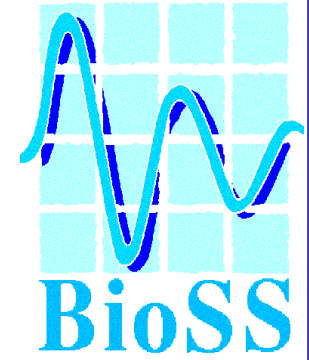


Inferring regulatory networks using multiple data sources.

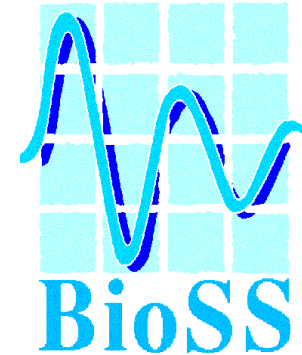
Adriano V. Werhli

Dirk Husmeier



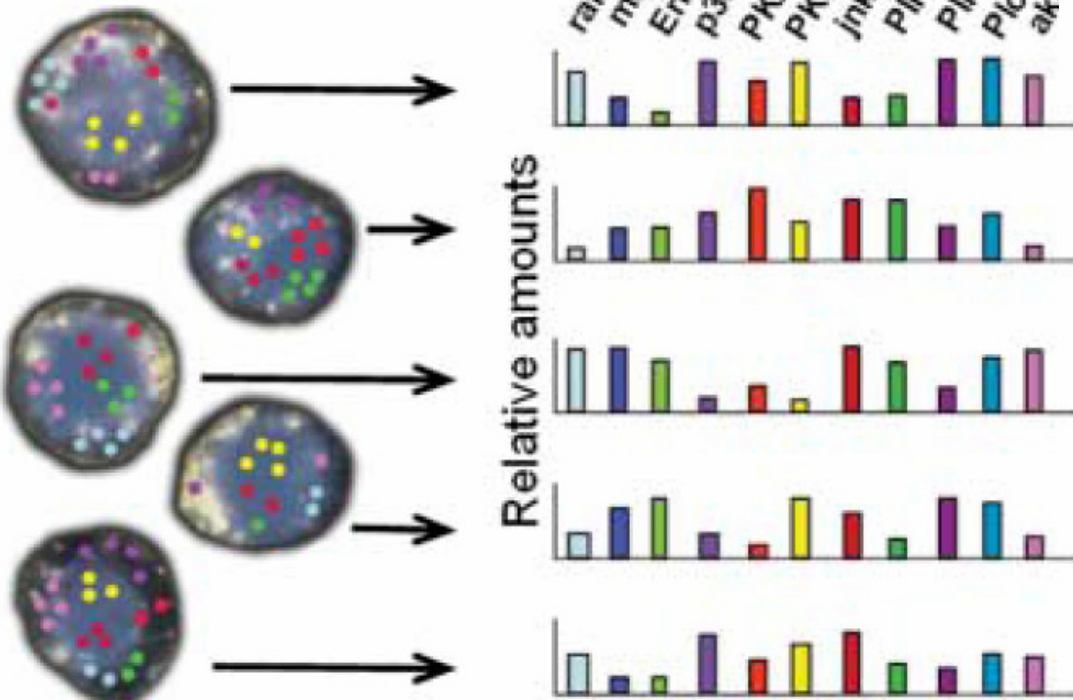
MOTIVATION

Data



2. Multiparameter
Flow Cytometry

3. Correlated phospho-
measures per cell



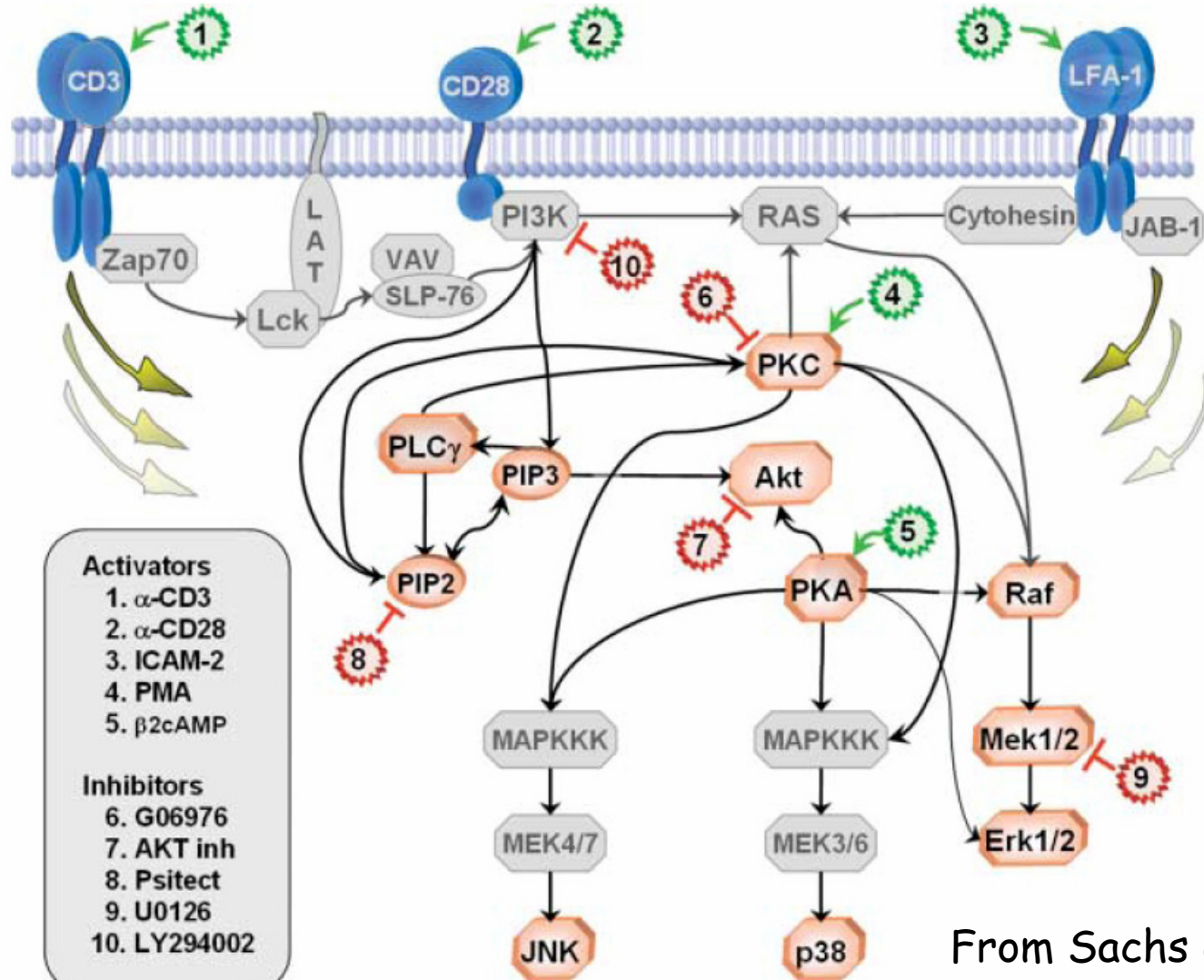
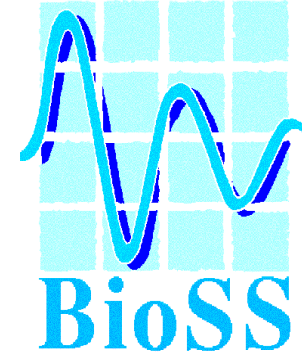
Causal Protein-Signaling Networks Derived from Multiparameter Single-Cell Data

Karen Sachs,^{1*} Omar Perez,^{2*} Dana Pe'er,^{3*}
Douglas A. Lauffenburger,^{1†} Garry P. Nolan^{2†}

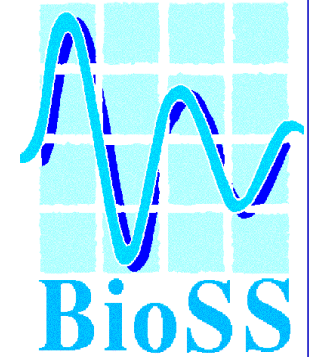
- Intracellular multicolour flow cytometry.
- Measured protein concentrations.
- 11 proteins X 1200 data points.

Accepted regulatory network

Classical Raf signalling network



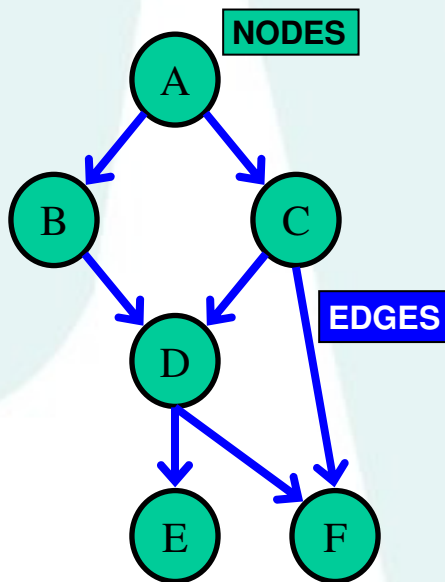
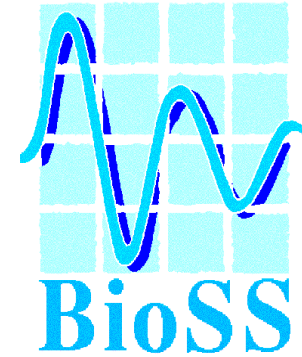
From Sachs et al Science 2005



Can we **reconstruct** the **network** from
the **data**?

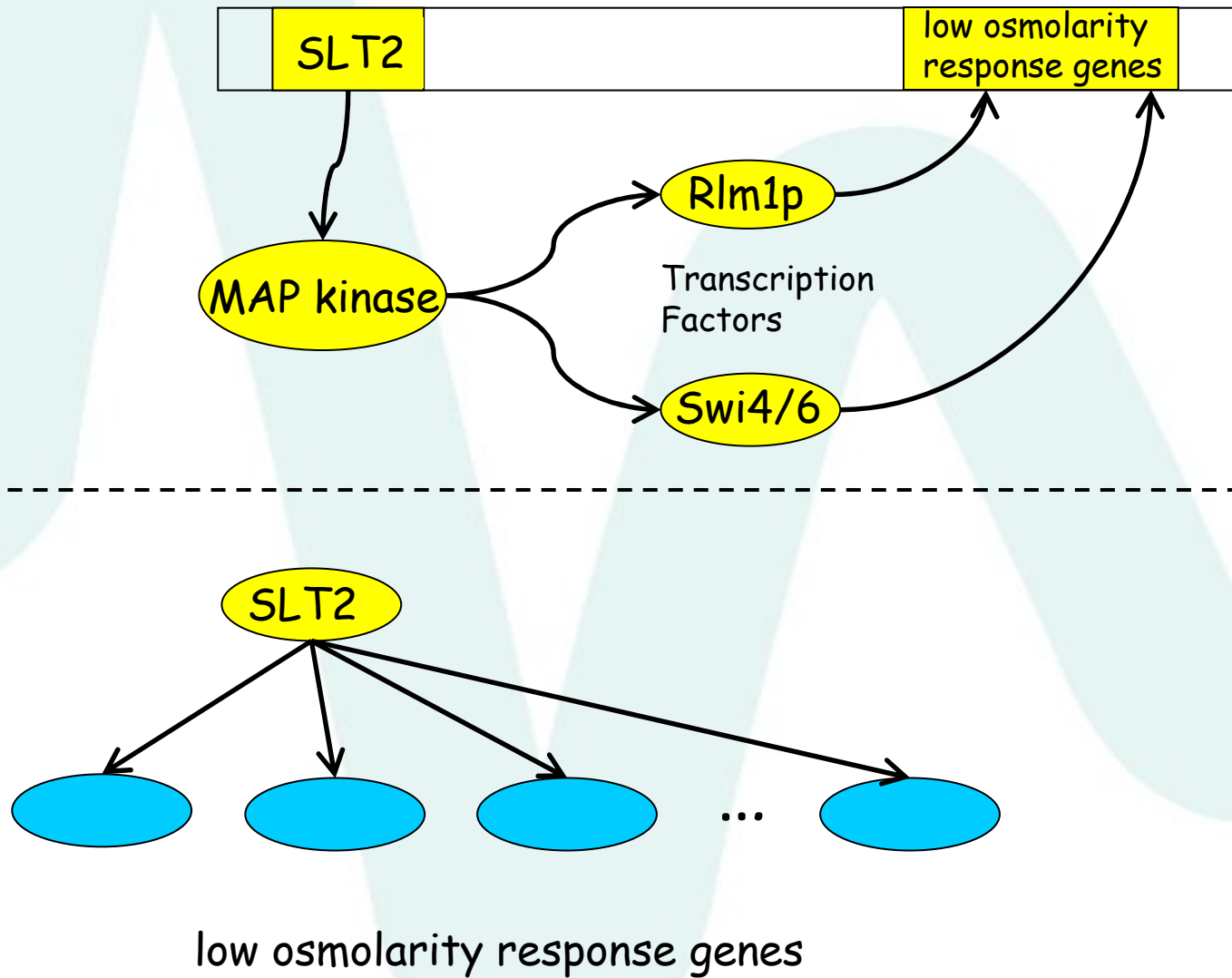
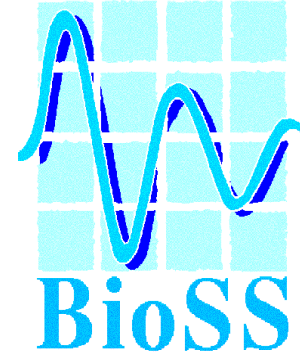
Can we **improve** the reconstructed
network by using **additional sources of
information** as prior biological
knowledge?

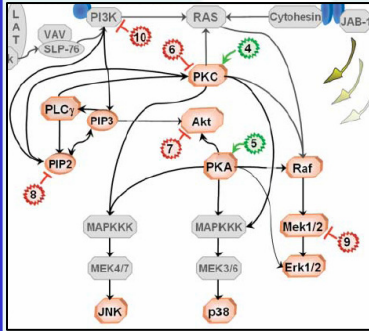
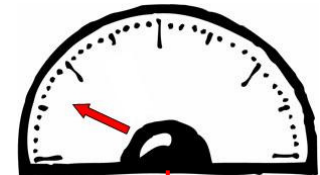
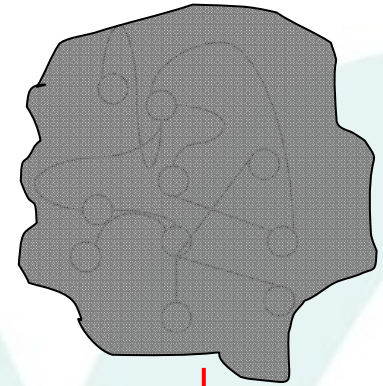
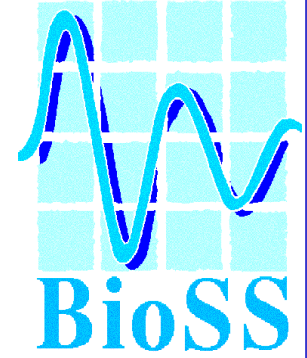
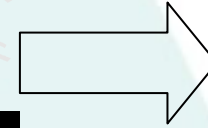
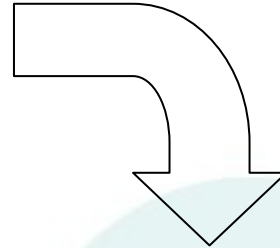
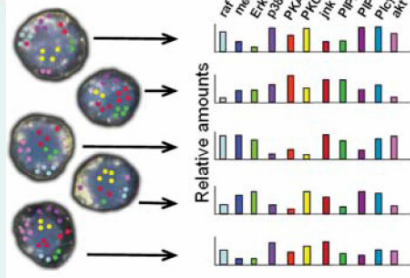
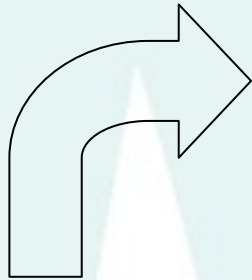
What is a Regulatory network?

