Gene Mapping: The Why and How of Multiple QTL

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- why: strategy
  - bias with single QTL
  - advantages of multiple QTL
- how: software
  - WinQTLCart intro
  - R/qtl demo
  - R/qtlbim demo

Real knowledge is to know the extent of one's ignorance.
Confucius (on a bench in Seattle)

outline

1. What is the goal of multiple QTL study?
2. Gene action and epistasis
3. Bayesian vs. classical QTL
4. QTL software options

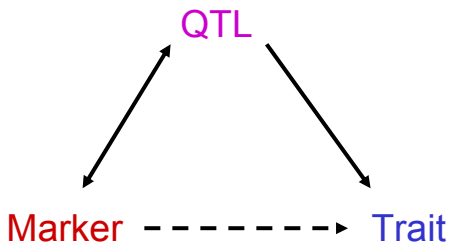
cross two inbred lines

→ linkage disequilibrium

→ associations

→ linked segregating QTL

(after Gary Churchill)

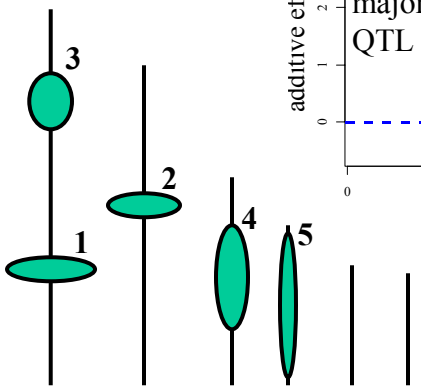


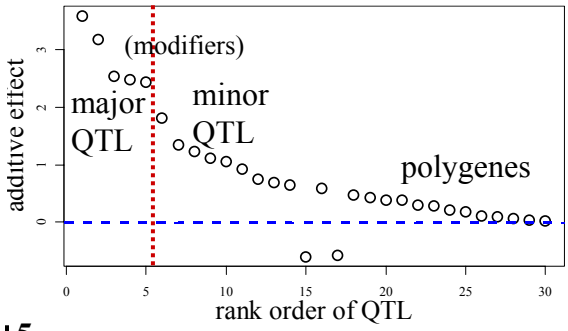
1. what is the goal of QTL study?

- uncover underlying biochemistry
  - identify how networks function, break down
  - find useful candidates for (medical) intervention
  - epistasis may play key role
  - statistical goal: maximize number of correctly identified QTL
- basic science/evolution
  - how is the genome organized?
  - identify units of natural selection
  - additive effects may be most important (Wright/Fisher debate)
  - statistical goal: maximize number of correctly identified QTL
- select "elite" individuals
  - predict phenotype (breeding value) using suite of characteristics (phenotypes) translated into a few QTL
  - statistical goal: mimimize prediction error

Pareto diagram of QTL effects

major QTL on linkage map





problems of single QTL approach

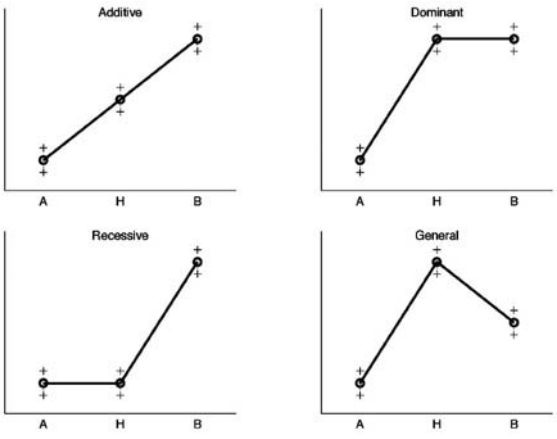
- wrong model: biased view
  - fool yourself: bad guess at locations, effects
  - detect ghost QTL between linked loci
  - miss epistasis completely
- low power
- bad science
  - use best tools for the job
  - maximize scarce research resources
  - leverage already big investment in experiment

advantages of multiple QTL approach

- improve statistical power, precision
  - increase number of QTL detected
  - better estimates of loci: less bias, smaller intervals
- improve inference of complex genetic architecture
  - patterns and individual elements of epistasis
  - appropriate estimates of means, variances, covariances
    - asymptotically unbiased, efficient
  - assess relative contributions of different QTL
- improve estimates of genotypic values
  - less bias (more accurate) and smaller variance (more precise)
  - mean squared error = MSE = $(\text{bias})^2$ + variance

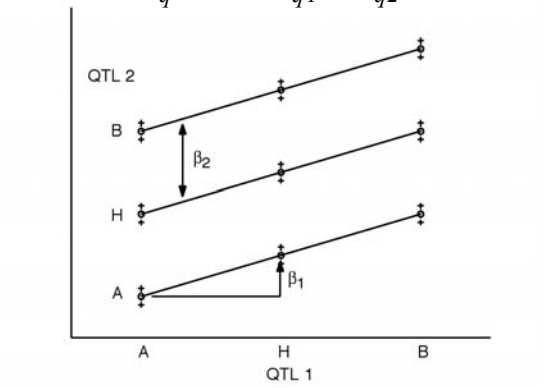
2. Gene Action and Epistasis

additive, dominant, recessive, general effects of a single QTL (Gary Churchill)



additive effects of two QTL (Gary Churchill)

$$\mu_q = \mu + \beta_{q1} + \beta_{q2}$$



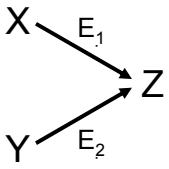
Epistasis (Gary Churchill)

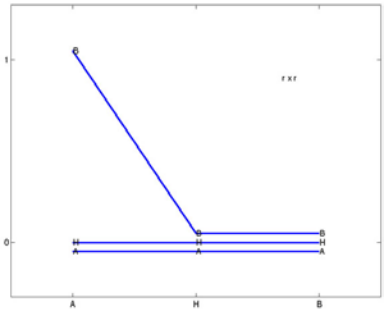
The allelic state at one locus can mask or uncover the effects of allelic variation at another.

- W. Bateson, 1907.

epistasis in parallel pathways (GAC)

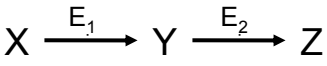
- Z keeps trait value low
- neither E_1 nor E_2 is rate limiting
- loss of function alleles are segregating from parent A at E_1 and from parent B at E_2

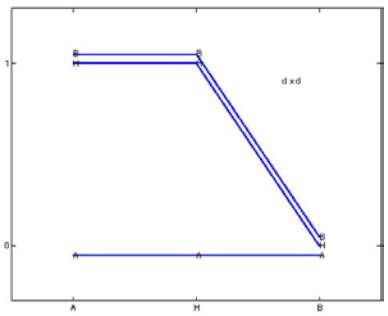




epistasis in a serial pathway (GAC)

- Z keeps trait value high
- neither E_1 nor E_2 is rate limiting
- loss of function alleles are segregating from parent B at E_1 and from parent A at E_2





epistatic interactions

- model space issues
  - 2-QTL interactions only?
    - or general interactions among multiple QTL?
  - partition of effects
    - Fisher-Cockerham or tree-structured or ?
- model search issues
  - epistasis between significant QTL
    - check all possible pairs when QTL included?
    - allow higher order epistasis?
  - epistasis with non-significant QTL
    - whole genome paired with each significant QTL?
    - pairs of non-significant QTL?
- see papers of Nengjun Yi (2000-7) in *Genetics*

limits of epistatic inference

- power to detect effects
  - epistatic model sizes grow quickly
    - $|A| = 3^{n.qtl}$ for general interactions
  - power tradeoff
    - depends sample size *vs.* model size
    - want $n / |A|$ to be fairly large (say > 5)
    - 3 QTL, $n = 100$ F2: $n / |A| \approx 4$
- rare genotypes may not be observed
  - *aa/BB & AA/bb* rare for linked loci
  - empty cells mess up balance
    - adjusted tests (type III) are wrong
  - confounds main effects & interactions

2 linked QTL empty cell with $n = 100$

	bb	*bB*	*BB*
aa	6	15	0
aA	15	25	15
AA	3	15	6

limits of multiple QTL?

