Mapping multiple QTL in experimental crosses

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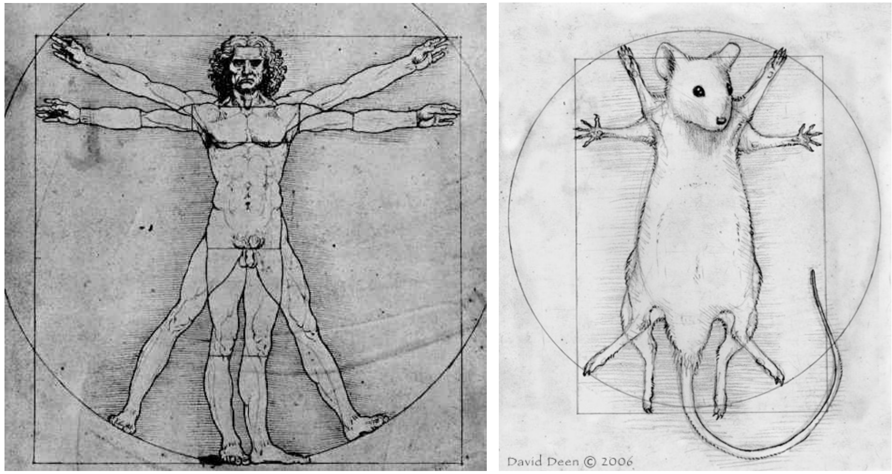
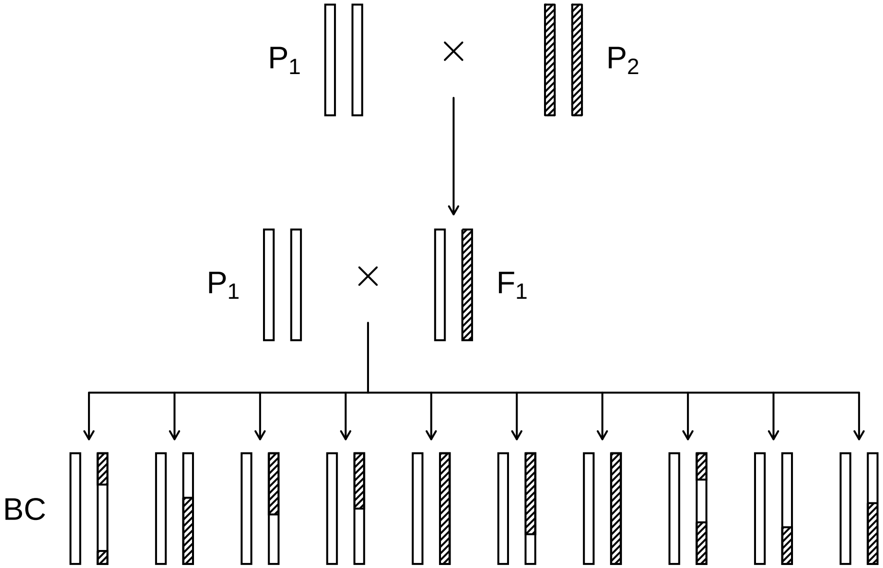
Human vs mouse

