# Integration of muliple tables

in

Methods to integrate multiple tables in biomedical studies to detect biomarkers and stratify individuals

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# Outline


1. Introduction
2. Integrating two or more omic datasets
3. RGCCA
4. SGCCA
5. Recommended lectures

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# Introduction

- Undersanding the genetic basis of complex traits is an open question for may researchers
- Recent advances in technology has made this problem even more complex by incorporating other pieces of information such as neuroimaging, daily measurements of enviromental exposures among others
- The main challenge is to analyze the vast amount of data that is being generated, particularly how to integrate information from different tables

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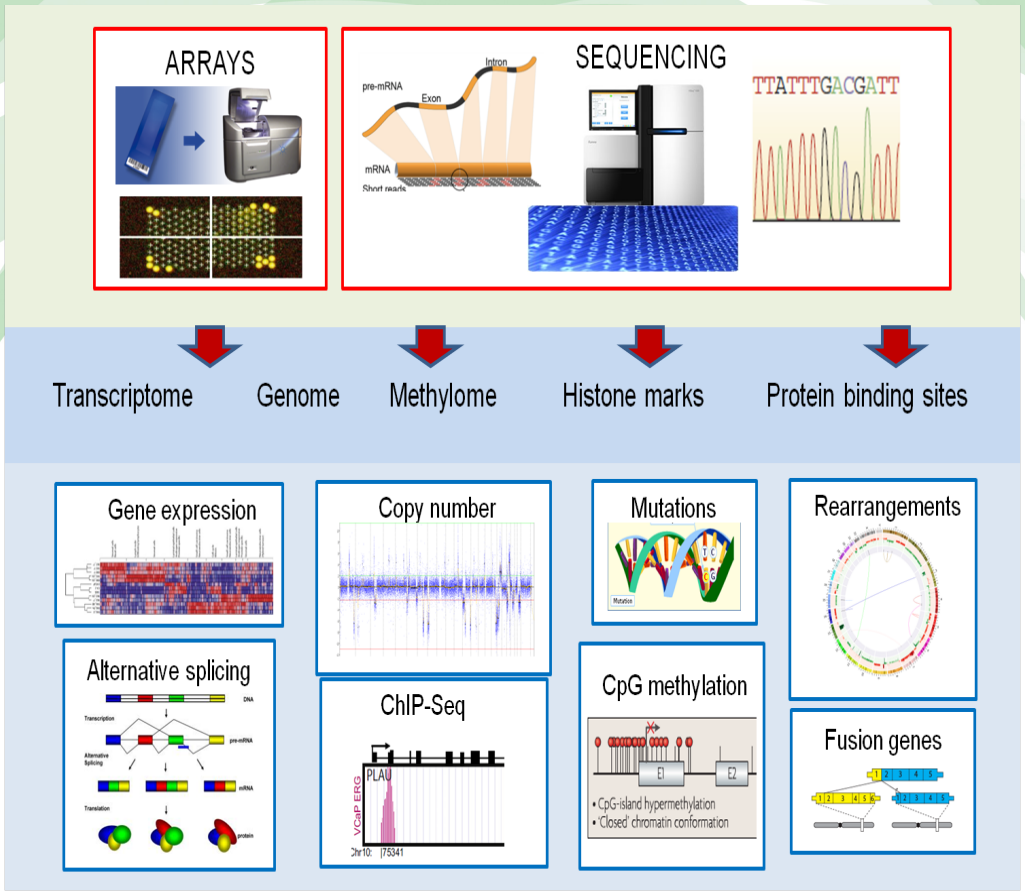
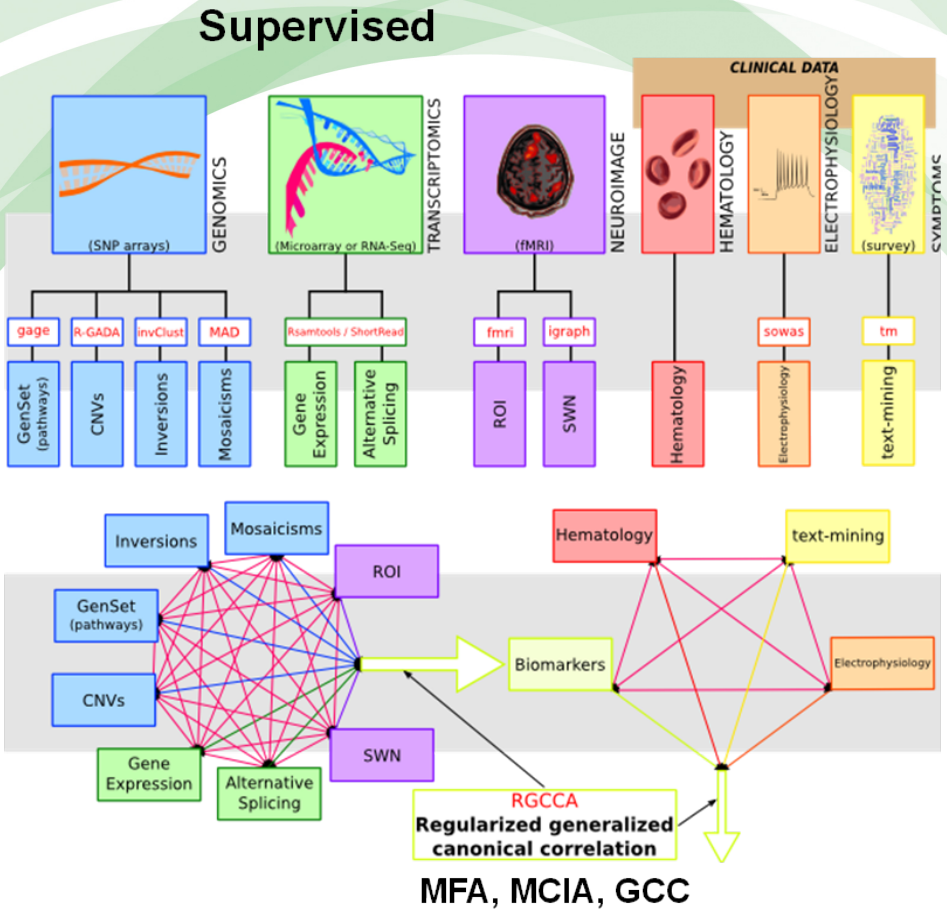
# Introduction




