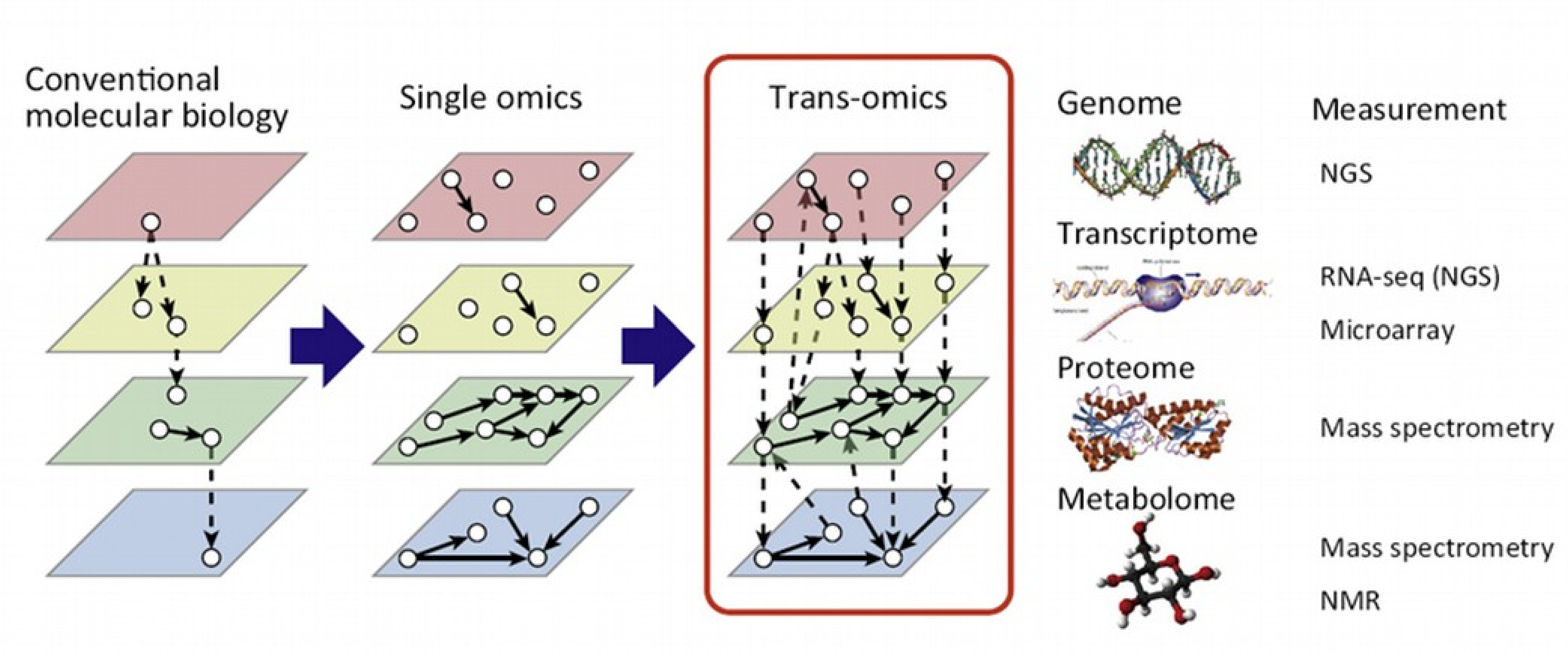
# Feature Selection and Supervised OMICs Integration

OMICs Integration and Systems Biology course
Nikolay Oskolkov, NBIS SciLifeLab
Lund, 5.10.2020

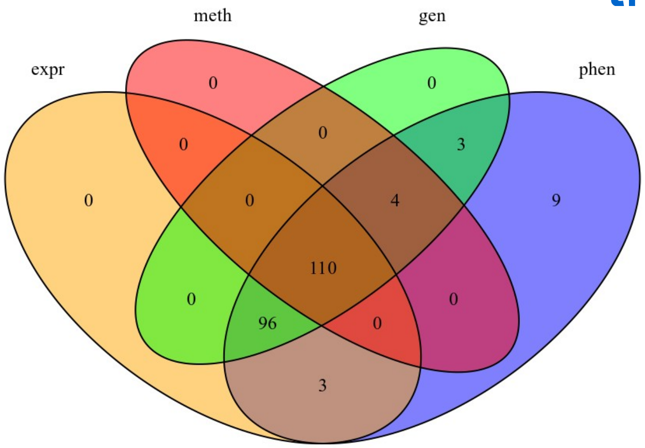


# What Method of Integration to Select?

| | Linear | Non-Linear |
|---|---|---|
| Supervised | PLS / OPLS / mixOmics, LASSO / Ridge / Elastic Net | Neural Networks, Random Forest, Bayesian Networks |
| Unsupervised | Factor Analysis / MOFA | Autoencoder, SNF, UMAP, Clustering of Clusters |

1) With ~110 samples it is a good idea to do **linear** OMICs integration
2) T2D is a phenotype of interest, therefore **supervised** integration

# Feature Pre-Selection to Overcome the Curse of Dimensionality



29% of Diabetics

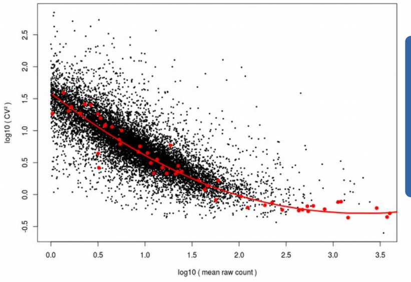
~~WGS (~30 mln dims)~~
~~BSseq (~30 mln dims)~~

Data Set (4 OMICs)

Train Set (n = 88)

Test Set (n = 22)

unsupervised



supervised

Feature Pre-Selection

Evaluation

OMICs Integration

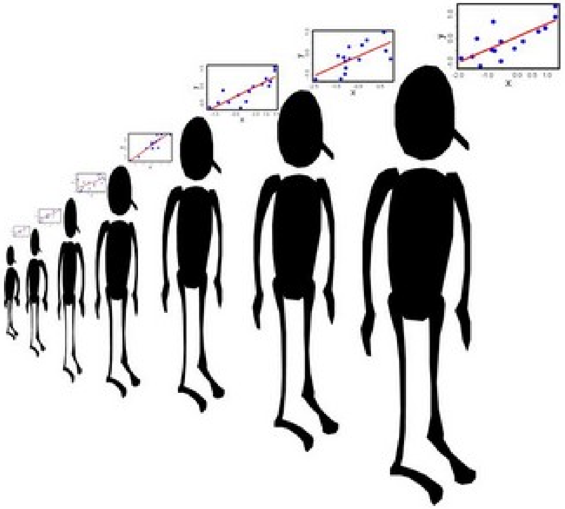
Trained Model

# Maximum Likelihood does not Stand Non-Independence in Data

```
##            n1         n2          n3           n4         n5
## p1 -0.6760258 -1.2307634  1.66039982  0.196033326 -0.2981471
## p2 -1.5834993  0.6494188 -0.01267663 -1.064763128 -0.1792141
## p3  0.3152418 -0.5791937 -1.79593465 -0.312303710  0.2671534
## p4 -0.9359010  0.1212546 -0.36279328 -0.553364109  1.0598898
## p5 -2.0411903  0.6899356 -1.03923098  0.008958754 -0.2249498
```

- Two types of non-independence in data
  - between samples
  - between features

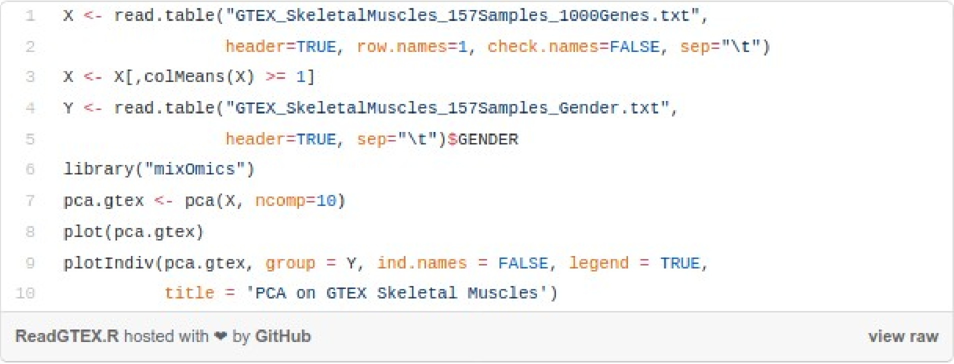
Random Effects



Lasso

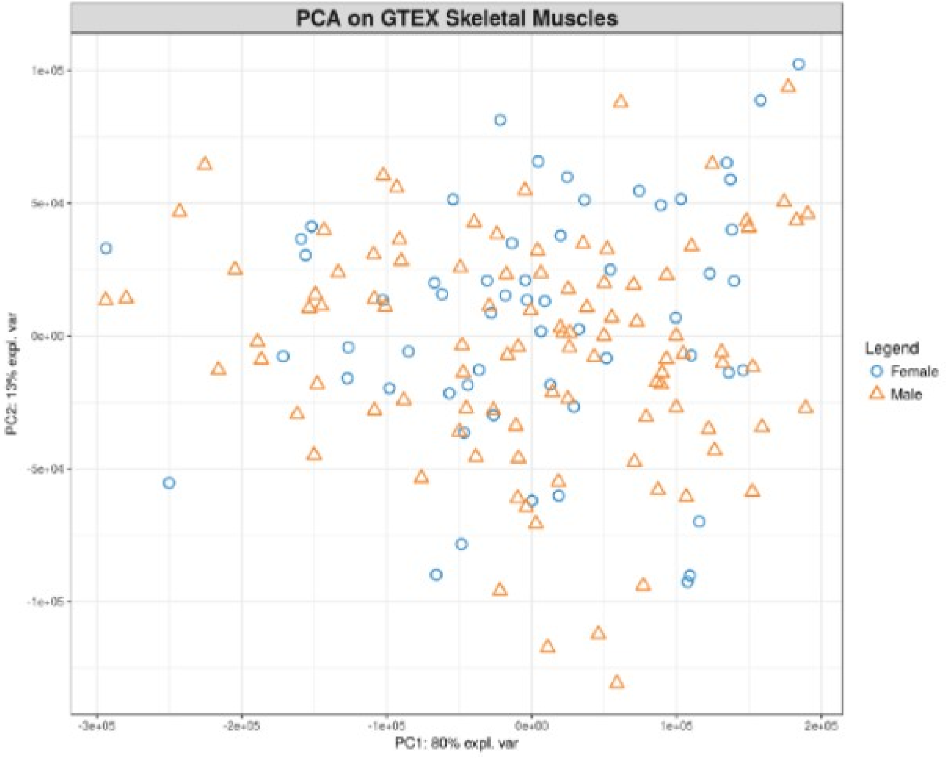
# Univariate and Multivariate Feature Selection