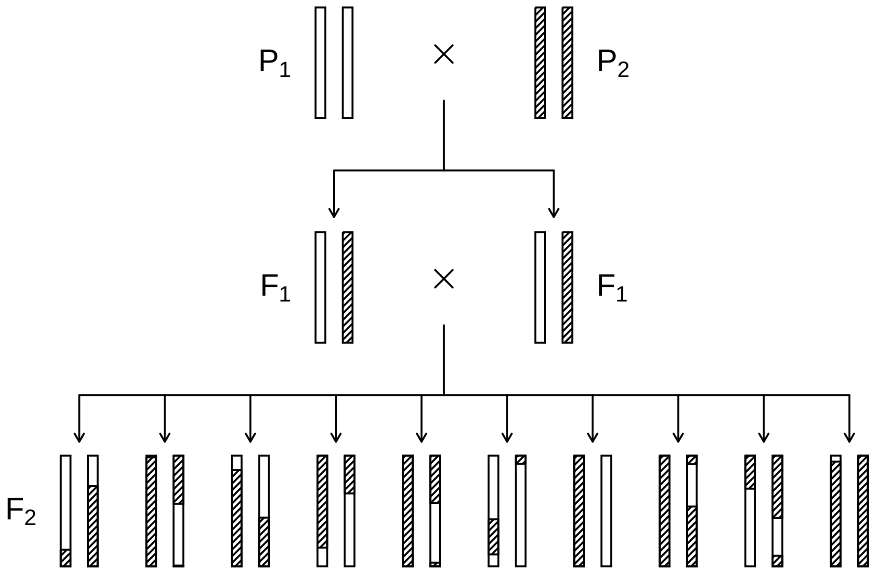


`www.daviddeen.com`

Backcross



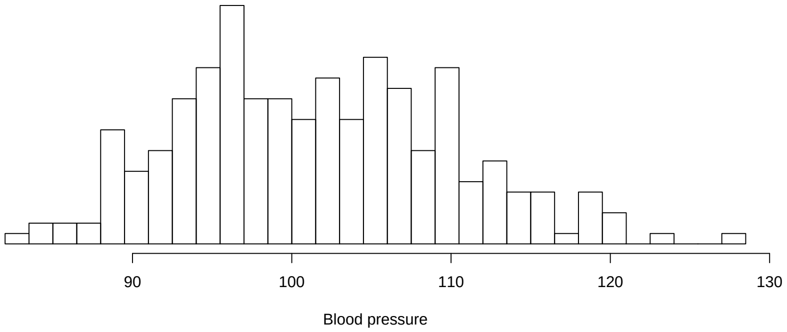
Intercross



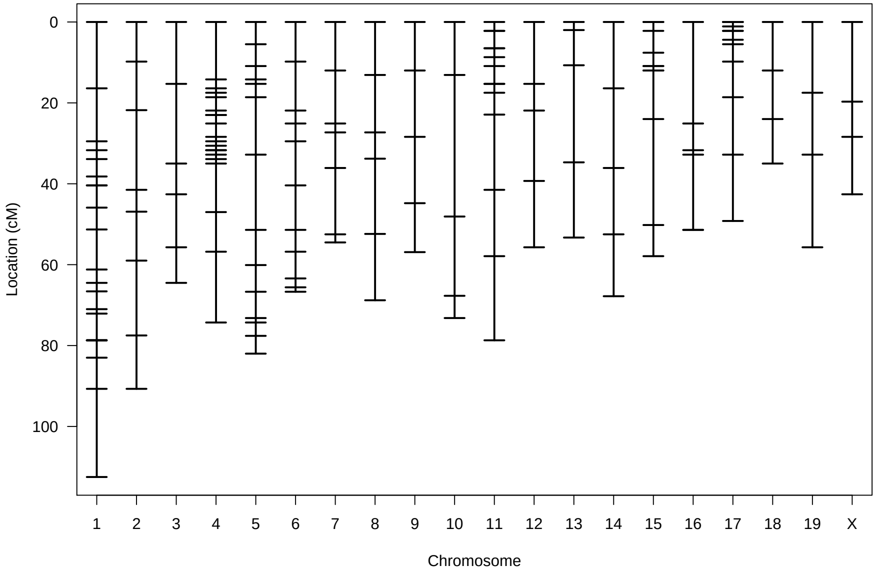
Phenotype data

Sugiyama et al. Genomics 71:70-77, 2001

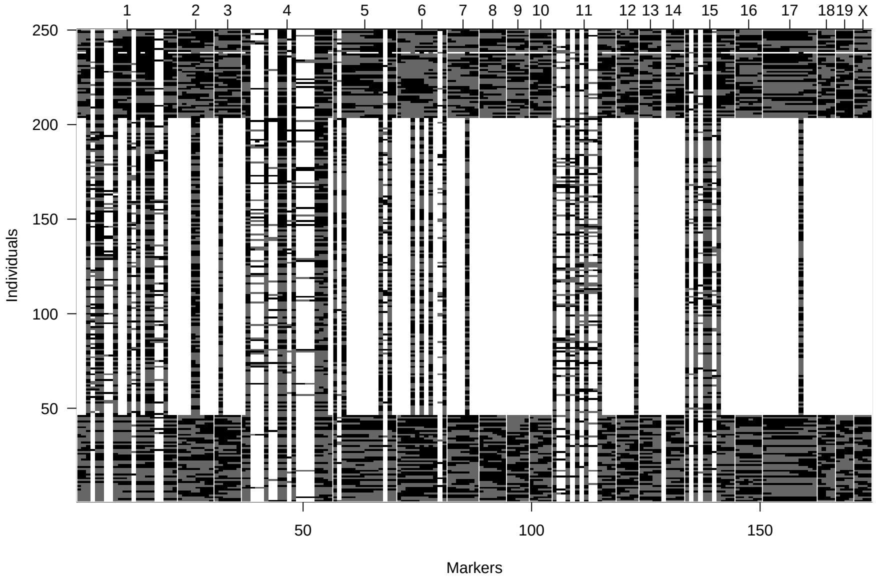
250 male mice from the backcross (A × B) × B
Blood pressure after two weeks drinking water with 1% NaCl



