Mapping multiple QTL in experimental crosses

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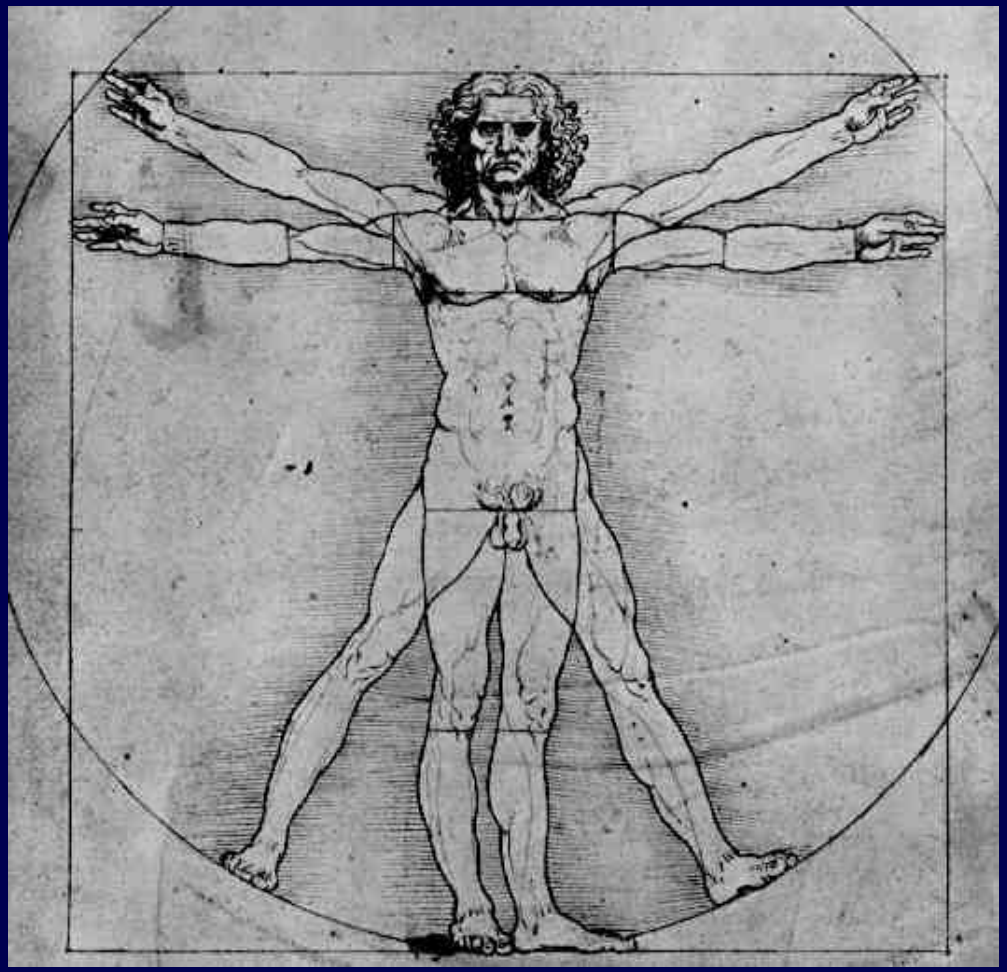
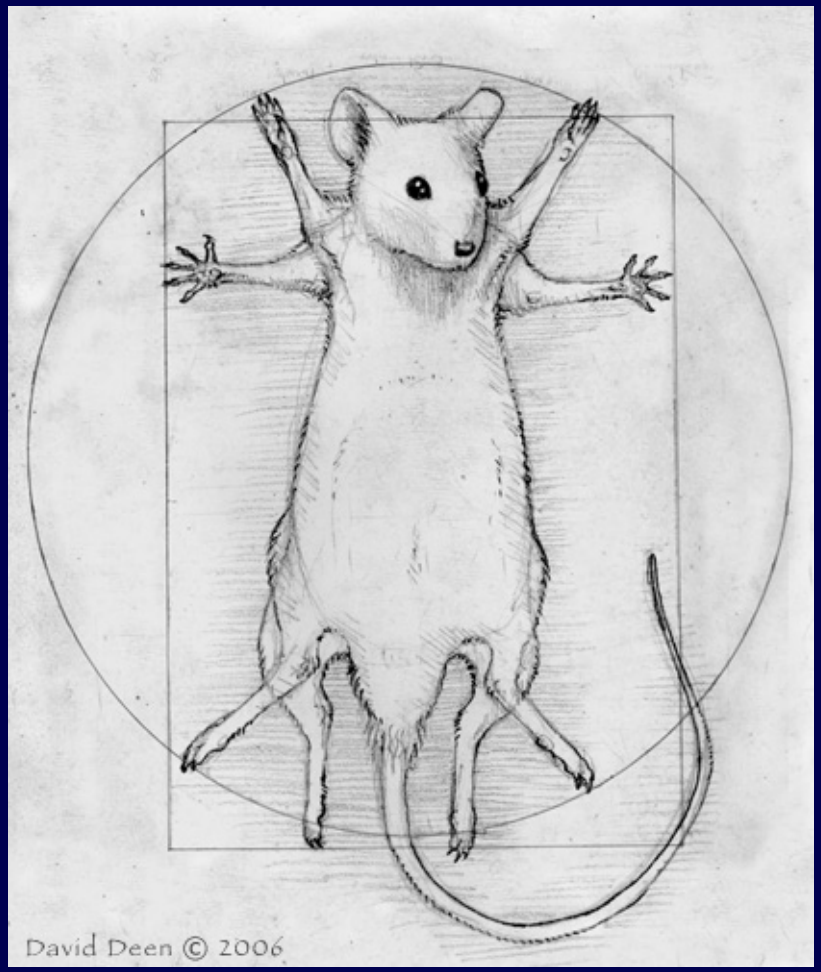
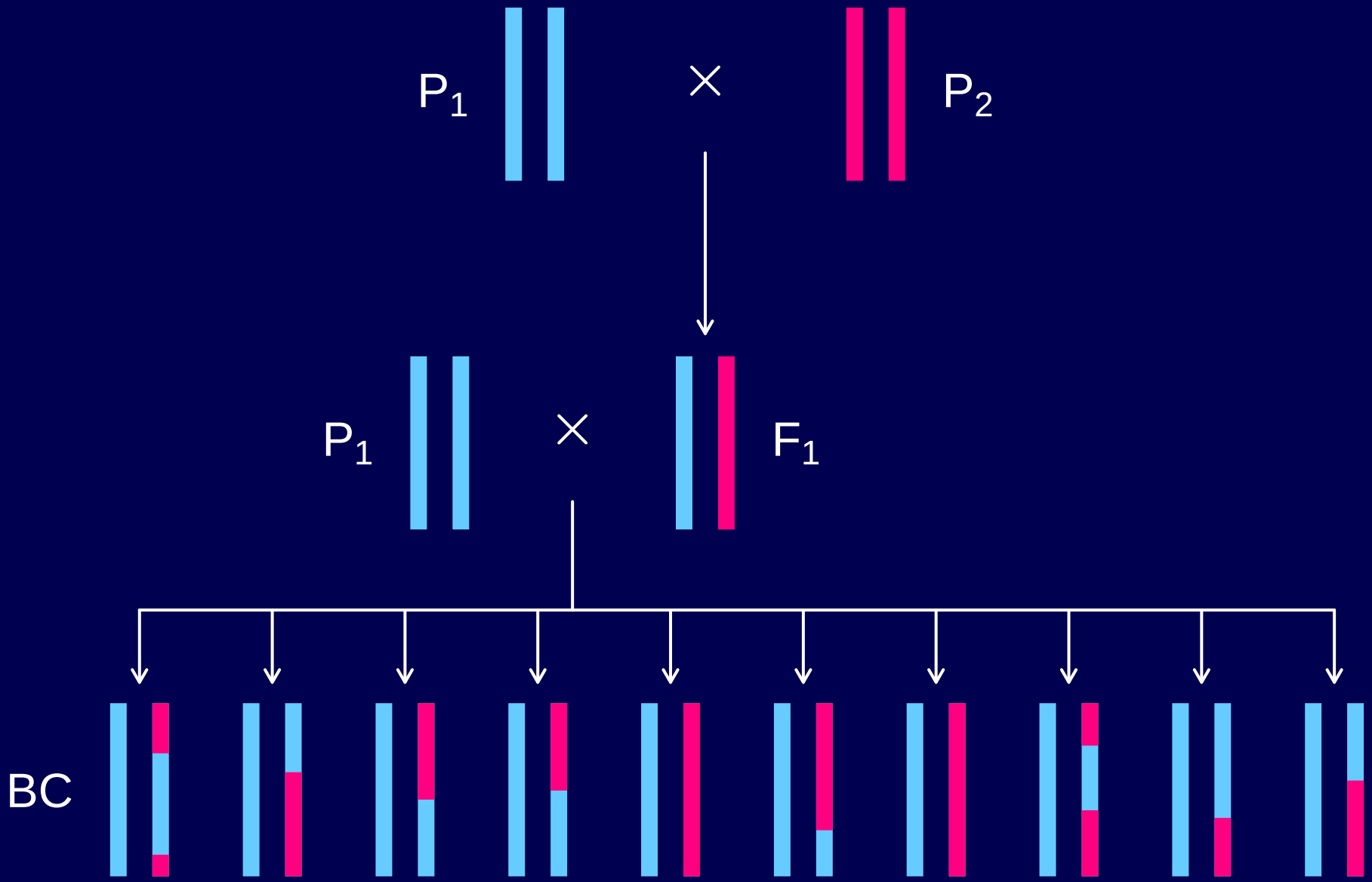
Human vs mouse



