Bayesian Network Modelling

with Examples in Genetics and Systems Biology

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What Are Bayesian Networks?

A Graph and a Probability Distribution

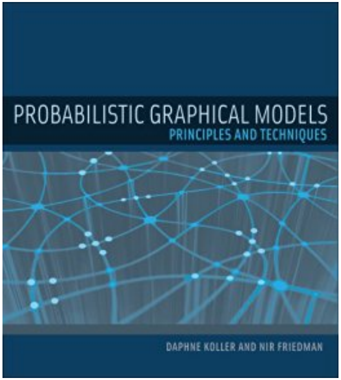
Bayesian networks (BNs) are defined by:

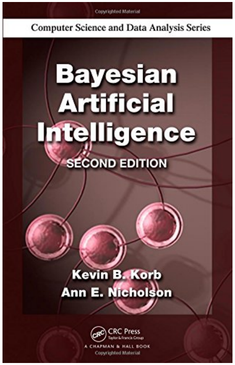
- a network structure, a directed acyclic graph $\mathcal{G} = (\mathbf{V}, A)$, in which each node $v_i \in \mathbf{V}$ corresponds to a random variable X_i;
- a global probability distribution $\mathbf{X}$ with parameters Θ, which can be factorised into smaller local probability distributions according to the arcs $a_{ij} \in A$ present in the graph.

The main role of the network structure is to express the conditional independence relationships among the variables in the model through graphical separation, thus specifying the factorisation of the global distribution:

$$\mathrm{P}(\mathbf{X}) = \prod_{i=1}^{p} \mathrm{P}(X_i \mid \Pi_{X_i}; \Theta_{X_i}) \quad \text{where} \quad \Pi_{X_i} = \{\text{parents of } X_i\}$$

Key Books to Reference


PROBABILISTIC GRAPHICAL MODELS
PRINCIPLES AND TECHNIQUES
DAPHNE KOLLER AND NIR FRIEDMAN

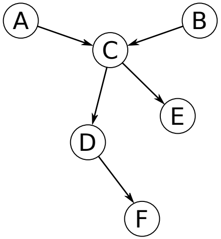

Computer Science and Data Analysis Series
Bayesian Artificial Intelligence
SECOND EDITION
Kevin B. Korb
Ann E. Nicholson
CRC Press

PROBABILISTIC REASONING IN INTELLIGENT SYSTEMS:
Networks of Plausible Inference
Revised & Updated
Judea Pearl
REVISED SECOND PRINTING

(Best perused as ebooks, the Koller & Friedman is $\approx 2{}^1\!/{}_2$ inches thick.)

How the DAG Maps to the Probability Distribution

DAG



$\Longrightarrow$

Graphical separation

$$
\begin{aligned}
&A \perp\!\!\!\perp_G B \\
&A \perp\!\!\!\perp_G D \mid C \\
&B \perp\!\!\!\perp_G D \mid C \\
&A \perp\!\!\!\perp_G E \mid C \\
&B \perp\!\!\!\perp_G E \mid C \\
&D \perp\!\!\!\perp_G E \mid C \\
&C \perp\!\!\!\perp_G F \mid D \\
&\ldots
\end{aligned}
$$

$\Longrightarrow$

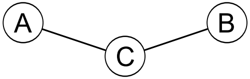
Probabilistic independence

$$
\begin{aligned}
&A \perp\!\!\!\perp_P B \\
&A \perp\!\!\!\perp_P D \mid C \\
&B \perp\!\!\!\perp_P D \mid C \\
&A \perp\!\!\!\perp_P E \mid C \\
&B \perp\!\!\!\perp_P E \mid C \\
&D \perp\!\!\!\perp_P E \mid C \\
&C \perp\!\!\!\perp_P F \mid D \\
&\ldots
\end{aligned}
$$

Formally, the DAG is an independence map of the probability distribution of $\mathbf{X}$, with graphical separation ($\perp\!\!\!\perp_G$) implying probabilistic independence ($\perp\!\!\!\perp_P$).

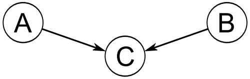
Graphical Separation in DAGs (Fundamental Connections)

separation (undirected graphs)

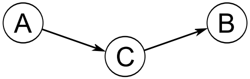


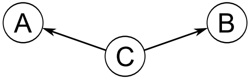
$$\mathbf{A} \perp\!\!\!\perp \mathbf{B} \mid \mathbf{C}$$
$$\mathrm{P}(\mathbf{A}, \mathbf{B}, \mathbf{C}) = \mathrm{P}(\mathbf{A} \mid \mathbf{C})\,\mathrm{P}(\mathbf{B} \mid \mathbf{C})\,\mathrm{P}(\mathbf{C})$$

d-separation (directed acyclic graphs)



$$\mathbf{A} \not\perp\!\!\!\perp \mathbf{B} \mid \mathbf{C}$$
$$\mathrm{P}(\mathbf{A}, \mathbf{B}, \mathbf{C}) = \mathrm{P}(\mathbf{C} \mid \mathbf{A}, \mathbf{B})\,\mathrm{P}(\mathbf{A})\,\mathrm{P}(\mathbf{B})$$





$$\mathbf{A} \perp\!\!\!\perp \mathbf{B} \mid \mathbf{C}$$
$$\begin{aligned}\mathrm{P}(\mathbf{A}, \mathbf{B}, \mathbf{C}) &= \\ &= \mathrm{P}(\mathbf{B} \mid \mathbf{C})\,\mathrm{P}(\mathbf{C} \mid \mathbf{A})\,\mathrm{P}(\mathbf{A}) \\ &= \mathrm{P}(\mathbf{A} \mid \mathbf{C})\,\mathrm{P}(\mathbf{B} \mid \mathbf{C})\,\mathrm{P}(\mathbf{C})\end{aligned}$$

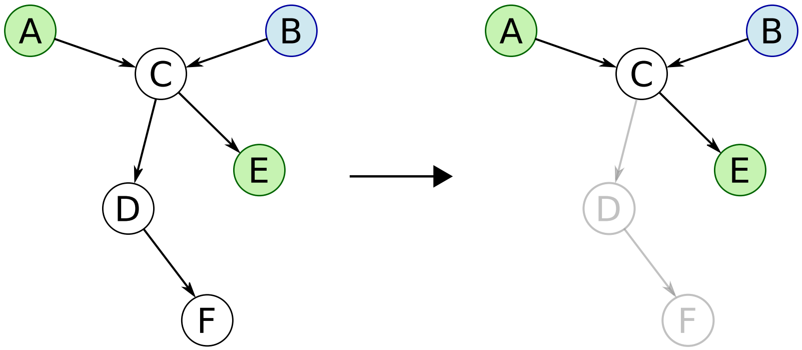
Graphical Separation in DAGs (General Case)

Now, in the general case we can extend the patterns from the fundamental connections and apply them to every possible path between **A** and **B** for a given **C**; this is how d-separation is defined.

