

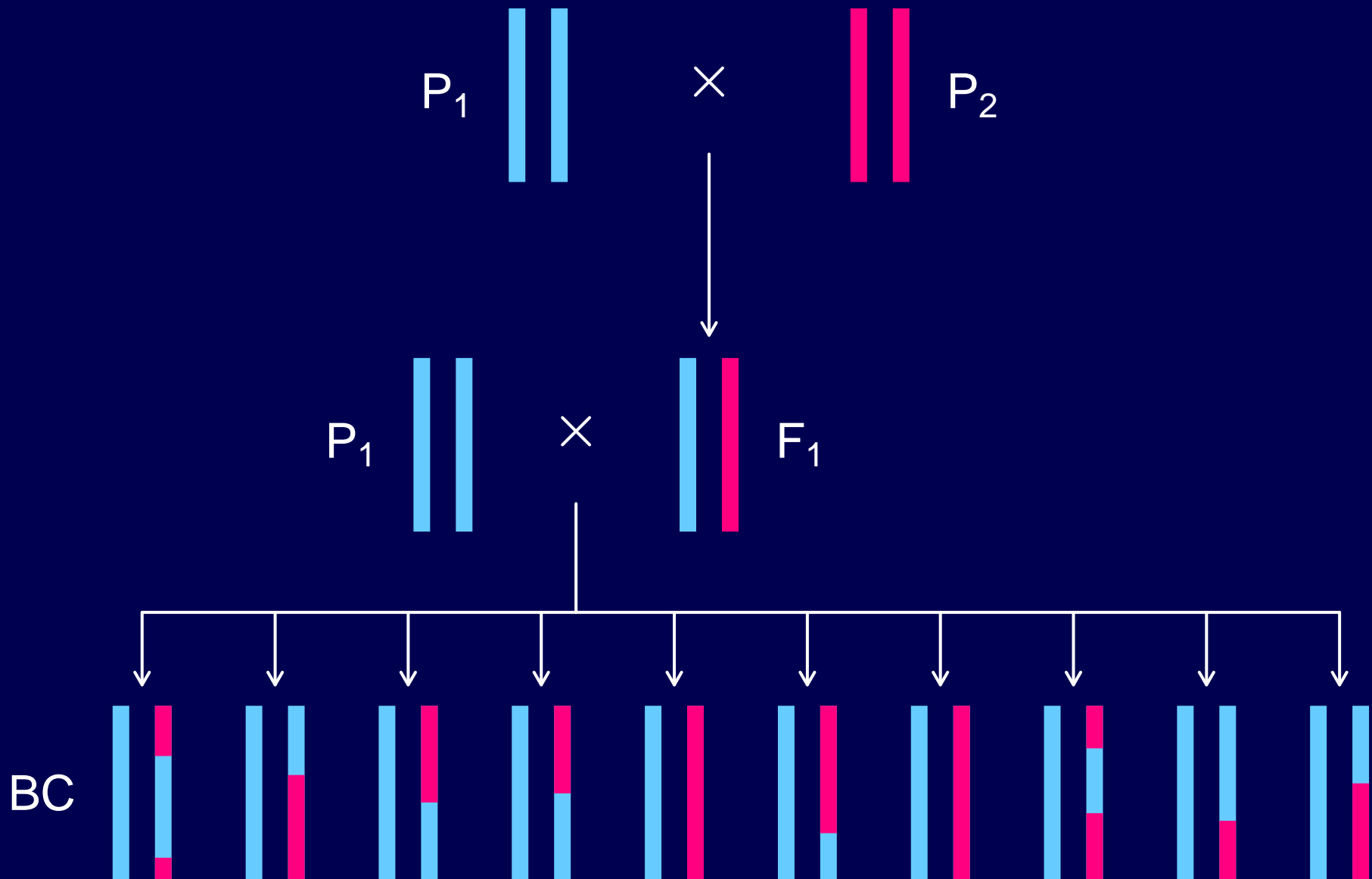
Mapping multiple QTL in experimental crosses

