# QTL mapping in mice: Review of single QTL methods

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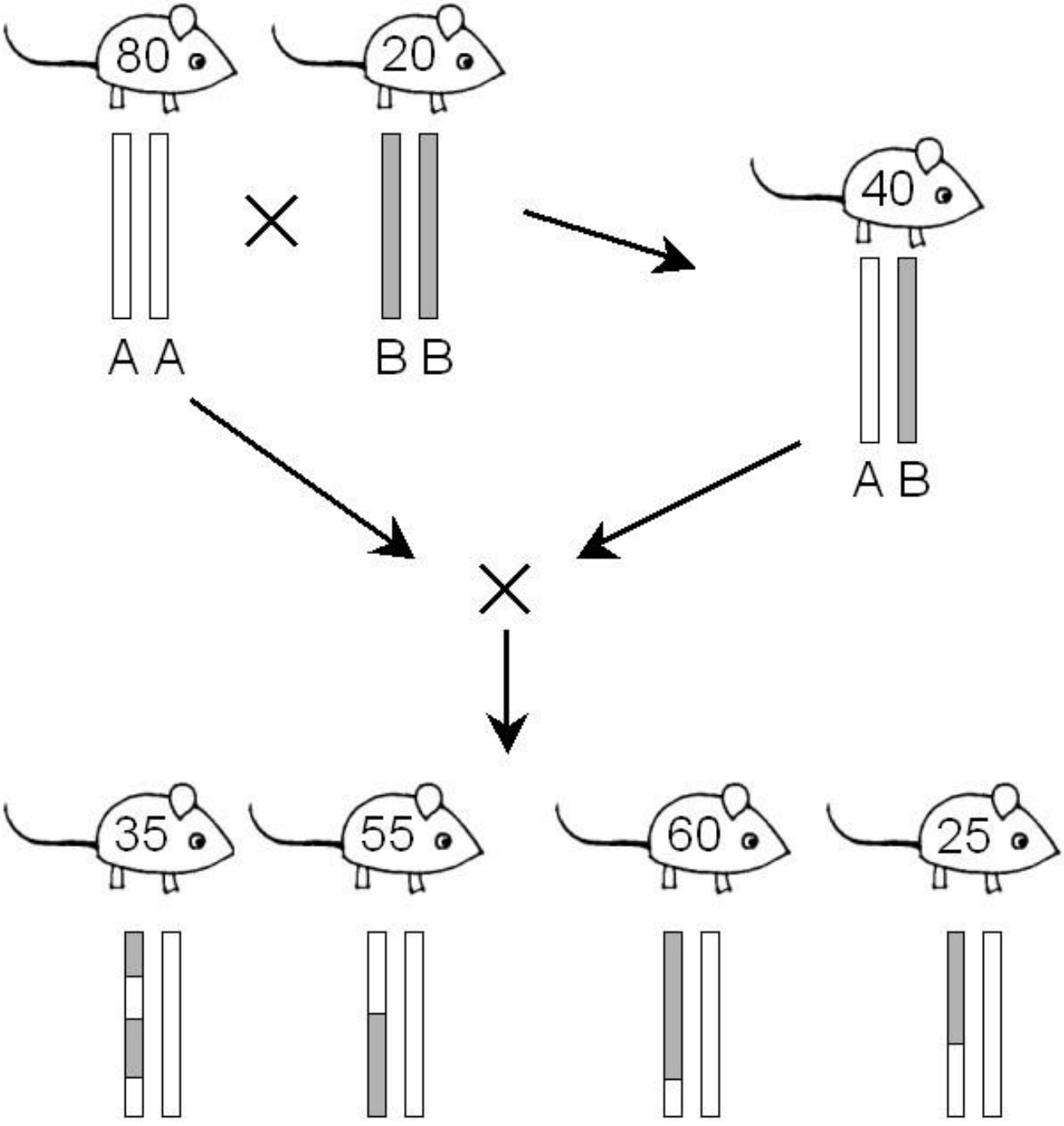
# Backcross experiment



