Mapping multiple QTL in experimental crosses

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Human vs mouse

www.daviddeen.com
Backcross

P₁ × P₂

F₁

BC
Intercross
Phenotype data


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

• Identify quantitative trait loci (QTL) (and interactions among QTL)

• Interval estimates of QTL location

• Estimated QTL effects
The missing data problem:Markers $\leftrightarrow$ QTL

The model selection problem:QTL, covariates $\rightarrow$ phenotype
• Split mice into groups according to genotype at a marker.
• Do a t-test / ANOVA.
• Repeat for each marker.
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

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

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

No QTL model: The phenotypes are iid \(N(\mu, \sigma^2)\).
LOD curves
Permutation test

- genotypes
- data
- markers
- individuals
- phenotypes
- LOD scores
- maximum LOD score
Permutation results

Genome-wide maximum LOD score
Estimated effects

Chr 1 @ 48 cM
- BB
- BA

Chr 4 @ 30 cM
- BB
- BA

Chr 6 @ 24 cM
- BB
- BA

Chr 15 @ 20 cM
- BB
- BA
Modeling multiple QTL

- Reduce residual variation $\rightarrow$ increased power
- Separate linked QTL
- Identify interactions among QTL (epistasis)
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
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
Automation

- Assistance to the masses
- Understanding performance
- Many phenotypes
Additive QTL

Simple situation:

- Dense markers
- Complete genotype data
- No epistasis

\[
y = \mu + \sum \beta_j q_j + \epsilon \quad \text{which } \beta_j \neq 0?
\]

\[
\text{LOD}_\delta(\gamma) = \text{LOD}(\gamma) - T |\gamma|
\]
Additive QTL

Simple situation:

- Dense markers
- Complete genotype data
- No epistasis

\[ y = \mu + \sum \beta_j q_j + \epsilon \]

which \( \beta_j \neq 0 \)?

\[ \text{LOD}_\delta(\gamma) = \text{LOD}(\gamma) - T |\gamma| \]

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

\[ \text{LOD}_\delta(\{\lambda\}) = \text{LOD}(\{\lambda\}) - T \]
Additive QTL

Simple situation:
- Dense markers
- Complete genotype data
- No epistasis

\[ y = \mu + \sum \beta_j q_j + \epsilon \]

which \( \beta_j \neq 0 \)?

\[ \text{LOD}_\delta(\gamma) = \text{LOD}(\gamma) - T |\gamma| \]

For the mouse genome:
\[ T = 2.69 \text{ (BC)} \text{ or } 3.52 \text{ (F}_2\text{)} \]
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

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

\[ \text{LOD}_{\delta \epsilon}(\gamma) = \text{LOD}(\gamma) - T_m |\gamma|_m + T_i |\gamma|_i \]

\[ T_m = \text{as chosen previously} \]

\[ T_i = ? \]
Imagine there are two additive QTL and consider a 2d, 2-QTL scan.

\[ T_i = 95\text{th percentile of the distribution of} \]
\[ \max \text{LOD}_f(s, t) - \max \text{LOD}_a(s, t) \]
Imagine there are two additive QTL and consider a 2d, 2-QTL scan.

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

For the mouse genome:

\[ T_m = 2.69 \text{ (BC)} \text{ or } 3.52 \text{ (F}_2\text{)} \]
\[ T_i^H = 2.62 \text{ (BC)} \text{ or } 4.28 \text{ (F}_2\text{)} \]
Imagine there is one QTL and consider a 2d, 2-QTL scan.

\[ T_m + T_i = 95\text{th percentile of the distribution of} \]
\[ \max \text{LOD}_f(s, t) - \max \text{LOD}_1(s) \]
Imagine there is one QTL and consider a 2d, 2-QTL scan.

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

For the mouse genome:

\[ T_m = 2.69 \text{ (BC)} \text{ or } 3.52 \text{ (F}_2\text{)} \]
\[ T_i^H = 2.62 \text{ (BC)} \text{ or } 4.28 \text{ (F}_2\text{)} \]
\[ T_i^L = 1.19 \text{ (BC)} \text{ or } 2.69 \text{ (F}_2\text{)} \]
Models as graphs

A

B

C

D
Results

LOD = 23.1
Results

LOD = 23.1
Results

\[ T_m = 2.69 \quad T_i^H = 2.62 \quad T_i^L = 1.19 \quad T_m + T_i^H = 5.31 \quad T_m + T_i^L = 3.88 \]
Add an interaction?

\[ T_m = 2.69 \quad T_i^H = 2.62 \quad T_i^L = 1.19 \quad T_m + T_i^H = 5.31 \quad T_m + T_i^L = 3.88 \]
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Add an interaction?

\[ T_m = 2.69 \quad T_{iH} = 2.62 \quad T_{iL} = 1.19 \quad T_m + T_{iH} = 5.31 \quad T_m + T_{iL} = 3.88 \]
Add an interaction?

1 4
0.2

6 15

\[ T_m = 2.69 \quad T_i^H = 2.62 \quad T_i^L = 1.19 \quad T_m + T_i^H = 5.31 \quad T_m + T_i^L = 3.88 \]
Add an interaction?

$T_m = 2.69 \quad T_i^H = 2.62 \quad T_i^L = 1.19 \quad T_m + T_i^H = 5.31 \quad T_m + T_i^L = 3.88$
Add another QTL?

\[ T_m = 2.69 \quad T_i^H = 2.62 \quad T_i^L = 1.19 \quad T_m + T_i^H = 5.31 \quad T_m + T_i^L = 3.88 \]
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Add another QTL?

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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
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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