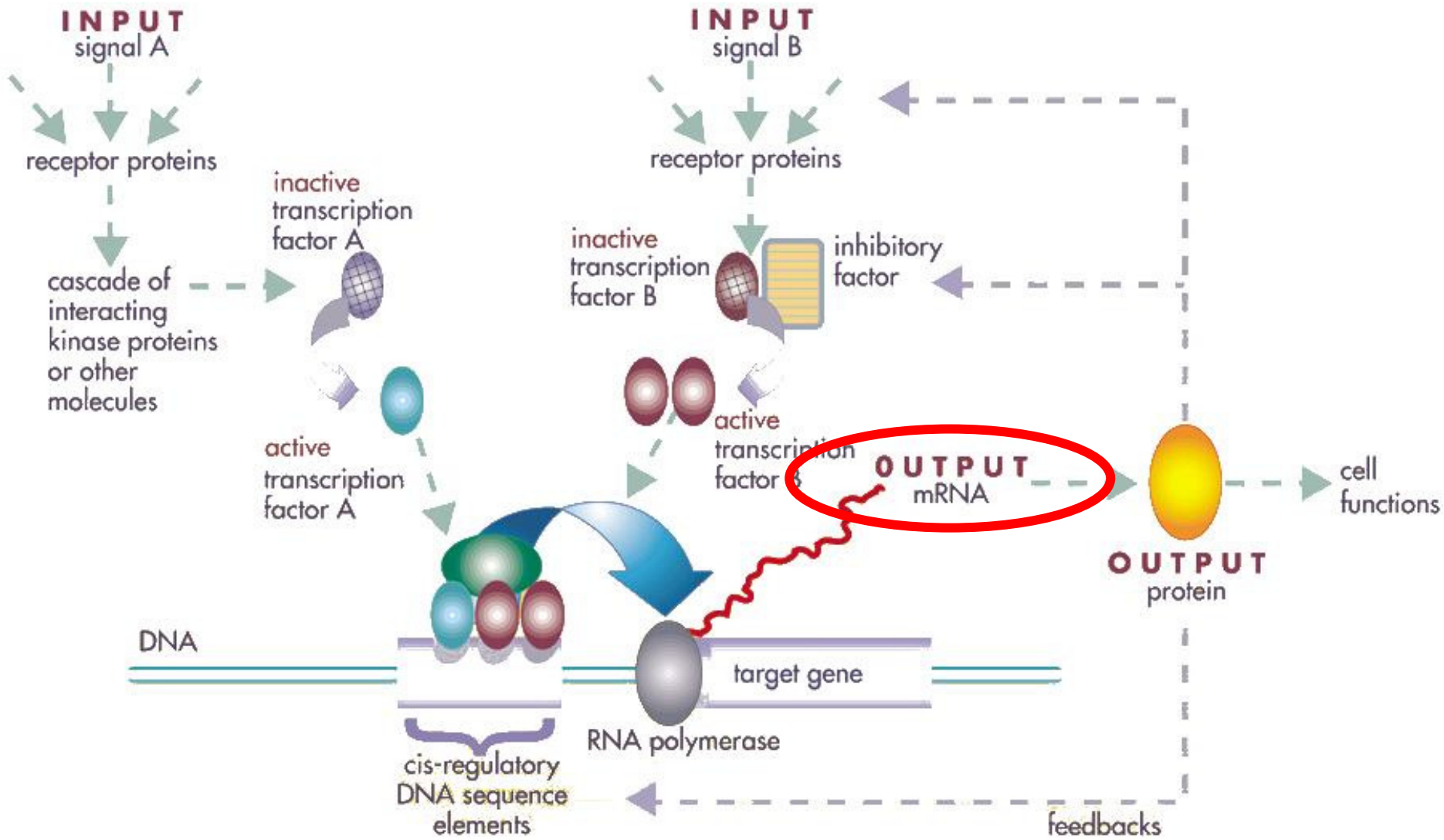
Computational Inference of Cellular Networks from Microarray Data

Achim Tresch

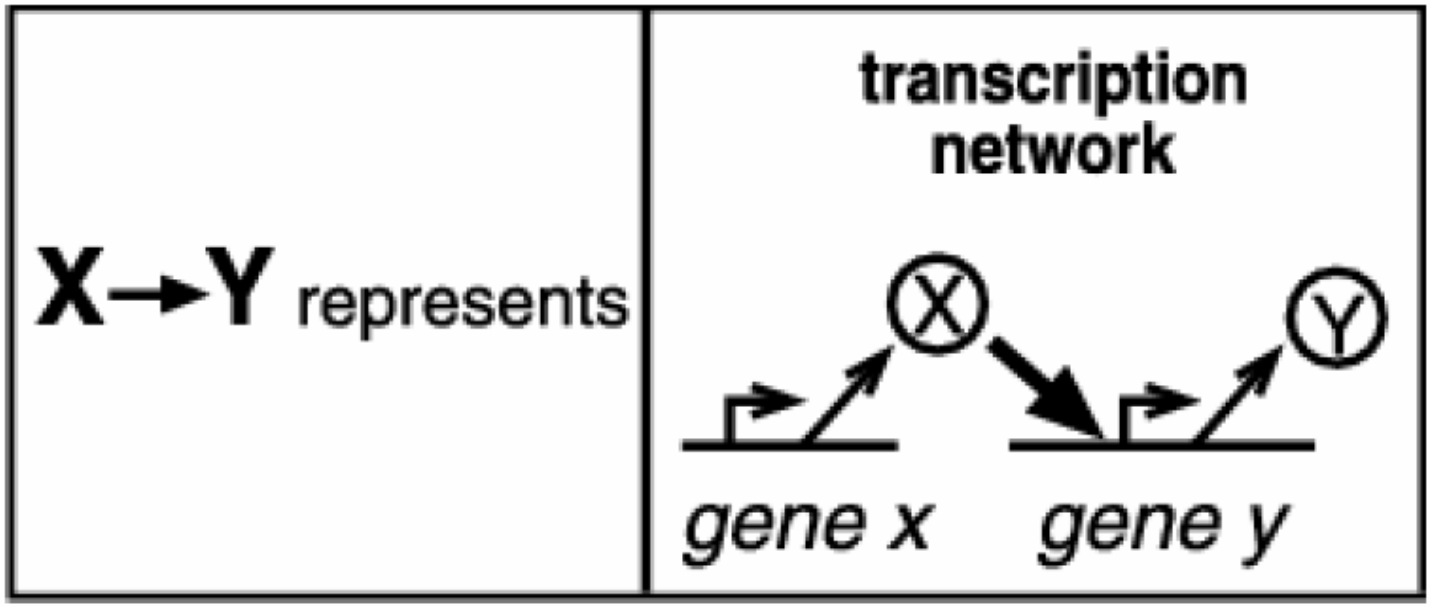
Topics

- **Biological networks vs. Network Models**
- **Learning Networks from non-interventional data:**
  - Gaussian Graphical Models
  - Bayesian Networks
- **Learning from interventional data:**
  - Pruning
  - Signal-Effects Model

Which biological Network?



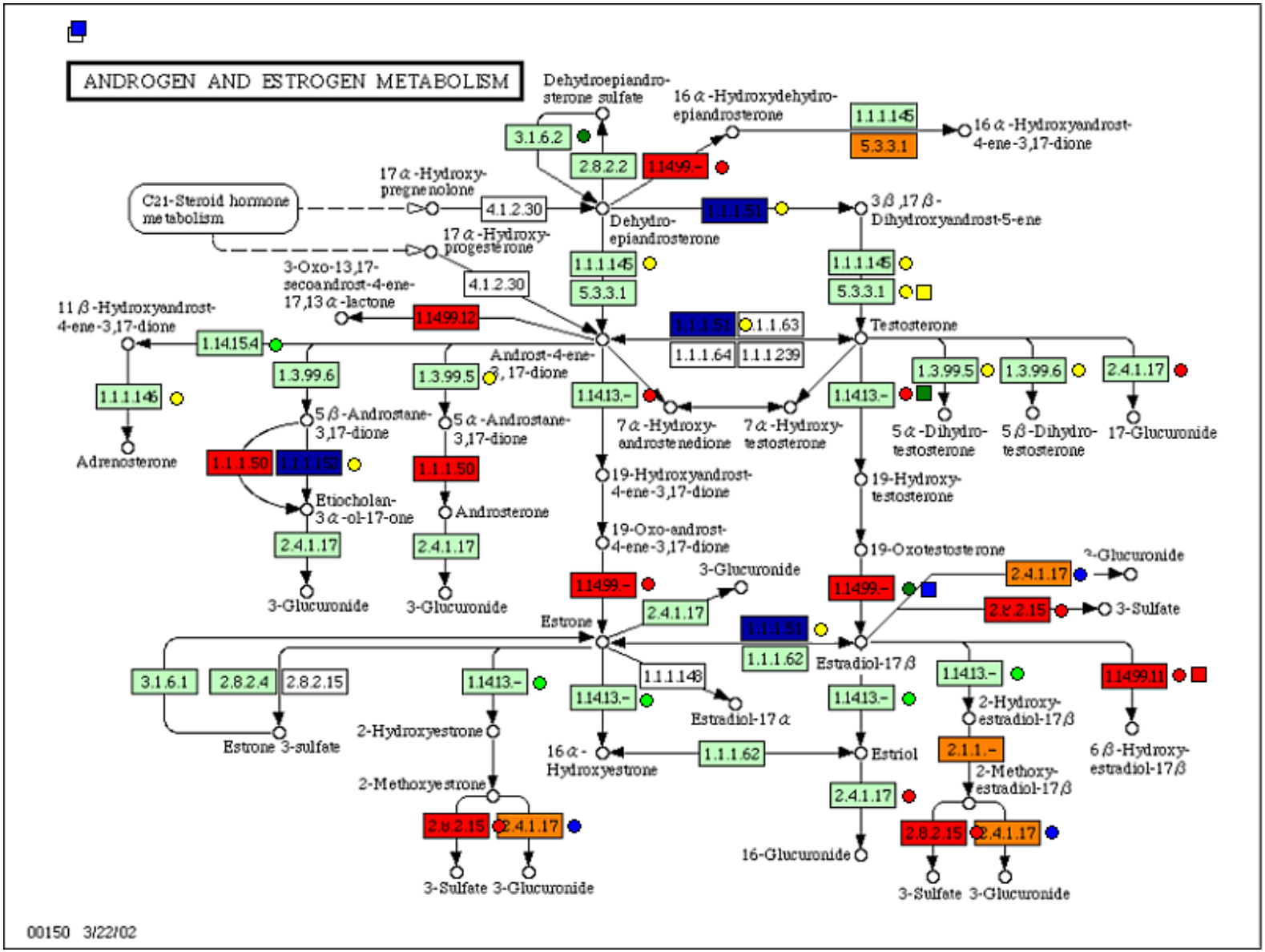
Transcription Networks



Nodes = transcription factors

Directed edge: X regulates transcription of Y

Transcription Networks



LEGEND

- high expression
- medium expression
- no difference
- low expression
- protein not found in array

