

# Introduction to QTL mapping in model organisms

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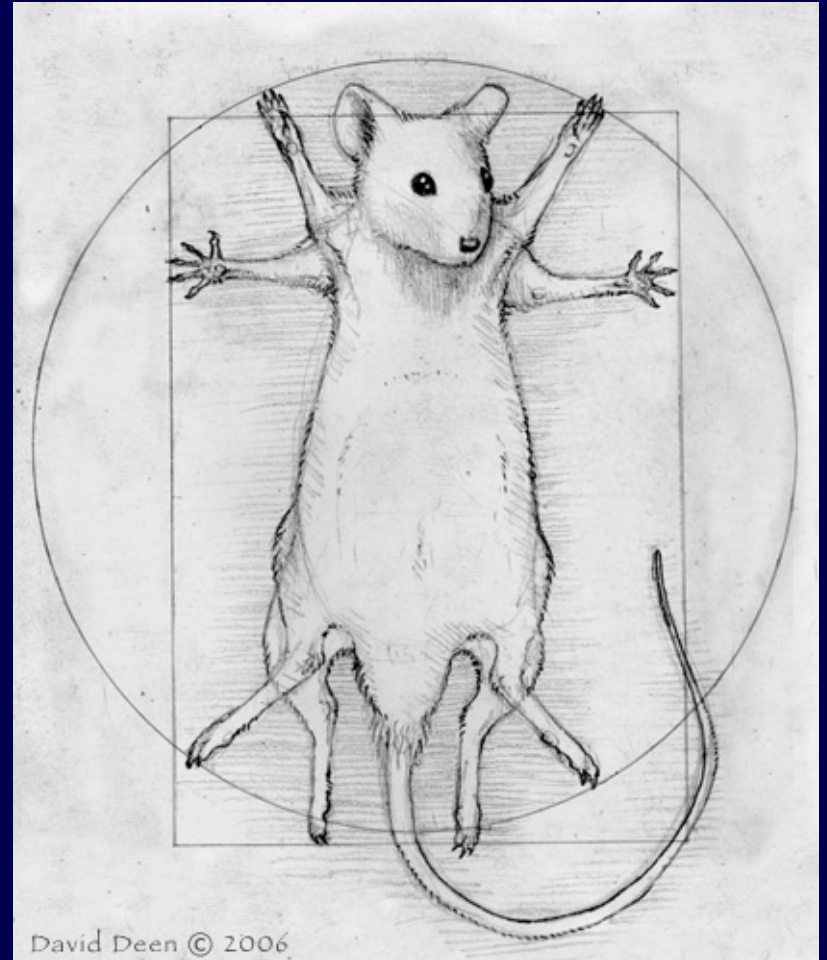
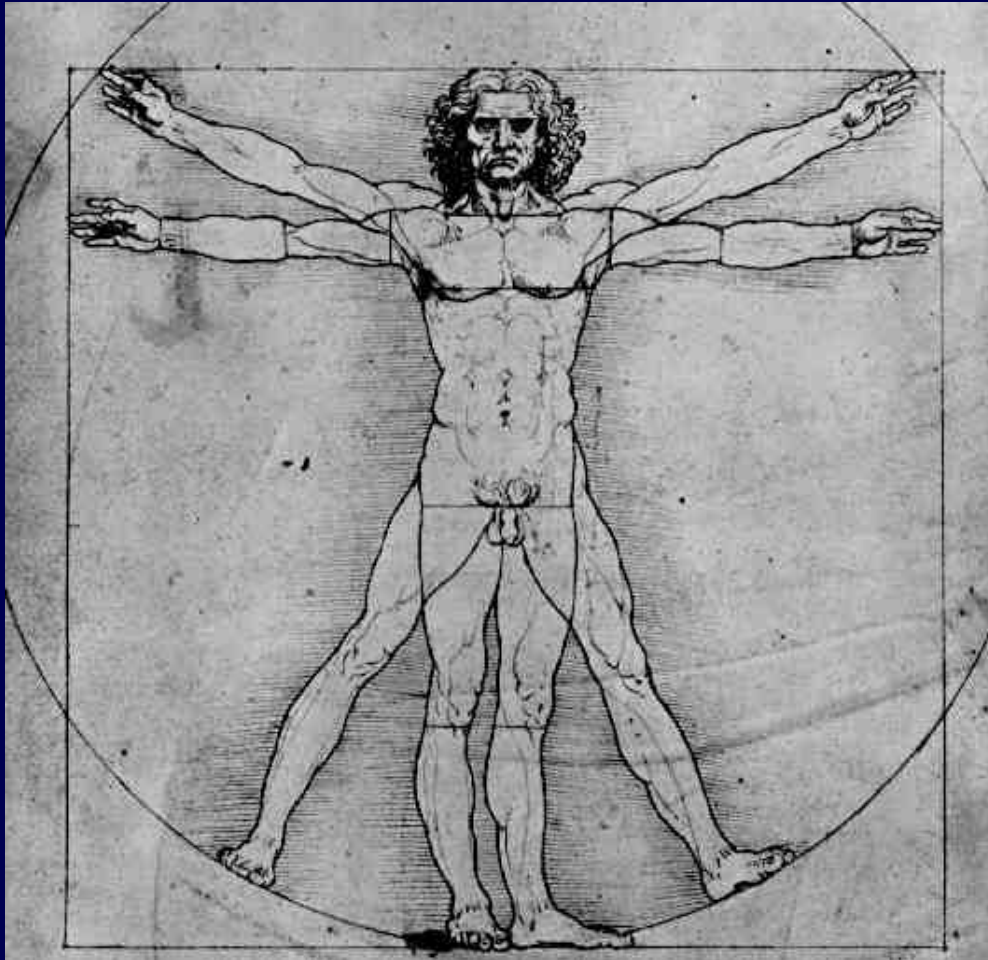
[kbroman.org](http://kbroman.org)

[github.com/kbroman](https://github.com/kbroman)

