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## Old wine in new bottles : Factorial analyses in the age of multi-omics

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# Old wine in new bottles : Factorial analyses in the age of multi-omics

12-16 june 2023

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25<sup>th</sup> Congress

**ASPA**2023

Monopoli (Bari, Italy), June 13-16, 2023



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la science pour la vie, l'humain, la terre

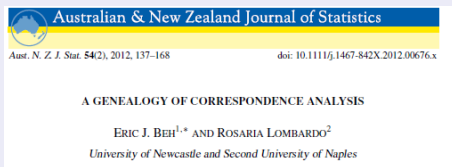
# Introduction

## A bit of history : Back to the sixties

And even before (Pearson (1901), Hotelling (1933), Fisher (1940))

- 1962. Tukey : The future of analysis.
- 60's. Benzecri : Multivariate descriptive analysis tools.

## Further reading



### 1. Introduction

In the beginning, there was no correspondence analysis. However, since the beginning of the 20<sup>th</sup> century some of the most influential UK statisticians (including R. A. Fisher, K. Pearson, F. Yates and G. U. Yule) recognised the need to find a way of measuring the association between categorical variables. Modern correspondence analysis has a long and

The impact of correspondence analysis would still continue to be felt throughout France and other parts of Europe. Countries such as Italy and The Netherlands would find themselves central to the development of correspondence analysis. For example, contributions by Italian researchers to the development of correspondence (in particular non-symmetrical correspondence analysis) include, but are not limited to, [105], [141], [145], [177] – [195],

# Data

- *The model must be data-driven, not the opposite, J P Benzécri*
- *Let the data speak for themselves, J W Tukey*
- Emphasis on visualization

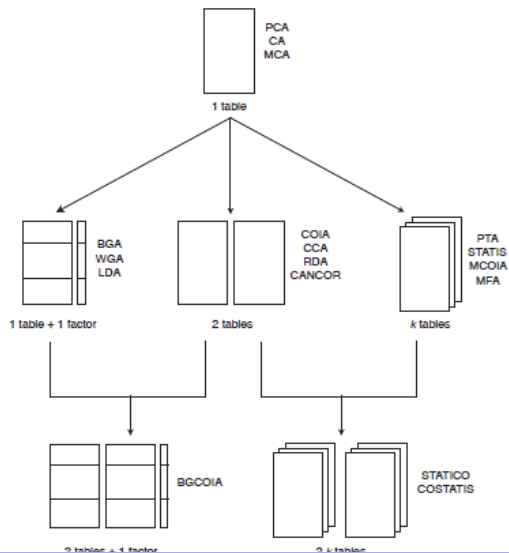
# Factorial Analyses

## Geometrical approach

- Data are represented by clouds of points in a multidimensional space
- Synthesis by dimensionality reduction
- Visualization by a factorial map / scatterplot
- One table
  - ▶ PCA, CA, MCA, MDS...

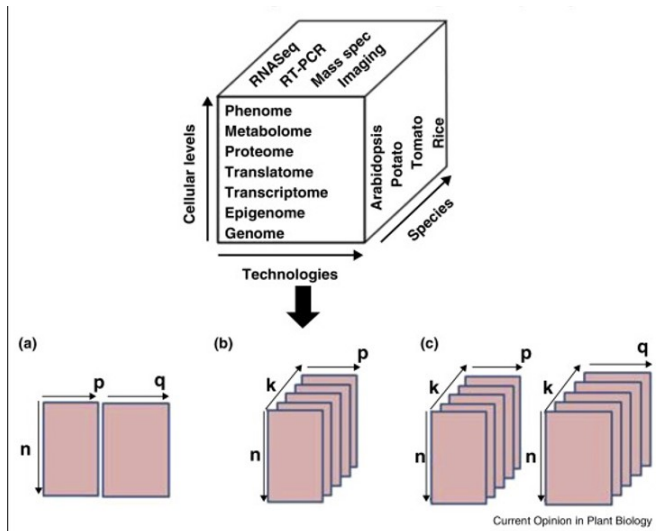
# The extensions

Thioulouse, 2011. Simultaneous analysis of a sequence of paired ecological tables: A comparison of several methods. Ann. Appl. Stat. 5 (4) 2300 - 2325



# Big Data, x-omics

D Rajusundaram and J Selbig, 2016. More effort, more results: recent advances in integrative omics data analysis.