TRANSCRIPTION FACTORS:

- Oct-1
- p107
- GATA-1
- Sp3
- Rb

DRUG TARGETS

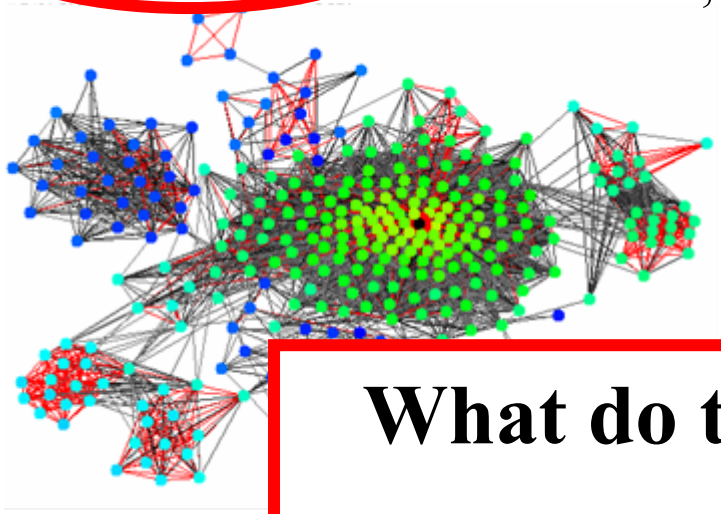
- thamoxifen
- flutamide
- anastrazole
- masterlone

From KEGG database

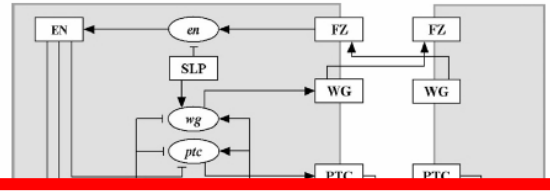
Which Network Model?

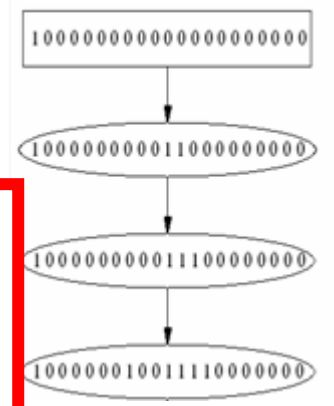
qualitative

Best suited for high dimensional, noisy data



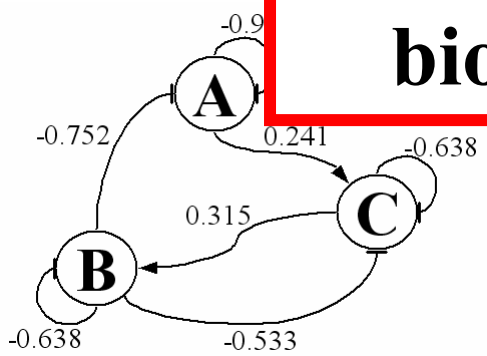
semiquantitative





What do the arrows mean?

Can they be ascribed a biological interpretation?



$$\frac{d[B]}{dt} = \frac{V_b}{1+\frac{K_{aC}}{[C]}} - k_b[B]$$

$$\frac{d[C]}{dt} = \frac{V_c}{\left(1+\frac{[B]}{K_{iB'}}\right)\left(1+\frac{K_{aA}}{[A]}\right)} - k_c[C]$$

quantitative

Qulitative Network Models

Possible Models include

- **Correlation Graphs**
- **Gaussian Graphical Models**
- **Bayesian Networks**

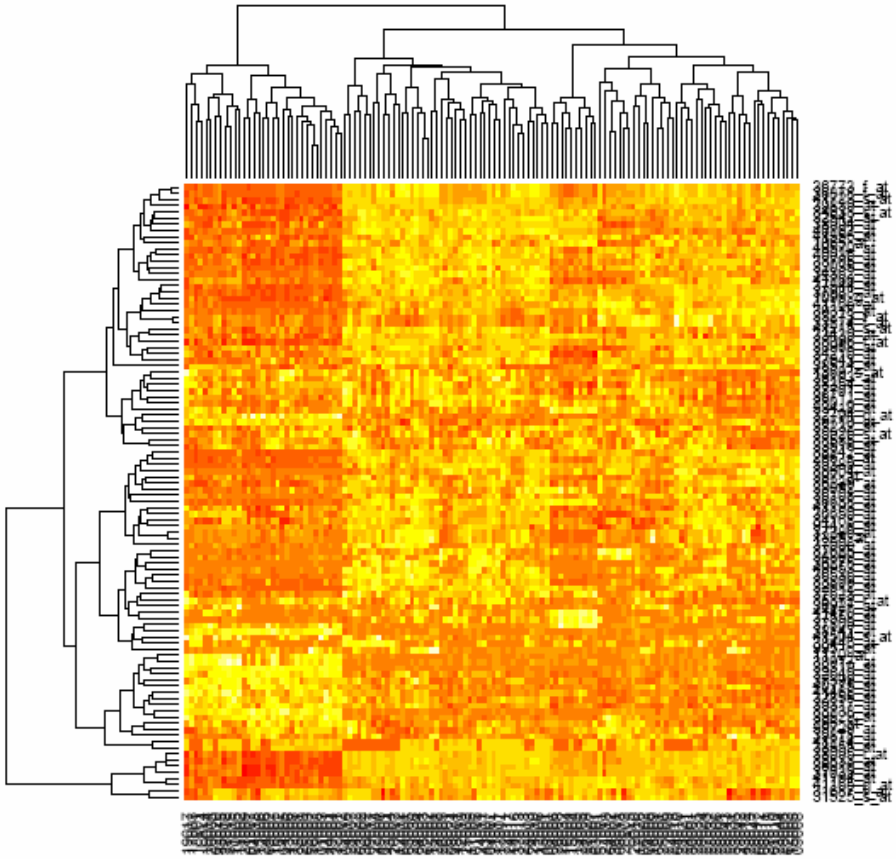
However: Correct Reconstruction of the complete regulatory network is impossible due to

- **Lack of data**
- **Measurement error**
- **Oversimple/wrong model assumptions**

“All models are wrong, some of them are useful“

(Edwards Deming, George Box)

Clustering by coexpression



Assumption:

Coexpression $\sim$ coregulation

If genes show the same expression profiles they follow the same regulatory regimes

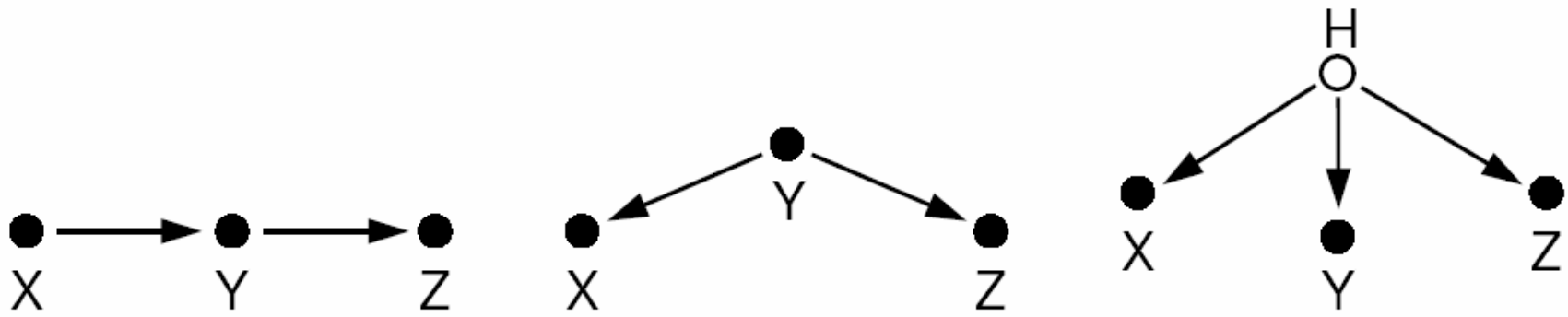
Correlation Graphs

- **An expression profile is a collection of expression vectors**
  $$\{ X_g = (X_{g,s})_{s \in \text{samples}} , g \in \text{Genes} \}$$
- **Correlation graph: Depict genes as vertices of a graph and draw an undirected edge (i, j) if some correlation measure (Pearson correlation, Spearman rank correlation, Kendall's tau) between X_i and X_j is sufficiently different from zero.**
- **Advantage: This representation of the marginal dependence structure is easy to interpret and can be accurately estimated even if p » N.**
- **Application: Stuart et al. (Science, 2003) build a graph from coexpression across multiple organisms.**

Problems of correlation based approaches

- **It is impossible to distinguish direct from indirect dependencies**

  Three reasons why X, Y , and Z may be highly correlated:



Possible remedies:

- **search for correlations which cannot be explained by other variables.**
- **measure effects of gene perturbations**

- **A strong correlation is not a strong evidence for regulatory dependence (lots of false positives) rather than a low correlation is a strong evidence for no regulatory edge.**

Conditional Independence

Be X, Y, Z random variables with joint distribution P.

X is conditionally independent of Y given Z

$$X \perp\!\!\!\perp Y \mid Z \quad \Leftrightarrow$$

$$P(X = x, Y = y | Z = z) = P(X = x | Z = z) \cdot P(Y = y | Z = z)$$
$$P(X = x | Y = y, Z = z) = P(X = x | Z = z)$$

In other words:

- **Knowing Z, knowing Y is irrelevant for knowing X (and vice versa).**
- **Z explains any observed dependence between X and Y .**

Gaussian Graphical Models (GGM)

Given a random vector $\mathbf{X} = (X_1, \ldots, X_p)$.

