Including prior knowledge in machine learning for genomic data

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Mines ParisTech / Curie Institute / Inserm

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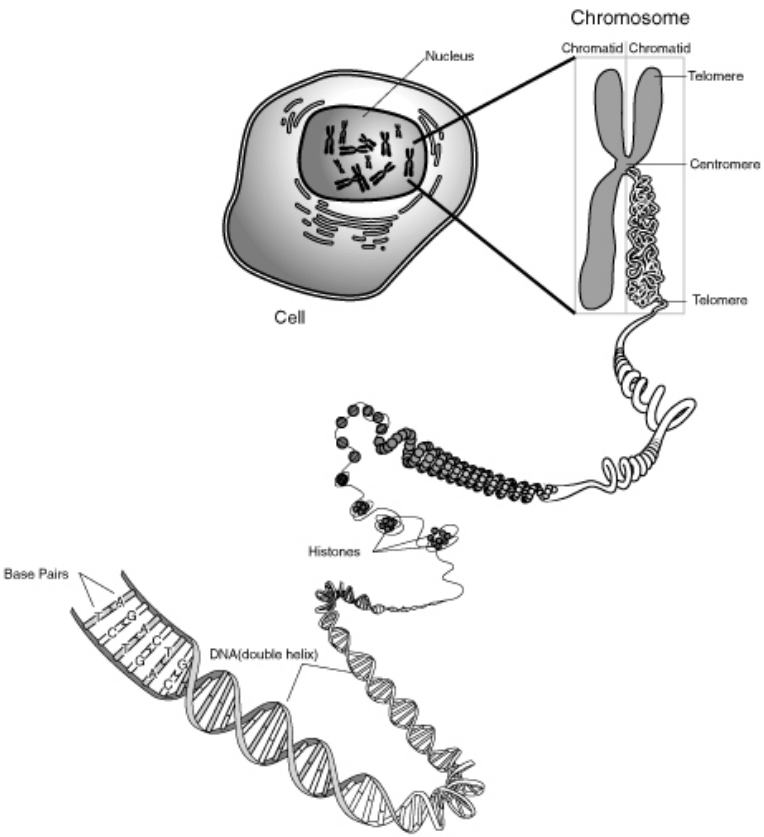
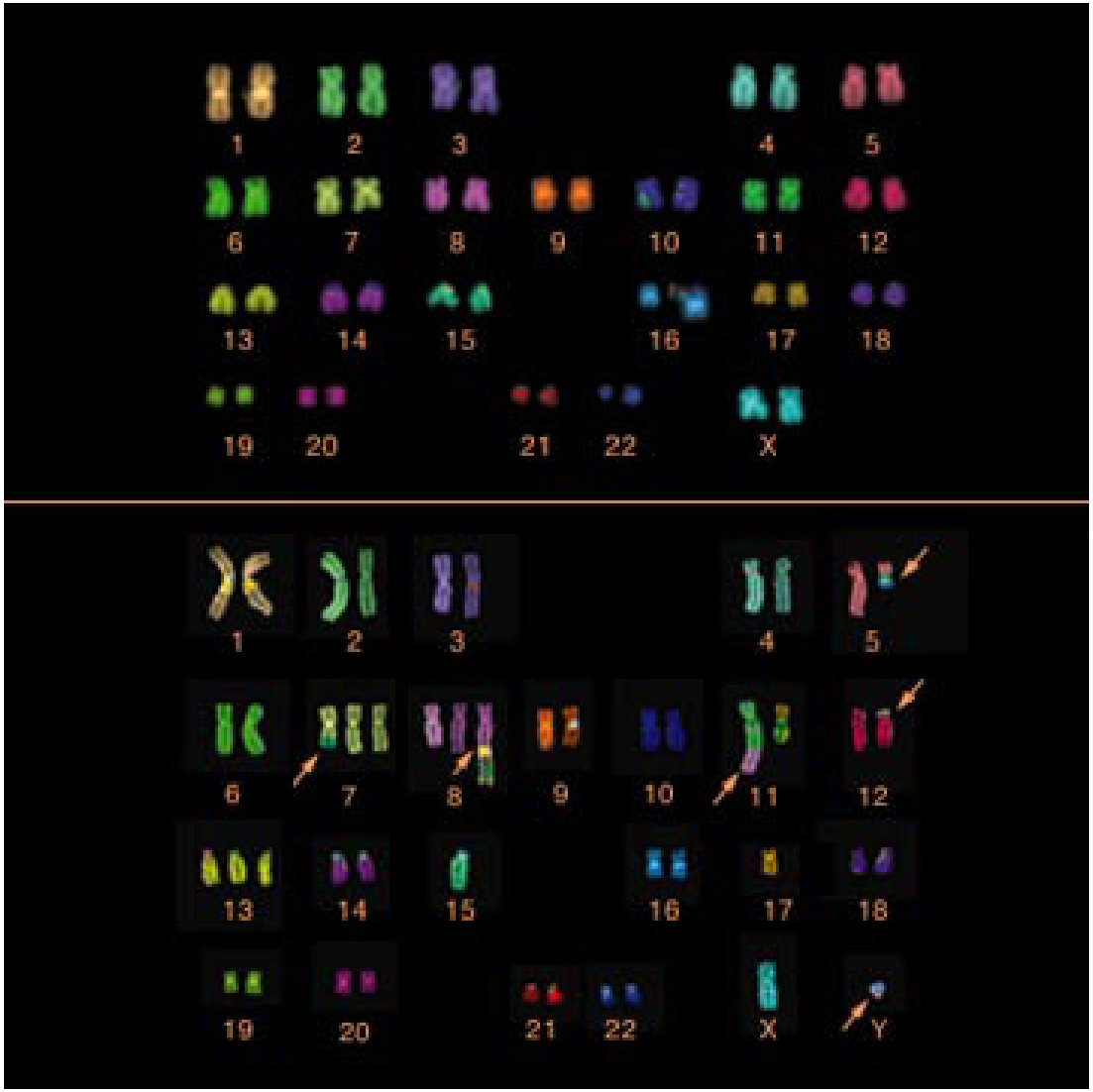
Outline

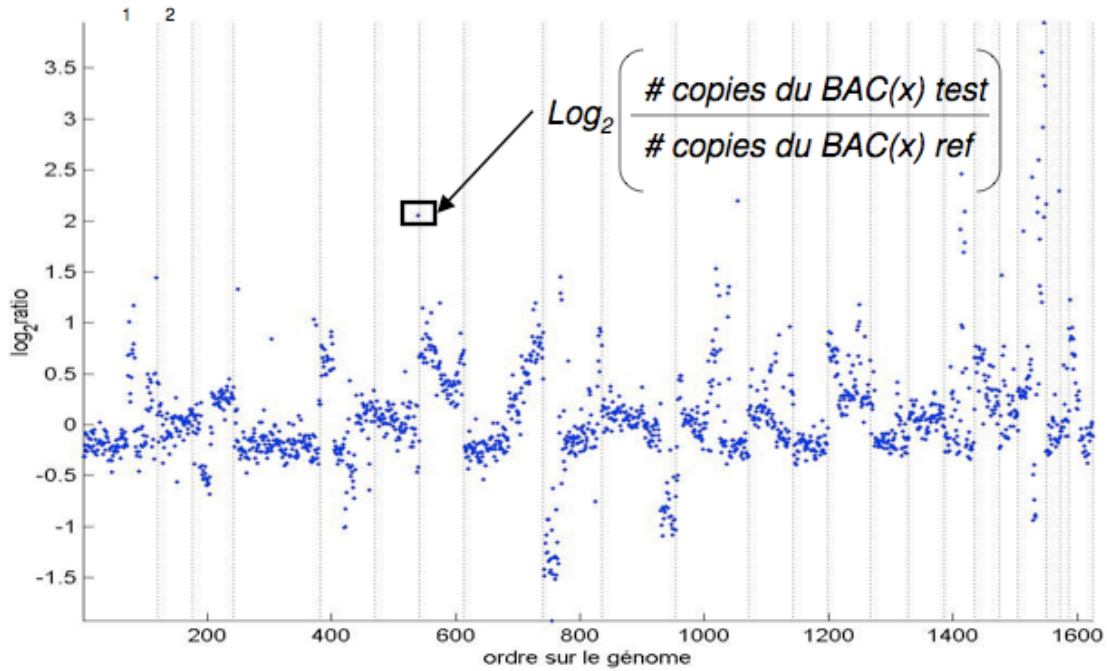
Outline

Chromosomic aberrations in cancer



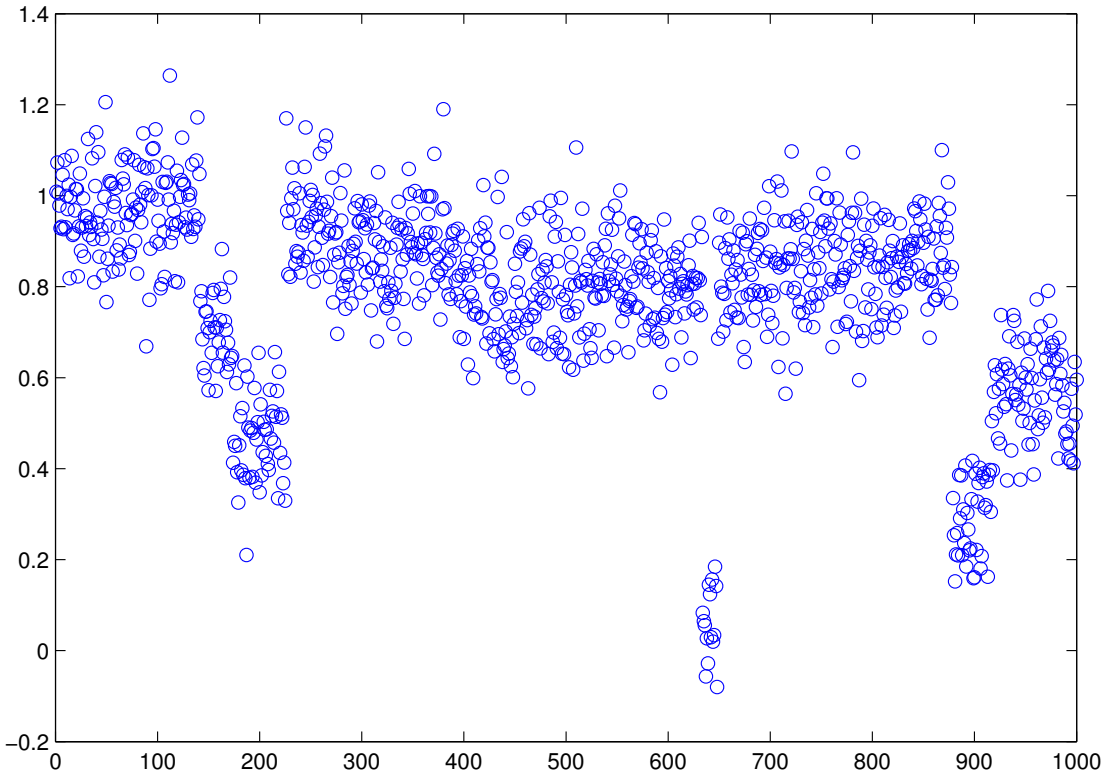


Comparative Genomic Hybridization (CGH)

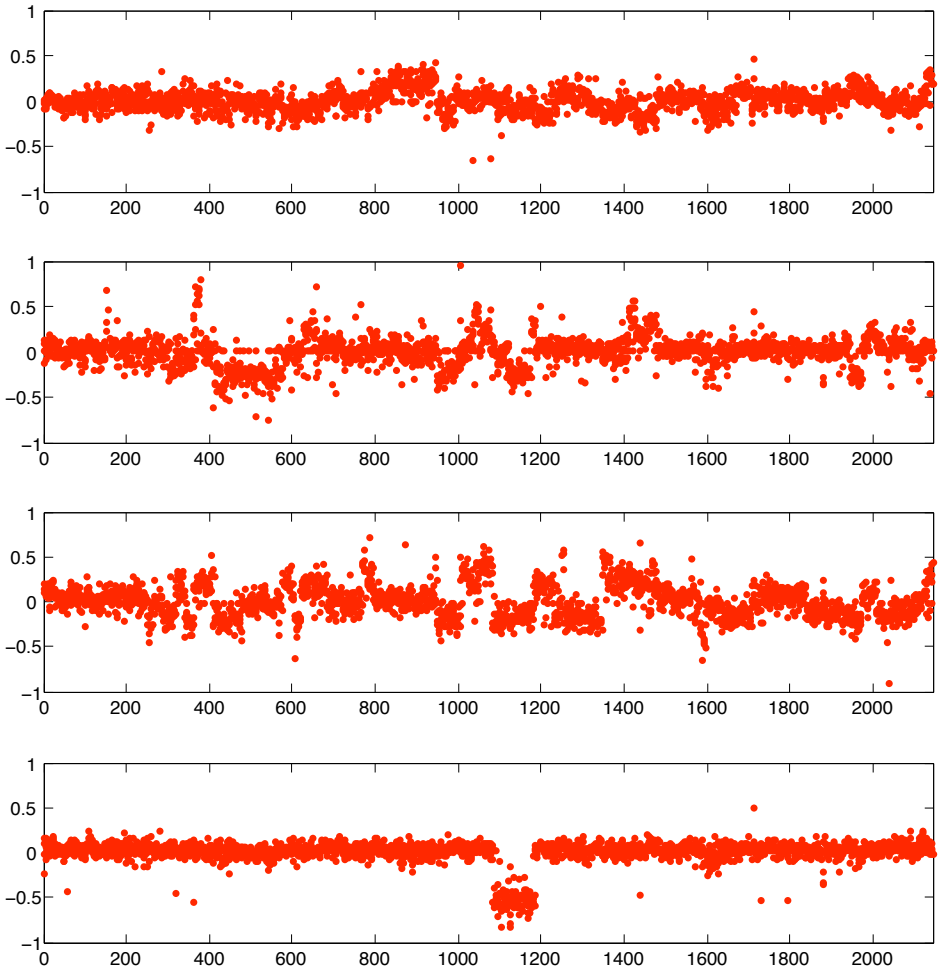


Jain et al. Genome research 2002 12:325-332

Can we identify breakpoints and "smooth" each profile?

