Learning with structured sparsity in computational biology

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Normal vs cancer cells

What goes wrong?
How to treat?
Biology is now quantitative, "high-throughput"
"The $1,000 genome, the $1 million interpretation" (B. Kopf)

High-dimensional, heterogeneous, structured data. "Large \( p \)"

http://aws.amazon.com/1000genomes/
In this talk

\[
\min_w R(w) + \lambda \Omega(w)
\]

where:

- \( w \) is the hypothesis we want to infer from data
- \( R(w) \) is a smooth convex "fitness" function
- \( \Omega(w) \) is a non-smooth convex penalty, which favors particular solution

1. Mapping DNA breakpoints in cancer genomes
2. Isoform detection from RNA-seq data
3. Learning molecular classifiers with network information
Outline

1. Mapping DNA breakpoints in cancer genomes
2. Isoform detection from RNA-seq data
3. Learning molecular classifiers with network information
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 $10^6 \sim 10^9$
For a signal $Y \in \mathbb{R}^p$, define an optimal approximation $\beta \in \mathbb{R}^p$ with $k$ breakpoints as the solution of

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

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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Promoting sparsity with the $\ell_1$ penalty

The $\ell_1$ 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 $\beta$ 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)
Solving TV signal approximator

\[ \min_{\beta \in \mathbb{R}^p} \| Y - \beta \|_2^2 \quad \text{such that} \quad \sum_{i=1}^{p-1} |\beta_{i+1} - \beta_i| \leq \mu \]

- 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 s for \( p = 10^5 \) (Friedman et al., 2007)
- For all \( \mu \) with the LARS in \( O(pK) \) (Harchaoui and Levy-Leduc, 2008)
- For all \( \mu \) in \( O(p \ln p) \) (Hoefling, 2009)
- For the first \( K \) change-points in \( O(p \ln K) \) (Bleakley and V., 2010)
Problem formulation

Let \( Y = (Y_1, \ldots, Y_n) \in \mathbb{R}^n \) be a signal that we wish to approximate by a piecewise-constant signal \( \mu \). We consider the following formulation [2]:

\[
\min_{\mu} \frac{1}{2} \| Y - \mu \|^2 + \lambda \sum_{i=1}^n |\mu_{i+1} - \mu_i|
\]

for \( i = 1 \) to \( k \) do

3: \( P \leftarrow \text{arg max}_{I \in P} \gamma(I^*) \)

6: \( P \leftarrow P \setminus \{I^*\} \)

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

end for

8: return \( P \)

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: \( P = \{I_0\} \)
3: for \( i = 1 \) to \( k \) do
4: \( I^* \leftarrow \text{arg max}_{I \in P} \gamma(I^*) \)
5: \( P \leftarrow P \setminus \{I^*\} \)
6: \( P \leftarrow P \cup \{I_L(I^*), I_R(I^*)\} \)
7: end for
8: return \( P \)

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

TV signal approximator performs "greedy" dichotomomic segmentation

Apparently greedy algorithm finds the global optimum!
TV signal approximator as dichotomic segmentation

Problem formulation

Let \( Y = (Y_1, \ldots, Y_n) \in \mathbb{R}^n \) a signal that we wish to approximate by a piecewise-constant signal \( \mu \). For integer \( k \), perform the dichotomic segmentation method.

We will investigate different function approximators, in particular the TV signal approximator as dichotomic segmentation.

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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 \( \mathcal{P} \)

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

TV signal approximator performs "greedy" dichotomic segmentation

Apparently greedy algorithm finds the global optimum!
Speed trial: 2 s. for $K = 100, \ p = 10^7$
Extension: cancer prognosis

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:** this is convex optimization problem that can be solved very efficiently with proximal optimization methods (V. and Bleakley, 2012)
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Prognostic in melanoma (Rapaport et al., 2008)
Extension: finding multiple change points shared by several profiles
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Define the "optimal" piecewise constant approximation $\hat{U} \in \mathbb{R}^{p \times n}$ of $Y$ as the solution of

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

- DP finds the solution in $O(p^2 kn)$ in time and $O(p^2)$ in memory
- But: does not scale to $p = 10^6 \sim 10^9$...
Selecting pre-defined groups of variables

Group lasso (Yuan & Lin, 2006)

If groups of covariates are likely to be selected together, the $\ell_1/\ell_2$-norm induces sparse solutions \textit{at the group level}:

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

$$
\Omega(w_1, w_2, w_3) = \|(w_1, w_2)\|_2 + \|w_3\|_2
= \sqrt{w_1^2 + w_2^2} + \sqrt{w_3^2}
$$
GFLseg (Bleakley and V., 2011)

