Prototype QTL Strategy: Phenotype bp in Cross hyper

Brian S. Yandell, W. Whipple Neely, Nengjun Yi

March 29, 2012

Automated Strategy

- Estimate positions and effects of main QTL.
- Find chromosomes with epistasis.
- Estimate epistatic pair positions and effects.
- Confirm genetic architecture with ANOVA.

Running Sweave

```
> library(qtlbim)

> qb.sweave(hyper, pheno.col = 1,
+  n.iter = 3000, n.draws = 8,
+  scan.type = "2logBF", hpd.level = 0.5,
+  threshold = c(upper = 2),
+  SweaveFile = "",
+  SweaveExtra = "/tmp/RtmpeXvCwQ/Rinst304c500c0ae7/qtlbim/external/hyper.slide.extra.Rnw",
+  PDFDir = "bpPDF",
+  remove.qb = TRUE)
```

Cross Object

```
> summary(cross)

    Backcross

    No. individuals:    250

    No. phenotypes:     2
    Percent phenotyped: 100 100

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

    Total markers:      170
    No. markers:        22 8 6 20 14 11 7 6 5 5 14 5 5 5 11 6 12 4 4
    Percent genotyped:  47.9
    Genotypes (%):      BB:50.1  BA:49.9
```

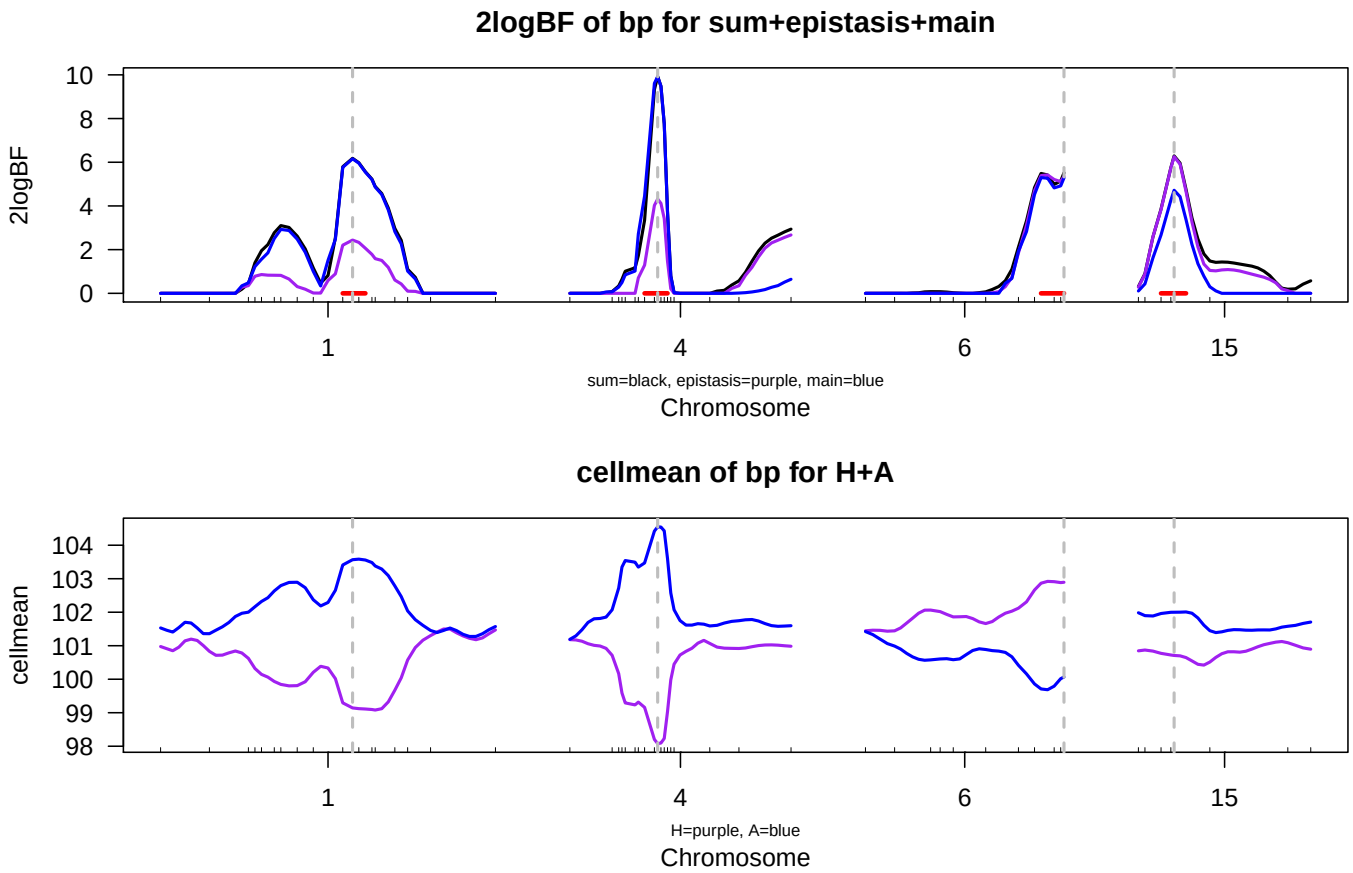
Create MCMC runs

```
> cross <- qb.genoprob(cross,step=2)
> cross.qb <- qb.mcmc(cross, pheno.col = pheno.col,
+   genoupdate=TRUE, n.iter = 3000, verbose=FALSE)
```

