

Causal Network Models for Correlated Quantitative Traits

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outline

- Correlation and causation
- Correlated traits in organized groups
 - modules and hotspots
 - Genetic vs. environmental correlation
- QTL-driven directed graphs
 - Assume QTLs known, causal network unknown
- Causal graphical models in systems genetics
 - QTLs unknown, causal network unknown
- Scaling up to larger networks
 - Searching the space of possible networks
 - Dealing with computation

“The old view of cause and effect ... could only fail; things are not in our experience either independent or causative. All classes of phenomena are linked together, and the problem in each case is how close is the degree of association.”

Karl Pearson (1911)
The Grammar of Science

“The ideal ... is the study of the direct influence of one condition on another ...[when] all other possible causes of variation are eliminated.... The degree of correlation between two variables ... [includes] all connecting paths of influence.... [Path coefficients combine] knowledge of ... correlation among the variables in a system with ... causal relations.

Sewall Wright (1921)
Correlation and causation. J Agric Res

"Causality is not mystical or metaphysical. It can be understood in terms of simple processes, and it can be expressed in a friendly mathematical language, ready for computer analysis."

Judea Pearl (2000)

Causality: Models, Reasoning and Inference

problems and controversies

- Correlation does not imply causation.
 - Common knowledge in field of statistics.
- Steady state (static) measures may not reflect dynamic processes.
 - Przytycka and Kim (2010) *BMC Biol*
- Population-based estimates (from a sample of individuals) may not reflect processes within an individual.

randomization and causation

- RA Fisher (1926) *Design of Experiments*
- control other known factors
- randomize assignment of treatment
 - no causal effect of individuals on treatment
 - no common cause of treatment and outcome
 - reduce chance correlation with unknown factors
- conclude outcome differences are caused by (due to) treatment

correlation and causation

- temporal aspect: cause before reaction
 - genotype (usually) drives phenotype
 - phenotypes in time series
 - *but* time order is not enough
- axioms of causality
 - transitive: if $A \rightarrow B$, $B \rightarrow C$, then $A \rightarrow C$
 - local (Markov): events have only proximate causes
 - asymmetric: if $A \rightarrow B$, then B cannot $\rightarrow A$
- Shipley (2000) *Cause and Correlation in Biology*

causation casts probability shadows

- causal relationship
 - $Y_1 \rightarrow Y_2 \rightarrow Y_3$
- conditional probability
 - $\Pr(Y_1) * \Pr(Y_2 | Y_1) * \Pr(Y_3 | Y_2)$
- linear model
 - $Y_1 = \mu_1 + e$
 - $Y_2 = \mu_2 + \beta_1 \cdot Y_1 + e$
- adding in QTLs: $Q_1 \rightarrow Y_1 \rightarrow Y_2 \leftarrow Q_2$
 - $Y_1 = \mu_1 + \theta_1 \cdot Q_1 + e$
 - $Y_2 = \mu_2 + \beta_1 \cdot Y_1 + \theta_2 \cdot Q_2 + e$

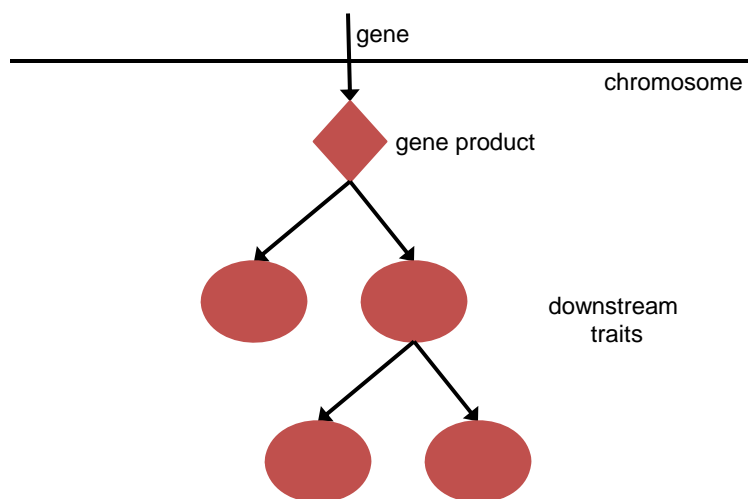
organizing correlated traits

- functional grouping from prior studies
 - GO, KEGG; KO panels; TF and PPI databases
- co-expression modules (Horvath talk today)
- eQTL hotspots (here briefly)
- traits used as covariates for other traits
 - does one trait essentially explain QTL of another?
- causal networks (here and Horvath talk)
 - modules of highly correlated traits

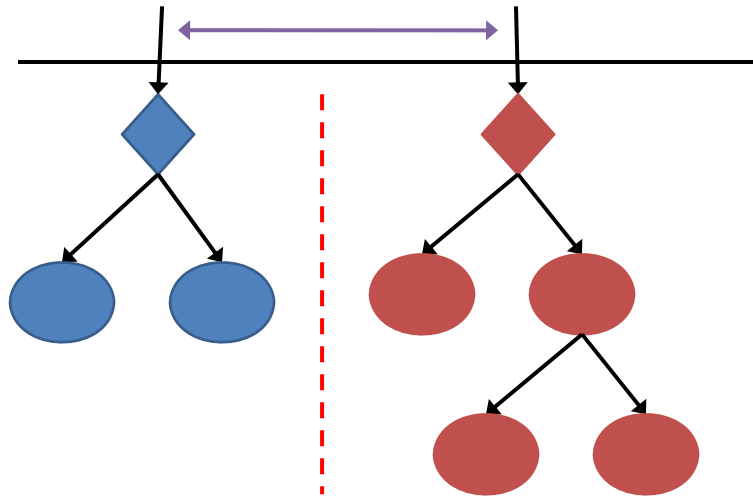
Correlated traits in a hotspot

- why are traits correlated?
 - Environmental: hotspot is spurious
 - One causal driver at locus
 - Traits organized in causal cascade
 - Multiple causal drivers at locus
 - Several closely linked driving genes
 - Correlation due to close linkage
 - Separate networks are not causally related

