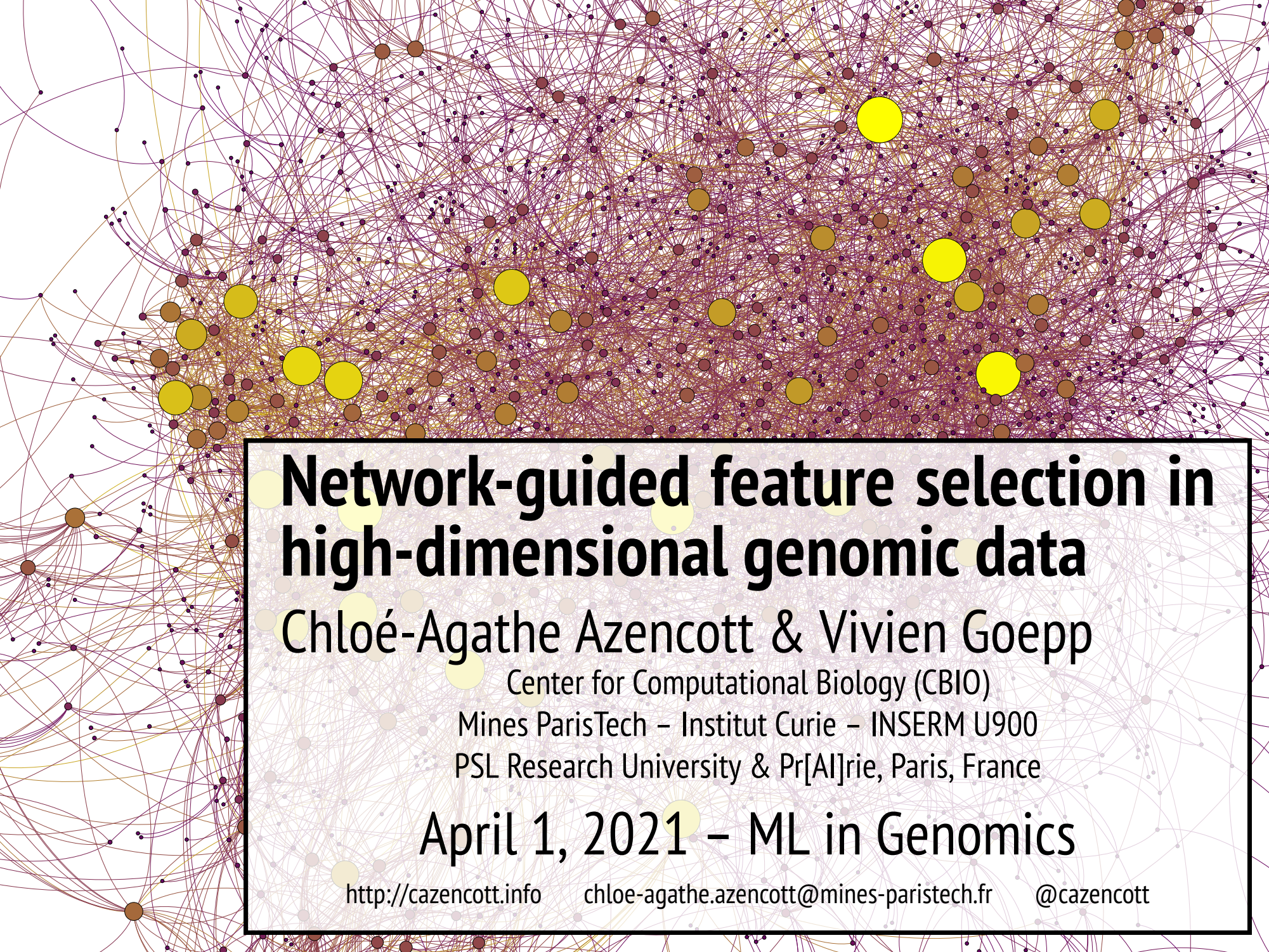

Network-guided feature selection in high-dimensional genomic data

Chloé-Agathe Azencott & Vivien Goepp

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April 1, 2021 – ML in Genomics

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About Chloé

Janvier 2020 **Habilitation à Diriger des Recherches**

Depuis 2019 **Chaire tremplin** à PrAIrie
Institut 3IA.

Depuis 2013 **Chargée de recherche** puis **Maîtresse-assistante** au CBIO

2011–2013 **Chargée de recherche post-doctorante**
Machine Learning for Computational Biology, MPI Tübingen (Allemagne).

2005–2010 **Doctorante**
Institute for Genomics and Bioinformatics, University of California Irvine (USA).

2002–2005 **Double diplôme Ingénieur & Master**
École Nationale Supérieure des Télécommunications de Bretagne
Informatique et Mathématiques.

About me

2020–2021 **Post-doctorant**
Center for Computational Biology, Mines Paristech & Institut Curie.

2016–2019 **Doctorant**
Université Paris-Descartes (*Université de Paris*).

2013–2016 **Double diplôme Ingénieur & Master**
Supélec
Master in Statistics

Precision Medicine

- **Adapt** treatment to the **genetic specificities** of the patient.

  E.g. Trastuzumab for HER2+ breast cancer.

[Li11 ; GVB13 ; AR15 ; Sch15]

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  Identify **similarities** between patients that exhibit similar phenotypes.

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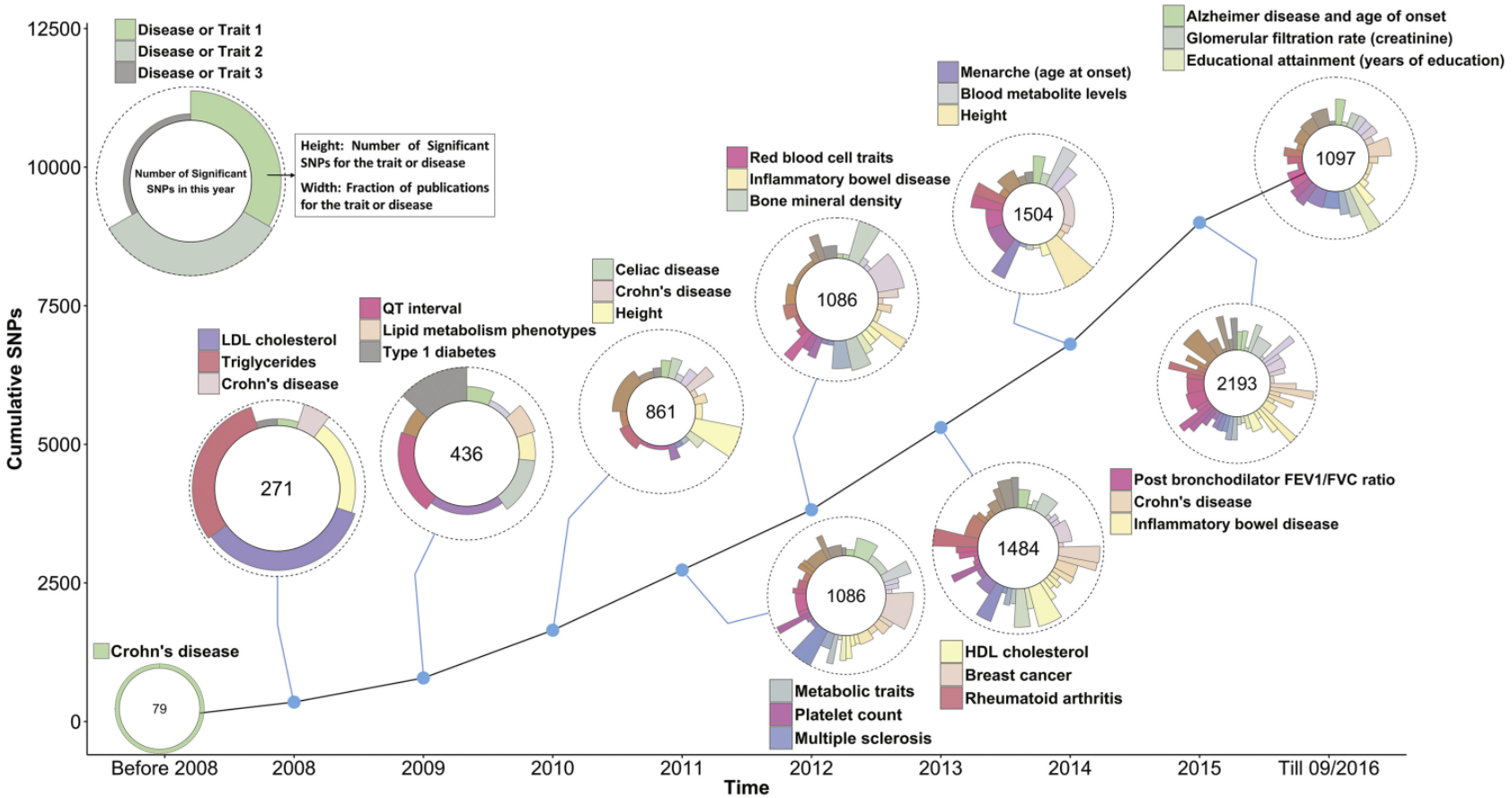
Data + Feature Selection

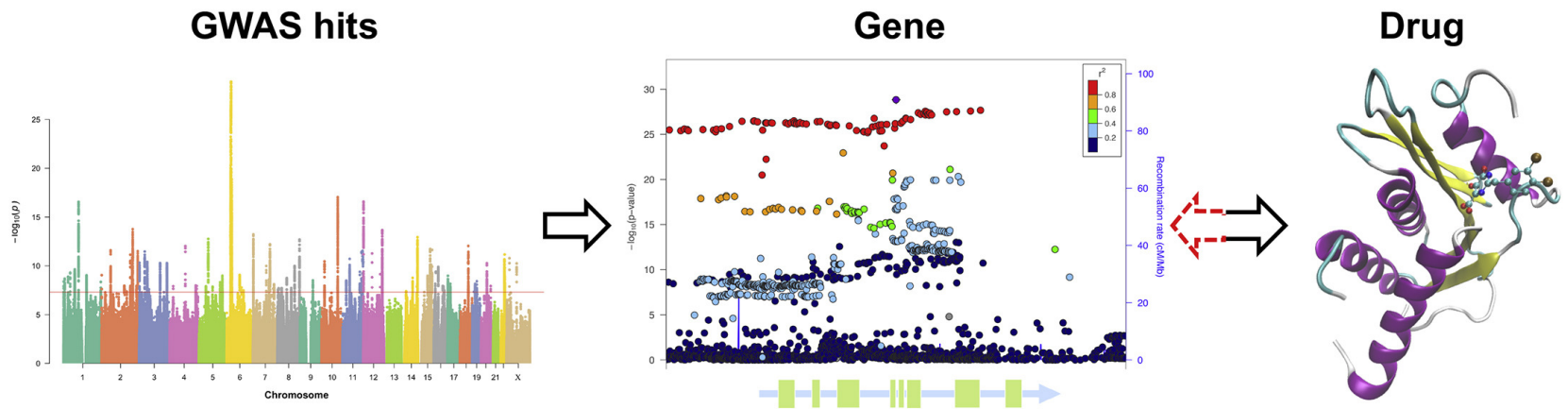
[Li11 ; GVB13 ; AR15 ; Sch15]

GWAS SNP-trait discovery timelime



Ref: [visscher2017]

From GWAS discoveries to drugs



Trait	Gene with GWAS hits	Known or candidate drug
Type 2 Diabetes	*SLC30A8/KCNJ11*	ZnT-8 antagonists/Glyburide
Rheumatoid Arthritis	*PADI4/IL6R*	BB-Cl-amidine/Tocilizumab
Ankylosing Spondylitis(AS)	*TNFR1/PTGER4/TYK2*	TNF-inhibitors/NSAIDs/fostamatinib
Psoriasis(Ps)	*IL23A*	Risankizumab
Osteoporosis	*RANKL/ESR1*	Denosumab/Raloxifene and HRT
Schizophrenia	*DRD2*	Anti-psychotics
LDL cholesterol	*HMGCR*	Pravastatin
AS, Ps, Psoriatic Arthritis	*IL12B*	Ustekinumab

Ref: [visscher2017]

