Analysis and inference of gene networks from genomic data

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Motivations

- Many heterogeneous data **about genes**: sequences, expression, evolution, structures, etc...
- More and more data **between genes**: interactome, pathways, regulation etc...
- **Goal**: propose a **formalism** and **algorithms** to **compare** these data, and to **infer** gene networks from high-throughput genomic data.
Example 1: Comparing gene expression and pathway databases

- Detect active pathways?
- Denoise expression data?
- Denoise pathway database?
- Find new pathways?
- Are there “correlations”?
Example 2:  
Gene network inference
Outline

- A direct approach to network inference
- Supervised network inference
- Extraction of pathway activity
- Learning from several heterogeneous data
Part 1

A direct approach to network inference
The problem
Related approaches

- Bayesian nets for regulatory networks (Friedman et al. 2000)
- Boolean networks (Akutsu, 2000)
- Joint graph method (Marcotte et al, 1999)
Network inference: the direct approach
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Evaluation of the performance: the ROC curve
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True Positives

False Positives
Evaluation of the performance : the ROC curve

True Positives

False Positives
Evaluation of the performance: the ROC curve

- True Positives
- False Positives
Evaluation of the performance : the ROC curve
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\[ ROC = \frac{21}{24} = 87.5\% \]
**Application: the metabolic gene network**

- **Glucose** to **Glucose−6P**
  - HKA, HKB, GLK1
  - PGM1, PGM2
- **Glucose−6P** to **Fructose−6P**
  - PGT1
- **Fructose−6P** to **Fructose−1,6P2**
  - PFK1, PFK2
  - FBP1
- **Glucose−1P** to **Glucose−6P**
  - GAL10
- **HKA1**, **PGM1**, **PGT1**, **PFK1**, **PFK2**
- **FBA1**

Link two genes when they can **catalyze two successive reactions**
Evaluation of the direct approach

The metabolic network of the yeast involves 769 genes. Each gene is represented by 157 expression measurements. (ROC=0.52)
Shortcuts of the direct approach

- What similarity measure between profiles should be used?
Shortcuts of the direct approach

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- Which network are we expecting to recover?
Shortcuts of the direct approach

- What similarity measure between profiles should be used?
- Which network are we expecting to recover?
- How to use prior knowledge about the network to be recovered?
Part 2

Supervised network inference
The supervised gene inference problem
The supervised gene inference problem
The idea in a nutshell

- Use the known network to “learn” a more relevant measure of similarity
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- For example, map the genes expression profiles to a different space, where the natural distance better fits the known network
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- For example, map the genes expression profiles to a different space, where the natural distance better fits the known network

- Then apply the direct strategy in the second space
Illustration
Illustration
Illustration
Illustration
Illustration

Φ
Illustration

\[ \Phi \]
Learning the mapping $\Phi$

- Let $x \in \mathbb{R}^p$ be an expression profile
Learning the mapping $\Phi$

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- Let us consider linear mappings:

$$\Phi(x) = (f_1(x), \ldots, f_d(x))' \in \mathbb{R}^d$$

made of linear features $f_i(x) = w_i^\top x$
Learning the mapping $\Phi$

- Let $x \in \mathbb{R}^p$ be an expression profile.
- Let us consider linear mappings:

$$\Phi(x) = (f_1(x), \ldots, f_d(x))' \in \mathbb{R}^d$$

made of linear features $f_i(x) = w_i^T x$.
- A feature $f : \mathbb{R}^p \to \mathbb{R}$ is “good” if connected genes in the known network have similar value.
"Good" features

- A "good" feature \( f(x) = w^\top x \) should minimize:

\[
R(f) = \frac{\sum_{i \sim j} (f(x_i) - f(x_j))^2}{\sum_{i=1}^{n} f(x_i)^2},
\]

