Prototype QTL Strategy: Phenotype bp in Cross hyper

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

October 18, 2006

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 = 64,
+  scan.type = "2logBF", hpd.level = 0.5,
+  threshold = c(upper = 2),
+  SweaveFile = "/tmp/Rinst1107343038/qtlbim/doc/hyperslide.Rnw",
+  SweaveExtra = "/tmp/Rinst1107343038/qtlbim/external/hyperslideextra.Rnw",
+  PDFDir = "bpPDF",
+  remove.qb = TRUE)
```

Cross Object

```
> summary(cross)

    Backcross

    No. individuals:    250

    No. phenotypes:     1
    Percent phenotyped: 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 (%):      AA:50.1  AB:49.9
```

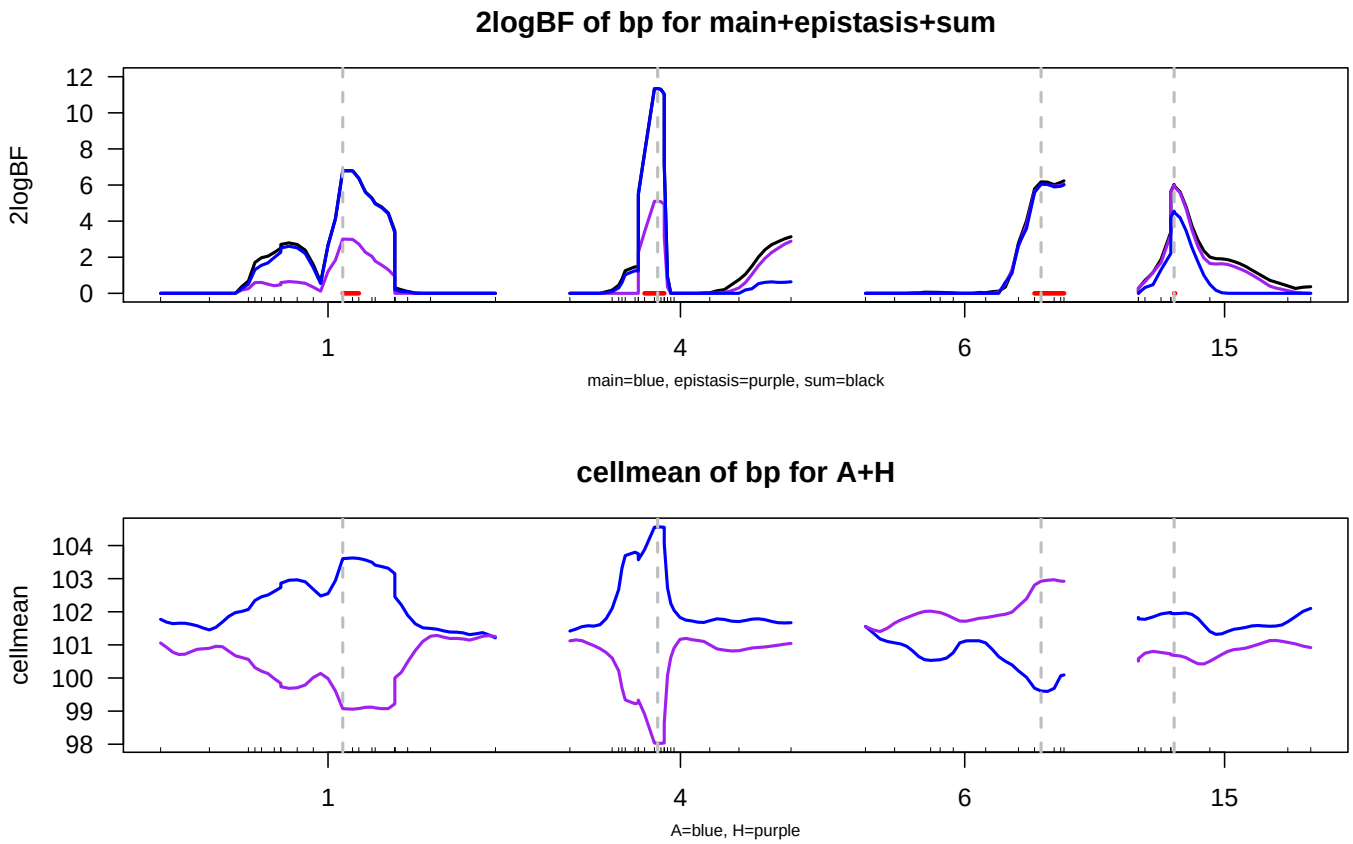
Create MCMC runs