A Gaussian graphical model [7, 4] is an **undirected graph** on vertex set V, with $|V| = p$.

To each vertex $i \in V$ corresponds a **random variable** $X_i \in \mathbf{X}$.

Draw an **edge** between vertices i and j if and only if

$$X_i \not\perp\!\!\!\perp X_j \mid \mathbf{X}_{\text{rest}},$$

where $\mathbf{X}_{\text{rest}} = \mathbf{X} \backslash \{X_i, X_j\}$.

Gaussian Graphical Models (GGM)

If we assume that the common expression distribution of all genes follows a multivariate Gaussian distribution (which is of course never the case), conditional independence can be assessed as follows:

1. First estimate the covariance matrix Σ by the sample covariance matrix

$$\hat{\Sigma} = \frac{1}{N-1}(X - \bar{X})^T(X - \bar{X}).$$

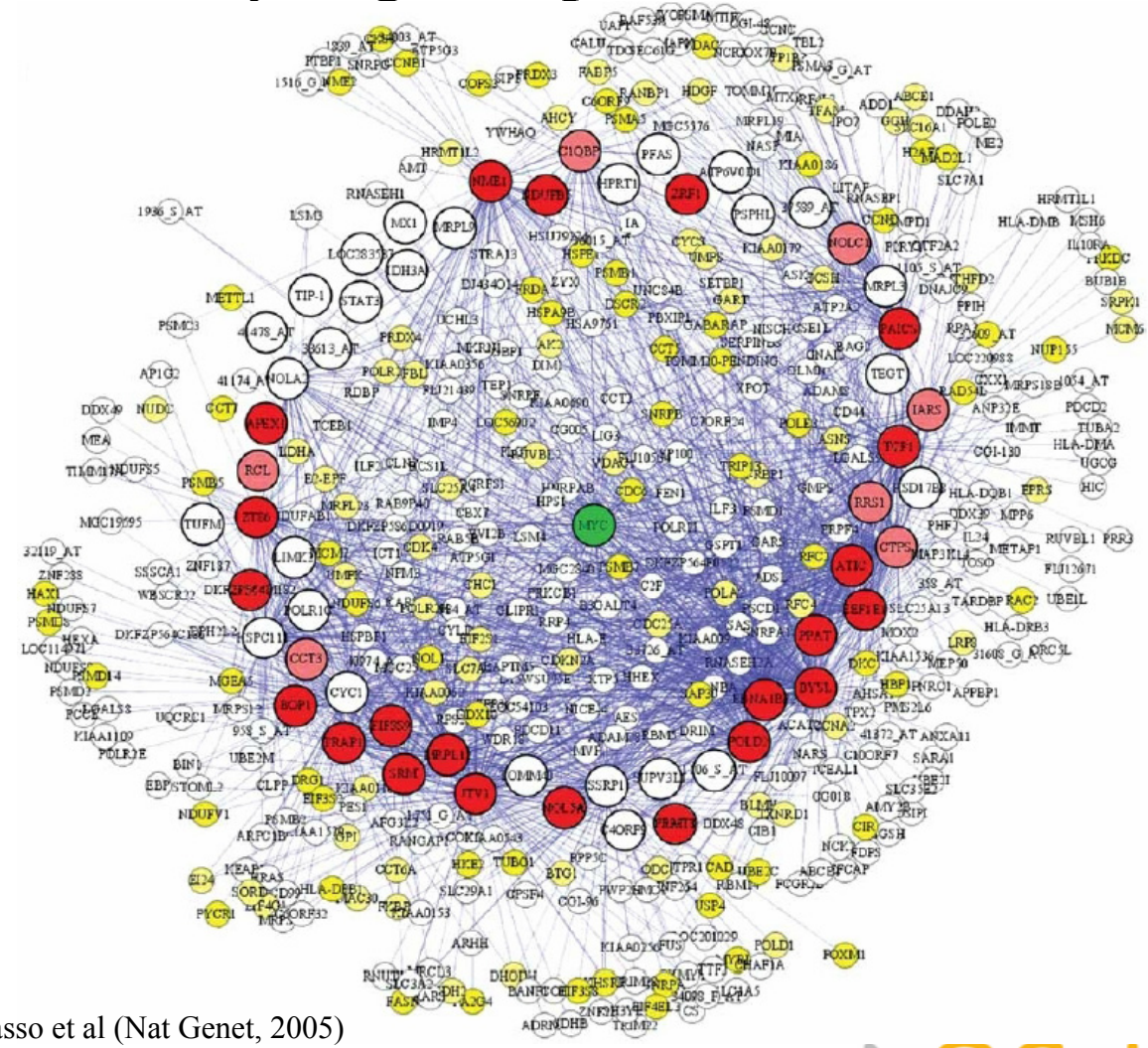
2. Invert $\hat{\Sigma}$ to obtain an estimate $\hat{K}$ of the precision matrix K.
3. Employ statistical tests [56] to decide, which entries in $\hat{K}$ are significantly different from zero.

What if p » N?

Full conditional relationships can only be accurately estimated if the number of samples N is relatively large compared to the number of variables p.

Thus, if p » N, you can . . .

- **use the Moore-Penrose pseudoinverse, bootstrap aggregation and shrinkage estimators to stabilize the result (e.g. Schäfer and Strimmer, Bioinformatics´05)**
- **resort to a simpler model that does not rely on full conditional independence**



Graph from Basso et al (Nat Genet, 2005)

Modified Gaussian Graphical Models (GGM)

We have seen methods to build graphs from

1. marginal dependencies

$$X_i \not\perp\!\!\!\perp X_j \mid \emptyset$$ Correlation Graphs

2. full conditional dependence

$$X_i \not\perp\!\!\!\perp X_j \mid X_{\text{rest}}$$ GGMs

3. first order dependencies

$$X_i \not\perp\!\!\!\perp X_j \mid X_k \quad \forall k \in \text{rest}$$ Wille / Bühlmann

4. This leads use to include **all higher order dependencies**

$$X_i \not\perp\!\!\!\perp X_j \mid \mathbf{X}_S \quad \text{for all } S \subseteq \text{rest}$$

All methods failed to accurately reconstruct networks, even if they were of very moderate size (~20)

Children depend on parents

The DAG defines families.

Relationships are further characterized by local probability distributions:

$$P(J) = \begin{cases} 1/4 & \text{spring} \\ 1/4 & \text{summer} \\ 1/4 & \text{autumn} \\ 1/4 & \text{winter} \end{cases}$$

J = Season

pa(J) = ∅

pa(S) = {J}

pa(R) = {J}

S = Sprinkler

R = Rain

pa(N) = {S,R}

W = Wet Lawn

$$P(S \mid J) = \begin{cases} J \setminus S & \text{on} & \text{off} \\ \text{spring} & 0.1 & 0.9 \\ \text{summer} & 0.5 & 0.5 \\ \text{autumn} & 0.1 & 0.9 \\ \text{winter} & 0 & 1 \end{cases}$$

$$P(R \mid J) = \begin{cases} J \setminus R & \text{rain} & \text{no rain} \\ \text{spring} & 0.3 & 0.7 \\ \text{summer} & 0.4 & 0.6 \\ \text{autumn} & 0.2 & 0.8 \\ \text{winter} & 0.1 & 0.9 \end{cases}$$

$$P(W \mid S,R) = \begin{cases} (S,R) \setminus W & \text{wet} & \text{dry} \\ (\text{on},\text{rain}) & 1 & 0 \\ (\text{on},\text{no rain}) & 1 & 0 \\ (\text{off},\text{rain}) & 0.9 & 0.1 \\ (\text{off},\text{no rain}) & 0.01 & 0.99 \end{cases}$$

The sprinkler network

Bayesian Networks: The Sprinkler Network

The common distribution of {J,S,R,N} can be coded by the graph topology and 3+4+4+4 =15 real numbers: (instead of 4·2·2·2-1 = 31 real numbers for an arbitrary distribution)

$$pa(.) = \begin{cases} J \mapsto \{\} \\ S \mapsto \{J\} \\ R \mapsto \{J\} \\ N \mapsto \{S, R\} \end{cases}$$

$$P(J) = \begin{cases} 1/4 & \text{spring} \\ 1/4 & \text{summer} \\ 1/4 & \text{autumn} \\ 1/4 & \text{winter} \end{cases}$$

$$P(S|J) = \begin{cases} J\backslash S & \text{on} & \text{off} \\ \text{spring} & 0.1 & 0.9 \\ \text{summer} & 0.5 & 0.5 \\ \text{autumn} & 0.1 & 0.9 \\ \text{winter} & 0 & 1 \end{cases}$$

$$P(R|J) = \begin{cases} J\backslash R & \text{rain} & \text{norain} \\ \text{spring} & 0.3 & 0.7 \\ \text{summer} & 0.4 & 0.6 \\ \text{autumn} & 0.2 & 0.8 \\ \text{winter} & 0.1 & 0.9 \end{cases}$$

$$P(N|S,R) = \begin{cases} (S,R)\backslash N & \text{wet} & \text{dry} \\ (\text{on,rain}) & 1 & 0 \\ (\text{on,norain}) & 1 & 0 \\ (\text{off,rain}) & 0.9 & 0.1 \\ (\text{off,norain}) & 0.01 & 0.99 \end{cases}$$

$$P(J = j, S = s, R = r, N = n) = P(N = n \mid S = s, R = r) \cdot P(S = s \mid J = j) \cdot P(R = r \mid J = j) \cdot P(J = j)$$

E.g.

$$\begin{aligned} P(J = \text{summer}, S = \text{off}, R = \text{rain}, N = \text{wet}) &= P(N = \text{wet} \mid S = \text{off}, R = \text{rain}) \cdot P(R = \text{rain} \mid J = \text{summer}) \\ &\quad \cdot P(S = \text{off} \mid J = \text{summer}) \cdot P(J = \text{summer}) \\ &= 0.9 \cdot 0.4 \cdot 0.5 \cdot 0.25 \\ &= 0.045 \end{aligned}$$

Bayesian Networks

Problems:

- **Given a directed acyclic graph (DAG), learn the local probability distributions and score the DAG according to its likelihood („how good does this graph fit the data“?) → Parameter estimation, Bayesian Dirichlet metric (Cooper, Herskovits 1992)**

- **Find the topology(-ies) for the underlying DAG**

The latter point is the crucial problem, since there may be DAGs that are equally likely, and there are in general billions of DAGs that score comparably well.

