On feature selection and pattern detection in high dimension

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Mines ParisTech / Curie Institute / Inserm

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Outline

1. Motivations
2. Feature selection
3. Issues in gene selection from expression data
4. Issues in gene network inference
5. Finding multiple change-points in a single profile
6. Finding multiple change-points shared by many signals
7. Supervised classification of genomic profiles
8. Learning molecular classifiers with network information
9. Conclusion
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Chromosomal aberrations in cancer

[Diagram of a cell and chromosome structure]

[Image of a karyotype with labeled chromosomes]
Comparative Genomic Hybridization (CGH)

Jain et al. Genome research 2002 12:325-332
Can we detect frequent breakpoints?

A collection of bladder tumour copy number profiles.
Can we detect discriminative patterns?

Aggressive (left) vs non-aggressive (right) melanoma.
DNA $\rightarrow$ RNA $\rightarrow$ protein

- CGH shows the (static) DNA
- Cancer cells have also abnormal (dynamic) gene expression (= transcription)
Tissue profiling with DNA chips

Data

- Gene expression measures for more than 10k genes
- Measured typically on less than 100 samples of two (or more) different classes (e.g., different tumors)
**Tissue classification from microarray data**

**Goal**
- Design a **classifier** to automatically assign a class to future samples from their expression profile
- **Interpret** biologically the differences between the classes

**Difficulty**
- Large dimension
- Few samples

---

**Feature selection**

### B

- C-myb (U22376)
- Proteasome iota (X59417)
- MB-1 (U005259)
- Cyclin D3 (M92287)
- Myosin light chain (M31211)
- RbAp48 (X74262)
- SNF2 (D25456)
- HkRt-1 (S50223)
- E2A (M31523)
- Inducible protein (L77738)
- Dynactin light chain (U32944)
- Topoisomerase II (Z15115)
- IRF2 (X15549)
- TFIEF (X63469)
- Acyl-Coenzyme A dehydrogenase (M91432)
- SNF2 (U29715)
- C2-ATPase (Z69881)
- SRP9 (U20998)
- MCM3 (D38073)
- Deoxyhypusine synthase (U26266)
- Op (H331303)
- Rabaptin-5 (Y08012)
- Heterochromatin protein 2 (U35451)
- IL-7 receptor (M29696)
- Adenosine deaminase (M13792)

### ALL

- Fumarase (M55150)
- Zyxin (X95735)
- LTC4 synthase (U50136)
- LYN (M16038)
- HoxA9 (U82759)
- CD13 (M21917)
- Adipin (M84526)
- Leptin receptor (Y12670)
- Cystatin C (M27801)
- Protocollin-1 (X17092)
- IL-8 precursor (Y00787)
- Azurocidin (M96326)
- g62 (U34675)
- CyP3 (M80254)
- MCL1 (L08246)
- ATPase (M62762)
- IL-8 (M28130)
- Cathernin D (M63138)
- Lecin (M57710)
- MAD-3 (M69043)
- CD11c (M81695)
- Ehp72 (X83116)
- Lysozyme (M19045)
- Propedrin (M83652)
- Catalase (X04085)
Can we detect predictive molecular signatures?

A. Gene-Expression Profiling

B. St. Gallen Criteria

P<0.001

Years

0 2 4 6 8 10 12

0.0 0.2 0.4 0.6 0.8 1.0

P=0.05

Years

0 2 4 6 8 10 12

0.0 0.2 0.4 0.6 0.8 1.0

J.P Vert (ParisTech)
Gene expression regulation

- gene regulatory sequences
- spacer DNA
- gene regulatory proteins
- general transcription factors
- RNA polymerase
- TATA box
- upstream
- promoter
- start of transcription
Gene regulatory network
Can we reconstruct the GRN from expression data?
Many problems...