one causal driver



two linked causal drivers pathways independent given drivers



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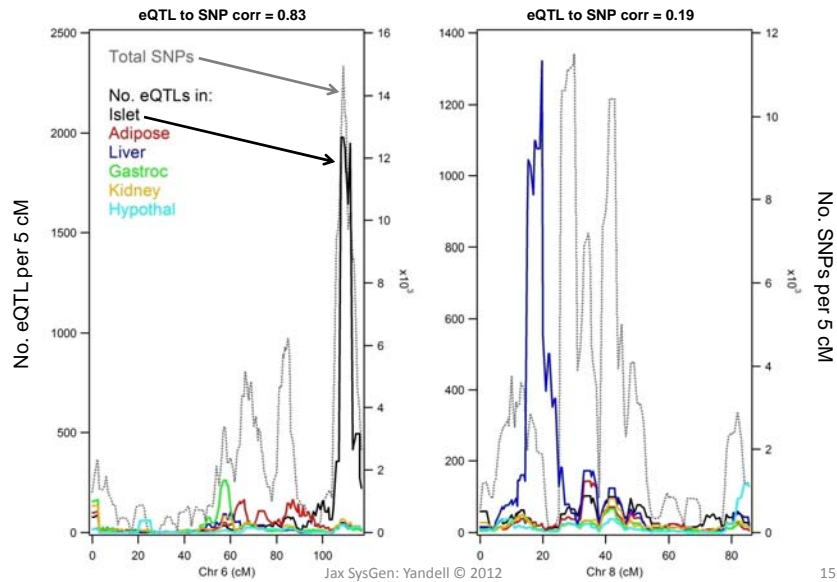
hotspots of correlated traits

- multiple correlated traits map to same locus
 - is this a real hotspot, or an artifact of correlation?
 - use QTL permutation across traits
- references
 - Breitling R, Li Y, Tesson BM, Fu J, Wu C, Wiltshire T, Gerrits A, Bystrykh LV, de Haan G, Su AI, Jansen RC (2008) Genetical Genomics: Spotlight on QTL Hotspots. *PLoS Genetics* 4: e1000232. [doi:10.1371/journal.pgen.1000232]
 - Chaibub Neto E, Keller MP, Broman AF, Attie AD, Jansen RC, Broman KW, Yandell BS, Quantile-based permutation thresholds for QTL hotspots. *Genetics* (in review).

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eQTL vs SNP architecture



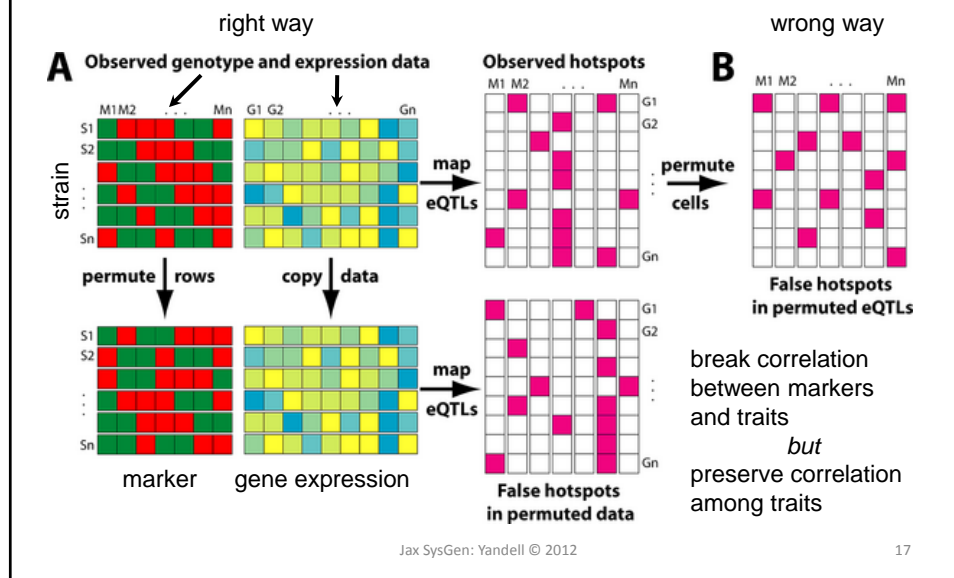
hotspot permutation test

(Breitling et al. Jansen 2008 *PLoS Genetics*)

- for original dataset and each permuted set:
 - Set single trait LOD threshold T
 - Could use Churchill-Doerge (1994) permutations
 - Count number of traits (N) with LOD above T
 - Do this at every marker (or pseudomarker)
 - Probably want to smooth counts somewhat
- find count with at most 5% of permuted sets above (critical value) as count threshold
- conclude original counts above threshold are real

permutation across traits

(Breitling et al. Jansen 2008 *PLoS Genetics*)

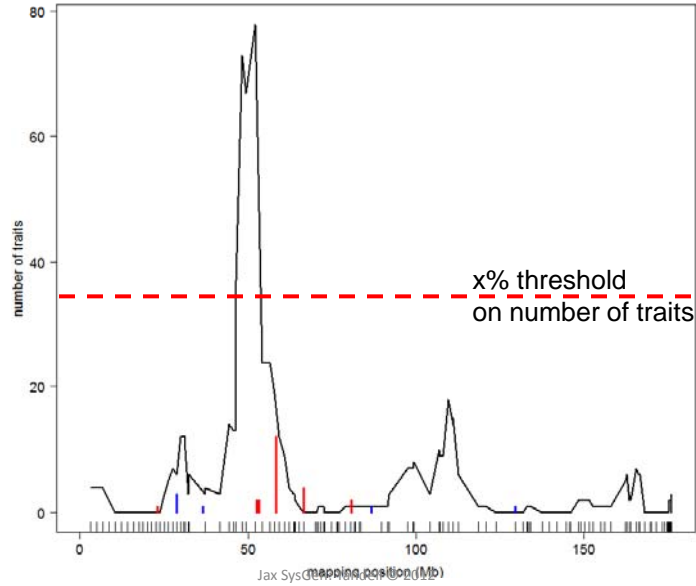


quality vs. quantity in hotspots

(Chaibub Neto et al. in review)

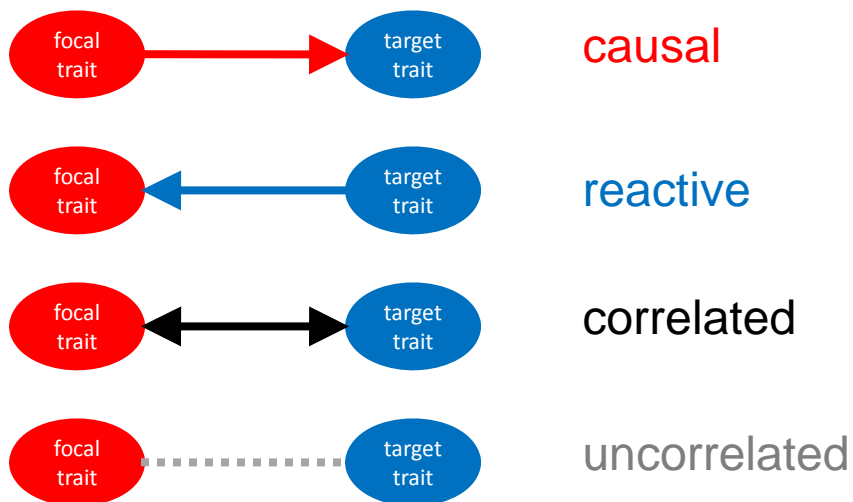
- detecting single trait with very large LOD
 - control FWER across genome
 - control FWER across all traits
- finding small “hotspots” with significant traits
 - all with large LODs
 - could indicate a strongly disrupted signal pathway
- sliding LOD threshold across hotspot sizes

