

Multiple Traits

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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 causality 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

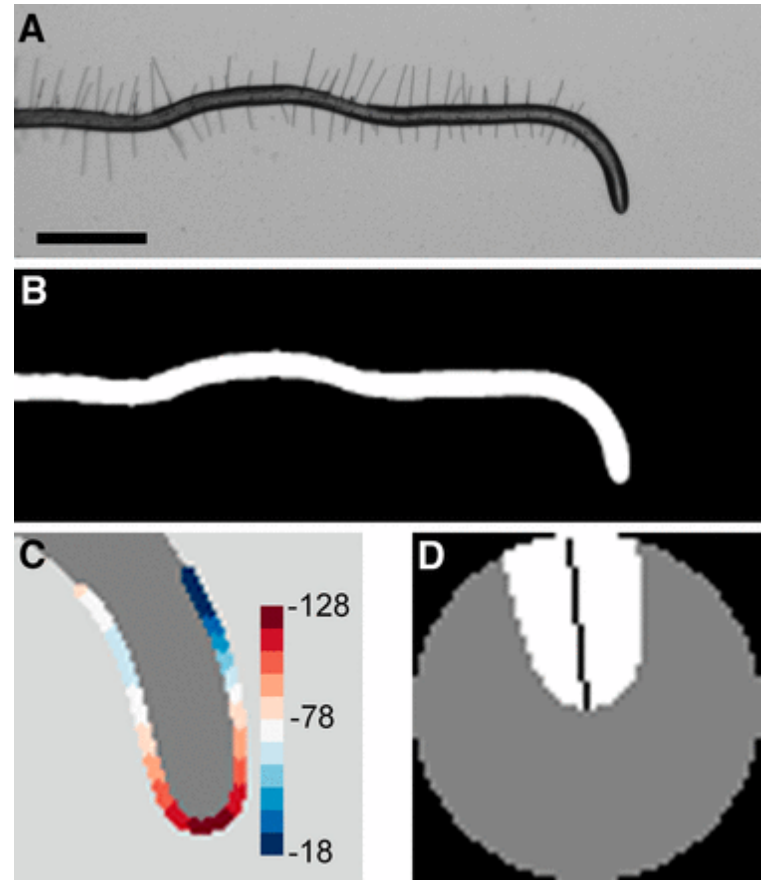
