

DNACopy: A Package for Analyzing DNA Copy Data

Venkatraman E. Seshan¹ and Adam B. Olshen²

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¹Department of Epidemiology and Biostatistics
Memorial Sloan-Kettering Cancer Center
`seshanv@mskcc.org`

²Department of Epidemiology and Biostatistics
University of California, San Francisco
`olshena@biostat.ucsf.edu`

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1 Overview

This document presents an overview of the DNACopy package. This package is for analyzing array DNA copy number data, which is usually (but not always) called array Comparative Genomic Hybridization (array CGH) data (Pinkel et al., 1998; Snijders et al., 2001; Lucito et al., 2003). It implements our methodology for finding change-points in these data (Olshen et al., 2004), which are points after which the (log) test over reference ratios have changed location. Our model is that the change-points correspond to positions where the underlying DNA copy number has changed. Therefore, change-points can be used to identify regions of gained and lost copy number. We also provide a function for making relevant plots of these data.

2 Data

We selected a subset of the data set presented in Snijders et al. (2001). We are calling this data set `coriell`. The data correspond to two array CGH studies of fibroblast cell

strains. In particular, we chose the studies **GM05296** and **GM13330**. After selecting only the mapped data from chromosomes 1-22 and X, there are 2271 data points. There is accompanying spectral karyotype data (not included), which can serve as a gold standard. The data can be found at http://www.nature.com/ng/journal/v29/n3/supinfo/ng754_S1.html

3 An Example

Here we perform an analysis on the **GM05296** array CGH study described above.

```
> library(DNAcopy)
> data(coriell)
```

Before segmentation the data needs to be made into a CNA object.

```
> CNA.object <- CNA(cbind(coriell$Coriell.05296),
+                   coriell$Chromosome, coriell$Position,
+                   data.type="logratio", sampleid="c05296")
```

We generally recommend smoothing single point outliers before analysis. It is a good idea to check that the smoothing is proper for a particular data set.

```
> smoothed.CNA.object <- smooth.CNA(CNA.object)
```

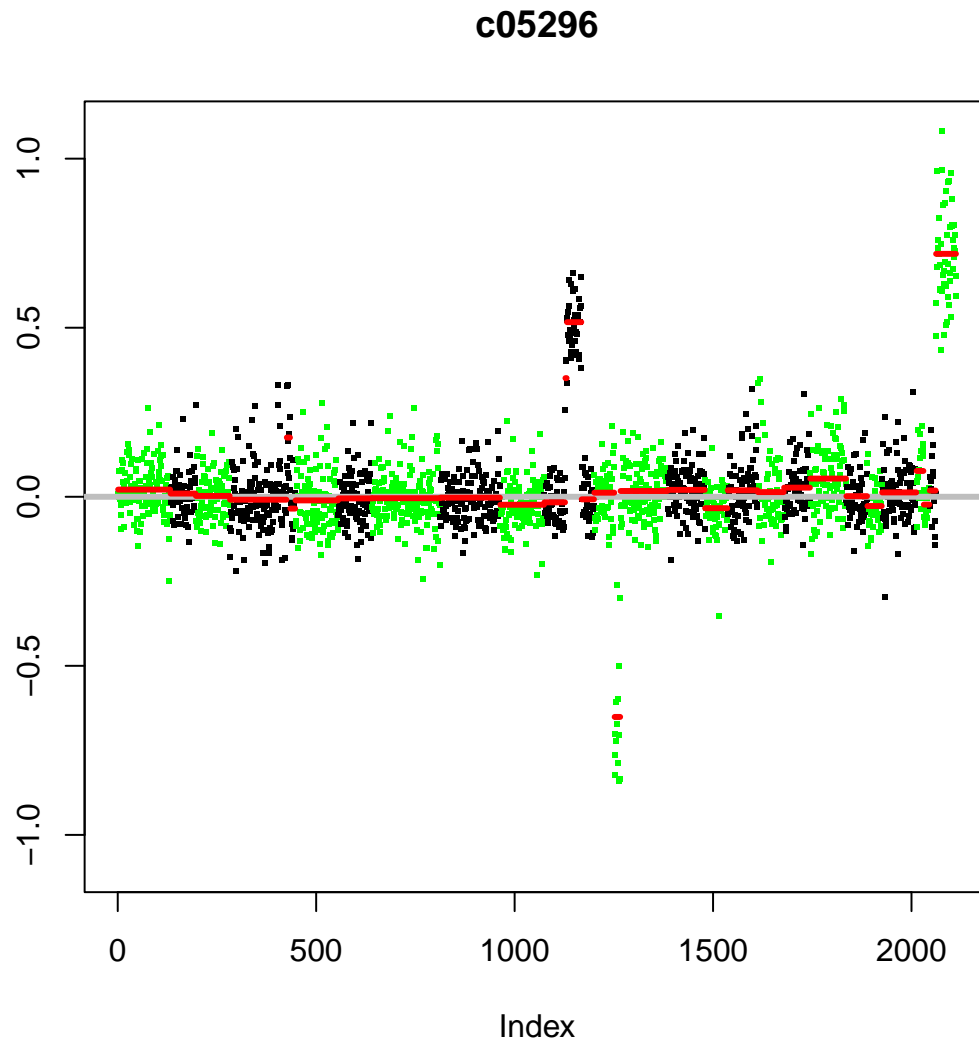
After smoothing, if necessary, the segmentation is run. Here the default parameters are used. A brief discussion of parameters that can be adjusted is in the Tips section.

```
> segment.smoothed.CNA.object <- segment(smoothed.CNA.object, verbose=1)
```

