

# snpBMA: a package for details genetic association analysis of densely typed genetic regions

Chris Wallace

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### 1 Bayesian Model Averaging and the BMA package

### 2 Priors

The choice of priors for SNP models with dense genotyping data is not obvious. The CRAN BMA package has as its default a prior that gives equal weight to all possible models. This seems unrealistic with genetic data - in a region of 100 SNPs, a model with all 100 should not have the same prior as a model with just one associated. An alternative is to decide a prior for the number of SNPs in each model. For example, we might specify a binomial prior

$$nsnps \sim Bin(nsnps.total, \pi)$$

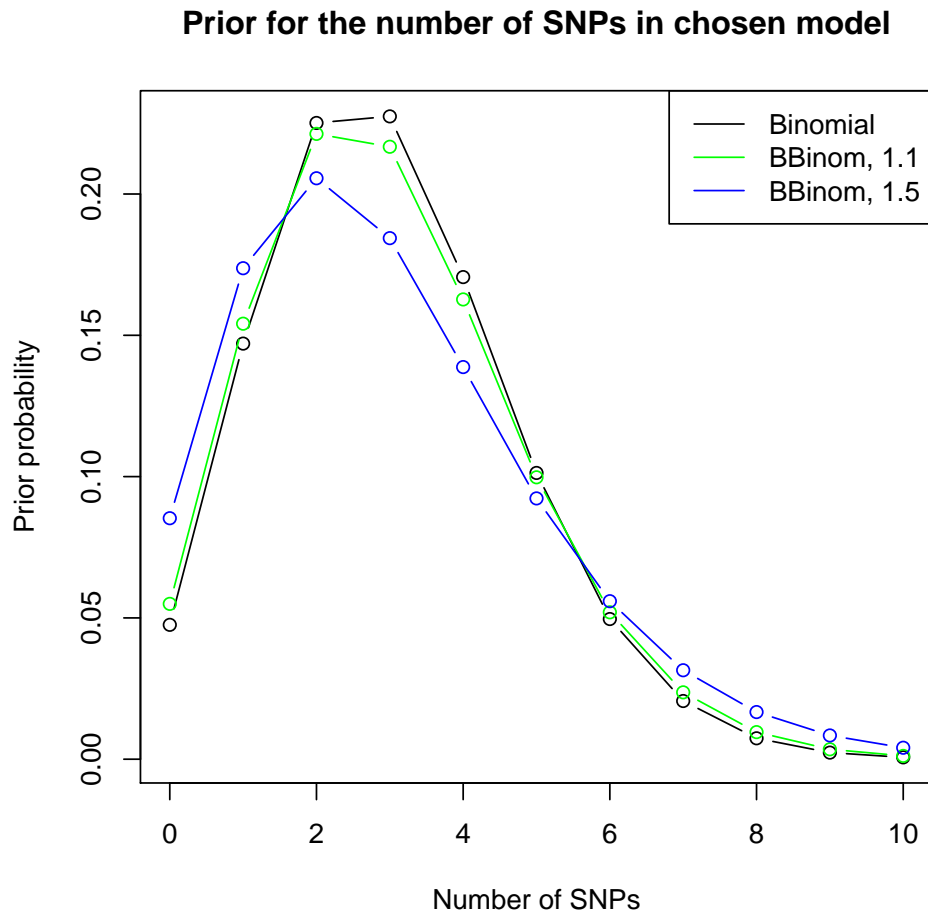
where  $\pi$  is chosen so that  $E(nsnps)$  is some sensible value. On the other hand, a binomial prior for the number of SNPs in a model may be considered too peaked if there is relatively little prior information about the number of causal SNPs, and, particularly if the posterior model choice is sensitive to this prior, it can be useful to consider a prior with greater spread. One such choice is the beta binomial model, under which the number of SNPs follows a binomial distribution with parameters  $nsnps.total$ ,  $\pi$  while  $\pi$  follows a beta distribution with parameters chosen so that the mean and the overdispersion (relative to a binomial distribution) are as specified. Functions exist in this package for both these models, and some examples are shown below, or, of course, you may specify your own (see below). It makes sense to specify, additionally, your prior for no SNPs being associated - this is unlikely to follow the same prior function as for one or more SNPs. This is the approach taken by [?].

```
> library(snpBMA)
> ## binomial prior assuming 100 SNPs in a region, 3 expected in preferred model
> ## low-ish prior (0.1) of no association in region
> p.binom <- prior.binomial(x=0:10, n=100, expected=3, value="prob", pi0=0.1)
> ## beta binomial, as above, allowing some overdispersion
> p.bb.1.1 <- prior.betabinomial(x=0:10, n=100, expected=3,
+                               overdispersion=1.1, value="prob", pi0=0.1)
> p.bb.1.5 <- prior.betabinomial(x=0:10, n=100, expected=3,
```

```

+                                     overdispersion=1.5, value="prob", pi0=0.1)
> ## plot
> plot(0:10, p.binom, type="b", main="Prior for the number of SNPs in chosen model",
+      xlab="Number of SNPs", ylab="Prior probability")
> lines(0:10, p.bb.1.1, col="green", type="b")
> lines(0:10, p.bb.1.5, col="blue", type="b")
> legend("topright", lty=rep(1,3),
+       col=c("black", "green", "blue"),
+       legend=c("Binomial", "BBinom, 1.1", "BBinom, 1.5"))

```



If we are prepared to assume all models with the same number of SNPs have equal priors (I pretty much am), then the simple thing is to say

$$\pi(M_{i,j}) = \frac{\pi(nsnps = i)}{\{M_{i,\cdot}\}}$$

The number of possible models grows exponentially with the number of SNPs in a model - note the plot below is on a log scale.

```

> mx <- sapply(0:10, function(i) max.models(n.snps=100, n.use=i))
> plot(0:10, log(mx), type="b", ylab="Log number of models",
+      main="Number of models for a fixed number of SNPs (log scale)",xlab="Number of SNPs")

```

As the number of possible models grows so quickly with the number of SNPs in a model, priors for individual models become very small very quickly.

```

> plot(0:10, p.bb.1.5/mx, type="b", main="Prior for each model of a given size",col="blue",
+      xlab="Number of SNPs", ylab="Prior probability")
> lines(0:10, p.bb.1.1/mx, col="green", type="b")
> lines(0:10, p.binom/mx, col="black", type="b")
> legend("topright",lty=rep(1,3),
+       col=c("black","green","blue"),
+       legend=c("Binomial", "BBinom, 1.1", "BBinom, 1.5"))

