Inferring and using biological networks

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We have many genes and proteins..
Network 1: protein-protein interaction
Network 2: metabolic network
Network 3: gene transcriptional regulatory network
Data available

*Biologists* have collected a lot of data about proteins. e.g.,

- Gene expression measurements
- Phylogenetic profiles
- Location of proteins/enzymes in the cell
Problem 1: how to infer relationships between genes from biological data?

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Problem 2: how to use biological networks to help in the analysis of genomic data?
Outline

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2. How to use biological networks to help in the analysis of genomic data?
Typical reverse engineering strategies

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

![Diagram showing the inference process in biological networks]
The known metabolic network of the yeast involves 769 proteins.

Predict edges from distances between a variety of genomic data (expression, localization, phylogenetic profiles, interactions).
Large-Scale Mapping and Validation of \textit{Escherichia coli} Transcriptional Regulation from a Compendium of Expression Profiles

Jeremiah J. Faith\(^1\), Boris Hayete\(^1\), Joshua T. Thaden\(^2,3\), Ilaria Mogno\(^2,4\), Jamey Wierzbowski\(^2,5\), Guillaume Cottarel\(^2,5\), Simon Kasif\(^1,2\), James J. Collins\(^1,2\), Timothy S. Gardner\(^1,2\)*
Change of paradigm

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.
Given a training set of patterns in two classes, learn to discriminate them

Many algorithms (ANN, SVM, Decision trees, ...)
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Interlude: Pattern recognition

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Given a training set of patterns in two classes, learn to discriminate them

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Interlude : Pattern recognition
Pattern recognition and graph inference

**Pattern recognition**
Associate a binary label $Y$ to each data $X$

**Graph inference**
Associate a binary label $Y$ to each pair of data $(X_1, X_2)$

**Two solutions**
- Consider each pair $(X_1, X_2)$ as a single data -> learning over pairs
- Reformulate the graph inference problem as a pattern recognition problem at the level of individual vertices -> local models
Pattern recognition and graph inference

**Pattern recognition**

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Pattern recognition for pairs

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
Pattern recognition for pairs

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Representing a pair

Concatenation?

A simple idea is to concatenate the vectors $u$ and $v$ to obtain a $2p$-dimensional vector of $(u, v)$:

$$\psi(u, v) = u \oplus v = \left( \begin{array}{c} u \\ v \end{array} \right).$$

Problem: a linear function then becomes additive...

$$f(u, v) = w^\top \psi(u, v) = w_1^\top u + w^\top v.$$
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Other representations for pairs

**Symmetric tensor product (Ben-Hur and Noble, 2006)**

\[ \psi(u, v) = (u \otimes v) + (v \otimes u) . \]

**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 \(C\)

**Metric learning (V. et al, 2007)**

\[ \psi(u, v) = (u - v) \otimes^2 . \]

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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.

![Graph diagram](image)
The idea (Bleakley et al., 2007)

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A few remarks about the local approach

- Weak hypothesis:
  - if A is connected to B,
  - if C is similar to B,
  - then A is likely to be connected to C.

- Computationally: much faster to train $N$ local models with $N$ training points each, than to train 1 model with $N^2$ training points.

- Caveats:
  - each local model may have very few training points
  - no sharing of information between different local models
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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)

- CLR
- SIRENE
- SIRENE−Bias

<table>
<thead>
<tr>
<th>Method</th>
<th>Recall at 60%</th>
<th>Recall at 80%</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIRENE</td>
<td><strong>44.5%</strong></td>
<td><strong>17.6%</strong></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>
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SIRENE = Supervised Inference of REgulatory NEtworks (Mordelet and V., 2008)
Prediction of missing enzyme genes in a bacterial metabolic network

Reconstruction of the lysine-degradation pathway of *Pseudomonas aeruginosa*

Yoshihiro Yamanishi\(^1\), Hisaaki Mihara\(^2\), Motoharu Osaki\(^2\), Hisashi Muramatsu\(^3\), Nobuyoshi Esaki\(^2\), Tetsuya Sato\(^1\), Yoshiyuki Hizukuri\(^1\), Susumu Goto\(^1\) and Minoru Kanehisa\(^1\)

1 Bioinformatics Center, Institute for Chemical Research, Kyoto University, Japan
2 Division of Environmental Chemistry, Institute for Chemical Research, Kyoto University, Japan
3 Department of Biology, Graduate School of Science, Osaka University, Japan
Applications: missing enzyme prediction
Prediction of nitrogen metabolism-related genes in *Anabaena* by kernel-based network analysis

Shinobu Okamoto¹*, Yoshihiro Yamanishi¹, Shigeki Ehira², Shuichi Kawashima³, Koichiro Tonomura¹**, and Minoru Kanehisa¹

¹ Bioinformatics Center, Institute for Chemical Research, Kyoto University, Uji, Japan
² Department of Biochemistry and Molecular Biology, Faculty of Science, Saitama University, Saitama, Japan
³ Human Genome Center, Institute of Medical Science, University of Tokyo, Meguro, Japan
Determination of the role of the bacterial peptidase PepF by statistical inference and further experimental validation

