Bayesian Quantitative Trait Loci Mapping

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What?

Quantitative Trait Loci (QTL) Mapping

What?

Quantitative Trait Loci (QTL) Mapping

QT
y_1
y_2
y_3
y_4
y_5
y_6
y_7
y_8
y_9
y_{10}

- Quantitative Traits *e.g.* Blood pressure, BMI, FatMass, complex diseases (Alzhiemers) etc.

What?

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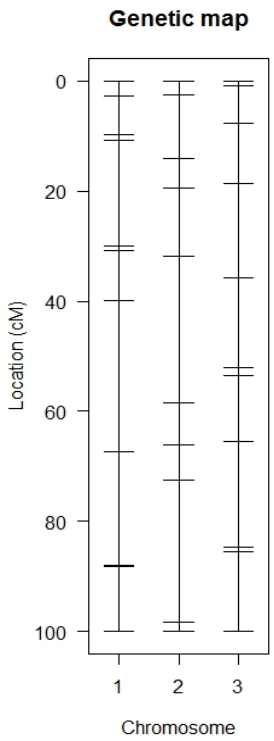
L



- Loci → Genomic positions influencing the traits

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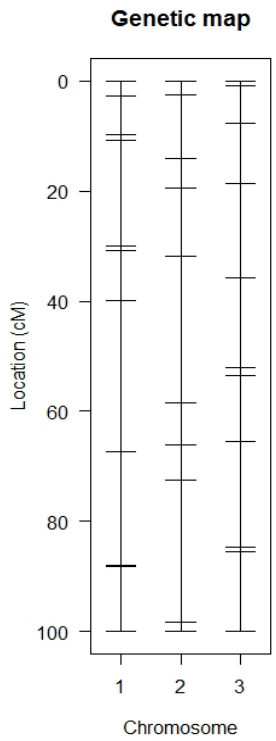
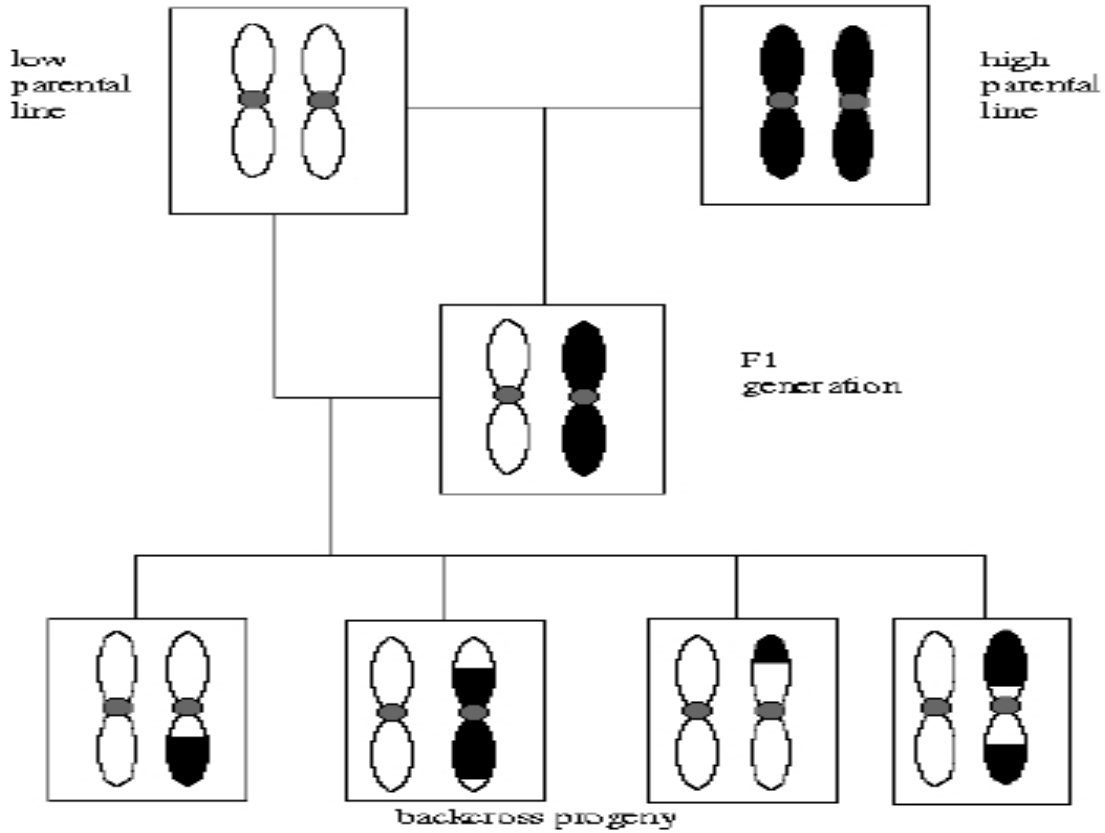


Mapping

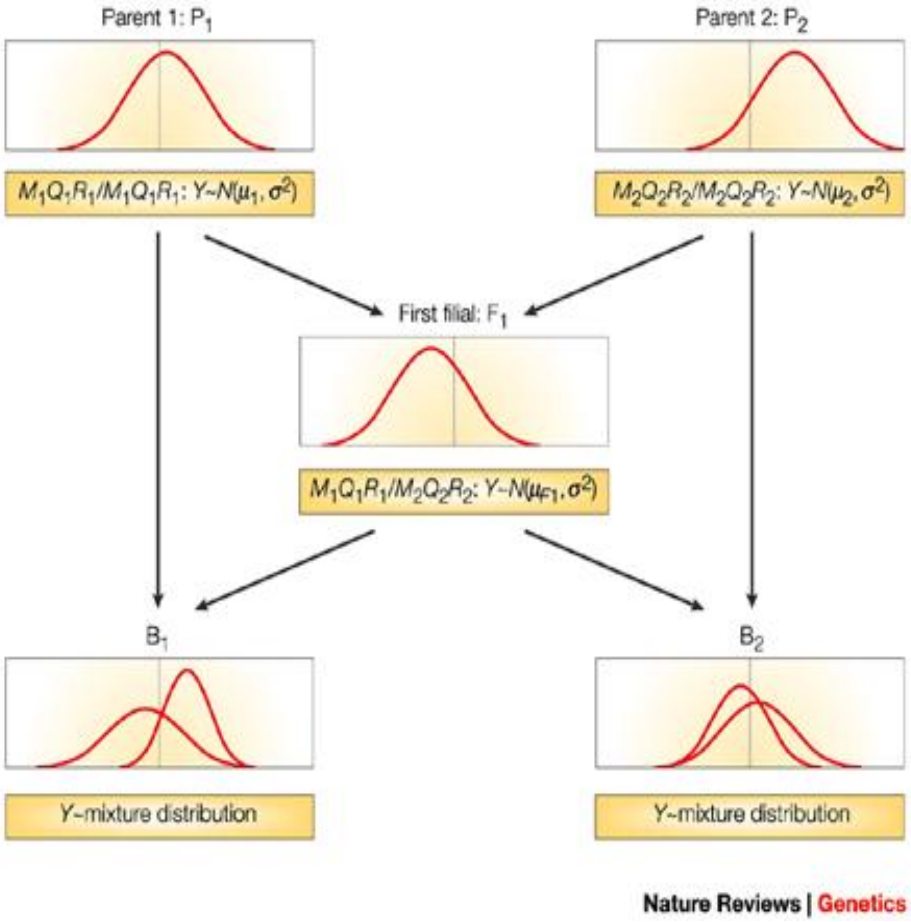
- Information from Quantitative traits combined with genetic information
- Try to map the positions of the genome influencing the traits

Genetic Design (Backcross Experiment)



- Broman, 1997

Backcross Experiment



Data

y_1	C1M1	C1M2	C2M1	C2M2	C15M2	C16M1	C19M1
8.8	AA	AA	AB	AA	AA	AB	AB
9.6	AA	AA	AB	AB	AB	AB	AB
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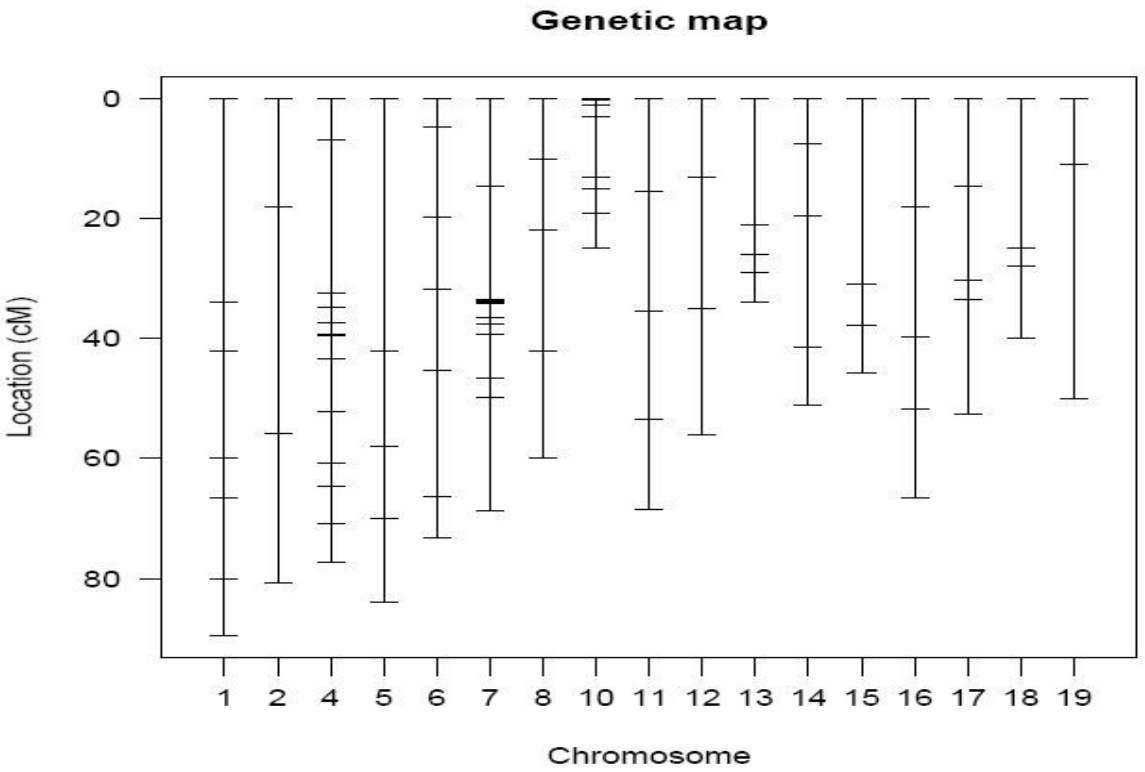

Genetic Model

Cockerham's Genetic Model

F_2

$$x^{add} = \begin{cases} 1 & \text{if AA} \\ 0 & \text{if Aa} \\ -1 & \text{if aa} \end{cases} \qquad x^{dom} = \begin{cases} 1/2 & \text{if Aa} \\ -1/2 & o.w \end{cases}$$

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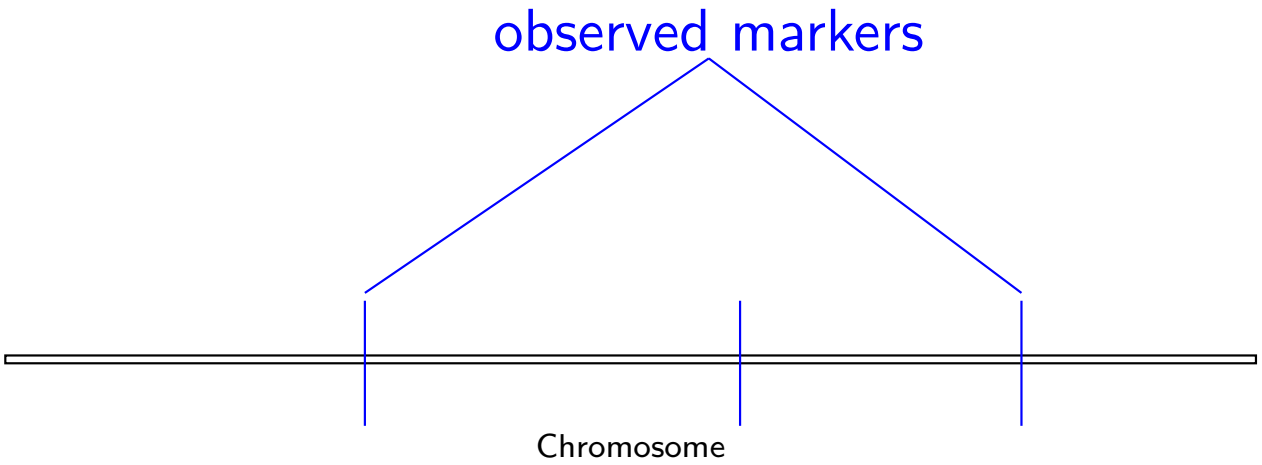
Advantages

- Orthogonal contrasts
- Can test non-nested models

Idea of Interval Mapping



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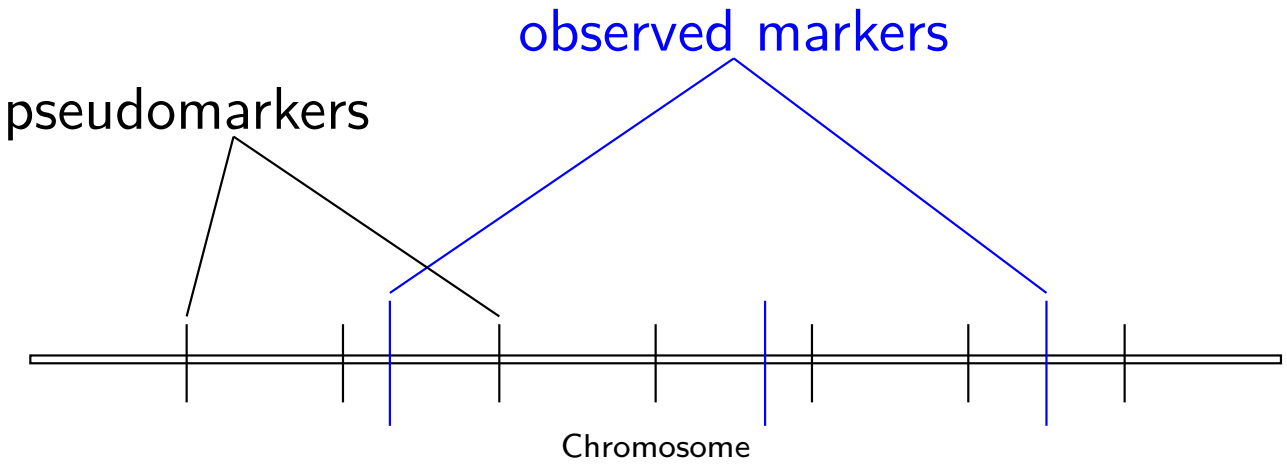

- Insert arbitrary positions (pseudomarkers) into marker intervals

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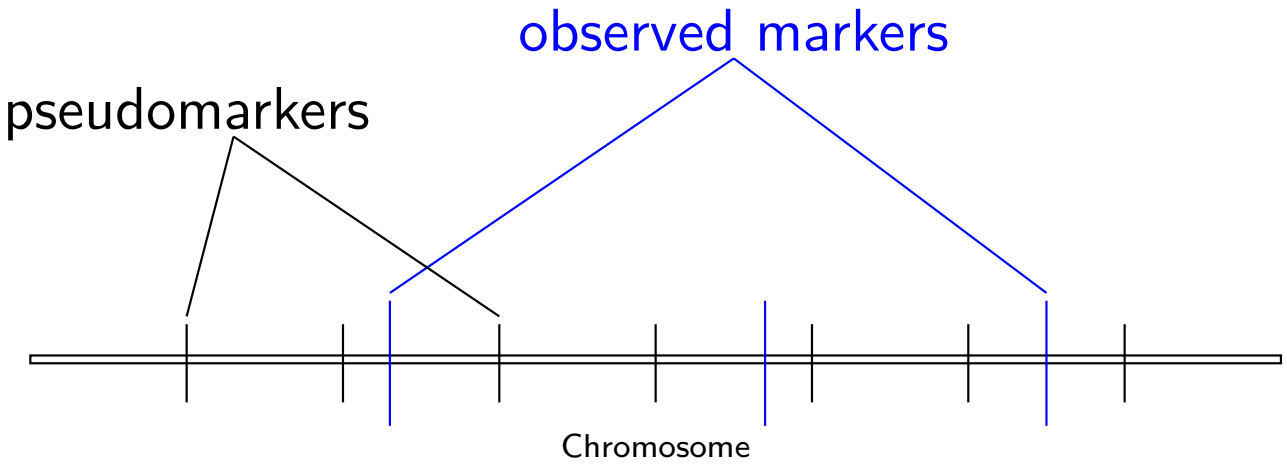

