

SMAP: A Segmental Maximum A Posteriori Approach to Array-CGH Copy Number Profiling

Robin Andersson, Jan Komorowski

October 26, 2021

The Linnaeus Centre for Bioinformatics,
Uppsala University, Uppsala, Sweden

`robin.andersson@lcb.uu.se`

Contents

1	Overview	1
2	Observations	1
3	A Hidden Markov Model for copy number assignments	4
4	Copy number profiling by segmental a posteriori maximization	5
5	Plotting results	7

1 Overview

This document describes classes and functions in the *SMAP* package for copy number profiling of array-CGH data. The data analyzed is glioblastoma multiforme sample *G24460* obtained from Teresita Diaz de Ståhl, Uppsala University, Sweden.

```
> library(SMAP)
```

2 Observations

The glioblastoma multiforme data is stored in a *data.frame* which needs to be converted to a *SMAPObservations* object prior to analysis. The required arguments for the *SMAPObservations* constructor function are:

value A numeric vector of intensity ratios for each clone on the array

chromosome A character vector of chromosomes annotated to the clones on the array

startPosition A numeric vector of start positions (bp) of the sequences corresponding to the clones on the array

endPosition A numeric vector of end positions (bp) of the sequences corresponding to the clones on the array

Optional data are:

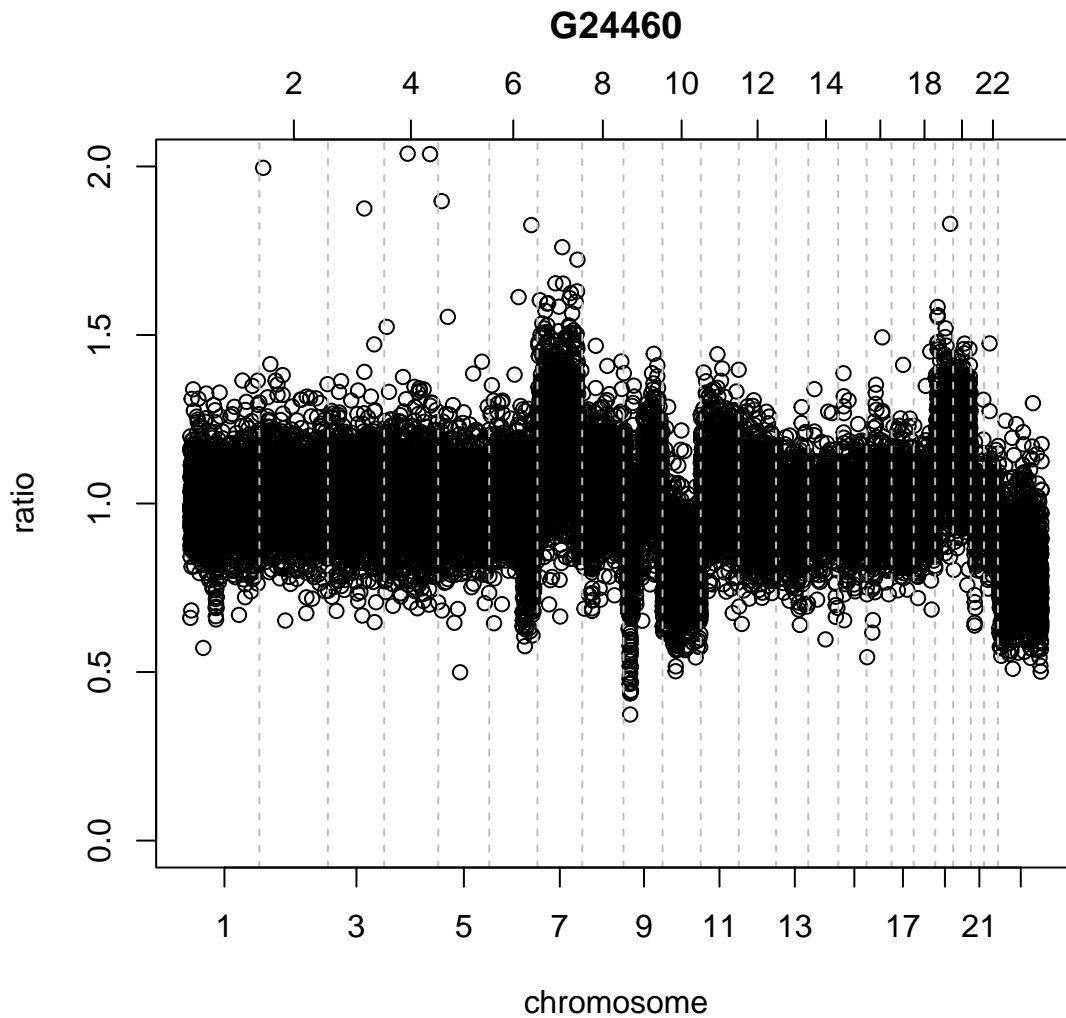
name The name (identifier) of the array

reporterId Identifiers of the clones on the array

```
> data(GBM)
> obs <- SMAPObservations(value=as.numeric(GBM[,2]),
+                          chromosome=as.character(GBM[,3]),
+                          startPosition=as.numeric(GBM[,4]),
+                          endPosition=as.numeric(GBM[,5]),
+                          name="G24460",
+                          reporterId=as.character(GBM[,1]))
```

The observations can be visualized by using the generic `plot` function on the *SMAPObservations* object. If multiple chromosomes are present, the chromosomes are separated by vertical dashed lines and indexed on the horizontal axis.

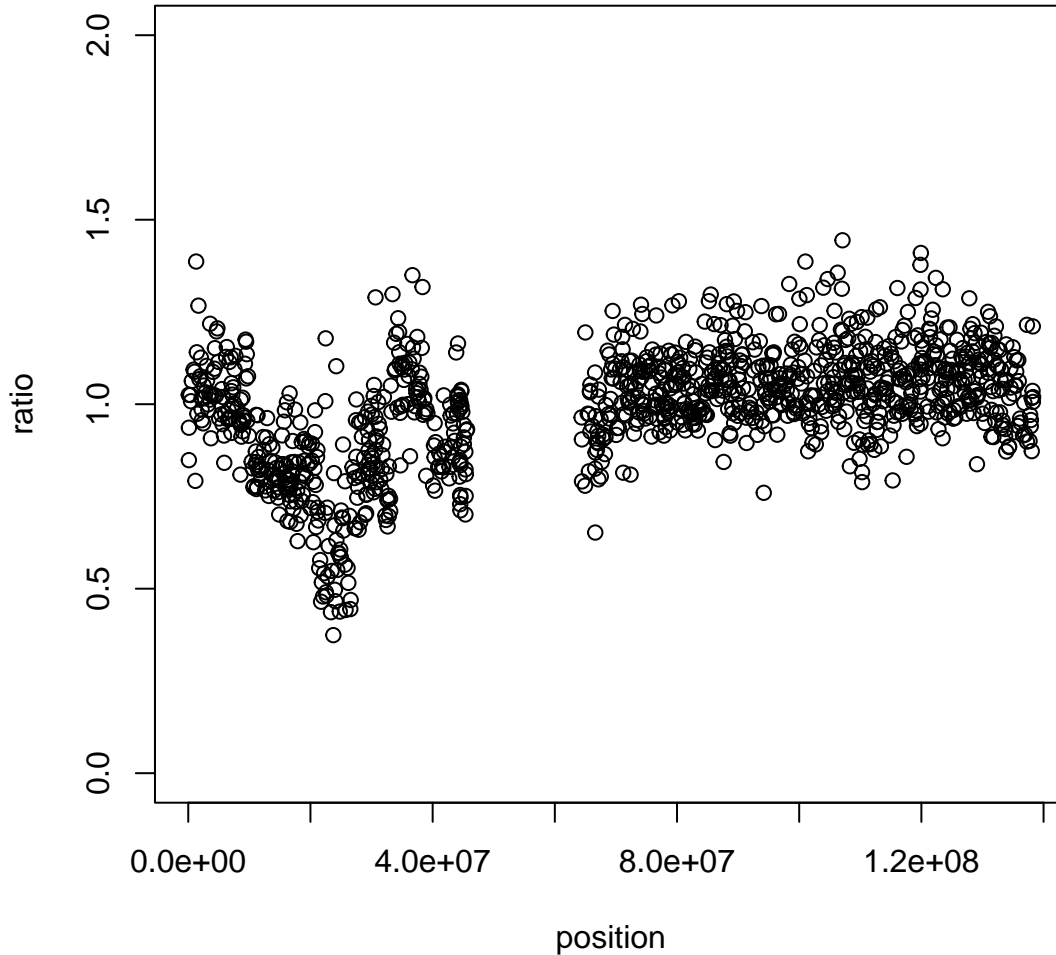
```
> plot(obs, ylab="ratio", ylim=c(0,2))
```



Subsets of observations may also be plotted using general subscripts. For instance, chromosome 9 may be plotted in the following manner:

```
> ids <- which(chromosome(obs) == "9")
> plot(obs[ids], ylab="ratio", ylim=c(0,2),
+ main=paste(name(obs), "chromosome 9"))
```

G24460 chromosome 9



The observations plotted in this example has been normalized using the `normalizeWithinArrays` function in the *limma* package.