1-D 2logBF Scan

```
> hpd.level

[1] 0.5

> scan.type

[1] "2logBF"

> cross.hpd <- qb.hpdone(cross.qb, hpd.level, scan.type)
> sum.one <- summary(cross.hpd)
> sum.one

   chr n.qtl  pos lo.50. hi.50. 2logBF       A       H
1    1 0.695 67.8   64.5   72.1  6.181 103.568  99.143
4    4 2.834 29.5   25.1   32.8  9.924 104.550  98.078
6    6 0.743 66.7   59.0   66.7  5.488  99.710 102.866
15  15 0.909 17.5   13.1   21.5  6.291 101.999 100.710

> chrs <- as.vector(sum.one[, "chr"])
> pos <- sum.one[, "pos"]

> plot(cross.hpd)
```

1-D Scan: 2logBF Profile



2-D: find epistatic pairs

```
> two <- qb.scantwo(cross.qb, chr = chrs, type = scan.type)
> sum.two <- summary(two,sort="upper",threshold=threshold,
+   refine = TRUE)
> sum.two

upper: 2logBF of bp for epistasis
lower: 2logBF of bp for full
Thresholds: upper=2

        n.qtl l.pos1 l.pos2 lower u.pos1 u.pos2 upper
c6 :c15 1.004   66.7   17.5 11.44   66.7   17.5 11.43
c4 :c6  1.185   29.5   59.0 13.77   74.3   61.2  7.49
c4 :c15 1.452   29.5   17.5 13.28   74.3   47.6  6.84
c15:c15 0.261   21.5   23.5  7.12   17.5   31.5  6.21
c1 :c4  1.817   67.8   29.5 14.41   72.1   29.5  6.10
c1 :c6  1.103   67.8   59.0 11.37   67.8   59.0  5.21
c1 :c1  0.366   43.7   77.6  7.48   39.4   77.6  5.20
c1 :c15 1.255   67.8   17.5 10.87   75.4   23.5  4.76
c4 :c4  0.417   29.5   74.3 11.00   28.4   49.5  4.76
c6 :c6  0.111   61.2   65.6  7.52   40.4   56.8  3.94
```

Initial Genetic Architecture

```
> cross.arch <- qb.arch(sum.two, chrs, pos)
> cross.arch

main QTL loci:
    [,1]    [,2]    [,3]    [,4]    [,5]    [,6]    [,7]    [,8]    [,9]
chr "1"     "1"     "15"    "15"    "4"     "4"     "4"     "6"     "6"
pos "39.35" "72.14" "21.50" "47.64" "29.13" "49.45" "74.30" "40.40" "62.08"

Epistatic pairs by qtl, chr, pos:
       qtla qtlb chra chrb  posa  posb
pair 1    3    9   15    6 21.50 62.08
pair 2    7    9    4    6 74.30 62.08
pair 3    4    7   15    4 47.64 74.30
pair 4    2    5    1    4 72.14 29.13
pair 5    2    9    1    6 72.14 62.08
pair 6    1    2    1    1 39.35 72.14
pair 7    2    3    1   15 72.14 21.50
pair 8    5    6    4    4 29.13 49.45
pair 9    8    9    6    6 40.40 62.08
Epistatic chromosomes by connected sets:
1,15,4,6
```

Construct QTL Object

use R/qtl tools to check model fit
first simulate missing markers
then construct QTL object

```
> cross.sub <- subset(cross, chr = unique(cross.arch$qtl$chr))
> n.draws

[1] 8

> cross.sub <- sim.geno(cross.sub, n.draws=n.draws, step=2, error=0.01)
> qtl <- makeqtl(cross.sub, as.character(cross.arch$qtl$chr), cross.arch$qtl$pos)
```

Stepwise Reduction

```
> cross.step <- step.fitqtl(cross.sub, qtl, pheno.col, cross.arch)

   drop           LOD      p
1  1@71.3:15@21.5 -0.13200 1.0000
2  1@71.3:15@21.5 -0.19300 1.0000
3  1@39.3:1@71.3   0.05330 0.6330
4  15@47.5         0.12800 0.4570
5  4@29.5:4@50.0   0.20300 0.3490
6  4@50.0          0.00857 0.8470
7  6@40.4:6@62.0   0.38800 0.1940
8  6@40.4          0.20700 0.3420
9  1@39.3:1@71.3   0.29500 0.2550
10 1@39.3:1@71.3   0.30600 0.2450
11 1@39.3:1@71.3   0.34600 0.2160
12 1@71.3:15@21.5  0.30000 0.2480
13 4@74.3          0.84200 0.0524

> summary(cross.step$fit)

       df         SS        MS      LOD    %var Pvalue(Chi2)    Pvalue(F)
Model   5  4891.591 978.31827 17.59622 27.6847 5.551115e-16 1.110223e-15
Error 244 12777.345  52.36617
Total 249 17668.936
```

