On Learning Gene Regulatory Networks with Only Positive Examples

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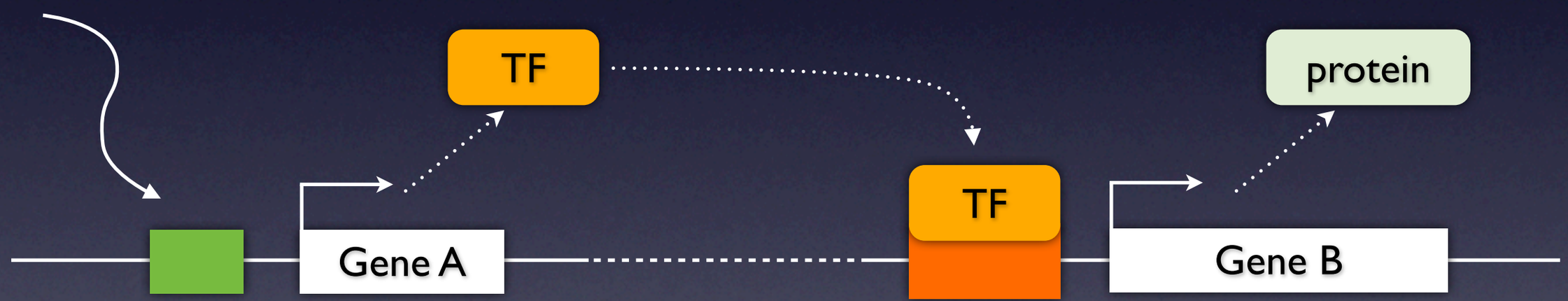
Outline

- Supervised inference of gene regulatory networks
- The positive only problem
- Negative selection approaches
- Effect on prediction accuracy
- Conclusions and future directions

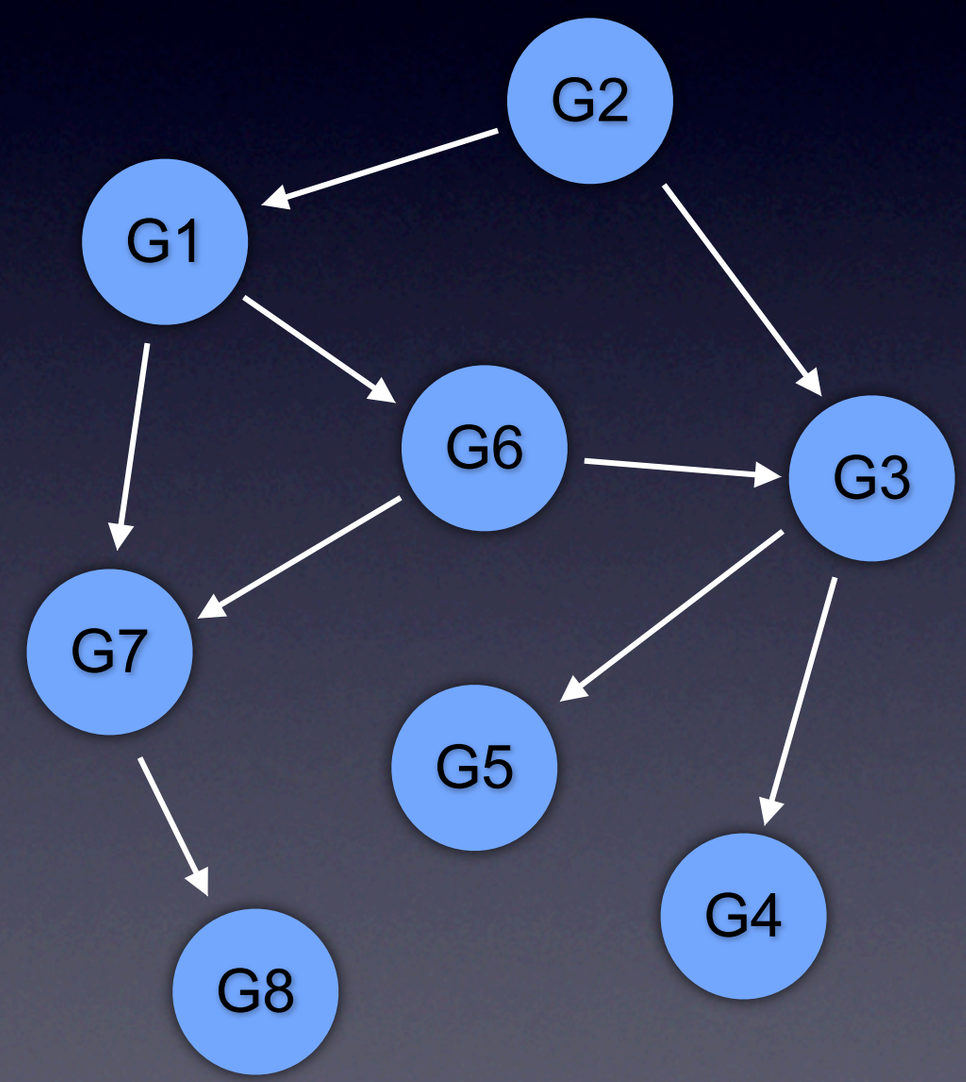
Gene Regulatory Network (GRN)

The network of transcription dependences among genes of an organism, known as transcription factors, and their binding sites.

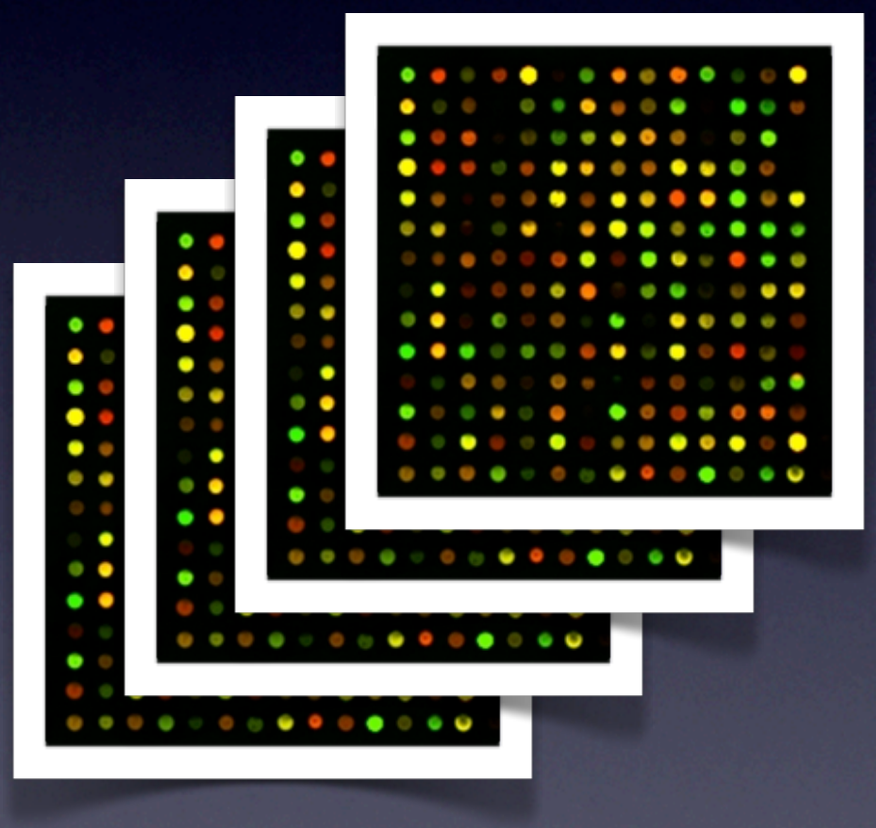


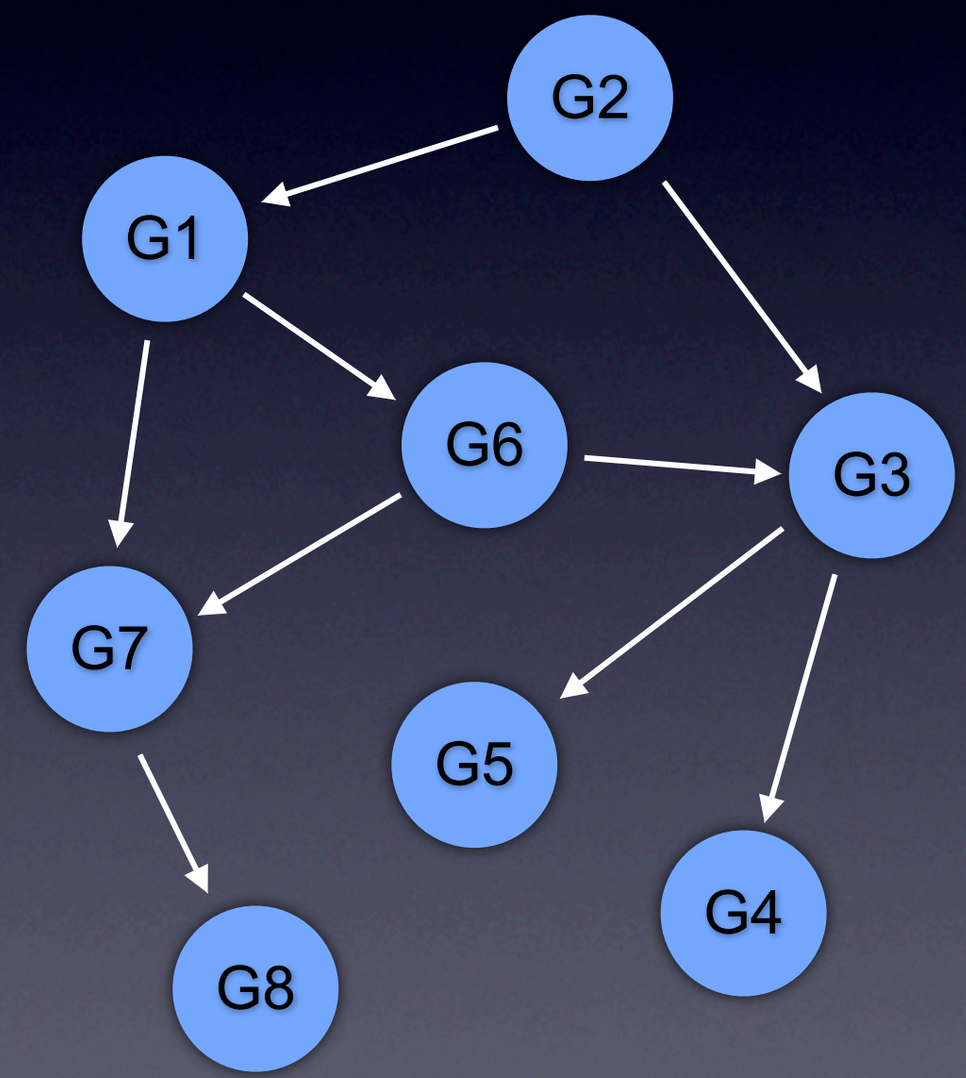
Gene Regulatory Network (GRN)

- A gene regulatory network can be represented as a graph G = (Vertices, Edges)
- Vertices = Genes
- Edges = Interactions



Inference of Gene regulatory networks





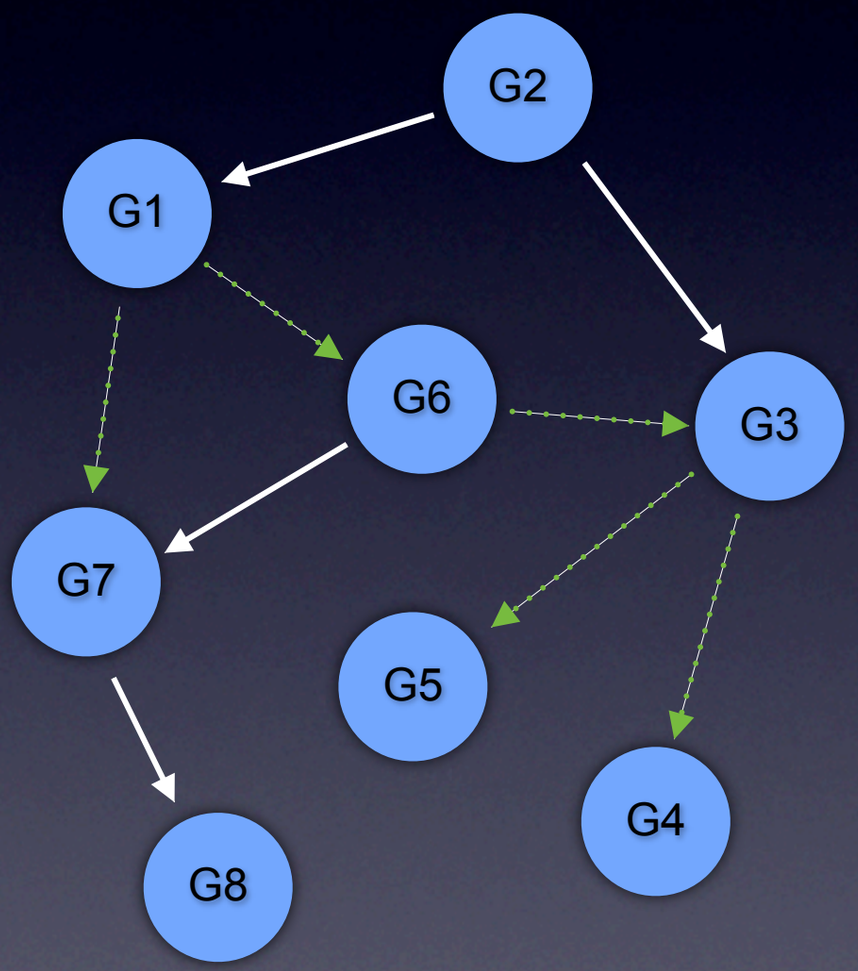
$$G_i = \{e_1, e_2, e_3, \ldots, e_n\}$$

GRN unsupervised inference

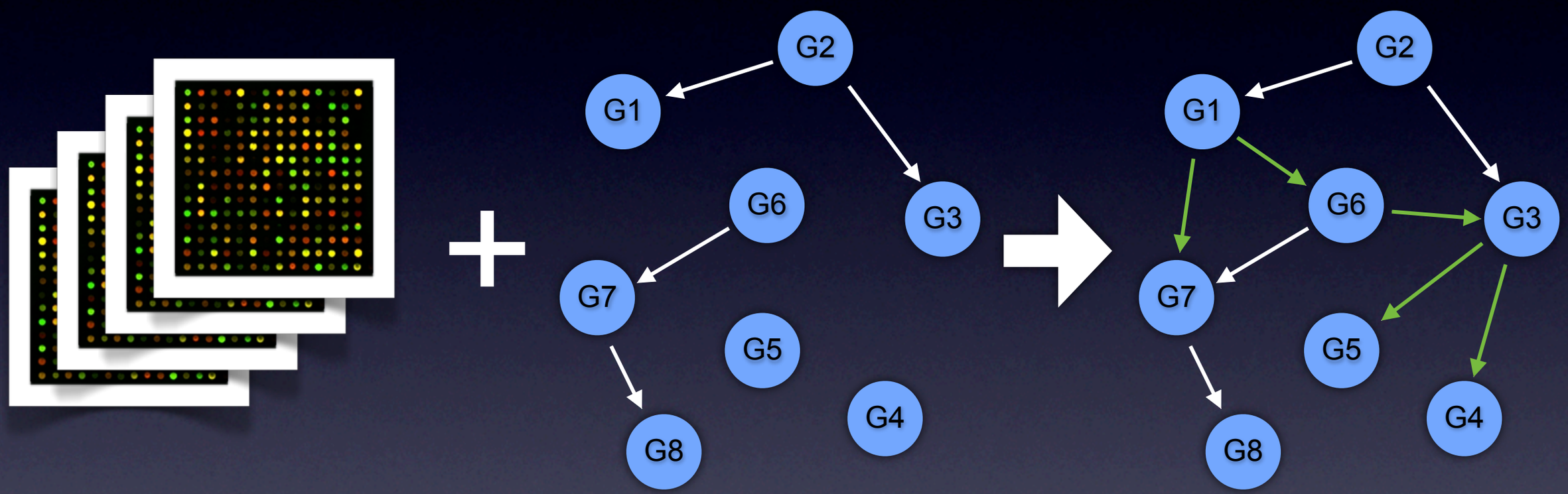
- Correlation models (eg. Mutual information)
- Bayesian Network
- Boolean networks
- ODE
- ...