100s-1000s of aberrations

# Introduction



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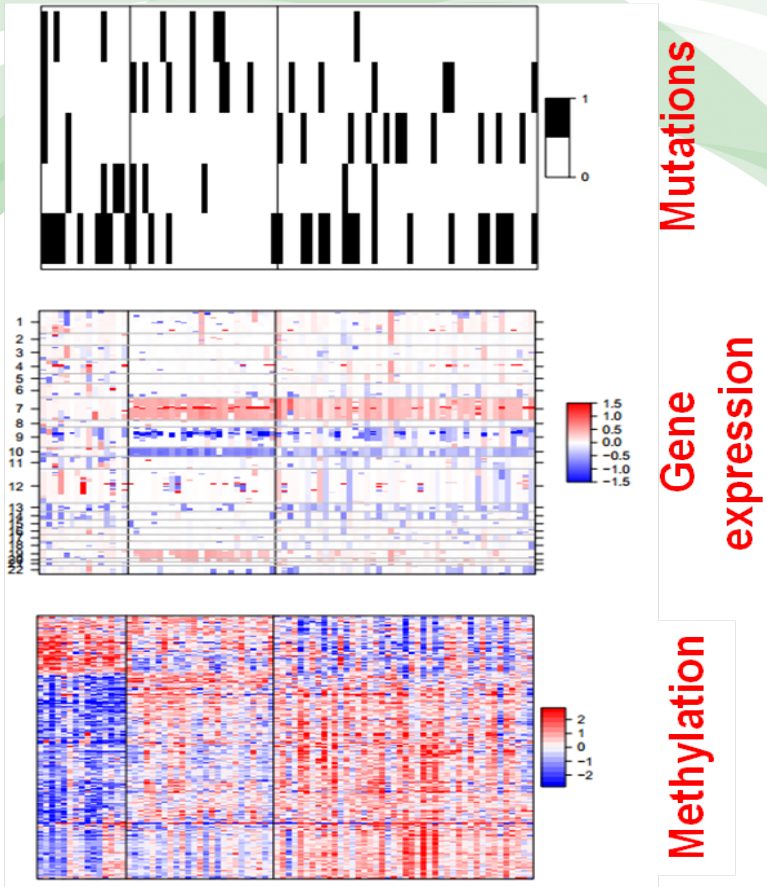
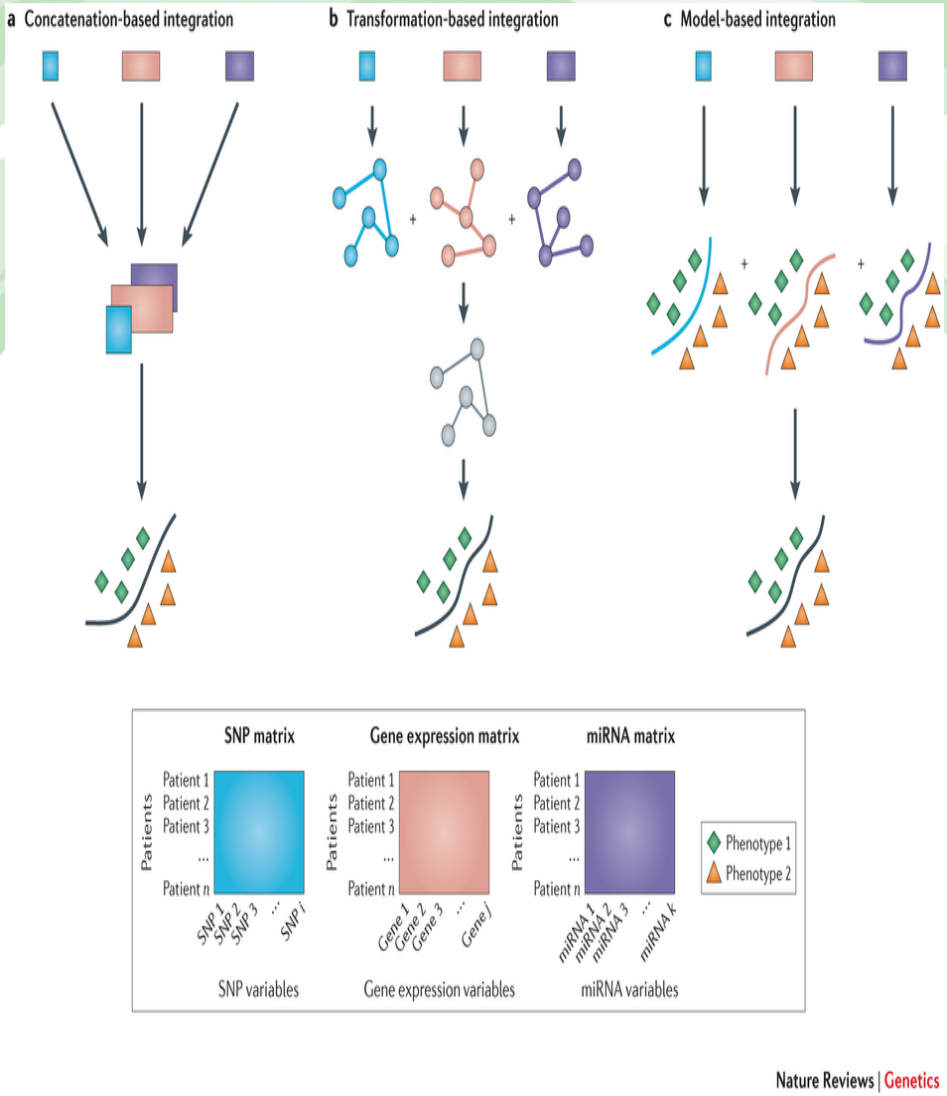


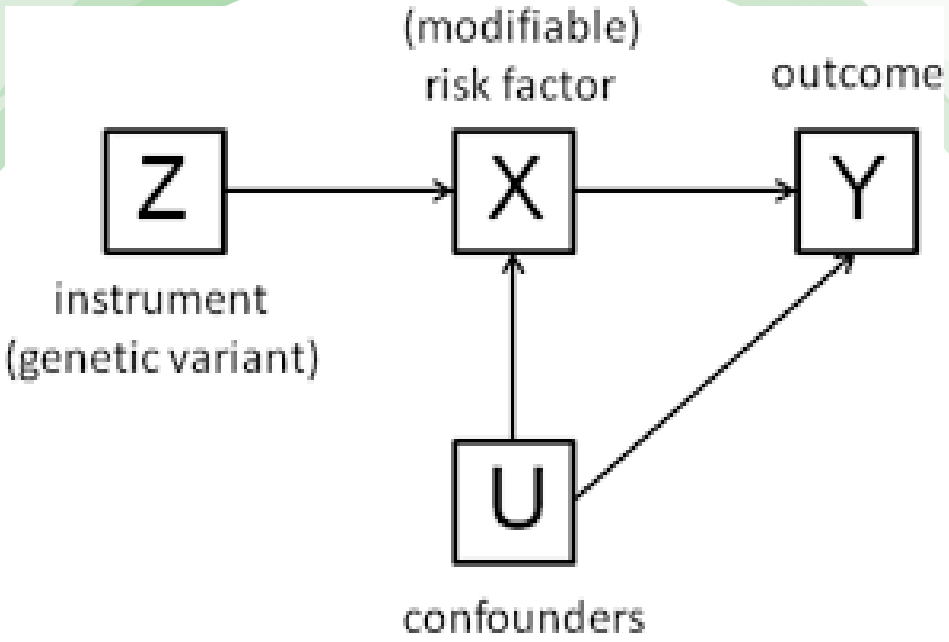
# Introduction

- Data integration (Integrative bioinformatics, integrated analysis, crossomics, multi-dataset analysis, data fusion, ...) is being crucial in Bioinformatics/Biology/Epidemiology
- Data integration may refer to different aspects
  - Computational combination of data (sets)
  - Simultaneous analysis of different variables from different tables, different time points, different tissues, ...
  - Provide biological insights by using information from existing databases (ENCODE, GTEX, KEGG, ...)
- Here we mean the process by which different types of data are combined as predictor variables to allow more thorough and comprehensive modelling of complex traits or phenotypes