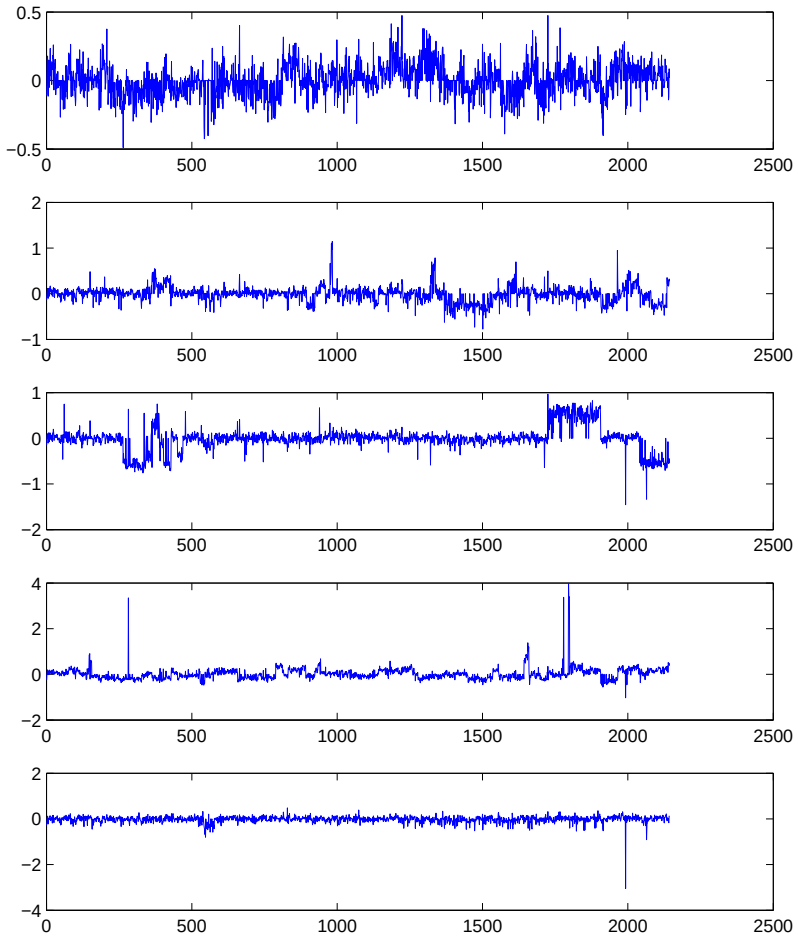


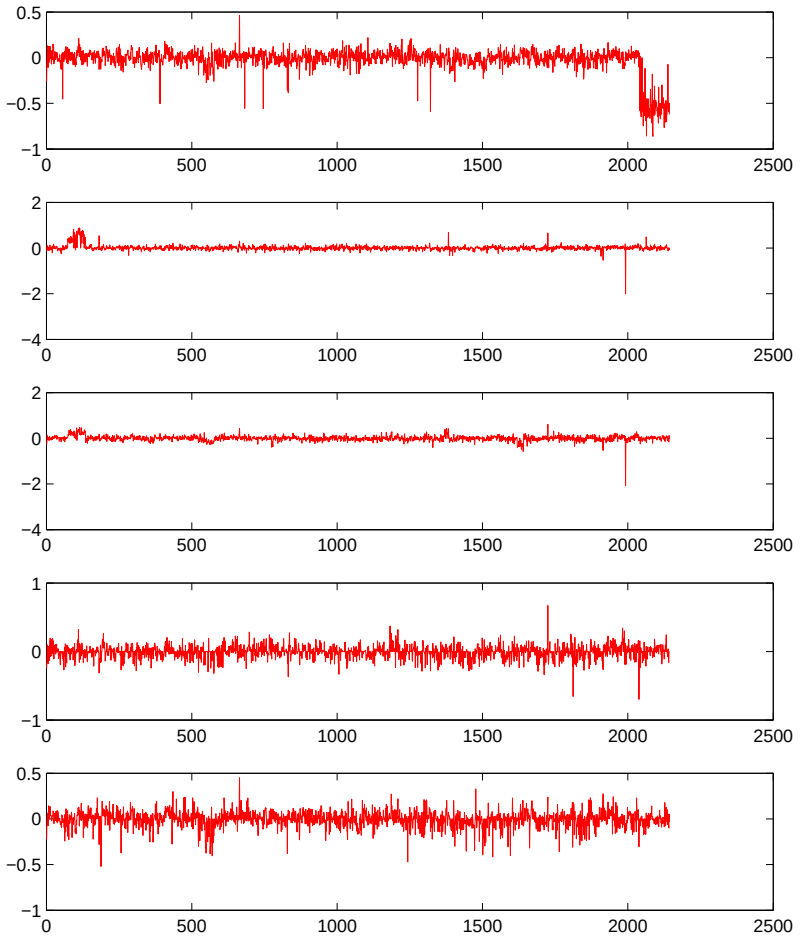
Can we detect frequent breakpoints?



A collection of bladder tumour copy number profiles.

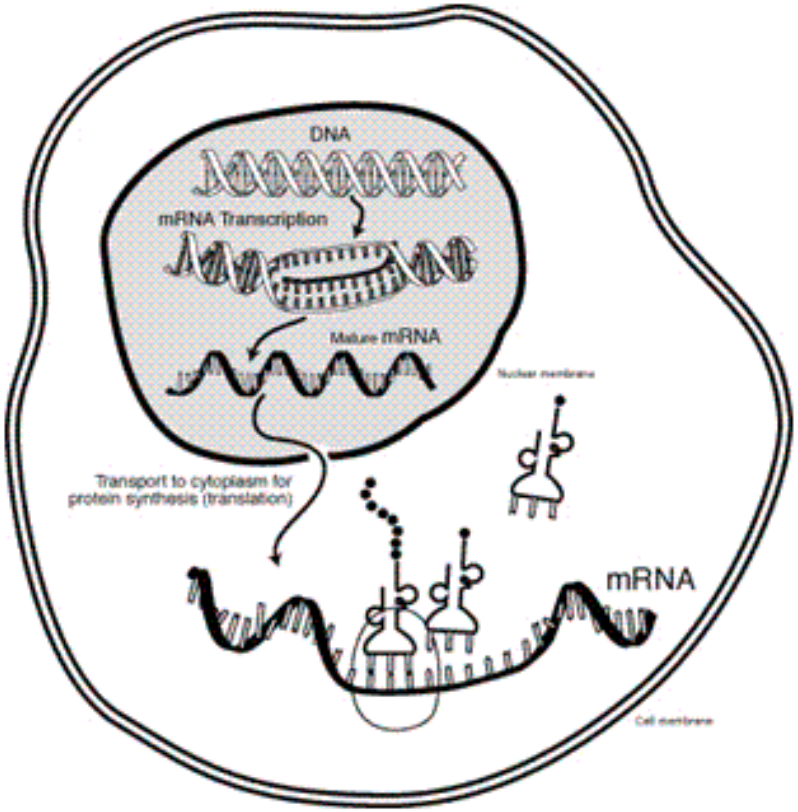
Can we detect discriminative patterns?

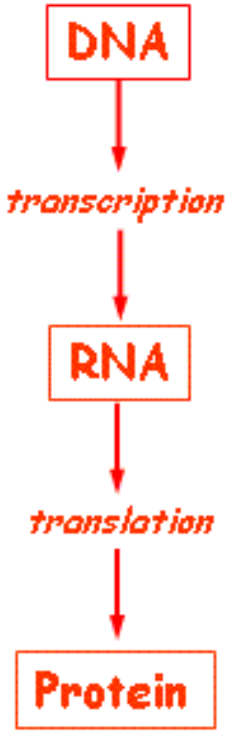




Aggressive (left) vs non-aggressive (right) melanoma.

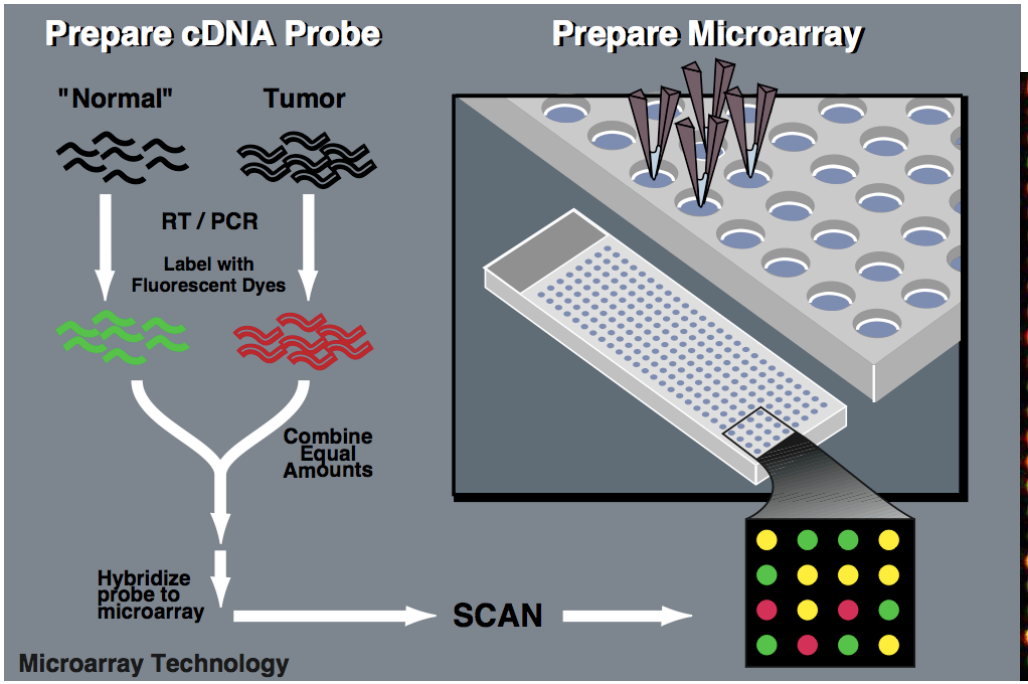
DNA → RNA → protein

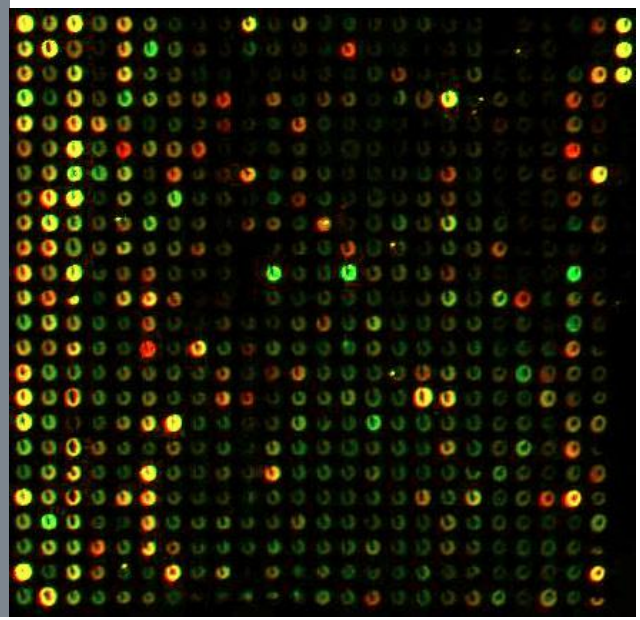




- CGH shows the (static) DNA
- Cancer cells have also abnormal (dynamic) gene expression (= transcription)

Tissue profiling with DNA chips

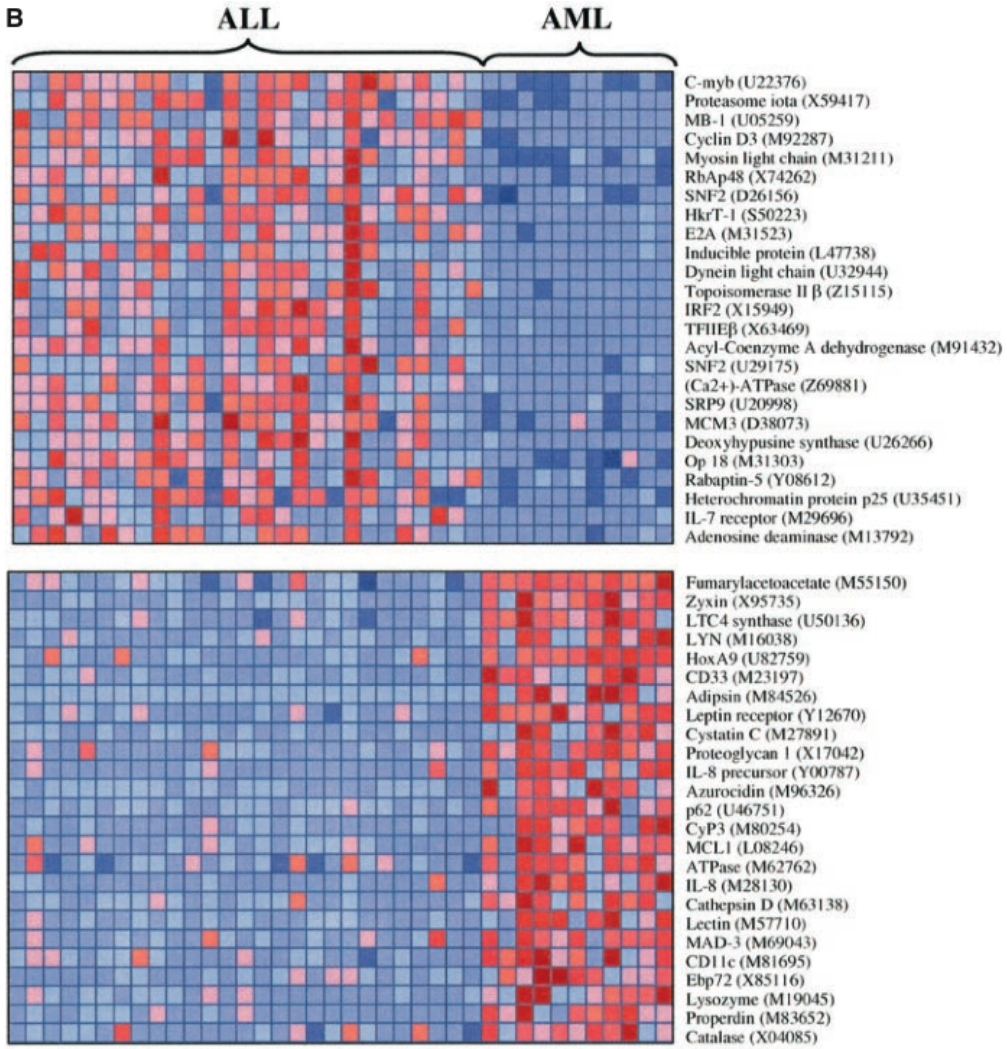




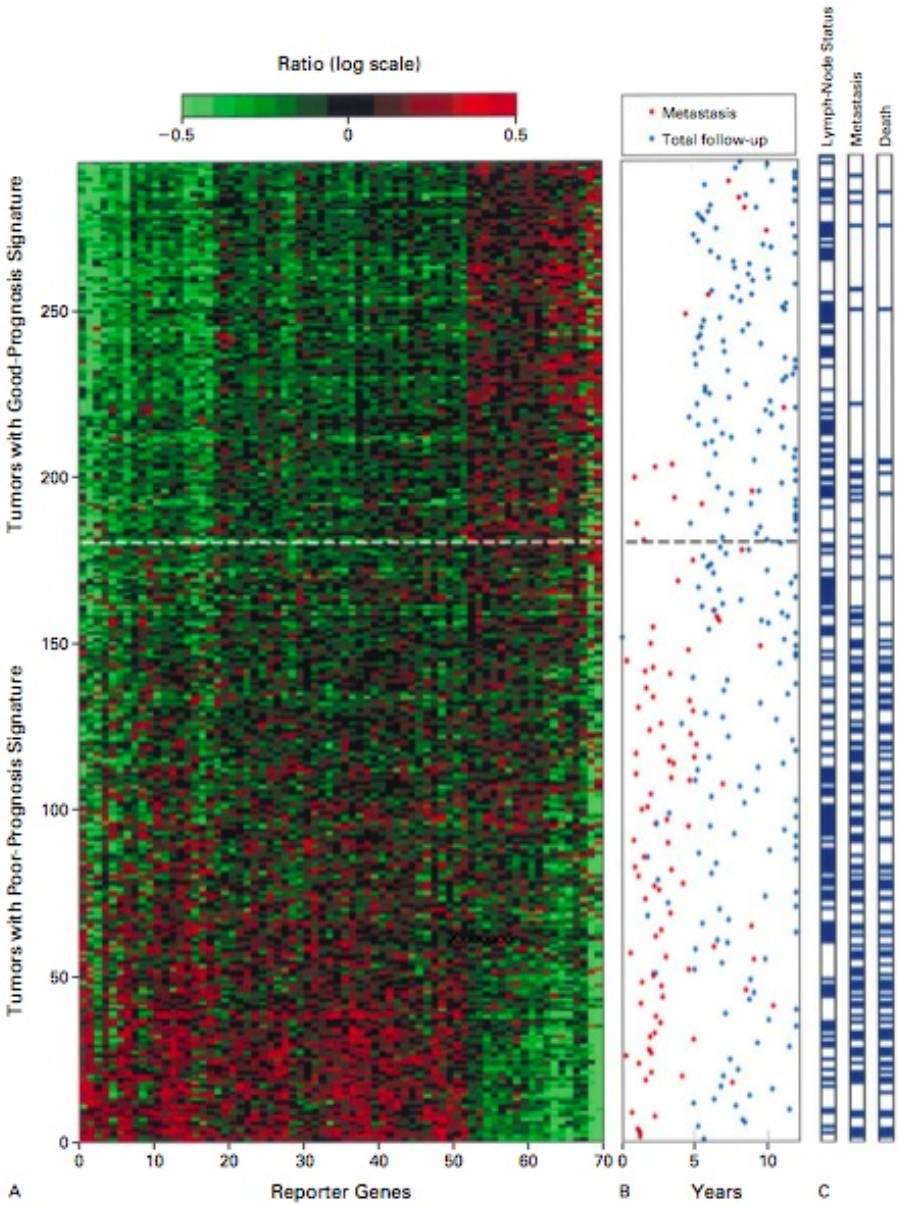
Data

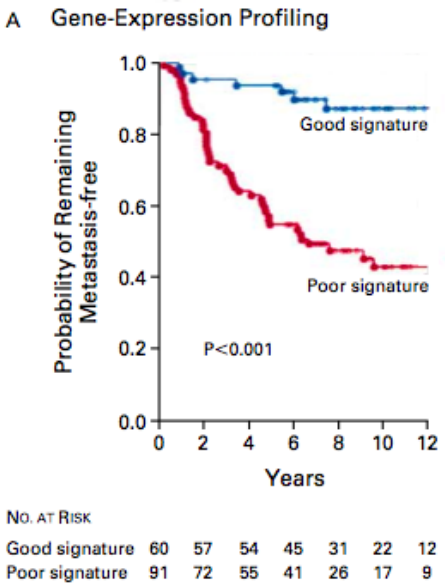
- Gene expression measures for more than $10k$ genes
- Measured typically on less than 100 samples of two (or more) different classes (e.g., different tumors)