goals with multiple traits

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

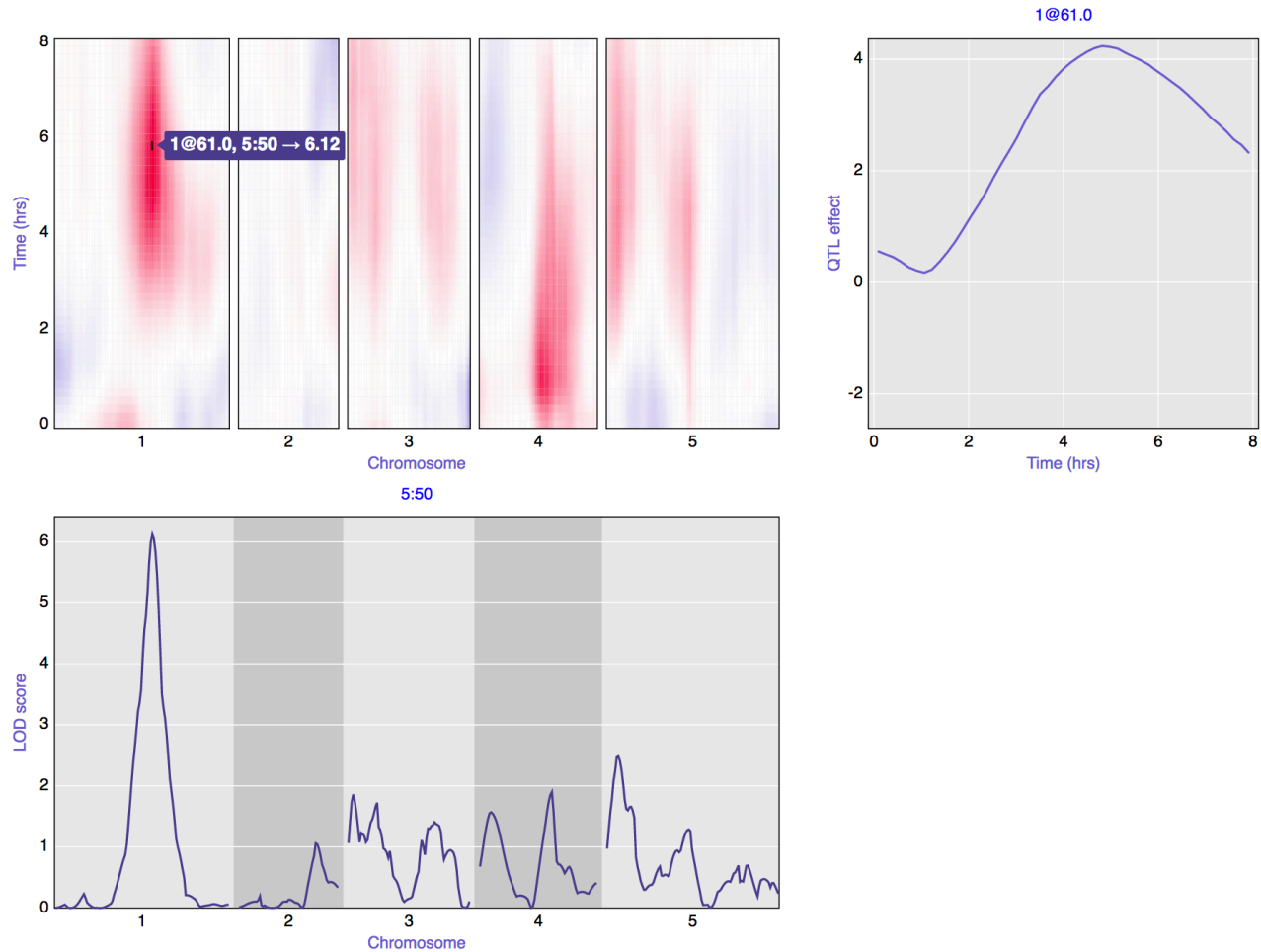
gravitopic response: root tip

- *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)