> *If* $\mathbf{A}$, $\mathbf{B}$ *and* $\mathbf{C}$ *are three disjoint subsets of nodes in a directed acyclic graph* $\mathcal{G}$, *then* $\mathbf{C}$ *is said to d-separate* $\mathbf{A}$ *from* $\mathbf{B}$, *denoted* $\mathbf{A} \perp\!\!\!\perp_G \mathbf{B} \mid \mathbf{C}$, *if along every path between a node in* $\mathbf{A}$ *and a node in* $\mathbf{B}$ *there is a node* v *satisfying one of the following two conditions:*
>
> 1. v *has converging edges (i.e. there are two edges pointing to* v *from the adjacent nodes in the path) and none of* v *or its descendants (i.e. the nodes that can be reached from* v*) are in* $\mathbf{C}$.
> 2. v *is in* $\mathbf{C}$ *and does not have converging edges.*

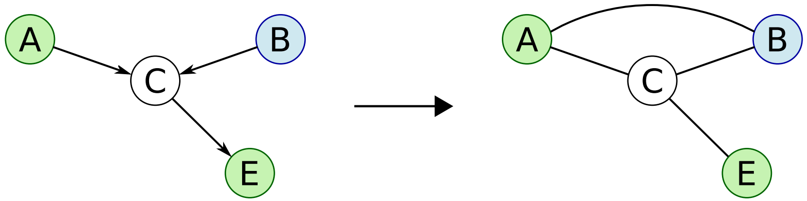
This definition clearly does not provide a computationally feasible approach to assess d-separation; but there are other ways.

A Simple Algorithm to Check D-Separation (I)



Say we want to check whether A and E are d-separated by B. First, we can drop all the nodes that are not ancestors (*i.e.* parents, parents' parents, etc.) of A, E and B since each node only depends on its parents.

A Simple Algorithm to Check D-Separation (II)

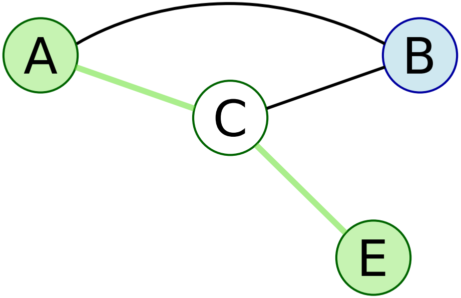


Transform the subgraph into its moral graph by

1. connecting all nodes that have one parent in common; and
2. removing all arc directions to obtain an undirected graph.

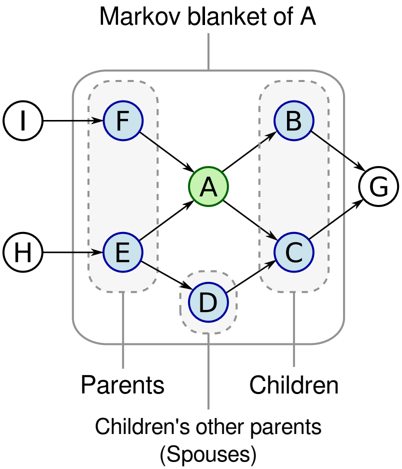
This transformation has the double effect of making the dependence between parents explicit by “marrying” them and of allowing us to use the classic definition of graphical separation.

A Simple Algorithm to Check D-Separation (III)



Finally, we can just perform *e.g.* a depth-first or breadth-first search and see if we can find an open path between A and B, that is, a path that is not blocked by C.

Completely D-Separating: Markov Blankets



We can easily use the DAG to solve the feature selection problem. The set of nodes that graphically isolates a target node from the rest of the DAG is called its Markov blanket and includes:

- its parents;
- its children;
- other nodes sharing a child.

Since $\perp\!\!\!\perp_G$ implies $\perp\!\!\!\perp_P$, we can restrict ourselves to the Markov blanket to perform any kind of inference on the target node, and disregard the rest.

Different DAGs, Same Distribution: Topological Ordering

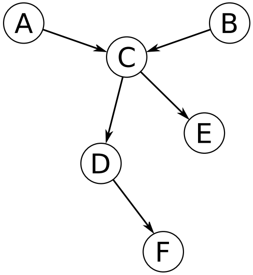
A DAG uniquely identifies a factorisation of $\mathrm{P}(\mathbf{X})$; the converse is not true. Consider again the DAG on the left:

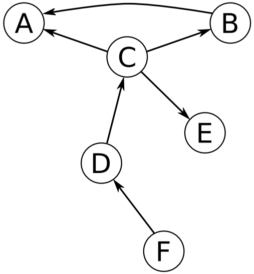
$$\mathrm{P}(\mathbf{X}) = \mathrm{P}(A)\,\mathrm{P}(B)\,\mathrm{P}(C \mid A, B)\,\mathrm{P}(D \mid C)\,\mathrm{P}(E \mid C)\,\mathrm{P}(F \mid D).$$

We can rearrange the dependencies using Bayes theorem to obtain:

$$\mathrm{P}(\mathbf{X}) = \mathrm{P}(A \mid B, C)\,\mathrm{P}(B \mid C)\,\mathrm{P}(C \mid D)\,\mathrm{P}(D \mid F)\,\mathrm{P}(E \mid C)\,\mathrm{P}(F),$$

which gives the DAG on the right, with a different topological ordering.





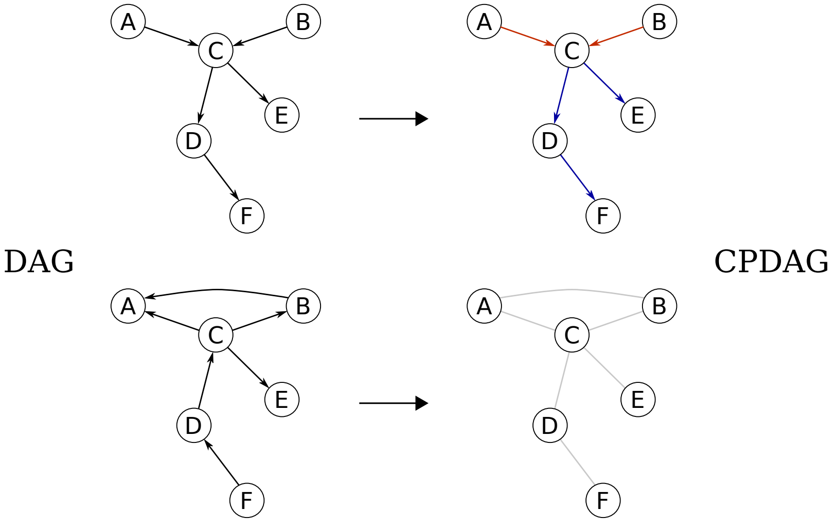
Different DAGs, Same Distribution: Equivalence Classes

On a smaller scale, even keeping the same underlying undirected graph we can reverse a number of arcs without changing the dependence structure of $\mathbf{X}$. Since the triplets $A \rightarrow B \rightarrow C$ and $A \leftarrow B \rightarrow C$ are probabilistically equivalent, we can reverse the directions of their arcs as we like as long as we do not create any new v-structure ($A \rightarrow B \leftarrow C$, with no arc between A and C).

