

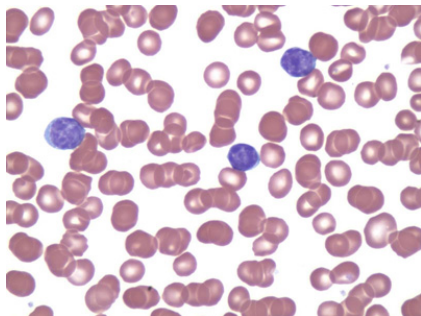
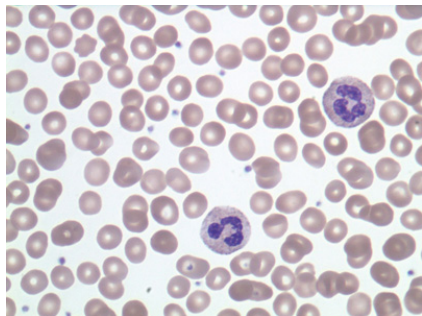
Fast sparse methods for genomics data

Jean-Philippe Vert



Optimization and Statistical Learning workshop,
Les Houches, January 6-11, 2013

Normal vs cancer cells

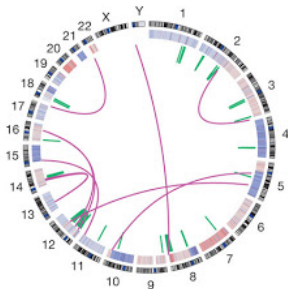
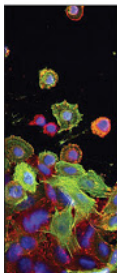


What goes wrong?
How to treat?

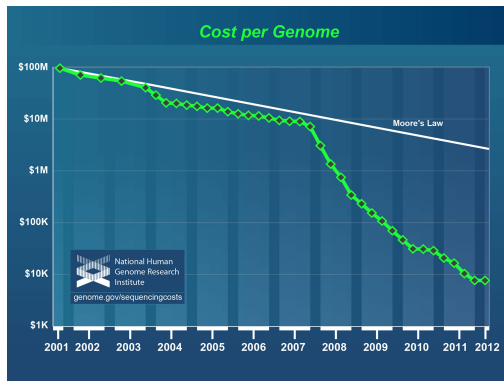
Biology is now quantitative, "high-throughput"



DOE Joint Genome Institute



Big data in biology

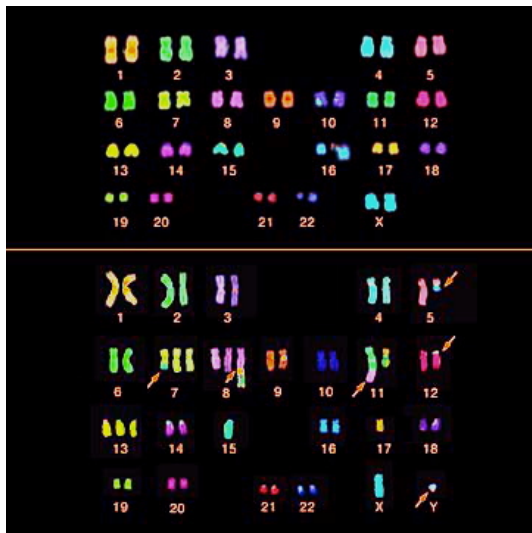
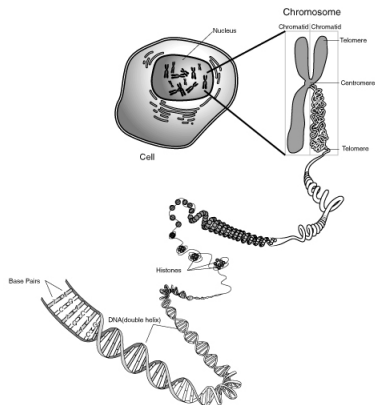


- "The \$1,000 genome, the \$1 million interpretation" (B. Kopf)
- High-dimensional, heterogeneous, structured data. **"Large p "**
- <http://aws.amazon.com/1000genomes/>

- 1 Mapping DNA breakpoints in cancer genomes (w. K Bleakley)
- 2 Isoform detection from RNA-seq data (w. E Bernard, J Mairal, L Jacob)

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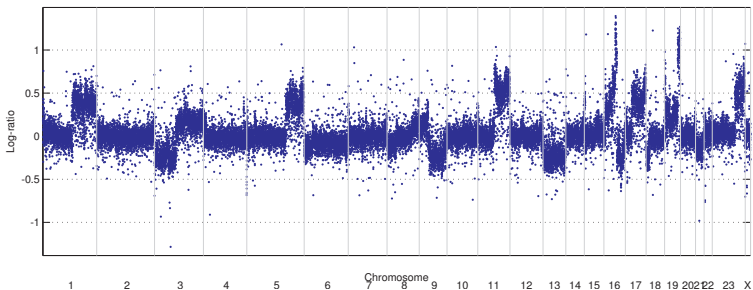
Chromosomal aberrations in cancer



