Detecting single QTL

Search for one QTL at fixed cM intervals across the genome

+ Estimate additive (and possibly dominance) effects of QTL at every putative QTL location

+ Identified QTL may be used as cofactors in consecutive analyses to remove background noise - often called Multiple QTL Mapping or **Composite interval mapping**

Detecting multiple QTL

II) Likelihood based Multiple QTL Method (Kao et al 1999)

+ Identification of regions with indications of QTL activity

+ Searches for multiple interacting QTL at fixed cM intervals in these regions

> Model selection

+ Yet not solved how to chose the significance threshold for these analyses

+ Very time consuming analysis, Many combinations possible randomization testing intractable

Detecting multiple QTL

Carlborg, O., Andersson, L. and Kinghorn, B.P. 2000. The use of a genetic algorithm for simultaneous mapping of multiple interacting quantitative trait loci. *Genetics*. In Press

A simultaneous search for multiple interacting QTL has higher power to detect QTL and estimates parameters better

Simultaneous mapping of multiple QTL can be used in practice if a better search algorithm is used

The genetic algorithms are good for QTL mapping since they are:

+ Robust
+ Easy to implement
+ Computationally efficient

Models of dominance and epistasis

Dominance:

$$\begin{pmatrix} II \\ Ii \\ ii \end{pmatrix} = \begin{pmatrix} \mu + A_i \\ \mu + D_i \\ \mu - A_i \end{pmatrix}$$

Use genetic markers for known QTL (*I*, *i*).

Use coefficients of expression for genome-wide effects

Epistasis (2-locus):

$$\begin{pmatrix} II\ JJ & II\ Jj & II\ jj \\ Ii\ JJ & Ii\ Jj & Ii\ jj \\ ii\ JJ & ii\ Jj & ii\ jj \end{pmatrix} = \begin{pmatrix} \mu + A_i + A_j + AA_{ij} & \mu + A_i + D_j + AD_{ij} & \mu + A_i - A_j - AA_{ij} \\ \mu + D_i + A_j + AD_{ji} & \mu + D_i + D_j + DD_{ij} & \mu + D_i - A_j - AD_{ji} \\ \mu - A_i + A_j - AA_{ij} & \mu - A_i + D_j - AD_{ij} & \mu - A_i - A_j + AA_{ij} \end{pmatrix}$$

… many parameters to estimate!

Detecting multiple QTL – epistatic models

Reasons for using an epistatic model when mapping multiple QTL:

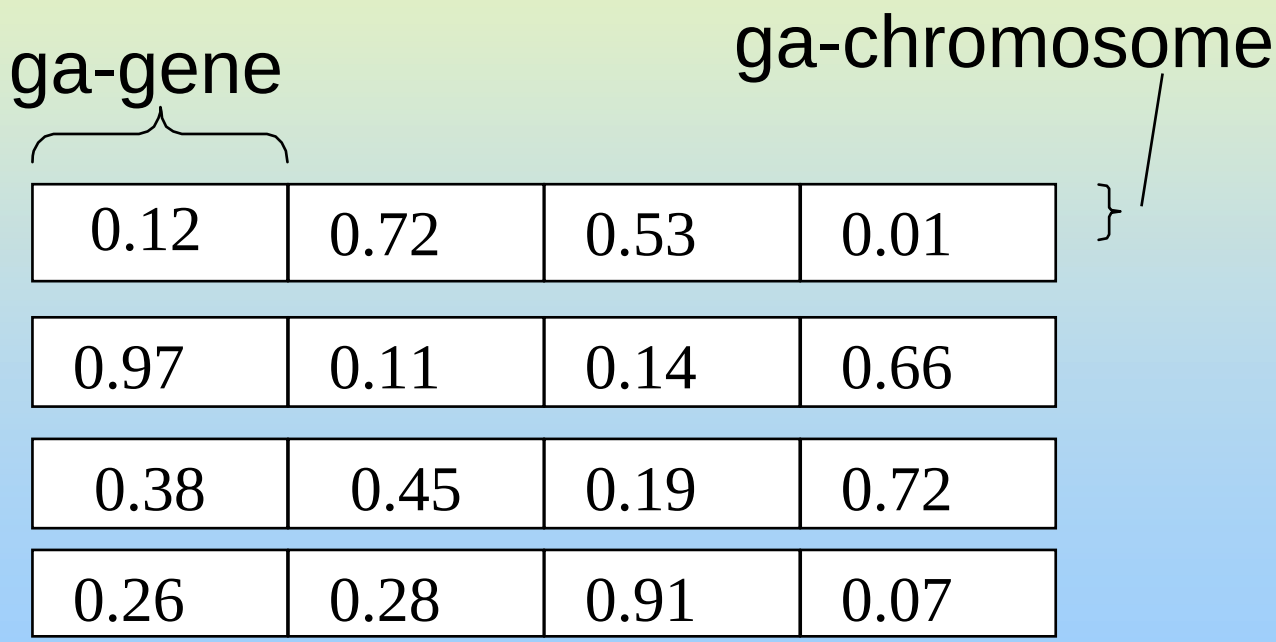
- Higher power to detect interacting QTL
- Better estimates of QTL effects

Classical epistatic interactions are e.g.