```
> 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

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

     chr n.qtl  pos lo.50% hi.50% 2logBF       A       H
<NA>   1 0.694 64.5   64.5   69.9  6.796 103.604  99.073
<NA>   4 3.460 29.5   25.1   31.7 11.347 104.561  98.026
<NA>   6 1.107 59.0   56.8   66.7  6.179  99.606 102.924
<NA>  15 0.341 17.5   17.5   17.5  6.032 101.940 100.692

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

> plot(cross.hpd, profile = scan.type)
```

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
```

	chr1	chr2	n.qtl	l.pos1	l.pos2	lower	u.pos1	u.pos2	upper
6:15	6	15	1.080	59.0	17.5	12.779	59.000	17.500	12.751
4:6	4	6	1.561	29.5	66.7	14.884	74.300	59.000	7.728
4:15	4	15	0.446	29.5	17.5	14.539	74.300	35.546	7.350
1:4	1	4	1.352	67.8	29.5	15.705	72.100	29.500	7.303
15:15	15	15	0.105	17.5	27.5	8.125	17.500	25.500	7.234
1:15	1	15	0.298	67.8	17.5	12.012	77.600	17.500	5.794
1:6	1	6	1.831	67.8	59.0	12.611	77.600	65.600	4.756
4:4	4	4	1.145	29.5	74.3	11.820	2.029	28.400	4.756
6:6	6	6	1.214	61.2	65.6	7.442	27.300	65.600	4.756
1:1	1	1	0.362	43.7	77.6	7.583	43.700	74.300	4.697

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  1.0  1.00 4.00  4.00  4.0  6.0  6.00 15.0 15.00
pos 43.7 73.22 2.03 29.13 74.3 27.3 61.64 19.1 35.55

Epistatic pairs by qtl, chr, pos:
  qtla qtlb chra chrb  posa  posb
1    7    8    6   15 61.64 19.10
2    5    7    4    6 74.30 61.64
3    5    9    4   15 74.30 35.55
4    2    4    1    4 73.22 29.13
5    2    8    1   15 73.22 19.10
6    2    7    1    6 73.22 61.64
7    3    4    4    4  2.03 29.13
8    6    7    6    6 27.30 61.64
9    1    2    1    1 43.70 73.22
Epistatic chromosomes by connected sets:
1,4,6,15
```

Construct QTL Object

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

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

[1] 64

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

Stepwise Reduction

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

  drop                    LOD   p
1 Chr1@73.22:Chr6@61.64 0.134 0.451
2 Chr6@27.3:Chr6@61.64  0.143 0.434
3 Chr6@27.3             0.185 0.373
4 Chr4@2.03:Chr4@29.13  0.331 0.232
5 Chr4@2.03             0.115 0.482
6 Chr1@73.22:Chr15@19.1 0.504 0.139
7 Chr1@43.7:Chr1@73.22  0.548 0.122
8 Chr1@73.22:Chr4@29.13 0.870 0.051

> summary(cross.step$fit)

       df         SS        MS      LOD     %var Pvalue(Chi2) Pvalue(F)
Model  10  7536.634 753.66344 30.18779 42.65471             0         0
Error 239 10132.302  42.39457
Total 249 17668.936
```

Stepwise Reduction

	df	Type III SS	LOD	%var	F value	Pvalue(F)	
Chr1@43.7	1	278.002	1.469	1.573	6.557	0.011060	*
Chr1@73.22	1	801.459	4.133	4.536	18.905	2.03e-05	***
Chr4@29.13	1	2553.941	12.203	14.454	60.242	2.44e-13	***
Chr4@74.3	3	1232.103	6.230	6.973	9.688	4.66e-06	***
Chr6@61.64	3	2130.566	10.360	12.058	16.752	6.55e-10	***
Chr15@19.1	2	1482.279	7.412	8.389	17.482	8.21e-08	***
Chr15@35.55	2	638.158	3.316	3.612	7.526	0.000676	***
Chr6@61.64:Chr15@19.1	1	1347.276	6.777	7.625	31.779	4.85e-08	***
Chr4@74.3:Chr6@61.64	1	390.074	2.051	2.208	9.201	0.002686	**
Chr4@74.3:Chr15@35.55	1	608.589	3.167	3.444	14.355	0.000192	***