- Regularisation: for statistical reasons, it is safer to minimize:

\[
\min_{f(x) = w^\top x} \frac{\sum_{i \sim j} (f(x_i) - f(x_j))^2 + \lambda \|w\|^2}{\sum_{i=1}^{n} f(x_i)^2},
\]
Influence of $\lambda$

- $\lambda \rightarrow +\infty$: PCA
  - Useful for noisy, high-dimensional data.
  - Used in spectral clustering. The graph does not play any role (unsupervised)

- $\lambda \rightarrow 0$: second smallest eigenvector of the graph
  - Useful to embed the graph in a Euclidean space (used in graph partitioning)
  - Sensitive to noise. Mapping of points outside of the graph unstable (overfitting)
Extracting successive features

- Successive features to form $\Phi$ can be obtained by:

$$w_i = \arg \min_{w \perp \{w_1, \ldots, w_{i-1}\}, \text{var}(f_w)=1} \left\{ \sum_{i \sim j} (f_w(x_i) - f_w(x_j))^2 + \lambda ||w||^2 \right\}.$$
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- Each features satisfies $w = \sum_i \alpha_i x_i$ (Representer theorem)
Solving the problem

- The problem can then be rewritten:

\[
\alpha_i = \arg\min_{\alpha \in \mathbb{R}^n, \alpha K_V \alpha_1 = \ldots = \alpha K_V \alpha_{i-1}} \left\{ \frac{\alpha^\top K_V L K_V \alpha + \lambda \alpha^\top K_V \alpha}{\alpha^\top K^2_V \alpha} \right\}
\]

where \( K_V \) is the centered \( n \times n \) matrix of inner products and \( L \) is the Laplacian of the graph.

- It is equivalent to solving the generalized eigenvalue problem:

\[
(L K_V + \lambda I) \alpha = \mu K_V \alpha.
\]
Evaluation of the supervised approach: effect of $\lambda$

Metabolic network, 10-fold cross-validation, 1 feature
Evaluation of the supervised approach: number of features ($\lambda = 2$)

![ROC as a function of number of features (lambda=2)]
Part 3

Extraction of pathway activity
The idea

- The previous approach is a way to extract features from gene expression data: $f(x) = w^\top x$.

- These features are smooth on the graph: connected nodes tend to have similar values.

- This is a way to detect “correlations” between gene expression data and metabolic network: typical activity patterns of typical pathways.
Experiment

- **Gene network**: two genes are linked if they catalyze successive reactions in the KEGG database (669 yeast genes)

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

Expression vs. Time

Graph showing changes in expression over time.
Learning from several heterogeneous data
Summary of the process
The “kernel trick”

- The matrix of similarity is $K_{i,j} = x_i^\top x_j$
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- However, more general measures are allowed: they simply must be symmetric positive definite

- This enables nonlinear features, as well as features from other types of data, as soon as a symmetric p.d. function $K(x, y)$ is defined
Several kernels have been developed recently:

- for phylogenetic profiles (JPV. 2004)
- for gene sequences (Leslie et al. 2003, Saigo et al. 2004, ...)
- for nodes in a network (Kondor et al. 2000)
Learning from heterogeneous data

- Suppose several data are available about the genes, e.g., expression, localization, structure, predicted interaction etc...

- Each data can be represented by a positive definite similarity matrix $K_1, \ldots, K_p$ called kernels

- Kernel can be combined by various operations, e.g., addition:

\[
K = \sum_{i=1}^{p} K_i
\]
Learning from heterogeneous data (unsupervised)
Learning from heterogeneous data (supervised)
The gene YJR137C was predicted in 09/2003 between \( EC : 1.8.4.8 \) and \( EC : 2.5.1.47 \). It was recently annotated as \( EC:1.8.1.2 \).
Conclusion
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- A new approach to feature extractions and supervised network inference, many possible variants and extensions

- Straightforward generalization to any network (e.g., interactome): the same data can be used to infer different networks

- Currently tested on characterization of tumor cells (with Institut Curie) and metabolism of P. falciparum (with Institut Pasteur).