Network Biology- part IV

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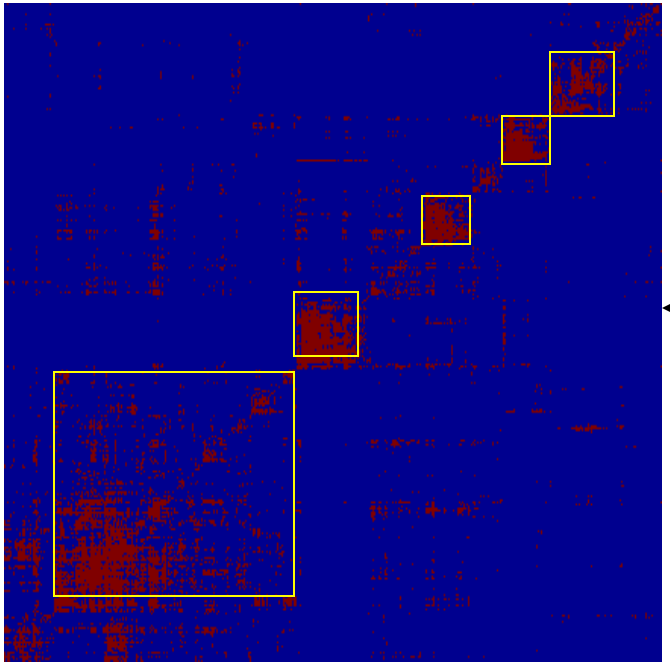
Biological networks/pathways

Data required to train models

Association networks ⟷ **Probabilistic causal networks**

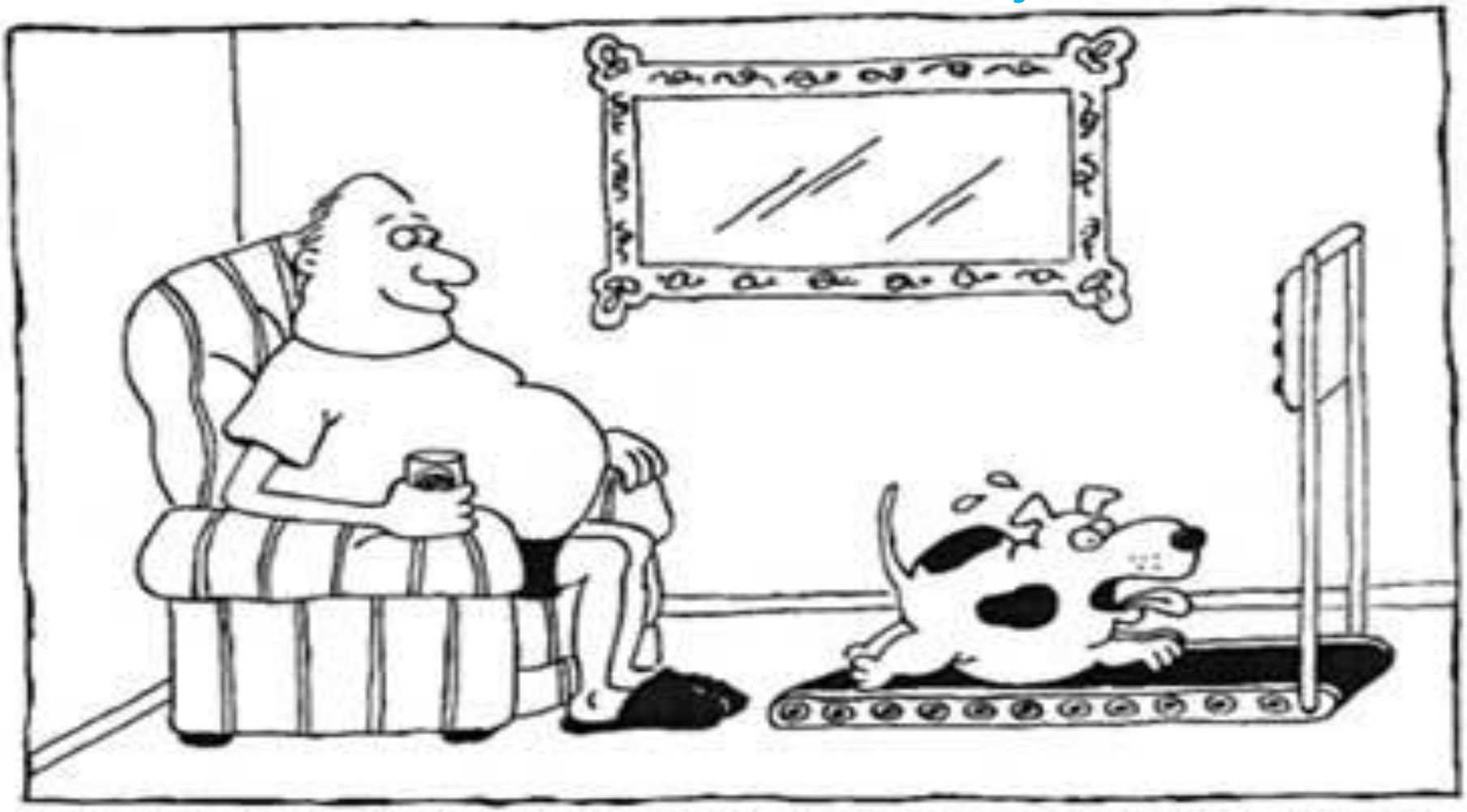
Biological details revealed

4267 top genes in BxH liver female rescan qtl overlap
(num(p(GGC)<1e-15)>100 ~abs(cor)>0.5886)



1. How do genes in the same module interact?
2. How do genes in different modules interact?
3. Can we make causal inferences to elucidate signaling pathway for disease targets?

