

polySegratioMM: An R library for Bayesian mixture models for marker dosage in autopolyploids

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It is well known that the dosage level of markers in autopolyploids and allopolyploids can be characterised by their observed segregation ratios. The related package `polySegratio` provides functions to allocate dosage by standard approaches and to simulate marker data sets for differing ploidies and levels of overdispersion. Note that these methods could equally well be applied to allopolyploids with specified expected segregation ratios. For details see `polySegratio`.

A Bayesian approach was proposed by Baker et al. (2010) where marker dosage estimation was obtained by fitting a finite mixture distribution.

This library calls the JAGS software for Bayesian calculation. JAGS 1.0 or higher must be installed following instructions from <http://mcmc-jags.sourceforge.net/>. Note that only the most recent version is used for testing with R. The JAGS executable must be in your path. Currently, no checking is carried out to ascertain whether or not JAGS is set up appropriately.

To use the library, you need to attach it with

```
> library(polySegratioMM)
```

1 Simulated data

Library functions are demonstrated on a simulated data set generated using the `sim.autoMarkers` function from the `polySegratio` package.

The following R code can be used to generate 500 markers for 200 autohexaploid individuals exhibiting overdispersion with the parameter `shape1 = 25`. The underlying percentages of single double and triple dose markers are 70%, 20% and 10%, respectively.

```
hexmarkers <- sim.autoMarkers(6,c(0.7,0.2,0.1),n.markers=500,n.individuals=200)
> ##<<simData, cache=true>>=
> ## simulate small autohexaploid data set of 500 markers for 200 individuals
> ## with %70 Single, %20 Double and %10 Triple Dose markers
> ## created with
```

```
> ## hexmarkers <- sim.autoMarkers(6,c(0.7,0.2,0.1),n.markers=500,n.individuals=200)
> ## save(hexmarkers, file="../../data/hexmarkers.RData")
> print(hexmarkers)
```

Autopolyploid dominant markers generated at Fri Jul 18 14:51:38 2008
with call:

```
sim.autoMarkers(ploidy.level = 6, dose.proportion = c(0.7, 0.2,
  0.1), n.markers = 500, n.individuals = 200)
```

Ploidy level is: 6 (Hexaploid)

Parents were set as heterogeneous for the markers

Theoretical segregation proportions:

ratio.SD	ratio.DD	ratio.TD	ploidy.level
"0.5"	"0.8"	"0.95"	"6"
ploidy.name	type.parents		
"Hexaploid"	"heterogeneous"		

Proportions in each dosage class:

SD	DD	TD
0.7	0.2	0.1

No. of markers generated from multinomial distribution:

No.markers	
SD	346
DD	103
TD	51

Data were generated for 200 individuals with 500 markers

A subset is:

	X.1	X.2	X.3	X.4	X.5	X.6	X.7	X.8	X.9	X.10	r	n	ratio	dose
M.1	1	0	0	1	0	1	0	1	1	1	108	200	0.54	SD
M.2	0	1	1	1	0	1	0	1	0	1	102	200	0.51	SD
M.3	1	0	0	1	0	0	0	1	1	1	103	200	0.515	SD
M.4	1	1	1	1	1	0	0	0	1	0	97	200	0.485	SD
M.5	0	0	1	1	0	0	1	1	0	1	99	200	0.495	SD
M.6	1	1	0	0	0	0	0	0	0	0	103	200	0.515	SD
M.7	1	1	0	0	0	1	0	0	1	1	101	200	0.505	SD
M.8	1	1	1	1	1	1	0	0	0	1	102	200	0.51	SD
M.9	0	1	1	1	1	0	0	1	1	0	110	200	0.55	SD
M.10	1	0	1	0	1	1	1	0	1	1	108	200	0.54	SD

Note that the segregation ratios for simulated or real data may be extracted by using `segregationRatios` which sets up the appropriate objects for testing marker dosage and plotting or summarising the marker data.

```
> sr <- segregationRatios(hexmarkers$markers)
```