Common disease common variant hypothesis

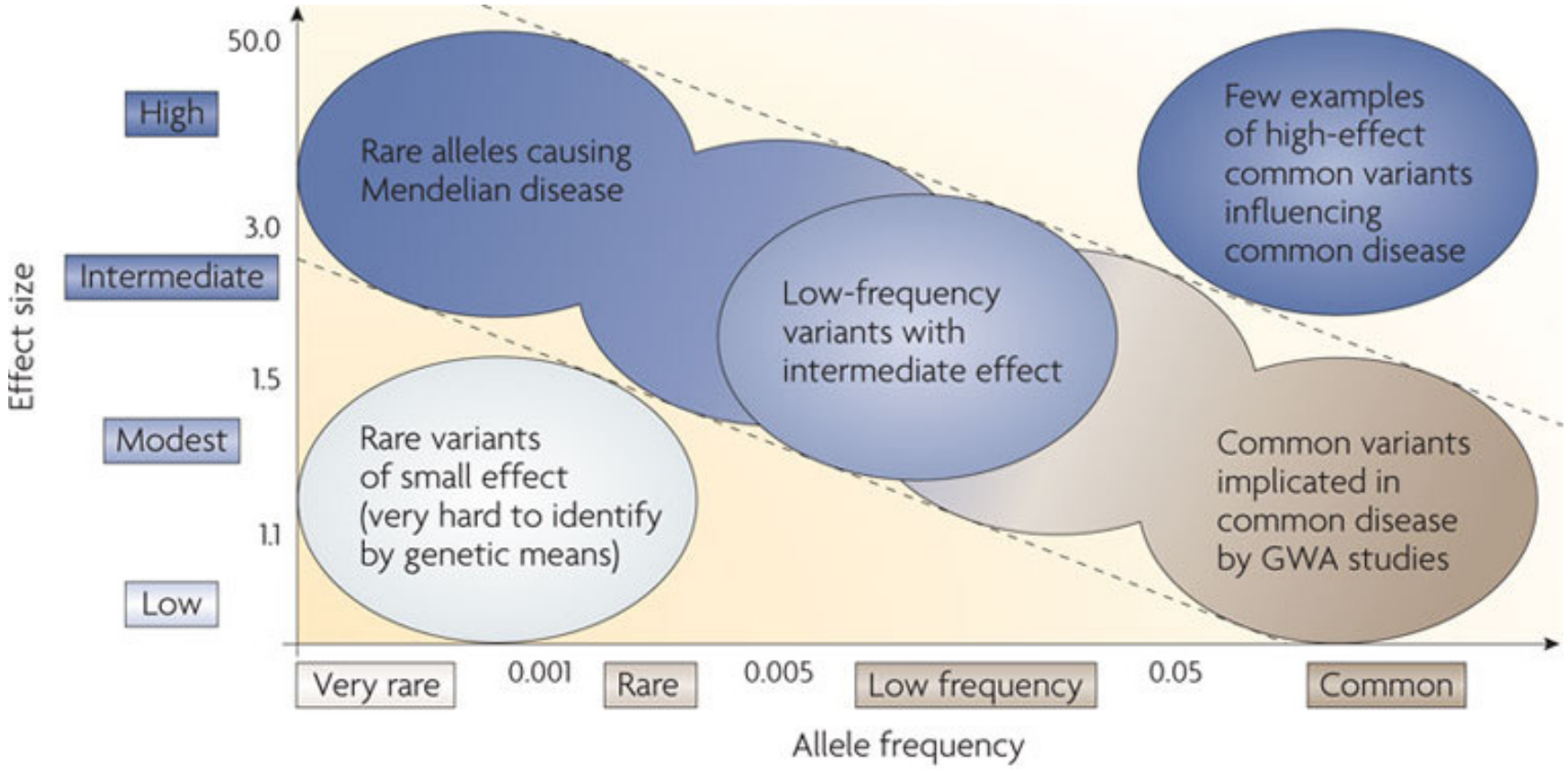


Image source: [Ant+10]

Genome-Wide Association Studies (GWAS)

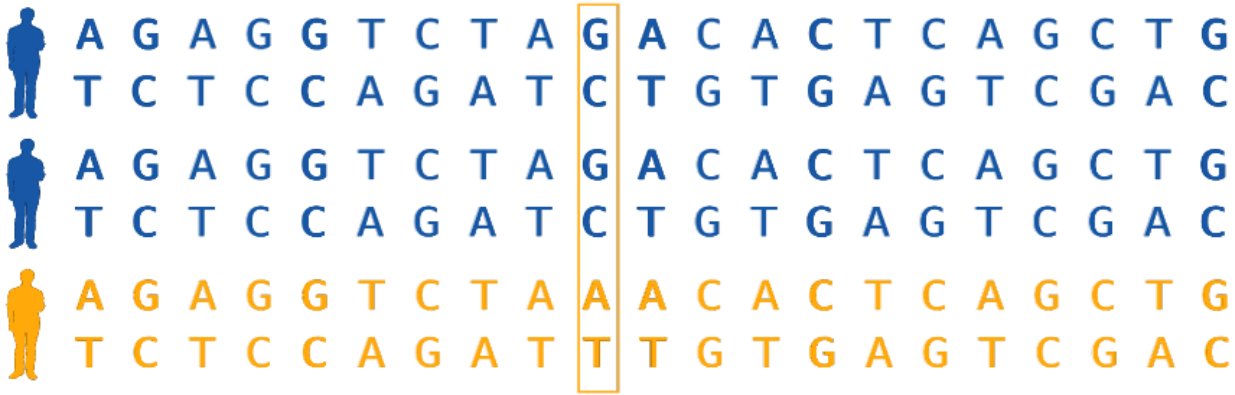


Image courtesy V. Bellón.

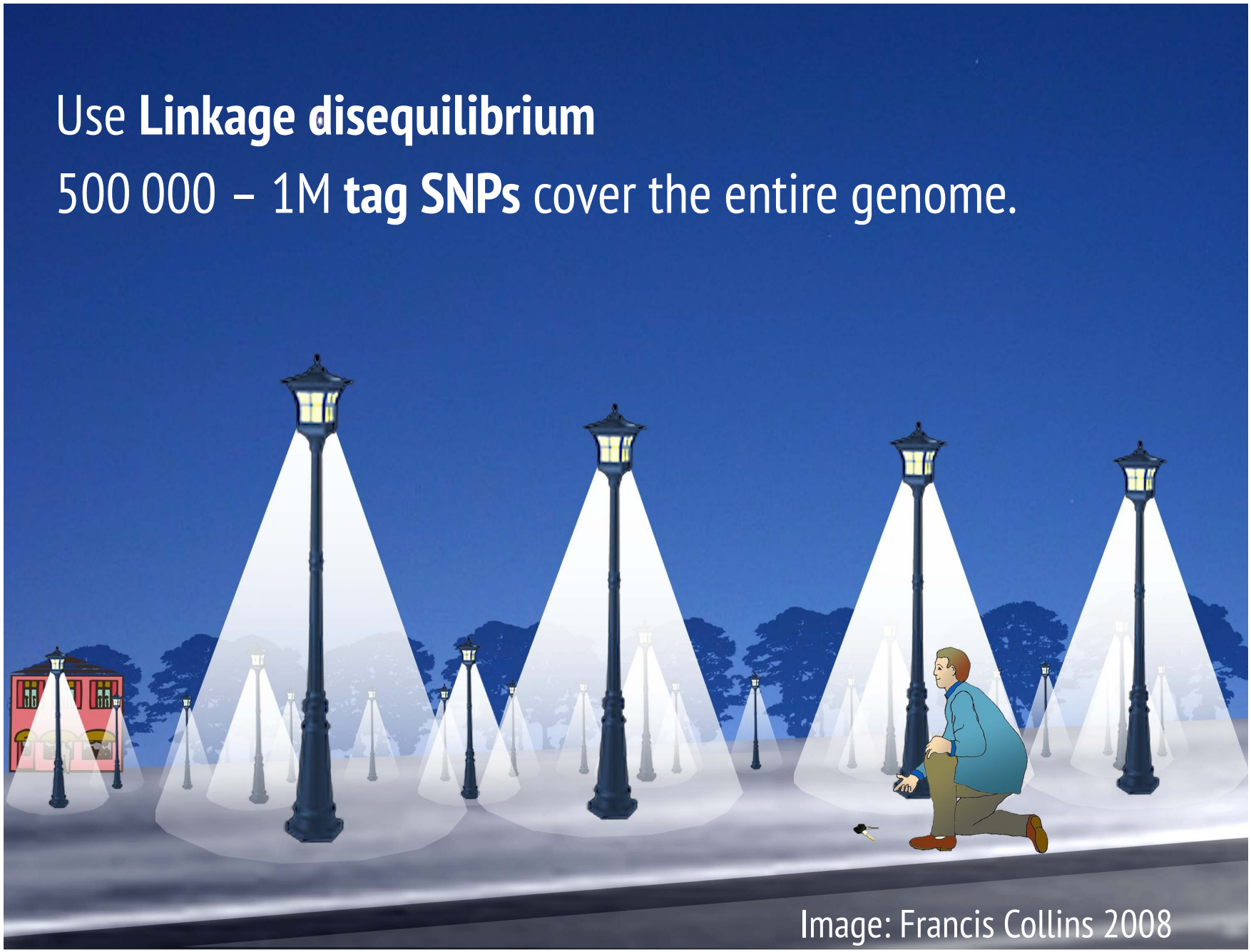
Which SNPs explain the phenotype?

p = 10^5 – 10^7 **SNPs** n = 10^3 – 10^5 **samples**

Single **N**ucleotide **P**olymorphisms $\mathcal{Y} = \{-1, 1\}$ or $\mathbb{R}$

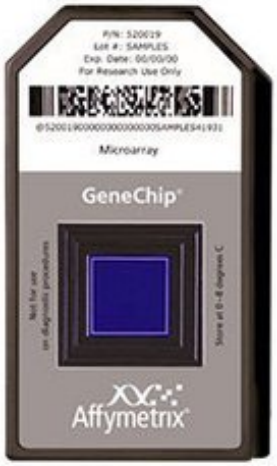
Data: $(X, \mathbf{y}) \in \{0, 1, 2\}^{n \times p} \times \mathcal{Y}^n$

Guilt by association



SNP genotyping

SNP microarray



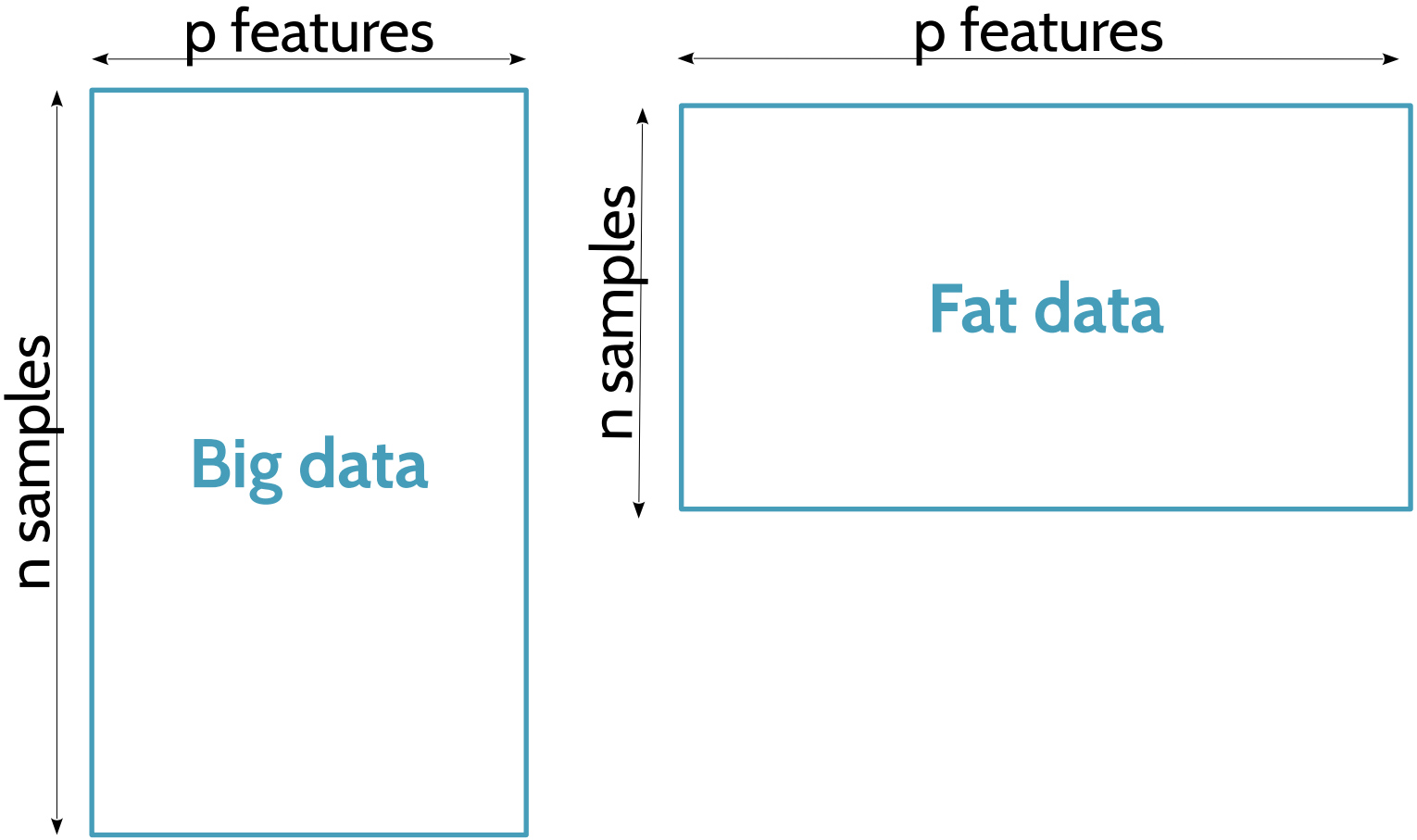
- Cheap
- Small data files
- 500K – 5M loci captured.

Whole-Genome Sequencing

- More expensive
- Large data files
- $\sim$ 3B loci captured (incl. rare variants).


