Intégration Multi-omiques

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UNIVERSITÉ LAVAL

Objectifs

- Comprendre les **enjeux** liés à l'intégration multi-omique.
- Être capable d'expliquer les différents **concepts** d'intégration multi-omique.
- Savoir appliquer la bonne **méthode** d'intégration en fonction des **données** disponibles.

Mise en contexte

- omique ? multi-omique ?
- Pourquoi ? Difficultés
- Ressources

Méthodes d'intégration

- Intégration Conceptuelle
- Intégration Statistique
- Intégration à base de modèle

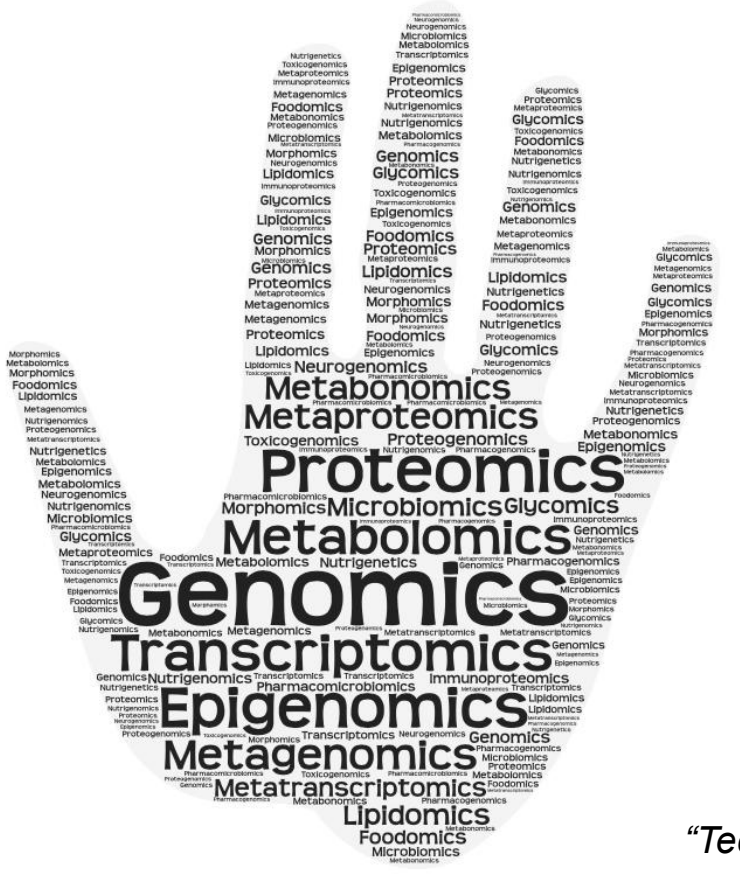
Méthodes Multivariées

- Analyse en Composante Principale
- Autres méthodes multivariés

Méthodes à base de réseaux biologiques

- Les réseaux en biologie
- Exploration des réseaux

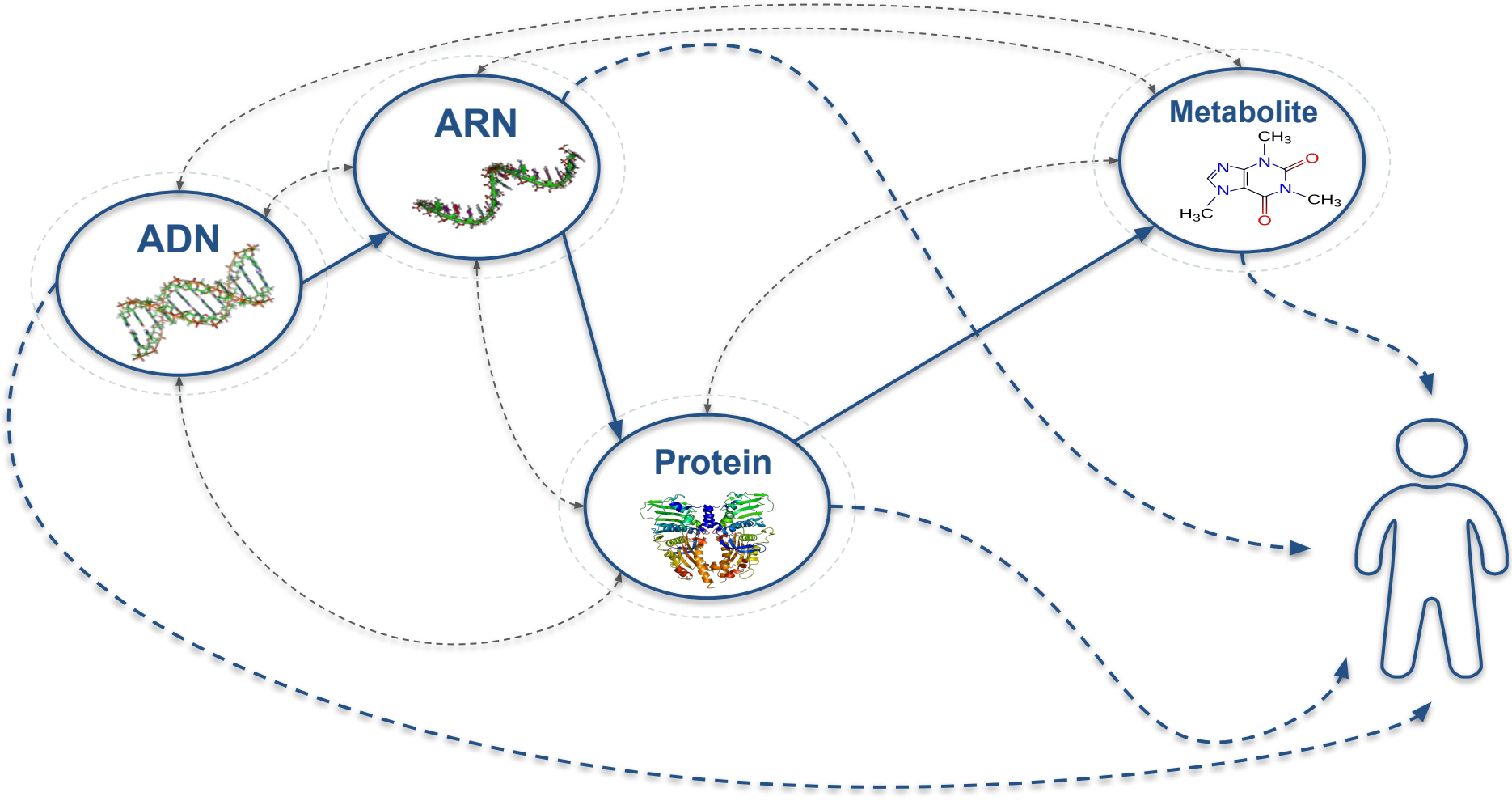
Qu'est-ce qu'un *omique* ?



- "Genomics" inventé dans les 70s
  (Thomas Roderick)
- D'autres termes:
  Protéomique, métabolomique, épigénomique, …
- "Méta"-omique
  Métagénomique, métaprotéomique, …
- Néologisme
  Morphomics, foodomics, ...

"Technologies omiques à haut débit"

Qu'est-ce que le *multi-omique* ?



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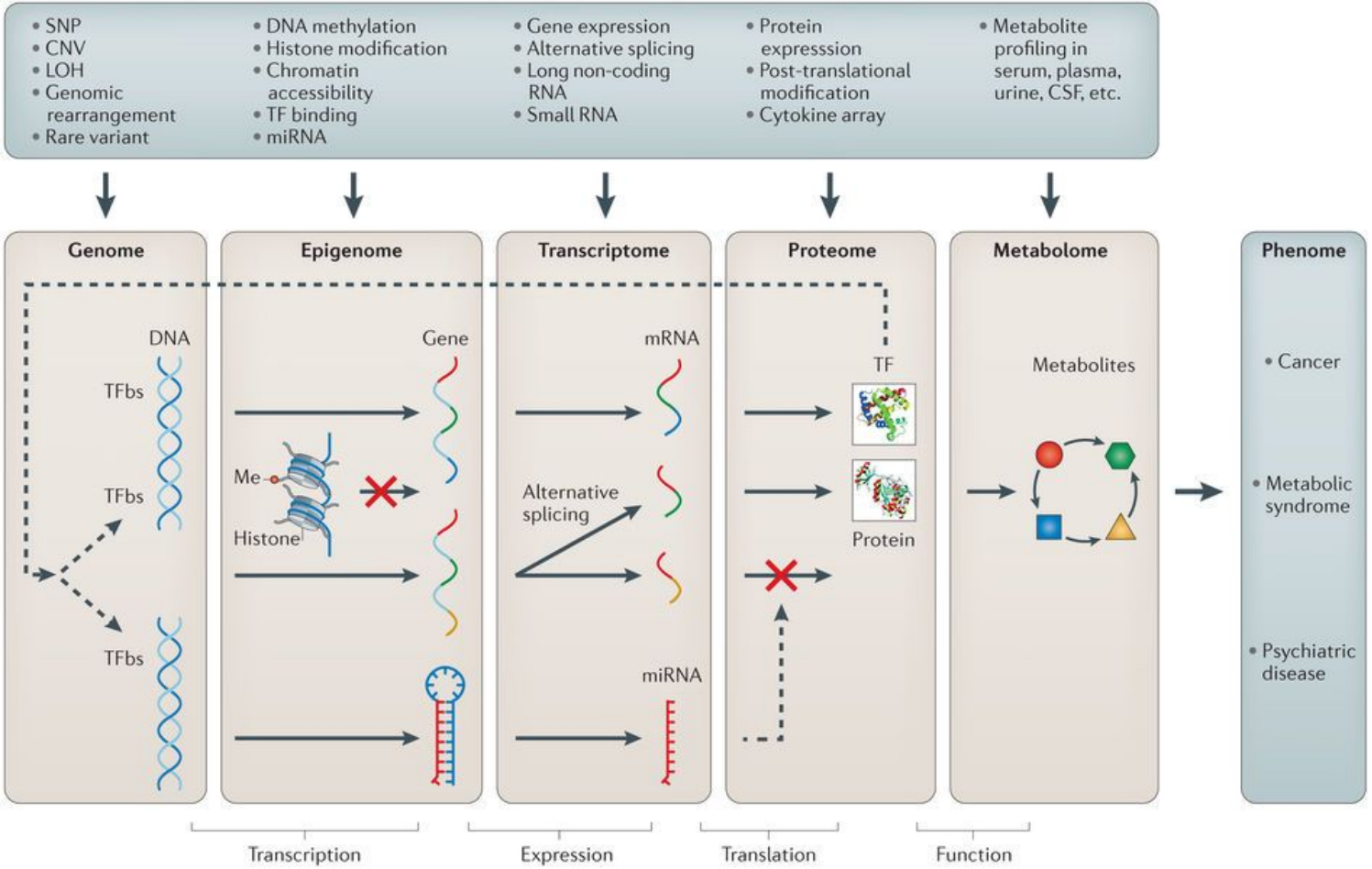

doi:10.1038/nrg3868
Nature Reviews | Genetics

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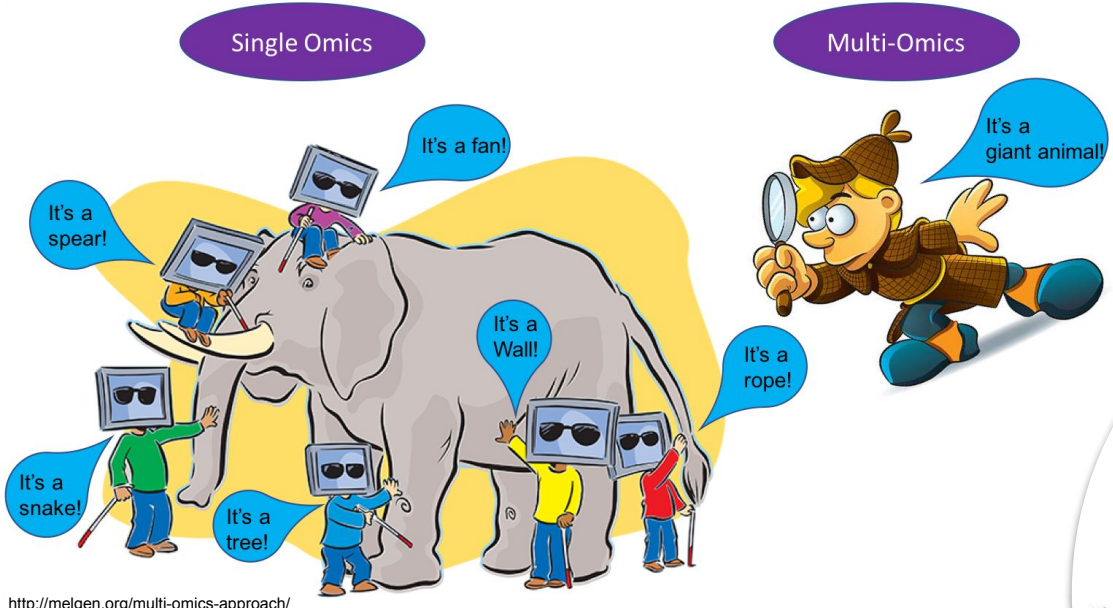
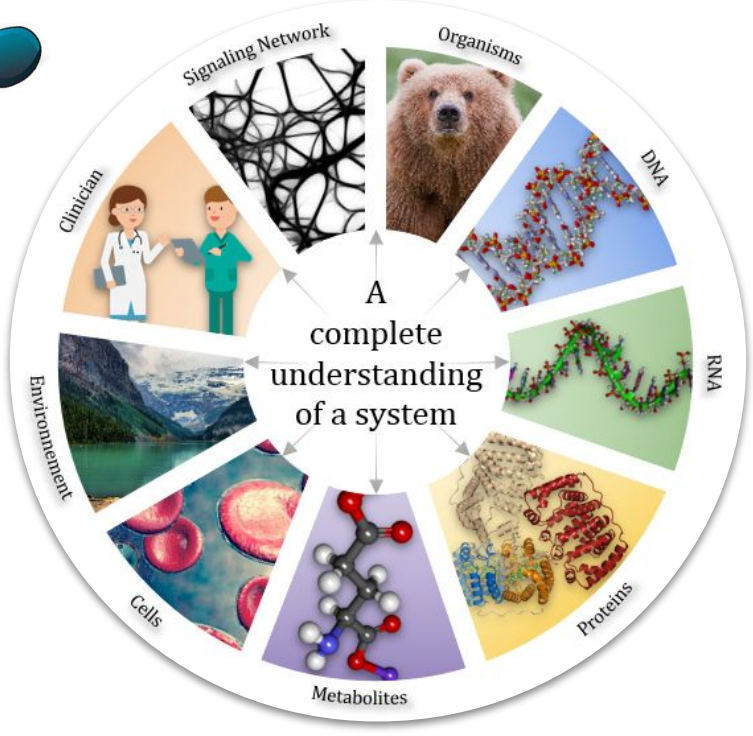
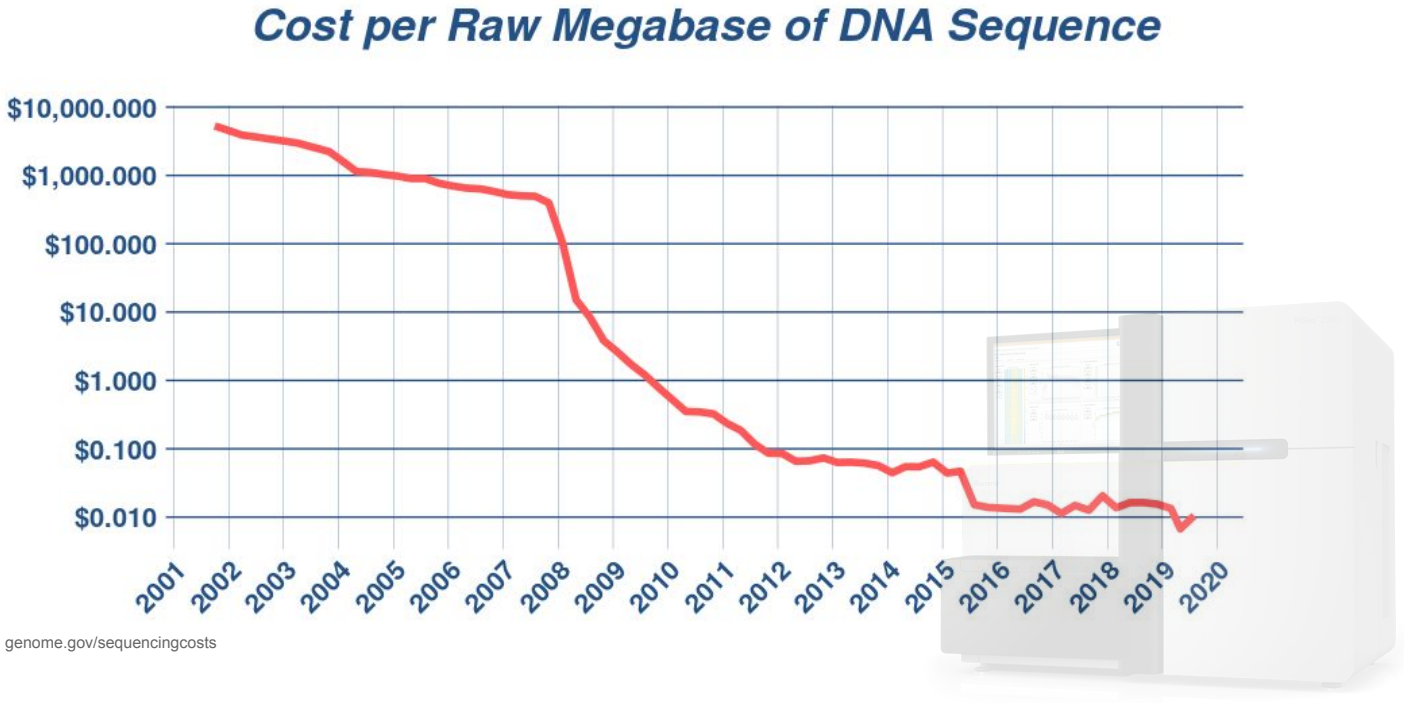


http://melgen.org/multi-omics-approach/

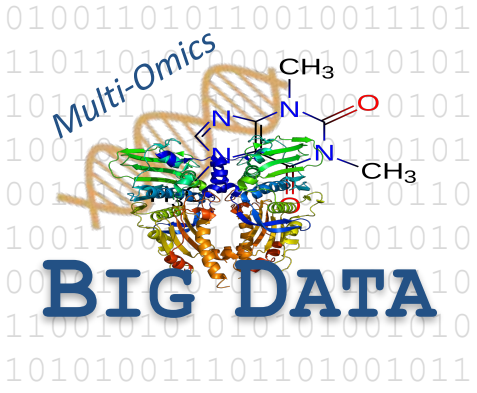
Approche **Réductionniste** (single-omic)
vs
Approche **Holistique** (multi-omic)

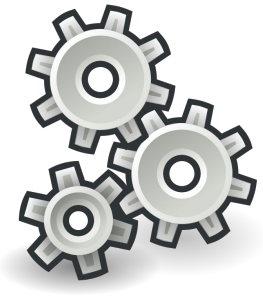


Pourquoi ?


Cost per Raw Megabase of DNA Sequence
$10,000.000
$1,000.000
$100.000
$10.000
$1.000
$0.100
$0.010
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020
genome.gov/sequencingcosts

Difficultés

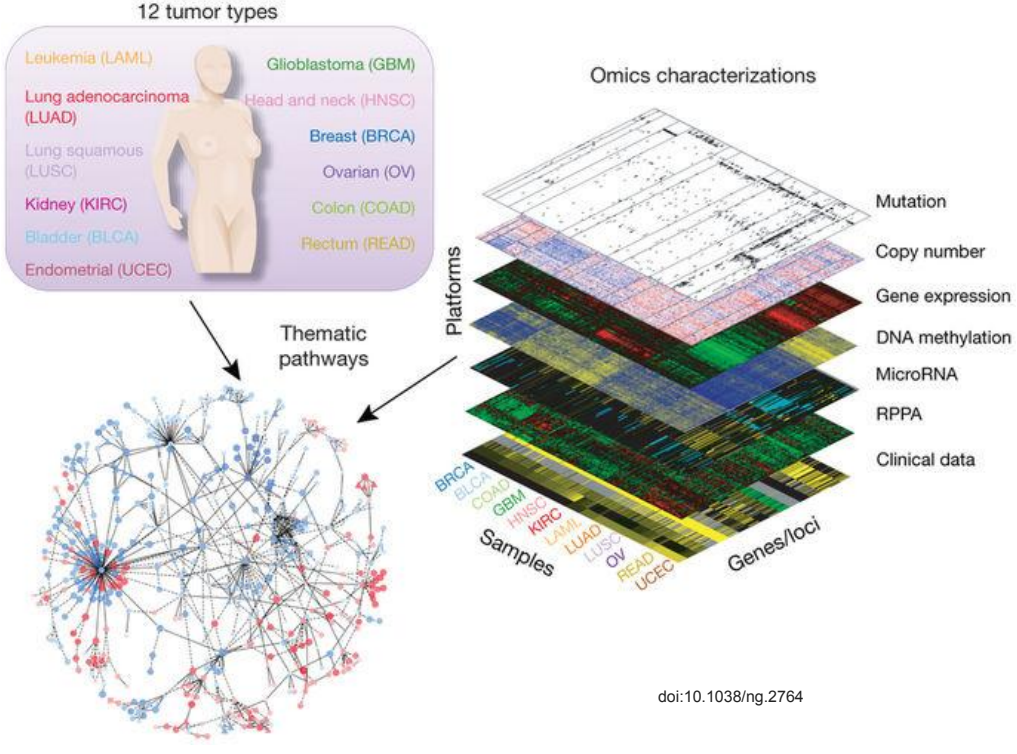


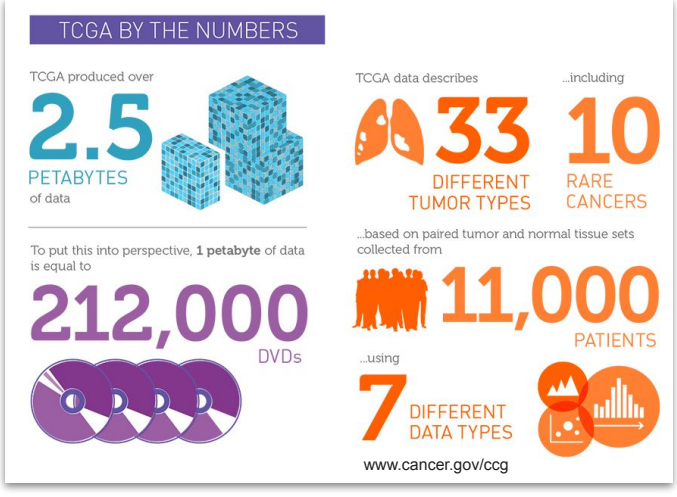


- Sources multiples et hétérogènes
- Puissance de calcul
- Interprétabilité
- Rester informé des avancées dans chaque domaines

Quelques ressources *multi-omique* ?

NIH **THE CANCER GENOME ATLAS**
National Cancer Institute
National Human Genome Research Institute





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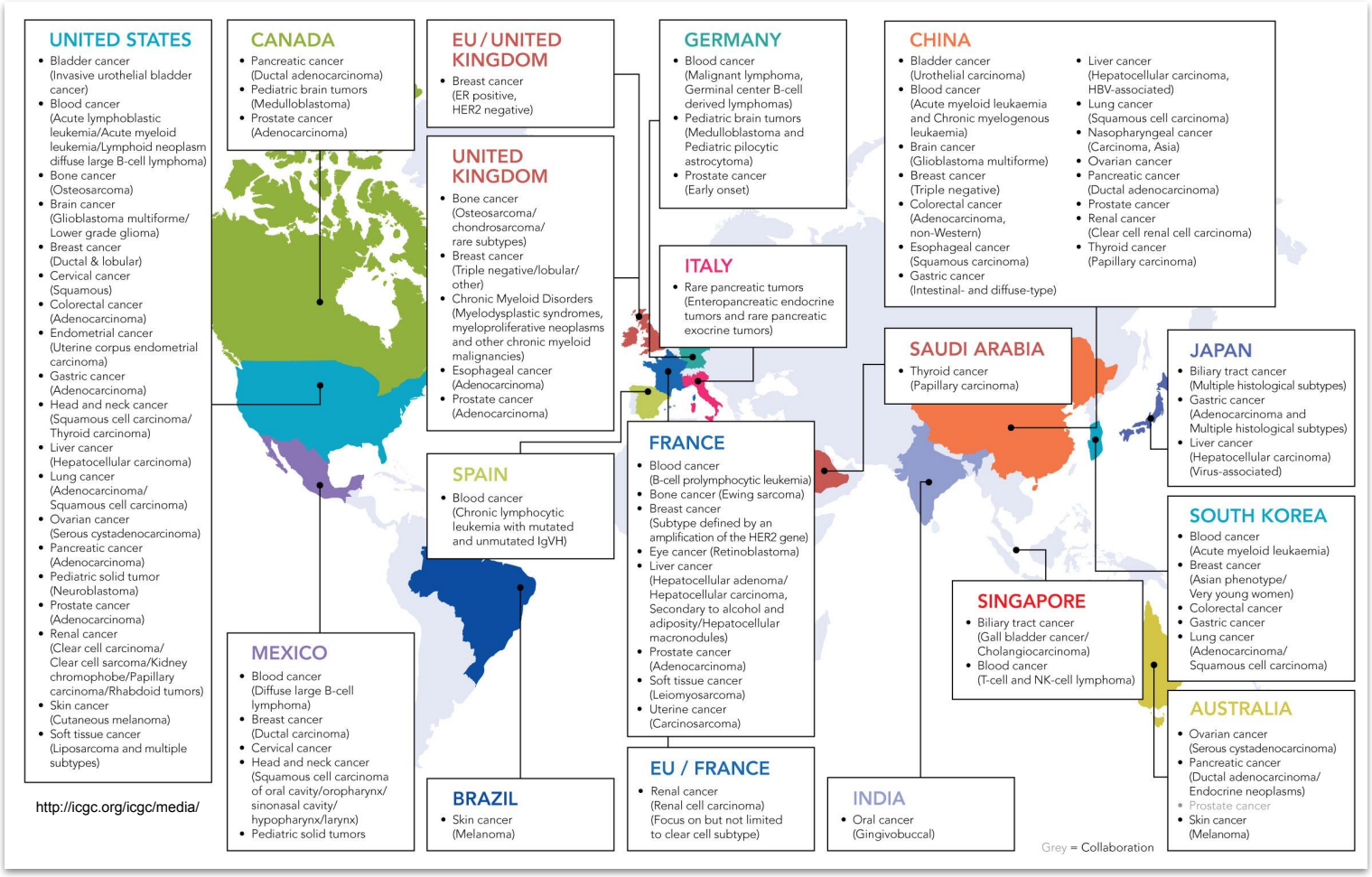
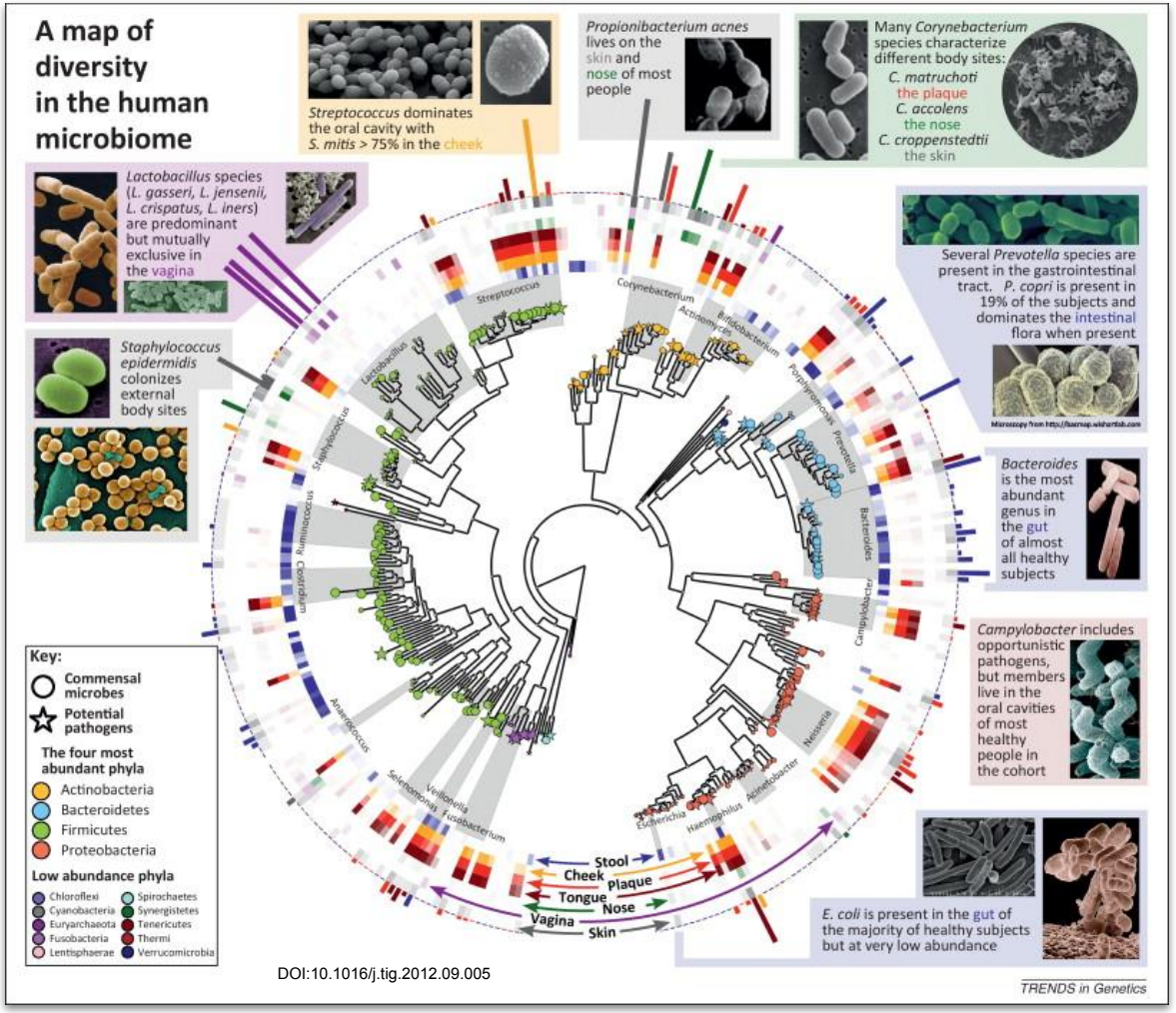
Quelques ressources *multi-omique* ?

