

Inference of biological networks

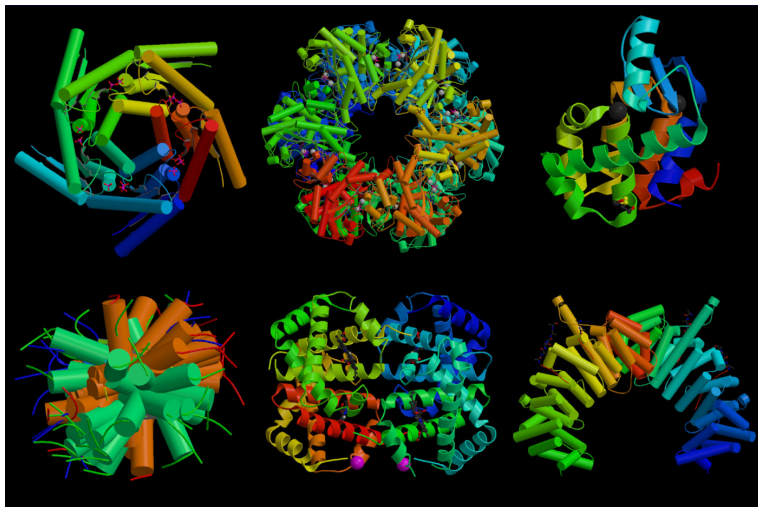
Jean-Philippe Vert

Jean-Philippe.Vert@mines-paristech.fr

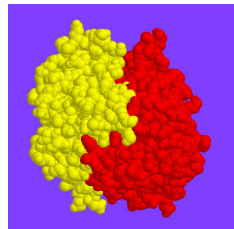
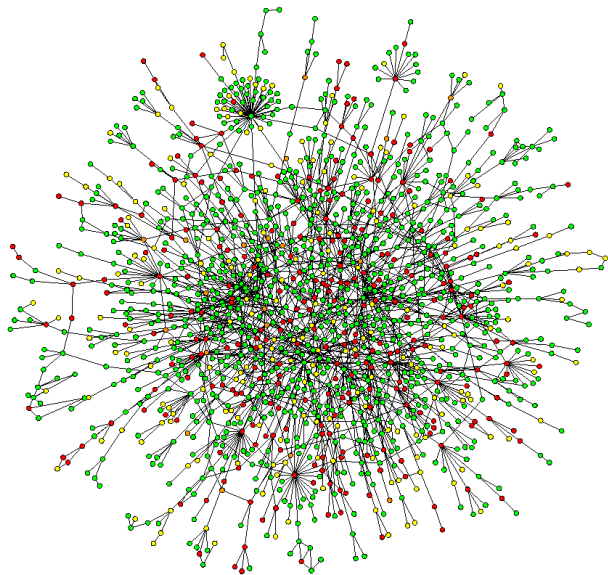
Mines ParisTech, Institut Curie, INSERM U900

"Advances in the Theory of Control, Signals, and Systems, with Physical Modeling" workshop, Bernoulli Center, EPFL, June 5, 2009.