Analyzing: c05296

There are a number of plots that can be made. The first is ordering the data by chromosome and map positions. The red lines correspond to mean values in segments. Note that the points are in alternate colors to indicate different chromosomes.

```
> plot(segment.smoothed.CNA.object, plot.type="w")
```



Another possibility is to plot by chromosome within a study.

```
> plot(segment.smoothed.CNA.object, plot.type="s")
```

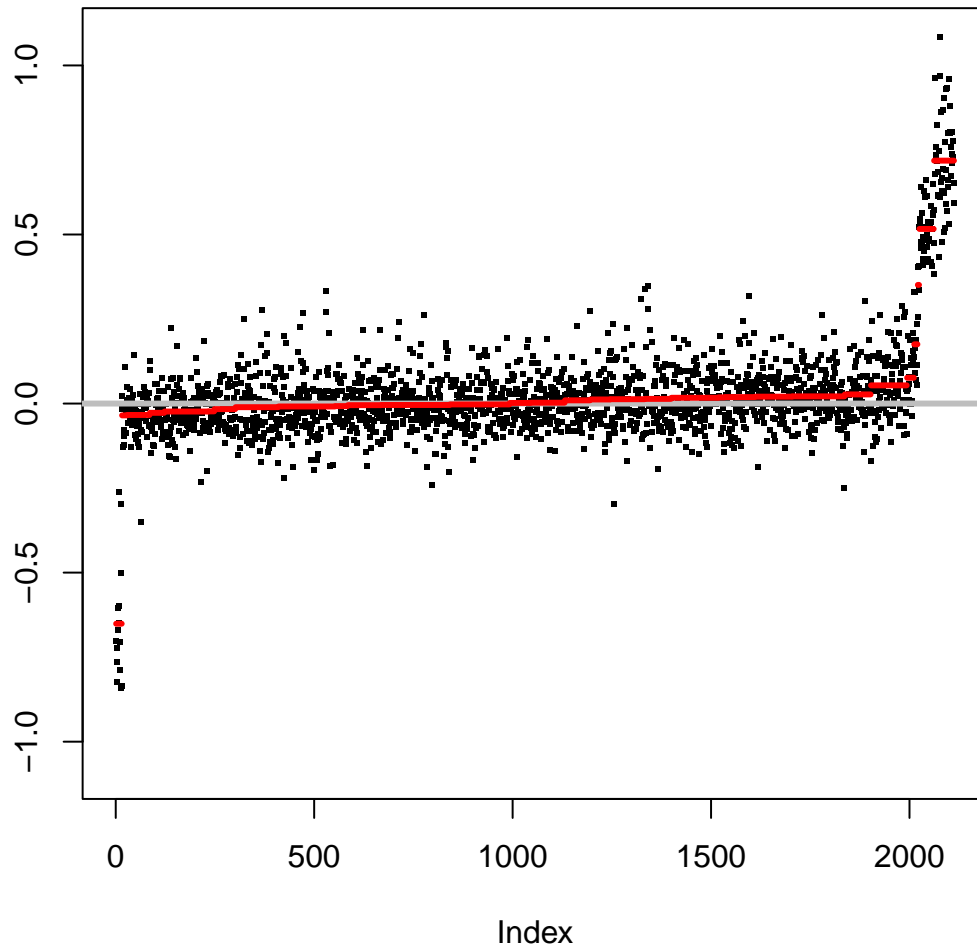
Setting multi-figure configuration



If there are multiple studies, one could plot by chromosome across studies using the option `plot.type='c'`. A final plot orders the segment by their chromosome means. One can take the plateaus in this plot to determine what the mean values should be for calling segments gains