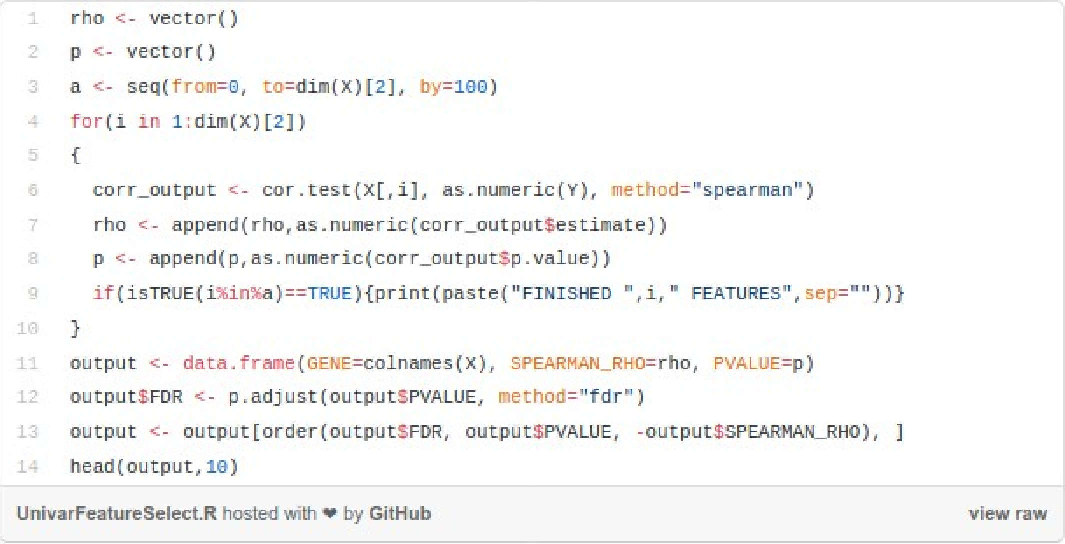
# Univariate Feature Selection



```r
X <- read.table("GTEX_SkeletalMuscles_157Samples_1000Genes.txt",
                header=TRUE, row.names=1, check.names=FALSE, sep="\t")
X <- X[,colMeans(X) >= 1]
Y <- read.table("GTEX_SkeletalMuscles_157Samples_Gender.txt",
                header=TRUE, sep="\t")$GENDER
library("mixOmics")
pca.gtex <- pca(X, ncomp=10)
plot(pca.gtex)
plotIndiv(pca.gtex, group = Y, ind.names = FALSE, legend = TRUE,
          title = 'PCA on GTEX Skeletal Muscles')
```

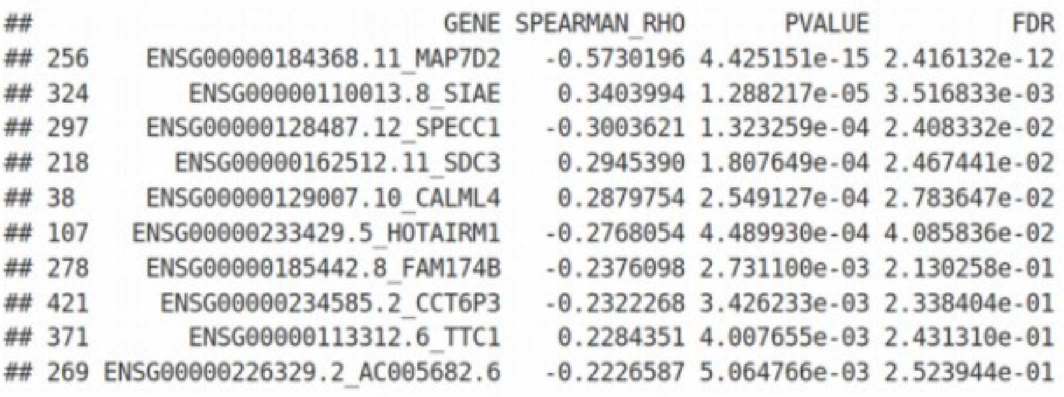
ReadGTEX.R hosted with ❤ by GitHub    view raw





```r
rho <- vector()
p <- vector()
a <- seq(from=0, to=dim(X)[2], by=100)
for(i in 1:dim(X)[2])
{
  corr_output <- cor.test(X[,i], as.numeric(Y), method="spearman")
  rho <- append(rho,as.numeric(corr_output$estimate))
  p <- append(p,as.numeric(corr_output$p.value))
  if(isTRUE(i%in%a)==TRUE){print(paste("FINISHED ",i," FEATURES",sep=""))}
}
output <- data.frame(GENE=colnames(X), SPEARMAN_RHO=rho, PVALUE=p)
output$FDR <- p.adjust(output$PVALUE, method="fdr")
output <- output[order(output$FDR, output$PVALUE, -output$SPEARMAN_RHO), ]
head(output,10)
```

UnivarFeatureSelect.R hosted with ❤ by GitHub    view raw



```
##                           GENE SPEARMAN_RHO       PVALUE          FDR
## 256     ENSG00000184368.11_MAP7D2   -0.5730196 4.425151e-15 2.416132e-12
## 324        ENSG00000110013.8_SIAE    0.3403994 1.288217e-05 3.516833e-03
## 297     ENSG00000128487.12_SPECC1   -0.3003621 1.323259e-04 2.408332e-02
## 218       ENSG00000162512.11_SDC3    0.2945390 1.807649e-04 2.467441e-02
## 38      ENSG00000129007.10_CALML4    0.2879754 2.549127e-04 2.783647e-02
## 107    ENSG00000233429.5_HOTAIRM1   -0.2768054 4.489930e-04 4.085836e-02
## 278     ENSG00000185442.8_FAM174B   -0.2376098 2.731100e-03 2.130258e-01
## 421       ENSG00000234585.2_CCT6P3   -0.2322268 3.426233e-03 2.338404e-01
## 371        ENSG00000113312.6_TTC1    0.2284351 4.007655e-03 2.431310e-01
## 269 ENSG00000226329.2_AC005682.6   -0.2226587 5.064766e-03 2.523944e-01
```

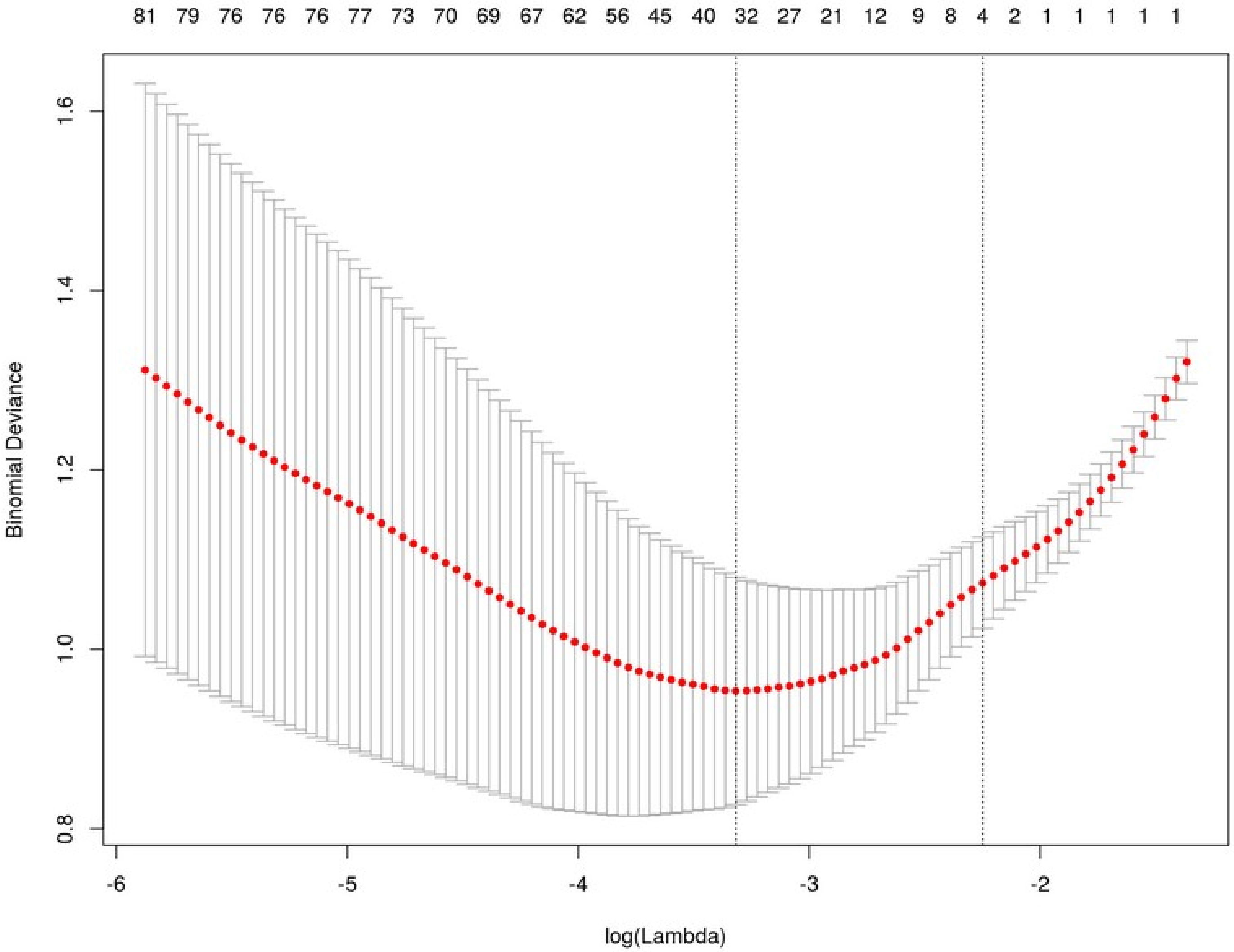
Generally acknowledged that univariate feature selection has a poor predictive capacity compared to multivariate feature selection

# Multivariate Feature Selection: LASSO

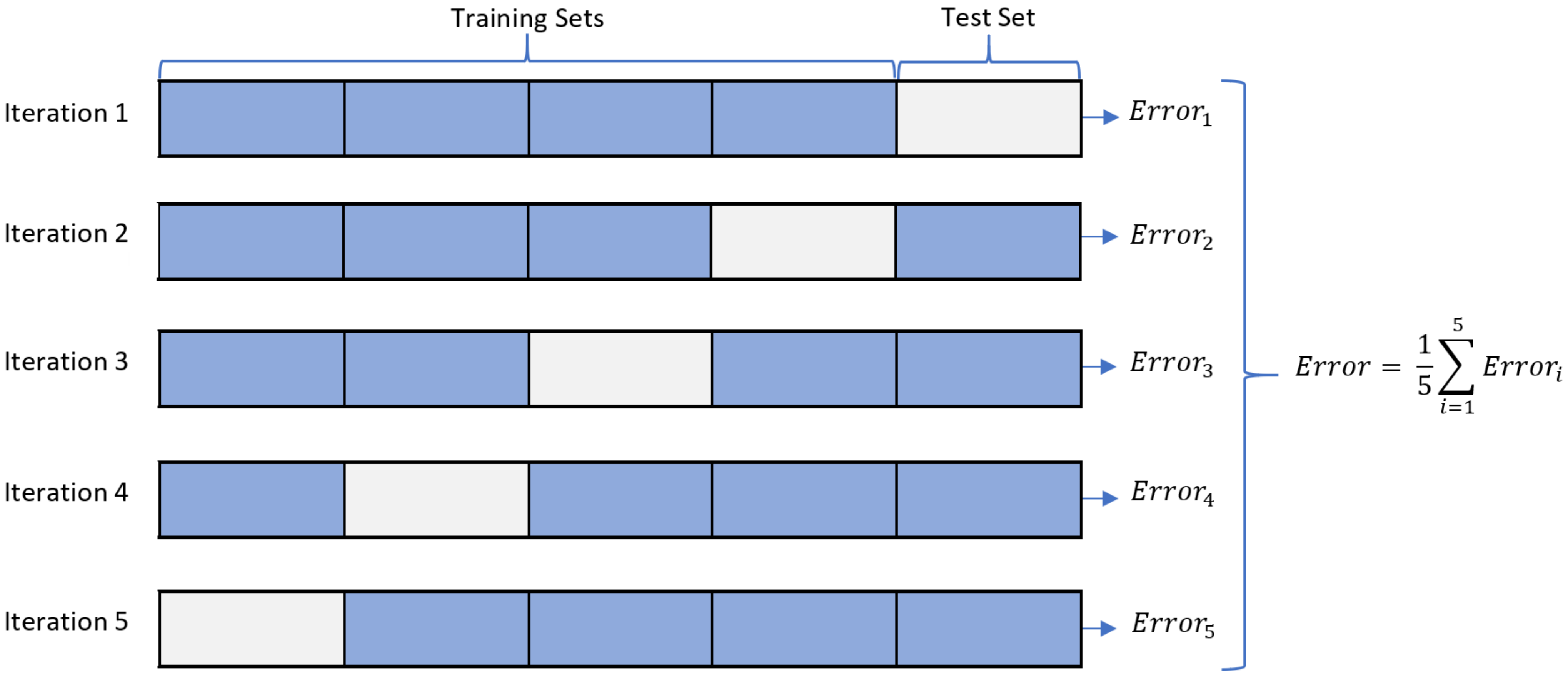
$$Y = \beta_1 X_1 + \beta_2 X_2 + \epsilon$$

$$\text{OLS} = (y - \beta_1 X_1 - \beta_2 X_2)^2$$

$$\text{Penalized OLS} = (y - \beta_1 X_1 - \beta_2 X_2)^2 + \lambda(|\beta_1| + |\beta_2|)$$



