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► **To cite this version:**

Quentin Grimonprez, Alain Celisse, Guillemette Marot. Analysis of genomic markers: Make it easy with the R package MPAGENOMICS. SMPGD 2014, Jan 2014, Paris, France. , 2014. hal-01091543

**HAL Id: hal-01091543**

**<https://hal.science/hal-01091543v1>**

Submitted on 5 Dec 2014

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# Analysis of genomic markers: Make it easy with the R package MPAGenomics



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## Context

### Data

Affymetrix genome-wide SNP6 arrays.

About 200 biological samples with two types of profiles :

- copy-number: ~ 1.8 million probes (SNPs + CN)
- allele B fraction: proportion of total signal from allele B (~ 930.000 SNPs).

### Goal

- Create an R package : pipeline for beginners in R to easily perform data analysis from genome-wide SNP arrays.
- Calibration method for the segmentation parameter.

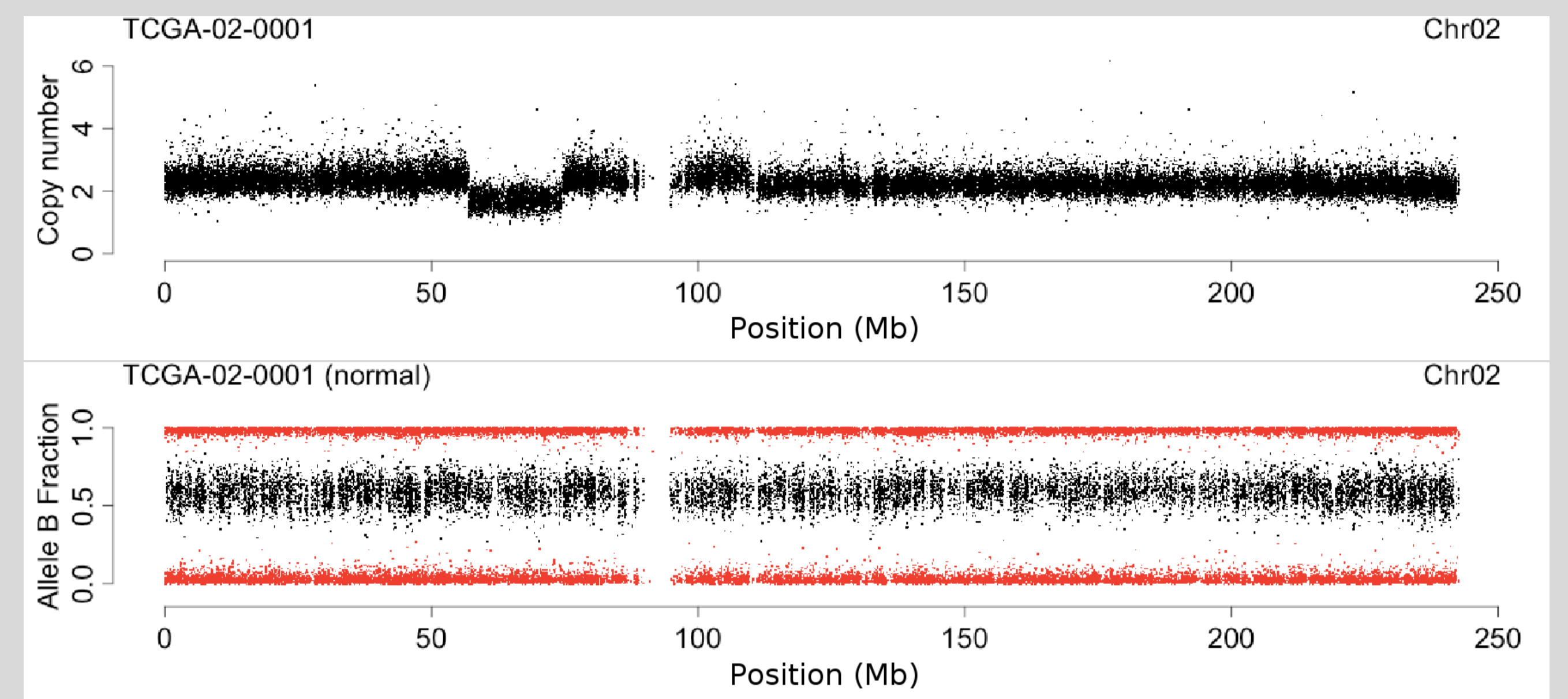


Figure 1: Top : Copy-number profile. Bottom : Allele B fraction profile : homozygous SNPs (red), heterozygous SNPs (black).

## Data Normalization

### Packages aroma

- Technical biases correction
- Copy-number & allele B fraction calculation
- *TumorBoost* : better allele B fraction correction for studies with matched normal-tumor samples

### Difficulties for beginners :

- Complicated internal documentation
- **Heavy architecture** to deal with
- No way to perform the whole analysis straightforwardly

### MPAGenomics contribution

1. Normalize data via MPAGenomics
  - Easily build architecture
  - Provide automatic wrappers of **aroma** functions
2. Provide normalized data

## Segmentation

### Copy-number

Copy-number signal is segmented by the PELT segmentation method from **changeoint** package (Killick et al., 2013).

### Allele B fraction

Heterozygous SNPs are kept and the signal is symmetrized. Then, the signal is segmented the same way as the copy-number signal.

### Calibration of $\lambda$ parameter in PELT

- PELT depends on a parameter to calibrate.
- MPAGenomics: **automatic calibration of  $\lambda$** .

## Calling method

- Assign labels (loss, normal or gain) to segments (copy-number).
- **CGHcall** package (van de Wiel et al., 2007).