# Data integration

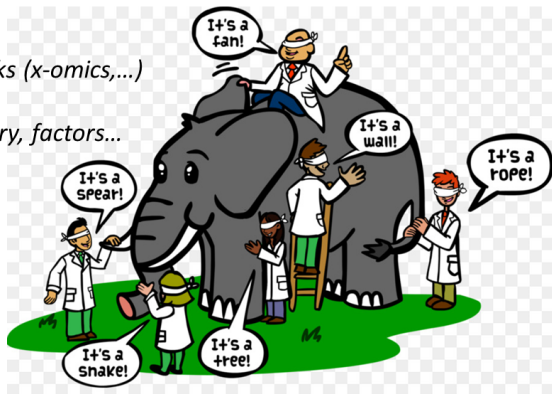
Different

- *variables in blocks (x-omics,...)*

Heterogeneous

- *continuous, binary, factors...*

...



# Data integration

## No structure, different data



Tail



Body



Trunk



Ear



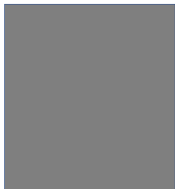
- Don't know it's an elephant (same phenomenon);
- Separate analyses-> different conclusions;
- How to combine conclusions?



# Data integration

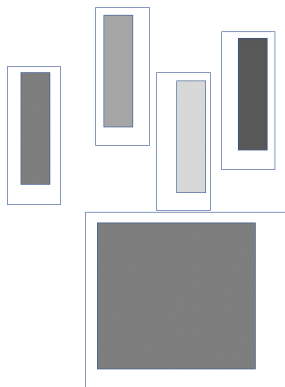
No structure, Everything is mixed

- Don't know it's an elephant (same phenomenon)
- But divided in different groups of data;
- Same analysis ? Lost specificities

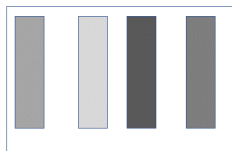


# Data integration

## Structure - multitable

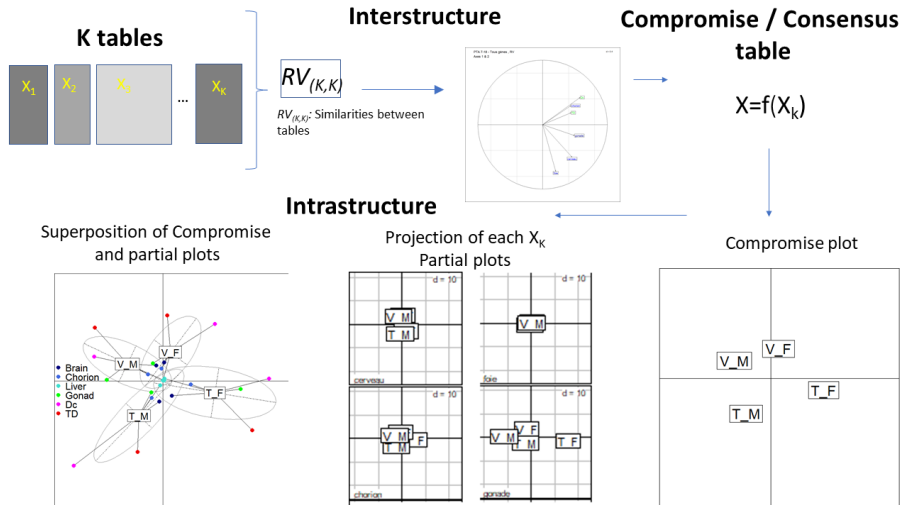


From  $k$  different analyses to a common analysis, that accounts for block specificities



# K-tables analysis at a glance:

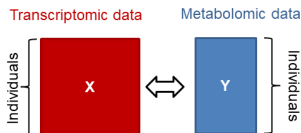
## Three steps



# Two Tables: Coinertia and Redundancy Analysis

- Assymetry: X explains Y: Redundancy Analysis (RDA)
- **Symmetry: same role for X and Y : Coinertia Analysis (COIA)**
- CoiA is to covariance what PCA is to variance

