*Data Science Summer School 2018*

# Machine learning for genetic data

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# Precision Medicine

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- **Data-driven** biology/medicine

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- **Data-driven** biology/medicine

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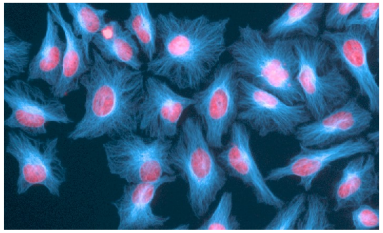
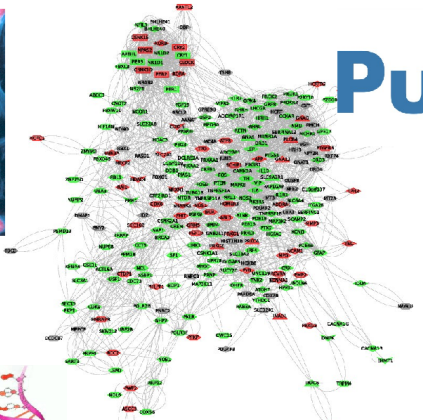
**Data** + **Feature Selection**

# Accumulating data



phenome

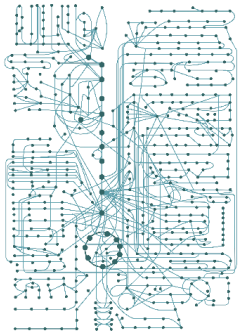


interactome

PubMed

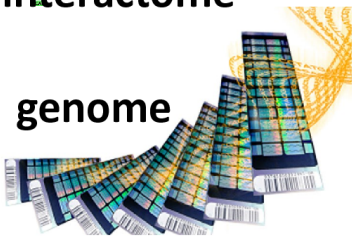
publications


transcriptome

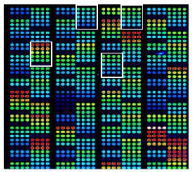


metabolome

methylome



genome



proteome

Image sources: ajc1@ flickr; Zlir'a@wikimedia

NIH THE CANCER GENOME ATLAS
National Cancer Institute
National Human Genome Research Institute

biobank uk
Improving the health of future generations

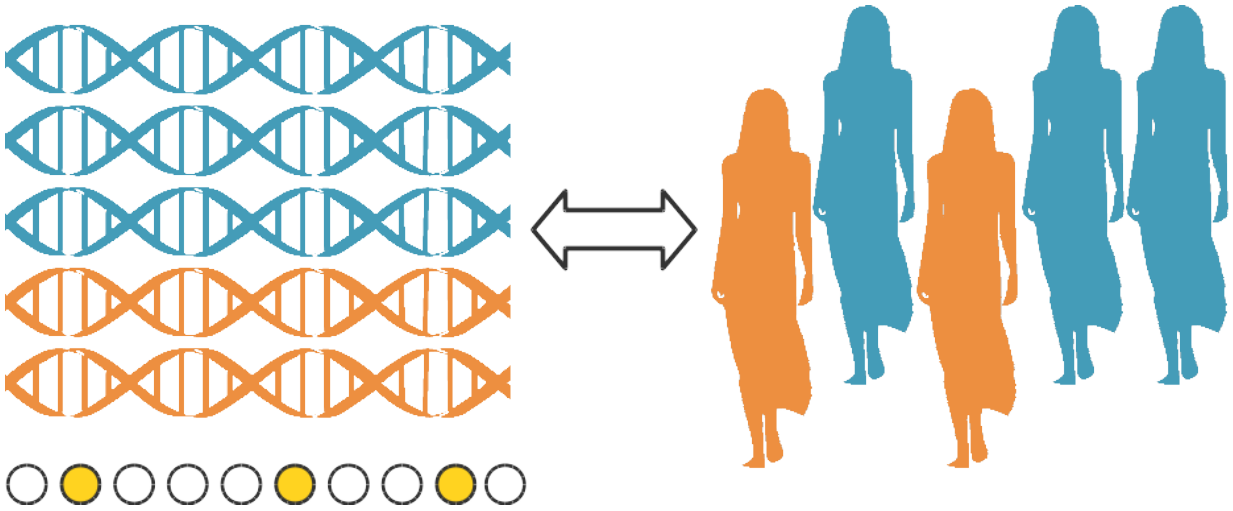
db GaP
GENOTYPES and PHENOTYPES

DREAM Challenges

*Ceci n'est pas* **du Big Data**

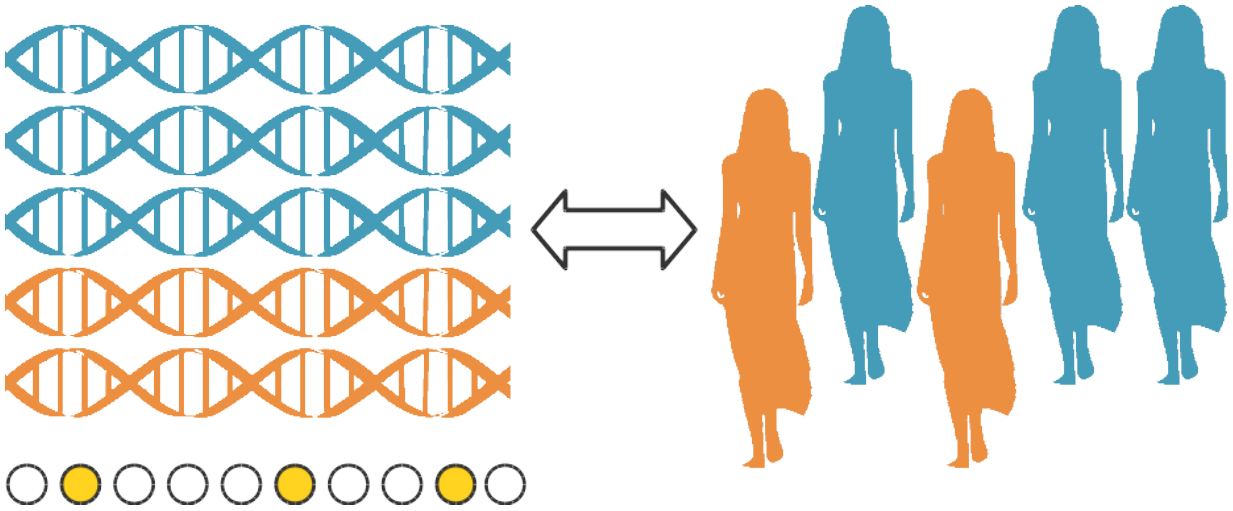
Magritte

# From genotype to phenotype



**Which genomic features explain the phenotype?**

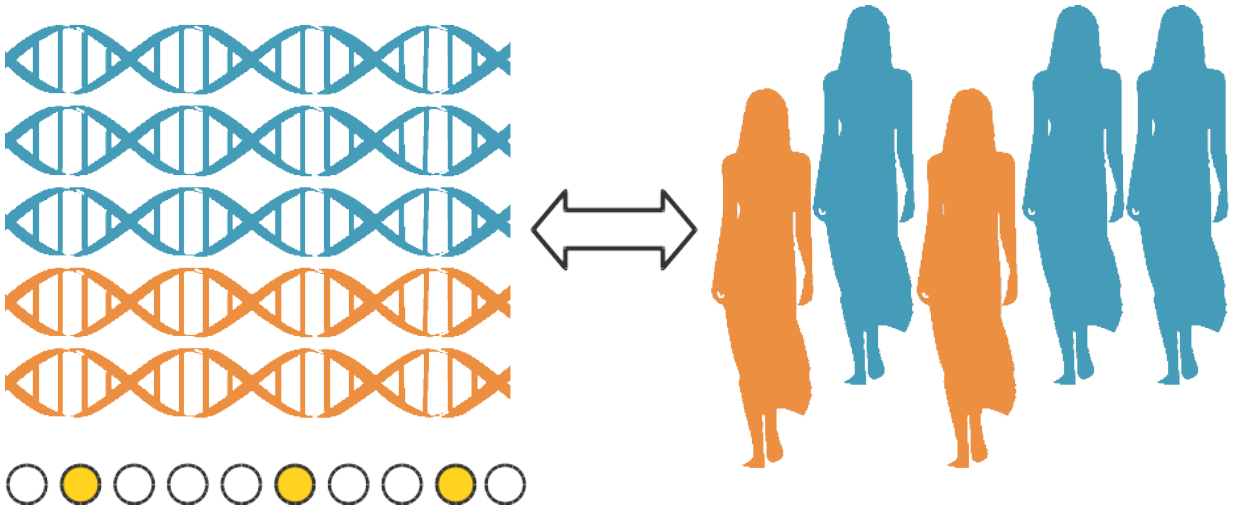
# From genotype to phenotype



**Which genomic features explain the phenotype?**

- 80 000 proteins
- 200 000 mRNA
- 10 million SNPs
- 28 million CpG islands

# From genotype to phenotype



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$p = 10^5 - 10^7$ **genomic features**

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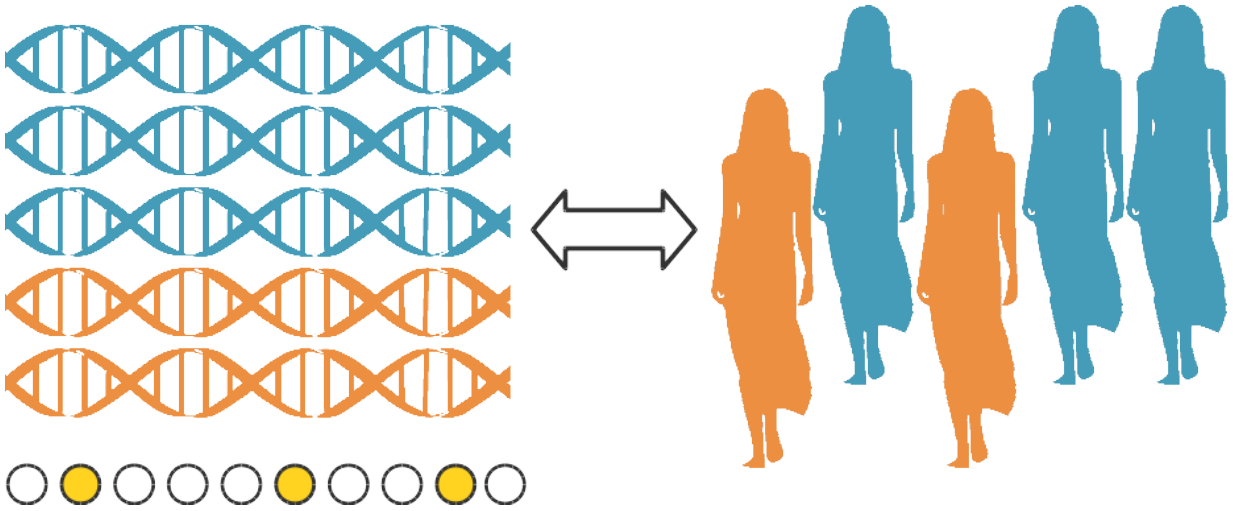

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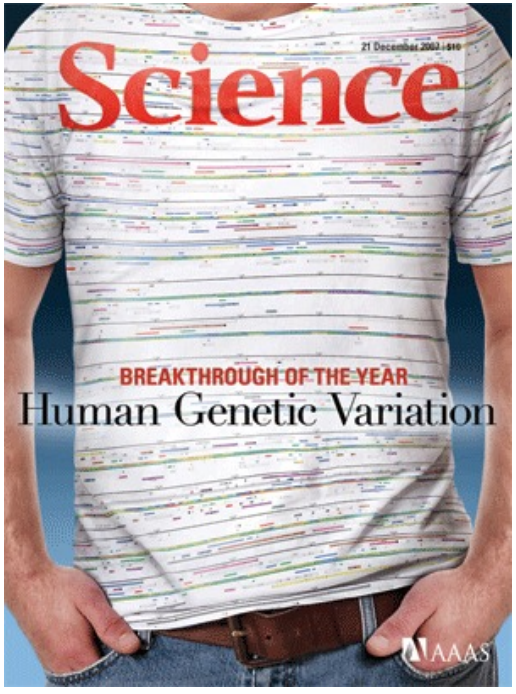
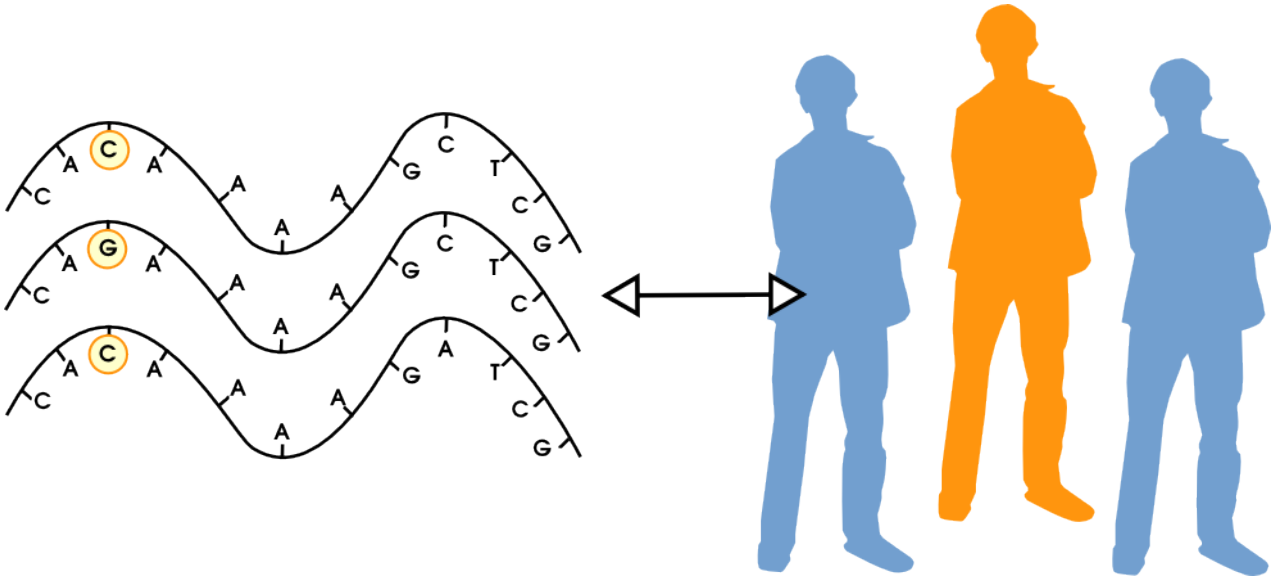
**High-dimensional** (large p), **low sample size** (small n) data.

# GWAS: Genome-Wide Association Studies



**Which genomic features explain the phenotype?**

$p = 10^5 - 10^7$ Single Nucleotide Polymorphisms (SNPs)

$n = 10^2 - 10^4$ samples

[Pen07; Man13; Vis+17]

# 1. Challenges of high-dimensional data

# Challenges of high-dimensional data

- **Computational challenges** for some algorithms

  **Linear regression:** inverting $X^\top X$ takes $\mathcal{O}(p^3)$ computations.

- The **curse of dimensionality** makes it hard to learn

- **Overfitting** is more likely

- **Ill-posed problems.**

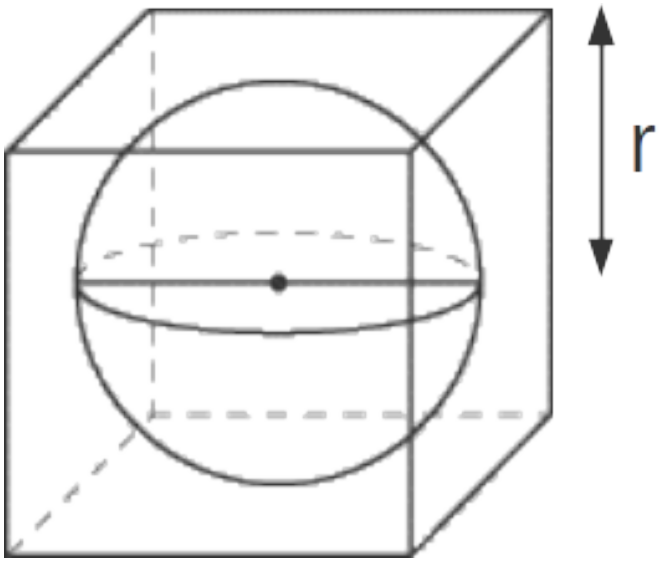
# The curse of dimensionality

- Methods and intuitions that work in low dimension **might not apply to higher dimensions.**

- **Hyperspace is very big and everything is far apart**

  Fraction of the points within a cube that fall outside the inscribed circle:

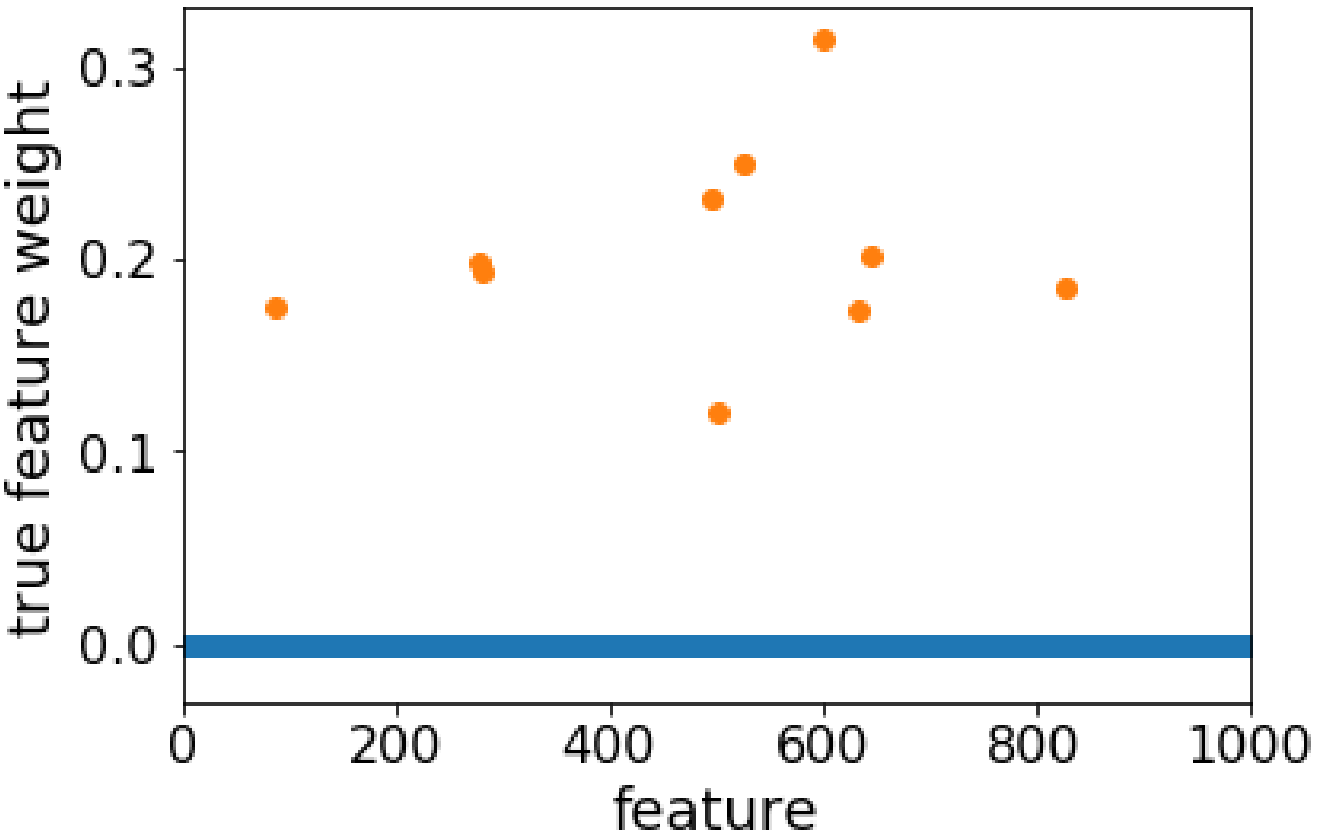
  - In two dimensions: $1 - \frac{\pi r^2}{4r^2} = 1 - \frac{\pi}{4}$
  - In three dimensions: $1 - \frac{4/3\pi r^3}{8r^3} = 1 - \frac{\pi}{6}$
  - In higher dimension: tends towards $1$.