+ Complementary epistasis (9:7)
+ Dominant epistasis (12:3:1)
+ Duplicate epistasis (15:1)
+ Recessive epistasis (9:3:4)
+ Inhibitory epistasis (13:3)

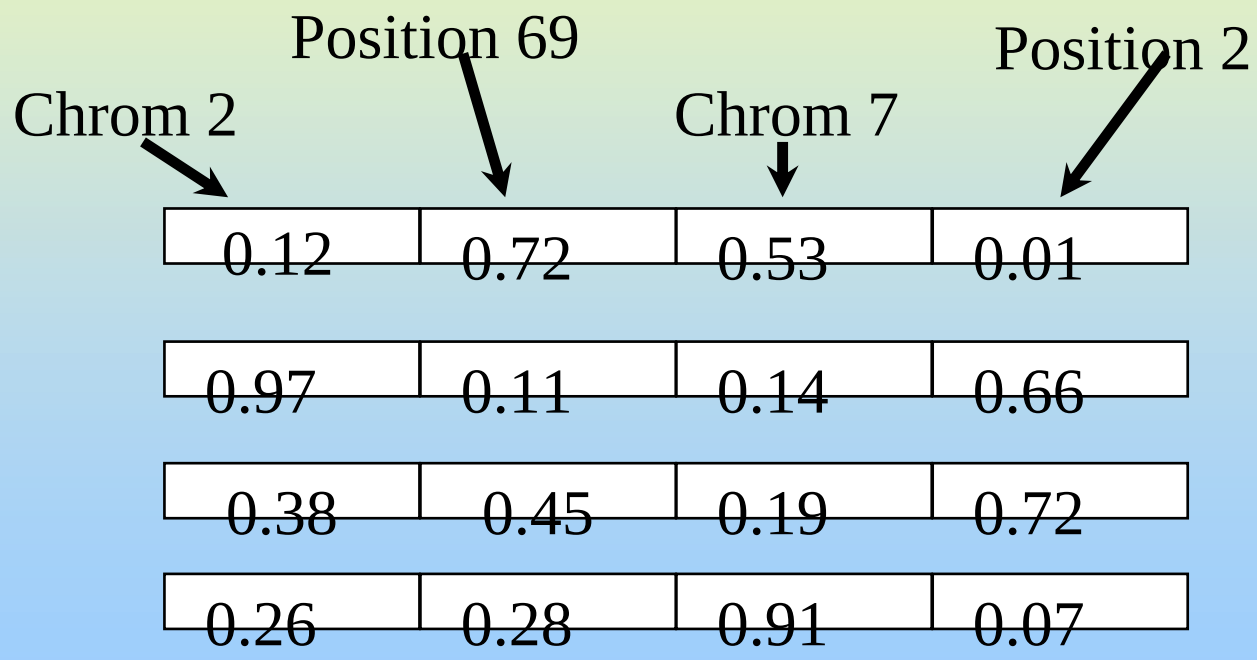
Implementation of genetic algorithm:

1) Generate a population of ga-chromosomes



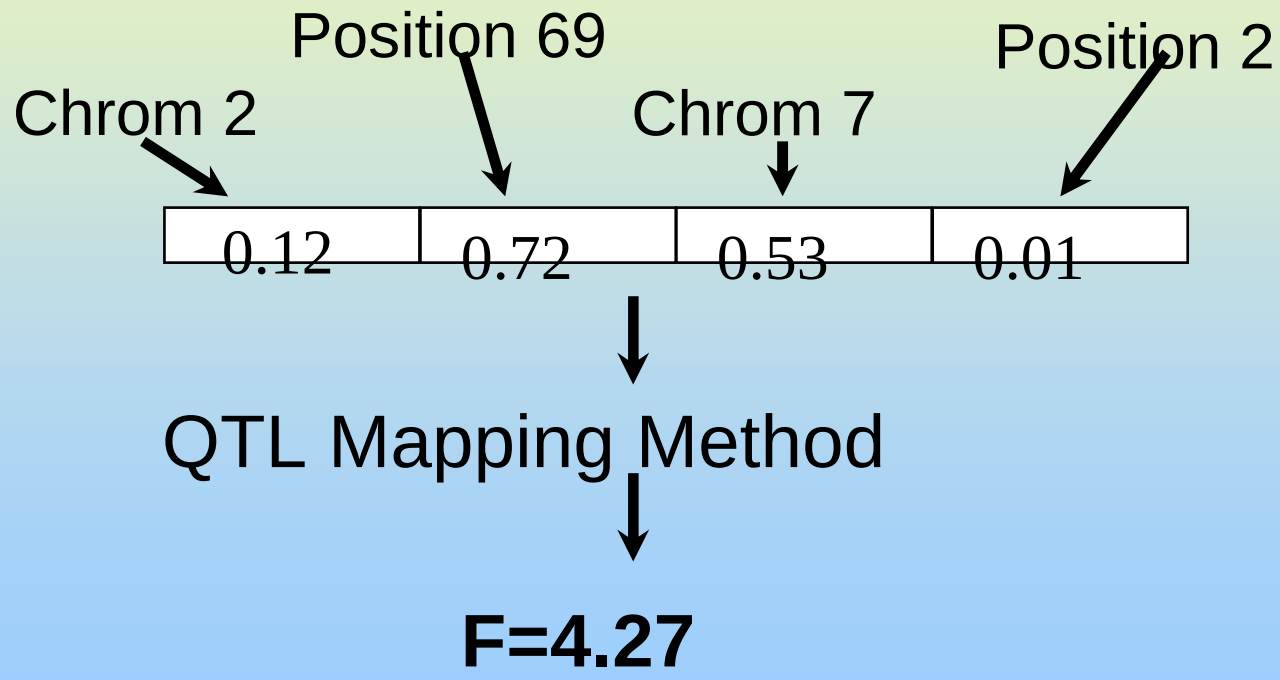
Implementation in QTL mapping:

2) Translate coded values to QTL positions



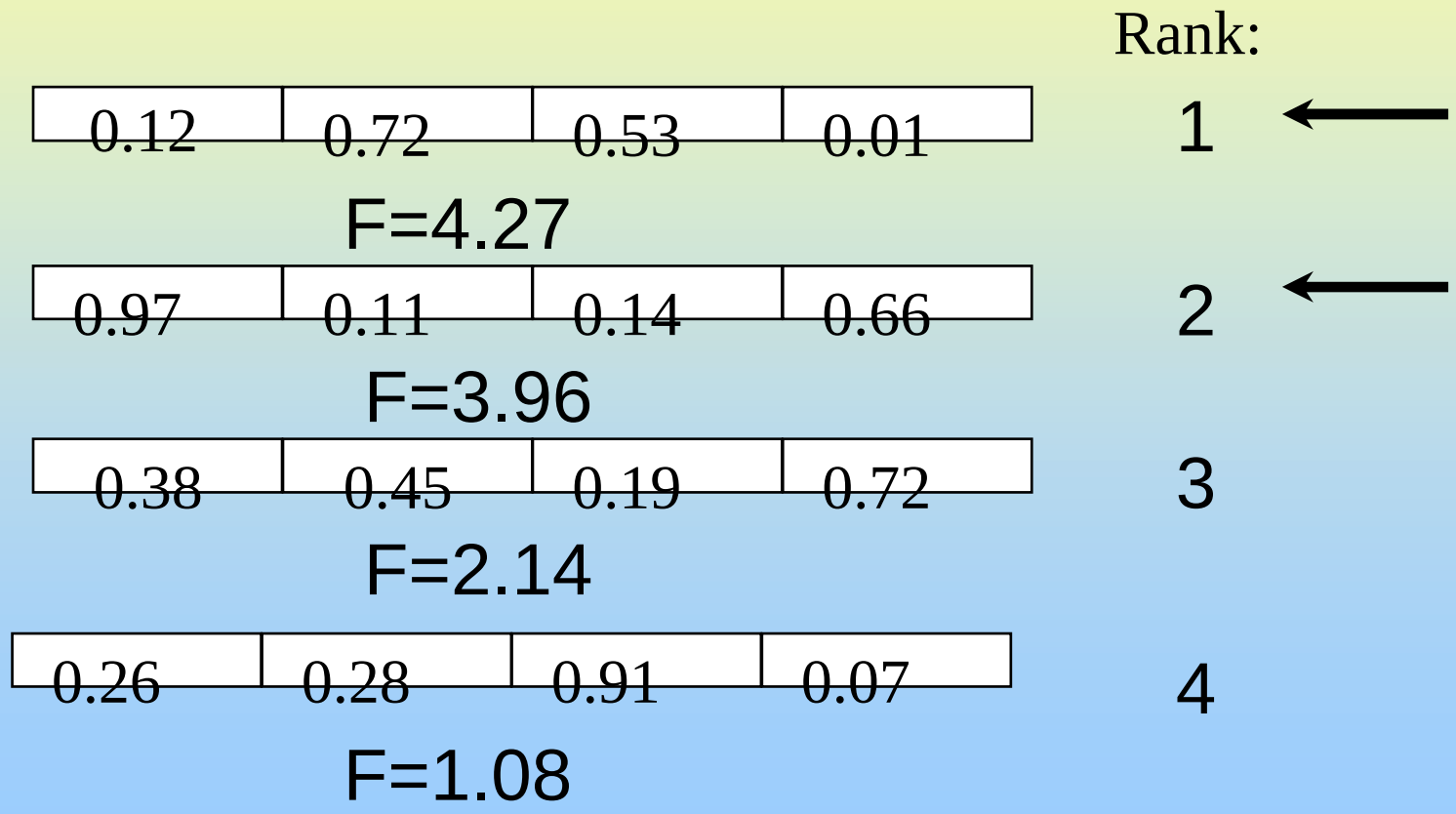
Implementation in QTL mapping:

3) Evaluate statistical fit for each ga-chromsome



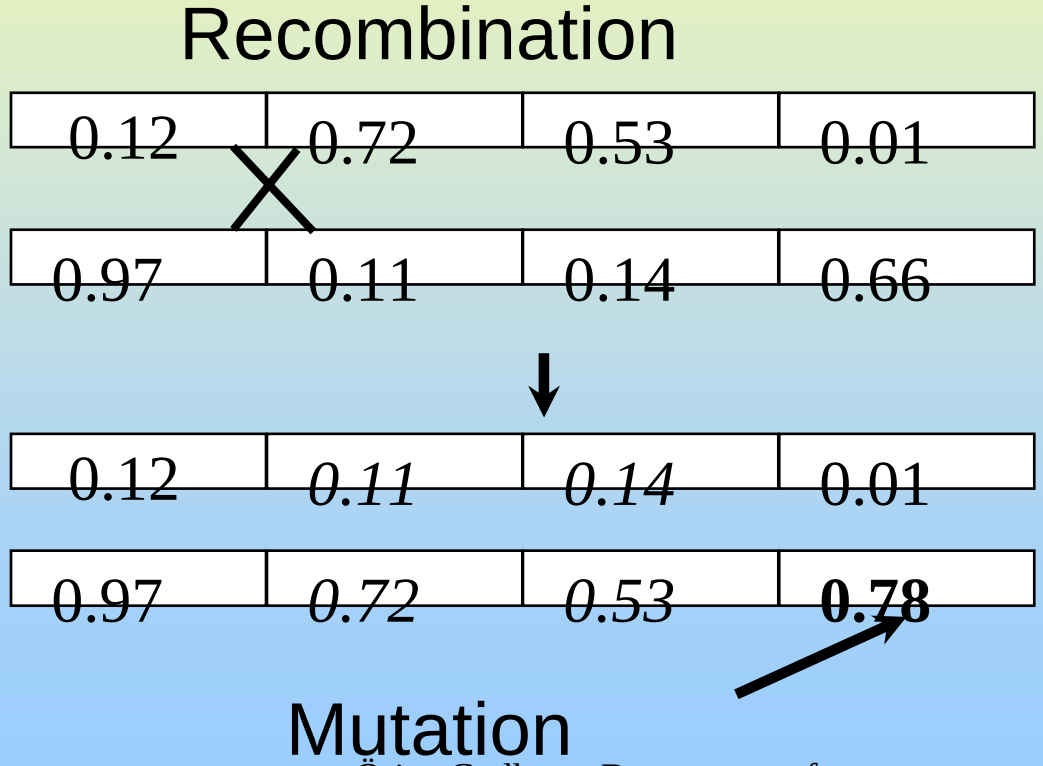
Implementation in QTL mapping:

4) Select good ga-chromosomes



Implementation in QTL mapping:

5) Generation of new ga-chromosomes (Breeding)