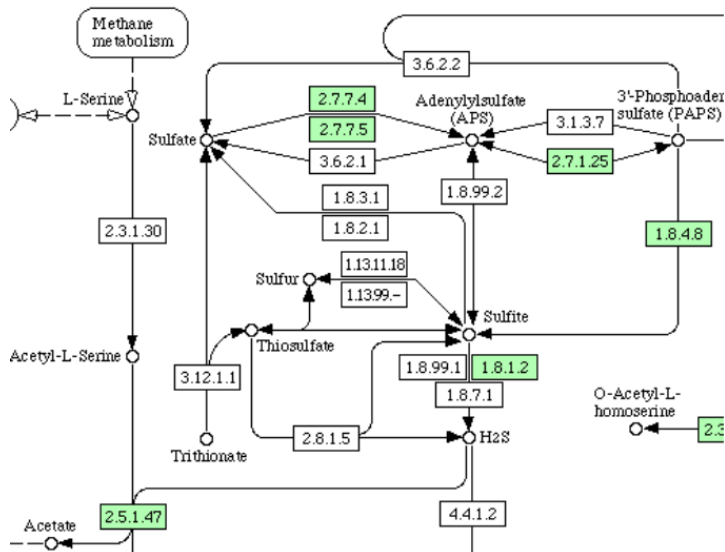
Proteins



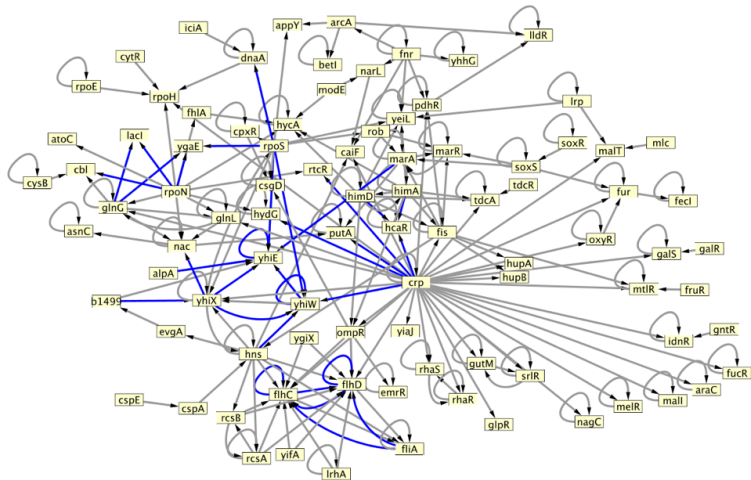
Network 1: protein-protein interaction



Network 2: metabolic network



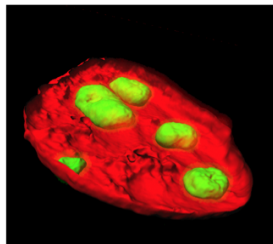
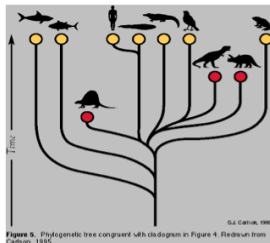
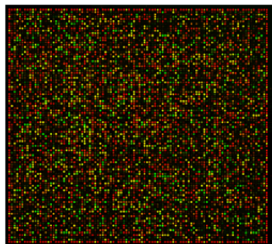
Network 3: gene regulatory network



Data available

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

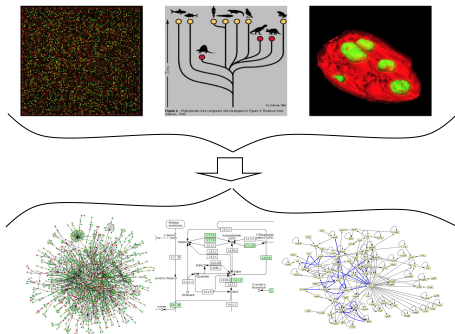
- Gene expression measurements
- Phylogenetic profiles
- Location of proteins/enzymes in the cell



How to use this information “intelligently” to find a good function that **predicts edges between nodes.**

Formalization

- $\mathcal{V} = \{1, \dots, N\}$ vertices (*e.g., genes, proteins*)
- $\mathcal{D} = (x_1, \dots, x_N) \in \mathcal{H}^N$ data about the vertices (\mathcal{H} Hilbert space)
- Goal: predict edges $\mathcal{E} \subset \mathcal{V} \times \mathcal{V}$.



Typical reverse-engineering strategies

- 1 Fit a **dynamical system** to time series (e.g., PDE, boolean networks, state-space models).
- 2 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

Typical reverse-engineering strategies

- 1 Fit a **dynamical system** to time series (e.g., PDE, boolean networks, state-space models).
- 2 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

Typical reverse-engineering strategies

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

Pros

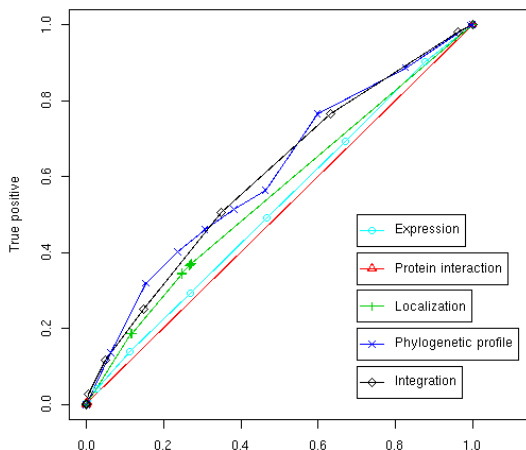
- **Excellent approach** if the model is correct and enough data are available
- **Interpretability** of the model
- Inclusion of **prior knowledge**

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

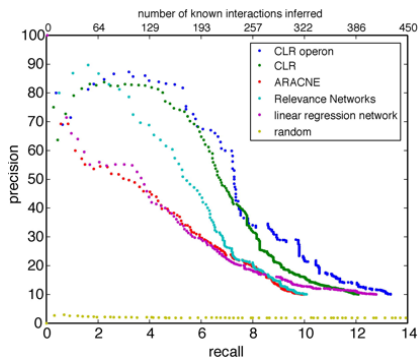
Does it work? Metabolic network...

- 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 *Escherichia coli* Transcriptional Regulation from a Compendium of Expression Profiles

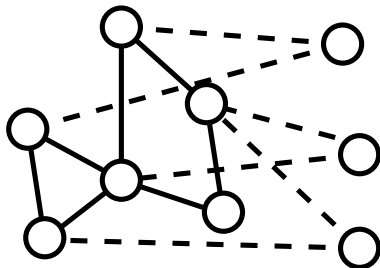
Jeremiah J. Faith¹, Boris Hayete¹, Joshua T. Thaden^{2,3}, Ilaria Mogno^{2,4}, Jamey Wierzbowski^{2,5}, Guillaume Cottarel^{2,5}, Simon Kasif^{1,2}, James J. Collins^{1,2}, Timothy S. Gardner^{1,2*}



Motivation

In actual applications,

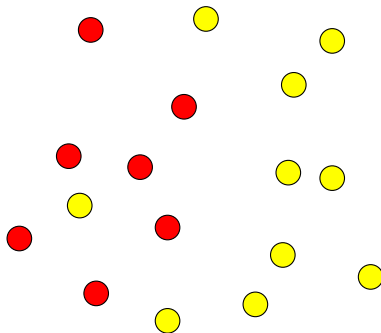
- we know in advance parts of the network to be inferred
- the problem is to add/remove nodes and edges using genomic data as side information