GRN supervised Inference

- Part of the network is known in advance from public databases (Eg. RegulonDB)



GRN supervised Inference



$$G_i = \{e_1, e_2, e_3, \ldots, e_n\}$$

$$T = \{(G_1, G_2), (G_2, G_3), (G_6, G_7), (G_7, G_8)\}$$

Binary classifier (SVM, Decision Tree, Neural Networks,...)

Related work

BIOINFORMATICS

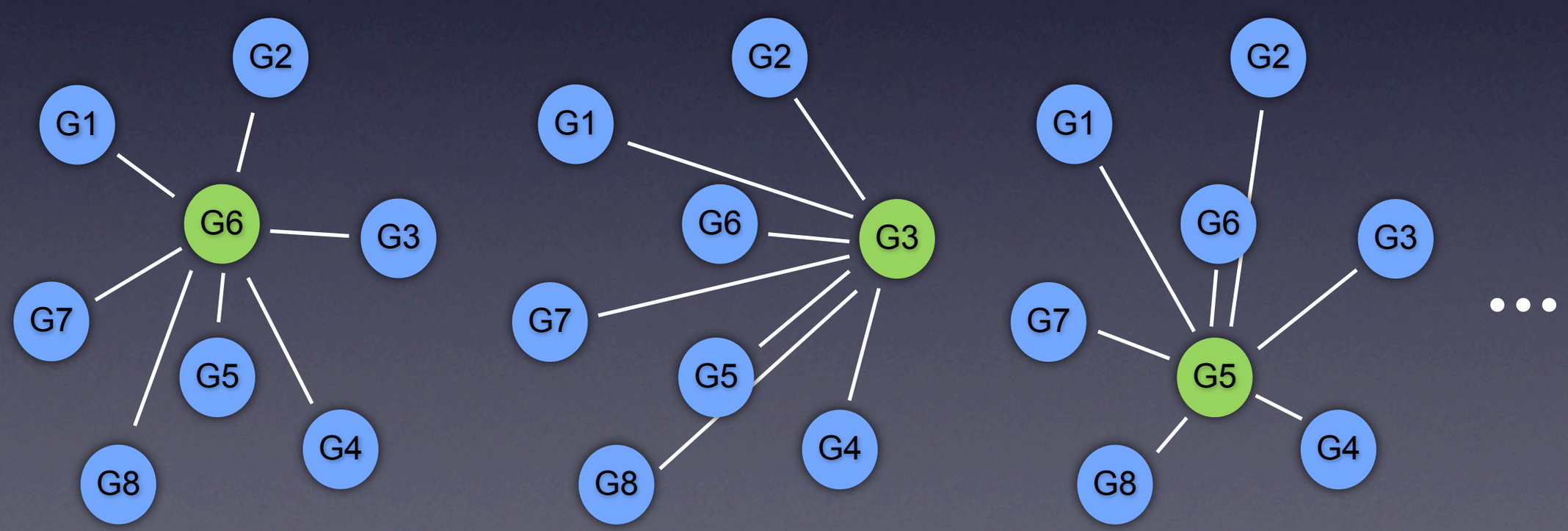
Vol. 24 ECCB 2008, pages i76–i82
doi:10.1093/bioinformatics/btn273

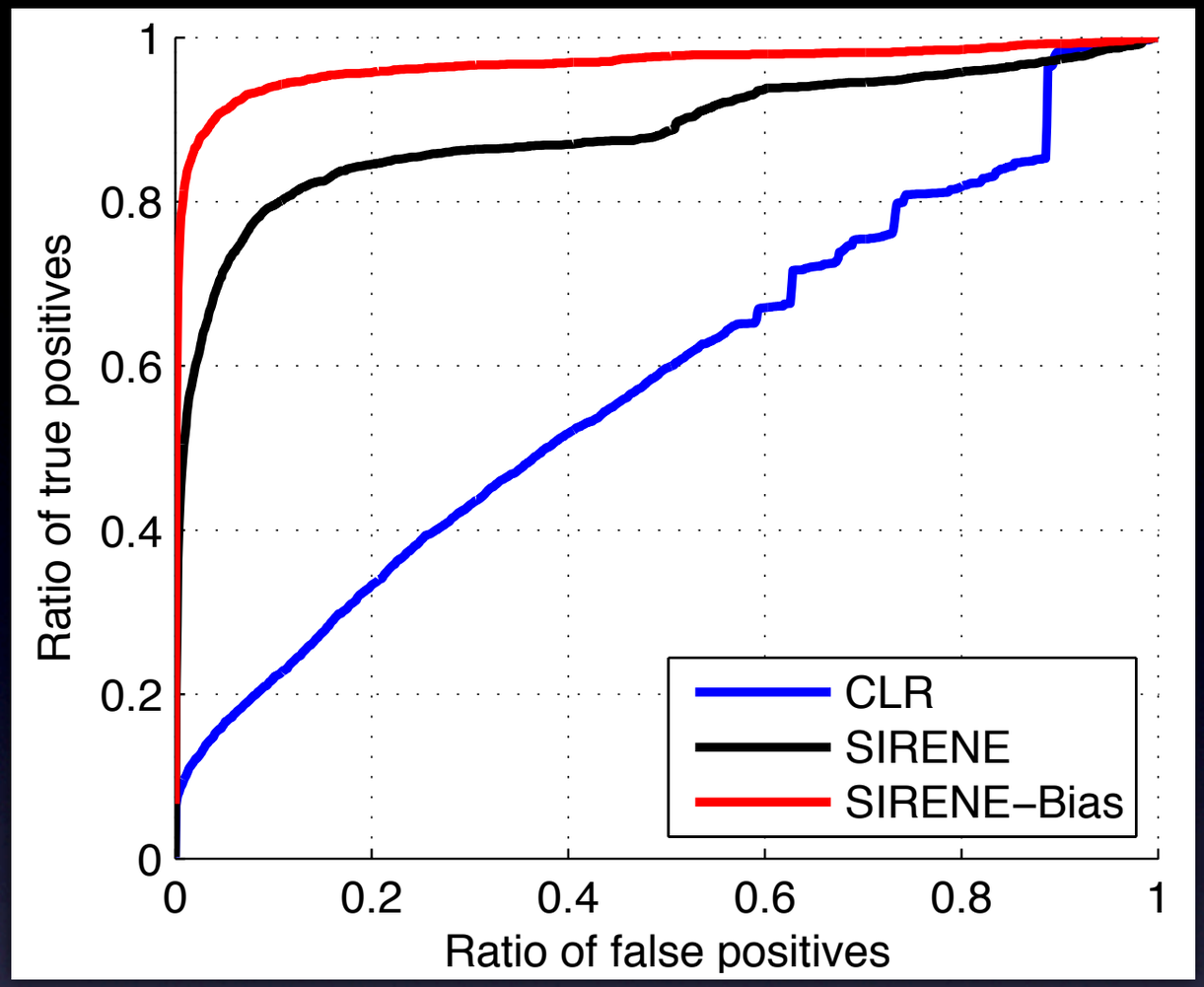
SIRENE: supervised inference of regulatory networks

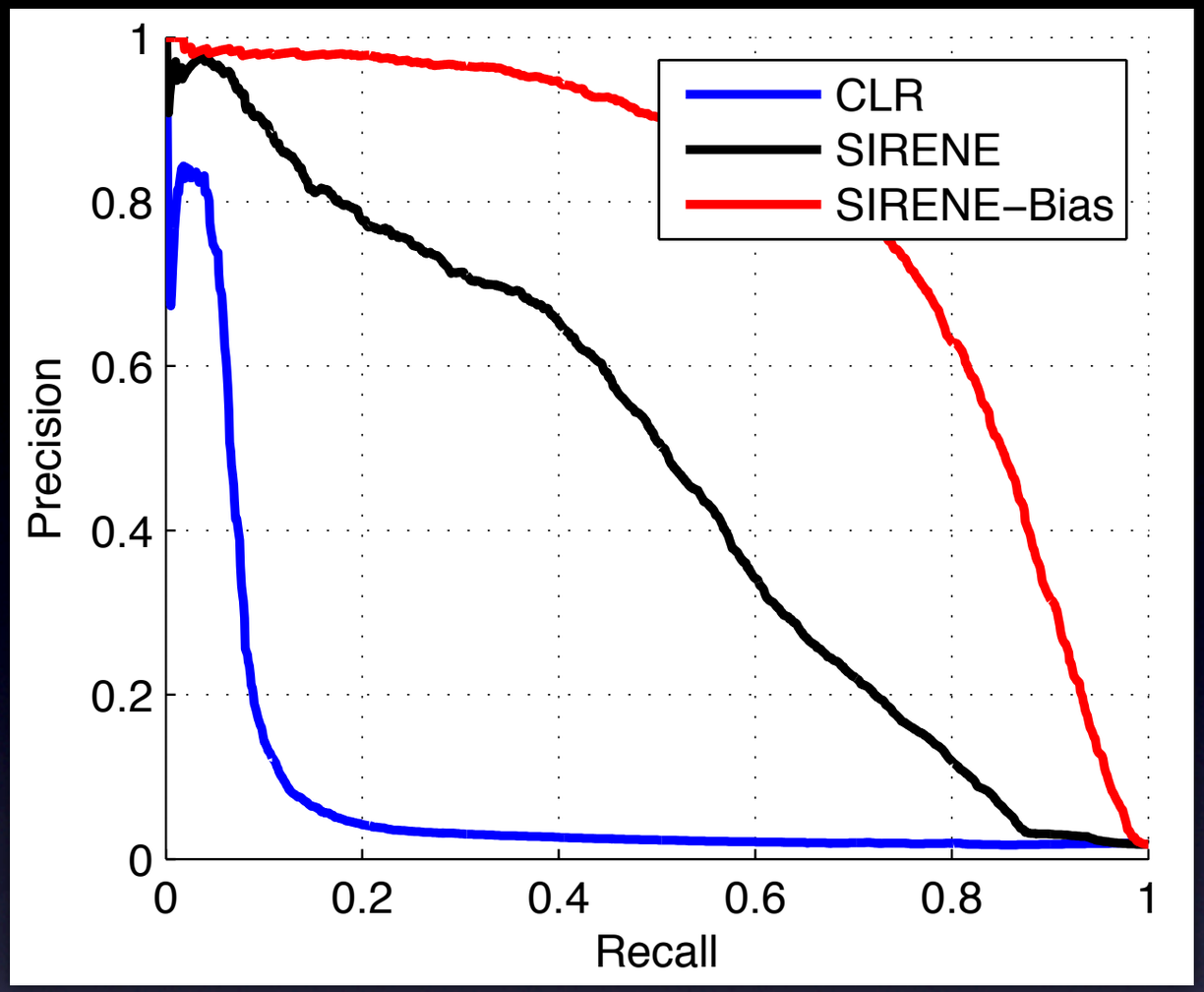
Fantine Mordelet[1,2,3,4,*] and Jean-Philippe Vert [1,2,3]

[1]Ecole des Mines de Paris, ParisTech, 35 rue Saint-Honoré, Fontainebleau F-77300, [2]Institut Curie, Paris F-75248, [3]INSERM, U900, Paris F-75248 and [4]CREST, INSEE, 3 av. Pierre Larousse, Malakoff, F-92240 France

- SIRENE approach
  - trains an SVM classifier for each gene and predicts which genes are regulated by that gene
  - combines all predicted regulations to obtain the full regulatory network



