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Comparison of segmentation methods in cancer samples

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2013-04-16

Outline

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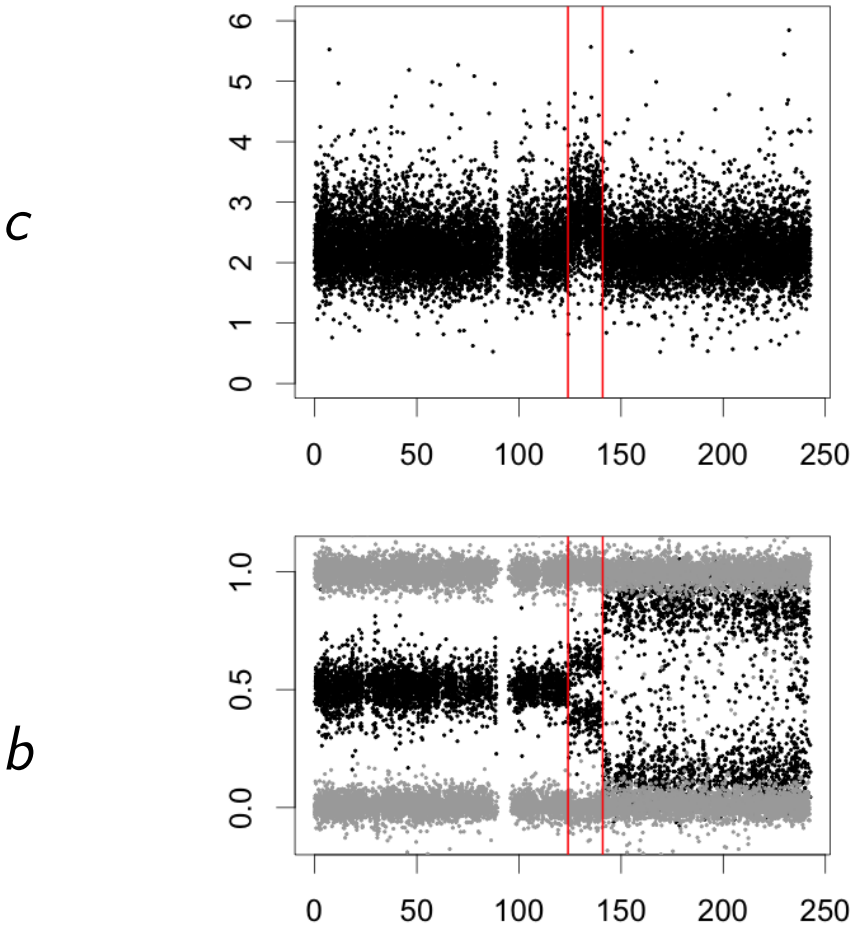
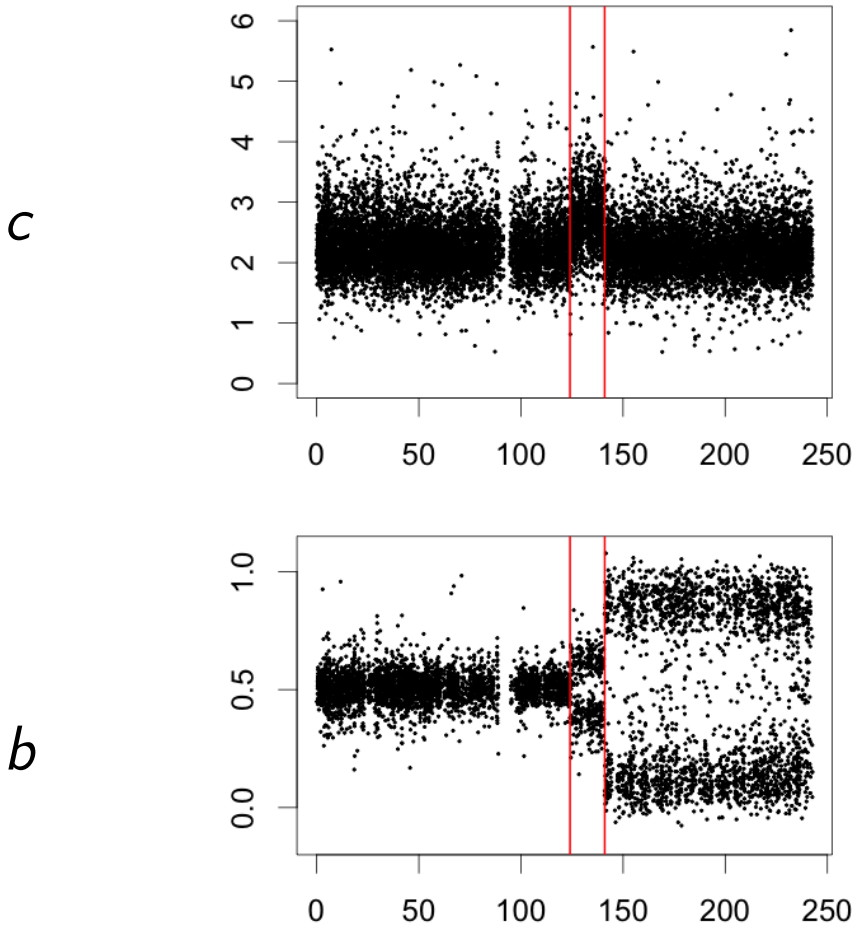


