Some contributions of machine learning to bioinformatics

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Where I come from

- A joint lab about “Cancer computational genomics, bioinformatics, biostatistics and epidemiology”
- Located in the Institut Curie, a major hospital and cancer research institute in Europe
- Hosted in a brand new building in the center of Paris (near Notre-Dame, Saint-Germain, Pantheon...)

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Our research

Main topics

- **Epidemiology** of cancer (eg, studies on etiology of breast cancer)
- **General biostatistics** (eg, clinical trials, risk modelling...)
- **Biostatistics and machine learning for bioinformatics** (high-throughput data processing, modeling, predictive models...)
- **Systems biology**: analysis, modeling, inference of important regulatory and signaling systems
- **IT**: software developments, DB, web
Main topics in machine learning / statistics

- Processing **high-throughput data** (normalization, analysis): transcriptome, genome (CGH/SNP), proteomics, kinome. High-throughput sequencing is coming soon.
- Making **predictive models**, in particular diagnosis / prognosis
- **Data mining** / integration of **heterogeneous** data
- **Structural bioinformatics**, protein-protein interactions, virtual screening, chemogenomics
Outline

1. Including prior knowledge in classification and regression
2. Virtual screening and chemogenomics
3. Inference on biological networks
4. Conclusion
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Including prior knowledge in classification and regression

Virtual screening and chemogenomics

Inference on biological networks

Conclusion
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 \( \beta_i \) quantifies the influence of feature \( i \) (but...)

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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 \( \beta \), e.g.:

\[ \Omega(\beta) \leq C. \]
A common method in statistics to learn with few samples in high dimension is to constrain the Euclidean norm of $\beta$

$$\Omega_{\text{ridge}}(\beta) = \| \beta \|^2_2 = \sum_{i=1}^{p} \beta_i^2,$$

(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 $\beta$: 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
Incorporating prior knowledge

The idea

- If we have a specific prior knowledge about the “correct” weights, it can be included in $\Omega$ in the constraint:

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

- If we design a convex function $\Omega$, then the algorithm boils down to a convex optimization problem (usually easy to solve).

- Similar to priors in Bayesian statistics
The problem

- 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?
- Prior knowledge: we expect $\beta$ to be sparse, and piecewise constant along the genome.
Example: CGH array classification

A solution (Rapaport et al., 2008)

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

- 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

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

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

\[ \Omega_{\text{graphfusion}}(\beta) = \sum_{i \sim j} |\beta_i - \beta_j| + \sum_i |\beta_i|. \]
Example: finding discriminant modules in gene networks

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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?

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:

$$K(x, x') = \Phi(x)^\top \Phi(x') = \sum_{i=1}^{p} \Phi_i(x) \Phi_i(x').$$
Example: 2D fragment kernel

- $\phi_d(x)$ is the vector of counts of all fragments of length $d$:
  
  $\phi_1(x) = (\#(C), \#(O), \#(N), \ldots)^\top$
  
  $\phi_2(x) = (\#(C-C), \#(C=O), \#(C-N), \ldots)^\top$ etc...

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

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

- \( K_{\text{fragment}} \) 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
Screening of inhibitors for 60 cancer cell lines (from Mahé and V., 2008)
Example: 3D pharmacophore kernel (Mahé et al., 2005)

\[ K(x, y) = \sum_{p_x \in P(x)} \sum_{p_y \in P(y)} \exp(-\gamma d(p_x, p_y)) . \]

### Results (accuracy)

<table>
<thead>
<tr>
<th>Kernel</th>
<th>BZR</th>
<th>COX</th>
<th>DHFR</th>
<th>ER</th>
</tr>
</thead>
<tbody>
<tr>
<td>2D (Tanimoto)</td>
<td>71.2</td>
<td>63.0</td>
<td>76.9</td>
<td>77.1</td>
</tr>
<tr>
<td>3D fingerprint</td>
<td>75.4</td>
<td>67.0</td>
<td>76.9</td>
<td>78.6</td>
</tr>
<tr>
<td>3D not discretized</td>
<td><strong>76.4</strong></td>
<td><strong>69.8</strong></td>
<td><strong>81.9</strong></td>
<td><strong>79.8</strong></td>
</tr>
</tbody>
</table>
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 $f(\text{target, ligand}) \in \{\text{bind, notbind}\}$
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 peptide recognition pocket)
- take a kernel to compare different epitopes (9-mer peptides)
- Combine them to learn the $f(\text{allele}, \text{epitope})$ function
- State-of-the-art performance
- Available at http://cbio.ensmp.fr/kiss
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).
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Biological networks
Our goal

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

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

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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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Main messages

1. Most methods developed so far are “de novo” (e.g., co-expression, Bayesian networks, mutual information nets, dynamical systems...)