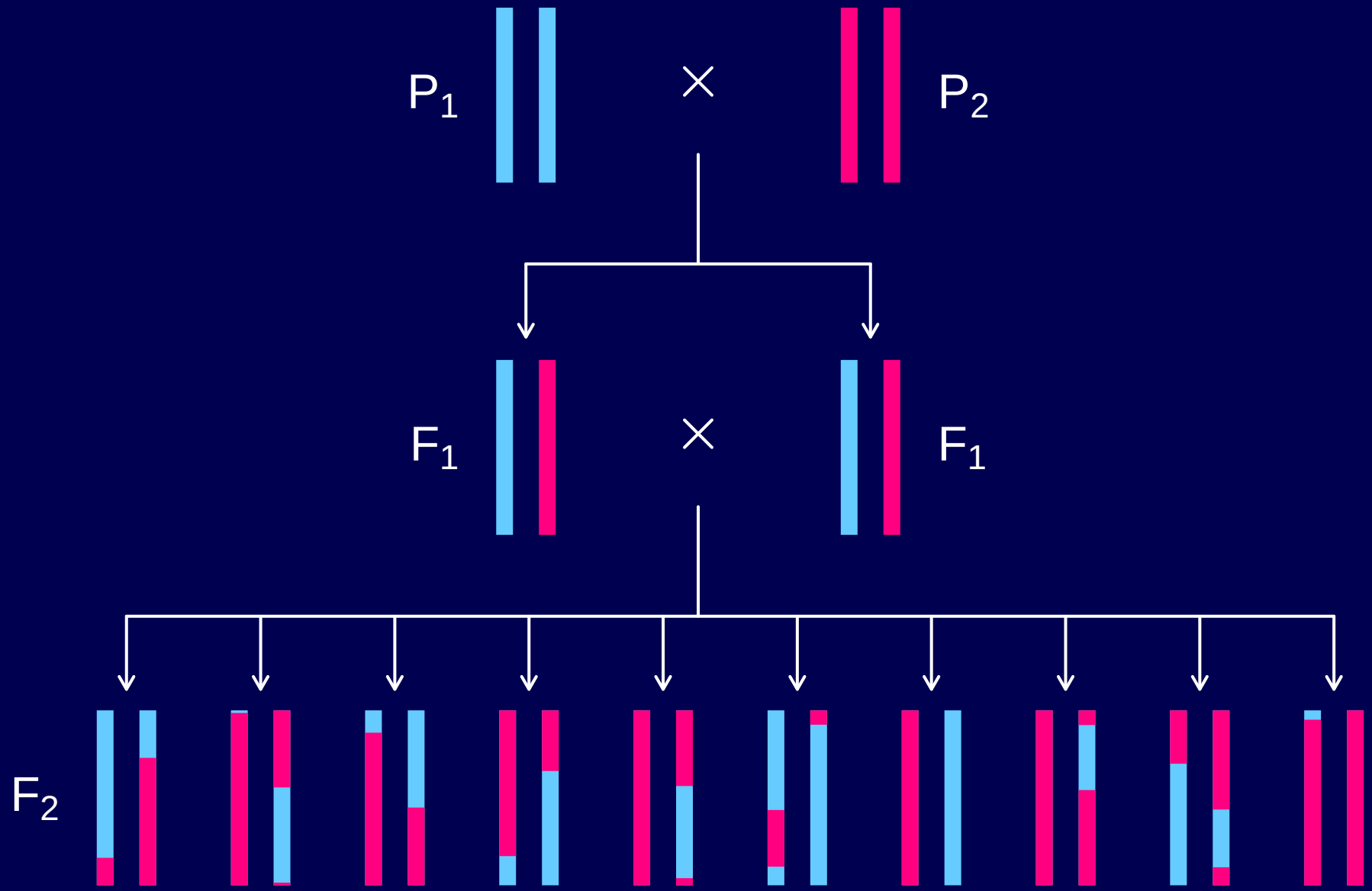


www.daviddeen.com

Backcross



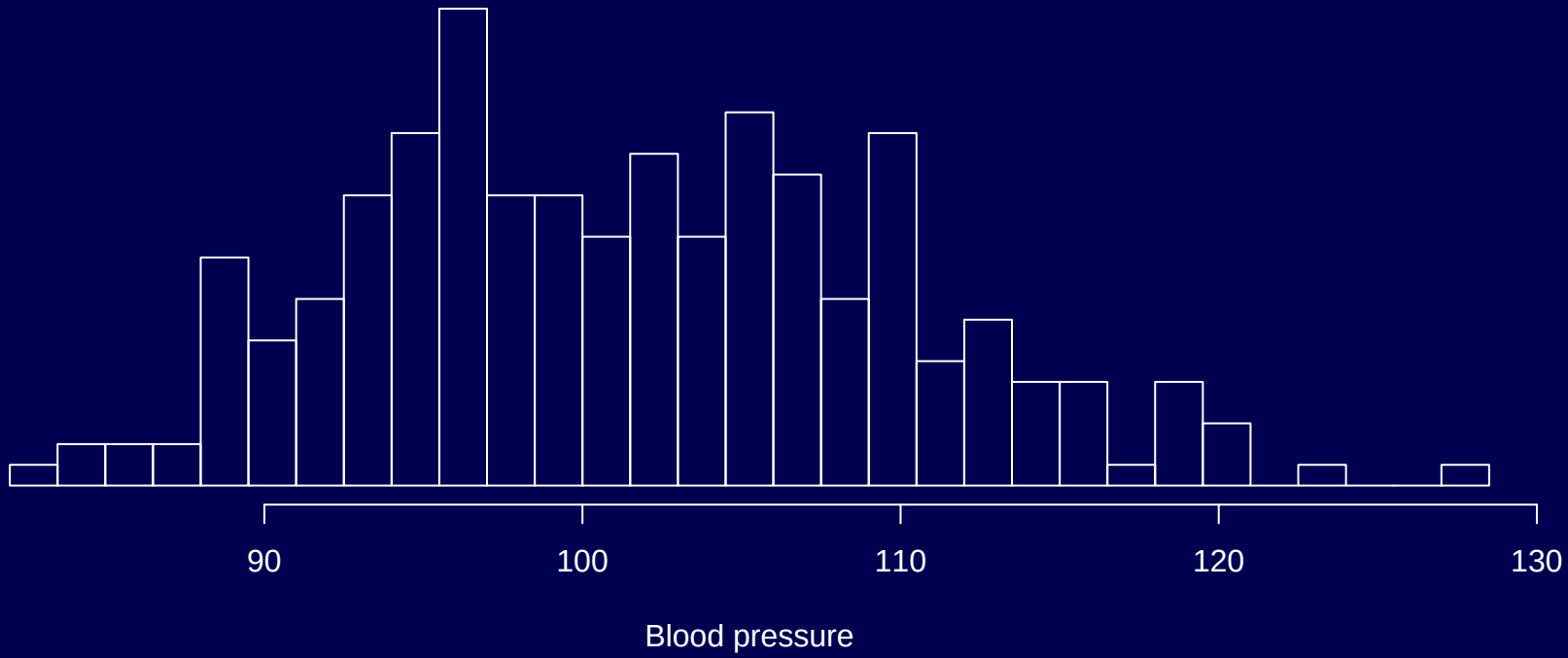
Intercross



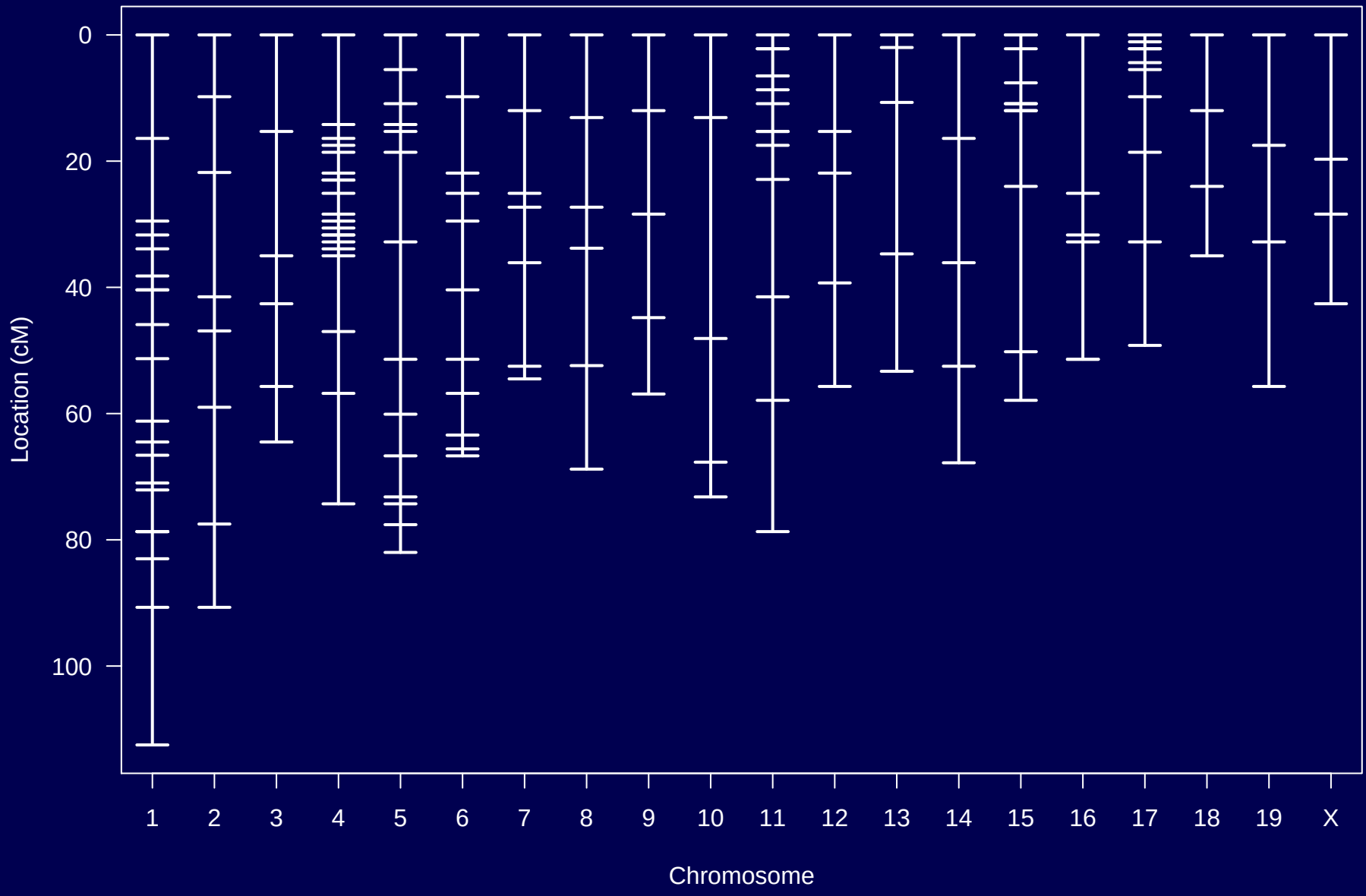
Phenotype data

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

