Machine Learning for Personalized Medicine

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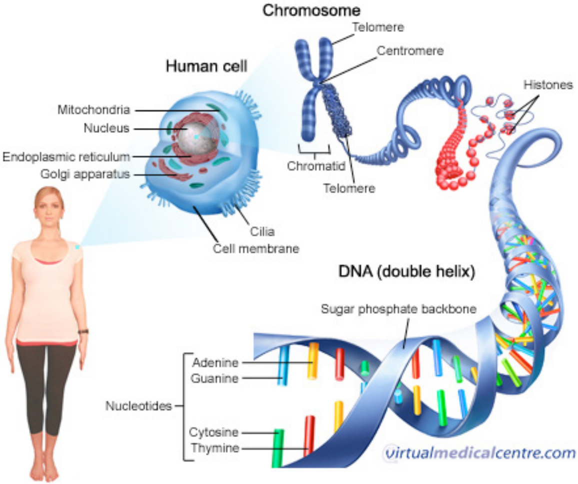
Together, let's beat cancer.

SeMoVi seminar, Grenoble, May 14, 2014

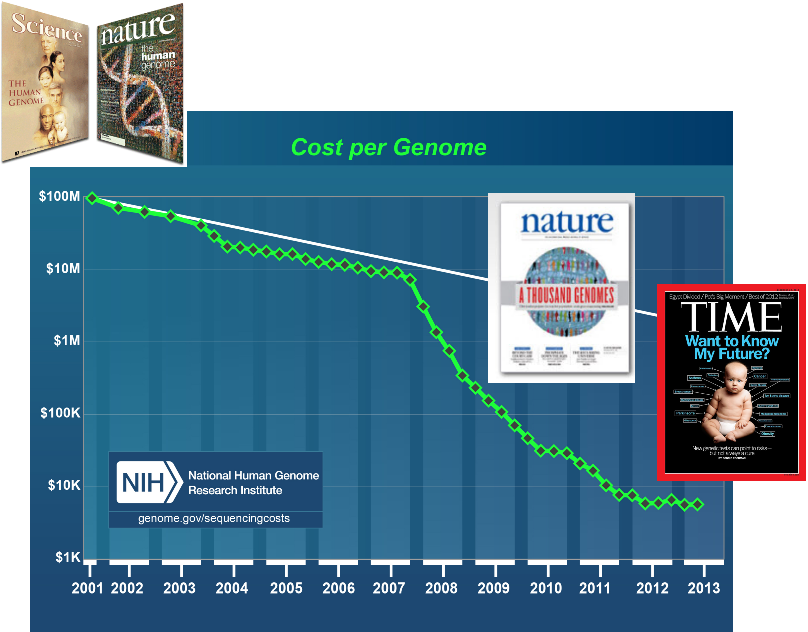
Complexity of life



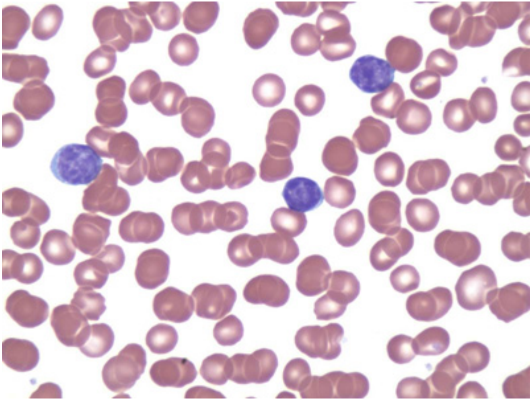
1 body = 10^{14} cells

1 cell = 6×10^{9} ACGT coding for $20,000$ genes

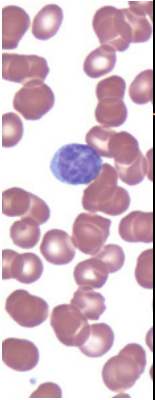
Sequencing revolution

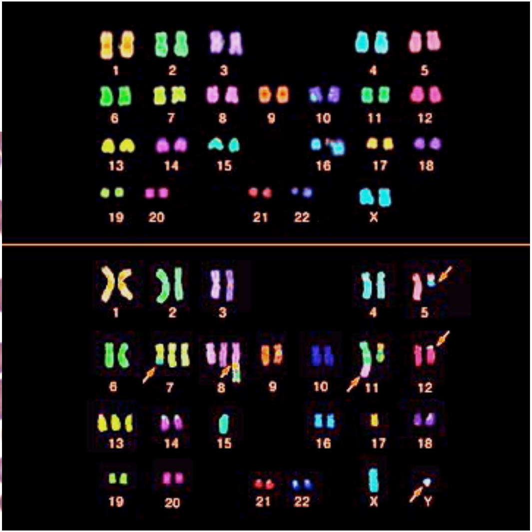


A cancer cell

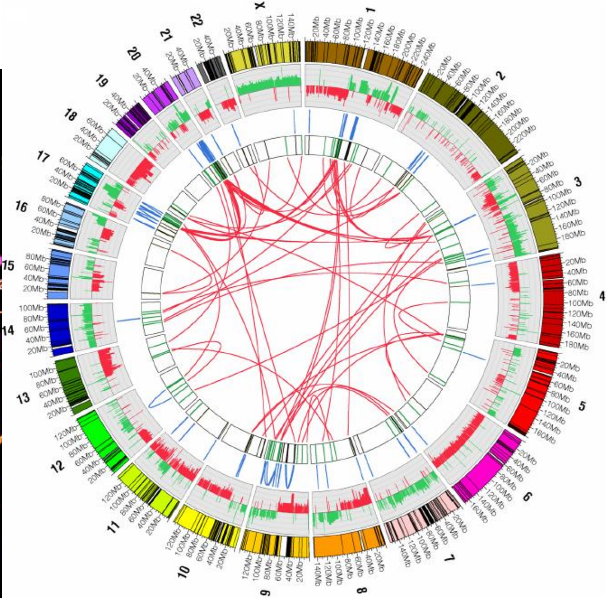


A cancer cell

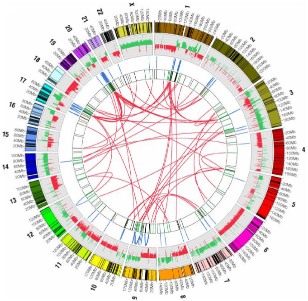




A cancer cell

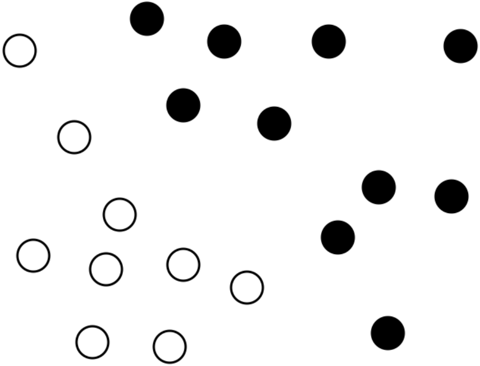


Opportunities

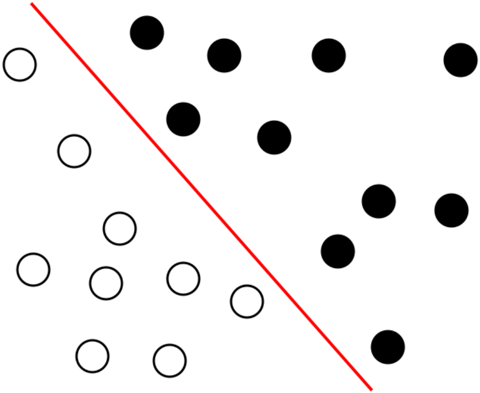


- What is your risk of developing a cancer? (*prevention*)
- After diagnosis and treatment, what is the risk of relapse? (*prognosis*)
- What specific treatment will cure your cancer? (*personalized medicine*)

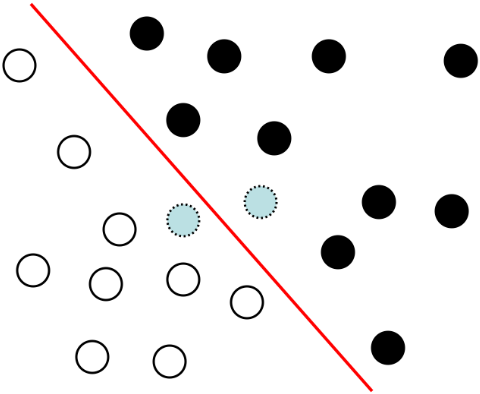
Machine learning formulation



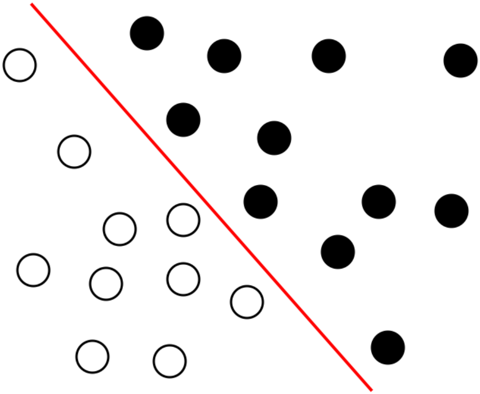
Machine learning formulation