Stepwise Reduction

	df	Type III SS	LOD	%var	F value	Pvalue(F)	
1@39.3	1	306.6	1.287	1.735	5.854	0.016269	*
1@71.3	1	593.2	2.464	3.357	11.328	0.000887	***
15@21.5	1	266.3	1.120	1.507	5.085	0.025014	*
4@29.5	1	2852.4	10.939	16.143	54.469	2.47e-12	***
6@62.0	1	509.7	2.124	2.885	9.734	0.002026	**

Reduced Genetic architecture

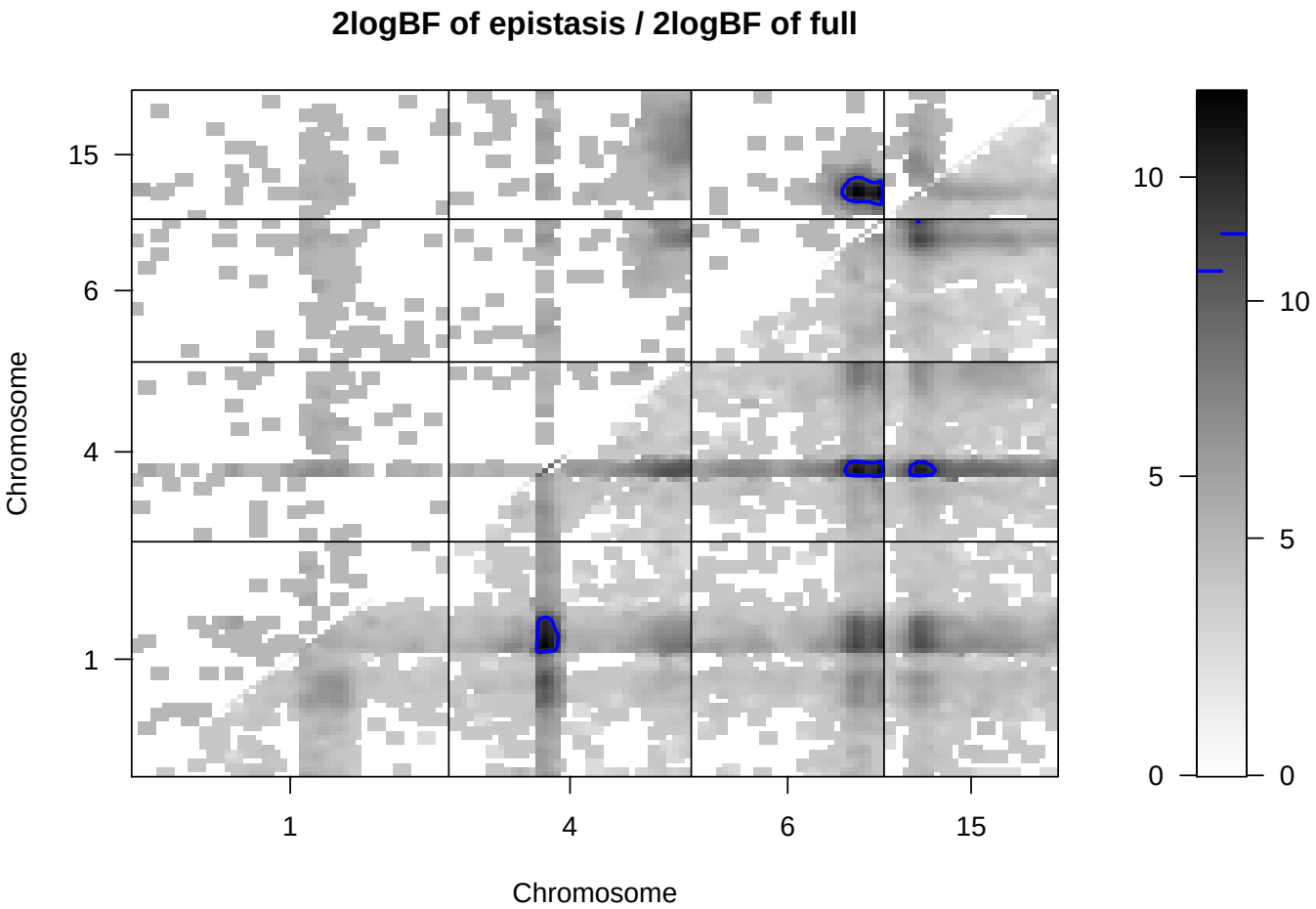
```
> cross.arch <- cross.step$arch
> cross.arch

main QTL loci:
    1       2       3       5       9
chr "1"     "1"     "15"    "4"     "6"
pos "39.35" "72.14" "21.50" "29.13" "62.08"

epistatic pairs: none
```

2-D Plots

2-D plots by cliques (if any epistasis)

```
> for(i in names(cross.arch$chr.by.set))
+   plot(two, chr = cross.arch$chr.by.set[[i]], smooth = 3,
+     col = "gray", contour = 3)
```