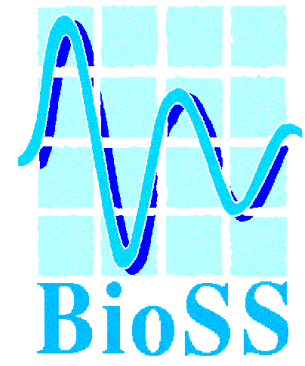
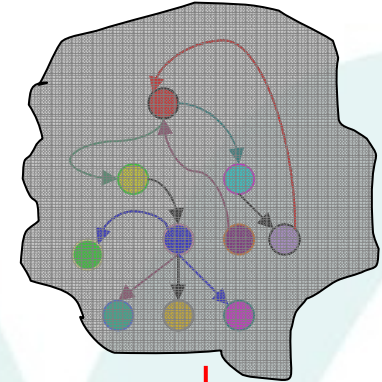
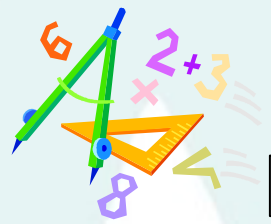
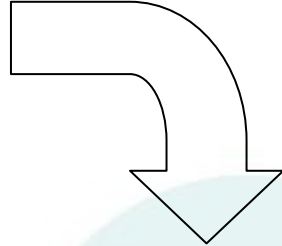
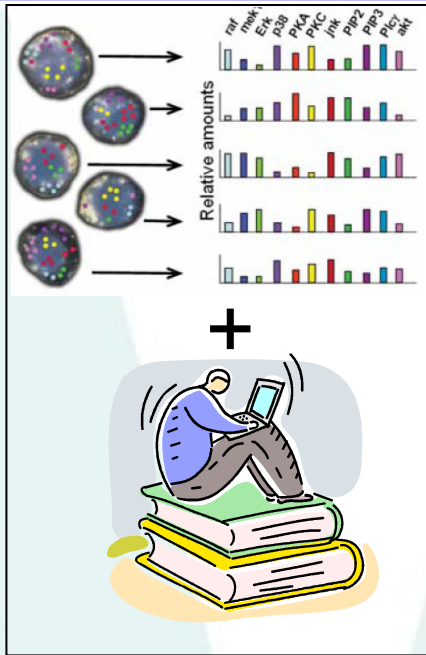
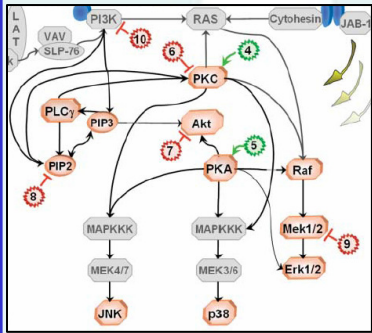


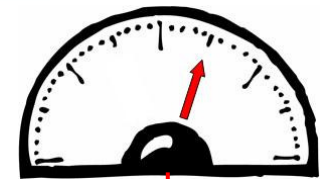
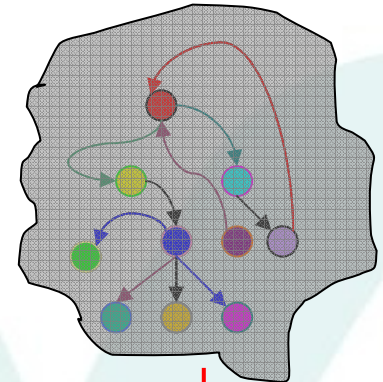
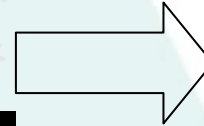
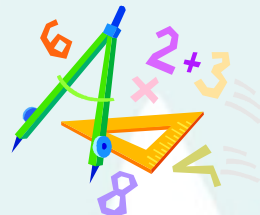
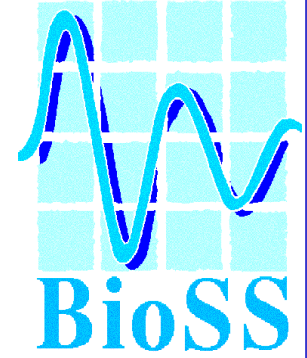
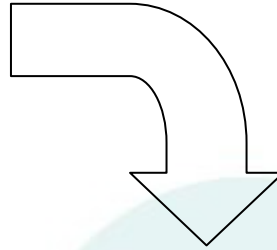
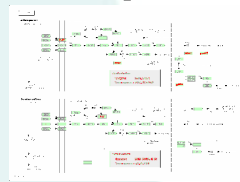
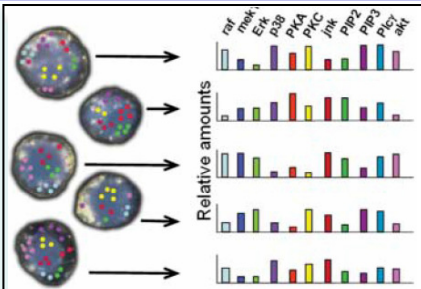
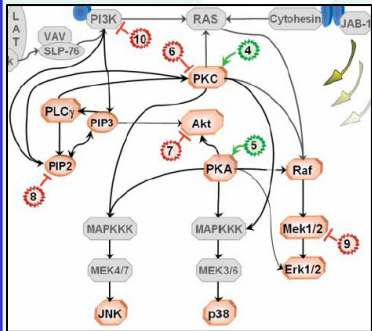
- Set of nodes that regulate each other.
- Edges represent putative causal relationships.
- Only measured elements are represented as nodes.
- Intermediary elements that are not measured are not represented.

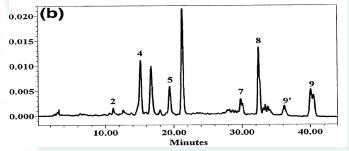
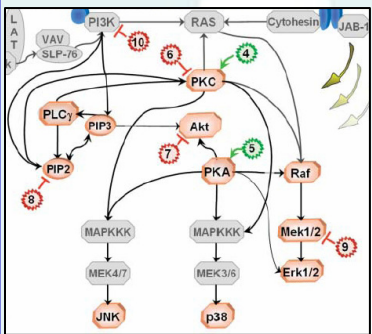
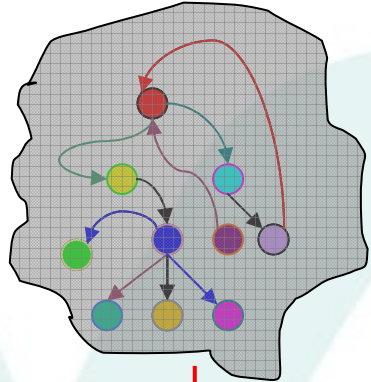
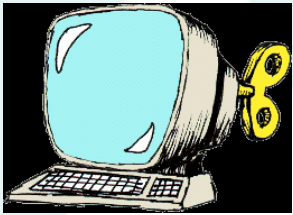
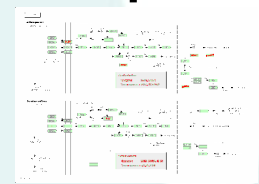
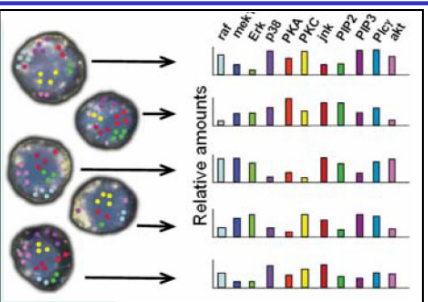
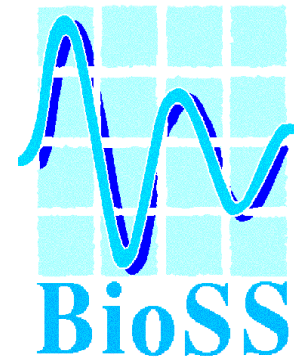
Regulatory network

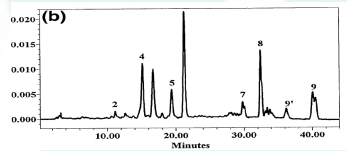
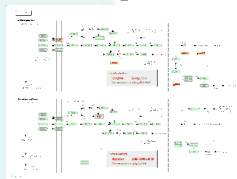
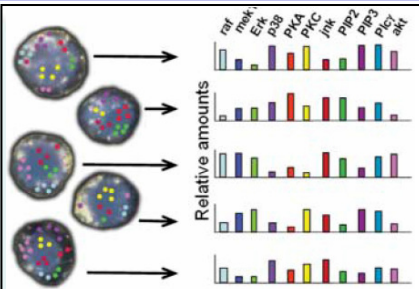
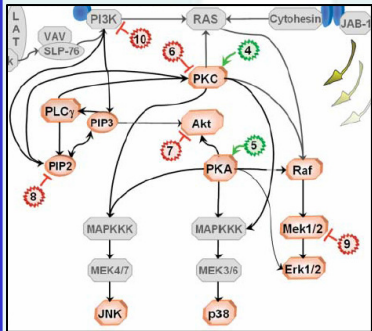






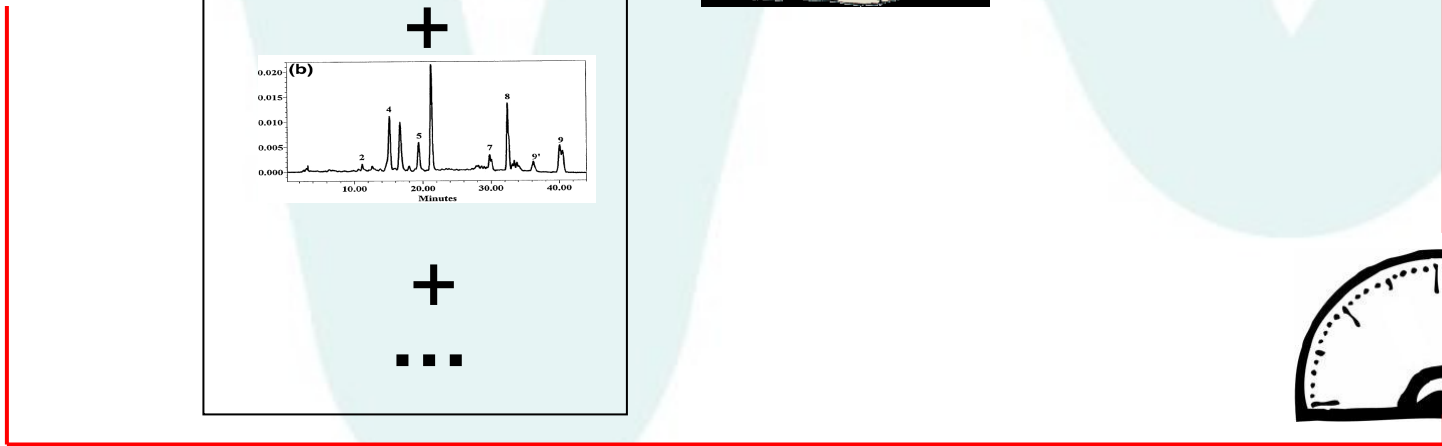
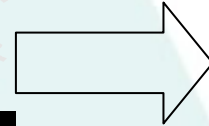
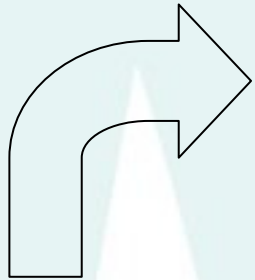
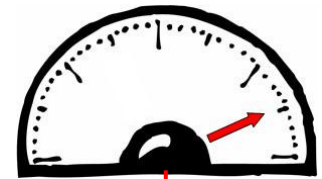
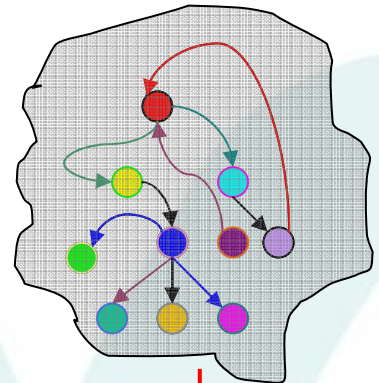
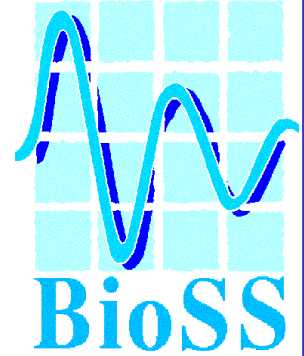
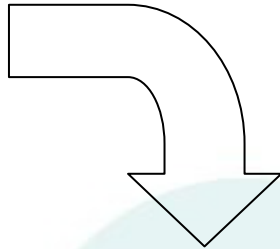


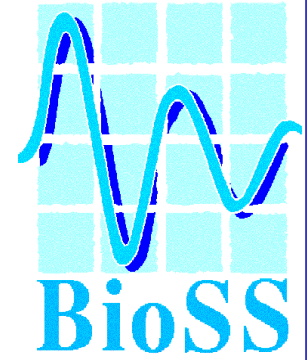




+

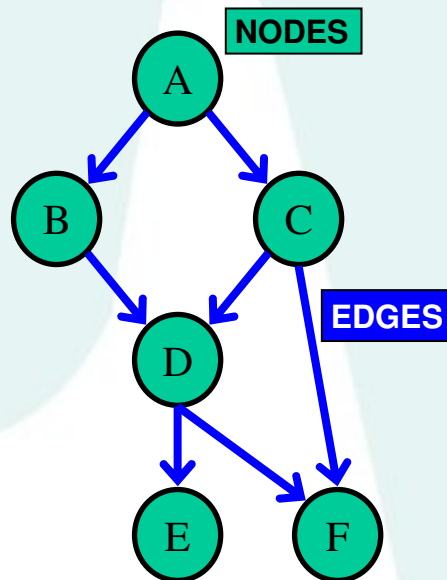
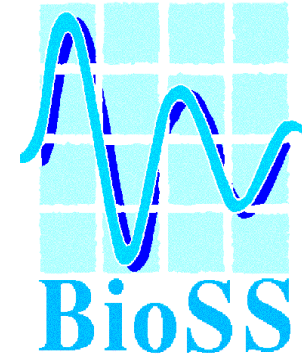
...





Methods

Bayesian networks



$$P(X_1, X_2, \dots, X_n) = \prod_{i=1}^n P(X_i | \mathcal{X}_{pa[i]})$$

Find the best **structure**

$$\mathcal{M}^* = \operatorname{argmax}_{\mathcal{M}} \{P(\mathcal{M} | \mathcal{D})\}$$

Find the best **parameters**

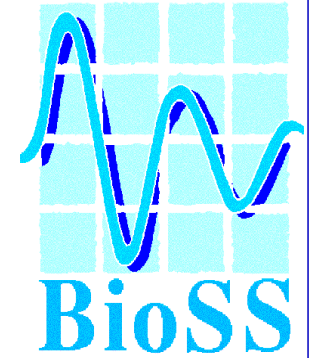
$$\mathbf{q} = \operatorname{argmax}_{\mathbf{q}} \{P(\mathbf{q} | \mathcal{M}^*, \mathcal{D})\}$$

$$P(\mathcal{M} | \mathcal{D}) \propto P(\mathcal{D} | \mathcal{M}) P(\mathcal{M})$$

$$P(\mathcal{D} | \mathcal{M}) = \int P(\mathcal{D} | \mathbf{q}, \mathcal{M}) P(\mathbf{q} | \mathcal{M}) d\mathbf{q}$$

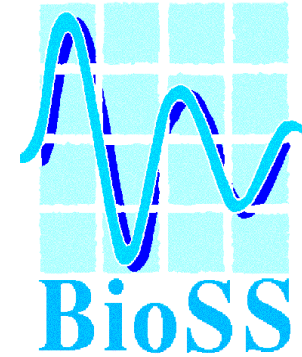
BGe - Bayesian Gaussian equivalence scores

BDe - Bayesian Discretized equivalence scores



One approach would be calculate $P(\mathcal{M}|\mathcal{D})$ to all possible structures \mathcal{M}^*

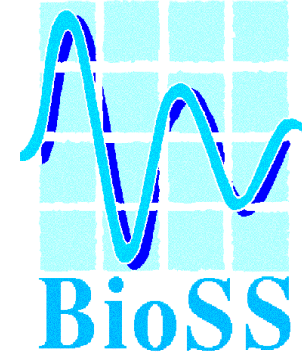
Problems:



One approach would be calculate $P(\mathcal{M}|\mathcal{D})$ to all possible structures \mathcal{M}^*

Problems:

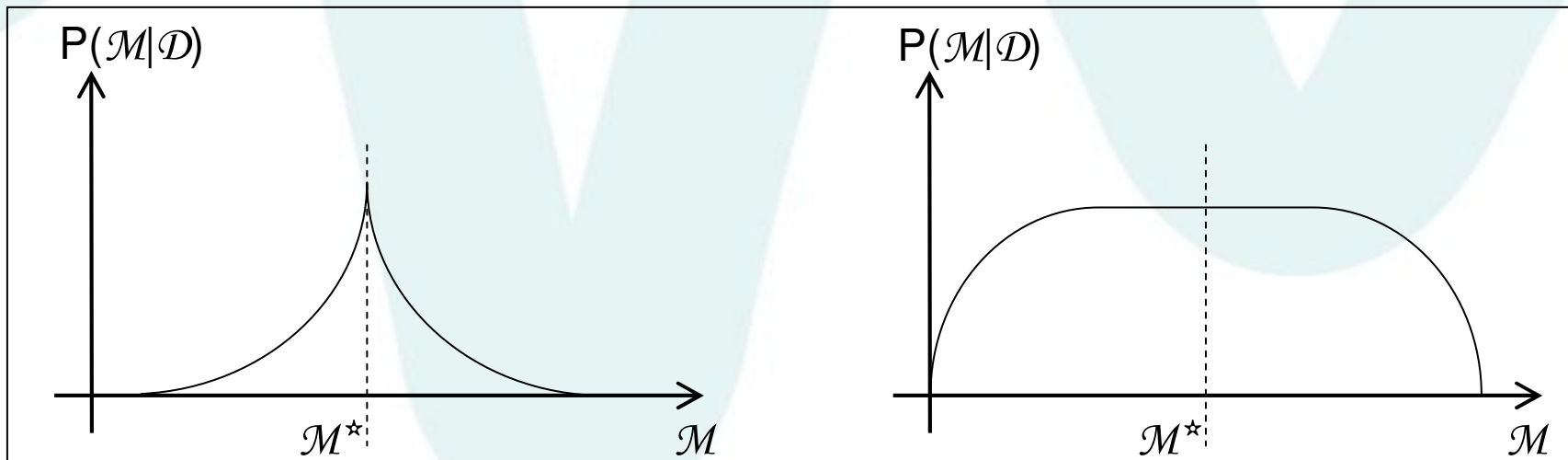
Number of nodes	2	4	6	8	10
Number of topologies	3	543	3.7×10^6	7.8×10^{11}	4.2×10^{18}



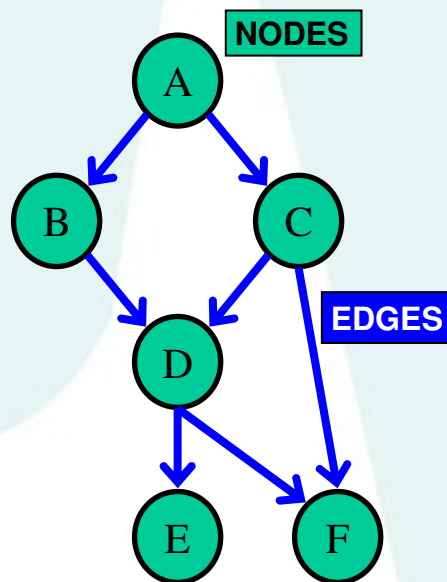
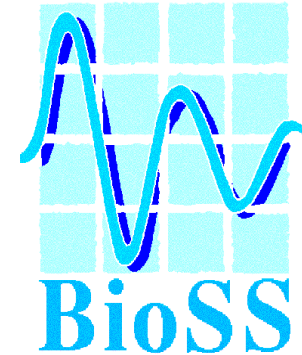
One approach would be calculate $P(\mathcal{M}|\mathcal{D})$ to all possible structures \mathcal{M}^*

Problems:

Number of nodes	2	4	6	8	10
Number of topologies	3	543	3.7×10^6	7.8×10^{11}	4.2×10^{18}



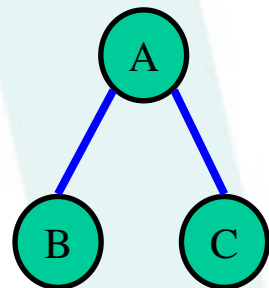
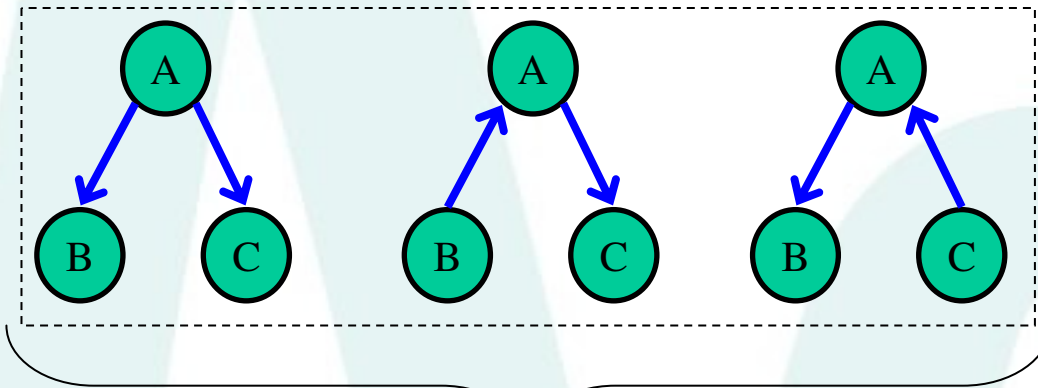
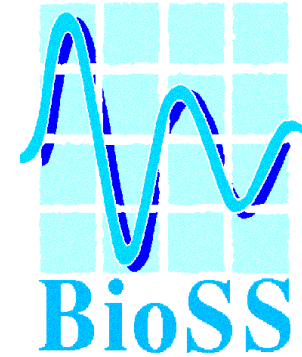
Bayesian networks + MCMC



- Marriage between graph theory and probability theory.
- It is possible to score a network in light of data. We can assert how well a particular network explains some observed data.
- We use Markov Chain Monte Carlo (MCMC) for sampling networks.
- There are problems with **equivalence** classes...

Bayesian networks

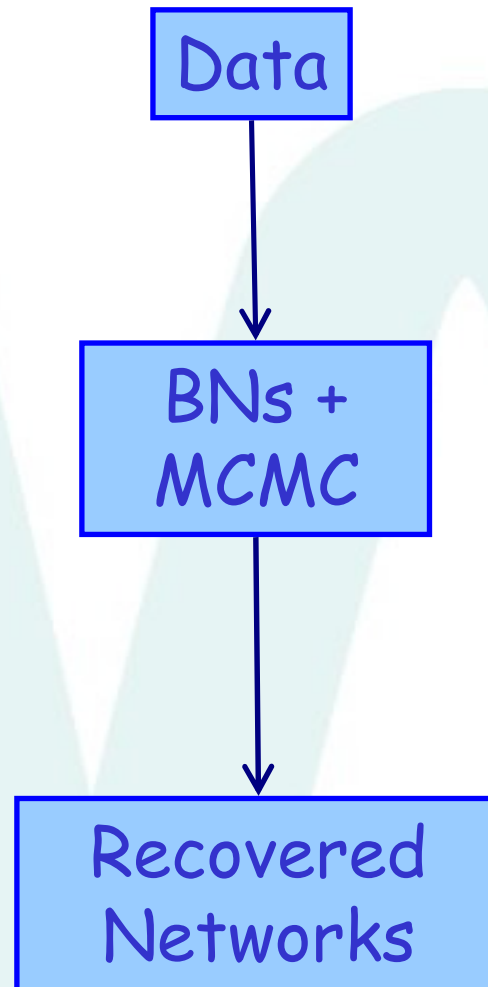
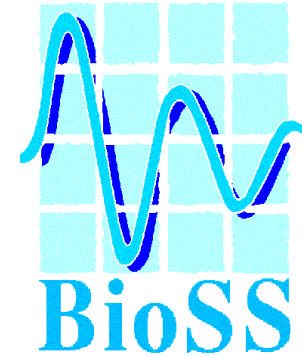
Equivalence classes

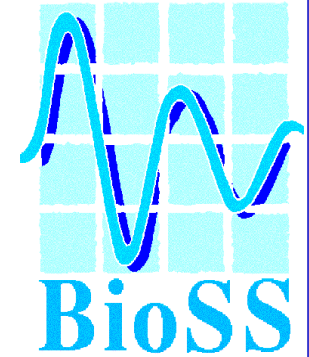


- Score of first three networks are the same.
- They can't be distinguished in light of the data.
- We can only learn the undirected graph.
- Unless... we use interventions or **prior knowledge**.

Bayesian networks

Summary

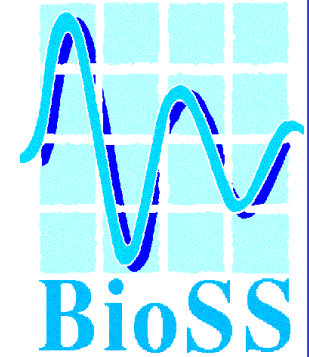




How can biological prior knowledge be integrated in the Bayesian networks?

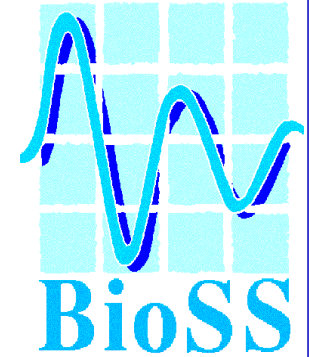
MCMC and Priors

$$A = \min \left\{ \frac{P(D|G')P(G')Q(G|G')}{P(D|G)P(G)Q(G'|G)}, 1 \right\}$$

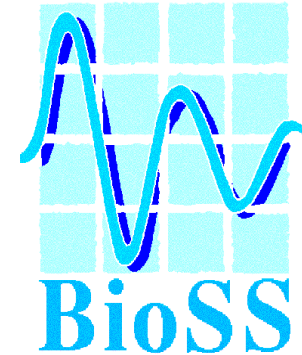


MCMC and Priors

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MCMC and Priors



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We model the prior with the Gibbs distribution:

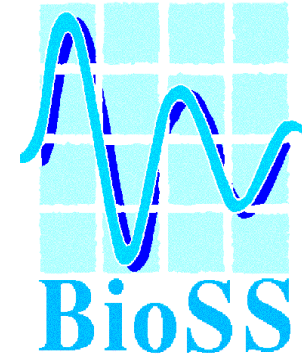
$$P(G|\beta) = \frac{e^{-\beta E(G)}}{Z(\beta)}$$

Where the partition function is:

$$Z(\beta) = \sum_{G \in \mathcal{G}} e^{-\beta E(G)}$$

Imoto,S., Higuchi,T., Goto,T., Kuhara,S. and Miyano,S. (2003) Combining microarrays and biological knowledge for estimating gene networks via Bayesian networks. *Proceedings IEEE Computer Society Bioinformatics Conference, (CSB'03)*, 104–113.

MCMC and Priors



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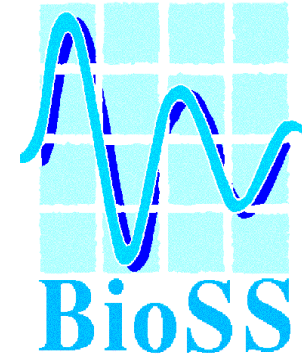
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Hyperparameter

Imoto,S., Higuchi,T., Goto,T., Kuhara,S. and Miyano,S. (2003) Combining microarrays and biological knowledge for estimating gene networks via Bayesian networks. *Proceedings IEEE Computer Society Bioinformatics Conference, (CSB'03)*, 104–113.

MCMC and Priors



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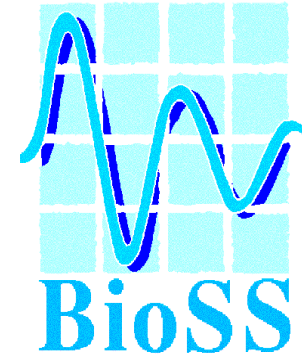
Where the partition function is:

$$Z(\beta) = \sum_{G \in \mathcal{G}} e^{-\beta E(G)}$$

The energy

Imoto,S., Higuchi,T., Goto,T., Kuhara,S. and Miyano,S. (2003) Combining microarrays and biological knowledge for estimating gene networks via Bayesian networks. *Proceedings IEEE Computer Society Bioinformatics Conference, (CSB'03)*, 104–113.

Biological Prior Knowledge



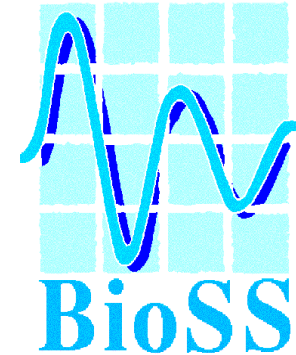
Biological prior knowledge matrix

$$B = \begin{pmatrix} b_{11} & b_{12} & b_{13} & \cdots & b_{1n} \\ b_{21} & b_{22} & b_{23} & \cdots & b_{2n} \\ b_{31} & b_{32} & b_{33} & \cdots & b_{3n} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ b_{n1} & b_{n2} & b_{n3} & \cdots & b_{nn} \end{pmatrix}$$

$$0 \leq b_{ij} \leq 1$$

b_{ij} Indicates some knowledge about the relationship between genes i and j

Biological Prior Knowledge



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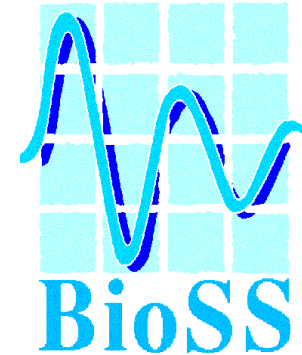
Define the energy of a Graph G

$$G = \begin{pmatrix} g_{11} & g_{12} & g_{13} & \cdots & g_{1n} \\ g_{21} & g_{22} & g_{23} & \cdots & g_{2n} \\ g_{31} & g_{32} & g_{33} & \cdots & g_{3n} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ g_{n1} & g_{n2} & g_{n3} & \cdots & g_{nn} \end{pmatrix}$$

$$g_{ij} \in \{0, 1\}$$

$$E(G) = \sum_{i,j=1}^N |B_{i,j} - G_{i,j}|$$

MCMC with **one** source of prior biological knowledge



Sample graph and the hyperparameter β .

$$A = \min \left\{ \frac{P(D|G')P(G'|\beta')P(\beta')}{P(D|G)P(G|\beta)P(\beta)}, 1 \right\}$$

Separate in two samples to improve the acceptance:

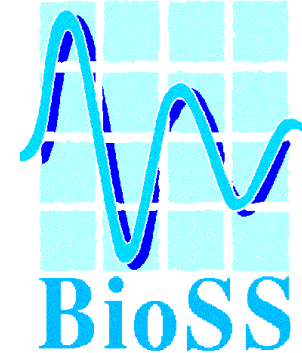
1. *Sample graph with β fixed.*
2. *Sample β with graph fixed.*

$$A_1 = \min \left\{ \frac{P(D|G')P(G'|\beta)}{P(D|G)P(G|\beta)}, 1 \right\}$$

$$A_2 = \min \left\{ \frac{P(G|\beta')P(\beta')}{P(G|\beta)P(\beta)}, 1 \right\}$$

$$A_2 = \min \left\{ \frac{e^{-\beta' E(G)} Z(\beta)}{Z(\beta') e^{-\beta E(G)}}, 1 \right\} = \min \left\{ e^{-E(G)(\beta' - \beta)} \frac{Z(\beta)}{Z(\beta')}, 1 \right\}$$

MCMC with **one** source of prior biological knowledge



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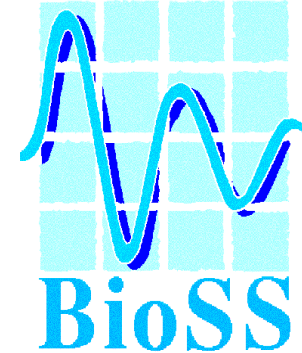
BGe
BDe

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MCMC with **one** source of prior biological knowledge



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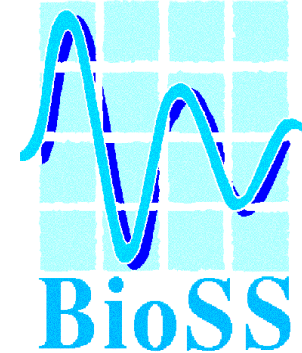
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$$A_2 = \min \left\{ \frac{P(G|\beta')P(\beta')}{P(G|\beta)P(\beta)}, 1 \right\}$$

$$e^{-\beta(E(G')-E(G))}$$

$$A_2 = \min \left\{ \frac{e^{-\beta' E(G)}}{Z(\beta')} \frac{Z(\beta)}{e^{-\beta E(G)}}, 1 \right\} = \min \left\{ e^{-E(G)(\beta'-\beta)} \frac{Z(\beta)}{Z(\beta')}, 1 \right\}$$

MCMC with **one** source of prior biological knowledge



Sample graph and the hyperparameter β .