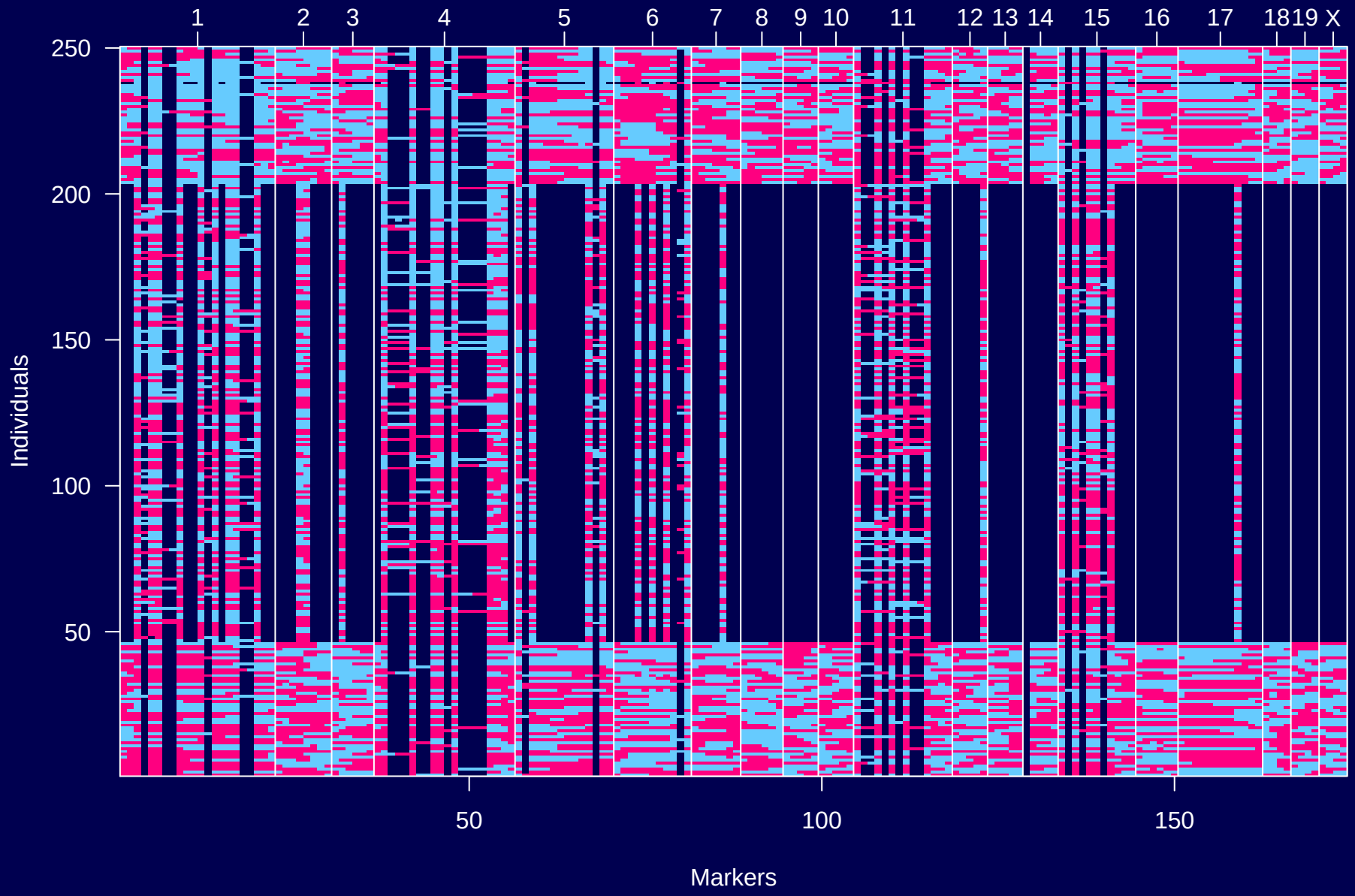
250 male mice from the backcross (A $\times$ B) $\times$ B
Blood pressure after two weeks drinking water with 1% NaCl



Genetic map


Location (cM)
0
20
40
60
80
100
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
X
Chromosome