# Types of meta-dimensional analyses

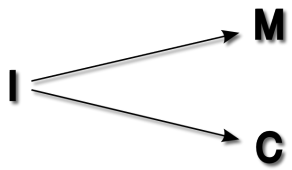


# Mendelian randomization



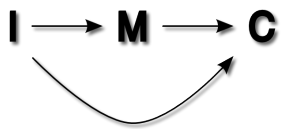
# Conditional Tests

A) Independencia / Asociación

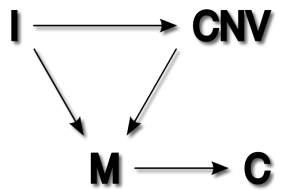



B) Causal


C) Causal / Asociación




D) Complejo



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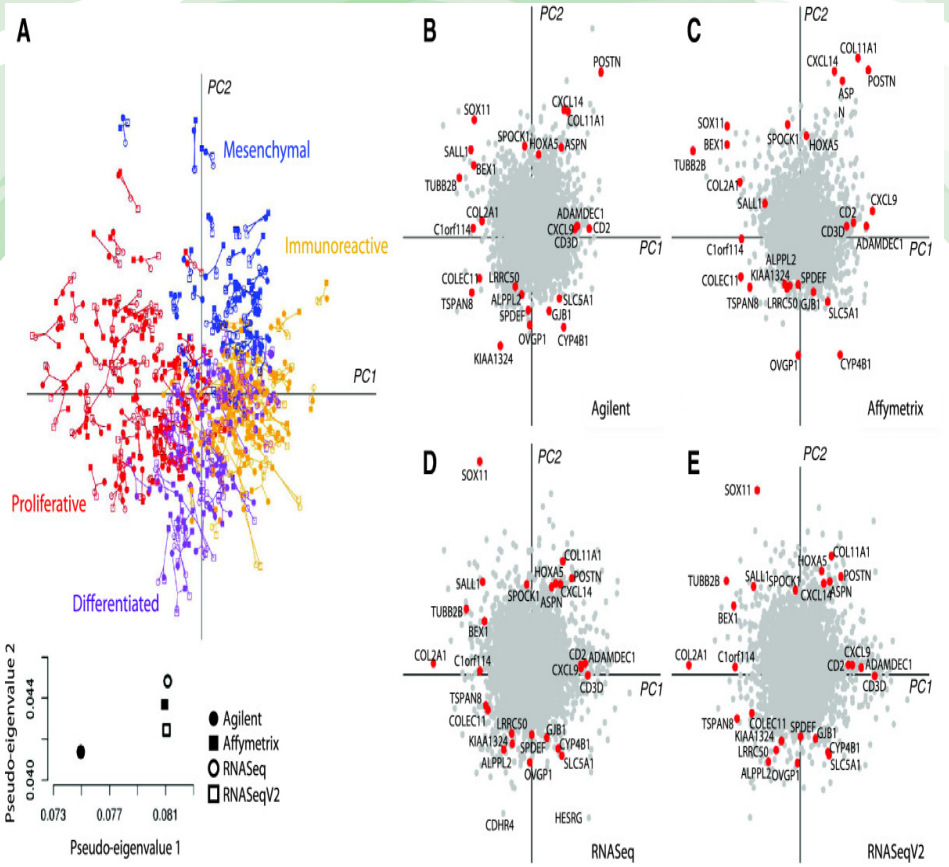
# Multiple dataset: dimensionality reduction



# Integrating two or more datasets

- There are methods based on dimension reduction techniques: generalized SVD, Co-Inertia Analysis (CIA), sparse or penalized extensions of Partial Least Squares (PLS), Canonical Correlation (CCA), Multiple Factor Analysis (MFA), Generalized Canonical Correlation (GCA)
- There are methods that are based on path modelling: structural equation models (SEM)
- Reguralized Generalized Canonical Correlation (RGCA) provides a unified framework for different approaches (Tenenhaus, M. and Tenenhaus, A. Psychometrika, 2011, 76(2):257-284). Other methods are special cases of RGCA.
- RGCA integrates a feature selection method, named sparse GCCA (SGCCA) (Tenenhaus, A et al. Biostatistics, 2014, 15(3):569-83).

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# Integrating two or more datasets

- Canonical Correlation can be seen as an extension of PCA for more than two tables $X$ and $Y$
- The two datasets can be decomposed as:

$$f = Xp$$

$$g = Yq$$

  where $p$ and $q$ are the loading vectors
- CCA searches for association or correlations among $X$ and $Y$ by

$$\arg\max_{p^i q^i} \text{cor}(Xp^i Yq^i)$$

  for the $i$-th component
- $Xp^i$ and $Yq^i$ are known as canonical variates and their correlations are the canonical correlations.

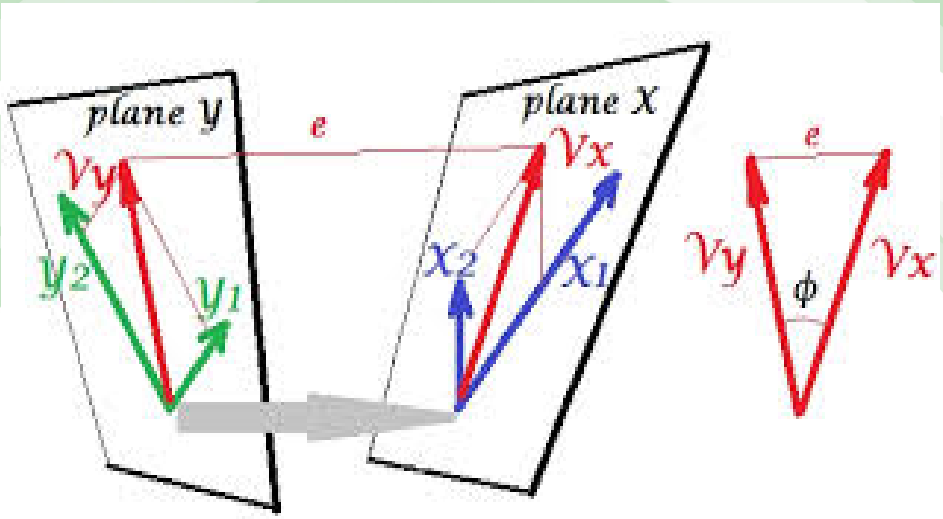
# Integrating two or more datasets

- ($p >> n$) is an issue. Additionally, there is often presence of multicollinearity within both sets of variables that requires a reguralization step.
- This may accomplished by addign a ridge penalty, that is, adding a multiple of the identity matrix to the correlation/covariance matrix.

$$\arg\max_{p^i q^i} \text{cor}(Xp^i Yq^i) + \lambda \mathbf{I}$$

- A sparse solution (filtering the number of variables) is the solution: pCCA, sCCA, CCA-l1, CCA-EN, CCA-group sparse have been used to integrate two omic data.

# Integrating two or more datasets




$V_y$ and $V_x$ are selected to maximize:

- Correlation (CCA)
- Squared Covariance (CIA)

$$\arg\max_{p^i q^i} \mathrm{cov}^2(Xp^i\, Yq^i)$$

# Canonical Correlation

- CCA has been used in omic data
- The main limitation is that the number of features generally greatly exceeds the number of observations
- Consequence 1: parameter estimation cannot be applied using standard methods
- Consequence 2: Most of markers are having no effect in the canonical axes (e.g. almost all components in a and b are 0)
- Penalized (sparse) CCA has been proposed
- Main advantages: More than two tables, easy interpretation (do not need computing p-values nor correcting for multiple comparisons)

# Sparse canonical correlation

$$
\begin{aligned}
U_1 &= a_{11}X_1 + a_{12}X_2 + \cdots + a_{1p}X_p \\
U_2 &= a_{21}X_1 + a_{22}X_2 + \cdots + a_{2p}X_p \\
&\vdots \\
U_p &= a_{p1}X_1 + a_{p2}X_2 + \cdots + a_{pp}X_p \\
\\
V_1 &= b_{11}Y_1 + b_{12}Y_2 + \cdots + b_{1q}Y_q \\
V_2 &= b_{21}Y_1 + b_{22}Y_2 + \cdots + b_{2q}Y_q \\
&\vdots \\
V_p &= b_{p1}Y_1 + b_{p2}Y_2 + \cdots + b_{pq}Y_q
\end{aligned}
$$

a and b for i-th cannonical variable is obtained by maximizing

$$\rho_i^* = \frac{\operatorname{cov}(U_i, V_i)}{\sqrt{\operatorname{var}(U_i)\operatorname{var}(V_i)}}$$

Subject to:

$\|a\|^2 \leq 1$ and $\|b\|^2 \leq 1$

# Co-Inertia

- CIA does not requires an inversion step of the covariance matrix; thus, regularization or penalization implementation is not required
- CIA can deal with disperse variables
- CIA does consider quantitative or qualitative variables
- Can weight cases
- The method provides the RV coefficient. This is a measure of global similarity between the datasets, and is a number between 0 and 1. The closer it is to 1 the greater the global similarity between the two datasets.

