A causal gene network with genetic variations incorporating biological knowledge and latent variables

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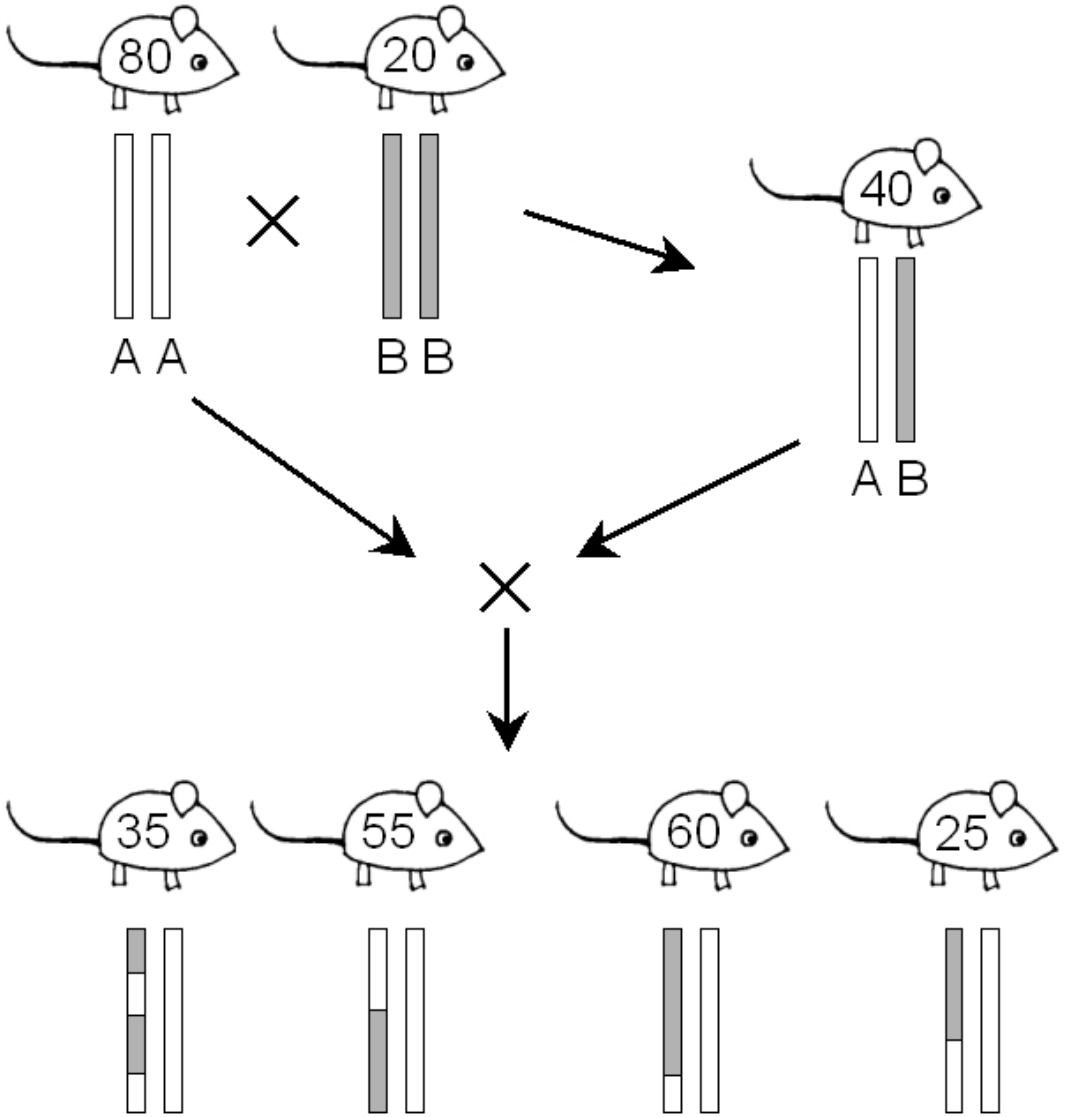
Experimental Cross Study



[Broman, K. W (2001) Lab Animal.]

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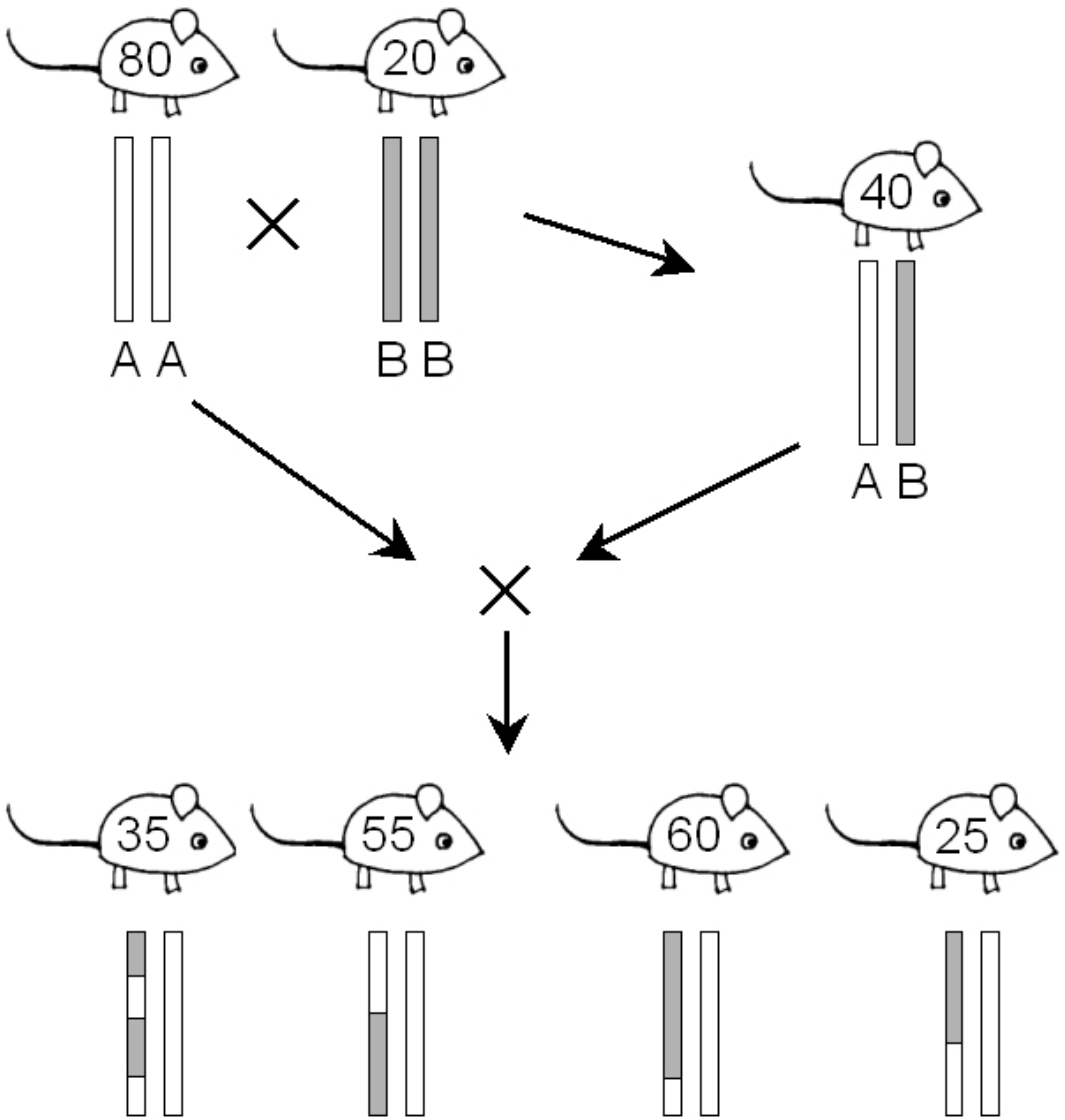

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$\Rightarrow$ Genotypes
Gene expressions
Phenotypes of interest

Outline

1. Bayesian network with genetic variations and biological knowledge
   - Background
   - Encoding of biological knowledge
   - Model (QTLnet-prior)
   - Implementation
   - Simulations
   - Yeast cell cycle analysis
2. A genetic network with latent variables
   - Motivation for latent variables
   - Introduction of ancestral graph
   - Model
   - Property and Theorems
   - Algorithm - MCMC
   - Simulations
   - Conclusion
3. Future Research Plan

I. A Bayesian network with genetic variations and biological knowledge

Background

A Bayesian Network is a probabilistic graphical model whose conditional independence is represented by a directed acyclic graph (DAG), G.

