R/qtl workshop
(part 2)

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

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

Chr 1 @ 48 cM

Chr 4 @ 30 cM

Chr 6 @ 24 cM

Chr 15 @ 20 cM

Genotype

blood pressure
Modeling multiple QTL

- Reduce residual variation $\rightarrow$ increased power
- Separate linked QTL
- Identify interactions among QTL (epistasis)
2-dim, 2-QTL scan

For all pairs of positions, fit the following models:

\[ H_f : y = \mu + \beta_1 q_1 + \beta_2 q_2 + \gamma q_1 q_2 + \epsilon \]
\[ H_a : y = \mu + \beta_1 q_1 + \beta_2 q_2 + \epsilon \]
\[ H_1 : y = \mu + \beta_1 q_1 + \epsilon \]
\[ H_0 : y = \mu + \epsilon \]

\( \log_{10} \) likelihoods:

\[ l_f(s, t) \quad l_a(s, t) \quad l_1(s) \quad l_0 \]
LOD scores:

$$\text{LOD}_f(s, t) = l_f(s, t) - l_0$$

$$\text{LOD}_a(s, t) = l_a(s, t) - l_0$$

$$\text{LOD}_i(s, t) = l_f(s, t) - l_a(s, t)$$

$$\text{LOD}_1(s) = l_1(s) - l_0$$
Results: $\text{LOD}_i$ and $\text{LOD}_f$
Results: $LOD_i$ and $LOD_f$
Summaries

Consider each pair of chromosomes, \((j, k)\), and let \(c(s)\) denote the chromosome for position \(s\).

\[
M_f(j, k) = \max_{c(s)=j, c(t)=k} \text{LOD}_f(s, t)
\]

\[
M_a(j, k) = \max_{c(s)=j, c(t)=k} \text{LOD}_a(s, t)
\]

\[
M_1(j, k) = \max_{c(s)=j \text{ or } k} \text{LOD}_1(s)
\]

\[
M_i(j, k) = M_f(j, k) - M_a(j, k)
\]

\[
M_{fv1}(j, k) = M_f(j, k) - M_1(j, k)
\]

\[
M_{av1}(j, k) = M_a(j, k) - M_1(j, k)
\]
Results: $LOD_i$ and $LOD_{fv1}$
[R/qtl]
A pair of chromosomes \((j, k)\) is considered interesting if:

\[
M_f(j, k) > T_f \quad \text{and} \quad \{ \ M_{fv1}(j, k) > T_{fv1} \quad \text{or} \quad M_i(j, k) > T_i \ \}\n\]

or

\[
M_a(j, k) > T_a \quad \text{and} \quad M_{av1}(j, k) > T_{av1}
\]

where the thresholds \((T_f, T_{fv1}, T_i, T_a, T_{av1})\) are determined by a permutation test with a 2d scan
## 2d scan summary

<table>
<thead>
<tr>
<th></th>
<th>pos1f</th>
<th>pos2f</th>
<th>lod.full</th>
<th>lod.fv1</th>
<th>lod.int</th>
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</thead>
<tbody>
<tr>
<td>c1:c4</td>
<td>71.3</td>
<td>30.0</td>
<td>14.36</td>
<td>6.78</td>
<td>0.27</td>
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<tr>
<td>c6:c15</td>
<td>55.0</td>
<td>20.5</td>
<td>6.91</td>
<td>4.95</td>
<td>2.92</td>
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<tr>
<td>c1:c1</td>
<td>39.3</td>
<td>78.3</td>
<td>5.10</td>
<td>1.58</td>
<td>0.09</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>pos1a</th>
<th>pos2a</th>
<th>lod.add</th>
<th>lod.av1</th>
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<tbody>
<tr>
<td>c1:c4</td>
<td>68.3</td>
<td>30.0</td>
<td>14.09</td>
<td>6.50</td>
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<tr>
<td>c6:c15</td>
<td>24.0</td>
<td>22.5</td>
<td>3.99</td>
<td>2.03</td>
</tr>
<tr>
<td>c1:c1</td>
<td>48.3</td>
<td>79.3</td>
<td>5.02</td>
<td>1.50</td>
</tr>
</tbody>
</table>
Estimated effects