This means that we can group DAGs into equivalence classes that are uniquely identified by the underlying undirected graph and the v-structures. The directions of other arcs can be either:

- uniquely identifiable because one of the directions would introduce cycles or new v-structures in the graph (compelled arcs);
- completely undetermined.

Completed Partially Directed Acyclic Graphs (CPDAGs)



What About the Probability Distributions?

The second component of a BN is the probability distribution $\mathrm{P}(\mathbf{X})$. The choice should such that the BN:

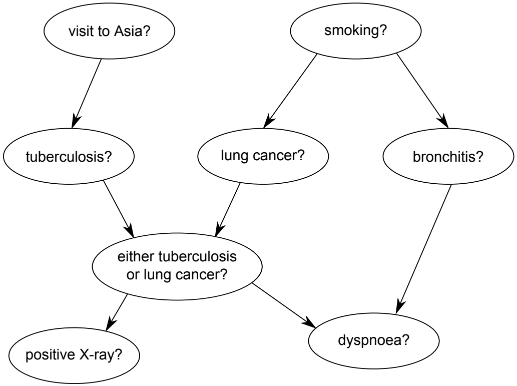
- can be learned efficiently from data;
- is flexible (distributional assumptions should not be too strict);
- is easy to query to perform inference.

The three most common choices in the literature (by far), are:

- discrete BNs (DBNs), in which $\mathbf{X}$ and the $X_i \mid \Pi_{X_i}$ are multinomial;
- Gaussian BNs (GBNs), in which $\mathbf{X}$ is multivariate normal and the $X_i \mid \Pi_{X_i}$ are univariate normal;
- conditional linear Gaussian BNs (CLGBNs), in which $\mathbf{X}$ is a mixture of multivariate normals and the $X_i \mid \Pi_{X_i}$ are either multinomial, univariate normal or mixtures of normals.

It has been proved in the literature that exact inference is possible in these three cases, hence their popularity.

Discrete Bayesian Networks



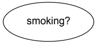
A classic example of DBN is the ASIA network from Lauritzen & Spiegelhalter (1988), which includes a collection of binary variables. It describes a simple diagnostic problem for tuberculosis and lung cancer.

Total parameters of $\mathbf{X}$: $2^8 - 1 = 255$

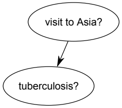
Conditional Probability Tables (CPTs)

visit to Asia?

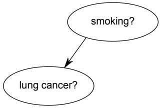
yes	no
0.01	0.99



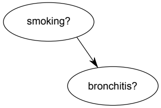
yes	no
0.50	0.50



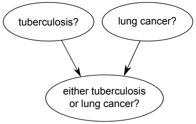
	yes	no
yes	0.05	0.95
no	0.01	0.99



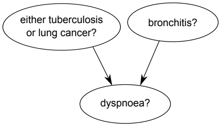
	yes	no
yes	0.10	0.90
no	0.01	0.99



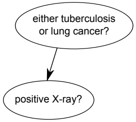
	yes	no
yes	0.60	0.40
no	0.30	0.70



	yes	no
yes:yes	1	0
yes:no	1	0
no:yes	1	0
no:no	0	1



	yes	no
yes:yes	0.90	0.10
yes:no	0.70	0.30
no:yes	0.80	0.20
no:no	0.10	0.90

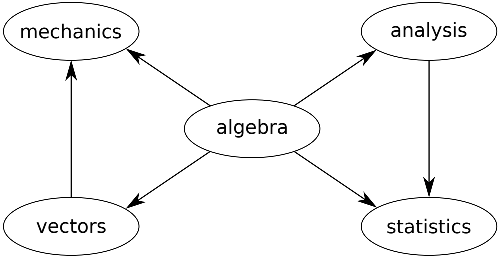


	yes	no
yes	0.98	0.02
no	0.05	0.95

The local distributions $X_i \mid \Pi_{X_i}$ take the form of conditional probability tables for each node given all the configurations of the values of its parents.

Overall parameters of the $X_i \mid \Pi_{X_i}$: 18

Gaussian Bayesian Networks



A classic example of GBN is the MARKS networks from Mardia, Kent & Bibby JM (1979), which describes the relationships between the marks on 5 math-related topics.

Assuming $X \sim N(\boldsymbol{\mu}, \Sigma)$, we can compute $\Omega = \Sigma^{-1}$. Then $\Omega_{ij} = 0$ implies $X_i \perp\!\!\!\perp_P X_j \mid \mathbf{X} \setminus \{X_, X_j\}$. The absence of an arc $X_i \to X_j$ in the DAG implies $X_i \perp\!\!\!\perp_G X_j \mid \mathbf{X} \setminus \{X_, X_j\}$, which in turn implies $X_i \perp\!\!\!\perp_P X_j \mid \mathbf{X} \setminus \{X_, X_j\}$.

Total parameters of $\mathbf{X}$: $5 + 15 = 20$

Partial Correlations and Linear Regressions

The local distributions $X_i \mid \Pi_{X_i}$ take the form of linear regression models with the Π_{X_i} acting as regressors and with independent error terms.

$$\begin{aligned}
\text{ALG} &= 50.60 + \varepsilon_{\text{ALG}} \sim N(0, 112.8) \\
\text{ANL} &= -3.57 + 0.99\text{ALG} + \varepsilon_{\text{ANL}} \sim N(0, 110.25) \\
\text{MECH} &= -12.36 + 0.54\text{ALG} + 0.46\text{VECT} + \varepsilon_{\text{MECH}} \sim N(0, 195.2) \\
\text{STAT} &= -11.19 + 0.76\text{ALG} + 0.31\text{ANL} + \varepsilon_{\text{STAT}} \sim N(0, 158.8) \\
\text{VECT} &= 12.41 + 0.75\text{ALG} + \varepsilon_{\text{VECT}} \sim N(0, 109.8)
\end{aligned}$$

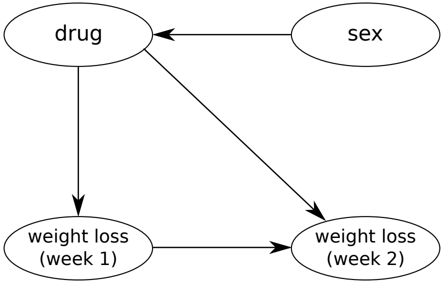
(That is because $\Omega_{ij} \propto \beta_j$ for X_i, so $\beta_j > 0$ if and only if $\Omega_{ij} > 0$. Also $\Omega_{ij} \propto \rho_{ij}$, the partial correlation between X_i and X_j, so we are implicitly assuming all probabilistic dependencies are linear.)

