CGHcall: Calling aberrations for array CGH tumor profiles.

Sjoerd Vosse and Mark van de Wiel

April 14, 2011

Department of Epidemiology & Biostatistics
VU University Medical Center

mark.vdwiel@vumc.nl

Contents

1 Overview

CGHcall allows users to make an objective and effective classification of their aCGH data into copy number states (loss, normal, gain or amplification). This document provides an overview on the usage of the CGHcall package. For more detailed information on the algorithm and assumptions we refer to the article (van de Wiel et al., 2007) and its supplementary material. As example data we attached the first five samples of the Wilting dataset (Wilting et al., 2006). After filtering and selecting only the autosomes 4709 datapoints remained.

2 Example

In this section we will use CGHcall to call and visualize the aberrations in the dataset described above. First, we load the package and the data:

```
> library(CGHcall)
> data(WiltingData)
> Wilting <- cghRaw(WiltingData)
```

Next, we apply the `preprocess` function which:

- removes data with unknown or invalid position information.
- shrinks the data to `nchrom` chromosomes.
- removes data with more than `maxmiss` % missing values.
- imputes missing values using `impute.knn` from the package `impute` (Troyanskaya et al., 2001).

```
> cghdata <- preprocess(Wilting, maxmiss = 30, nchrom = 22)
```

```
Changing impute.knn parameter k from 10 to 4 due to small sample size.
```

To be able to compare profiles they need to be normalized. In this package we provide very basic global median or mode normalization. Of course, other methods can be used outside this package. This function also contains smoothing of outliers as implemented in the DNAcopy package (Venkatraman and Olshen, 2007). Furthermore, when the proportion of tumor cells is not 100% the ratios can be corrected. See the article and the supplementary material for more information on cellularity correction (van de Wiel et al., 2007).

```
> tumor.prop <- c(0.75, 0.9, 0.8, 1, 1)
> norm.cghdata <- normalize(cghdata, method = "median", cellularity = tumor.prop,
+     smoothOutliers = TRUE)
```

```
Applying median normalization ...
Smoothing outliers ...
Adjusting for cellularity ...
Cellularity sample 1 :  0.75
Cellularity sample 2 :  0.9
Cellularity sample 3 :  0.8
Cellularity sample 4 :  1
Cellularity sample 5 :  1
```

The next step is segmentation of the data. This package only provides a simple wrapper function that applies the `DNAcopy` algorithm (Venkatraman and Olshen, 2007). Again, other segmentation algorithms may be used. To save time we will limit our analysis to the first two samples from here on.

```
> norm.cghdata <- norm.cghdata[, 1:2]
> seg.cghdata <- segmentData(norm.cghdata, method = "DNAcopy")

Start data segmentation ..
Analyzing: Sample.1
Analyzing: Sample.2
```

Post-segmentation normalization allows to better set the zero level after segmentation

```
> postseg.cghdata <- postsegnormalize(seg.cghdata)
```

Now that the data have been normalized and segments have been defined, we need to determine which segments should be classified as losses, normal, gains or amplifications.

```
> result <- CGHcall(postseg.cghdata)

[1] "changed"
EM algorithm started ...
[1] "Total number of segments present in the data: 113"
[1] "Number of segments used for fitting the model: 113"
         used (Mb) gc trigger (Mb) max used (Mb)
Ncells 447839 12.0     741108 19.8   741108 19.8
Vcells 393693  3.1     905753  7.0   905753  7.0
Calling iteration 1 :
     j        rl       mudl       musl        mun       mug      mudg      mua
[1,] 2 -3770.814 -0.8429234 -0.2959666 0.01151765 0.3355313 0.5735946 1.073453
           sddl       sdsl        sdn       sdg      sddg       sda
[1,] 0.08667158 0.08609276 0.08947486 0.1710695 0.1713615 0.1713616
         used (Mb) gc trigger (Mb) max used (Mb)
Ncells 448270 12.0     741108 19.8   741108 19.8
Vcells 394551  3.1     905753  7.0   905753  7.0
Calling iteration 2 :
     j        rl      mudl      musl        mun       mug      mudg      mua
[1,] 2 -3769.749 -0.848933 -0.294113 0.01683709 0.3371155 0.5763027 1.076157
```

```
          sddl       sdsl        sdn      sdg      sddg       sda
[1,] 0.08073707 0.08011538 0.08195825 0.170614 0.1709068 0.1709068
Computing posterior probabilities for all segments ...
Total time: 1 minutes
```