Network identification

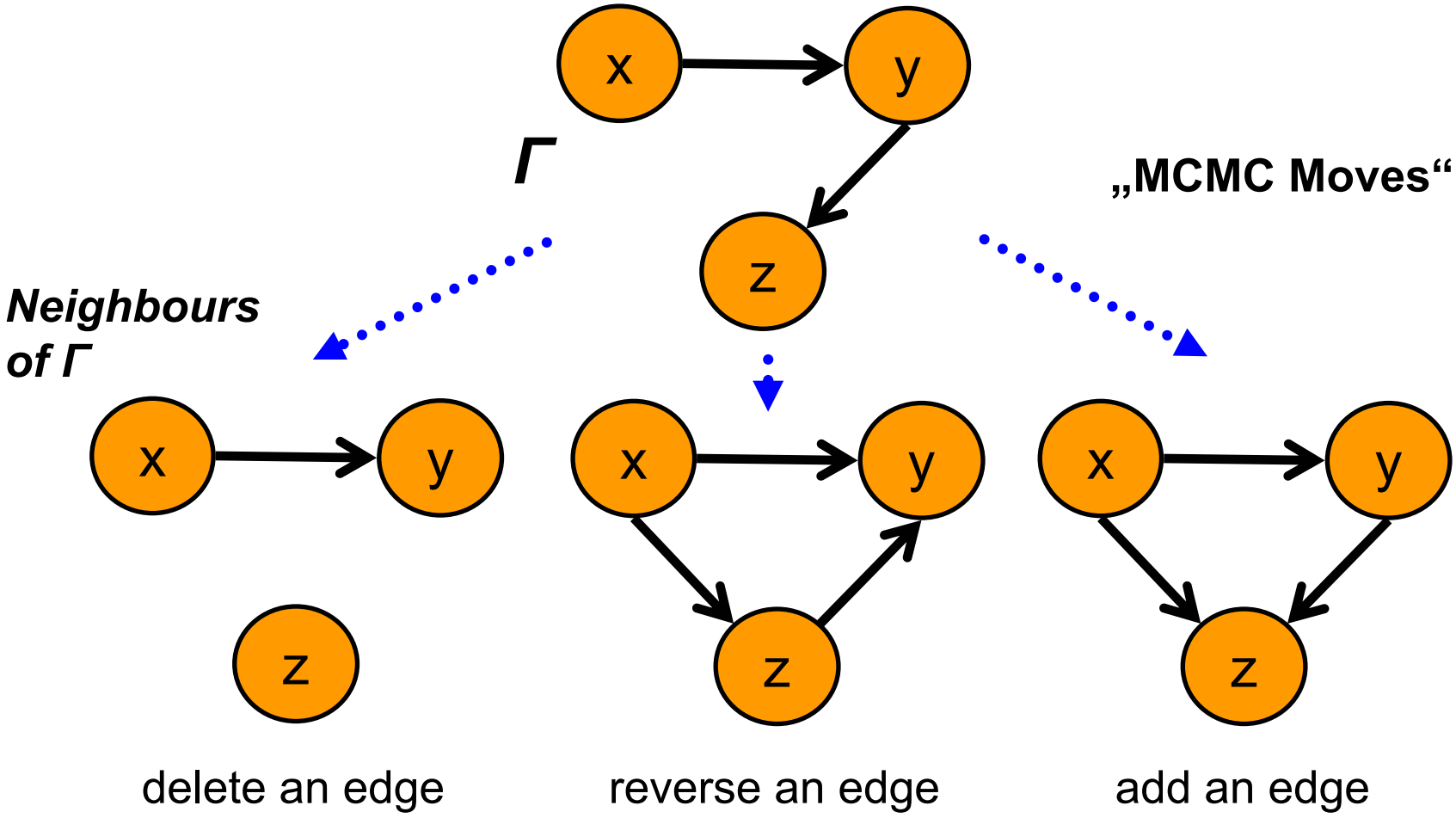
- **Model Selection:**
  Find a model wíth maximal (or at least exceptionally high) posterior probability P(Γ|Data) and assume that this ist the true network topology

- **Model Averaging:**
  Draw a large number of random samples Γ from the distribution P(Γ |Data) and approximate P(edge present | Data) by the sum

$$P(e \mid D) = \sum_{\Gamma \in \text{DAGs}} I(e \in \Gamma) P(\Gamma \mid D) \approx \frac{1}{\#\text{samples}} \sum_{\Gamma \in \text{samples}} I(e \in \Gamma) P(\Gamma \mid D)$$

MCMC sampling of directed acyclic graphs

Wander through the space of all possible topologies



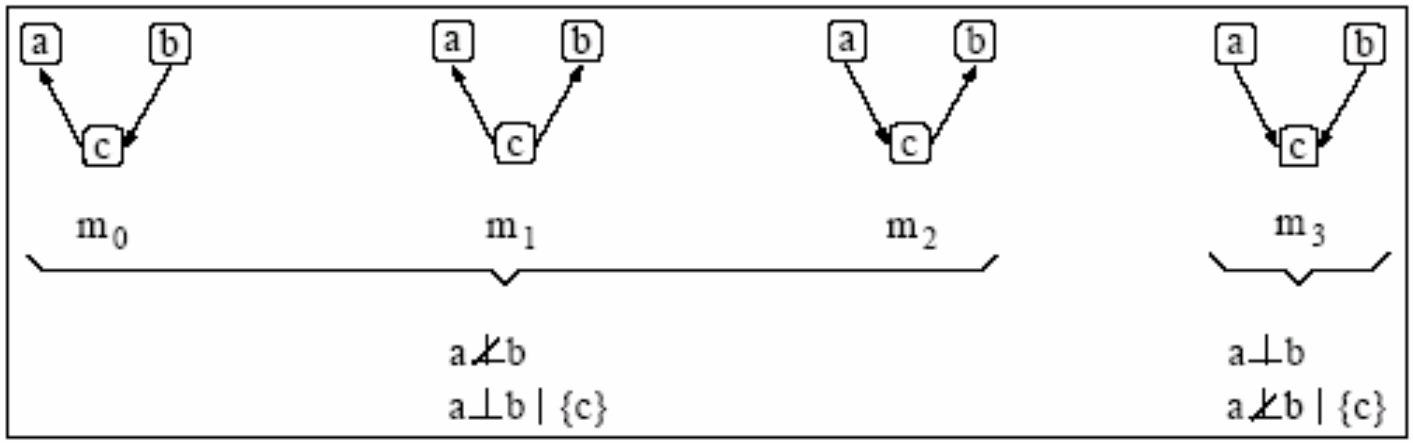
Causality in Bayesian Networks: Likelihood equivalence

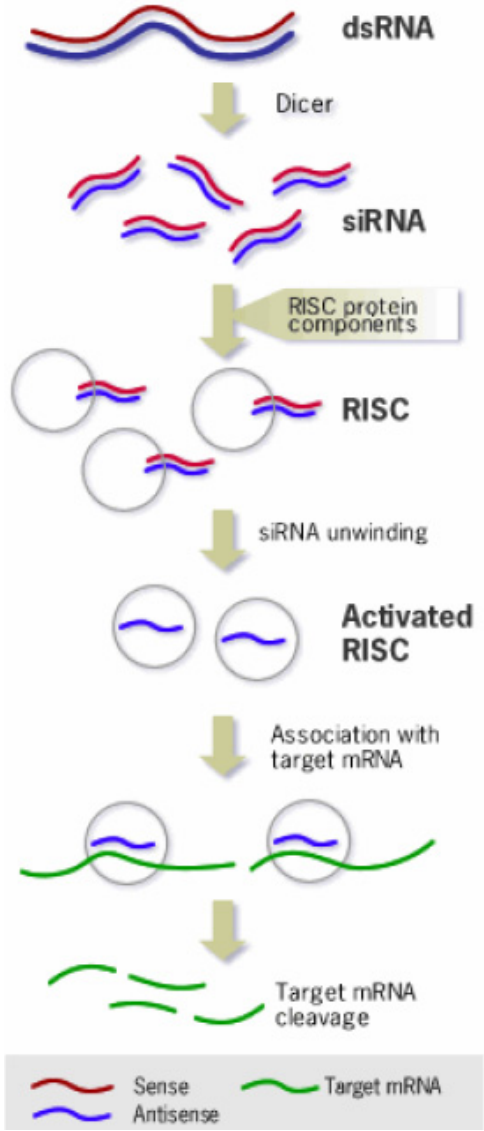
Examples of equivalent and non-equivalent graphs

$$P(a,b,c) = \underbrace{P(a\,|\,c)P(c\,|\,b)P(b)}_{m_0} = \underbrace{P(a\,|\,c)P(b\,|\,c)P(c)}_{m_1} = \underbrace{P(c\,|\,a)P(b\,|\,c)p(a)}_{m_2}$$

$$P(a,b,c) = \underbrace{P(c\,|\,a,b)P(a)P(b)}_{m_3}$$

Each common distribution *P(a,b,c),* that can be modelled with BN m_0 can also be modelled with m_1 and m_2 , and vice versa. However there exist distributions P*(a,b,c),* which can be modeled with BN m_3, but not with m_0 .





