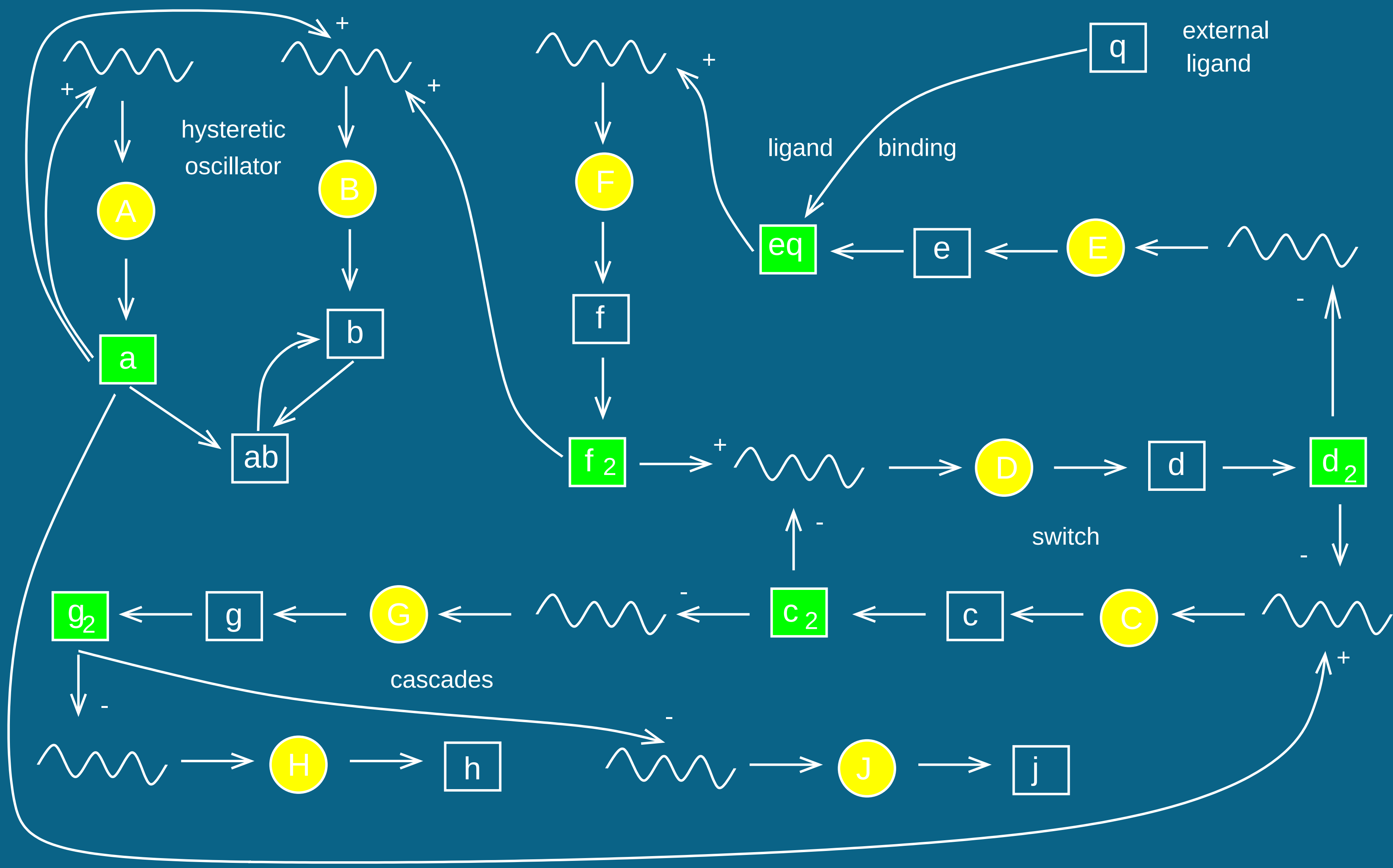
# Reverse engineering of gene regulatory networks

Dirk Husmeier
Biomathematics & Statistics Scotland (BioSS)
JCMB, The King's Buildings, Edinburgh EH9 3JZ, UK
http://www.bioss.ac.uk/∼dirk



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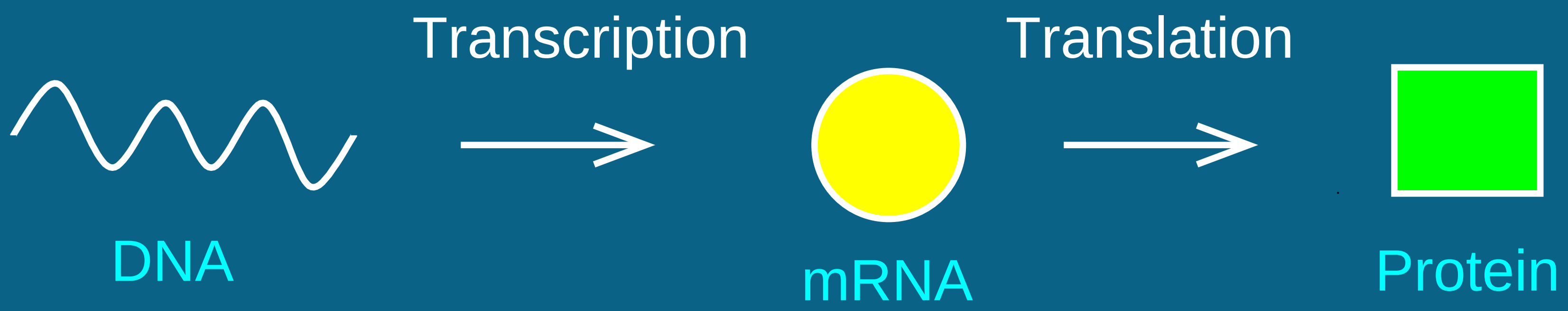
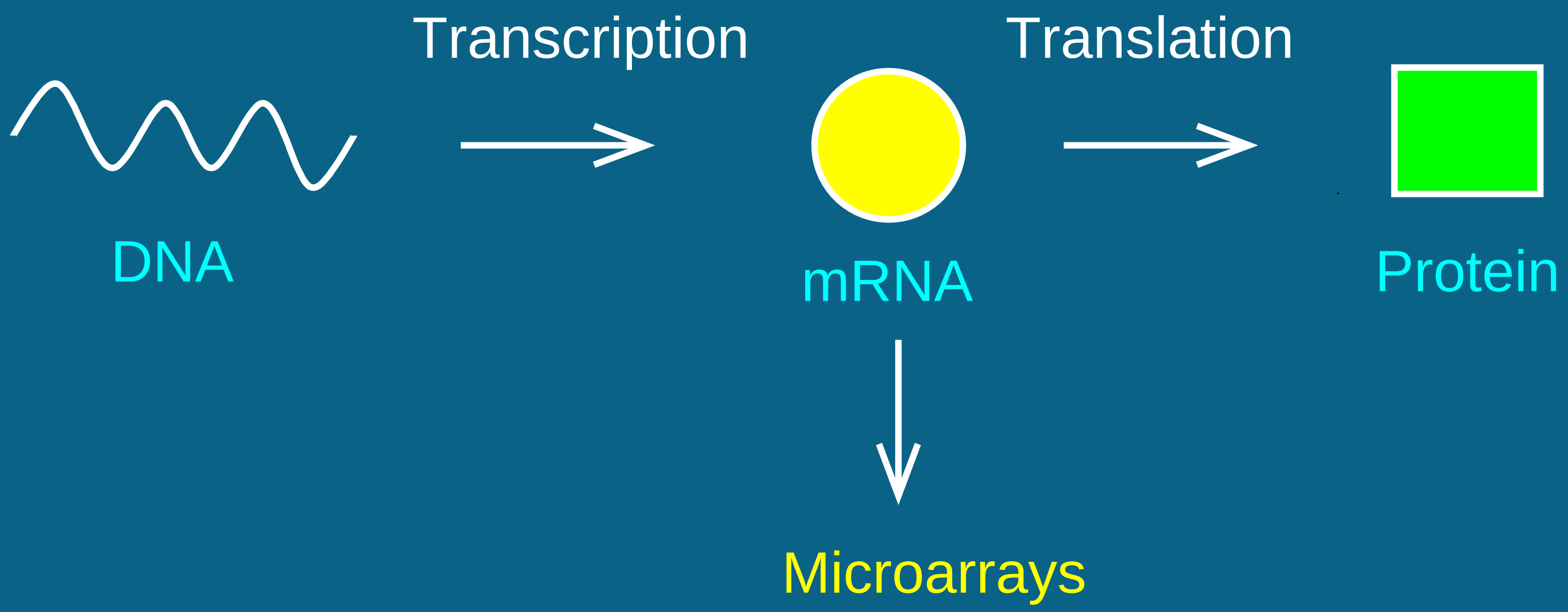

Transcription
Translation
DNA
mRNA
Protein


Transcription
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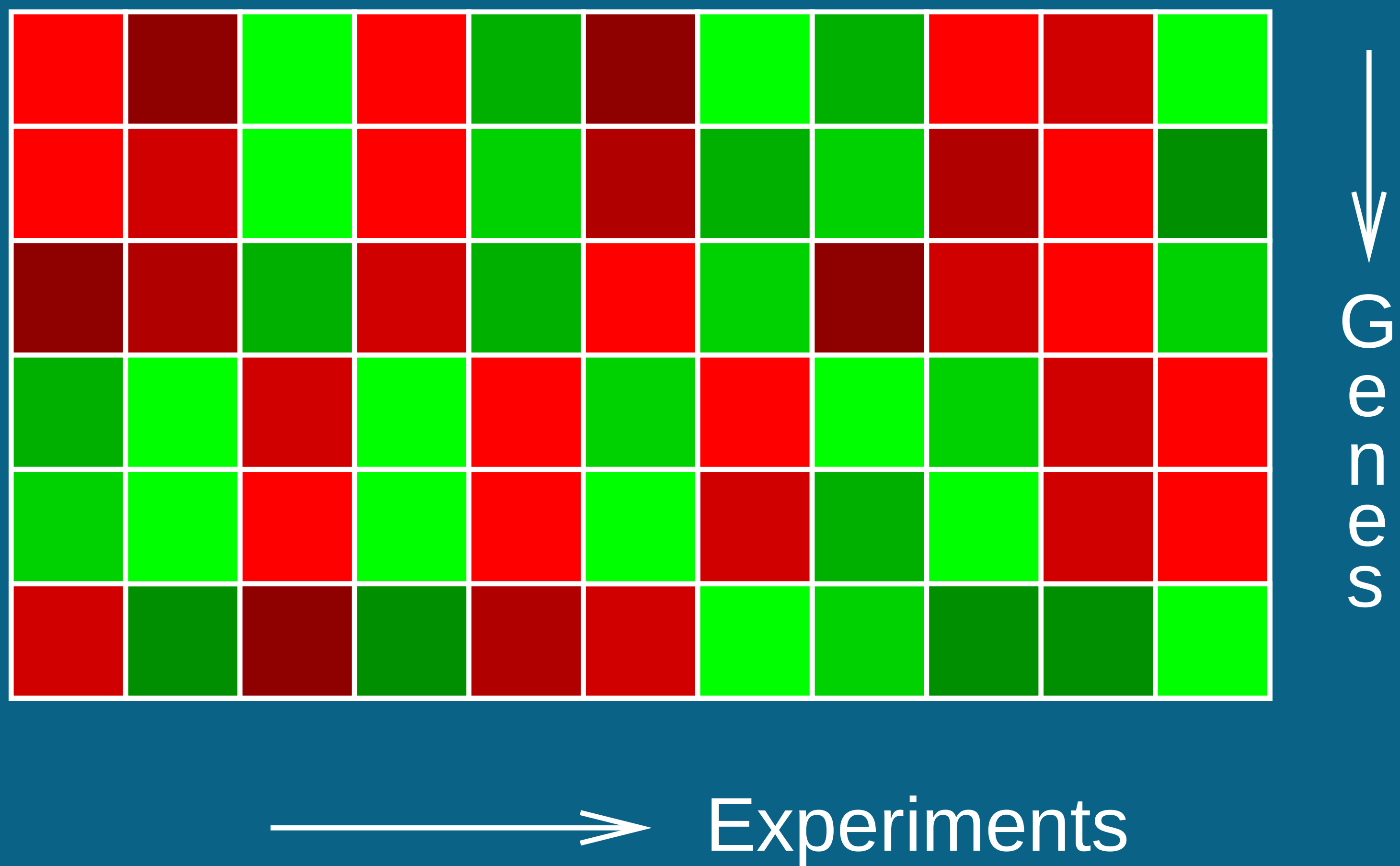
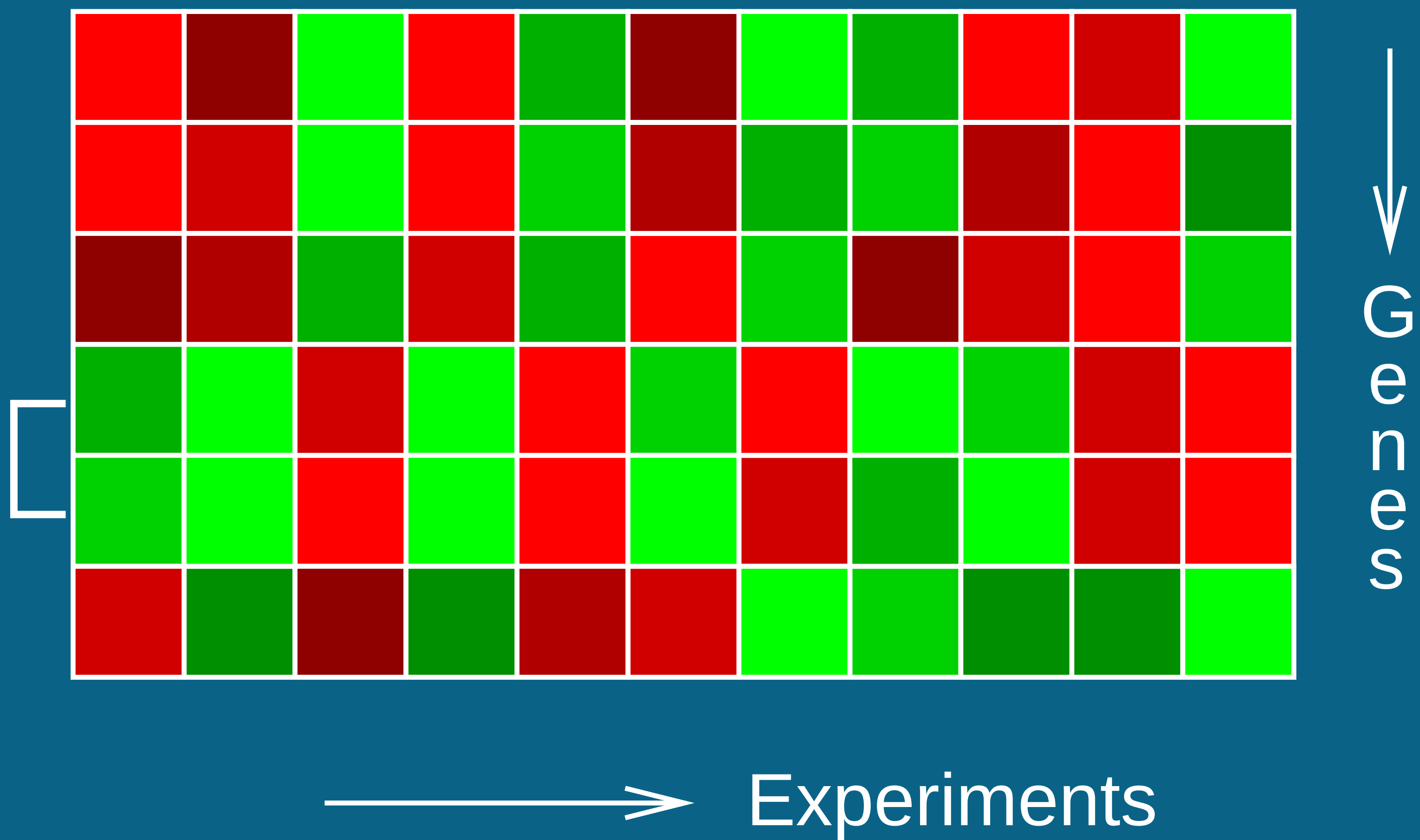
Protein
Microarrays


Genes
Experiments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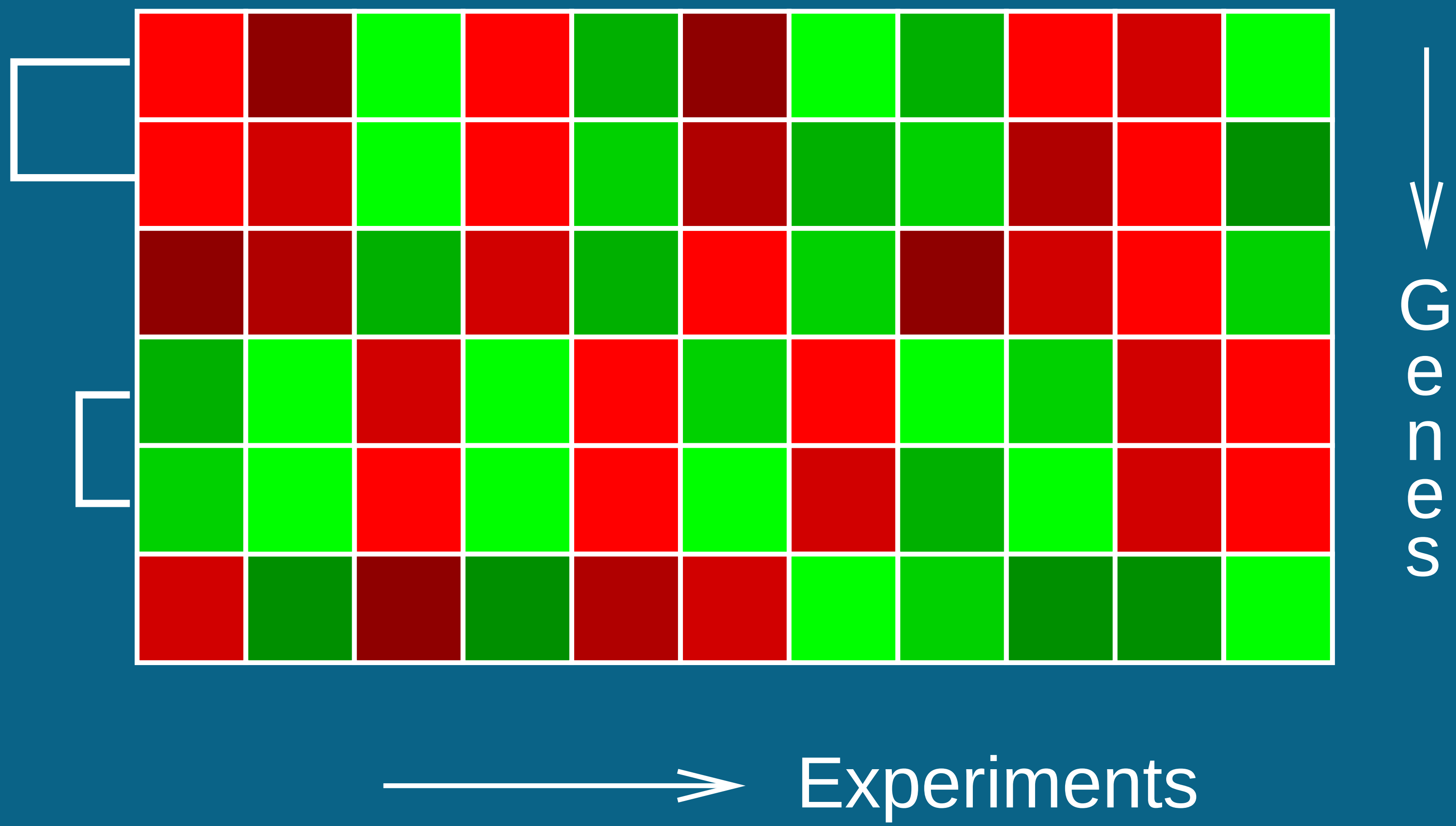
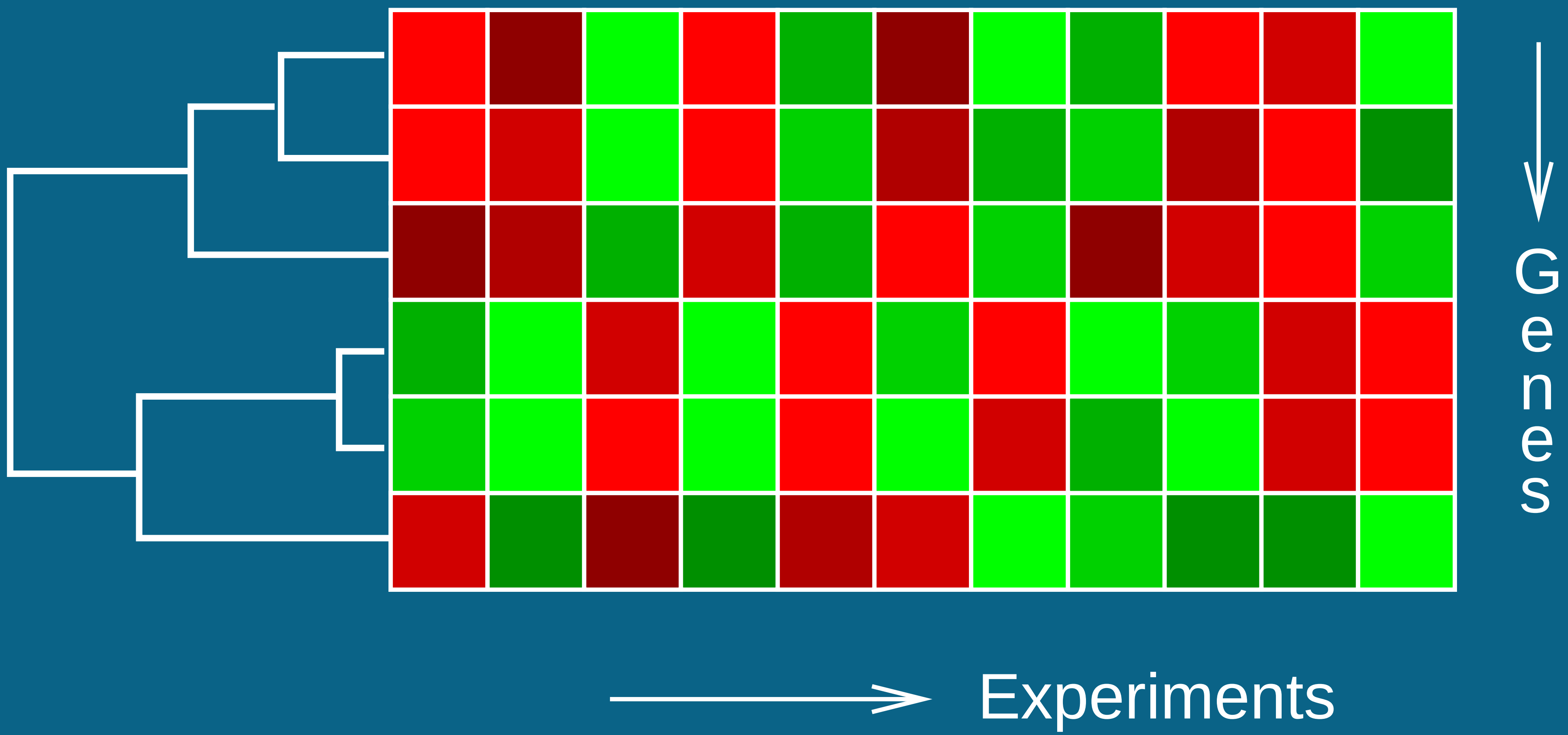

Genes
Experiments


Genes
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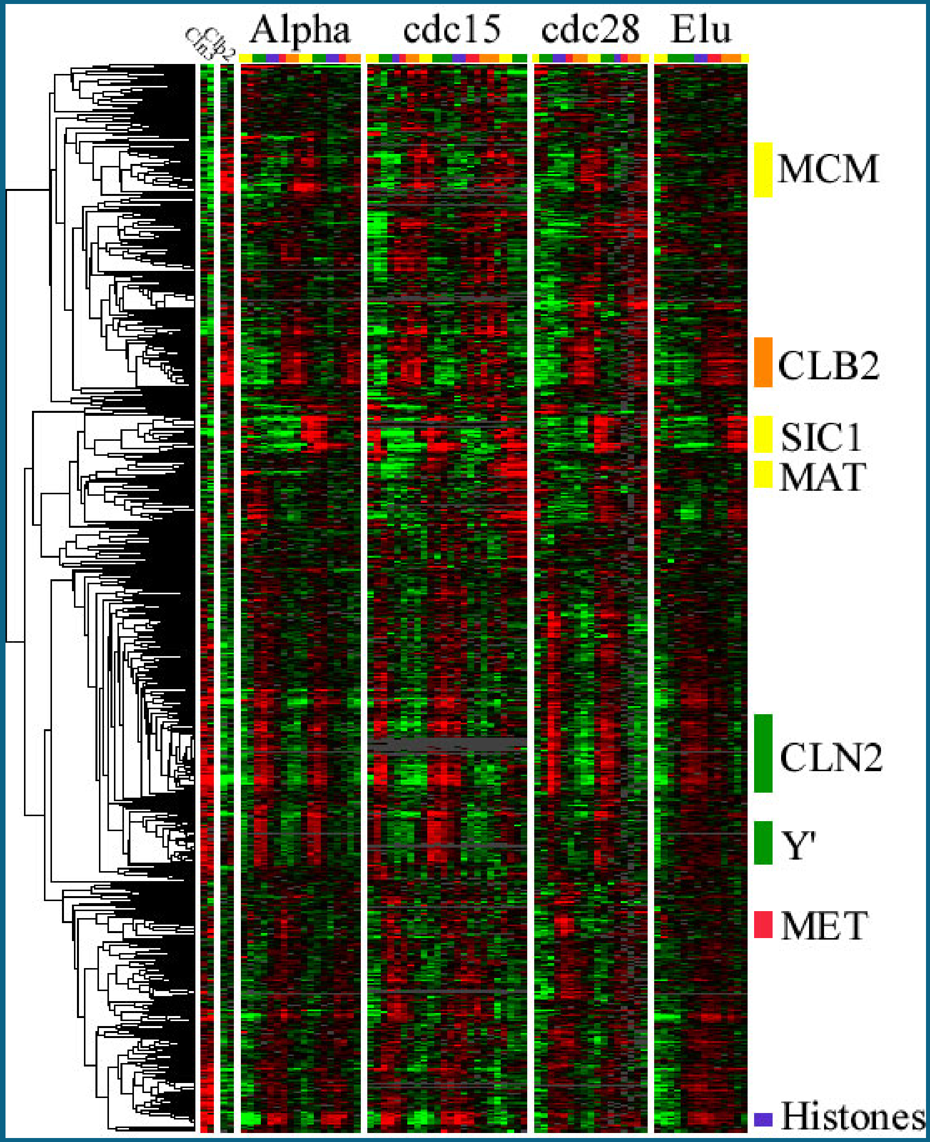



From Spellman et al., http://cellcycle-www.stanford.edu/

# Advantage of clustering

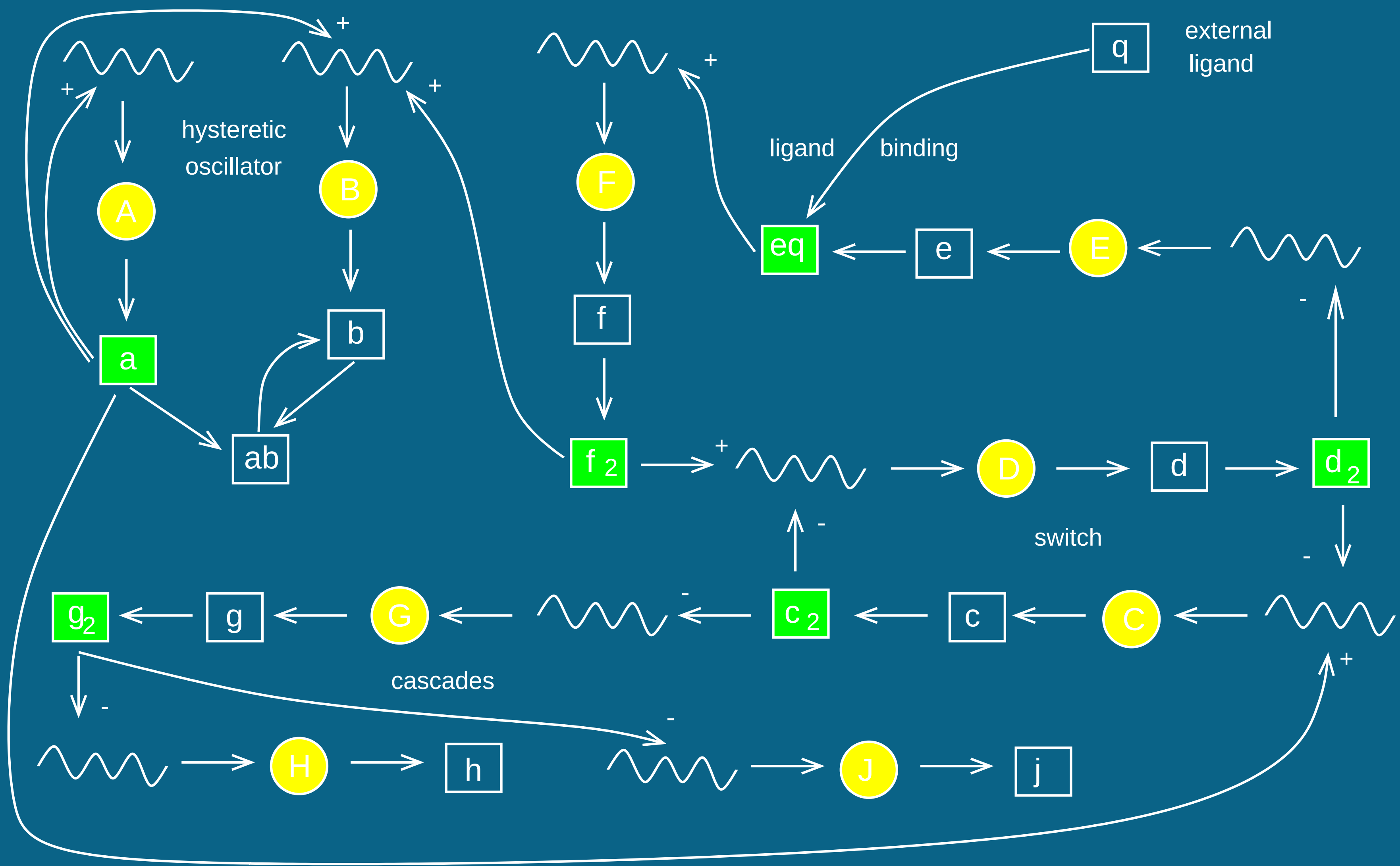
Fast, computationally cheap

**Advantage of clustering**

Fast, computationally cheap

**Shortcoming of clustering**

It is **NOT** reverse engineering



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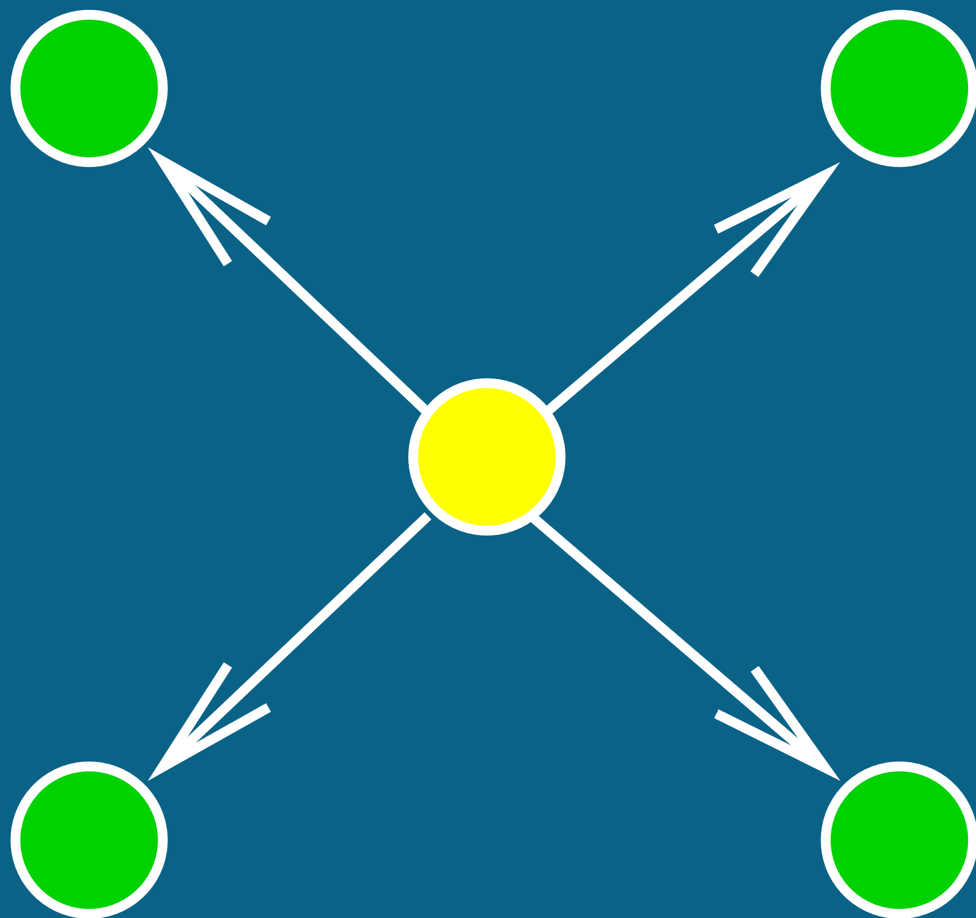

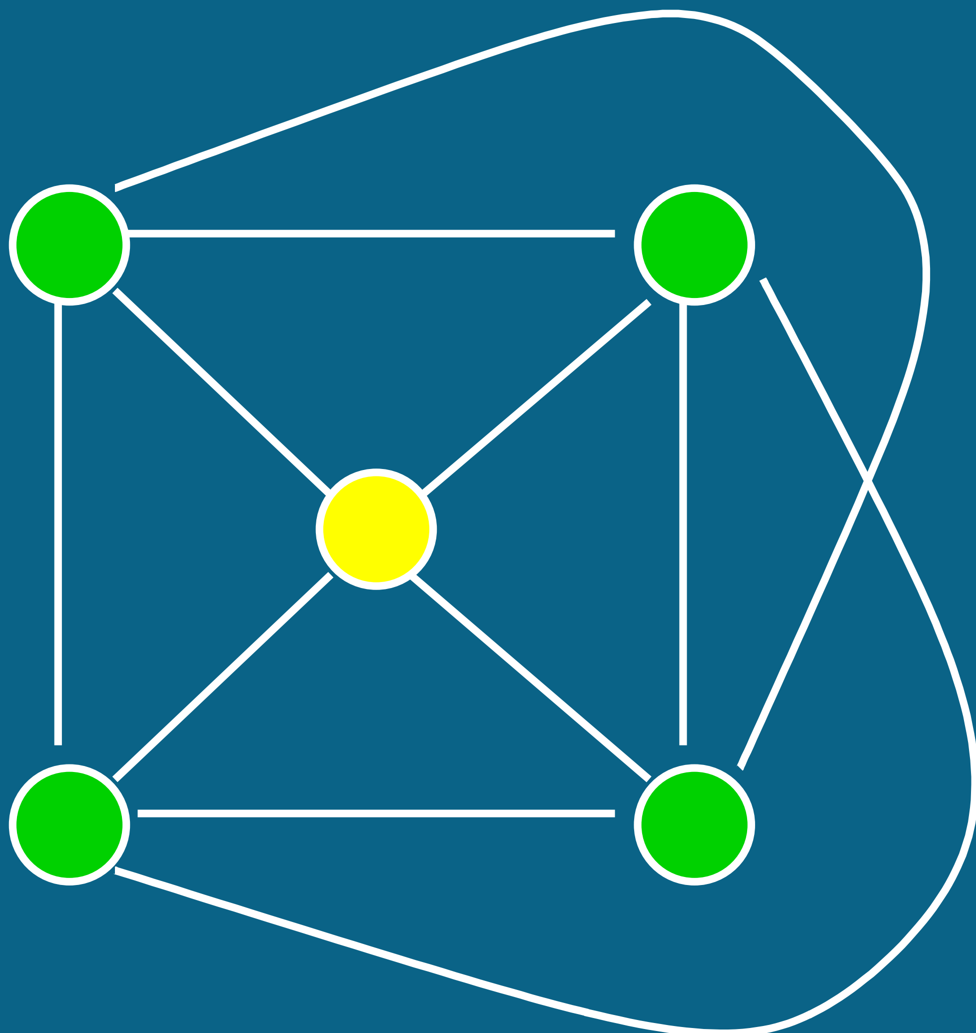

## Reverse engineering

Learn the network structure from gene expression data.

Problem: Noise, sparse data

# Bayesian networks

Probabilistic framework for
robust inference of interactions
in the presence of noise

Nir Friedman et al. (2000)
Journal of Computational Biology 7: 601-620

# Outline of the talk

- Recapitulation: Bayesian networks
- Reverse engineering:
  Learning networks from data
- Application to the yeast cell cycle
- Estimating the accuracy of inference

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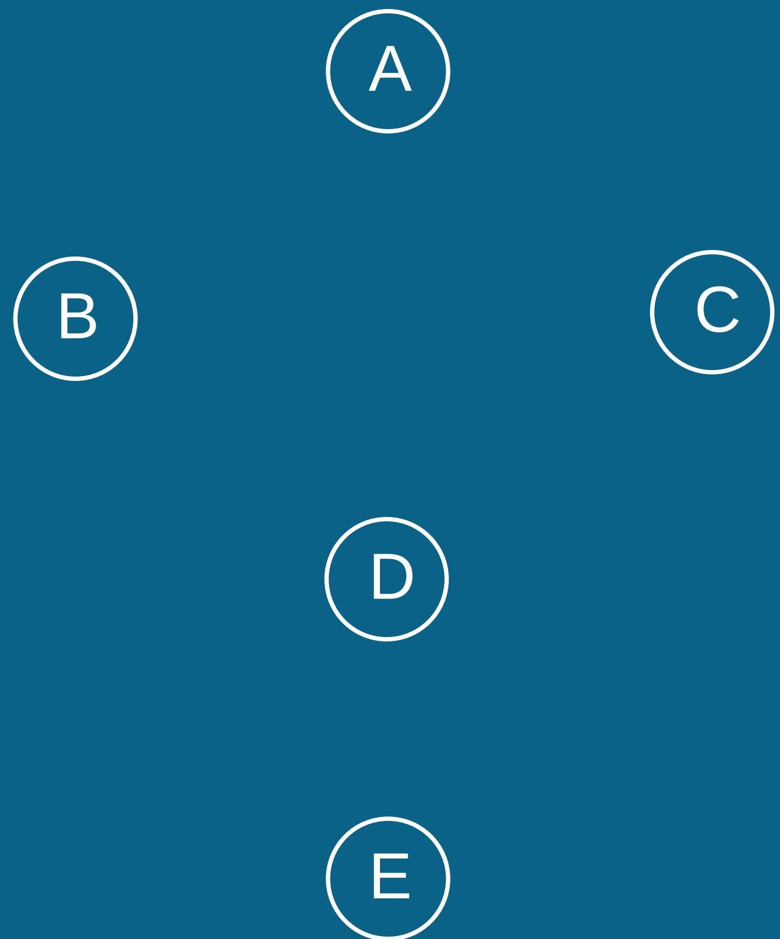
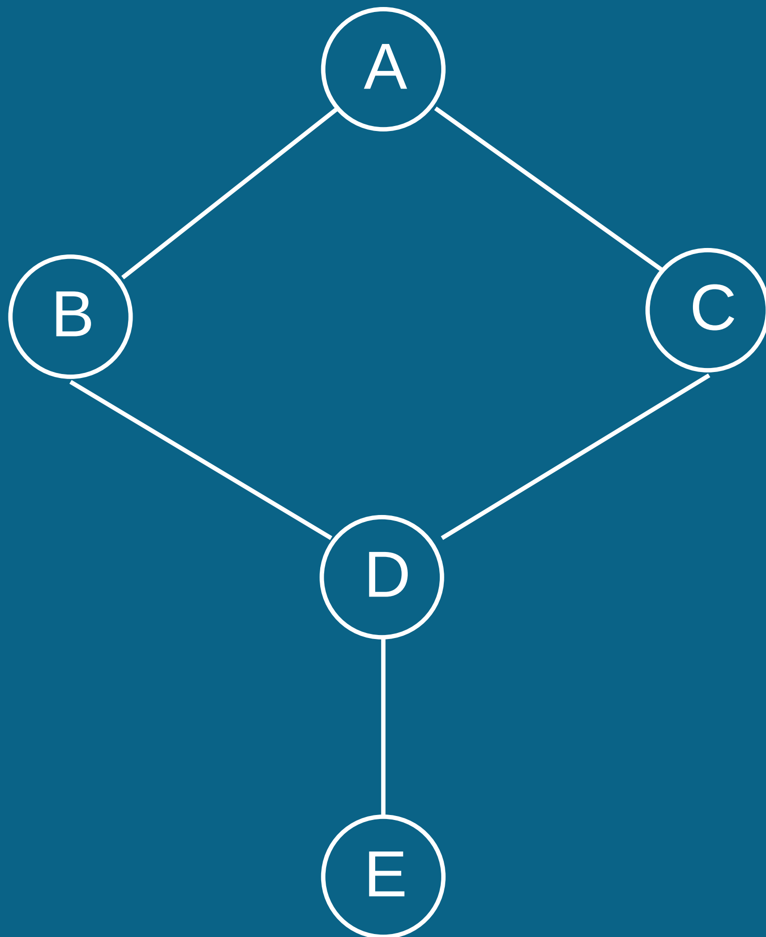
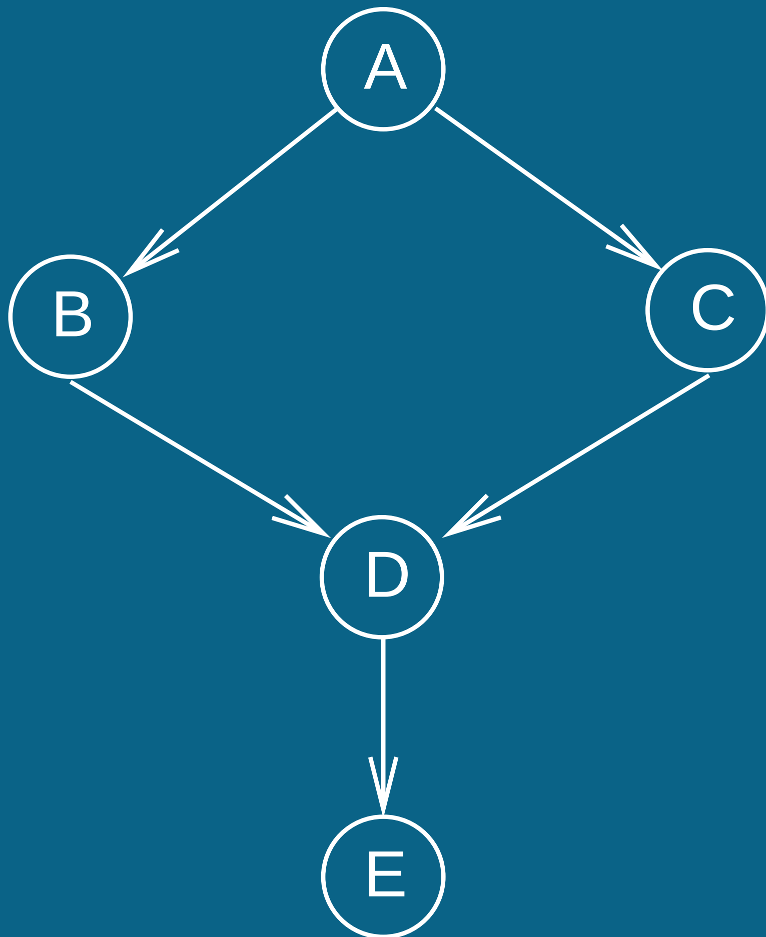