BxH ApoE-/- chr 2: hotspot



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causal model selection choices in context of larger, unknown network



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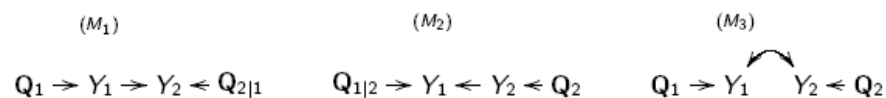
causal architecture

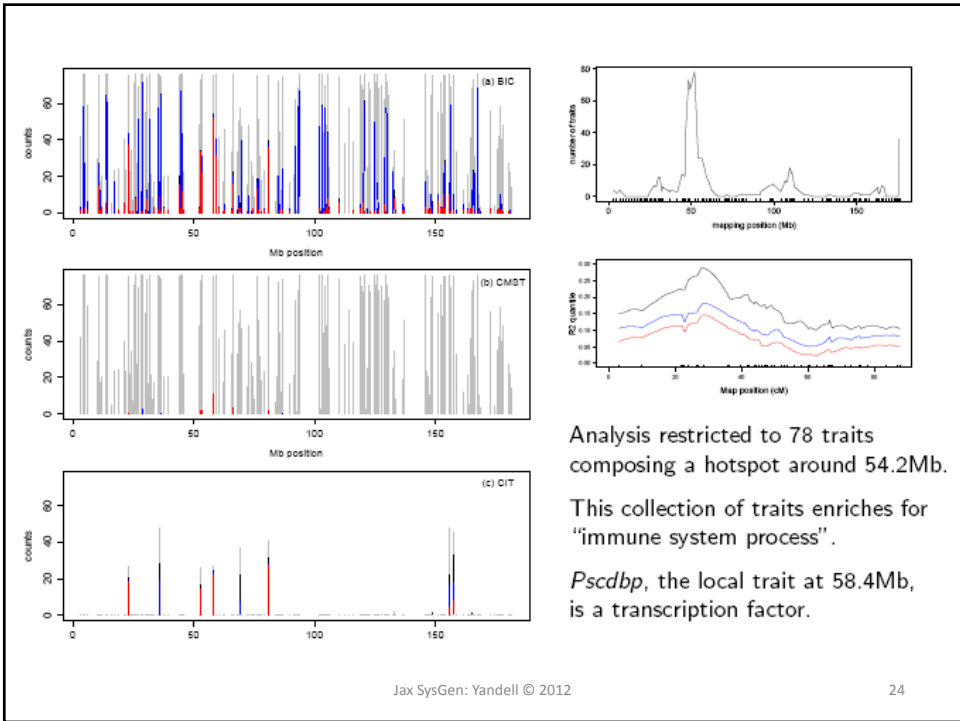
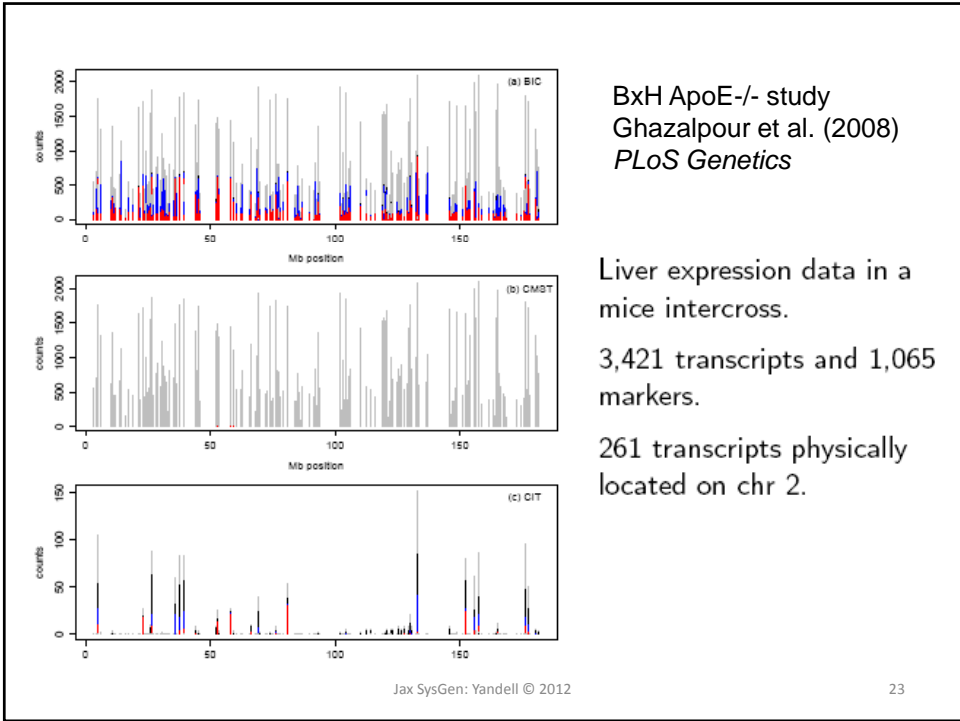
- how many traits are up/downstream of a trait?
 - focal trait causal to downstream target traits
 - record count at Mb position of focal gene
 - red = downstream, blue = upstream
- what set of target traits to consider?
 - all traits
 - traits in module or hotspot