International Cancer Genome Consortium



Quelques ressources *multi-omique* ?

https://hmpdacc.org



High Throughput Technology

	Gene-1	Gene-2	Gene-3	Gene-4
A	10	5	6	0
B	42	49	2	9
...				

	Prot-1	Prot-2	Prot-3
A	2	9	5
B	8	3	0
...			

	Metab-1	Metab-2	Metab-3	Metab-4	Metab-5
A	58	89	32	73	51
B	72	104	99	43	16
...					

"Bloc"

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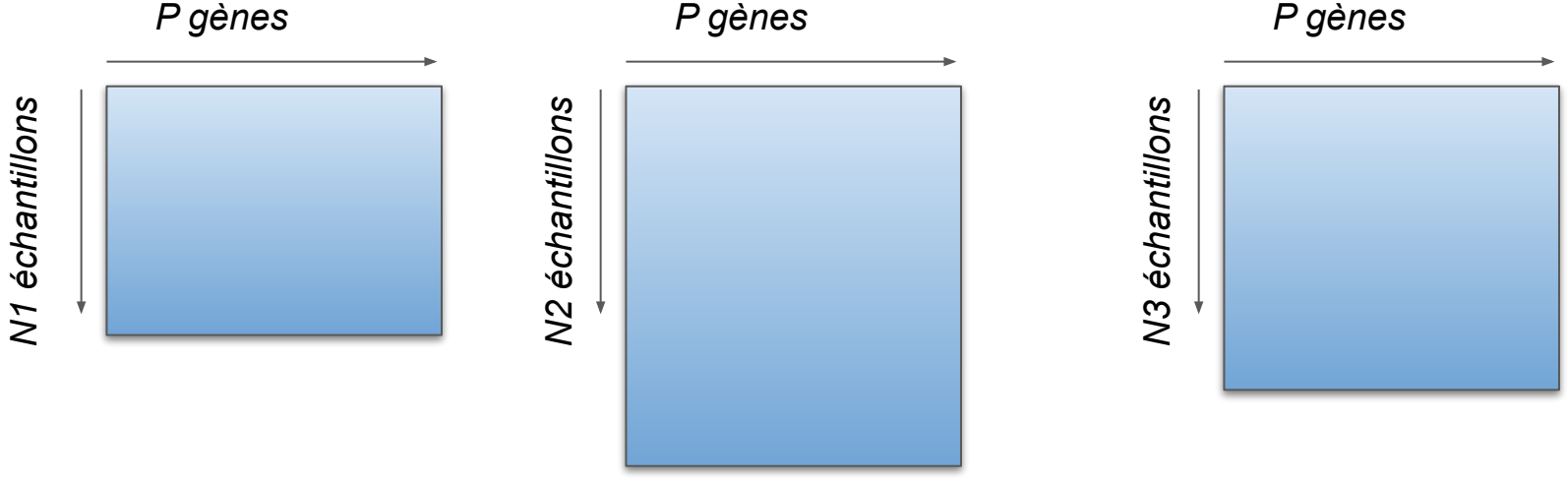
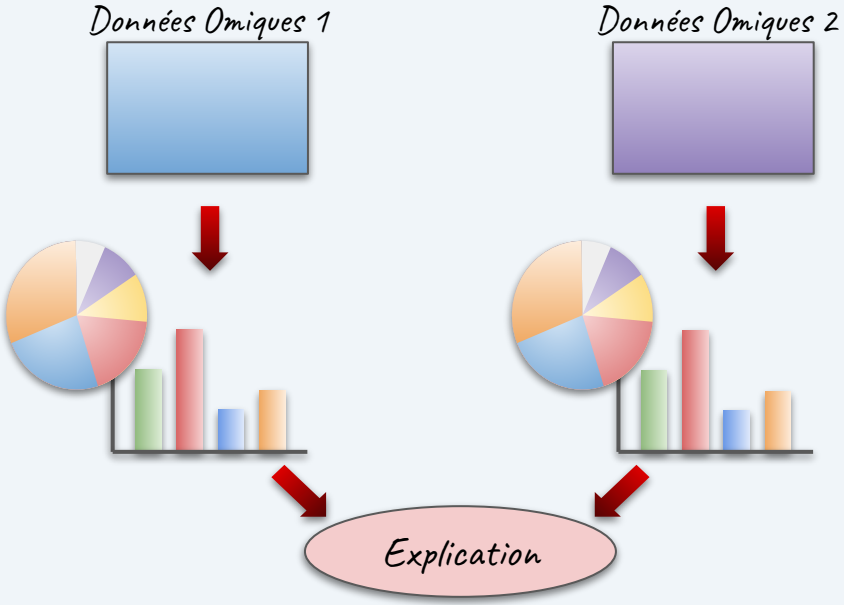
N-Intégration

P-Intégration

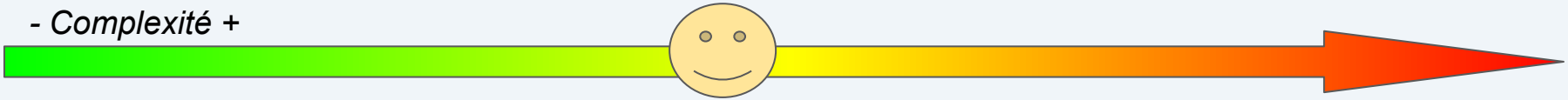


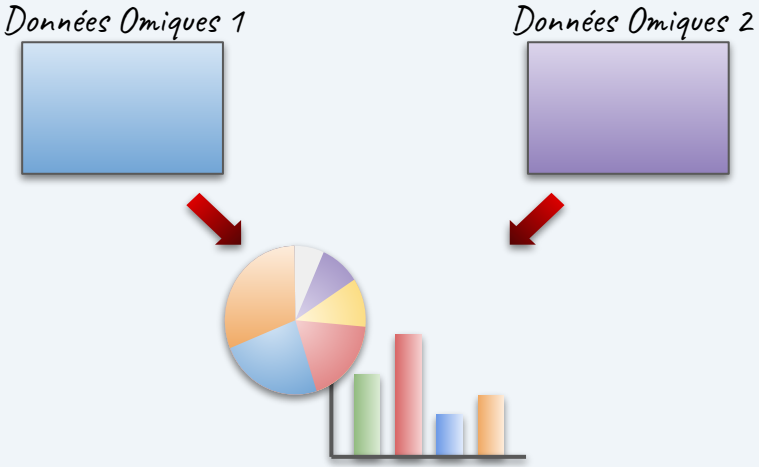
Intégration Conceptuelle



- Analyse de chaque omique séparément
- Manque les relations entre les données

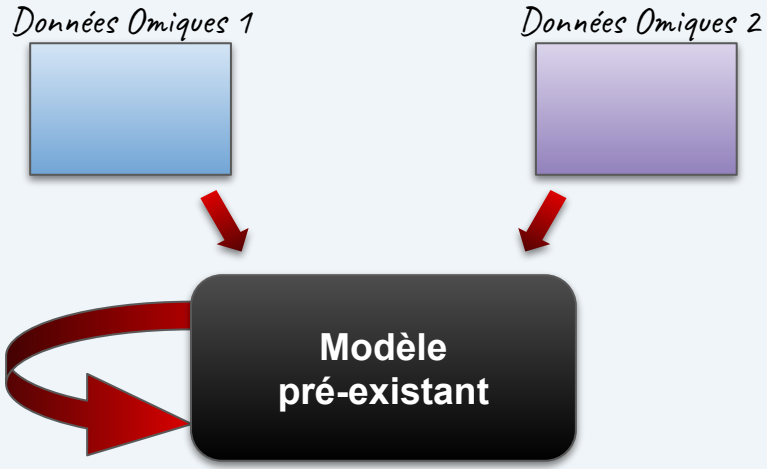
Intégration Statistique





- Forme d'intégration la plus commune
- Différentes méthodes :
  - Corrélation
  - Concaténation
  - Multivariée
  - Pathways Biologiques

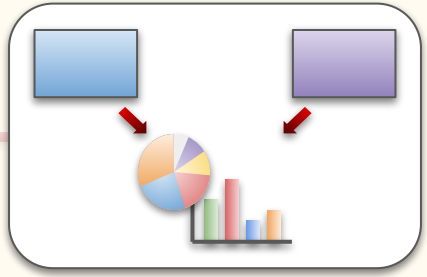
Intégration à base de Modèles



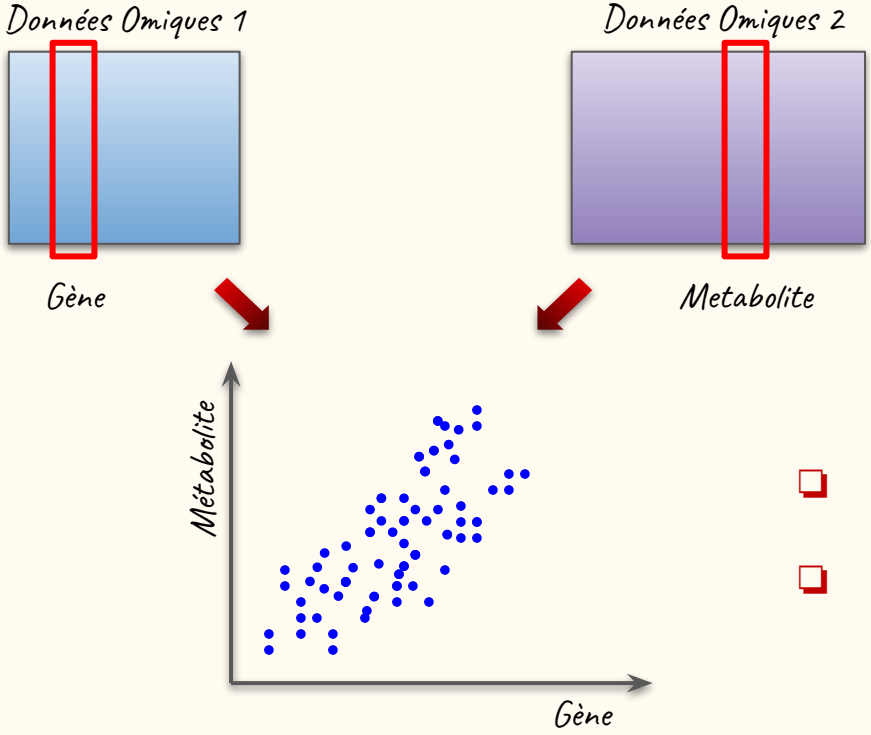
- Idéal à atteindre …

  … mais difficilement atteignable aujourd'hui

Intégration Statistique

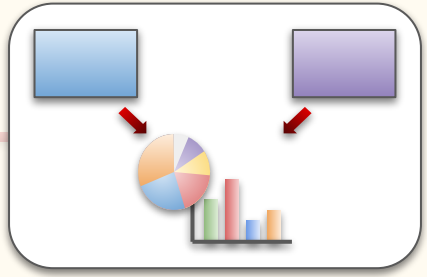


A) Corrélation

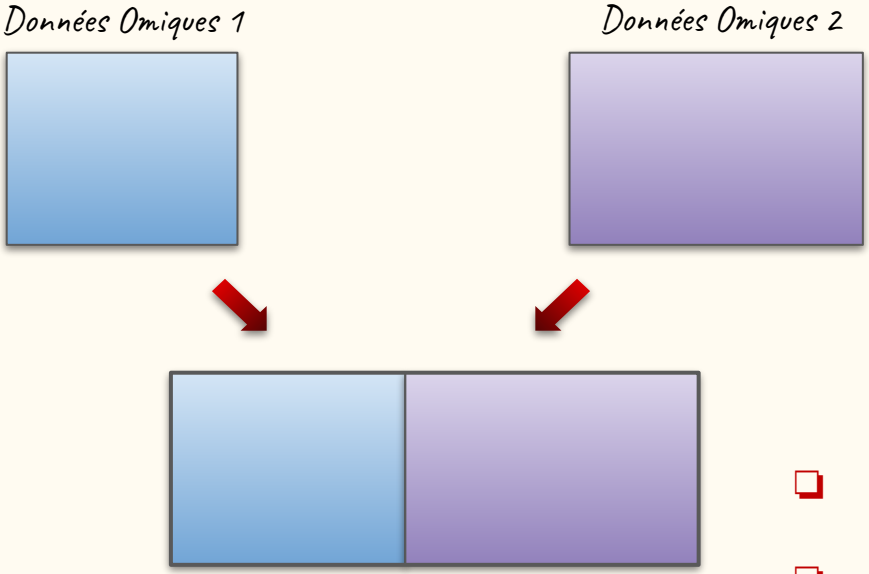


- Méthode la plus simple et plus utilisée
- Corrélation de **Pearson** ou **Spearman**

Intégration Statistique

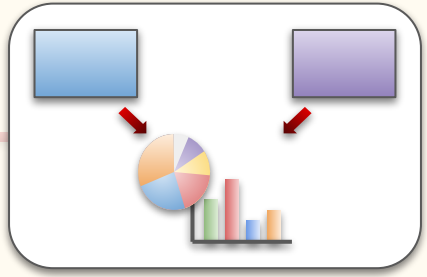


B) Concaténation

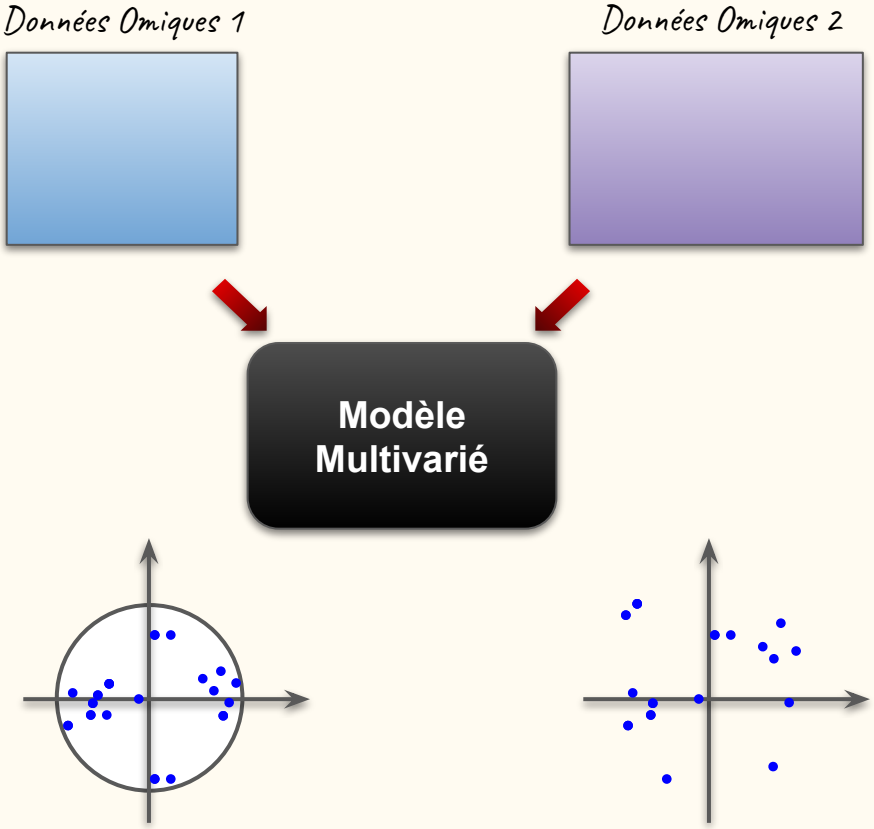


- Concaténation des données en une table
- **Machine Learning**
- Mais : poids des données, sources hétérogènes, schéma de valeurs attendues, ….

Intégration Statistique

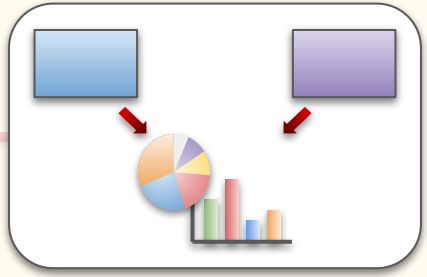


C) Multivarié

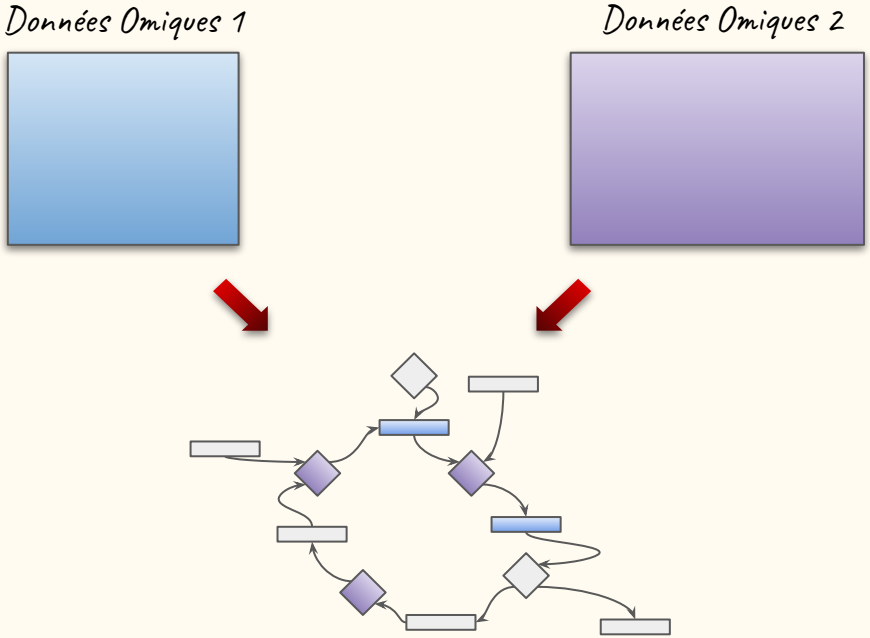


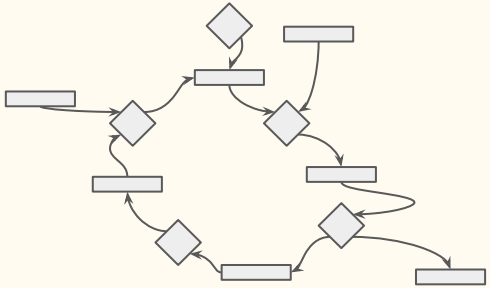
- Méthodes puissantes et à la mode
- Technique de PCA, PLS, …
- Covariance, correlation

Intégration Statistique



D) Pathways Biologiques





- "*Knowledge driven*"
- Modules fonctionnelles
- Enrichissement

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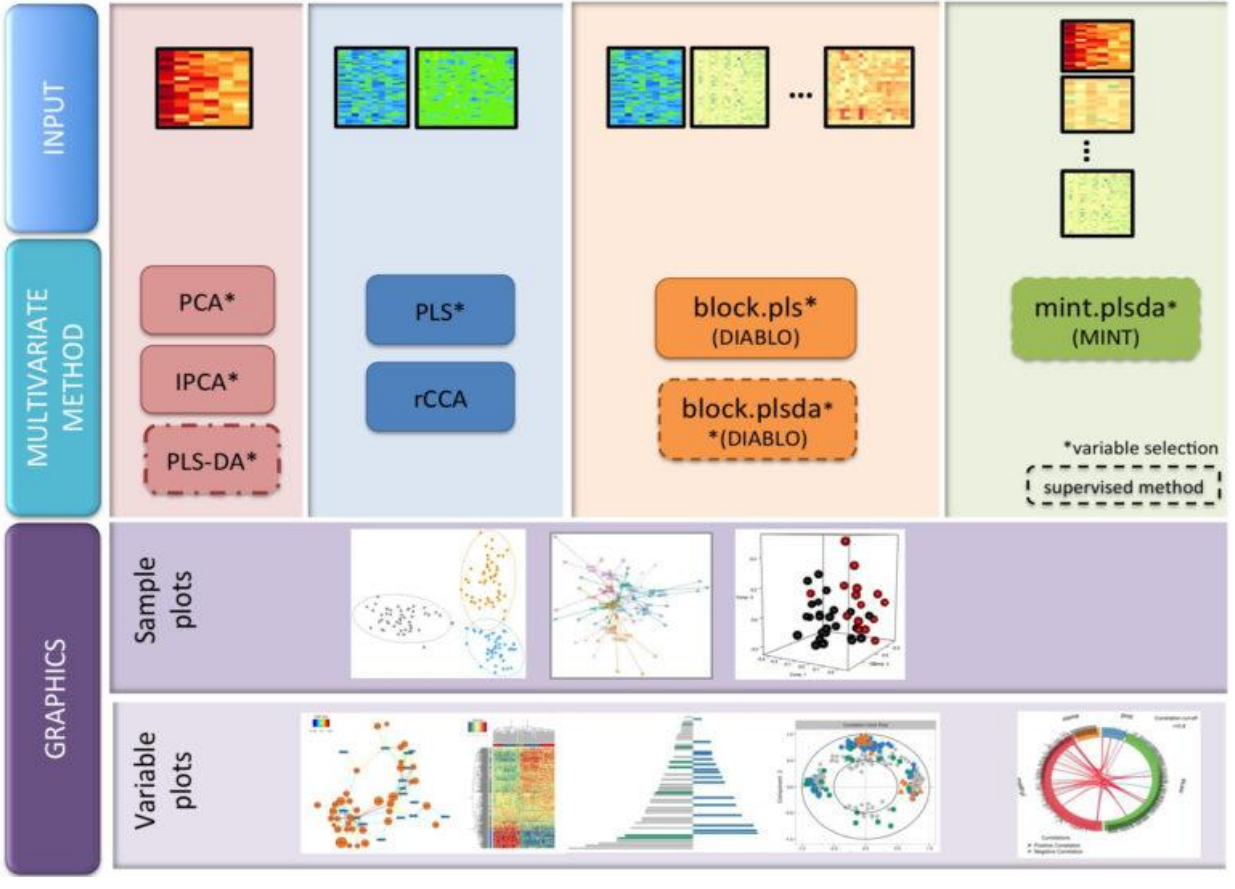
Choix des méthodes Multivariées

mixOmics

Exploration and

Integration of

Omics datasets



L'Analyse en Composante Principale

Les données

Men

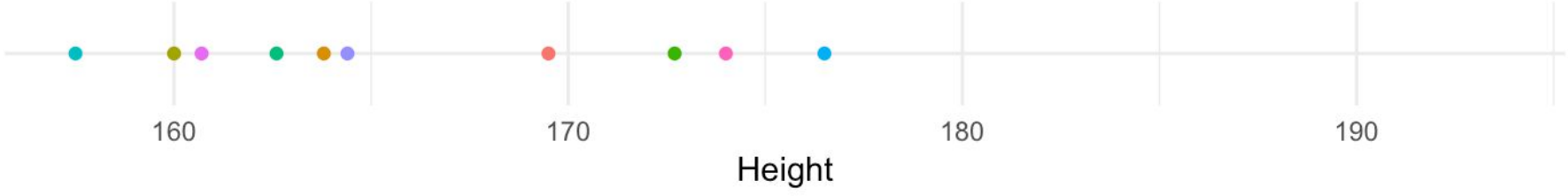
ID	Shoulders	Chest	Waist	Mass	Height
M1	106.2	89.5	71.5	65.6	174.0
M2	110.5	97.0	79.0	71.8	175.3
M3	115.1	97.5	83.2	80.7	193.5
M4	104.5	97.0	77.8	72.6	186.5
M5	107.5	97.5	80.0	78.8	187.2
M6	119.8	99.9	82.5	74.8	181.5
M7	123.5	106.9	82.0	86.4	184.0
M8	120.4	102.5	76.8	78.4	184.5
M9	111.0	91.0	68.5	62.0	175.0
M10	119.5	93.5	77.5	81.6	184.0

Women

ID	Shoulders	Chest	Waist	Mass	Height
W1	105.0	89.0	71.2	67.3	169.5
W2	100.2	94.1	79.6	75.5	160.0
W3	99.1	90.8	77.9	68.2	172.7
W4	107.6	97.0	69.6	61.4	162.6
W5	104.0	95.4	86.0	76.8	157.5
W6	108.4	91.8	69.9	71.8	176.5
W7	99.3	87.3	63.5	55.5	164.4
W8	91.9	78.1	57.9	48.6	160.7
W9	107.1	90.9	72.2	66.4	174.0
W10	100.5	97.1	80.4	67.3	163.8

L’Analyse en Composante Principale

Comment représenter les données ?