- limits of statistical inference
  - power to detect QTL depends on many things
    - larger sample, higher heritability, smaller environmental variation
  - difficult to sort out effects of closely linked loci
  - "best" model balances data fit against model size
- limits of biological utility
  - marker assisted selection (Bernardo 2001 *Crop Sci*)
    - 10 QTL ok, 50 QTL are too many
    - phenotype better predictor than genotype when too many QTL
    - increasing sample size may not give multiple QTL any advantage
  - hard to select many QTL simultaneously
    - 3^m possible genotypes to choose from

QTL below detection level?

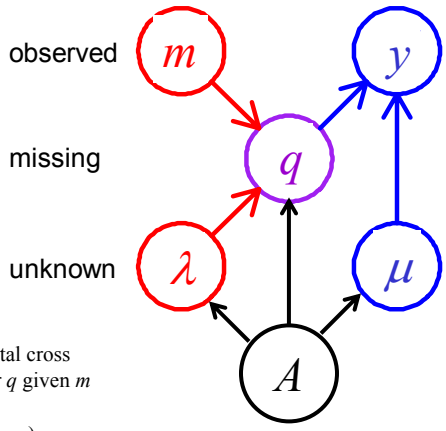
- problem of selection bias
  - QTL of modest effect only detected sometimes
  - effects overestimated when detected
  - repeat studies may fail to detect these QTL
- think of probability of detecting QTL
  - avoids sharp in/out dichotomy
  - avoid pitfalls of one "best" model
  - examine "better" models with more probable QTL
- rethink formal approach for QTL
  - directly allow uncertainty in genetic architecture
  - QTL model selection over genetic architecture

3. Bayesian vs. classical QTL study

- classical study
  - ***maximize*** over unknown effects
  - ***test*** for detection of QTL at loci
  - model selection in stepwise fashion
- Bayesian study
  - ***average*** over unknown effects
  - ***estimate*** chance of detecting QTL
  - sample all possible models
- both approaches
  - average over missing QTL genotypes
  - scan over possible loci

QTL model selection: key players

- observed measurements
  - y = phenotypic trait
  - m = markers & linkage map
  - i = individual index $(1,\ldots,n)$
- missing data
  - missing marker data
  - q = QT genotypes
    - alleles QQ, Qq, or qq at locus
- unknown quantities
  - λ = QT locus (or loci)
  - μ = phenotype model parameters
  - A = QTL model/genetic architecture
- $\Pr(q|m,\lambda,A)$ genotype model
  - grounded by linkage map, experimental cross
  - recombination yields multinomial for q given m
- $\Pr(y|q,\mu,A)$ phenotype model
  - distribution shape (assumed normal here)
  - unknown parameters μ (could be non-parametric)



after
Sen Churchill (2001)

Bayes posterior vs. maximum likelihood

- LOD: classical Log ODds
  - maximize likelihood over effects μ
  - `R/qtl scanone/scantwo: method = "em"`
- *LPD*: Bayesian *L*og *P*osterior *D*ensity
  - average posterior over effects μ
  - `R/qtl scanone/scantwo: method = "imp"`

$$\mathrm{LOD}(\lambda) = \log_{10}\{\max_{\mu} \mathrm{pr}(y \mid m, \mu, \lambda)\} + c$$

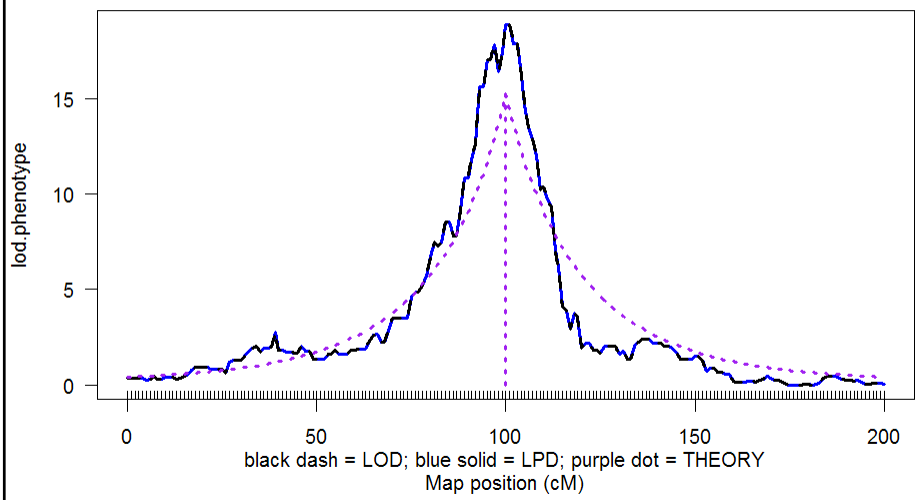
$$\mathrm{LPD}(\lambda) = \log_{10}\{\mathrm{pr}(\lambda \mid m) \int \mathrm{pr}(y \mid m, \mu, \lambda)\mathrm{pr}(\mu) d\mu\} + C$$

likelihood mixes over missing QTL genotypes:

$$\mathrm{pr}(y \mid m, \mu, \lambda) = \sum_q \mathrm{pr}(y \mid q, \mu)\mathrm{pr}(q \mid m, \lambda)$$

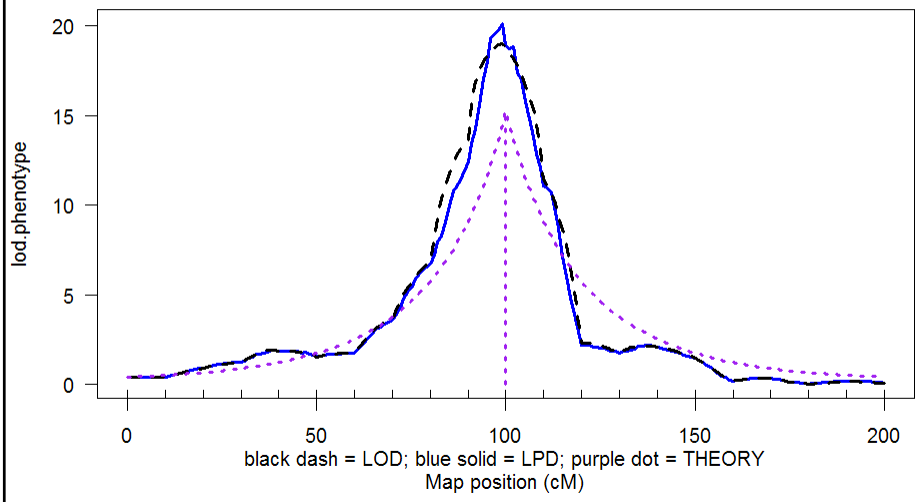
LOD & LPD: 1 QTL

n.ind = 100, 1 cM marker spacing



LOD & LPD: 1 QTL

n.ind = 100, 10 cM marker spacing



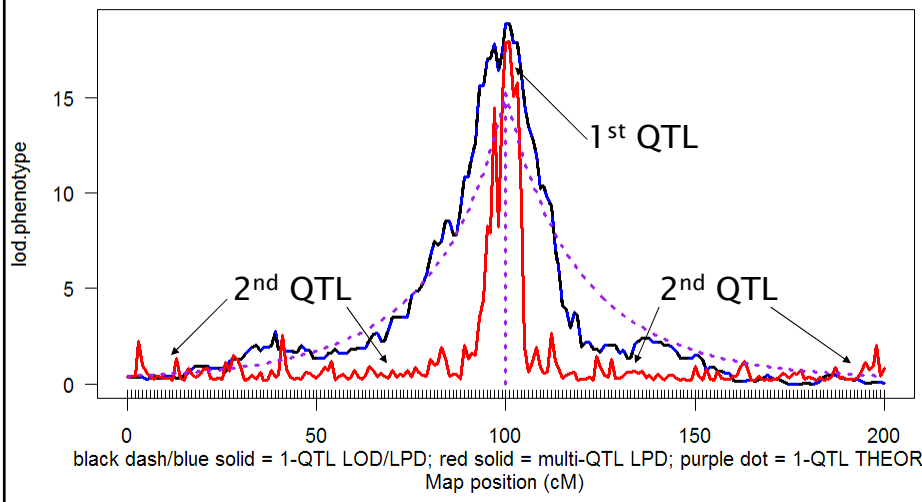
marginal LOD or LPD

- compare two architectures at each locus
  - with (A_2) or without (A_1) another QTL at separate locus λ_2
    - preserve model hierarchy (e.g. drop any epistasis with QTL at λ_2)
  - with (A_2) or without (A_1) epistasis with second locus λ_2
- allow for multiple QTL besides locus being scanned
  - allow for QTL at all other loci λ_1 in architecture A_1
- use marginal LOD, LPD or other diagnostic
  - posterior, Bayes factor, heritability

$$\mathrm{LOD}(\lambda_1, \lambda_2 \mid A_2) - \mathrm{LOD}(\lambda_1 \mid A_1)$$
$$\mathrm{LPD}(\lambda_1, \lambda_2 \mid A_2) - \mathrm{LPD}(\lambda_1 \mid A_1)$$