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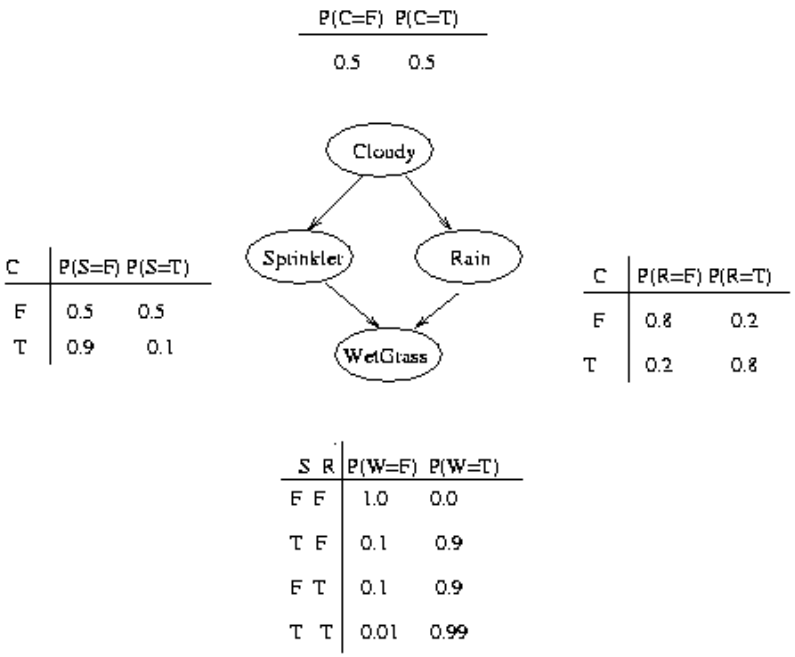

picture from `http://www.cs.ubc.ca/~murphyk/Bayes/bnintro.html`

u $\longrightarrow$ **v**

technical definition: Y_v is conditionally dependent on Y_u

interpretation: Y_v is causally dependent on Y_u.

Properties of Bayesian network

Local directed Markov property Each variable is independent of its nondescendant variables conditional on its parent variables.

$$Y_t \perp Y_{V \setminus de(t)} | Y_{pa(t)} \quad \text{for all } t \in V$$

where $de(t)$ is the set of descendants of t, $pa(t)$ is the set of parents of t, V is the set of all nodes in a DAG G, and $Y_{pa(t)} = \{Y_i : i \in pa(t)\}$.

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Factorization theorem.

$$\begin{aligned} P(Y_1, \ldots, Y_T) &= \prod_{t=1}^{T} P(Y_t | Y_{t-1}, \ldots, Y_1) \\ &= \prod_{t=1}^{T} P(Y_t | Y_{pa(t)}) \end{aligned}$$

Previous Work

- Friedman et al. (2000): a Bayesian network from microarray data with time-series measurements
- Chaibub Neto et al. (2010): a Bayesian network of phenotypes and causal QTLs
- Werhli and Husmeier (2007): a Bayesian network of phenotypes adjusted by prior Biological knowledge
- Zhu et al. (2008): Incorporate genetic variation and biological knowledge. But, network is constructed by piecewise merging.

Likelihood equivalence

Network Structure	Joint Likelihood
$G_Y^1 = Y1 \rightarrow Y_2 \rightarrow Y_3$	$P(Y_3\|Y_2)P(Y_2\|Y_1)P(Y_1) = P(Y_3\|Y_2)P(Y_2, Y_1)$
$G_Y^2 = Y1 \rightarrow Y_2 \leftarrow Y_3$	$P(Y_2\|Y_3, Y_1)P(Y_1)P(Y_3)$
$G_Y^3 = Y1 \leftarrow Y_2 \rightarrow Y_3$	$P(Y_2)P(Y_3\|Y_2)P(Y_1\|Y_2) = P(Y_3\|Y_2)P(Y_2, Y_1)$

G_Y^1 and G_Y^3 are likelihood equivalent.

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causal QTL

Phenotypes are causally dependent on QTLs.

1. In Biology, genotypes influence phenotypes, not the other way. $Q \rightarrow Y$.
2. Alleles are randomized during meiosis.

Extended Network Structure	Joint Likelihood
$G^1 = Q \rightarrow Y1 \rightarrow Y_2 \rightarrow Y_3$	$P(Y_3\|Y_2)P(Y_2\|Y_1)P(Y_1\|Q)P(Q)$
$G^3 = Q \rightarrow Y1 \leftarrow Y_2 \rightarrow Y_3$	$P(Y_2)P(Y_3\|Y_2)P(Y_1\|Y_2,Q)P(Q)$

Adding QTL can distinguish G^1 and G^3 by likelihoods.

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Biological knowledge

If $P(u \rightarrow v) > P(u \leftarrow v)$ by prior biological knowledge,

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and $P(Y|u \rightarrow v) = P(Y|u \leftarrow v)$,

Biological knowledge

If $P(u \rightarrow v) > P(u \leftarrow v)$ by prior biological knowledge,
and $P(Y|u \rightarrow v) = P(Y|u \leftarrow v)$,
then posterior $P(u \rightarrow v|Y) > P(u \leftarrow v|Y)$.

- Transcription factor binding
- Protein-protein interaction

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Encoding of Biological Knowledge, B

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Transcription factor and DNA binding Suppose we have a p-value about whether a transcription factor binds to a certain DNA location. As in Bernard and Hartemink (2005), we assume

$$P_\lambda(P_{ij} = p | G(i,j) = 1) = \frac{\lambda e^{-\lambda p}}{1 - e^{-\lambda}}$$
$$P_\lambda(P_{ij} = p | G(i,j) = 0) = 1.$$

We assume $P(G_{i,j} = 1) = P(G_{i,j} = 0) = 1/2$. Then, the presence of an edge after observing p-value is

$$P(G(i,j) = 1 | P_{ij} = p) = \frac{1}{\lambda_H - \lambda_L} \int_{\lambda_L}^{\lambda_H} \frac{\lambda e^{-\lambda p}}{\lambda e^{-\lambda p} + (1 - e^{-\lambda})} d\lambda$$

$B(i,j) := P(G(i,j) = 1 | P_{ij} = p)$.

Encoding protein-protein interaction A Bayes classifier by Jansen et al. (2003) to combine heterogeneous interaction data.

$$O_{posterior} = \frac{P(pos|f_1, \ldots, f_L)}{P(neg|f_1, \ldots, f_L)} = O_{prior} \times LR$$
$$= \frac{P(pos)}{P(neg)} \times \frac{P(f_1, \ldots, f_L|pos)}{P(f_1, \ldots, f_L|neg)}.$$

$P(f_1, \ldots, f_L|pos)$ is obtained in the positive gold standard.

