Comparison of Association Mapping Methods in Cattle Population

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Approaches to Mapping

1. Candidate gene studies
    - Association
    - Resequencing approaches

2. Genome-wide studies
    - Linkage analysis
    - Genome-wide association studies [Linkage disequilibrium (LD) mapping]

Association mapping

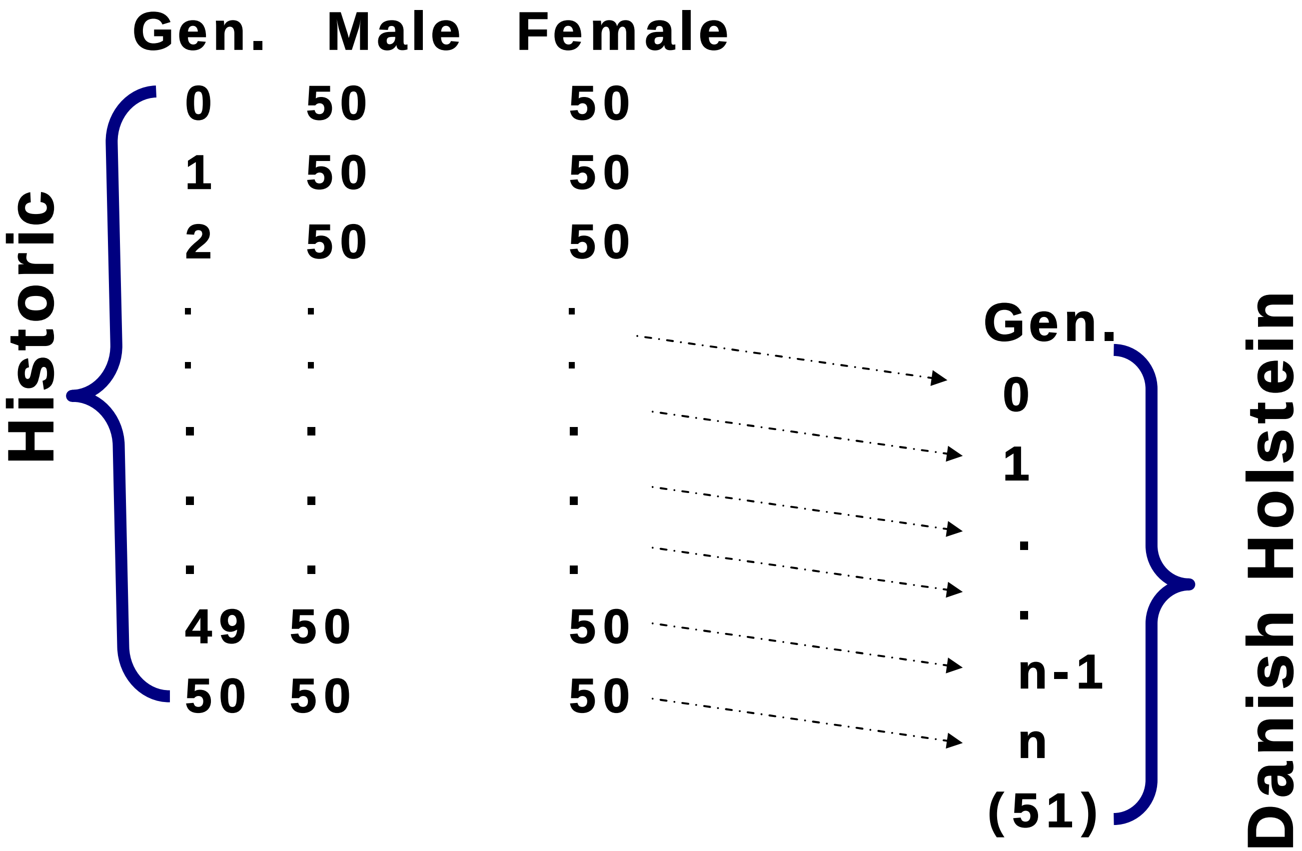
- Marker alleles are correlated with a trait on a population level
- Does not necessarily imply that markers are linked to (are close to) genes influencing the trait.
- Approaches
  - Case-control study
  - Family based methods

Limitation in cattle

- Complex pedigree
- Population structure
- Complex traits with very many genes individually of small effect
- Environmental influence
- Genetic heterogeneity underlying phenotype

