Model selection for QTL mapping

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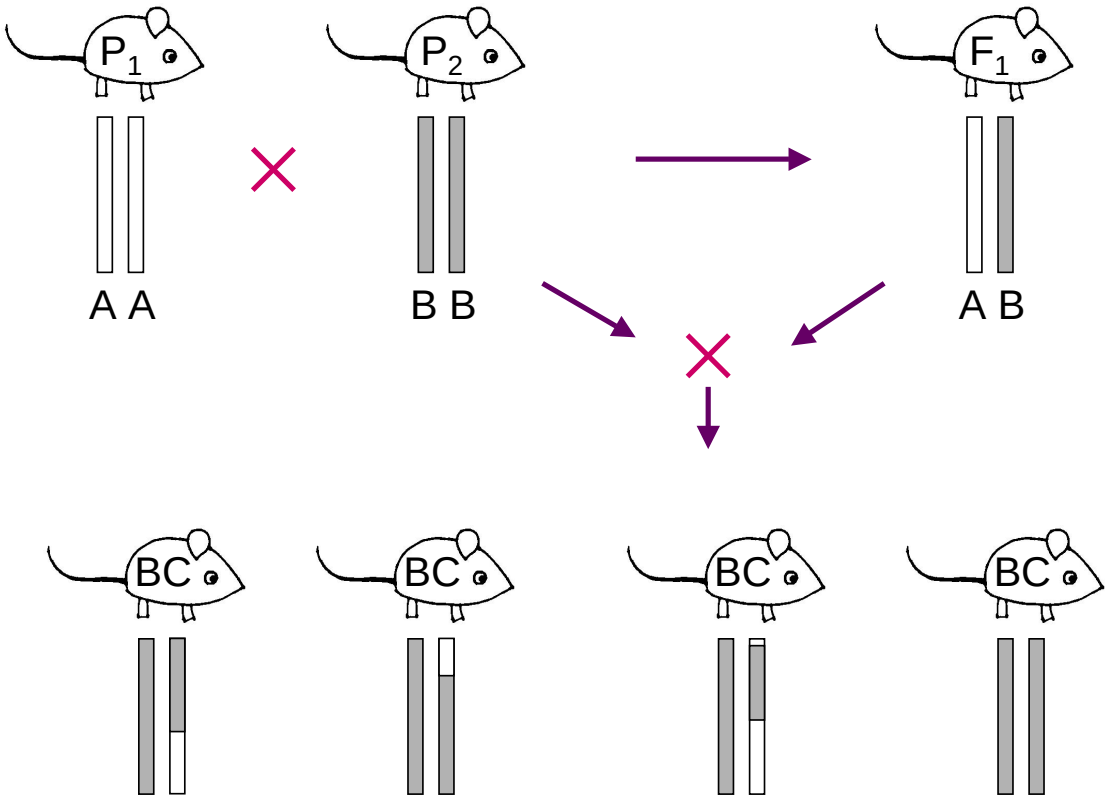
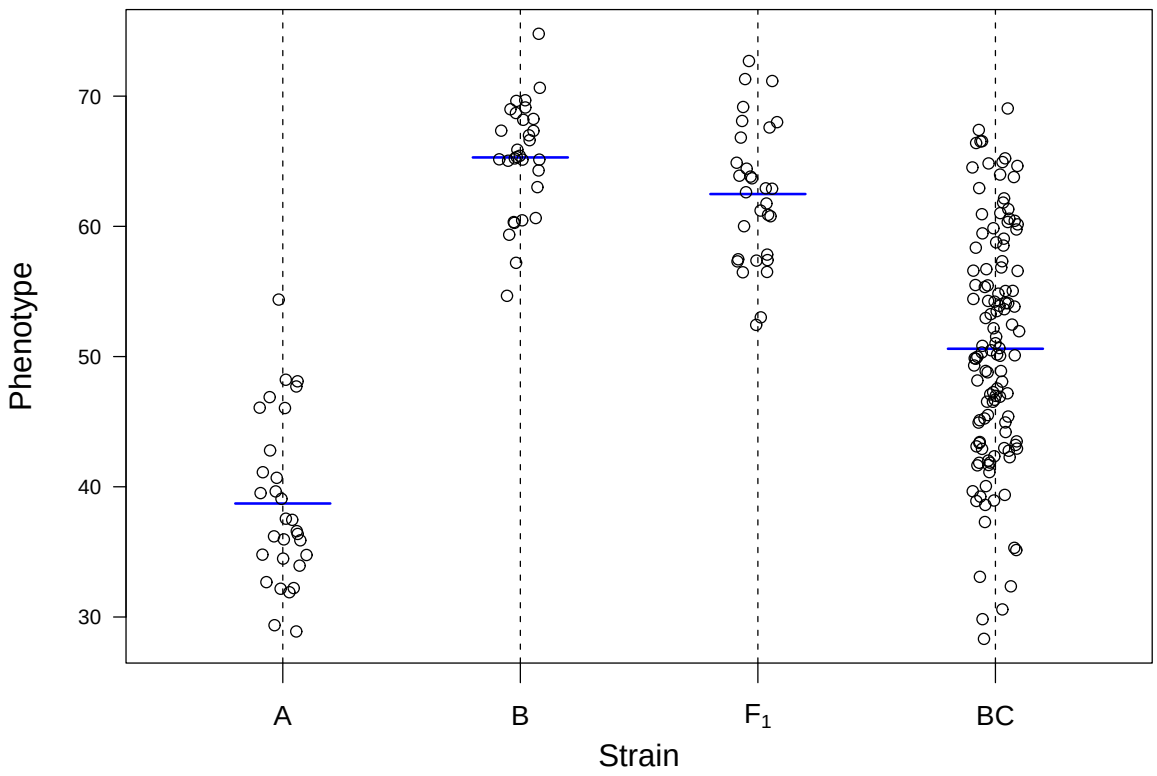
Backcross experiment