2-D Plots: clique 1

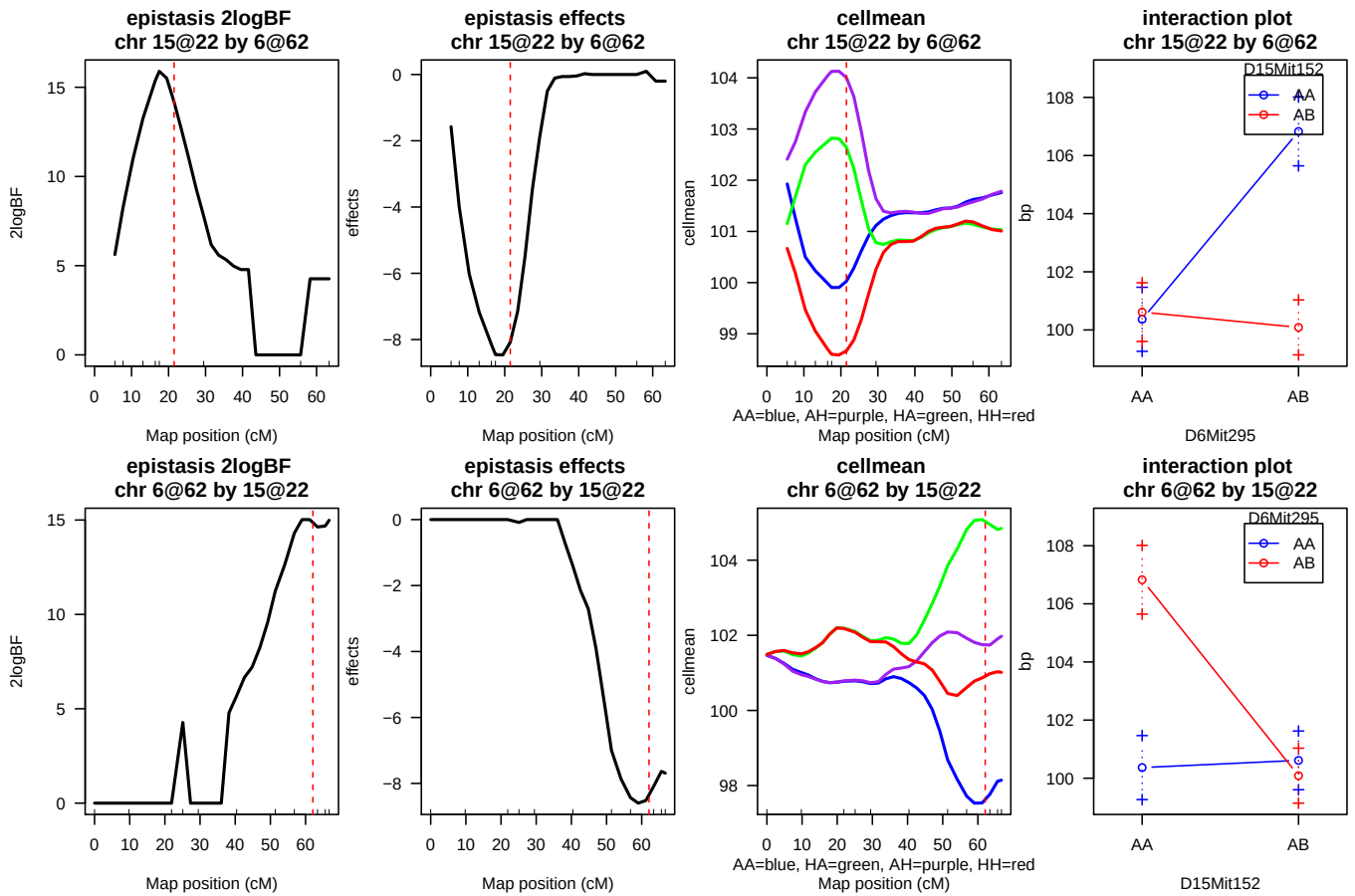


Slice Each Epistatic Pair

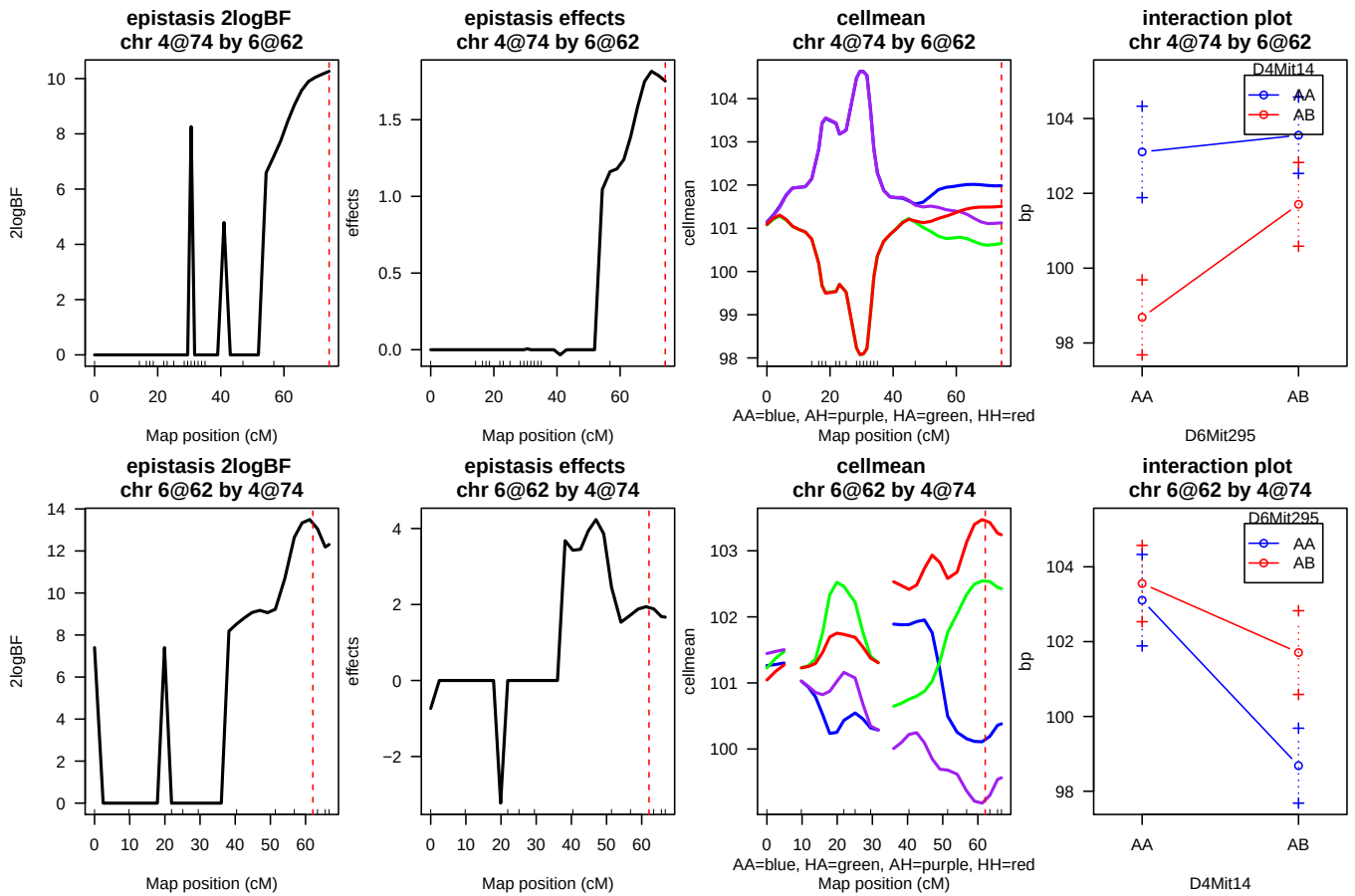
show detail plots for epistatic pairs (if any)

```
> if(!is.null(cross.arch$pair.by.chr)) {
+  for(i in seq(nrow(cross.arch$pair.by.chr$chr))) {
+    chri <- cross.arch$pair.by.chr$chr[i,]
+    posi <- cross.arch$pair.by.chr$pos[i,]
+    if(chri[1] != chri[2])
+      plot(qb.slicetwo(cross.qb, chri, posi, scan.type))
+  }
+}
```