## Markers selection

### Strategy

- Select genomic markers (e.g. SNPs or CNV) associated with a response  $y$ .
- Lasso method for sparse selection (few markers) with  $\rho > 0$  :

$$\sum_{i=1}^I (y_i - (X\beta)_i)^2 + \rho \sum_{p=1}^P |\beta_p|$$

### Implementation in MPAGenomics

- **Linear regression**: HDPenReg for **huge amount** of variables (HDPenReg: R package, C++ implementation of LARS (Efron et al., 2004)).
- **Logistic regression**: wrapper of **glmnet** R package (Friedman et al., 2010).
- Choice of  $\rho$  by  $k$ -fold cross validation.

## Calibration of $\lambda$ (segmentation)

- PELT **default parameter is misleading**.
- MPAGenomics: automatic data-driven choice of  $\lambda$

### Strategy

1. Grid of  $\lambda$ :  $0 < \lambda_1 < \lambda_2 < \dots < \lambda_{\max}$ .
2. Run PELT for each  $\lambda_i$  (see Figure 2 left).
3. Choose  $\lambda$  corresponding to the widest range such that the number of segments is constant ( $> 1$ ).

### Sample-specific parameter versus common $\lambda$

#### 1. Common $\lambda$ :

- Compute the signal-to-noise ratio (SNR) for each profile.
- Cluster profiles according to SNR (Gaussian mixture).
- For each cluster, choose  $\lambda$ .

#### 2. Sample-specific $\lambda$ :

MPAGenomics provides an **automatic choice of  $\lambda$  for each profile**.

### Sample-specific parameter versus common $\lambda$

Common  $\lambda$  within each cluster is misleading (Figure 2 right).

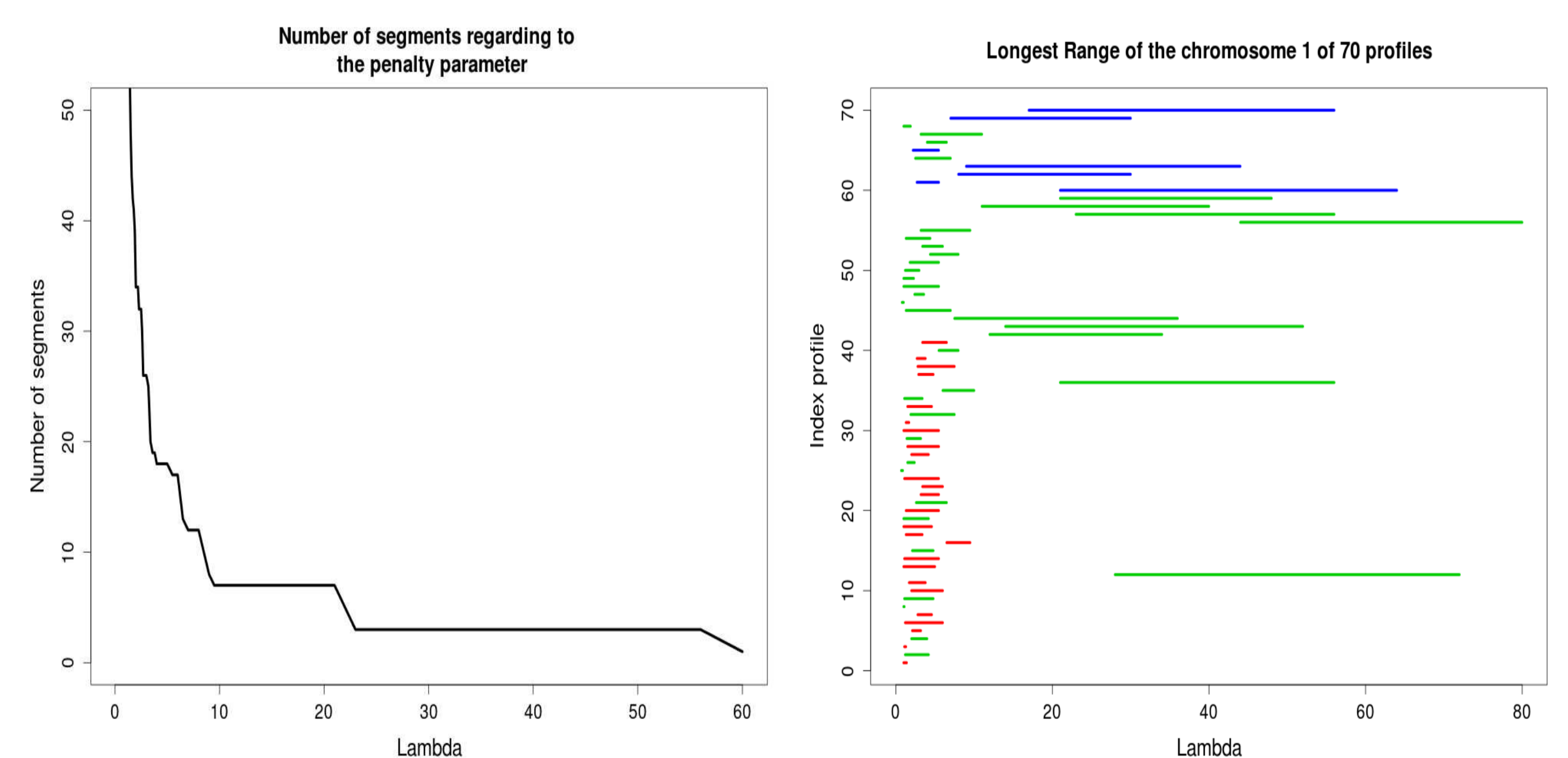


Figure 2: Left: Number of segments versus  $\lambda$  (chromosome 1). Right: Ranges of optimal  $\lambda$  for each profile. Color indicates a given signal-to-noise ratio (red;green;blue).

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