Inference of biological networks with supervised machine learning

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Outline

1. Inference of biological networks
2. Supervised methods
3. Applications
4. Conclusion

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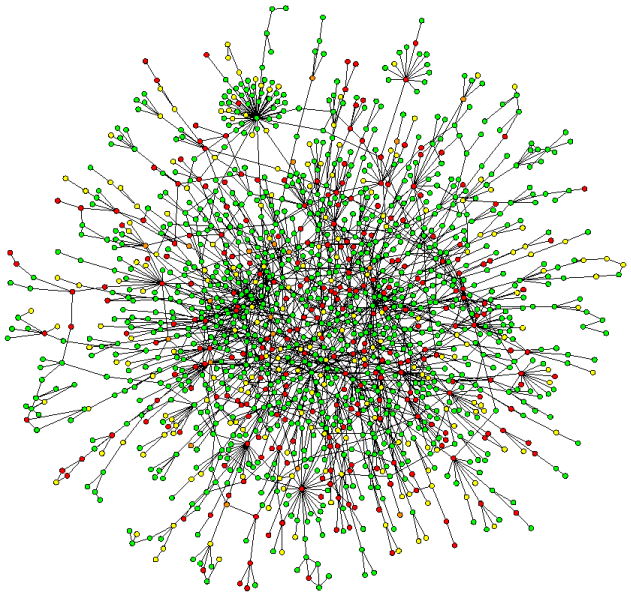
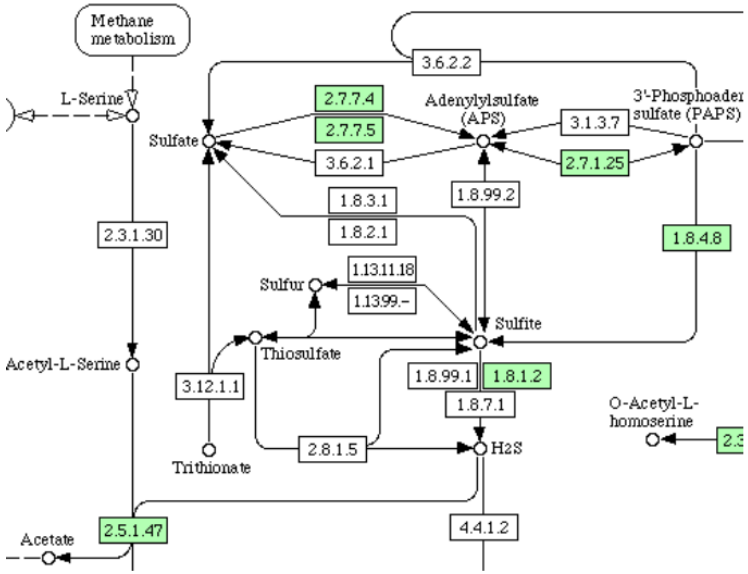
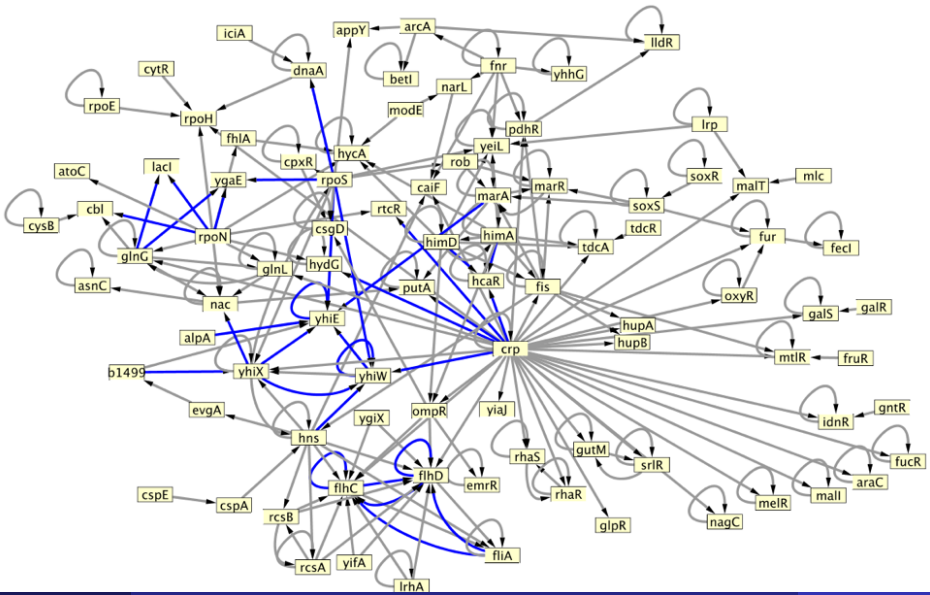
Biological networks



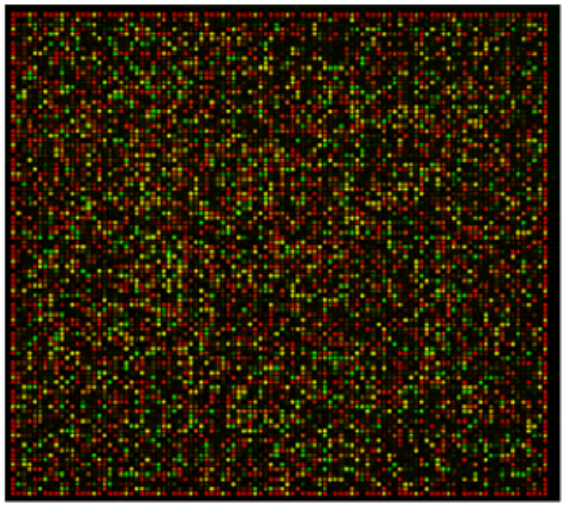




Data available

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

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



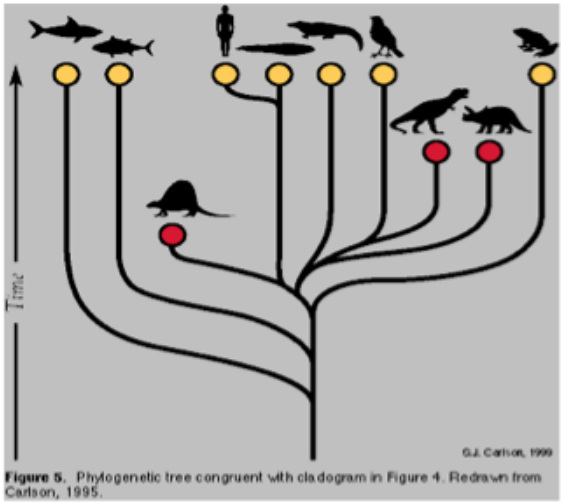
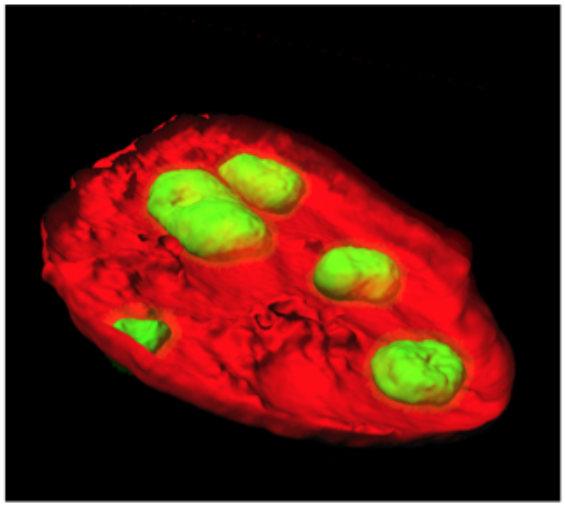
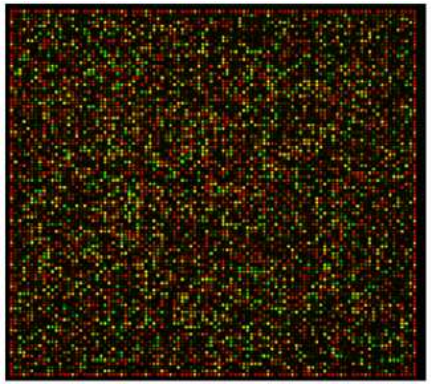


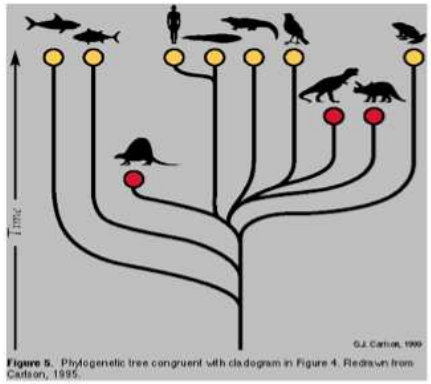
Figure 5. Phylogenetic tree congruent with cladogram in Figure 4. Redrawn from Carlson, 1995.



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

Our goal




Time
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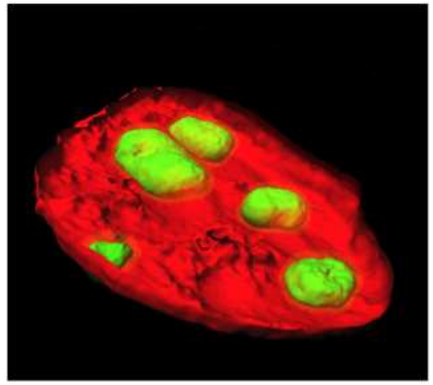
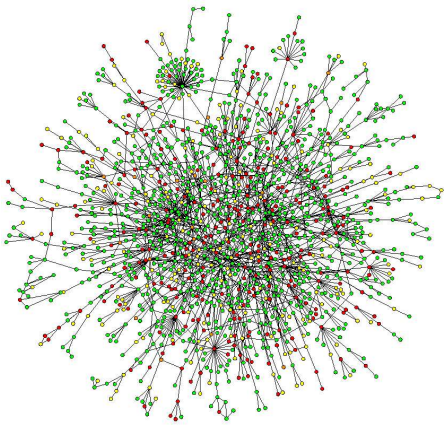
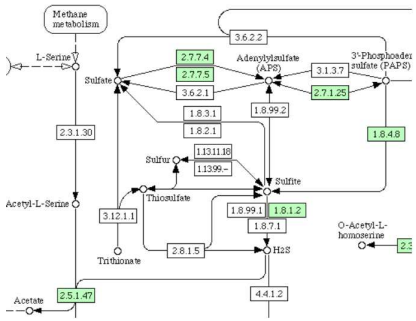
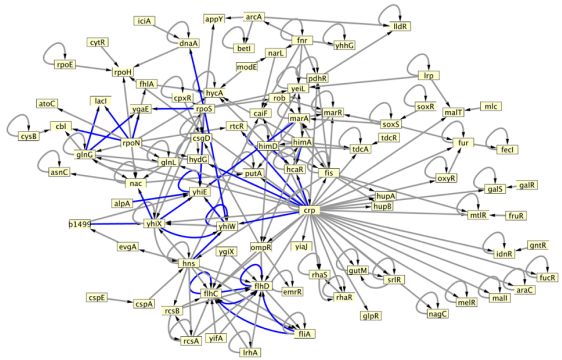





Methane metabolism
L-Serine
Sulfate
Adenylylsulfate (APS)
3'-Phosphoadenylsulfate (PAPS)
Acetyl-L-Serine
Thiosulfate
Sulfur
Sulfite
Trithionate
H2S
O-Acetyl-L-homoserine
Acetate



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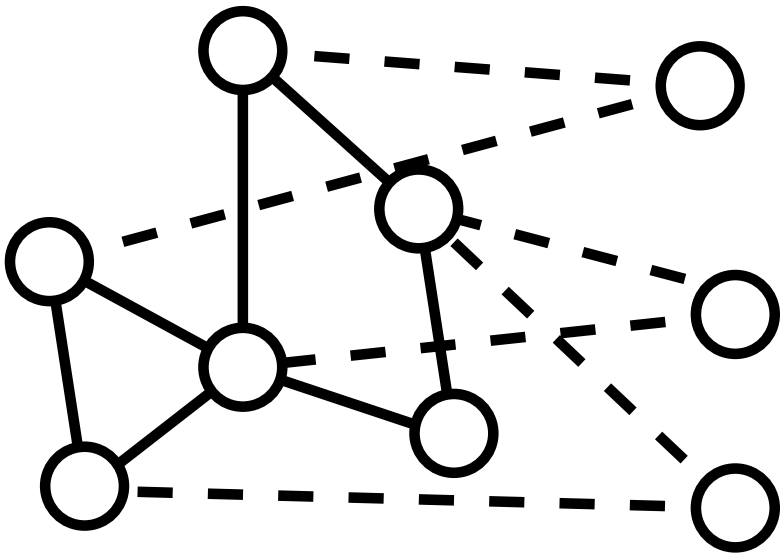
Supervised methods

Motivation

In actual applications,

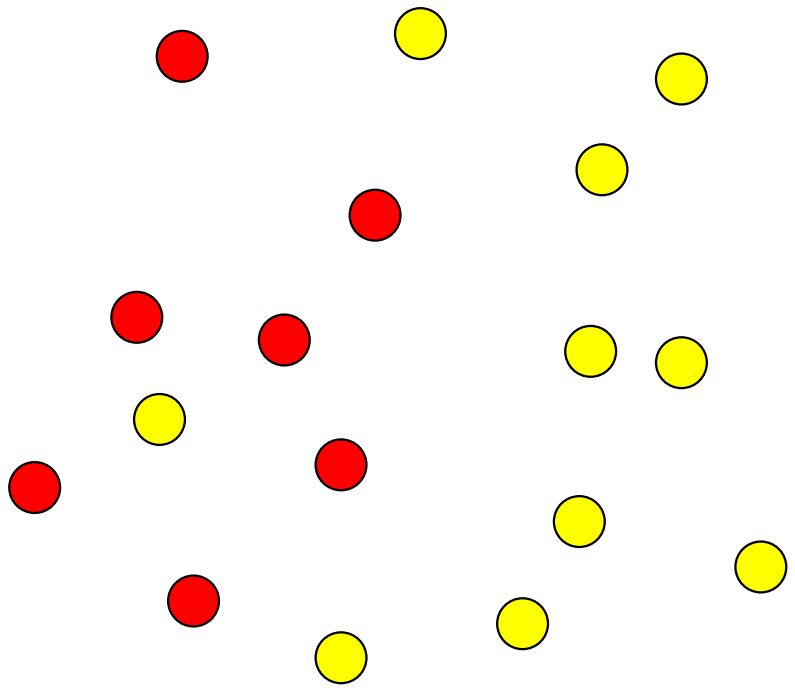
- we know in advance parts of the network to be inferred
- the problem is to add/remove nodes and edges using genomic data as side information



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 tress, ...)