Overall parameters of the $X_i \mid \Pi_{X_i}$: $11 + 5 = 16$

Conditional Linear Gaussian Bayesian Networks

CLGBNs contain both discrete and continuous nodes, and combine DBNs and GBNs as follows to obtain a mixture-of-Gaussians network:

- continuous nodes cannot be parents of discrete nodes;
- the local distribution of each discrete node is a CPT;
- the local distribution of each continuous node is a set of linear regression models, one for each configurations of the discrete parents, with the continuous parents acting as regressors.



One of the classic examples is the RATS' WEIGHTS network from Edwards (1995), which describes weight loss in a drug trial performed on rats.

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Mixtures of Linear Regressions

The resulting local distribution for the first weight loss for drugs D$_1$, D$_2$ and D$_3$ is:

$$\begin{aligned}
\mathsf{W}_{1,\mathrm{D}_1} &= 7 + \varepsilon_{\mathrm{D}_1} \sim N(0, 2.5) \\
\mathsf{W}_{1,\mathrm{D}_2} &= 7.50 + \varepsilon_{\mathrm{D}_2} \sim N(0, 2) \\
\mathsf{W}_{1,\mathrm{D}_3} &= 14.75 + \varepsilon_{\mathrm{D}_3} \sim N(0, 11)
\end{aligned}$$

with just the intercepts since the node has no continuous parents. The local distribution for the second loss is:

$$\begin{aligned}
\mathsf{W}_{2,\mathrm{D}_1} &= 1.02 + 0.89\beta_{\mathrm{W}_1} + \varepsilon_{\mathrm{D}_1} \sim N(0, 3.2) \\
\mathsf{W}_{2,\mathrm{D}_2} &= -1.68 + 1.35\beta_{\mathrm{W}_1} + \varepsilon_{\mathrm{D}_2} \sim N(0, 4) \\
\mathsf{W}_{2,\mathrm{D}_3} &= -1.83 + 0.82\beta_{\mathrm{W}_1} + \varepsilon_{\mathrm{D}_3} \sim N(0, 1.9)
\end{aligned}$$

Overall, they look like random effect models with random intercepts and random slopes.

Case Study:
A Protein Signalling Network

Source and Overview of the Data

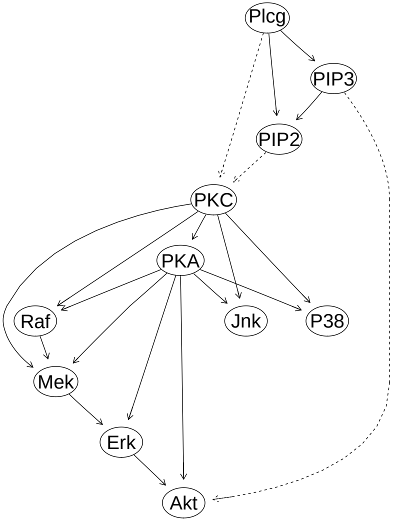
Causal Protein-Signalling Networks Derived from Multiparameter Single Cell Data
Karen Sachs, *et al.*, Science, **308**, 523 (2005);
DOI: 10.1126/science.1105809

That's a landmark paper in applying BNs because it highlights the use of interventional data; and because results are validated using existing literature. The data consist in the 5400 simultaneous measurements of 11 phosphorylated proteins and phospholypids:

- 1800 data subject only to general stimolatory cues, so that the protein signalling paths are active;
- 600 data with with specific stimolatory/inhibitory cues for each of the following 4 proteins: Mek, PIP2, Akt, PKA;
- 1200 data with specific cues for PKA.

The goal of the analysis is to learn what relationships link these 11 proteins, that is, the signalling pathways they are part of.

Analysis and Validated Network



1. Outliers were removed and the data were discretised, since it was impossible to model them with a GBN.

2. A large number of DAGs were learned and averaged to produce a more robust model. The averaged DAG was created using the arcs present in at least 85% of the DAGs.

3. The validity of the averaged BN was evaluated against established signalling pathways from literature.

Bayesian Network Structure Learning

Learning a BN $\mathcal{B} = (\mathcal{G}, \Theta)$ from a data set $\mathcal{D}$ is performed in two steps:

$$\underbrace{\mathrm{P}(\mathcal{B} \mid \mathcal{D}) = \mathrm{P}(\mathcal{G}, \Theta \mid \mathcal{D})}_{\text{learning}} = \underbrace{\mathrm{P}(\mathcal{G} \mid \mathcal{D})}_{\text{structure learning}} \cdot \underbrace{\mathrm{P}(\Theta \mid \mathcal{G}, \mathcal{D})}_{\text{parameter learning}} .$$

In a Bayesian setting structure learning consists in finding the DAG with the best $\mathrm{P}(\mathcal{G} \mid \mathcal{D})$. We can decompose $\mathrm{P}(\mathcal{G} \mid \mathcal{D})$ into

$$\mathrm{P}(\mathcal{G} \mid \mathcal{D}) \propto \mathrm{P}(\mathcal{G})\,\mathrm{P}(\mathcal{D} \mid \mathcal{G}) = \mathrm{P}(\mathcal{G}) \int \mathrm{P}(\mathcal{D} \mid \mathcal{G}, \Theta)\,\mathrm{P}(\Theta \mid \mathcal{G}) d\Theta$$

where $\mathrm{P}(\mathcal{G})$ is the prior distribution over the space of the DAGs and $\mathrm{P}(\mathcal{D} \mid \mathcal{G})$ is the marginal likelihood of the data given $\mathcal{G}$ averaged over all possible parameter sets Θ; and then

$$\mathrm{P}(\mathcal{D} \mid \mathcal{G}) = \prod_{i=1}^{N} \left[\int \mathrm{P}(X_i \mid \Pi_{X_i}, \Theta_{X_i})\,\mathrm{P}(\Theta_{X_i} \mid \Pi_{X_i}) d\Theta_{X_i} \right] .$$

