Analyse multi-patients de données génomiques

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SUMMARY

1 Introduction

Introduction

Data

- Patients with leukemia (about 300).
- Profiles obtained using SNP arrays with DNA from patients at diagnosis and at remission.
- Informations about the relapse of patients.

Goal

- Select important markers for predicting the relapse of patients.

Partners

- Laboratoire d'hématologie, CHRU Lille.
- Plate-forme de génomique fonctionnelle et structurale, Université Lille 2.

2
Markers selection

Markers selection

- Select genomic markers (e.g. SNPs or CNV) associated with a response $y \in \mathbb{R}^p$.
- $X \in \mathcal{M}_{n,p}(\mathbb{R})$ containing the different signals.
- Lasso [Tibshirani, 1994] method for sparse selection (few markers) with $\lambda > 0$:

$$\hat{\beta} = \arg\min_{\beta \in \mathbb{R}^p} \|y - X\beta\|_2^2 + \lambda \|\beta\|_1$$

R packages

- Package `glmnet` for logistic regression [Friedman et al., 2010]
- Re-implementation of LARS algorithm [Efron et al., 2004] for linear regression

R Package `HDPenReg`

- Lars algorithm in C++ with R interface
- Choice of λ by k-fold cross validation.
- Faster than `lars` package
- Work with bigger data than `lars` package

Conclusion

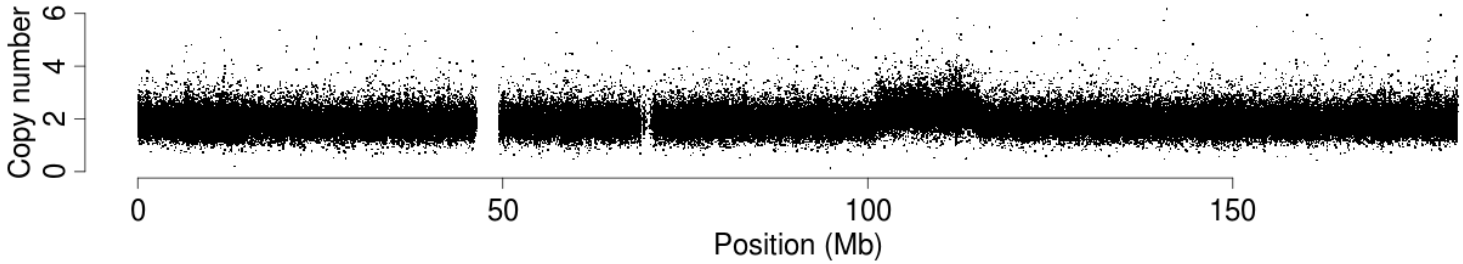
- No interesting results
- According to M.D., an abnormality is present in 5-10% of patients at the same position. The number of abnormalities is more important.

3
Segmentation & Calling

Segmentation

Goal

- Segment copy-number signal



Segmentation

Statistic modeling

- $y = (y_1, \ldots, y_n)$ a signal of length n
- Let $r_1, r_2, \ldots, r_{K-1}$ position of breakpoints
- Let $\mu_1, \mu_2, \ldots, \mu_K$ means of segments
- $\forall t \in s_i = [r_i, r_{i+1}[\,, y_t = \mu_i + N_t$ où $N_t \sim \mathcal{N}(0, \sigma^2)$
  $i = 1, \ldots, K-1$

Maximum of likelihood

- Maximize : $\log p(y; R, \mu) = \sum_{k=1}^{K} \sum_{t \in s_k} \log\, p(y_t; \mu_k) + Pen$
- In Gaussian case :
  $\log p(y; R, \mu) = C_1 - C_2 \sum_{k=1}^{K} \sum_{t \in s_k} (y_t - \mu_k)^2$