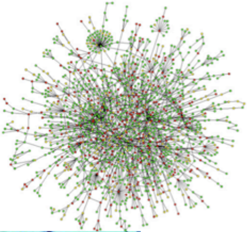
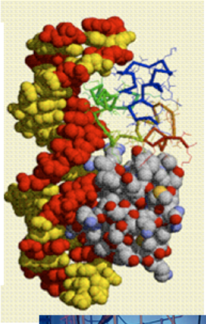
Machine learning formulation

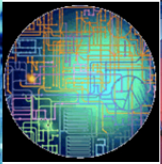


Machine learning formulation

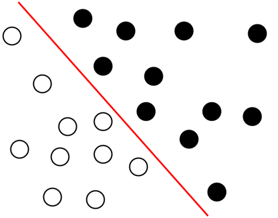


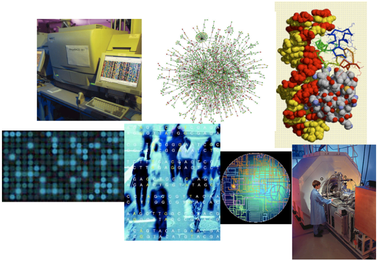
On real data...

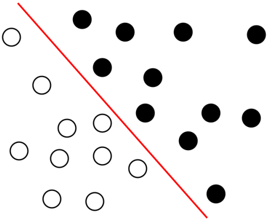

Challenges





- High dimension
- Few samples
- Structured data
- Heterogeneous data
- Prior knowledge
- Fast and scalable implementations
- Interpretable models

Learning with regularization



Learn

$$f_\beta(x) = \beta^\top x$$

by solving

$$\min_{\beta \in \mathbb{R}^p} R(f_\beta) + \lambda \Omega(\beta)$$

- $R(f_\beta)$ empirical risk
- $\Omega(\beta)$ penalty

Outline

1. Learning molecular classifiers with network information
2. Kernel bilinear regression for toxicogenomics

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1 Learning molecular classifiers with network information

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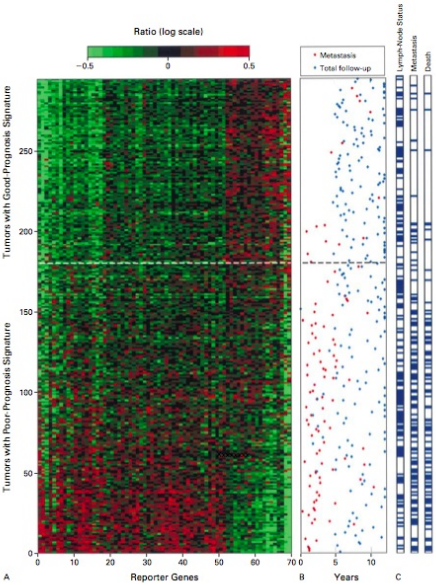
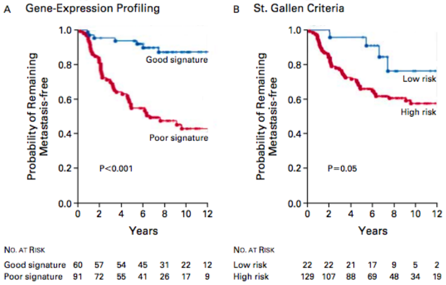
Breast cancer prognosis

