Supervised inference of biological networks

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Machine Learning in Systems Biology (MLSB 2007), Evry, France, September 24th, 2007

Outline

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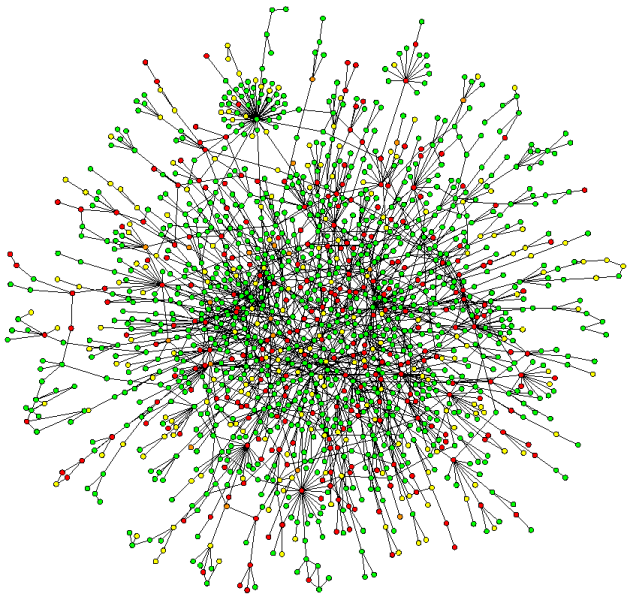
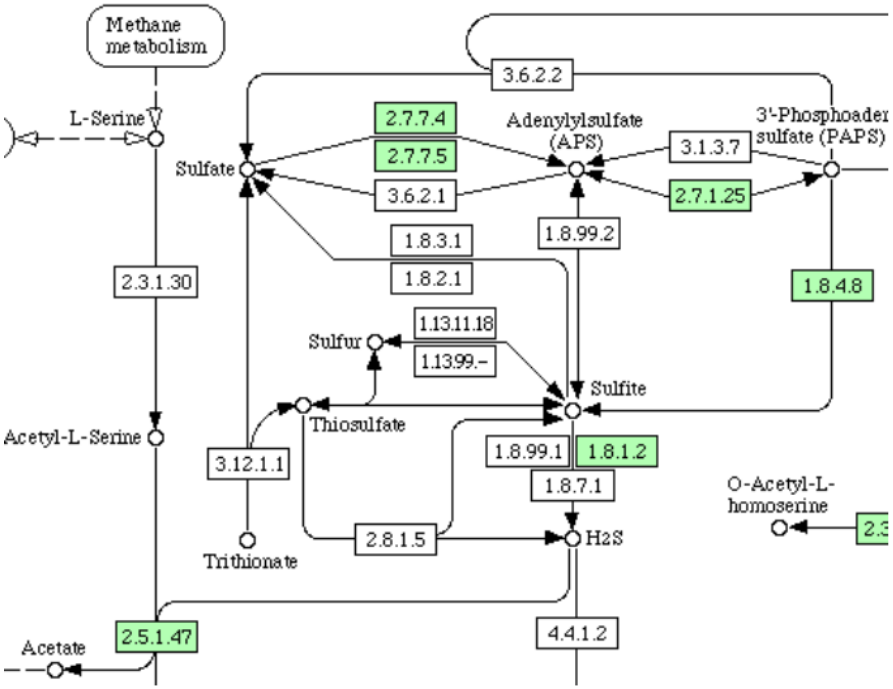
Biological networks

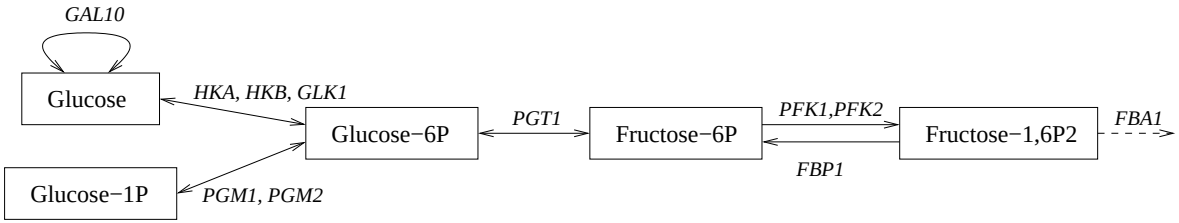


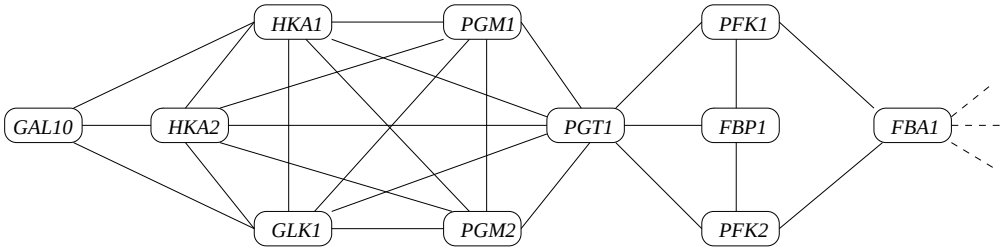


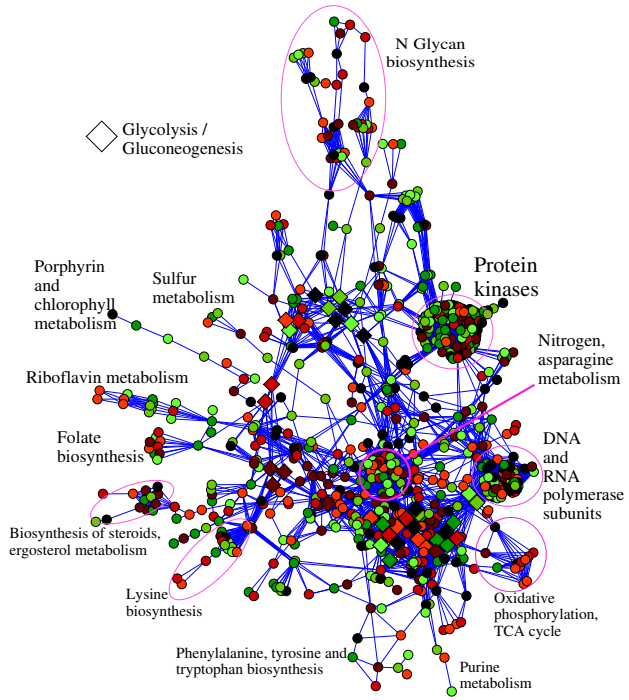
Many interesting biological situations can be represented as network:

- Protein-protein interactions,
- Metabolic pathways,
- Signaling pathways, ...

Example: metabolic network







- Vertices are enzymes
- Edges connect two enzymes when they catalyze two successive reactions

What are the challenges?

Questions

1. Given a newly discovered protein (e.g. from genome sequencing), predict which known ones are connected to it
2. Discover new functional relationships (new edges) between already known proteins.

Applications

- Genome annotation
- Elucidation of new pathways
- Prediction of new binding partners
- Identification of new candidate drug targets

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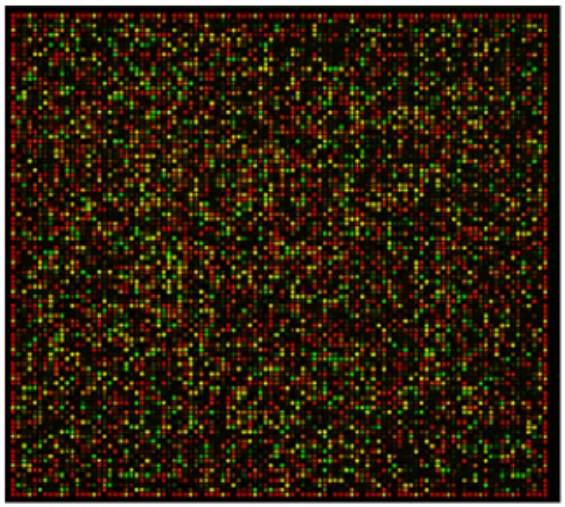
How can bioinformatics help?

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

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



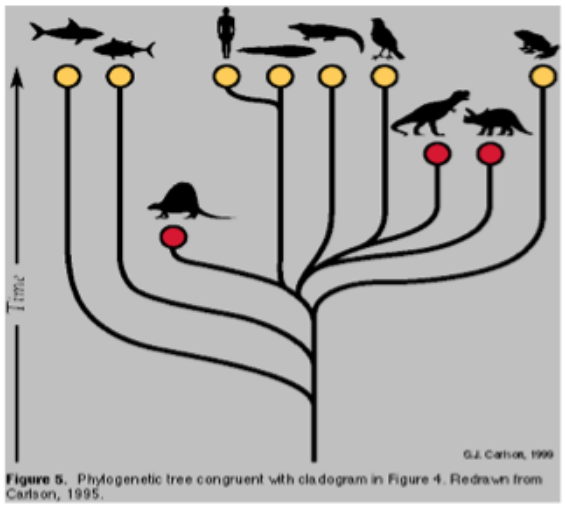
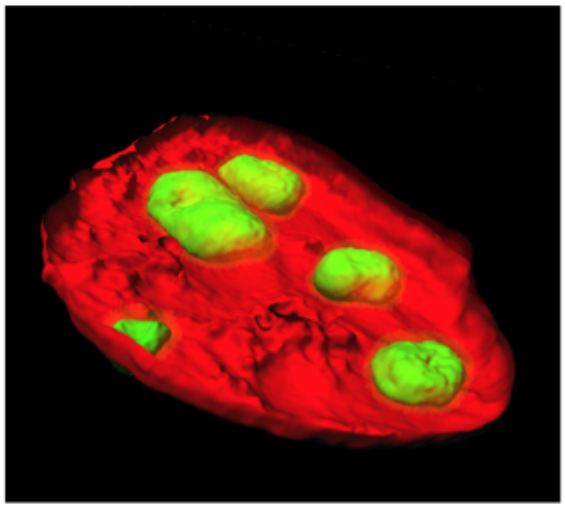
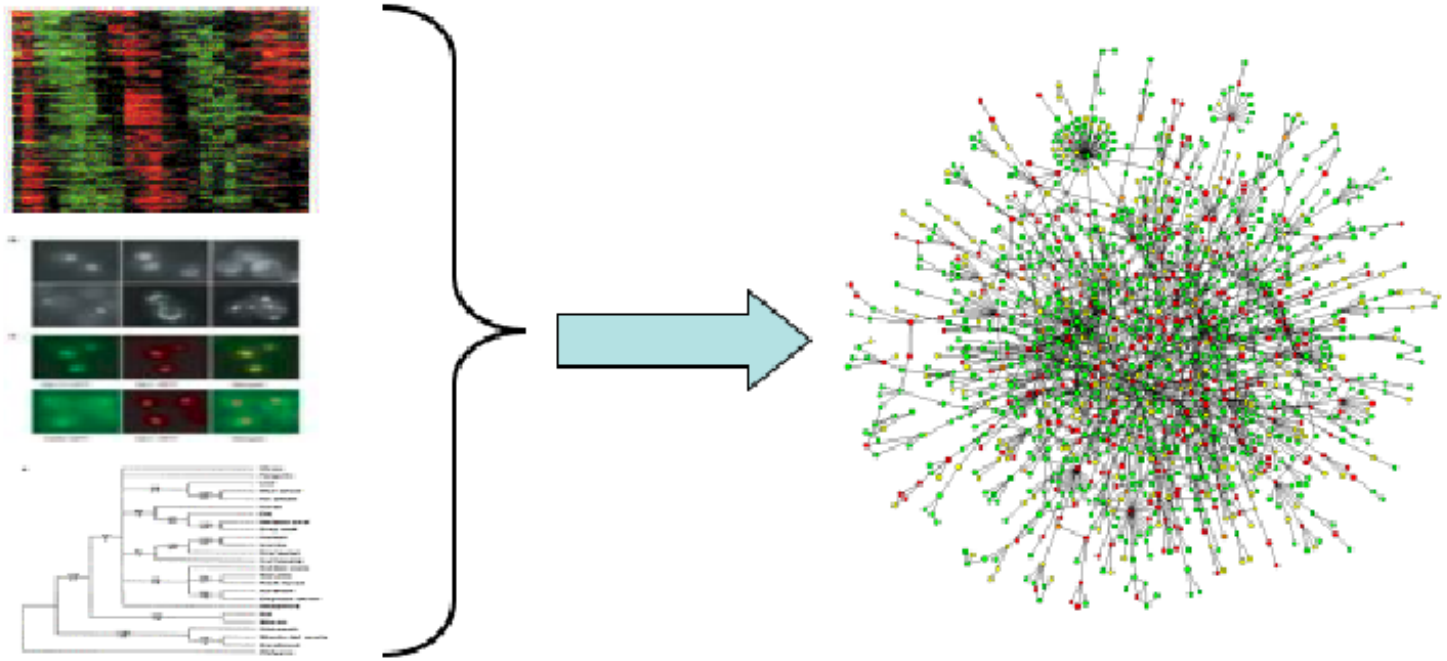


Figure 5. Phylogenetic tree congruent with cladogram in Figure 4. Redrawn from Carlson, 1995.



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

Our goal: Summary



Data

- Gene expression,
- Gene sequence,
- Protein localization, ...

Graph

- Protein-protein interactions,
- Metabolic pathways,
- Signaling pathways, ...

Outline

Unsupervised inference

Setting

- Given data about the genes proteins...
- Infer the edges between genes and proteins
- Note that the graph is considered completely unknown in the inference process

Strategies for inference

- Model-based : fit a "model" involving a graph to the data
- Similarity-based : connect "similar" nodes

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Model-based approaches

Strategy

1. Define a model to explain the data with a graph
2. Fit the model to the data to infer a graph

Examples

- Dynamical system to model gene expression time series (boolean network, PDE, state-space models...)
- Statistical models where the graph represents conditional independence relationships among random variables (Bayesian networks, LASSO, ...)

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Model-based approaches

Pros

- Best 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

Similarity-based approaches

Rationale

Genes functionally related are likely to be co-regulated, co-localized, present in the same organisms...

Strategy

1. Define a distance between proteins from the genomic data
2. Predict an edge if the distance is below a threshold

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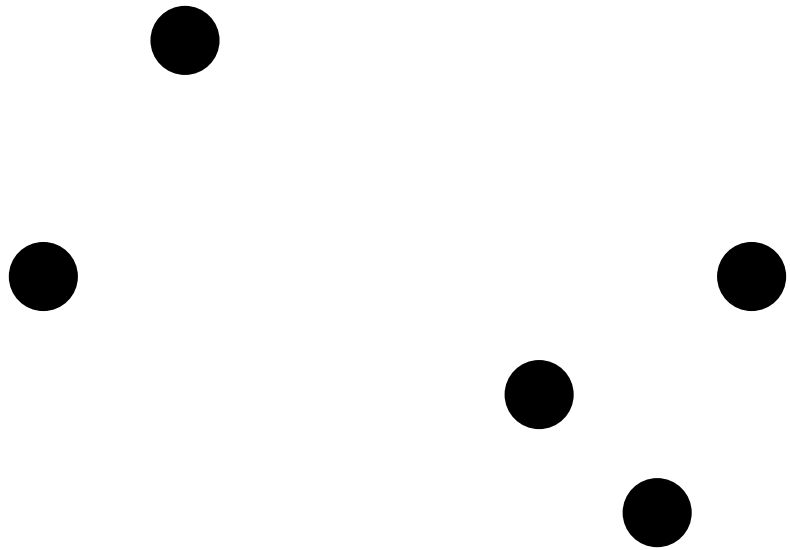

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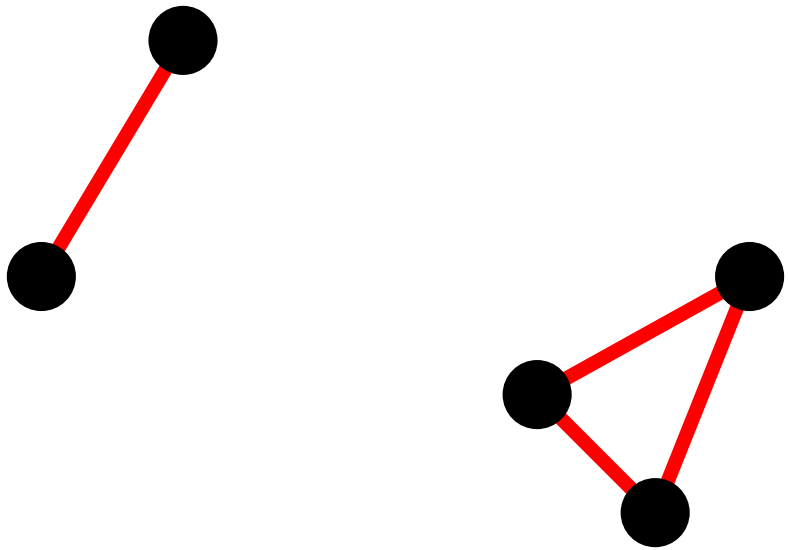
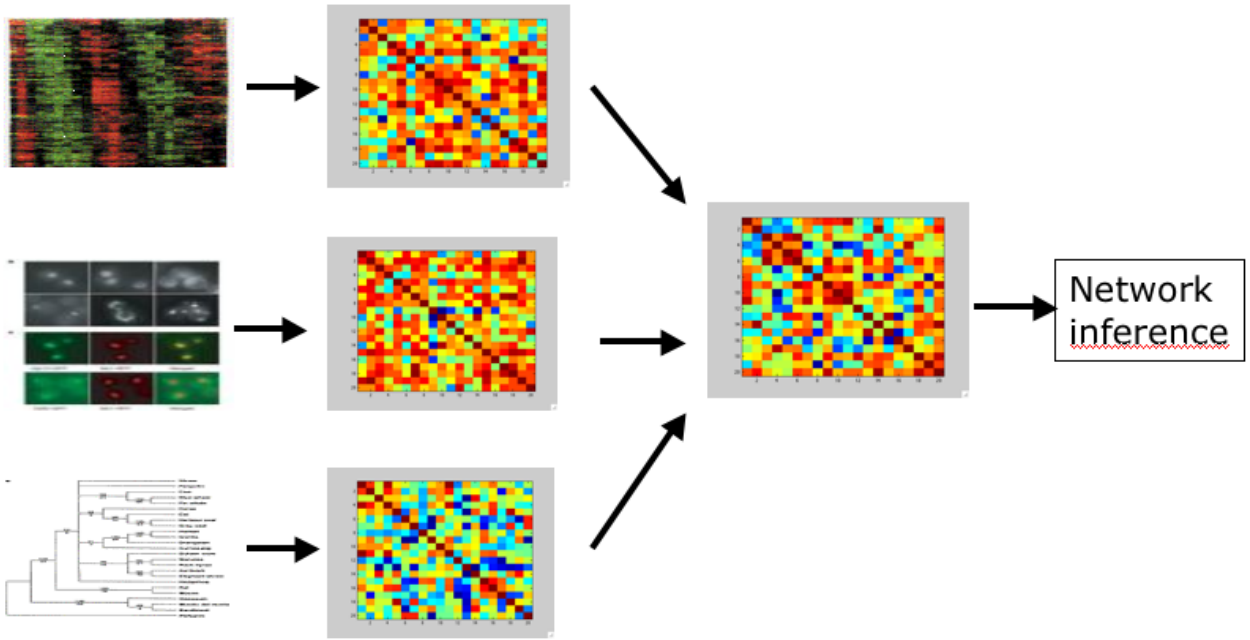


Integrations of genomic data

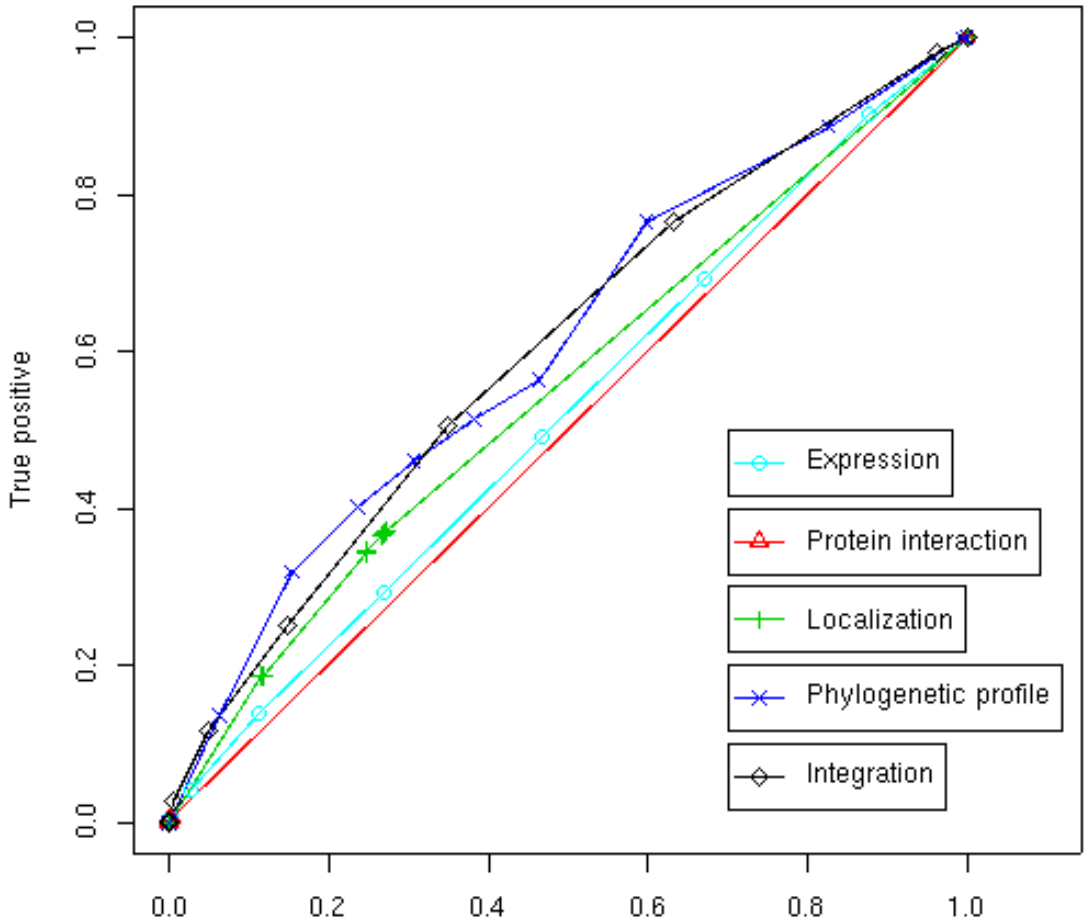
Data representation a distances

- We assume that each type of data (expression, sequences...) defines a distance between genes.
- Many such distances exist (cf kernel methods).
- Data integration is easily obtained by summing the distance to obtain an "integrated" distance



Evaluation on metabolic network reconstruction

- 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).