For instance, as seen in Figure 1, segregation ratios may be plotted with

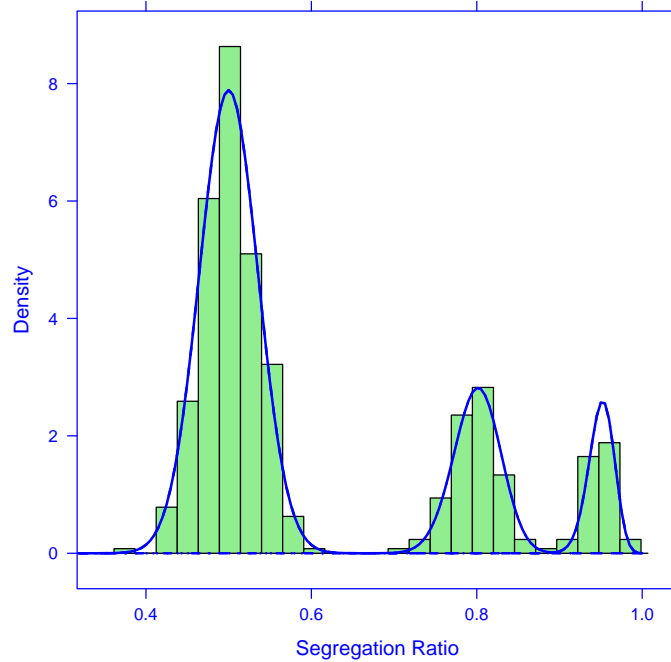


Figure 1: Segregation ratios of 500 simulated markers from 200 autohexaploid individuals. Percentages of single double and triple dose markers are 70%, 20% and 10%, respectively. Data were generated assuming no overdispersion.

```
plotTheoretical(ploidy.level=6, seg.ratios=sr,
  expected.segratio=NULL, proportions=c(0.7,0.2,0.1),
  n.individuals=200)
```

On the other hand, consider a similar data set that exhibits overdispersion. This may be simulated as follows

```
hexmarkers.overdisp <- sim.autoMarkers(6,c(0.7,0.2,0.1),n.markers=500,n.individuals=200,
  overdispersion=TRUE, shape1=30)
```

```
> sr.overdisp <- segregationRatios(hexmarkers.overdisp$markers)
```

The histogram of marker segregation ratios, which is a useful graphical method for identifying overdispersion or outliers, is seen in Figure 2. Note that, due to overdispersion the theoretical distribution is narrower than the observed data.

2 A Bayesian mixture model approach

For the j^{th} marker $j = 1 \dots n$, we assume the observed number r_j of dominant markers out of N_j lines follows a binomial distribution denoted $Bin(N_j, P_k)$.

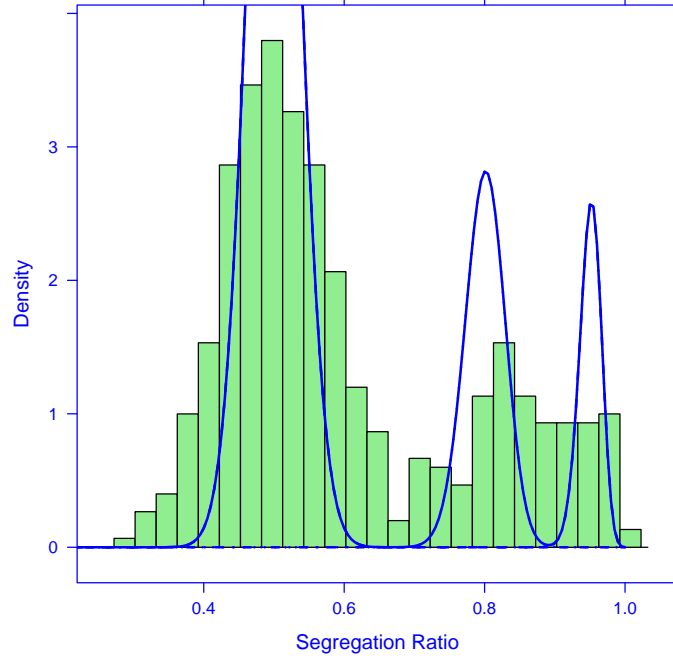


Figure 2: Segregation ratios of 500 simulated markers from 200 autohexaploid individuals. Percentages of single double and triple dose markers are 70%, 20% and 10%, respectively. Data were generated from the Beta-Binomial distribution assuming a shape parameter shape1 of 30.

If we knew the dosage k then, following Ripol et al. (1999), the expected value of P_k may be written as

$$P_k(k|m, x) = 1 - \frac{\binom{m-k}{mx}}{\binom{m}{mx}}, k = 0 \dots m/2 \quad (1)$$

where m is the ploidy level or number of homologous chromosomes and the monoploid number x is the number of chromosomes in a basic set. Note that for diploids $m = 2$, tetraploids $m = 4$, octaploids then $m = 8$ and so on and also that if there are no marker data missing then N_j is simply the number of progeny.