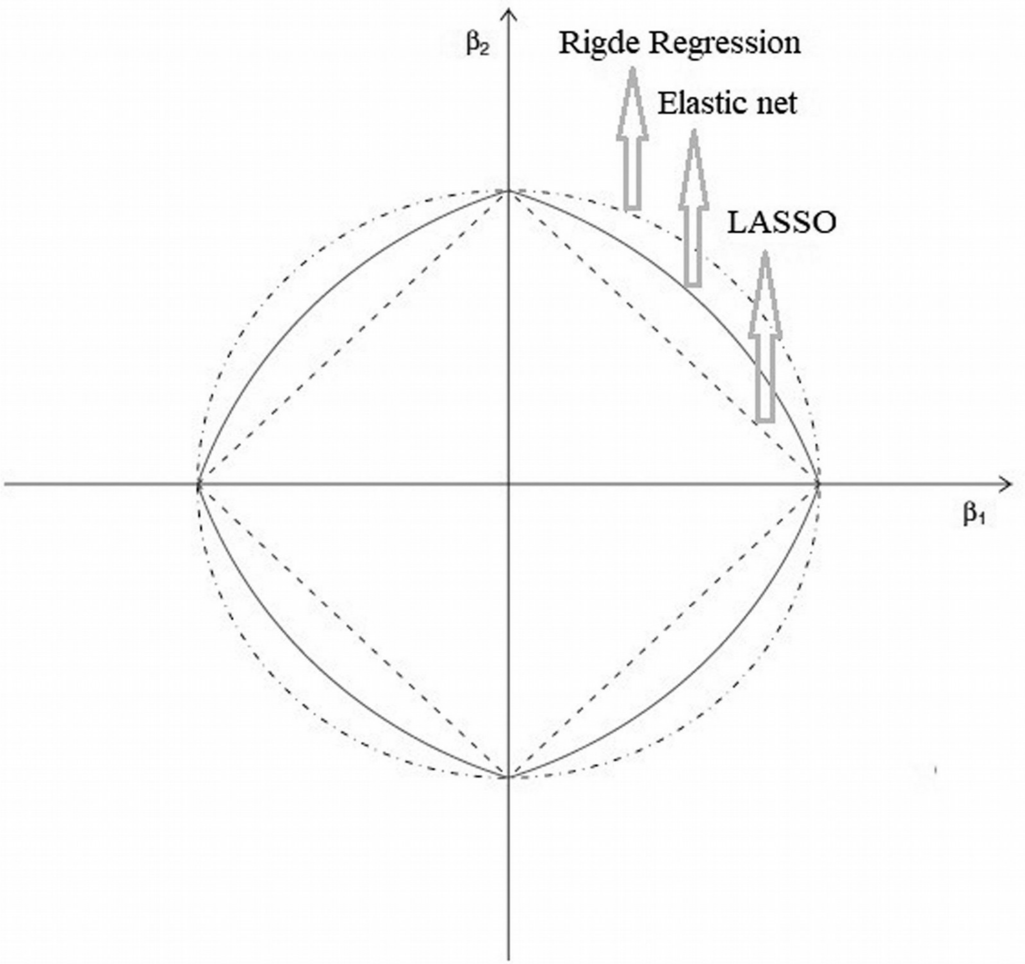
# K-fold Cross Validation



$$Error = \frac{1}{5}\sum_{i=1}^{5} Error_i$$

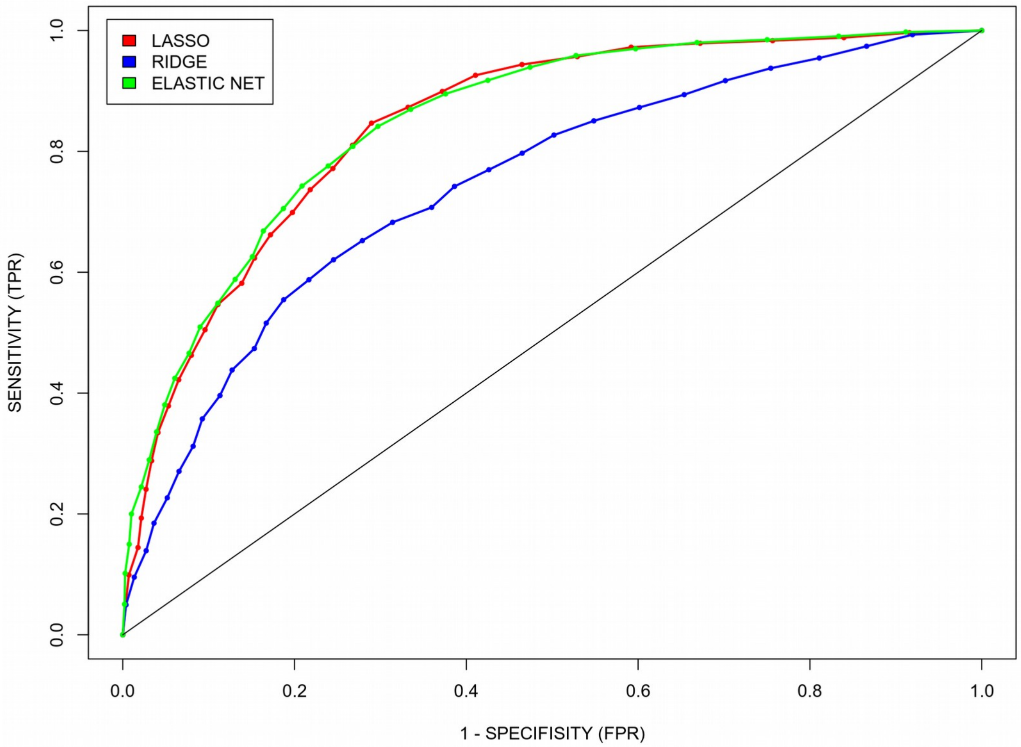
Cross-validation is a standard way to tune model hyperparameters such as λ in LASSO

# Difference between Lasso, Ridge, and Elastic Net



$$\text{Lasso} : |\beta_1| + |\beta_2| \le \lambda$$

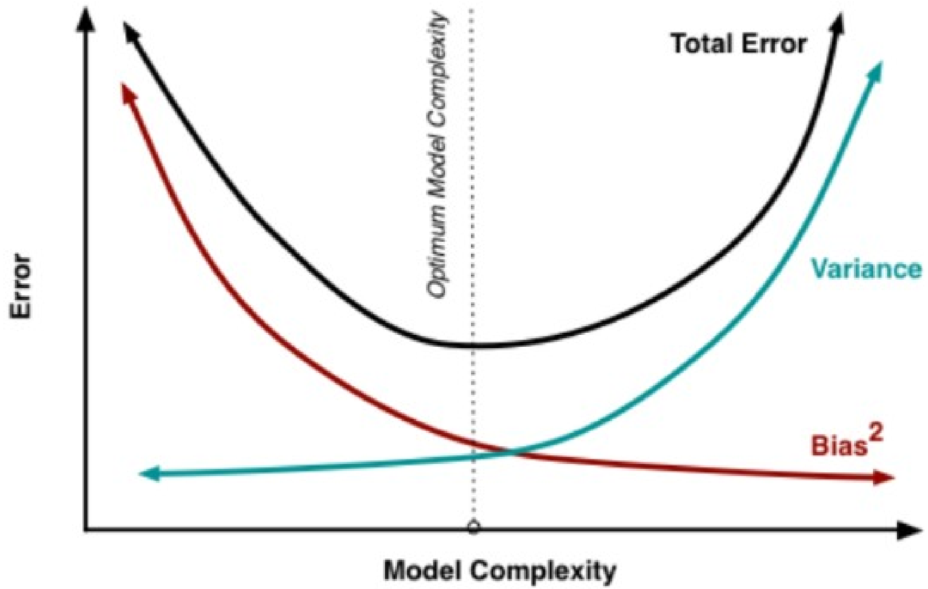
$$\text{Ridge} : \beta_1^2 + \beta_2^2 \le \lambda$$