Replace

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

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?
GFLseg (Bleakley and V., 2011)

Replace

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

by

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

GFLseg = Group Fused Lasso segmentation

Questions

- Practice: can we solve it efficiently?
- Theory: does it recover the correct segmentation?
GFLseg as a group Lasso problem

- Make the change of variables:

\[ \gamma = U_{1,:}, \]
\[ \beta_{i,:} = w_i (U_{i+1,:} - U_{i,:}) \quad \text{for } i = 1, \ldots, p - 1. \]

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

\[
\min_{\beta \in \mathbb{R}^{(p-1) \times n}} \| \tilde{Y} - \tilde{X} \beta \|^2 + \lambda \sum_{i=1}^{p-1} \| \beta_{i,:} \|, 
\]

where \( \tilde{Y} \) is the centered signal matrix and \( \tilde{X} \) is a particular \((p - 1) \times (p - 1)\) design matrix.
TV approximator implementation

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

**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
Proof: computational tricks...

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

- For any \( R \in \mathbb{R}^{p \times n} \), we can compute \( C = \bar{X}^\top R \) in \( O(np) \) operations and memory.

- For any two subset of indices \( A = (a_1, \ldots, a_{|A|}) \) and \( B = (b_1, \ldots, b_{|B|}) \) in \([1, p - 1]\), we can compute \( \bar{X}_{\cdot, A}^\top \bar{X}_{\cdot, B} \) in \( O(|A||B|) \) in time and memory.

- For any \( A = (a_1, \ldots, a_{|A|}) \), set of distinct indices with \( 1 \leq a_1 < \ldots < a_{|A|} \leq p - 1 \), and for any \(|A| \times n\) matrix \( R \), we can compute \( C = \left( \bar{X}_{\cdot, A}^\top \bar{X}_{\cdot, A} \right)^{-1} R \) 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 $(\beta_i)_{i=1,\ldots,n}$ s.t. $\bar{\beta}^2 = \lim_{k \to \infty} \frac{1}{n} \sum_{i=1}^{n} \beta_i^2$
- corrupted by i.i.d. Gaussian noise of variance $\sigma^2$

Does the TV approximator correctly estimate the first change-point as $p$ increases?
Consistency of the unweighted TV approximator

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

**Theorem**

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

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

- correct estimation on \([p\epsilon, p(1 - \epsilon)]\) with \( \epsilon = \sqrt{\frac{\sigma^2}{2p\beta^2}} + o(p^{-1/2}) \).
- 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 \( n \to +\infty \).

- 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 $F_i = \| \hat{c}_{i,j} \|^2$, where

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

$\hat{c}$ is Gaussian, and $F_i$ is follows a non-central $\chi^2$ 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.
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 \( \{10, 20, \ldots, 90\} \) and the variance $\sigma^2$ 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
1. Mapping DNA breakpoints in cancer genomes

2. Isoform detection from RNA-seq data

3. Learning molecular classifiers with network information
Central dogma

DNA

transcription

RNA

translation

Protein
Alternative splicing: 1 gene = many proteins
The isoform identification and quantification problem

Given a biological sample (e.g., cancer tissue), can we:

1. identify the isoform(s) of each gene present in the sample?
2. quantify their abundance?
RNA-seq measures mRNA abundance by sequencing short fragments.
RNA-seq and alternative splicing

(Costa et al., 2011)
From RNA-seq to isoforms

**RNA sample**

**transcripts**

**reads**

50-200pb

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**Transcripts Quantification using annotations**

- RQuant (Bohnert et al. 2009)
- FluxCapacitor (Montgomery et al. 2010)
- IsoEM (Nicolae et al. 2011)
- eXpress (Roberts et al. 2013)

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**De Novo approaches**

- OASES (Schultz et al. 2012)
- Trinity (Grabherr et al. 2011)
- Kissplice (Sacomoto et al. 2012)

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**Genome-based Transcripts Reconstruction**

