Statistical Machine Learning Methods for Bioinformatics

VII. Introduction to Bayesian Network Theory and Applications

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Opening Statements

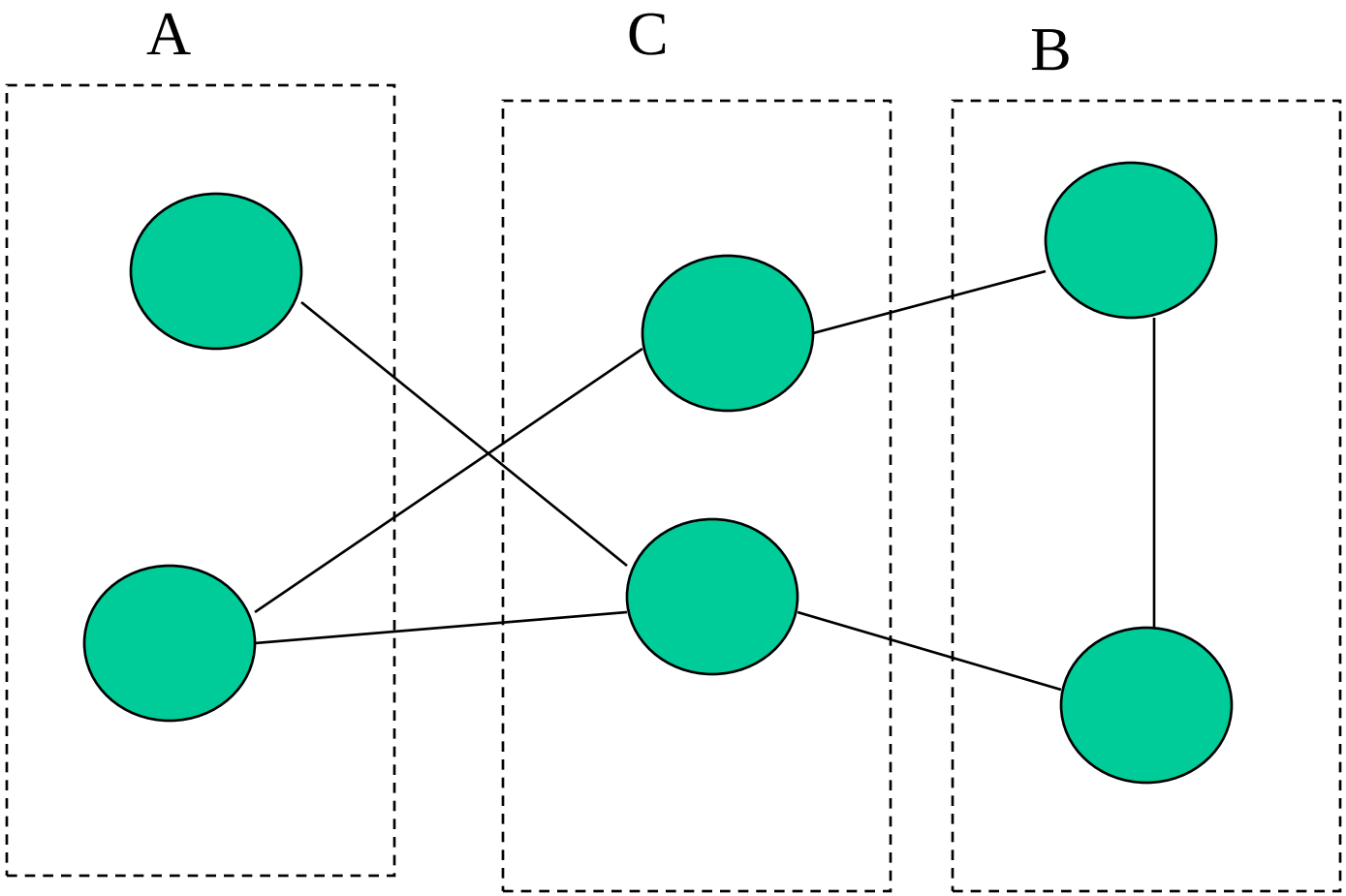
- These slides are just a quick introduction to the Bayesian networks and their applications in bioinformatics due to the time limit.
- For the in-depth treatment of Bayesian networks, students are advised to read the books and papers listed at the course web site and the Kevin Murphy's introduction.
- Thanks to **Kevin Murphy**'s excellent introduction tutorial: http://www.cs.ubc.ca/~murphyk/Bayes/bnintro.html

Definition of Graphical Model

- Probabilistic graphical models are graphs in which nodes represent random variables, and the (lack of) arcs represent dependence (conditional independence).
- It provides a compact representation of joint probability distribution

Markov Random Fields

- Undirected graphical models (also called Markov networks)
- Two sets of nodes A and B are conditionally independent give a third set C if all paths between A and B are separated by a node C.
- Popular with the physics and vision communities.