# Data and Goals

## Phenotypes

$y_i$ = phenotype for mouse *i*

## Marker genotypes

$x_{ik}$ = 1/0 if *i* is AB/AA at marker *k*

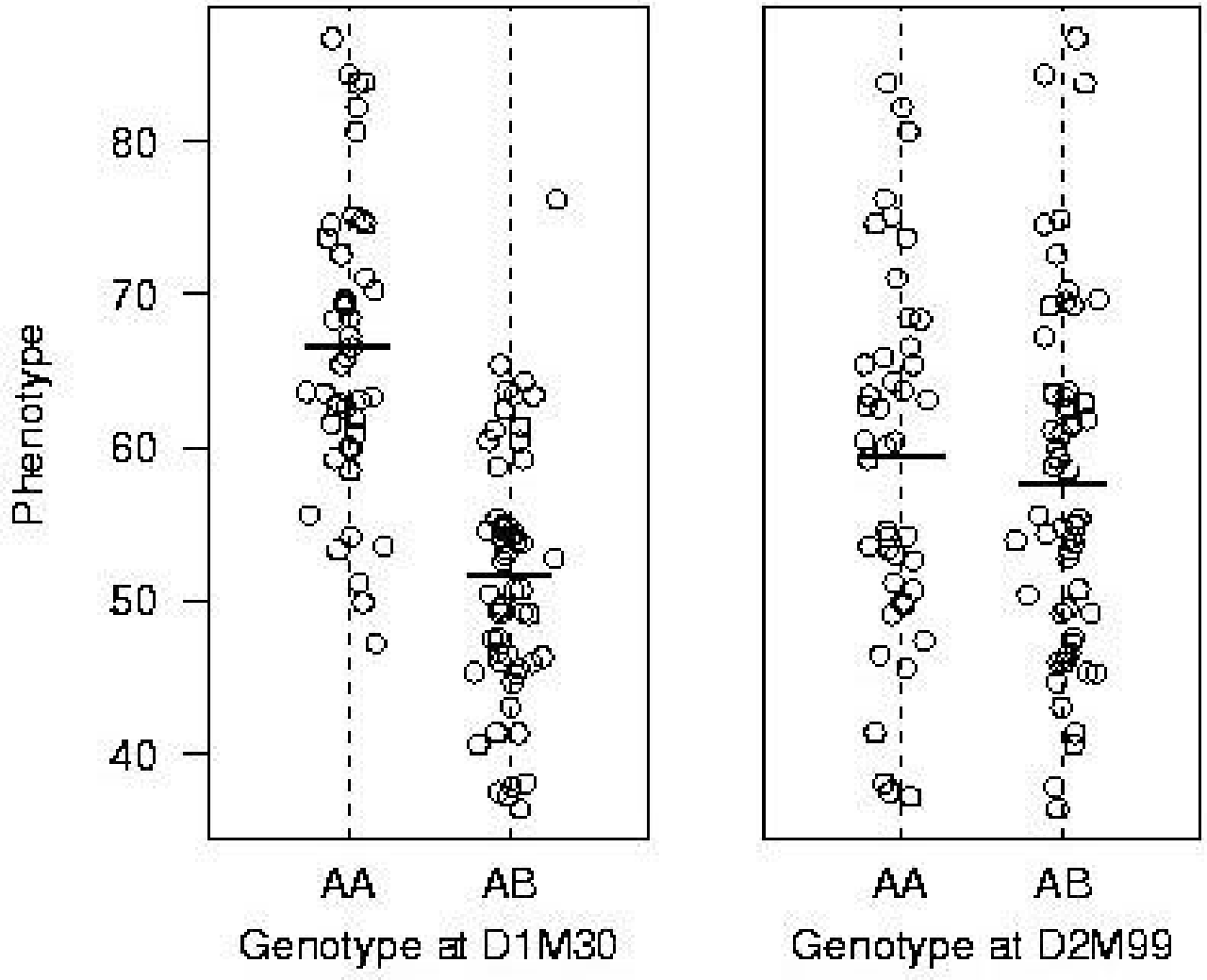
## Genetic map

Locations of markers

## Goals:

- Identify the genomic regions (QTLs) contributing to variation in the phenotype
- Identify at least one QTL
- Form confidence interval for QTL location
- Estimate QTL effects

# The simplest method: ANOVA




- Split mice into groups according to their genotypes at a marker
- Do a t-test / ANOVA
- Repeat for each typed marker

# ANOVA at marker loci

## Advantages

- Simple
- Easily incorporate covariates
- Easily extended to more complex models