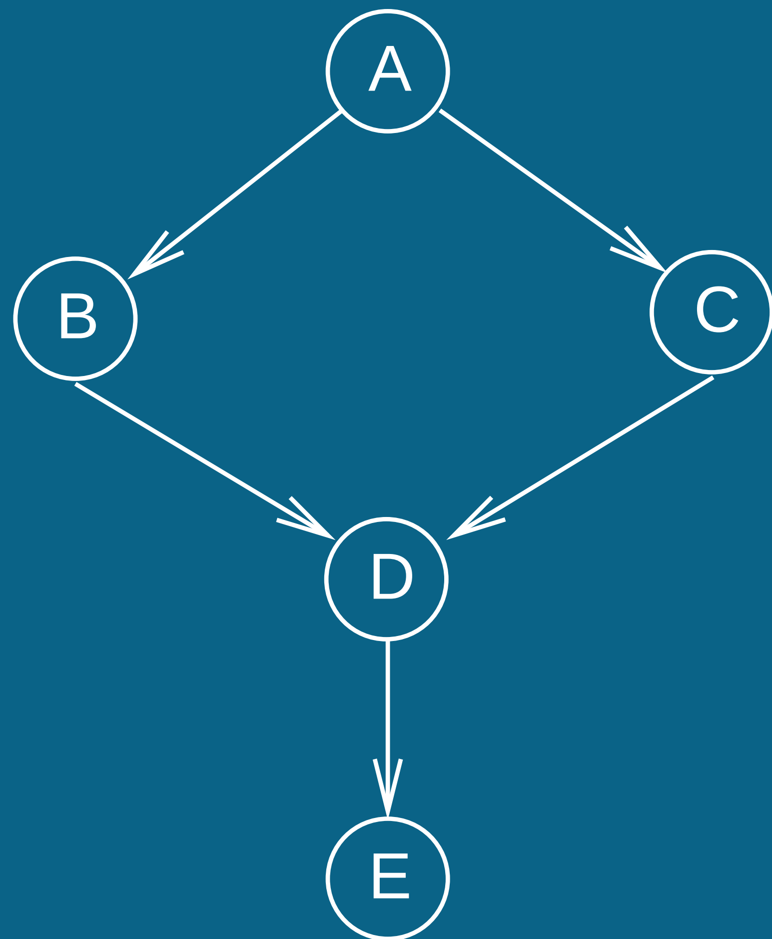

Nodes



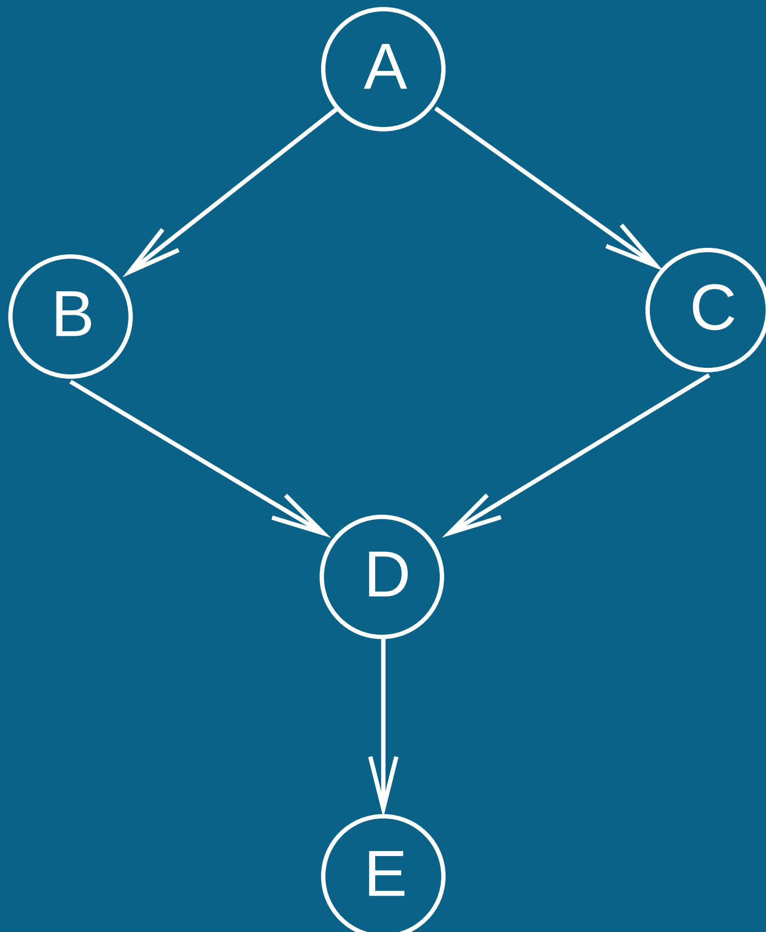

Edges



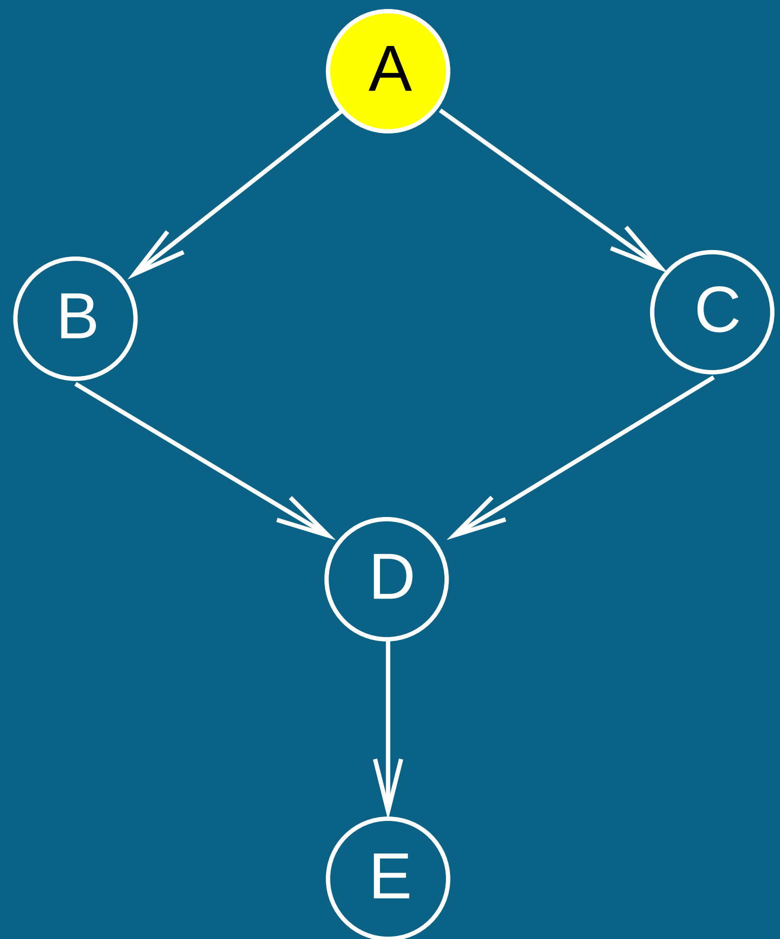

Edges = directed




$$P(A,B,C,D,E) = \prod_i P(\text{node}_i|\text{parents}_i)$$

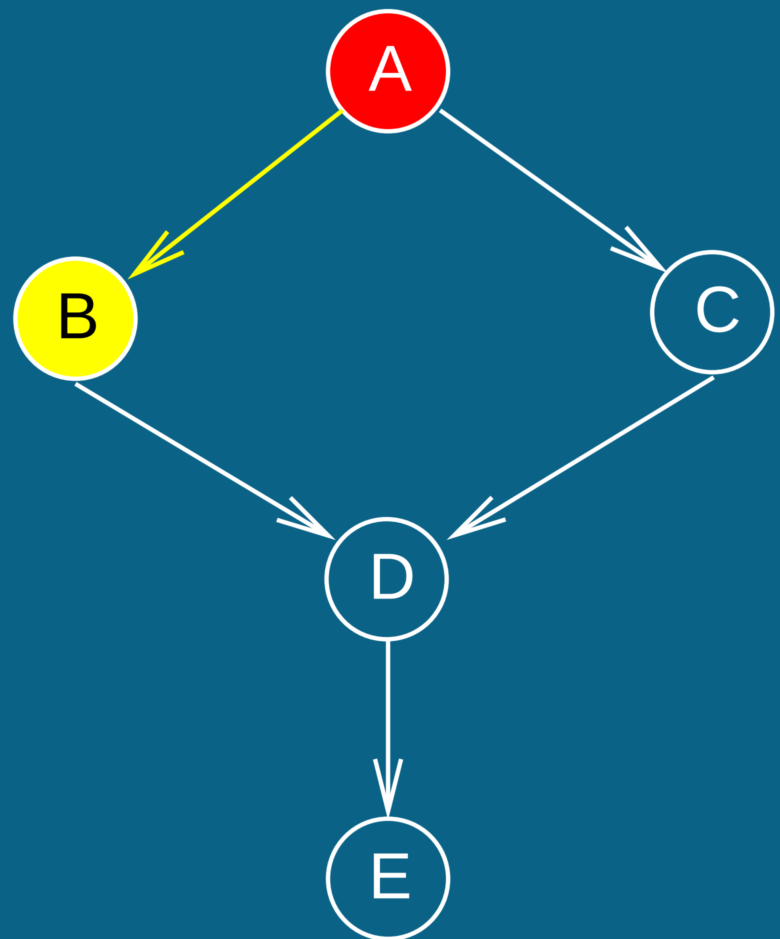



$$P(A, B, C, D, E) =$$



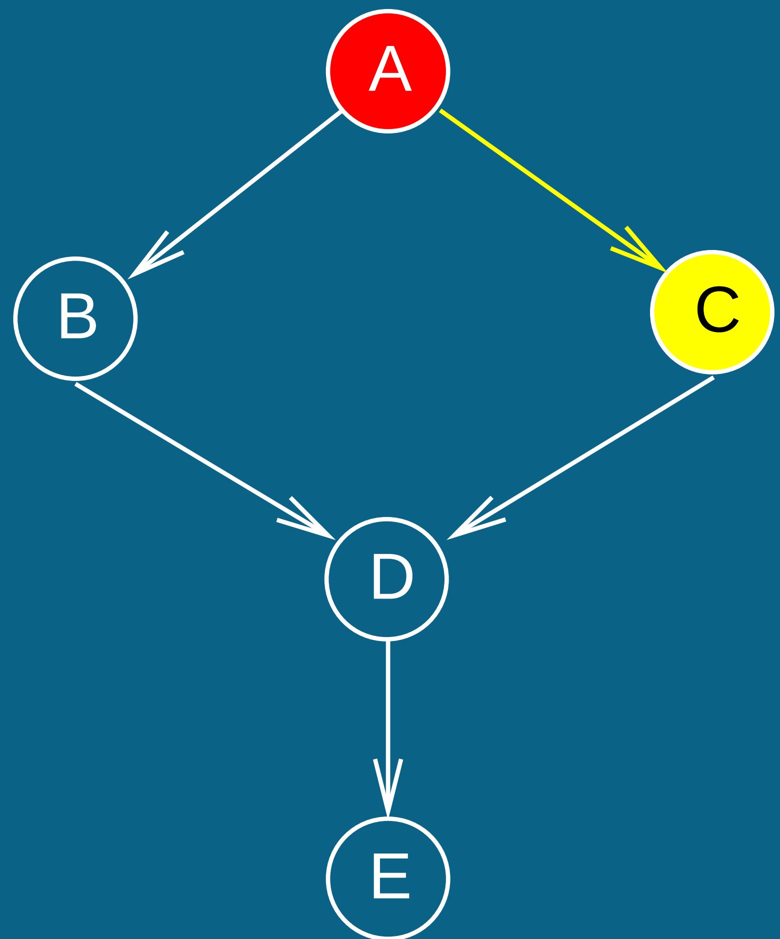

$$P(A, B, C, D, E) =$$

$$P(A)$$



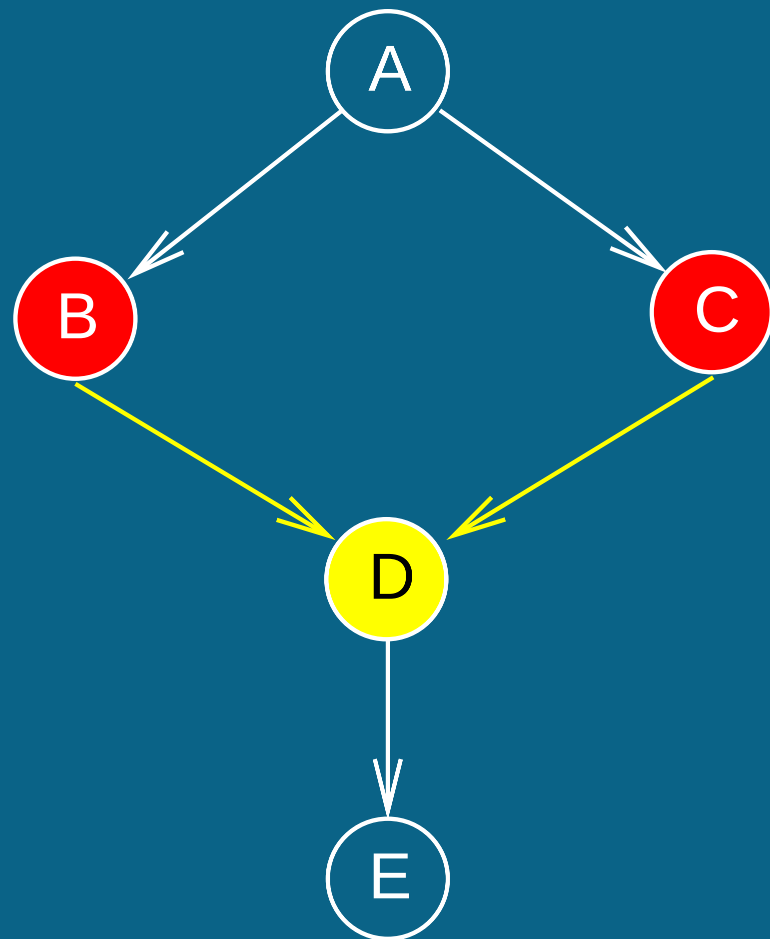

$$P(A, B, C, D, E) =$$

$$P(A)P(B|A)$$



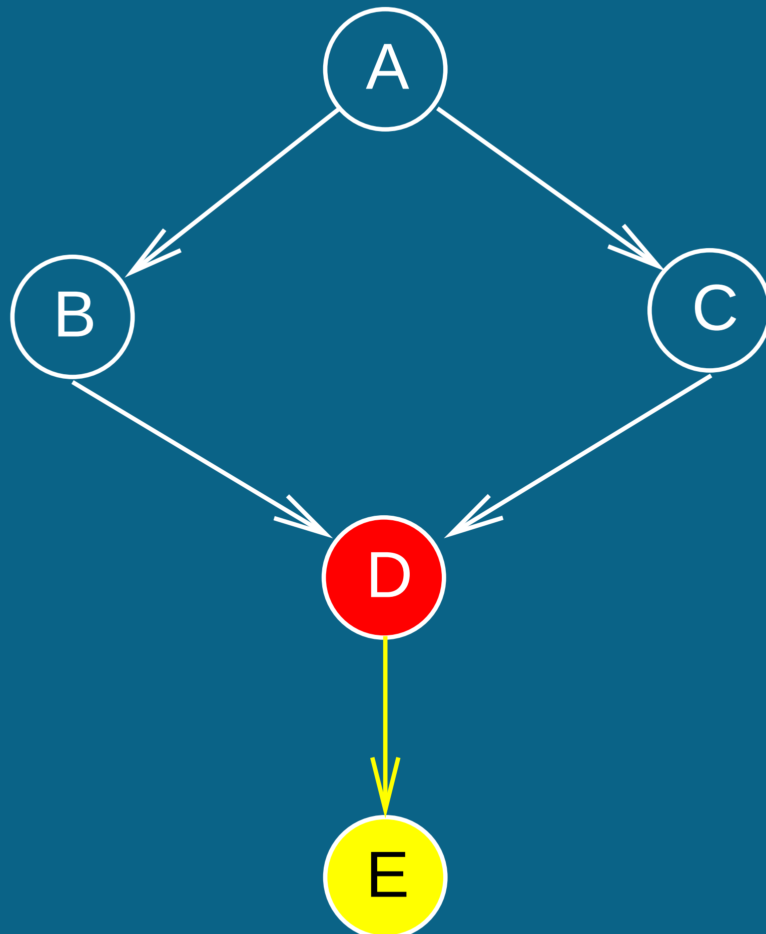

$$P(A, B, C, D, E) =$$

$$P(A)P(B|A)P(C|A)$$




$$P(A, B, C, D, E) =$$

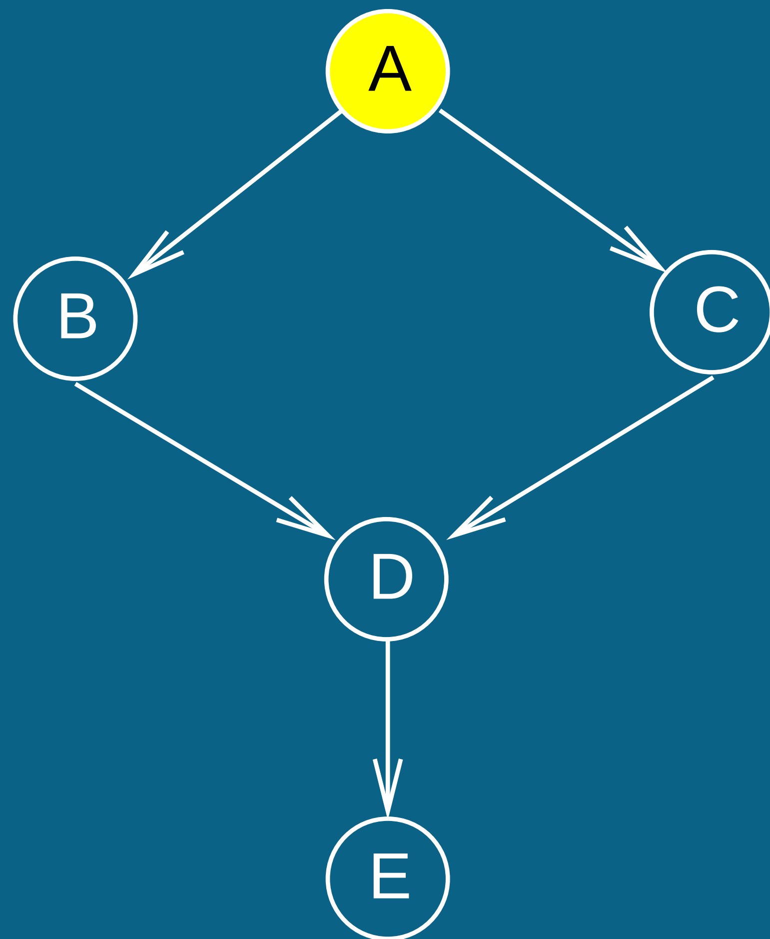
$$P(A)P(B|A)P(C|A)P(D|B, C)$$



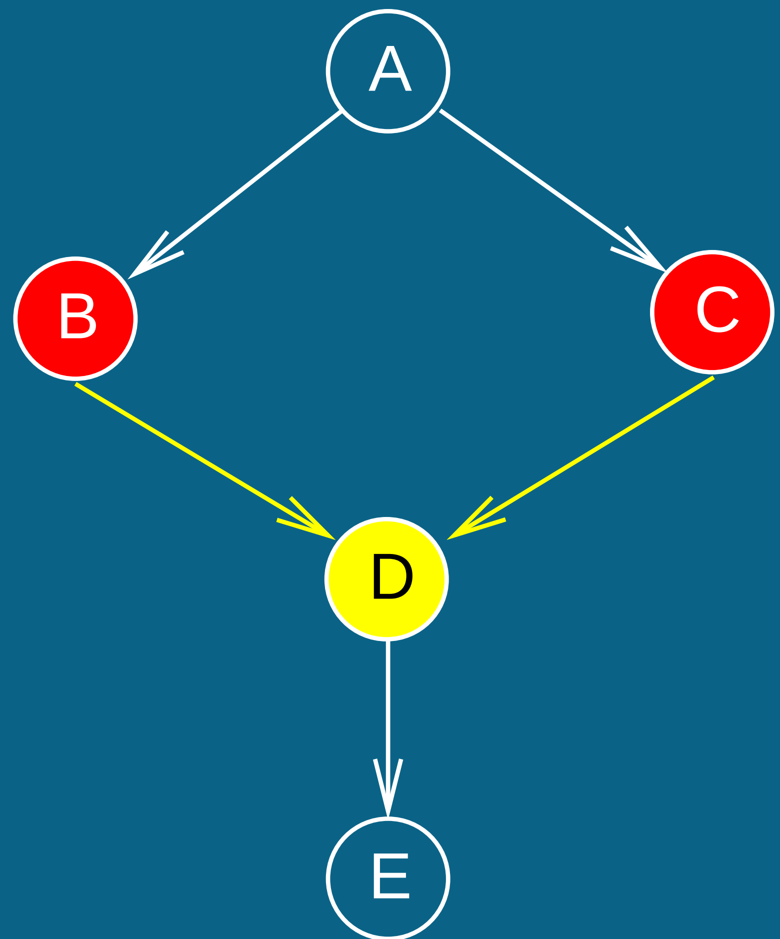

$$P(A, B, C, D, E) =$$

$$P(A)P(B|A)P(C|A)P(D|B, C)P(E|D)$$

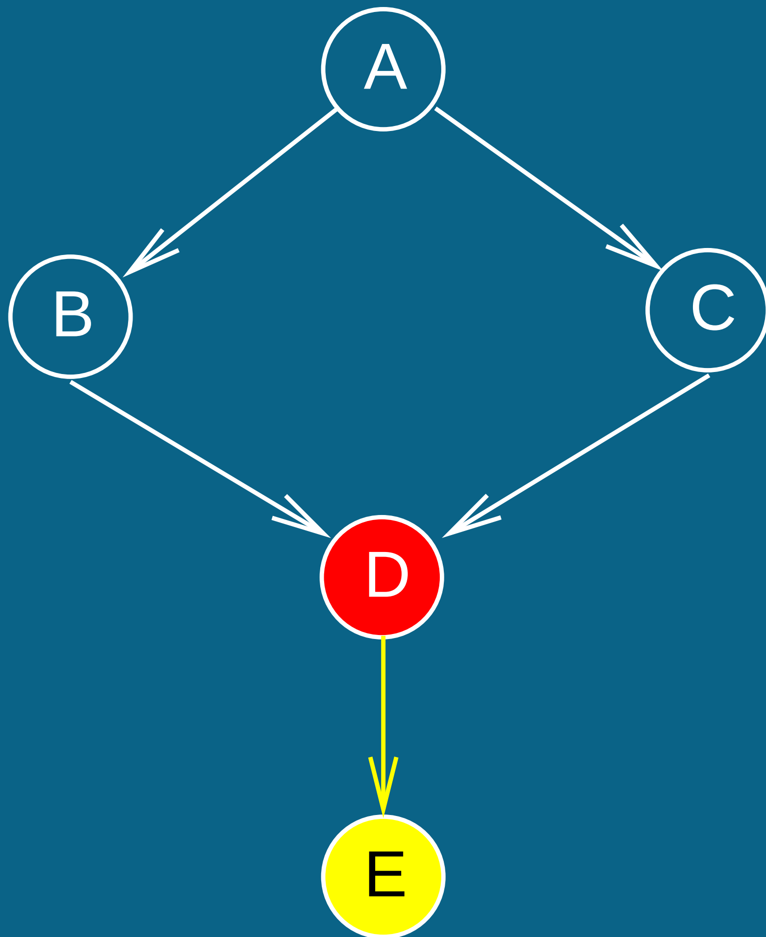
# Biological interpretation



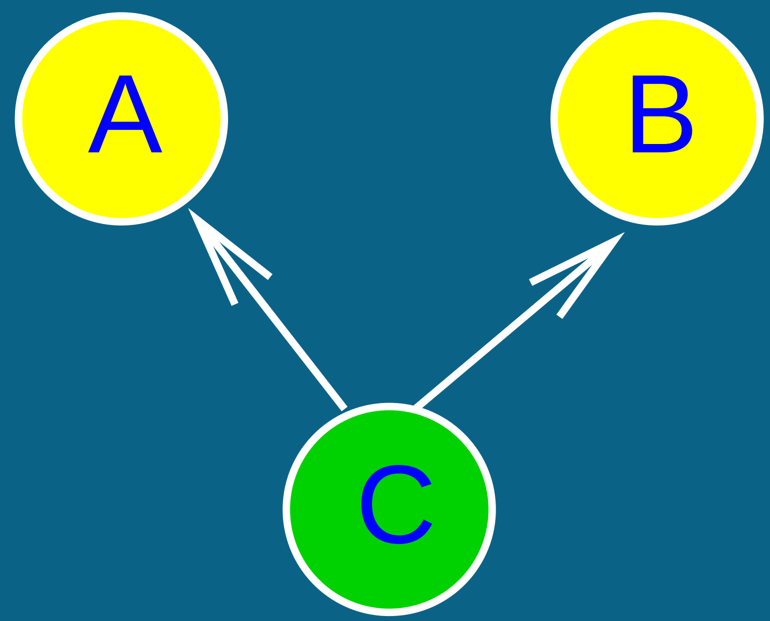

Initiation of cell (sub-)cycle

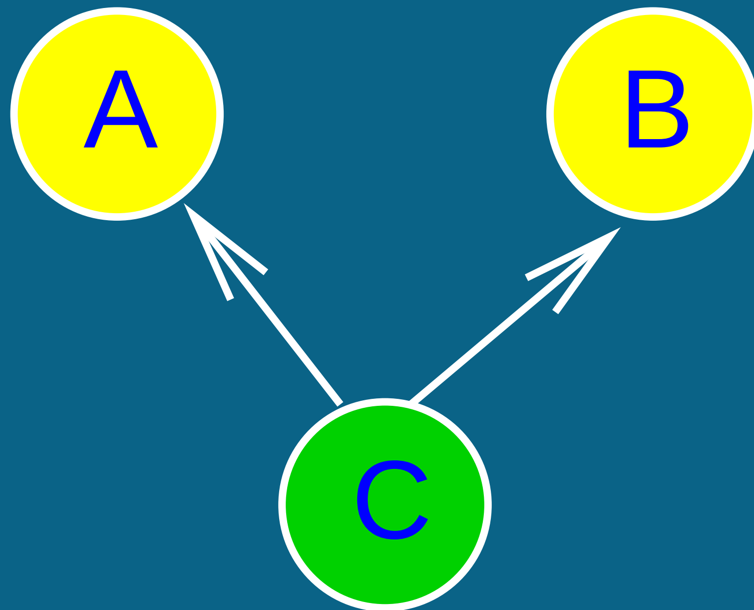



Co-regulation

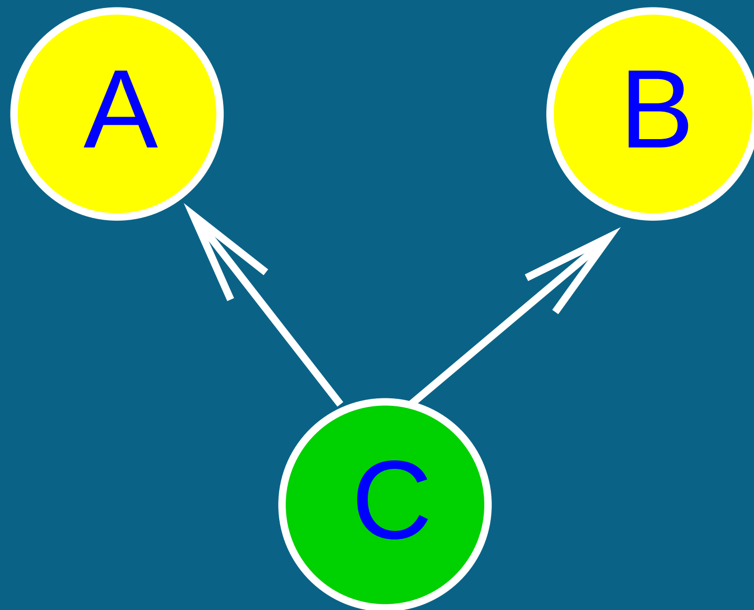



Mediation


A
B
C

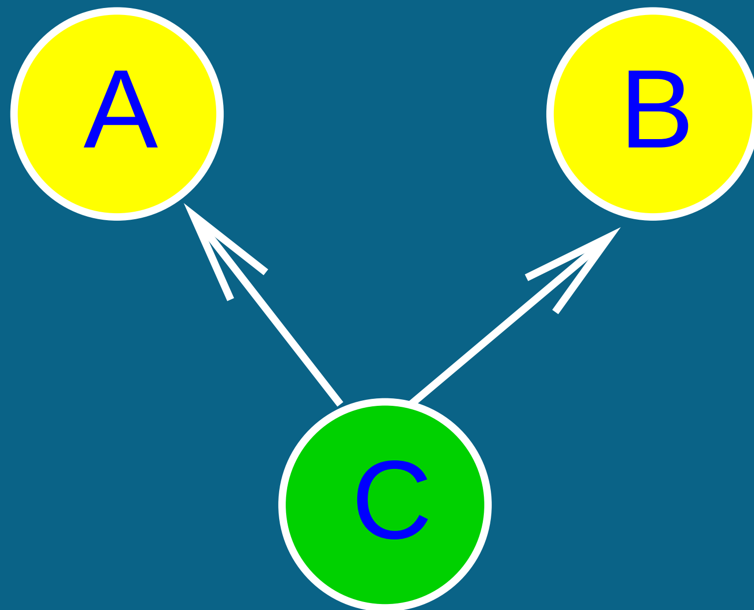



$$P(A, B, C) = P(A|C)P(B|C)P(C)$$




$$P(A, B, C) = P(A|C)P(B|C)P(C)$$

$$P(A, B|C) = \frac{P(A, B, C)}{P(C)} = P(A|C)P(B|C)$$




$$P(A,B,C) = P(A|C)P(B|C)P(C)$$

$$P(A,B|C) = \frac{P(A,B,C)}{P(C)} = P(A|C)P(B|C)$$

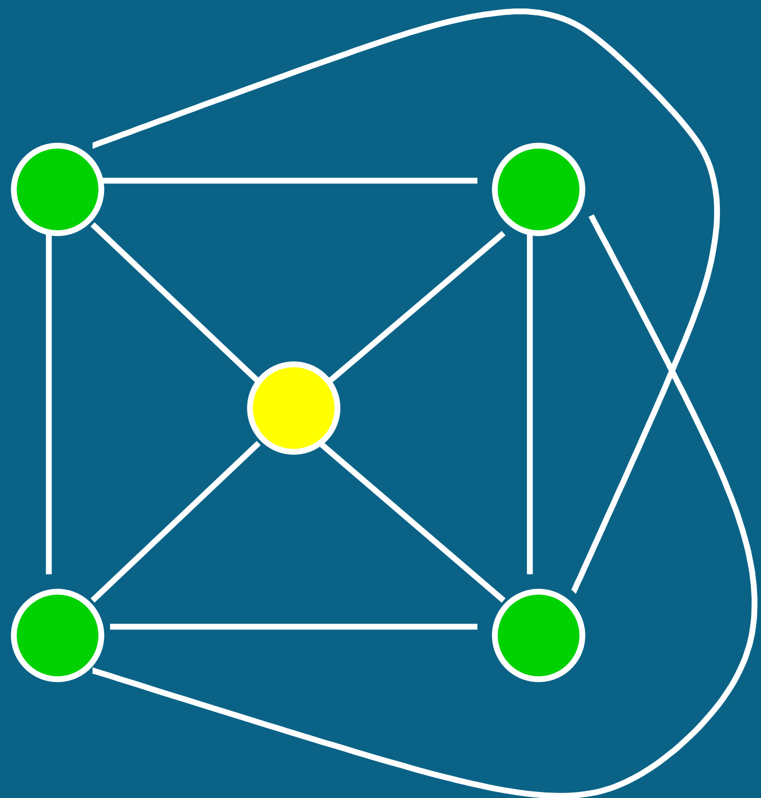
But: $P(A,B) \neq P(A)P(B)$

# Biological example

Yeast cell cycle

Clustering

Spellman et al. 1998
Molecular Biology of the Cell 9 (12) :3273-97



SLT2 clusters with low-osmolarity response genes

# Biological example

Yeast cell cycle

Nir Friedman et al. (2000)

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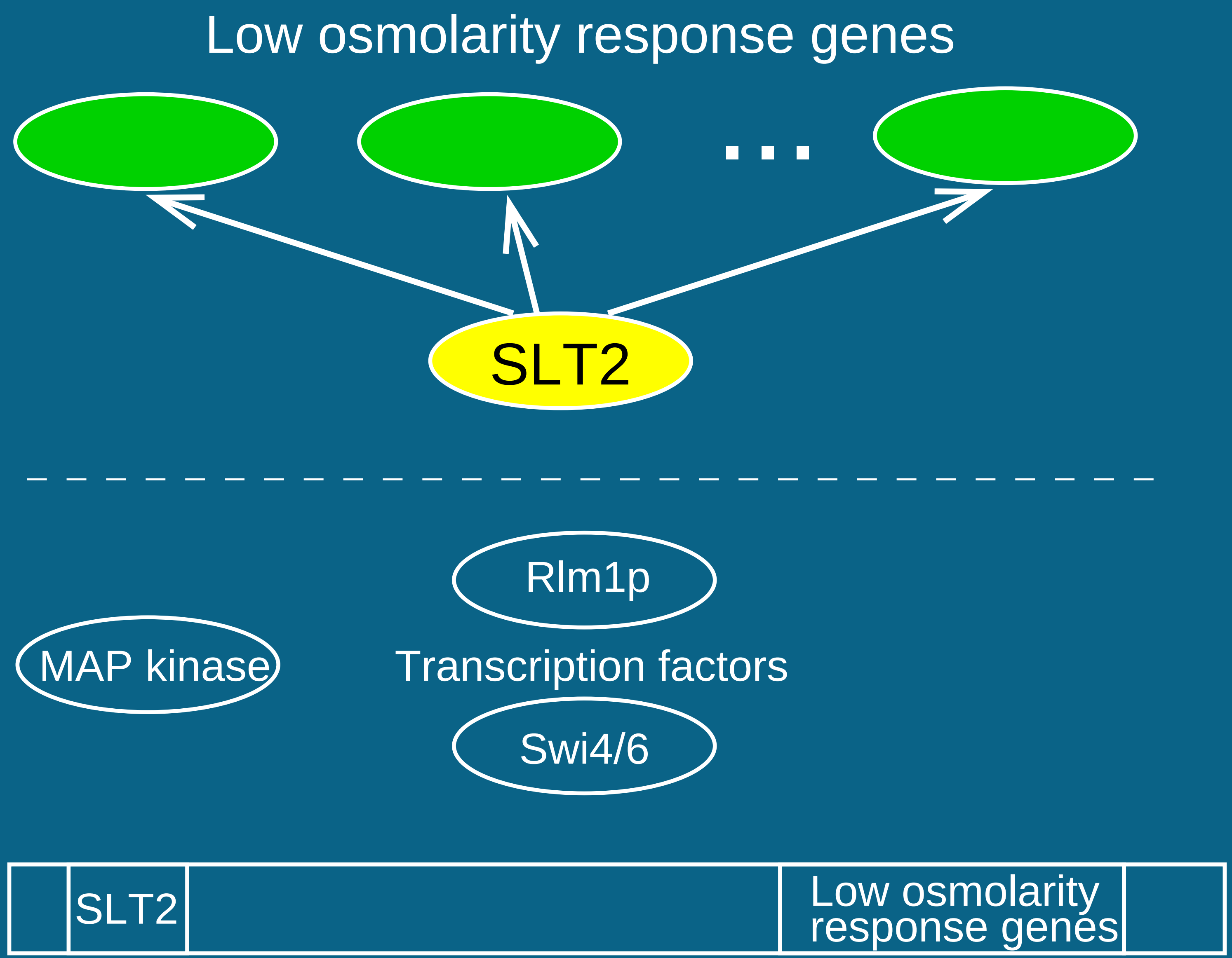
Low osmolarity response genes
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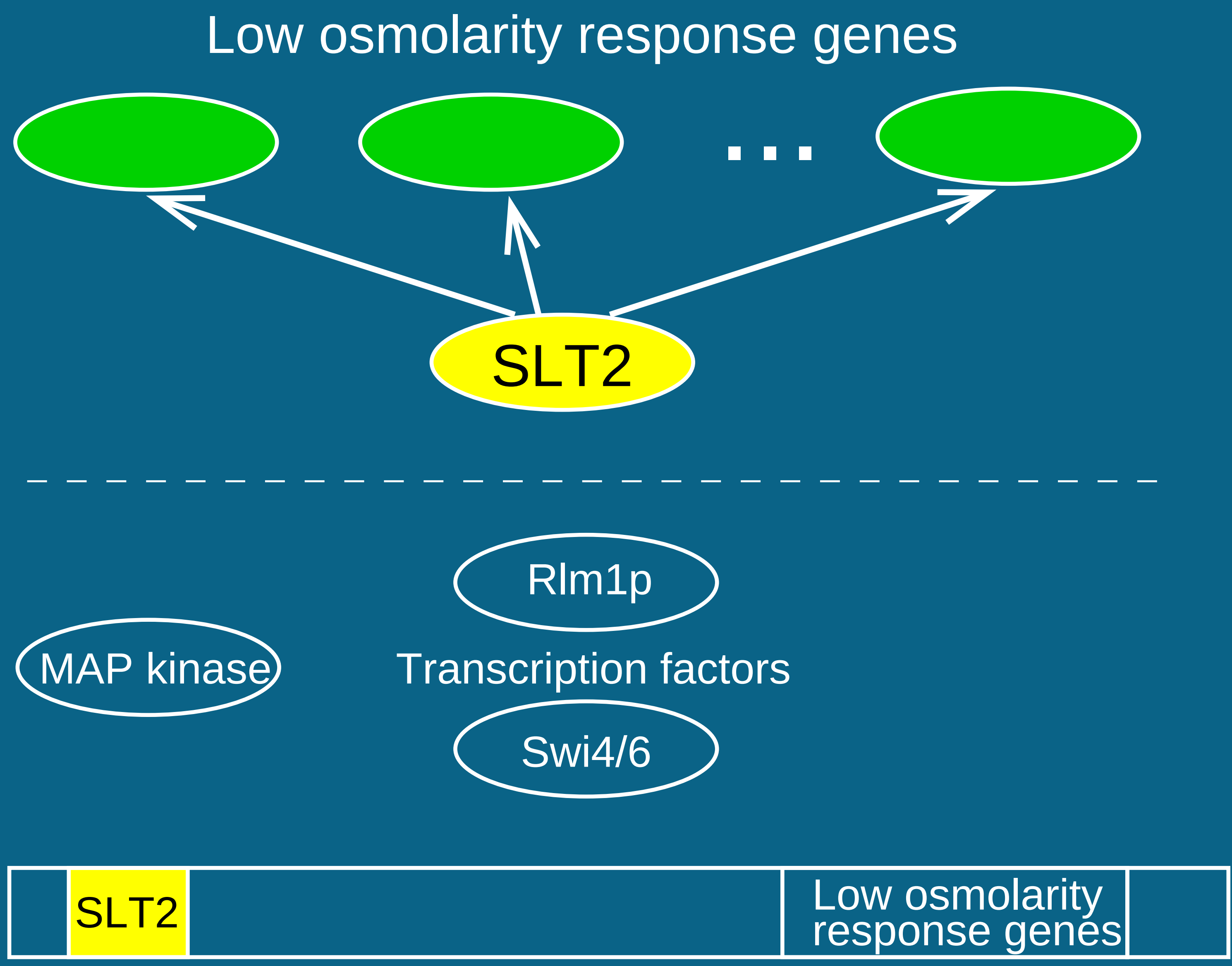
SLT2
Rlm1p
MAP kinase
Transcription factors
Swi4/6
SLT2
Low osmolarity response genes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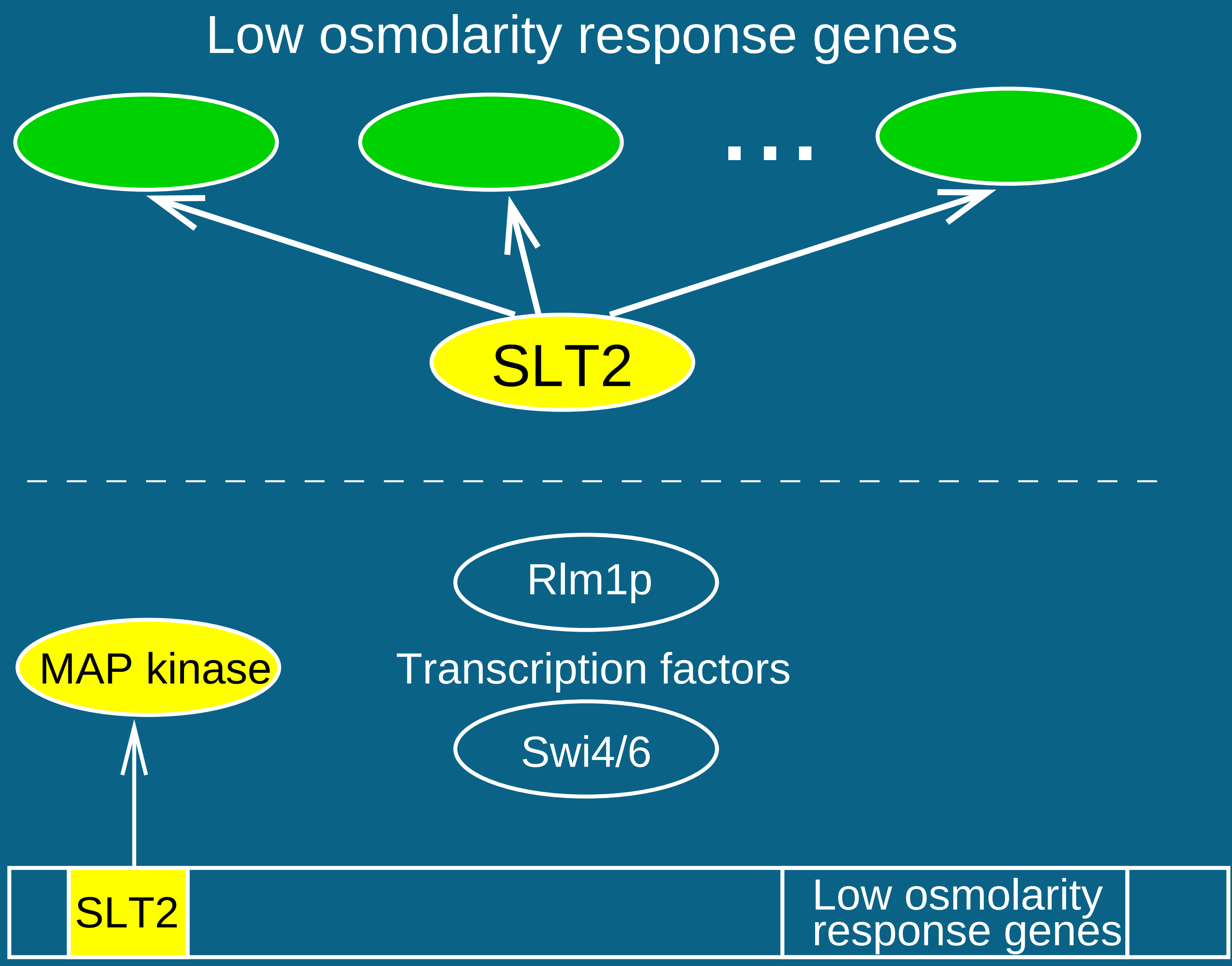
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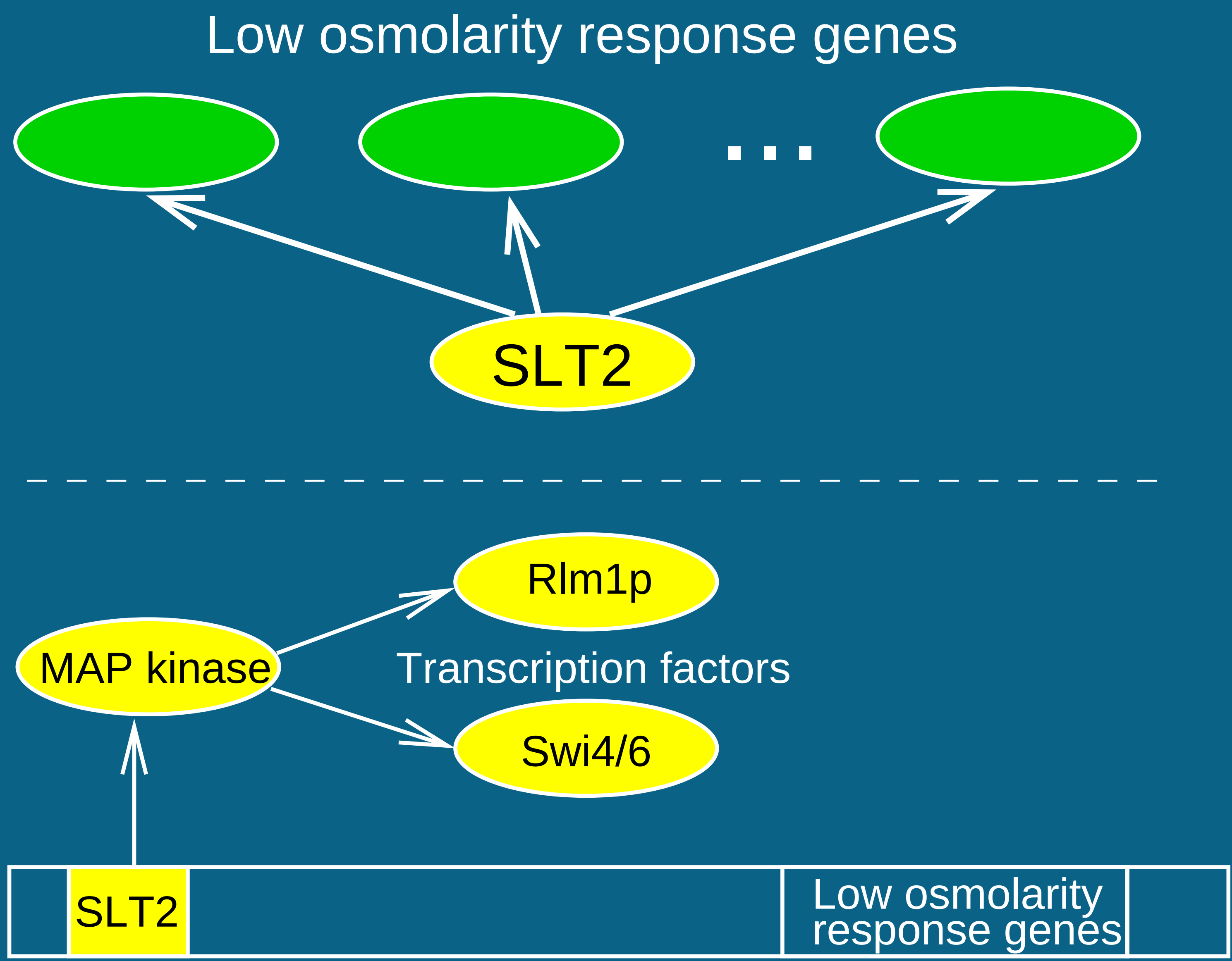
Low osmolarity response genes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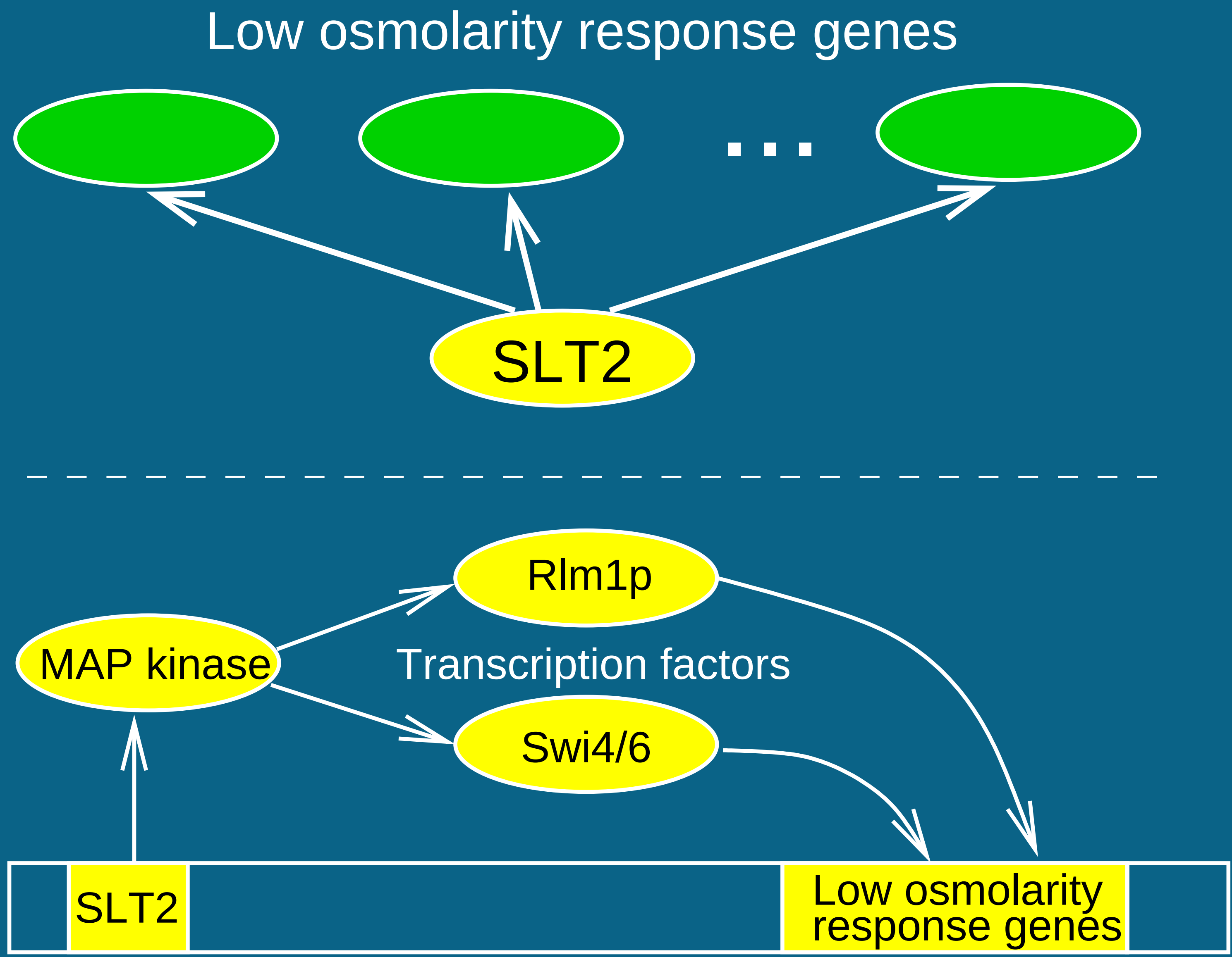

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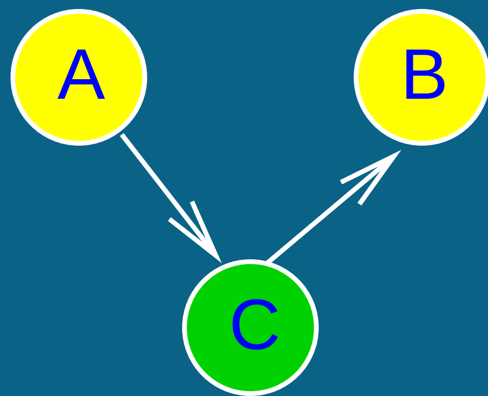
Swi4/6
SLT2
Low osmolarity response genes

Can we learn causal relationships
from conditional dependencies ?