Classification accuracy is not all, interpretation is necessary

Common topic: detect predictive variables / patterns

Need for efficient and scalable algorithms
Classification and regression

**Input**
- $\mathcal{X}$ the space of patterns (typically, $\mathcal{X} = \mathbb{R}^p$)
- $\mathcal{Y}$ the space of response or labels
  - Classification or pattern recognition: $\mathcal{Y} = \{-1, 1\}$
  - Regression: $\mathcal{Y} = \mathbb{R}$
- $S = \{(x_1, y_1), \ldots, (x_n, y_n)\}$ a training set in $(\mathcal{X} \times \mathcal{Y})^n$

**Output**
- A function $f : \mathcal{X} \rightarrow \mathcal{Y}$ to predict the output associated to any new pattern $x \in \mathcal{X}$ by $f(x)$
Estimate a function $f(x)$ that only depends on a subset $S \subset [1, p]$ of the variables.

**Why?**

- **Statistics**: a way to control the complexity of the search space, can improve accuracy by reducing the estimation error. Especially relevant in high dimension, and if we believe that there exist good sparse models.

- **Interpretation**: the selected variables in $S$ are interesting to understand the physical/biological structure of the problem, and suggest further investigations.

- **Practical**: a small set $S$ can lead to cheap implementations of the predictor, e.g., dedicated chips for prognosis.
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- **Practical**: a small set $S$ can lead to cheap implementations of the predictor, e.g., dedicated chips for prognosis.
In best subset selection, we must solve the problem:

$$\min R(f_\beta) \quad \text{s.t.} \quad \| \beta \|_0 \leq k$$

for $k = 1, \ldots, p$, and $R$ is an empirical risk.

The state-of-the-art is branch-and-bound optimization, known as *leaps and bound* for least squares (Furnival and Wilson, 1974).

This is usually a NP-hard problem, feasible for $p$ as large as 30 or 40.
To work with more variables, we must use different methods. The state-of-the-art is split among

1. **Filter methods**: the predictors are preprocessed and ranked from the most relevant to the less relevant. The subsets are then obtained from this list, starting from the top.

2. **Wrapper method**: here the feature selection is iterative, and uses a learning algorithm in the inner loop

3. **Embedded methods**: here the feature selection is part of the learning algorithm itself

Additionally, **ensemble feature learning** has been proposed as a useful meta-method for feature selection.
Filter methods

- Associate a score $S(i)$ to each feature $i$, then rank the features by decreasing score.

- Many scores / criteria can be used
  - Loss of the ERM trained on a single feature
  - Statistical tests (Fisher, T-test)
  - Other performance criteria of the ERM restricted to a single feature (AUC, ...)
  - Information theoretical criteria (mutual information...)

Pros

Simple, scalable, good empirical success

Cons

- Selection of redundant features
- Some variables useless alone can become useful together
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Wrapper methods

The idea

- A greedy approach to

\[
\min R^n(f_\beta) \quad \text{s.t.} \quad \| \beta \|_0 \leq k
\]

- For a given set of selected features, we know how to minimize \( R^n(f) \)

- We iteratively try to find a good set of features, by adding/removing features which contribute most to decrease the risk (using ERM as an internal loop)
Two flavors of wrapper methods

Forward stepwise selection
- Start from no features
- Sequentially add into the model the feature that most improves the fit

Backward stepwise selection (if \( n > p \))
- Start from all features
- Sequentially removes from the model the feature that least degrades the fit

Other variants
Hybrid stepwise selection strategies that consider both forward and backward moves at each stage, and make the "best" move
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Embedded methods

- Decision trees
- Sparsity-inducing convex penalties, e.g.

\[
\min R(f_\beta) \quad \text{s.t.} \quad \| \beta \|_1 \leq k
\]
Ensemble feature selection

1. For $t = 1, \ldots, T$, randomly subsample samples and/or variables
2. For each $t$, select a subset of variables $S_t$
3. Aggregate all $S_t$ to obtain the final list of variables

Examples:
- Random forests
- Stability selection
Ensemble feature selection

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Examples:
- Random forests
- Stability selection
A well-studied problem, with many solutions that vary in computational complexity and theoretical guarantees

Feature selection in the "small n large p" setting has been studied a lot recently, mostly for embedded methods (lasso...) and largely motivated by applications in biology

Ensemble feature selection has been put forward recently (stability selection, bolasso...), but limited theoretical results and validations

The theoretical validity of different methods on real data is often hard to check
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Prognostic molecular signatures

