. Then combine predictions for ranking candidate edges.



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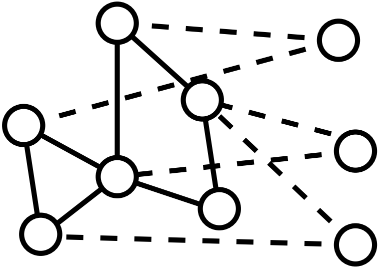
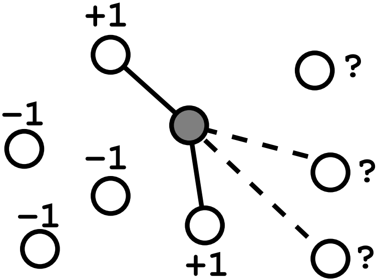
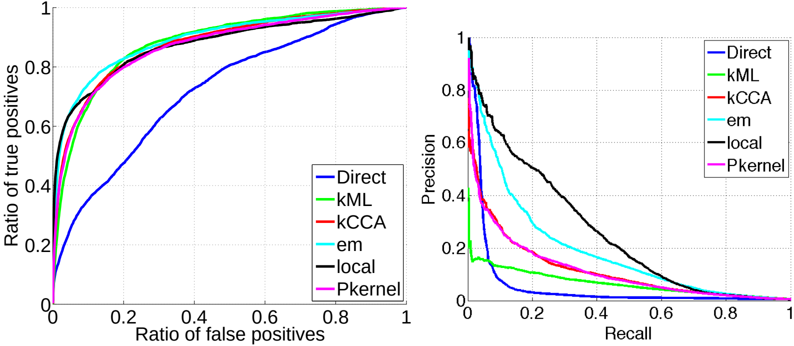


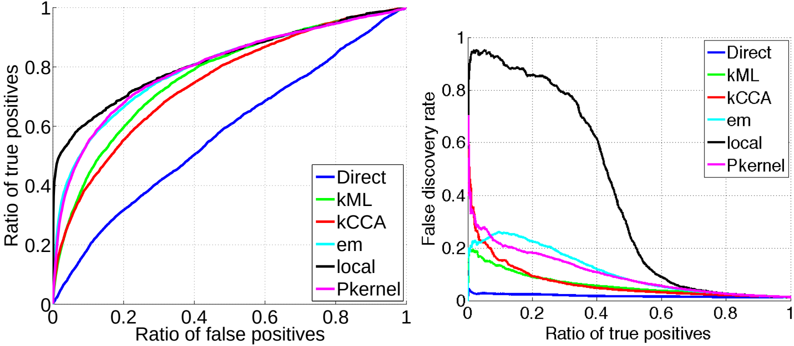


Results: protein-protein interaction (yeast)



(from Bleakley et al., 2007)

Results: metabolic gene network (yeast)



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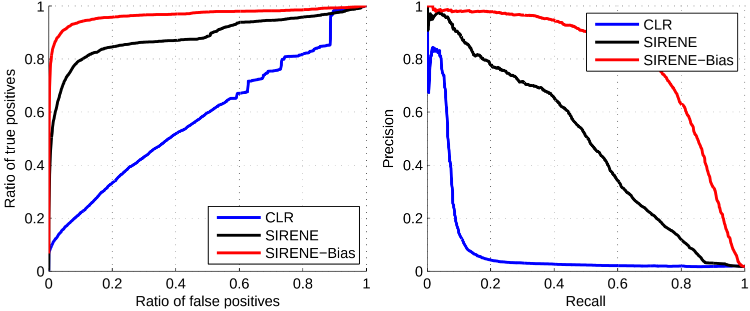
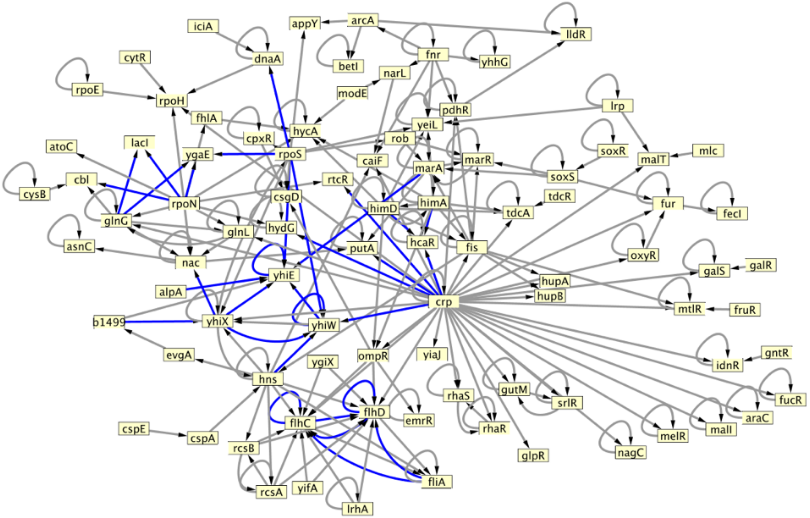
Results: regulatory network (E. coli)