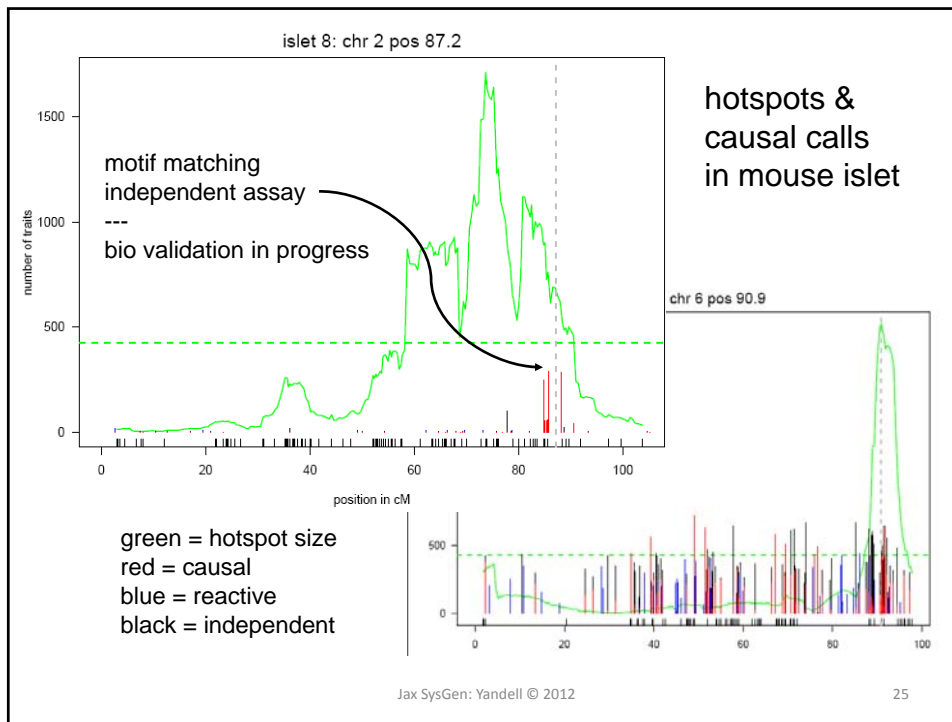
causal architecture references

- BIC: Schadt et al. (2005) *Nature Genet*
- CIT: Millstein et al. (2009) *BMC Genet*
- Aten et al. Horvath (2008) *BMC Sys Bio*
- CMST: Chaibub Neto et al. (2010) PhD thesis

Extends Vuong's model selection tests to the comparison of 3, possibly **misspecified**, models.



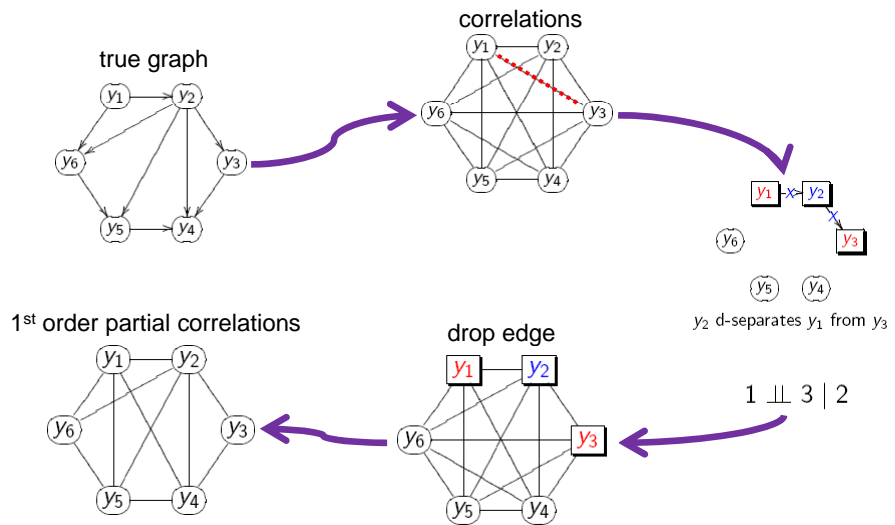




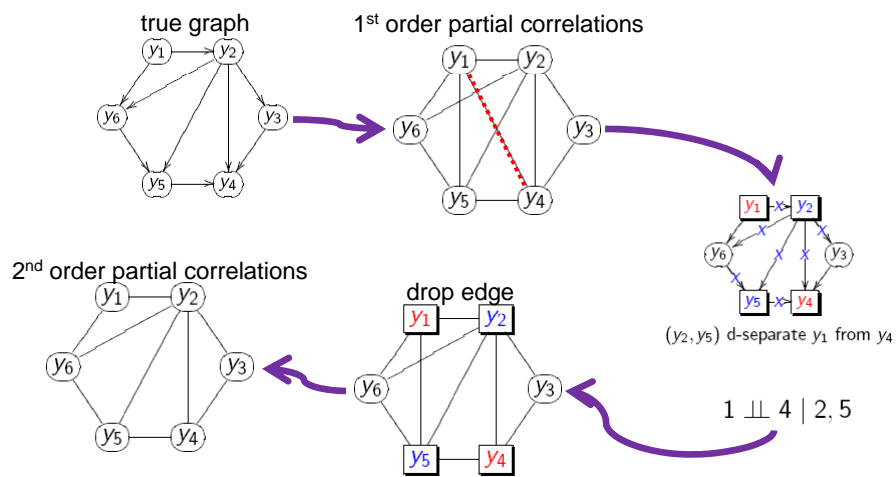
QTL-driven directed graphs

- given genetic architecture (QTLs), what causal network structure is supported by data?
- R/qdg available at www.github.org/byandell
- references
 - Chaibub Neto, Ferrara, Attie, Yandell (2008) Inferring causal phenotype networks from segregating populations. *Genetics* 179: 1089-1100. [doi:genetics.107.085167]
 - Ferrara et al. Attie (2008) Genetic networks of liver metabolism revealed by integration of metabolic and transcriptomic profiling. *PLoS Genet* 4: e1000034. [doi:10.1371/journal.pgen.1000034]

partial correlation (PC) skeleton



partial correlation (PC) skeleton

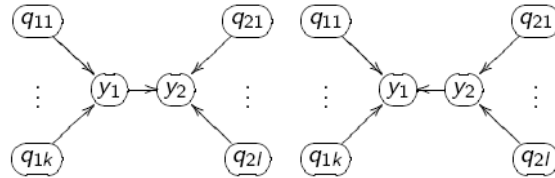


edge direction: which is causal?