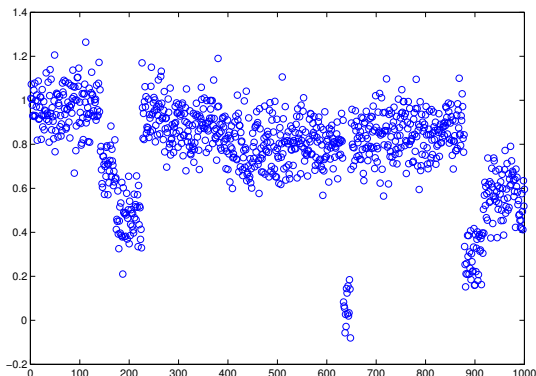
Comparative Genomic Hybridization (CGH)

Motivation

- Comparative genomic hybridization (CGH) data measure the **DNA copy number** along the genome
- Very useful, in particular in cancer research to observe systematically variants in DNA content

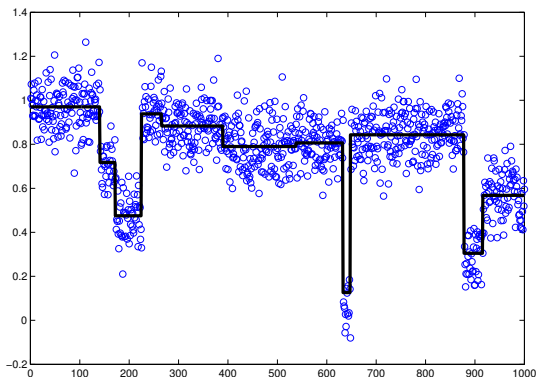


Can we identify breakpoints and "smooth" each profile?



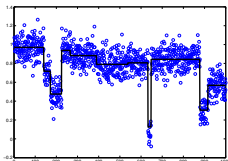
- A classical **multiple change-point detection** problem
- Should scale to lengths of order $10^6 \sim 10^9$

Can we identify breakpoints and "smooth" each profile?



- A classical **multiple change-point detection** problem
- Should scale to lengths of order $10^6 \sim 10^9$

An optimal solution

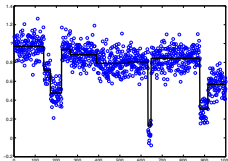


- For a signal $Y \in \mathbb{R}^p$, define an optimal approximation $\beta \in \mathbb{R}^p$ with k breakpoints as the solution of

$$\min_{\beta \in \mathbb{R}^p} \|Y - \beta\|^2 \quad \text{such that} \quad \sum_{i=1}^{p-1} \mathbf{1}(\beta_{i+1} \neq \beta_i) \leq k$$

- This is an optimization problem over the $\binom{p}{k}$ partitions...
- Dynamic programming finds the solution in $O(p^2 k)$ in time and $O(p^2)$ in memory
- But: does not scale to $p = 10^6 \sim 10^9$...

An optimal solution

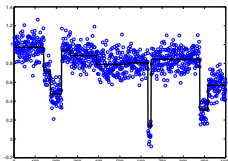


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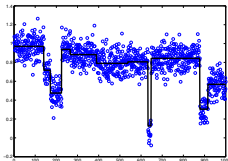


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Promoting sparsity with the ℓ_1 penalty

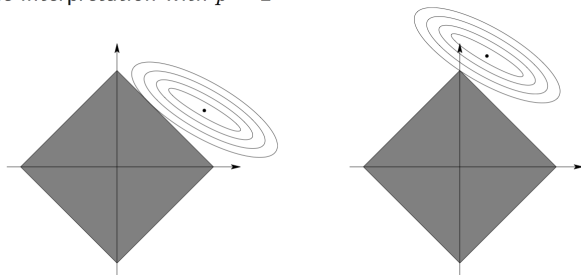
The ℓ_1 penalty (Tibshirani, 1996; Chen et al., 1998)

If $R(\beta)$ is convex and "smooth", the solution of

$$\min_{\beta \in \mathbb{R}^p} R(\beta) + \lambda \sum_{i=1}^p |\beta_i|$$

is usually **sparse**.

Geometric interpretation with $p = 2$



The total variation / variable fusion penalty

If $R(\beta)$ is convex and "smooth", the solution of

$$\min_{\beta \in \mathbb{R}^p} R(\beta) + \lambda \sum_{i=1}^{p-1} |\beta_{i+1} - \beta_i|$$

is usually piecewise constant (Rudin et al., 1992; Land and Friedman, 1996).

