Multi-omic data analysis

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1. Introduction
2. Multi-staged analysis
3. Meta-dimensional analysis
   - One omic dataset: dimensionality reduction
   - Integrating two or more omic datasets
4. Recommended lectures

Outline

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2. Multi-staged analysis
3. Meta-dimensional analysis
   - One omic dataset: dimensionality reduction
   - Integrating two or more omic datasets
4. Recommended lectures

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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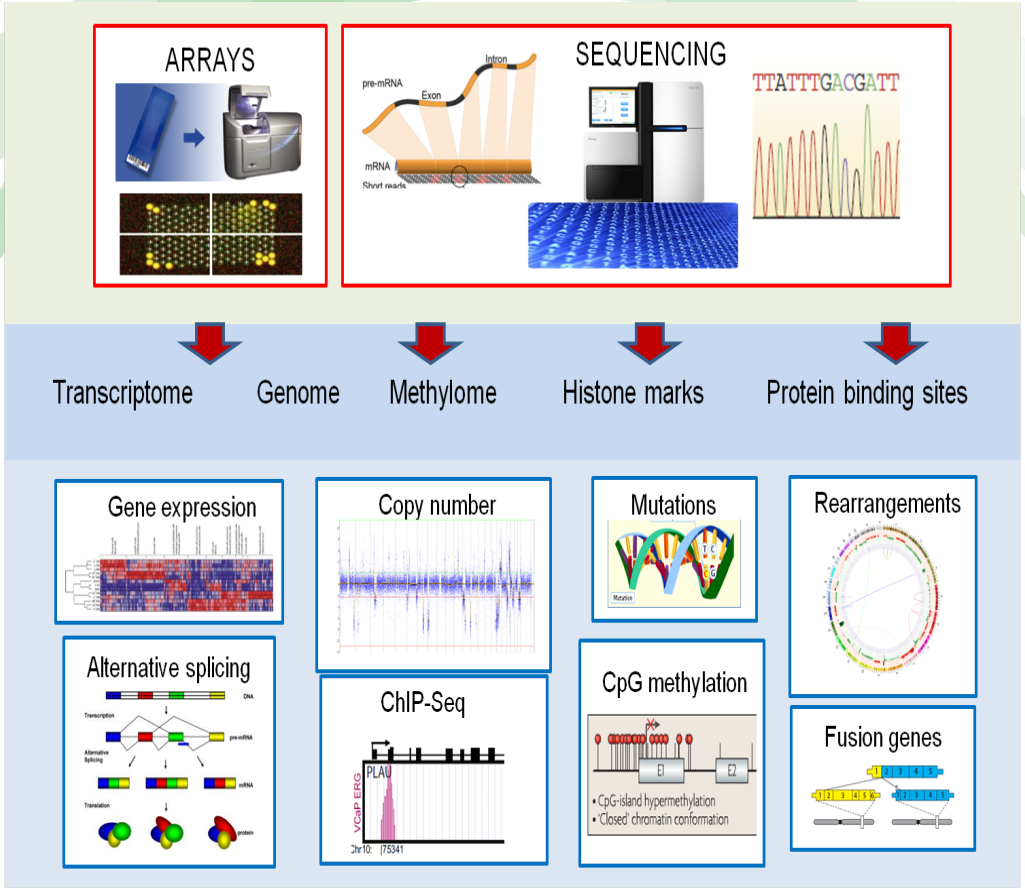
Introduction



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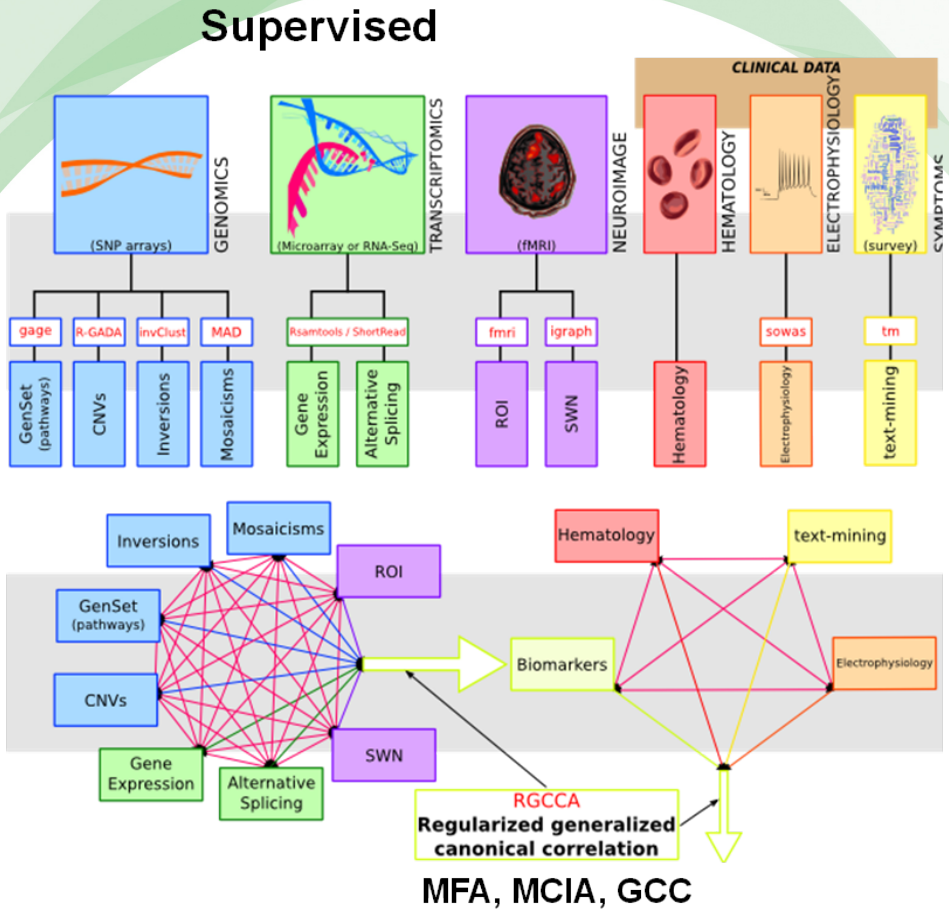

Introduction

- 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 omic data are combined as predictor variables to allow more thorough and comprehensive modelling of complex traits or phenotypes

Introduction

- Multi-staged analysis: Involves integrating information using a stepwise or hierarchical analysis approach
- Meta-dimensional analysis: Refers to the concept of integrating multiple different data types to build a multivariate model associated with a given outcome

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Multi-staged analysis

- Genomic variation analysis approaches: Triangle approach
  1. SNPs are associated with the phenotype of interesed and filtered based on p-values
  2. Significant SNPs are tested for association with another level of omic data (i.e eQTLs)
  3. Omic data used in step 2 are then tested for correlation with phenotype of interest
- Domain knowledge-guided approaches: Integration of functional and pathway information
  1. Significant results (regions of interest) are annotated in databases such as ENCODE, Roadmap Epigenomic Project, KEGG, ...
  2. We an determine whether those regions are within pathways and/or overlaping with functional units, sucha as transcription factors binding, hyper- or hypo-methylated regions
  3. Overlaping regions are then correlated with the phenotype of interest
  4. The main limitation is that this method is biased by current knowledge

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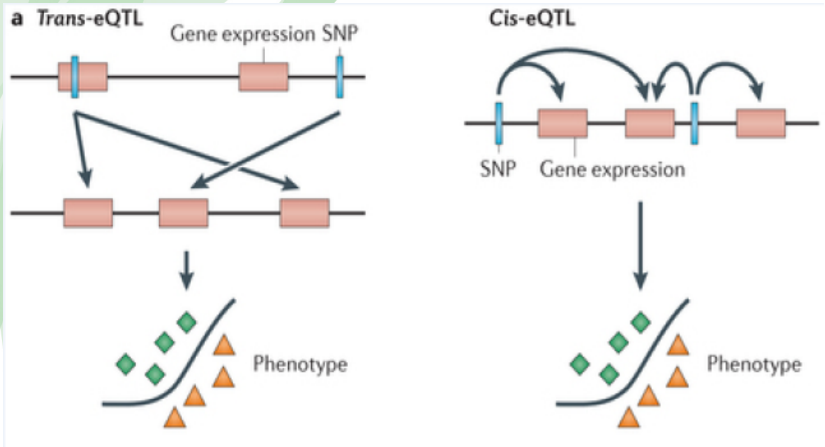
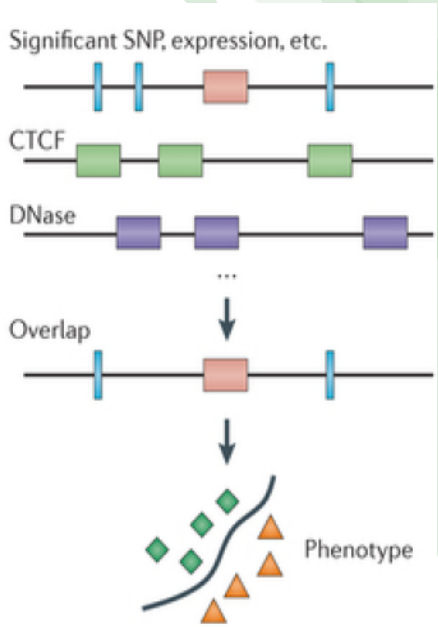
Types of multi-staged analyses