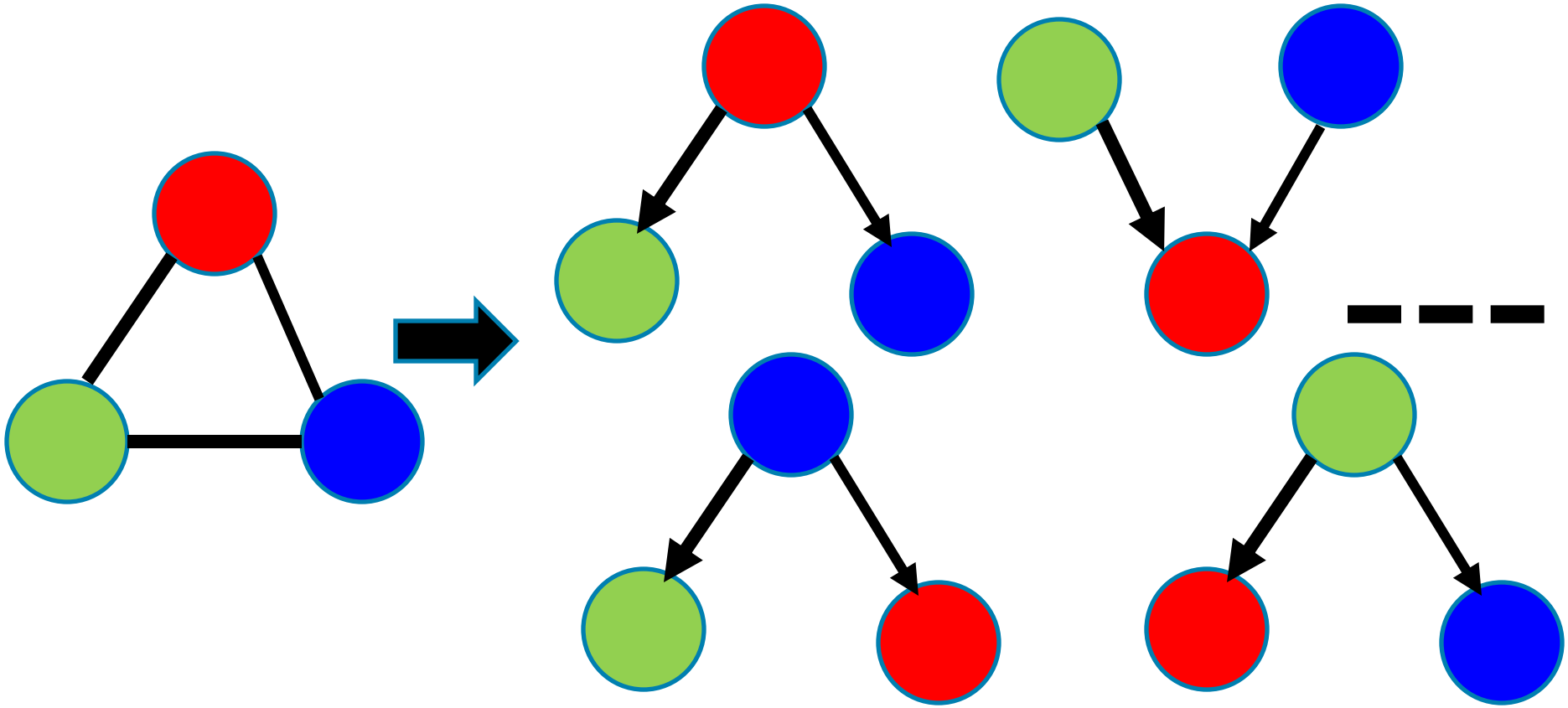
Association vs Causality



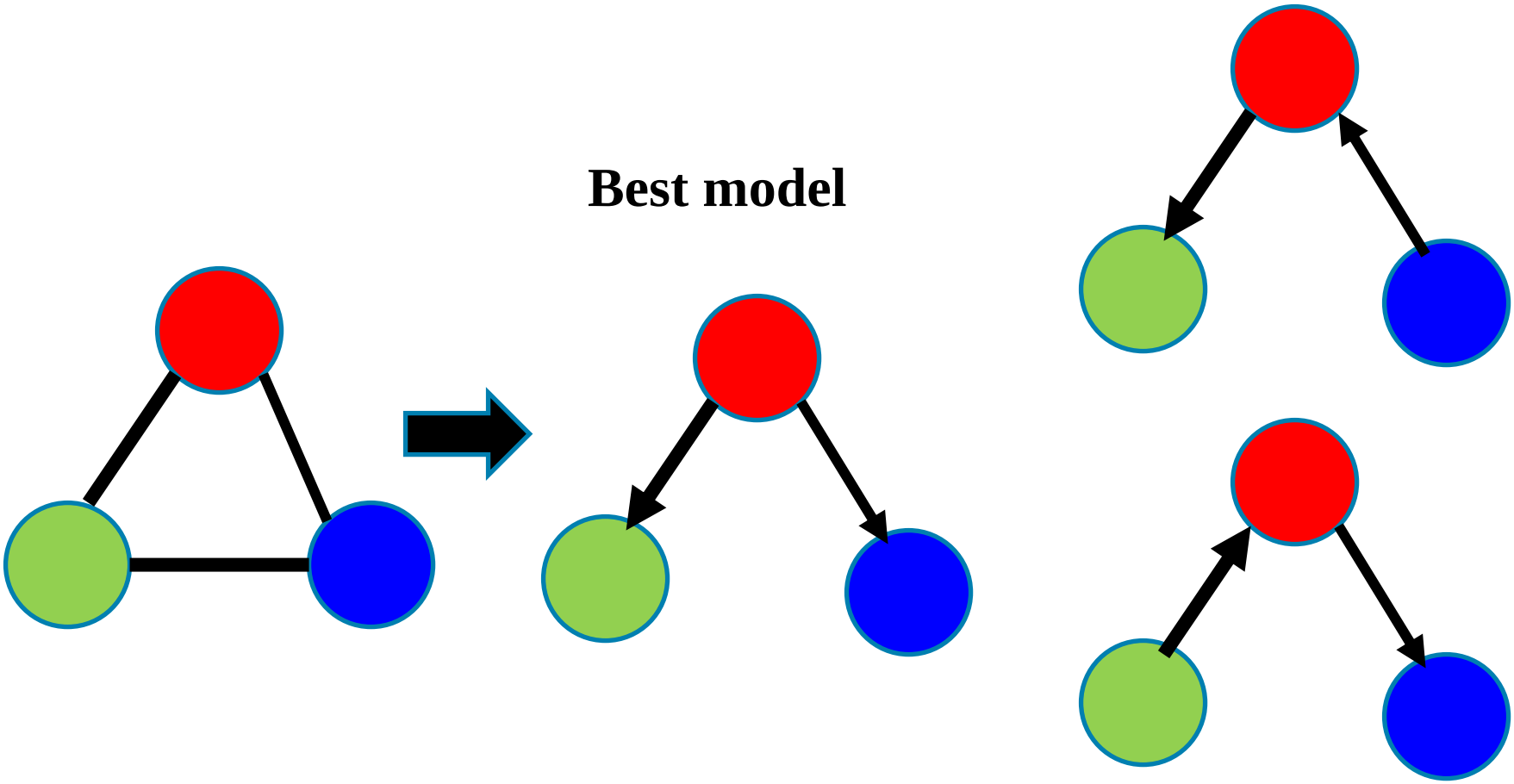
WHEN INFORMED BY HIS DOCTOR OF THE CORRELATION BETWEEN FAT DOGS AND THEIR MASTERS, BRIAN SET OUT IMMEDIATELY TO RECTIFY HIS WEIGHT PROBLEM.

From Stephen Friend

A simple biological question: are there causal/reactive relationships?



A Bayesian network approach:

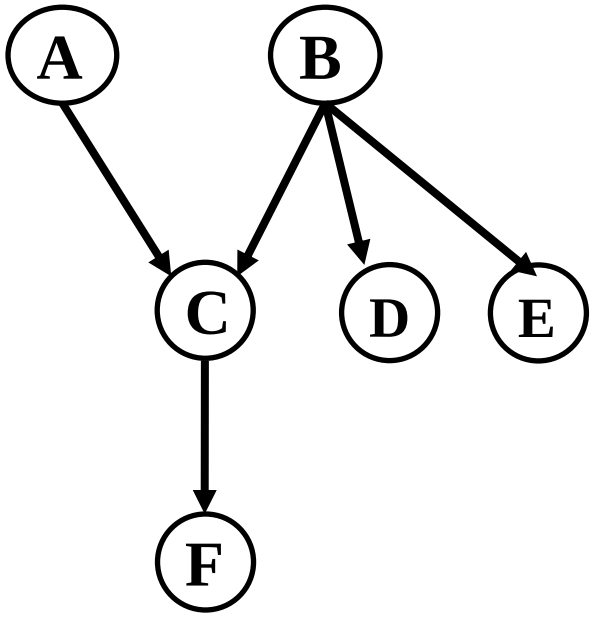


What are Bayesian networks?

- A Bayesian network is an expert system that captures all existing knowledge;
- They are also called **belief** networks, Bayesian belief networks, **causal probabilistic** networks;

- A Bayesian network consists of
  - a **directed** acyclic graph (a set of nodes and directed edges connecting nodes)--DAG
  - A set of conditional probability tables (for discrete data) or probability density functions (for continuous data)