# Can we learn causal relationships from conditional dependencies ?

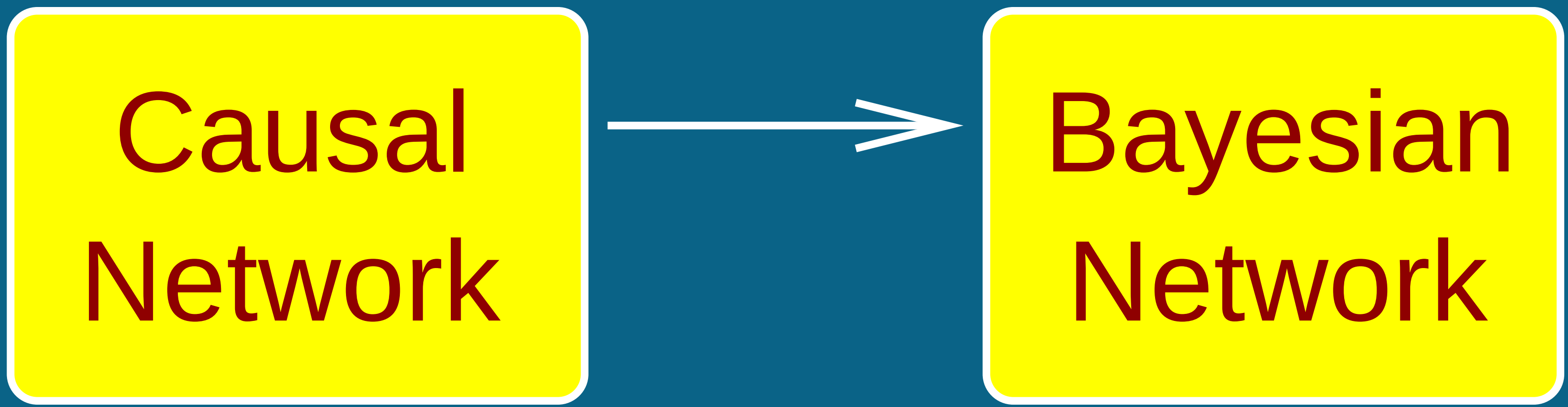



Bayesian network:
A node is independent of its nondescendants, given its parents.

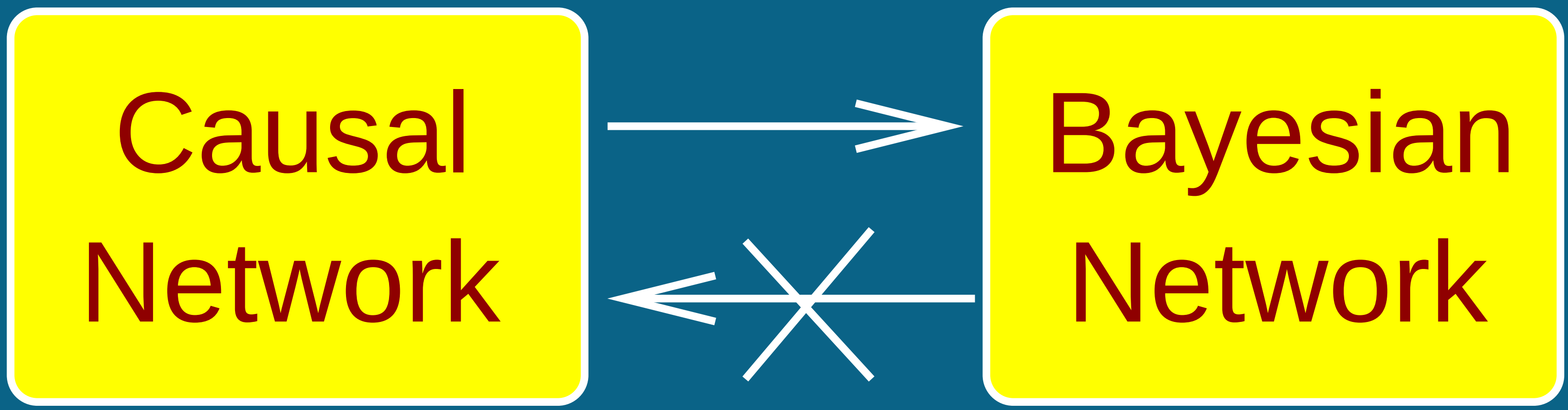
Causal network:
A node is independent of its earlier causes, given its immediate causes.

Causal Network

Bayesian Network



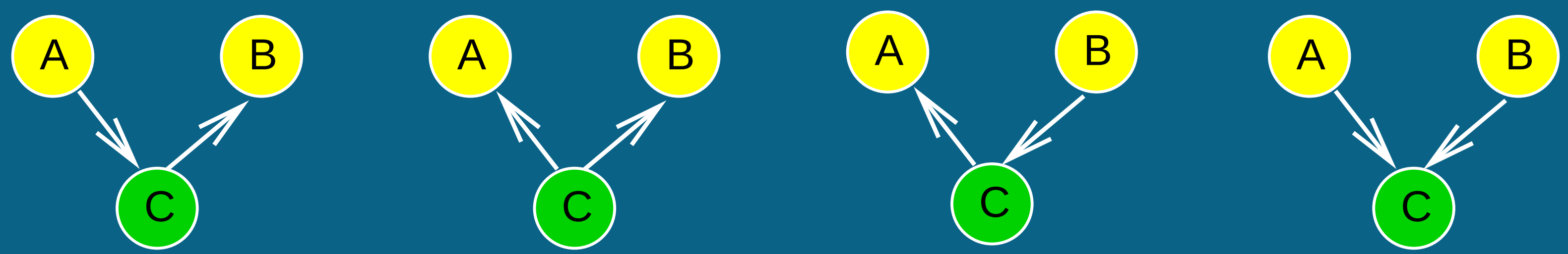
Causal Network
Bayesian Network


Causal Network
Bayesian Network

# Equivalence classes

and

# PDAGs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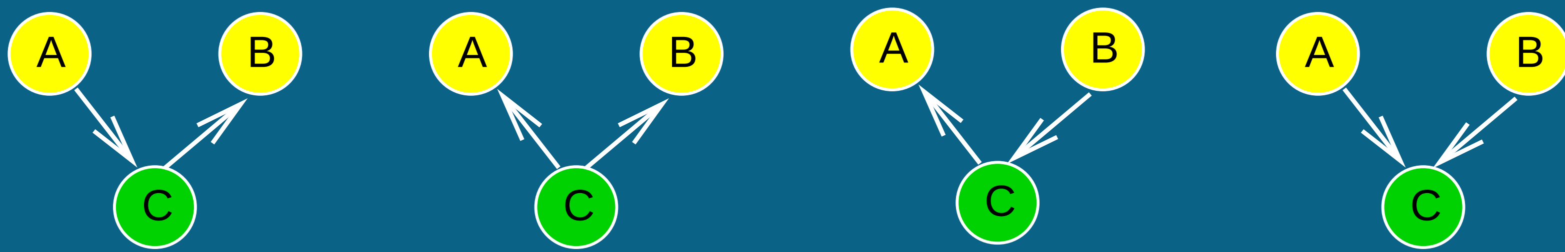
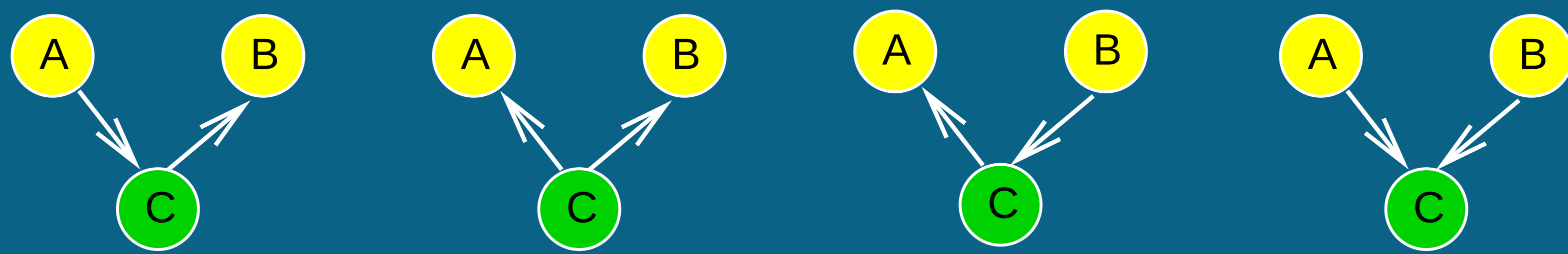
A
B
C




P(A,B,C) =

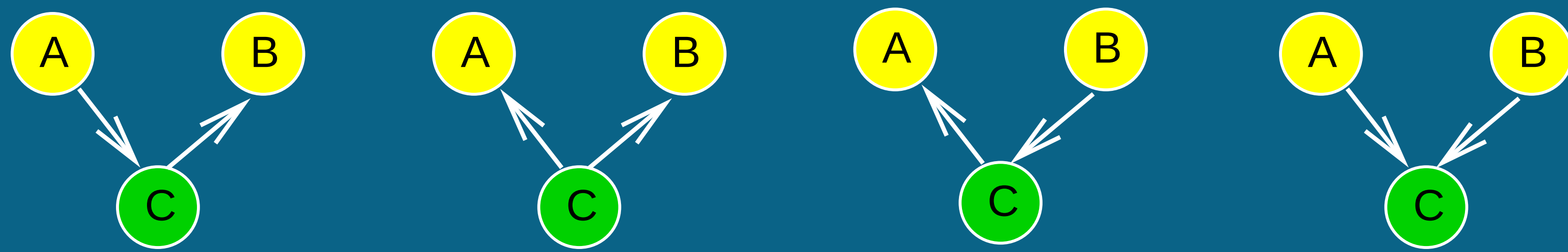
P(B|C) P(C|A) P(A)    P(A|C) P(B|C) P(C)    P(A|C) P(C|B) P(B)    P(C|A,B) P(A) P(B)




$$P(A,B,C) =$$

$P(B|C)\ P(C|A)\ P(A)$     $P(A|C)\ P(B|C)\ P(C)$     $P(A|C)\ P(C|B)\ P(B)$     $P(C|A,B)\ P(A)\ P(B)$

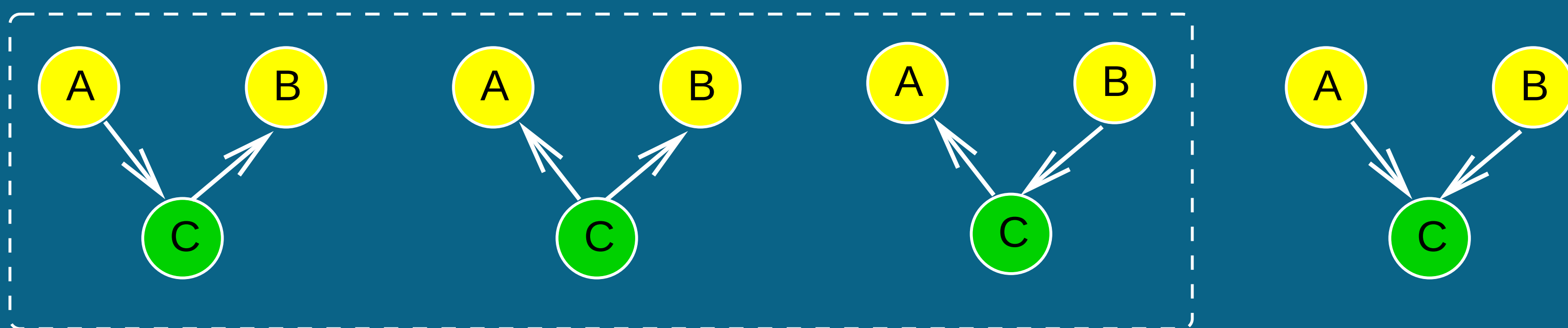
$P(A|C)\ P(C)$     $P(B|C)\ P(C)$

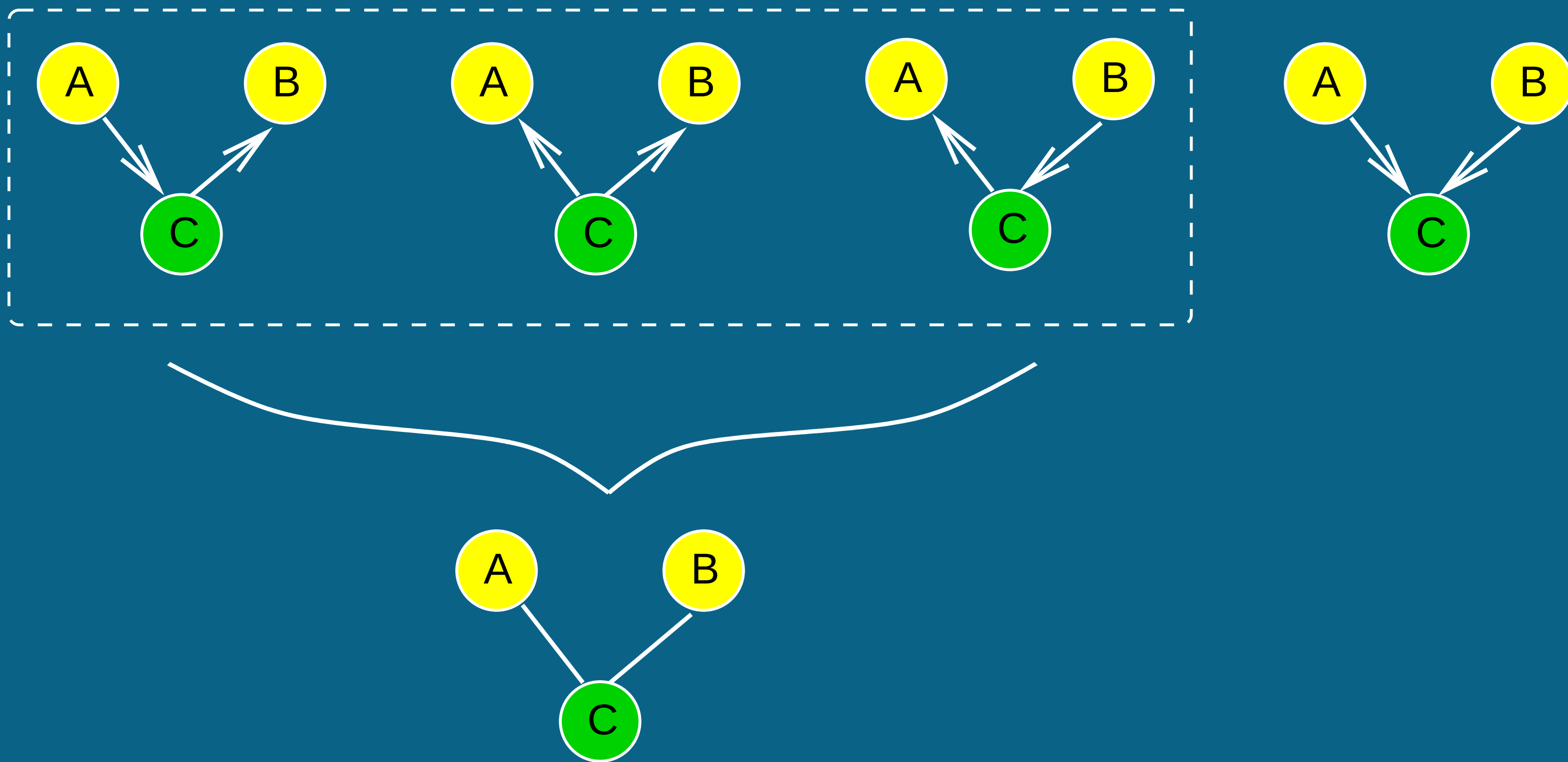



P(A,B,C) =

P(B|C) P(C|A) P(A) P(A|C) P(B|C) P(C) P(A|C) P(C|B) P(B) P(C|A,B) P(A) P(B)

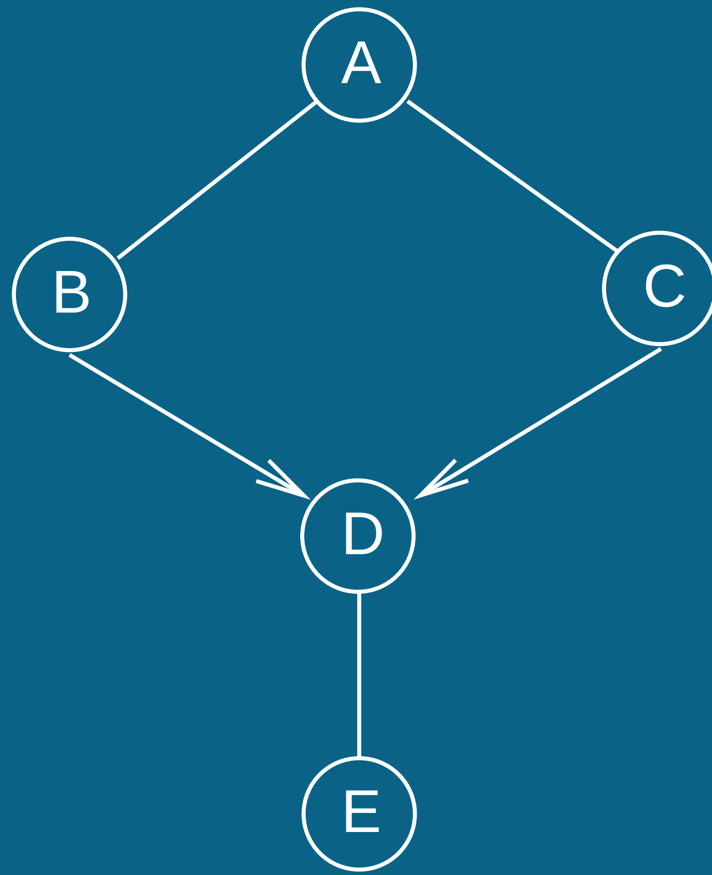
P(A|C) P(C) P(B|C) P(C)






- Two DAGs are equivalent iff they have the same skeleton (= the underlying undirected graph) and the same v-structure.
- v-structure: Converging directed edges into the same node without an edge between the parents.

An equivalence class of DAGs can be represented by a PDAG (partially directed acyclic graph).




We can only learn PDAGs from the data!

- Observation: A passive measurement of the domain of interest.
- Intervention: Setting the values of some variables using forces outside the causal model, e.g., gene knockout or over-expression

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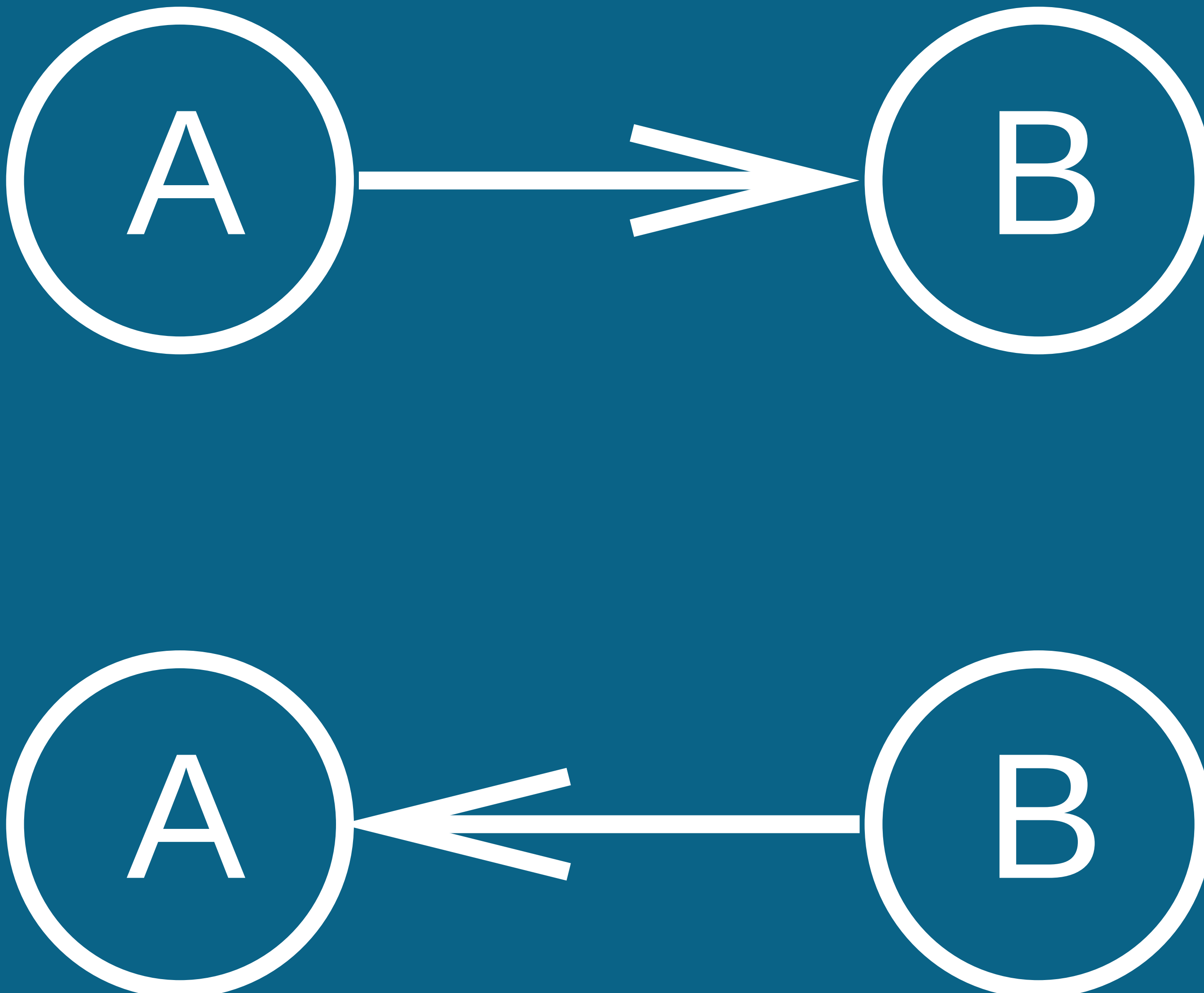
- Intervention: Setting the values of some variables using forces outside the causal model, e.g., gene knockout or over-expression
- Interventions can destroy the symmetry within an equivalent class.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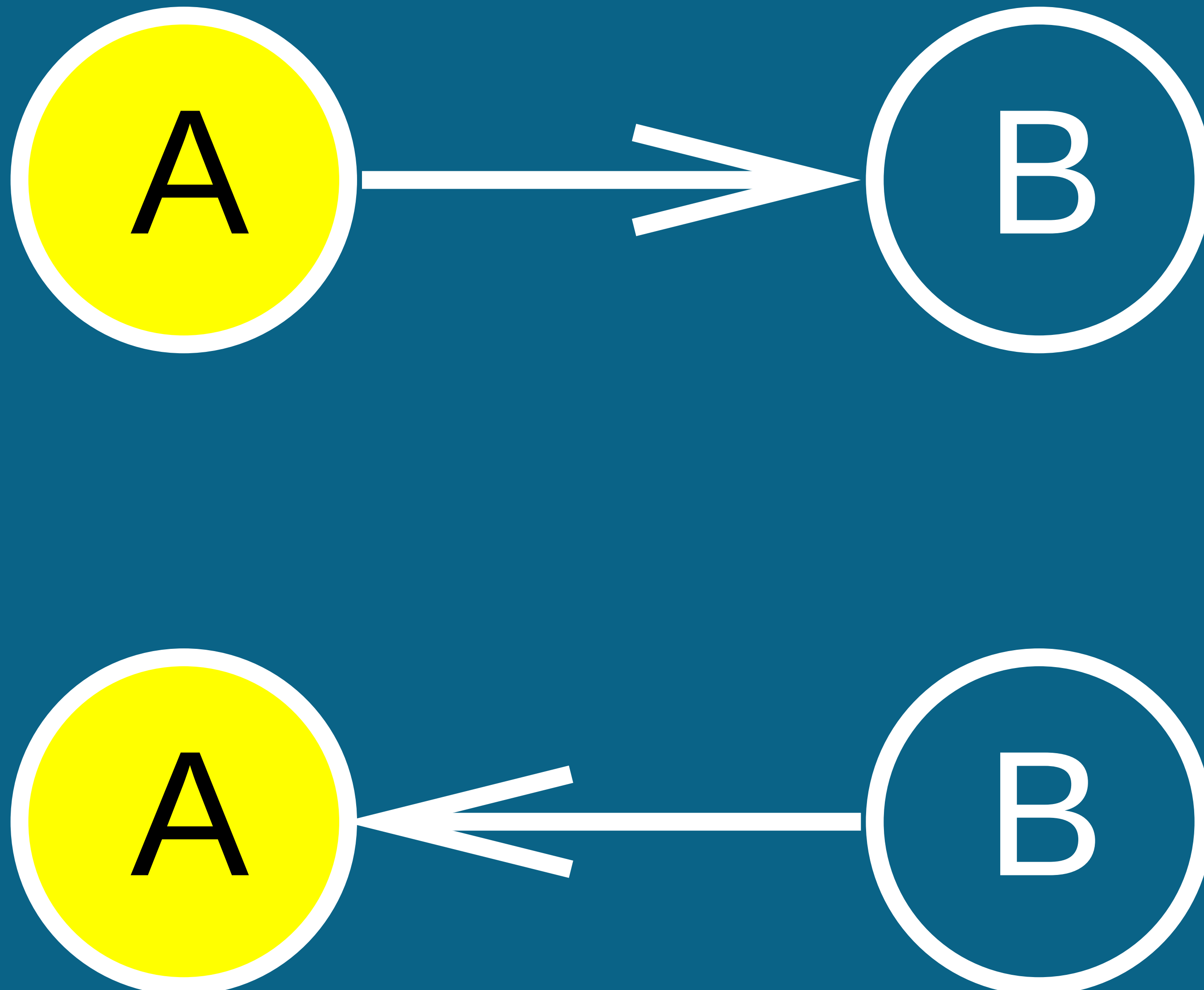
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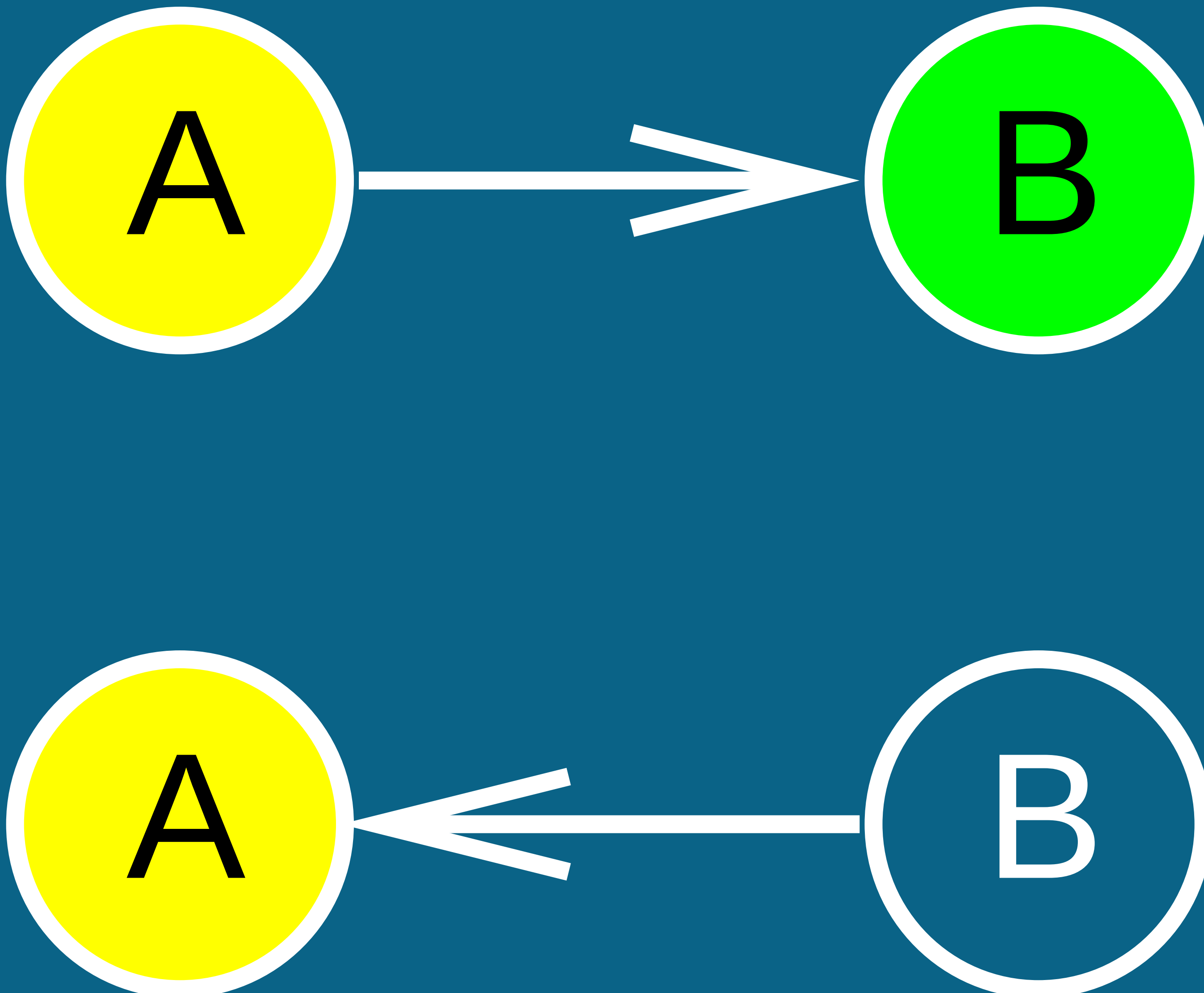

A
B
A
B

# Learning with interventions

No intervention:

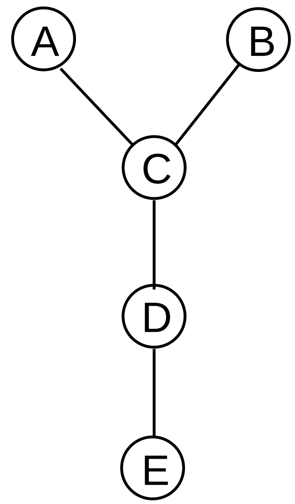
$$P(D|M) = \prod_i P(X_i|Pa(X_i))$$

Two models $\mathcal{M}$, $\mathcal{M}'$ with the same score are structure equivalent.

$Int$: Set of interventions $\longrightarrow$ Modified score:

$$P(D|M) = \prod_{i, X_i \notin Int} P(X_i|Pa(X_i))$$

This score is no longer structure equivalent.


A
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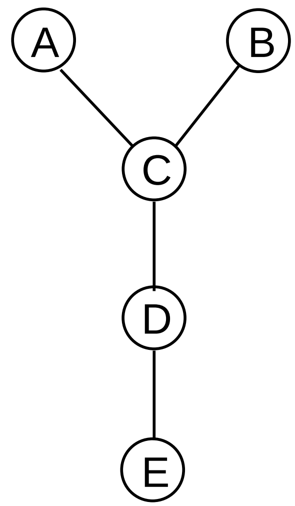
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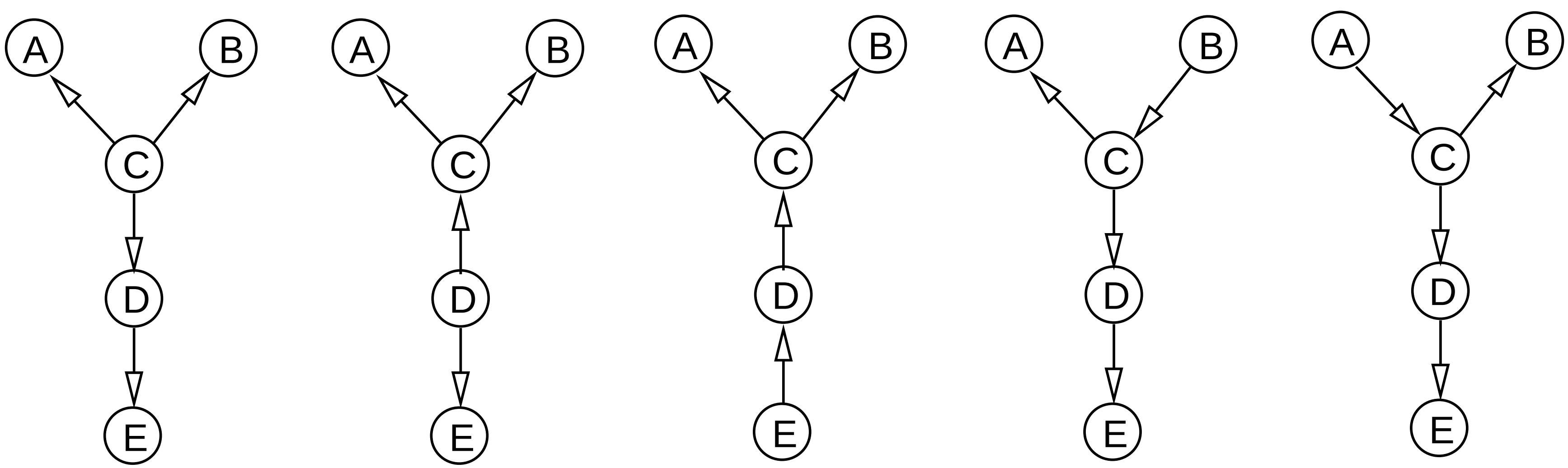
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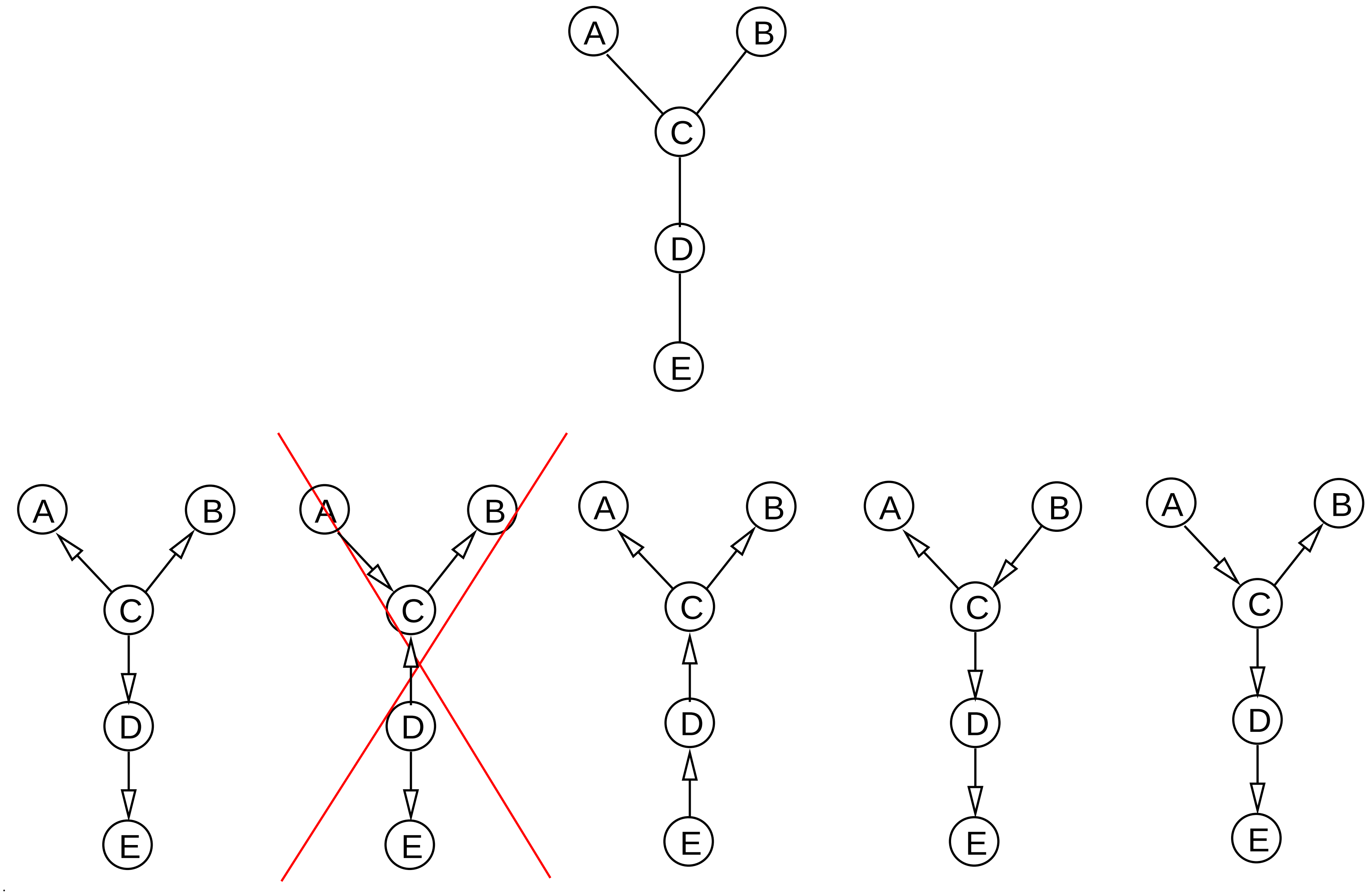
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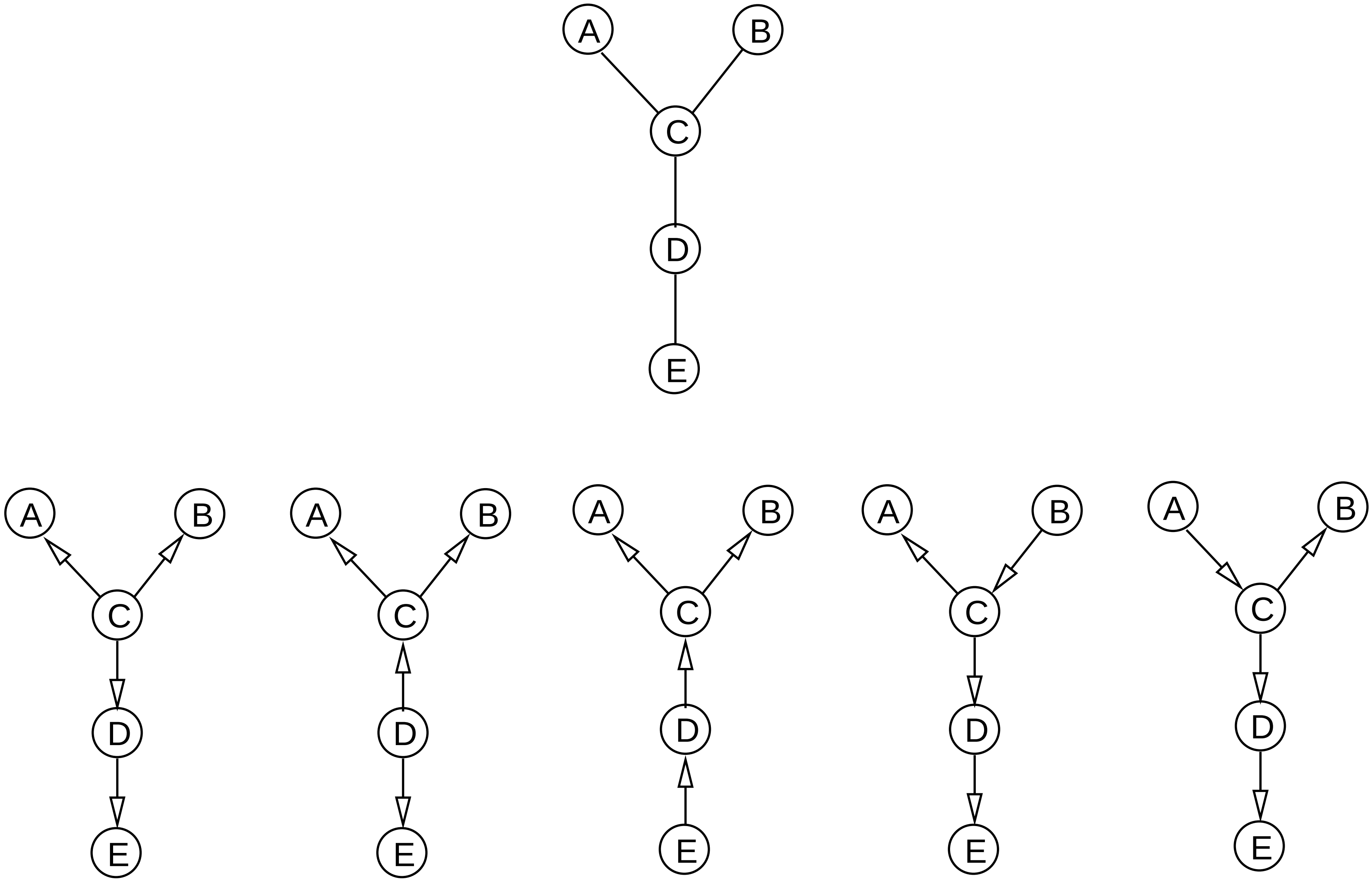
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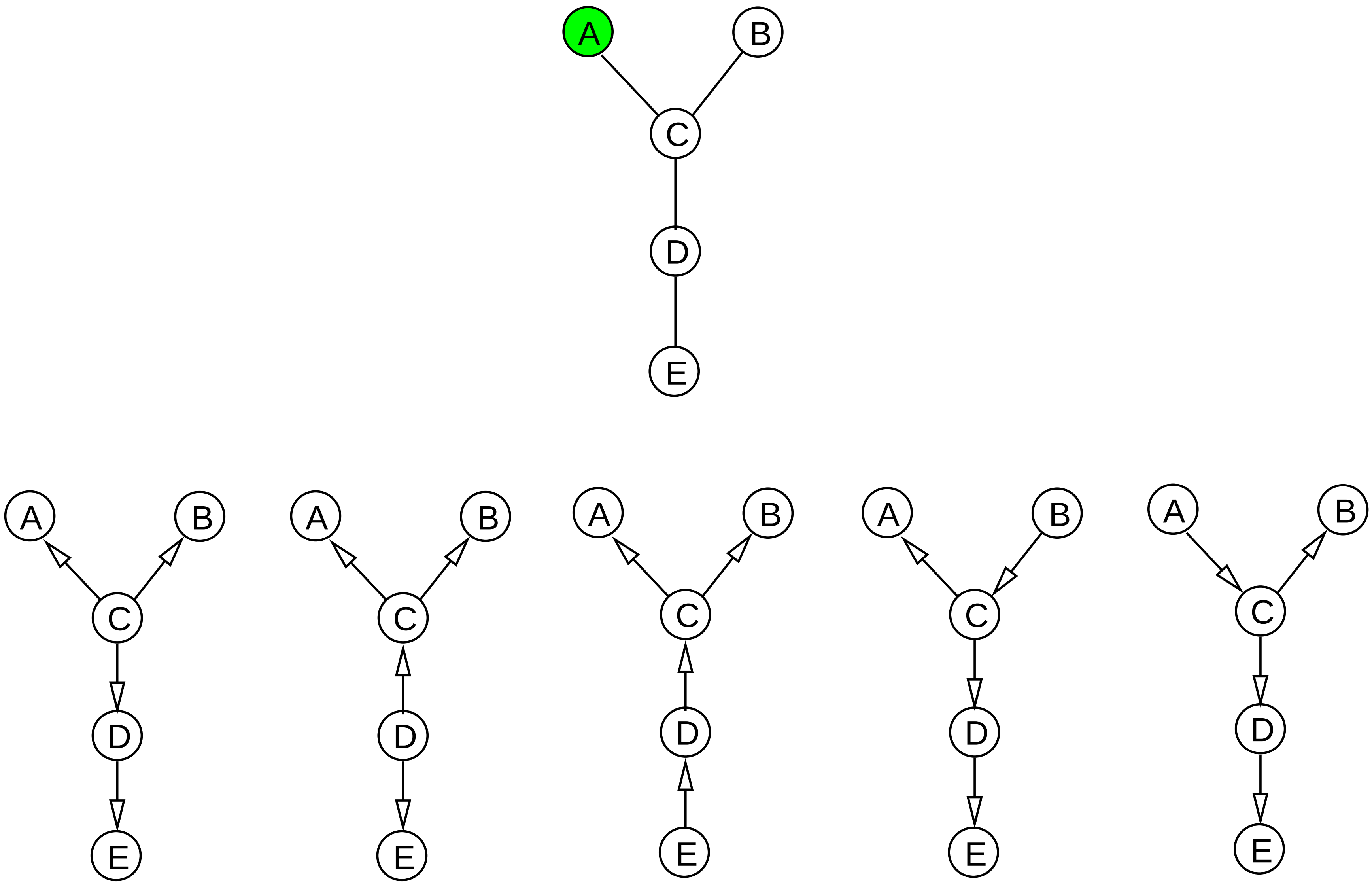