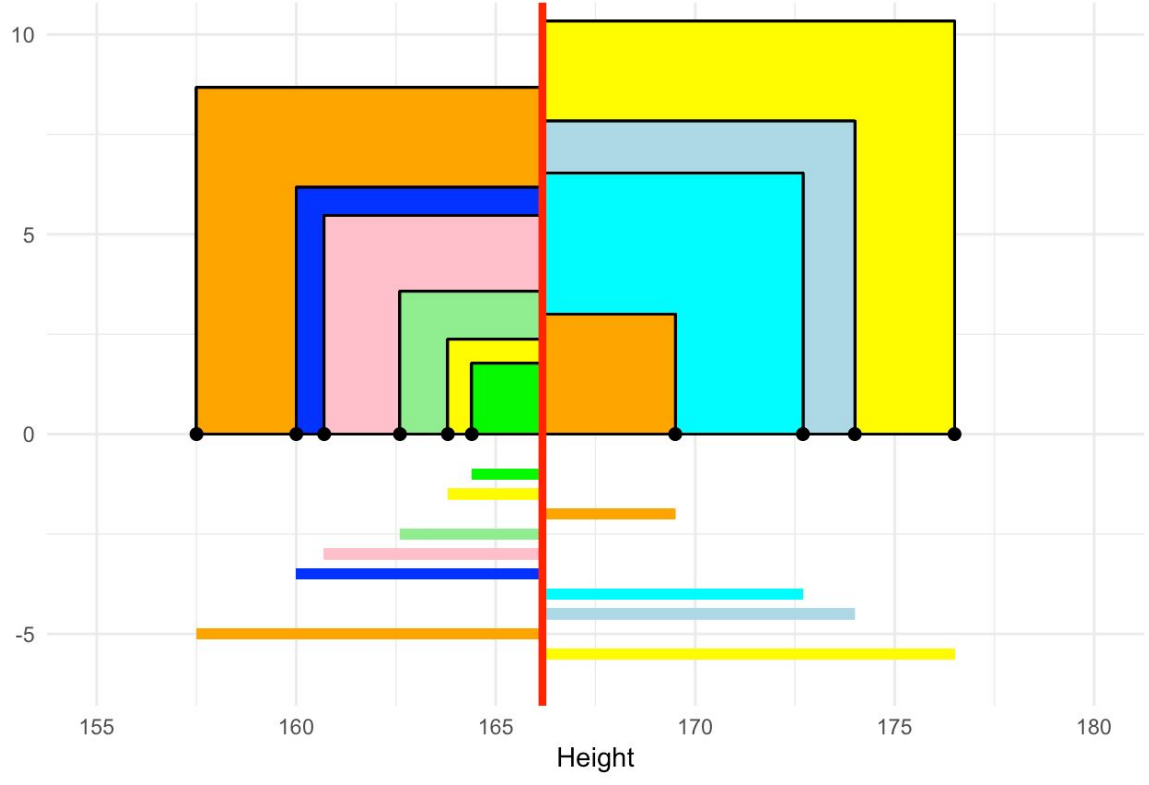
L'Analyse en Composante Principale

Indicateur de dispersion

- La **moyenne** $\bar{x} = \frac{1}{n}\left(\sum_{i=1}^{n} x_i\right) = \frac{x_1 + x_2 + \cdots + x_n}{n}$
- L'**étendue** $E = x_{\max} - x_{\min}$
- La **variance** $V = \frac{1}{n}\sum_{i=1}^{n}(x_i - \overline{x})^2$
- L'**écart-type** $\sigma = \sqrt{V} = \sqrt{\frac{1}{n}\sum_{i=1}^{n}(x_i - \overline{x})^2}$

L’Analyse en Composante Principale

Variance et Écart-type



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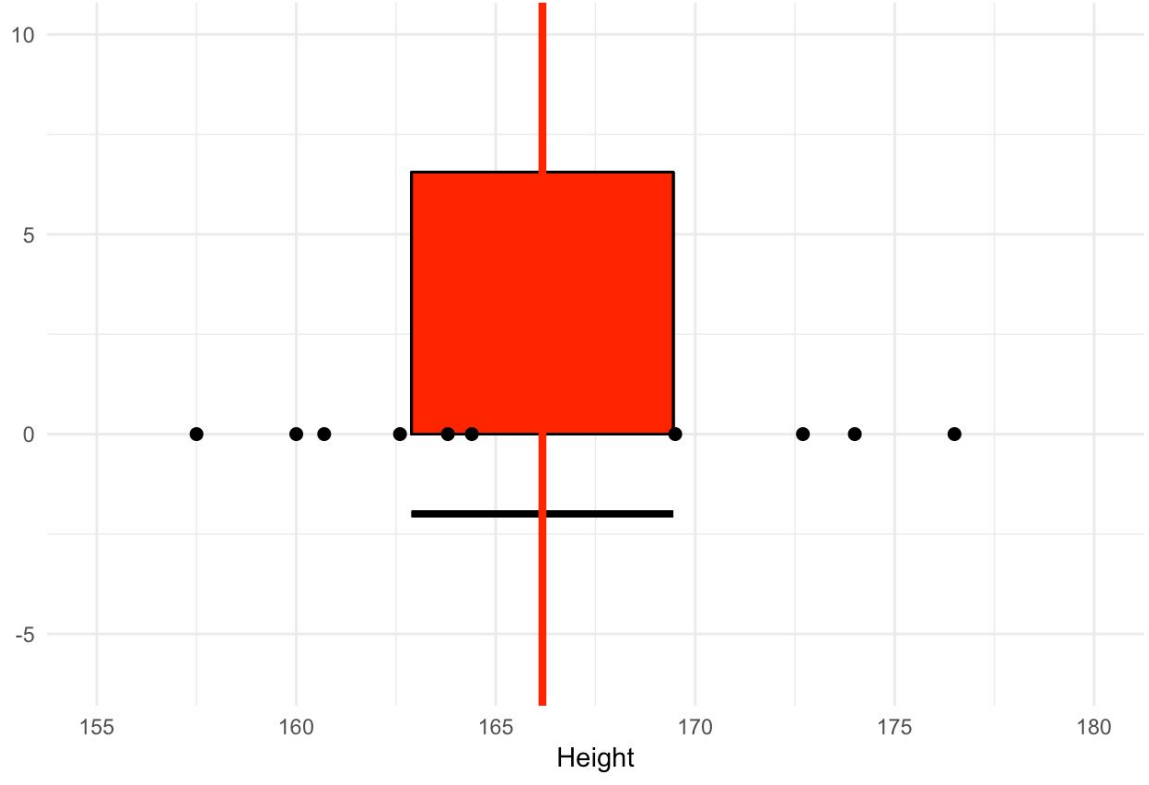
Variance et Écart-type



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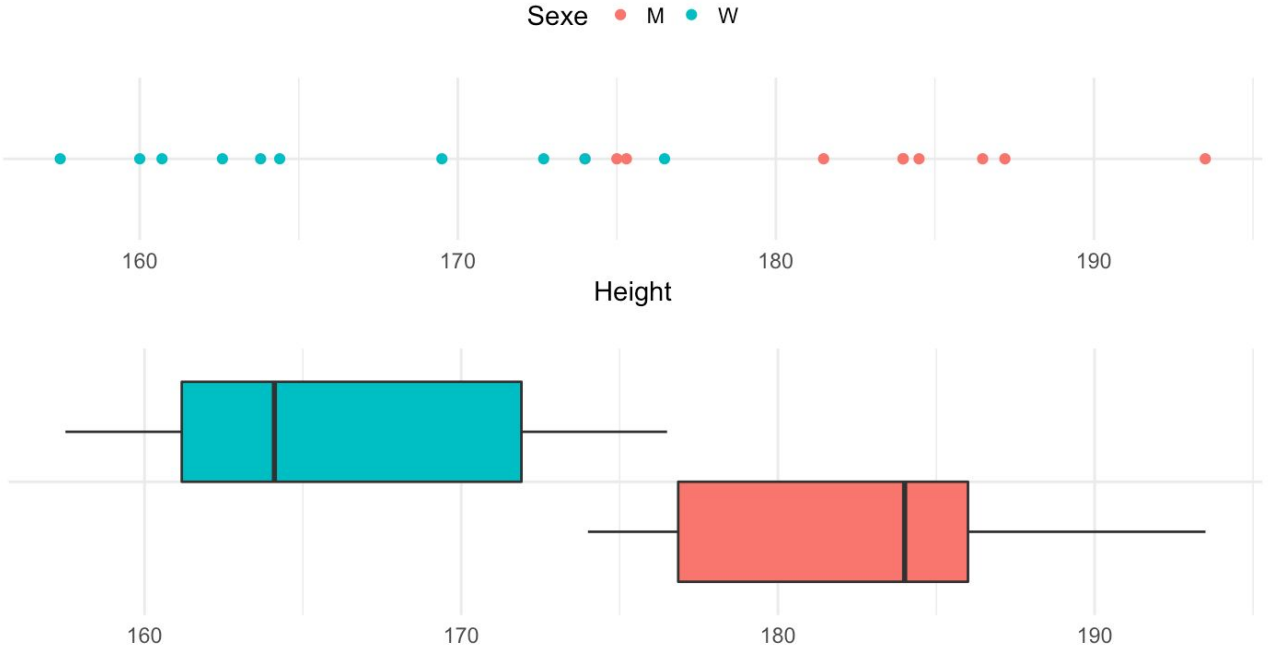
1D



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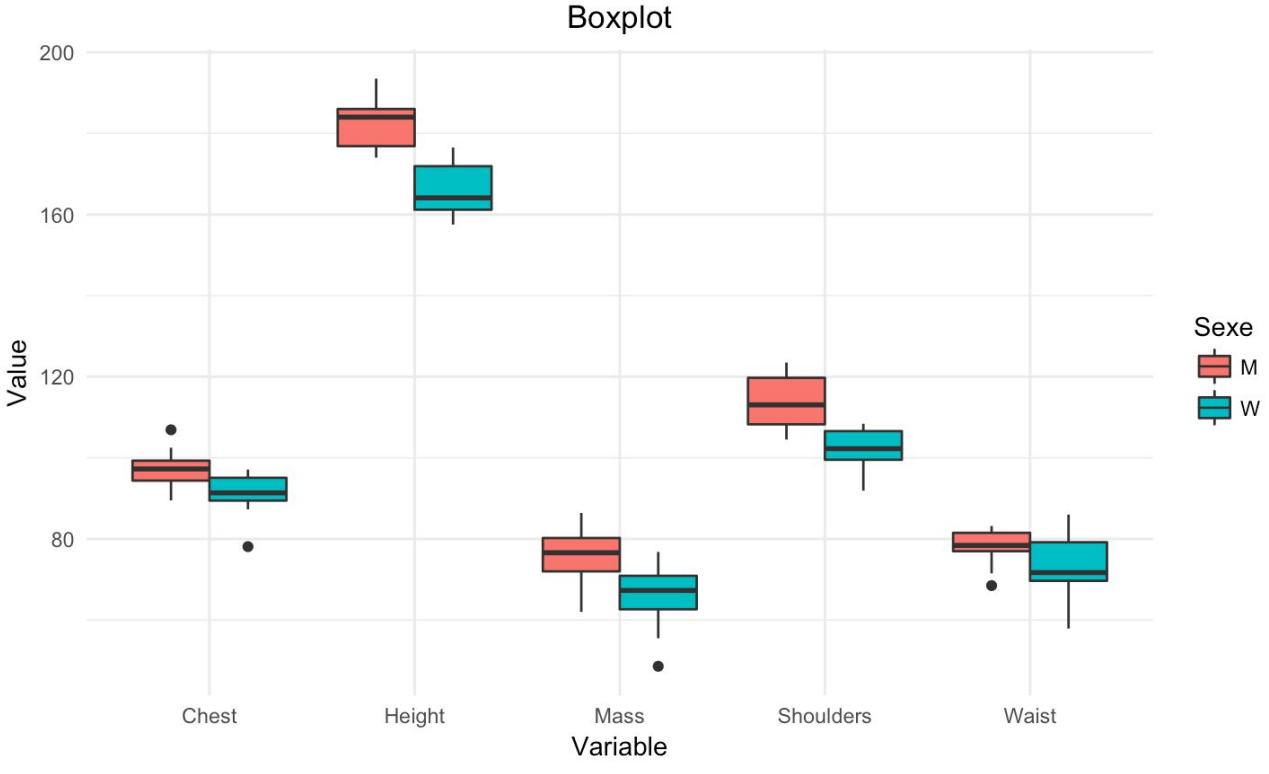
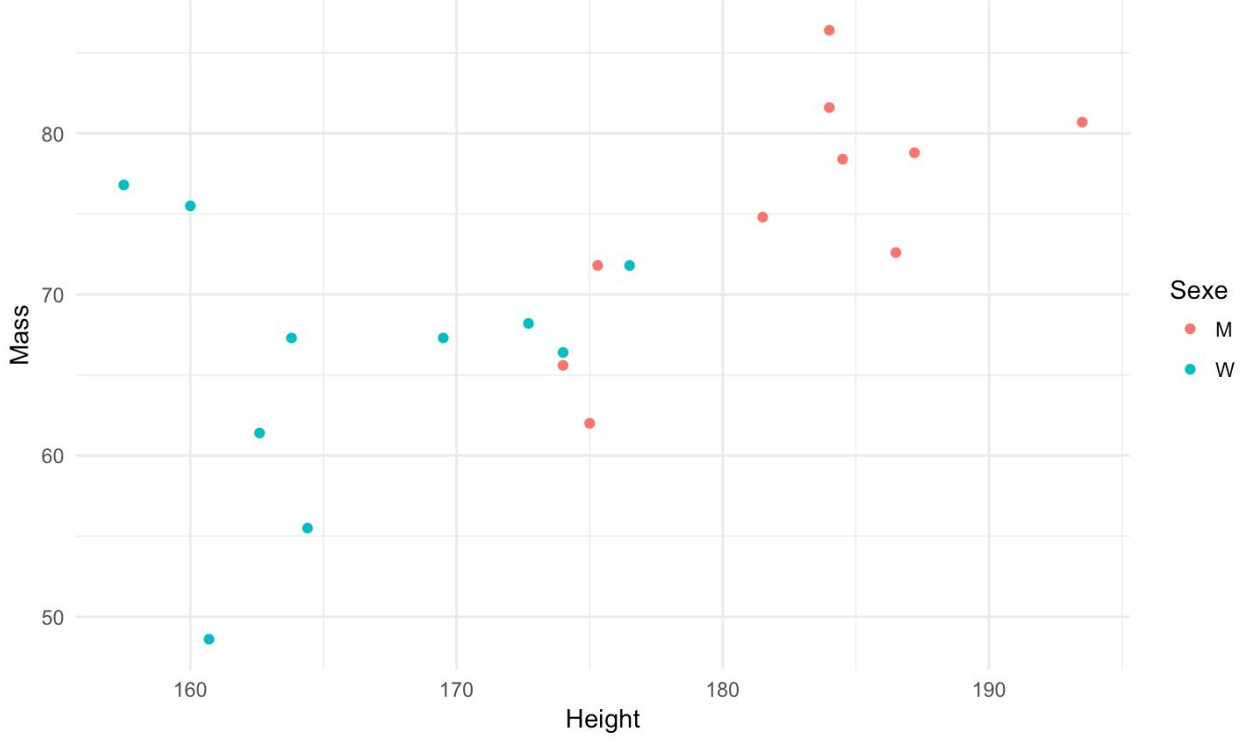


L’Analyse en Composante Principale

Comment représenter les données ?

2D



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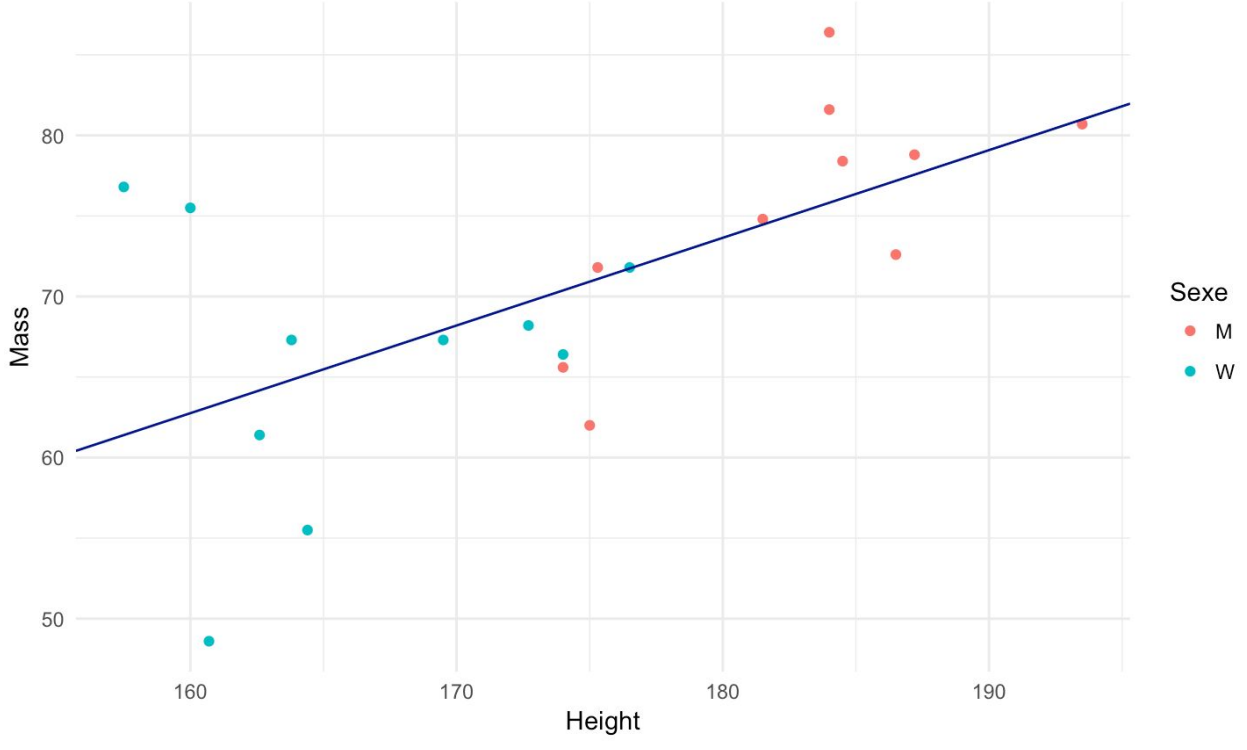

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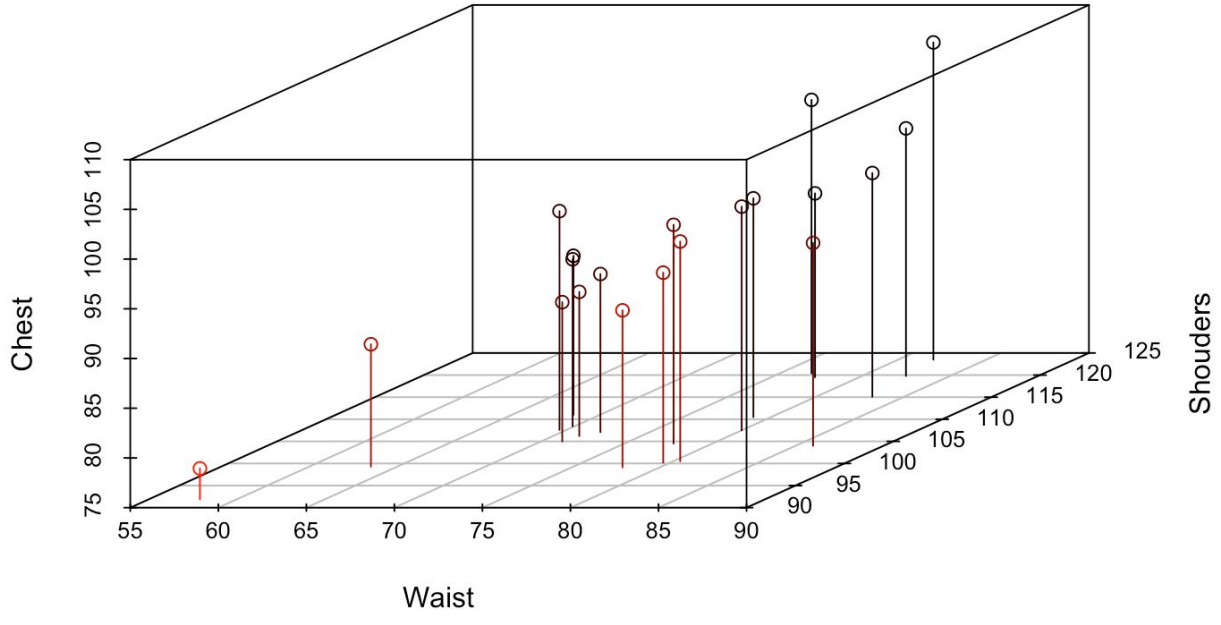

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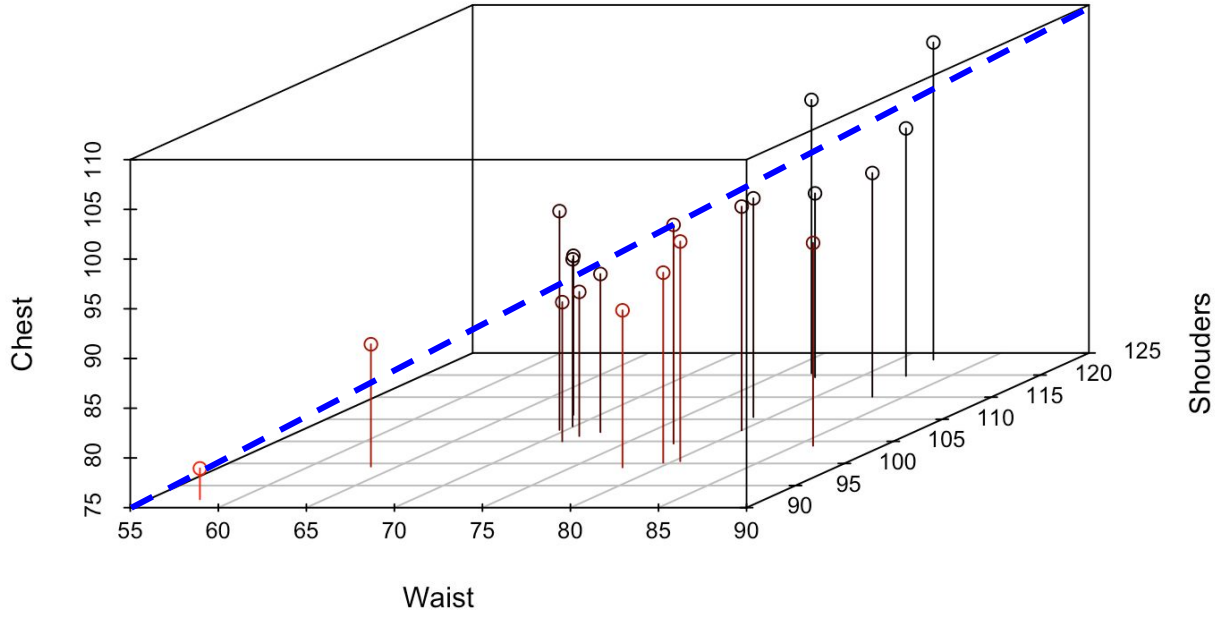

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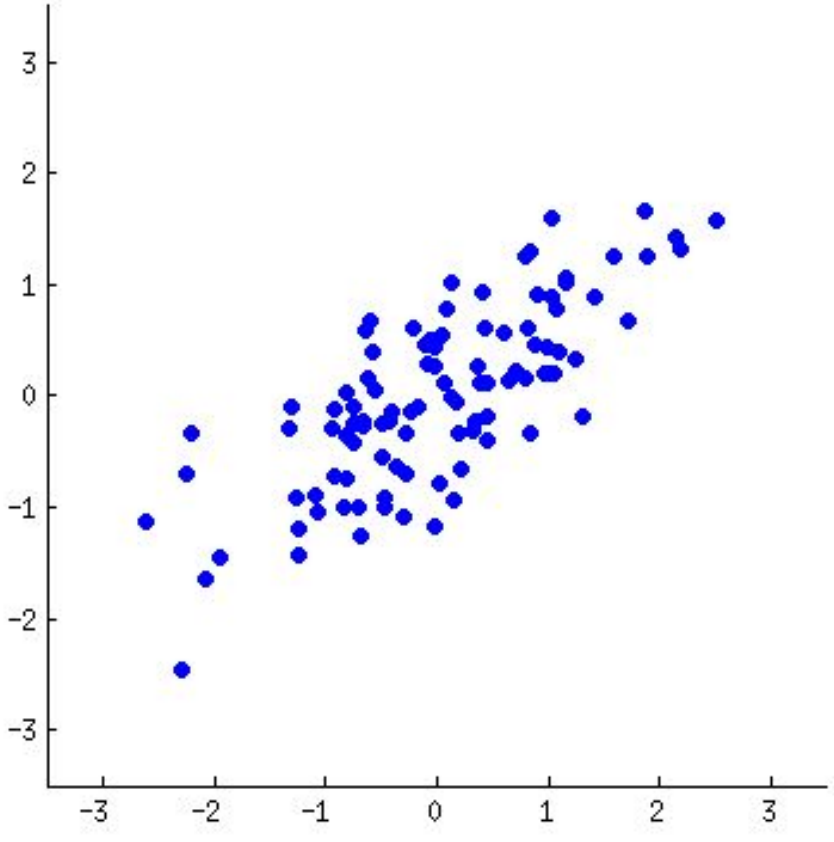
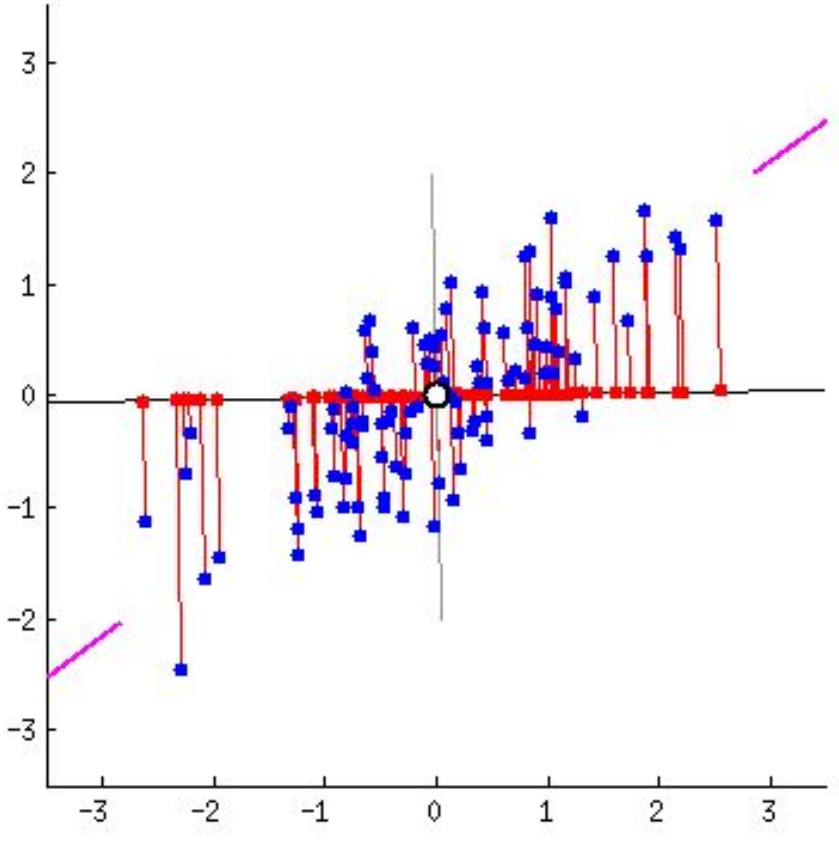


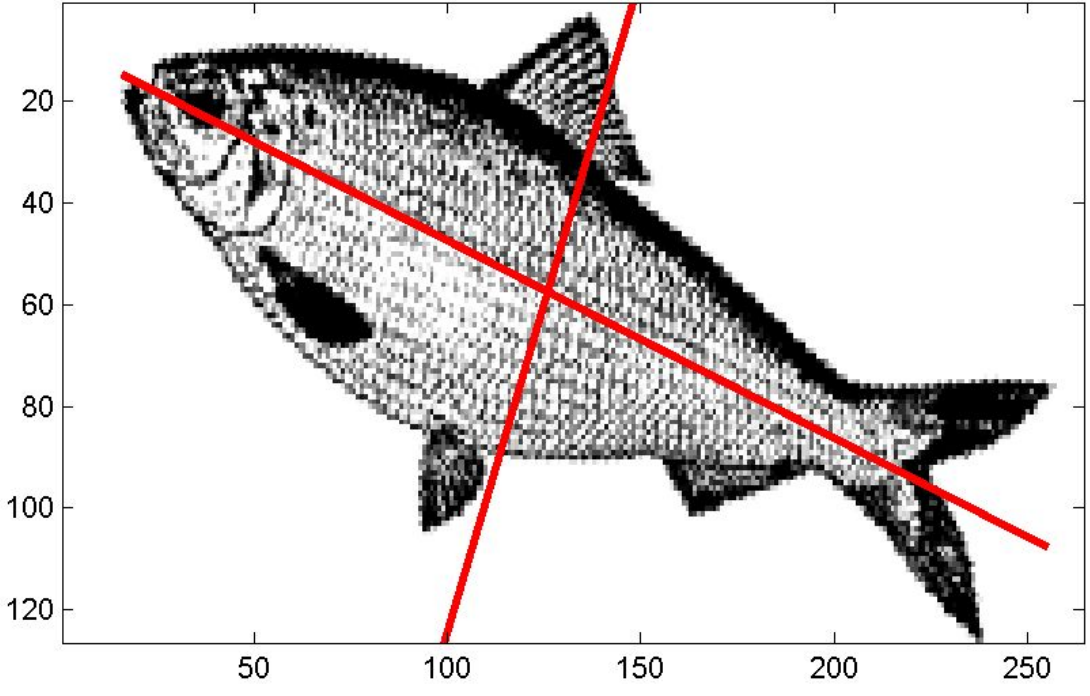
https://stats.stackexchange.com/questions/2691/making-sense-of-principal-component-analysis-eigenvectors-eigenvalues

L’Analyse en Composante Principale



https://stats.stackexchange.com/questions/2691/making-sense-of-principal-component-analysis-eigenvectors-eigenvalues

L’Analyse en Composante Principale



https://upload.wikimedia.org/wikipedia/commons/9/90/PCA_fish.png

L'Analyse en Composante Principale

X =

	Gene-A	Gene-B	Gene-C
Ech1	10	5	6
ECh2	42	49	2
...			

components =

	PC1	PC2	PC3
Ech1	6.1	1.2	1.5
ECh2	42.9	8.6	2.5
...			