Data Simulation

Generations and individuals



Historic

Gen.	Male	Female
0	50	50
1	50	50
2	50	50
.	.	.
.	.	.
.	.	.
.	.	.
.	.	.
49	50	50
50	50	50

Danish Holstein

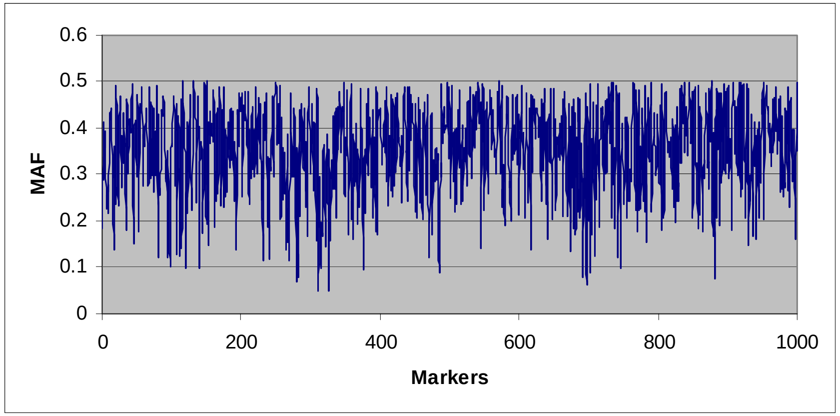
Gen.
0
1
.
.
n-1
n
(51)

Marker & QTL

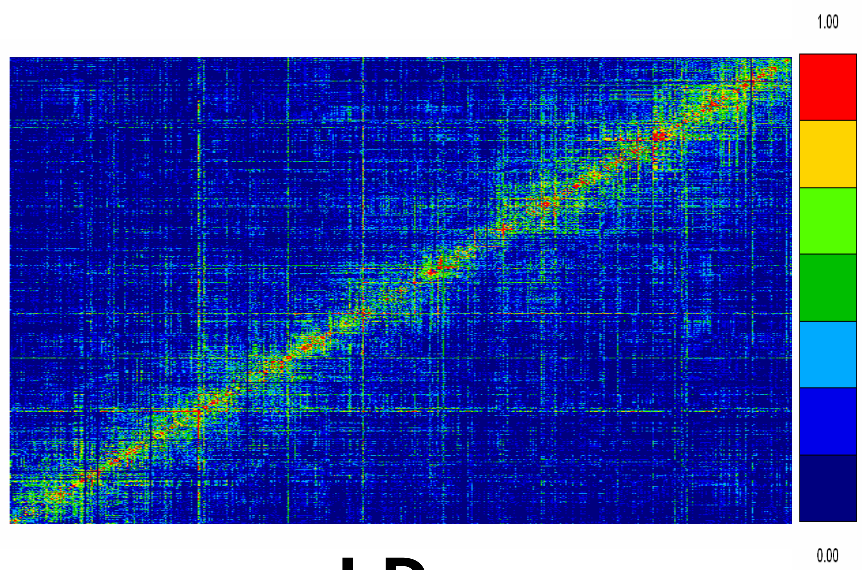
- 5 chromosomes 100 cM each
- 5000 biallelic markers
- 15 QTL with known position and effects
  - 1 QTL with 10%, 4 QTL with 5% and 10 QTL with 2% genetic variance
- Chromosome-5 had no QTL

Population evolves over 50 generations

- LD structure (drift, recombination)
- Allele frequencies change



MAF



LD

Phenotypes

- Heritability of the trait : 30%
- 50% genetic variance comes from 15 QTL, rest 50% was polygenic
- Breeding values were simulated assuming 100 daughters per sire
- 2000 individuals were selected randomly from 136 families
- 25 replications