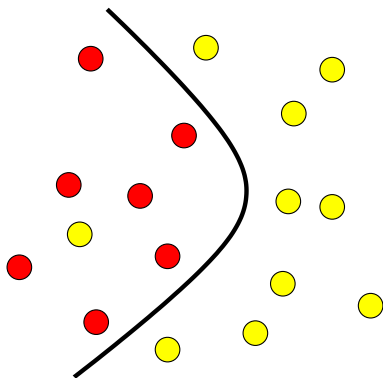
Supervised method

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

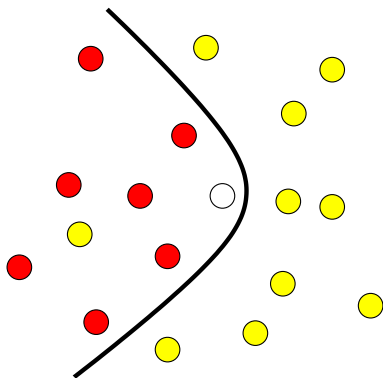
Pattern recognition



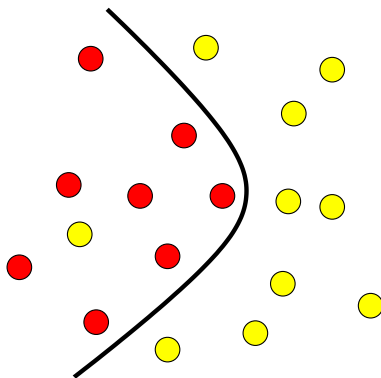
- Given a training set of patterns in two classes, learn to discriminate them
- Many algorithms (ANN, SVM, Decision trees, ...)



- Given a training set of patterns in two classes, learn to discriminate them
- Many algorithms (ANN, SVM, Decision trees, ...)



- Given a training set of patterns in two classes, learn to discriminate them
- Many algorithms (ANN, SVM, Decision trees, ...)



- Given a training set of patterns in two classes, learn to discriminate them
- Many algorithms (ANN, SVM, Decision trees, ...)

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

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)

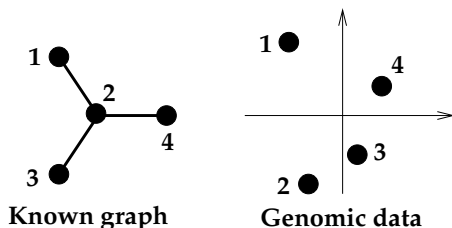
Two solutions

- 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 for pairs

Formulation and basic issue

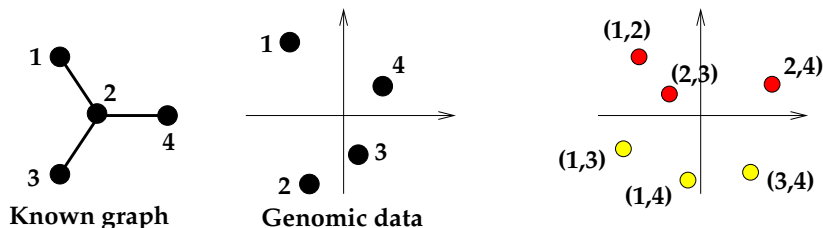
- A pair can be **connected (1)** or **not connected (-1)**
- From the known subgraph we can **extract examples** of connected and non-connected pairs
- However the genomic data characterize **individual** proteins; we need to work with **pairs** of proteins instead!



Pattern recognition for pairs

Formulation and basic issue

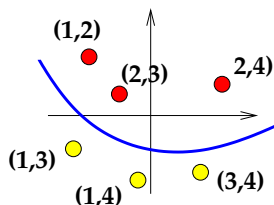
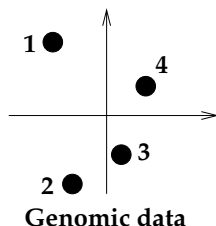
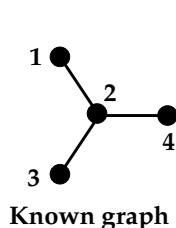
- A pair can be **connected (1)** or **not connected (-1)**
- From the known subgraph we can **extract examples** of connected and non-connected pairs
- However the genomic data characterize **individual** proteins; we need to work with **pairs** of proteins instead!



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!



Representing a pair as a vector

- Each individual protein is represented by a vector $v \in \mathbb{R}^p$
- We must represent a pair of proteins (u, v) by a vector $\psi(u, v) \in \mathbb{R}^q$ in order to estimate a linear classifier
- **Question: how build $\psi(u, v)$ from u and v ?**

Direct sum

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

$$\psi(u, v) = u \oplus v = \begin{pmatrix} u \\ v \end{pmatrix}.$$

- **Problem:** a linear function then becomes **additive**...

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

Direct sum

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

$$\psi(u, v) = u \oplus v = \begin{pmatrix} u \\ v \end{pmatrix}.$$

- **Problem**: a linear function then becomes **additive**...

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

Direct product

- Alternatively, make the **direct product**, i.e., the p^2 -dimensional vector whose entries are all products of entries of u by entries of v :

$$\psi(u, v) = u \otimes v$$

- **Problem**: can get really large-dimensional...
- **Good news**: inner product factorizes:

$$(u_1 \otimes v_1)^\top (u_2 \otimes v_2) = (u_1^\top u_2) \times (v_1^\top v_2),$$

which is good for algorithms that use only inner products (SVM...)