Gain in computing speed …

Genetic algorithm versus exhaustive search

In a genome size of 2000 cM:

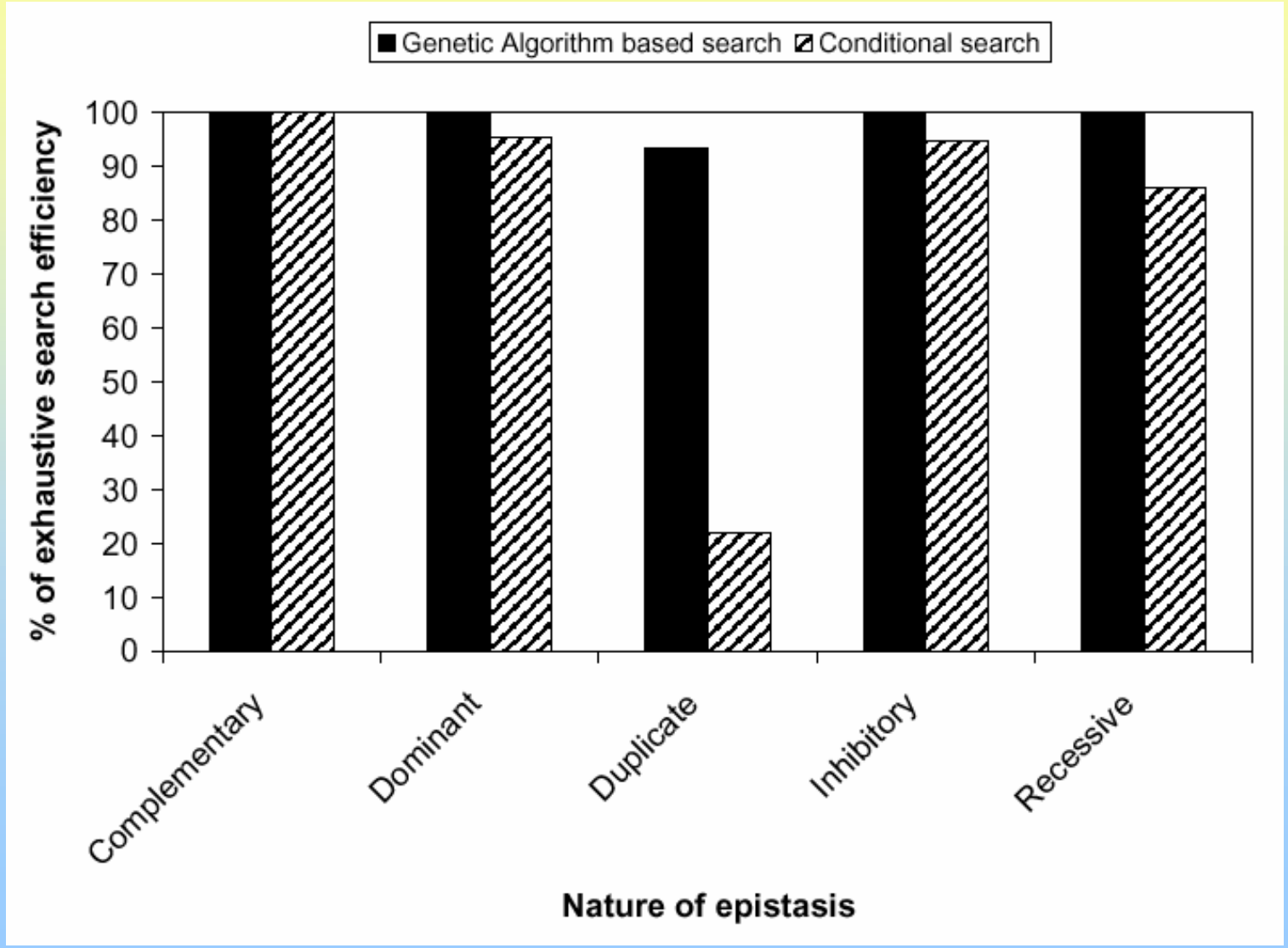
+ For 2 QTL improvement by factor 120

+ For 3 QTL improvement by factor 65,000

+ For 4 QTL improvement by factor 1.7×10^7