Liliana LOPEZ KLEINE\textsuperscript{1,2}, Alain TRUBUIL\textsuperscript{1}, Véronique MONNET\textsuperscript{2}

\textsuperscript{1}Unité de Mathématiques et Informatiques Appliquées. INRA Jouy en Josas 78352, France.
\textsuperscript{2}Unité de Biochimie Bactérienne. INRA Jouy en Josas 78352, France.
Prediction at 60% precision, restricted to transcription factors (from Mordelet and V., 2008).
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Tissue classification from microarray data

**Goal**

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

**Issue**

- 20K+ genes but only <100 tumours
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...)

![Diagram of linear classification](image)

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Linear classifiers

Training the model

- Minimize an empirical risk on the training samples:

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

- ... subject to some constraint on \( \beta \), e.g.:

\[
\Omega(\beta) \leq C.
\]
Classical penalties

- **Feature selection** (NP-hard, many greedy variants exist):

\[
\Omega_{\text{Best subset selection}}(\beta) = \| \beta \|_0 = \sum_{i=1}^{p} \mathbf{1}(\beta_i > 0).
\]

- **Small weights** (SVM, ridge regression, ...):

\[
\Omega_{\text{ridge}}(\beta) = \| \beta \|_2^2 = \sum_{i=1}^{p} \beta_i^2.
\]

- **Sparsity-inducing convex priors** (computationally tractable + feature selection):

\[
\Omega_{\text{LASSO}}(\beta) = \| \beta \|_1 = \sum_{i=1}^{p} |\beta_i|.
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Why LASSO leads to sparse solutions

Geometric interpretation with $p = 2$
How protein networks can help us

- Basic biological functions usually involve the coordinated action of several proteins:
  - Formation of protein complexes
  - Activation of metabolic, signalling or regulatory pathways
- Many pathways and protein-protein interactions are already known
- Hypothesis: the signature should be “coherent” with respect to this prior knowledge
Example: smooth signature

- Hypothesis: adjacent genes should have similar weights in the signature
- Penalty function (Rapaport et al., 2007):

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

1. Use the gene network to extract the “important information” in gene expression profiles by **Fourier analysis** on the graph.
2. Learn a linear classifier on the **smooth components** with classical ridge penalty.
Illustration (yeast, high vs. low irradiation doses)

- Glycolysis / Gluconeogenesis
- N Glycan biosynthesis
- Protein kinases
- Porphyrin and chlorophyll metabolism
- Riboflavin metabolism
- Folate biosynthesis
- Biosynthesis of steroids, ergosterol metabolism
- Lysine biosynthesis
- Phenylalanine, tyrosine and tryptophan biosynthesis
- Purine metabolism
- Nitrogen, asparagine metabolism
- DNA and RNA polymerase subunits
- Oxidative phosphorylation, TCA cycle
Spectral analysis of gene expression profiles using gene networks

Fig. 5. ... work was supported by the grant ACI-IMPBIO-2004-47 of the French Ministry for Research and New Technologies.
Example: smooth and sparse signature

- **Hypothesis:**
  - The signature should be **sparse** (gene selection)
  - **Connected genes** should have the same weight

- **Penalty function (Rapaport et al., 2008):**

\[
\Omega_{\text{piecewiseconstant}}(\beta) = \sum_{i \sim j} |\beta_i - \beta_j| + \lambda \sum_i |\beta_i|.
\]

Geometric interpretation with \( p = 2 \)
Hypothesis:

- the signature should be **sparse** (gene selection)
- selected genes should form **dense connected components** (without any constraint of their relative weights)

Penalty function (Jacob et al., 2009):

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

\[
\Omega_{\text{union}}(\beta) = \sup_{\alpha \in \mathbb{R}^p : \forall i \sim j, \|\alpha_i^2 + \alpha_j^2\| \leq 1} \alpha^\top \beta.
\]
Graph LASSO leads to structured sparsity

Groups (1, 2) and (2, 3). Left: $\Omega_{\text{intersection}}(\beta)$. Right: $\Omega_{\text{union}}(\beta)$. Vertical axis is $\beta_2$. 
A supervised machine learning formulation leads to promising results on the problem of inferring unknown relationships between genes and proteins.

Conversely, biological networks can help fighting the curse of dimensionality for classification of high-dimensional genomic data.

All this is progressing very quickly these days!
People I need to thank

- **Graph inference**: Yoshihiro Yamanishi, Minoru Kanehisa (Univ. Kyoto), Jian Qian, Bill Noble (Univ. Washington), Kevin Bleakley, Gerard Biau (Univ. Montpellier), Fantine Mordelelt (ParisTech)
- **Using graphs**: Franck Rapaport, Emmanuel Barillot, Andrei Zinovyev (Institut Curie), Laurent Jacob (ParisTech), Guillaume Obozinski (Berkeley / INRIA)