Since the dosage of each marker is unknown, we rely on the missing data representation of Dempster et al. (1977) and Tanner and Wong (1987) which is commonly adopted for MCMC computation in finite mixture models. An indicator variable z_j corresponding to unknown marker dosage class k is introduced where $z_j = k$ if the marker has dose k . For the K components with $K \leq m/2$, consider the logit transformation of the true segregation proportions P_k for dose $k, k = 1 \dots K$. The the logit transformed segregation ratio ω_k

is then

$$\omega_k = \log\left(\frac{P_k}{1 - P_k}\right). \quad (2)$$

Let $z = (z_1 \dots z_n)^T$ be a vector of unknown dosages (labelled $1, 2 \dots K$ corresponding to simplex, duplex, triplex markers and so on), then r_j is binomially distributed with known size parameter N_j and unknown proportion parameter ω_{z_j} which is the segregation ratio for marker dosage z_j . Hence, given marker dosage z_j then

$$r_j | z_j \sim \text{Bin}\left(N_j, \omega_{z_j}\right), \quad (3)$$

where

$$\text{logit}(\omega_{z_j}) = \log\left(\frac{\omega_{z_j}}{1 - \omega_{z_j}}\right) \sim N(\mu_{z_j}, \tau_{z_j}^{-1})$$

where μ_k and τ_k are the mean and precision ($\tau_k = 1/\sigma_k^2$) of marker dosage class k on the logit scale.

Since the dosage is unknown, for the autohexaploid data generated here then for the $\text{logit}(\omega_{z_k})$ can be modelled as a finite mixture of 3 normals

$$\text{logit}(\omega_{z_j}) \sim \pi_1 N(\mu_1, \tau_1^{-1}) + \pi_2 N(\mu_2, \tau_2^{-1}) + \dots + \pi_K N(\mu_K, \tau_K^{-1}) \quad (4)$$

where μ_k is the mean and τ_k is the precision of component k on the logit scale, and π_k are the mixing proportions of the three components with $\sum_{k=1}^K \pi_k = 1$. The probability density function $f(x)$ of $\text{logit}(\omega_k)$ is

$$f(x) = \sum_{k=1}^K \pi_k \phi(x | \mu_k, \tau_k^{-1}) \quad (5)$$

where ϕ is the normal cumulative distribution function with parameters mean μ_k and variance $\sigma_k^2 = \tau_k^{-1}$.

Simulation studies suggested that incorporating strong prior information, such as the expected distributions of Haldane (1930) provided the best method of allocating dosage. Further details may be found in Baker et al. (2010).

3 Specifying a model

A mixture model may be set up with `setModel`. By default, only two parameters are required, namely the `ploidy.level` or the number of homologous chromosomes set either as a numeric or as a character string and also `n.components` or the number of components for mixture model (less than or equal to maximum number of possible dosages). By default, strong priors are set by using the formulae of Haldane (1930) for the expected numbers and ratios of offspring for various parental configurations of autopolyploids.

For the autohexaploid data generated above, the models are set with

```
> x.mod1 <- setModel(3,6) # autohexaploid model with 3 components
```

The R object `x.mod1` contains components describing aspects of the model such as the number of components, ploidy, expected segregation ratios and so on. Note that the `str` command is useful for displaying the internal structure of any R object.

4 Fitting a mixture model

While various options are available for fine tuning the MCMC process, the simplest way to fit a mixture model to allocate marker dosages is with the wrapper function `runSegratioMM` as follows:

```
mcmcHexRun <- runSegratioMM(sr.overdisp, x.mod1)
```

which automatically determines starting values, priors, length of burn in, number of iterations, and other parameters as well as producing summary statistics and diagnostic plots.

To run JAGS without producing plots then set the `plots` option to `FALSE`. For the overdispersed data running this command produced the following selected output. While selected output is printed here the simple command `print(mcmcHexRun)` would produce the following output and more.