What went wrong?

Limitations

- Is the assumption that “similar proteins are connected” correct and sufficient?
- Is the Euclidean distance the “correct” way to compare genomic data?
- Perhaps the network inferred is interesting, but not related to the metabolic network?

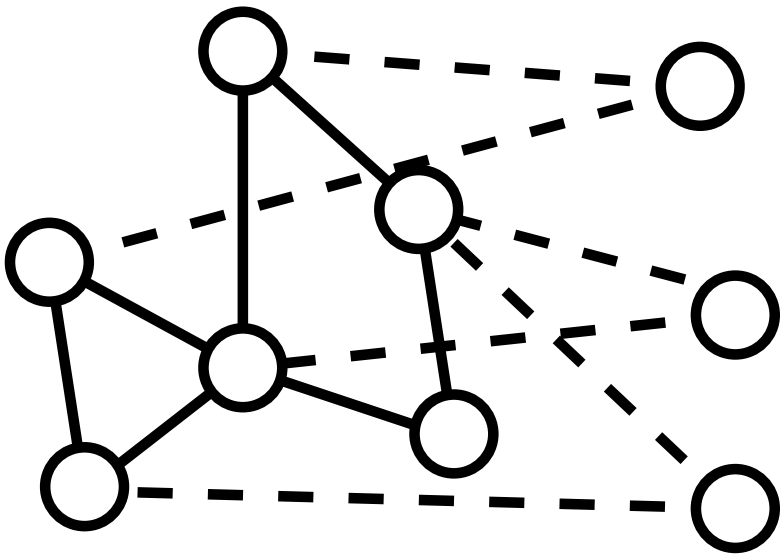
Outline

Setting

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

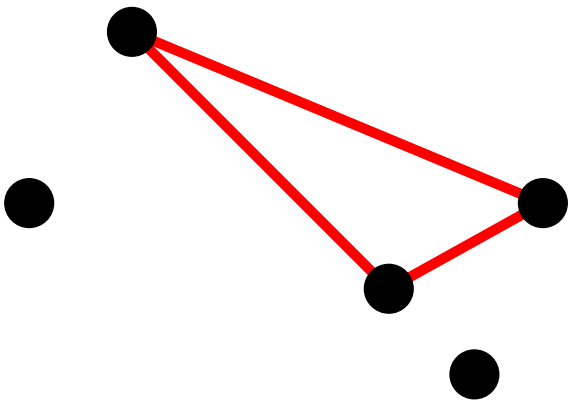
- Given genomic data and the currently known network...
- Infer missing edges between current nodes and additional nodes.

Outline

Metric learning

Idea

- The direct similarity-based method fails because the distance metric used might not be adapted to the inference of the targeted protein network.
- Solution: use the known subnetwork to refine the distance measure, before applying the similarity-based method



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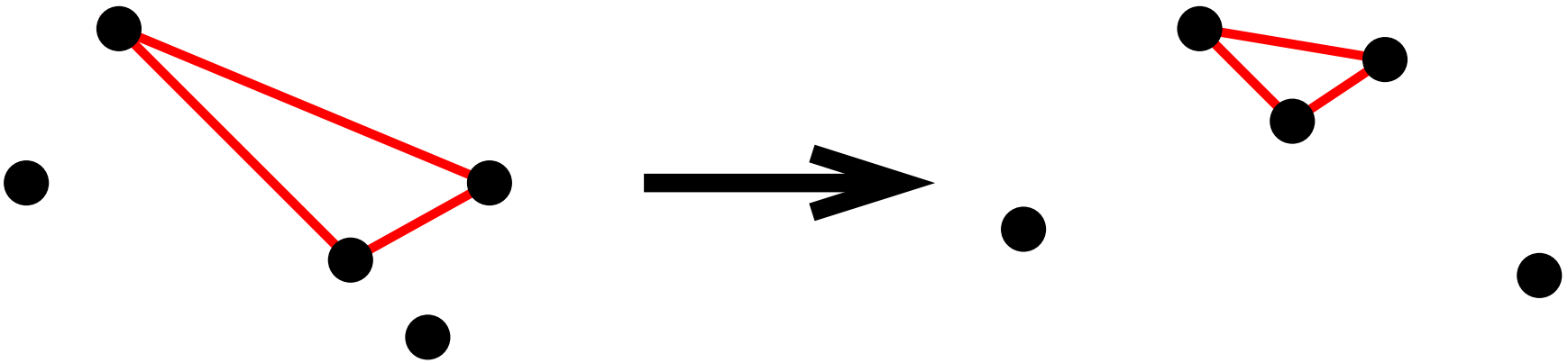

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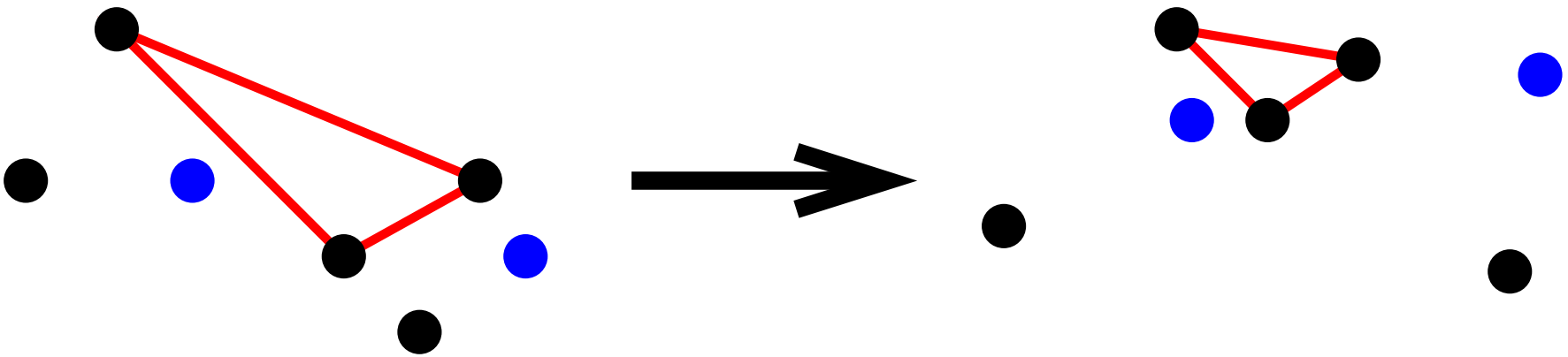

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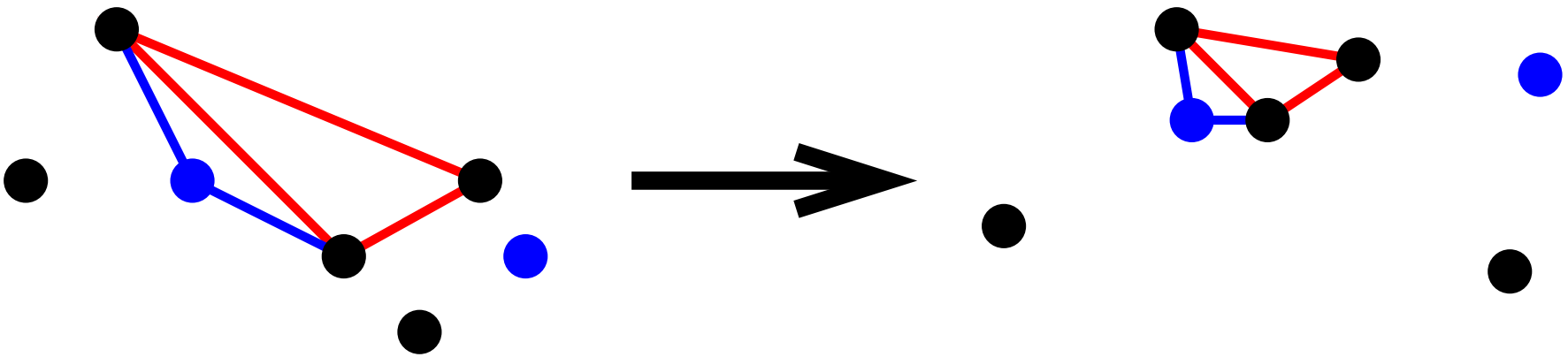
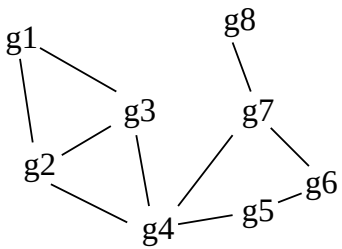
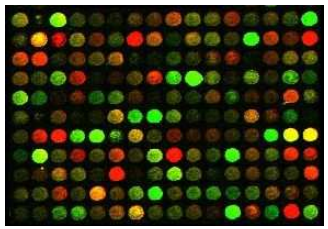


Metric learning by kernel CCA (Yamanishi et al., 2004)

- Embed both the graph and the genomic data in Hilbert spaces.
- Find subspaces in the Hilbert spaces where the graph distance and the genomic data distance match (kernel CCA)
- Use the metric of the genomic data subspace for network inference with the direct method.





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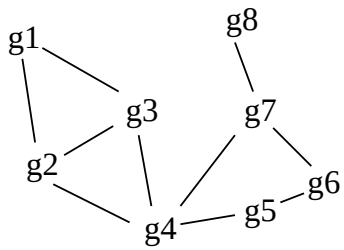

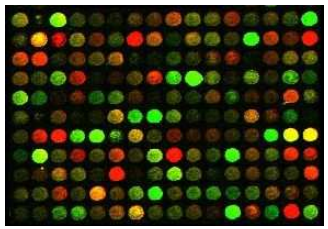

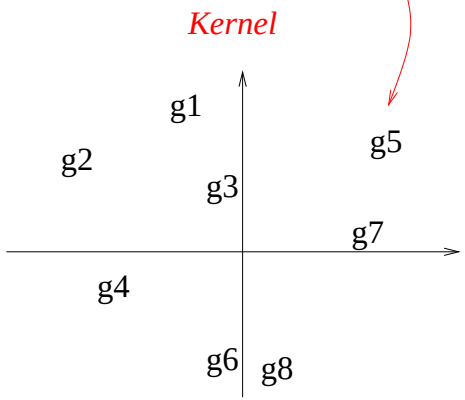

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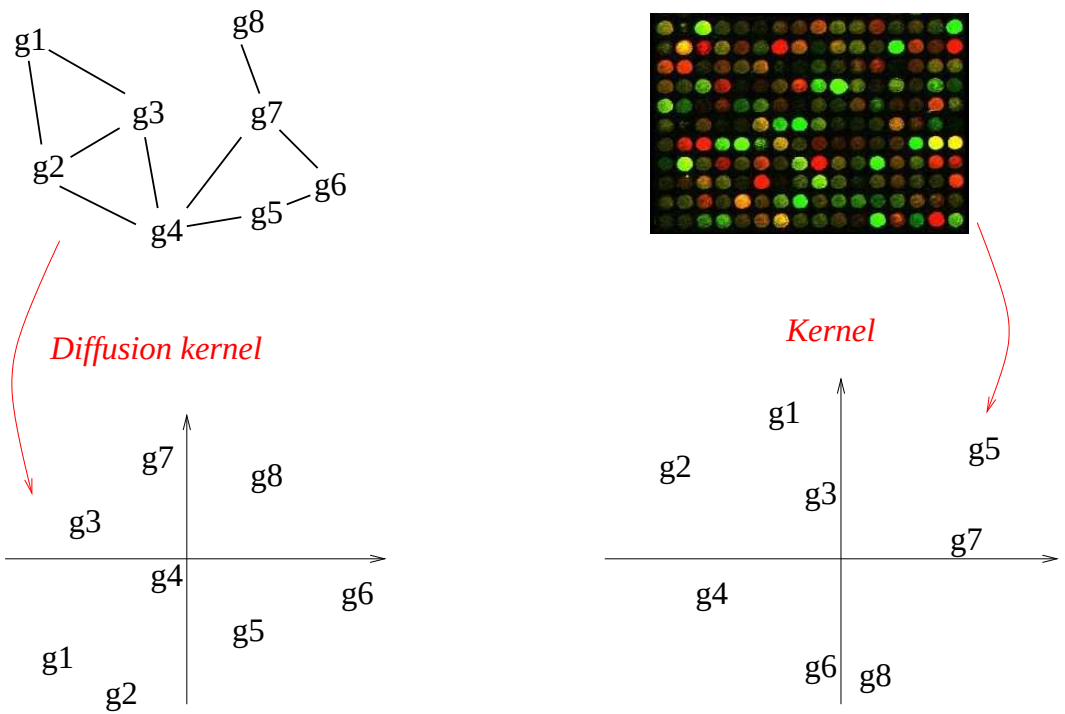

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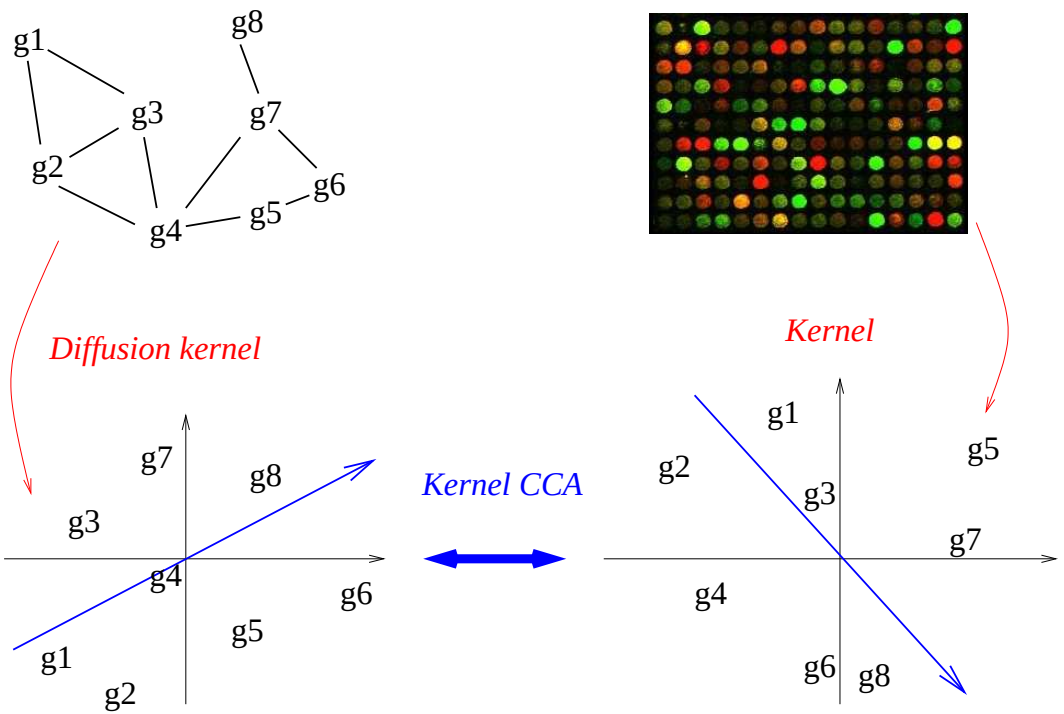

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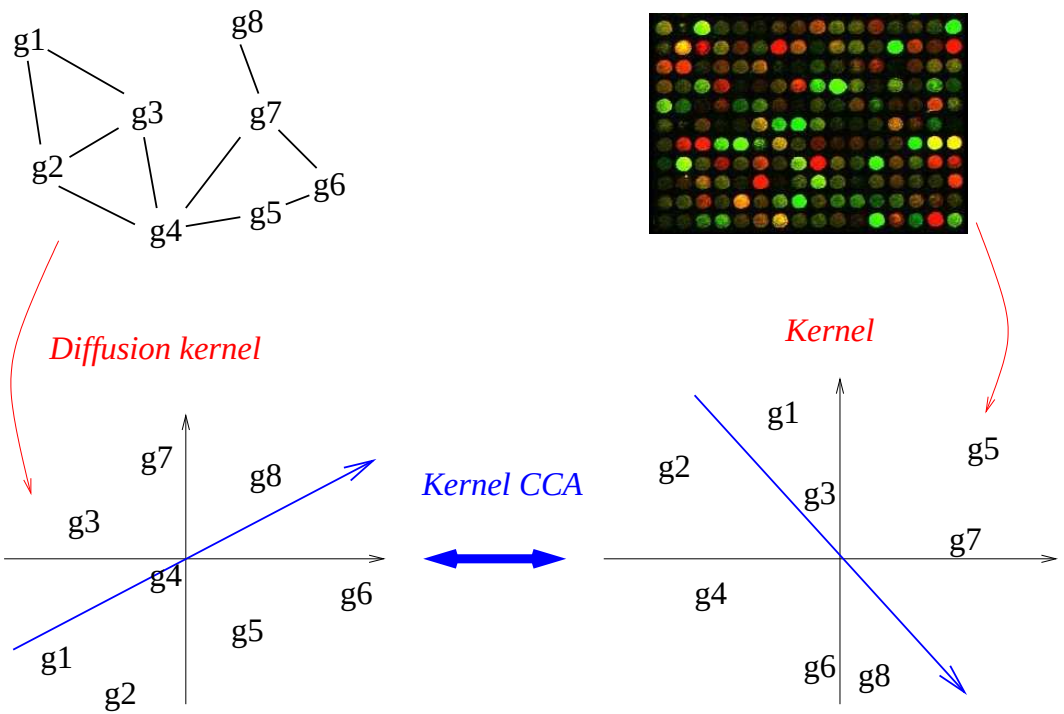


Kernel metric learning (V. and Yamanishi, 2005)

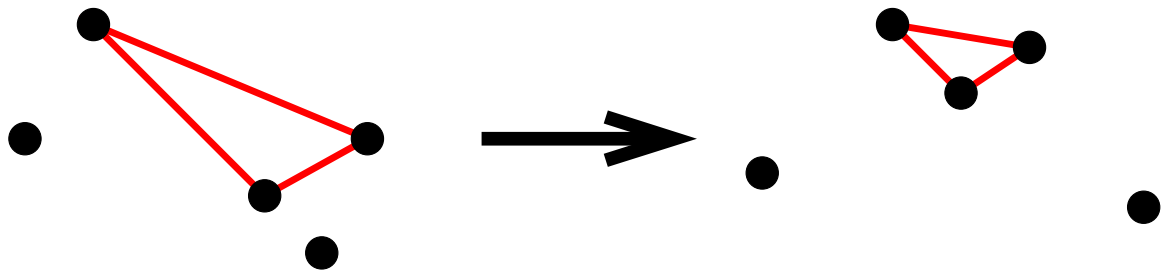
Kernel metric learning

- Criterion: connected points should be near each other after mapping to a new d-dimensional Euclidean space.
- Add regularization to deal with high dimensions.
- Mapping $f(x) = (f_1(x), \ldots, f_d(x))$ with:

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

- Interpolates between (kernel) PCA ($\lambda = \infty$) and graph embedding ($\lambda = 0$).
- Equivalent to a generalized eigenvalue problem.

Metric learning: Summary



- Solves an important question of the similarity-based approach: which distance should be used?
- Virtually any algorithm for distance metric learning can be used
- But... do we really need to follow the similarity-based approach to infer graphs?