# Data analysis illustration

- Data from the Cancer Genome Atlas (TCGA) will be analyzed.
- A subset of the TCGA breast cancer study from Nature 2012 publication have been selected.
- Data `https://tcga-data.nci.nih.gov/docs/publications/brca_`
- Available data are: miRNA, miRNAprecursor, RNAseq, Methylation, proteins from a RPPA array, and GISTIC SNP calls (CNA and LOH). Clinical data are also available.
- We are interested in comparing women with ER+ vs ER-.

```
load("data/breast_TCGA.RData")
group <- droplevels(breast_multi$clin$ER.Status)
```

# Canonical Correlation: gene expression and proteins

```
require(CCA)
df1 <- t(breast_multi$RNAseq)[,1:1000]
df2 <- t(breast_multi$RPPA)
```

```
resCC <- cc(df1, df2)
```

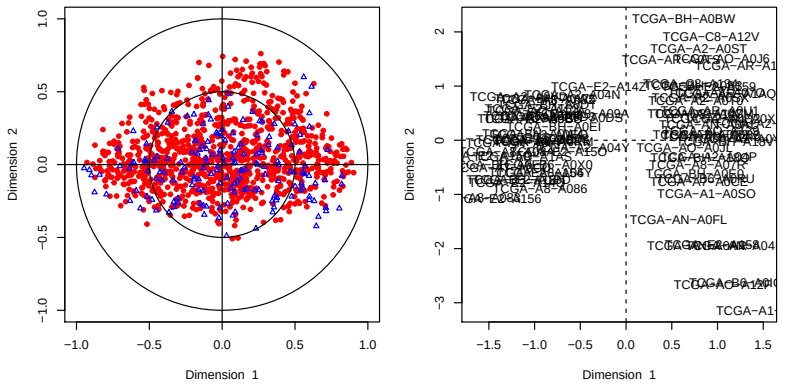
```
Error en chol.default(Bmat) :
  la submatriz de orden 81 no es definida positiva
```

```
resRCC <- rcc(df1, df2, 0.2, 0.1)
```

```
regul <- estim.regul(df1, df2)
resRCC2 <- rcc(df1, df2, regul$lambda1, regul$lambda2)
```

```
plt.cc(resRCC)
```

# Canonical Correlation: gene expression and proteins



# Canonical Correlation: gene expression and proteins

```
require(PMA)
ddlist <- list(df1, df2)
perm.out <- MultiCCA.permute(ddlist,
                             type=c("standard", "standard"),
                             trace=FALSE)
```

```
resMultiCCA <- MultiCCA(ddlist,
                        penalty=perm.out$bestpenalties,
                        ws=perm.out$ws.init,
                        type=c("standard", "standard"),
                        ncomponents=1, trace=FALSE, standardize=TRUE)
```

NOTE: setting `type` equal to "ordered" allows to consider that features are correlated (e.g. genomic regions)

# Canonical Correlation: gene expression and proteins

```
rownames(resMultiCCA$ws[[1]]) <- colnames(df1)
rownames(resMultiCCA$ws[[2]]) <- colnames(df2)
head(resMultiCCA$ws[[1]])
```

```
##                  [,1]
## CREB3L1   0.030502191
## PNMA1     0.035339312
## MMP2      0.000000000
## C10orf90 -0.009616231
## GPR98     0.049652420
## APBB2     0.084521773
```

```
head(resMultiCCA$ws[[2]])
```

```
##                    [,1]
## c.Myc       -0.03022533
## HER3         0.00000000
## XBP1         0.00000000
## Fibronectin  0.00000000
## PAI.1        0.00000000
## p21          0.00000000
```

NOTE: we are interested in selecting those features having a coefficient (`ws`) different from 0.

# Co-inertia: gene expression and proteins

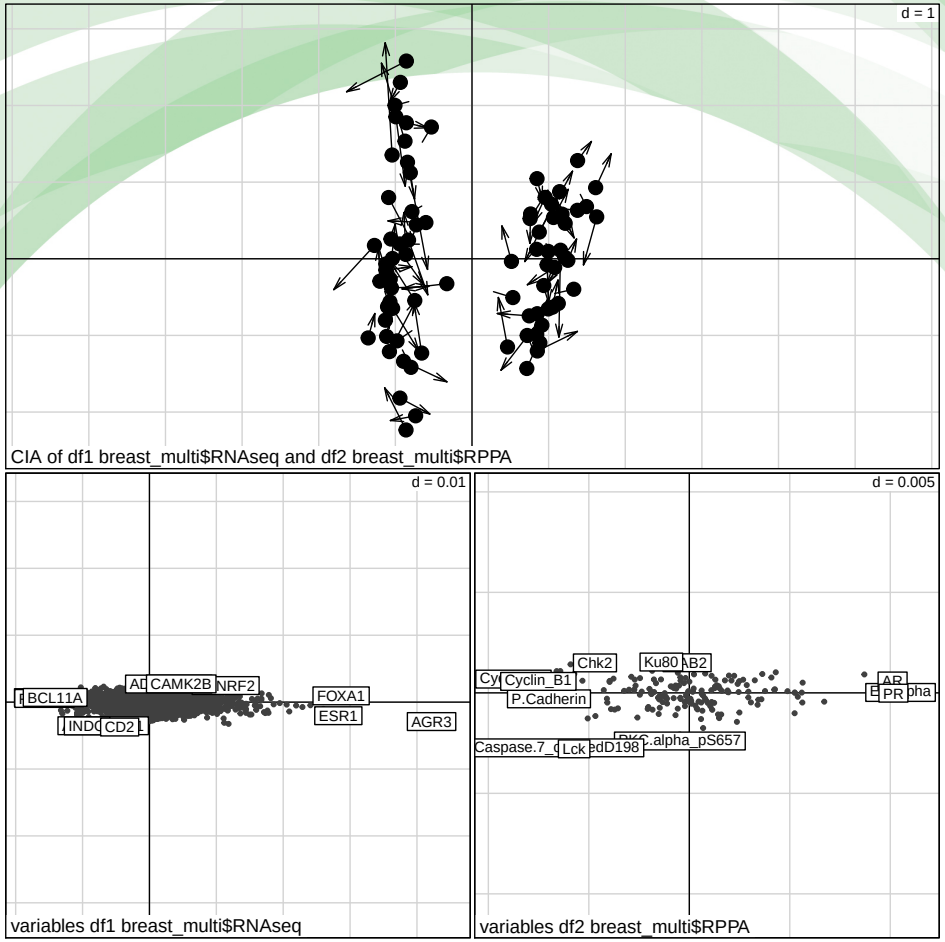
Let us load required packages (coinertia and multiple coinertia)

```
library(made4)
library(omicade4)
```

```
resCIA <- cia(breast_multi$RNAseq, breast_multi$RPPA)
```

```
plot(resCIA, classvec=group, nlab=3, clab=0, cpoint=3 )
```

# Co-inertia: gene expression and proteins



# Co-inertia: gene expression and proteins

Top-5 features of the first axis (positive side) can be retrieve by

```
topVar(resCIA, axis=1, topN=5, end="positive")
```

```
##   ax1_df1_positive ax1_df2_positive
## 1             AGR3         ER.alpha
## 2            FOXA1               PR
## 3             ESR1               AR
## 4             AGR2           INPP4B
## 5         C1orf64            GATA3
```

# Co-inertia: gene expression and proteins

Top-5 features of the first axis (negative side) can be retrieve by

```
topVar(resCIA, axis=1, topN=5, end="negative")
```

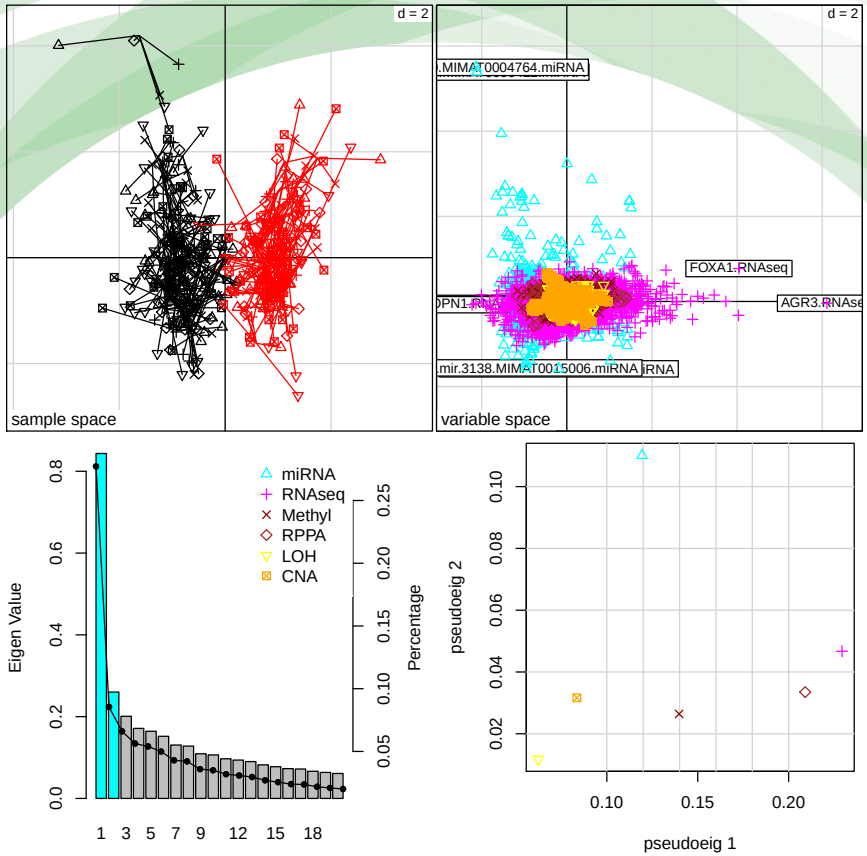
```
##   ax1_df1_negative      ax1_df2_negative
## 1            ROPN1             Cyclin_E1
## 2          ROPN1B             Cyclin_B1
## 3          BCL11A            P.Cadherin
## 4            ART3                  MSH6
## 5           SFRP1 Caspase.7_cleavedD198
```