0.2 x *(a1)*

Gene-A
10
42

\+ 0.7 x *(a2)*

Gene-B
5
49

\+ 0.1 x *(a3)*

Gene-C
6
2

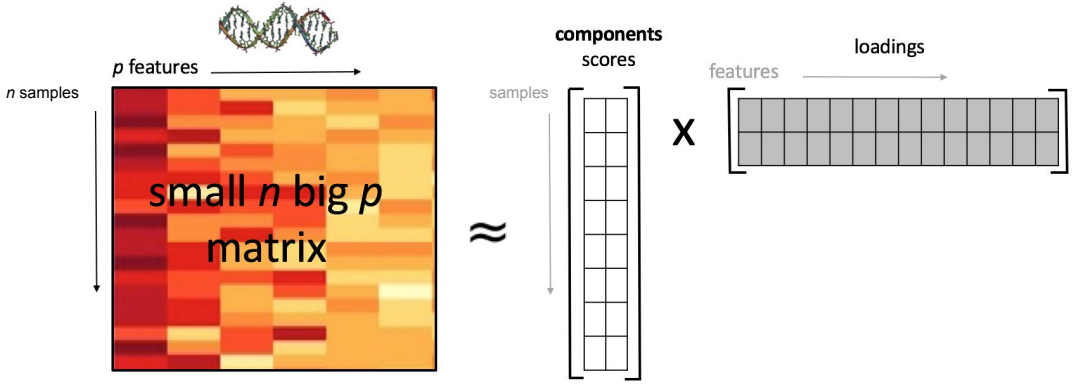
=

Linear Comb.
6.1
42.9

a = loading vectors

= PC

L'Analyse en Composante Principale



$$\arg \max_{||a^h||=1} \text{var}(Xa^h)$$

Solved with SVD:

$$X = U\Delta A^T$$

Singular vectors:

- $T = U\Delta$, T contains the PCs $\boldsymbol{t}^h$
- A contains the loading vectors $\boldsymbol{a}^h$

Singular values:

- Δ diagonal matrix with $\sqrt{\delta_h}$

PCA dimension: $h = 1..H$

X (n x p) is decomposed into:

- **principal components PC**
- **loading vectors associated to each PC**

=> such that var(PC) is max.

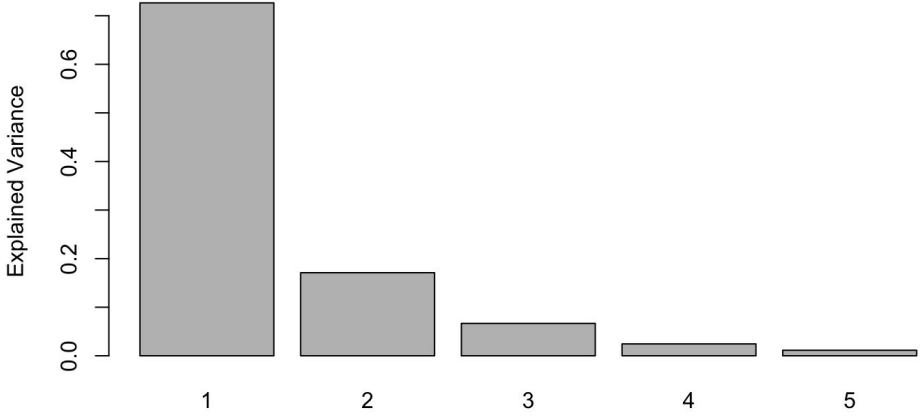
The variance of the first principal component $\boldsymbol{t}^1$ is the largest ($= \delta_1$).

The eigenvalues δ_h decrease and correspond to the explained variance per component.

Slide from K-A Lê Cao

Exemple d'ACP - Nombre de composantes

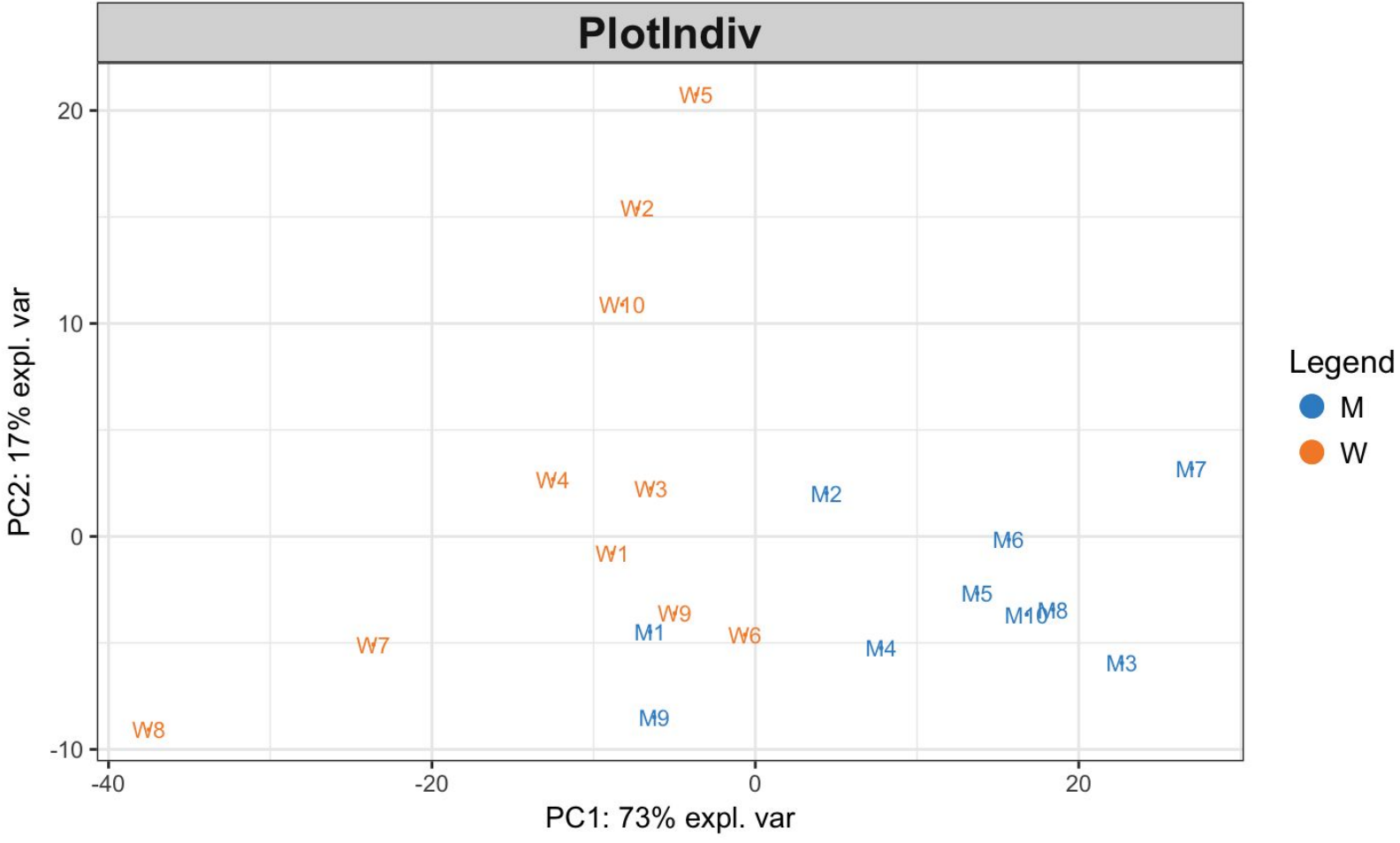
```
## Eigenvalues for the first 5 principal components, see object$sdev^2:
##        PC1        PC2        PC3        PC4        PC5
## 255.655833  60.183388  23.484105   8.607990   4.010947
##
## Proportion of explained variance for the first 5 principal components, see object$explained_variance:
##        PC1        PC2        PC3        PC4        PC5
## 0.72641413 0.17100358 0.06672715 0.02445853 0.01139661
##
## Cumulative proportion explained variance for the first 5 principal components, see object$cum.var:
##       PC1       PC2       PC3       PC4       PC5
## 0.7264141 0.8974177 0.9641449 0.9886034 1.0000000
```



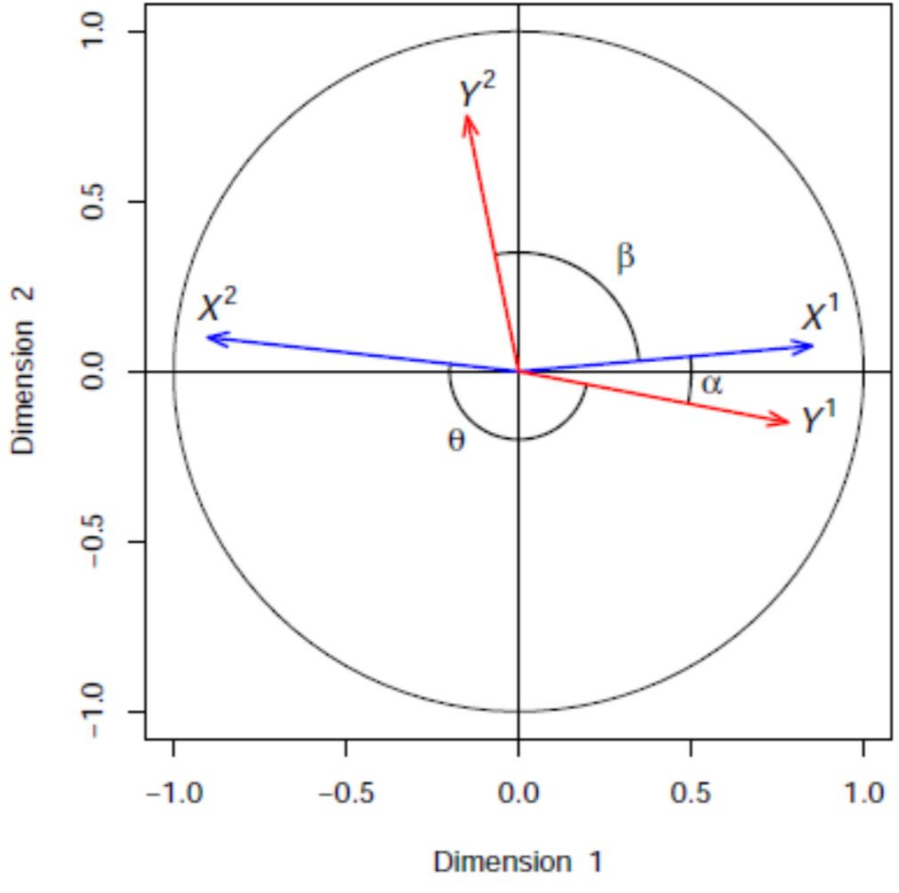
- Critère de Kaiser
- Seuil de variance expliquée
- Critère du coude

```
> plot(pca.res)
```

Exemple d'ACP - graphe des individus

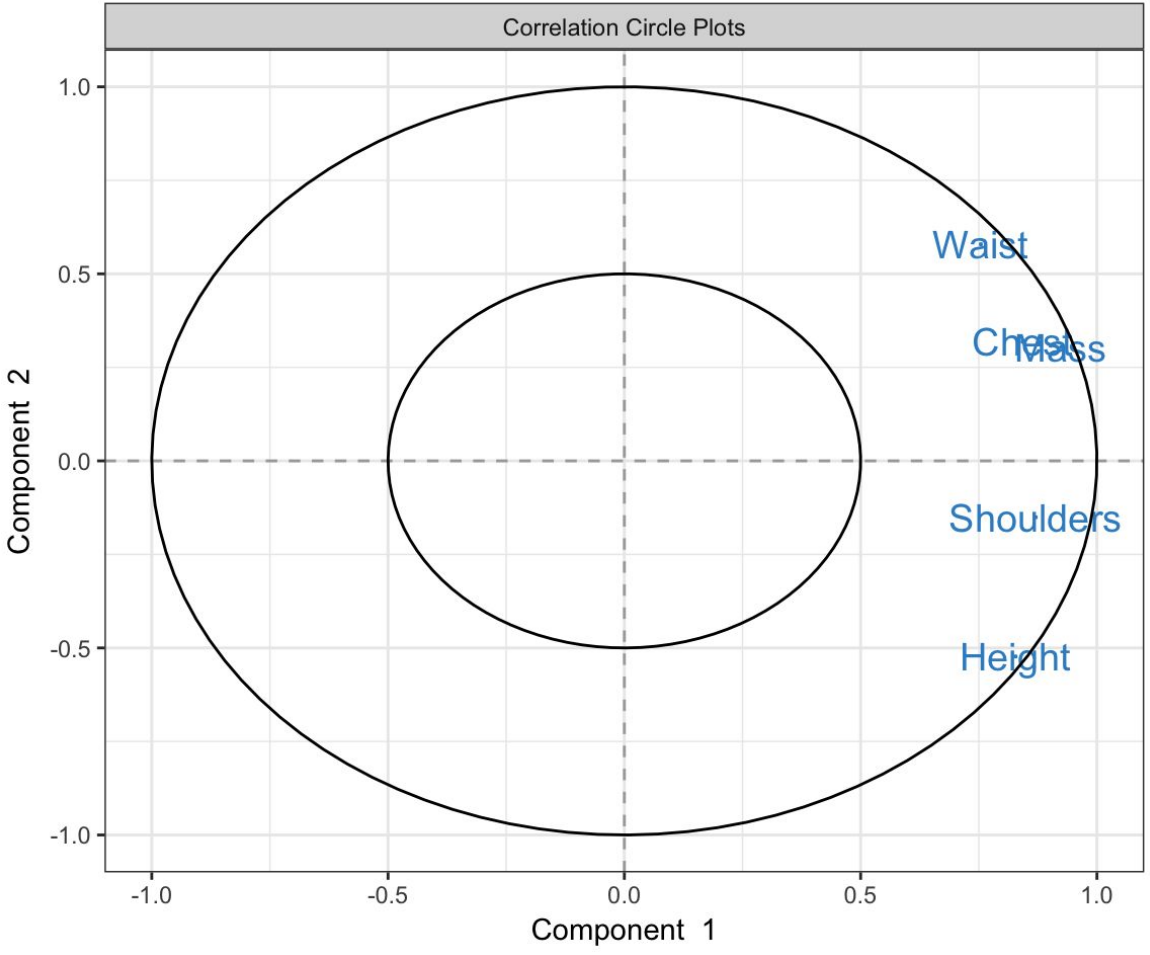


Exemple d'ACP - graphe des variables

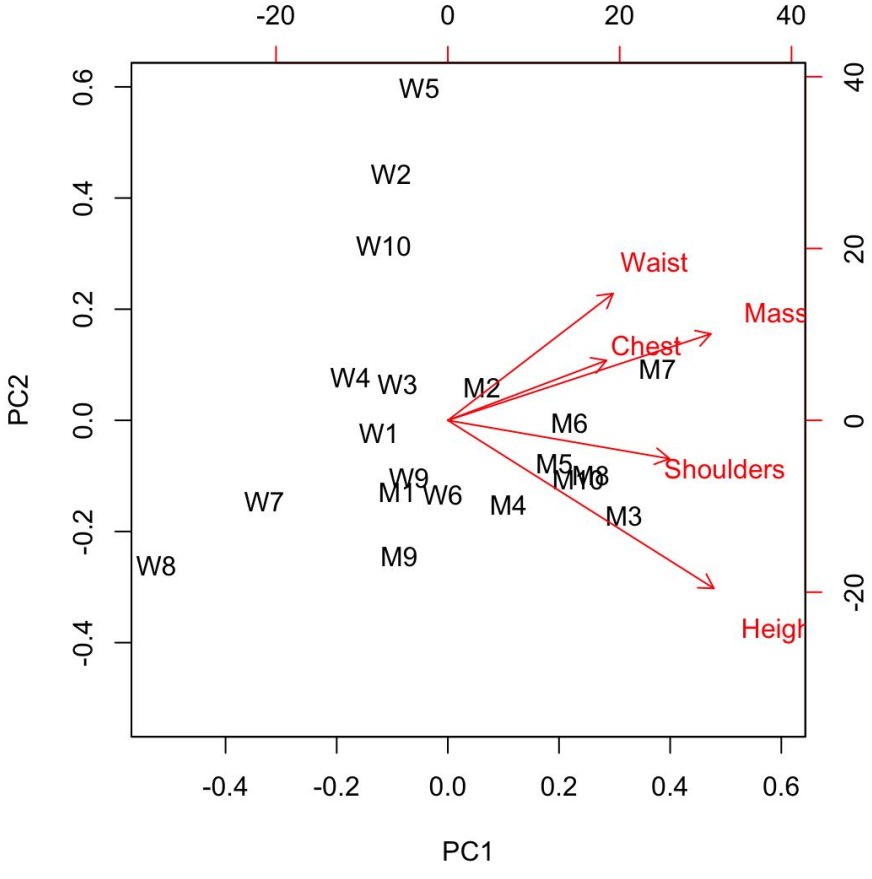


- Hypersphères des corrélations
- Corrélation entre 1 variables :
  - positive
  - négative
  - nulle
- Contribution aux axes

Exemple d'ACP - graphe des variables



Exemple d'ACP - biplot



N-Intégration

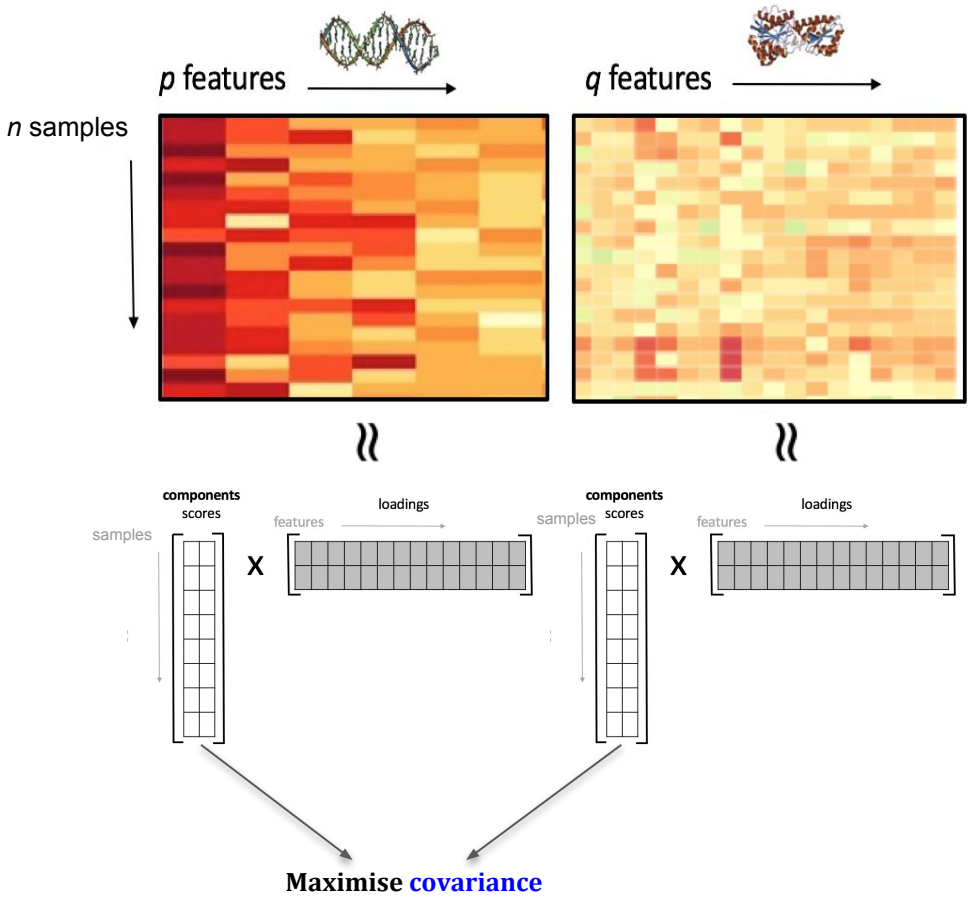
P-Intégration

PLS: Projection on Latent Structures

PLS maximises the **covariance** between 2 sets of data

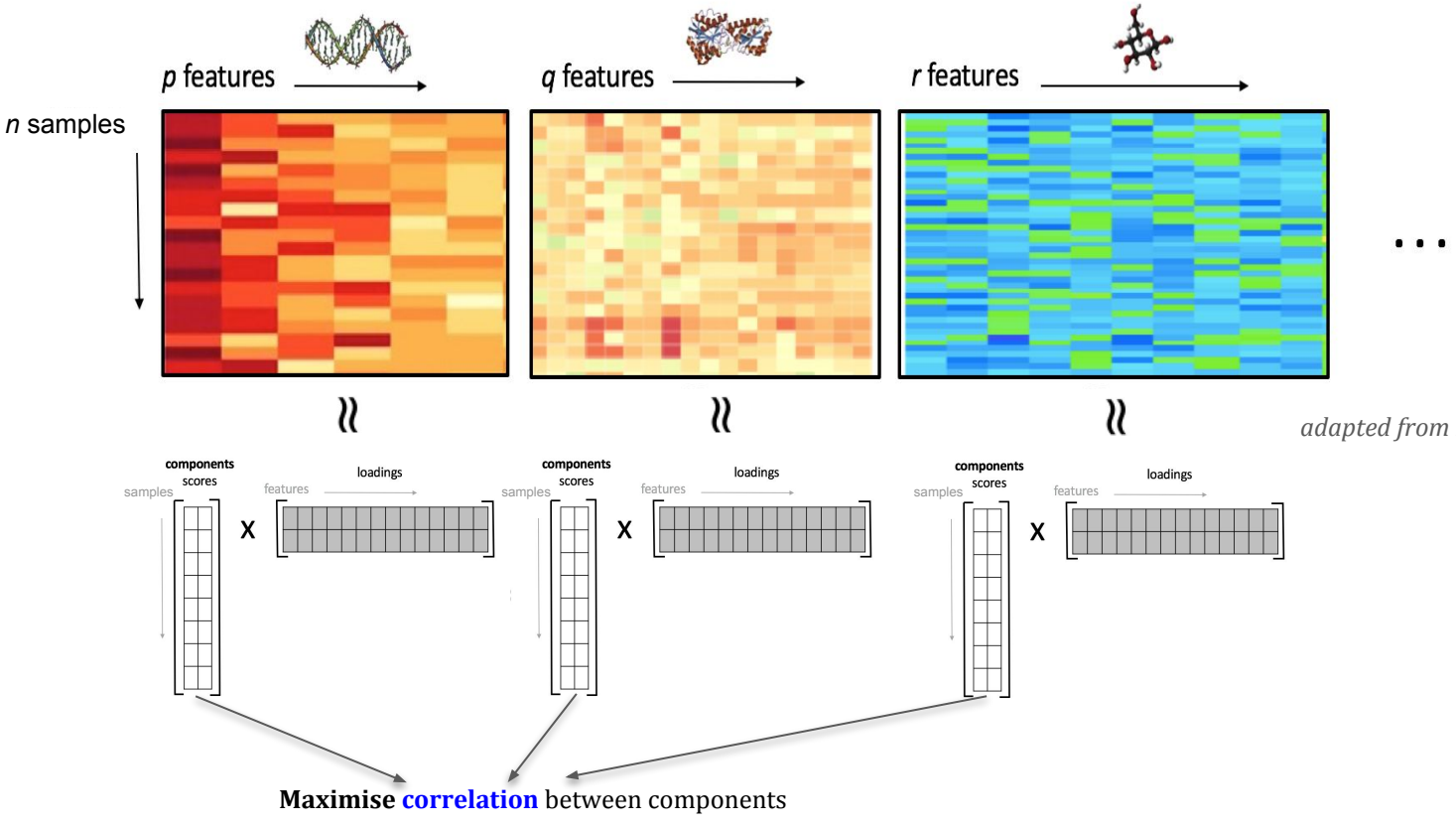
$$\arg \max_{||a^h||=1, ||b^h||=1} \text{cov}(Xa^h, Yb^h)$$