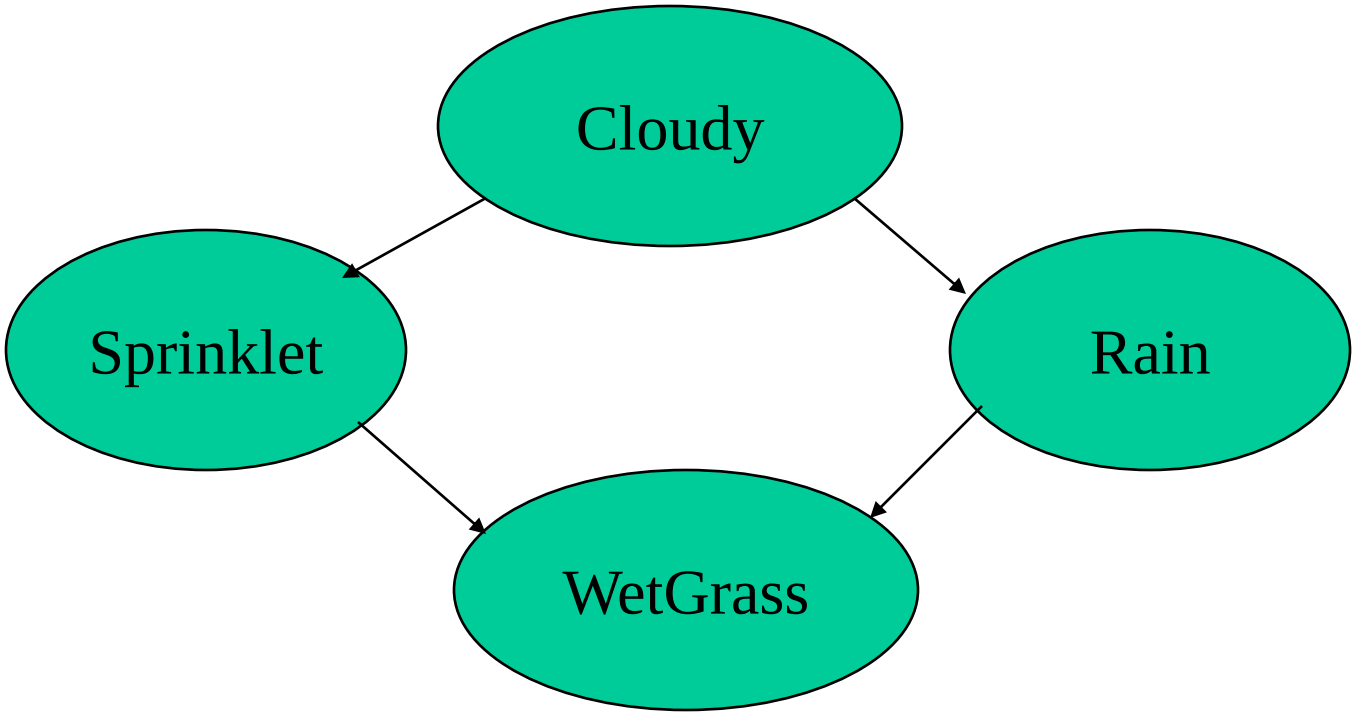


$$A \perp B \mid C$$

Bayesian Networks

- Directed graphical models (also called Belief Networks)
- Popular with AI and statistics communities.
- A model with both directed and undirected arcs is called a chain graph

Bayesian Network Example



Comparison of Directed and Undirected Graphical Models

- Independence relationship of directed graph is more complicated.
- A -> B can encode causal relationship
- Directed models can encode deterministic relationship, and are easier to learn (fit to data).

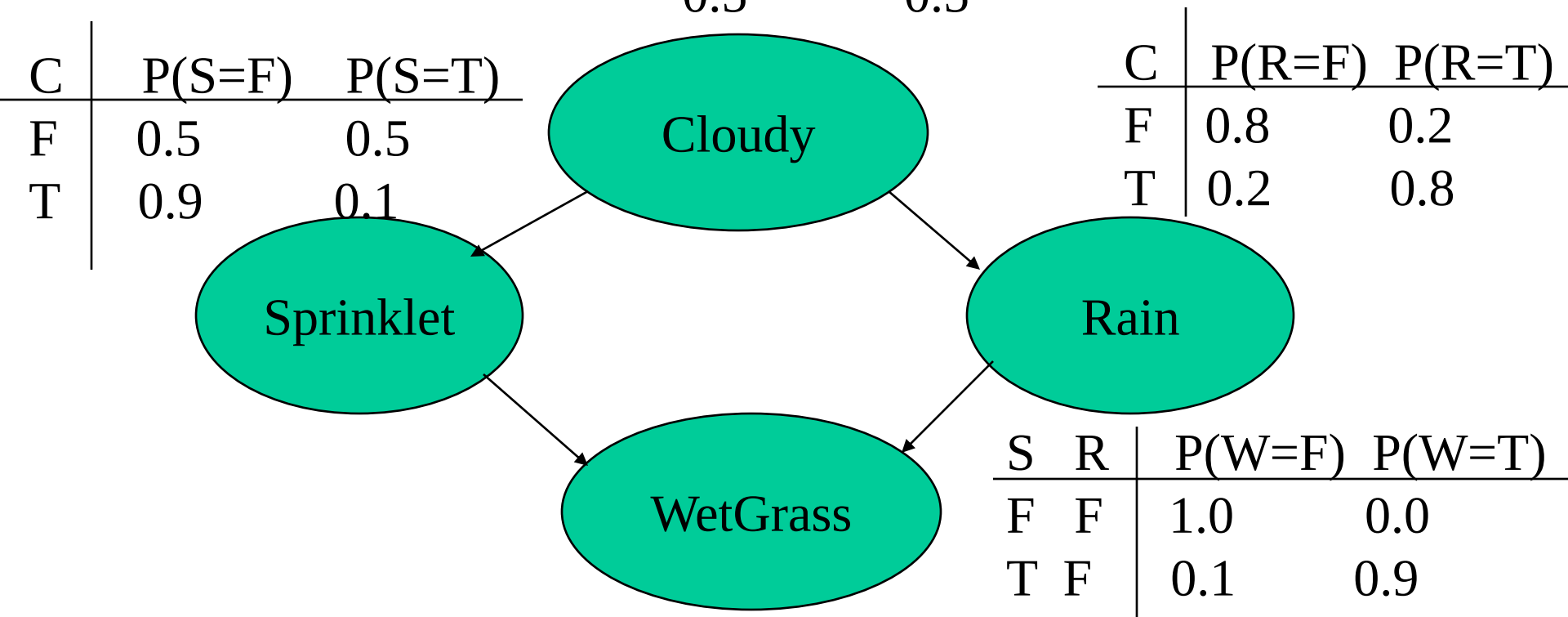
Advantages of BN

- Compact & intuitive representation
- Captures causal relationships
- Efficient model learning (parameters and structure)
- Deals with noisy data
- Integration of prior knowledge
- Effective inference algorithms

N. Friedman, 2005

Conditional Probability Distribution

- Discrete variable: CPT, conditional probability table



The Simplest Conditional Independence in BN

- A node is independent of its ancestors given its parents, where the ancestor / parent relationship is with respect to some fixed topological ordering of the nodes
- The joint probability is the product of the conditional probability
- For previous examples: $P(C, S, R, W) = P(C) * P(S|C) * P(R|C,S) * P(W|C, S, R) = P(C) * P(S|C) * P(R|C) * P(W|S,R)$.

Compact Representation of Joint Probability

- In general, if we had n binary nodes, the full joint would require $O(2^n)$ space to represent, assuming each node has two possible values. But the factored form would require $O(n2^k)$ space to represent, where k is the maximum fan-in of a node.
- Fewer parameters makes learning easier.

Inference

- Probabilistic inference is one of the most common tasks we wish to solve using BN.
- Question: Suppose we observe the fact that the grass is wet. There are two possible causes for this: either it is raining, or the sprinkler is on. Which is more likely?
- We can use Bayes's rule to compute the posterior probability of each explanation.

$$\Pr(S=1|W=1) = \frac{\Pr(S=1,W=1)}{\Pr(W=1)} = \frac{\sum_{c,r}\Pr(C=c,S=1,R=r,W=1)}{\Pr(W=1)} = 0.2781/0.6471 = 0.430$$

$$\Pr(R=1|W=1) = \frac{\Pr(R=1,W=1)}{\Pr(W=1)} = \frac{\sum_{c,s}\Pr(C=c,S=s,R=1,W=1)}{\Pr(W=1)} = 0.4581/0.6471 = 0.708$$

where

$$\Pr(W=1) = \sum_{c,r,s}\Pr(C=c,S=s,R=r,W=1) = 0.6471$$

P(W=1) is a normalizing constant, equal to the probability (likelihood) of the data. So we see it is more likely that the grass is wet because it is raining.