# Large p, small n data

**Simulation:** n=150, p=1000, 10 causal features.

$$y = \sum_{j=1}^{p} w_j x_j + \epsilon$$



# Qualitative GWAS

**Binary** phenotype, i.e. case/controls encoded as 1/0.

- **Contingency table**

| | AA | Aa | aa |
|---|---|---|---|
| Cases | | | |
| Ctrls | | | |

| | 0 | 1 |
|---|---|---|
| Cases | a | b |
| Ctrls | c | d |

**Statistical tests:** $\chi^2$, Cochran-Armitage trend test, etc.

- **Logistic regression**

$$\text{logit}(p(y|X)) = \beta_0 + \beta_1 X$$

- **Odds-ratio**

$$\underbrace{\frac{\text{P(0|case)}}{\text{P(0|ctrl)}}}_{\text{odds of 0 in cases}} \Big/ \underbrace{\frac{\text{P(1|case)}}{\text{P(1|ctrl)}}}_{\text{odds of 1 in cases}} = \frac{ad}{bc}$$

# Quantitative GWAS

- **Linear regression**

$$y = \beta_0 + \beta_1 X$$

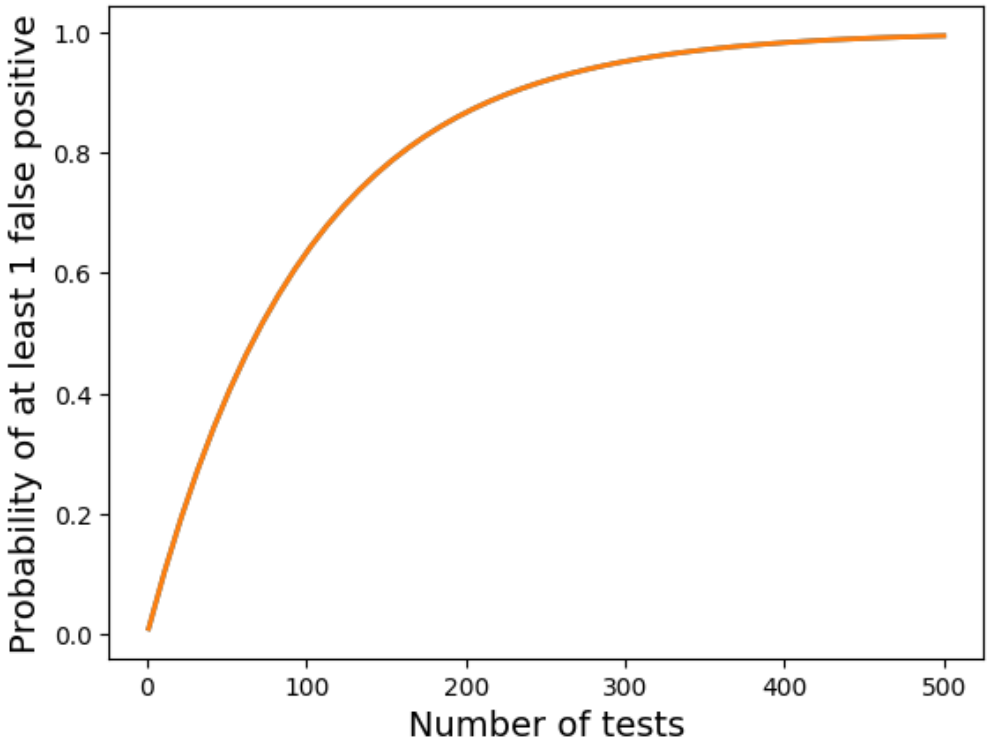
- p-value: Is $\hat{\beta}_1$ significantly different from 0?

  **Wald test:** compare $\frac{\hat{\beta}_1^2}{\text{Var}(\hat{\beta}_1)}$ to a $\chi^2$ distribution.

- **Effect size:** $\beta_1$.

# Multiple Hypothesis Testing

- Probability of having **at least one false positive:**
  - For **one** test: $\alpha$
  - For **p** tests: $1 - (1 - \alpha)^p$




- Controlling **Family-Wise Error Rate** (FWER)

  $\text{FWER} = P(|\text{FP}| \geq 1)$

  FP = number of false positives (Type I errors)

- **Bonferroni** correction: $\alpha \rightarrow \frac{\alpha}{p}$

# Simulation

**t-test:** For each feature,

- fit $y \sim w_j x_j + b_j$
- test whether $w_j \neq 0$.

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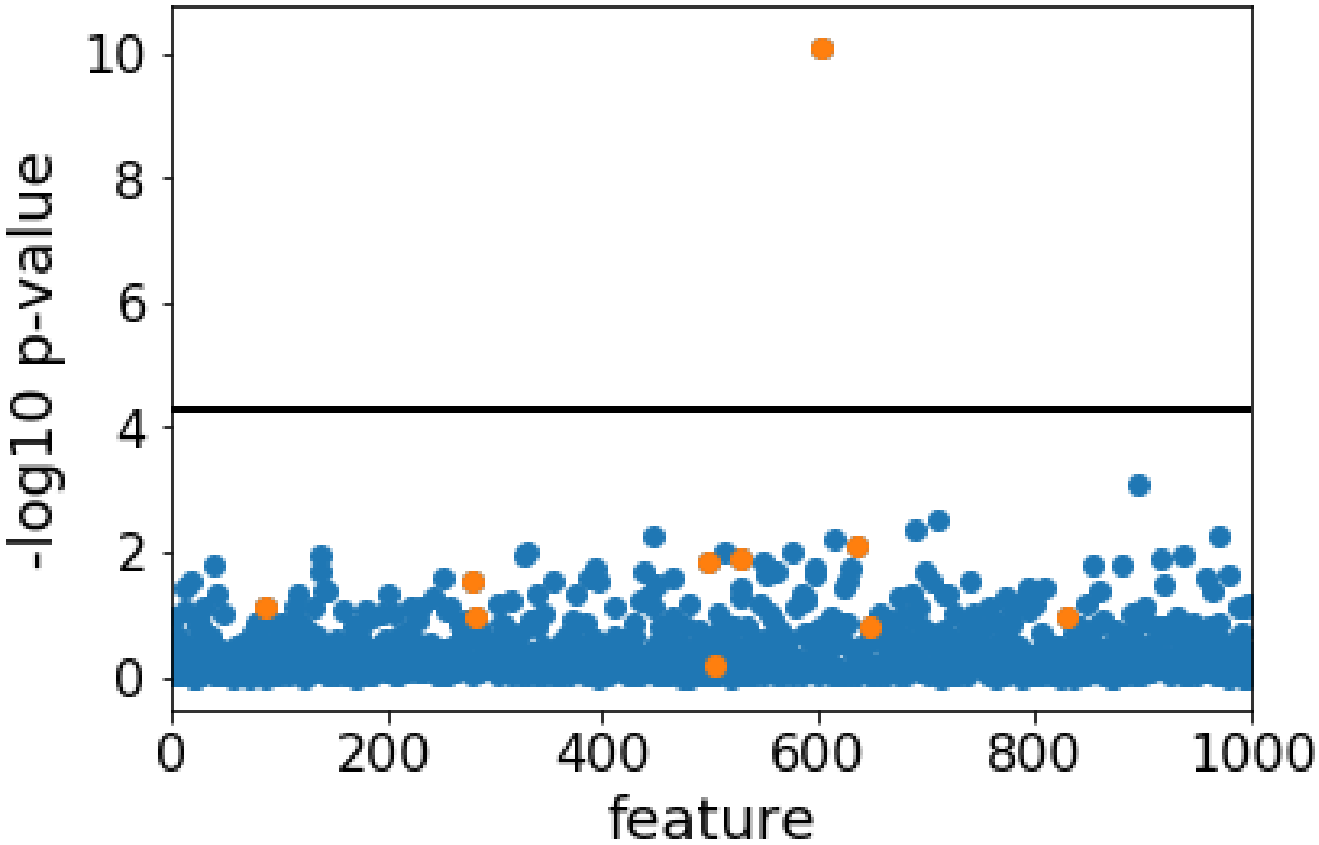

# Missing heritability

GWAS **fail to explain** most of the **inheritable variability** of complex traits.

Many possible reasons:

- non-genetic / non-SNP factors
- heterogeneity of the phenotype
- rare SNPs
- weak effect sizes
- **few samples in high dimension ($p \gg n$)**
- **joint effets of multiple SNPs.**

Ref: [Man+09]

# Simulation

**Linear regression:** Fit $y \sim \sum_{j=1}^{p} w_j x_j + b$.

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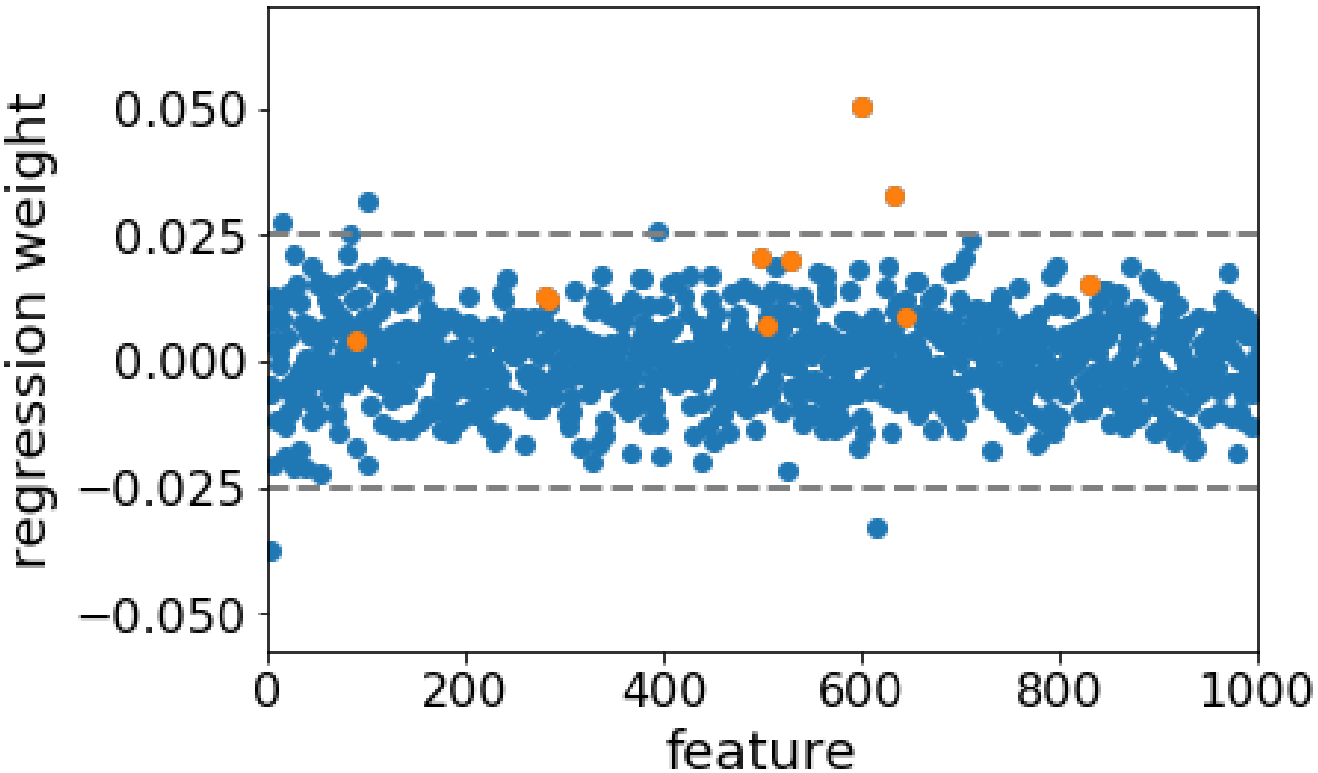

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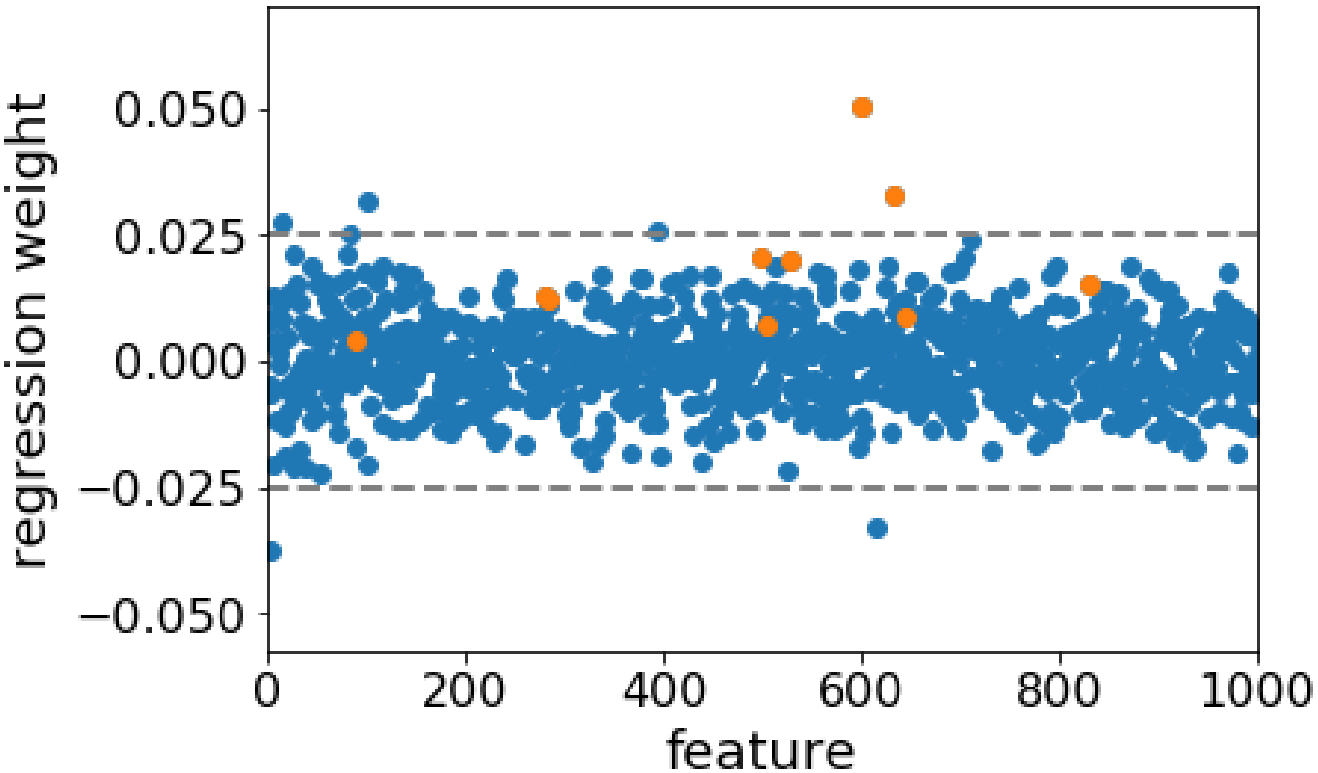
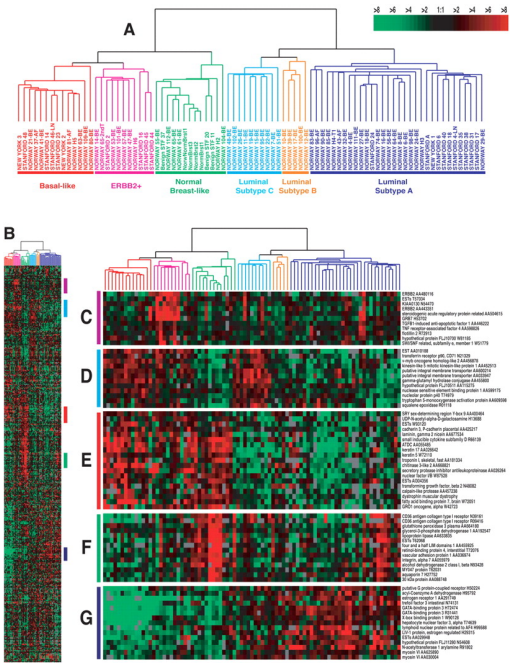
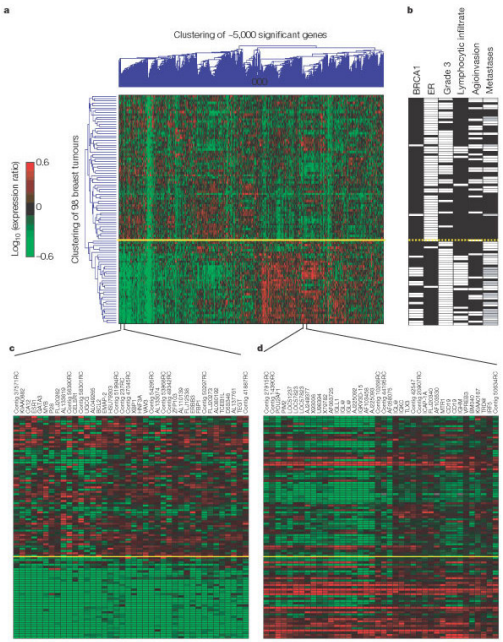



- RMSE on test set: 0.21.

# Molecular signatures stability

**Stability (robustness):** find similar answers on different data sets linked to the same biological question.

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PLoS COMPUTATIONAL BIOLOGY

## Most Random Gene Expression Signatures Are Significantly Associated with Breast Cancer Outcome

David Venet[1], Jacques E. Dumont[2], Vincent Detours[2,3]*

# Molecular signatures stability

- **Correction** to Snyder, A. et al. "Genetic basis for clinical response to CTLA-4 blockade in melanoma", NEJM (2014)

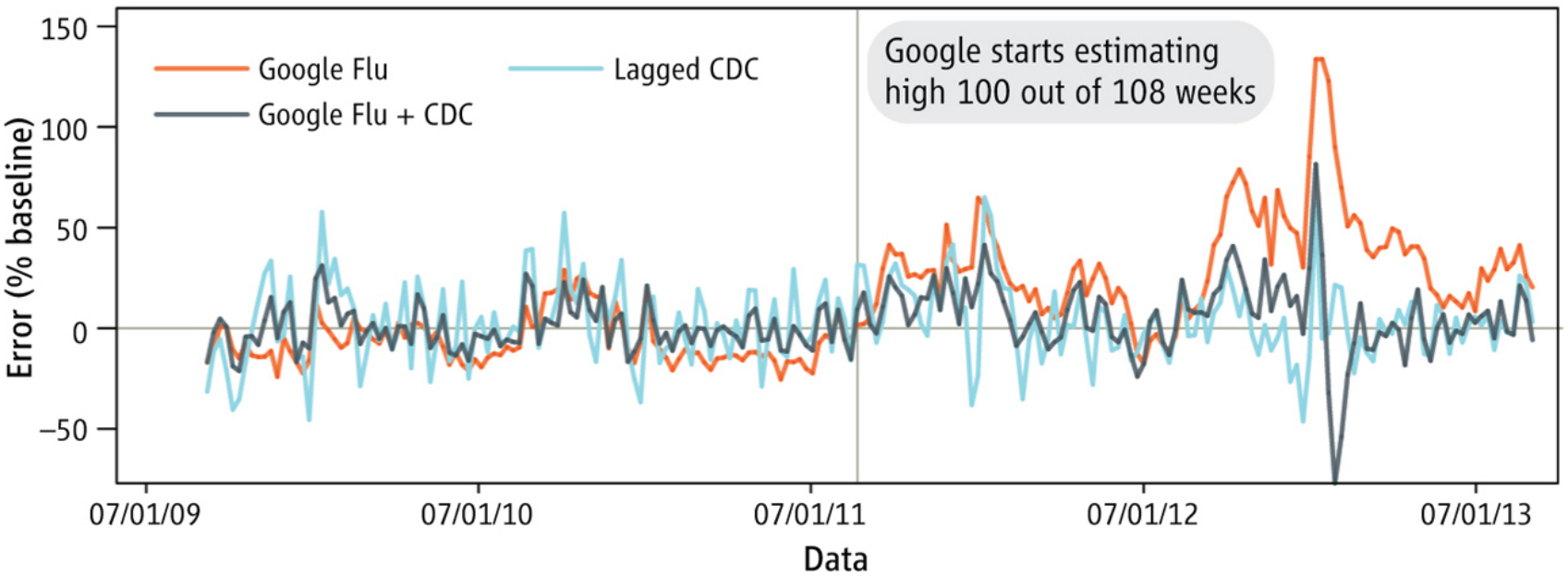
the full text of the article at NEJM.org. Some readers were confused by our incomplete description of part of the data analysis and our use of the term "validation set." We acknowledge that our use of "validation set" was not appropriate in the context of the search for a neoantigen signature, since information from both data sets was used to derive the results. Here,

In the article, we did not use "validation set" in the conventional way that the term is typically used in biomarker studies — namely, as an entirely independent data set in which findings from the discovery set are either confirmed or refuted. Rather, the term was carried over from

# Google Flu Trends

D. Lazer, R. Kennedy, G. King and A. Vespignani. **The Parable of Google Flu: Traps in Big Data Analysis.** Science 2014

- **p = 50 million** search terms
- **n = 1152** data points




- Predictive search terms include keywords related to high school basketball.

