Multitask group Lasso for Genome Wide Association Studies in diverse populations

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U900 Lab meeting

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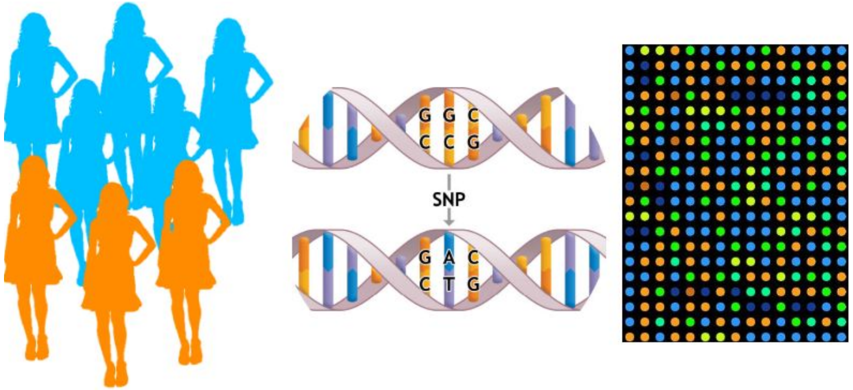
Genome Wide Association Studies



Goal: Find association between the genotype and the phenotype.

- The genotype: Single Nucleotide Polymorphism (SNP) arrays.
- The phenotype:
  - Quantitative: BMI, weight, height, etc.
  - Qualitative: Case-control study

Challenges in GWAS analysis

- **Microarray data: SNP arrays**

Curse of dimensionality (p>>N): $p \approx 10^5 - 10^7\ ,\ N \approx 10^2 - 10^4$

01

Single marker analysis

Testing each SNP individually

02

Population stratification

Difference in allele frequencies between subpopulations

03

Linkage disequilibrium

Dependence relationship between two alleles at two different loci

04

Computational limitations

For complex methods:

- Memory errors
- Very slow

05

Lack of stability

Susceptibility to small perturbations in the data set

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From GWAS to Machine Learning

- **Single-marker analysis:**

Given a phenotype y, $\mathbf{X}$ is the genotype matrix:

For each feature $\mathbf{X}_j$, we fit a **single-predictor** equation $\mathbf{y} = \beta_0 + \beta_j \mathbf{X}_j + \varepsilon \Rightarrow$ **p-value from a t-test** against an intercept-only model $H_0 = \{\beta_j = 0\}$.

- **Multi-variate approach:** Feature selection based on regularization

- Regularization: adding a penalty term

$$\underset{\beta \in \mathbb{R}^p}{\operatorname{argmin}} \underbrace{\mathcal{L}\left(y, \beta X_j\right)}_{\text{loss}} + \underbrace{\lambda \Omega\left(\beta_1, \beta_2, \ldots, \beta_j\right)}_{\text{regularization term}}$$

where β is a $p \times 1$ vector corresponds to the SNP effects

Ω is the regularizer

λ is the penalization term

- Lasso: shrinkage and feature selection (L1-regularization)

$$\underset{\beta \in \mathbb{R}^p}{\operatorname{argmin}} \underbrace{\mathcal{L}\left(y, \beta X_j\right)}_{\text{loss}} + \underbrace{\lambda \sum_{j=1}^{p} \left|\beta_j\right|}_{\text{sparsity}}$$

- Group lasso: allow predefined groups of covariates to be jointly selected

$$\underset{\beta \in \mathbb{R}^p}{\operatorname{argmin}} \underbrace{\mathcal{L}\left(y, \beta X_j\right)}_{\text{loss}} + \underbrace{\lambda \sum_{g \in \mathcal{G}} \sqrt{p_g} \left\|\beta_g\right\|_2}_{\text{sparsity at the group level}}$$

where $\mathcal{G}$ is the set of groups

β_g is β restricted to the SNPs in g

$\sqrt{p_g}$ scales the penalization factor according to the group size

From GWAS to Machine Learning

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- **Multi-task lasso:** allows fitting multiple regression problems jointly

$$\underset{\beta\in\mathbb{R}^{T\times p}}{\operatorname{argmin}}\, \underbrace{\sum_{t=1}^{T}\frac{1}{n_t}\sum_{m=1}^{n_t}\mathcal{L}\left(y^{(tm)},\left(\beta_0^{(t)}+\sum_{j=1}^{p}\beta_j^{(t)}X_j^{(tm)}\right)\right)}_{\text{loss}} + \underbrace{\lambda\sum_{j=0}^{p}\sum_{t=1}^{T}\left|\beta_j^{(t)}\right|}_{\text{task sharing}}$$

where T is the number of tasks to learn the training set

$\left\{\left(x_{tm},y_{tm}\right) \text{ for } t=1..T \text{ and } m=1..n_t\right\}$

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Population stratification

Population stratification refers to the presence of differences in allele frequencies between subpopulations due to different ancestry.

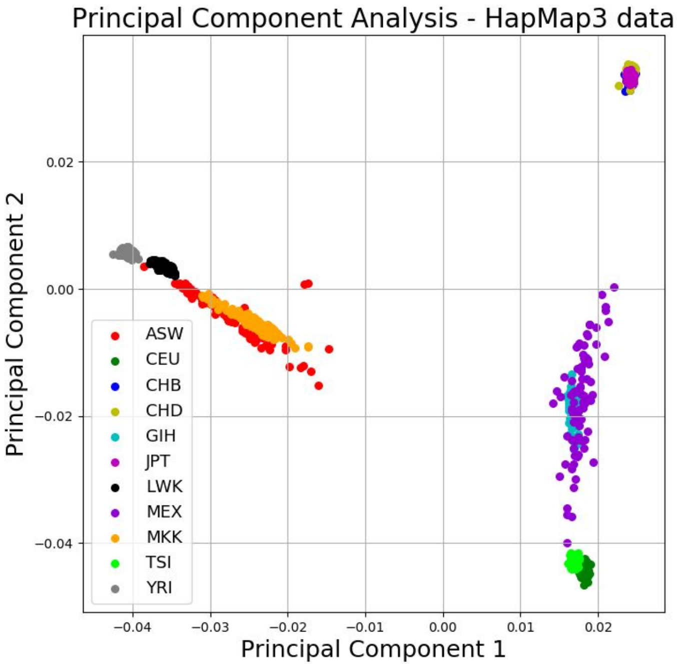
- **State-of-the art adjustment methods**
  - PCA-based methods