Direct product

- Alternatively, make the **direct product**, i.e., the p^2 -dimensional vector whose entries are all products of entries of u by entries of v :

$$\psi(u, v) = u \otimes v$$

- **Problem**: can get really large-dimensional...
- **Good news**: inner product factorizes:

$$(u_1 \otimes v_1)^\top (u_2 \otimes v_2) = (u_1^\top u_2) \times (v_1^\top v_2),$$

which is good for algorithms that use only inner products (SVM...)

Direct product

- Alternatively, make the **direct product**, i.e., the p^2 -dimensional vector whose entries are all products of entries of u by entries of v :

$$\psi(u, v) = u \otimes v$$

- **Problem**: can get really large-dimensional...
- **Good news**: inner product factorizes:

$$(u_1 \otimes v_1)^\top (u_2 \otimes v_2) = (u_1^\top u_2) \times (v_1^\top v_2),$$

which is good for algorithms that use only inner products (SVM...)

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)

$$\psi(u, v) = (u - v)^{\otimes 2} .$$

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 $D - C$.

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)

$$\psi(u, v) = (u - v)^{\otimes 2} .$$

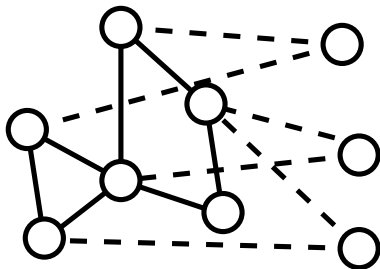
Intuition: a pair (A, B) is similar to a pair (C, D) if:

- $A - B$ is similar to $C - D$, **or**...
- $A - B$ is similar to $D - C$.

Supervised inference with local models

The idea (Bleakley et al., 2007)

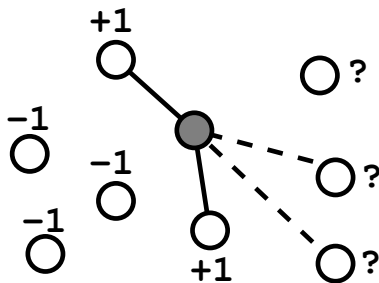
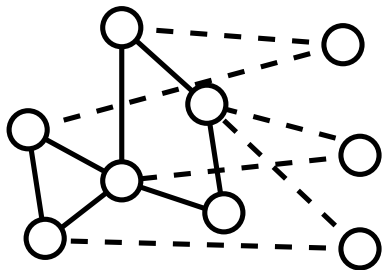
- Motivation: define **specific models** for **each target node** to discriminate between its neighbors and the others
- Treat each node independently from the other. Then **combine** predictions for ranking candidate edges.



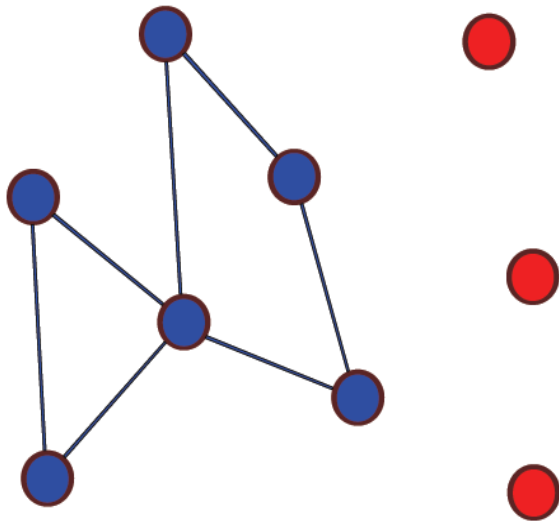
Supervised inference with local models

The idea (Bleakley et al., 2007)

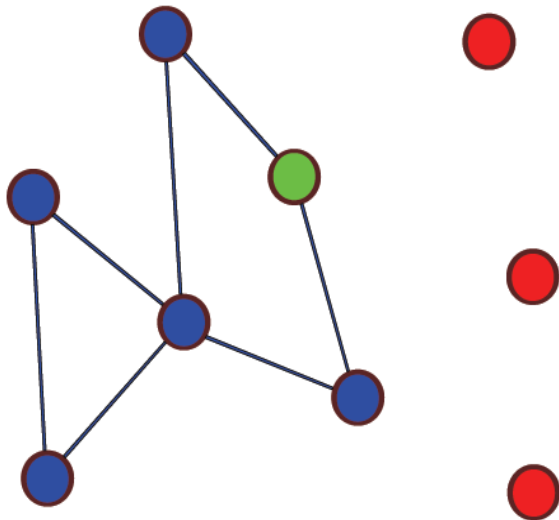
- Motivation: define **specific models** for **each target node** to discriminate between its neighbors and the others
- Treat each node independently from the other. Then **combine** predictions for ranking candidate edges.