Trait distributions



Data and Goals

Phenotypes: y_i = trait value for mouse i

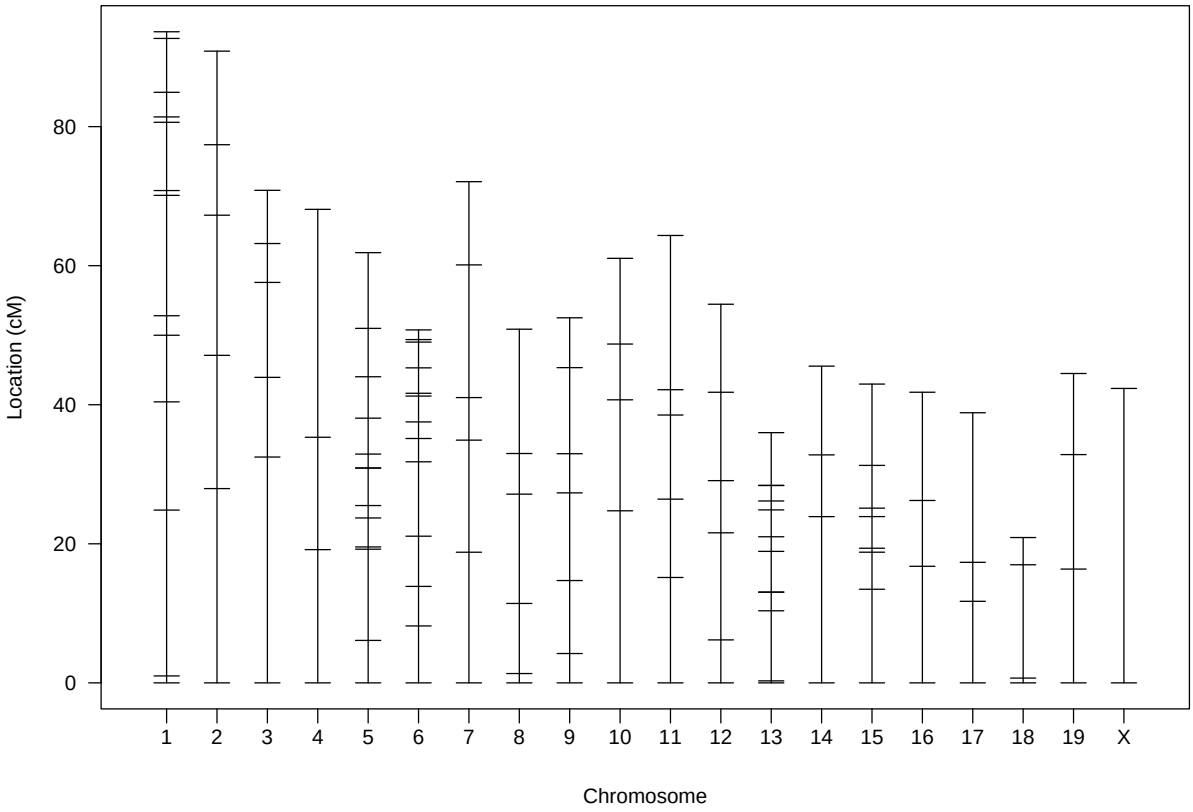
Genotypes: x_{ij} = 1/0 if mouse i is BB/AB at marker j (for a backcross)

Genetic map: Locations of markers

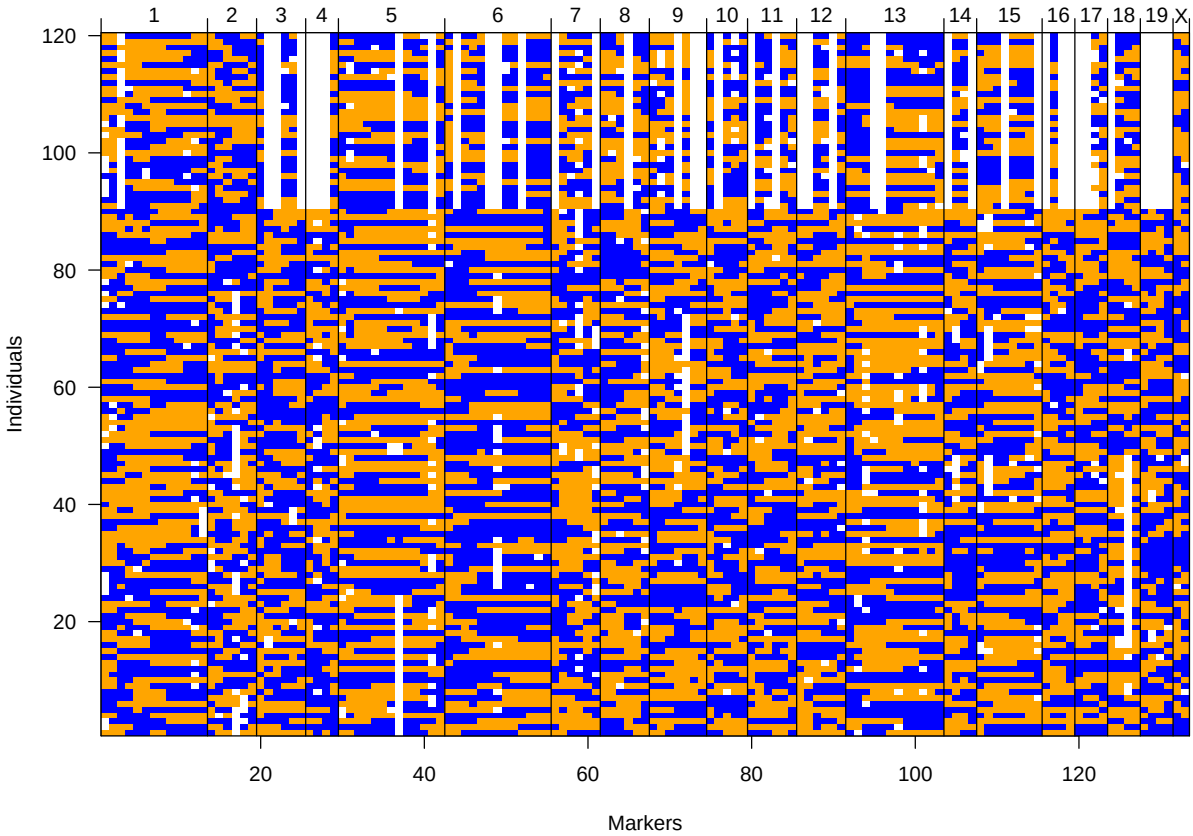
Goals:

- Identify the (or at least one) genomic regions (QTLs) that contribute to variation in the trait.
- Form confidence intervals for QTL locations.
- Estimate QTL effects.

Genetic map



Genotype data



Models: Recombination

We assume no crossover interference.

$\Longrightarrow$ Points of exchange (crossovers) are according to a Poisson process.

$\Longrightarrow$ The $\{x_{ij}\}$ (marker genotypes) form a Markov chain

Models: Genotype $\longleftrightarrow$ Phenotype

Let y = phenotype
g = whole genome genotype

Imagine a small number of QTLs with genotypes $g_1, \ldots, g_p$.
(2^p distinct genotypes)

$$\mathrm{E}(y|g) = \mu_{g_1,\ldots,g_p} \qquad \mathrm{var}(y|g) = \sigma^2_{g_1,\ldots,g_p}$$

Models: Genotype $\longleftrightarrow$ Phenotype

Homoscedasticity (constant variance): $\sigma_g^2 \equiv \sigma^2$

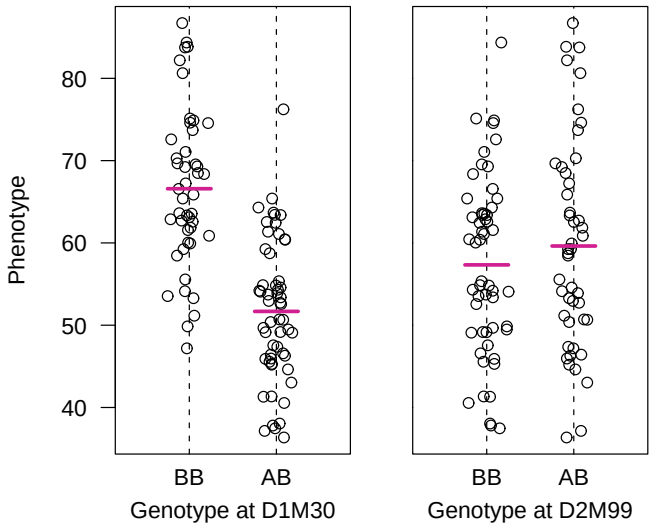
Normally distributed residual variation: $y|g \sim N(\mu_g, \sigma^2)$.

Additivity: $\mu_{g_1,\ldots,g_p} = \mu + \sum_{j=1}^{p} \Delta_j \, g_j$ ($g_j = 1$ or 0)

Epistasis: Any deviations from additivity.