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Backcross

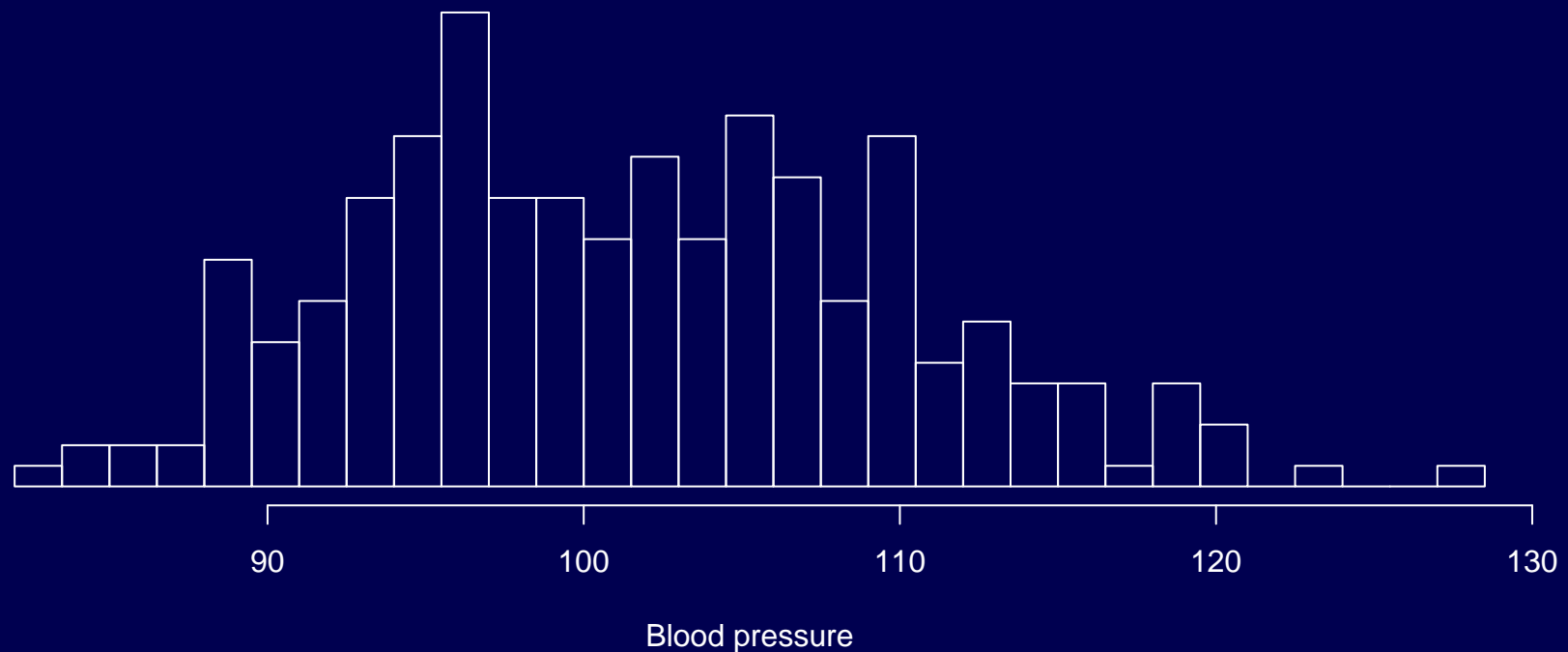


Phenotype data

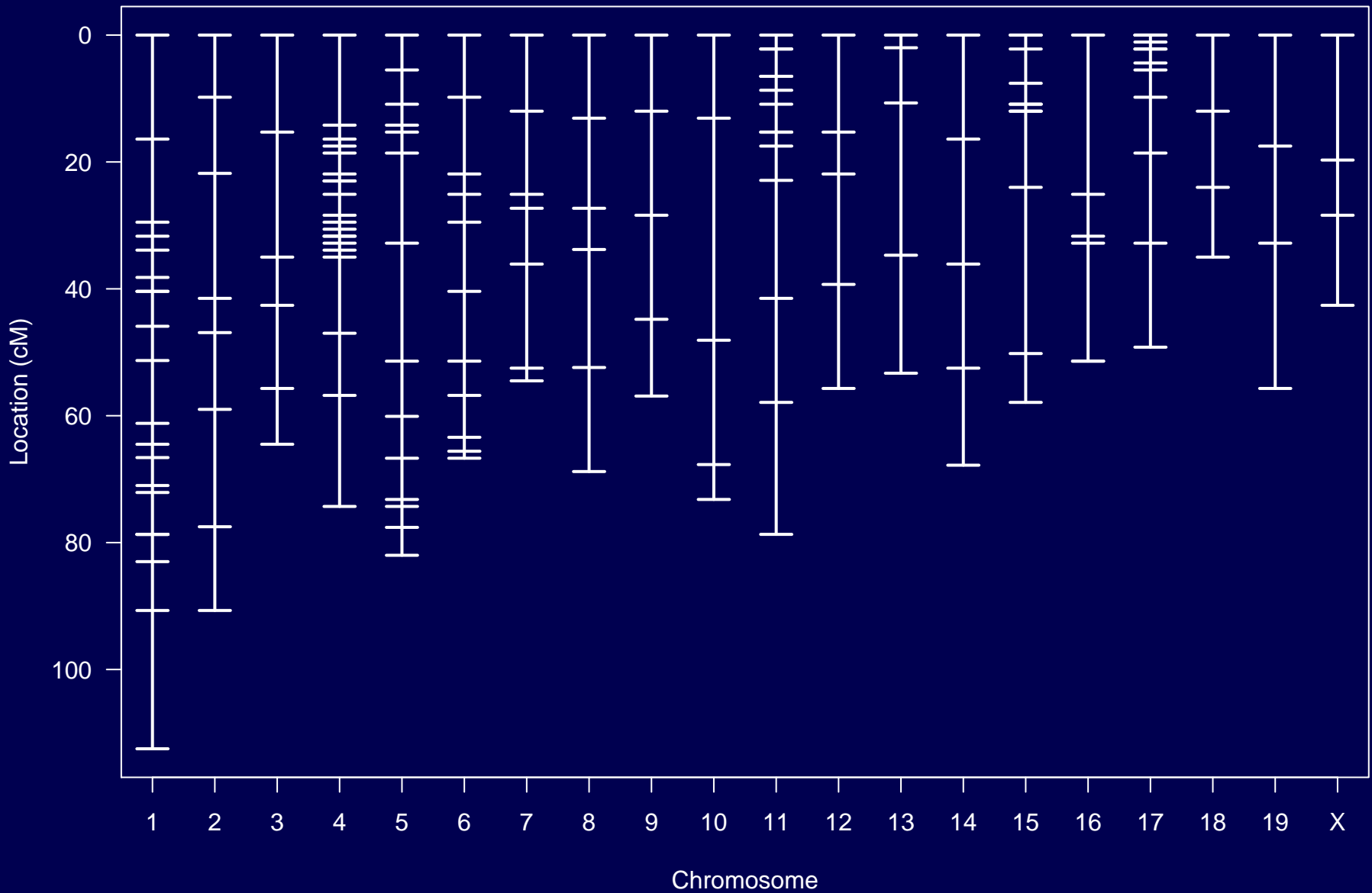
Sugiyama et al. Genomics 71:70-77, 2001

250 male mice from the backcross $(A \times B) \times B$

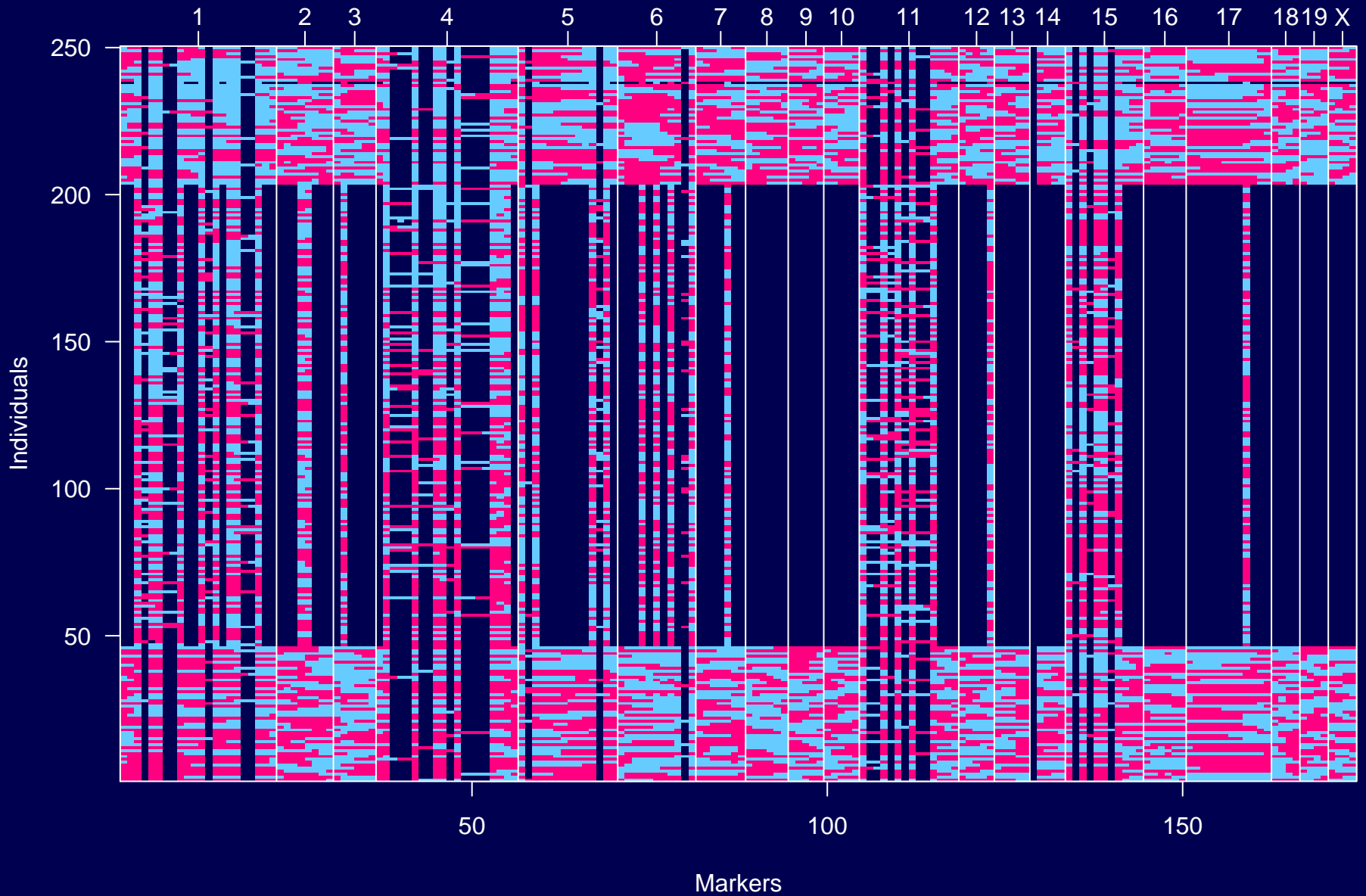
Blood pressure after two weeks drinking water with 1% NaCl