    Include Principal components (PCs) as covariates

    - Logistic Regression + Top PCs[1,2]
    - EIGENSTRAT[3]: multi-linear regression + 10 PCs

  - Linear mixed models

    Fast-LMM[4]



[1] Need et al.,A genome-wide investigation of snps and cnvs in schizophrenia. 2009, *PLoS Genet*.

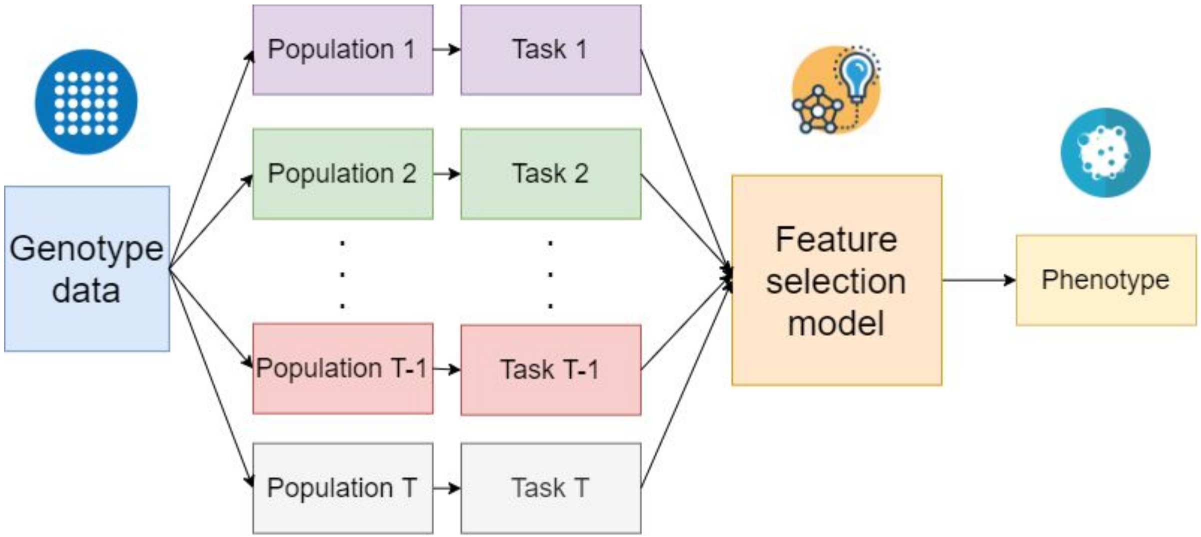
[2] Zeggini et al., Meta-analysis of genome-wide association data and large-scale replication identifies additional susceptibility loci for type 2 diabetes. 2008, *Nat Genet.*

[3] Price et al.,Principal components analysis corrects for stratification in genome-wide association studies. *Nat Genet.*

[4] Lippert et al., FaST linear mixed models for genome-wide association studies. 2011. *Nat Methods.*

Population stratification

- **Proposed adjustment method**: subpopulations assignment in multitask framework



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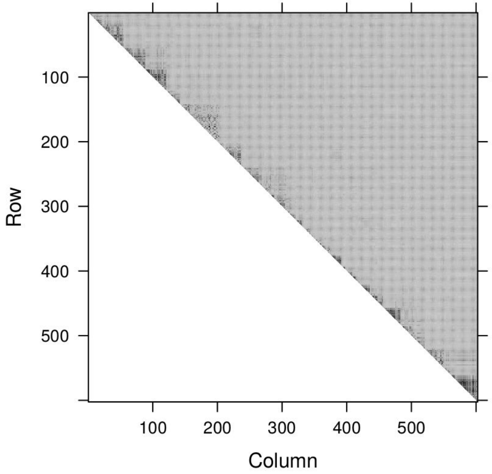
Linkage Disequilibrium groups clustering

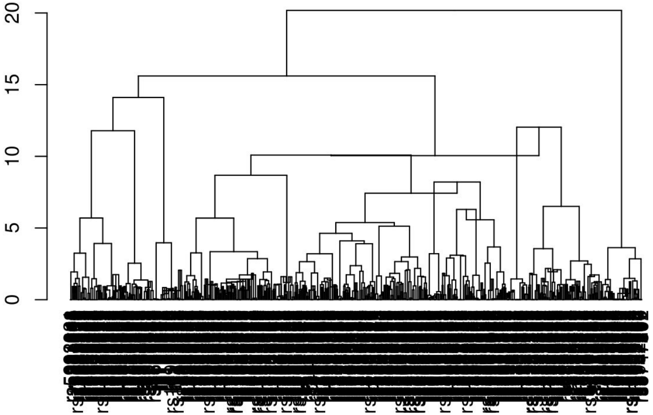
Linkage Disequilibrium (LD):

- Tendency of alleles to be transmitted together, more often that expected by chance alone.
- Usually caused by close proximity of genes in the same chromosome.