# More than two tables

```
resMCIA <- mcia( breast_multi[ c(1,3,4,5,6,7) ] )
```

```
plot(resMCIA, axes=1:2, sample.lab=FALSE, sample.legend=FALSE,
     phenovec=group, gene.nlab=2,
     df.color=c("cyan", "magenta", "red4", "brown","yellow", "orange")
     df.pch=2:7)
```

# More than two tables



# More than two tables

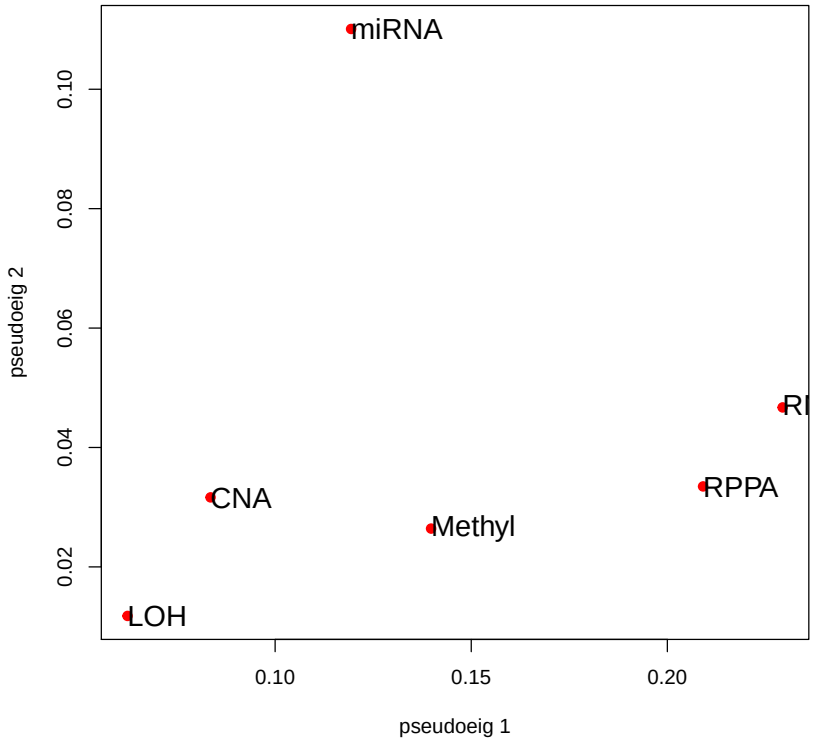
Top-5 features of the first axis (positive side) can be retrieve by

```
topVar(resMCIA, end="positive", axis=1, topN=5)
```

```
##                 ax1_miRNA_positive ax1_RNAseq_positive ax1_Methyl_po
## 1 hsa.mir.4254.MIMAT0016884.miRNA          AGR3.RNAseq   cg08097882.
## 2 hsa.mir.3945.MIMAT0018361.miRNA         FOXA1.RNAseq   cg09952204.
## 3 hsa.mir.302b.MIMAT0000715.miRNA          ESR1.RNAseq   cg04988423.
## 4 hsa.mir.1265.MIMAT0005918.miRNA          AGR2.RNAseq   cg00679738.
## 5 hsa.mir.3171.MIMAT0015046.miRNA      C1orf64.RNAseq   cg12601757.
##   ax1_RPPA_positive ax1_LOH_positive ax1_CNA_positive
## 1     ER.alpha.RPPA        X4006.LOH        X8374.CNA
## 2           AR.RPPA        X4007.LOH        X8381.CNA
## 3           PR.RPPA        X4008.LOH        X8382.CNA
## 4       INPP4B.RPPA        X4009.LOH        X8383.CNA
## 5        GATA3.RPPA        X4010.LOH        X8384.CNA
```

# More than two tables

```
plot(resMCIA$mcoa$cov2,  xlab = "pseudoeig 1",
     ylab = "pseudoeig 2", pch=19, col="red")
text(resMCIA$mcoa$cov2, labels=rownames(resMCIA$mcoa$cov2),
     cex=1.4, adj=0)
```



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# RGCCA

- RGCCA allows to combine tables with different types of variables between blocks
- The objective of RGCCA is to find, for each block (talbe), a weighted composite of variables (called block component) $\mathbf{y}_j = \mathbf{X}_j\mathbf{a}_j, j = 1, \ldots, J$ (where $\mathbf{a}_j$ is a column-vector with $p_j$ elements) summarizing the relevant information between and within the blocks.
- The block components are obtained such that (i) block components explain well their own block and/or (ii) block components that are assumed to be connected are highly correlated.
- RGCCA has been extended to integrate a variable selection procedure, called SGCCA, allowing the identification of the most relevant features.

# RGCCA

RGCCA (Tenenhaus, M. et al. Psychometrika, 2001 and Tenenhaus A et al, Psychometrika, 2017) is defined as the next optimization problem:

$$\underset{\mathbf{a}_1,\mathbf{a}_2,\ldots,\mathbf{a}_J}{\text{maximize}} \sum_{j,k=1}^{J} c_{jk} g(\text{cov}(\mathbf{X}_j\mathbf{a}_j, \mathbf{X}_k\mathbf{a}_k))$$

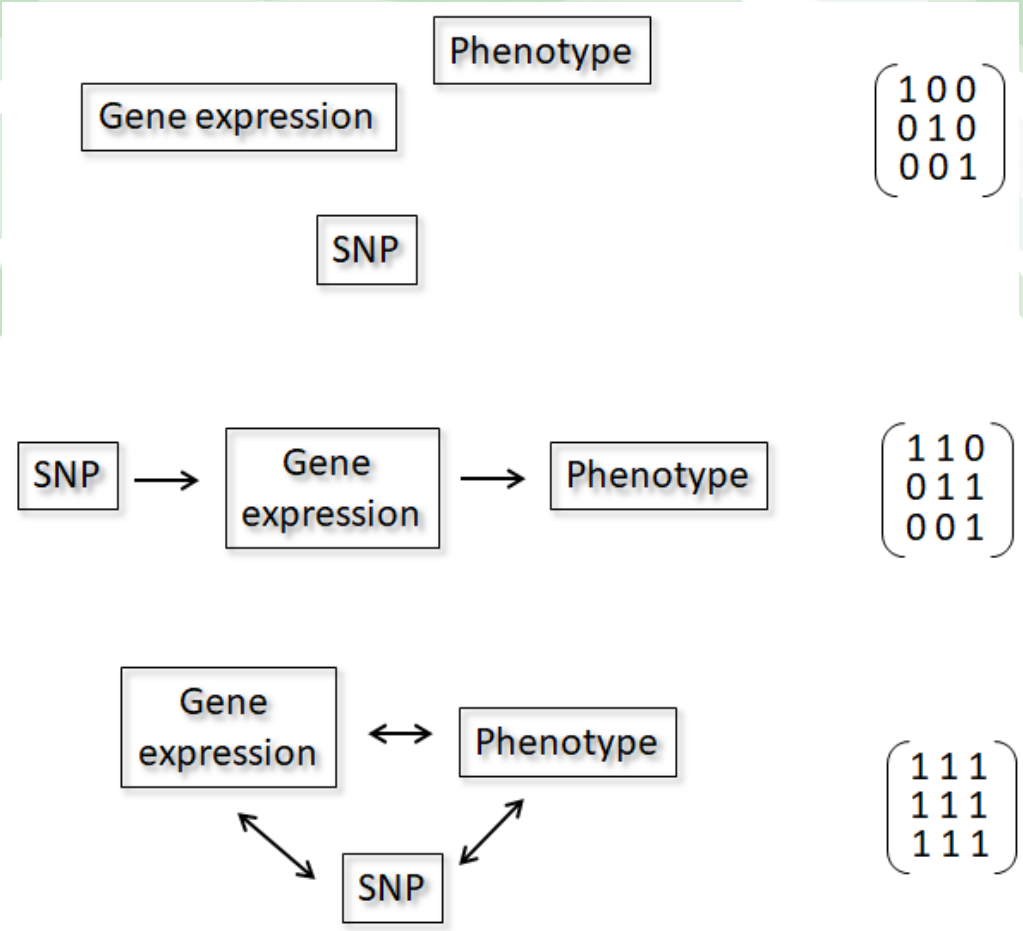
$$\text{s.t.} \quad (1\text{-}\tau_j)\text{var}(\mathbf{X}_j\mathbf{a}_j) + \tau_j\|\mathbf{a}_j\|^2 = 1, j = 1, \ldots, J$$