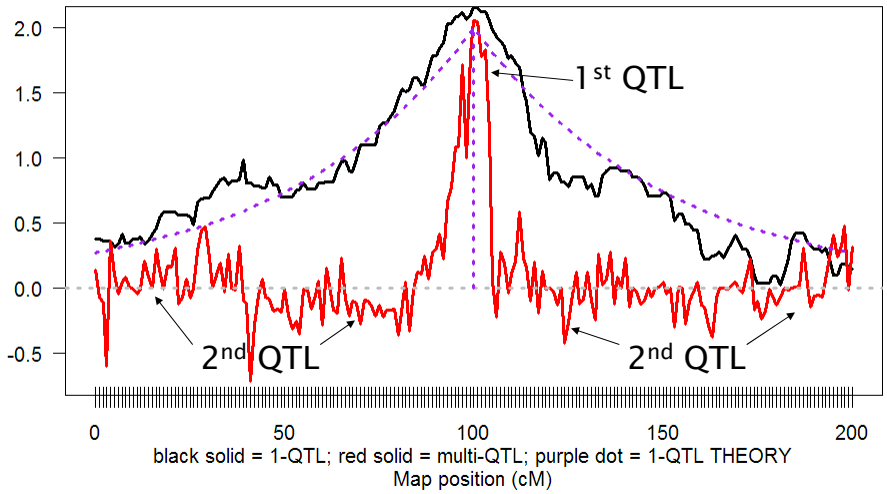
LPD: 1 QTL vs. multi-QTL

marginal contribution to LPD from QTL at λ



substitution effect: 1 QTL vs. multi-QTL

single QTL effect vs. marginal effect from QTL at λ



comparing models

- balance model fit against model complexity
  - want to fit data well (maximum likelihood)
  - without getting too complicated a model

	smaller model	**bigger model**
fit model	miss key features	fits better
estimate phenotype	may be biased	no bias
predict new data	may be biased	no bias
interpret model	easier	more complicated
estimate effects	low variance	high variance

information criteria
to balance fit against complexity

- classical information criteria
  - penalize likelihood L by model size $|A|$
  - IC = $-2 \log L(A \mid y) + \text{penalty}(A)$
  - maximize over unknowns
- Bayes factors
  - marginal posteriors $\text{pr}(y \mid A)$
  - average over unknowns

4. QTL software options

- methods
  - approximate QTL by markers
  - exact multiple QTL interval mapping
- software platforms
  - MapMaker/QTL (obsolete)
  - QTLCart (statgen.ncsu.edu/qtlcart)
  - R/qtl (www.rqtl.org)
  - R/qtlbim (www.qtlbim.org)
  - Yandell, Bradbury (2007) book chapter

approximate QTL methods

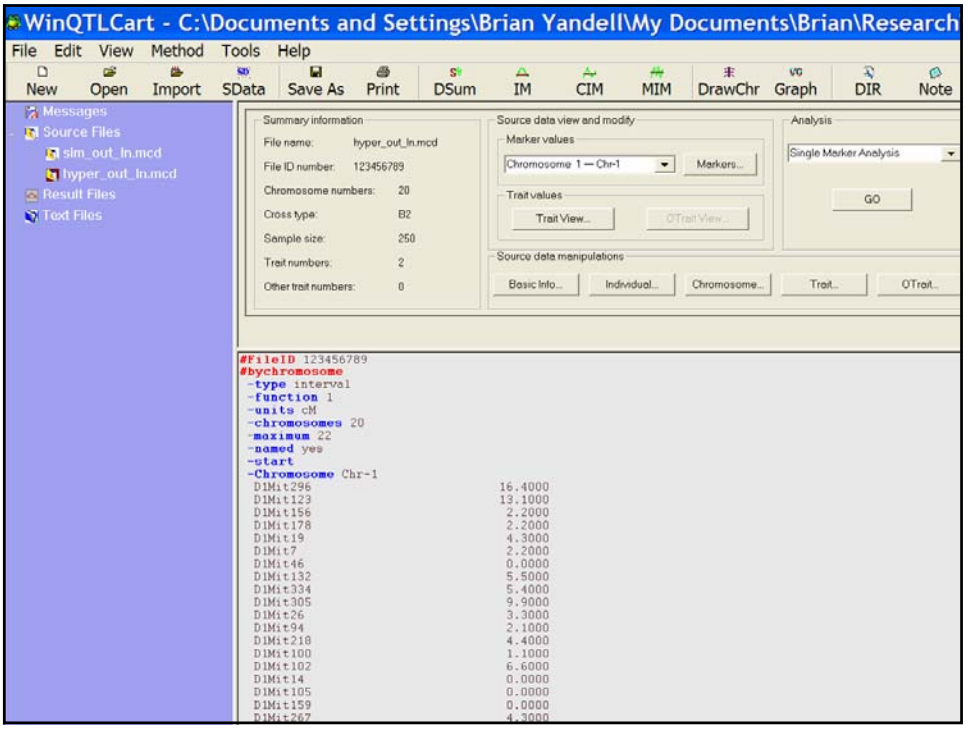
- marker regression
  - locus & effect confounded
  - lose power with missing data
- Haley-Knott (least squares) regression
  - correct mean, wrong variance
  - biased by pattern of missing data (Kao 2000)
- extended HK regression
  - correct mean and variance
  - minimizes bias issue (R/qtl "ehk" method)
- composite interval mapping (QTLCart)
  - use markers to approximate other QTL
  - properties depend on marker spacing, missing data

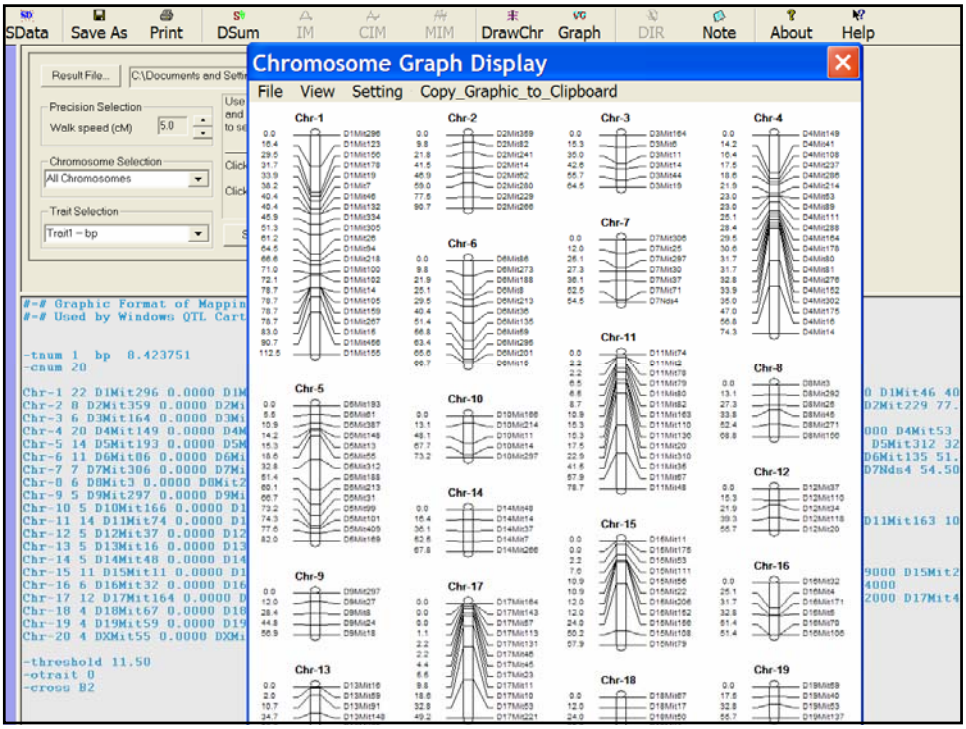
exact QTL methods

- interval mapping (Lander, Botstein 1989)
  - scan whole genome for single QTL
  - bias for linked QTL, low power
- multiple interval mapping (Kao, Zeng, Teasdale 1999)
  - sequential scan of all QTL
  - stepwise model selection
- multiple imputation (Sen, Churchill 2001)
  - fill in (impute) missing genotypes along genome
  - average over multiple imputations
- Bayesian interval mapping (Yi et al. 2005)
  - sample most likely models
  - marginal scans conditional on other QTL