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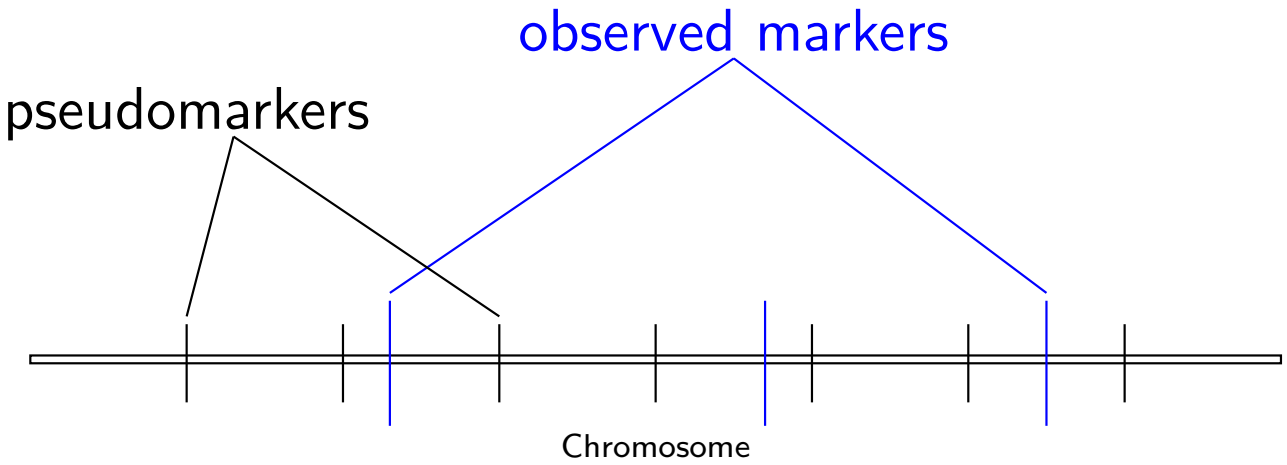

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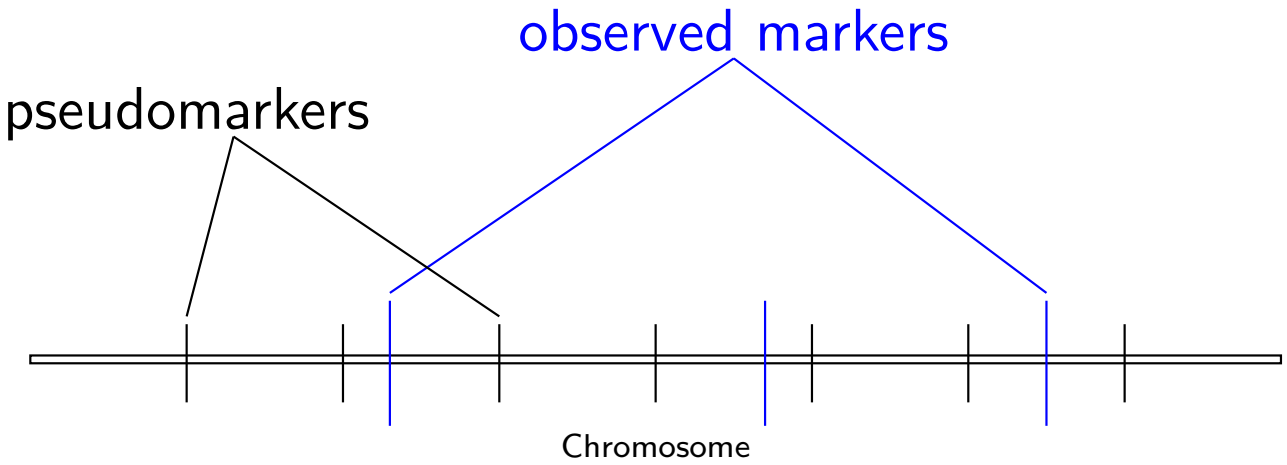

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- Enables us to detect QTL within marker intervals
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- Pseudomarkers not observed – Hidden Markov Model to reconstruct genotypes

Challenges in QTL Mapping

Complex Traits

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- interacting network of multiple genes and environmental factors

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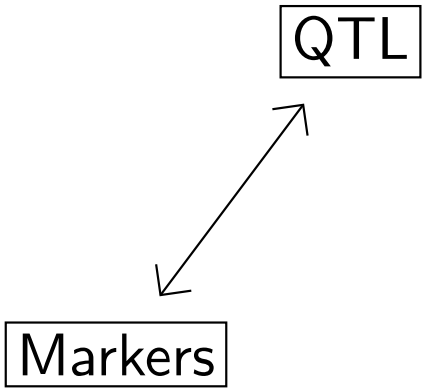
- For a BC (backcross) population with 40 genetic markers
- $2^{40} = 10^{12} = 1,000,000,000,000$ models

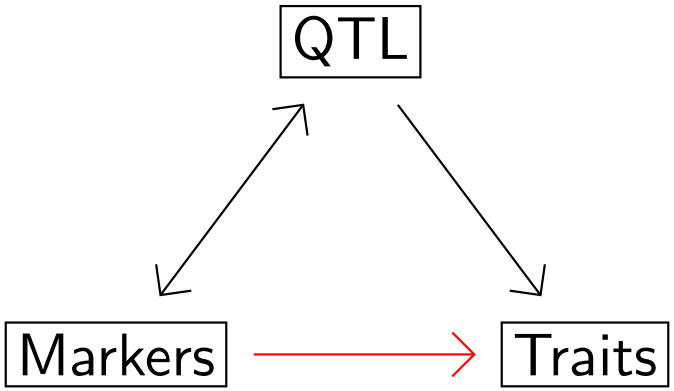
Statistical structure



Two aspects of the QTL mapping problem

1. The missing data problem: Markers $\leftrightarrow$ QTL

Statistical structure



Two aspects of the QTL mapping problem

1. The missing data problem: Markers $\leftrightarrow$ QTL
2. The model selection problem: QTL $\rightarrow$ Traits

Classical QTL Mapping Methods

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  - high dimensional system viewed from margins
  - marginal subsystem tells us very little about the full system

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- EM or least squares to analyze

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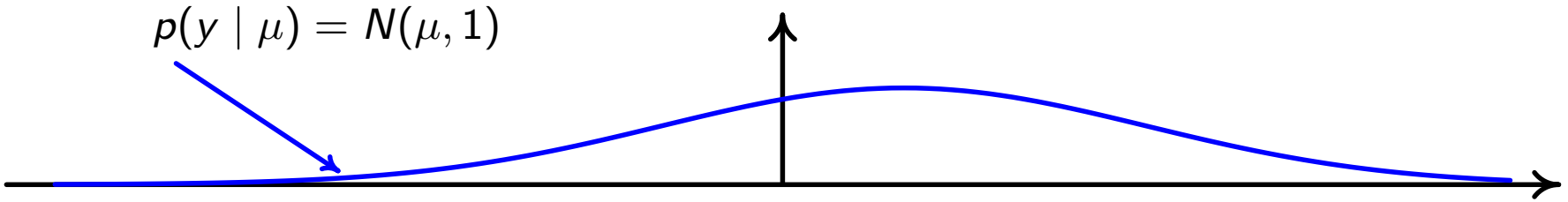
  - model uncertainty ignored
  - many competing models equally fit data
- lot of judgement involved in the process

Bayesian Idea



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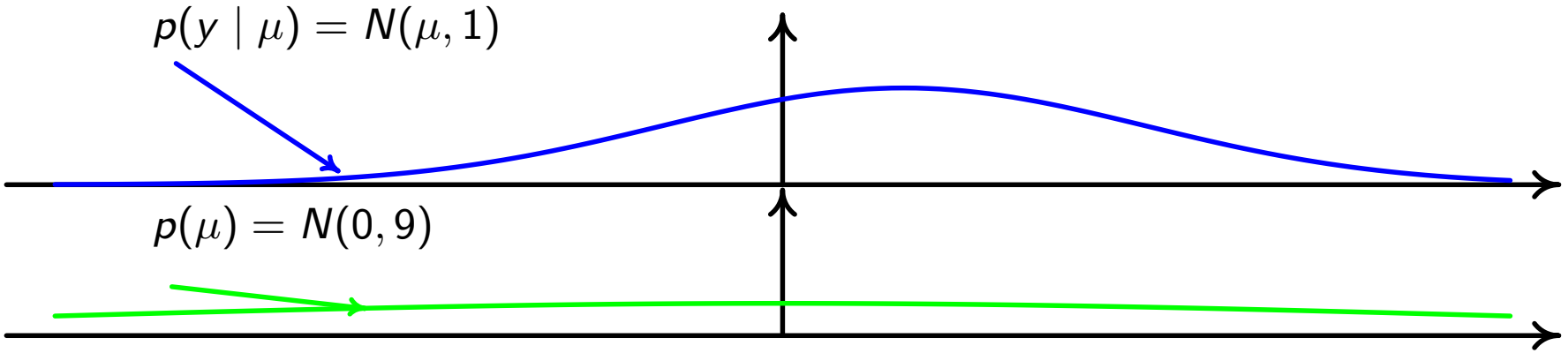

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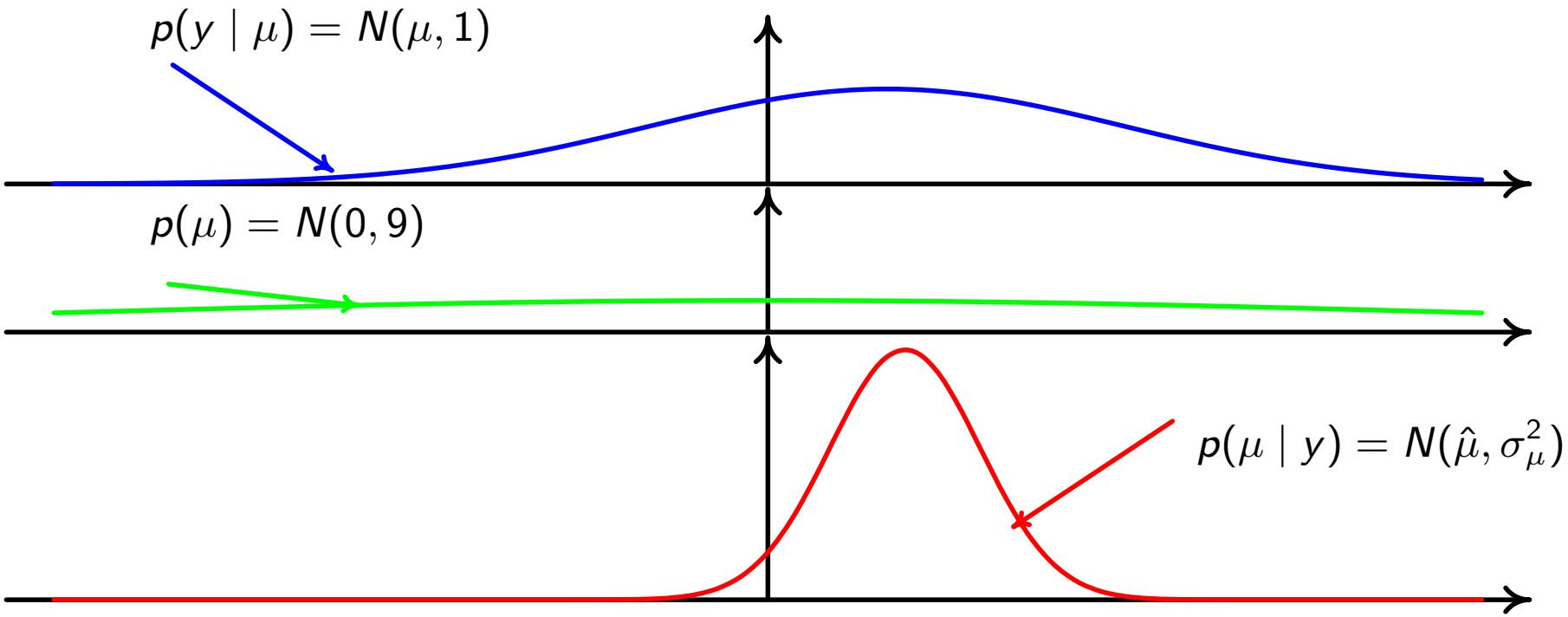

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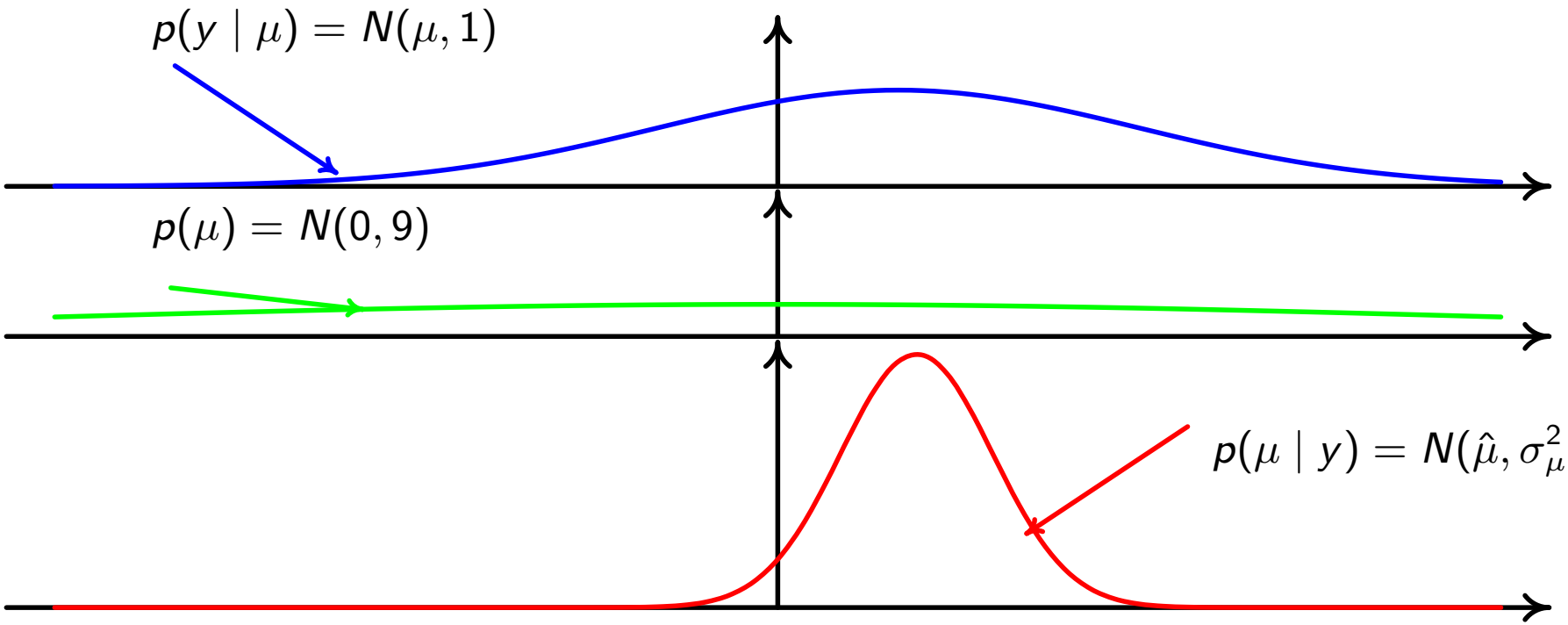
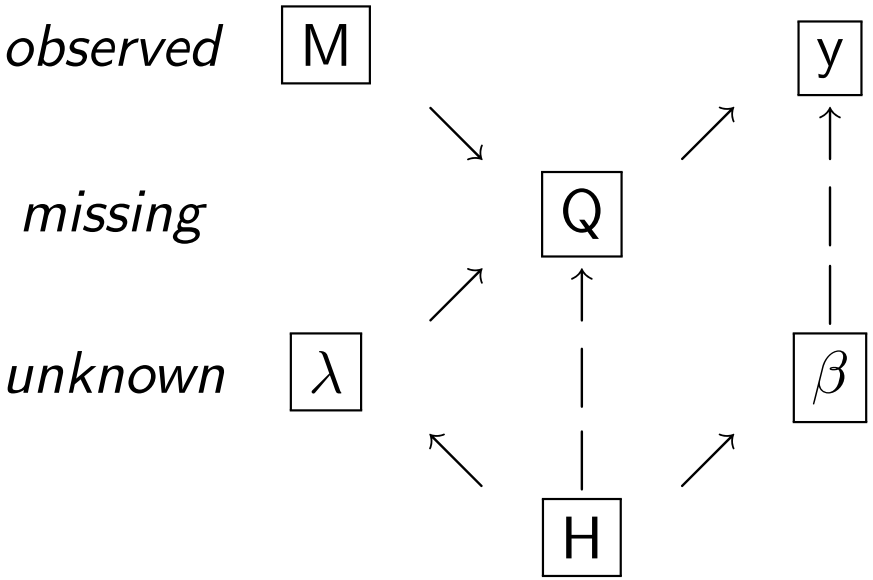


Bayes Theorem

$$P(B_1 \mid A) = \frac{P(A \mid B_1)P(B_1)}{P(A \mid B_1)P(B_1) + P(A \mid B_2)P(B_2)}$$

Bayesian Interval Mapping Framework



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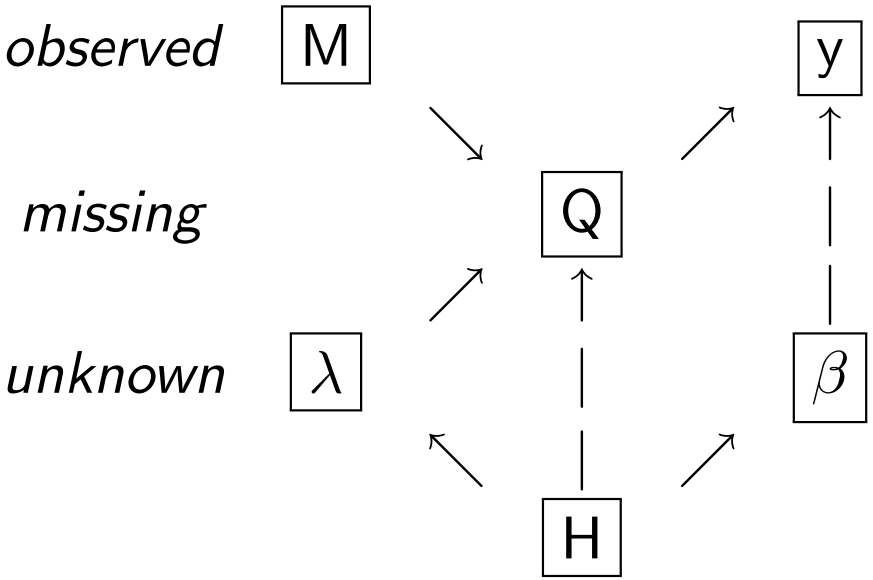