Reduced Genetic architecture

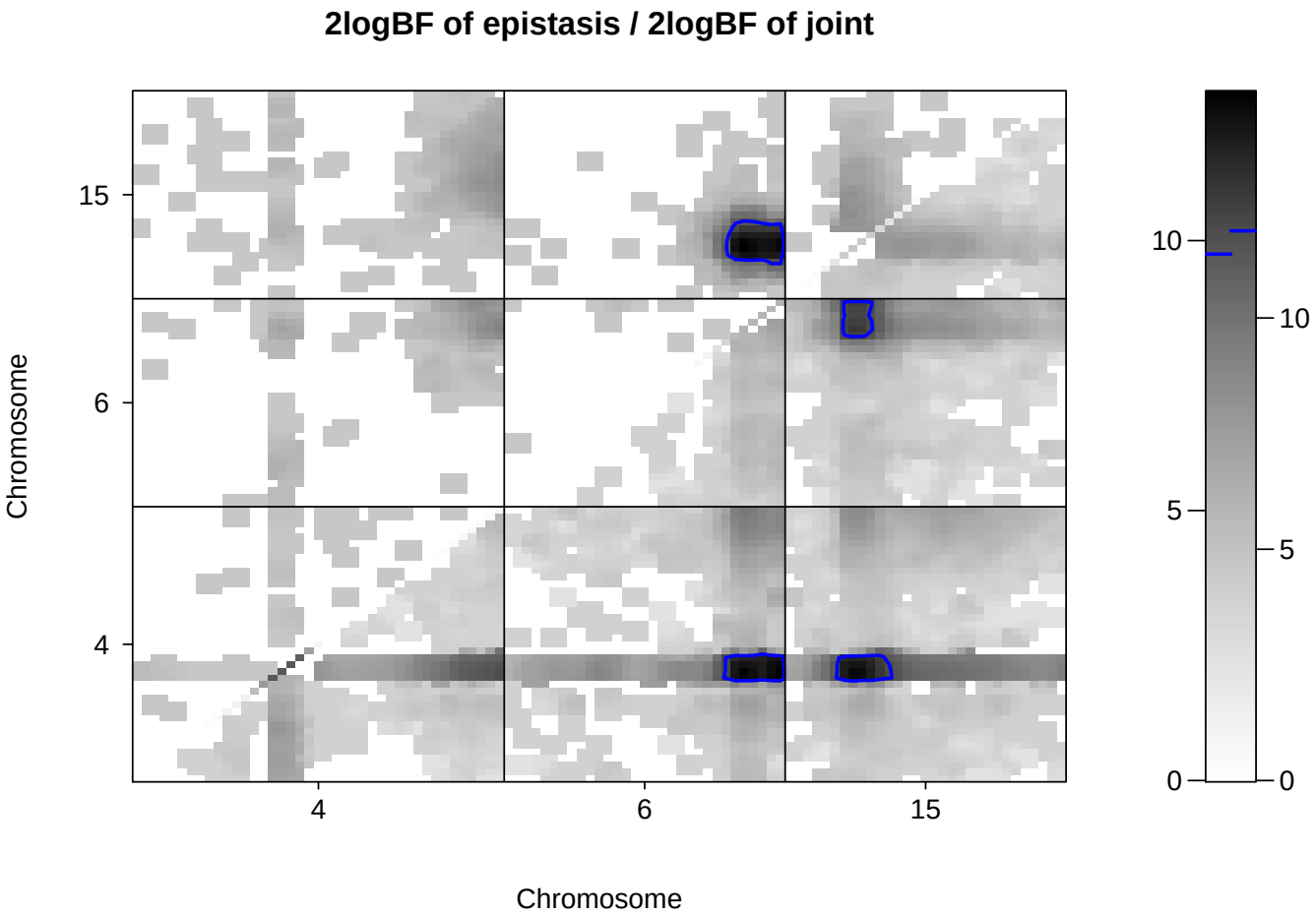
```
> cross.arch <- cross.step$arch
> cross.arch

main QTL loci:
       1     2     4    5     7    8     9
chr  1.0  1.00  4.00  4.0  6.00 15.0 15.00
pos 43.7 73.22 29.13 74.3 61.64 19.1 35.55

Epistatic pairs by qtl, chr, pos:
  q1 q2 chra chrb  posa  posb
1  7  8    6   15 61.64 19.10
2  5  7    4    6 74.30 61.64
3  5  9    4   15 74.30 35.55
Epistatic chromosomes by connected sets:
4,6,15
```