Loading vectors obtained from $\texttt{svd}(X_1^T X_2)$

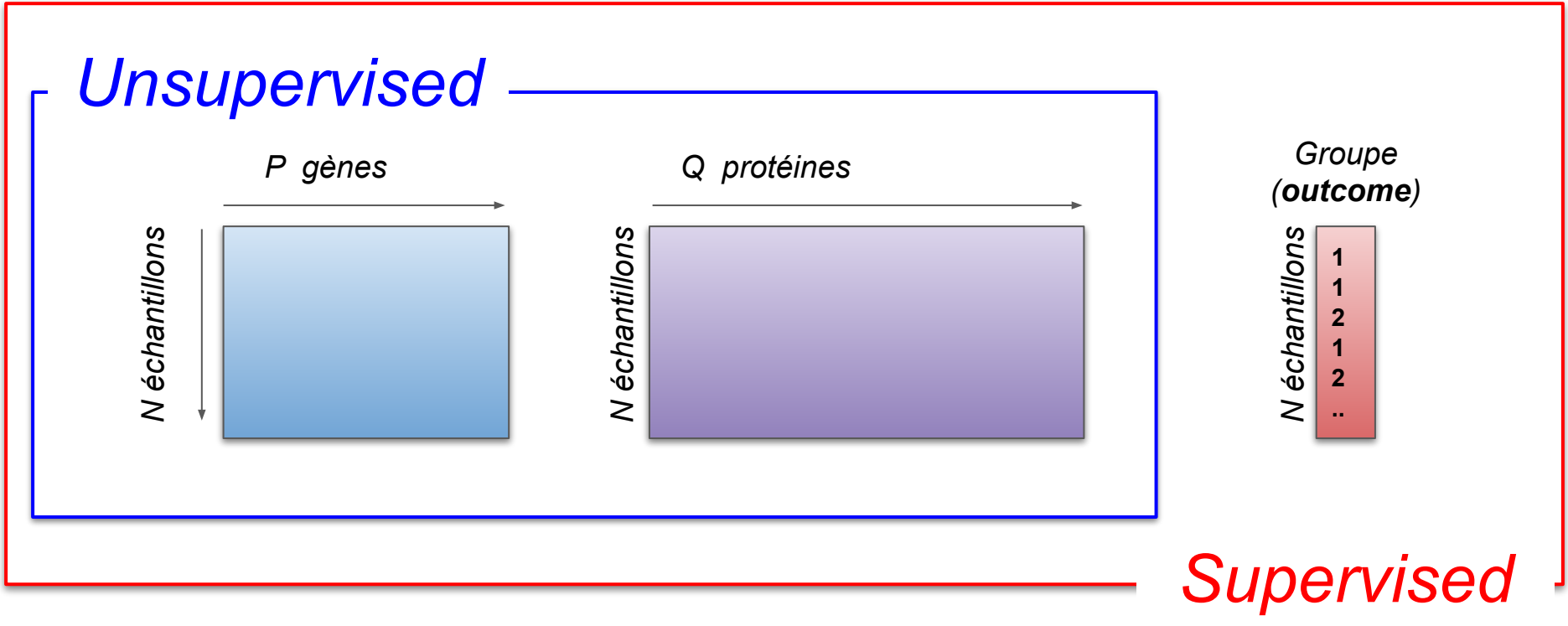


Adapted from K-A Lê Cao

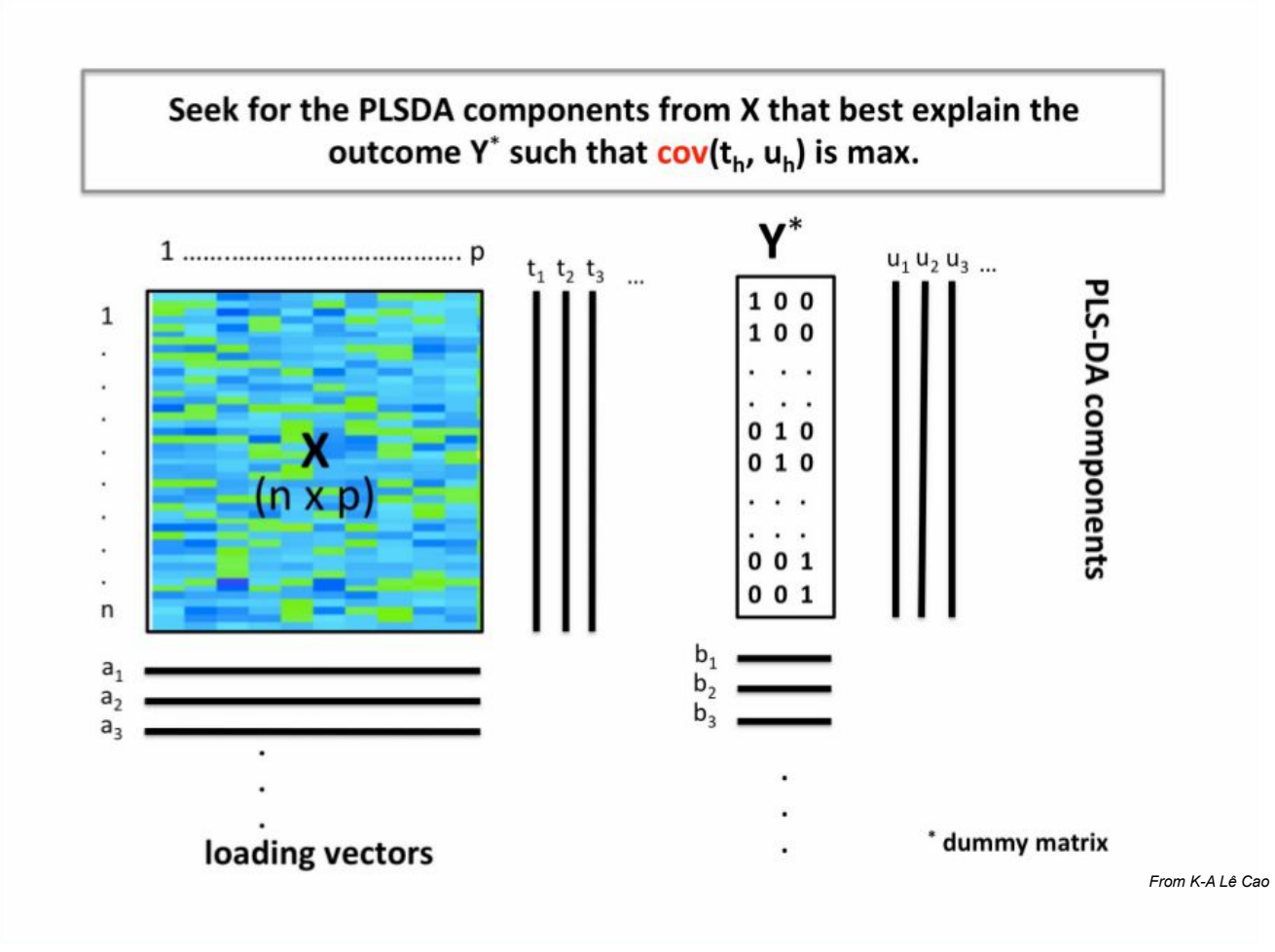
Multi-block PLS



adapted from K-A Lê Cao


Unsupervised
P gènes
N échantillons
Q protéines
N échantillons
Groupe
(outcome)
N échantillons
1
1
2
1
2
..
Supervised

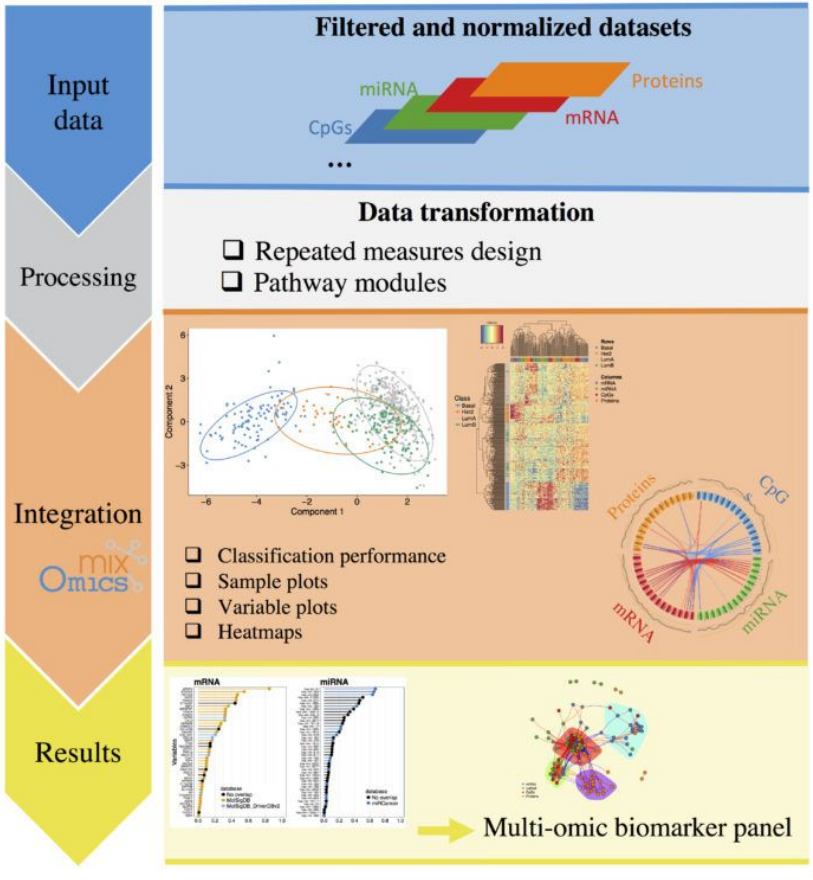
PLS - Discriminant Analysis (PLS-DA)



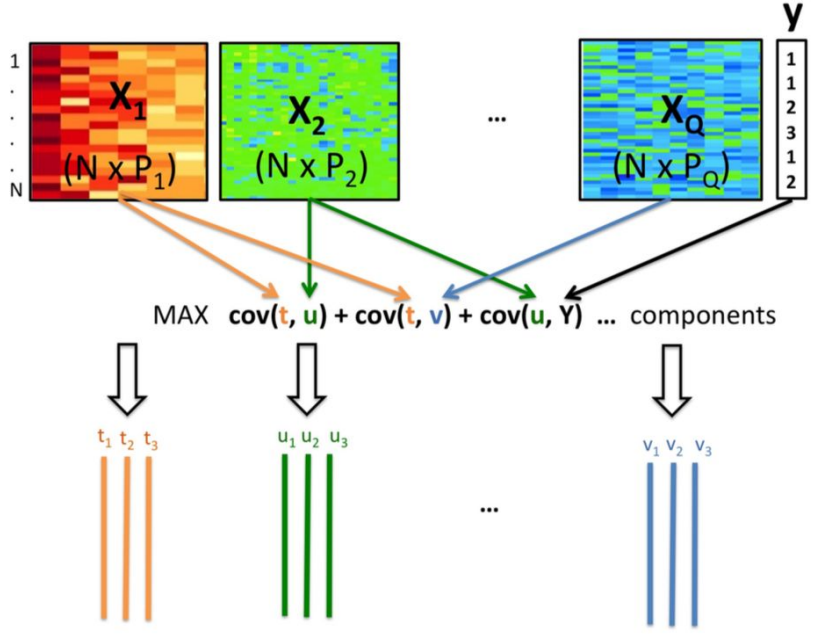
From K-A Lê Cao

DIABLO

Data Integration Analysis for Biomarker discovery using Latent Variables approaches for Omics studies

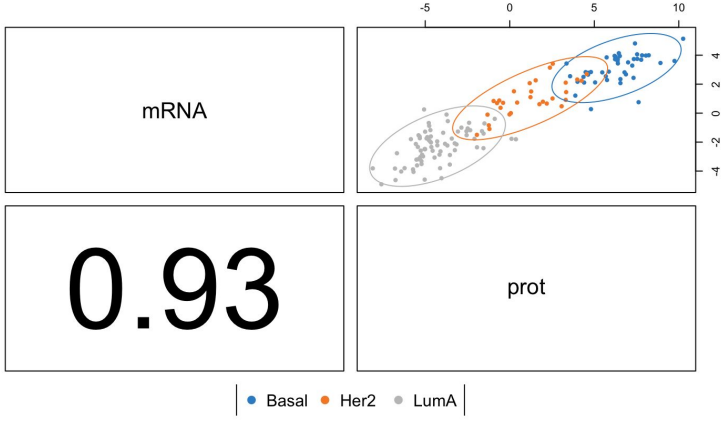


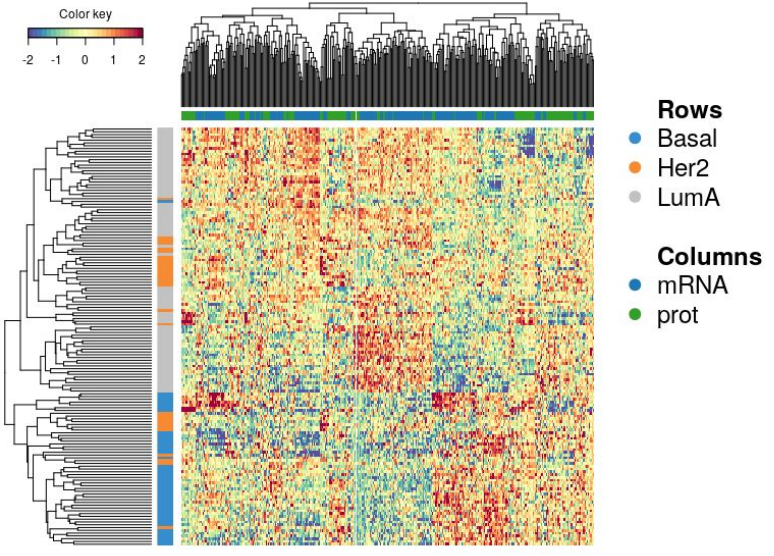
D I A B L O

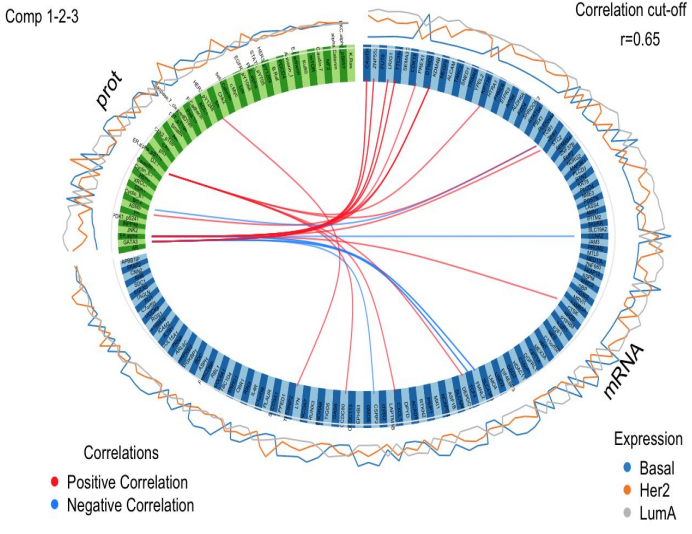


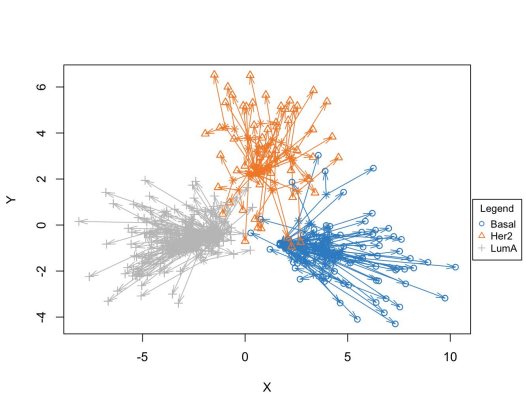
From K-A Lê Cao

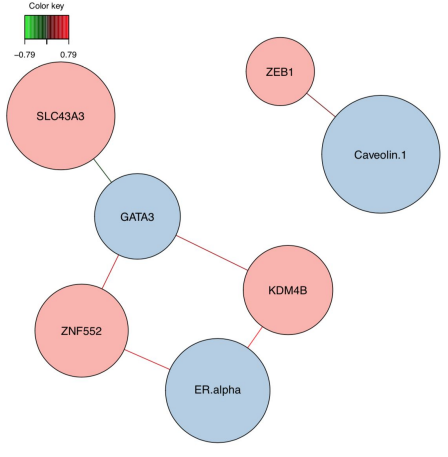
DIABLO


mRNA
0.93
prot
Basal
Her2
LumA


Color key
Rows
Basal
Her2
LumA
Columns
mRNA
prot

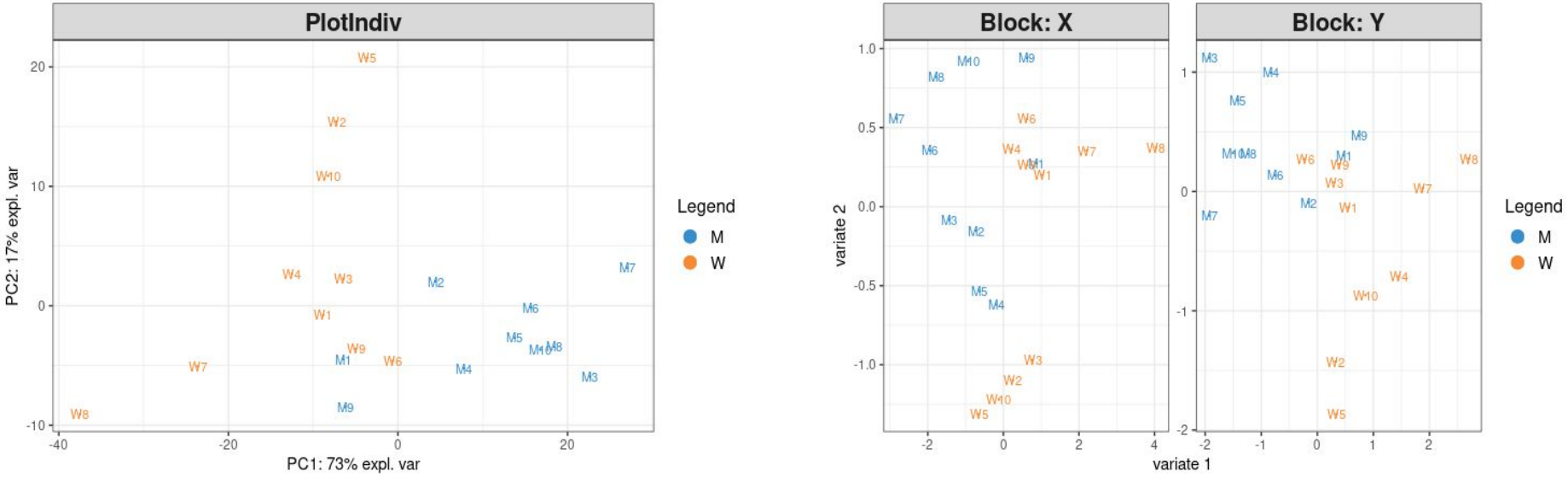

Comp 1-2-3
Correlation cut-off
r=0.65
prot
mRNA
Correlations
Positive Correlation
Negative Correlation
Expression
Basal
Her2
LumA


Legend
Basal
Her2
LumA
X
Y


Color key
SLC43A3
ZEB1
Caveolin.1
GATA3
KDM4B
ZNF552
ER.alpha

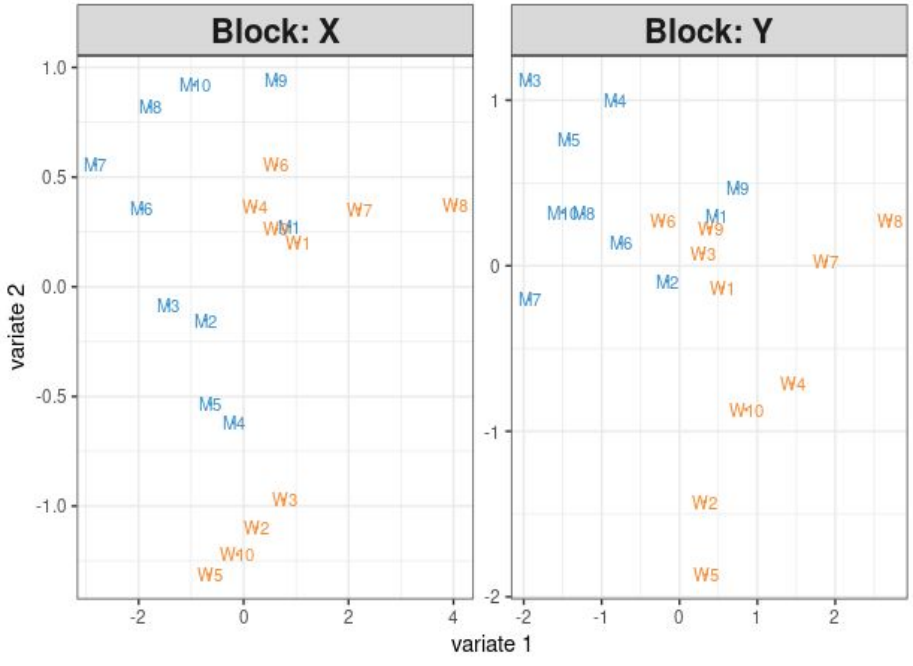
mixOmics Graphical Output

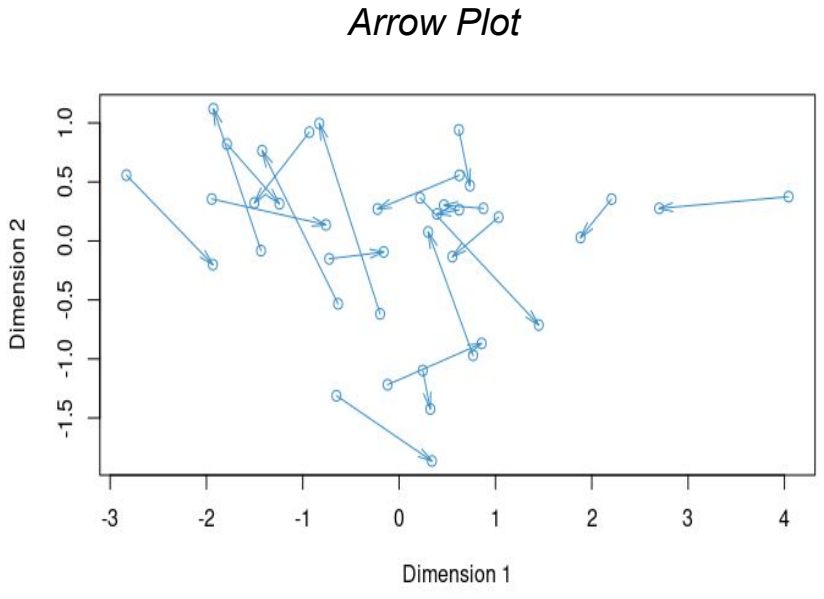
1. Samples plots



- Projection des échantillons (samples) dans l'espace produit par les nouvelles variables instrumentales (components, latent structures, …)
- similarité entre les échantillons (clustering)
- autres méthodes pour représenter les échantillons dans mixOmics: *plotArrow* (paired: X -> Y)

```
> plotIndiv(...)
```



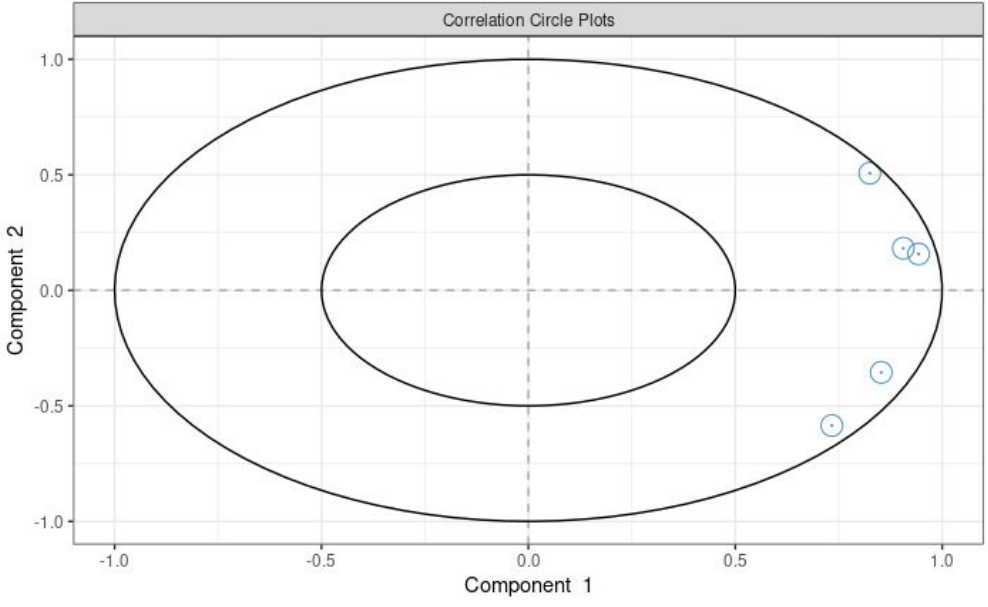


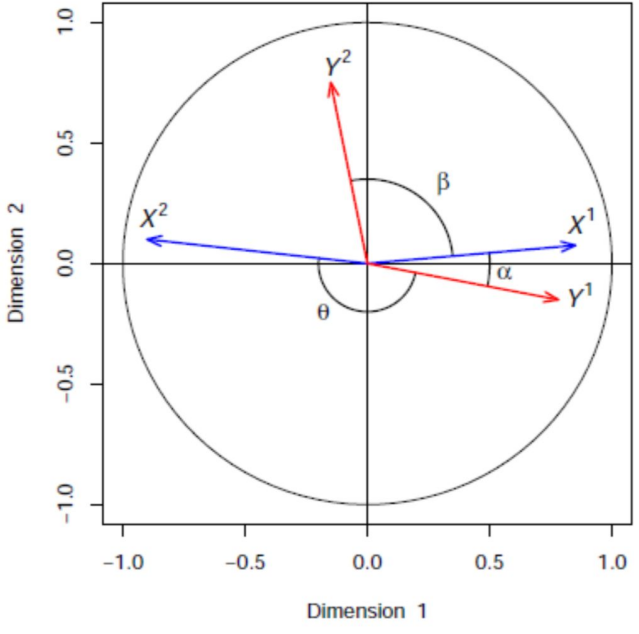
- 2 *blocs*
- 1 flèche = 1 échantillon.
- Origine = l'emplacement de l'échantillon en X, la pointe = l'emplacement dans Y
- Courtes flèches = X et Y sont en accord pour cet échantillon et inversement.

```
> plotArrow(...)
```

2. Variables plots

Circle Correlation plot

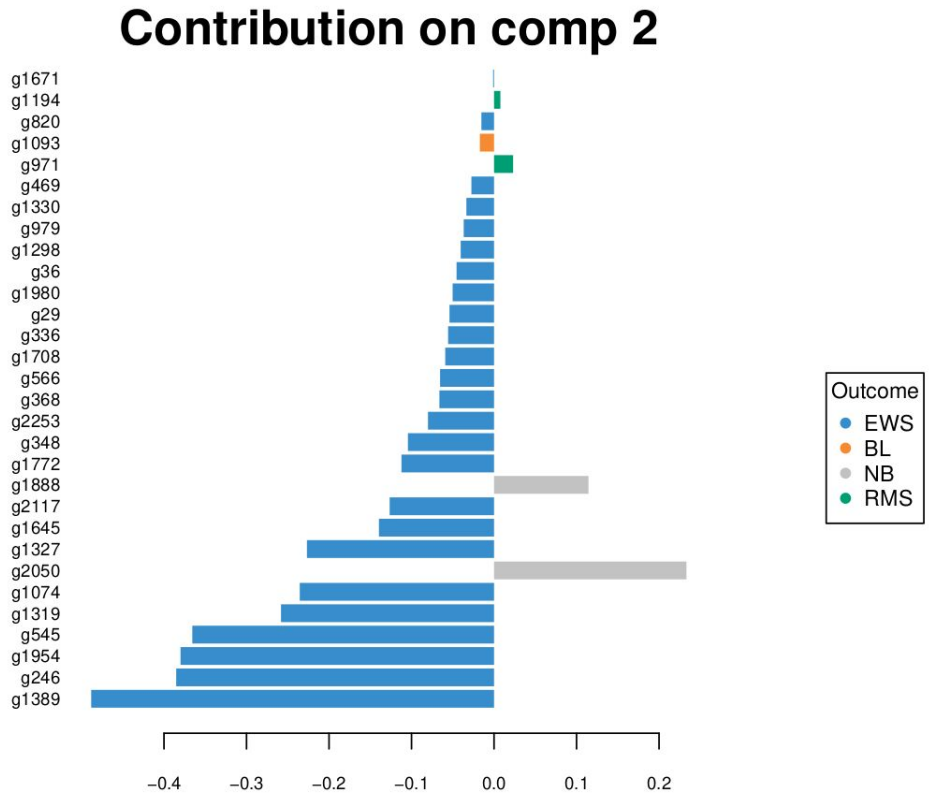




- Visualise les relations entre les variables et les composantes (*structure latentes*)
- Importance de la longueur du vecteur et du cosinus de l'angle avec l'axe
- Montre l'importance des variables / contribution par rapport aux composantes

```
> plotVar(...)
```