- Observed: y (traits) and M (marker and linkage map)

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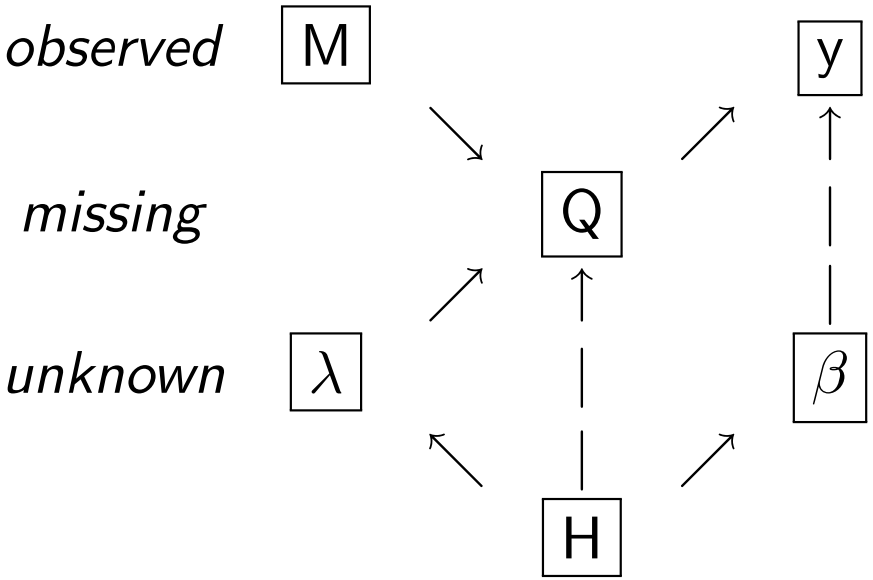

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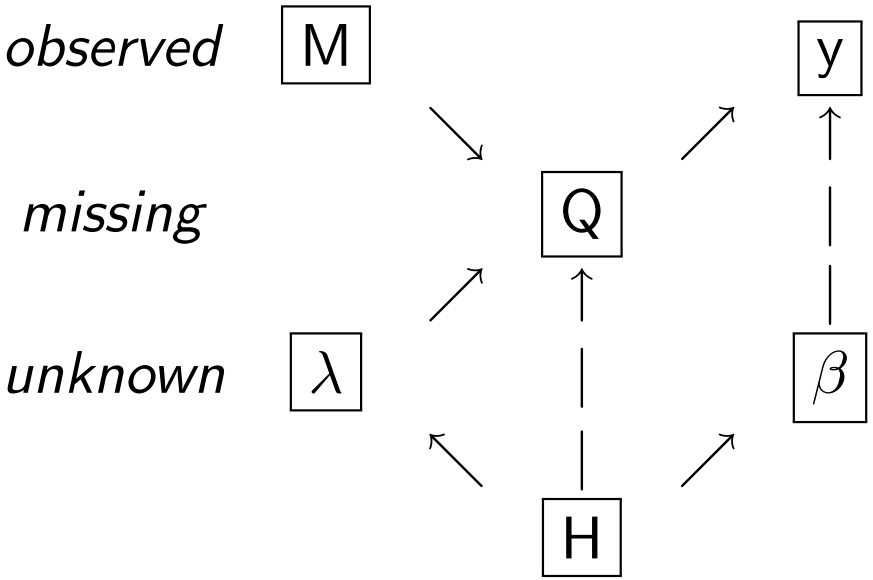

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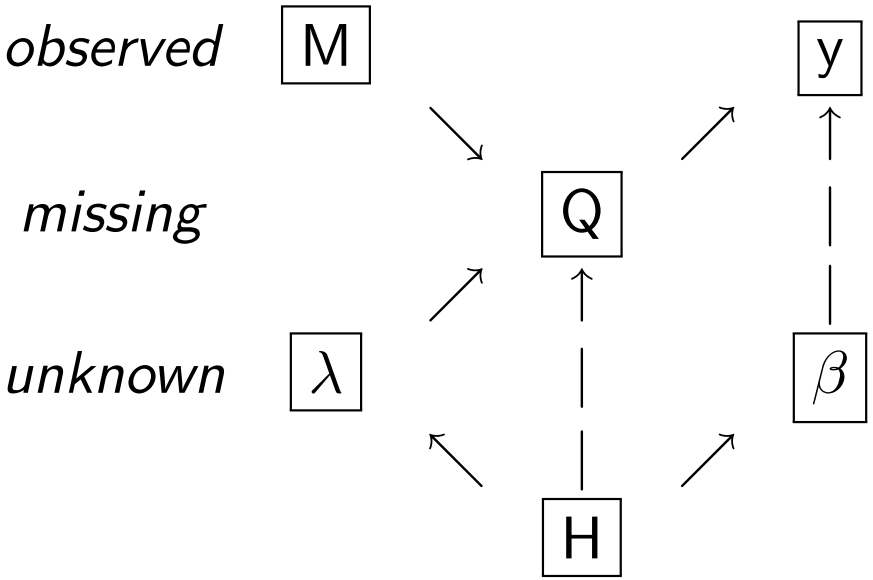

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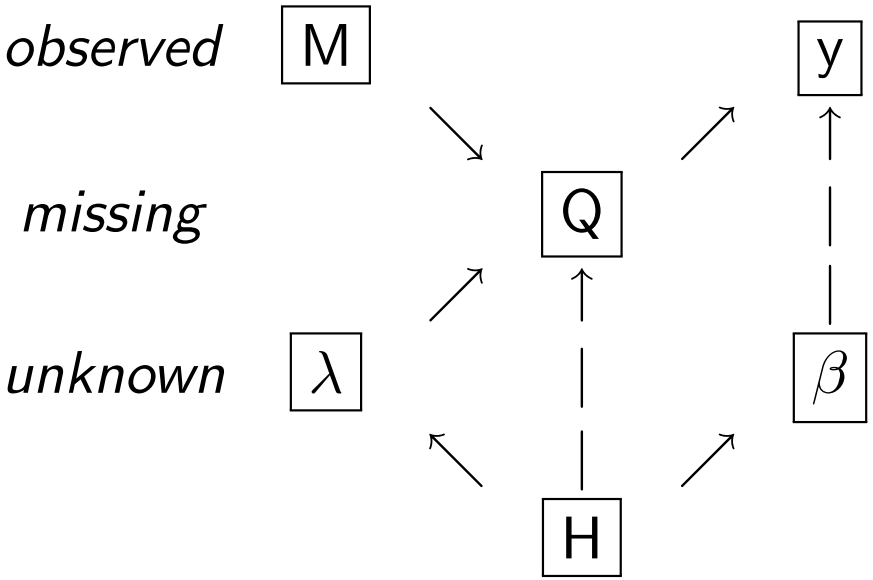

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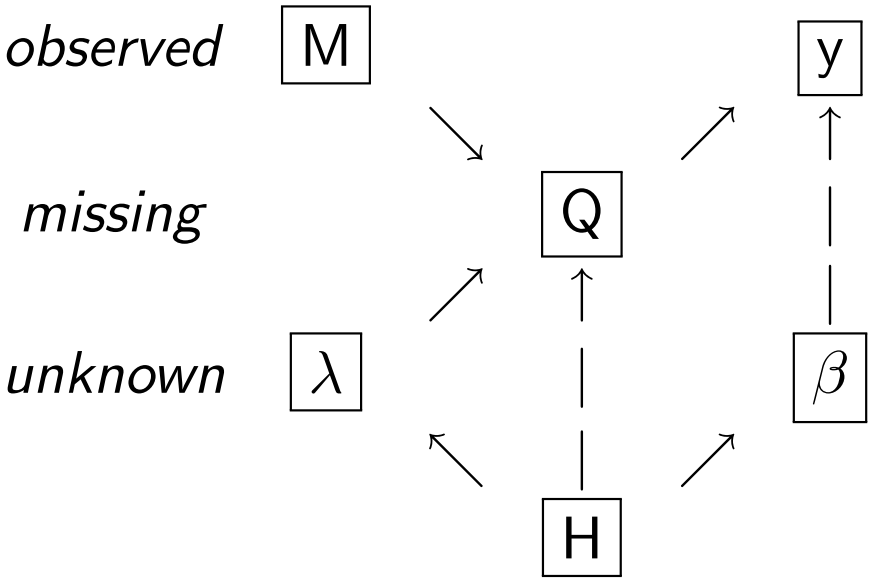

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posterior = likelihood × prior

$$p(\lambda, \beta, H, Q \mid y, M) \propto p(y \mid \beta, \lambda, Q, H) p(Q \mid M, \lambda, H) p(\beta, \lambda, H)$$

Advantages of a Bayesian approach

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- Easily extensible to a wide range of problems, *e.g* analyzing ordinal traits using the threshold model.
- Problem: A full Bayesian analysis can be computationally intensive and hence slow.

Bayesian QTL Mapping for Multiple Traits

Samprit Banerjee and Nengjun Yi

Dept. of Biostatistics
University of Alabama, Birmingham

Why Multiple Traits?

y_1	y_2	C1M1	C1M2	C2M1	C2M2	C15M2	C16M1	C19M1
8.8	7.8	AA	AA	AB	AA	AA	AB	AB
9.6	10.1	AA	AA	AB	AB	AB	AB	AB
10.6	9.9	AB	AB	AA	AA	AB	AA	AA
11.1	10.9	AB	AB	AA	AB	AB	AA	AA

- Typically data on more than one phenotype (correlated) are collected *e.g.* BMI, fatmass etc.

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  - pleiotropy
    - one gene, affecting both traits indicating common biochemical pathways
  - close linkage
    - two tightly linked genes resulting in collinear genotypes

Multivariate Model

We wish to investigate the performance of two multivariate models.

1. Traditional Multivariate Model - for a simple case of two traits and two QTL:

$$Y_1 = \beta_{11} Q_1 + \beta_{21} Q_2 + \epsilon$$
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Composite Model Space Approach

Markers	C1M1	C1M2	C2M1	C2M2	C15M2	C16M1	C19M1
γ_{y_1}	0	0	1	0	0	1	1
γ_{y_2}	0	0	1	0	1	0	0

- Assign indicators Γ to the putative loci

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- Impose a constraint on the number of detectable QTL (say L)
  - reduces the search space drastically
  - efficient way to walk through the space of models, spending more time on "good" models
- Remarkable feature achieved by augmenting the variable dimension space $(\Gamma, \lambda_\Gamma, \beta_\Gamma)$ to the fixed dimension model (Γ, λ, β)

Seemingly Unrelated Regression (SUR) Model

We consider two different SUR model

1. Modeling different loci for all traits (SURd)

	QTL_1	QTL_2	QTL_3	QTL_4
λ_{y_1}	λ_{11}	λ_{12}	λ_{13}	λ_{14}
λ_{y_2}	λ_{21}	λ_{22}	λ_{23}	λ_{24}
γ_{y_1}	0	1	1	0
γ_{y_2}	1	0	1	0

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λ_{y_2}	λ_1	λ_2	λ_3	λ_4
γ_{y_1}	0	1	1	0
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Choice of Priors

Prior on β

- batches k=add,dom,add-add interaction etc.
- $\beta_k \sim \mathcal{N}(0, \sigma_k^2)$ and $\sigma_k^2 \sim Inv - \chi^2(\nu_k, s_k^2)$
- s_k^2 controls the prior heritability per effect $s_k^2 = (\nu_k - 2)E(h_j)V_p/(\nu_k V_j)$

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Prior on number of QTL (ℓ)

- $\ell \sim Poission(\ell_0)$
- Choice of $L = \ell_0 + 3\sqrt{\ell_0}$

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- independent priors on QTL positions and indicators

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Prior on Σ_ϵ^{-1}

- $p(\Sigma_\epsilon) \propto |\Sigma_\epsilon|^{-\frac{M+1}{2}}$

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- independent priors on QTL positions and indicators

MCMC Idea

Marginal Posterior

$$p(\beta_1 \mid y) = \int_{\beta_2} \dots \int_{\beta_J} \int_{\mu} \int_{\sigma} \int_{\Sigma_\epsilon^{-1}} \int_{g} p(\beta, \mu, \sigma, \Sigma_\epsilon^{-1}, g, \lambda, \mid y) d\beta_2 \dots d\beta_J d\mu d\sigma d\Sigma_\epsilon^{-1} dg$$

- Ugly posterior: analytical calculations not possible

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- Ugly posterior: analytical calculations not possible
- Direct sampling from posterior not possible
- Construct a Markov chain, $\{X_i\}_{i=0}^{\infty}$ so that $lim_i P(X_i = x) = \pi(x)$
- Generate Monte carlo samples to approximate the posterior.

MCMC

- Draw $\beta_j|\beta_{-j} \sim \mathcal{N}(\beta_j^*, \sigma^2_{\beta_j})$

MCMC

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  2. QTL currently not in the model

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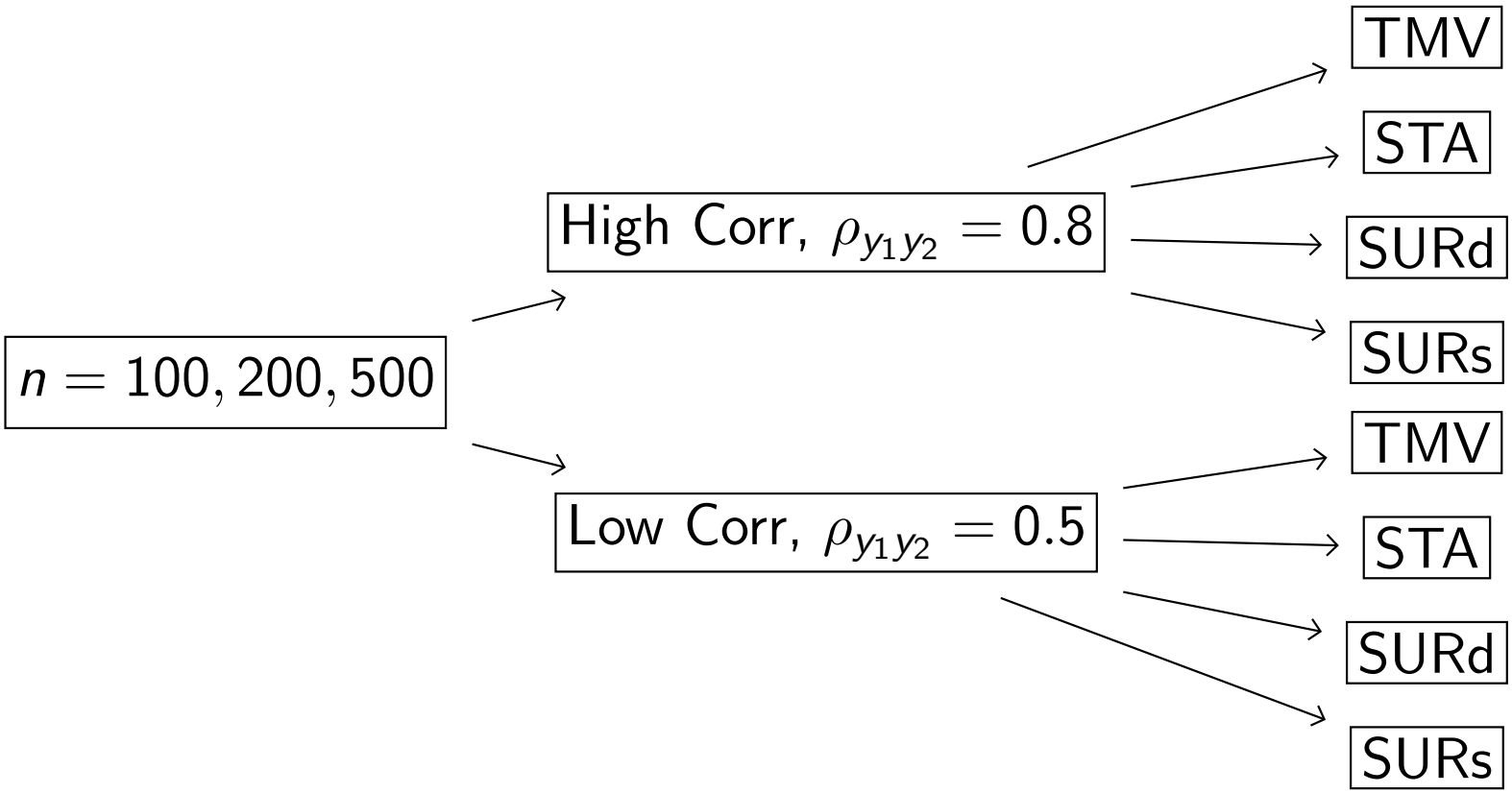
- Update locations λ fine tune in the nearby region
- Update indicators γ
  1. QTL currently in the model
     - position and genotypes already generated in the preceding step
  2. QTL currently not in the model
     - generate new QTL from its prior distribution and generate genotypes for all individuals