Method	Recall at 60%	Recall at 80%
SIRENE	**44.5%**	**17.6%**
CLR	7.5%	5.5%
Relevance networks	4.7%	3.3%
ARACNe	1%	0%
Bayesian network	1%	0%

SIRENE = Supervised Inference of REgulatory NEtworks (Mordelet and V., 2008)

Results: predicted regulatory network (E. coli)



Prediction at 60% precision, restricted to transcription factors (from Mordelet and V., 2008).

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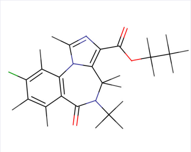
Virtual screening

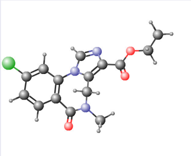
Objective

Build models to predict biochemical properties of small molecules from their structures.

Structures

$C_{15}H_{14}ClN_3O_3$

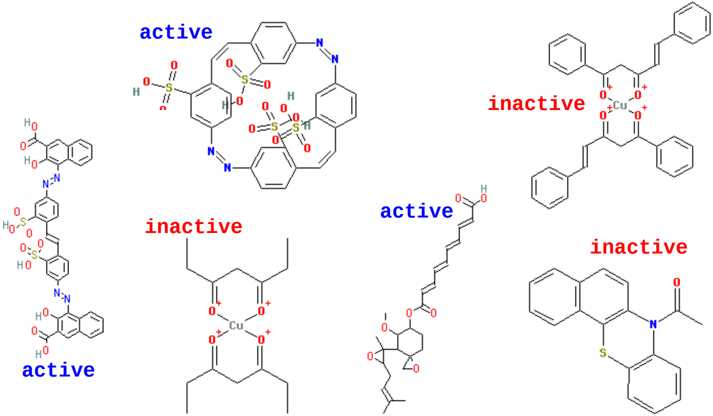




Properties

- binding to a therapeutic target,
- pharmacokinetics (ADME),
- toxicity...

Ligand-Based Virtual Screening and QSAR



NCI AIDS screen results (from http://cactus.nci.nih.gov).

Formalization

The problem

- Given a set of training instances $(x_1, y_1), \ldots, (x_n, y_n)$, where x_i's are graphs and y_i's are continuous or discrete variables of interest,
- Estimate a function

$$y = f(x)$$

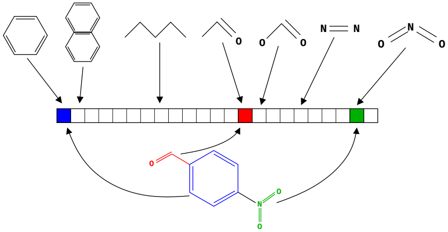
  where x is any graph to be labeled.
- This is a classical regression or pattern recognition problem over the set of graphs.