Genetic map



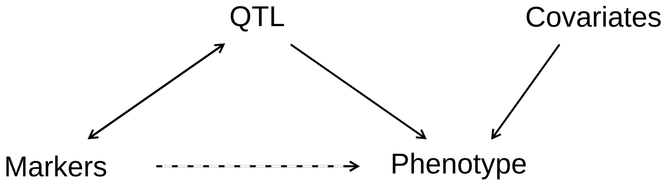
Genotype data



Goals

- Identify quantitative trait loci (QTL)
  (and interactions among QTL)
- Interval estimates of QTL location
- Estimated QTL effects

Statistical structure



QTL

Covariates

Markers

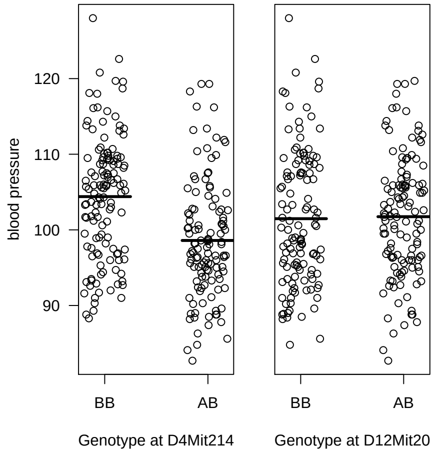
Phenotype

The missing data problem: Markers ⟷ QTL

The model selection problem: QTL, covariates ⟶ phenotype

ANOVA at marker loci

- Split mice into groups according to genotype at a marker.
- Do a t-test / ANOVA.
- Repeat for each marker.



Interval mapping

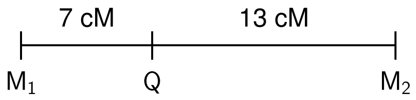
Lander & Botstein (1989)

- Assume a single QTL model.
- Consider each position in the genome, one at a time, as the location of the putative QTL.
- Let $q = 0/1$ if the (unobserved) QTL genotype is BB/AB.
  (Or 0/1/2 if the QTL genotype is AA/AB/BB in an intercross.)

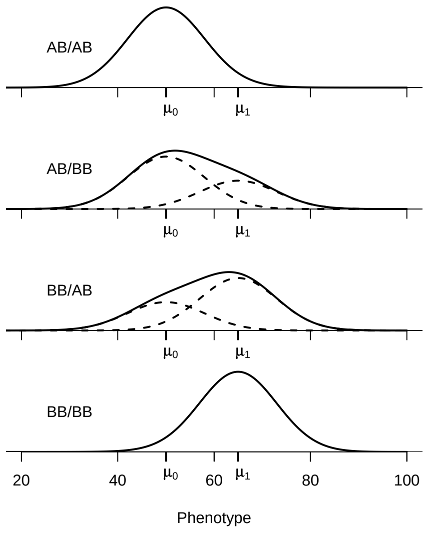
  Assume $y \mid q \sim N(\mu_q, \sigma)$
- Calculate $p_q = \Pr(q \mid \text{marker data})$.

  $y \mid \text{marker data} \sim \sum_q p_q \, \phi(y \mid \mu_q, \sigma)$

The normal mixtures



- Two markers separated by 20 cM, with the QTL closer to the left marker.
- The figure at right shows the distributions of the phenotype conditional on the genotypes at the two markers.
- The dashed curves correspond to the components of the mixtures.