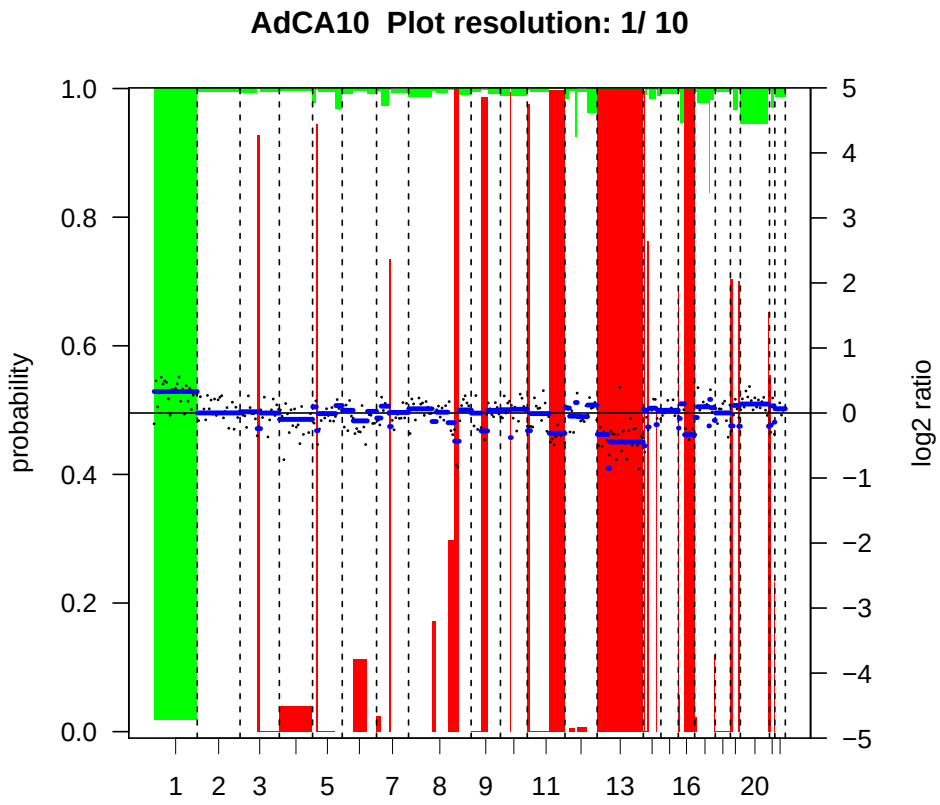
In CGHcall version >=2.9.0 the result of CGHcall needs to be converted to a call object. This can be a large object for large arrays.

```
> result <- ExpandCGHcall(result, postseg.cghdata)

[1] 1
         used (Mb) gc trigger (Mb) max used (Mb)
Ncells 449596 12.1     818163 21.9   818163 21.9
Vcells 419766  3.3     905753  7.0   905753  7.0
         used (Mb) gc trigger (Mb) max used (Mb)
Ncells 449606 12.1     818163 21.9   818163 21.9
Vcells 433977  3.4     905753  7.0   905753  7.0
         used (Mb) gc trigger (Mb) max used (Mb)
Ncells 449605 12.1     818163 21.9   818163 21.9
Vcells 433976  3.4     905753  7.0   905753  7.0
         used (Mb) gc trigger (Mb) max used (Mb)
Ncells 449623 12.1     818163 21.9   818163 21.9
Vcells 455290  3.5     905753  7.0   905753  7.0
         used (Mb) gc trigger (Mb) max used (Mb)
Ncells 449939 12.1     818163 21.9   818163 21.9
Vcells 457102  3.5     905753  7.0   905753  7.0
         used (Mb) gc trigger (Mb) max used (Mb)
Ncells 449947 12.1     818163 21.9   818163 21.9
Vcells 458881  3.6     905753  7.0   905753  7.0
         used (Mb) gc trigger (Mb) max used (Mb)
Ncells 449955 12.1     818163 21.9   818163 21.9
Vcells 460660  3.6     905753  7.0   905753  7.0
         used (Mb) gc trigger (Mb) max used (Mb)
Ncells 449963 12.1     818163 21.9   818163 21.9
Vcells 462439  3.6     905753  7.0   905753  7.0
         used (Mb) gc trigger (Mb) max used (Mb)
Ncells 449967 12.1     818163 21.9   818163 21.9
Vcells 464217  3.6     905753  7.0   905753  7.0
         used (Mb) gc trigger (Mb) max used (Mb)
Ncells 449994 12.1     818163 21.9   818163 21.9
```