(a) Genomic variation analysis



(b) Domain knowledge-guided



Genomic variation example

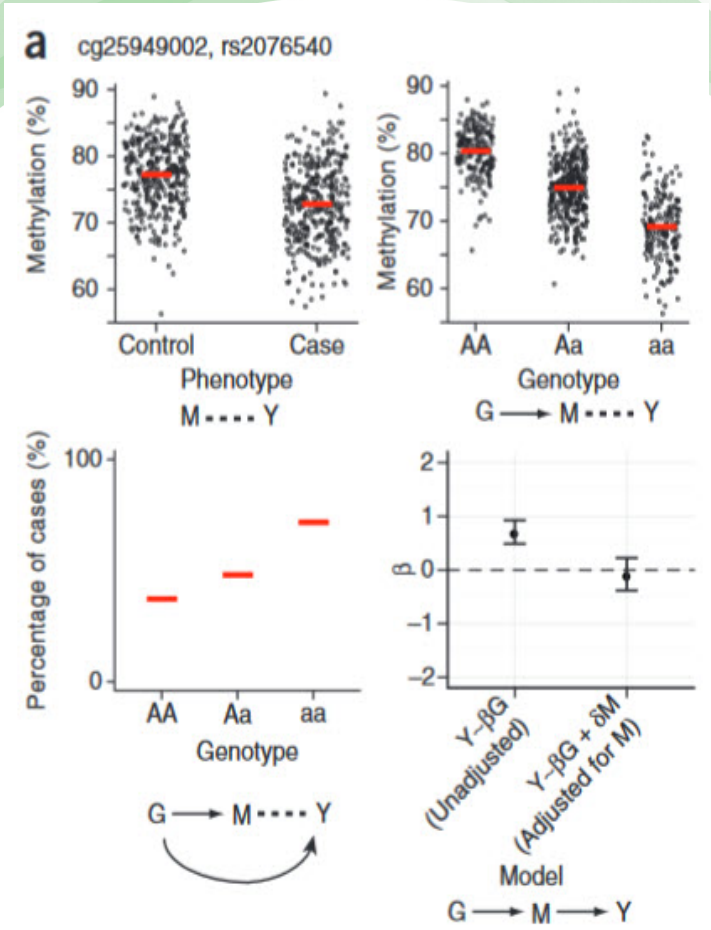
ARTICLES

nature biotechnology

Epigenome-wide association data implicate DNA methylation as an intermediary of genetic risk in rheumatoid arthritis

Yun Liu[1,2,12], Martin J Aryee[1,3,12], Leonid Padyukov[4,5,12], M Daniele Fallin[1,6,7,12], Espen Hesselberg[4,5], Arni Runarsson[1,2], Lovisa Reinius[8], Nathalie Acevedo[9], Margaret Taub[1,6], Marcus Ronninger[4,5], Klementy Shchetynsky[4,5], Annika Scheynius[9], Juha Kere[8], Lars Alfredsson[10], Lars Klareskog[4,5], Tomas J Ekström[5,11] & Andrew P Feinberg[1,2,6]

Genomic variation example

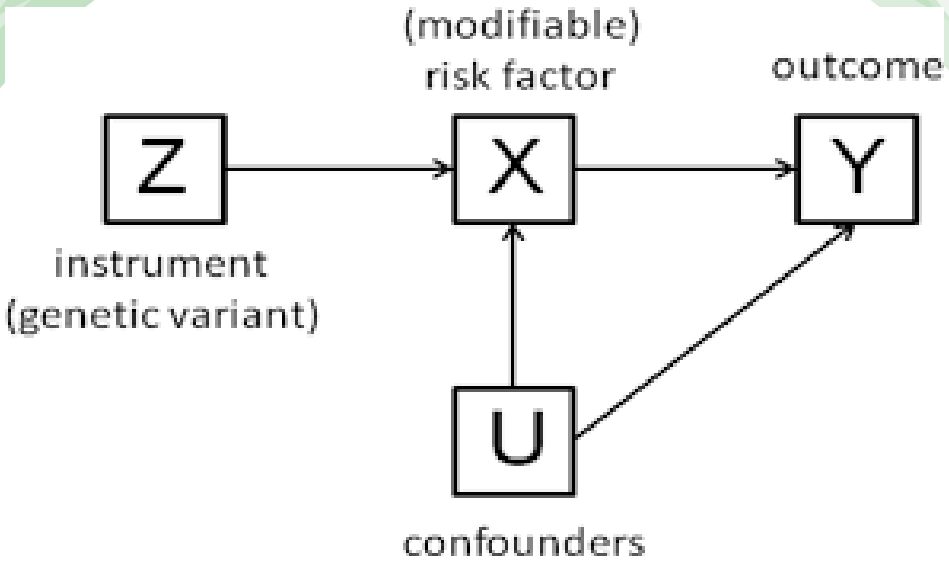


Genomic variation example

- Mediation analysis
- Mendelian randomization (MR)
- Conditional Independent test (CIT)

Mediation: `https://cran.r-project.org/web/packages/mediation/vignettes/mediation.pdf` MR: `https://cran.r-project.org/web/packages/MendelianRandomization/vignettes/Vignette_MR.pdf` CIT:`https://cran.r-project.org/web/packages/cit/`