QTL software platforms

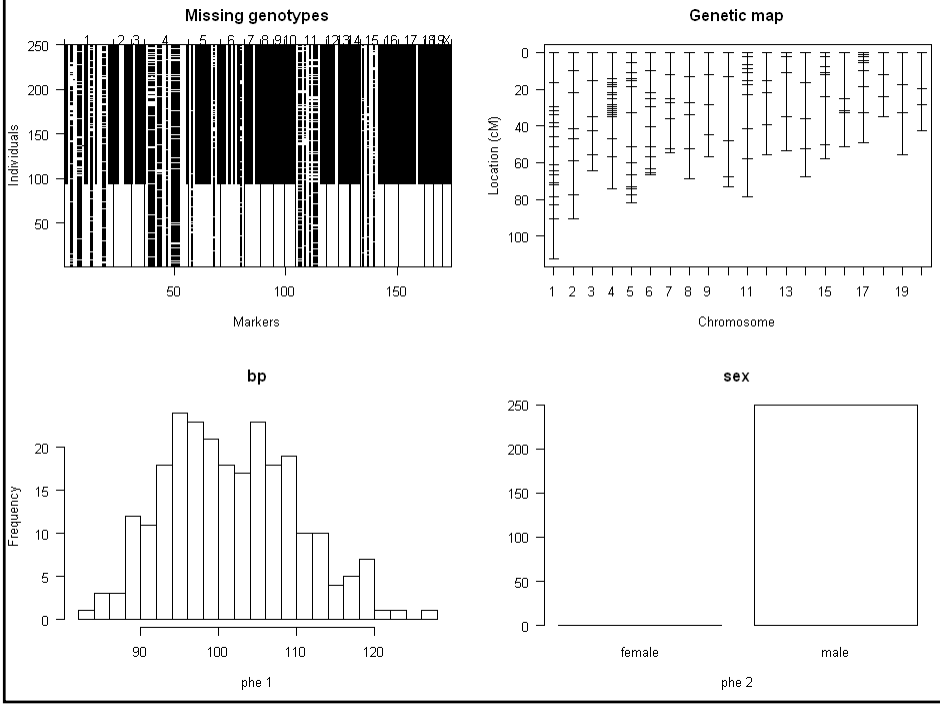
- QTLCart (statgen.ncsu.edu/qtlcart)
  - includes features of original MapMaker/QTL
    - not designed for building a linkage map
  - easy to use Windows version WinQTLCart
  - based on Lander-Botstein maximum likelihood LOD
    - extended to marker cofactors (CIM) and multiple QTL (MIM)
    - epistasis, some covariates (GxE)
    - stepwise model selection using information criteria
  - some multiple trait options
  - OK graphics
- R/qtl (www.rqtl.org)
  - includes functionality of classical interval mapping
  - many useful tools to check genotype data, build linkage maps
  - excellent graphics
  - several methods for 1-QTL and 2-QTL mapping
    - epistasis, covariates (GxE)
  - tools available for multiple QTL model selection

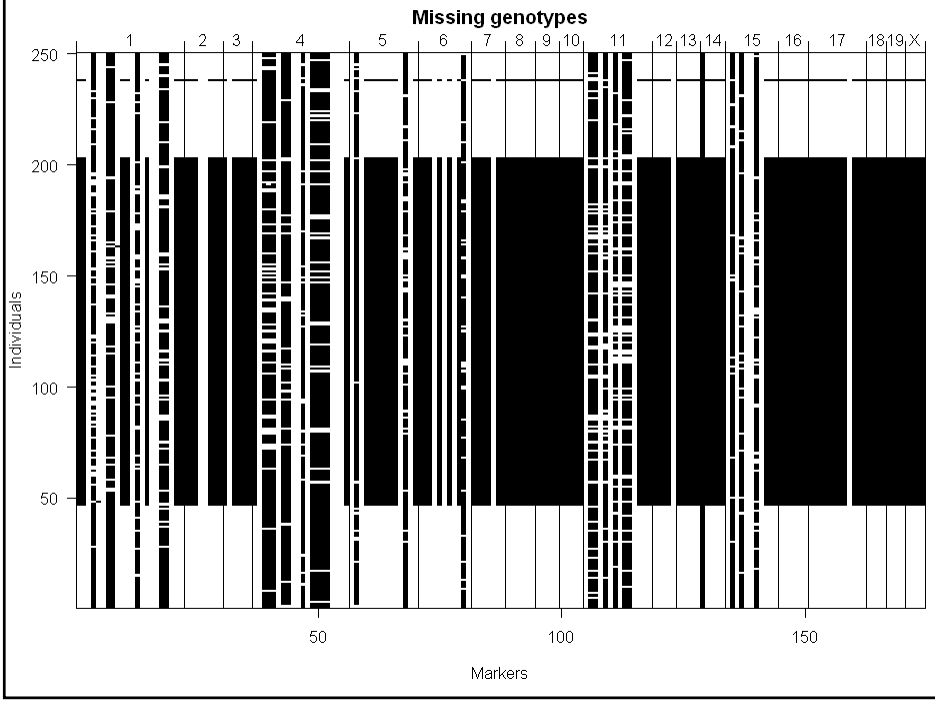

WinQTLCart - C:\Documents and Settings\Brian Yandell\My Documents\Brian\Research
File Edit View Method Tools Help
New Open Import SData Save As Print DSum IM CIM MIM DrawChr Graph DIR Note
Messages
Source Files
slm_out_ln.mcd
hyper_out_ln.mcd
Result Files
Text Files
Summary information
File name: hyper_out_ln.mcd
File ID number: 123456789
Chromosome numbers: 20
Cross type: B2
Sample size: 250
Trait numbers: 2
Other trait numbers: 0
Source data view and modify
Marker values
Chromosome 1 — Chr-1
Markers...
Trait values
Trait View...
OTrait View...
Source data manipulations
Basic Info...
Individual...
Chromosome...
Trait...
OTrait...
Analysis
Single Marker Analysis
GO
#FileID 123456789
#bychromosome
-type interval
-function 1
-units cM
-chromosomes 20
-maximum 22
-named yes
-start
-Chromosome Chr-1
D1Mit296 16.4000
D1Mit123 13.1000
D1Mit156 2.2000
D1Mit178 2.2000
D1Mit19 4.3000
D1Mit7 2.2000
D1Mit46 0.0000
D1Mit132 5.5000
D1Mit334 5.4000
D1Mit305 9.9000
D1Mit26 3.3000
D1Mit94 2.1000
D1Mit210 4.4000
D1Mit100 1.1000
D1Mit102 6.6000
D1Mit14 0.0000
D1Mit105 0.0000
D1Mit159 0.0000
D1Mit267 4.3000