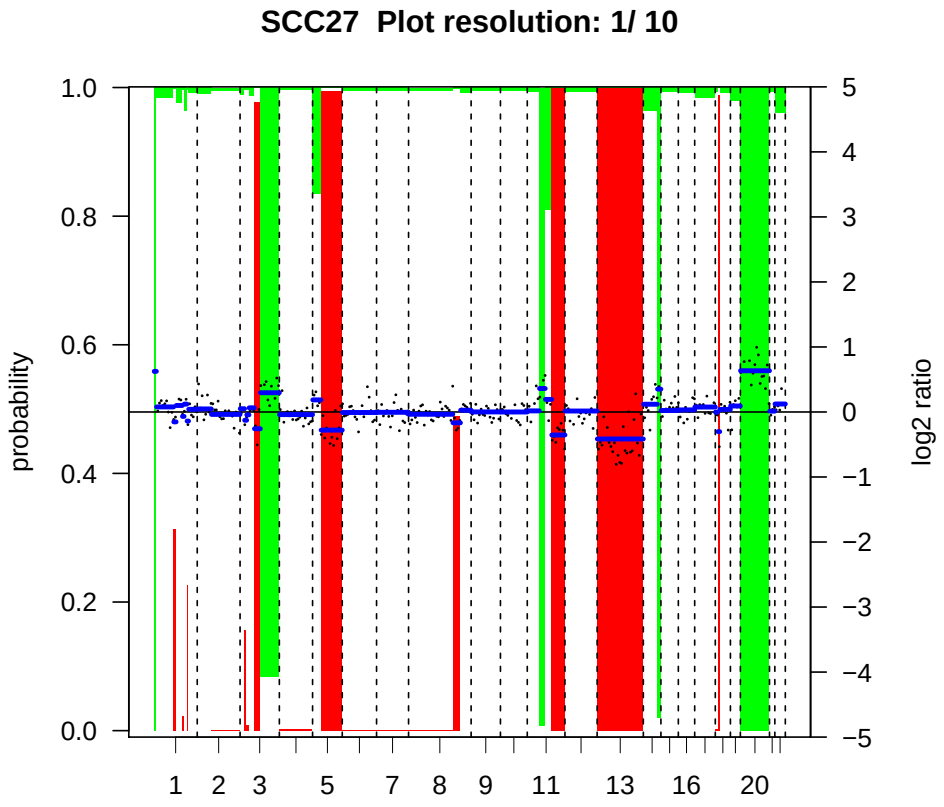
```
Vcells 480226  3.7    1031040  7.9   905753  7.0
         used (Mb) gc trigger (Mb) max used (Mb)
Ncells 450683 12.1     818163 21.9   818163 21.9
Vcells 487635  3.8    1031040  7.9   905753  7.0
[1] 2
         used (Mb) gc trigger (Mb) max used (Mb)
Ncells 450687 12.1     818163 21.9   818163 21.9
Vcells 501844  3.9    1031040  7.9   905753  7.0
         used (Mb) gc trigger (Mb) max used (Mb)
Ncells 450688 12.1     818163 21.9   818163 21.9
Vcells 501845  3.9    1031040  7.9  1027757  7.9
         used (Mb) gc trigger (Mb) max used (Mb)
Ncells 450687 12.1     818163 21.9   818163 21.9
Vcells 501844  3.9    1031040  7.9  1027757  7.9
         used (Mb) gc trigger (Mb) max used (Mb)
Ncells 450691 12.1     818163 21.9   818163 21.9
Vcells 505397  3.9    1031040  7.9  1027757  7.9
         used (Mb) gc trigger (Mb) max used (Mb)
Ncells 450687 12.1     818163 21.9   818163 21.9
Vcells 501844  3.9    1031040  7.9  1027757  7.9
         used (Mb) gc trigger (Mb) max used (Mb)
Ncells 450695 12.1     818163 21.9   818163 21.9
Vcells 503623  3.9    1031040  7.9  1027757  7.9
         used (Mb) gc trigger (Mb) max used (Mb)
Ncells 450703 12.1     818163 21.9   818163 21.9
Vcells 505402  3.9    1031040  7.9  1027757  7.9
         used (Mb) gc trigger (Mb) max used (Mb)
Ncells 450711 12.1     818163 21.9   818163 21.9
Vcells 507181  3.9    1031040  7.9  1027757  7.9
         used (Mb) gc trigger (Mb) max used (Mb)
Ncells 450715 12.1     818163 21.9   818163 21.9
Vcells 508959  3.9    1031040  7.9  1027757  7.9
         used (Mb) gc trigger (Mb) max used (Mb)
Ncells 450742 12.1     818163 21.9   818163 21.9
Vcells 524968  4.1    1031040  7.9  1027757  7.9
         used (Mb) gc trigger (Mb) max used (Mb)
Ncells 453739 12.2     818163 21.9   818163 21.9
Vcells 512984  4.0    1031040  7.9  1030937  7.9
FINISHED!
Total time: 0 minutes
```