Proof:

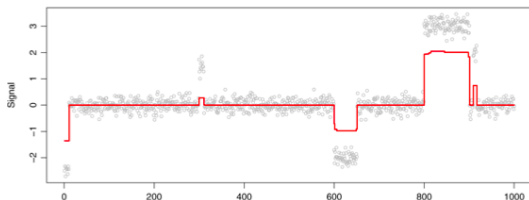
- Change of variable $u_i = \beta_{i+1} - \beta_i$, $u_0 = \beta_1$
- We obtain a Lasso problem in $u \in \mathbb{R}^{p-1}$
- u sparse means β piecewise constant

TV signal approximator

$$\min_{\beta \in \mathbb{R}^p} \|Y - \beta\|^2 \quad \text{such that} \quad \sum_{i=1}^{p-1} |\beta_{i+1} - \beta_i| \leq \mu$$

Adding additional constraints does not change the change-points:

- $\sum_{i=1}^p |\beta_i| \leq \nu$ (Tibshirani et al., 2005; Tibshirani and Wang, 2008)
- $\sum_{i=1}^p \beta_i^2 \leq \nu$ (Mairal et al. 2010)



$$\min_{\beta \in \mathbb{R}^p} \|Y - \beta\|^2 \quad \text{such that} \quad \sum_{i=1}^{p-1} |\beta_{i+1} - \beta_i| \leq \mu$$

- QP with sparse linear constraints in $O(p^2)$ -> 135 min for $p = 10^5$ (Tibshirani and Wang, 2008)
- Coordinate descent-like method $O(p)$? -> 3s for $p = 10^5$ (Friedman et al., 2007)
- With the LARS in $O(pk)$ (Harchaoui and Levy-Leduc, 2008)
- For all μ in $O(p \ln p)$ (Hoefling, 2009)
- For the first k change-points in $O(p \ln k)$ (Bleakley and V., 2010)

Theorem (V. and Bleakley, 2010; see also Hoefling, 2009)

TV signal approximator performs "greedy" dichotomic segmentation

Algorithm 1 Greedy dichotomic segmentation

Require: k number of intervals, $\gamma(I)$ gain function to split an interval I into $I_L(I), I_R(I)$

1: I_0 represents the interval $[1, n]$

2: $\mathcal{P} = \{I_0\}$

3: **for** $i = 1$ to k **do**

4: $I^* \leftarrow \arg \max_{I \in \mathcal{P}} \gamma(I^*)$

5: $\mathcal{P} \leftarrow \mathcal{P} \setminus \{I^*\}$

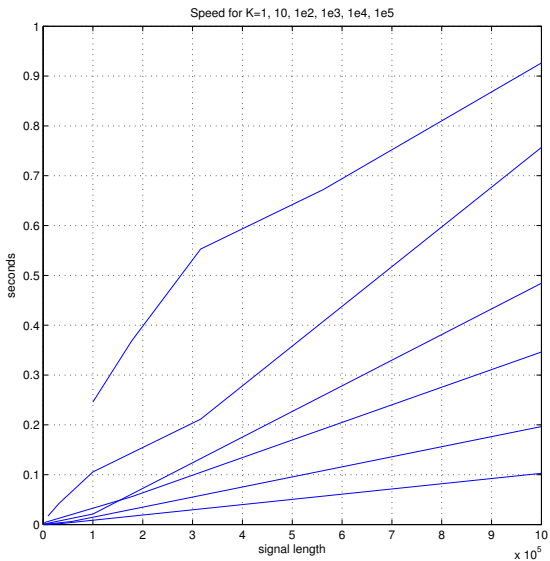
6: $\mathcal{P} \leftarrow \mathcal{P} \cup \{I_L(I^*), I_R(I^*)\}$

7: **end for**

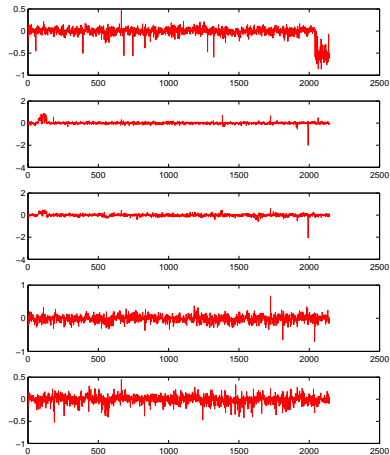
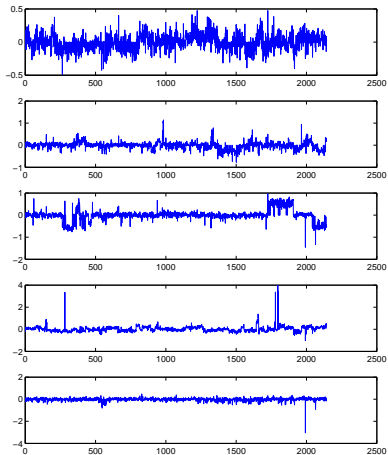
8: **return** \mathcal{P}

Apparently greedy algorithm finds the global optimum!