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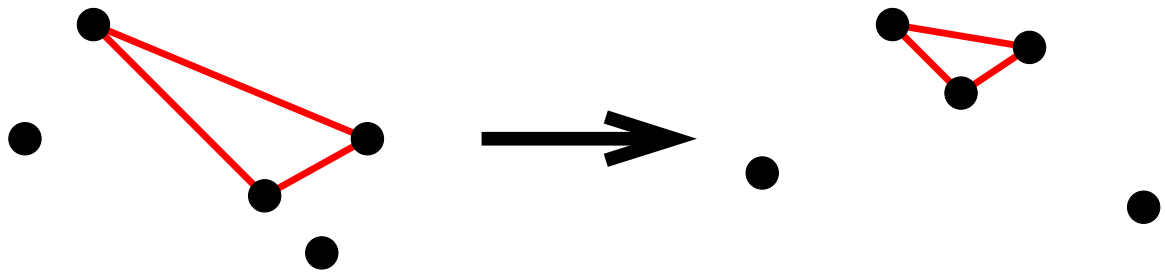

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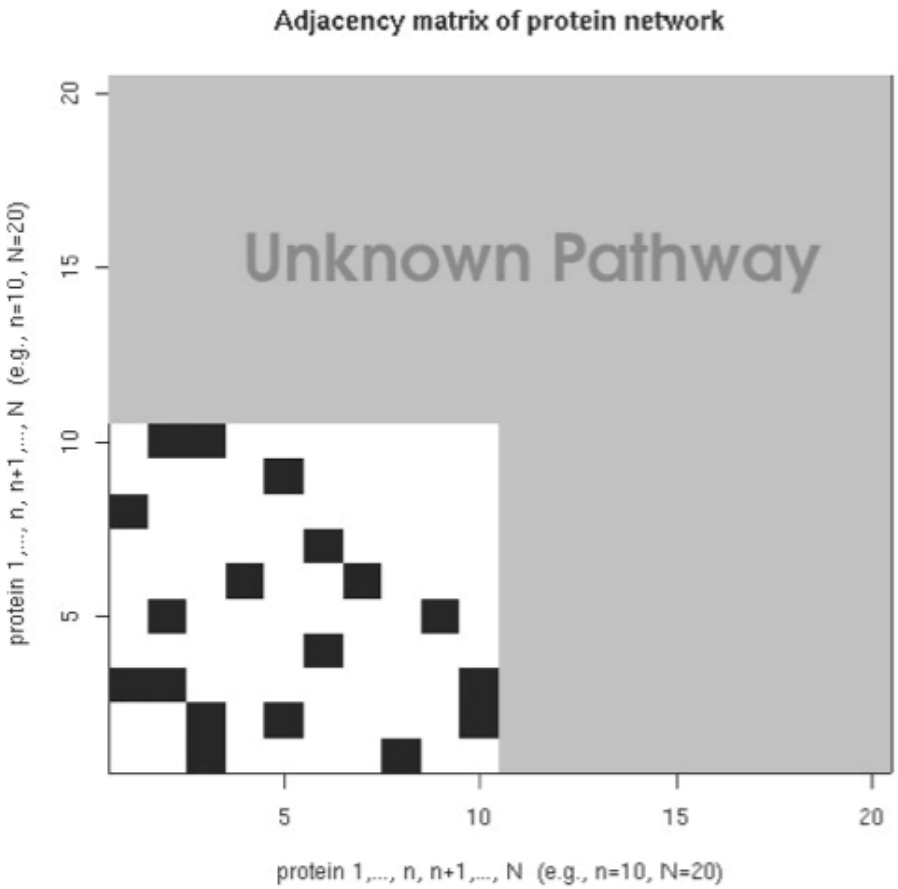
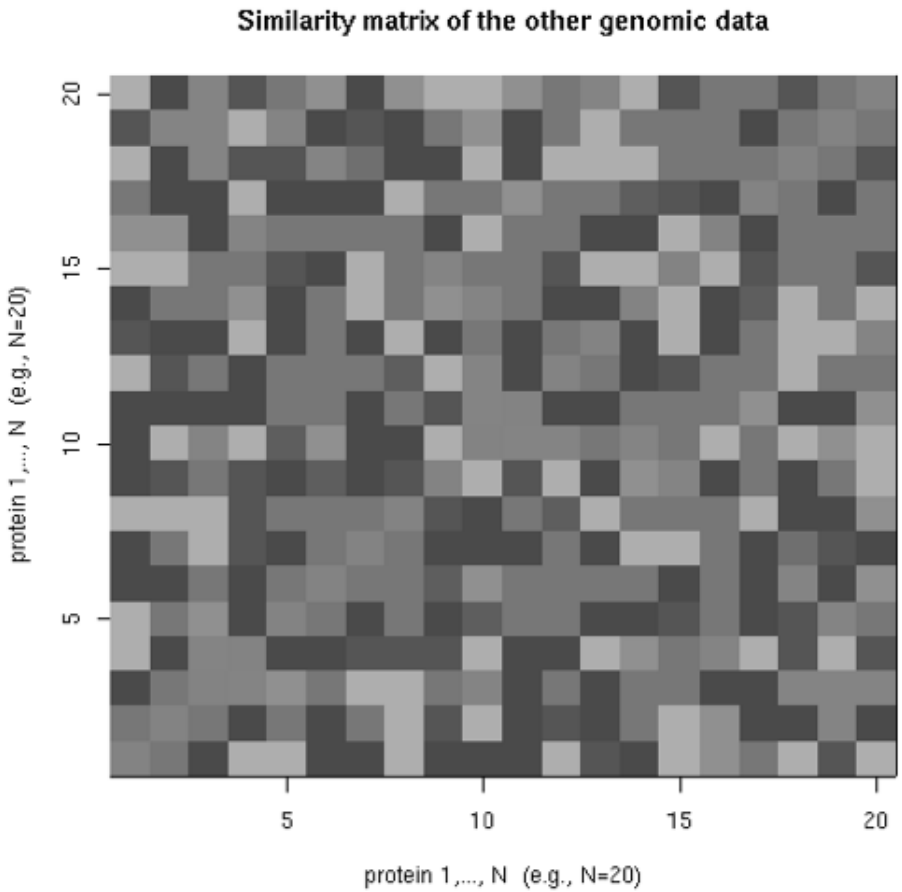
Matrix completion

Idea

- Goal: Fill missing entries in the adjacency matrix directly
- Use genomic data matrix (similarity/distance) as side information



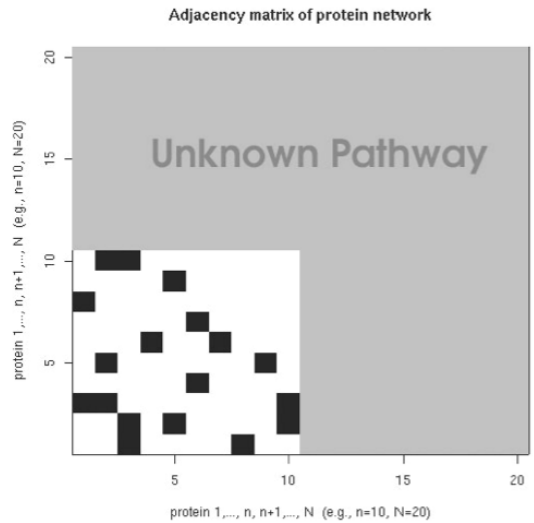


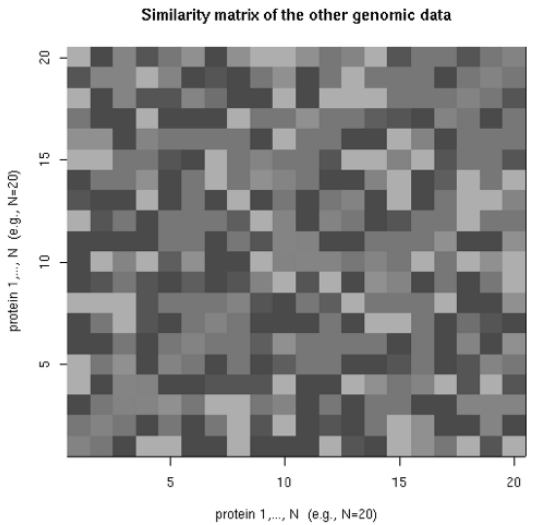
Matrix completion by em algorithm (Kato et al., 2005)

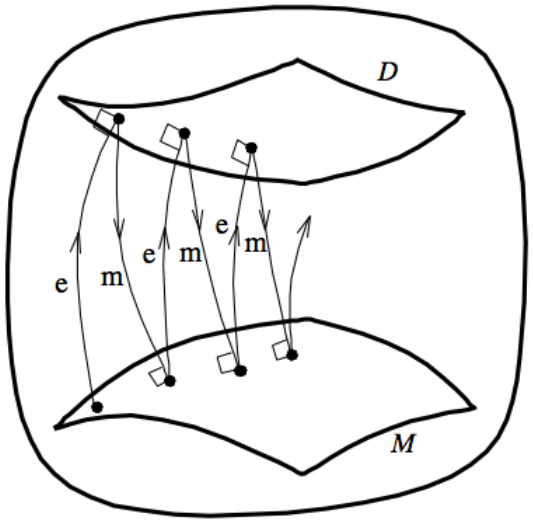
Method

- $\mathcal{M}$ is the set of matrices obtained when missing entries are filled
- $\mathcal{D}$ is the set of spectral variants of the genomic data matrix
- Find the completed matrix M by solving

$$\min_{M \in \mathcal{M}, D \in \mathcal{D}} KL(D, M)$$







Matrix completion by kernel matrix regression (Yamanishi and V., 2007)

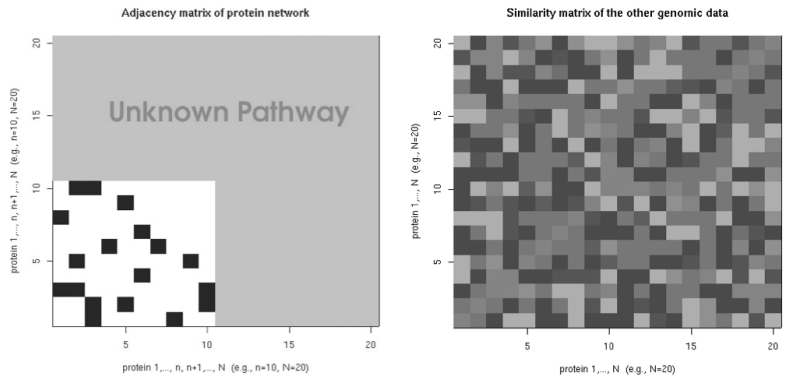
Method

- Embed the genomic data to a Hilbert space $\mathcal{H}$
- Formulate the problem as a bivariate regression problem:

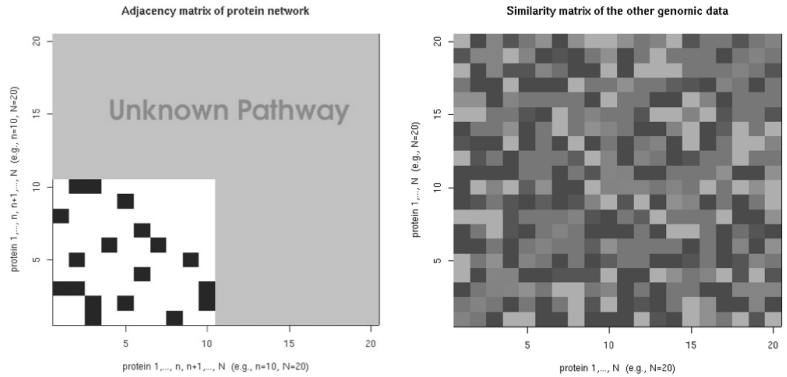
$$M(x, y) = u(x)^\top u(y) + \epsilon \,,$$

where $u : \mathcal{H} \to \mathbb{R}^d$.

- A variant of the em algorithm, using the Euclidean geometry instead of the information geometry.



Matrix completion : Summary



- Algebric formulation of the problem
- Use specific geometries of the set of matrices (information geometry, Forbenius distances)
- However not really motivated by biological motivations
- In fact closely related to metric learning approaches (central role of spectral decomposition)

Outline

Pattern recognition


APPLE


APPLE


PEAR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APPLE


PEAR


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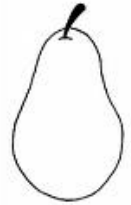
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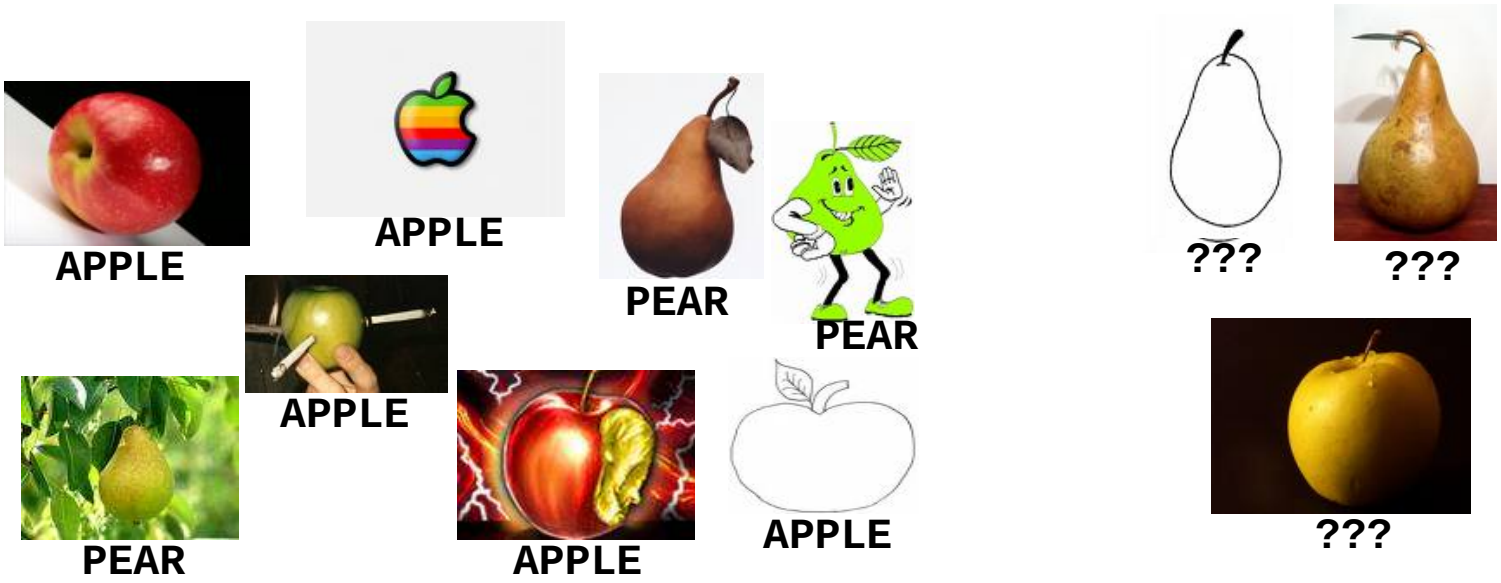
- Input variables $\mathbf{x} \in \mathcal{X}$, Output $y \in \{-1, 1\}$.
- Training set $\mathcal{S} = \{(\mathbf{x}_1, y_1), \ldots, (\mathbf{x}_n, y_n)\}$.
- Goal: learn a function $f : \mathcal{X} \mapsto \{-1, 1\}$
- Many powerful algorithms! Logistic regression, nearest neighbors, ANN, decision trees, SVM

Pattern recognition



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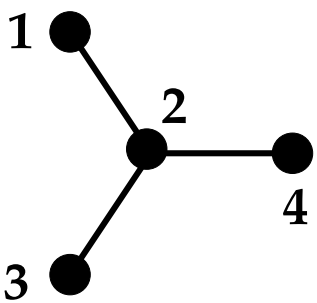
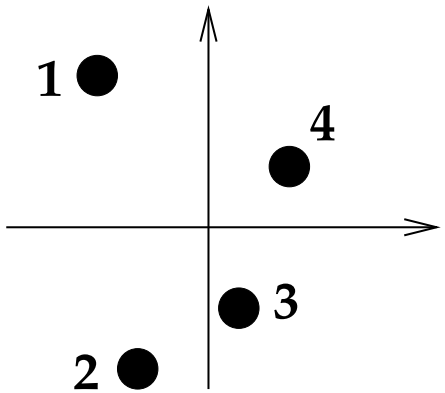
Pattern recognition for supervised graph inference

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

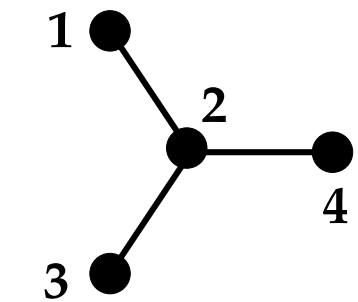


Genomic data

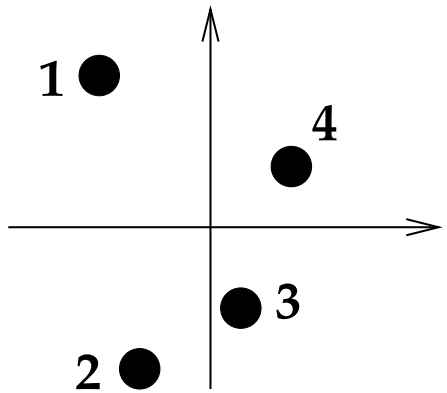
Pattern recognition for supervised graph inference

Formulation and basic issue

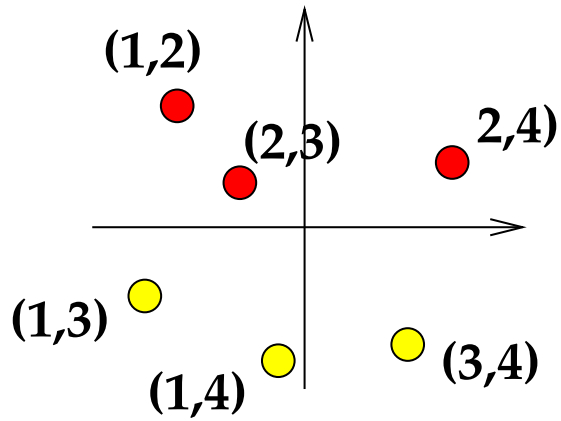
- A pair can be connected (1) or not connected (-1)
- From the known subgraph we can extract examples of connected and non-connected pairs
- However the genomic data characterize individual proteins; we need to work with pairs of proteins instead!



Known graph



Genomic data



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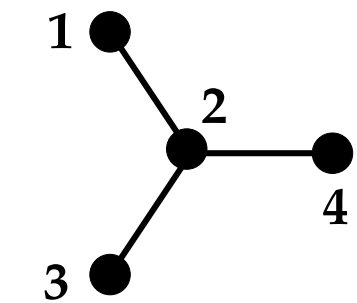

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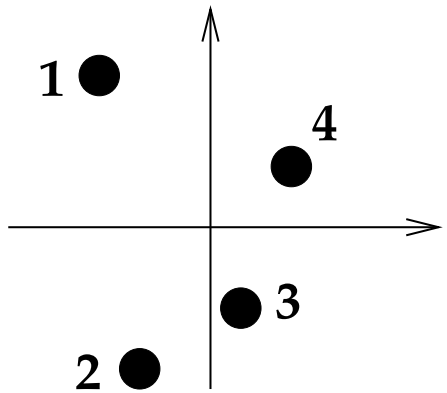

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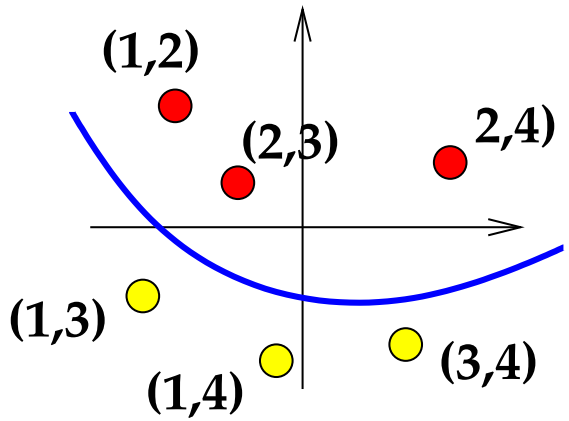

Tensor product SVM (Ben-Hur and Noble, 2006)

- 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
- Formally, define a similarity between pairs from a similarity between individuals by

$$K_{TPPK}((a,b),(c,d)) = K(a,c)K(b,d) + K(a,d)K(b,c) \; .$$

- If K is a positive definite kernel for individuals then K_{TPPK} is a p.d. kernel for pairs which can be used by SVM
- This amounts to representing a pair (a, b) by the symmetrized tensor product:

$$(a,b) \to (a \otimes b) \oplus (b \otimes a) \; .$$

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Metric learning pairwise SVM (V. et al, 2007)

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Remarks about pattern recognition for pairs

Pros

- The objective function is exactly what we want (discriminate between connected and non-connected pairs)
- We can use state-of-the-art powerful algorithms for graph inference (e.g., SVM)

Cons

- We need to deduce an embedding for pairs from data about individuals.
- There are many training examples ($N(N-1)/2$) which can be a problem of pattern recognition algorithms in terms of computation time and memory
- The result is a global model over the graph; however the presence or absence of a connection may also depend on the "position" of the connection in the graph.