A Bayesian network



DAG

$$p(C \mid A, B)$$

$$p(\mathrm{D} \mid B)$$

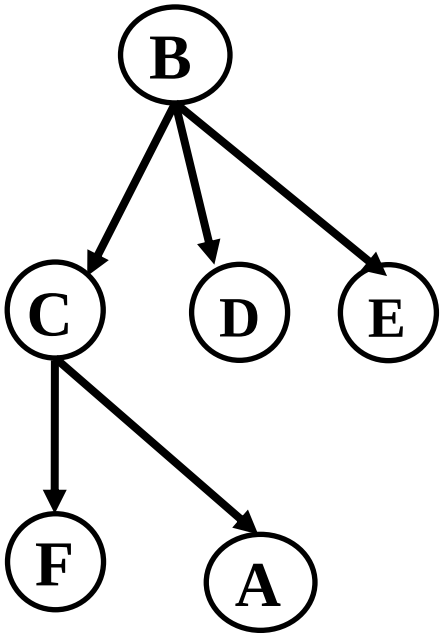
$$p(\mathrm{E} \mid B)$$

$$p(\mathrm{F} \mid \mathrm{C})$$

Conditional probability tables

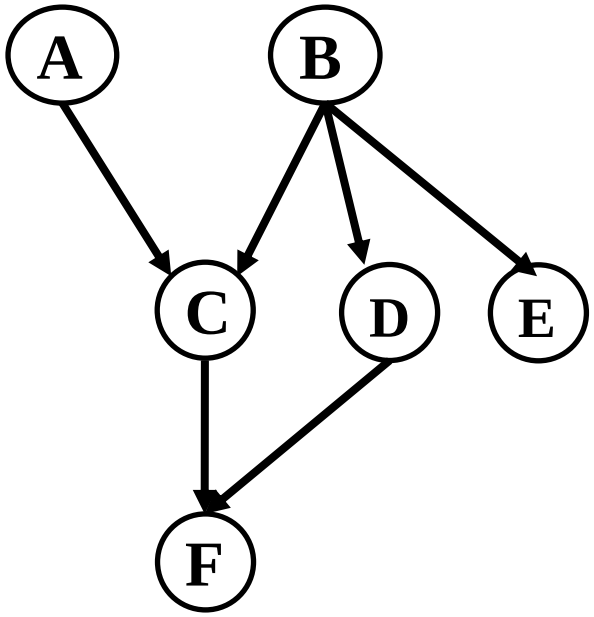
Bayesian network

- **A tree is a Bayesian network**



Bayesian network

- **A Bayesian network is not a tree**



Bayesian network

- **Conventional Notations**

$$p(\mathbf{A}) = \prod_i p(A_i \mid pa(A_i))$$

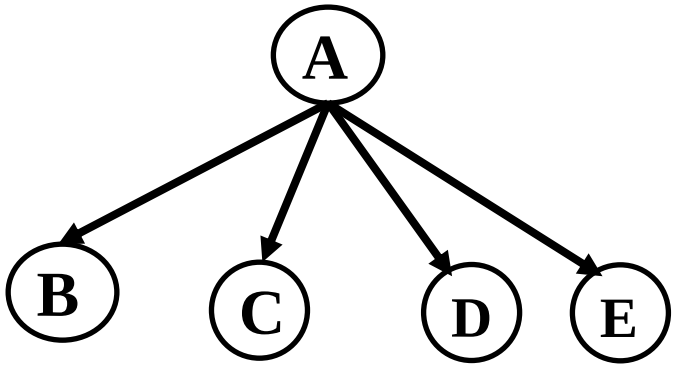
$\mathbf{A} = \{A_1, A_2, \ldots, A_n\}$ are nodes.

$p(\mathbf{A})$ is the joint probability of nodes $\mathbf{A}$.

$pa(A_i)$ are parent nodes of A_i.

Bayesian network

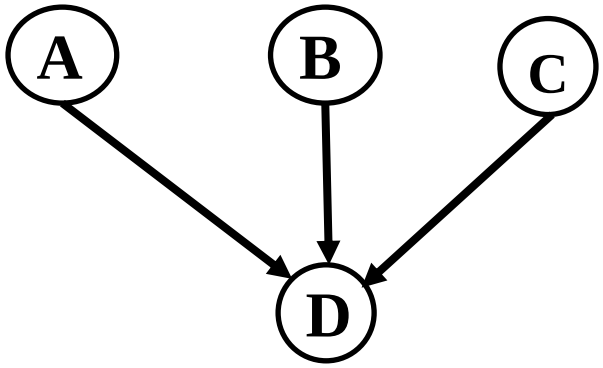
- **A diverging structure**



out-degree =4

Bayesian network

- **A converging structure**



in-degree =3

Bayesian network

- **Why a DAG is required?**

$$p(\mathbf{A}) = \prod_i p(A_i \mid pa(A_i))$$

- **It is guaranteed that <u>there is a node Aj in a DAG that has no child.</u>**

$$\begin{aligned} p(\mathbf{A}) &= p(\mathbf{A} \setminus \{A_j\})\, p(A_j \mid \mathbf{A} \setminus \{A_j\}) \\ &= p(\mathbf{A} \setminus \{A_j\})\, p(A_j \mid pa(A_j)) \\ &= \left(\prod_{i \neq j} p(A_i \mid pa(A_i))\right) * p(A_j \mid pa(A_j)) \end{aligned}$$

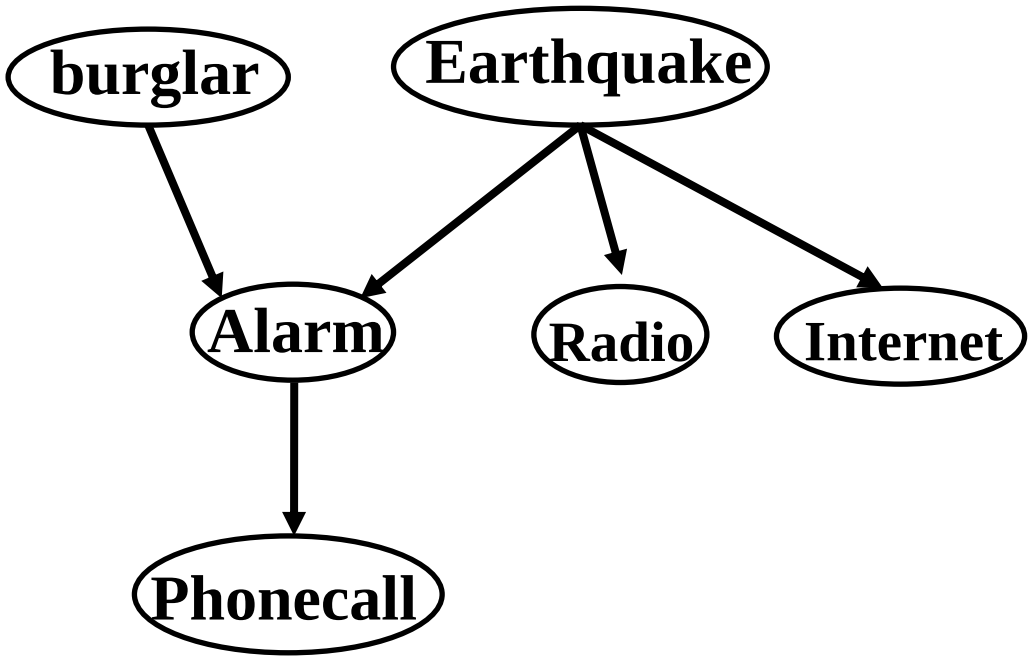
Bayesian network: usages

- Bayesian networks can be used to predict outcomes or diagnose causal effects (if structures are known)