$$M_1 : (y_1) \rightarrow (y_2) \quad M_2 : (y_1) \leftarrow (y_2)$$

the above models are likelihood equivalent,

$$f(y_1)f(y_2 | y_1) = f(y_1, y_2) = f(y_2)f(y_1 | y_2)$$

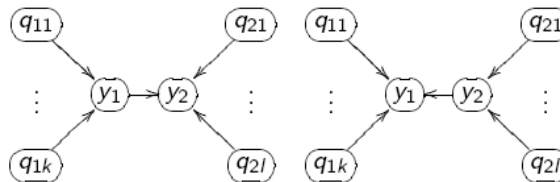


not likelihood equivalent **due to QTL**

$$f(\mathbf{q}_1)f(y_1 | \mathbf{q}_1)f(y_2 | y_1, \mathbf{q}_2)f(\mathbf{q}_2) \neq f(\mathbf{q}_2)f(y_2 | \mathbf{q}_2)f(y_1 | y_2, \mathbf{q}_1)f(\mathbf{q}_1)$$

test edge direction using LOD score

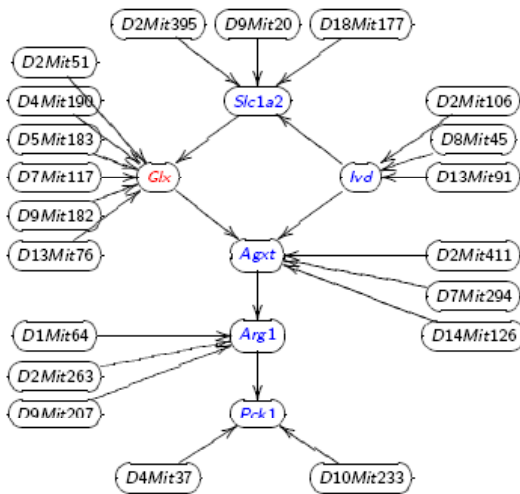
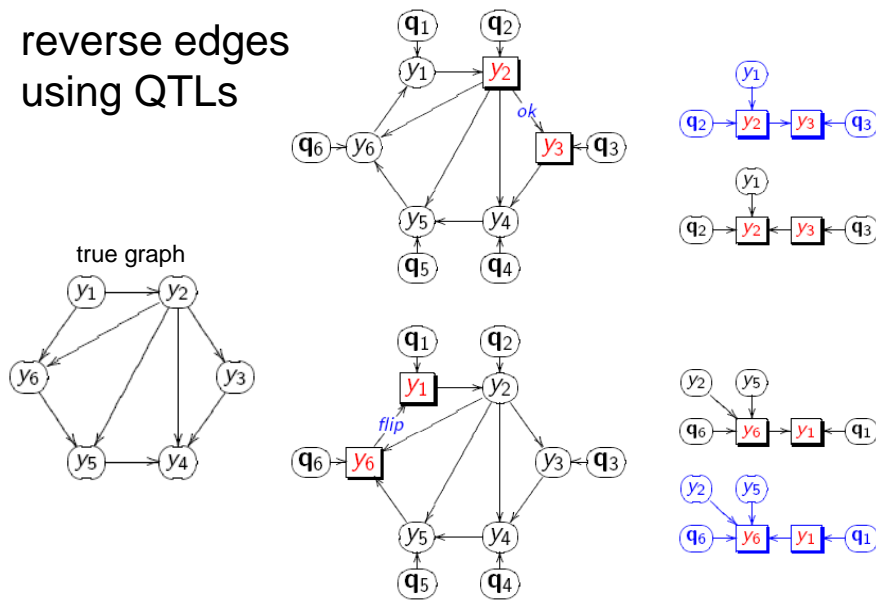
$$LOD = \log_{10} \left\{ \frac{\prod_{i=1}^n f(y_{1i} | \mathbf{q}_{1i})f(y_{2i} | y_{1i}, \mathbf{q}_{2i})}{\prod_{i=1}^n f(y_{2i} | \mathbf{q}_{2i})f(y_{1i} | y_{2i}, \mathbf{q}_{1i})} \right\}$$



not likelihood equivalent because

$$f(\mathbf{q}_1)f(y_1 | \mathbf{q}_1)f(y_2 | y_1, \mathbf{q}_2)f(\mathbf{q}_2) \neq f(\mathbf{q}_2)f(y_2 | \mathbf{q}_2)f(y_1 | y_2, \mathbf{q}_1)f(\mathbf{q}_1)$$

reverse edges using QTLs



- ▶ We constructed a network from metabolites and transcripts involved in liver metabolism.
- ▶ We validated this network with *in vitro* experiments (Ferrara et al 2008). Four out of six predictions were confirmed.

causal graphical models in systems genetics

- What if genetic architecture and causal network are unknown?
 - jointly infer both using iteration
- Chaibub Neto, Keller, Attie, Yandell (2010) Causal Graphical Models in Systems Genetics: a unified framework for joint inference of causal network and genetic architecture for correlated phenotypes. *Ann Appl Statist* 4: 320-339. [doi:10.1214/09-AOAS288]
- R/qtlnet available from www.github.org/byandell
- Related references
 - Schadt et al. Lusi (2005 *Nat Genet*); Li et al. Churchill (2006 *Genetics*); Chen Emmert-Streib Storey (2007 *Genome Bio*); Liu de la Fuente Hoeschele (2008 *Genetics*); Winrow et al. Turek (2009 *PLoS ONE*); Hageman et al. Churchill (2011 *Genetics*)

Basic idea of QTLnet

- iterate between finding QTL and network
- genetic architecture given causal network
 - trait y depends on parents $pa(y)$ in network
 - QTL for y found conditional on $pa(y)$
 - Parents $pa(y)$ are interacting covariates for QTL scan
- causal network given genetic architecture
 - build (adjust) causal network given QTL
 - each direction change may alter neighbor edges

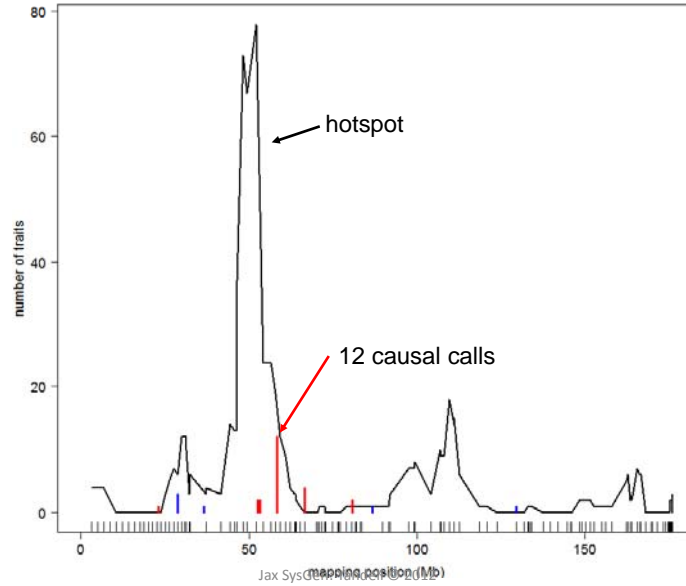
missing data method: MCMC

- known phenotypes Y , genotypes Q
- unknown graph G
- want to study $\Pr(Y | G, Q)$
- break down in terms of individual edges
 - $\Pr(Y|G,Q) = \text{sum of } \Pr(Y_i | \text{pa}(Y_i), Q)$
- sample new values for individual edges
 - given current value of all other edges
- repeat many times and average results

