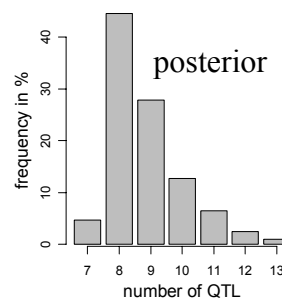


examples in detail

- simulation study (after Stephens & Fisch (1998))
- days to flower for *Brassica napus* (plant) ($n = 108$)
 - single chromosome with 2 linked loci
 - whole genome
- gonad shape in *Drosophila* spp. (insect) ($n = 1000$)
 - multiple traits reduced by PC
 - many QTL and epistasis
- expression phenotype (SCD1) in mice ($n = 108$)
 - multiple QTL and epistasis
- obesity in mice ($n = 421$)
 - epistatic QTLs with no main effects

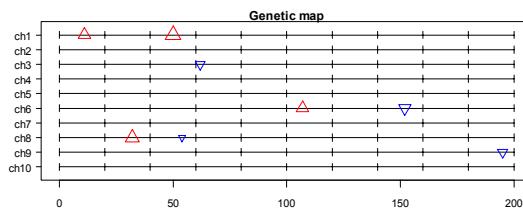
simulation with 8 QTL

- simulated F2 intercross, 8 QTL
 - (Stephens, Fisch 1998)
 - $n=200$, heritability = 50%
 - detected 3 QTL
- increase to detect all 8
 - $n=500$, heritability to 97%



QTL chr loci effect

1	1	11	-3
2	1	50	-5
3	3	62	+2
4	6	107	-3
5	6	152	+3
6	8	32	-4
7	8	54	+1
8	9	195	+2



loci pattern across genome

- notice which chromosomes have persistent loci
- best pattern found 42% of the time

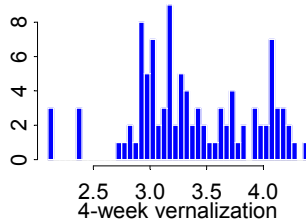
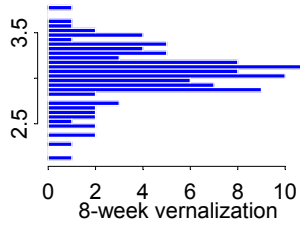
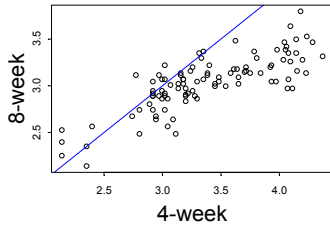
Chromosome

<u>m</u>	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	<u>7</u>	<u>8</u>	<u>9</u>	<u>10</u>	<u>Count of 8000</u>
8	2	0	1	0	0	2	0	2	1	0	3371
9	3	0	1	0	0	2	0	2	1	0	751
7	2	0	1	0	0	2	0	1	1	0	377
9	2	0	1	0	0	2	0	2	1	0	218
9	2	0	1	0	0	3	0	2	1	0	218
9	2	0	1	0	0	2	0	2	2	0	198

Brassica napus: 1 chromosome

- 4-week & 8-week vernalization effect
 - log(days to flower)
- genetic cross of
 - Stellar (annual canola)
 - Major (biennial rapeseed)
- 105 F1-derived double haploid (DH) lines
 - homozygous at every locus (*QQ* or *qq*)
- 10 molecular markers (RFLPs) on LG9
 - two QTLs inferred on LG9 (now chromosome N2)
 - corroborated by Butruille (1998)
 - exploiting synteny with *Arabidopsis thaliana*

Brassica 4- & 8-week data

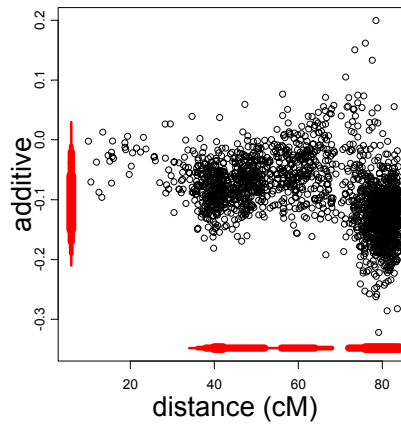
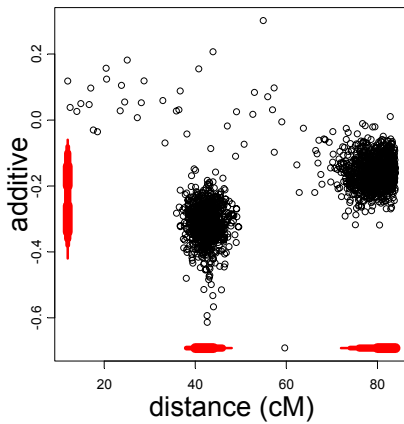


