QTL mapping in multi-parent populations

Karl Broman

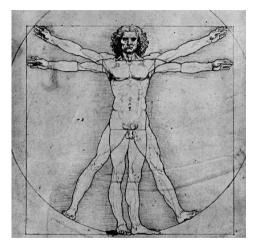
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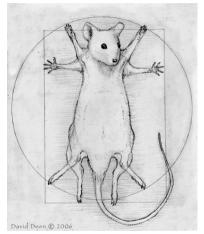
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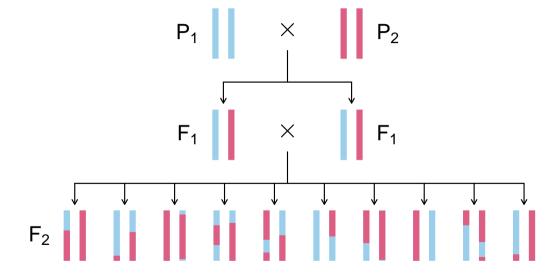




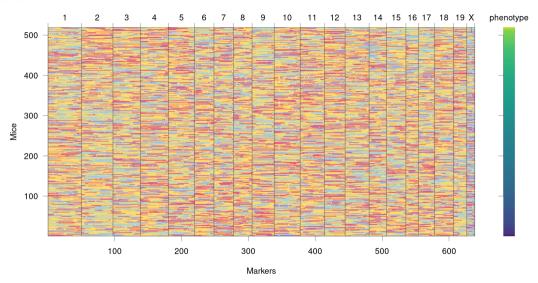


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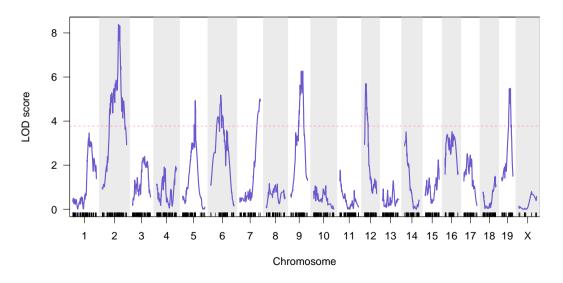
Intercross