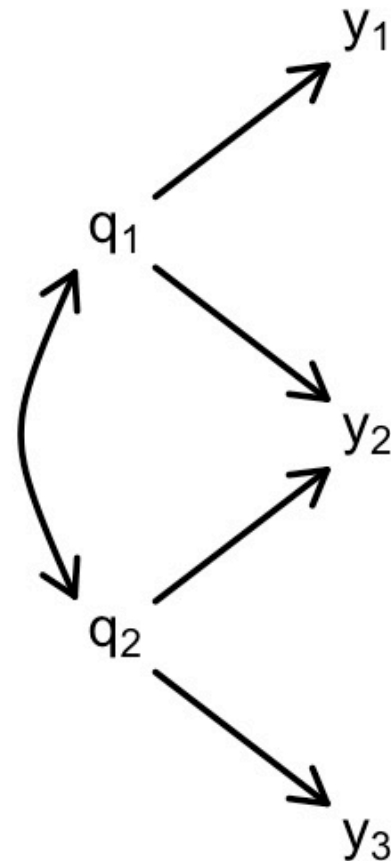
gravitropic response over time



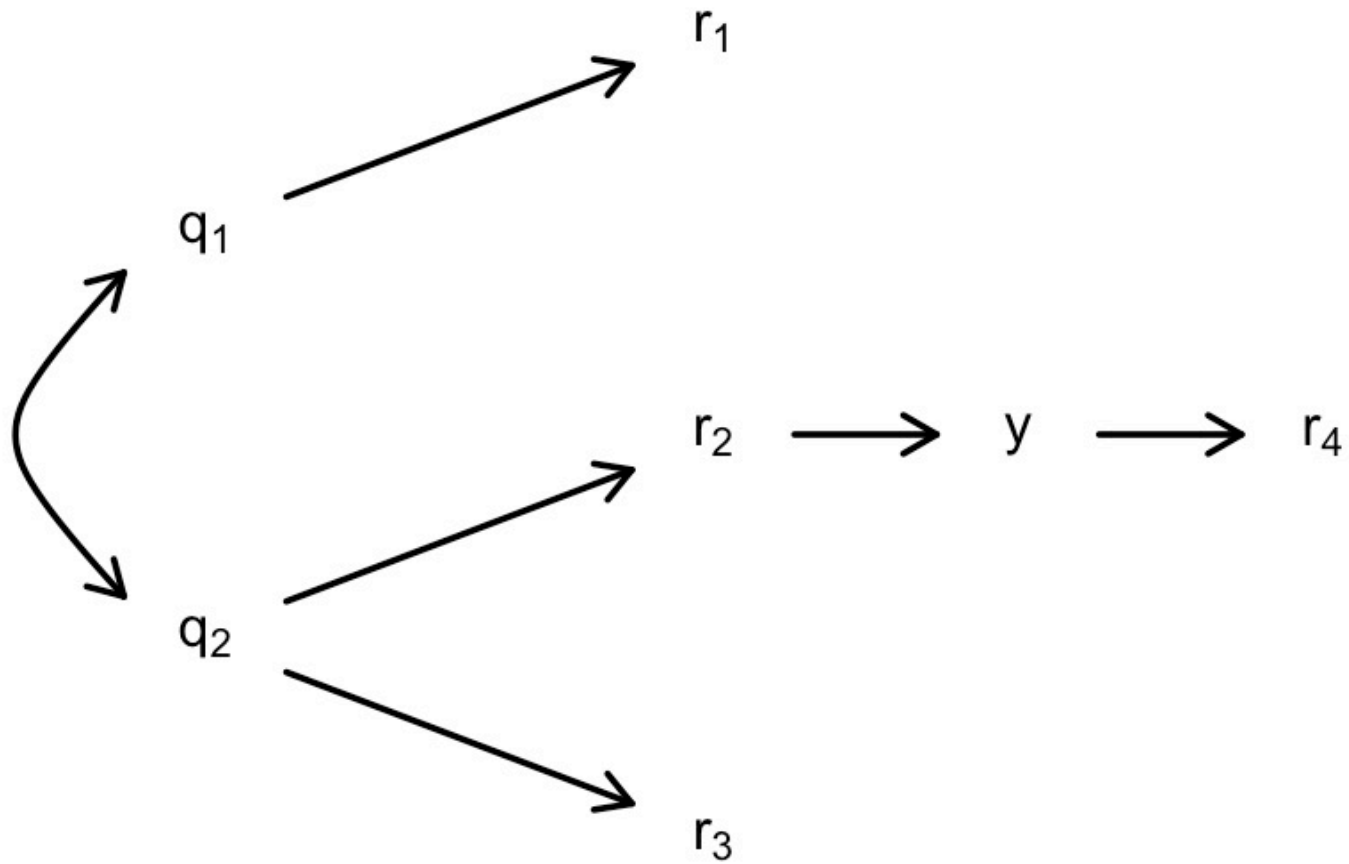
Moore, Johnson, Kwak, Livny, Broman, Spalding (2013)

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:

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

$$\text{LOD} = (n/2) \log_{10}(\text{RSS}_0/\text{RSS}_1)$$

multiple traits:

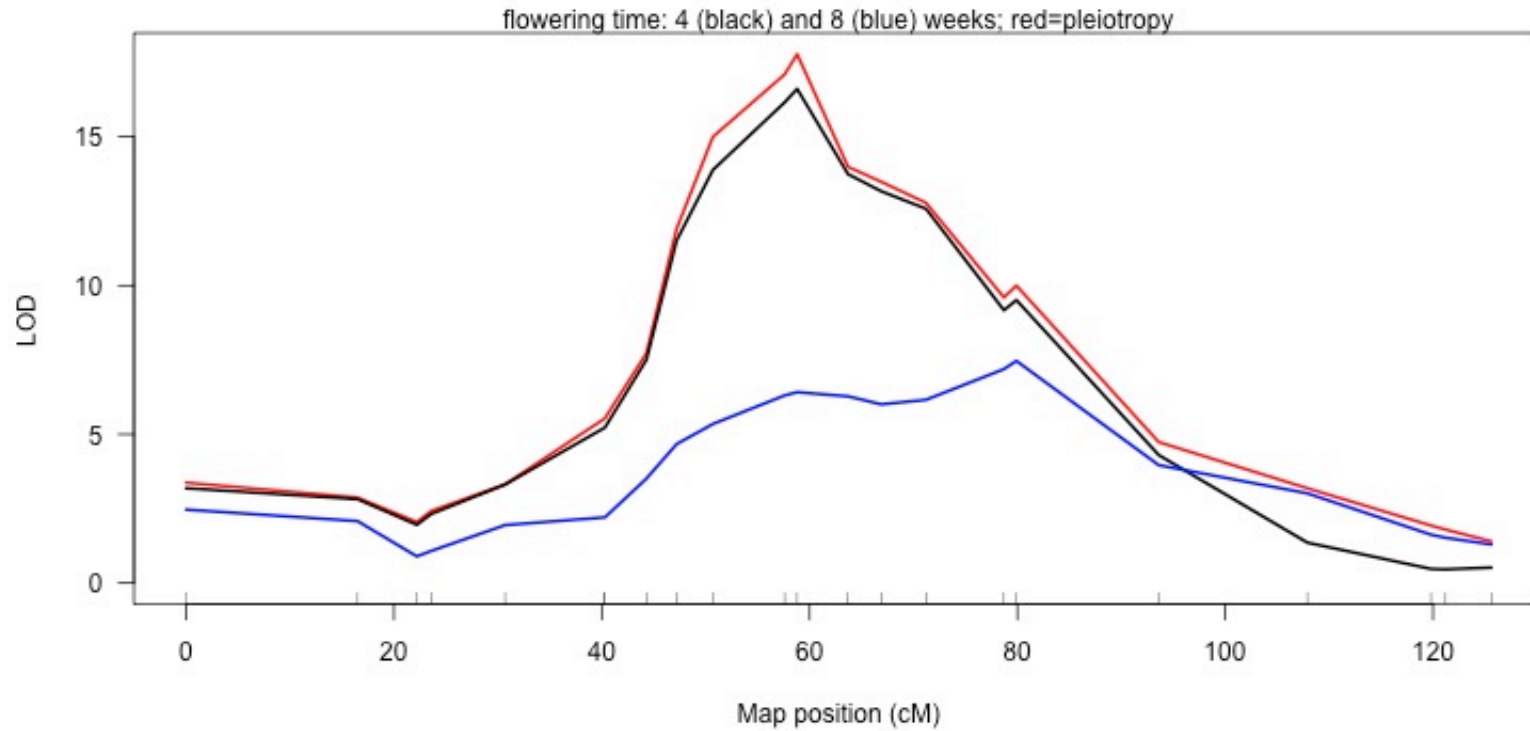
$$Y = Q\beta + E, \quad E \sim \text{MVN}(0, \Sigma)$$

$$\text{LOD} = (n/2) \log_{10}(|\hat{\Sigma}_0|/|\hat{\Sigma}_1|)$$

pleiotropy?