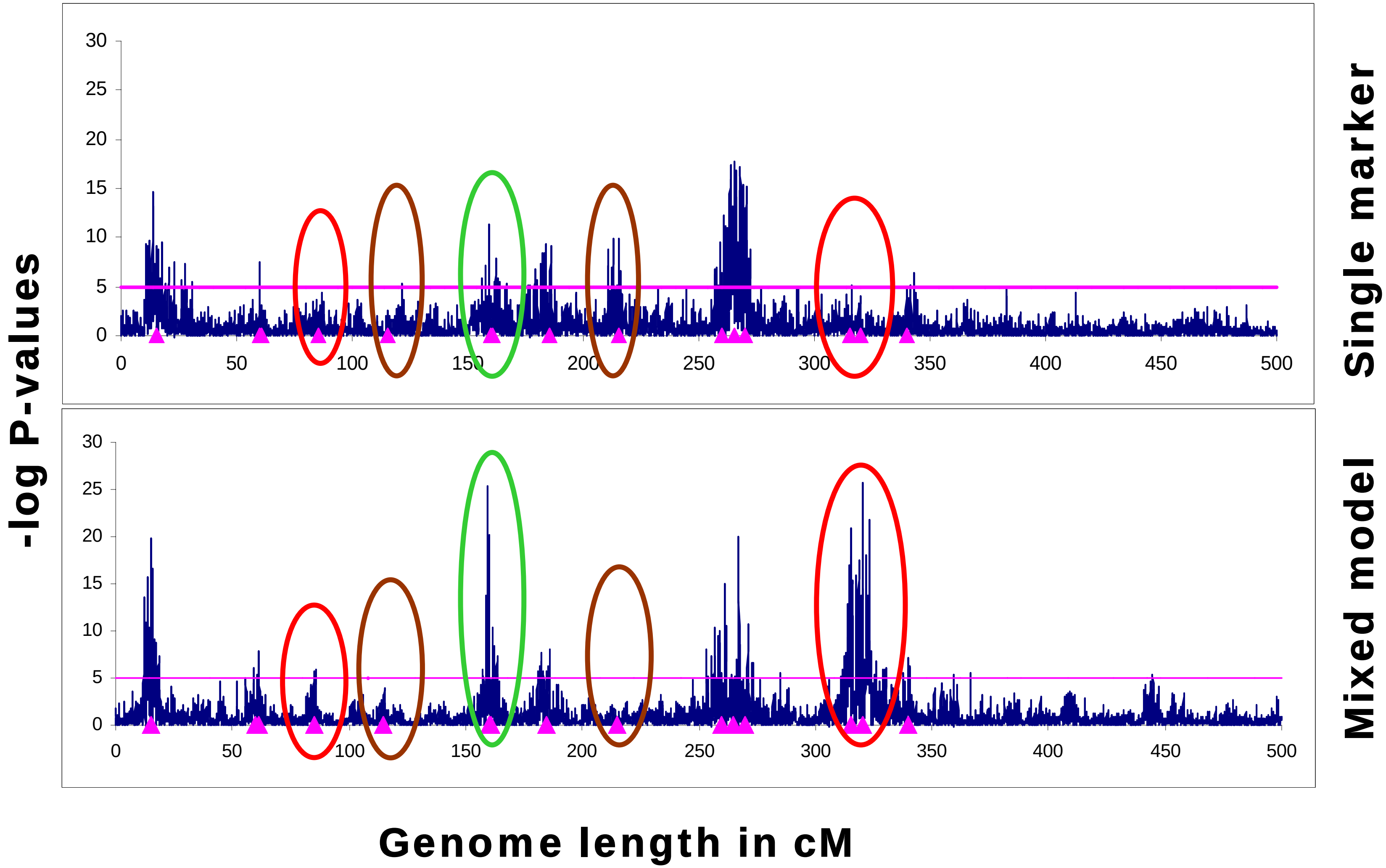
Association Analysis