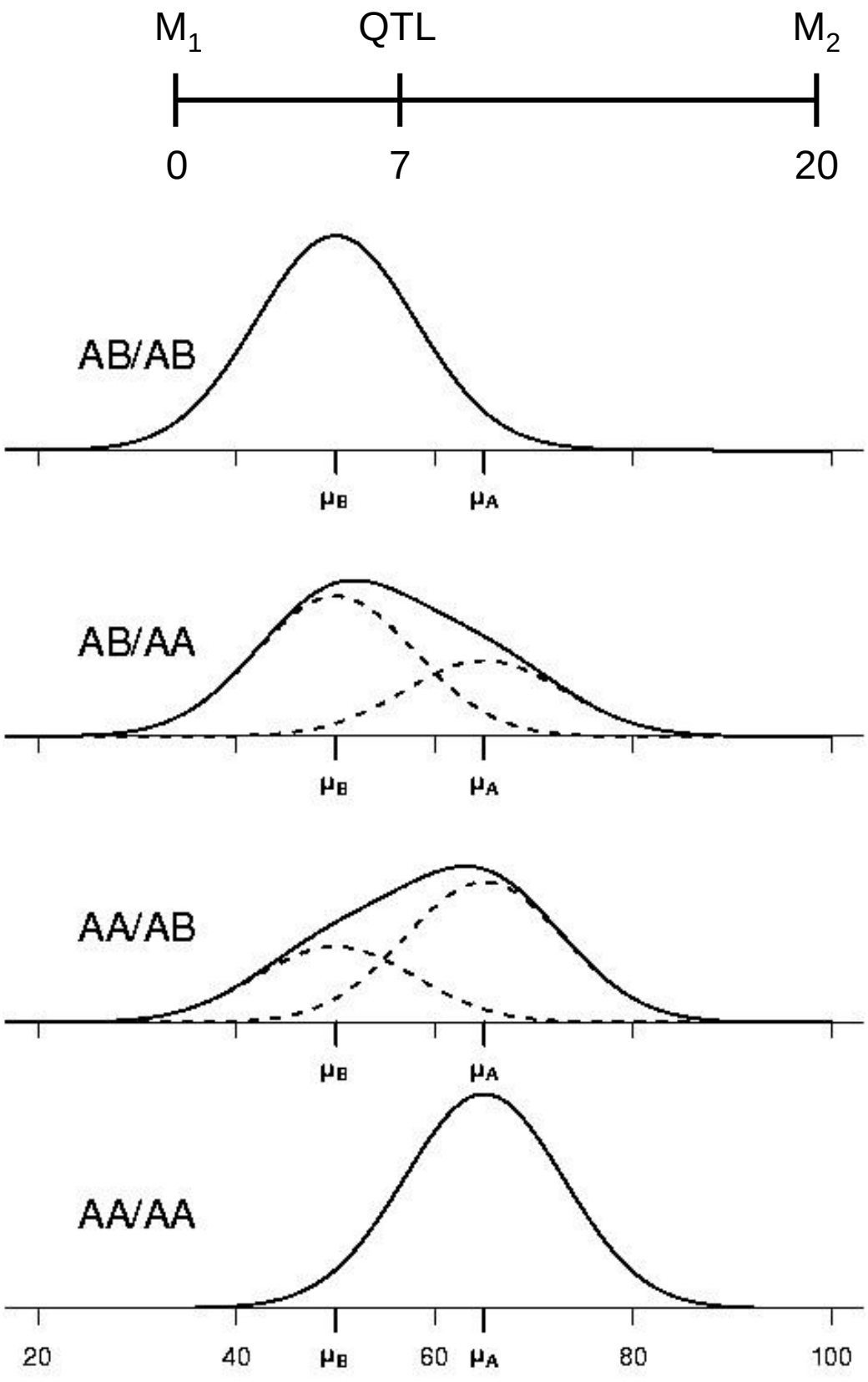
## Disadvantages

- 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 and Botstein 1989

- Consider any one position in the genome as the location for a putative QTL
- For a particular mouse, let z = 1/0 if (unobserved) genotype at QTL is AB/AA
- Calculate Pr(z = 1 | marker data)
  - Assume no meiotic interference
  - Need only consider flanking typed markers
  - May allow for the presence of genotyping errors
- Given genotype at the QTL, phenotype is distributed as normal( $\mu + \Delta z, \sigma^2$ )
- Given marker data, phenotype follows a *mixture* of normal distributions


M1
QTL
M2
0
7
20
AB/AB
μB
μA
AB/AA
μB
μA
AA/AB
μB
μA
AA/AA
20
40
μB
60
μA
80
100
Phenotype