Classical approaches

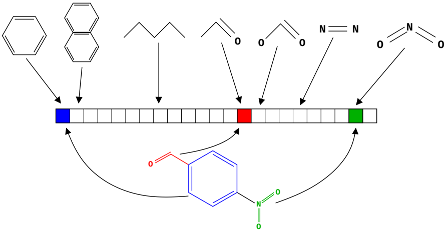
Two steps

1. Map each molecule to a vector of fixed dimension using molecular descriptors
   - Global properties of the molecules (mass, logP...)
   - 2D and 3D descriptors (substructures, fragments, ...)
2. Apply an algorithm for regression or pattern recognition.
   - PLS, ANN, ...

Example: 2D structural keys



Which descriptors?



Difficulties

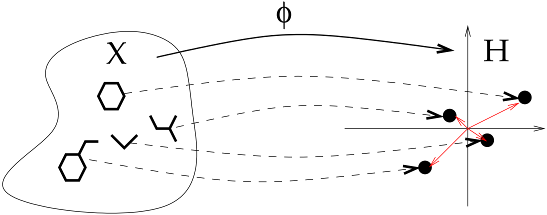
- Many descriptors are needed to characterize various features (in particular for 2D and 3D descriptors)
- But too many descriptors are harmful for memory storage, computation speed, statistical estimation

Kernels

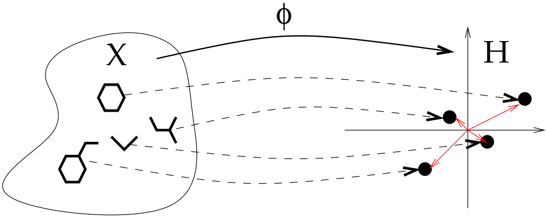
Definition

- Let $\Phi(x) = (\Phi_1(x), \ldots, \Phi_p(x))$ be a vector representation of the molecule x
- The kernel between two molecules is defined by:

$$K(x, x') = \Phi(x)^\top \Phi(x') = \sum_{i=1}^{p} \Phi_i(x)\Phi_i(x') \, .$$



The kernel trick

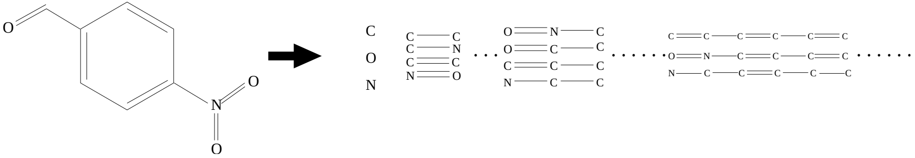


$$K(x,x') = \Phi(x)^\top \Phi(x')$$

The trick

- Many linear algorithms for regression or pattern recognition can be expressed only in terms of inner products between vectors
- Computing the kernel is often more efficient than computing $\Phi(x)$, especially in high or infinite dimensions!

Example: 2D fragment kernel



- $\phi_d(x)$ is the vector of counts of all fragments of length d:

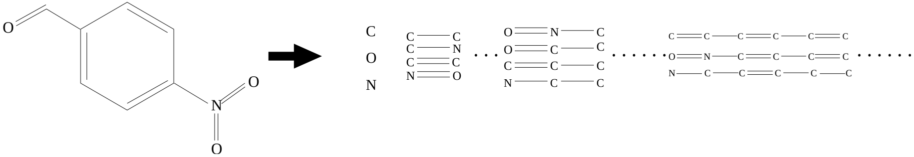
$$\phi_1(x) = (\quad \texttt{\#(C),\#(O),\#(N),} \quad \ldots)^\top$$

$$\phi_2(x) = (\quad \texttt{\#(C-C),\#(C=O),\#(C-N),} \quad \ldots)^\top \quad \text{etc...}$$

- The 2D fragment kernel is defined, for $\lambda < 1$, by

$$K_{fragment}(x, x') = \sum_{d=1}^{\infty} r(\lambda) \phi_d(x)^\top \phi_d(x') \,.$$