@kwbroman

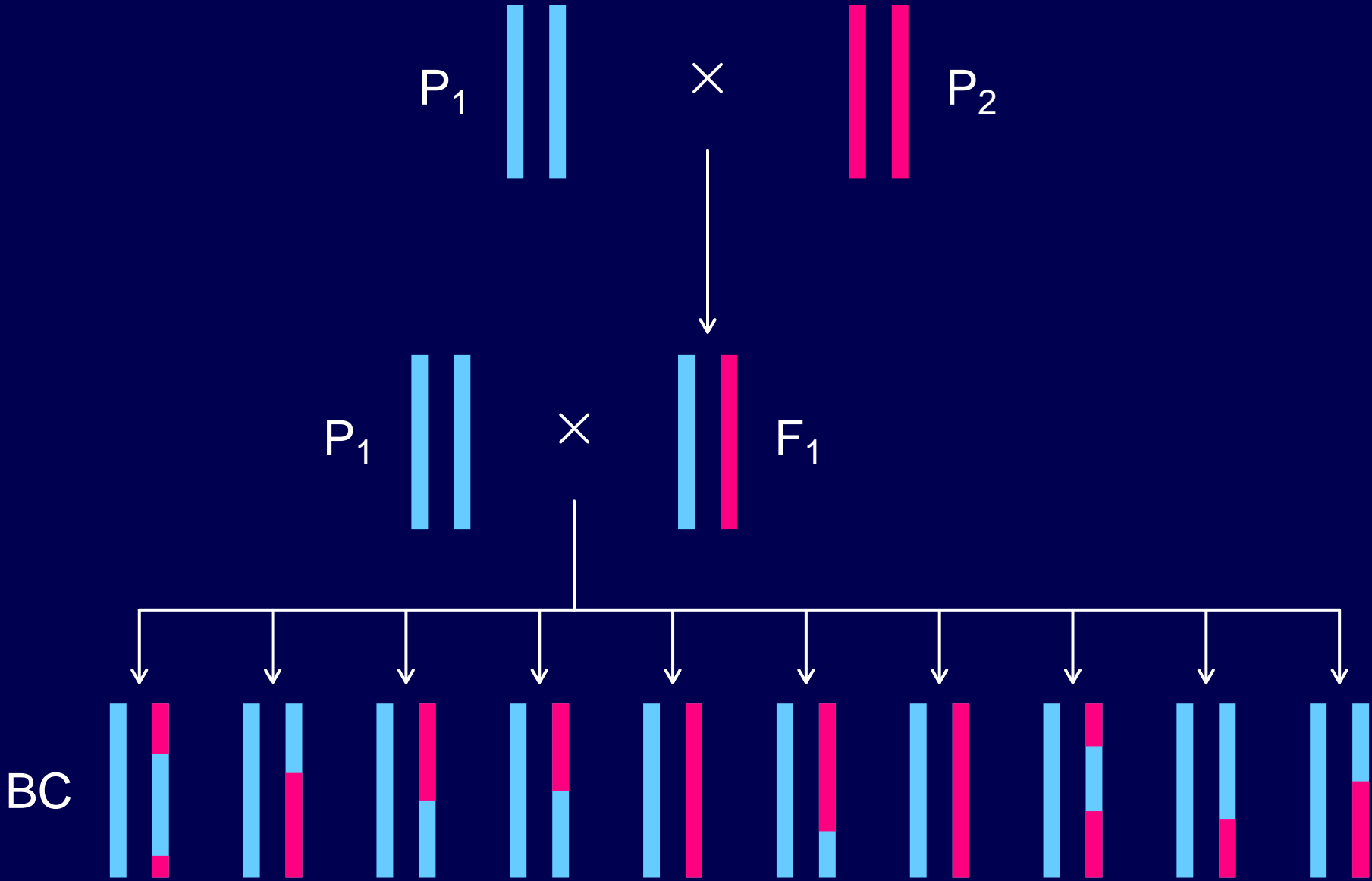


# Human vs mouse

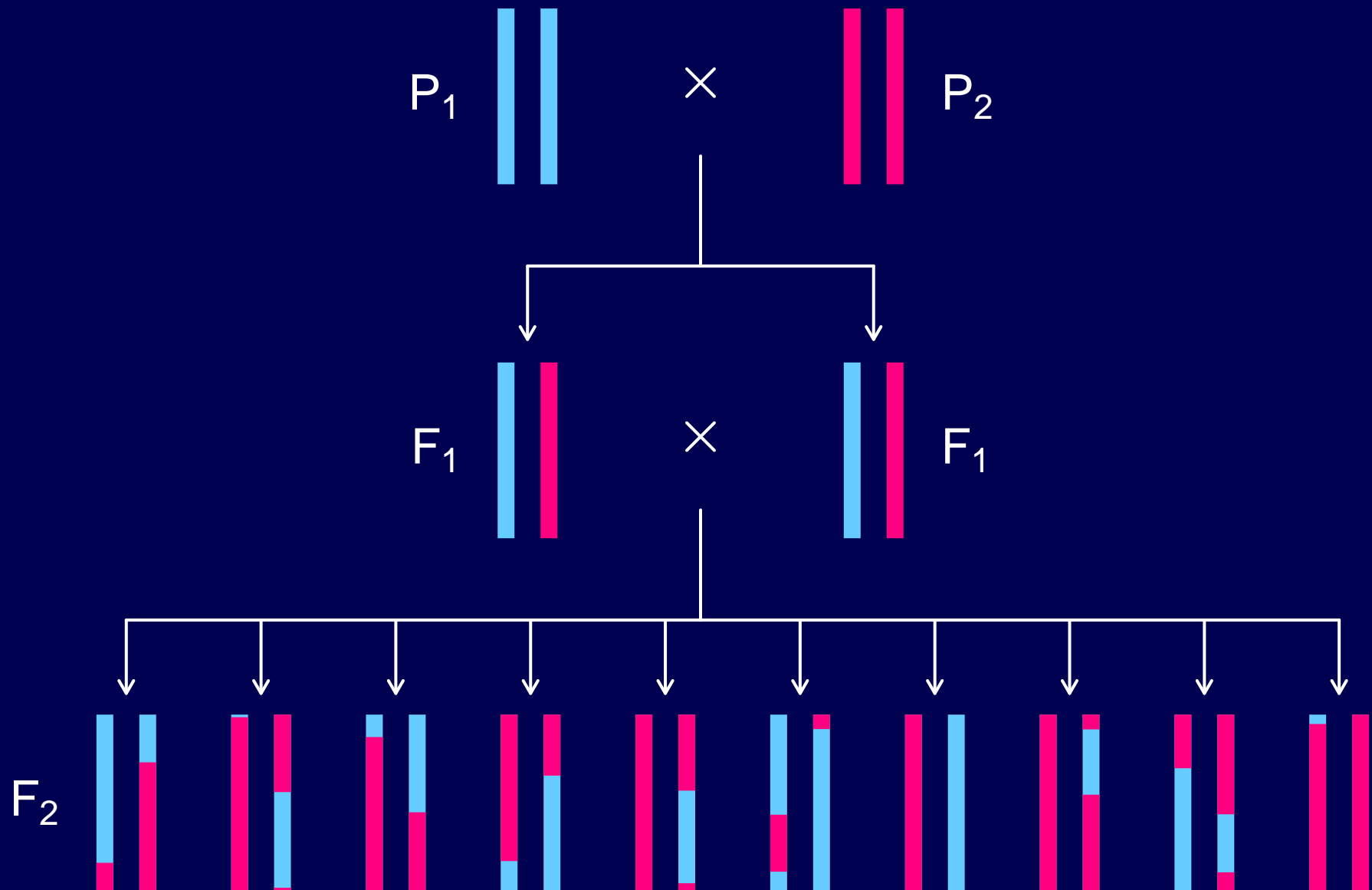


[www.daviddeen.com](http://www.daviddeen.com)

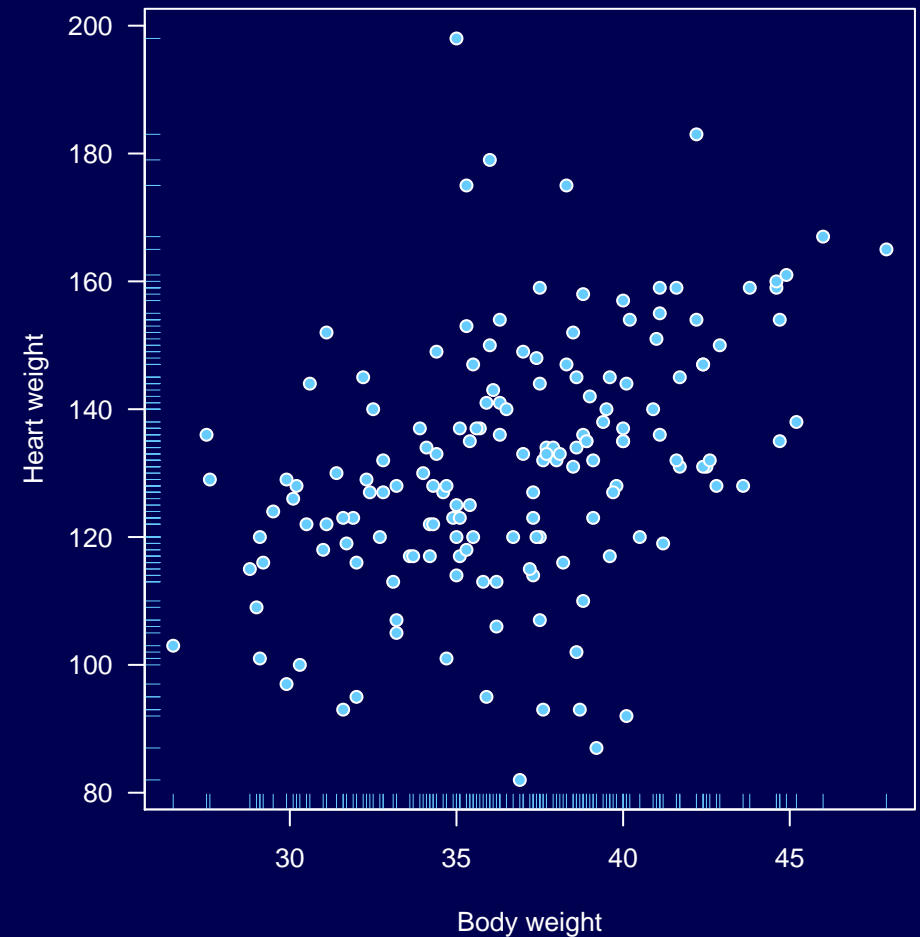
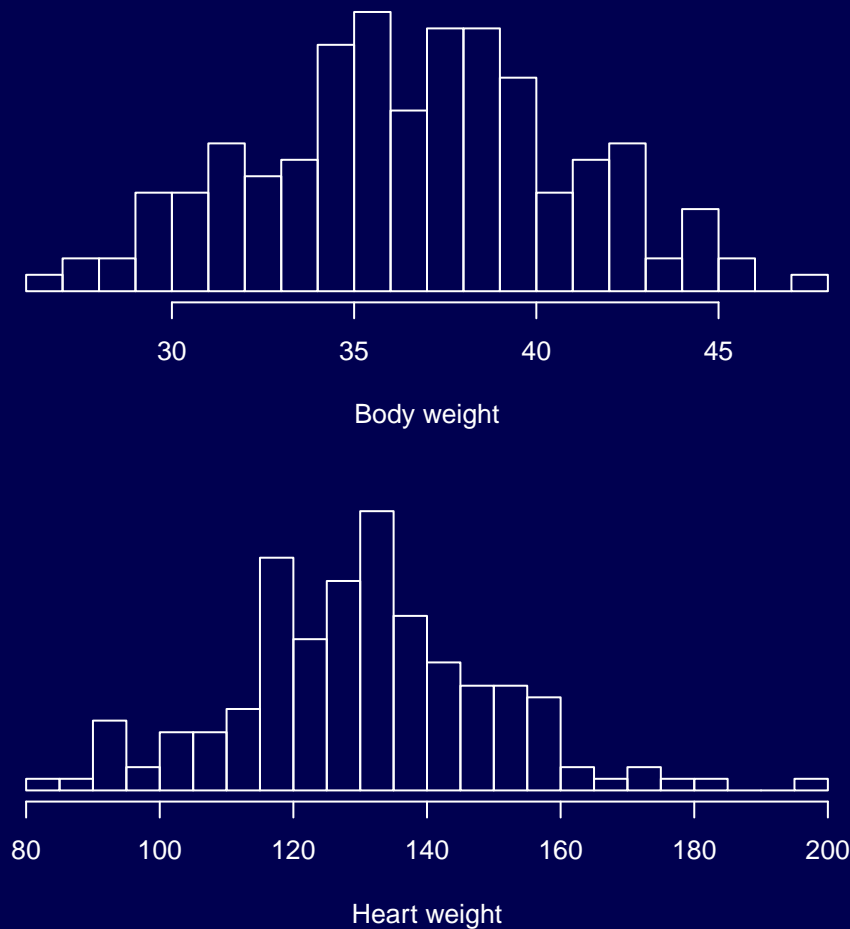
# Backcross