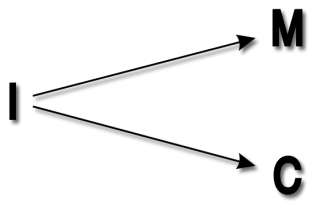
Mediation analysis



See file `mediation.html`

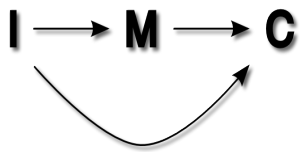
Conditional Independent Test

A) Independencia / Asociación

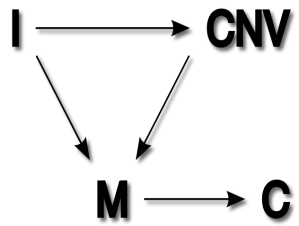


B) Causal

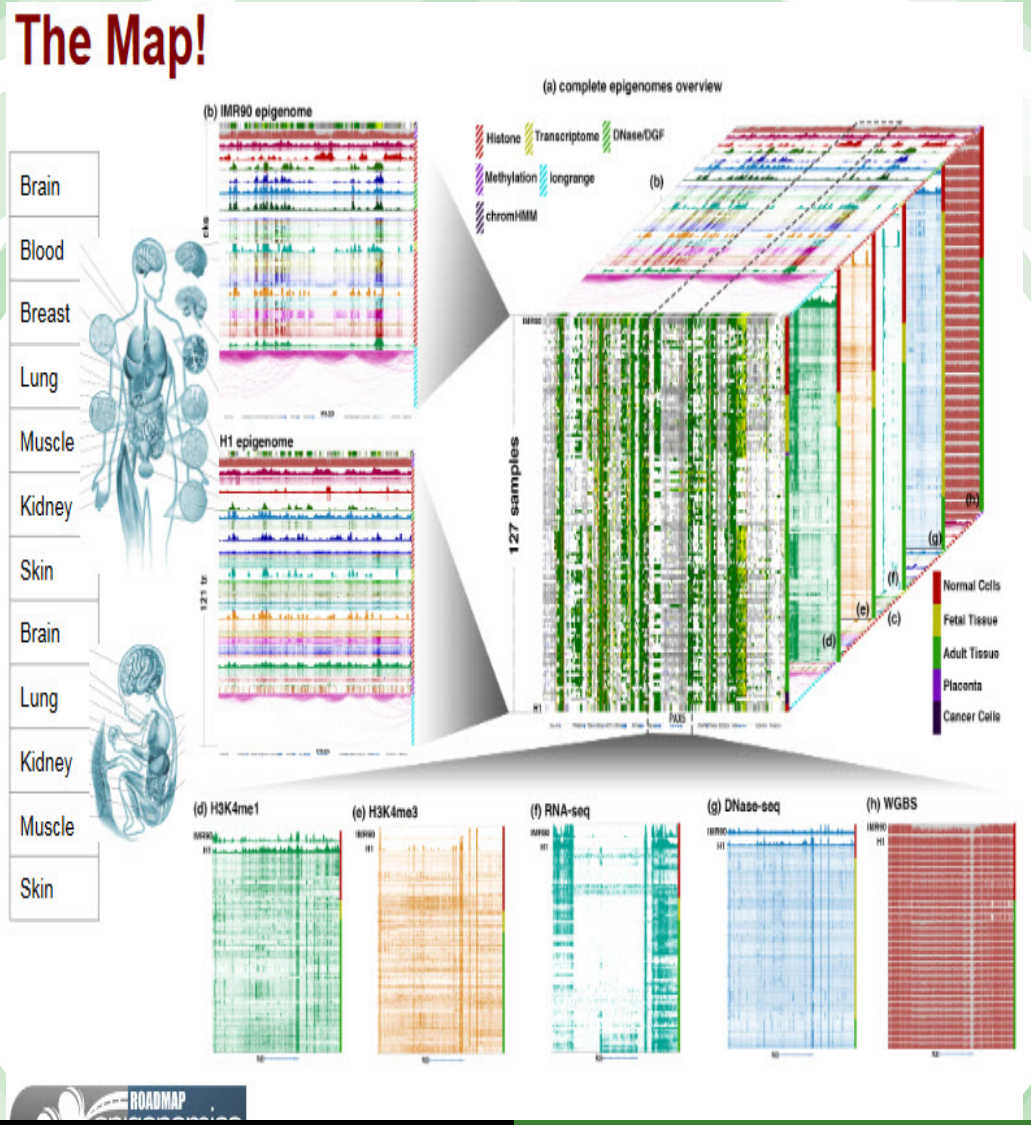
C) Causal / Asociación



D) Complejo



Domain knowledge-guided



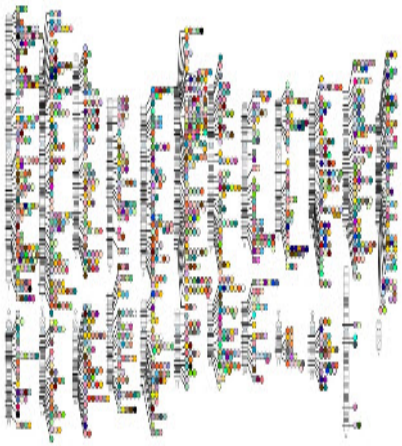
The RoadMap Epigenomics

- Marking of functional genomic elements
- Environmental exposures
- Understanding development and differentiation
- Regenerative medicine (stem and iPS cells)
- Human disease
- Interpreting GWAS
- Biomarkers, diagnostics and therapies
- Exploring cross-talk between epigenomic mechanisms

Domain knowledge-guided

Using Epigenomic Data to Interpret GWAS Data

Gene variants in human disease



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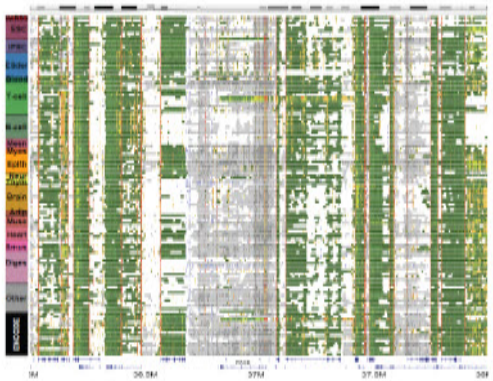
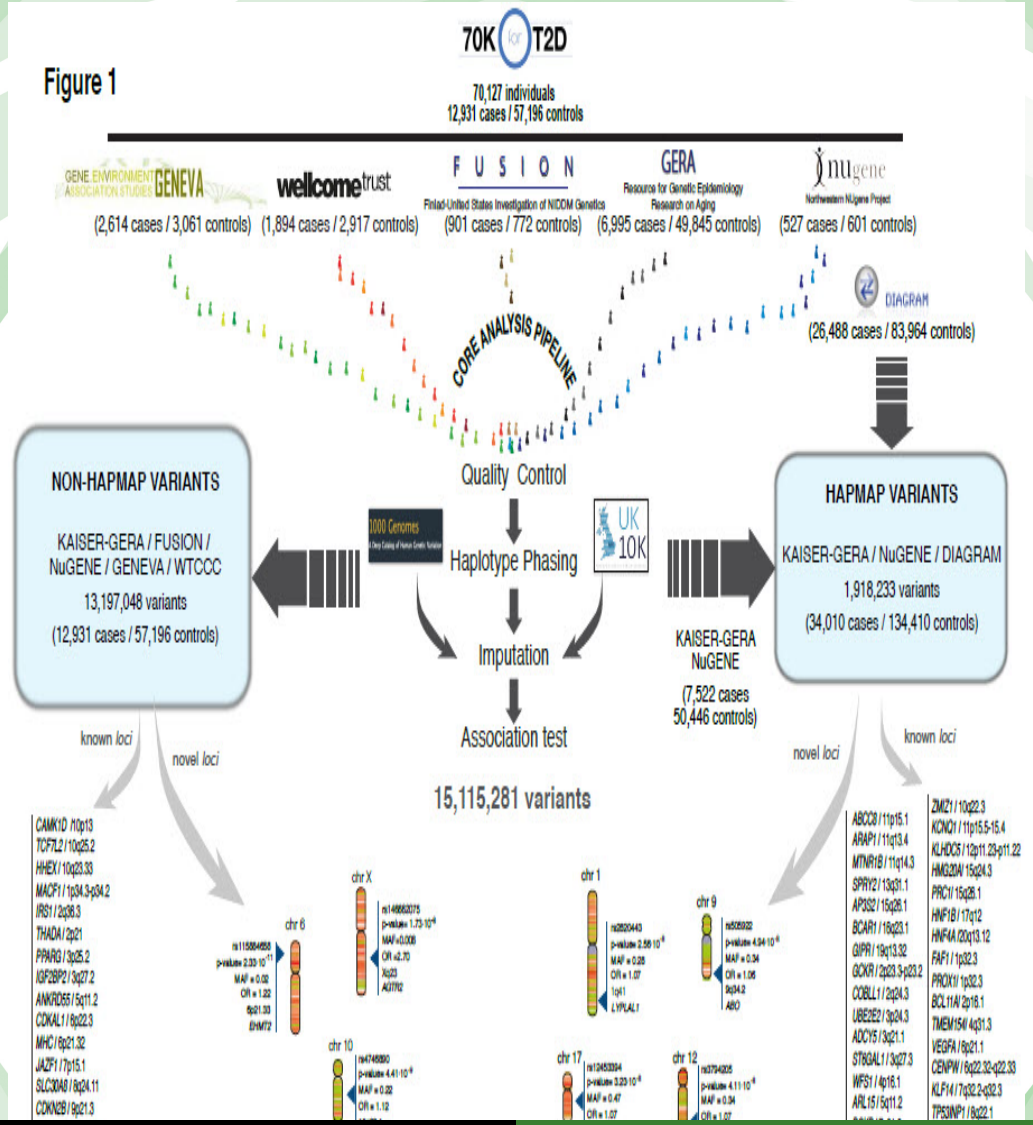
Epigenomic data for many normal human cell/tissue types



- 77% of disease variants are in/near enhancer elements or promoters*
- Variants are in regulatory regions NOT protein coding regions
- Generate hypotheses about function

Domain knowledge-guided



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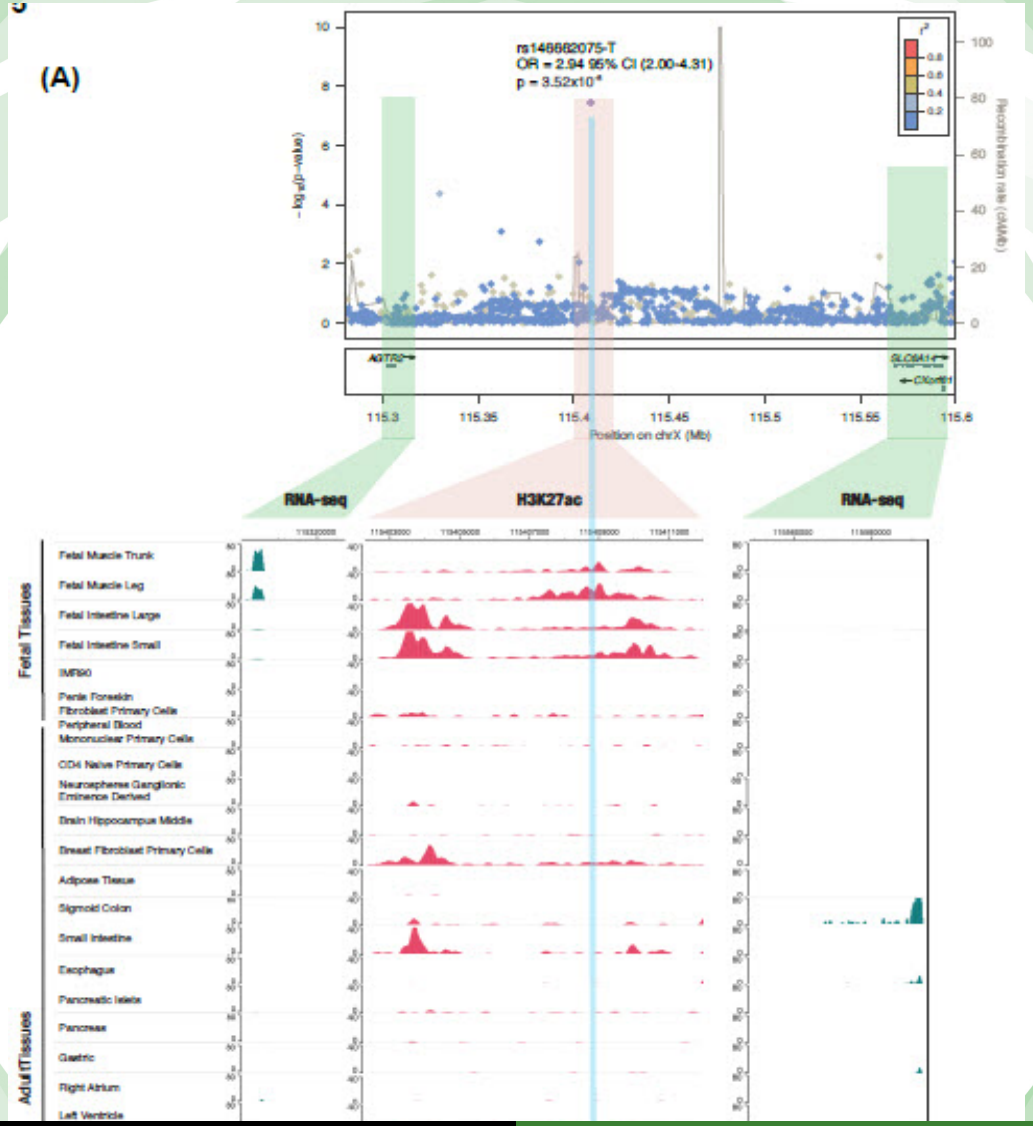