Genetic map



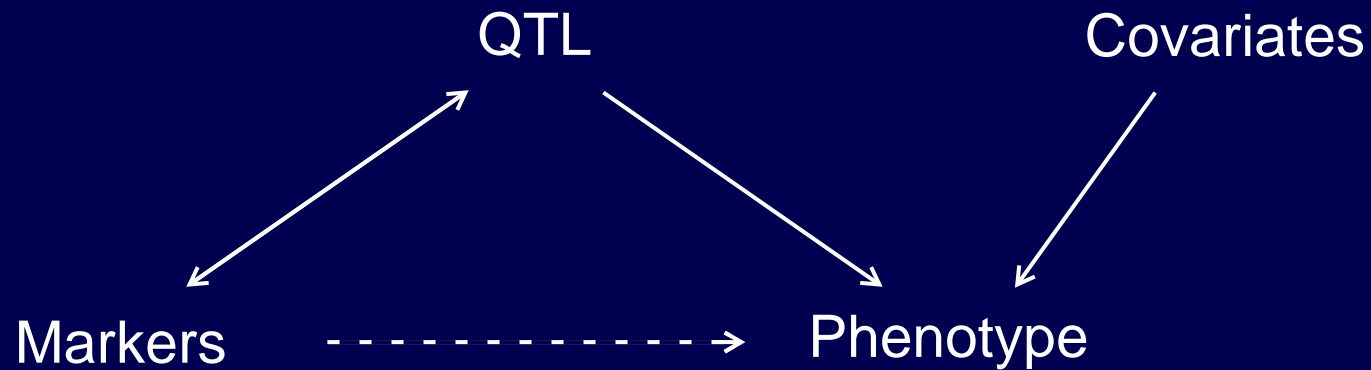
Genotype data



Goals

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

Two problems



The missing data problem:

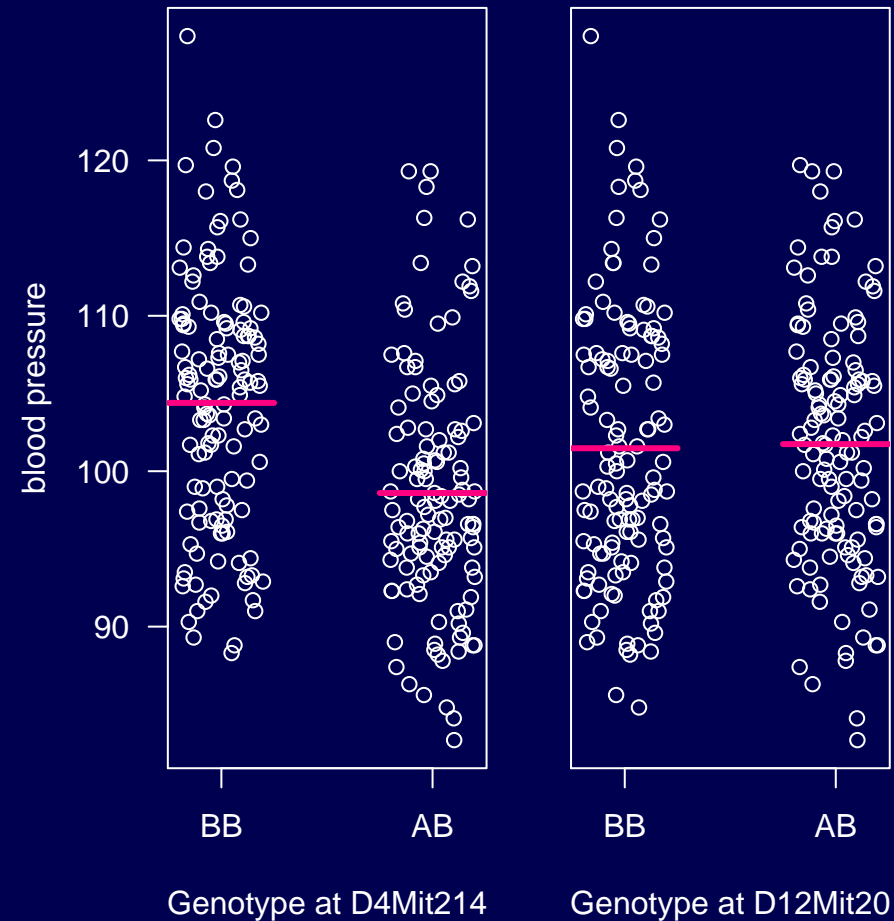
Markers \longleftrightarrow QTL

The model selection problem:

QTL, covariates \longrightarrow 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.)