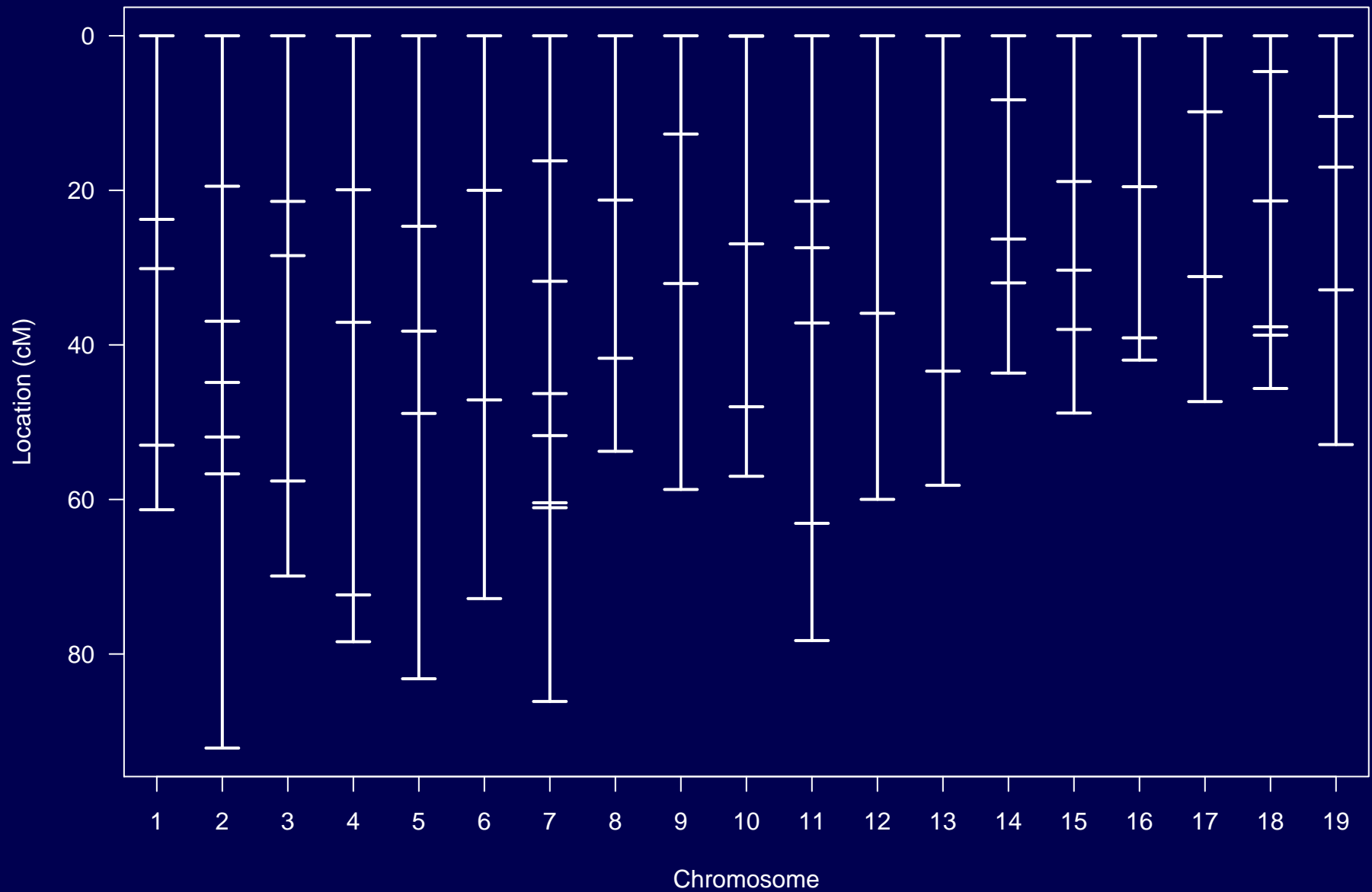
# Intercross



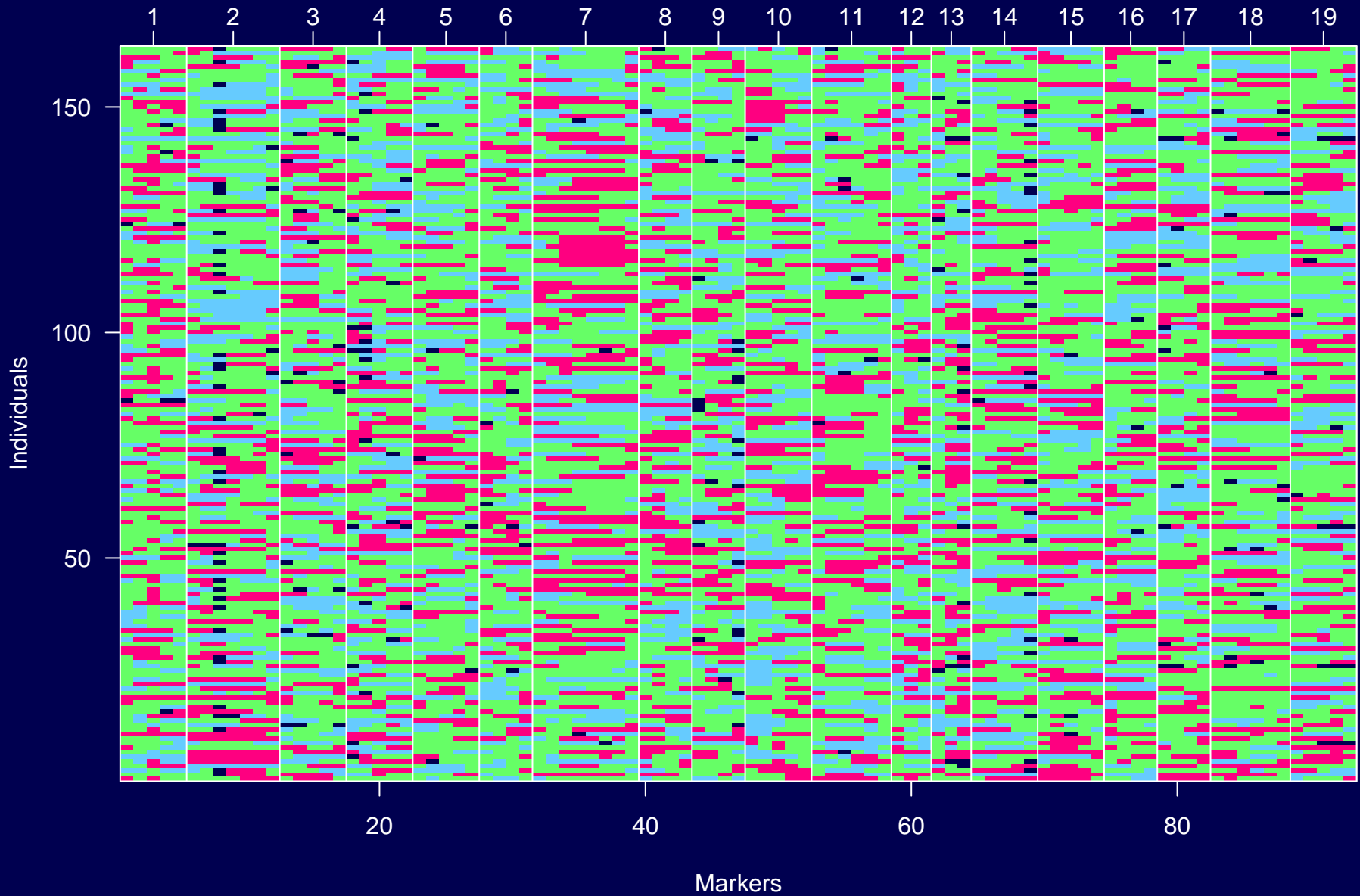
# Phenotype data



# Genetic map



# Genotype data

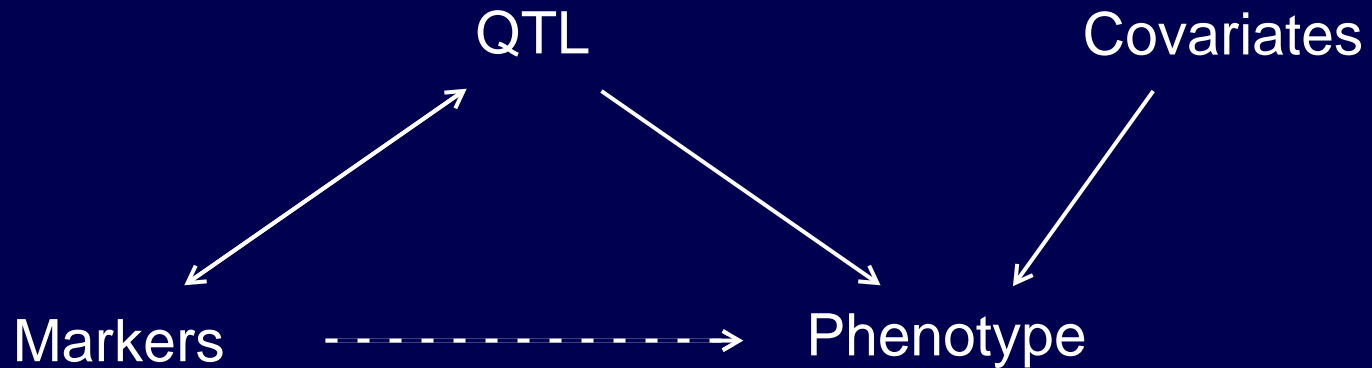




# Goals

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

# Statistical structure



The missing data problem:

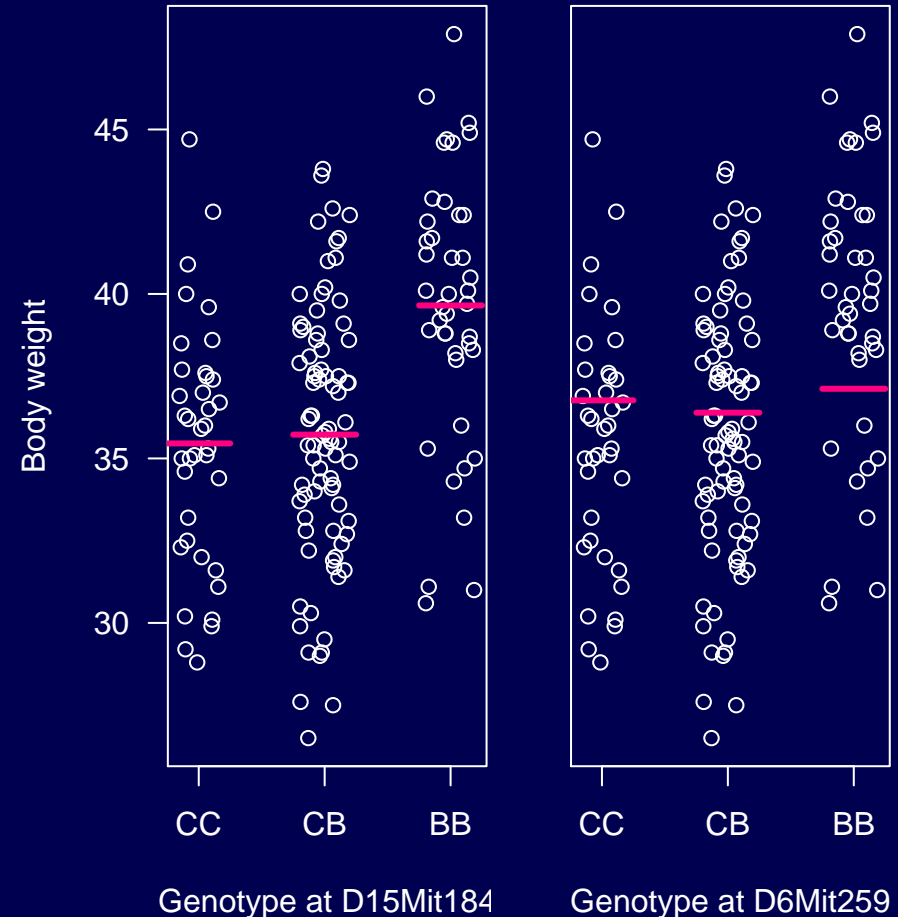
Markers  $\longleftrightarrow$  QTL

The model selection problem:

QTL, covariates  $\longrightarrow$  phenotype

# ANOVA at marker loci

- Also known as **marker regression**.
- Split mice into groups according to genotype at a marker.
- Do a t-test / ANOVA.
- Repeat for each marker.



# ANOVA at marker loci

## Advantages

- Simple.
- Easily incorporates covariates.
- Easily extended to more complex models.
- Doesn't require a genetic map.

## Disadvantages

- Must exclude individuals with missing genotype data.
- Imperfect information about QTL location.
- Suffers in low density scans.
- Only considers one QTL at a time.

# Interval mapping

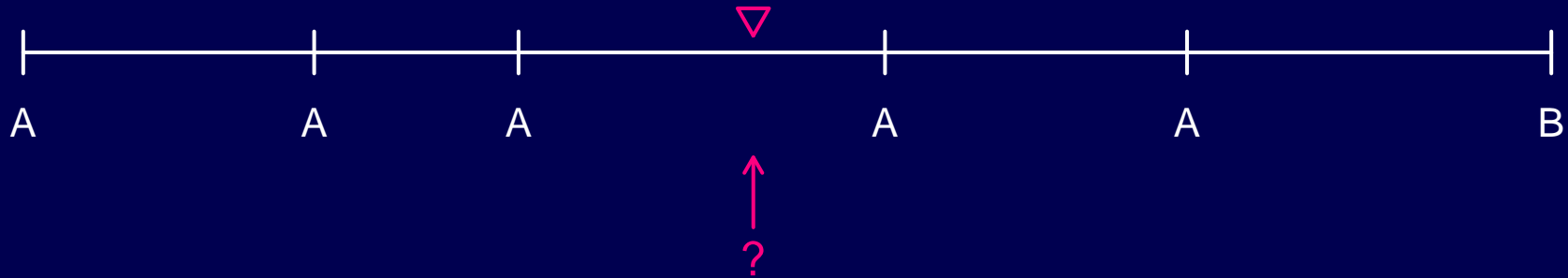
## Lander & Botstein (1989)

- Assume a **single** QTL model.
- Each position in the genome, one at a time, is posited as the putative QTL.
- Let  $q = 1/0$  if the (unobserved) QTL genotype is BB/AB.  
(Or 2/1/0 if the QTL genotype is BB/AB/AA in an intercross.)

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

- Given genotypes at linked markers,  $y \sim$  mixture of normal dist'ns with mixing proportions  $\Pr(q \mid \text{marker data})$

# Genotype probabilities



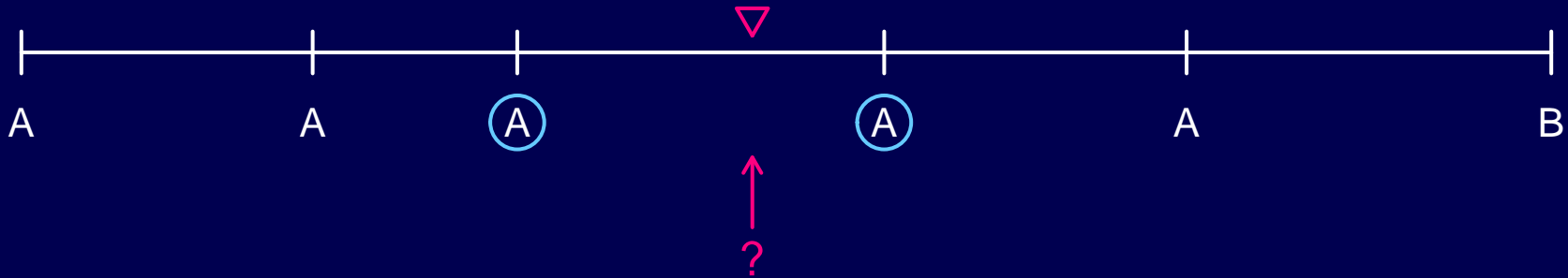
Calculate  $\Pr(q \mid \text{marker data})$ , assuming

- No crossover interference
- No genotyping errors

Or use the **hidden Markov model (HMM)** technology

- To allow for genotyping errors
- To incorporate dominant markers
- (Still assume no crossover interference.)