# RGCCA

- The scheme function $g$ is any continuous convex function and allows to consider different optimization criteria.
  - identity (horst scheme, leading to maximizing the sum of covariances between block components)
  - the absolute value (centroid scheme, yielding maximization of the sum of the absolute values of the covariances)
  - the square function (factorial scheme, thereby maximizing the sum of squared covariances)
  - any even integer $m$, $g(x) = x^m$
- A fair model is a model where all blocks contribute equally to the solution ($m = 1$)
- $m > 1$ is preferable if the user wants to discriminate between blocks.
- In practice, $m$ is equal to 1, 2 or 4. The higher the value of $m$ the more the method acts as block selector

The design matrix **C** is a symmetric $J \times J$ matrix of nonnegative elements describing the network of connections between blocks that the user wants to take into account. Usually, $c_{jk} = 1$ for two connected blocks and 0 otherwise.

# RGCCA


Phenotype
Gene expression
SNP
1 0 0
0 1 0
0 0 1
SNP
Gene expression
Phenotype
1 1 0
0 1 1
0 0 1
Gene expression
Phenotype
SNP
1 1 1
1 1 1
1 1 1

# RGCCA

The $\tau_j$ are called shrinkage parameters ranging from 0 to 1 and interpolate smoothly between maximizing the covariance and maximizing the correlation

- $\tau_j = 1$ yields the maximization of a covariance-based criterion. It is recommended when the user wants a stable component (large variance) while simultaneously taking into account the correlations between blocks. The user must, however, be aware that variance dominates over correlation.
- $\tau_j = 0$ yields the maximization of a correlation-based criterion. It is recommended when the user wants to maximize correlations between connected components. This option can yield unstable solutions in case of multi-collinearity and cannot be used when a data block is rank deficient (e.g. $n < p_j$).
- $0 < \tau_j < 1$ is a good compromise between variance and correlation: the block components are simultaneously stable and as well correlated as possible with their connected block components. This setting can be used when the data block is rank deficient.

# PCA as RGCCA

Principal Component Analysis is defined as the following optimization problem

$$\underset{\mathbf{a}}{\text{maximize}} \ \text{var}(\mathbf{Xa}) \ \text{s.t.} \ \|\mathbf{a}\| = 1$$

and is obtained with the ‘rgcca()‘ function as follows:

```
# Design matrix C
# Shrinkage parameters tau = c(tau1, tau2)

pca.with.rgcca = rgcca(A = list(X, X),
                       C = matrix(c(0, 1, 1, 0), 2, 2),
                       tau = c(1, 1))
```

# CCA as RGCCA

Canonical Correlation Analysis is defined as the following optimization problem

$$\underset{\mathbf{a}_1,\mathbf{a}_2}{\text{maximize}} \quad \text{cor}\left(\mathbf{X}_1\mathbf{a}_1, \mathbf{X}_2\mathbf{a}_2\right) \text{ s.t. } \text{var}(\mathbf{X}_1\mathbf{a}_1) = \text{var}(\mathbf{X}_2\mathbf{a}_2) = 1$$

and is obtained with the 'rgcca()' function as follows:

```
# X1 = Block1 and X2 = Block2
# Design matrix C
# Shrinkage parameters tau = c(tau1, tau2)

cca.with.rgcca = rgcca(A= list(X1, X2),
                       C = matrix(c(0, 1, 1, 0), 2, 2),
                       tau = c(0, 0))
```

# PLS as RGCCA

PLS regression is defined as the following optimization problem

$$\underset{\mathbf{a}_1,\mathbf{a}_2}{\text{maximize}} \quad \text{cov}\left(\mathbf{X}_1\mathbf{a}_1, \mathbf{X}_2\mathbf{a}_2\right) \text{ s.t. } \|\mathbf{a}_1\| = \|\mathbf{a}_2\| = 1$$

and is obtained with the ‘rgcca()‘ function as follows:

```
# X1 = Block1 and X2 = Block2
# Design matrix C
# Shrinkage parameters tau = c(tau1, tau2)

pls.with.rgcca = rgcca(A= list(X1, X2),
                       C = matrix(c(0, 1, 1, 0), 2, 2),
                       tau = c(1, 1))
```

# RDA as RGCCA

Redundancy Analysis of $\mathbf{X}_1$ with respect to $\mathbf{X}_2$ is defined as the following optimization problem

$$\underset{\mathbf{a}_1,\mathbf{a}_2}{\text{maximize}} \quad \text{cor}\left(\mathbf{X}_1\mathbf{a}_1, \mathbf{X}_2\mathbf{a}_2\right) \times \text{var}\left(\mathbf{X}_1\mathbf{a}_1\right)^{1/2} \text{ s.t. } \|\mathbf{a}_1\| = \text{var}(\mathbf{X}_2\mathbf{a}_2) = 1$$

and is obtained with the 'rgcca()' function as follows:

```
# X1 = Block1 and X2 = Block2
# Design matrix C
# Shrinkage parameters tau = c(tau1, tau2)

ra.with.rgcca = rgcca(A= list(X1, X2),
                      C = matrix(c(0, 1, 1, 0), 2, 2),
                      tau = c(1, 0))
```

# GCCA as RGCCA

For Generalized Canonical Correlation Analysis (GCCA), a superblock $\mathbf{X}_{J+1} = [\mathbf{X}_1, \ldots, \mathbf{X}_J]$ defined as the concatenation of all the blocks is introduced. GCCA is defined as the following optimization problem

$$\underset{\mathbf{a}_1,\mathbf{a}_2,\ldots,\mathbf{a}_J}{\text{maximize}} \sum_{j=1}^{J} \text{cor}^2(\mathbf{X}_j\mathbf{a}_j, \mathbf{X}_{J+1}\mathbf{a}_{J+1}) \text{ s.t } \text{var}(\mathbf{X}_j\mathbf{a}_j) = 1, j = 1, \ldots, J+1$$

and is obtained with the ‘rgcca()‘ function as follows:

```
# X1 = Block1, ..., XJ = BlockJ, X_{J+1} = [X1, ..., XJ]
# (J+1)*(J+1) Design matrix C
C = matrix(c(0, 0, 0, ..., 0, 1,
             0, 0, 0, ..., 0, 1,
                    ...
             1, 1, 1, ..., 1, 0), J+1, J+1)
# Shrinkage parameters tau = c(tau1, ...,  tauJ, tau_{J+1})
gcca.with.rgcca = rgcca(A= list(X1, ..., XJ, cbind(X1, ..., XJ)),
                        C = C, tau = rep(0, J+1),
                        scheme = "factorial")
```

