QTL Mapping II:

Model Selection

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Outline

- The model selection problem:
  - Class of models
  - Compare models
  - Search model space
  - Assess the performance of a procedure
- A simulation study

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 QTLs are well-supported?

  Is there evidence for QTL-QTL interactions?

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

Perfect data situation

To ease discussion, we'll focus on a simple special case:

- Complete marker genotype data
- Markers are only putative QTLs
- Normally distributed residuals

Example model (in a backcross):

$y_i = \mu + \Delta_1 q_{i1} + \Delta_2 q_{i2} + \Delta_3 q_{i3} + \epsilon_i$ ϵ_i are iid N(0,σ^2)

q_j are 0/1 variables (QTL genotypes)

μ, Δ's are parameters, estimated by least squares

Fitted values: $\hat{y}_i = \hat{\mu} + \hat{\Delta}_1 q_{i1} + \hat{\Delta}_2 q_{i2} + \hat{\Delta}_3 q_{i3}$

RSS = $\sum_i (y_i - \hat{y}_i)^2$ indicates model fit.

Model selection

1. Class of models
2. Compare models
3. Search model space
4. Assess performance of a procedure

Note:

2 and 4 are much the same.

There might be a 0th item: Method for model fitting.
(e.g., imputation, EM, etc.)

Class of models

- Additive models

$$y = \mu + \sum_j \Delta_j q_j + \epsilon$$

- Also pairwise interactions

  Preserve hierarchy: if include interaction, also include both main effects.

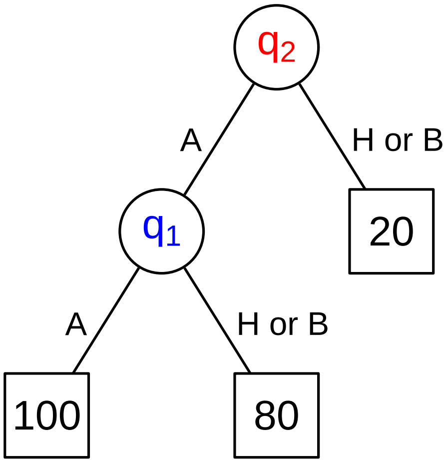
- Also higher-order interactions

  Again, preserve hierarchy.

- Regression trees

Example regression tree

		QTL 1		
		A	H	B
QTL 2	A	100	80	80
	H	20	20	20
	B	20	20	20



Intercrosses: class of models

- Always bring in both degrees of freedom with a QTL

  or

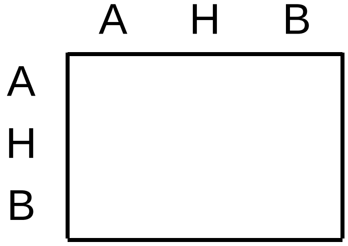
  Try to distinguish additivity/dominance/recessiveness?

A	H	B

- Always bring in all four d.f. with a QTL:QTL interaction

  or

  Try to distinguish ways to subdivide the 3×3 table?



Compare models

- Imagine you could fit all possible models; which would you like best?
- This issue is like LOD thresholds, but more complicated.
- For models with the same number of parameters (QTLs and interactions), we prefer that with the “best fit” (smallest RSS or largest likelihood).
- If you fit more parameters, you’ll get a “better fit.”
  - How much better, before including additional terms?
  - I like a form of penalized likelihood.
- Note: Bayesians must also confront this issue (through the prior on models).

The additive QTL case

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 $\Delta_j \neq 0$?

$$\text{BIC}_\delta = \log \text{RSS} \; + \; \text{no. markers} \; \times \left(\delta \times \frac{\log n}{n} \right)$$

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.

BIC$_\delta$ $\longleftrightarrow$ conditional LOD

Conditional LOD score:

$$\text{LOD}(x_k^\star \mid x_1^\star, \ldots, x_{k-1}^\star) \;=\; \frac{n}{2}\,\log_{10}\left\{\frac{\text{RSS}(x_1^\star, \ldots, x_{k-1}^\star)}{\text{RSS}(x_1^\star, \ldots, x_k^\star)}\right\}$$

Minimizing BIC$_\delta$ is approximately equivalent to choosing the largest k such that

$$\text{LOD}(x_k^\star \mid x_1^\star, \ldots, x_{k-1}^\star) \;\geq\; \frac{\delta}{2}\,\log_{10} n$$

Choice of δ

Smaller δ: include more loci; higher false positive rate

Larger δ: include fewer loci; lower false positive rate

Let L = 95% genome-wide LOD threshold

(compare single-QTL models to the null model)

Choose $\delta = 2\,L / \log_{10} n$

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

Search model space

- Consider the case of additive QTL models, with 100 putative QTLs.
- There are $2^{100} \approx 10^{30}$ possible models, far more than can be inspected individually.
- Need a way to search through this space, to find the good ones.
- This is really a matter of "grunt work." (More is better; the tradeoff is with computational time.)