Large p, small n data

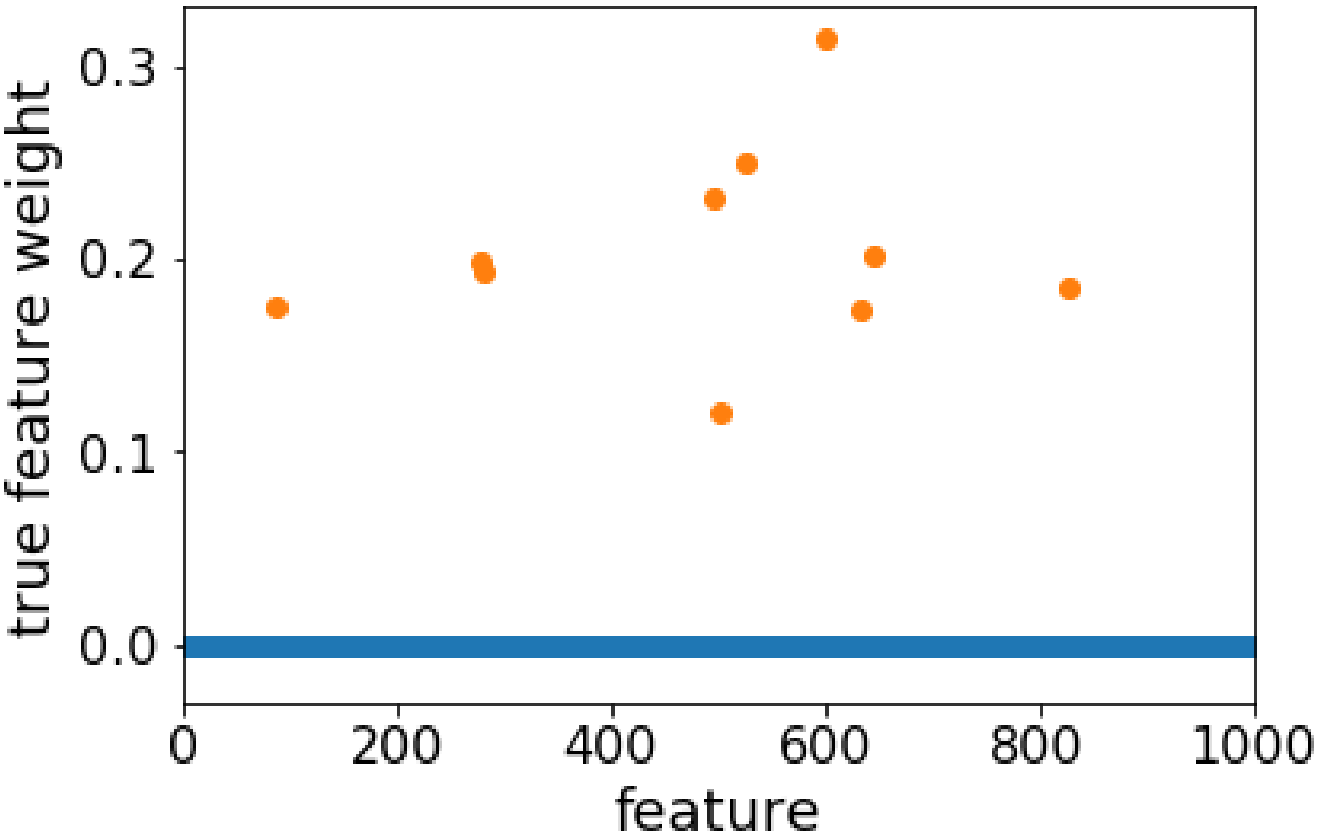
High-dimensional data with low sample size



Large p, small n data

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

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



Simulation

t-test: For each feature x_j,

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

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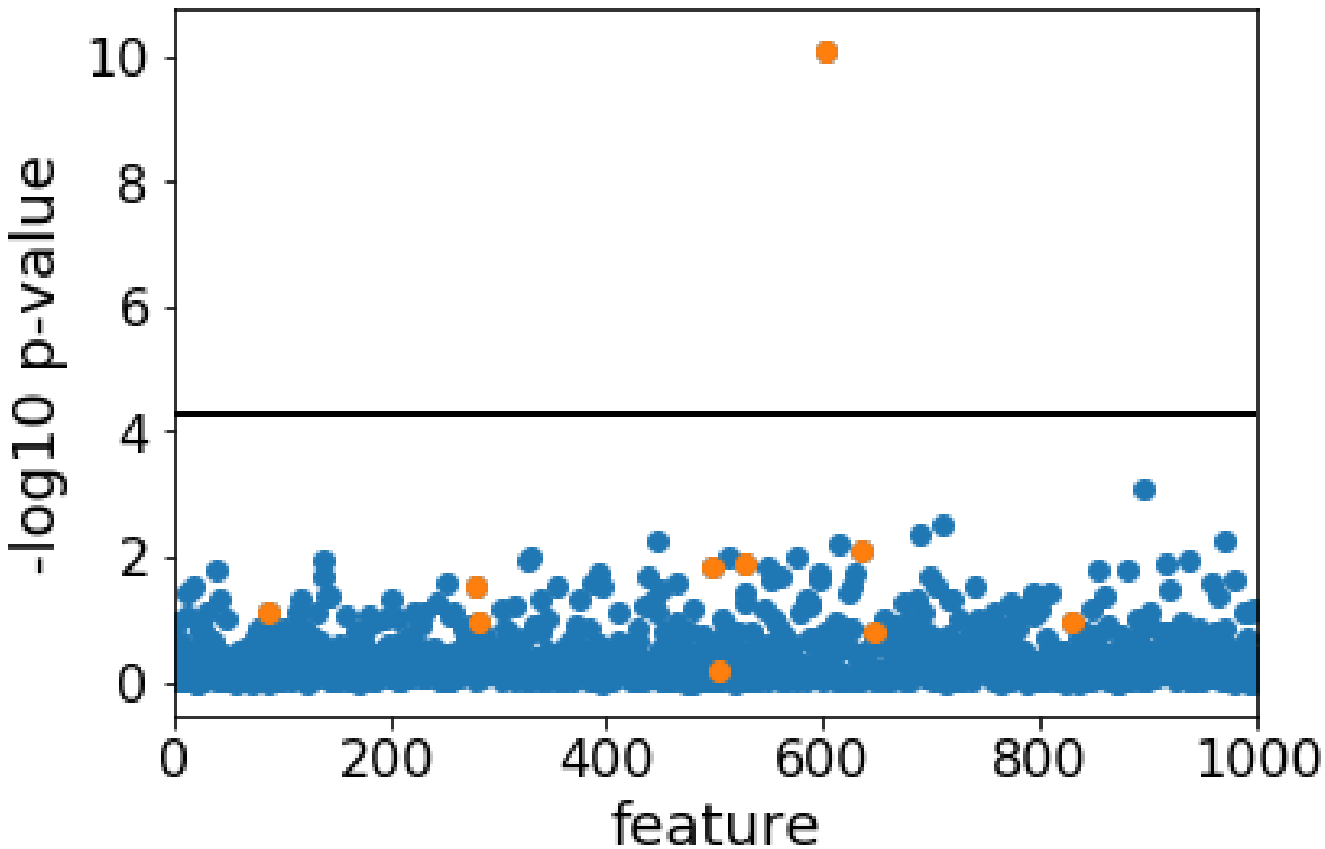

Simulation

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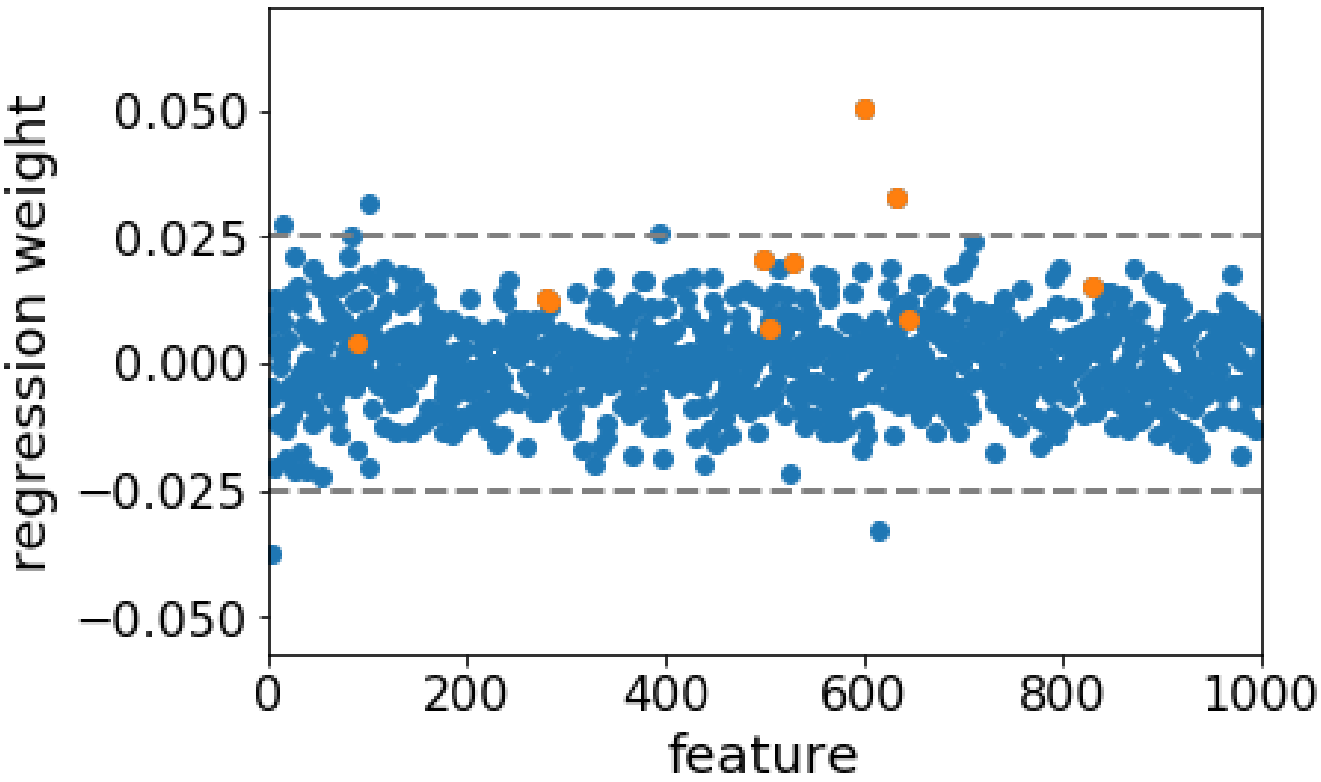

Molecular signatures stability

- **Stability (robustness):** find similar answers on different data sets linked to the same biological question.
- **Example:** predicting apparition of distant metastasis at 5 years in breast cancer.
  - **2001:** a signature of **456** genes [Sør+01]

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  - **2002:** a signature of **70** genes [VV+02]
  - Overlap: **17** genes [ED+05]
  - Most **random** signatures of 70 genes predict outcome well [VDD11]

Encoding SNPs

AA, Aa and aa must be represented as numbers.

- **Allelic dosage / Codominance** model:
  AA = 0 Aa = 1 aa = 2
- **Dominance** model:
  AA = 0 Aa = 1 aa = 1
- **Recessive** model:
  AA = 0 Aa = 0 aa = 1
- **Dummy encoding:**
  AA = 0, 0 Aa = 0, 1 aa = 1, 1
  Covers all above models, but with twice as many variables.

Qualitative GWAS

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

- Is the SNP **significantly associated** with the phenotype?
- **Contingency table**

	AA	Aa	aa
Cases			
Ctrls			

	0	1
Cases	a	b
Ctrls	c	d

Statistical tests: χ^2, Cochran-Armitage trend test, etc.

- **Logistic regression**

$$\text{logit}(P(\text{case}|x)) = \beta_0 + \beta_1 x$$

Is $\hat{\beta}_1$ significantly different from 0?

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

Interlude – Fitting a regression

- **Univariate linear regression:**
  - **Model:** $f(x) = \beta_0 + \beta_1 x$
  - **Data:** n samples $(x_1, y_1), (x_2, y_2) \ldots, (x_n, y_n)$
  - **Fitting** = finding β_0 and β_1: minimize the sum of squared errors
    Least squares fit (Gauss/Legendre)

$$\hat{\beta}_0, \hat{\beta}_1 = \arg\min_{\beta_0, \beta_1} \sum_{i=1}^{n} (y_i - f(x_i))^2$$

$$\hat{\beta}_0, \hat{\beta}_1 = \arg\min_{\beta_0, \beta_1} \sum_{i=1}^{n} (y_i - (\beta_0 + \beta_1 x_i))^2$$

- Can be solved **analytically**.

Interlude – Fitting a regression

- **Multivariate linear regression:**
  - **Model:** $f(x) = \beta_0 + \beta_1 x_1 + \cdots + \beta_p x_p$
  - **Data:** n samples
    $((x_{11}, x_{12}, \ldots, x_{1p}), y_1), \ldots, ((x_{n1}, x_{n2}, \ldots, x_{np}), y_n)$
  - **Fitting** = finding $\beta_0, \beta_1, \ldots, \beta_p$: minimize the sum of squared errors
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$$\hat{\beta}_0, \hat{\beta}_1 = \arg\min_{\beta_0, \beta_1} \sum_{i=1}^{n} \left(y_i - \left(\beta_0 + \sum_{j=1}^{p} \beta_j x_{ij} \right) \right)^2$$

- Can be solved **analytically** or by **gradient descent.**

Interlude – Fitting a regression

- **Multivariate logistic regression:**
  - **Model:** $f(x) = \text{logistic}\left(\beta_0 + \beta_1 x_1 + \cdots + \beta_p x_p\right)$
    - $\text{logistic}(u) = \frac{1}{1+\exp(-u)}$ transforms a number between $-\infty$ and $+\infty$ into a number between 0 and 1.
    - f models the probability that $y = 1$.
  - **Data:** n samples
    $((x_{11}, x_{12}, \ldots, x_{1p}), y_1), \ldots, ((x_{n1}, x_{n2}, \ldots, x_{np}), y_n)$
  - **Fitting** = finding $\beta_0, \beta_1, \ldots, \beta_p$: minimize the sum of **logistic** errors

$$\hat{\boldsymbol{\beta}} = \arg\min_{\boldsymbol{\beta} \in \mathbb{R}^{p+1}} \sum_{i=1}^{n} \log\left(1 + \exp(-y_i f(x_i))\right)$$

y_i = -1 for controls, 1 for cases

- Can be solved by **gradient descent.**

Qualitative GWAS

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

- What is the **effect** of the SNP on the phenotype?
- **Contingency table**

	AA	Aa	aa
Cases			
Ctrls			

	0	1
Cases	a	b
Ctrls	c	d

- **Odds-ratio**

$$\underbrace{\frac{P(0|case)}{P(0|ctrl)}}_{\text{odds of 0 in cases}} \Big/ \underbrace{\frac{P(1|case)}{P(1|ctrl)}}_{\text{odds of 1 in cases}} = \frac{a\ d}{b\ c}$$

Quantitative GWAS

- Is the SNP **significantly associated** with the phenotype?
- **Linear regression**

$$y = \beta_0 + \beta_1 x$$

Is $\hat{\beta}_1$ significantly different from 0?

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

- What is the **effect** of the SNP on the phenotype?
- **Effect size:** $\hat{\beta}_1$.

Hypothesis testing

Do my observations support my new discovery?