# MCIA as RGCCA

For Multiple Co-Inertia Analysis (MCIA) a superblock $\mathbf{X}_{J+1} = [\mathbf{X}_1, \ldots, \mathbf{X}_J$ defined as the concatenation of all the blocks is introduced. MCIA is defined as the following optimization problem

$$\underset{\mathbf{a}_1,\mathbf{a}_2,\ldots,\mathbf{a}_J}{\text{maximize}} \sum_{j=1}^{J} \text{cor}^2(\mathbf{X}_j\mathbf{a}_j, \mathbf{X}_{J+1}\mathbf{a}_{J+1}) \times \text{var}(\mathbf{X}_j\mathbf{a}_j), \quad \text{s.t } \|\mathbf{a}_j\| = 1, j = 1, \ldots, J \text{ and} \tag{1}$$

and is obtained with the 'rgcca()' function as follows:

```
# X1 = Block1, ..., XJ = BlockJ, X_{J+1} = [X1, ..., XJ]
# (J+1)*(J+1) Design matrix C
C = matrix(c(0, 0, 0, ..., 0, 1,
             0, 0, 0, ..., 0, 1,
                ...
             1, 1, 1, ..., 1, 0), J+1, J+1)
# Shrinkage parameters tau = c(tau1, ..., tauJ, tau_{J+1})
mcoa.with.rgcca = rgcca(A= list(X1, ..., XJ, cbind(X1, ..., XJ)),
                        C = C, tau = c(rep(1, J), 0),
                        scheme = "factorial")
```

# RGCCA data analysis

Data must be preprocessed to ensure comparability between variables. Standardization is applied (zero mean and unit variance).

```
library(RGCCA)
load("data/breast_TCGA.RData")
X <- t(breast_multi$RNAseq)
Y <- t(breast_multi$miRNA)
Z <- t(breast_multi$RPPA)
A <- list(rnaseq=X, miRNA=Y, RPPA=Z)
A <- lapply(A, scale)
```

NOTE: A possible strategy is to standardize the variables and then to divide each block by the square root of its number of variables. This two-step procedure leads to $\mathrm{tr}(\mathbf{X}_j^t \mathbf{X}_j) = n$ for each block (i.e. the sum of the eigenvalues of the covariance matrix of $\mathbf{X}_j$ is equal to 1 whatever the block). Such a preprocessing is reached by setting the 'scale' argument to 'TRUE' (default value) in the 'rgcca()' and 'sgcca()' functions.

# RGCCA data analysis

Let us assume that both miRNA and mRNa are affecting the protein levels. Therefore the **C** matrix will be

```
C <- matrix(c(1,0,1,0,1,1,0,0,1), nrow=3, byrow = TRUE)
C
```

```
##      [,1] [,2] [,3]
## [1,]    1    0    1
## [2,]    0    1    1
## [3,]    0    0    1
```

# RGCCA data analysis

RGCCA using the defined design matrix **C**, the factorial scheme ($g(x) = x^2$) and mode B for all blocks (full correlation criterion) is obtained by

```
rgcca.factorial <- rgcca(A, C=C, tau = rep(0, 3),
                         scheme ="factorial", ncomp=c(2,2,2),
                         scale = FALSE, verbose = FALSE)
```

The weight vectors, solution of the optimization problemare obtained as:

```
rgcca.factorial$a # weight vectors
```

# RGCCA data analysis

The block-components are also avalaible as output of ‘rgcca‘. The first components of each block are given by:

```
Y.block <- rgcca.factorial$Y
lapply(Y.block, head)

## [[1]]
##                    comp1      comp2
## TCGA-C8-A12V -1.4043762 -0.5590542
## TCGA-A2-A0ST -1.3471553 -2.3964964
## TCGA-E2-A159 -0.5738528  0.8281707
## TCGA-BH-A0BW -0.2061025  0.4681924
## TCGA-A2-A0SX -0.8960506  0.1448149
## TCGA-AR-A1AI -1.2582255  0.4333885
##
## [[2]]
##                    comp1      comp2
## TCGA-C8-A12V -1.4043119 -0.5584358
## TCGA-A2-A0ST -1.3470213 -2.3960350
## TCGA-E2-A159 -0.5738116  0.8287364
## TCGA-BH-A0BW -0.2062718  0.4694125
## TCGA-A2-A0SX -0.8958721  0.1451569
## TCGA-AR-A1AI -1.2582603  0.4338262
##
## [[3]]
##                    comp1      comp2
```

# RGCCA data analysis

Information about Average Variance Explained (AVE)
- The AVE of block $\mathbf{X}_j$, denoted by AVE($\mathbf{X}_j$), is defined as:

$$\text{AVE}(\mathbf{X}_j) = 1/p_j \sum_{h=1}^{p_j} cor^2(\mathbf{x}_{jh}, \mathbf{y}_j)$$

AVE($\mathbf{X}_j$) varies between 0 and 1 and reflects the proportion of variance captured by $\mathbf{y}_j$.
- For all blocks:

$$\text{AVE(outermodel)} = \left(1/\sum_j p_j\right) \sum_j p_j \text{AVE}(\mathbf{X}_j)$$

- For the inner model:

$$\text{AVE(innermodel)} = \left(1/\sum_{j<k} c_{jk}\right) \sum_{j<k} c_{jk} \text{cor}^2(\mathbf{y}_j, \mathbf{y}_k)$$

# RGCCA data analysis

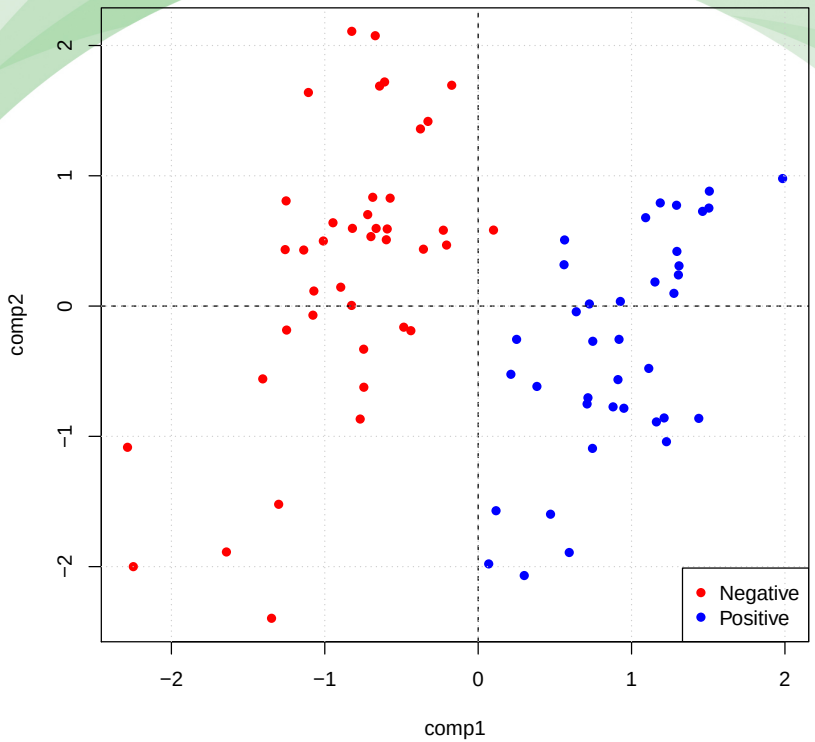
```
rgcca.factorial$AVE

## $AVE_X
## $AVE_X[[1]]
##     comp1     comp2
## 0.1470807 0.0303539
##
## $AVE_X[[2]]
##      comp1      comp2
## 0.06683530 0.02441686
##
## $AVE_X[[3]]
##      comp1      comp2
## 0.17983101 0.07924063
##
##
## $AVE_outer_model
## [1] 0.14088037 0.03060966
##
## $AVE_inner_model
## [1] 1 1
```

# RGCCA data analysis

## Plot individuals

```
source("R/plotInd.R")
plotInd(rgcca.factorial, group)
```

# RGCCA data analysis



# RGCCA data analysis

Features first axis right side (e.g. ER+)

```
source("R/topVars.R")
topVars(rgcca.factorial, axis=1, end="pos", topN=5)

##       table_1   table_2                       table_3
## top_1 "PGLYRP2" "hsa-mir-29b-2.MIMAT0004515" "ER.alpha"
## top_2 "TMEM163" "hsa-mir-29c.MIMAT0004673"   "PR"
## top_3 "CYP4F11" "hsa-mir-190b.MIMAT0004929"  "GATA3"
## top_4 "FDXR"    "hsa-mir-664.MIMAT0005949"   "AR"
## top_5 "WBSCR17" "hsa-mir-342.MIMAT0004694"   "INPP4B"
```