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

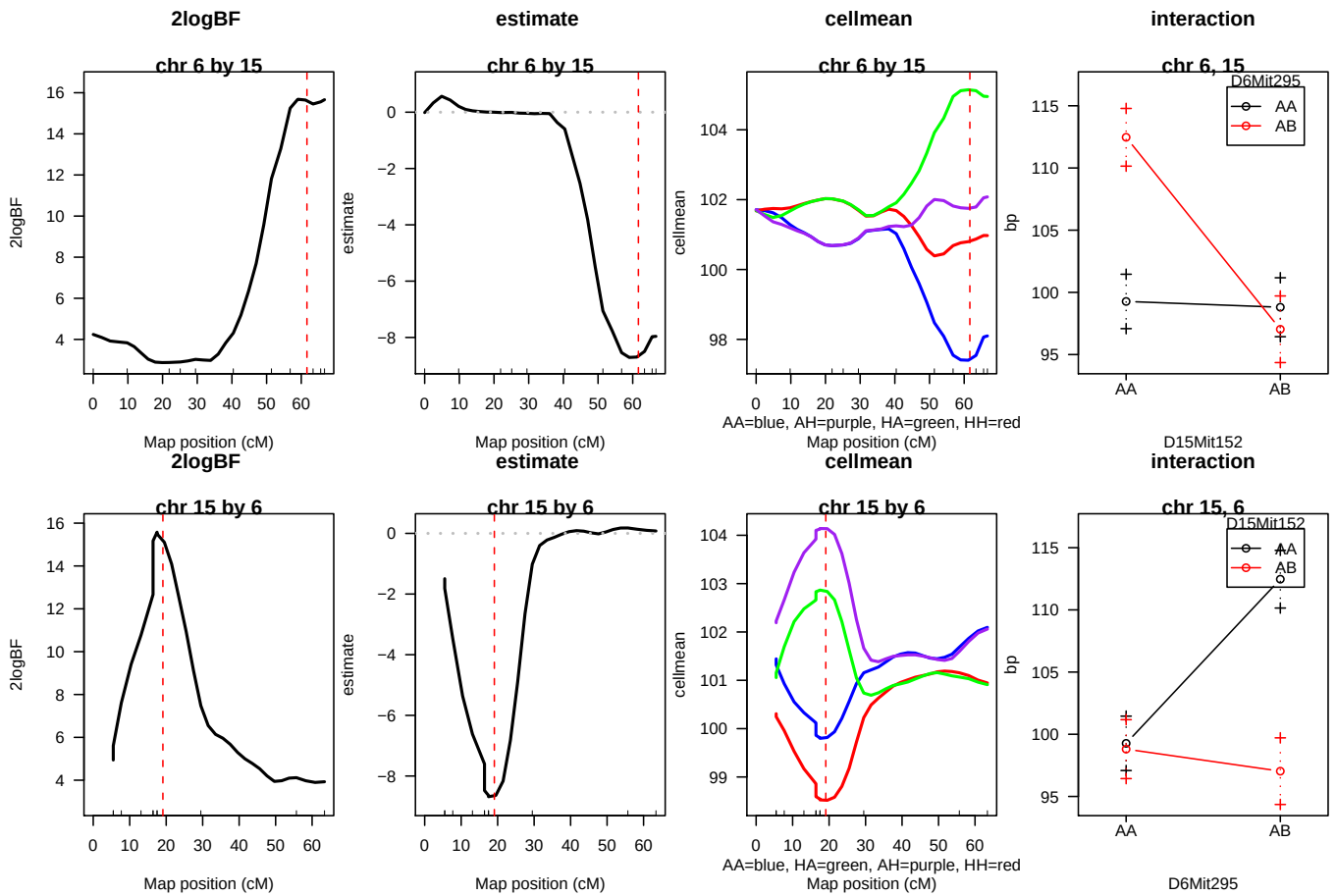


Slice Each Epistatic Pair

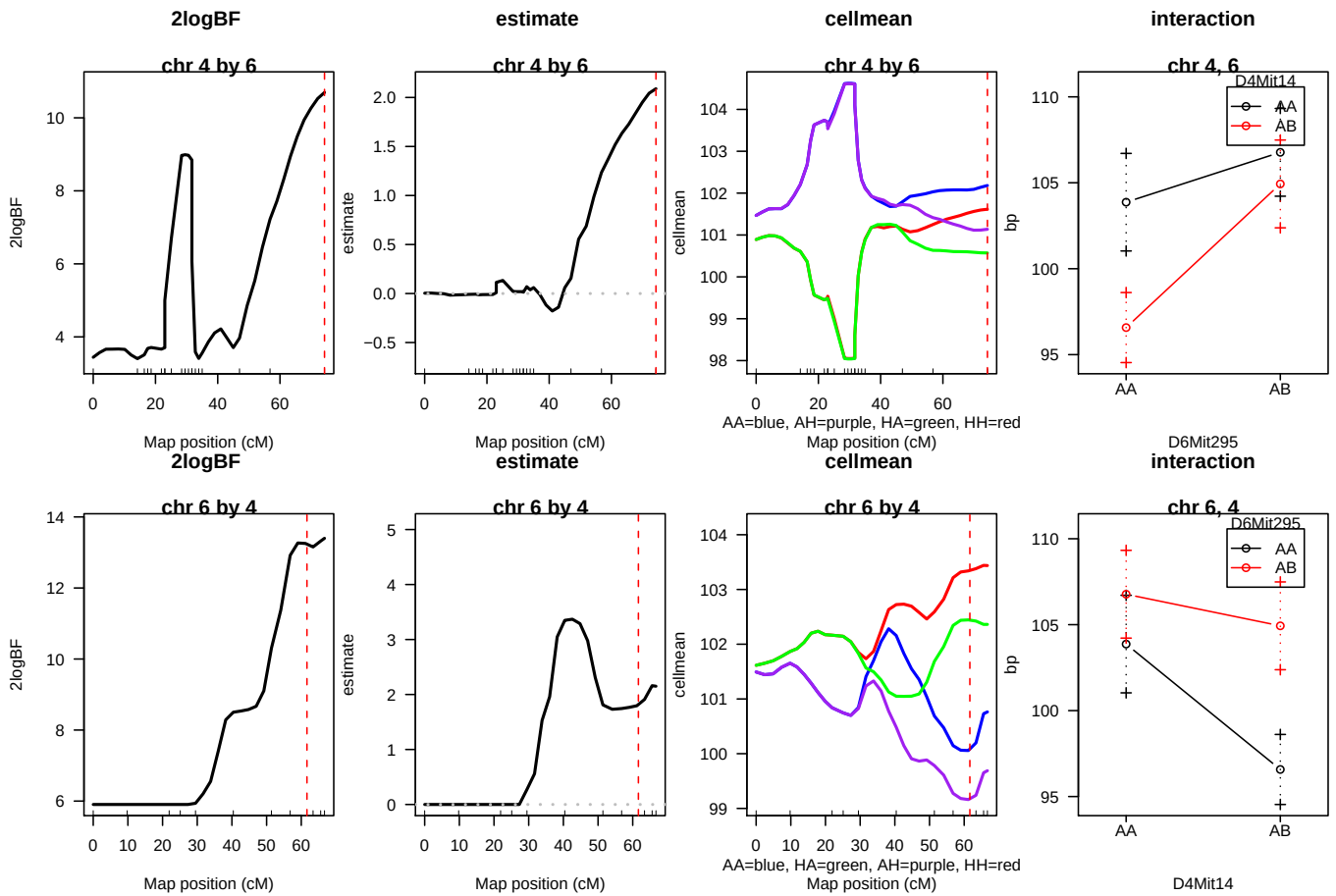
show detail plots for epistatic pairs (if any)

```
> 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,]
+    plot(qb.slicetwo(cross.qb, chri, posi, scan.type))
+  }
+}
```