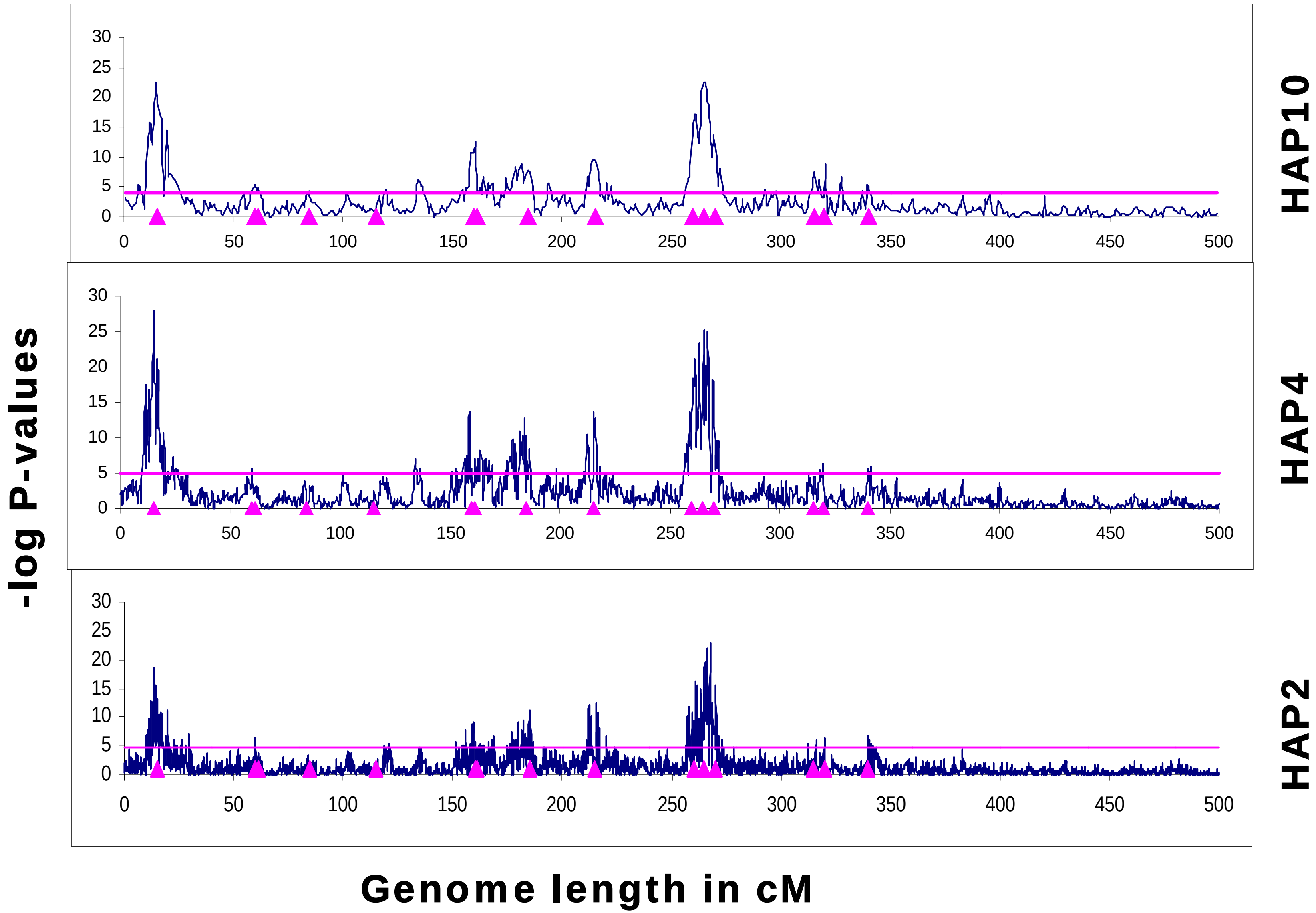
Methods

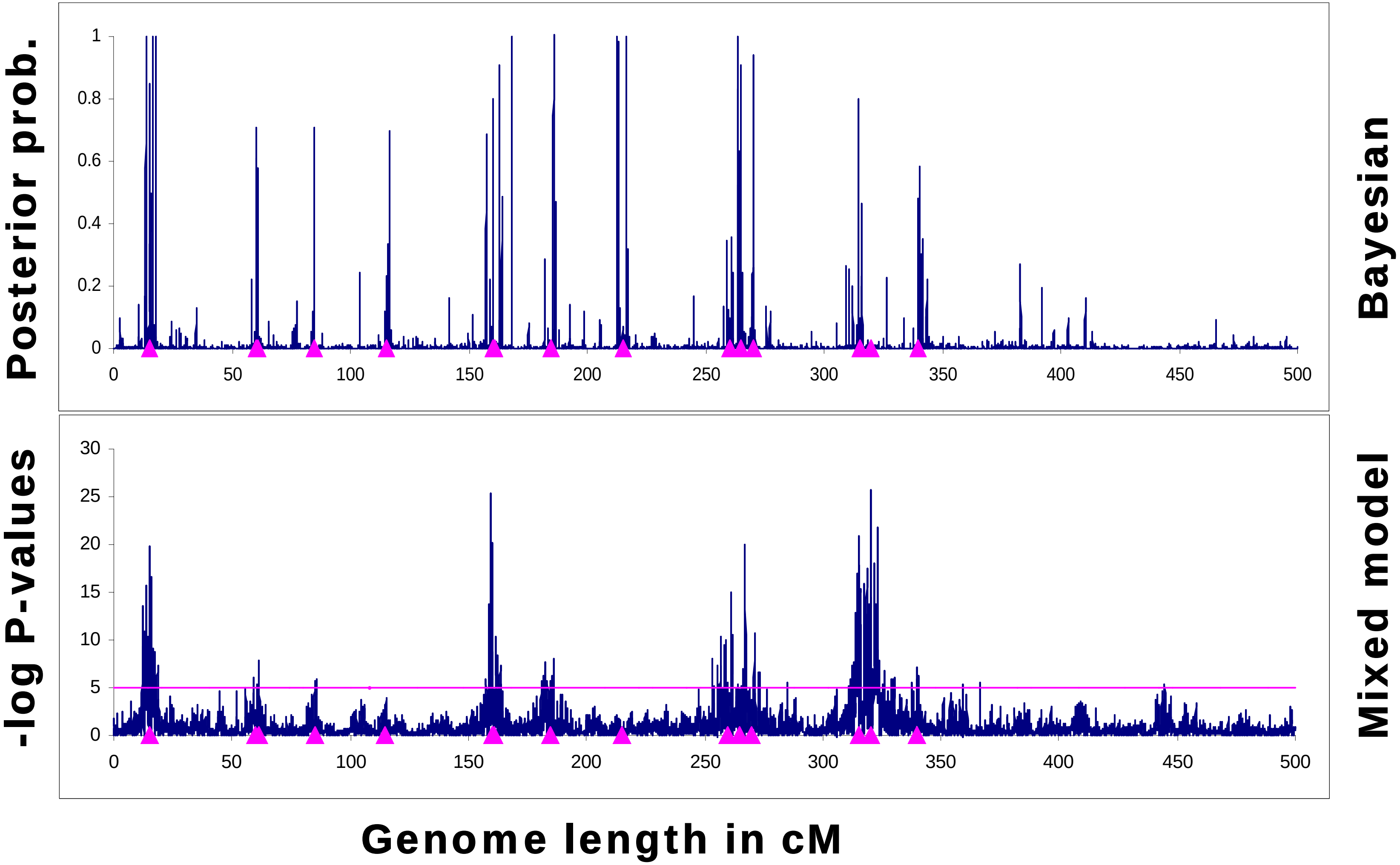
- Linear models (*TASSEL/R*)
  - Phenotype = Sire + genotype/haplotype