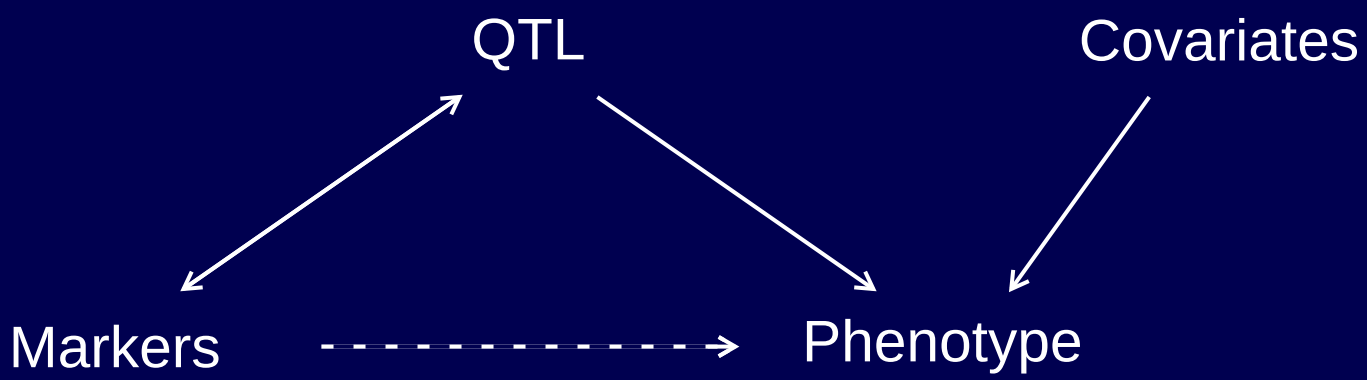
Genotype data



Goals

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

Statistical structure

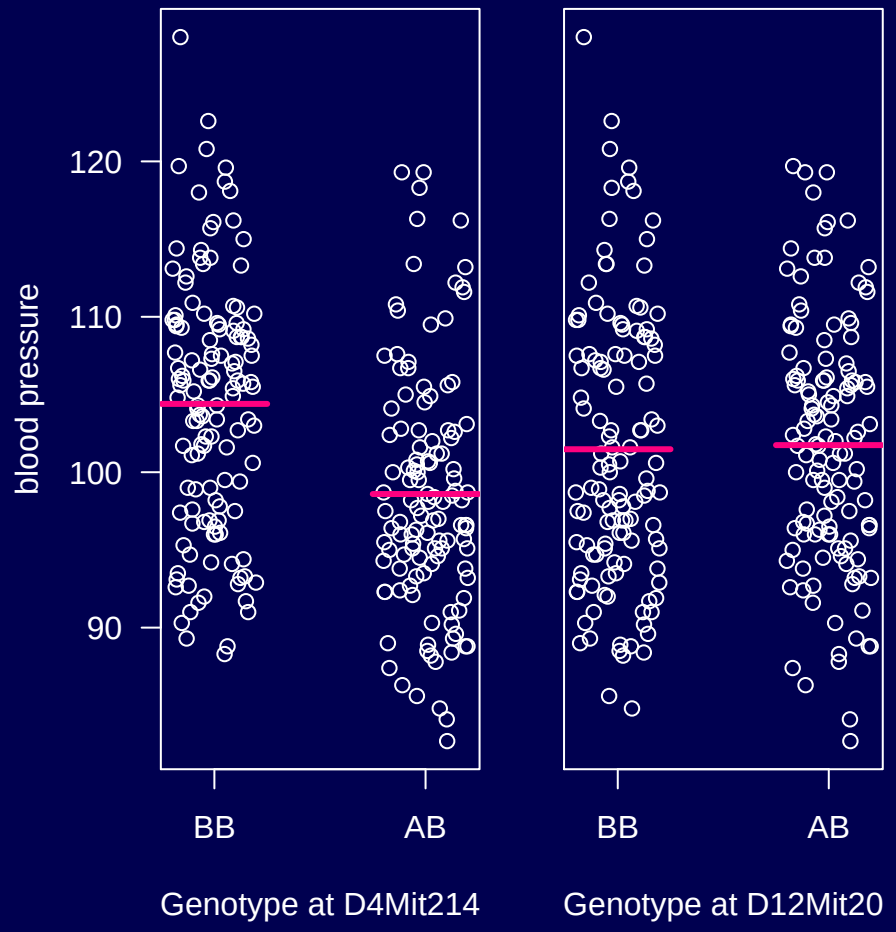


The missing data problem: Markers $\longleftrightarrow$ QTL

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

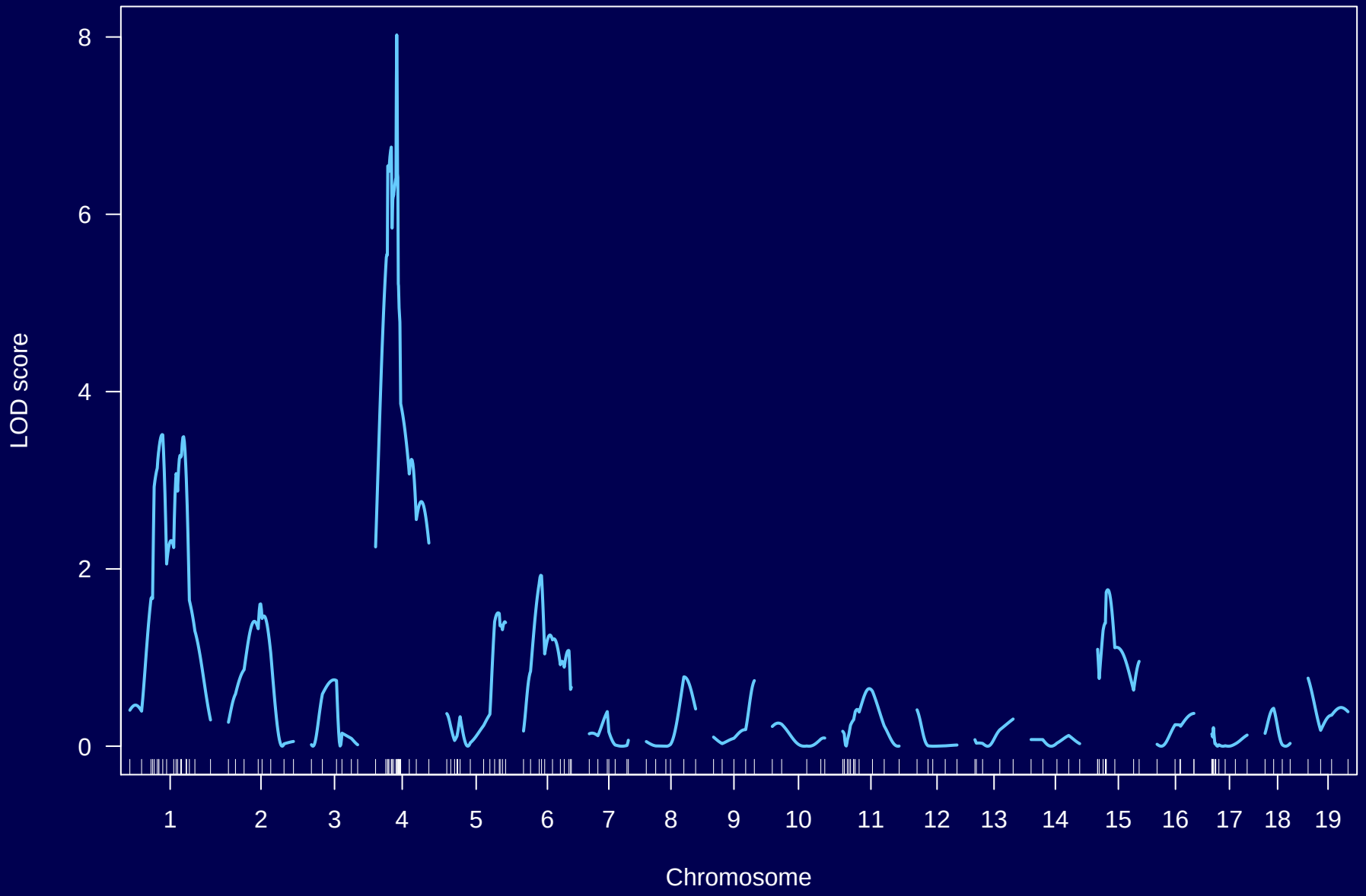
Lander & Botstein (1989)

- 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.)