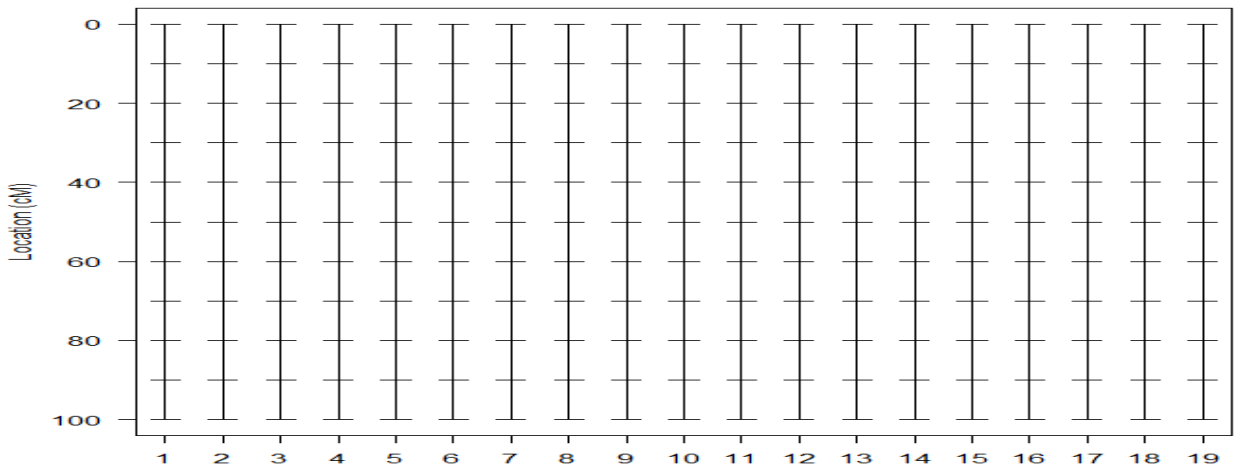
R/qtlbim

Our method has been (and is being) implemented in R/qtlbim (**B**ayesian **I**nterval **M**apping for **QTL**)

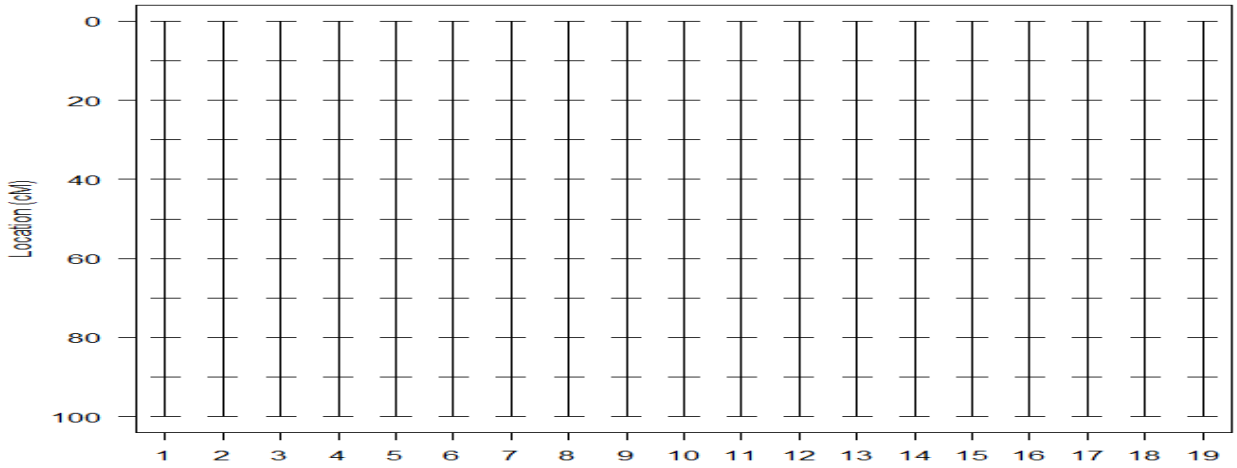
- add-on package for R, freely available, distributable and extensible.
- computationally intensive algorithms written in C while graphics in R and built on top of R/qtl (Broman)
- Collaboration of Dr. Nengjun Yi (UAB) and Dr. Brian Yandell (UW-Madison)
  - Tapan Mehta, Ramprasad Venkataraman, Daniel Shriner and Samprit Banerjee (UAB)
  - Jee Young Moon, William Whipple Neely (UW-Madison)
  - NIH R01 grant (PI: Yi)
  - Released through CRAN in Sept. 2006
- Website: http://www.qtlbim.org/.


$n = 100, 200, 500$
High Corr, $\rho_{y_1 y_2} = 0.8$
Low Corr, $\rho_{y_1 y_2} = 0.5$
TMV
STA
SURd
SURs
TMV
STA
SURd
SURs

Simulation Design



Simulation Design



	Q_1	Q_2	Q_3	Q_4	Q_5	Q_6
Chr	1	1	2	2	3	4
Pos(cM)	22	55	22	65	65	45
y_1	0.8	0.6	0	0	0.8	0.6
y_2	0	0	-0.8	-0.6	0.8	0.6
y_1	8.8%	4.9%	0	0	8.8%	4.9%
y_2	0	0	9.3%	5.2%	9.3%	5.2%

	Q_1	Q_2	Q_3	Q_4	Q_5	Q_6
Chr	1	1	2	2	3	4
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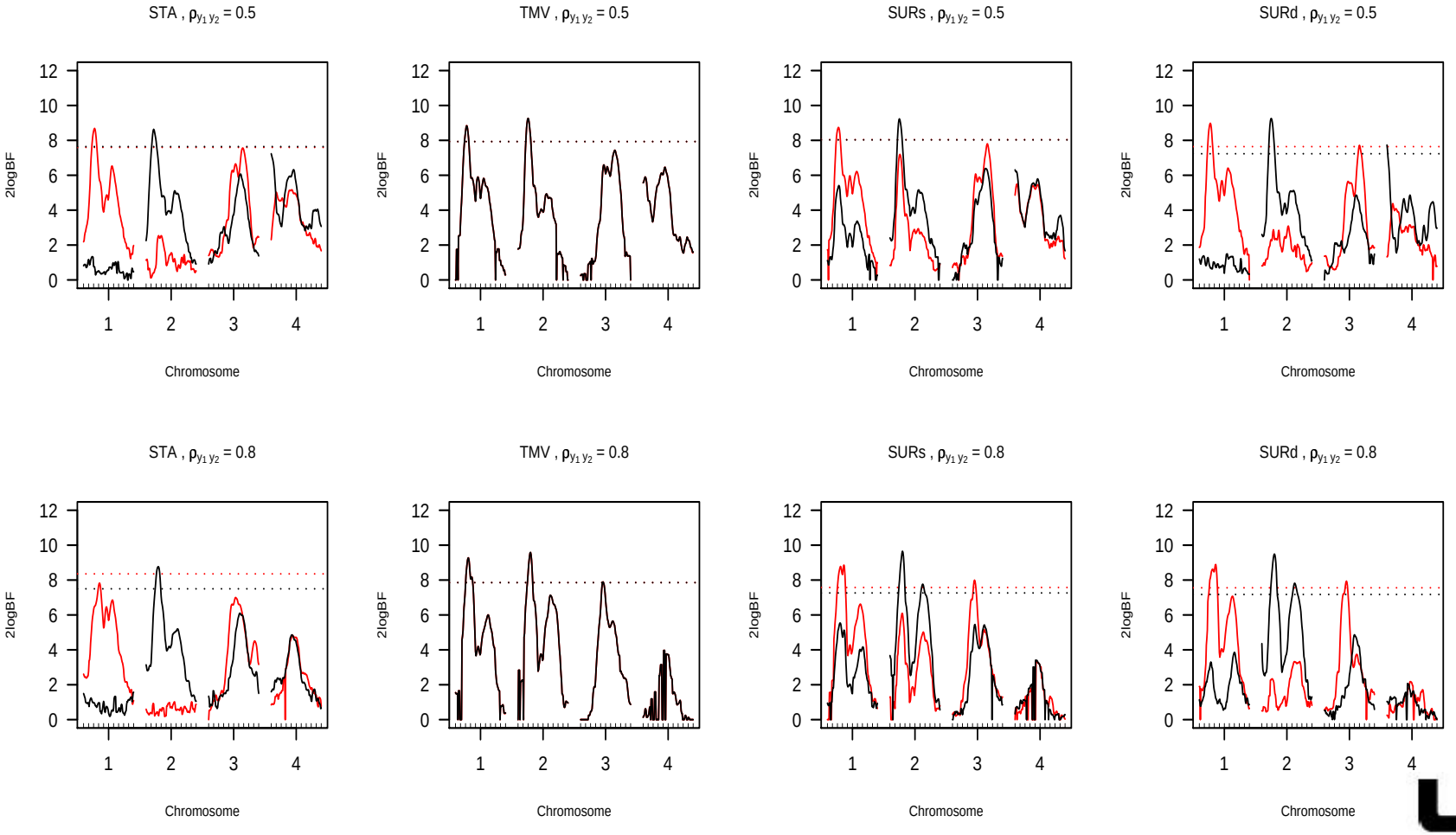
$N = 100$
$\longrightarrow$ Y_1
$\longrightarrow$ Y_2



	Q_1	Q_2	Q_3	Q_4	Q_5	Q_6
Chr	1	1	2	2	3	4
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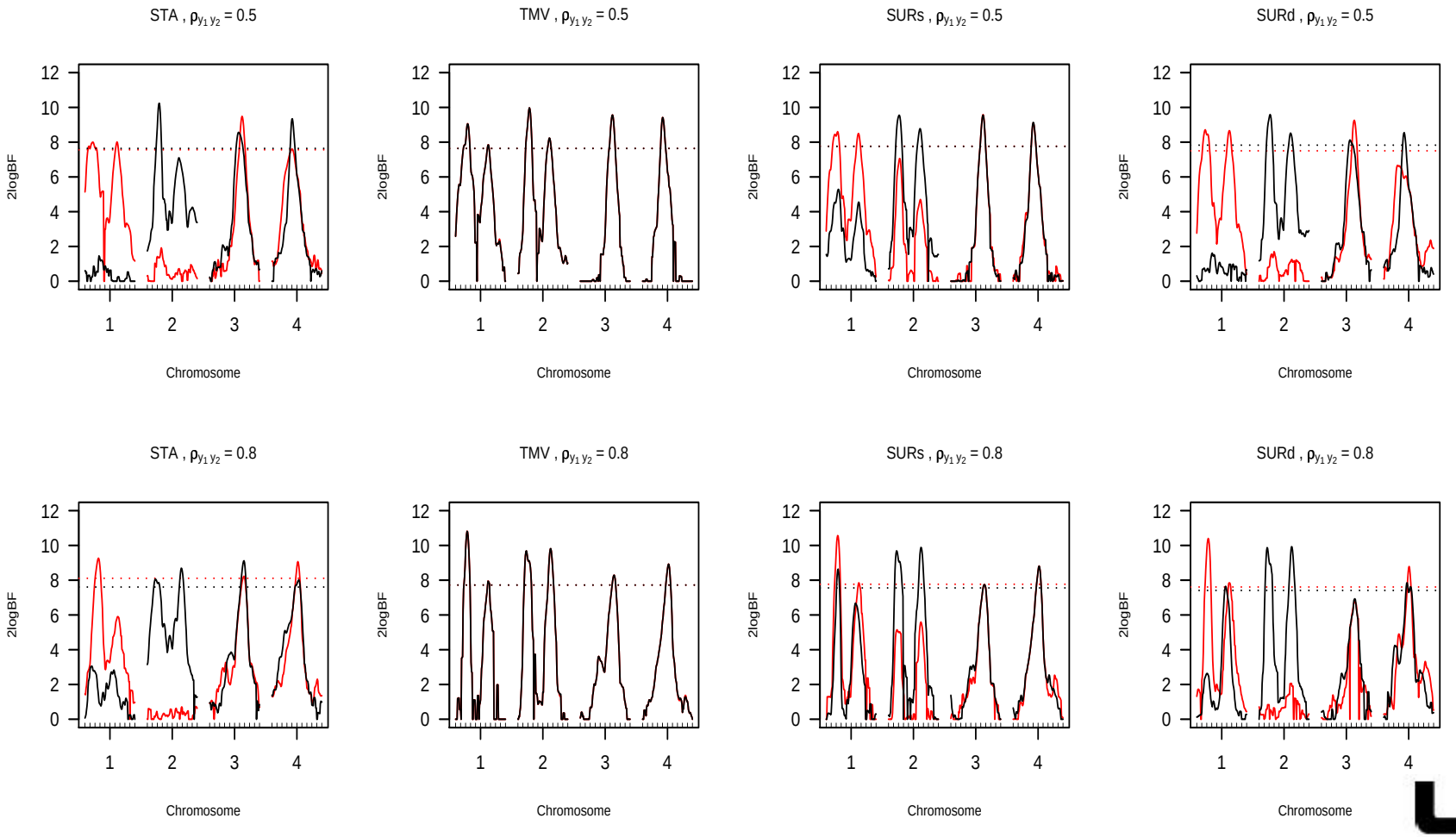
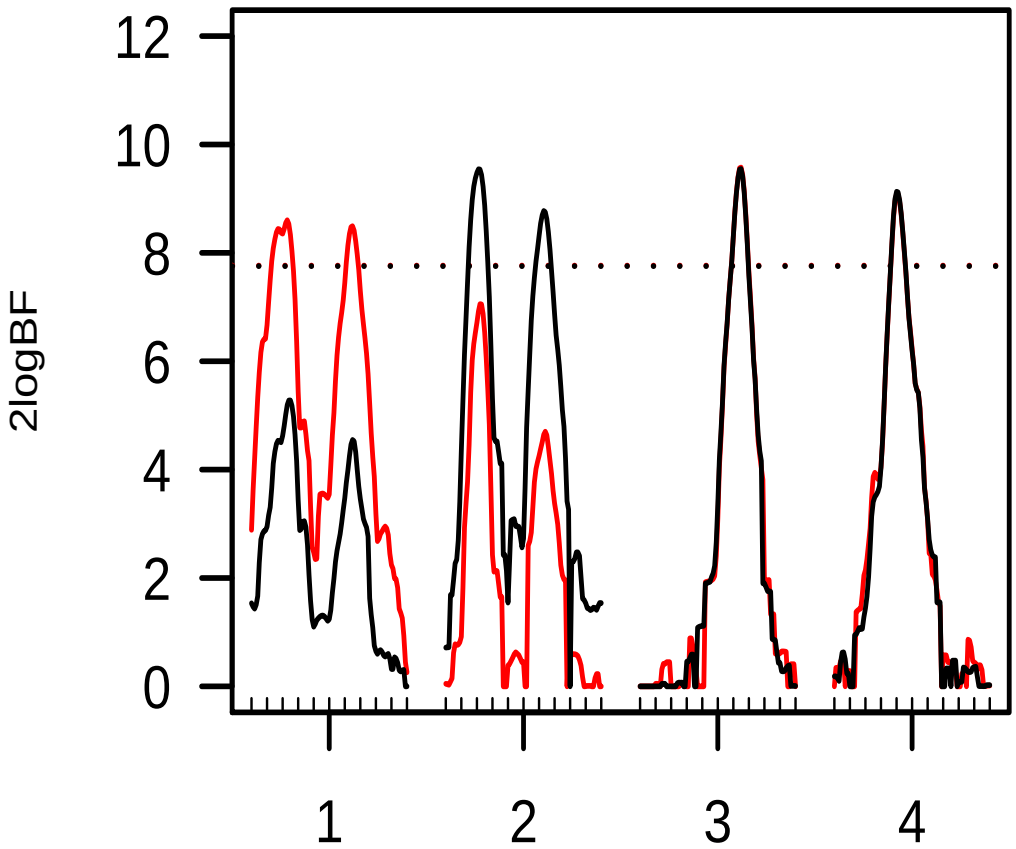
$N = 200$