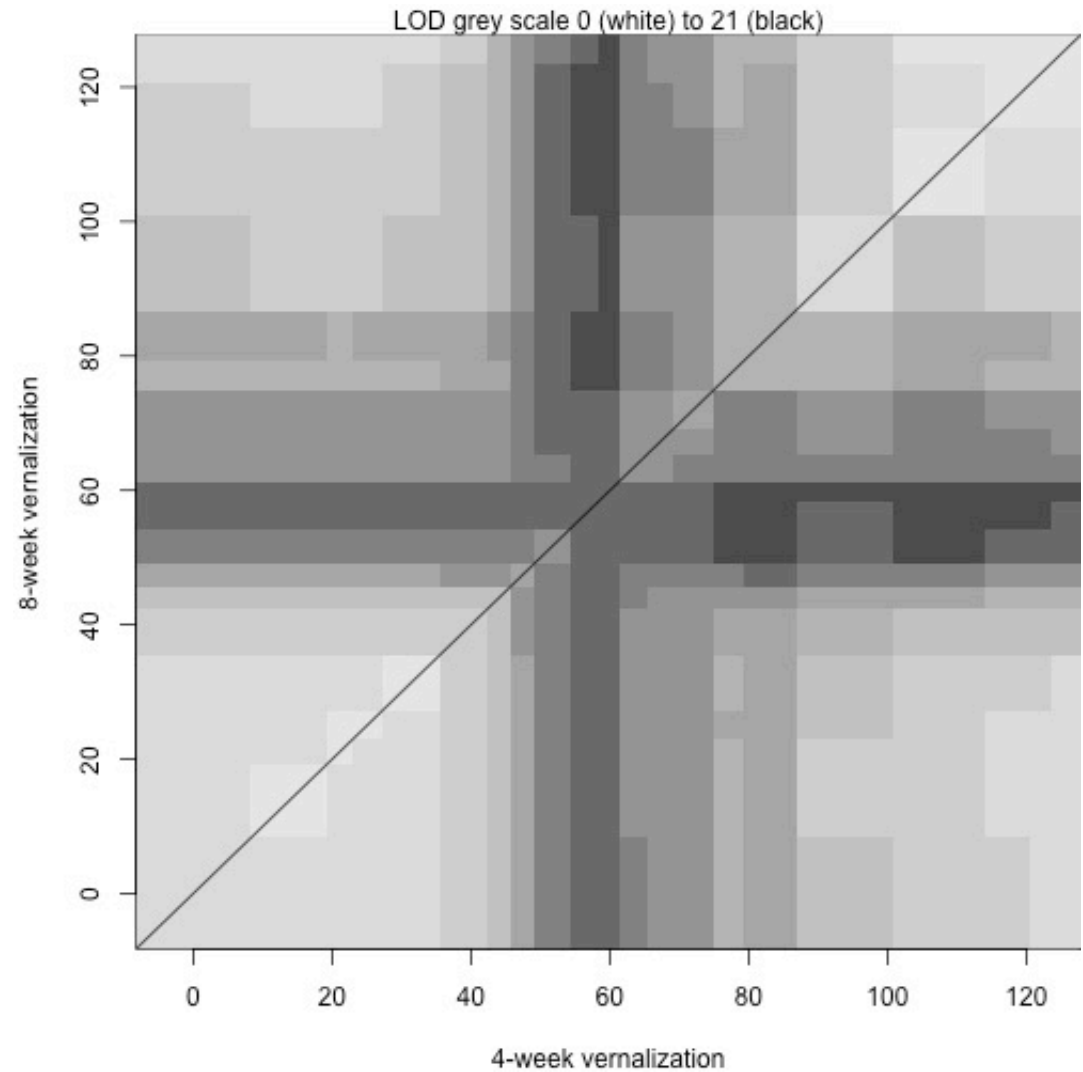
- consider two traits and one chromosome
- assume each affected by a single QTL
- 1-D scan for single QTL assumed to affect both
- 2-D scan over chromosome
 - separate axes for each trait
 - or profile each trait across other trait
- significance?
 - parametric bootstrap using fitted single-QTL model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

