

Prototype QTL Strategy: Phenotype bp in Cross hyper

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

October 10, 2006

Overview

Initialization

1-D & 2-D Scans

Anova Fit

User Customized Section

Conclusion

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/Rinst2351176914/qtlbim/doc/hyperslide.Rnw",
+ SweaveExtra = "/tmp/Rinst2351176914/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

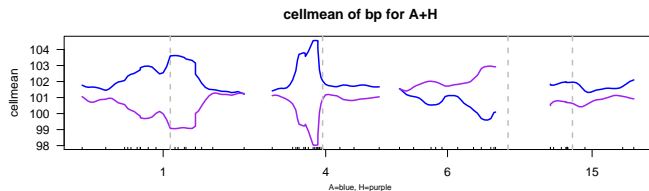
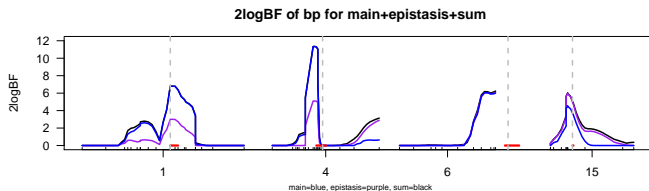
> cross.hpd <- qb.hpdone(cross.qb, hpd.level)
> sum.one <- summary(cross.hpd)
> sum.one
```

	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.qt1	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	1.145	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	0.298	29.5	74.3	11.820	2.029	30.600	4.756
6:6	6	6	1.214	61.2	65.6	7.442	27.300	66.700	4.756
1:1	1	1	0.362	43.7	77.6	7.583	43.700	75.400	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	73.44	2.03	29.87	74.3	27.3	61.86	19.1	35.55

Epistatic pairs by qtl, chr, pos:

	qtl	qtlb	chra	chrb	posa	posb
1	7	8	6	15	61.86	19.10
2	5	7	4	6	74.30	61.86
3	5	9	4	15	74.30	35.55
4	2	4	1	4	73.44	29.87
5	2	8	1	15	73.44	19.10
6	2	7	1	6	73.44	61.86
7	3	4	4	4	2.03	29.87
8	6	7	6	6	27.30	61.86
9	1	2	1	1	43.70	73.44

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$qt1$chr)
> n.draws

[1] 64

> cross.sub <- sim.geno(cross.sub, n.draws = n.draws, step = 2,
+   error = 0.01)
> qt1 <- makeqtl(cross.sub, cross.arch$qt1$chr, cross.arch$qt1$pos)
> cross.sub <- clean(cross.sub)
```

Stepwise Reduction

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

	drop	LOD	p
1	Chr1@73.44:Chr6@61.86	0.0686	0.589
2	Chr6@27.3:Chr6@61.86	0.1920	0.366
3	Chr4@2.03:Chr4@29.87	0.2310	0.320
4	Chr4@2.03	0.2100	0.342
5	Chr1@73.44:Chr15@19.1	0.2340	0.315
6	Chr1@43.7:Chr1@73.44	0.2640	0.285
7	Chr6@27.3	0.4840	0.146
8	Chr1@73.44:Chr4@29.87	0.4650	0.154

```
> summary(cross.step$fit)
```

	df	SS	MS	LOD	%var	Pvalue(Chi2)	Pvalue(F)
Model	10	7183.00	718.29997	28.32540	40.65327	0	0
Error	239	10485.94	43.87421				
Total	249	17668.94					

Stepwise Reduction

	df	Type III SS	LOD	%var	F value	Pvalue(F)
Chr1@43.7	1	181.0779	0.9295	1.0248	4.127	0.043305 *
Chr1@73.44	1	833.1147	4.1504	4.7151	18.989	1.95e-05 ***
Chr4@29.87	1	2318.2468	10.8431	13.1205	52.838	5.12e-12 ***
Chr4@74.3	3	930.7226	4.6165	5.2676	7.071	0.000143 ***
Chr6@61.86	3	2006.0875	9.5032	11.3538	15.241	4.16e-09 ***
Chr15@19.1	2	1400.7465	6.8067	7.9277	15.963	3.11e-07 ***
Chr15@35.55	2	512.6109	2.5910	2.9012	5.842	0.003334 **
Chr6@61.86:Chr15@19.1	1	1244.8886	6.0902	7.0456	28.374	2.31e-07 ***
Chr4@74.3:Chr6@61.86	1	334.0786	1.7026	1.8908	7.614	0.006239 **
Chr4@74.3:Chr15@35.55	1	467.7187	2.3690	2.6471	10.660	0.001255 **