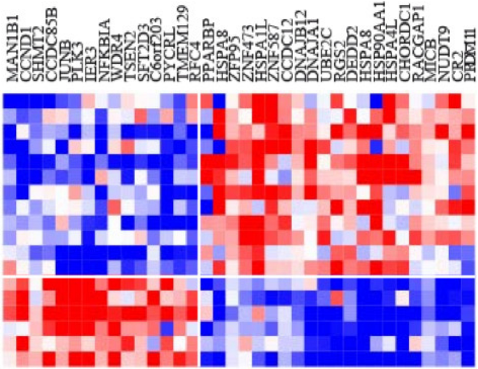




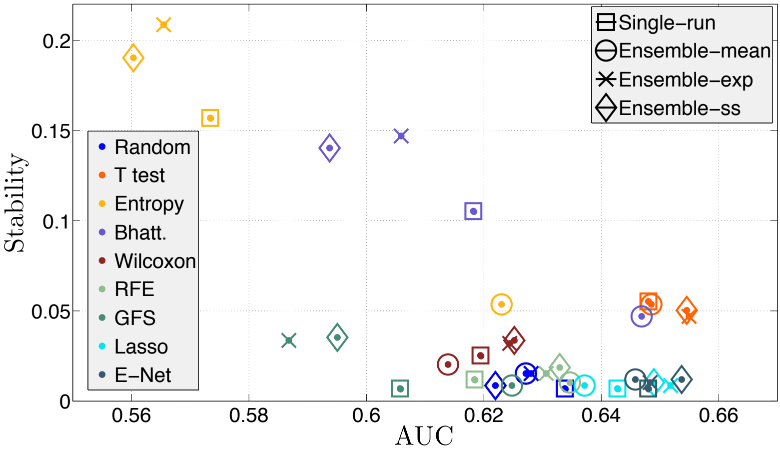
Gene selection, molecular signature

The idea

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

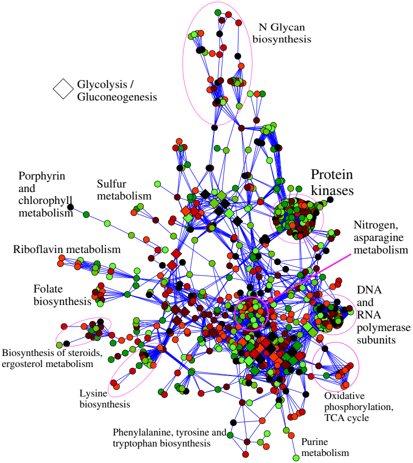


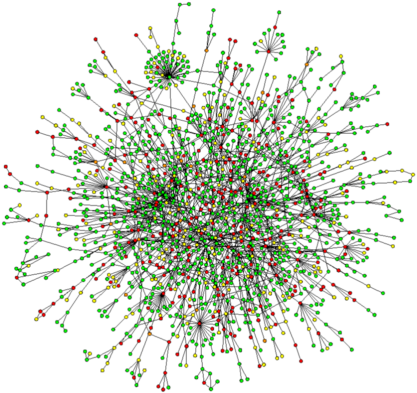
Lack of stability of signatures



Haury et al. (2011)

Gene networks

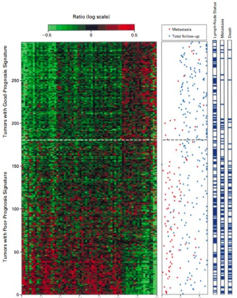


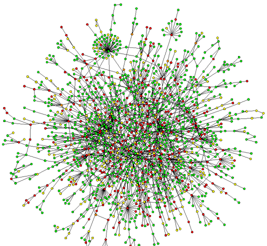


Gene networks and expression data

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

$$f_\beta(x) = \beta^\top x \qquad \min_\beta R(f_\beta) + \lambda\Omega(\beta)$$

Prior hypothesis

Genes near each other on the graph should have similar weigths.

An idea (Rapaport et al., 2007)

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

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

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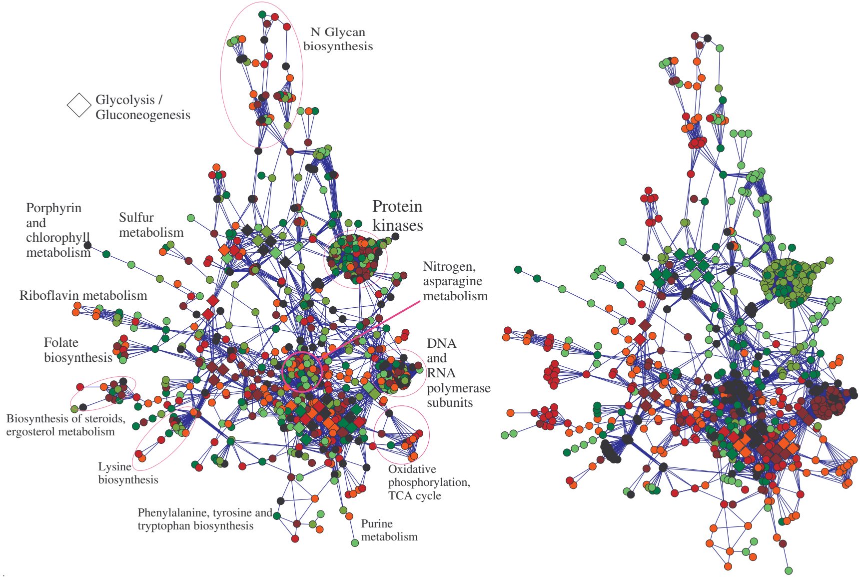
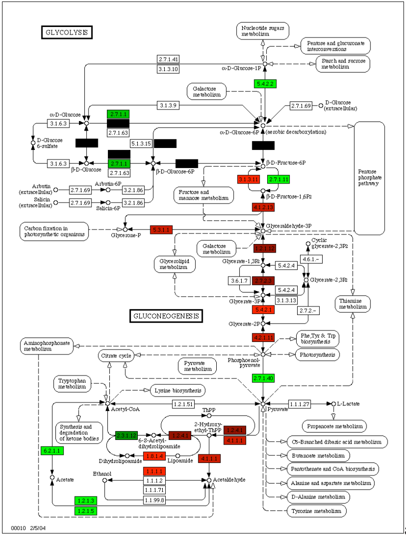
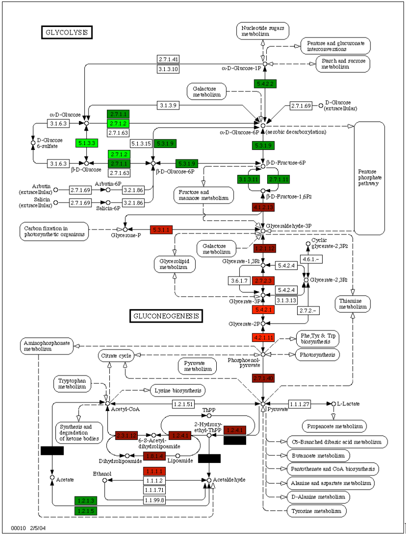
Classifiers