summaries of raw data
joint scatter plots
(identity line)
separate histograms

Brassica credible regions

4-week

8-week



B. napus 8-week vernalization whole genome study

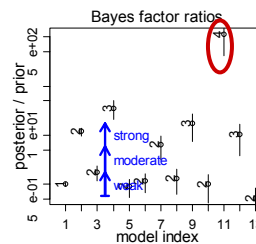
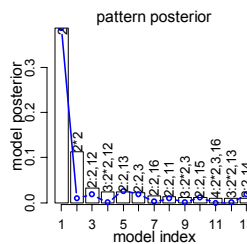
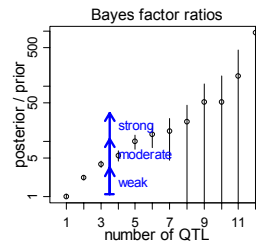
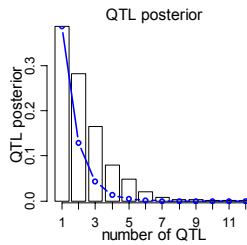
- 108 plants from double haploid
 - similar genetics to backcross: follow 1 gamete
 - parents are Major (biennial) and Stellar (annual)
- 300 markers across genome
 - 19 chromosomes
 - average 6cM between markers
 - median 3.8cM, max 34cM
 - 83% markers genotyped
- phenotype is days to flowering
 - after 8 weeks of vernalization (cooling)
 - Stellar parent requires vernalization to flower
- Ferreira et al. (1994); Kole et al. (2001); Schranz et al. (2002)

Bayesian model assessment

row 1: # QTL
row 2: pattern

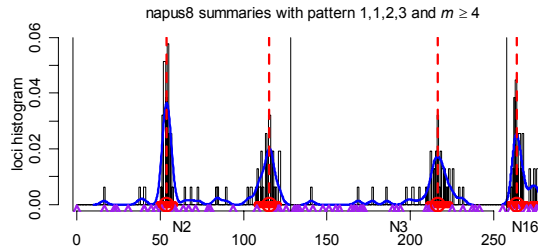
col 1: posterior
col 2: Bayes factor
note error bars on bf

evidence suggests
4-5 QTL
N2(2-3), N3, N16

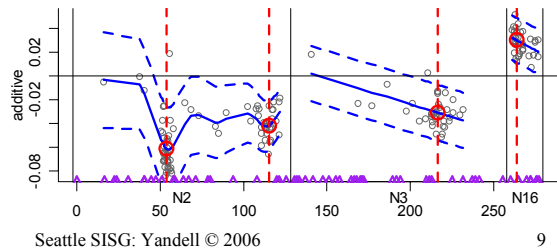


Bayesian estimates of loci & effects

histogram of loci
blue line is density
red lines at estimates



estimate additive effects
(red circles)
grey points sampled
from posterior
blue line is cubic spline
dashed line for 2 SD



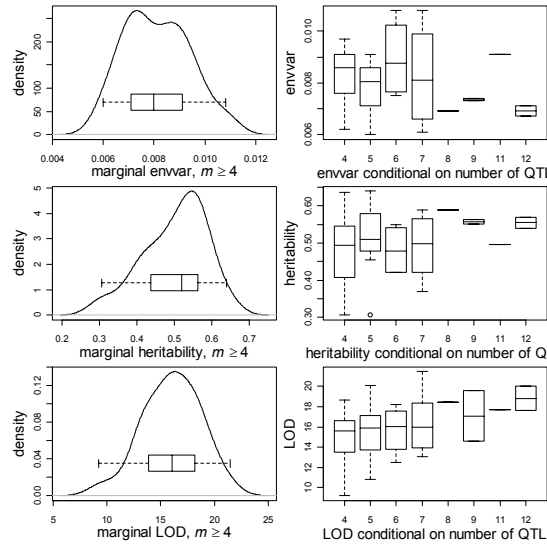
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Bayesian model diagnostics

pattern: N2(2),N3,N16
col 1: density
col 2: boxplots by m

environmental variance
 $\sigma^2 = .008$, $\sigma = .09$
heritability
 $h^2 = 52\%$
LOD = 16
(highly significant)

but note change with m



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10

shape phenotype in BC study indexed by PC1

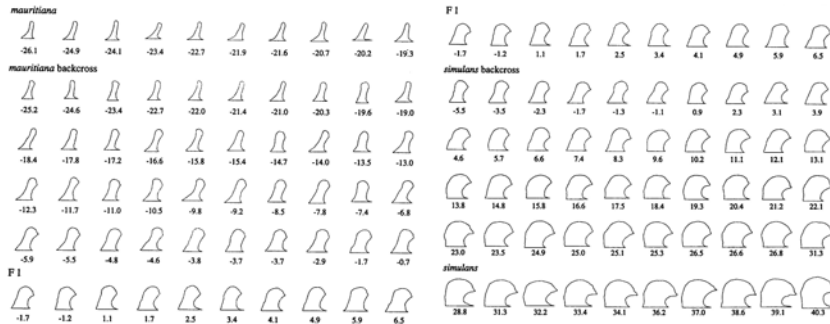


FIGURE 6.—Outlines of the posterior lobe from a sample of individuals from each of the five groups: pure *mauritiana*, *mauritiana* backcross, *F1*, *simulans* backcross, and pure *simulans*. Within each group, the outlines are presented in order of their PC1 score (sampled at even intervals from the range of variation). The number below each specimen is its PC1 score. The outlines are drawn to scale with the origin at the centroid of each outline and with all baselines parallel.