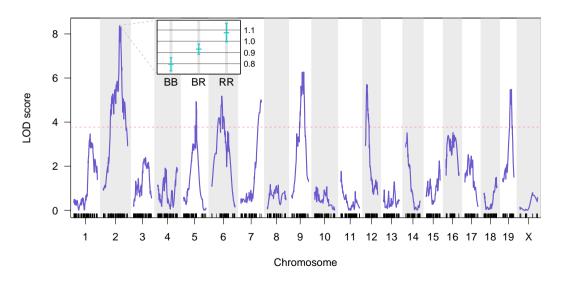
Data



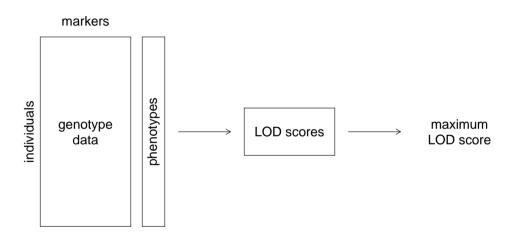
Genome scan



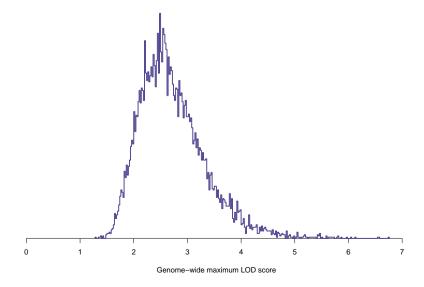
Genome scan



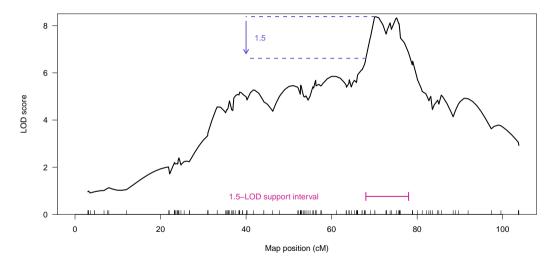
Permutation test



Permutation distribution



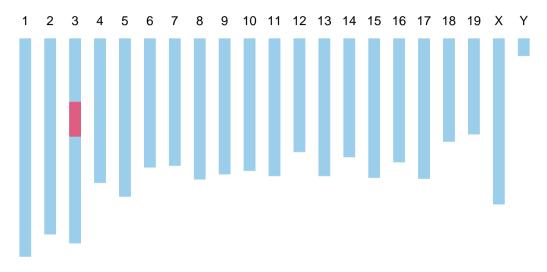
QTL intervals



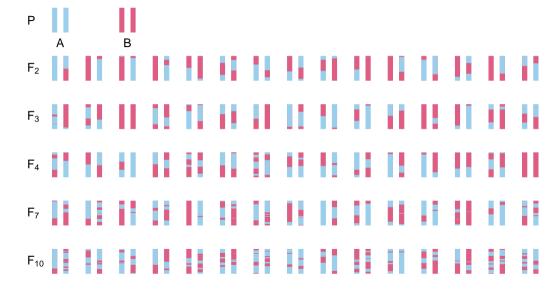
Multiple QTL models

- ► Reduce residual variation greater power
- Separate linked QTL
- ► Identify interactions (epistasis)

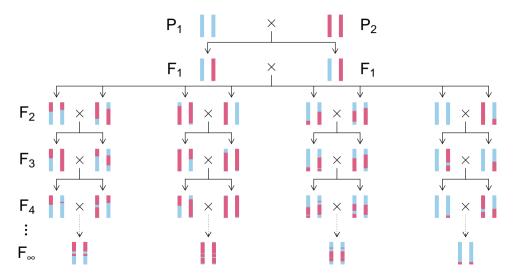
Congenic line



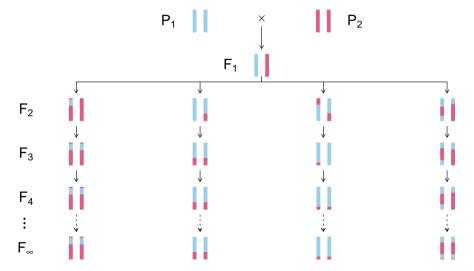
Advanced intercross lines



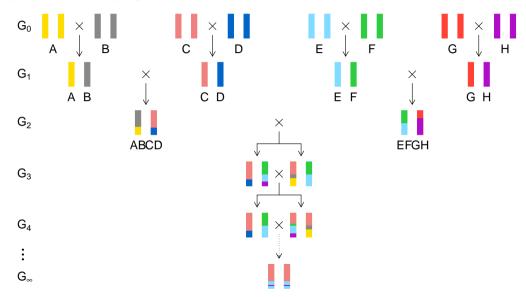
Recombinant inbred lines



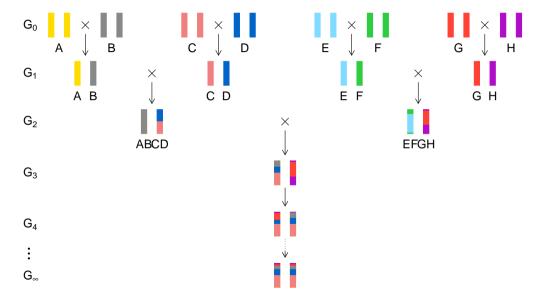
Recombinant inbred lines (selfing)