SData Save As Print DSum IM CIM MIM DrawChr Graph DIR Note About Help
Result File...
C:\Documents and Setti
Precision Selection
Walk speed (cM) 5.0
Chromosome Selection
All Chromosomes
Trait Selection
Trait1 – bp
#-# Graphic Format of Mappin
#-# Used by Windows QTL Cart
-tnum 1 bp 8.423751
-cnum 20
Chr-1 22 D1Mit296 0.0000 D1M
Chr-2 8 D2Mit359 0.0000 D2Mi
Chr-3 6 D3Mit164 0.0000 D3Mi
Chr-4 20 D4Mit149 0.0000 D4M
Chr-5 14 D5Mit193 0.0000 D5M
Chr-6 11 D6Mit06 0.0000 D6Mi
Chr-7 7 D7Mit306 0.0000 D7Mi
Chr-8 6 D8Mit3 0.0000 D8Mit2
Chr-9 5 D9Mit297 0.0000 D9Mi
Chr-10 5 D10Mit166 0.0000 D1
Chr-11 14 D11Mit74 0.0000 D1
Chr-12 5 D12Mit37 0.0000 D12
Chr-13 5 D13Mit16 0.0000 D13
Chr-14 5 D14Mit48 0.0000 D14
Chr-15 11 D15Mit11 0.0000 D1
Chr-16 6 D16Mit32 0.0000 D16
Chr-17 12 D17Mit164 0.0000 D
Chr-18 4 D18Mit67 0.0000 D18
Chr-19 4 D19Mit59 0.0000 D19
Chr-20 4 DXMit55 0.0000 DXMi
-threshold 11.50
-otrait 0
-cross B2
Chromosome Graph Display
File View Setting Copy_Graphic_to_Clipboard
Chr-1
Chr-2
Chr-3
Chr-4
Chr-5
Chr-6
Chr-7
Chr-8
Chr-9
Chr-10
Chr-11
Chr-12
Chr-13
Chr-14
Chr-15
Chr-16
Chr-17
Chr-18
Chr-19
0 D1Mit46 40
D2Mit229 77.
000 D4Mit53
D5Mit312 32
D6Mit135 51.
D7Nds4 54.50
D11Mit163 10
9000 D15Mit2
4000
2000 D17Mit4

R/qtl tutorial (www.rqtl.org)

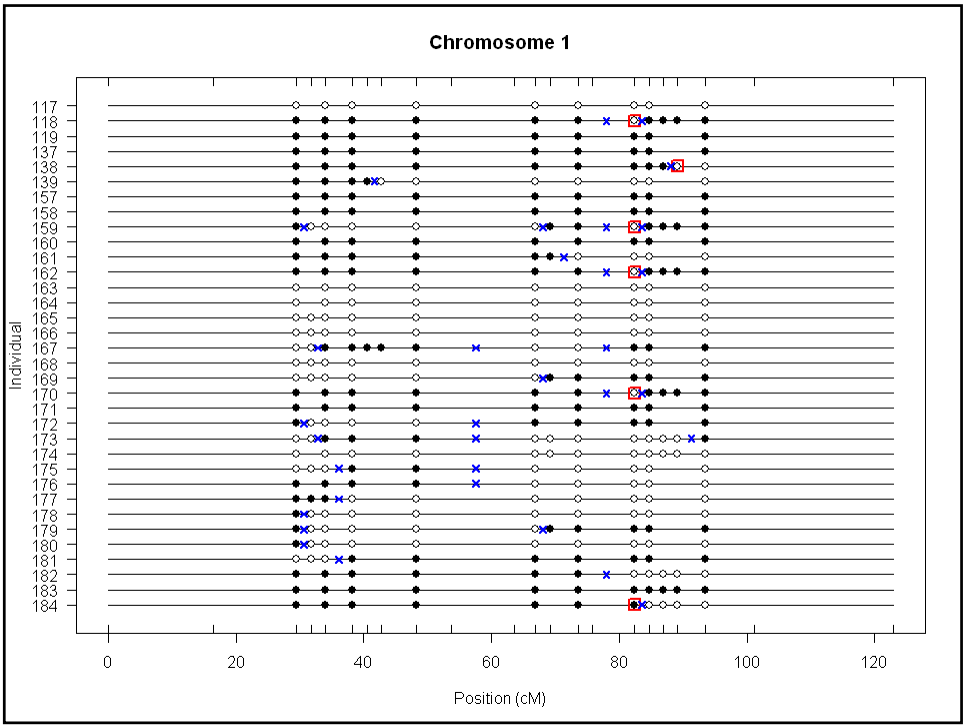
```
> library(qtl)
> data(hyper)
> summary(hyper)
    Backcross

    No. individuals:    250

    No. phenotypes:     2
    Percent phenotyped: 100 100

    No. chromosomes:    20
        Autosomes:      1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19
        X chr:          X

    Total markers:      174
    No. markers:        22 8 6 20 14 11 7 6 5 5 14 5 5 5 11 6 12 4 4 4
    Percent genotyped:  47.7
    Genotypes (%):      AA:50.2  AB:49.8
> plot(hyper)
> plot.missing(hyper, reorder = TRUE)
```



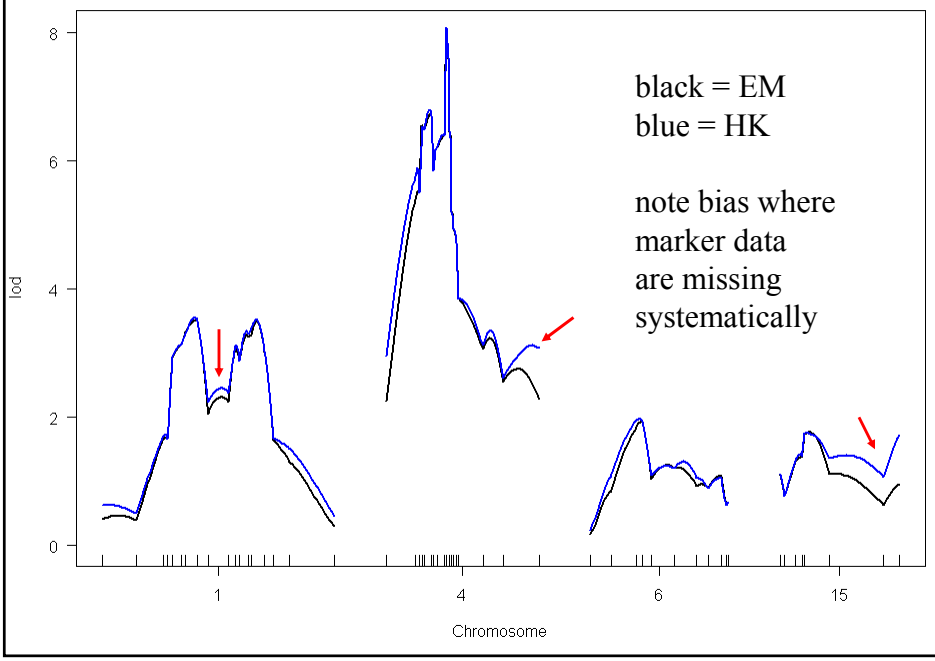
R/qtl: find genotyping errors

```
> hyper <- calc.errorlod(hyper, error.prob=0.01)
> top.errorlod(hyper)
   chr  id    marker errorlod
1    1 118   D1Mit14 8.372794
2    1 162   D1Mit14 8.372794
3    1 170   D1Mit14 8.372794
4    1 159   D1Mit14 8.350341
5    1  73   D1Mit14 6.165395
6    1  65   D1Mit14 6.165395
7    1  88   D1Mit14 6.165395
8    1 184   D1Mit14 6.151606
9    1 241   D1Mit14 6.151606
...
16   1 215  D1Mit267 5.822192
17   1 108  D1Mit267 5.822192
18   1 138  D1Mit267 5.822192
19   1 226  D1Mit267 5.822192
20   1 199  D1Mit267 5.819250
21   1  84  D1Mit267 5.808400
> plot.geno(hyper, chr=1, ind=c(117:119,137:139,157:184))
```