Classifier



a)



b)

Spectral penalty as a kernel

Theorem

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

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

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

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

and where

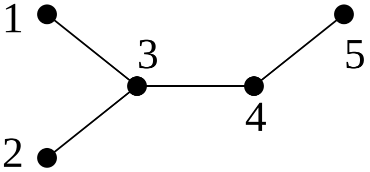
$$\Phi(x)^\top \Phi(x') = x^\top K_G x'$$

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

Graph Laplacian

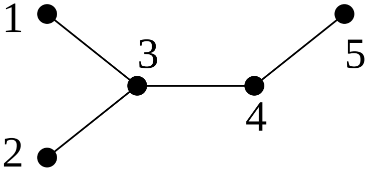
Definition

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



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

Pseufo-inverse of the Laplacian



$$L^* = \begin{pmatrix} 0.88 & -0.12 & 0.08 & -0.32 & -0.52 \\ -0.12 & 0.88 & 0.08 & -0.32 & -0.52 \\ 0.08 & 0.08 & 0.28 & -0.12 & -0.32 \\ -0.32 & -0.32 & -0.12 & 0.48 & 0.28 \\ -0.52 & -0.52 & -0.32 & 0.28 & 1.08 \end{pmatrix}$$

Other penalties with kernels

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

with:

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

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

- The diffusion kernel:

$$K_G = \exp_M(-2tL) .$$

penalizes high frequencies of β in the Fourier domain.

Other penalties without kernels

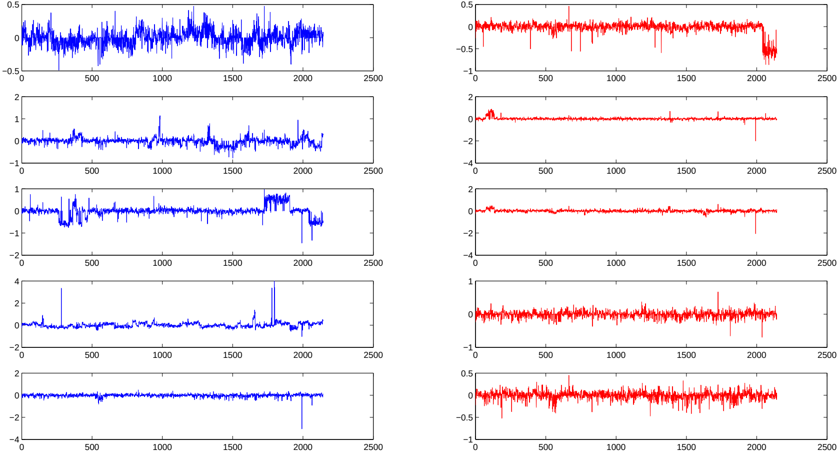
- Gene selection + Piecewise constant on the graph

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

- Gene selection + smooth on the graph

$$\Omega(\beta) = \sum_{i \sim j} \left(\beta_i - \beta_j\right)^2 + \sum_{i=1}^{p} |\, \beta_i \,|$$

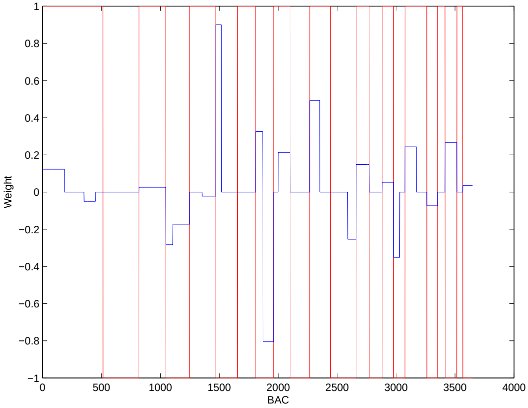
Example: classification of DNA copy number profiles



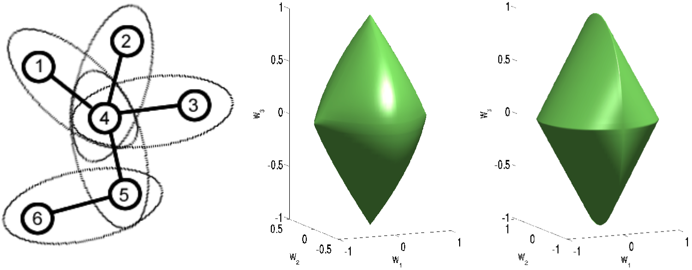
Aggressive (left) vs non-aggressive (right) melanoma

Fused lasso solution (Rapaport et al., 2008)

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



Graph-based structured feature selection

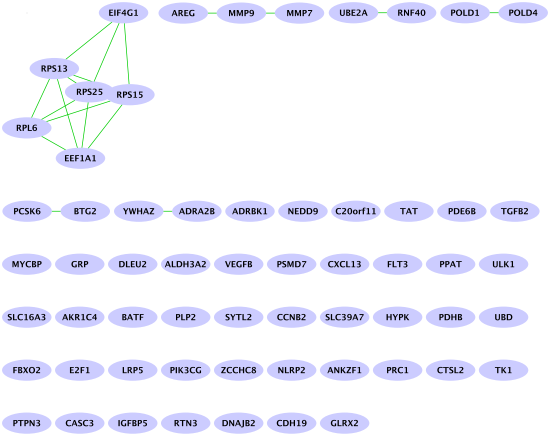


Graph lasso(s)

$$\Omega_1(\beta) = \sum_{i \sim j} \sqrt{\beta_i^2 + \beta_j^2}\,, \quad \text{(Jenatton et al., 2009)}$$