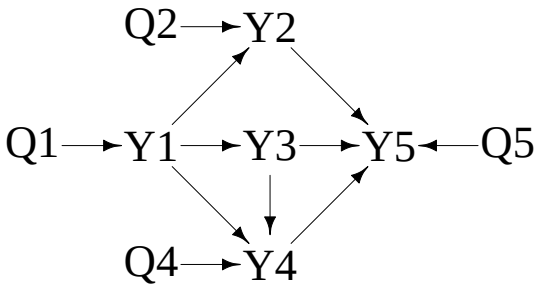
$$B(i,j) = B(j,i) := \frac{O_{posterior}}{1 + O_{posterior}} = P(pos|f_1, \ldots, f_L).$$

Our Model - QTLnet-prior

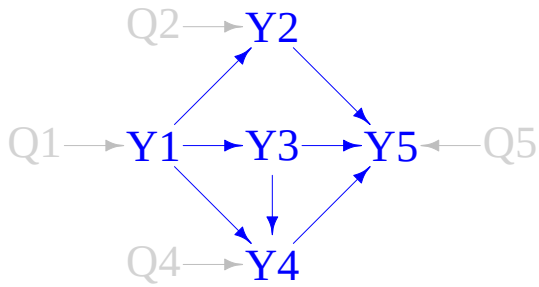
We incorporate both causal QTLs and biological knowledge to infer a Bayesian network of phenotypes.

$$
\begin{aligned}
P(G, W|Y, X, B) &\propto P(Y|G, W, X, B)P(G, W|X, B) \\
&= P(Y|G, X)P(G_Y, W|X, B)P(G_{Q\to Y}|X, B) \\
&= P(Y|G, X)P(G_Y, W|B)P(G_{Q\to Y}|X) \\
&= P(Y|G, X)P(G_Y|W, B)P(W|B)P(G_{Q\to Y}|X)
\end{aligned}
$$

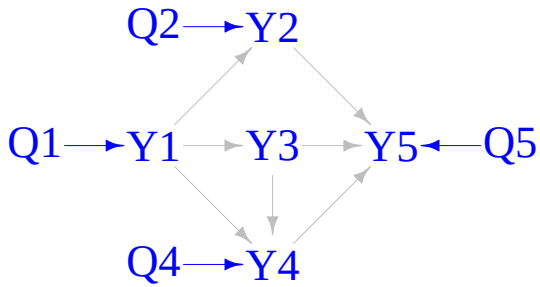
G	a Bayesian network of phenotypes and causal QTLs
G_Y	a subgraph of G composed of phenotype nodes and edges between phenotypes
$G_{Q\to Y}$	a subgraph of G composed of phenotypes and causal QTL nodes and edges from QTL to phenotypes
B	a matrix of biological knowledge
W	weight of biological knowledge
Y	expression data
X	genetic variation information


Q2
Y2
Q1
Y1
Y3
Y5
Q5
Q4
Y4

G


Q2
Y2
Q1
Y1
Y3
Y5
Q5
Q4
Y4

G_Y


Q2
Y2
Q1
Y1
Y3
Y5
Q5
Q4
Y4

$G_{Q \to Y}$

A Bayesian network of phenotypes with causal QTLS, $P(Y|G, X)$

We assume the following family of distribution for phenotypes by Chibub Neto et. al (2010)

$$y_{ti} = \mu^*_{ti} + \sum_{v \in pa(t)} \beta_{tv} y_{vi} + \epsilon_{ti}, \quad \epsilon_{ti} \sim N(0, \sigma^2_t)$$

where $\mu^*_{ti} = \mu_t + X_i \; diag(\gamma_t) \; \theta_t$, μ_t is the overall mean for a trait t,
θ_t is a column vector of all genetic effects,
X_i is a row vector for individual i from X,
β_{tv} is the partial regression coefficients relating phenotype t with phenotype v,
ϵ_{ti} is the associated independent normal error term.

Joint likelihood is obtained by multiplying all the likelihoods for all traits by factorization theorem.
Marginal likelihood is

$$P(Y|G, X) = \int P(Y|G, X, \theta_G) P(\theta_G|G) d\theta_G.$$

Prior on phenotype network structures, $P(G_Y|B, W)$

Assume a Gibbs distribution for the network structure to integrate biological knowledge from Werhli and Husmeier (2007).

$$P(G_Y|B, W) = \frac{\exp(-W\mathcal{E}(G_Y))}{Z(W)}, \quad G_Y \in \mathcal{DAG}$$

$$\text{where } \mathcal{E}(G_Y) = \sum_{i,j=1}^{T} |B(i,j) - G_Y(i,j)|.$$

where B is an encoding of biological knowledge ranging from 0 to 1 and G_Y is an adjacency matrix. $G_Y(i,j) = 1$ means the presence of the directed edge from node i to j.
W controls the contribution of biological knowledge.

- $W \to \infty$: prior on network structures peaks at the biological knowledge
- $W \to 0$: influence of knowledge gets negligible. Uniform distribution

Prior on biological knowledge weights, $P(W|B)$ and Prior on genetic architectures, $P(G_{Q \rightarrow Y})$

$$P(W|B) \sim \exp(-W)$$
$$P(G_{Q \rightarrow Y}) \sim \textit{Uniform}$$

Markov Chain Monte Carlo Sampling

1. Sample a new network structure of phenotypes G_Y^{new} from a network structure proposal distribution $R(G_Y^{new} | G_Y^{old})$.

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3. Accept the new extended network structure G^{new} composed of G_Y^{new} and $G_{Q\rightarrow Y}^{new}$ given the biological knowledge weights W with a probability $A_G = \min\{1, \frac{P(Y|G^{new},X)P(G_Y^{new}|B,W)P(G_{Q\rightarrow Y}^{new})}{P(Y|G^{old},X)P(G_Y^{old}|B,W)P(G_{Q\rightarrow Y}^{old})} \frac{R(G_Y^{old}|G_Y^{new})R(G_{Q\rightarrow Y}^{old}|G_{Q\rightarrow Y}^{new})}{R(G_Y^{new}|G_Y^{old})R(G_{Q\rightarrow Y}^{new}|G_{Q\rightarrow Y}^{old})}\}$.

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4. For each biological knowledge k,
   1. Sample a new W_k^{new} of biological knowledge weight from a proposal distribution, $R(W_k^{new}|W_k^{old})$.
   2. Accept the new biological weight W_k^{new} given phenotype network G_Y with a probability
   $$A_{W_k} = \min\{1, \frac{P(G_Y|W_k^{new},W_{-k}^{old},B)}{P(G_Y|W^{old},B)} \frac{P(W_k^{new}|B)}{P(W_k^{old}|B)} \frac{R(W_k^{old}|W_k^{new})}{R(W_k^{new}|W_k^{old})}\}.$$

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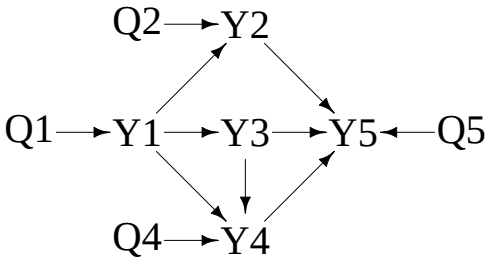
5. Iterate the steps 1-4 until the chain converges.