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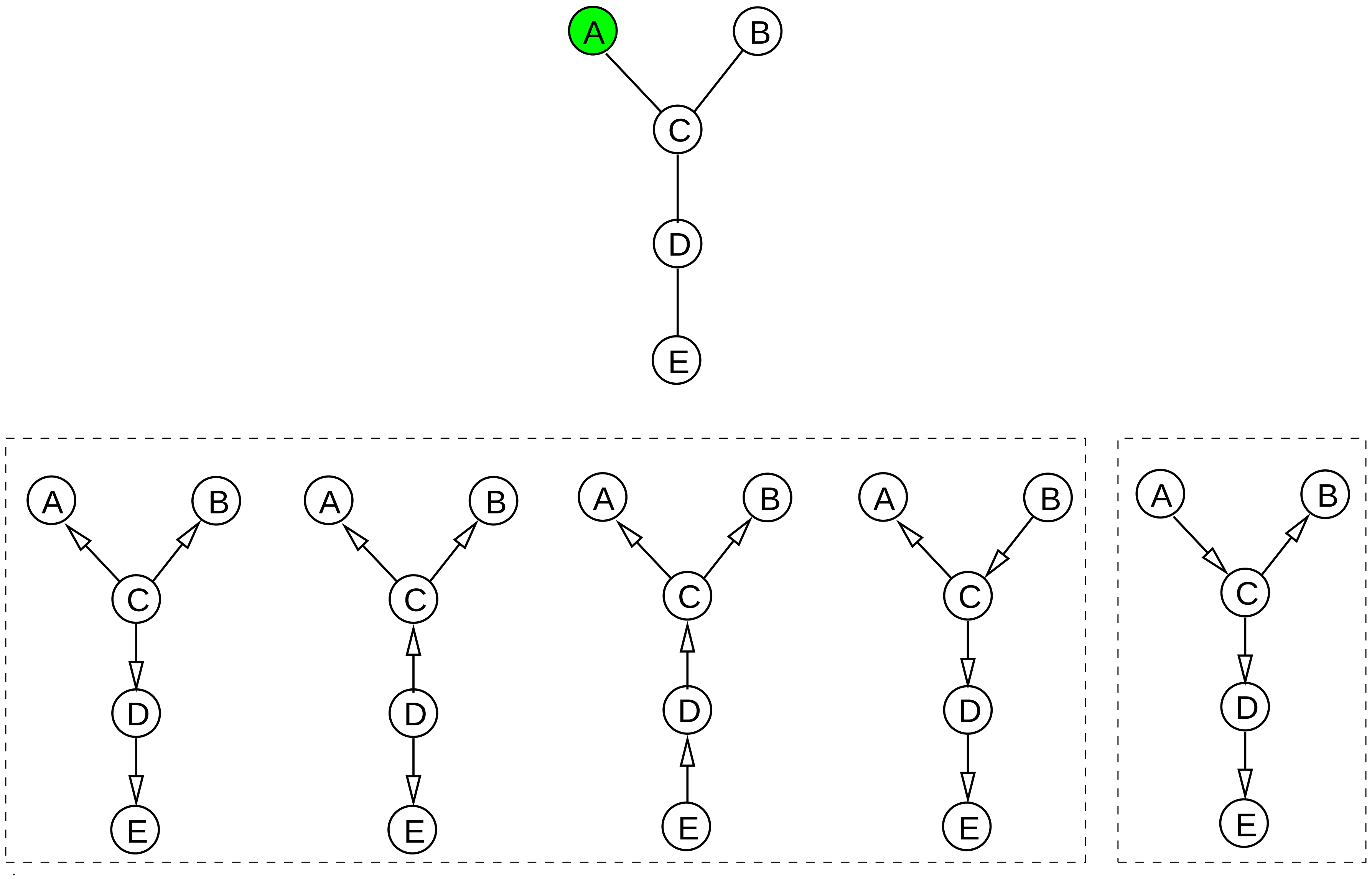
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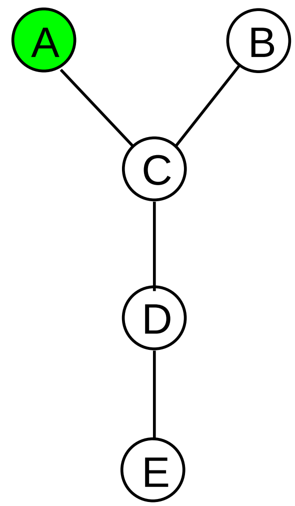
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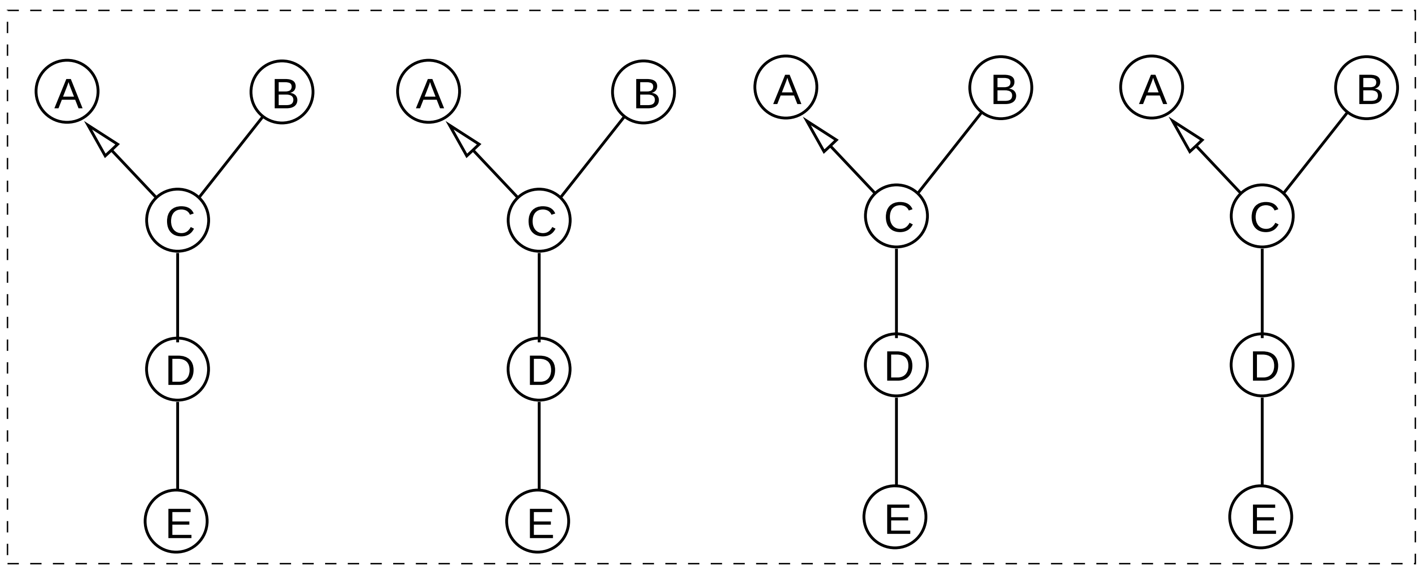
A
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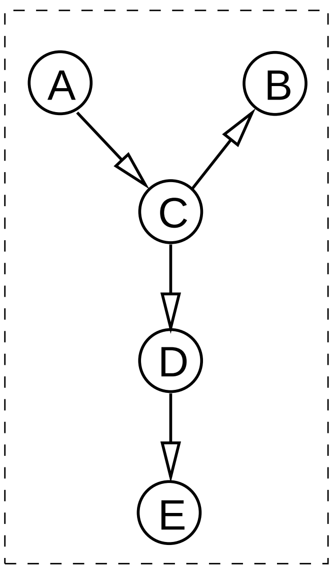
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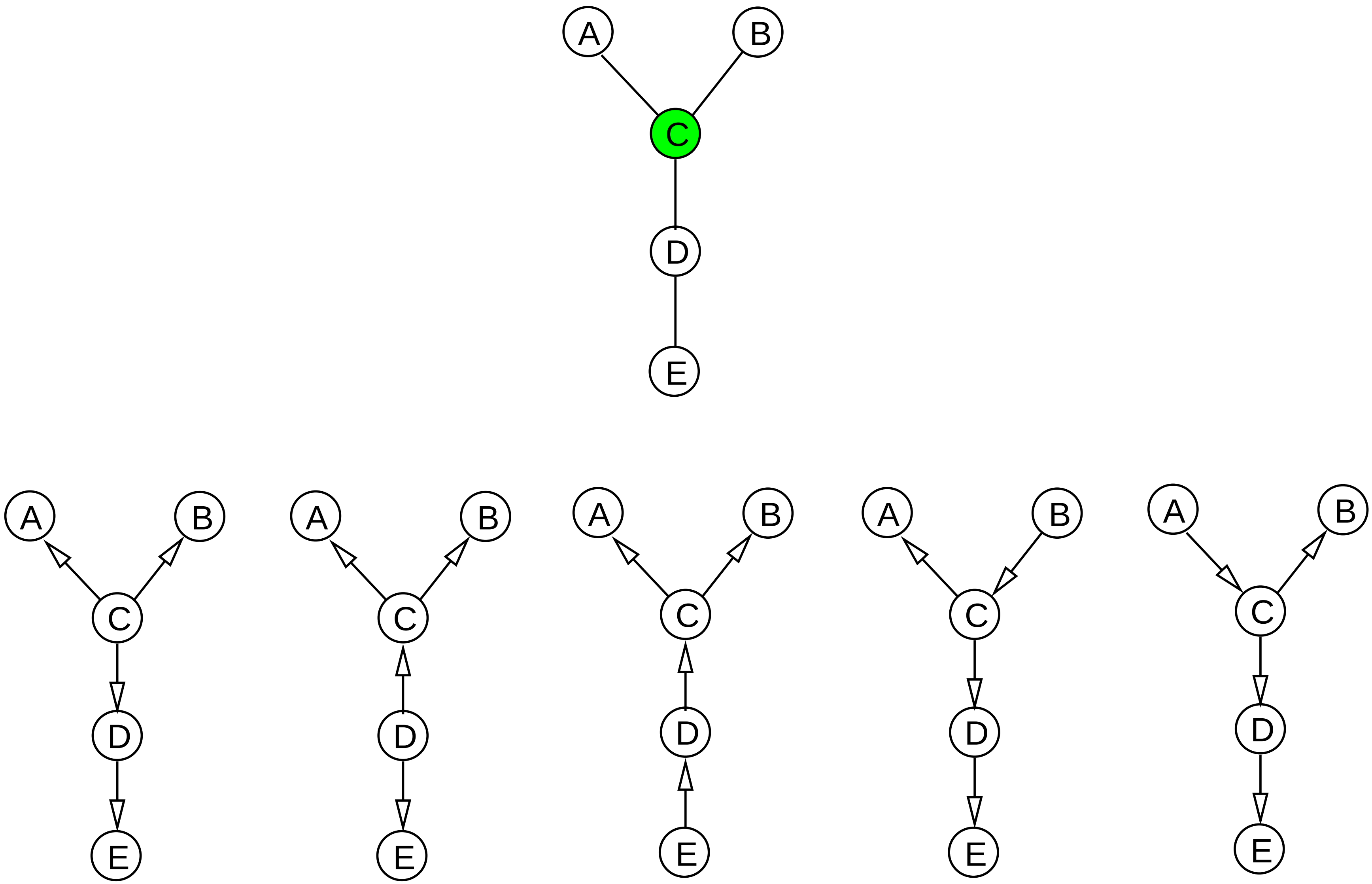
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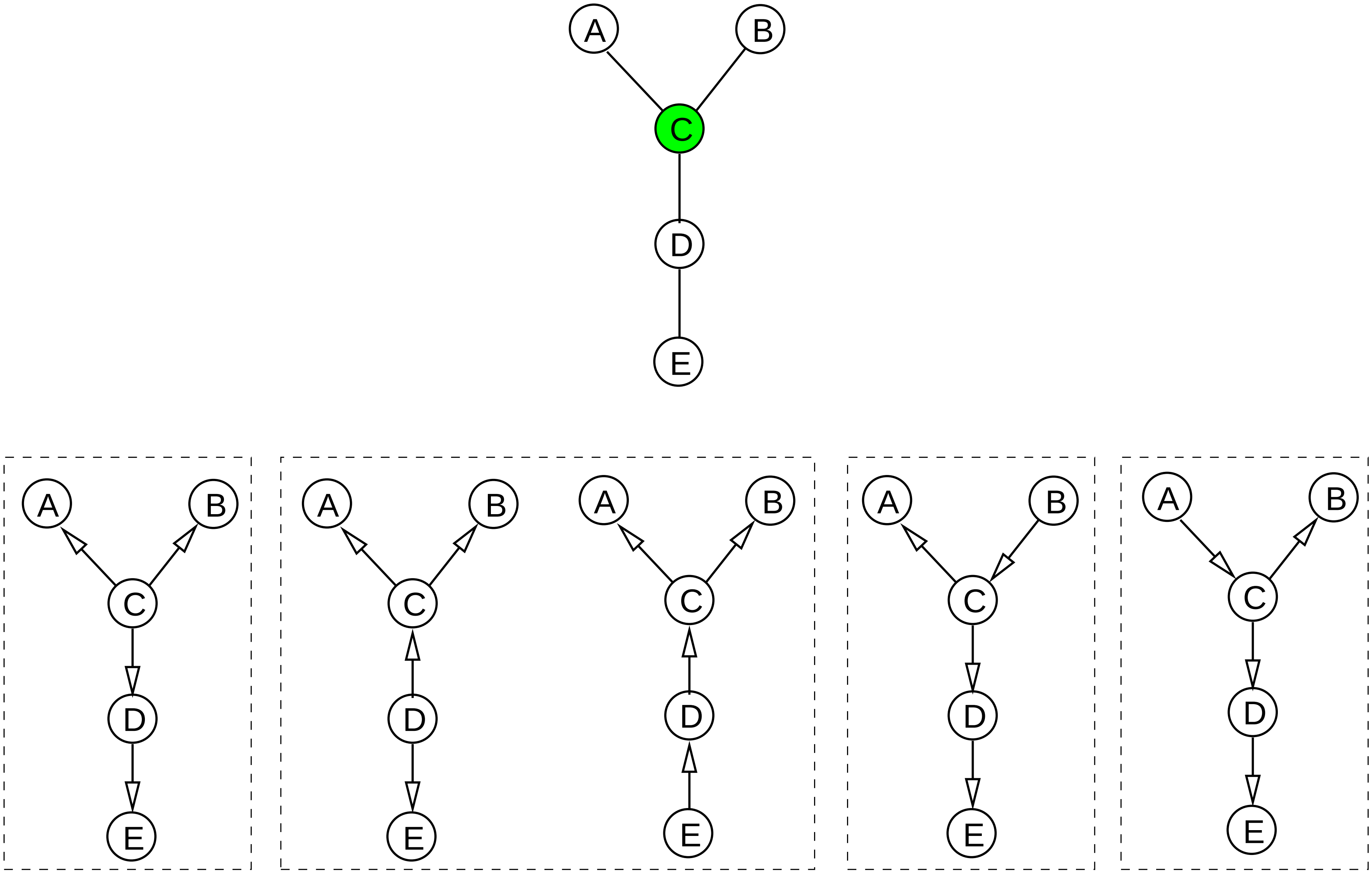
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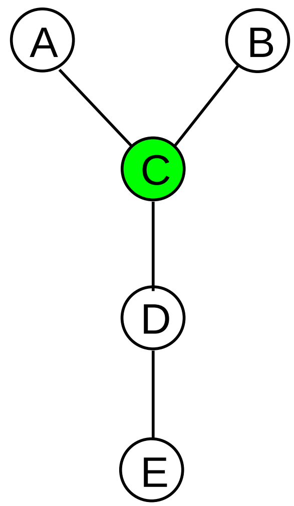
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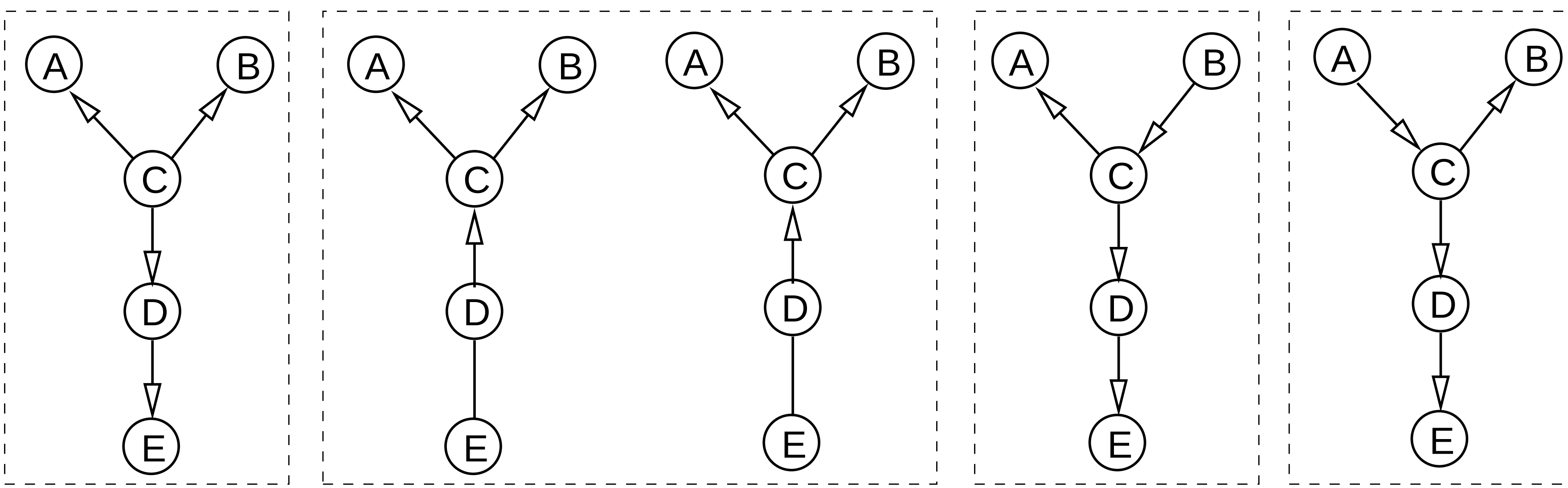
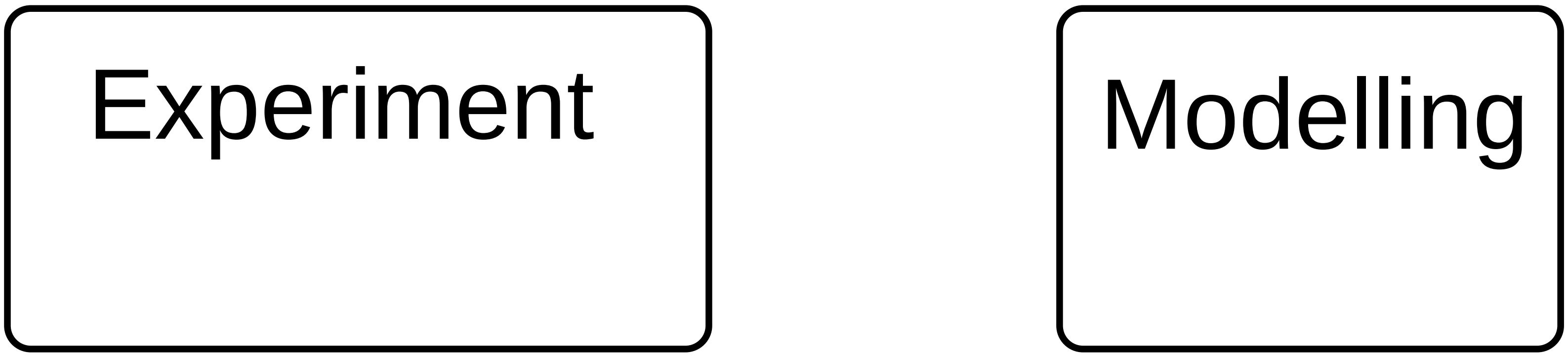
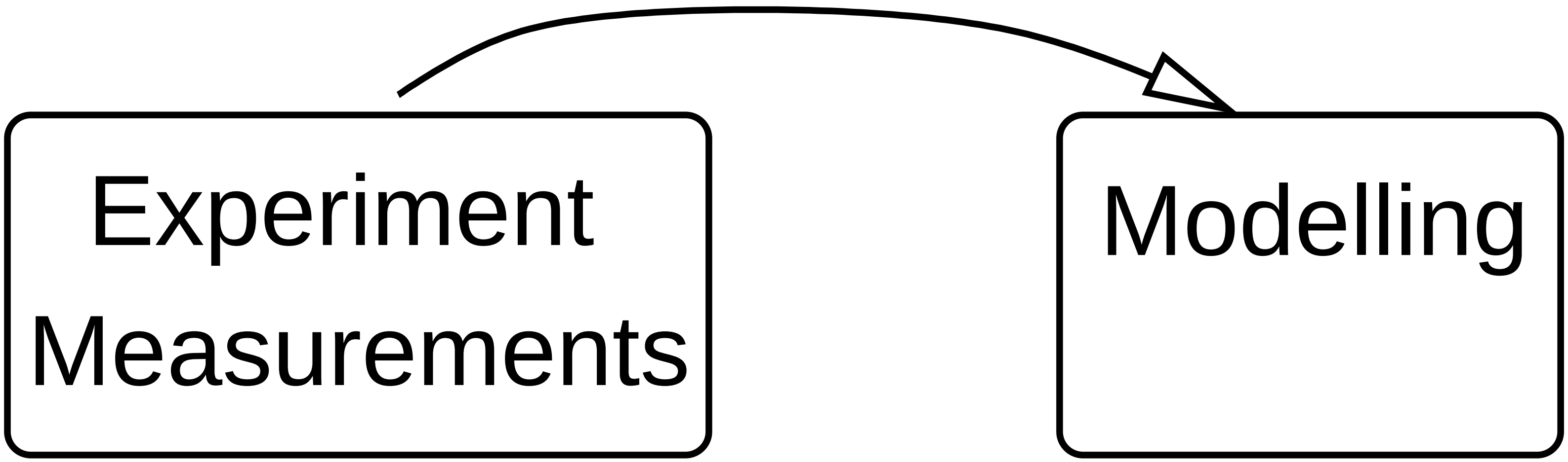

A
B
C
D
E

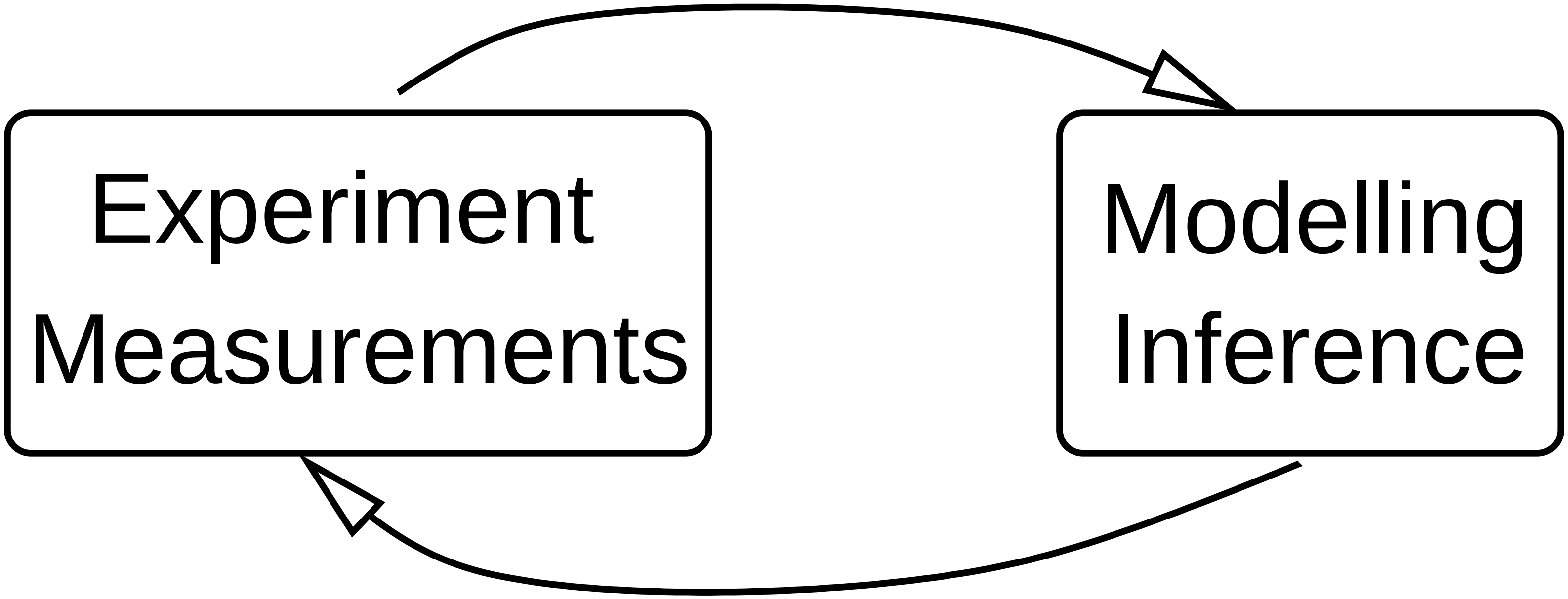
# Active learning

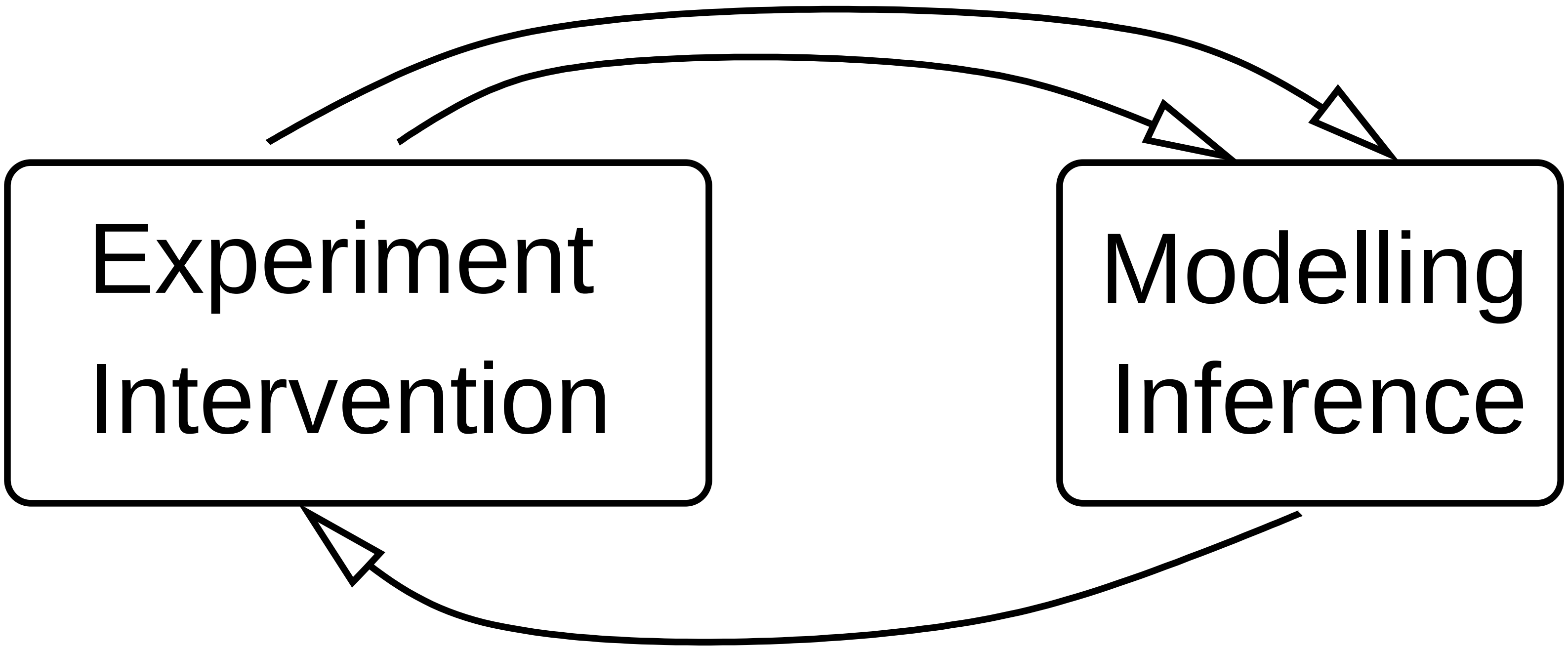
Based on preliminary inference:

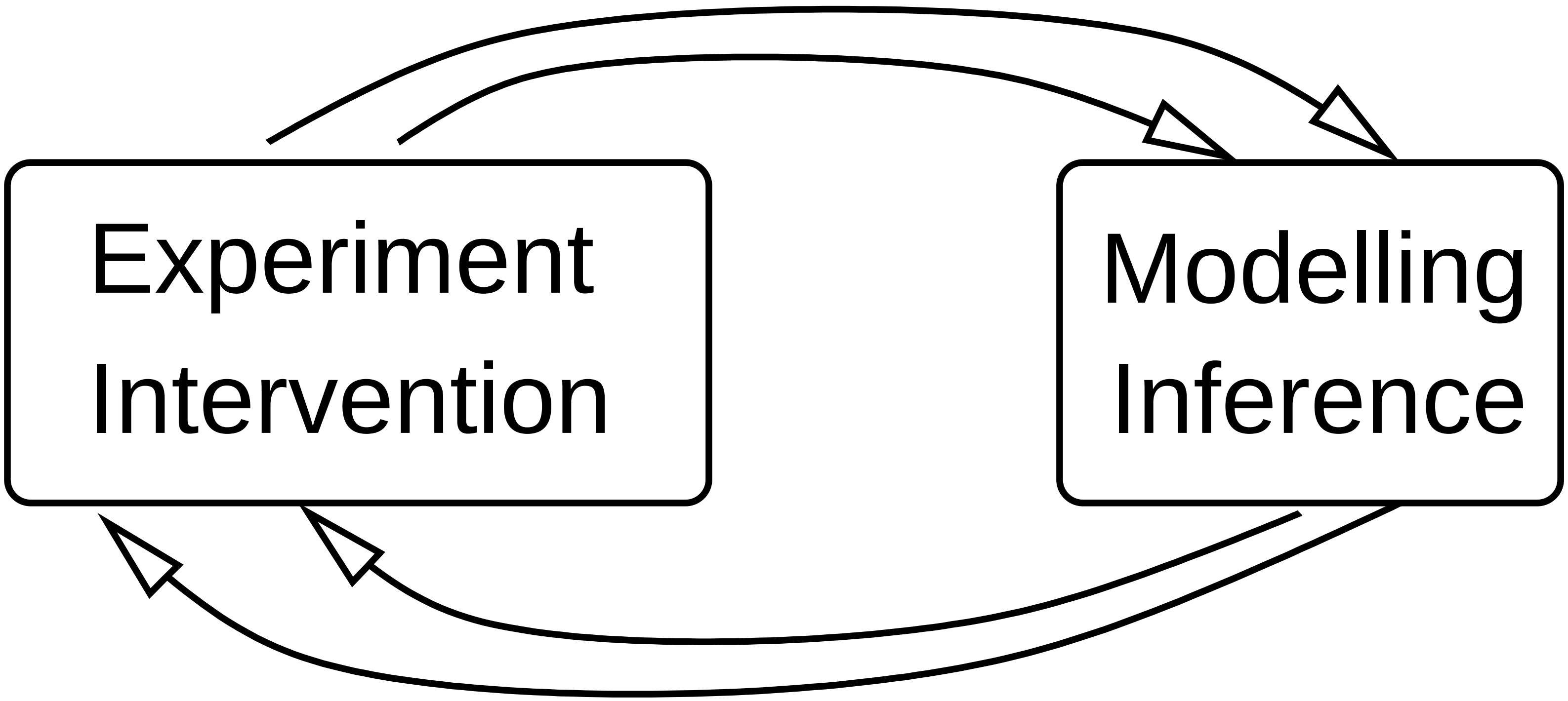
Predict the intervention that maximizes the information content of the expected response.


Experiment
Modelling


Experiment
Measurements
Modelling


Experiment
Measurements
Modelling
Inference


Experiment
Intervention
Modelling
Inference


Experiment
Intervention
Modelling
Inference

# Reconstructing gene networks by passive and active Bayesian learning

PhD thesis

Iosifina Pournara

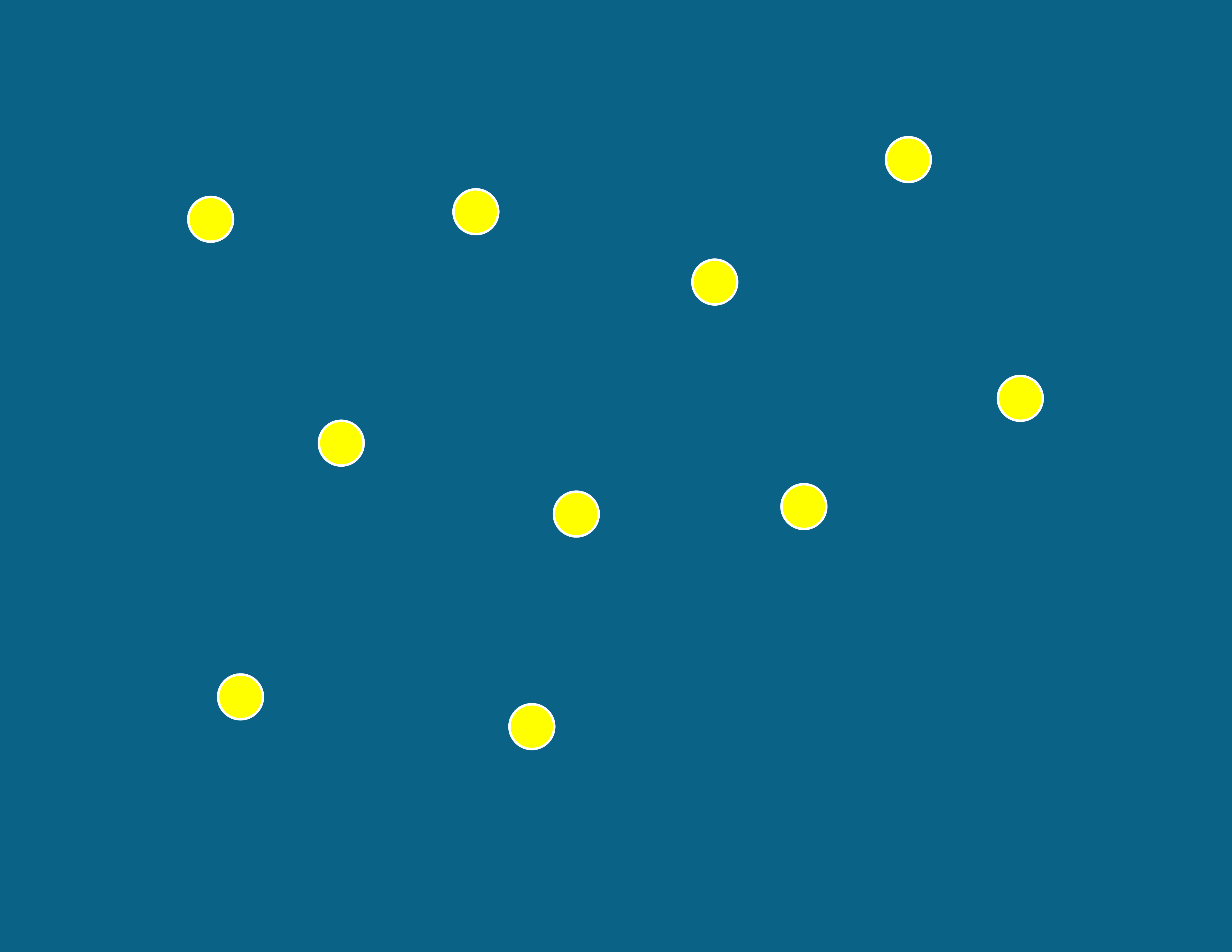
Birbeck College London, January 2005

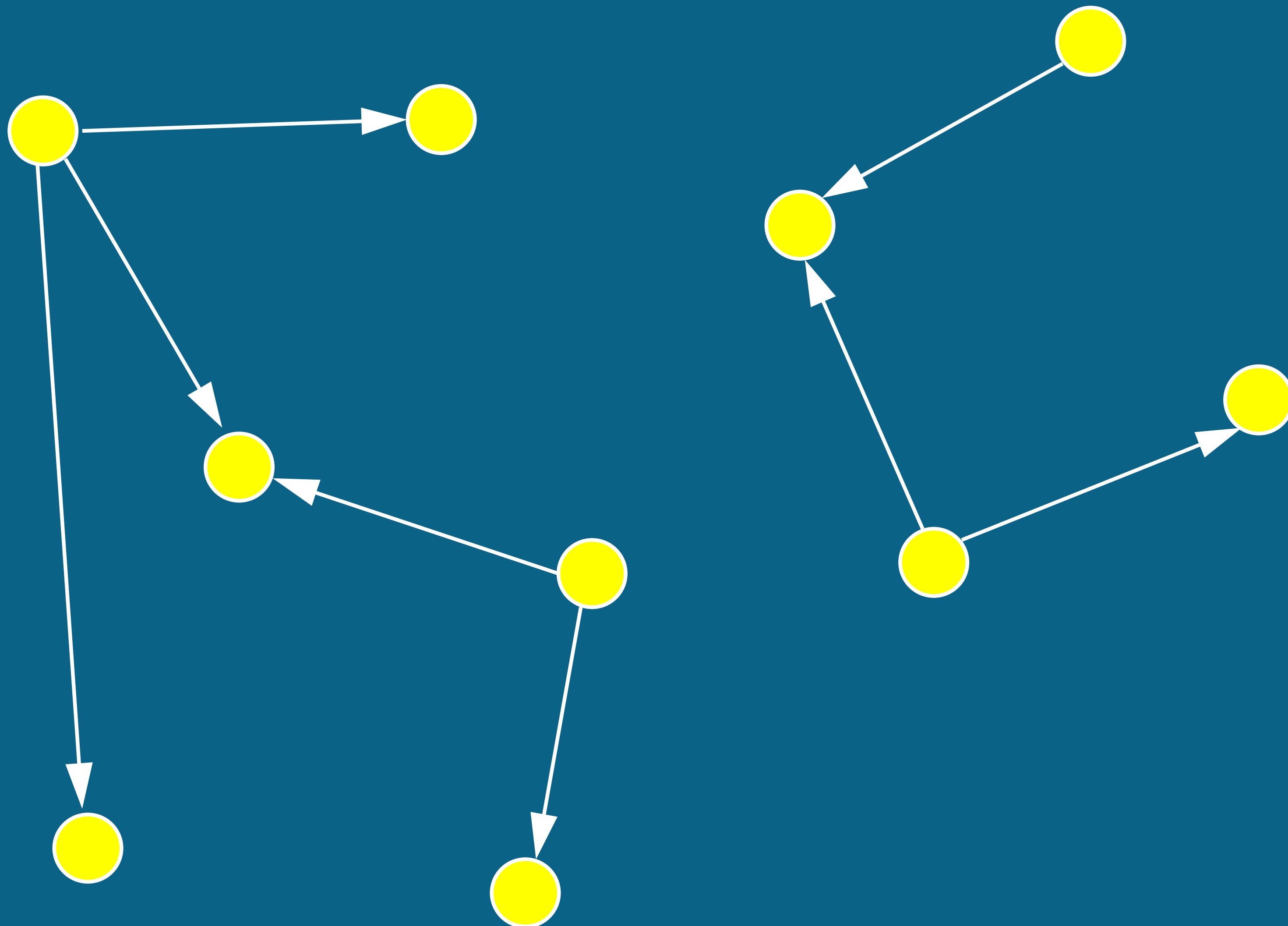
# Dynamic Bayesian Networks

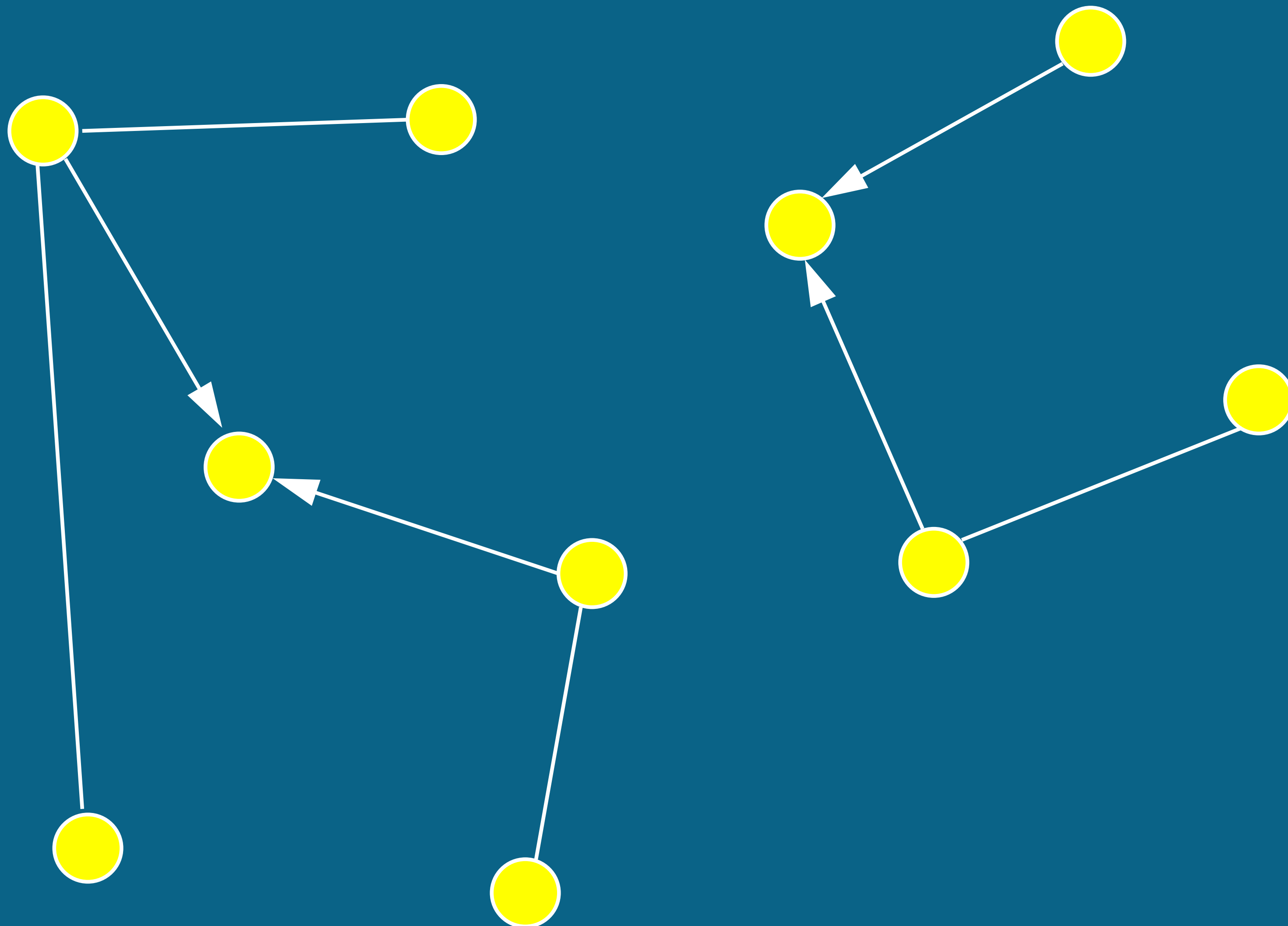
## Dynamic Bayesian Networks

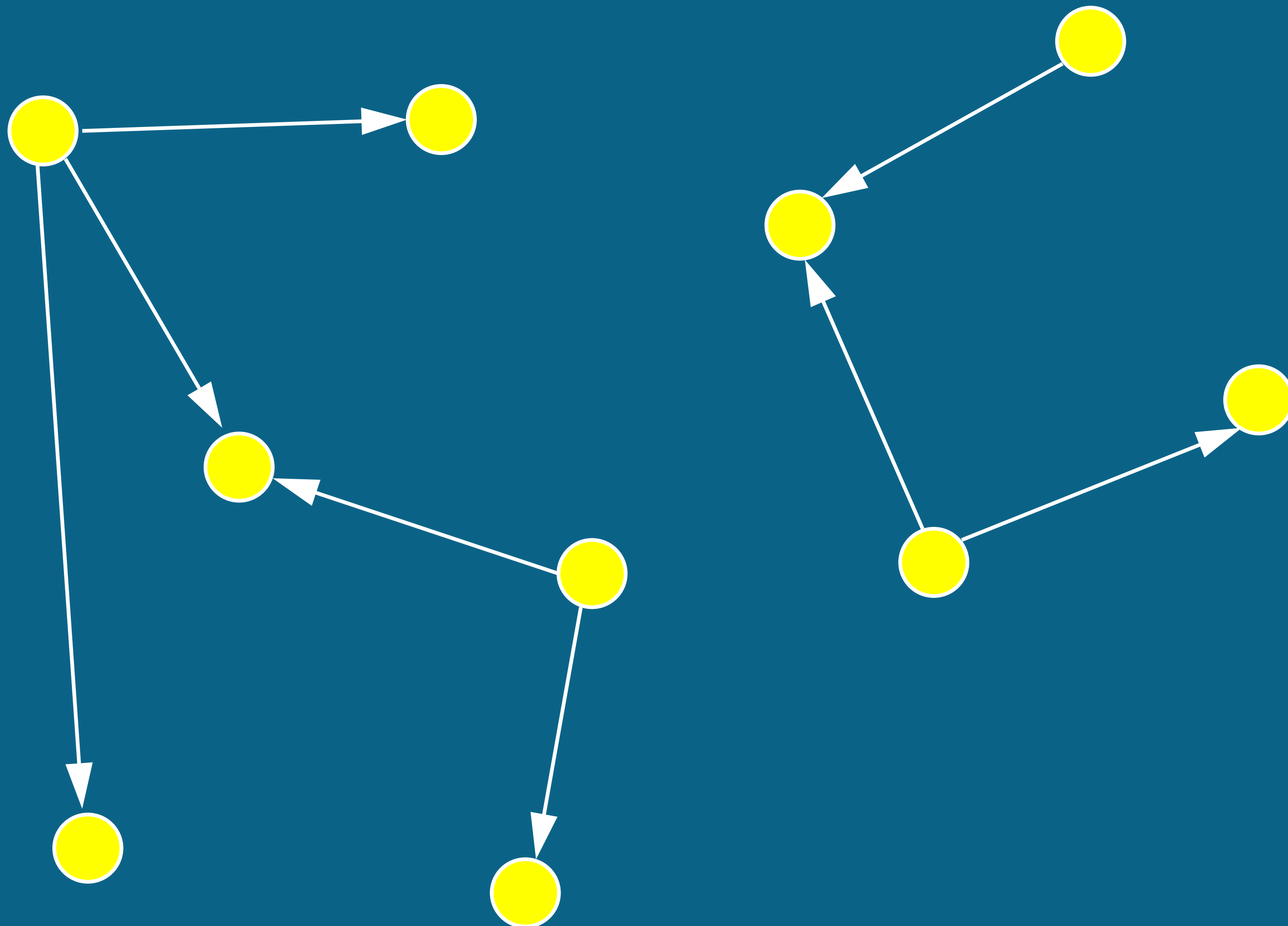
Symmetry breaking by the direction of time:
Cause precedes its effect

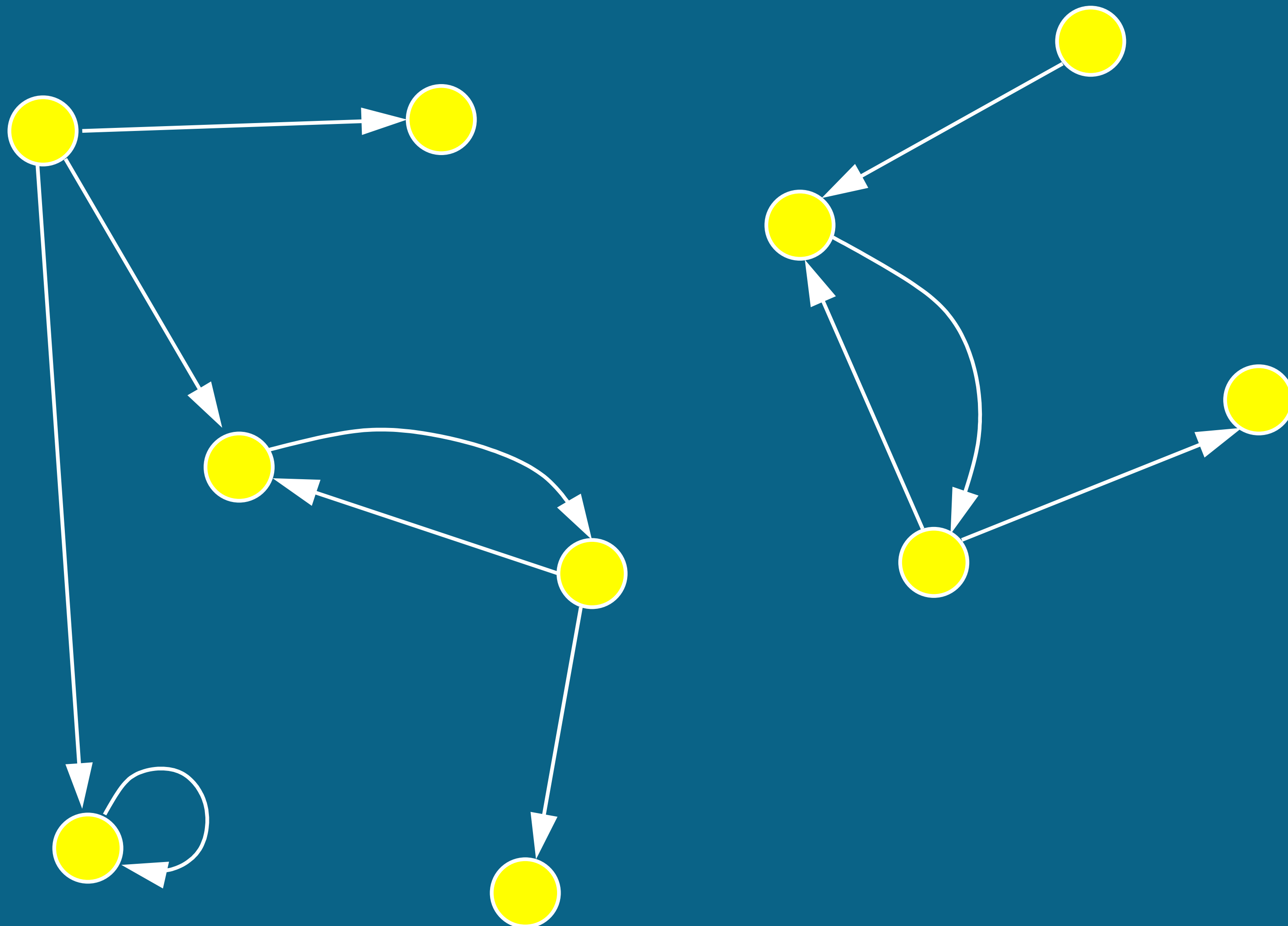
Modelling recurrent structures and
feedback loops