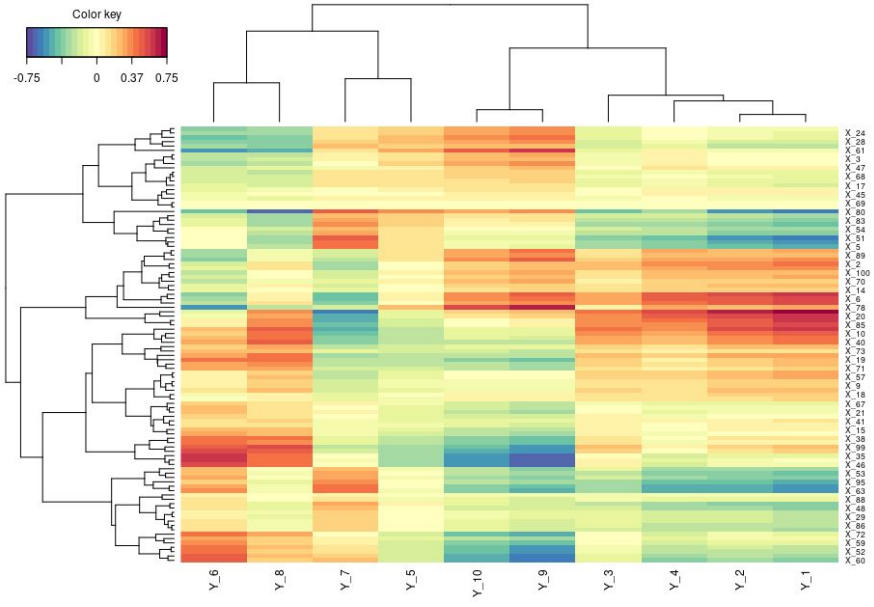
Loading plot

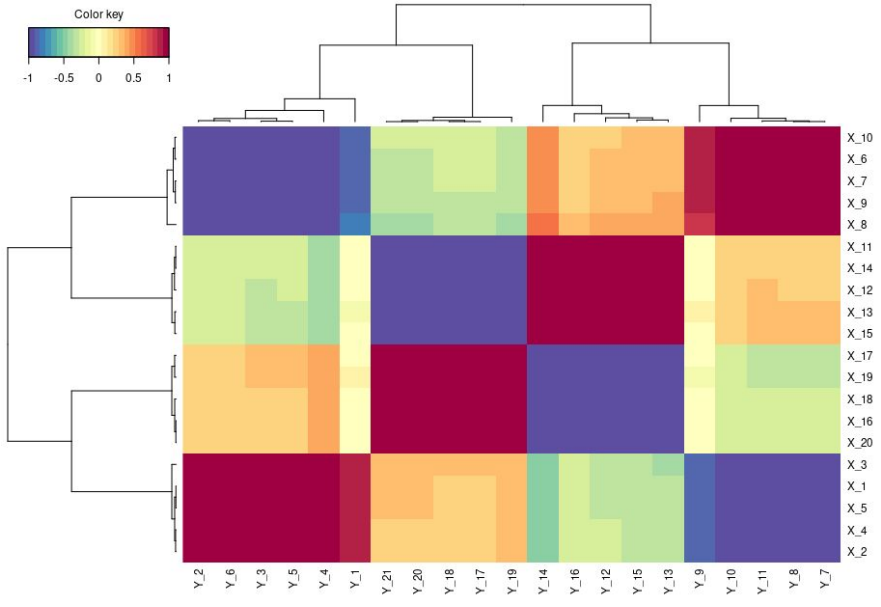


- Très similaire au *CCplot*
- Importance des variables chaque composantes (taille des barres)
- Ordonnée par ordre d'importance
- en mode *supervisé*, la couleur correspond au groupe le plus proche

```
> plotLoadings(...)
```

Clustered Image Map

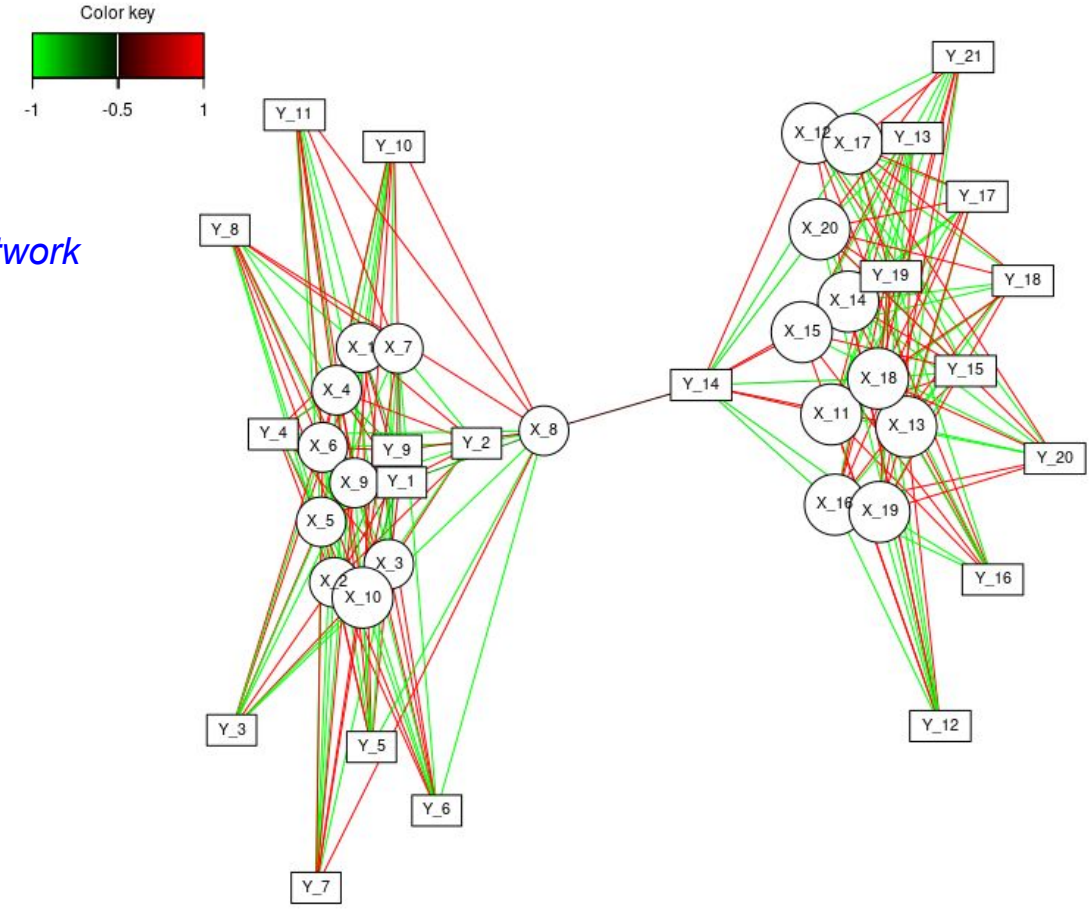




- Correlation = couleur
- Montre la corrélation entre des ensembles de variables de type différents (2 blocs)
- Clusters
- Dendrogramme

```
> cim(...)
```

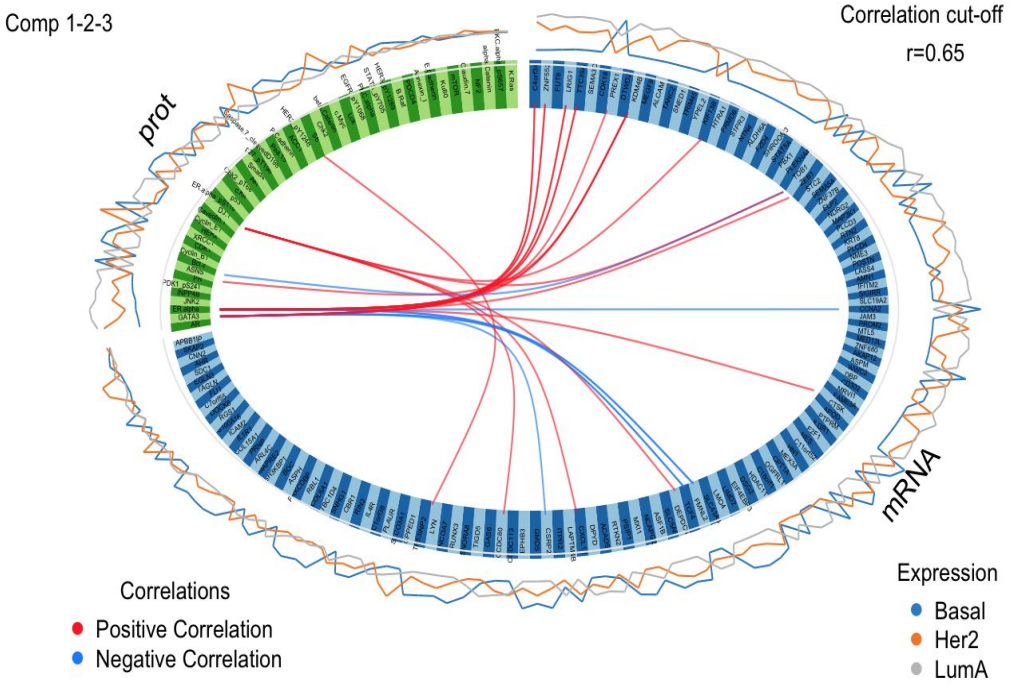
Relevance Network



- Montre la corrélation entre 2 variables (2 à 2) par un lien (tous les blocs).
- Corrélation = couleur du lien *(positif/négatif, fort/faible)*
- choix du *cutoff* *(affichage des liens)*
- Recherche de clique / sous-réseau

```
> network(...)
```

Circos plot



- Montre les associations / corrélation entre les blocs
- Corrélation = lien au centre (cutoff)
- Bordure externe = Intensité de l'expression *(par groupe en supervisé)*

```
> circos(...)
```

Mise en contexte

- omique ? multi-omique ?
- Pourquoi ? Difficultés
- Ressources

Méthodes d'intégration

- Intégration Conceptuelle
- Intégration Statistique
- Intégration à base de modèle

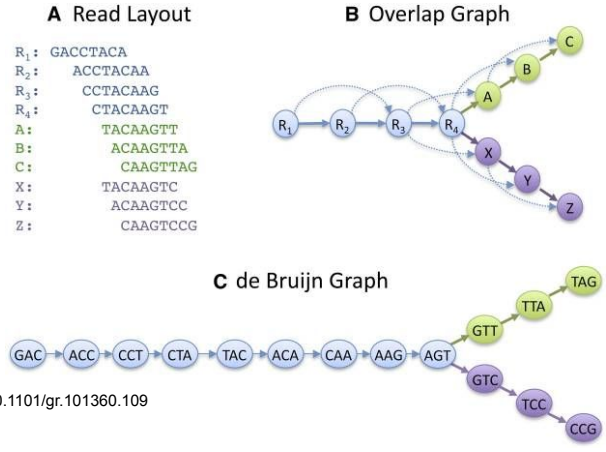
Méthodes Multivariées

- Analyse en Composante Principale
- Autres méthodes multivariés

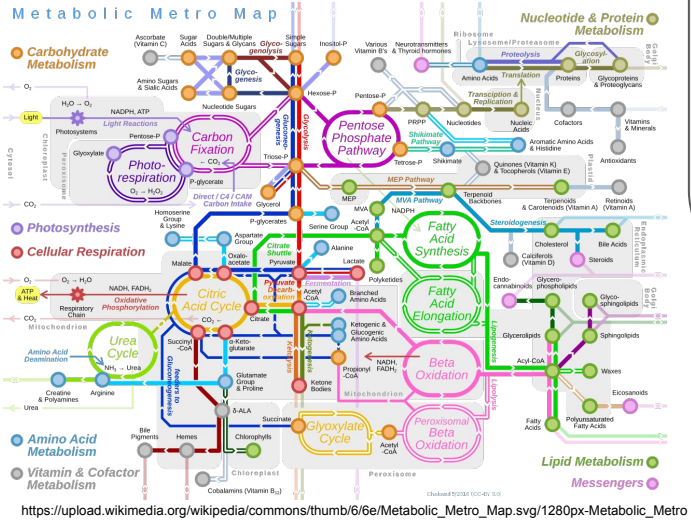
Méthodes à base de réseaux biologiques

- Les réseaux en biologie
- Exploration des réseaux

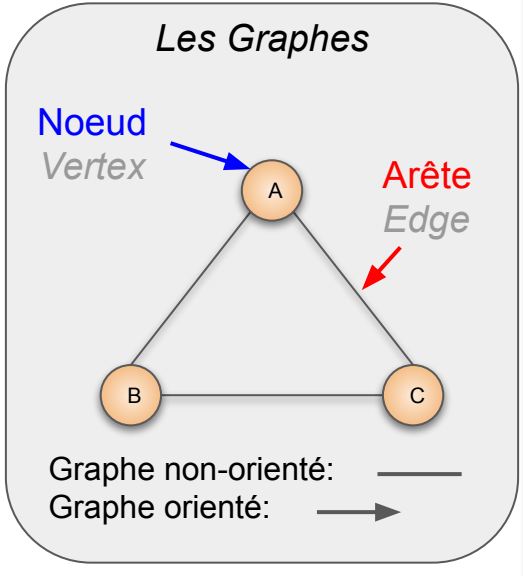
Les Réseaux en Biologie

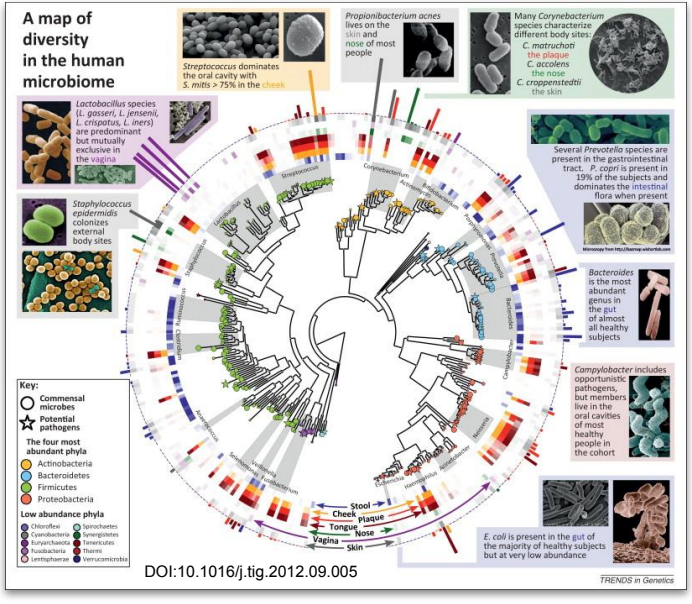


DOI: 10.1101/gr.101360.109



https://upload.wikimedia.org/wikipedia/commons/thumb/6/6e/Metabolic_Metro_Map.svg/1280px-Metabolic_Metro_Map.svg.png





DOI:10.1016/j.tig.2012.09.005

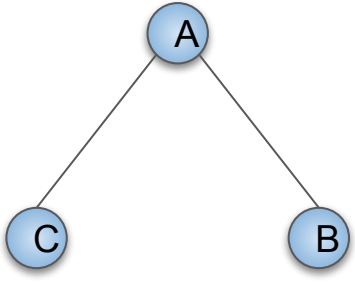
Gene Co-Expression / Regulation Network

	Gene-A	Gene-B	Gene-C
Ech1	10	5	6
ECh2	42	49	2
...			

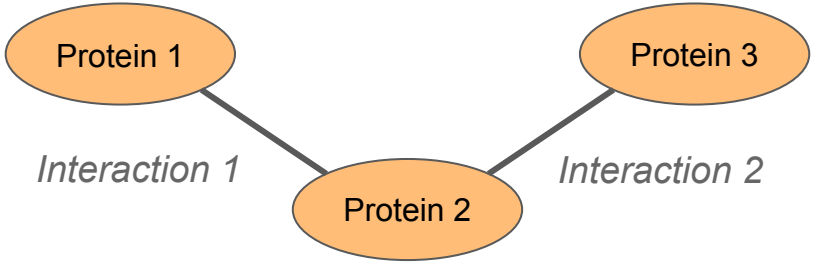
Matrice d'adjacence

	Gene-A	Gene-B	Gene-C
Gene-A	1	1	1
Gene-B	1	1	0
Gene-C	1	0	1

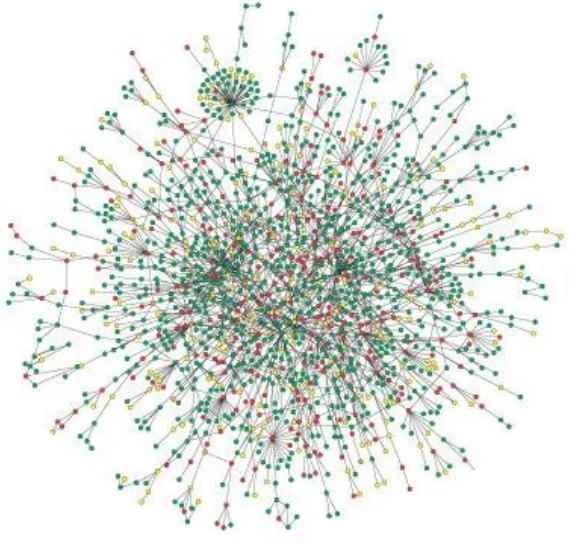
1: connecté 0: pas connecté



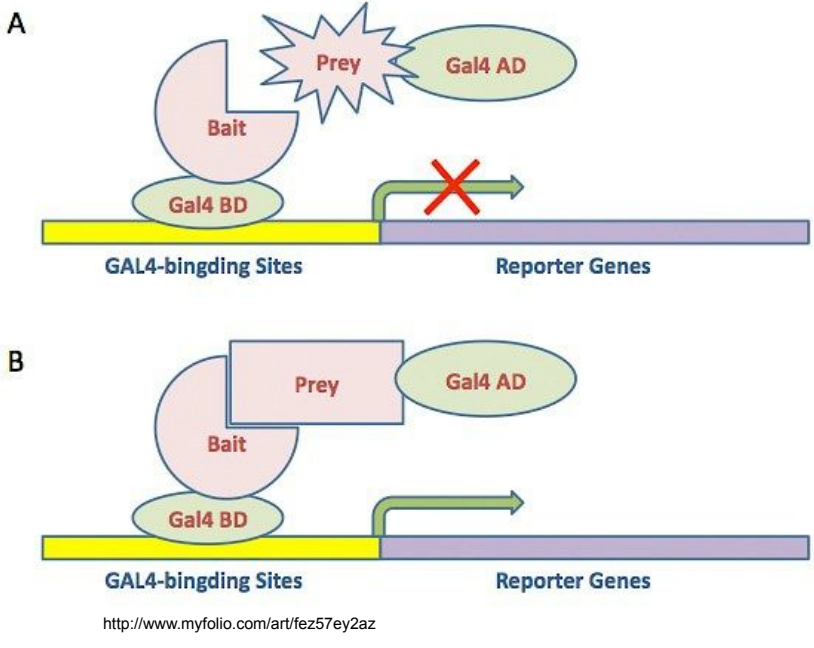
Réseaux d'interaction Protéine-Protéine (PPi)



Interaction = (activation, binding to, phosphorylation…)



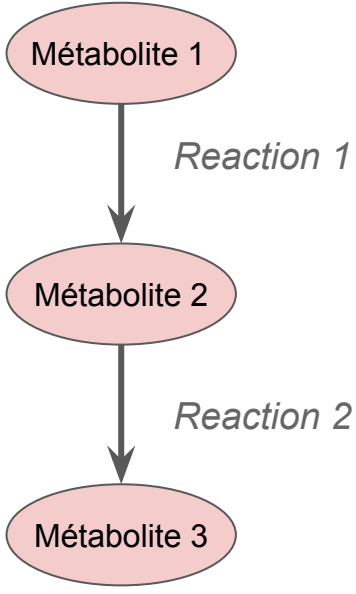
Two-hybrid screening

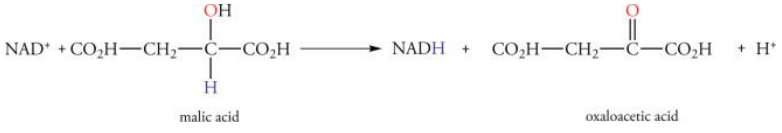


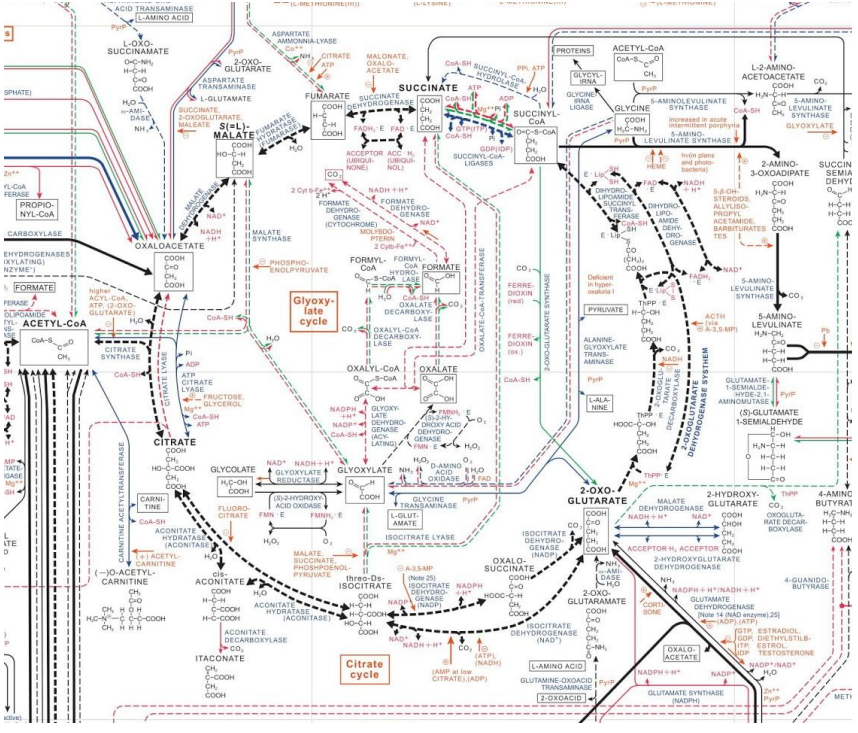
http://www.myfolio.com/art/fez57ey2az

Jeong, H., Mason, S. P., Barabási, A. L., & Oltvai, Z. N. (2001). Lethality and centrality in protein networks. Nature, 411(6833), 41.

Metabolic Pathways

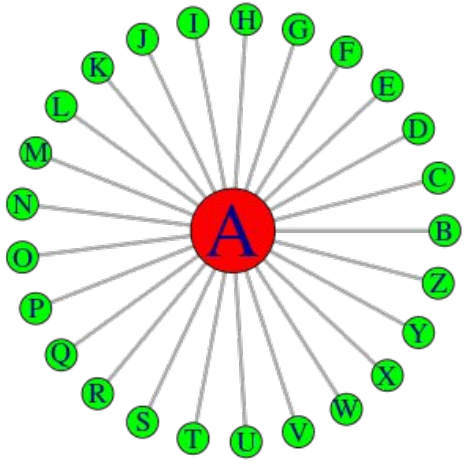






Interaction = (synthesis, oxydation, hydratation, decarboxylation, ...)

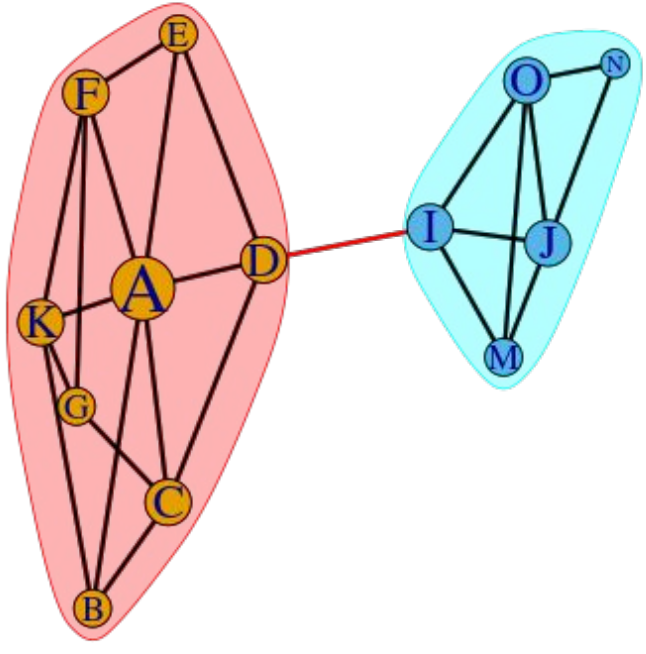
Analyse de Topologie



- Degree distribution

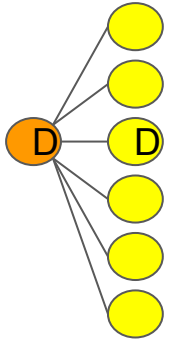
- Modularity
- Hierarchy
- Centrality
- ...