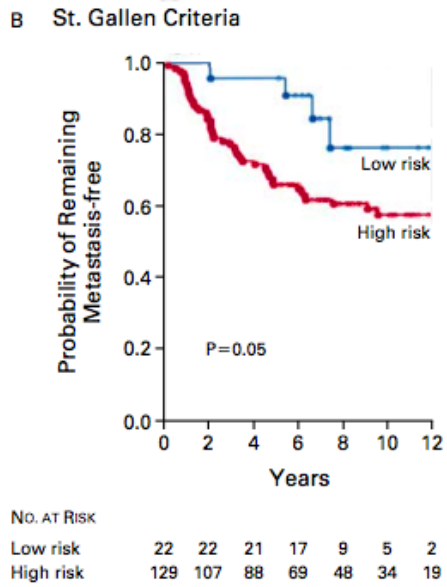
Can we identify the cancer subtype? (diagnosis)



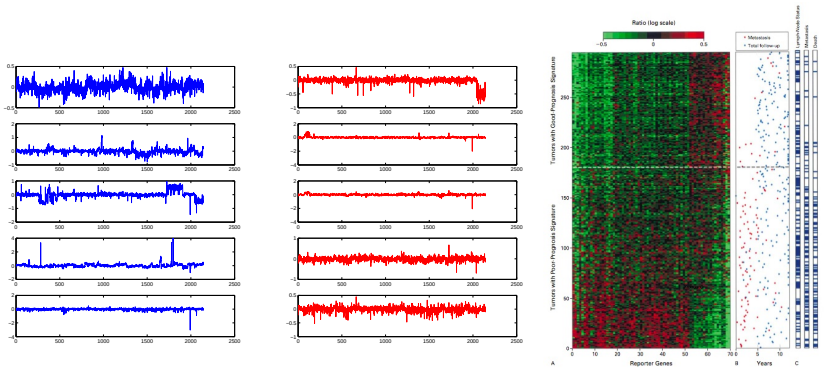
Can we predict the future evolution? (prognosis)







Summary

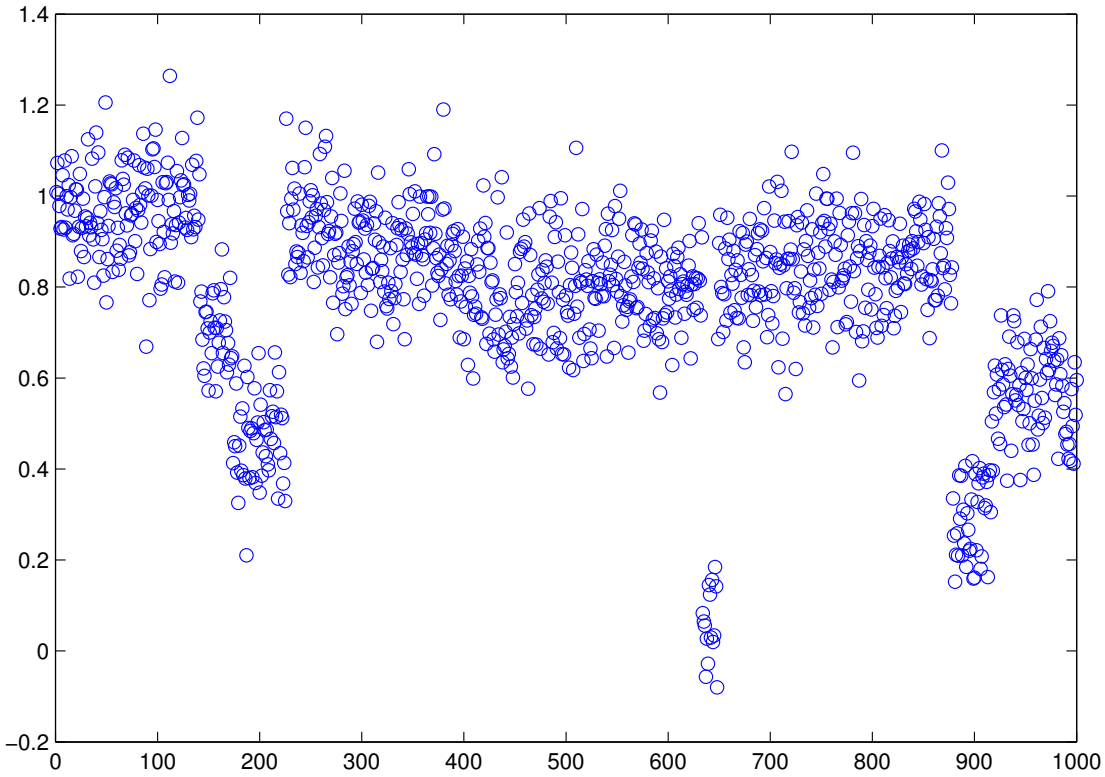


- Many problems...
- Data are high-dimensional, but "structured"
- Classification accuracy is not all, interpretation is necessary (pattern discovery)
- A general strategy

$$\min R(\beta) + \lambda\Omega(\beta)$$

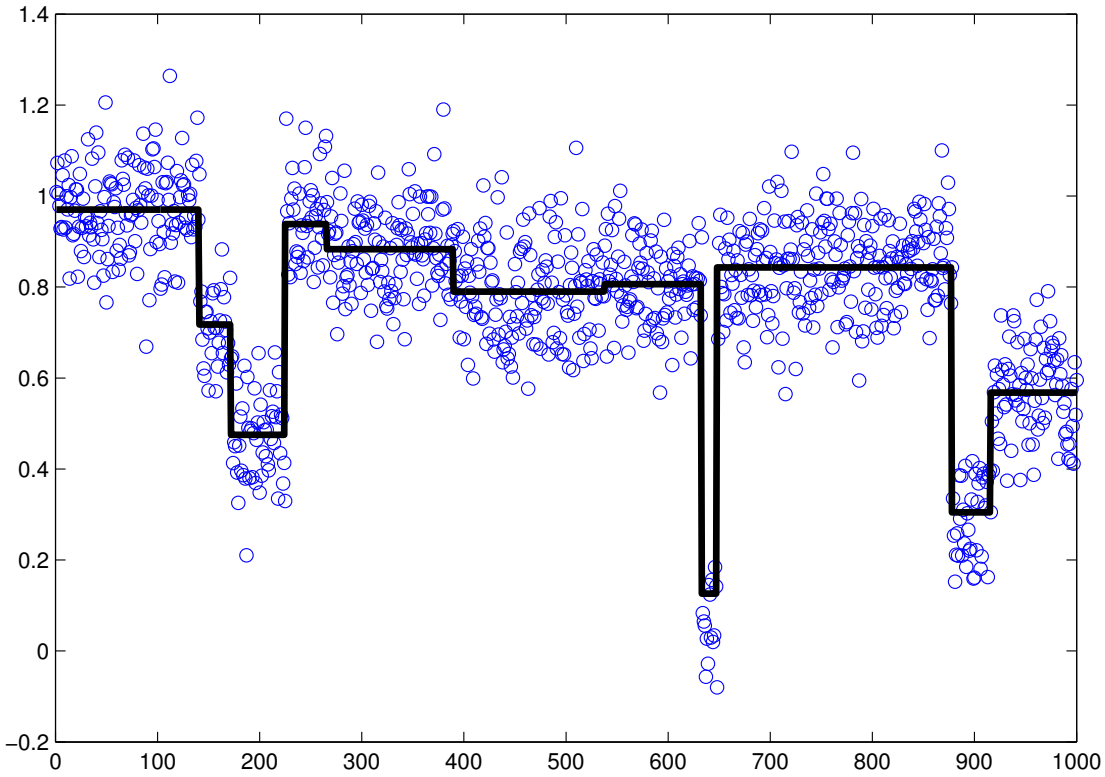
Outline

The problem



- 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.

The problem



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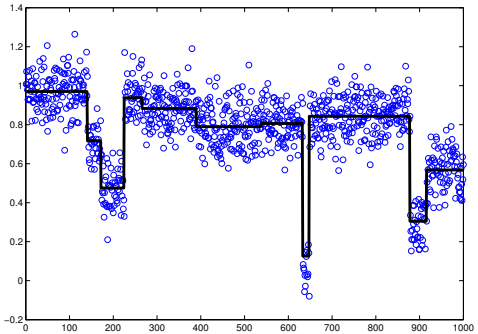
An optimal solution?

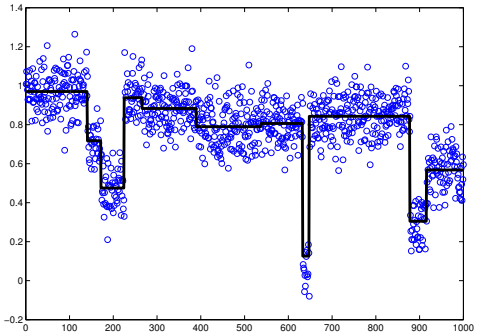


- We can define an "optimal" piecewise constant approximation $\hat{U} \in \mathbb{R}^p$ as the solution of

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

- 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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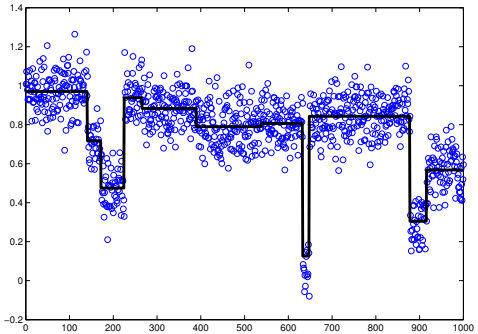

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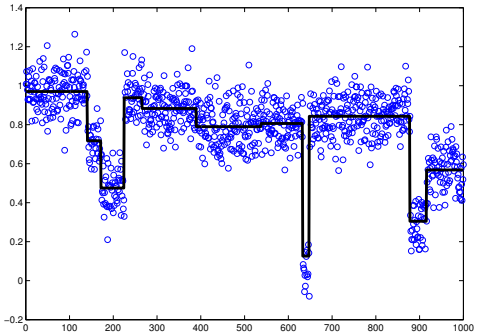

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Promoting sparsity with the ℓ_1 penalty

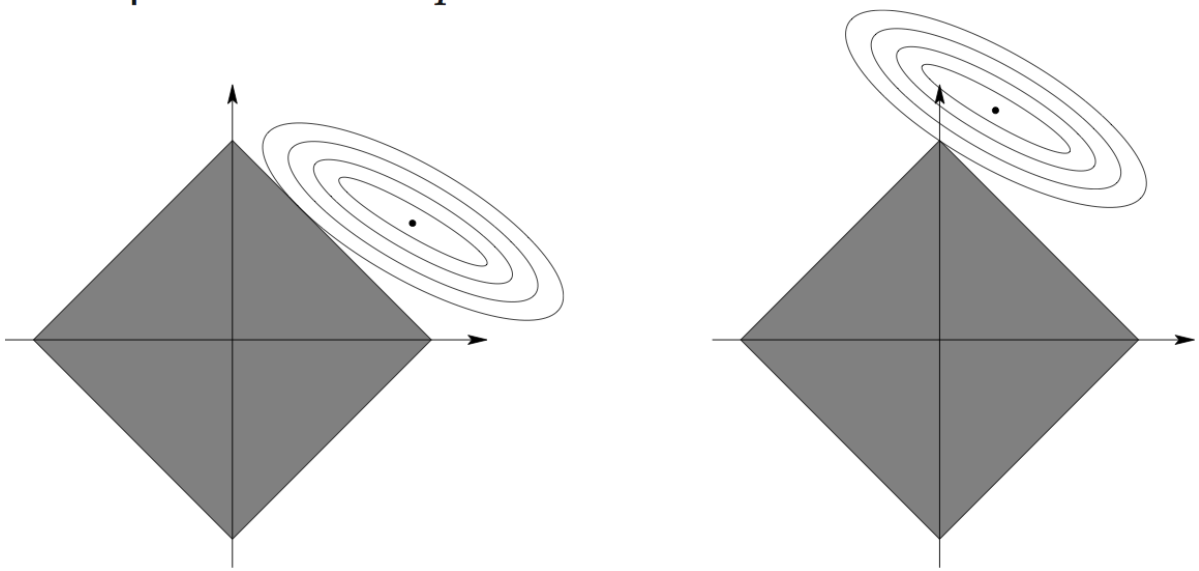
The ℓ_1 penalty (Tibshirani, 1996; Chen et al., 1998)

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 $p = 2$



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:

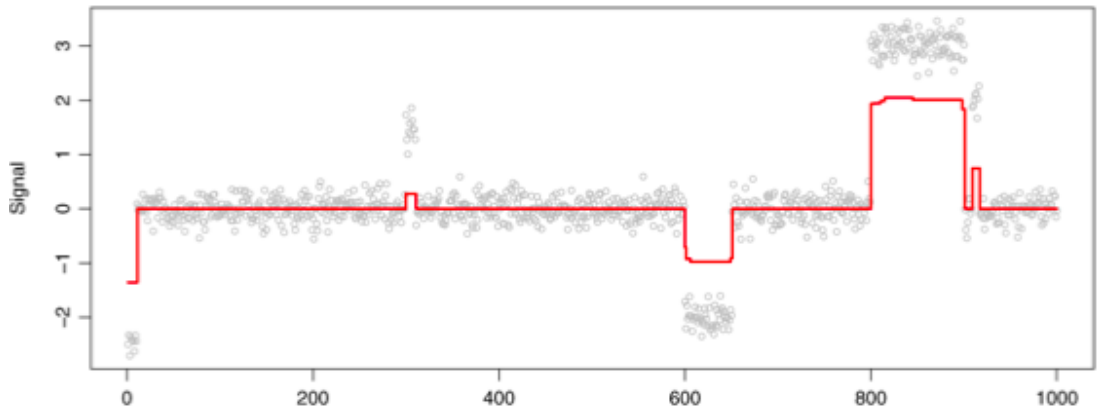
- Change of variable $u_i = \beta_{i+1} - \beta_i$, $u_0 = \beta_1$
- We obtain a Lasso problem in $u \in \mathbb{R}^{p-1}$
- u sparse means β piecewise constant

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)