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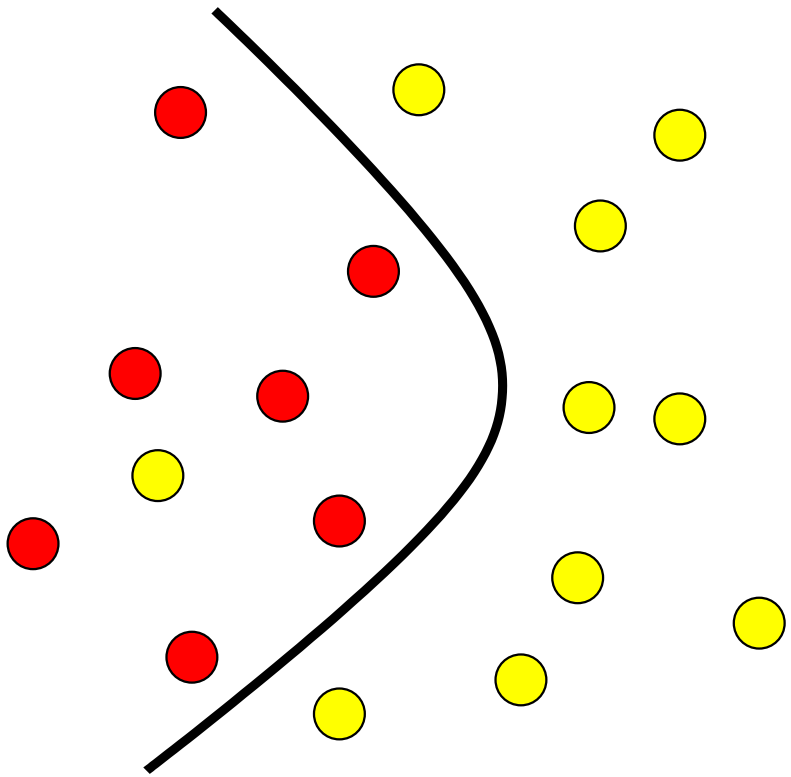

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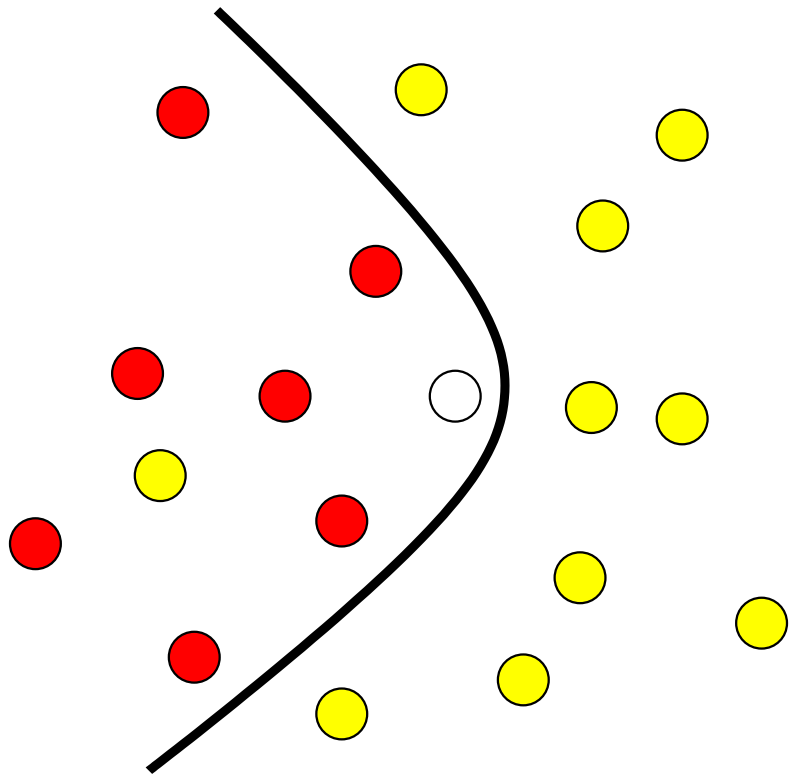

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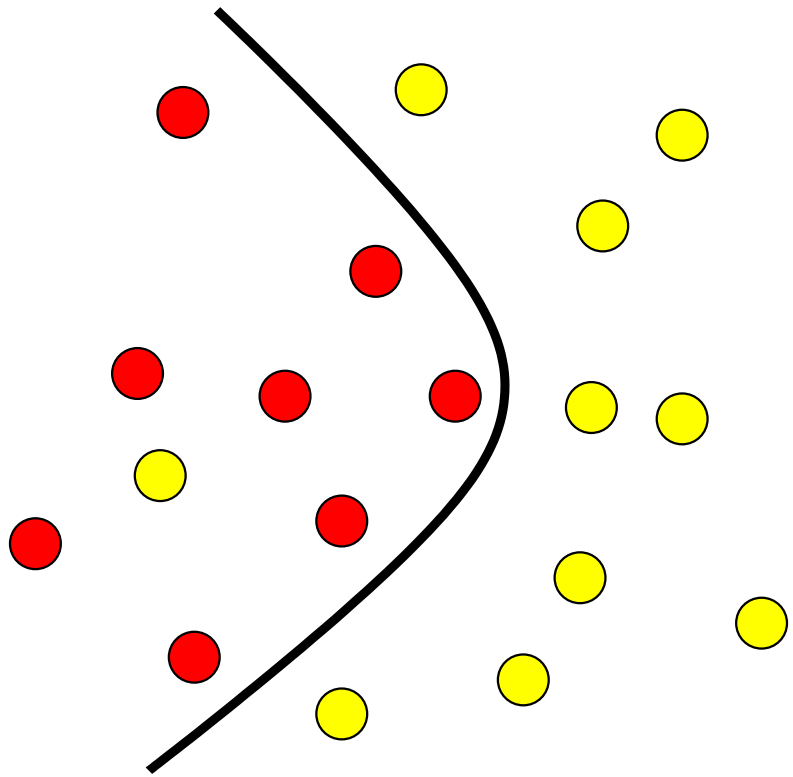

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Pattern recognition and graph inference

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

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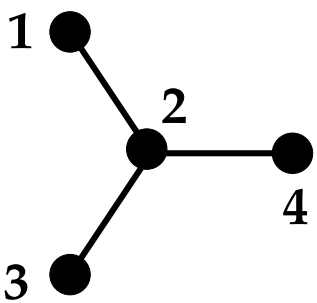
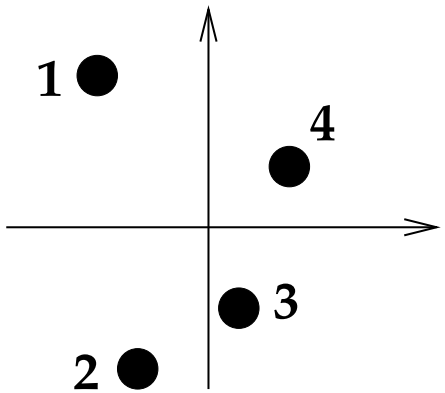
Pattern recognition for pairs

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

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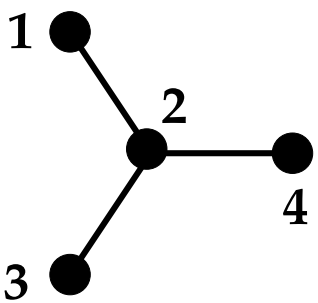

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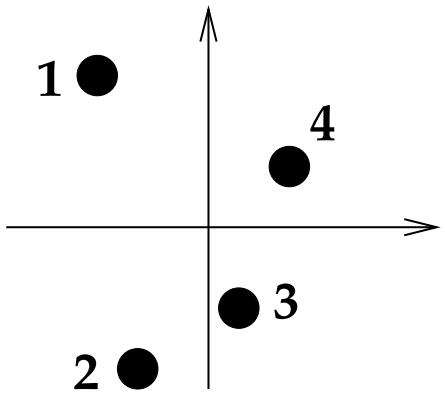

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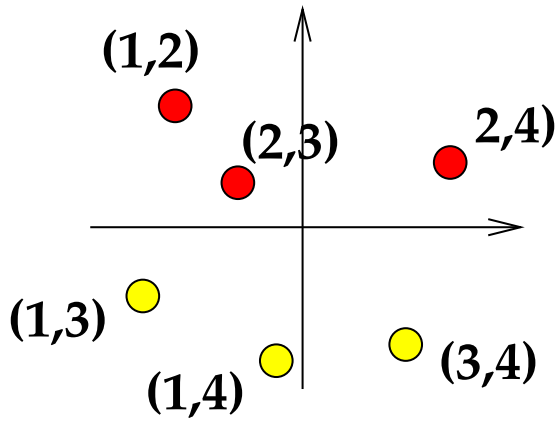

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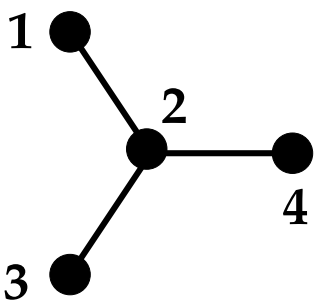

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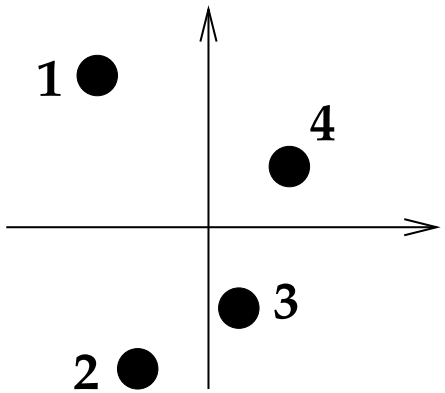

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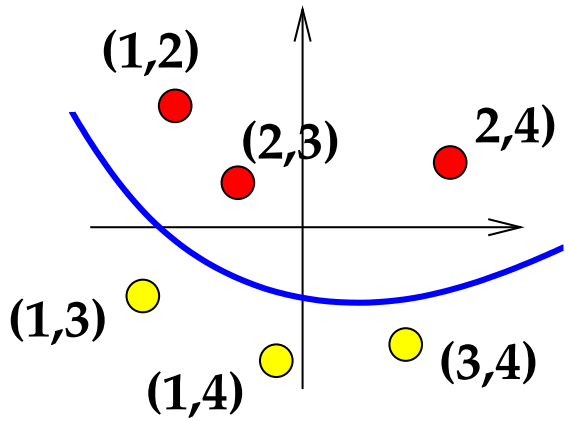

Pattern recognition for pairs

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?

Representing a pair

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...

$$f(u, v) = w^\top \psi(u, v) = w_1^\top u + w_2^\top v .$$

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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:

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

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

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Other represention for pair

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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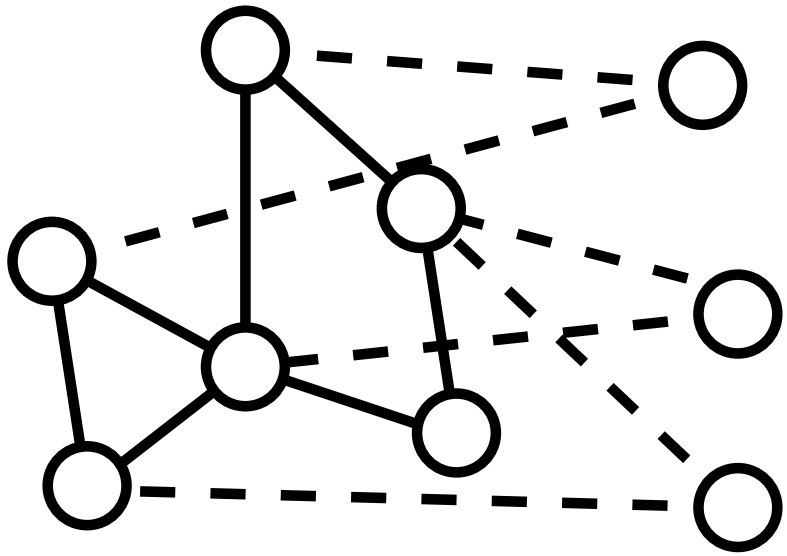
Supervised inference with local models

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.