Methods of model search

- Forward selection
  - Find the best single-QTL model: $q_1^\star$.
  - Find the best two-QTL model that includes $q_1^\star$: $(q_1^\star, q_2^\star)$.
  - Find the best three-QTL model that includes $q_1^\star, q_2^\star$: $(q_1^\star, q_2^\star, q_3^\star)$.
  - Etc.
- Backward elimination
- Forward selection followed by backward elimination
- Stepwise selection
- Randomized algorithms (e.g., MCMC, genetic algorithms, etc.)

Assess performance

- Selection of a model includes two types of errors:
  - Missing 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.
- You can't know the performance of your procedure with your data—you need to know the truth.
- You can know:
  - How a particular procedure performs in simulated cases
  - How a procedure performs in simulated data close to what you've inferred

Science isn't really model selection

I've said here: pick a good model

Really:

- Want to guide future experiments
- Want some understanding of the uncertainty in different aspects of the chosen model

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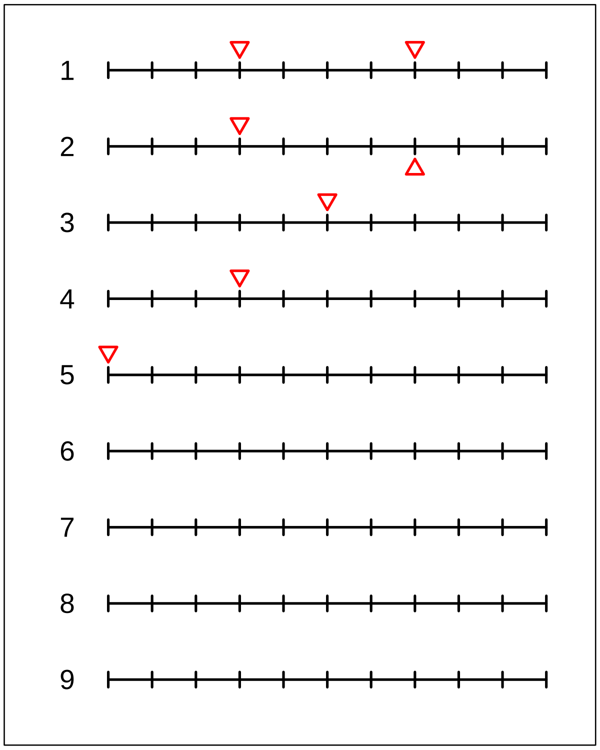
A simulation study

- 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$_\delta$
- Backward elimination with BIC$_\delta$
- FS followed by BE with BIC$_\delta$
- MCMC with BIC$_\delta$

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

A simplified version of CIM

Select a set of markers, S

(e.g., by FS to a fixed number)

For each marker, x, in the genome:

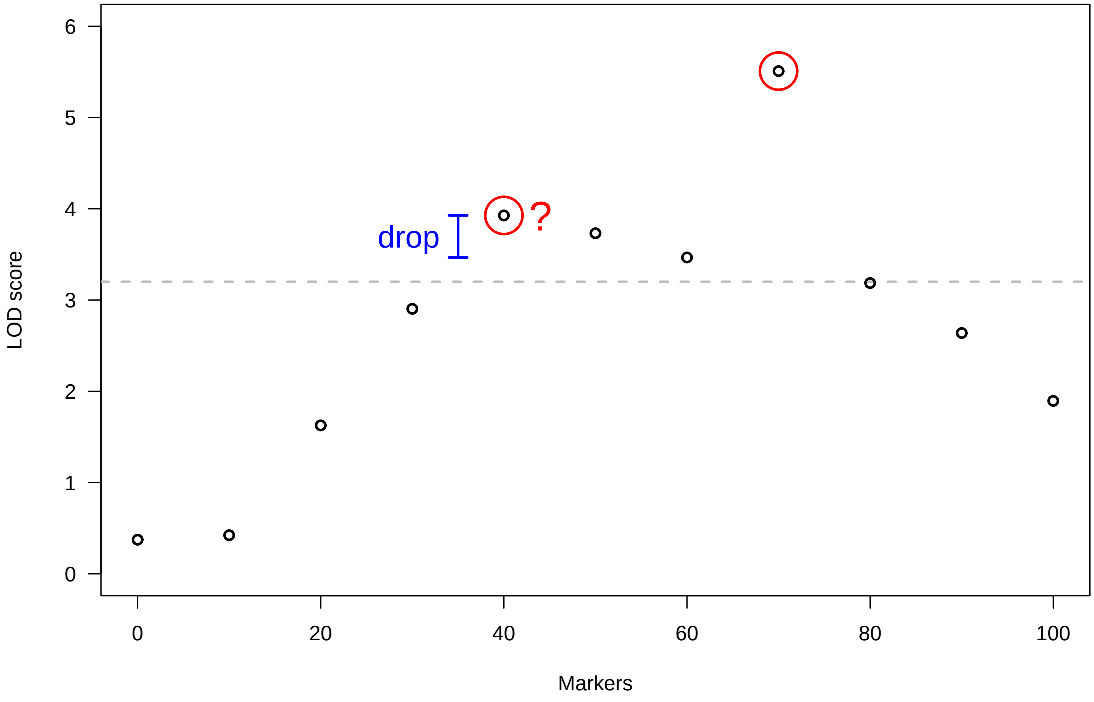
(a) If $x \notin S$, calculate LOD$(x \mid S)$

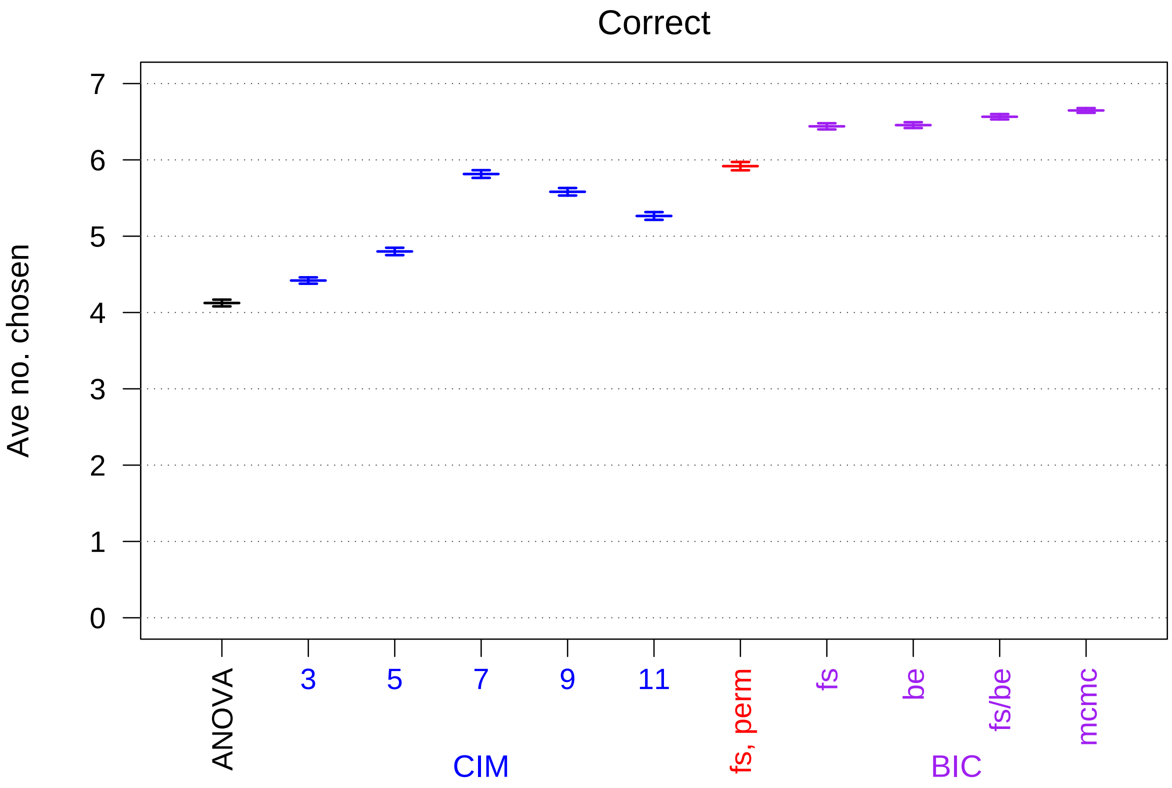
(b) If $x \in S$, calculate LOD$(x \mid S \setminus \{x\})$