Explaining Away

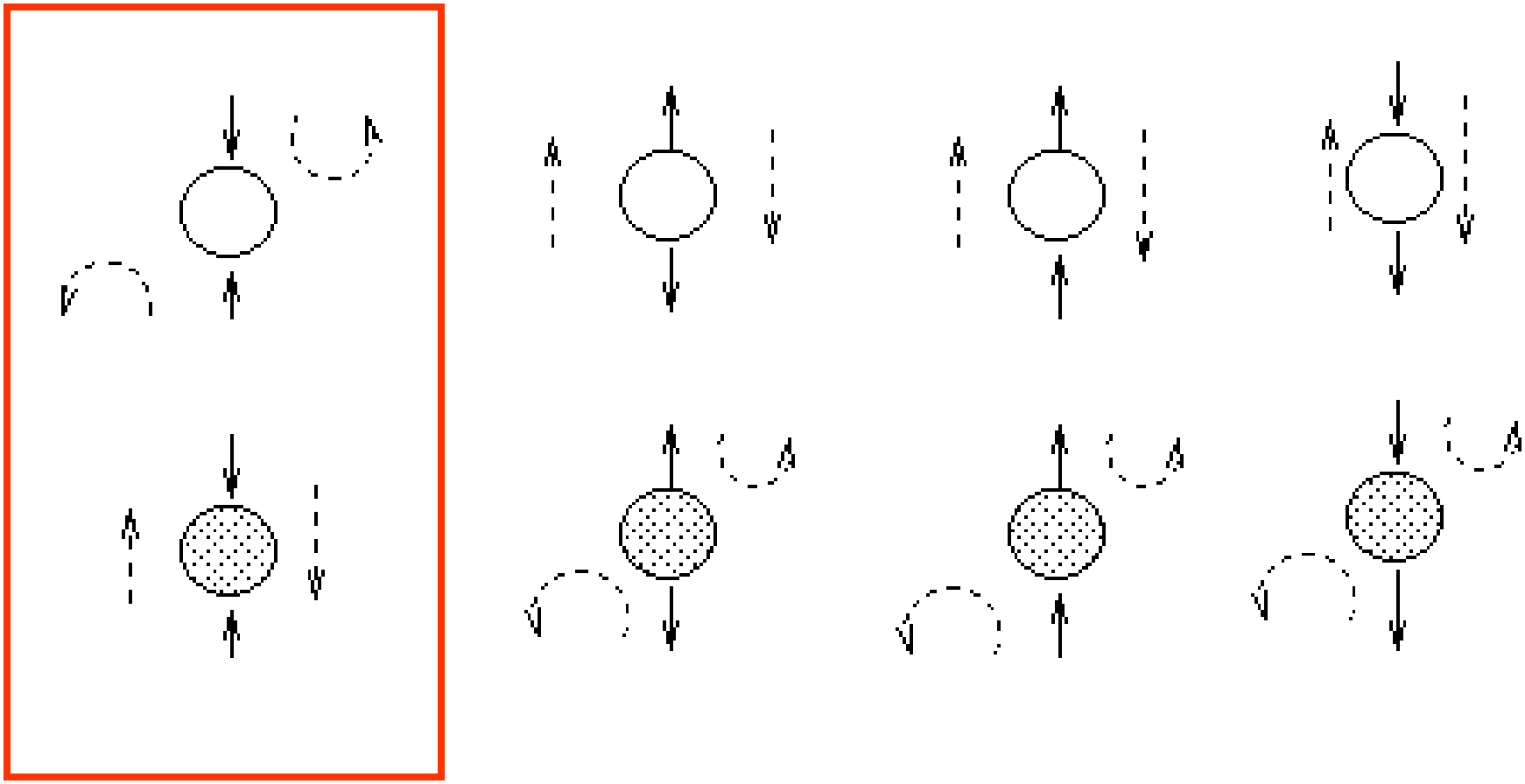
- S and R are the two causes competing to explain the observed data.
- So if w is not observed, S and R are marginally independent.
- If w is observed, S and R become conditionally dependent. $P(S=1|W=1, R=1) = 0.1945 < P(S=1|W=1)$
- This is called “explaining away”. In statistics, it is known as Berkson’s paradox, or “selection bias”.

Top-Down and Bottom-Up Reasoning

- Bottom up: In the water sprinkler example, we had evidence of an effect (wet grass), and inferred the most likely cause.
- Top down: We can compute the probability that the grass will be wet given that it is cloudy. (how causes generate effects).

Conditional Independence in BN

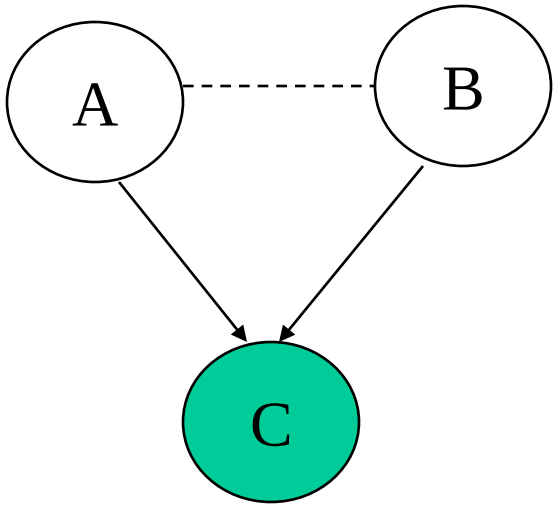
- **Bayes Ball** algorithm (due to Ross Shachter)
- Two (sets of) nodes A and B are conditionally independent (d-separated) given a set of C if and only if there is no way for a ball to get from A to B in a graph, where the allowable movements of ball are shown in the following figures.



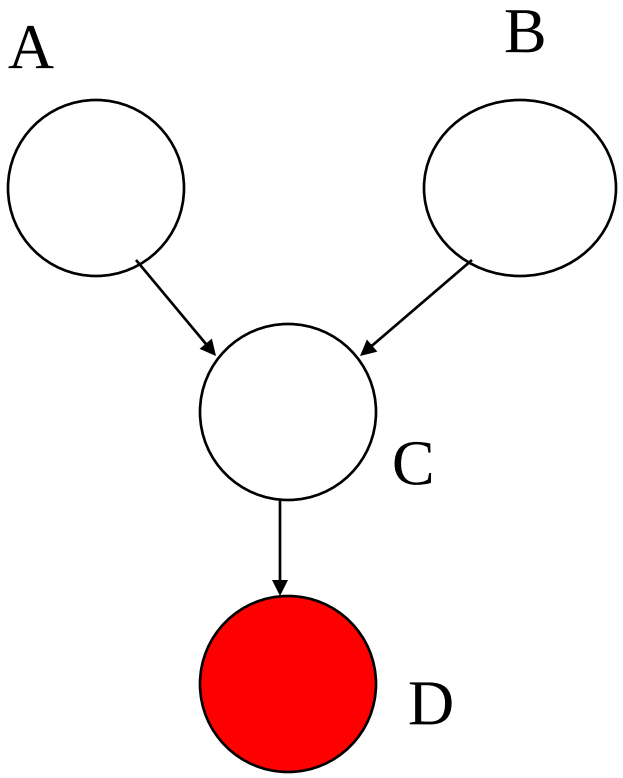
In the first column, when we have two arrows converging on a node X. If X is hidden, its parents are marginally independent. But if X is observed, the parents become dependent, and the ball pass through. **Why**?