pleiotropy in flowering time



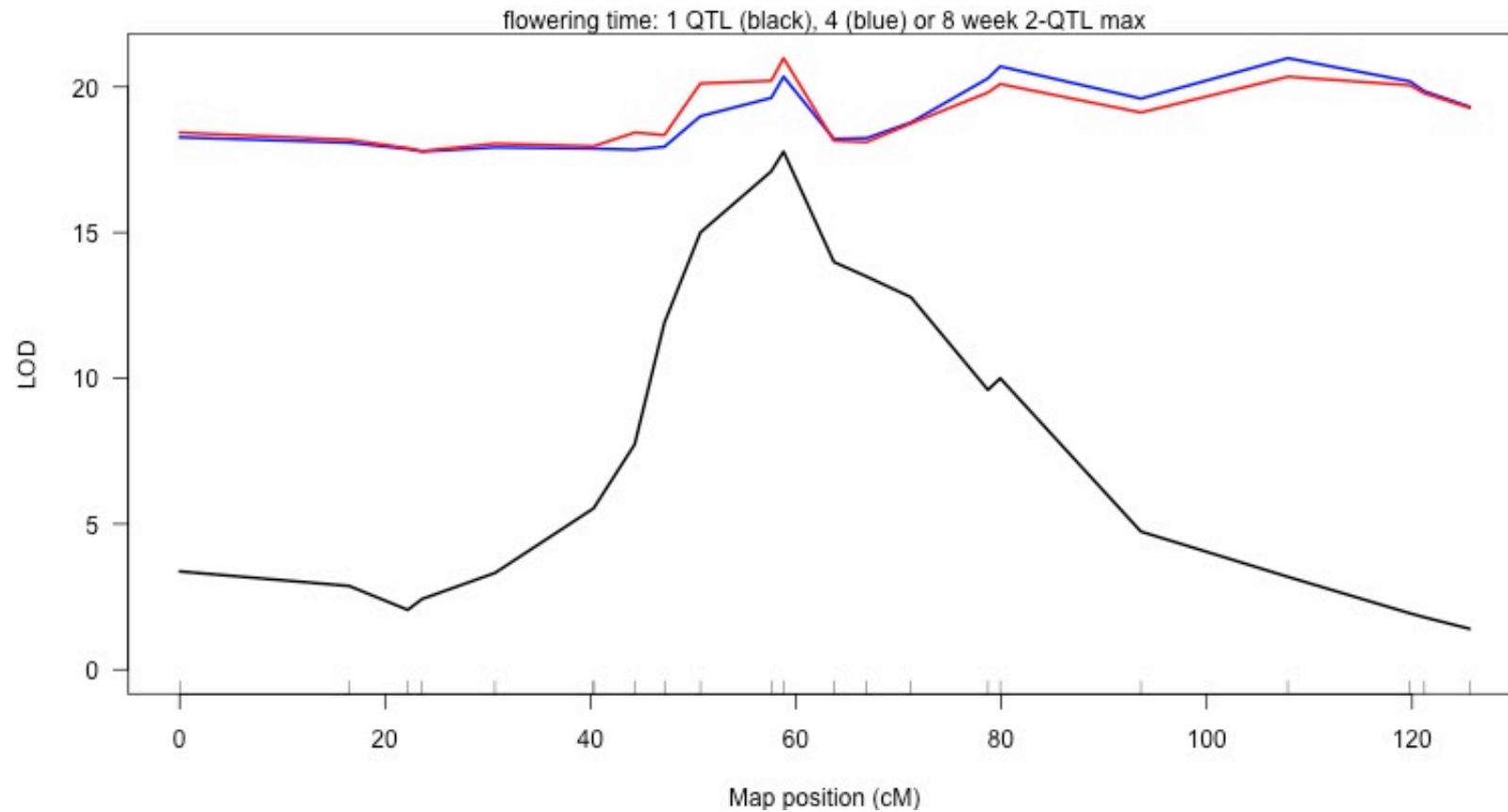
pleiotropy in flowering time

- 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

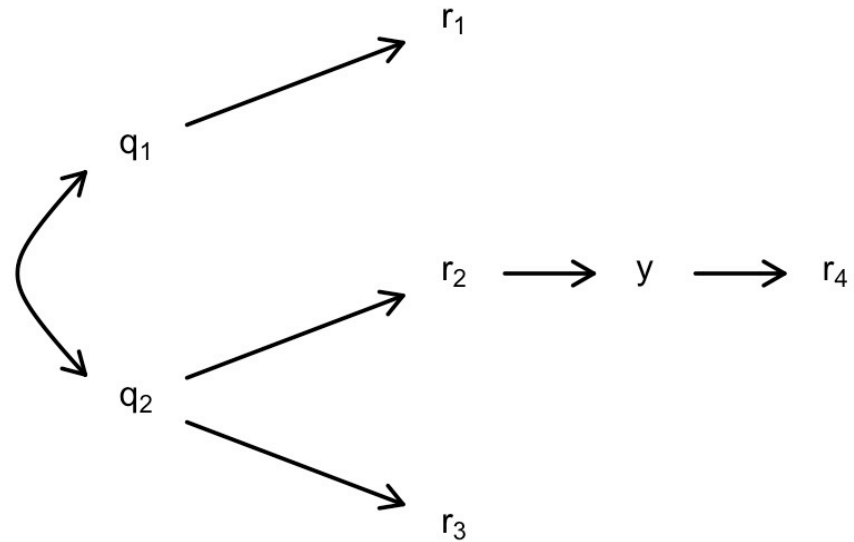
- q_j = genotype (QTL)
- r_k = RNA expression
- y = physiology

QTLs: $r_j = \mu_{q_j} + e_j$

linkage: $\text{cor}(q_1, q_2)$