A Gene-Expression Profiling

B St. Gallen Criteria

Probability of Remaining Metastasis-free

Years

Years

NO. AT RISK
Good signature 91 72 55 41 26 17 9 5 2
Poor signature 50 57 54 45 31 22 12
NO. AT RISK
Low risk 22 22 21 17 9 5 2
High risk 120 107 68 60 48 34 19

P<0.001

P=0.05
Prognostic molecular signatures

Gene expression profiling predicts clinical outcome of breast cancer

Laura J. van 't Veer†, Hengyue Dai†, Marc J. van de Vijver†, Yudong D. He†, Augustinus A. M. Hart†, Mao Mao†, Hans L. Peterse*, Karin van der Kooy†, Matthew J. Marton‡, Anko T. Witteveen‡, George J. Schreiber‡, Ron M. Kerkhoven‡, Chris Roberts‡, Peter S. Linsley‡, René Bernards‡ & Stephen H. Friend‡.

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Gene-expression profiles to predict distant metastasis of lymph-node-negative primary breast cancer

Yixin Wang, Jan G M Klijn, Yi Zhang, Aniera M Sleuwer, Maxime P Look, Fei Yang, Dmitri Taltyov, Mieke Timmermans, Marion E Meijer-van Gelder, Jack Yu, Tim Jatkoe, Ets M J J Berns, David Atkins, John A Foekens

- Two signatures in clinical trial for breast cancer (70 and 76 genes)
- Only 3 genes in common... Why?
  - Different cohorts of patients?
  - Different technologies and experimental protocols?
  - Different algorithm for feature selection?
  - Other?
Unstability of molecular signatures

- Wang dataset: $n = 286, \ p = 8141$
- Pearson correlation with the output on 2 random subsamples of 143 samples:
Comparison of feature selection methods

Haury et al. (2011)
Lessons learned...

- Difficult problem!
- Unstability mostly due to statistical issues
- Filter methods (t-test) current method of choice
- Ensemble feature selection not really useful
The problem

Predict the GRN from a matrix $X \in \mathbb{R}^{n \times p}$ of expression data.
Predict regulations between "dependent" genes

If $A$ regulates $B$, we expect their expressions to be dependent across experiments.

Detect the dependency by various measures, e.g., Euclidean distance, correlation, mutual information...
Validation

Application: E coli regulatory network: 154 TF targeting 1164 genes through 3293 regulations
The dynamic equation of the mRNA concentration of a gene is of the form:

\[ \frac{dX}{dt} = f(X, R) \]

where \( R \) represent the set of concentrations of transcription factors that regulate \( X \).

At steady state, \( \frac{dX}{dt} = 0 = f(X, R) \)

If we linearize \( f(X, R) = 0 \) we get linear relation of the form

\[ X = \sum_{i \in R} \beta_i X_i \]

This suggests to look for transcription factors whose expression is sufficient to explain the expression of \( X \) across different experiments.
RF (Huynh-Thu et al., 2010) and Lasso+stability selection (Haury et al., 2011) ranked 1st and 2nd at the 2010 DREAM5 in silico network inference challenge
Lessons learned...

- Again, very difficult problem! (recall around 10% in the best case...)
- State-of-the-art express GRN network as feature selection (perhaps not the best idea?)
- Ensemble feature selection seems to work best
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Let $Y \in \mathbb{R}^p$ the signal

We want to find a piecewise constant approximation $\hat{U} \in \mathbb{R}^p$ with at most $k$ change-points.
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We can define an "optimal" piecewise constant approximation $\hat{U} \in \mathbb{R}^p$ as the solution of

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

This is an optimization problem over the $\binom{p}{k}$ partitions...

Dynamic programming finds the solution in $O(p^2k)$ in time and $O(p^2)$ in memory.