The summary of processing times:

```
> print(mcmcHexRun$run.jags)
```

```
CMD File: test.cmd
```

```
JAGS started at Fri Jul 18 14:51:41 2008
```

```
JAGS run completed successfully at Fri Jul 18 14:55:47 2008
```

```
Elapsed times:
```

```
  user  system elapsed
228.0  228.0   246.4
```

And summary statistics for the posterior distributions of selected parameters:

```
> print(mcmcHexRun$summary)
```

```
$statistics
```

	Mean	SD	Naive SE	Time-series SE
P[1]	0.72356	0.02064	0.0002919	0.0003616
P[2]	0.19709	0.01906	0.0002695	0.0005650
P[3]	0.07935	0.01336	0.0001890	0.0006636
mu[1]	0.02381	0.01696	0.0002398	0.0006163
mu[2]	1.54959	0.04421	0.0006253	0.0031491
mu[3]	3.16008	0.08879	0.0012557	0.0074792
sigma	0.27012	0.01215	0.0001718	0.0005203

```
$quantiles
```

	2.5%	25%	50%	75%	97.5%
P[1]	0.681698	0.70954	0.72439	0.73818	0.76208

```

P[2] 0.161445 0.18404 0.19643 0.20946 0.23651
P[3] 0.054776 0.07029 0.07876 0.08805 0.10753
mu[1] -0.008683 0.01177 0.02381 0.03529 0.05805
mu[2] 1.464629 1.51904 1.54875 1.57957 1.63693
mu[3] 2.995540 3.09972 3.15792 3.21625 3.34191
sigma 0.247668 0.26165 0.26998 0.27826 0.29443

```

```

$start
[1] 0

```

```

$end
[1] 4999

```

```

$thin
[1] 1

```

```

$nchain
[1] 1

```

```

attr("class")
[1] "summarySegratioMCMC"

```

Note that MCMC convergence diagnostic output is produced automatically. Assessing convergence is crucial in MCMC and poor convergence may result in mis-allocated marker dosages. The diagnostic statistics indicate that convergence was achieved.

```
> print(mcmcHexRun$diagnostics)
```

```

$raftery
$raftery[[1]]

```

```

Quantile (q) = 0.025
Accuracy (r) = +/- 0.005
Probability (s) = 0.95

```

	Burn-in (M)	Total (N)	Lower bound (Nmin)	Dependence factor (I)
P[1]	2	3803	3746	1.020
P[2]	2	3930	3746	1.050
P[3]	2	3680	3746	0.982
mu[1]	4	4713	3746	1.260
mu[2]	10	11010	3746	2.940
mu[3]	18	19611	3746	5.240
sigma	10	10754	3746	2.870

```

$geweke

```

```
$geweke[[1]]
```

```
Fraction in 1st window = 0.1
```

```
Fraction in 2nd window = 0.5
```

```

P[1]    P[2]    P[3]    mu[1]    mu[2]    mu[3]    sigma
1.3314 -1.9552  1.4159  1.7912 -0.7923 -0.9007 -1.0033

```

```
$heidel
```

```
$heidel[[1]]
```

	Stationarity test	start iteration	p-value
P[1]	passed	1	0.348
P[2]	passed	1	0.904
P[3]	passed	1	0.547
mu[1]	passed	1	0.387
mu[2]	passed	1	0.465
mu[3]	passed	1	0.374
sigma	passed	1	0.913

	Halfwidth test	Mean	Halfwidth
P[1]	passed	0.7236	0.000709
P[2]	passed	0.1971	0.001107
P[3]	passed	0.0794	0.001301
mu[1]	passed	0.0238	0.001208
mu[2]	passed	1.5496	0.006172
mu[3]	passed	3.1601	0.014659
sigma	passed	0.2701	0.001020

```
$hpd
```

```
$hpd[[1]]
```

	lower	upper
P[1]	0.68391	0.76365
P[2]	0.15950	0.23382
P[3]	0.05438	0.10695
mu[1]	-0.01018	0.05593
mu[2]	1.46539	1.63737
mu[3]	2.99198	3.33813
sigma	0.24697	0.29359

```
attr("Probability")
[1] 0.95
```