# Interval mapping

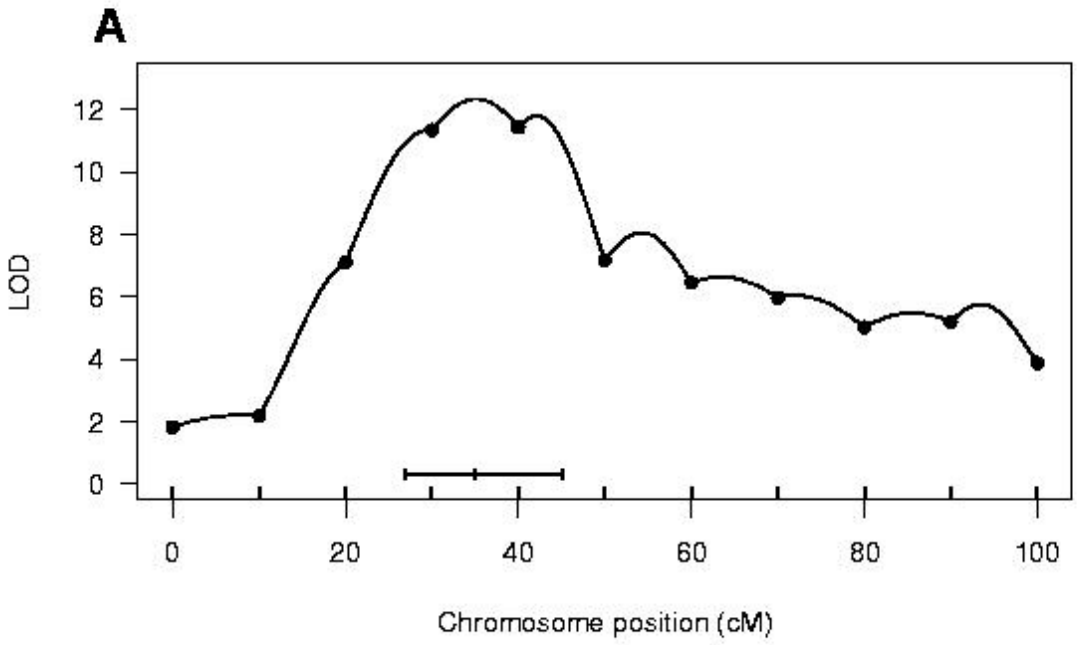
## Estimation and LOD scores

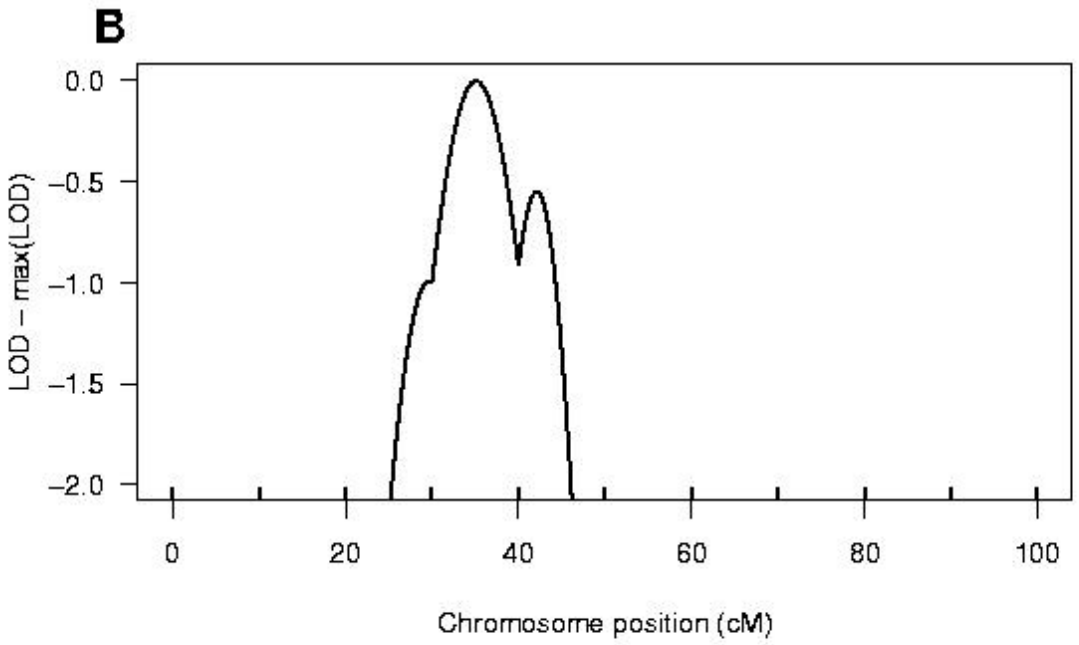
- Use a version of the EM algorithm to obtain estimates of $\mu_{AA}$, $\mu_{AB}$, and $\sigma$ (an *iterative* algorithm)
- Calculate the LOD score

$$\text{LOD} = \log_{10}\left\{\frac{\Pr(\text{data} \mid \hat{\mu}_{AA}, \hat{\mu}_{AB}, \hat{\sigma})}{\Pr(\text{data} \mid \text{no QTL})}\right\}$$

- Repeat for all other genomic positions (in practice, at 0.5 cM steps along genome)

# A simulated example



# Interval mapping

## Advantages

- Make proper account of missing data
- Can allow for the presence of genotyping errors
- Pretty pictures
- Higher power in low-density scans
- Improved estimate of QTL location

## Disadvantages

- Greater computational effort
- Requires specialized software
- More difficult to include covariates
- Only considers one QTL at a time

# Haley-Knott regression

- An approximation of IM
- Regress phenotypes on Pr(z = 1 | marker data)
  - Like assuming Normal($\mu + \Delta$ p, $\sigma$) rather than a mixture of Normal($\mu$, $\sigma$) and Normal($\mu + \Delta$, $\sigma$)
  - Like a half-step of the EM algorithm

## Advantages

- Fast
- Nearly IM if not *too* much missing data
- Can easily incorporate covariates