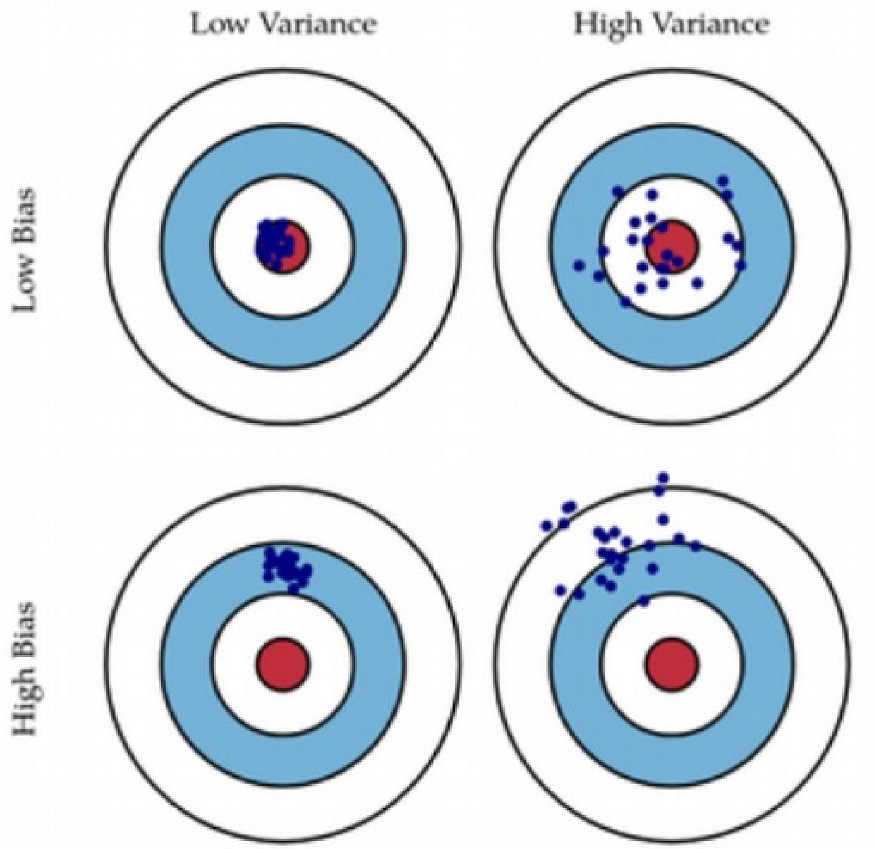


Lasso is more conservative

Ridge is more permissive

# Penalized Regression Interpretation



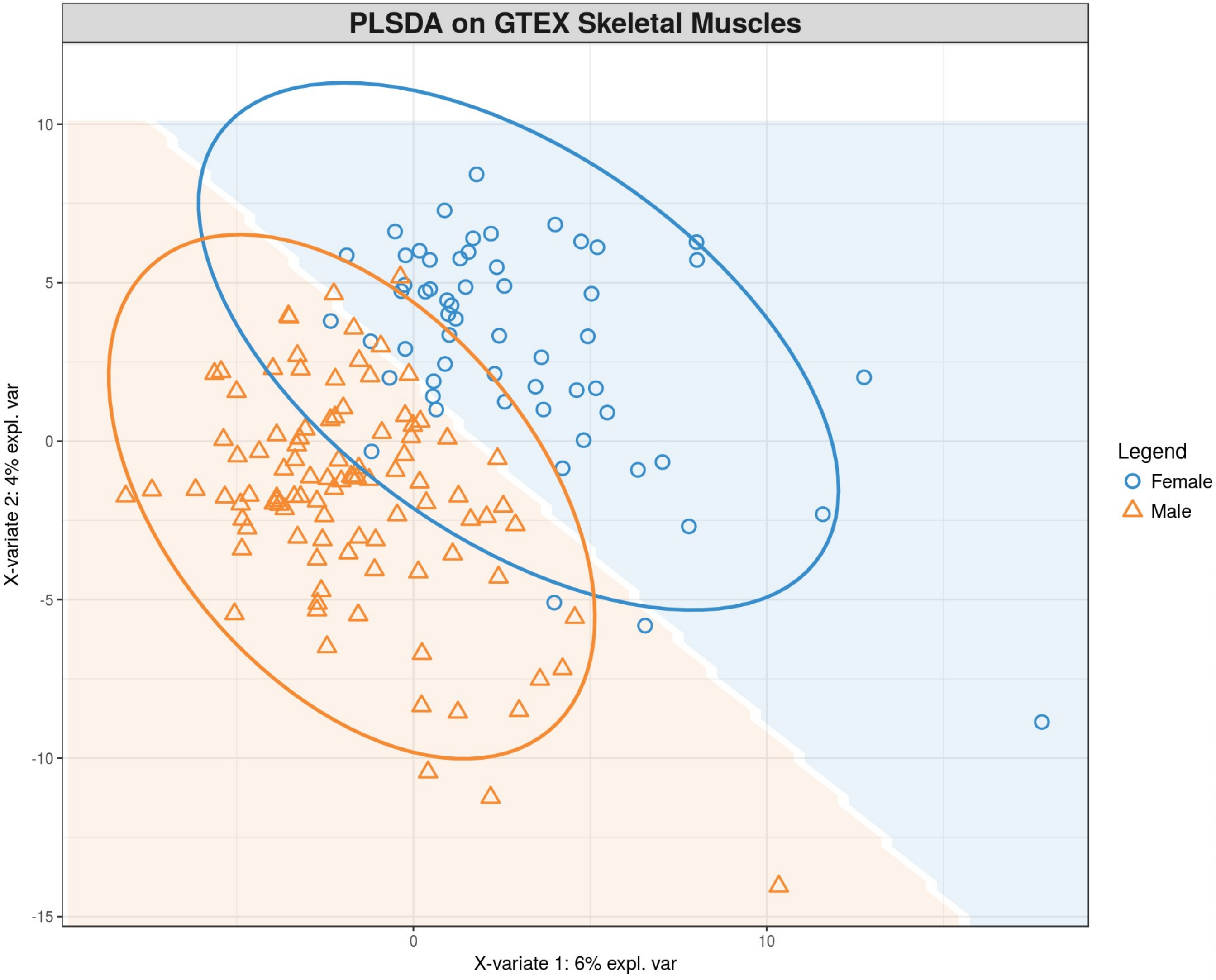


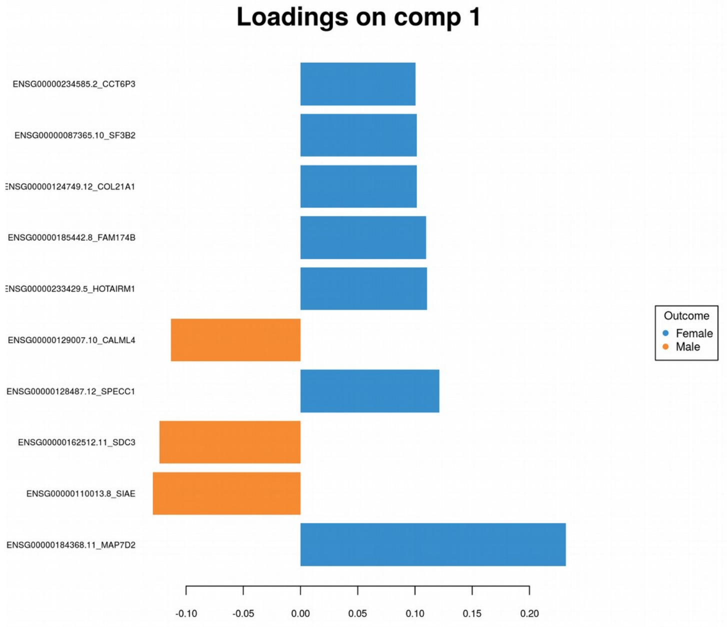
$$Y = f(X) \Longrightarrow \text{Reality}$$

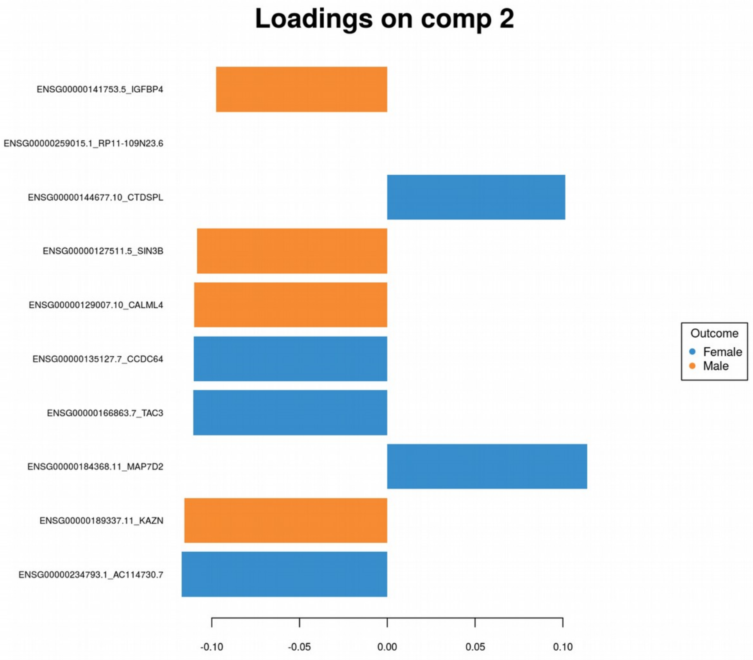
$$\mathrm{Y} = \hat{\mathrm{f}}\,(\mathrm{X}) + \mathrm{Error} \Longrightarrow \mathrm{Model}$$

$$\mathrm{Error}^2 = (\mathrm{Y} - \hat{\mathrm{f}}\,(\mathrm{X}))^2 = \mathrm{Bias}^2 + \mathrm{Variance}$$