But: does not scale to $p = 10^6 \sim 10^9$...
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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 $p = 2$
Efficiency computation of the regularization path

\[
\min_{\beta \in \mathbb{R}^p} \| Y - X\beta \|^2 + \lambda \sum_{i=1}^{p} |\beta_i |
\]  

1. No explicit solution, but this is just a **quadratic program**.
2. **LARS** (Efron et al., 2004) provides a fast algorithm to compute the solution for all \(\lambda\)'s simultaneously (regularization path).
Promoting piecewise constant profiles penalty

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

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

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

- 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)
Greedy dichotomic segmentation

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

1: \( I_0 \) represents the interval \([1, p]\)
2: \( P = \{ I_0 \} \)
3: **for** \( i = 1 \) to \( k \) **do**
4: \( l^* \leftarrow \operatorname{arg\,max}_{l \in P} \gamma(l^*) \)
5: \( P \leftarrow P \setminus \{ l^* \} \)
6: \( P \leftarrow P \cup \{ I_L(l^*), I_R(l^*) \} \)
7: **end for**
8: **return** \( P \)
From greedy segmentation to TV approximator

**Theorem**

*TV approximator is a greedy dichotomic segmentation.*

**Consequences:**

- Good: very fast methods for TV approximator
- Good: we can analyze this greedy method by expressing the solution as the global minimum of an objective function
- Bad: TV approximator is no more than a greedy method...
From greedy segmentation to TV approximator

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Technical details

- Represent an interval $[u + 1, v]$ by a quadruplet $I = (u, v, \sigma_u, \sigma_v)$ where $\sigma_u, \sigma_v \in \{-1, 0, 1\}$
- Let $F_u = \sum_{i=1}^{u} Y_u$, and for $u < k < v$, $\sigma \in \{-1, 1\}$

$$f_I(k, \sigma) = \begin{cases} 
\sigma A_k / 2 & \text{if } \sigma_u = \sigma_v \neq 0, \\
A_k / (\sigma - B_k) & \text{otherwise},
\end{cases}$$

where

$$A_k = -F_k + \frac{(v - k) F_u + (k - u) F_v}{v - u},$$
$$B_k = \frac{(v - k) \sigma_u + (k - u) \sigma_v}{v - u}.$$
Then the functions $\gamma(I)$, $I_L(I)$ and $I_R(I)$ are respectively given by:

$$
\gamma(I) = \max_{k \in [u+1, v-1], \sigma \in \{-1, 1\}} f_l(k, \sigma),
$$

$$(k^*, \sigma^*) = \arg\max_{k \in [u+1, v-1], \sigma \in \{-1, 1\}} f_l(k, \sigma),$$

$$I_L(I) = (u, k^*, \sigma_u, \sigma^*)$$

$$I_R(I) = (k^*, v, \sigma^*, \sigma_v).$$
Homotopy method (LARS)

Similar to Harchaoui and Levy-Leduc (2008), removing superfluous computations

The next breakpoint in a segment, and the $\mu$ where it appears, is independent of events in other segments
Speed trial: 2 s. for $K = 100, p = 10^7$
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Let $Y \in \mathbb{R}^{p \times n}$ the $n$ signals of length $p$

We want to find a piecewise constant approximation $\hat{U} \in \mathbb{R}^{p \times n}$ with at most $k$ change-points.
"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

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

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}:

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

$$\Omega(w_1, w_2, w_3) = \|(w_1, w_2)\|_2 + \|w_3\|_2$$

$$= \sqrt{w_1^2 + w_2^2} + \sqrt{w_3^2}$$
TV approximator for many signals

- Replace

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

by

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

Questions

- Practice: can we solve it efficiently?
- Theory: does it benefit from increasing \( p \) (for \( n \) fixed)?
TV approximator as a group Lasso problem

Make the change of variables:

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

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

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

where \( \bar{Y} \) is the centered signal matrix and \( \bar{X} \) is a particular \( (p - 1) \times (p - 1) \) design matrix.
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 $\bar{X}_{\bullet,A} \bar{X}_{\bullet,B}$ 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 $C = \left(\bar{X}_{\bullet,A} \bar{X}_{\bullet,A}\right)^{-1} R$ in $O(|A|n)$ in time and memory.
Consistency for a single change-point

Suppose a single change-point:

- at position $u = \alpha p$
- with increments $(\beta_i)_{i=1,...,n}$ 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

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

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

\[ w_i = \sqrt{\frac{i(p - i)}{p}} \]