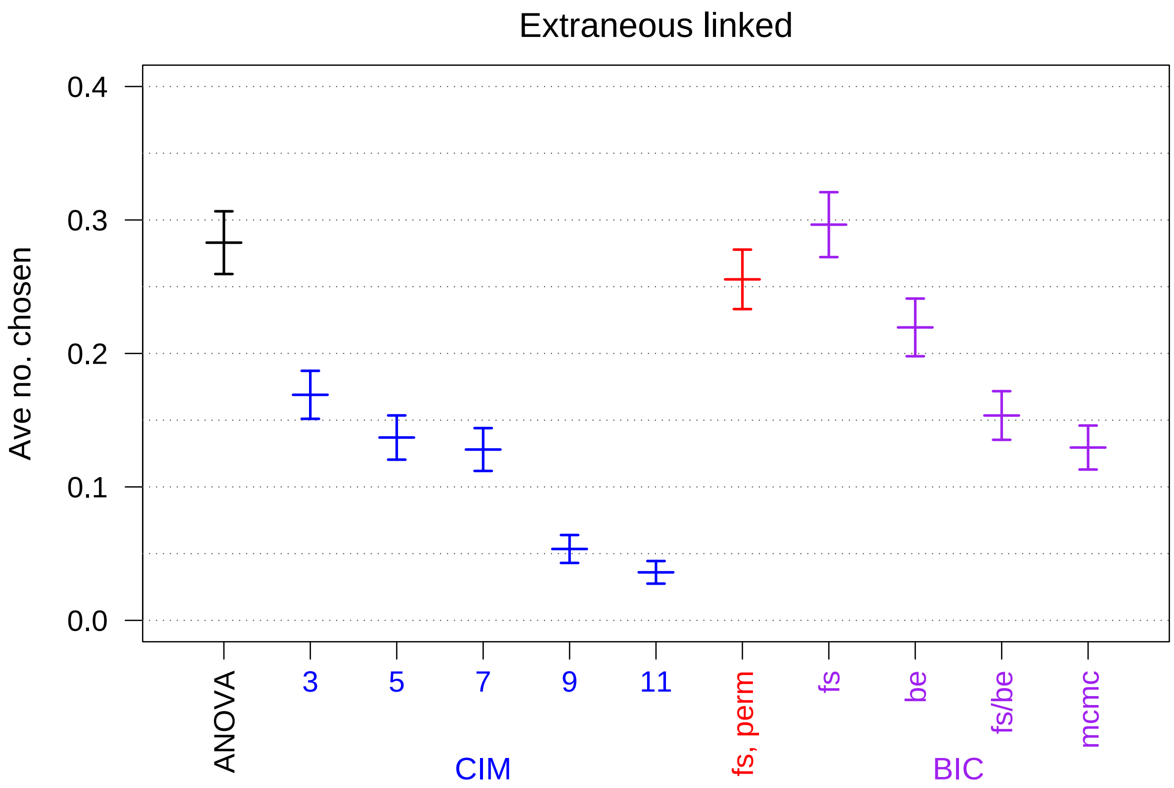
Compare to a genome-wide threshold.

(Take into account the choice of S.)

IM / CIM ⟶ model


LOD score
Markers
0
1
2
3
4
5
6
0
20
40
60
80
100
drop
?