# Multivariate Feature Selection: PLS

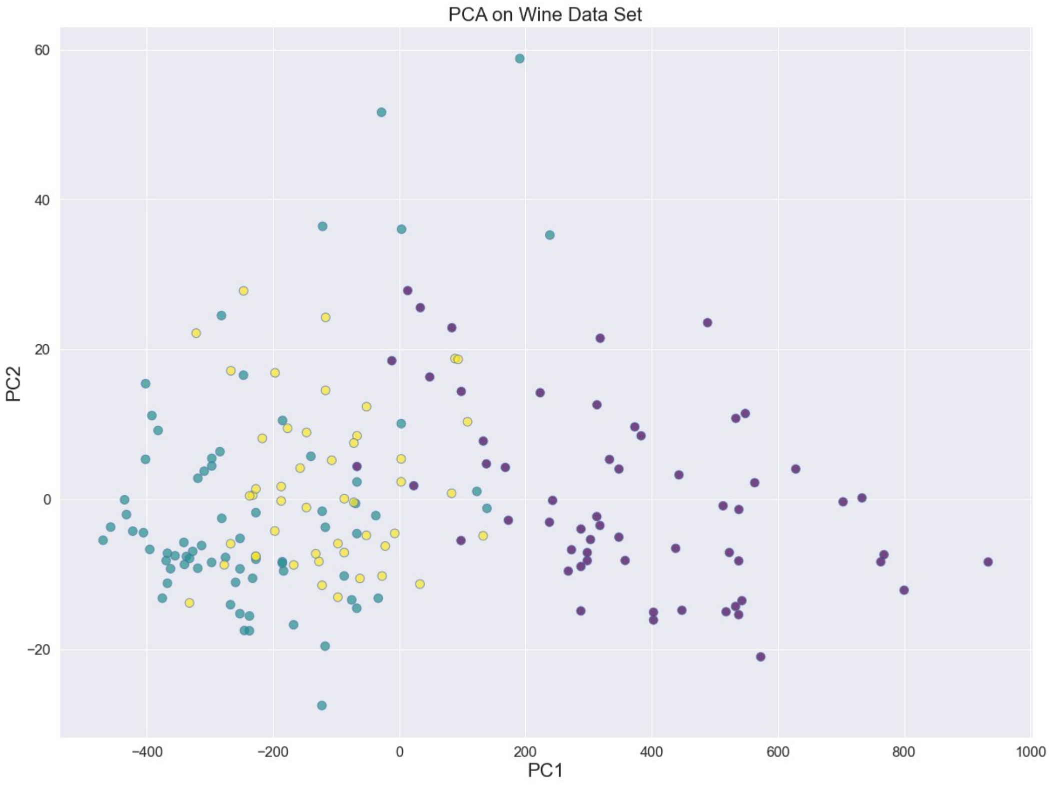


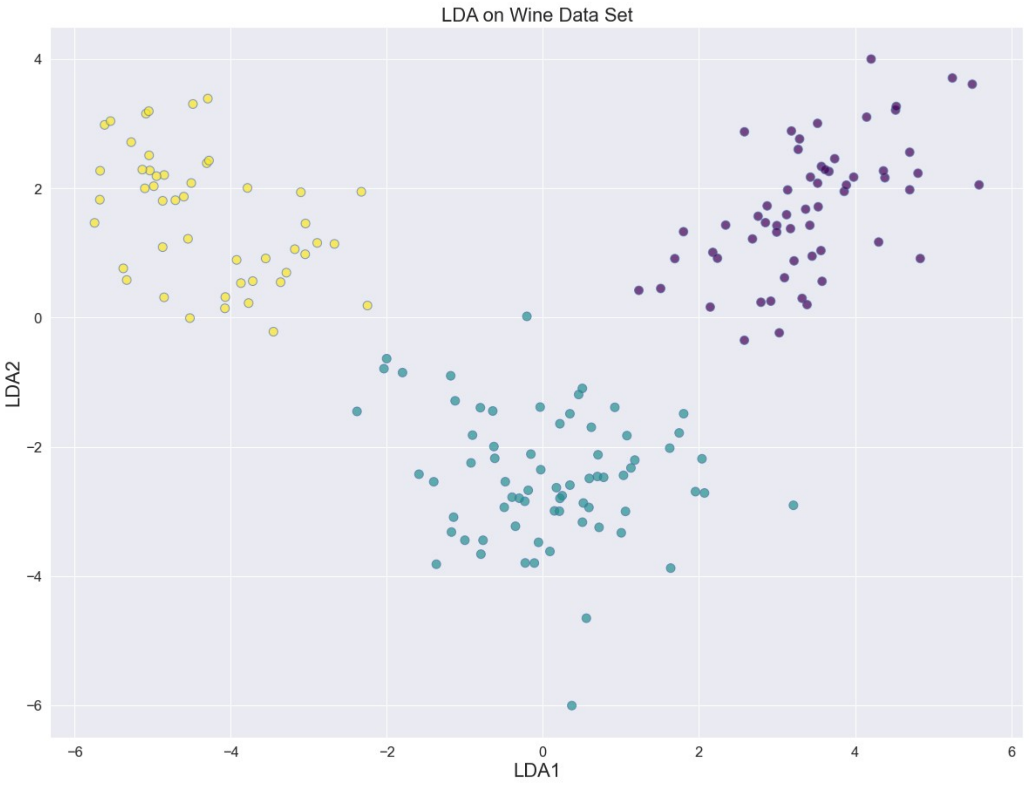




Select features that separate two groups of samples the most

# Multivariate Feature Selection: Linear Discriminant Analysis (LDA)

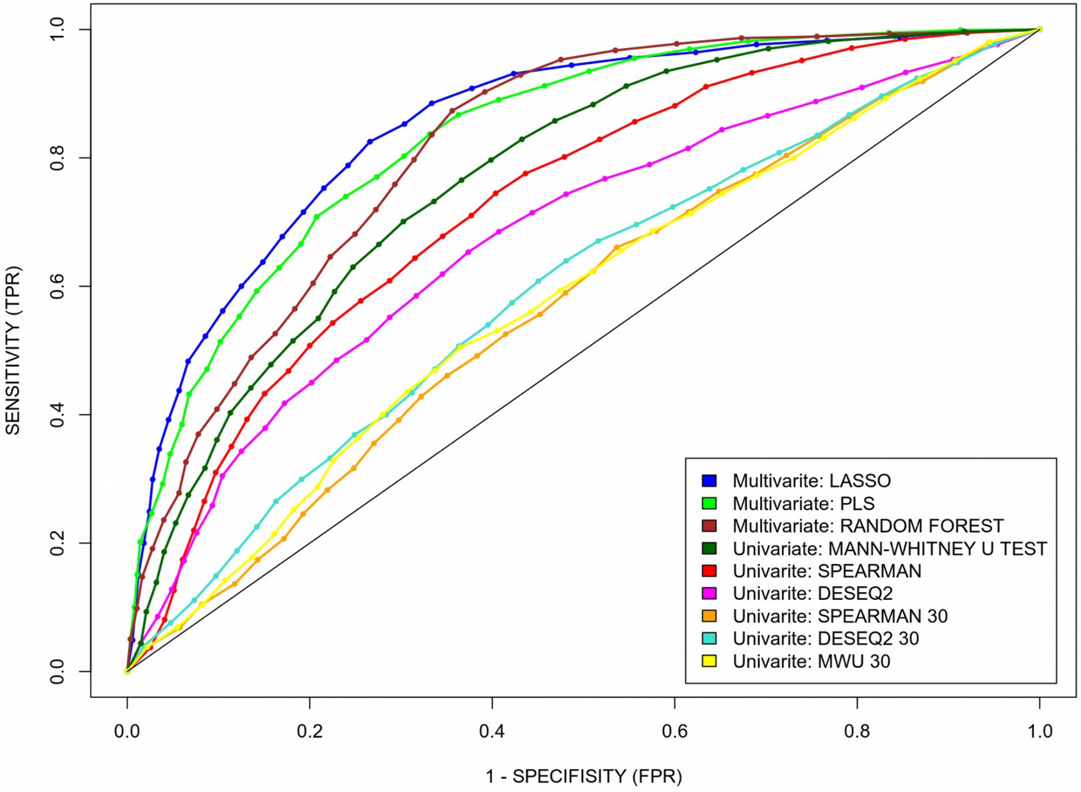




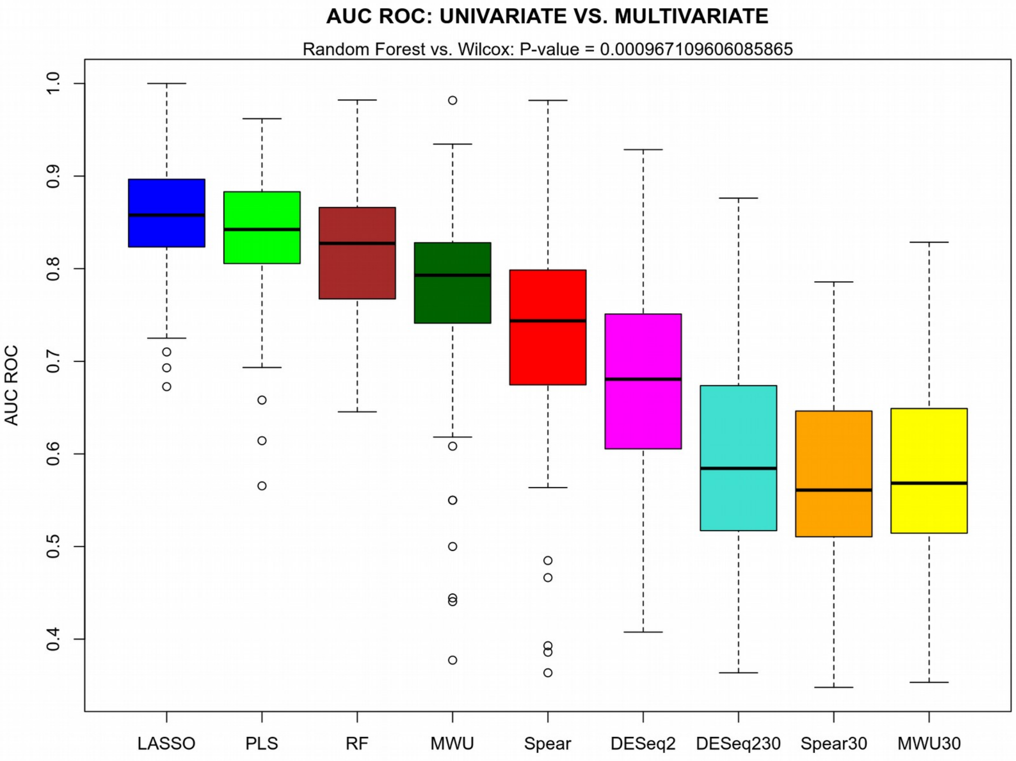
Minimize variance within clusters and maximize variance between clusters

Similar to what ANOVA / t-test is doing, therefore LINEAR Discriminant Analysis (LDA)

# Univariate vs. Multivariate Prediction



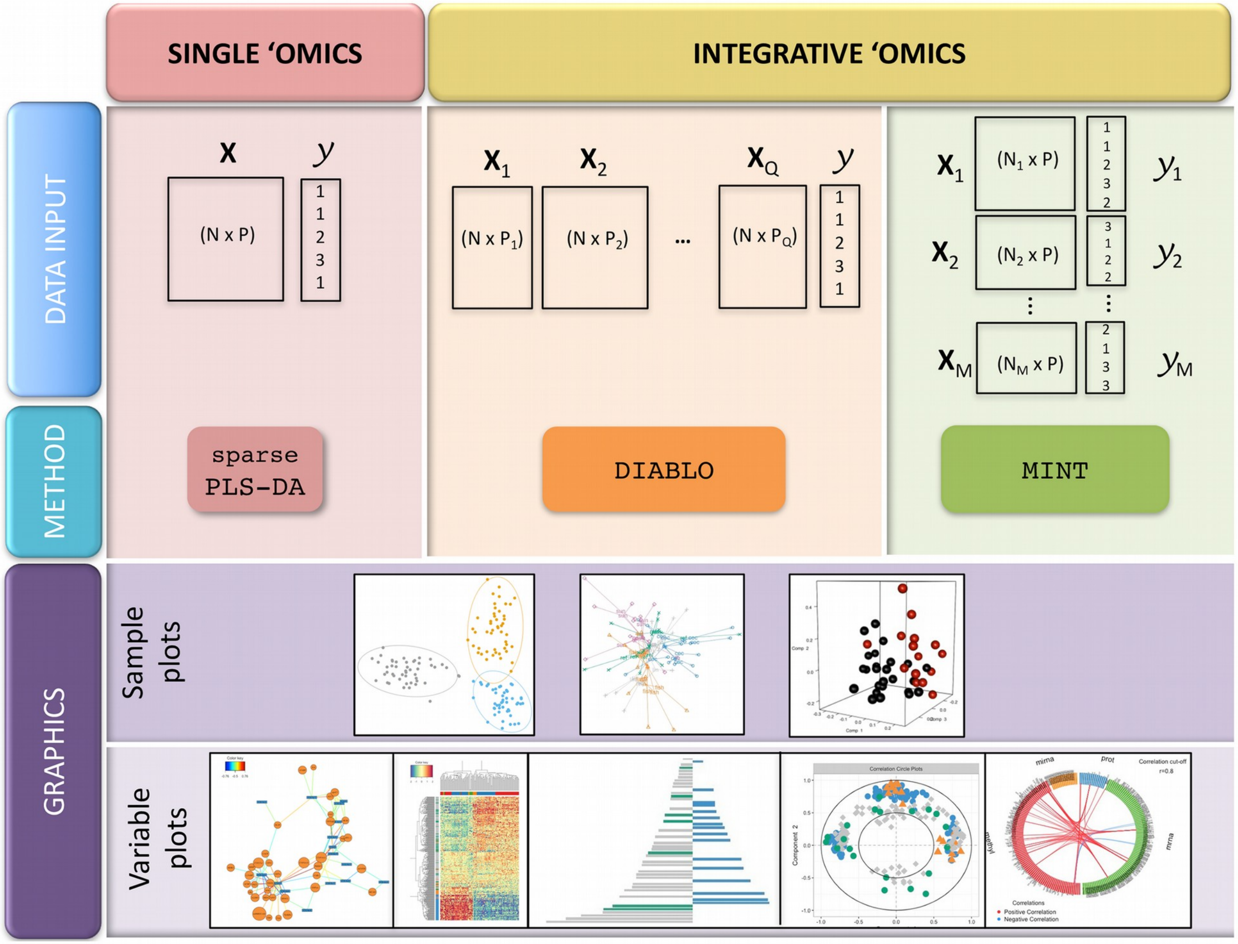
Multivariate methods (LASSO, PLS, RanFor) have significantly higher AUC ROC than univariate methods (Spear, MWU, DESeq2) on skeletal muscle gene expression data

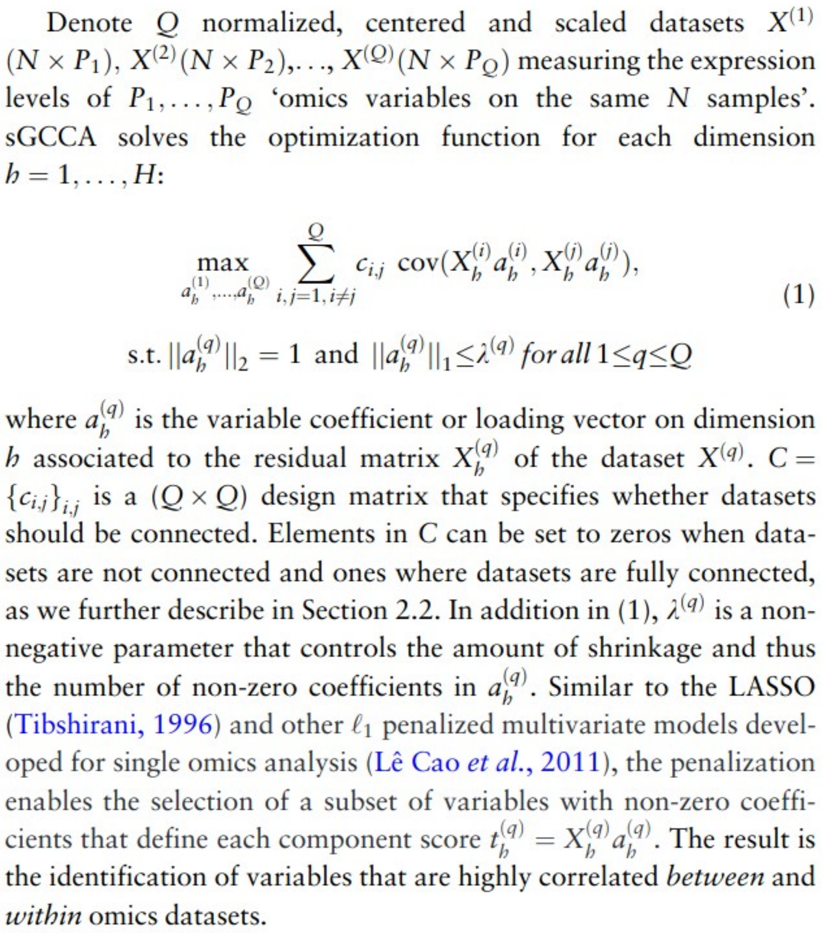


If you find a data set where it is not true, please let me know

# DIABLO Omics Integration

# DIABLO PLS-Based Algorithm





Denote $Q$ normalized, centered and scaled datasets $X^{(1)}$ $(N \times P_1)$, $X^{(2)}(N \times P_2)$,..., $X^{(Q)}(N \times P_Q)$ measuring the expression levels of $P_1, \dots, P_Q$ 'omics variables on the same $N$ samples'. sGCCA solves the optimization function for each dimension $h = 1, \dots, H$:

