CGHcall: Calling aberrations for array CGH tumor profiles.

Sjoerd Vosse and Mark van de Wiel

October 31, 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, smoothO
```

```
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 506579 27.1     899071 48.1   818163 43.7
Vcells 908810  7.0    1598044 12.2  1597828 12.2
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 507030 27.1     899071 48.1   899071 48.1
Vcells 909866  7.0    1598044 12.2  1597828 12.2
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)
```

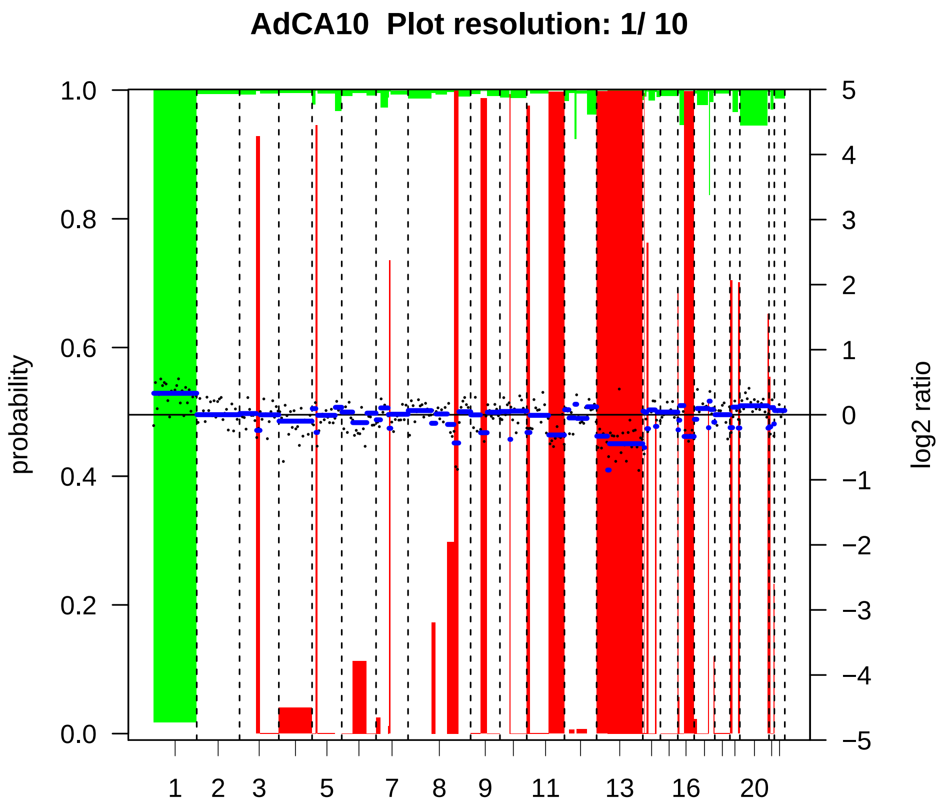
```
[1] 1
         used (Mb) gc trigger (Mb) max used (Mb)
Ncells 508364 27.2     899071 48.1   899071 48.1
Vcells 941857  7.2    1598044 12.2  1597828 12.2
         used (Mb) gc trigger (Mb) max used (Mb)
Ncells 508374 27.2     899071 48.1   899071 48.1
Vcells 956066  7.3    1598044 12.2  1598037 12.2
         used (Mb) gc trigger (Mb) max used (Mb)
Ncells 508373 27.2     899071 48.1   899071 48.1
Vcells 956065  7.3    1598044 12.2  1598037 12.2
         used (Mb) gc trigger (Mb) max used (Mb)
Ncells 508391 27.2     899071 48.1   899071 48.1
Vcells 977379  7.5    1757946 13.5  1598037 12.2
         used (Mb) gc trigger (Mb) max used (Mb)
Ncells 508864 27.2     899071 48.1   899071 48.1
Vcells 981641  7.5    1757946 13.5  1598037 12.2
         used (Mb) gc trigger (Mb) max used (Mb)
Ncells 508872 27.2     899071 48.1   899071 48.1
Vcells 985197  7.6    1757946 13.5  1598037 12.2
         used (Mb) gc trigger (Mb) max used (Mb)
Ncells 508880 27.2     899071 48.1   899071 48.1
Vcells 988753  7.6    1757946 13.5  1598037 12.2
         used (Mb) gc trigger (Mb) max used (Mb)
Ncells 508888 27.2     899071 48.1   899071 48.1
Vcells 992309  7.6    1757946 13.5  1598037 12.2
         used (Mb) gc trigger (Mb) max used (Mb)
Ncells 508892 27.2     899071 48.1   899071 48.1
Vcells 995864  7.6    1757946 13.5  1598037 12.2
          used (Mb) gc trigger (Mb) max used (Mb)
Ncells  508919 27.2     899071 48.1   899071 48.1
Vcells 1017217  7.8    1757946 13.5  1598037 12.2
          used (Mb) gc trigger (Mb) max used (Mb)
Ncells  509676 27.3     899071 48.1   899071 48.1
Vcells 1026496  7.9    1757946 13.5  1598037 12.2
[1] 2
```