## Disadvantages

- Only *nearly* IM

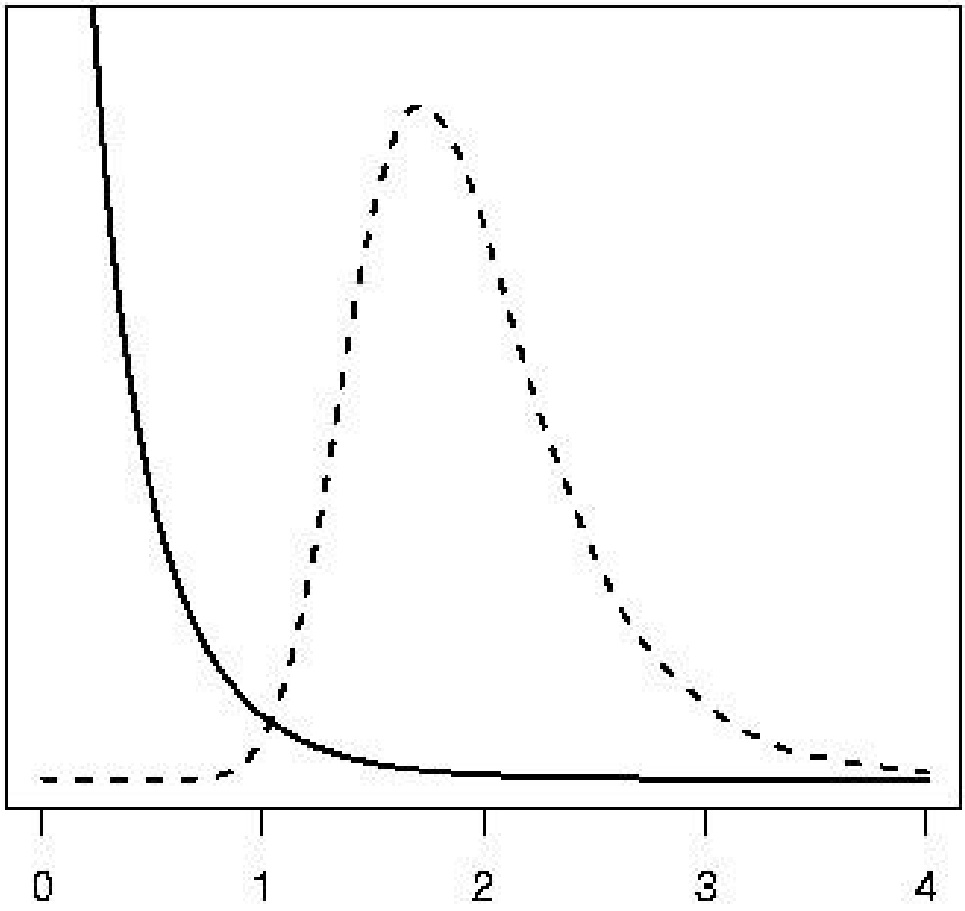
# Statistical significance

Large LOD score $\Rightarrow$ evidence for QTL

**Question**: How large is large?

**Answer 1**: Consider distribution of LOD score if there were no QTL

**Answer 2**: Consider distribution of **maximum** LOD score



# More on LOD thresholds

## Appropriate threshold depends on:

- Size of genome
- Number of typed markers
- Pattern of missing data
- Stringency of significance threshold
- Type of cross (e.g. $F_2$ vs BC)
- Etc.

## Methods for obtaining thresholds

- Analytical calculations (assuming dense map of markers)
- Computer simulations
- Permutation/randomization test