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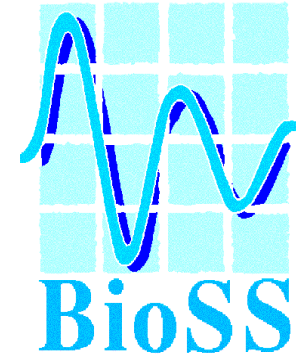
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$$e^{-\beta(E(G')-E(G))}$$

$$A_2 = \min \left\{ \frac{P(G|\beta')P(\beta')}{P(G|\beta)P(\beta)}, 1 \right\}$$

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MCMC with **one** source of prior biological knowledge



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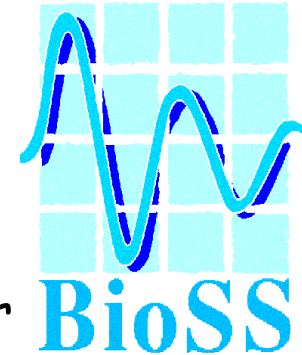
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MCMC with **one** source of prior biological knowledge



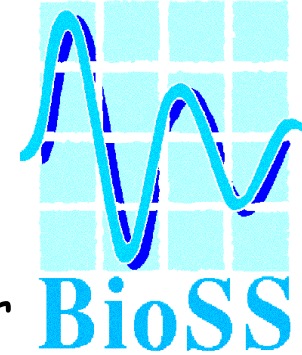
- How to calculate the partition function? How to sum over all possible graphs?

$$E(G) = \sum_{i,j=1}^N |B_{i,j} - G_{i,j}|$$

Rewrite the energy as a function of nodes and parent sets

$$E(G) = \sum_{n=1}^N \mathcal{E}(n, \pi_n [G])$$

MCMC with **one** source of prior biological knowledge



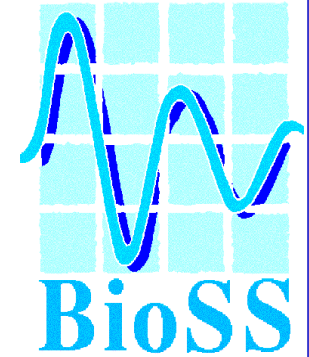
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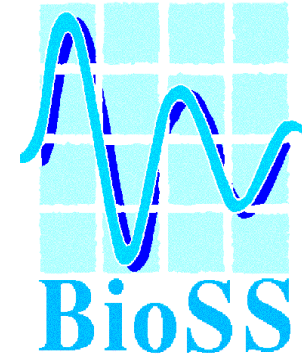
$$E(G) = \sum_{n=1}^N \mathcal{E}(n, \pi_n [G])$$

$$\begin{aligned} Z &= \sum_{G \in \mathcal{G}} e^{-\beta E(G)} \\ &\approx \sum_{\pi_1} \dots \sum_{\pi_N} e^{-\beta(\mathcal{E}(1, \pi_1) + \dots + \mathcal{E}(N, \pi_N))} \\ &\approx \prod_n \sum_{\pi_n} e^{-\beta \mathcal{E}(n, \pi_n)} \end{aligned}$$



How can we integrate **multiple** sources
of biological prior knowledge?

MCMC with **multiple** sources of prior biological knowledge



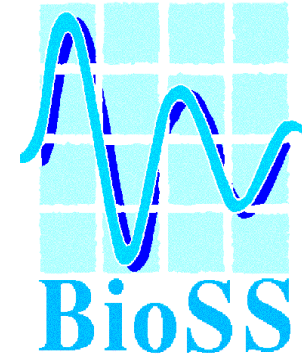
We model the prior with the Gibbs distribution:

$$P(G|\beta_1, \beta_2) = \frac{e^{-\{E(G_1)\beta_1 + E(G_2)\beta_2\}}}{Z(\beta_1, \beta_2)}$$

Where the partition function is:

$$Z(\beta_1, \beta_2) = \sum_{G \in \mathcal{G}} e^{-\{E(G_1)\beta_1 + E(G_2)\beta_2\}}$$

MCMC with **multiple** sources of prior biological knowledge



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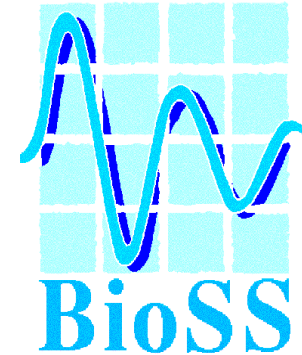
$$Z(\beta_1, \beta_2) = \sum_{G \in \mathcal{G}} e^{-\{E(G_1)\beta_1 + E(G_2)\beta_2\}}$$

$$E_1(G) = \sum_{n=1}^N \mathcal{E}_1(n, \pi_n[G])$$

$$E_2(G) = \sum_{n=1}^N \mathcal{E}_2(n, \pi_n[G])$$

$$\begin{aligned} Z &= \sum_{G \in \mathcal{G}} e^{-\{\beta_1 E_1(G) + \beta_2 E_2(G)\}} \\ &\approx \sum_{\pi_1} \dots \sum_{\pi_N} e^{-\{\beta_1 [\mathcal{E}_1(1, \pi_1) + \dots + \mathcal{E}_1(N, \pi_N)] + \beta_2 [\mathcal{E}_2(1, \pi_1) + \dots + \mathcal{E}_2(N, \pi_N)]\}} \\ &\approx \prod_n \sum_{\pi_n} e^{-\{\beta_1 \mathcal{E}_1(n, \pi_n) + \beta_2 \mathcal{E}_2(n, \pi_n)\}} \end{aligned}$$

MCMC with **multiple** sources of prior biological knowledge



Sample graph and the parameters β_1 and β_2

$$A = \min \left\{ \frac{P(D|G')P(G'|\beta'_1, \beta'_2)}{P(D|G)P(G|\beta_1, \beta_2)}, 1 \right\}$$

Separate in three samples to improve the acceptance:

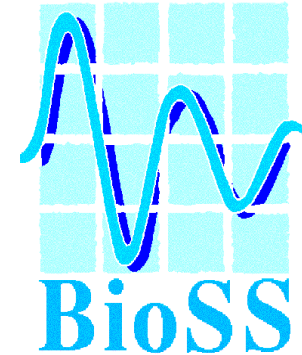
1. *Sample graph with β_1 and β_2 fixed.*
2. *Sample β_1 with graph and β_2 fixed.*
3. *Sample β_2 with graph and β_1 fixed.*

$$A_1 = \min \left\{ \frac{P(D|G')P(G'|\beta_1, \beta_2)}{P(D|G)P(G|\beta_1, \beta_2)}, 1 \right\}$$

$$A_2 = \min \left\{ \frac{P(G|\beta'_1, \beta_2)}{P(G|\beta_1, \beta_2)}, 1 \right\}$$

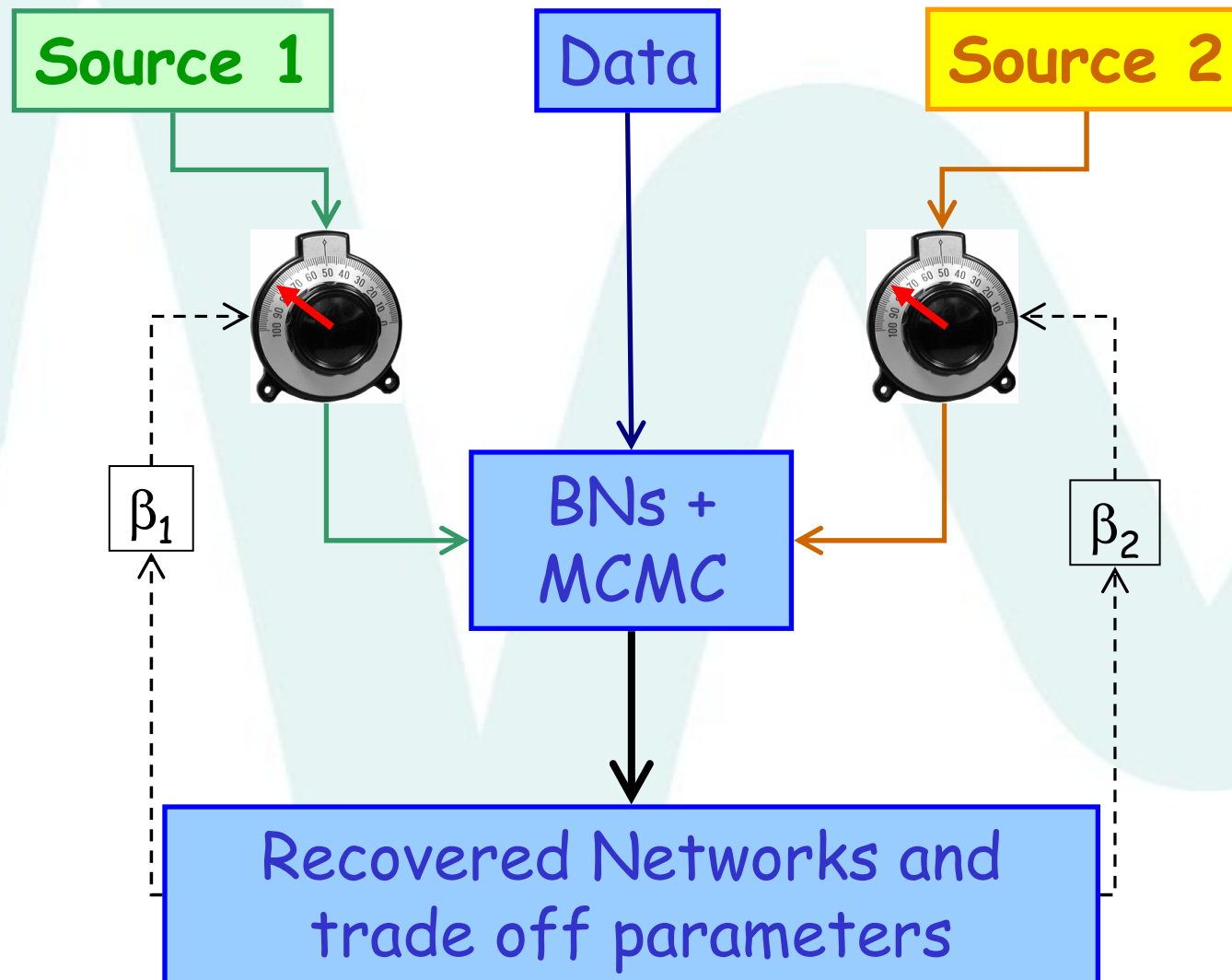
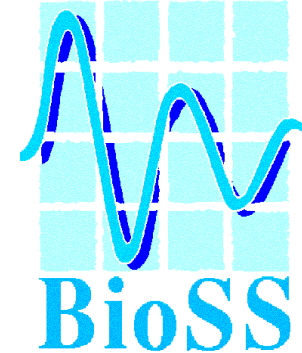
$$A_3 = \min \left\{ \frac{P(G|\beta_1, \beta'_2)}{P(G|\beta_1, \beta_2)}, 1 \right\}$$

Bayesian networks with prior biological knowledge

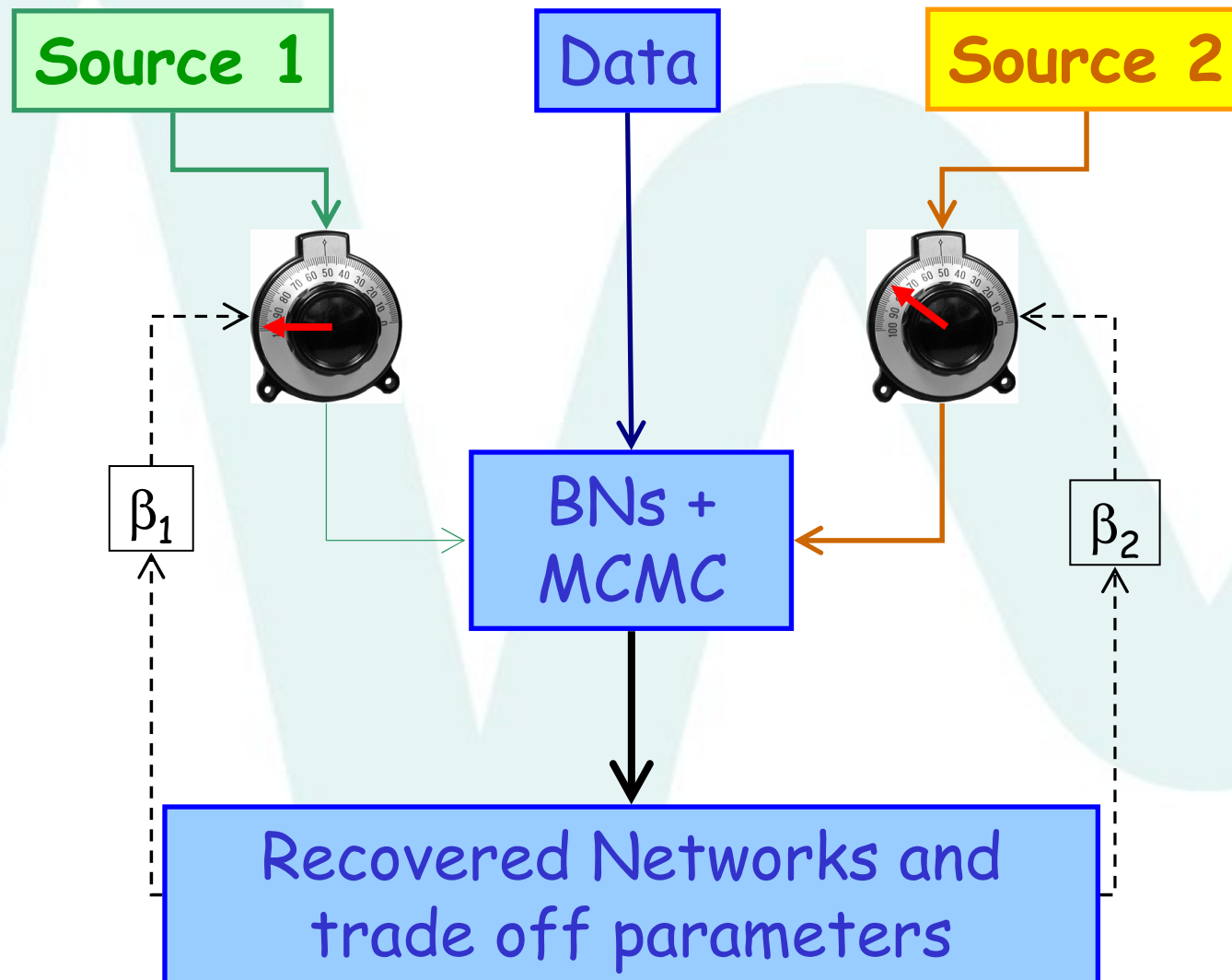
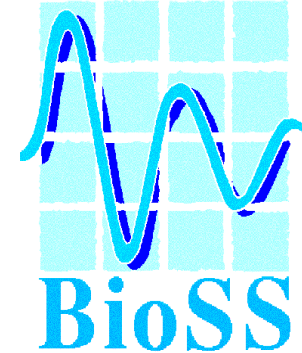


- Prior biological knowledge: Information about the interaction between nodes.
- In our simulations we use two distinct sources of biological prior knowledge.
- Each source of biological prior knowledge is associated with its own **trade-off hyperparameter**: β_1 and β_2 .
- Trade off hyperparameter indicates how much biological prior information is used.
- Trade off hyperparameters are sampled. They are **not** set by the user!