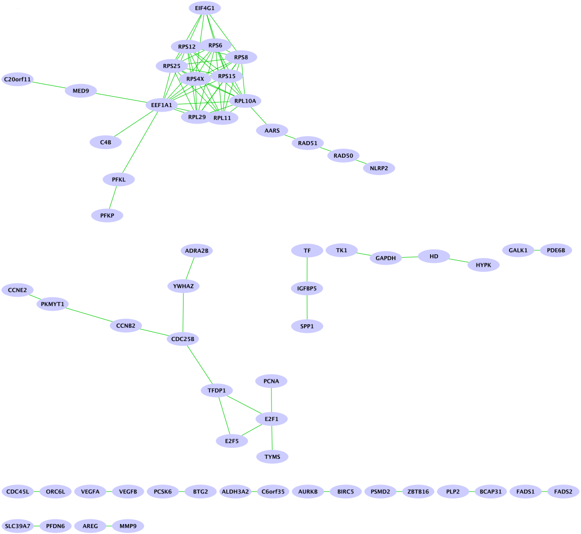
$$\Omega_2(\beta) = \sup_{\alpha \in \mathbb{R}^p : \forall i \sim j, \|\alpha_i^2 + \alpha_j^2\| \leq 1} \alpha^\top \beta\,. \quad \text{(Jacob et al., 2008)}$$

Lasso signature (accuracy 0.61)



Breast cancer prognosis

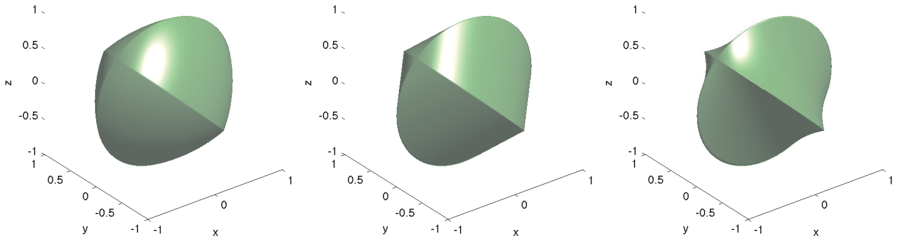
Graph Lasso signature (accuracy 0.64)



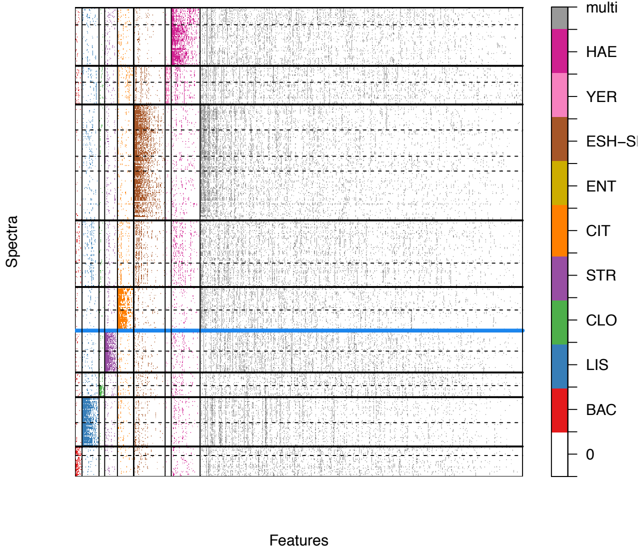
Breast cancer prognosis

Disjoint feature selection (Vervier et al., 2014)

$$W = (w_i)_{i \in V} \in \mathbb{R}^{p \times V} \qquad \Omega(W) = \min_{-H \leq W \leq H} \sum_{i \sim j} K_{ij} \left| h_i^\top h_j \right|$$



Example: multiclass classification of MS spectra



(Vervier et al, 2013, unpublished)

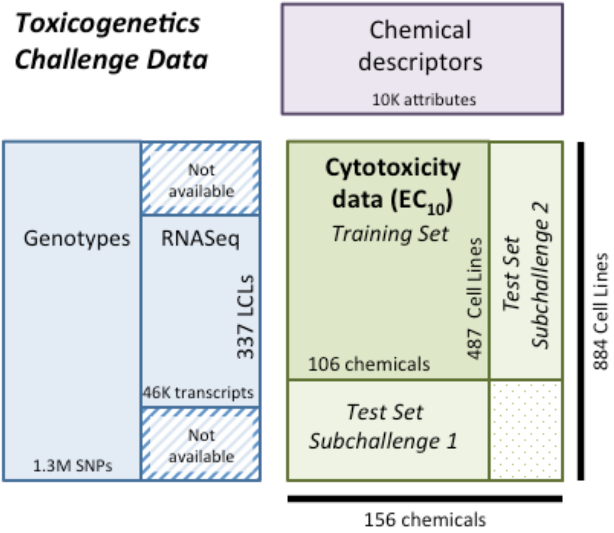
Outline

1. Learning molecular classifiers with network information

2. Kernel bilinear regression for toxicogenomics

Pharmacogenomics / Toxicogenomics

DREAM8 Toxicogenetics challenge



Genotypes from the 1000 genome project
RNASeq from the Geuvadis project

Bilinear regression

- Cell line X, chemical Y, toxicity Z.
- Bilinear regression model:

$$Z = f(X, Y) + b(Y) + \epsilon\,,$$

- Estimation by kernel ridge regression:

$$\min_{f \in \mathcal{H}, b \in \mathbb{R}^p} \sum_{i=1}^{n} \sum_{j=1}^{p} \left(f(x_i, y_j) + b_j - z_{ij} \right)^2 + \lambda \|f\|^2\,,$$

Solving in $O(max(n, p)^3)$

Theorem 1. *Let $Z \in \mathbb{R}^{n\times p}$ be the response matrix, and $K_X \in \mathbb{R}^{n\times n}$ and $K_Y \in \mathbb{R}^{p\times p}$ be the kernel Gram matrices of the n cell lines and p chemicals, with respective eigenvalue decompositions $K_X = U_X D_X U_X^\top$ and $K_Y = U_Y D_Y U_Y^\top$. Let $\gamma = U_X^\top \mathbf{1}_n$ and $S \in \mathbb{R}^{n\times p}$ be defined by $S_{ij} = 1/\left(\lambda + D_X^i D_Y^j\right)$, where D_X^i (resp. D_Y^i) denotes the i-th diagonal term of D_X (resp. D_Y). Then the solution (f^*, b^*) of (2) is given by*

$$b^* = U_Y Diag\left(S^\top \gamma^{\circ 2}\right)^{-1}\left(S^\top \circ \left(U_Y^\top Z^\top U_X\right)\right)\gamma \tag{3}$$