```

Instead, we suggest using the priors above to fix the relative odds of a model having  $m$  SNPs to a model with zero SNPs.

```

> ## binomial prior assuming 100 SNPs in a region, 3 expected in preferred model
> odds.binom <- prior.binomial(x=0:10, n=100, expected=3, value="odds", pi0=0.1)
> ## beta binomial, as above, allowing some overdispersion
> odds.bb.1.1 <- prior.betabinomial(x=0:10, n=100, expected=3,
+                                 overdispersion=1.1, value="odds", pi0=0.1)
> odds.bb.1.5 <- prior.betabinomial(x=0:10, n=100, expected=3,
+                                 overdispersion=1.5, value="odds", pi0=0.1)
> plot(0:10, odds.binom, type="b", main="Prior odds for each model of a given size")
> lines(0:10, odds.bb.1.1, col="green", type="b")
> lines(0:10, odds.bb.1.5, col="blue", type="b")
> legend("topright",lty=rep(1,3),
+       col=c("black","green","blue"),
+       legend=c("Binomial", "BBinom, 1.1", "BBinom, 1.5"))

```

### 3 Simulate some data

We start with using some sample data from the `snpStats` package including 20 SNPs, and simulating a quantitative trait that depends on 3 causal SNPs.

```

> library(snpStats)
> data(for.exercise, package="snpStats")
> set.seed(12346)
> X <- snps.10[,101:120]
> n <- nrow(X)
> causal <- c("rs1555897","rs7069505")
> Y <- rnorm(n,mean=as.numeric(X[,causal[1]]))*sqrt(0.2) +
+   rnorm(n,mean=as.numeric(X[,causal[2]]))*sqrt(0.2) +
+   rnorm(n)*sqrt(0.6)

```

X contains some missing genotypes, but no SNPs with such a low call rate we would worry in a large study. Still, the rest of the analysis is easier to interpret for the purposes of a vignette if we fill in the missing values.

```
> summary(col.summary(X))
```

Calls		Call.rate		Certain.calls		RAF	
Min.	:984.0	Min.	:0.9840	Min.	:1	Min.	:0.04651
1st Qu.:	988.5	1st Qu.:	0.9885	1st Qu.:	1	1st Qu.:	0.16658
Median	:989.0	Median	:0.9890	Median	:1	Median	:0.41617
Mean	:989.7	Mean	:0.9897	Mean	:1	Mean	:0.41482
3rd Qu.:	990.0	3rd Qu.:	0.9900	3rd Qu.:	1	3rd Qu.:	0.62680
Max.	:998.0	Max.	:0.9980	Max.	:1	Max.	:0.84747
MAF		P.AA		P.AB		P.BB	
Min.	:0.04651	Min.	:0.01921	Min.	:0.08898	Min.	:0.002022
1st Qu.:	0.14523	1st Qu.:	0.14170	1st Qu.:	0.22626	1st Qu.:	0.029575
Median	:0.31430	Median	:0.33984	Median	:0.42095	Median	:0.172658
Mean	:0.27944	Mean	:0.40774	Mean	:0.35487	Mean	:0.237383
3rd Qu.:	0.37406	3rd Qu.:	0.69520	3rd Qu.:	0.47258	3rd Qu.:	0.392982
Max.	:0.49298	Max.	:0.90900	Max.	:0.50101	Max.	:0.732323
z.HWE							
Min.	:-3.5140						
1st Qu.:	:-1.1135						
Median	: 0.1907						
Mean	:-0.4489						
3rd Qu.:	: 0.4224						
Max.	: 1.1354						

```
> X <- impute.missing(X)
```

```
20 to impute
```

```
1 .SNPs tagged by multiple tag haplotypes (saturated model): 1
2 .SNPs tagged by multiple tag haplotypes (saturated model): 1
3 .SNPs tagged by multiple tag haplotypes (saturated model): 1
4 .SNPs tagged by a single SNP: 1
5 .SNPs tagged by a single SNP: 1
6 .SNPs tagged by a single SNP: 1
7 .SNPs tagged by a single SNP: 1
8 .SNPs tagged by multiple tag haplotypes (saturated model): 1
9 .SNPs tagged by multiple tag haplotypes (saturated model): 1
10 .SNPs tagged by multiple tag haplotypes (saturated model): 1
11 .SNPs tagged by multiple tag haplotypes (saturated model): 1
12 .SNPs tagged by multiple tag haplotypes (saturated model): 1
13 .SNPs tagged by multiple tag haplotypes (saturated model): 1
14 .SNPs tagged by multiple tag haplotypes (saturated model): 1
15 .SNPs tagged by multiple tag haplotypes (saturated model): 1
```

```

16 .SNPs tagged by multiple tag haplotypes (saturated model): 1
17 .SNPs tagged by multiple tag haplotypes (saturated model): 1
18 .SNPs tagged by multiple tag haplotypes (saturated model): 1
19 .SNPs tagged by multiple tag haplotypes (saturated model): 1
20 .SNPs tagged by multiple tag haplotypes (saturated model): 1