Liu et al. (1996) *Genetics*

shape phenotype via PC

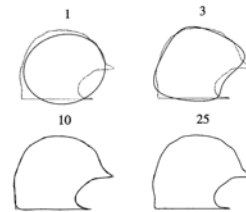
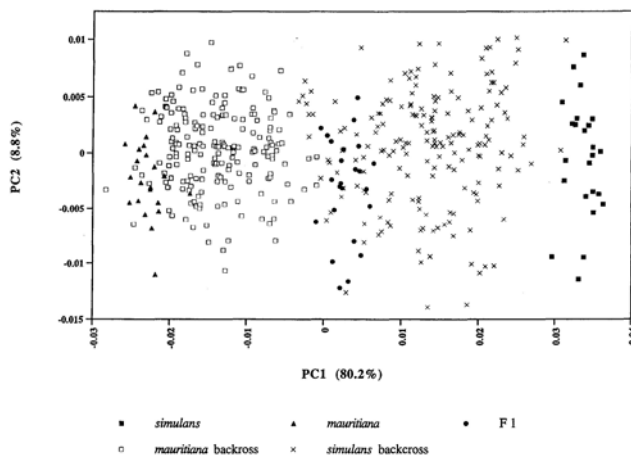


FIGURE 2.—The effect of harmonic number on the accuracy of reconstruction of a posterior lobe outline by elliptical Fourier analysis.

FIGURE 5.—A plot of the first two principal components of the Fourier coefficients from posterior lobe outlines. Many individuals from each of five genotypic classes are represented. Each point represents an average of scores from the left and right sides of an individual (with a few exceptions for which the score is from one side only). The percentage of variation in the Fourier coefficients accounted for by each principal component is given in parentheses. Liu et al. (1996) *Genetics*

Zeng et al. (2000) CIM vs. MIM

composite interval mapping
(Liu et al. 1996)
narrow peaks
miss some QTL

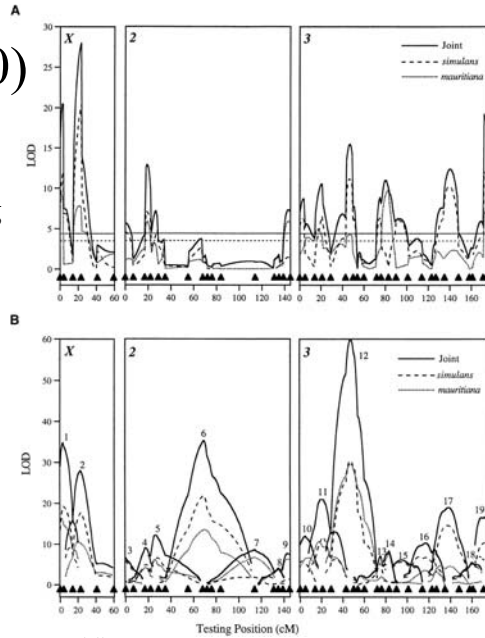
multiple interval mapping
(Zeng et al. 2000)
triangular peaks

both conditional 1-D scans
fixing all other "QTL"

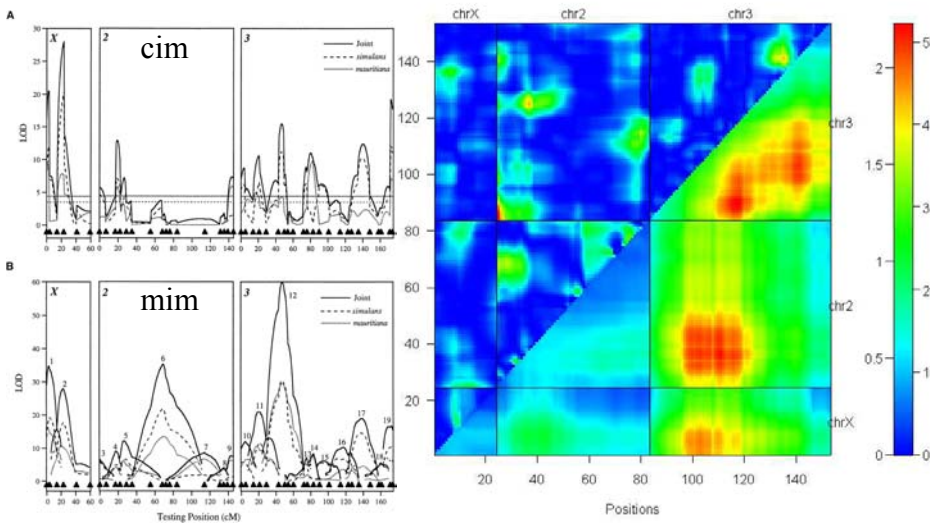
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13