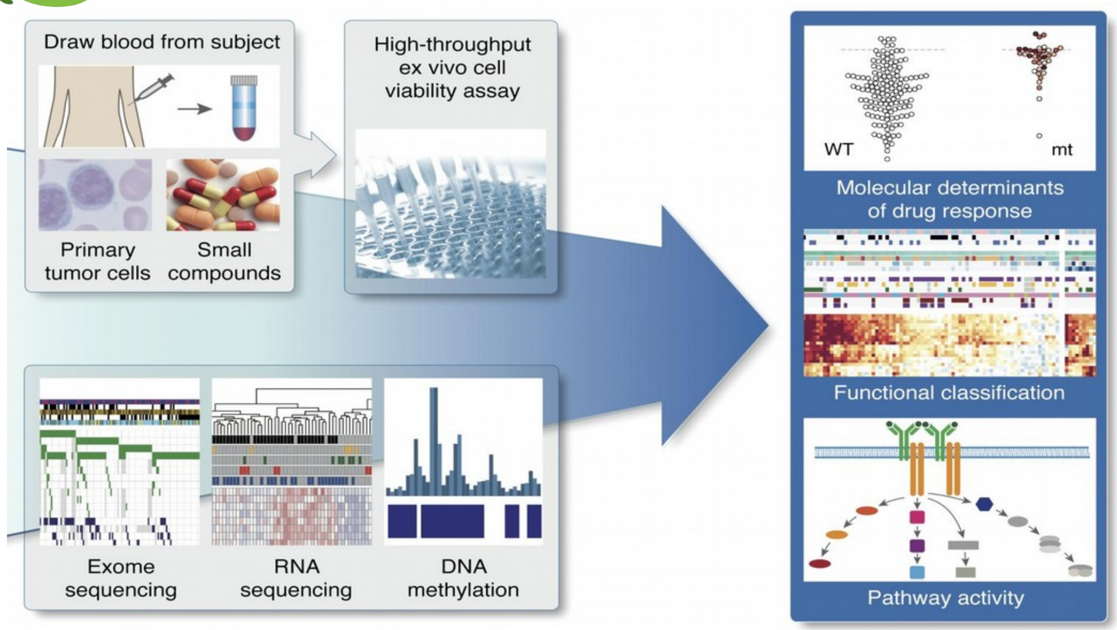
$$\max_{a_h^{(1)},\dots,a_h^{(Q)}} \sum_{i,j=1, i\neq j}^{Q} c_{i,j}\ \mathrm{cov}(X_h^{(i)}a_h^{(i)}, X_h^{(j)}a_h^{(j)}), \qquad (1)$$

$$\text{s.t. } \|a_h^{(q)}\|_2 = 1 \text{ and } \|a_h^{(q)}\|_1 \le \lambda^{(q)} \textit{ for all } 1 \le q \le Q$$

where $a_h^{(q)}$ is the variable coefficient or loading vector on dimension $h$ associated to the residual matrix $X_h^{(q)}$ of the dataset $X^{(q)}$. $C = \{c_{i,j}\}_{i,j}$ is a $(Q \times Q)$ design matrix that specifies whether datasets should be connected. Elements in C can be set to zeros when datasets are not connected and ones where datasets are fully connected, as we further describe in Section 2.2. In addition in (1), $\lambda^{(q)}$ is a non-negative parameter that controls the amount of shrinkage and thus the number of non-zero coefficients in $a_h^{(q)}$. Similar to the LASSO (Tibshirani, 1996) and other $\ell_1$ penalized multivariate models developed for single omics analysis (Lê Cao *et al.*, 2011), the penalization enables the selection of a subset of variables with non-zero coefficients that define each component score $t_h^{(q)} = X_h^{(q)}a_h^{(q)}$. The result is the identification of variables that are highly correlated *between* and *within* omics datasets.

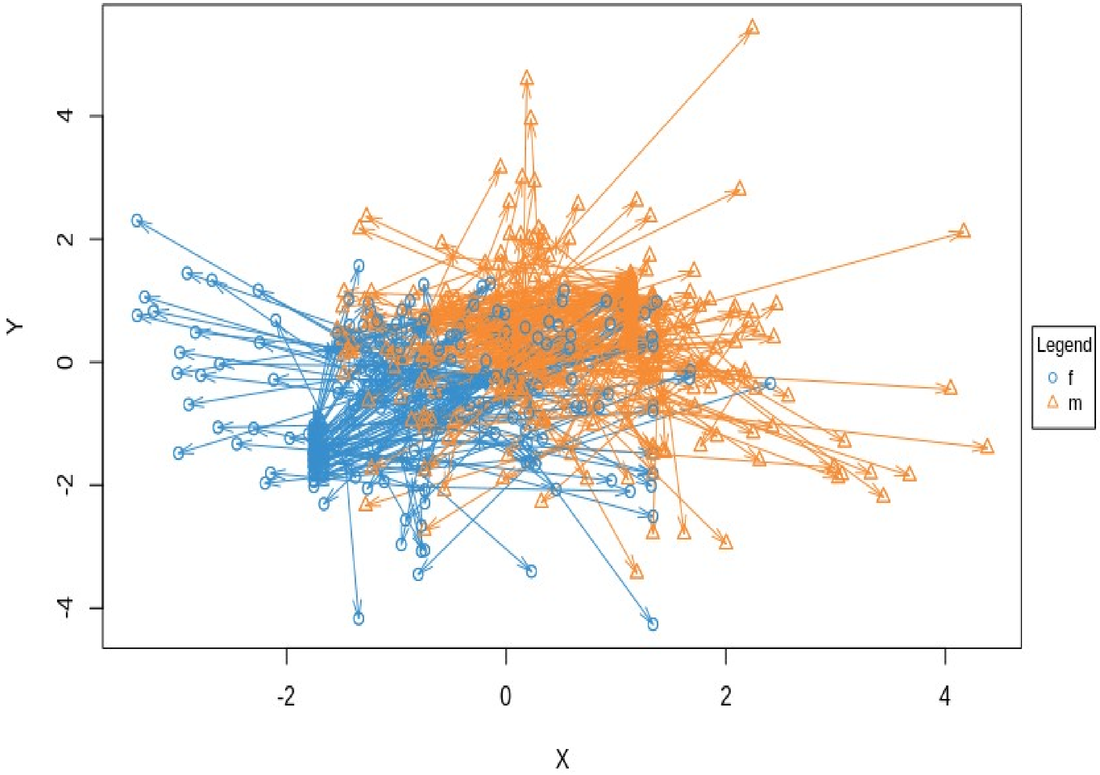
$$\max_{\beta} \mathrm{cov}(X, Y) \Longrightarrow \hat{\beta}$$

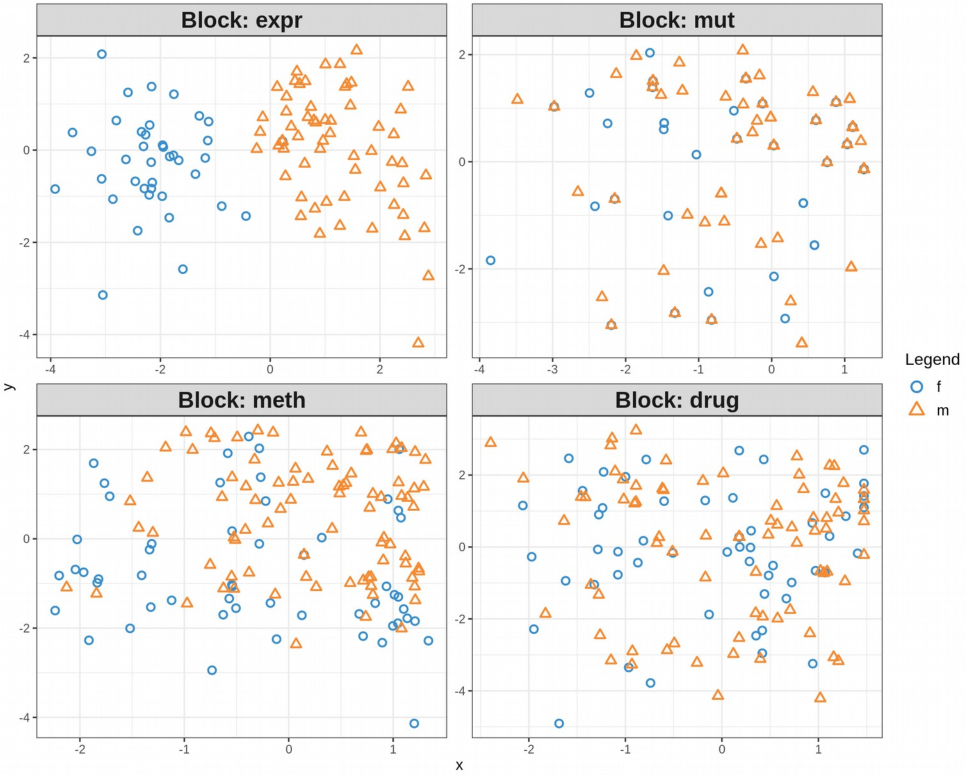
# DIABLO Omics Integration



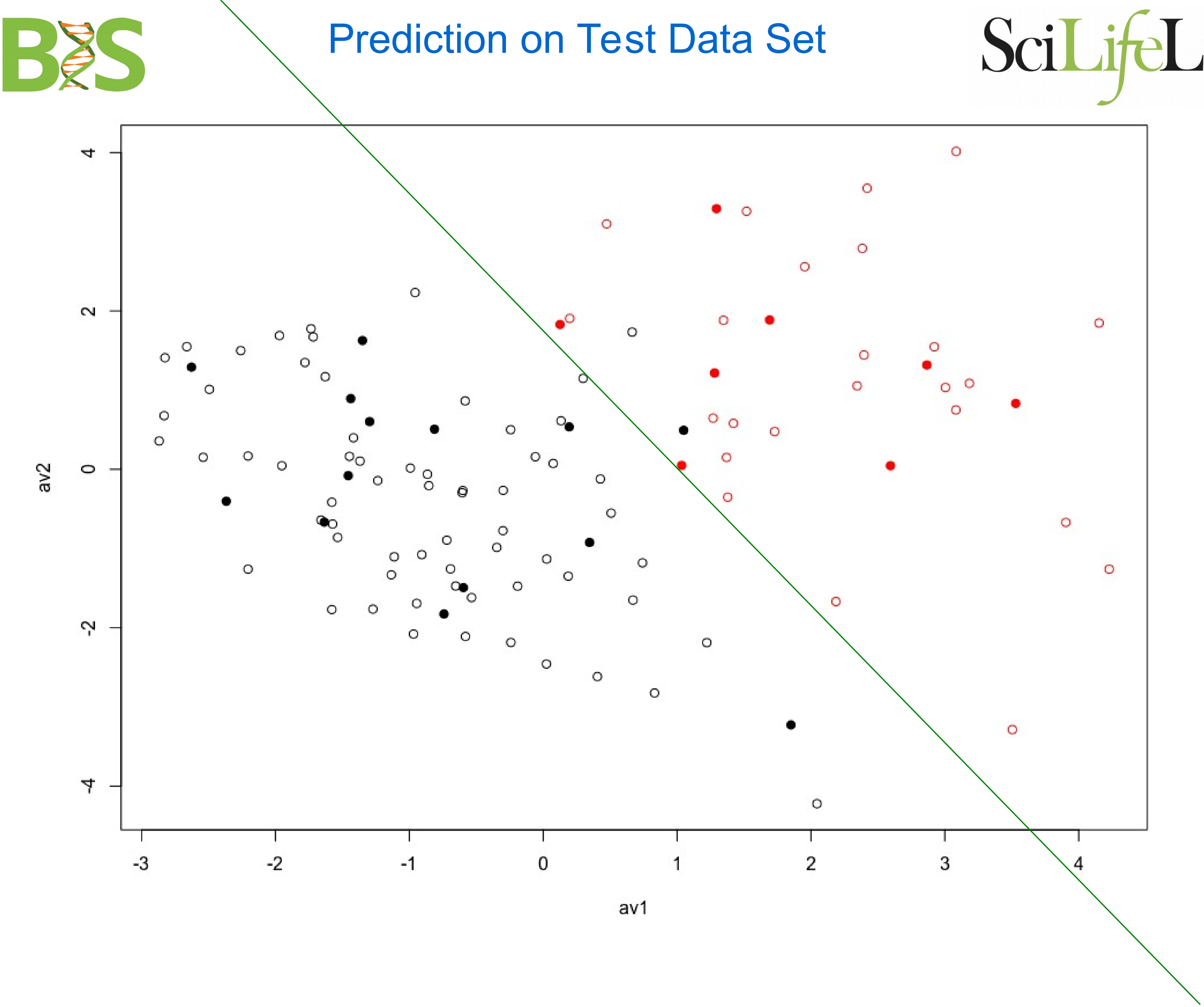
Chronic Lymphocytic Leukaemia (CLL):