Hierarchical clustering approach[1]

Performing a **spatially-constrained hierarchical clustering**





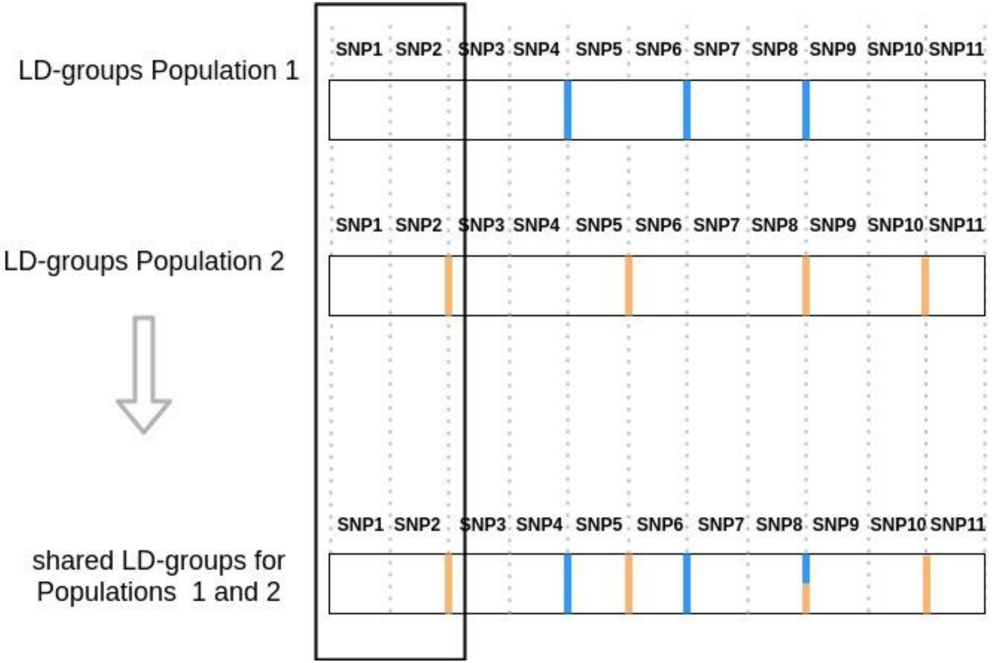
⇒ Selection at the **LD-group level** instead of single-SNP level.

[1] Ambroise et al.., Adjacency-constrained hierarchical clustering of a band similarity matrix with application to genomics. 2019. arXiv:1902.01596v1 [math.ST].

Linkage Disequilibrium groups clustering

- **Choice of LD-groups**

Linkage disequilibrium is different in different populations


LD-groups Population 1
SNP1 SNP2 SNP3 SNP4 SNP5 SNP6 SNP7 SNP8 SNP9 SNP10 SNP11
LD-groups Population 2
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shared LD-groups for Populations 1 and 2
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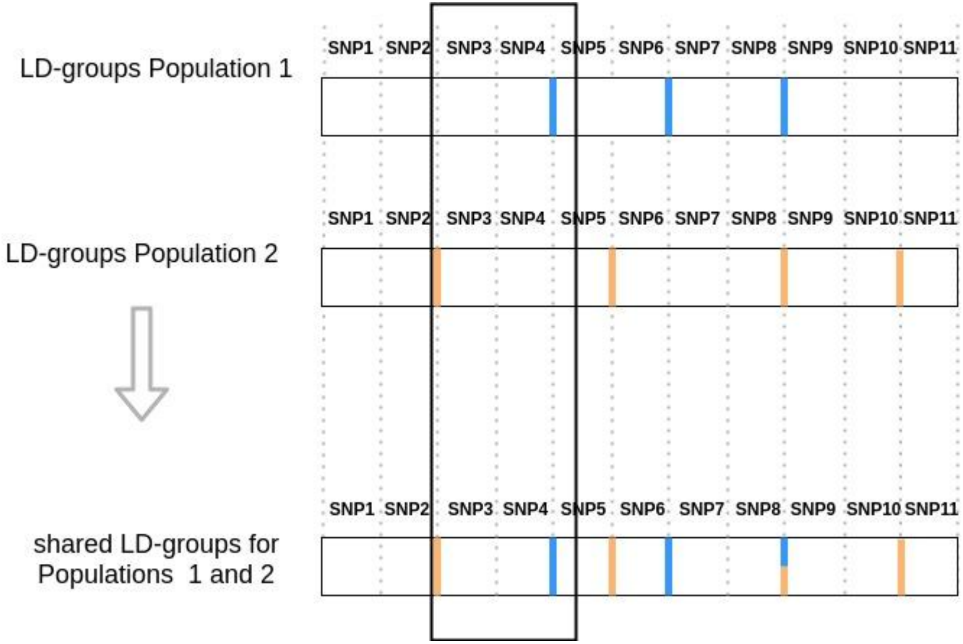
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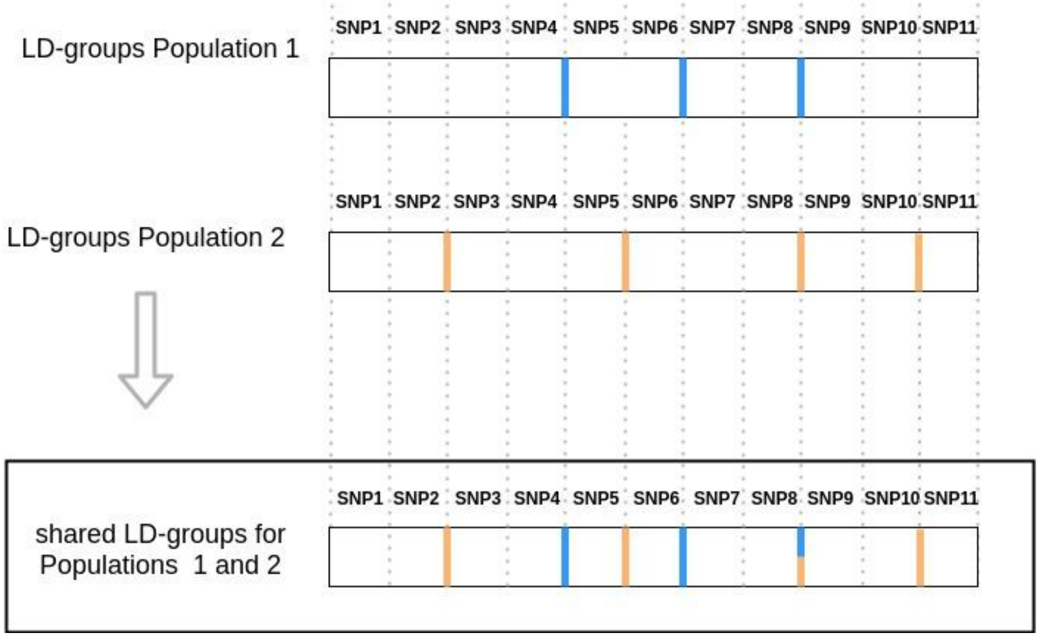
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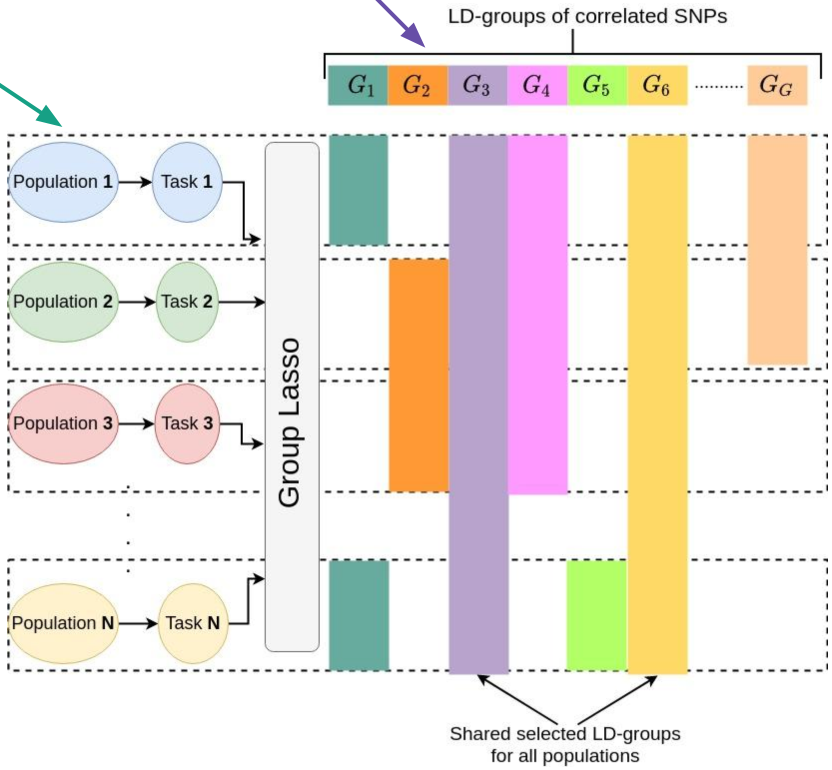
Multitask group Lasso for Genome Wide Association studies in diverse populations