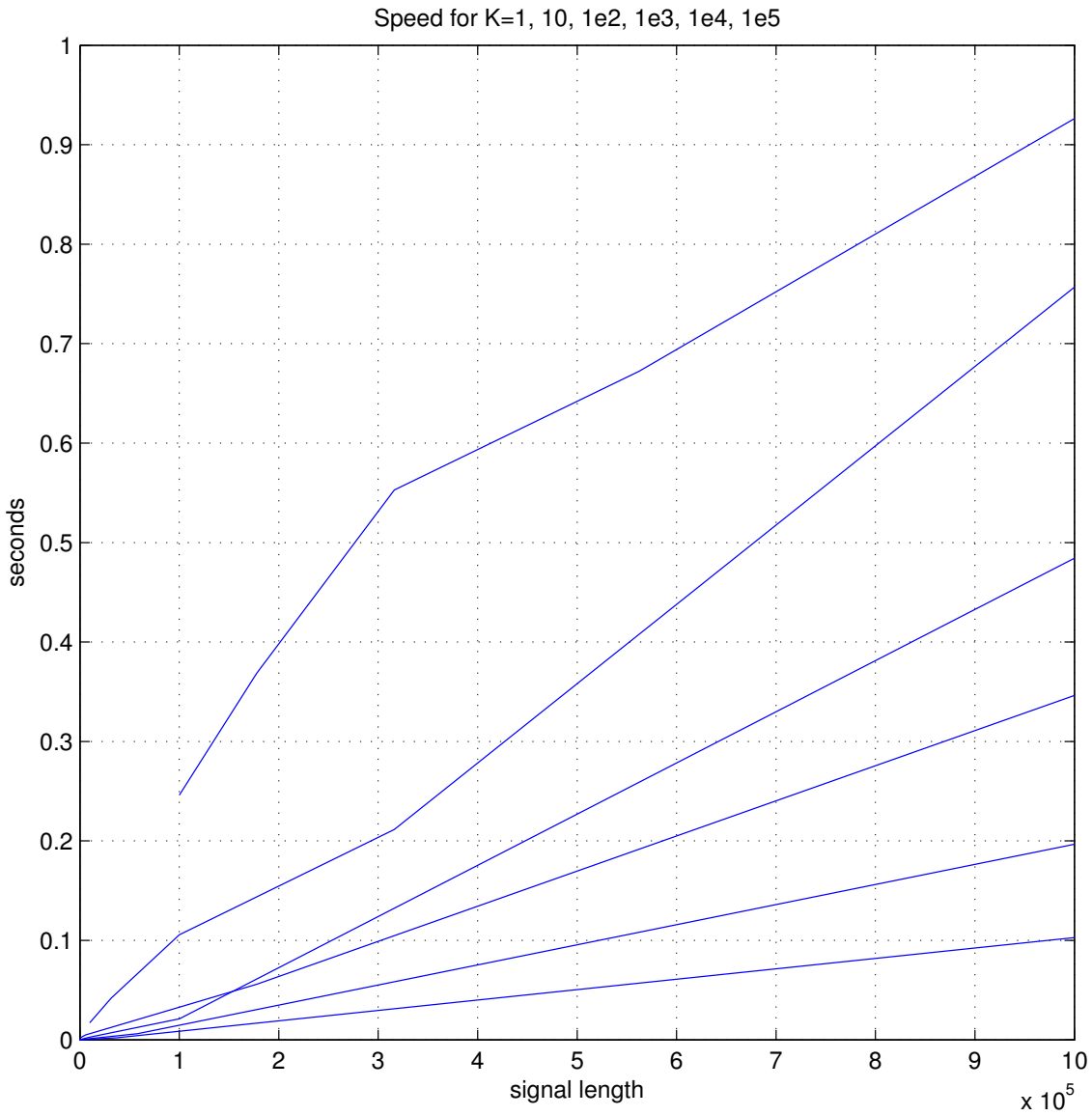


Solving TV signal approximator

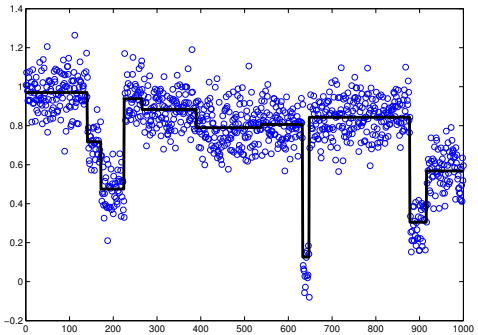
$$\min_{\beta \in \mathbb{R}^p} \| Y - \beta \|^2 \quad \text{such that} \quad \sum_{i=1}^{p-1} | \beta_{i+1} - \beta_i | \leq \mu$$

- 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 μ 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)

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



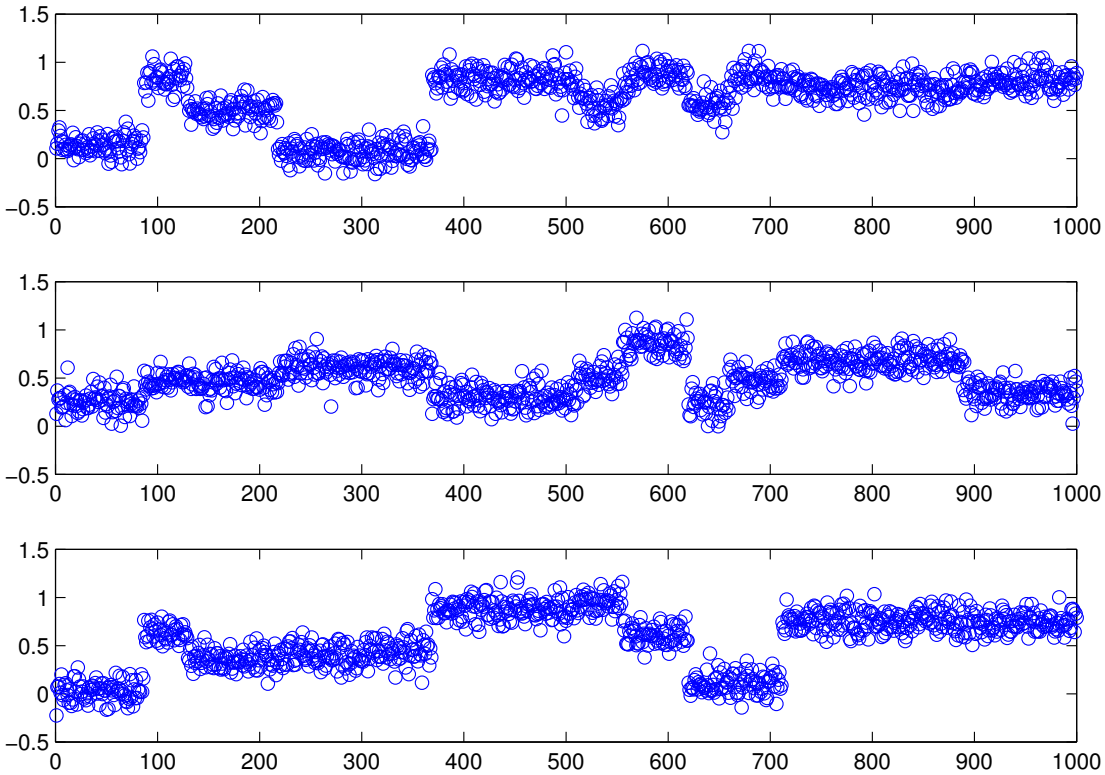
Summary



- A fast method for multiple change-point detection
- An embedded method that boils down to a dichotomic wrapper method (very different from dynamic programming)

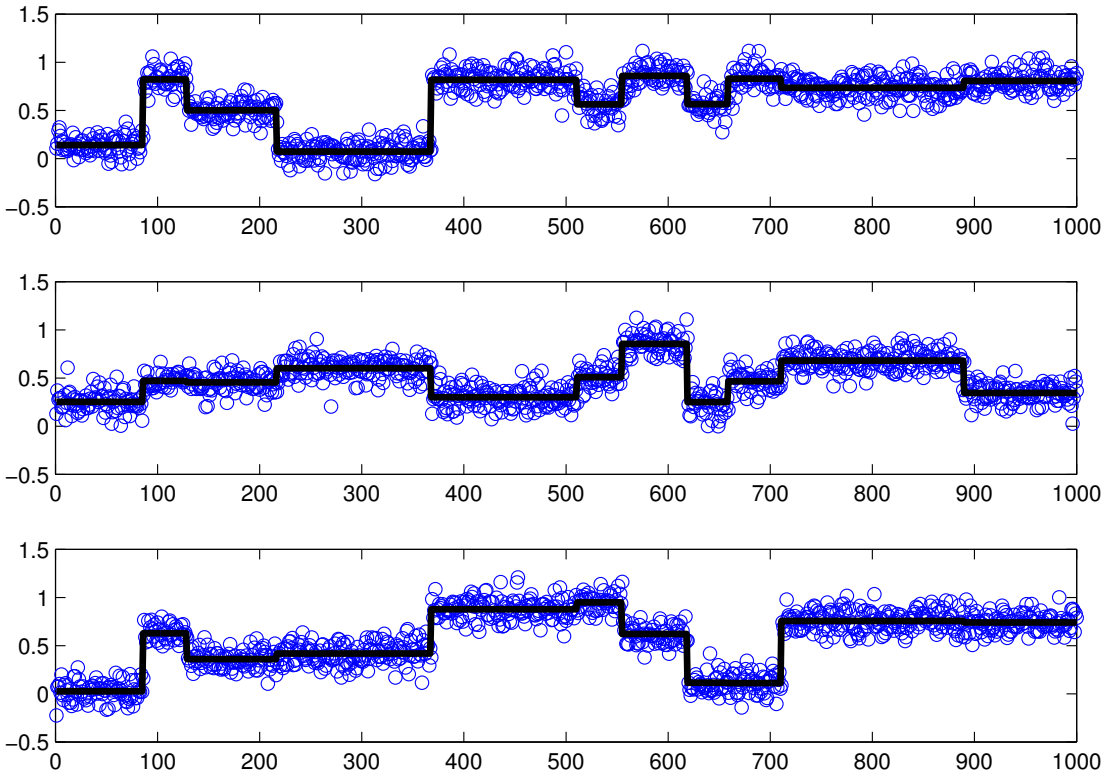
Outline

The problem



- 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.

The problem



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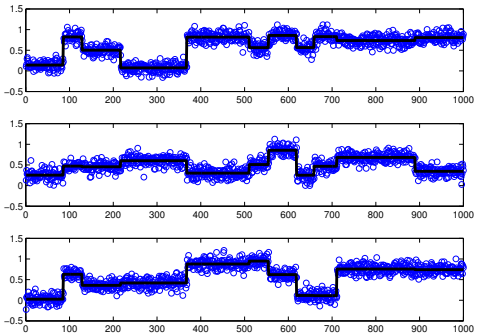
"Optimal" segmentation by dynamic programming



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

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

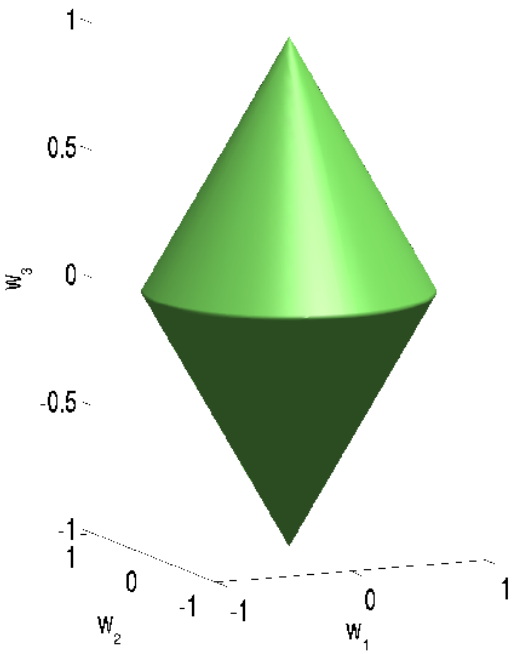
- DP finds the solution in $O(p^2 kn)$ in time and $O(p^2)$ in memory
- But: does not scale to $p = 10^6 \sim 10^9$...

Selecting pre-defined groups of variables

Group lasso (Yuan & Lin, 2006)

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

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



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

TV approximator for many signals

- Replace

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

by

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

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:

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

- 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.

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...

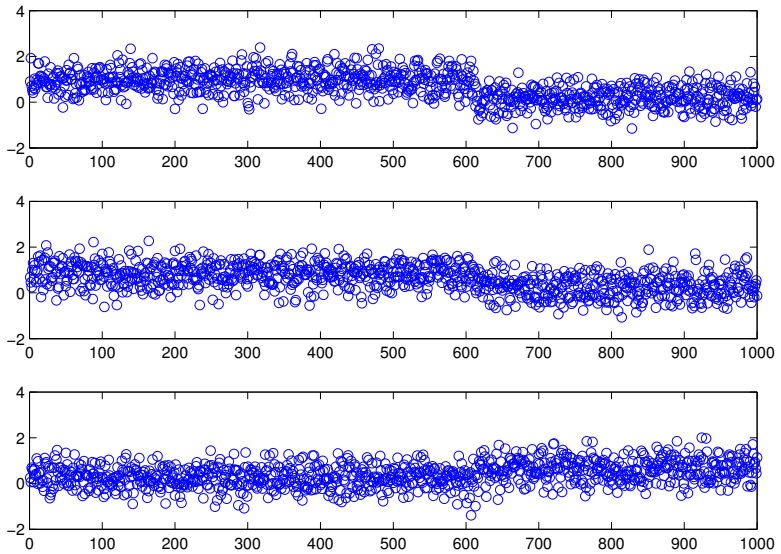
Although $\bar{X}$ is $(p-1) \times (p-1)$:

- 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 $\bar{X}^\top_{\bullet,A} \bar{X}_{\bullet,B}$ 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 $C = \left(\bar{X}^\top_{\bullet,A} \bar{X}_{\bullet,A}\right)^{-1} R$ 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 $(\beta_i)_{i=1,\dots,n}$ 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 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* $n \to +\infty$ *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* $n \to +\infty$.

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

Proof sketch

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

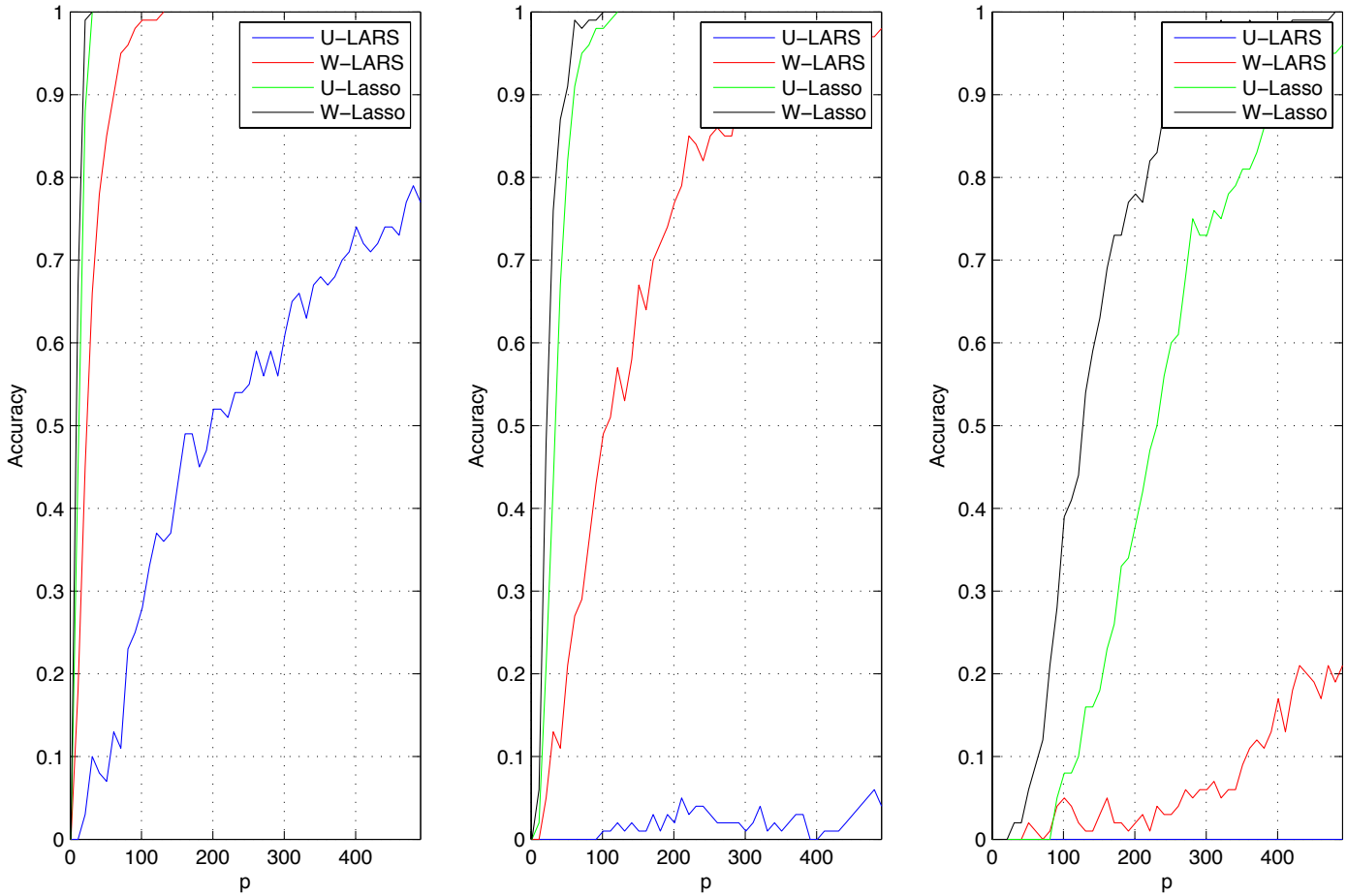
$$\hat{c} = \bar{X}^\top \bar{Y} = \bar{X}^\top \bar{X} \beta^* + \bar{X}^\top W \,.$$