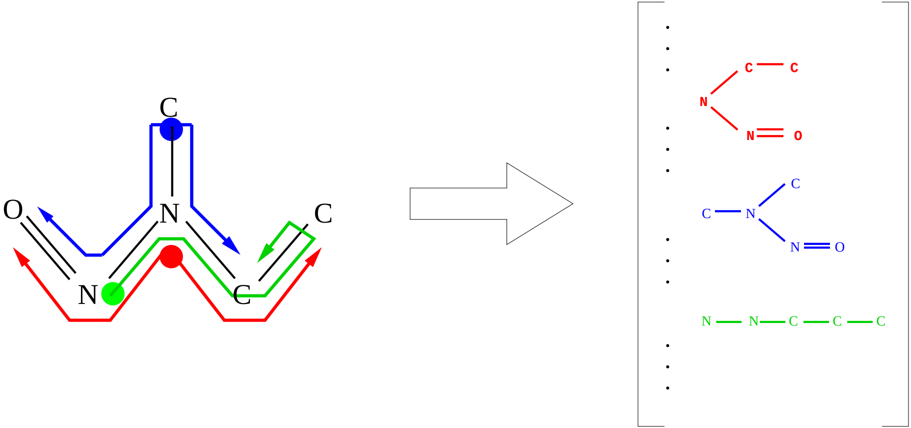
Example: 2D fragment kernel



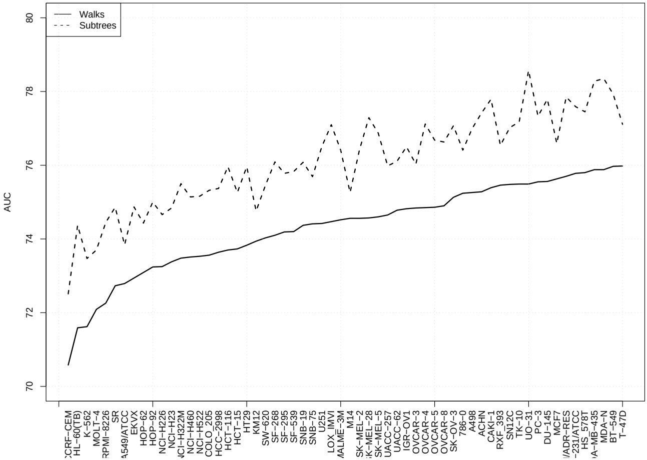
In practice

- $K_{fragment}$ can be computed efficiently (geometric kernel, random walk kernel...) although the feature space has infinite dimension.
- Increasing the specificity of atom labels improves performance
- Selecting only “non-tottering” fragments can be done efficiently and improves performance.

Example: 2D subtree kernel

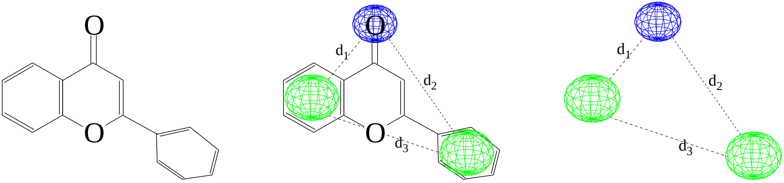


2D Subtree vs fragment kernels (Mahé and V, 2007)



Screening of inhibitors for 60 cancer cell lines (from Mahé and V., 2008)

Example: 3D pharmacophore kernel (Mahé et al., 2005)



$$K(x,y) = \sum_{p_x \in \mathcal{P}(x)} \sum_{p_y \in \mathcal{P}(y)} \exp\left(-\gamma d\left(p_x, p_y\right)\right) .$$

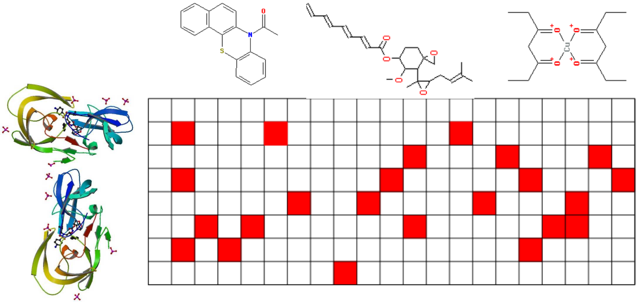
Results (accuracy)

