Machine learning approaches for reconstruction of genetic networks

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Motivations: systems biology

- Gene expression
- Sequence
- Protein structure
- Protein localization, etc...
- Regulatory network
- Signaling pathways
- Metabolic pathways
- Interaction network, etc...
Mains approaches

1. Direct approach = connect similar proteins.

2. Model-based approach = fit an a priori defined model (Bayesian network, dynamical system..).

3. Indirect approach = connect pairs of proteins similar to connected pairs.

Machine learning is present in all 3 approaches.
Indirect approach

- Classical setting of **supervised pattern recognition**: “given a training set of connected and non-connected pairs, learn to predict whether new pairs are connected or not”.

- Need to extend the representation of points to the representation of **pairs of points**.

- Example: a **pairwise kernel** (Ben-Hur and Noble, 2004):

\[
K_p ((u_1, u_2), (v_1, v_2)) = K(u_1, v_1)K(u_2, v_2) + K(u_1, v_2)K(u_2, v_1)
\]
Direct approach

- The simplest and most natural approach.

- Define a **measure of similarity** (e.g., correlation coefficient between expression profiles) and **connect the most similar pairs**.

- Usually **unsupervised**, but..
Performance of unsupervised direct approach

The metabolic network of the yeast involves 769 genes. Each gene is represented by 157 expression measurements. (ROC=0.52)
What is wrong?

- What similarity measure between profiles should be use?
What is wrong?

- What *similarity measure* between profiles should be used?
- *Which network* are we expecting to recover?
Supervised direct approach

- Given a set of known interacting pairs, we can learn how to measure their similarities before connecting similar pairs.

- Typical problem of distance metric learning.
Supervised direct approach

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![Diagram with nodes and edges illustrating the supervised direct approach.](image-url)
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Part 2

Supervised direct inference by generalized KPCA
Explicit mapping $\Phi$

- Let $x \in \mathbb{R}^p$ be a genomic data (e.g., expression profile)
Explicit 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 $f_i(x) = w_i^\top x$
Explicit mapping $\Phi$

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  \[
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  \]
  made of linear features
  \[
  f_i(x) = w_i^\top x
  \]
- 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 $f(x) = w^T x$ should minimize:

$$R(f) = \frac{\sum_{i \sim j} (f(x_i) - f(x_j))^2 - \sum_{i \neq j} (f(x_i) - f(x_j))^2}{\sum_{i=1}^{n} f(x_i)^2}$$
“Good” features

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

\[
R(f) = \frac{\sum_{i \sim j} (f(x_i) - f(x_j))^2 - \sum_{i \not\sim j} (f(x_i) - f(x_j))^2}{\sum_{i=1}^n f(x_i)^2}
\]

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

\[
\min_{f(x) = w^\top x} R(f) + \lambda \frac{\|w\|^2}{\sum_{i=1}^n f(x_i)^2}
\]
Influence of \( \lambda \)

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

- \( \lambda \to 0 \): 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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- Generalizes Principal Component Analysis (PCA)
Limitations

- How to generalize to non-linear features?
- How to process non-vectorial data (sequences, phylogenetic profiles, ...)


Overcoming the limitations

- Remember:

\[
\begin{align*}
\mathbf{w}_i &= \arg \min_{w \perp \{w_1, \ldots, w_{i-1}\}, \text{var}(f_w)=1} \left\{ \sum_{i \sim j} (f_w(x_i) - f_w(x_j))^2 + \lambda \|w\|^2 \right\}.
\end{align*}
\]

- In order to allow nonlinear features, we need to replace:

  - \(\|w\|^2\) by \(\|f\|^2\)
  - \(w_i \perp w_j\) by \(f_i \perp f_j\)
Positive definite kernels