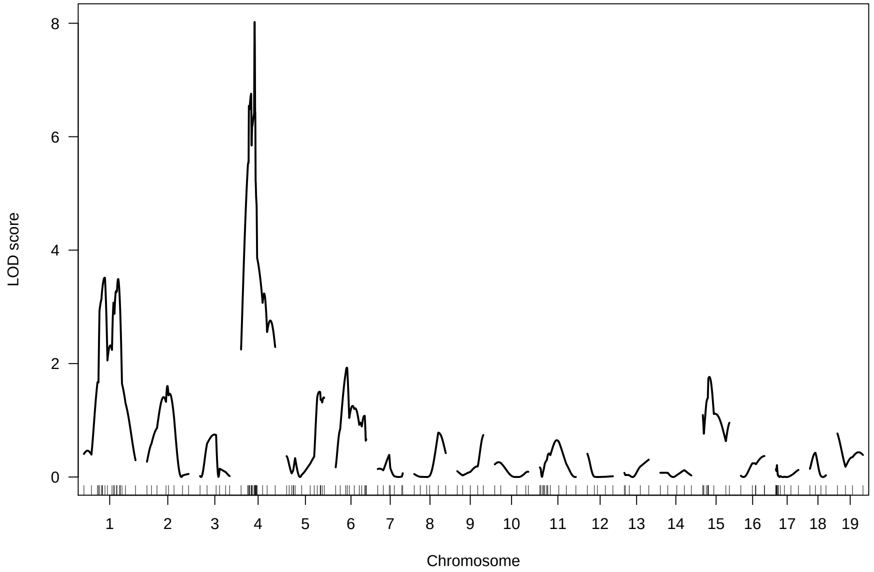
LOD scores

$$\begin{aligned}\text{LOD}(\lambda) &= \log_{10} \text{ likelihood ratio comparing the hypothesis of a} \\ &\quad \text{QTL at position } \lambda \text{ versus that of no QTL} \\ &= \log_{10}\left\{\frac{\Pr(y|\text{QTL at } \lambda, \hat{\mu}_{q\lambda}, \hat{\sigma}_\lambda)}{\Pr(y|\text{no QTL}, \hat{\mu}, \hat{\sigma})}\right\}\end{aligned}$$

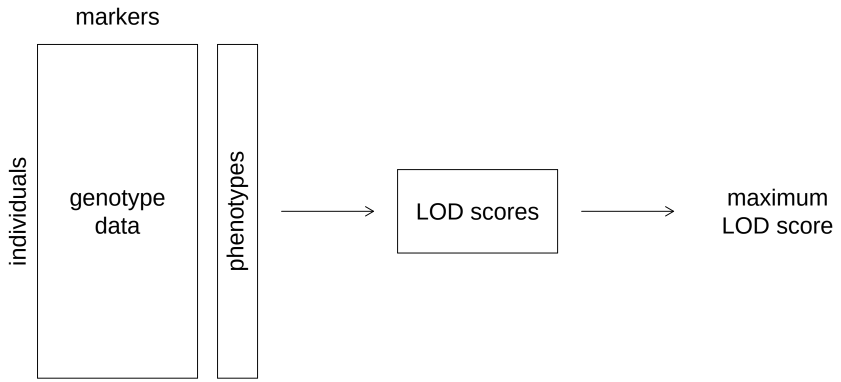
$\hat{\mu}_{q\lambda}, \hat{\sigma}_\lambda$ are the MLEs, assuming a single QTL at position λ.

No QTL model: The phenotypes are iid $N(\mu, \sigma^2)$.