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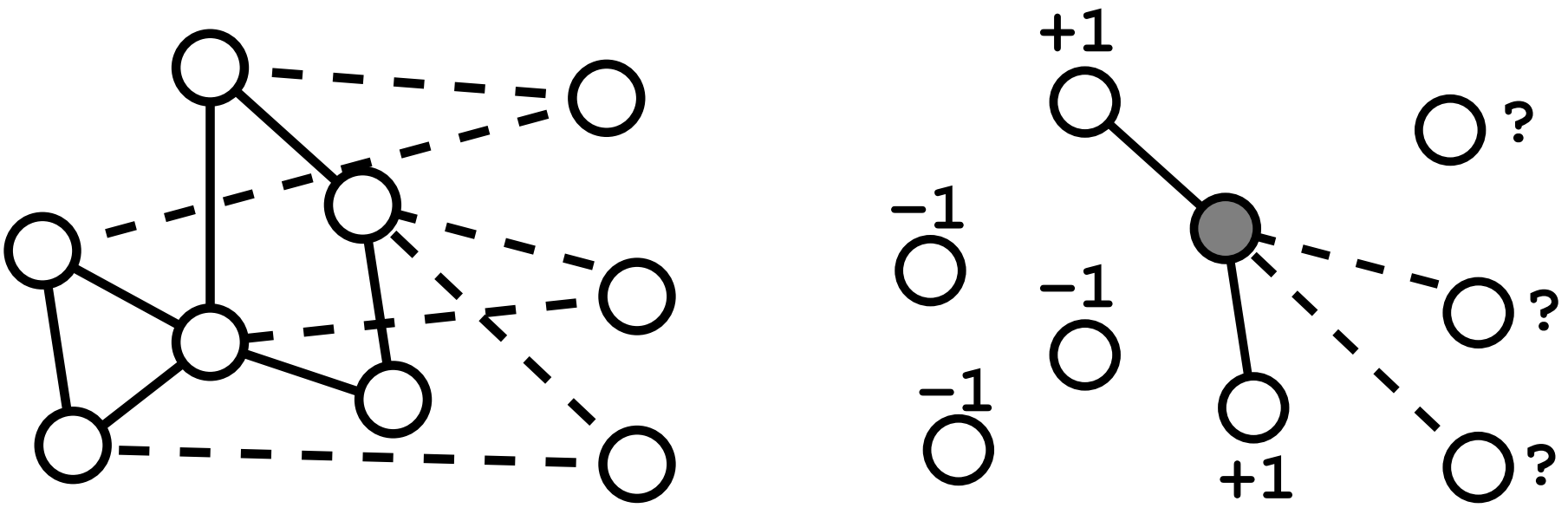
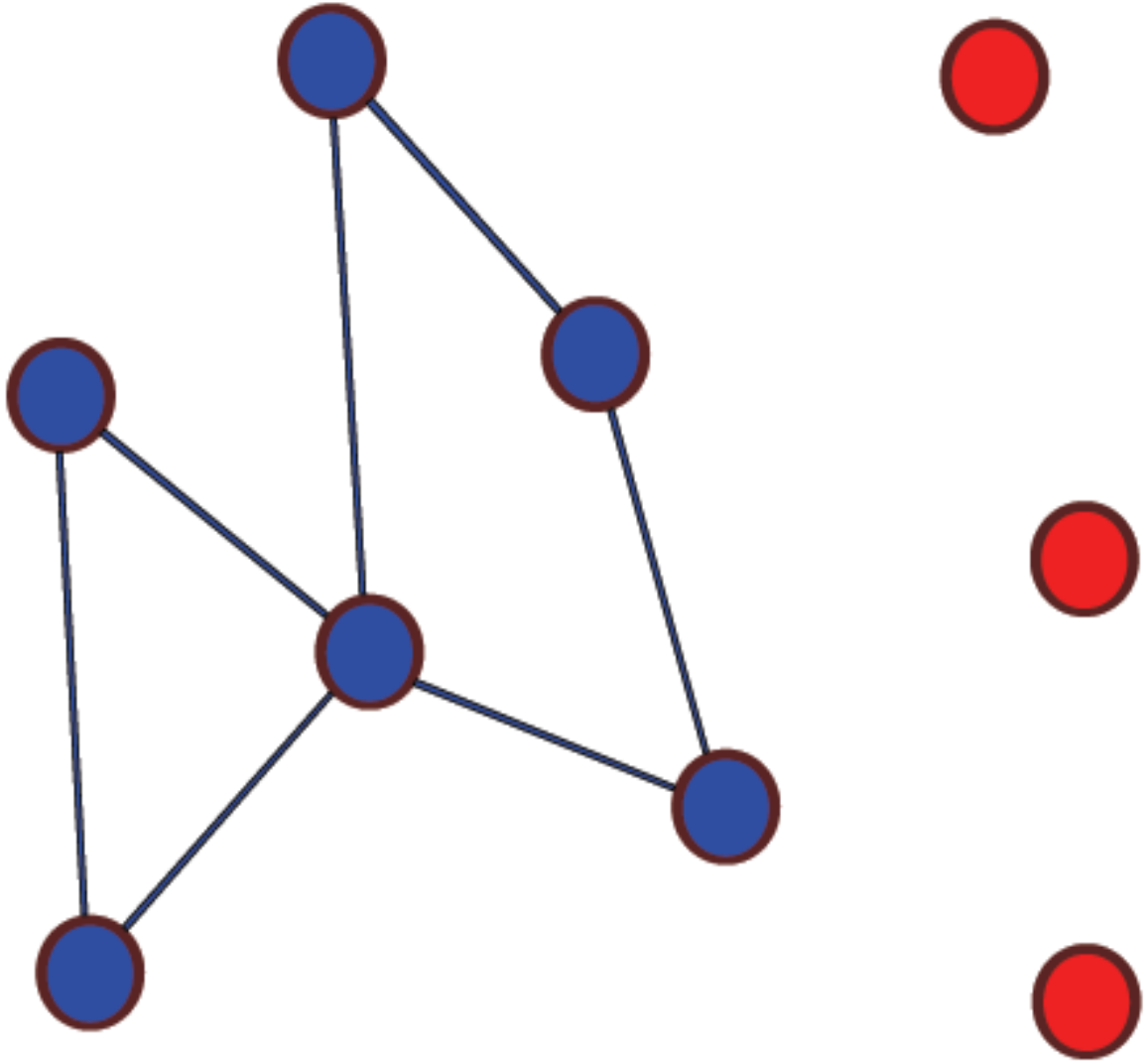


The LOCAL model



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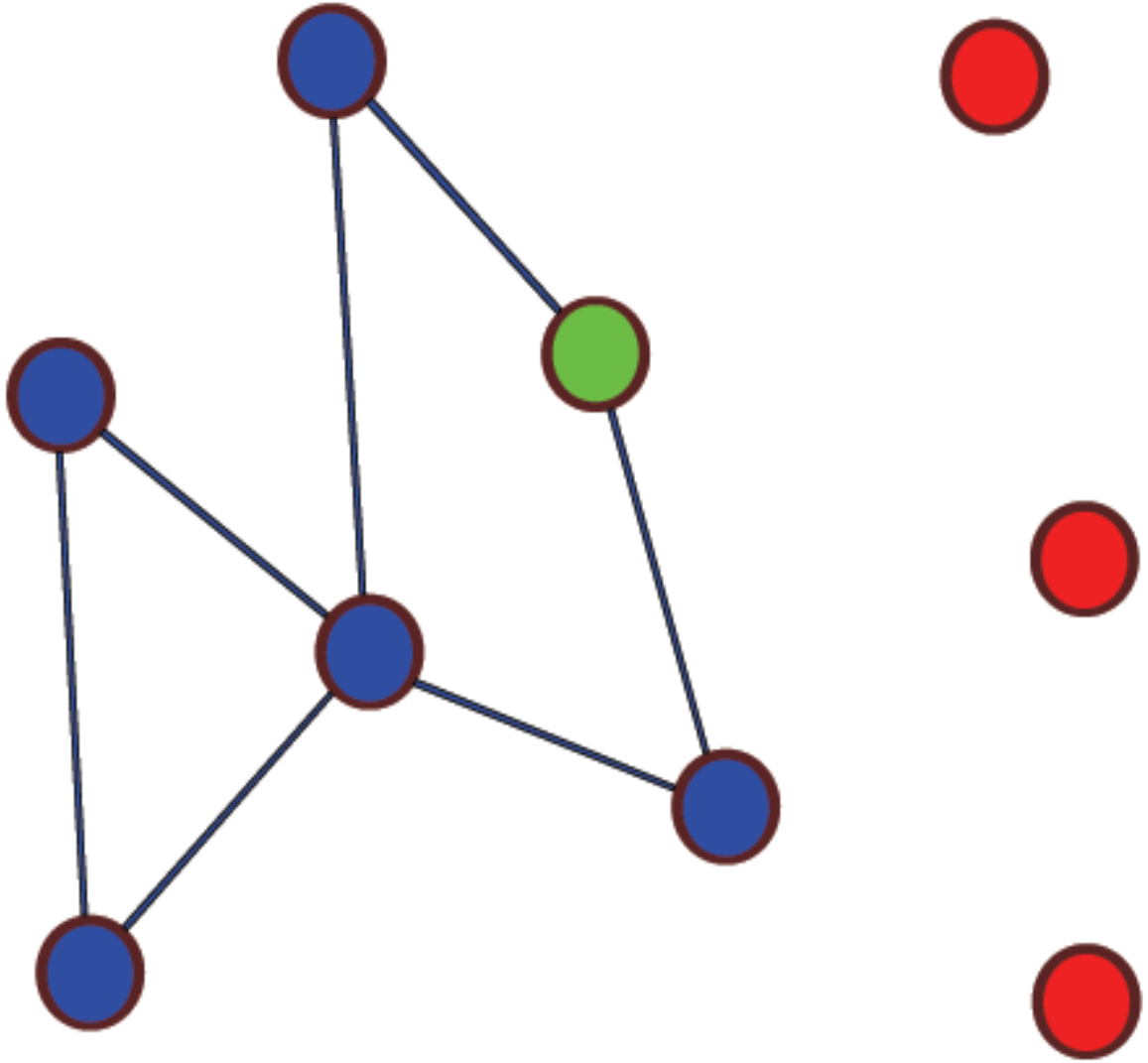

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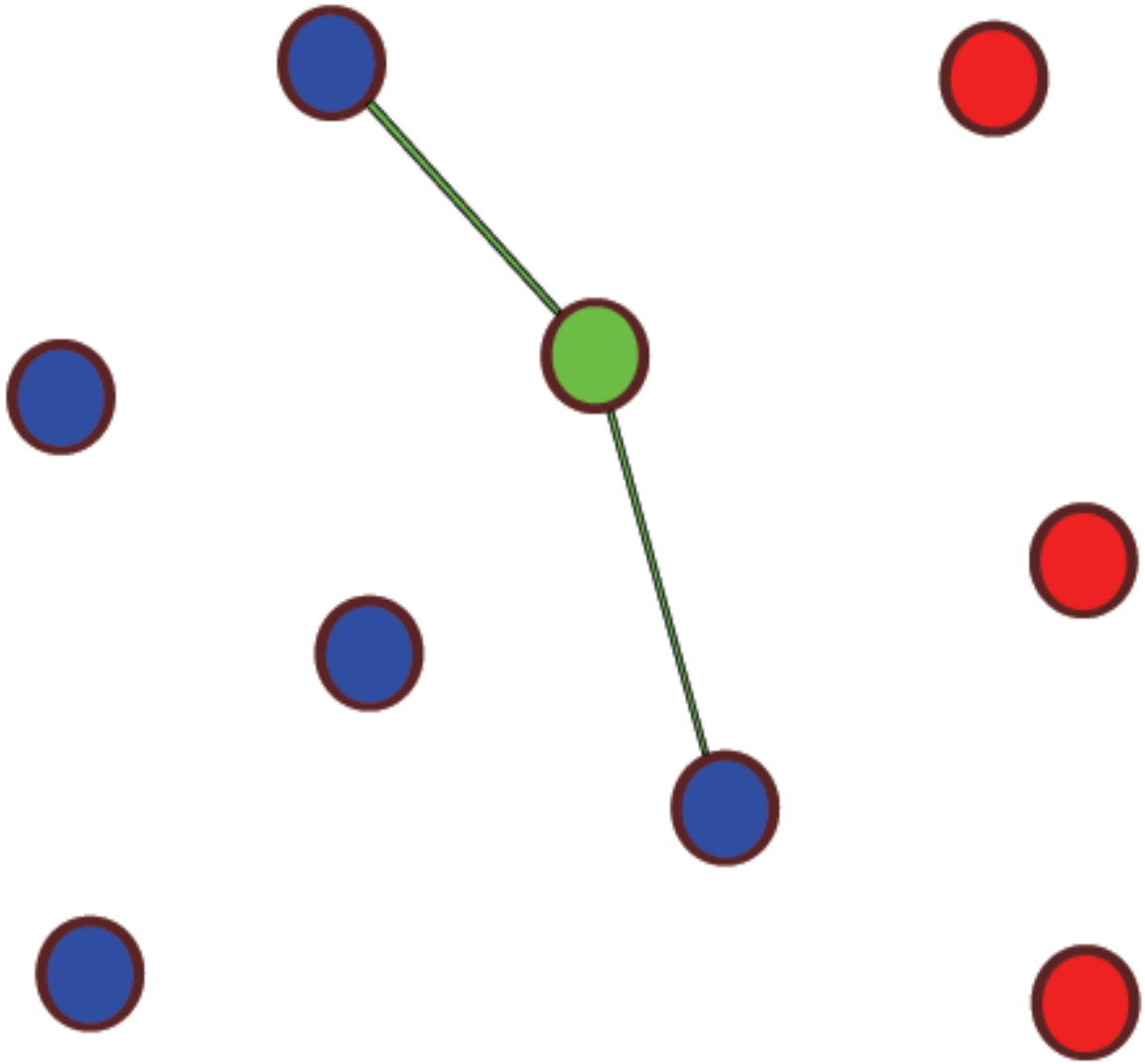