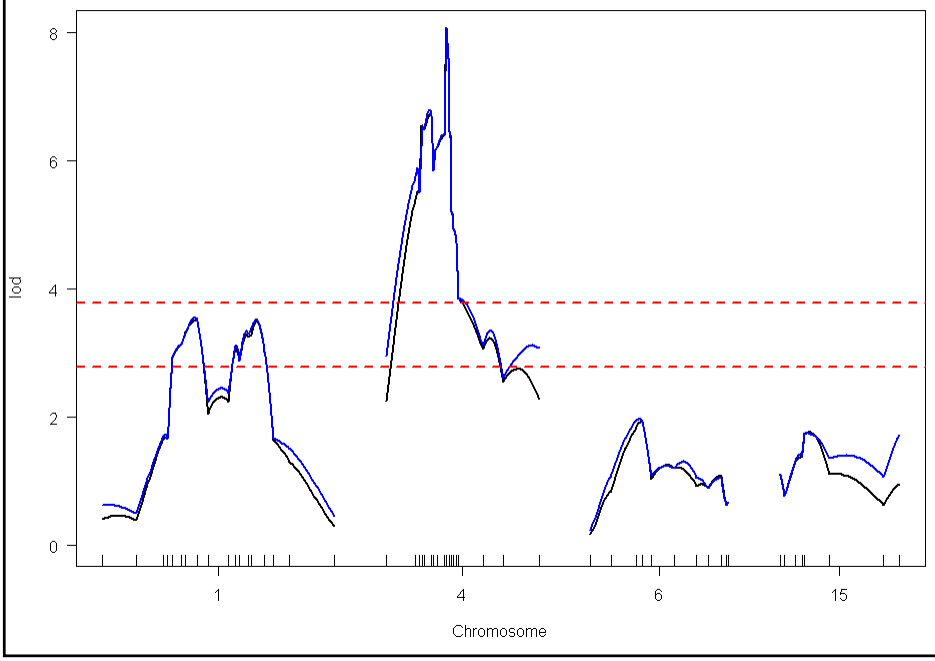
R/qtl: 1 QTL interval mapping

```
> hyper <- calc.genoprob(hyper, step=1,
  error.prob=0.01)
> out.em <- scanone(hyper)
> out.hk <- scanone(hyper, method="hk")
> summary(out.em, threshold=3)
          chr  pos  lod
c1.loc45    1 48.3 3.52
D4Mit164    4 29.5 8.02
> summary(out.hk, threshold=3)
          chr  pos  lod
c1.loc45    1 48.3 3.55
D4Mit164    4 29.5 8.09
```



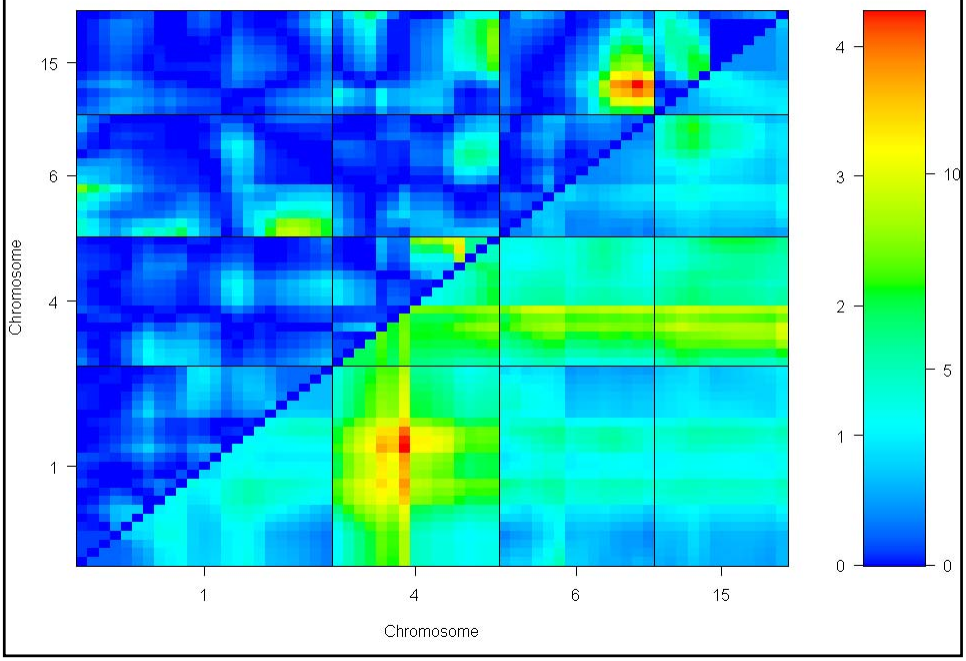
R/qtl: permutation threshold

```
> operm.hk <- scanone(hyper, method="hk",
  n.perm=1000)
Doing permutation in batch mode ...
> summary(operm.hk, alpha=c(0.01,0.05))
LOD thresholds (1000 permutations)
    lod
1% 3.79
5% 2.78
> summary(out.hk, perms=operm.hk, alpha=0.05,
  pvalues=TRUE)
  chr  pos  lod  pval
1   1 48.3 3.55 0.015
2   4 29.5 8.09 0.000
```



R/qtl: 2 QTL scan

```
> hyper <- calc.genoprob(hyper, step=5, error.prob=0.01)
>
> out2.hk <- scantwo(hyper, method="hk")
 --Running scanone
 --Running scantwo
 (1,1)
 (1,2)
...
 (19,19)
 (19,X)
 (X,X)
> summary(out2.hk, thresholds=c(6.0, 4.7, 4.4, 4.7, 2.6))
        pos1f pos2f lod.full lod.fv1 lod.int     pos1a pos2a lod.add lod.av1
c1 :c4   68.3  30.0    14.13    6.51   0.225      68.3  30.0   13.90   6.288
c2 :c19  47.7   0.0     6.71    5.01   3.458      52.7   0.0    3.25   1.552
c3 :c3   37.2  42.2     6.10    5.08   0.226      37.2  42.2    5.87   4.853
c6 :c15  60.0  20.5     7.17    5.22   3.237      25.0  20.5    3.93   1.984
c9 :c18  67.0  37.2     6.31    4.79   4.083      67.0  12.2    2.23   0.708
c12:c19   1.1  40.0     6.48    4.79   4.090       1.1   0.0    2.39   0.697
> plot(out2.hk, chr=c(1,4,6,15))
```



R/qtl: ANOVA imputation at QTL

```
> hyper <- sim.geno(hyper, step=2, n.draws=16, error.prob=0.01)
> qtl <- makeqtl(hyper, chr = c(1, 1, 4, 6, 15), pos = c(50, 76, 30, 70, 20))

> my.formula <- y ~ Q1 + Q2 + Q3 + Q4 + Q5 + Q4:Q5
> out.fitqtl <- fitqtl(hyper$pheno[,1], qtl, formula=my.formula)
> summary(out.fitqtl)

Full model result
----------------------------------
Model formula is:  y ~ Q1 + Q2 + Q3 + Q4 + Q5 + Q4:Q5

       df        SS        MS      LOD     %var Pvalue(Chi2) Pvalue(F)
Model   6  5789.089 964.84822 21.54994 32.76422            0         0
Error 243 11879.847  48.88826
Total 249 17668.936

Drop one QTL at a time ANOVA table:
----------------------------------
                 df Type III SS      LOD     %var F value Pvalue(F)
Chr1@50           1     297.149    1.341    1.682   6.078   0.01438 *
Chr1@76           1     520.664    2.329    2.947  10.650   0.00126 **
Chr4@30           1    2842.089   11.644   16.085  58.134  5.50e-13 ***
Chr6@70           2    1435.721    6.194    8.126  14.684  9.55e-07 ***
Chr15@20          2    1083.842    4.740    6.134  11.085  2.47e-05 ***
Chr6@70:Chr15@20  1     955.268    4.199    5.406  19.540  1.49e-05 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

R/qtlbim (www.qtlbim.org)

- cross-compatible with R/qtl
- model selection for genetic architecture
  - epistasis, fixed & random covariates, GxE
  - samples multiple genetic architectures
  - examines summaries over nested models
- extensive graphics

R/qtlbim: tutorial

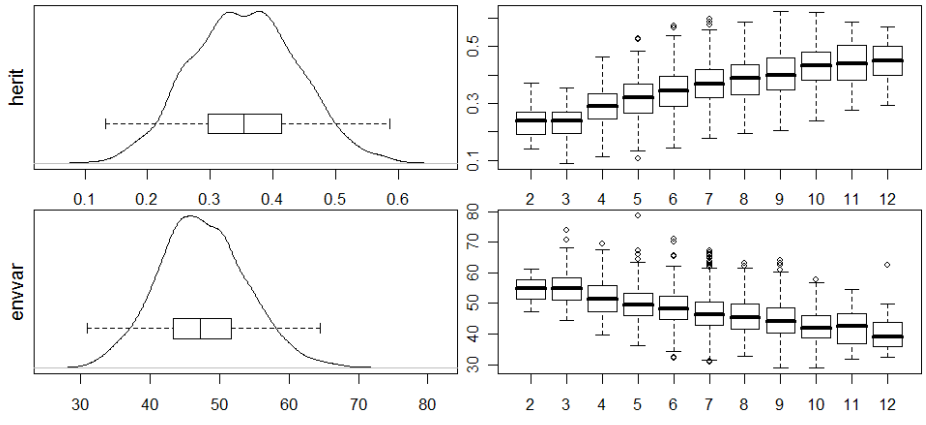
(www.stat.wisc.edu/~yandell/qtlbim)

```
> data(hyper)
## Drop X chromosome (for now).
> hyper <- subset(hyper, chr=1:19)
> hyper <- qb.genoprob(hyper, step=2)
## This is the time-consuming step:
> qbHyper <- qb.mcmc(hyper, pheno.col = 1)
## Here we get stored samples.
> qb.load(hyper, qbHyper)
> summary(qbHyper)
```

R/qtlbim: initial summaries

```
> summary(qbHyper)
Bayesian model selection QTL mapping object qbHyper on cross object hyper
had 3000 iterations recorded at each 40 steps with 1200 burn-in steps.