Domain knowledge-guided

Let us assume that we want to extract biological information (eQTL, LD, motifs, ...) from large genomic projects such as ENCODE, the 1000 Genomes Project, Roadmap Epigenomics Project and others on the 15 SNPs obtained in paper *Verweij et al. Identification of 15 novel risk loci for coronary artery disease and genetic risk of recurrent events, atrial fibrillation and heart failure. Sci Rep, 7, Article number: 2761 (2017)*.

```
library(haploR)
x <- queryHaploreg(query=c(c("rs11810571", "rs7623687", "rs142695226",
                             "rs433903", "rs10857147", "rs11723436",
                             "rs35879803", "rs35541991", "rs1351525",
                             "rs11170820", "rs2244608", "rs3832966",
                             "rs33928862", "rs7500448", "rs138120077")
```

Domain knowledge-guided

We can ask, for instance, information about motifs, gwas, gene name and Enhancer histone marks of those SNPs that are in high LD (>0.9). Notice that the name of all possible variables can shown by typing `names(x)`.

```
sel <- as.numeric(x$r2) > 0.9
x2 <- x[sel, c("pos_hg38", "rsID", "Motifs", "gwas",
               "GENCODE_name", "Enhancer_histone_marks")]
x2
```

```
## # A tibble: 258 x 6
##    pos_hg38  rsID       Motifs              gwas  GENCODE_name Enhan
##    <fct>     <fct>      <fct>               <fct> <fct>        <fct>
##  1 75148524  rs10138183 Nanog_disc2         .     TMED10       ""
##  2 75166305  rs10149880 ERalpha-a_disc2;H~  .     TMED10       ""
##  3 75139089  rs1047418  Irf_disc5;RBP-Jka~  .     TMED10       ""
##  4 22606797  rs10485012 AP-4_1;Nkx2_11;Nk~  .     RP1-309H15.2 ""
##  5 145859799 rs10519748 .                   .     ZNF827       ""
##  6 151773603 rs1054479  Hoxa13;Pou2f2_kno~  .     TDRKH        ""
##  7 151788316 rs10788809 Foxj2_1;SP1_disc1   .     TDRKH        ""
##  8 13266391  rs10832011 Pax-4_1            .     ARNTL        ""
```

Domain knowledge-guided

eQTLs can also be depict by

```
x3 <- x[, c("rsID", "eQTL")]
x3
```

```
## # A tibble: 258 x 2
##    rsID       eQTL
##    <fct>      <fct>
##  1 rs10138183 GTEx2015_v6,Adipose_Subcutaneous,EIF2B2,3.37702382515
##  2 rs10149880 GTEx2015_v6,Adipose_Subcutaneous,EIF2B2,5.49512183025
##  3 rs1047418  GTEx2015_v6,Adipose_Subcutaneous,EIF2B2,1.19295941493
##  4 rs10485012 .
##  5 rs10519748 GTEx2015_v6,Artery_Tibial,ZNF827,8.660298945898e-06
##  6 rs1054479  GTEx2015_v6,Adipose_Subcutaneous,RP11-98D18.9,2.12743
##  7 rs10788809 GTEx2015_v6,Adipose_Subcutaneous,RP11-98D18.9,1.16363
##  8 rs10832011 GTEx2015_v6,Whole_Blood,ARNTL,1.999398908862 88e-10;La
##  9 rs10832012 GTEx2015_v6,Whole_Blood,ARNTL,8.81903348679608e-09
## 10 rs10832013 GTEx2015_v6,Whole_Blood,ARNTL,8.8679461832997e-11;Lap
## # ... with 248 more rows
```

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Meta-dimensional analysis

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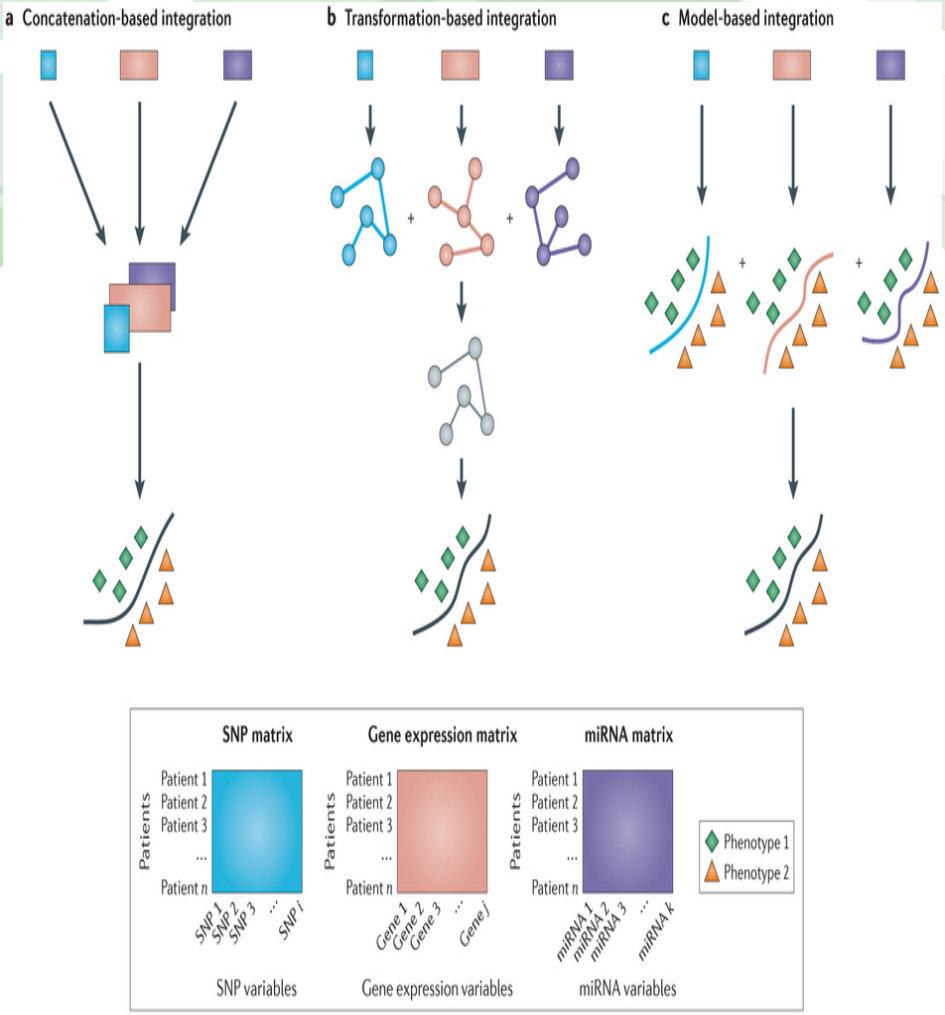
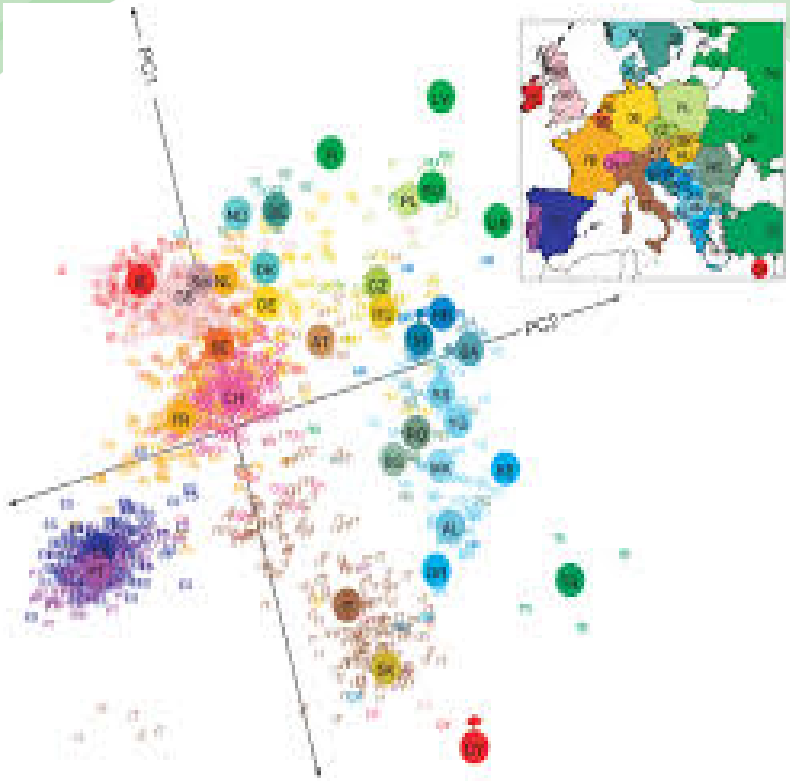
Types of meta-dimensional analyses