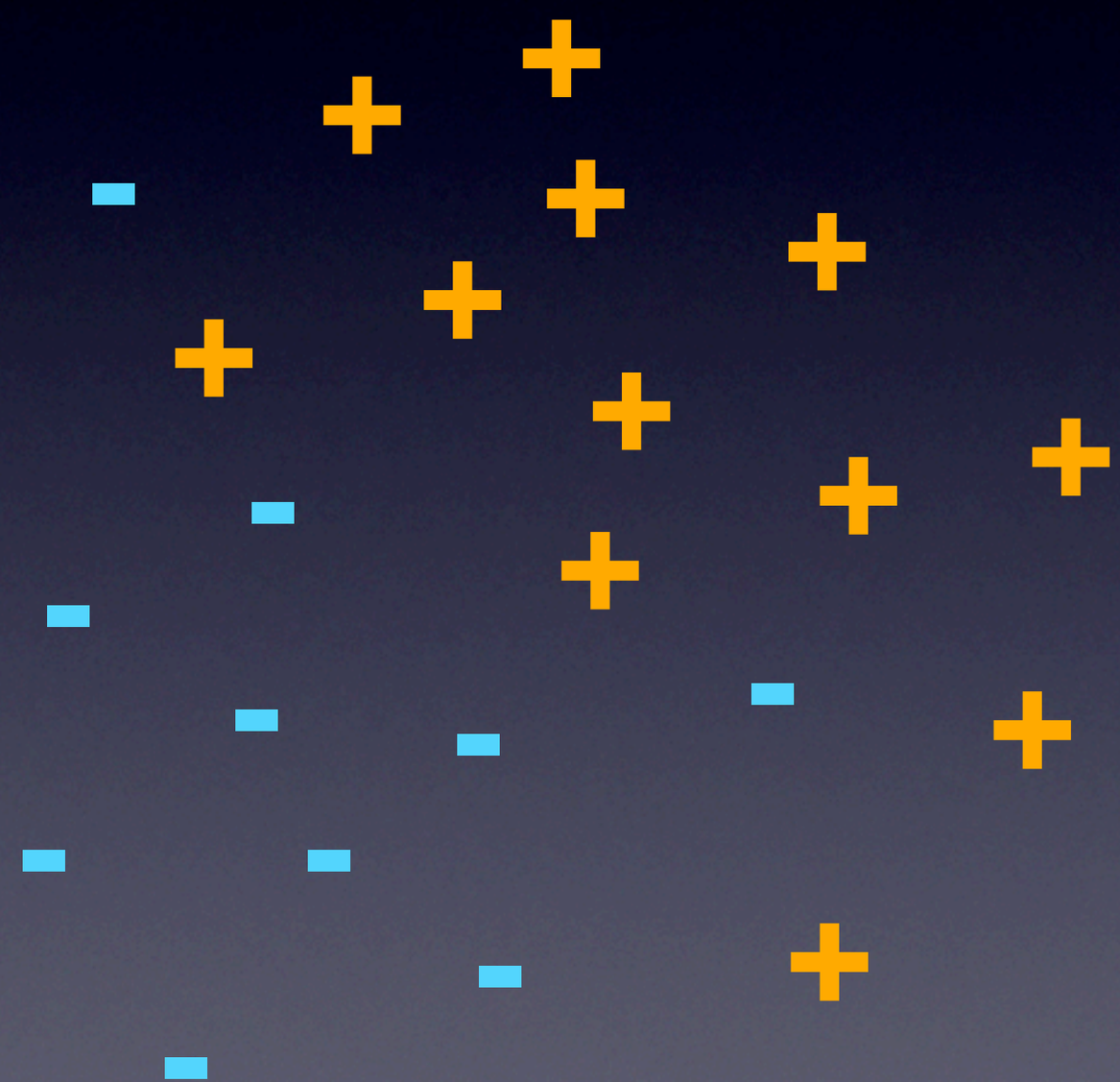




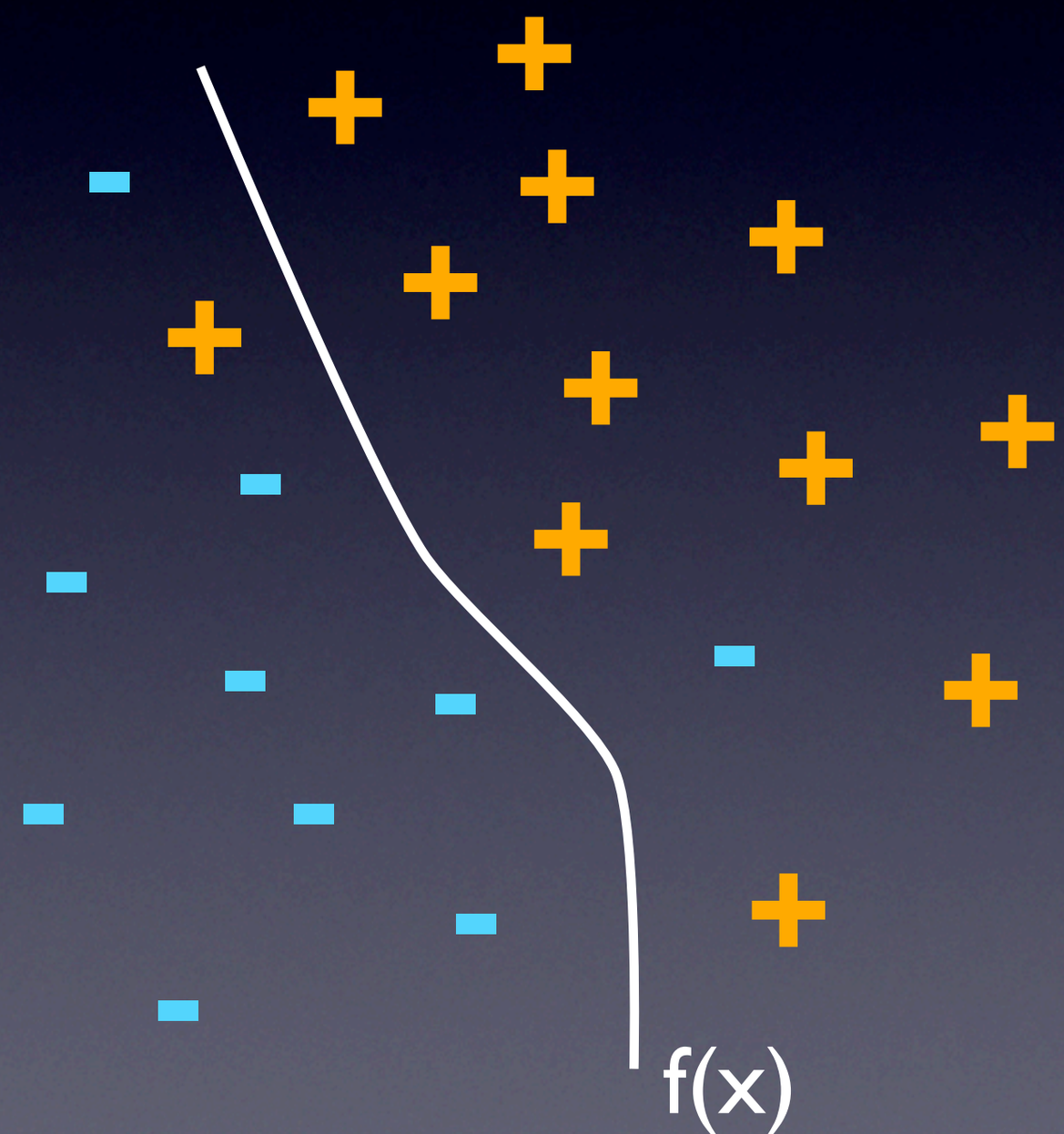
Method	Recall at 60% of Precision	Recall at 80% of Precision
SIRENE	44.5%	17.6%
CLR	7.5%	5.5%
Relevance networks	4.7%	3.3%
ARACNe	1%	0%
Bayesian network	1%	0%

Compared with unsupervised methods (Mordelet and Vert, 2008)

