

# Inferring Causal Phenotype Networks

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# outline

- QTL-driven directed graphs
  - Assume QTLs known, network unknown
  - Infer links (edges) between pairs of phenotypes (nodes)
    - Based on partial correlation
  - Infer causal direction for edges
  - Chaibub et al. (2008 *Genetics*)
  - Software R/qdg available on CRAN
- Causal graphical models in systems genetics
  - QTLs unknown, network unknown
  - Infer both genetic architecture (QTLs) and pathways (networks)
  - Chaibub et al. (2010 *Ann Appl Statist*)
  - Software R/qtlnet ([www.stat.wisc.edu/~yandell/sysgen/qtlnet](http://www.stat.wisc.edu/~yandell/sysgen/qtlnet))

# QTL-driven directed graphs

- See edited slides by Elias Chaibub Neto
  - BIOCOMP 2008 talk
  - Chaibub Neto, Ferrara, Attie, Yandell (2008) Inferring causal phenotype networks from segregating populations. *Genetics* 179: 1089-1100.
  - Ferrara et al. Attie (2008) Genetic networks of liver metabolism revealed by integration of metabolic and transcriptomic profiling. *PLoS Genet* 4: e1000034.

# causal graphical models in systems genetics

- 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)
- 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*)
- Jointly infer unknowns of interest
  - genetic architecture
  - causal network

# Basic idea of QTLnet

- 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

# MCMC for QTLnet

- Propose new causal network with simple changes to current network
  - Change edge direction
  - Add or drop edge
- Find any new genetic architectures (QTLs)
  - Update phenotypes whose parents  $pa(y)$  change in new network
- Compute likelihood for new network and QTL
- Accept or reject new network and QTL
  - Usual Metropolis-Hastings idea

# Future work

- Incorporate latent variables
  - Aten et al. Horvath (2008 *BMC Sys Biol*)
- Allow for prior information about network
  - Werhli and Husmeier (2007 *SAGMB*); Dittrich et al. Müller (2008 *Bioinfo*); Zhu et al. Schadt (2008 *Nat Genet*); Lee et al. Koller (2009 *PLoS Genet*); Thomas et al. Portier (2009 *Genome Bio*); Wu et al. Lin (2009 *Bioinfo*)
- Improve algorithm efficiency
  - Ramp up to 1000s of phenotypes
- Extend to outbred crosses, humans