Let's **put this to the test.**

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- **Alternate hypothesis** $\mathcal{H}_1$: The thing you'd like to prove.
- **Test statistic** Q : a random variable of known distribution under $\mathcal{H}_0$.
- **Significance threshold** α : probability of rejecting $\mathcal{H}_0$ when it is correct.
- **p-value:** $\mathbb{P}_{\mathcal{H}_0}(|Q| > q_0)$

  should be $\leq \alpha$ to reject $\mathcal{H}_0$

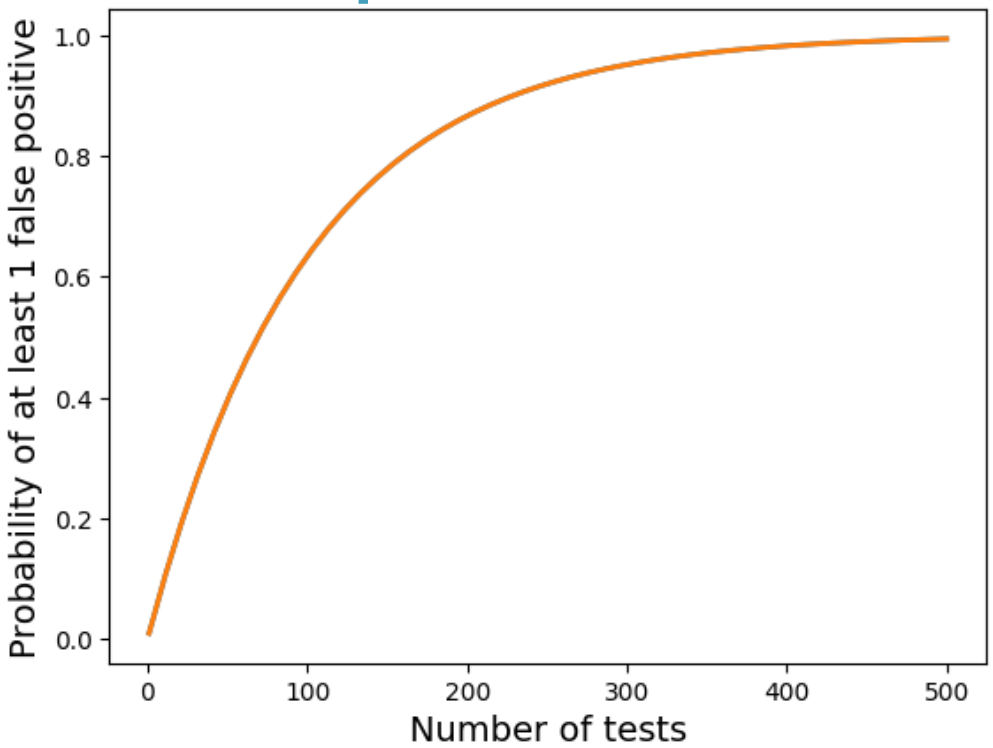
  i.e. **the probability to obtain a result at least as extreme as the one observed.**

Multiple Hypothesis Testing

- Probability of having **at least one false positive:**
  - For **one** test: α
  - For **p** tests:

Multiple Hypothesis Testing

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

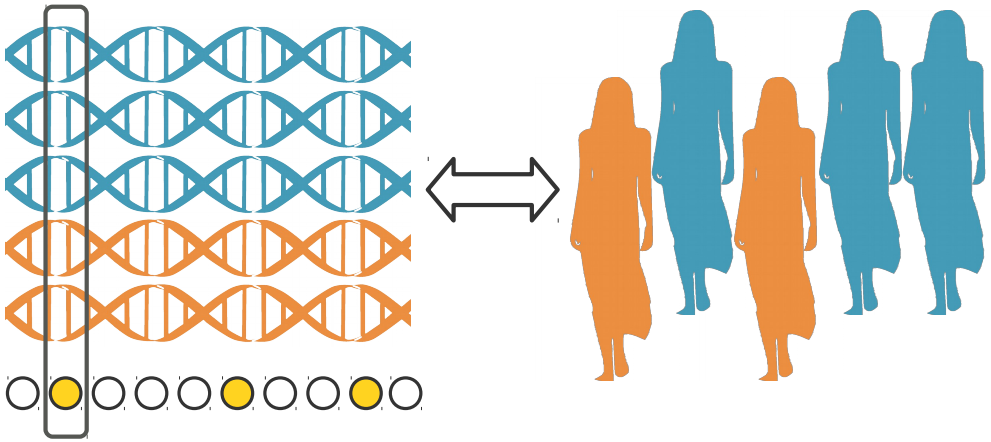


- Controlling **Family-Wise Error Rate** (FWER)
  - FWER $= \mathbb{P}(|\text{FP}| \geq 1)$
    FP = number of false positives (Type I errors)
  - **Bonferroni** correction: $\alpha \rightarrow \frac{\alpha}{p}$

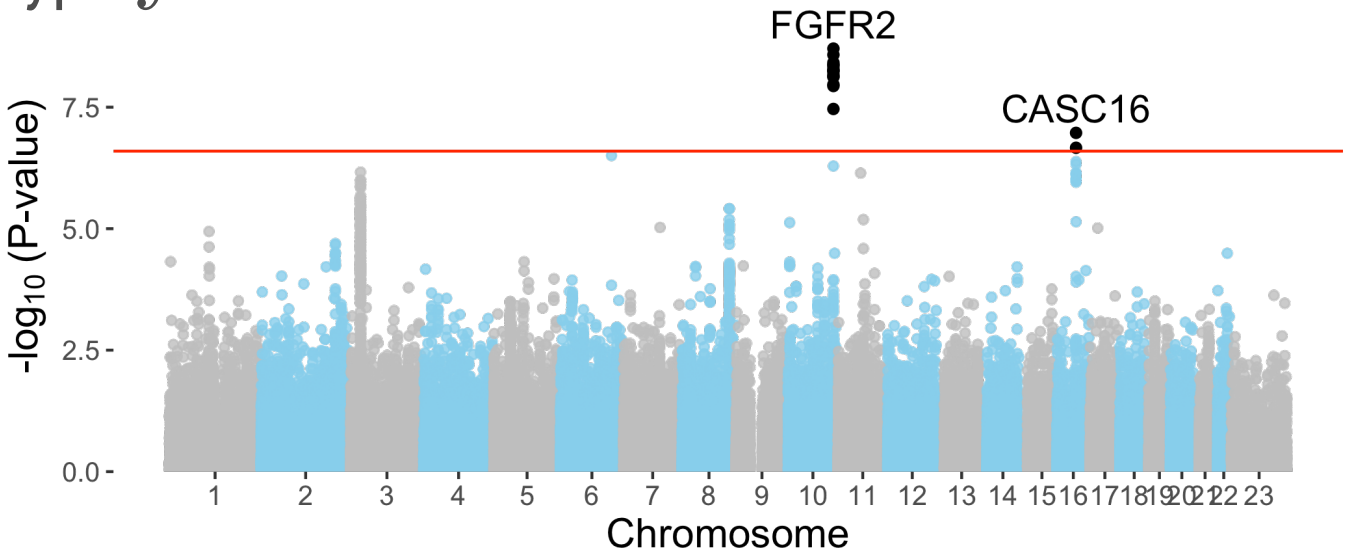
Back to

Large p, small n data

State-of-the-art: Statistical tests



- **Statistical test** of association between **each SNP** $\mathbf{x}_j$ and the phenotype $\mathbf{y}$.



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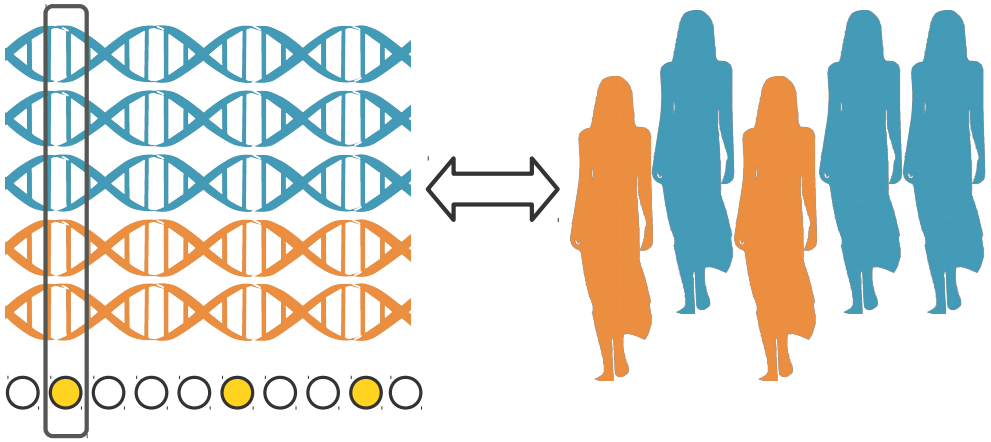

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Limitations:

☹ Lack of **statistical power;**

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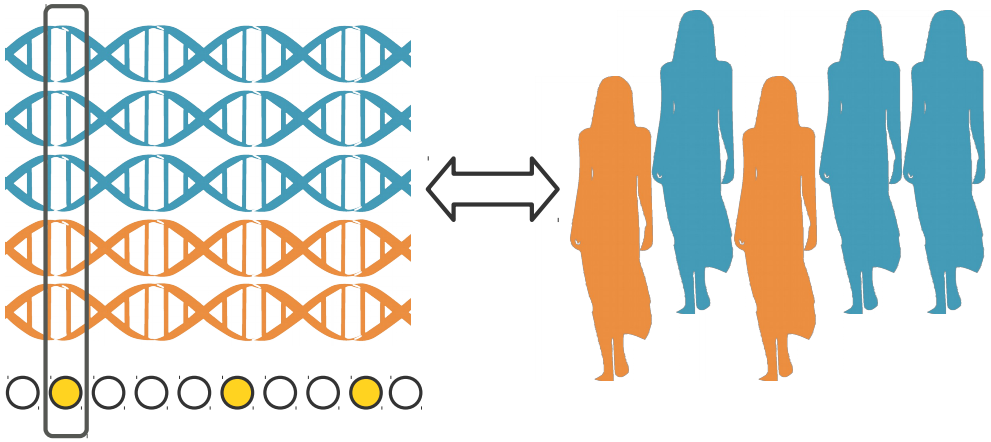

- **Statistical test** of association between **each SNP** $\mathbf{x}_j$ and the phenotype $\mathbf{y}$.

Limitations:

☹ Lack of **statistical power;**

☹ Consider SNPs **independently from each other.**

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.**

Contributions

Feature selection in high-dimensional genomic data

1. Using **biological networks** to integrate **prior knowledge.**
2. Considering **multiple related phenotypes** at once.
3. Modeling **nonlinearities.**

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   (But we won't talk about this today.)

Reducing p

Integrating prior knowledge

- **Regularization**

$$\arg\min_{\mathbf{w}\in\mathbb{R}^p} \underbrace{\sum_{i=1}^{n}\left(y^i - \sum_{j=1}^{p} w_j x_{ij}\right)^2}_{\text{loss}}$$

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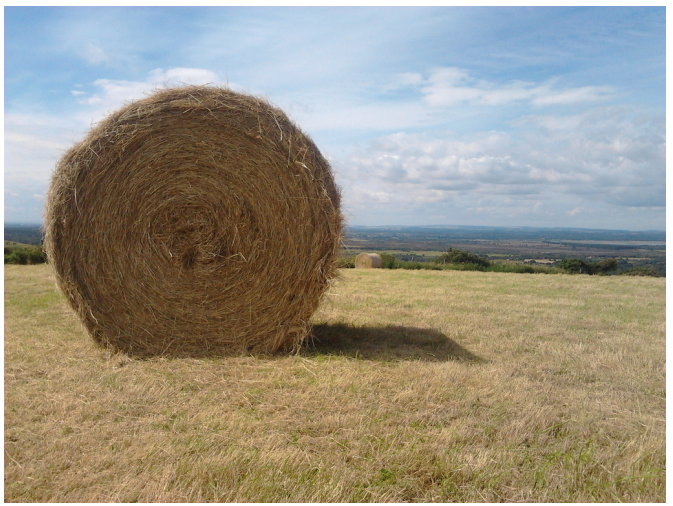

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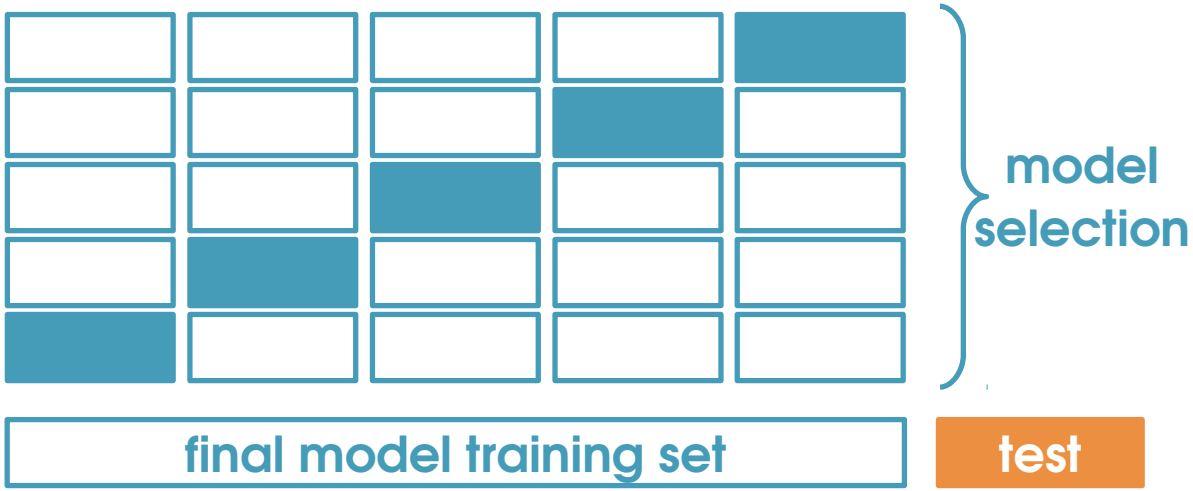
- Set the **regularization hyperparameter** by **cross-validation**



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- **Sparsity:** many features are assigned a weight of 0. They can be removed from the model.