Speed trial : 2 s. for $k = 100$, $p = 10^7$

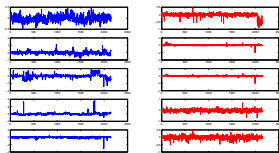


Extension 1: linear discrimination / regression



Aggressive (left) vs non-aggressive (right) melanoma

Fused lasso for supervised classification

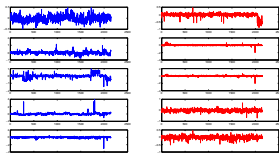


- **Idea:** find a linear predictor $f(Y) = \beta^T Y$ that best discriminates the aggressive vs non-aggressive samples, subject to the constraints that it should be sparse and piecewise constant
- **Mathematically:**

$$\min_{\beta \in \mathbb{R}^p} R(\beta) + \lambda_1 \|\beta\|_1 + \lambda_2 \|\beta\|_{TV}$$

- **Computationally:** proximal methods

Fused lasso for supervised classification

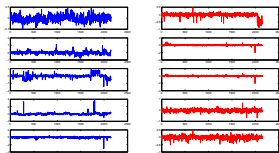


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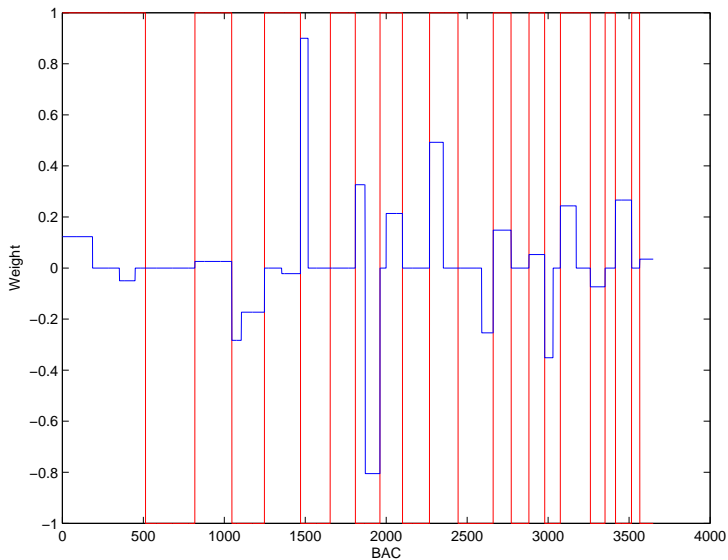


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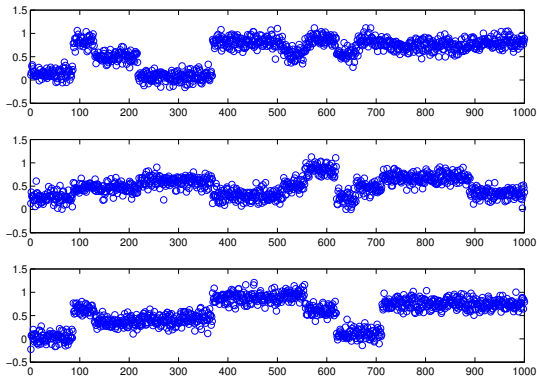
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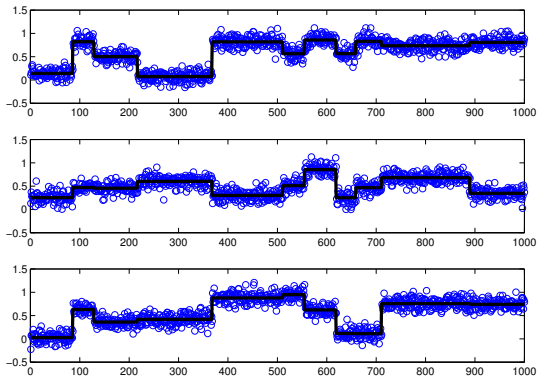
Prognosis in melanoma (Rapaport et al., 2008)



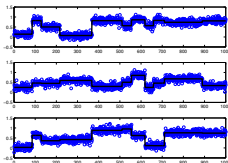
Extension 2: finding multiple change points shared by several profiles



Extension 2: finding multiple change points shared by several profiles



"Optimal" segmentation by dynamic programming



- Define the "optimal" piecewise constant approximation $\hat{U} \in \mathbb{R}^{p \times n}$ of Y as the solution of

$$\min_{U \in \mathbb{R}^{p \times n}} \|Y - U\|^2 \quad \text{such that} \quad \sum_{i=1}^{p-1} \mathbf{1}(U_{i+1, \bullet} \neq U_{i, \bullet}) \leq k$$

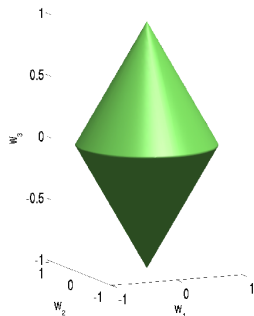
- DP finds the solution in $O(p^2 kn)$ in time and $O(p^2)$ in memory
- But: does not scale to $p = 10^6 \sim 10^9 \dots$

Selecting pre-defined groups of variables

Group lasso (Yuan & Lin, 2006)

If groups of covariates are likely to be selected together, the l_1/l_2 -norm induces sparse solutions *at the group level*:

$$\Omega_{group}(w) = \sum_g \|w_g\|_2$$



$$\begin{aligned}\Omega(w_1, w_2, w_3) &= \|(w_1, w_2)\|_2 + \|w_3\|_2 \\ &= \sqrt{w_1^2 + w_2^2} + \sqrt{w_3^2}\end{aligned}$$

Replace

$$\min_{U \in \mathbb{R}^{p \times n}} \|Y - U\|^2 \quad \text{such that} \quad \sum_{i=1}^{p-1} \mathbf{1}(U_{i+1, \bullet} \neq U_{i, \bullet}) \leq k$$

by

$$\min_{U \in \mathbb{R}^{p \times n}} \|Y - U\|^2 \quad \text{such that} \quad \sum_{i=1}^{p-1} w_i \|U_{i+1, \bullet} - U_{i, \bullet}\| \leq \mu$$

GFLseg = Group Fused Lasso segmentation

Questions

- Practice: can we solve it efficiently?
- Theory: does it recover the correct segmentation?