- $\hat{c}$ is Gaussian, and F_i is 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 $G_u = \max_i G_i$

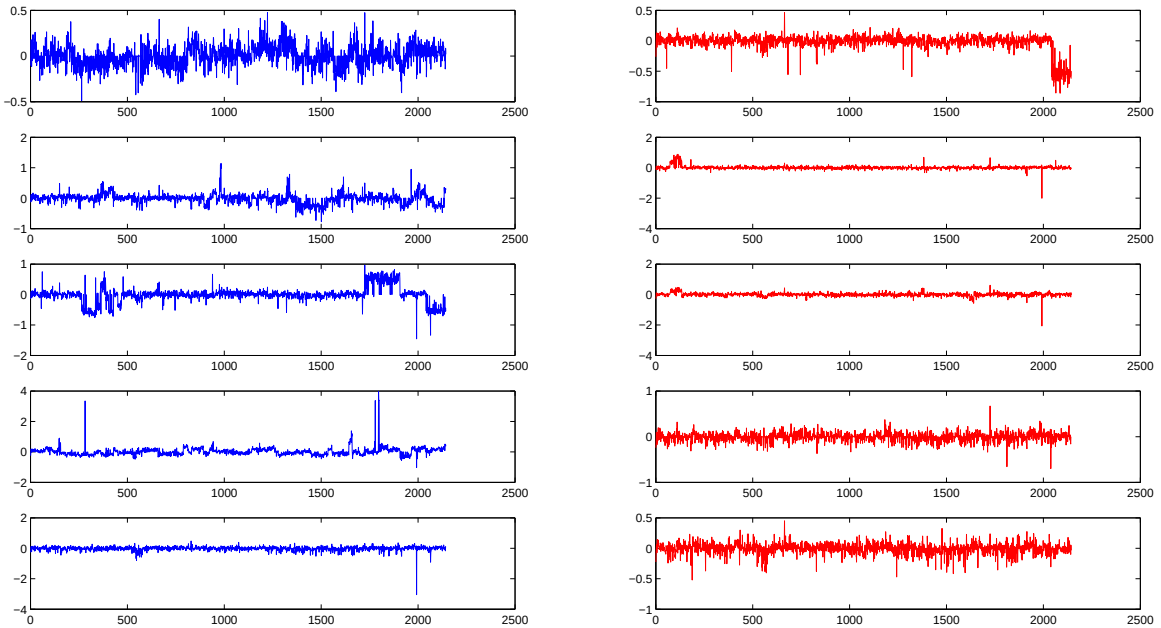
Consistent estimation of more change-points?



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

Outline

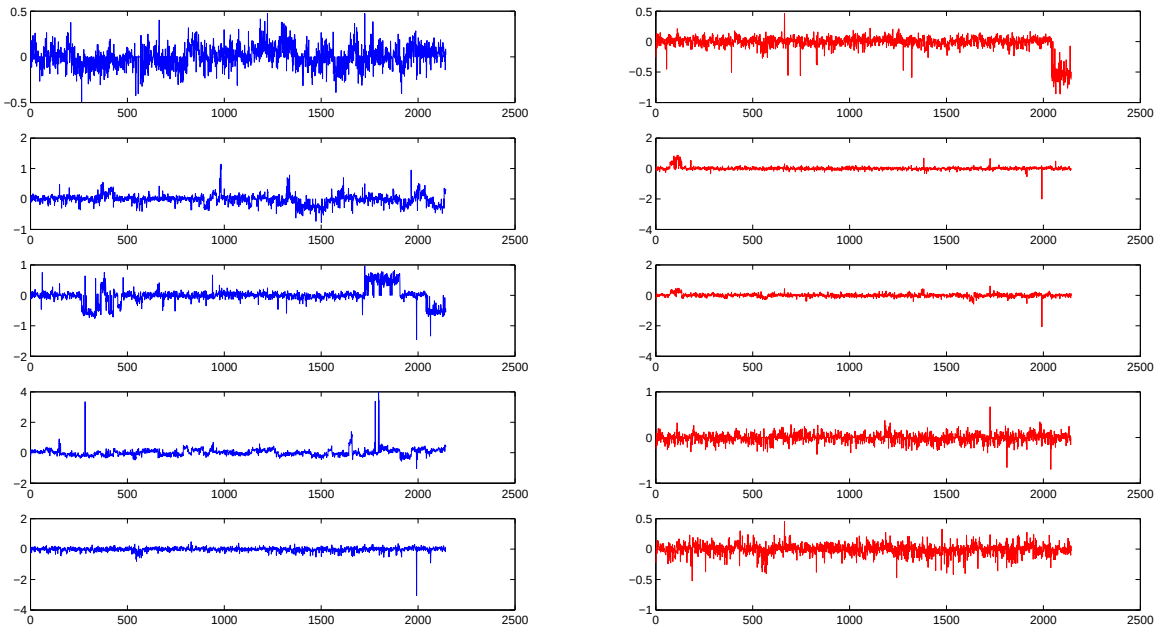
The problem



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

Prior knowledge

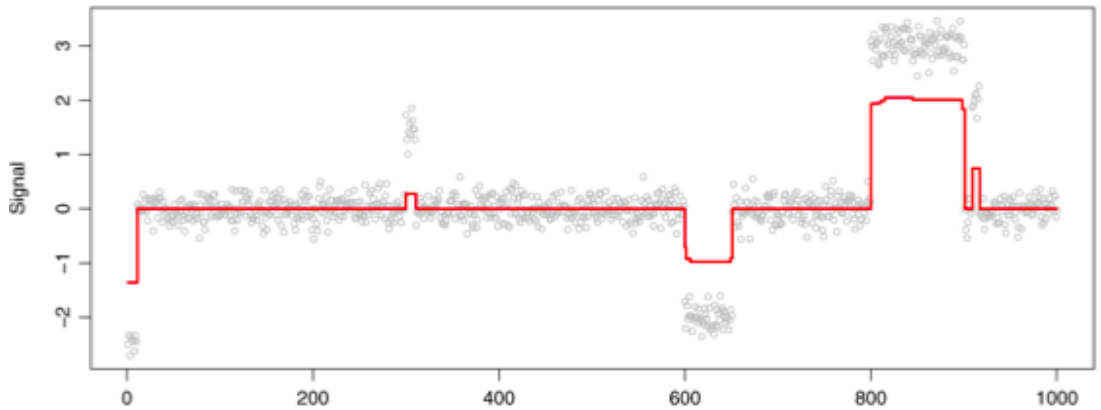
- Sparsity : not all positions should be discriminative, and we want to identify the predictive region (presence of oncogenes or tumor suppressor genes?)
- Piecewise constant : within a selected region, all probes should contribute equally



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

Implementation

- When ℓ is the hinge loss (fused SVM), this is a linear program -> up to $p = 10^3 \sim 10^4$
- When ℓ is convex and smooth (logistic, quadratic), efficient implementation with proximal methods -> up to $p = 10^8 \sim 10^9$

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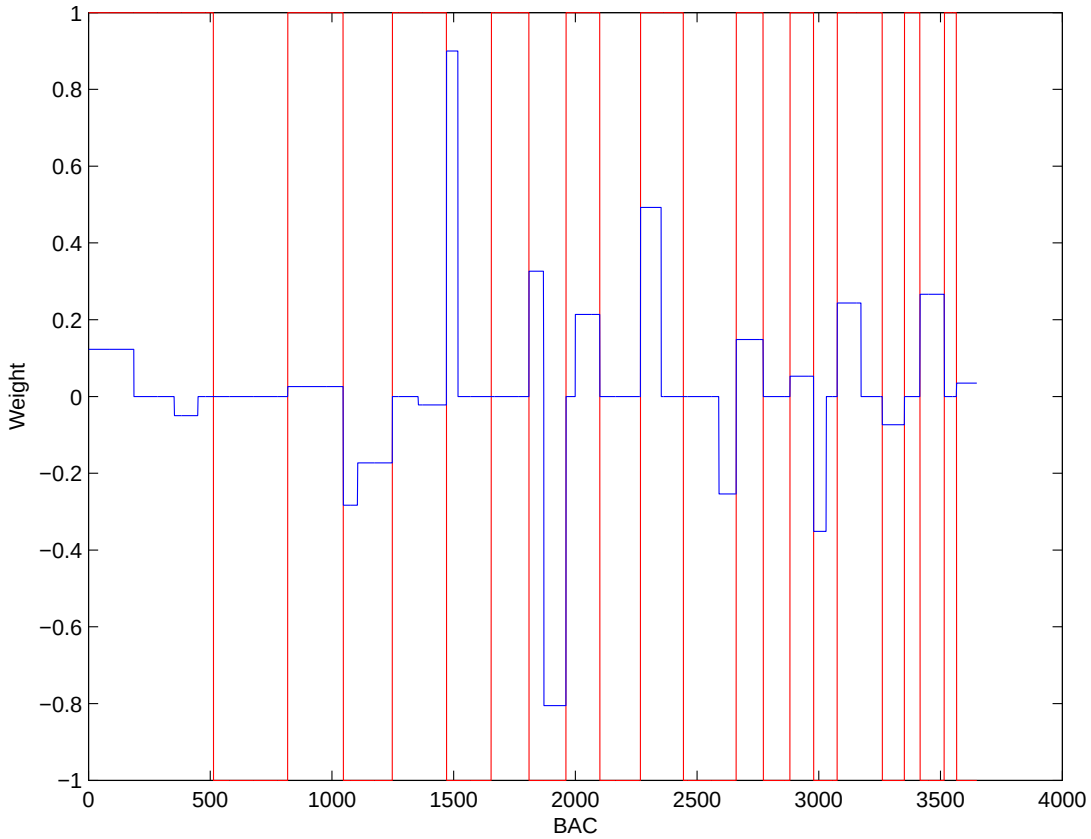
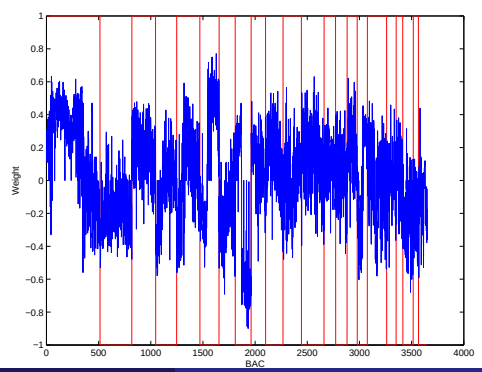
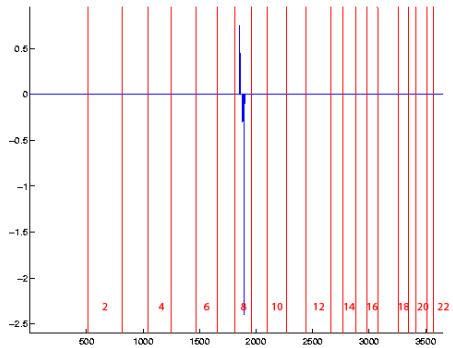
Example: predicting metastasis in melanoma