Simulations



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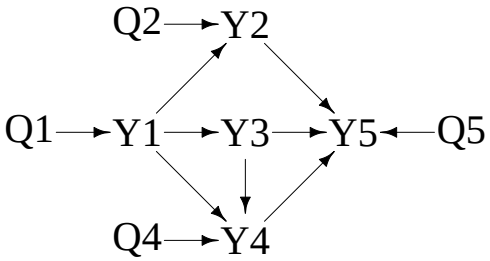

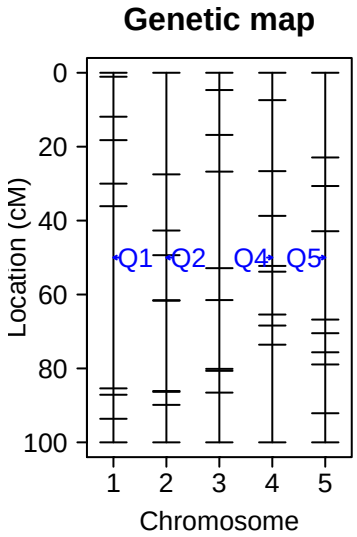

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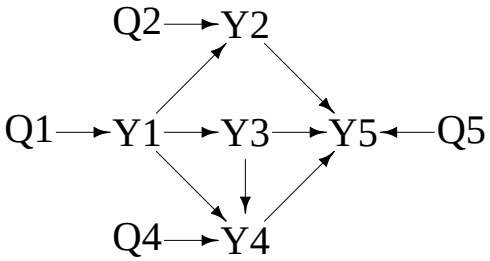
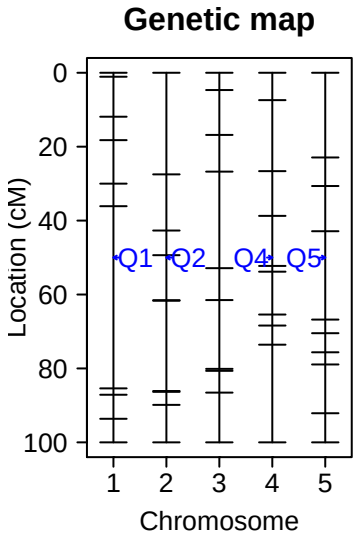
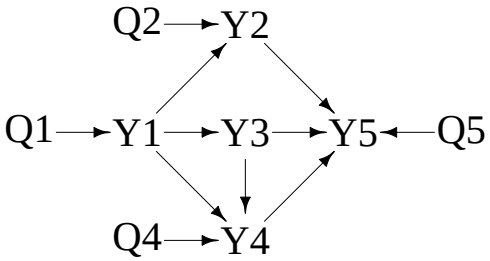
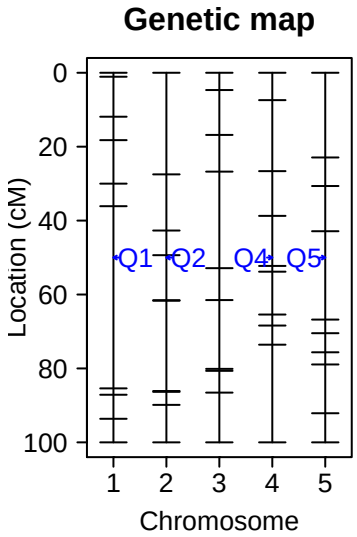




$\longrightarrow$ X for 500 mice in F2 population

Simulations

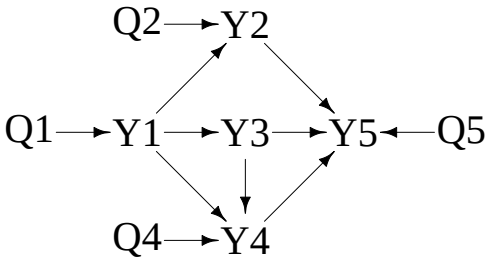


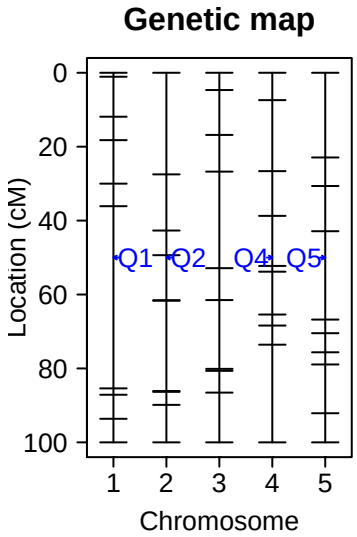


$\longrightarrow$ X for 500 mice in F2 population

$$\xrightarrow[\substack{\theta_{add} \sim U[0,0.5] \\ \theta_{dominance} \sim U[0,0.25] \\ \beta_{tv} \sim U[-0.5,0.5]}]{} \begin{pmatrix} Y_1 \\ Y_2 \\ Y_3 \\ Y_4 \\ Y_5 \end{pmatrix}$$ for 500 mice.

Simulations





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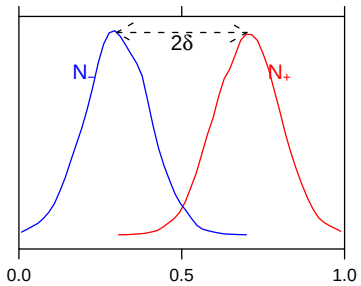
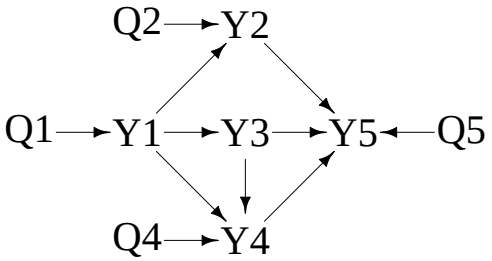
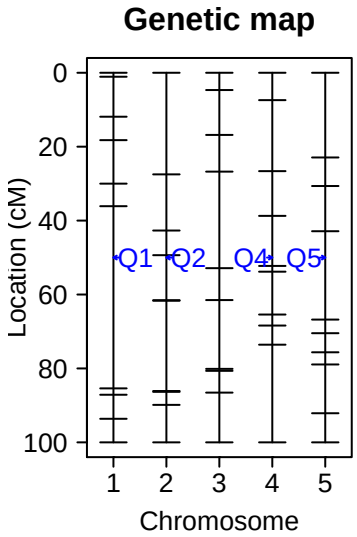
$$G_Y = \begin{array}{c} \\ Y_1 \\ Y_2 \\ Y_3 \\ Y_4 \\ Y_5 \end{array} \begin{array}{c} \begin{array}{ccccc} Y_1 & Y_2 & Y_3 & Y_4 & Y_5 \end{array} \\ \begin{pmatrix} & 1 & 1 & 1 & 0 \\ 0 & & 0 & 0 & 1 \\ 0 & 0 & & 1 & 1 \\ 0 & 0 & 0 & & 1 \\ 0 & 0 & 0 & 0 & \end{pmatrix} \end{array}$$



$$\xrightarrow[Blue \sim N_-]{Red \sim N_+}$$ B $= \begin{pmatrix} & x & x & x & x \\ x & & x & x & x \\ x & x & & x & x \\ x & x & x & & x \\ x & x & x & x & \end{pmatrix}$

Simulations





$\longrightarrow$ X for 500 mice in F2 population

$\xrightarrow[\theta_{dominance} \sim U[0,0.25]]{\theta_{add} \sim U[0,0.5]}$ $\begin{pmatrix} Y_1 \\ Y_2 \\ Y_3 \\ Y_4 \\ Y_5 \end{pmatrix}$ for 500 mice.