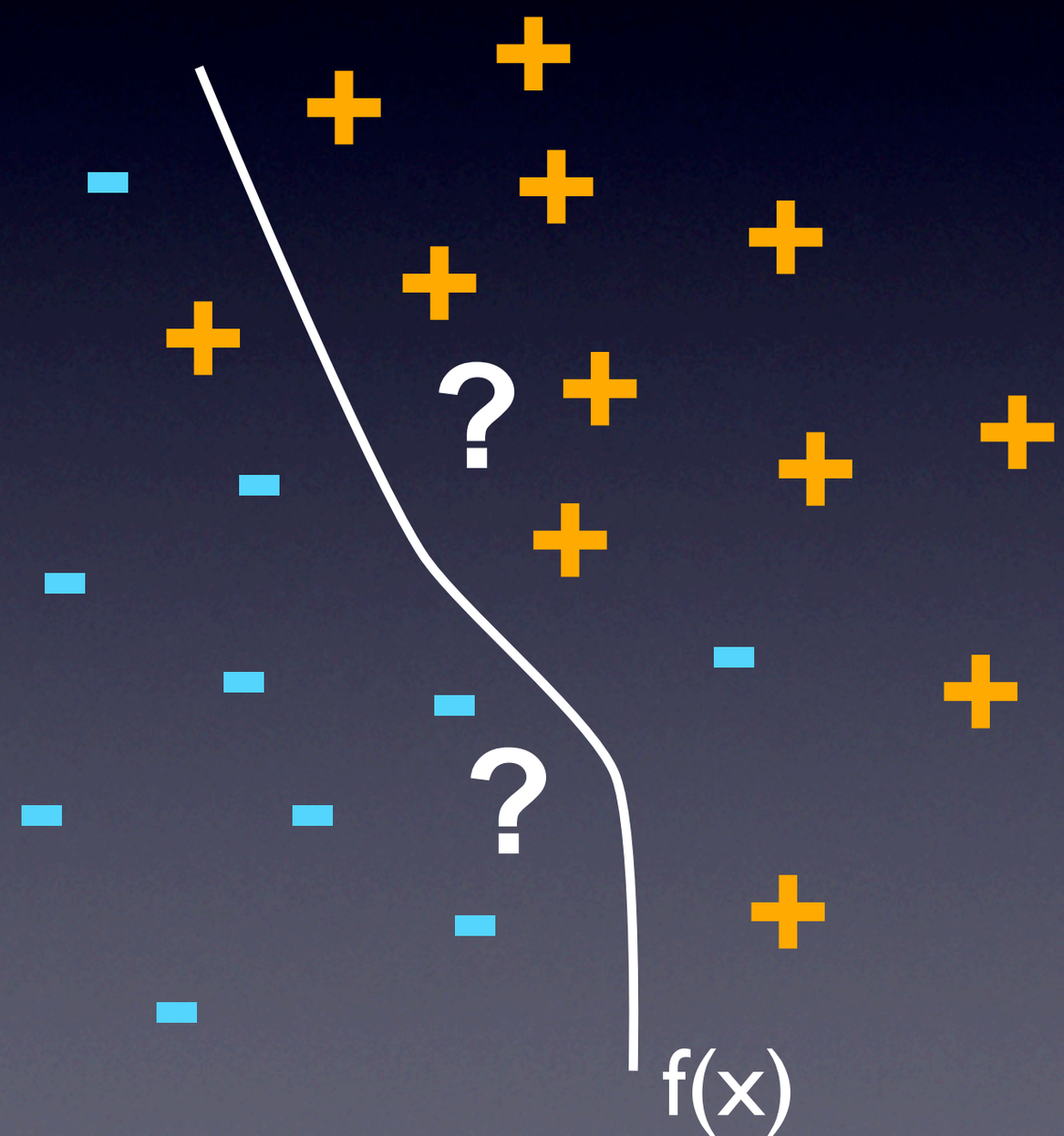
Supervised learning



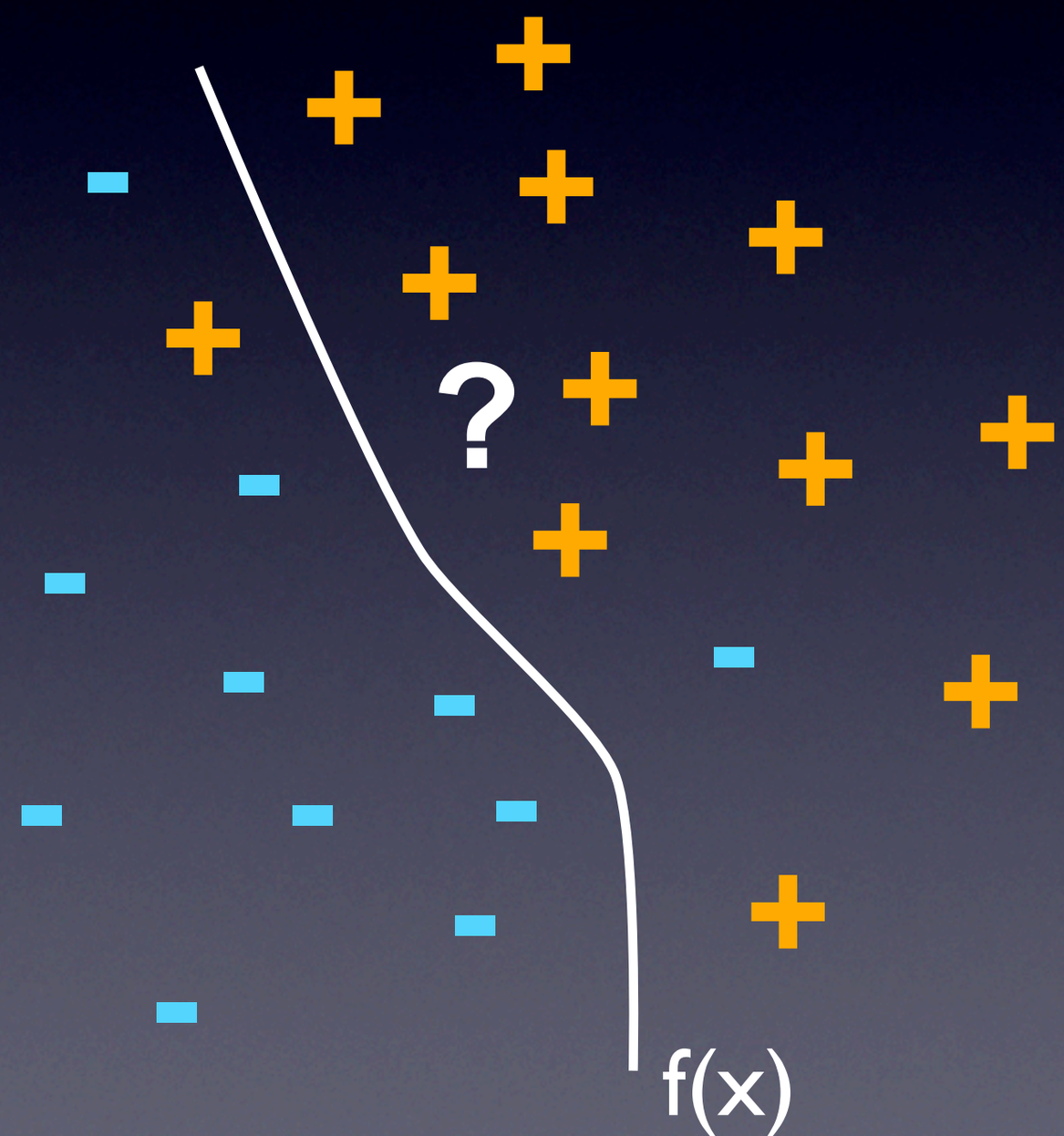
Supervised learning



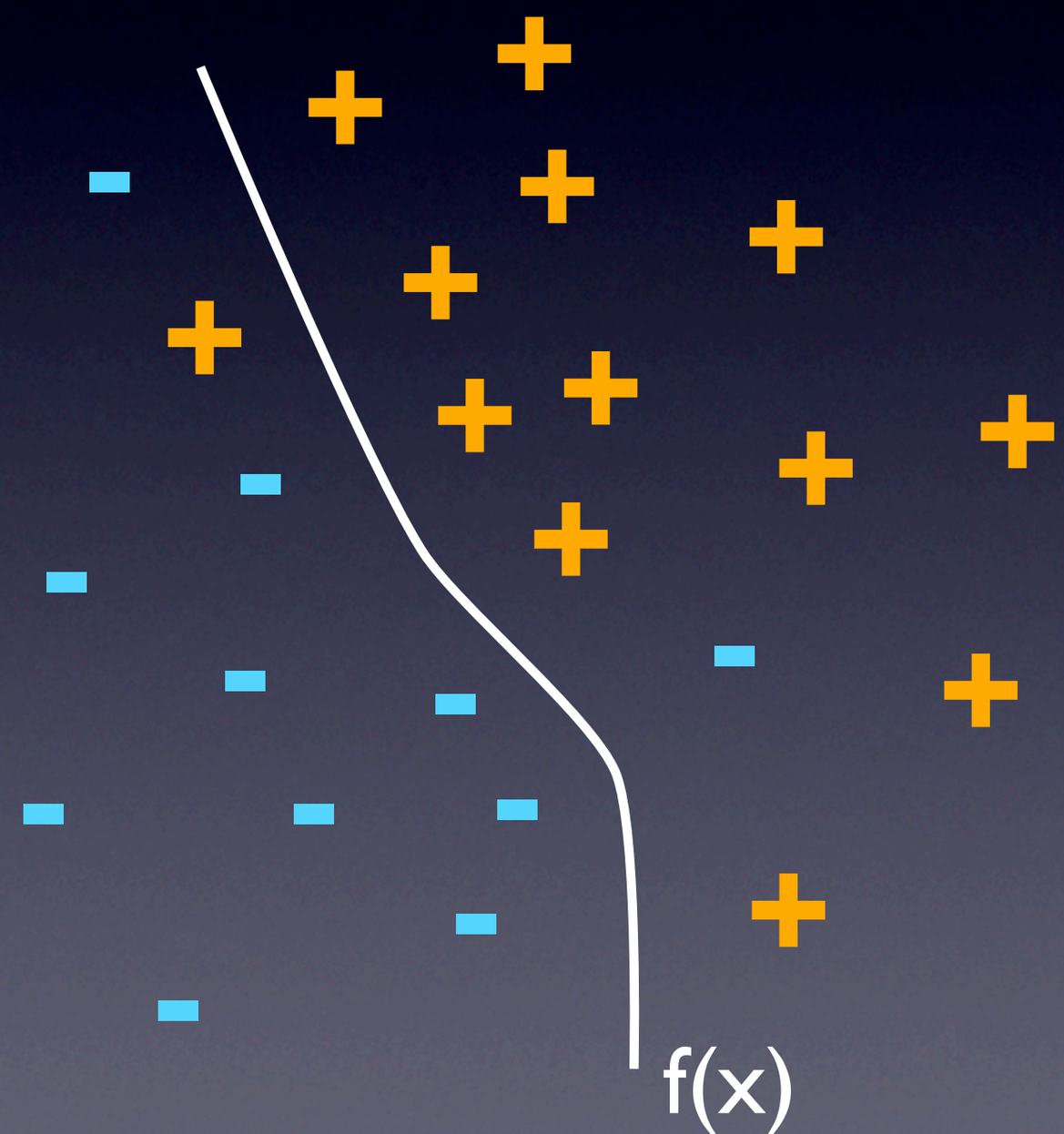
Supervised learning



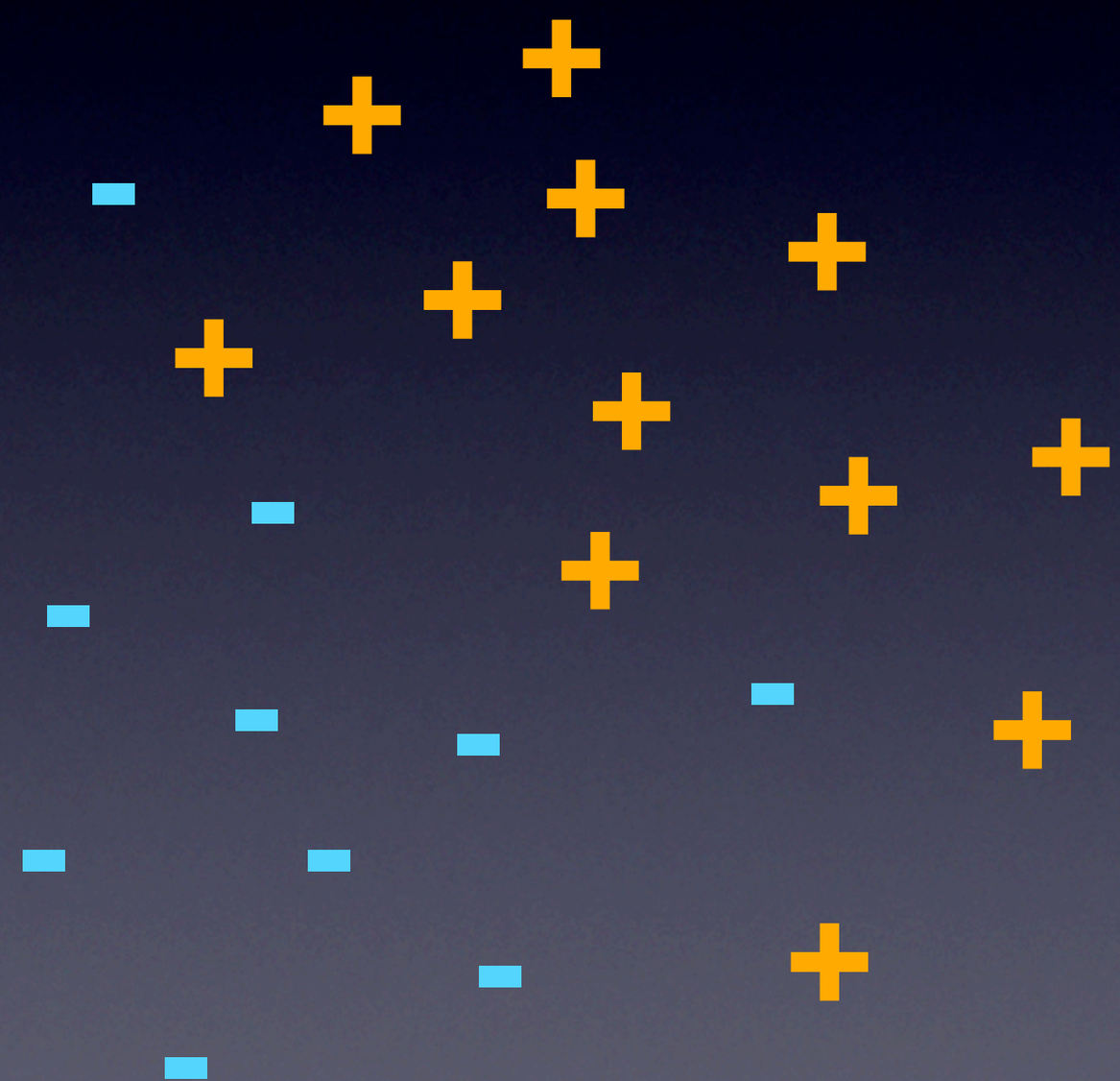
Supervised learning



Supervised learning



Supervised learning with unlabeled data



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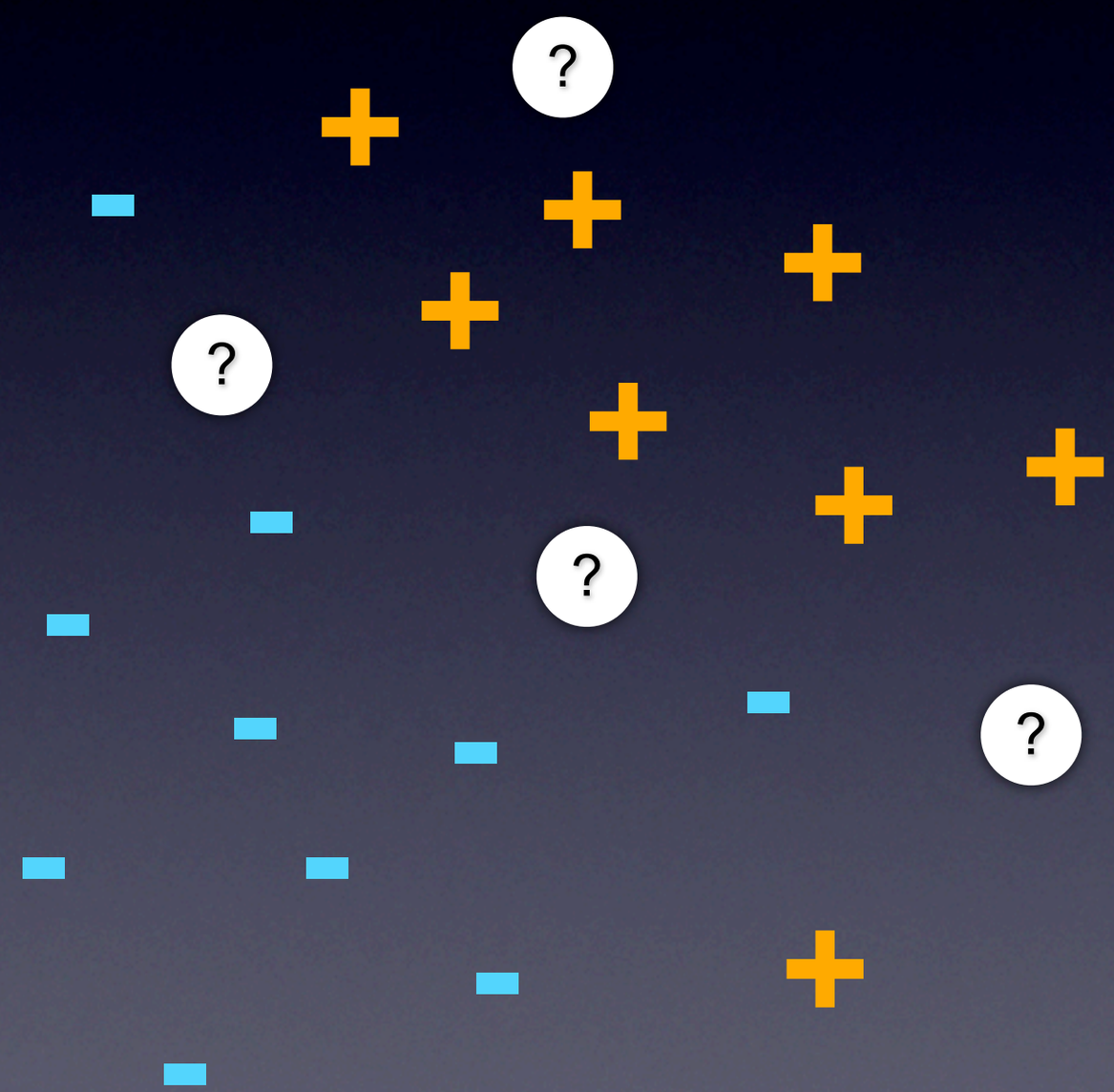

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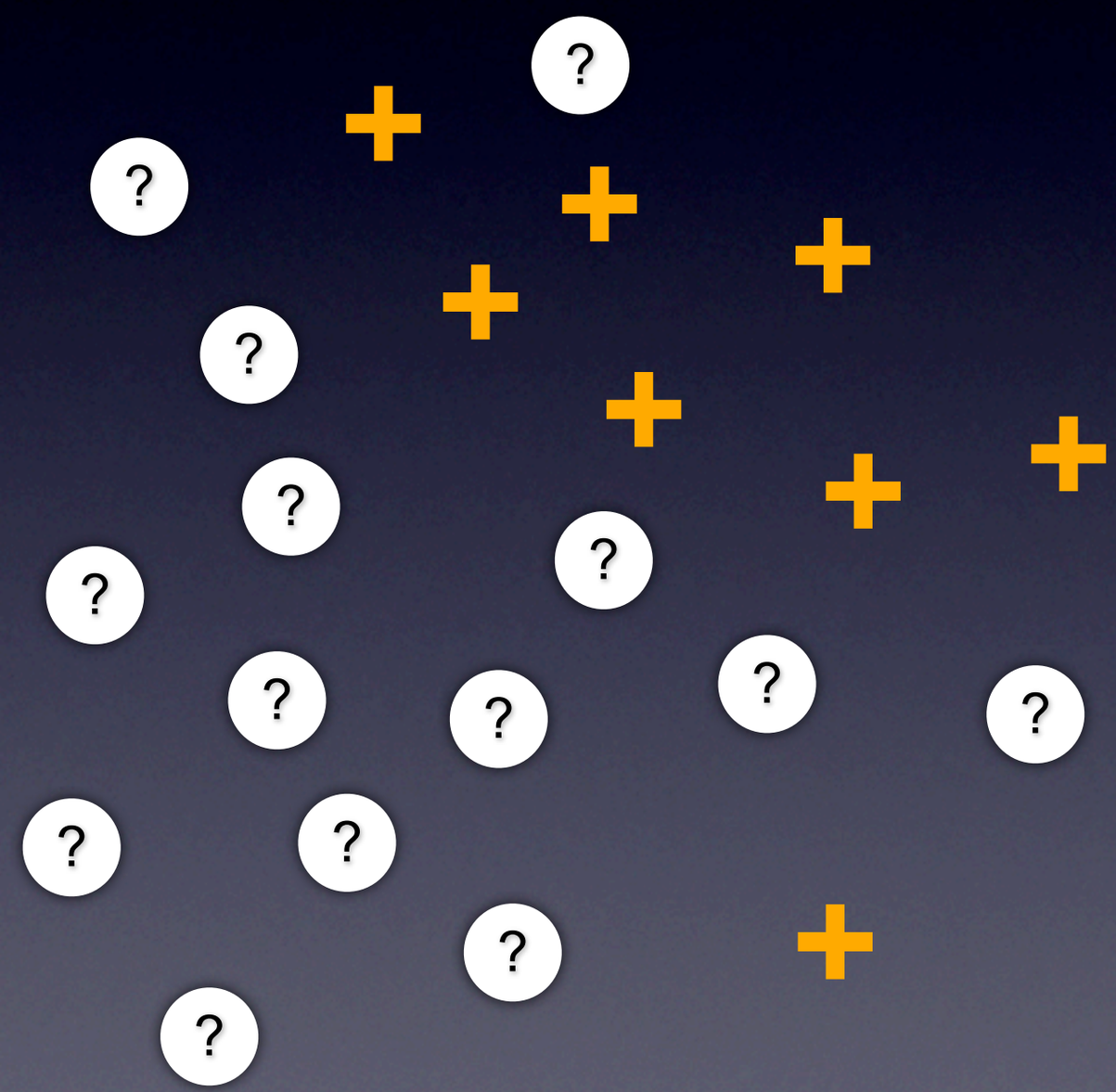
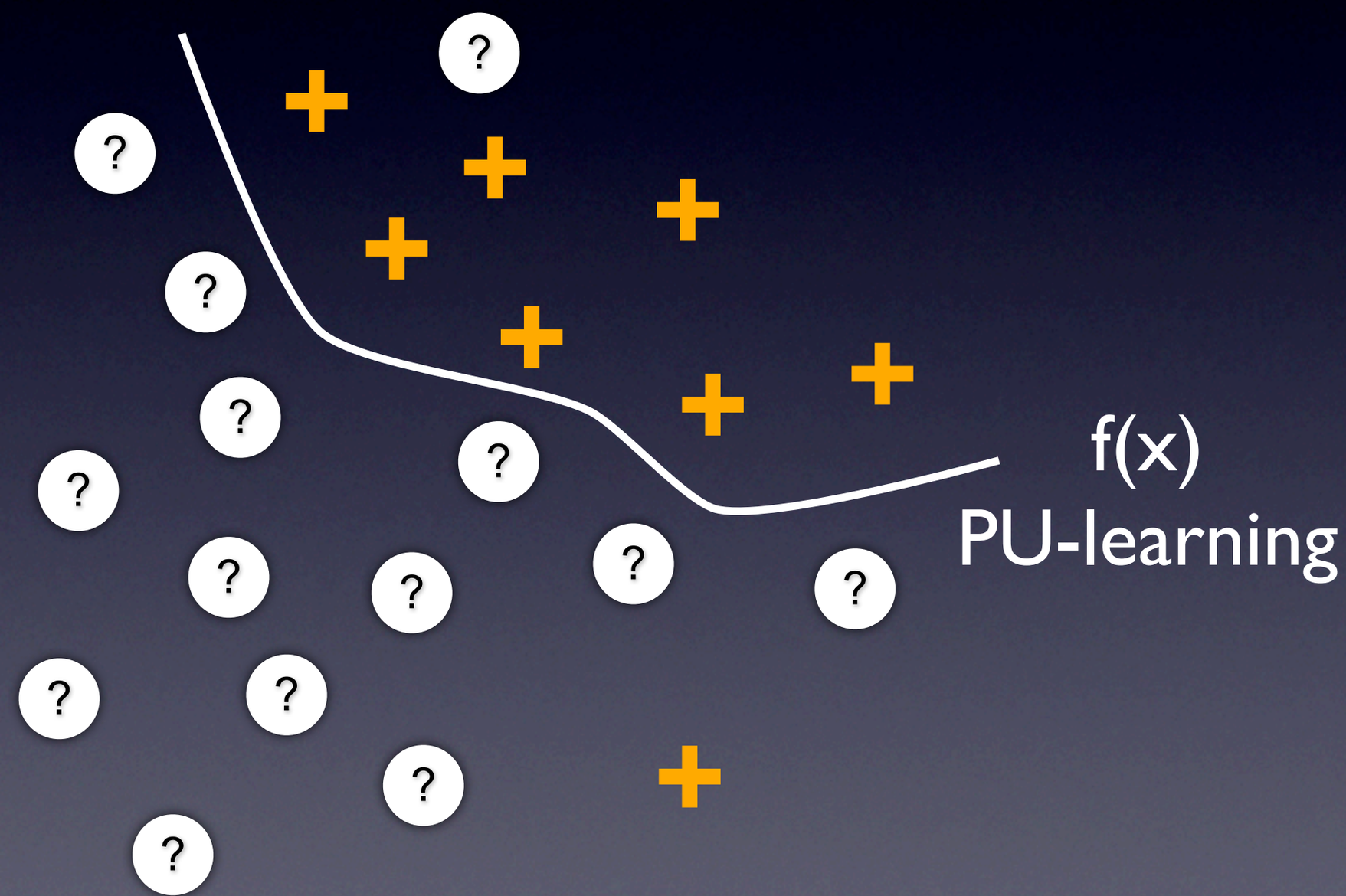
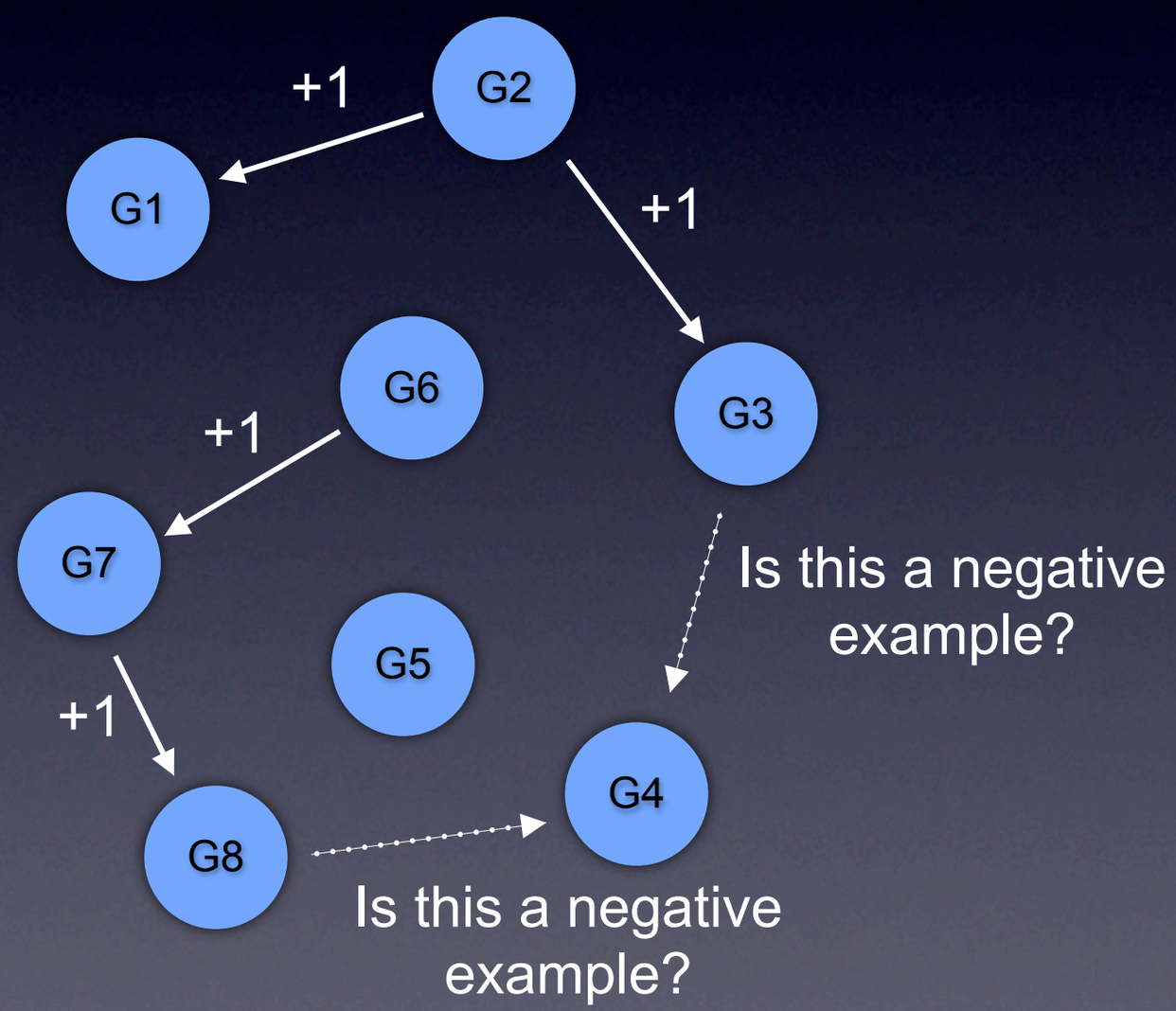