The simplest method: ANOVA

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

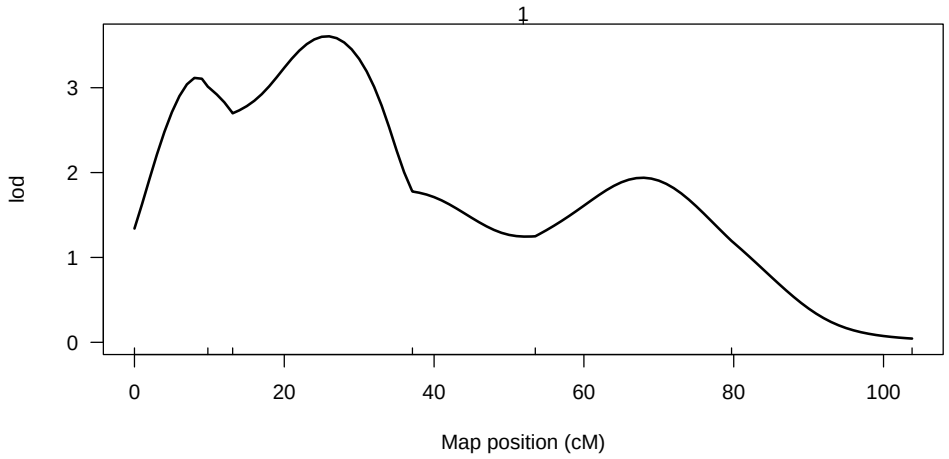


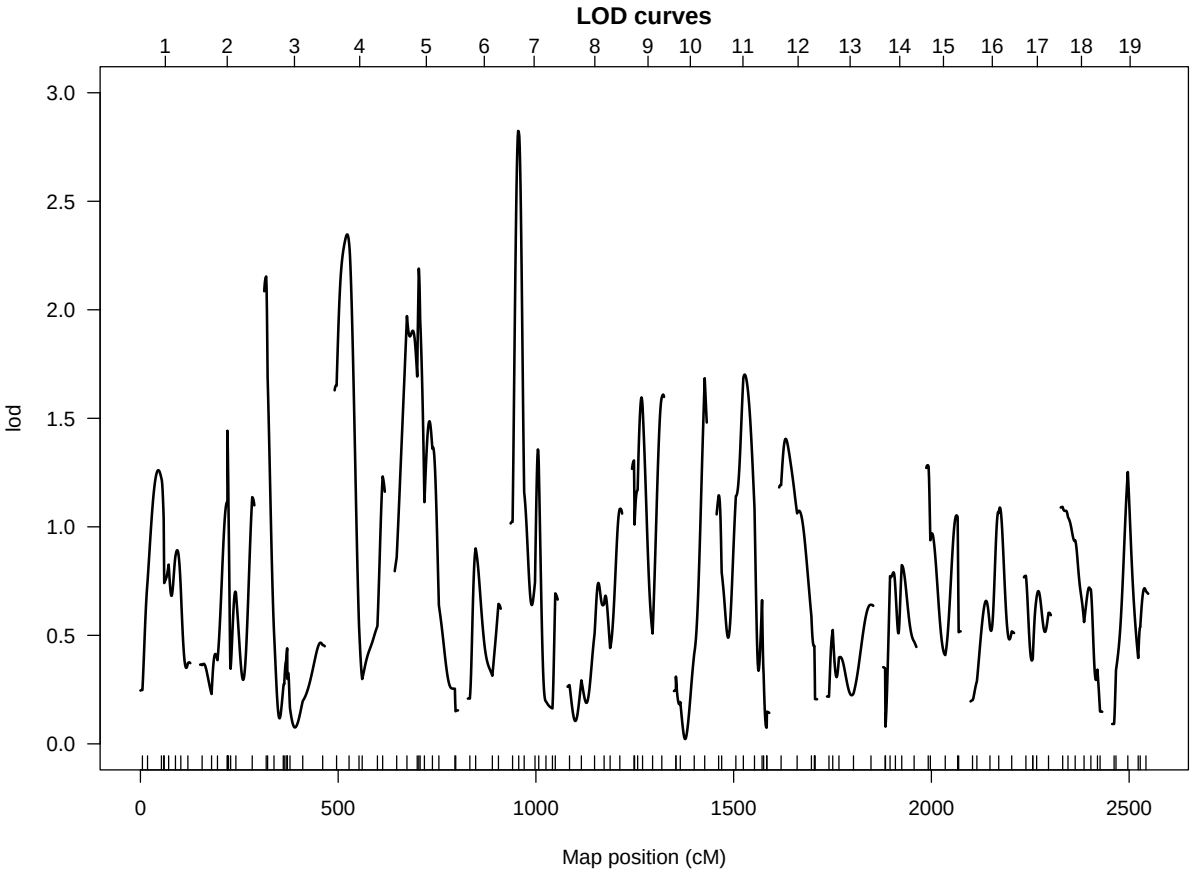
LOD score = $\log_{10}$ likelihood ratio comparing single-QTL model to "no QTL anywhere."

Interval mapping (IM)

Lander & Botstein (1989)

- Take account of missing genotype data
- Interpolate between markers
- Maximum likelihood under a mixture model





LOD thresholds

LOD threshold = 95 %ile of distr'n of max LOD, genome-wide, if there are no QTLs anywhere

Derivation:
- Analytical calculations
- Simulations
- Permutation tests

Multiple QTL methods

Why consider multiple QTLs at once?

- Reduce residual variation.
- Separate linked QTLs.
- Investigate interactions between QTLs (epistasis).

Abstractions / simplifications

- Complete marker data
- QTLs are at the marker loci
- QTLs act additively

The problem

n backcross mice; M markers

x_{ij} = genotype (1/0) of mouse i at marker j

y_i = phenotype (trait value) of mouse i

$$y_i = \mu + \sum_{j=1}^{M} \Delta_j \, x_{ij} + \epsilon_i$$

Which $\Delta_j \neq 0$?

$\longrightarrow$ **Model selection in regression**

How is this problem different?

- Relationship among the x's
- Find a good model vs. minimize prediction error

Model selection

- Select class of models
  - Additive models
  - Add've plus pairwise interactions
  - Regression trees
- Search model space
  - Forward selection (FS)
  - Backward elimination (BE)
  - FS followed by BE
  - MCMC
- Compare models
  - $\text{BIC}_\delta(\gamma) = \log \text{RSS}(\gamma) + |\gamma| \, (\delta \, \frac{\log n}{n})$
  - Sequential permutation tests
- Assess performance
  - Maximize no. QTLs found; control false positive rate

Why BIC$_\delta$?

- For a fixed no. markers, letting $n \to \infty$, BIC$_\delta$ is consistent.
- There exists a prior (on models + coefficients) for which BIC$_\delta$ is the –log posterior.
- BIC$_\delta$ is essentially equivalent to use of a threshold on the conditional LOD score
- It performs well.