gene expression (RNAseq), mutations, methylation, drug response

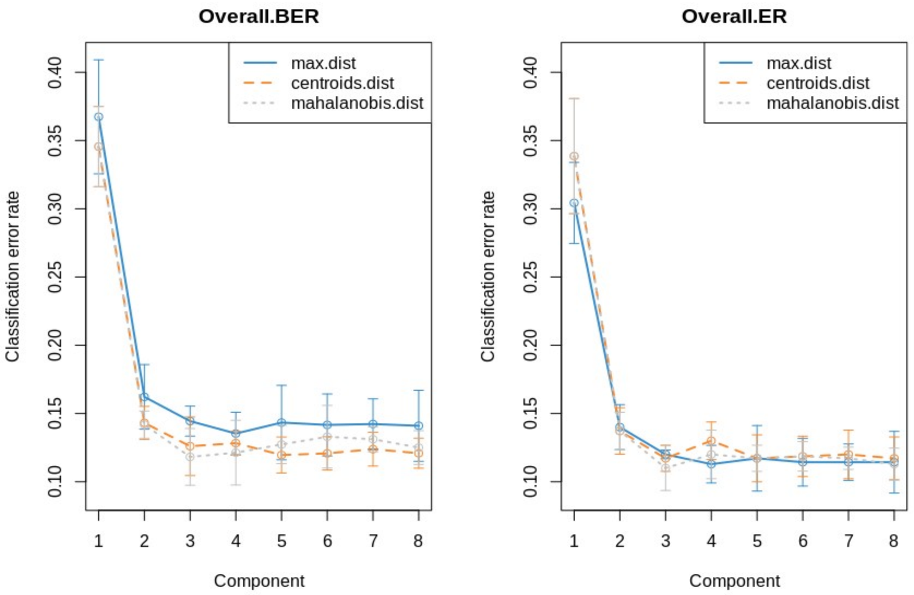


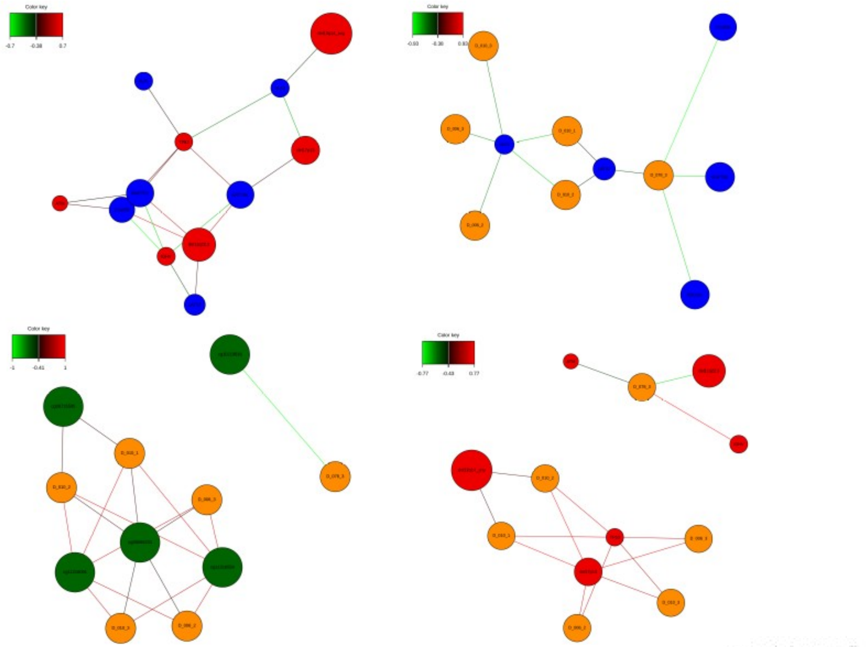


# Prediction on Test Data Set



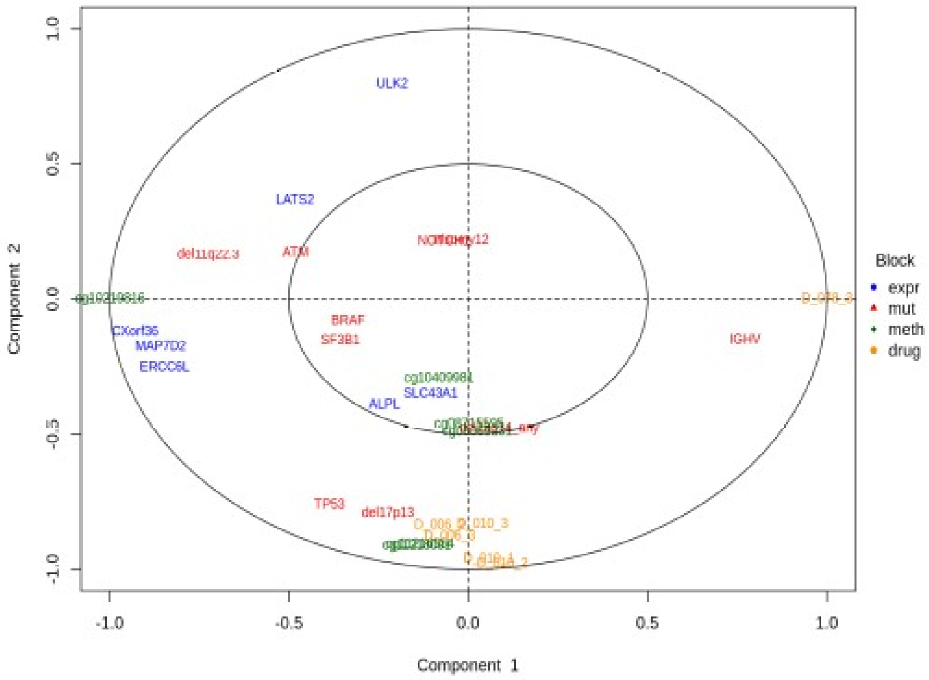
# DIABLO Visualization



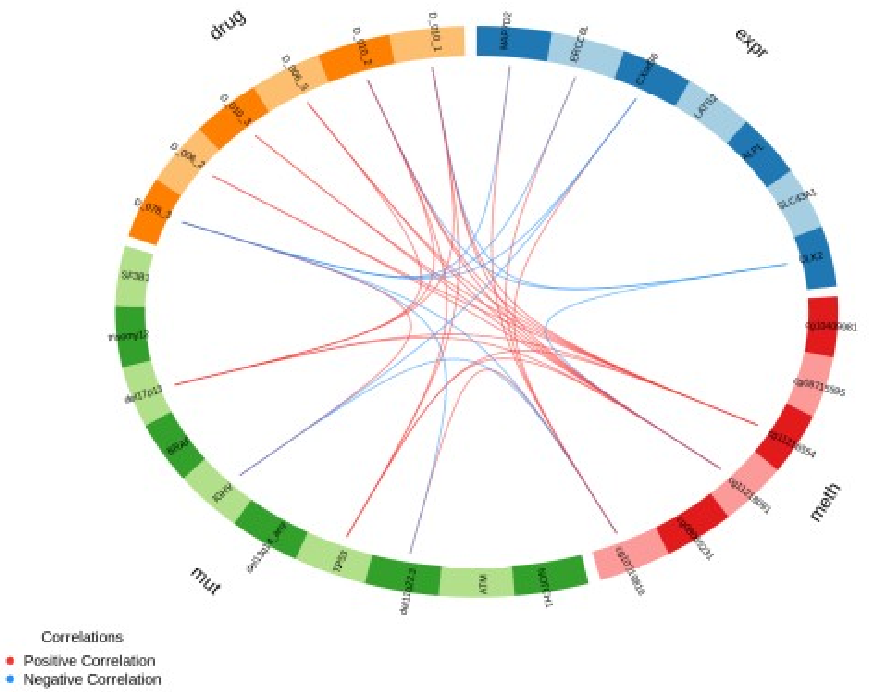


Correlation Circle Plots

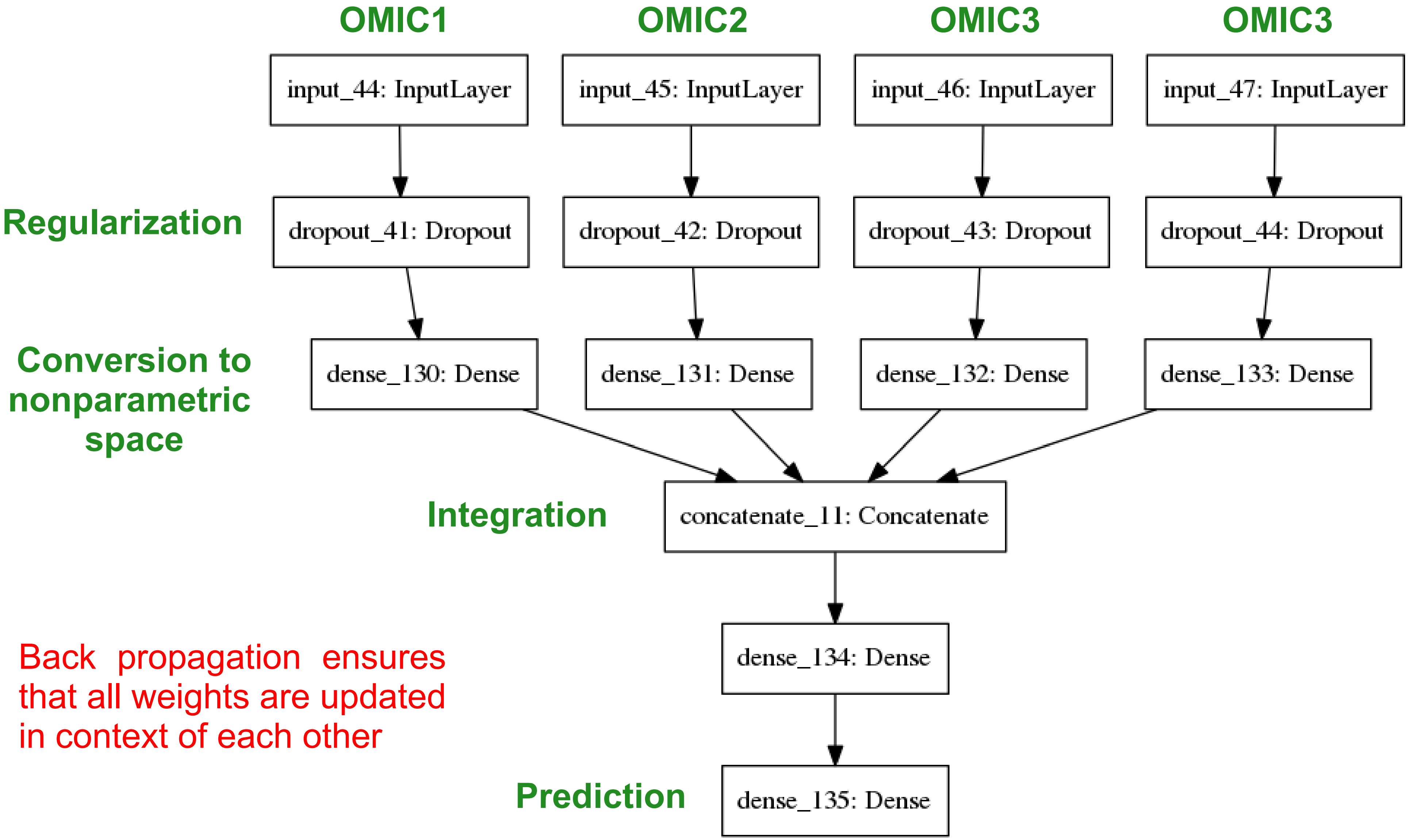
Comp 1-2



Correlation cut-off
r=0.7

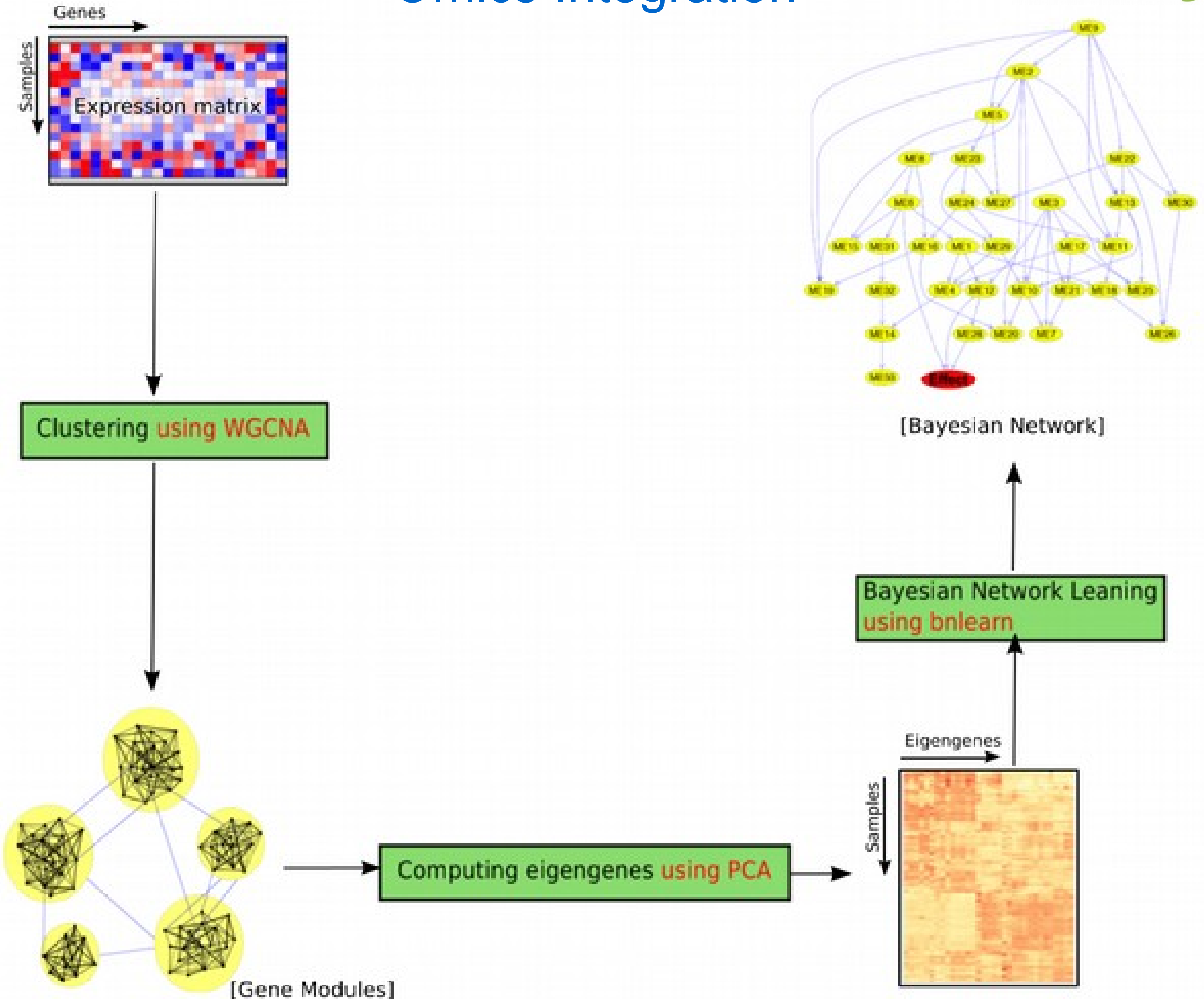


# Deep Learning for Omics Integration



Back propagation ensures that all weights are updated in context of each other

# Bayesian Networks for Omics Integration

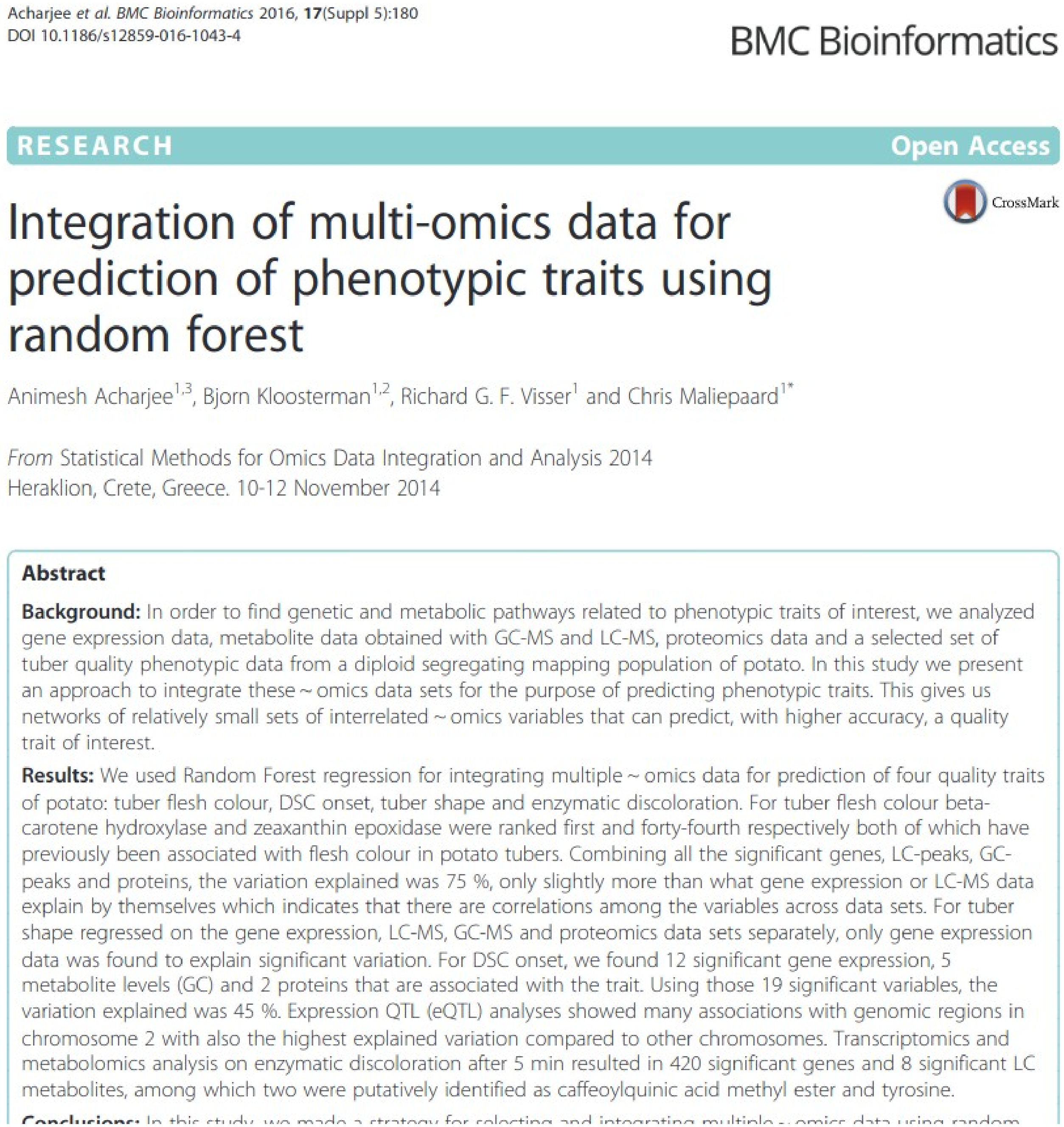


Clustering using WGCNA

Computing eigengenes using PCA

Bayesian Network Leaning using bnlearn

# Random Forest for Omics Integration



Acharjee *et al. BMC Bioinformatics* 2016, **17**(Suppl 5):180
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BMC Bioinformatics

RESEARCH Open Access

## Integration of multi-omics data for prediction of phenotypic traits using random forest

Animesh Acharjee[1,3], Bjorn Kloosterman[1,2], Richard G. F. Visser[1] and Chris Maliepaard[1*]

*From* Statistical Methods for Omics Data Integration and Analysis 2014
Heraklion, Crete, Greece. 10-12 November 2014

**Abstract**

**Background:** In order to find genetic and metabolic pathways related to phenotypic traits of interest, we analyzed gene expression data, metabolite data obtained with GC-MS and LC-MS, proteomics data and a selected set of tuber quality phenotypic data from a diploid segregating mapping population of potato. In this study we present an approach to integrate these ~ omics data sets for the purpose of predicting phenotypic traits. This gives us networks of relatively small sets of interrelated ~ omics variables that can predict, with higher accuracy, a quality trait of interest.