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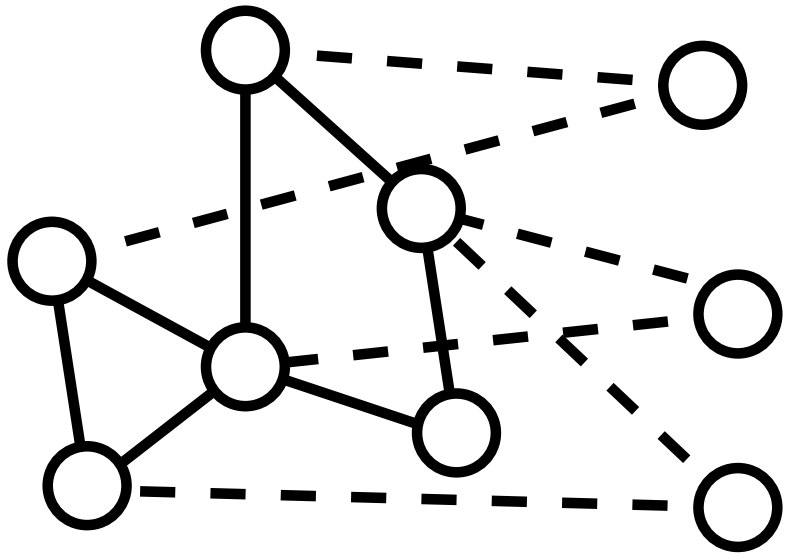
Outline

Local pattern recognition (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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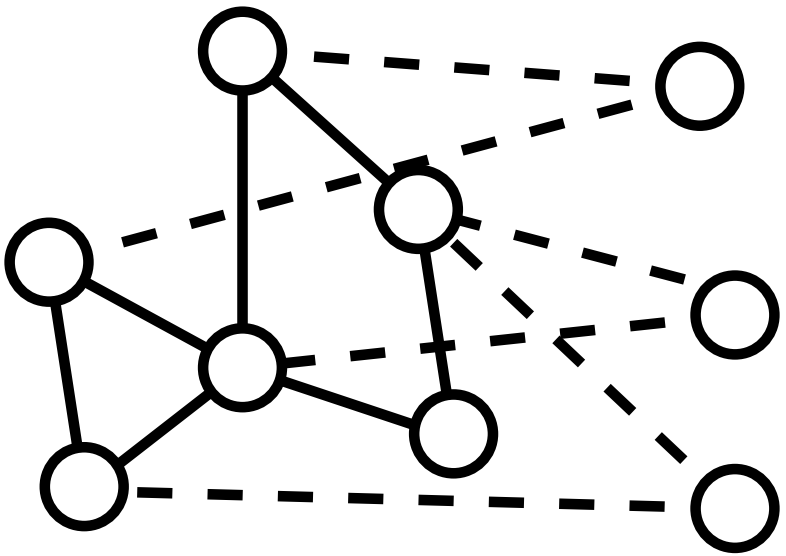
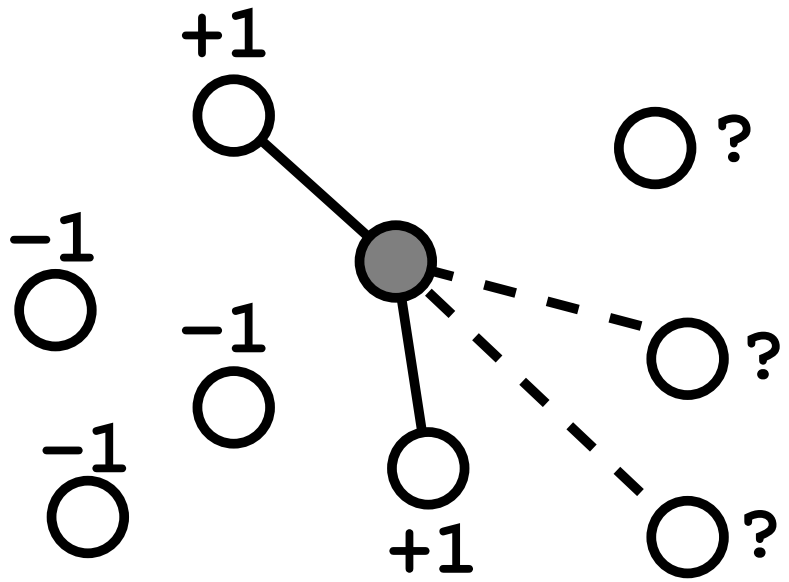
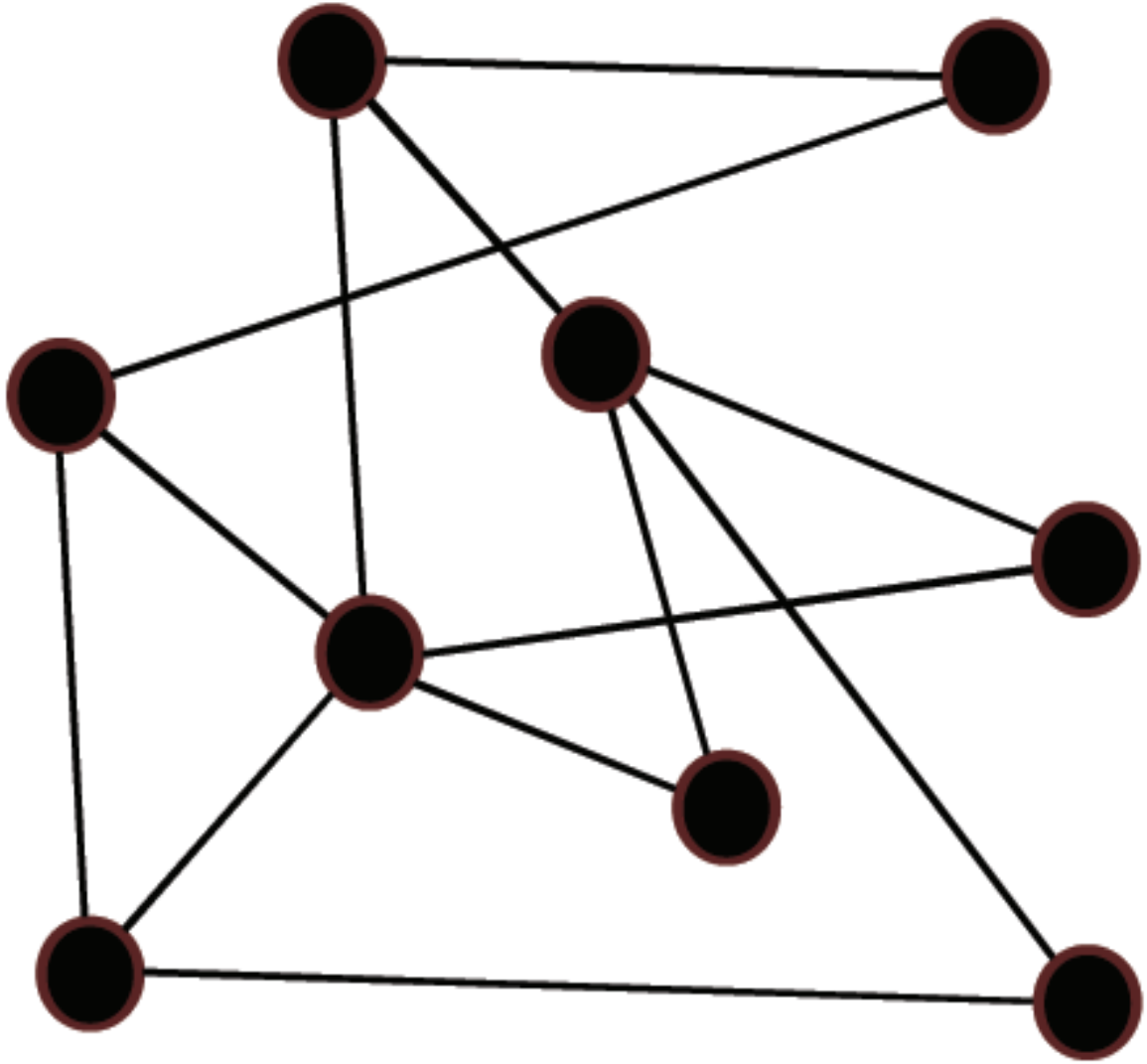
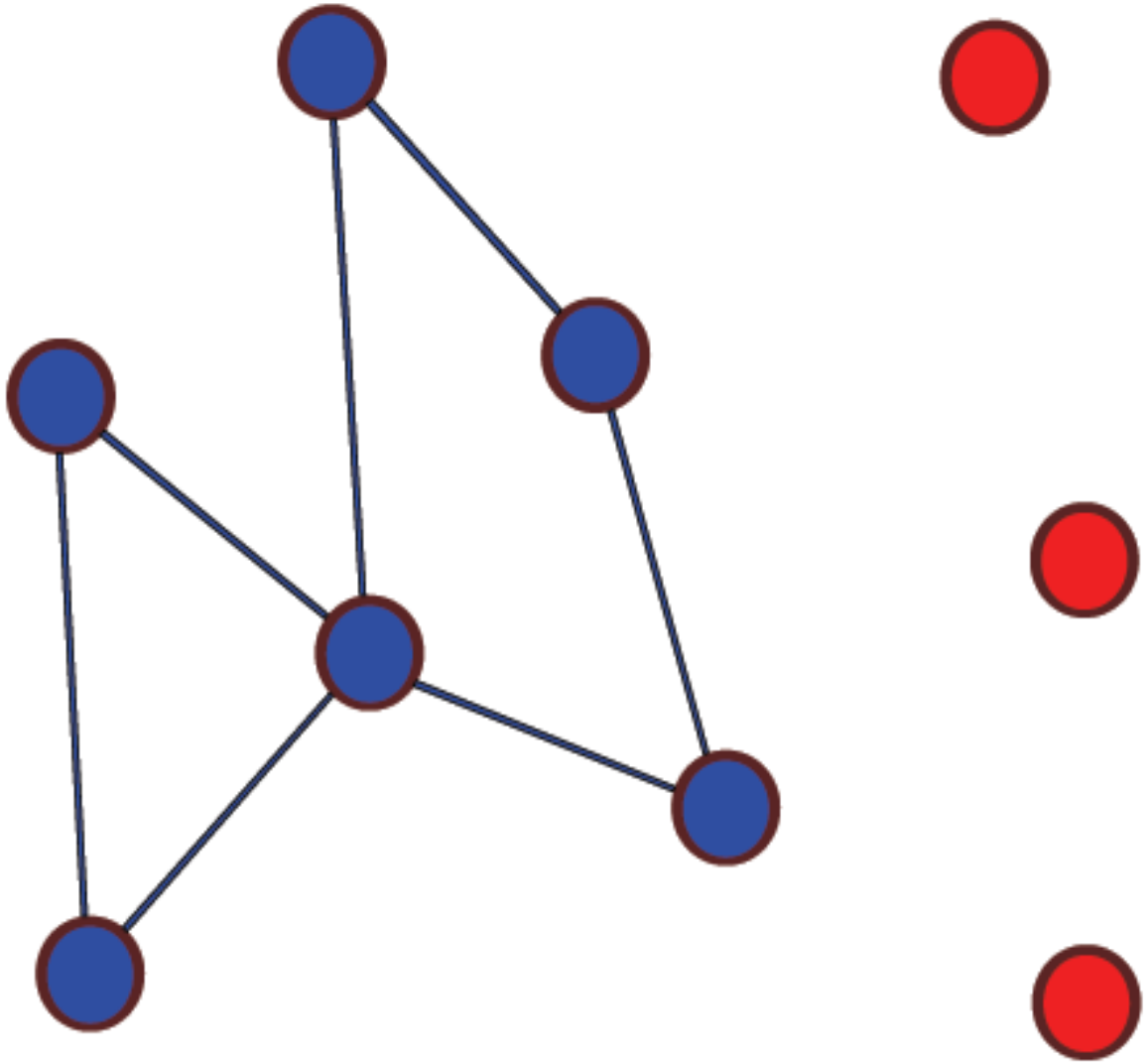




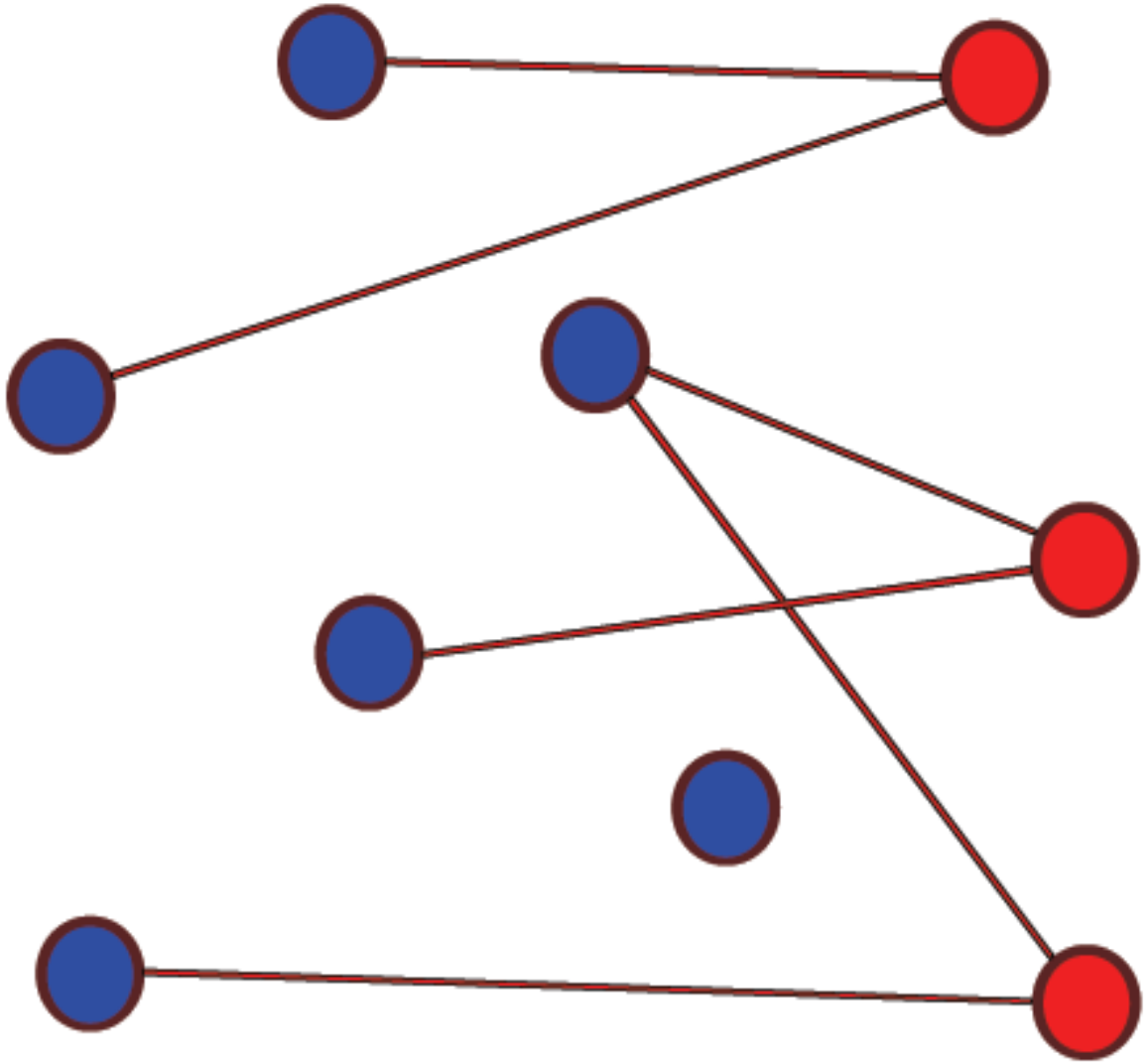
The LOCAL model



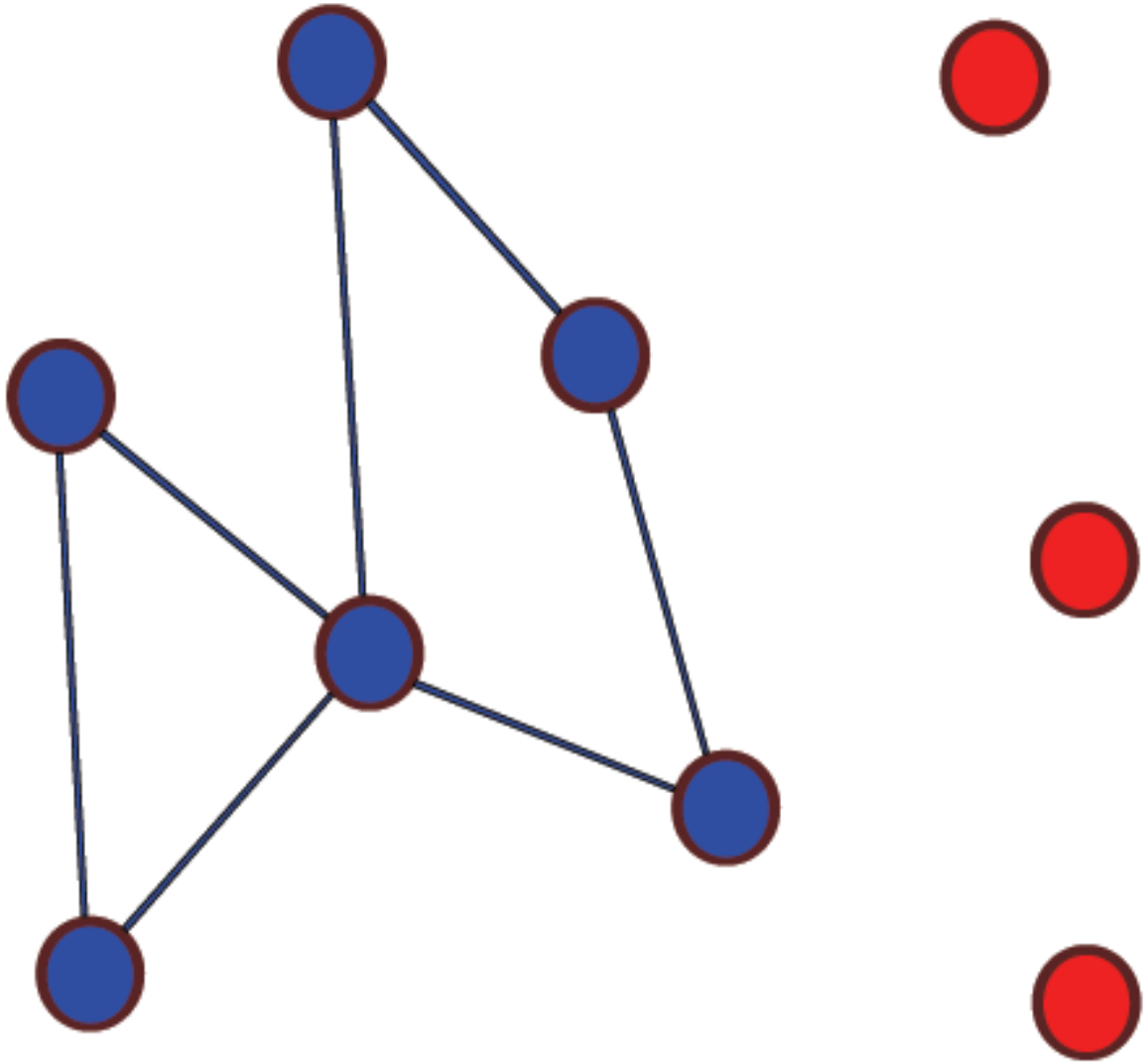
The LOCAL model: training edges



The LOCAL model: testing edges



The LOCAL model: learning



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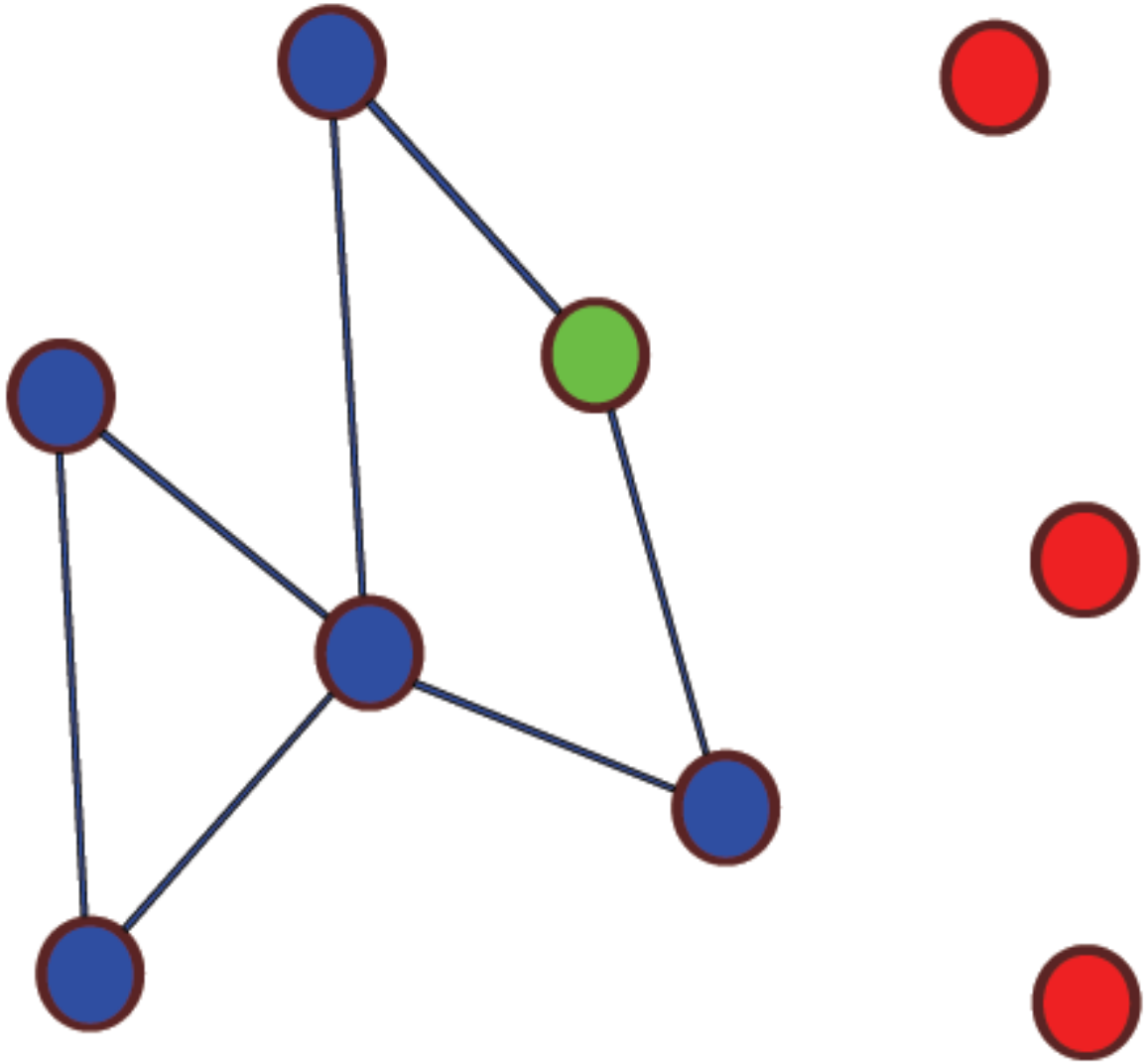