CIM, MIM and IM pairscan

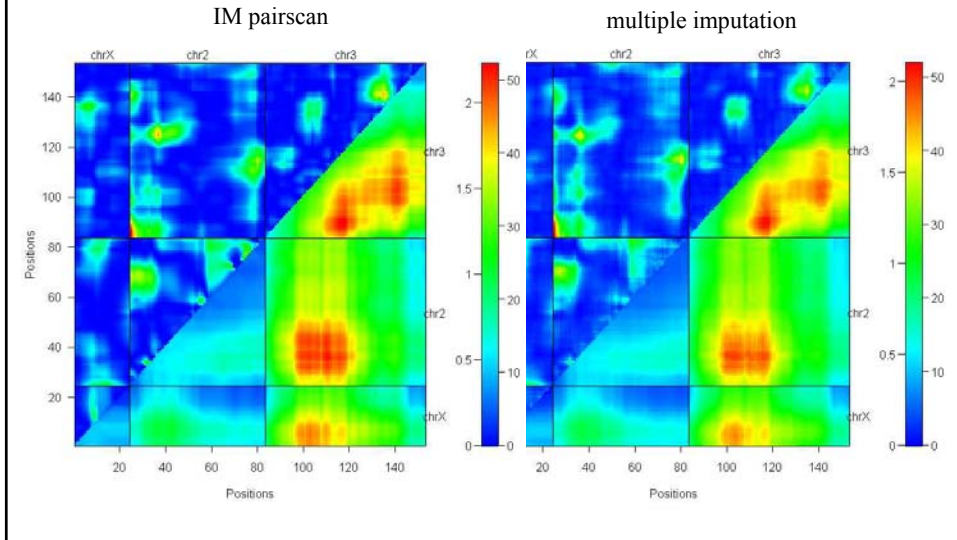


QTL 2: Data

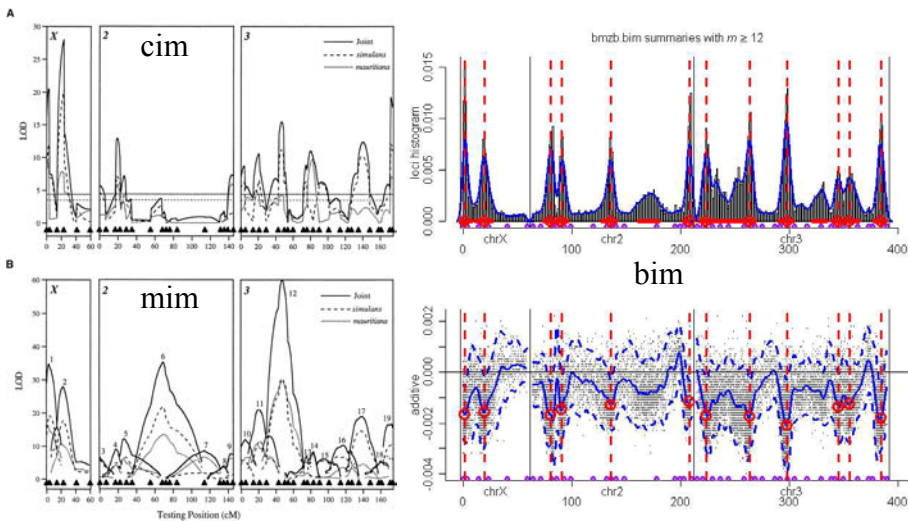
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14

2 QTL + epistasis: IM versus multiple imputation



multiple QTL: CIM, MIM and BIM



studying diabetes in an F2

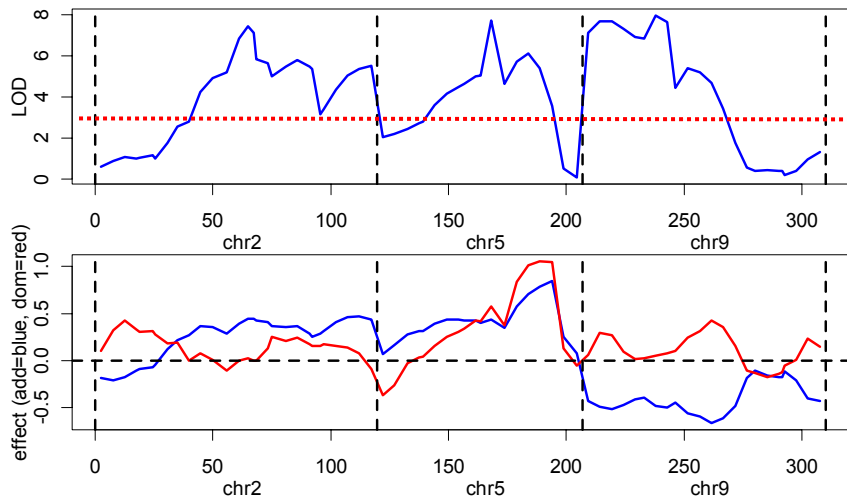
- segregating cross of inbred lines
 - B6.ob x BTBR.ob → F1 → F2
 - selected mice with ob/ob alleles at leptin gene (chr 6)
 - measured and mapped body weight, insulin, glucose at various ages (Stoehr et al. 2000 Diabetes)
 - sacrificed at 14 weeks, tissues preserved
- gene expression data
 - Affymetrix microarrays on parental strains, F1
 - key tissues: adipose, liver, muscle, β -cells
 - novel discoveries of differential expression (Nadler et al. 2000 PNAS; Lan et al. 2002 in review; Ntambi et al. 2002 PNAS)
 - RT-PCR on 108 F2 mice liver tissues
 - 15 genes, selected as important in diabetes pathways
 - SCD1, PEPCK, ACO, FAS, GPAT, PPARgamma, PPARalpha, G6Pase, PDI,...

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17

Multiple Interval Mapping (QTLCart) SCD1: multiple QTL plus epistasis!