Comments

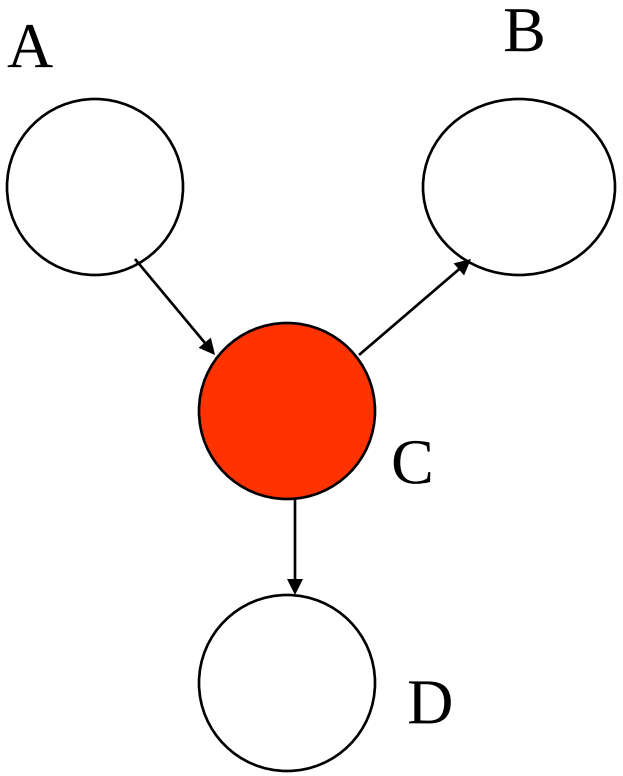
If the previous graph is undirected, the child would always separate the parents; hence when converting a directed graph to an undirected graph, we must add links between “unmarried” parents who share a common child (i.e., “**moralize**” the graph) to prevent us reading off incorrect independence statements.



Example



Is A independent B given D?



Is A independent of B given C

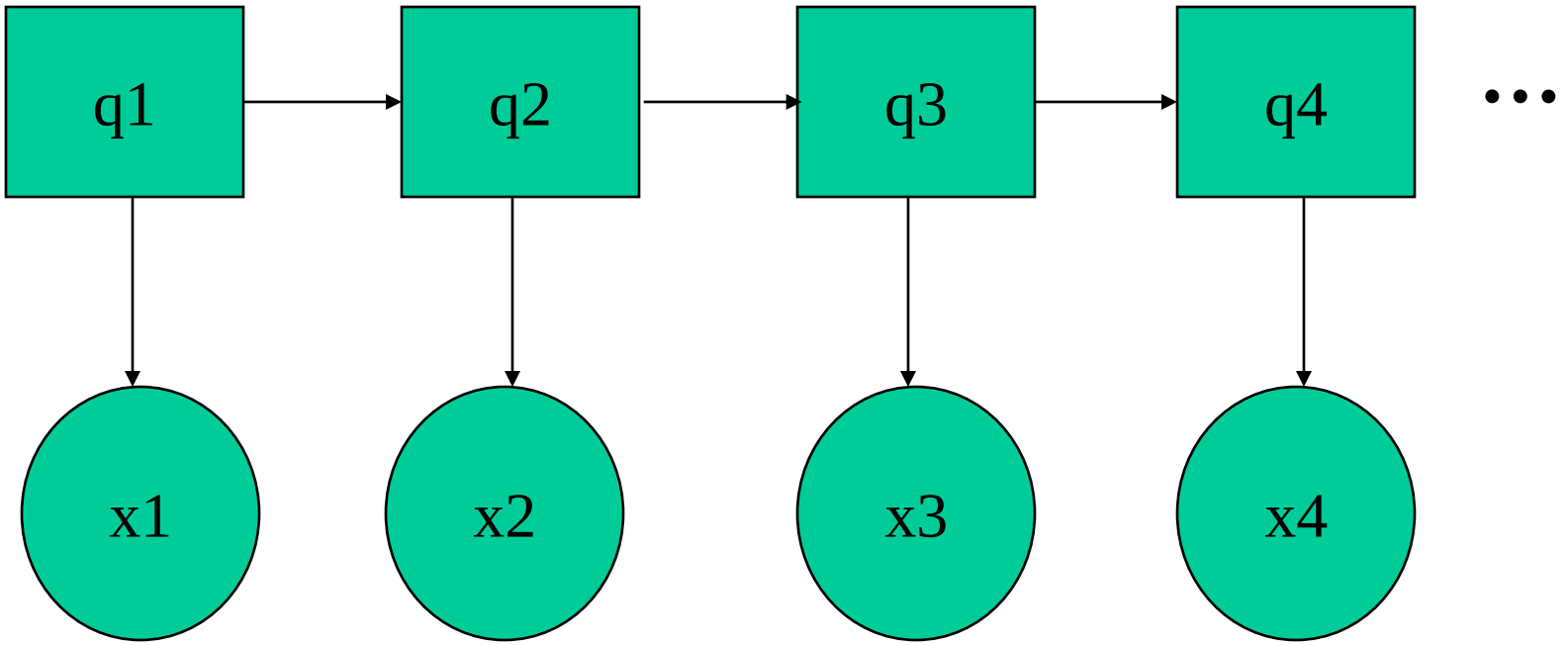
Bayes Nets with Discrete and Continuous Nodes

- It is possible to create Bayesian networks with continuous valued nodes. The most common distribution for such variable is the Gaussian.
- For discrete nodes with continuous parents, we can use logistic / softmax distribution.
- Using multinomial, conditional Gaussians, and softmax distribution, we can have a rich toolbox for making complex models.
- For a good review: A Unifying Review of Linear Gaussian Models, S. Roweis & Z. Ghahramani. Neural Computation, 1999.

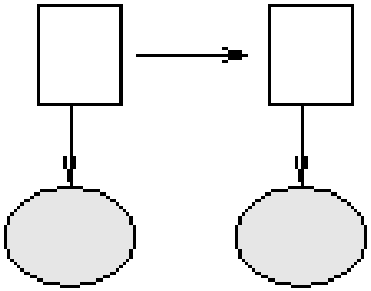
Dynamic Bayesian Networks

- DBNs are directed graphical models of stochastic processes.
- Examples: hidden Markov models and linear dynamical systems.

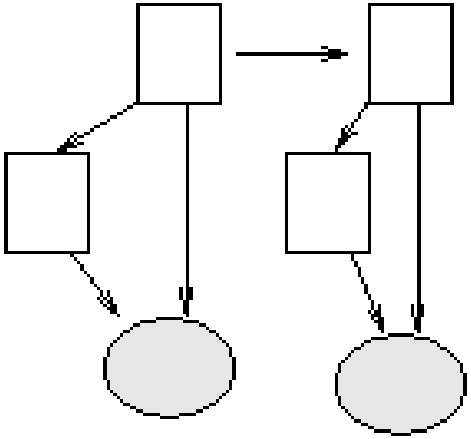
Hidden Markov Model (A New View)



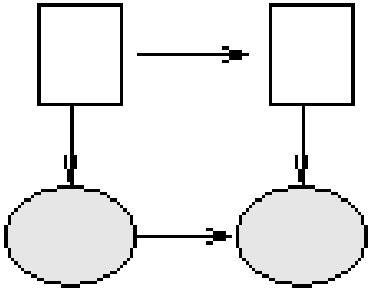
We have “unrolled” the model for 4 “time slices” -- the structure and parameters are assumed to repeat as the model is unrolled further. Hence to specify a DBN, we need to define the intra-slice topology (within a slice), the inter-slice topology (between two slices).