LOD curves



Permutation test



markers

individuals

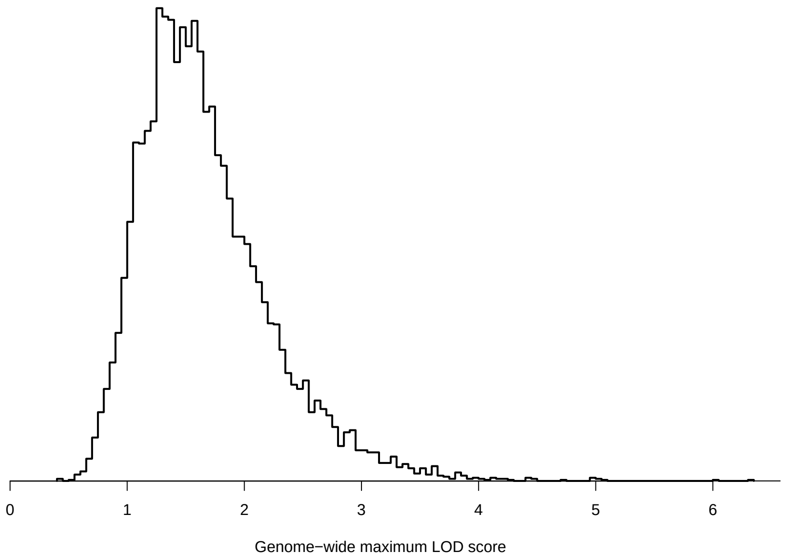
genotype data

phenotypes

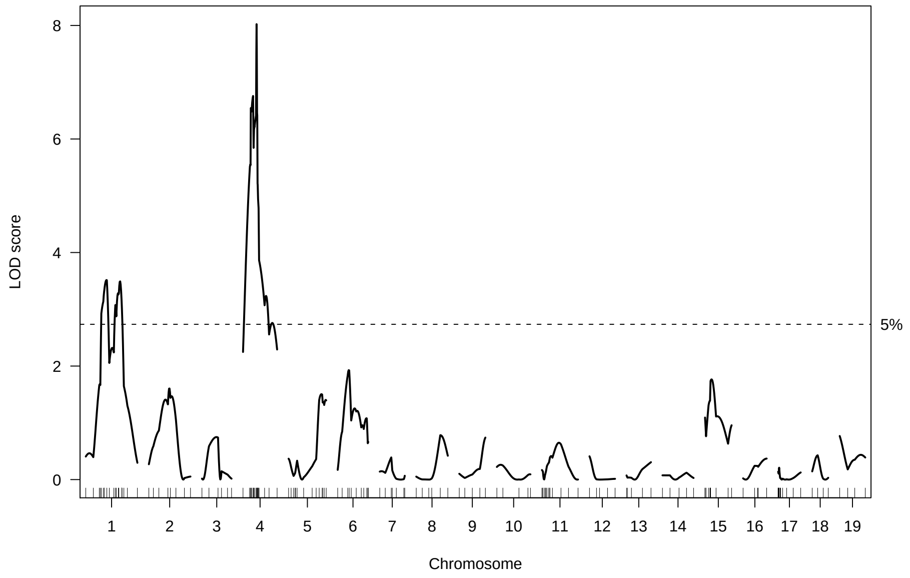
LOD scores

maximum LOD score

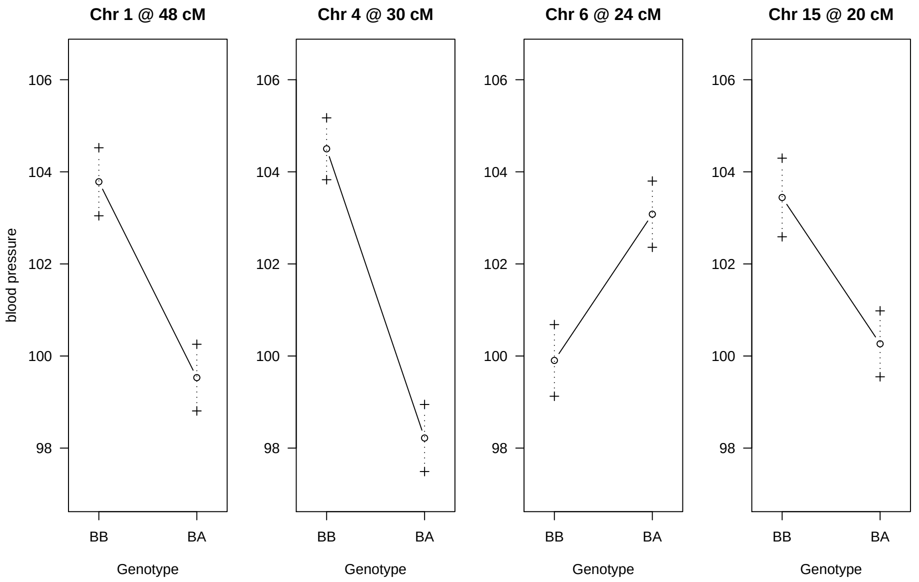
Permutation results



LOD curves



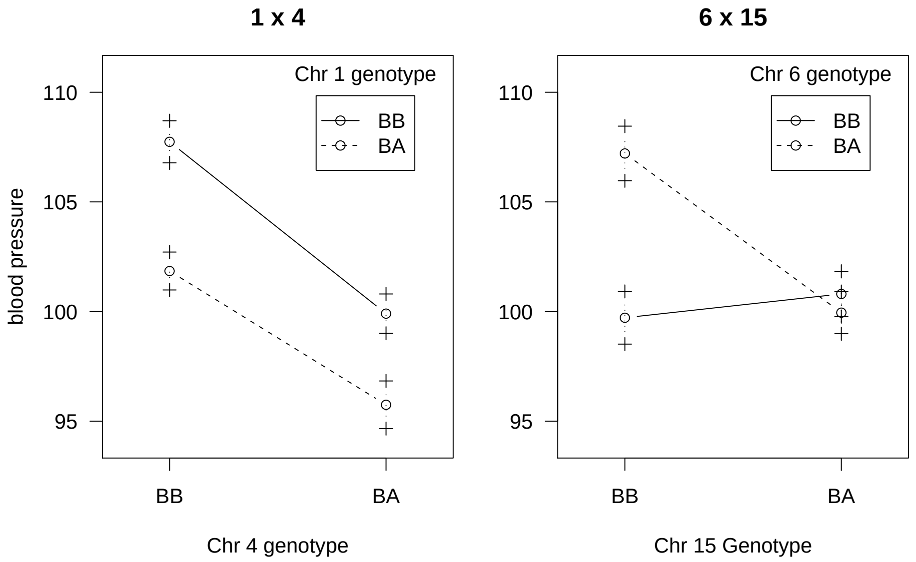
Estimated effects



Modeling multiple QTL

- Reduce residual variation ⟶ increased power
- Separate linked QTL
- Identify interactions among QTL (epistasis)

Estimated effects



Hypothesis testing?

- In the past, QTL mapping has been regarded as a task of hypothesis testing.

  Is this a QTL?

  Much of the focus has been on adjusting for test multiplicity.

- It is better to view the problem as one of model selection.

  What set of QTL are well supported?
  Is there evidence for QTL-QTL interactions?

  Model $=$ a defined set of QTL and QTL-QTL interactions
  (and possibly covariates and QTL-covariate interactions).

Model selection

- Class of models
  - Additive models
  - + pairwise interactions
  - + higher-order interactions
  - Regression trees
- Model fit
  - Maximum likelihood
  - Haley-Knott regression
  - extended Haley-Knott
  - Multiple imputation
  - MCMC
- Model comparison
  - Estimated prediction error
  - AIC, BIC, penalized likelihood
  - Bayes
- Model search
  - Forward selection
  - Backward elimination
  - Stepwise selection
  - Randomized algorithms

Target

- Selection of a model includes two types of errors:
  - Miss important terms (QTLs or interactions)
  - Include extraneous terms
- Unlike in hypothesis testing, we can make both errors at the same time.