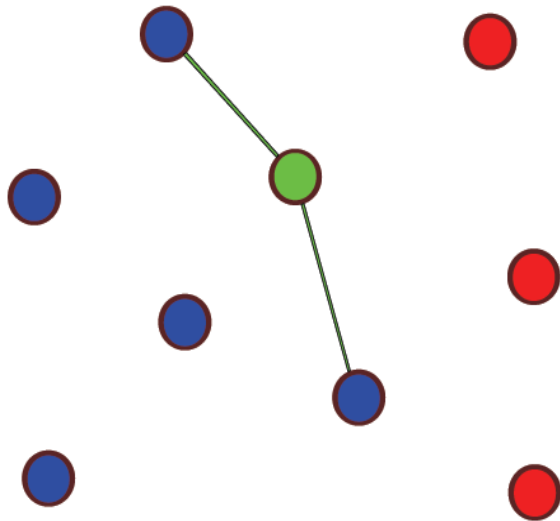
The LOCAL model



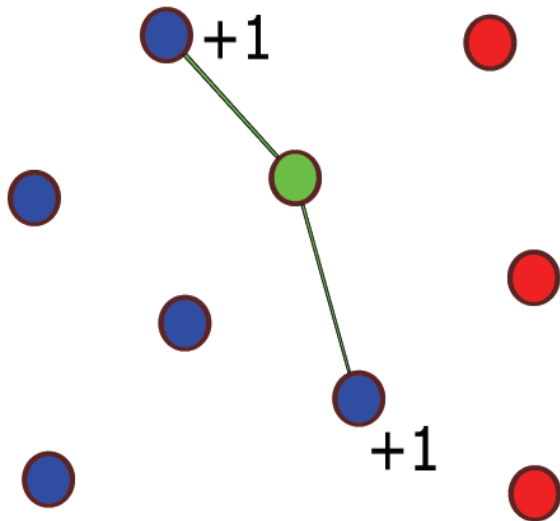
The LOCAL model



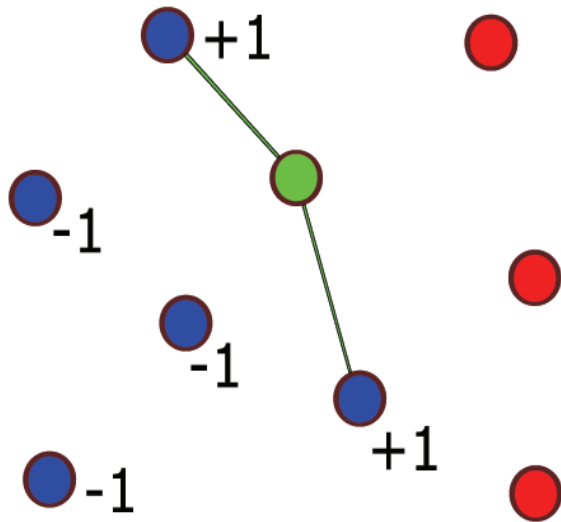
The LOCAL model



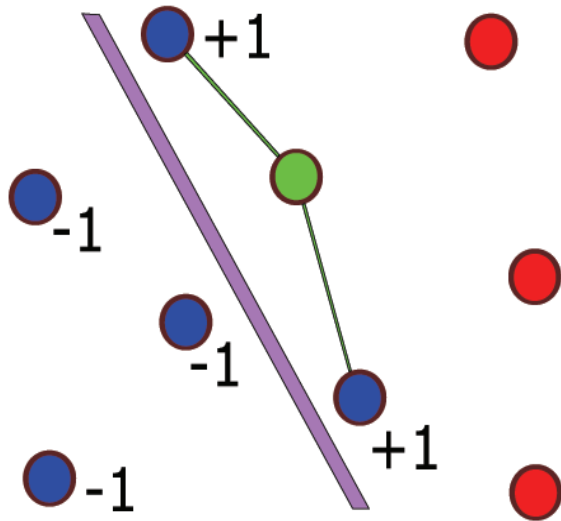
The LOCAL model



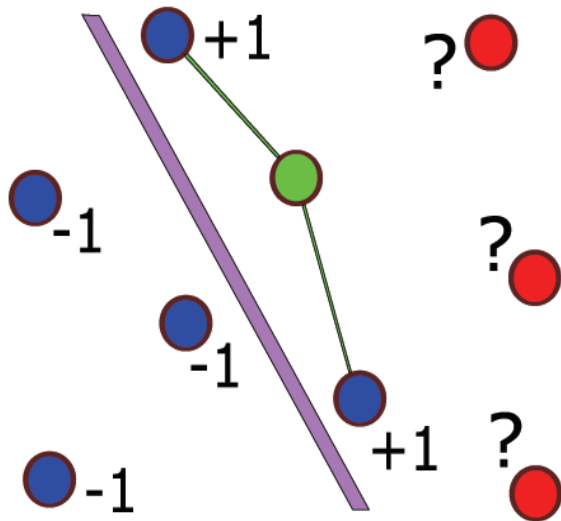
The LOCAL model



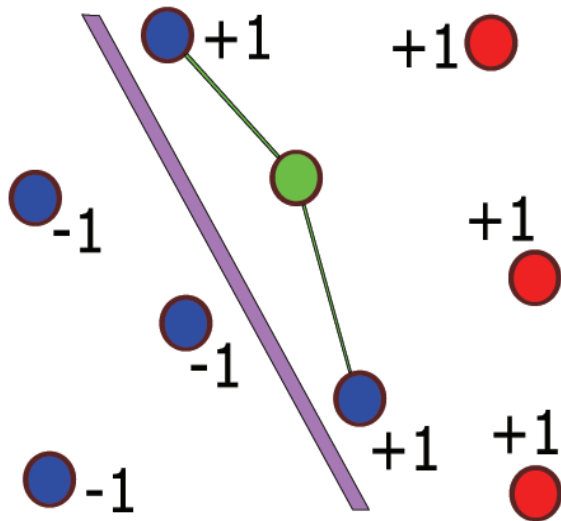
The LOCAL model



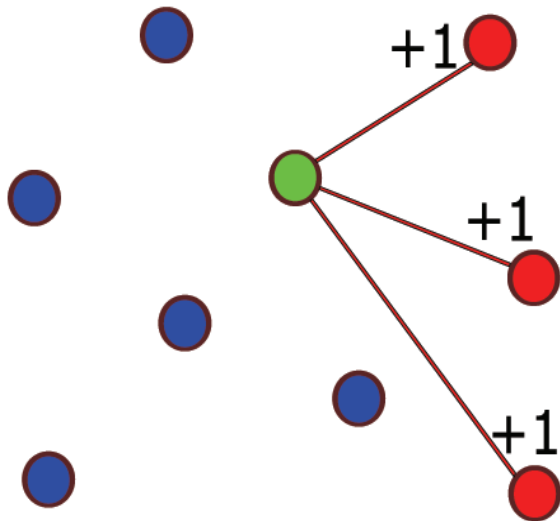
The LOCAL model



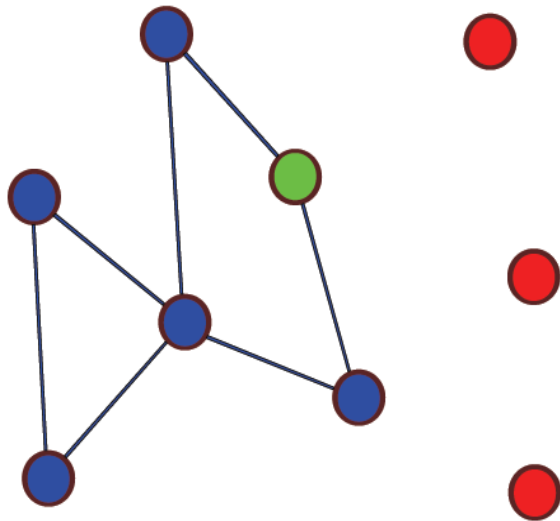
The LOCAL model



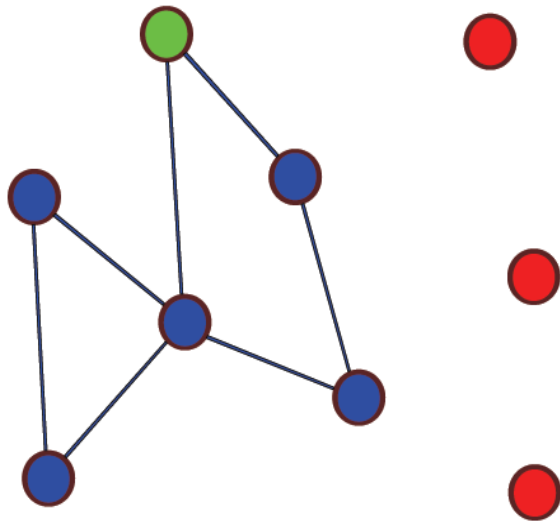
The LOCAL model



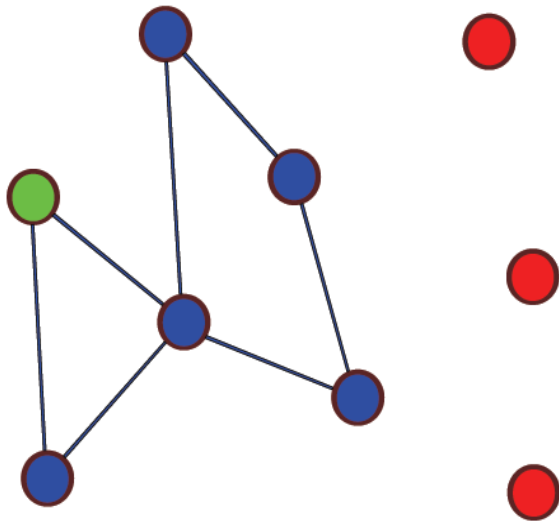
The LOCAL model



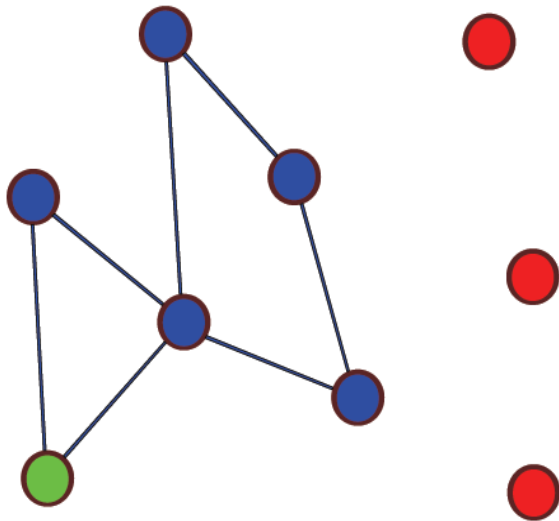