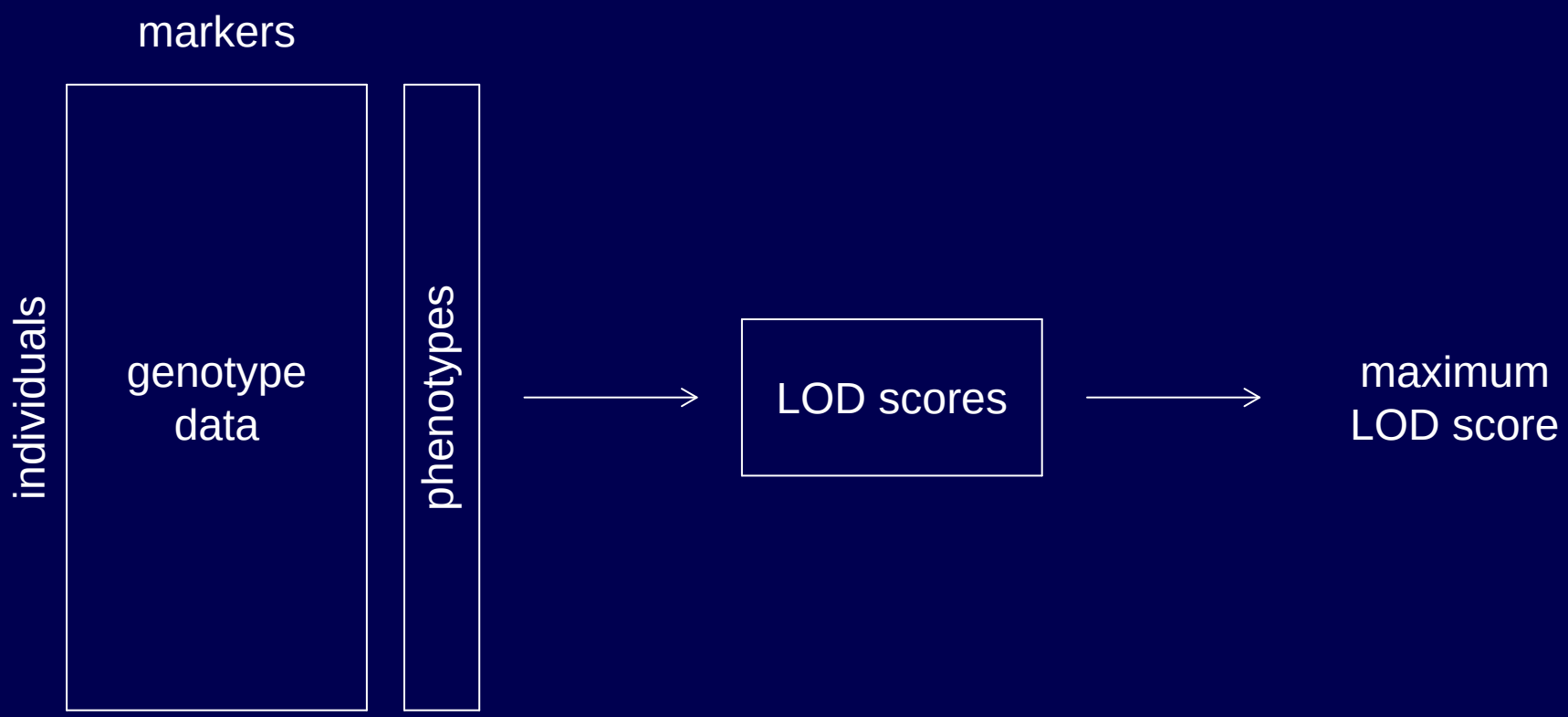
  Assume $y \mid q \sim N(\mu_q, \sigma)$
- Calculate $p_q = \Pr(q \mid \text{marker data})$.

  $y \mid \text{marker data} \sim \sum_q p_q \, \phi(y \mid \mu_q, \sigma)$
- $\text{LOD}(\lambda) = \log_{10} \left\{ \frac{\Pr(y|\text{QTL at } \lambda, \hat{\mu}_{q\lambda}, \hat{\sigma}_\lambda)}{\Pr(y|\text{no QTL}, \hat{\mu}, \hat{\sigma})} \right\}$

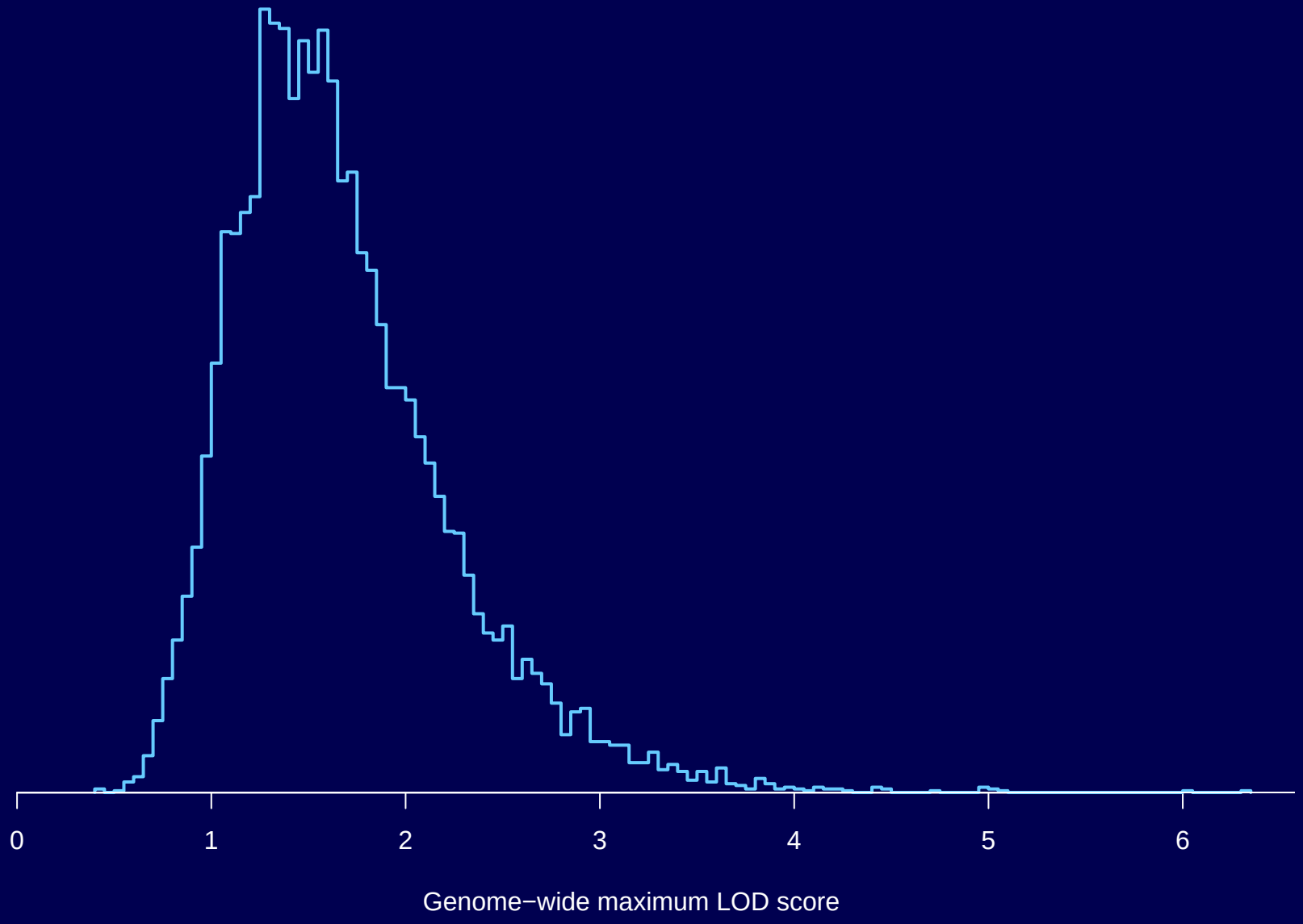
LOD curves


LOD score
0
2
4
6
8
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
Chromosome