Choice of δ

Larger δ: include more loci; higher false positive rate

Smaller δ: include fewer loci; lower false positive rate

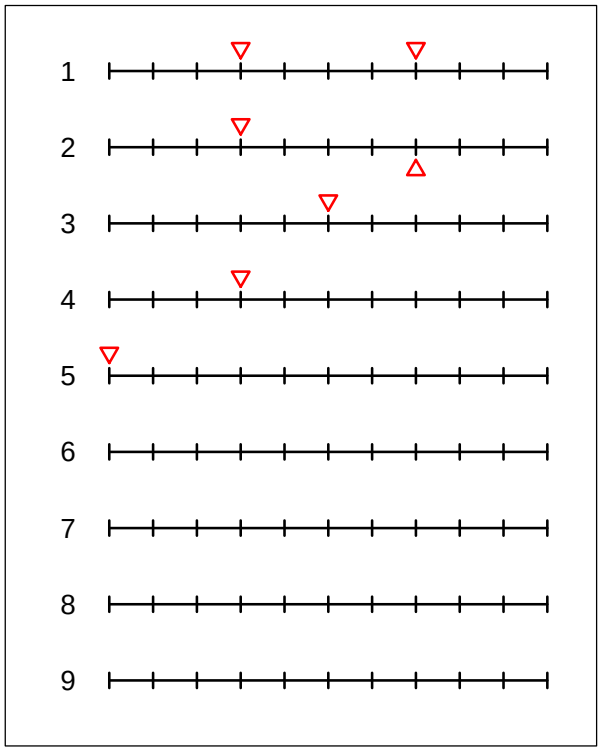
Let *L* = 95% genome-wide LOD threshold
(compare single-QTL models to the null model)

Choose δ = 2 *L* / $\log_{10} n$

With this choice of δ, in the absence of QTLs, we'll include at least one extraneous locus, 5% of the time.

Simulations

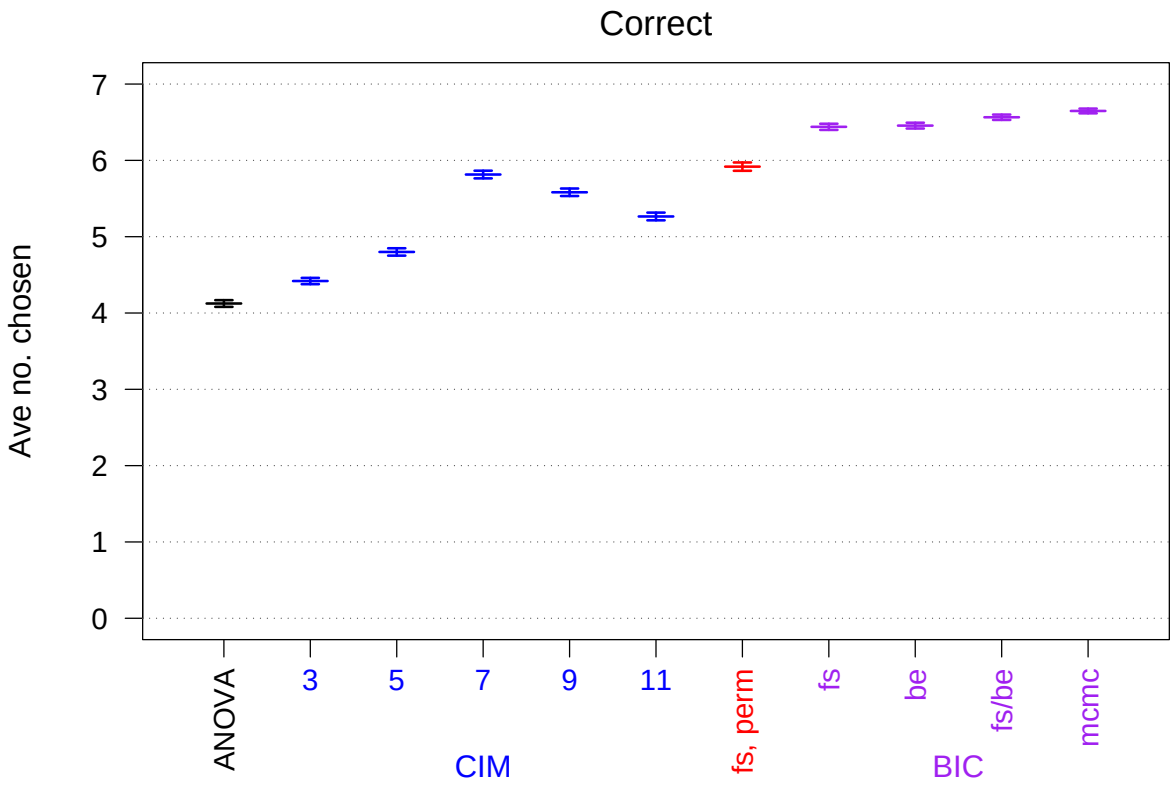
- Backcross with n=250
- No crossover interference
- 9 chr, each 100 cM
- Markers at 10 cM spacing; complete genotype data
- 7 QTLs
  - One pair in coupling
  - One pair in repulsion
  - Three unlinked QTLs
- Heritability = 50%
- 2000 simulation replicates