- Shortest path
- Clustering

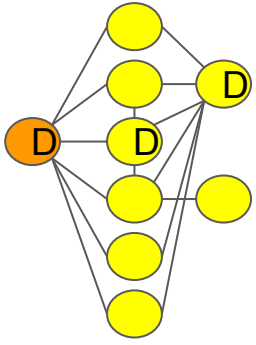


Analyse de Topologie

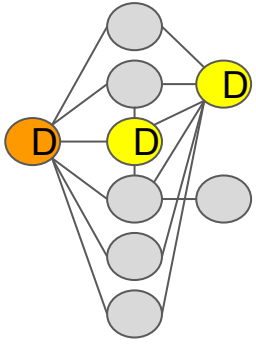
- Random Walk



Direct neighbors
- False positives
- False negatives

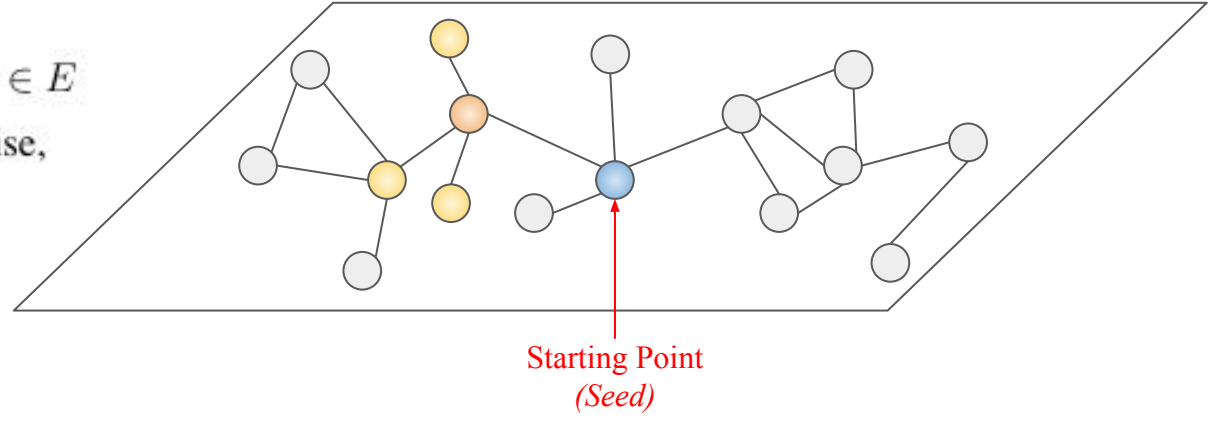


Shortest Path
- *Small world*
- False positives



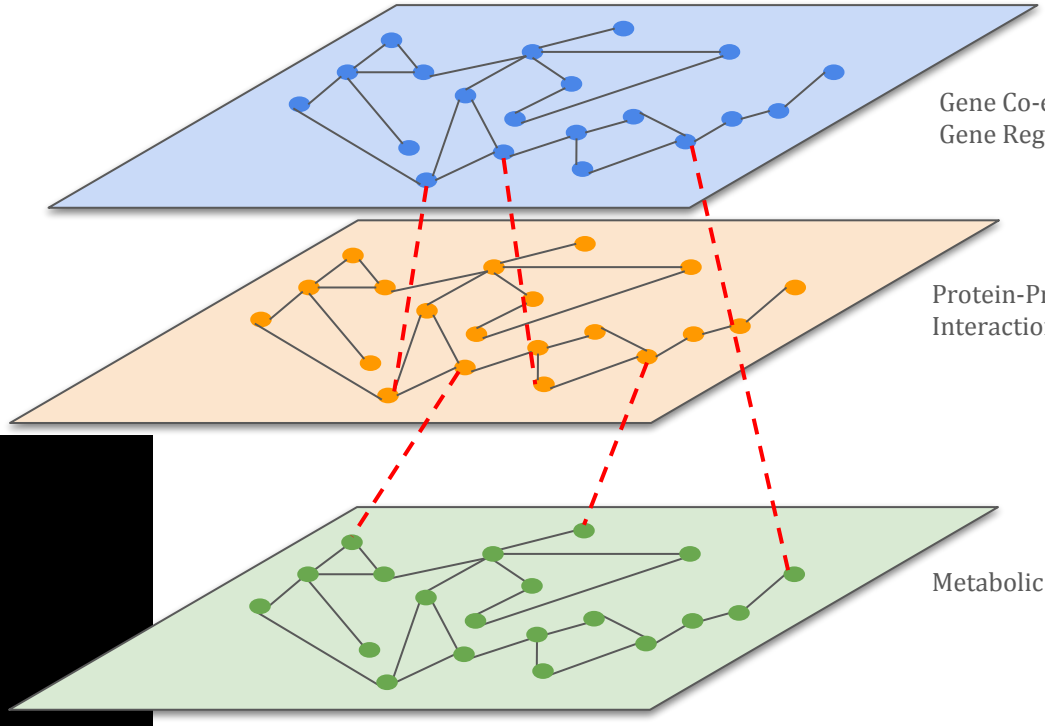
Network Propagation
- Random Walk
- Node Ranking

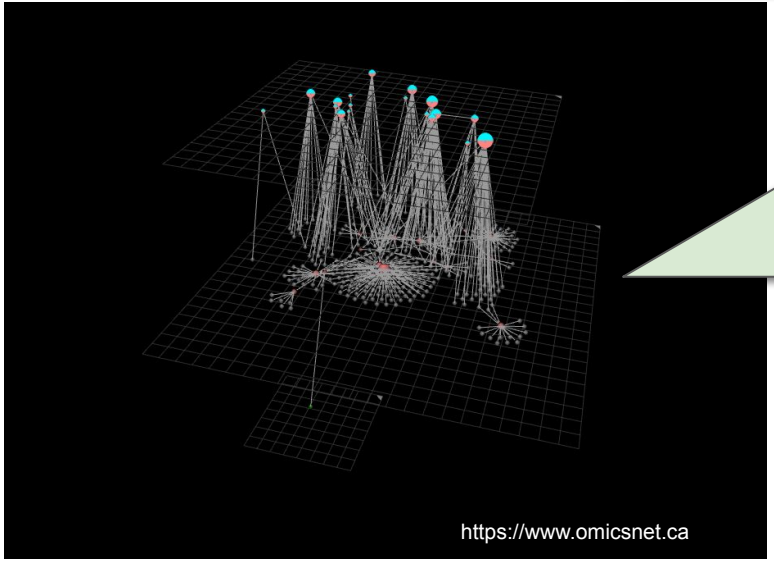
$$\mathbb{P}(v_{t+1} = y | v_t = x) = \begin{cases} \frac{1}{d(x)} & \text{if}(x, y) \in E \\ 0 & \text{otherwise,} \end{cases}$$



Multi-Omics Networks

Multi-Layered





Multiplex Heterogeneous Network

Mise en contexte

- omique ? multi-omique ?
- Pourquoi ? Difficultés
- Ressources

Méthodes d'intégration

- Intégration Conceptuelle
- Intégration Statistique
- Intégration à base de modèle

Méthodes Multivariées

- Analyse en Composante Principale
- Autres méthodes multivariés

Méthodes à base de réseaux biologiques

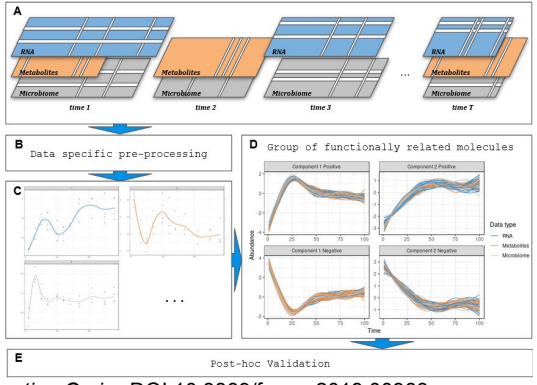
- Les réseaux en biologie
- Exploration des réseaux

Dernières tendances

- Omiques inhabituels
  - Microbiome: iHMP (https://www.hmpdacc.org/ihmp/)

- Aspect Longitudinale
  - Suivre la dynamique des systèmes (complexe) au niveau moléculaire

- Méthode d'exploration des graphes
  - (Random Walk, …)

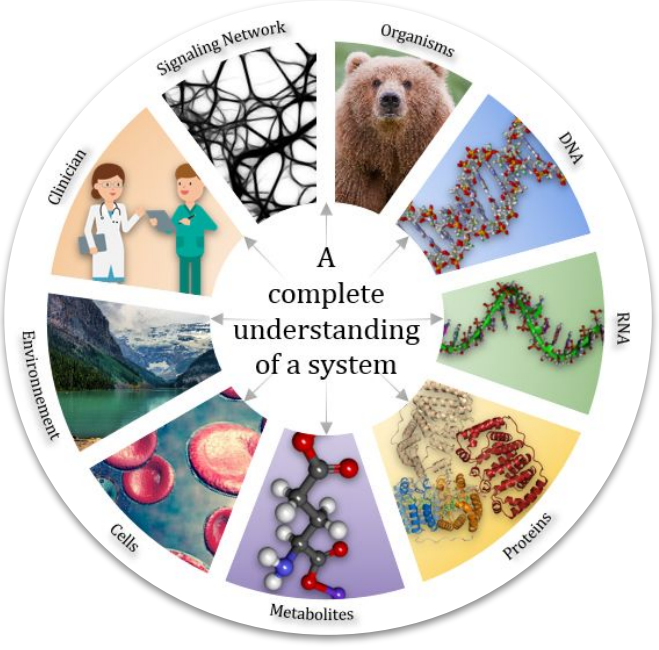


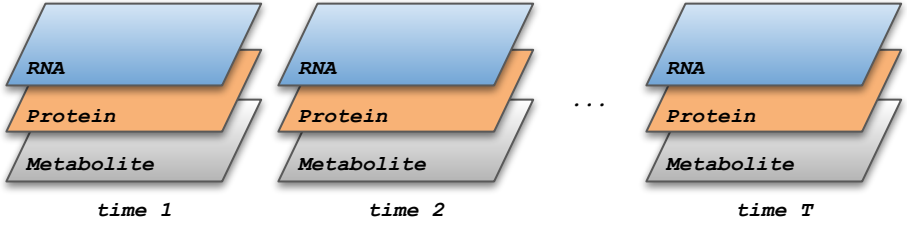
timeOmics DOI:10.3389/fgene.2019.00963

Intégration longitudinale

New experimental **design**

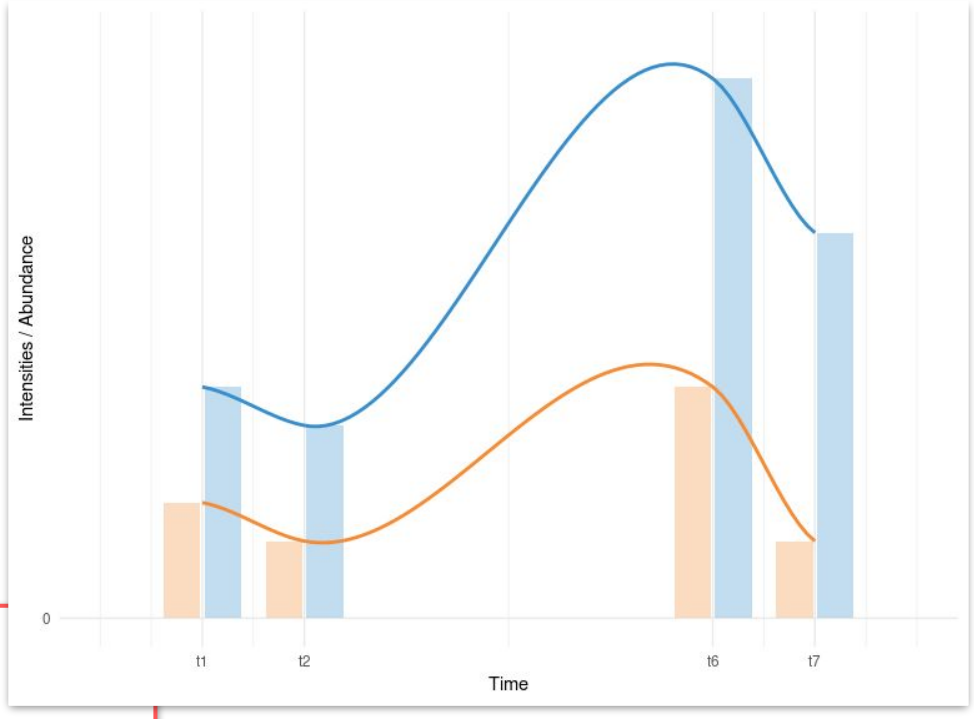
Multi-OMICS **time** series data





Intégration longitudinale

- Time effect
  - between two time points
  - between intervals of time points
- Group effect
- **Detect similar pattern**

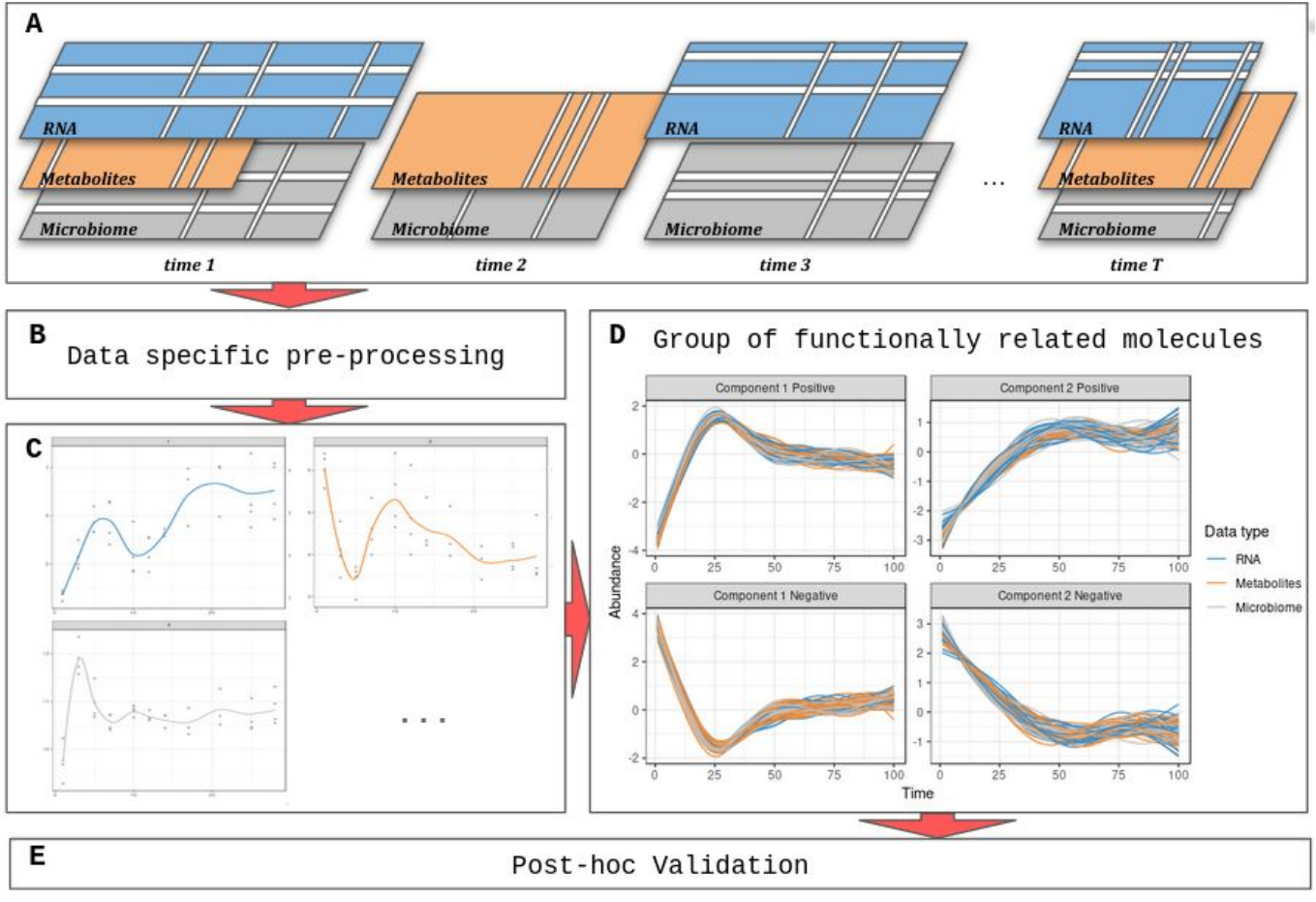


Why cluster data ?

- Group molecules with similar expression profile
- Functionally related
- Can be used to infer regulatory relationships

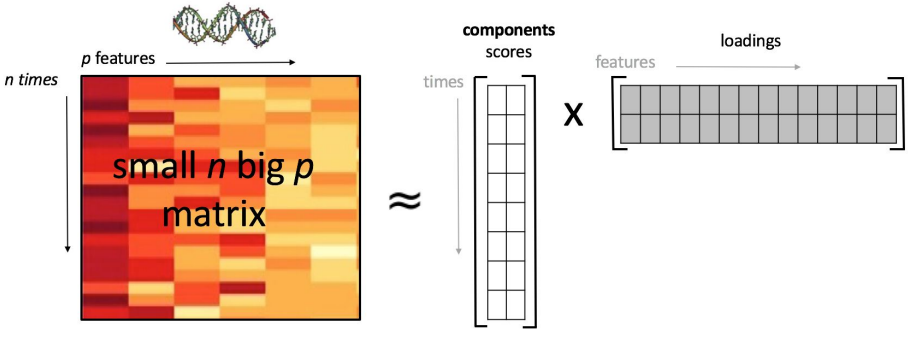
timeOmics

A. Data Acquisition
B. Pre-processing
C. Modelling and Filtering
D. Clustering / Integration
E. Validation



timeOmics DOI:10.3389/fgene.2019.00963

Principal Component Analysis - PCA

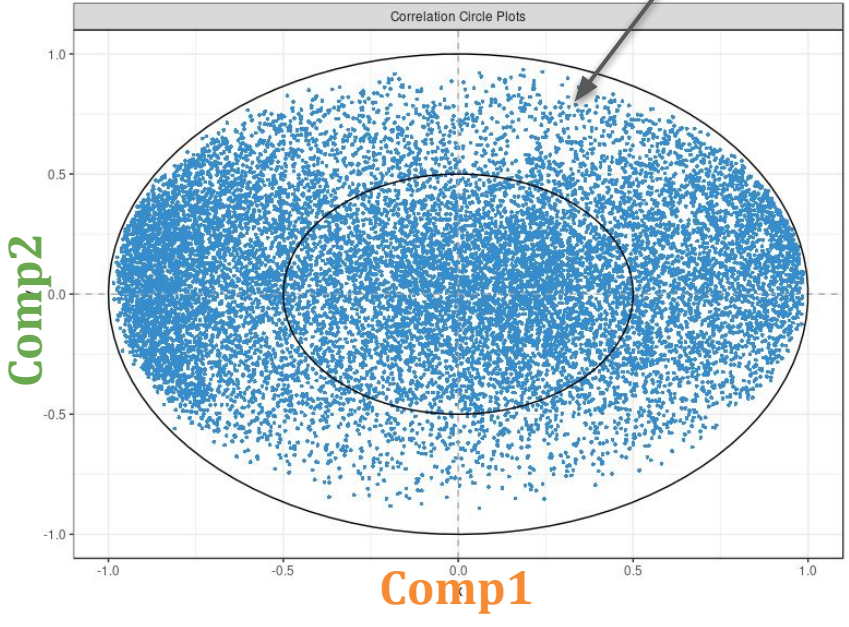


- Block = OTU table
- Unsupervised
- Dimension reduction
- Maximize **variance**

(`mixOmics` R package)

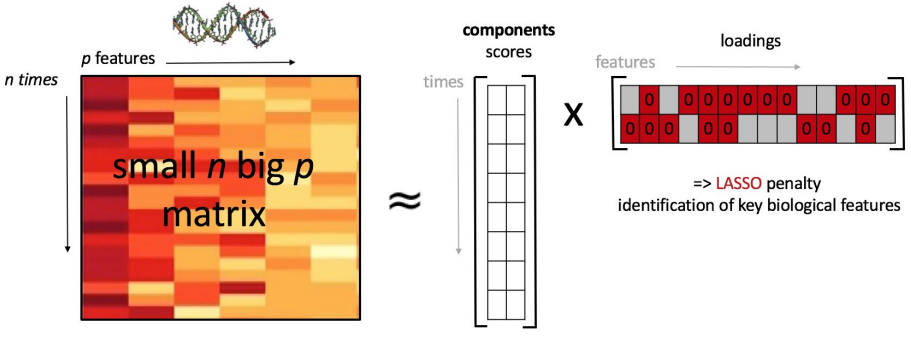
1 point = 1 time profile (genes, proteins, ...)

Circle Correlation Plot



timeOmics

sparse Principal Component Analysis - sPCA

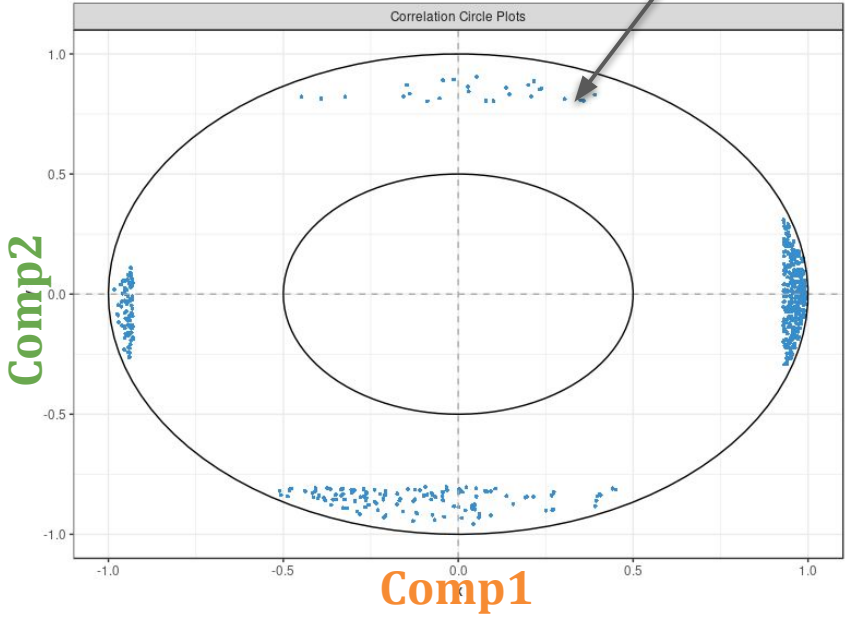


- Block = OTU table
- Unsupervised
- Dimension reduction
- Maximize **variance**
- Sparse version for **feature selection**

(`mixOmics` R package)

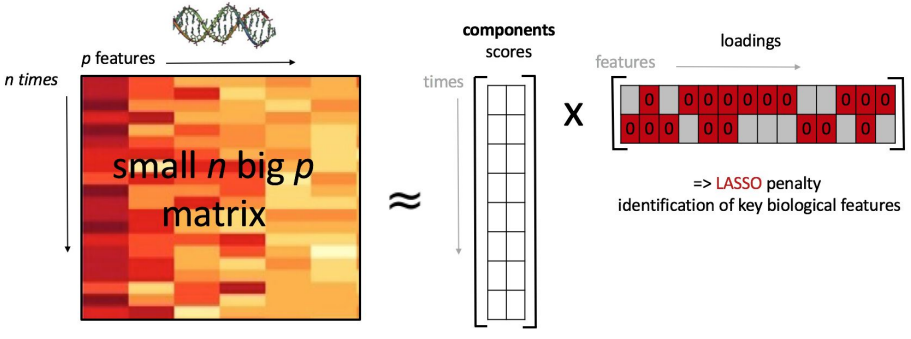
1 point = 1 time profile (genes, proteins, ...)

Circle Correlation Plot

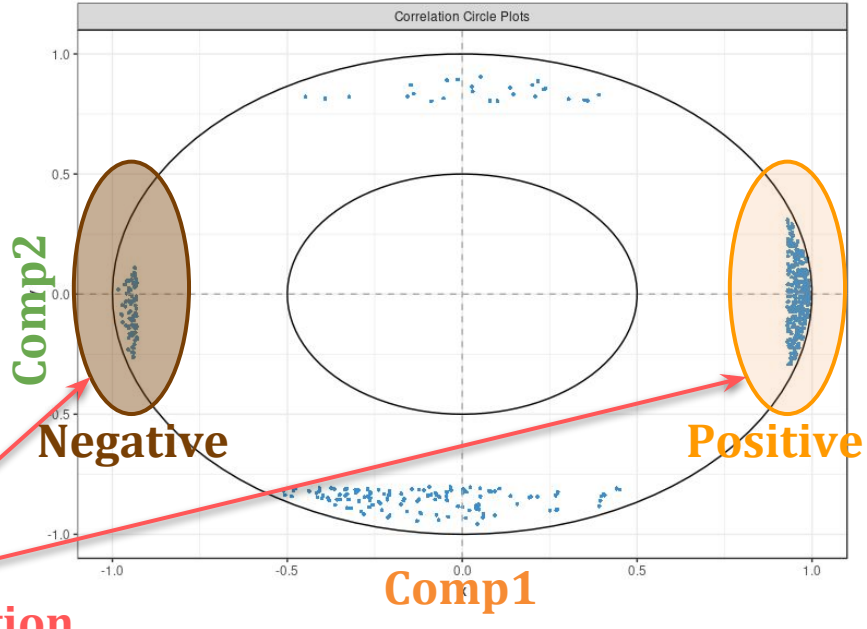


timeOmics

sparse Principal Component Analysis - sPCA



Circle Correlation Plot



Each component selects **2 clusters of OTUs**

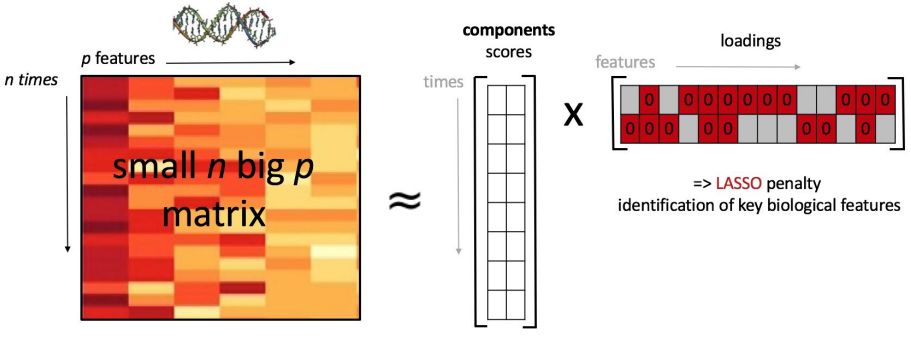
- Positively correlated
- Negatively correlated

Negative Correlation

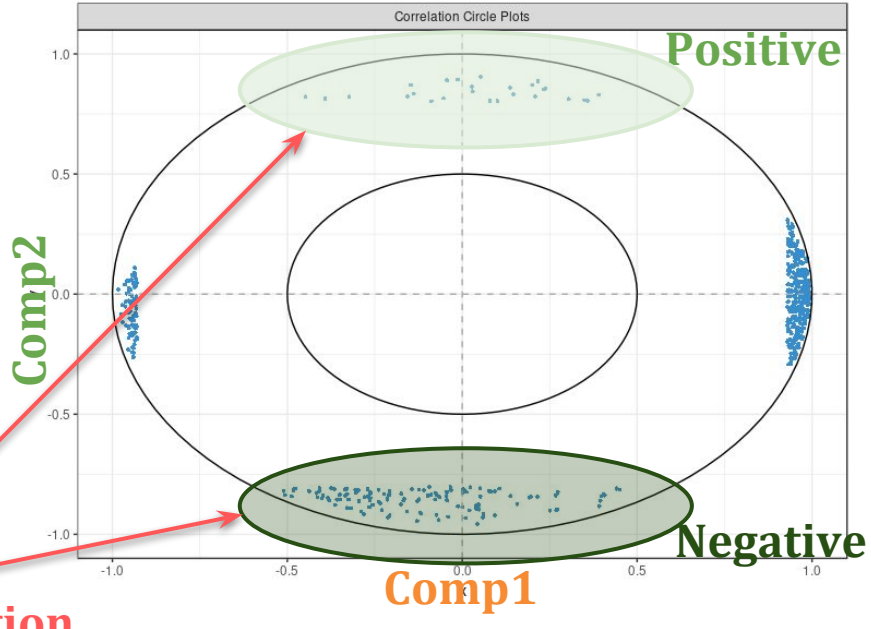
Two clusters identified on **comp 1**

timeOmics

sparse Principal Component Analysis - sPCA



Circle Correlation Plot



Each component selects **2 clusters of OTUs**

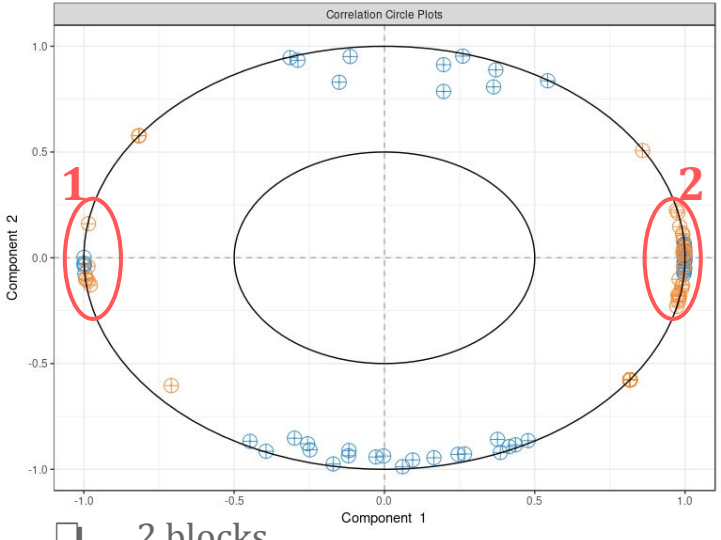
- Positively correlated
- Negatively correlated