And finally, summaries of marker dosage allocations are produced:


```

> print(mcmcHexRun$doses)

Dosages for chain: 1
Thresholds set at:
[1] 0.50 0.60 0.70 0.80 0.90 0.95 0.99
A random sample of posterior probabilities and classifications
      SD      DD      TD 0.5 0.6 0.7 0.8 0.9 0.95 0.99 maxPostP
M.48  0.9998 0.0002 0.0000  1  1  1  1  1  1  1  1
M.50  0.9932 0.0068 0.0000  1  1  1  1  1  1  1  1
M.97  1.0000 0.0000 0.0000  1  1  1  1  1  1  1  1
M.117 1.0000 0.0000 0.0000  1  1  1  1  1  1  1  1
M.130 1.0000 0.0000 0.0000  1  1  1  1  1  1  1  1
M.134 1.0000 0.0000 0.0000  1  1  1  1  1  1  1  1
M.152 1.0000 0.0000 0.0000  1  1  1  1  1  1  1  1
M.195 0.9830 0.0170 0.0000  1  1  1  1  1  1  .  1
M.199 1.0000 0.0000 0.0000  1  1  1  1  1  1  1  1
M.250 0.5302 0.4698 0.0000  1  .  .  .  .  .  .  1
M.263 1.0000 0.0000 0.0000  1  1  1  1  1  1  1  1
M.269 1.0000 0.0000 0.0000  1  1  1  1  1  1  1  1
M.329 1.0000 0.0000 0.0000  1  1  1  1  1  1  1  1
M.340 1.0000 0.0000 0.0000  1  1  1  1  1  1  1  1
M.355 0.0892 0.9108 0.0000  2  2  2  2  2  .  .  2
M.359 0.0000 1.0000 0.0000  2  2  2  2  2  2  2  2
M.416 0.4616 0.5384 0.0000  2  .  .  .  .  .  .  2
M.434 0.6678 0.3322 0.0000  1  1  .  .  .  .  .  1
M.446 0.1732 0.8268 0.0000  2  2  2  2  .  .  .  2
M.460 0.0000 0.0184 0.9816  3  3  3  3  3  3  .  3

Maximum posterior probabilities for 500 markers
      Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
0.502  1.000  1.000  0.980  1.000  1.000

Proportion of genes classified using maximum posterior probability
      SD      DD      TD
0.724 0.194 0.082
Total proportion of markers classified: 1
Call:
dosagesJagsMix(mcmc.mixture = read.jags, jags.control = jags.control,
  seg.ratio = seg.ratios)

```

Note that simply plotting `mcmcHexRun` will produce a histogram of segregation proportions and the fitted model but that other plots are easily produced.

When the `plots` option of `runSegratioMM` is set to the default value of `TRUE`, numerous plots are produced including trace and density plots from the CODA package. These may also be extracted manually but the process is somewhat more complicated. For instance to obtain trace and density plots for the parameters p_1 , μ_1 , σ_1 and for the 140th marker, as shown in Figure 3, then CODA may be used directly by following command.

NULL

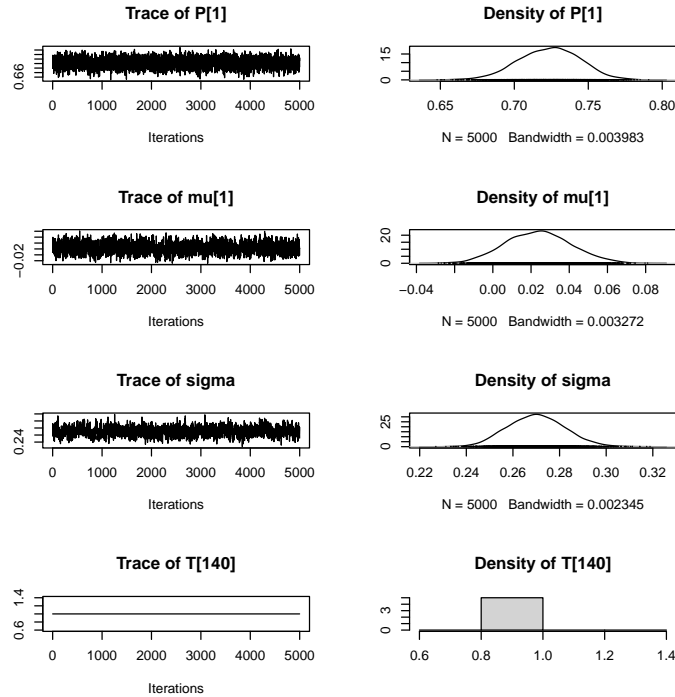


Figure 3: Trace and posterior density plots for the parameters p_1 , μ_1 , σ and for the 140th marker for the overdispersed data.

```
plot(mcmcHexRun$mcmc.mixture$mcmc.list[[1]][,c("P[1]", "mu[1]", "sigma", "T[140]")])
```

The histogram of segregation proportions with fitted and theoretical values shown in Figure 4 may be obtained by setting the theoretical option to TRUE as follows.

```
print(plot(mcmcHexRun, theoretical=TRUE))
```