- Identify as many correct terms as possible, while controlling the rate of inclusion of extraneous terms.

What is special here?

- Goal: identify the major players
- A continuum of ordinal-valued covariates (the genetic loci)
- Association among the covariates
  - Loci on different chromosomes are independent
  - Along chromosome, a very simple (and known) correlation structure

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Automation

- Assistance to the masses
- Understanding performance
- Many phenotypes

Additive QTL

Simple situation:

- Dense markers
- Complete genotype data
- No epistasis

$$y = \mu + \sum \beta_j q_j + \epsilon \qquad \text{which } \beta_j \neq 0?$$

$\text{LOD}_\delta(\gamma) = \text{LOD}(\gamma) - T\,|\gamma|$

0 vs 1 QTL: $\text{LOD}_\delta(\emptyset) = 0$

$\text{LOD}_\delta(\{\lambda\}) = \text{LOD}(\{\lambda\}) - T$

Experience

- Controls rate of inclusion of extraneous terms
- Forward selection over-selects
- Forward selection followed by backward elimination works as well as MCMC
- Need to define performance criteria
- Need large-scale simulations

Broman & Speed, JRSS B 64:641-656, 2002

Epistasis

$$y = \mu + \sum \beta_j q_j + \sum \gamma_{jk} q_j q_k + \epsilon$$

$$\mathrm{LOD}_{\delta\epsilon}(\gamma) = \mathrm{LOD}(\gamma) - T_m |\gamma|_m + T_i |\gamma|_i$$

T_m = as chosen previously

T_i = ?

Idea 1

Imagine there are two additive QTL and consider a 2d, 2-QTL scan.

T_i = 95th percentile of the distribution of
$\max \mathrm{LOD}_f(s,t) - \max \mathrm{LOD}_a(s,t)$

For the mouse genome:

T_m = 2.69 (BC) or 3.52 (F_2)

T_i^H = 2.62 (BC) or 4.28 (F_2)

Idea 2

Imagine there is one QTL and consider a 2d, 2-QTL scan.