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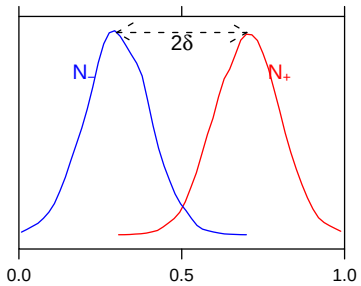

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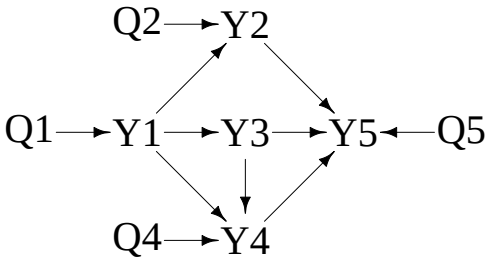
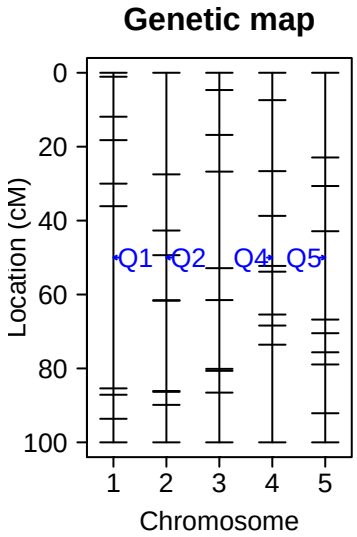
X, Y, B are simulated for 100 times

Simulations

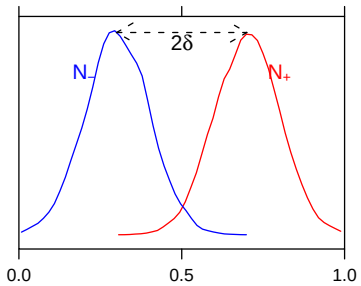




$\longrightarrow$ X for 500 mice in F2 population

$$\xrightarrow[\substack{\theta_{add} \sim U[0,0.5] \\ \theta_{dominance} \sim U[0,0.25] \\ \beta_{tv} \sim U[-0.5,0.5]}]{} \begin{pmatrix} Y_1 \\ Y_2 \\ Y_3 \\ Y_4 \\ Y_5 \end{pmatrix}$$ for 500 mice.

$$G_Y = \begin{array}{c} \\ Y_1 \\ Y_2 \\ Y_3 \\ Y_4 \\ Y_5 \end{array} \begin{array}{c} \begin{array}{ccccc} Y_1 & Y_2 & Y_3 & Y_4 & Y_5 \end{array} \\ \begin{pmatrix} & 1 & 1 & 1 & 0 \\ 0 & & 0 & 0 & 1 \\ 0 & 0 & & 1 & 1 \\ 0 & 0 & 0 & & 1 \\ 0 & 0 & 0 & 0 & \end{pmatrix} \end{array}$$



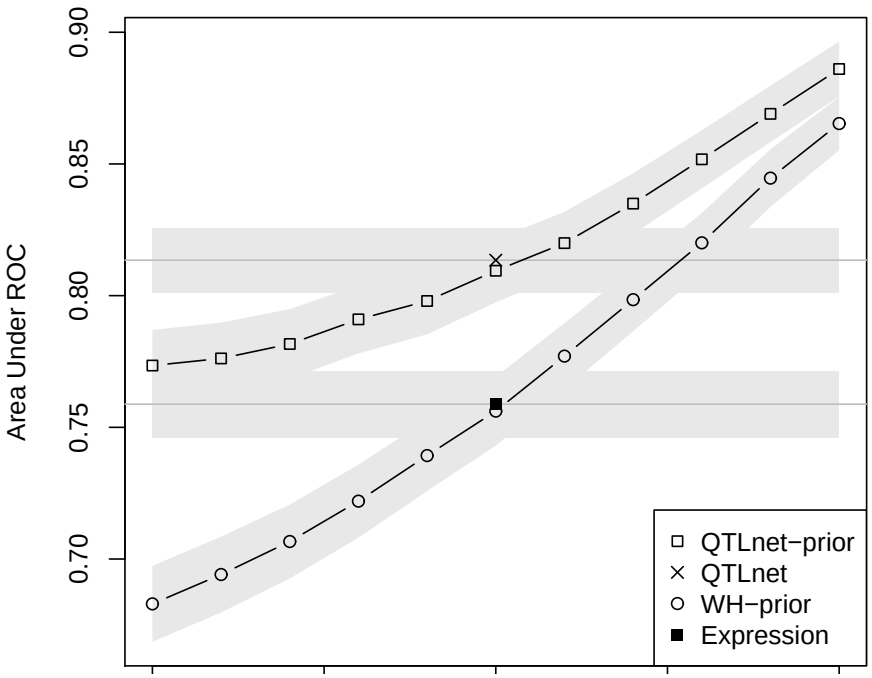
$\xrightarrow[Blue \sim N_-]{Red \sim N_+}$ B $= \begin{pmatrix} & x & x & x & x \\ x & & x & x & x \\ x & x & & x & x \\ x & x & x & & x \\ x & x & x & x & \end{pmatrix}$

X, Y, B are simulated for 100 times

for each $\delta \in \{\pm 0.5, \pm 0.25, \pm 0.2, \pm 0.15, \pm 0.1, \pm 0.05, 0\}$.

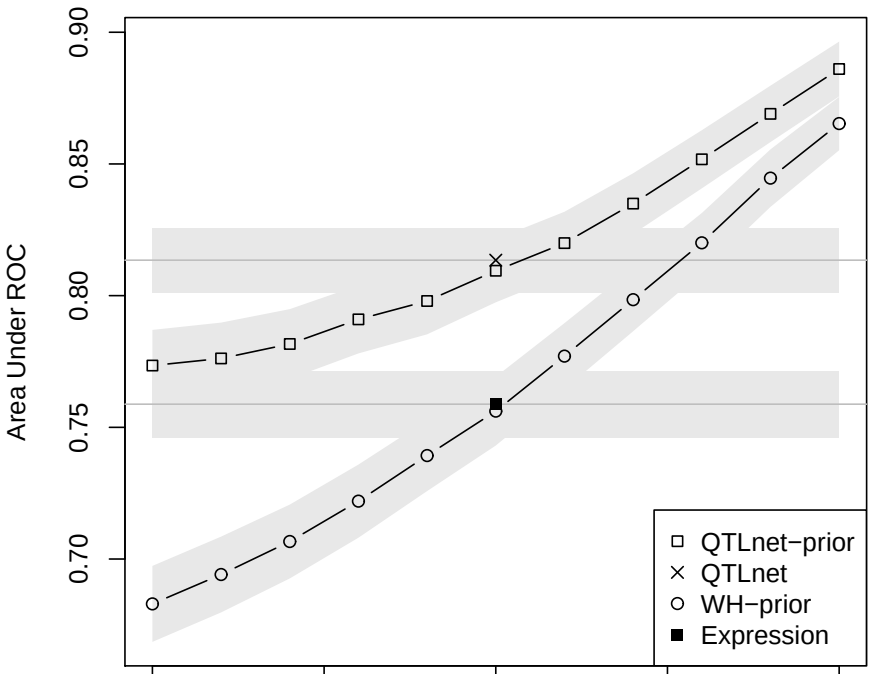
Method	Genetic Variation Information	Biological Knowledge
QTLnet-prior	YES	YES
QTLnet	YES	NO
WH-prior	NO	YES
Expression	NO	NO