```

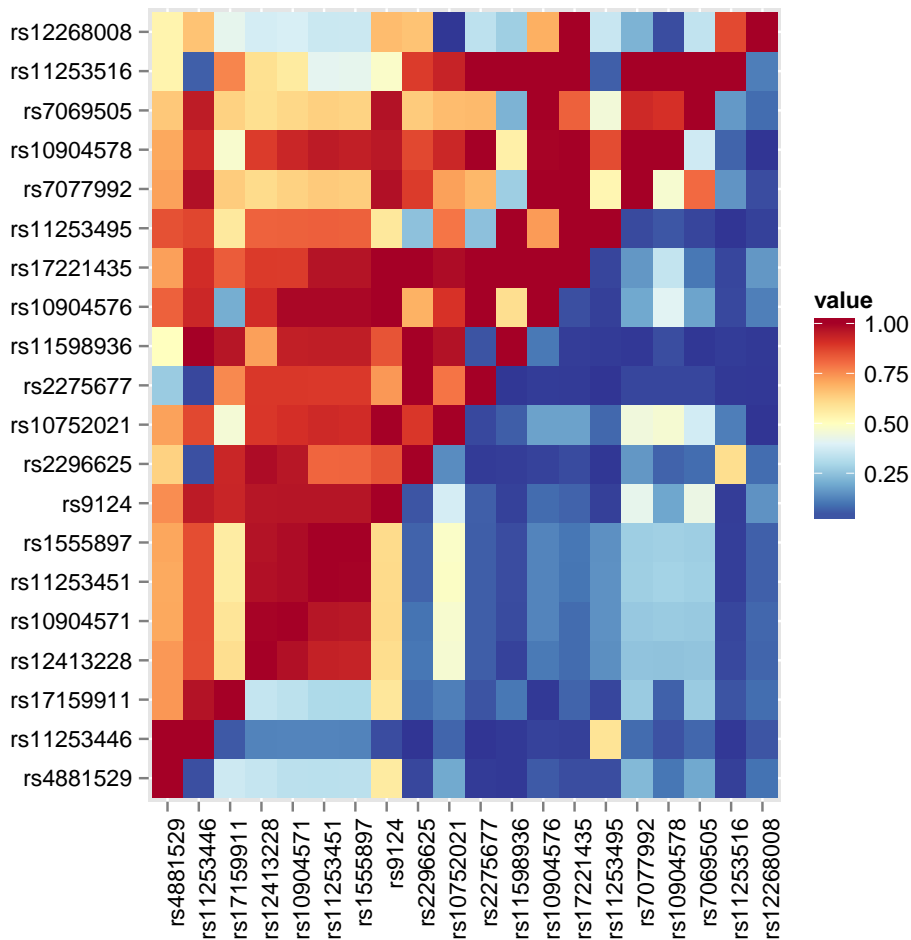
```
coercing object of mode numeric to SnpMatrix
```

```
> summary(col.summary(X))
```

Calls		Call.rate	Certain.calls	RAF	MAF		
Min.	:1000	Min.	:1	Min.	:0.0460	Min.	:0.0460
1st Qu.:	1000	1st Qu.:	1	1st Qu.:	0.1660	1st Qu.:	0.1457
Median	:1000	Median	:1	Median	:0.4158	Median	:0.3145
Mean	:1000	Mean	:1	Mean	:0.4145	Mean	:0.2794
3rd Qu.:	1000	3rd Qu.:	1	3rd Qu.:	0.6269	3rd Qu.:	0.3739
Max.	:1000	Max.	:1	Max.	:0.8465	Max.	:0.4940
P.AA		P.AB	P.BB	z.HWE			
Min.	:0.0200	Min.	:0.0880	Min.	:0.00200	Min.	:-3.5284
1st Qu.:	0.1410	1st Qu.:	0.2268	1st Qu.:	0.02925	1st Qu.:	-1.0185
Median	:0.3400	Median	:0.4220	Median	:0.17150	Median	: 0.2031
Mean	:0.4079	Mean	:0.3551	Mean	:0.23700	Mean	:-0.4348
3rd Qu.:	0.6957	3rd Qu.:	0.4733	3rd Qu.:	0.39275	3rd Qu.:	0.3971
Max.	:0.9100	Max.	:0.5020	Max.	:0.73100	Max.	: 1.1292

Looking at the LD, we see this is a region in which  $D'$  (above the diagonal) is very high, whilst  $r^2$  can be high between some SNPs, and with moderately strong  $r^2 \simeq 0.7$  between two of our causal SNPs:

```
> ld <- show.ld(X=X)
```



#### 4 A full BMA analysis using SNP tagging to quickly cover the model space

Bayesian model averaging approaches can be slow when the number of SNPs is very large, as the number of models grows rapidly. The simulated data are deliberately small here, so that you can compare the effect of the different ways we tackle this, which fall into three categories.

First, a strategy we recommend by default, is to cover the model space more rapidly by focusing on a tagging subset of SNPs, then expand to include the tagged SNPs only in the neighbourhood of supported models. Tags can be selected using the `tag` function, where `tag.threshold` sets the  $r^2$  threshold used to group SNPs. This function makes use of `hclust` to do the grouping. We can see that not all of our causal SNPs will be analysed directly, but some through tags. Usually a `tag.threshold` of 0.8 might be a sensible choice, lower values will cover the model space faster, but at the risk of missing true causal variants.

```
> tags <- tag(X, tag.threshold=0.8)
> tags[causal]
```

```
rs1555897    rs7069505
"rs12413228" "rs7077992"
```

In this case tagging means neither causal SNP is included directly in the set of SNPs we use to build our sets of models. We start with all possible one SNP models:

```
> ## make a snpBMAdata set
> data <- make.data(X, Y, tags=tags, family="gaussian")
```

Keeping 1000 of 1000 samples and 16 SNPs

```
> ## Calculate Bayes Factors for all one SNP models
> bma.1 <- bma.nsnps(data, nsnps=1)
```

groups not needed, creating a model matrix of 16 x 16 .  
Evaluating 16 models

```
> ## Summarise the SNPs with greatest support
> head(ss1 <- snp.summary(bma.1))
```

```
6 x 3 Matrix of class "dgeMatrix"
      twologB10-phi1 twologB10-phi2 twologB10-phi3
rs12413228      189.62567      188.71710      186.54791
rs10752021      180.17636      179.26334      177.09185
rs7077992       165.90851      164.98879      162.81383
rs9124          165.00678      164.08664      161.91146
rs10904578     149.16509      148.23750      146.05847
rs4881529       97.23981       96.28782       94.09615
```

Although the `bma.nsnps()` function works for any number of SNPs, it can be simpler to think of growing your BMA models from a parent generation (here, all possible one SNP models) to a child generation (here, all possible two SNP models).

```
> bma.2 <- bma.grow(data=data, bma=bma.1)
```

Evaluating 120 models

```
> bma.3 <- bma.grow(data=data, bma=bma.2)
```

Evaluating 560 models

## 4.1 Visualizing the results

It can be nice to visualize the support across these generations of models graphically. So far, we have assumed each model within a generation has an equal prior, which seems reasonable in the absence of specific information about the likely impact of each SNP. However, it doesn't seem reasonable that all models, regardless of the number of SNPs, should have equal priors. Models with smaller numbers of SNPs should be favoured. We can implement this by specifying a prior for the number of SNPs in a model. `snpBMA` has two functions to do this, or you can just create your own numeric vector.

```

> ## assume a binomial prior for the number of SNPs with expectation of
> ## 2 causal SNPs ie exactly the scenario simulated!
> prior.odds <- prior.binomial(1:10, n=ncol(X), expected=2, value="odds", pi0=0.1)
> ## also consider a prior with expectation of 4 causal
> ## SNPs to examine the effect of varying the prior
> prior.alt <- prior.binomial(1:10, n=ncol(X), expected=4, value="odds", pi0=0.1)