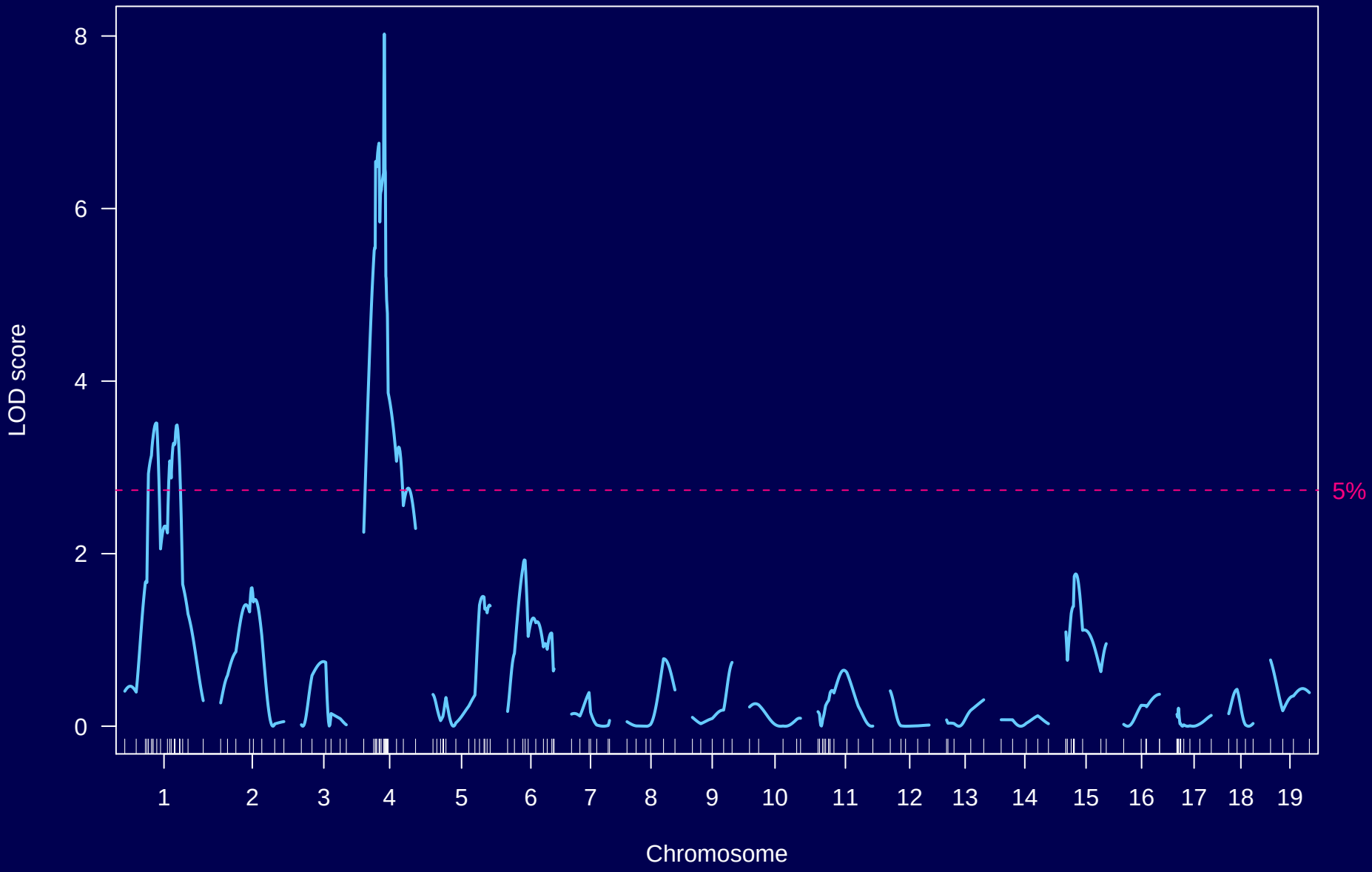
Permutation test



Permutation results



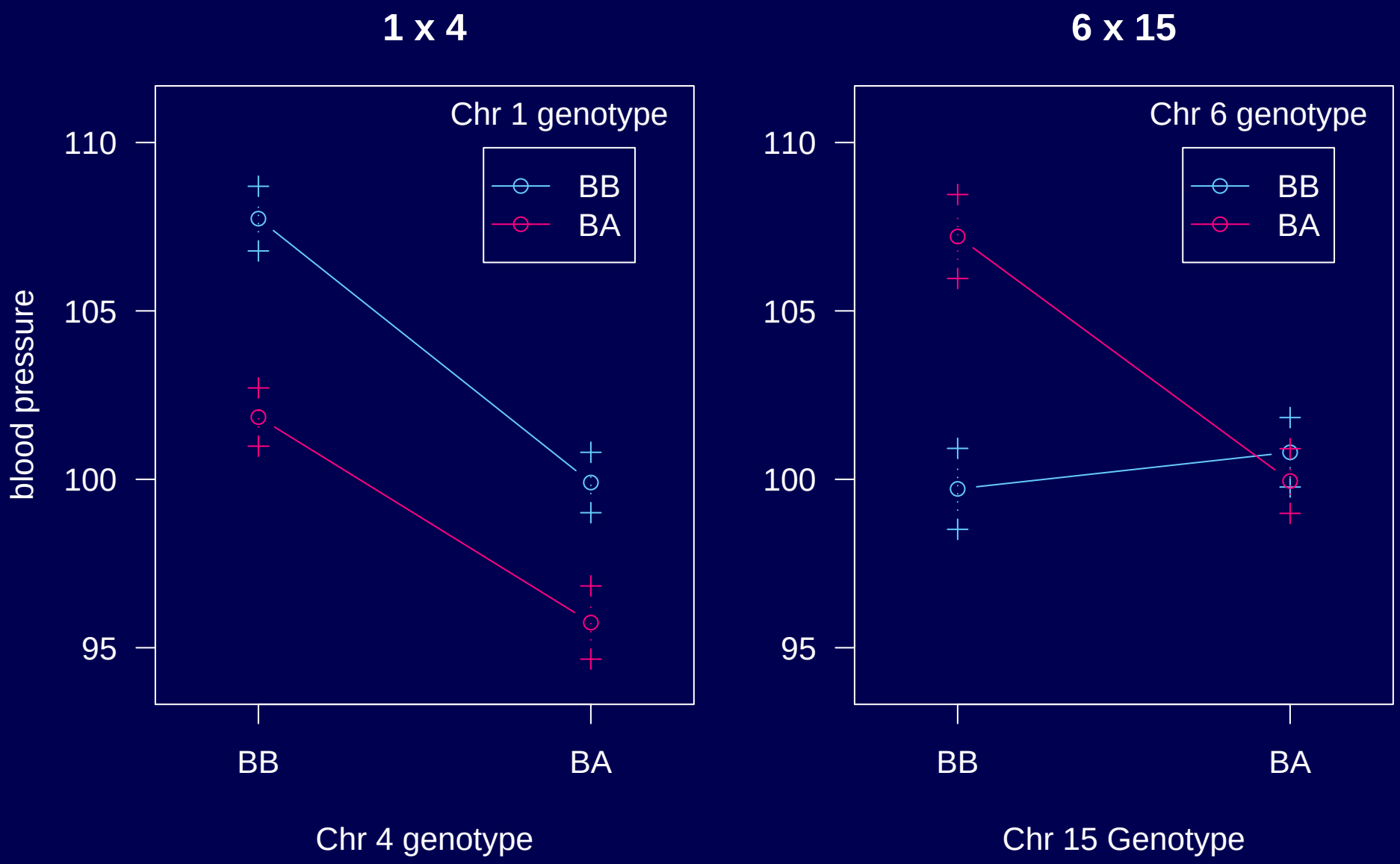
LOD curves


LOD score
8
6
4
2
0
5%
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
Chromosome

Modeling multiple QTL

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

Estimated effects



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
  - Impose hierarchy on interactions?
  - Don't allow QTL to be to 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
- 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.
- 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

Automation

- Assistance to the masses
- Understanding performance
- Many phenotypes

Additive QTL

Simple situation:

- Dense markers
- Complete genotype data
- No epistasis

$$\mathsf{y} = \mu + \sum \beta_{\mathsf{j}}\, \mathsf{q}_{\mathsf{j}} + \epsilon \qquad \text{which } \beta_{\mathsf{j}} \neq 0?$$

$$\mathsf{pLOD}(\gamma) = \mathsf{LOD}(\gamma) - \mathsf{T}\,|\gamma|$$

Additive QTL

Simple situation:

- Dense markers
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$$y = \mu + \sum \beta_j q_j + \epsilon \qquad \text{which } \beta_j \neq 0?$$

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

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

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

Additive QTL

Simple situation:

- Dense markers
- Complete genotype data
- No epistasis

$$y = \mu + \sum \beta_j q_j + \epsilon \qquad \text{which } \beta_j \neq 0?$$

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

For the mouse genome:

T = 2.69 (BC) or 3.52 (F_2)

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

Epistasis

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

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

T_m = as chosen previously

T_i = ?

