Learning smoothing models of copy number profiles using breakpoint annotations

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Introduction: how to detect breakpoints in copy number?

Breakpoint annotations: a new method for smoothing model selection and validation

Definitions and results on the neuroblastoma data with several common smoothing models

Conclusions and future work
Motivation: tumor genome copy number analysis

- Comparative genomic hybridization microarrays (aCGH) allow genome-wide copy number analysis since logratio is proportional to DNA copy number (Pinkel et al., 1998).
- Tumors often contain breakpoints, amplifications, and deletions at specific chromosomal locations that we would like to detect.
- Which genomic alterations are linked with good or bad patient outcome?
- To answer clinical questions like this one, we first need to accurately detect these genomic alterations.
aCGH neuroblastoma copy number data
Copy number profiles are predictive of progression in neuroblastoma


2 types of profiles:

- Segmental: deletion 1p 3p 11q, gain 1q 2p 17q. Bad outcome. In this talk “breakpoints.”
But which model to use to detect breakpoints?

- GLAD: adaptive weights smoothing (Hupé et al., 2004)
- DNAcopy: circular binary segmentation (Venkatraman and Olshen, 2007)
- cghFLasso: fused lasso signal approximator with heuristics (Tibshirani and Wang, 2007)
- HaarSeg: wavelet smoothing (Ben-Yaacov and Eldar, 2008)
- flsa: fused lasso signal approximator path algorithm (Hoefling 2009)
- cghseg: pruned dynamic programming (Rigaill 2010)

How to define which model is best?
And how to choose the degree of smoothness?
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Which model segments these the best? (demo)
Answer: annotate the profiles!
cghseg.k smoothing for lambda=10^-3.48

position on chromosome (mega base pairs)

logratio

annotation
red breakpoint
gray normal
cghseg.k smoothing for lambda=10^{−1.96}
Choose the smoothing model that minimizes error with respect to breakpoint annotations.

![Graph showing number of annotations inconsistent with model smoothing against log10(smoothness parameter).](image)

- More breakpoints: log10(smoothness parameter) > -1.96
- Fewer breakpoints: log10(smoothness parameter) < -1.96
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Definition of breakpoints in smoothing models

Consider just one copy number profile.

For the \( d \) probes corresponding to chromosome \( c \), let

\[
\begin{align*}
    p_1 & \leq \ldots \leq p_d \in \mathbb{N} & \text{positions on chromosome } c \\
    y_1 & , \ldots , y_d \in \mathbb{R} & \text{logratio measurements} \\
    \hat{y}_1^\lambda & , \ldots , \hat{y}_d^\lambda \in \mathbb{R} & \text{smoothed profile (solid blue lines)}
\end{align*}
\]

Breakpoints predicted on chromosome \( c \):

\[
\hat{B}_c^\lambda = \left\{ \frac{(p_j + p_{j+1})}{2} \mid \hat{y}_j^\lambda \neq \hat{y}_{j+1}^\lambda, \ \forall j = 1, \ldots, d - 1 \right\}
\]

Then, we define \( \hat{B}^\lambda \) to be the complete set of genomic breakpoints predicted by algorithm \( \lambda \), over all chromosomes \( c \) (dashed vertical blue lines).
## Gudrun and Isabelle annotated 6 regions on each profile

<table>
<thead>
<tr>
<th>$k$</th>
<th>min $ = r_k$</th>
<th>max $ = \bar{r}_k$</th>
<th>chrom $c_k$</th>
<th>breakpoint</th>
<th>normal</th>
<th>(all)</th>
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<tbody>
<tr>
<td>1</td>
<td>0.00</td>
<td>125.00</td>
<td>1</td>
<td>103</td>
<td>464</td>
<td>567</td>
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<td>93.30</td>
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<td>50.40</td>
<td>4</td>
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<td>569</td>
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<tr>
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<td>135.01</td>
<td>11</td>
<td>107</td>
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<td>571</td>
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<td>6</td>
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<td>81.20</td>
<td>17</td>
<td>175</td>
<td>388</td>
<td>563</td>
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</tbody>
</table>

(all) 573 2845 3418

![Graph showing ratio vs. position on chromosome for each profile with annotations for breakpoints and normal regions.](attachment:image.png)
Quantify agreement to breakpoint annotations

Let $b_i^k \subset \mathbb{N}$ be the set of breakpoint counts annotated in region $k$ for profile $i$, i.e. $\{0\}$ for “normal” and $\{1, 2, \ldots \}$ for “breakpoint”. Let $\hat{b}_i^k(\lambda)$ be the number of breakpoints in this region predicted by the model with smoothness parameter $\lambda$.