2. However most real-world application fit the “supervised” framework

3. Solving the “supervised” problem is much easier (and more efficient) than the “de novo” problem. It requires less hypothesis.
De novo methods

Typical strategies

- Fit a dynamical system to time series (e.g., PDE, boolean networks, state-space models)
- Detect statistical conditional independence or dependency (Bayesian network, mutual information networks, co-expression)

Pros

- Excellent approach if the model is correct and enough data are available
- Interpretability of the model
- Inclusion of prior knowledge

Cons

- Specific to particular data and networks
- Needs a correct model!
- Difficult integration of heterogeneous data
- Often needs a lot of data and long computation time
Motivation

In actual applications,

- we know in advance parts of the network to be inferred
- the problem is to add/remove nodes and edges using genomic data as side information

Supervised method

- Given genomic data and the currently known network...
- Infer **missing edges** between current nodes and additional nodes.
Idea

- The direct similarity-based method fails because the distance metric used might not be adapted to the inference of the targeted protein network.
- Solution: use the known subnetwork to refine the distance measure, before applying the similarity-based method.
- Examples: kernels CCA (Yamanishi et al. 2004), kernel metric learning (V and Yamanishi, 2005)
Supervised approach by Metric learning

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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!
Supervised inference by pattern recognition

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Known graph

Genomic data

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Formulation and basic issue

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- 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!
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) \rightarrow (a \otimes b) \oplus (b \otimes a) .
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Formally, define a similarity between pairs from a similarity between individuals by

\[
K_{MLPK} \left( ((a, b), (c, d)) \right) = (K(a, c) + K(b, d) - K(a, c) - K(b, d))^2.
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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:

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(a, b) \rightarrow (a - b)^\otimes 2.
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Metric learning pairwise SVM (V. et al, 2007)

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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.
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.

![Diagram of a network with nodes and edges labeled with +1 or -1, indicating positive or negative predictions.](image-url)
The LOCAL model
The LOCAL model
The LOCAL model
The LOCAL model
The LOCAL model
The LOCAL model
The LOCAL model
The LOCAL model
The LOCAL model
The LOCAL model
The LOCAL model
The LOCAL model
The LOCAL model
The LOCAL model
Results: protein-protein interaction (yeast)

(from Bleakley et al., 2007)
Results: metabolic gene network (yeast)

(from Bleakley et al., 2007)
Results: regulatory network (E. coli)

<table>
<thead>
<tr>
<th>Method</th>
<th>Recall at 60%</th>
<th>Recall at 80%</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIRENE</td>
<td>44.5%</td>
<td>17.6%</td>
</tr>
<tr>
<td>CLR</td>
<td>7.5%</td>
<td>5.5%</td>
</tr>
<tr>
<td>Relevance networks</td>
<td>4.7%</td>
<td>3.3%</td>
</tr>
<tr>
<td>ARACNe</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Bayesian network</td>
<td>1%</td>
<td>0%</td>
</tr>
</tbody>
</table>

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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Modern machine learning methods for regression / classification lend themselves well to the integration of prior knowledge in the penalization / regularization function, in particular for feature selection / grouping. Applications in array CGH classification, siRNA design, microarray classification with gene networks.

Kernel methods (eg SVM) allow to manipulate complex objects (eg molecules, biological sequences) as soon as kernels can be defined and computed. Applications in virtual screening, QSAR, chemogenomics.

Inference of biological networks can be formulated as a supervised problem if the graph is partly known, and powerful methods can be applied. Application in PPI, metabolic and regulatory networks inference.
# People I need to thank

## Including prior knowledge in penalization
- Franck Rapaport, Emmanuel Barillot, Andrei Zynoviev, Christian Lajaunie, Yves Vandenbrouck, Nicolas Foveau...

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