Plus: GA method has finer resolution

Results from genome scan

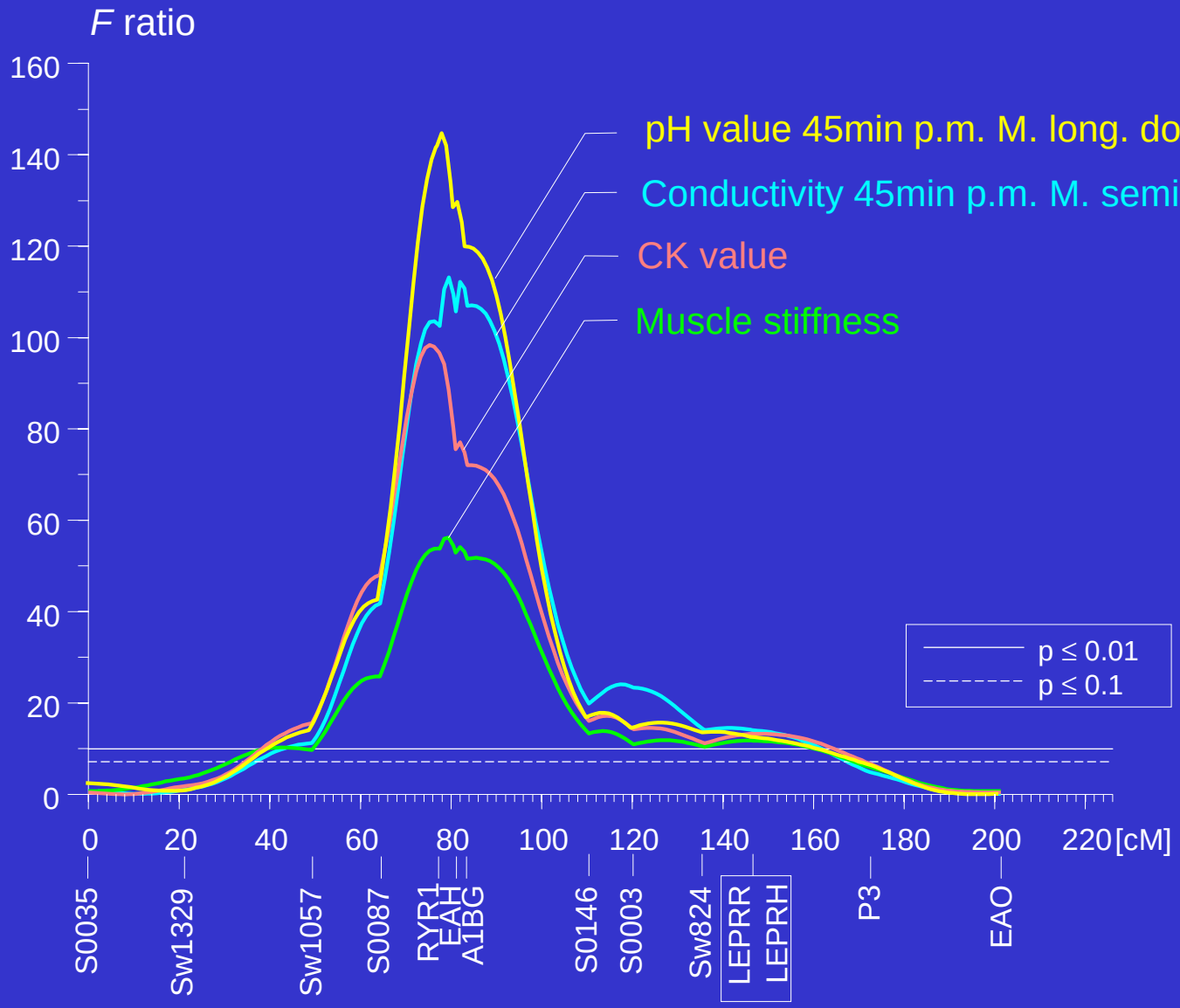


Multiple trait

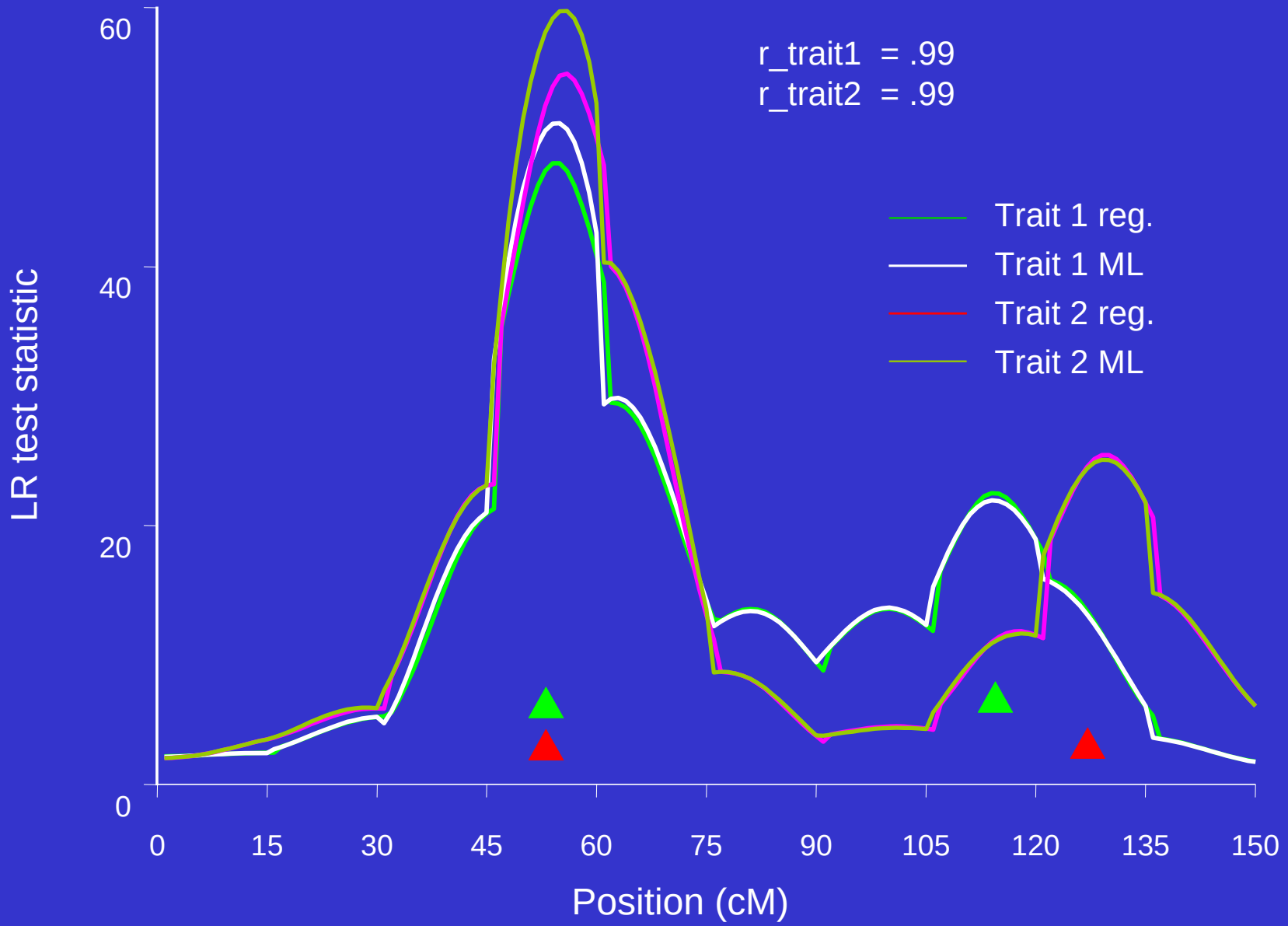
- Increased power from using multiple traits
- testing models regarding genetic correlation
  - pleiotropy or close linkage