```

See the help for `prior.betabinomial` to understand the other function available, and the difference to a binomial prior.

```

> ## create a graph of BMA results so far
> results <- stack(bma.1,bma.2,bma.3)
> g<-graphBMA(bma.list=results, priors=prior.odds)
> ## g is an igraph, so you can do all the usual stuff with it:
> g

```

```
[[1]]
```

```
[1] 696
```

```
[[2]]
```

```
[1] FALSE
```

```
[[3]]
```

```

[1] 16 16 17 17 18 18 19 19 20 20 21 21 22 22 23 23 24 24
[19] 25 25 26 26 27 27 28 28 29 29 30 30 31 31 32 32 33 33
[37] 34 34 35 35 36 36 37 37 38 38 39 39 40 40 41 41 42 42
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```



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[221] 7.567172e+36 8.737872e+27 1.973599e+37 6.033389e+37 7.751399e+25  
[226] 4.329958e+23 2.449372e+30 4.677979e+38 6.597443e+37 3.524525e+28  
[231] 1.128274e+31 1.354094e+44 4.637666e+38 4.735290e+28 2.492459e+24  
[236] 1.290851e+41 8.509725e+36 6.788992e+36 3.674167e+37 4.057074e+38  
[241] 4.258139e+23 8.092233e+38 2.596751e+40 2.720107e+31 6.790818e+43  
[246] 3.031632e+24 3.854705e+30 1.540072e+32 1.223734e+29 8.546301e+24  
[251] 3.828678e+46 2.478334e+41 5.182429e+31 1.738564e+25 3.552277e+41  
[256] 2.776586e+46 3.023250e+46 2.743986e+38 2.329605e+38 1.403569e+40  
[261] 5.094901e+42 5.834284e+38 9.932464e+50 1.286386e+47 1.635509e+45  
[266] 3.221418e+38 2.414745e+46 2.050532e+46 1.453133e+40 1.474270e+40  
[271] 2.422381e+41 4.262922e+43 4.042860e+40 1.004697e+51 2.361261e+47  
[276] 1.298789e+45 1.414226e+40 5.964861e+41 4.986842e-01 1.034994e-02  
[281] 4.717201e+08 1.173564e+11 6.328961e-02 3.359072e+45 1.200634e+30  
[286] 4.601937e-01 2.167875e+05 2.922323e+36 5.824673e+36 1.195240e+37  
[291] 2.162608e+37 2.853831e+36 1.187621e+43 6.367435e+39 1.838181e+38  
[296] 1.818861e+39 1.602082e-01 3.749859e+09 5.302868e+11 6.702098e-01  
[301] 1.151459e+41 1.143512e+29 1.720764e+01 5.849056e+03 7.985132e+08  
[306] 1.606750e+12 2.641282e-02 8.631455e+40 1.069467e+29 2.080514e-01  
[311] 3.885908e+02 2.472467e+28 2.291806e+09 1.047750e+41 1.417637e+29  
[316] 1.225014e+09 8.418420e+09 3.255345e+11 1.929267e+41 1.801460e+29  
[321] 2.437995e+11 2.893155e+26 1.765214e+41 1.669008e+29 1.634661e+00  
[326] 1.591036e+03 2.081637e+41 2.011963e+43 7.809478e+42 1.963849e+29  
[331] 1.813740e+33 7.190173e+08 7.075351e+40 3.766382e+47 7.541978e+46  
[336] 6.665788e+38 1.073539e+39 1.018448e+41 2.913123e+42 1.058746e+39  
[341] 2.042751e+50 2.855452e+47 1.604229e+46 5.826255e+38 5.102786e+38  
[346] 1.340742e+46 3.870079e+32 5.069885e+32 8.468564e+35 3.717013e+38  
[351] 7.343438e+38 2.008737e+41 2.495000e+45 1.069069e+38 1.333155e+33  
[356] 2.302333e+44 1.080929e+23 6.454222e+29 1.328654e+31 5.758004e+26  
[361] 7.250045e+29 5.679275e+36 1.545698e+40 3.200322e+24 1.164261e+24



[366] 4.281837e+43 1.205596e+44 6.985073e+44 1.099161e+44 5.703328e+43  
[371] 4.827085e+45 4.980575e+46 5.039138e+43 3.550027e+44 6.097909e+23  
[376] 2.497198e+27 2.359967e+24 7.041086e+22 1.178380e+36 1.162763e+40  
[381] 9.875225e+23 1.258437e+17 4.090651e+29 3.151643e+31 6.822495e+28  
[386] 1.029910e+38 2.850887e+41 2.739512e+30 7.394790e+23 1.055574e+39  
[391] 1.706405e+31 3.396209e+37 1.164867e+40 1.361916e+31 7.471085e+27  
[396] 7.822612e+27 3.708379e+37 1.087946e+40 9.731090e+27 5.983134e+28  
[401] 1.209119e+43 9.751765e+40 2.325568e+30 1.680254e+23 1.104234e+42  
[406] 1.508236e+36 1.364773e+36 2.485551e+40 6.529043e+40 5.506397e+25  
[411] 4.518788e+48 2.152737e+47 6.321310e+40 4.705244e+40 1.430079e+42  
[416] 3.861149e+44 1.214269e+41 2.623469e+50 2.676952e+48 1.446120e+47  
[421] 9.895358e+40 7.000024e+45 1.217502e+45 2.503163e+45 2.971027e+45  
[426] 2.246948e+46 2.718209e+46 5.862568e+50 7.534446e+47 4.636152e+45  
[431] 6.360362e+45 7.750140e+44 2.035990e+45 1.781735e+45 1.441028e+46  
[436] 2.359943e+46 9.710252e+50 4.802274e+47 6.617079e+45 3.143728e+45  
[441] 5.793570e+37 2.769546e+39 9.078614e+41 4.237856e+38 1.888648e+50  
[446] 1.110243e+46 1.165988e+44 5.740412e+37 5.247790e+39 8.196401e+41  
[451] 3.422899e+38 1.489154e+50 1.545045e+46 1.827331e+44 5.387606e+37  
[456] 9.042071e+45 1.679681e+40 1.660068e+50 1.869104e+46 2.788989e+44  
[461] 3.248220e+39 8.421486e+42 7.794618e+50 2.169297e+46 9.577485e+45  
[466] 3.000769e+43 2.425442e+50 1.408741e+47 1.536567e+45 4.243688e+38  
[471] 9.724386e+50 5.958940e+50 1.663544e+50 3.609183e+47 2.216471e+46  
[476] 1.397240e+45 3.917438e+45 1.822602e+38 2.050516e+38 6.272474e+39  
[481] 1.520259e+41 2.000317e+45 2.639781e+41 5.561734e+45 6.679091e+38  
[486] 2.045915e+38 2.625933e+45 6.809577e+45 6.140505e+45 3.511630e+46  
[491] 1.351940e+46 1.334332e+47 1.832169e+48 3.344139e+45 3.845873e+45  
[496] 2.556113e+32 3.467632e+35 2.487963e+38 4.940757e+38 1.328734e+41  
[501] 1.497928e+45 4.044064e+37 9.742765e+32 5.415852e+35 3.244708e+38  
[506] 4.895159e+38 1.308797e+41 1.544620e+45 4.195155e+37 9.071155e+32  
[511] 3.375503e+44 2.483224e+40 4.500829e+41 2.312783e+45 1.165559e+39  
[516] 6.840191e+36 2.866386e+42 1.564855e+43 2.275116e+45 1.581057e+41  
[521] 8.786068e+38 1.335201e+48 7.869964e+46 1.442893e+44 8.030473e+38  
[526] 9.299783e+45 3.350362e+41 2.078068e+41 4.549456e+45 1.171538e+45  
[531] 4.830021e+37 3.280937e+40 1.067204e+41 1.228153e+41 8.651565e+41  
[536] 2.949910e+41 2.458203e+48 1.093613e+44 9.771982e+40 6.117727e+41  
[541] 9.756077e-03 7.131482e+08 7.208121e+10 3.731643e+00 5.755468e+35  
[546] 1.271834e+30 4.370695e-01 3.232330e+02 1.089629e+08 6.673596e+11  
[551] 5.834830e-02 1.203083e+36 1.352145e+30 1.055055e-02 8.086168e+00  
[556] 2.886180e+29 2.008375e+09 1.646742e+36 2.357313e+30 3.911008e+08  
[561] 6.911817e+08 2.094867e+11 1.218442e+38 3.225091e+30 9.458205e+11  
[566] 1.582895e+24 8.272369e+41 1.234778e+30 3.010244e+00 2.076993e+05  
[571] 2.297826e+40 1.249436e+36 6.383038e+35 2.616883e+30 1.382328e+33  
[576] 3.233539e+04 2.657181e+36 4.748184e+36 8.591538e+36 1.370403e+36  
[581] 5.663556e+41 1.844300e+39 2.844721e+37 1.892712e+39 3.405418e+37  
[586] 1.067890e+37 2.931921e+36 6.795726e+41 6.514425e+39 8.647850e+37