Replace

$$\min_{U \in \mathbb{R}^{p \times n}} \|Y - U\|^2 \quad \text{such that} \quad \sum_{i=1}^{p-1} \mathbf{1}(U_{i+1, \bullet} \neq U_{i, \bullet}) \leq k$$

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GFLseg = Group Fused Lasso segmentation

Questions

- Practice: can we solve it efficiently?
- Theory: does it recover the correct segmentation?

- Make the change of variables:

$$\begin{aligned}\gamma &= U_{1,\bullet}, \\ \beta_{i,\bullet} &= w_i (U_{i+1,\bullet} - U_{i,\bullet}) \quad \text{for } i = 1, \dots, p-1.\end{aligned}$$

- TV approximator is then equivalent to the following group Lasso problem (Yuan and Lin, 2006):

$$\min_{\beta \in \mathbb{R}^{(p-1) \times n}} \|\bar{Y} - \bar{X}\beta\|^2 + \lambda \sum_{i=1}^{p-1} \|\beta_{i,\bullet}\|,$$

where \bar{Y} is the centered signal matrix and \bar{X} is a particular $(p-1) \times (p-1)$ design matrix.

$$\min_{\beta \in \mathbb{R}^{(p-1) \times n}} \|\bar{Y} - \bar{X}\beta\|^2 + \lambda \sum_{i=1}^{p-1} \|\beta_{i,\bullet}\|,$$

Theorem

The TV approximator can be solved efficiently:

- "approximately" with the group LARS in $O(npk)$ in time and $O(np)$ in memory
- "exactly" with a block coordinate descent + active set method in $O(np)$ in memory

Although \bar{X} is $(p-1) \times (p-1)$:

- For any $R \in \mathbb{R}^{p \times n}$, we can compute $C = \bar{X}^T R$ in $O(np)$ operations and memory
- For any two subset of indices $A = (a_1, \dots, a_{|A|})$ and $B = (b_1, \dots, b_{|B|})$ in $[1, p-1]$, we can compute $\bar{X}_{\bullet, A}^T \bar{X}_{\bullet, B}$ in $O(|A||B|)$ in time and memory
- For any $A = (a_1, \dots, a_{|A|})$, set of distinct indices with $1 \leq a_1 < \dots < a_{|A|} \leq p-1$, and for any $|A| \times n$ matrix R , we can compute $C = \left(\bar{X}_{\bullet, A}^T \bar{X}_{\bullet, A} \right)^{-1} R$ in $O(|A|n)$ in time and memory

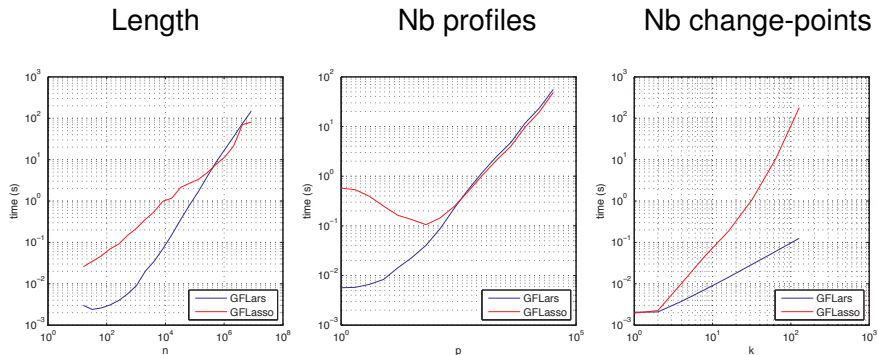
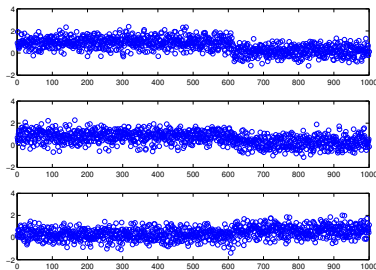


Figure 2: **Speed trials for group fused LARS (top row) and Lasso (bottom row).** *Left column:* varying n , with fixed $p = 10$ and $k = 10$; *center column:* varying p , with fixed $n = 1000$ and $k = 10$; *right column:* varying k , with fixed $n = 1000$ and $p = 10$. Figure axes are log-log. Results are averaged over 100 trials.

Consistency

Suppose a single change-point:

- at position $u = \alpha p$
- with increments $(\beta_i)_{i=1,\dots,n}$ s.t. $\bar{\beta}^2 = \lim_{k \rightarrow \infty} \frac{1}{n} \sum_{i=1}^n \beta_i^2$
- corrupted by i.i.d. Gaussian noise of variance σ^2



Does the TV approximator correctly estimate the first change-point as p increases?