Multitask group Lasso where **tasks** correspond to **subpopulations** and **groups** correspond to **LD-groups** of strongly correlated SNPs

$$\min_{B\in\mathbb{R}^{T\times(p+1)}} \boxed{\sum_{t=1}^{T}} \underbrace{\frac{1}{n_t}\sum_{m=1}^{n_t}\mathscr{L}\left(y^{(tm)},\left(\beta_0^{(t)}+\sum_{j=1}^{p}\beta_j^{(t)}x_j^{(tm)}\right)\right)}_{\textbf{loss for each task}} + \lambda \underbrace{\boxed{\sum_{g=1}^{G}}\sqrt{p_g}\boxed{\boxed{\|B_g\|}_F}}_{\textbf{sparsity at the LD-group level across tasks}}$$

where

- $\boldsymbol{\beta}^{(t)} \in \mathbb{R}^{p+1}$ is a task-specific vector of regression coefficients
- $\mathscr{L}$ is the loss function (quadratic or logistic regression)
- B_g is a $T \times p_g$ matrix of the regression coefficients, across all tasks T, for the SNPs of LD-group g
- λ is the penalization parameter
- $\sqrt{p_g}$ scales the penalization factor according the group size



⇒ Selection of LD-groups associated with **the phenotype** **across all tasks/populations**, or **specifically for some tasks/populations**

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Gap Safe screening rules

Gap Safe Screening rules[1]**:** eliminates features with associated coefficients are proved to be zero at the optimum in order to obtain **more speed up** and to **avoid memory errors**.

Ignoring some variables by exploiting geometric properties of the dual formulation of the following optimization problem:

$$\widehat{\beta}^{(\lambda)} \in \underset{\beta \in \mathbb{R}^p}{\operatorname{argmin}} P_{\lambda}(\beta)\,, \text{ for } P_{\lambda}(\beta) := F(\beta) + \lambda\Omega(\beta) := \sum_{i=1}^{n} f_i\left(x_i^{\top}\beta\right) + \lambda\Omega(\beta)$$

where $f_i : \mathbb{R} \mapsto \mathbb{R}$ *are convex and differentiable functions and* $\Omega : \mathbb{R}^p \mapsto \mathbb{R}_+$ *is a group-decomposable norm:* $\Omega(\beta) = \sum_{g \in \mathscr{G}} \Omega_g(\beta_g)$
with Ω_g *a norm of* $\mathbb{R}^{n_g}$

[1] Ndiaye et al.,Gap Safe Screening Rules for Sparsity Enforcing Penalties. 2017, *Journal of Machine Learning Research 18*.