causal: $y = r_2 + e_2$

reactive: $r_4 = a + by + e_4$



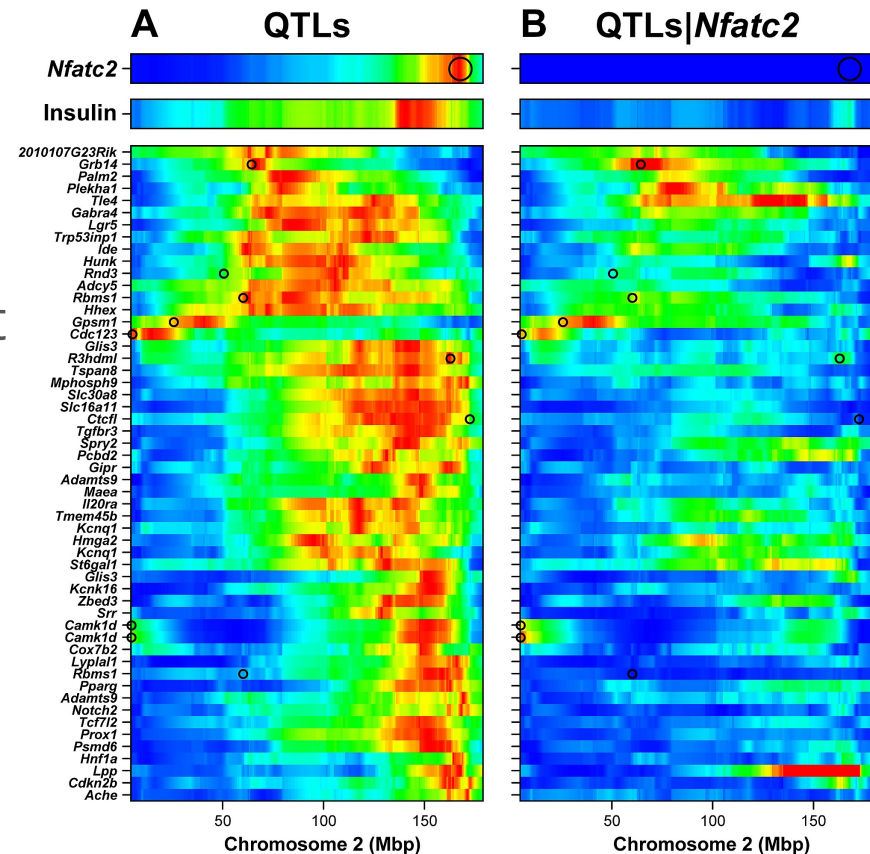
$$\text{pr}(Q, R, Y) = \text{pr}(q_1, q_2)\text{pr}(y_1 | q_1)\text{pr}(r_2 | q_2)\text{pr}(r_3 | q_2)\text{pr}(y | r_2)\text{pr}(r_4 | y)$$

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?