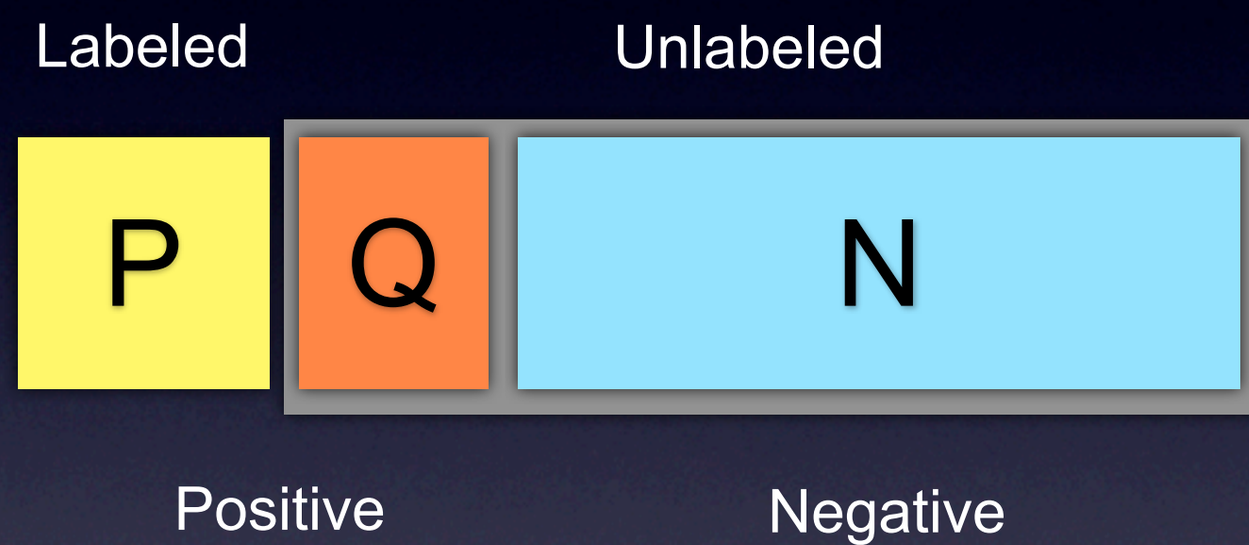
Supervised learning with unlabeled data



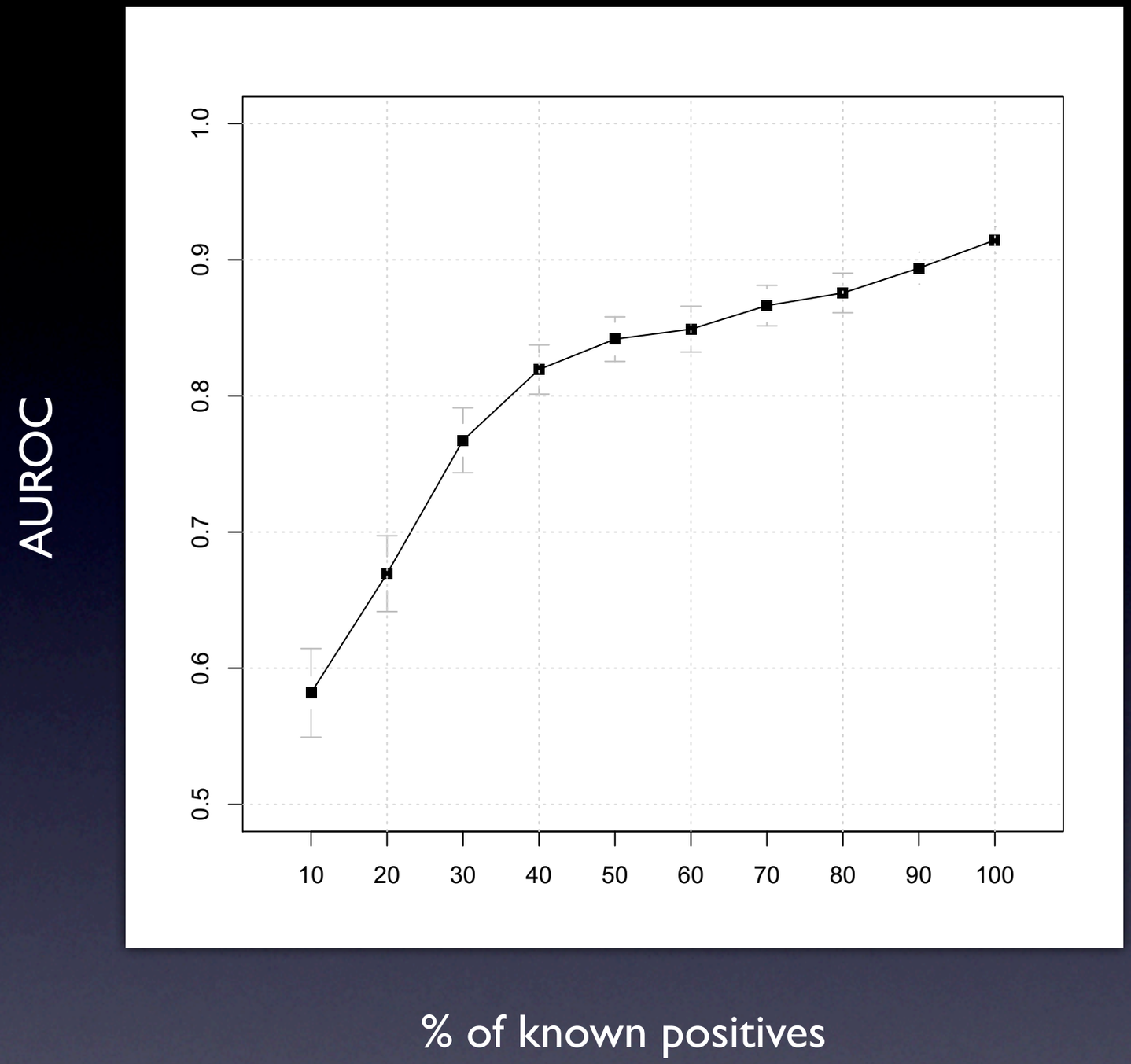
Supervised learning of gene regulatory networks



Training set



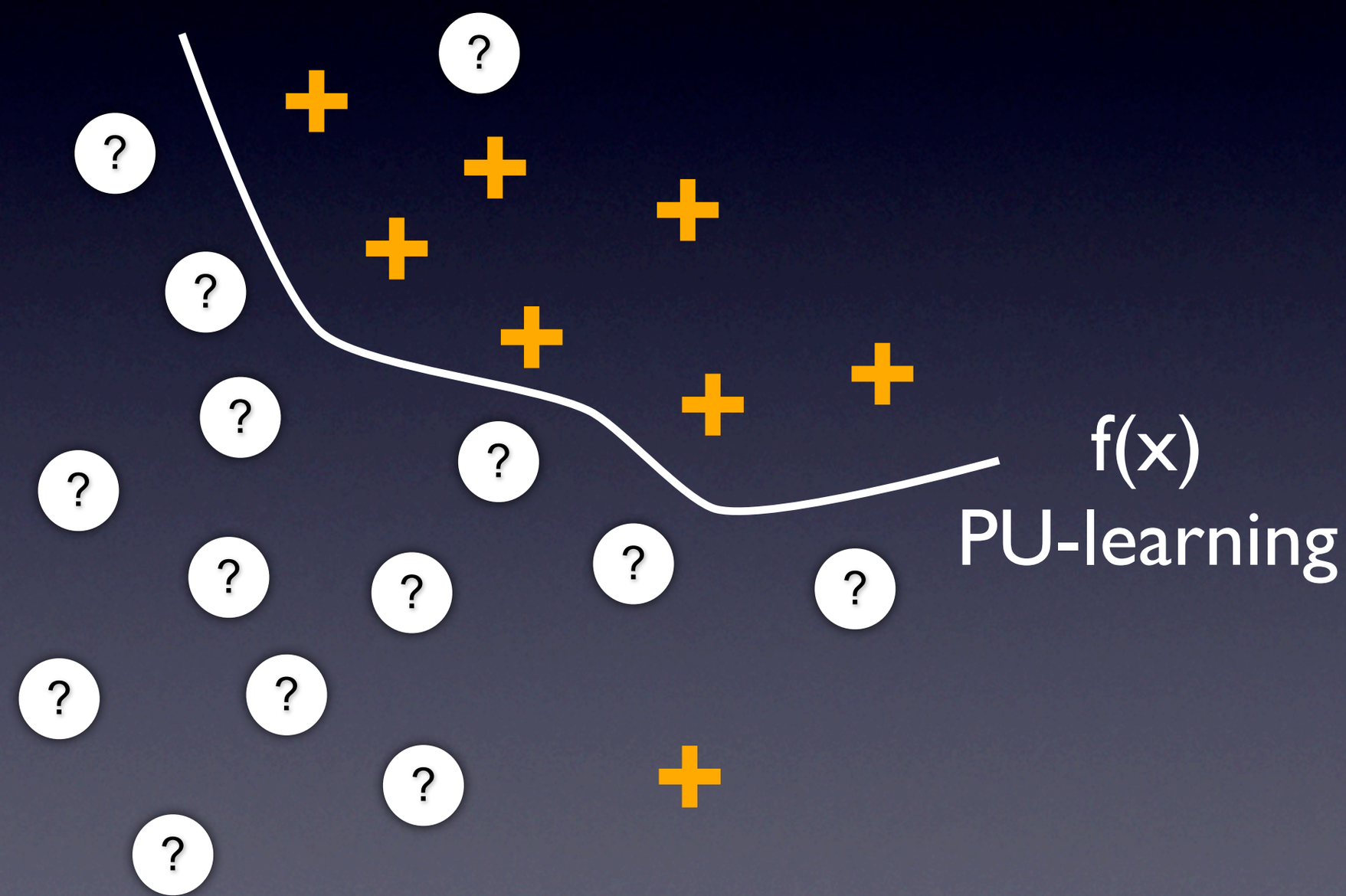
% of Known Positives $\frac{|P|}{|P \cup Q|}$



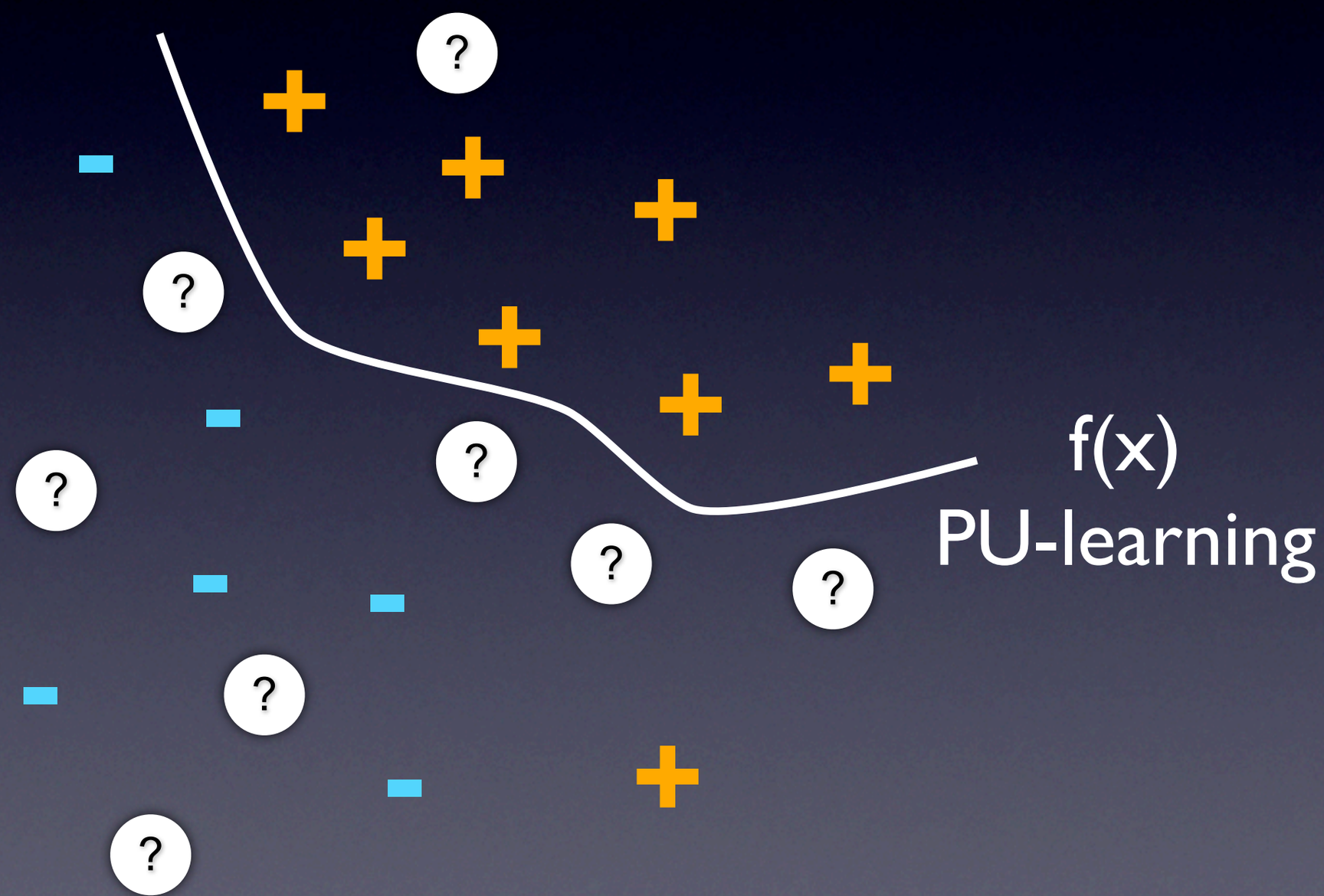
Effect of PU-learning

E.coli dataset [J.J. Faith *et al.*, 2007]