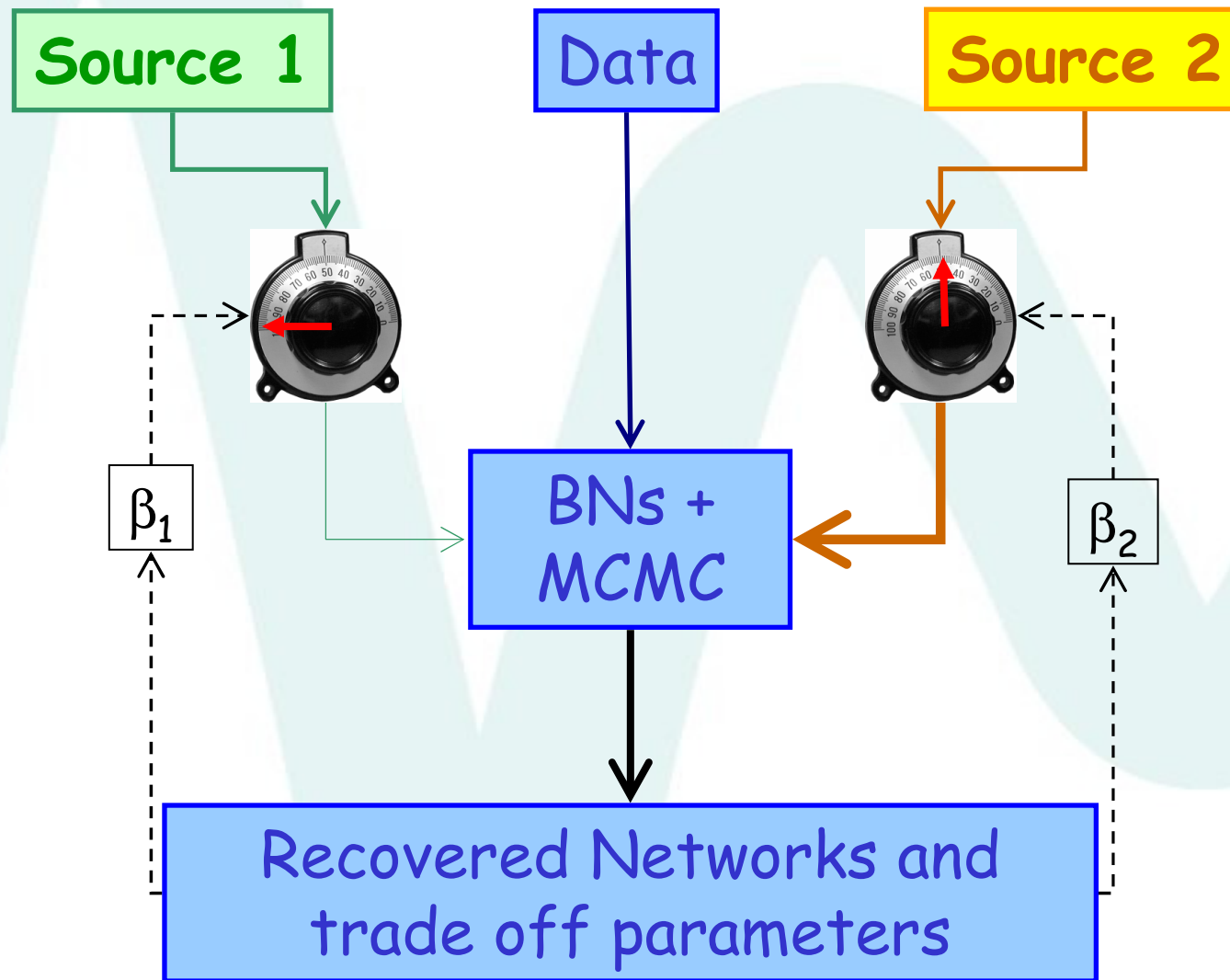
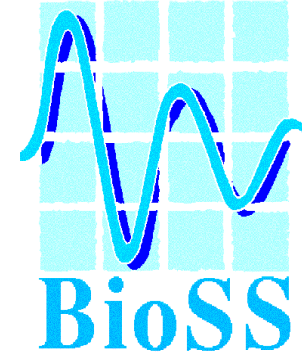
Bayesian networks with two sources of prior

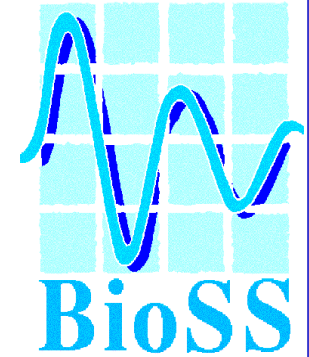


Bayesian networks with two sources of prior



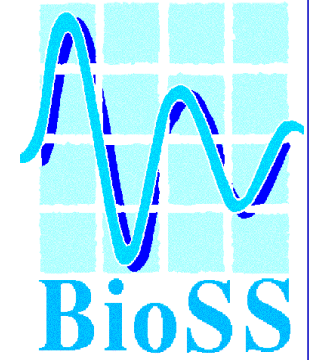
Bayesian networks with two sources of prior





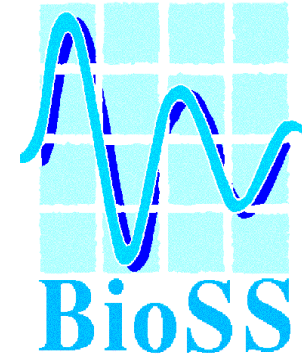
I presented the method and how it is supposed to work.

Is it what we get when applying it to real data?



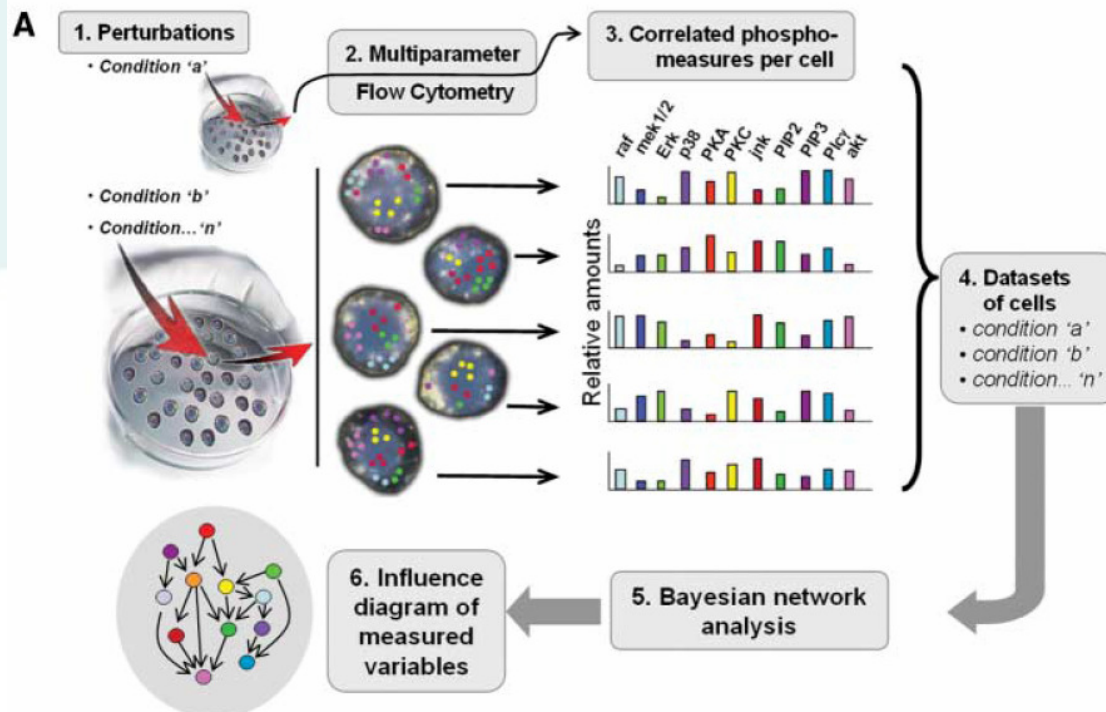
Application

The data



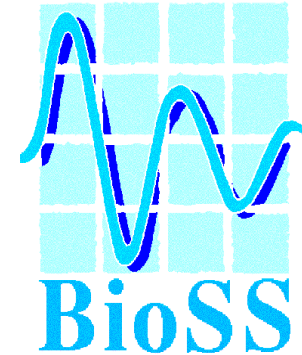
Causal Protein-Signaling Networks Derived from Multiparameter Single-Cell Data

Karen Sachs,^{1*} Omar Perez,^{2*} Dana Pe'er,^{3*}
Douglas A. Lauffenburger,^{1†} Garry P. Nolan^{2†}



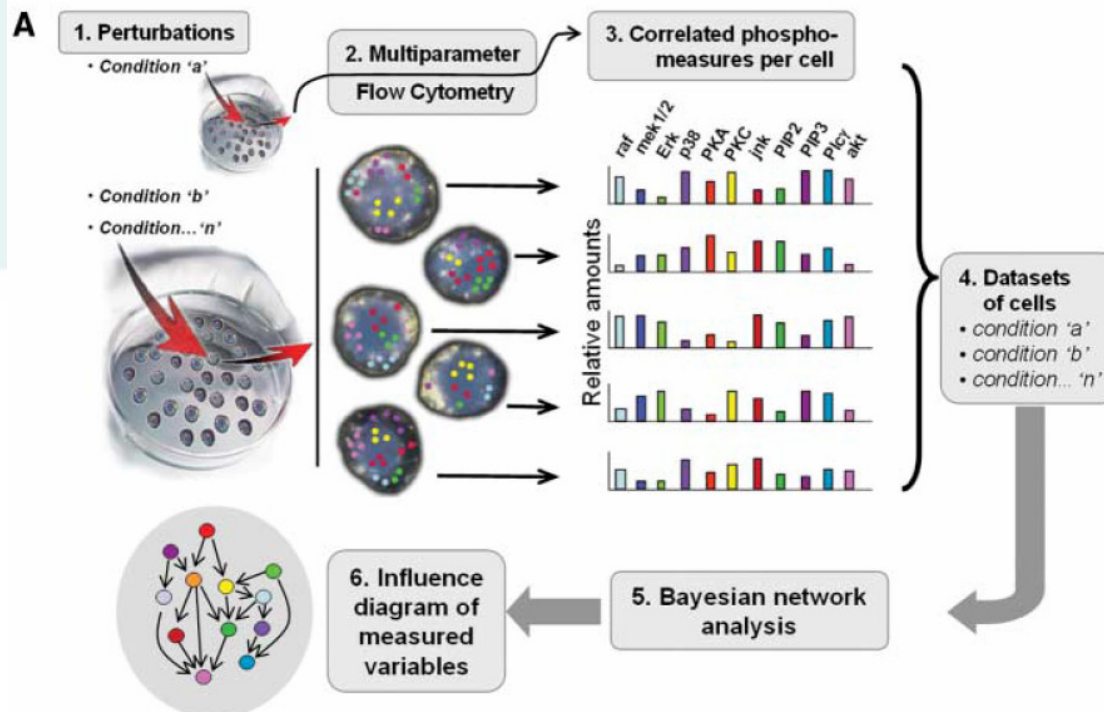
- Data available:
 - Intracellular multicolour flow cytometry.
 - Measured protein concentrations.
 - 11 X 1200 data points.
- We sample 5 data sets with 100 data points each.

The data



Causal Protein-Signaling Networks Derived from Multiparameter Single-Cell Data

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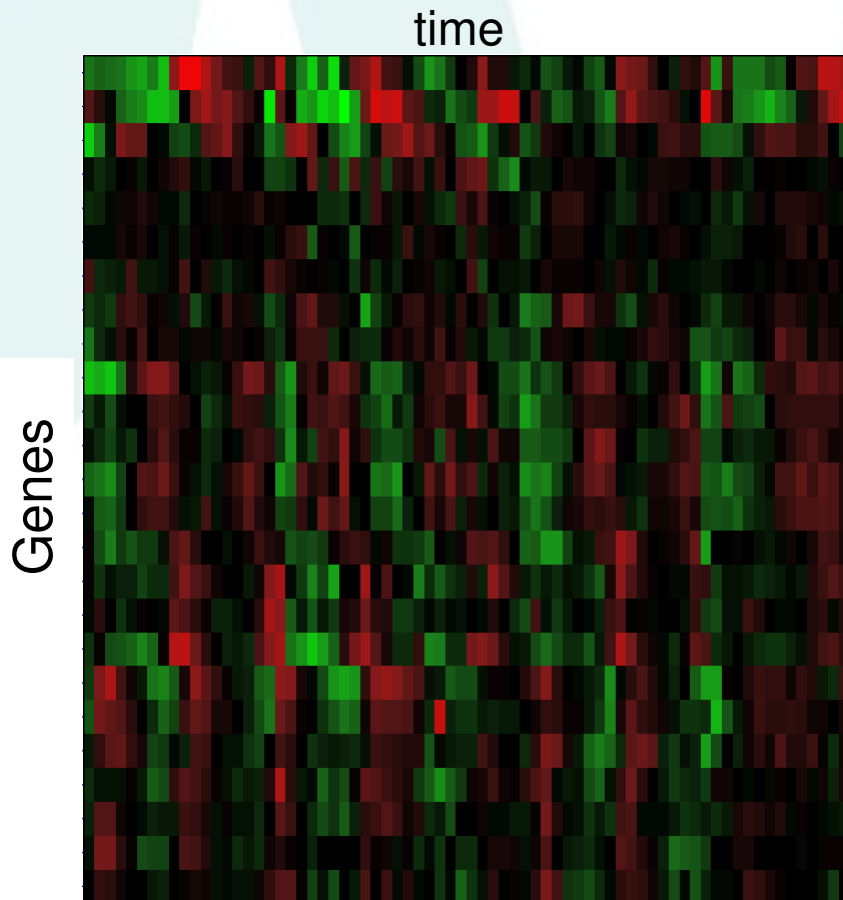
Why we don't use all the data?

Microarray example

Spellman et al (1998)

Cell cycle

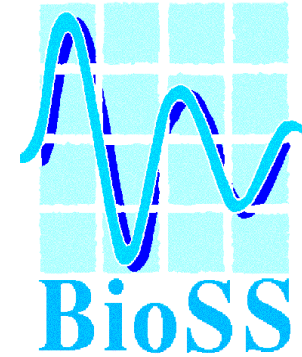
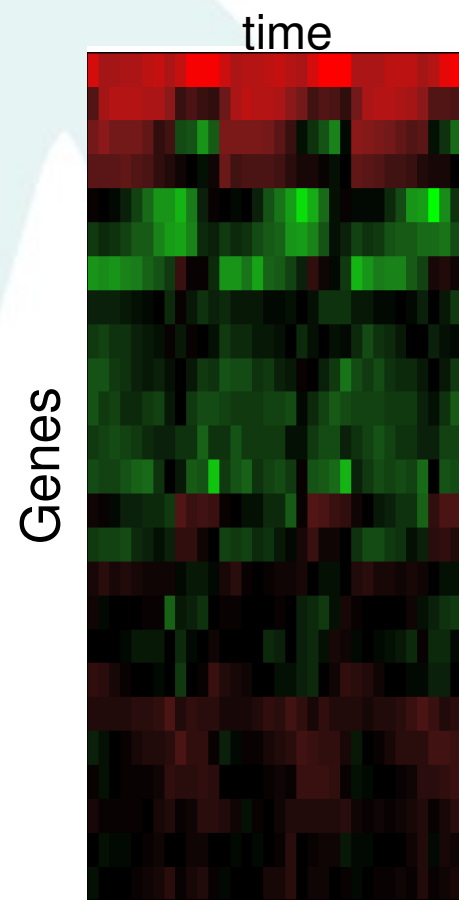
73 samples



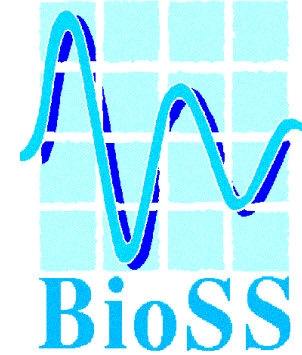
Tu et al (2005)