Idea 1

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

T_i = 95th percentile of the distribution of

$$\max \mathrm{LOD}_f(\lambda_1, \lambda_2) - \max \mathrm{LOD}_a(\lambda_1, \lambda_2)$$

Idea 1

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

T_i = 95th percentile of the distribution of

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For the mouse genome:

T_m = 2.69 (BC) or 3.52 (F_2)

T_i^H = 2.62 (BC) or 4.28 (F_2)

Idea 2

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

$T_m + T_i$ = 95th percentile of the distribution of

$$\max \mathrm{LOD}_f(\lambda_1, \lambda_2) - \max \mathrm{LOD}_1(\lambda)$$

Idea 2

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

$T_m + T_i$ = 95th percentile of the distribution of

$$\max \mathrm{LOD}_f(\lambda_1, \lambda_2) - \max \mathrm{LOD}_1(\lambda)$$

For the mouse genome:

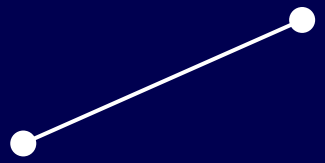
T_m = 2.69 (BC) or 3.52 (F_2)

T_i^H = 2.62 (BC) or 4.28 (F_2)

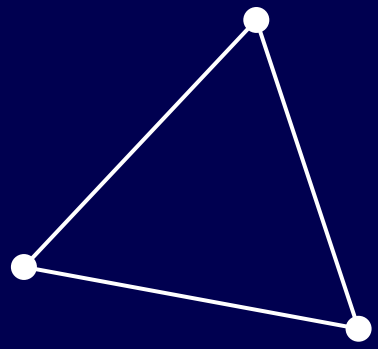
T_i^L = 1.19 (BC) or 2.69 (F_2)

Models as graphs

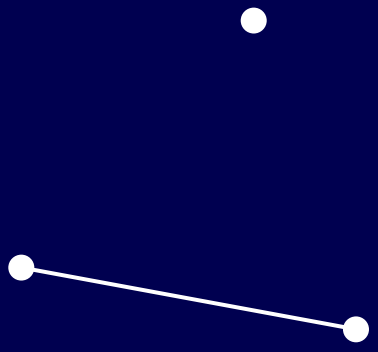
A



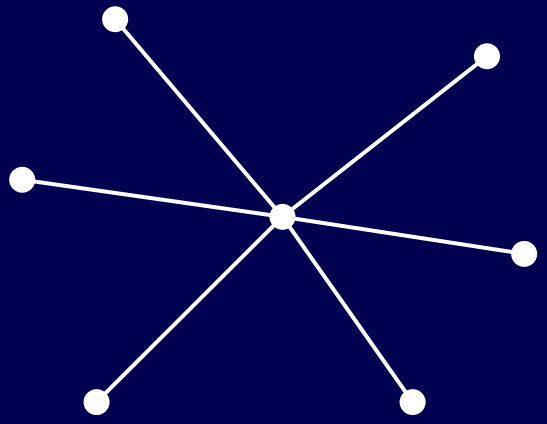
C



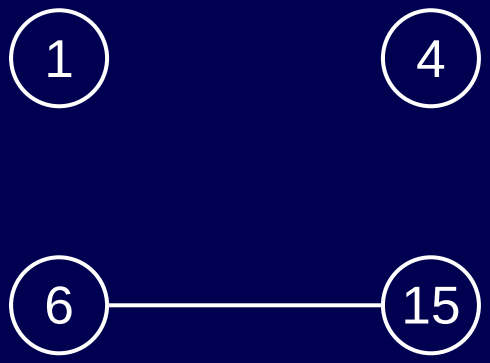
B



D

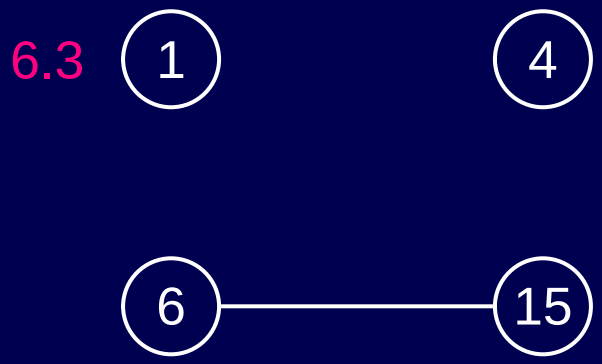


Results



LOD = 23.1

Drop one term?



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

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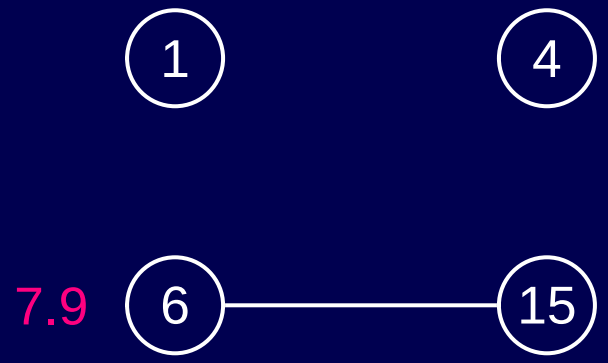

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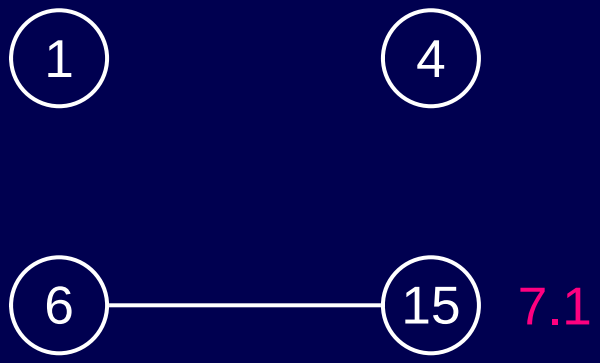
Drop one term?



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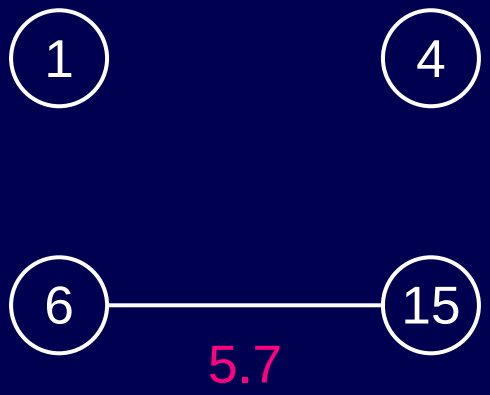

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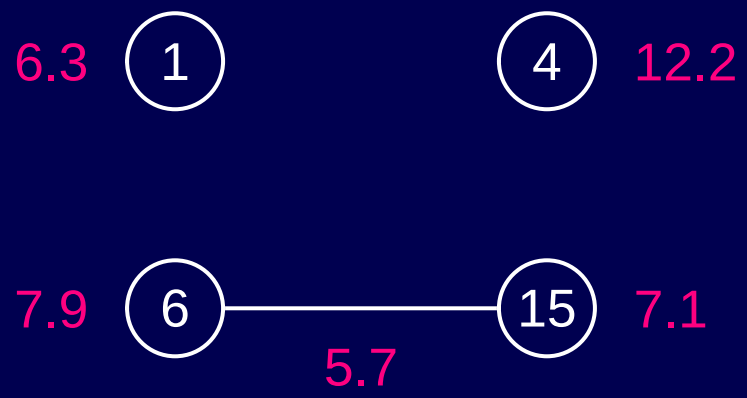
Drop one at time



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Add an interaction?