# LOD support intervals

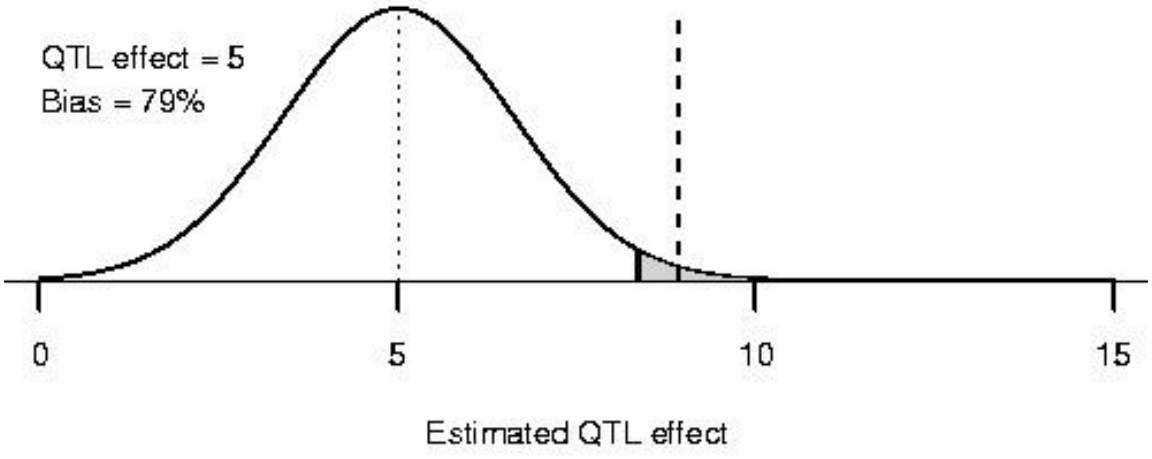
## 1.5-LOD support interval =

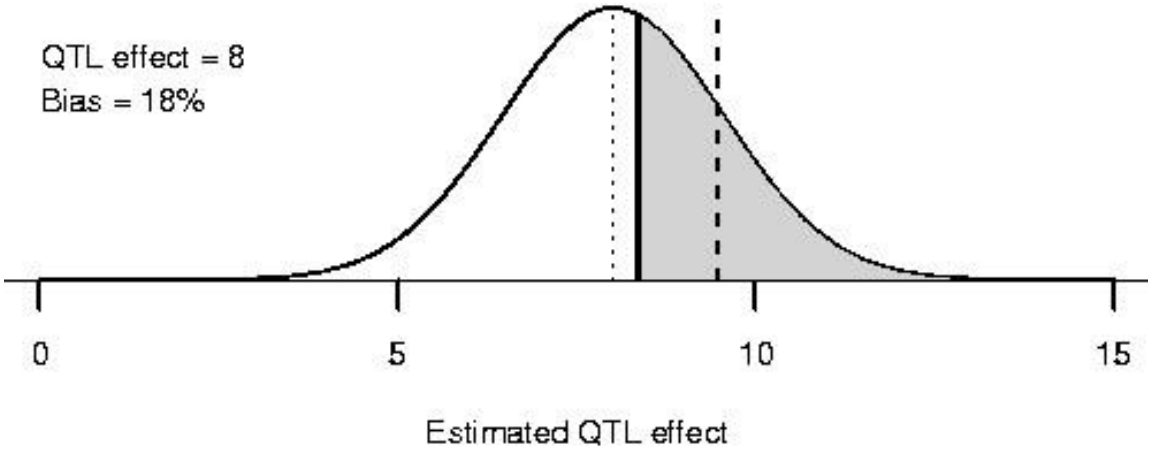
- Interval in which LOD score is within 1.5 of its maximum
- Indicates plausible location for QTL