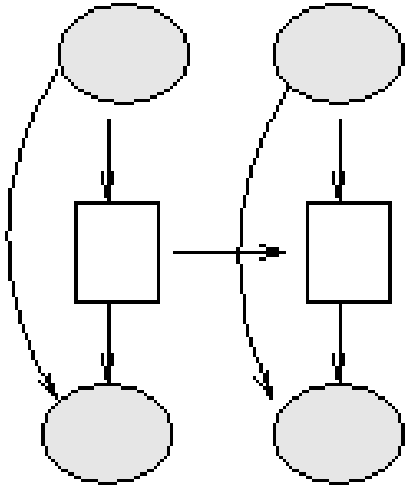
HMM with Gaussian output



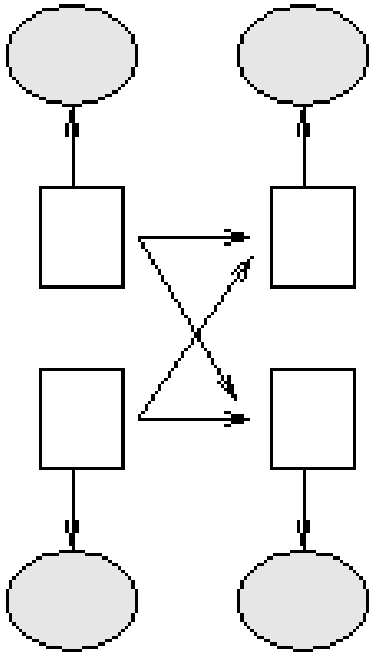
HMM with mixture of Gaussians output



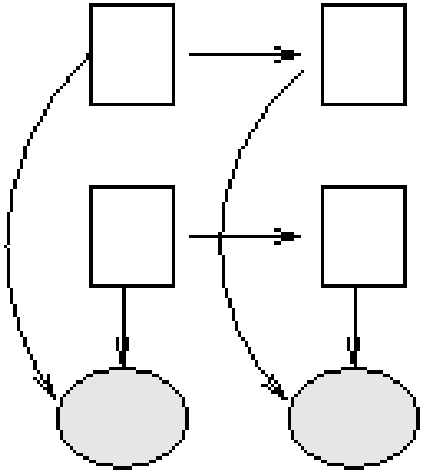
Auto Regressive HMM



Input–output HMM



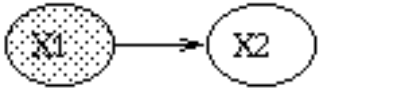
Coupled HMM



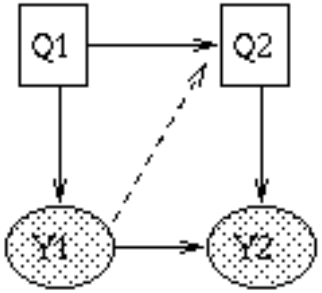
Factorial HMM

Linear Dynamic Systems (LDSs) and Kalman Filters

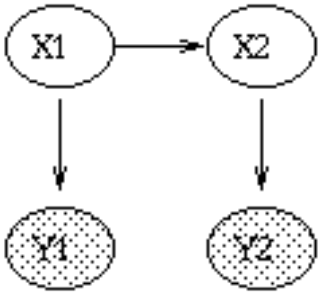
- A linear dynamical system (LDS) has the same topology as an HMM, but all nodes are assumed to have linear-Gaussian distributions, i.e., $x(t+1) = A*x(t) + w(t)$, $w \sim N(0, Q)$, $x(0) \sim N(\text{init\_x}, \text{init\_v})$, $y(t) = C*x(t) + v(t)$, $v \sim N(0, R)$



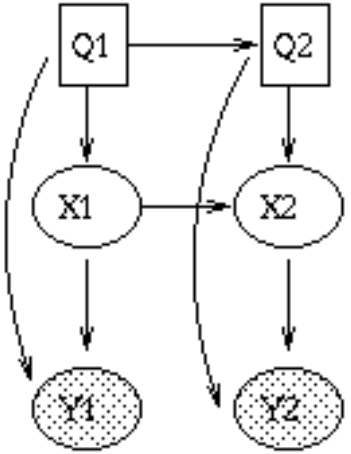
Auto Regressive model AR(1)