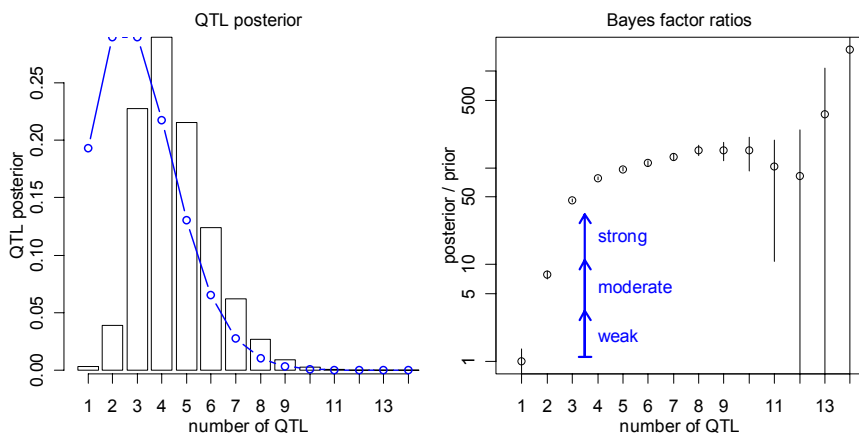


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18

Bayesian model assessment: number of QTL for SCD1

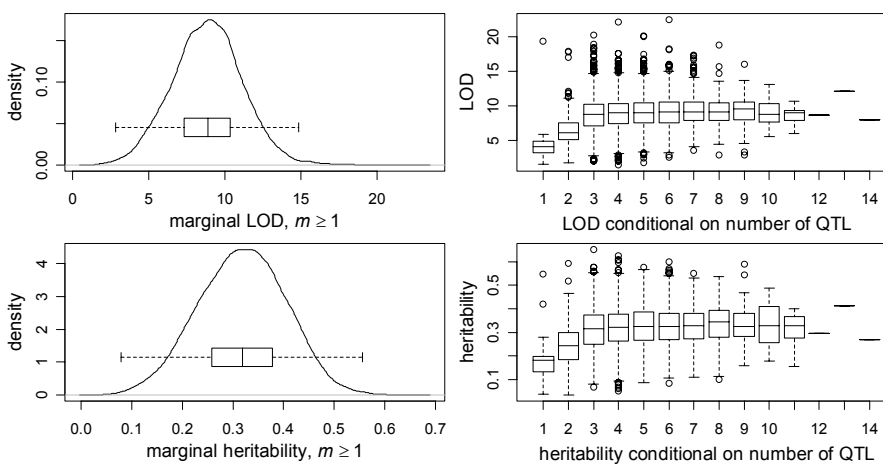


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19

Bayesian LOD and h^2 for SCD1

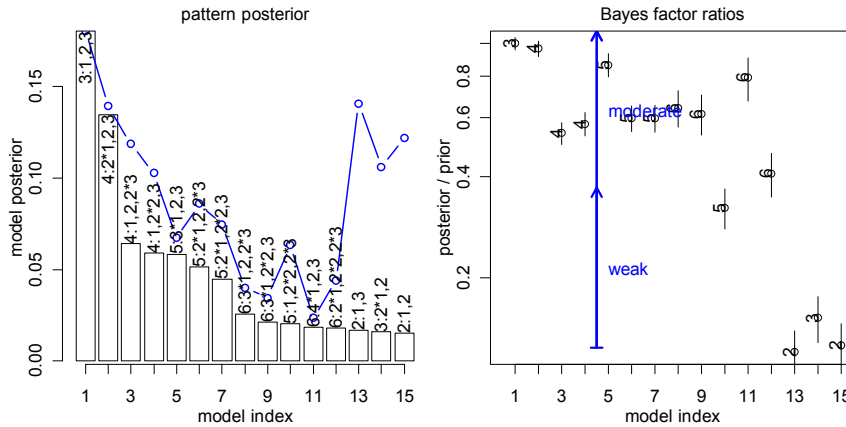


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Bayesian model assessment: chromosome QTL pattern for SCD1

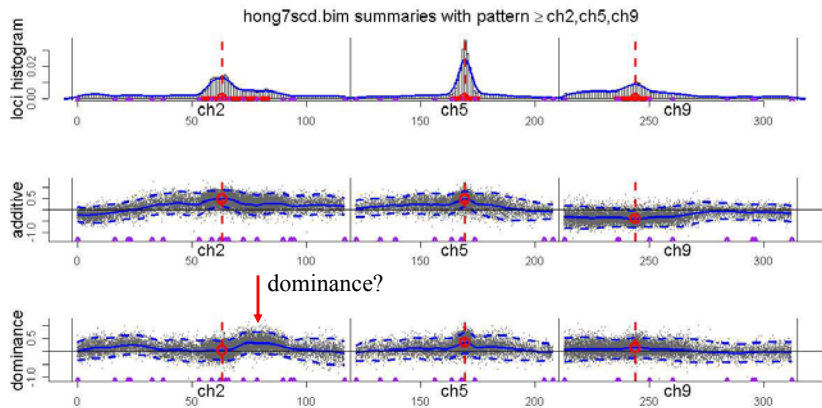


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trans-acting QTL for SCD1 (no epistasis yet: see Yi, Xu, Allison 2003)

