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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.

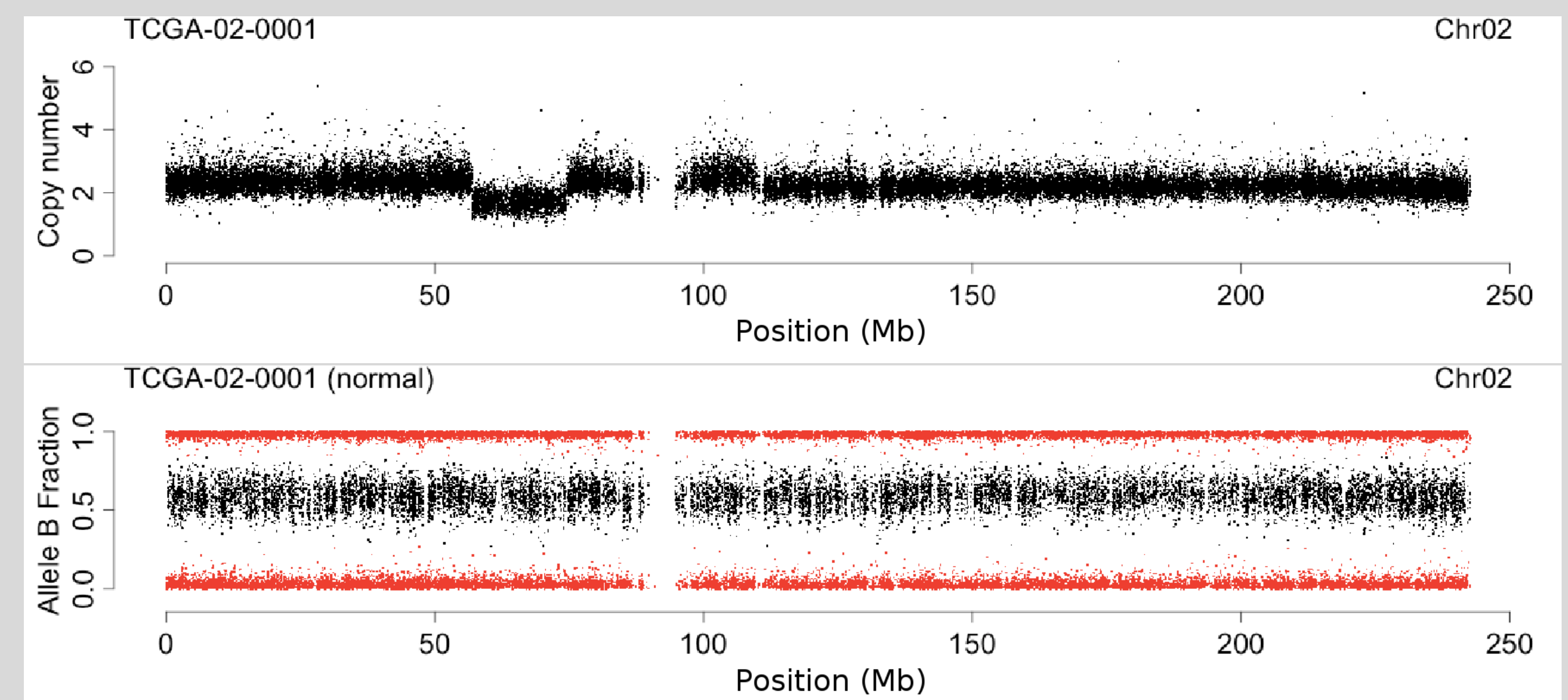


Figure 1: Top : Copy-number profile. Bottom : Allele B fraction profile : homozygous SNPs (red), heterozygous SNPs (black).

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 **changepoint** 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 λ parameter in PELT

- PELT depends on a parameter to calibrate.
- **MPAGenomics**: **automatic calibration of λ** .

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 ρ by k -fold cross validation.

Calibration of λ (segmentation)

- PELT **default parameter is misleading**.
- **MPAGenomics**: automatic data-driven choice of λ

Strategy

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

Sample-specific parameter versus common λ

1. **Common λ** :
 - Compute the signal-to-noise ratio (SNR) for each profile.
 - Cluster profiles according to SNR (Gaussian mixture).
 - For each cluster, choose λ .
2. **Sample-specific λ** :
MPAGenomics provides an **automatic choice of λ for each profile**.