Simulation

Lasso regression: Minimize

$$\sum_{i=1}^{n} \left(y^i - \sum_{j=1}^{p} w_j x_{ij} \right)^2 + \lambda \sum_{j=1}^{p} |w_j|$$

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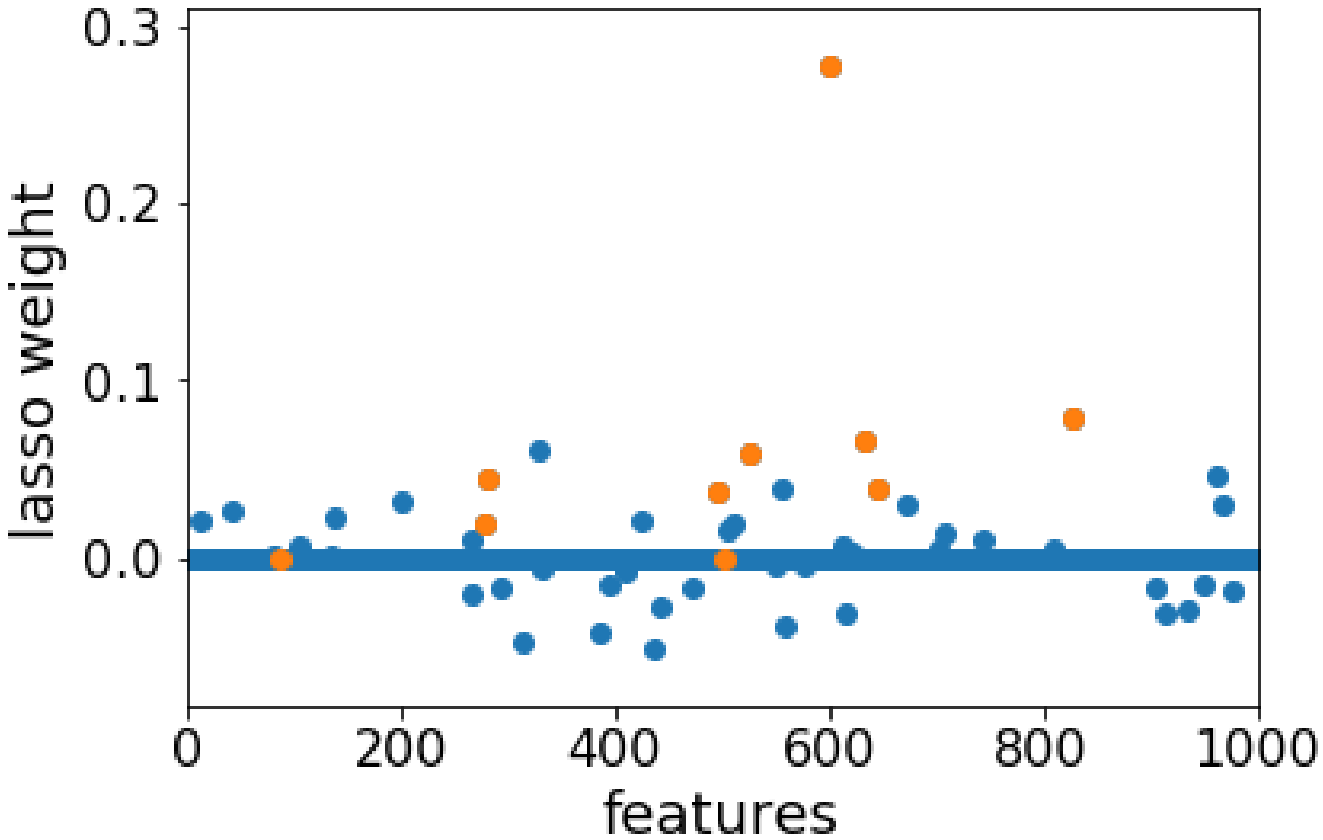
Lasso regression: Minimize

$$\sum_{i=1}^{n} \left(y^i - \sum_{j=1}^{p} w_j x_{ij} \right)^2 + \lambda \sum_{j=1}^{p} |w_j|$$



Stability

- Lasso tends to be **unstable:**
  - Randomly picks one of several correlated variables.
  - Different results on similar data sets.
- **Elastic net** combines ℓ_2 shrinkage with lasso [ZH05]

$$\arg\min_{\mathbf{w}\in\mathbb{R}^p} \sum_{i=1}^{n} \left(y^i - \sum_{j=1}^{p} w_j x_{ij} \right)^2 + \lambda \left((1-\alpha) \sum_{j=1}^{p} |w_j| + \alpha \sum_{j=1}^{p} w_j^2 \right)$$

- **Stability selection** [MB10]
  - Repeat on multiple bootstrap samples of the data.
  - Only keep the features that are selected often.

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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 [Loc+14 ; Lee+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.

Network view of complex diseases

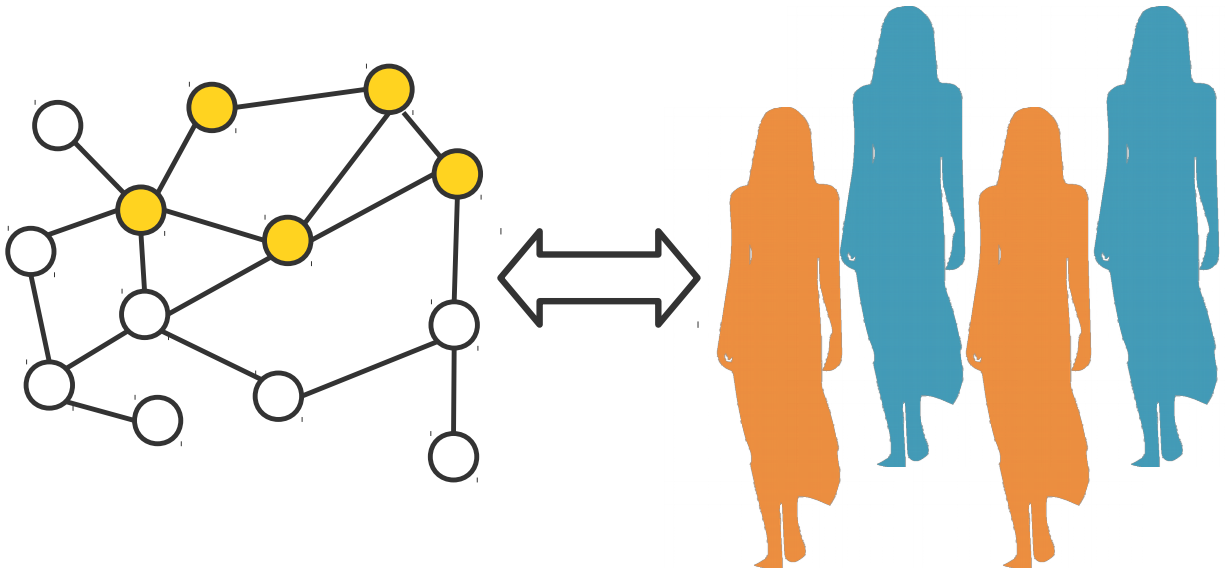
- Biology emerges from the **interplay** of multiple entities.

  DNA, RNA, proteins, metabolites + environment

- **Biological networks:**
  - **Nodes:** genes, proteins, etc.
  - **Edges:** biological relationships between two nodes.
  - E.g. **protein-protein interaction networks**, **gene regulatory networks**, **gene co-expression networks**, etc.
- **Biological networks** help understanding disease
  - Understand mutations **in their genomic context.**
  - Multiple ways of producing the same symptoms.
  - **Local hypothesis:** genes involved in disease interact with each other.
    [VCB11 ; Bar+12 ; Fur13 ; Cow+17 ; Hua+18]

Network-guided biomarker discovery

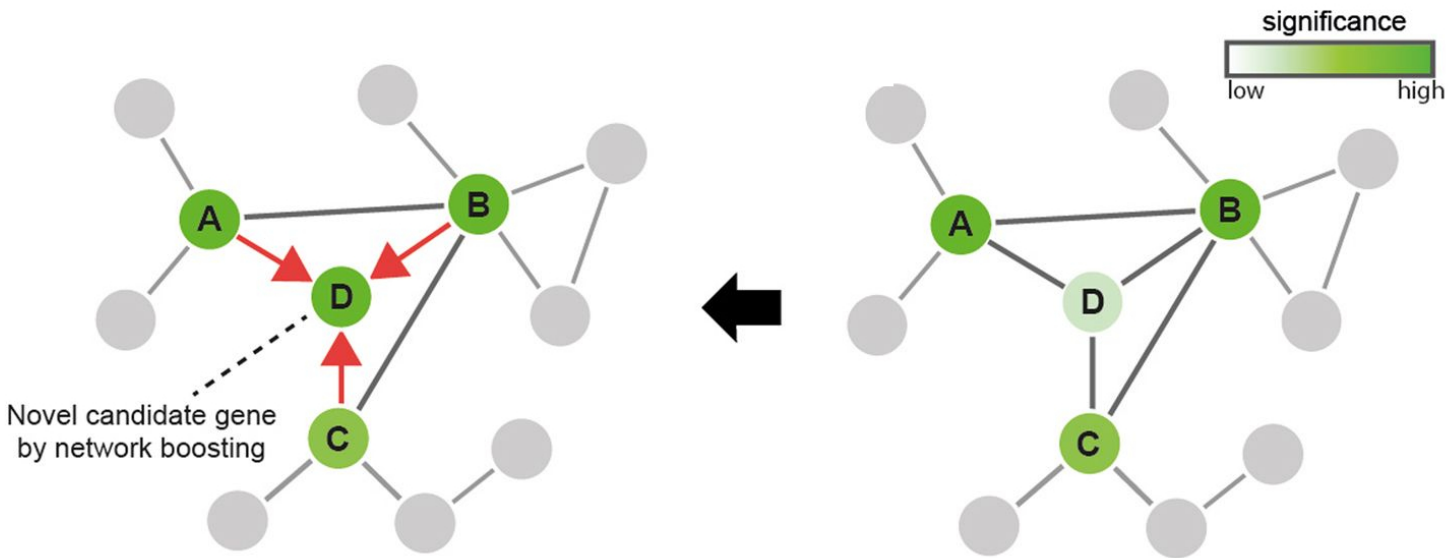
- Goal: Find a **set of explanatory features** compatible with a **given network** structure.



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

Network-guided GWAS

- **Map SNPs to genes** according to genomic position.
- **Combine** SNP p-values into **gene p-values.**
- Find networks **enriched** in genes with low p-values.



Guilt by association [LL18]

Finding high-scoring modules in PPI networks

Transform SNP p-values into gene p-values

- **Map SNP to genes:** position on the genomic sequence.
- **Aggregate p-values:** VEGAS2 [MM15]

Find high-scoring modules

- **dmGWAS:** greedy "seed and extend" heuristic [JZ14]
- **heinz:** Prize-Collecting Steiner Tree Problem [Dit+08]
- **HotNet2:** based on a heat diffusion process [Lei+15]
- **LEAN:** focus on star subnetworks [Gwi+17]

dmGWAS

- Use **biological networks** to analyze the output of a GWAS
- Find **modules** (subnetworks) enriched in small p-values
- SNPs p-values $\rightarrow$ genes p-values

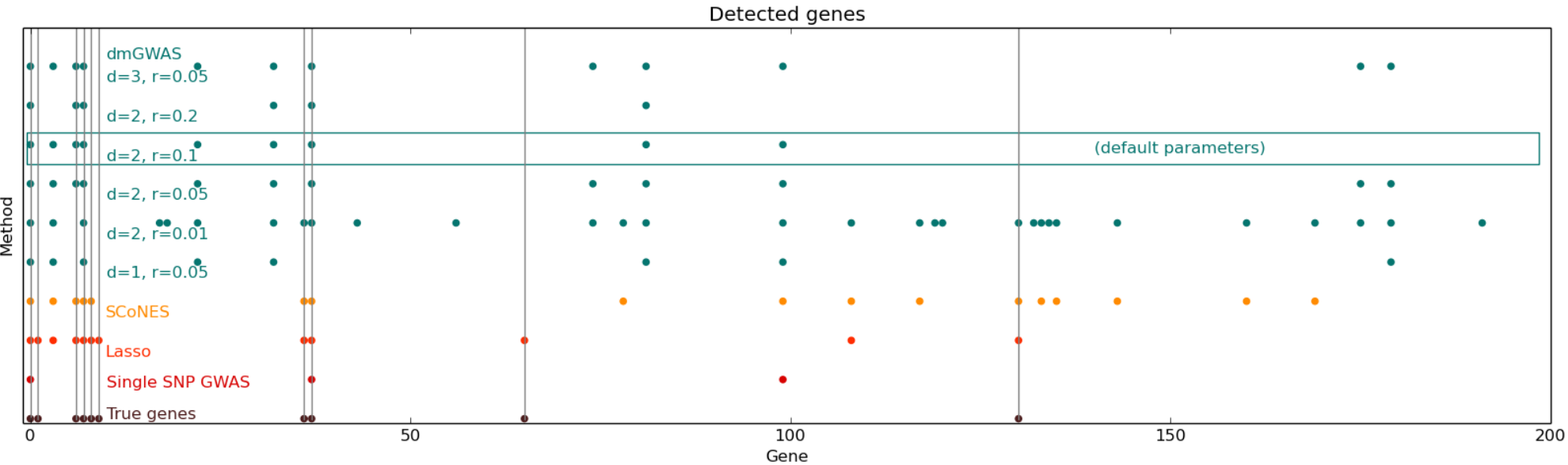
  20kb window, **min** p-value
- module z-score: $Z(\mathcal{S}) = \frac{\sum_{i \in \mathcal{S}} z_i}{\sqrt{|\mathcal{S}|}}$
- greedy search strategy:
  - each gene = seed
  - add neighbor i (within distance $\boldsymbol{d}$) if $Z(\mathcal{S} \cup i) \geq Z(\mathcal{S}) \times (1 + \boldsymbol{r})$
  - keep modules with more than **5** nodes
  - $Z(\mathcal{S}) \rightarrow Z_N(\mathcal{S}) = \frac{Z(\mathcal{S}) - \mu}{\sigma}$ (compare to random modules of size $|\mathcal{S}|$)
  - only keep top **1%** of modules (according to Z_N)
  - only keep modules that are significantly associated with the phenotype.

dmGWAS

Simulation: n=100, p=1000, 10 **causal SNPs**, y = X**w** + e.