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 $F_i = \| \hat{c}_{i,*} \|^2$, 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

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

We then just check when $G_u = \max_i G_i$
Consistent estimation of more change-points?

\[ p = 100, \ k = 10, \ \bar{\beta}^2 = 1, \ \sigma^2 \in \{0.05; 0.2; 1\} \]
Motivations

Feature selection

Issues in gene selection from expression data

Issues in gene network inference

Finding multiple change-points in a single profile

Finding multiple change-points shared by many signals

Supervised classification of genomic profiles

Learning molecular classifiers with network information

Conclusion
The problem

- $x_1, \ldots, x_n \in \mathbb{R}^p$ the $n$ profiles of length $p$
- $y_1, \ldots, y_n \in [-1, 1]$ the labels
- We want to learn a function $f : \mathbb{R}^p \rightarrow [-1, 1]$
Prior knowledge

- **Sparsity**: not all positions should be discriminative, and we want to identify the predictive region (presence of oncogenes or tumor suppressor genes?)
- **Piecewise constant**: within a selected region, all probes should contribute equally
Fused Lasso signal approximator (Tibshirani et al., 2005)

\[
\min_{\beta \in \mathbb{R}^p} \sum_{i=1}^{p} (y_i - \beta_i)^2 + \lambda_1 \sum_{i=1}^{p} |\beta_i| + \lambda_2 \sum_{i=1}^{p-1} |\beta_{i+1} - \beta_i|.
\]

- First term leads to **sparse** solutions
- Second term leads to **piecewise constant** solutions
Fused lasso for supervised classification (Rapaport et al., 2008)

\[
\min_{\beta \in \mathbb{R}^p} \sum_{i=1}^{n} \ell \left( y_i, \beta^\top x_i \right) + \lambda_1 \sum_{i=1}^{p} |\beta_i| + \lambda_2 \sum_{i=1}^{p-1} |\beta_{i+1} - \beta_i|.
\]

where \( \ell \) is, e.g., the hinge loss \( \ell(y, t) = \max(1 - yt, 0) \).

Implementation

- When \( \ell \) is the hinge loss (fused SVM), this is a linear program \( \rightarrow \) up to \( p = 10^3 \sim 10^4 \)
- When \( \ell \) is convex and smooth (logistic, quadratic), efficient implementation with proximal methods \( \rightarrow \) up to \( p = 10^8 \sim 10^9 \)
Fused lasso for supervised classification (Rapaport et al., 2008)

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**Implementation**

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- When \(\ell\) is convex and smooth (logistic, quadratic), efficient implementation with proximal methods -> up to \(p = 10^8 \sim 10^9\)
Example: predicting metastasis in melanoma
Molecular diagnosis / prognosis / theragnosis

Feature selection
Gene networks

- **Glycolysis / Gluconeogenesis**
- **Porphyrin and chlorophyll metabolism**
- **Sulfur metabolism**
- **Riboflavin metabolism**
- **Folate biosynthesis**
- **Biosynthesis of steroids, ergosterol metabolism**
- **Lysine biosynthesis**
- **Phenylalanine, tyrosine and tryptophan biosynthesis**
- **Purine metabolism**
- **N Glycan biosynthesis**
- **Protein kinases**
- **Nitrogen, asparagine metabolism**
- **DNA and RNA polymerase subunits**
- **Oxidative phosphorylation, TCA cycle**
- **Porphyrin and chlorophyll metabolism**
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- **DNA and RNA polymerase subunits**
- **Oxidative phosphorylation, TCA cycle**

J.P Vert (ParisTech)
Gene networks and expression data

Motivation

- Basic biological functions usually involve the **coordinated action of several proteins**:
  - Formation of **protein complexes**
  - Activation of metabolic, signalling or regulatory **pathways**
- Many pathways and protein-protein interactions are **already known**
- **Hypothesis**: the weights of the classifier should be “coherent” with respect to this **prior knowledge**
Graph-based penalty

\[ \min_{\beta} R(\beta) + \lambda \Omega_G(\beta) \]

**Hypothesis**

We would like to design penalties \( \Omega_G(\beta) \) to promote one of the following hypothesis:

- **Hypothesis 1**: genes near each other on the graph should have similar weights (but we do not try to select only a few genes), i.e., the classifier should be smooth on the graph.