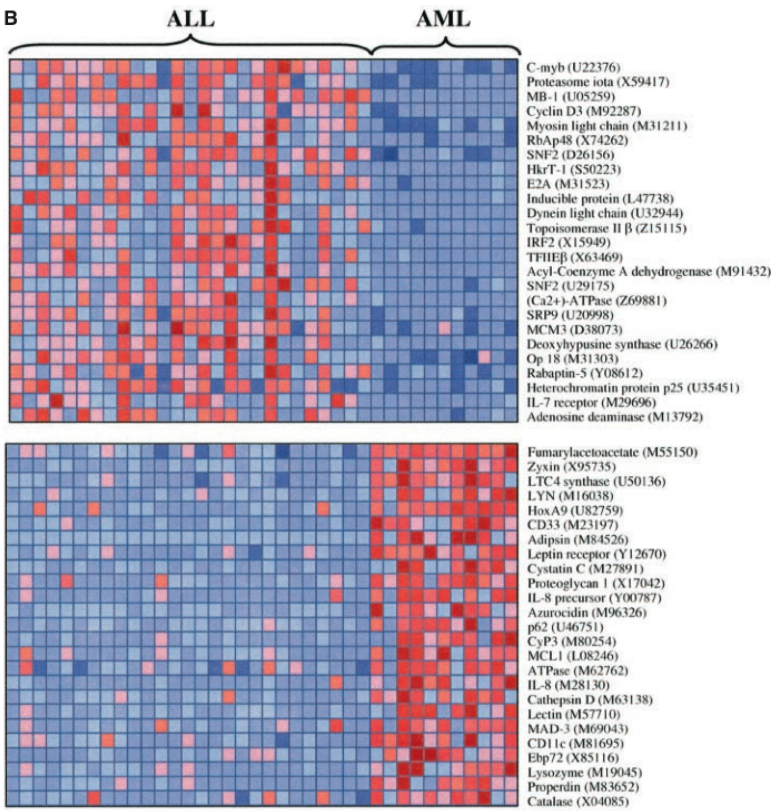


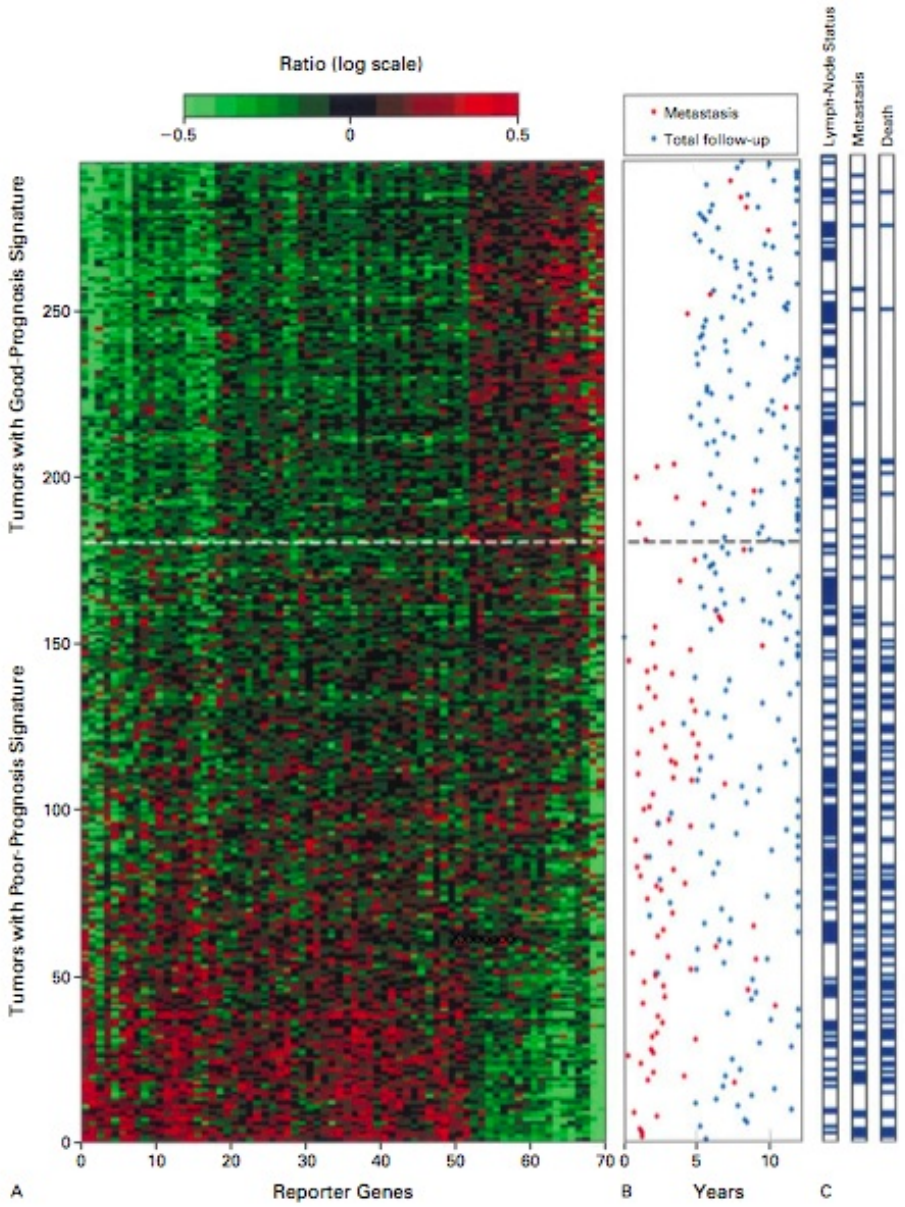




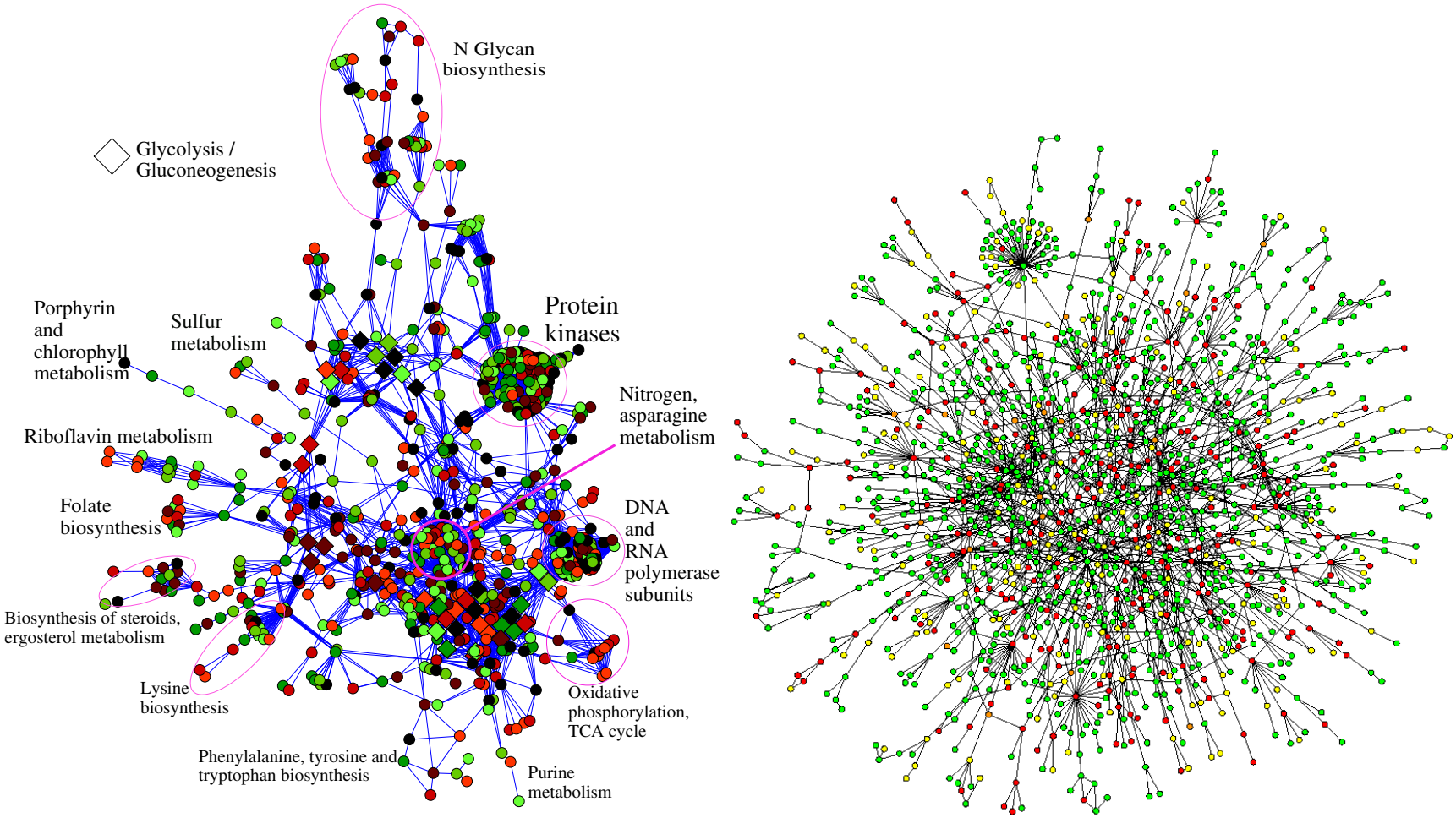
Outline

Molecular diagnosis / prognosis / theragnosis





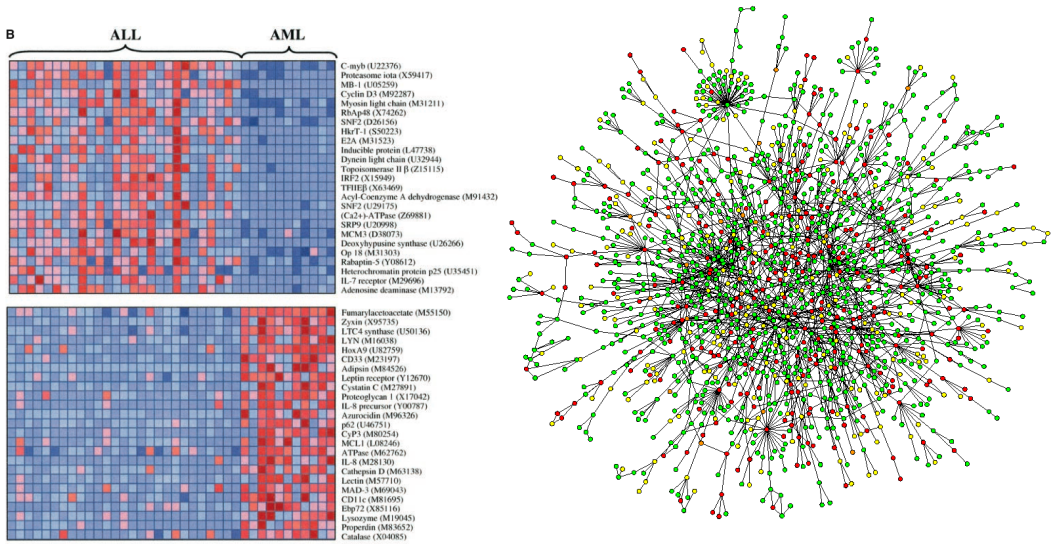
Gene networks



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 weigths.

An idea (Rapaport et al., 2007)

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

$$\min_{\beta \in \mathbb{R}^p} R(\beta) + \lambda \sum_{i \sim j} (\beta_i - \beta_j)^2 \,.$$

Graph based penalty

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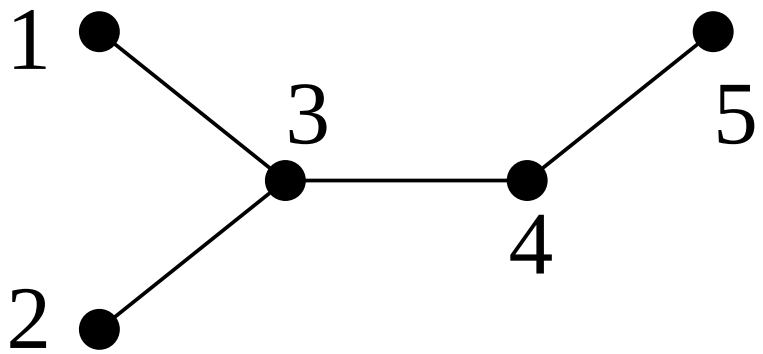
Graph Laplacian

Definition

The Laplacian of the graph is the matrix $L = D - A$.



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

Spectral penalty as a kernel

Theorem

The function $f(x) = \beta^\top x$ where b is solution of

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

is equal to $g(x) = \gamma^\top \Phi(x)$ where γ is solution of

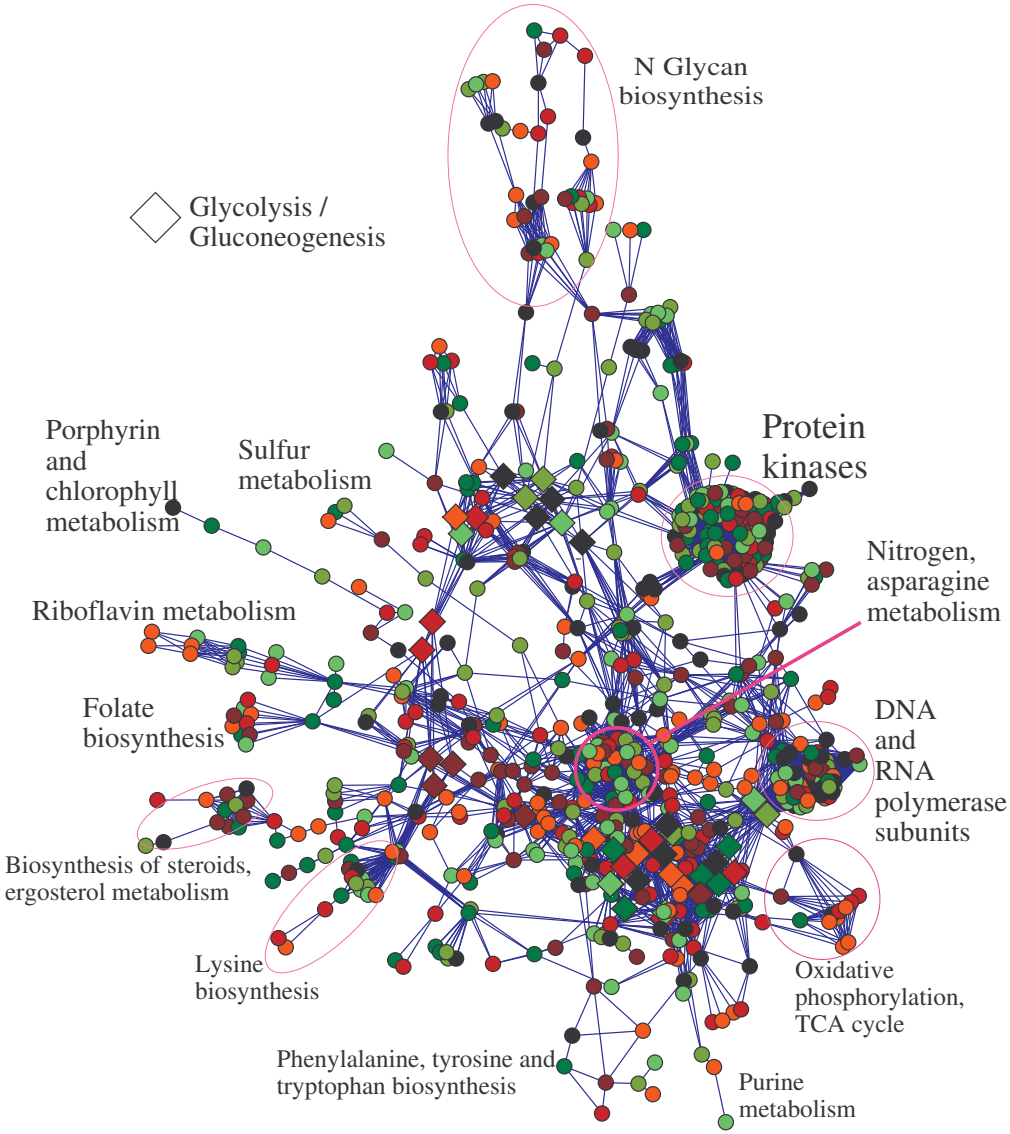
$$\min_{\gamma \in \mathbb{R}^p} \frac{1}{n} \sum_{i=1}^{n} l\left(\gamma^\top \Phi(x_i), y_i\right) + \lambda \gamma^\top \gamma \,,$$

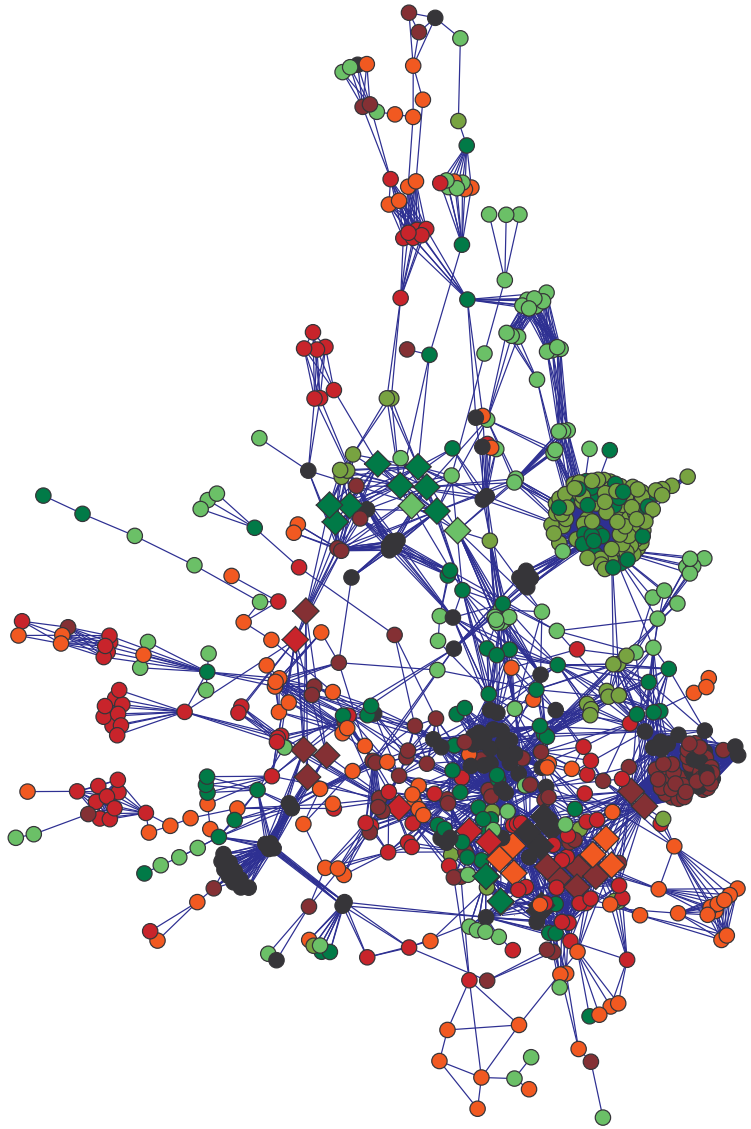
and where

$$\Phi(x)^\top \Phi(x') = x^\top K_G x'$$

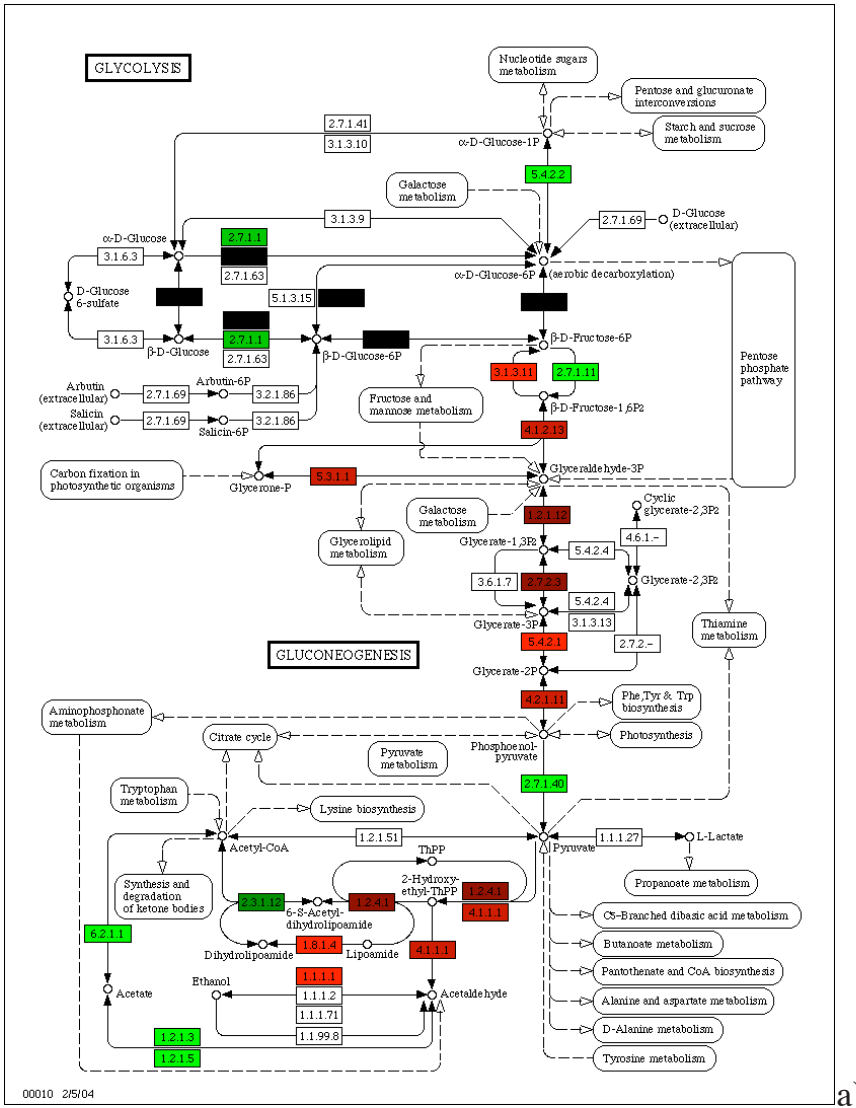
for $K_G = L^*$, the pseudo-inverse of the graph Laplacian.