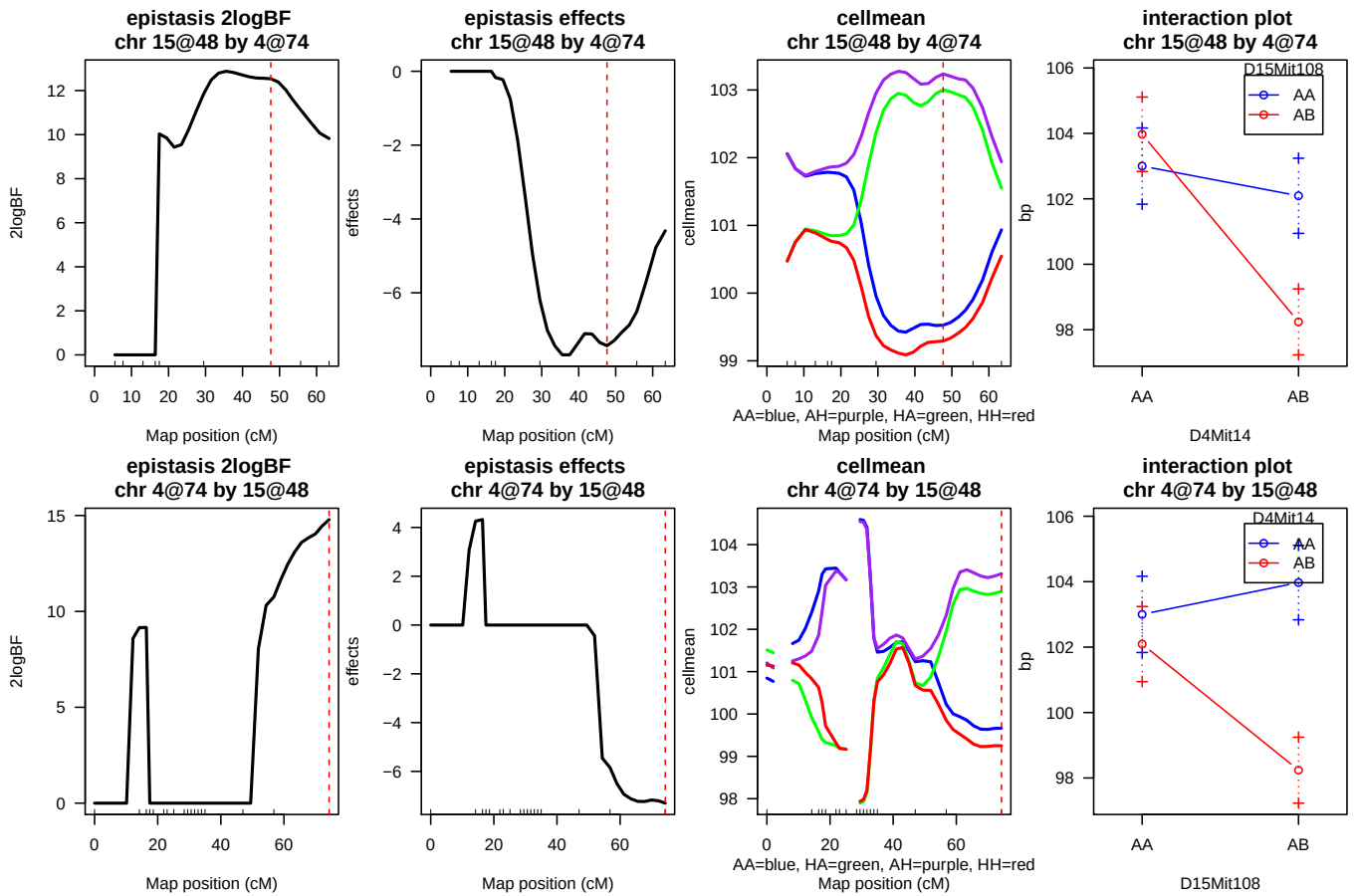
Epistatic Pair 15 and 6



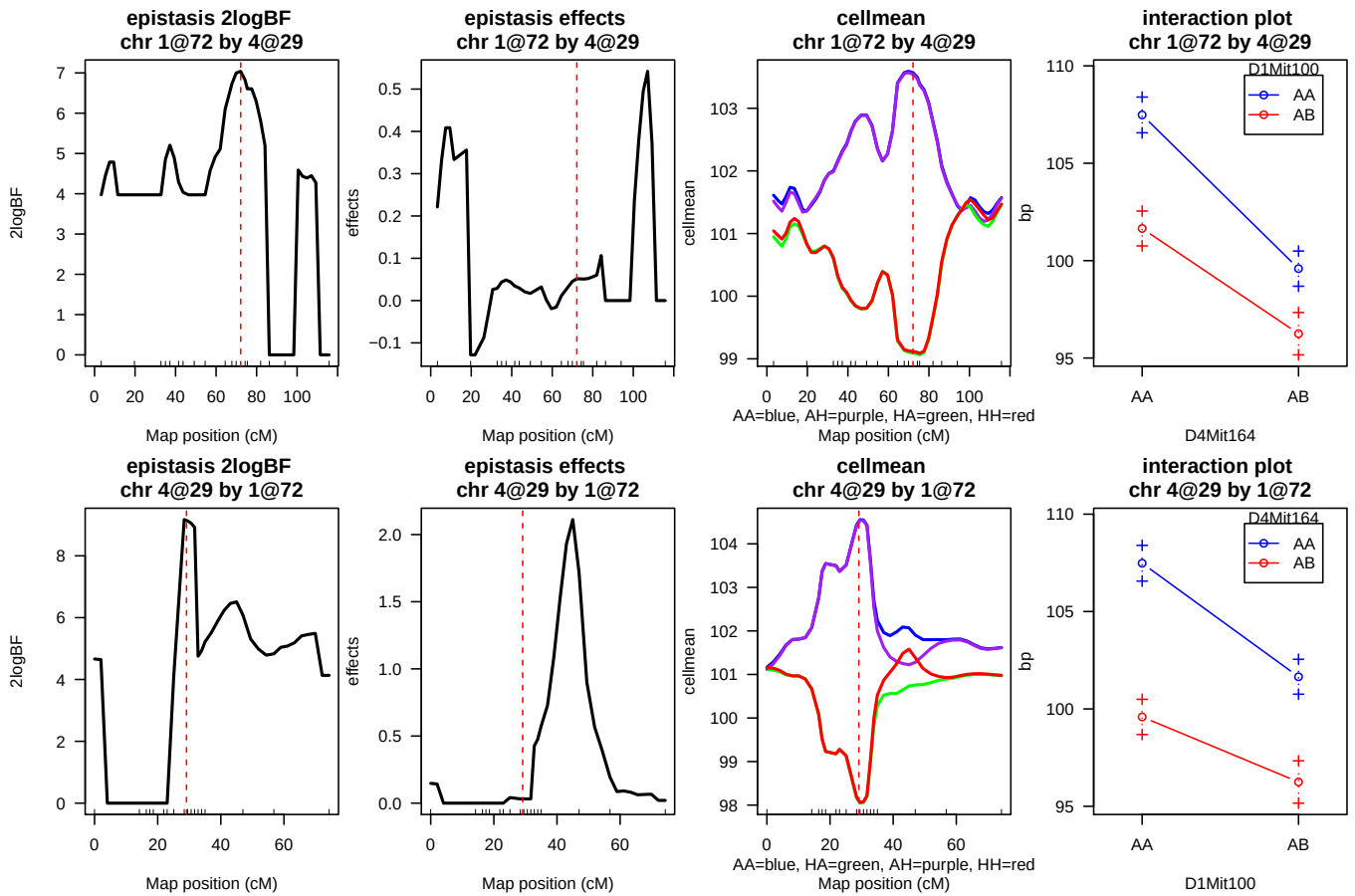
Epistatic Pair 4 and 6



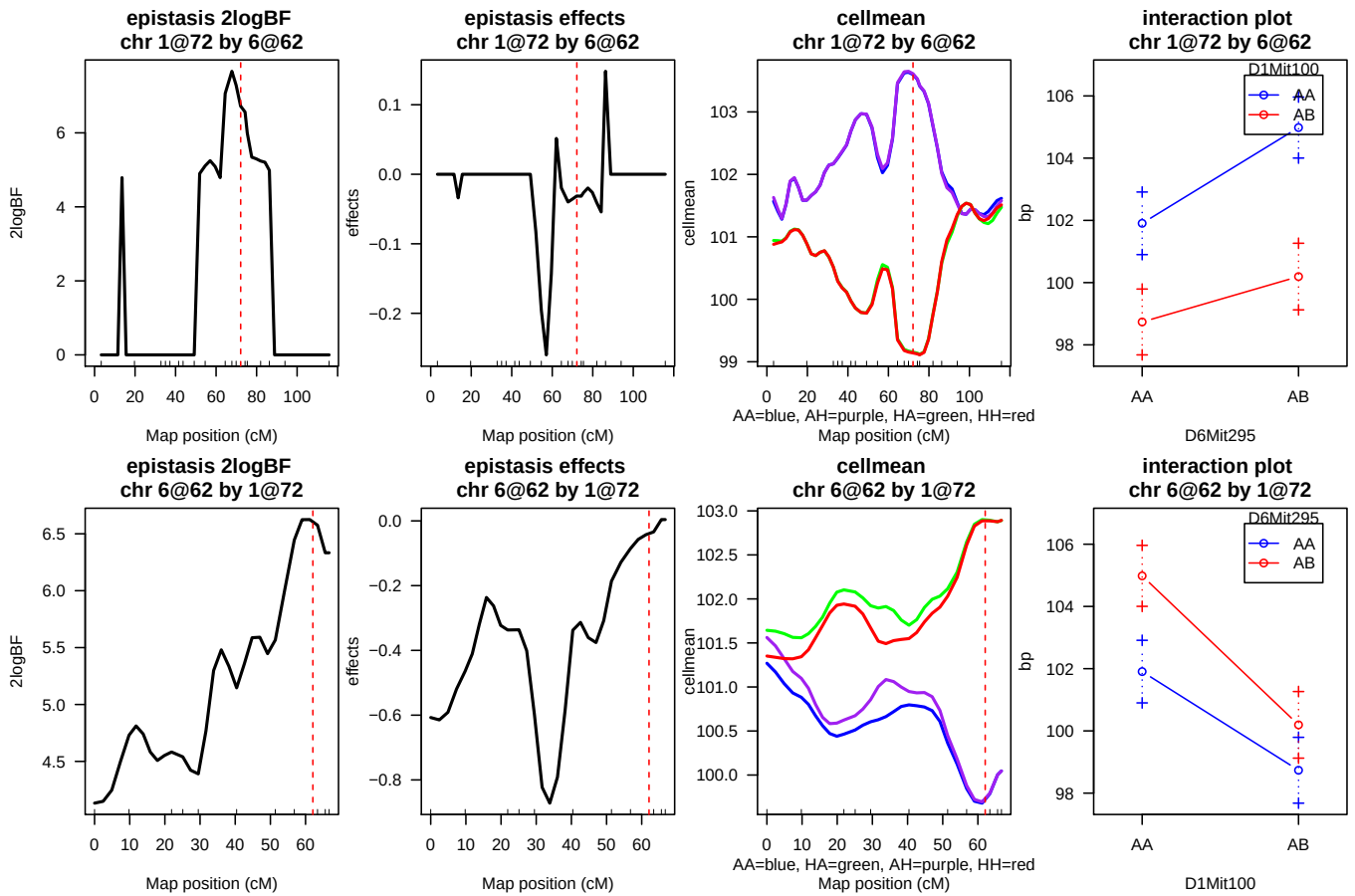
Epistatic Pair 15 and 4



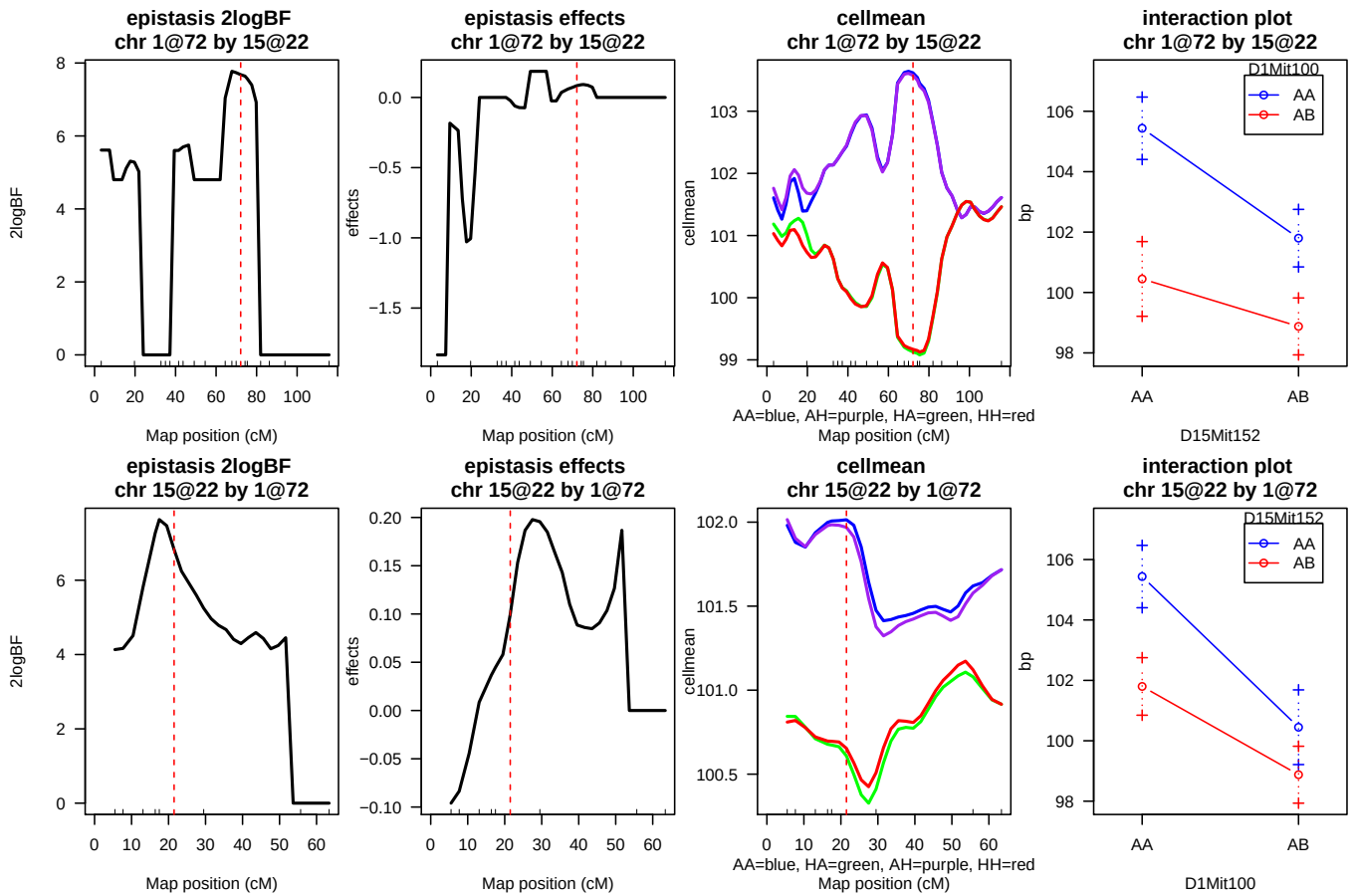
Epistatic Pair 1 and 4



Epistatic Pair 1 and 6



Epistatic Pair 1 and 15



Compare with Literature

Sugiyama et al. (2002) found:
two main QTLs on 1 4
two epistatic pairs with 6.15, 7.15
compare to present model:

```
> arch3 <- qb.arch(cross.step,main=c(1,4),
+   epistasis = data.frame(q1 = c(6,7),q2 = rep(15,2)))
> arch3
```

Sugiyama Model

```
> cross.step2 <- step.fitqtl(cross.sub, qtl, pheno.col, arch3)
> summary(cross.step2$fit)
```

Sugiyama vs. Automata

formal comparison with automated model

```
> anova(cross.step, cross.step2)
```

final tasks:
externally rename file .tex to bp.tex
and run pdflatex twice on it
remove objects created by R/qtlbim if desired

```
> file.rename(".tex", "bp.tex")
> invisible(system("pdflatex bp.tex",intern=TRUE))
> invisible(system("pdflatex bp.tex",intern=TRUE))

> remove.qb

[1] FALSE

> if(remove.qb) {
+   qb.remove(cross.qb)
+   rm(cross, cross.sub, pheno.col, threshold, n.iter, n.draws, remove.qb)
+ }
```