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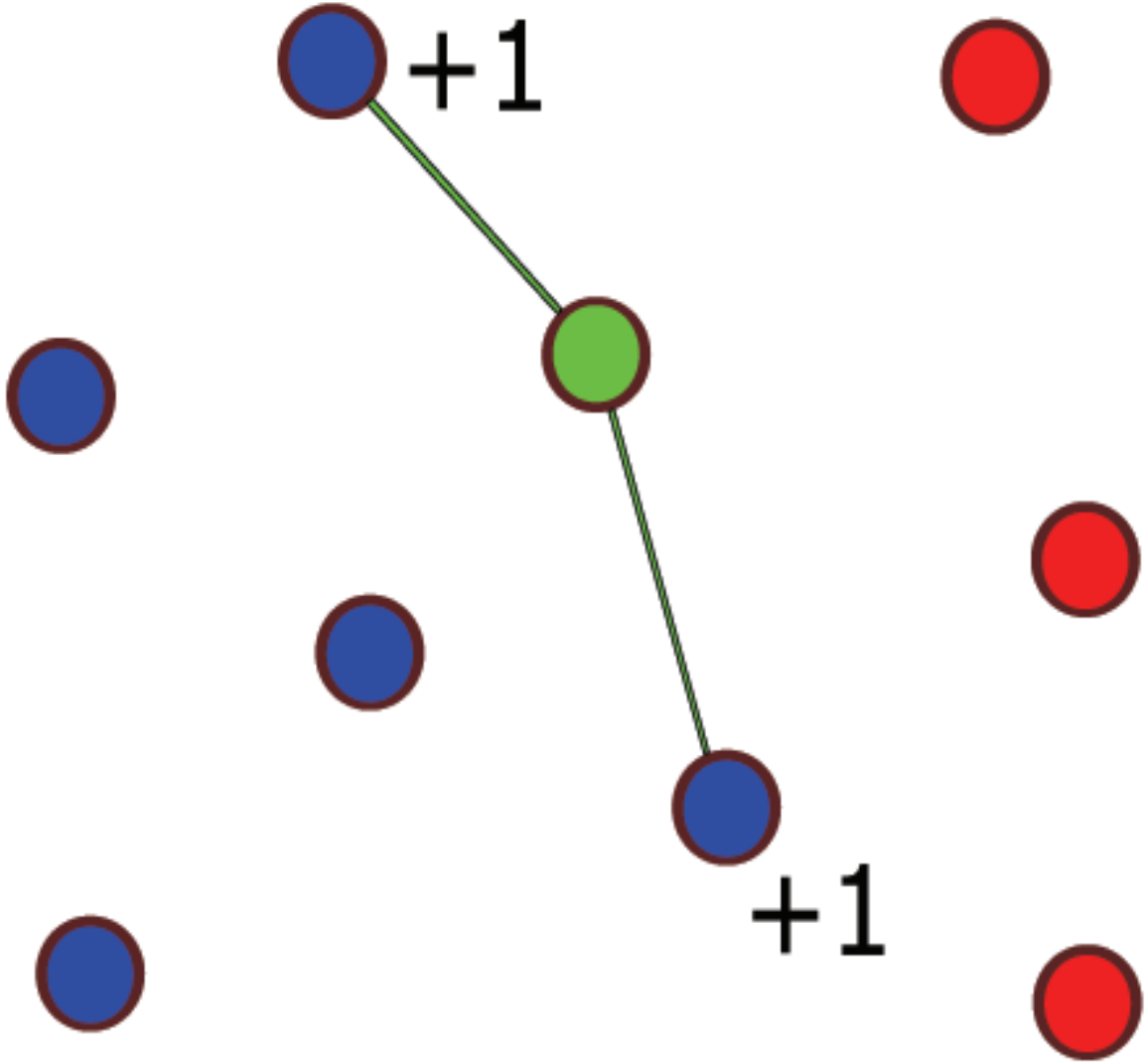

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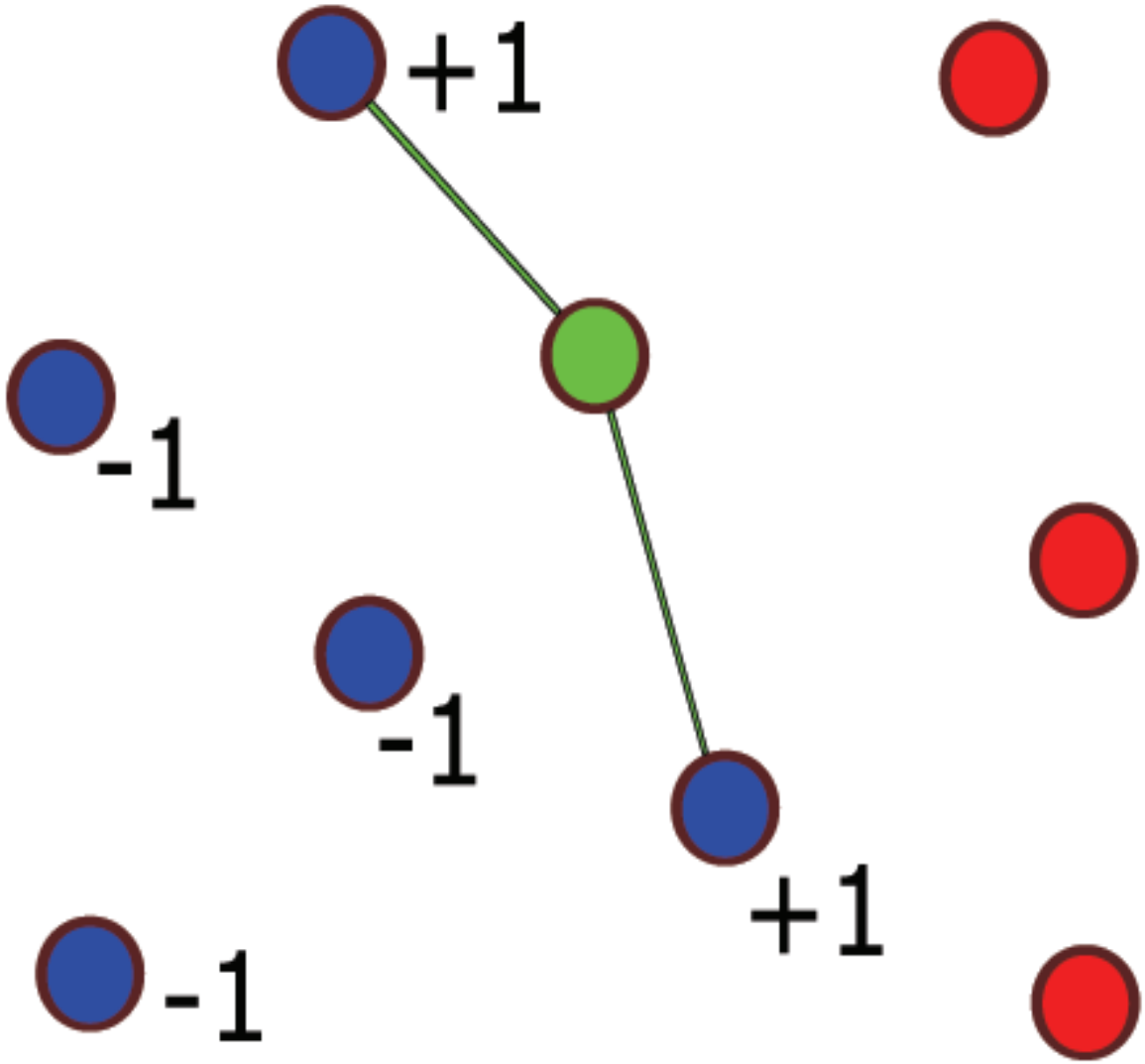

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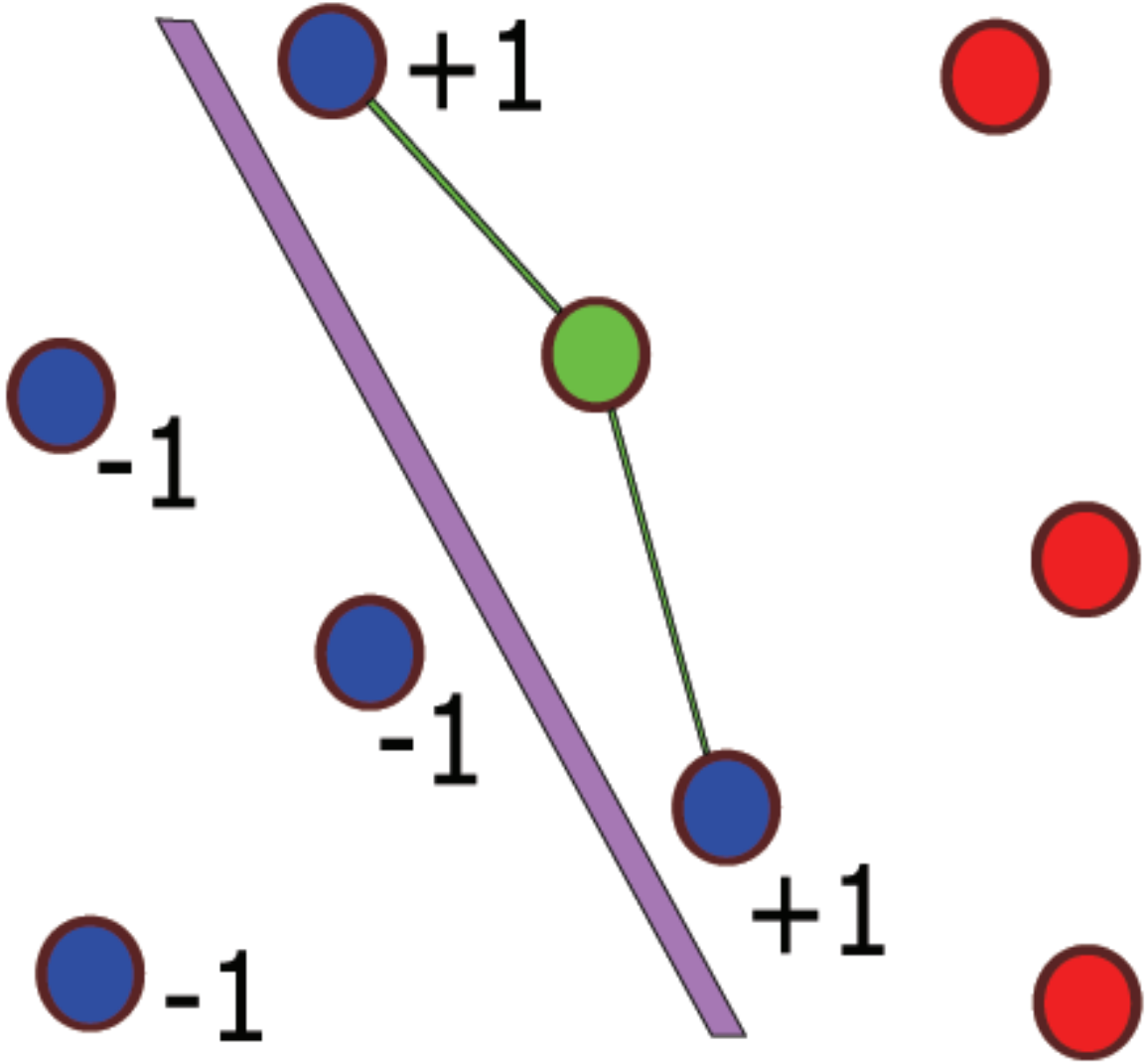

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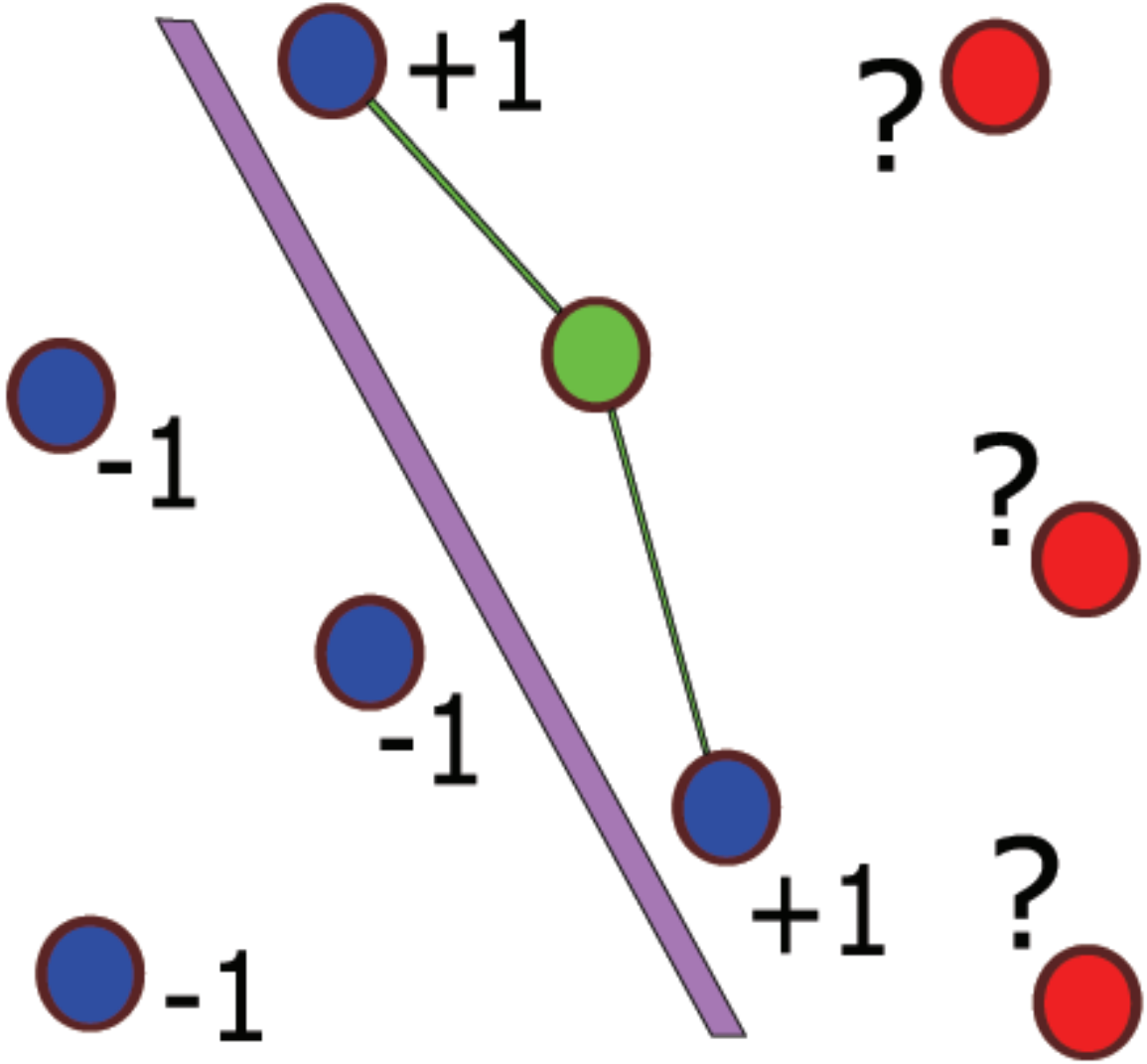