Let $\mathcal{X}$ be a set (not necessarily vectors) endowed with a symmetric measure of similarity $k : \mathcal{X}^2 \rightarrow \mathbb{R}$ that satisfies:

$$\sum_{i=1}^{n} \sum_{j=1}^{n} c_i c_j k(x_i, x_j) \geq 0$$

for any $n \geq 0, (x_1, \ldots, x_n) \in \mathcal{X}$ and $(a_1, \ldots, a_n) \in \mathbb{R}$

- $k(x, y) = x \cdot y$ for $\mathcal{X} = \mathbb{R}^d$
- $k(x, y) = \exp\left(-\|x - y\|^2/(2\sigma^2)\right)$ for $\mathcal{X} = \mathbb{R}^d$
Reproducing kernel Hilbert space

- A p.d. kernel defines a **Hilbert space** of functions \( f : \mathcal{X} \to \mathbb{R} \) obtained by completing the span of \( \{ k(x, \cdot), x \in \mathcal{X} \} \).

- The norm of a function \( f(x) = \sum_{i=1}^{n} c_i k(x_i, x) \) is:

\[
\| f \|_k^2 = \sum_{i,j=1}^{n} c_i c_j k(x_i, x_j).
\]

- This space is called the **reproducing kernel Hilbert space** (RKHS).
Example: linear RKHS

For $\mathcal{X} = \mathbb{R}^d$ and $k(x, y) = x \cdot y$, we have:

- $f(x) = \sum_{i=1}^n c_i x_i \cdot x = f_w(x)$ with $w = \sum_{i=1}^n c_i x_i$.
- $\|f\|_k^2 = \sum_{i,j=1}^n c_i c_j x_i \cdot x_j = \|w\|^2$
- If $f(x) = w \cdot x$ and $g(x) = v \cdot x$ then:

  \[ \langle f, g \rangle_k = w \cdot v \]
Graph-driven feature extraction in RKHS

- For a general set $\mathcal{X}$ endowed with a p.d. kernel $k$ we therefore have the following graph-driven feature extractor:

$$f_i = \arg \min_{f \perp \{f_1, \ldots, f_{i-1}\}, \text{var}(f) = 1} \left\{ \sum_{i \sim j} (f(x_i) - f(x_j))^2 + \lambda \|f\|^2_k \right\}.$$

- The values at the minima (the spectrum) quantifies how much the graph fits the data.
Solving the problem

- By the representer theorem, $f_i$ can be expanded as:

$$f_i(x) = \sum_{j=1}^{n} \alpha_{i,j} k(x_i, x).$$

- This shows that

$$< f_i, f_j >_k = \alpha_i^\top K \alpha_j$$

and

$$\|f_i\|_k^2 = \alpha_i^\top K \alpha_i$$

(1)
Solving the problem (cont.)

• The problem can then be rewritten:

\[ \alpha_i = \arg \min_{\alpha \in \mathbb{R}^n, \alpha K_V \alpha_1 = \ldots = \alpha K_V \alpha_{i-1} = 0} \left\{ \frac{\alpha^\top K_V L K_V \alpha + \lambda \alpha^\top K_V \alpha}{\alpha^\top K_V^2 \alpha} \right\} \]

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

• It is equivalent to solving the generalized eigenvalue problem:

\[ (L K_V + \lambda I) \alpha = \mu K_V \alpha. \]
Kernels

Several similarity 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 $K_1, \ldots, K_p$

• 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)
Part 3

Supervised direct inference by metric learning pairwise kernel
Limitations of GKPCA

- Requires the training set to be made of the presence / absence of edges among a particular subset of genes

- Discrepancy between the objective function and the goal of edge inference

- Requires the tuning of two regularization parameters ($d$ and $\lambda$)
Objective function