**Results:** We used Random Forest regression for integrating multiple ~ omics data for prediction of four quality traits of potato: tuber flesh colour, DSC onset, tuber shape and enzymatic discoloration. For tuber flesh colour beta-carotene hydroxylase and zeaxanthin epoxidase were ranked first and forty-fourth respectively both of which have previously been associated with flesh colour in potato tubers. Combining all the significant genes, LC-peaks, GC-peaks and proteins, the variation explained was 75 %, only slightly more than what gene expression or LC-MS data explain by themselves which indicates that there are correlations among the variables across data sets. For tuber shape regressed on the gene expression, LC-MS, GC-MS and proteomics data sets separately, only gene expression data was found to explain significant variation. For DSC onset, we found 12 significant gene expression, 5 metabolite levels (GC) and 2 proteins that are associated with the trait. Using those 19 significant variables, the variation explained was 45 %. Expression QTL (eQTL) analyses showed many associations with genomic regions in chromosome 2 with also the highest explained variation compared to other chromosomes. Transcriptomics and metabolomics analysis on enzymatic discoloration after 5 min resulted in 420 significant genes and 8 significant LC metabolites, among which two were putatively identified as caffeoylquinic acid methyl ester and tyrosine.

**Conclusions:** In this study, we made a strategy for selecting and integrating multiple ~ omics data using random

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