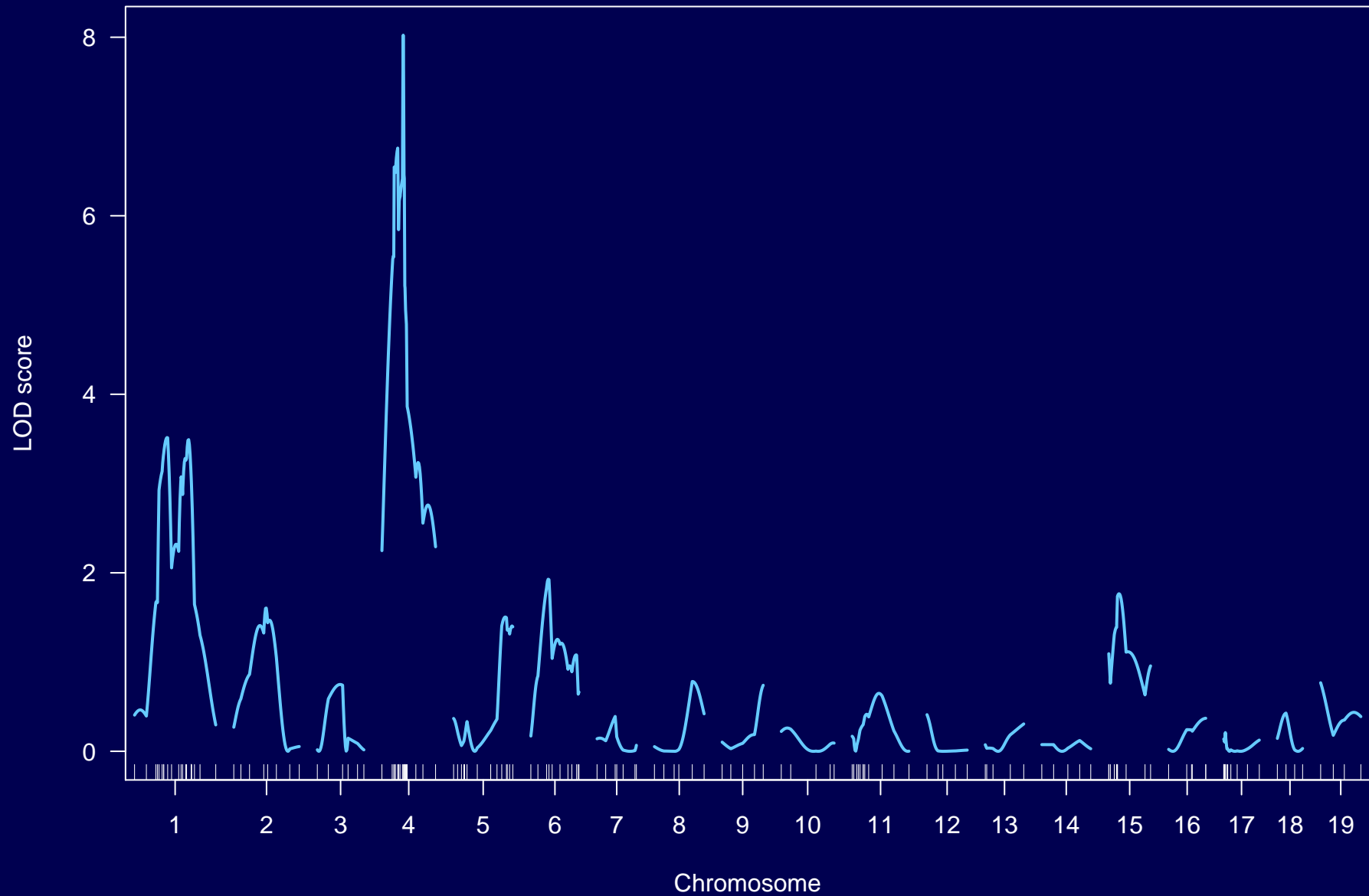
Assume $y \mid q \sim N(\mu_q, \sigma)$

- Calculate $p_q = \Pr(q \mid \text{marker data})$.

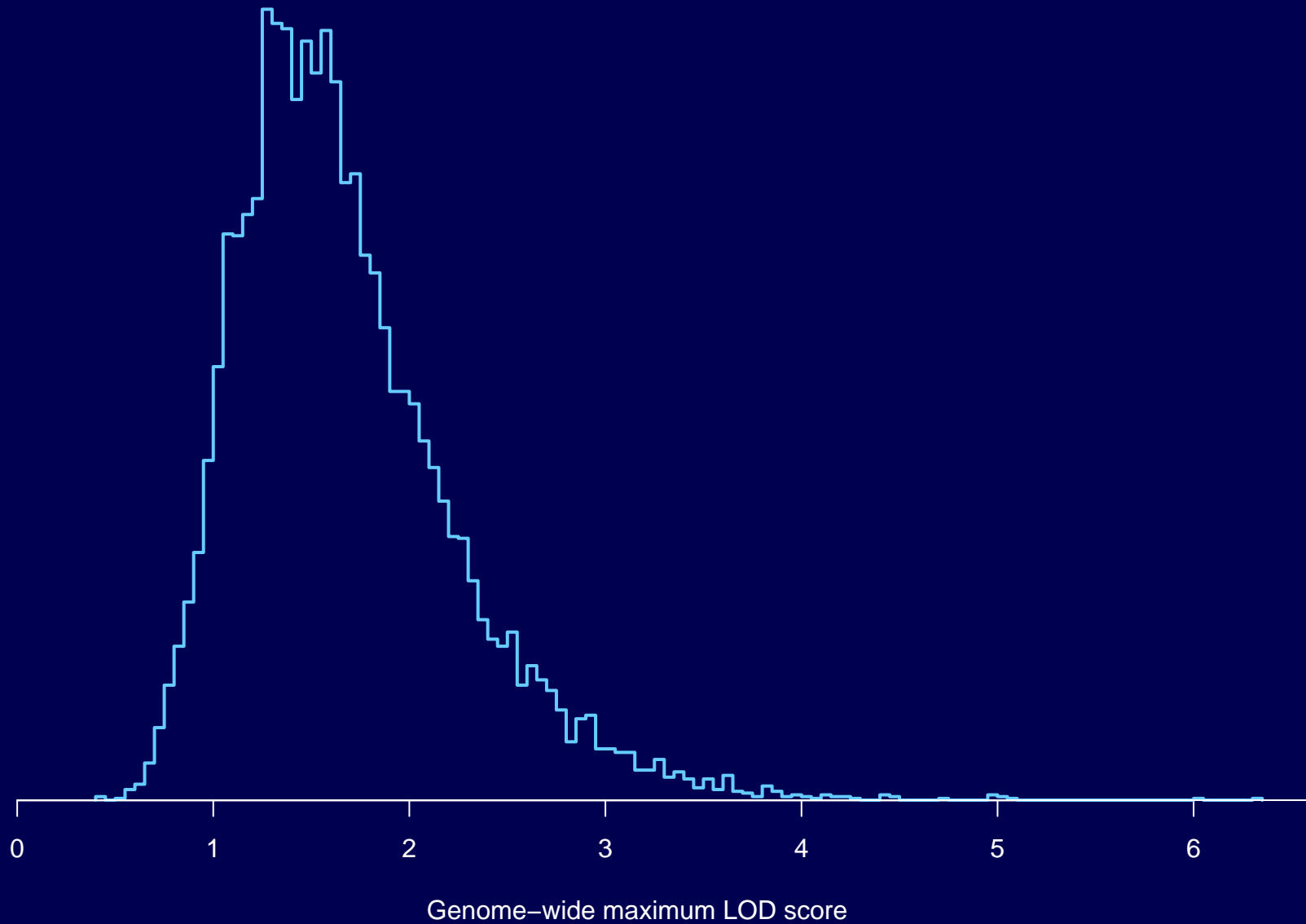
$$y \mid \text{marker data} \sim \sum_q p_q \phi(y \mid \mu_q, \sigma)$$