$\longrightarrow Y_1$

$\longrightarrow Y_2$



SURs , $\rho_{y_1 y_2} = 0.5$



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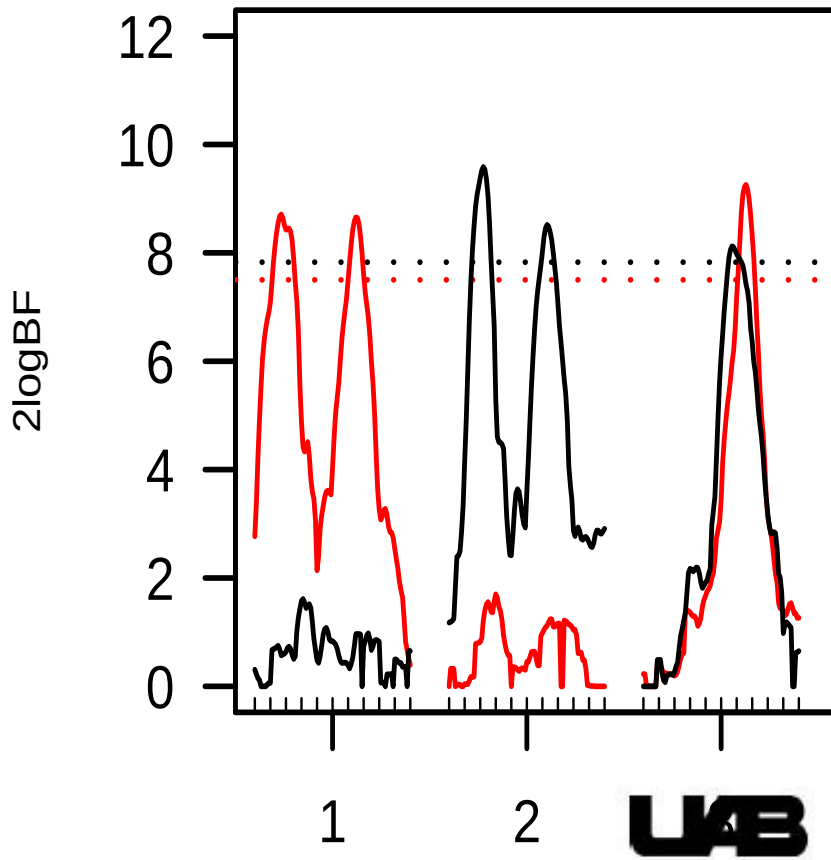
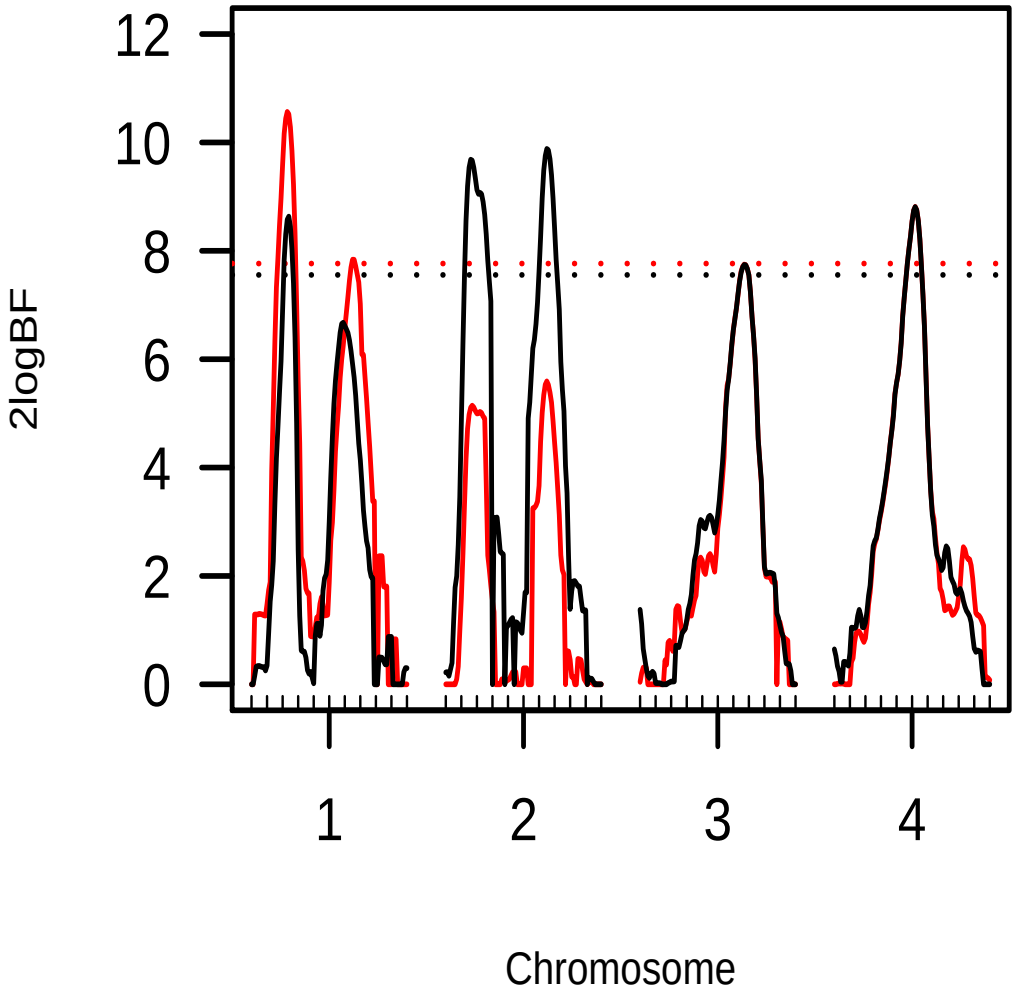


SURs , $\rho_{y_1 y_2} = 0.8$



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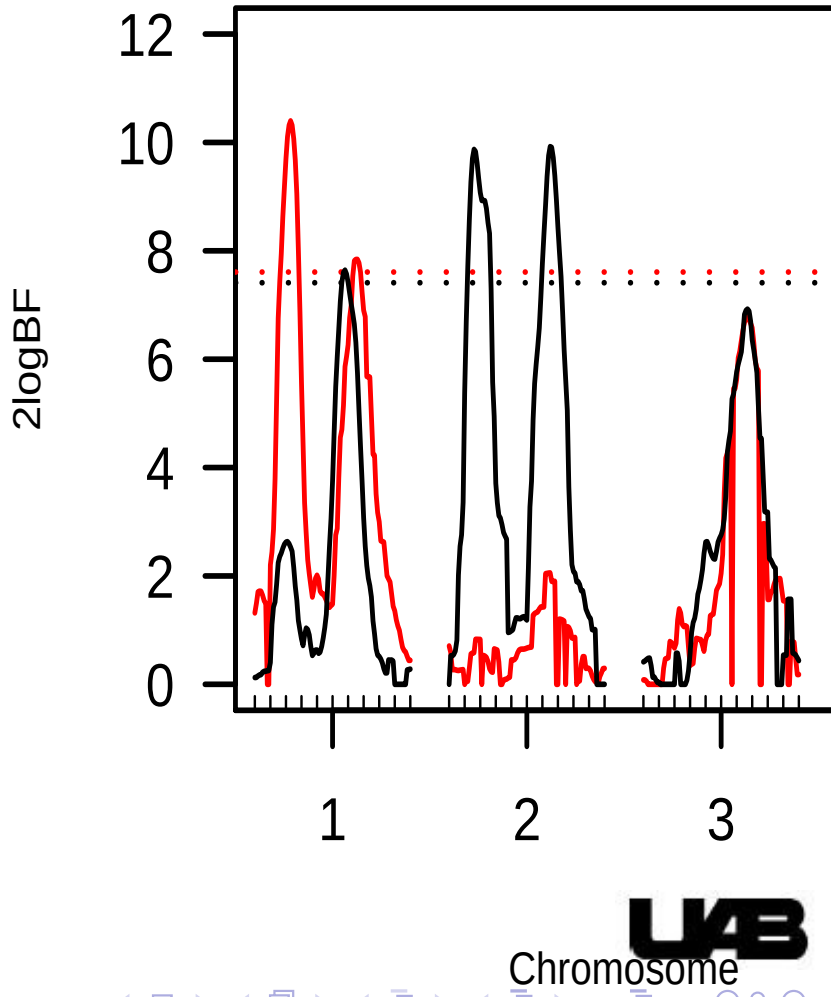
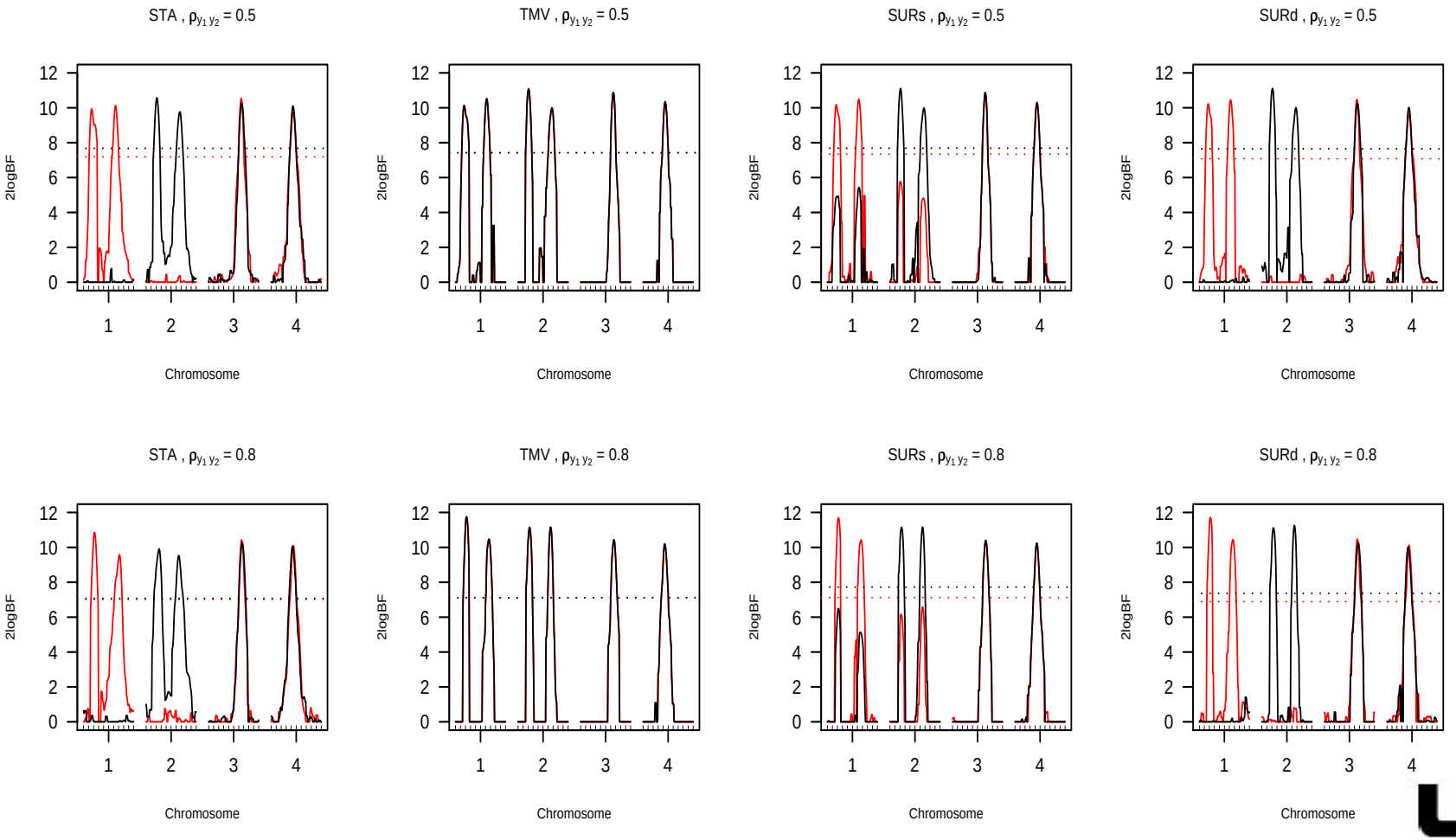


	Q_1	Q_2	Q_3	Q_4	Q_5	Q_6
Chr	1	1	2	2	3	4
Pos(cM)	22	55	22	65	65	45

$N =$ 500
$\longrightarrow$ Y_1
$\longrightarrow$ Y_2



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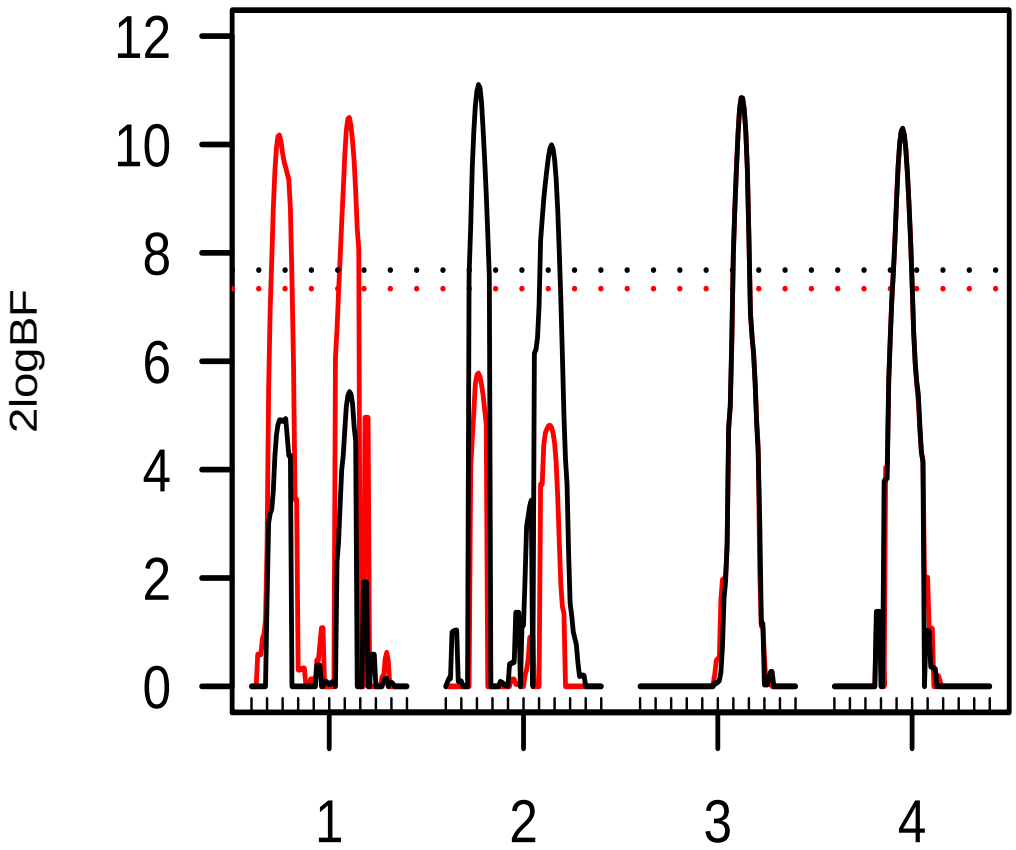

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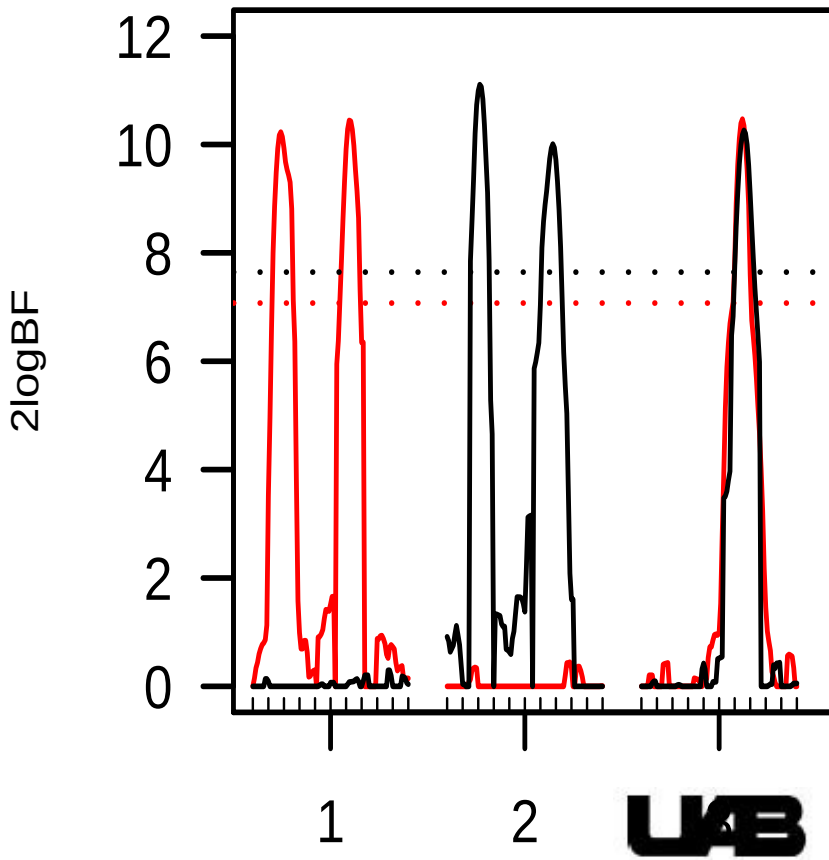

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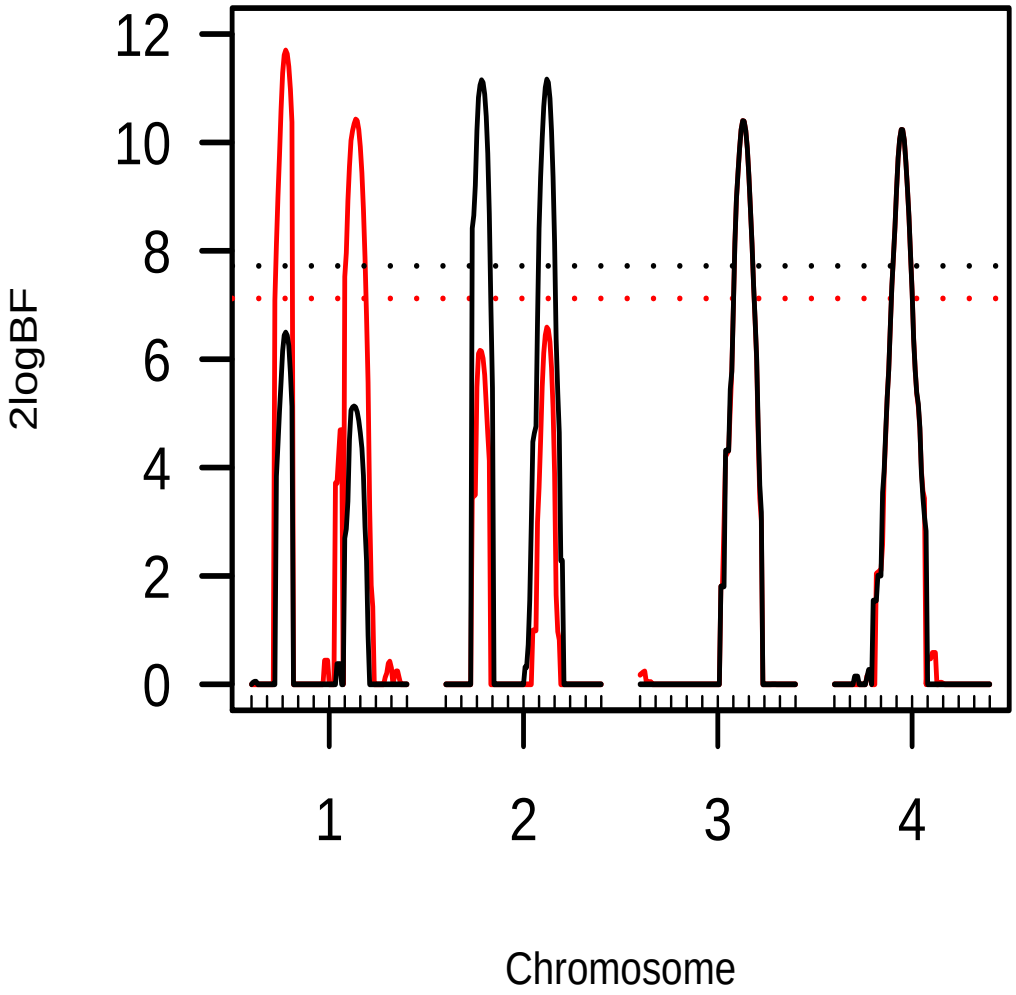