MCMC steps for QTLnet

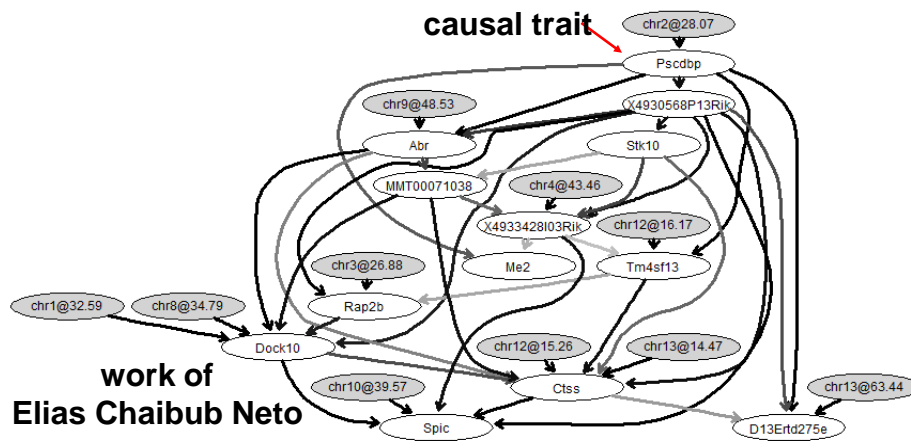
- propose new causal network G
 - with simple changes to current network:
 - change edge direction
 - add or drop edge
- find any new genetic architectures Q
 - update phenotypes when parents $\text{pa}(y)$ change in new G
- compute likelihood for new network and QTL
 - $\Pr(Y | G, Q)$
- accept or reject new network and QTL
 - usual Metropolis-Hastings idea

BxH ApoE-/- chr 2: causal architecture



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BxH ApoE-/- causal network for transcription factor Pscdbp



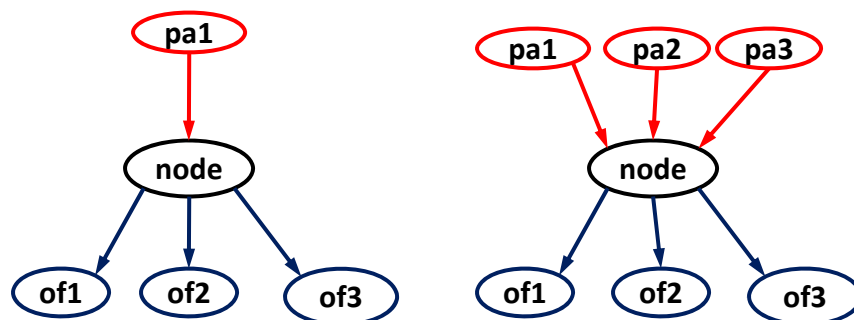
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scaling up to larger networks

- reduce complexity of graphs
 - use prior knowledge to constrain valid edges
 - restrict number of causal edges into each node
- make task parallel: run on many machines
 - pre-compute conditional probabilities
 - run multiple parallel Markov chains
- rethink approach
 - LASSO, sparse PLS, other optimization methods

graph complexity with node parents



how many node parents?

- how many edges per node? (fan-in)
 - few parents directly affect one node
 - many offspring affected by one node

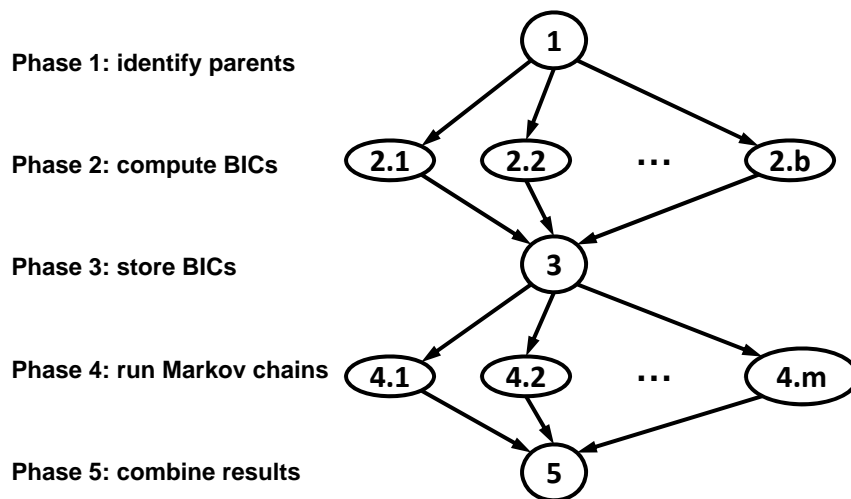
BIC computations by maximum number of parents

#	3	4	5	6	all
10	1,300	2,560	3,820	4,660	5,120
20	23,200	100,720	333,280	875,920	10.5M
30	122,700	835,230	4.40M	18.6M	16.1B
40	396,800	3.69M	26.7M	157M	22.0T
50	982,500	11.6M	107M	806M	28.1Q

BIC computation

- each trait (node) has a linear model
 - $Y \sim \text{QTL} + \text{pa}(Y) + \text{other covariates}$
- BIC = LOD – penalty
 - BIC balances data fit to model complexity
 - penalty increases with number of parents
- limit complexity by allowing only 3-4 parents