- Mixed model (*DMU*)
  - Phenotype= Fixed factors + polygene + SNP

- Bayesian approach (*iBays*)
  - Phenotype= Fixed factors + Polygene + ΣSNP

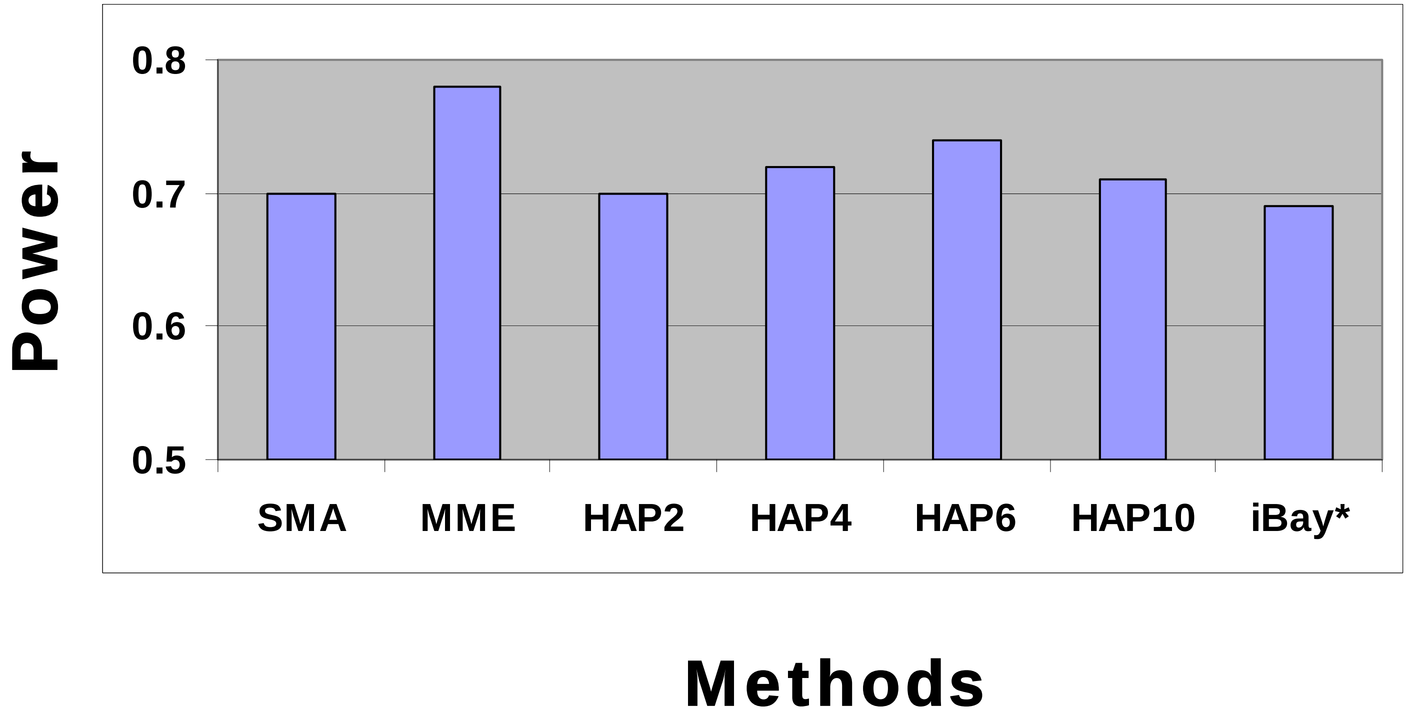

-log P-values
Single marker
Mixed model
Genome length in cM
30
25
20
15
10
5
0
0
50
100
150
200
250
300
350
400
450
500


-log P-values
HAP10
30
25
20
15
10
5
0
0
50
100
150
200
250
300
350
400
450
500
HAP4
30
25
20
15
10
5
0
0
50
100
150
200
250
300
350
400
450
500
HAP2
30
25
20
15
10
5
0
0
50
100
150
200
250
300
350
400
450
500
Genome length in cM


Posterior prob.
1
0.8
0.6
0.4
0.2
0
0
50
100
150
200
250
300
350
400
450
500
Bayesian
-log P-values
30
25
20
15
10
5
0
0
50
100
150
200
250
300
350
400
450
500
Mixed model
Genome length in cM