```
          used (Mb) gc trigger (Mb) max used (Mb)
Ncells  509680 27.3     899071 48.1   899071 48.1
Vcells 1040705  8.0    1757946 13.5  1598037 12.2
          used (Mb) gc trigger (Mb) max used (Mb)
Ncells  509681 27.3     899071 48.1   899071 48.1
Vcells 1040706  8.0    1757946 13.5  1726662 13.2
          used (Mb) gc trigger (Mb) max used (Mb)
Ncells  509680 27.3     899071 48.1   899071 48.1
Vcells 1040705  8.0    1757946 13.5  1726662 13.2
          used (Mb) gc trigger (Mb) max used (Mb)
Ncells  509684 27.3     899071 48.1   899071 48.1
Vcells 1044258  8.0    1757946 13.5  1726662 13.2
          used (Mb) gc trigger (Mb) max used (Mb)
Ncells  509680 27.3     899071 48.1   899071 48.1
Vcells 1040705  8.0    1757946 13.5  1726662 13.2
          used (Mb) gc trigger (Mb) max used (Mb)
Ncells  509688 27.3     899071 48.1   899071 48.1
Vcells 1044261  8.0    1757946 13.5  1726662 13.2
          used (Mb) gc trigger (Mb) max used (Mb)
Ncells  509696 27.3     899071 48.1   899071 48.1
Vcells 1047817  8.0    1757946 13.5  1726662 13.2
          used (Mb) gc trigger (Mb) max used (Mb)
Ncells  509704 27.3     899071 48.1   899071 48.1
Vcells 1051373  8.1    1757946 13.5  1726662 13.2
          used (Mb) gc trigger (Mb) max used (Mb)
Ncells  509708 27.3     899071 48.1   899071 48.1
Vcells 1054928  8.1    1757946 13.5  1726662 13.2
          used (Mb) gc trigger (Mb) max used (Mb)
Ncells  509735 27.3     899071 48.1   899071 48.1
Vcells 1076281  8.3    1925843 14.7  1726662 13.2
          used (Mb) gc trigger (Mb) max used (Mb)
Ncells  512873 27.4     899071 48.1   899071 48.1
Vcells 1056808  8.1    1925843 14.7  1925191 14.7
FINISHED!
Total time: 0 minutes
```

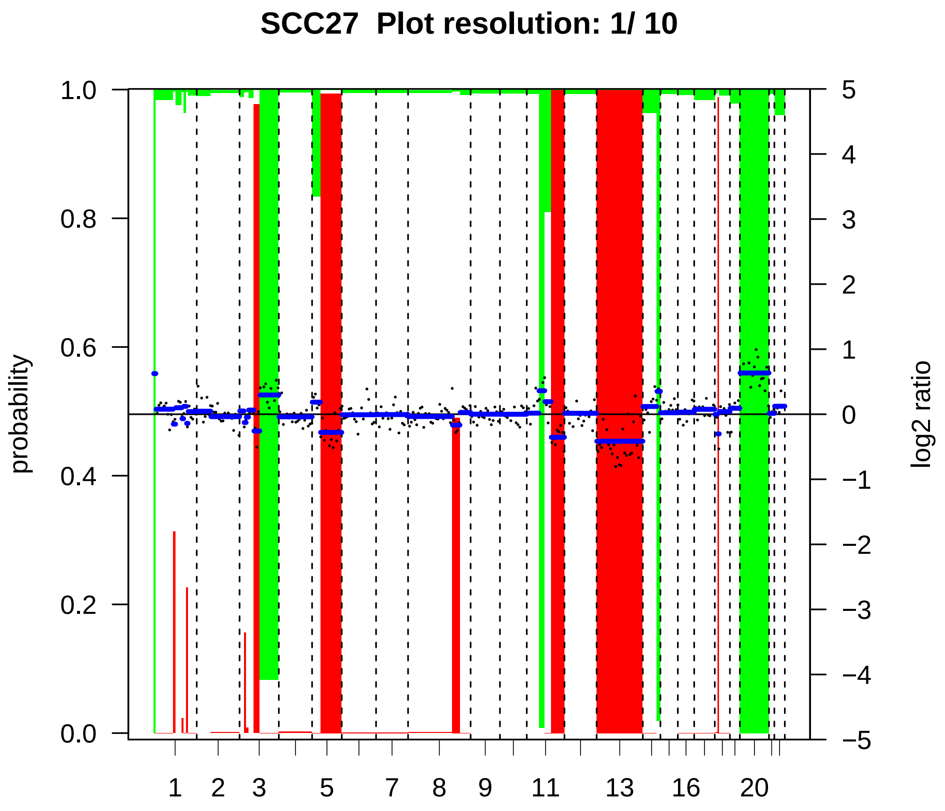
To visualize the results per profile we use the `plotProfile` function:

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