Consistency of the unweighted TV approximator

$$\min_{U \in \mathbb{R}^{p \times n}} \|Y - U\|^2 \quad \text{such that} \quad \sum_{i=1}^{p-1} \|U_{i+1, \bullet} - U_{i, \bullet}\| \leq \mu$$

Theorem

The unweighted TV approximator finds the correct change-point with probability tending to 1 (resp. 0) as $n \rightarrow +\infty$ if $\sigma^2 < \tilde{\sigma}_\alpha^2$ (resp. $\sigma^2 > \tilde{\sigma}_\alpha^2$), where

$$\tilde{\sigma}_\alpha^2 = p\bar{\beta}^2 \frac{(1 - \alpha)^2 (\alpha - \frac{1}{2p})}{\alpha - \frac{1}{2} - \frac{1}{2p}}.$$

- correct estimation on $[p\epsilon, p(1 - \epsilon)]$ with $\epsilon = \sqrt{\frac{\sigma^2}{2p\bar{\beta}^2}} + o(p^{-1/2})$.
- wrong estimation near the boundaries

Consistency of the weighted TV approximator

$$\min_{U \in \mathbb{R}^{p \times n}} \|Y - U\|^2 \quad \text{such that} \quad \sum_{i=1}^{p-1} w_i \|U_{i+1, \bullet} - U_{i, \bullet}\| \leq \mu$$

Theorem

The weighted TV approximator with weights

$$\forall i \in [1, p-1], \quad w_i = \sqrt{\frac{i(p-i)}{p}}$$

correctly finds the first change-point with probability tending to 1 as $n \rightarrow +\infty$.

- we see the benefit of increasing n
- we see the benefit of adding weights to the TV penalty

- The first change-point \hat{i} found by TV approximator maximizes $F_i = \|\hat{c}_{i,\bullet}\|^2$, where

$$\hat{c} = \bar{X}^\top \bar{Y} = \bar{X}^\top \bar{X} \beta^* + \bar{X}^\top W.$$

- \hat{c} is Gaussian, and F_i follows a non-central χ^2 distribution with

$$G_i = \frac{EF_i}{p} = \frac{i(p-i)}{pw_i^2} \sigma^2 + \frac{\bar{\beta}^2}{w_i^2 w_u^2 p^2} \times \begin{cases} i^2 (p-u)^2 & \text{if } i \leq u, \\ u^2 (p-i)^2 & \text{otherwise.} \end{cases}$$

- We then just check when $G_u = \max_i G_i$

Consistency for a single change-point

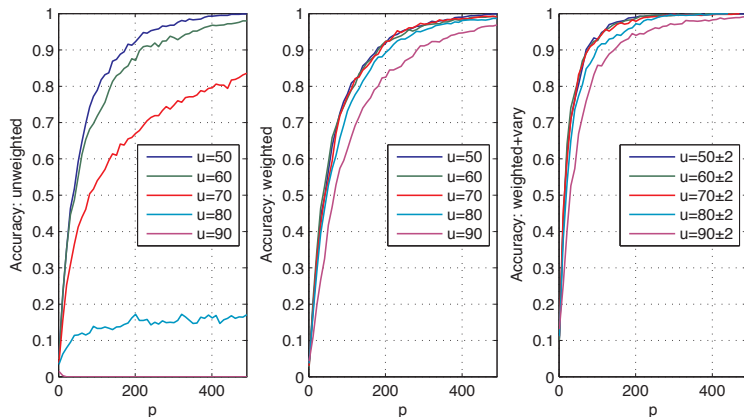


Figure 3: **Single change-point accuracy for the group fused Lasso.** Accuracy as a function of the number of profiles p when the change-point is placed in a variety of positions $u = 50$ to $u = 90$ (left and centre plots, resp. unweighted and weighted group fused Lasso), or: $u = 50 \pm 2$ to $u = 90 \pm 2$ (right plot, weighted with varying change-point location), for a signal of length 100.

Estimation of several change-points

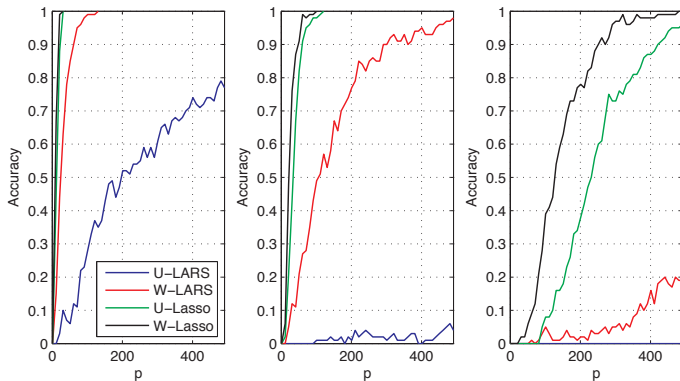
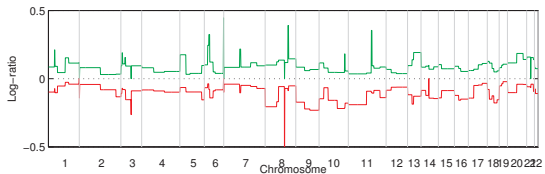
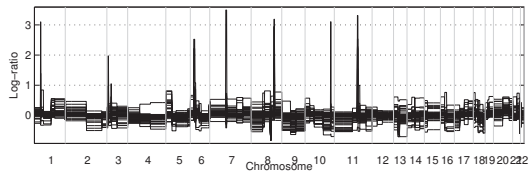
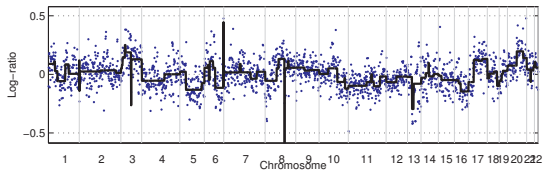