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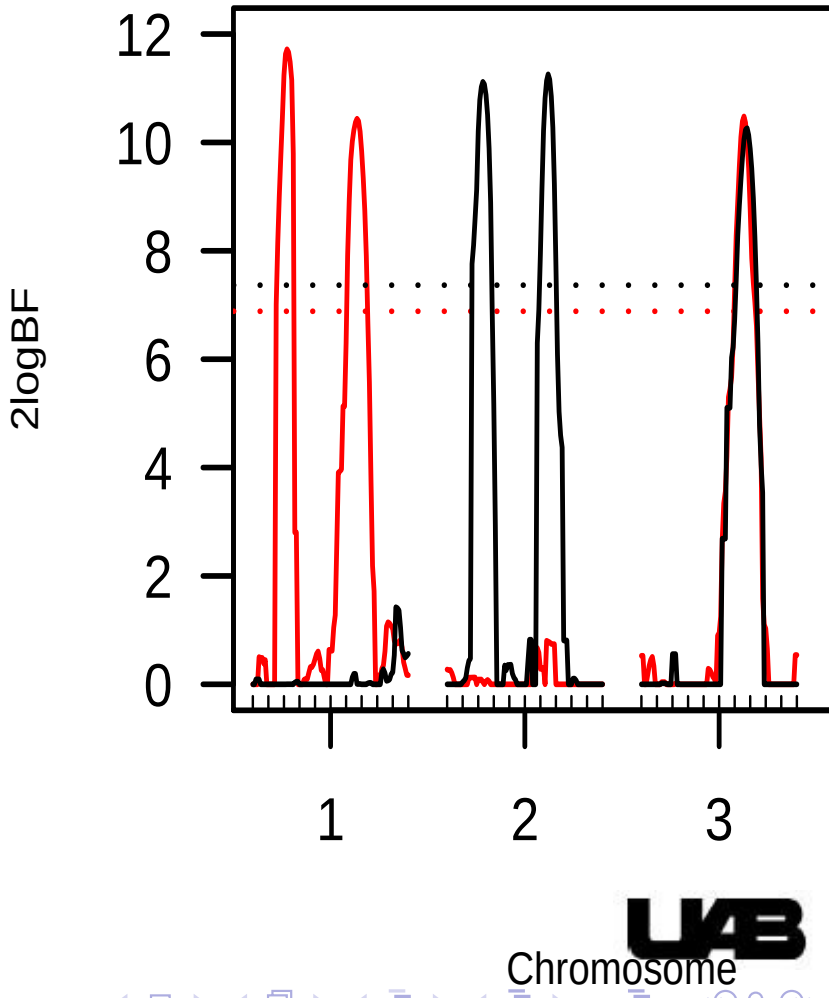
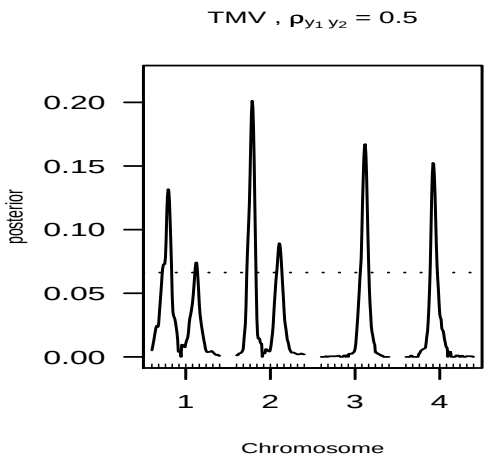
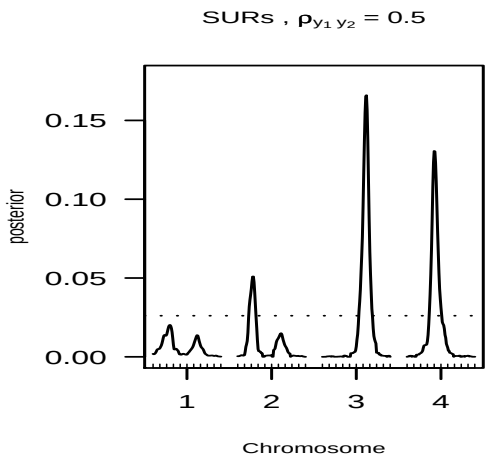
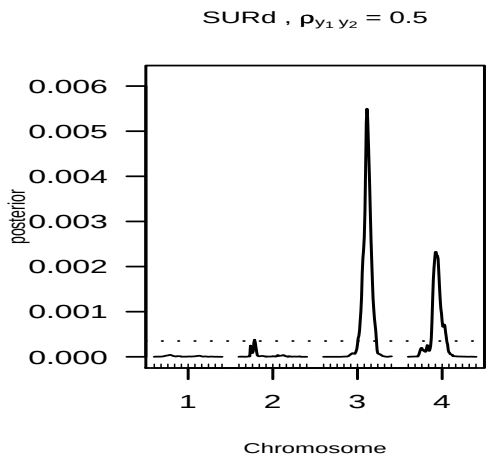


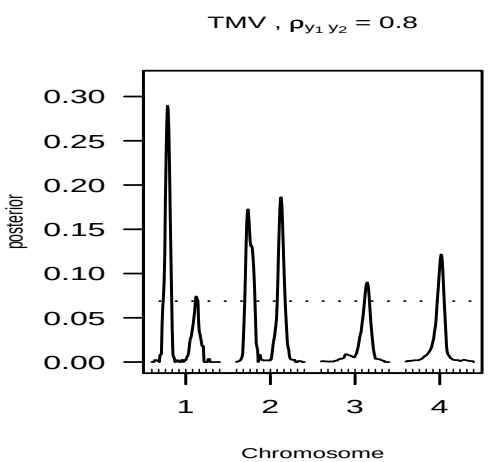
	Q_1	Q_2	Q_3	Q_4	Q_5	Q_6
Chr	1	1	2	2	3	4
Pos(cM)	22	55	22	65	65	45

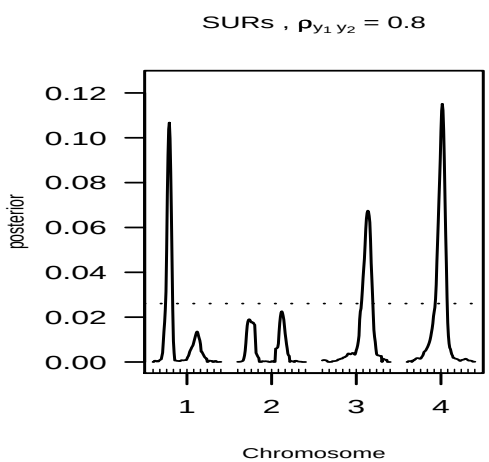
N=200

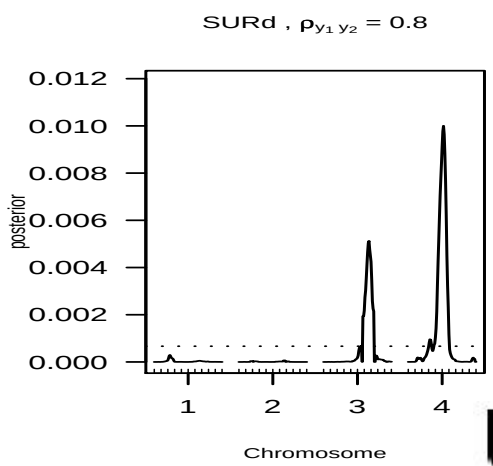












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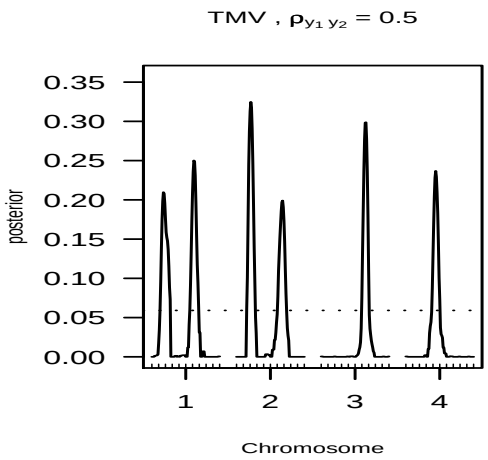
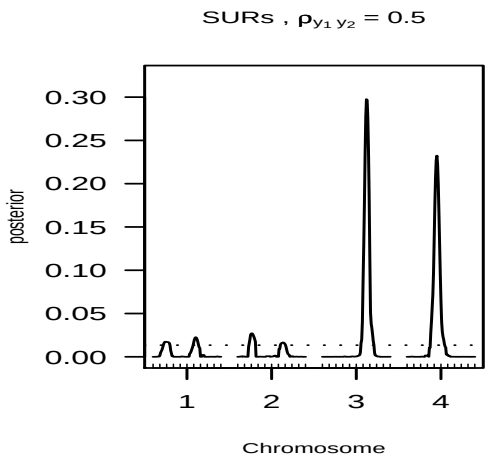
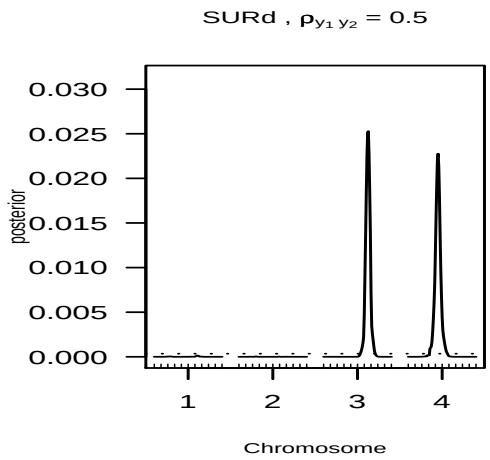
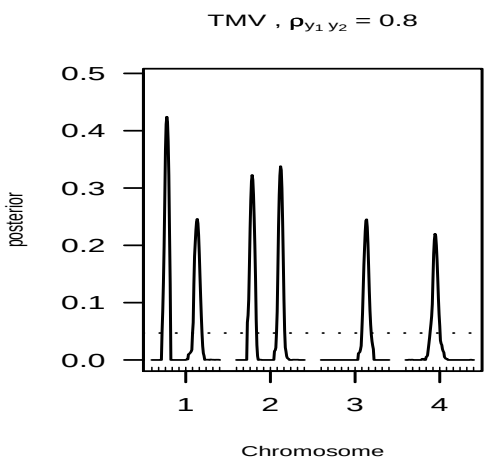
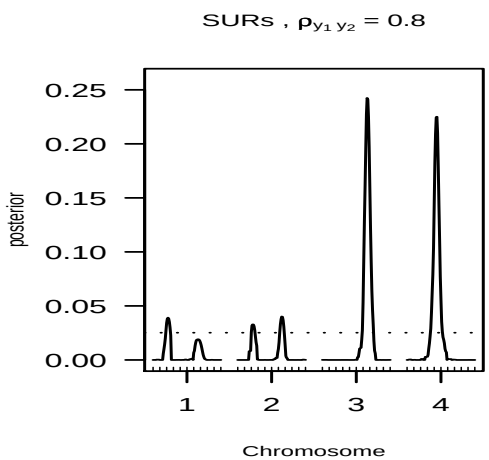
N=500

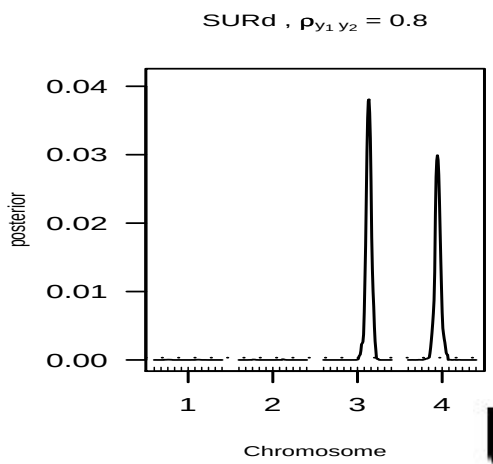












Average correct and incorrect QTL detected for y_2

	Correct				Incorrect			
$(n, \rho_{y_1 y_2})$	STA	TMV	*SURs*	*SURd*	STA	TMV	*SURs*	*SURd*
$(100, 0.5)$	0.65	0.8	0.67	0.64	0.7	1.34	0.45	0.65
$(100, 0.8)$	0.34	1.01	1.02	0.97	0.24	1.85	0.75	0.54
$(200, 0.5)$	1.69	2.13	2.12	1.78	1.06	2.53	0.78	1.02
$(200, 0.8)$	1.51	2.6	2.56	2.24	0.63	2.92	0.73	0.72
$(500, 0.5)$	3.54	3.72	3.76	3.66	1.01	3.1	0.83	1.22
$(500, 0.8)$	3.55	3.81	3.78	3.67	1.1	3.14	1.03	1.01

Average MCMC time

	STA	TMV	SURs	SURd
VLN:LR	1.17	0.96	1.10	1.18
VLN:HR	1.18	0.98	1.09	1.16
LN:LR	2.47	1.99	2.23	2.52
LN:HR	2.48	2.06	2.22	2.45
HN:LR	6.94	6.14	6.51	7.76
HN:HR	6.92	6.11	6.45	7.51

Comparison between methods

- STA - not powerful in low sample sizes

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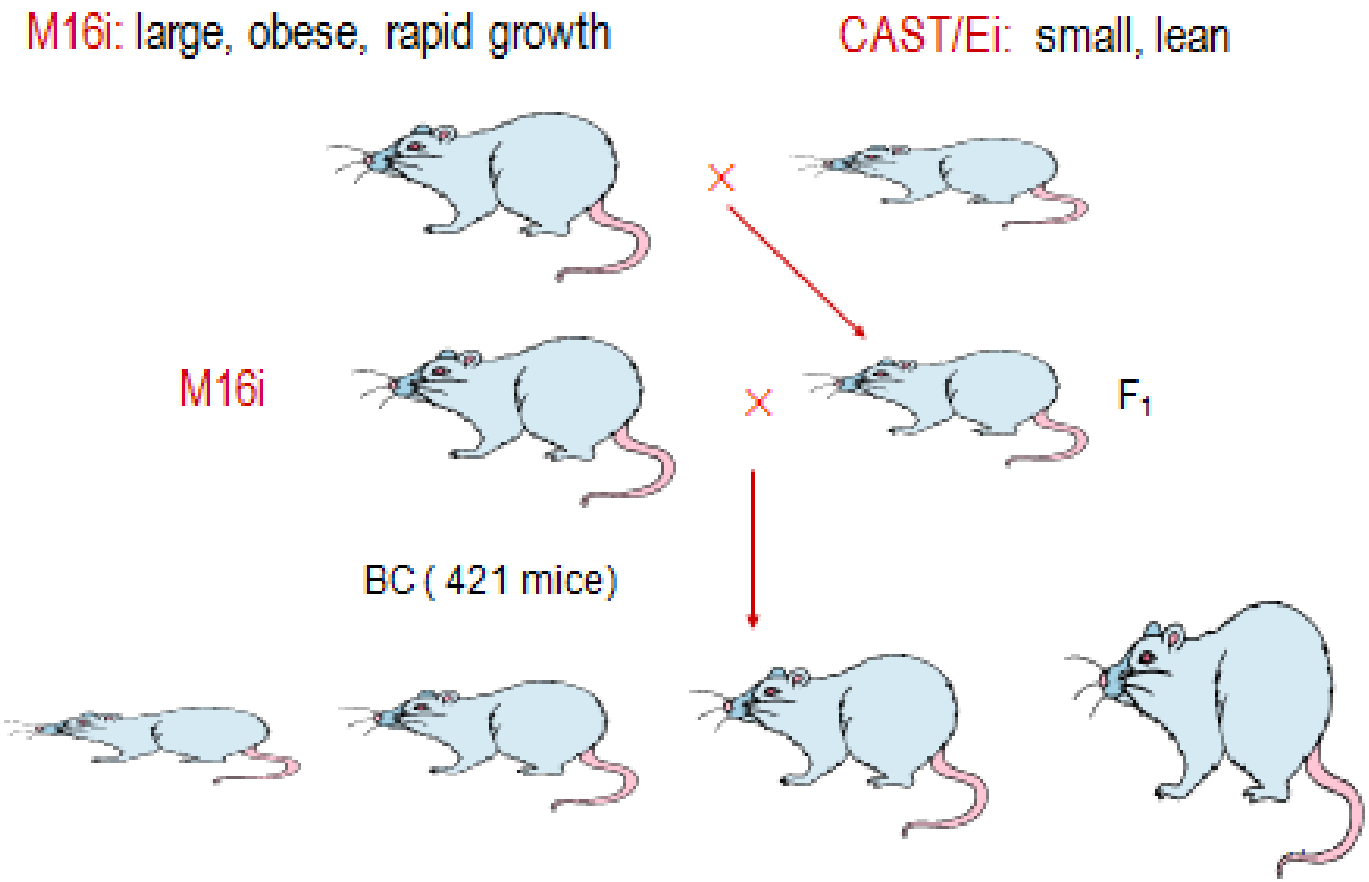
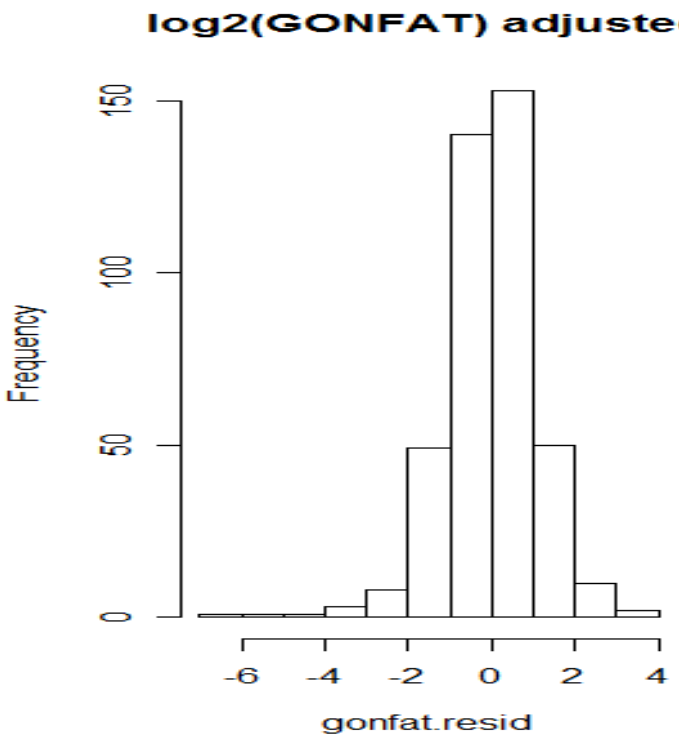
Comparison between methods