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

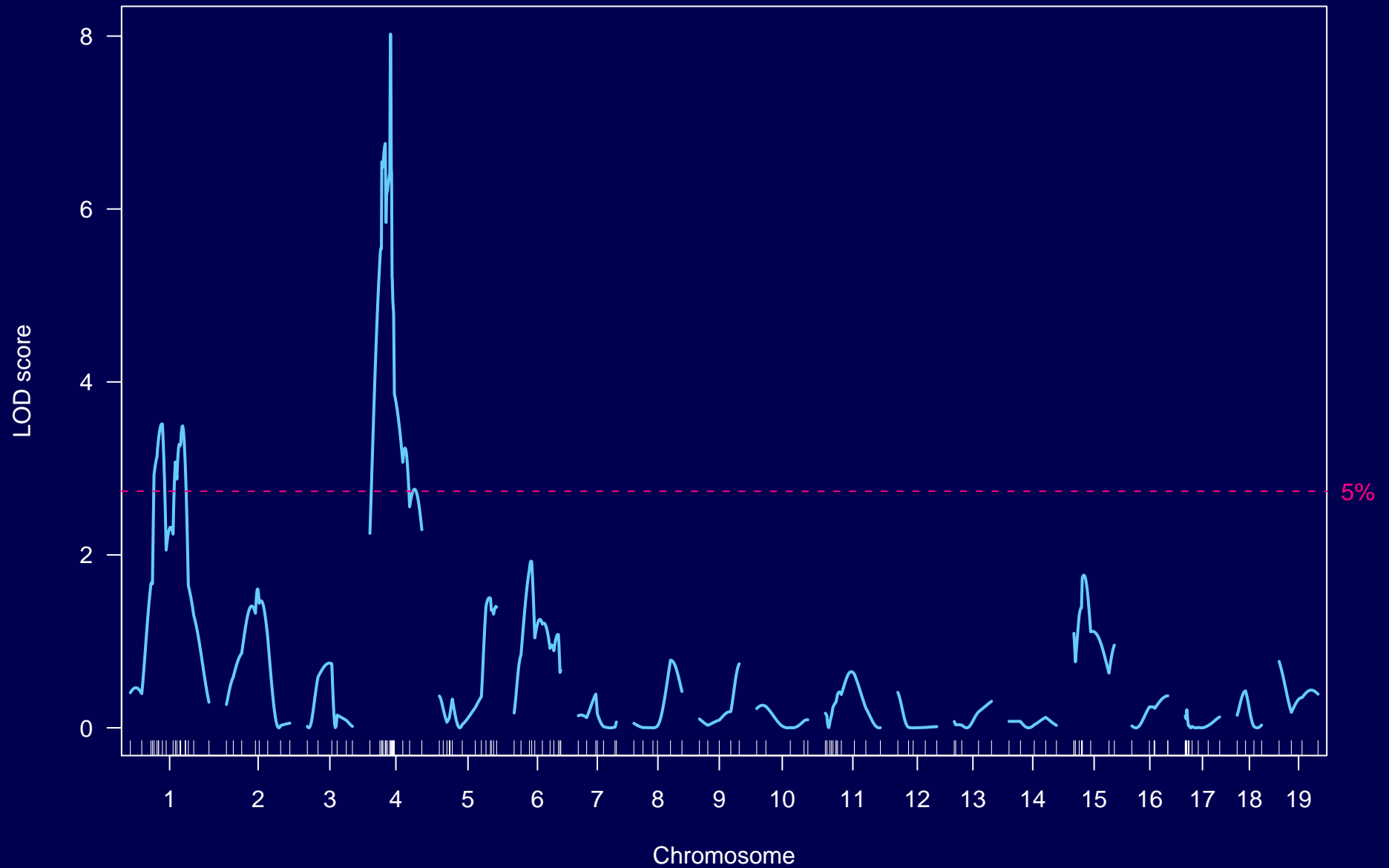
LOD curves



Permutation results



LOD curves

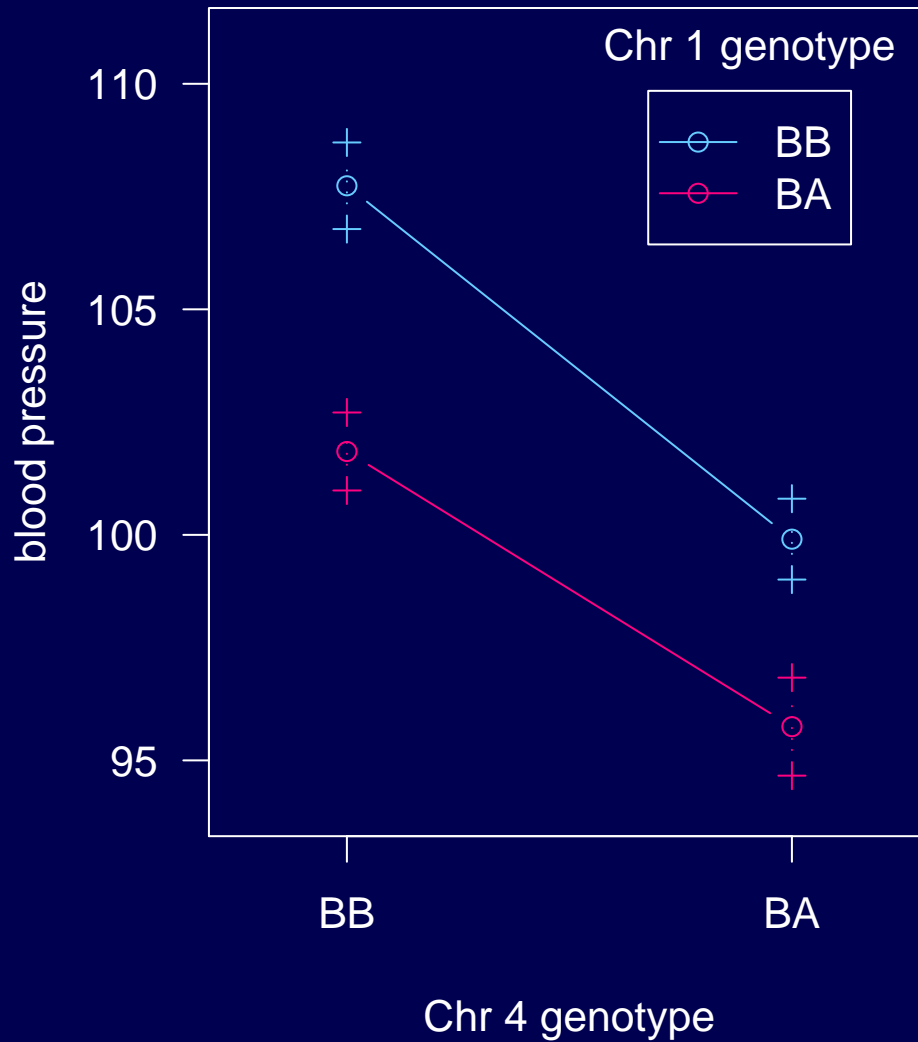


Modeling multiple QTL

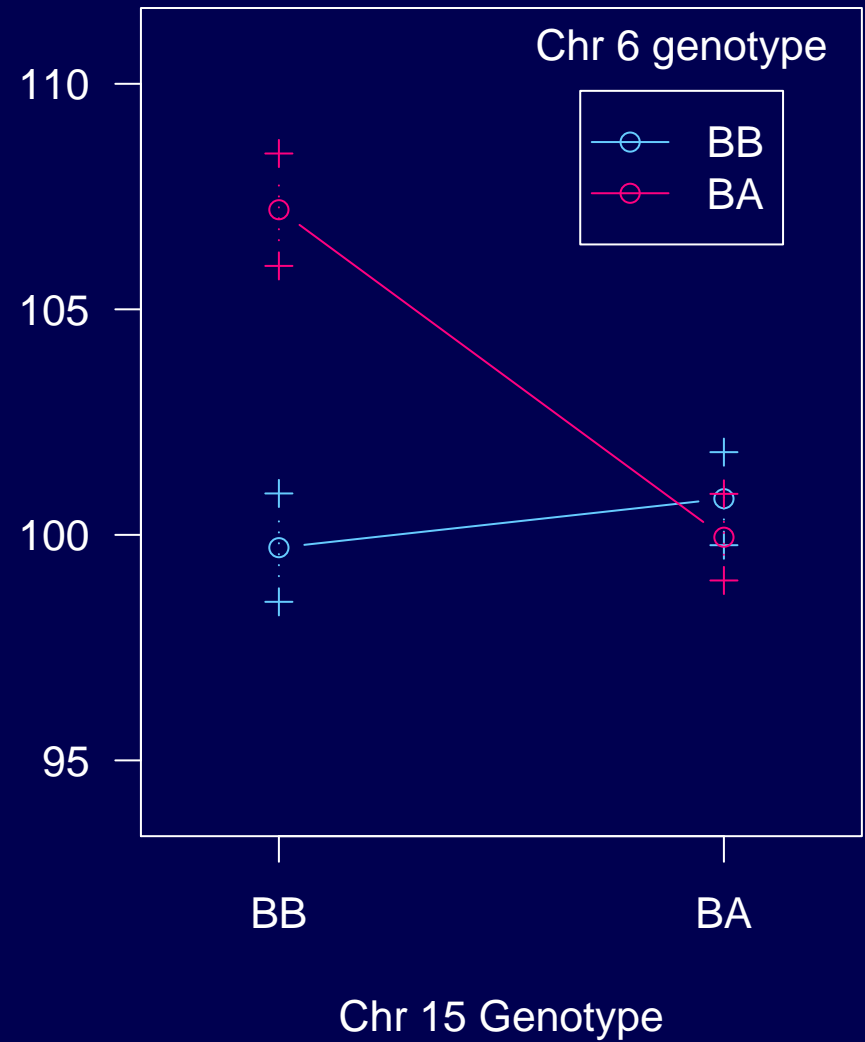
- Reduce residual variation \longrightarrow increased power
- Separate linked QTL
- Identify interactions among QTL (epistasis)

Estimated effects

1 x 4



6 x 15



Model selection

- Class of models
 - Additive models
 - + pairwise interactions
 - + higher-order interactions
 - Impose hierarchy on interactions?
 - Don't allow QTL to be too close
- 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 (QTL or interactions)
 - Include extraneous terms
- Identify as many correct terms as possible, while controlling the rate of inclusion of extraneous terms.
- Want the major players; correct identification of interactions is of secondary importance.