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	73.44	29.87	74.3	61.86	19.1	35.55

Epistatic pairs by qtl, chr, pos:

	q1	q2	chra	chrb	posa	posb
1	7	8	6	15	61.86	19.10
2	5	7	4	6	74.30	61.86
3	5	9	4	15	74.30	35.55

Epistatic chromosomes by connected sets:

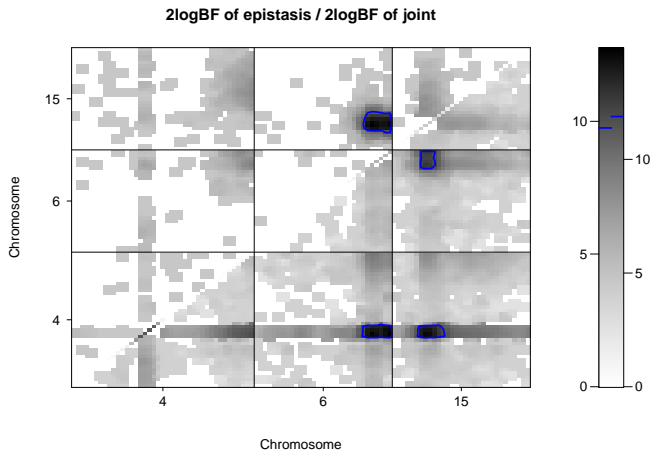
4,6,15

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

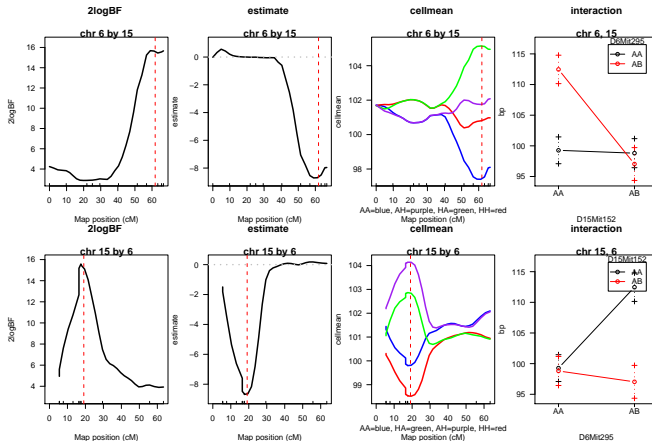


Slice Each Epistatic Pair

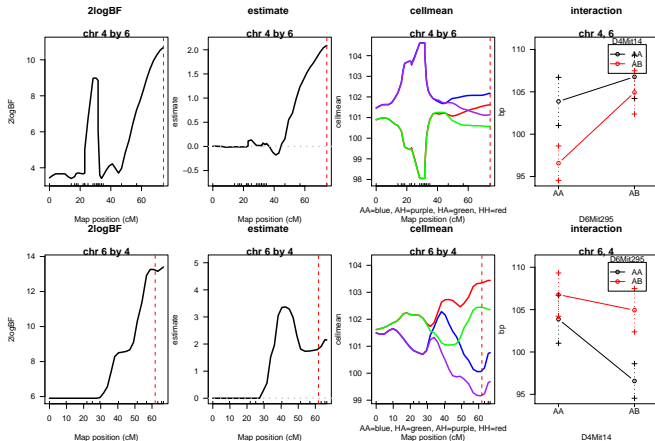
show detail plots for epistatic pairs (if any)

```
> 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))  
+   }  
+}
```

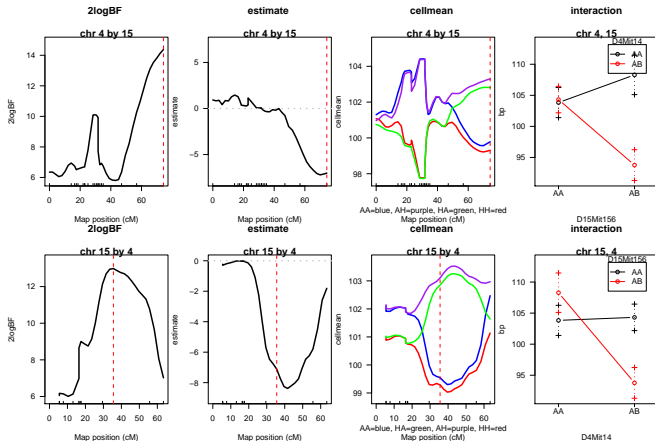
Epistatic Pair 6 and 15



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/qt1bim 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)
+ }
```