ROC curves



Area under ROC curves

ROC curves



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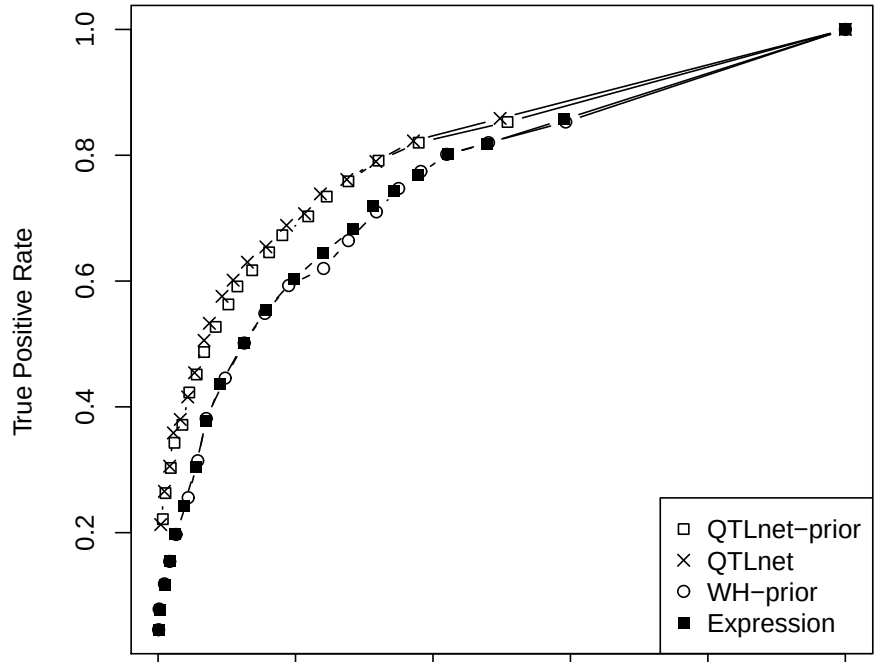
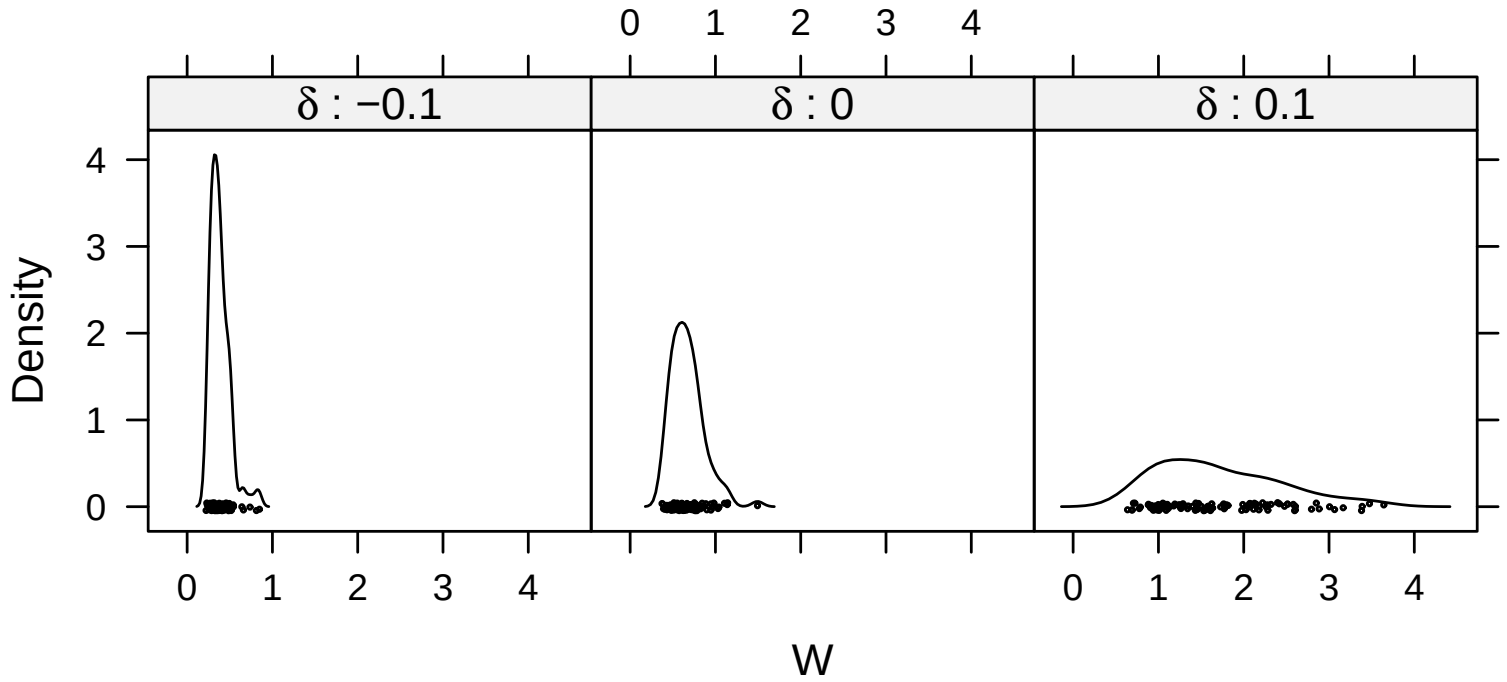


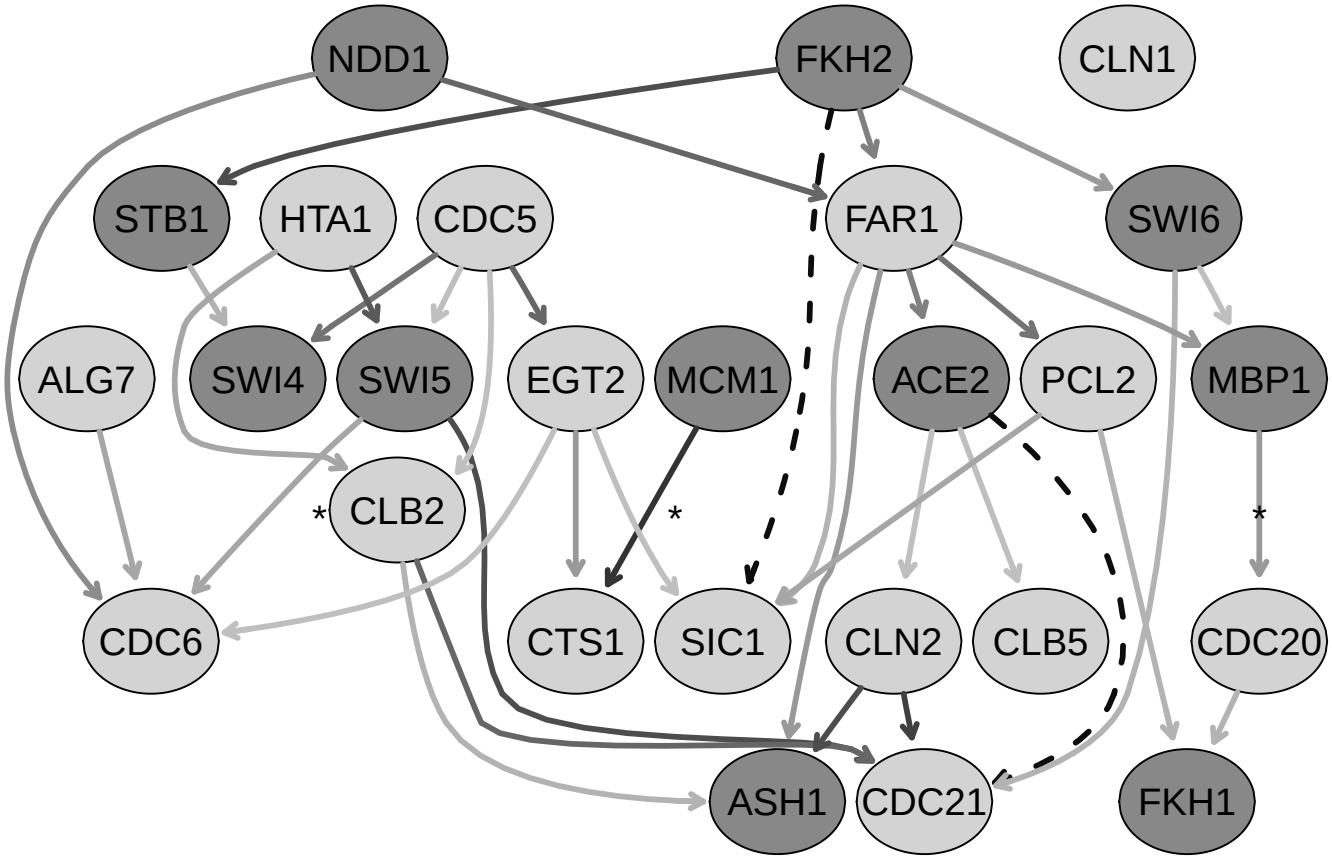
QTLnet-prior, WH-prior ($\delta = 0$) vs. QTLnet, Expression