```
[591] 9.816267e+39 1.502697e+39 5.267185e+36 5.827873e+41 2.031093e+39
[596] 1.887677e+38 1.857791e+39 1.086825e+37 1.120963e+42 2.127567e+39
[601] 3.748994e+38 2.680401e+43 3.014244e+42 2.965014e+39 8.838287e+37
[606] 1.629408e+39 3.401451e+42 6.242228e+44 2.179398e+43 2.010924e+41
[611] 8.058558e+42 3.314140e+39 6.754634e+08 2.323369e+12 8.466525e-01
[616] 8.314799e+32 1.363255e+29 3.806287e-01 1.456227e+00 3.262137e+28
[621] 1.642142e+10 2.287558e+33 1.854010e+29 2.498983e+09 1.667546e+09
[626] 1.087527e+12 3.105556e+34 2.334510e+29 2.422366e+11 4.443194e+23
[631] 5.148178e+38 1.325205e+29 1.567326e+02 6.138474e+03 8.685952e+36
[636] 7.262166e+33 1.862606e+33 2.284172e+29 9.978765e+32 1.061266e+06
[641] 2.632639e+28 3.196069e+09 1.671541e+33 1.639829e+29 2.910373e+08
[646] 3.439582e+08 2.881259e+12 5.611152e+34 1.993119e+29 7.197163e+11
[651] 4.387920e+24 3.294403e+38 1.235190e+29 1.417338e+00 3.418062e+02
[656] 7.438106e+36 1.107399e+34 1.657748e+33 2.334987e+29 1.581264e+33
[661] 1.457365e+04 3.091987e+28 8.763004e+36 7.804406e+29 4.405093e+28
[666] 1.213051e+35 4.172328e+38 1.583802e+29 5.723692e+09 2.066383e+10
[671] 1.255651e+37 2.926148e+34 3.252227e+33 3.303042e+29 8.111846e+34
[676] 1.025074e+10 1.344853e+39 2.015806e+29 5.333827e+11 2.989866e+25
[681] 1.445104e+37 5.944779e+35 2.220598e+37 4.213167e+29 4.705642e+35
[686] 2.951557e+27 4.543721e+39 1.028884e+40 4.501258e+39 2.109977e+29
[691] 1.768759e+33 6.937356e+08 3.523836e+38 2.737983e+38 8.045724e+33
[696] 1.202317e+33
```