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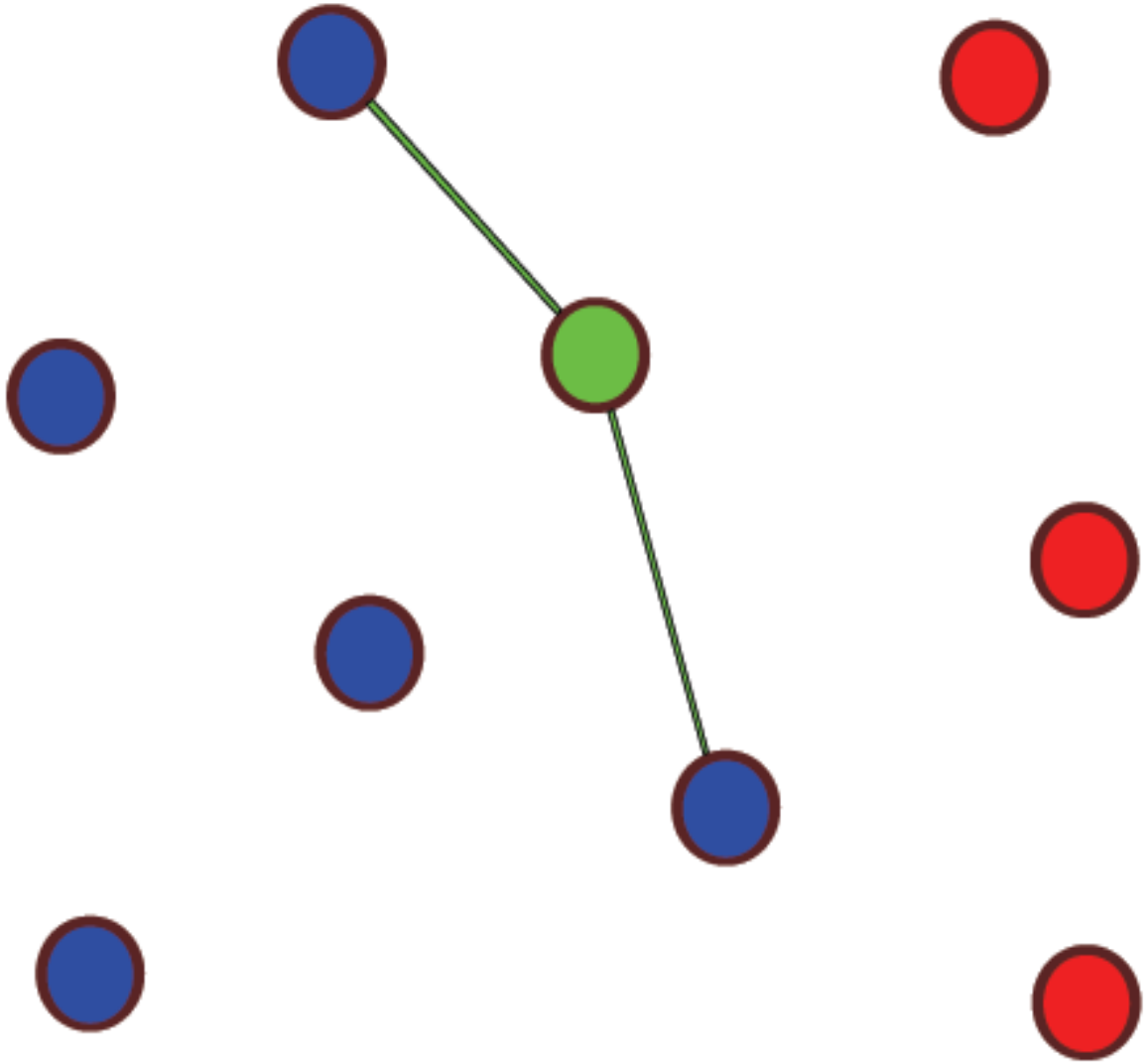

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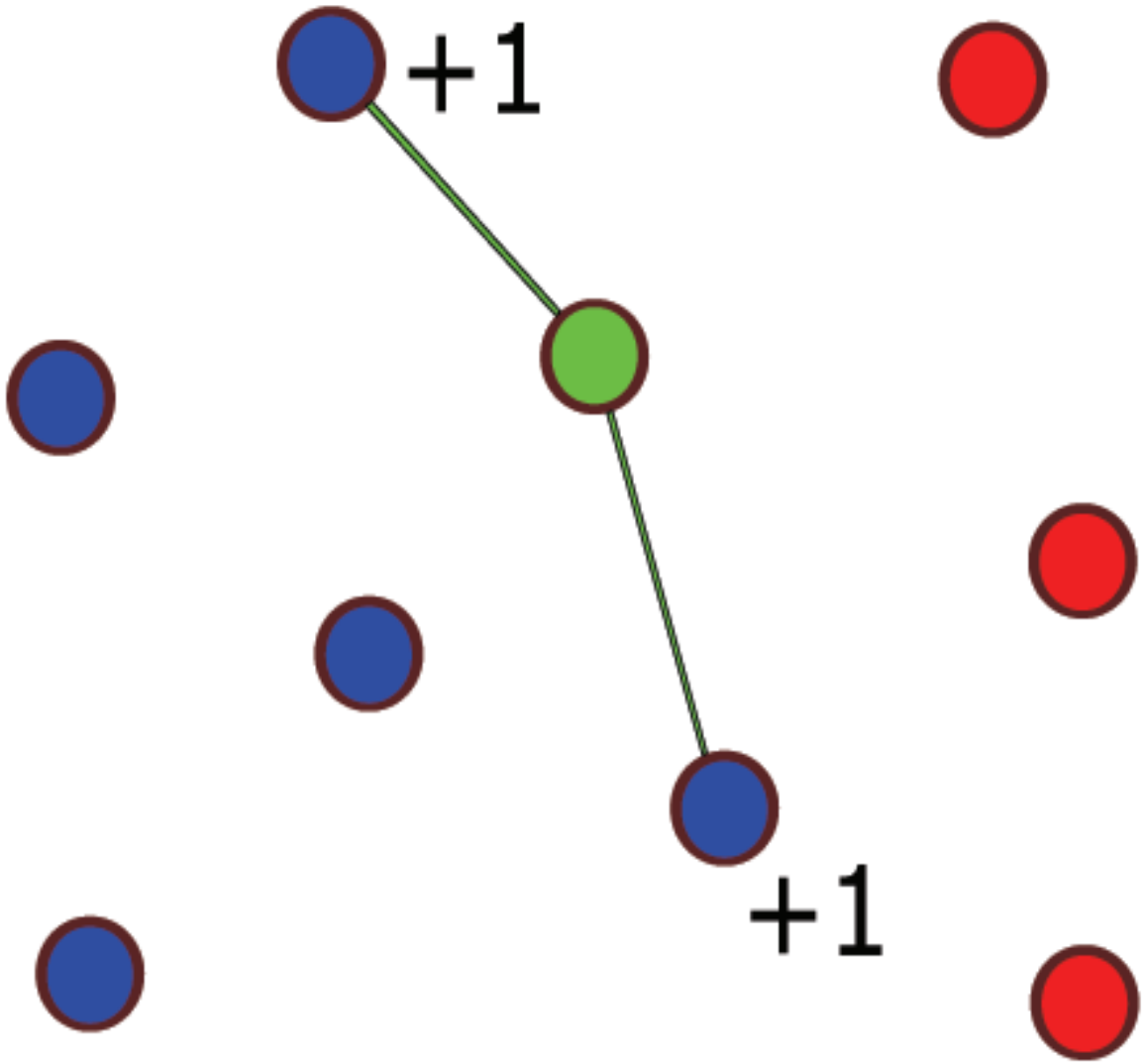

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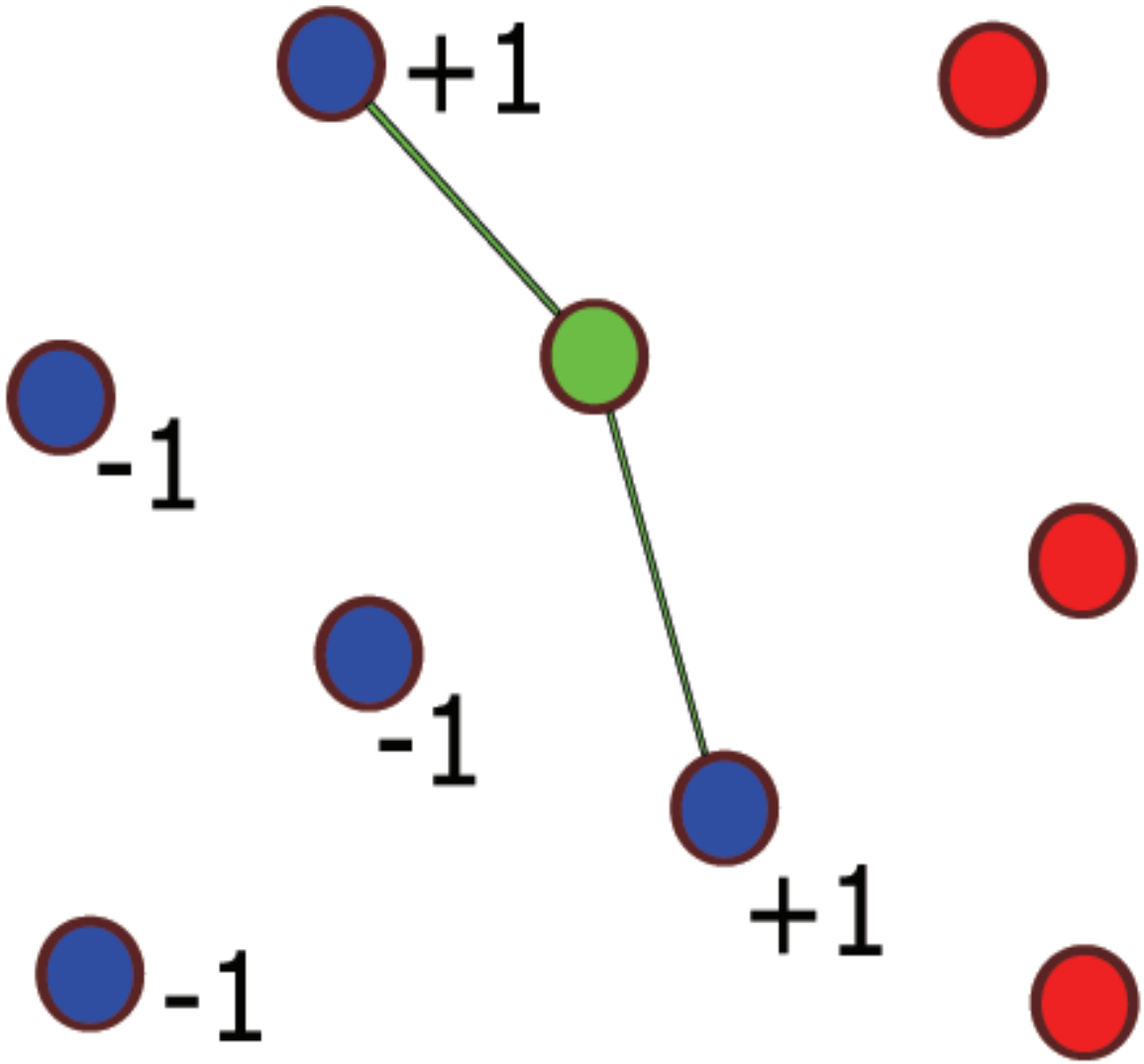
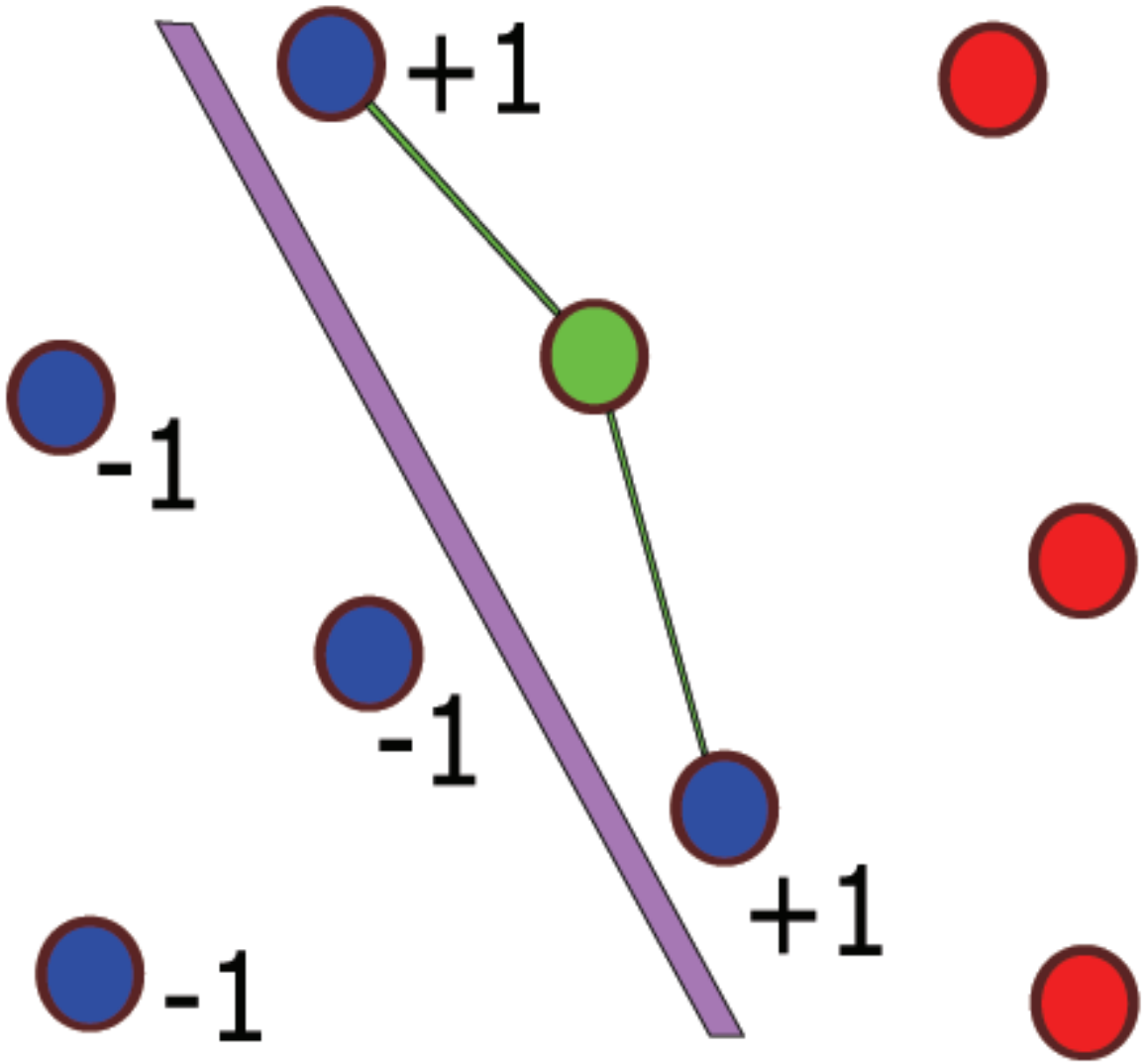
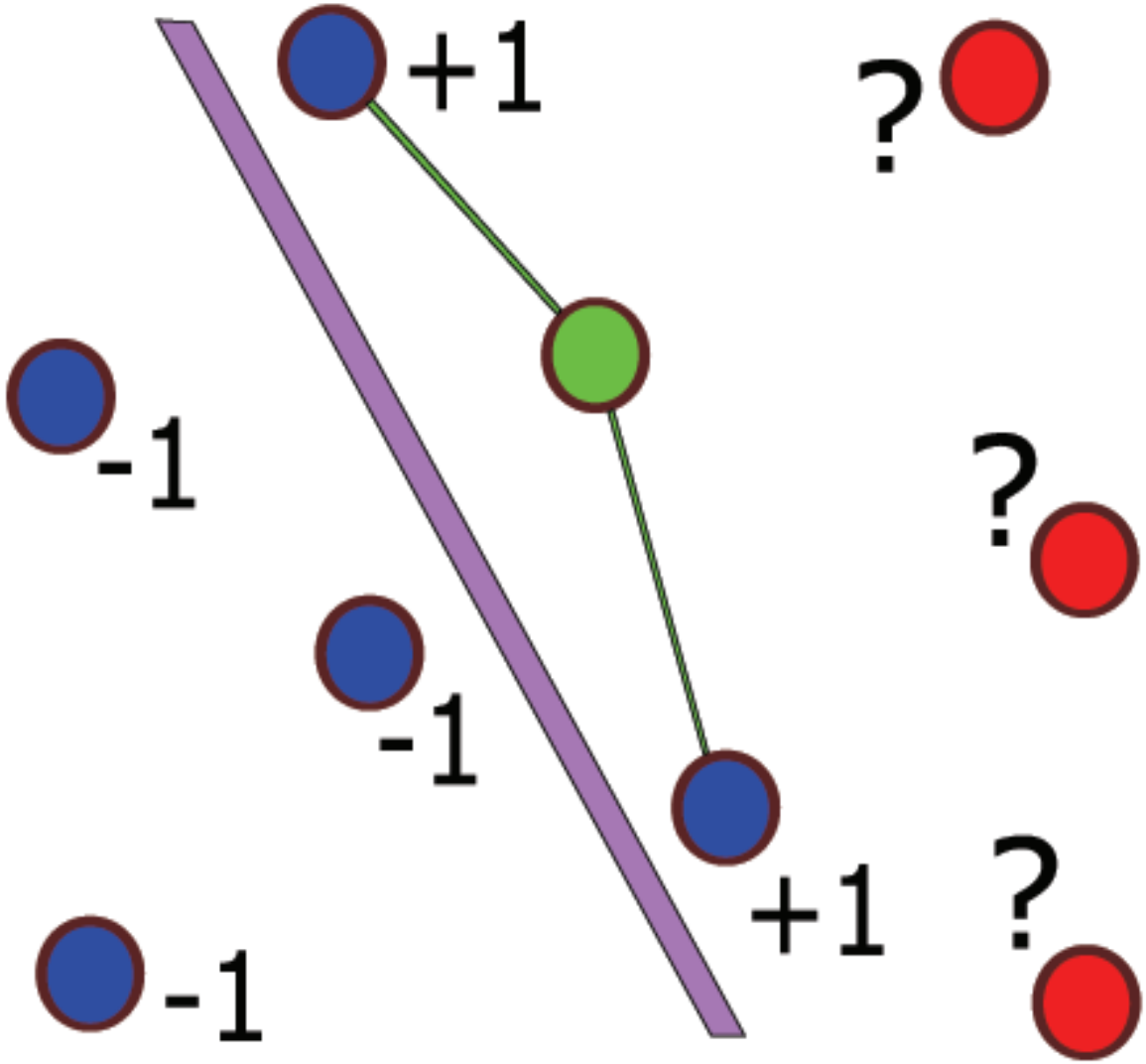