**CoIA** allows to identify relationships between two datasets by maximizing the covariance between them.



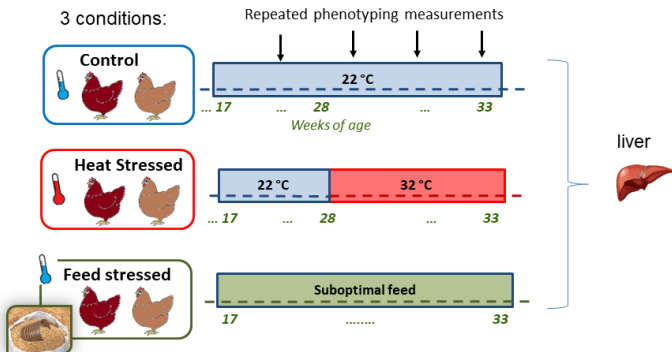
- Relationships between X and Y
- No constraints on the number of variables of X and Y

# Coinertia : an example

An integrated metabolomic and transcriptomic analysis evaluating heat and feed stress in layer chickens (Zerjal and Laloë, 2019)

**Chicken Model:** 2 Rhode Island Red lines divergently selected for low (R-) and high (R+) residual feed intake (50 animals per line and condition).

3 conditions:



# Coinertia

## Transcriptomic and metabolomics analysis

8 animals per line and condition

### Total RNA

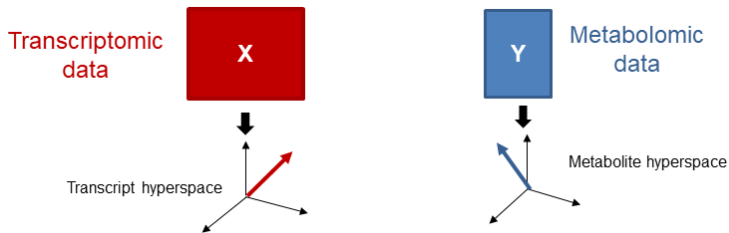
12873 expressed genes

### Metabolome

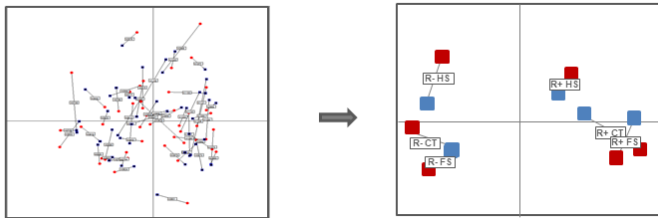
142 NMR buckets



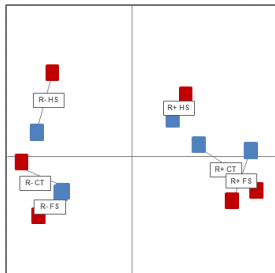
# Results: A simultaneous representation



Summarize the common structure existing in the two datasets



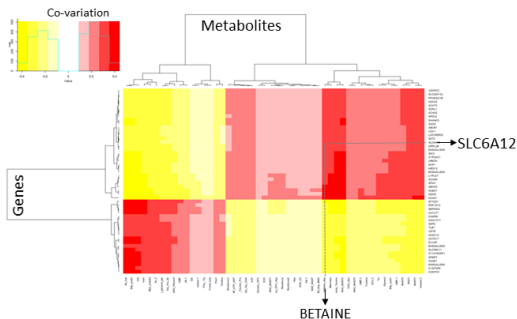
## Results: A simultaneous representation



- The transcriptomics and the metabolomics data are impacted by both “line” and “stress” but the impact of the stresses is not of the same amplitude
- The heat stress seems to impact more the liver transcriptome and the metabolome than the feed stress
- The transcriptome seems to be more impacted than the metabolome

# Results: Detection of covariant variables

Estimation of co-variation of related biological compounds under heat stress

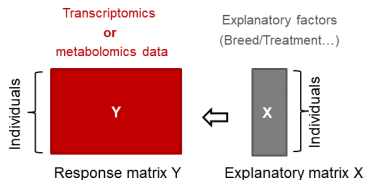


SLC6A12 encodes for a membrane transporter of betaine. In liver cells, SLC6A12 and betaine may have a role in volume regulation for cell survival under stress.