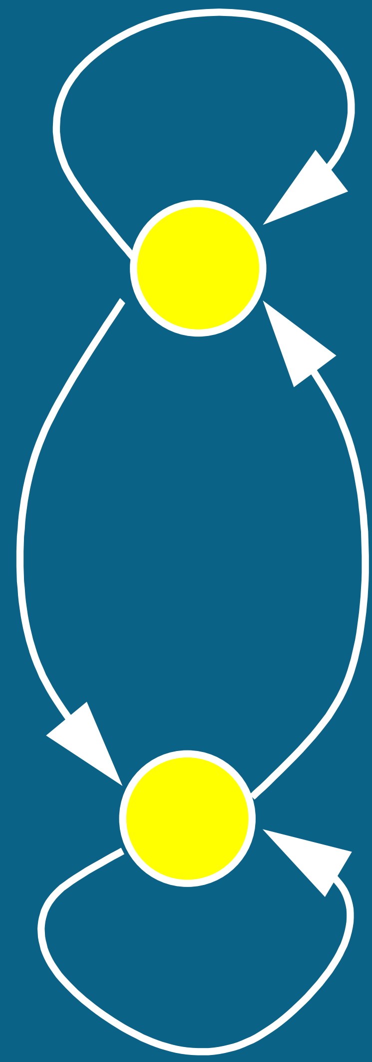


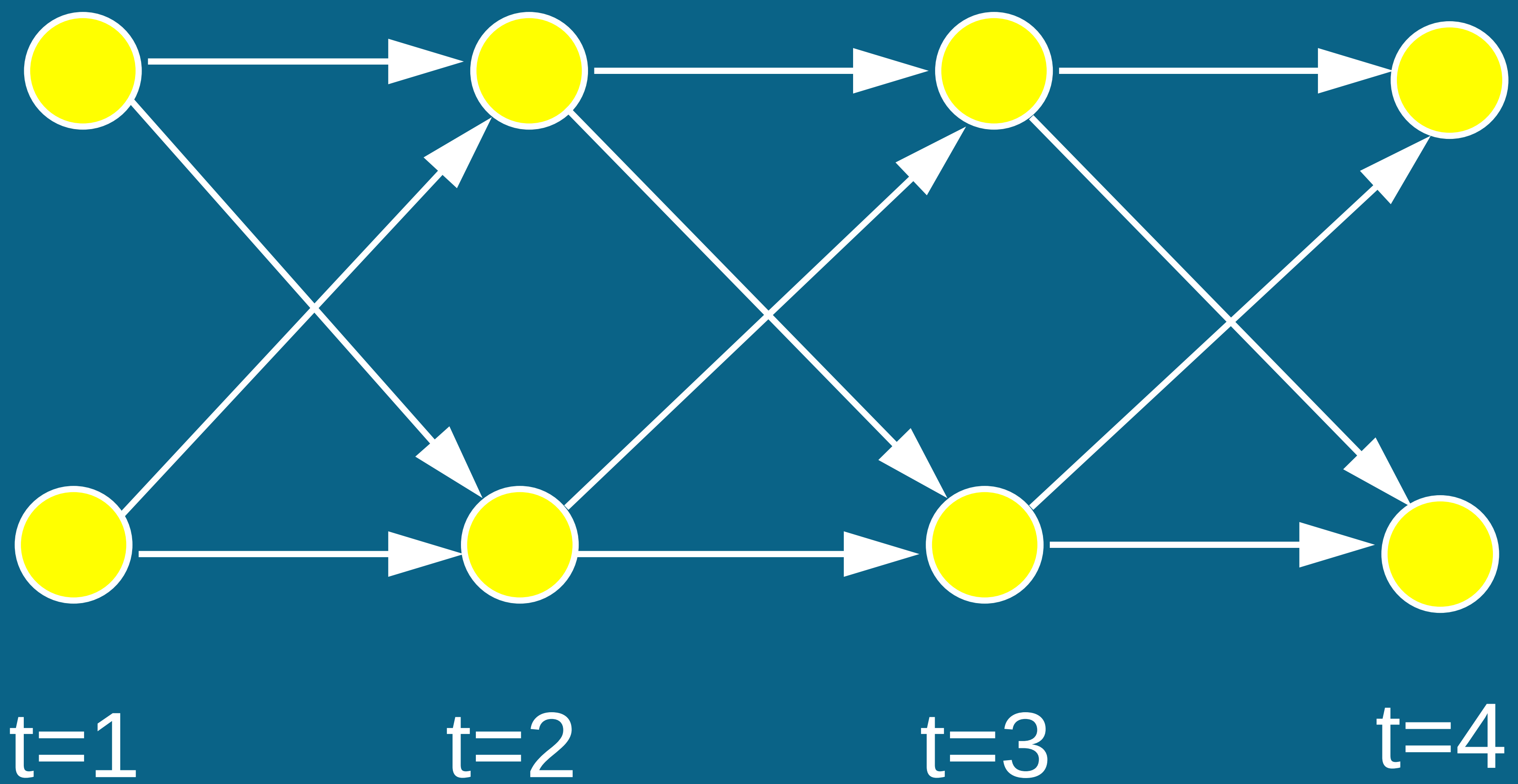











t=1
t=2
t=3
t=4

# Outline of the talk

- Recapitulation: Bayesian networks
- **Reverse engineering:**
  **Learning networks from data**
- Application to the yeast cell cycle
- Estimating the accuracy of inference

# Learning from data

# Learning from data

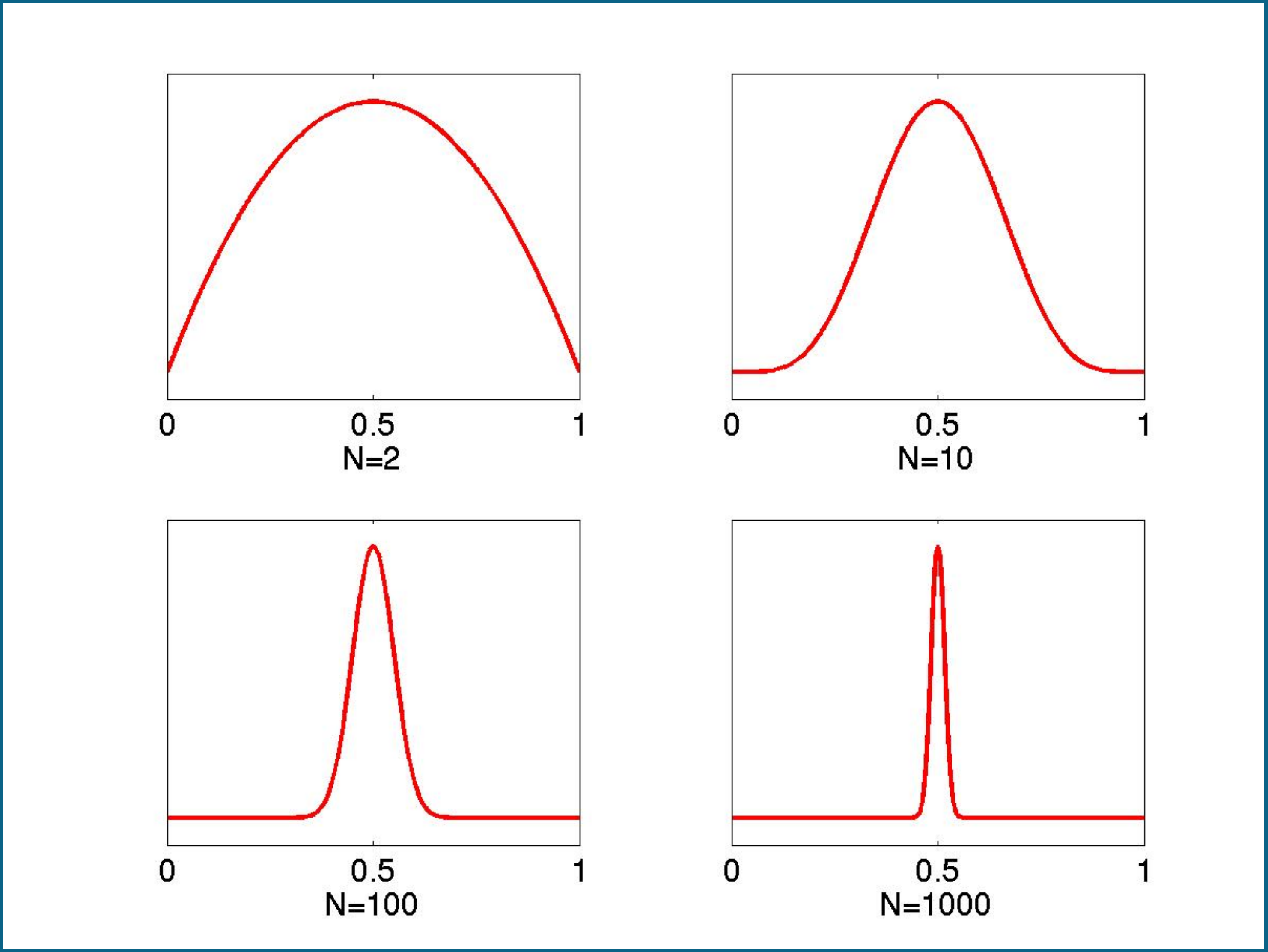
Heads Tails

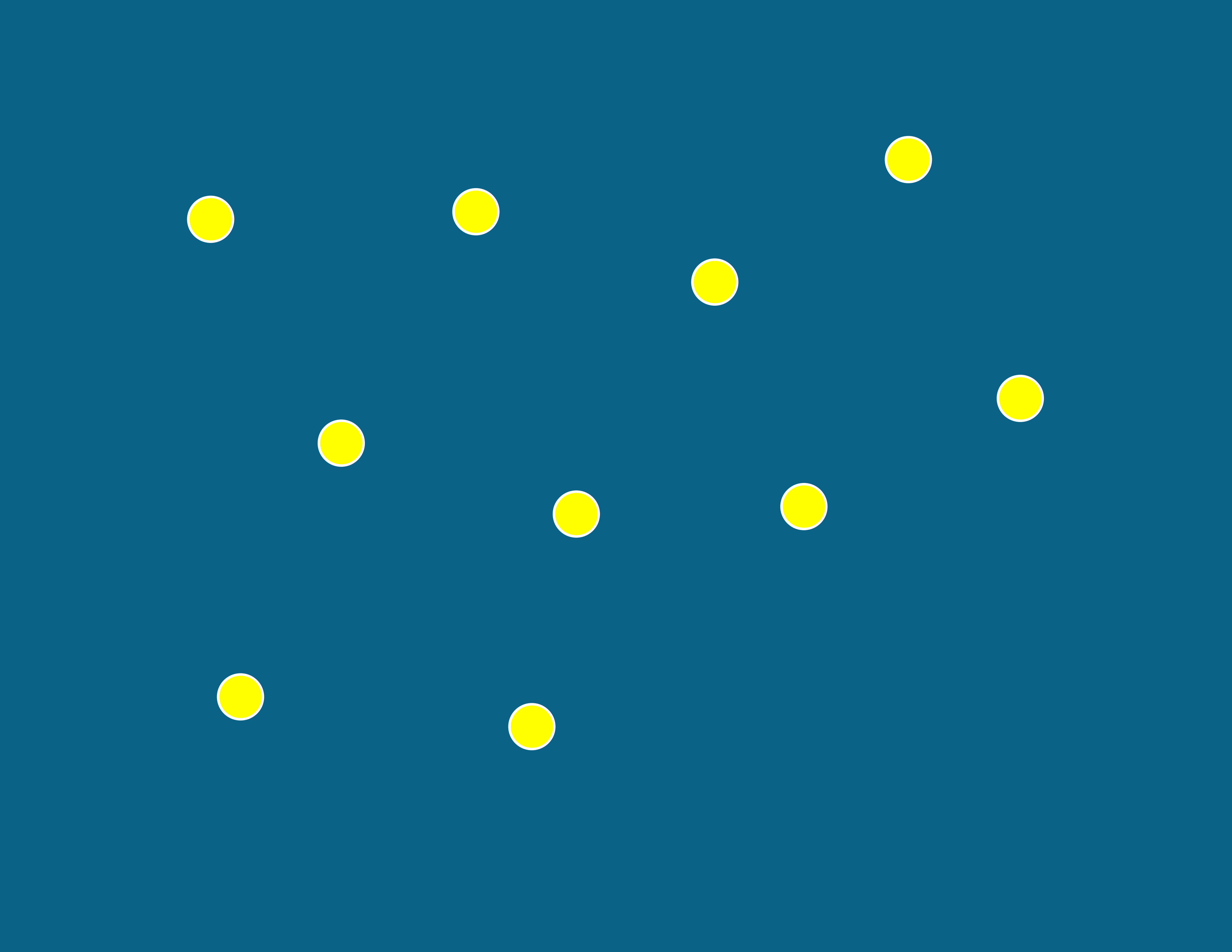
Probability $\theta$ $1-\theta$

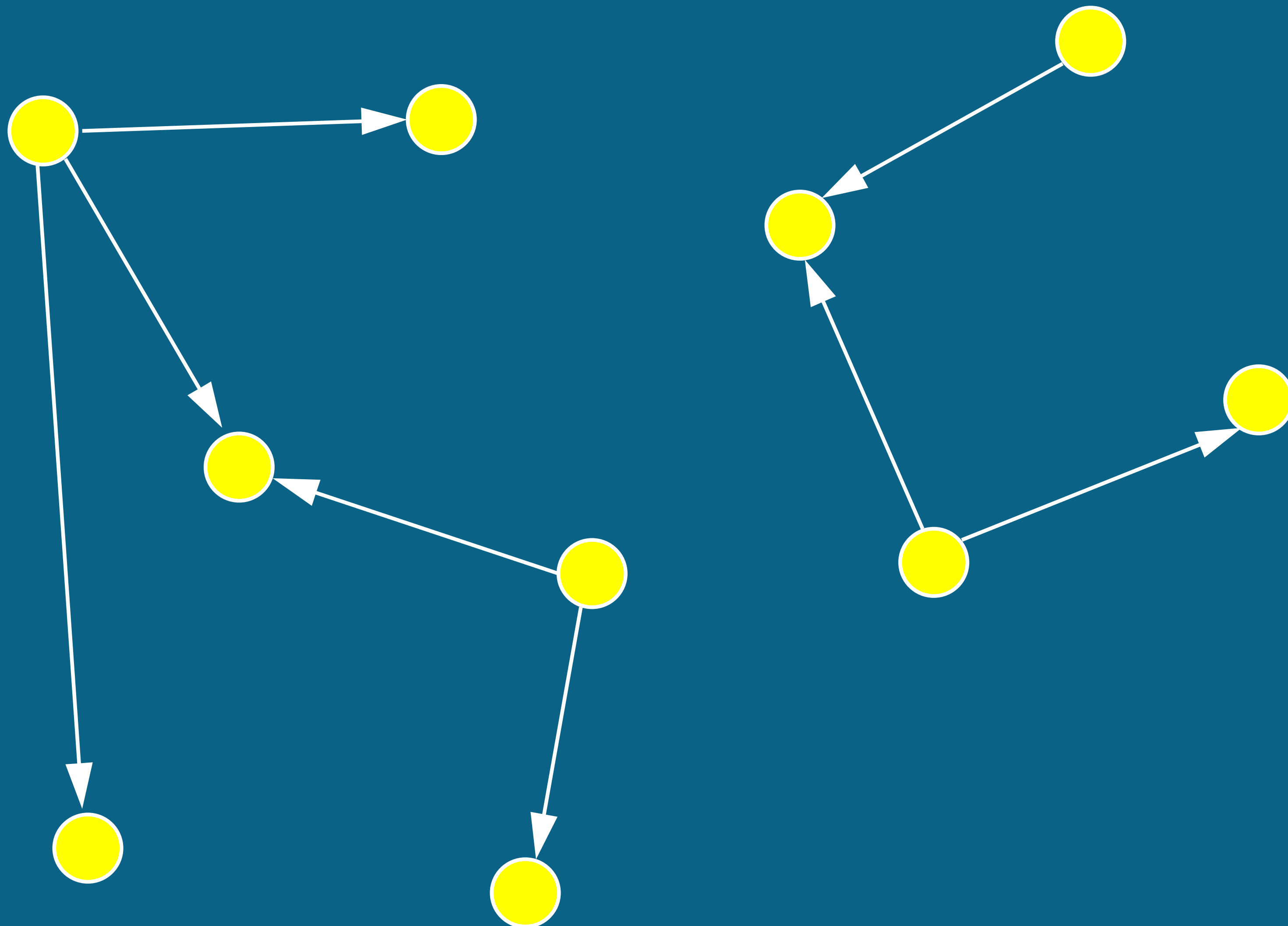
Data

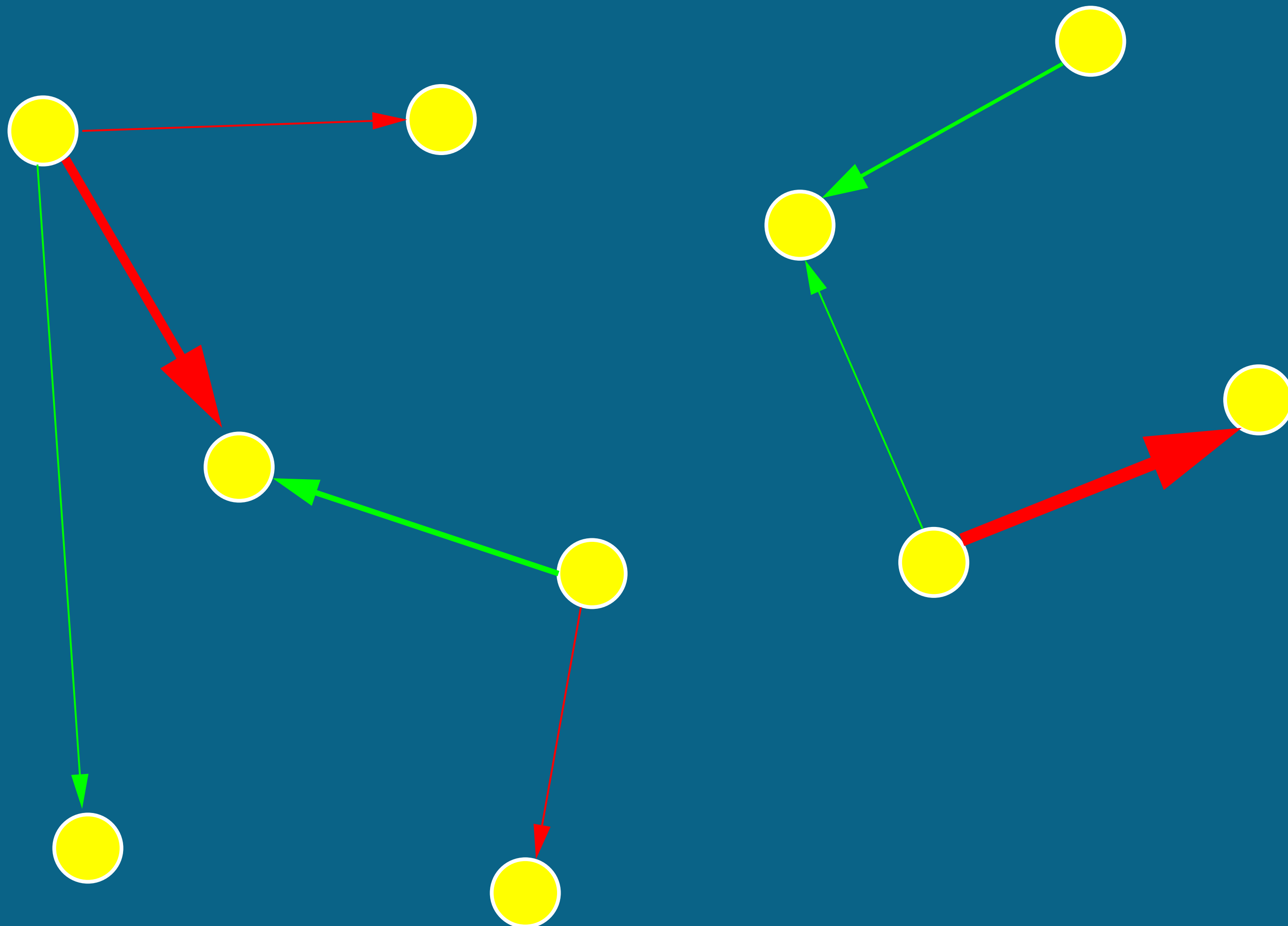
N tosses, k observations of "heads"

Example: $P(\theta|D)$ for equal numbers of heads and tails









# Classical learning paradigm

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Find the best network structure $M$:

$$M^* = \text{argmax}\{P(M|D)\}$$

## Classical learning paradigm

Find the best network structure $M$:

$$M^* = \mathrm{argmax}\{P(M|D)\}$$

Find the best parameters $\theta^*$

$$\theta^* = \mathrm{argmax}\{P(\theta|D, M^*)\}$$

Find the best model $M$, that is, the best network

$$P(M|D) \propto P(D|M)P(M)$$

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$$P(M|D) \propto P(D|M)P(M)$$

$$P(D|M) = \int P(D|\theta, M)P(\theta|M)d\theta$$

When is the integral analytically tractable?

Find the best model $M$, that is, the best network

$$P(M|D) \propto P(D|M)P(M)$$

$$P(D|M) = \int P(D|\theta, M)P(\theta|M)d\theta$$

When is the integral analytically tractable?

- Complete observation: No missing values.
- $P(D|\theta, M)$ and $P(\theta|M)$ must satisfy certain regularity conditions.
- Examples: Multinomial with a Dirchlet prior, linear Gaussian with a normal-gamma prior.

## Naive approach

- Compute $P(M|D)$ for all possible network structures $M$ .
- Select network structure $M^*$ that maximizes $P(M|D)$

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- Compute $P(M|D)$ for all possible network structures $M$ .
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### Problem 1:

Number of different network structures increases super-exponentially with the number of nodes.

| N of nodes | 2 | 4 | 6 | 8 | 10 |
|---|---|---|---|---|---|
| N of structures | $3$ | $543$ | $3.7 \times 10^6$ | $7.8 \times 10^{11}$ | $4.2 \times 10^{18}$ |

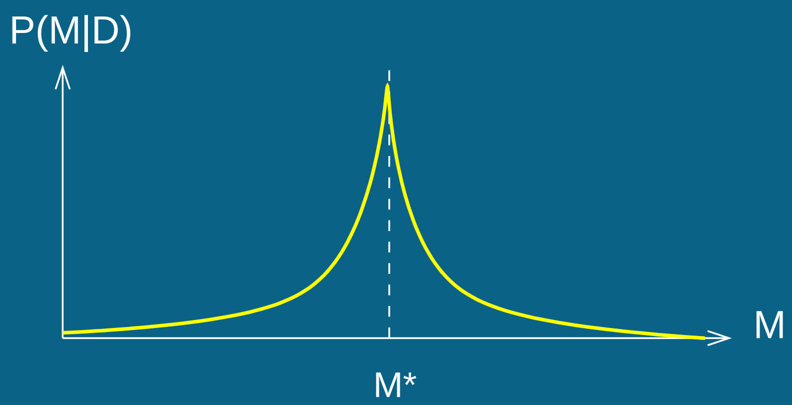
$\longrightarrow$ Optimization problem intractable for large N of nodes

## Naive approach

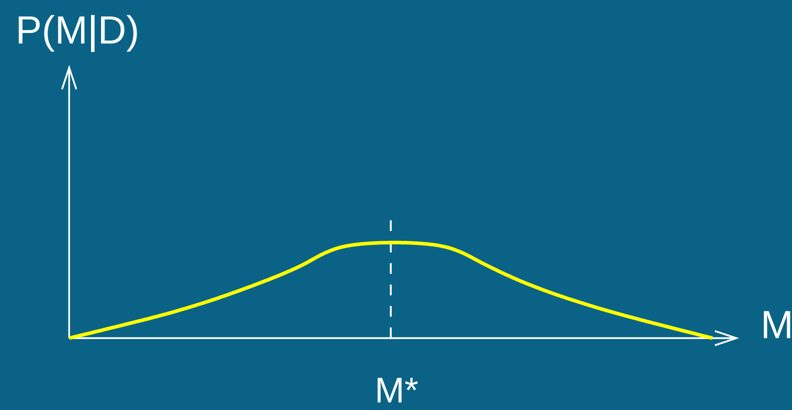
- Compute $P(M|D)$ for all possible network structures $M$ .
- Select network structure $M^*$ that maximizes $P(M|D)$

**Problem 2:**

Data are sparse $\longrightarrow$ Intrinsic uncertainty of inference




Large data set D:
Best network structure M* well defined




Small data set D:
Intrinsic uncertainty about M*

Objective: Sample from the posterior distribution

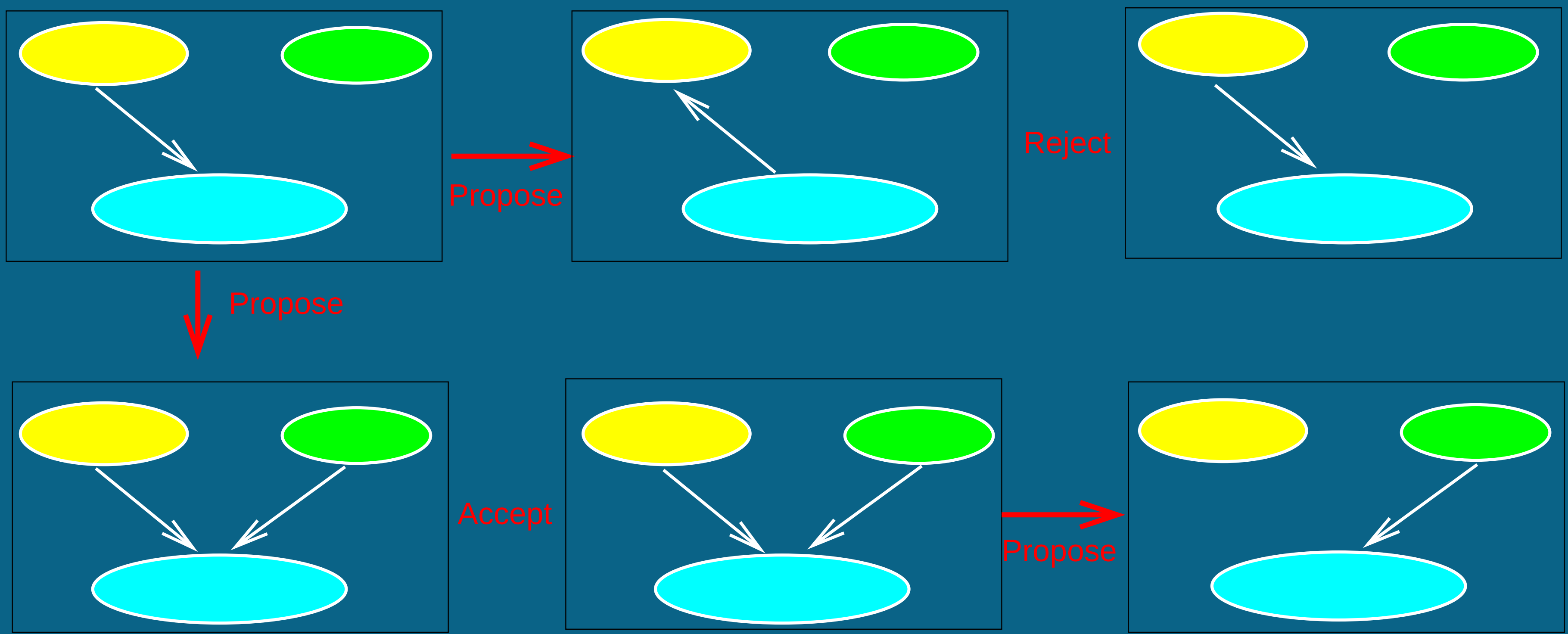
$$P(M_k|D) = \frac{P(D|M_k)P(M_k)}{\sum_i P(D|M_i)P(M_i)}$$

Direct approach intractable due to $\sum_i P(D|M_i)P(M_i)$

Markov chain Monte Carlo (MCMC):

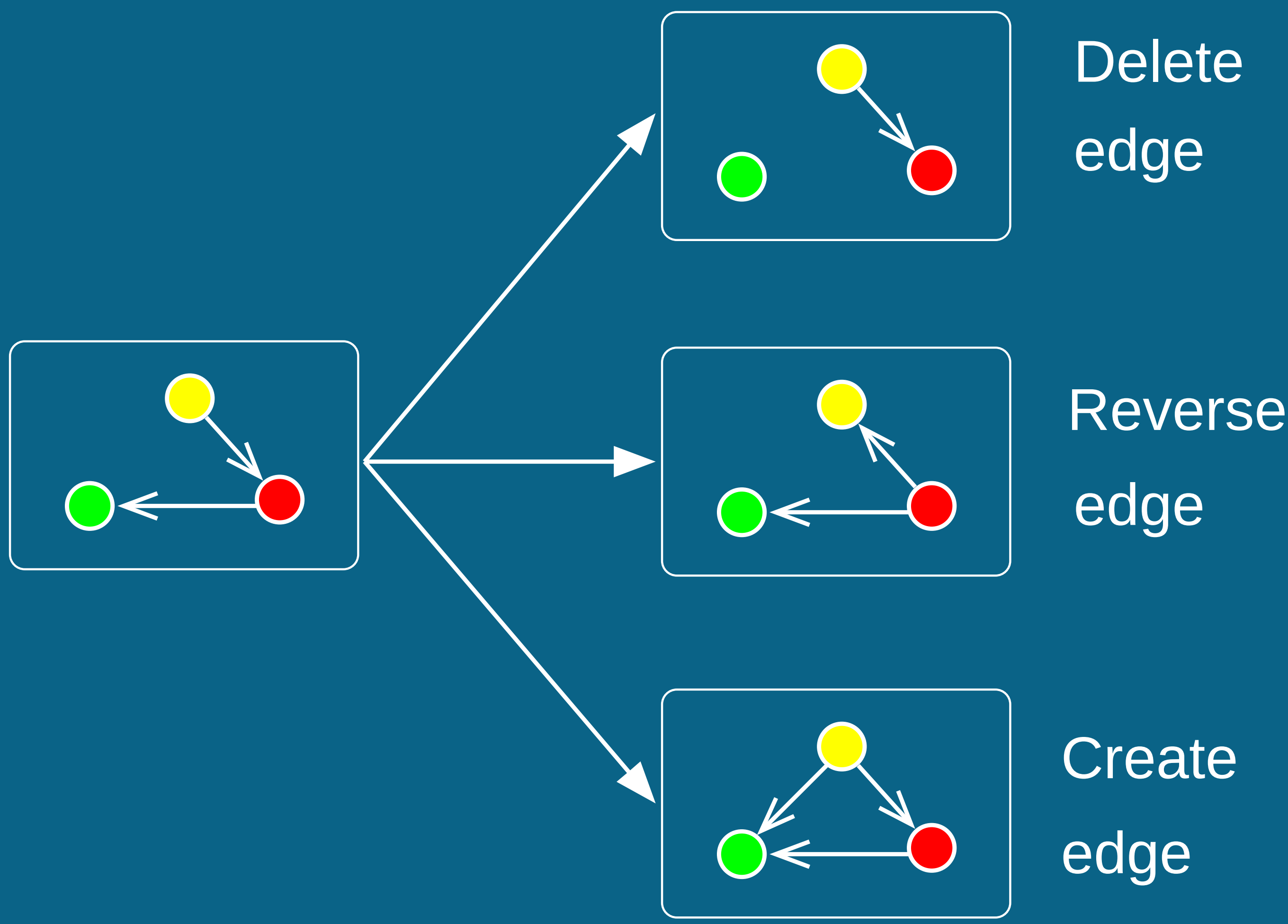
- Proposal move: Given network $M_{old}$, propose a new network $M_{new}$ with probability $Q(M_{new}|M_{old})$.
- Acceptance/Rejection: Accept this new network with probability $\min\left\{1, \frac{P(M_{new}|D)}{P(M_{old}|D)} \times \frac{Q(M_{old}|M_{new})}{Q(M_{new}|M_{old})}\right\}$

# Markov chain Monte Carlo (MCMC)




Accept move with probability: $\min\left\{1, \frac{P(D|M_{new})P(M_{new})}{P(D|M_{old})P(M_{old})} \times \frac{Q(M_{old}|M_{new})}{Q(M_{new}|M_{old})}\right\}$

# MCMC moves



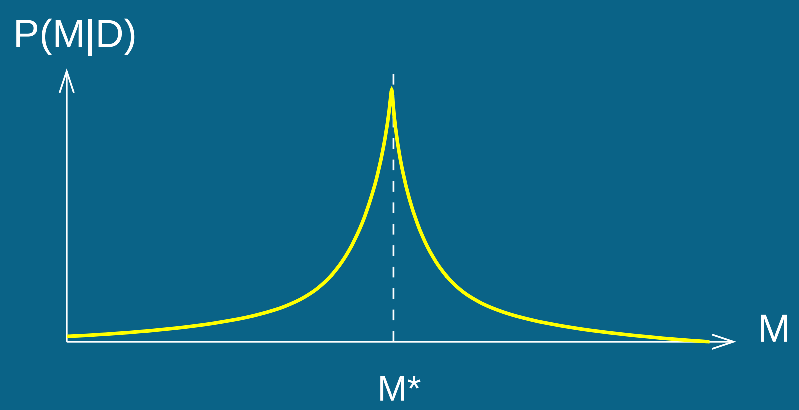
Study with Marco Grzegorczyk and Wolfgang Urfer (Dortmund University)

Carcinogenesis in kidney

- 100 genes
- 60 kidney cancer patients
- MCMC: 100,000 Metropolis-Hastings steps

# Problem: Statistical significance of the networks

- Complex models: Transcript levels of hundreds of genes.
- Sparse data: Typically a few dozen samples.



Large data set D:
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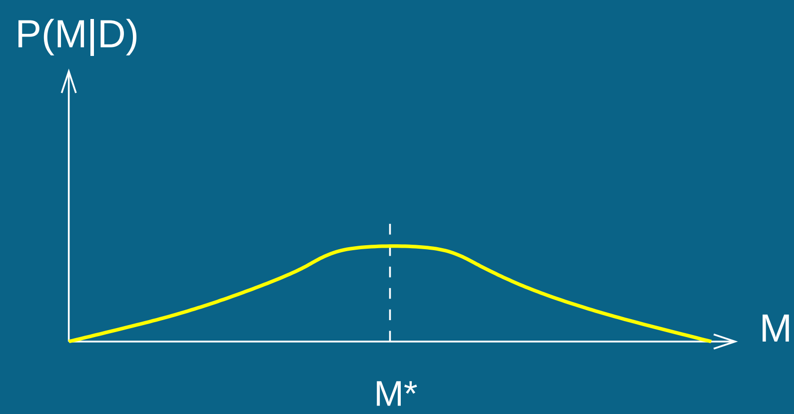
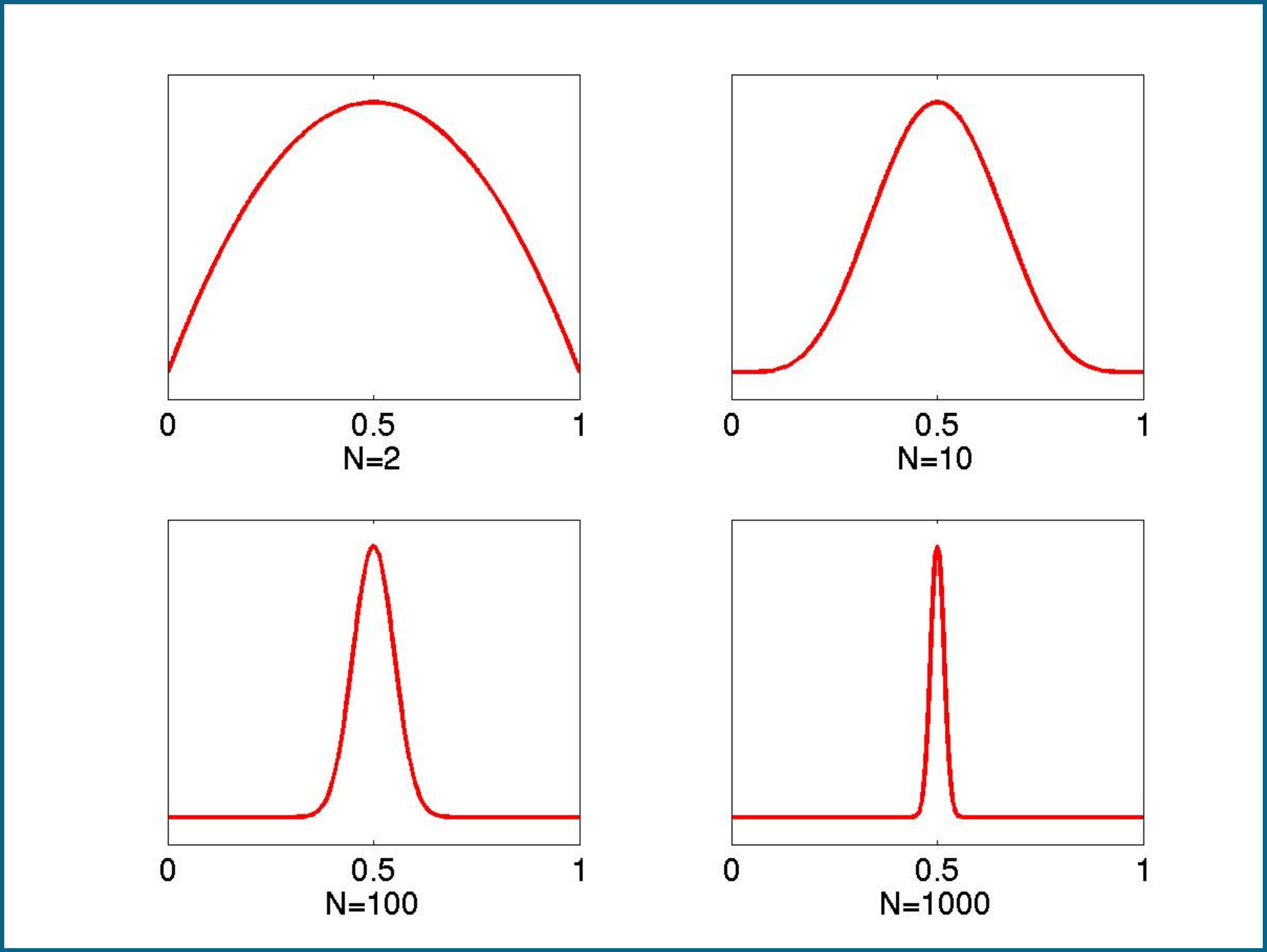


Small data set D:
Intrinsic uncertainty about M*

- Posterior probability $P(M|D)$ diffuse: Global network inference is meaningless.

## Example: $P(\theta|D)$ for equal numbers of heads and tails



Solution: Focus on features and subnetworks

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Feature: Indicator variable for a property of interest,
e.g.: Are X and Y close neighbours in the network?

$$f(M) = \begin{cases} 1 \text{ if } M \text{ satisfies the feature} \\ 0 \text{ otherwise} \end{cases}$$

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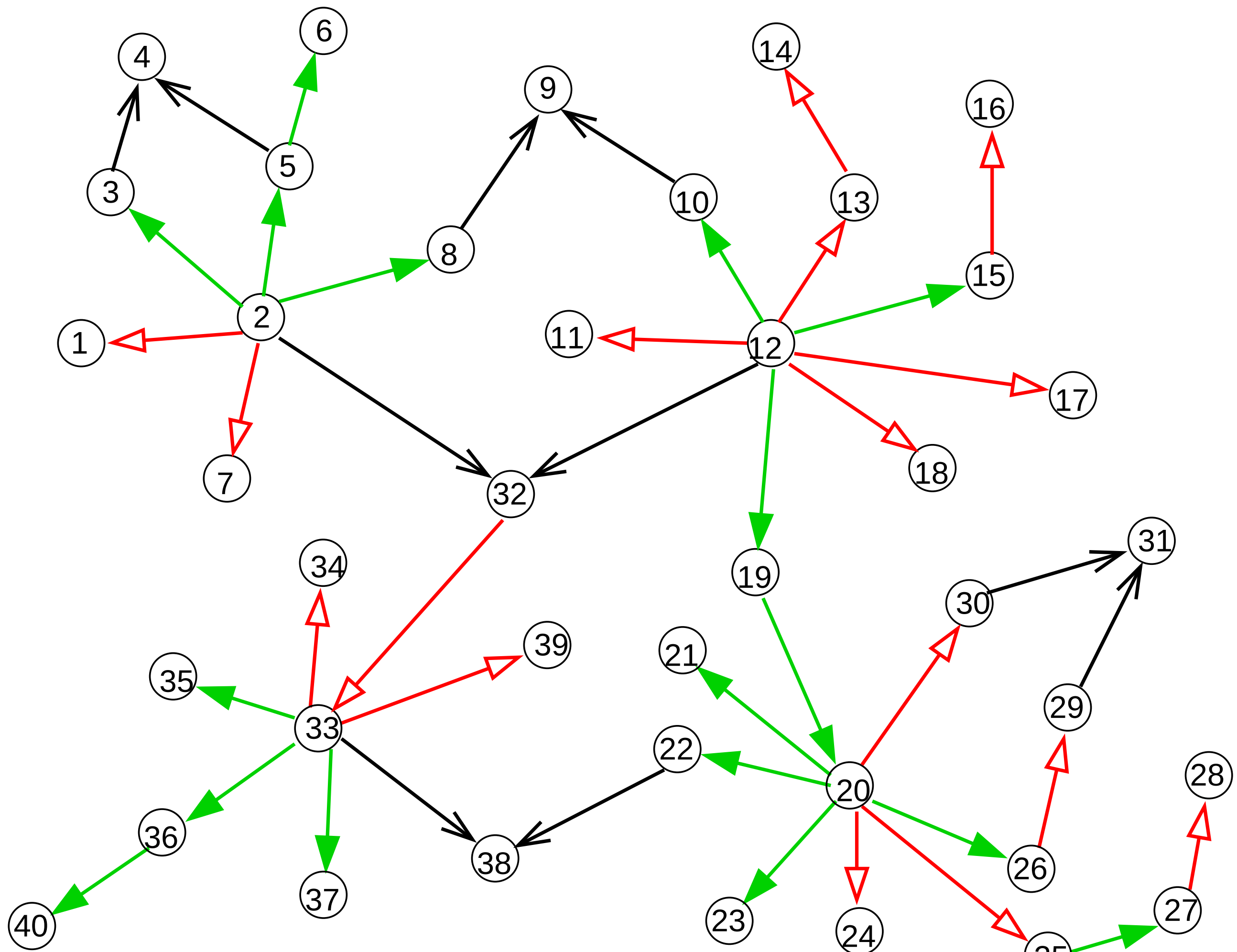
$$f(M) = \begin{cases} 1 \text{ if } M \text{ satisfies the feature} \\ 0 \text{ otherwise} \end{cases}$$

Posterior probability of features: $P(f|D) = \sum_{M} f(M) P(M|D)$

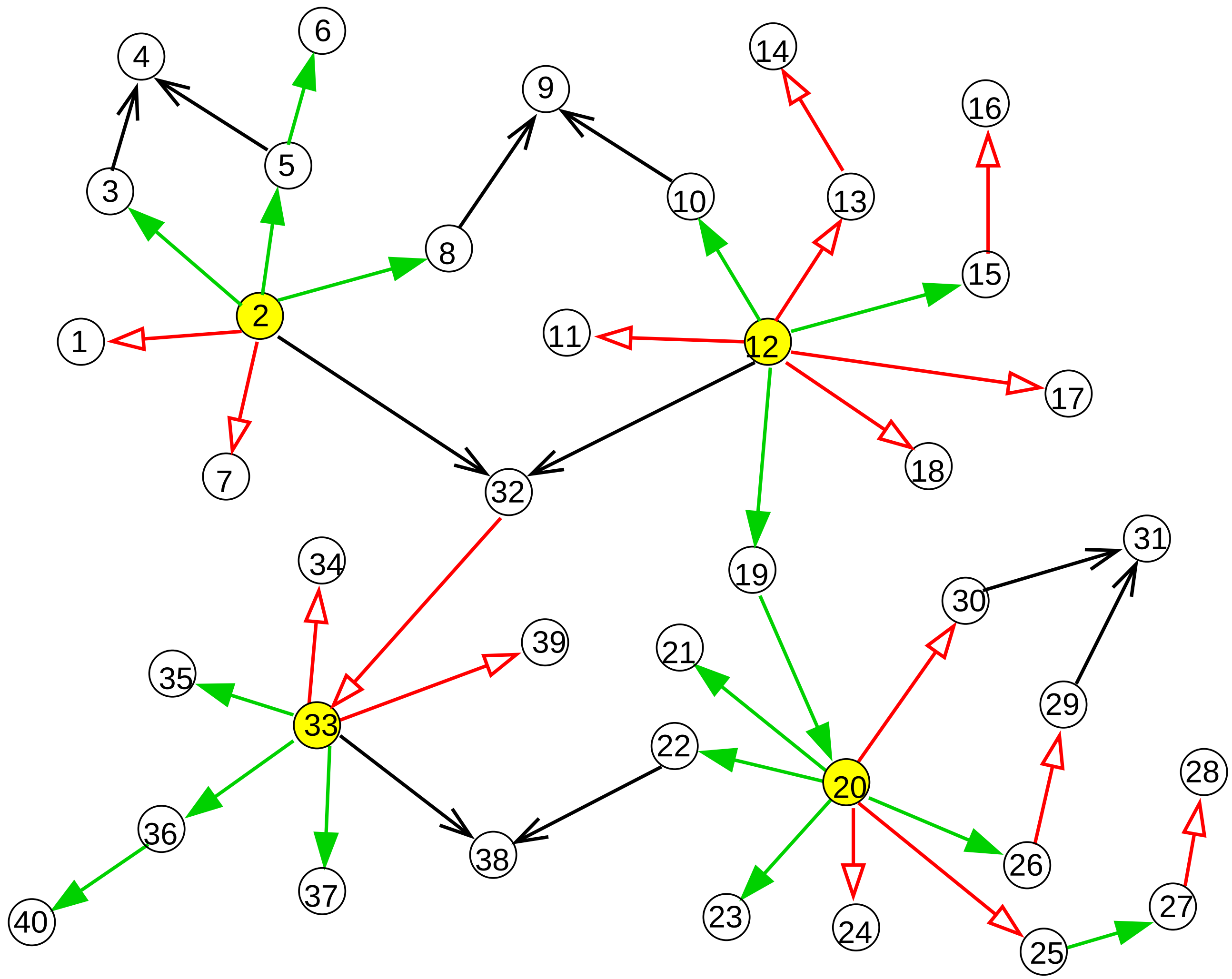
Approximate this sum with MCMC: $P(f|D) = \frac{1}{T} \sum_{i=1}^{T} f(M_i)$

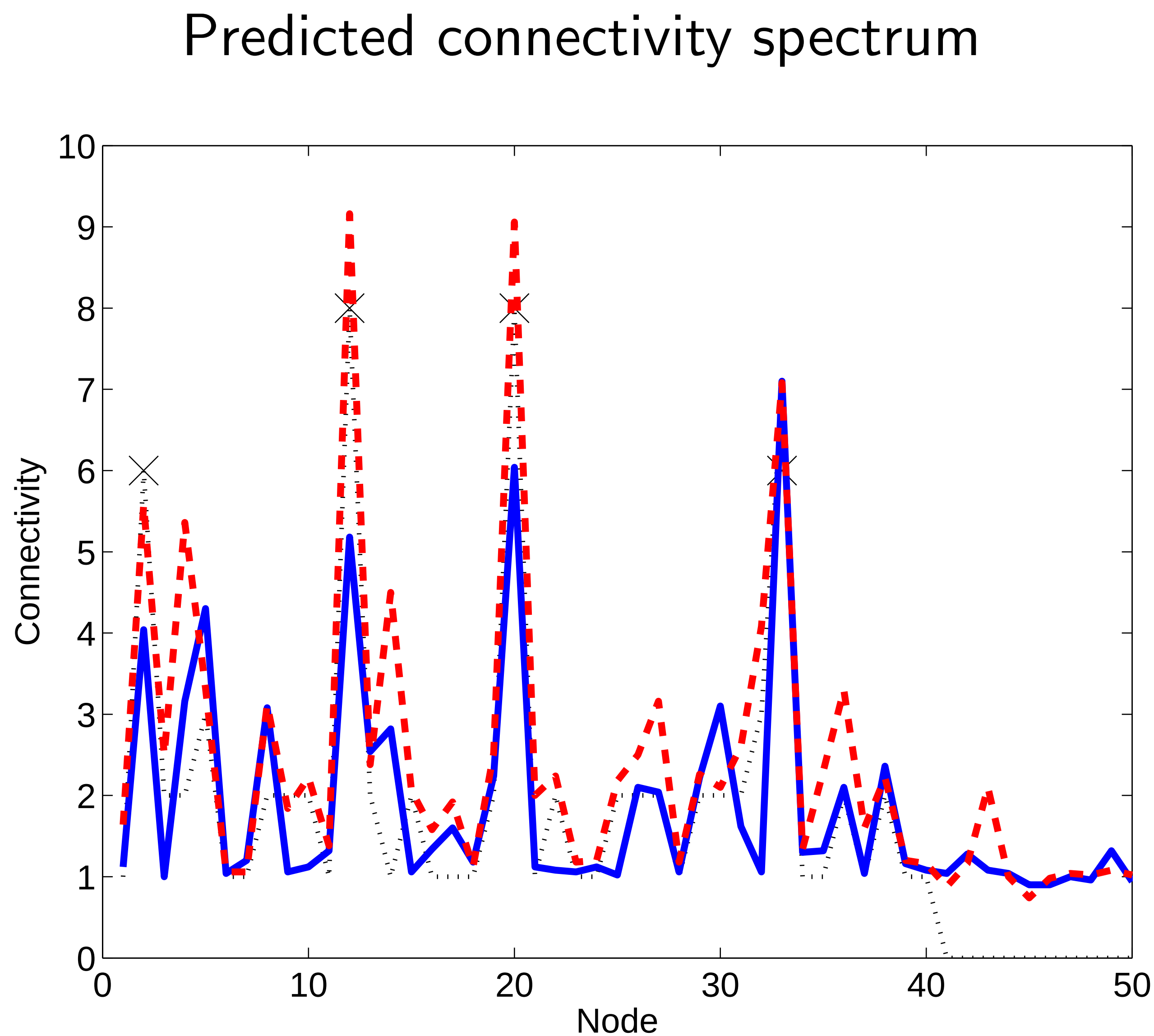
where $\{M_i\}$ is a sample from the posterior obtained with MCMC.