- Bayesian networks can be used to discover causal relationships (if structures are not known)

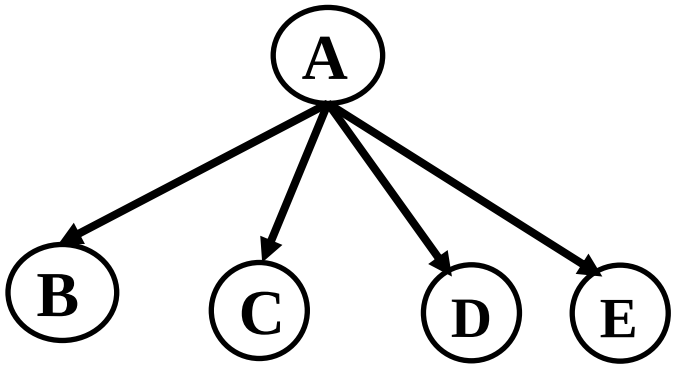
Bayesian network: an example

- **A burglar alarm system**



Bayesian network: a classifier

- **What is a naïve Bayes net**

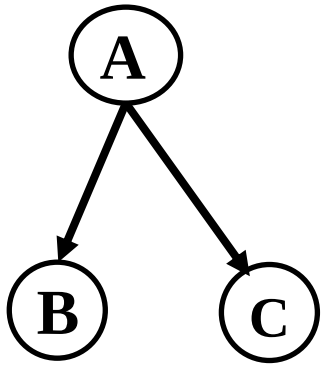


$$p(A,B,C,D,E) = p(B \mid A)p(C \mid A)p(D \mid A)p(E \mid A)p(A)$$

$$p(A \mid B,C,D) = \frac{p(A,B,C,D,E)}{p(B,C,D,E)}$$

Bayesian network

