Prototype QTL Strategy: Phenotype bp in Cross hyper

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April 11, 2008

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Anova Fit
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   Initialization

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Automated Strategy

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

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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/Rinst3021484561/qtlbim/external/hyper.slide.extra.Rnw",
+  PDFDir = "bpPDF",
+  remove.qb = TRUE)
```

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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
```

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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)
```

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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 0.826 67.8   64.5   74.3  6.181 103.568  99.143
4    4 3.035 29.5   23.0   31.7  9.970 104.552  98.073
6    6 0.873 66.7   56.8   66.7  5.488  99.710 102.866
15  15 0.395 17.5   17.5   19.5  5.448 101.993 100.703

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

> plot(cross.hpd)
```
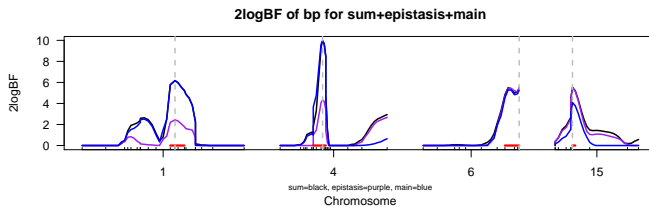
1-D Scan: 2logBF Profile

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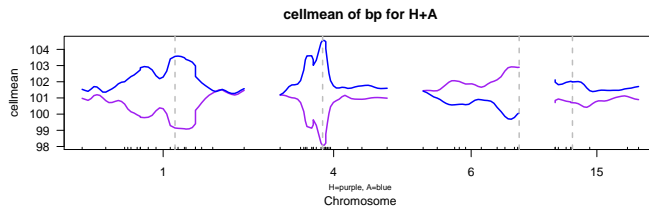
2-D: find epistatic pairs

```
> 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   59.0   17.5 11.89   59.0   17.5 11.90
c4 :c6  1.185   29.5   59.0 13.77   74.3   61.2  7.49
c4 :c15 1.452   29.5   17.5 13.61   74.3   47.6  6.84
c15:c15 0.261   17.5   33.5  7.54   17.5   31.5  6.52
c1 :c4  1.817   67.8   29.5 14.41   72.1   29.5  6.10
c1 :c15 1.255   67.8   17.5 11.20   72.1   17.5  5.23
c1 :c6  1.103   67.8   59.0 11.37   67.8   59.0  5.21
c1 :c1  0.366   43.7   77.6  7.46   39.4   77.6  5.20
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"    "15"    "4"     "4"     "4"     "6"
pos "39.35" "71.48" "17.50" "31.52" "47.64" "29.13" "49.45" "74.30" "40.40"
    [,10]
chr "6"
pos "60.54"


Epistatic pairs by qtl, chr, pos:
        qtla qtlb chra chrb  posa  posb
pair 1     3   10   15    6  17.50 60.54
pair 2     8   10   15    4  74.30 60.54
pair 3     5    8   15    4  47.64 74.30
pair 4     3    4   15   15  17.50 31.52
pair 5     2    6    1    4  71.48 29.13
pair 6     2    3    1   15  71.48 17.50
pair 7     2   10    1    6  71.48 60.54
pair 8     1    2    1    1  39.35 71.48
pair 9     6    7    4    4  29.13 49.45
pair 10    9   10    6    6  40.40 60.54
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)
> cross.sub <- clean(cross.sub)
```

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Stepwise Reduction

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

    drop                    LOD       p
1   Chr1@71.3:Chr15@17.5  -0.09030  1.000
2   Chr1@71.3:Chr15@17.5  -0.09670  1.000
3   Chr15@47.5             0.03700  0.692
4   Chr1@71.3:Chr15@17.5   0.05390  0.632
5   Chr15@31.5            -0.06120  1.000
6   Chr4@29.5:Chr4@50     -0.00191  1.000
7   Chr4@50                0.11400  0.483
8   Chr1@71.3:Chr6@60      0.27400  0.275
9   Chr1@71.3:Chr15@17.5   0.20900  0.340
10  Chr1@71.3:Chr15@17.5   0.22300  0.324
11  Chr1@39.3:Chr1@71.3    0.46800  0.151
12  Chr1@39.3:Chr1@71.3    0.20300  0.344
13  Chr6@40.4:Chr6@60      0.39200  0.188
14  Chr6@40.4              0.05840  0.610

> summary(cross.step$fit)

        df       SS       MS      LOD     %var  Pvalue(Chi2)   Pvalue(F)
Model    6  4970.311  828.38514  17.93171  28.13022  9.992007e-16  2.331468e-15
Error  243  12698.625  52.25772
Total  249  17668.936
```

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```
            df Type III SS     LOD    %var F value Pvalue(F)
Chr1@39.3    1    268.505    1.136    1.520    5.138  0.024286 *
Chr1@71.3    1    616.272    2.573    3.488   11.793  0.000699 ***
Chr15@17.5   1    253.773    1.074    1.436    4.856  0.028486 *
Chr4@29.5    1   2218.614    8.741   12.557   42.455  4.13e-10 ***
Chr4@74.3    1    215.147    0.912    1.218    4.117  0.043544 *
Chr6@60      1    409.326    1.722    2.317    7.833  0.005542 **
```

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Reduced Genetic architecture