## Model network, data set size: $N = 50$



Model network, data set size: $N = 50$




Predicted connectivity spectrum
Connectivity
Node
0
1
2
3
4
5
6
7
8
9
10
0
10
20
30
40
50

# Outline of the talk

- Recapitulation: Bayesian networks
- Reverse engineering:
  Learning networks from data
- **Application to the yeast cell cycle**
- Estimating the accuracy of inference

# Experimental Results

- Friedman, Linial, Nachman, Pe'er (2000)
  Journal of Computational Biology 7: 601-620

- Pe'er, Regev, Elidan, Friedman (2001)
  Bioinformatics S1: 215-224

- Friedman & Koller (2003)
  Machine Learning 50: 95-126

- Yeast cell cycle (*S. cerevisiae*).
- Six time series under different experimental conditions, altogether 76 gene expression measurements.
- 800 genes.
- No biological prior knowledge.
- Do not take into account the temporal aspect of the measurements. Introduce an additional root node representing the cell cycle phase.
- Discretization: Underexpressed (-1), normal (0), overexpressed (1).

# Order relations

- Is A an ancestor of B in all the networks of a given equivalence class?
- Does the network contain a directed path from A to B?

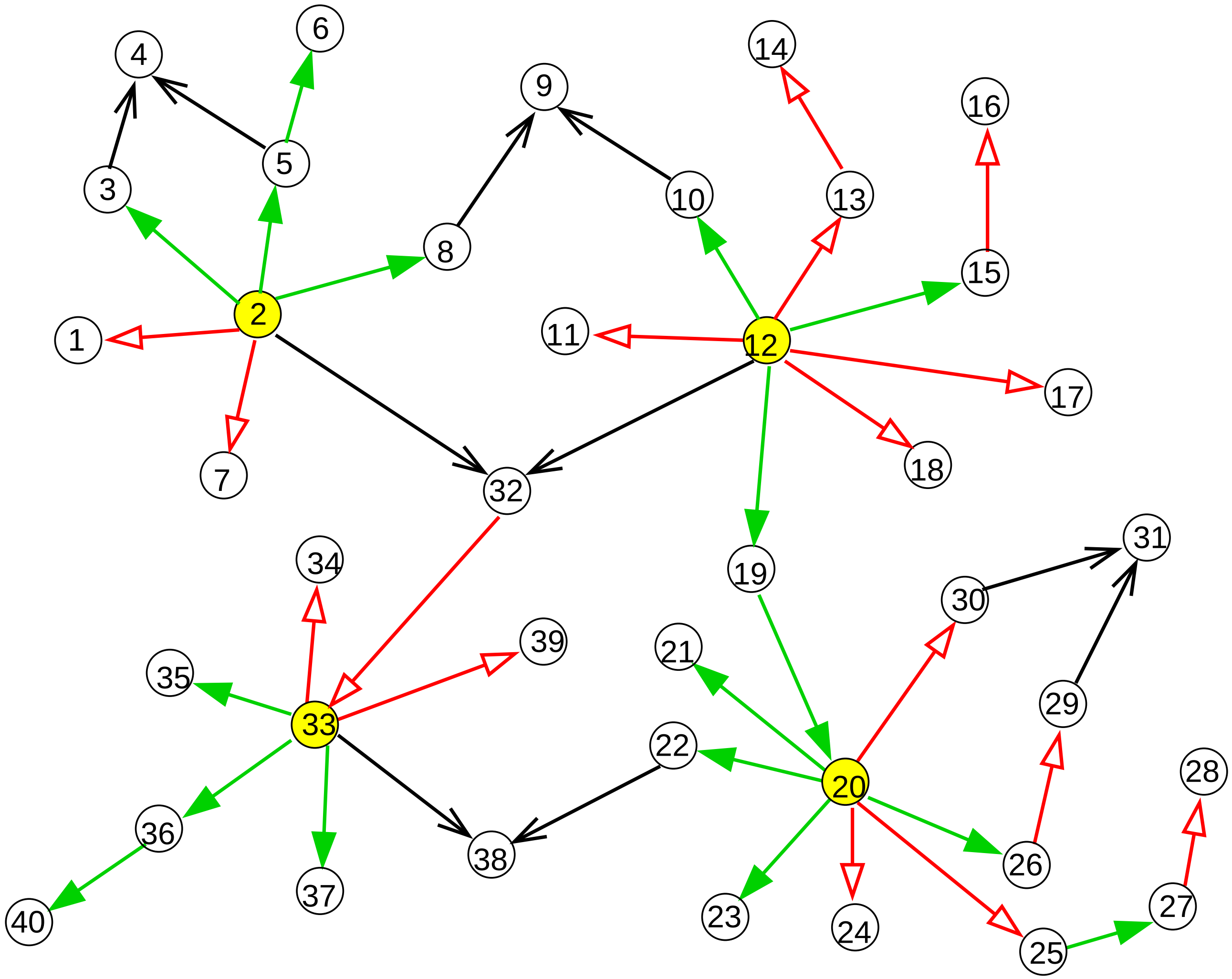
  Indication that A might be a causal ancestor of B.

# Order relations

Confidence in X being an ancestor of Y:
$P(X \to Y|D)$

Dominance score of X: $\sum_Y P(X \to Y|D)$

Genes with high dominance scores are indicative of potential causal sources of the cell cycle process.



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38
39
40

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# Order relations

Confidence in X being an ancestor of Y:
$P(X \to Y|D)$

Dominance score of X: $\sum_{Y} P(X \to Y|D)$

Genes with high dominance scores are indicative of potential causal sources of the cell cycle process.

Finding: Only a few genes dominate the order.

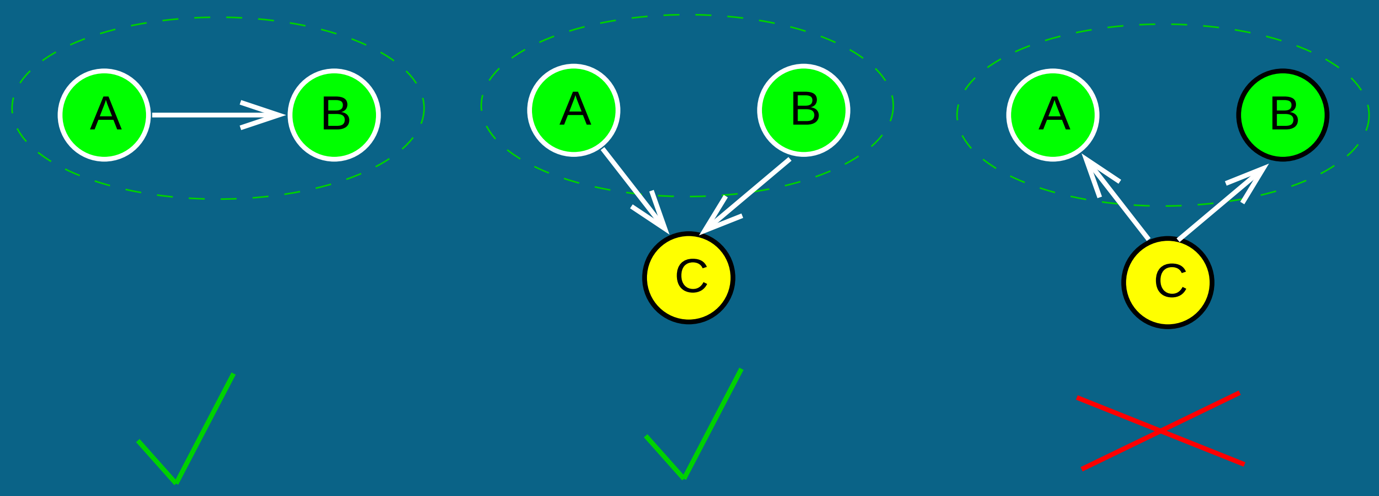
## Dominant genes in the ordering relations

| | |
|---|---|
| CLN1 | Role in cell cycle start |
| CLN2 | Role in cell cycle start |
| CDC5 | Cell cycle control, required for exit from mitosis |
| RAD53 | Cell cycle control: checkpoint function |
| RFA2 | Involved in nucleotide excision repair |
| PLO30 | Required for DNA replication and repair |
| MSH6 | Required for mismatch repair in mitosis and meiosis |

DNA repair is associated with transcription initiation: DNA areas which are more active in transcription are also repaired more frequently.

# Markov neighbours

- Variables that are not separated by any other measured variable in the domain.




- Indication that two genes are related in some joint biological interaction or process.
- Parent-child: One gene regulating another.
- Spouse relations: Two genes co-regulating another.

# Markov relations

$P(X \leftrightarrow Y|D)$: Indication that genes are functionally related.

- Most Markov pairs: Intracluster pairings with high correlation in their expression.

- But: Genes where $P(X \leftrightarrow Y|D)$ is high and correlation is low.

| | |
|---|---|
| FAR1 | Role in a mating type switch |
| ASH1 | Role in a mating type switch |
| LAC1 | GPI transport protein |
| YNL300W | Modified by GPI |
| SAG1 | Induces the mating process |
| MF-ALPHA-1 | Participates in the mating process |

# Markov relations

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|---|---|
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| LAC1 | GPI transport protein |
| YNL300W | Modified by GPI |
| SAG1 | Induces the mating process |
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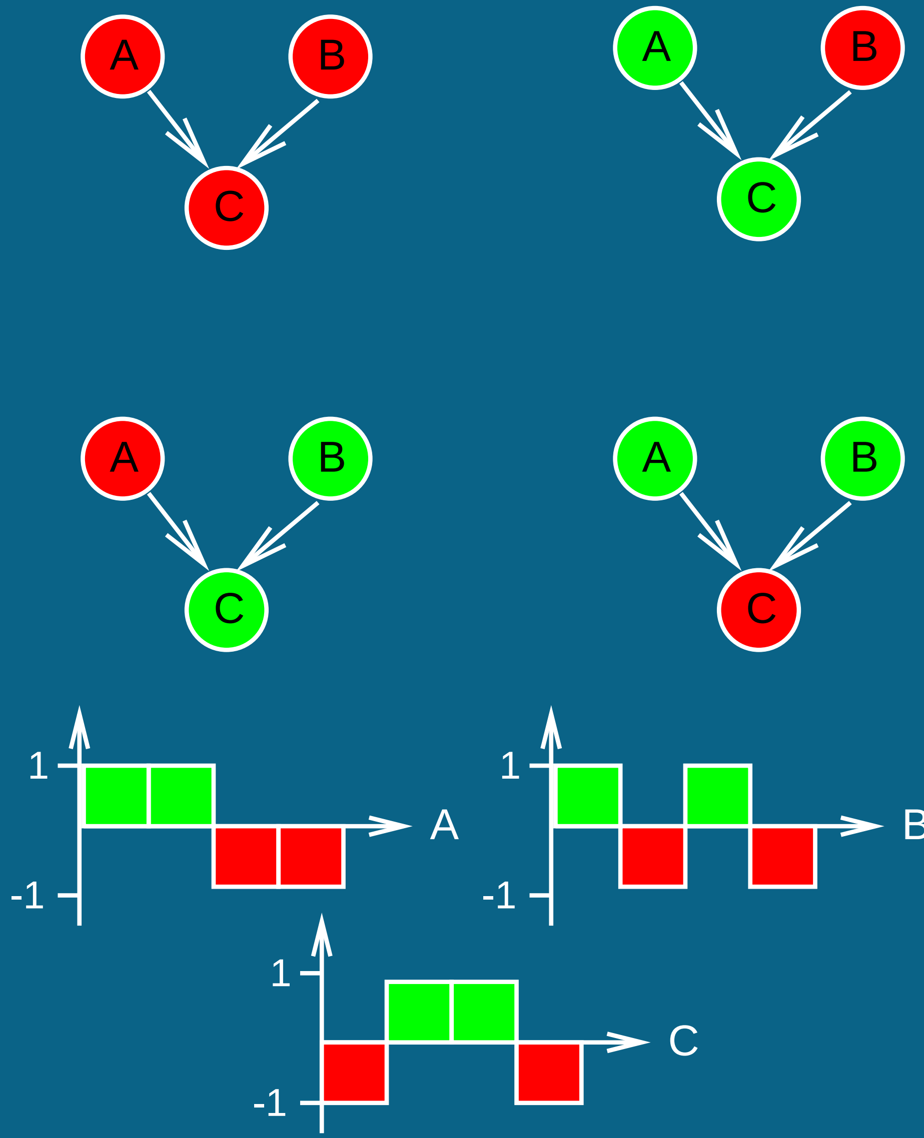
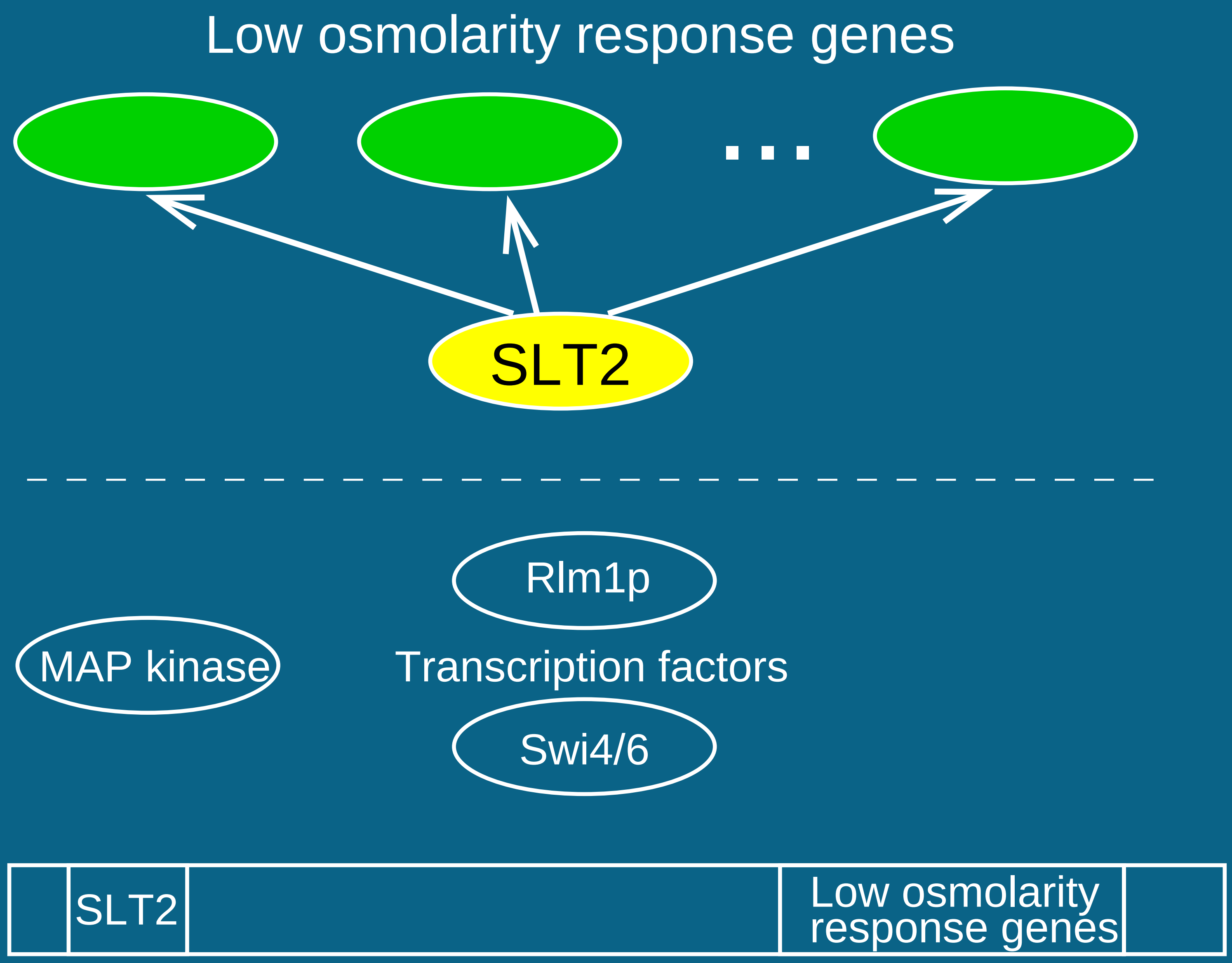
Advantage of Bayesian networks: context-specific and non-linear.

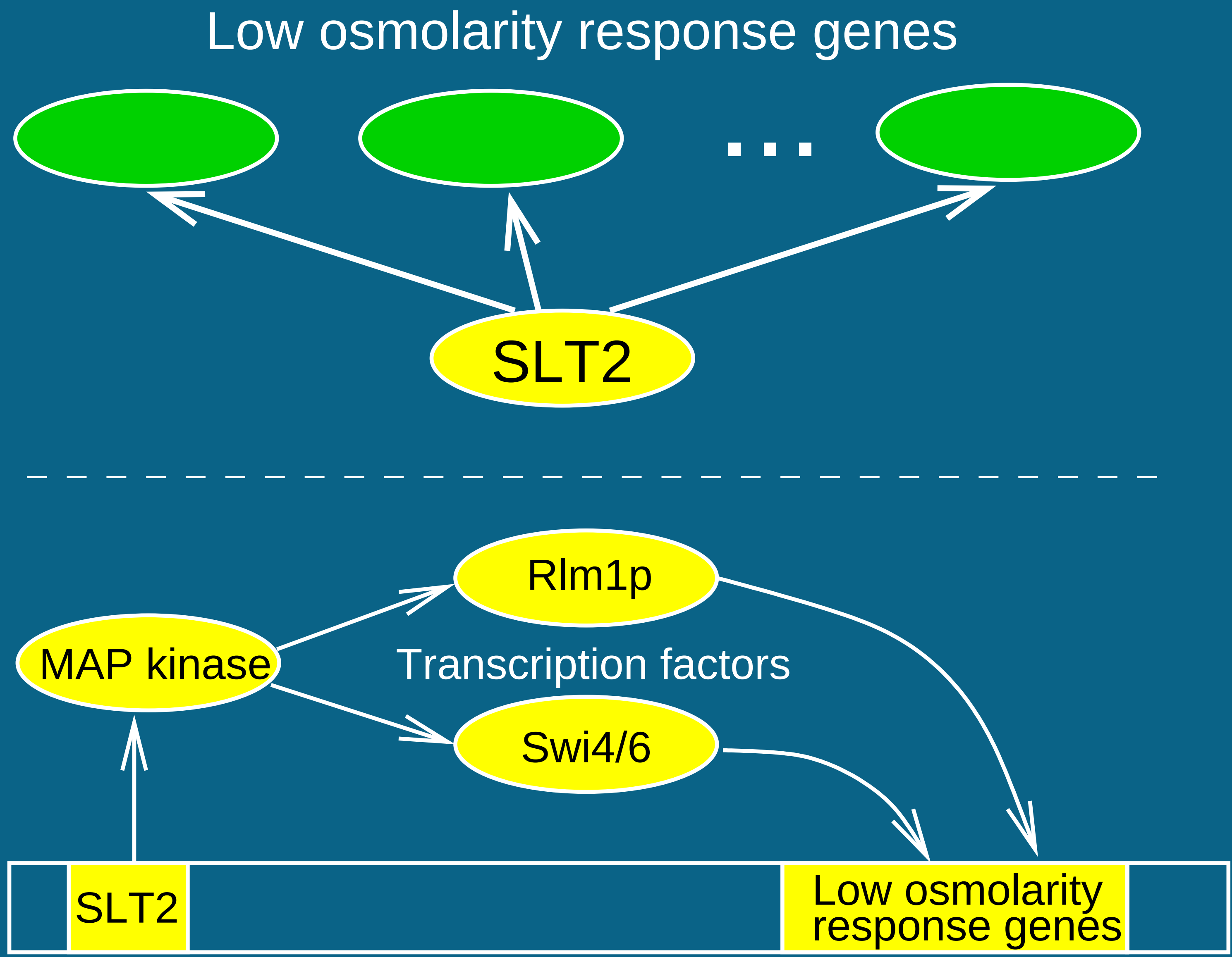

A
B
C
A
B
C
A
B
C
A
B
C
1
-1
A
1
-1
B
1
-1
C

# Separator relations

and

# subnetworks


Low osmolarity response genes
...
SLT2
Rlm1p
MAP kinase
Transcription factors
Swi4/6
SLT2
Low osmolarity response genes



Low osmolarity response genes
...
SLT2
Rlm1p
MAP kinase
Transcription factors
Swi4/6
SLT2
Low osmolarity response genes

# Outline of the talk

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- **Estimating the accuracy of inference**

Dirk Husmeier (2003)

Bioinformatics 19, 2271-2282

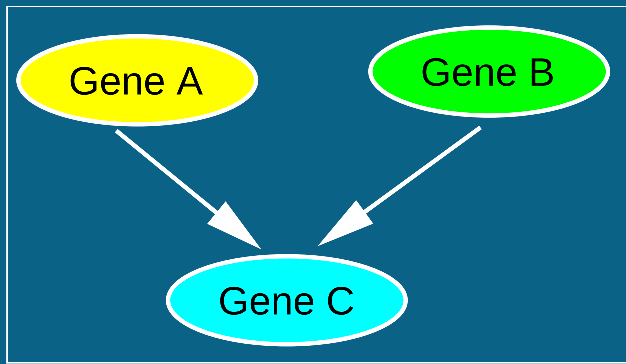
**Disadvantage** of **real data:**

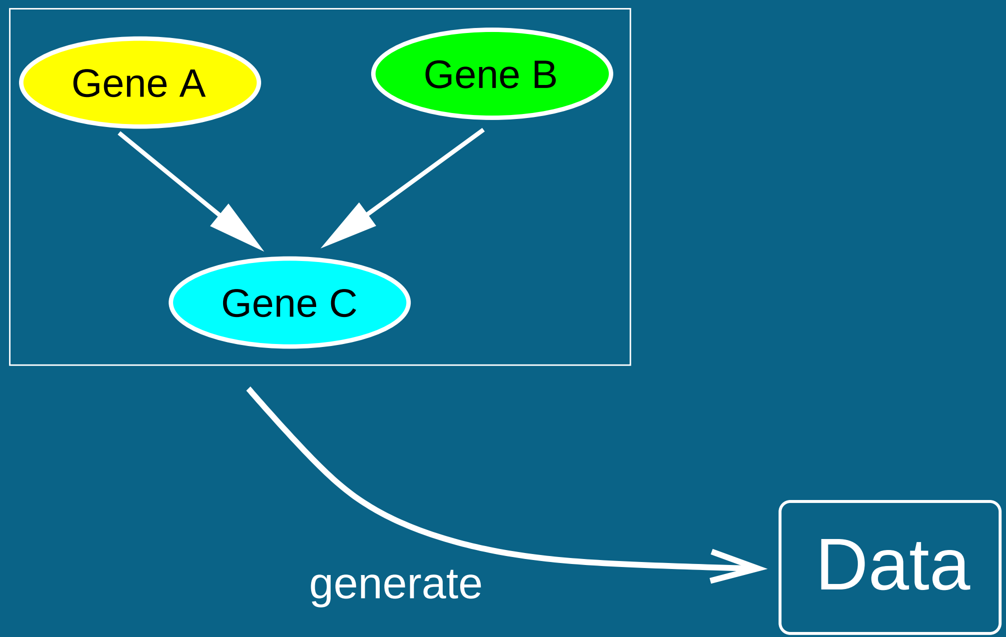
No gold standards !

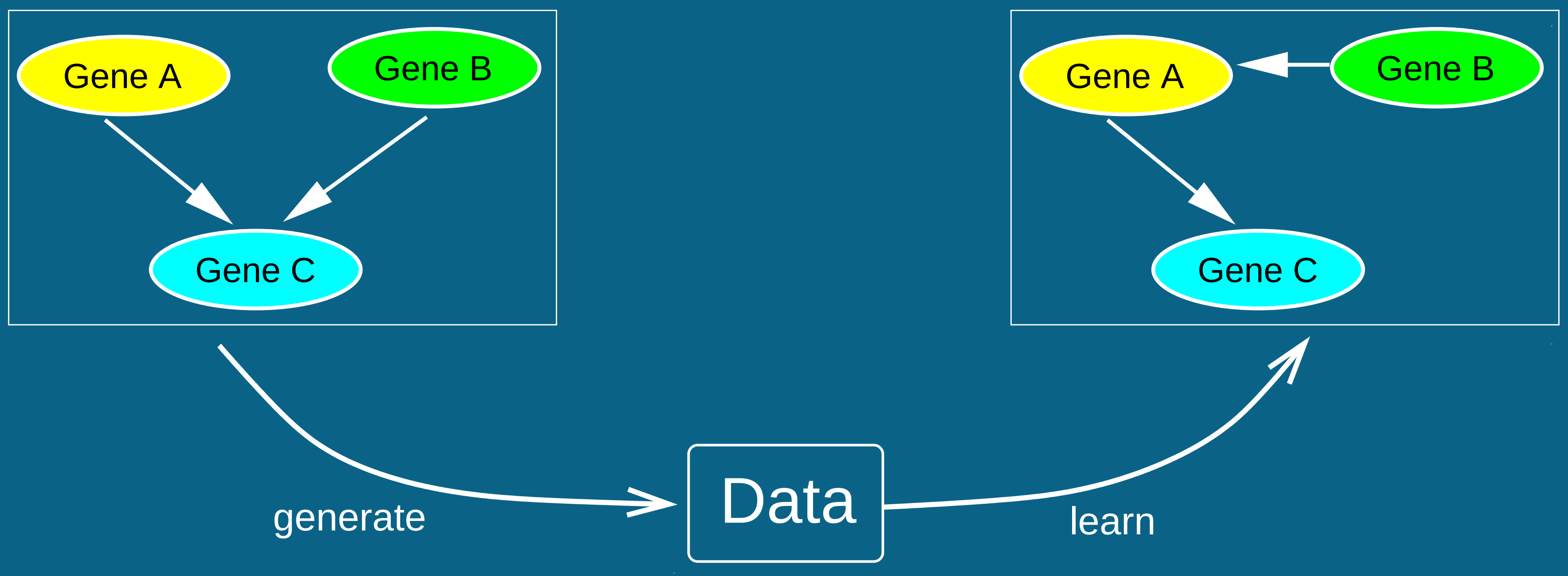
It may be possible to

estimate the **sensitivity**,

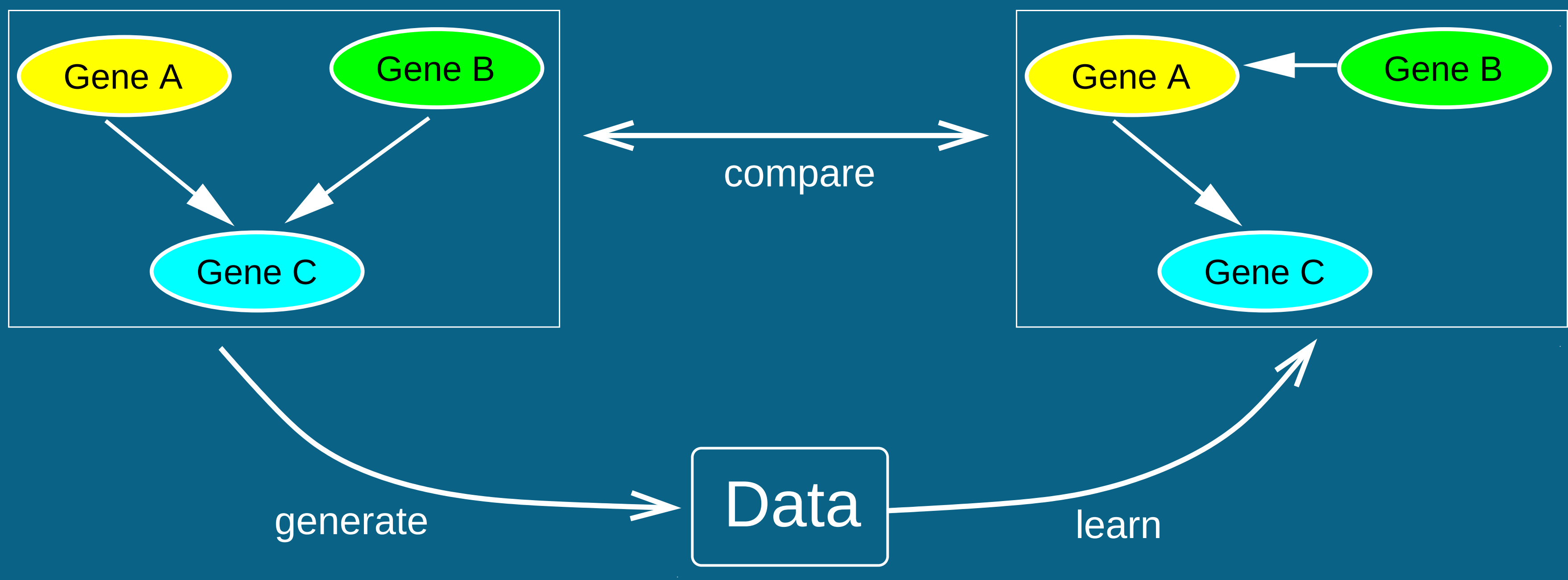
but not the **specificity**.

