Mapping multiple QTL in experimental crosses

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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

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

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Markers

Phenotype

Covariates

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 $p_q = \Pr(q \mid \text{marker data})$.
- $y \mid \text{marker data} \sim \sum p_q \phi(y \mid \mu_q, \sigma)$
LOD scores

$\text{LOD}(\lambda) = \log_{10} \text{likelihood ratio comparing the hypothesis of a QTL at position } \lambda \text{ versus that of no QTL}$

$= \log_{10} \left\{ \frac{\Pr(y|\text{QTL at } \lambda, \hat{\mu}_q, \hat{\sigma}_\lambda)}{\Pr(y|\text{no QTL}, \hat{\mu}, \hat{\sigma})} \right\}$

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

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

Permutation test

markers

phenotypes

LOD scores

maximum LOD score

Genome−wide maximum LOD score

Permutation results

LOD curves
LOD curves

Modeling multiple QTL

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

Estimated effects

Chr 1 @ 48 cM
Chr 4 @ 30 cM
Chr 6 @ 24 cM
Chr 15 @ 20 cM

Estimated effects

1 x 4
6 x 15
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
**Automation**

- Assistance to the masses
- Understanding performance
- Many phenotypes

**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

**Additive QTL**

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

\[ y = \mu + \sum \beta_j q_j + \epsilon \] where \( \beta_j \neq 0 \)

\[ \text{LOD}_{\delta}(\gamma) = \text{LOD}(\gamma) \bigg|_{\gamma} - T_{m} |\gamma|_{m} + T_{i} |\gamma|_{i} \]

\[ T_{m} = \text{as chosen previously} \]

\[ T_{i} = ? \]

**Epistasis**

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

\[ \text{LOD}_{\delta}(\gamma) = \text{LOD}(\gamma) \bigg|_{\gamma} - T_{m} |\gamma|_{m} + T_{i} |\gamma|_{i} \]

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

**Experience**

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Idea 1

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

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

For the mouse genome:

- \[ T_m = 2.69 \text{ (BC) or } 3.52 \text{ (F}_2\text{)} \]
- \[ T_i^{HI} = 2.62 \text{ (BC) or } 4.28 \text{ (F}_2\text{)} \]

Idea 2

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

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

For the mouse genome:

- \[ T_m = 2.69 \text{ (BC) or } 3.52 \text{ (F}_2\text{)} \]
- \[ T_i^{HI} = 2.62 \text{ (BC) or } 4.28 \text{ (F}_2\text{)} \]
- \[ T_i = 1.19 \text{ (BC) or } 2.69 \text{ (F}_2\text{)} \]

Results

\[ \begin{align*}
T_m &= 2.69 \\
T_i^{HI} &= 2.62 \\
T_i &= 1.19 \\
T_m + T_i^{HI} &= 5.31 \\
T_m + T_i &= 3.88
\end{align*} \]
Add an interaction?

\[
\begin{align*}
T_m &= 2.69 & T_i^H &= 2.62 & T_i &= 1.19 & T_m + T_i^H &= 5.31 & T_m + T_i &= 3.88 \\
1 & \quad 4 \\
6 & \quad 15
\end{align*}
\]

Add another QTL?

\[
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T_m &= 2.69 & T_i^H &= 2.62 & T_i &= 1.19 & T_m + T_i^H &= 5.31 & T_m + T_i &= 3.88 \\
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Add a pair of QTL?

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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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