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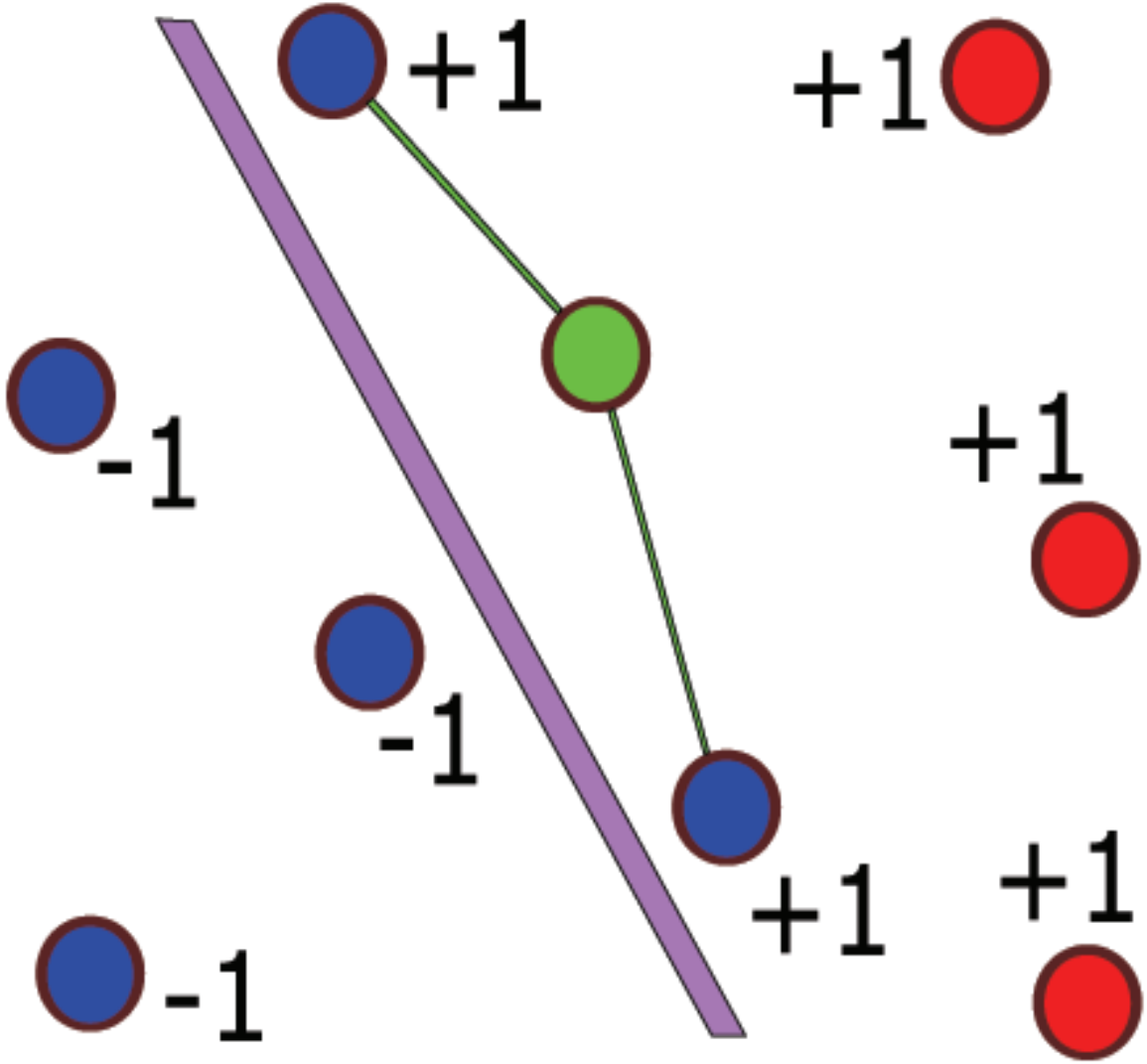

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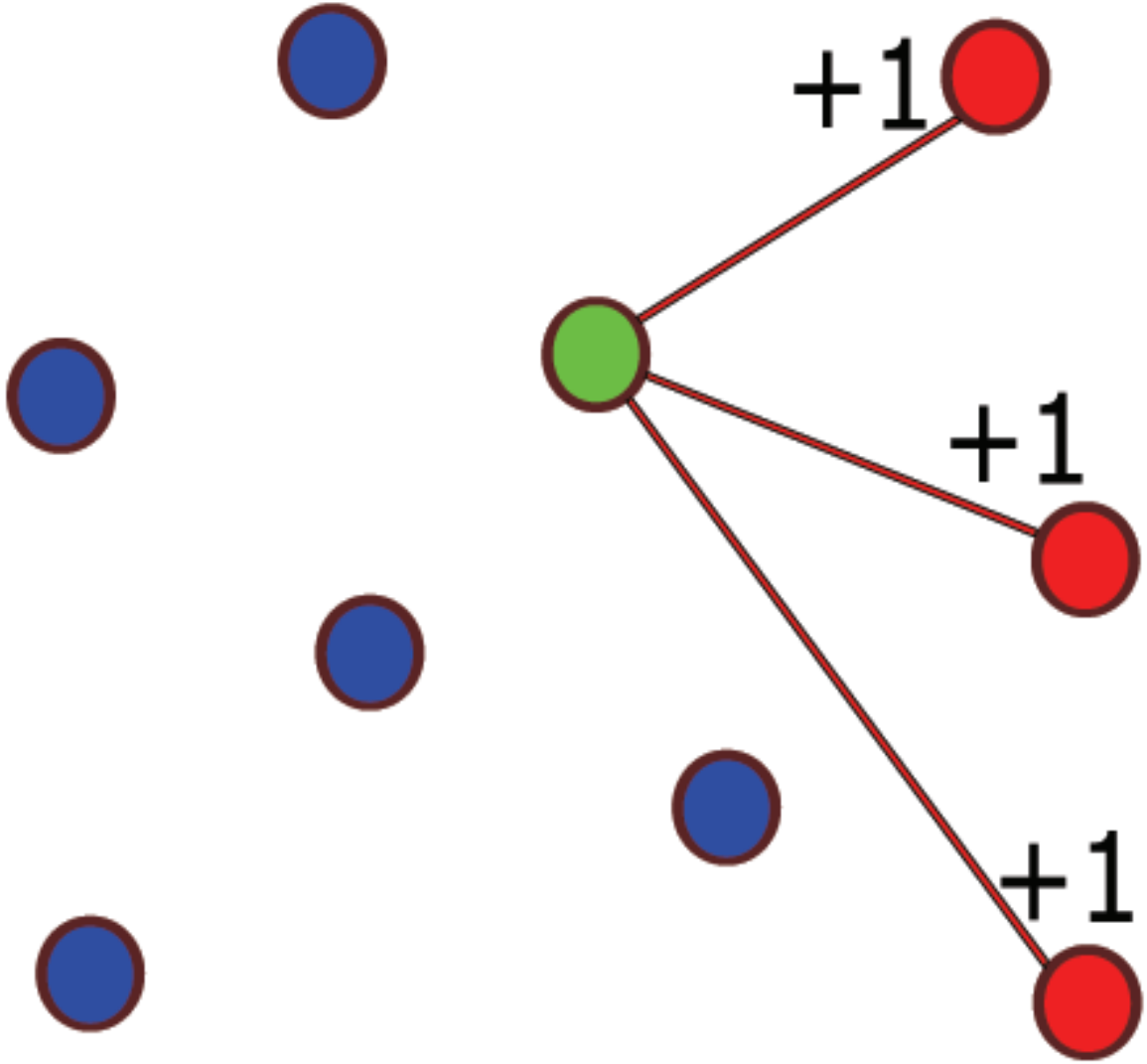

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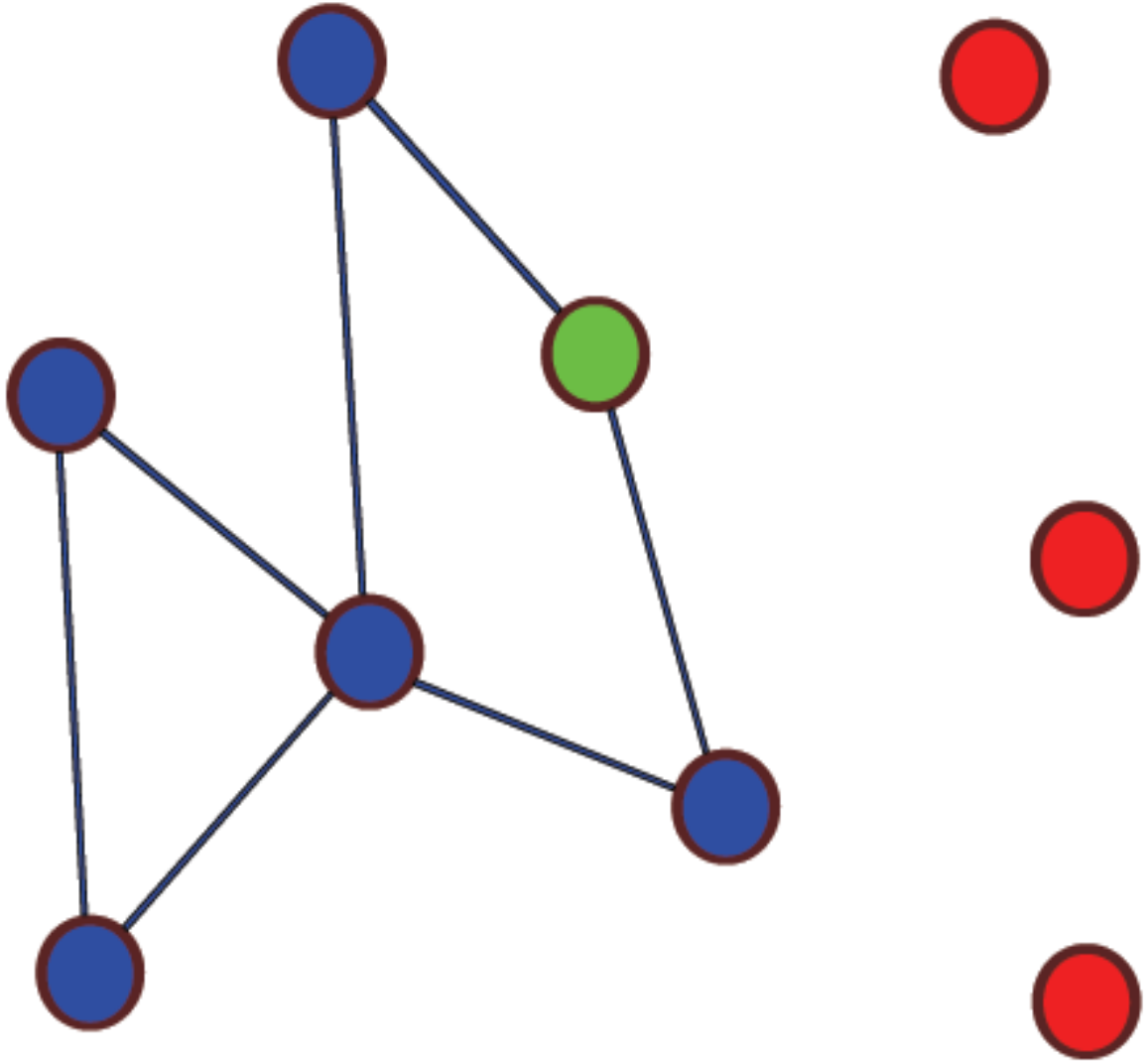