The LOCAL model: decision boundary



The LOCAL model: testing



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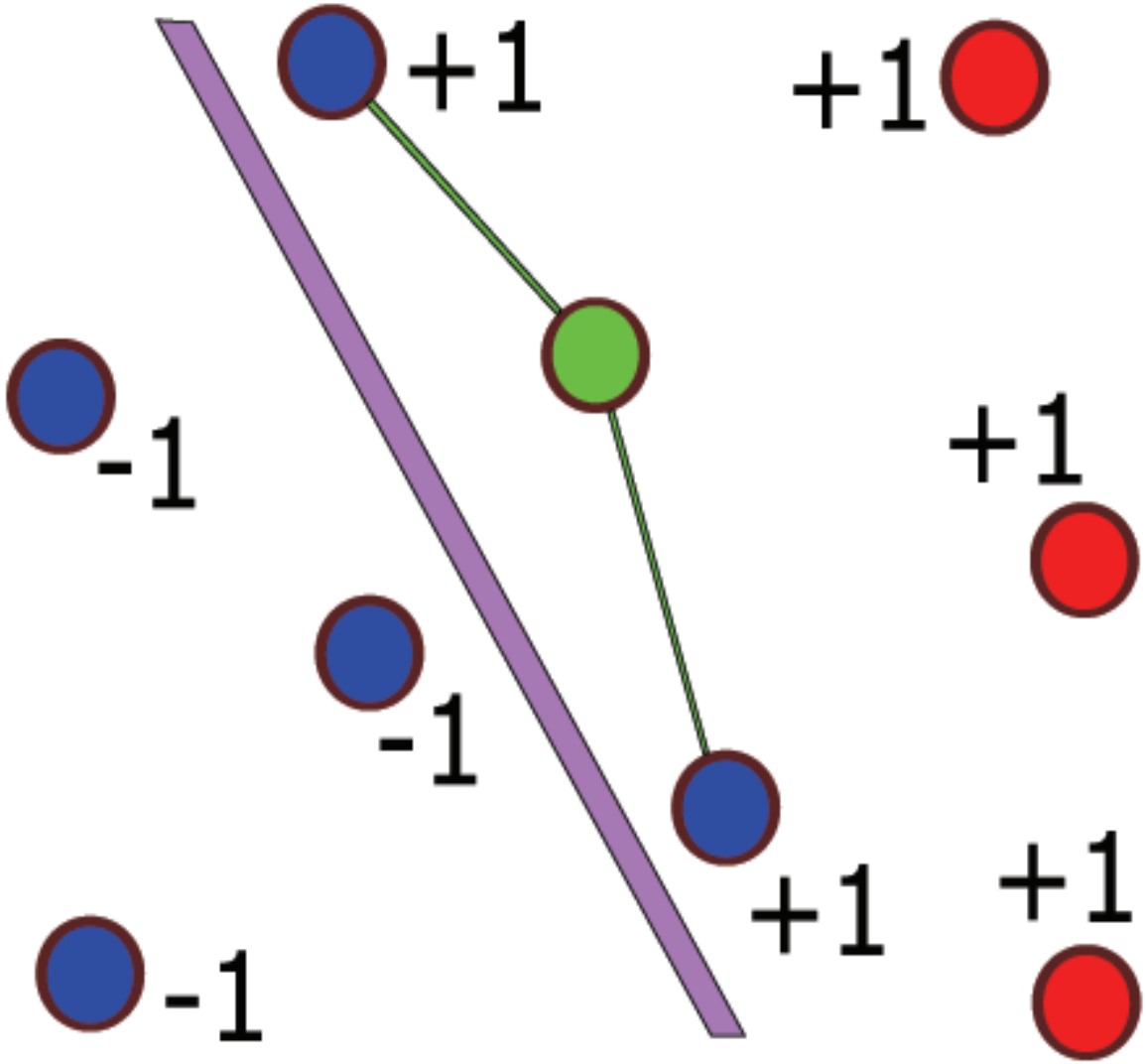
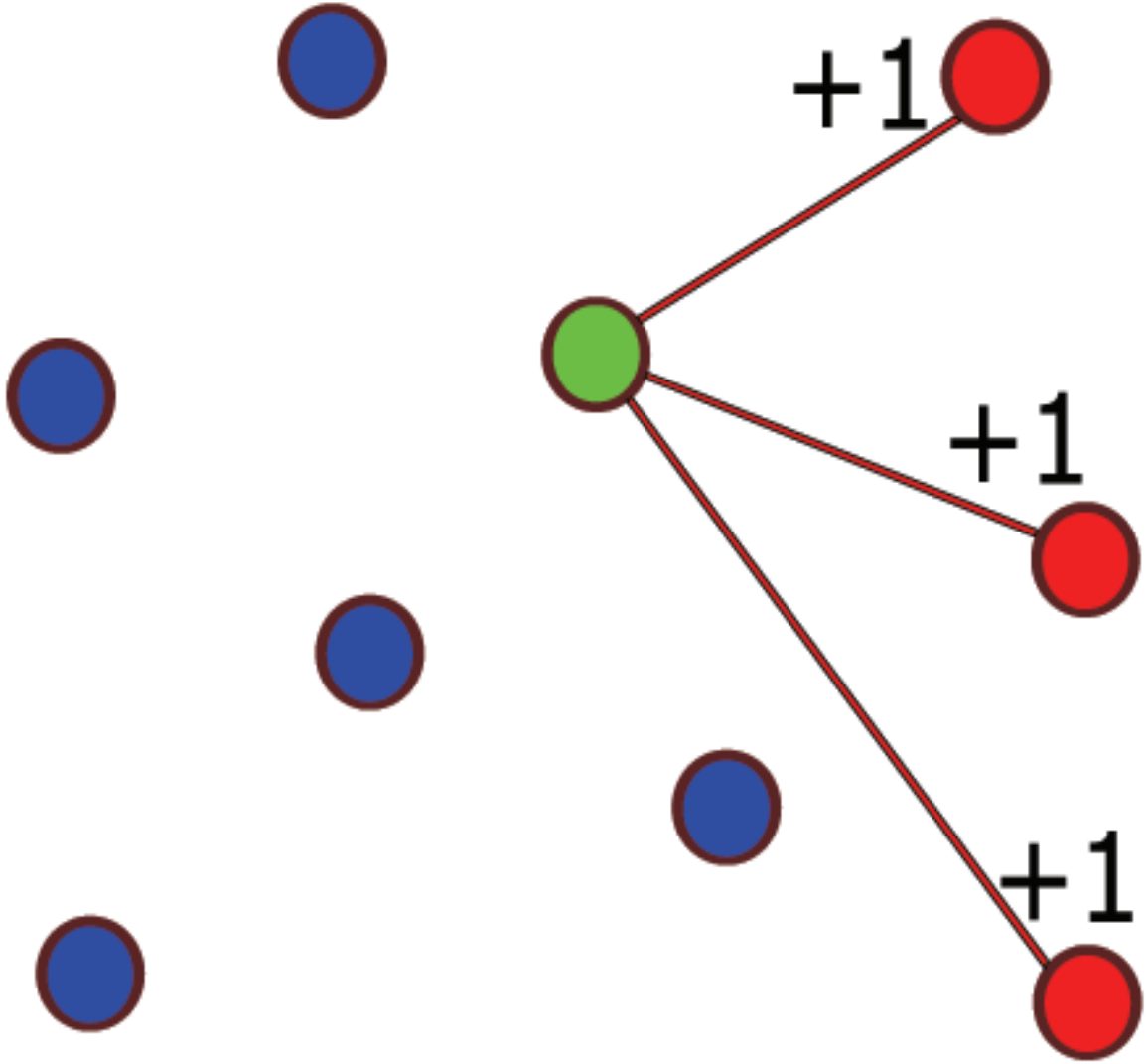
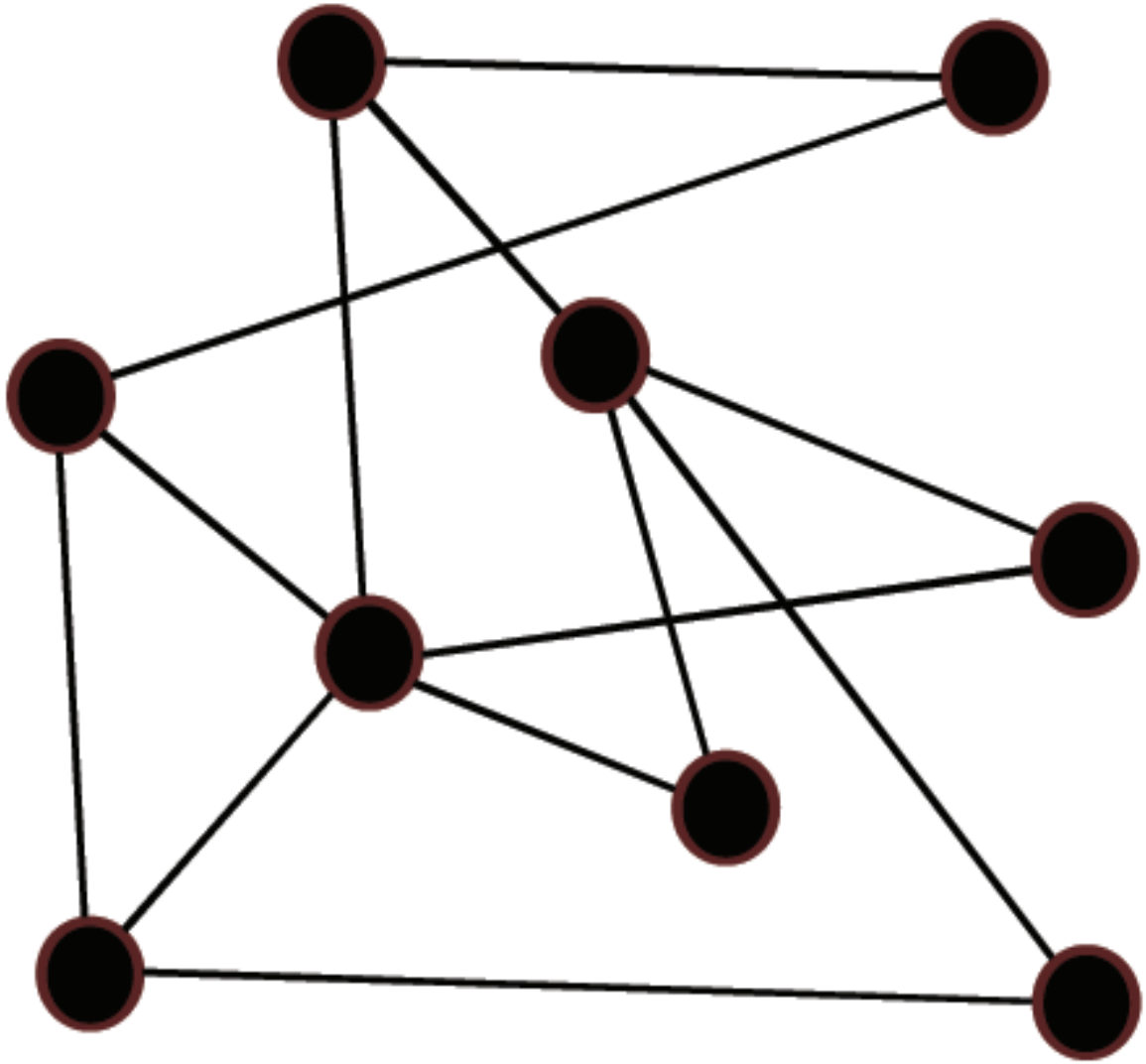


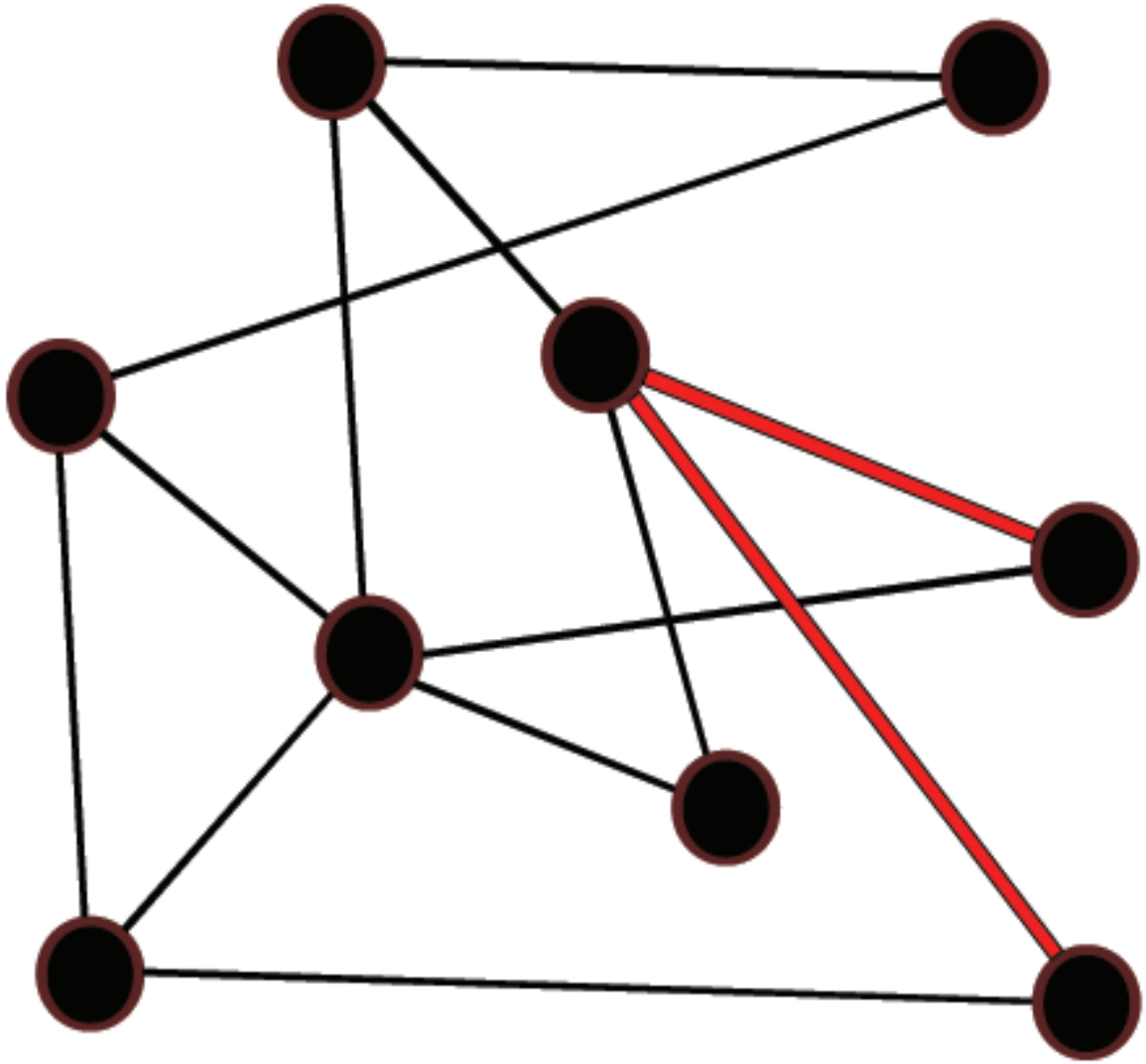
The LOCAL model: Predictions



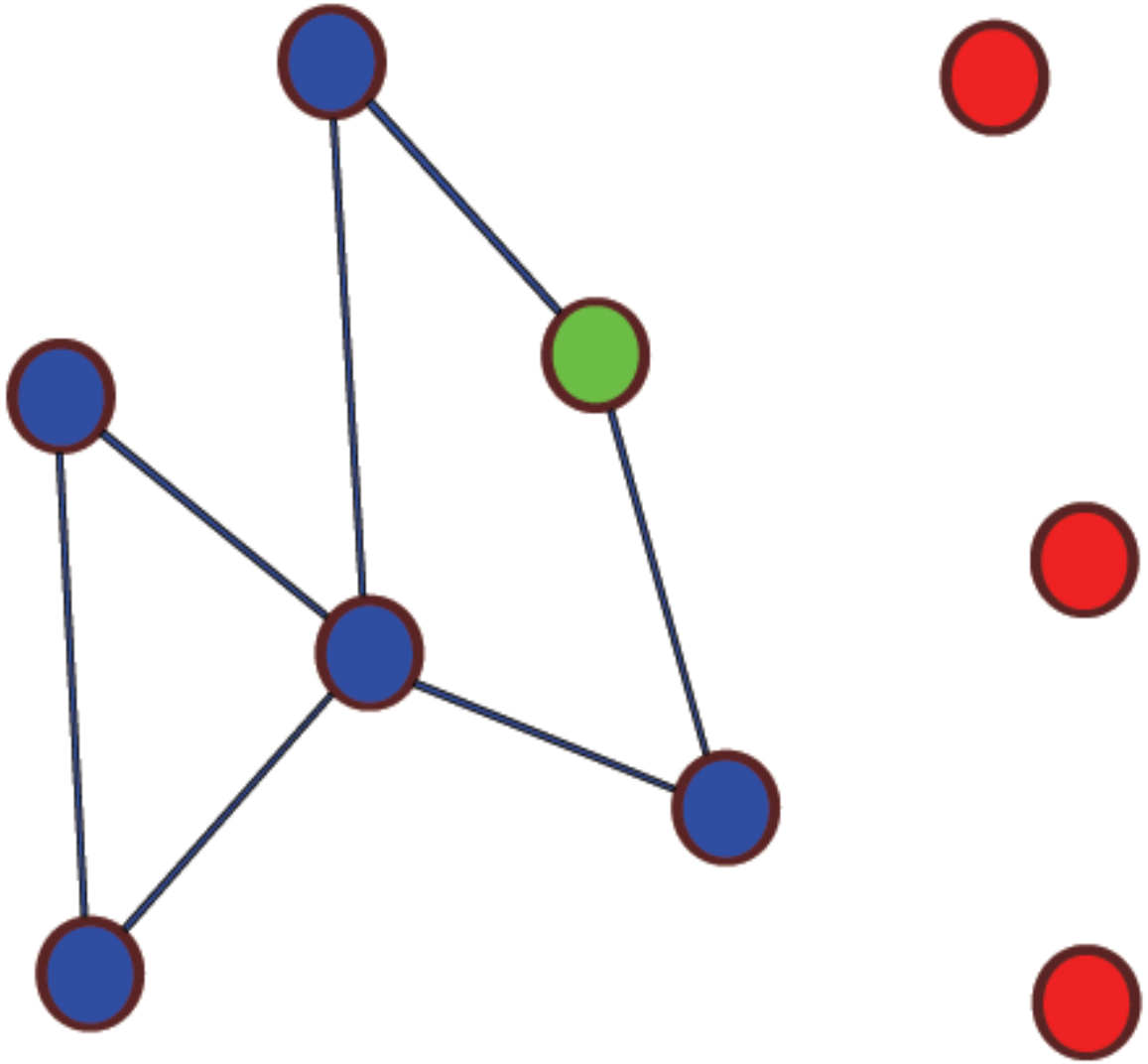
The LOCAL model: target graph



The LOCAL model: Two correct edges, one error



The LOCAL model: Do same for each learning node



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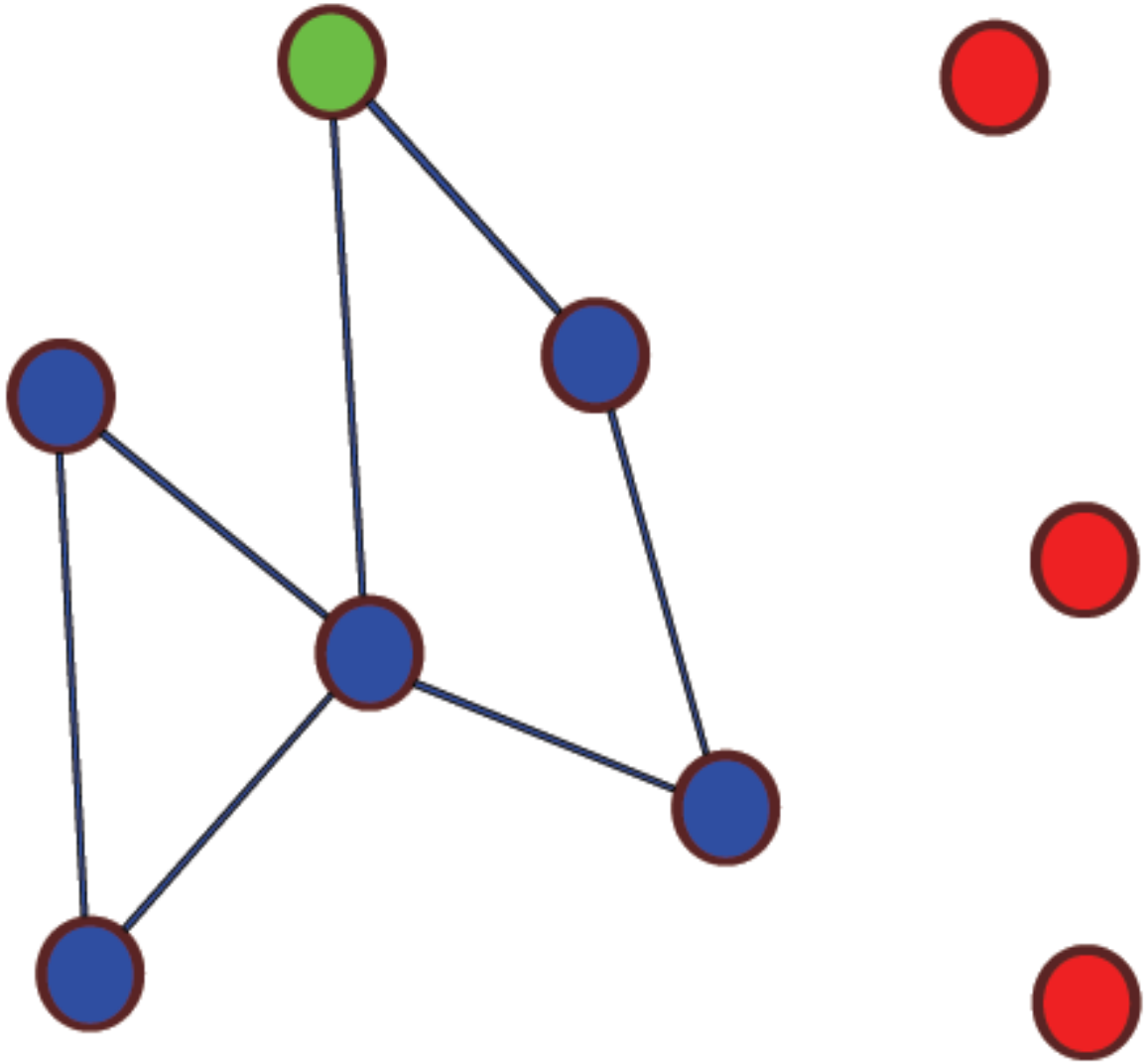