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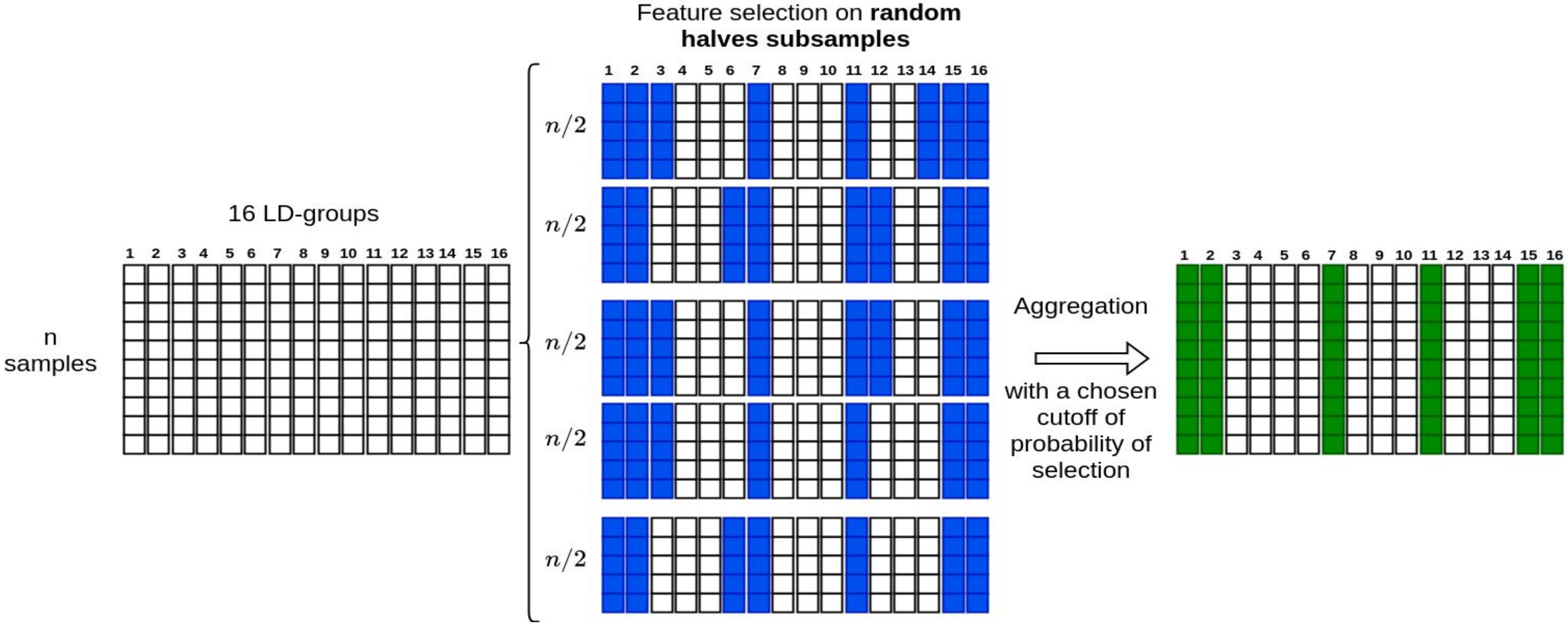
Stability Selection

Stability selection[1]**: bootstrap aggregation** procedure where feature selection is performed repeatedly on bootstrap subsamples, and the results of all repetitions are aggregated. It allows a **precise statement** of the significance of the selected features set and **reduce false positives**.


Feature selection on **random halves subsamples**
16 LD-groups
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
n samples
$n/2$
$n/2$
$n/2$
$n/2$
$n/2$
Aggregation
with a chosen cutoff of probability of selection

[1] Meinshausen et al,. Stability selection. 2010. *Journal of the Royal Statistical Society Series B-Statistical Methodology*.

MuGLasso implementation

- Datasets

Realistic simulated data using GWAsimulator[1]

- **Dimension:** 4,000 samples x 1,400,000 SNPs
- **Populations:** 2000 European (CEU), 2000 African (YRI)
- **Phenotype:** 1100 CEU cases, 900 CEU controls, 900 YRI cases, 1100 controls.
- **Disease loci:** chromosomes: **2** (located on 1,000-50,000 SNPs), **12** (located on 10-40,000 SNPs), **19** (1000-50,000 SNPs), **21** (10-10,000 SNPs) and **22** (10-2000 SNPs)

Real data: DRIVE Breast Cancer OncoArray[2]

- **Dimension:** 28,281 samples x 528,620 SNPs
- **Phenotype:** 13,846 cases and 14,435 controls
- **Populations:** USA – Uganda – Nigeria – Cameroon – Australia – Denmark

[1] Li et al., GWAsimulator: a rapid whole-genome simulation program. 2008 *Bioinformatics, Volume 24, Issue 1, 1 January 2008, Pages 140–142.*

[2] DRIVE: "General Research Use" dataset in DRIVE Breast Cancer OncoArray Genotypes, available from dbGaP (study accession: phs001265/GRU), accessed under project #17707.

MuGLasso implementation

- Quality control and preprocessing
  - MAF < 5%
  - HWE-P-Value < 0.0001
  - Remove samples with missing case/control criterion
  - Sex check
  - Remove samples and/or variants with high genotypic missing rate
  - Imputation of missing values: IMPUTE2

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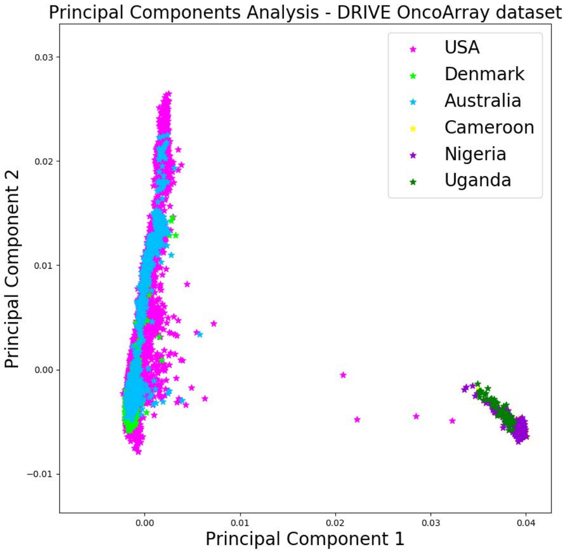
- Subpopulations definition