```
Plotting sample AdCA10
```



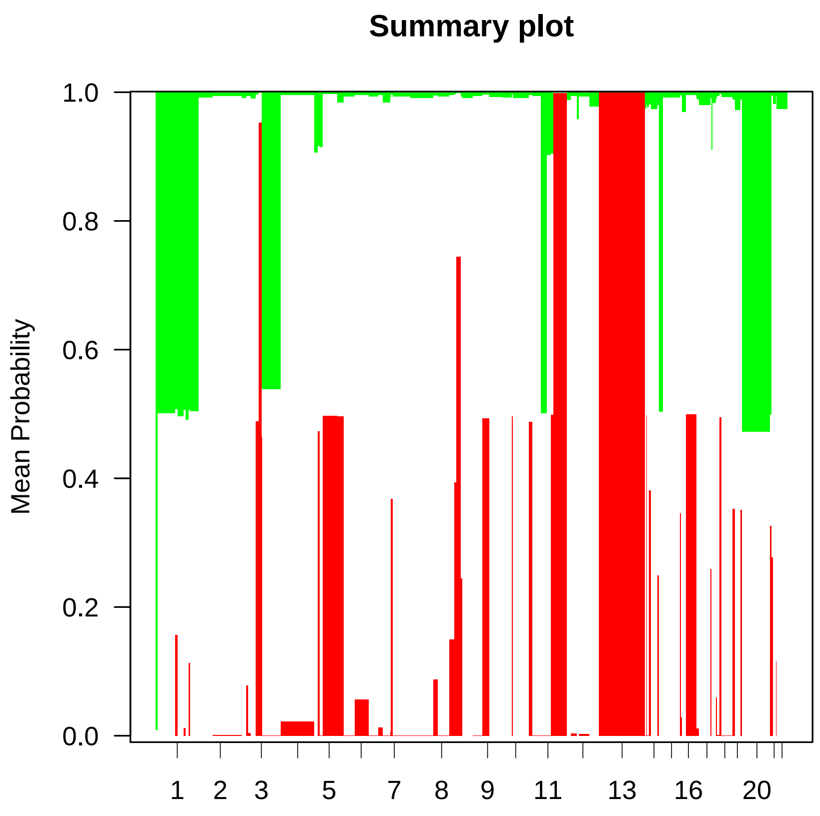
```
> plot(result[,2])

Plotting sample SCC27
```



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

```
> summaryPlot(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.