1 x 4

Chr 1 genotype

6 x 15

Chr 6 genotype

Chr 4 genotype

Chr 15 Genotype
Chr 1: LOD$_i$ and LOD$_{av1}$
[R/qtl]
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
Exploratory methods

- Condition on a large-effect QTL
  - Reduce residual variation
  - Conditional LOD score:
    \[
    \text{LOD}(q_2 \mid q_1) = \log_{10} \left\{ \frac{\text{Pr}(\text{data} \mid q_1, q_2)}{\text{Pr}(\text{data} \mid q_1)} \right\}
    \]

- Piece together the putative QTL from the 1d and 2d scans
  - Omit loci that no longer look interesting (drop-one-at-a-time analysis)
  - Study potential interactions among the identified loci
  - Scan for additional loci (perhaps allowing interactions), conditional on these
## Drop-one-QTL table

<table>
<thead>
<tr>
<th>df</th>
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<th>%var</th>
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<tr>
<td>1068.3</td>
<td>6.30</td>
<td>11.0</td>
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<tr>
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<td>12.21</td>
<td>20.1</td>
</tr>
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<td>6061.0</td>
<td>7.93</td>
<td>13.6</td>
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<td>7.14</td>
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<td>6061.0 : 15017.5</td>
<td>5.68</td>
<td>9.9</td>
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</table>
[R/qtl]
Automation

- Assistance to non-specialists
- Understanding performance
- Many phenotypes
Additive QTL

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

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

which \( \beta_j \neq 0? \)

\[ pLOD(\gamma) = LOD(\gamma) - T|\gamma| \]
Additive QTL

Simple situation:

- Dense markers
- Complete genotype data
- No epistasis

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

\[ pLOD(\gamma) = LOD(\gamma) - T |\gamma| \]

0 vs 1 QTL: \[ pLOD(\emptyset) = 0 \]

\[ pLOD(\{\lambda\}) = LOD(\lambda) - T \]
Additive QTL

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

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

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

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
[R/qtl]
Epistasis

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

\[ pLOD(\gamma) = LOD(\gamma) - T_m |\gamma_m| - T_i |\gamma_i| \]

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

\[ T_i = ? \]
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:

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

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

\[ T_m + T_i = 95\text{th percentile of the distribution of} \]
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For the mouse genome:

\[ T_m = 2.69 \ (\text{BC}) \text{ or } 3.52 \ (F_2) \]
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\[ T_i^L = 1.19 \ (\text{BC}) \text{ or } 2.69 \ (F_2) \]
Models as graphs

A

B

C

D
Results

LOD = 23.1
Results

\[ T_m = 2.69 \quad T_i^H = 2.62 \quad T_i^L = 1.19 \quad T_m + T_i^H = 5.31 \quad T_m + T_i^L = 3.88 \quad 2T_m = 5.38 \]

LOD = 23.1
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Profile LOD curves
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Add another QTL?

\[ T_m = 2.69 \quad T_i^H = 2.62 \quad T_i^L = 1.19 \quad T_m + T_i^H = 5.31 \quad T_m + T_i^L = 3.88 \quad 2T_m = 5.38 \]
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Add a pair of QTL?

\[ T_m = 2.69 \quad T_i^H = 2.62 \quad T_i^L = 1.19 \quad T_m + T_i^H = 5.31 \quad T_m + T_i^L = 3.88 \quad 2T_m = 5.38 \]
• QTL mapping is a model selection problem

• The criterion for comparing models is most important

• We’re focusing on a penalized likelihood method, with penalties derived from permutation tests with 1d and 2d scans

• Manichaikul et al., Genetics 181:1077–1086, 2009