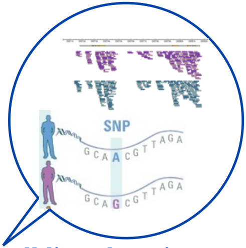
and

$$\forall (x, y) \in \mathcal{X} \times \mathcal{Y}, \quad f^*(x, y) = \sum_{i=1}^{n}\sum_{j=1}^{p} \alpha_{i,j}^* K_X(x_i, x) K_Y(y_i, y)\,, \tag{4}$$

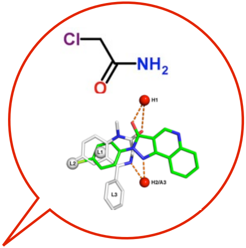
where

$$\alpha^* = U_X\left(S \circ \left(U_X^\top\left(Z - \mathbf{1}_n b^{*\top}\right)U_Y\right)\right)U_Y^\top\,. \tag{5}$$

Kernel Trick

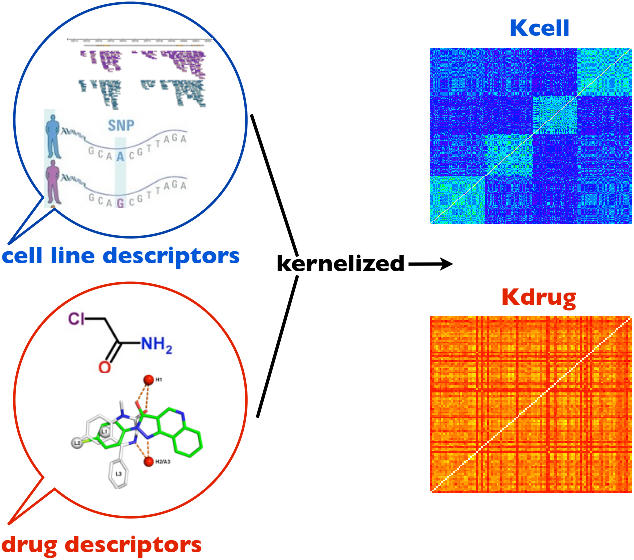


cell line descriptors



drug descriptors

Kernel Trick



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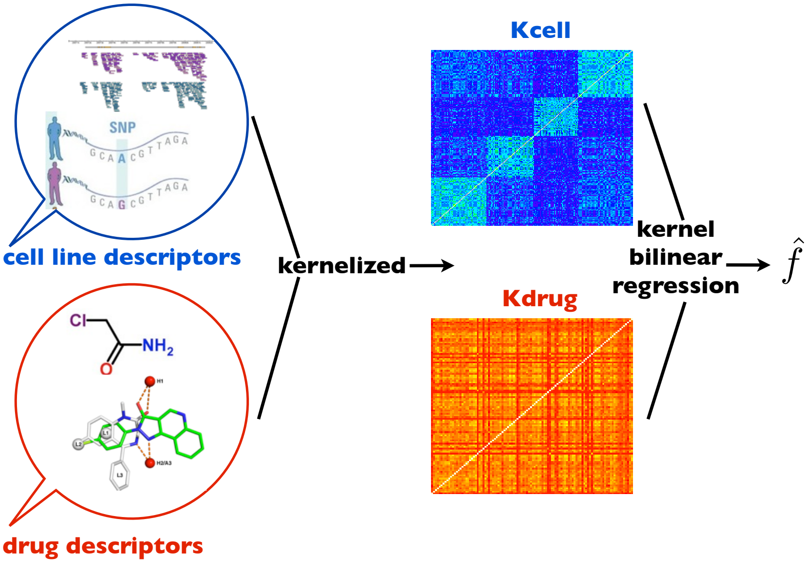

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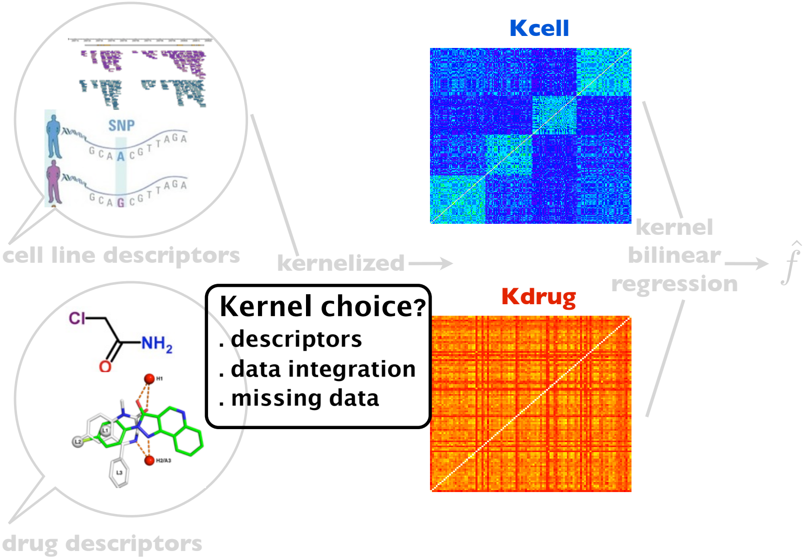

Kernel choice

1. $\mathbf{K}_{\text{cell}}$:
   $\Longrightarrow$ 29 cell line kernels tested
   $\Longrightarrow$ 1 kernel that *integrate all information*
   $\Longrightarrow$ deal with missing data
2. $\mathbf{K}_{\text{drug}}$:
   $\Longrightarrow$ 48 drug kernels tested
   $\Longrightarrow$ multi-task kernels

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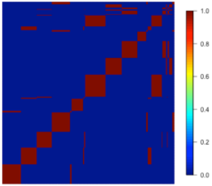
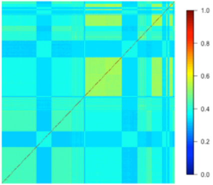
Cell line data integration