3 A Hidden Markov Model for copy number assignments

SMAP uses a Hidden Markov Model (HMM) to model the copy number assignments. We recommend using a six state model describing states corresponding to homozygous deletions, normal, one copy gain, two copy gain, and amplification. A *SMAPHMM* class is used in the *SMAP* package to manage HMMs and initiated using the `SMAPHMM` function. The required arguments to `SMAPHMM` are:

noStates The number of hidden states in the HMM

Phi A $noStates * 2$ matrix of Gaussian distributions associated with each hidden state, the first

column described means and the second described standard deviations

Optional arguments to `SMAPHMM` are:

A A $noStates \times noStates$ transition probability matrix (probabilities of moving between states in the HMM)

Pi A numeric vector of initial probabilities (probabilities of starting in each state)

initTrans The probability of changing state in the HMM (used if *A* is *NULL*), defaults to $0.2/(noStates - 1)$ which means the probability of staying in the same state is 0.8

Initiate a *SMAPHMM* Hidden Markov Model object with 6 states:

```
> init.means <- c(0.4, 0.7, 1, 1.3, 1.6, 3)
> init.sds <- rep(0.1, 6)
> phi <- cbind(init.means, init.sds)
> hmm <- SMAPHMM(noStates=6, Phi=phi, initTrans=0.02)
> hmm
```

An object of class "SMAPHMM"

Slot "A":

```
      1  2  3  4  5  6
1 0.90 0.02 0.02 0.02 0.02 0.02
2 0.02 0.90 0.02 0.02 0.02 0.02
3 0.02 0.02 0.90 0.02 0.02 0.02
4 0.02 0.02 0.02 0.90 0.02 0.02
5 0.02 0.02 0.02 0.02 0.90 0.02
6 0.02 0.02 0.02 0.02 0.02 0.90
```

Slot "Pi":

```
[1] 0.1666667 0.1666667 0.1666667 0.1666667 0.1666667 0.1666667
```

Slot "Phi":

```
  mean SD
1  0.4 0.1
2  0.7 0.1
3  1.0 0.1
4  1.3 0.1
5  1.6 0.1
6  3.0 0.1
```

4 Copy number profiling by segmental a posteriori maximization

Given a set of observations O and a HMM λ , the `smap` function finds the most probable state sequence Q (assignment of clones to HMM states) in the HMM by maximizing the joint posterior probability of Q and λ given O . This is done by, starting with an initial estimate of the HMM, alternating optimization of the joint posterior probability over Q and λ until no further improvements can be made or a maximum number of iterations has been reached. Optimization over Q and λ is done using the Viterbi algorithm and a gradient descent scheme with individual learning rate adaptation, respectively.

The `smap` function requires the following arguments:

x A *SMAPHMM* object

Obs A *SMAPObservations* object

Other arguments (default values) are:

eta (0.005) Initial learning rate in the gradient descent optimization

overlap (TRUE) If *TRUE*, genomic overlap of clones is considered in the optimization

distance (TRUE) If *TRUE*, genomic distance between clones is considered in the optimization, in terms of distance based transition probabilities

chrom.wise (FALSE) If *TRUE*, the observations are analyzed chromosome-wise rather than genome-wise

verbose (1) Specifies the amount of output produced; 0 means no information and 3 a lot of information

L (5000000) A positive length parameter that controls the convergence of distance based transition probabilities towards $1 / noStates(x)$

All arguments are described in detail in the man pages for **smap**.

The choice of parameters sent to the **smap** function as well as the initial HMM used may influence the results. A too high or too low value of *eta* may reduce the ability to fit the HMM to the data. The initial estimates of changing state in the HMM may also influence the results. A too high value may find too much variation in the data whereas a too small value may restrain the ability of finding true variations in the data. If *chrom.wise* is set to *FALSE* (recommended), one HMM is fit to all data which controls the adaptation of HMM parameters to local non-biological trends which may be present in some chromosome only. If set to *TRUE*, one HMM per chromosome is trained and the resulting state distributions may conflict between chromosomes.

The *overlap* argument specifies whether overlap should be taken into account during optimization. If set to *TRUE*, each observation is considered to be drawn from a mixture of distributions where the mixture proportions are determined in terms of relative overlap between clones.