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

main QTL loci:
      1        2        3        6        8        10
chr "1"      "1"      "15"     "4"      "4"      "6"
pos "39.35"  "71.48"  "17.50"  "29.13"  "74.30"  "60.54"

epistatic pairs: none
```
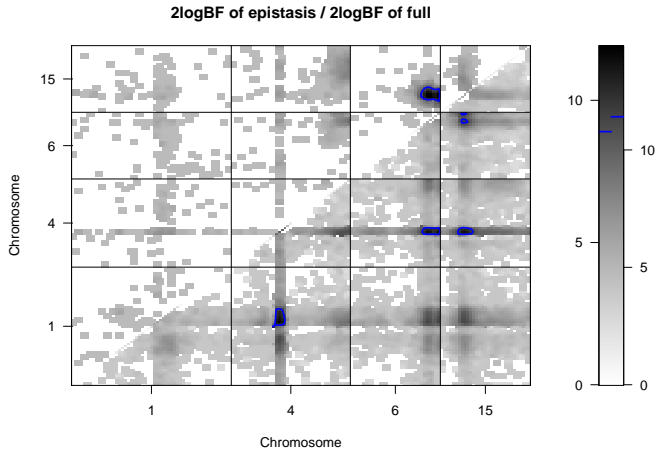
2-D Plots

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)
```

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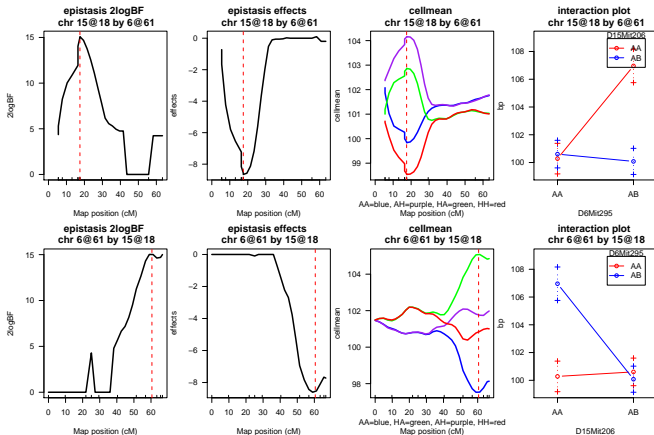1-D & 2-D Scans
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2-D Plots: clique 1

2logBF of epistasis / 2logBF of full

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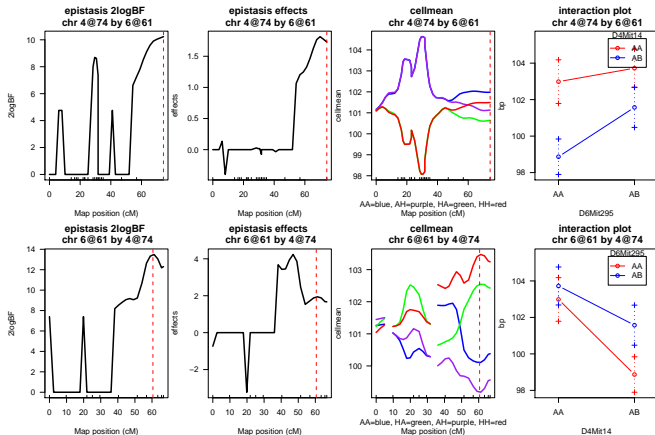Conclusion

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))
+ }
+}
```
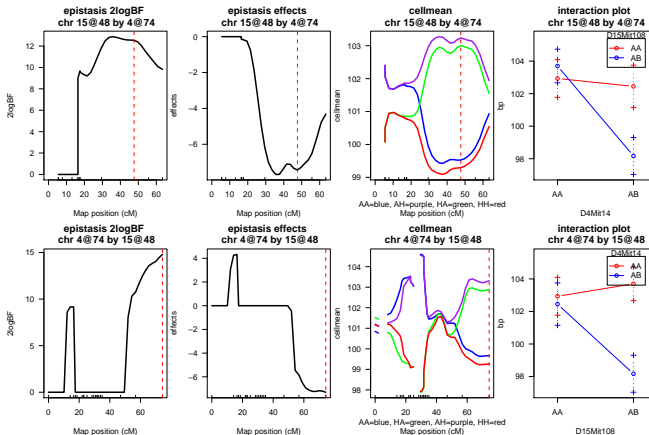
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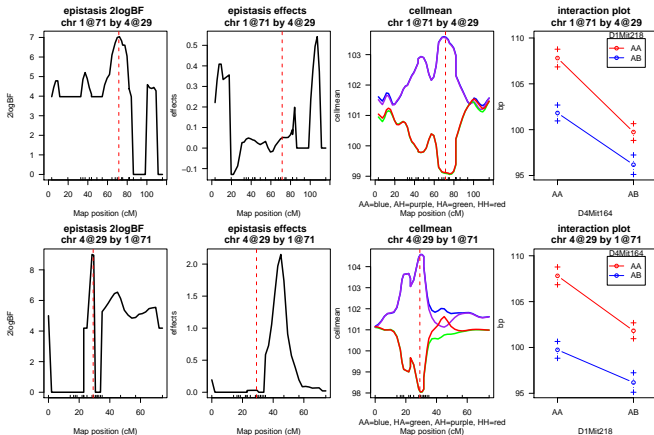1-D & 2-D Scans
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Epistatic Pair 15 and 6

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Epistatic Pair 4 and 6

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Epistatic Pair 15 and 4

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Epistatic Pair 1 and 4

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Epistatic Pair 1 and 15

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Epistatic Pair 1 and 6

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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)
```

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Sugiyama vs. Automata

formal comparison with automated model

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

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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)
+ }
```