Kernel	BZR	COX	DHFR	ER
2D (Tanimoto)	71.2	63.0	76.9	77.1
3D fingerprint	75.4	67.0	76.9	78.6
3D not discretized	**76.4**	**69.8**	**81.9**	**79.8**

Chemogenomics

The problem

- Similar targets bind similar ligands
- Instead of focusing on each target individually, can we screen the biological space (target families) vs the chemical space (ligands)?
- Mathematically, learn $f(\textit{target}, \textit{ligand}) \in \{\textit{bind}, \textit{notbind}\}$



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Chemogenomics with SVM

Tensor product SVM

- Take the kernel:

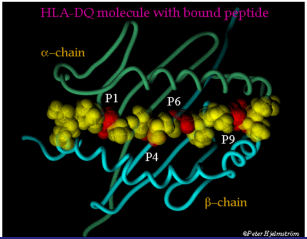
$$K\left((t,l),(t',l')\right) = K_t(t,t')K_l(l,l')\,.$$

- Equivalently, represent a pair (t,l) by the vector $\phi_t(t) \otimes \phi_l(l)$
- Allows to use any kernel for proteins K_t with any kernel for small molecules K_l
- When K_t is the Dirac kernel, we recover the classical paradigm: each target is treated independently from the others.
- Otherwise, information is shared across targets. The more similar the targets, the more they share information.

Example: MHC-I epitope prediction across different alleles

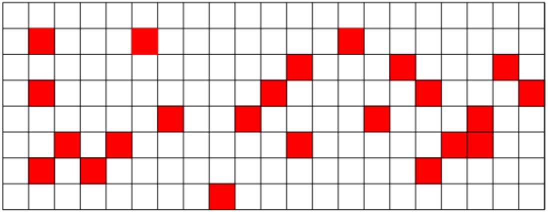
The approach (Jacob and V., 2007)

- take a kernel to compare different MHC-I alleles (e.g., based on the amino-acids in the paptide recognition pocket)
- take a kernel to compare different epitopes (9-mer peptides)
- Combine them to learn the $f(allele, epitope)$ function
- State-of-the-art performance
- Available at `http://cbio.ensmp.fr/kiss`



Generalization: collaborative filtering with attributes

- General problem: learn $f(x, y)$ with a kernel K_x for x and a kernel K_y for y.
- SVM with a tensor product kernel $K_x \otimes K_y$ is a particular case of something more general: estimating an operator with a spectral regularization.
- Other spectral regularization are possible (e.g., trace norm) and lead to efficient algorithms
- More details in Abernethy et al. (2008).



Outline

1 Supervised classification of genomic data

2 Inference of biological networks

3 Virtual screening and chemogenomics

4 Conclusion

Conclusion

- Modern machine learning methods for regression / classification lend themselves well to the integration of prior knowledge in the penalization / regularization function.
- Inference of biological networks can be formulated in the framework of pattern recognition.
- Kernel methods (eg SVM) allow to manipulate complex objects (eg molecules, biological sequences) as soon as kernels can be defined and computed.

People I need to thank

Including prior knowledge in penalization

Franck Rapaport, Emmanuel Barillot, Andrei Zynoviev, Christian Lajaunie, Yves Vandenbrouck, Nicolas Foveau...

Virtual screening, kernels etc..

Pierre Mahé, Laurent Jacob, Liva Ralaivola, Véronique Stoven, Brice Hoffman, Martial Hue, Francis Bach, Jacob Abernethy, Theos Evgeniou...

Network inference

Kevin Bleakley, Fantine Mordelet, Yoshihiro Yamanihi, Gérard Biau, Minoru Kanehisa, William Noble, Jian Qiu...