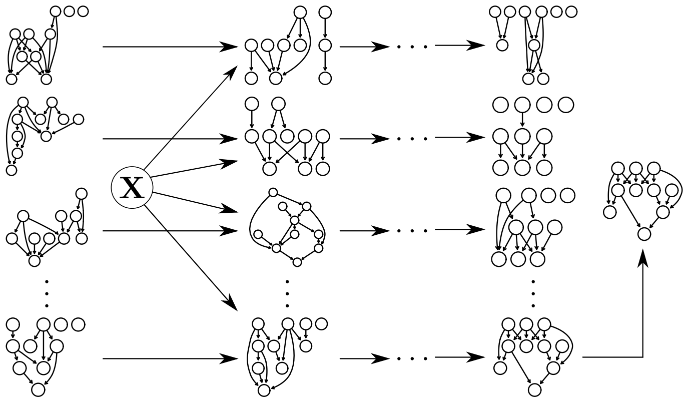
The Hill-Climbing Algorithm

The most common score-based structure learning algorithm, in which we are looking for the DAG that maximises a score such as the posterior $\mathrm{P}(\mathcal{G} \mid \mathcal{D})$ or BIC, is a greedy search such as hill-climbing:

```
1. Choose an initial DAG $\mathcal{G}$, usually (but not necessarily) empty.
2. Compute the score of $\mathcal{G}$, denoted as $Score_{\mathcal{G}} = \mathrm{Score}(\mathcal{G})$.
3. Set $maxscore = Score_{\mathcal{G}}$.
4. Repeat the following steps as long as $maxscore$ increases:
   4.1 for every possible arc addition, deletion or reversal not introducing
       cycles:
       4.1.1 compute the score of the modified DAG $\mathcal{G}^*$, $Score_{\mathcal{G}^*} = \mathrm{Score}(\mathcal{G}^*)$:
       4.1.2 if $Score_{\mathcal{G}^*} > Score_{\mathcal{G}}$, set $\mathcal{G} = \mathcal{G}^*$ and $Score_{\mathcal{G}} = Score_{\mathcal{G}^*}$.
   4.2 update $maxscore$ with the new value of $Score_{\mathcal{G}}$.
5. Return the DAG $\mathcal{G}$.
```

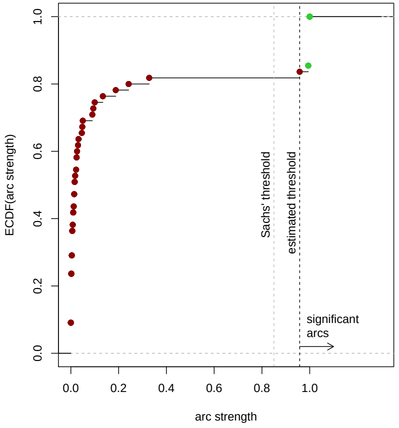
Only one local distribution changes in each step, which makes algorithm computationally efficient and easy to speed up with caching.

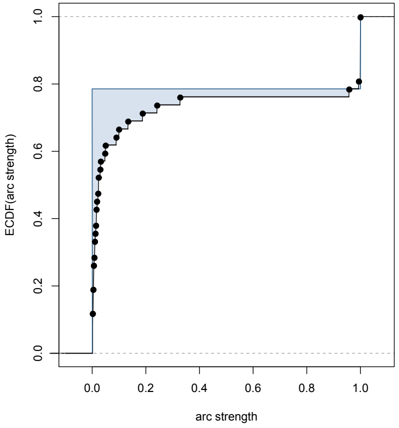
Learning Multiple DAGs from the Data



Searching from different starting points increases our coverage of the space of the possible DAGs; the frequency with which an arc appears is a measure of the strength of the dependence.

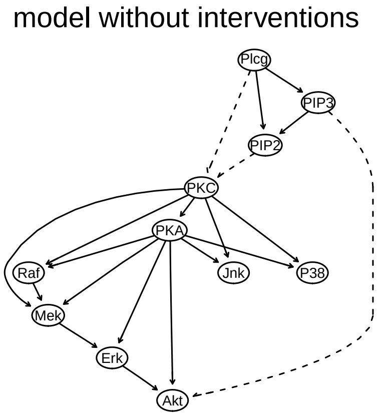
Model Averaging for DAGs

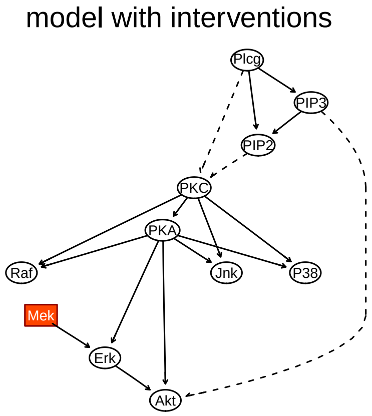




Arcs with significant strength can be identified using a threshold estimated from the data by minimising the distance from the observed ECDF and the ideal, asymptotic one (the blue area in the right panel).

Combining Observational and Interventional Data

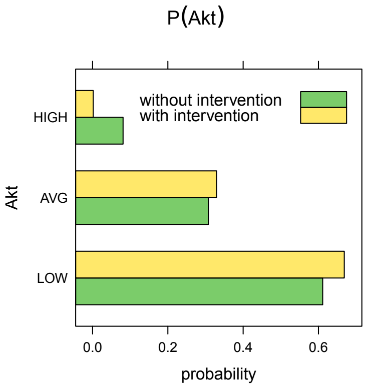


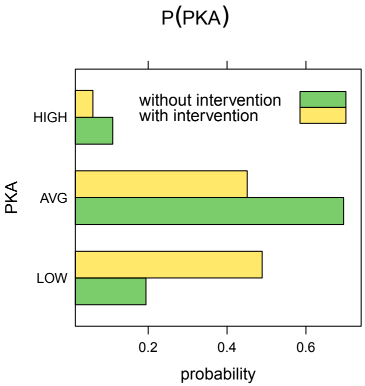


Observations must be scored taking into account the effects of the interventions, which break biological pathways; the overall network score is a mixture of scores adjusted for each experiment.

Using The Protein Network to Plan Experiments

This idea goes by the name of hypothesis generation: using a statistical model to decide which follow-up experiments to perform. BNs are especially easy to use for this because they automate the computation of arbitrary events.





Conditional Probability Queries

DBNs, GBNs, CLGBNs all have exact inference algorithms to compute conditional probabilities for an event given some evidence. However, approximate inference scales better and the same algorithms can be used for all kinds of BNs. An example is likelihood weighting below.

Input: a BN $\mathcal{B} = (\mathcal{G}, \Theta)$, an query $\mathbf{Q} = \mathbf{q}$ and a set of evidence $\mathbf{E}$
Output: an approximate estimate of $\mathrm{P}(\mathbf{Q} \mid \mathbf{E}, G, \Theta)$.

```
1. Order the $X_i$ according to the topological ordering in $\mathcal{G}$.
2. Set $w_{\mathbf{E}} = 0$ and $w_{\mathbf{E},\mathbf{q}} = 0$.
3. For a suitably large number of samples $\mathbf{x} = (x_1, \ldots, x_p)$:
    3.1 generate $x_{(i)}, i = 1, \ldots, p$ from $X_{(i)} \mid \Pi_{X_{(i)}}$ using the values
        $e_1, \ldots, e_k$ specified by the hard evidence $\mathbf{E}$ for $X_{i_1}, \ldots, X_{i_k}$.
    3.2 compute the weight $w_{\mathbf{x}} = \prod \mathrm{P}(X_{i^*} = e_* \mid \Pi_{X_{i^*}})$
    3.3 set $w_{\mathbf{E}} = w_{\mathbf{E}} + w_{\mathbf{x}}$;
    3.4 if $\mathbf{x}$ includes $\mathbf{Q} = \mathbf{q}$ , set $w_{\mathbf{E},\mathbf{q}} = w_{\mathbf{E},\mathbf{q}} + w_{\mathbf{x}}$.
4. Estimate $\mathrm{P}(\mathbf{Q} \mid \mathbf{E}, G, \Theta)$ with $w_{\mathbf{E},\mathbf{q}} / w_{\mathbf{E}}$.
```

Case Study:
Genome-Wide Predictions

MAGIC Populations: Wheat and Rice

Sequence data (*e.g.* SNP markers) is routinely used in statistical genetics to understand the genetic basis of human diseases, and to breed traits of commercial interest in plants and animals. Multiparent (MAGIC) populations are ideal for the latter. Here we consider two:

- A winter wheat population: 721 varieties, 16K markers, 7 traits.
- An indica rice population: 1087 varieties, 4K markers, 10 traits.