# Measuring stability

- **Similarity between two sets of selected features: Jaccard's index**

$$J(\mathcal{S}, \mathcal{S}') = \frac{|\mathcal{S} \cap \mathcal{S}'|}{|\mathcal{S} \cup \mathcal{S}'|}$$

- **Kuncheva's consistency index** [Kun07]

$$I_C(\mathcal{S}, \mathcal{S}') = \frac{\text{Observed}(|\mathcal{S} \cap \mathcal{S}'|) - \text{Expected}(|\mathcal{S} \cap \mathcal{S}'|)}{\text{Maximum}(|\mathcal{S} \cap \mathcal{S}'|) - \text{Expected}(|\mathcal{S} \cap \mathcal{S}'|)}$$

$$\text{Maximum}(|\mathcal{S} \cap \mathcal{S}'|) = \min(|\mathcal{S}|, |\mathcal{S}'|) \qquad \text{Expected}(|\mathcal{S} \cap \mathcal{S}'|) = \frac{|\mathcal{S}||\mathcal{S}'|}{p}$$

- **Similarity between $k$ sets of selected features:**

$$I_C(\mathcal{S}_1, \mathcal{S}_2, \ldots, \mathcal{S}_k) = \frac{k(k-1)}{2} \sum_{i=1}^{k} \sum_{j=i+1}^{k} I_C(\mathcal{S}_i, \mathcal{S}_j)$$

# 2. Reducing p: Regularization

# Dimensionality reduction

- **Feature selection:** Keep relevant features only
  - **Filter approaches:** Apply a statistical test to assign a score to each feature.
  - **Wrapper approaches:** Use a greedy search to find the "best" set of features for a given predictive model.
  - **Embedded approaches:** Fit a **sparse** model, i.e. that is encouraged to not use all the features.
- **Feature extraction:** Project the data on a new space
  - Creates new features, which makes interpretability harder.
  - **Matrice factorization techniques:** PCA, factorial analysis, NMF, kPCA.
  - **Manifold learning:** Multidimensional scaling, t-SNE.
  - **Autoencoders.**

# Integrating prior knowledge

- **Regularization**

$$\arg\min_{\mathbf{w}\in\mathbb{R}^p} \underbrace{||\mathbf{y}-\mathbf{w}X||_2^2}_{\text{loss}}$$

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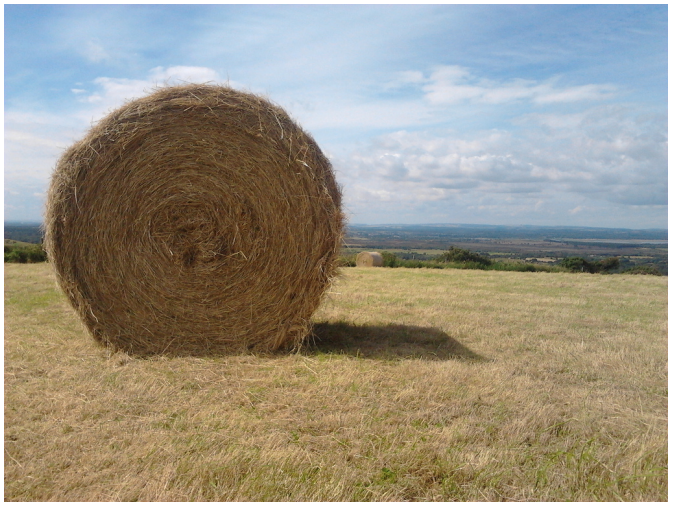

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- **Lasso**

$$\arg\min_{\mathbf{w}\in\mathbb{R}^p} \underbrace{||\mathbf{y}-\mathbf{w}X||_2^2}_{\text{loss}} + \lambda \underbrace{\sum_{j=1}^{p} |w_j|}_{\text{sparsity}}$$

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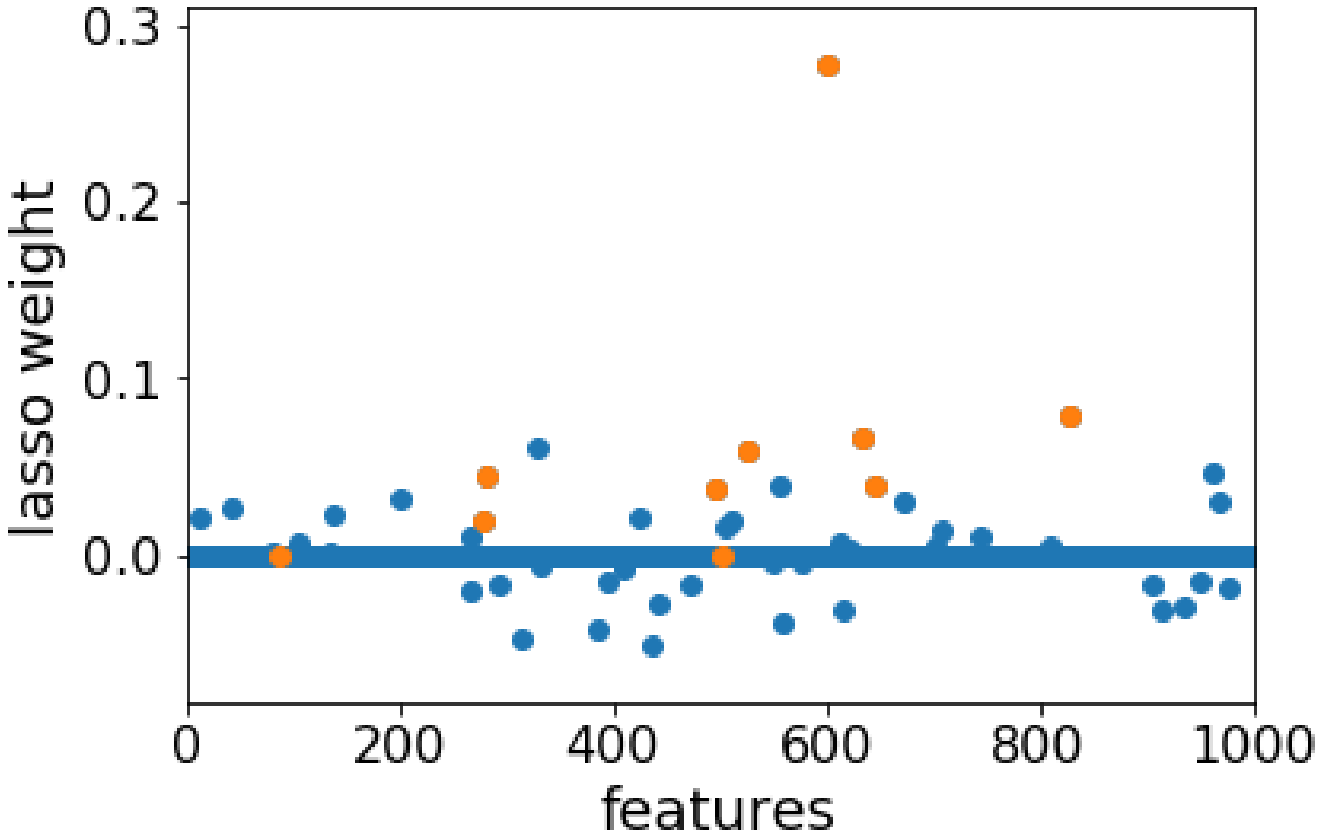
- **Sparsity:** many features are assigned a weight of 0.

  They can be removed from the model.

# Simulation

## Lasso regression:




– 55 features have non-zero weights.

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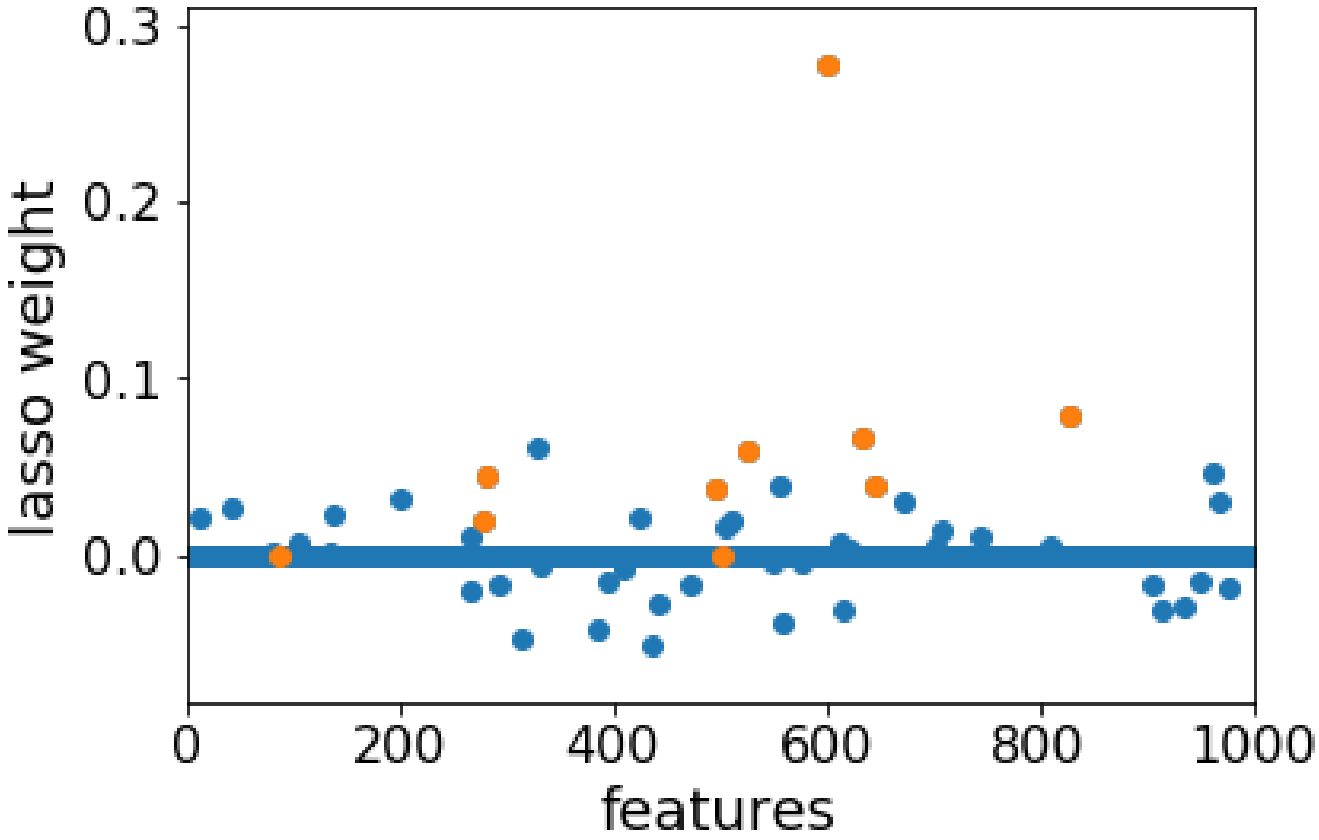


- 55 features have non-zero weights.
- RMSE on test set: 0.19.

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[Ioa05; Nuz14; Hea+15; Hol18]

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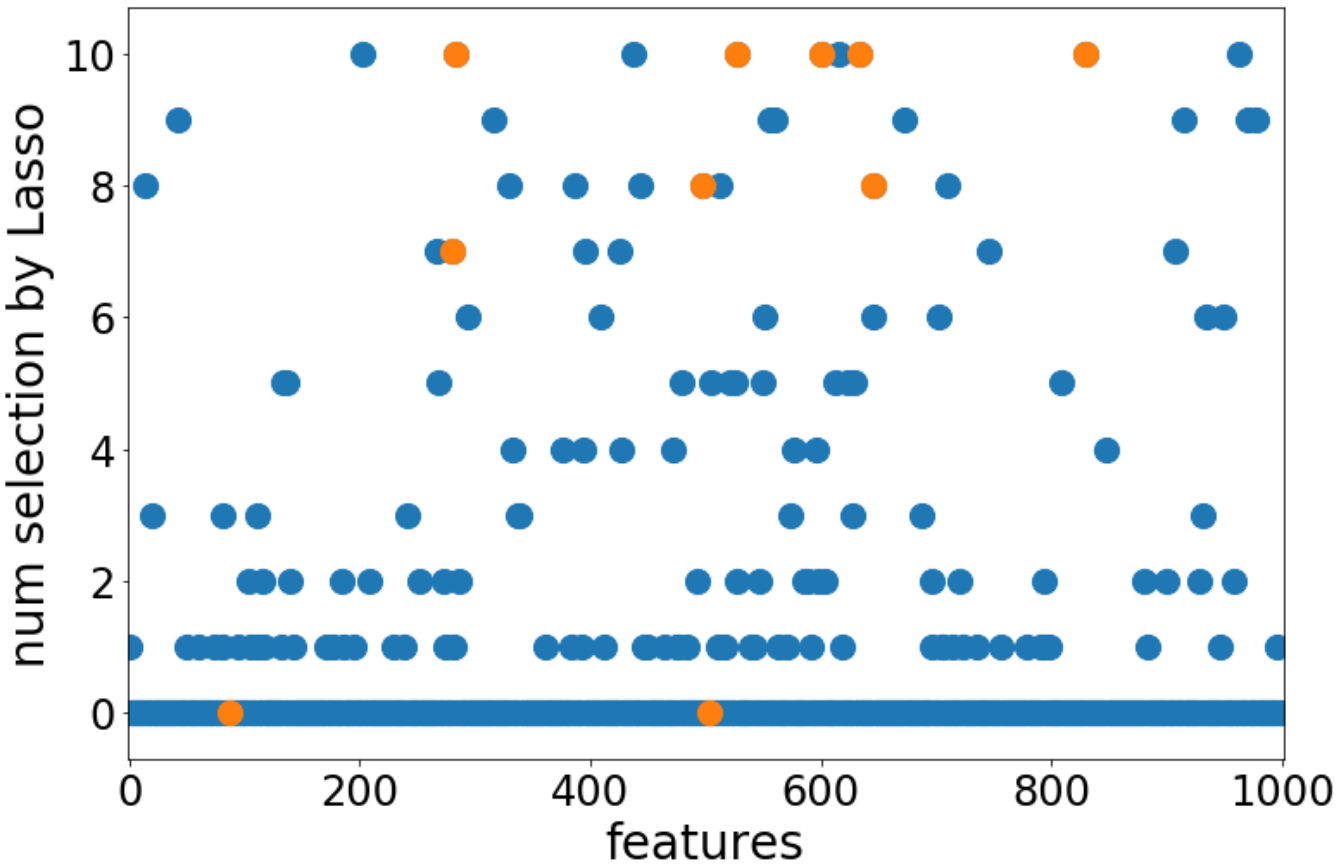
  [Ioa05; Nuz14; Hea+15; Hol18]

- For the **lasso**, possible but computationally intensive

  R. Lockhart et al. **A significance test for the lasso.** Annals of Stats 2014.

# Stability

10-fold cross-validation: how often was each feature selected?




**Consistency index:** 0.58.

# Elastic Net

- **Lasso**

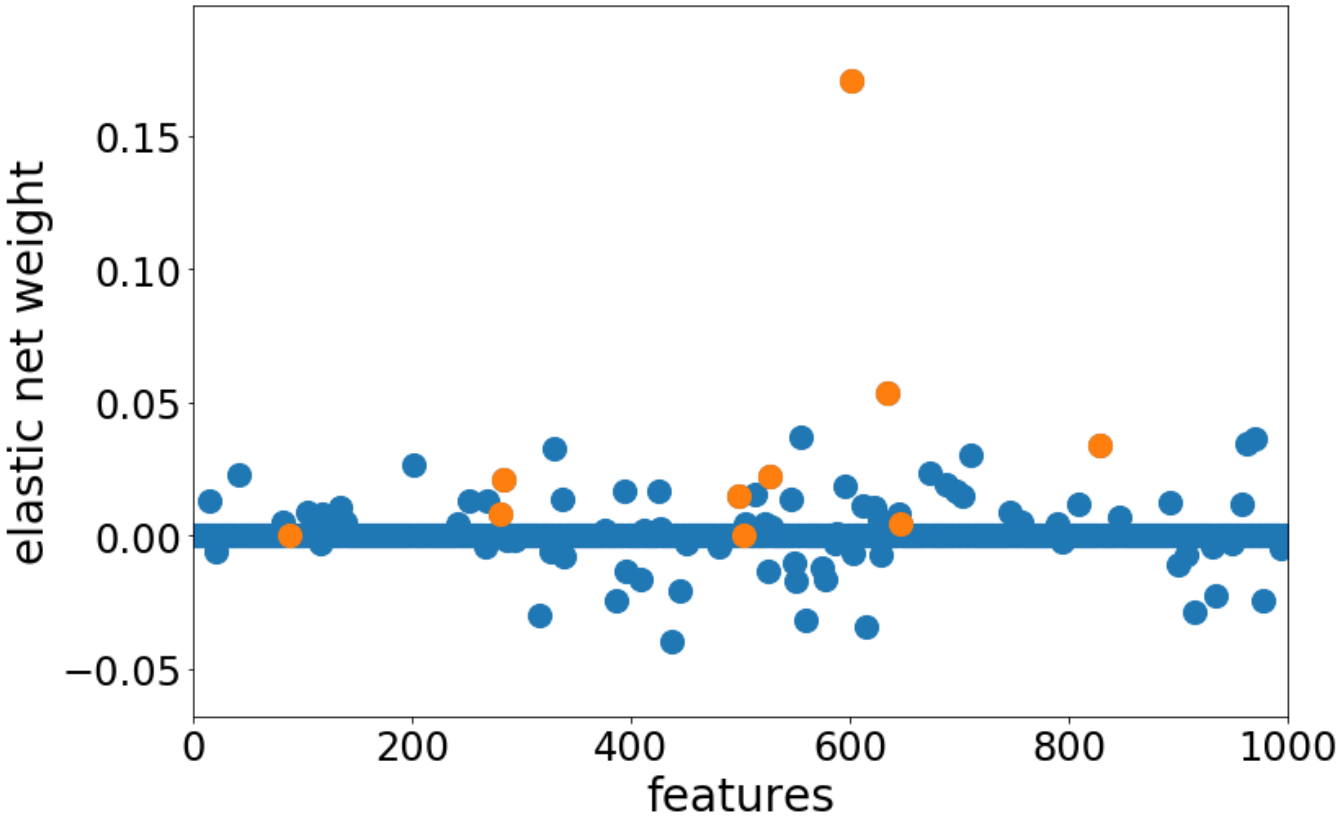
$$\underset{\mathbf{w}\in\mathbb{R}^p}{\arg\min} \underbrace{||\mathbf{y}-\mathbf{w}X||_2^2}_{\text{loss}} + \lambda \underbrace{\sum_{j=1}^{p}|w_j|}_{\text{sparsity}}$$

- **Elastic Net:** [ZH05]

$$\underset{\mathbf{w}\in\mathbb{R}^p}{\arg\min} \underbrace{||\mathbf{y}-\mathbf{w}X||_2^2}_{\text{loss}} + \lambda \left( \underbrace{\alpha \sum_{j=1}^{p}|w_j|}_{\text{sparsity}} + (1-\alpha) \underbrace{\sum_{j=1}^{p} w_j^2}_{\text{weight decay}} \right)$$

# Simulation

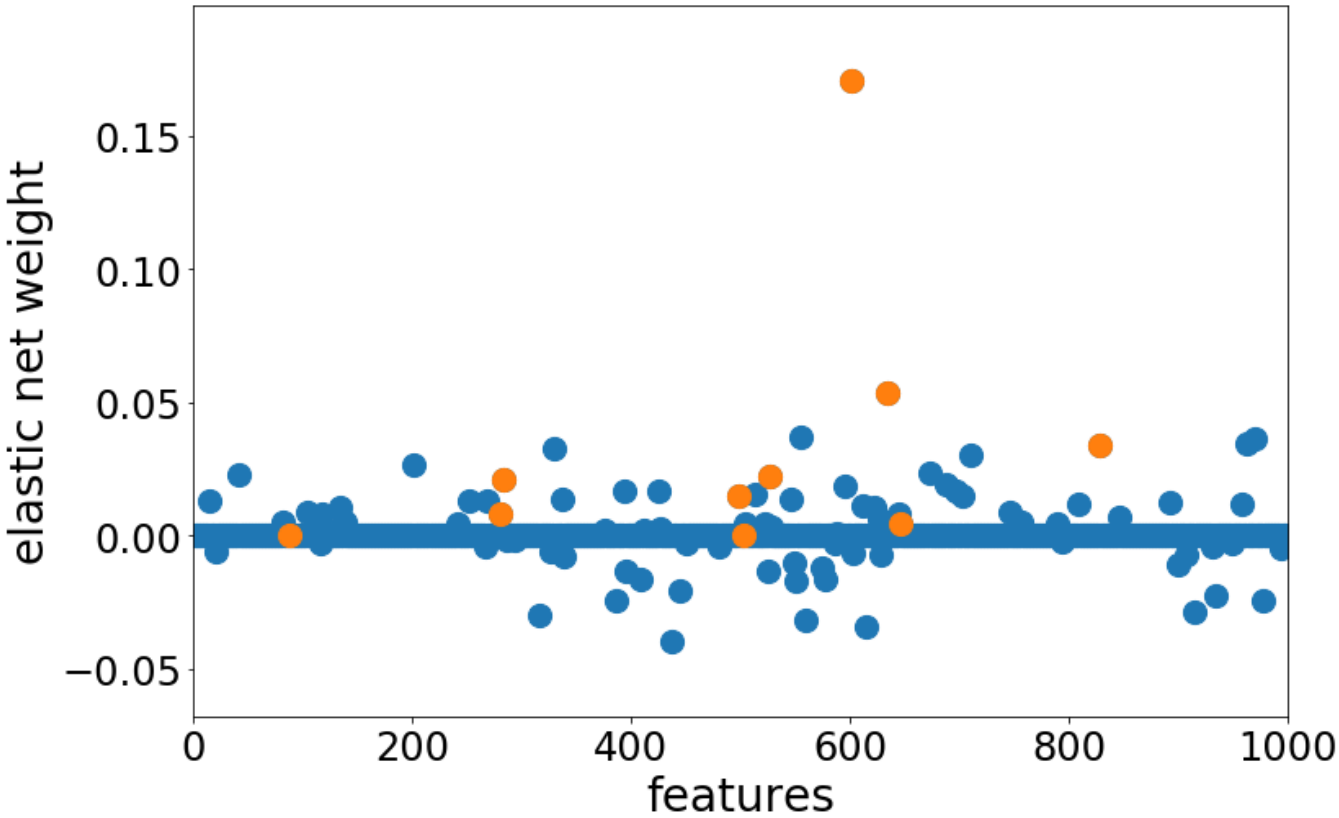
## Elastic net:




– 92 features have non-zero weights.