$T_m + T_i$ = 95th percentile of the distribution of
$\max \mathrm{LOD}_f(s,t) - \max \mathrm{LOD}_1(s)$

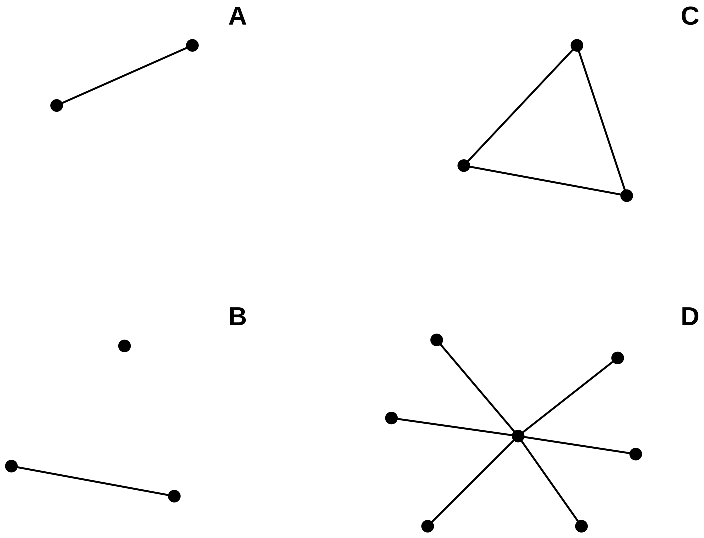
For the mouse genome:

T_m = 2.69 (BC) or 3.52 (F_2)

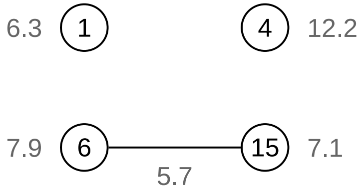
T_i^H = 2.62 (BC) or 4.28 (F_2)

T_i^L = 1.19 (BC) or 2.69 (F_2)

Models as graphs

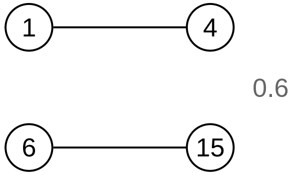


Results



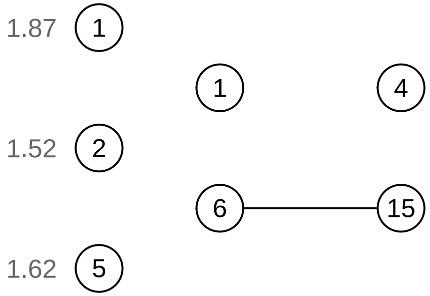
$T_m = 2.69$ $T_i^H = 2.62$ $T_i^L = 1.19$ $T_m + T_i^H = 5.31$ $T_m + T_i^L = 3.88$

Add an interaction?



$T_m = 2.69$ $T_i^H = 2.62$ $T_i^L = 1.19$ $T_m + T_i^H = 5.31$ $T_m + T_i^L = 3.88$

Add another QTL?



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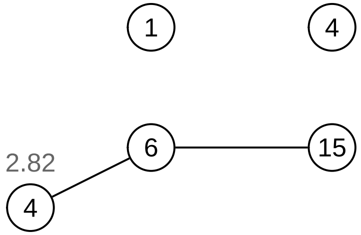
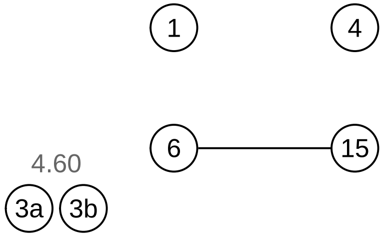
Add another QTL?



$T_m = 2.69$ $T_i^H = 2.62$ $T_i^L = 1.19$ $T_m + T_i^H = 5.31$ $T_m + T_i^L = 3.88$

Add a pair of QTL?



$T_m = 2.69 \quad T_i^H = 2.62 \quad T_i^L = 1.19 \quad T_m + T_i^H = 5.31 \quad T_m + T_i^L = 3.88$

To do

- Improve search procedures
- Study performance
  (especially relative to other approaches)
- Measuring model uncertainty
- Measuring uncertainty in QTL location

Summary

- QTL mapping is a model selection problem
- The criterion for comparing models is most important
- We're focusing on a penalized likelihood method
  and are close to a practiceable solution

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