Metabolic cycle

36 samples

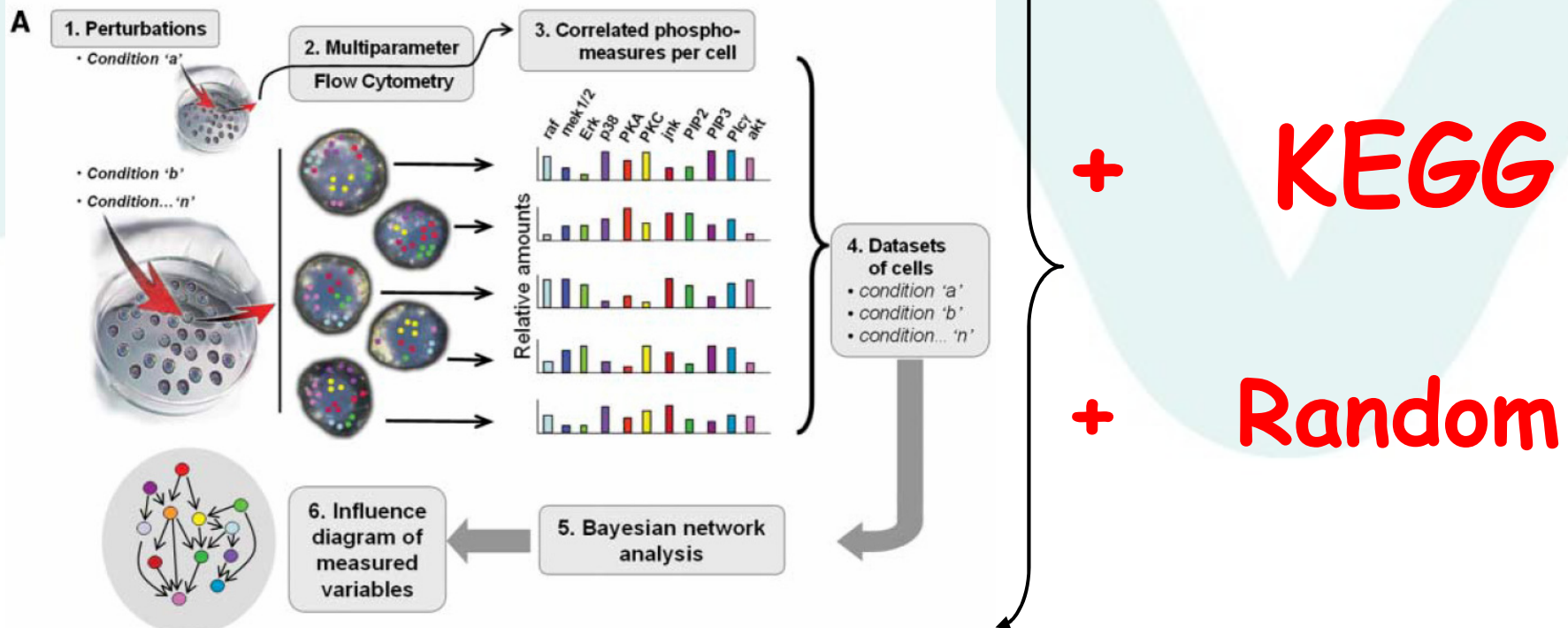


The data and the priors



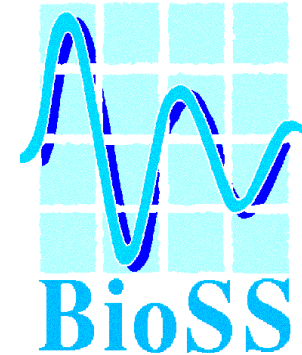
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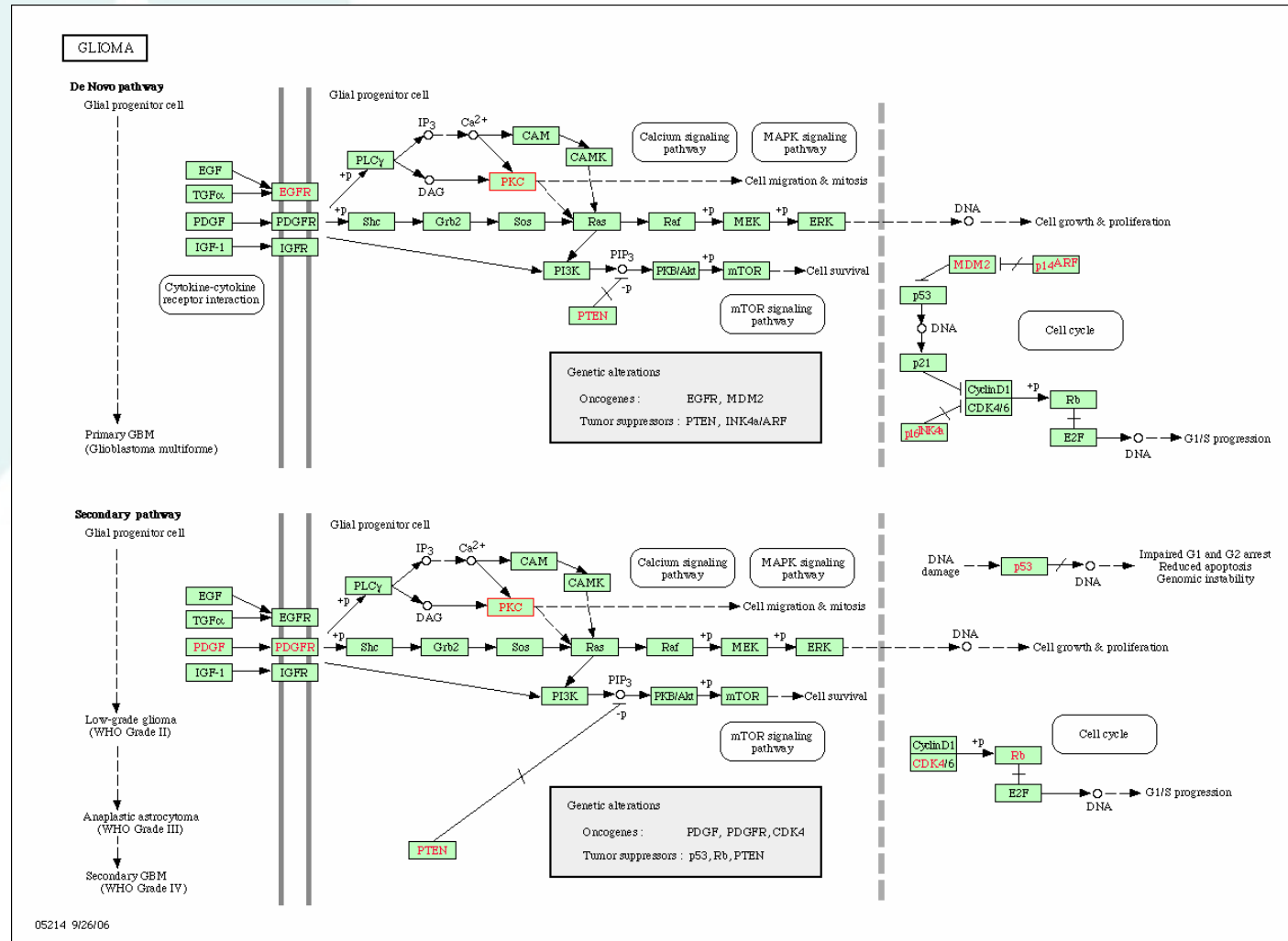
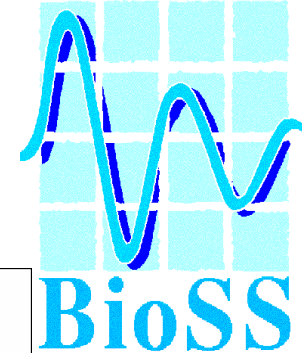
The data and the priors

<http://www.genome.jp/kegg/>

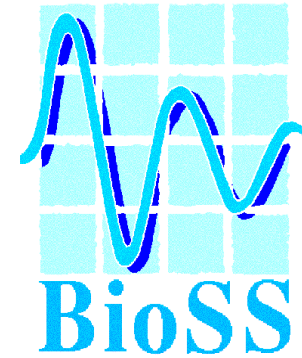


KEGG PATHWAYS are a collection of manually drawn pathway maps representing our knowledge of molecular interactions and reaction networks.

The data and the priors



The data and the priors

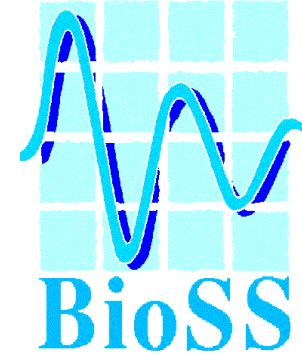


Define by M_{ij} the total number of times a pair of genes i and j appears in a pathway, and by m_{ij} the number of times the genes are connected by a (directed) edge in the KEGG pathway. The elements B_{ij} of the prior knowledge matrix are then defined by

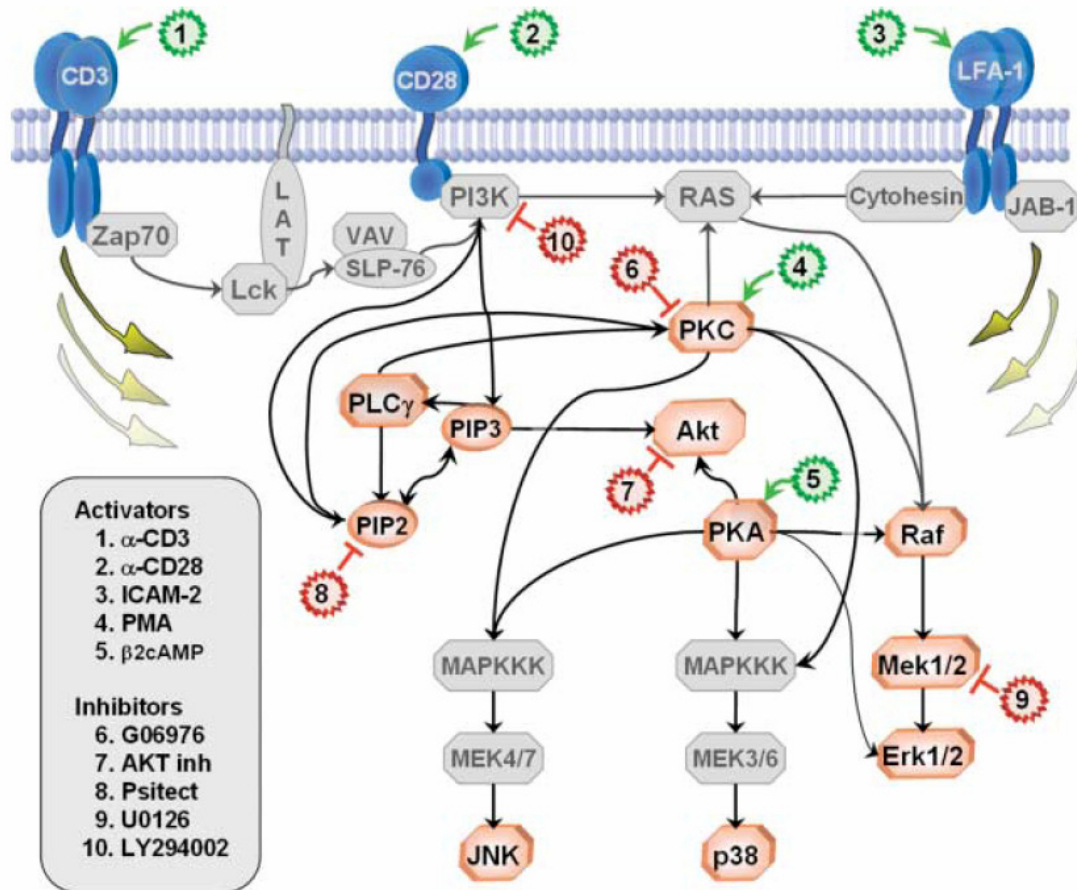
$$B_{ij} = \frac{m_{ij}}{M_{ij}} \quad (43)$$

If a pair of genes is not found in any of the KEGG pathways, we set the respective prior association to $B_{ij} = 0.5$, implying that we have no information about this relationship.

Accepted regulatory network



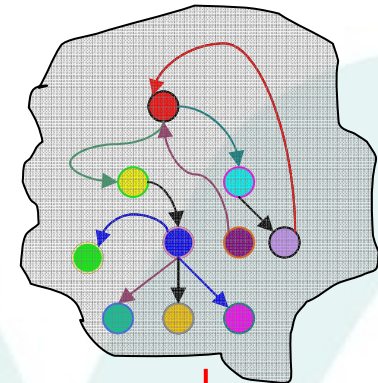
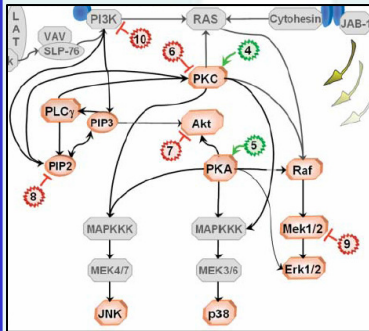
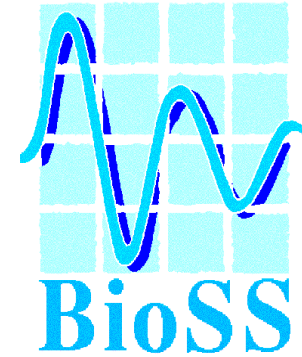
Classical Raf signalling network



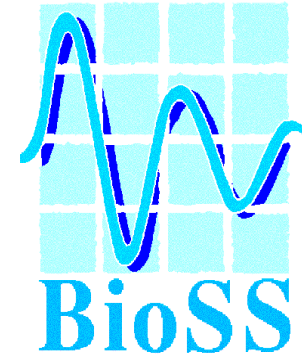
Why
rediscover a
known
network?

From Sachs et al Science 2005

How to compare the recovered networks?