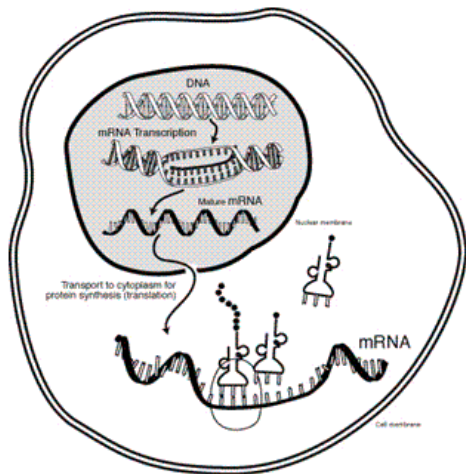
Figure 4: **Multiple change-point accuracy.** Accuracy as a function of the number of profiles p when change-points are placed at the nine positions $\{10, 20, \dots, 90\}$ and the variance σ^2 of the centered Gaussian noise is either 0.05 (left), 0.2 (center) and 1 (right). The profile length is 100.

Application: detection of frequent abnormalities

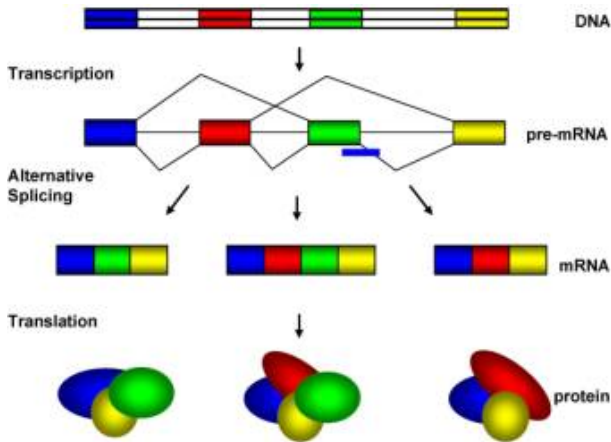


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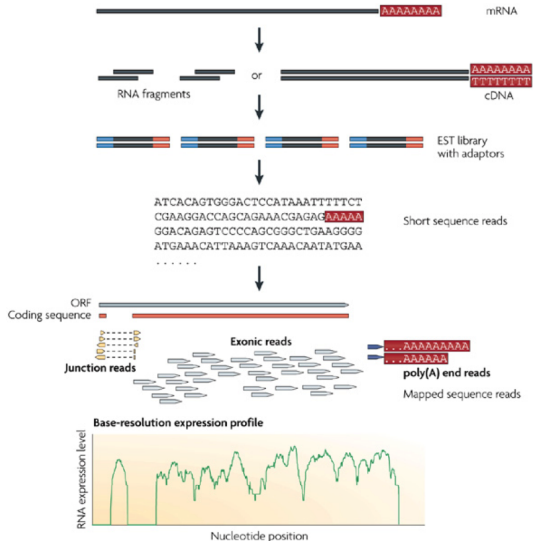
Central dogma



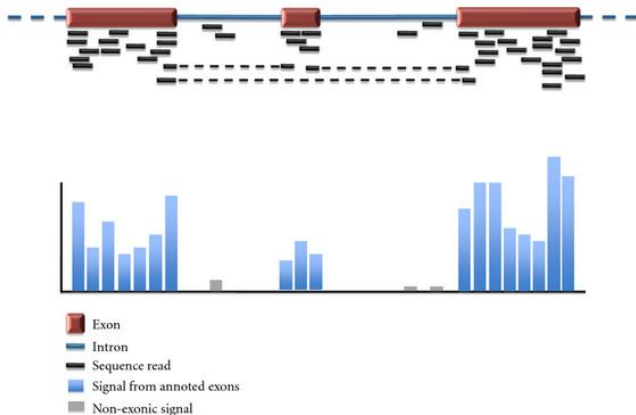
Alternative splicing: 1 gene = many proteins