- **How to train a Bayesian network**

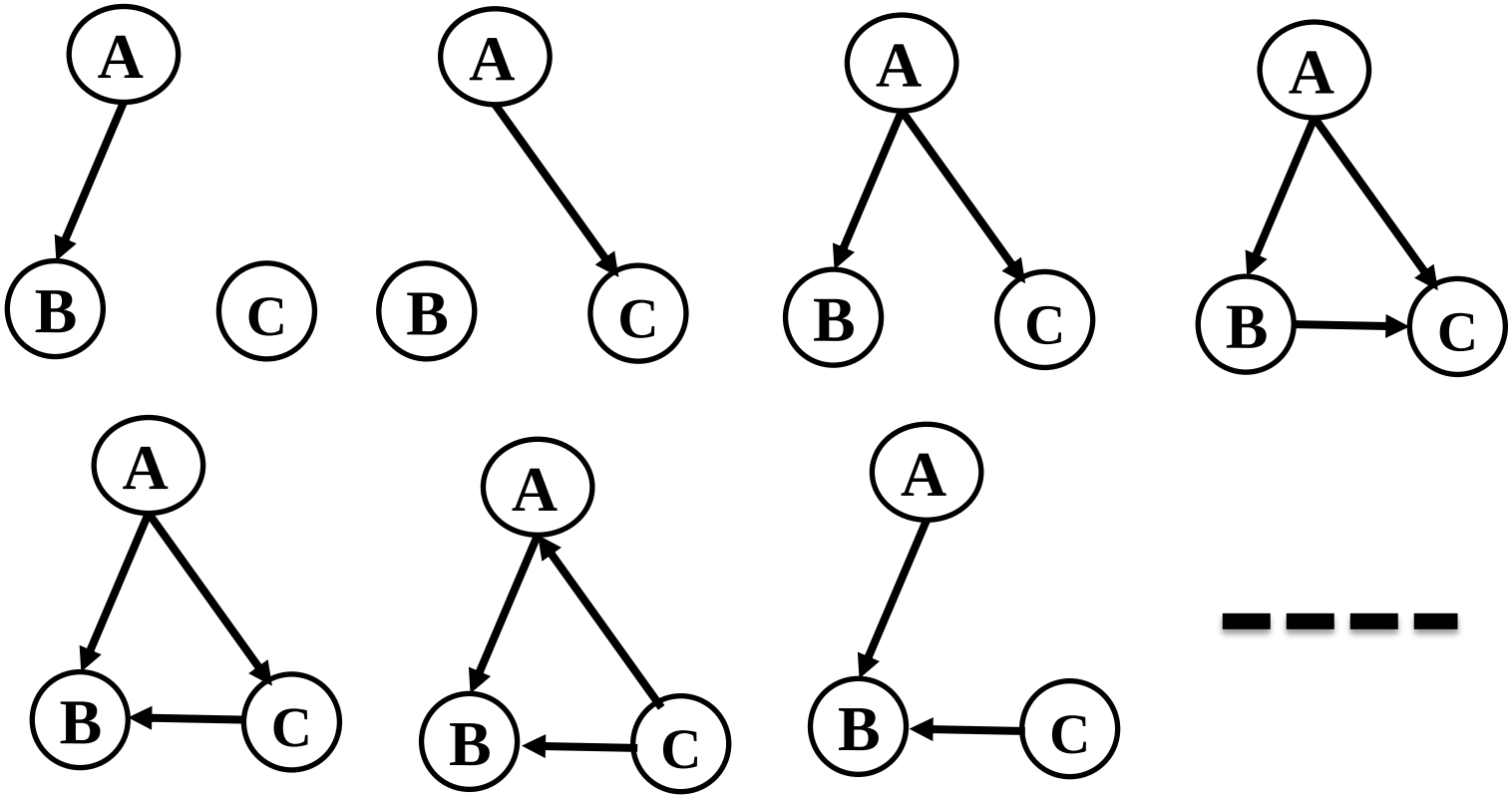


	A=a1	A=a2	A=a3
B=b1	7	12	25
B=b2	20	30	28
B=b3	25	20	6

	A=a1	A=a2	A=a3
C=c1	15	8	20
C=c2	11	25	18
C=c3	27	10	16

Bayesian network

- **How to construct a Bayesian network? Enumerating possible structures**



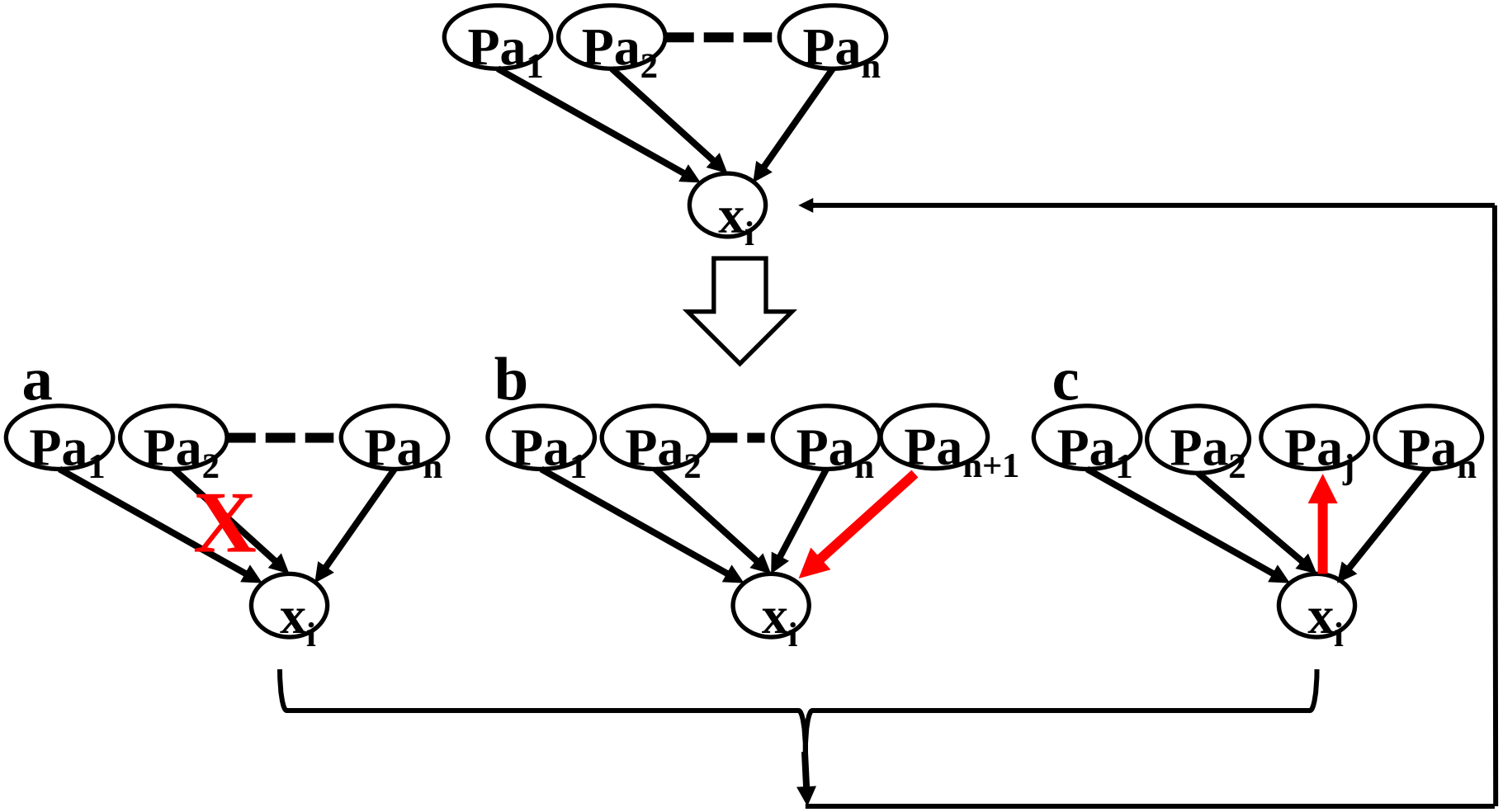
Bayesian network

- **How to construct a Bayesian network? Enumerating all possible structures is impossible**