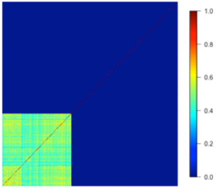
Covariates
. linear kernel



SNPs
. 10 gaussian kernels



RNA-seq
. 10 gaussian kernels



Cell line data integration

Covariates
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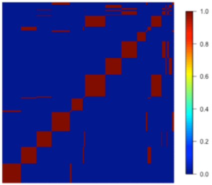

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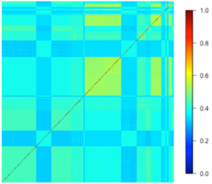

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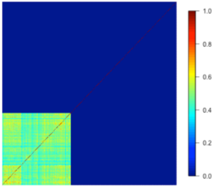
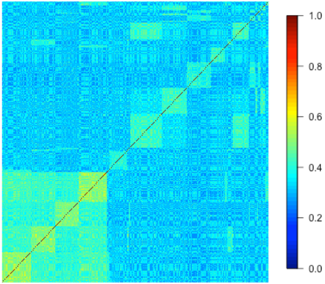
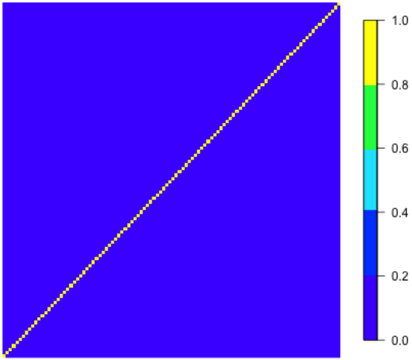


Integrated kernel



Multi-task drug kernels

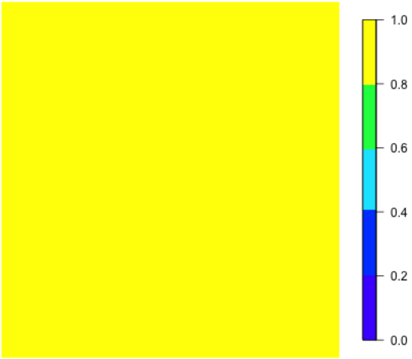
1. **Dirac**
2. Multi-Task
3. Feature-based
4. Empirical
5. Integrated



independent regression for each drug

Multi-task drug kernels

1. Dirac
2. **Multi-Task**
3. Feature-based
4. Empirical
5. Integrated



sharing information across drugs

Multi-task drug kernels

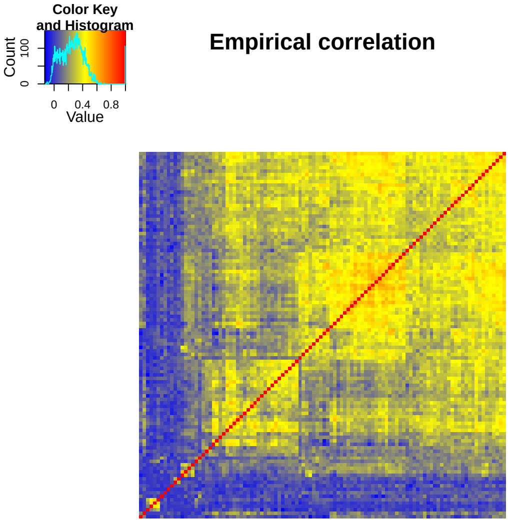
1. Dirac
2. Multi-Task
3. **Feature-based**
4. Empirical
5. Integrated

Linear kernel and 10 gaussian kernels based on features:

- CDK (160 descriptors) and SIRMS (9272 descriptors)
- Graph kernel for molecules (2D walk kernel)
- Fingerprint of 2D substructures (881 descriptors)
- Ability to bind human proteins (1554 descriptors)

Multi-task drug kernels

1. Dirac
2. Multi-Task
3. Feature-based
4. **Empirical**
5. Integrated



Multi-task drug kernels

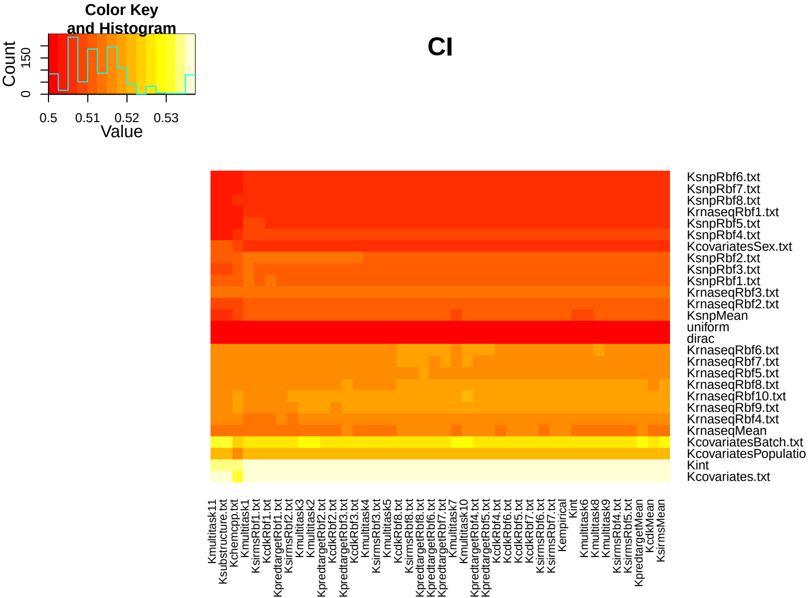
1. Dirac
2. Multi-Task
3. Feature-based
4. Empirical
5. **Integrated**