Phenotypic traits include flowering time, height, yield, a number of disease scores; and physical and quality traits for grains in rice.
The goal of the analysis is to find key markers controlling the traits; the causal relationships between them; keep a good predictive accuracy.

Genetics Society of America

Multiple Quantitative Trait Analysis Using Bayesian Networks
Marco Scutari, *et al.*, Genetics, **198**, 129–137 (2014);
DOI: 10.1534/genetics.114.165704

Bayesian Networks for Selection and Association Studies

If we have a set of traits and markers for each variety, all we need are the Markov blankets of the traits; most markers are discarded in the process. Using common sense, we can make some assumptions:

- traits can depend on markers, but not vice versa;
- dependencies between traits should follow the order of the respective measurements (*e.g.* longitudinal traits, traits measured before and after harvest, etc.);
- dependencies in multiple kinds of genetic data (*e.g.* SNP + gene expression or SNPs + methylation) should follow the central dogma of molecular biology.

Assumptions on the direction of the dependencies allow to reduce Markov blankets learning to learning the parents and the children of each trait, which is a much simpler task.

Parametric Assumptions

In the spirit of classic additive genetics models, we use a Gaussian BN. Then the local distribution of each trait T_i is a linear regression model

$$\begin{aligned} T_i &= \boldsymbol{\mu}_{T_i} + \Pi_{T_i}\boldsymbol{\beta}_{T_i} + \boldsymbol{\varepsilon}_{T_i} \\ &= \boldsymbol{\mu}_{T_i} + \underbrace{T_j\beta_{T_j} + \ldots + T_k\beta_{T_k}}_{\text{traits}} + \underbrace{G_l\beta_{G_l} + \ldots + G_m\beta_{G_m}}_{\text{markers}} + \boldsymbol{\varepsilon}_{T_i} \end{aligned}$$

and the local distribution of each marker G_i is likewise

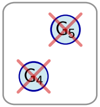
$$\begin{aligned} G_i &= \boldsymbol{\mu}_{G_i} + \Pi_{G_i}\boldsymbol{\beta}_{G_i} + \boldsymbol{\varepsilon}_{G_i} = \\ &= \boldsymbol{\mu}_{G_i} + \underbrace{G_l\beta_{G_l} + \ldots + G_m\beta_{G_m}}_{\text{markers}} + \boldsymbol{\varepsilon}_{G_i} \end{aligned}$$

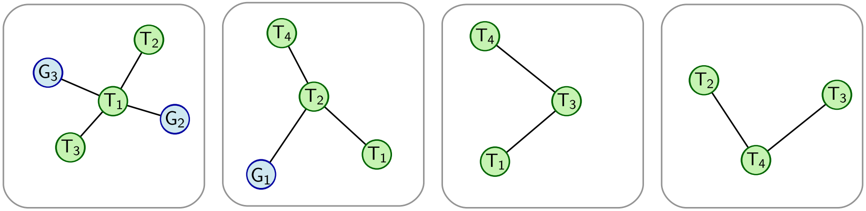
in which the regressors (Π_{T_i} or Π_{G_i}) are treated as fixed effects. Π_{T_i} can be interpreted as causal effects for the traits, Π_{G_i} as markers being in linkage disequilibrium with each other.

Learning the Bayesian Network (I)

1. Feature Selection.
   1.1 Independently learn the parents and the children of each trait with the SI-HITON-PC algorithm; children can only be other traits, parents are mostly markers, spouses can be either. Both are selected using the exact Student's t test for partial correlations.
   1.2 Drop all the markers that are not parents of any trait.

Redundant markers that are not in the Markov blanket of any trait

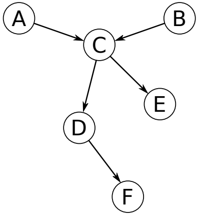




Parents and children of T_1 Parents and children of T_2 Parents and children of T_3 Parents and children of T_4

Constraint-Based Structure Learning Algorithms

CPDAG



$\Longleftarrow$

Graphical separation

$A \perp\!\!\!\perp_G B$
$A \perp\!\!\!\perp_G D \mid C$
$B \perp\!\!\!\perp_G D \mid C$
$A \perp\!\!\!\perp_G E \mid C$
$B \perp\!\!\!\perp_G E \mid C$
$D \perp\!\!\!\perp_G E \mid C$
$C \perp\!\!\!\perp_G F \mid D$
$\ldots$

$\Longleftarrow$

Conditional independence tests

$p_{A \perp\!\!\!\perp B} < \alpha$
$p_{A \perp\!\!\!\perp E} < \alpha$
$\vdots$
$p_{A \perp\!\!\!\perp E|C} < \alpha$
$p_{B \perp\!\!\!\perp E|D} < \alpha$
$p_{A \perp\!\!\!\perp B|C} > \alpha$
$p_{E \perp\!\!\!\perp F|D} < \alpha$
$\vdots$
$p_{F \perp\!\!\!\perp E|CD}$

The mapping between edges and conditional independence relationships lies at the core of BNs; therefore, one way to learn the structure of a BN is to check which such relationships hold using a suitable conditional independence test. Such an approach results in a set of conditional independence constraints that identify a single equivalence class.