```
[[9]][[4]]
```

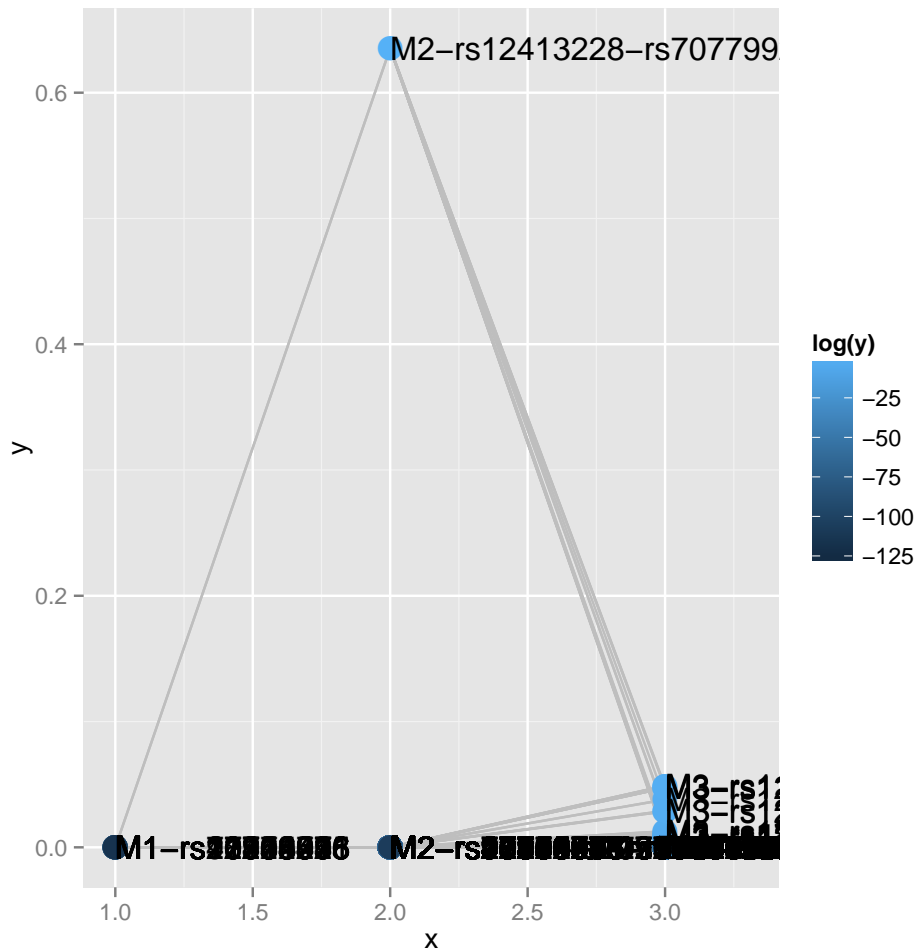
```
list()
```

```
attr(,"class")
```

```
[1] "igraph"
```

```
> ## visualize
```

```
> graphView(g)
```



This shows the models according to posterior probabilities **across the model space visited**. One model stands out, with the tags of our causal SNPs. Similar information can be obtained from writing the top models to screen

```
> top.models(results, priors=prior.odds, n=20)
```

	PP_phi=phi.1	PP_phi=phi.2	PP_phi=phi.3
rs12413228-rs7077992	0.5135056451	6.353348e-01	8.407343e-01
rs11253446-rs9124-rs7077992	0.0646995686	4.891916e-02	2.145439e-02
rs11253446-rs12413228-rs7077992	0.0644578569	4.836163e-02	2.112522e-02
rs12413228-rs7077992-rs10904578	0.0635417270	4.734849e-02	2.060945e-02
rs12413228-rs10752021-rs7077992	0.0635466069	4.727967e-02	2.056324e-02
rs12413228-rs17221435-rs7077992	0.0507554806	3.795236e-02	1.654927e-02
rs12413228-rs7077992-rs11253516	0.0386474352	2.901436e-02	1.267804e-02
rs12413228-rs2296625-rs7077992	0.0379696617	2.854512e-02	1.248199e-02
rs12413228-rs9124-rs7077992	0.0169984688	1.277379e-02	5.584527e-03
rs12413228-rs11253495-rs7077992	0.0157549933	1.180959e-02	5.156128e-03
rs17159911-rs12413228-rs7077992	0.0132335905	9.946249e-03	4.348659e-03

```

rs4881529-rs12413228-rs7077992 0.0122595414 9.199372e-03 4.018763e-03
rs12413228-rs2275677-rs7077992 0.0122488867 9.195914e-03 4.018251e-03
rs12413228-rs7077992-rs12268008 0.0107909617 8.099875e-03 3.538988e-03
rs12413228-rs10904576-rs7077992 0.0107745721 8.082949e-03 3.530555e-03
rs12413228-rs11598936-rs7077992 0.0096657350 7.250762e-03 3.166975e-03
rs12413228-rs9124-rs2296625 0.0002915435 2.200219e-04 9.640133e-05
rs12413228-rs9124-rs10904578 0.0001760543 1.303420e-04 5.654432e-05
rs2296625-rs10752021-rs7077992 0.0001577420 1.196910e-04 5.258925e-05
rs9124-rs10752021-rs10904578 0.0001204382 8.920917e-05 3.870983e-05

```

and a character vector of the SNPs forming these models can be found by `#BEGINSRC R :ravel label=top.snps top.snps(results, priors=prior.odds, n=16) # n refers to number of #+ENDSRC`

## 4.2 Add back in the tagged SNPs

We used tagging to span the space quickly. Once we have found our favoured models, it makes sense to see how the tagged SNPs in LD with SNPs in those models change things. There are a couple of subtleties here to be aware of however:

1. the X matrix must be of full rank, which means a small amount of tagging may always be necessary, say at  $r^2=0.99$
2. when two SNPs are in strong LD, fitting both in the model can make the model uninterpretable. With `snpBMA` you can group SNPs so that at most one of each group is included in any single model. The default grouping threshold is  $r^2=0.8$ , but the optimal value will depend on your data: with many subjects a higher threshold may be appropriate, as the SNPs become statistically distinguishable.

```

> ## First, tag at r2=0.99
> tags.99 <- tag(X, 0.99)
> ## group remaining snps at r2=0.8, using the first set of tags above as indices
> groups <- group.tags(tags, keep=tags.99)
> length(groups)

```

```
[1] 16
```

```
> data.99 <- make.data(X, Y, tags=tags.99, family="gaussian")
```

Keeping 1000 of 1000 samples and 19 SNPs

Now we decide which tag SNP groups we would like to "expand". Because we are keen not to miss the true causal variants, we choose any SNPs in the top 16 models, after which the posterior probabilities really do appear to tail off, and refit all models including these tagged SNPs in their groups:

```

> expand.snps <- top.snps(results, prior.odds, nmodels=17)
> bma.e1 <- bma.expand(data.99, bma.1, groups=groups[expand.snps])

```

Evaluating 19 models