# Genotype probabilities



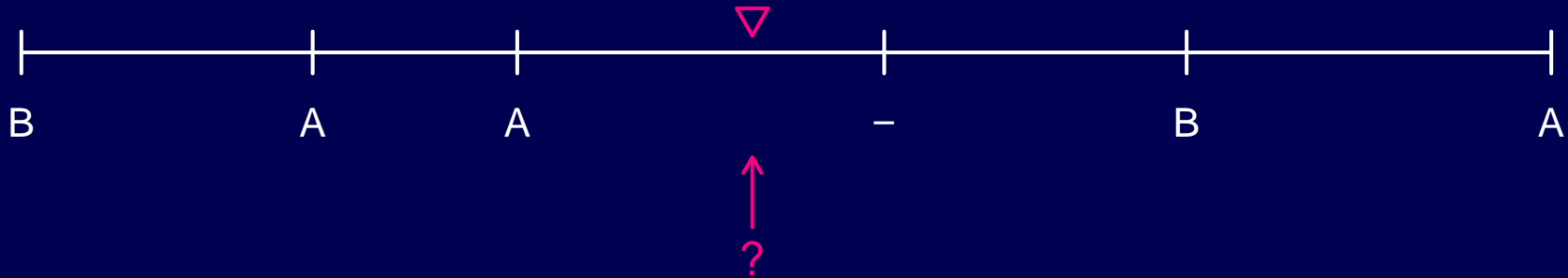
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# Genotype probabilities



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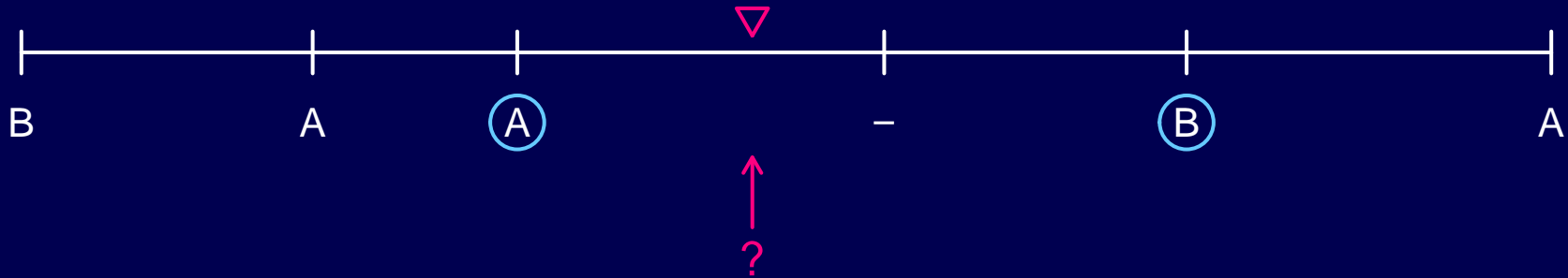
- No crossover interference
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# Genotype probabilities



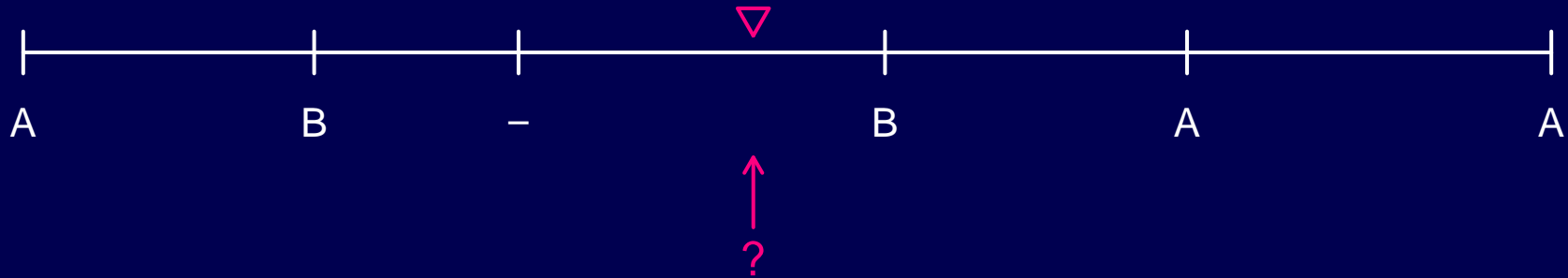
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# Genotype probabilities



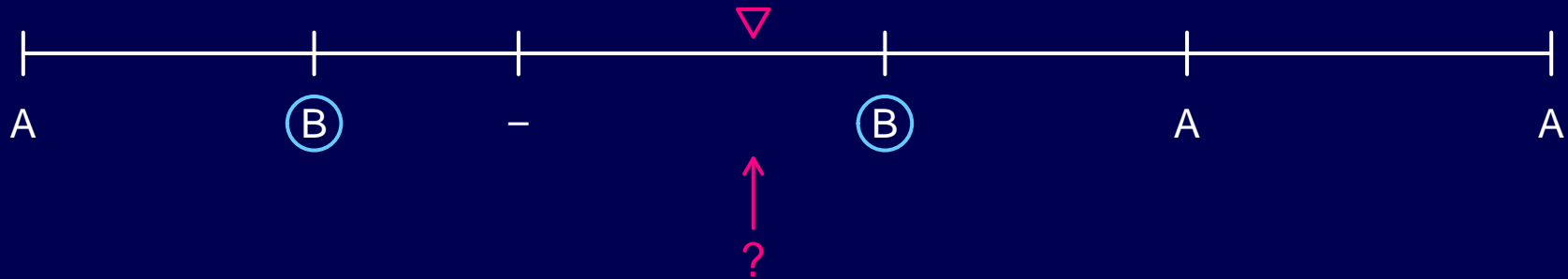
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# Genotype probabilities



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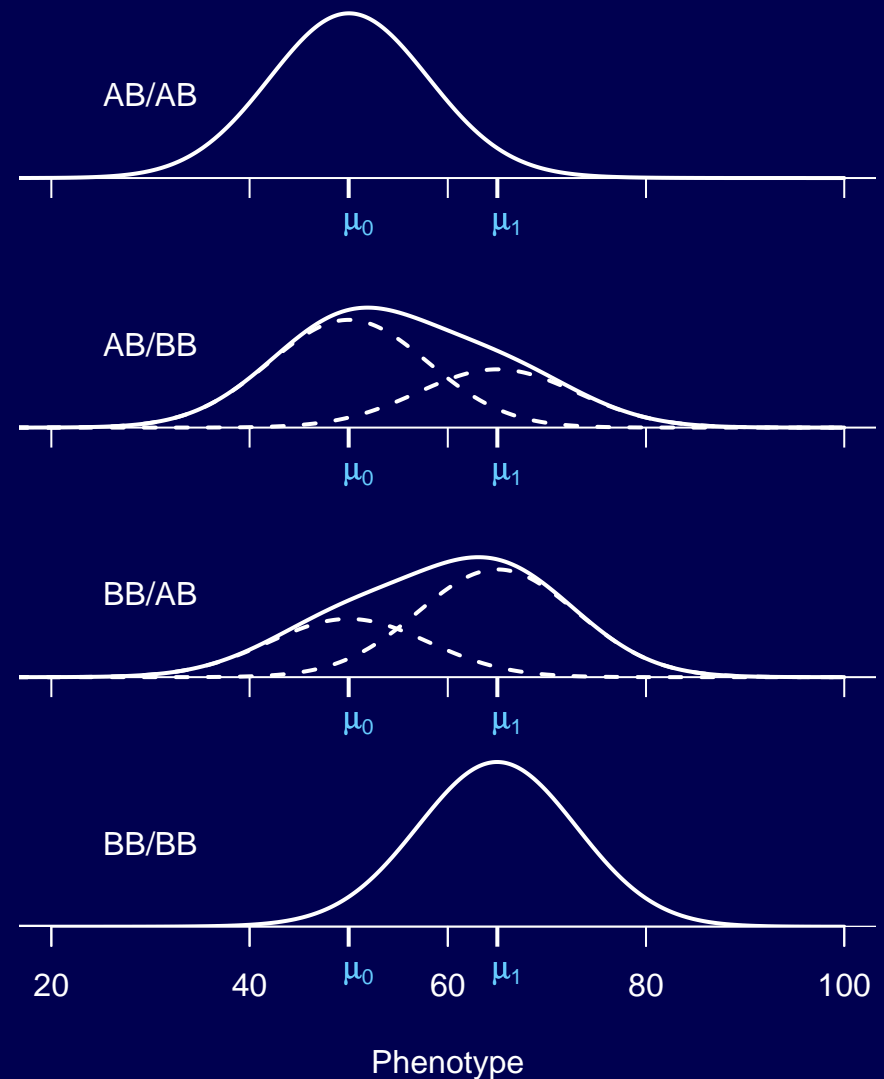
Or use the **hidden Markov model (HMM)** technology

- To allow for genotyping errors
- To incorporate dominant markers
- (Still assume no crossover interference.)

# The normal mixtures



- Two markers separated by 20 cM, with the QTL closer to the left marker.
- The figure at right shows the distributions of the phenotype conditional on the genotypes at the two markers.
- The dashed curves correspond to the components of the mixtures.



# Interval mapping

Let  $p_{ij} = \Pr(q_i = j | \text{marker data})$

$$y_i | q_i \sim N(\mu_{q_i}, \sigma^2)$$

$$\Pr(y_i | \text{marker data}, \mu_0, \mu_1, \sigma) = \sum_j p_{ij} f(y_i; \mu_j, \sigma)$$

$$\text{where } f(y; \mu, \sigma) = \exp[-(y - \mu)^2 / (2\sigma^2)] / \sqrt{2\pi\sigma^2}$$

**Log likelihood:**  $l(\mu_0, \mu_1, \sigma) = \sum_i \log \Pr(y_i | \text{marker data}, \mu_0, \mu_1, \sigma)$

Maximum likelihood estimates (**MLEs**) of  $\mu_0, \mu_1, \sigma$ :

values for which  $l(\mu_0, \mu_1, \sigma)$  is maximized.

# EM algorithm

Dempster et al. (1977)

E step:

$$\begin{aligned}\text{Let } w_{ij}^{(k)} &= \Pr(q_i = j | y_i, \text{marker data}, \hat{\mu}_0^{(k-1)}, \hat{\mu}_1^{(k-1)}, \hat{\sigma}^{(k-1)}) \\ &= \frac{p_{ij} f(y_i; \hat{\mu}_j^{(k-1)}, \hat{\sigma}^{(k-1)})}{\sum_j p_{ij} f(y_i; \hat{\mu}_j^{(k-1)}, \hat{\sigma}^{(k-1)})}\end{aligned}$$