# Redundancy Analysis

- Symmetry: same role for X and Y : Coinertia Analysis (COIA)
- Assymetry: X explains Y: Redundancy Analysis (RDA)

**RDA** allows to summarize the variation in a set of response variables (Y) that can be explained by a set of explanatory variables (X).



- Linear model approach applied to a multivariate context
- Constraints on the number of variables for the X matrix

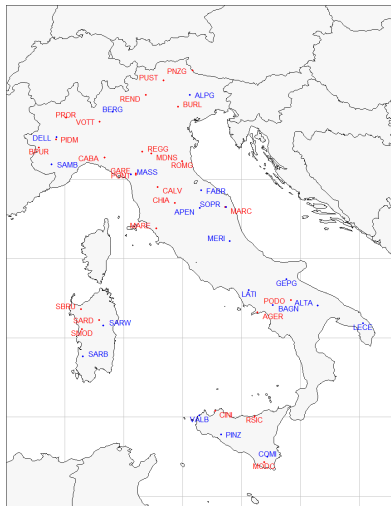
# Redundancy analysis

- Multivariate linear modelling
- Anova table
- Significance tests (permutation);
- Percentage of inertia due to
  - ▶ the model
  - ▶ the axes
  - ▶ the different factors in the model
  - ▶ Inertia % =  $F_{st}$

# RDA and environmental genomics

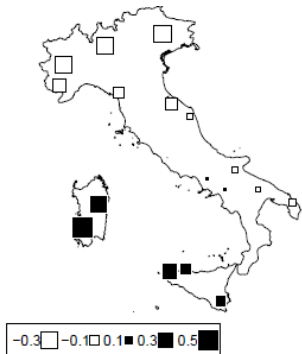
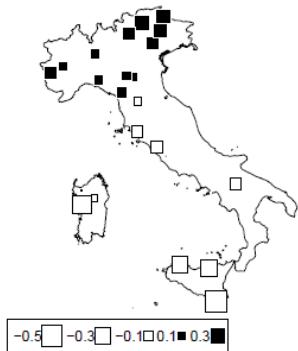
## spatio-climatic structuration of Italian cattle and sheep

Senczuk et al, 2022. How Geography and Climate Shaped the Genomic Diversity of Italian Local Cattle and Sheep Breeds. *Animals*, 12(17), 2198.



## geographical structuration of Italian cattle and sheep

How cattle (left) and sheep (right) are structured according to geography (latitude+longitude)



# geographical structuration of Italian cattle and sheep

## Inertia components (geography)

		Cattle (Fst = 0.177)		Sheep (Fst = 0.144)	
RDA Component		% Inertia	<i>p</i> -Value	%	<i>p</i> -Value
Geog (Lat*Long)	RDA1	7.5	0.03	11.5	< 0.01
	RDA2	4.6	0.66	8.1	0.02
	RDA3	2.6	0.97	6.7	0.14
	Total	14.7		26.3	

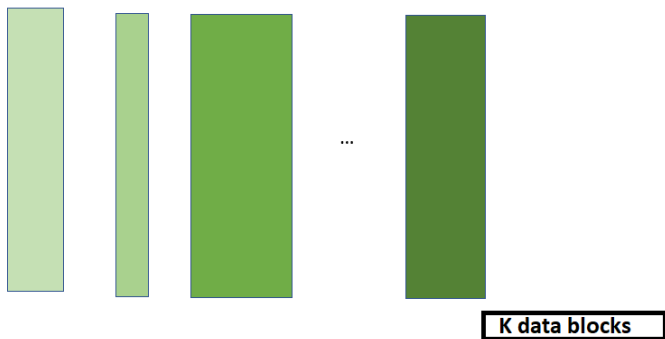
- Cattle : 14,7 %
- Sheeps : 26,3 %
- Simplistic modelling of geography (Latitude:Longitude).
- Spatial PCA, neighbouring graphs. Laloë et al. 2010. Spatial trends of genetic variation of domestic ruminants in Europe. Diversity, 2(6), 932-945.