# Simulation

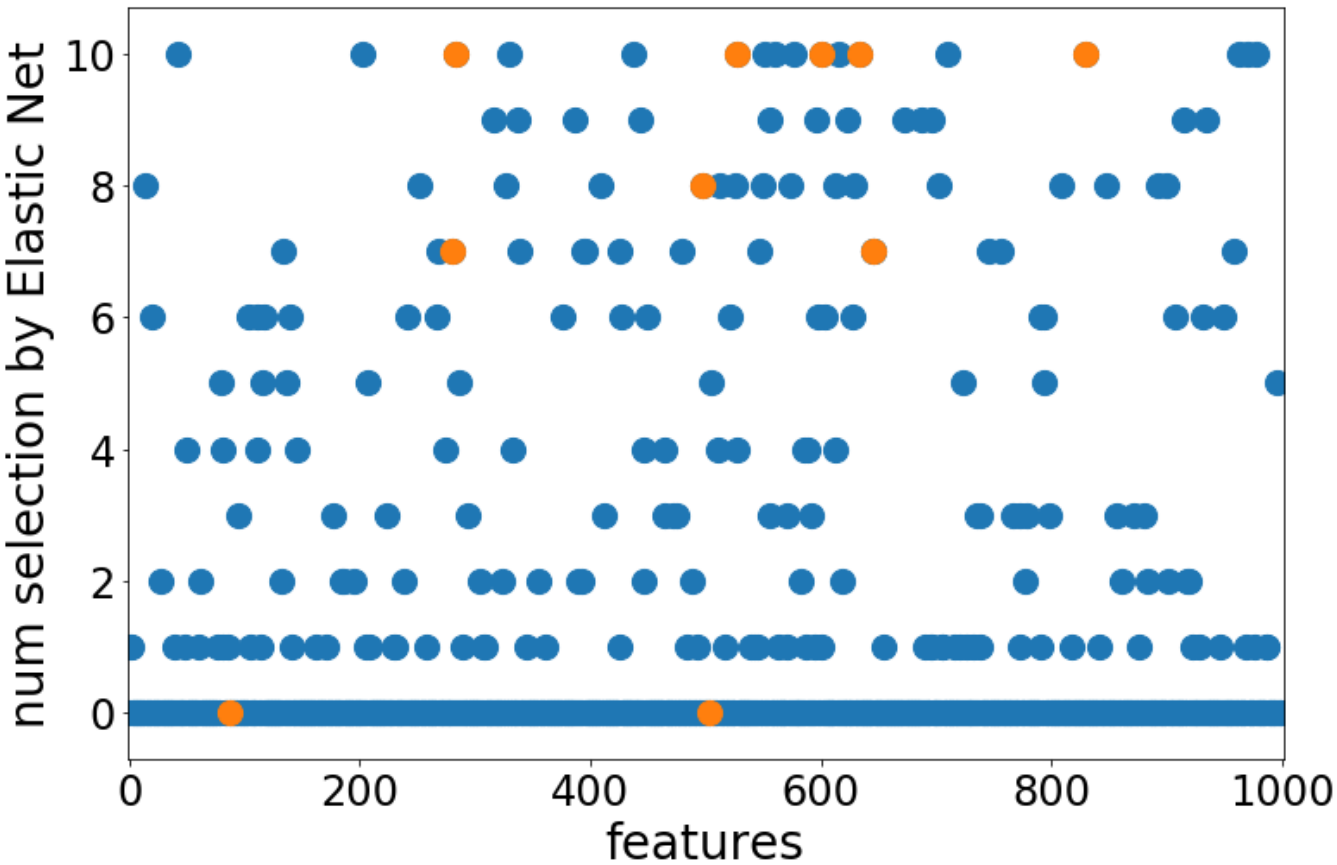
## Elastic net:




- 92 features have non-zero weights.
- RMSE on test set: 0.20.

# Stability

10-fold cross-validation: how often was each feature selected?




**Consistency index:** 0.62.

# Stability selection with the lasso

- Repeat:
  - randomly **subsample the training data** $I \subset \{1, 2, \ldots, n\}$
  - randomly **scale the regularizer** $s_j \in \{s, 1\}$ (Bernouilli; $0 < s < 1$)
  - fit a lasso

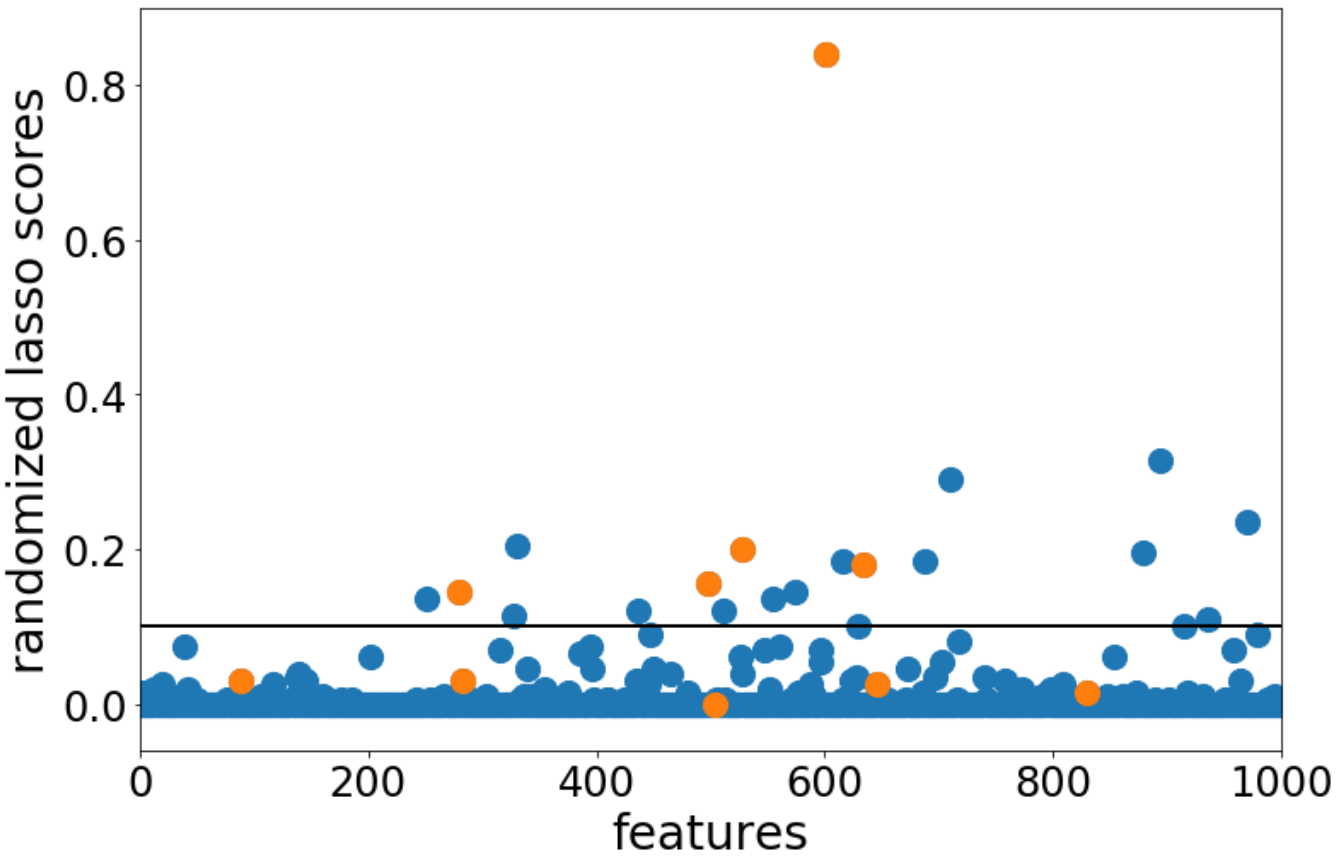
$$\underset{\mathbf{w} \in \mathbb{R}^p}{\arg\min} \underbrace{\frac{1}{|I|} \sum_{i \in I} \left( y_i - \sum_{j=1}^{p} w_j x_{ij} \right)^2}_{\text{loss}} + \lambda \underbrace{\sum_{j=1}^{p} \frac{|w_j|}{s_j}}_{\text{sparsity}}$$

- Select features that appear in **multiple models.**

[MB10; SS13; AL11; DP15; NB16]

# Simulation

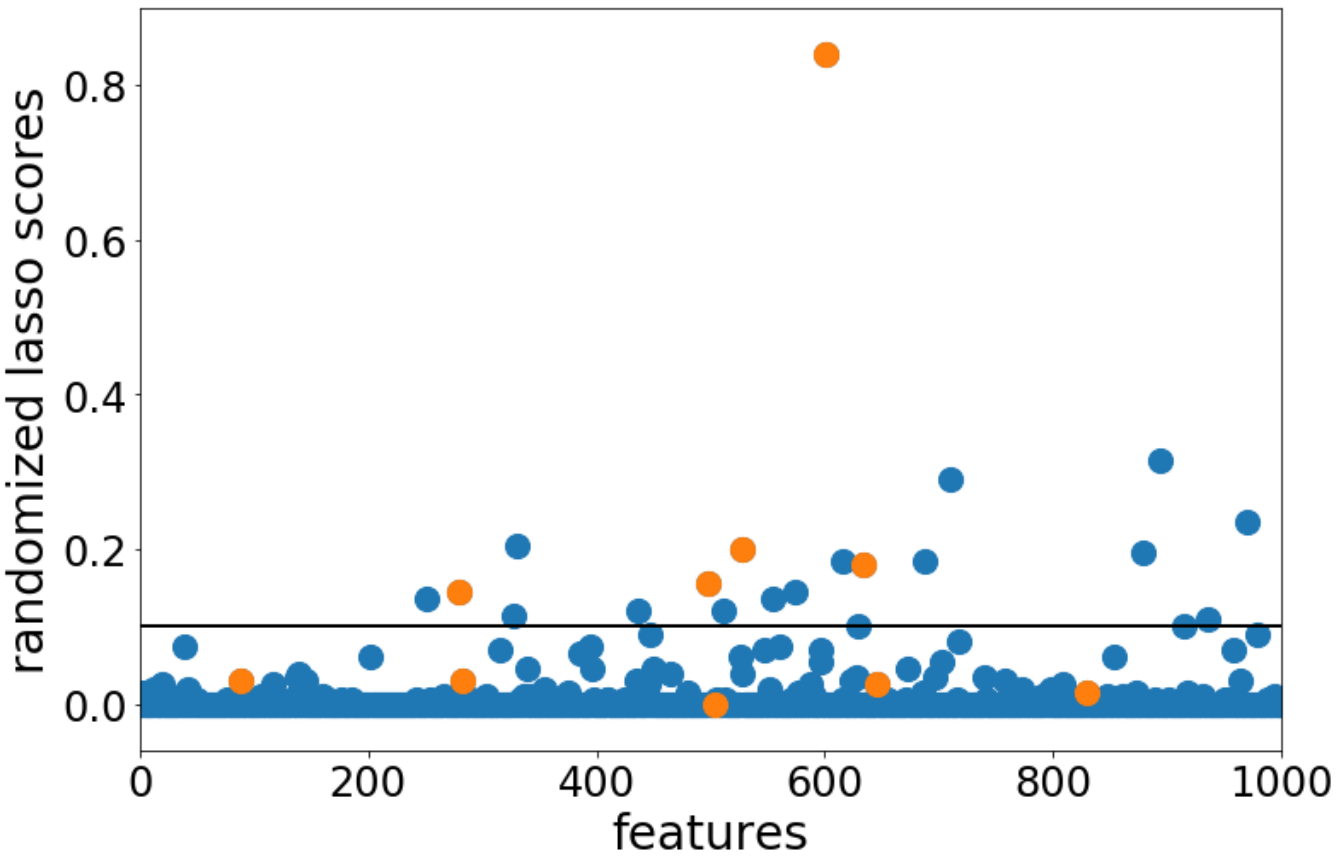
## Stability selection lasso




19 features are selected in more than 10% of the folds.

# Simulation

## Stability selection lasso




19 features are selected in more than 10% of the folds.

- RMSE on test set: 0.16.

# Integrating prior knowledge

**Use prior knowledge as a constraint on the selected features**

- **Consistant** with previously established knowledge
- Increases **interpretability** and **statistical power.**

Prior knowledge can be represented as **structure:**

- Linear structure of the DNA
- **Groups:** e.g. pathways
- **Networks:** molecular, 3D structure.

# Integrating prior group knowledge

- **Group lasso**

$$\underset{\mathbf{w}\in\mathbb{R}^p}{\arg\min} \underbrace{||\mathbf{y}-\mathbf{w}X||_2^2}_{\text{loss}} + \lambda \underbrace{\sum_{j=1}^{p}|w_j|}_{\text{sparsity}} + \eta \underbrace{\sum_{g\in\mathcal{G}}||\mathbf{w}_g||}_{\text{grouping}}$$

- **Overlapping group lasso** for when a feature can belong to multiple groups

$$\underset{\mathbf{w}\in\mathbb{R}^p}{\arg\min} \underbrace{||\mathbf{y}-\mathbf{w}X||_2^2}_{\text{loss}} + \lambda \underbrace{\sum_{j=1}^{p}|w_j|}_{\text{sparsity}} + \eta \underbrace{\sum_{g\in\mathcal{G}}\sum_{\mathbf{x}\in\mathcal{V}_\mathcal{G},\sum_{g\in\mathcal{G}}\mathbf{x}_g=\mathbf{w}}||\mathbf{x}_g||}_{\text{grouping}}$$

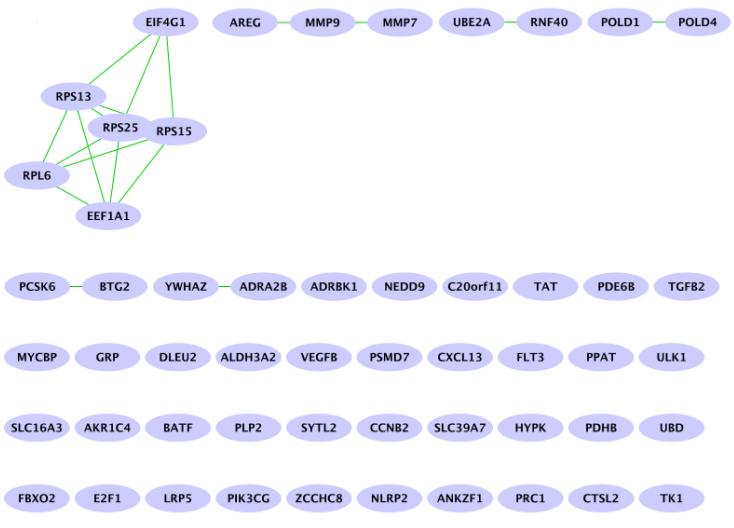
# Gene selection with the Graph lasso

icml2009

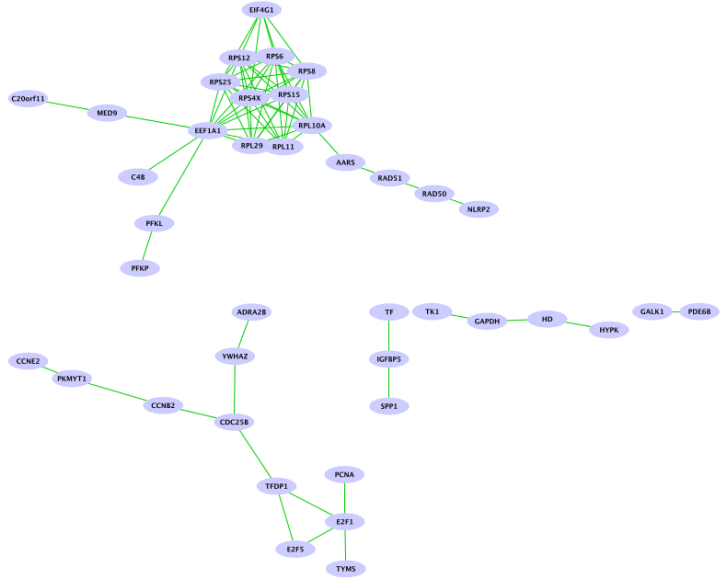
**Group Lasso with Overlaps and Graph Lasso**

*Laurent Jacob, Guillaume Obozinski and Jean-Philippe Vert*

## Lasso



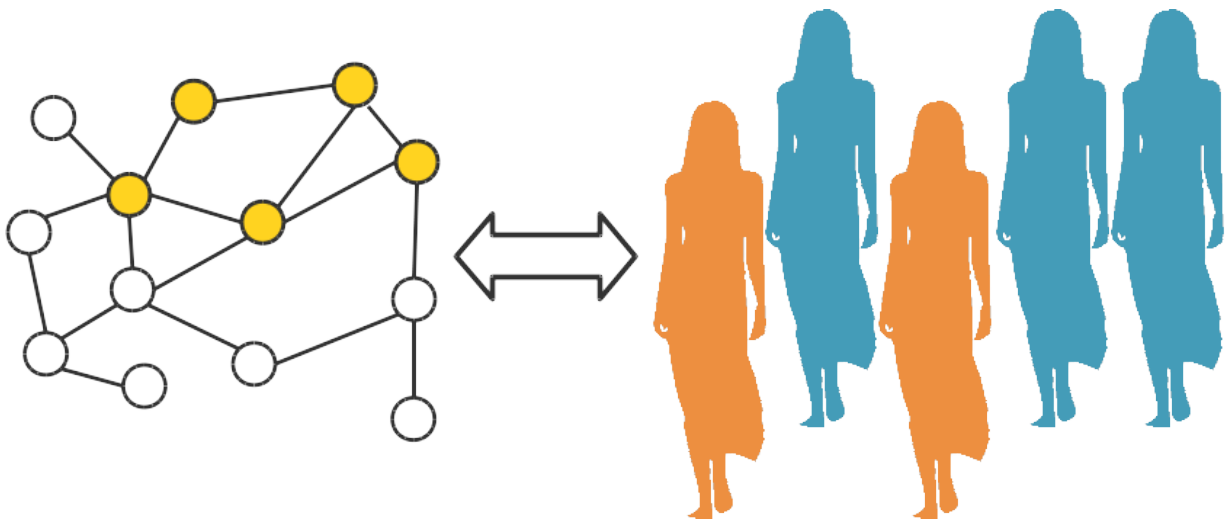

## Graph Lasso




Ref: [JOV09]

# Network-guided biomarker discovery

Goal: Find a **set of explanatory features** compatible with a **given network** structure.