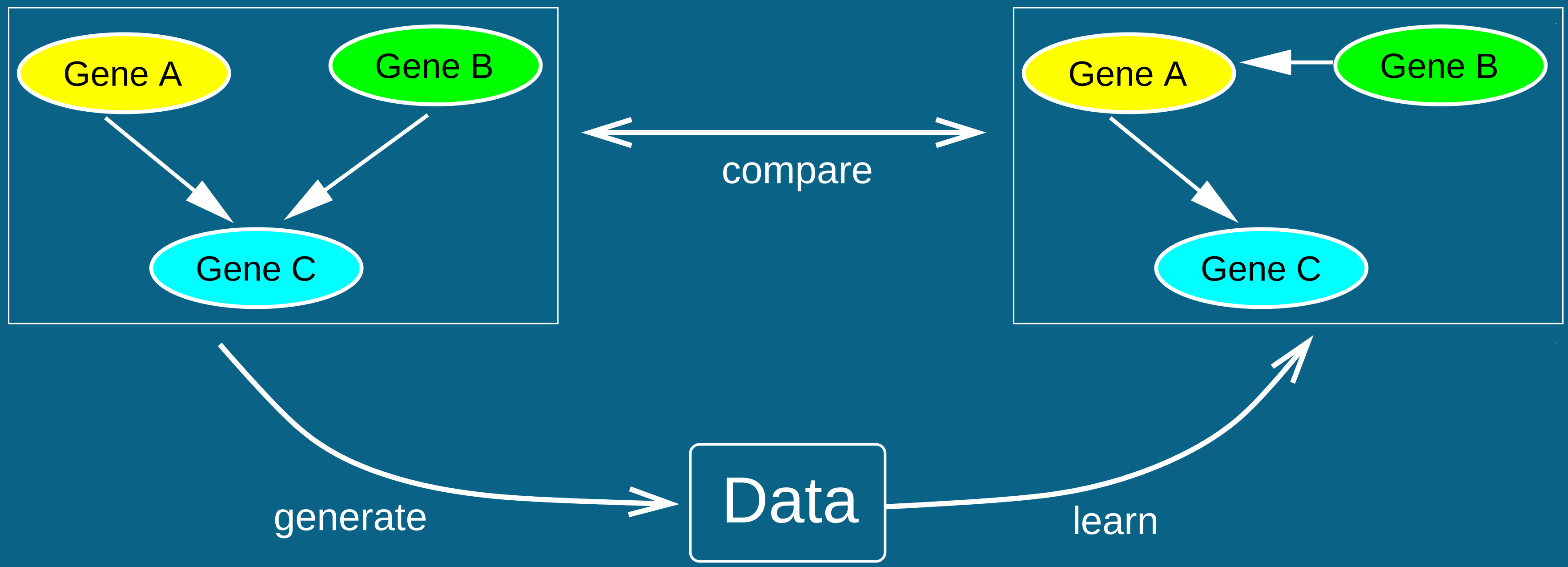

Gene A
Gene B
Gene C


Gene A
Gene B
Gene C
generate
Data

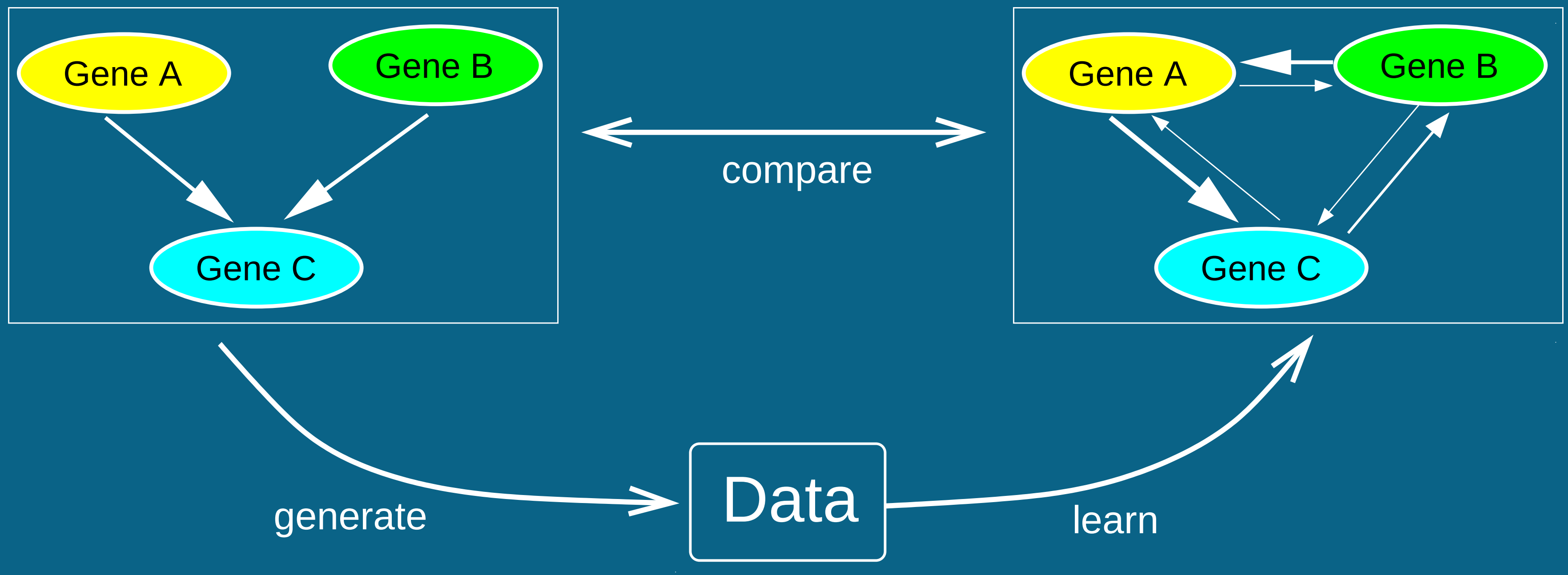


Gene A
Gene B
Gene C
generate
Data
learn
Gene A
Gene B
Gene C

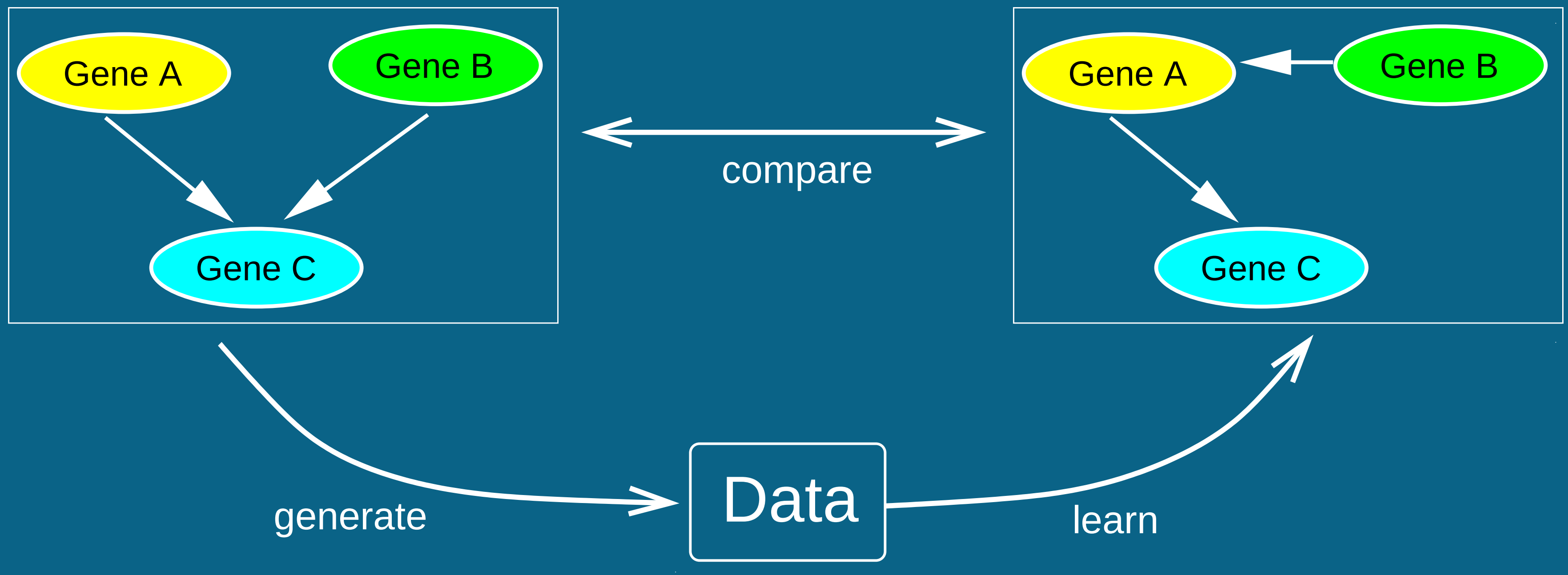

Gene A
Gene B
Gene C
compare
Gene A
Gene B
Gene C
generate
Data
learn



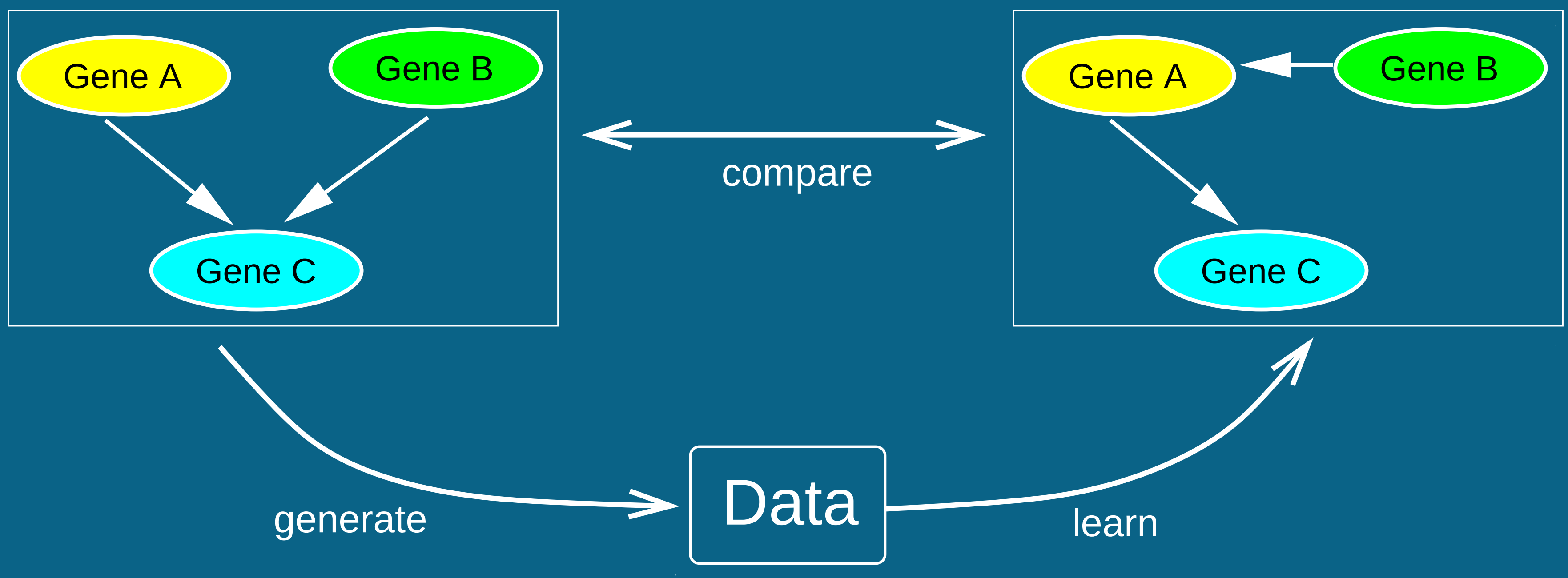

Deterministic inference




# Probabilistic inference



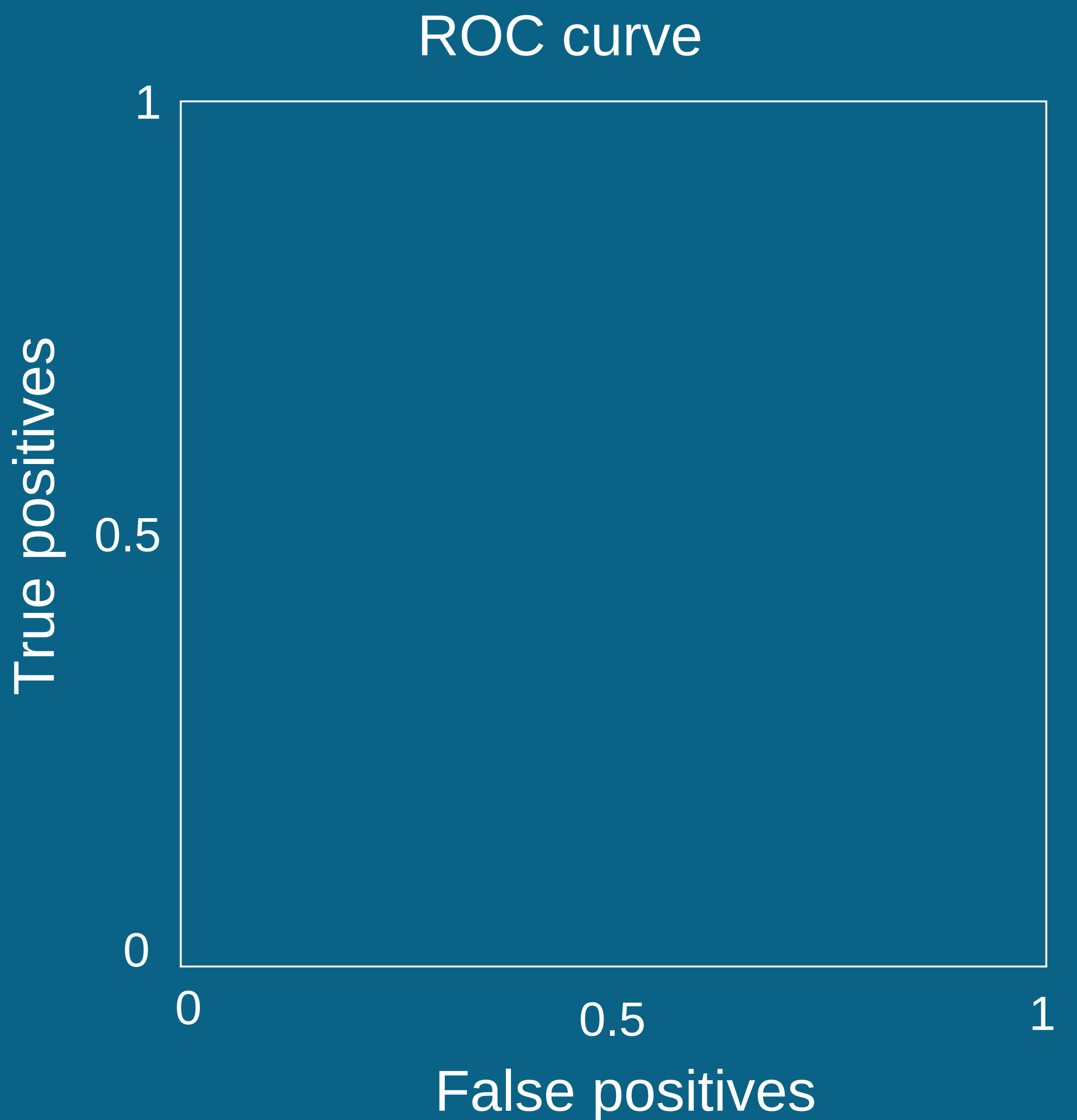

Thresholding

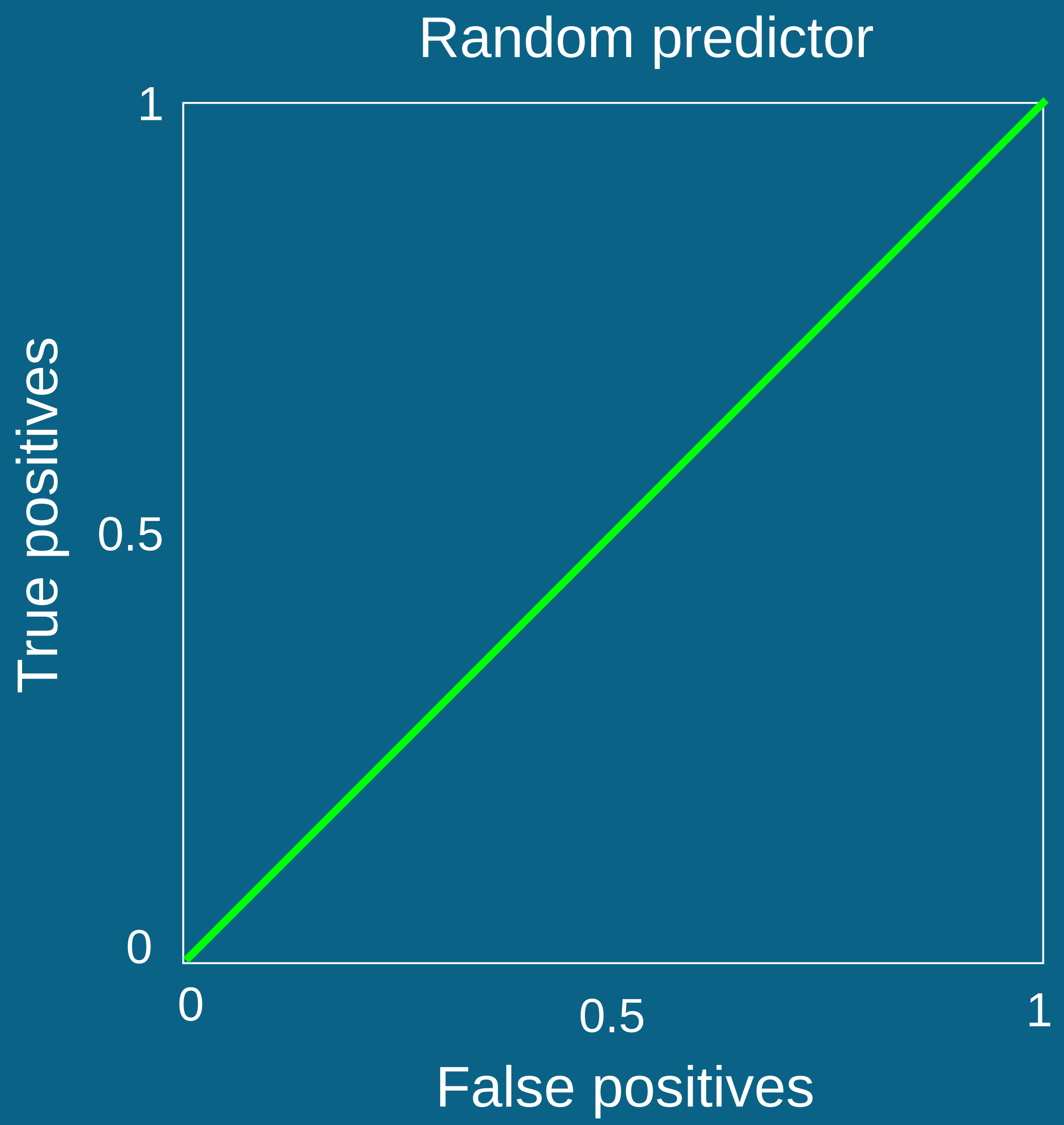



Thresholding

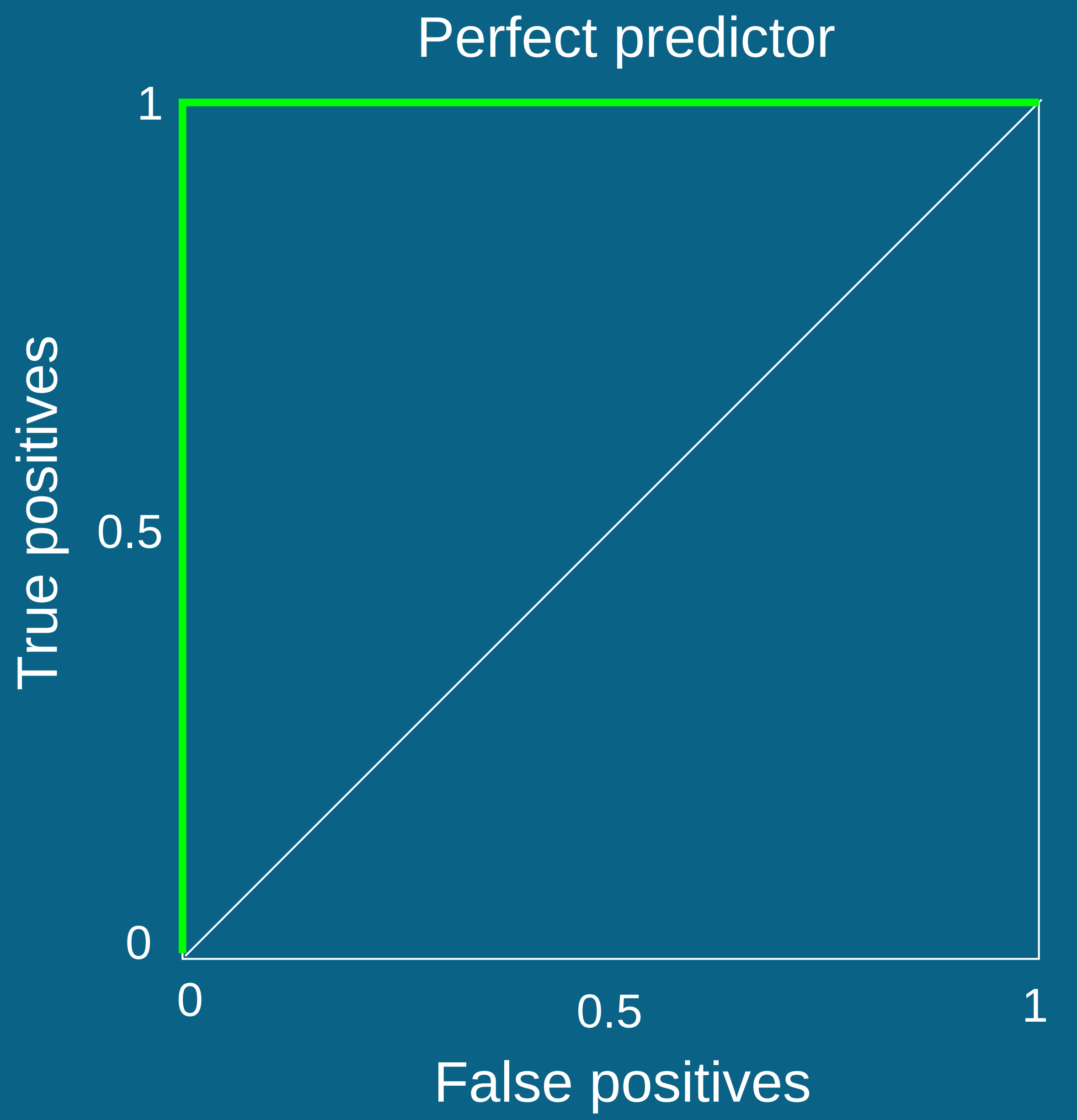
True positives

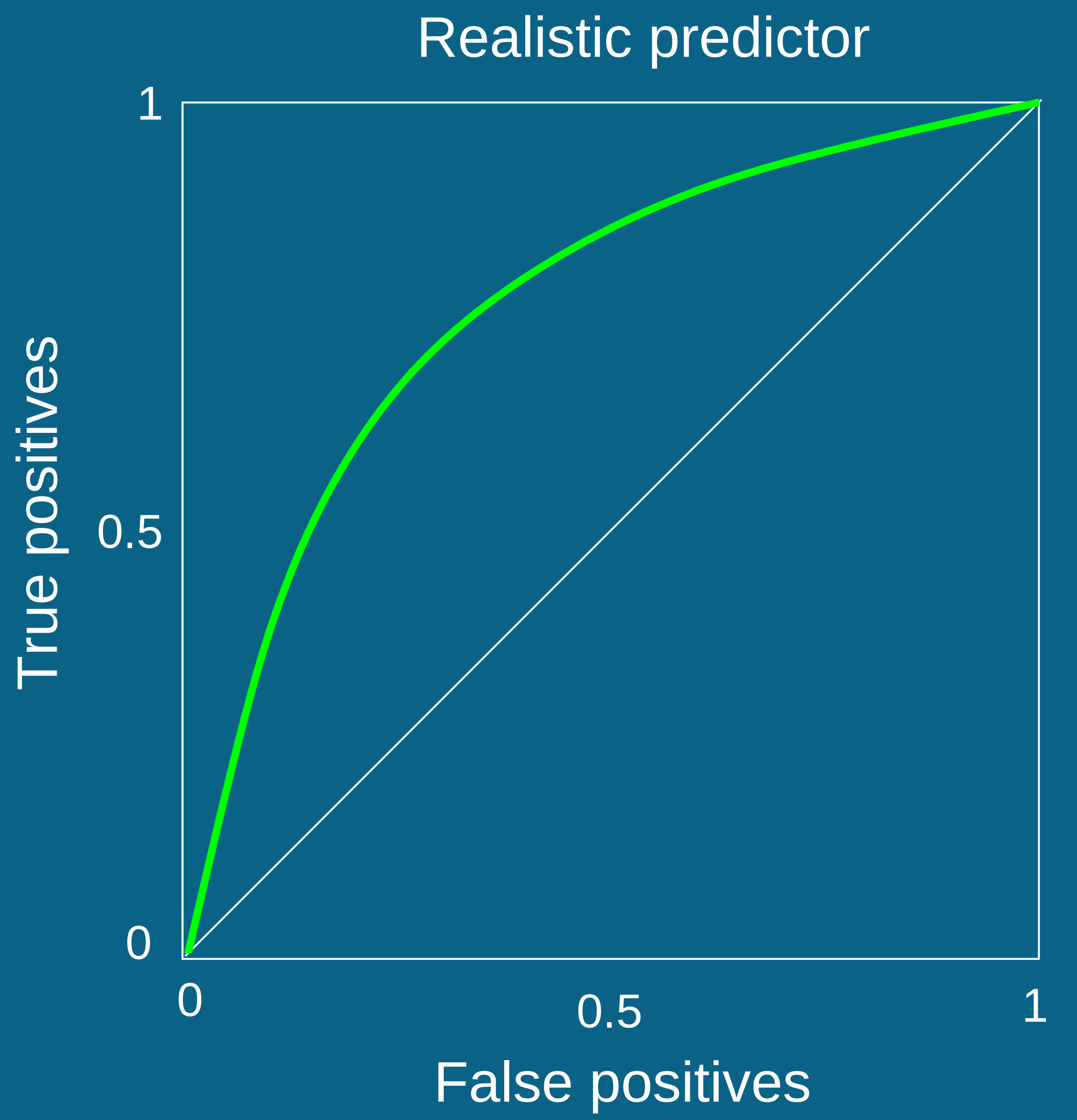
False positives


ROC curve
1
0.5
0
True positives
0
0.5
1
False positives

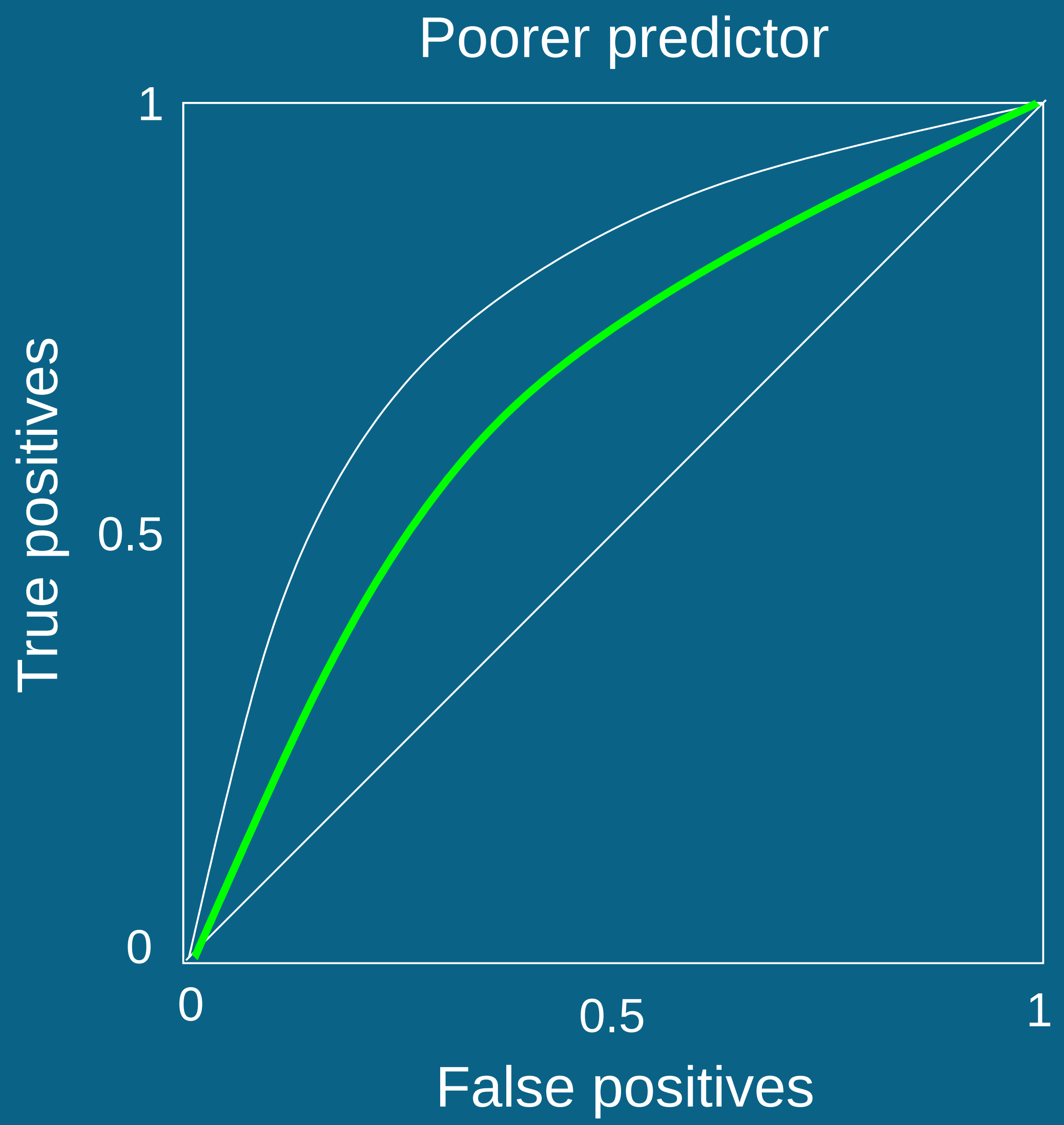


Random predictor
True positives
1
0.5
0
0
0.5
1
False positives


Perfect predictor
1
0.5
0
True positives
0
0.5
1
False positives


Realistic predictor
1
0.5
0
True positives
0
0.5
1
False positives

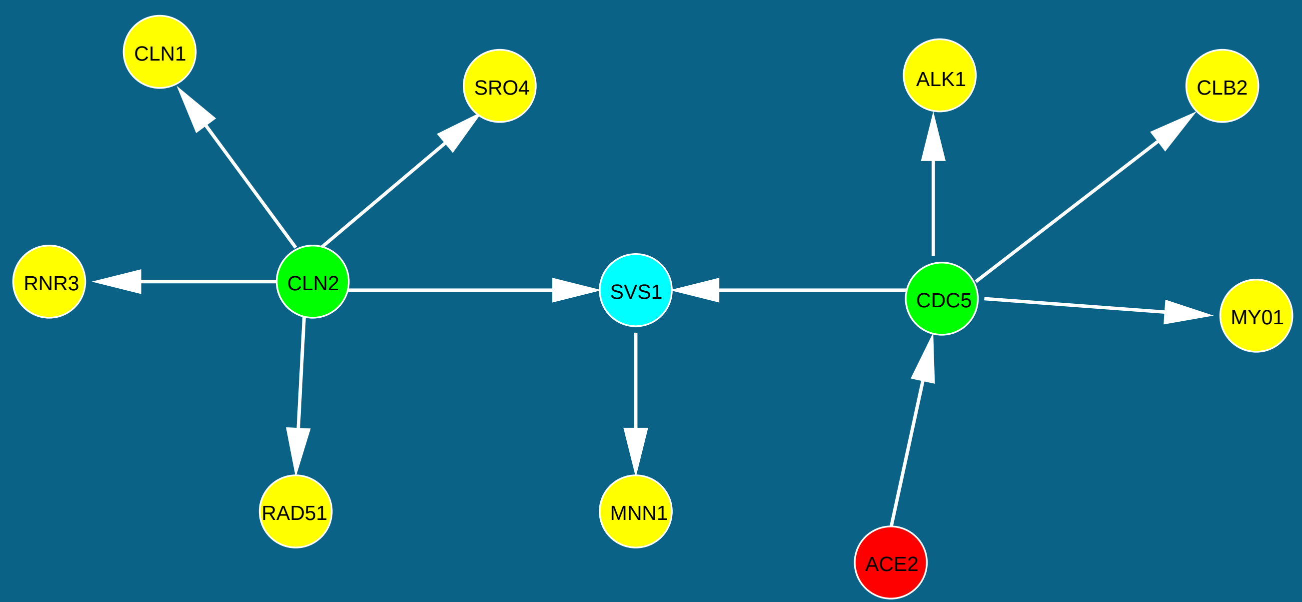

Better predictor
1
0.5
0
True positives
0
0.5
1
False positives



Poorer predictor
True positives
False positives
1
0.5
0
0
0.5
1

**Data:** binary

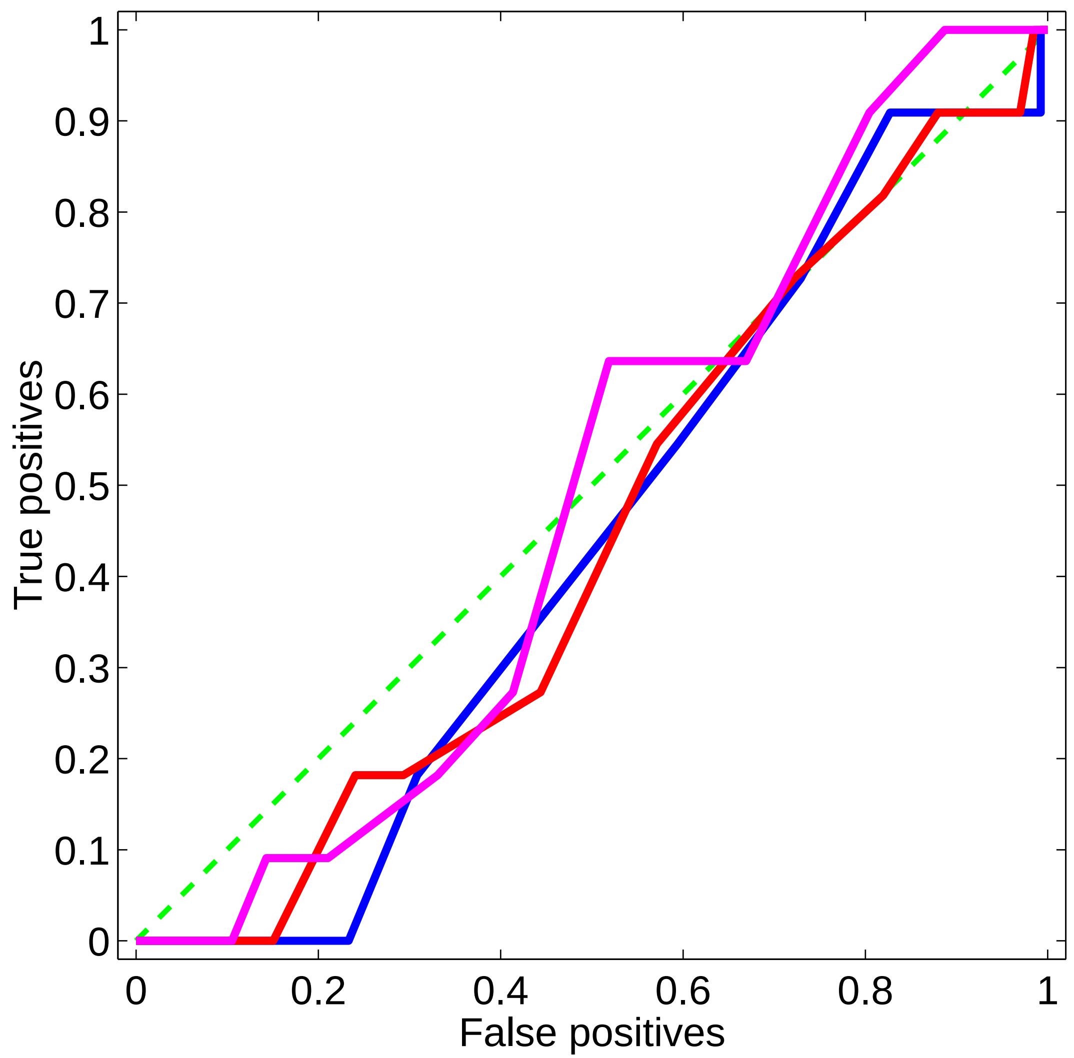
**Model:**



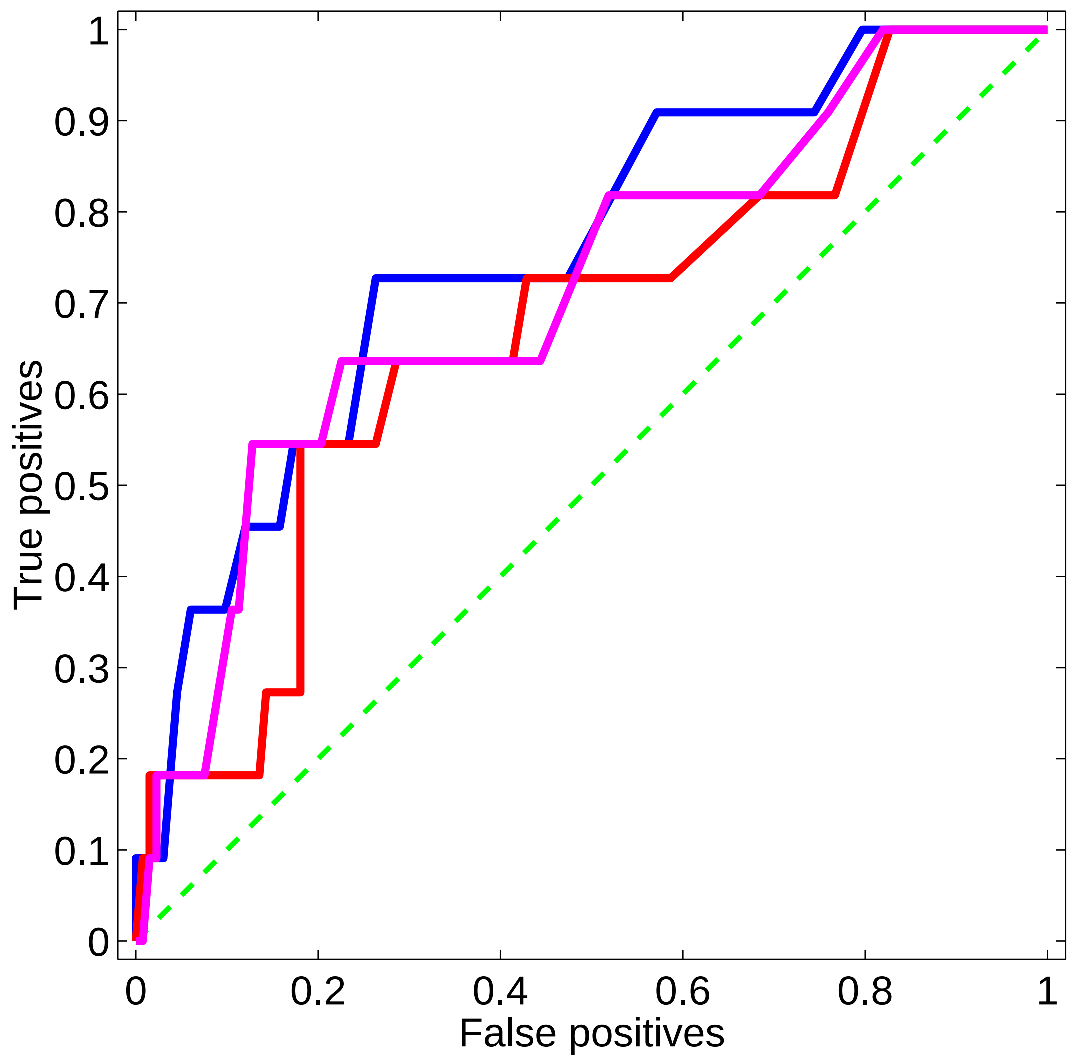

**Parameters:**

Noisy boolean: $P \in \{0.1, 0.9\}$

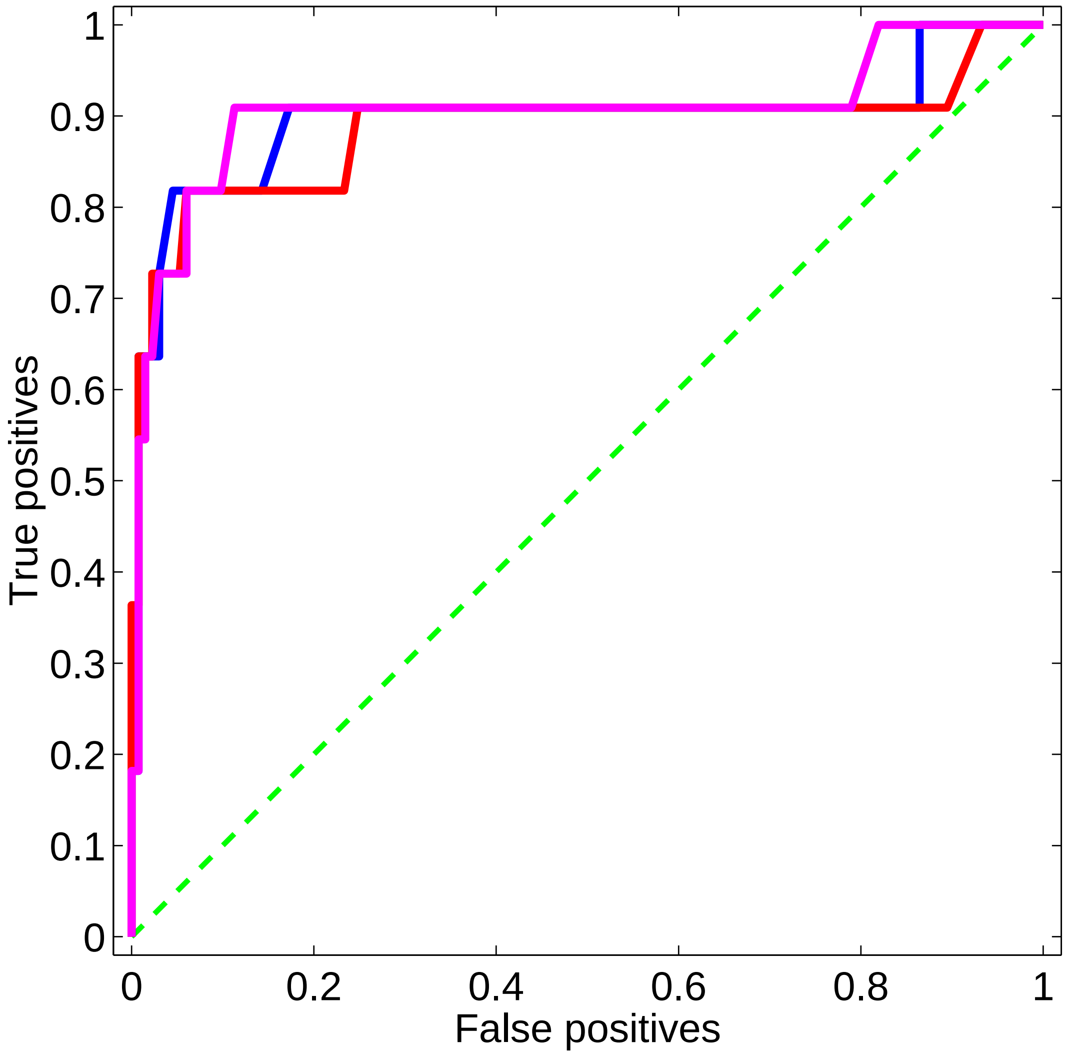
# ROC curve: Sample size= 3



# ROC curve: Sample size= 6

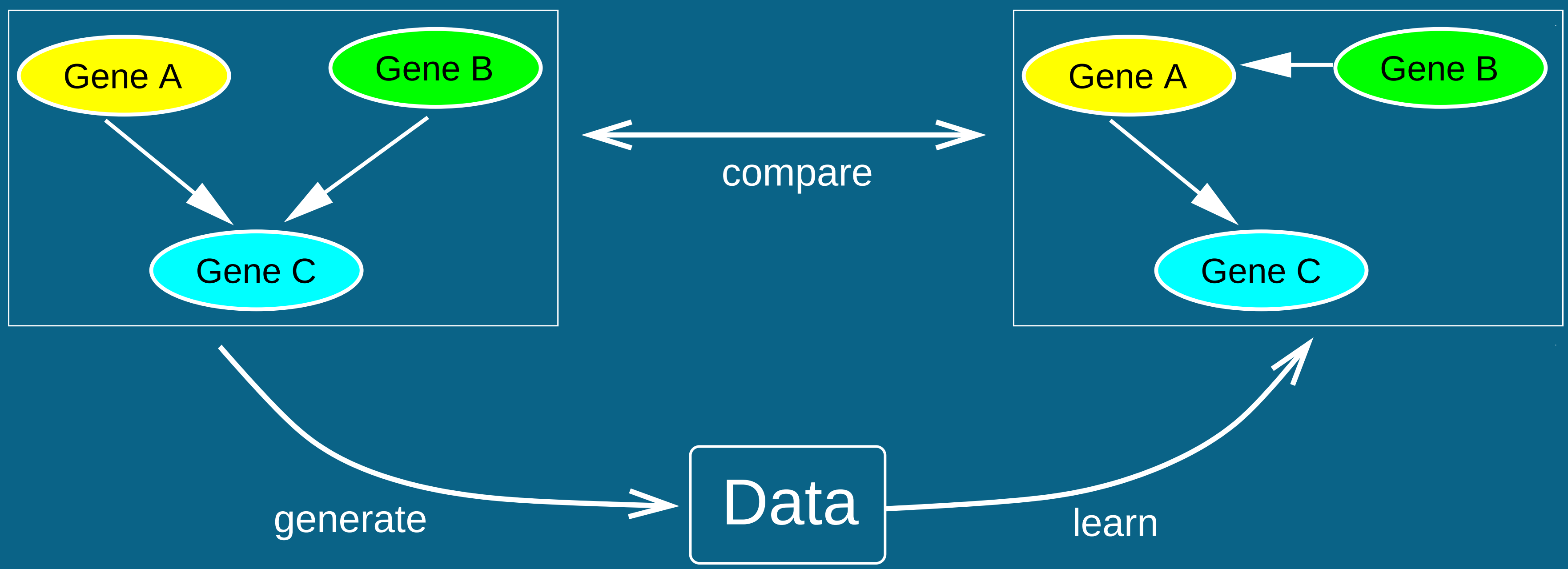


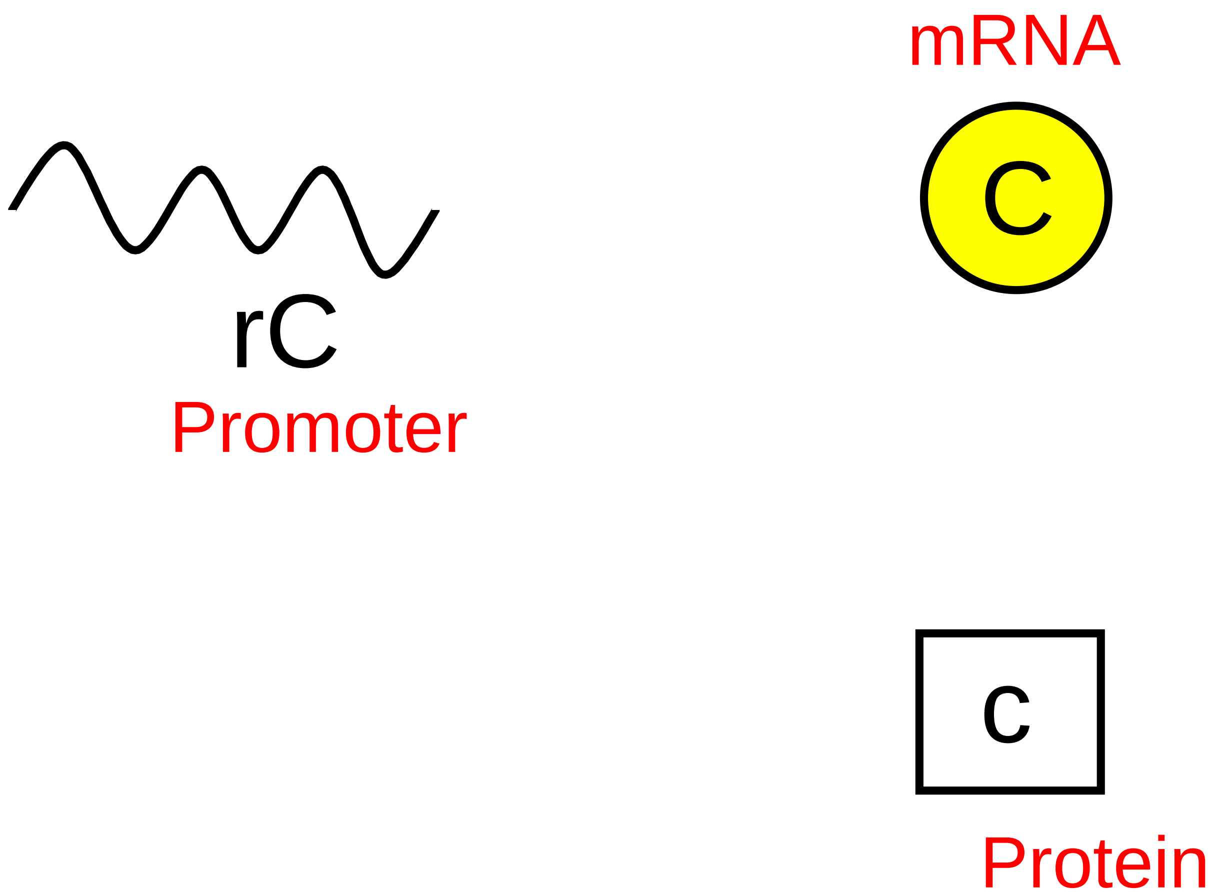
# ROC curve: Sample size= 12

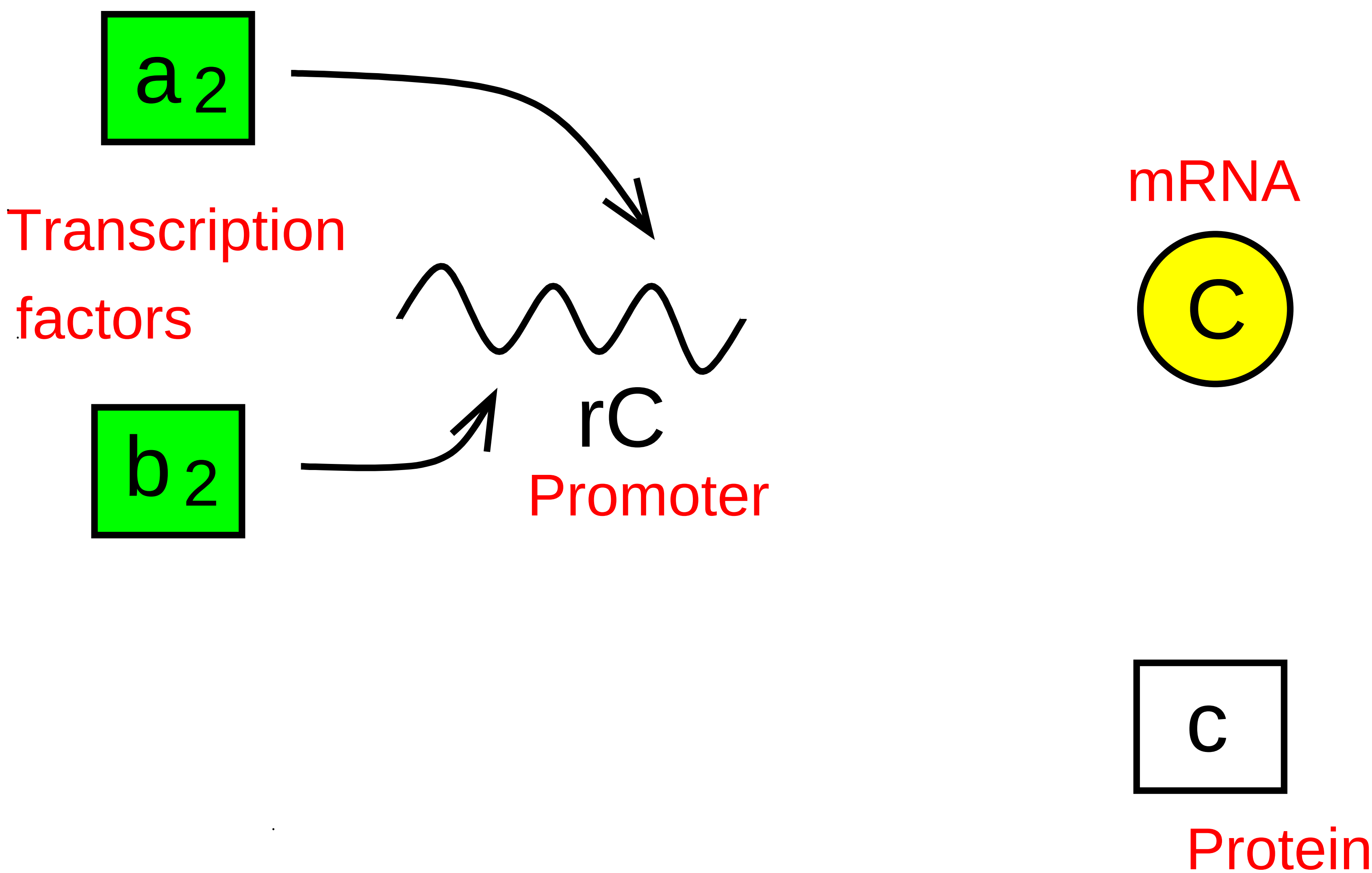


Disadvantage:

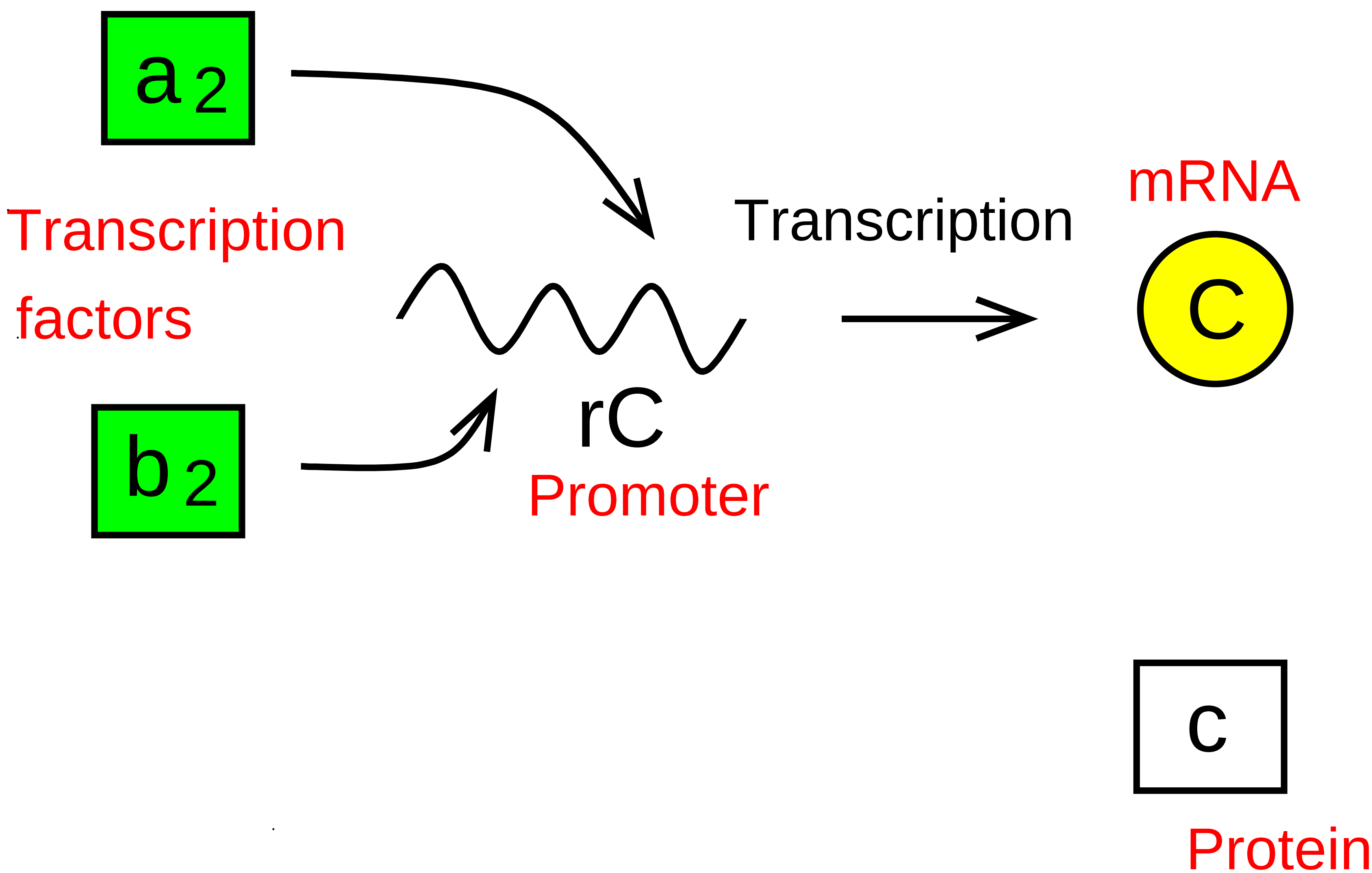
Unrealistic, no mismatch between the model used for data generation and the model used for inference.

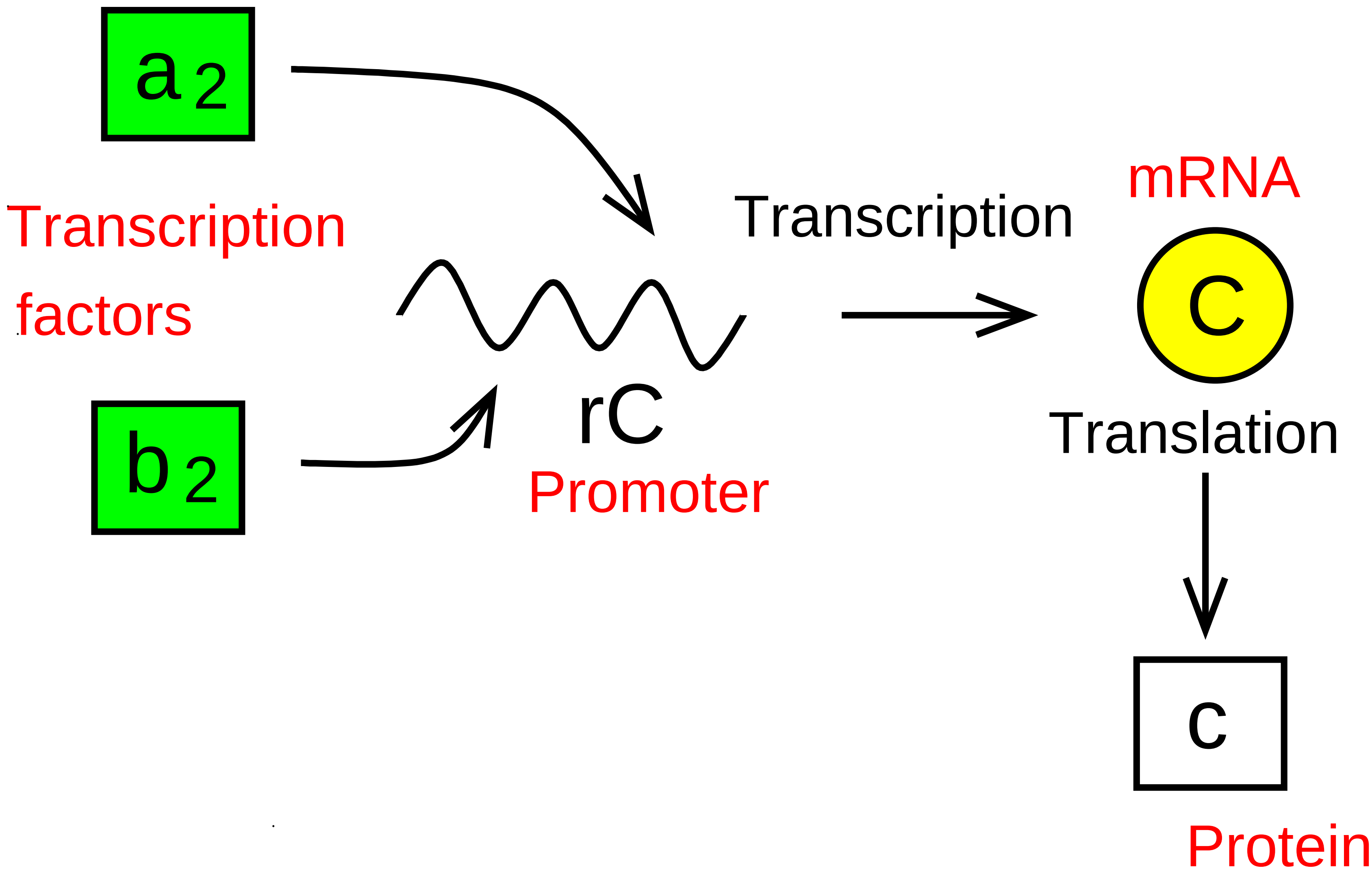


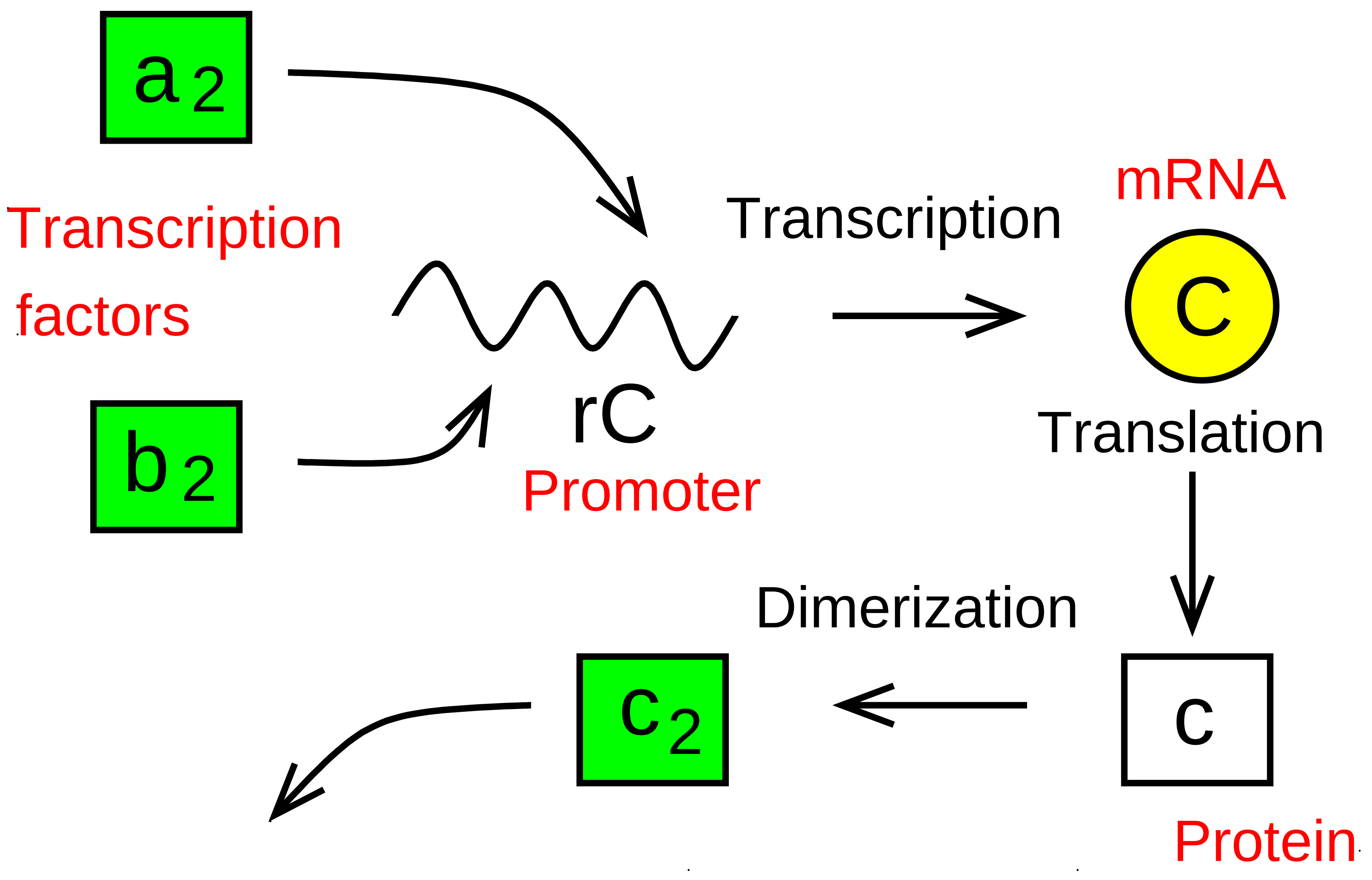

mRNA
C
rC
Promoter
c
Protein



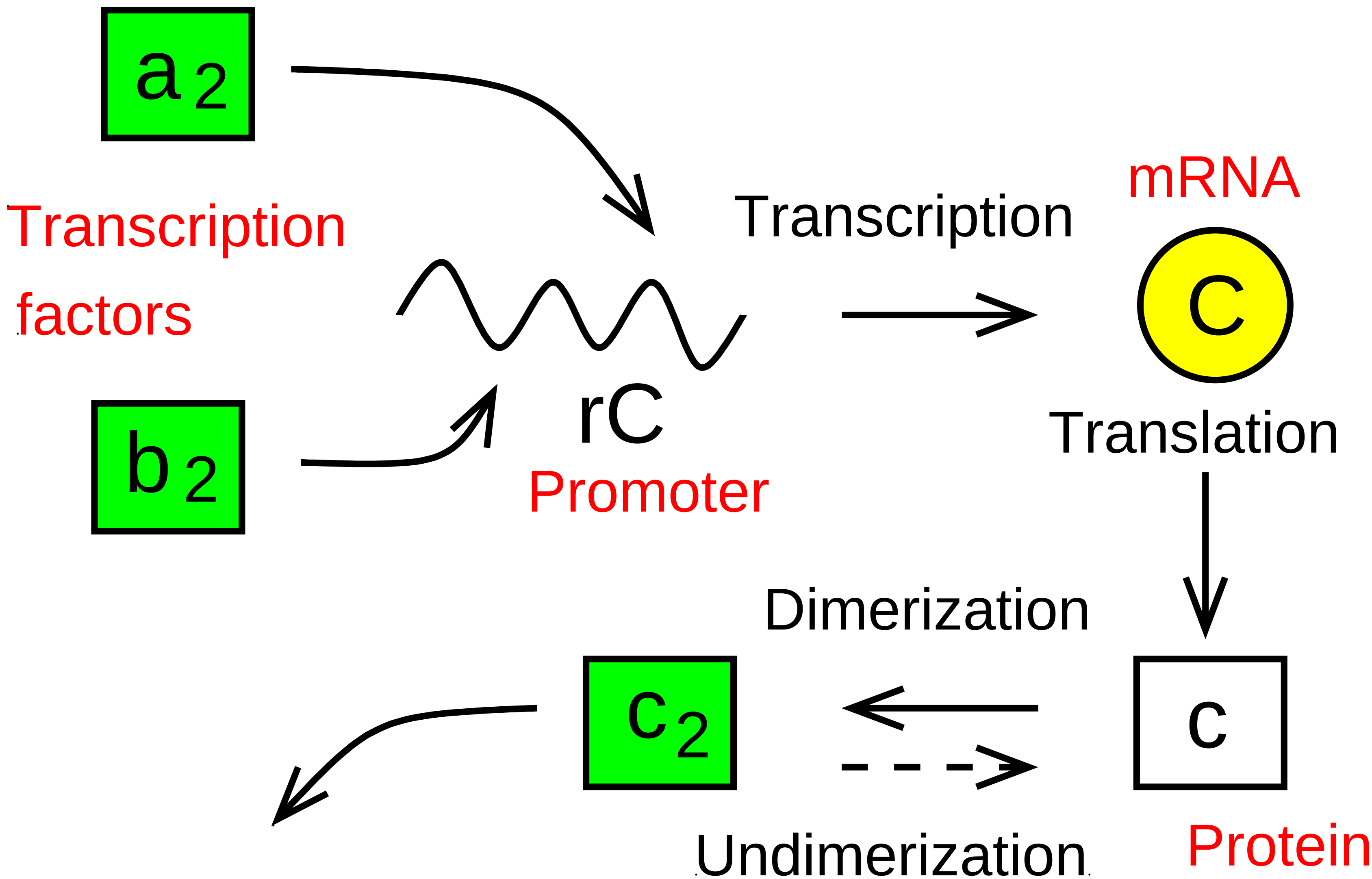
$a_2$
Transcription
factors
$b_2$
rC
Promoter
mRNA
C
c
Protein