# K-Tables Analysis

## Multiple Factor Analysis (MFA, Escofier and Pagès, 1997)

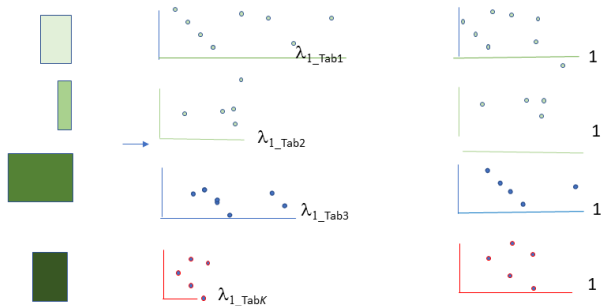
Same observations,  $K$  data tables



# MFA

## a weighted PCA

Ponderation by  $1/\lambda_1$   
Scale of the first axis  
of each block PCA

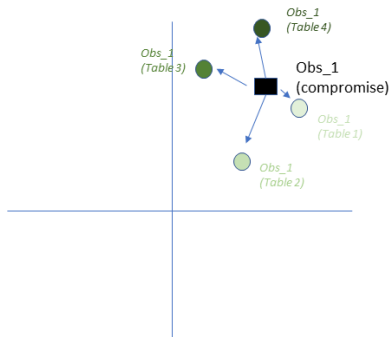


# MFA

## A simultaneous representation of the compromise and the partial analyses

### MFA :

- PCA on the concatenation of weighted tables -> compromise
- Projection of tables on the compromise -> partial points

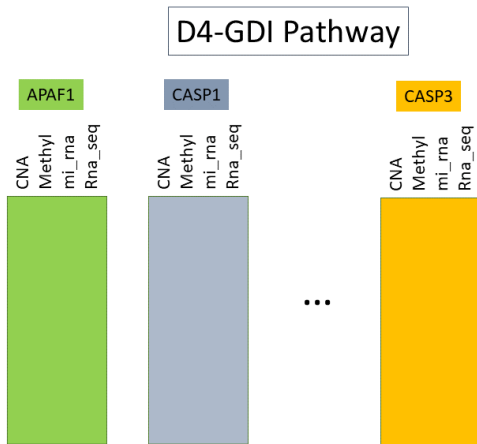


- Observations :
  - \* A compromise point
  - \*  $K$  partial points

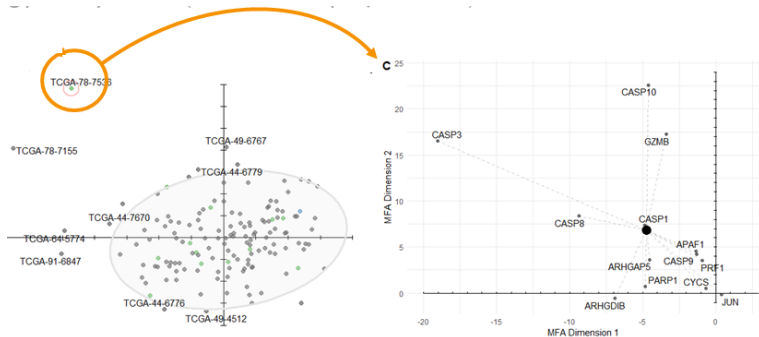
*The compromise point :  
barycenter of the partial points  
cloud*

# Individualized multi-omic pathway deviation scores using multiple factor analysis. An example on TCGA data

Rau et al 2022. Individualized multi-omic pathway deviation scores using multiple factor analysis. Biostatistics, 23(2), 362-379.



# Individualized multi-omic pathway deviation scores using multiple factor analysis. An example on TCGA data



# A modern approach

- No matrix inversion step
  - ▶ Big Data / Computing
  - ▶  $p \gg n$
- No (or a few) assumptions on distributions
- Focus on visualization

# Versatility

- Mixing quantitative and qualitative
- Various designs
  - ▶ Two tables (Coinertia)
  - ▶ Sequences of tables (Multiple Factor Analysis)
  - ▶ Data cubes (Partial Triadic Analysis)
- Supervised version: modelling, prediction...
  - ▶ Two or three tables (Redundancy Analysis)
  - ▶ k- tables (Multiblock Redundancy Analysis)

## References / R packages

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- vegan <http://cran.r-project.org/web/packages/vegan/>