parallel phases for larger projects

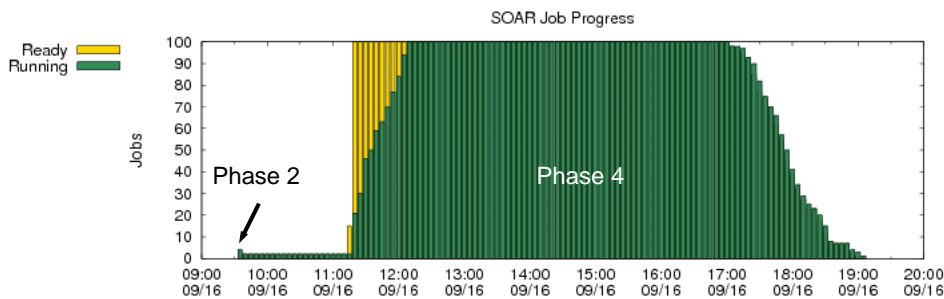


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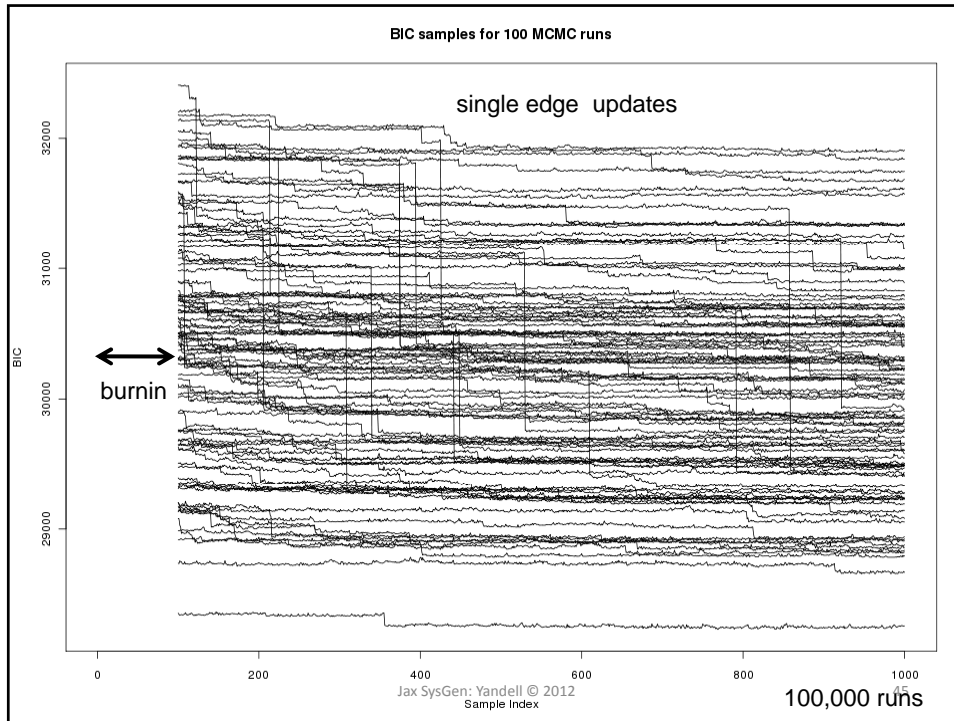
parallel implementation

- R/qtlnet available at www.github.org/byandell
- Condor cluster: chtc.cs.wisc.edu
 - System Of Automated Runs (SOAR)
 - ~2000 cores in pool shared by many scientists
 - automated run of new jobs placed in project

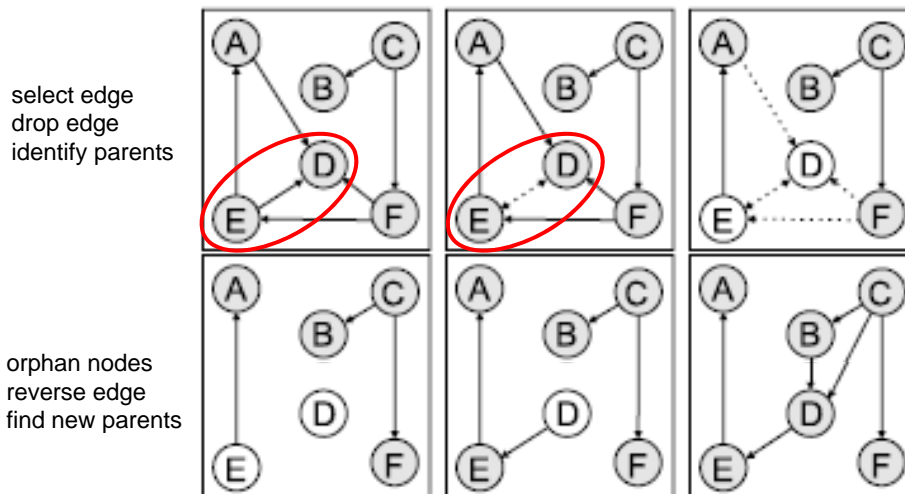


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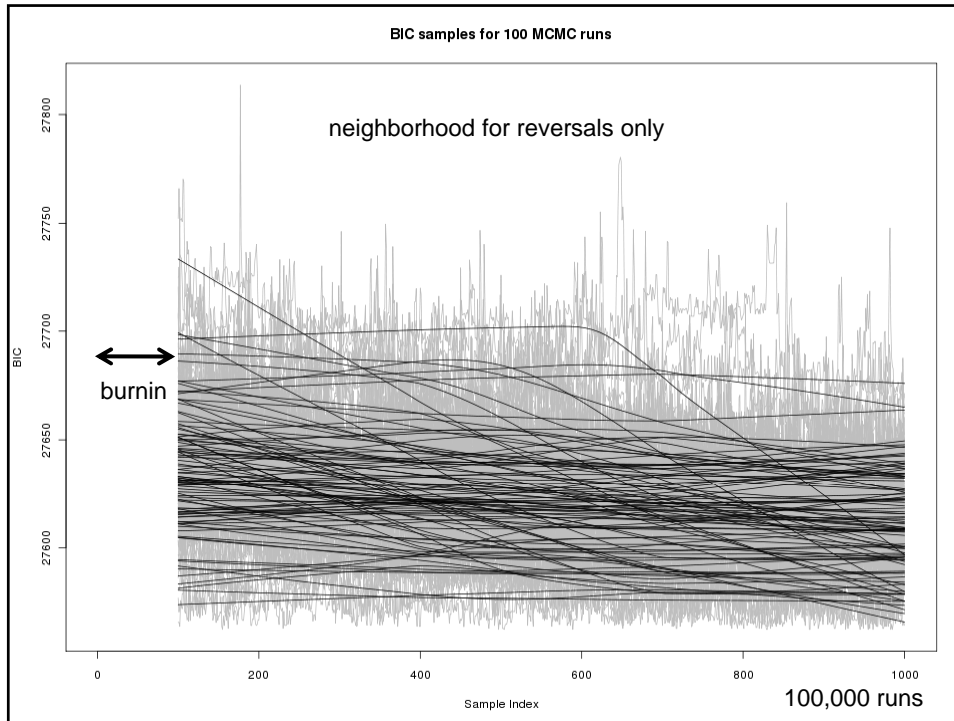
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neighborhood edge reversal



Grzegorzczak M. and Husmeier D. (2008) *Machine Learning* 71 (2-3), 265-305.