- Scripture (Guttman et al. 2010)
- Cufflinks (Trapnell et al. 2010)
- IsoLasso (Li et al. 2011a)
- NSMAP (Xia et al. 2011)
- SLIDE (Li et al. 2011b)
- iReckon (Mezlini et al. 2012)
- FlipFlop
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:

$$
\begin{pmatrix}
\text{exon}_1 & \cdots & \text{exon}_e & \text{junction}_{1,2} & \cdots & \text{junction}_{e_1,e}
\end{pmatrix}
$$

$$
\begin{pmatrix}
\text{isoform}_1 & \begin{pmatrix} 1 & \cdots & 1 & 1 & \cdots & 1 \end{pmatrix} \\
\text{isoform}_2 & \begin{pmatrix} 1 & \cdots & 0 & 1 & \cdots & 0 \end{pmatrix} \\
\vdots & \begin{pmatrix} \vdots & \cdots & \vdots & \cdots \end{pmatrix} \\
\text{isoform}_c & \begin{pmatrix} 0 & \cdots & 1 & 0 & \cdots & 0 \end{pmatrix}
\end{pmatrix}
$$

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

Goal: estimate $\phi$ from the observed reads on each exon/junction
Isoform deconvolution with the Lasso

Estimate $\phi$ 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

\[
\min_{\phi \in \mathbb{R}^c_+} R(U^\top \phi) + \lambda \| \phi \|_1
\]

is equivalent to

\[
\min_{f \text{ flow}} R(f) + \lambda f_t
\]
FlipFlop (Bernard, Jacob, Mairal and V., 2012)

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

- Cufflink: *a priori* selection of isoforms (minimum graph cover)
- IsoLasso: pre-filtering of candidate isoforms using various heuristics
- NSMAP, SLIDE: limit the maximum number of exons
- FlipFlop: exact optimization without pre-filtering in polynomial time
Simulated data (hg19, 1137 genes on chr1, 1 million 75 bp single-end reads by transcript levels).
Speed trial

![Graph showing elapsed time vs. number of exons for different tools: Flipflop, NSMAP, IsoLasso, Cufflinks, FlipFlop, NSMAP, SLIDE. The graph is divided into four categories: 2–5 exons, 5–10 exons, 10–20 exons, and 20–116 exons. The y-axis represents CPU time (ms) by gene, and the x-axis represents the number of exons. The graph shows a comparison of tool performance across different exon counts.]
Outline

1. Mapping DNA breakpoints in cancer genomes
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The idea

- We look for a **limited set** of genes that are sufficient for prediction.
- Selected genes should inform us about the underlying biology.
Lack of stability of signatures

Haury et al. (2011)
Gene networks, gene groups

Glycolysis / Gluconeogenesis

N-Glycan biosynthesis

Protein kinases

DNA and RNA polymerase subunits

Glycogen metabolism

Sulfur metabolism

Riboflavin metabolism

Folate biosynthesis

Biosynthesis of steroids, ergosterol metabolism

Lysine biosynthesis

Phenylalanine, tyrosine and tryptophan biosynthesis

Purine metabolism

Oxidative phosphorylation, TCA cycle

DNA and RNA polymerase subunits

Nitrogen, asparagine metabolism

Protein kinases

Porphyrin and chlorophyll metabolism

Muscle cell differentiation

Cell cycle

Focal adhesion

IGF, ...

JP Vert (ParisTech)
Structured feature selection

- Basic biological functions usually involve the coordinated action of several proteins:
  - Formation of protein complexes
  - Activation of metabolic, signalling or regulatory pathways
- How to perform structured feature selection, such that selected genes
  - belong to only a few groups?
  - form a small number of connected components on the graph?
Selecting pre-defined groups of variables

Group lasso (Yuan & Lin, 2006)

If groups of covariates are likely to be selected together, the $\ell_1/\ell_2$-norm induces sparse solutions at the group level:

$$\Omega_{\text{group}}(\mathbf{w}) = \sum_{g} \| w_g \|_2$$

$$\Omega(w_1, w_2, w_3) = \| (w_1, w_2) \|_2 + \| w_3 \|_2$$
Group lasso with overlapping groups

Idea 1: shrink groups to zero (Jenatton et al., 2009)

- \( \Omega_{\text{group}}(w) = \sum_g \| w_g \|_2 \) sets groups to 0.
- One variable is selected \( \iff \) all the groups to which it belongs are selected.

