Detecting single QTL

Search for one QTL at fixed cM intervals across the genome

+ Estimate additive (and possibly dominance) effects of QTL at every putative QTL location

+ Identified QTL may be used as cofactors in consecutive analyses to remove background noise - often called Multiple QTL Mapping or **Composite interval mapping**
Detecting multiple QTL

II) Likelihood based Multiple QTL Method (Kao et al, 1999)

+ Identification of regions with indications of QTL activity

+ Searches for multiple interacting QTL at fixed cM intervals in these regions

> Model selection

+ Yet not solved how to chose the significance threshold for these analyses

+ Very time consuming analysis, Many combinations possible
  randomization testing intractable
Detecting multiple QTL


A simultaneous search for multiple interacting QTL has higher power to detect QTL and estimates parameters better

Simultaneous mapping of multiple QTL can be used in practice if a better search algorithm is used

The genetic algorithms are good for QTL mapping since they are:

+ Robust
+ Easy to implement
+ Computationally efficient
Models of dominance and epistasis

**Dominance:**
\[
\begin{pmatrix}
II \\
Ii \\
ii
\end{pmatrix} = \begin{pmatrix}
\mu + A_i \\
\mu + D_i \\
\mu - A_i
\end{pmatrix}
\]

Use genetic markers for known QTL \((I, i)\).

Use coefficients of expression for genome-wide effects.

**Epistasis (2-locus):**
\[
\begin{pmatrix}
II JJ \\
II Jj \\
II jj \\
Ii JJ \\
Ii Jj \\
Ii jj \\
iI JJ \\
iI Jj \\
iI jj
\end{pmatrix} = \begin{pmatrix}
\mu + A_i + A_j + AA_{ij} & \mu + A_i + D_j + AD_{ij} & \mu + A_i - A_j - AA_{ij} \\
\mu + D_i + A_j + AD_{ji} & \mu + D_i + D_j + DD_{ij} & \mu + D_i - A_j - AD_{ji} \\
\mu - A_i + A_j - AA_{ij} & \mu - A_i + D_j - AD_{ij} & \mu - A_i - A_j + AA_{ij}
\end{pmatrix}
\]

... many parameters to estimate!
Detecting multiple QTL – epistatic models

Reasons for using an epistatic model when mapping multiple QTL:

- Higher power to detect interacting QTL
- Better estimates of QTL effects

Classical epistatic interactions are e.g.
- Complementary epistasis (9:7)
- Dominant epistasis (12:3:1)
- Duplicate epistasis (15:1)
- Recessive epistasis (9:3:4)
- Inhibitory epistasis (13:3)
**Implementation of genetic algorithm:**

1) Generate a population of ga-chromosomes

<table>
<thead>
<tr>
<th>ga-gene</th>
<th>ga-chromosome</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.12</td>
<td>0.72 0.53 0.01</td>
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<tr>
<td>0.97</td>
<td>0.11 0.14 0.66</td>
</tr>
<tr>
<td>0.38</td>
<td>0.45 0.19 0.72</td>
</tr>
<tr>
<td>0.26</td>
<td>0.28 0.91 0.07</td>
</tr>
</tbody>
</table>
Implementation in QTL mapping:

2) Translate coded values to QTL positions

<table>
<thead>
<tr>
<th>Chrom 2</th>
<th>Position 69</th>
<th>Chrom 7</th>
<th>Position 2</th>
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</thead>
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<td>0.91</td>
<td>0.07</td>
</tr>
</tbody>
</table>
Implementation in QTL mapping:

3) Evaluate statistical fit for each ga-chromosome

Chrom 2

Position 69

Chrom 7

Position 2

QTL Mapping Method

F=4.27
Implementation in QTL mapping:

4) Select good ga-chromosomes

<table>
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<th>0.53</th>
<th>0.01</th>
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<tbody>
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<th>0.91</th>
<th>0.07</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>1.08</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Rank:

1. 4
2. 3
3. 2
4. 1
Implementation in QTL mapping:

5) Generation of new ga-chromosomes (Breeding)