One omic dataset: dimensionality reduction



One omic dataset: dimensionality reduction

- Used to study tissue, cell attributes or cancer signatures with regard to abundance of mRNAs, proteins and metabolites
- Given an omic data set X, which is a $n \times p$ matrix, of n individuals and p features

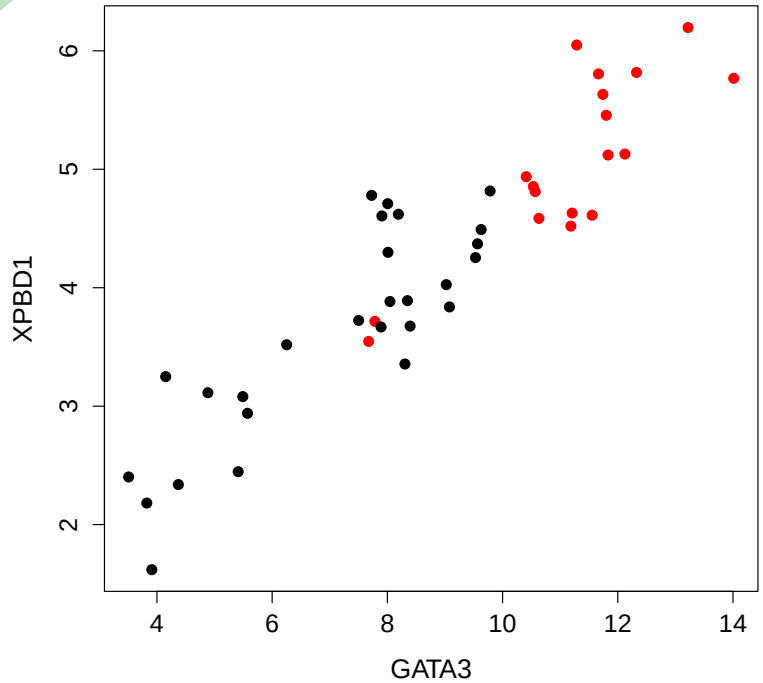
$$X = (x_1, x_2, \ldots, x_p)$$

- we look for new variables that are linear combinations of the original variables $f = q_1 X_1 + q_2 X_2 + \ldots + q_p X_p$ or $f = Xq$ where q are know as loadings.
- We introduce the restriction that for ith component, q's should maximize the variance components of f's

$$\arg\max_{q^i} \text{var}(Xq^i)$$

and q's has to be orthogonal to each other.

One omic dataset: dimensionality reduction



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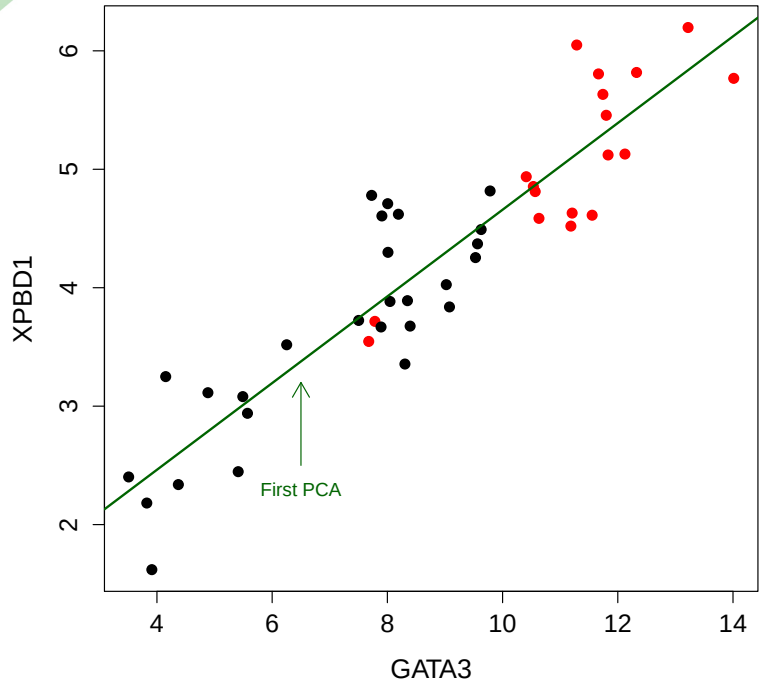

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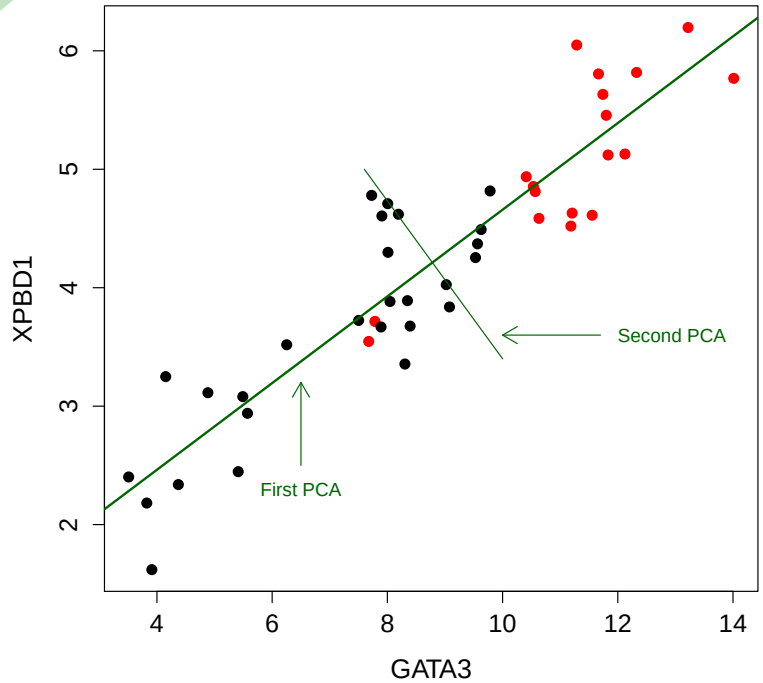

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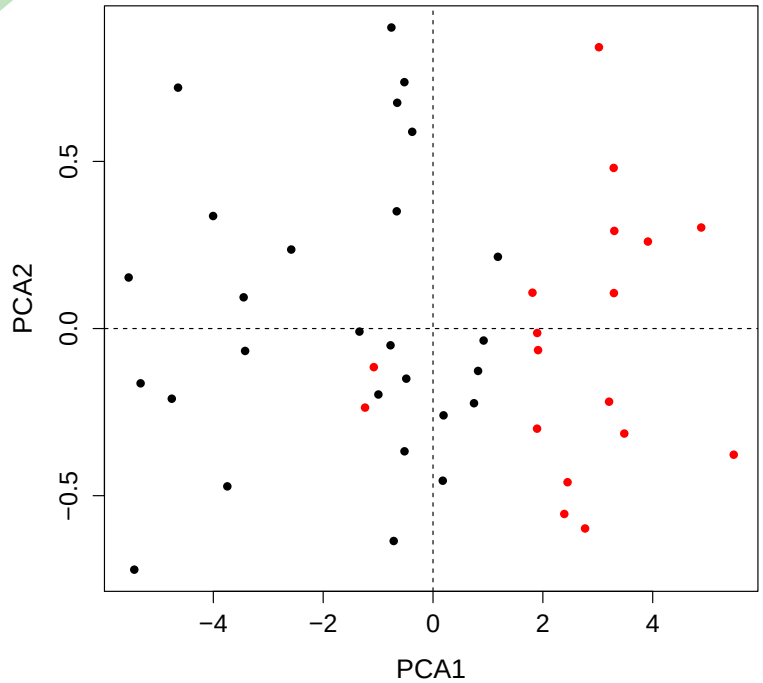
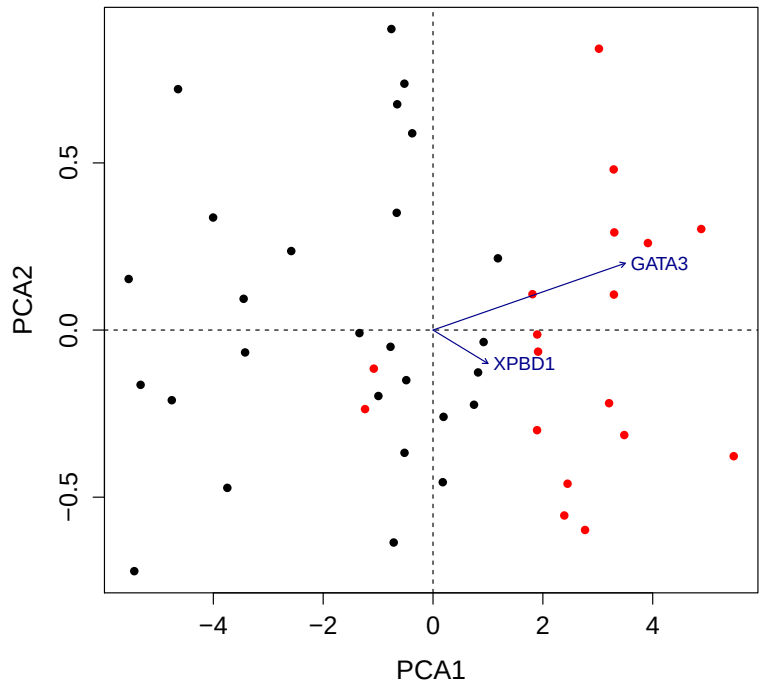