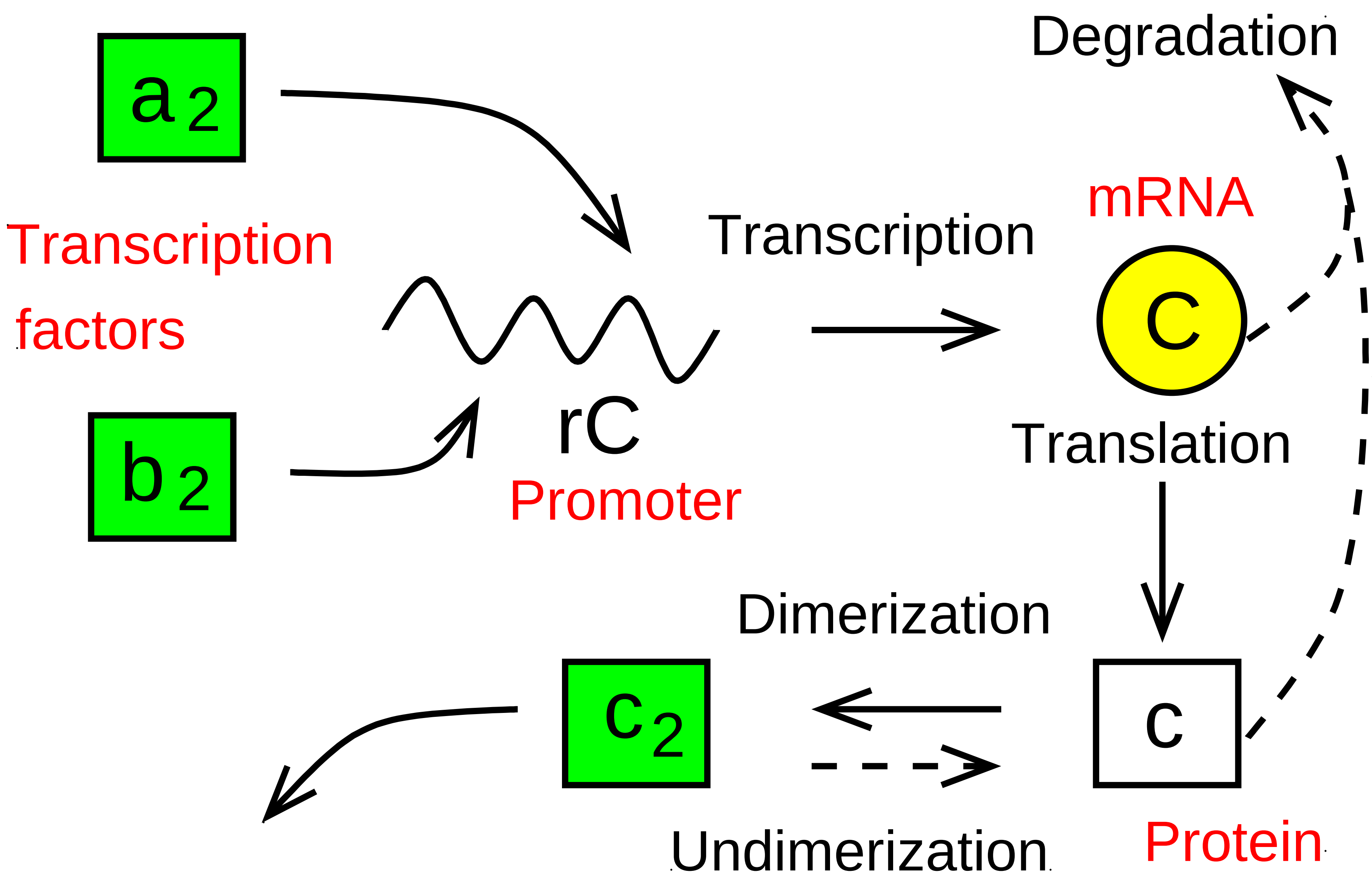

a 2
Transcription
factors
b 2
rC
Promoter
Transcription
mRNA
c
c
Protein


a 2
Transcription
factors
b 2
rC
Promoter
Transcription
mRNA
c
Translation
c
Protein

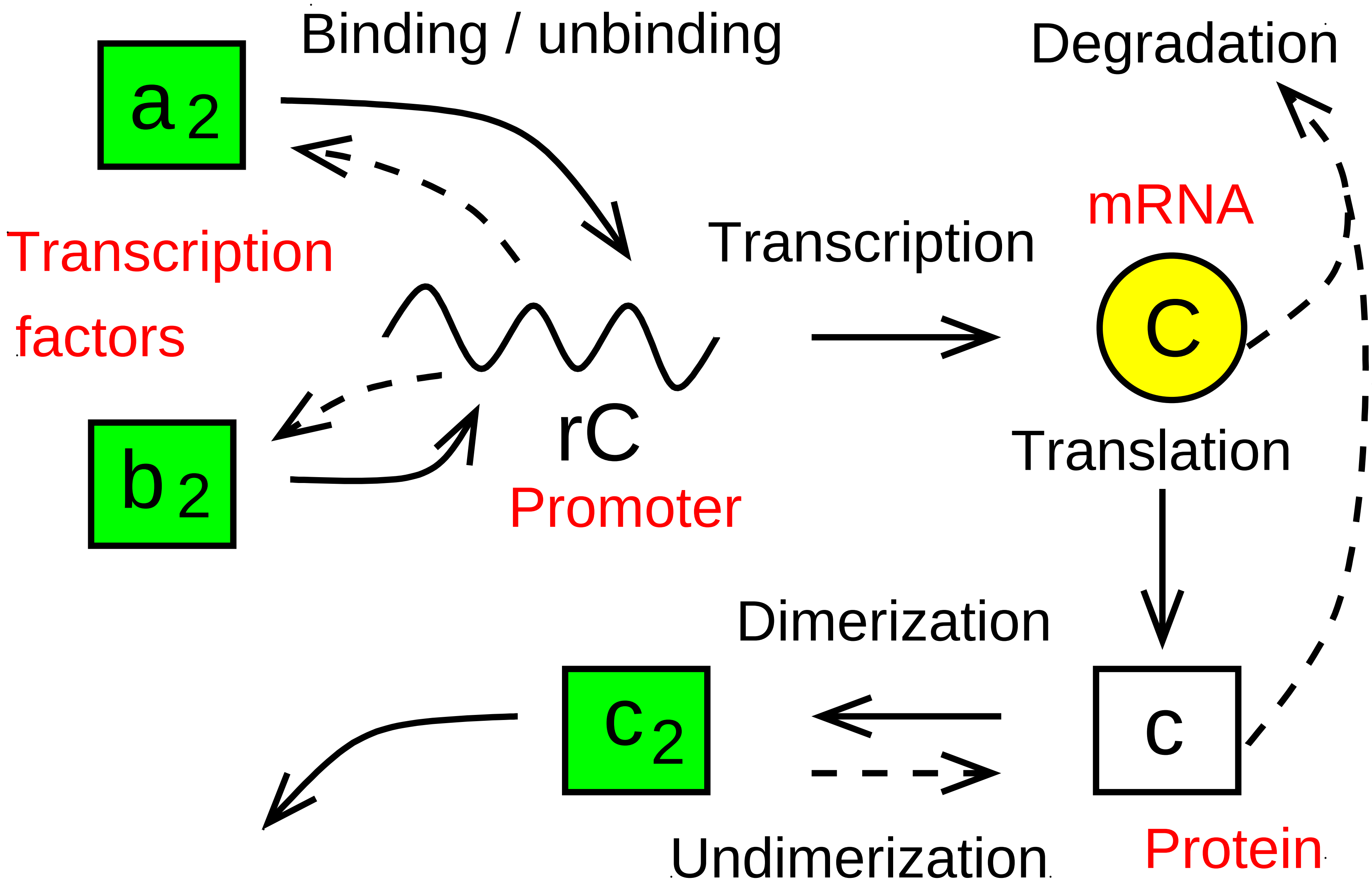


a2
Transcription factors
b2
rC
Promoter
Transcription
mRNA
c
Translation
Dimerization
c2
c
Protein


a2
Transcription
factors
b2
rC
Promoter
Transcription
mRNA
c
Translation
Dimerization
c2
c
Undimerization
Protein



a2
Transcription factors
b2
rC
Promoter
Transcription
mRNA
c
Degradation
Translation
c
Protein
Dimerization
Undimerization
c2

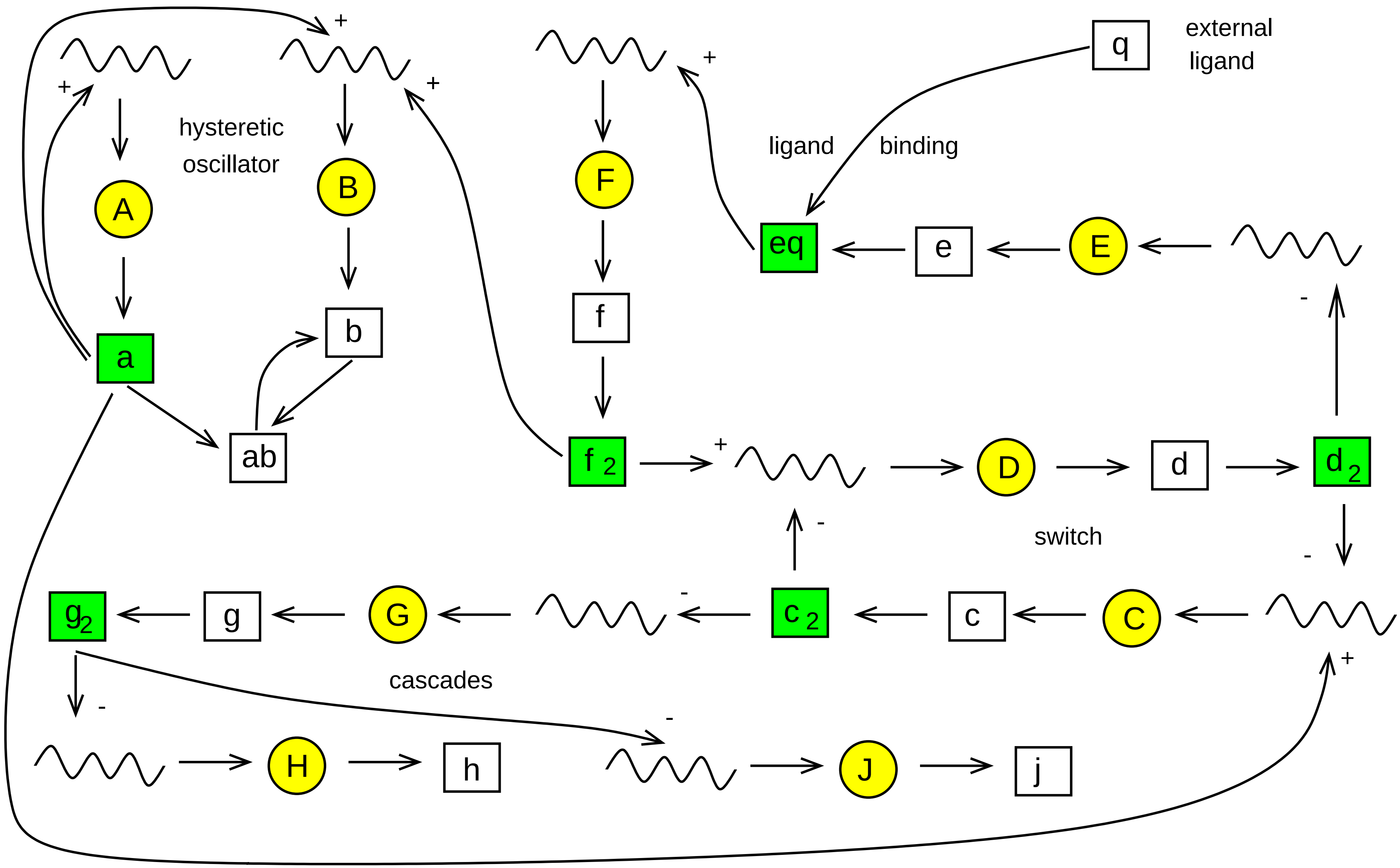

Binding / unbinding
Degradation
$a_2$
mRNA
Transcription
Transcription
factors
c
rC
Translation
$b_2$
Promoter
Dimerization
$c_2$
c
Undimerization
Protein

$$\frac{d}{dt}[a2.rC] = \lambda^{+}_{a_2.rC}[a_2][rC] - \lambda^{-}_{a_2.rC}[a_2.rC]$$

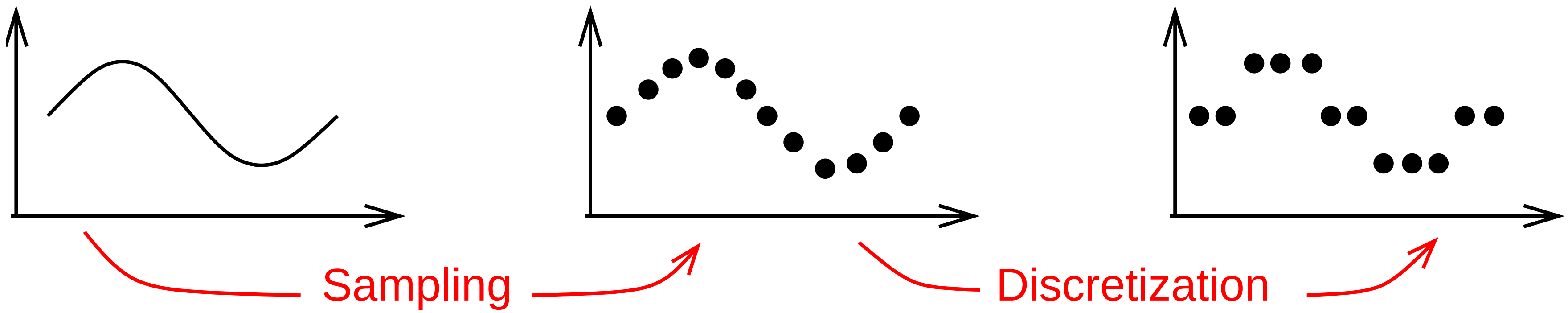
$$\frac{d}{dt}[C] = \lambda_{rC}[rC] + \lambda_{a_2.rC}[a_2.rC] + \lambda_{b_2.rC}[b_2.rC] - \lambda_{C}[C]$$

$$\frac{d}{dt}[c] = \lambda_{Cc}[C] - \lambda_{c}[c]$$

$$\frac{d}{dt}[c_2] = \lambda^{+}_{cc}[c]^2 - \lambda^{-}_{cc}[c_2]$$

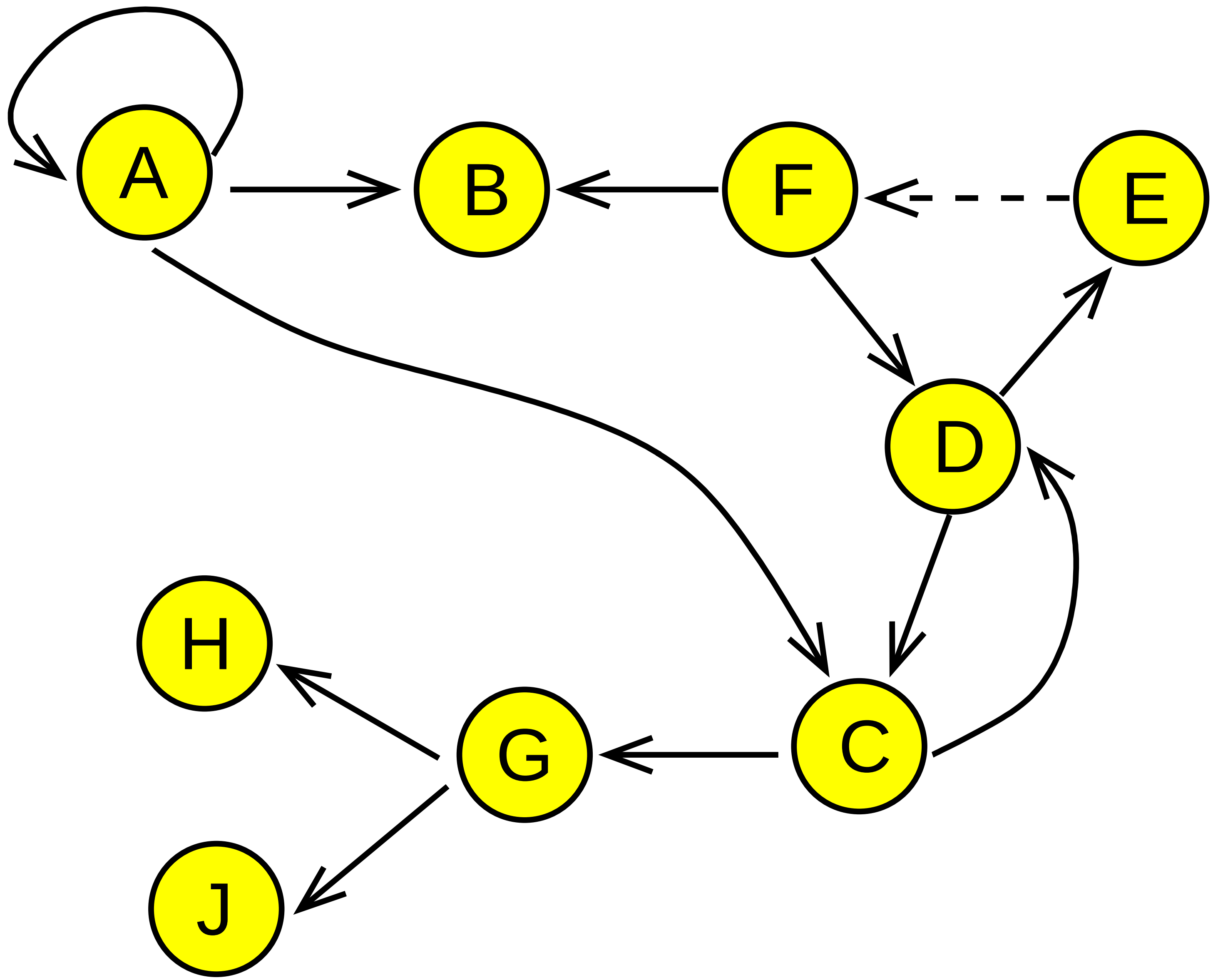


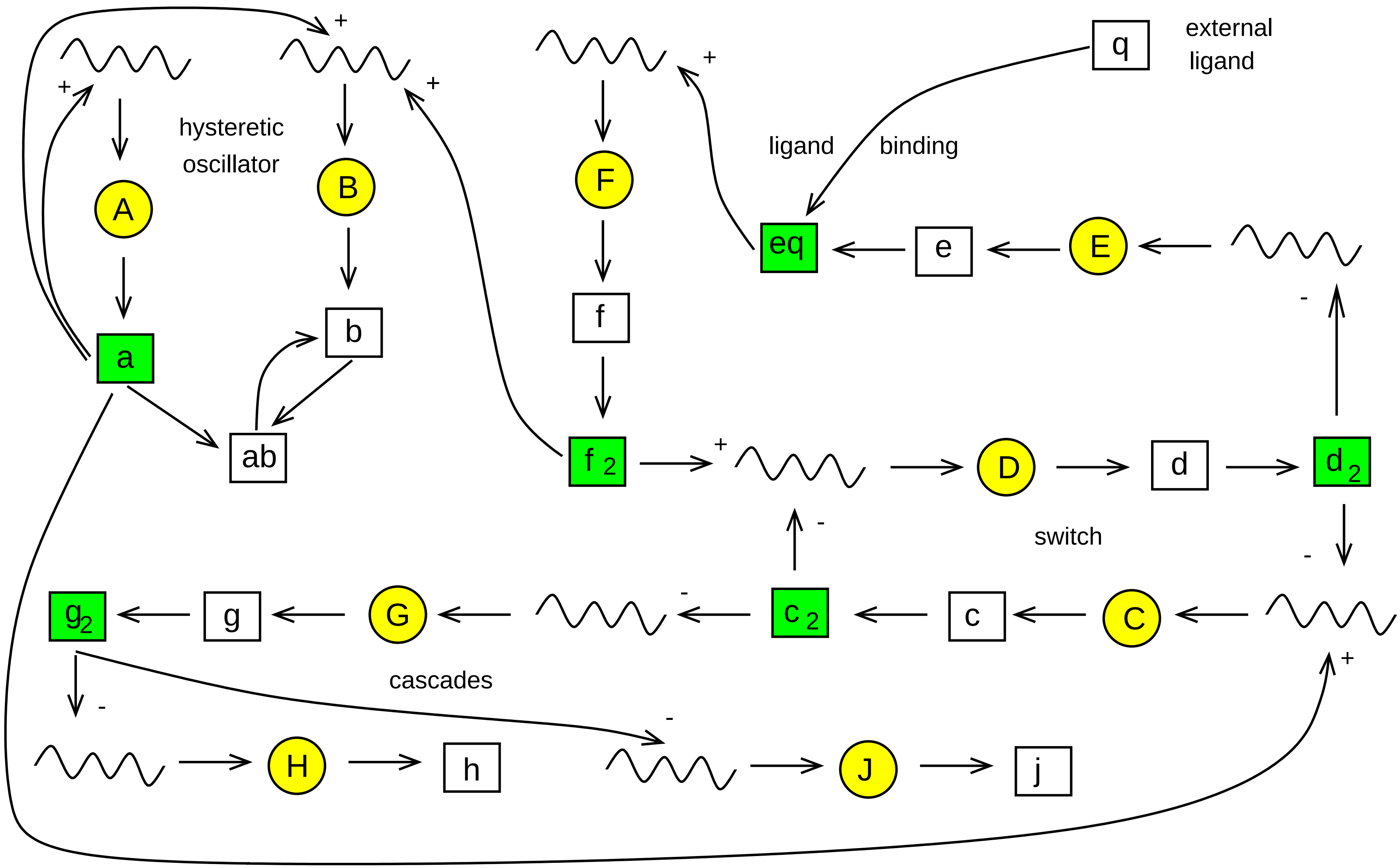

Zak et al., Int. Conf. Sys. Biol., 2001




12 time points

Recover the true genetic network
with
reverse engineering.


A
B
F
E
D
H
G
C
J



hysteretic
oscillator
A
a
B
b
ab
F
f
f 2
ligand
binding
q
external
ligand
eq
e
E
D
d
d 2
switch
C
c
c 2
G
g
g2
cascades
H
h
J
j
+
-

# Simulation Experiments

Ligand injection for 10 minutes.

## Equilibrium

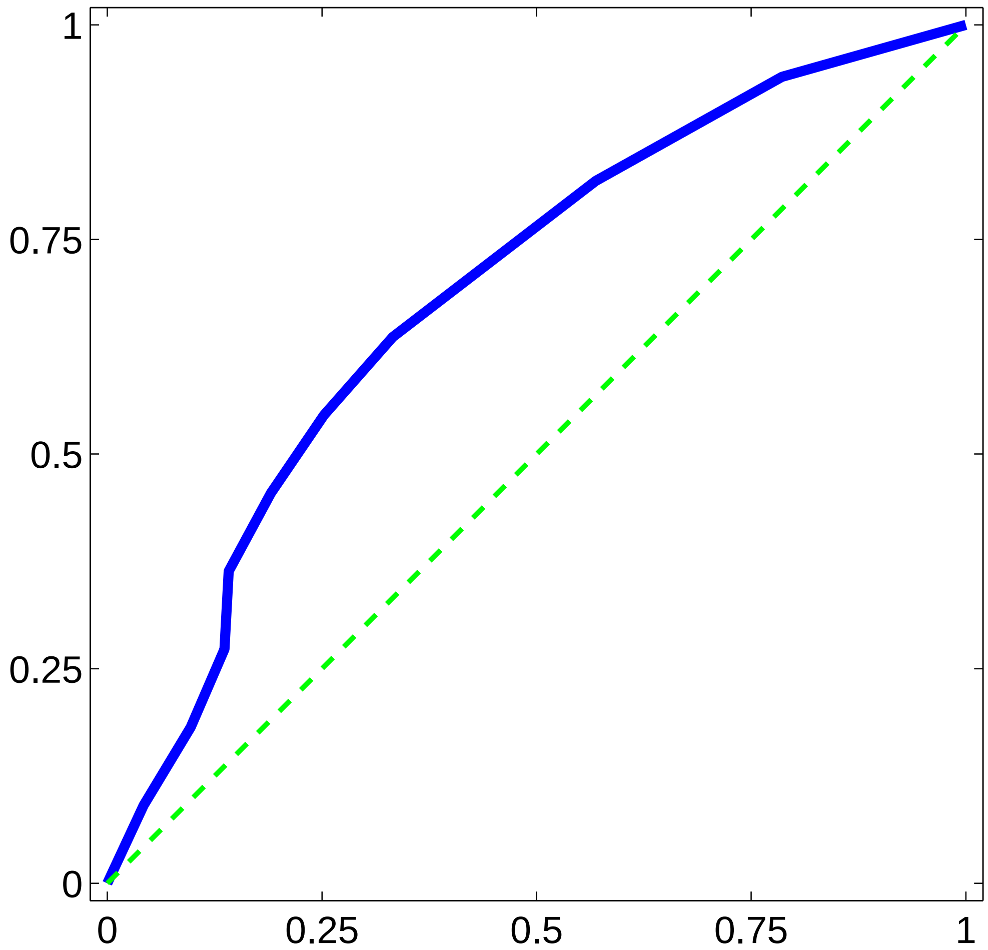
12 data points collected over 4000 min in equi-distant intervals.

## Disequilibrium

12 data points collected over 500 min in equi-distant intervals.

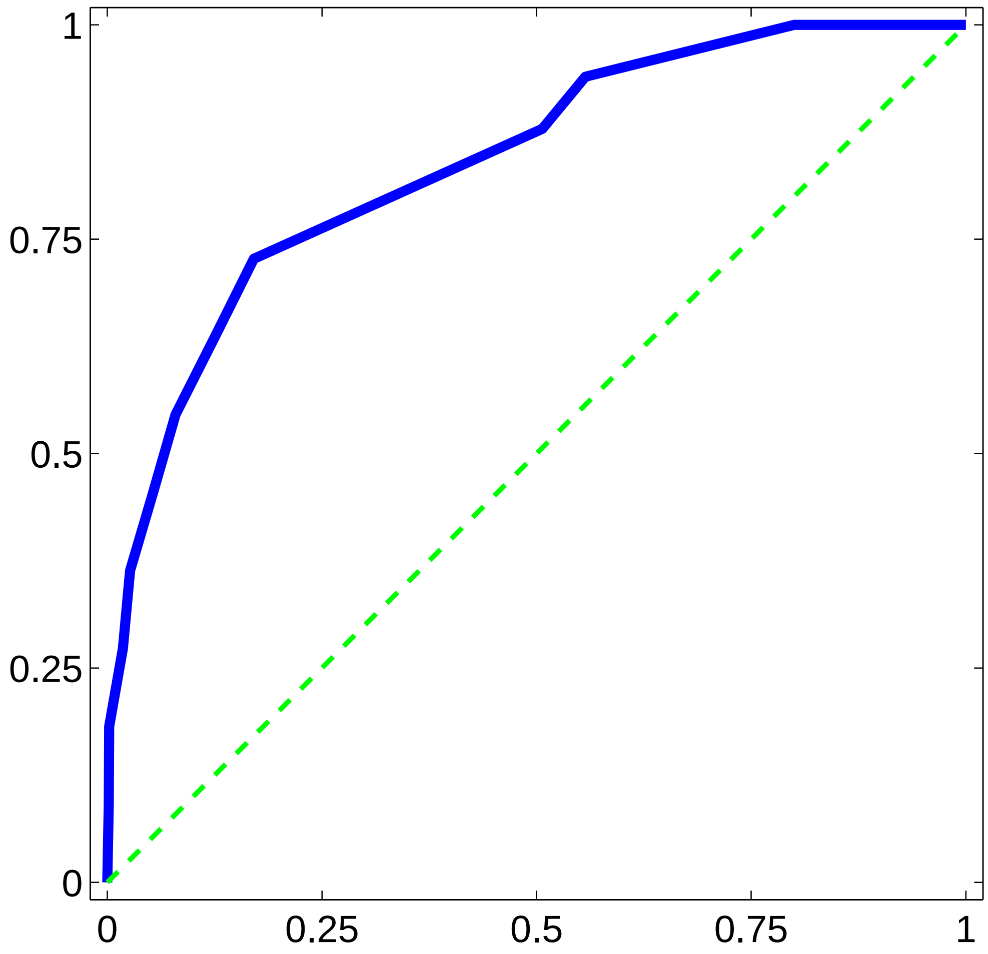
# ROC curve: Equilibrium

True positives (vertical axis) $\longleftrightarrow$ False positives (horizontal axis)



# ROC curve: Disequilibrium

True positives (vertical axis) $\longleftrightarrow$ False positives (horizontal axis)



# Sequence information

$$\frac{P(y \rightarrow rX | r \in B[y])}{P(y \rightarrow rX | r \notin B[y])} = 2$$

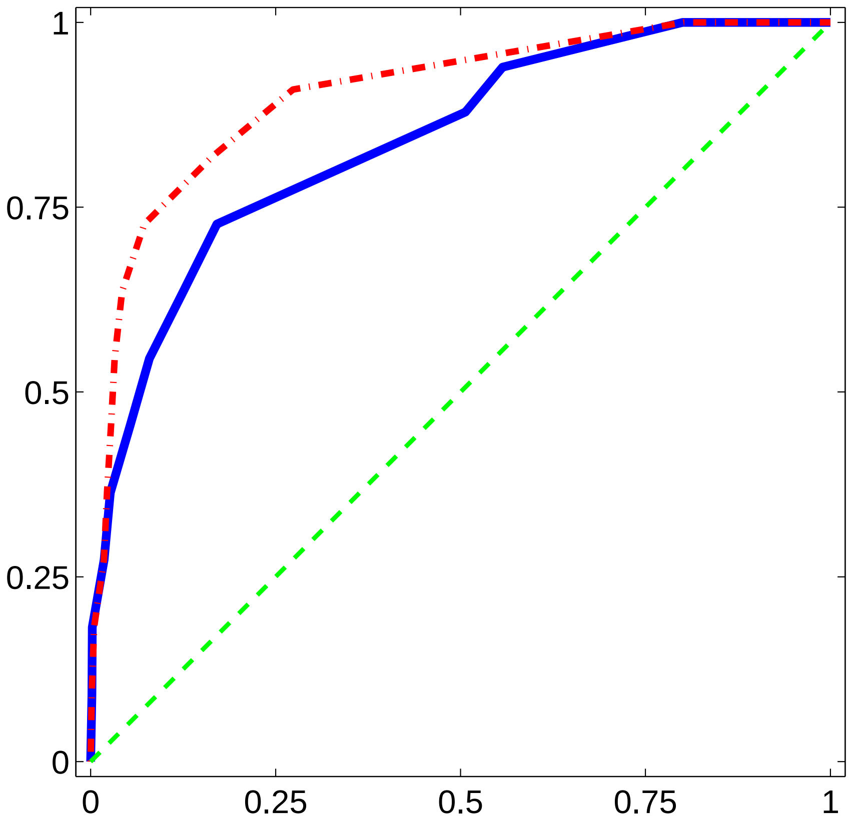
$y \rightarrow rX$ denotes the event that transcription factor $y$ binds to the promoter $r$ upstream of gene $X$, and $B[y]$ is the set of (known) binding motifs for $y$.

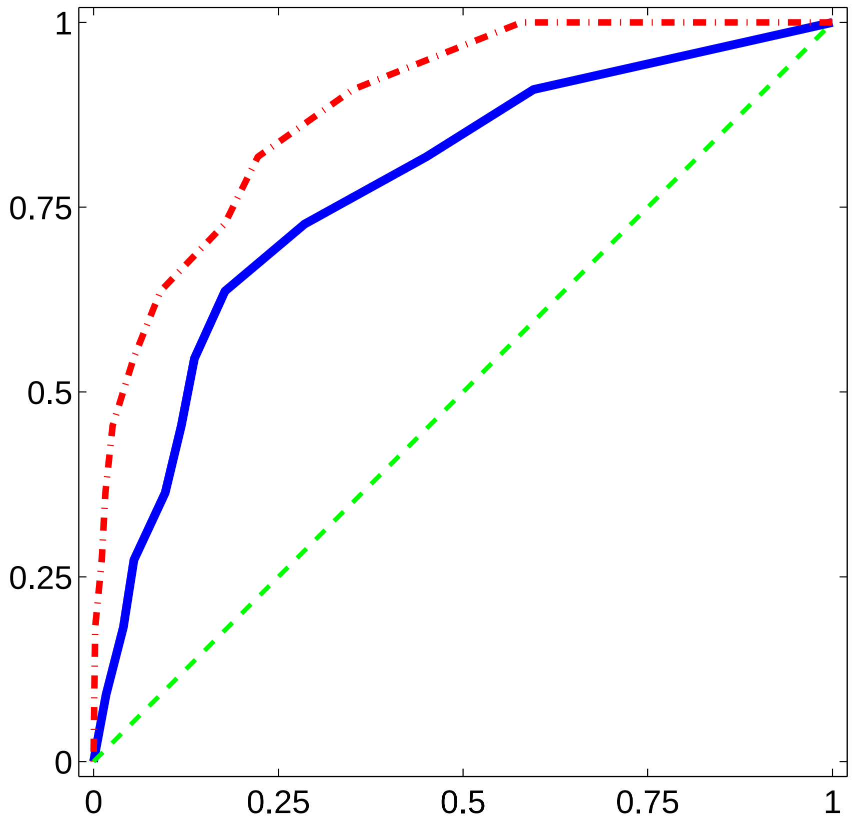
In words: The equation expresses that on identifying a binding motif for transcription factor $y$ in the upstream region of gene $X$, this transcription factor is twice as likely to bind to $X$ than in the absence of such a motif.

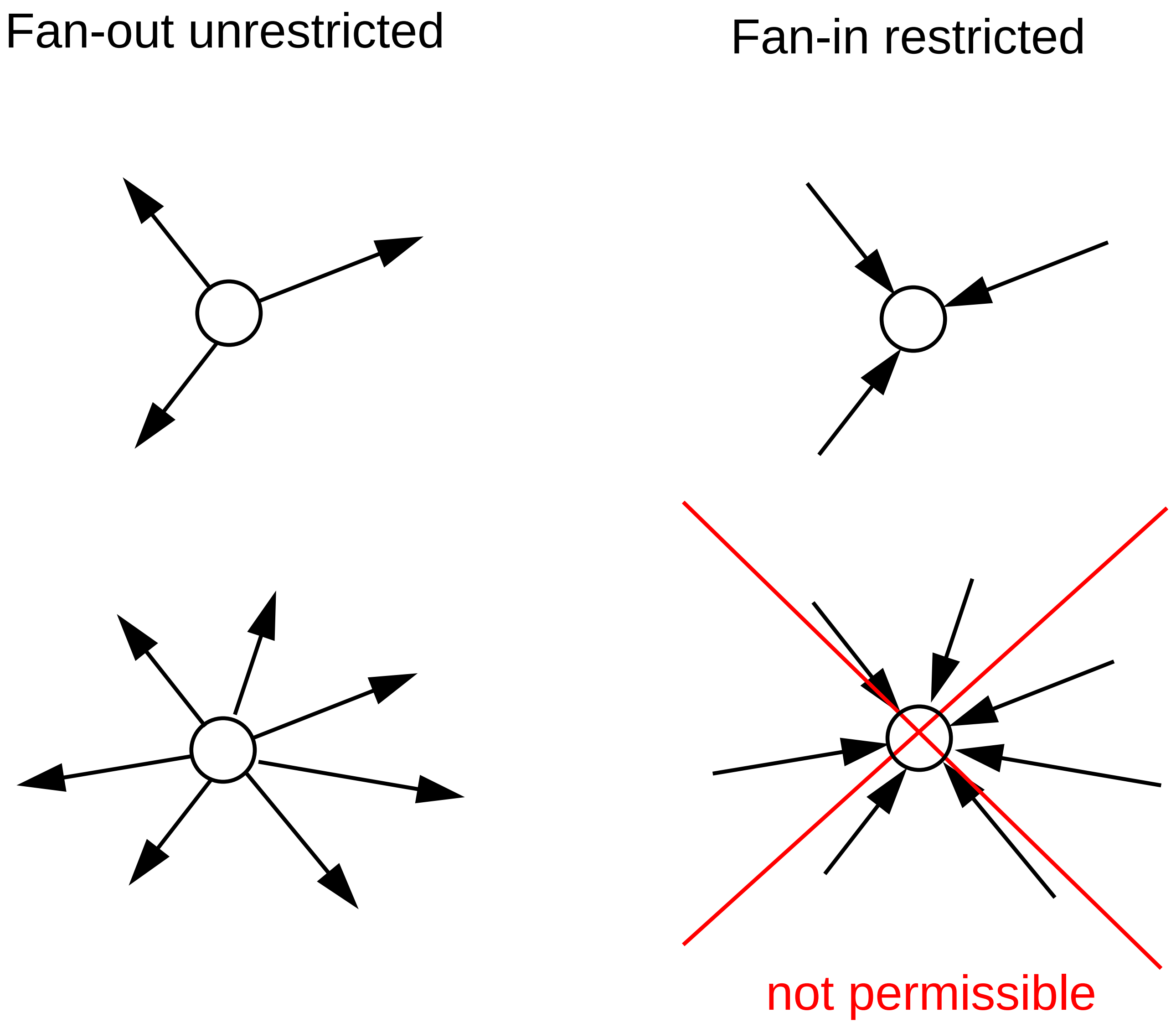
# ROC curves

True positives (vertical axis) $\longleftrightarrow$ False positives (horizontal axis)

Left: max fan-in $= 2$ Right: max fan-in $= 3$




Fan-out unrestricted
Fan-in restricted
not permissible

# Comparison with alternative schemes

Marco Grzegorczyk (Dortmund University)

Adriano Werhli (BioSS)

# Comparison with alternative schemes

Marco Grzegorczyk (Dortmund University)

Adriano Werhli (BioSS)

## Segment polarity network

Dassow et al., Nature 2000

## Simulation: steady state, sigma-pi

Schilstra & Bolouri

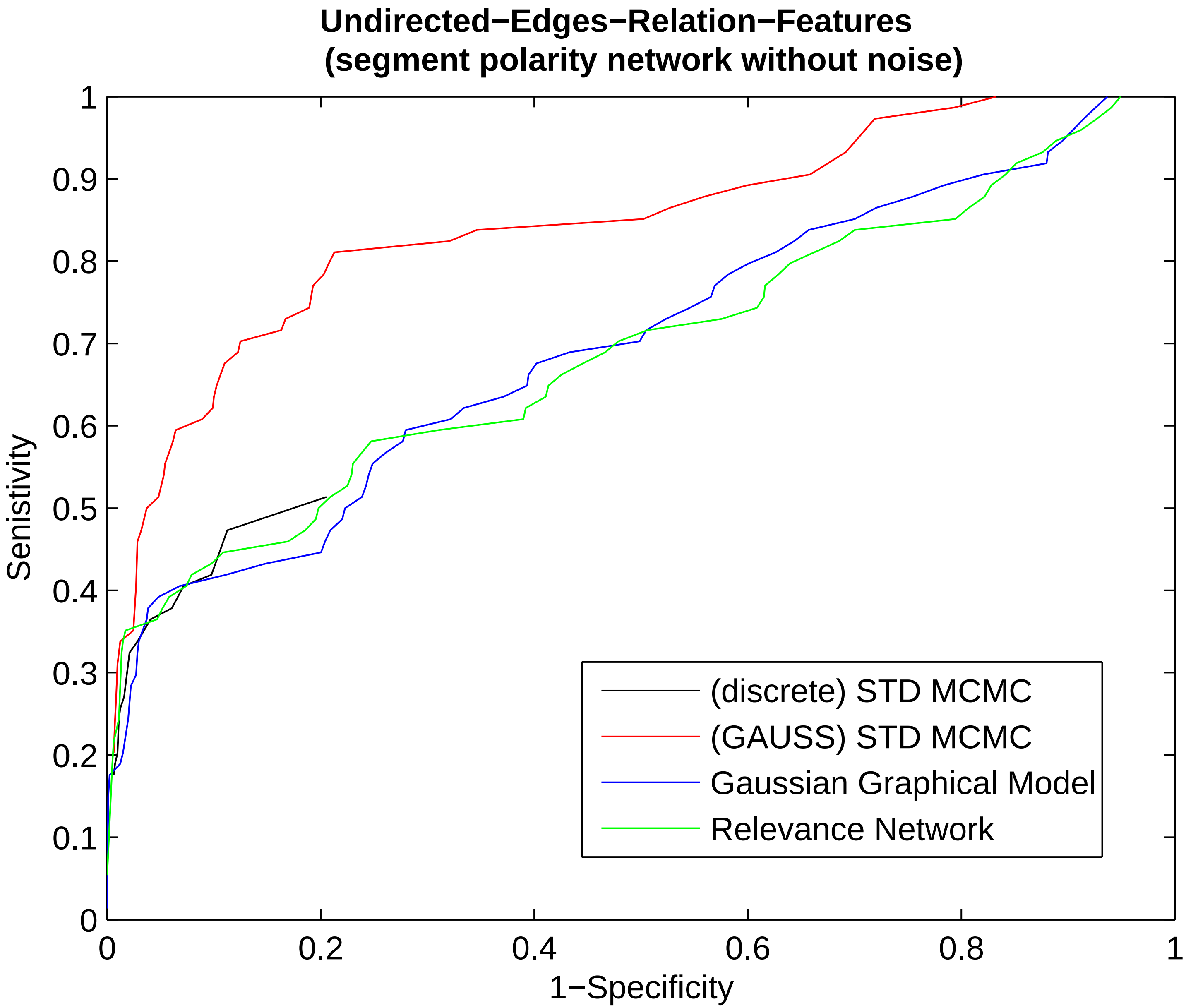
42 nodes, 100 observations

42 nodes, 100 observations

Comparison with alternative schemes

- Mutual information relevance networks
  Butte & Kohane
  Pacific Symposium on Biocomputing 2000

- Gaussian graphical models
  Schafer & Strimmer
  Bioinformatics 2004



Undirected−Edges−Relation−Features
(segment polarity network without noise)
Senistivity
1−Specificity
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
0.2
0.4
0.6
0.8
1
(discrete) STD MCMC
(GAUSS) STD MCMC
Gaussian Graphical Model
Relevance Network

# Conclusions

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- Learning the global network $\longrightarrow$ impossible
- Intrinsic uncertainty due to lack of data

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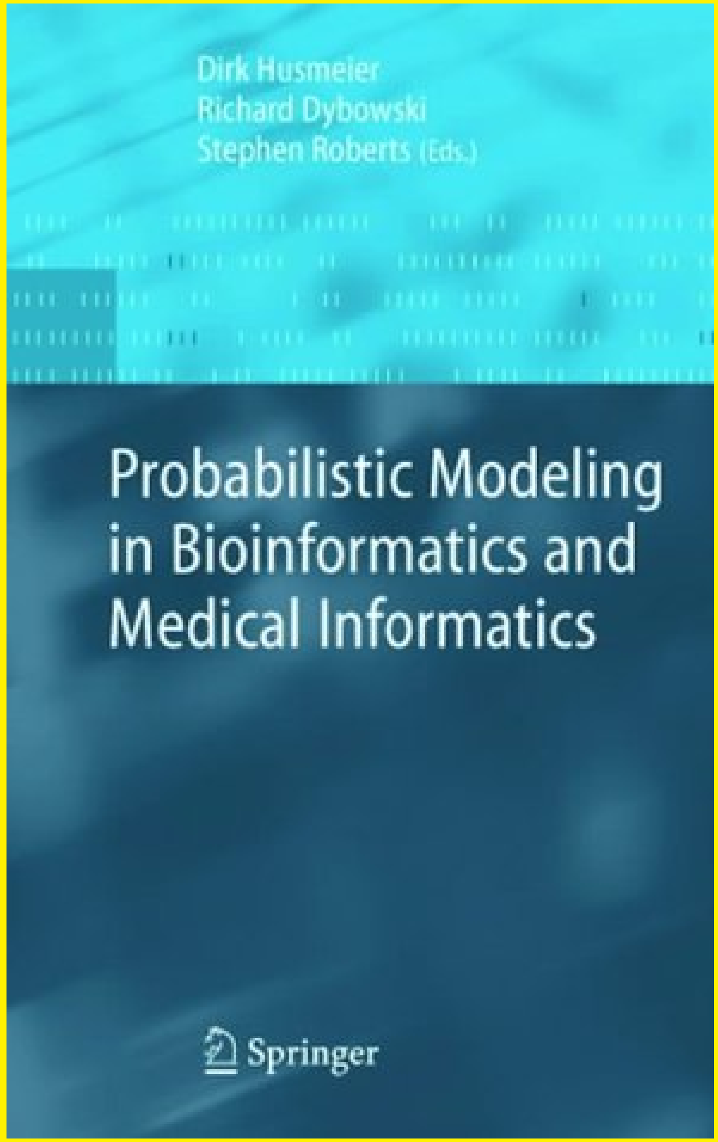
- Learning the global network $\longrightarrow$ impossible
- Intrinsic uncertainty due to lack of data
- Inference local substructures possible.
- Bayesian networks
  outperform alternative approaches.
- Integrating post-genomic data.


Dirk Husmeier
Richard Dybowski
Stephen Roberts (Eds.)
Probabilistic Modeling in Bioinformatics and Medical Informatics
Springer