  Assign subpopulations in Multitask framework according to PCA patterns


Principal Components Analysis - DRIVE OncoArray dataset

POP1: USA, Denmark and Australia and **POP2:** Cameroon, Nigeria and Uganda

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- Evaluation of Multi-task group Lasso
  - **Validation using simulated data**

    Generate simulations with specified multi locus disease model in specified regions

    ⇒ Compute **false positives rate**
  - **Estimation of the stability of the selection** [1,2]

    $$Stability = \widehat{\Phi}(s_1, s_2, \dots s_M) = \frac{1}{M(M-1)} \sum_i \sum_{j \neq i} sim(s_i, s_j)$$
  - **Comparison with the state-of-the art methods**

[1] Kuncheva et Al., A stability index for feature selection. 2008, *IASTED International Conference on Artificial Intelligence and Applications*.

[2] Nogueira et Al., On the Stability of Feature Selection Algorithms. 2018, *Journal of Machine Learning Reasearch 18.*

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  - **Comparison with the state-of-the art methods**

1. **Adjusted Lasso: after PCA adjustment** for population stratification at the **SNP level**
2. **Adjusted group Lasso: after PCA adjustment** for population stratification at **LD-groups level**
3. **Stratified group Lasso** for each subpopulation at **LD-groups level**
4. **Stratified Lasso** for each subpopulation at **the SNP level**
5. **Adjusted GWAS:** Classic GWAS after PCA adjustment

[1] Kuncheva et Al., A stability index for feature selection. 2008, *IASTED International Conference on Artificial Intelligence and Applications*.

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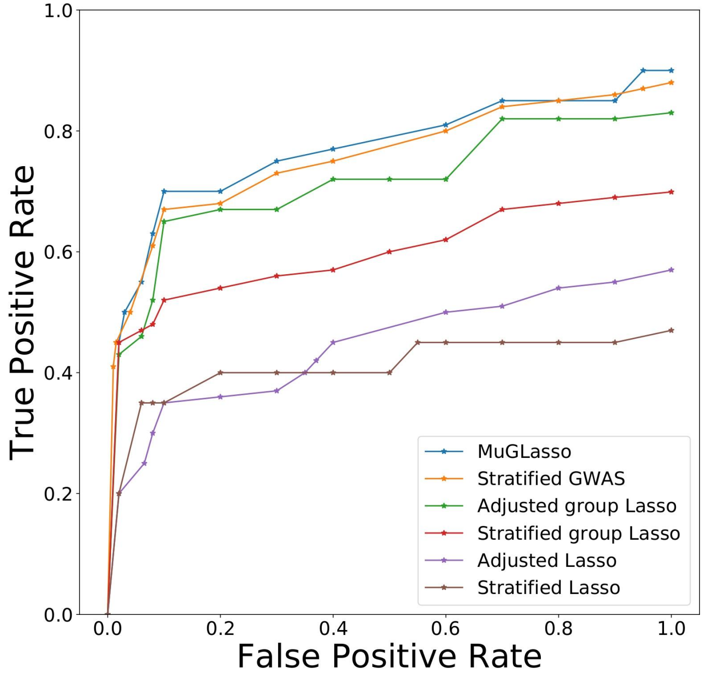
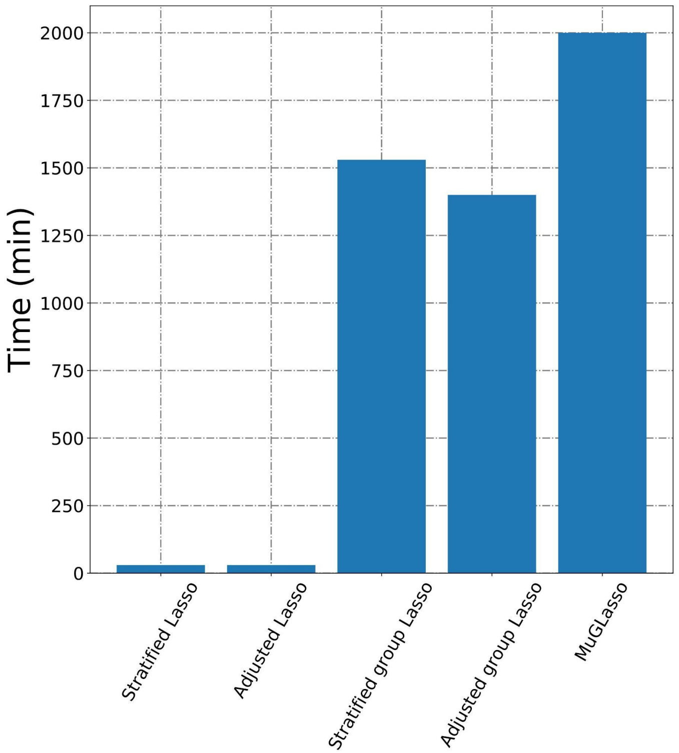
  - **Comparison with the state-of-the art methods**
  - **Computational time**

[1] Kuncheva et Al., A stability index for feature selection. 2008, *IASTED International Conference on Artificial Intelligence and Applications*.