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

Additive QTL

Simple situation:

- Dense markers
- Complete genotype data
- No epistasis

$$y = \mu + \sum \beta_j \mathbf{q}_j + \epsilon \quad \text{which } \beta_j \neq 0?$$

$$\text{pLOD}(\gamma) = \text{LOD}(\gamma) - \mathbf{T} |\gamma|$$

Additive QTL

Simple situation:

- Dense markers
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$$\text{pLOD}(\gamma) = \text{LOD}(\gamma) - \mathbf{T} |\gamma|$$

$$0 \text{ vs } 1 \text{ QTL: } \text{pLOD}(\emptyset) = 0$$

$$\text{pLOD}(\{\lambda\}) = \text{LOD}(\{\lambda\}) - \mathbf{T}$$

Additive QTL

Simple situation:

- Dense markers
- Complete genotype data
- No epistasis

$$y = \mu + \sum \beta_j \mathbf{q}_j + \epsilon \quad \text{which } \beta_j \neq 0?$$

$$\text{pLOD}(\gamma) = \text{LOD}(\gamma) - \mathbf{T} |\gamma|$$

For the mouse genome:

$$\mathbf{T} = 2.69 \text{ (BC) or } 3.52 \text{ (F}_2\text{)}$$

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

Epistasis

$$y = \mu + \sum \beta_j \mathbf{q}_j + \sum \gamma_{jk} \mathbf{q}_j \mathbf{q}_k + \epsilon$$

$$\text{pLOD}(\gamma) = \text{LOD}(\gamma) - T_m |\gamma|_m - T_i |\gamma|_i$$

T_m = as chosen previously

T_i = ?

Idea 1

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

$$T_i = 95\text{th percentile of the distribution of} \\ \max \text{LOD}_f(\lambda_1, \lambda_2) - \max \text{LOD}_a(\lambda_1, \lambda_2)$$

Idea 1

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

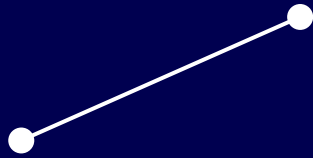
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For the mouse genome:

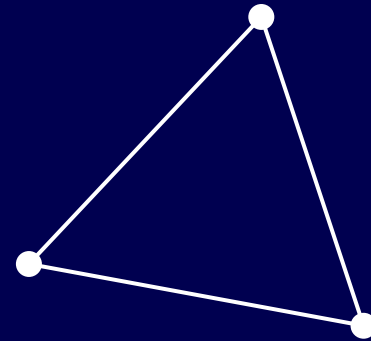
$$T_m = 2.69 \text{ (BC) or } 3.52 \text{ (F}_2\text{)}$$

$$T_i^H = 2.62 \text{ (BC) or } 4.28 \text{ (F}_2\text{)}$$

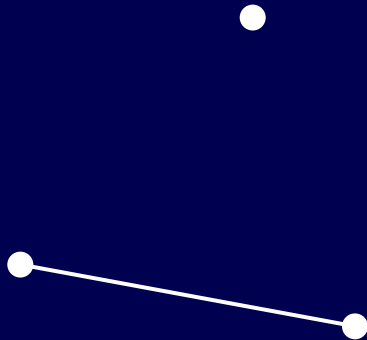
Models as graphs



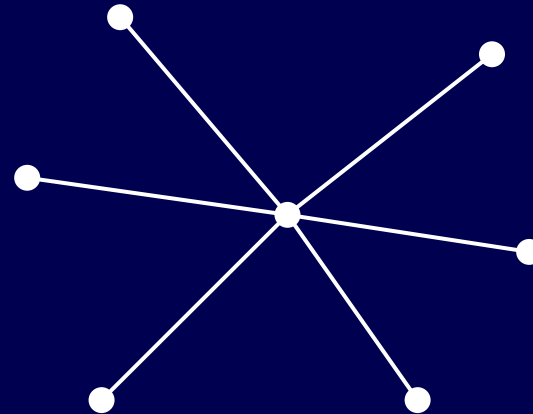
A



C



B



D

Idea 2

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

$$T_m + T_i = 95\text{th percentile of the distribution of} \\ \max \text{LOD}_f(\lambda_1, \lambda_2) - \max \text{LOD}_1(\lambda)$$

Idea 2

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

$$T_m + T_i = 95\text{th percentile of the distribution of} \\ \max \text{LOD}_f(\lambda_1, \lambda_2) - \max \text{LOD}_1(\lambda)$$

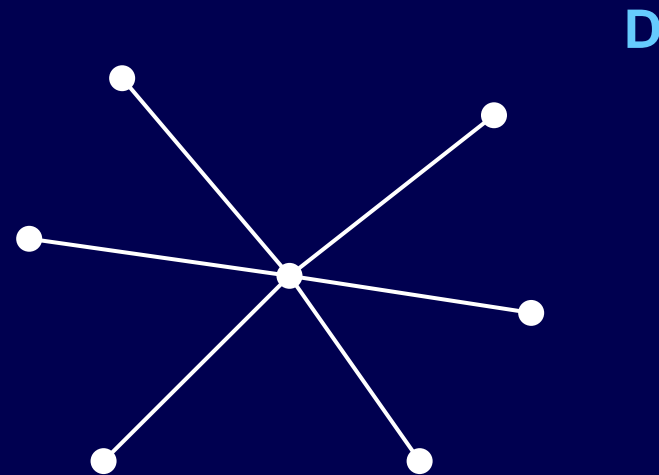
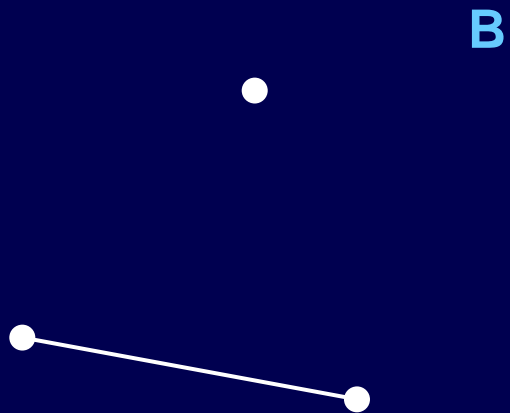
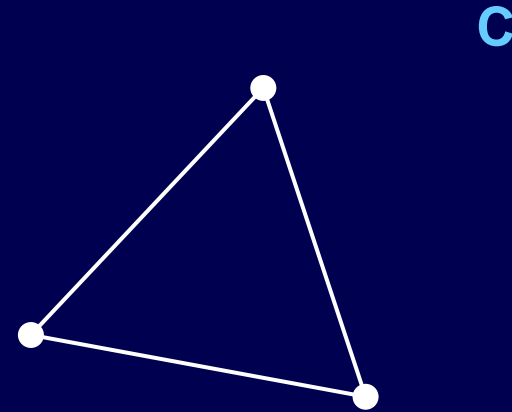
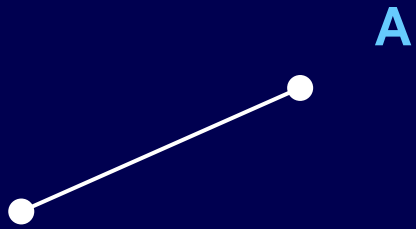
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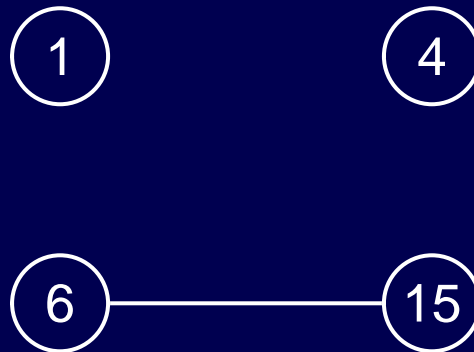
$$T_i^H = 2.62 \text{ (BC) or } 4.28 \text{ (F}_2\text{)}$$