Switching AR model

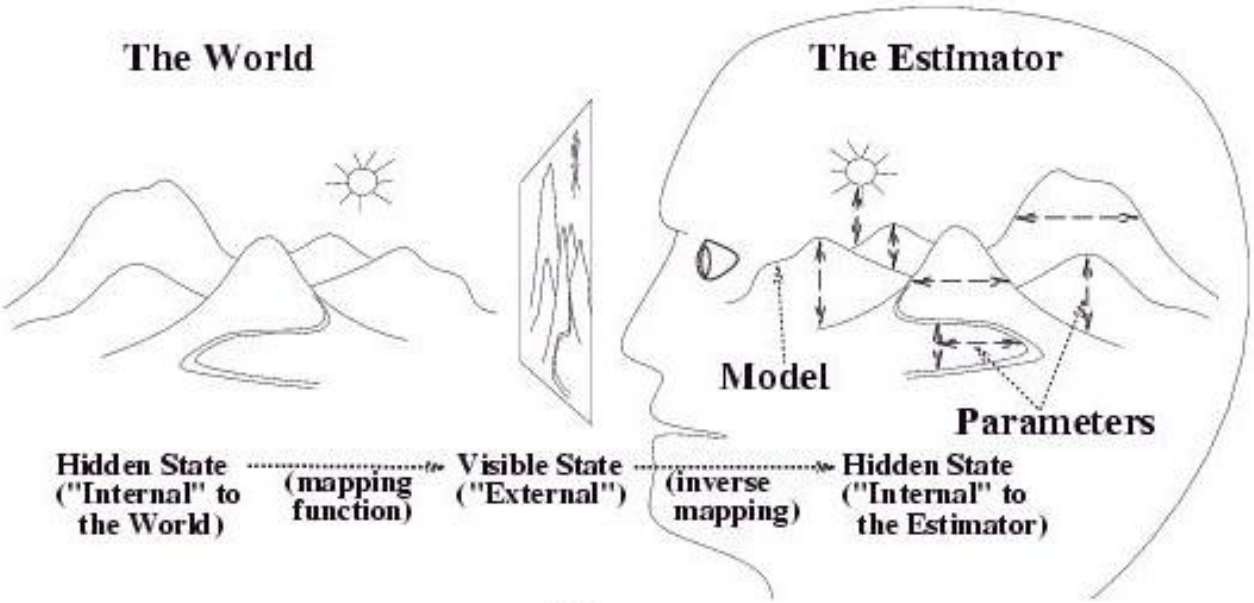


Kalman filter model

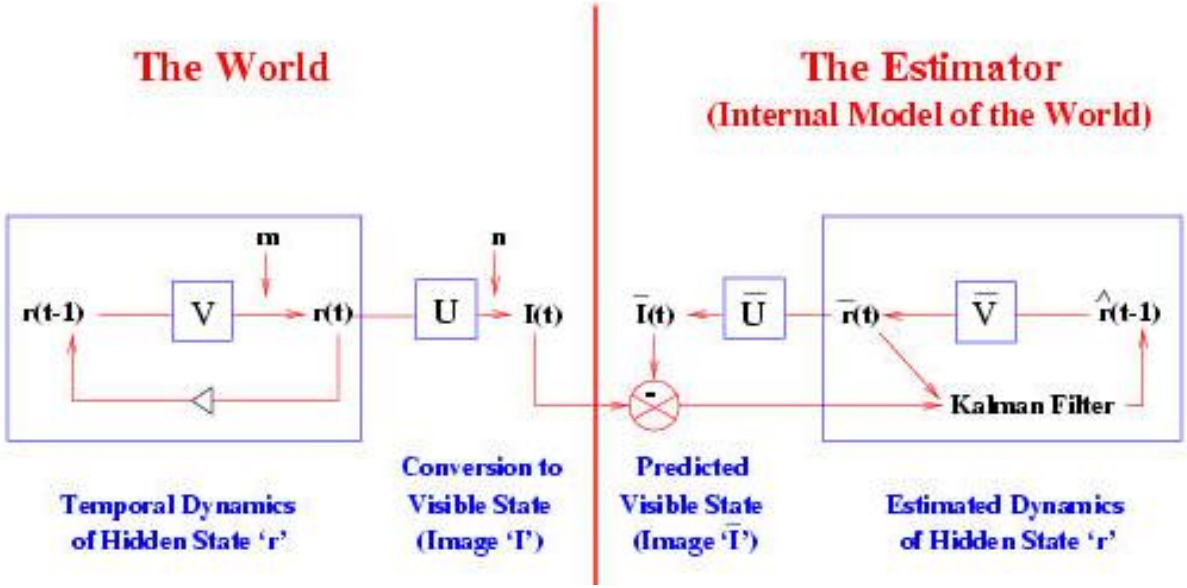


Switching Kalman filter

The Kalman filter has been proposed as a model for how the Brain integrates visual cues over time to infer the state of the World, although the reality is obviously more complicated. Kalman filter is also used in tacking of objects.


The World
The Estimator
Model
Parameters
Hidden State ("Internal" to the World)
(mapping function)
Visible State ("External")
(inverse mapping)
Hidden State ("Internal" to the Estimator)

(a)


The World
The Estimator
(Internal Model of the World)
m
n
r(t-1)
V
r(t)
U
I(t)
Ī(t)
Ū
r̄(t)
V̄
r̂(t-1)
-
Kalman Filter
Temporal Dynamics of Hidden State 'r'
Conversion to Visible State (Image 'I')
Predicted Visible State (Image 'Ī')
Estimated Dynamics of Hidden State 'r'

Efficient Inference Algorithms

- A simple summation of joint probability distribution (JPD) over all variables can answer all possible inference queries by marginalization, but takes exponential time.
- For a Bayes net, we can sometime use the factored representation of the JPD to do marginalization efficiently. The key idea is to "push sums" as far as possible when summing out irrelevant terms.

Variable Elimination: Water Sprinkler Network

$$\begin{aligned}
\Pr(W = w) &= \sum_c \sum_s \sum_r \Pr(C = c, S = s, R = r, W = w) \\
&= \sum_c \sum_s \sum_r \Pr(C = c) \times \Pr(S = s|C = c) \times \Pr(R = r|C = c) \times \Pr(W = w|S = s, R = r) \\
&= \sum_c \Pr(C = c) \sum_s \Pr(S = s|C = c) \sum_r \Pr(R = r|C = c) \times \Pr(W = w|S = s, R = r)
\end{aligned}$$

Notice that, as we perform the innermost sums, we create new terms, which need to be summed over in turn e.g.,

$$\Pr(W = w) = \sum_c \Pr(C = c) \sum_s \Pr(S = s|C = c) \times T1(c, w, s)$$

where

$$T1(c, w, s) = \sum_r \Pr(R = r|C = c) \times \Pr(W = w|S = s, R = r)$$

Continuing in this way,

$$\Pr(W = w) = \sum_c \Pr(C = c) \times T2(c, w)$$

where

$$T2(c, w) = \sum_s \Pr(S = s|C = c) \times T1(c, w, s)$$

- The principle of distributing sums over products can be generalized greatly to apply to any commutative summing. This forms the basis of many common algorithms, such as Viterbi decoding and the Fast Fourier Transform.
- The amount of work we perform when computing a marginal is bounded by the size of the largest term that we encounter. Choosing a summation (elimination) ordering to minimize this is NP-hard, although greedy algorithms work well in practice.

Dynamic Programming and Local Message Passing

- To compute several marginals at the same time, we can use DP to avoid redundant computation that would be involved if we used variable elimination repeatedly.
- If the underlying undirected graph of the BN is acyclic (i.e. a tree), we can use a local message passing algorithm due to Perl. It is a generalization of the well-known forwards-backwards algorithm for HMMs (chains).

Local Message Passing

- If the BN has undirected cycles (as in the water sprinkler example), local message passing algorithms run the risk of double counting (e.g. the information from S and R flowing into W is not independent, because it came from a common cause, C).
- The most common approach is therefore to convert the BN into a tree, by clustering nodes together, to form what is called a **junction tree**, then running a local message passing algorithm on the tree.
- The running time of the DP algorithm is exponential in the size of the largest cluster (these clusters correspond to the intermediate terms created by variable elimination). The size is called the **induced width** of the graph. Minimizing this is NP hard.

Approximation Algorithms

- Exact inference is still very slow in some practical problems such as multivariate time-series or image analysis due to large induced width.
- Major approximation techniques: Variational methods, Sampling (Monte Carlo) methods, loopy belief propagation

Learning of BN

- The graph topology of BN
- The parameters of each CPD
- Learning structure is much harder than learning parameters
- Learning when some of nodes are hidden or we have missing data, is much harder than when everything is observed.

