Unraveling Complex Gene-Phenotype Relationships using Multi-Phenotype Association (MPA) Decomposition

Background

Genome Wide Association Studies (GWAS) results often reveal single nucleotide polymorphisms (SNPs) or genes that associate with multiple phenotypes (MPA), often indicating a pleiotropy effect. There are several modes, or signatures, of pleiotropy that imply different potential genetic mechanisms. Modifications to a gene with pleiotropic effects can potentially have impact on multiple traits, so is important to understand these patterns.

Approach

- We represented GWAS results (SNP-to-phenotype) as bipartite networks
- We then constructed modules from SNPs and genes that shared associations with similar sets of phenotypes. These modules provide network entities that tie together groups of SNPs, genes and phenotypes for network analysis

Outcome

- Developed MPA Decomposition, a new network-based approach which enables rapid detection of pleiotropic genes and their mode of pleiotropy on a genome-wide scale
- In *Populus trichocarpa*, genes with Type II pleiotropy appear to be enriched for many developmental functions

Significance

- This method should prove invaluable in the interpretation of large GWAS datasets and aid in future synthetic biology efforts by highlighting potential off-target phenotypic effects.

Signature decomposition example. Two Poplar genes, Potri.013G092400 (A) and Potri.001G419800 (B) have the same surrounding network topology in the gene-phenotype network in that they are both connected to two phenotypes. Projecting the genes into powerset space through MPA decomposition of the gene-phenotype network indicates that they exhibit different MPA signatures: Potri.013G092400 exhibits a type 1 MPA signature (C), containing a SNP associating with two phenotypes (E), while Potri.001G419800 exhibits a type 2 MPA signature (D) containing two SNPs, each with a different phenotype association (F). For example Type I pleiotropy exists due to one SNP within a gene associating with multiple traits, while Type II exists when multiple SNPs within a gene associate with one trait each.