[2] Nogueira et Al., On the Stability of Feature Selection Algorithms. 2018, *Journal of Machine Learning Reasearch 18.*

MuGLasso outperforms the state-of-the-art methods on simulated data

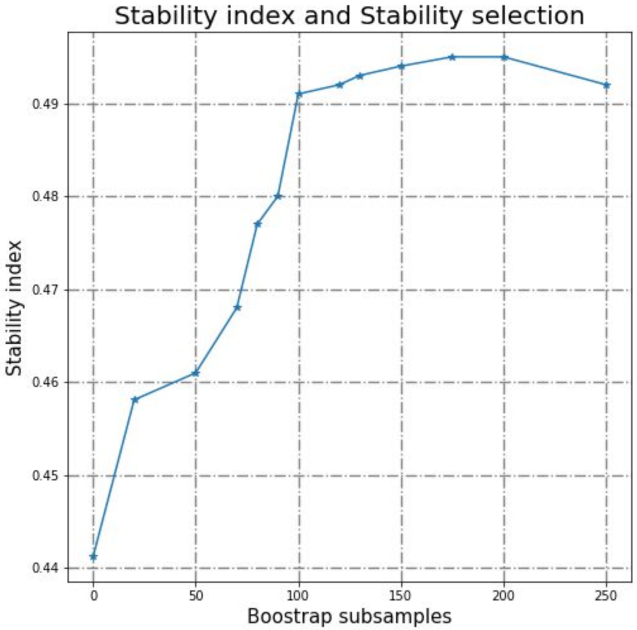




MuGLasso improve the stability of the selection on DRIVE data

Real data: DRIVE Breast Cancer OncoArray[1]: n=28,282 ; p=313,237 ; LD-groups = 17,782

Methods	Number of selected LD-groups	Stability index	Selection level
MuGLasso (100 boostraps)	62	0.4312	LD-groups
Adjusted group Lasso	59	0.3234	LD-groups
Stratified group Lasso	58	0.2498	LD-groups
Adjusted Lasso	41	0.2068	Single-SNP
Stratified Lasso	38	0.1581	Single-SNP
Adjusted GWAS	16	-	Single-SNP



⇒ The feature selection at the LD-groups level alleviate the curse of dimensionality and the lack of stability.

[1] DRIVE: "General Research Use" dataset in DRIVE Breast Cancer OncoArray Genotypes, available from dbGaP (study accession: phs001265/GRU), accessed under project #17707.

Breast cancer risk loci detected by MuGLasso on DRIVE

- All SNPs/genes found by adjusted GWAS were also selected by MuGLasso.
- **9 genes** were discovered by adjusted GWAS and 32 genes were discovered by MuGLasso.
- **17 of 32 genes** had been previously identified by a meta-GWAS containing the DRIVE data.
- **7 genes** were found in the literature prior evidence of relationship with breast cancer risk or tumor growth.

Genes found by adjusted GWAS	**ITPR1, MRPS30, MAP3K1, SETD9, MIER3, EBF1, FGFR2, TOX3, MKL1**
Genes found by MuGLasso	**ITPR1, MRPS30, MAP3K1, SETD9, MIER3, EBF1, FGFR2, TOX3, MKL1**, **ADSL**, **ASTN2**, C7orf73, **CACNA1I**, **CCDC170**, **CCDC91**, CCSER1, CD2AP, **CDYL2**, **DIRC3**, **ELL**, **ESR1**, **FTO**, **GRHL1**, HK1, HRSP12, **KCNU1**, LUC7L3, MED21, **NEK10**, **NUP205**, **PAX9**, **POP1**,**PPFIBP1**, **PTHLH**, REP15, **SGSM3**, **SSBP4**, **TGFBR2**, **TNRC6B**, **ZMIZ1**, **ZNF365**

Genes discovered for subpopulation POP1	**ESR1**, **SGSM3**, MED21, REP15
Genes discovered for subpopulation POP2	**DIRC3**, LUC7L3

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Conclusion and future work

01

Multi-variate approach

- Consider the effect of SNPs jointly

02

Multitask assignment

- Address population stratification by assigning an input task to each subpopulation

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LD-groups clustering

- Address high correlation between SNPs
- Alleviate the curse of dimensionality

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Safe screening rules

- Speed up the solvers and avoid memory errors in high scale

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Stability selection

- Improve the stability of the feature selection using subsampling procedure

Paper: Multitask group Lasso for Genome Wide Association Studies in diverse populations, published in PSB 2022, https://www.biorxiv.org/content/10.1101/2021.08.02.454499
Code: https://github.com/asmanouira/MuGLasso_GWAS
Contact: asma.nouira@mines-paristech.fr
asma.nouira@curie.fr

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Future work

Sparse MuGLasso (SMuG Lasso)

- Add an L1-norm sparsity penalty to improve the LD-groups selection for specific-populations
- Extend MuGLasso to general applications

Paper: Multitask group Lasso for Genome Wide Association Studies in diverse populations, published in PSB 2022, https://www.biorxiv.org/content/10.1101/2021.08.02.454499
Code: https://github.com/asmanouira/MuGLasso_GWAS
Contact: asma.nouira@mines-paristech.fr
asma.nouira@curie.fr

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- GWAS team

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THANK YOU!

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For group Lasso: the data fitting term is $F(\beta) = \frac{\mathscr{L}\left(y, \beta X_j\right)}{2}$,

The *L1/L2-norm* is defined by $\Omega(\beta) = \Omega_w(\beta)$:

$$\Omega_w(\beta) := \sum_{g \in \mathcal{G}} w_g \|\beta_g\|_2 \quad \text{and} \quad \Omega_w^D(\xi) := \max_{g \in \mathcal{G}} \frac{\|\xi_g\|_2}{w_g}$$

where $w = (w_g)_{g \in \mathcal{G}}$ *are weights satisfying* $w_g > 0$ *for all* $g \in \mathcal{G}$ *and* $\Omega_w^D(\xi)$ *is the dual norm along the regularization path.*

[1] Ndiaye et al.,Gap Safe Screening Rules for Sparsity Enforcing Penalties. 2017, *Journal of Machine Learning Research 18*.