```
> bma.e2 <- bma.expand(data.99, bma.2, groups=groups[expand.snps])
```

Evaluating 167 models

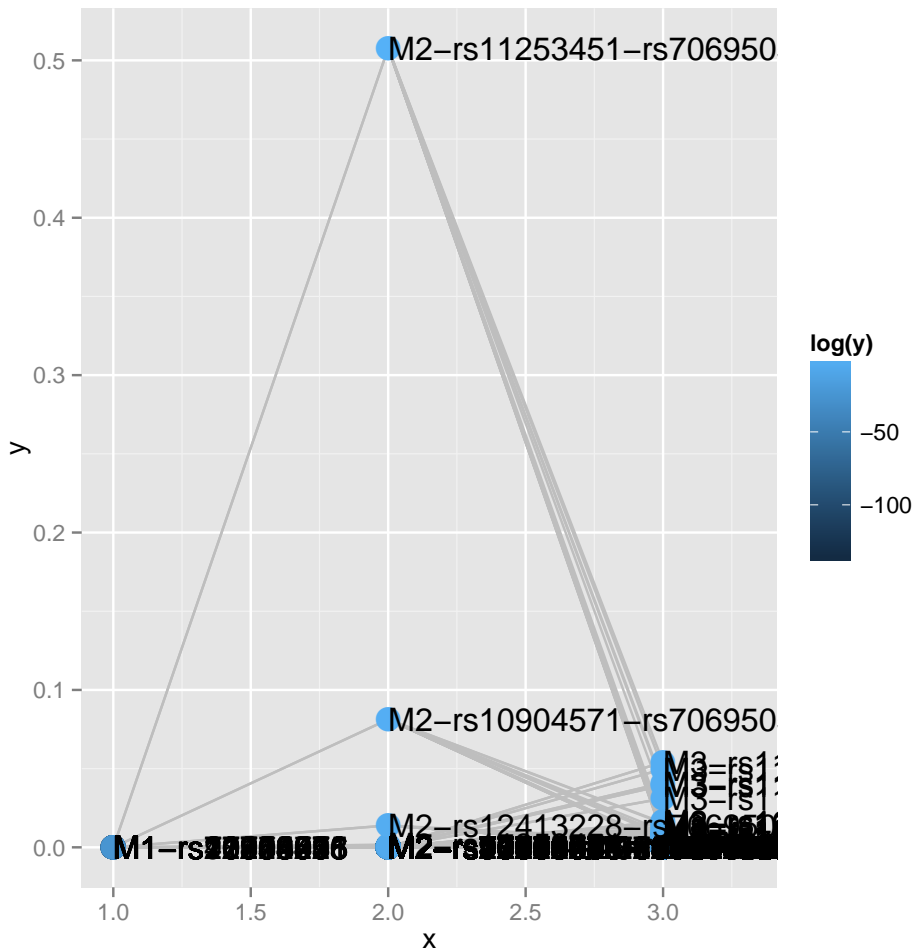
```
> bma.e3 <- bma.expand(data.99, bma.3, groups=groups[expand.snps])
```

Evaluating 903 models

You can see the model space grows much more quickly. But the end result is not dissimilar. The top model is now rs11253451-rs7069505. rs7069505 is one of the causal SNPs, and rs11253451 tags the other (rs1555897), at  $r^2=1$ .

```
> ## create a graph of BMA results so far
> expand.results <- stack(bma.e1,bma.e2,bma.e3)
> g.expand<-graphBMA(expand.results, prior.odds)
> ## visualize
> graphView(g.expand)
> top.models(expand.results, prior.odds)
```

	PP_phi=phi.1	PP_phi=phi.2	PP_phi=phi.3
rs11253451-rs7069505	0.40376004	0.50769188	0.69064645
rs10904571-rs7069505	0.06464480	0.08127372	0.11055400
rs11253451-rs7069505-rs11253446	0.07090410	0.05410507	0.02430552
rs11253451-rs7069505-rs17221435	0.06549112	0.04976490	0.02230718
rs11253451-rs7069505-rs10752021	0.05400202	0.04084564	0.01826548
rs11253451-rs7069505-rs2296625	0.05150494	0.03935315	0.01769045



## 5 Speedup 2: excluding SNPs with low single SNP support

An additional, fairly brute force, way to prune the model space is to exclude all SNPs with very limited single SNP support. In this case, we drop SNPs that have a 2 log Bayes Factor (versus the null model with no SNPs)  $< 2.2$ , a threshold previously described as "weak support" (TODO:REF).

```
> ## define the list of SNPs to drop
> max.bf <- apply(ss1,1,max)
> snps.drop <- rownames(ss1)[ max.bf < 0 ]
> snps.drop
```

```
[1] "rs2296625" "rs11598936"
```

Then we can assess all two SNP models excluding those in `snps.drop`. We will also analyse the complete set of data, so the two approaches can be compared. To do this, we need to prune the snps included in the `bma.1` object and the `data` object.

```
> ## generate a new set of tags and snpBMAdata object
> data2 <- snps.prune.data(data, snps.drop)
```

Keeping 1000 of 1000 samples and 14 SNPs

```
> bma.2 <- bma.nsnps(data, nsnps=2)
```

groups not needed, creating a model matrix of 120 x 16 .  
Evaluating 120 models

```
> bma.2d <- bma.nsnps(data2, nsnps=2)
```

groups not needed, creating a model matrix of 91 x 14 .  
Evaluating 91 models

```
> ## compare top models
> top.models(bma.2)
```

	rs12413228	rs9124	rs2296625	rs10752021	rs7077992	rs10904578	twologB10-phi1
[1,]	1	0	0	0	1	0	239.8248
[2,]	1	0	0	0	0	1	220.3352
[3,]	0	1	0	1	0	0	217.8585
[4,]	1	0	1	0	0	0	216.3604
[5,]	0	1	0	0	0	1	216.0529
[6,]	1	0	0	1	0	0	215.4962

	twologB10-phi2	twologB10-phi3
[1,]	237.9051	233.5136
[2,]	218.4076	214.0120
[3,]	215.9272	211.5297
[4,]	214.4915	210.1263
[5,]	214.1268	209.7321
[6,]	213.5593	209.1589

```
> top.models(bma.2d)
```

	rs12413228	rs9124	rs10752021	rs7077992	rs10904578	rs11253516
[1,]	1	0	0	1	0	0
[2,]	1	0	0	0	1	0
[3,]	0	1	1	0	0	0
[4,]	0	1	0	0	1	0
[5,]	1	0	1	0	0	0
[6,]	1	0	0	0	0	1

	twologB10-phi1	twologB10-phi2	twologB10-phi3
[1,]	239.8248	237.9051	233.5136
[2,]	220.3352	218.4076	214.0120
[3,]	217.8585	215.9272	211.5297
[4,]	216.0529	214.1268	209.7321
[5,]	215.4962	213.5593	209.1589
[6,]	211.6803	209.7966	205.4237

## 6 Speedup 3: excluding descendants of less likely model paths

Models with two or more SNPs can be thought of as children of many parent models. If a two SNP model contains SNPs A and B, then its parents are the single SNP models containing either A or B. Each parent model has many potential children. Thus the model space can be partitioned into generations, with each generation containing a fixed number of SNPs. Any two or more SNP model can be reached via multiple paths in this model space.

[?] proposed that where child models had a parent with greater support than the child, no further "grandchild" models would be worth considering. This is quite a broad pruning. We choose to implement a variation where the future generation models are excluded if a child model has a parent model with  $f$ -fold greater support, and have set the default at  $f = 10$ .

Here, we compare the child and parent models in `bma.1` and `bma.2d` to determine the set of models we will not explore. One way to implement this would be to determine all the possible three SNP models, then delete those that are children of the dropped models. But a faster way is to drop these models from the `bma2` object, then use `bma.grow()` to automatically fit all the child models of those which remain.