The LOCAL model



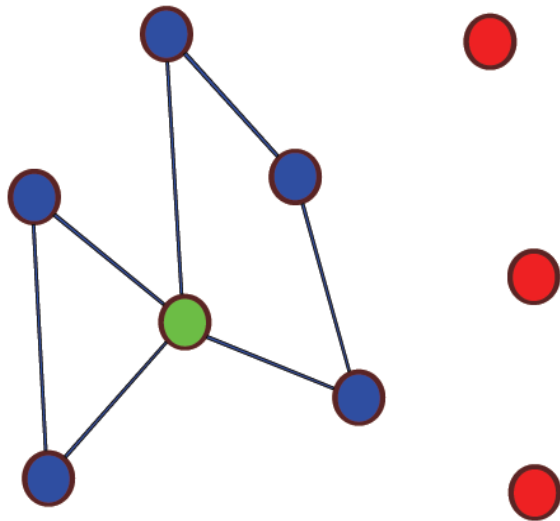
The LOCAL model



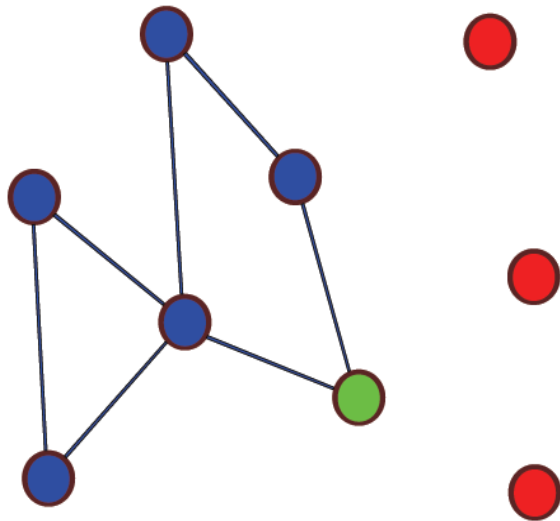
The LOCAL model



The LOCAL model



The LOCAL model

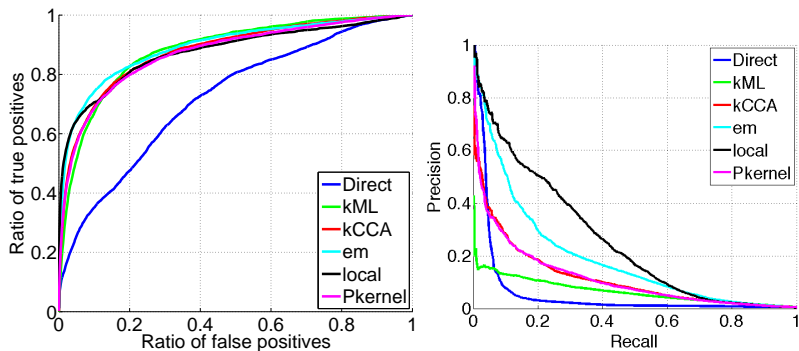


- **Weak hypothesis:**
 - if A is connected to B,
 - if C is similar to B,
 - then A is likely to be connected to C.
- **Computationally:** much faster to train N local models with N training points each, than to train 1 model with N^2 training points.
- **Caveats:**
 - each local model may have very few training points
 - no sharing of information between different local models