The Semi-Interleaved HITON-PC Algorithm

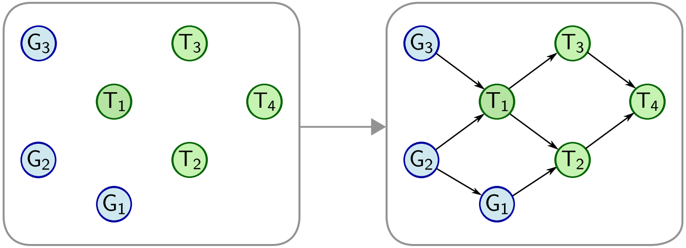
Input: each trait T_i in turn, other traits (T_j) and all markers (G_l), a significance threshold α.
Output: the set $\mathbf{CPC}$ parents and children of T_i in the BN.

```
1. Perform a marginal independence test between $T_i$ and each $T_j$ ($T_i \perp\!\!\!\perp T_j$)
   and $G_l$ ($T_i \perp\!\!\!\perp G_l$) in turn.
2. Discard all $T_j$ and $G_l$ whose p-values are greater than $\alpha$.
3. Set $\mathbf{CPC} = \{\varnothing\}$.
4. For each the $T_j$ and $G_l$ in order of increasing p-value:
    4.1 Perform a conditional independence test between $T_i$ and $T_j/G_l$
        conditional on all possible subsets $\mathbf{Z}$ of the current $\mathbf{CPC}$
        ($T_i \perp\!\!\!\perp T_j \mid \mathbf{Z} \subseteq \mathbf{CPC}$ or $T_i \perp\!\!\!\perp G_l \mid \mathbf{Z} \subseteq \mathbf{CPC}$).
    4.2 If the p-value is smaller than $\alpha$ for all subsets then
        $\mathbf{CPC} = \mathbf{CPC} \cup \{T_j\}$ or $\mathbf{CPC} = \mathbf{CPC} \cup \{G_l\}$.
```

NOTE: the algorithm is defined for a generic independence test, you can plug in any test that is appropriate for the data.

Learning the Bayesian Network (II)

2. Structure Learning. Learn the structure of the network from the nodes selected in the previous step, setting the directions of the arcs according to the assumptions above. The optimal structure can be identified with a suitable goodness-of-fit criterion such as BIC. This follows the spirit of other hybrid approaches that have shown to be well-performing in literature.

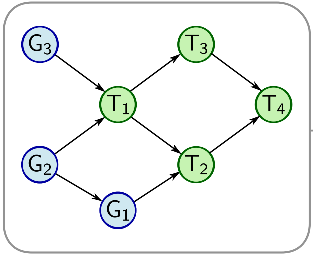


Empty network

Learned network

Learning the Bayesian Network (III)

3. Parameter Learning. Learn the parameters: each local distribution is a linear regression and the global distribution is a hierarchical linear model. Typically least squares works well because SI-HITON-PC selects sets of weakly correlated parents; ridge regression can be used otherwise.

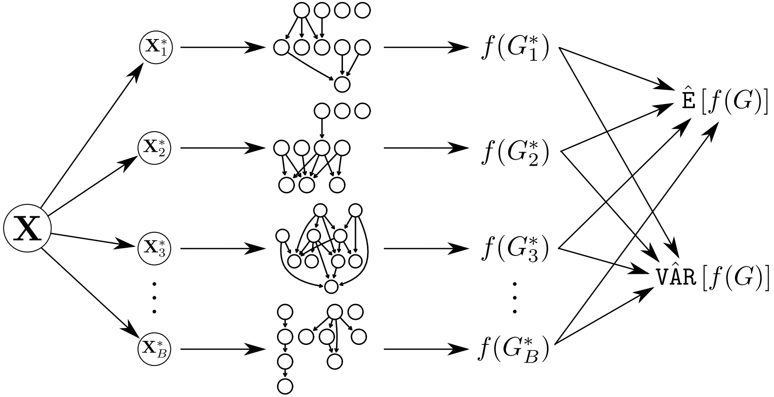


Learned network

$$
\begin{aligned}
G_1 &= \mu_{G_1} + G_2\beta_{G_2} + \varepsilon_{G_1}\\
G_2 &= \mu_{G_2} + \varepsilon_{G_2}\\
G_3 &= \mu_{G_3} + \varepsilon_{G_3}\\
T_1 &= \mu_{T_1} + G_2\beta_{G_2} + G_3\beta_{G_3} + \varepsilon_{T_1}\\
T_2 &= \mu_{T_2} + T_1\beta_{T_1} + G_1\beta_{G_1} + \varepsilon_{T_2}\\
T_3 &= \mu_{T_3} + T_1\beta_{T_1} + \varepsilon_{T_3}\\
T_4 &= \mu_{T_4} + T_2\beta_{T_2} + T_3\beta_{T_3} + \varepsilon_{T_4}
\end{aligned}
$$

Local distributions

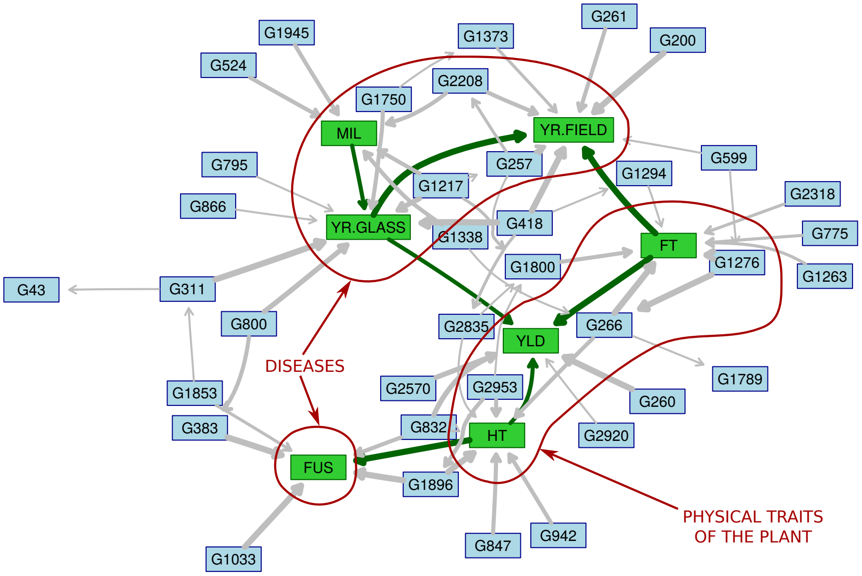
Model Averaging and Assessing Predictive Accuracy



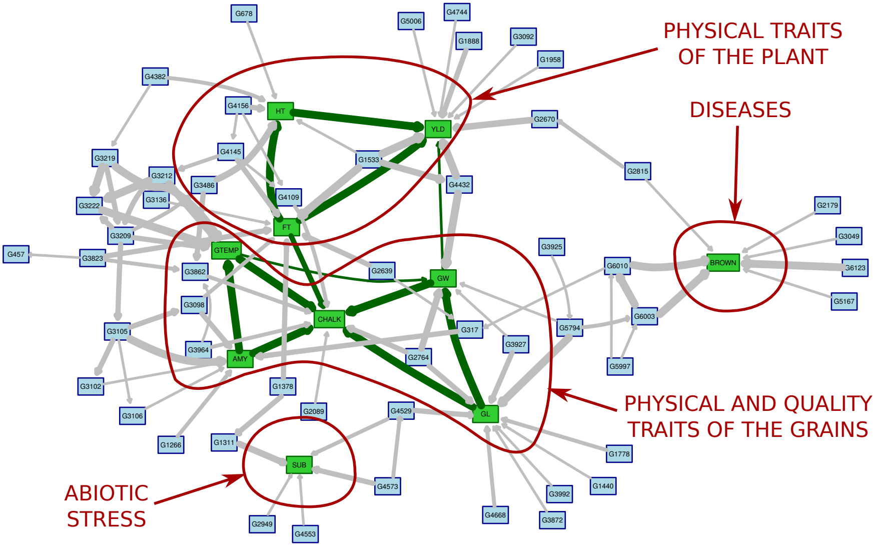
We perform all the above in 10 runs of 10-fold cross-validation to

- assess predictive accuracy with *e.g.* predictive correlation;
- obtain a set of DAGs to produce an averaged, de-noised consensus DAG with model averaging.