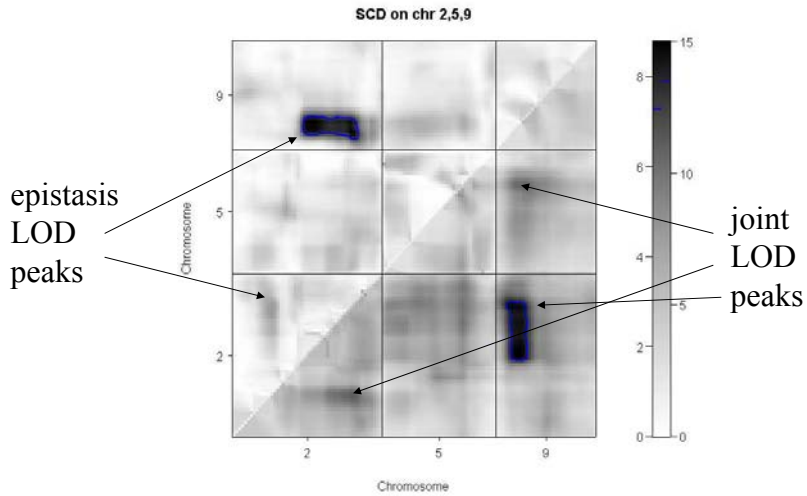


QTL 2: Data

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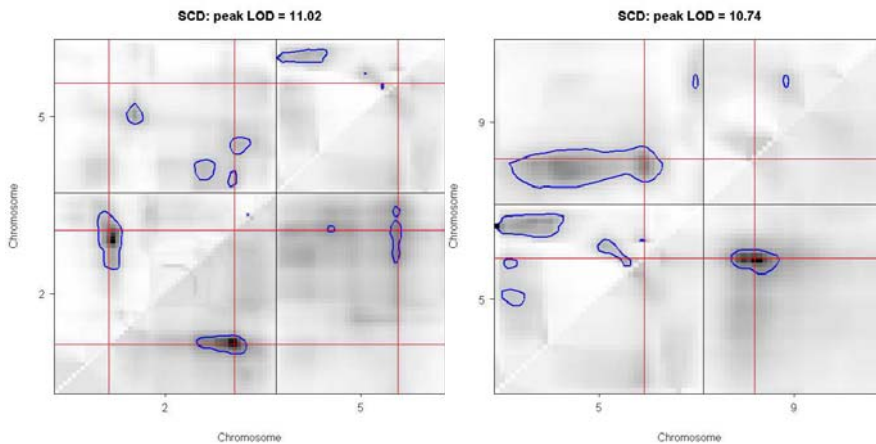
22

2-D scan: assumes only 2 QTL!



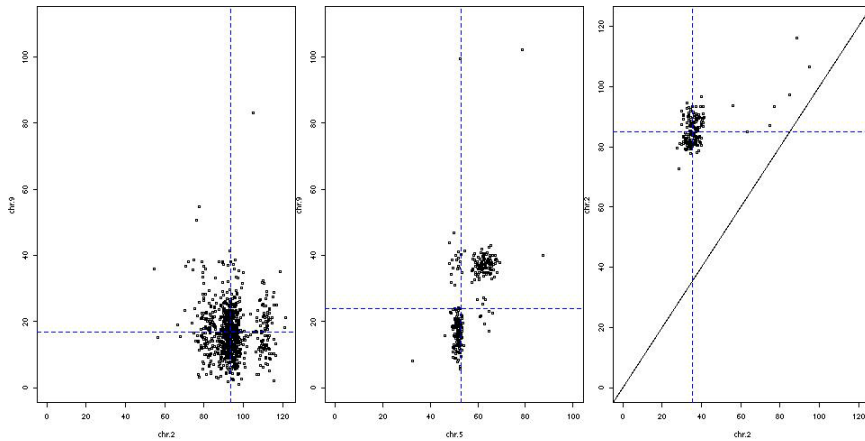
23

sub-peaks can be easily overlooked!