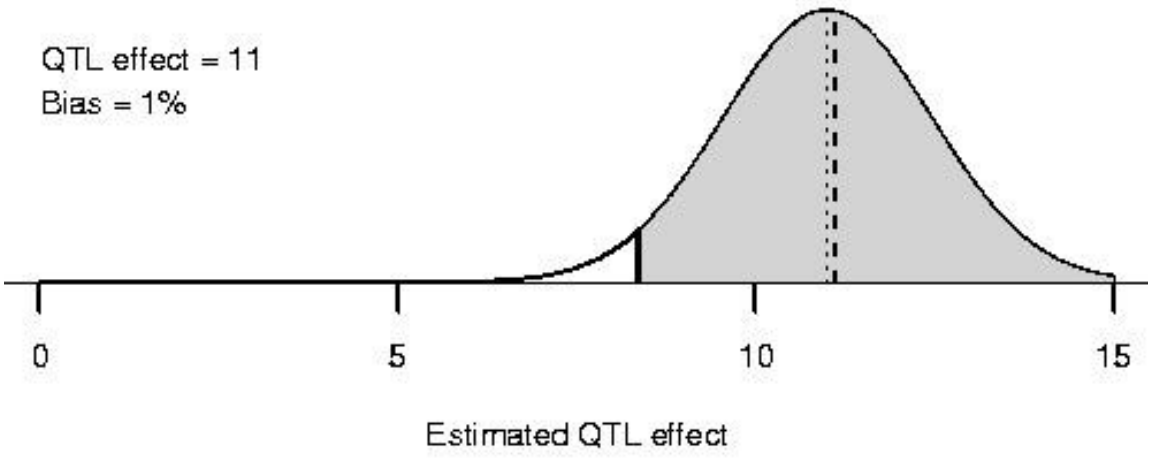
## Plot LOD score with maximum at 0

→ Valuable tool for depicting evidence for QTL location

# Selection bias in QTL effects

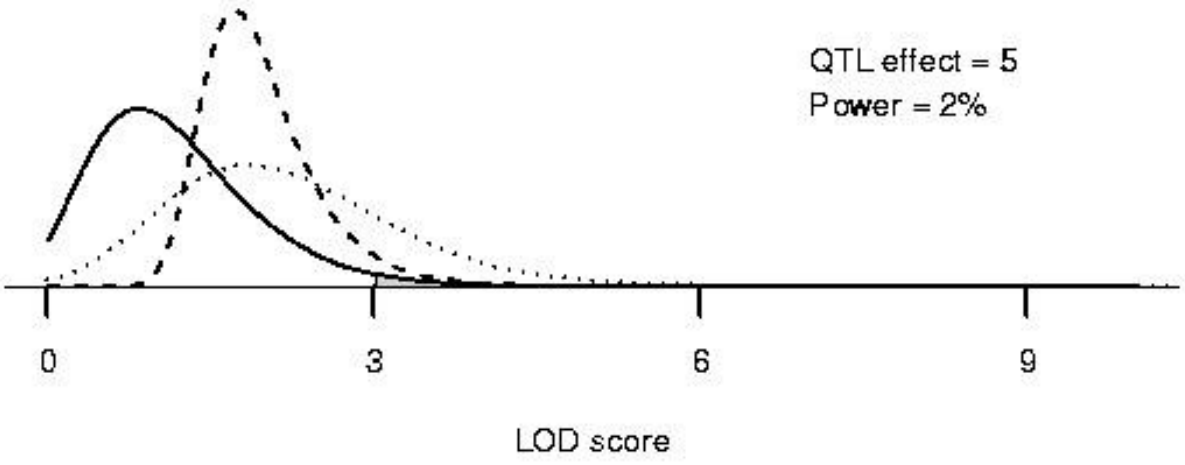


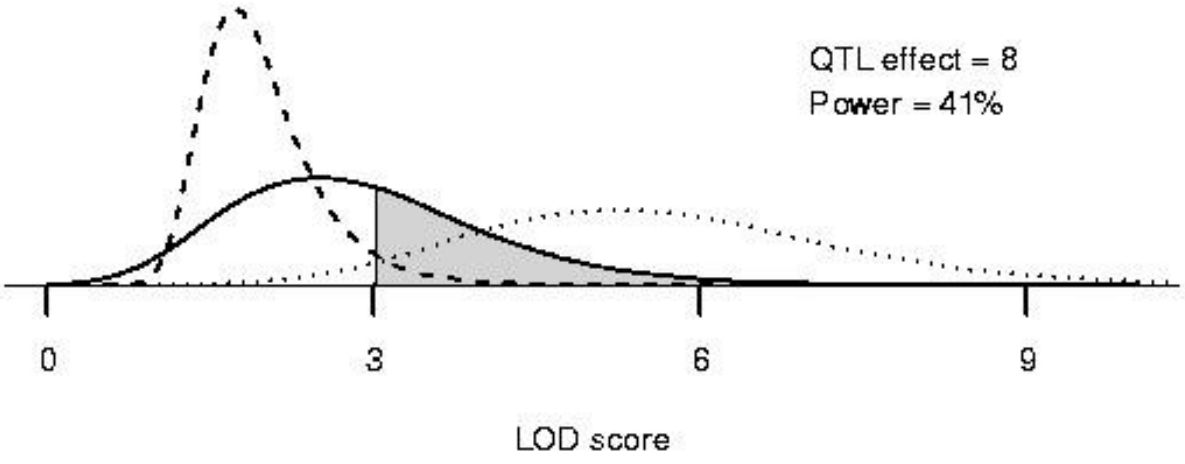



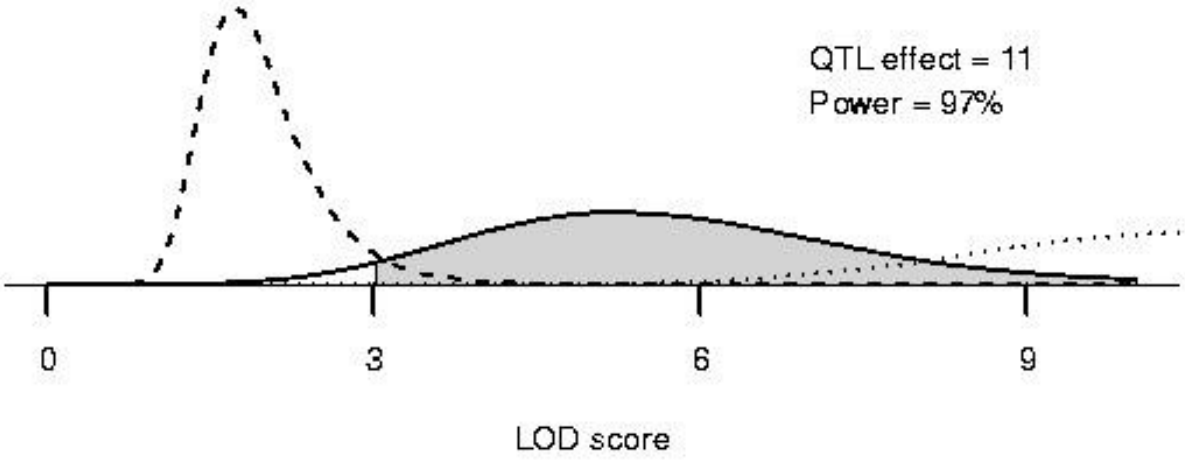



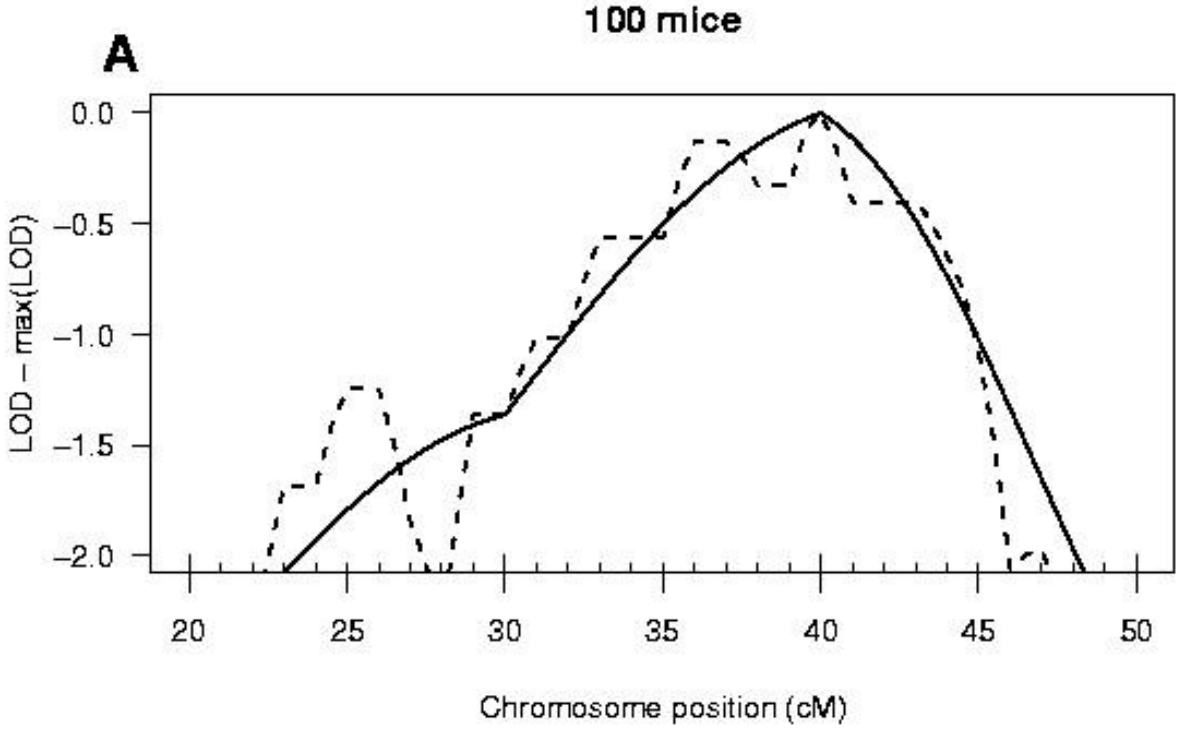
# Summary

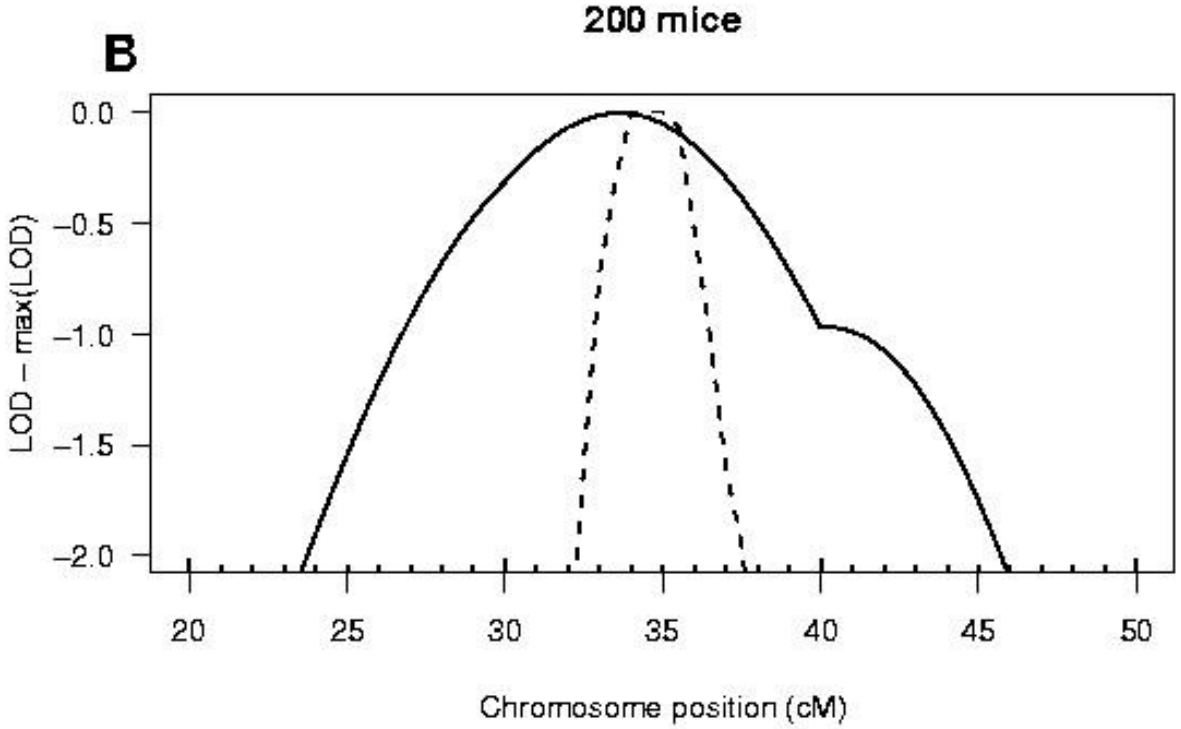
- **Simplest method: ANOVA**
  - Suffers in the presence of missing genotype data and/or low-density map
- **Interval mapping**
  - Makes proper account of missing data
  - More computationally intensive
  - Still only considers single QTLs
- **Statistical significance**
  - Adjust for multiple testing
  - Permutation tests
- **QTL location**: LOD support intervals
  - Plot LOD curve re-centered so max=0
- **Selection bias**
  - Est'd QTL effects may be too large


QTL effect = 5
Power = 2%
0
3
6
9
LOD score


QTL effect = 8
Power = 41%
0
3
6
9
LOD score


QTL effect = 11
Power = 97%
0
3
6
9
LOD score


100 mice
A
0.0
−0.5
−1.0
−1.5
−2.0
LOD − max(LOD)
20
25
30
35
40
45
50
Chromosome position (cM)


200 mice
B
0.0
−0.5
−1.0
−1.5
−2.0
LOD − max(LOD)
20
25
30
35
40
45
50
Chromosome position (cM)