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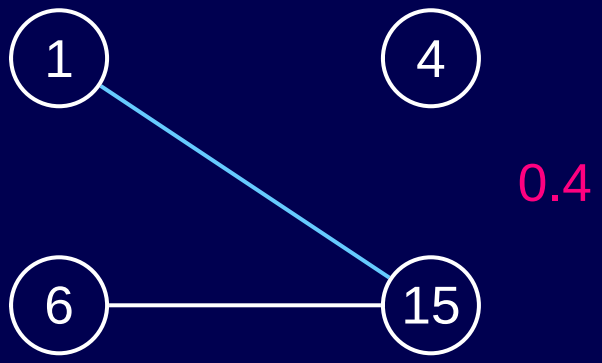

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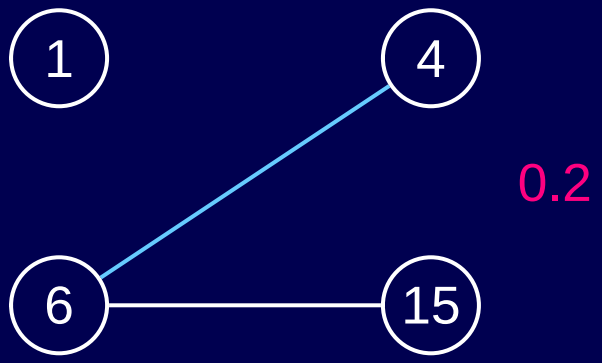

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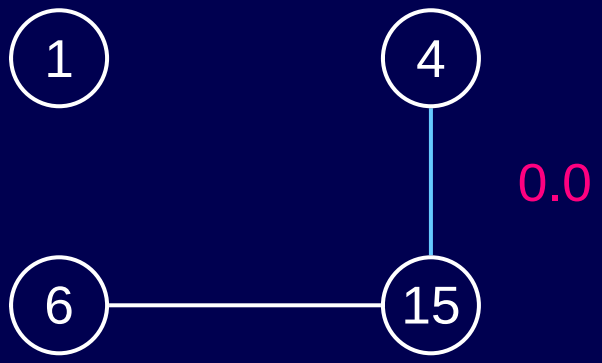

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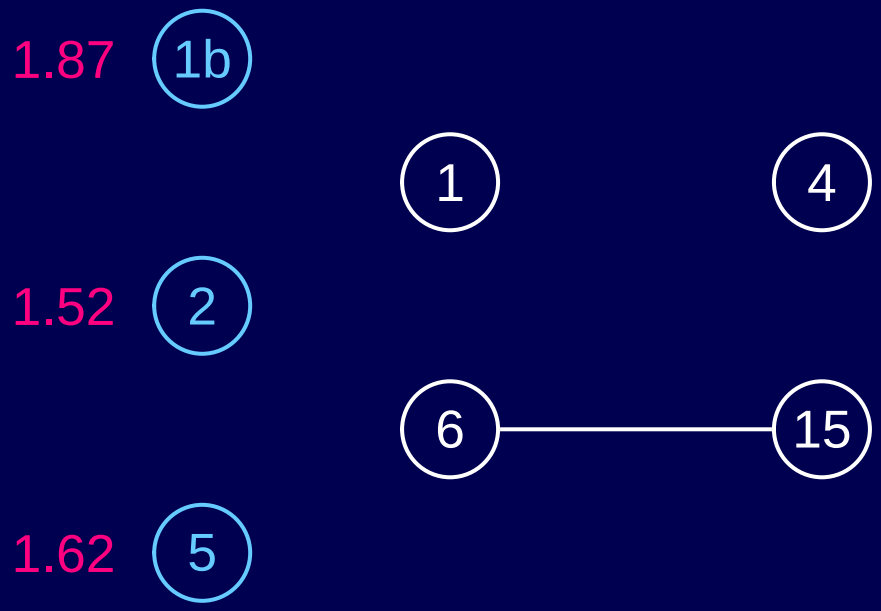
Add another QTL?



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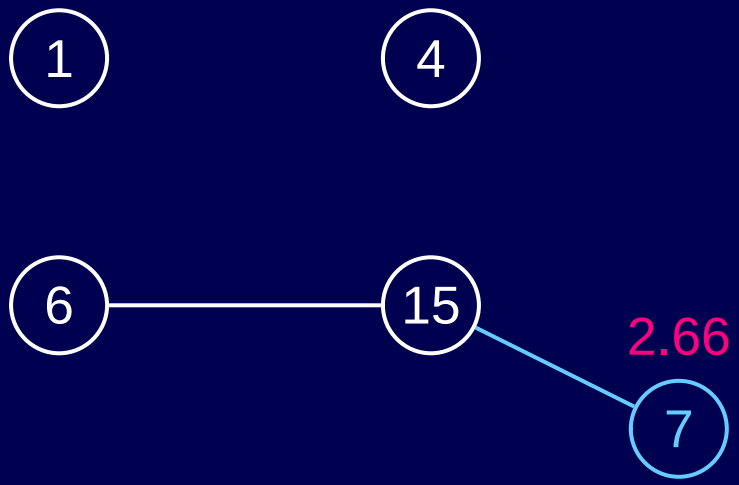

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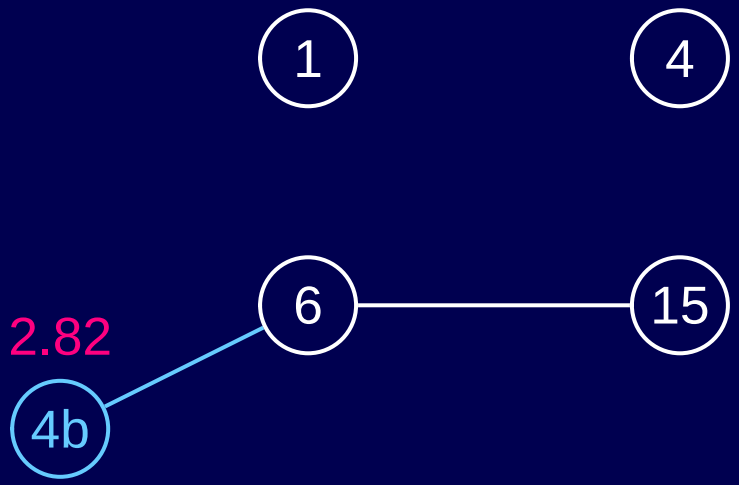

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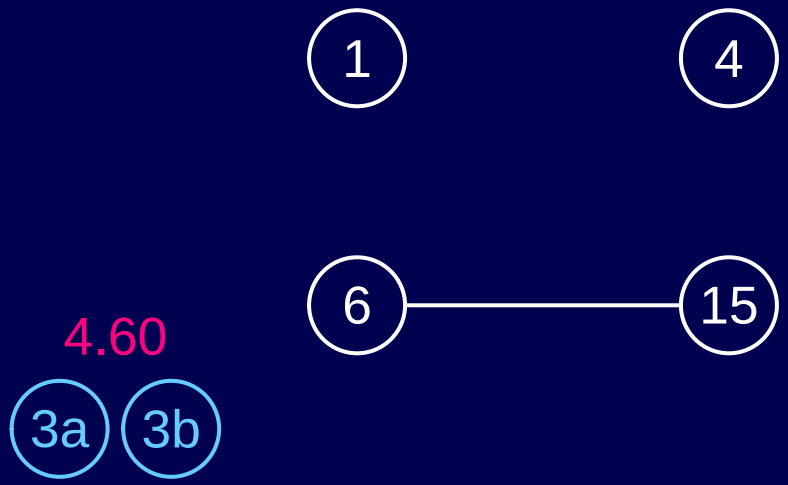
Add a pair of QTL?



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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

Ani Manichaikul	Johns Hopkins University (now at University of Virginia)
Gary Churchill	Jackson Laboratory
Śaunak Sen	University of California, San Francisco
Terry Speed	University of California, Berkeley
Brian Yandell	University of Wisconsin – Madison
Fumihiro Sugiyama	now at University of Tsukuba, Japan
Bev Paigen	Jackson Laboratory

Bayes/MCMC

Advantages

- All analysis aspects combined
- More fully captures uncertainty
- More clean expression of uncertainty

Disadvantages

- May require a specialist
- Prior specification is difficult
- Bayes factors can be difficult to interpret
- Can be difficult to assess performance