Diagnostic summaries:
          nqtl    mean envvar varadd  varaa    var
Min.     2.000  97.42  28.07  5.112  0.000  5.112
1st Qu.  5.000 101.00  44.33 17.010  1.639 20.180
Median   7.000 101.30  48.57 20.060  4.580 25.160
Mean     6.543 101.30  48.80 20.310  5.321 25.630
3rd Qu.  8.000 101.70  53.11 23.480  7.862 30.370
Max.    13.000 103.90  74.03 51.730 34.940 65.220

Percentages for number of QTL detected:
 2  3  4  5  6  7  8  9 10 11 12 13
 2  3  9 14 21 19 17 10  4  1  0  0

Percentages for number of epistatic pairs detected:
pairs
 1  2  3  4  5  6
29 31 23 11  5  1

Percentages for common epistatic pairs:
 6.15  4.15   4.6   1.7 15.15   1.4   1.6   4.9  1.15  1.17   1.5  5.11   1.2  7.15   1.1
   63    18    10     6     6     5     4     4     3     3     2     2     2     2     2
> plot(qb.diag(qbHyper, items = c("herit", "envvar")))
```

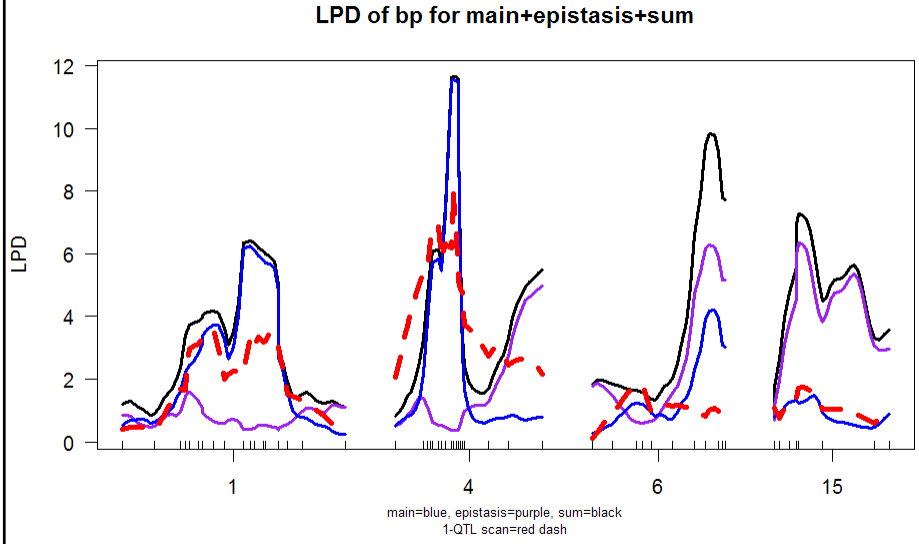

diagnostic summaries



R/qtlbim: 1-D (*not* 1-QTL!) scan

```
> one <- qb.scanone(qbHyper, chr = c(1,4,6,15),
  type = "LPD")
> summary(one)
LPD of bp for main,epistasis,sum

     n.qtl  pos m.pos e.pos  main epistasis   sum
c1   1.331 64.5  64.5  67.8  6.10     0.442  6.27
c4   1.377 29.5  29.5  29.5 11.49     0.375 11.61
c6   0.838 59.0  59.0  59.0  3.99     6.265  9.60
c15 0.961 17.5  17.5  17.5  1.30     6.325  7.28
> plot(one)
> plot(out.em, chr=c(1,4,6,15), add = TRUE, col =
  "red", lty = 2)
```

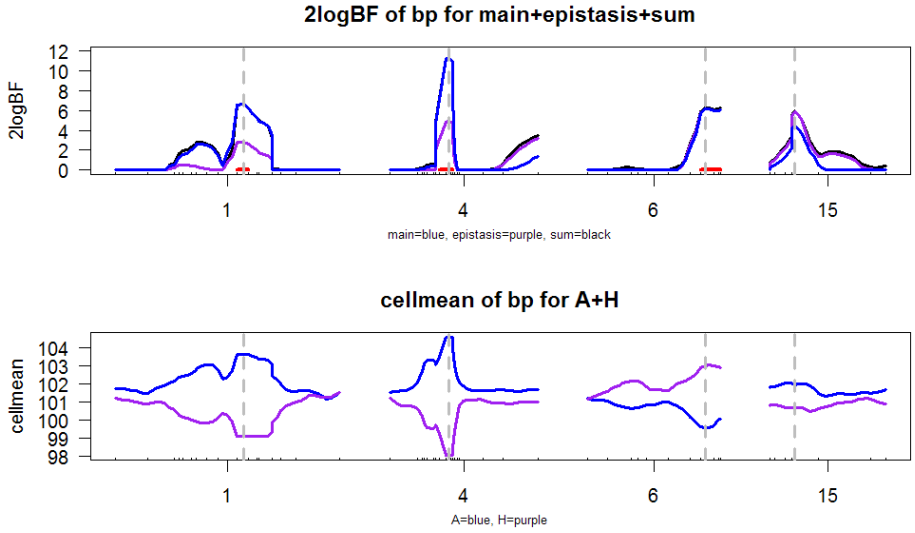

hyper data: scanone



R/qtlbim: automated QTL selection

```
> hpd <- qb.hpdone(qbHyper, profile = "2logBF")
> summary(hpd)
   chr n.qtl  pos lo.50% hi.50% 2logBF       A       H
1    1 0.829 64.5   64.5   72.1  6.692 103.611  99.090
4    4 3.228 29.5   25.1   31.7 11.169 104.584  98.020
6    6 1.033 59.0   56.8   66.7  6.054  99.637 102.965
15  15 0.159 17.5   17.5   17.5  5.837 101.972 100.702
> plot(hpd)
```

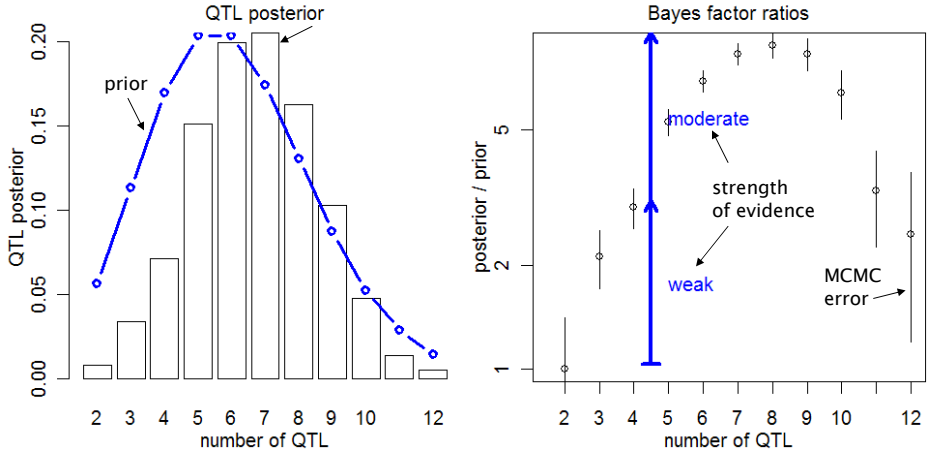

2log(BF) scan with 50% HPD region



R/qtlbim: Bayes Factor evaluations