$$K_{int} = \sum_i K_i$$

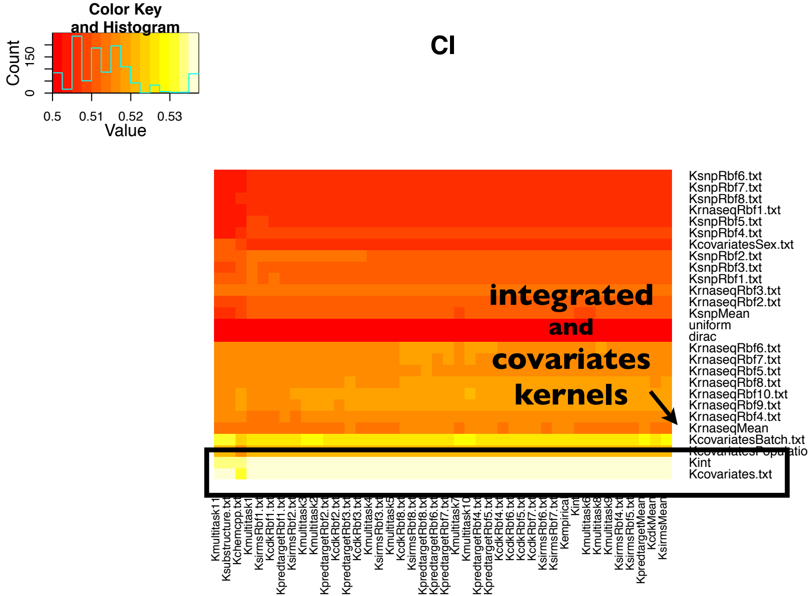
Integrated kernel:

- Combine all information on drugs

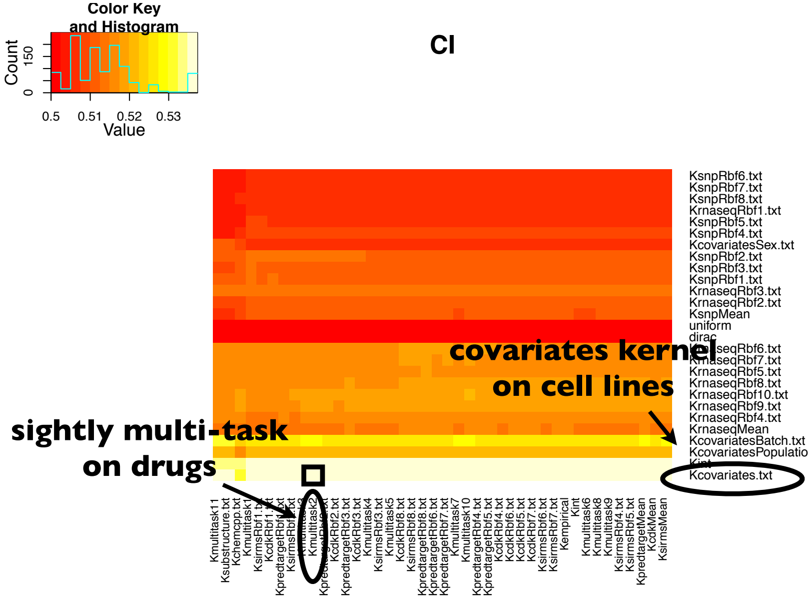
29x48 kernel combinations: CV results



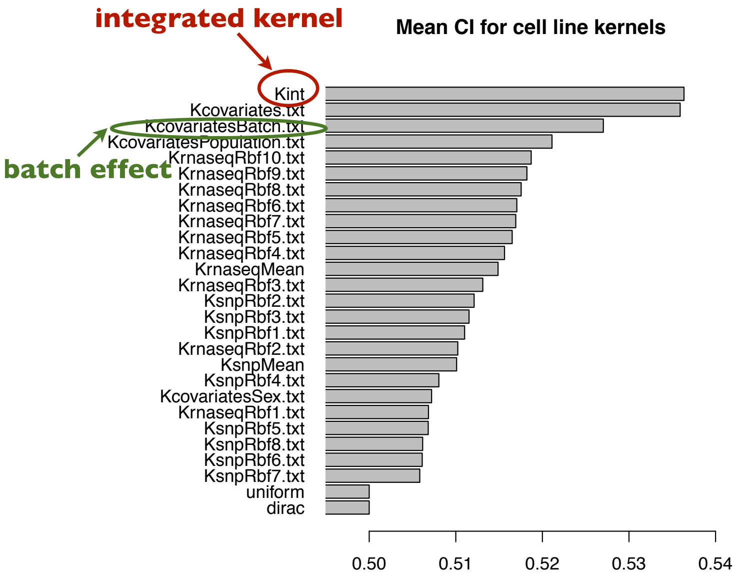
29x48 kernel combinations: CV results



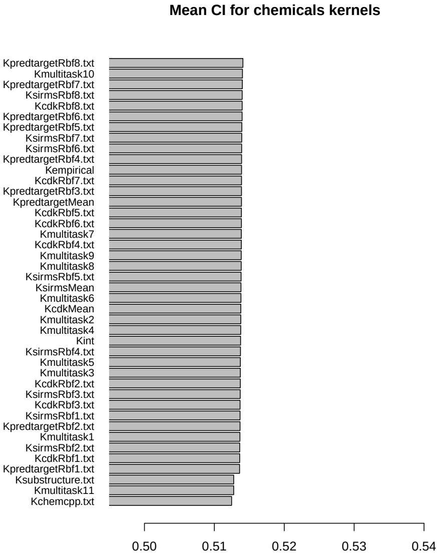
29x48 kernel combinations: CV results



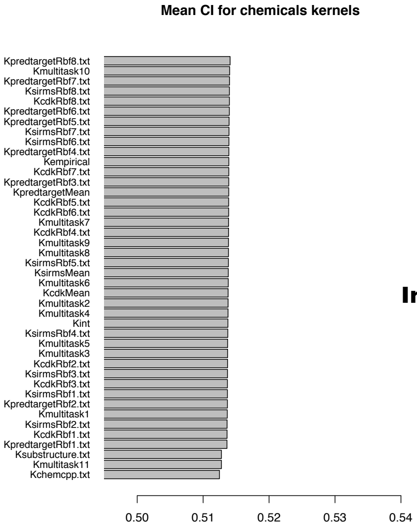
Kernel on cell lines: CV results



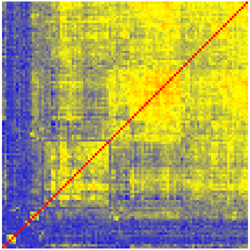
Kernel on drugs: CV results



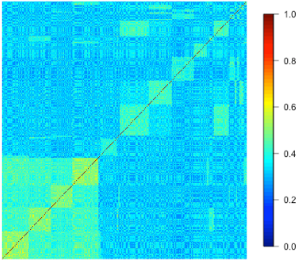
Final Submission (ranked 2nd)



Empirical kernel on drugs



Integrated kernel on cell lines



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