```
> ## prune the bma.2d object
> bma.2dd <- models.prune(parents=bma.1, children=bma.2d,
+                          prior.parents=prior.odds[1],
+                          prior.children=prior.odds[2])

Identified 27 of 91 models with pp(parent) > 10 * pp(child)

> ## grow the BMA to a third generation
> bma.3dd <- bma.grow(data2, bma.2dd)

Evaluating 355 models

> ## for comparison, without pruning, we could use tagging only...
> bma.3 <- bma.nsnps(data, nsnps=3)

groups not needed, creating a model matrix of 560 x 16 .
Evaluating 560 models

> ## ... or tagging + excluding poorly supported single SNPs
> bma.3d <- bma.nsnps(data2, nsnps=3)

groups not needed, creating a model matrix of 364 x 14 .
Evaluating 364 models

> ## this should be the same as growing from the bma.2d object
> bma.3d2 <- bma.grow(data2, bma.2d)

Evaluating 364 models

> top.models(bma.3d)
```



```

rs11253446 rs12413228 rs9124 rs10752021 rs17221435 rs7077992 rs10904578
[1,] 1 0 1 0 0 1 0
[2,] 1 1 0 0 0 1 0
[3,] 0 1 0 0 0 1 1
[4,] 0 1 0 1 0 1 0
[5,] 0 1 0 0 1 1 0
[6,] 0 1 0 0 0 1 0
rs11253516 twologB10-phi1 twologB10-phi2 twologB10-phi3
[1,] 0 236.4928 233.5881 226.9879
[2,] 0 236.4853 233.5652 226.9569
[3,] 0 236.4566 233.5228 226.9075
[4,] 0 236.4568 233.5199 226.9030
[5,] 0 236.0073 233.0804 226.4687
[6,] 1 235.4622 232.5433 225.9357

```

```
> top.models(bma.3d2)
```

```

rs11253446 rs12413228 rs9124 rs10752021 rs17221435 rs7077992 rs10904578
[1,] 1 0 1 0 0 1 0
[2,] 1 1 0 0 0 1 0
[3,] 0 1 0 0 0 1 1
[4,] 0 1 0 1 0 1 0
[5,] 0 1 0 0 1 1 0
[6,] 0 1 0 0 0 1 0
rs11253516 twologB10-phi1 twologB10-phi2 twologB10-phi3
[1,] 0 236.4928 233.5881 226.9879
[2,] 0 236.4853 233.5652 226.9569
[3,] 0 236.4566 233.5228 226.9075
[4,] 0 236.4568 233.5199 226.9030
[5,] 0 236.0073 233.0804 226.4687
[6,] 1 235.4622 232.5433 225.9357

```

## 7 Automating the analysis

There are a lot of steps above. It's good to understand the detail of how we approach the problem, but once you understand it, it can be tedious to run each step. `snpBMA` will have a function, `bma.auto()`, that should automate much of this.

TODO!!!

```

\bibliographystyle{plain}
\bibliography{ProbePosition}

```

## 8 Stratified analysis

There is another data class, `snpBMAstrat`, which is used to store data for when a stratified analysis is needed. The stratification is based on the following factorization of the Bayes Factor

$$\frac{P(D|M_1)}{P(D|M_2)} = \frac{P(D_1|M_1) \times P(D_2|M_1)}{P(D_1|M_2) \times P(D_2|M_2)}$$

where  $D$  represents the data, which can be stratified into two independent datasets  $D_1$ ,  $D_2$ , and  $M_1$ ,  $M_2$  represent models under consideration. Strata may be, for example, batch in biological assays.

To define such data, we do

```
> sdata <- make.data(X,Y,tags=tags,family="gaussian",
+                   strata=rep(c(1,2),length=nrow(X)))
```

Keeping 1000 of 1000 samples and 16 SNPs

Analysis of the stratified and unstratified datasets here should produce similar results, as there is no intrinsic difference between the distribution of  $Y$  between strata.

```
> data <- make.data(X,Y,tags=tags,family="gaussian")
```

Keeping 1000 of 1000 samples and 16 SNPs

```
> bma.1 <- bma.nsnps(data, nsnps=1)
```

```
groups not needed, creating a model matrix of 16 x 16 .
Evaluating 16 models
```

```
> sbma.1 <- bma.nsnps(sdata, nsnps=1)
```

```
groups not needed, creating a model matrix of 16 x 16 .
Stratum 1      Evaluating 16 models
2              Evaluating 16 models
```

```
> top.models(bma.1)
```

	rs4881529	rs12413228	rs9124	rs10752021	rs7077992	rs10904578	twologB10-phi1
[1,]	0	1	0	0	0	0	189.62567
[2,]	0	0	0	1	0	0	180.17636
[3,]	0	0	0	0	1	0	165.90851
[4,]	0	0	1	0	0	0	165.00678
[5,]	0	0	0	0	0	1	149.16509
[6,]	1	0	0	0	0	0	97.23981
	twologB10-phi2	twologB10-phi3					
[1,]	188.71710	186.54791					
[2,]	179.26334	177.09185					
[3,]	164.98879	162.81383					
[4,]	164.08664	161.91146					
[5,]	148.23750	146.05847					
[6,]	96.28782	94.09615					

```
> top.models(sbma.1)
```

```
rs4881529 rs12413228 rs9124 rs10752021 rs7077992 rs10904578 twologB10-phi1
[1,]      0          1      0          0          0          0          185.80689
[2,]      0          0      0          1          0          0          174.95889
[3,]      0          0      0          0          1          0          160.44461
[4,]      0          0      1          0          0          0          160.05983
[5,]      0          0      0          0          0          1          143.90646
[6,]      1          0      0          0          0          0          93.60258

twologB10-phi2 twologB10-phi3
[1,]      183.99282      179.6561
[2,]      173.13472      168.7928
[3,]      158.60694      154.2580
[4,]      158.22171      153.8725
[5,]      142.05305      137.6959
[6,]       91.70189       87.3203
```