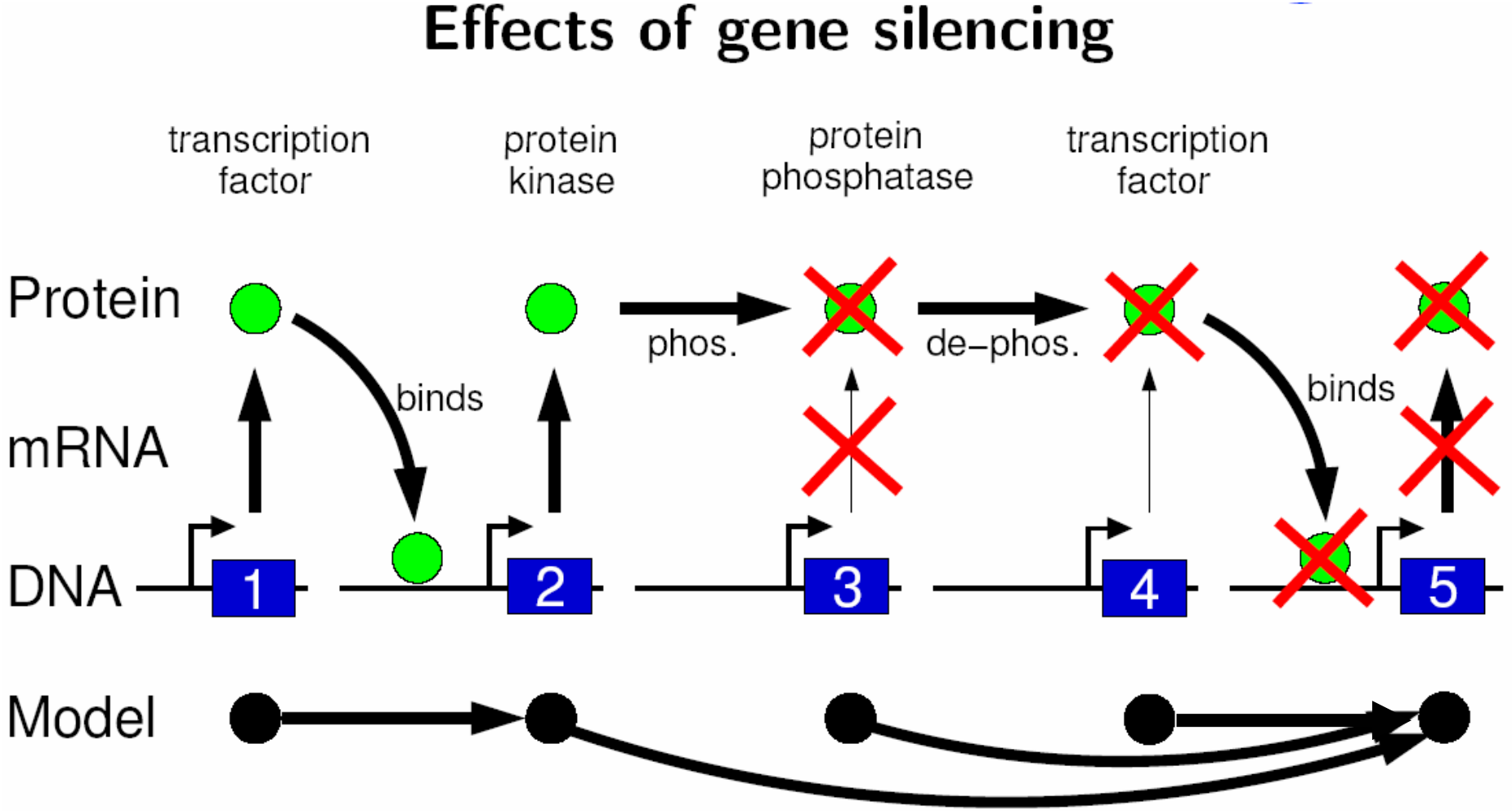
RNAi kills the messenger

(A. Fire, C. Mello, Nobel prize 2006)

1. **Double-stranded RNAs** (dsRNAs) get processed into **small interfering RNAs** (siRNAs).
2. siRNAs assemble into **RNA-induced silencing complexes** (RISCs).
3. The siRNA strands guide the RISCs to **complementary RNA molecules**, . . .
4. . . . where they **cleave and destroy** the cognate RNA.

Figure from http://www.ambion.com

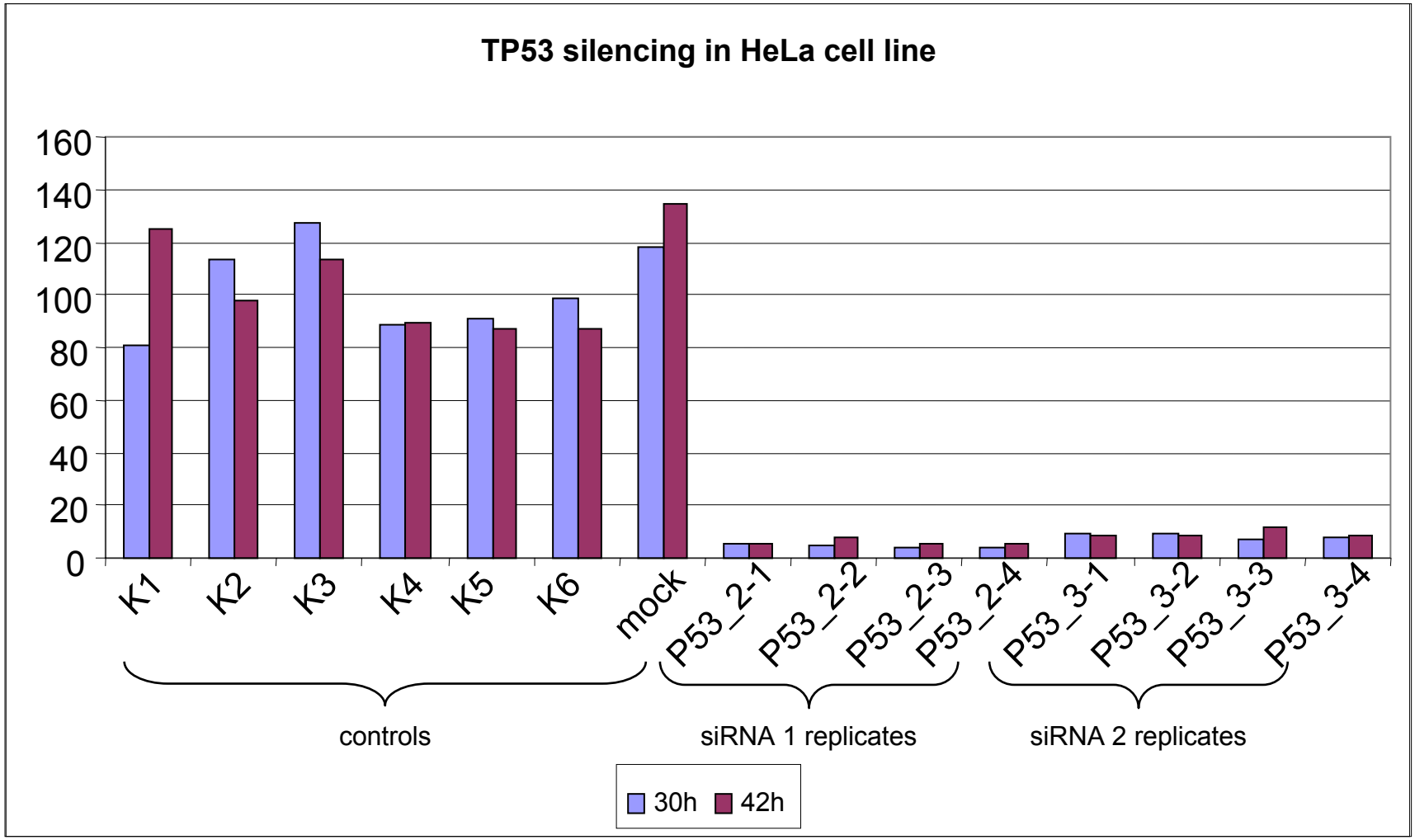
Learning from interventional data



Proof-of-principle Experiment

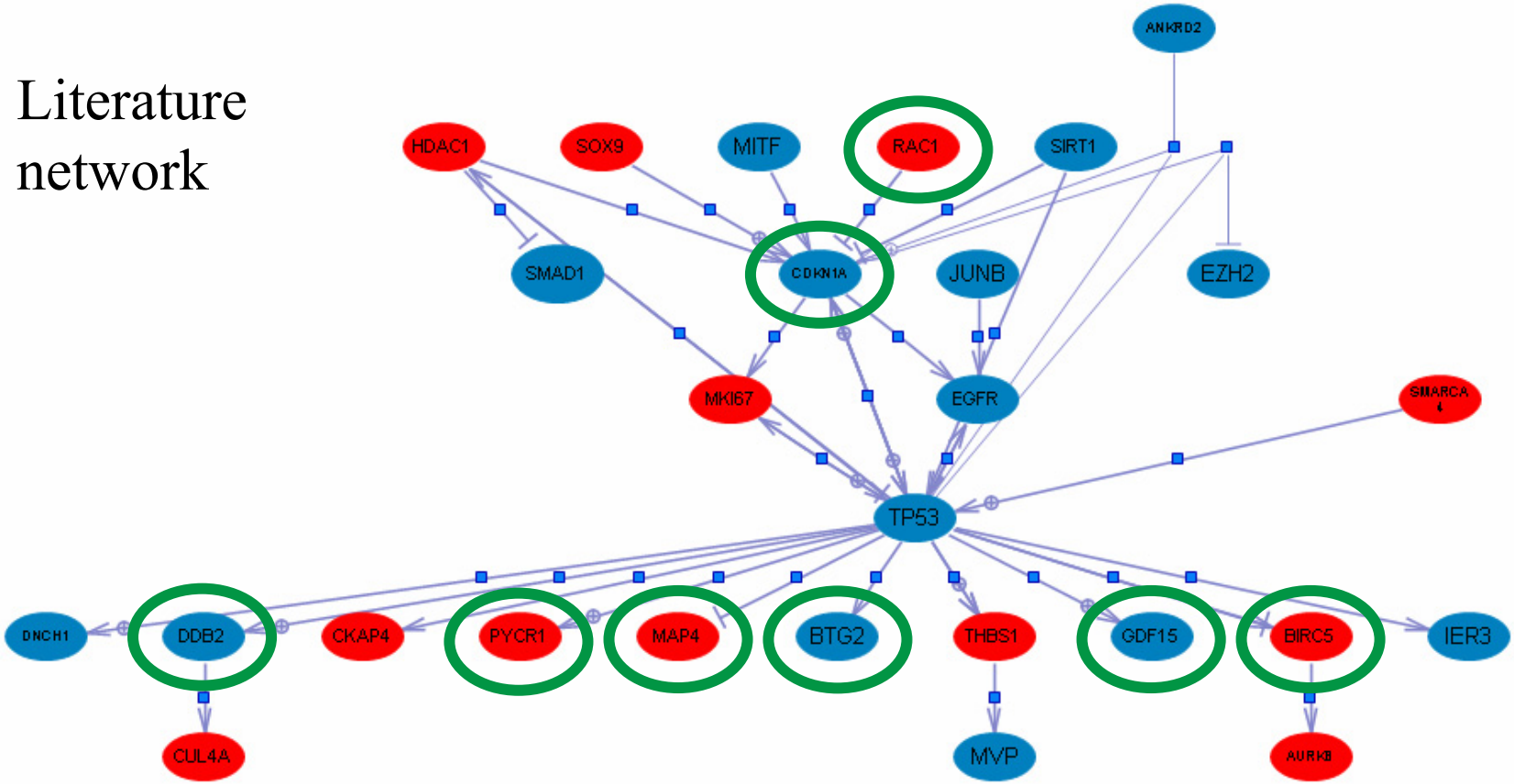
- TP53 chosen as model-gene for siRNA mediated knock-down
- nuclear protein, DNA-binding, postulated to bind as tetramer, activates expression of downstream genes that inhibit growth and/or invasion, thus function as a tumor suppressor
- very well known in literature, ease to find interaction partners
- Transfection of siRNA into HeLa cell line using HiPerFect transfection-reagent (HeLa cell line known to show very good transfection efficiencies)
- Minimal concentration of siRNA used to reduce possible off-target effects
- Measurement of silencing efficiency regarding mRNA of TP53 using qRT-PCR