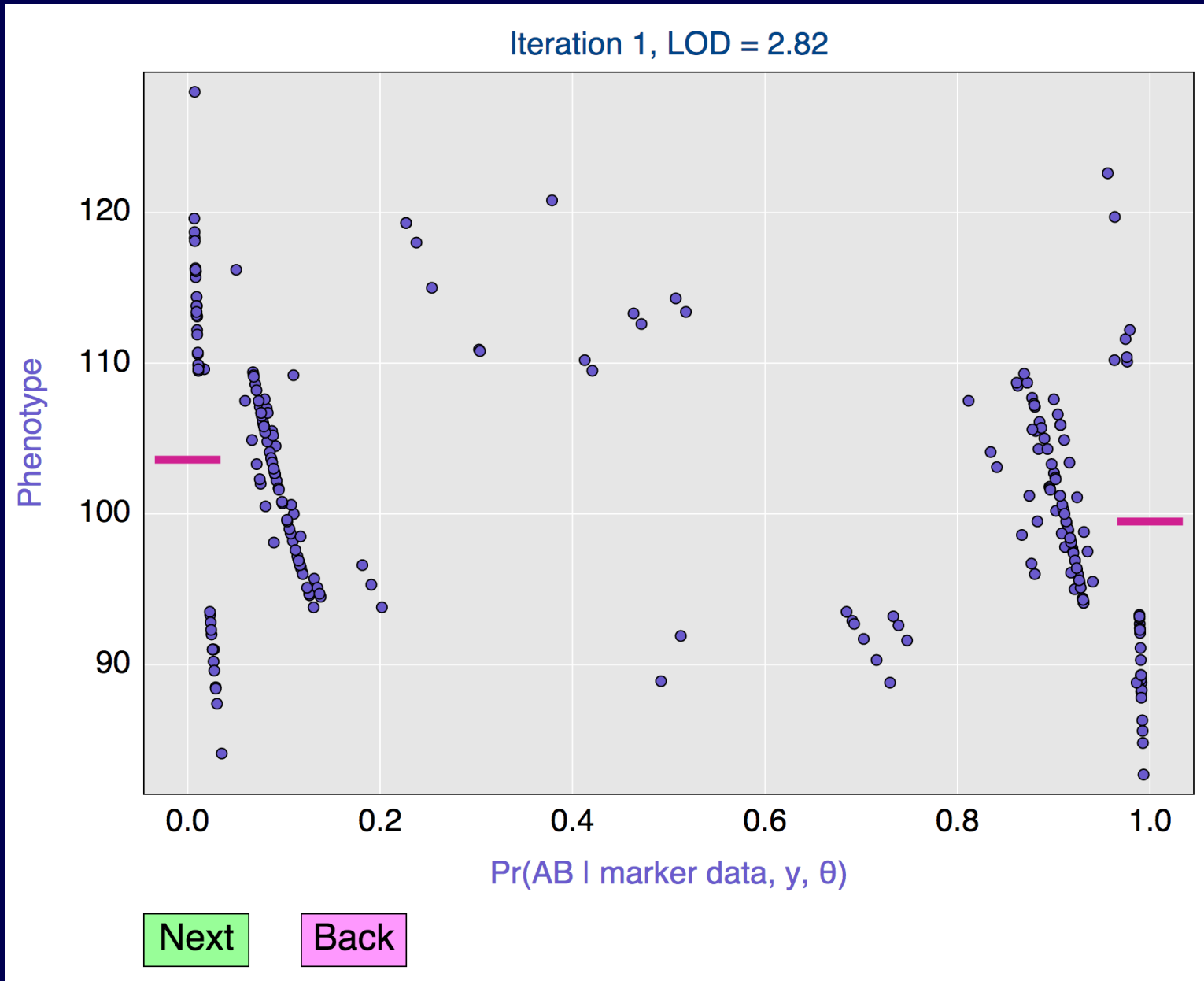
M step:

$$\begin{aligned}\text{Let } \hat{\mu}_j^{(k)} &= \sum_i y_i w_{ij}^{(k)} / \sum_i w_{ij}^{(k)} \\ \hat{\sigma}^{(k)} &= \sqrt{\sum_i \sum_j w_{ij}^{(k)} (y_i - \hat{\mu}_j^{(k)})^2 / n}\end{aligned}$$

The algorithm:

Start with  $w_{ij}^{(1)} = p_{ij}$ ; iterate the E & M steps until convergence.

# Interactive illustration



# LOD scores

The LOD score is a measure of the **strength of evidence** for the presence of a QTL at a particular location.

$\text{LOD}(\lambda) = \log_{10}$  likelihood ratio comparing the hypothesis of a QTL at position  $\lambda$  versus that of no QTL

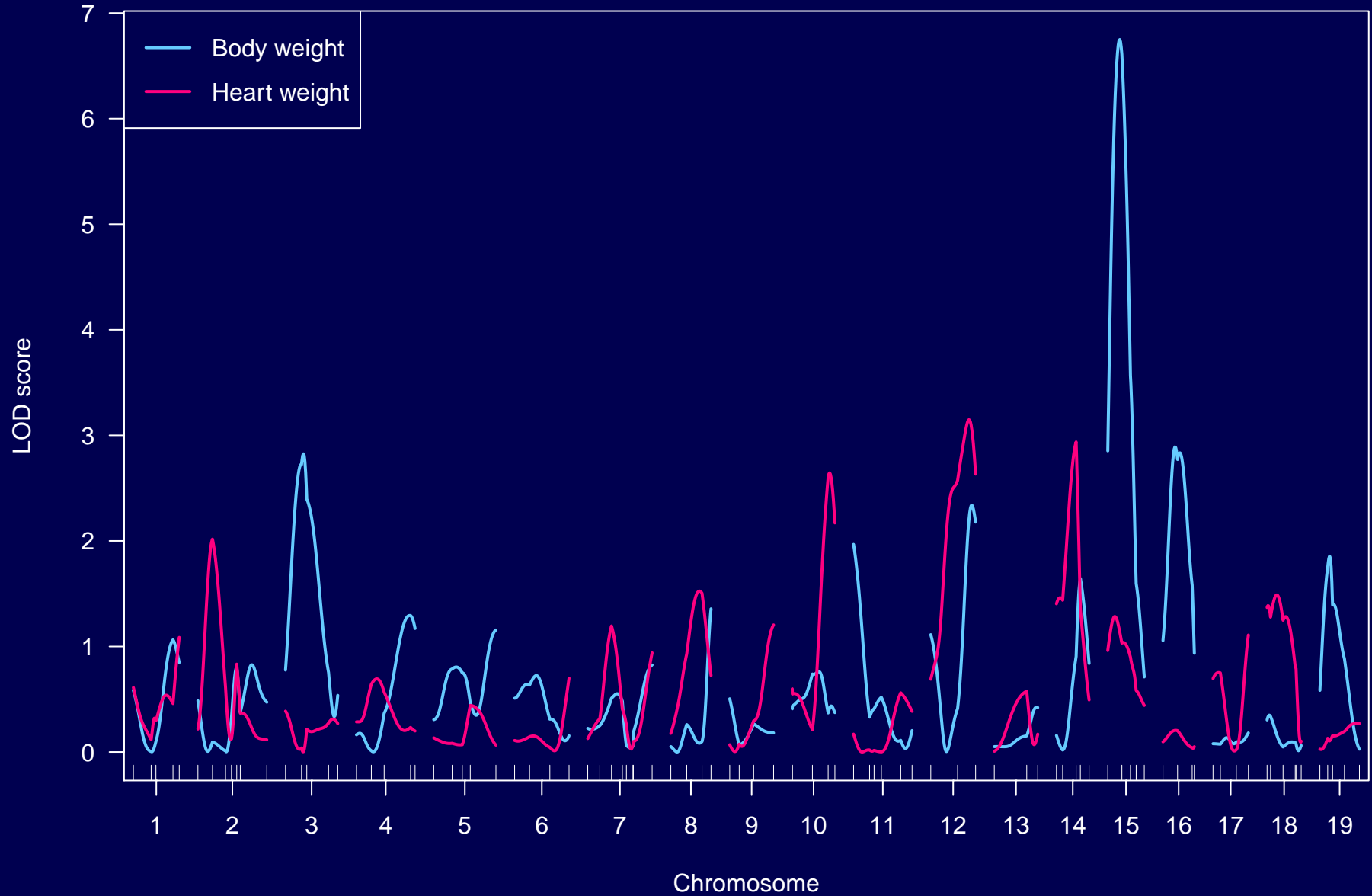
$$= \log_{10} \left\{ \frac{\text{Pr}(\mathbf{y} | \text{QTL at } \lambda, \hat{\mu}_{0\lambda}, \hat{\mu}_{1\lambda}, \hat{\sigma}_{\lambda})}{\text{Pr}(\mathbf{y} | \text{no QTL}, \hat{\mu}, \hat{\sigma})} \right\}$$

$\hat{\mu}_{0\lambda}, \hat{\mu}_{1\lambda}, \hat{\sigma}_{\lambda}$  are the MLEs, assuming a single QTL at position  $\lambda$ .

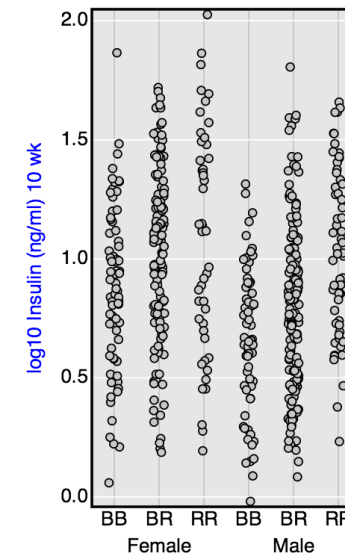
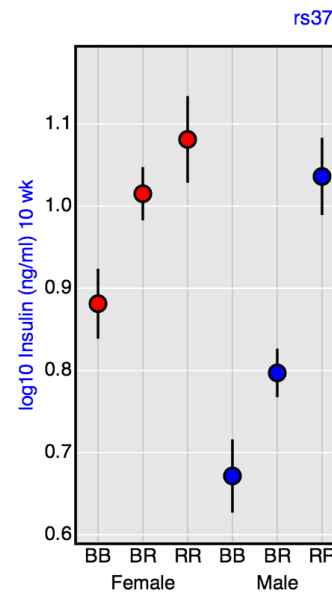
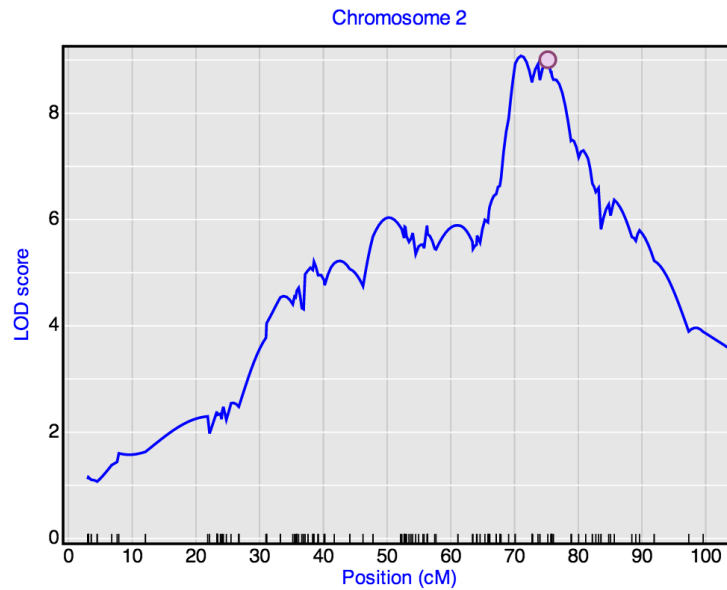
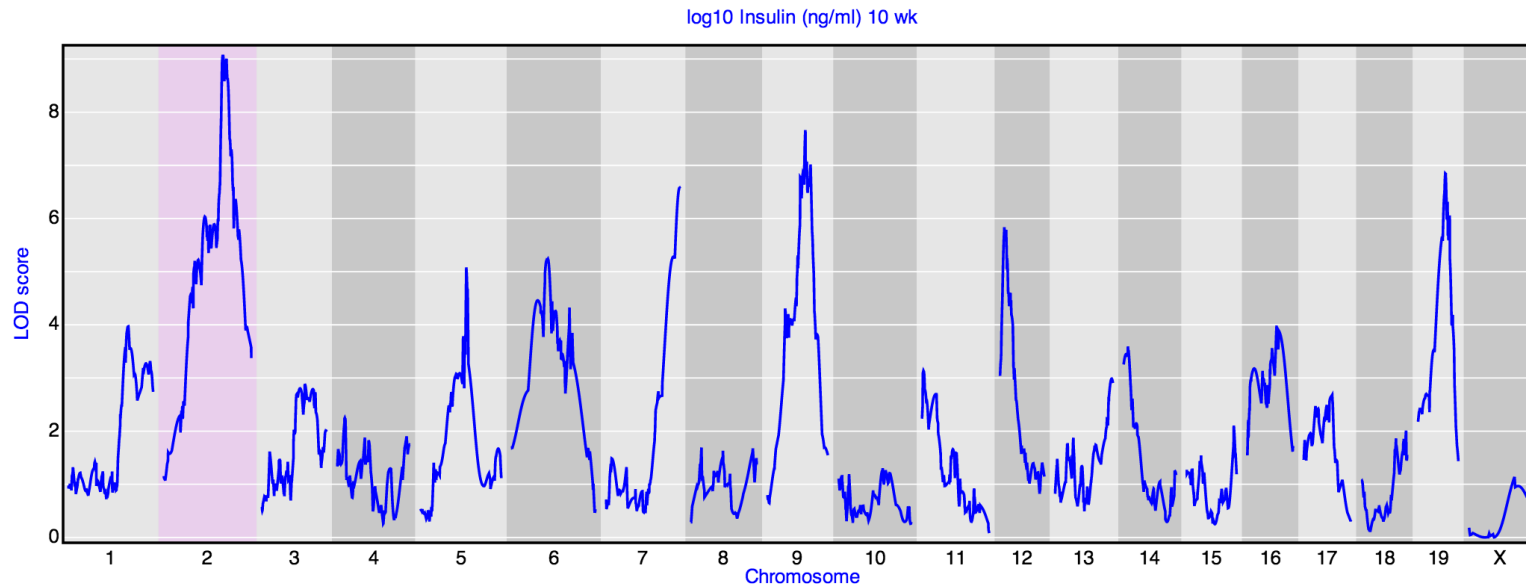
No QTL model: The phenotypes are independent and identically distributed (iid)  $N(\mu, \sigma^2)$ .