limits of causal inference

unfaithful: false positive edges

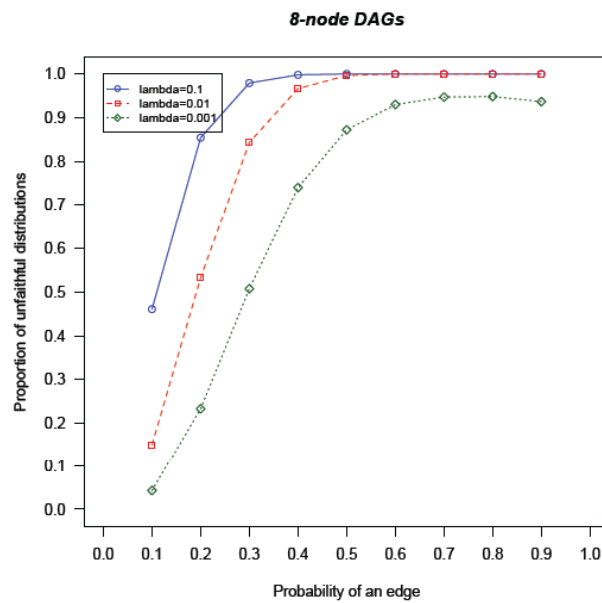
$$\lambda = \min | \text{cor}(Y_i, Y_j) |$$

$$\lambda = c \cdot \text{sqrt}(dp/n)$$

$d = \text{max degree}$

$p = \# \text{ nodes}$

$n = \text{sample size}$



Uhler, Raskutti, Buhlmann, Yu (2012 arxiv)

how to use functional information?

- functional grouping from prior studies
 - may or may not indicate direction
 - gene ontology (GO), KEGG
 - knockout (KO) panels
 - protein-protein interaction (PPI) database
 - transcription factor (TF) database
- methods using only this information
- priors for QTL-driven causal networks
 - more weight to local (*cis*) QTLs?

modeling biological knowledge

- infer graph G from biological knowledge B
 - $\Pr(G | B, W) = \exp(-W * |B-G|) / \text{constant}$
 - B = prob of edge given TF, PPI, KO database
 - derived using previous experiments, papers, etc.
 - G = 0-1 matrix for graph with directed edges
- W = inferred weight of biological knowledge
 - $W=0$: no influence; W large: assumed correct
 - $P(W|B) = \phi \exp(-\phi W)$ exponential
- Werhli and Husmeier (2007) *J Bioinfo Comput Biol*

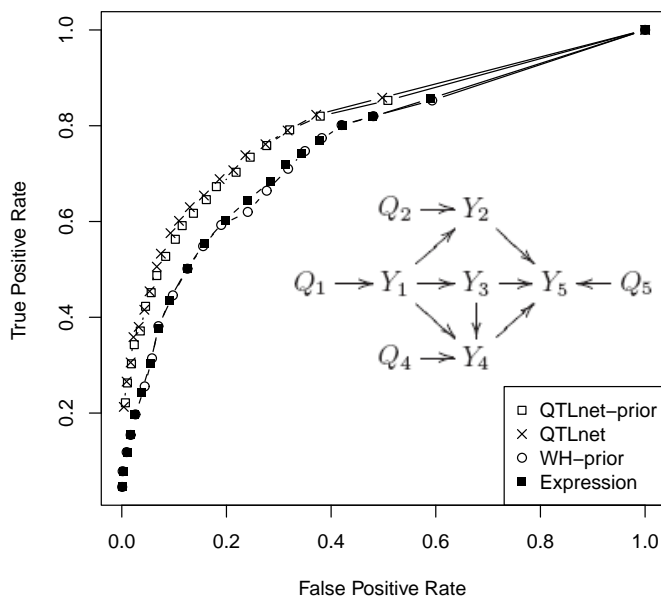
combining eQTL and bio knowledge

- probability for graph G and bio-weights W
 - given phenotypes Y , genotypes X , bio info B
- $\Pr(G, W \mid Y, Q, B) = \Pr(Y \mid G, Q) \Pr(G \mid B, W) \Pr(W \mid B)$
 - $\Pr(Y \mid G, Q)$ is genetic architecture (QTLs)
 - using parent nodes of each trait as covariates
 - $\Pr(G \mid B, W)$ is relation of graph to biological info
 - see previous slides
 - put priors on QTL based on proximity, biological info
- related ref: Kim et al. Przytycka (2010) *RECOMB*

ROC curve simulation

open =
QTLnet

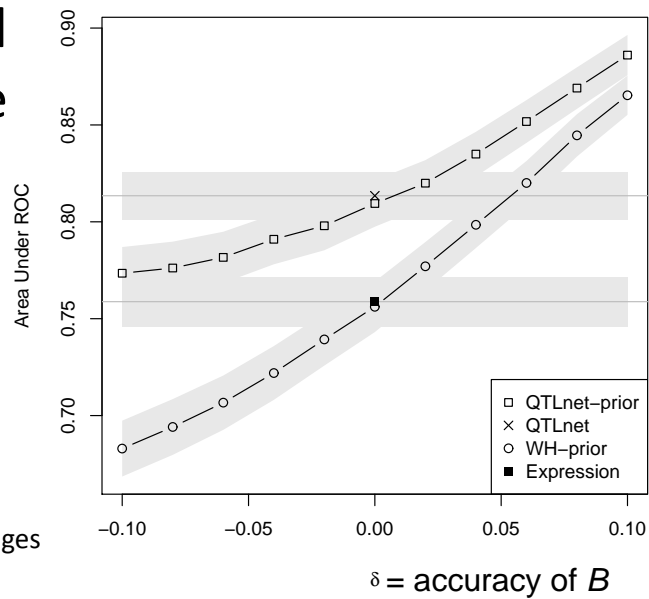
closed =
phenotypes
only



integrated
ROC curve

2x2:
genetics
pathways

probability classifier
ranks true > false edges



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QTL software on CRAN

- R/qtlhot: hotspots & causal architecture
 - map hotspots, permutation tests
 - causal model selection tests
- R/qtlnet: QTL-driven phenotype networks
 - infer QTLs and directed graphs
 - coming: prior biological information
- R/qtlbim: Bayesian Interval Mapping for QTL
 - multiple QTL inference, graphical diagnostics
 - see earlier Jax talks for details

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many thanks!

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 - Chris Plaisier (Institute for Systems Biology, Seattle)
 - Elias Chaibub Neto (Sage Bionetworks, Seattle)
 - Jee Young Moon (grad student)
 - Xinwei Deng (VA Tech Asst Prof)
 - and many more!