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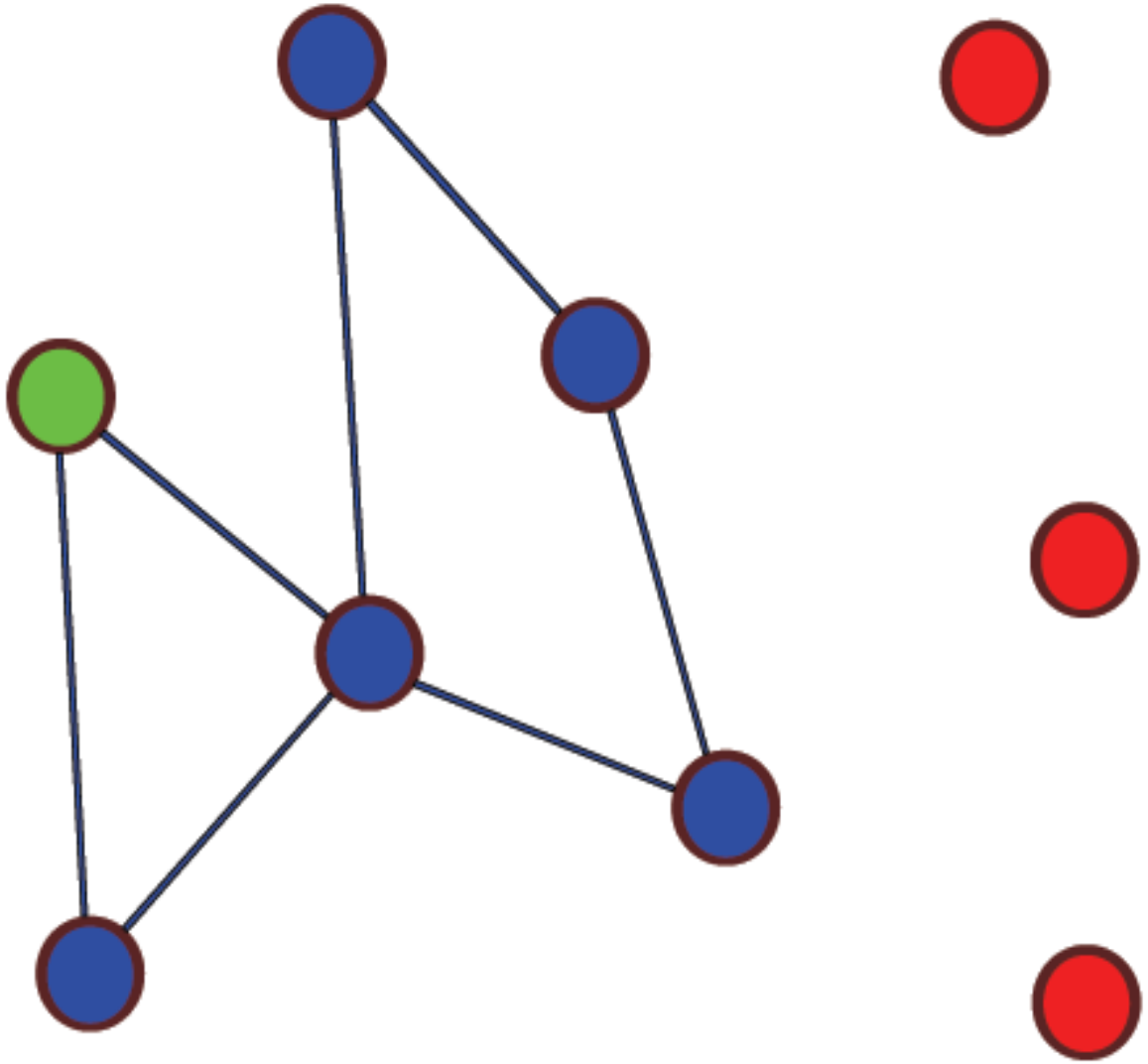

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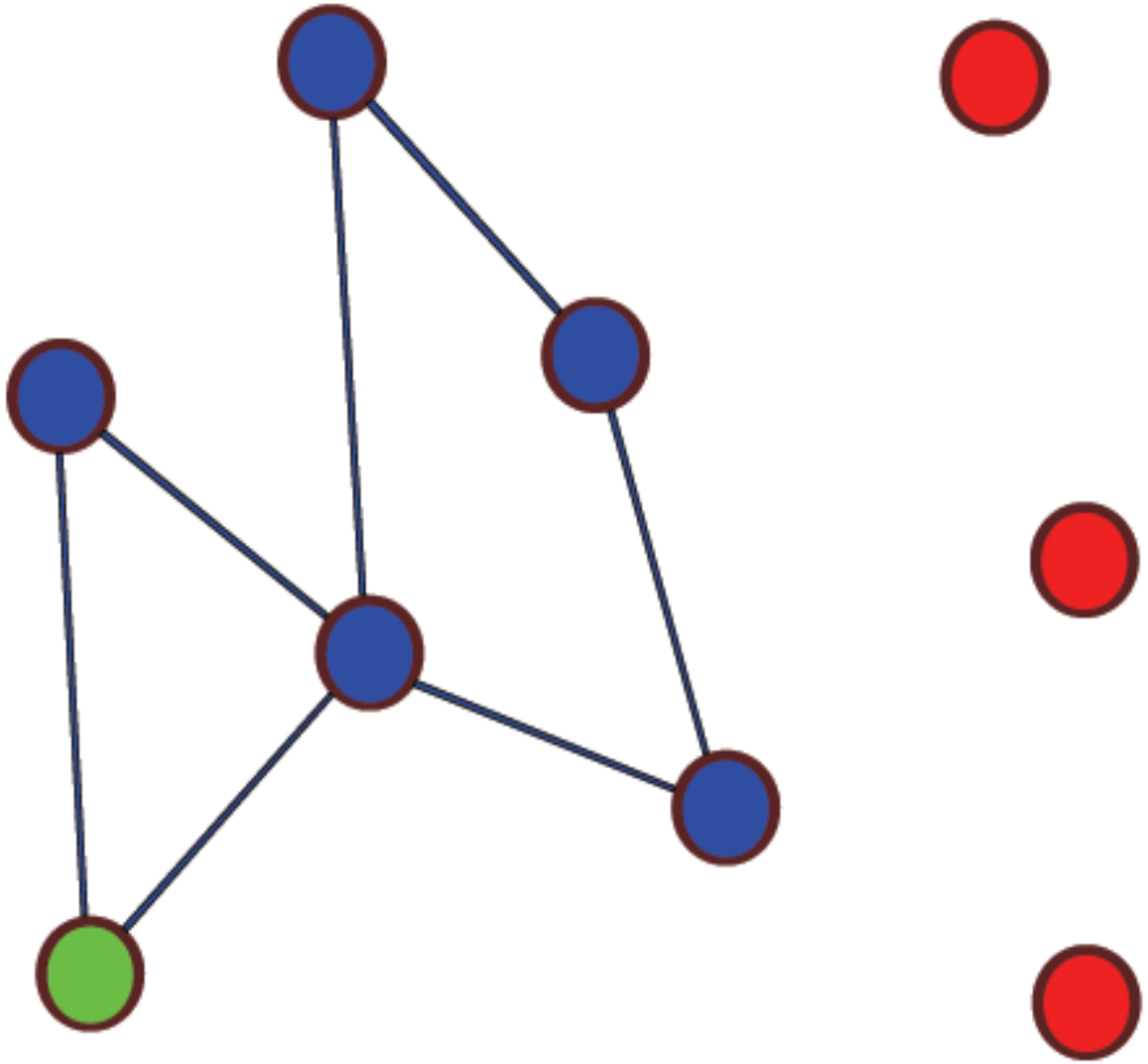

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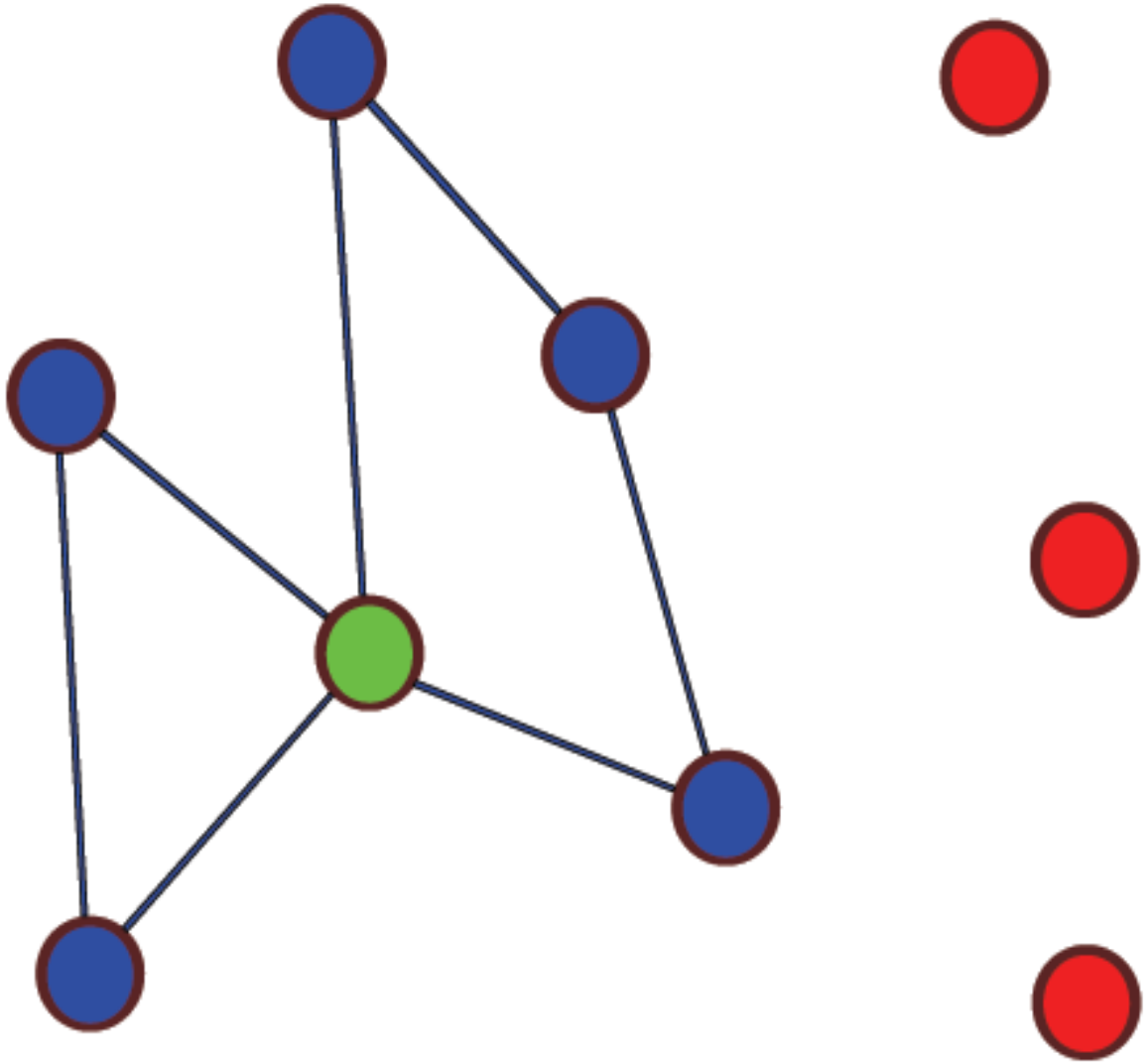

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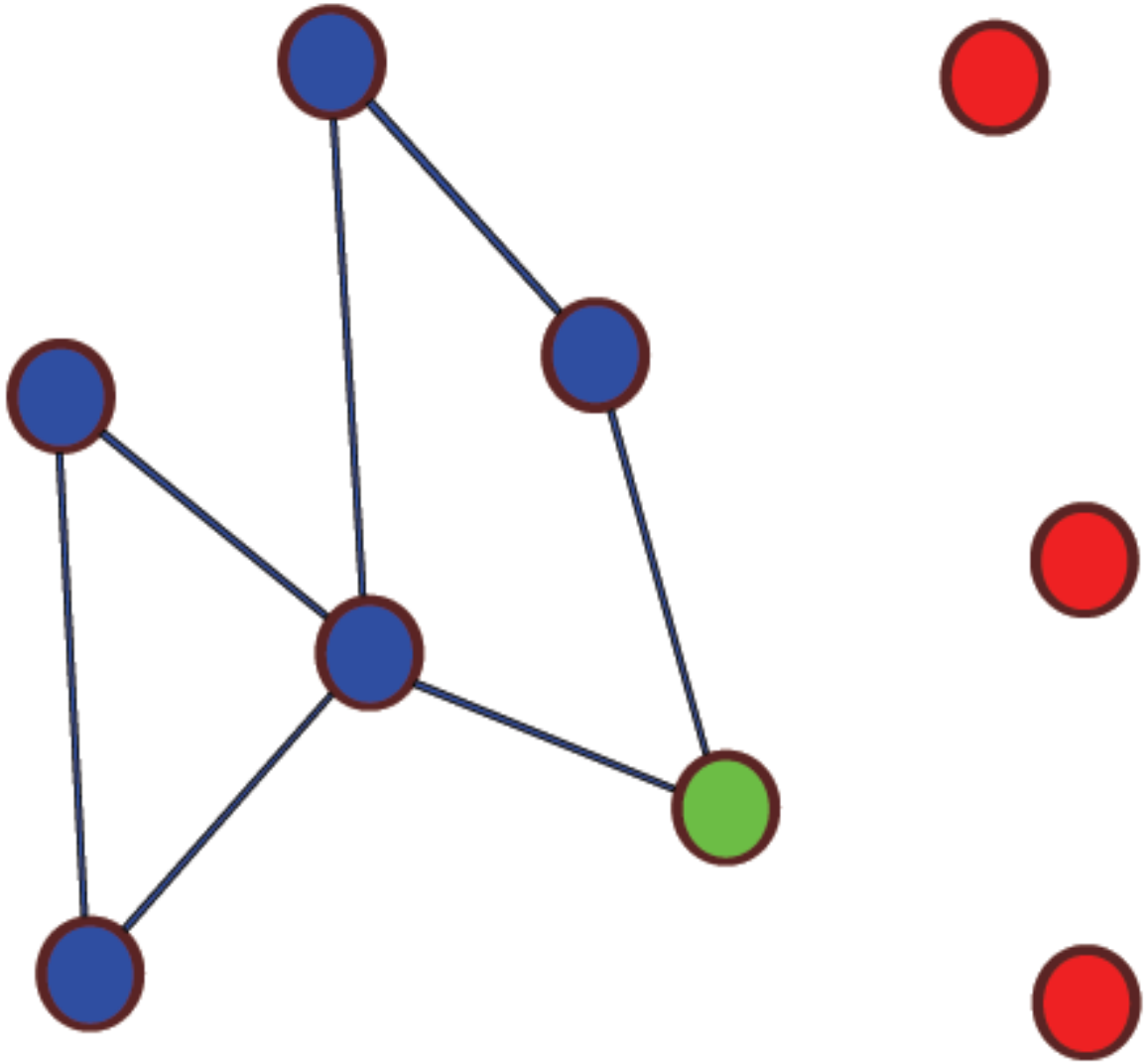

Local predictions: pros and cons

Pros

- Allow very different models for nearby nodes on the graph
- Faster to train n models with n examples than 1 model with n^2 examples
- No need for tricky embedding of pairs: each model works at the level of individuals.

Cons

- Few positive examples available for some nodes
- We must rank pairs based on scores obtained on different models $\Longrightarrow$ scores must be calibrated.
- If we have two new proteins, no simple way to predict an edge between them.

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Outline

Experiments

Network

- Metabolic network (668 vertices, 2782 edges)
- Protein-protein interaction network (984 vertices, 2438 edges)

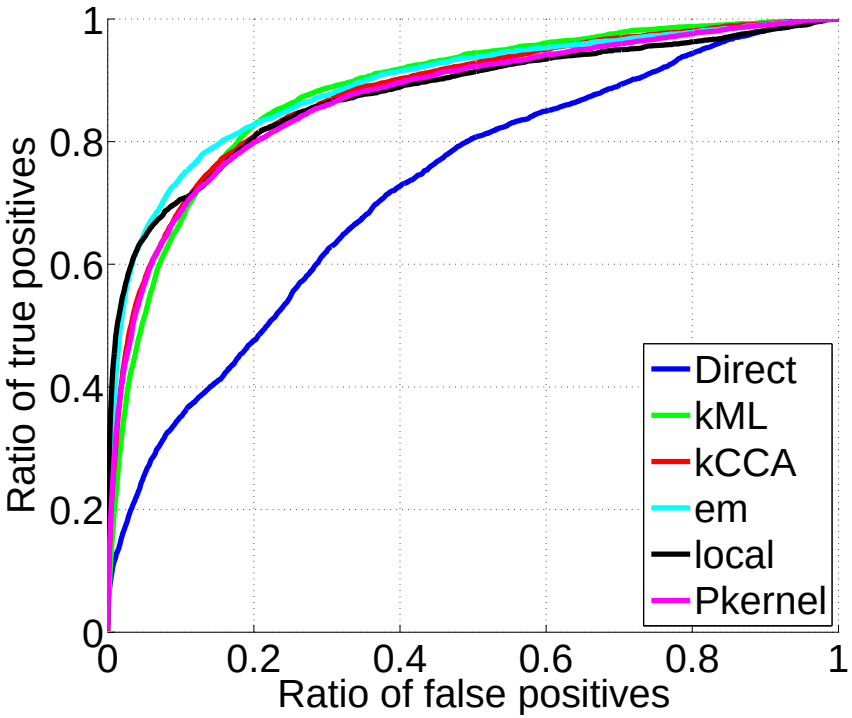
Data (yeast)

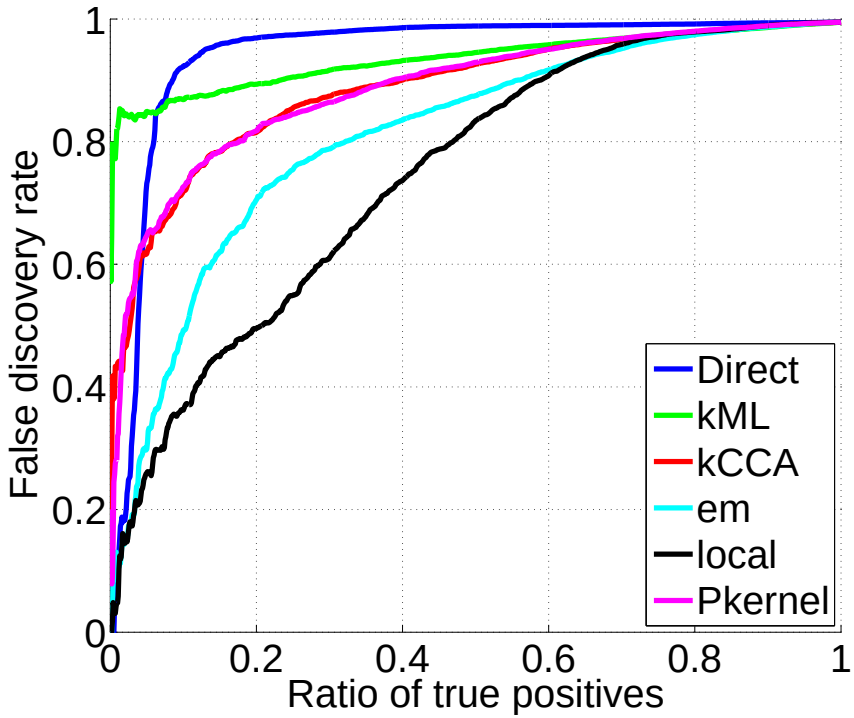
- Gene expression (157 experiments)
- Phylogenetic profile (145 organisms)
- Cellular localization (23 intracellular locations)
- Yeast two-hybrid data (2438 interactions among 984 proteins)