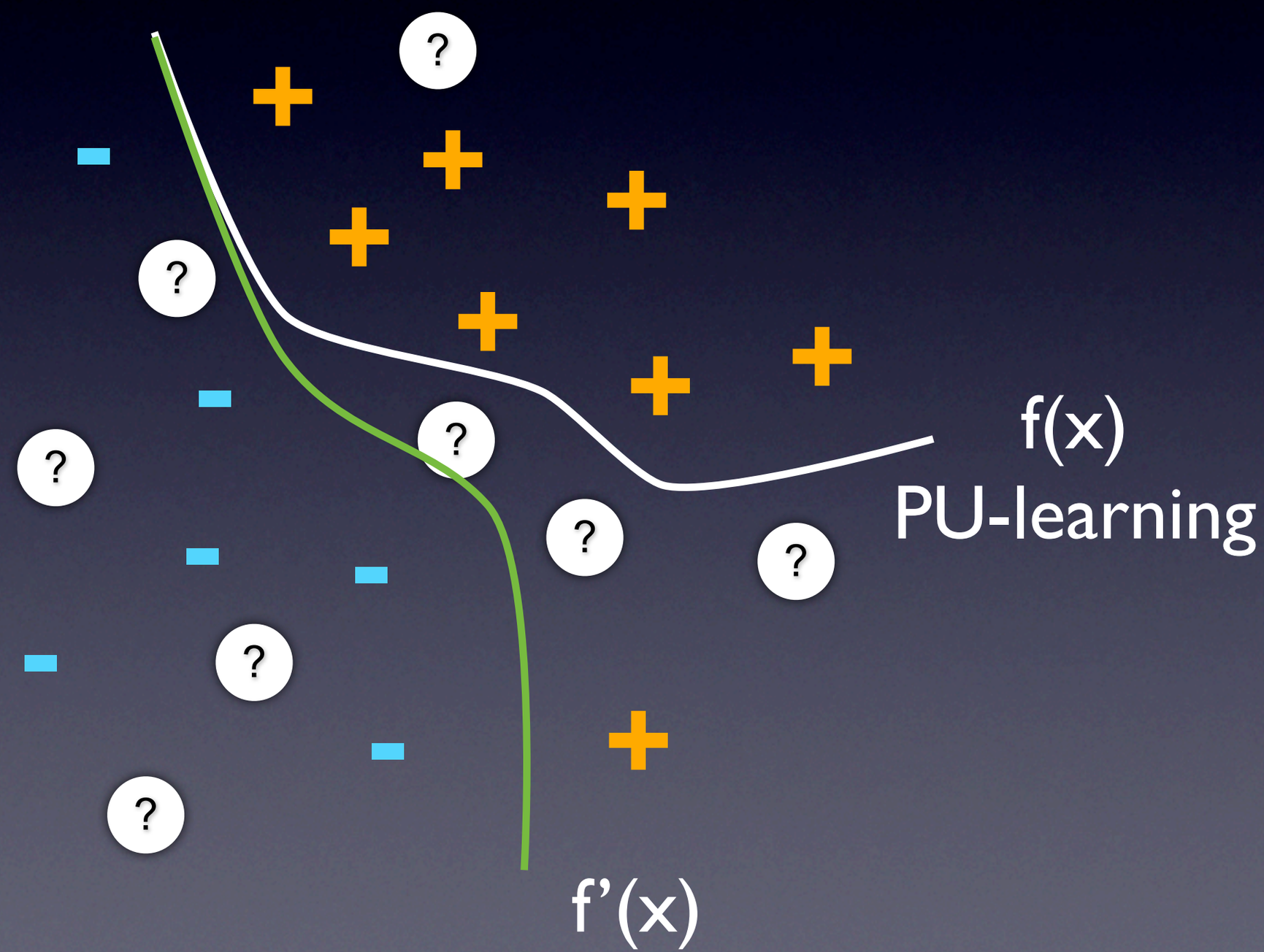
Reliable negative selection



Reliable negative selection



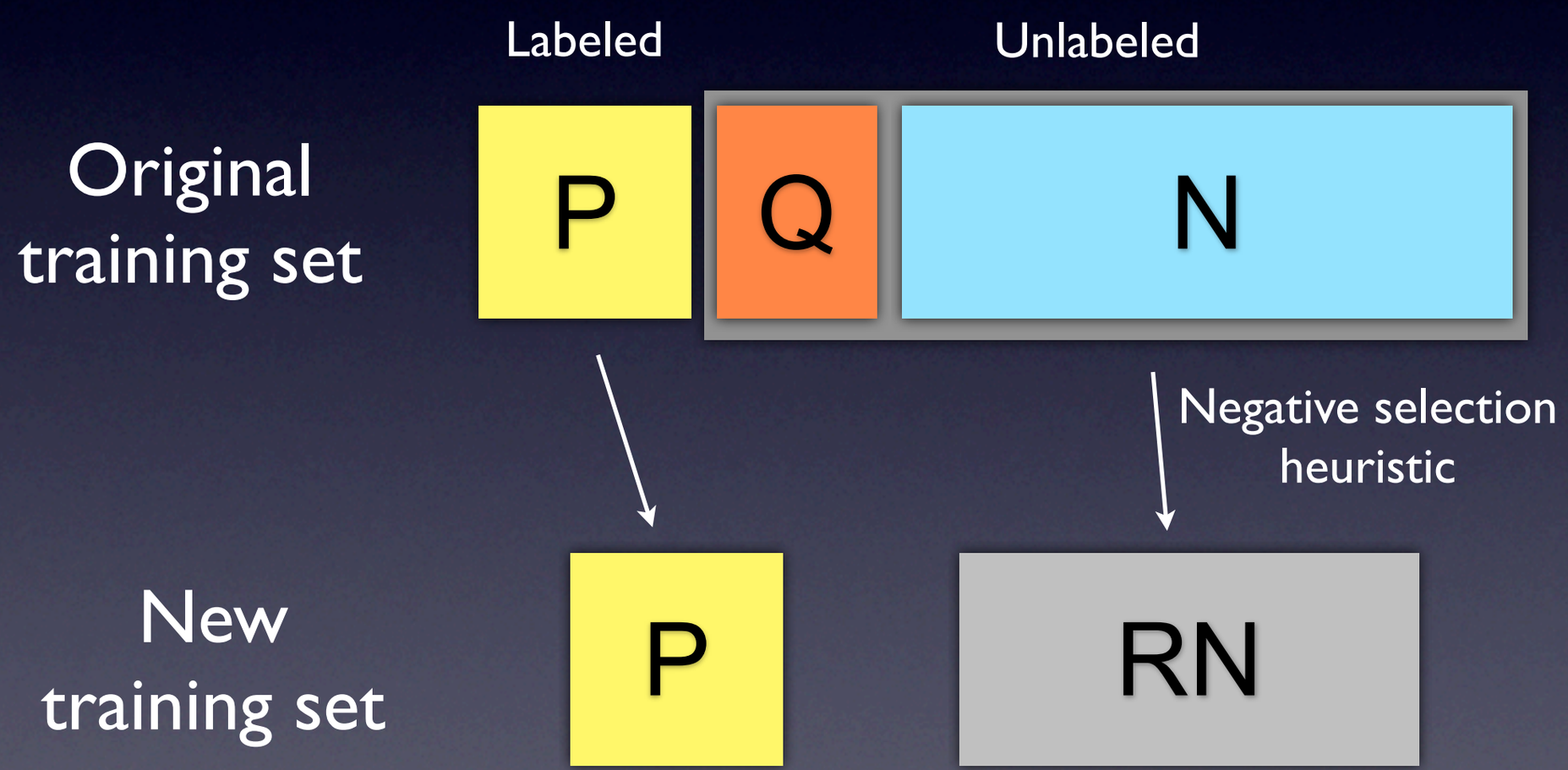
Reliable negative selection



Reliable negative selection in text mining

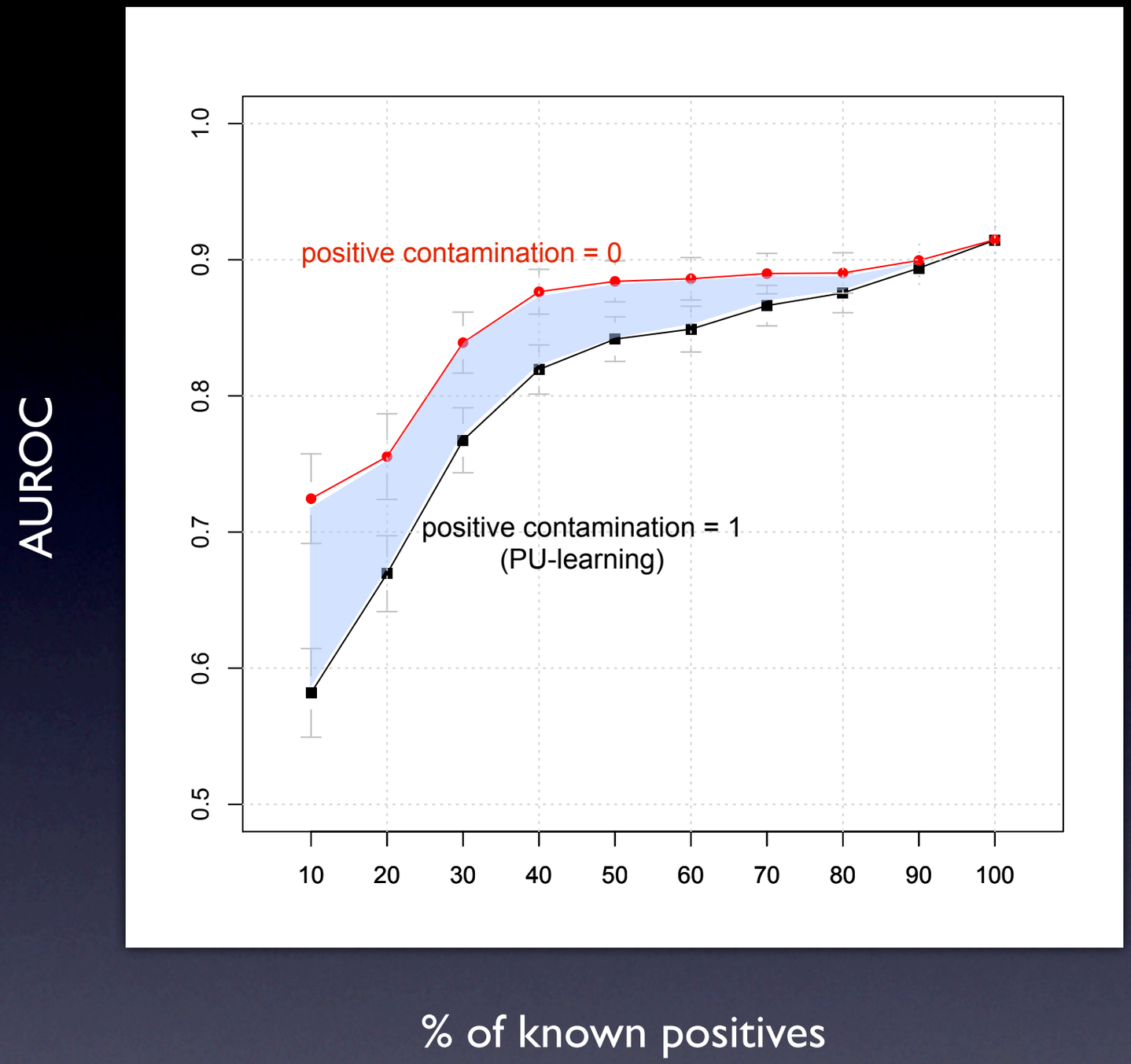
- B. Liu et al. Building Text Classifiers Using Positive and Unlabeled Examples, in ICDM 2003
- Yu et al. PEBL: Positive Example Based Learning for Web Page Classification Using SVM, in KDD 2002
- Denis et al. Text classification from positive and unlabeled Examples, in IPMU 2002

Methods based on reliable negative selection



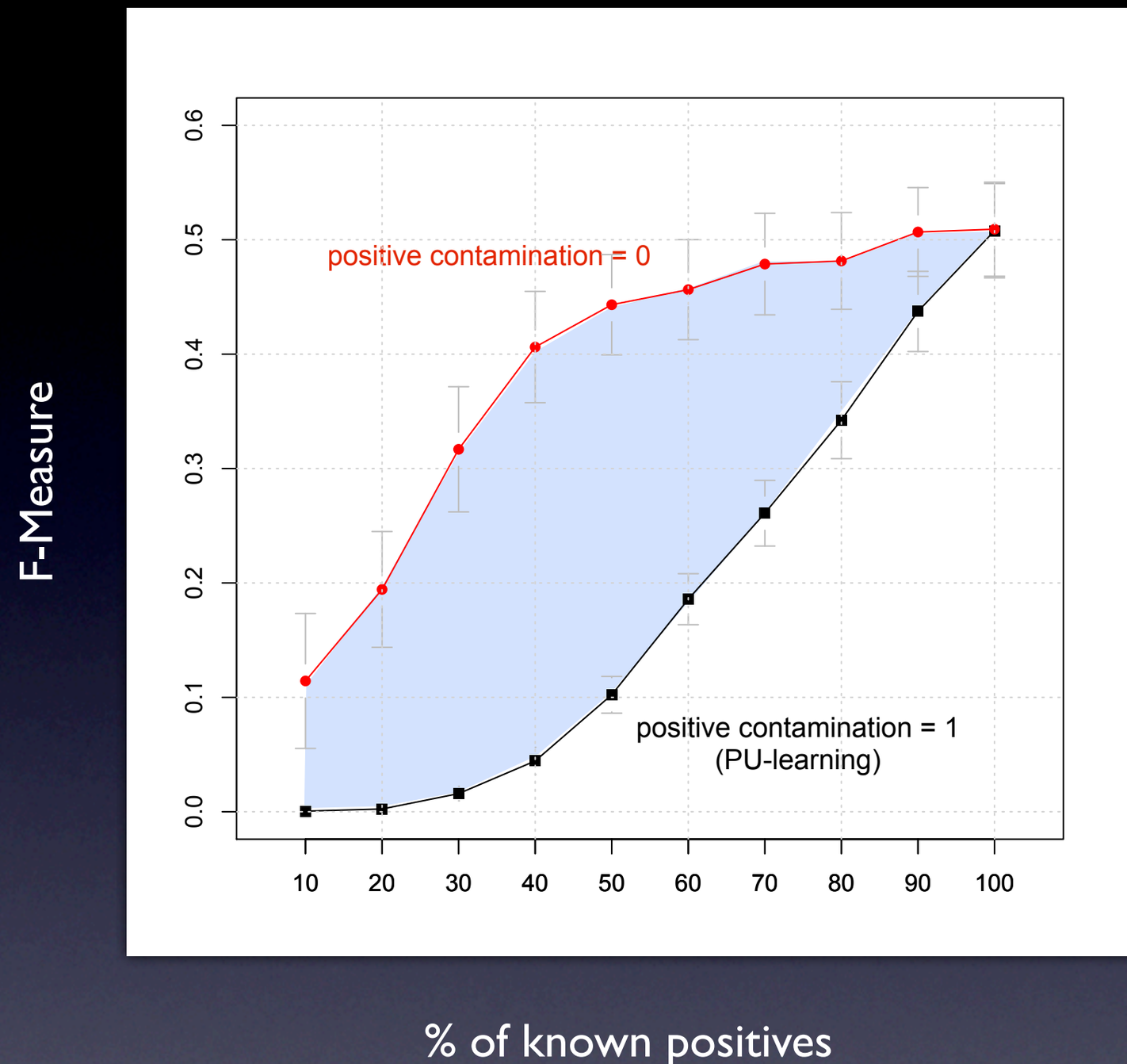
Quality of RN

- RN could be contaminated with positives embedded in unlabeled data
- The <u>fraction of positive contamination</u> is the ratio between the number of positives in RN and the total number of unknown positives |Q|