5 Assigning marker dosage

Marker dosages allocations may be obtained directly from the object `mcmcHexRun`. The dosage with maximum posterior probability is simply `mcmcHexRun$doses$max.post.dosage`. A more conservative allocation is obtained by using `mcmcHexRun$doses$dosage[, "0.8"]` whereby the dosage with posterior probability over 0.8 is employed. For instance, to tabulate the number of markers (including those not allocated a dosage which are labelled NA) the `table` command can be employed.

```
> cat("Employing maximum posterior probability\n")
```

```
Employing maximum posterior probability
```

Warning: component proportions normalised, now:

```
P[1] P[2] P[3]
0.72356 0.19709 0.07935
```

PlotTheoretical Warning: Binomial mixture density is only approximate on logit scale

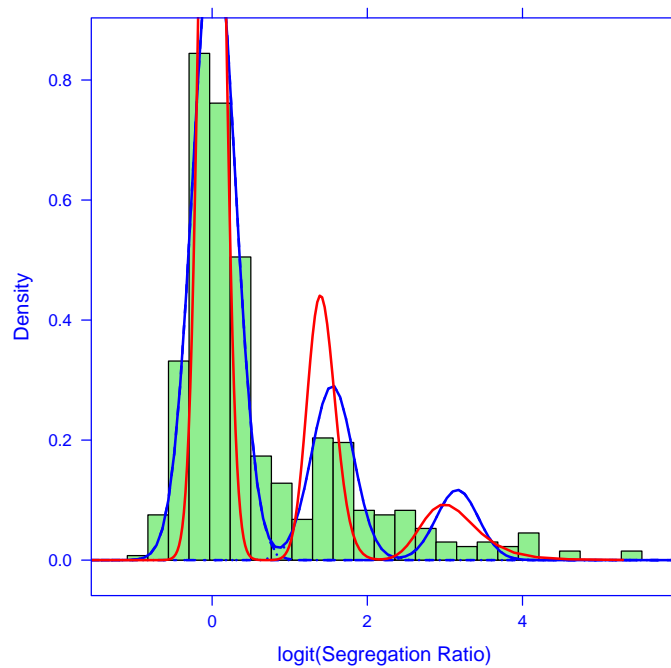


Figure 4: Fitted (blue) and theoretical (red) distributions for simulated segregation ratios with overdispersion for 500 markers from 200 individuals.

```
> table(Dose=mcmcHexRun$doses$max.post.dosage, exclude=NULL)
```

```
Dose
  1  2  3
362 97 41
```

```
> cat("Employing posterior probability > 0.8\n")
```

```
Employing posterior probability > 0.8
```

```
> table(Dose=mcmcHexRun$doses$dosage[,"0.8"], exclude=NULL)
```

```
Dose
  1  2  3 <NA>
358 89 34  19
```

And of course since the data were simulated we can compare the estimated and true dosages obtained as `hexmarkers.overdisp>true.doses$dosage` via

cross tabulation. Doses can also be obtained for the standard χ^2 test by using the `test.segRatio` command from the `polySegratio` library.

```
> cat("Employing theChi squared test\n")
```

Employing theChi squared test

```
> dose.chi <- test.segRatio(sr.overdisp, ploidy.level = 6)
```

```
> table(Chi2Dose=dose.chi$dosage, True=hexmarkers.overdisp>true.doses$dosage, exclude=NULL)
```

	True		
Chi2Dose	1	2	3
1	223	2	0
2	0	54	5
3	0	3	27
<NA>	130	39	17

```
> cat("Employing maximum posterior probability\n")
```

Employing maximum posterior probability

```
> table(MixtureDose=mcmcHexRun$doses$max.post.dosage, True=hexmarkers.overdisp>true.doses$d
```

```
+ exclude=NULL)
```

	True		
MixtureDose	1	2	3
1	353	9	0
2	0	86	11
3	0	3	38

```
> cat("Employing posterior probability > 0.8\n")
```

Employing posterior probability > 0.8

```
> table(MixtureDose=mcmcHexRun$doses$dosage[,"0.8"], True=hexmarkers.overdisp>true.doses$d
```

```
+ exclude=NULL)
```

	True		
MixtureDose	1	2	3
1	352	6	0
2	0	78	11
3	0	2	32
<NA>	1	12	6

These tables show that far fewer markers are allocated a dosage using the standard χ^2 test than by the mixture model. Fewer markers were misclassified using a posterior probability threshold of 0.8 rather than the maximum posterior probability as a basis for allocating dosage.

References

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5.1 Acknowledgments

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