Negative Correlation

Two clusters identified on **comp 2**

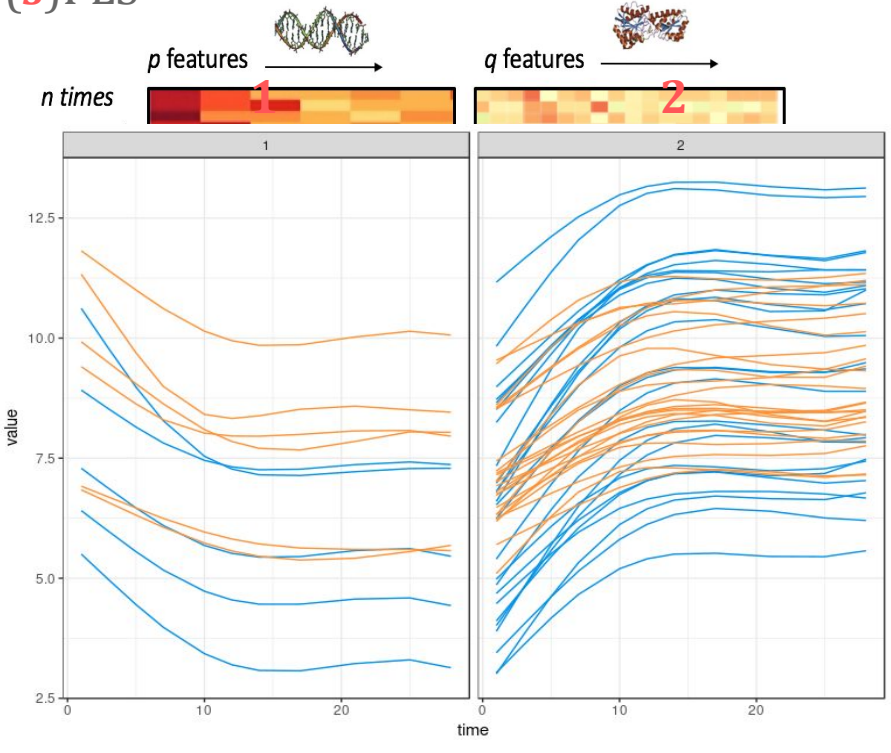
timeOmics

(***sparse***) Projection on Latent Structures - (***s***)PLS



- 2 blocks
- sparse PLS = feature extraction

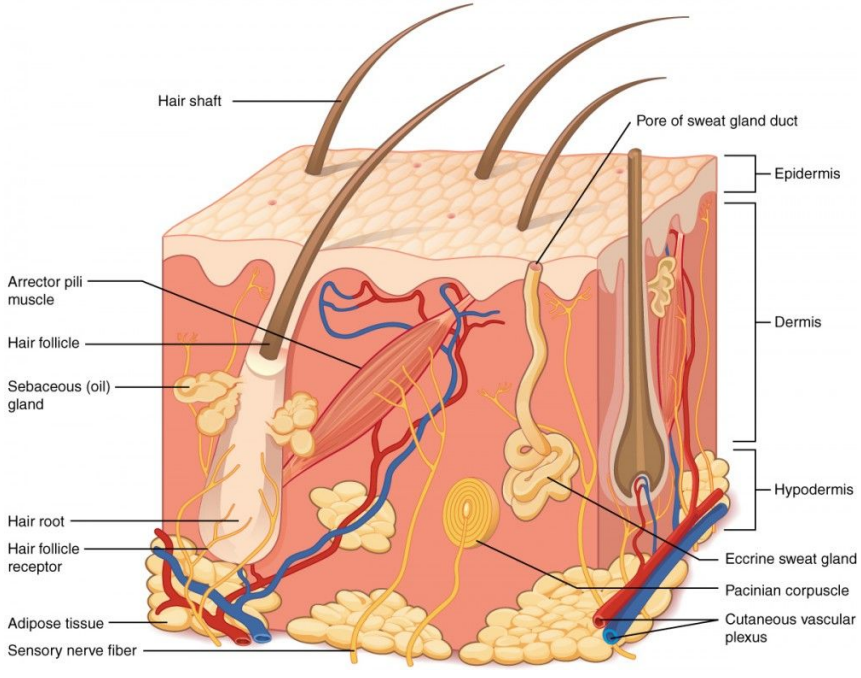
(`mixOmics` R package)



Example: *epidermis reconstruction*

Main function of the human skin:

- ❑ Organ of Sensation
- ❑ Thermo-regulation
- ❑ Secretion
- ❑ Immunité
- ❑ Psycological
- ❑ **Protection**

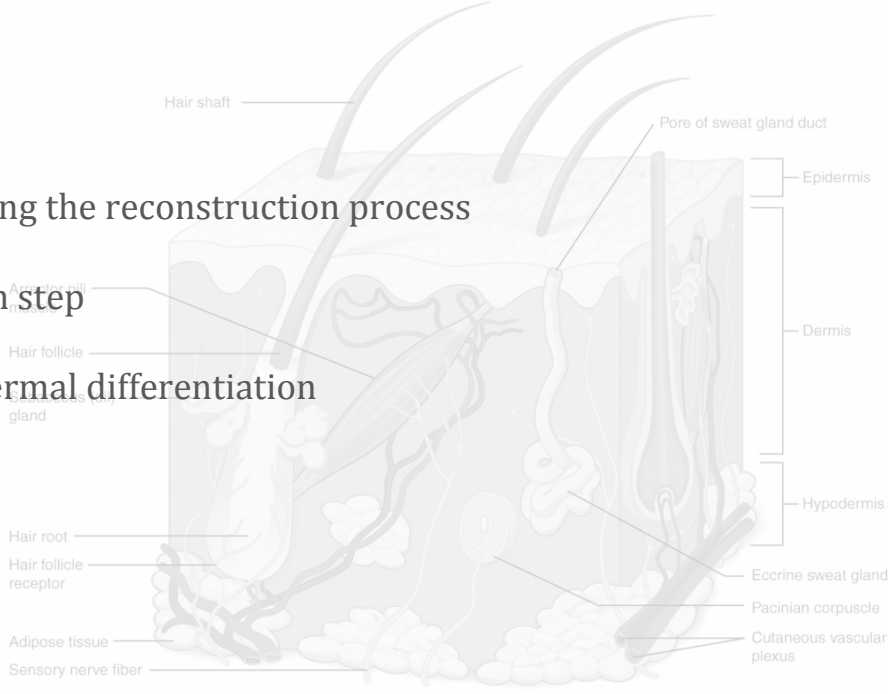


High capacity for regeneration

We aim to study the kinetics of epidermal differentiation during the reconstruction process.

Example: *epidermis reconstruction*

- Understand the epidermal differentiation during the reconstruction process
- Identify key biological players involved in each step
- Identify key and transitional steps of the epidermal differentiation
- Identify key missing players

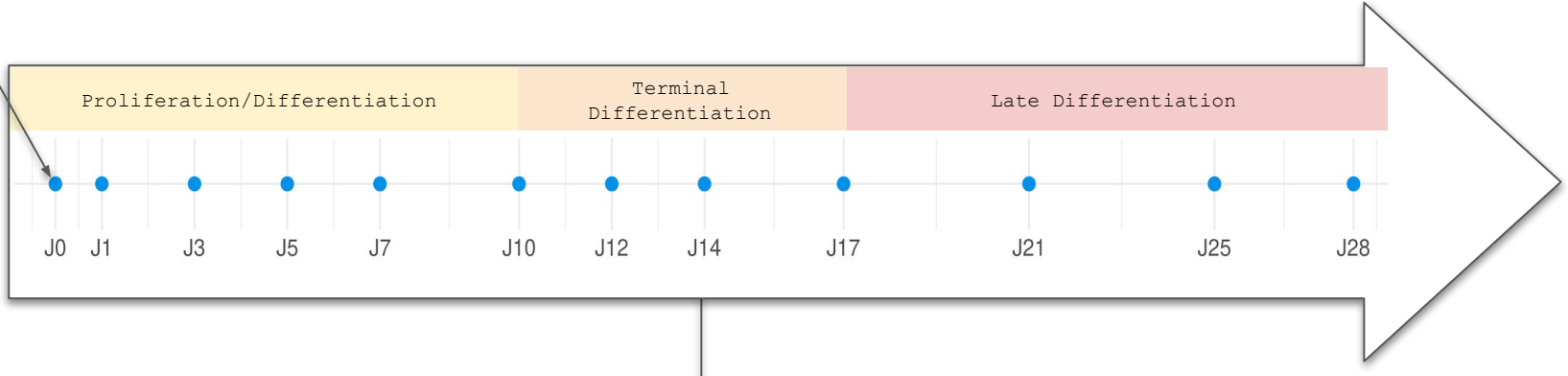


Example: *epidermis reconstruction*

NHEK seeding

x4 Biological Replicates
(4 donors)

CHAIRE DE RECHERCHE ET D'INNOVATION L'ORÉAL EN BIOLOGIE NUMÉRIQUE
AFFILIÉ À UNIVERSITÉ LAVAL

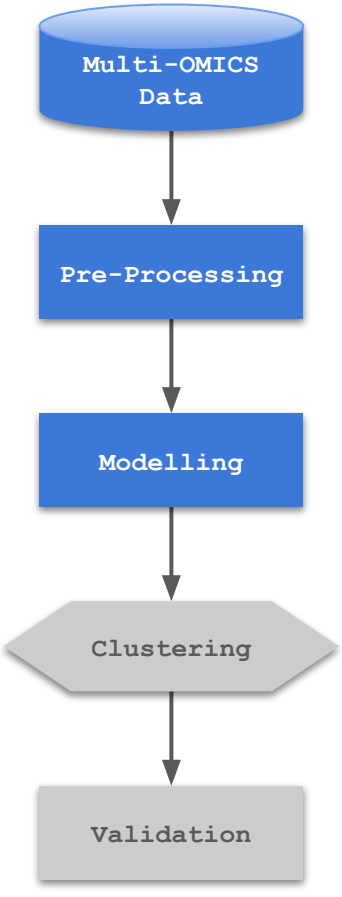


12 timepoints

- ❑ **Transcriptomics**
  (mRNA, miRNA)
- ❑ **Proteomics**
- ❑ **Metabolomics**

\+ *Histology and Microscopy*

Example: *epidermis reconstruction*



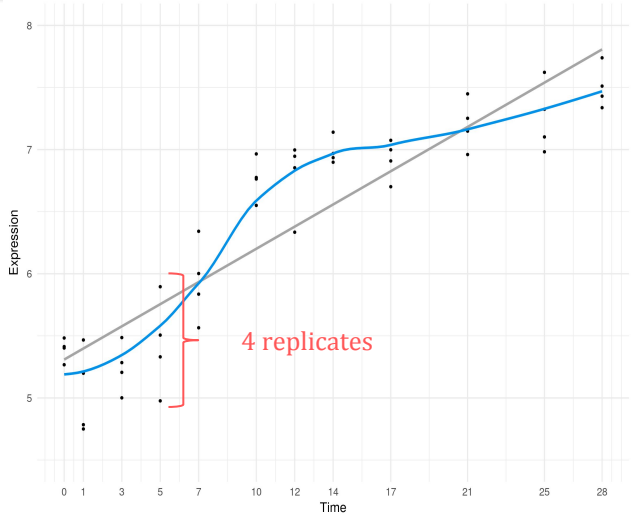
OMICS	# Molecules	# Molecule after filtering
mRNA	15,348	1,979 *(13%)*
miRNA	896	171 *(19%)*
Proteomics	1,820	987 *(54%)*
Metabolomics	428	338 *(79%)*

Filtering

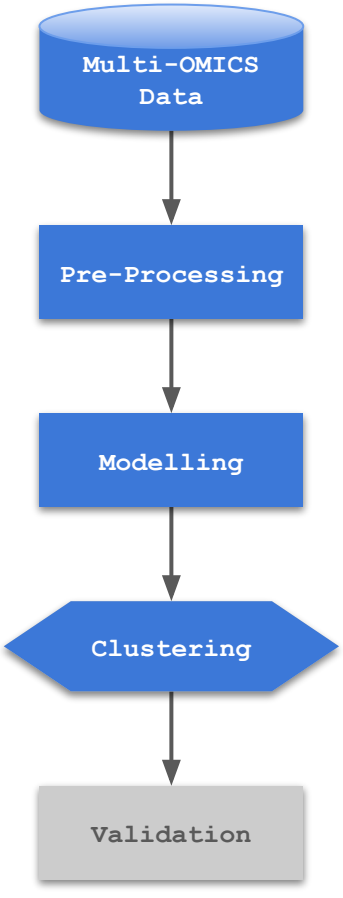
- ❑ *"flat"* profiles
- ❑ Molecules with no D.E. in time

Modelling

- ❑ Linear Mixed Model Spline
- ❑ Filter noisy profile

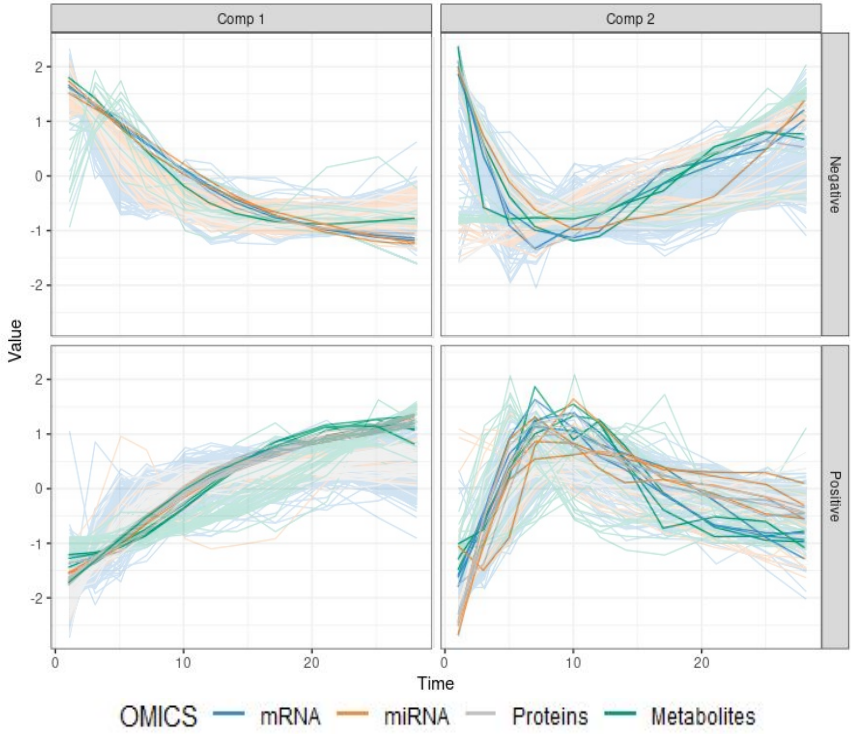


Example: *epidermis reconstruction*



Cluster -1 *(Comp1 Neg)*
mRNA: 418 *(5)*
miRNA: 87 *(18)*
Proteins: 179 *(5)*
Metabolites: 62 *(16)*

Multi-OMICS (sparse) clusters

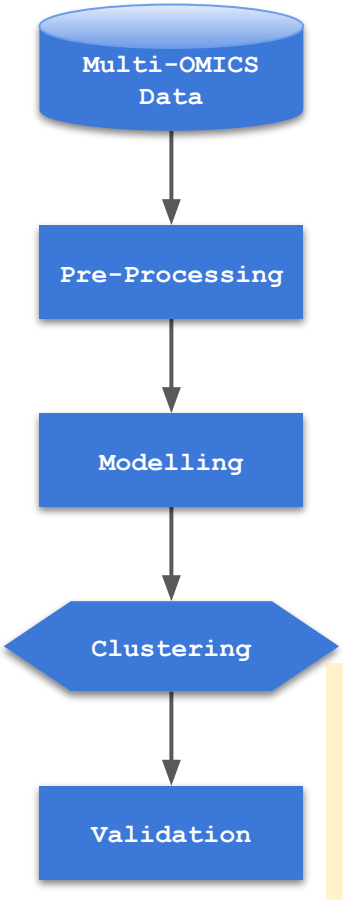


Cluster -2 *(Comp2 Neg)*
mRNA: 228 *(7)*
miRNA: 10 *(7)*
Proteins: 197 *(3)*
Metabolites: 58 *(6)*

Cluster 1 *(Comp1 Pos)*
mRNA: 898 *(10)*
miRNA: 21 *(17)*
Proteins: 317 *(20)*
Metabolites: 127 *(9)*

Cluster 2 *(Comp2 Pos)*
mRNA: 435 *(8)*
miRNA: 53 *(8)*
Proteins: 294 *(12)*
Metabolites: 91 *(9)*

Example: *epidermis reconstruction*

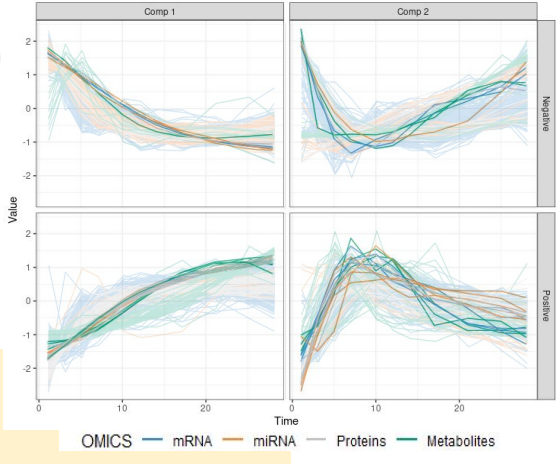


- **Single OMIC enrichment**
  Hypergeometric test against OMIC specific background set
  (Gene Ontology BP, Kegg, Reactome, WikiPathways)
- **Multi-OMICS enrichment**
  significant function represented by different omics
  (Fisher's combined probability test)

(`grofiler2` `FELLA`R packages)

Cluster -1
(mRNA-miRNA-proteins): regulation of cell migration (10e-16), anatomical structure morphogenesis (10e-21), ...
(all): Focal adhesion (10e-9)
(mRNA): angiogenesis (10e-4), nervous system development (10e-4)

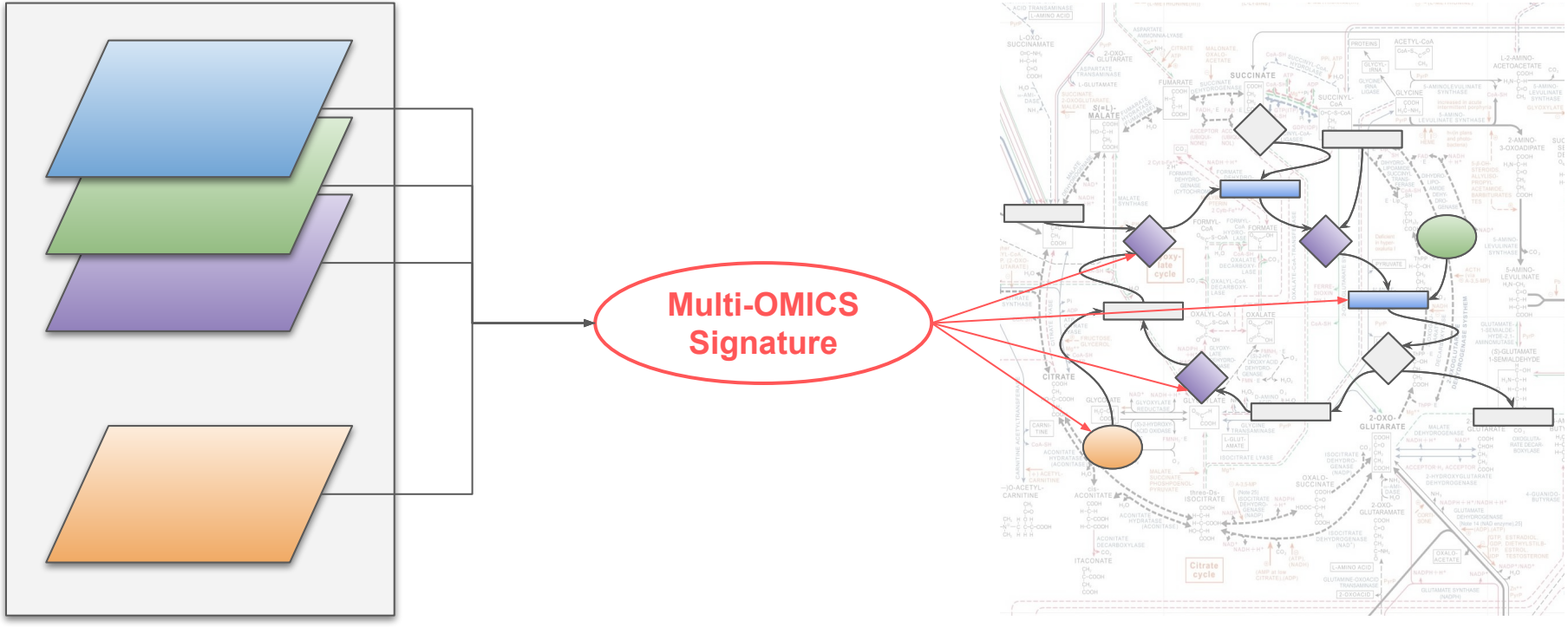
Cluster -2
(mRNA-miRNA-proteins): Extracellular matrix organization (10e-7)
(metabolite): Glycosphingolipid biosynthesis (10e-4)
(proteins): cornification (10e-5), keratinization (10e-4)



Cluster 1
(mRNA-miRNA-proteins):
Keratinisation (10e-36),
Cornification (10e-24), **epidermis** development (10e-22), ...
(all): Sphyngolipid metabolism (10e-4), ...

Cluster 2
(mRNA-miRNA-proteins): **cornification** (10e-26), epithelial cell differentiation (10e-17), tissue development (10e-13)

Example: *epidermis reconstruction*

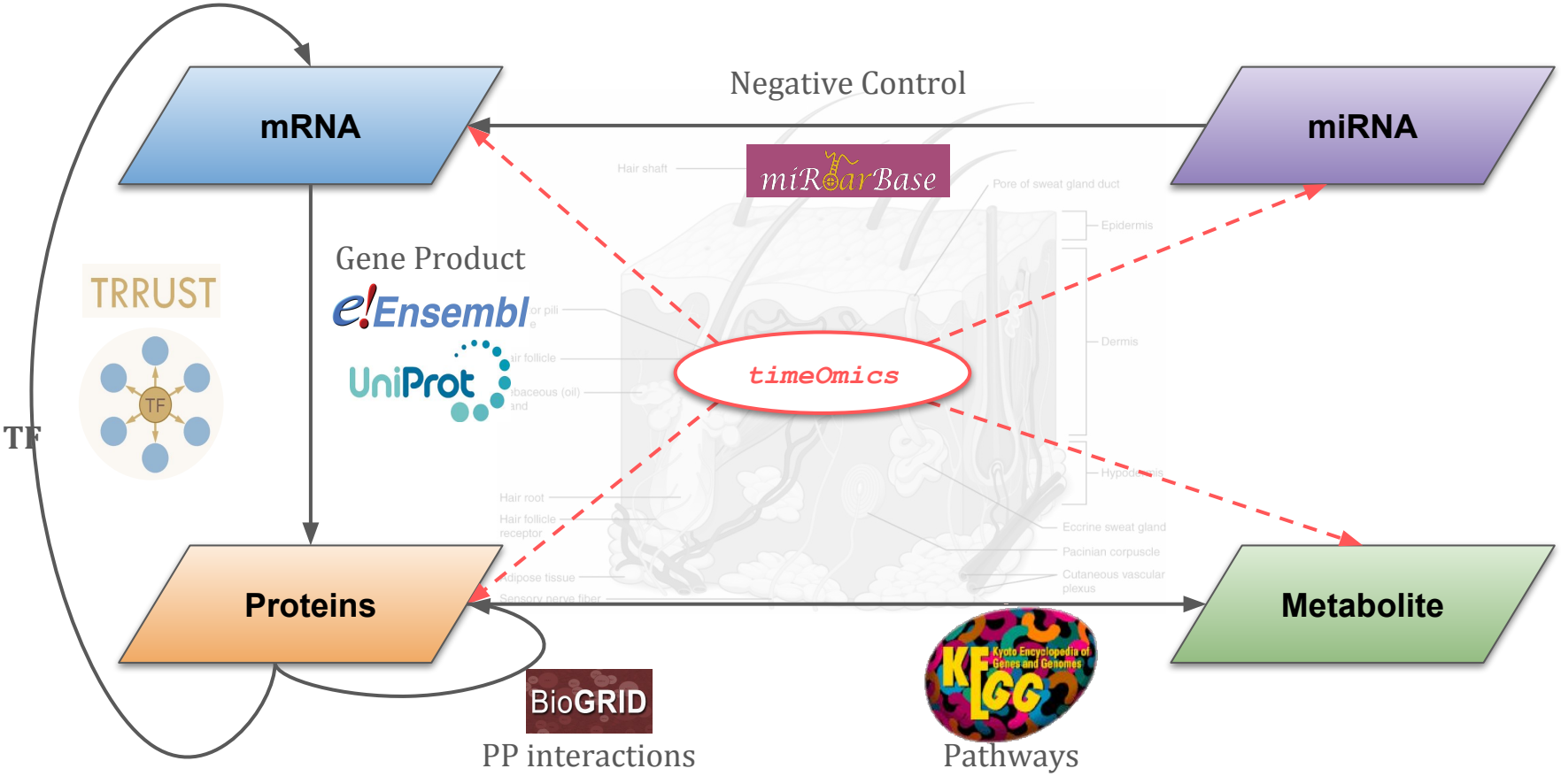


Multi-OMICS Data

timeOmics

Knowledge

Example: *epidermis reconstruction*



- http://melgen.org/multi-omics-approach/

- Huang S, Chaudhary K, Garmire LX. More Is Better: Recent Progress in Multi-Omics Data Integration Methods. Frontiers in Genetics. 2017;8:84. doi:10.3389/fgene.2017.00084.

- Hasin, Y., Seldin, M., & Lusis, A. (2017). Multi-omics approaches to disease. Genome biology, 18(1), 83.

- Cavill, R., Jennen, D., Kleinjans, J., & Briedé, J. J. (2015). Transcriptomic and metabolomic data integration. Briefings in bioinformatics, 17(5), 891-901.

- Wanichthanarak, K., Fahrmann, J. F., & Grapov, D. (2015). Genomic, proteomic, and metabolomic data integration strategies. Biomarker insights, 10(Suppl 4), 1.

- https://www.frontiersin.org/research-topics/2280/multi-omic-data-integration

- http://mixomics.org

- L'analyse en Composante Principale, Sébastien Déjean - math.univ-toulouse.fr