- **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

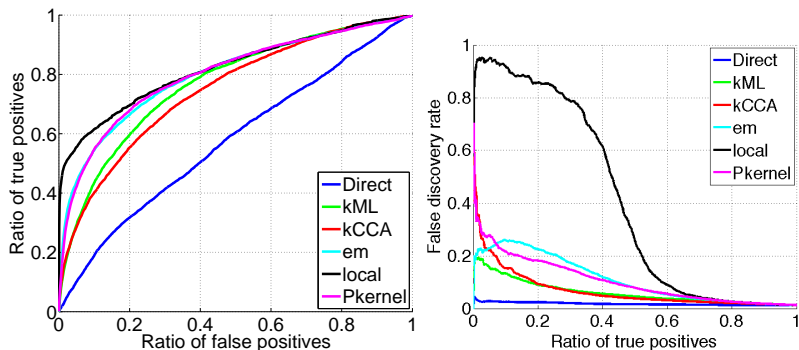
- **Weak hypothesis:**
 - if A is connected to B,
 - if C is similar to B,
 - then A is likely to be connected to C.
- **Computationally:** much faster to train N local models with N training points each, than to train 1 model with N^2 training points.
- **Caveats:**
 - each local model may have very few training points
 - no sharing of information between different local models

Results: protein-protein interaction (yeast)



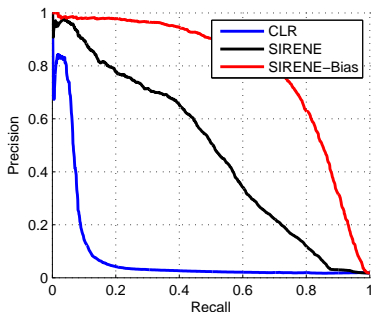
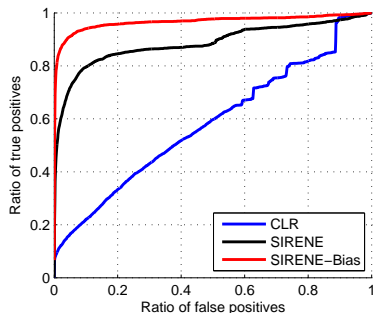
(from Bleakley et al., 2007)