QTL Map of Chromosome 6 in Family WxP
Stress Reaction and Meat Quality Traits

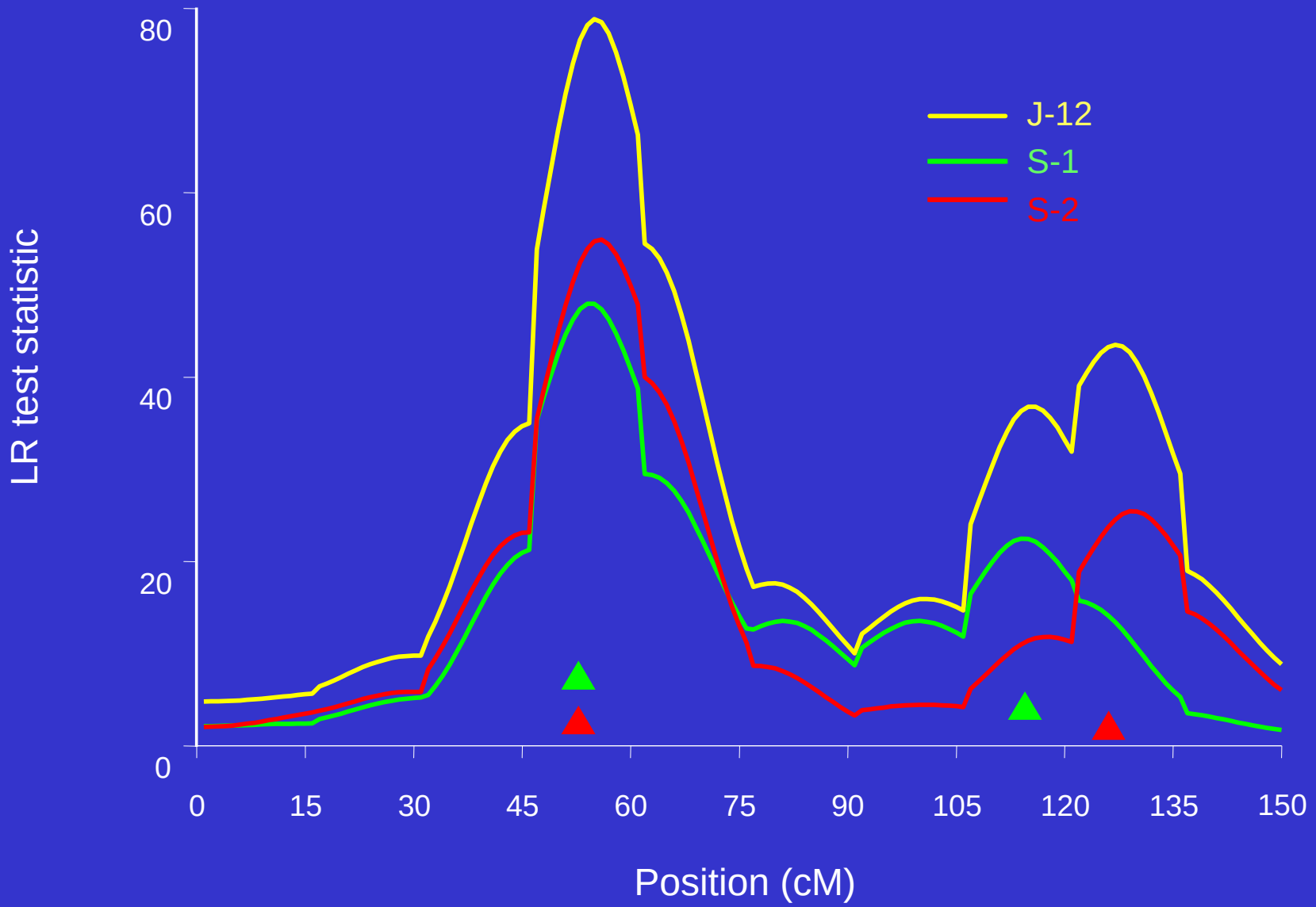
F ratio testing the hypothesis of a single QTL at a given position on the chromosome



ML and regression for single traits (CIM)



Joint mapping *vs.* separate mapping using regression (CIM)



Properties of the joint analysis

a) $r = 0$ — **if traits uncorrelated**

$LR_j \approx LR_{S1} + LR_{S2}$ — **i.e. increased power**

b) $\beta_2 = 0$ — **if only one trait affected**

$LR_j \approx LR_{S1}/(1-r)^2 \geq LR_{S1}$ — **increased power**

c)

$LR_j \geq \text{maximum}[LR_{S1}, LR_{S2}]$

d) $r\,\beta_1\,\beta_2 < 0$ **(i.e r and** $\beta_1\,\beta_2$ **have different signs)**

