Multiple Traits

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January 2017
why study multiple traits?

- We may not know ...
  - how to measure (quality, shape, taste)
  - when to measure (development, season, kinetics)
  - what to measure (molecular pathways)
- We are interested in many things
  - individuals expensive
  - multiple measurements cheap (high throughput)
- causal relationships among traits
  - pleiotropy vs close linkage
  - indirect effect of QTL via other trait
  - untangle genetic & environment correlation
multiple traits and GxE

- same phenotype in multiple environments
  - does genetic response depend on environment?
  - comparing 2 (or more) environments
  - trends across a cline or gradient
- multiple phenotypes
  - does one trait affect others (directly)?
  - leveraging similar biological function
  - correlation and causalty models
what affects outcomes?

- **Time**
  - development, growth, aging, senescence
  - physiology, reaction to stimuli
  - evolution, selection

- **Space**
  - geography, altitude, longitude, height, gravity
  - soil structure, plant density
  - seed & pollen (plant part) dispersal

- **Stress**
  - physiology, nutrients, light, heat, water
  - weeds, herbivores, pollinators
  - disease, pests, parasites, harvesting
goals with multiple traits

- use multiple phenotypes to improve QTL detection
- do traits share QTL (pleiotropy)?
- causal relationships among traits?
- effects of QTL across time
gravitropic response: root tip

- *Arabidopsis thaliana* Ler x Cvi
  - 92 NIL; 2525 seedlings
  - 162 RILs; 2132 (RIL1) or 2325 (RIL2) seedlings
- genotypes: 102 (NIL) or 234 (RILs) markers on 5 chr
- root tip angles every 2 min

Moore, Johnson, Kwak, Livny, Broman, Spalding (2013)
gravitropic response over time

Moore, Johnson, Kwak, Livny, Broman, Spalding (2013)
pleiotropy?

- $y_1$ & $y_2$ are pleiotropic
  - both depend on $q_1$
  - $\text{cor}(y_1, y_2 | q_1) = 0$
- $y_2$ & $y_3$ are pleiotropic
  - both depend on $q_2$
  - $\text{cor}(y_2, y_3 | q_2) = 0$
- $y_1$ & $y_3$ have linked QTLs
  - $\text{cor}(q_1, q_2)$ via linkage
  - $\text{cor}(y_1, y_3)$ indirect
close linkage?
basic multiple trait model

one trait:

\[ y = q\beta + e, \quad e \sim N(0, \sigma^2) \]

\[ \text{LOD} = \left( \frac{n}{2} \right) \log_{10} \left( \frac{\text{RSS}_0}{\text{RSS}_1} \right) \]

multiple traits:

\[ Y = Q\beta + E, \quad E \sim \text{MVN}(0, \Sigma) \]

\[ \text{LOD} = \left( \frac{n}{2} \right) \log_{10} \left( \frac{|\hat{\Sigma}_0|}{|\hat{\Sigma}_1|} \right) \]
pleiotropy?

- consider two traits and one chromosome
- assume each affected by a single QTL
- 1-D scan for single QTL assumed to affect both
- 2-D scan over chromosome
  - separate axes for each trait
  - or profile each trait across other trait
- significance?
  - parametric bootstrap using fitted single-QTL model
  - stratified (within QTL genotype) permutation test
pleiotropy in flowering time
pleiotropy in flowering time

- allow 2 QTL per trait
- is 1 enough?
- or are there 2 QTL?
pleiotropy in flowering time

profile LOD of each trait with respect to the other
causal models

- All ... phenomena are linked together, and the problem ... is how close is the degree of association. Karl Pearson (1911)
- direct influence of one condition on another ... [through] all connecting paths of influence ... among the variables in a system with ... causal relations. Sewall Wright (1921)
- Causality is not mystical or metaphysical. It can be understood in terms of simple processes ... in a friendly mathematical language, ready for computer analysis. Judea Pearl (2000)
causal relations

- $q_j = \text{genotype (QTL)}$
- $r_k = \text{RNA expression}$
- $y = \text{physiology}$

QTLs: $r_j = \mu_{qj} + e_j$
linkage: $\text{cor}(q_1, q_2)$
causal: $y = r_2 + e_2$
reactive: $r_4 = a + by + e_4$

$$\Pr(Q, R, Y) = \Pr(q_1, q_2)\Pr(y_1 | q_1)\Pr(r_2 | q_2)\Pr(r_3 | q_2)\Pr(y | r_2)\Pr(r_4 | y)$$
Nfatc2 impact on LOD

- 500 mice F2: B6 x BTBR obese
- diabetes & obesity
- insulin resistance
- 130+ mRNA expression hot spot
- Nfatc2 as key driver

Keller et al. Yandell, Kendziorski, Attie (2016)
PLoS Gen
Nfatc2 causal architecture

is gene mRNA causal (red) or reactive (blue) to other mRNA?