IGF selection \( \Rightarrow \) selection of unwanted groups

Removal of any group containing a gene \( \Rightarrow \) the weight of the gene is 0.
Group lasso with overlapping groups

Idea 2: latent group Lasso (Jacob et al., 2009)

\[ \Omega^G_{\text{latent}}(w) \triangleq \min_v \sum_{g \in G} \| v_g \|_2 \]
\[ w = \sum_{g \in G} v_g \]
\[ \text{supp}(v_g) \subseteq g. \]

Properties

- Resulting support is a *union* of groups in \( G \).
- Possible to select one variable without selecting all the groups containing it.
- Equivalent to group lasso when there is no overlap.
Overlap and group unity balls

Balls for $\Omega^G_{\text{group}}(\cdot)$ (middle) and $\Omega^G_{\text{latent}}(\cdot)$ (right) for the groups $G = \{\{1, 2\}, \{2, 3\}\}$ where $w_2$ is represented as the vertical coordinate. Left: group-lasso ($G = \{\{1, 2\}, \{3\}\}$), for comparison.
Theoretical results

Consistency in group support (Jacob et al., 2009)

- Let $\tilde{w}$ be the true parameter vector.
- Assume that there exists a unique decomposition $\tilde{v}_g$ such that $\tilde{w} = \sum_g \tilde{v}_g$ and $\Omega^G_{\text{latent}}(\tilde{w}) = \sum \|\tilde{v}_g\|_2$.
- Consider the regularized empirical risk minimization problem $L(w) + \lambda \Omega^G_{\text{latent}}(w)$.

Then
- under appropriate mutual incoherence conditions on $X$,
- as $n \to \infty$,
- with very high probability,
the optimal solution $\hat{w}$ admits a unique decomposition $(\hat{v}_g)_{g \in G}$ such that
$$\{g \in G| \hat{v}_g \neq 0\} = \{g \in G| \tilde{v}_g \neq 0\}.$$
Theoretical results

Consistency in group support (Jacob et al., 2009)

Let \( \bar{w} \) be the true parameter vector.

Assume that there exists a unique decomposition \( \bar{v}_g \) such that
\[
\bar{w} = \sum_g \bar{v}_g \text{ and } \Omega_{\text{latent}}^G (\bar{w}) = \sum \|\bar{v}_g\|_2.
\]

Consider the regularized empirical risk minimization problem
\[
L(w) + \lambda \Omega_{\text{latent}}^G (w).
\]

Then

under appropriate mutual incoherence conditions on \( X \),

as \( n \to \infty \),

with very high probability,

the optimal solution \( \hat{w} \) admits a unique decomposition \( (\hat{v}_g)_{g \in G} \) such that
\[
\{ g \in G \mid \hat{v}_g \neq 0 \} = \{ g \in G \mid \bar{v}_g \neq 0 \}.
\]
Experiments

Synthetic data: overlapping groups

- 10 groups of 10 variables with 2 variables of overlap between two successive groups: \{1, \ldots, 10\}, \{9, \ldots, 18\}, \ldots, \{73, \ldots, 82\}.
- Support: union of 4th and 5th groups.
- Learn from 100 training points.

Frequency of selection of each variable with the lasso (left) and $\Omega^G_{\text{latent}} (\cdot)$ (middle), comparison of the RMSE of both methods (right).
Graph lasso

Two solutions

$$\Omega^g_{\text{group}}(\beta) = \sum_{i \sim j} \sqrt{\beta_i^2 + \beta_j^2},$$

$$\Omega^g_{\text{latent}}(\beta) = \sup_{\alpha \in \mathbb{R}^p: \forall i \sim j, \|\alpha_i^2 + \alpha_j^2\| \leq 1} \alpha^T \beta.$$
Preliminary results

Breast cancer data

- Gene expression data for 8,141 genes in 295 breast cancer tumors.
- Canonical pathways from MSigDB containing 639 groups of genes, 637 of which involve genes from our study.

<table>
<thead>
<tr>
<th>Method</th>
<th>$\ell_1$</th>
<th>$\Omega_{\text{LATENT}}(\cdot)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Error</td>
<td>0.38 ± 0.04</td>
<td>0.36 ± 0.03</td>
</tr>
<tr>
<td>Mean # Path.</td>
<td>130</td>
<td>30</td>
</tr>
</tbody>
</table>

- Graph on the genes.

<table>
<thead>
<tr>
<th>Method</th>
<th>$\ell_1$</th>
<th>$\Omega_{\text{graph}}(\cdot)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Error</td>
<td>0.39 ± 0.04</td>
<td>0.36 ± 0.01</td>
</tr>
<tr>
<td>Av. Size C.C.</td>
<td>1.03</td>
<td>1.30</td>
</tr>
</tbody>
</table>
Conclusions

- Convex sparsity-inducing penalties as a way to incorporate prior knowledge
- Specific implementations for specific problems:
  - greedy dichotomic segmentation for fused lasso
  - fast group Lasso for joint segmentation
  - network flow optimization of lasso over the paths of a graph
  - efficient proximity operator computation of latent group lasso
- Often, feature selection is consistent (although we pay a price when features are very correlated), stability selection may help
- Numerous applications in bioinformatics and beyond!
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