Recombination

\[
\begin{array}{cccc}
0.12 & 0.72 & 0.53 & 0.01 \\
\times & & & \\
0.97 & 0.11 & 0.14 & 0.66 \\
\end{array}
\]

Mutation

\[
\begin{array}{cccc}
0.12 & 0.11 & 0.14 & 0.01 \\
0.97 & 0.72 & 0.53 & 0.78 \\
\end{array}
\]
Gain in computing speed …

Genetic algorithm versus exhaustive search

In a genome size of 2000 cM:

+ For 2 QTL improvement by factor 120
+ For 3 QTL improvement by factor 65,000
+ For 4 QTL improvement by factor $1.7 \times 10^7$

Plus: GA method has finer resolution
Results from genome scan

- Genetic Algorithm based search
- Conditional search

% of exhaustive search efficiency

Nature of epistasis

Complementary, Dominant, Duplicate, Inhibitory, Recessive
Multiple trait

• Increased power from using multiple traits

• testing models regarding genetic correlation
  – pleiotropy or close linkage
QTL Map of Chromosome 6 in Family WxP
Stress Reaction and Meat Quality Traits

$F$ ratio testing the hypothesis of a single QTL at a given position on the chromosome

$p \leq 0.01$

$p \leq 0.1$

- pH value 45min p.m. M. long. dorsi
- Conductivity 45min p.m. M. semim.
- CK value
- Muscle stiffness

Gene markers:
- S0035
- Sw1329
- Sw1057
- S0087
- RYR1EAHA1BG
- S0146
- S0003
- Sw824
- LEPRR
- LEPRH
- P3
- EAO

[cM]
ML and regression for single traits (CIM)

\[ r_{\text{trait1}} = .99 \]
\[ r_{\text{trait2}} = .99 \]
Joint mapping vs. separate mapping using regression (CIM)
Properties of the joint analysis

a) $r = 0$ if traits uncorrelated

$$LR_j \approx LR_{S1} + LR_{S2}$$

i.e. increased power

b) $\beta_2 = 0$ if only one trait affected

$$LR_j \approx LR_{S1}/(1-r)^2 \geq LR_{S1}$$

increased power

c) $LR_j \geq \text{maximum}[LR_{S1}, LR_{S2}]$

d) $r \beta_1 \beta_2 < 0$ (i.e. $r$ and $\beta_1 \beta_2$ have different signs)

$$LR_j > LR_{S1} + LR_{S2}$$
Testing for linked TL vs pleiotropic QTL

$H_0$: position 1 = position 2
$H_1$: position 1 \neq position 2

Testing different genetic models

Existence of epistasis

QTL affecting single traits vs. QTL affecting multiple traits
Joint mapping vs. separate mapping using regression (CIM)
Approximate LR test statistic using regression

Single trait analysis:

\[ LR \approx n \log_e \left( \frac{RSS_{\text{reduced}}}{RSS_{\text{full}}} \right) \]

Multiple trait analysis:

\[ LR \approx n \log_e \left( \frac{\Sigma_{\text{reduced}}}{\Sigma_{\text{full}}} \right) \]

Test pleiotropy vs. close linkage

\[ \Sigma = \begin{bmatrix} RSS_{11} & RSP_{12} \\ RSP_{12} & RSS_{22} \end{bmatrix} \]

\[ H_0 = p(1) = p(2) \]

\[ H_1 = p(1) \neq p(2) \]
Joint mapping on 2 traits by ML and regression (IM)

\[ r = 0.9967 \]
Multiple trait analysis using logistic regression

Henshall and Goddard, 1999

- Regress QTL genotype on phenotype rather than the other way around.

\[ Y = \text{Phenotype} + e \quad \text{Y- Binomial} \]

- Just as simple as regression but more ML properties
- Method accounts for selection in phenotypes
  - (think of selective genotyping)
Regression method: Genotype probabilities ...

Prior distribution for animals not expressing the effect.

Prior distribution for animals expressing the effect

Probability of expressing effect as a function of phenotypic merit. This is the height of the smaller distribution divided by sum of the heights of both distributions.
Multiple trait

• Increased power from using multiple traits

• testing models regarding genetic correlation
  – pleiotropy or close linkage