or losses. In this case, maybe 0.4 for gains and -0.6 for losses. For most data, these plateaus are much closer to zero. The next generation of this software will have automatic methods for calling gains and losses.

```
> plot(segment.smoothed.CNA.object, plot.type="p")
```

c05296



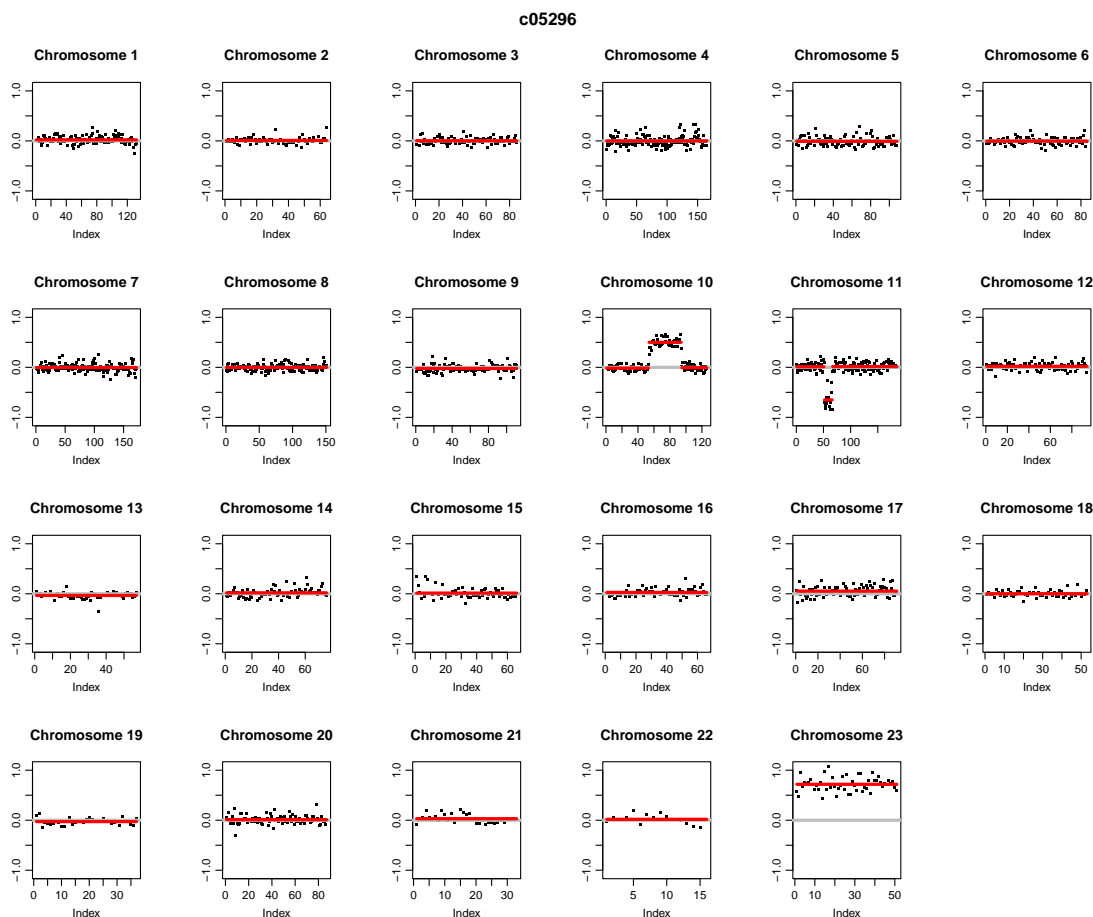
Change-points are often found due to local trends in the data. An undo method is needed to get rid of unnecessary change-points. Below all splits that are not at least three SDs apart are removed. The following plot shows that all splits not corresponding to the gold standard results have been removed.

```
> sdundo.CNA.object <- segment(smoothed.CNA.object,  
+                               undo.splits="sdundo",  
+                               undo.SD=3,verbose=1)
```