Proof-of-principle Experiment



Proof of principle: The TP53 network

Literature network



increase

decrease

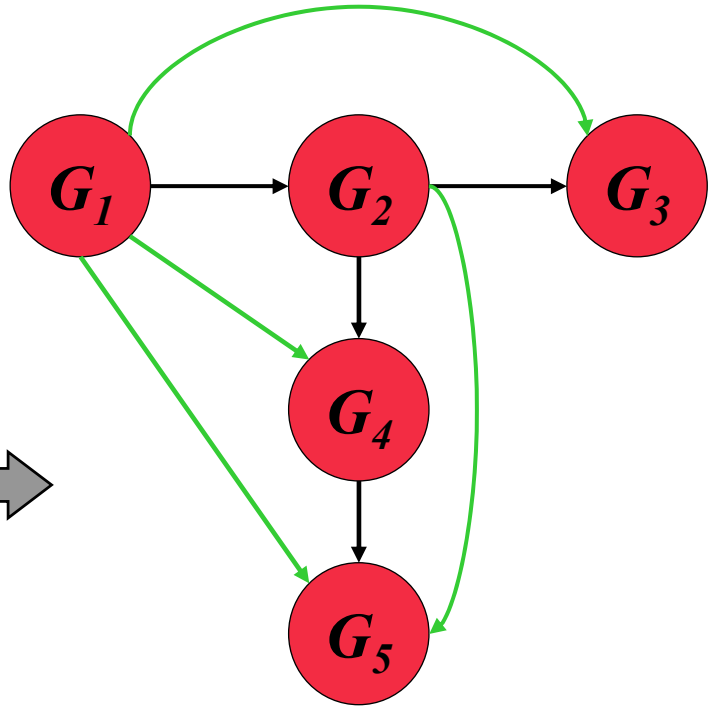
found by siRNA experiment

Pruning of Gene interaction Graphs

observations list

Pertur-bation	Effect
G_1	G_2 , G_3 , G_4 , G_5
G_2	G_3 , G_4 , G_5
G_3	-
G_4	G_5
G_5	-

Interaction graph



necessarily direct interactions

optional, possibly indirect interactions

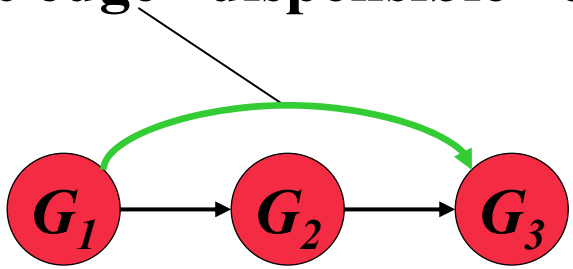
Pruning of Gene interaction Graphs

Given a gene interaction graph, find edges that survive Occam's razor (14th century):

"***non est ponenda pluritas sine necessitate***"

(pluralities ought not to be proposed without necessity)

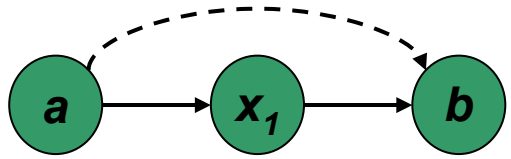
Is this edge "dispensible" or not?



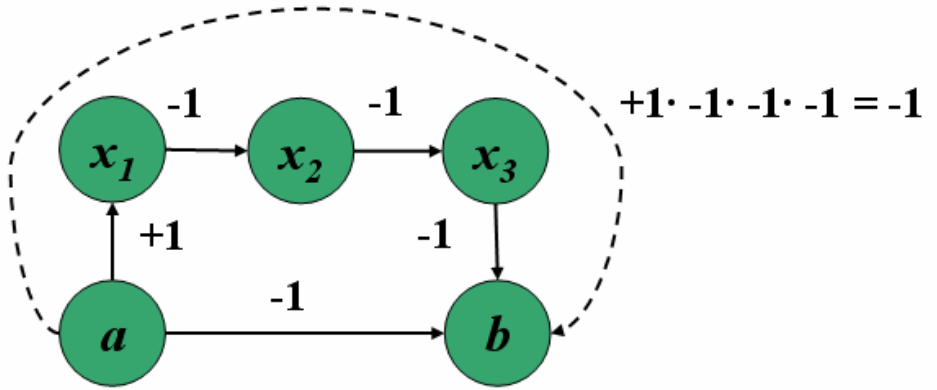
Need for algorithm to define and find
minimal consistent and biologically meaningful graph

Finding non-necessary edges

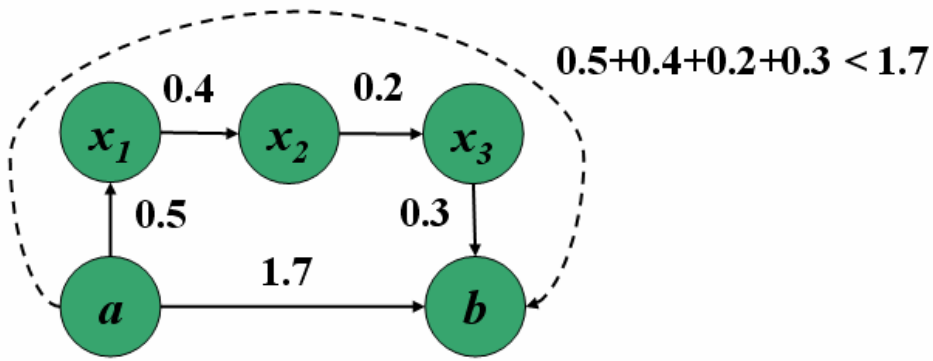
- "Trivial".
  Remove all edges a→b for which there exists a bypass (a longer way from a to b). [Wagner, 2002]



- "Signs".
  Let every edge of the observational graph hava a sign +1 or –1 according to the direction of the regulatory effect.
  Remove a→b if product of all signs along the path a→... →b equals the sign of the edge a→b [Tringe et al., 2004]

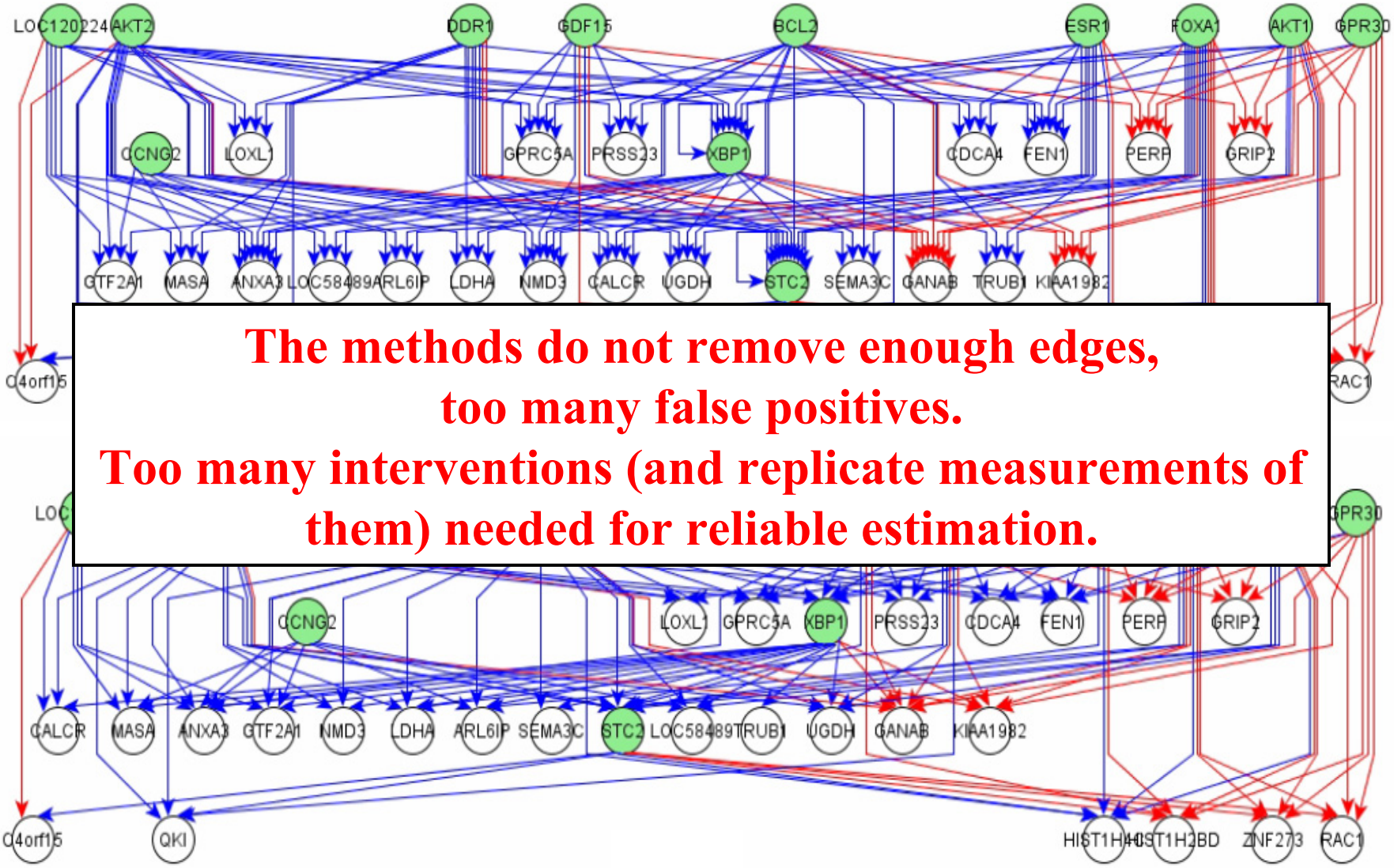


- "Weights".
  Let every edge be weighted with a non-negative number. Edges with low weights are meant to represent edges for which there is strong evidence for a direct regulatory interaction.
  Remove a→b if sum of the weights along the path a→... →b is smaller than the weight of the edge a→b
  [Tresch et al.]