Results: metabolic gene network (yeast)



(from Bleakley et al., 2007)

Results: regulatory network (E. coli)



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)

Prediction of missing enzyme genes in a bacterial metabolic network

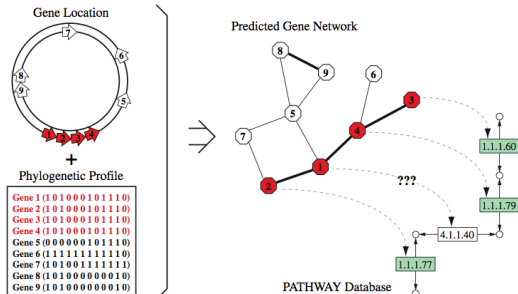
Reconstruction of the lysine-degradation pathway of *Pseudomonas aeruginosa*

Yoshihiro Yamanishi¹, Hisaaki Mihara², Motoharu Osaki², Hisashi Muramatsu³, Nobuyoshi Esaki², Tetsuya Sato¹, Yoshiyuki Hizukuri¹, Susumu Goto¹ and Minoru Kanehisa¹

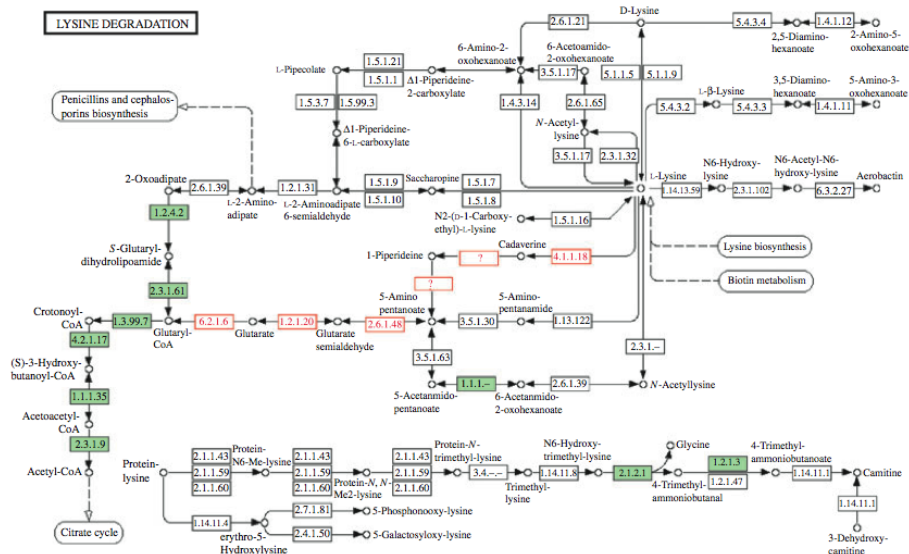
¹ Bioinformatics Center, Institute for Chemical Research, Kyoto University, Japan

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



RESEARCH ARTICLE

Prediction of nitrogen metabolism-related genes in *Anabaena* by kernel-based network analysis

Shinobu Okamoto^{1*}, Yoshihiro Yamanishi¹, Shigeki Ehira², Shuichi Kawashima³, Koichiro Tonomura^{1**} 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

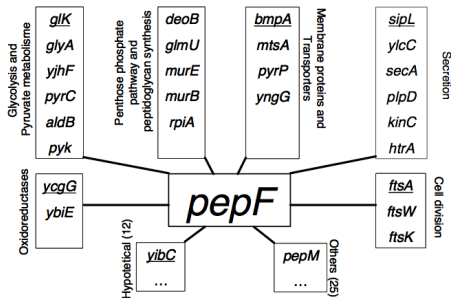
³ Human Genome Center, Institute of Medical Science, University of Tokyo, Meguro, Japan

Determination of the role of the bacterial peptidase PepF by statistical inference and further experimental validation

Liliana LOPEZ KLEINE^{1,2}, Alain TRUBUIL¹, Véronique MONNET²

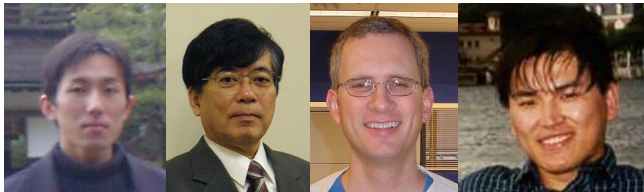
¹Unité de Mathématiques et Informatiques Appliquées. INRA Jouy en Josas 78352, France.

²Unité de Biochimie Bactérienne. INRA Jouy en Josas 78352, France.



- When the network is known in part, **supervised** methods can be more adapted than unsupervised ones.
- A **variety of methods** have been investigated recently (metric learning, matrix completion, pattern recognition).
 - work for **any network**
 - work with **any data**
 - can **integrate heterogeneous data**, which strongly improves performance
- Current research: infer edges simultaneously with global constraints on the graph?

People I need to thank



- Yoshihiro Yamanishi, Minoru Kanehisa (Univ. Kyoto): kCCA, kML
- Jian Qian, Bill Noble (Univ. Washington): pairwise SVM
- Kevin Bleakley, Gerard Biau (Univ. Montpellier), Fantine Mordelet (ParisTech/Curie): local SVM