Chromosome 2 (Mb)

Breakpoints occur at exact same position in the two dimensions



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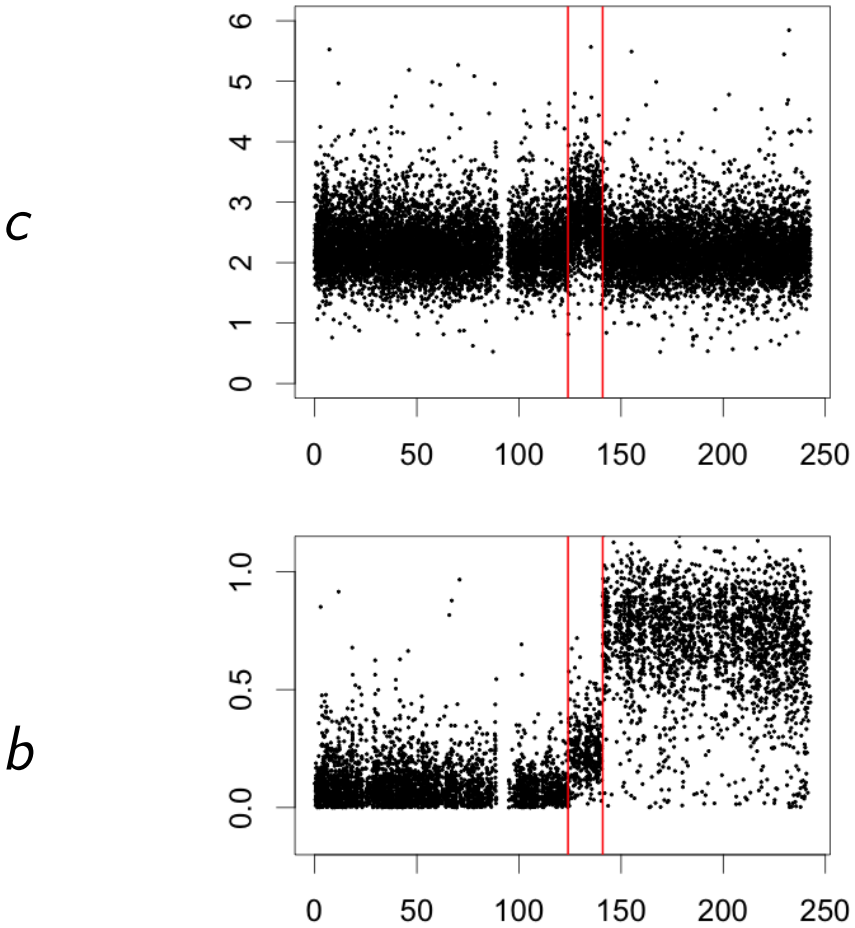

Chromosome 2 (Mb)

Breakpoints occur at exact same position in the two dimensions

Goal of DNA copy number studies : Identification of altered genome regions.