SNPs belong to 200 genes, connected on a Barabási-Albert small-world network.

- Ideal lasso situation (simulated according to linear model).
- dmGWAS:
  - which genes are selected **depends a lot on the parameters**
  - **high FDR**, rather **low power.**



Integrating prior network knowledge

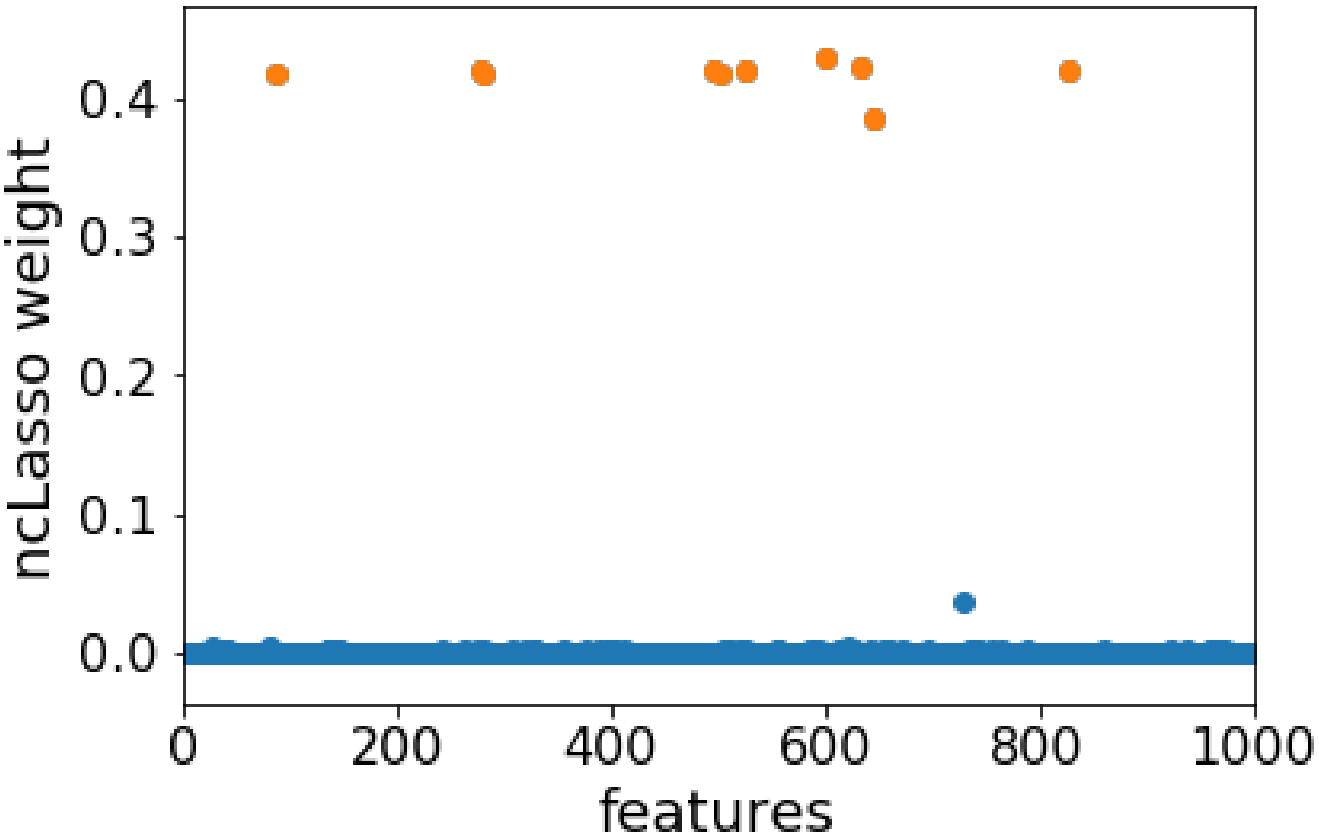
- **Network-constrained lasso** [LL08 ; LL10]

$$\underset{\mathbf{w}\in\mathbb{R}^p}{\arg\min} \underbrace{\sum_{i=1}^{n}\left(y^i - \sum_{j=1}^{p} w_j x_{ij}\right)^2}_{\text{loss}} + \lambda \underbrace{\sum_{j=1}^{p}|w_j|}_{\text{sparsity}} + \eta \underbrace{\sum_{j=1}^{p}\sum_{k=1}^{p} w_j L_{jk} w_k}_{\text{connectivity}}$$

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

Simulation

Network-constrained lasso



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**

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

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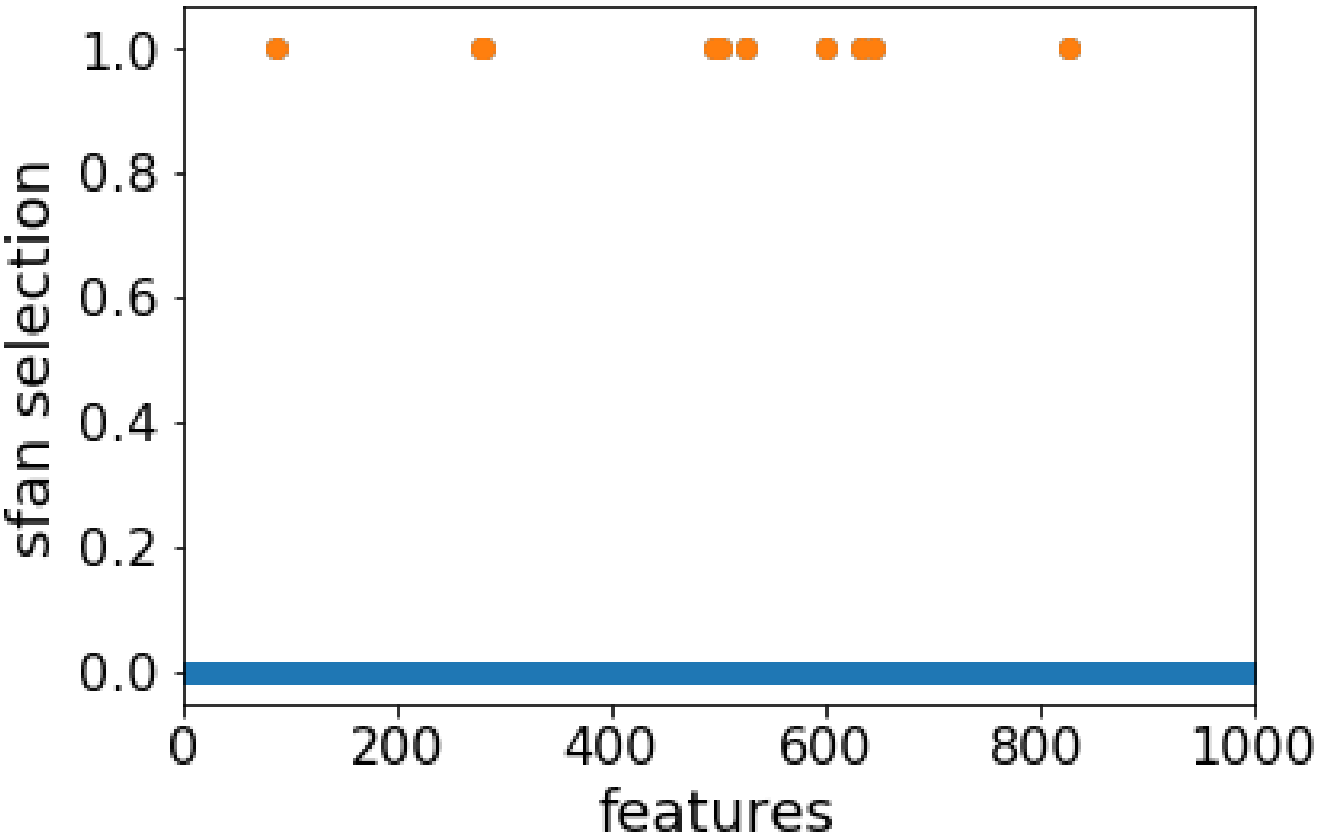
SConES: Selecting **Con**nected **E**xplanatory **S**NPs.

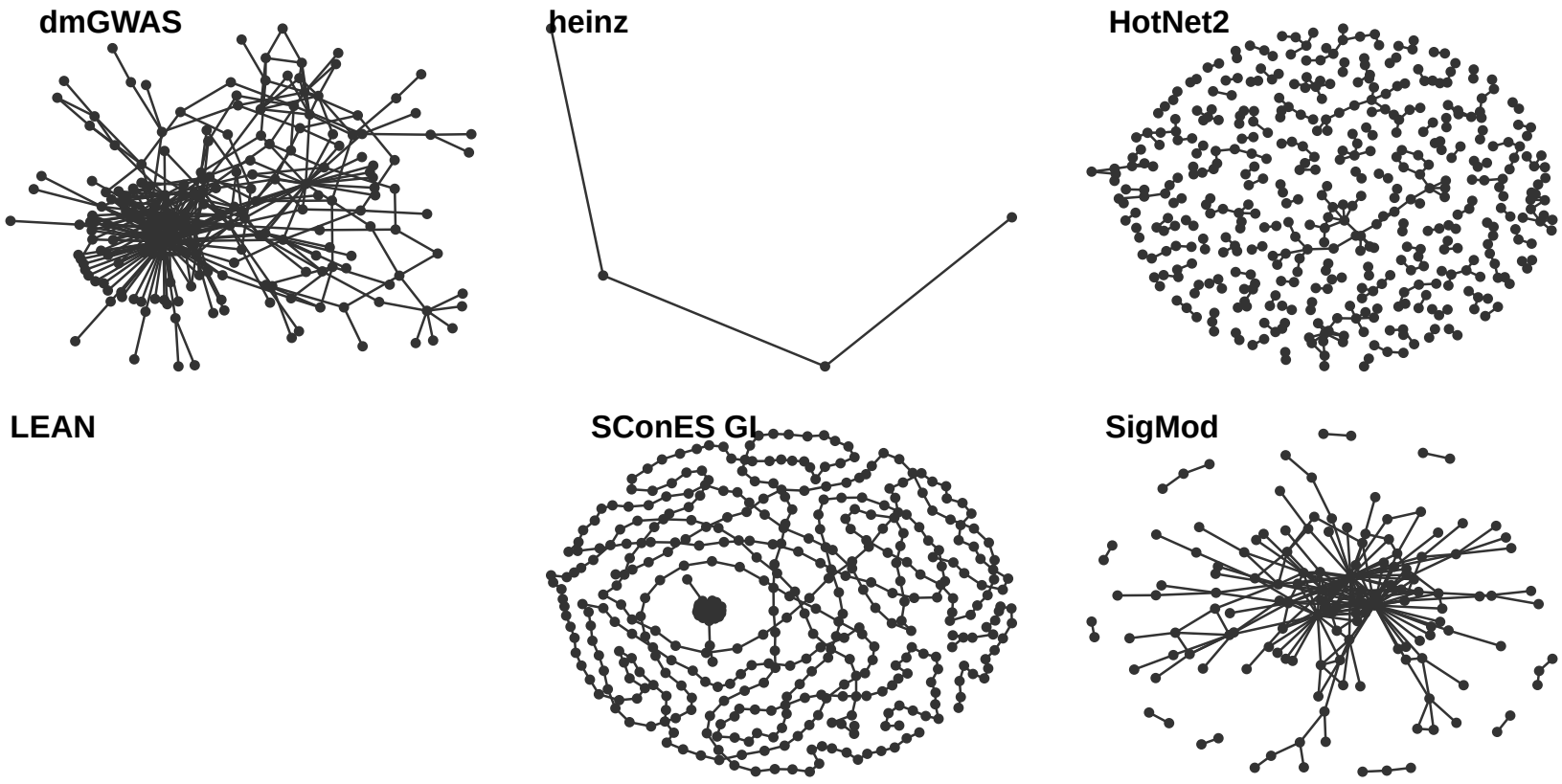
C.-A. Azencott, D. Grimm, et al. **Efficient network-guided multi-locus association mapping with graph cuts**. Bioinformatics 2013
https://github.com/chagaz/scones Bioconductor/martini