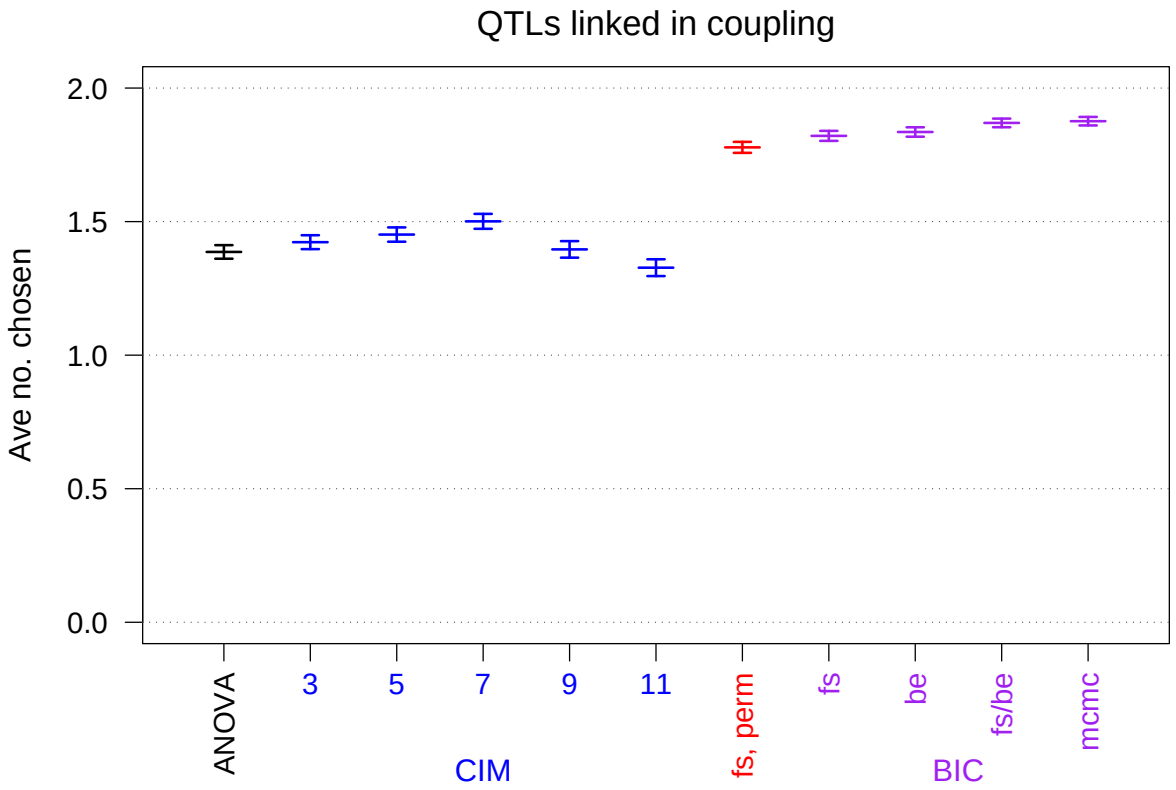


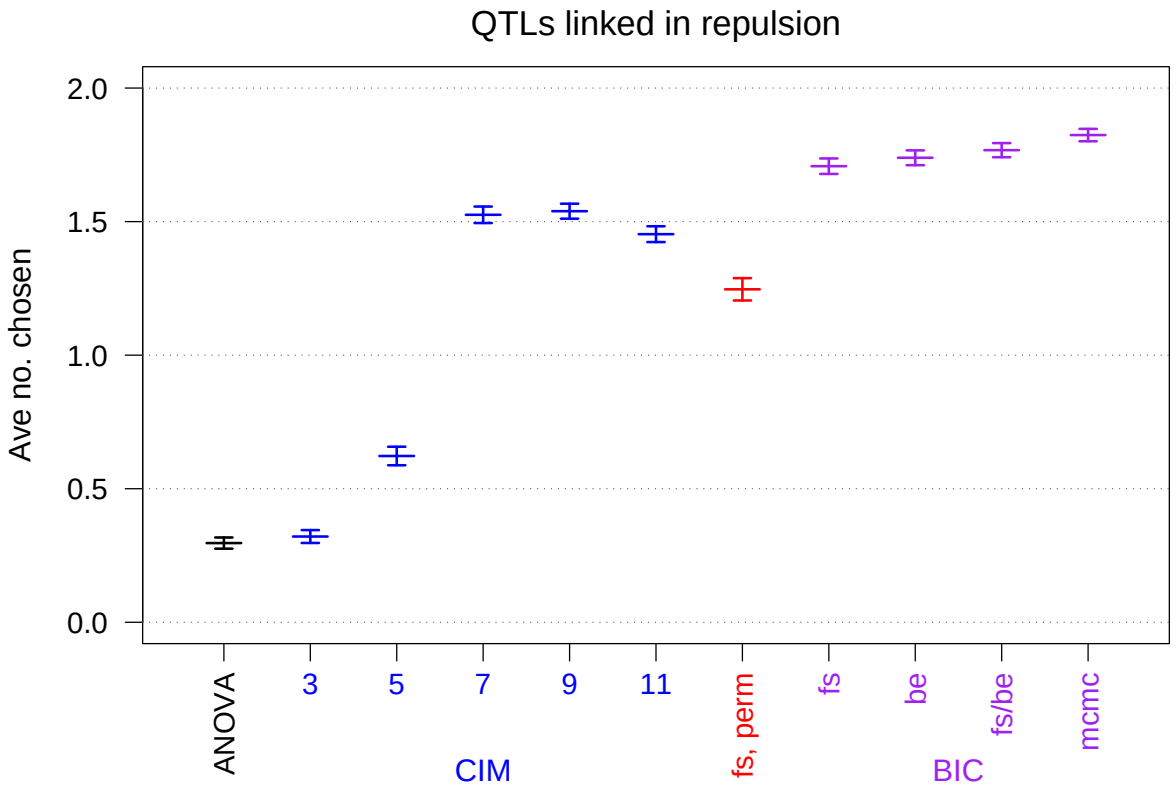
Methods

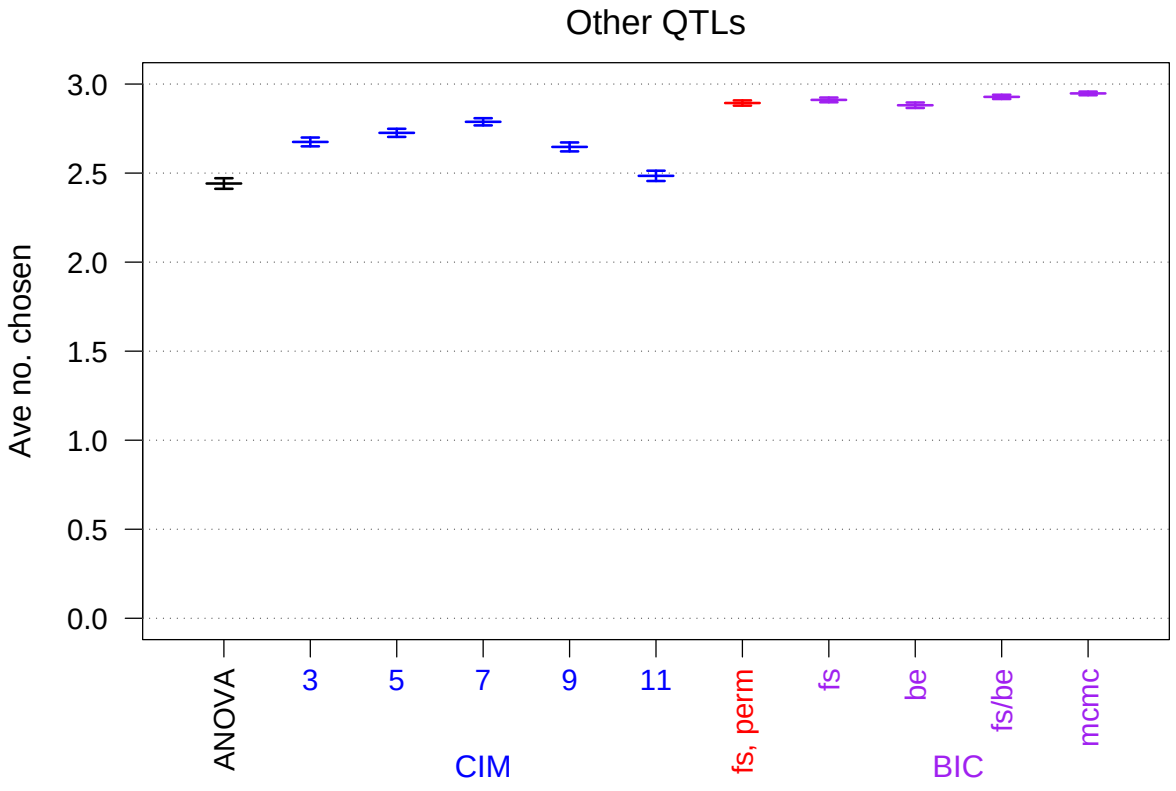
- ANOVA at marker loci
- Composite interval mapping (CIM)
- Forward selection with permutation tests
- Forward selection with BIC_δ