C.-A. Azencott, Network-guided biomarker discovery, LNCS 2016

# Integrating prior network knowledge

- **Network-constrained lasso** [LL08]

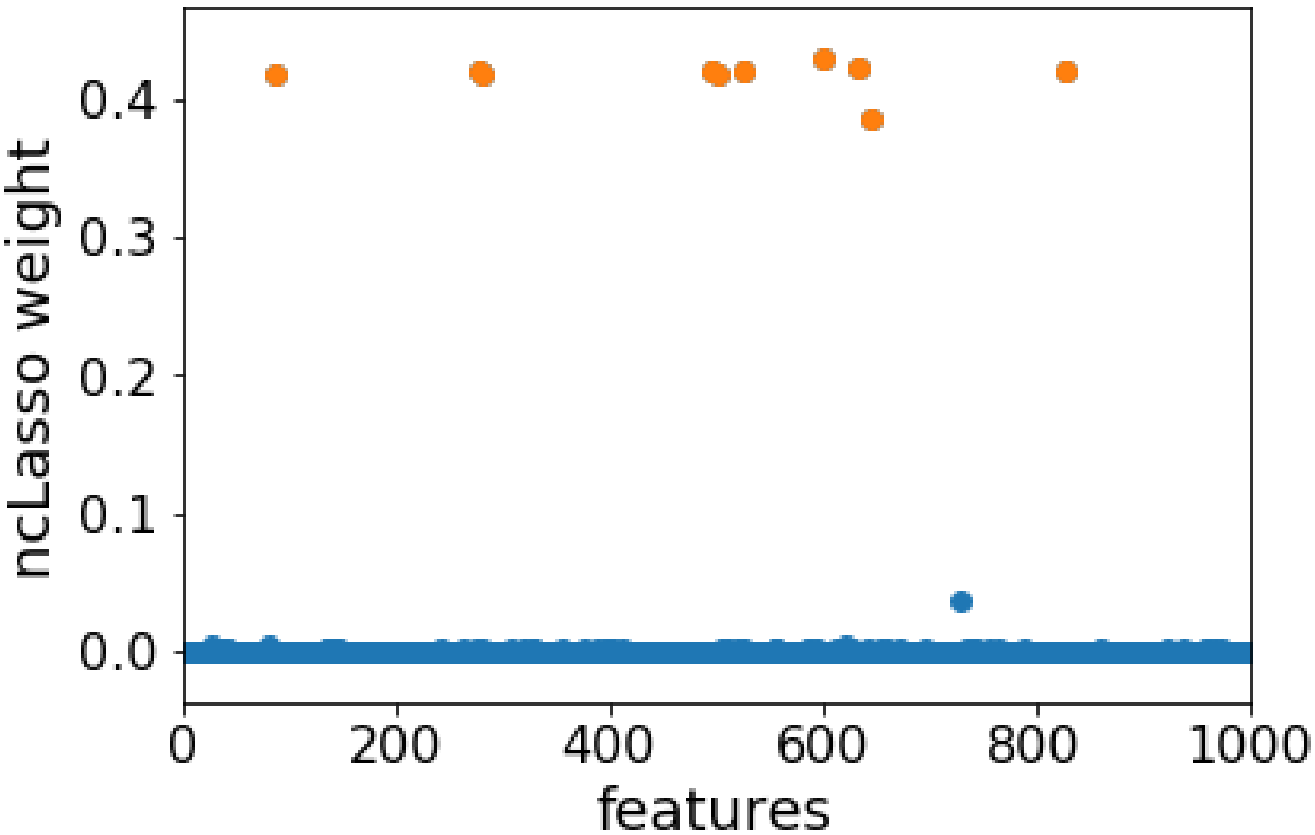
$$\underset{\mathbf{w}\in\mathbb{R}^p}{\arg\min} \underbrace{||\mathbf{y}-\mathbf{w}X||_2^2}_{\text{loss}} + \lambda \underbrace{\sum_{j=1}^{p}|w_j|}_{\text{sparsity}} + \eta \underbrace{\sum_{j=1}^{p}\sum_{k=1}^{p} w_j L_{jk} w_k}_{\text{connectivity}}$$

- **Graph Laplacian** $L$ ensures $w$ varies **smoothly** on the network.

$$L_{jk} = \begin{cases} 1 & \text{if } j = k \\ -W_{jk}/\sqrt{d_j d_j} & \text{if } j \neq k \\ 0 & \text{otherwise.} \end{cases}$$

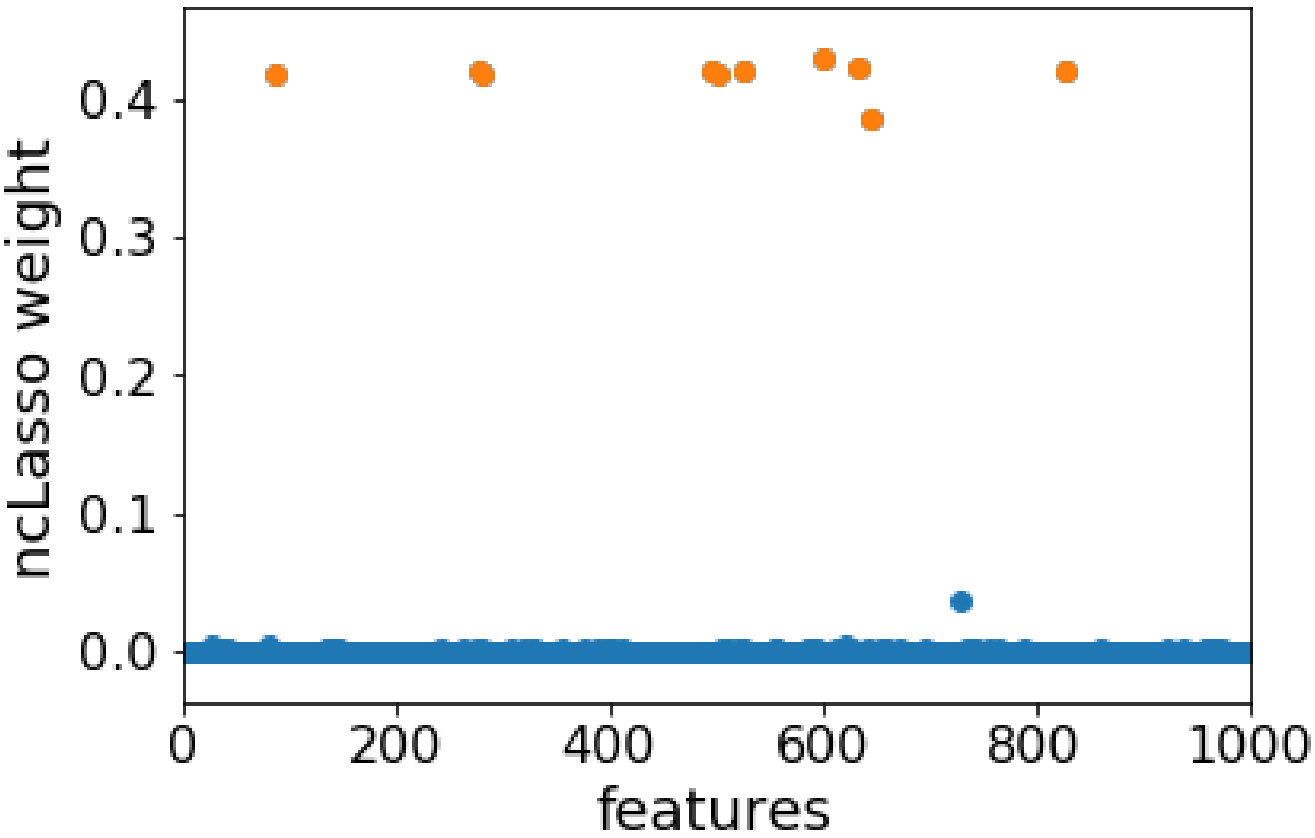
# Simulation

## Network-constrained lasso



# Simulation

## Network-constrained lasso




- RMSE on test set: 0.14.

# Integrating prior network knowledge

- **Regularized relevance** Set $\mathcal{V}$ of $p$ variables.

$$\arg\max_{\mathcal{S}\subseteq\mathcal{V}} \underbrace{R(\mathcal{S})}_{\text{relevance}} - \lambda \underbrace{\Omega(\mathcal{S})}_{\text{regularizer}}$$

- **Network-regularized relevance**

$$\arg\max_{\mathcal{S}\subseteq\mathcal{V}} \underbrace{R(\mathcal{S})}_{\text{relevance}} - \lambda \underbrace{|\mathcal{S}|}_{\text{sparsity}} - \eta \underbrace{\sum_{j\in\mathcal{S}}\sum_{k\notin\mathcal{S}} W_{jk}}_{\text{connectivity}}$$

# Integrating prior network knowledge

- **Regularized relevance** Set $\mathcal{V}$ of $p$ variables.

$$\arg\max_{\mathcal{S}\subseteq\mathcal{V}} \underbrace{R(\mathcal{S})}_{\text{relevance}} - \lambda \underbrace{\Omega(\mathcal{S})}_{\text{regularizer}}$$

- **Network-regularized relevance**

$$\arg\max_{\mathcal{S}\subseteq\mathcal{V}} \underbrace{R(\mathcal{S})}_{\text{relevance}} - \lambda \underbrace{|\mathcal{S}|}_{\text{sparsity}} - \eta \underbrace{\sum_{j\in\mathcal{S}}\sum_{k\notin\mathcal{S}} W_{jk}}_{\text{connectivity}}$$

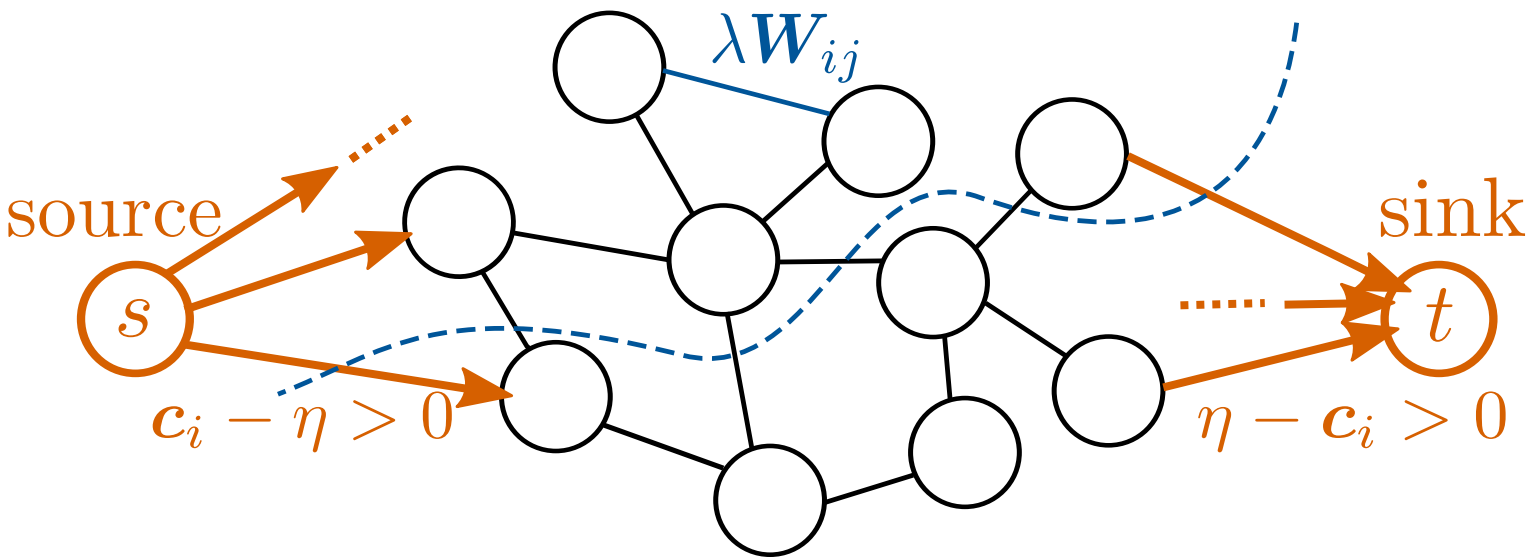
**SConES: S**electing **Con**nected **E**xplanatory **S**NPs.

C.-A. Azencott, D. Grimm, M. Sugiyama, Y. Kawahara and K. Borgwardt (2013) **Efficient network-guided multi-locus association mapping with graph cuts**, Bioinformatics 29 (13), i171–i179 doi:10.1093/bioinformatics/btt238 [Aze+13]
https://github.com/chagaz/scones Bioconductor/martini

# Minimum cut reformulation

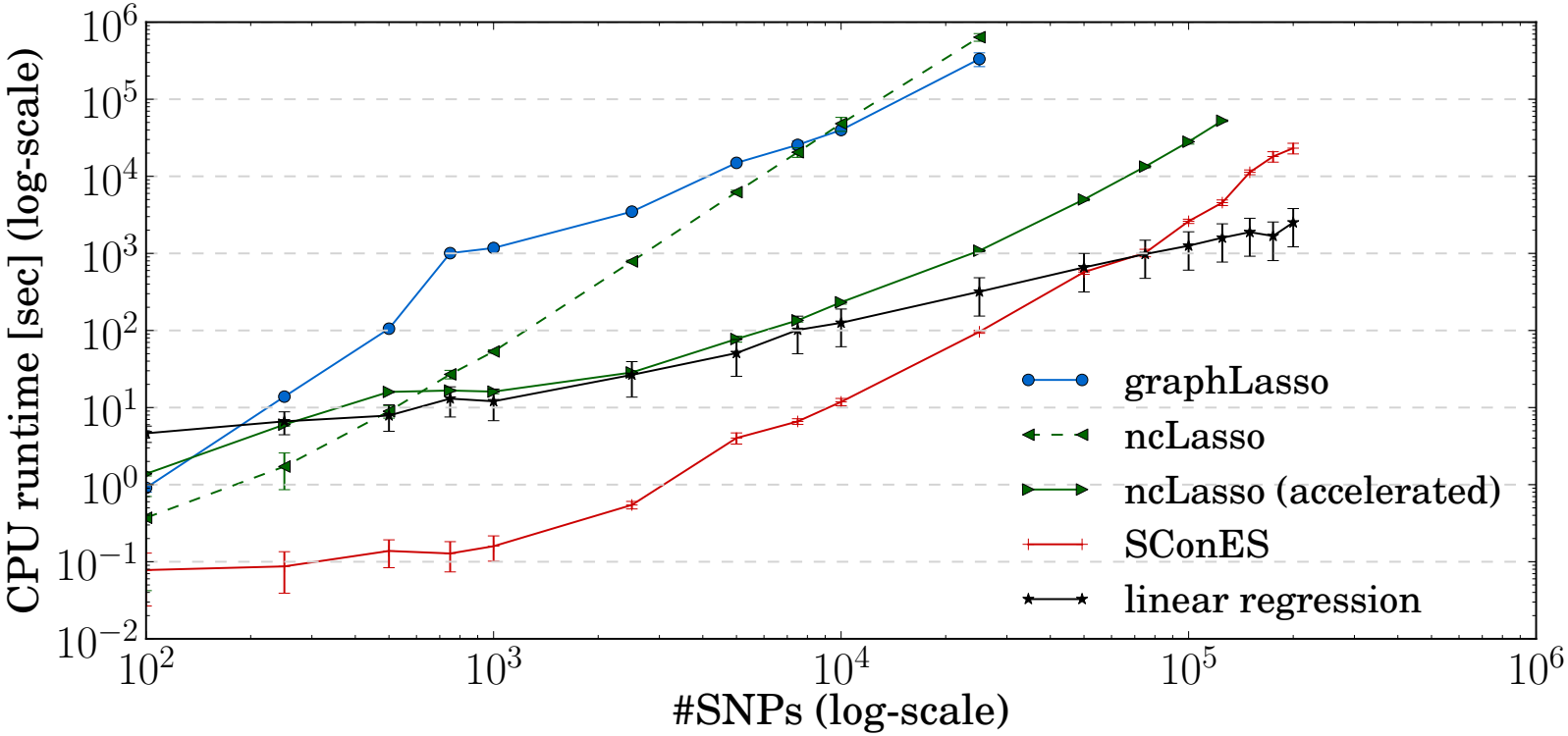
The graph-regularized maximization of score $Q(*)$ is equivalent to a $s/t$-min-cut for a graph with adjacency matrix $\mathbf{A}$ and two additional nodes $s$ and $t$, where $\mathbf{A}_{ij} = \lambda \mathbf{W}_{ij}$ for $1 \leq i, j \leq p$ and the weights of the edges adjacent to nodes $s$ and $t$ are defined as

$$\mathbf{A}_{si} = \begin{cases} c_i - \eta & \text{if } c_i > \eta \\ 0 & \text{otherwise} \end{cases} \quad \text{and} \quad \mathbf{A}_{it} = \begin{cases} \eta - c_i & \text{if } c_i < \eta \\ 0 & \text{otherwise} \end{cases}.$$




**SConES: S**electing **Con**nected **E**xplanatory **S**NPs.

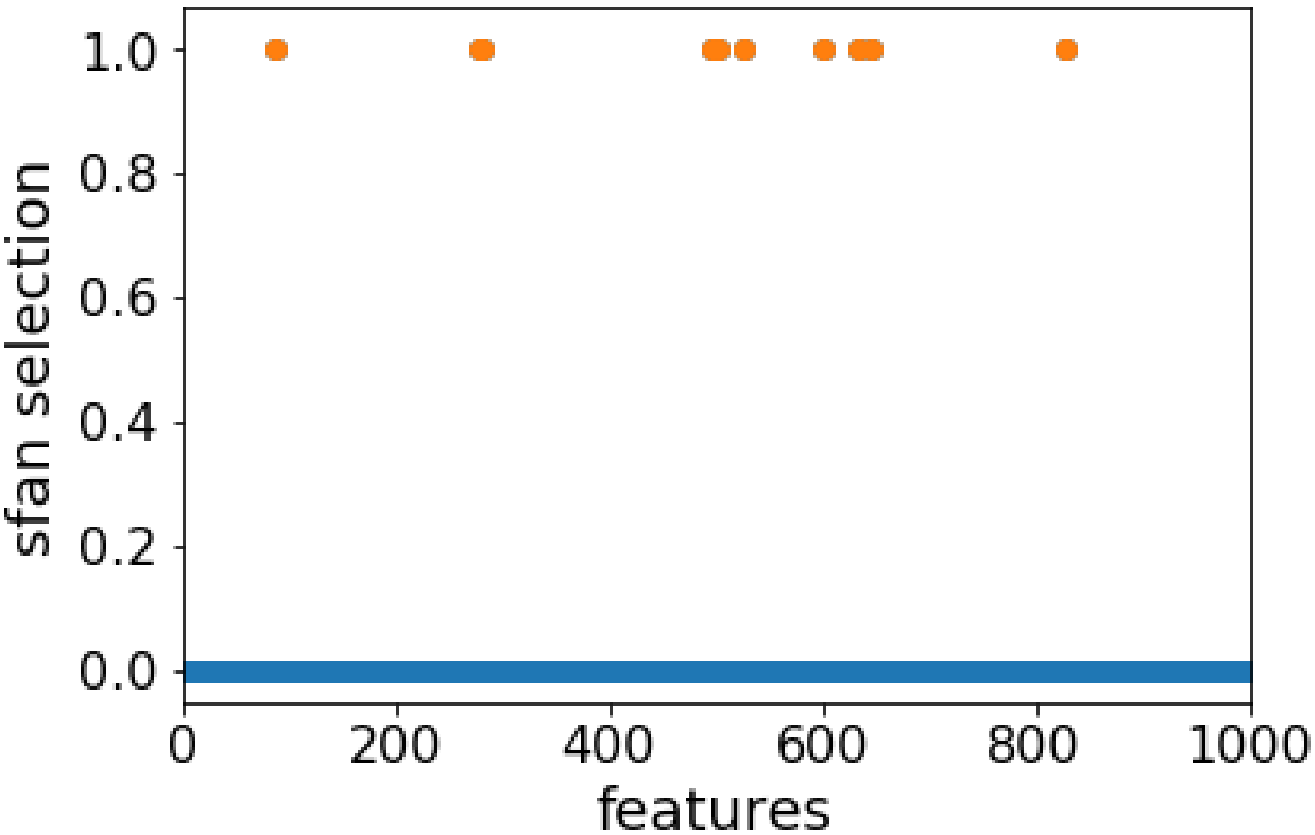
# Runtime




$n = 200$ exponential random network (2 % density)