The error function for one profile $i$ and one region $k$:

$$E_{i}^{k}(\lambda) = \begin{cases} 0 & \text{if } \hat{b}_i^k(\lambda) \in b_i^k \\ 1 & \text{otherwise} \end{cases}$$

The local error function for one profile $i$:

$$E_i^{\text{local}}(\lambda) = \sum_k E_{i}^{k}(\lambda)$$

The global error function for all profiles:

$$E^{\text{global}}(\lambda) = \sum_i E_i^{\text{local}}(\lambda)$$
Questions we can answer using these data

1. Can we find a model with smoothness $\hat{\lambda}$ that is consistent with all the annotations?
2. If not, would it be good to use profile-specific smoothness parameters $\hat{\lambda}_i$?
3. How much time do we need to spend creating the annotation database?
Run each algorithm with a range of parameters, select model by minimizing annotation error

Result 1: no model is consistent with all the annotations, but cghseg.k has the lowest training error.
Details of the cghseg.k model

1. Segment each signal $y \in \mathbb{R}^d$ using pruned DP to get the smoothed signal $\hat{\beta}(y, k) \in \mathbb{R}^d$ for $k \in \{1, \ldots, k_{\text{max}}\}$ segments.

2. For any $\lambda > 0$, define optimal number of segments

$$k^*(y, \lambda) = \arg \min_{k \in \{1, \ldots, k_{\text{max}}\}} \lambda k + ||y - \hat{\beta}(y, k)||^2 / d$$  \hspace{1cm} (1)

3. For any $\lambda > 0$, define the optimal smoothing

$$\hat{y}^\lambda = \hat{\beta}(y, k^*(y, \lambda))$$  \hspace{1cm} (2)

4. Discretize $\lambda \in \{10^{-5}, \ldots, 10^0\}$ and calculate $\hat{y}^\lambda$ for each.
Profile-specific smoothness parameters can decrease the training error, but is that good?

- More breakpoints
- Fewer breakpoints
- Log10(smoothing parameter)

- Errors
- False positive
- False negative

- Global model
- Local model for profile 375
- Local model for profile 362

- cghseg.k flsa.norm dnacopy.sd glad.lambdabreak

- Percent incorrectly predicted annotations in training set

- Statistics
Annotations can be used for model selection and validation

Set of all profiles and annotations

<table>
<thead>
<tr>
<th>train</th>
<th>test</th>
</tr>
</thead>
</table>

BIC, AIC, etc. → CV → Annotations → Selected model, degree of smoothness

Fit model with selected degree of smoothness on test profiles, evaluate using test annotations
Cross-validation on regions and profiles

- Leave-one-out
- n/1-fold
- n/2-fold
- n/3-fold

Tumor/copy number profile

Annotated region

Set
- Test
- Train
## Leave-one-out cross-validation on regions

<table>
<thead>
<tr>
<th></th>
<th>Global</th>
<th></th>
<th>Local</th>
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<td>FN</td>
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<td>11.6</td>
<td>11.1</td>
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<td>20.0</td>
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<td>12.3</td>
<td>23.0</td>
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<td>15.1</td>
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<tr>
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<td>97.2</td>
</tr>
</tbody>
</table>

* no smoothness parameter to select using annotations.

Result 2: local models trained on 1 profile overfit with many false positives.

So how many annotations are needed for a good model?
Cross-validation on regions and profiles

- leave-one-out
- n/1-fold
- n/2-fold
- n/3-fold

Annotated region

Tumor/copy number profile

Set
- Test
- Train

Annotated region
How many annotations for a good generalization error?

Result 3: only a few annotations needed to get low breakpoint detection error.
Can we find a model with smoothness $\hat{\lambda}$ that is consistent with all the annotations? No, but cghseg.k has the lowest training error.

If not, would it be good to use profile-specific smoothness parameters $\hat{\lambda}_i$? No, since this local model overfits with many false positives.

How much time do we need to spend creating the annotation database? Not much, since only a few profiles need to be annotated in order to accurately generalize to un-annotated profiles.
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Conclusions

- Annotations can be quickly produced using a GUI.
- Only a few annotations are necessary to get a good global smoothing model.
- Annotations are useful for:
  - Selecting the model and degree of smoothness.
  - Validating the model generalization ability.
  - Collaborating with biologists.

Availability:

- Learning smoothing models of copy number profiles using breakpoint annotations, HAL preprint 00663790.
- CRAN: library(bams) "breakpoint annotation model smoothing" to reproduce figures and tables from the article.
- CRAN: data(neuroblastoma,package="neuroblastoma")
- PyPI: annotate_regions GUI.
Future work and questions

▶ Annotations to quantify accuracy of copy number calling models.
▶ Joint modeling of logratio, annotations, and clinical outcome?
▶ Can other modeling strategies lower the breakpoint detection error?
▶ Can an active learning strategy be used to more quickly lower the error?
▶ Supervised, interactive smoothing model building using breakpoint annotations.