24

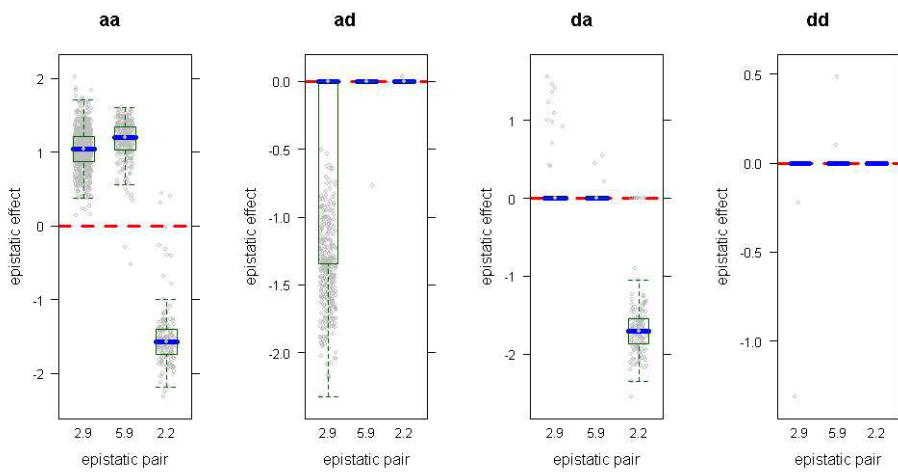
epistatic model fit



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Cockerham epistatic effects



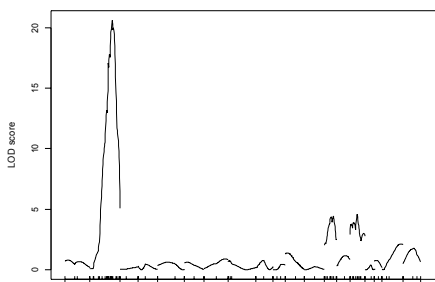
QTL 2: Data

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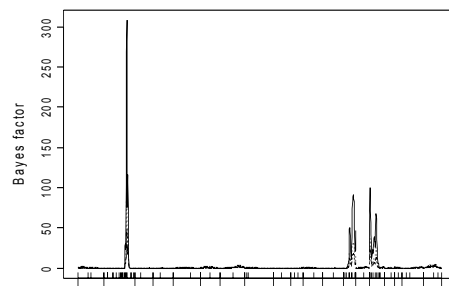
obesity in CAST/Ei BC onto M16i

- 421 mice (Daniel Pomp)
 - (213 male, 208 female)
- 92 microsatellites on 19 chromosomes
 - 1214 cM map
- subcutaneous fat pads
 - pre-adjusted for sex and dam effects
- Yi, Yandell, Churchill, Allison, Eisen, Pomp (2005) *Genetics* (in press)

non-epistatic analysis

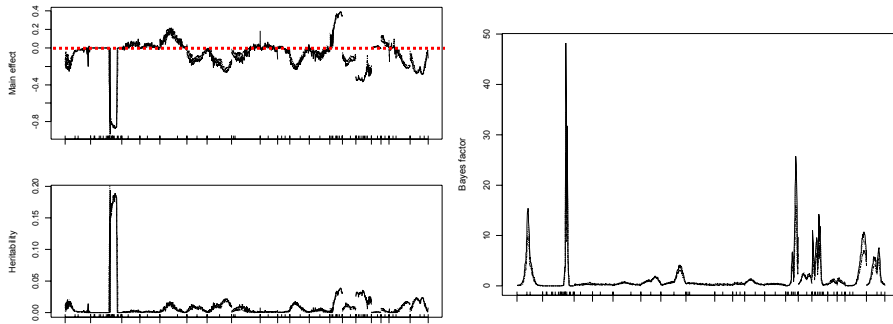


single QTL LOD profile



multiple QTL
Bayes factor profile

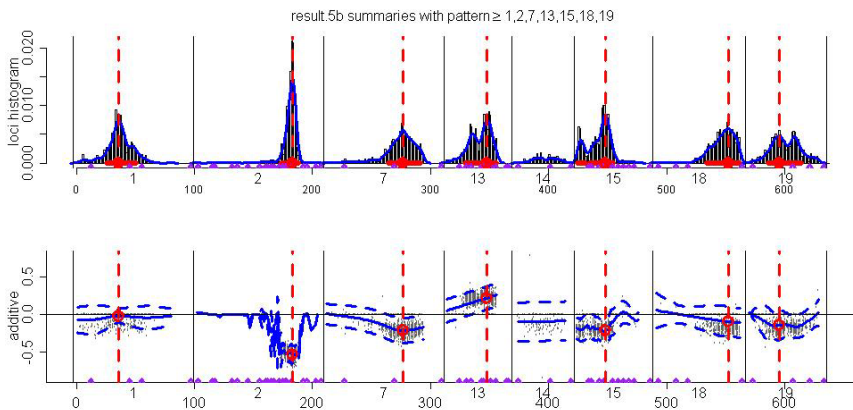
posterior profile of main effects in epistatic analysis



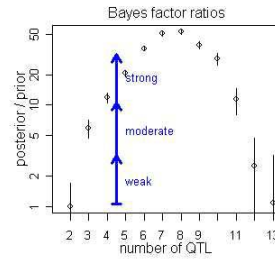
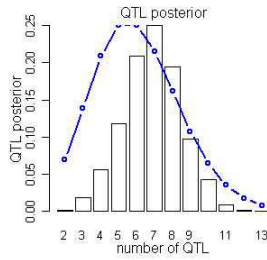
main effects & heritability profile

Bayes factor profile

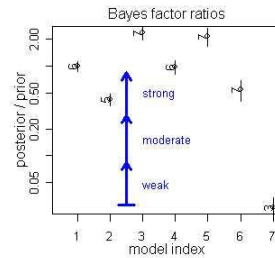
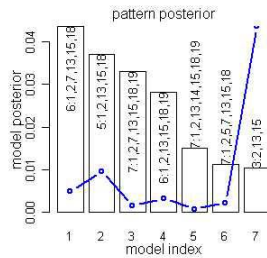
posterior profile of main effects in epistatic analysis



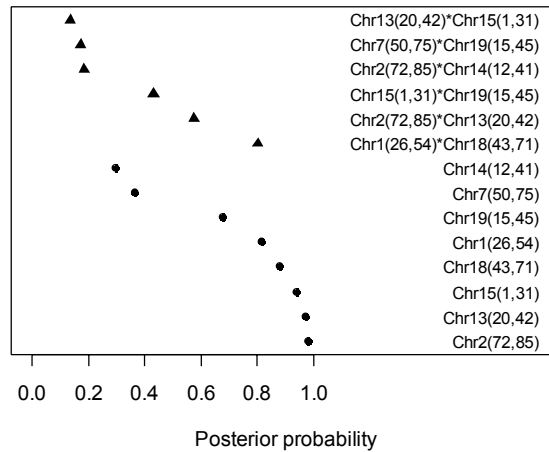
model selection
via
Bayes factors
for
epistatic model