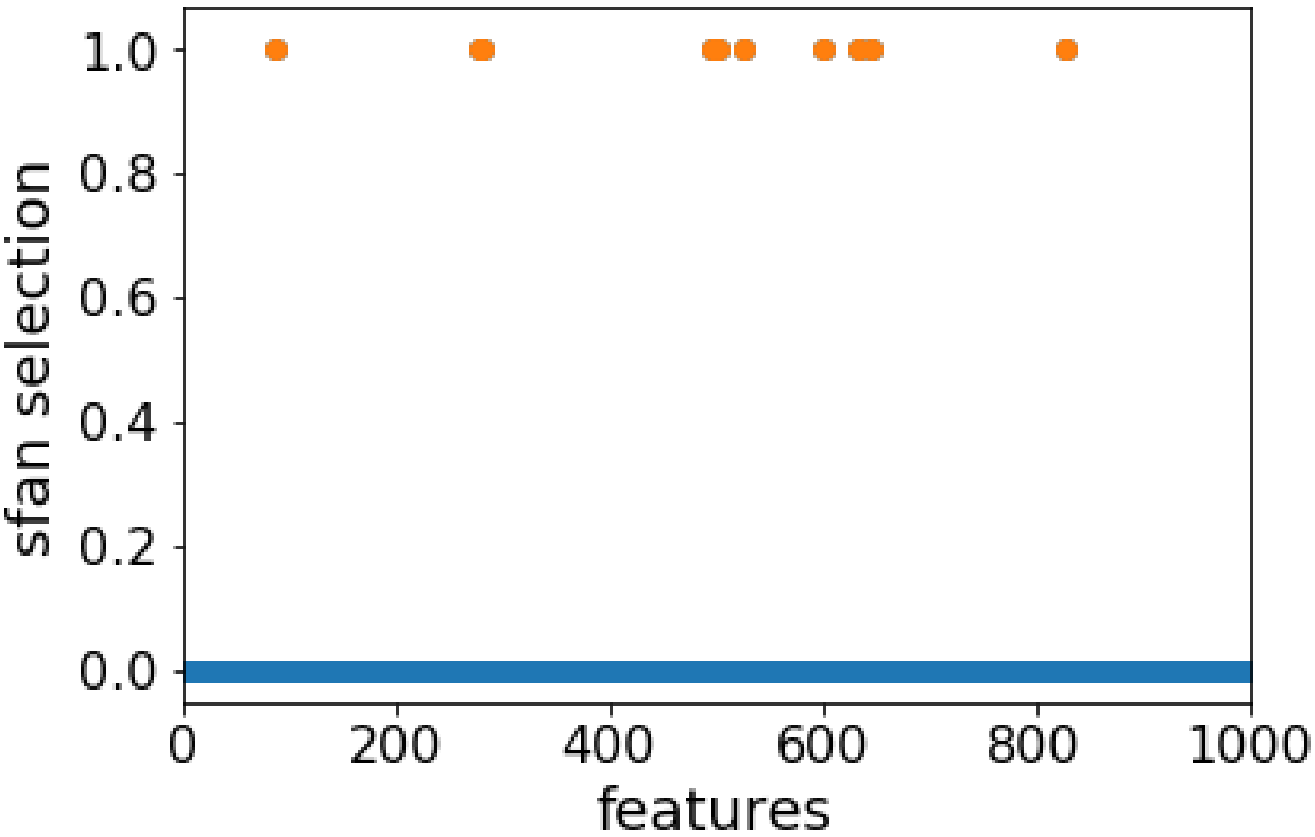
# Simulation

## SConES



# Simulation

## SConES

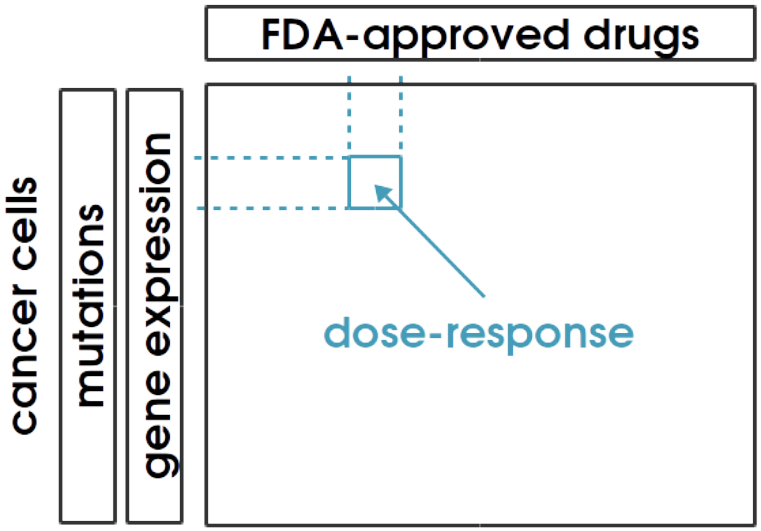



– RMSE on test set: 0.10.

# 3. Increasing n: Multitask approaches

# Multitask machine learning

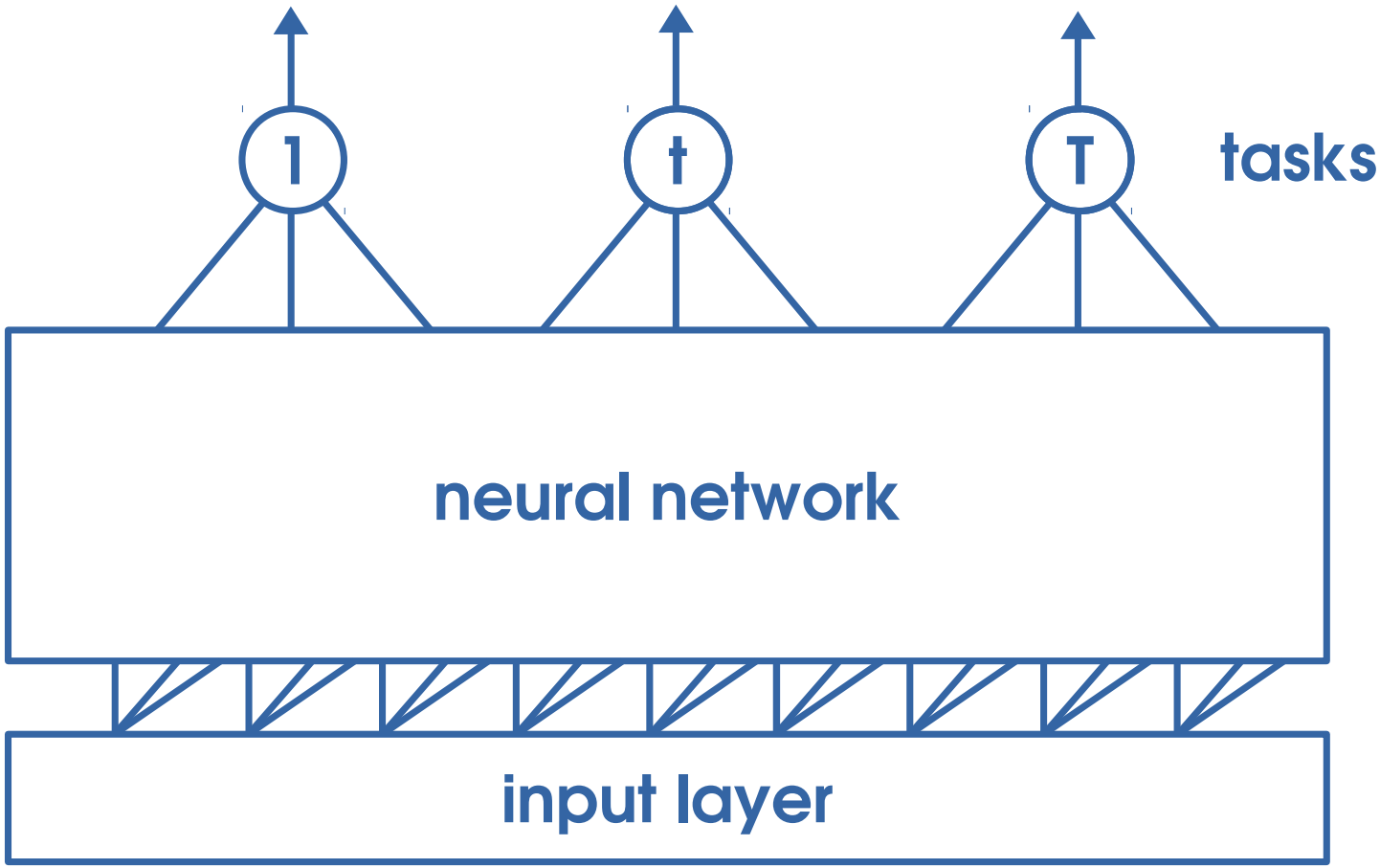
- Solve **multiple related tasks** simultaneously
  - QSAR for multiple related assays
  - **Pharmacogenetics / toxicogenetics / chemogenomics:** predict the response of a cell line to multiple drugs [Edu+15; Dre16; Ior+16]




  - x = a cell line, described by **multiomics features**
  - $y_t$ = **dose-response** to a given drug
  - t = **drug**

# Multitask neural networks

One output unit per task [Car97]



# Multitask linear regression

Group regularization [OTJ06]

linear predictor for task t

weight of feature j for task t

feature j of sample i

$$f_t(x_i) = \sum_{j=1}^{p} w_{tj} x_{ij}$$

$$\min \sum_{t=1}^{T} \boxed{\frac{1}{n_T} \sum_{i=1}^{n_T} (y_i - f_t(x_i))^2} + \lambda \boxed{\sum_{j=1}^{p} \sum_{t=1}^{T} w_{tj}^2}$$

least squares error

**regularization term:** same non-zero weights across tasks

- **Same features selected across tasks**
- The more **similar** the tasks, the more **similar** the features?

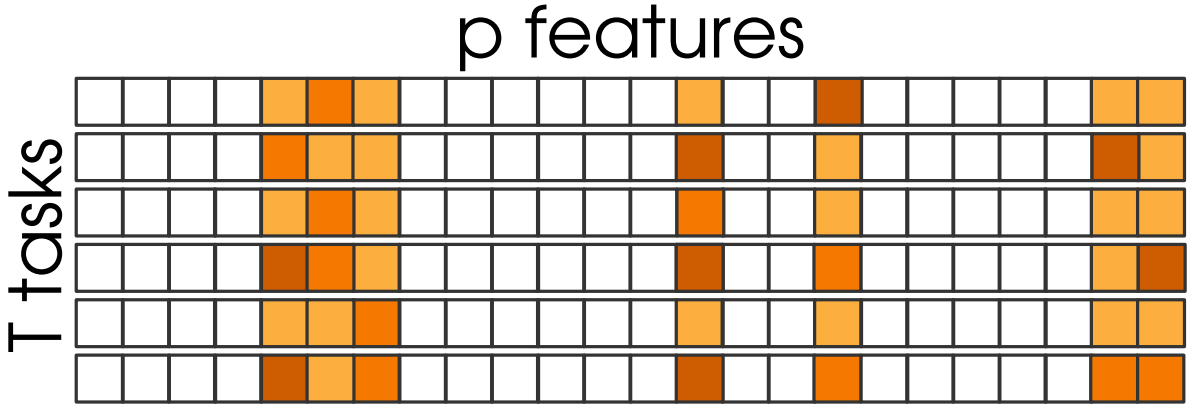
V. Bellón, C.-A. Azencott, and V. Stoven (2016) **Multitask feature selection with task descriptors.** PSB

# Multiplicative Multitask Lasso

- **Multitask Lasso** [OTJ06]

$$\underset{\beta \in \mathbb{R}^{T \times p}}{\arg\min} \underbrace{\sum_{t=1}^{T} \frac{1}{n_t} \sum_{m=1}^{n_t} \left( y_{tm} - \sum_{j=1}^{p} \beta_{tj} x_{tmj} \right)^2}_{\text{loss}} + \underbrace{\lambda \sum_{j=1}^{p} ||\beta_j^2||_2}_{\text{task sharing}}$$

  - Selects the **same features across tasks**
  - Controls weights magnitude ($\ell_2$ shrinkage).

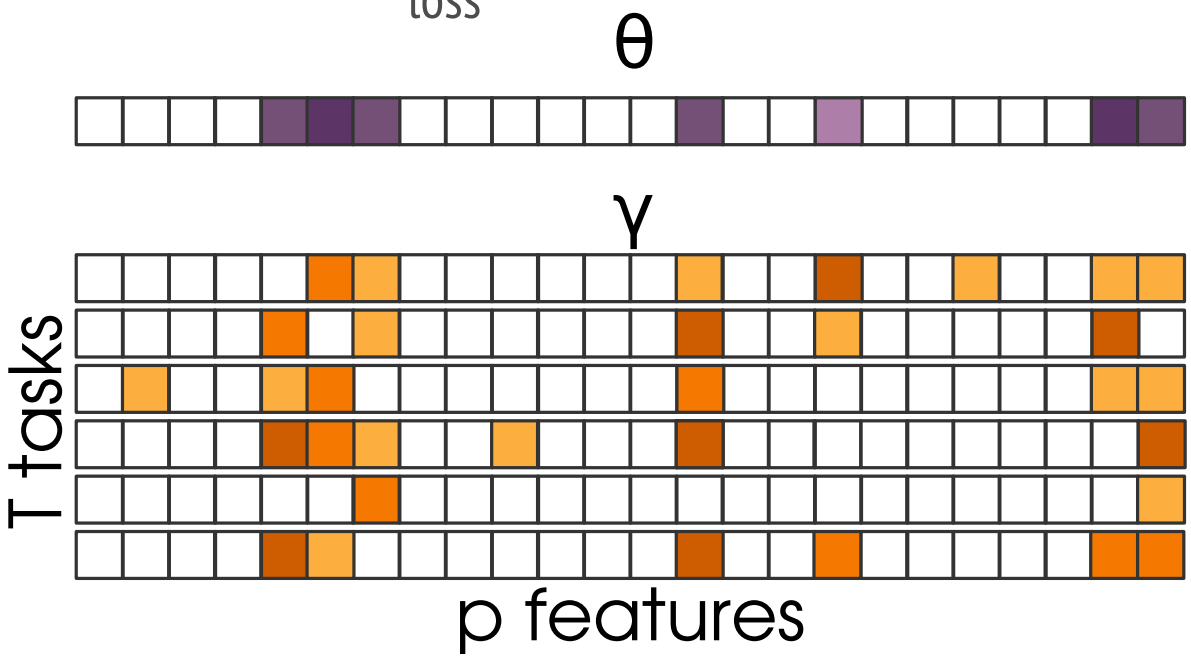


# Multiplicative Multitask Lasso

– **Multilevel Multitask Lasso** [SL12]

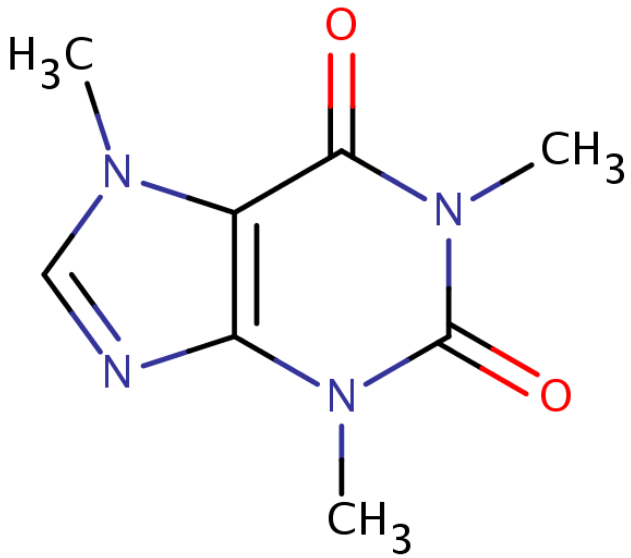
Modulate a sparse, global, task-independent effect $\theta_j$ with a task-specific $\gamma_{tj}$.

$$\underset{\boldsymbol{\theta}\in\mathbb{R}_+^p,\boldsymbol{\gamma}\in\mathbb{R}^{T\times p}}{\arg\min} \underbrace{\sum_{t=1}^{T}\frac{1}{n_t}\sum_{m=1}^{n_t}\left(y_{tm}-\sum_{j=1}^{p}\theta_j\gamma_{tj}x_{tmj}\right)^2}_{\text{loss}} + \underbrace{\lambda_1\,||\boldsymbol{\theta}||_1}_{\text{sparsity}} + \underbrace{\lambda_2\sum_{j=1}^{p}\sum_{t=1}^{T}|\gamma_{tj}|}_{\text{task sharing}}$$



# Task relatedness

- **Tasks that are "more similar" should share more features**
- Large literature on **chemical compounds representation** and **similarity**
  - Using the **molecular graph**
  - 3D structure, physico-chemical descriptors, etc.




C.-A. Azencott et al. (2007) **One- to four-dimensional kernels for virtual screening and the prediction of physical, chemical and biological properties** JCIM

# Expert knowledge descriptors

- **DRAGON** descriptors
  - 3224 molecular features
  - atom types, functional group counts, topological descriptors
- **PowerMV**
  - 1000+ descriptors
  - atom-based, fragment-based, real-valued descriptors
  - includes: partial charges, electronegativities, estimated solubility

**Hard to define/compute and potentially incomplete.**

# Molecular fingerprints

- Define **feature vectors** that record the presence/absence (or number of occurrences) of pre-determined molecular features in a compound.

$$\phi(A) = (\phi_s(A))_{s \text{ feature}}$$

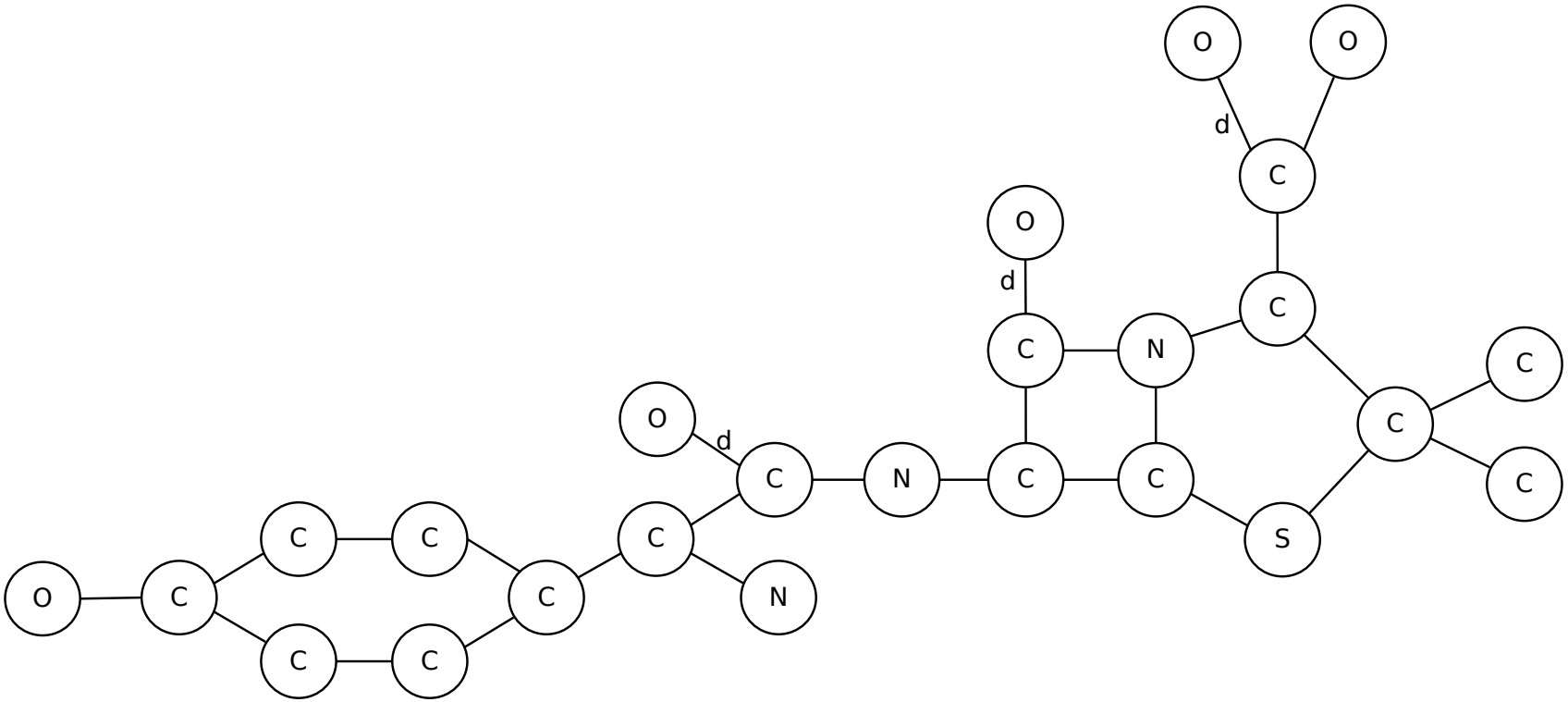
where

$$\phi_s(A) = \begin{cases} 1 & \text{if } s \text{ occurs in } A \\ 0 & \text{otherwise} \end{cases}$$