Analyzing: c05296

```
> plot(sdundo.CNA.object,plot.type="s")
```

Setting multi-figure configuration



4 Tips

A function that may be of interest that has not been mentioned is `subset.CNA`. It allows for subsetting of a CNA object by chromosome and sample so that segmentation does not have to be run on a whole data set. Similarly, `subset.DNACopy` allows subsetting of DNACopy objects, which contain the output of segmentation.

The original default segmentation algorithm, because it was based on permutation, took $O(N^2)$ computations, where N is the number of markers on a chromosome. The new default algorithm is much faster. It includes a hybrid approach to compute the p -value for segmenting based partly on permutation and partly on a Gaussian approximation (available in all versions after 1.2.0) and a stopping rule (available in all versions after 1.5.0) to declare change when there is a strong evidence for its presence (Venkatraman and Olshen, 2007). We no longer recommend using overlapping windows for larger data sets. It is still possible to run the full permutations analysis using the option `p.method='perm'`. If the new algorithm is still too slow, one can reduce the number of permutations in the hybrid method using the parameter `nperm` (default is 10,000). However, the lower `alpha` (the significance level for the test to accept change-points) is, the more permutations that are needed. The stopping boundary needs to be computed for any choice of `nperm` and `alpha` which is not the default

which is done automatically within the function `segment` or can be done externally using the function `getbdry` and passed on to `segment`.

References

- Lucito, R., Healey, J., Alexander, J., Reiner, A., Esposito, D., Chi, M., Rodgers, L., Brady, A., Sebat, J., Troge, J., West, J., Rostan, S., Nguyen, K., Powers, S., Ye, K., Olshen, A., Venkatraman, E., Norton, L., and Wigler, M. (2003). Representational oligonucleotide microarray analysis: a high resolution method to detect genome copy number variation. *Nat. Genet.*, 13:2291–305.
- Olshen, A. B., Venkatraman, E. S., Lucito, R., and Wigler, M. (2004). Circular binary segmentation for the analysis of array-based dna copy number data. *Biostatistics*, 5:557–72.
- Pinkel, D., Segraves, R., Sudar, D., Clark, S., Poole, I., Kowbel, D., Collins, C., Kuo, W. L., Chen, C., Zhai, Y., Dairkee, S. H., Ljung, B. M., Gray, J. W., and Albertson, D. G. (1998). High resolution analysis of dna copy number variation using comparative genomic hybridization to microarrays. *Nat. Genet.*, 20:207–211.
- Snijders, A. M., Nowak, N., Segraves, R., Blackwood, S., Brown, N., Conroy, J., Hamilton, G., Hindle, A. K., Huey, B., Kimura, K., S, S. L., Myambo, K., Palmer, J., Ylstra, B., Yue, J. P., Gray, J. W., Jain, A. N., Pinkel, D., and Albertson, D. G. (2001). Assembly of microarrays for genome-wide measurement of dna copy number. *Nat. Genet.*, 29:263–4.
- Venkatraman, E. S. and Olshen, A. B. (2007). A faster circular binary segmentation algorithm for the analysis of array cgh data. *Bioinformatics*, 23:657–63.