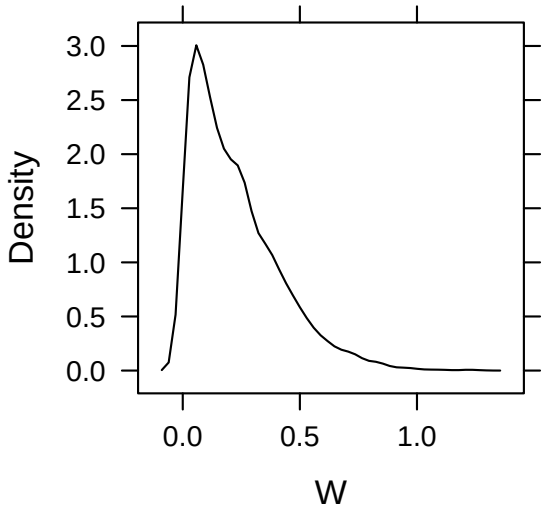
Convergence of W



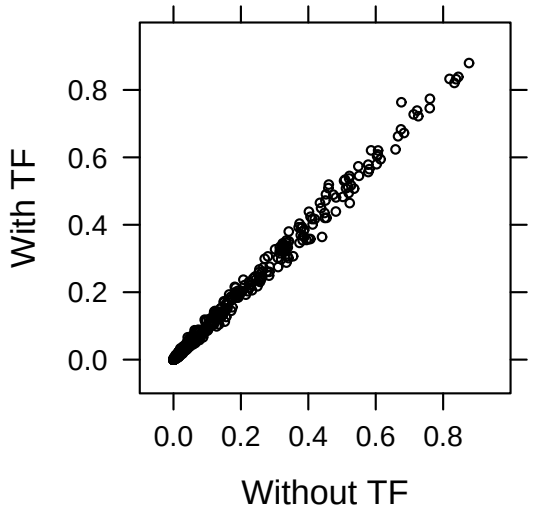
The distribution of median W of posterior sample by QTLnet-prior inference.

Yeast cell cycle analysis





The posterior distribution of weight W of TF-binding



Comparison of posterior probability of every possible edge

Conclusion

- When the prior knowledge is correct, the performance (area under ROC curve, proportion of recovered edges) is improved by prior knowledge. QTL mapping does not improve the performance.
- When the prior knowledge is incorrect, QTL mapping is important.
- When the prior knowledge is noninformative, we lose some power, but not too much.

References

- Friedman, N., Linial, M., Nachman, I., and Pe'er, D. (2000) Using bayesian networks to analyze expression data. *Journal of Computational Biology*, 7(3-4):601–620.
- Chaibub Neto, E., Keller, M. P., Attie, A. D., and S., Y. B. (2010) Causal graphical models in systems genetics: A unified framework for joint inference of causal network and genetic architecture for correlated phenotypes. *Ann. Appl. Stat.*, 4(1).
- Werhli, A. V. and Husmeier, D. (2007) Reconstructing gene regulatory networks with Bayesian networks by combining expression data with multiple sources of prior knowledge. *Statistical Applications in Genetics and Molecular Biology*, 6.
- Zhu, J., Zhang, B., Smith, E. N., Drees, B., Brem, R. B., Kruglyak, L., Bumgarner, R. E., and Schadt, E. E. (2008) Integrating large-scale functional genomic data to dissect the complexity of yeast regulatory networks. *Nat Genet*, 40(7):854–861.

II. A causal gene network with genetic variations and latent variables

Motivation for latent variables

1. There could be unmeasured variables in a network.
2. Inference of a network may be done on a subset of candidate variables.

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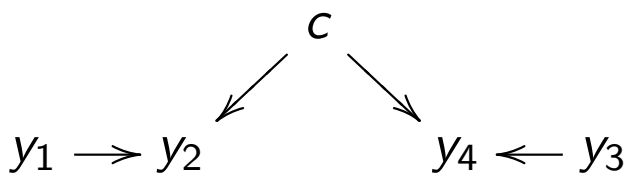

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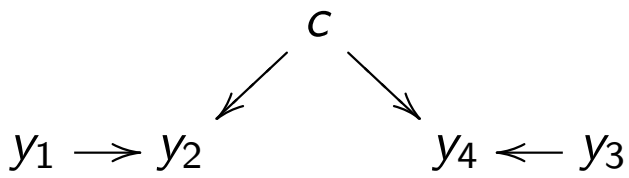

Let $\{y_1, y_2, y_3, y_4\}$: observed, c : unmeasured.
Conditional independence relations of observed variables:

$$y_2 \not\perp y_4 | \{y_1, y_3\}$$
$$y_1 \not\perp y_2 \qquad y_3 \not\perp y_4$$
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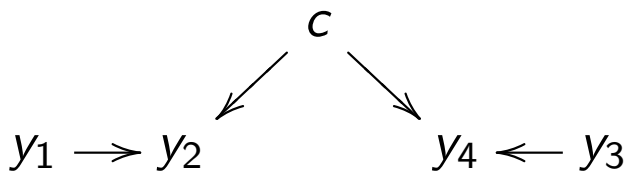

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Then, $y_1 \rightarrow y_2 \leftarrow y_4$ and $y_3 \rightarrow y_4 \leftarrow y_2$.

Introduction of ancestral graph

An ancestral graph is a graph whose vertexes are connected by at most one of undirected (—), directed ($\rightarrow$) or bidirected ($\leftrightarrow$) edges.

- Bidirected ($\leftrightarrow$) edges are associated with marginalization.
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An ancestral graph holds the following conditions:

- there are no directed cycles;
- whenever there is an edge $x \leftrightarrow y$, then there is no directed path from x to y, or from y to x;
- if there is an undirected edge x — y then there are no vertex v such that $v \leftrightarrow x$, $v \leftrightarrow y$, $v \rightarrow x$, or $v \rightarrow y$.