- Backward elimination with BIC_δ
- FS followed by BE with BIC_δ
- MCMC with BIC_δ

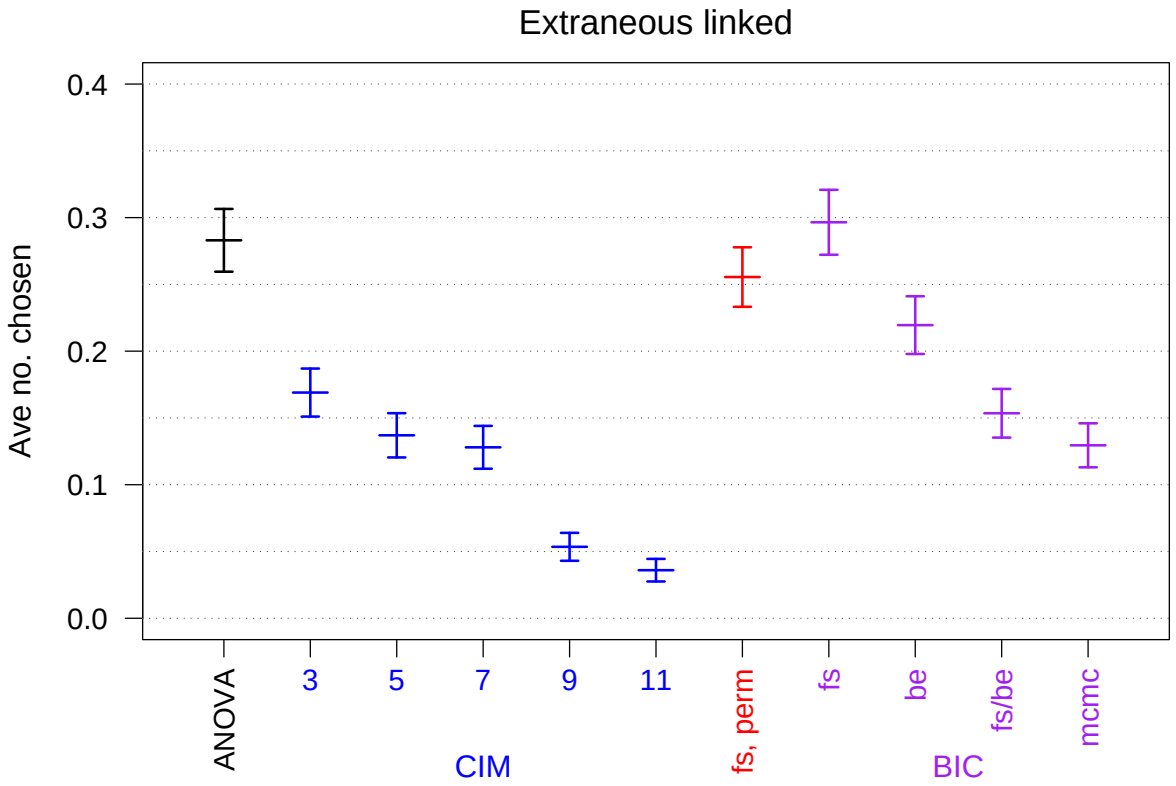
$\longrightarrow$ A selected marker is deemed correct if it is within 10 cM of a QTL (i.e., correct or adjacent)