After a linear mapping $\Phi(x) = Ax$ the square Euclidean distance is:

$$d_M(x, x') = (x - x')^\top M(x - x')$$

$$= tr \left( M(x - x')(x - x')^\top \right),$$

with $M = A^\top A \succ 0$. Direct edge inference is possible if, for example,

$$d_\phi(x_i, x_j) \begin{cases} 
\leq \gamma - 1 & \text{for } x_i \sim x_j , \\
\geq \gamma + 1 & \text{for } x_i \not\sim x_j . 
\end{cases}$$
Large-margin metric learning

In the spirit of SVM, this suggests the following optimization problem:

Minimize \( \| M \|_{Fro}^2 + C \sum \zeta_{i,j} \)

subject to \( \zeta_{i,j} \geq 0, \quad \forall (i, j) \)
\( d_M(x_i, x_j) \leq \gamma - 1 + \zeta_{i,j}, \quad i \sim j \)
\( d_M(x_i, x_j) \geq \gamma + 1 - \zeta_{i,j}, \quad i \not\sim j \)
\( M \succ 0. \)
SVM formulation

If we relax the constraint $M \succ 0$ this is equivalent to a SVM:

$$\text{Minimize} \quad \| M \|_{Fro}^2 + C \sum_{(i,j)} \zeta_{i,j}$$

subject to

$\zeta_{i,j} \geq 0, \quad \forall (i,j)$

$$< M, D_{i,j} >_{Fro} - \gamma \leq -1 + \zeta_{i,j}, \quad i \sim j$$

$$< M, D_{i,j} >_{Fro} - \gamma \geq 1 - \zeta_{i,j}, \quad i \not\sim j.$$
Inner product for pairs

The inner product between two pairs for this SVM is:

$$K_p ((x_1, x_2), (x_3, x_4))$$

$$= \langle D_{x_1, x_2}, D_{x_3, x_4} \rangle_{Fro}$$

$$= Tr ace \left( (x_1 - x_2) (x_1 - x_2)^\top (x_3 - x_4) (x_3 - x_4)^\top \right)$$

$$= \left( (x_1 - x_2)^\top (x_3 - x_4) \right)^2$$

$$= \left( x_1^\top x_3 - x_1^\top x_4 - x_2^\top x_3 + x_2^\top x_4 \right)^2.$$
Metric learning pairwise kernel

If we start from a kernel $K_g$ between single genes, this formulation is therefore a SVM to discriminate between connected and non-connected pairs with the following pairwise kernel:

\[
K_{MLPK} \left( (x_1, x_2), (x_3, x_4) \right) \\
= (K_g(x_1, x_3) - K_g(x_1, x_4) - K_g(x_2, x_3) + K_g(x_2, x_4))^2.
\]

To be compared, e.g., with the pairwise kernel:

\[
K_p \left( (x_1, x_2), (x_3, x_4) \right) = K(x_1, x_3)K(x_2, x_4) + K(x_1, x_4)K(x_2, x_3).
\]
Experimental results

Prediction of the co-complex protein network for the yeast from various protein data (AUC performance in cross-validation)

<table>
<thead>
<tr>
<th>Data</th>
<th>$K_p$</th>
<th>$K_{MLPK}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-regulation (Chip-chip)</td>
<td>0.68</td>
<td>0.90</td>
</tr>
<tr>
<td>Co-localization</td>
<td>0.83</td>
<td>0.78</td>
</tr>
<tr>
<td>PFAM kernel</td>
<td>0.92</td>
<td>0.98</td>
</tr>
<tr>
<td>PSI-BLAST kernel</td>
<td>0.94</td>
<td>0.97</td>
</tr>
</tbody>
</table>
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4. Data integration with kernels is simple and powerful
Conclusion

1. **Supervised inference** is better than unsupervised

2. Supervised graph inference can be performed by **distance metric learning**

3. Different formulations lead to different algorithms. **New pairwise kernel.**

4. **Data integration with kernels** is simple and powerful

5. **Few assumptions** about the network to infer (works well for the metabolic network and the protein interaction network)
Thanks

- Yoshihiro Yamanishi (Kyodai) : generalized KPCA
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