Tresch et al, unpublished

Unpruned vs. Pruned Network



The methods do not remove enough edges, too many false positives.
Too many interventions (and replicate measurements of them) needed for reliable estimation.

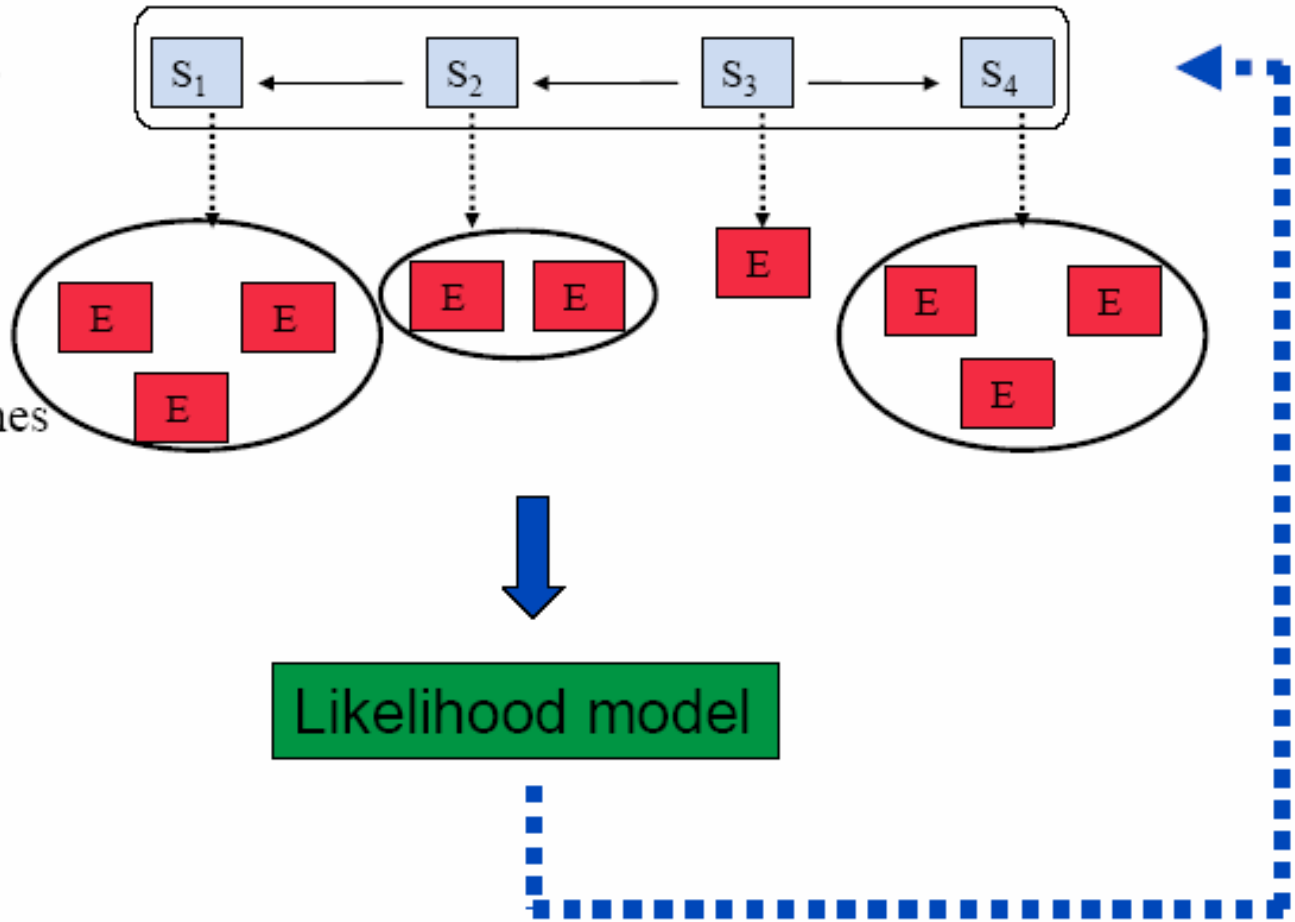
The Signal-Effects Model

1. Choose **candidate network topology** of silenced genes (S-genes)

2. Attach effected genes (E-genes)

3. Calculate score using Bayesian statistics

4. Propose different topology



Markowetz et al., Bioinformatics, 2005

Pathways from RNAi data – an example

Response to microbial challenge

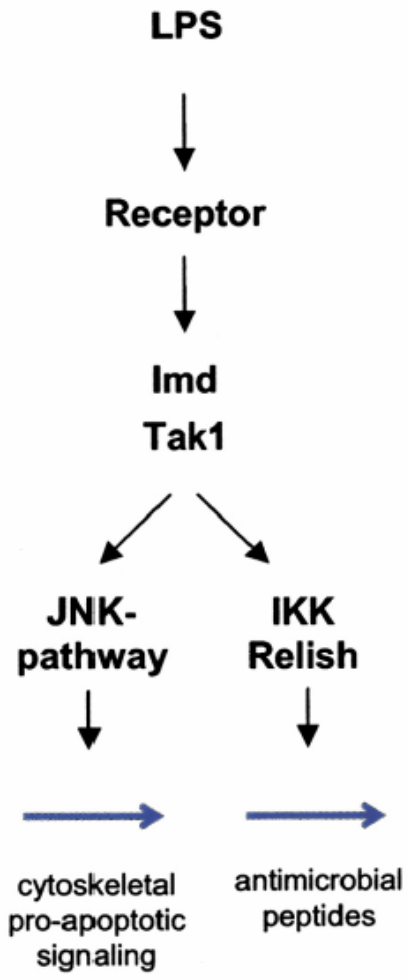
(Boutros *et al.*, Dev Cell, 2002)

Columns: silenced genes.

Rows: effects on other genes.

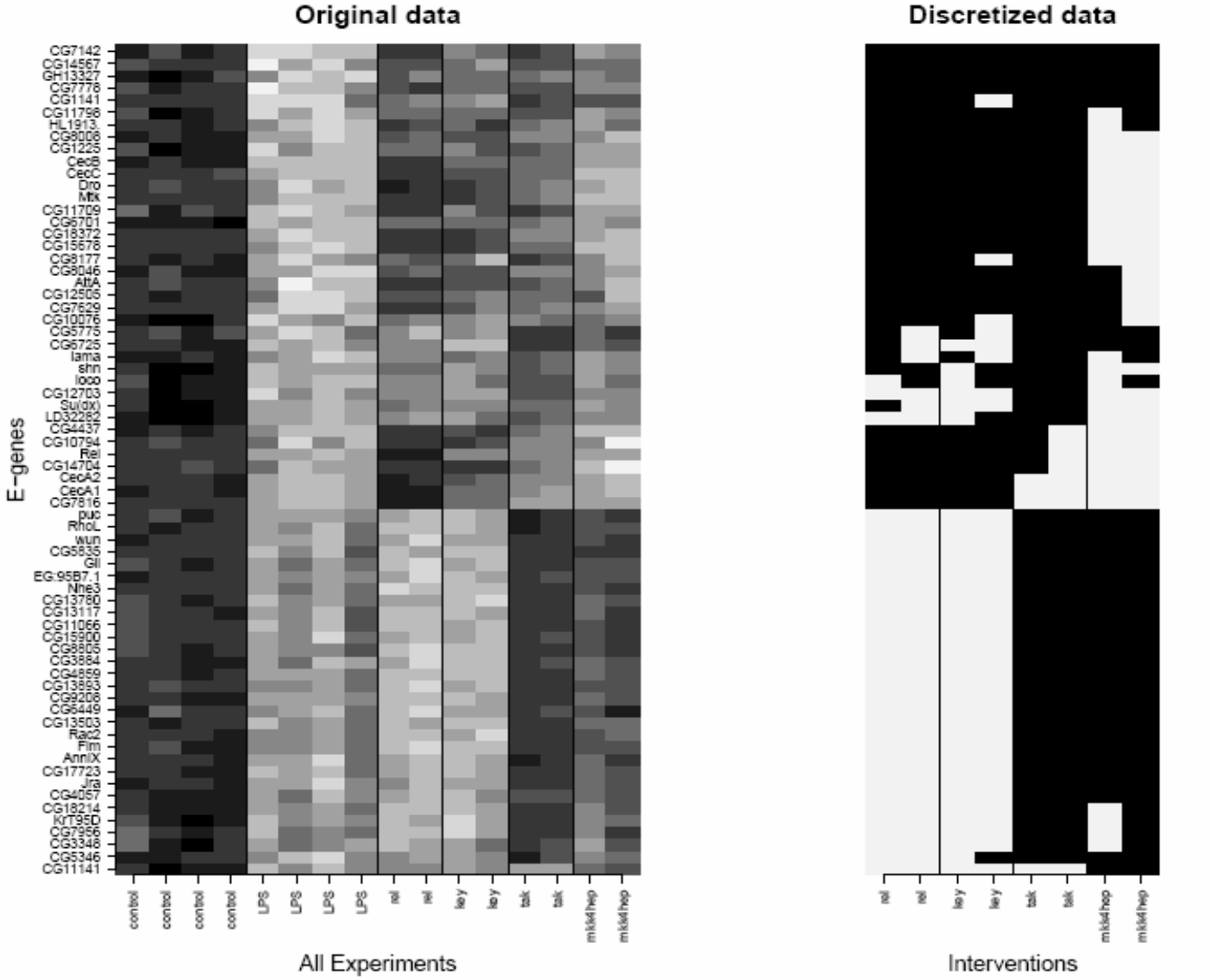
Results:

1. Silencing tak1 reduces expression of all LPS-inducible transcripts.
2. Silencing rel (key) or mkk4/hep reduces expression of separate sets of induced transcripts.