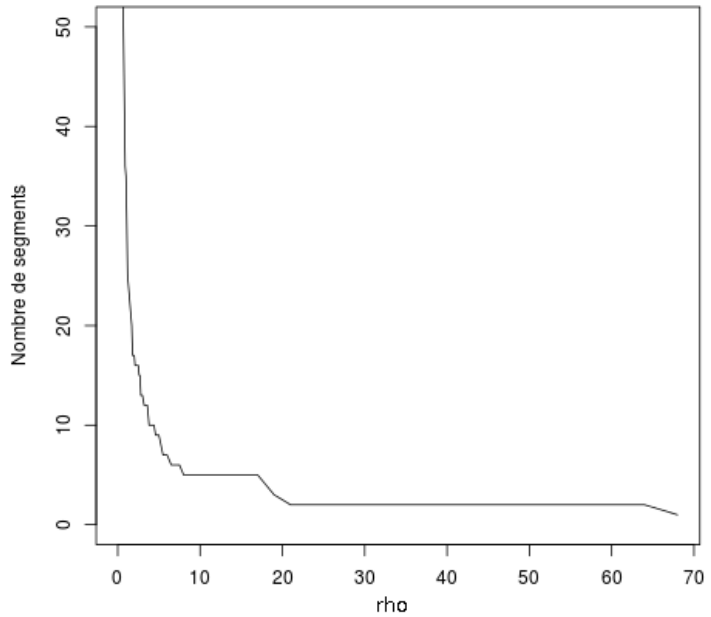
Method recommanded in [Hocking et al., 2013]

- PELT method [Killick et al., 2012] from `changepoint` package
- Default parameter for each profile and each chromosome
  $\Rightarrow$ In practise, over-segmentation of our data.
- Calibrate the penalty parameter ρ of the penalty $\rho \log(n)$ according to the data

Calibration of PELT parameter

Sample specific parameter

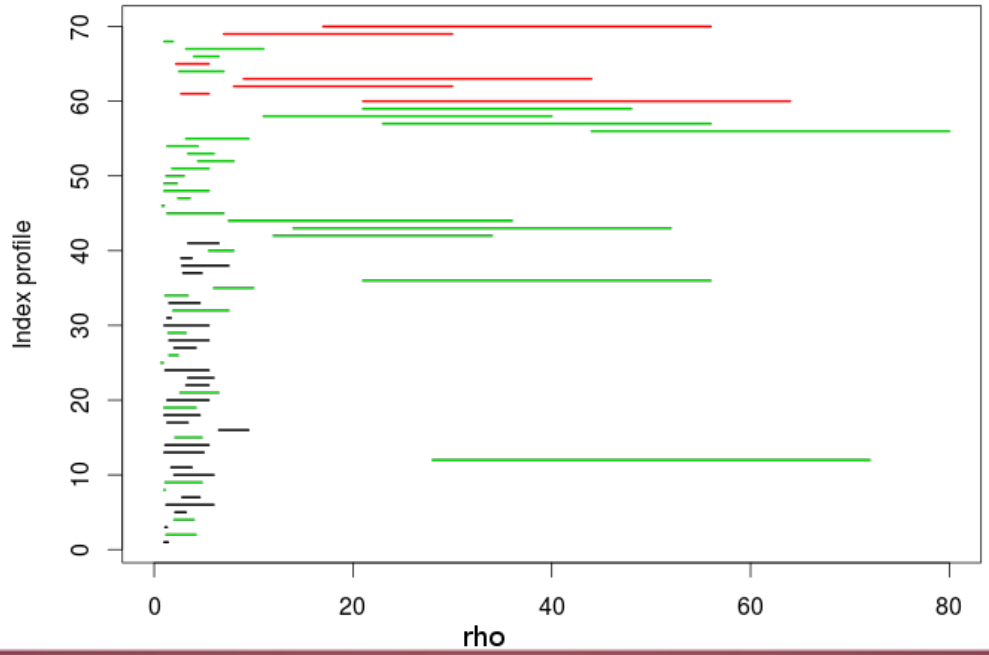
- Grid of ρ : $0 < \rho_1 < \cdots < \rho_{\text{max}}$
- Run PELT for each ρ_i
- Choose ρ corresponding to the widest range such that the number of segments is constant



Calibration of PELT parameter

Common parameter by group of variance

- Compute variance for each sample
- Cluster profiles according to variance with a Gaussian Mixture Model
- For each cluster, choose ρ