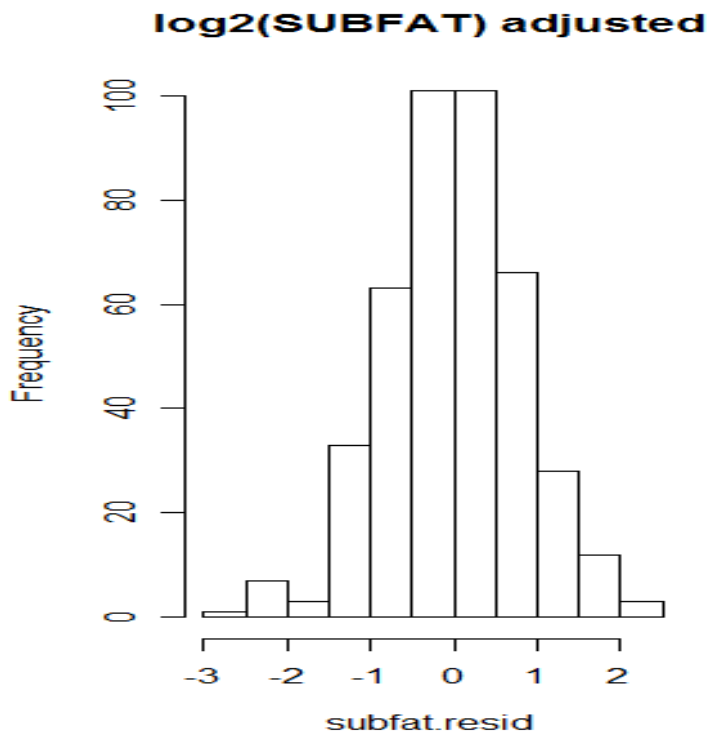
- STA - not powerful in low sample sizes
- TMV - too many incorrect detections
- SUR - both SUR models performed well
- Recommend SURd as SURs can favor QTL of no effect on one trait but having large effect on the other.

Real Data Set

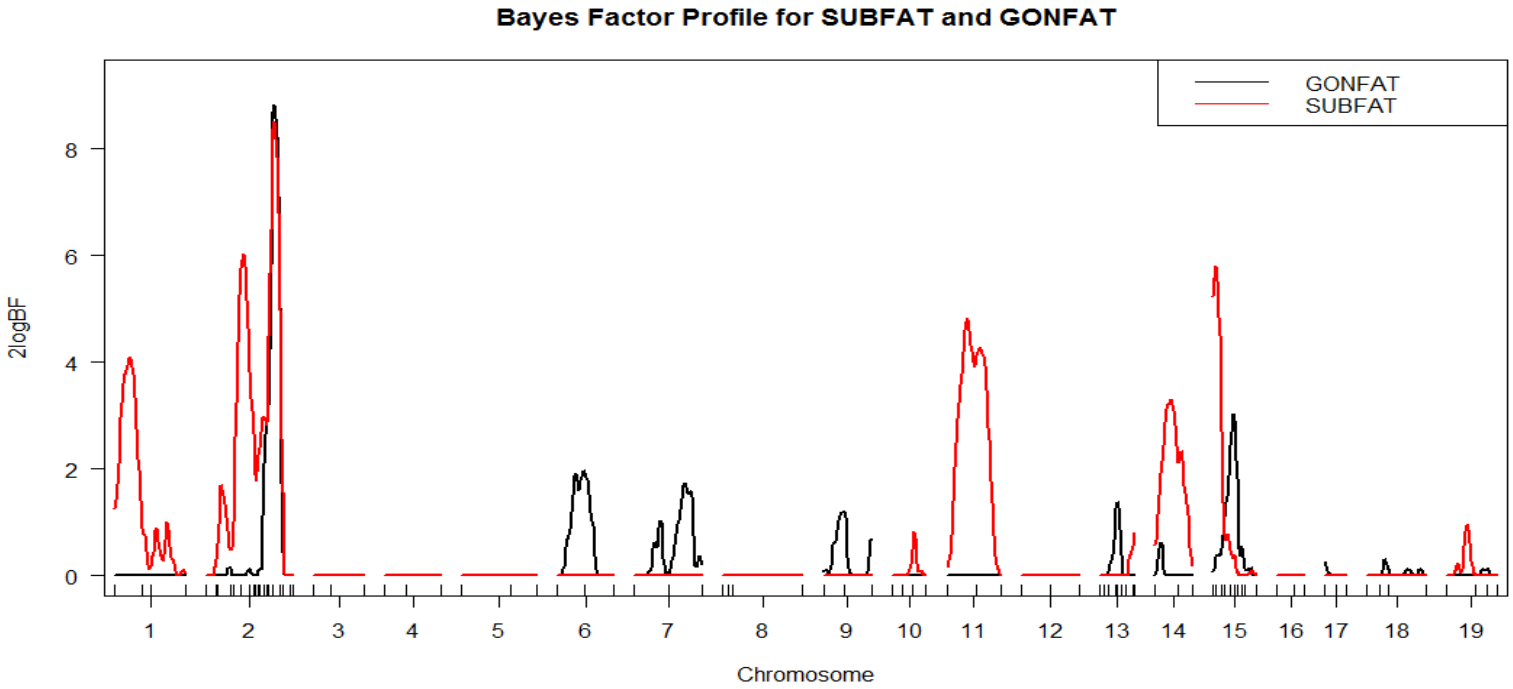


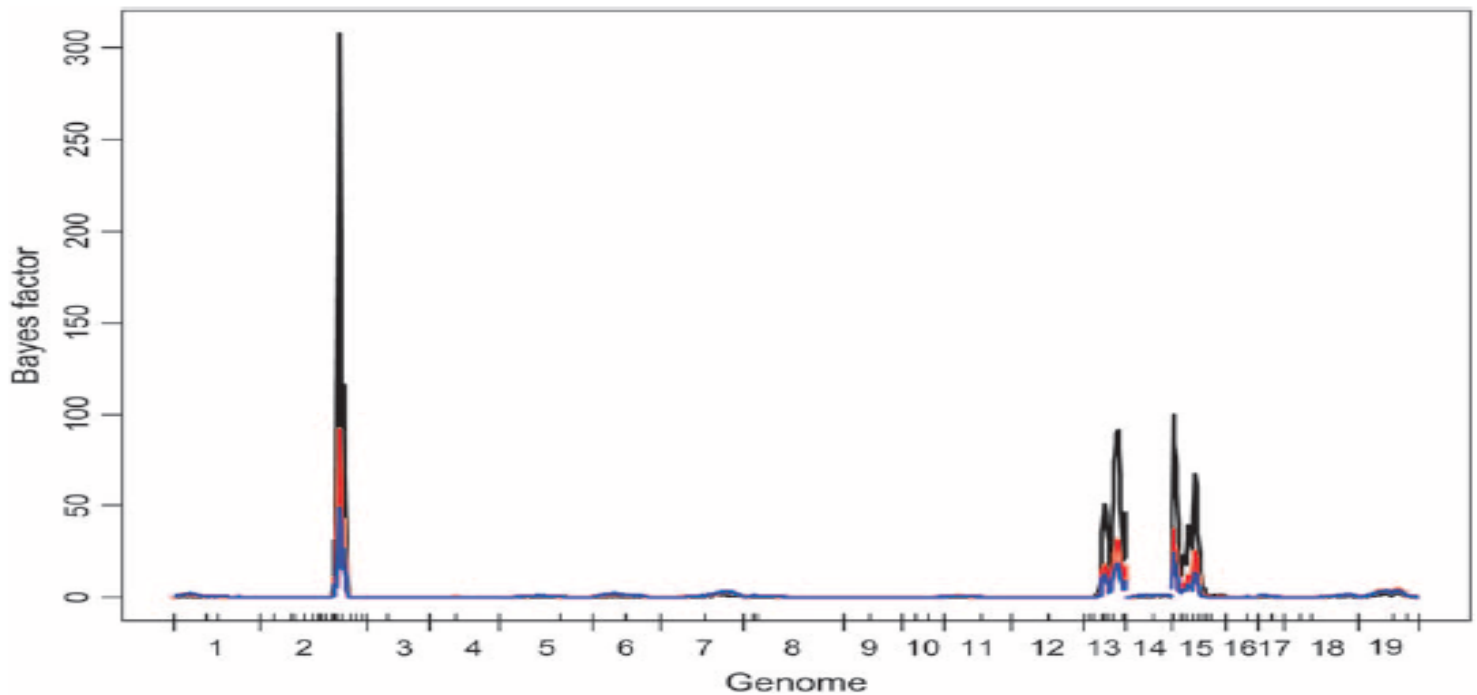
Trait Phenotype



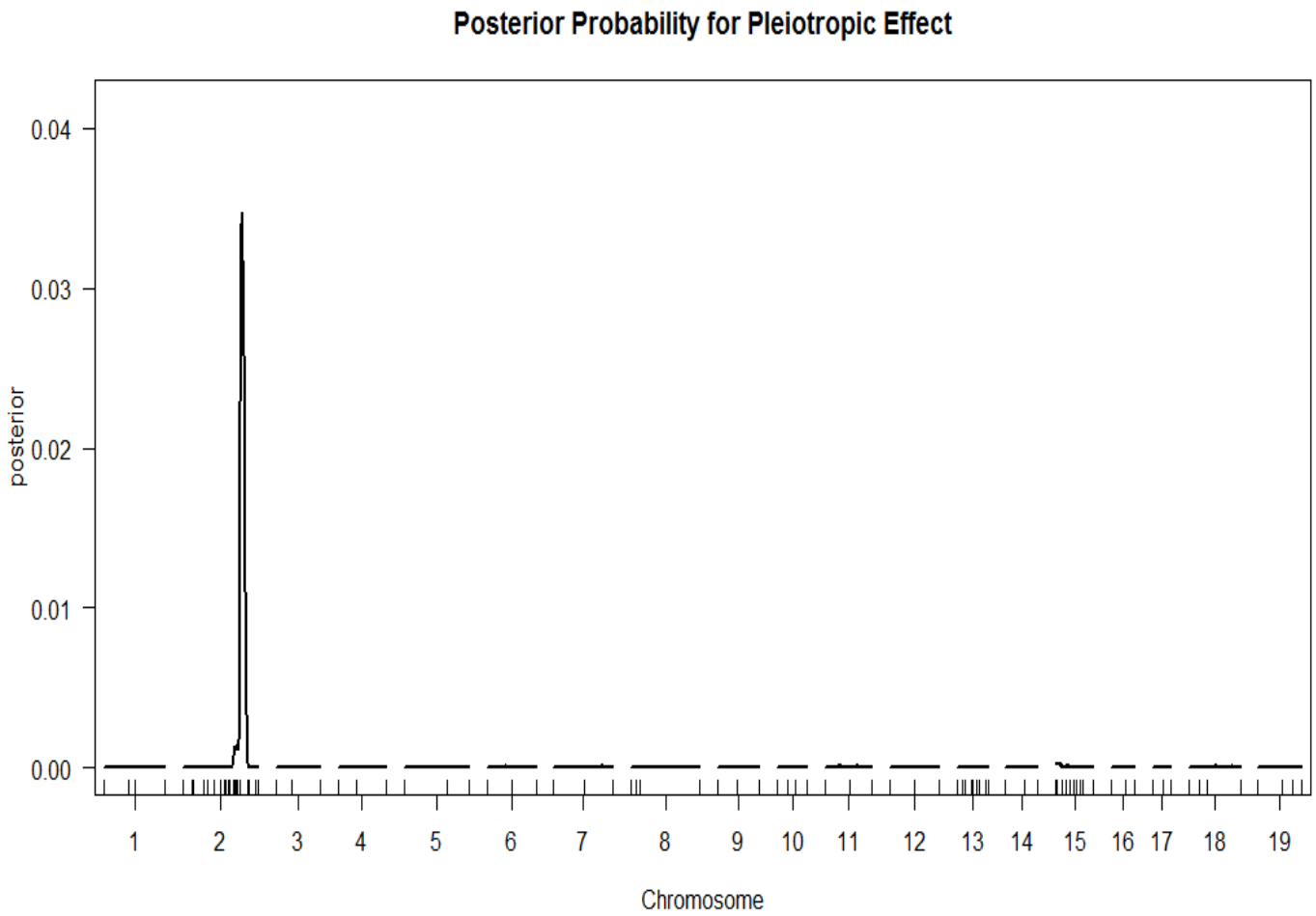


- GONFAT → Right Gonadal fat pad
- SUBFAT → Subcutaneous fat pad


Bayes Factor Profile for SUBFAT and GONFAT
GONFAT
SUBFAT
2logBF
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


Bayes factor
0
50
100
150
200
250
300
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 1617 18 19
Genome

Pleiotropic Effect



Conclusion

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  - ultimate goal in QTL mapping
- A comprehensive genome-wide search strategy to map multiple interacting QTL in correlated traits.

Future Research

- Gene-gene (epistasis) and gene-environment (GxE) interactions; covariates

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- eQTL?

Large-Scale Hierarchical Generalized Linear Models for Genome-wide QTL Mapping

Samprit Banerjee and Nengjun Yi

Dept. of Biostatistics
University of Alabama, Birmingham

GLM

- Some traits are non-normal, e.g. binary, poisson etc.

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Linear Models

$$E(y \mid X) = X\beta$$

GLM

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Linear Models

$$E(y \mid X) = X\beta$$

Generalized Linear Models

1. Linear predictor: $\eta = X\beta$
2. Link function: $E(y \mid X) = g^{-1}(\eta)$
3. Dist. of outcome variable: $p(y \mid X\beta, \phi) = \prod_{i=1}^{n} p(y_i \mid X_i\beta, \phi)$

Link function

GLM

$$\eta = g(\mu), \qquad \textit{where} \qquad \mu = E(y \mid X)$$

- Identity $\longrightarrow g(\mu) = \mu$
- Logit $\longrightarrow g(\mu) = log(\frac{\mu}{1-\mu})$
- Probit $\longrightarrow g(\mu) = \Phi^{-1}(\mu)$
- Logarithm $\longrightarrow g(\mu) = log(\mu)$

GLM

Linear Predictor

$$\eta = \beta_0 + X_E\beta_E + X_G\beta_G + X_{GG}\beta_{GG} + X_{GE}\beta_{GE}$$

- E = environmental effects

GLM

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- G = genetic effects *e.g.* main effects including additive and dominant effects of markers and pseudomarkers

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Conventional GLM

Problem

$$p \ggg n$$

Number of predictors $\ggg$ Sample size

- Classical maximum likelihood method breaks down.