Known Structure, Full Observability

- Maximize log-likelihood of training data D is sum of terms, one for each node:

$$L = \frac{1}{N} \sum_{i=1}^{n} \sum_{l=1}^{s} \log P(X_i | \mathrm{Pa}(X_i), D_l)$$

- Maximize the contribution of the log-likelihood of each node independently. For discrete variables, we just simply count the observations.

$$\Pr(W = w | S = s, R = r) \approx N(W = w, S = s, R = r) / N(S = s, R = r)$$

Known Structure, Partial Observability

- When some nodes are hidden, we can use EM algorithm to find a locally optimal Maximum Likelihood Estimate of the parameters
- For instance, Welch-Baum algorithm for HMM learning. (see slides of HMM theory)

More Complicated Learning

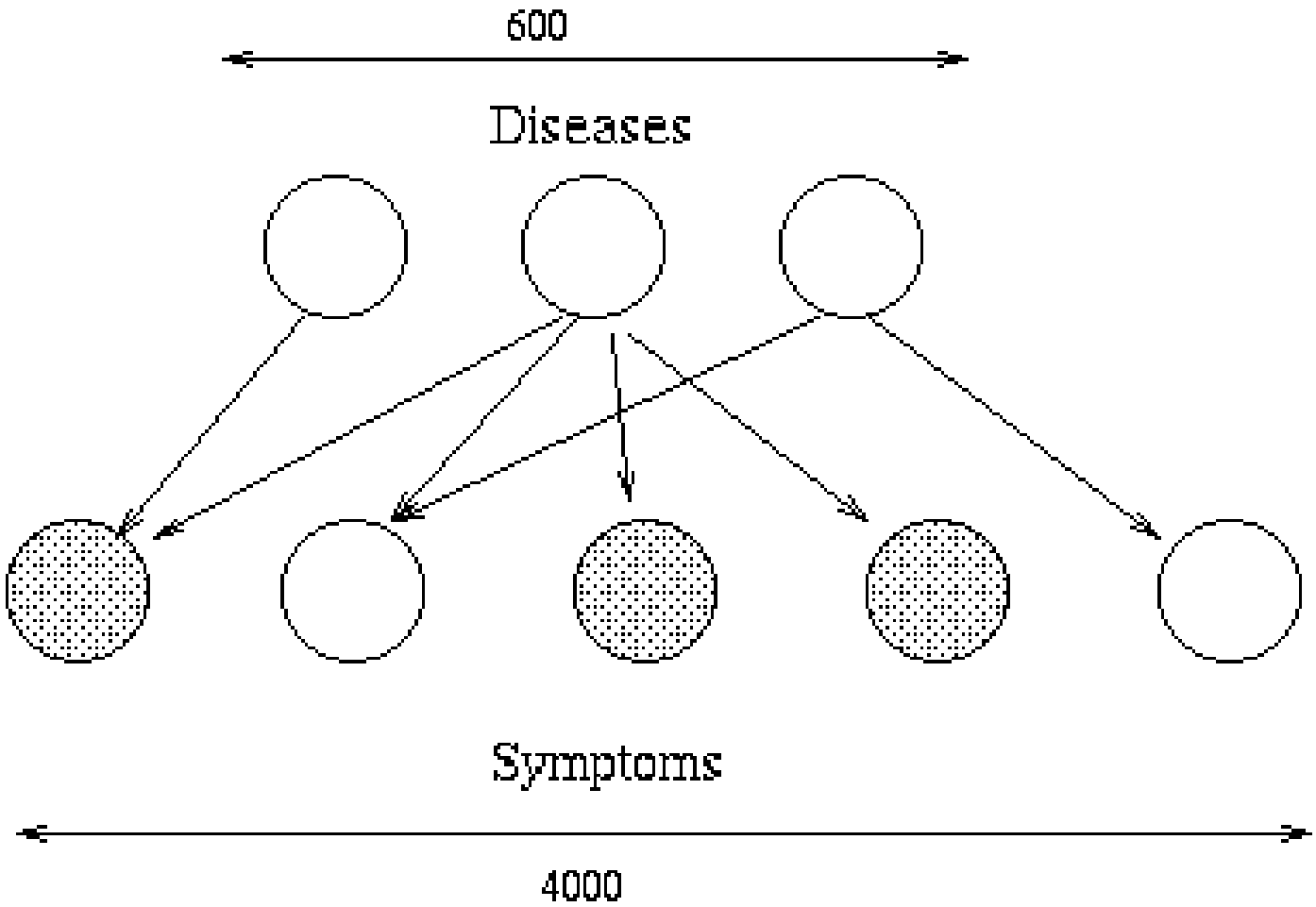
- **Unknown structure, full observability** (model selection, search the best model is NP hard. Number of DAGs on N variables is super-exponential in N)
- **Unknown structure, partial observability** (Search + EM algorithm)
- Further reading on learning:

  (1) W. L. Buntine, Operations for Learning with Graphical Models, J. AI Research, 1994

  (2) D. Heckerman, A tutorial on learning with Bayesian networks, 1996.

General Application Examples

- Microsoft Answer Wizard of Office 95, 97 and over 30 technical support troubleshooters
- Vista system by Eric Horvitz, a decision-theoretic system that has been used at NASA mission control center in Houston for several years. (provide advices on the likelihood of alternative failures of the space shuttle's propulsion systems)
- Quick medical reference model: model the relationship between diseases and symptoms.



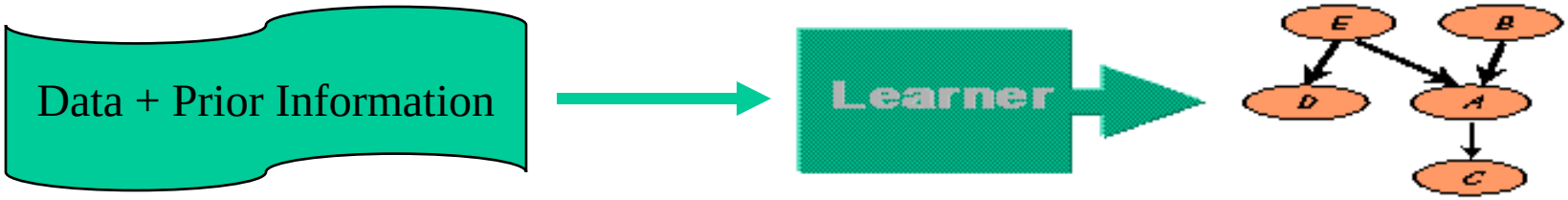
Infer the posterior probability P(disease | symptom)

Discovery of Regulatory Mechanism / Network of Genes

- A long term goal of Systems Biology is to discover the causal processes among genes, proteins, and other molecules in cells
- Can this be done (in part) by using data from high throughput experiments, such as microarrays?
- Clustering can group genes with similar expression patterns, but does not reveal structural relations between genes
- Bayesian Network (BN) is a probabilistic framework capable of learning complex relations between genes

Learning BN from Gene Expression Data

Measured expression level of each gene (discretized) → Random variables Affecting on another