Classifiers

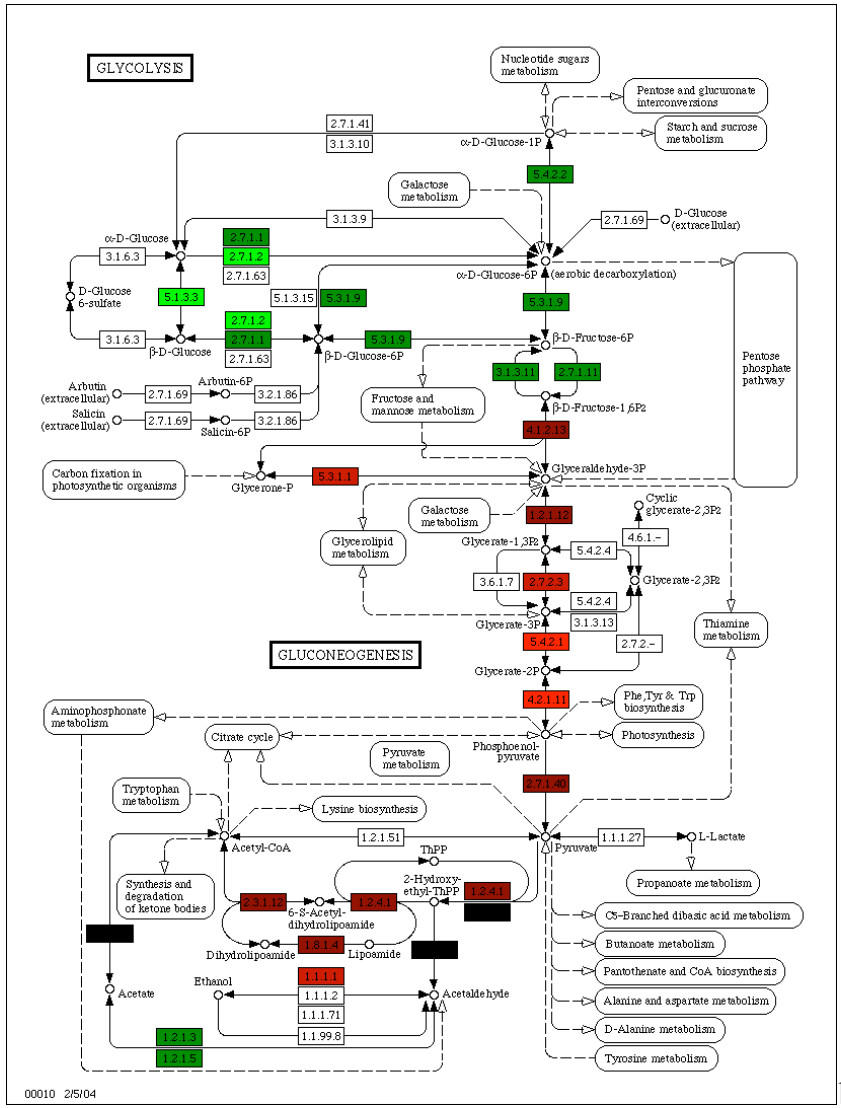




Classifier



a)



b)

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 β in the Fourier domain.

Other penalties without kernels

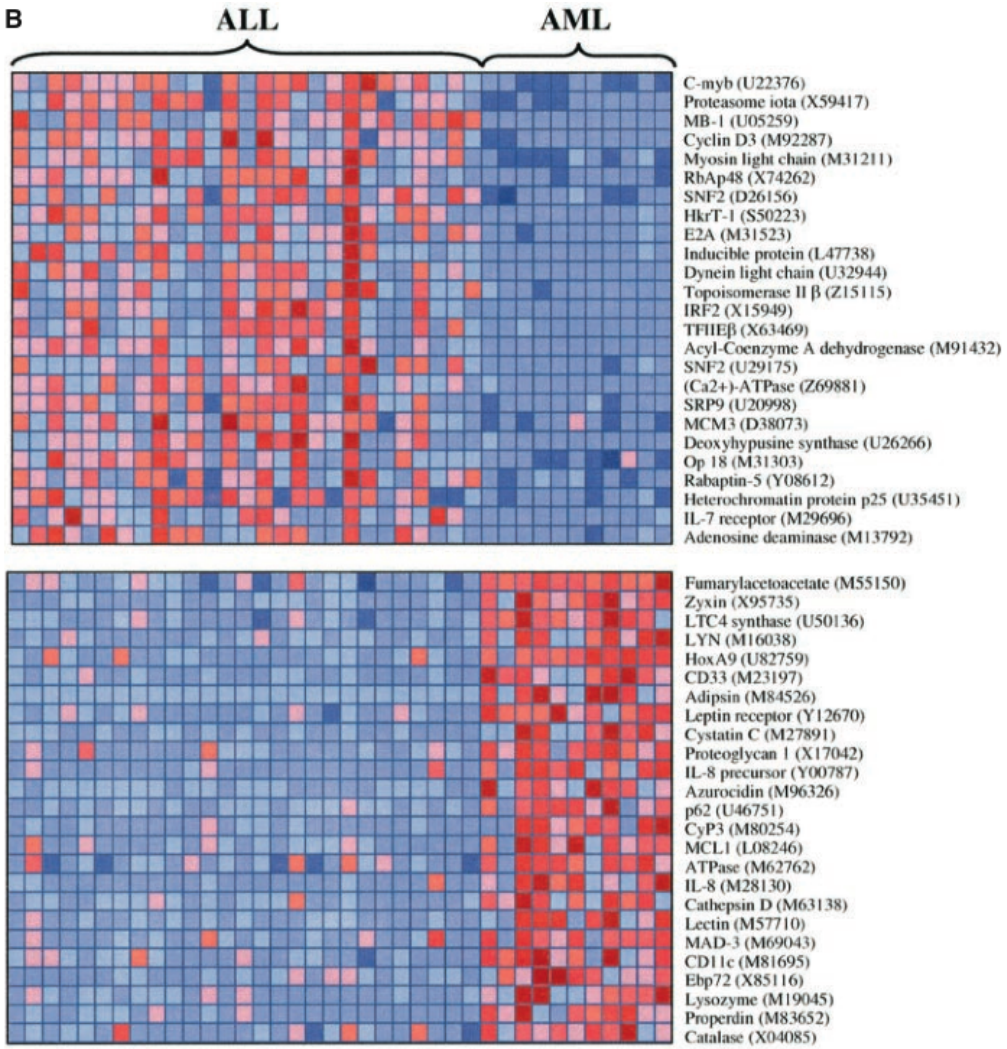
- Gene selection + Piecewise constant on the graph

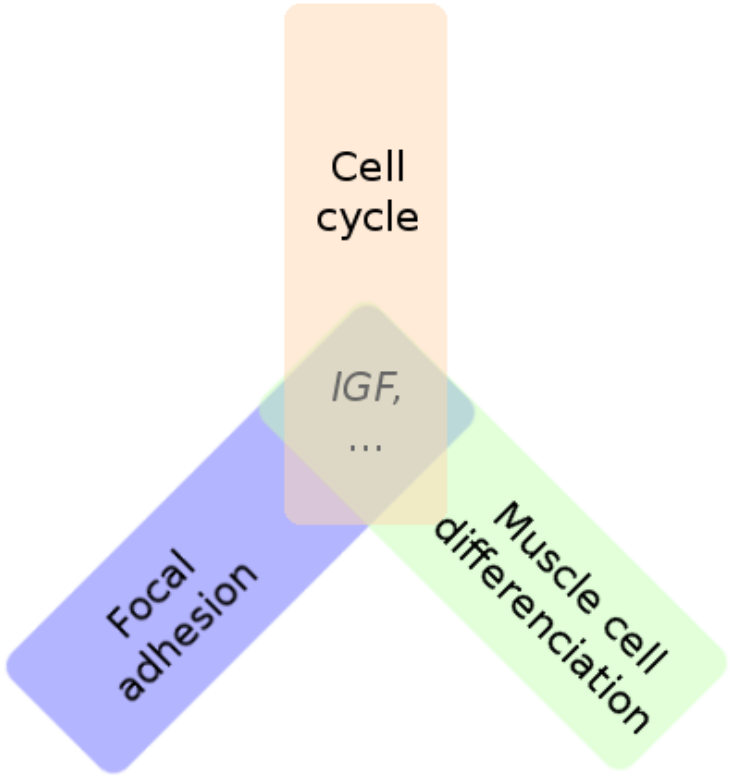
$$\Omega(\beta) = \sum_{i \sim j} |\beta_i - \beta_j| + \sum_{i=1}^{p} |\beta_i|$$

- 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?



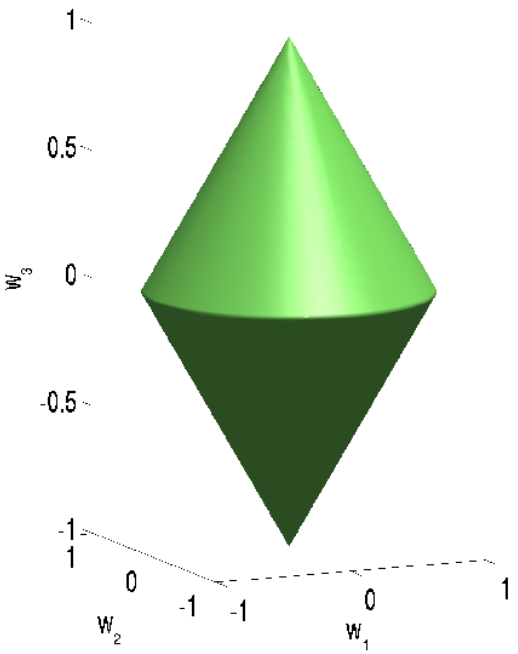


Selecting pre-defined groups of variables

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*:

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

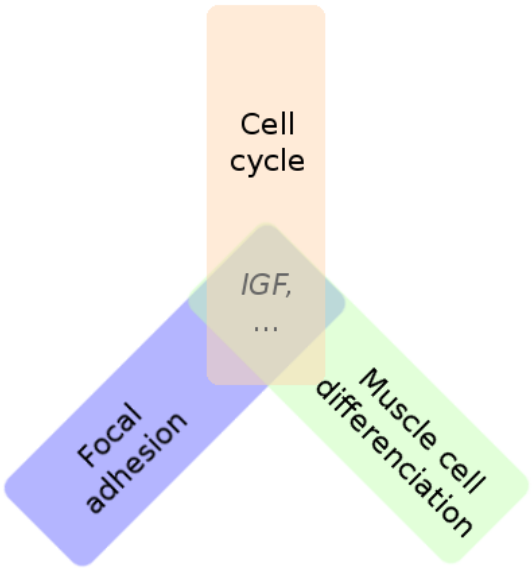


$$\Omega(w_1, w_2, w_3) = \|(w_1, w_2)\|_2 + \|w_3\|_2$$

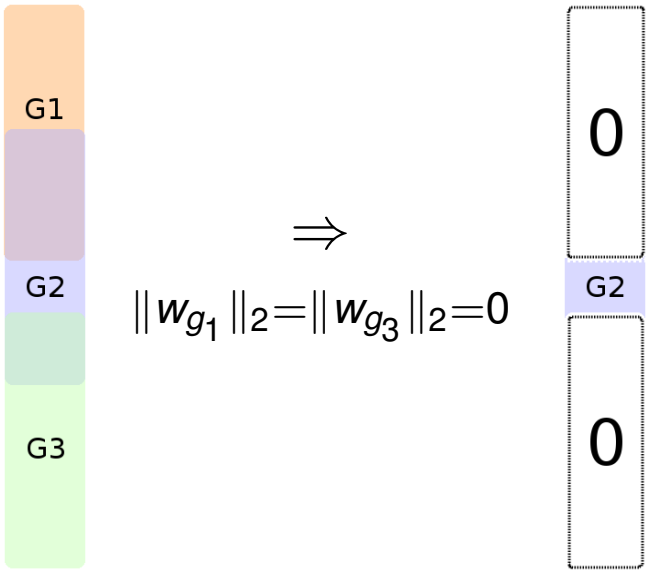
What if a gene belongs to several groups?

Issue of using the group-lasso

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



IGF selection $\Rightarrow$ selection of unwanted groups



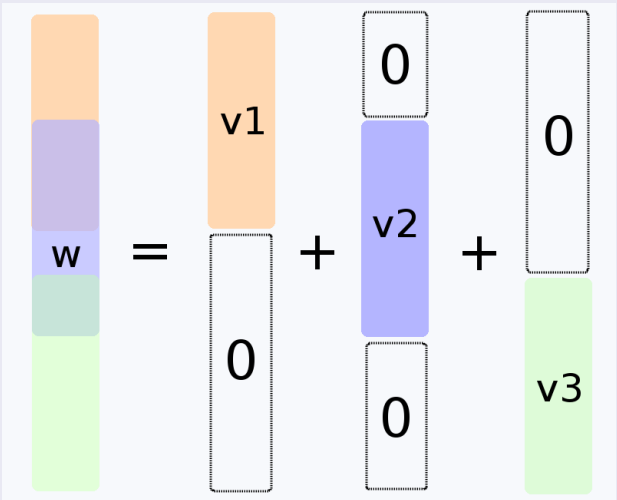
Removal of *any* group containing a gene $\Rightarrow$ the weight of the gene is 0.