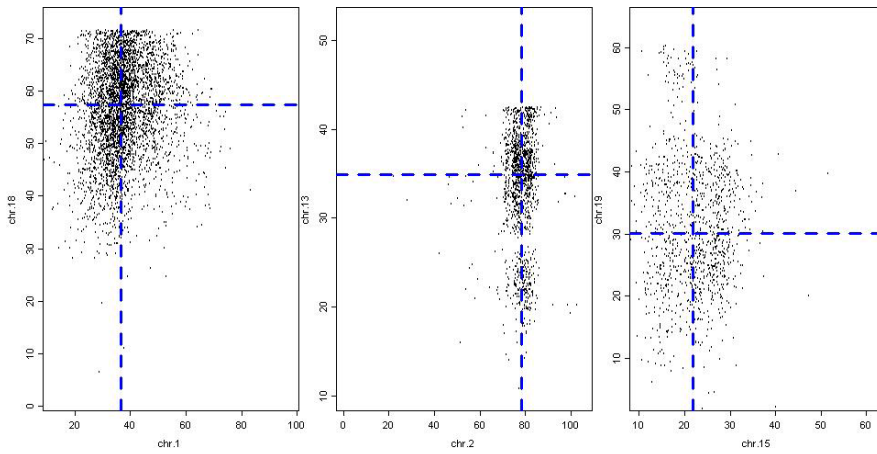
number of QTL
QTL pattern



posterior probability of effects



scatterplot estimates of epistatic loci

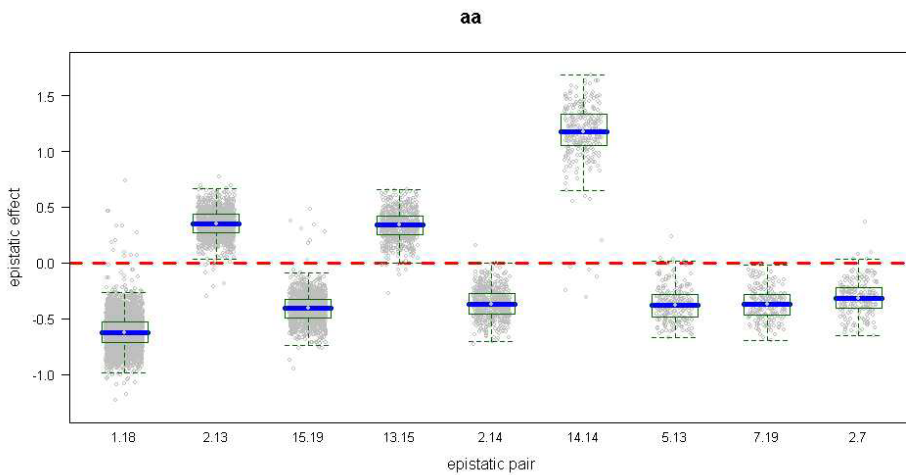


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33

stronger epistatic effects

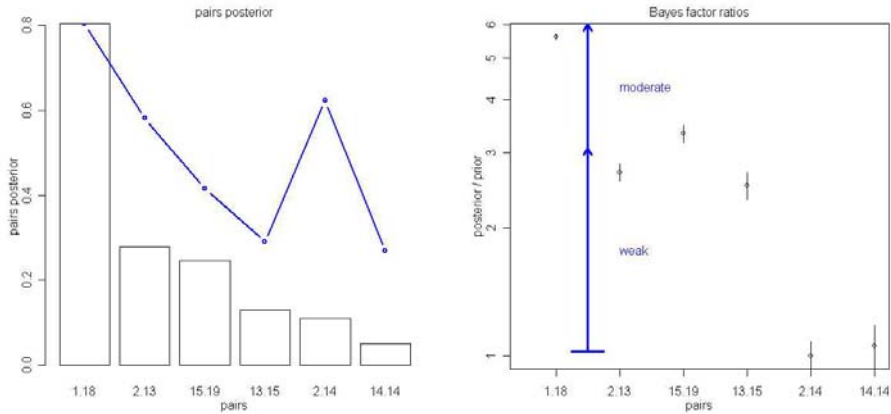


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model selection for pairs



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35

our RJ-MCMC software

- R: www.r-project.org
 - freely available statistical computing application R
 - library(bim) builds on Broman's library(qtl)
- QTLCart: statgen.ncsu.edu/qtlcart
 - Bmapqtl incorporated into QTLCart (S Wang 2003)
- www.stat.wisc.edu/~yandell/qtl/software/bmqtl
- R/bim
 - initially designed by JM Satagopan (1996)
 - major revision and extension by PJ Gaffney (2001)
 - whole genome, multivariate and long range updates
 - speed improvements, pre-burnin
 - built as official R library (H Wu, Yandell, Gaffney, CF Jin 2003)
- R/bmqtl
 - collaboration with N Yi, H Wu, GA Churchill
 - initial working module: Winter 2005
 - improved module and official release: Summer/Fall 2005
 - major NIH grant (PI: Yi)

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36