WHEAT: a Bayesian Network (44 nodes, 66 arcs)



RICE: a Bayesian Network (64 nodes, 102 arcs)



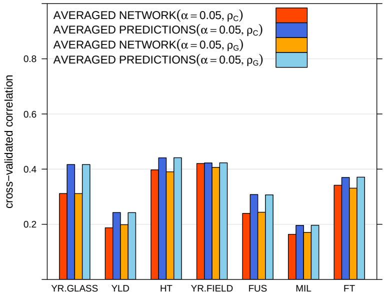
Predicting Traits for New Individuals

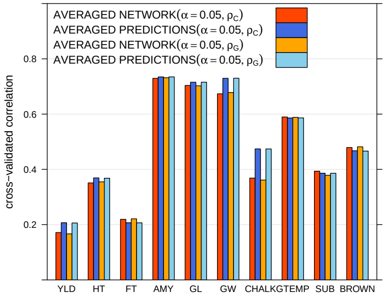
We can predict the traits:

1. from the averaged consensus network;
2. from each of the 10×10 networks we learn during cross-validation, and average the predictions for each new individual and trait.

Option 2. almost always provides better accuracy than option 1., especially for polygenic traits; 10×10 networks can cover the genome much better, and we have to learn them anyway.

So: averaged network for interpretation, ensemble of networks for predictions.



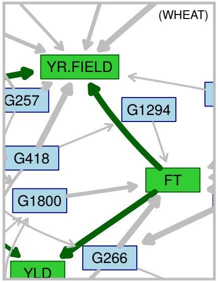


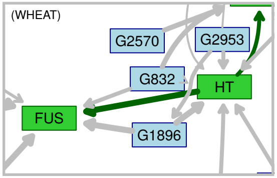
Causal Relationships Between Traits

One of the key properties of BNs is their ability of capturing the direction of the causal relationships among traits in the absence of latent confounders (the experimental design behind the data collection should take care of a number of them).

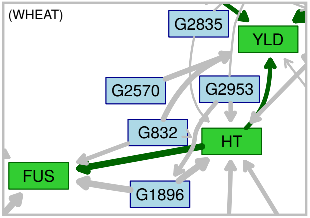
It works because each trait will have at least one incoming arc from the markers, say $G_l \rightarrow T_j$, and then $(G_l \rightarrow) T_j \leftarrow T_k$ and $(G_l \rightarrow) T_j \rightarrow T_k$ are not probabilistically equivalent. So the network can

- suggest the direction of novel relationships;
- confirm the direction of known relationships, troubleshooting the experimental design and data collection.





Spotting Confounding Effects

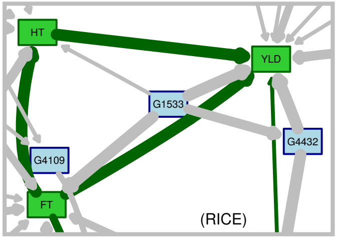


Traits can interact in complex ways that may not be obvious when they are studied individually, but that can be explained by considering neighbouring variables in the network.
An example: in the WHEAT data, the difference in the mean YLD between the bottom and top quartiles of the FUS disease scores is +0.08.

So apparently FUS is associated with increased YLD! What we are actually measuring is the confounding effect of HT (FUS $\leftarrow$ HT $\rightarrow$ YLD); conditional on each quartile of HT, FUS has a negative effect on YLD ranging from −0.04 to −0.06. This is reassuring since it is known that susceptibility to fusarium is positively related to HT, which in turn affects YLD.

Disentangling Pleiotropic Effects

When a marker is shown to be associated to multiple traits, we should separate its direct and indirect effects on each of the traits. (Especially if the traits themselves are linked!) Take for example G1533 in the RICE data set: it is putative causal for YLD, HT and FT.



- The difference in mean between the two homozygotes is +4.5cm in HT, +2.28 weeks in FT and +0.28 t/ha in YLD.
- Controlling for YLD and FT, the difference for HT halves (+2.1cm);
- Controlling for YLD and HT, the difference for FT is about the same (+2.3 weeks);
- Controlling for HT and FT the difference for YLD halves (+0.16 t/ha).

So, the model suggests the marker is causal for FT and that the effect on the other traits is partly indirect. This agrees from the p-values from an independent association study (FT: 5.87e-28 $<$ YLD: 4.18e-10, HT:1e-11).

Identifying Causal (Sets of) Markers

Compared to additive regression models, BNs make it trivial to compute:

- posterior probability of association for a marker and a trait after all the other markers and traits are taken into account to rule out linkage disequilibrium, confounding, pleiotropy, etc.;
- expected allele counts n_{LOW} and n_{HIGH} for a marker and low/high values of a set of traits ($n_{\mathrm{LOW}} - n_{\mathrm{HIGH}}$ should be large if the marker tags a causal variant and thus should show which allele is favourable).

	G1778	G3872	G4529	G1440	G5794
SMALL GRAINS	0.00	0.78	0.29	0.16	0.74
LARGE GRAINS	2.00	0.47	0.63	0.35	0.12
	G4668	G2764	G3927	G3992	G4432
SMALL GRAINS	0.24	0.29	0.18	0.09	0.00
LARGE GRAINS	0.17	0.00	0.62	0.29	0.82

SMALL GRAINS = bottom 10% GL, bottom 10% GW in the RICE data.
LARGE GRAINS = top 10% GL, top 10% GW.

Conclusions

Conclusions and Remarks

- BNs provide an intuitive representation of the relationships linking heterogeneous sets of variables, which we can use for qualitative and causal reasoning.
- We can learn BNs from data while including prior knowledge as needed to improve the quality of the model.
- BNs subsume a large number of probabilistic models and thus can readily incorporate other techniques from statistics and computer science (via information theory).
- For most tasks we can start just reusing state-of-the-art, general purpose algorithms.
- Once learned, BNs provide a flexible tool for inference, while maintaining good predictive power.
- Markov blankets are a valuable tool for feature selection, and make it possible to learn just part of the BN depending on the goals of the analysis.

That's all, Thanks!