$$T_i^L = 1.19 \text{ (BC) or } 2.69 \text{ (F}_2\text{)}$$

Models as graphs

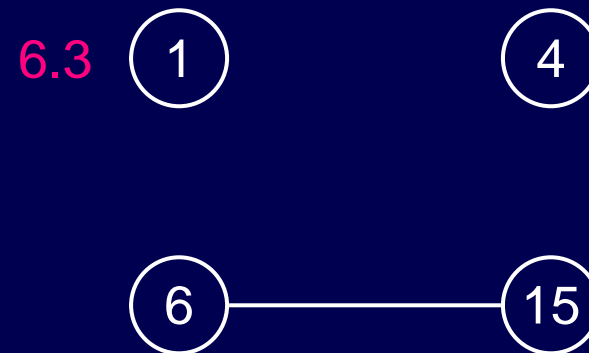


Results



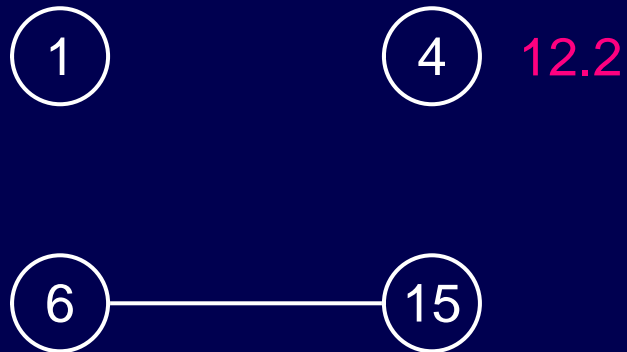
LOD = 23.1

Drop one term?



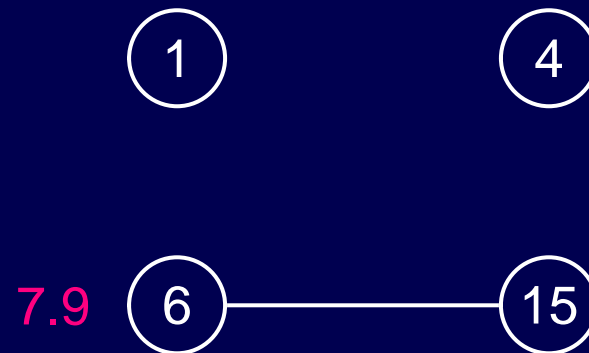
$$T_m = 2.69 \quad T_i^H = 2.62 \quad T_i^L = 1.19 \quad T_m + T_i^H = 5.31 \quad T_m + T_i^L = 3.88 \quad 2T_m = 5.38$$

Drop one term?



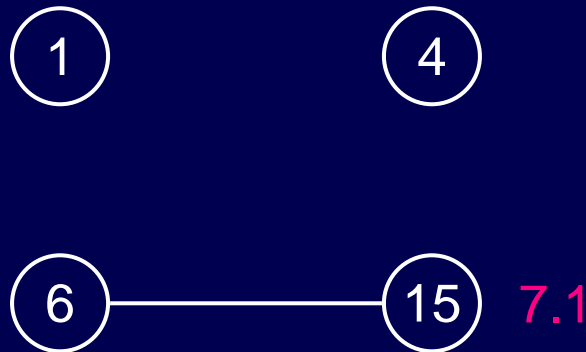
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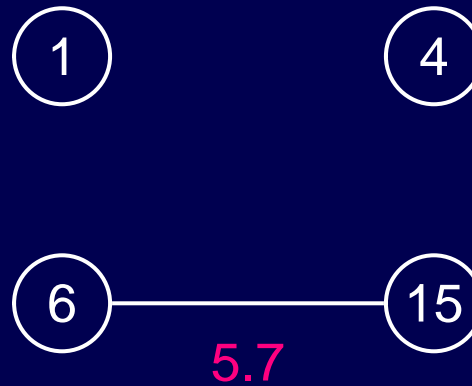
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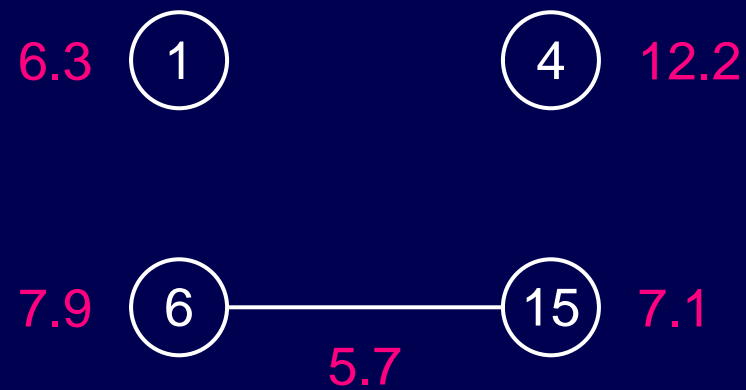
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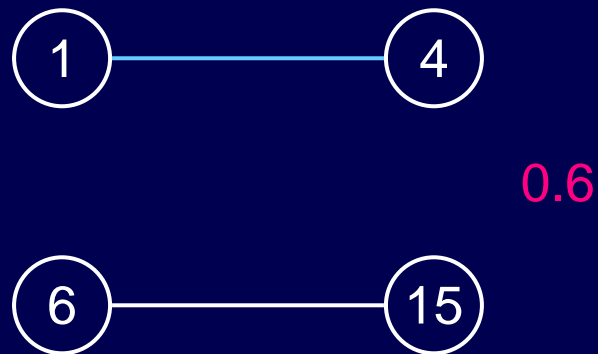
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Drop one at time



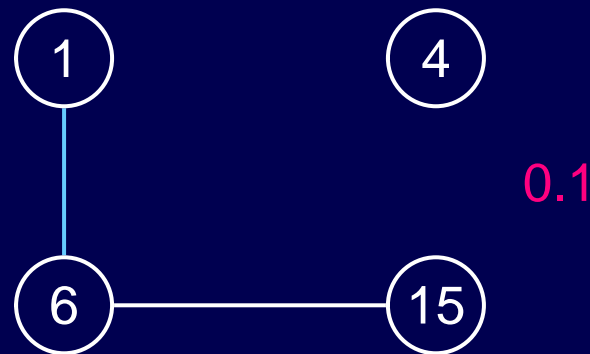
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Add an interaction?