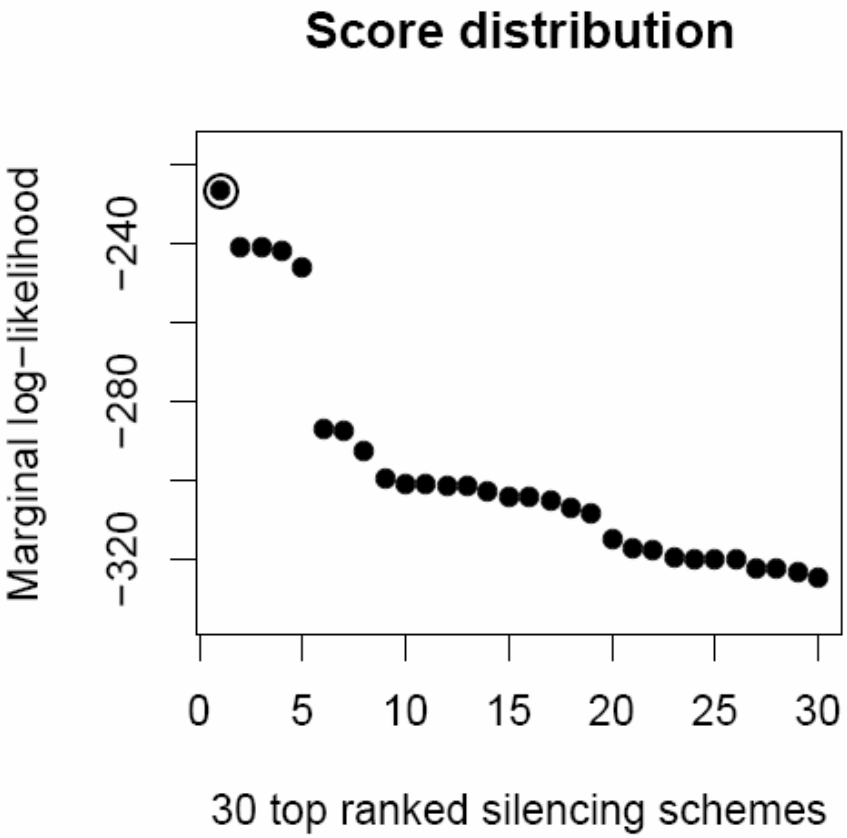


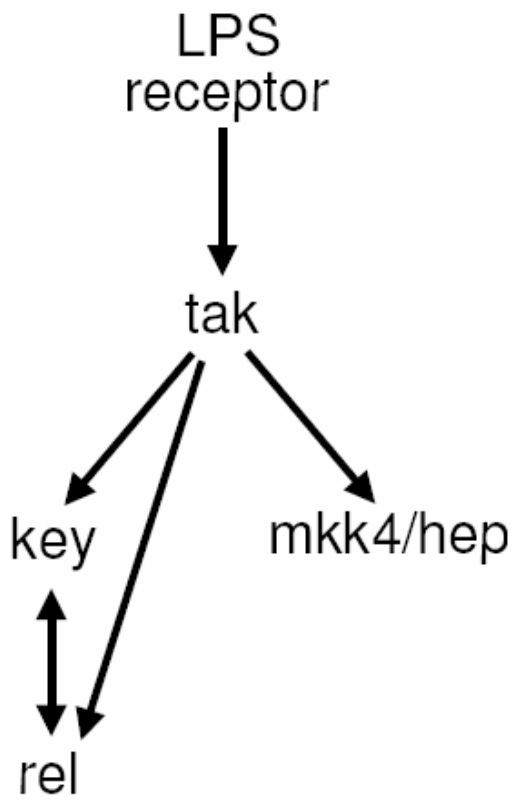
Figures from (Boutros *et al.*, 2002)

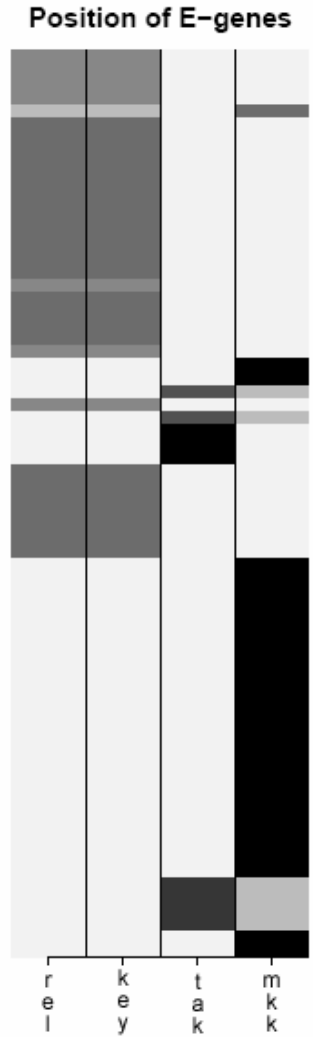
Application to Drosophila data



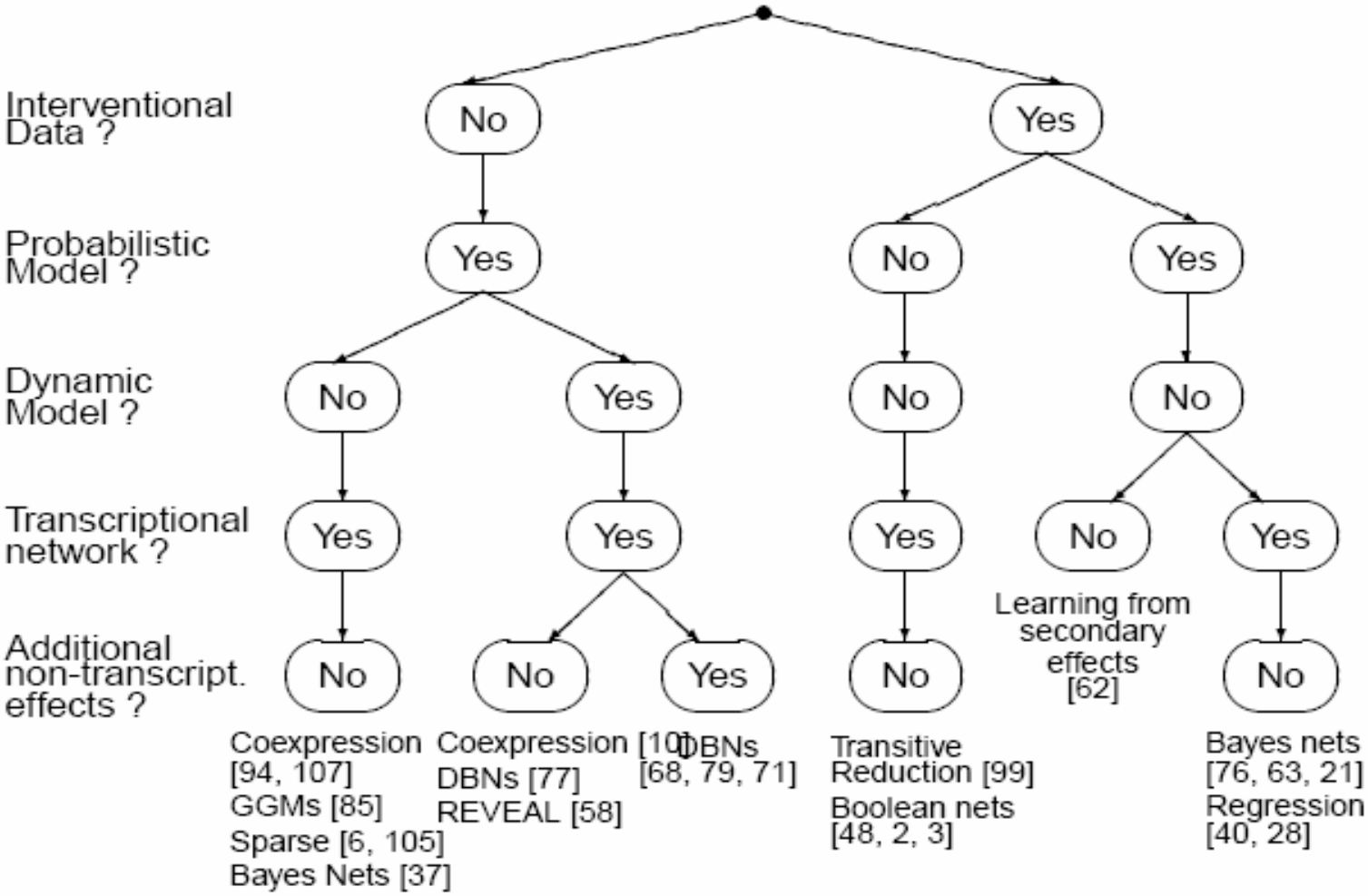
Application to Drosophila data







Survey of network models



Florian Markowetz, *Computational Inference of Cellular Pathways*, 2005 Oct 5

Networks in R/Bioconductor

- graph: basic class definitions and functionality
- RBGL: interface to graph algorithms (e.g. shortest path, connectivity)
- Rgraphviz: rendering functionality Different layout algorithms. Node plotting, line type, colour etc. can be controlled by the user.
- dynamicGraph: visualize interactive Graphs with TclTK.
- KEGGSOAP: Connecting to the KEGG database.
- GeneTS: Estimate GGMs from Microarray Data.

Pathways and Visualization Tools

- **Some Pathway Databases:**
  - **KEGG (http://www.genome.jp/kegg)**
  - **TRANSPATH (http://www.biobase.de)**
  - **Biocarta (http://www.biocarta.com)**
  - **Reactome (http://www.reactome.org)**
  - **HumanCyc (http://humancyc.org)**
  - **Signal Transduktion Knowledge Environment (http://stke.sciencemag.org)**

- **Software tools**
  - **GeneMAPP (www.genemapp.org)**
  - **GoMiner (http://discover.nci.nih.gov/gominer)**
  - **Bioconductor/Graphviz (http://www.bioconductor.org)**
  - **Cytoscape (http://www.cytoscape.org)**

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