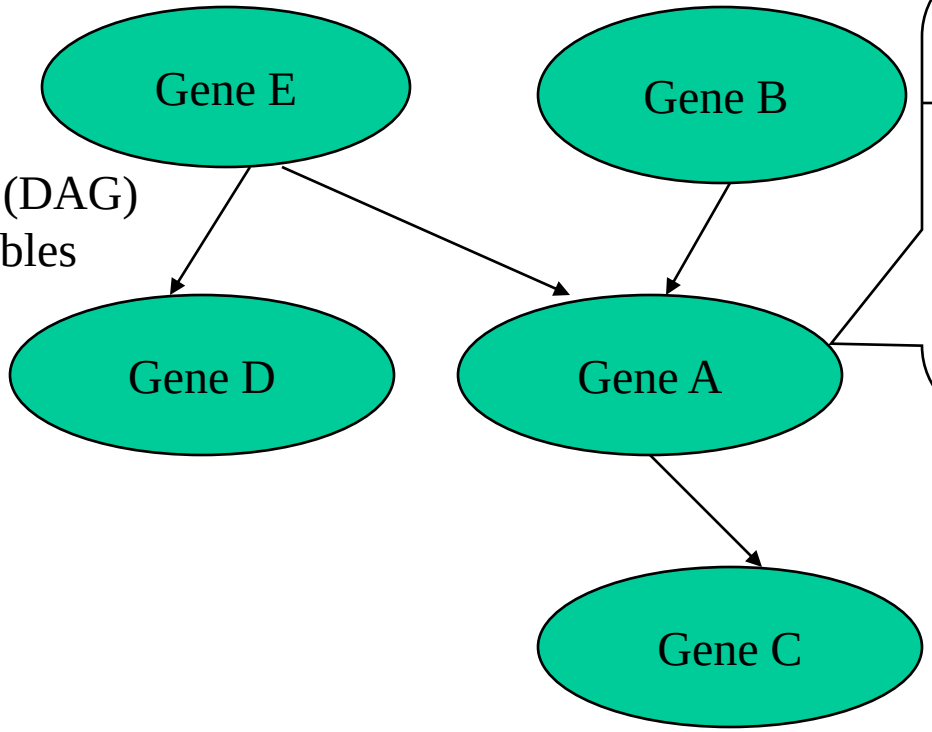


Learn parameters (conditional probabilities) from data
Learn structure (casual relation) from data
Make inference given a learned BN model

N. Friedman, 2005

Gene Bayesian Network

Qualitative Part:
Directed acyclic Graph (DAG)
• Nodes – random variables
•Edges – direct (causal) influence



E	B	P(A|E,B)	
		1	0
0	1	0.9	0.1
1	0	0.2	0.8
1	1	0.9	0.1
0	0	0.01	0.99

Quantitative part
•Local conditional probability

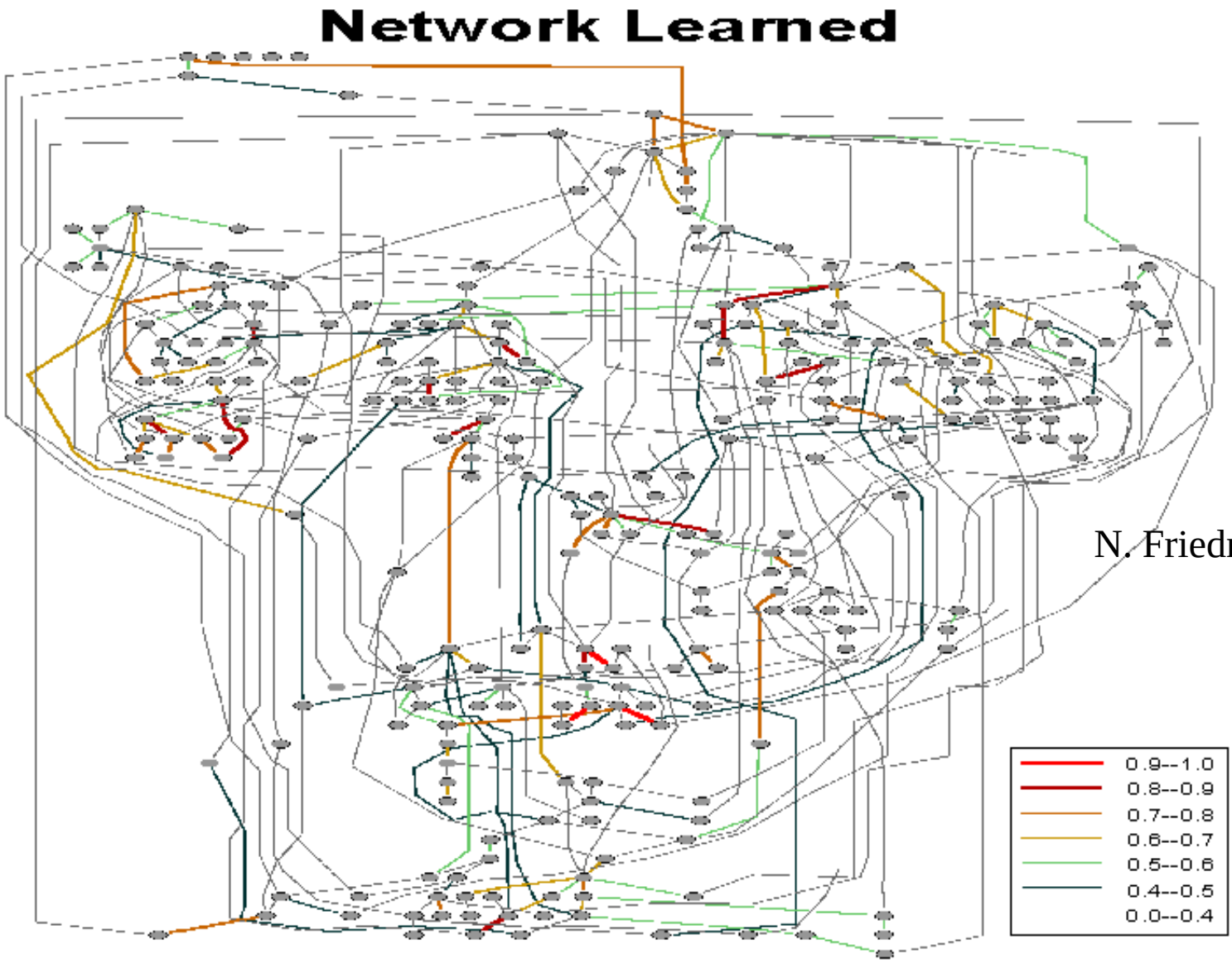
Challenges of Gene Bayesian Network

- Massive number of variables (genes)
- Small number of samples (dozens)
- Sparse networks (only a small number of genes directly affect one another)
- Two crucial aspects: computational complexity and statistical significance of relations in learned models

N. Friedman, 2005

Solutions

- **Sparse candidate algorithm** (by Nir Friedman): Choose a small candidate set for direct influence for each gene. Find optimal BN constrained on candidates. Iteratively improve candidate set.
- **Bootstrap confidence estimate**: use re-sampling to generate perturbations of training data. Use the number of times a relation (or feature) is repeated among networks learned from these datasets to estimate confidence of Bayesian network features.



N. Friedman, 2005

Data: 76 samples of 250 cell-cycle related genes in yeast genome
Discretized into 3 expression levels. Run 100 bootstrap using sparse learning algorithm.
Compute the confidence of features (relations). Most high confident relations make bio-senses.

Important References: BN in Bioinformatics

- N. Friedman. *Inferring cellular networks using probabilistic graphical models*, Science, v303 p799, 6 Feb 2004.
- E. Segal et al.. *Module networks: identifying regulatory modules and their condition-specific regulators from gene expression data*. Nature Genetics, 2003.