# Outline

1 Introduction
2 Integrating two or more omic datasets
3 RGCCA
4 SGCCA
5 Recommended lectures

# SGCCA data analysis

SGCCA extends RGCCA to address the issue of variable selection. Specifically, RGCCA with all $\tau_j = 1$ equal to 1 is combined with an L1-penalty that gives rise to SGCCA (Tenenhaus et al, Biostatistics, 2014). The SGCCA optimization problem is defined as follows:

$$\underset{\mathbf{a}_1,\mathbf{a}_2,\ldots,\mathbf{a}_J}{\text{maximize}} \sum_{j,k=1}^{J} c_{jk} g(\text{cov}(\mathbf{X}_j\mathbf{a}_j, \mathbf{X}_k\mathbf{a}_k)) \text{ s.t. } \|\mathbf{a}_j\|_2 = 1 \text{ and } \|\mathbf{a}_j\|_1 \leq s_j, j = 1, \ldots,$$

where $s_j$ is a user defined positive constant that determines the amount of sparsity for $\mathbf{a}_j, j = 1, \ldots, J$. The smaller the $s_j$, the larger the degree of sparsity for $\mathbf{a}_j$. The sparsity parameter $s_j$ is usually set based on cross-validation procedures. Alternatively, values of $s_j$ can simply be chosen to result in desired amounts of sparsity.

# SGCCA data analysis

Let us assume we are interested in this analysis (prediction problem)

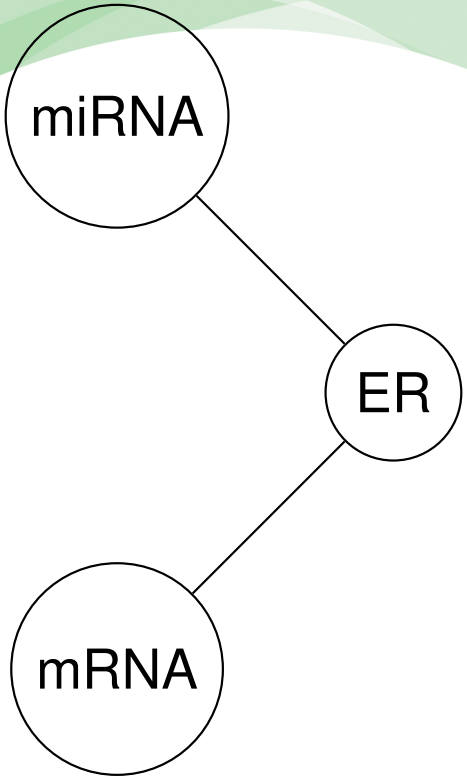



Figure: between-block connection for Breast TCGA data.

# SGCCA data analysis

```
X <- t(breast_multi$RNAseq)
Y <- t(breast_multi$miRNA)
AA <- list(rnaseq=X, miRNA=Y, group=as.numeric(group)-1)
C <-  matrix(c(0, 0, 1, 0, 0, 1, 1, 1, 0), 3, 3)
C
```

```
##      [,1] [,2] [,3]
## [1,]    0    0    1
## [2,]    0    0    1
## [3,]    1    1    0
```

# SGCCA data analysis

Let us estimate the weights for the 1st component

```
sgcca.breast = sgcca(AA, C, c1 = c(.071,.2, 1),
                     ncomp = c(1, 1, 1),
                     scheme = "centroid",
                     scale = TRUE,
                     verbose = FALSE)
```

# SGCCA data analysis

The mRNA associated with ER+ (i.e, positive part of first axis) are (NOTE:results are ordered)

```
source("R/selectVars.R")
ans <- selectVars(sgcca.breast, table=1, axis=1, end="pos")
length(ans)

## [1] 50

ans

##  [1] "CA12"     "FSIP1"    "AGR3"     "ESR1"     "SCUBE2"   "TBC1D9
##  [7] "MLPH"     "FOXA1"    "NAT1"     "C6orf97"  "ABCC8"    "SLC7A8
## [13] "XBP1"     "THSD4"    "INPP4B"   "AGR2"     "C1orf64"  "ABAT"
## [19] "EVL"      "ANXA9"    "IL6ST"    "ERBB4"    "PGR"      "SUSD3"
## [25] "UGCG"     "IGFALS"   "GATA3"    "ACADSB"   "C4orf18"  "NOSTRI
## [31] "SLC39A6"  "TMEM25"   "WFS1"     "STH"      "MAPT"     "KIAA13
## [37] "ENPP1"    "PREX1"    "ABCC11"   "GRPR"     "ANKRD30A" "C14orf
## [43] "JMJD2B"   "C3orf18"  "DNAJC12"  "SIDT1"    "C16orf45" "KRT18"
## [49] "ANKRA2"   "PH-4"
```

# SGCCA data analysis

The miRNA associated with ER+ (e.g. positive part of the first axis) are (NOTE:results are ordered)

```
ans <- selectVars(sgcca.breast, table=2, axis=1, end="pos")
length(ans)

## [1] 5

ans

## [1] "hsa-mir-190b.MIMAT0004929"  "hsa-mir-342.MIMAT0004694"
## [3] "hsa-mir-29b-2.MIMAT0004515" "hsa-mir-29c.MIMAT0004673"
## [5] "hsa-mir-431.MIMAT0004757"
```

# Concluding remarks

Correlation $Y = X$

Multiple correlation $Y = X_1 X_2 X_3 \cdots X_k$

Canonical correlation $Y_1 Y_2 Y_3 \cdots Y_j = X_1 X_2 X_3 \cdots X_k$

- Co-inertia analysis (CIA) is similar to CCA but it optimizes the squared covariance between the eigenvectors while CC optimizes the correlation.
- CIA can be applied to datasets where the number of variables (genes) far exceeds the number of samples (arrays) such is the case in several omic data, while CCA requires a regularized version to be implemented.
- Sparse and reguralized methods requires a tuning parameter. This makes these methods computing demanding.

# Take home messages

- Multivariate methods are purely descriptive methods that do not test a hypothesis to generate a p-value.
- They are not optimized for variable of biomarkers discovery, though the introduction of sparsity in variable loadings may help in the selection of variables forn downstream analyses.
- Number of variables in omic data is a challenge to tradicional visualization tools. New `R` packages including `ggord` are being developed to address this issue.
- Dynamic visualization is possible using `ggvis`, `ploty`, `explor` and other packages.
- Projection in the same space of variable annotation (GO or Reactome) may help to determine gene sets or patwhays associated with our traits.

# Outline

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# Recommended lectures


- Millstein et al. (2009). Disentangling molecular relationships with a causal inference test. BMC Bioinf, 10:23.
- Ebrahim and Smith (2008). Mendelian randomization: can genetic epidemiology help redress the failure of observational epidemiology?. Hum Genet, 123:15-33.
- Liu et al. (2013). Epifenome-wide association data implicate DNA methylation as an intermediary of genetic risk in rheumatoid arthritis. Nat Biotech, 31(2):142-148.
- Voight et al. (2012). Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study. Lancet, 380(9841): 572-580.
- Meng et al. (2014). A multivariate approach to the integration of multi-omics datasets. BMC Bioinf, 15:162.
- Witten et al. (2009). A Penalized Matrix Decomposition, with Applications to Sparse Principal Components and Canonical Correlation Analysis. Biostatistics, 10(3):515-34.
- Meng et al. (2016). Dimension reduction techniques for the integrative analysis of multi-omics data. Brief Bioinform, 17(4): 628-641.
- Tenenhaus A. and Tenenhaus M. (2011). Regularized Generalized Canonical Correlation Analysis. Psychometrika, 76: 257-84.
- Tenenhaus et al. (2014). Variable Selection for Generalized Canonical Correlation Analysis. Biostatistics 15(3):569-83.