- **Hypothesis 2**: genes selected in the signature should be connected to each other, or be in a few known functional groups, without necessarily having similar weights.
Graph based penalty

Prior hypothesis
Genes near each other on the graph should have similar weights.

An idea (Rapaport et al., 2007)

\[ \Omega_{\text{spectral}}(\beta) = \sum_{i \sim j} (\beta_i - \beta_j)^2, \]

\[ \min_{\beta \in \mathbb{R}^p} R(\beta) + \lambda \sum_{i \sim j} (\beta_i - \beta_j)^2. \]
Graph based penalty

Prior hypothesis
Genes near each other on the graph should have similar weights.

An idea (Rapaport et al., 2007)

\[
\Omega_{\text{spectral}}(\beta) = \sum_{i \sim j} (\beta_i - \beta_j)^2 ,
\]

\[
\min_{\beta \in \mathbb{R}^p} R(\beta) + \lambda \sum_{i \sim j} (\beta_i - \beta_j)^2 .
\]
The Laplacian of the graph is the matrix \( L = D - A \).

\[
L = D - A = \begin{pmatrix}
1 & 0 & -1 & 0 & 0 \\
0 & 1 & -1 & 0 & 0 \\
-1 & -1 & 3 & -1 & 0 \\
0 & 0 & -1 & 2 & -1 \\
0 & 0 & 0 & 1 & 1 \\
\end{pmatrix}
\]
Theorem

The function \( f(x) = \beta^T x \) where \( \beta \) is solution of

\[
\min_{\beta \in \mathbb{R}^p} \frac{1}{n} \sum_{i=1}^{n} l \left( \beta^T x_i, y_i \right) + \lambda \sum_{i \sim j} (\beta_i - \beta_j)^2
\]

is equal to \( g(x) = \gamma^T \Phi(x) \) where \( \gamma \) is solution of

\[
\min_{\gamma \in \mathbb{R}^p} \frac{1}{n} \sum_{i=1}^{n} l \left( \gamma^T \Phi(x_i), y_i \right) + \lambda \gamma^T \gamma,
\]

and where

\[
\Phi(x)^T \Phi(x') = x^T K_G x'
\]

for \( K_G = L^* \), the pseudo-inverse of the graph Laplacian.
Rapaport et al.

Glycan biosynthesis
Protein kinases
DNA and RNA polymerase subunits

Glycolysis / Gluconeogenesis
Porphyrin and chlorophyll metabolism
Riboflavin metabolism
Folate biosynthesis
Biosynthesis of steroids, ergosterol metabolism
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N Glycan biosynthesis
Nitrogen, asparagine metabolism
DNA and RNA polymerase subunits
Oxidative phosphorylation, TCA cycle
Purine metabolism
Spectral analysis of gene expression profiles using gene networks

Fig. 5. ... work was supported by the grant ACI-IMPBIO-2004-47
Other penalties with kernels

\[
\Phi(x)^\top \Phi(x') = x^\top K_G x'
\]

with:

- \( K_G = (c + L)^{-1} \) leads to

\[
\Omega(\beta) = c \sum_{i=1}^{p} \beta_i^2 + \sum_{i \sim j} (\beta_i - \beta_j)^2 .
\]

- The diffusion kernel:

\[
K_G = \exp_M(-2tL) .
\]

penalizes high frequencies of \( \beta \) in the Fourier domain.
Other penalties without kernels

- Gene selection + Piecewise constant on the graph

\[ \Omega(\beta) = \sum_{i \sim j} |\beta_i - \beta_j| + \sum_{i=1}^{p} |\beta_i| \]

- Gene selection + smooth on the graph

\[ \Omega(\beta) = \sum_{i \sim j} (\beta_i - \beta_j)^2 + \sum_{i=1}^{p} |\beta_i| \]
How to select jointly genes belonging to predefined pathways?