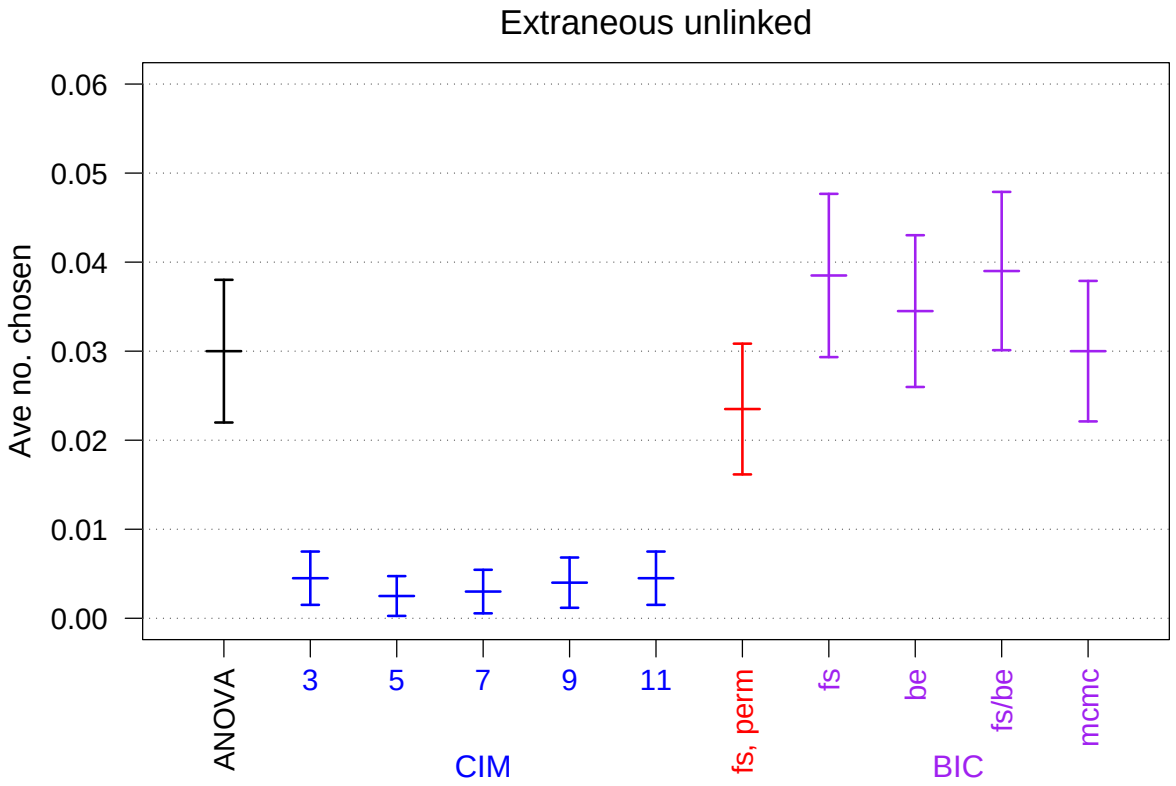

Correct
Ave no. chosen
0
1
2
3
4
5
6
7
ANOVA
3
5
7
9
11
fs, perm
fs
be
fs/be
mcmc
CIM
BIC


QTLs linked in coupling
Ave no. chosen
0.0
0.5
1.0
1.5
2.0
ANOVA
3
5
7
9
11
fs, perm
fs
be
fs/be
mcmc
CIM
BIC


QTLs linked in repulsion
Ave no. chosen
2.0
1.5
1.0
0.5
0.0
ANOVA
3
5
7
9
11
fs, perm
fs
be
fs/be
mcmc
CIM
BIC


Other QTLs
Ave no. chosen
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ANOVA
3
5
7
9
11
fs, perm
fs
be
fs/be
mcmc
CIM
BIC


Extraneous linked
Ave no. chosen
0.0
0.1
0.2
0.3
0.4
ANOVA
3
5
7
9
11
fs, perm
fs
be
fs/be
mcmc
CIM
BIC


Extraneous unlinked
Ave no. chosen
0.00
0.01
0.02
0.03
0.04
0.05
0.06
ANOVA
3
5
7
9
11
fs, perm
fs
be
fs/be
mcmc
CIM
BIC

Summary

- QTL mapping is a model selection problem.
- Key issue: the comparison of models.
- Large-scale simulations are important.
- More refined procedures do not necessarily give improved results.

- BIC_δ with forward selection followed by backward elimination works quite well.