# LOD curves



# Interactive plot



# Interval mapping

## Advantages

- Takes proper account of missing data.
- Allows examination of positions between markers.
- Gives improved estimates of QTL effects.
- Provides pretty graphs.

## Disadvantages

- Increased computation time.
- Requires specialized software.
- Difficult to generalize.
- Only considers one QTL at a time.

# LOD thresholds

Large LOD scores indicate evidence for the presence of a QTL

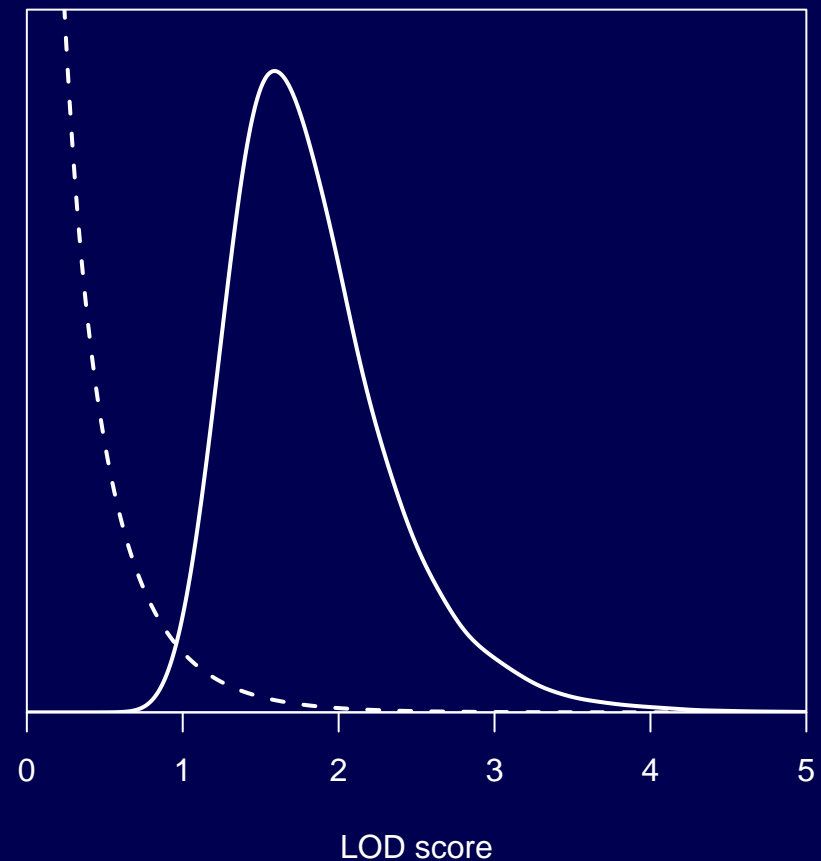
Question: How large is large?

**LOD threshold** = 95 %ile of distr'n of max LOD, genome-wide, if there are no QTLs anywhere

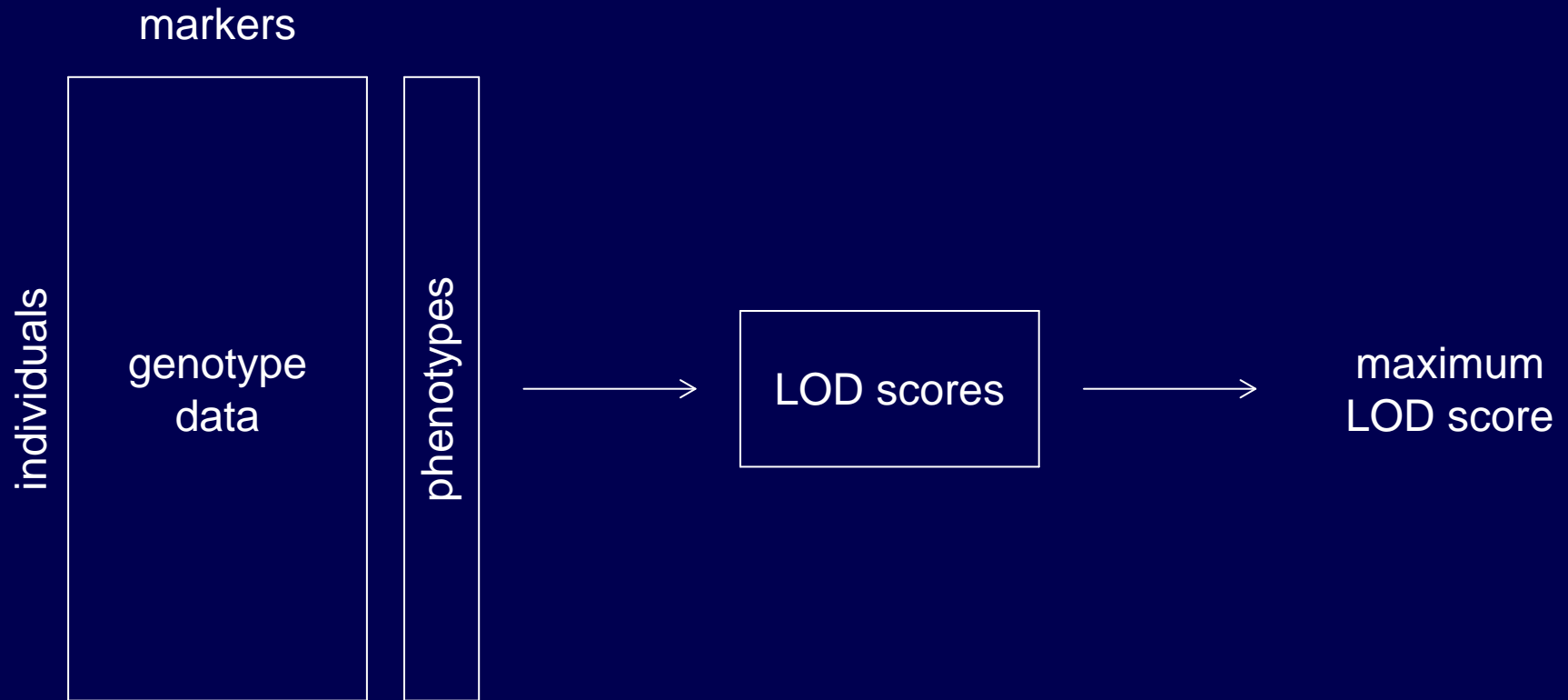
- Derivation:**
- Analytical calculations (L & B 1989)
  - Simulations (L & B 1989)
  - Permutation tests (Churchill & Doerge 1994)

# Null distribution of the LOD score

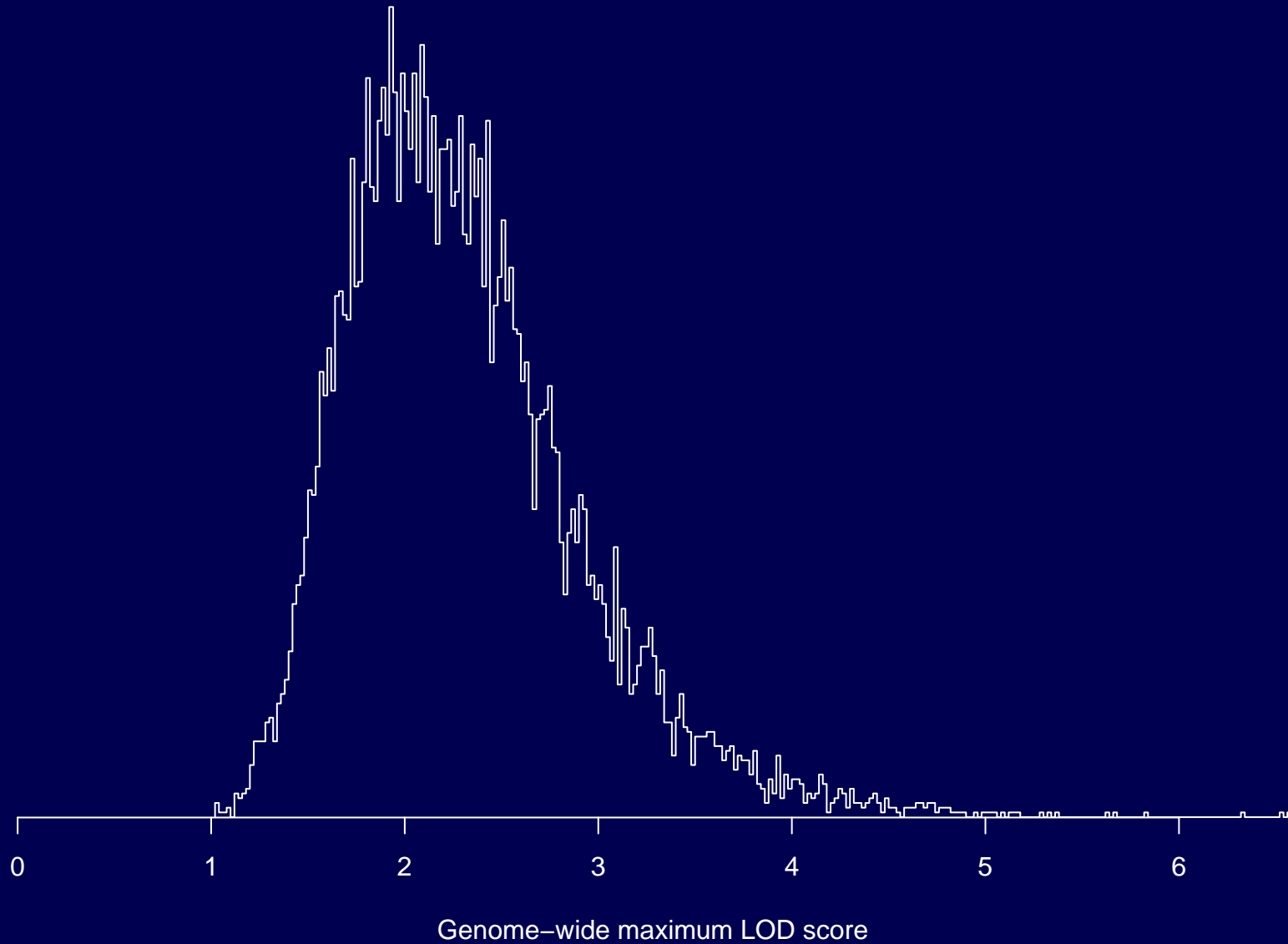
- Null distribution derived by computer simulation of backcross with genome of typical size.
- Dashed curve: distribution of LOD score at any one point.
- Solid curve: distribution of maximum LOD score, genome-wide.