One omic dataset: dimensionality reduction

Data visualization: biplot



One omic dataset: dimensionality reduction

- There are other thechniques such as: Principal co-ordinate analysis (PCoA), correspondence analysis (CA) and nonsymetrical correspondence analysis (NSCA).
- They can be applied to other types of data (e.g. non-continuous). PCoA can also be applied to binary or count data.
- PCA is designed to analyze multi-normal distributed data. If data are skweed, contain extreme outliers, or display nonlinear trends, other methods such as Multidimendional Scaling (MDS)
- Nonnegative matrix factorization (NMF) and Independent Component Analysis (ICA) are applied when orthogonality or independence acrross components are not hold.

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One omic dataset: dimensionality reduction

- Solving the problem for the *i*-th component

$$\arg\max_{q^i} \text{var}(Xq^i)$$

  uses SVD decomposition and it requires and inversion step that can be problematic when $p >> n$
- Several extensions based on reguralization step or L-1 penalization (Least Absolute Shrinkage and Selection Operator, LASSO) can be applied
- Sparse, penalized and reguralized extensions of PCA and related method have been proposed in omic data analysis, recently (sPCA)

Multi-omic real data

- 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.

Multi-omic real data

Data can be loaded into R by executing:

```
load("data/breast_TCGA_subset_multi_omic.RData")
summary(breast_multi)

##                 Length Class      Mode
## miRNA              79 data.frame list
## miRNAprecursor     79 data.frame list
## RNAseq         791580 -none-     numeric
## Methyl             79 data.frame list
## RPPA               79 data.frame list
## LOH            996348 -none-     numeric
## CNA            934649 -none-     numeric
## clin               29 data.frame list
```

PCA analysis

```
require(ade4)
dim(breast_multi$RNAseq)

## [1] 10020    79
```

```
breastPCA<-dudi.pca(breast_multi$RNAseq,
            scannf=FALSE, nf=5)
```

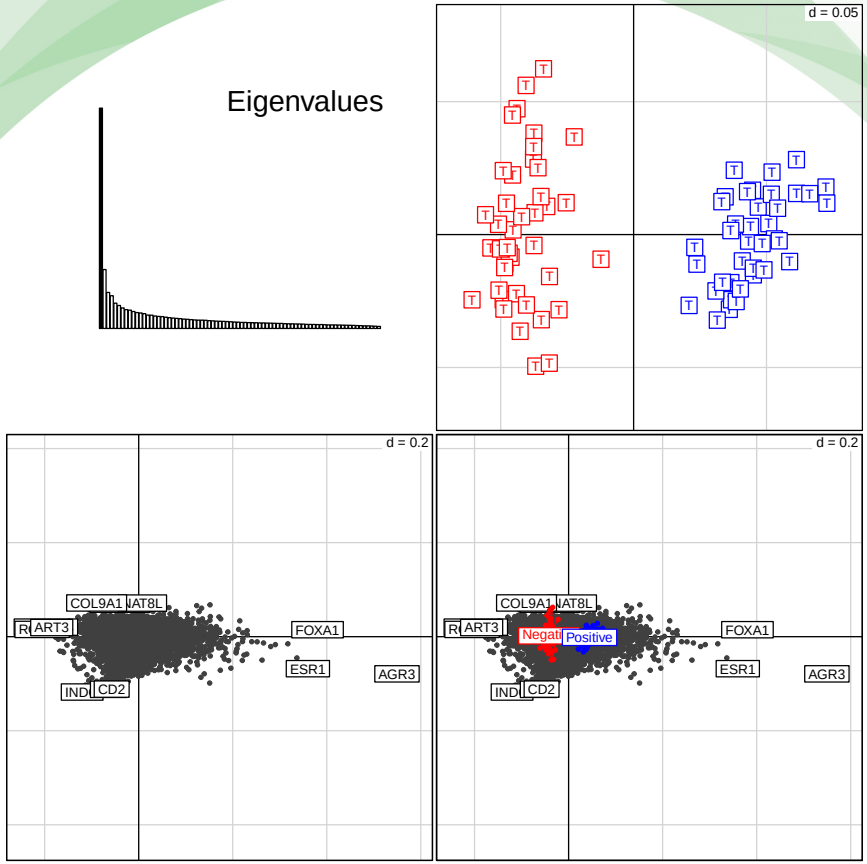
PCA analysis

There is a BioC package called made4 which is a wrapper oround ade4 that utilizes Bioconductor data classes (such as `ExpressionSet` to help visualizing the results). They key function ir `ord`. The panels shows plot of eignevalues, projections of samples, projections of genes and biplot.

```
require(made4)
```

```
group<-droplevels(breast_multi$clin$ER.Status)
out <- ord(breast_multi$RNAseq, classvec=group)
plot(out, nlab=3, arraylabels=rep("T", 79))
```

PCA analysis

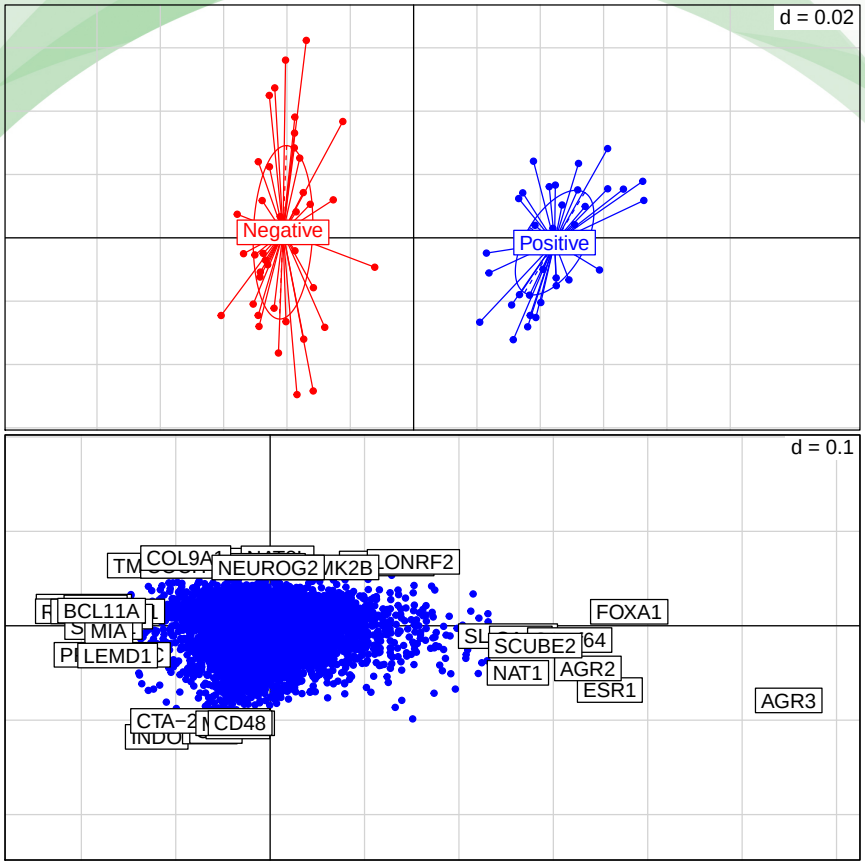


PCA analysis

Sample and genes projections can also be plotted using another wrapper around `ade4` package. By default the top-10 more important genes for each axis are highlighted.

```
par(mfrow=c(2,1))
plotarrays(out$ord$co, classvec=group)
plotgenes(out, col="blue")
```

PCA analysis



PCA analysis

A list of variables with higher loadings on axes can be obtained using the following function

```
ax1 <- topgenes(out, axis=1, n=5)
ax2 <- topgenes(out, axis=2, n=5)
cbind(ax1, ax2)

##        ax1        ax2
##  [1,] "ROPN1B"   "SH3GL2"
##  [2,] "ROPN1"    "SLITRK6"
##  [3,] "FOXA1"    "LONRF2"
##  [4,] "SFRP1"    "IL7R"
##  [5,] "ESR1"     "INDO"
##  [6,] "AGR3"     "NAT8L"
##  [7,] "AGR2"     "UBD"
##  [8,] "C1orf64"  "CD2"
##  [9,] "ART3"     "CD69"
## [10,] "BCL11A"   "COL9A1"
```