- Understand tumor progression
- Lead to personalized therapies

We focused on identification of breakpoints

- Genomic signals from SNP arrays are bivariate
- Breakpoints occur exactly at the same position in the two-dimensions

Outline

A change-point model

- Biological assumption : DNA copy numbers or symmetrized B allele frequency are piecewise constant
- Statistical model for K change points at $(t_1, ...t_K)$:

$$\forall j = 1, \ldots, n \qquad c_j = \gamma_j + \epsilon_j$$

where $\forall k \in \{1, \ldots, K+1\}, \forall j \in [t_{k-1}, t_k[\qquad \gamma_j = \Gamma_k$

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Complexity

- Challenges : K and $(t_1, ...t_K)$ are unknown
- For a fixed K , the number of possible partitions : $C_{n-1}^K = \mathcal{O}(n^{K-1})$

State of the art : Exact solution

One dimension

- [Picard et al. (2005)] : complexity in $\mathcal{O}(Kn^2)$
- [Rigaill et al.(2010)] : mean complexity in $\mathcal{O}(Knlog(n))$

Two dimensions

- Extension of [Picard et al. (2005)] : complexity in $\mathcal{O}(dKn^2)$ for smaller problems
- [Mosen-Ansorena, D et al (2013)] : complexity in $\mathcal{O}(dKnl)$ where l is the maximum length of segments

State of the art : Heuristics

Type	Name	Method	Dimension
Convex relaxation	FLASSO	total variation distance with a complexity in $\mathcal{O}(Kn)$	1 d
	GFLASSO	Group fused Lasso solved by LARS $\mathcal{O}(Knd)$	$\geq$2 d
Binary segmentation	CBS	Circular binary segmentation	1d
	CART	Classification and regression tree	1 d
	MCBS	Multivariate circular binary segmentation	$\geq$2 d
	PSCBS	CBS on copy number then on B allele frequency	2 d
	RBS	Recursive binary segmentation in 2 dimensions adaptation of CART	2 d
Other	PSCN	HMM (hidden Markov Model)	2 d

Two-step approaches for joint segmentation

[Gey,S and Lebarbier,E (2008)] and [Bleakley and Vert(2011)] proposed two-step approaches.
So, we implemented a fast joint segmentation using CART in 2d following by a pruning.
First step :

- Running a fast but approximate segmentation method (RBS)

Second step

- Pruning the final set of breakpoints using dynamic programming that is slower but exact

Binary Segmentation

- Take the simple case : dimension is equal to 1 ($d = 1$) :
- Hypothesis : $\mathcal{H}_0$: No breakpoint vs $\mathcal{H}_1$: Exactly one breakpoint.
- The likelihood ratio statistic is given by $\max_{1 \leq i \leq n} |Z_i|$

$$Z_i = \frac{\left(\frac{S_i}{i} - \frac{S_n - S_i}{n-i}\right)}{\sqrt{\frac{1}{i} + \frac{1}{n-i}}}, \tag{1}$$

And $S_i = \sum_{1 \leq l \leq i} y_l$

If ($d > 1$) : the likelihood ratio statistic becomes $\max_{1 \leq i \leq n} \|Z_i\|_2^2$

First step : Recursive Binary Segmentation (RBS)

Complexity : $O(dnlog(K))$

- First breakpoint
- For each i : we compute Z_i : $t_1 = \arg\max_{1 \leq i \leq n} \|Z_i\|_2^2$

fig/RBS0.pdf

fig/RBS1.pdf

First step : Recursive Binary Segmentation (RBS)