Effect of positive contamination

E.coli dataset [J.J. Faith *et al.*, 2007]



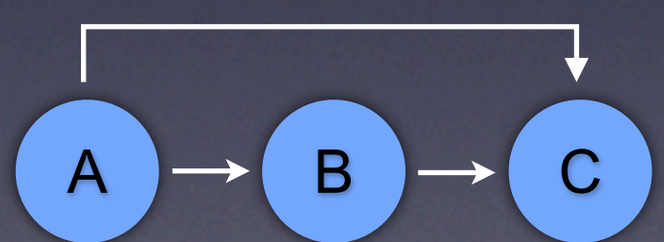
Effect of positive contamination

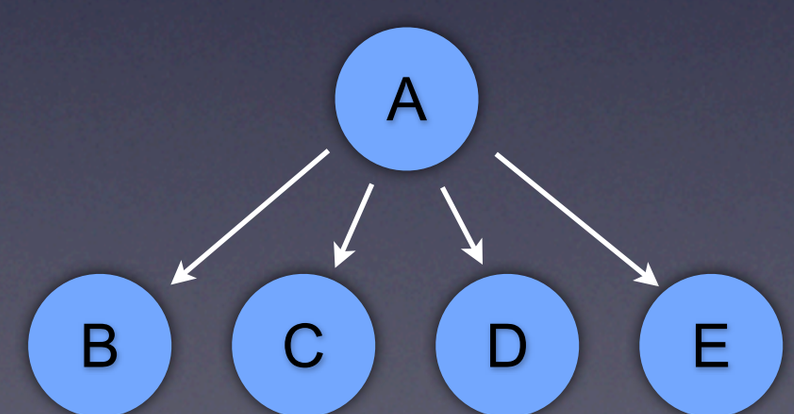
E.coli dataset [J.J. Faith *et al.*, 2007]

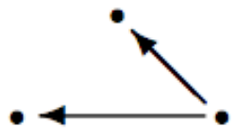
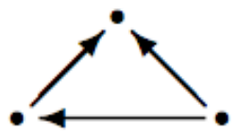
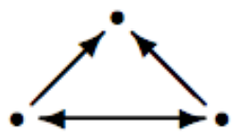
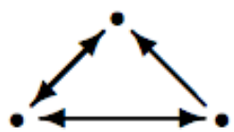
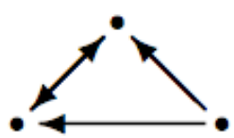
Network topology based heuristics

Network motifs

Network motifs are small connected subnetworks a network exhibits in a significant higher or lower occurrences than would be expected just by chance





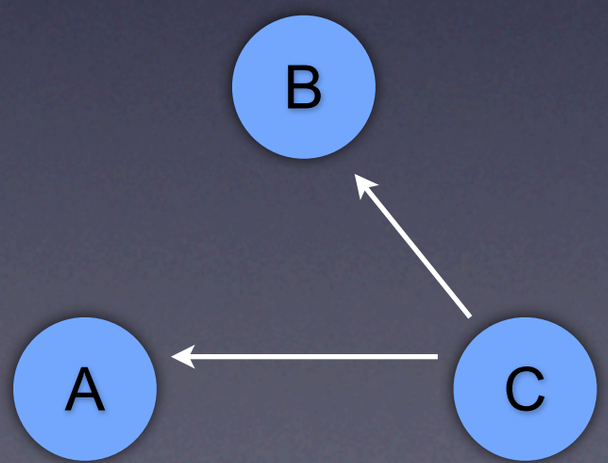
No.	Motif	E. coli Z-score	E. coli Freq.	S. cerevisiae Z-score	S. cerevisiae Freq.
1		20.343	97.467%	16.918	93.82%
2		13.295	0.318%	10.827	0.298%
3		14.401	0.105%	27.202	0.032%
4		2.058	<0.001%	4.233	<0.001%
5		4.533	0.004%	4.068	<0.001%

B. Goemann, E. Wingender, and A. P. Potapov, “An approach to evaluate the topological significance of motifs and other patterns in regulatory networks.” *BMC System Biology*, vol. 3, no. 53, May 2009.

S. S. Shen-Orr, R. Milo, S. Mangan, and U. Alon, “Network motifs in the transcriptional regulation network of escherichia coli,” *Nature Genetics*, vol. 31, no. 1, pp. 64–68, May 2002.

Network Motifs Heuristic

- For each three genes sub networks T:
- If matches a network motifs M then considers all connections not present in M as negatives



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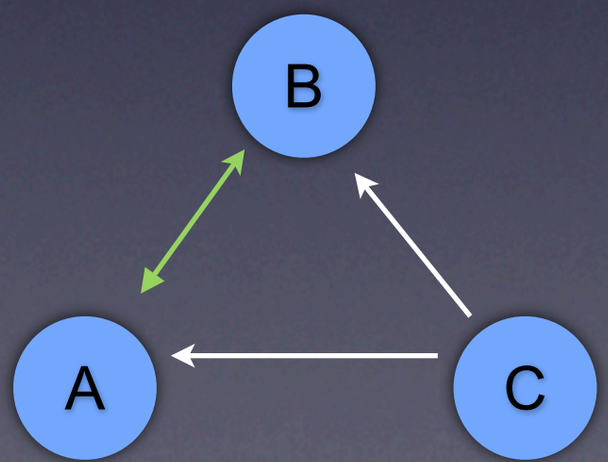

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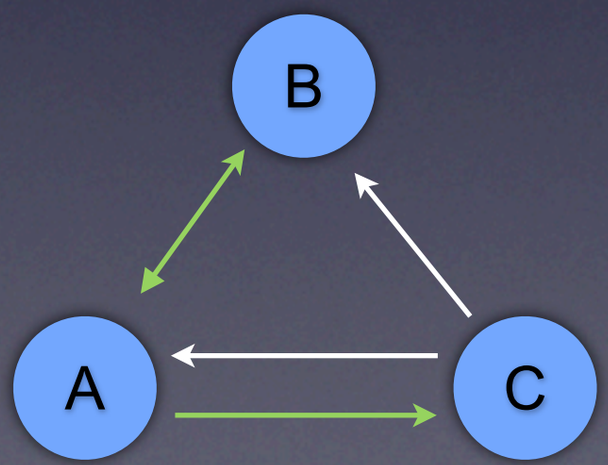

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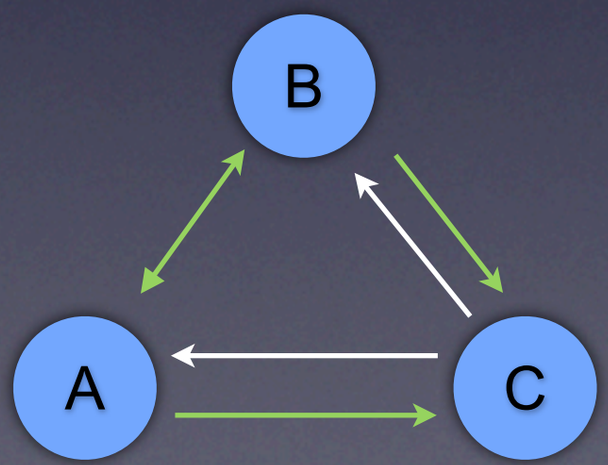
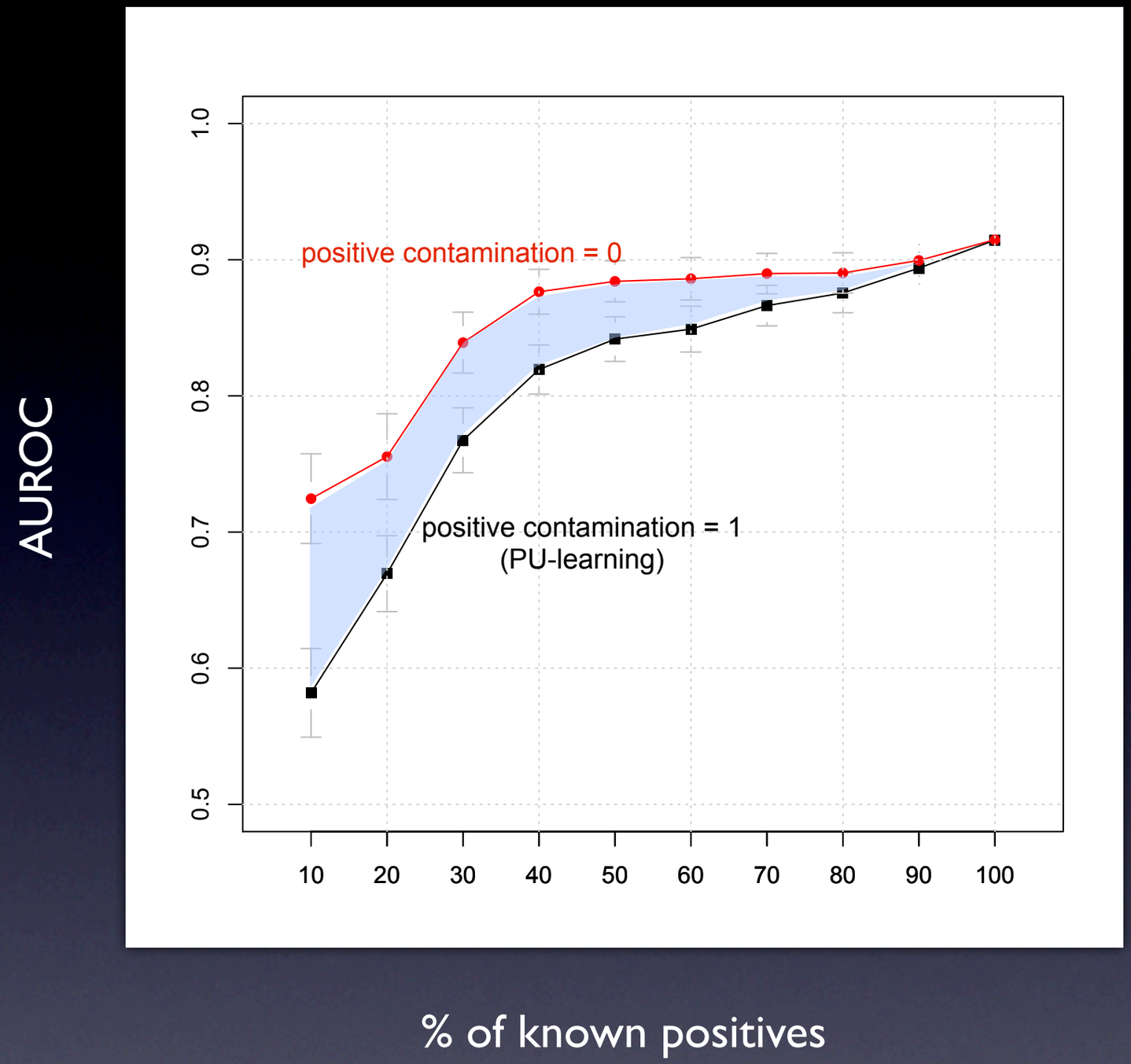
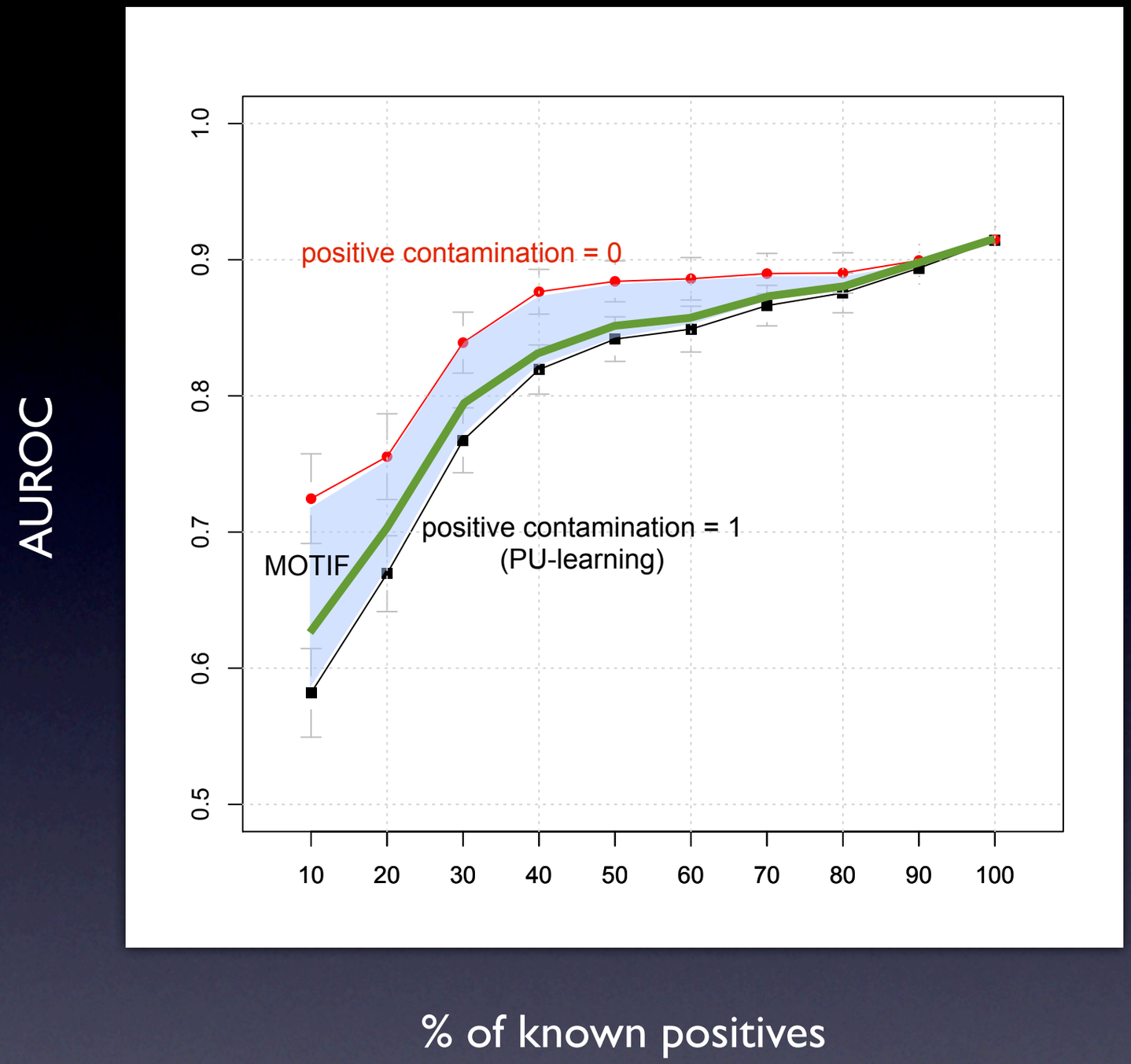




MOTIF selection performance

E.coli dataset [J.J. Faith *et al.*, 2007 and RegulonDB]