Simulation

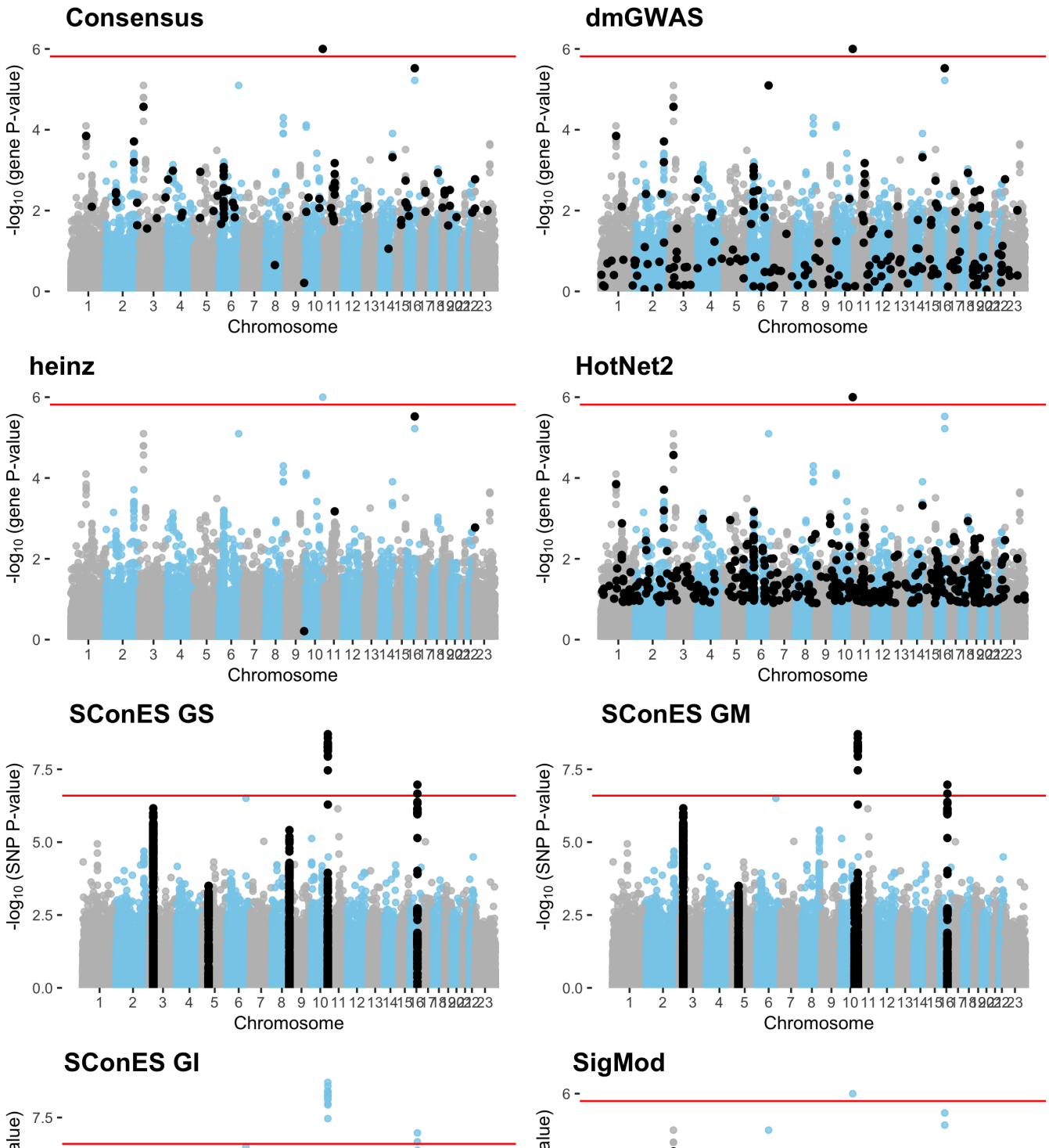
SConES



Other network-based methods



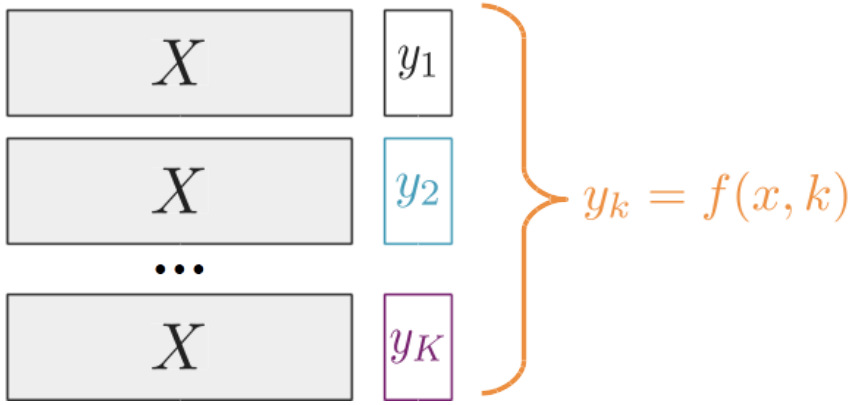
H. Climente-González et al. (2020). **Combining network-guided GWAS to discover susceptibility mechanisms for breast cancer,** BioRxiv.

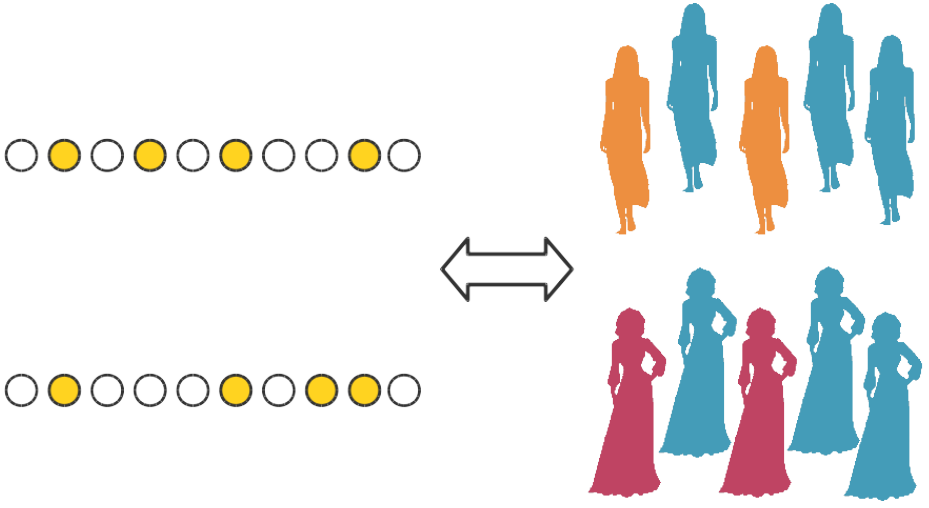

Consensus
dmGWAS
heinz
HotNet2
SConES GS
SConES GM
SConES GI
SigMod
-log10 (gene P-value)
-log10 (SNP P-value)
Chromosome

Increasing n

Multi-task approaches

Increase sample size by **jointly** performing feature selection for **multiple related phenotypes**



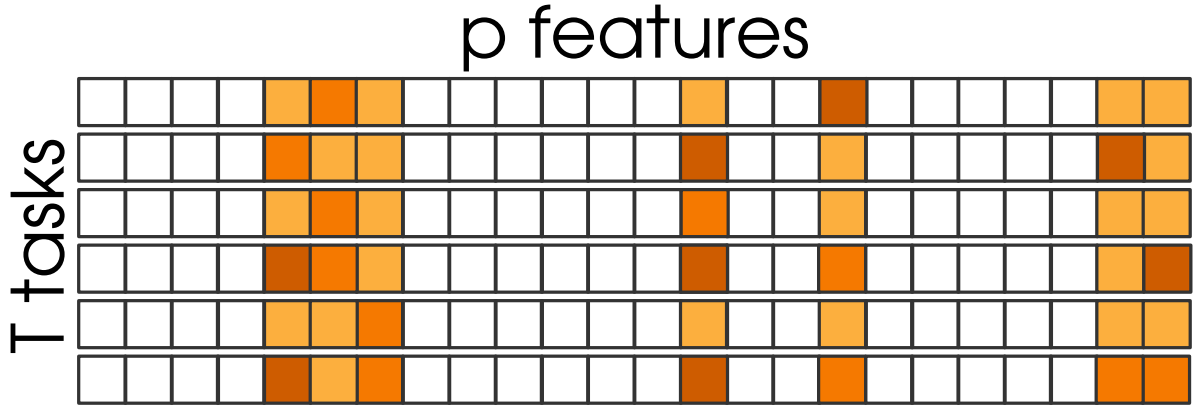


Multitask Lasso [OTJ06]

- T **related phenotypes** $\mathbf{y}_1 \in \mathcal{Y}^{n_1}, \ldots, \mathbf{y}_T \in \mathcal{Y}^{n_T}$

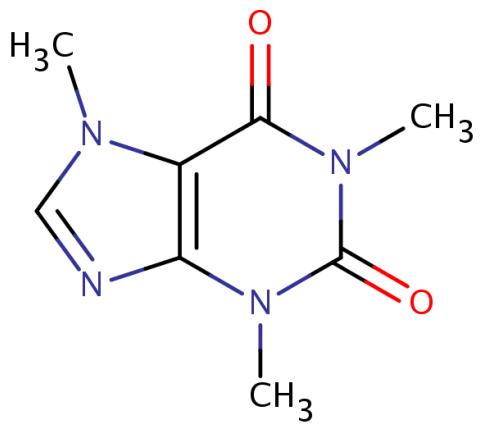
$$\underset{\boldsymbol{\beta} \in \mathbb{R}^{T \times p}}{\arg\min} \underbrace{\sum_{t=1}^{T} \frac{1}{n_t} \sum_{i=1}^{n_t} \left(y_{ti} - \sum_{j=1}^{p} w_{tj} x_{tij} \right)^2}_{\text{loss}} + \underbrace{\lambda \sum_{j=1}^{p} \sqrt{\sum_{t=1}^{T} w_{tj}^2}}_{\text{task sharing}}$$

- Selects the **same features across tasks**
- Controls weights magnitude (ℓ_2 shrinkage).



Task relatedness

- **Tasks that are "more similar" should share more features.**
- E.g. **response to treatment.**
- **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

Multi-SConES

- T **related phenotypes** $\mathbf{y}_1 \in \mathcal{Y}^{n_1}, \ldots, \mathbf{y}_T \in \mathcal{Y}^{n_T}$
- T SNP-SNP **networks** $W^t \in \mathbb{R}^{p \times p}$
- SNPs: $X \in \{0, 1, 2\}^{n \times p}$ $\qquad n = \sum_{t=1}^{T} n_t$
- Goal: obtain **similar sets of features** on related tasks.

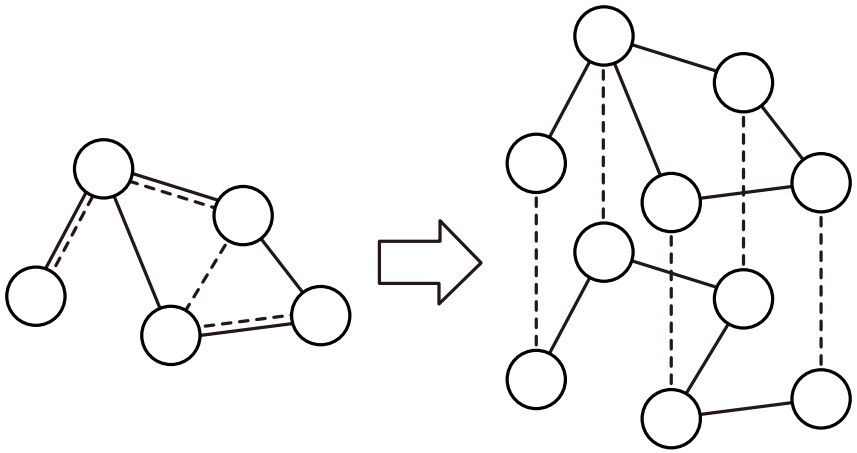
$$\underset{\mathcal{S}_1,\ldots,\mathcal{S}_T \subseteq \mathcal{V}}{\arg\max} \sum_{t=1}^{T} \left(\sum_{j \in \mathcal{S}_t} c_j^t - \eta \left|\mathcal{S}_t\right| - \lambda \sum_{j \in \mathcal{S}_t} \sum_{k \notin \mathcal{S}_t} W_{jk}^t \right) \underbrace{- \mu \sum_{t=1}^{T} \sum_{u=t+1}^{T} \left|\mathcal{S}_t \,\Delta\, \mathcal{S}_u\right|}_{\text{task sharing}}.$$

$$\mathcal{S} \,\Delta\, \mathcal{S}' = (\mathcal{S} \cup \mathcal{S}') \setminus (\mathcal{S} \cap \mathcal{S}') \qquad \text{(symmetric difference)}$$

Multi-SConES

$$\underset{\mathcal{S}_1,\ldots,\mathcal{S}_T \subseteq \mathcal{V}}{\arg\max} \sum_{t=1}^{T} \left(\sum_{j \in \mathcal{S}_t} c_j^t - \eta \left| \mathcal{S}_t \right| - \lambda \sum_{j \in \mathcal{S}_t} \sum_{k \notin \mathcal{S}_t} W_{jk}^t \right) \underbrace{- \mu \sum_{t=1}^{T} \sum_{u=t+1}^{T} \left| \mathcal{S}_t \,\Delta\, \mathcal{S}_u \right|}_{\text{task sharing}}.$$

- Can be reduced to single-task by building a **meta-network.**



Leveraging similarity between tasks

Task similarity: $\Sigma \in \mathbb{R}^{T \times T}$.

$$\underset{\mathcal{S}_1,\ldots,\mathcal{S}_T \subseteq \mathcal{V}}{\arg\max} \sum_{t=1}^{T} \left(\sum_{j \in \mathcal{S}_t} c_j - \eta \left| \mathcal{S}_t \right| - \lambda \sum_{j \in \mathcal{S}_t} \sum_{k \notin \mathcal{S}_t} W_{jk}^t \right) \underbrace{- \mu \sum_{t=1}^{T} \sum_{u=1}^{T} \left| \mathcal{S}_t \, \Delta \, \mathcal{S}_u \right| \Sigma_{tu}}_{\text{task sharing}}.$$

Can also be reformulated as a maxflow/mincut problem.

Multi-SConES: Selecting Connected Explanatory SNPs across Multiple related phenotypes

- ☺ selects connected, explanatory SNPs;
- ☺ benefits from using **multiple related tasks;**
- ☹ only scales up to **small number of tasks.**

- M. Sugiyama, C.-A. Azencott, D. Grimm, Y. Kawahara and K. Borgwardt (2014) **Multi-task feature selection on multiple networks via maximum flows**, SIAM ICDM, 199–207
- https://github.com/mahito-sugiyama/Multi-SConES
- https://github.com/chagaz/sfan

Feature selection in genomic data ($p \gg n$)

1. Using **biological networks** to integrate **prior knowledge.**

   SConES

   - Using constraints built from biological networks helps feature selection.
   - Flexibility is required as they are noisy and incomplete.

Feature selection in genomic data ($p \gg n$)

1. Using **biological networks** to integrate **prior knowledge.**

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   - Flexibility is required as they are noisy and incomplete.