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$$p \ggg n$$

Number of predictors $\ggg$ Sample size

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- Number of unknowns more that number of equations

Hierarchical Models

Solution

Informative prior distribution on coefficient (β) that favors sparseness

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Prior on β

$$\beta_j \mid \tau_j^2 \sim N(0, \tau_j^2)$$
$$\tau_j^2 \mid \nu_j, s_j^2 \sim Inv - \chi^2(\nu_j, s_j^2)$$

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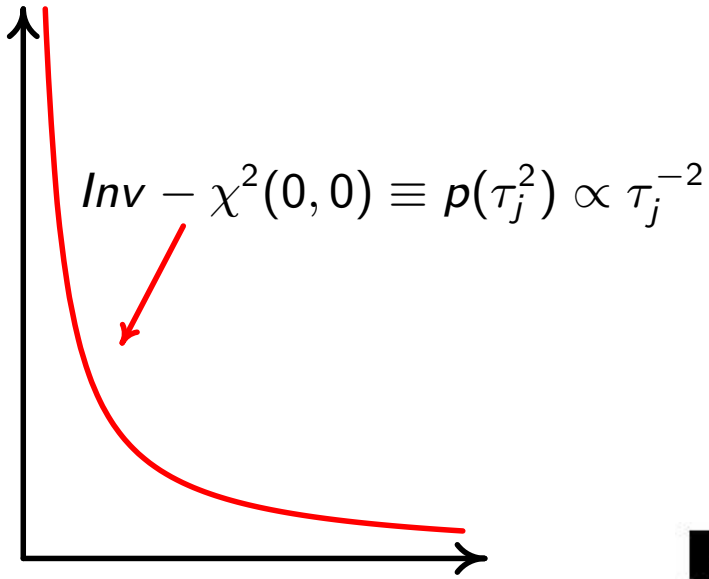

Another prior for β

Prior II on β

$$\beta_j \mid \tau_j^2 \sim N(0, \tau_j^2)$$
$$\tau_j^2 \mid \lambda \sim Expon(\tau_j^2 \mid \frac{\lambda^2}{2}) = \frac{\lambda^2}{2} e^{-\lambda^2 \tau_j^2/2}$$

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LASSO prior: LASSO estimates $\equiv$ Bayesian posterior modes (Tibshirani 1996)

Idea of Shrinkage

Variable Selection

Markers	C1M1	C1M2	C2M1	C2M2	C15M2	C16M1
γ_y	0	0	1	0	1	1

Shrinkage

Markers	C1M1	C1M2	C1M3	C1M4	$\cdots$	C19M100
β	0	0	0.2	0.3	$\cdots$	0.1

Where prior variance of $\beta < 0.001$ set $\beta = 0$

Unknown Variance

Prior on β

$$\beta_j \mid \tau_j^2 \sim N(0, \tau_j^2) \qquad \tau_j^2 \mid \nu_j, s_j^2 \sim Inv - \chi^2(\nu_j, s_j^2)$$

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- In classical GLM, the likelihood is approximated by weighted normal likelihood and estimates are obtained
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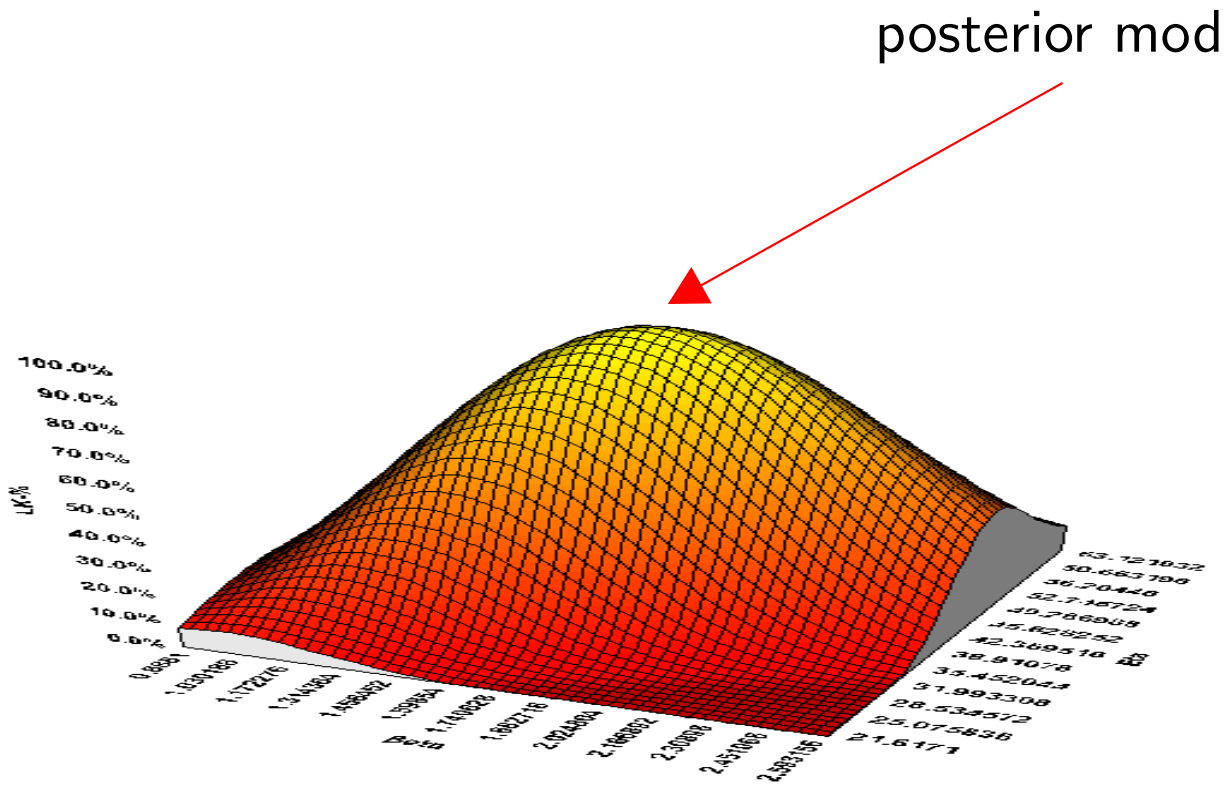
- EM (Expectation Maximization) algorithm

EM idea



EM algorithm calculates the posterior mode of (β, ϕ, s^2) averaging over $\tau_j^2,\ j = 1, .., J$

Model fitting strategy

Concern

Large number of markers: main effects, gene-gene (epistasis) and gene-environment (GxE) interactions

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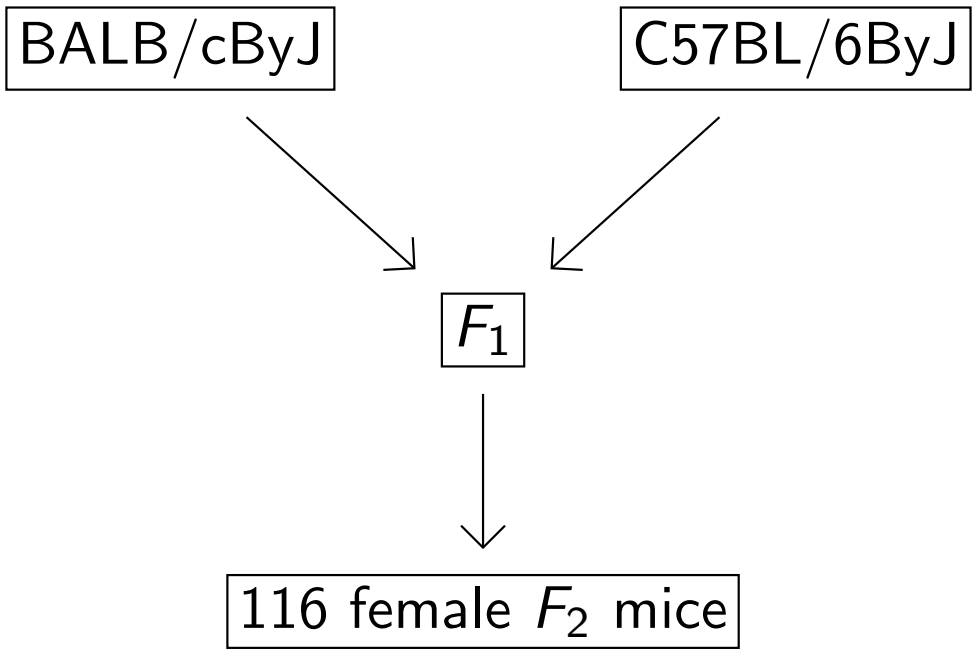
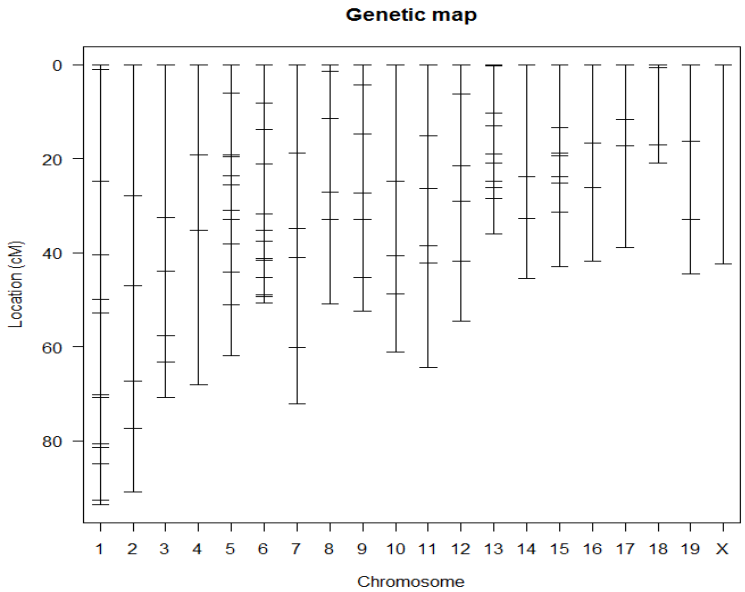
Listeria Monocytogenes Dataset

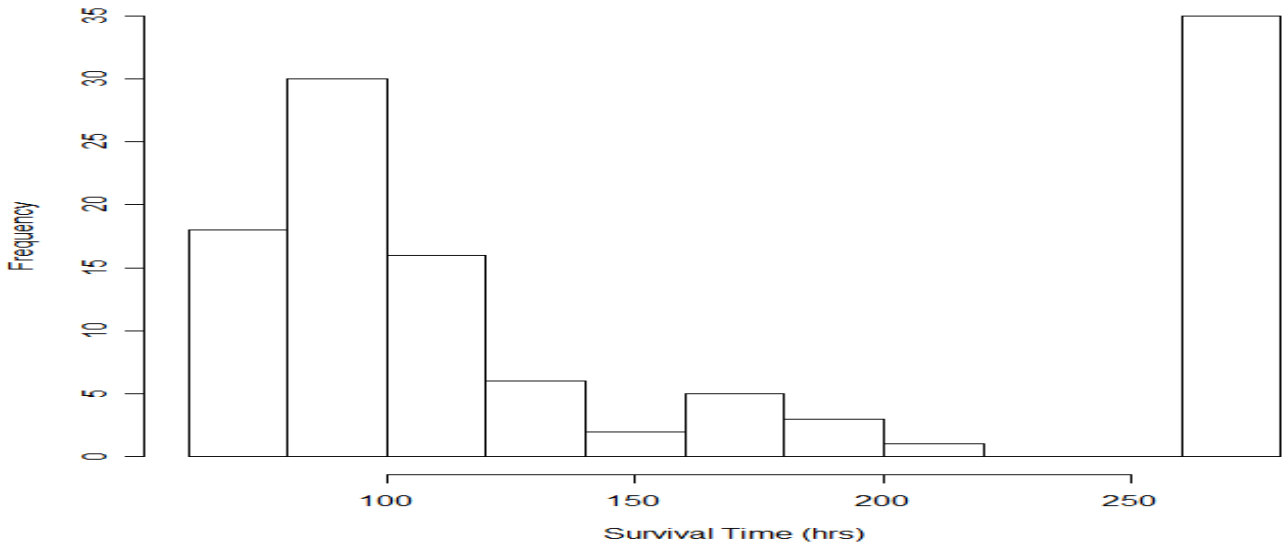




133 genetic markers

Trait Phenotype

Time to death following Listeria monocytogenes



Binary Trait

Survival $= 1/0$
Probit link

Continuous Trait

Analyzing dead mice (81) only (Time to infection (T) < 264)

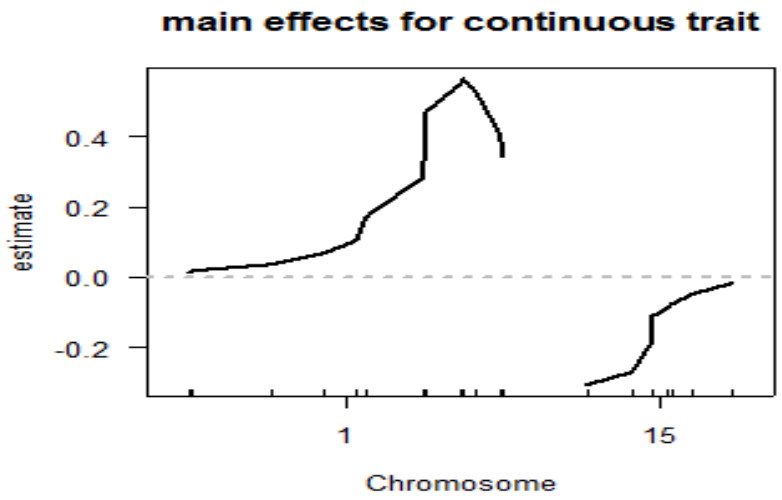
Results

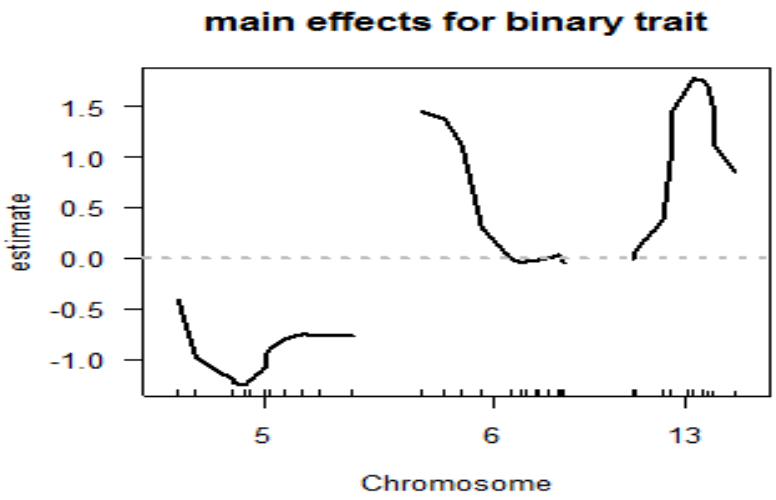
Binary Traits

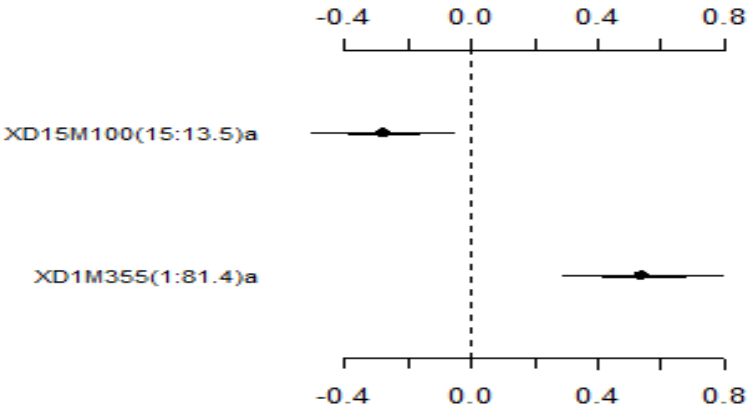
	Estimate	Std. Error	z-value	$Pr(>\|z\|)$
(Intercept)	-0.4947	0.1538	-3.216	0.001300
D5M91(5:32.9)a	-1.0962	0.2414	-4.540	5.62e-06
D6M188(6:18.2)a	0.8330	0.2331	3.574	0.000352
D13M99(13:18.9)a	0.9269	0.2216	4.182	2.89e-05

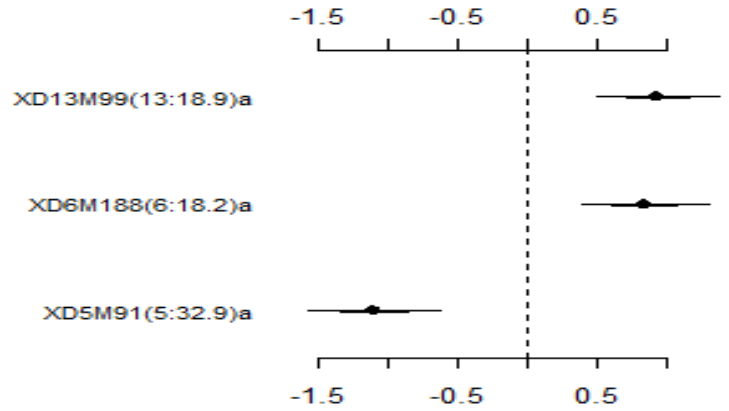
Continuous Traits

	Estimate	Std. Error	t-value	$Pr(>\|t\|)$
(Intercept)	0.02616	0.09274	0.282	0.7786
D1M355(1:81.4)a	0.54642	0.12867	4.247	5.74e-05
D15M100(15:13.5)a	-0.27828	0.11341	-2.454	0.0163


main effects for continuous trait
estimate
0.4
0.2
0.0
-0.2
1
15
Chromosome


main effects for binary trait
estimate
1.5
1.0
0.5
0.0
-0.5
-1.0
5
6
13
Chromosome


-0.4
0.0
0.4
0.8
XD15M100(15:13.5)a
XD1M355(1:81.4)a
-0.4
0.0
0.4
0.8


-1.5
-0.5
0.5
XD13M99(13:18.9)a
XD6M188(6:18.2)a
XD5M91(5:32.9)a
-1.5
-0.5
0.5

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