J.P. Vert (ParisTech)

Feature selection

Paris 7 Point de vue 86 / 100
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}:

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

$$\Omega(w_1, w_2, w_3) = \|(w_1, w_2)\|_2 + \|w_3\|_2$$
What if a gene belongs to several groups?

**Issue of using the group-lasso**

- $\Omega_{\text{group}}(w) = \sum_g \| w_g \|_2$ 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.
Overlap norm (Jacob et al., 2009)

An idea
Introduce latent variables $v_g$:

$$\begin{aligned}
\min_{w,v} & \quad L(w) + \lambda \sum_{g \in G} \|v_g\|_2 \\
\text{s.t.} & \quad w = \sum_{g \in G} v_g \\
& \quad \text{supp}(v_g) \subseteq g.
\end{aligned}$$

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.
A new norm

Overlap norm

\[
\begin{align*}
\min_{w,v} & \quad L(w) + \lambda \sum_{g \in G} \| v_g \|_2 \\
= & \quad \min_{w} L(w) + \lambda \Omega_{\text{overlap}}(w)
\end{align*}
\]

with

\[
\Omega_{\text{overlap}}(w) \triangleq \min_v \sum_{g \in G} \| v_g \|_2 \\
= \sum_{g \in G} v_g \\
\text{supp} (v_g) \subseteq g.
\]

Property

- \(\Omega_{\text{overlap}}(w)\) is a norm of \(w\).
- \(\Omega_{\text{overlap}}(.)\) associates to \(w\) a specific (not necessarily unique) decomposition \((v_g)_{g \in G}\) which is the argmin of (*)
Overlap and group unity balls

Balls for $\Omega_{\text{group}}^G (\cdot)$ (middle) and $\Omega_{\text{overlap}}^G (\cdot)$ (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 $\bar{w}$ be the true parameter vector.
- Assume that there exists a unique decomposition $\bar{v}_g$ such that $\bar{w} = \sum_g \bar{v}_g$ and $\Omega^G_{\text{overlap}}(\bar{w}) = \sum \|\bar{v}_g\|_2$.
- Consider the regularized empirical risk minimization problem $L(w) + \lambda \Omega^G_{\text{overlap}}(w)$.

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

$$\{g \in G | \hat{v}_g \neq 0\} = \{g \in G | \bar{v}_g \neq 0\}.$$
Theoretical results

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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 4\textsuperscript{th} and 5\textsuperscript{th} groups.
- Learn from 100 training points.

Frequency of selection of each variable with the lasso (left) and \(\Omega_{\text{overlap}}^G\) (middle), comparison of the RMSE of both methods (right).
Graph lasso

Two solutions

\[ \Omega_{\text{intersection}}(\beta) = \sum_{i \sim j} \sqrt{\beta_i^2 + \beta_j^2}, \]

\[ \Omega_{\text{union}}(\beta) = \sup_{\alpha \in \mathbb{R}^p : \forall i \sim j, \|\alpha_i^2 + \alpha_j^2\| \leq 1} \alpha^T \beta. \]
Graph lasso vs kernel on graph

**Graph lasso:**

$$\Omega_{\text{graph lasso}}(w) = \sum_{i \sim j} \sqrt{w_i^2 + w_j^2}.$$  

This constrains the **sparsity**, not the values.

**Graph kernel**

$$\Omega_{\text{graph kernel}}(w) = \sum_{i \sim j} (w_i - w_j)^2.$$  

This constrains the values (**smoothness**), not the sparsity.
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>$\Omega_{\text{OVERLAP}}(\cdot)$</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>
Outline

1. Motivations
2. Feature selection
3. Issues in gene selection from expression data
4. Issues in gene network inference
5. Finding multiple change-points in a single profile
6. Finding multiple change-points shared by many signals
7. Supervised classification of genomic profiles
8. Learning molecular classifiers with network information
9. Conclusion
Feature / pattern selection in high dimension is central for many applications

People excited about embedded methods (convex optimization), ensemble methods... but many disappointing results when tested on real data
  - Filter methods not so bad
  - Ensemble learning useful?

Need for more theory to explain practical observations, suggest new methods

Structured sparsity / pattern discovery is a promising direction

Need to adjust the difficulty of the inference problem to the data available