# Examples of molecular fingerprints

- **MACCS keys**: answers to a set of true/false questions about a chemical structure
  - "Are there fewer than 3 oxygen atoms?"
  - "Is there at least one halogen atom present?"
  - . . .
- **PubChem Substructure Fingerprints** (aka **CACTVS Subgraph Keys)**: presence/absence of molecular substructures, e.g.:
  - individual atoms of a given type
  - rings of a given size containing given atoms
  - more general patterns involving several bonds and atom types

# The molecular graph I




undirected labeled graph

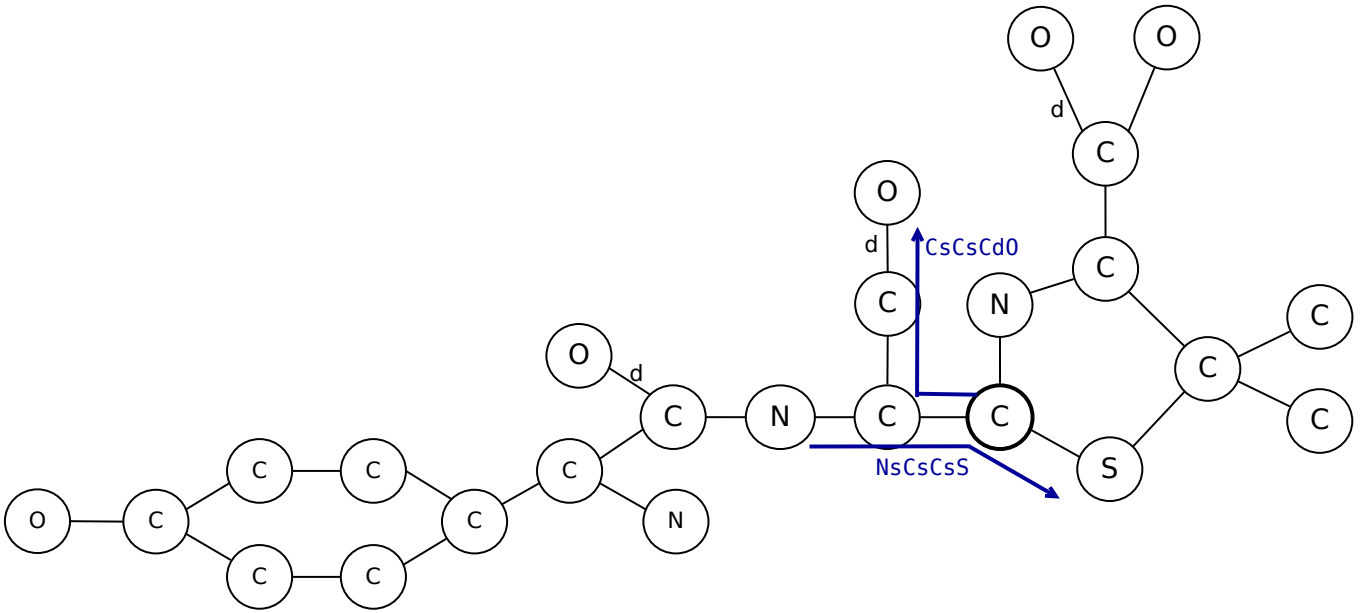
# The molecular graph II

Examples of labels:

- The **element**
- The **binding affinity**
  E.g. XSCORE: polar, hydrophobic, hydrogen-bond donating, hydrogen-bond accepting, other.
- The **element-hybridization state**
  E.g. Csp3, Nsp2.
- SYBYL: 53 labels
  E.g. sp3 carbon, trigonal planar nitrogen, halogen, sulfoxide sulfur.

# Paths fingerprints

- **Path fingerprints:** Labeled **paths** (or **walks**)

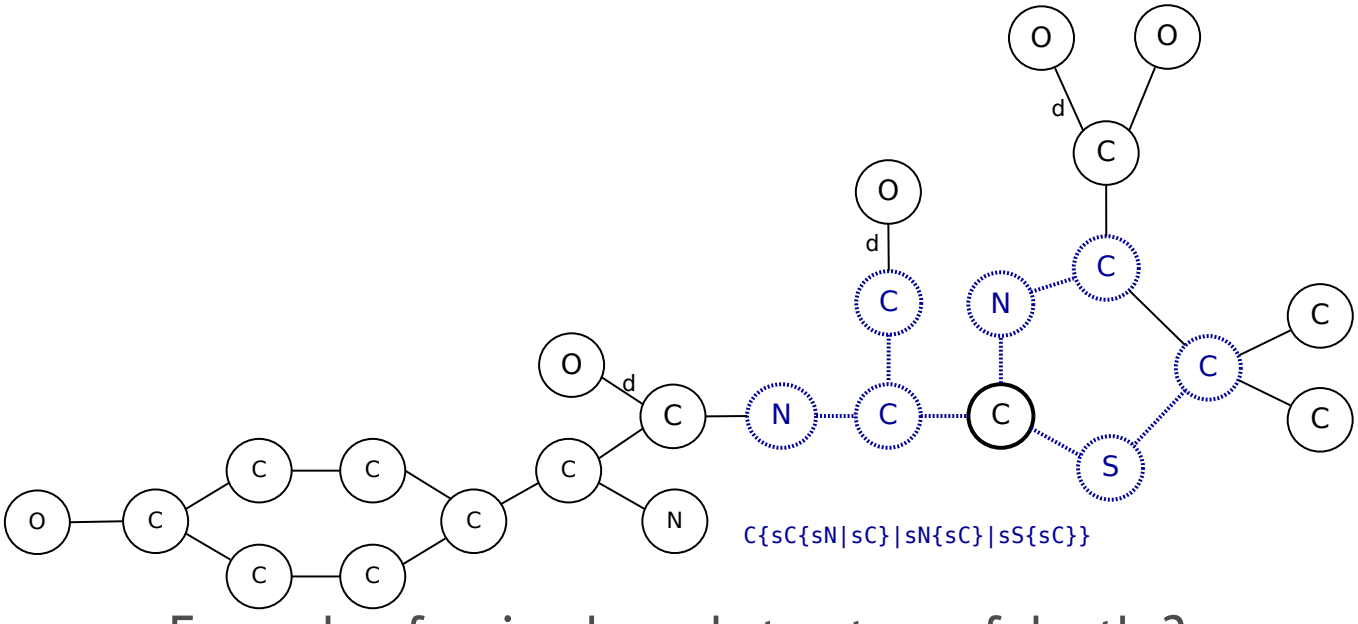



Some sub-paths of length 3

- Each entry of the fingerprint (feature vector) records the presence/absence of a given path in the molecular graph.

# Circular fingerprints

- Labeled **sub-trees**: **Extended-Connectivity** (or **Circular**) features




Example of a circular substructure of depth 2

- Each entry of the fingerprint (feature vector) records the presence/absence of a given tree (EC pattern) in the molecular graph.

# Similarity between two fingerprints

- Idea: Compare the number of entries that are **common** to the two fingerprints.
- **Binary** fingerprints $\mathcal{X} = \{0,1\}^p$ : **Tanimoto similarity**

$$s(x,z) = \frac{\sum_{j=1}^{p}(x_j \text{ AND } z_j)}{\sum_{j=1}^{p}(x_j \text{ OR } z_j)}$$

- **Count** fingerpritns $\mathcal{X} = \mathbb{N}^p$ : **Minmax similarity**

$$s(x,z) = \frac{\sum_{j=1}^{p}\min(x_j,z_j)}{\sum_{j=1}^{p}\max(x_j,z_j)}$$

- For a binary fingerprint, Tanimoto = MinMax.
- Tanimoto and MinMax are **kernels** and can be computed efficiently!

# Limitations

These representations do not model

- **accessible surface**
- **3D configuration**
  - Information can be difficult to get (use simulations)
  - Multiple conformations
- **stereoisomers**

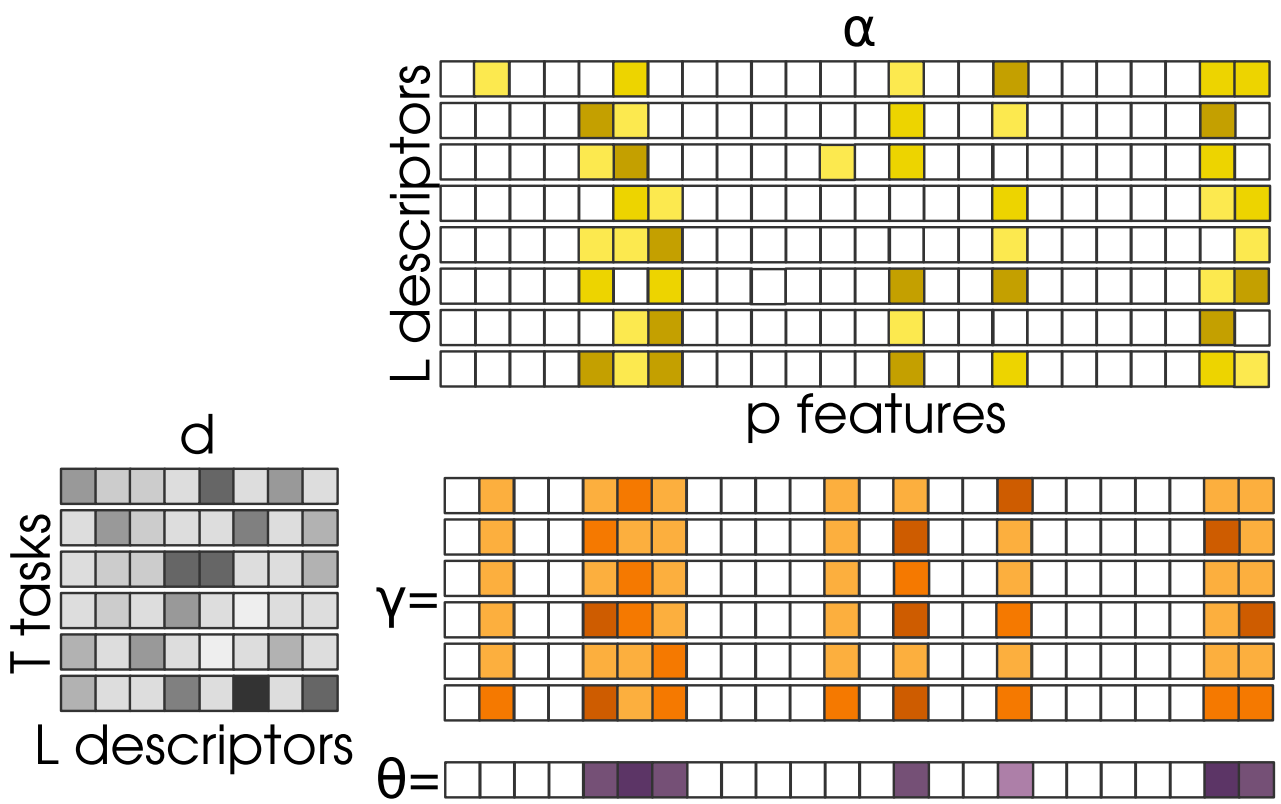
# What about large molecules?

- **Drug-like** compounds: typically about 22 heavy atoms
- What about proteins?
- **Sequence-based** representations
  - **Local Alignment kernel:** based on the Smith-Waterman alignment algorithm [Sai+04]
  - **String kernels:** [Les+04]
    - use all possible sequences of amino acids of fixed length k
    - soft penalization of mismatches
- Use **hierarchy** from the Enzyme Commission [JV08]
- Use the **3D binding pocket** information [Kel+06]

# Multiplicative Multitask Lasso with Task Descriptors

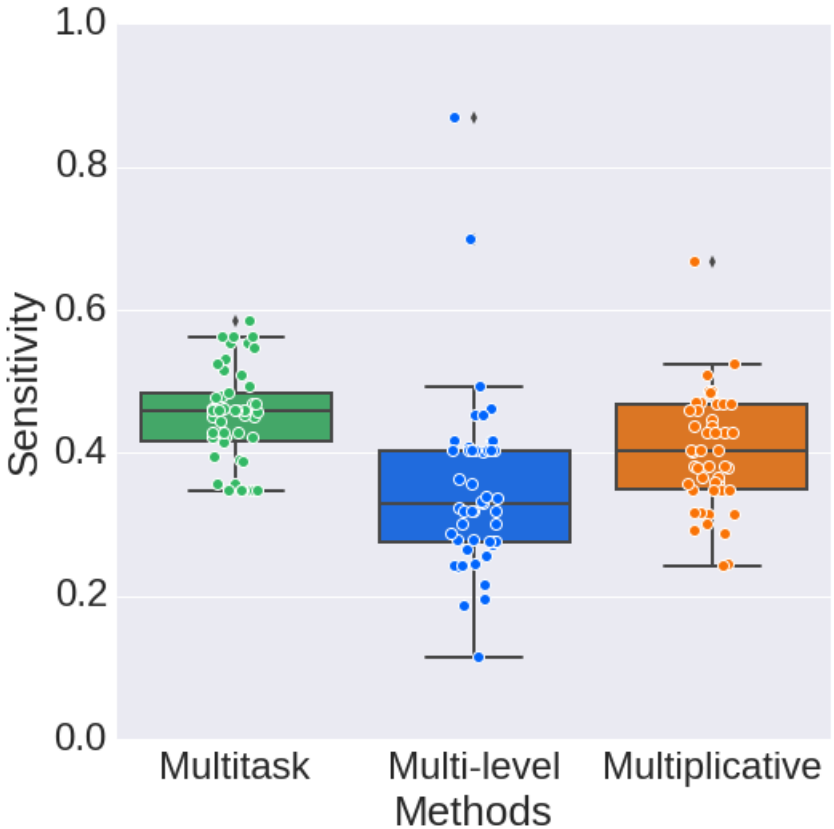
Tasks are described by $\boldsymbol{d} \in \mathbb{R}^{T \times L}$ Hypothesis: $\gamma_{tj} = \sum_{l=1}^{L} \alpha_{jl} d_{tl}$.

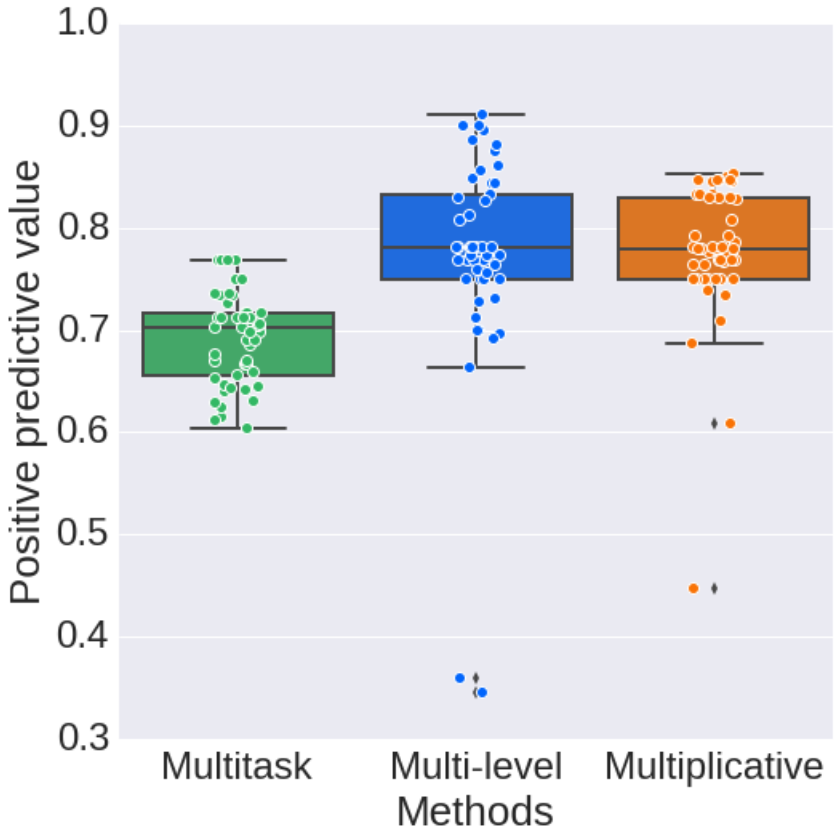
$$\underset{\boldsymbol{\theta} \in \mathbb{R}_+^p, \alpha \in \mathbb{R}^{p \times L}}{\arg\min} \underbrace{\sum_{t=1}^{T} \frac{1}{n_t} \sum_{m=1}^{n_t} \left( y_{tm} - \sum_{j=1}^{p} \theta_j \left( \sum_{l=1}^{L} \alpha_{jl} d_{tl} \right) x_{tmj} \right)^2}_{\text{loss}} + \underbrace{\lambda_1 ||\theta||_1}_{\text{sparsity}} + \underbrace{\lambda_2 \sum_{j=1}^{p} \sum_{l=1}^{L} |\alpha_{jl}|}_{\text{task sharing}}$$



# Performance of MMLD

- On **simulations:**

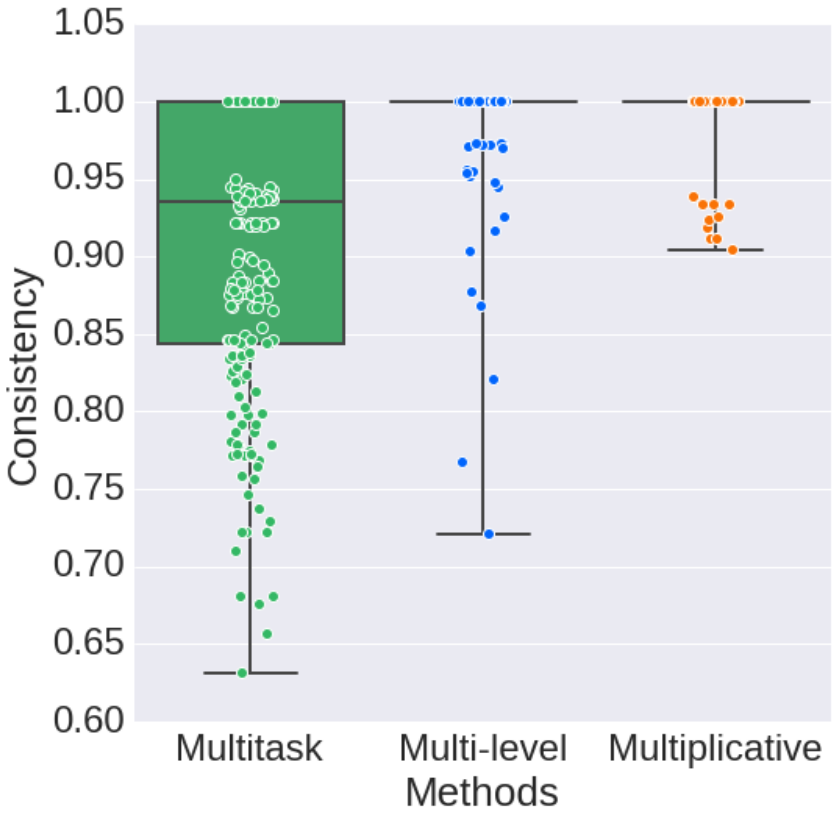


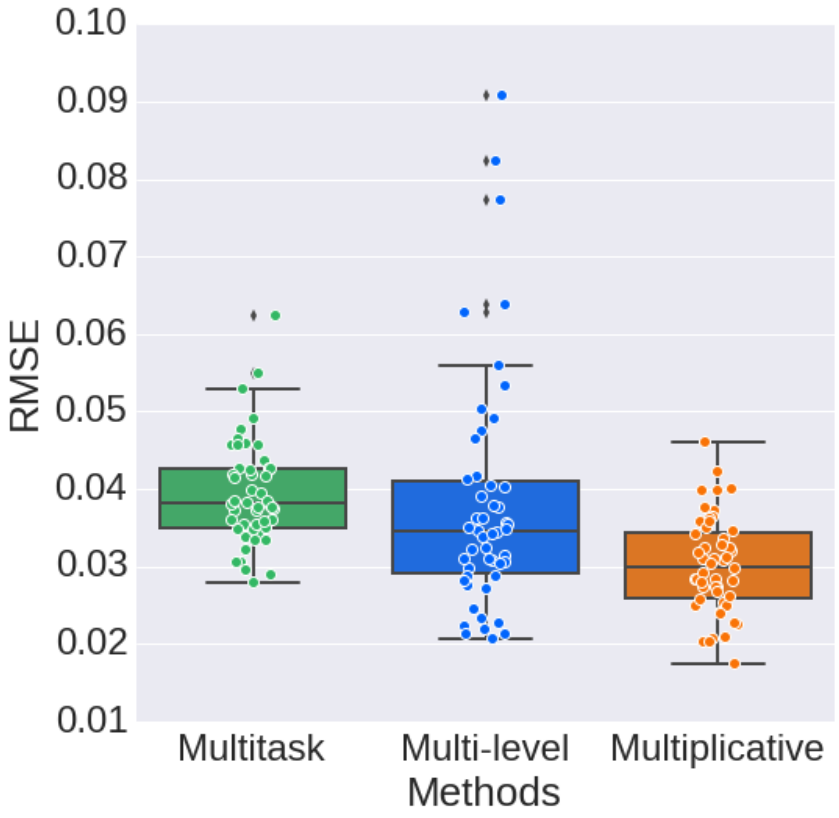




- **Sparser** solution
- Better **recovery of true features** (higher PPV)