Run **smap** on the *SMAPHMM* and *SMAPObservations* objects.

```
> profile <- smap(hmm, obs, verbose=2)
```

```
Calculating overlaps
```

```
RUNNING SMAP ON 'G24460'
```

```
init P: -160886.218423
```

```
Iteration 1, P: -140380.311018
```

```
Iteration 2, P: -133481.492709
```

```
Iteration 3, P: -133481.492709
```

```
Optimal P: -133481.492709 found after 2 iterations
```

The result of the **smap** run may be retrieved by accessing the *Q* slot of the resulting *SMAPProfile* object.

```
> Q(profile)
```

The resulting (adapted) HMM may be examined by accessing the HMM slot of the *SMAPProfile*.

```
> Phi(HMM(profile))
```

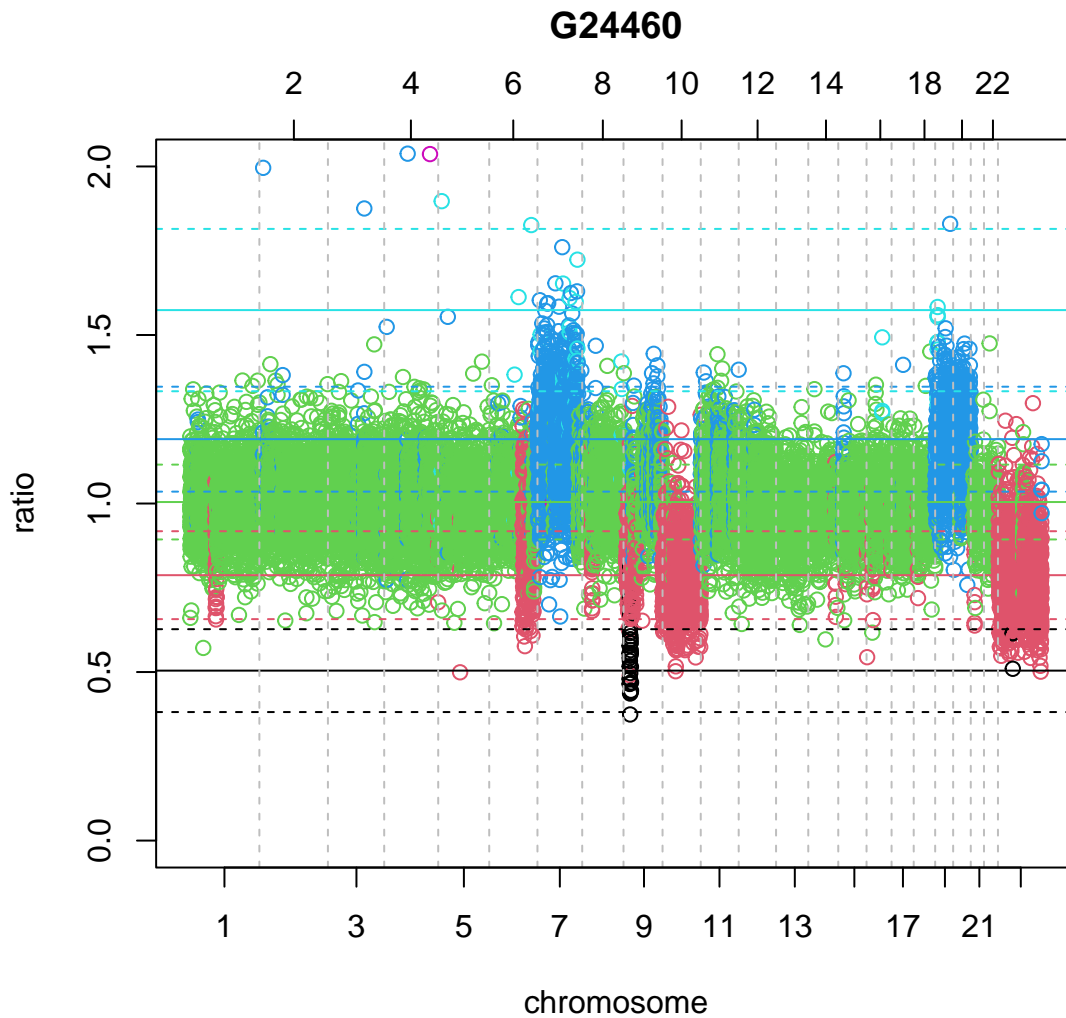
	mean	SD
1	0.5042062	0.1229025
2	0.7873844	0.1304443
3	1.0043969	0.1110023
4	1.1909501	0.1556679
5	1.5739008	0.2408134
6	2.9986192	0.7516224

5 Plotting results

The results of the `smap` run may be visualized using the generic `plot` function.