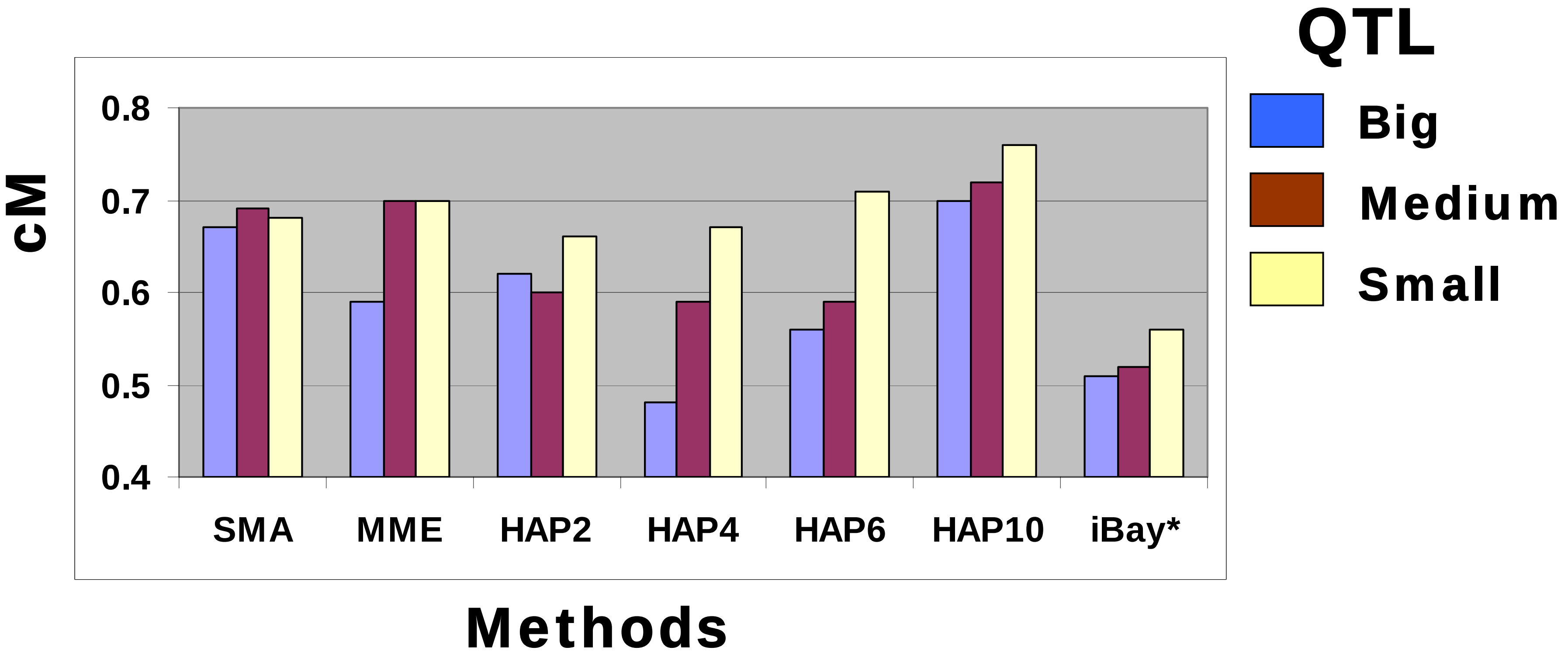
Power (QTL with 2% genetic variance)

A QTL was identified if a markers within 2cM region of the QTL location was significant



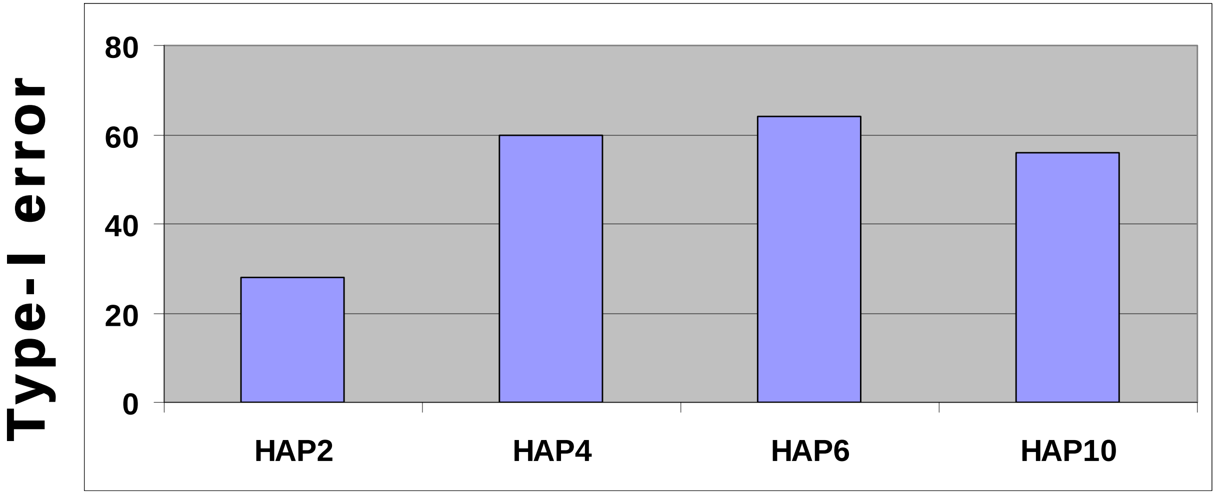
Mean error of QTL position

Precision was quantified as mean absolute error of position estimate



False Positives

- Single marker analysis and mixed model approach had type-I rate within expected limit
- Haplotype methods had very high Type-I error



Conclusions

- Mixed model approach had highest power in association mapping for QTL
- In general, Bayesian approach gave more precise location estimate
- The magnitude of QTL effect had little impact on precision
- Haplotype based methods had very high false positive rates