# Performance of MMLD

- On **simulations:**

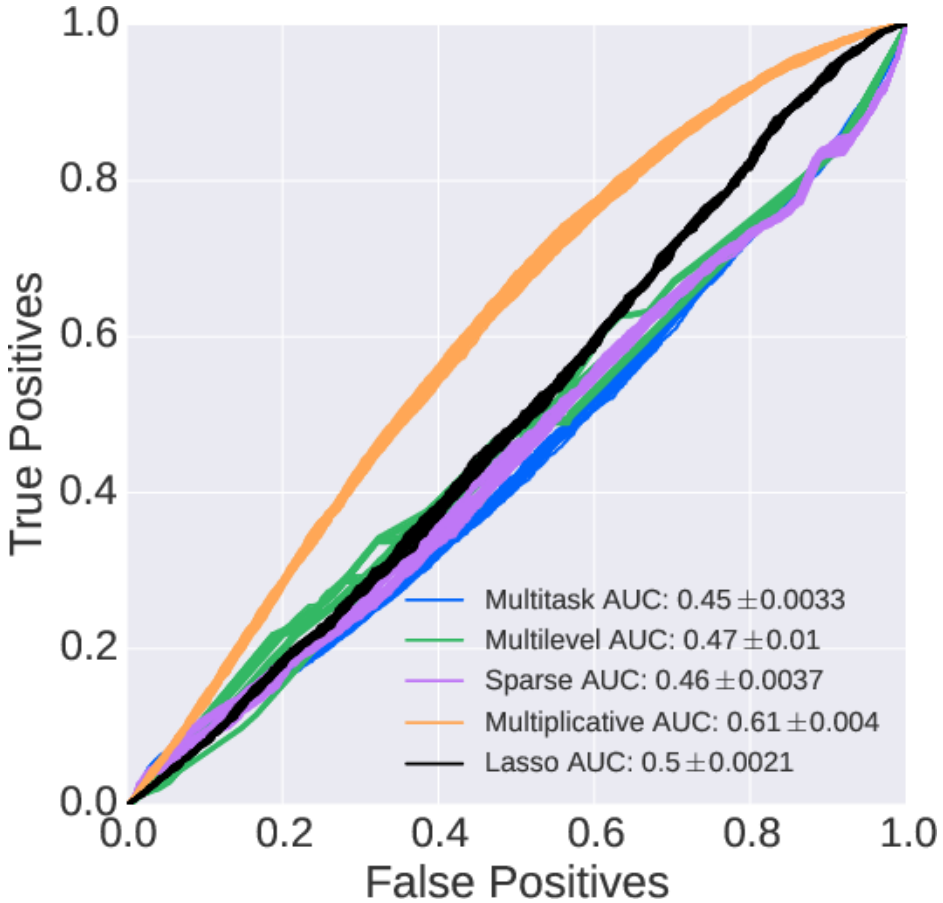



- Improved **stability** (consistency)
- Better **predictivity** (RMSE).

# Performance of MMLD

– Making predictions for tasks for which you have **no data.**




V. Bellón, V. Stoven, and C.-A. Azencott (2016) **Multitask feature selection with task descriptors**, PSB.

https://github.com/vmolina/MultitaskDescriptor

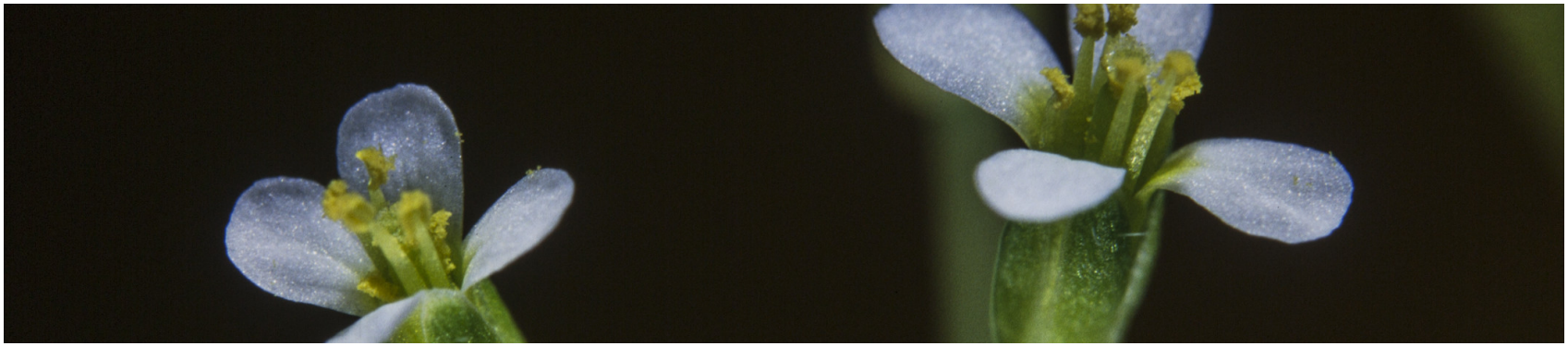
# Randomized MMLD

- **Stability:** Selecting the same features on multiple related data sets (or multiple subsets of the same data set)
- Crucial for **interpretability**
- **Randomized Lasso:** Summarize many repetitions on subsamples of the data in a consensus feature selection [MB10].

  $\Rightarrow$ **Randomized MMLD**

# Experimental results

*Arabidopsis thaliana* genotypes



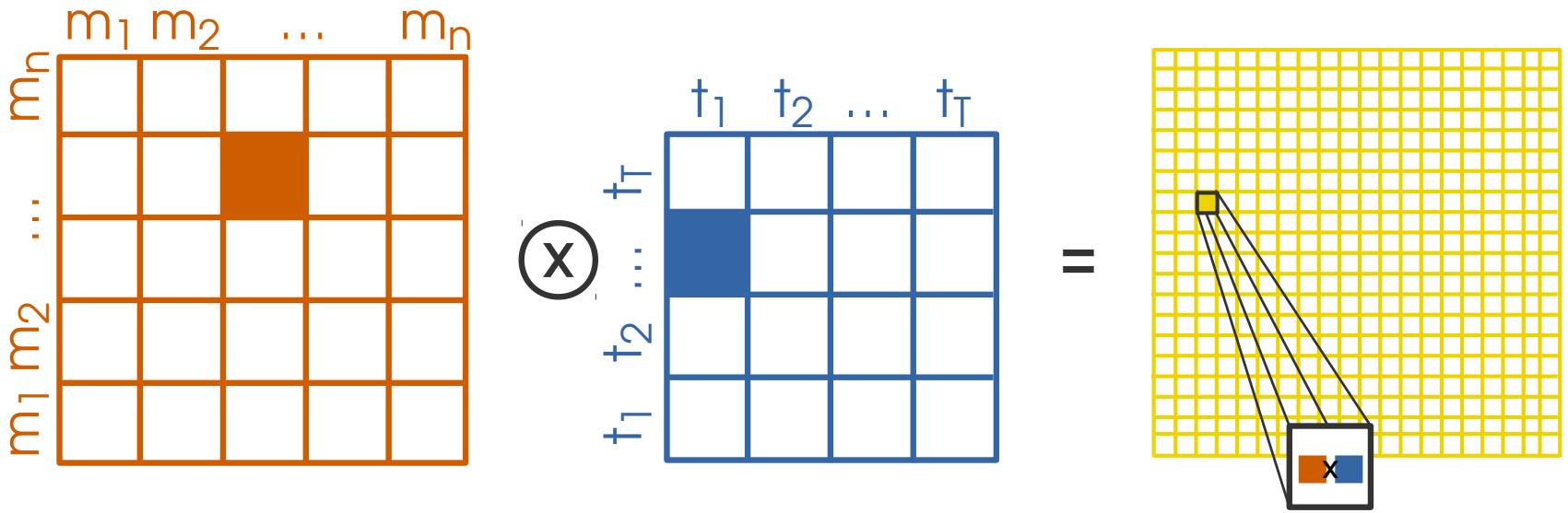
- 6 flowering time phenotypes (= tasks)
- $\sim$ 180 samples per task, $\sim$ 280 000 SNPs
- **candidate SNPs** = SNPs from genes known to be related to flowering time.

| | # Selected SNPS | Consistency | Consistency on candidate SNPs |
|---|---|---|---|
| Lasso | $871 \pm 12$ | $0.21 \pm 0.04$ | $0.01 \pm 0.01$ |
| MMLD | $616 \pm 71$ | $0.18 \pm 0.03$ | $0.01 \pm 0.07$ |
| Randomized MMLD | $2295 \pm 118$ | $0.37 \pm 0.02$ | $0.45 \pm 0.13$ |

# Multitask kernel methods

## Kronecker kernel:

$K((mol1, task1), (mol2, task2)) = K_{mol}(mol1, mol2) \times K_{task}(task1, task2)$




## Computational issues:

- n molecules, T tasks $\Rightarrow$ nT observations
- Can be solved by using **mostly nearby observations**

  B. Playe, C.-A. Azencott, and V. Stoven (2017) **Efficient multi-task chemogenomics for drug specificity prediction.** bioRxiv

# Conclusion

- Applying **machine learning** to **genomics data** is challenging because of the **dimensionality of the data**
- "Large p, small n" problem
- Reducing p: **interpretable dimensionality reduction**

  $\Rightarrow$ **regularization**
- Increasing n: **multi-task** approaches.

# Current ML challenges

- **Robustness/stability**

  Recovering the same biomarkers when the data changes slightly.

- **Complex interaction patterns**

  - Limited to additive or quadrative effects
  - Little existing work on complex ML models.

- **Statistical significance**

  - Computing p-values
  - Correcting for multiple hypotheses
  - Controlling false discovery rate.

# 4. A few hot topics around ML and health

# Further challenges: Privacy

- More data $\rightarrow$ Data sharing $\rightarrow$ **ethical** concerns
- How to learn from **privacy-protected** patient data?

C.-A. Azencott. **Machine learning and genomics: precision medicine vs. patient privacy.** Phil Trans Roy Soc A 2018.

# Further challenges: Heterogeneity

- Multiple relevant **data sources** and **types**
- Multiple (unknown) **populations** of samples.

**Tumor heterogeneity**

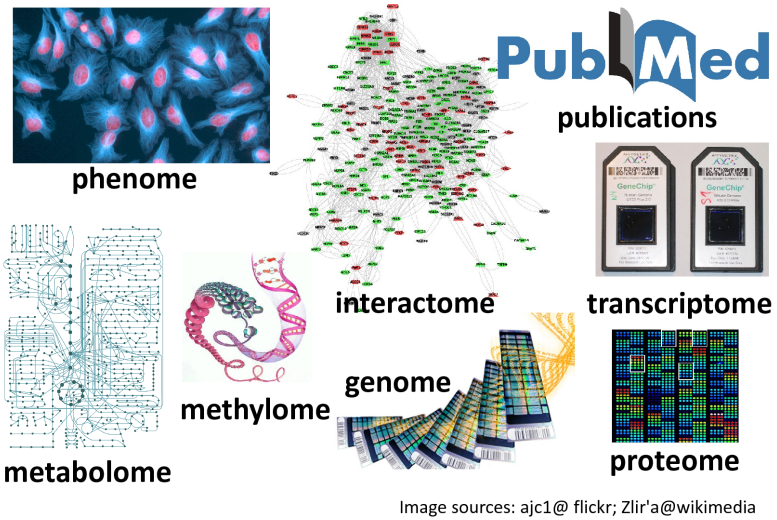
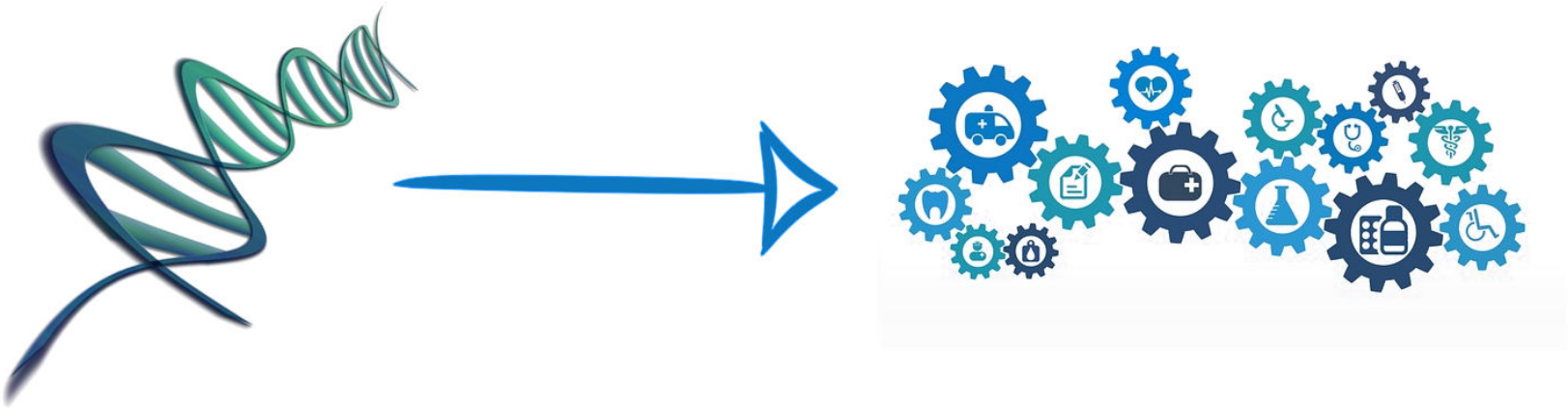



Image sources: ajc1@ flickr; Zlir'a@wikimedia

**Heterogeneous data sources**

[GBG16]

# Further challenges: Risk prediction



- State of the art: **Polygenic Risk Scores**

  **Linear** combination of SNPs with high p-values (**summary statistics**)
  Weighted by log odd ratios / univariate linear regression coefficients.

- **Complex models** slow to adopt – **reliability?** [Oks+14; SS17]

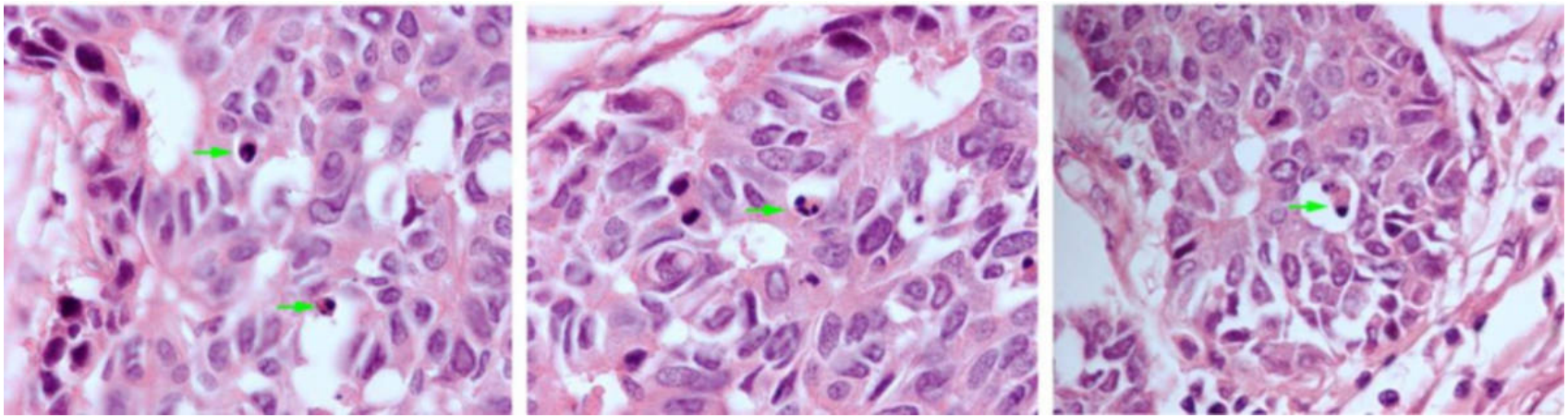
# Further challenges: Bioimage informatics

High-throughput **molecular** and **cellular** images

- **Subcellular location** analysis
- **High-content screening**
- Segmentation, tracking, registration.

**BioImage Informatics** `http://bioimageinformatics.org/`

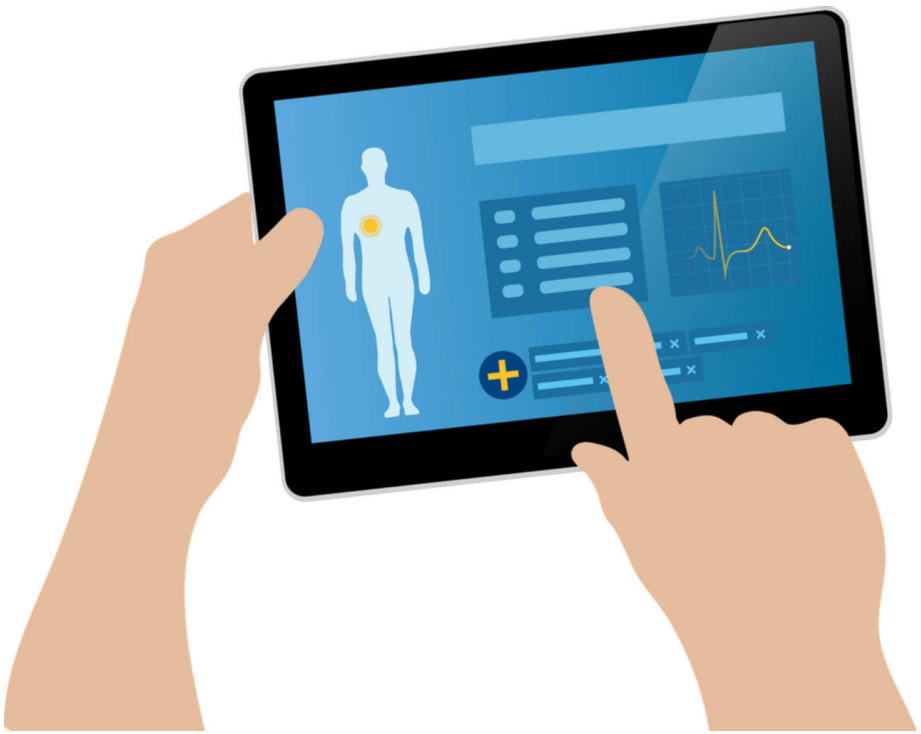
[Est+17; Che+18]



**Detecting cells undergoing apoptosis**

# Further challenges: Electronic health records

- **Clinical notes:** incomplete, imbalanced, time series
- Combine **text** + **images** + **genetics**
- Assisting **evidence-based medicine**



[Mio+16; Raj+18]

# Molecules

- **Representation learning:**
  - Use deep learning to **learn better representations** of molecular graphs [LPB13; Duv+15; Col+17a; HYL17]
  - But not only deep learning
    S. Rensi and R. B. Altman (2017) **Shallow Representation Learning via Kernel PCA Improves QSAR Modelability.** JCIM 57 (8), 1859–1967
- Use **(deep) generative models** to come up with new chemicals (still very much exploratory) [Kad+17; CKK17]
- **Deep learning**
  - **ML Docking:** Protein-ligand docking from 3D representations [Rag+16]
  - Y. Xu et al. (2017) **Demystifying Multitask Deep Neural Networks for Quantitative Structure-Activity Relationships.** JCIM Article ASAP.

# A few starting places

## Data and Challenges

- **DREAM Challenges:** Crowdsourcing challenges for biology and medicine `http://dreamchallenges.org/`
- **Epidemium:** Cancer research through data challenges `http://www.epidemium.cc/`
- **MIMIC:** Deidentified electronic health records `https://mimic.physionet.org/`
- **BioImage Informatics Challenges** `https://bii.eecs.wsu.edu/challenges/`

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