Model

Y_{ti} be the phenotype for individual i and trait t.
Each phenotype is modeled as follows:

$$Y_{ti} = \mu^*_{ti} + \sum_{v \in pa(t)} \beta_{tv} Y_{vi} + \epsilon_{ti},$$

where $pa(t) = \{v : v \to t\}$ and $\mu^*_{ti} = \mu_t + X_i \; diag(\gamma_t) \; \theta_t$ is the QTL effect.

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$$\epsilon \sim N_T(0, \Omega),$$

where

$\Omega(t, s) = 0$ iff there is no bidirected edge between t and s.

QTLs to distinguish Markov equivalent directed ancestral graphs.

Theorem

Consider a class of Markov equivalent directed maximal ancestral graphs $\mathcal{G}_{\mathcal{Y}}$. Let Y_1 and Y_2 be any two adjacent nodes in the graphs in $\mathcal{G}_{\mathcal{Y}}$. Assume that for each such pair there exists at least two variables, Q_1 directly affecting Y_1 but not Y_2 and Q_2 directly affecting Y_2 but not Y_1. Let $\mathcal{G}$ represent the class of extended graphs. Then the graphs in $\mathcal{G}$ are not Markov equivalent.

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$Y_1 \rightarrow Y_2$, $Y_1 \leftarrow Y_2$ and $Y_1 \leftrightarrow Y_2$
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$Q_1 \rightarrow Y_1 \rightarrow Y_2 \leftarrow Q_2$ versus $Q_1 \rightarrow Y_1 \leftarrow Y_2 \leftarrow Q_2$ versus $Q_1 \rightarrow Y_1 \leftrightarrow Y_2 \leftarrow Q_2$.

Search algorithms

1. Constraint-based search : Conditional independence tests for a pair of nodes, Removes edges, orient edges (FCI)
2. Likelihood-based search : Search over DMAG models by their likelihoods

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Markov equivalence of G_1 and $G_2 \Leftrightarrow$ Distribution equivalence of G_1 and G_2 in a (parametric) family F?

1. Markov equivalence: G_1 and G_2 represent the same set of conditional independence relations.
2. Distribution equivalence with respect to F: $\forall \theta_{G_1}$, there exists a θ_{G_2} such that $p(Y \mid \theta_{G_1}, G_1) = p(Y \mid \theta_{G_2}, G_2)$, and vice versa.
   They represent the same set of joint probability distributions.

Parametric Family

$$Y_{ti} = \mu^*_{ti} + \sum_{v \in pa(t)} \beta_{tv} Y_{vi} + \epsilon_{ti}$$

$\epsilon \sim N_T(0, \Omega)$

$\Omega(t, s) = 0$ iff there is no bidirected edge between t and s.

Property

A set of linear equations and correlated errors fall into a homogeneous conditional Gaussian (HCG) family.

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A conditional Gaussian (CG) family : the joint distribution of continuous variables are Gaussian conditional on discrete variables.
A homogeneous conditional Gaussian (HCG) family: the covariance in the conditional Gaussian distribution is independent of discrete variable values.

Markov equivalence $\Leftrightarrow$ Distribution equivalence in a HCG family

Theorem

For two Markov equivalent DMAGs G_1 and G_2, G_1 and G_2 differ only by $t \rightarrow v$ in G_1 and $t \leftrightarrow v$ in G_2. In a Gaussian distribution family, suppose the recursive equations for G_1 regarding t and v is represented by

$$Y_t = \mu_t + B_t(Y_{pa(t)} - \mu_{pa(t)}) + \epsilon_t$$
$$Y_v = \mu_v + B_v(Y_{pa(v)\setminus\{t\}} - \mu_{pa(v)}) + b_{tv}(Y_t - \mu_t) + \epsilon_v$$

where $cov(\epsilon_t, \epsilon_v) = 0$. Then, the re-parametrization below for G_2 regarding t and v gives out the same joint probability to the joint probability of G_1.

$$Y_t = \mu_t^* + B_t^*(Y_{pa(t)} - \mu_{pa(t)}^*) + \epsilon_t^*$$
$$Y_v = \mu_v^* + B_v^*(Y_{pa(v)\setminus\{t\}} - \mu_{pa(v)}^*) + \epsilon_v^*$$

where

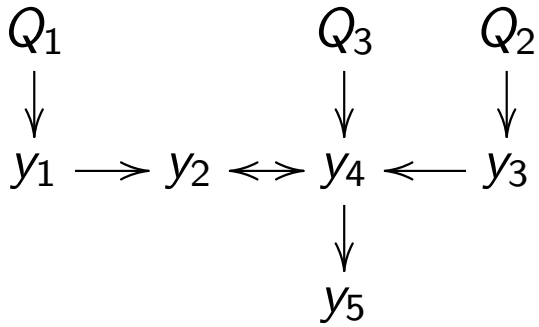
1. $B_v^* = B_v + b_{tv}B_t$
2. $var(\epsilon_v^*) = \sigma_v + b_{tv}^2\sigma_t$
3. $cov(\epsilon_v^*, \epsilon_{sp(v)}) = \sigma_{v,sp(v)} + b_{tv}\sigma_{t,sp(v)}$
4. $cov(\epsilon_t, \epsilon_v^*) = b_{tv}\sigma_t$
5. $B_t^* = B_t$
6. $Var(\epsilon_t^*) = \sigma_t$
7. $cov(\epsilon_t^*, \epsilon_{sp(t)}) = \sigma_{t,sp(t)}$.

Algorithm - MCMC

1. Divide a DMAG G_0 into bidirected graph G_0^B and directed graph and G_0^D.
2. Propose a new directed graph G^D from G_0^D by a DAG proposal distribution $R(G^D|G_0^D)$.
3. For each node, get a list of ancestors or descendants in G^D. Then, get a list of possible bidirected edges in $G \setminus G^D$. Propose new bidirected edges G^B by Bernoulli distribution for each possible bidirected edge with probability pB.
4. If $G = G^D \oplus G^B$ is not a maximal ancestral graph, make it to be maximal: $Max(G)$. Obtain several G^B and their proposal probabilities to become equivalent to $Max(G)$. Its proposal distribution is $R(Max(G)|G^D)$.
5. Accept the new DMAG $G_1 = Max(G)$ with a probability,

$$\min\{1, \frac{P(Y|G_1)}{P(Y|G_0)} \frac{R(G_0^D|G_1^D)R(G_0|G_0^D)}{R(G_1^D|G_0^D)R(G_0|G_1^D)}\}.$$

Simulations



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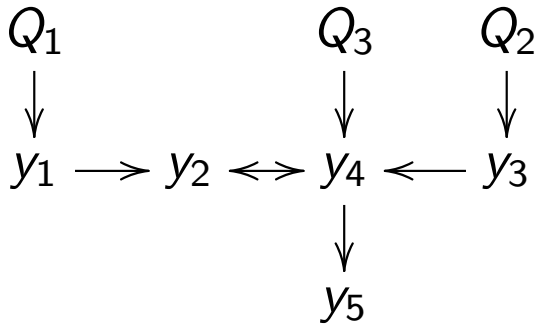

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Preliminary Result: The inferred skeleton has 1.35 edge difference to the true skeleton on average from 20 simulations.

Conclusion

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- Distribution equivalence in a HCG family $\Leftrightarrow$ Markov equivalence.

References

- Richardson, T. S. and Spirtes, P. (2002) Ancestral graph Markov models. *The Annals of Statistics*, 30(4):962–1030.
- Ali, R. A., Richardson, T. S., Spirtes, P. (2009) Markov equivalence for ancestral graphs. *Annals of Statistics*, 37(5B):2808–2837.
- Lauritzen, S. L. Lauritzen. Graphical Models. Oxford University Press, 1996

Future Research Plan