Sparse PCA analysis

Witten D, Tibshirani R, Hastie T (Biostatistics, 2009, 10(3):515-534) presented a penalized matrix decomposition for computing a rank-K approximation for a matrix based on L1-penalization. The method is also extended to Canonical Correlation Analysis (CCA).

```
require(PMA)
dd <- t(breast_multi$RNAseq)
sout <- SPC(dd, sumabsv=3,
            K=2, orth=TRUE)

## 12345678910
## 12345678910111213141516171819 20
```

NOTE: `subabsv` argument controls the degree of sparsity. It can be tuned by using `SPC.cv` function

Sparse PCA analysis

```
rownames(sout$u) <- rownames(dd)
rownames(sout$v) <- colnames(dd)
head(sout$u)
```

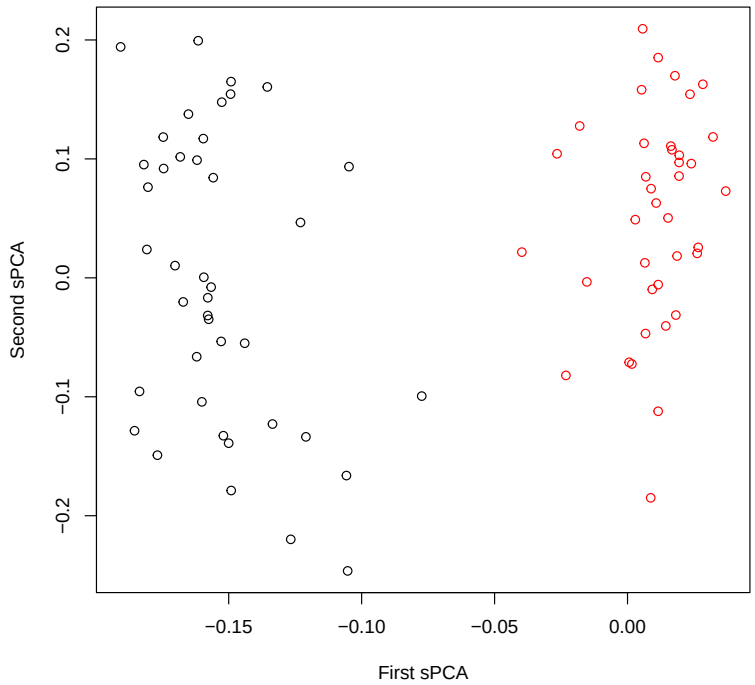
```
##                      [,1]       [,2]
## TCGA-C8-A12V -0.1266630 -0.2198702
## TCGA-A2-A0ST -0.1052587 -0.2464092
## TCGA-E2-A159 -0.1057203 -0.1662398
## TCGA-BH-A0BW -0.1335251 -0.1229296
## TCGA-A2-A0SX -0.1520058 -0.1327320
## TCGA-AR-A1AI -0.1768082 -0.1491056
```

```
head(sout$v)
```

```
##          [,1] [,2]
## CREB3L1     0    0
## PNMA1       0    0
## MMP2        0    0
## C10orf90    0    0
## GPR98       0    0
## APBB2       0    0
```

Sparse PCA analysis

```
plot(sout$u, type="n", xlab="First sPCA", ylab="Second sPCA")
points(sout$u, col=as.numeric(group))
```



Sparse PCA analysis

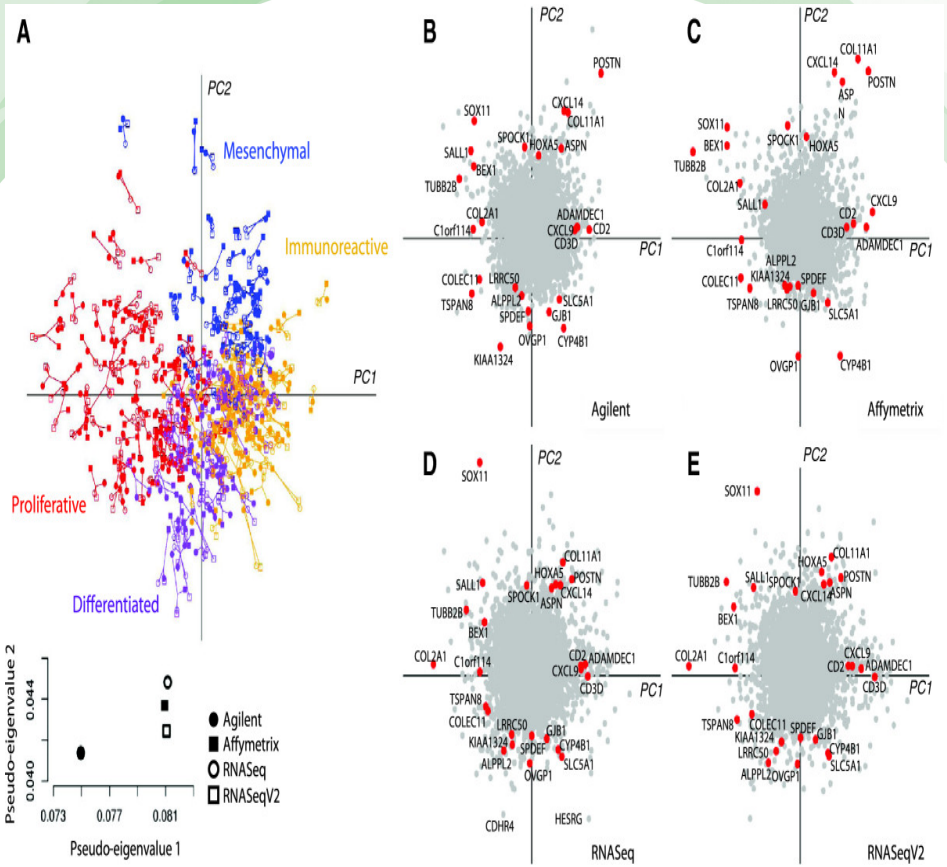
```
ss <- sout$v[,1]
ss[ss!=0]
```

```
##       FSIP1      ROPN1B     SLC44A4       ROPN1       FOXA1     SCGB2A2
##  0.12976786 -0.20047758  0.09854402 -0.22180706  0.35283734  0.02914304
##        CA12     HORMAD1        TFF3      ABCC11        ESR1        AGR3
##  0.08389962 -0.11978720  0.01092539  0.01843790  0.26810418  0.69491639
##        AGR2     C1orf64     SCUBE2        ART3
##  0.29917578  0.23368898  0.05023190 -0.18825577
```

```
ax1
```

```
##  [1] "ROPN1B"   "ROPN1"    "FOXA1"    "SFRP1"    "ESR1"     "AGR3"     "AGR2"
##  [8] "C1orf64" "ART3"     "BCL11A"
```

One omic dataset: dimensionality reduction



Integrating two or more omic 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 omic 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.

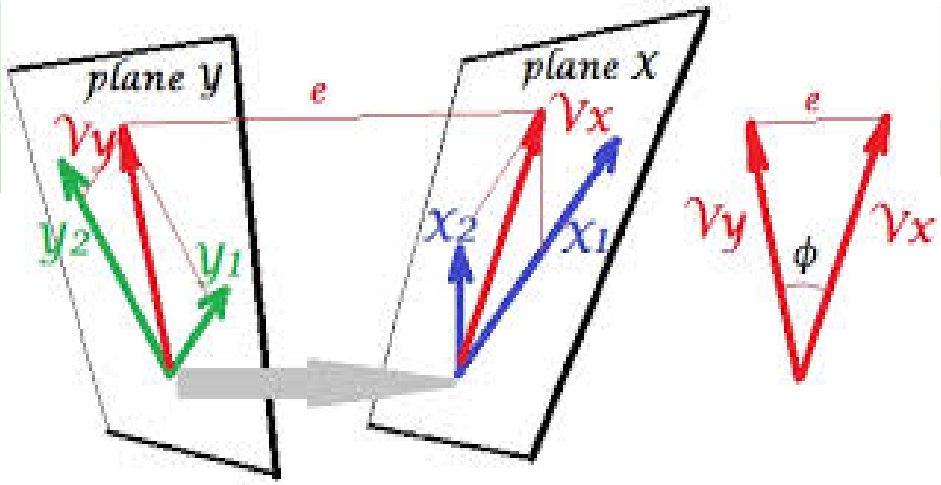
Integrating two or more omic datasets

- ($p >> n$) 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 omic 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

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

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.