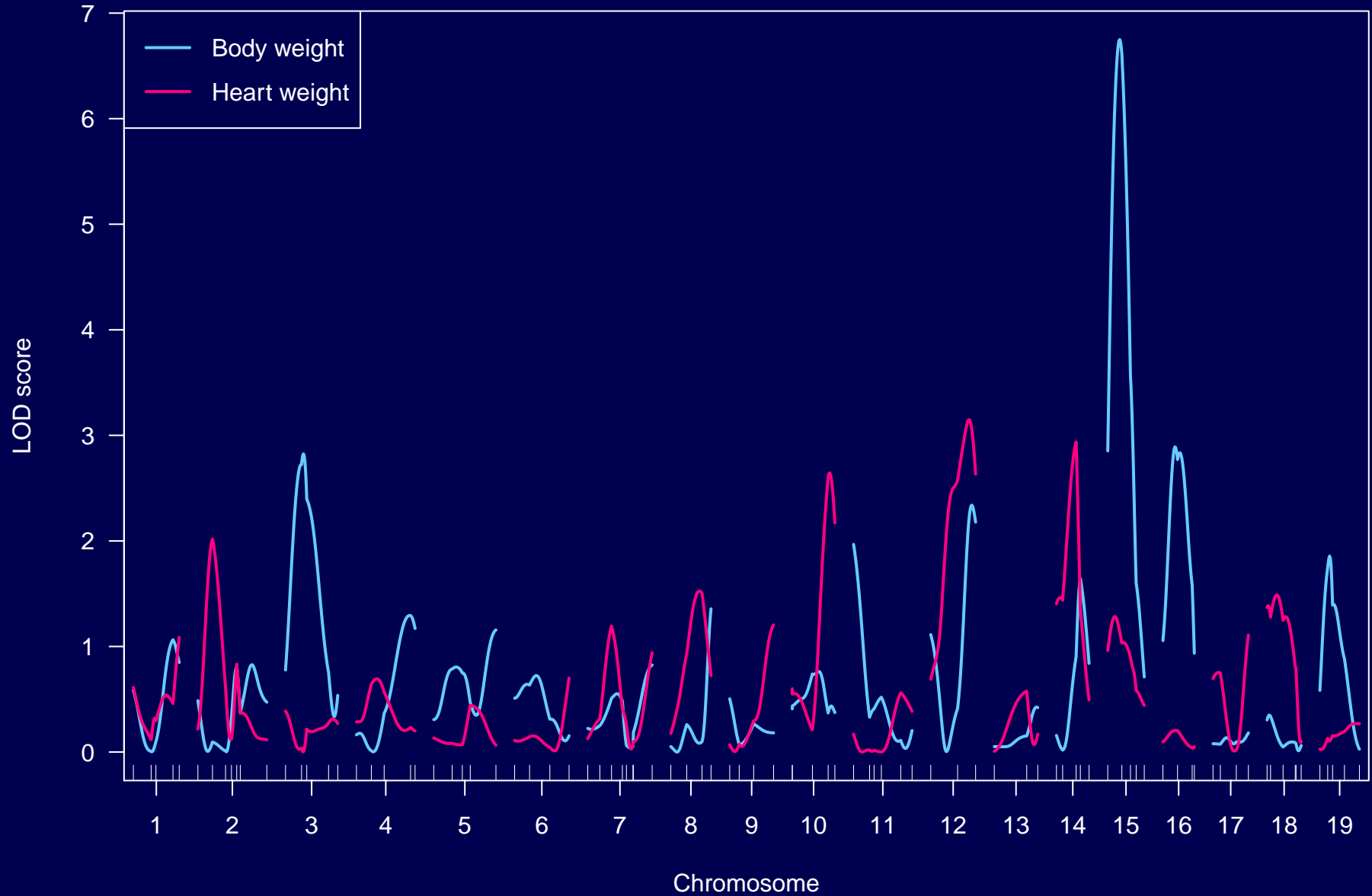
# Permutation test



# Permutation results

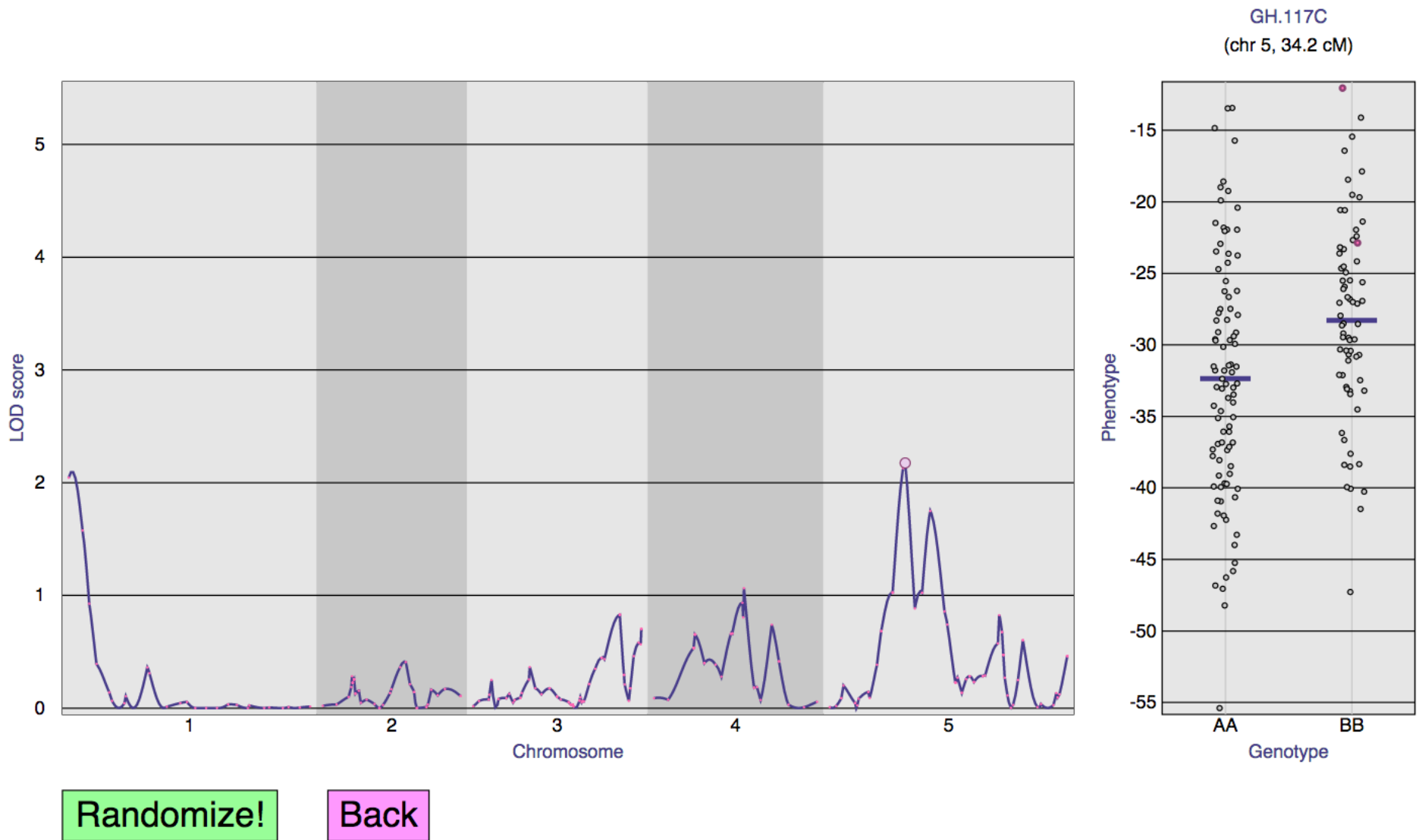


# LOD curves

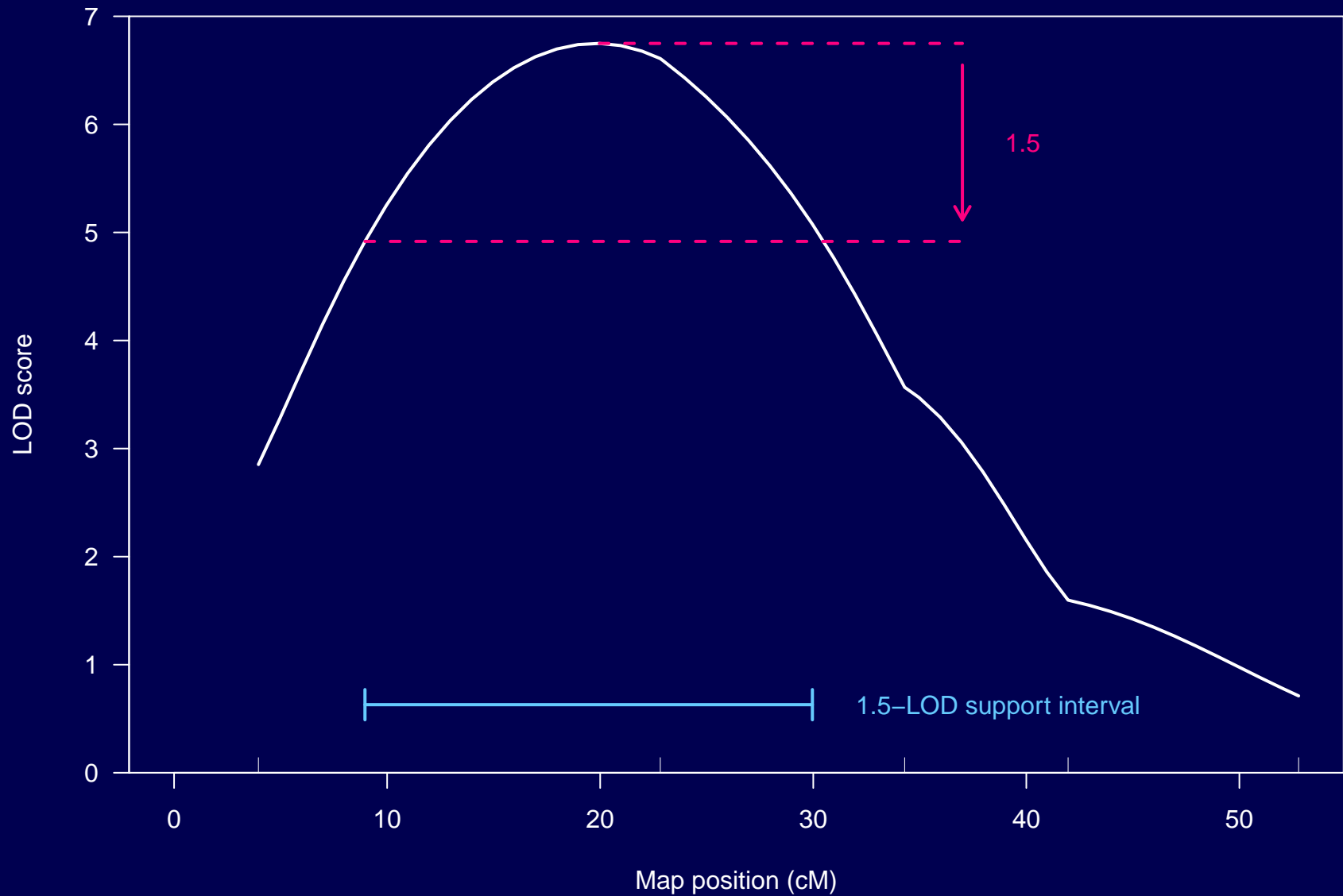




# Interactive plot



# LOD support intervals

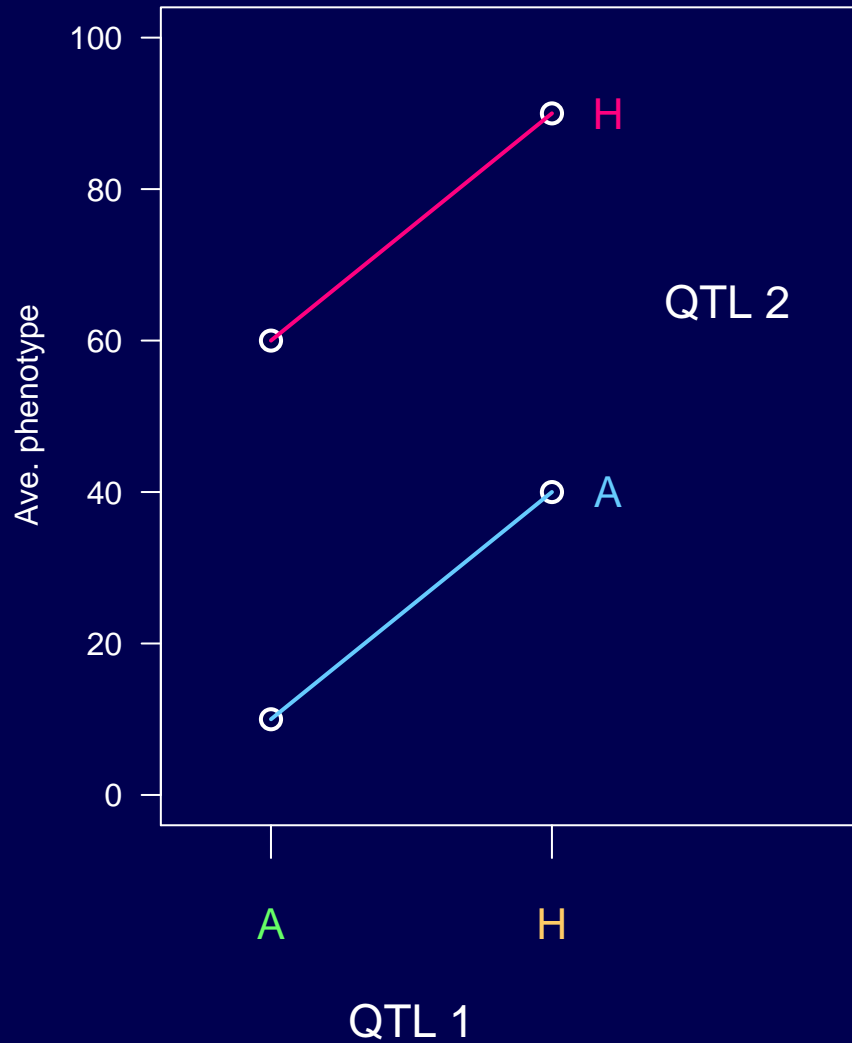


# Modelling multiple QTL

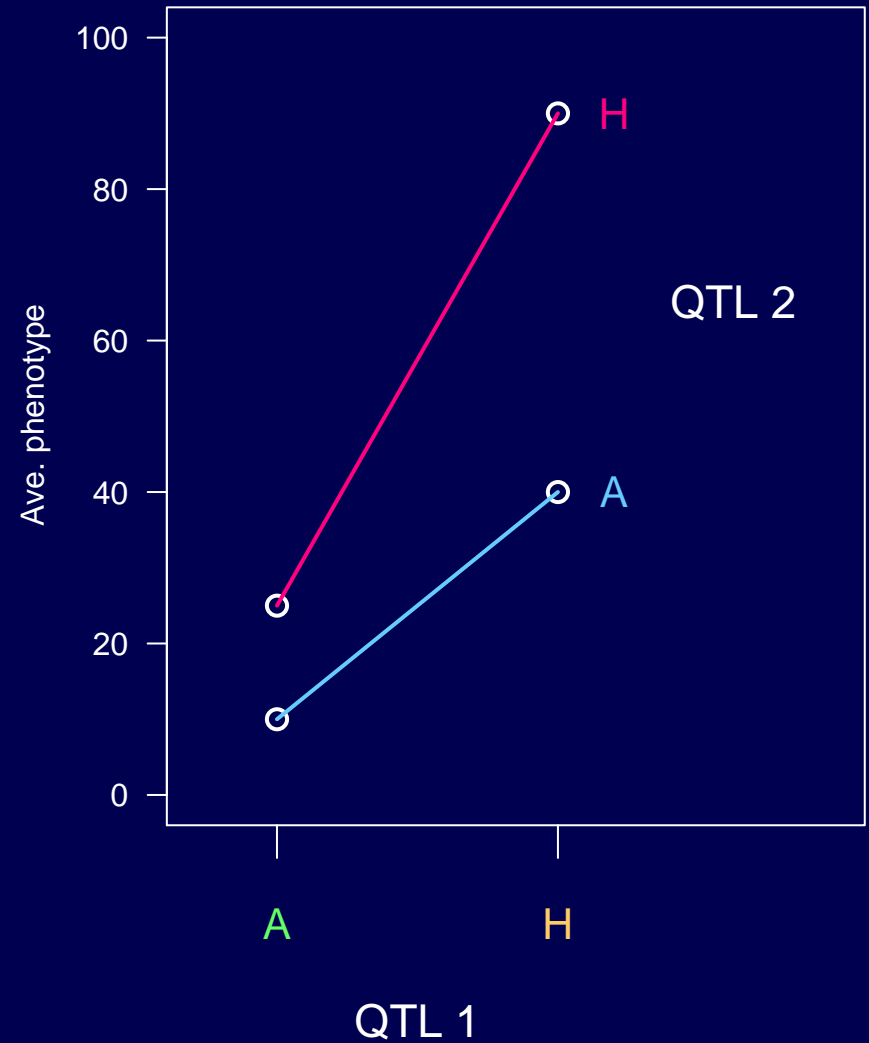
- Reduce residual variation  $\implies$  increased power