$LR_j > LR_{S1} + LR_{S2}$

Testing for linked TL vs pleiotropic QTL

H_0: position 1 = position 2

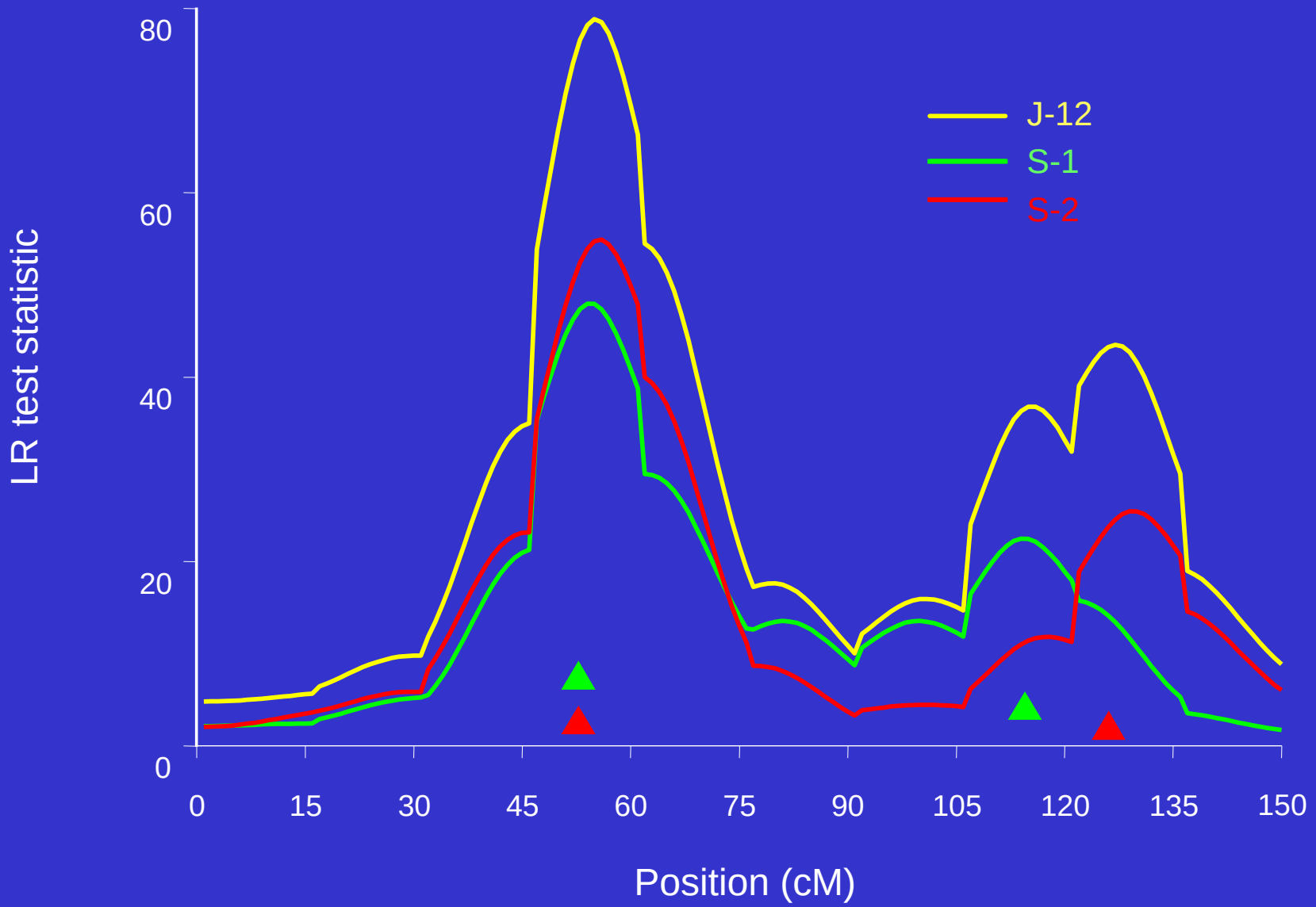
H_1: position 1 ≠ position 2

Testing different genetic models

Existence of epistasis

QTL affecting single traits vs. QTL affecting multiple traits

Joint mapping *vs.* separate mapping using regression (CIM)



Approximate LR test statistic using regression

Single trait analysis:

$$LR \approx n \log_e \left[\frac{RSS_{reduced}}{RSS_{full}} \right]$$

Multiple trait analysis:

$$LR \approx n \log_e \frac{\left| \Sigma_{reduced} \right|}{\left| \Sigma_{full} \right|}$$