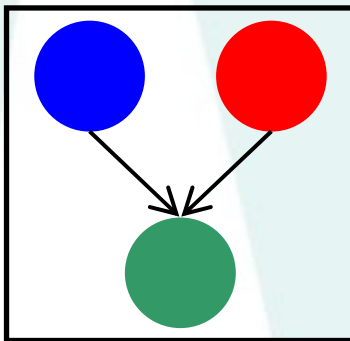


Performance evaluation

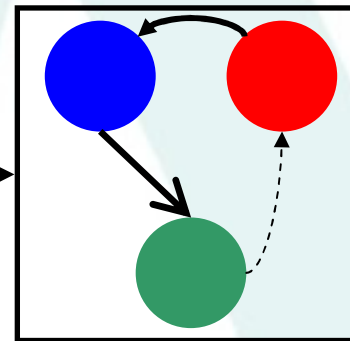


Thresholding

True network



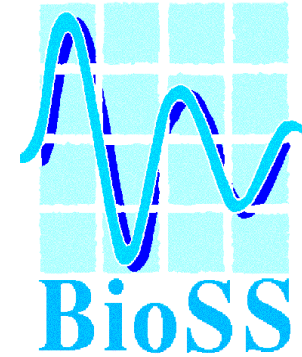
Predicted network



compare

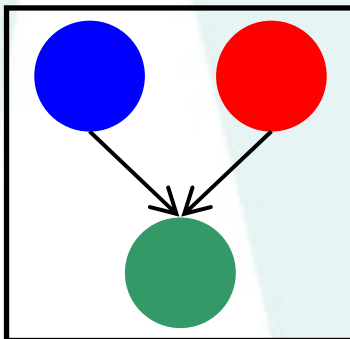


Performance evaluation

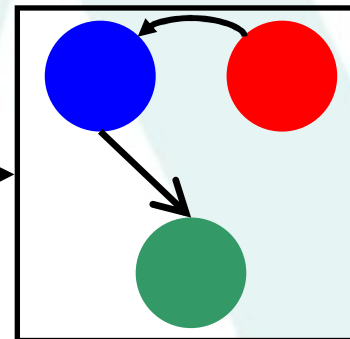


Thresholding

True network



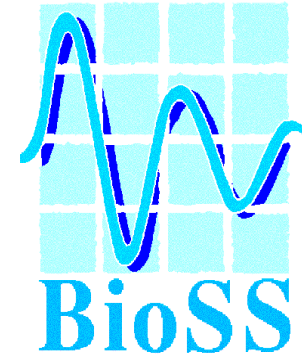
Predicted network



compare

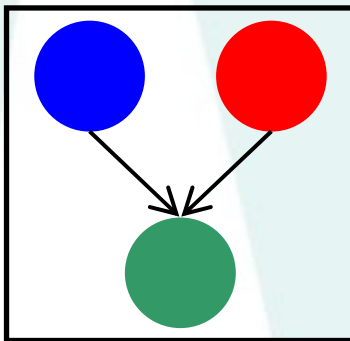


Performance evaluation

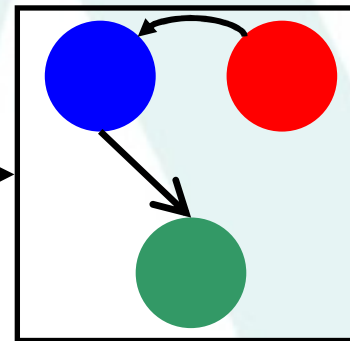


Counting

True network



Predicted network

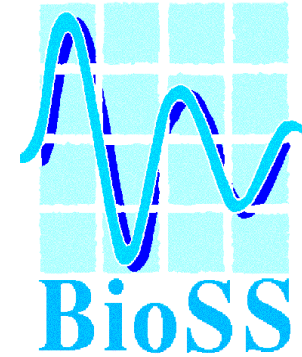


compare

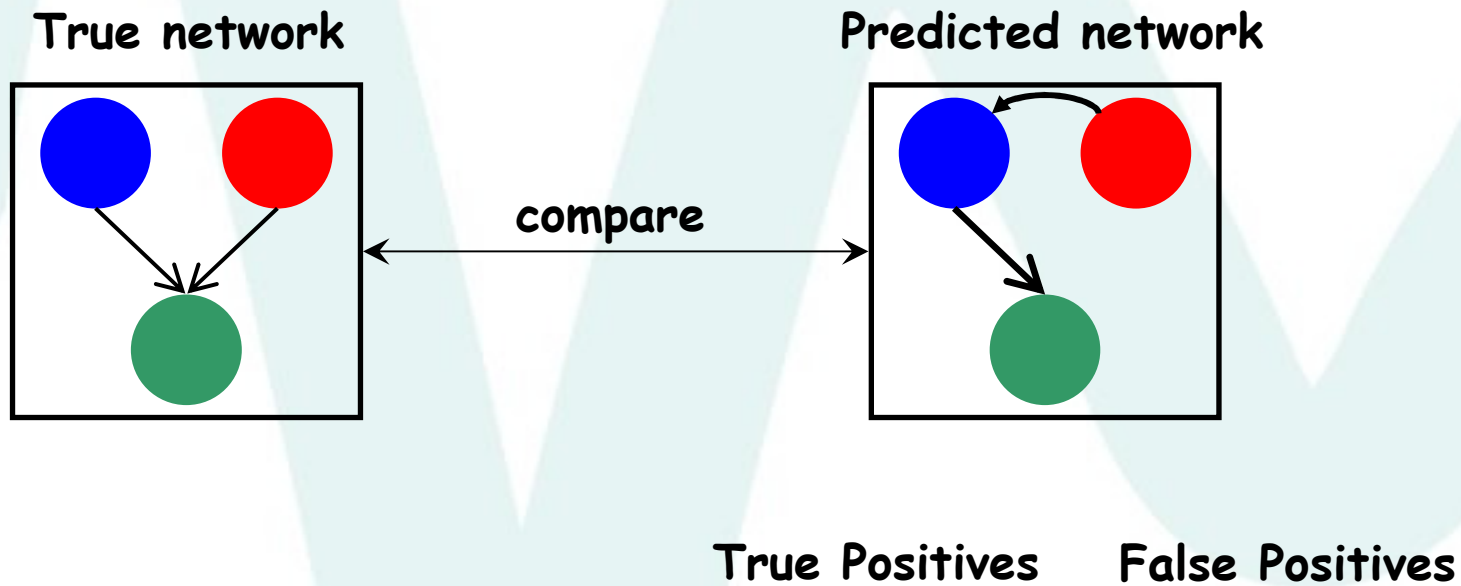
True Positives

False Positives

Performance evaluation



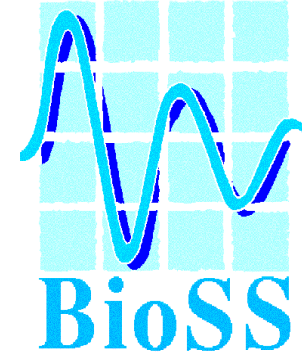
Counting



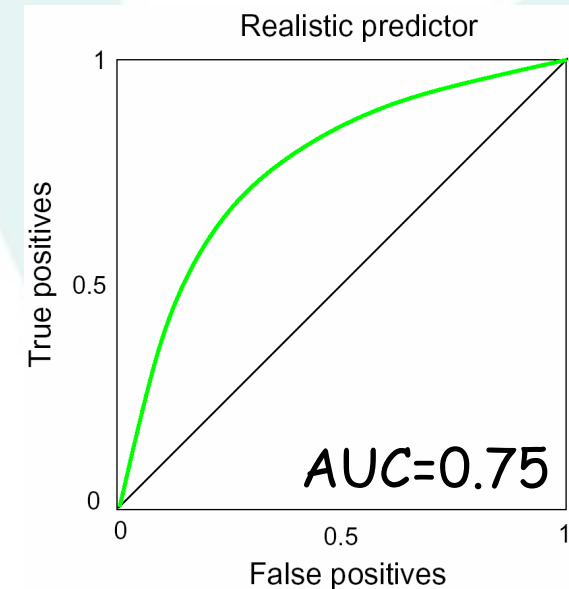
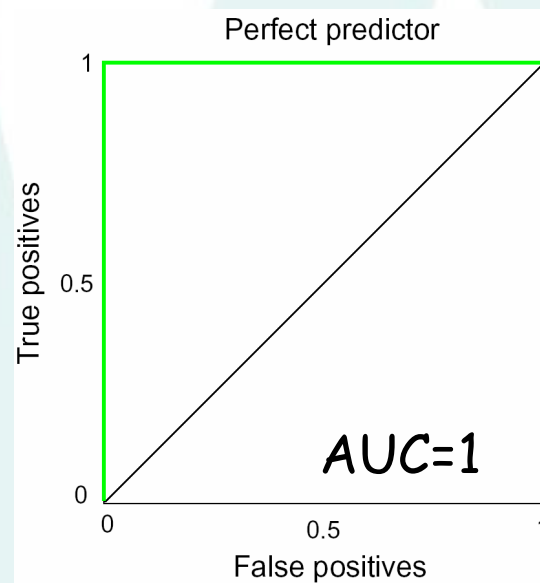
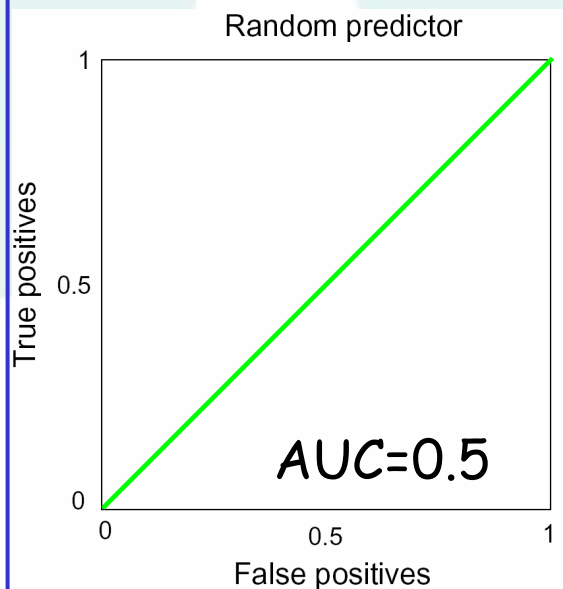
DGE - Consider edge directions

UGE - Discard the edge directions

How to compare the recovered networks?

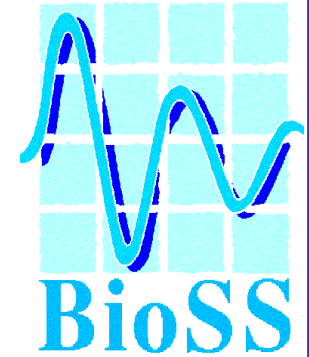


- We use the Area Under the Receiver Operating Characteristic Curve (ROC).
- ROC curves:

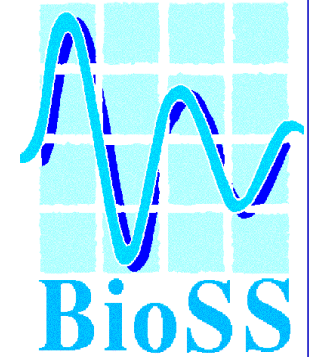


- We call the area *AUC*

Evaluation 2: TP scores



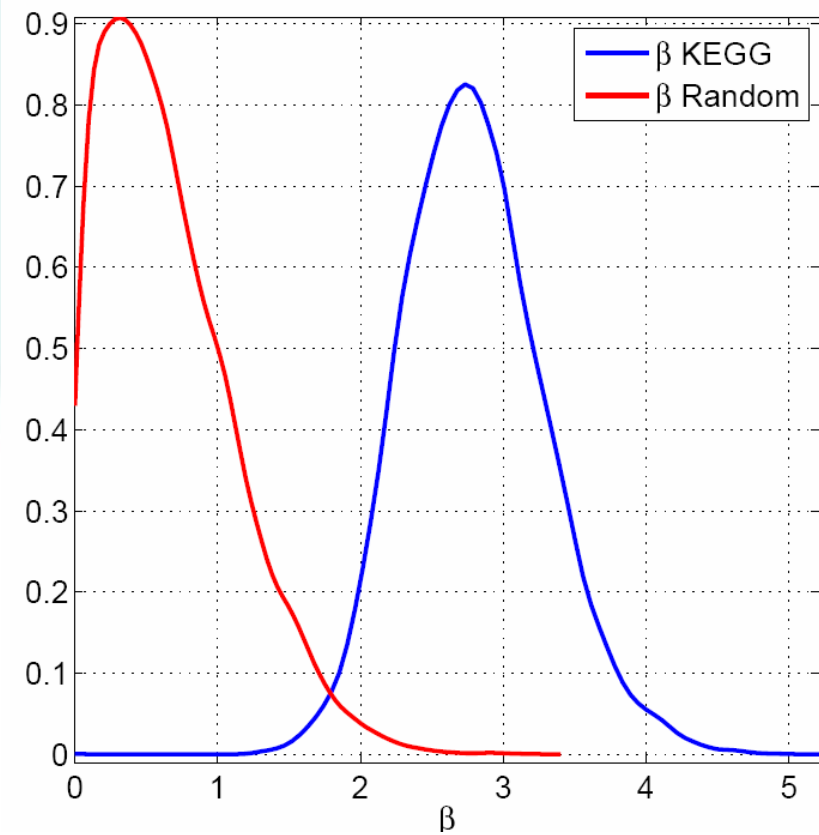
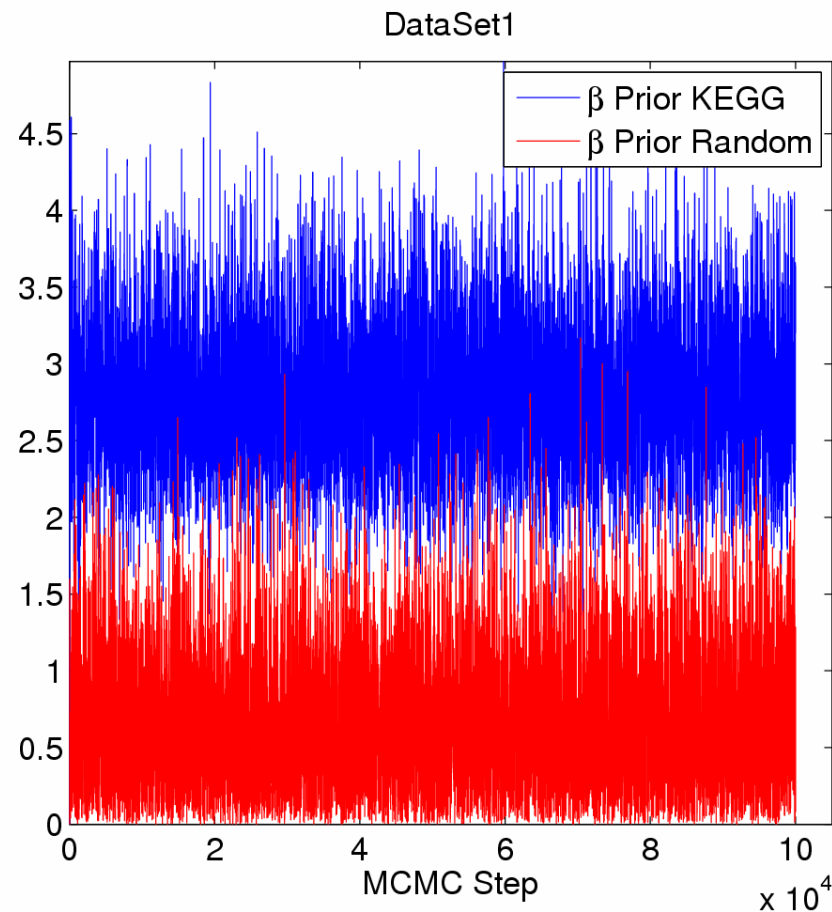
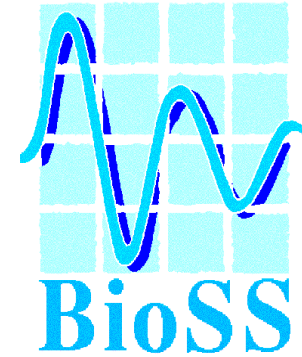
We **set** the **threshold** such that we obtained 5 spurious edges (**5 FPs**) and counted the corresponding number of true edges (**TP count**).

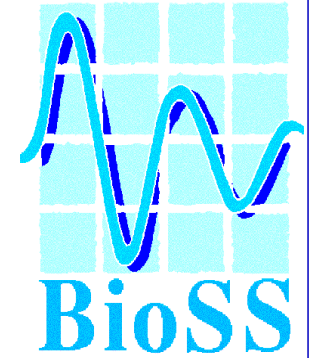


We have the **data sets** and **two different** sources of prior one of which is random.

How the sampled trade off hyperparameters look like?

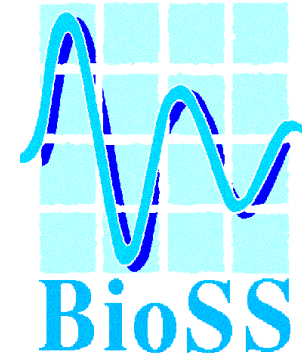
Typical sampled values of the hyperparameters



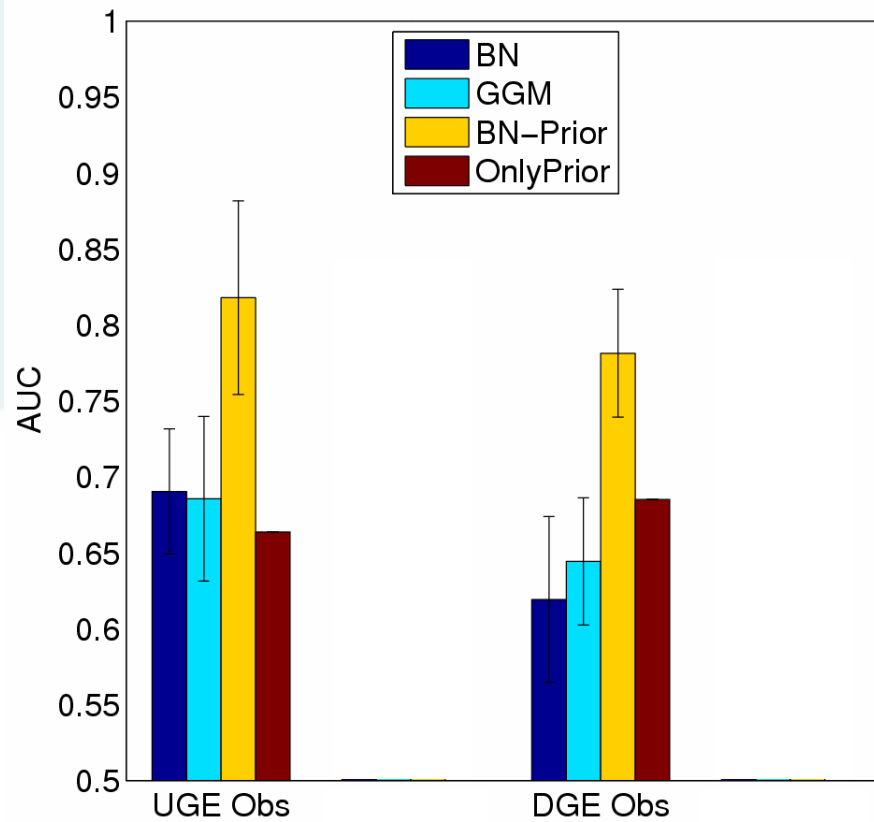


And the reconstructed network?