Calling

Goals

- Put a label on each segment (gain, loss, ...)
- Isolate non-normal segments

Method

- CGHcall package [van de Wiel et al., 2007]
- based on Gaussian Mixture Model

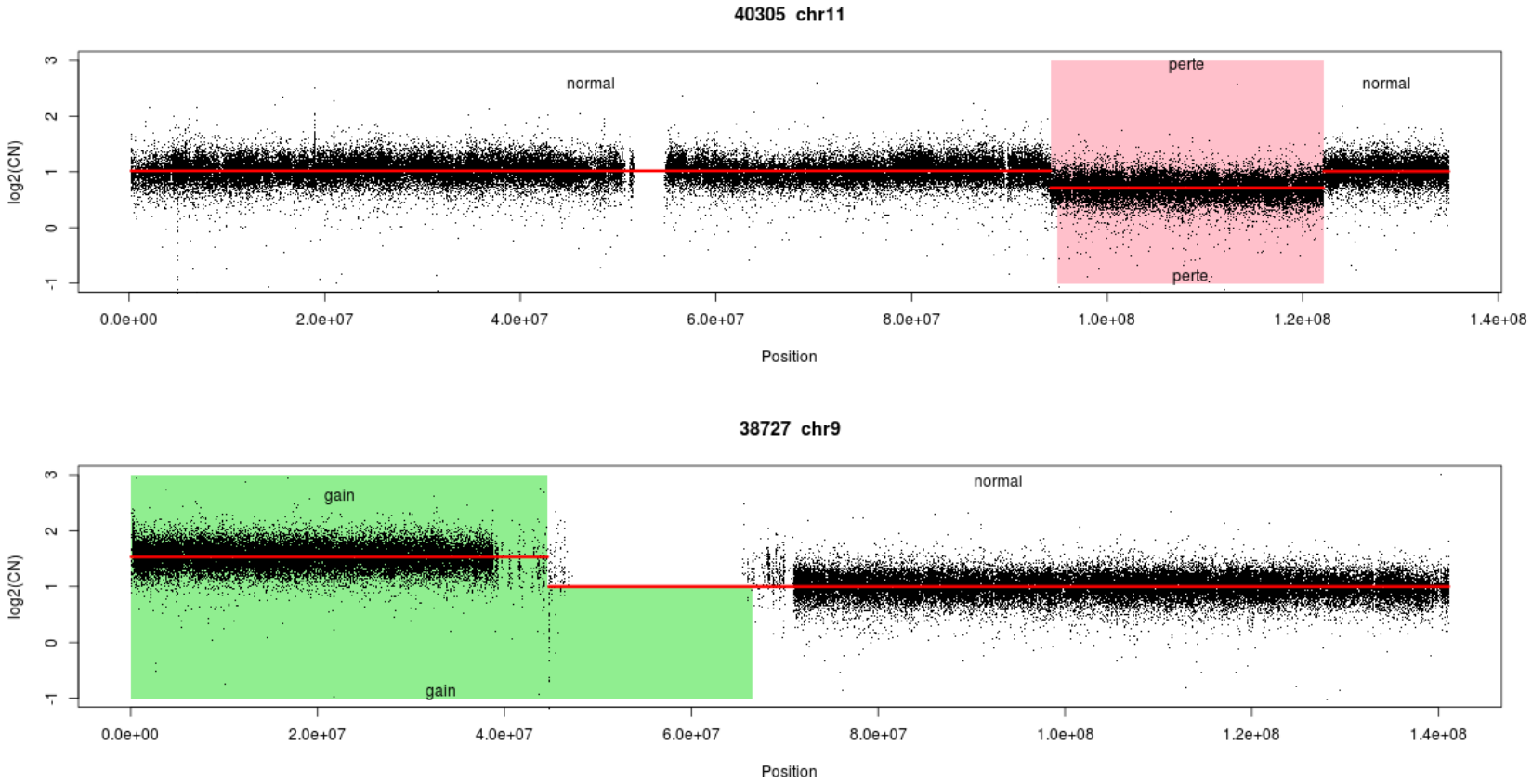
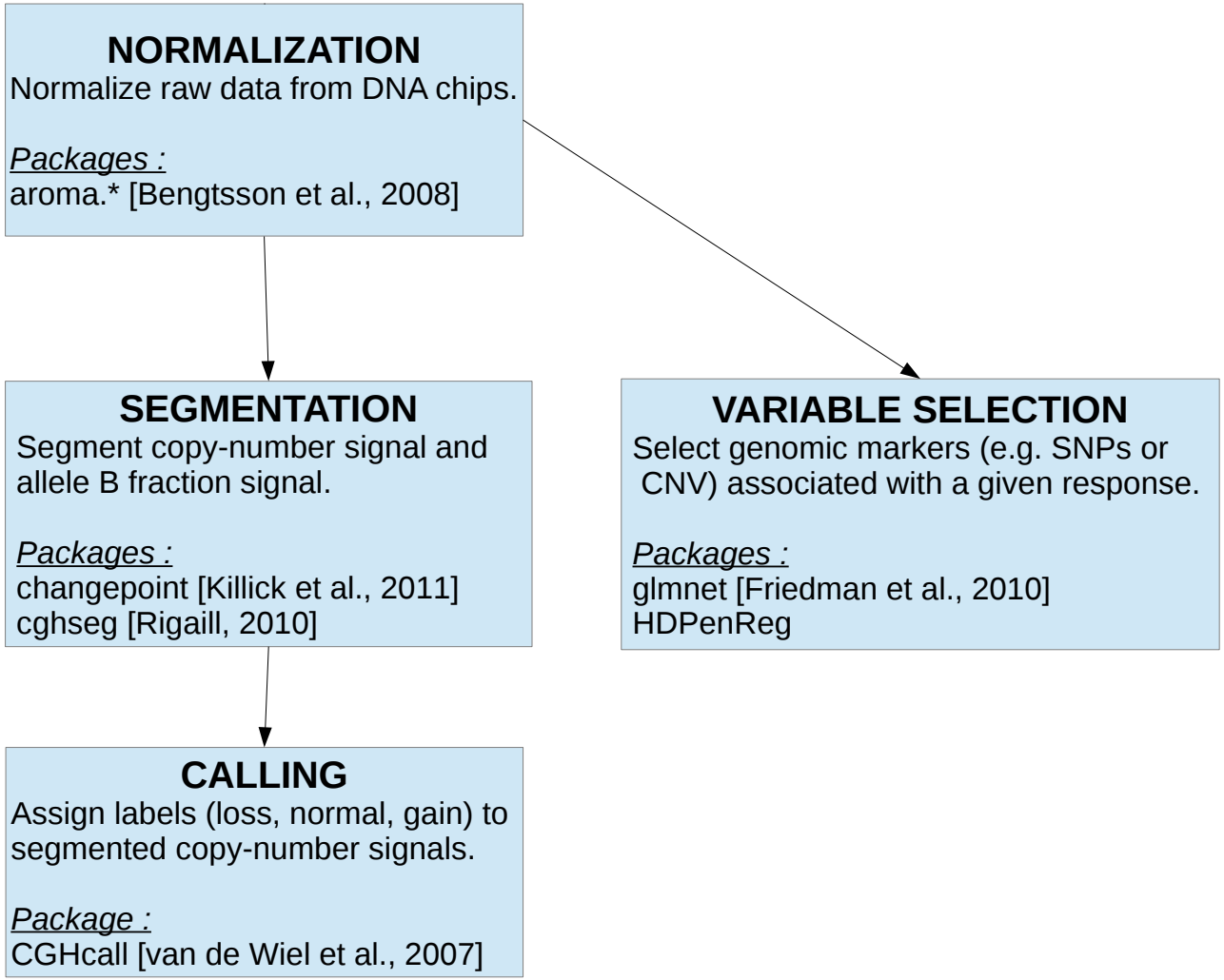


FIGURE: Examples of segmented and annotated signals. On each graph, CGHcall annotation vs human annotation.

4
MPAgenomics package

MPAgenomics package



5 Conclusion

Conclusion

Easy way to perform automatically multi-patients analysis

R Packages

- `HDPenReg` available on R-forge
- `MPAgenomics` available on R-forge $\Rightarrow$ `https://r-forge.r-project.org/R/?group_id=1658`

Futures Development

- Galaxy interface
- Joint segmentation

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