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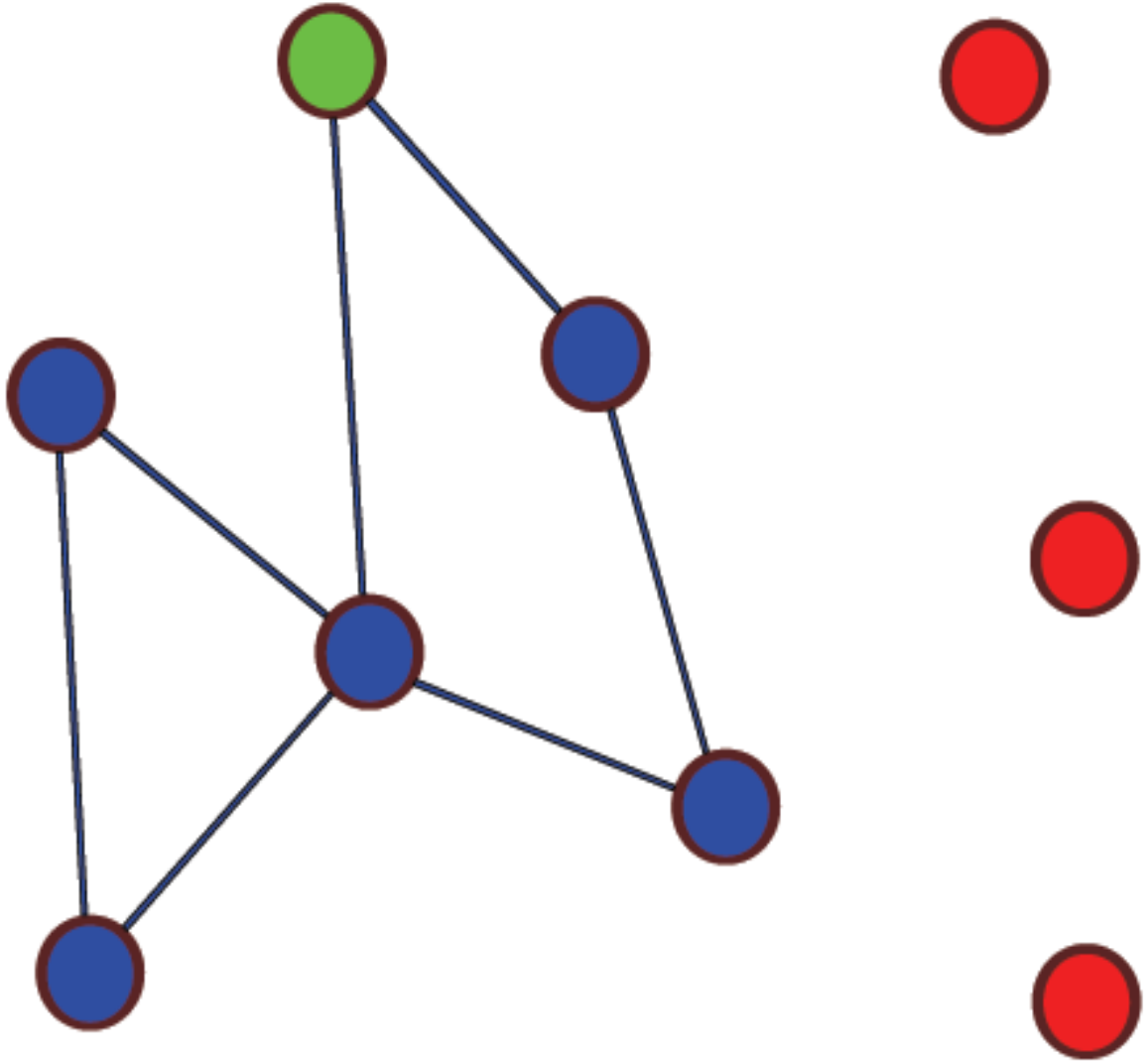

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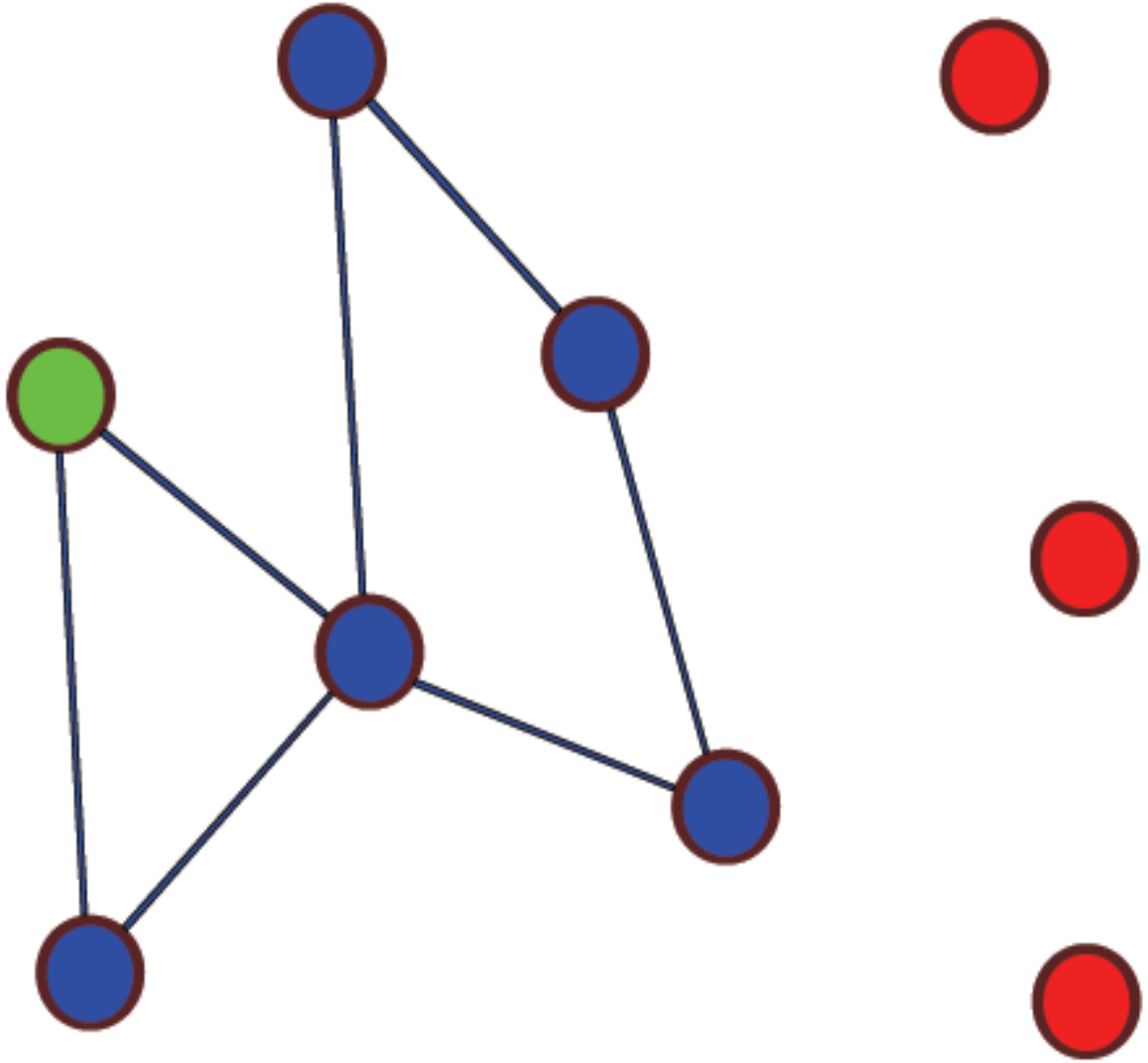

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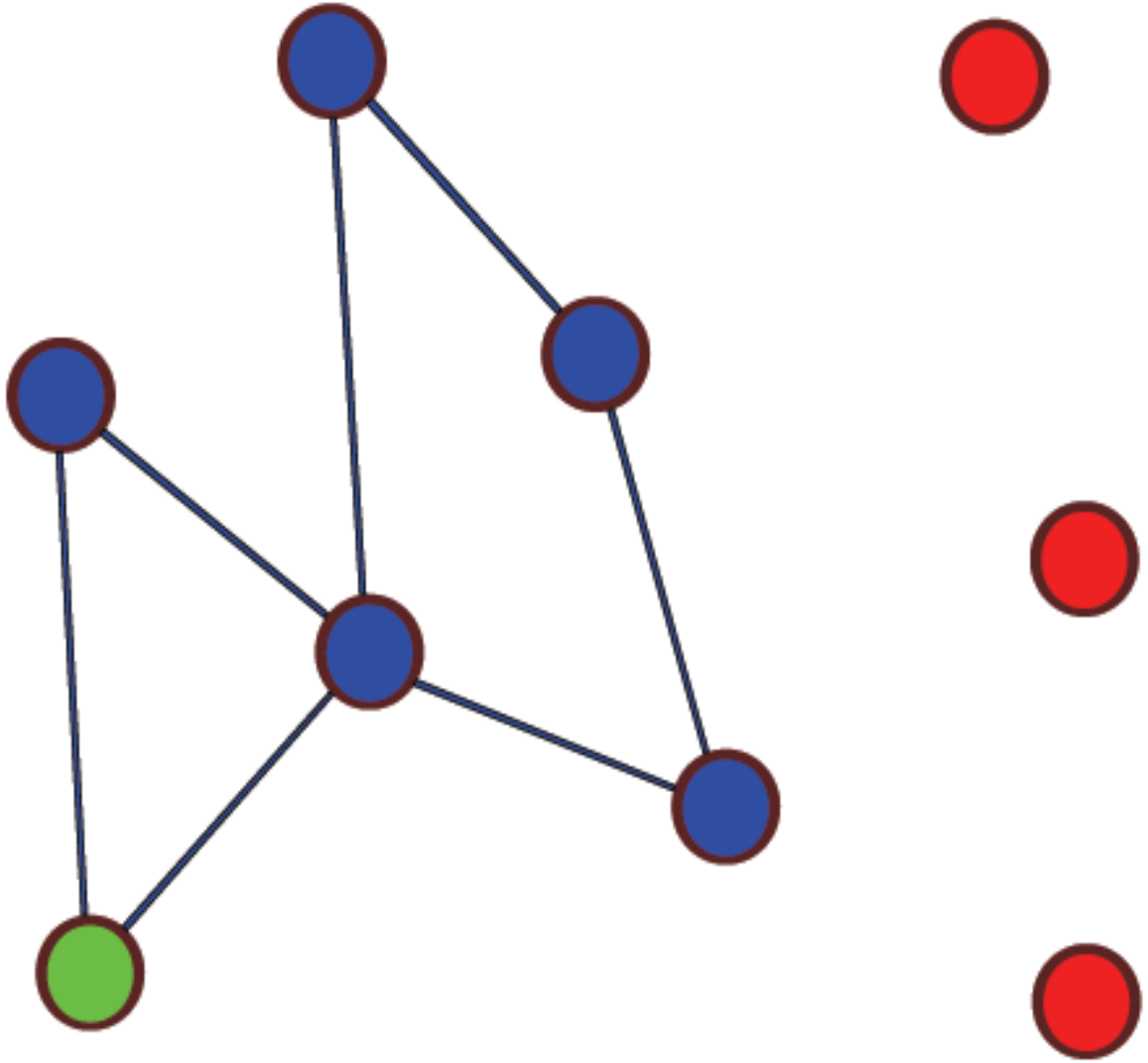

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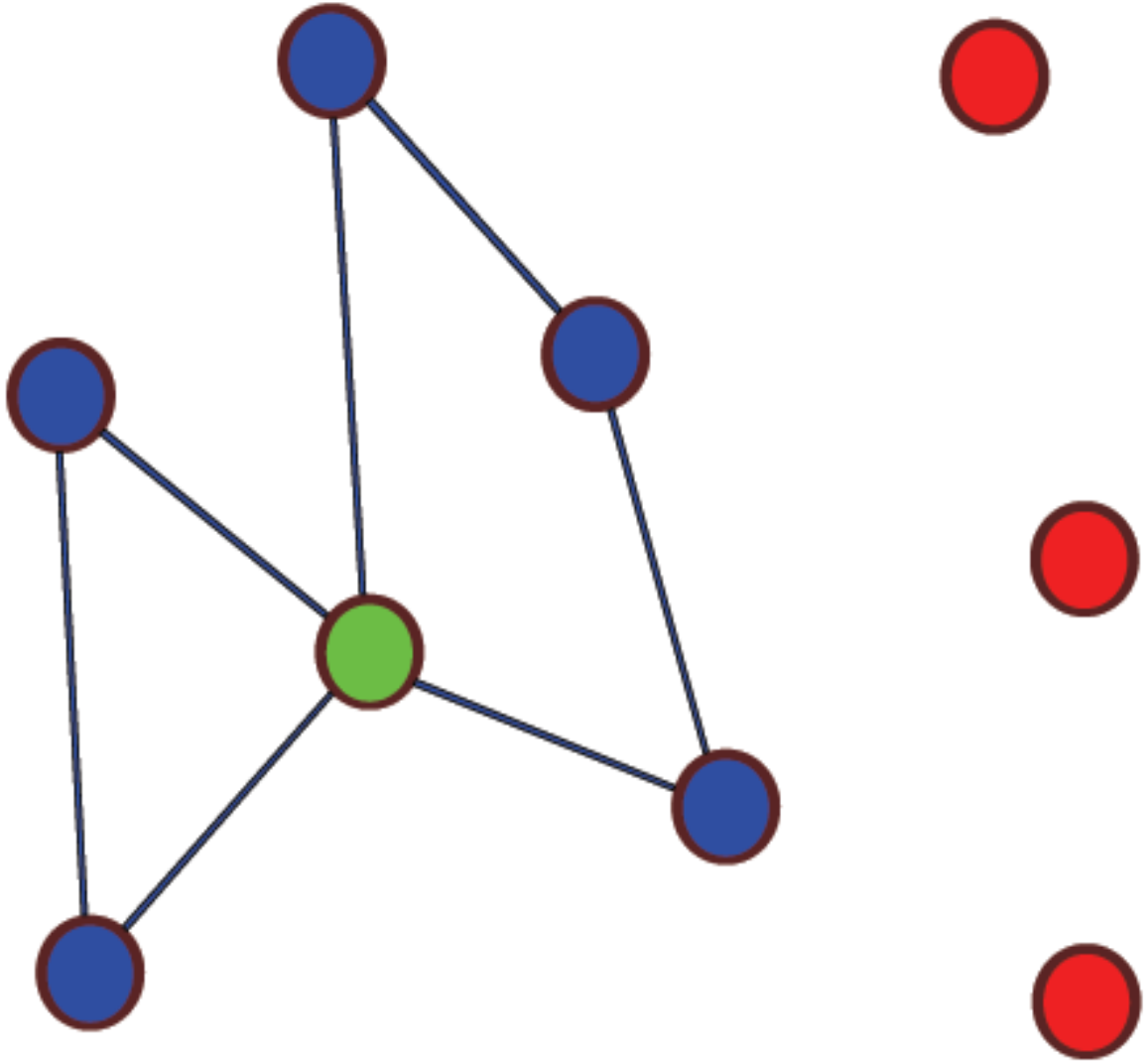