- Separate linked QTL
- Identify interactions among QTL

# Epistasis in BC

Additive

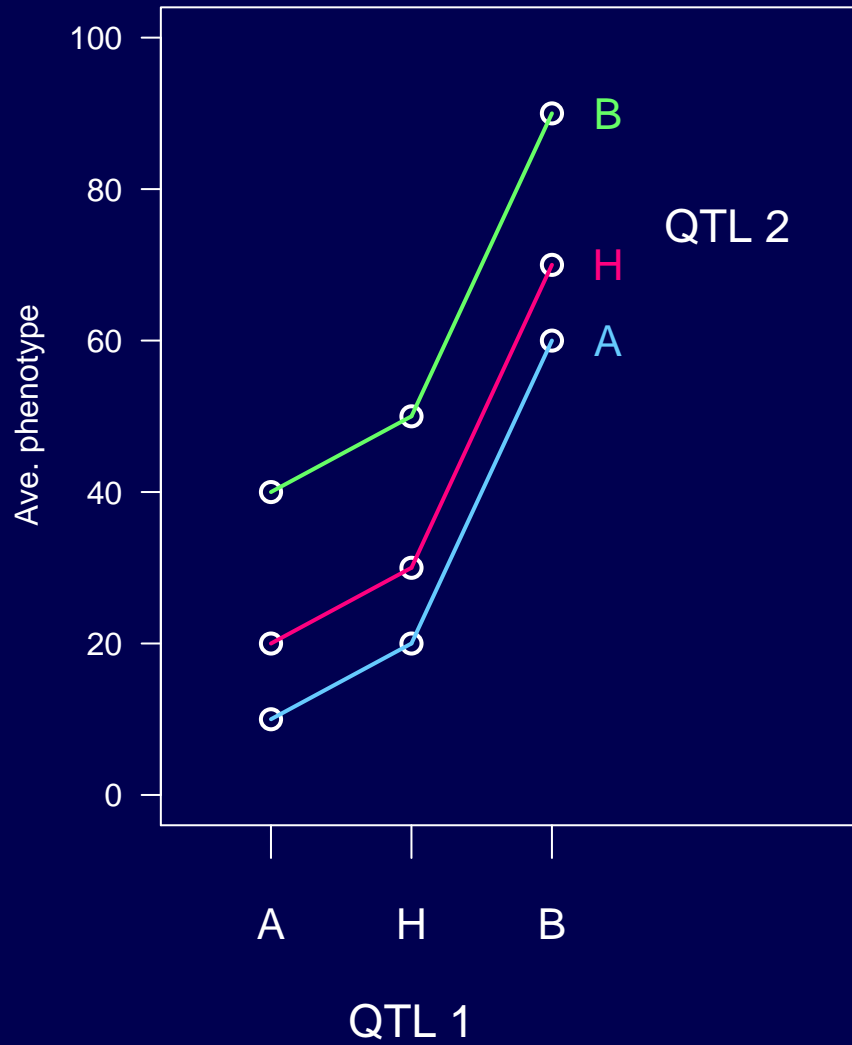


Epistatic

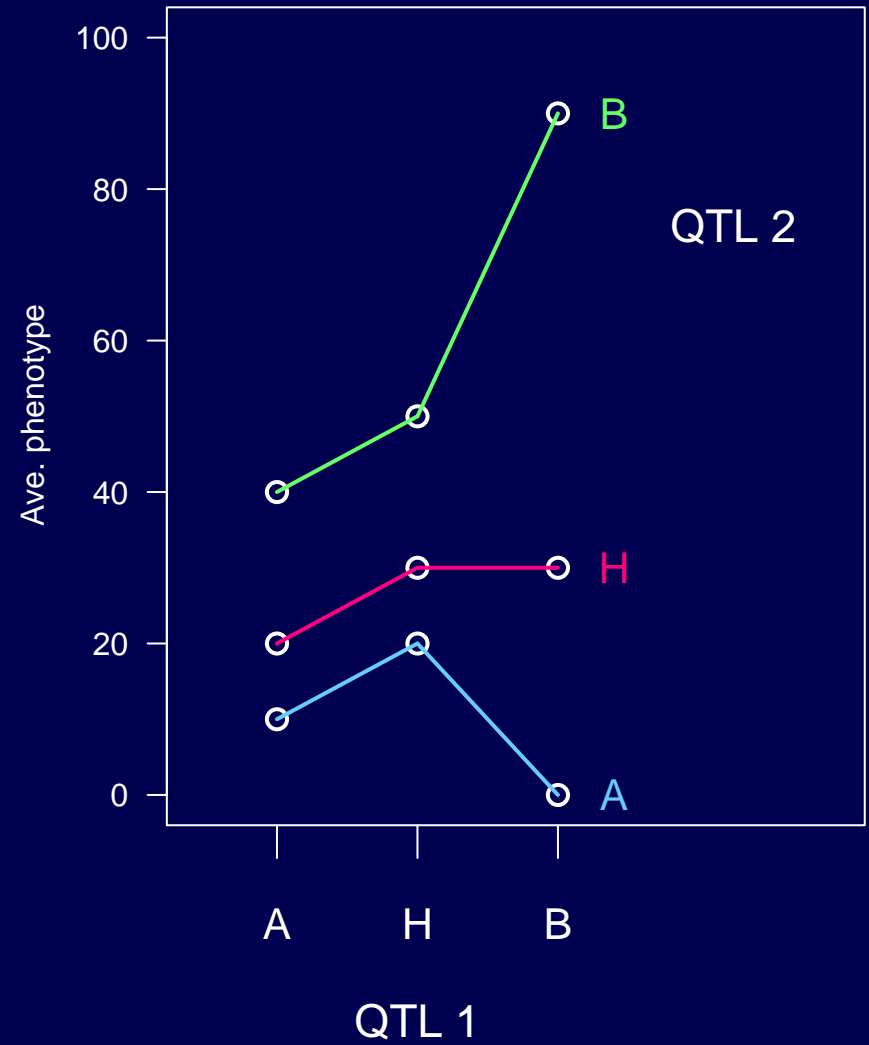


# Epistasis in F<sub>2</sub>

Additive



Epistatic



# References

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*An old but excellent general genetics textbook with a very interesting discussion of epistasis.*