Canonical Correlation: gene expression and proteins

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

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

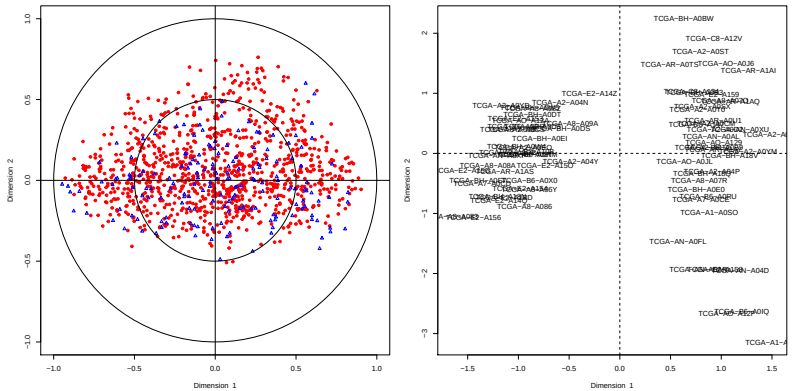
```
Error en chol.default(Bmat) :
  la submatriz de orden 81 no es definida positiva
```

```
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   0.03812575
## PNMA1     0.04078831
## MMP2      0.02402715
## C10orf90 -0.02896362
## GPR98     0.04723420
## APBB2     0.06279879
```

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

```
##                   [,1]
## c.Myc       -0.07099252
## HER3         0.02652238
## XBP1         0.00000000
## Fibronectin  0.01527691
## PAI.1       -0.02319958
## p21          0.02415011
```

Co-inertia: gene expression and proteins

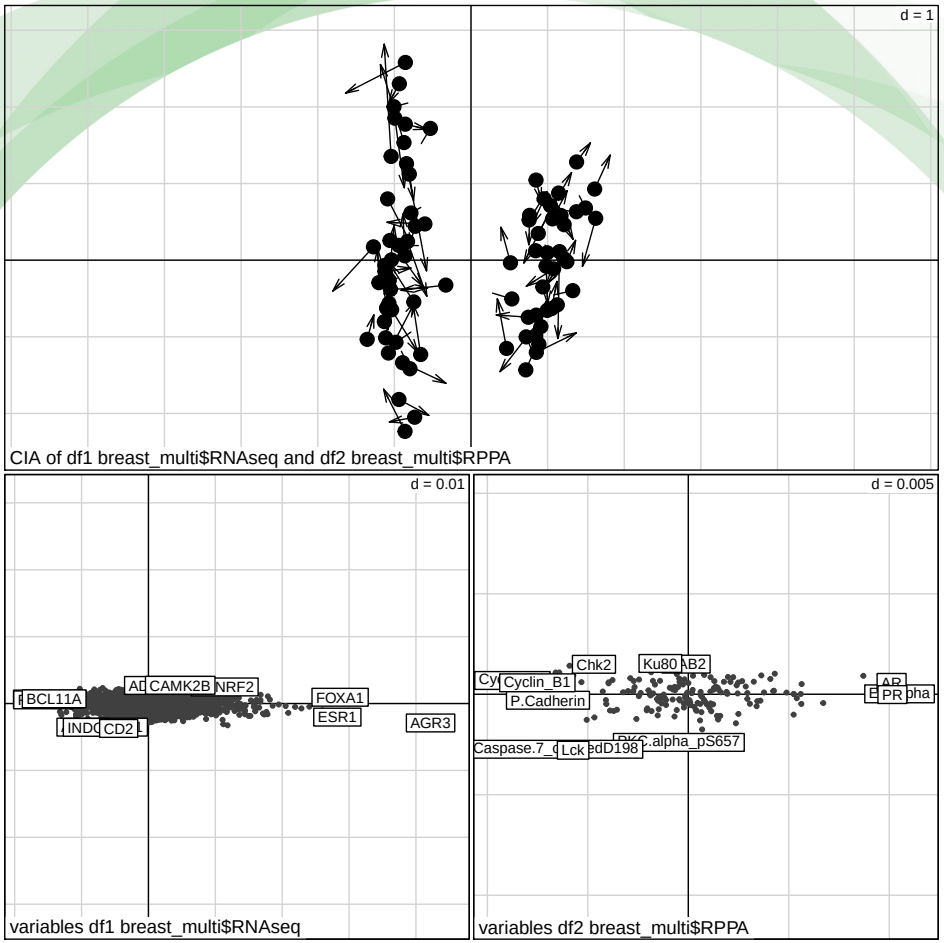
Let us load required packages (coinertia and multiple coinertia)

```
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

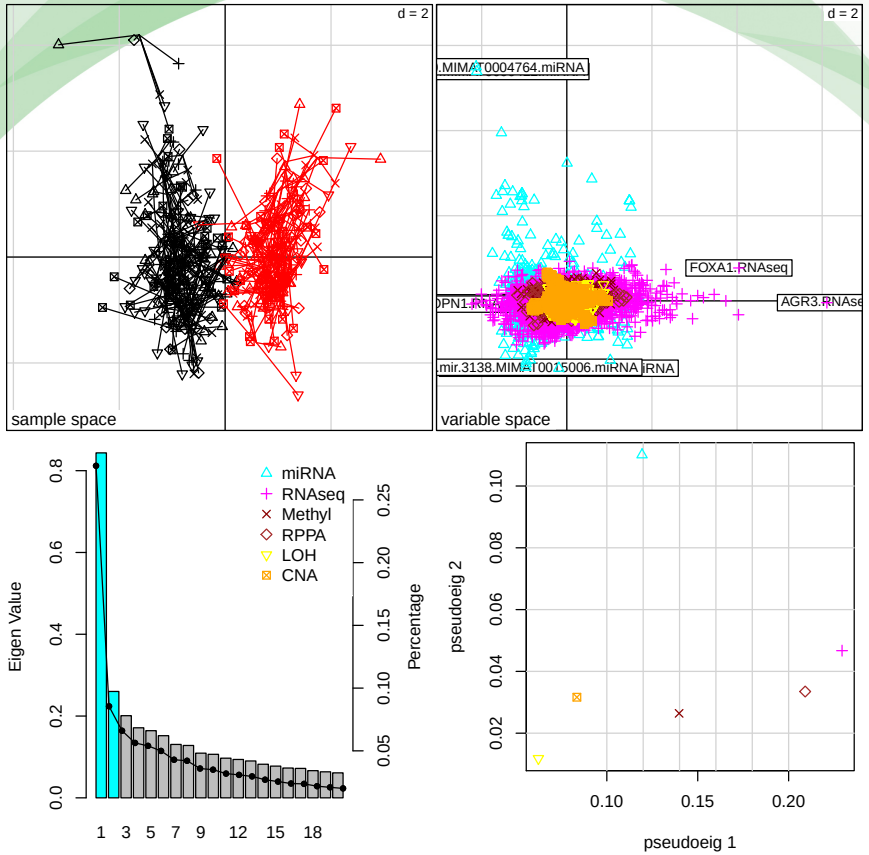
```
topVar(resCIA, axis=1, topN=5, end="negative")

##   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

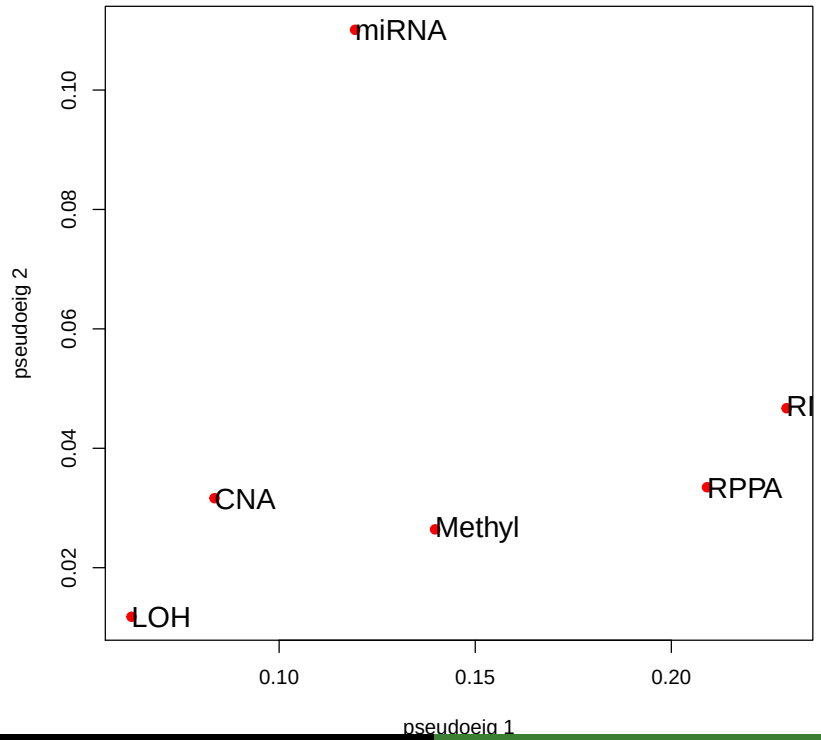
Top-5 features of the first axis (positive side) can be retrieve by

```
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)
```



Take home messages

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

1. Introduction
2. Multi-staged analysis
3. Meta-dimensional analysis
   - One omic dataset: dimensionality reduction
   - Integrating two or more omic datasets
4. Recommended lectures

Recommended lectures

- Richmond et al. (2016). Challenges and novel approaches for investigating molecular mediation. Hum Mol Genet, 25(R2):R149-R156.
- 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.