Complexity : $O(dnlog(K))$

- First breakpoint
- For each i : we compute Z_i : $t_1 = \arg\max_{1 \leq i \leq n} \|Z_i\|_2^2$

fig/RBS2.pdf

First step : Recursive Binary Segmentation (RBS)

- Second breakpoint :
  - $\max_{1 \leq i \leq t_1} \|Z_i\|_2^2$
  - $\max_{t_1 < i \leq n} \|Z_i\|_2^2$
- Compute RSE for each segment.
- Keep the RSE which bring the maximum gain
- Add the breakpoint to the active set

fig/RBS3.pdf

First step : Recursive Binary Segmentation (RBS)

- Second breakpoint :
  - $\max_{1 \leq i \leq t_1} \|Z_i\|_2^2$
  - $\max_{t_1 < i \leq n} \|Z_i\|_2^2$
- Compute RSE for each segment.
- Keep the RSE which bring the maximum gain
- Add the breakpoint to the active set

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First step : Recursive Binary Segmentation (RBS)

- Third breakpoint :
  - $\max_{1 \leq i \leq t_1} \|Z_i\|_2^2$
  - $\max_{t_1 < i \leq t_2} \|Z_i\|_2^2$
  - $\max_{t_2 < i \leq n} \|Z_i\|_2^2$
- Compute RSE for each segment.
- Keep the RSE which bring the maximum gain
- Add the breakpoint to the active set

fig/RBS5.pdf

First step : Recursive Binary Segmentation (RBS)

- Third breakpoint :
  - $\max_{1 \leq i \leq t_1} \|Z_i\|_2^2$
  - $\max_{t_1 < i \leq t_2} \|Z_i\|_2^2$
  - $\max_{t_2 < i \leq n} \|Z_i\|_2^2$
- Compute RSE for each segment.
- Keep the RSE which bring the maximum gain
- Add the breakpoint to the active set

fig/RBS6.pdf

First step : Recursive Binary Segmentation (RBS)

- Third breakpoint :
  - $\max_{1 \leq i \leq t_1} \|Z_i\|_2^2$
  - $\max_{t_1 < i \leq t_2} \|Z_i\|_2^2$
  - $\max_{t_2 < i \leq n} \|Z_i\|_2^2$
- Compute RSE for each segment.
- Keep the RSE which bring the maximum gain
- Add the breakpoint to the active set

fig/RBS7.pdf

Outline

Simulated data creation

How did we create the simulated data ?

- From a real data set
  - For each technology (Illumina or Affymetrix) we have
    - Several data sets with various level of contamination by normal cells
    - Illumina : 34, 50, 79 and 100% of tumor cells
    - Affymetrix : 30, 50, 70 and 100% of tumor cells.
- Breakpoints are known
- State of segments are also known

Affymetrix

fig/profileAffy50100.pdf

Illumina

fig/profileIllu50100.pdf

fig/TNTP.pdf

Illumina : Use 2 dimensions provides good results

100 profiles, $n = 5000$, $K = 5$, purity = 79%, precision = 1

fig/figIllumina/CRL2324,BAF,ROC,n=5000,K=5,regSize=0,minL=

fig/figIllumina/CRL2324,BAF,ROC

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fig/figIllumina/CRL2324,BAF,ROC,n=5000,K=5,regSize=0,minL=

fig/figIllumina/CRL2324,BAF,ROC

Illumina : Univariate methods are as good as bivariate

100 profiles, $n = 5000$, $K = 5$, purity = 100%, precision = 1

fig/figIllumina/CRL2324,BAF,ROC,n=5000,K=5,regSize=0,minL=

fig/figIllumina/CRL2324,BAF,ROC

Outline

Conclusion

Results

- Creation of realistic simulated data
- R package development 'jointSeg' on R-forge. https ://r-forge.r-project.org/R/ ?group_id=1562
- Bivariate methods are not uniformly better than univariate
- No superiority of one method

Perspective

- Kernel approaches
- Labelling
- Other applications (several profiles, methylation data)

Thanks to Pierre Neuvial, Guillem Rigaill and Cyril Dalmasso

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