To visualize the results per profile we use the `plotProfile` function:

```
> plot(result[, 1])

Plotting sample AdCA10
```

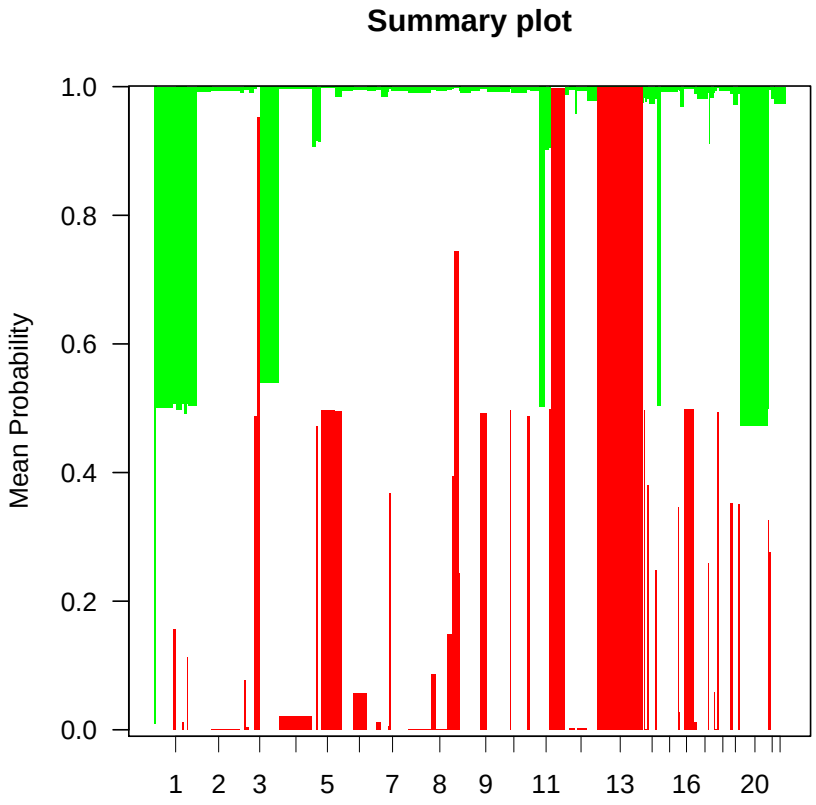


```
> plot(result[, 2])

Plotting sample SCC27
```



Alternatively, we can create a summary plot of all the samples:

```
> plot.summary(result)

Adding sample AdCA10 to summary plot.
Adding sample SCC27 to summary plot.
```



References

Troyanskaya, O., Cantor, M., Sherlock, G., Brown, P., Hastie, T., Tibshirani, R., Botstein, D., and Altman, R. B. (2001). Missing value estimation methods for DNA microarrays. *Bioinformatics*, 17:520–525.

van de Wiel, M. A., Kim, K. I., Vosse, S. J., van Wieringen, W. N., Wilting, S. M., and Ylstra, B. (2007). CGHcall: calling aberrations for array CGH tumor profiles. *Bioinformatics*, 23:892–894.

Venkatraman, E. S. and Olshen, A. B. (2007). A faster circular binary segmentation algorithm for the analysis of array CGH data. *Bioinformatics*, 23:657–663.

Wilting, S. M., Snijders, P. J. F., Meijer, G. A., Ylstra, B., van den Ijssel, P. R. L. A., Snijders, A. M., Albertson, D. G., Coffa, J., Schouten, J. P., van de Wiel, M. A., Meijer, C. J. L. M., and Steenbergen, R. D. M. (2006). Increased gene copy numbers at chromosome 20q are frequent in both squamous cell carcinomas and adenocarcinomas of the cervix. *J Pathol*, 209:220–230.