RNA-seq measures RNA abundance

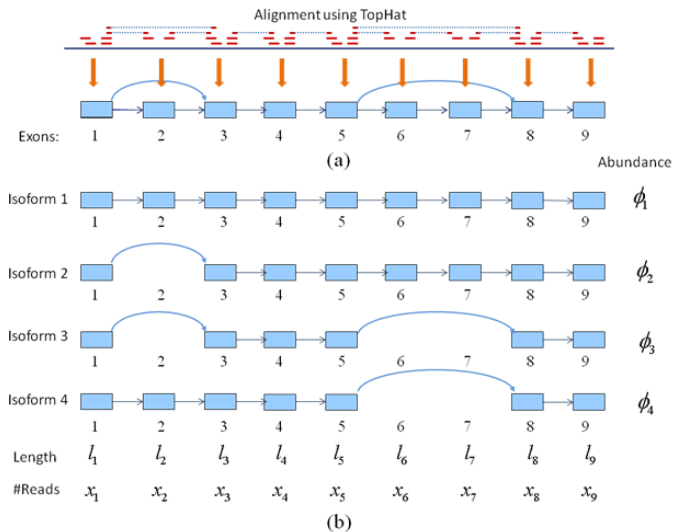


RNA-seq and alternative splicing



(Costa et al., 2011)

The isoform deconvolution problem



(Xia et al., 2011)

More formally

e exons

c candidate isoforms (up to $2^e - 1$)

$\phi \in \mathbb{R}_+^c$ the vector of abundance of isoforms (unknown!)

U binary matrix:

$$\begin{array}{l} \text{isoform}_1 \\ \text{isoform}_2 \\ \vdots \\ \text{isoform}_c \end{array} \begin{pmatrix} \text{exon}_1 & \cdots & \text{exon}_e & \text{junction}_{1,2} & \cdots & \text{junction}_{e_1,e} \\ 1 & \cdots & 1 & 1 & \cdots & 1 \\ 1 & \cdots & 0 & 1 & \cdots & 0 \\ \vdots & \cdots & & & \cdots & \\ 0 & \cdots & 1 & 0 & \cdots & 0 \end{pmatrix}$$

$U^T \phi$ the abundance of each exon/junction.

Goal: estimate ϕ from the observed reads on each exon/junction

Estimate ϕ sparse by solving:

$$\min_{\phi \in \mathbb{R}_+^c} R(U^T \phi) + \lambda \|\phi\|_1$$

- IsoLasso (Li et al., 2011)
- NSMAP (Xia et al., 2011)
- SLIDE (Li et al., 2011)

Works well BUT computationally challenging to enumerate all candidate isoforms (up to 2^e) for large genes!

Fast isoform deconvolution with the Lasso

Theorem (Bernard, Mairal, Jacob and V., 2012)

The isoform deconvolution problem

$$\min_{\phi \in \mathbb{R}_+^c} R(U^T \phi) + \lambda \|\phi\|_1$$

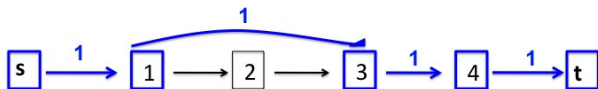
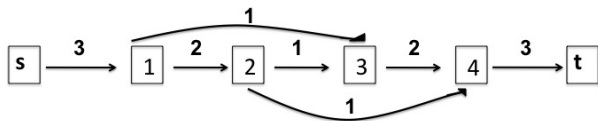
can be solved in **polynomial time** in the number of exon.

Key ideas

- 1 $U^T \phi$ corresponds to a **flow** on the graph
- 2 Reformulation as a **convex cost flow problem** (Mairal and Yu, 2012)
- 3 Recover isoforms by flow decomposition algorithm

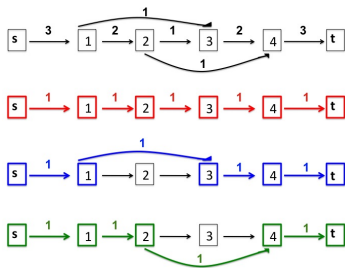
"Feature selection on an exponential number of features in polynomial time"

From isoforms to flows



- Isoforms are paths
- Linear combinations of isoforms are flows

Isoform deconvolution as convex cost flow problem

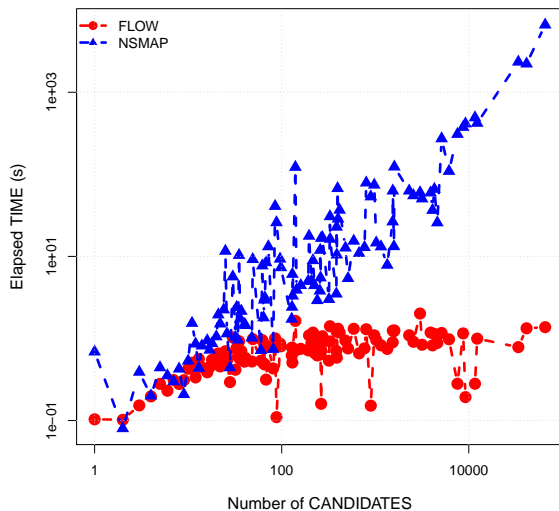


$$\min_{\phi \in \mathbb{R}_+^c} R(U^T \phi) + \lambda \|\phi\|_1$$

is equivalent to

$$\min_{f \text{ flow}} R(f) + \lambda f_t$$

Speed trial



Thanks!



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