$$\sim N^N,\ N\ is\ the\ number\ of\ nodes$$

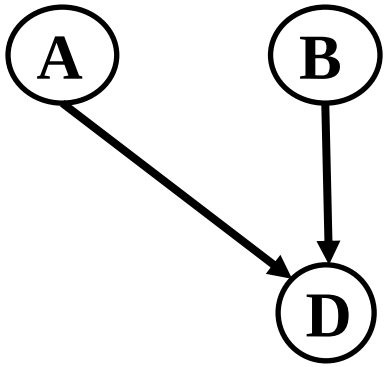
Bayesian network

- How to construct a Bayesian network? Heuristic approach

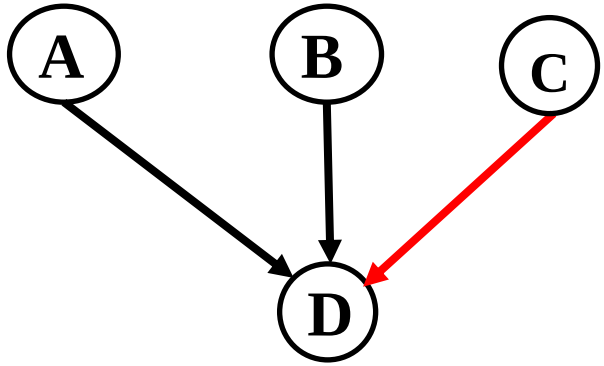


Bayesian network

- **How to construct a Bayesian network? Heuristic approach**



Parameters to estimate=3x3x3



Parameters to estimate=3x3x3x3

Bayesian network

- **How to construct a Bayesian network? Heuristic approach**

$$p(M \mid D) = \frac{p(D \mid M)\, p(M)}{p(D)}$$

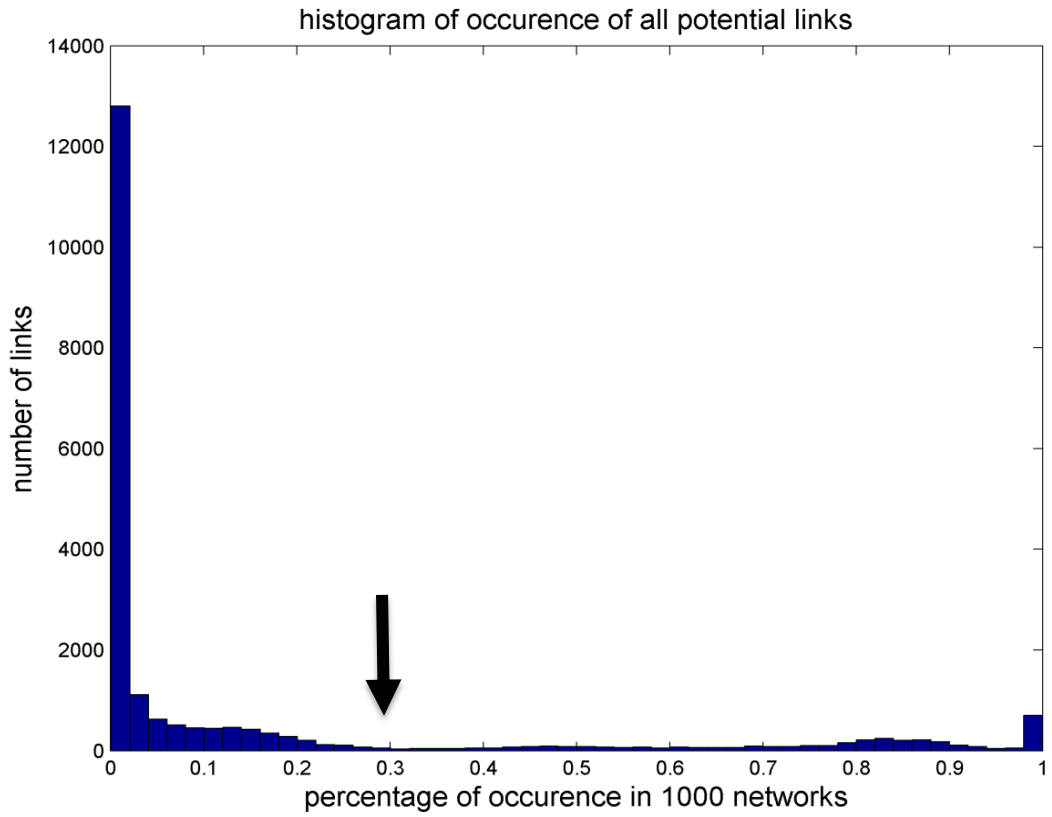
$$\mathrm{BIC} = -2 \ln p(D \mid \hat{M}) + k \ln(n)$$

n : number of samples

k : number of parameters to estimate

Bayesian network

- **How to construct a Bayesian network? averaging**



Zhu et al., PLoS CompBio, 2007
Zhu et al., Nature Genetics, 2008

Bayesian network

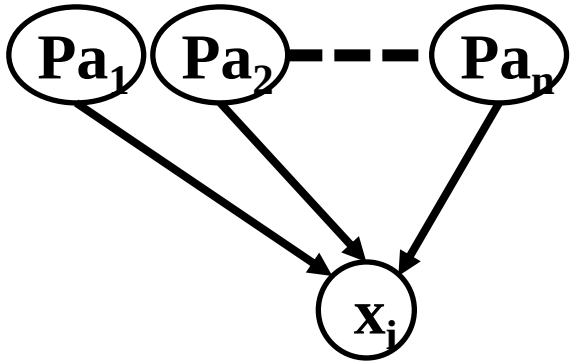
- **How to construct a Bayesian network? Enforcing DAG after averaging**

1. **Calculate shortest distance**
2. **Identify loops**
3. **Remove the weakest link in a loop**
4. **Go to step 1**