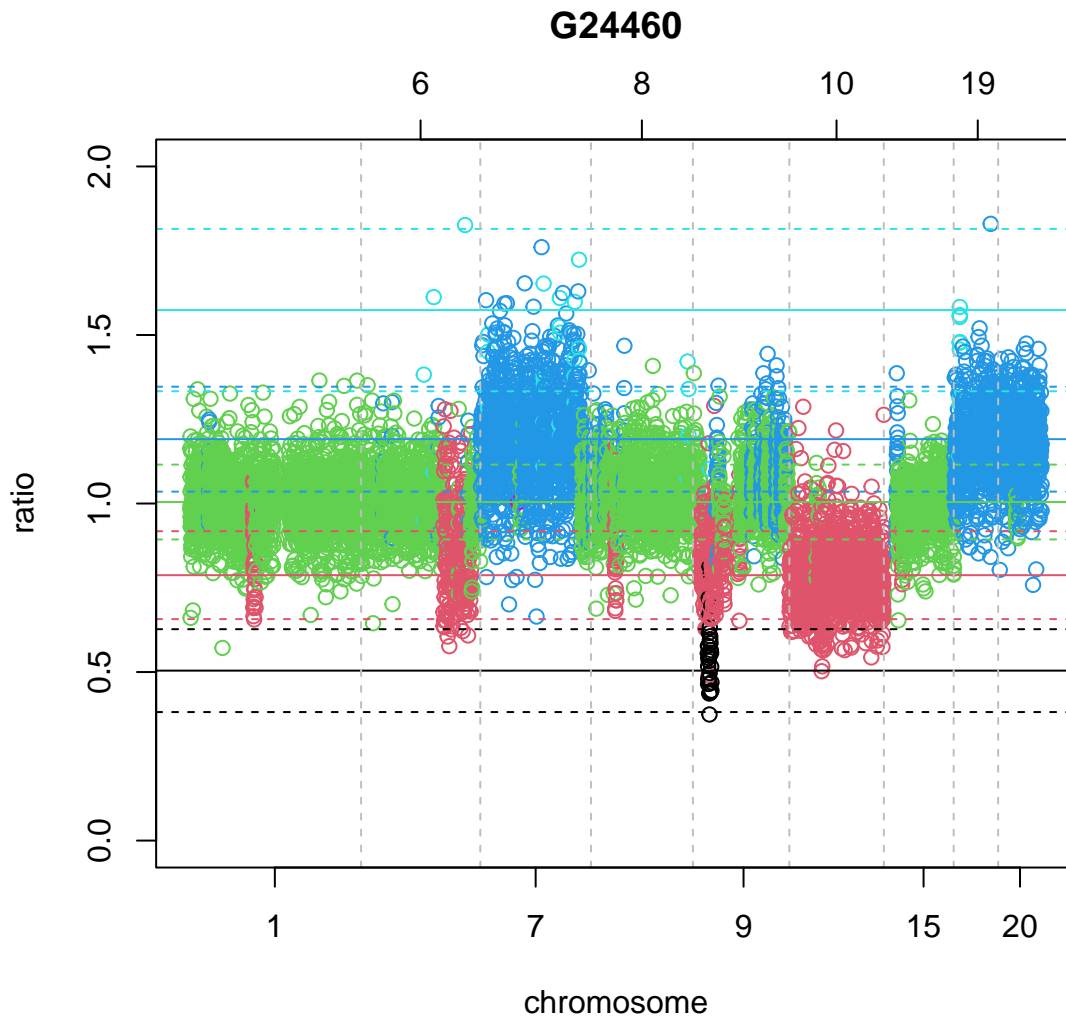
Plot results of all data:

```
> ## Plot results of all data:  
> plot(profile, ylab="ratio", ylim=c(0,2))
```



Plot chromosomes with aberrations

```
> ## Plot chromosomes with aberrations:
> chrom.selection <- as.character(c(1, 6, 7, 8, 9, 10, 15, 19, 20))
> selection <- which(chromosome(obs) %in% chrom.selection)
> plot(profile[selection], ylab="ratio", ylim=c(0, 2))
```

Plot all chromosomes with aberrations separately:

```
> ## Plot all chromosomes separately:
> par(mfrow=c(3, 3))
> for (c in chrom.selection) {
+   ids <- which(chromosome(obs) == c)
+   plot(profile[ids], ylab="ratio", ylim=c(0, 2), main=c)
+ }
```