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


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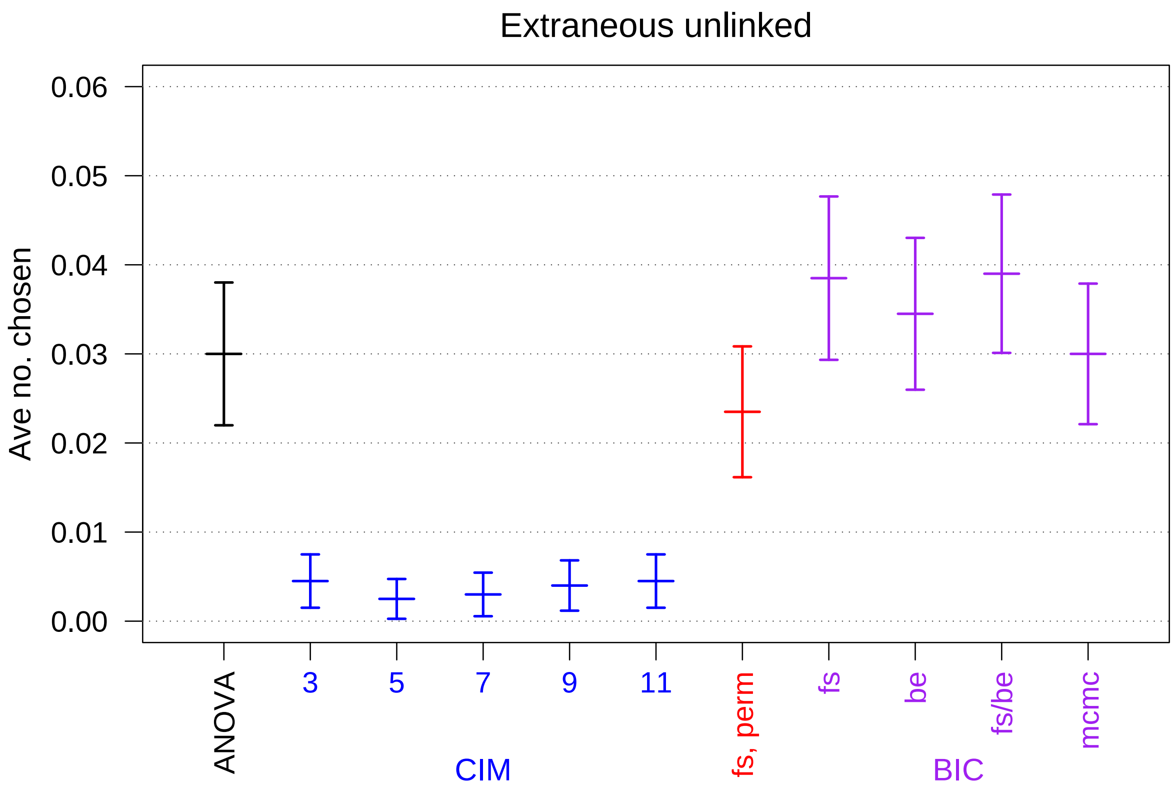
11
fs, perm
fs
be
fs/be
mcmc
CIM
BIC