```
> tmp <- qb.BayesFactor(qbHyper)
> summary(tmp)
$nqtl

$pattern
                  posterior    prior     bf   bfse
7:2*1,2*15,2*4,6    0.00500 3.17e-07 220.00 56.700
6:1,2*15,2*4,6      0.01400 1.02e-06 192.00 29.400
7:1,2*15,2*4,5,6    0.00600 4.49e-07 186.00 43.800
7:1,2*15,2,2*4,6    0.00433 5.39e-07 112.00 31.000
5:1,15,2*4,6        0.00867 5.81e-06  20.80  4.060
5:1,15,4,2*6        0.00733 5.22e-06  19.60  4.170
4:1,15,4,6          0.03770 2.71e-05  19.40  1.790

$chrom
   posterior  prior    bf  bfse
4     0.2100 0.0595 15.00 0.529
15    0.1470 0.0464 13.40 0.589
6     0.1280 0.0534 10.10 0.483
1     0.2030 0.0901  9.55 0.345
> plot(tmp)
```

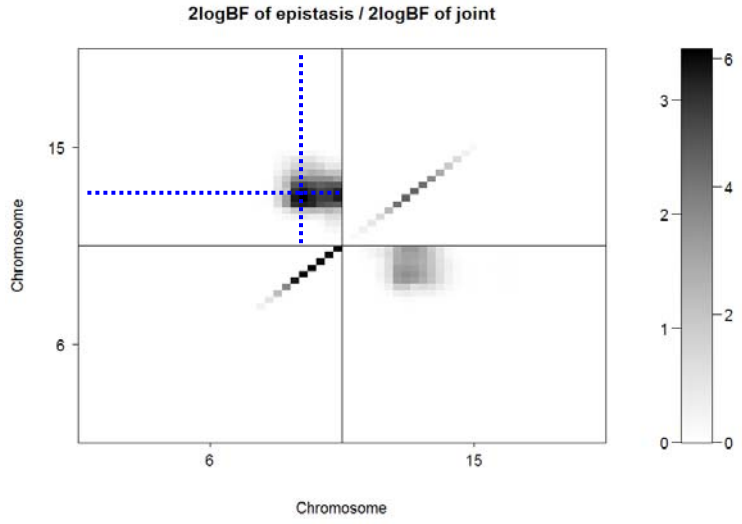

hyper: number of QTL posterior, prior, Bayes factors



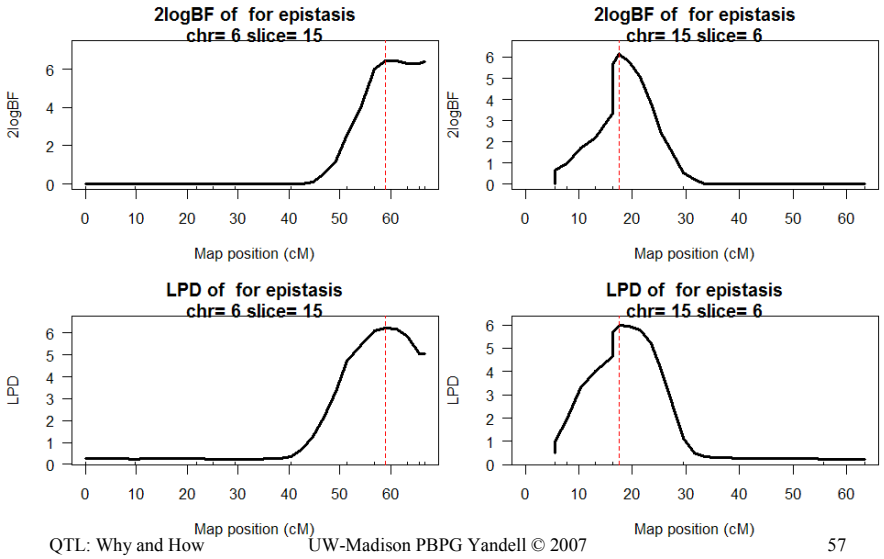
R/qtlbim: 2-D (*not* 2-QTL) scans

```
> two <- qb.scantwo(qbHyper, chr = c(6,15),
  type = "2logBF")
> plot(two)
> plot(two, chr = 6, slice = 15, show.locus =
  FALSE)
> plot(two, chr = 15, slice = 6, show.locus =
  FALSE)
> two <- qb.scantwo(qbHyper, chr = c(6,15),
  type = "LPD")
> plot(two, chr = 6, slice = 15, show.locus =
  FALSE)
> plot(two, chr = 15, slice = 6, show.locus =
  FALSE)
```


2-D plot of 2logBF: chr 6 & 15



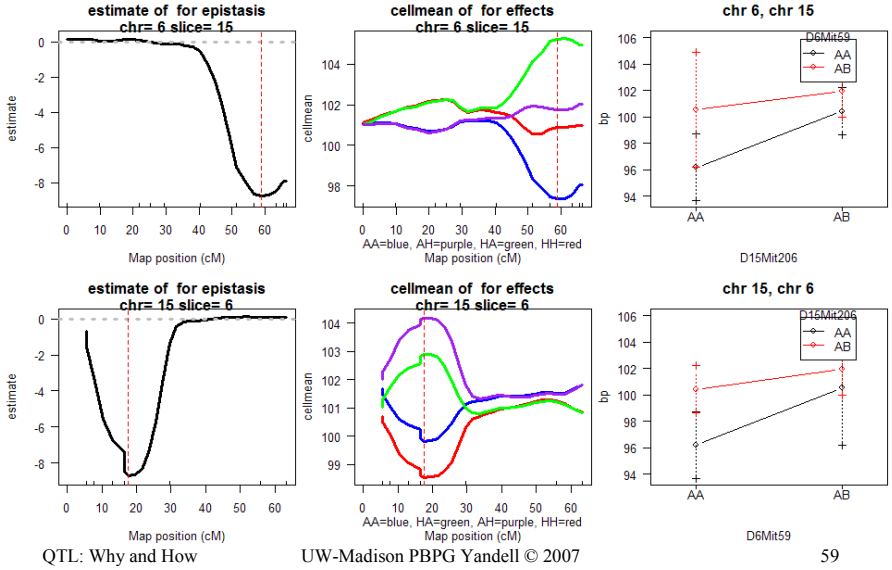
1-D Slices of 2-D scans: chr 6 & 15



R/qtlbim: slice of epistasis

```
> slice = qb.slicetwo(qbHyper, c(6,15), c(59,19.5))
> summary(slice)
2logBF of bp for epistasis

    n.qtl  pos m.pos e.pos epistasis slice
c6  0.838 59.0  59.0  66.7      15.8  18.1
c15 0.961 17.5  17.5  17.5      15.5  60.6

cellmean of bp for AA,HA,AH,HH

    n.qtl  pos m.pos   AA  HA  AH    HH slice
c6  0.838 59.0  59.0 97.4 105 102 100.8  18.1
c15 0.961 17.5  17.5 99.8 103 104  98.5  60.6

estimate of bp for epistasis

    n.qtl  pos m.pos e.pos epistasis slice
c6  0.838 59.0  59.0  66.7     -7.86  18.1
c15 0.961 17.5  17.5  17.5     -8.72  60.6
> plot(slice, figs = c("effects", "cellmean", "effectplot"))
```

1-D Slices of 2-D scans: chr 6 & 15



selected publications

www.stat.wisc.edu/~yandell/statgen

- Broman et al. (2003 *Bioinformatics*)
  - R/qtl introduction
- Broman (2001 *Lab Animal*)
  - nice overview of QTL issues
- Basten, Weir, Zeng (1995) *QTL Cartographer*
- Yandell, Bradbury (2007) *Plant Map* book chapter
  - overview/comparison of QTL methods
- Yandell et al. (2007 *Bioinformatics*)
  - R/qtlbim introduction
- Yi et al. (2005 *Genetics*)
  - methodology of R/qtlbim

many thanks

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- Nengjun Yi
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- Daniel Shriner
- Ram Venkataraman
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- Hao Wu
- Hyuna Yang
- Randy von Smith

Alan Attie
- Jonathan Stoehr
- Hong Lan
- Susie Clee
- Jessica Byers
- Mark Gray-Keller

Tom Osborn
- David Butruille
- Marcio Ferrera
- Josh Udahl
- Pablo Quijada

UW-Madison Stats

Yandell lab
- Jaya Satagopan
- Fei Zou
- Patrick Gaffney
- Chunfang Jin
- Elias Chaibub
- W Whipple Neely
- Jee Young Moon

Michael Newton

Christina Kendziorski

Daniel Gianola
- Liang Li
- Daniel Sorensen

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