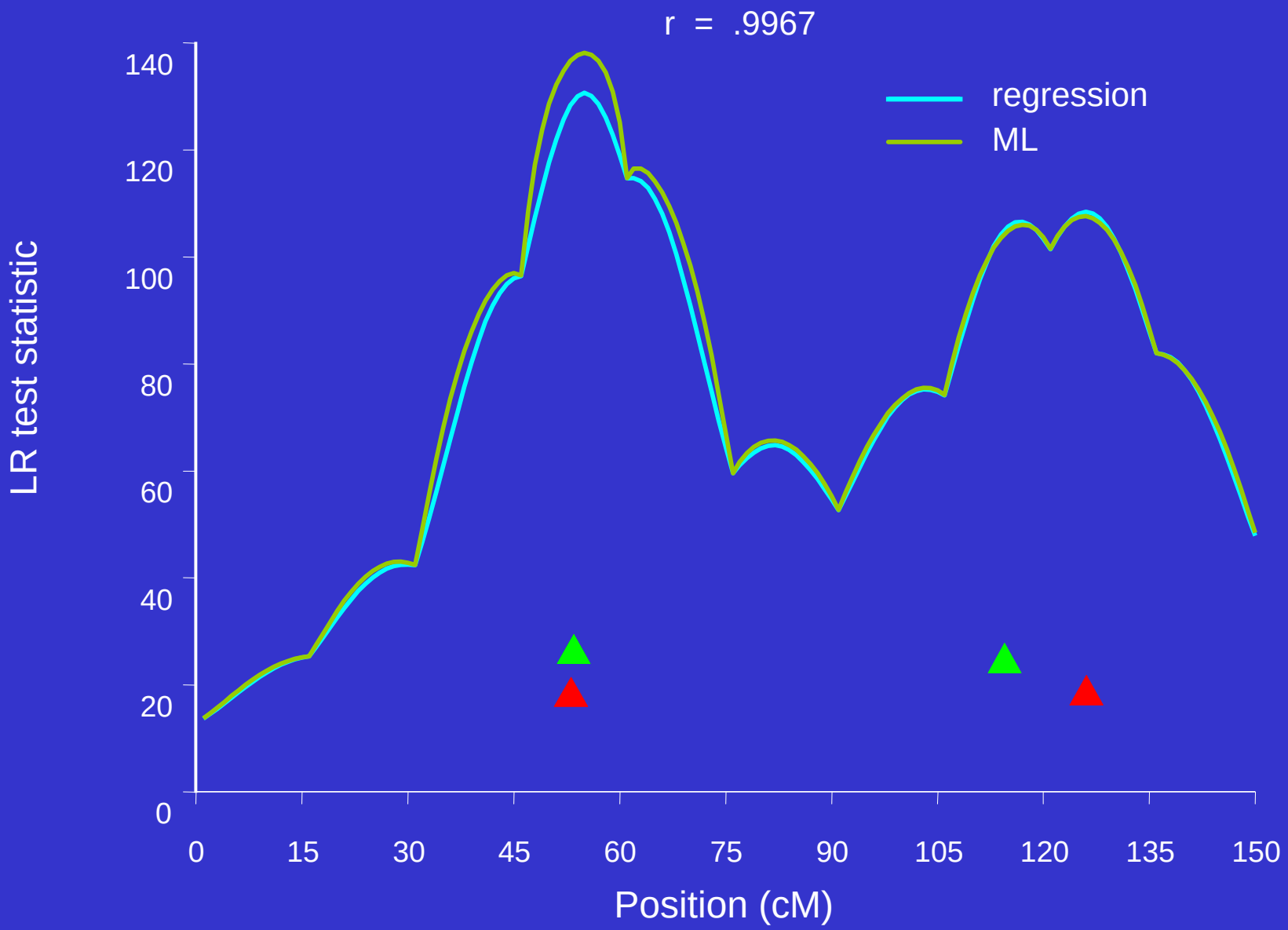
Test pleiotropy *vs*. close linkage

$$\left| \Sigma \right| = \begin{vmatrix} RSS_{11} & RSP_{12} \\ RSP_{12} & RSS_{22} \end{vmatrix}$$

$H_0 = p(1) = p(2)$

$H_1 = p(1) \neq p(2)$

Joint mapping on 2 traits by ML and regression (IM)



Multiple trait analysis using logistic regression

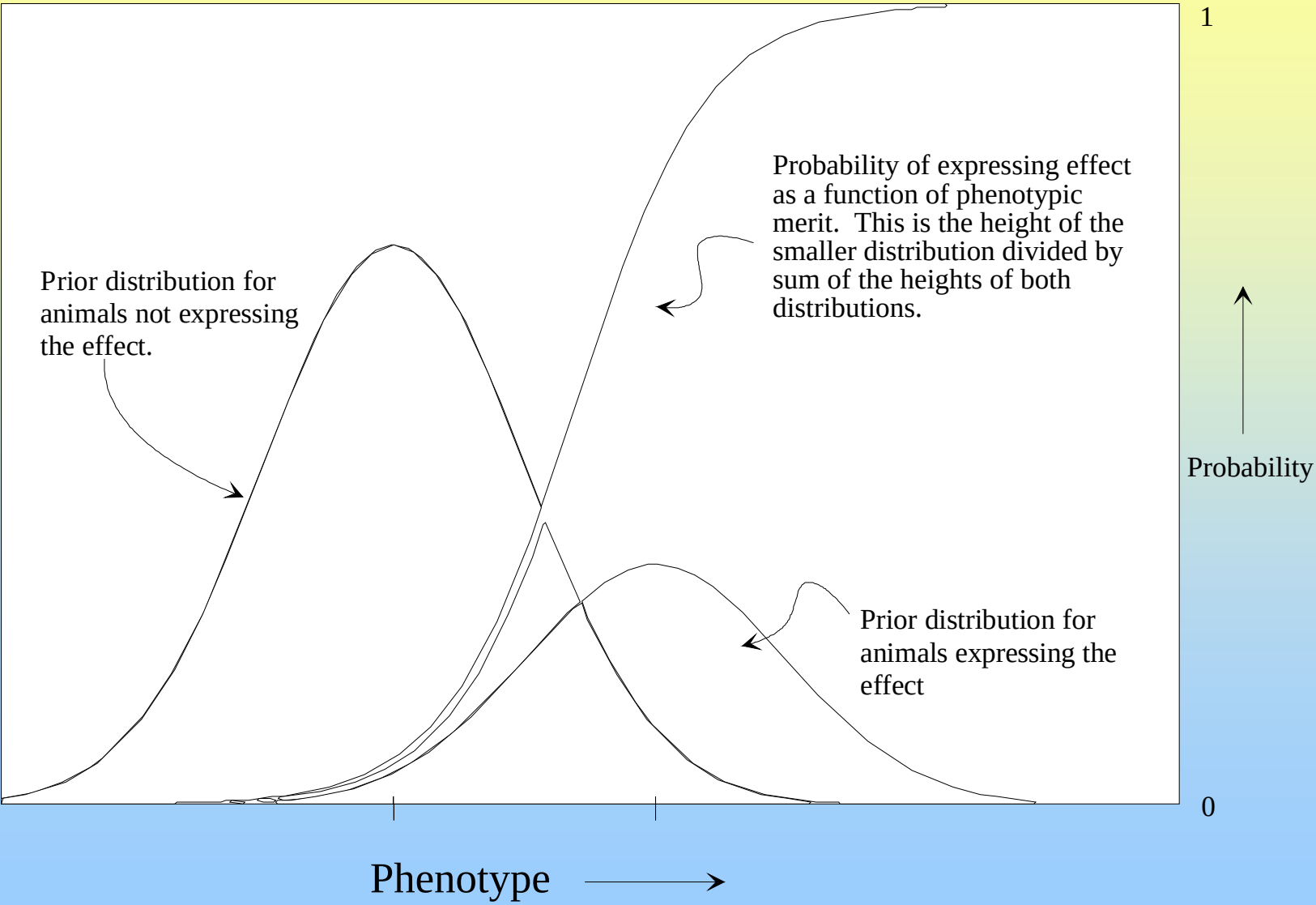
Henshall and Goddard, 1999

- Regress QTL genotype on phenotype rather than the other way around.

  Y = Phenotype + e Y- Binomial

  – Just as simple as regression but more ML properties
  – Method accounts for selection in phenotypes
    - (think of selective genotyping)

Regression method: Genotype probabilities ...



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