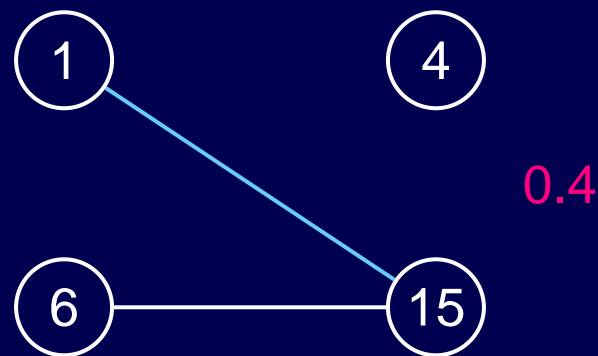
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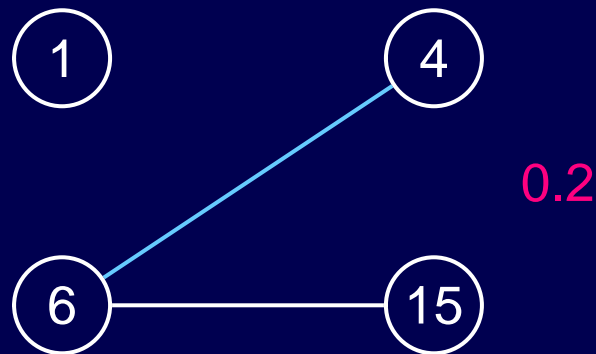
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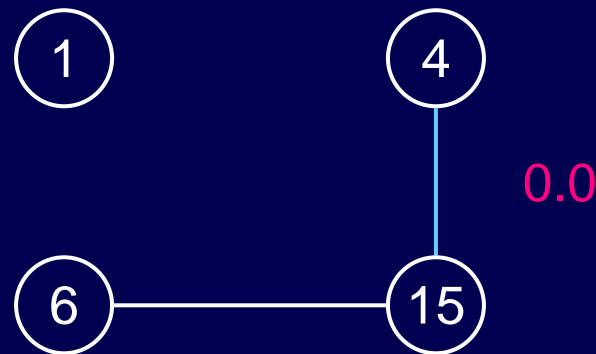
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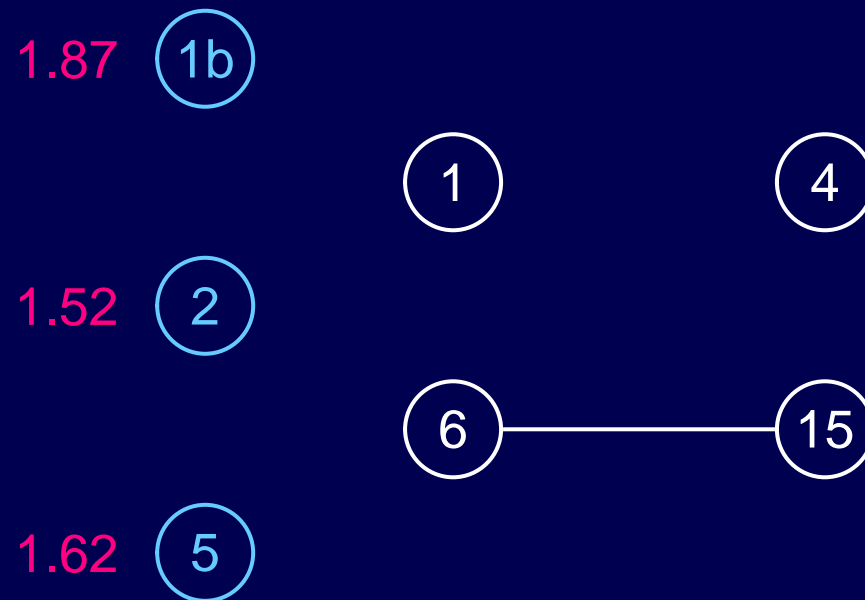
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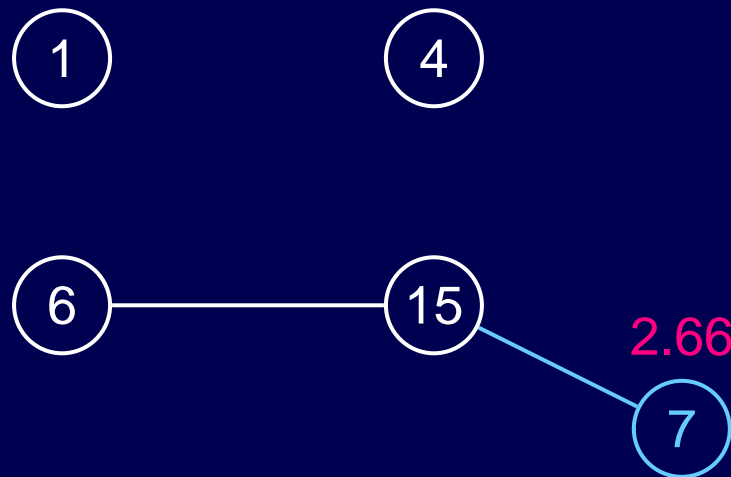
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Add another QTL?



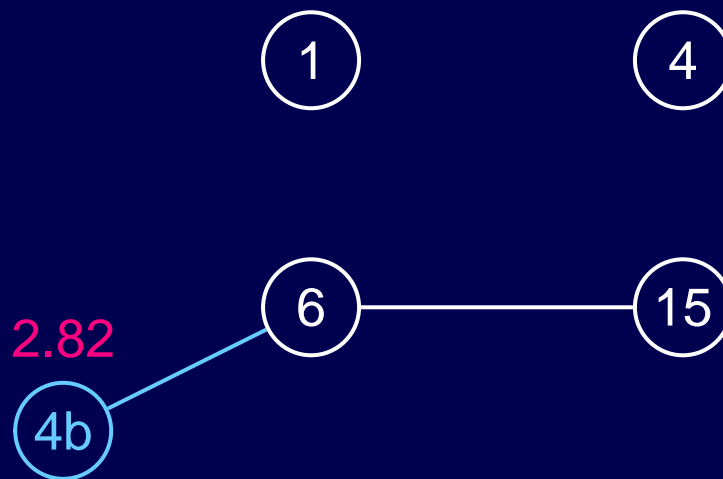
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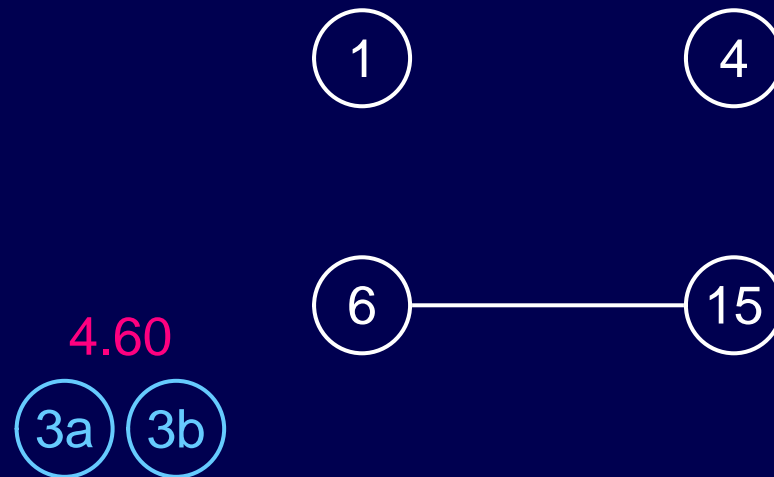
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Add a pair of QTL?



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

To do

- Study performance
(especially relative to other approaches)
- Improve search procedures
- Measuring model uncertainty
- Measuring uncertainty in QTL location
- Covariates and QTL \times covariate interactions
- That evil X chromosome
- Treat linked QTL differently?

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 believe we have a practiceable solution

Acknowledgments

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Fumihiko Sugiyama	now at University of Tsukuba, Japan
Bev Paigen	Jackson Laboratory