Stability Selection

Stability selection[1]**: bootstrap aggregation** procedure where feature selection is performed repeatedly on bootstrap subsamples, and the results of all repetitions are aggregated. It allows a **precise statement** of the significance of the selected features set and **reduce false positives**.

Procedure:

- Identify $S=\left\{k:\beta_k \neq 0\right\}$ a set of non-zero inputs of a sparse parameter vector β of observed data (X, y)
- Feature selection is performed on randomly $\left|\mathrm{I}\right| = \frac{n}{2}$ of observations, where $\mathrm{I} \subset \{1, \dots, n\}$
- Selection Path: Probability of the selection of a feature $k \in \{1, \dots, p\}$

  $\pi_k^\lambda = Pr^*\left[k \in \widehat{S}^\lambda(I)\right]$, where $\widehat{S}^\lambda(\mathrm{I}) \subset \{1, \dots, p\}$ denotes the selected features by a subsample I

  ⇒ Captures random selection within feature selection algorithms

- For a chosen cut-off $\frac{1}{2} \leq \pi_{thre} \leq 1$, the set of stable features is:

$$\widehat{S}^{stable} = \left\{k:\ \pi_k^\lambda \geq \pi_{thre}\right\}$$

⇒ Only variables that are selected consistently across all the random halves remain.

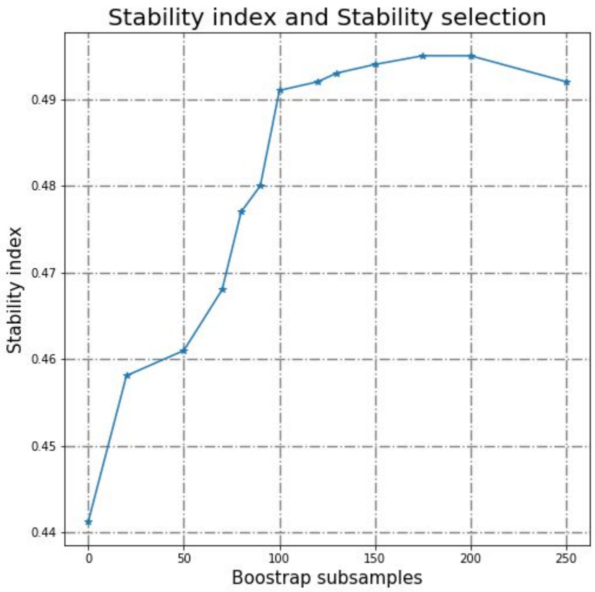
[1] Meinshausen et al,. Stability selection. 2010. *Journal of the Royal Statistical Society Series B-Statistical Methodology*.

Multitask group Lasso results and comparison

Multitask group Lasso is **more stable** than the state-of-the-art methods.

Simulated data: n=4,000 ; p=1,000,000 ; LD-groups number = 35,792 groups

Methods	Number of selected LD-groups	Number of selected SNPs	Stability index	Selection level
MuGLasso (100 boostraps)	5,623	155,312	0.4912	LD-groups
Adjusted group Lasso	6,054	162,104	0.4134	LD-groups
Stratified group Lasso	4,836	154,732	0.3398	LD-groups
Adjusted Lasso	5,379	158,856	0.2368	Single-SNP
Stratified Lasso	5,704	168,158	0.1742	Single-SNP
Adjusted GWAS	5,063	141,340	-	Single-SNP



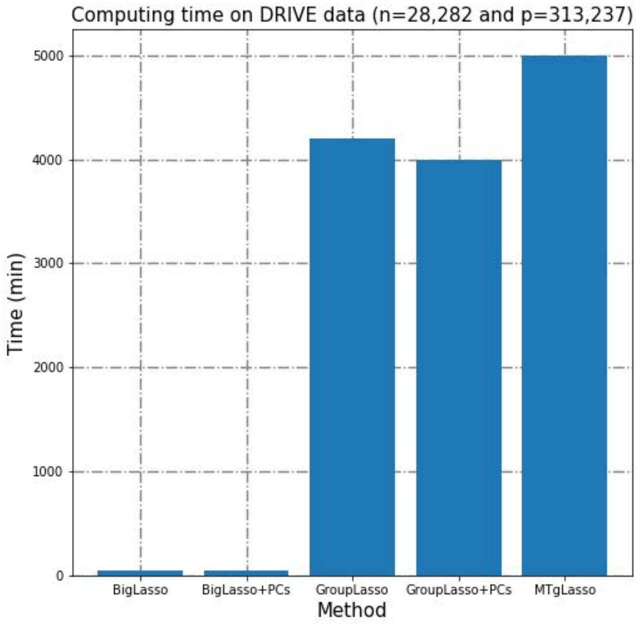
⇒ The feature selection at the LD-groups level alleviate the curse of dimensionality and the lack of stability.

Multitask group Lasso results and comparison

Multitask group Lasso is **more stable** than the state-of-the-art methods.

Real data: DRIVE Breast Cancer OncoArray[1] n=28,282 ; p=313,237 ; LD-groups number = 17,782 groups

Methods	Number of selected LD-groups	Number of selected SNPs	Stability index	Selection level
MuGLasso (100 boostraps)	62	1,357	0.4312	LD-groups
Adjusted group Lasso	59	1,293	0.3234	LD-groups
Stratified group Lasso	58	1,119	0.2498	LD-groups
Adjusted Lasso	41	874	0.2068	Single-SNP
Stratified Lasso	38	789	0.1581	Single-SNP
Adjusted GWAS	16	306	-	Singlle-SNP



[1] DRIVE: "General Research Use" dataset in DRIVE Breast Cancer OncoArray Genotypes, available from dbGaP (study accession: phs001265/GRU), accessed under project #17707.