Overlap norm (Jacob et al., 2009)

An idea

Introduce latent variables v_g:

$$\begin{cases} \min_{w,v} L(w) + \lambda \sum_{g \in \mathcal{G}} \|v_g\|_2 \\ w = \sum_{g \in \mathcal{G}} v_g \\ \text{supp}\left(v_g\right) \subseteq g. \end{cases}$$



Properties

- Resulting support is a *union* of groups in $\mathcal{G}$.
- 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

$$\begin{cases} \min_{w,v} L(w) + \lambda \sum_{g \in \mathcal{G}} \|v_g\|_2 \\ w = \sum_{g \in \mathcal{G}} v_g \\ \text{supp}\left(v_g\right) \subseteq g. \end{cases} = \min_w L(w) + \lambda \Omega_{overlap}(w)$$

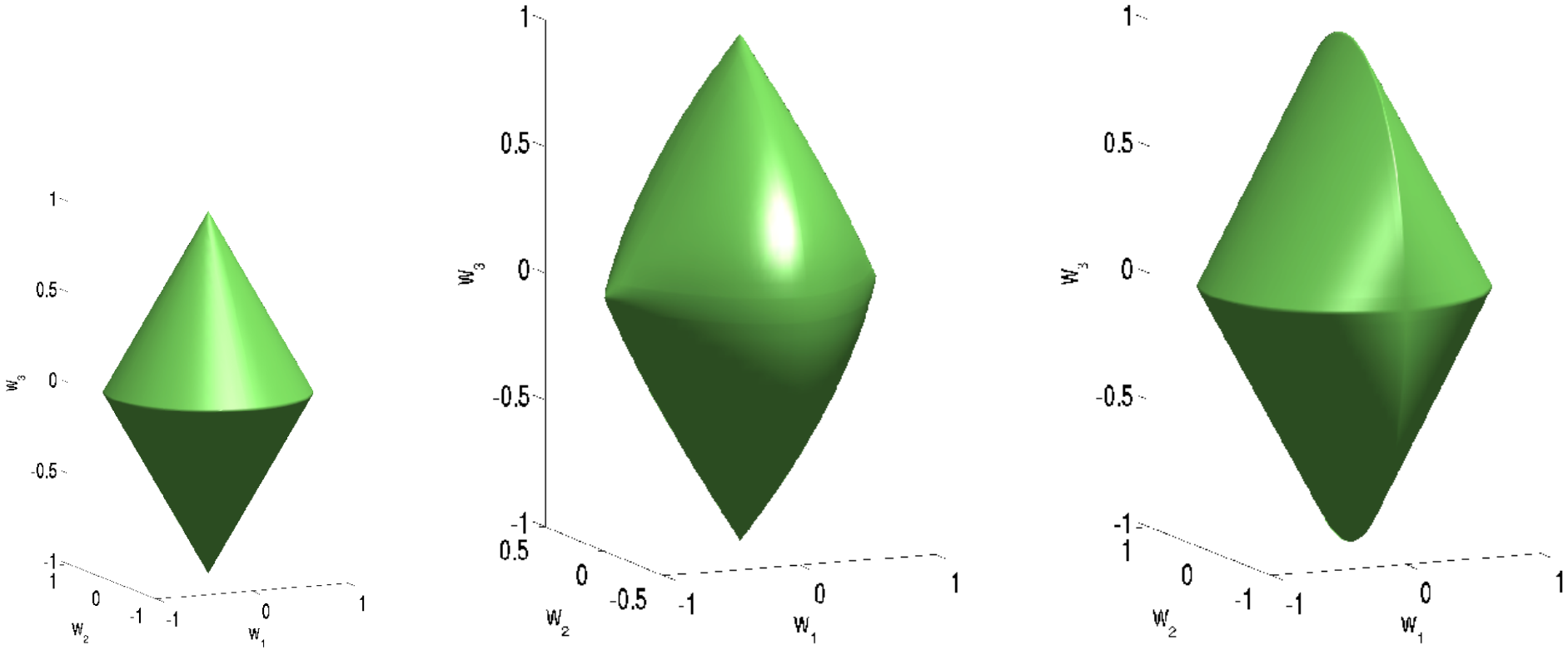
with

$$\Omega_{overlap}(w) \triangleq \begin{cases} \min_v \sum_{g \in \mathcal{G}} \|v_g\|_2 \\ w = \sum_{g \in \mathcal{G}} v_g \\ \text{supp}\left(v_g\right) \subseteq g. \end{cases} \quad (*)$$

Property

- $\Omega_{overlap}(w)$ is a norm of w.
- $\Omega_{overlap}(.)$ associates to w a specific (not necessarily unique) decomposition $(v_g)_{g \in \mathcal{G}}$ which is the argmin of $(*)$.

Overlap and group unity balls



Balls for $\Omega^{\mathcal{G}}_{\text{group}}(\cdot)$ (middle) and $\Omega^{\mathcal{G}}_{\text{overlap}}(\cdot)$ (right) for the groups $\mathcal{G} = \{\{1,2\},\{2,3\}\}$ where w_2 is represented as the vertical coordinate. Left: group-lasso ($\mathcal{G} = \{\{1,2\},\{3\}\}$), 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 $\Omega^{\mathcal{G}}_{\text{overlap}}(\bar{w}) = \sum \|\bar{v}_g\|_2$.
- Consider the regularized empirical risk minimization problem $L(w) + \lambda \Omega^{\mathcal{G}}_{\text{overlap}}(w)$.

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 $(\hat{v}_g)_{g \in \mathcal{G}}$ such that

$$\left\{ g \in \mathcal{G} | \hat{v}_g \neq 0 \right\} = \left\{ g \in \mathcal{G} | \bar{v}_g \neq 0 \right\}.$$

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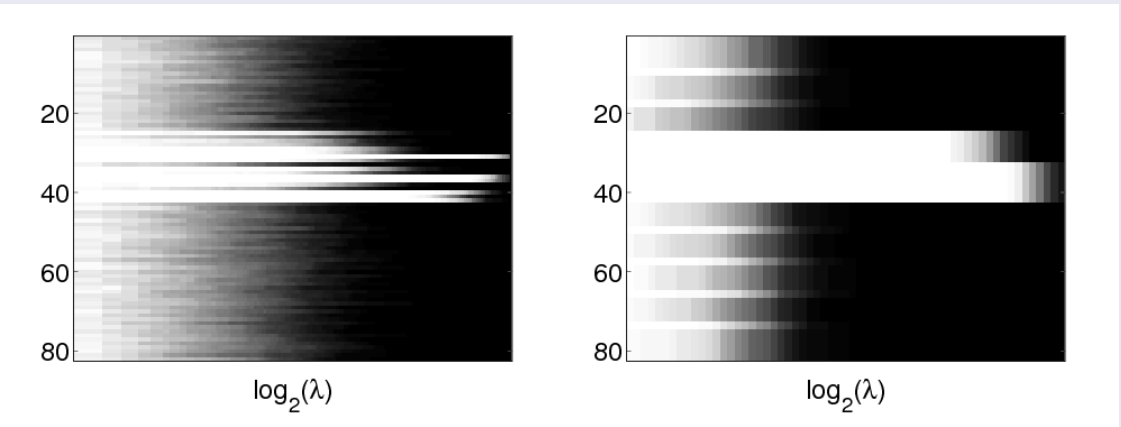
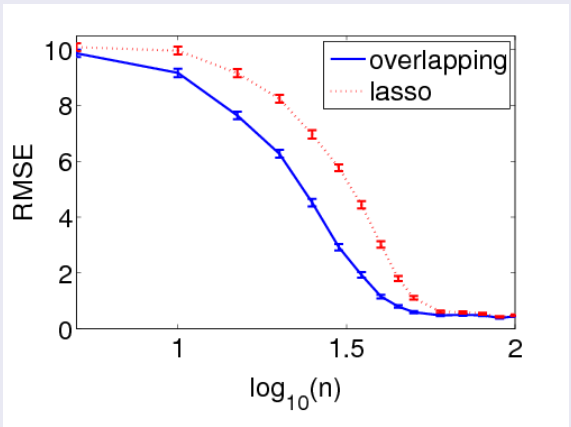
Experiments

Synthetic data: overlapping groups

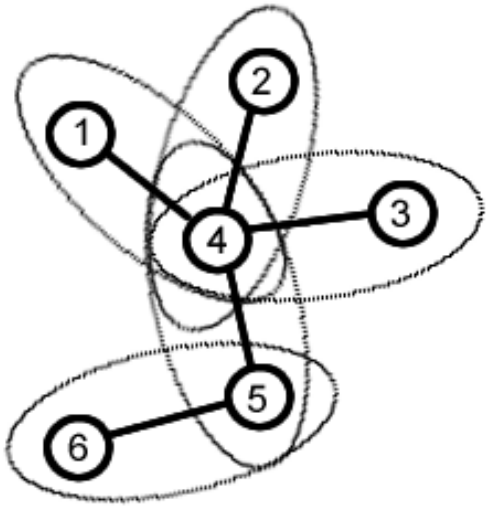
- 10 groups of 10 variables with 2 variables of overlap between two successive groups :$\{1, \ldots, 10\}, \{9, \ldots, 18\}, \ldots, \{73, \ldots, 82\}$.
- Support: union of 4*th* and 5*th* groups.
- Learn from 100 training points.





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

Graph lasso



Two solutions

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

$$\Omega_{union}(\beta) = \sup_{\alpha \in \mathbb{R}^p : \forall i \sim j, \|\alpha_i^2 + \alpha_j^2\| \leq 1} \alpha^\top \beta\,.$$

Graph lasso vs kernel on graph

- Graph lasso:

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

  constrains the sparsity, not the values
- Graph kernel

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

  constrains the values (smoothness), not the sparsity

Preliminary results

Breast cancer data

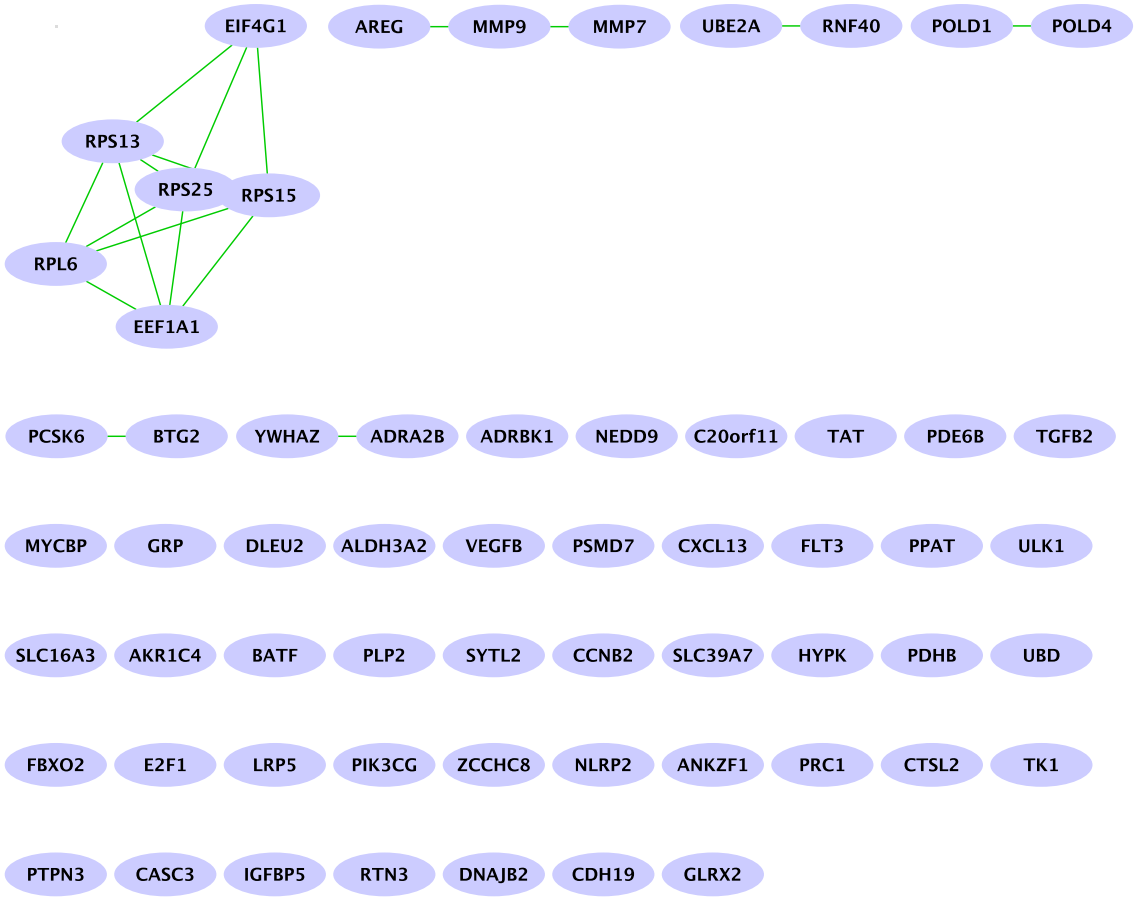
- Gene expression data for 8,141 genes in 295 breast cancer tumors.
- Canonical pathways from MSigDB containing 639 groups of genes, 637 of which involve genes from our study.

METHOD	ℓ_1	$\Omega^{\mathcal{G}}_{\text{OVERLAP}}(.)$
ERROR	0.38 ± 0.04	0.36 ± 0.03
MEAN $\sharp$ PATH.	130	30

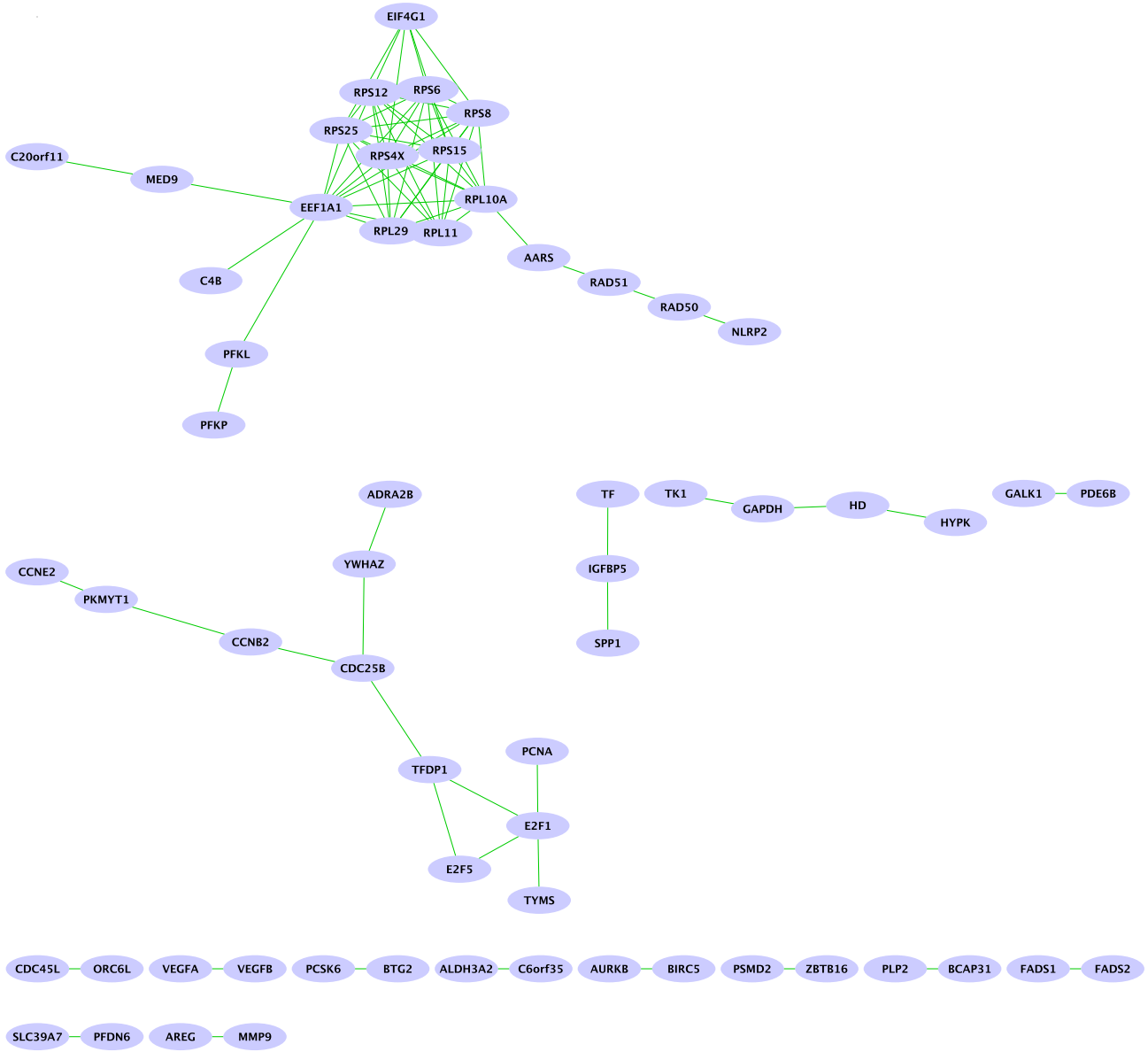
- Graph on the genes.

METHOD	ℓ_1	$\Omega_{graph}(.)$
ERROR	0.39 ± 0.04	0.36 ± 0.01
AV. SIZE C.C.	1.03	1.30

Lasso signature



Graph Lasso signature



Outline

Conclusions

- Feature / pattern selection in high dimension is central for many applications
- Convex sparsity-inducing penalties or positive definite kernels are promising
- Success stories remain limited on real data...
- Need to adjust the complexity of the model to the data available