Extraneous unlinked
Ave no. chosen
0.00
0.01
0.02
0.03
0.04
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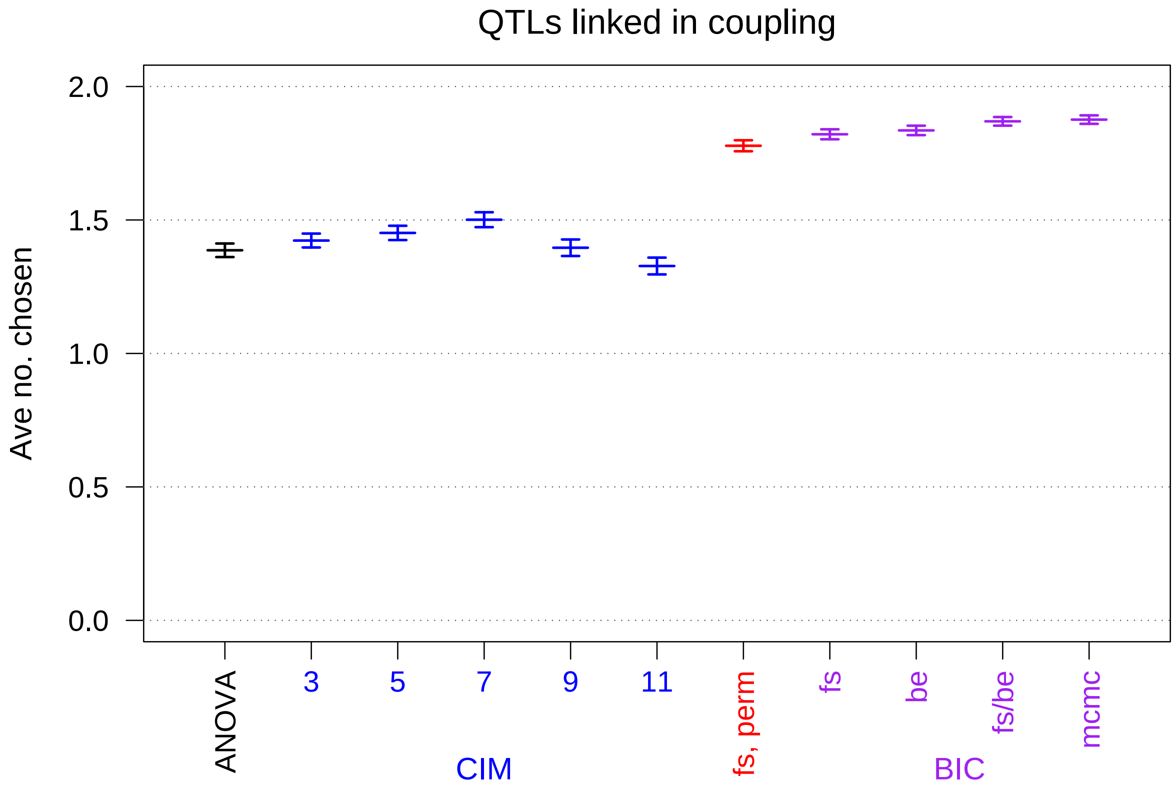
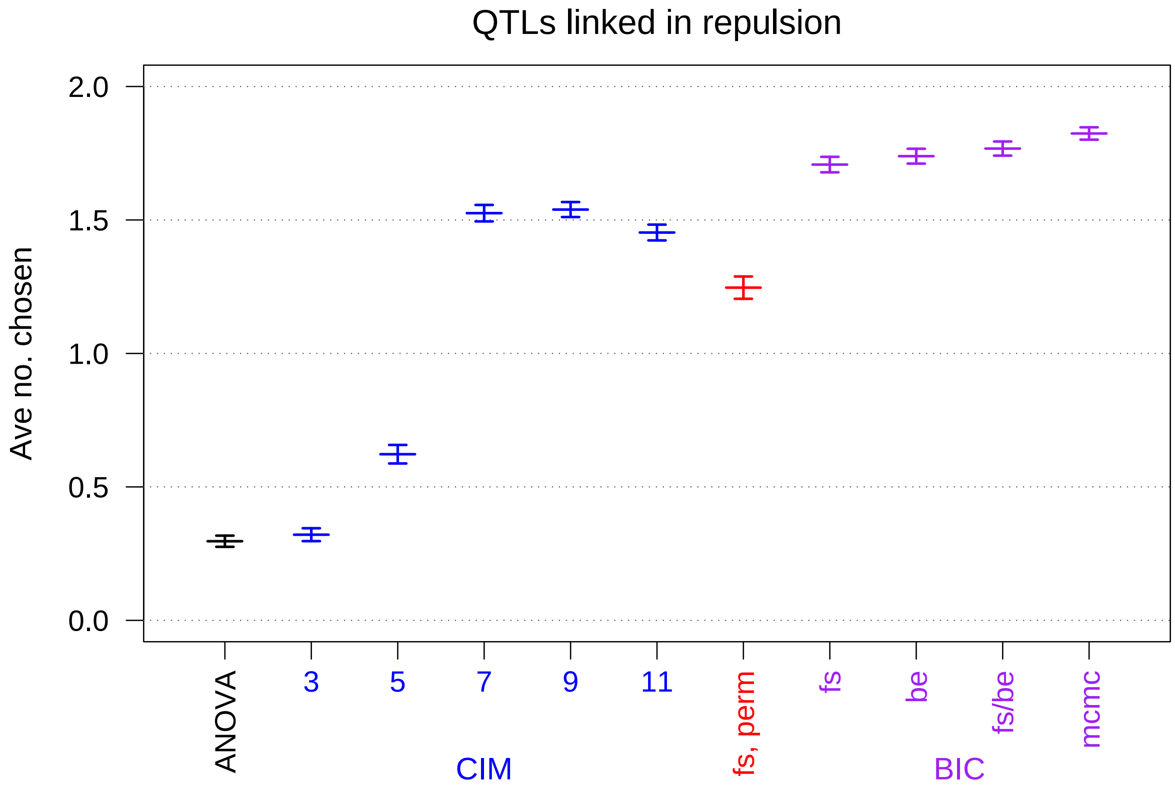
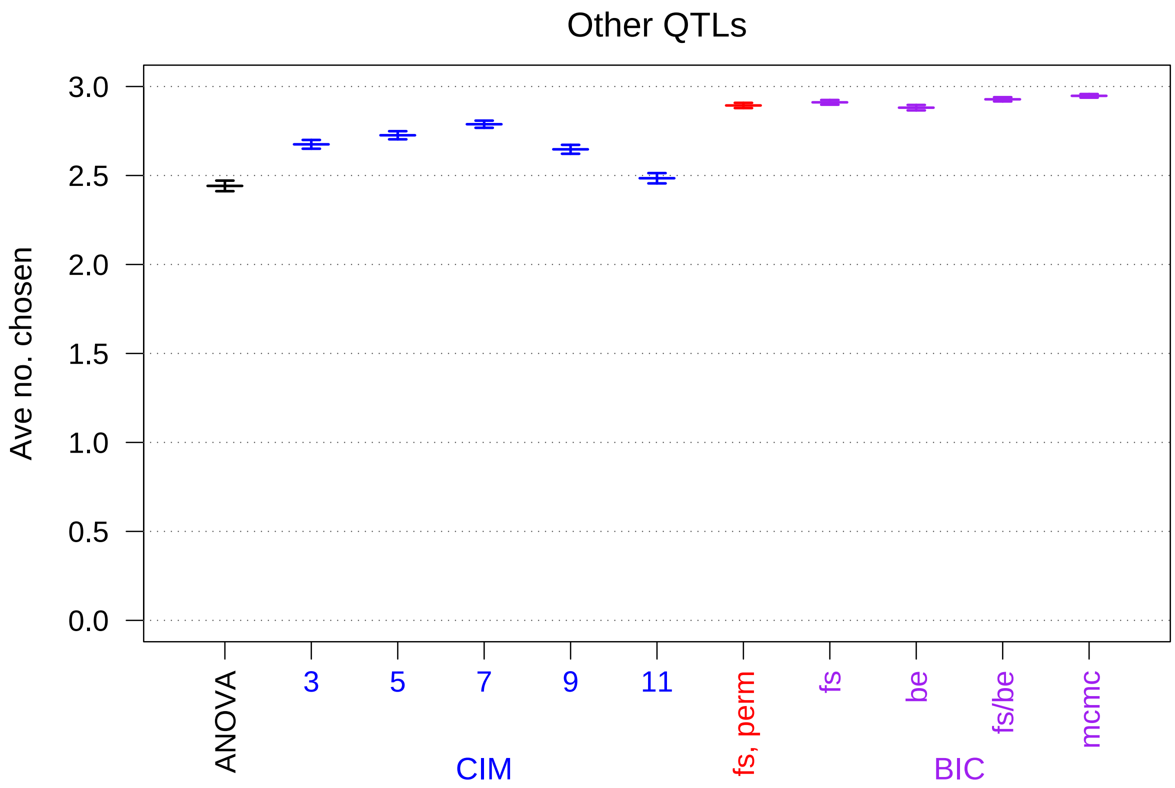
CIM
BIC


QTLs linked in coupling


QTLs linked in repulsion



Summary

- QTL mapping is a model selection problem (rather than hypothesis testing).
- Model selection =
  - Select a class of models
  - Select a criterion for comparing models
  - Select a method of searching model space
  - Figure out how your procedure performs
- Key issue: the comparison of models.
- Large-scale computer simulations are necessary for assessing the performance of procedures

References

- Broman KW, Speed TP (2002) A model selection approach for the identification of quantitative trait loci in experimental crosses. J Roy Stat Soc B, to appear. [See `http:/www.biostat.jhsph.edu/~kbroman/publications`]

  A paper, soon to appear, containing the simulation study described above.

- Zeng ZB, Kao CH, Basten CJ (1999) Estimating the genetic architecture of quantitative traits. Genetical Research 74: 279–289

  Another paper on the model selection aspects of QTL mapping.

- Miller AJ (2002) *Subset selection in regression*, 2nd edition. Chapman & Hall, New York

  A good book on model selection in regression; this new edition has just been printed.