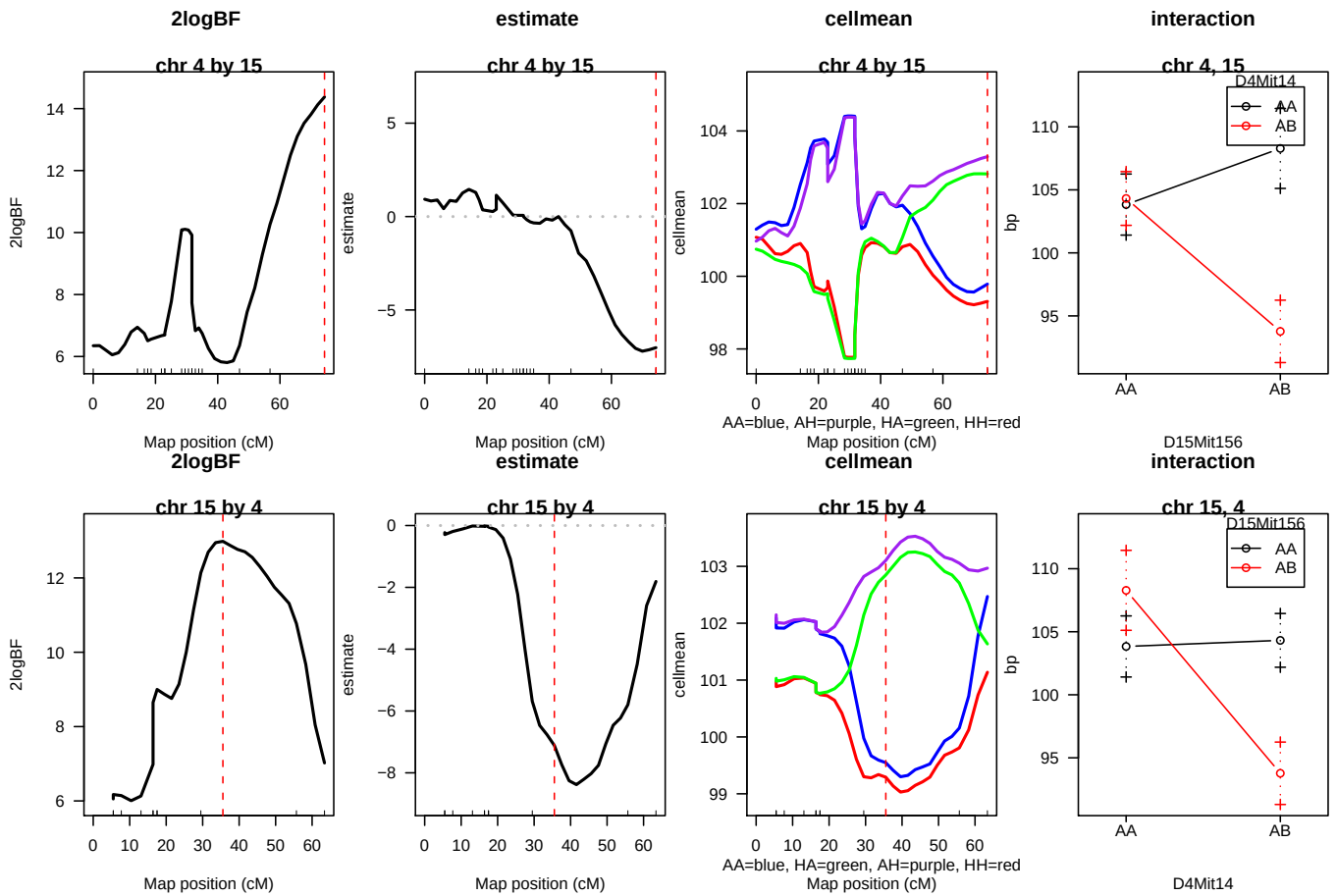
Epistatic Pair 6 and 15



Epistatic Pair 4 and 6



Epistatic Pair 4 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 hyperslide.tex to bp.tex
and run pdflatex twice on it
remove objects created by R/qtlbim if desired

```
> file.rename("hyperslide.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)
+ }
```