Sample-specific parameter versus common λ

Common λ within each cluster is misleading (Figure 2 right).

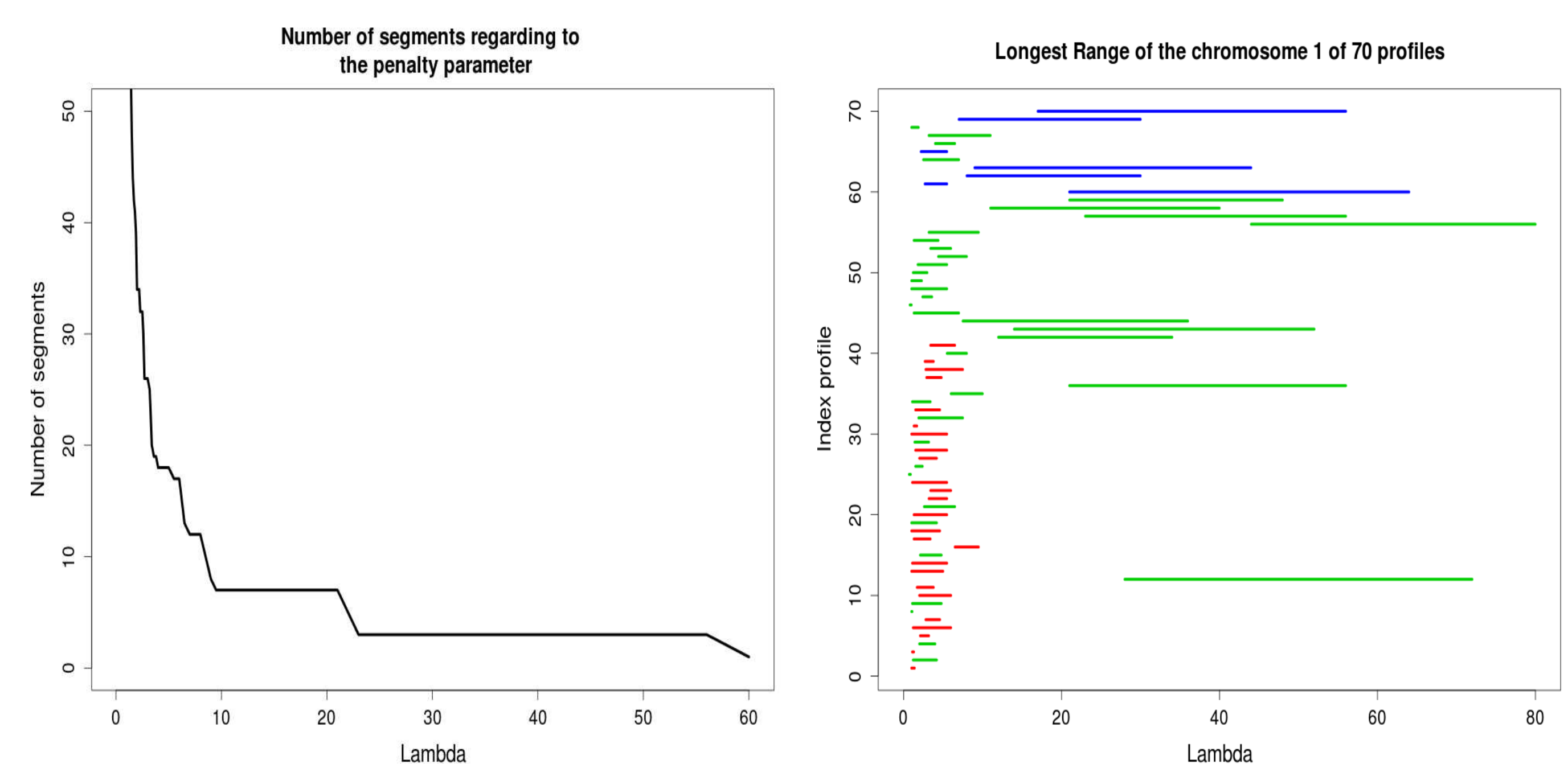


Figure 2: Left: Number of segments versus λ (chromosome 1). Right: Ranges of optimal λ for each profile. Color indicates a given signal-to-noise ratio (red|green|blue).

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