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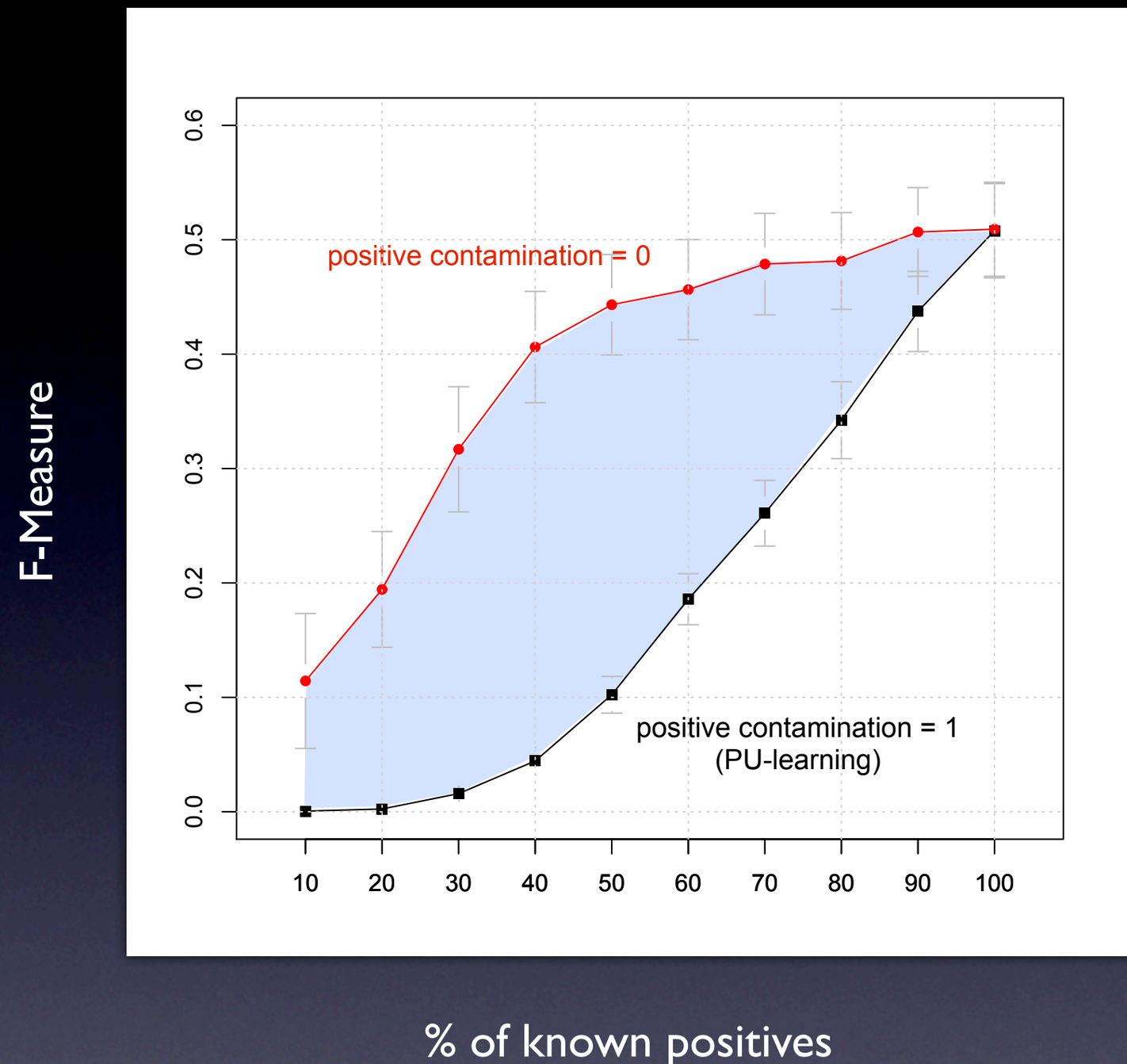
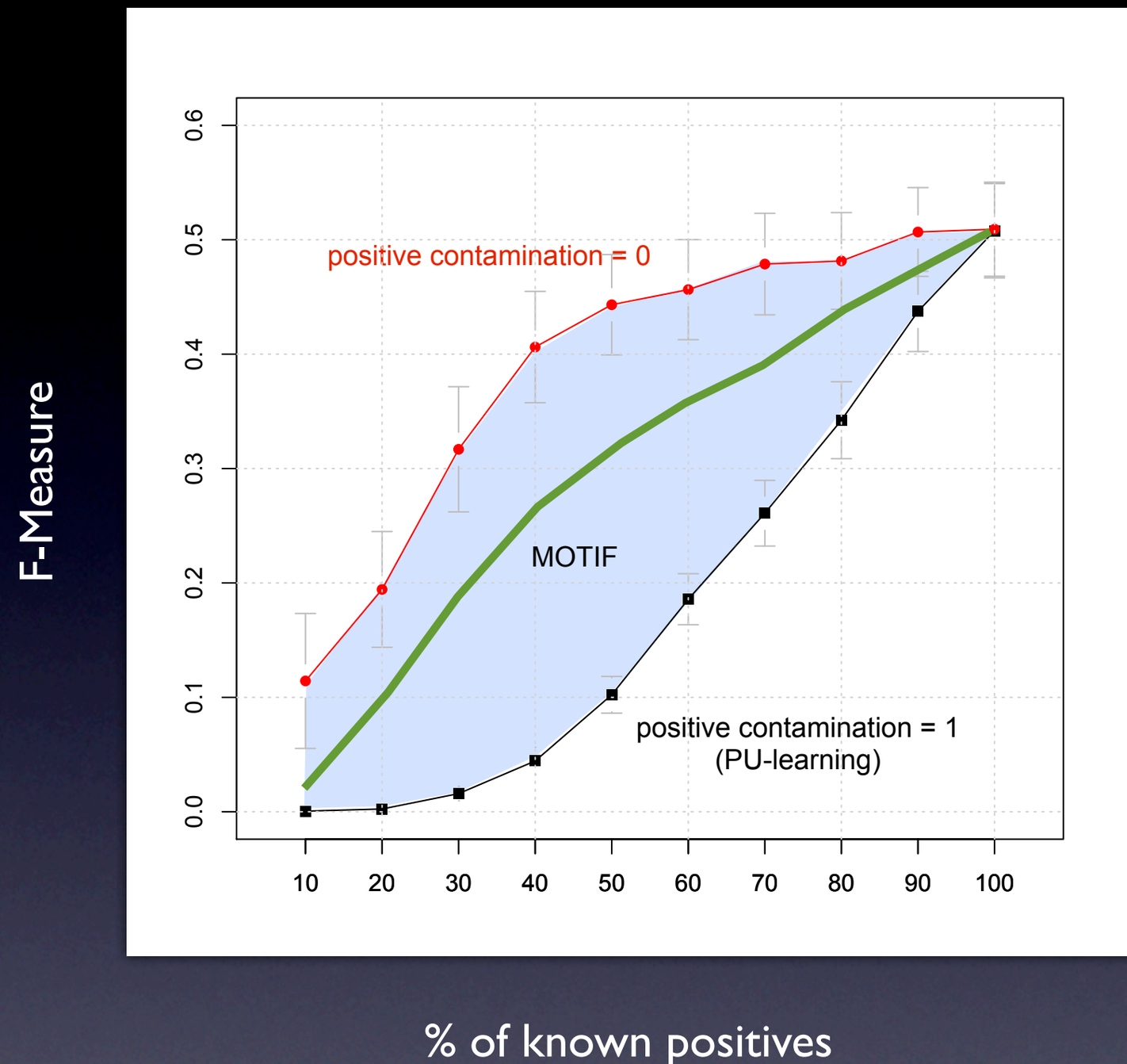


Effect of positive contamination

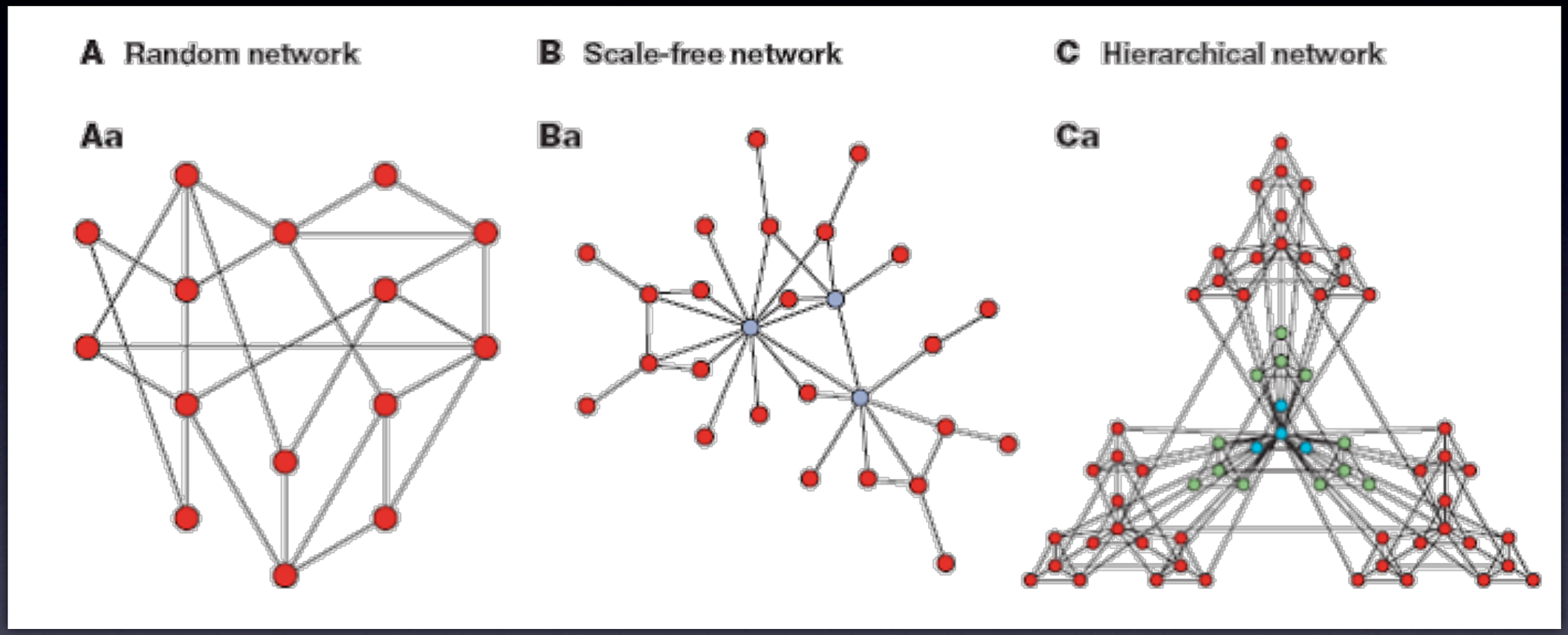
E.coli dataset [J.J. Faith *et al.*, 2007]



Effect of positive contamination

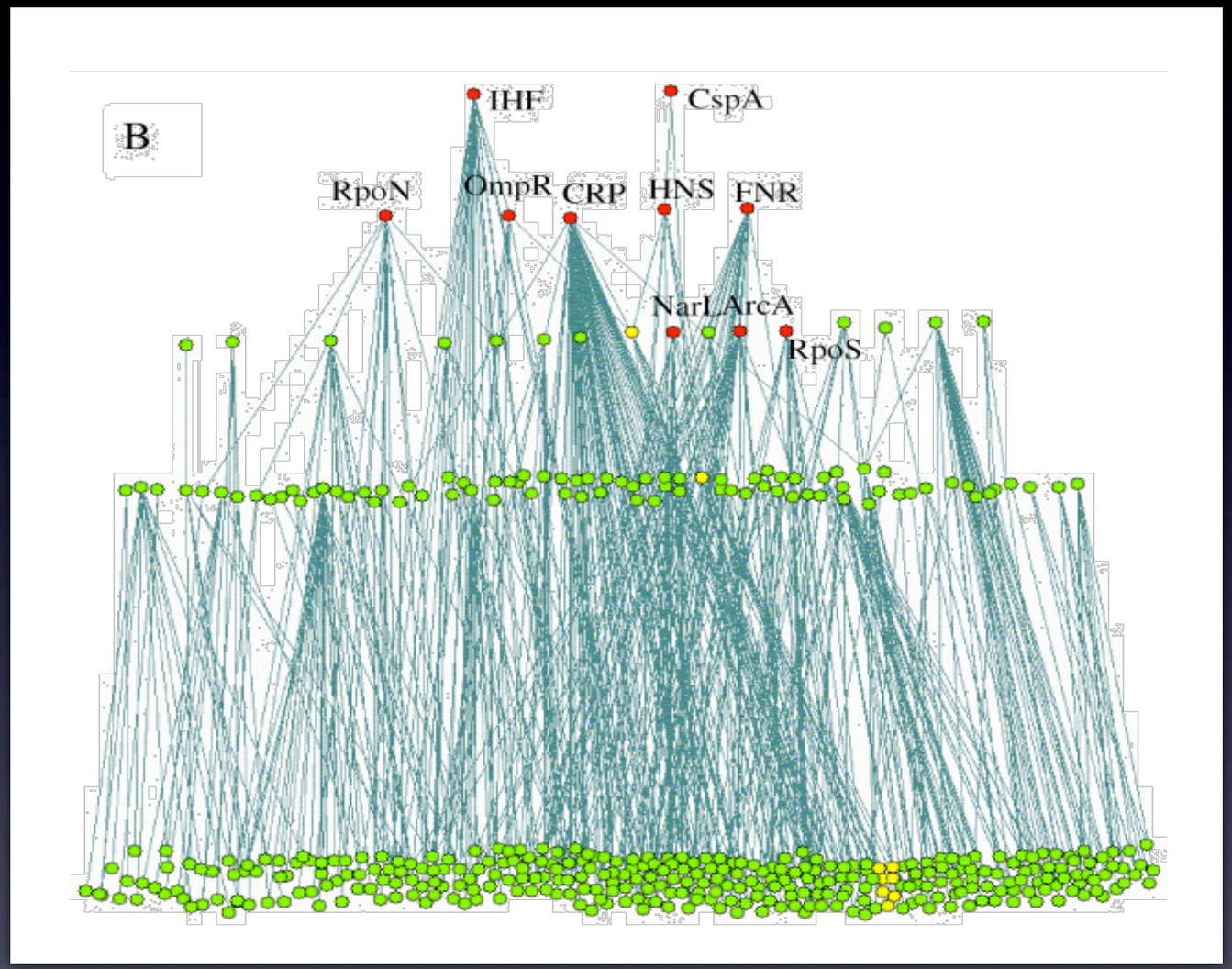
E.coli dataset [J.J. Faith *et al.*, 2007]

Scale free networks



Albert-László Barabási and Zoltán N. Oltvai
Network biology: Understanding the cell's functional organization
Nature Reviews Genetics 5, 101-113 (2004)

Hierarchical networks

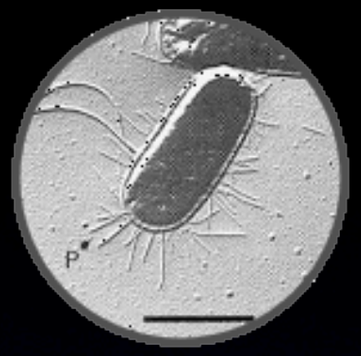


Hong-Wu Ma, Jan Buer, and An-Ping Zeng

Hierarchical structure and modules in the Escherichia coli transcriptional regulatory network revealed by a new top-down approach

BMC Bioinformatics 2004 5:199

Experimental data



- 445 Affymetrix Antisense2 microarray expression profiles for 4345 genes of E.coli [J.J. Faith *et al.*, 2007]
- Data were standardized (i.e. zero mean unit standard deviation)
- Regulations extracted from RegulonDB (v. 5) between 154 Transcription Factors and 1211 genes

Summary and conclusions

- Learning gene regulations is affected by the problem of learning from positive only data
- At least for E.coli
  - The study of positive contamination shows that there is room for new heuristics
  - Topology based heuristics (eg. motifs) have shown promising results.
- Open issues arise on higher level organisms where gene interactions are more complex