Zhu et al., PLoS CompBio, 2007

Bayesian network

- **How to construct a Bayesian network? Upper limit on in-degree**



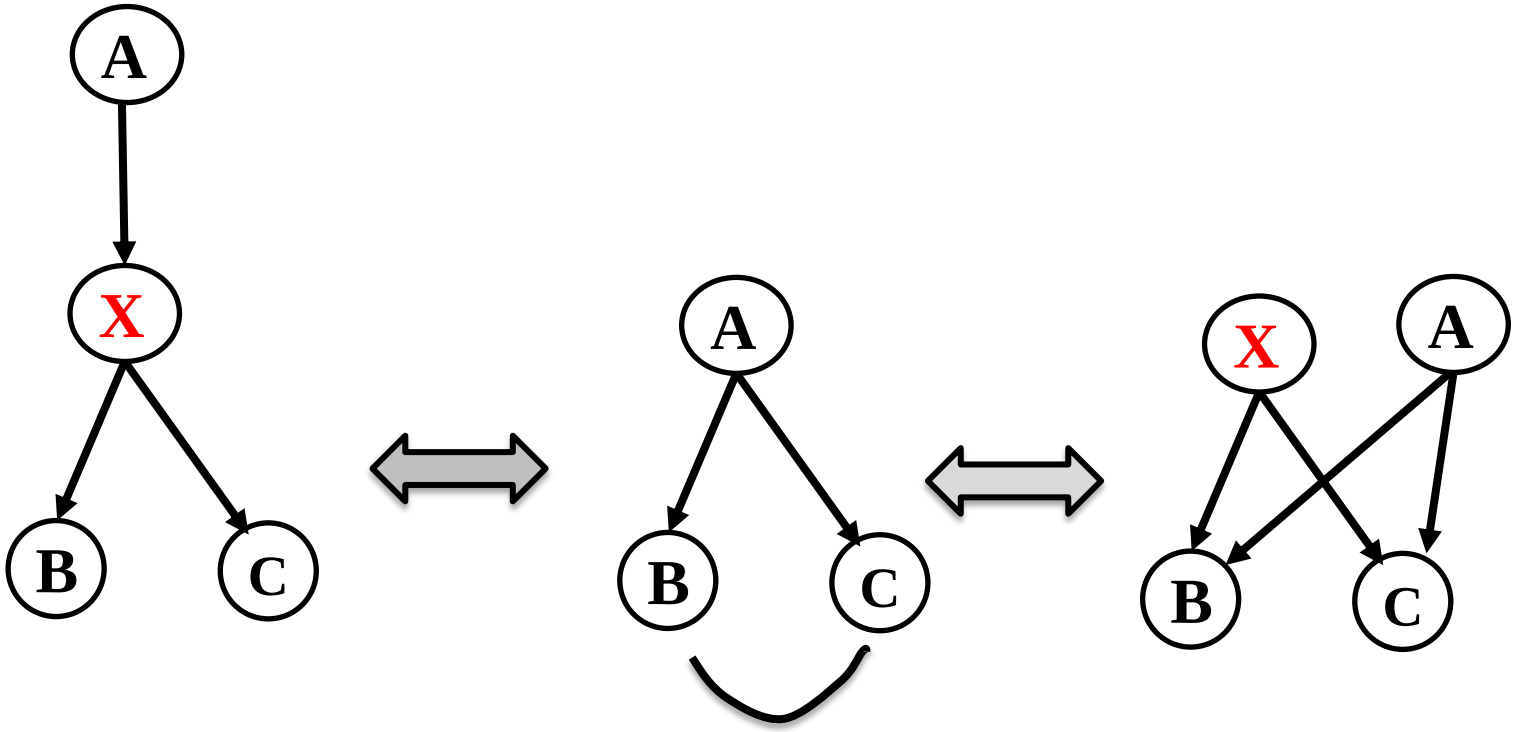
Parameters to estimate= 3^{n+1}

Bayesian network

- **Continuous vs discrete models**
- **Discrete model is faster, easier to capture high order interactions**
- **Any discretization lost information**

Bayesian network

- **Missing information**



Bayesian network

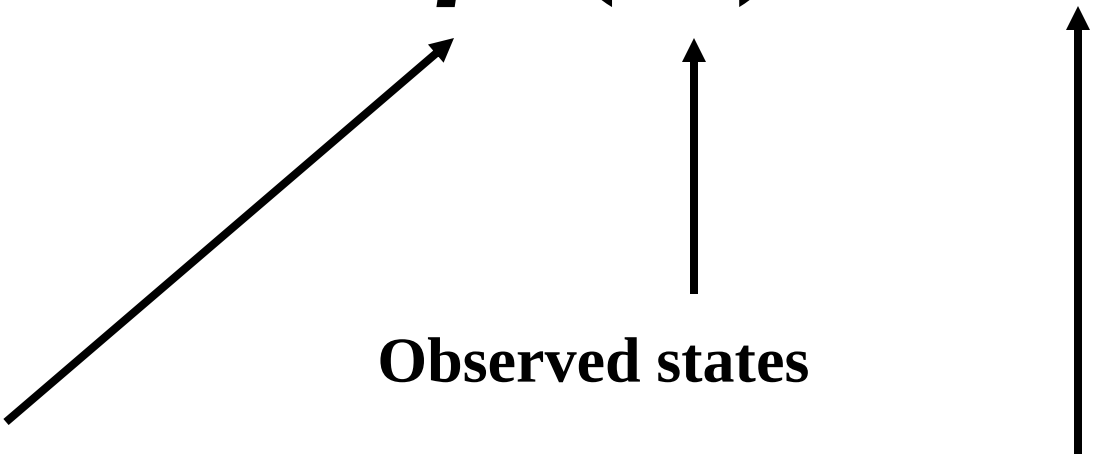
- **Biological network is context specific**
- **Bayesian network is just a snapshot under a specific condition**

Other ways to infer causal networks

- **Boolean network, Graphic Gaussian model**
- **Conditional Mutual Information**
- **ODE model**
- **Structural equation**

modeling by differential equations

$$dx/dt = f(x) + u$$



Gardner et al, Science, 2003

modeling by ordinary differential equations (ODE)

- Assume static state dx/dt=0
- Assume linear relationships f(x)=Ax

$$Ax + u = 0$$

regulatory matrix

$$x + A^{-1}u = 0$$

response matrix

ODE: advantages and disadvantages

- **Advantages**:
  - Simple
  - Can model feedback loops
- **Disadvantages**:
  - Need large amount of data
  - Need even more data to capture non-linear relationships

Aknowledgements

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