2. Considering **multiple related phenotypes** at once.

   Multi-SConES, **MMLD**

   - Jointly selecting features for related tasks alleviates the $p \gg n$ issue.
   - Using task descriptors can improve both selection and prediction.


Where next?

GWAS questions

- **Linkage disequilibrium**
  - **Pick one SNP** per block? **Combine SNPs** within the same block?
  - How do you **define** a block?

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  - **Separate** the data in homogeneous populations?
  - Incorporate population as **covariates?**
  - Use **multitask / multidomain** approaches?

    Work in progress with A Nouira.

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    Work in progress with A Nouira.
- **SNP-SNP network construction**
  - **SNP-to-gene mapping:** genomic coordinates? known eQTLs? 3D info?

    D. Duroux et al. (2020). **Interpretable network-guided epistasis detection,** BioRxiv
  - Underlying **gene-gene networks:** PPIN? Regulatory networks?

    Work in progress with H Climente-González, D Duroux, K Van Steen.

Stable feature selection

- **Stability**
  - How do you **enforce** stability?
  - Measure stability at the **level** of SNPs? Genes? Pathways?

    Work in progress with A Nouira.

Multiview feature selection

- **Multiomics:**
  - Jointly consider SNPs and gene expression, methylation patterns, etc.
  - Integration through **SNP-to-gene mapping?**
- **Multimodality:** select features on
  - Lab results.
  - Time series: patient trajectories, accelerometer data.
  - Free-form medical text.
  - Images.

  Work in progress with A Recanati, NM Mbaye, E Dumas, RT2 lab.
- **Data privacy**
  - Learning from **federated** data sets without compromising privacy.

  Work in progress with A Recanati.

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- **Sancare**
- **Sanofi-Adventis**

Thank You

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cazencott.info & goepp.github.io

References I

[AL11] David H. Alexander et Kenneth Lange. "Stability selection for genome-wide association". In : *Genetic Epidemiology* 35.7 (2011), p. 722-728.

[Ant+10] Stylianos E. Antonarakis et al. "Mendelian disorders and multifactorial traits: the big divide or one for all?" In : *Nature Reviews Genetics* 11.5 (2010), p. 380-384.

[AR15] Samuel J. Aronson et Heidi L. Rehm. "Building the foundation for genomics in precision medicine". In : *Nature* 526.7573 (2015), p. 336-342.

[Aze+13] Chloé-Agathe Azencott et al. "Efficient network-guided multi-locus association mapping with graph cuts". In : *Bioinformatics* 29.13 (2013), p. i171-i179.

[Aze16] Chloé-Agathe Azencott. "Network-guided biomarker discovery". In : *Machine Learning for Health Informatics*. Lecture Notes in Computer Science 9605. Springer International Publishing, 2016.

[Aze18] Chloé-Agathe Azencott. "Machine learning and genomics: precision medicine vs. patient privacy". In : *Philosophical Transactions of the Royal Society A* (2018).

[Bar+12] Fredrik Barrenäs et al. "Highly interconnected genes in disease-specific networks are enriched for disease-associated polymorphisms". In : *Genome Biology* 13 (2012), R46.

[BR17] Rina Foygel Barber et Aaditya Ramdas. "The p-filter: multilayer false discovery rate control for grouped hypotheses". In : *J. R. Stat. Soc. B* 79.4 (2017), p. 1247-1268.

References II

[Brz+17] Damian Brzyski et al. "Controlling the Rate of GWAS False Discoveries". In : *Genetics* 205.1 (2017). PMID: 27784720, p. 61-75.

[BSA16] Victor Bellon, Véronique Stoven et Chloé-Agathe Azencott. "Multitask feature selection with task descriptors". In : *Pacific Symposium on Biocomputing*. T. 21. 2016, p. 261-272.

[CA17] Héctor Climente et Chloé-Agathe Azencott. *martini: GWAS incorporating networks in R*. 2017. url : `https://bioconductor.org/packages/devel/bioc/html/martini.html`.

[CH+08] Gerda Claeskens, Nils Lid Hjort et al. "Model selection and model averaging". In : *Cambridge Books* (2008).

[Che+18] Po-Hsuan Cameron Chen et al. *An Augmented Reality Microscope for Real-time Automated Detection of Cancer*. Rapp. tech. Google AI Healthcare, 2018.

[Cla+08] Robert Clarke et al. "The properties of high-dimensional data spaces: implications for exploring gene and protein expression data". In : *Nature Reviews Cancer* 8.1 (2008), p. 37-49.

[Cow+17] Lenore Cowen et al. "Network propagation: a universal amplifier of genetic associations". In : *Nature Reviews Genetics* 18.9 (2017), p. 551-562.

[Dit+08] Marcus T. Dittrich et al. "Identifying functional modules in protein-protein interaction networks: an integrated exact approach". In : *Bioinformatics* 24.13 (2008), p. i223-i231.

References III

[DP15] Nicoletta Dessì et Barbara Pes. "Stability in Biomarker Discovery: Does Ensemble Feature Selection Really Help?" In : *Current Approaches in Applied Artificial Intelligence*. Lecture Notes in Computer Science 9101. DOI: 10.1007/978-3-319-19066-2_19. 2015, p. 191-200.

[Dro+16] Alexandre Drouin et al. "Predictive computational phenotyping and biomarker discovery using reference-free genome comparisons". In : *BMC Genomics* 17 (2016), p. 754.

[ED+05] Liat Ein-Dor et al. "Outcome signature genes in breast cancer: is there a unique set?" In : *Bioinformatics* 21.2 (2005), p. 171-178.

[Edu+15] Federica Eduati et al. "Opportunities and limitations in the prediction of population responses to toxic compounds assessed through a collaborative competition". In : *Nature Biotechnology* 33.9 (2015), p. 933-940. doi : `doi:10.1137/1.9781611973440.23`.

[Est+17] Andre Esteva et al. "Dermatologist-level classification of skin cancer with deep neural networks". In : *Nature* 542.7639 (2017), p. 115.

[Fur13] Laura I. Furlong. "Human diseases through the lens of network biology". In : *Trends in Genetics* 29.3 (2013), p. 150-159.

[GBG16] Laura Gay, Ann-Marie Baker et Trevor A Graham. "Tumour cell heterogeneity". In : *F1000Research* 5 (2016).

References IV

[Gra+15] G'Sell Max Grazier et al. "Sequential selection procedures and false discovery rate control". In : *Journal of the Royal Statistical Society: Series B (Statistical Methodology)* 78.2 (2015), p. 423-444.

[GVB13] Levi A. Garraway, Jaap Verweij et Karla V. Ballman. "Precision oncology: an overview". In : *J. Clin. Oncol.* 31.15 (2013), p. 1803-1805.

[Gwi+17] Frederik Gwinner et al. "Network-based analysis of omics data: the LEAN method". In : *Bioinformatics* 33.5 (2017), p. 701-709.

[Hea+15] Megan L Head et al. "The extent and consequences of p-hacking in science". In : *PLoS biology* 13.3 (2015), e1002106.

[Hol18] Susan Holmes. "Statistical proof? The problem of irreproducibility.". In : *Bulletin (New Series) of the American Mathematical Society* 55.1 (2018).

[Hua+18] Justin K. Huang et al. "Systematic evaluation of molecular networks for discovery of disease genes". In : *Cell Systems* 6.4 (2018), 484-495.e5.

[Ioa05] John PA Ioannidis. "Why most published research findings are false". In : *PLoS medicine* 2.8 (2005), e124.

[JOV09] L. Jacob, G. Obozinski et J.-P. Vert. "Group lasso with overlap and graph lasso". In : *ICML*. 2009, p. 433-440.

References V

[JZ14] Peilin Jia et Zhongming Zhao. "Network-assisted analysis to prioritize GWAS results: principles, methods and perspectives". In : *Human Genetics* 133.2 (2014), p. 125-138.

[Laz+14] David Lazer et al. "The parable of Google Flu: traps in big data analysis". In : *Science* 343.6176 (2014), p. 1203-1205.

[Lee+16] J. D. Lee et al. "Exact post-selection inference, with application to the lasso". In : *The Annals of Statistics* 44.3 (2016), p. 907-927.

[Lei+15] Mark D. M. Leiserson et al. "Pan-cancer network analysis identifies combinations of rare somatic mutations across pathways and protein complexes". In : *Nature Genetics* 47 (2015), p. 106-114.

[Li11] C. Li. "Personalized medicine – the promised land: are we there yet?" In : *Clinical Genetics* 79.5 (2011), p. 403-412.

[LL08] C. Li et H. Li. "Network-constrained regularization and variable selection for analysis of genomic data". In : *Bioinformatics* 24.9 (2008), p. 1175-1182.

[LL10] Caiyan Li et Hongzhe Li. "Variable selection and regression analysis for graph-structured covariates with an application to genomics". In : *The annals of applied statistics* 4.3 (2010), p. 1498-1516.

[LL18] Tak Lee et Insuk Lee. "araGWAB: Network-based boosting of genome-wide association studies in Arabidopsis thaliana". In : *Scientific reports* 8.1 (2018), p. 1-6.

References VI

[Loc+14] Richard Lockhart et al. "A significance test for the lasso". In : *Annals of statistics* 42.2 (2014), p. 413.

[MB10] Nicolai Meinshausen et Peter Bühlmann. "Stability selection". In : *Journal of the Royal Statistical Society: Series B (Statistical Methodology)* 72.4 (2010). issn : 1467-9868.

[Mio+16] Riccardo Miotto et al. "Deep patient: an unsupervised representation to predict the future of patients from the electronic health records". In : *Scientific reports* 6 (2016), p. 26094.

[MM15] Aniket Mishra et Stuart Macgregor. "VEGAS2: software for more flexible gene-based testing". In : *Twin Research and Human Genetics* 18.1 (2015), p. 86-91.

[NB16] Sarah Nogueira et Gavin Brown. "Measuring the stability of feature selection". In : *Machine Learning and Knowledge Discovery in Databases*. Lecture Notes in Computer Science 9852. Springer International Publishing, 2016, p. 442-457.

[Nie+15] Clément Niel et al. "A survey about methods dedicated to epistasis detection". In : *Bioinformatics and Computational Biology* (2015), p. 285.

[Nuz14] Regina Nuzzo. "Scientific method: statistical errors". In : *Nature News* 506.7487 (2014), p. 150.

[Oks+14] Sebastian Okser et al. "Regularized machine learning in the genetic prediction of complex traits". In : *PLoS genetics* 10.11 (2014), e1004754.

References VII

[OTJ06] Guillaume Obozinski, Ben Taskar et Michael I. Jordan. *Multi-task feature selection.* Rapp. tech. UC Berkeley, 2006.

[Pen07] Elizabeth Pennisi. "Human Genetic Variation". In : *Science* 318.5858 (2007), p. 1842-1843.

[Raj+18] Alvin Rajkomar et al. "Scalable and accurate deep learning with electronic health records". In : *NPJ Digital Medicine* 1.1 (2018), p. 18.

[Sch15] Nicholas J. Schork. "Personalized medicine: Time for one-person trials". In : *Nature News* 520.7549 (2015), p. 609.

[SL12] Grzegorz Swirszcz et Aurelie C. Lozano. "Multi-level lasso for sparse multi-task regression". In : *Proceedings of the 29th International Conference on Machine Learning (ICML-12)*. 2012, p. 361-368.

[Sli+19] Lotfi Slim et al. "kernelPSI: a post-selection inference framework for nonlinear variable selection". In : *Proceedings of the Thirty-Sixth International Conference on Machine Learning (ICML)*. T. 97. 2019, p. 5857-5865.

[Sny+14] Alexandra Snyder et al. "Genetic basis for clinical response to CTLA-4 blockade in melanoma". In : *New England Journal of Medicine* 371.23 (2014), p. 2189-2199.

References VIII

[Sør+01] Therese Sørlie et al. "Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications". In : *Proceedings of the National Academy of Sciences* 98.19 (2001), p. 10869-10874.

[SS17] Hon-Cheong So et Pak C Sham. "Improving polygenic risk prediction from summary statistics by an empirical Bayes approach". In : *Scientific Reports* 7 (2017), p. 41262.

[Sug+14] Mahito Sugiyama et al. "Multi-task feature selection on multiple networks via maximum flows". In : *SIAM ICDM*. 2014, p. 199-207.

[Suz+17] Shinya Suzumura et al. "Selective inference for sparse high-order interaction models". In : *PMLR*. 2017, p. 3338-3347.

[Ter+16] Aika Terada et al. "LAMPLINK: detection of statistically significant SNP combinations from GWAS data". In : *Bioinformatics* (2016), btw418.

[Tib94] Robert Tibshirani. "Regression shrinkage and selection via the lasso". In : *J. R. Stat. Soc.* 58 (1994), p. 267-288.

[VCB11] Marc Vidal, Michael E. Cusick et Albert-László Barabási. "Interactome networks and human disease". In : *Cell* 144.6 (2011), p. 986-998. (Visité le 05/02/2020).

References IX

[VDD11] David Venet, Jacques E. Dumont et Vincent Detours. "Most random gene expression signatures are significantly associated with breast cancer outcome". In : *PLoS Computational Biology* 7.10 (2011), e1002240.

[VV+02] Laura J Van't Veer et al. "Gene expression profiling predicts clinical outcome of breast cancer". In : *nature* 415.6871 (2002), p. 530.

[WL+16] Ronald L Wasserstein, Nicole A Lazar et al. "The ASA's statement on p-values: context, process, and purpose". In : *The American Statistician* 70.2 (2016), p. 129-133.

[YL06] Ming Yuan et Yi Lin. "Model selection and estimation in regression with grouped variables". In : *Journal of the Royal Statistical Society: Series B (Statistical Methodology)* 68.1 (2006), p. 49-67.

[ZH05] Hui Zou et Trevor Hastie. "Regularization and variable selection via the elastic net". In : *Journal of the Royal Statistical Society: Series B (Statistical Methodology)* 67.2 (2005), p. 301-320.