Method

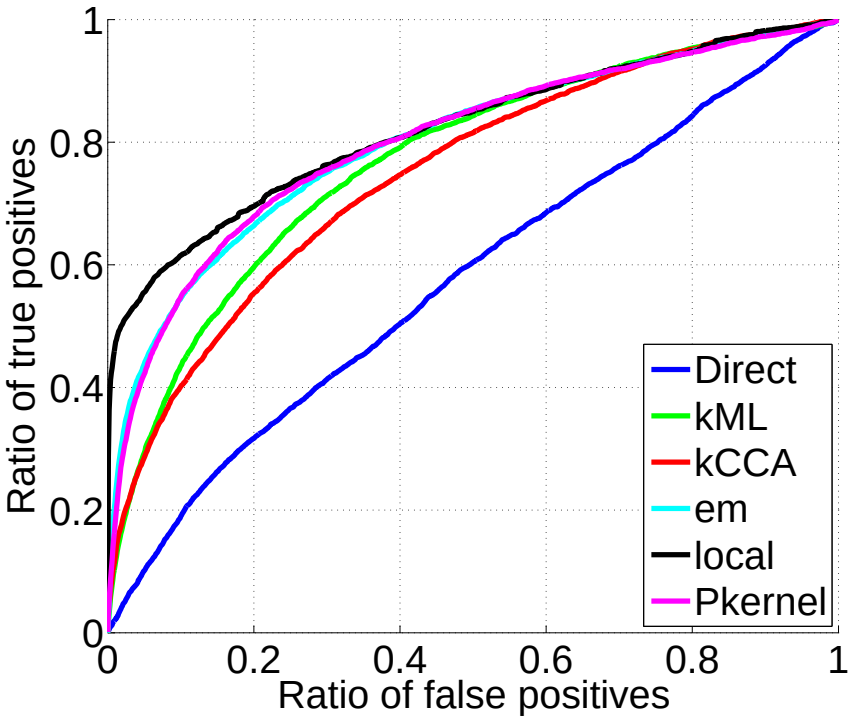
- 5-fold cross-validation
- Predict edges between test set and training set

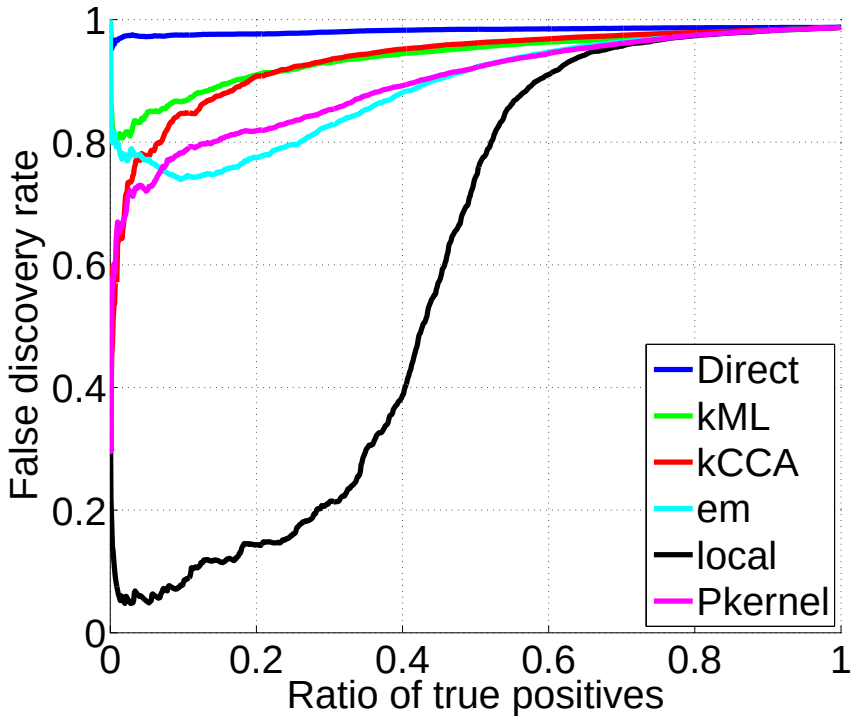
Results: protein-protein interaction



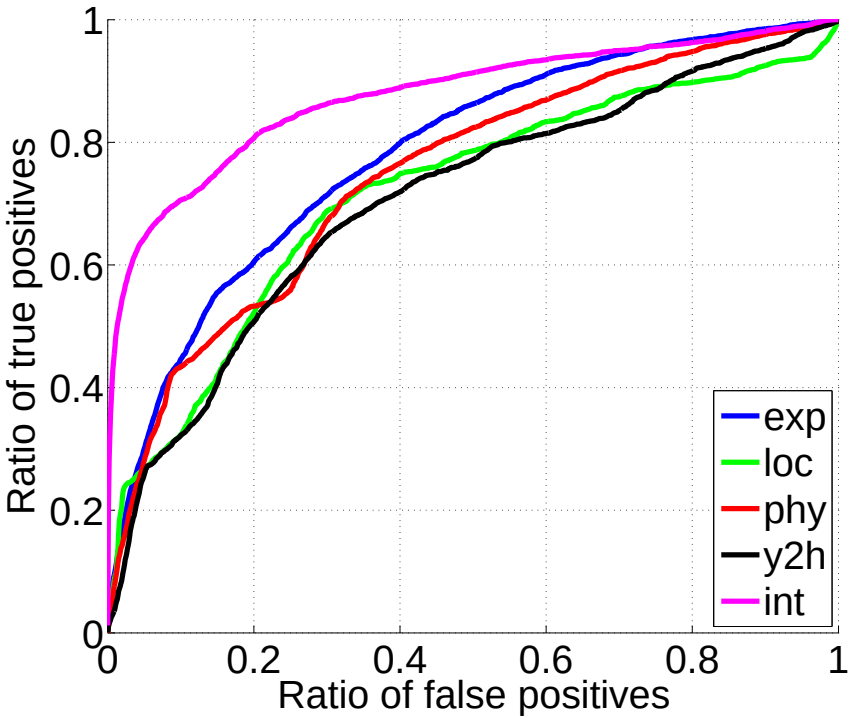


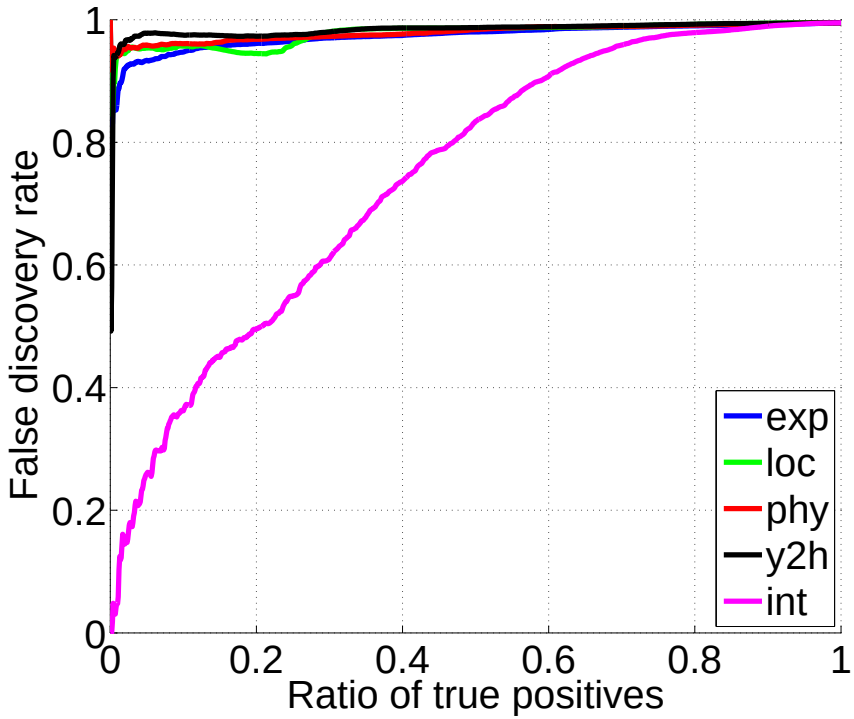
Results: metabolic gene network





Results: effect of data integration





Local SVM, protein-protein interaction network.

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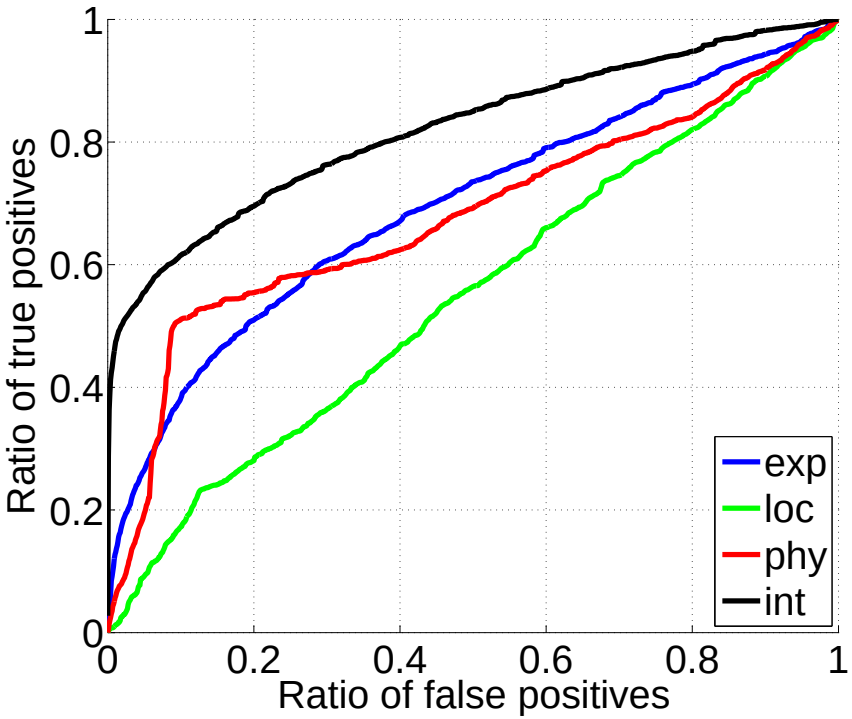
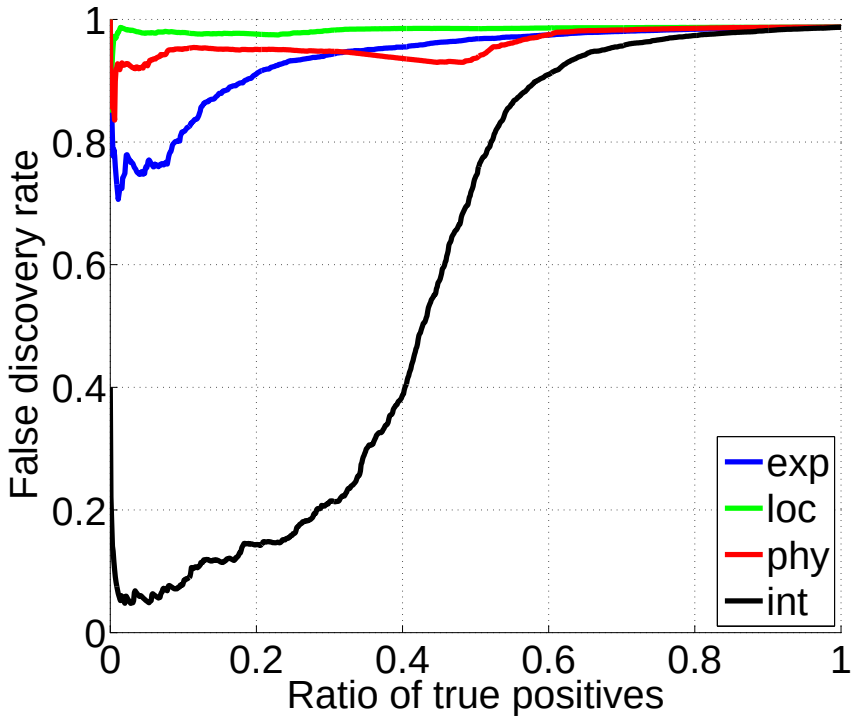




Local SVM, metabolic gene network.

Experiments: Summary

- Supervised approaches work much better than the baseline direct approach
- Data integration is easy and very powerful
- Good results obtained on two apparently very different networks (metabolic, physical interactions)
- The LOCAL method wins the benchmark competition

Applications: missing enzyme prediction

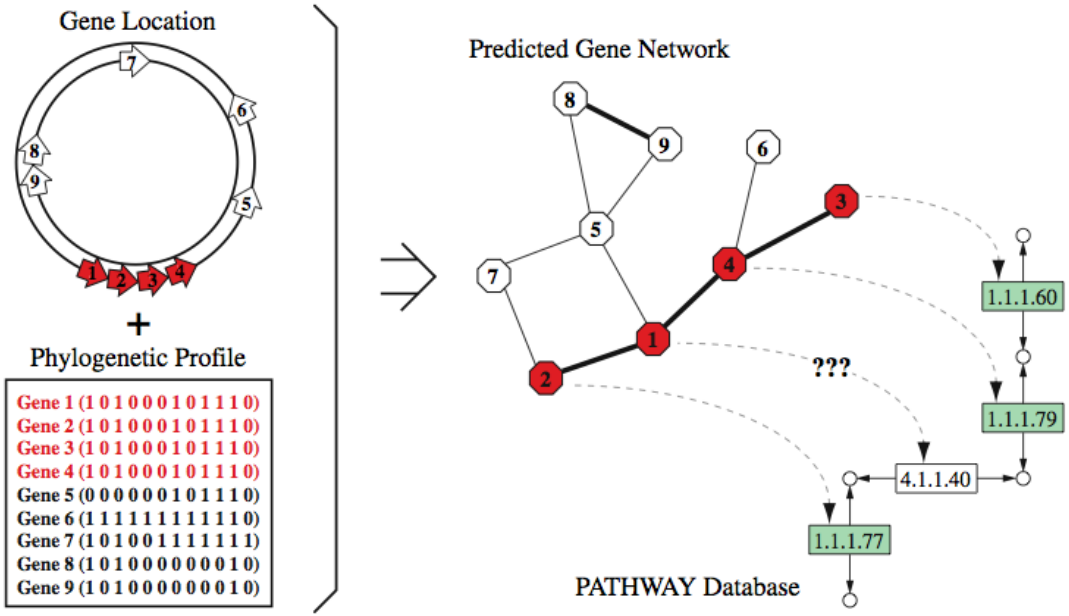
the FEBS Journal

Prediction of missing enzyme genes in a bacterial metabolic network

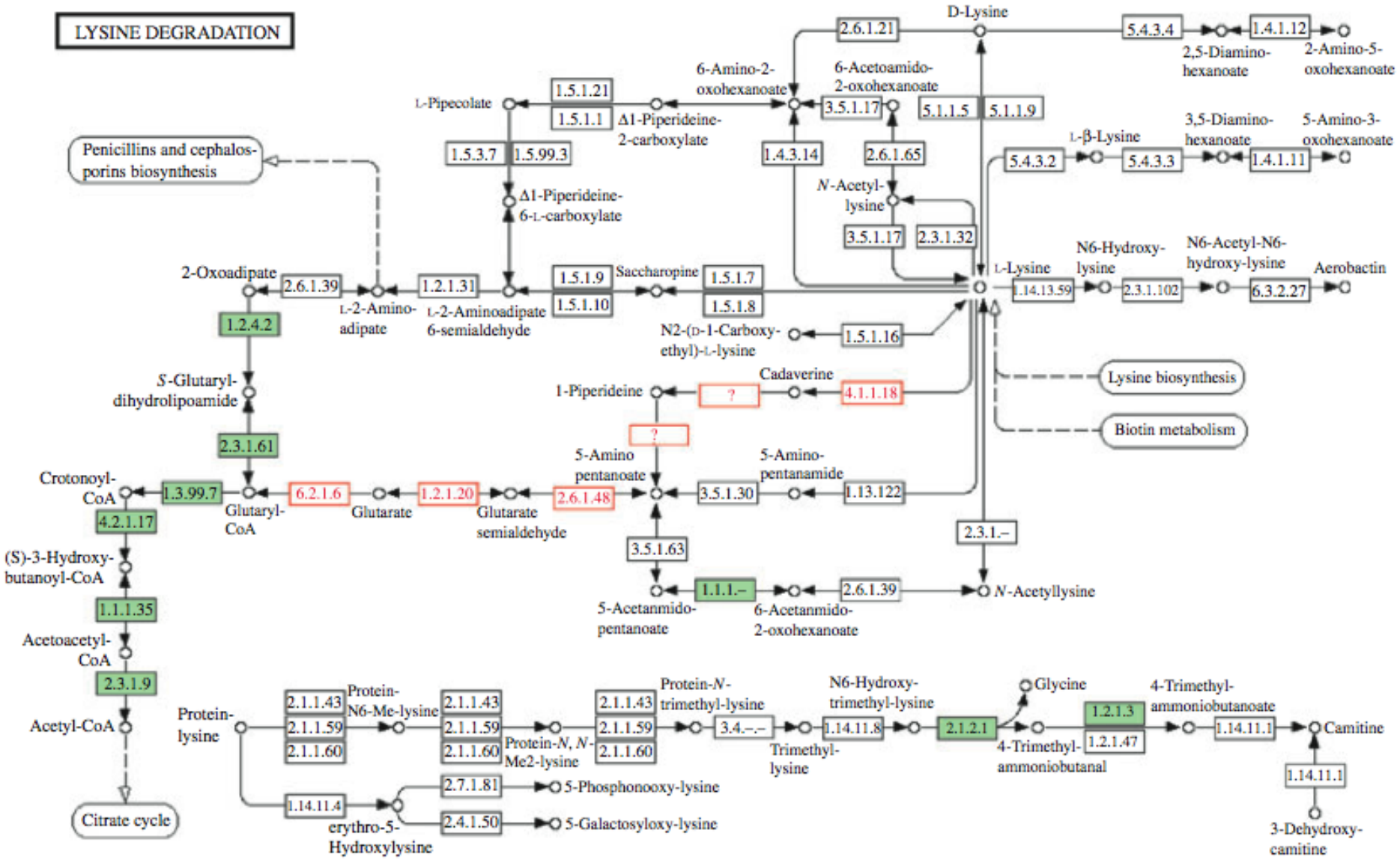
Reconstruction of the lysine-degradation pathway of *Pseudomonas aeruginosa*

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
[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

Applications: function annotation

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

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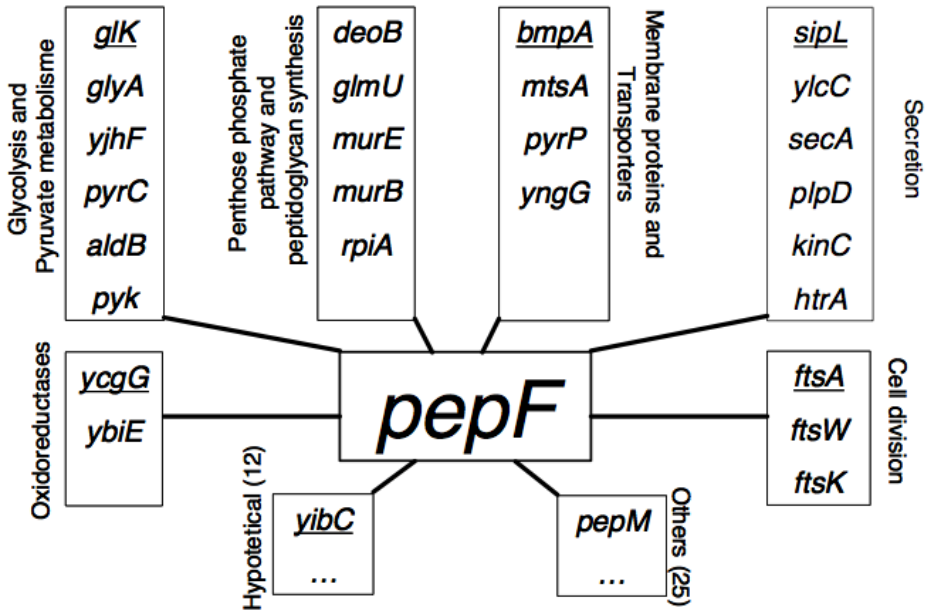

Outline

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 network and PPI network) is the local pattern recognition approach.
- It reaches high performance on the benchmarks: 45% of all true edges of the metabolic gene network are retrieved at a FDR below 50% (for the yeast).
- These methods:
  - work for any network
  - work with any data
  - can integrate heterogeneous data, which strongly improves performance

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): local SVM