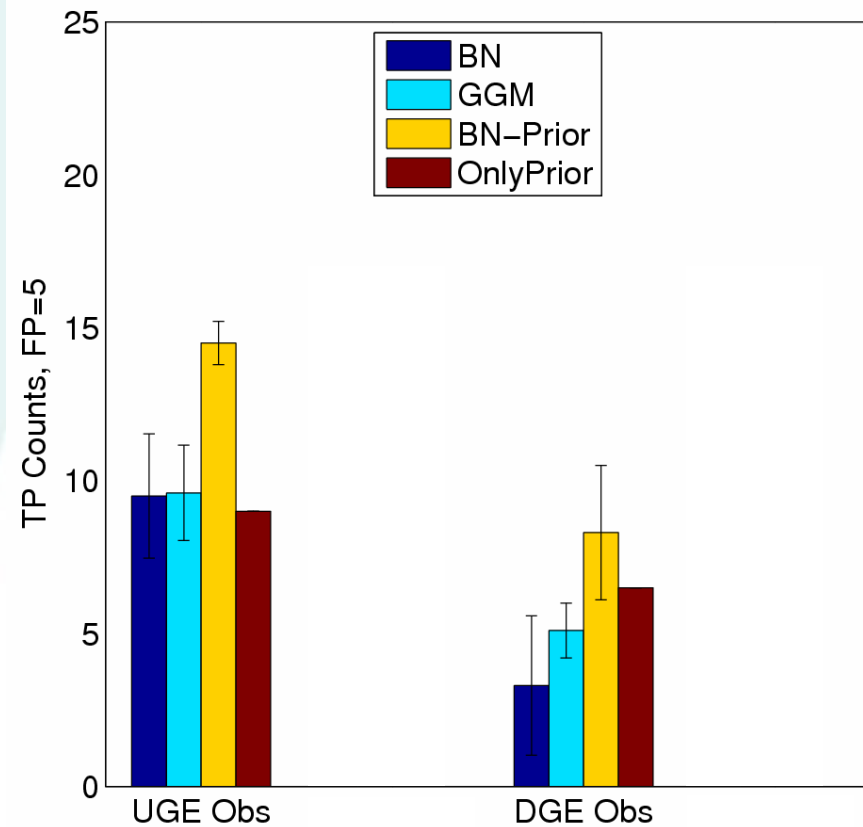
Flow cytometry data and KEGG

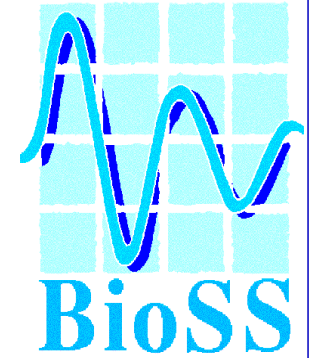


Real Data – AUC



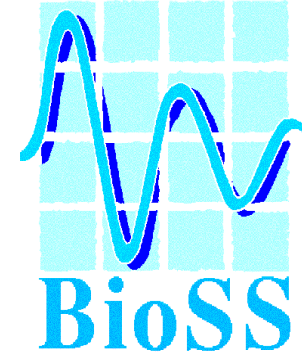
Real Data – TP



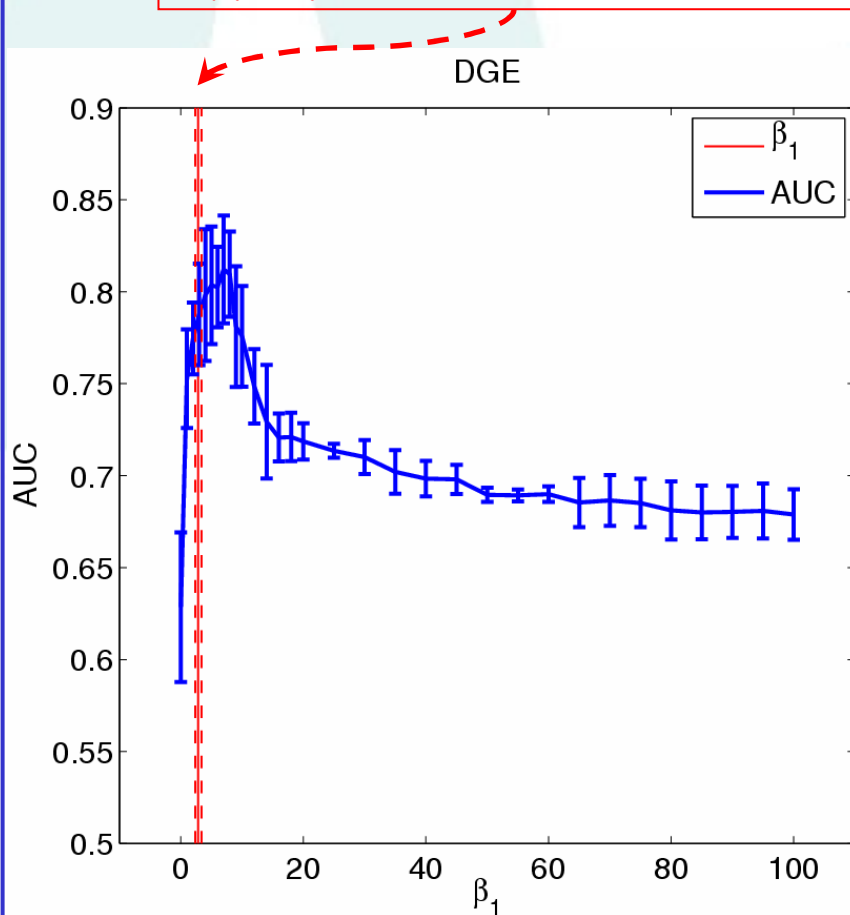


Are the trade off hyperparameters optimal?

Learning the trade off parameters on **real** data

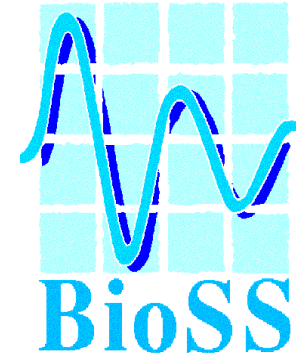


mean and standard deviation
of the sampled trade off
hyperparameter

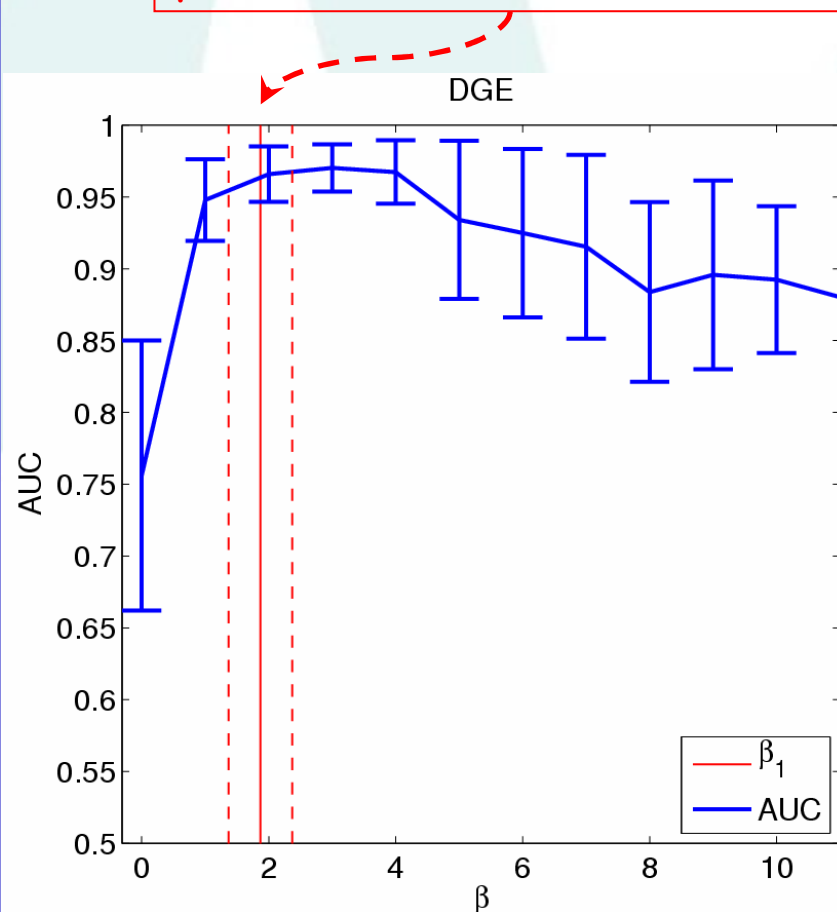


- Is the accepted network completely correct?

Learning the trade off parameters on *simulated* data



mean and standard deviation
of the sampled trade off
parameter



- We simulated data from the accepted network structure.
- We are sure that we don't have any mismatch between the data and the network we use to calculate the AUC scores.
- Now the sampled trade off parameter is optimal

New evidence for the accepted network

Regulation of Raf-1 by Direct Feedback Phosphorylation. *Molecular Cell*, Vol. 17, 2005 Dougherty et al

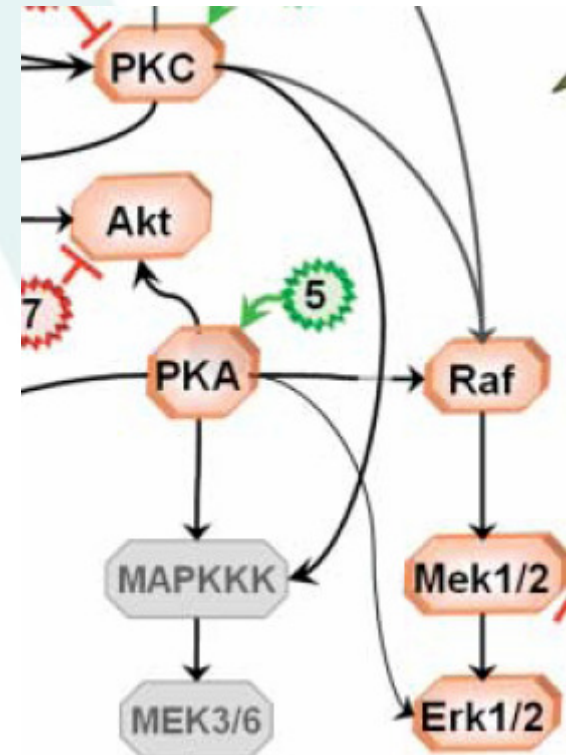
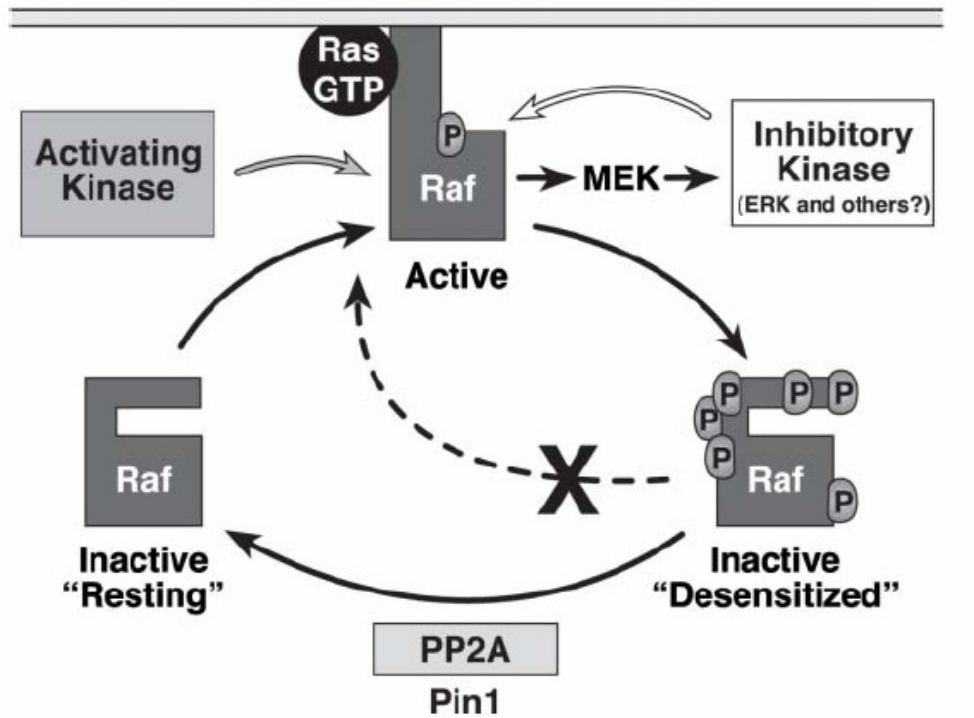
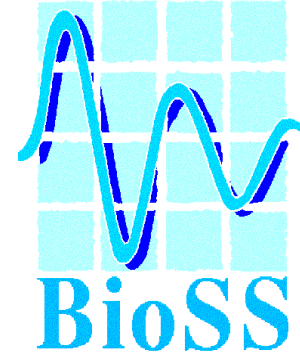


Figure 7. A Model for Raf-1 Regulation by Feedback Phosphorylation

New evidence for the accepted network

Regulation of Raf-1 by Direct Feedback Phosphorylation. *Molecular Cell*, Vol. 17, 2005 Dougherty et al

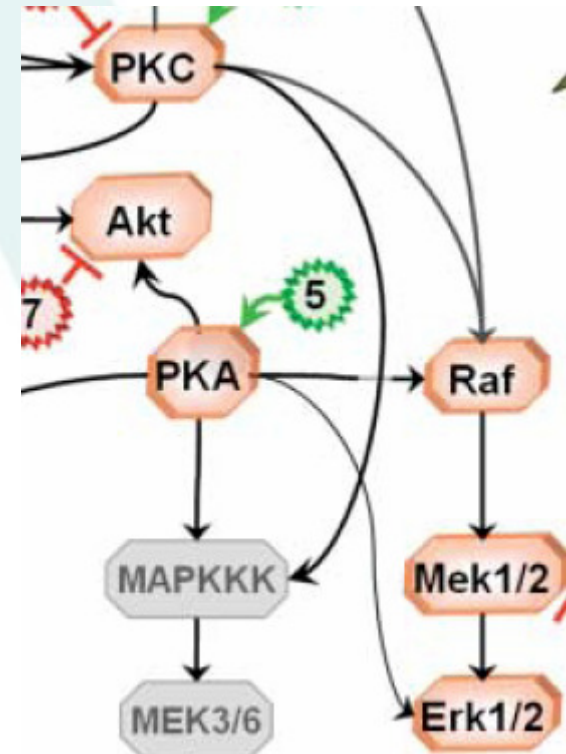
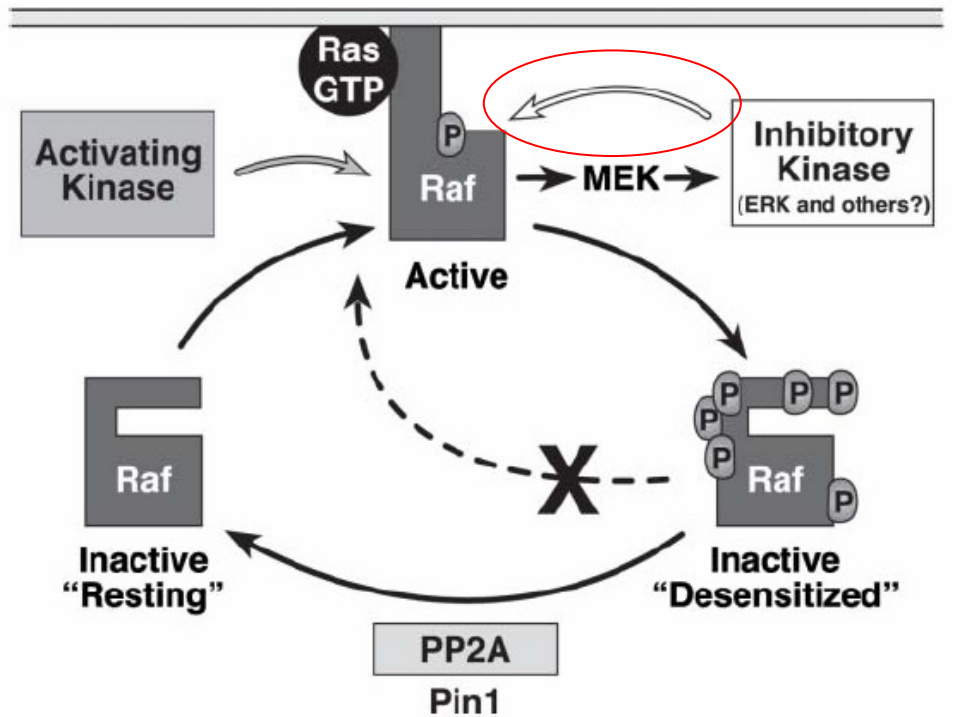
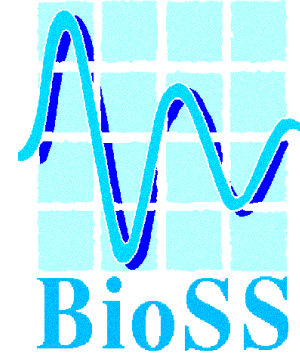
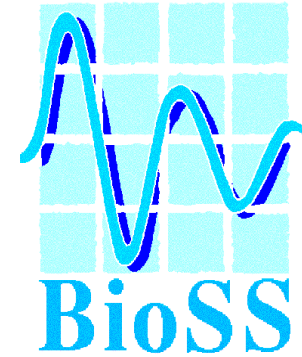


Figure 7. A Model for Raf-1 Regulation by Feedback Phosphorylation

Summary



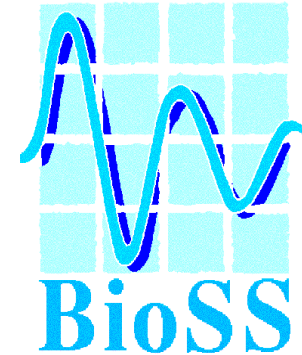
- Extended method can distinguish between good and bad sources of prior.
- Application to real data leads to significantly improved results.
- Trade off parameters are close to the optimal. Differences can be explained by the inconsistencies in the accepted network.

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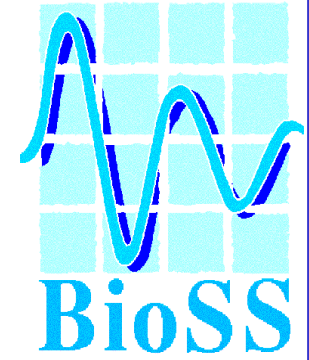


Reconstructing Gene Regulatory Networks
with Bayesian Networks by Combining
Expression Data with Multiple Sources of
Prior Knowledge

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Dirk Husmeier†

<http://www.bepress.com/sagmb/vol6/iss1/art15/>



Thank you