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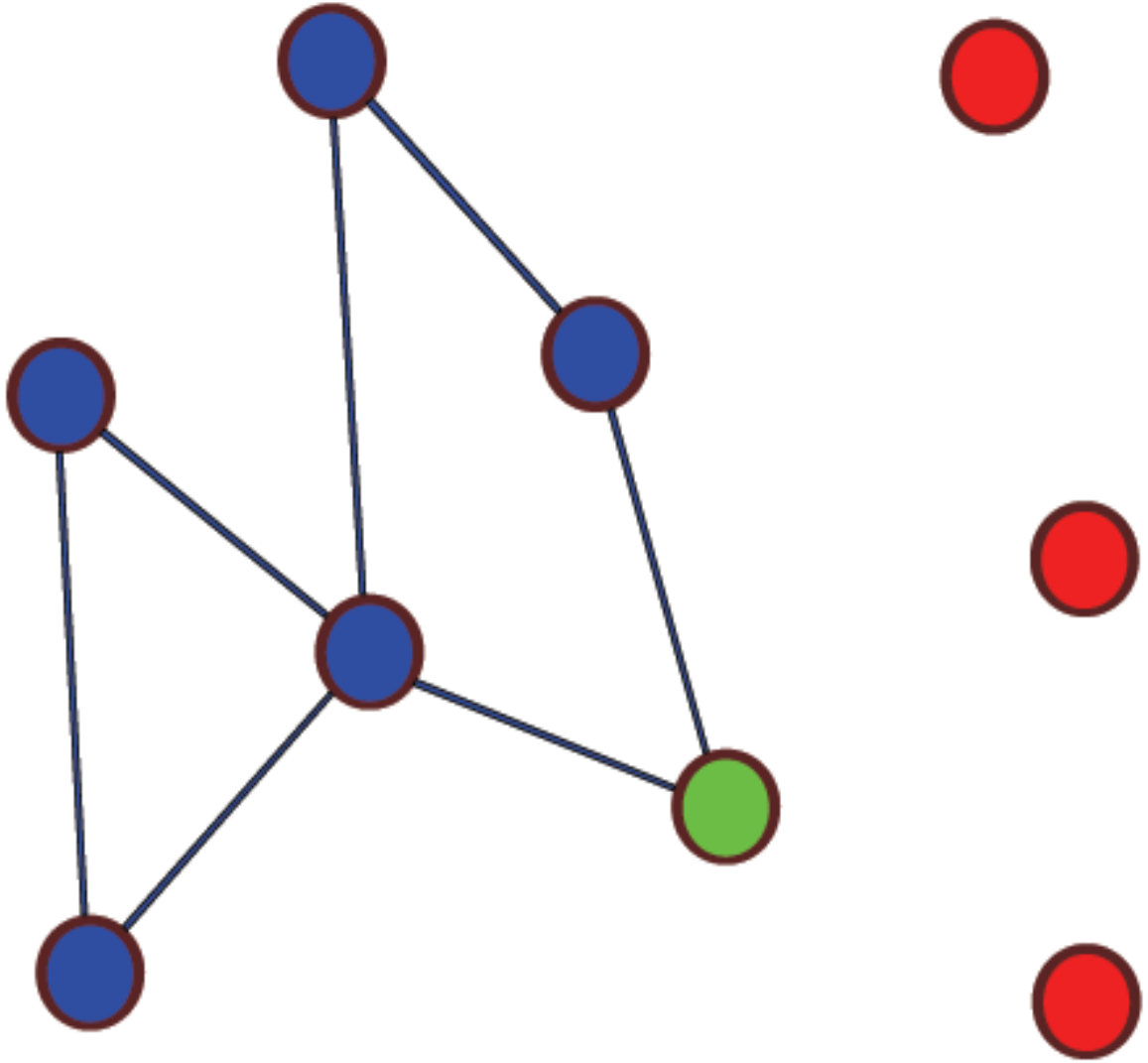

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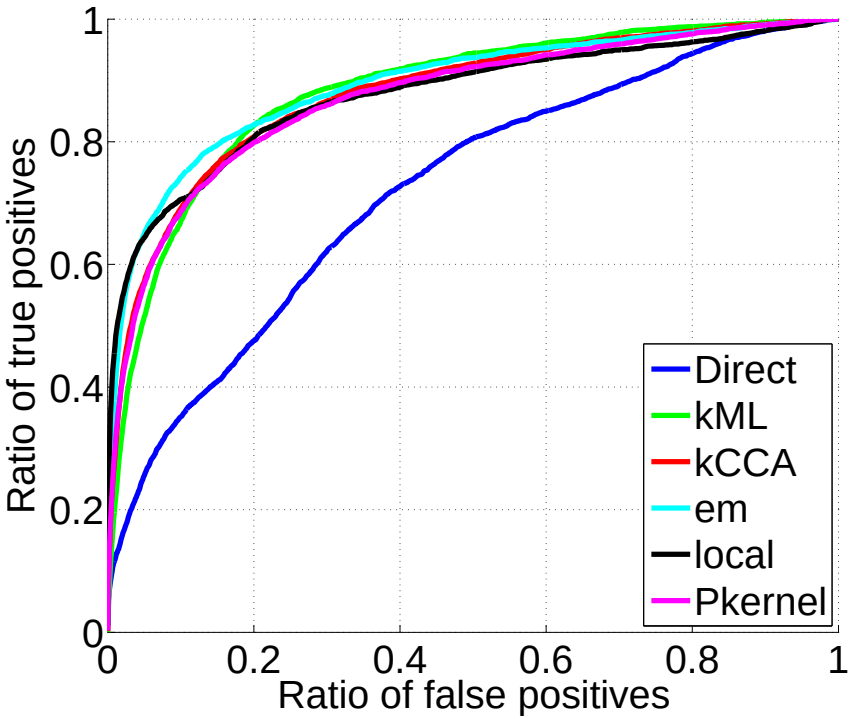
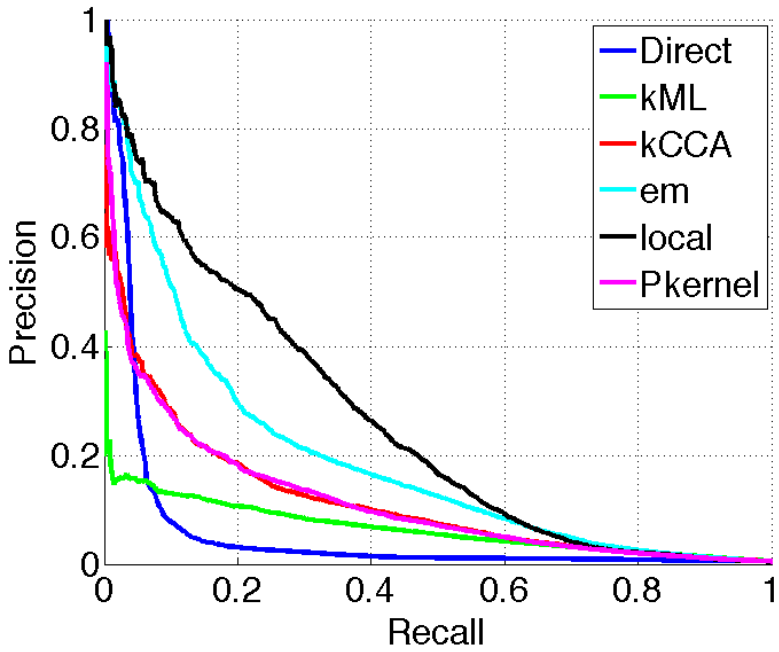
4. Conclusion

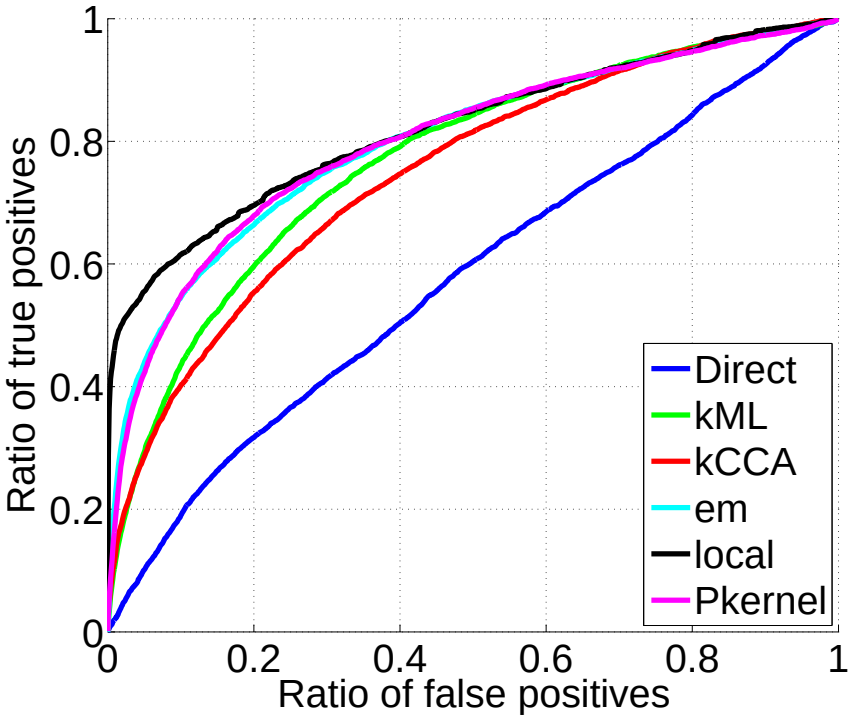
Results: protein-protein interaction (yeast)

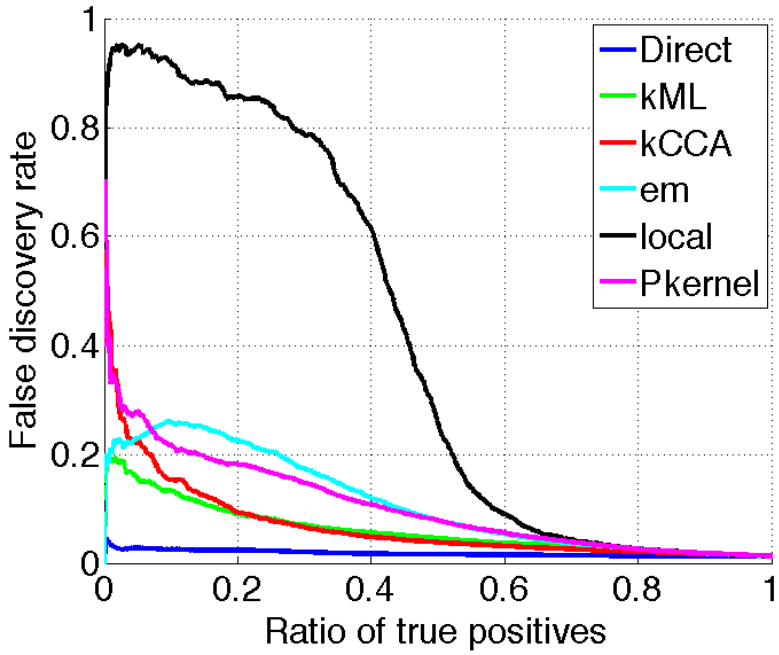




(from Bleakley et al., 2007)

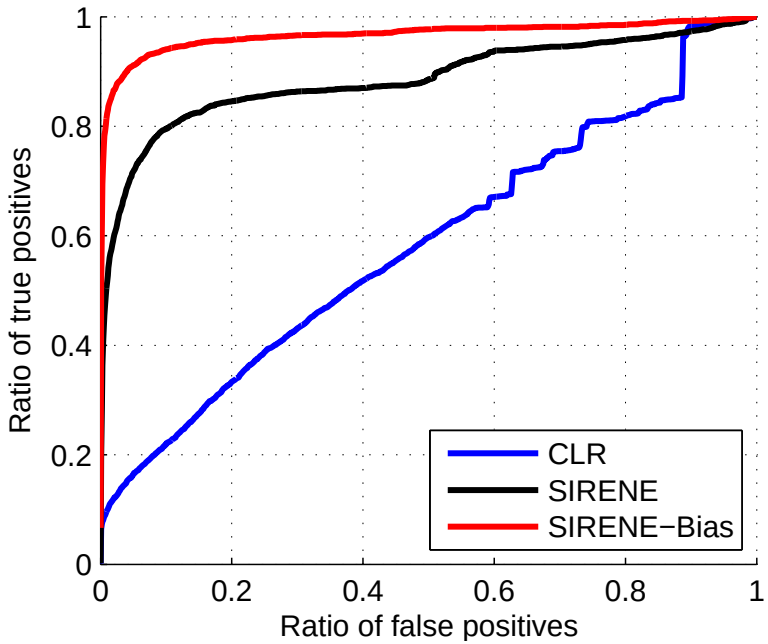
Results: metabolic gene network (yeast)

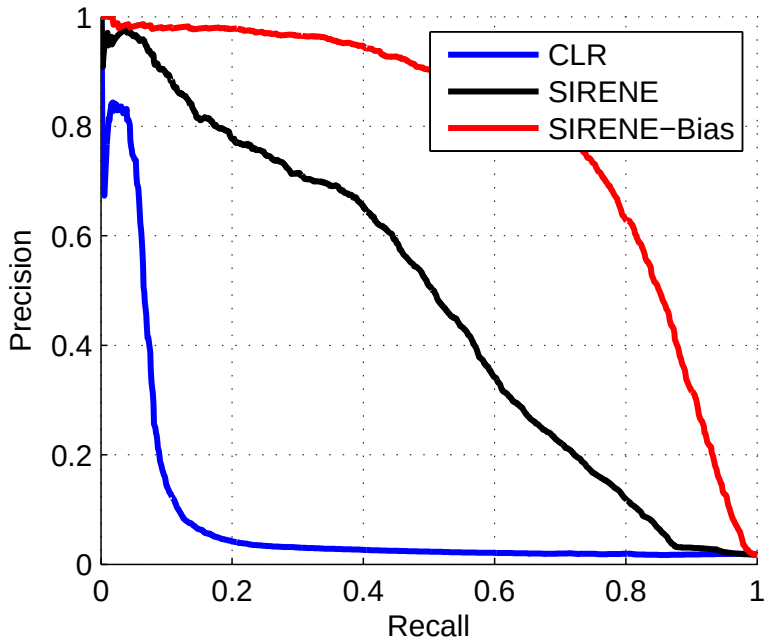




(from Bleakley et al., 2007)