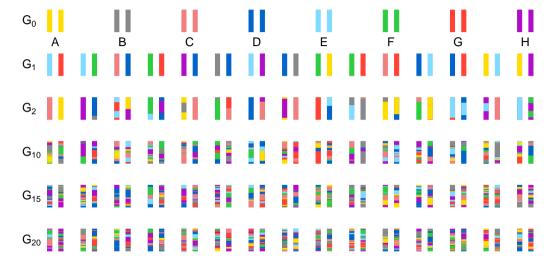
Collaborative Cross



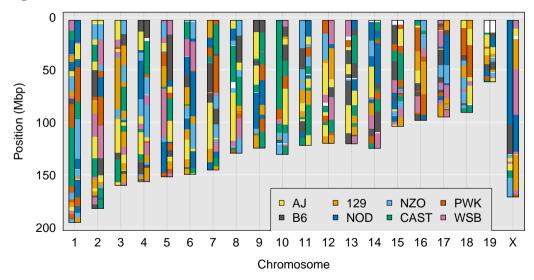
MAGIC lines



Heterogeneous Stock/Diversity outbreds



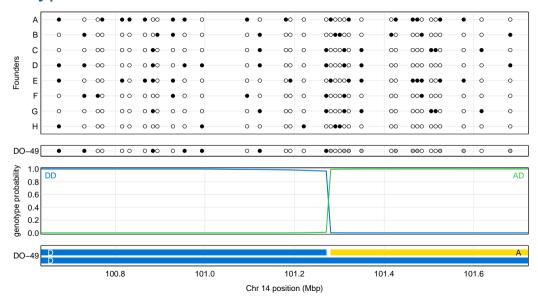
DO genome



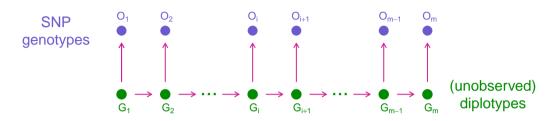
QTL analysis in DO

- ► Genotype reconstruction
- ► Treatment of QTL genotype
- Kinship correction

Genotype reconstruction



Hidden Markov model

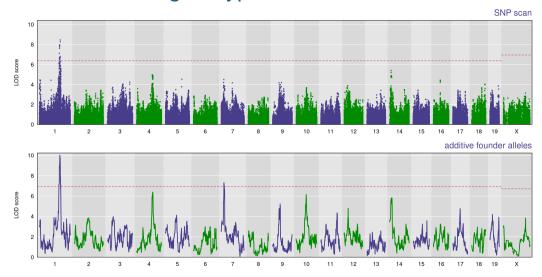


Initial
$$\pi(g) = \Pr(G_1 = g)$$

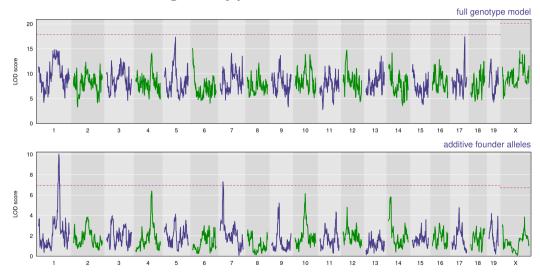
Transition $t_i(g,g') = \Pr(G_{i+1} = g' \mid G_i = g)$

Emission $e_i(g) = \Pr(O_i \mid G_i = g)$

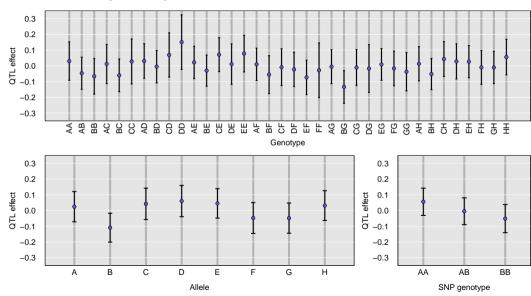
Treatment of QTL genotypes



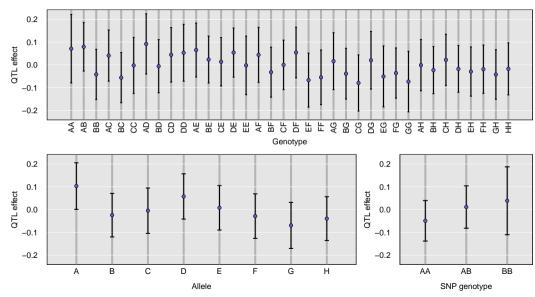
Treatment of QTL genotypes



QTL effects (chr 1)



QTL effects (chr 7)



Linear mixed model

$$\mathbf{y}_{i} = \mu + \sum_{\mathbf{k}} \beta_{\mathbf{k}} \mathbf{q}_{i\mathbf{k}} + \epsilon_{i} \qquad \epsilon_{i} \sim \mathbf{N}(0, \sigma_{\mathbf{e}}^{2})$$

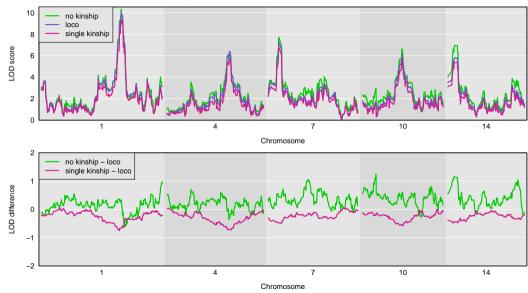
$$= \mu + \qquad \eta_{i} \qquad + \epsilon_{i} \qquad \eta_{i} \sim \mathbf{N}(0, \sigma_{\mathbf{p}}^{2})$$

$$\mathbf{cov}(\eta_{i}, \eta_{j}) = \sigma_{\mathbf{p}}^{2} (2\mathbf{k}_{ij})$$

Kinship and LOCO

- ▶ kinship coefficient measures similarity of two individuals' genomes
- generally estimated from genotype data
- ▶ generally using the "leave one chromosome out (loco)" method
 - Estimate kinship using all chromosomes except the one being scanned

LM vs LMM vs LOCO



Research topics

- ► Identifying the causal polymorphisms
- ▶ Joint analysis of high-dimensional outcomes
- Use of intermediate biochemical traits
- ► Cross-species analyses
- ▶ QTL × QTL interactions (epistasis)
- ► QTL × covariate interactions (e.g. sex, diet, or environment)

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