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)

Applications: missing enzyme prediction

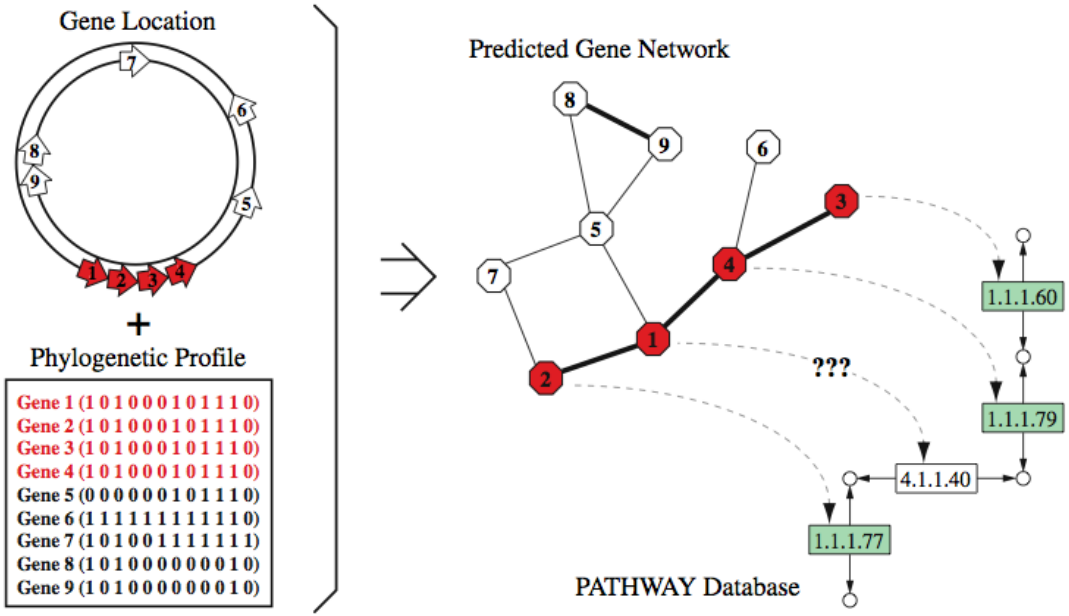
the FEBS Journal

Prediction of missing enzyme genes in a bacterial metabolic network

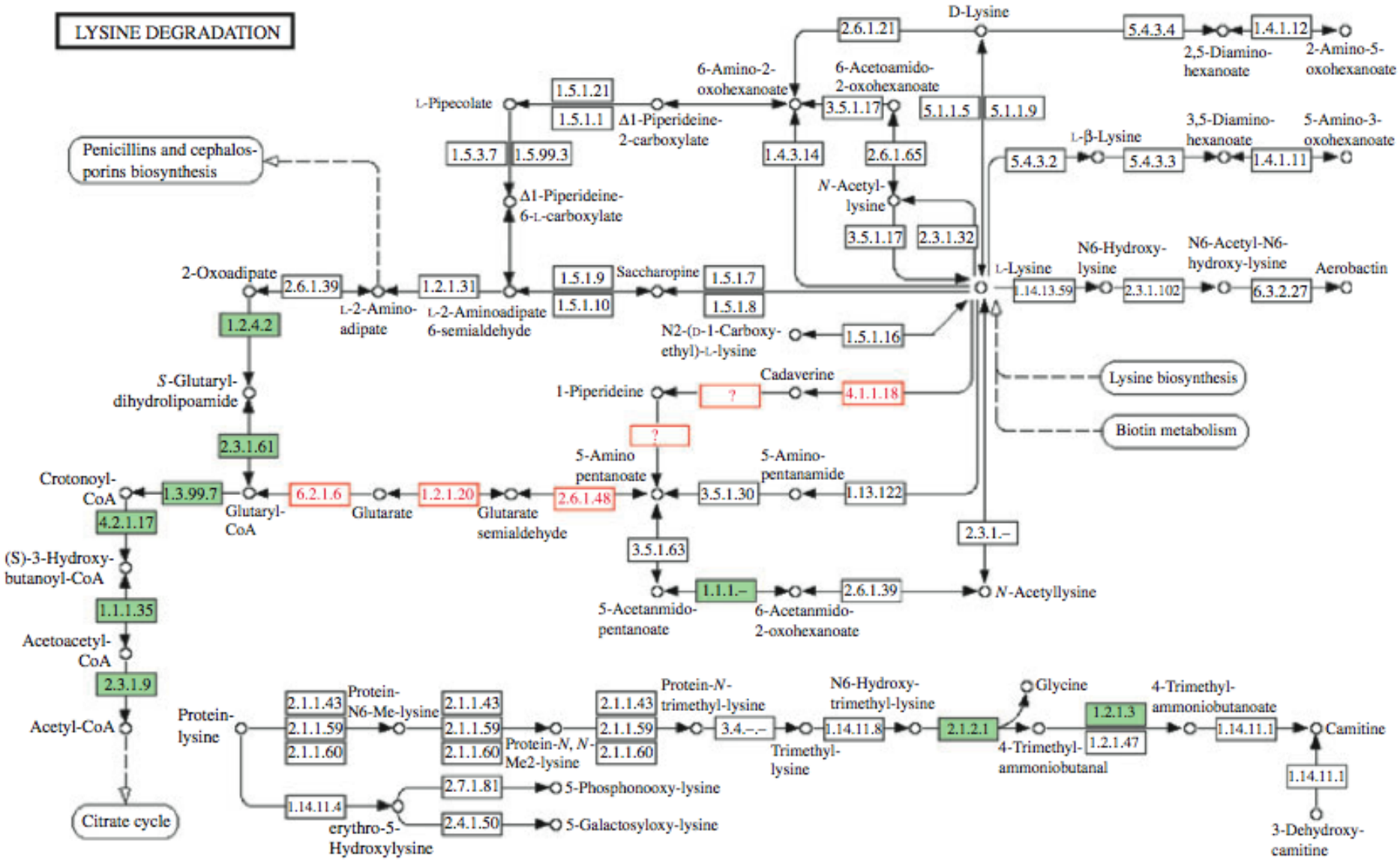
Reconstruction of the lysine-degradation pathway of *Pseudomonas aeruginosa*

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



Applications: missing enzyme prediction

900 DOI 10.1002/pmic.200600862 *Proteomics* 2007, *7*, 900–909

RESEARCH ARTICLE

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

Shinobu Okamoto[1], Yoshihiro Yamanishi[1], Shigeki Ehira[2], Shuichi Kawashima[3], Koichiro Tonomura[1]** and Minoru Kanehisa[1]*

[1] Bioinformatics Center, Institute for Chemical Research, Kyoto University, Uji, Japan
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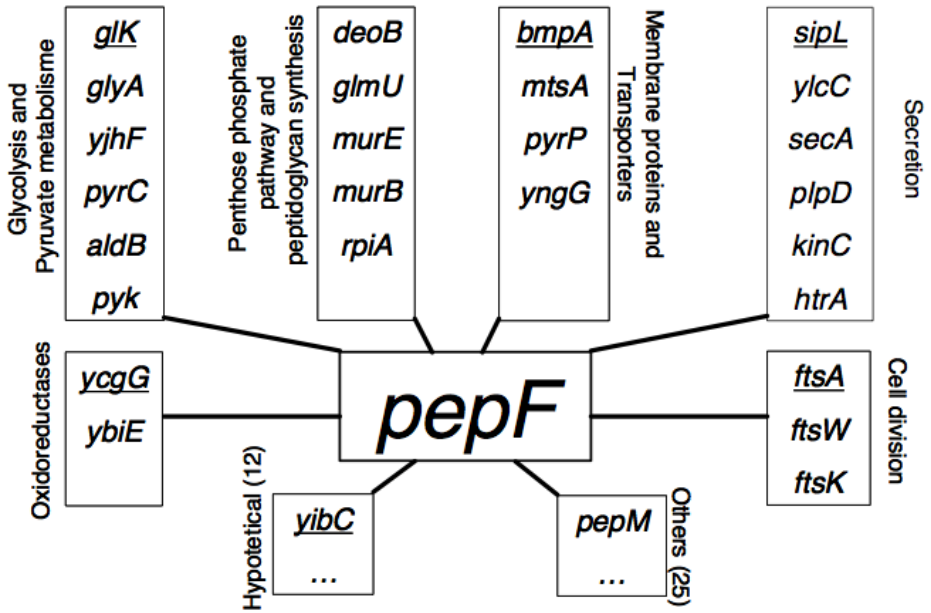
[3] Human Genome Center, Institute of Medical Science, University of Tokyo, Meguro, Japan

Applications: function annotation

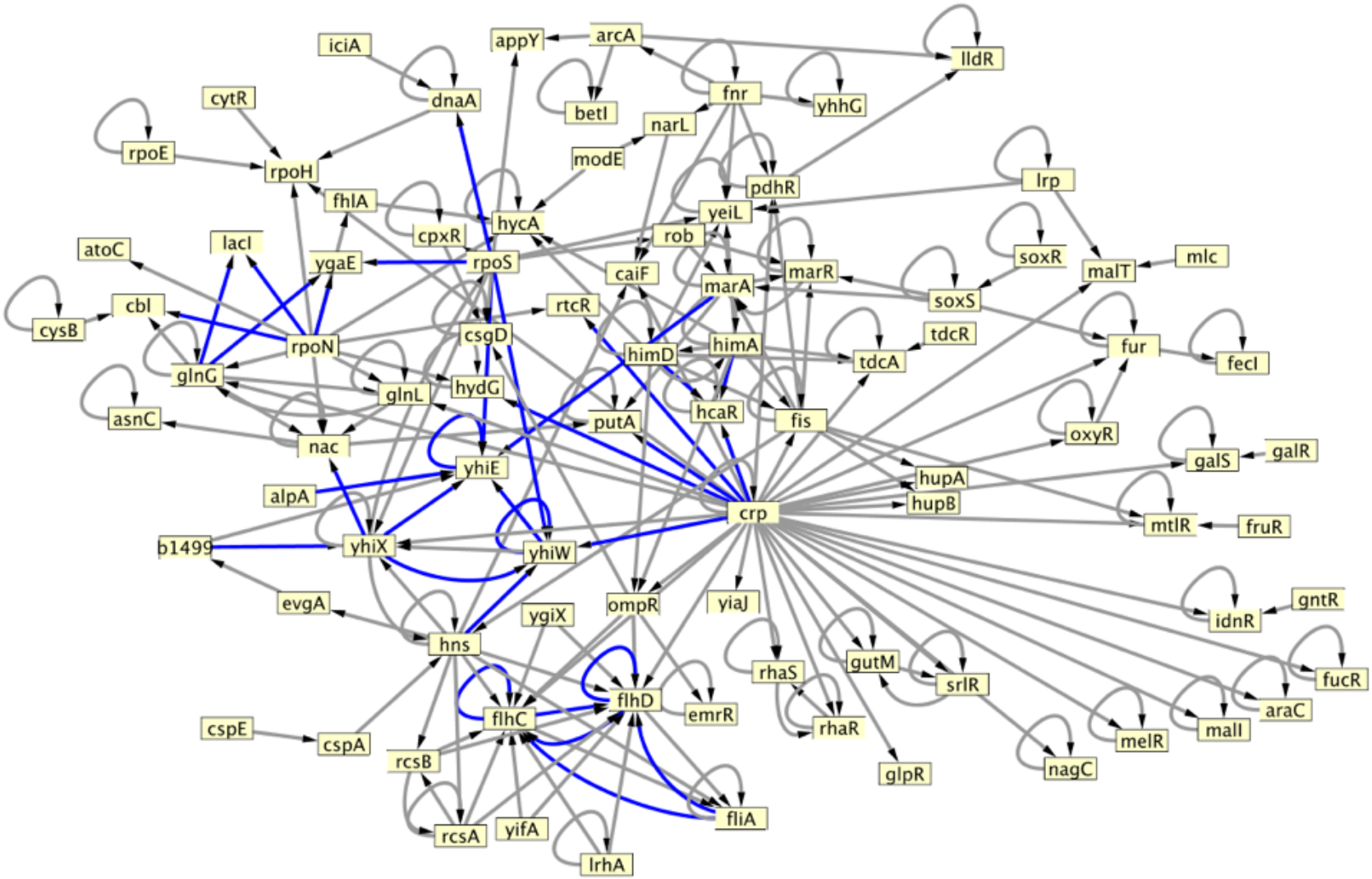
Determination of the role of the bacterial peptidase PepF by statistical inference and further experimental validation

Liliana LOPEZ KLEINE[1,2], Alain TRUBUIL[1], Véronique MONNET[2]

[1]Unité de Mathématiques et Informatiques Appliquées. INRA Jouy en Josas 78352, France.
[2]Unité de Biochimie Bactérienne. INRA Jouy en Josas 78352, France.



Application: predicted regulatory network (E. coli)



Prediction at 60% precision, restricted to transcription factors (from Mordelet and V., 2008).

Outline

1. Inference of biological networks
2. Supervised methods
3. Applications
4. Conclusion

Take-home messages

- 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).
- The current winner on our benchmarks (metabolic, PPI and regulatory networks) is the local pattern recognition approach, which reaches high performance
- These methods:
  - work for any network
  - work with any data
  - can integrate heterogeneous data, which strongly improves performance

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