UNIVERSITÉ DE GENÈVE

ISPSO
INSTITUT DES SCIENCES PHARMACEUTIQUES DE SUISSE OCCIDENTALE

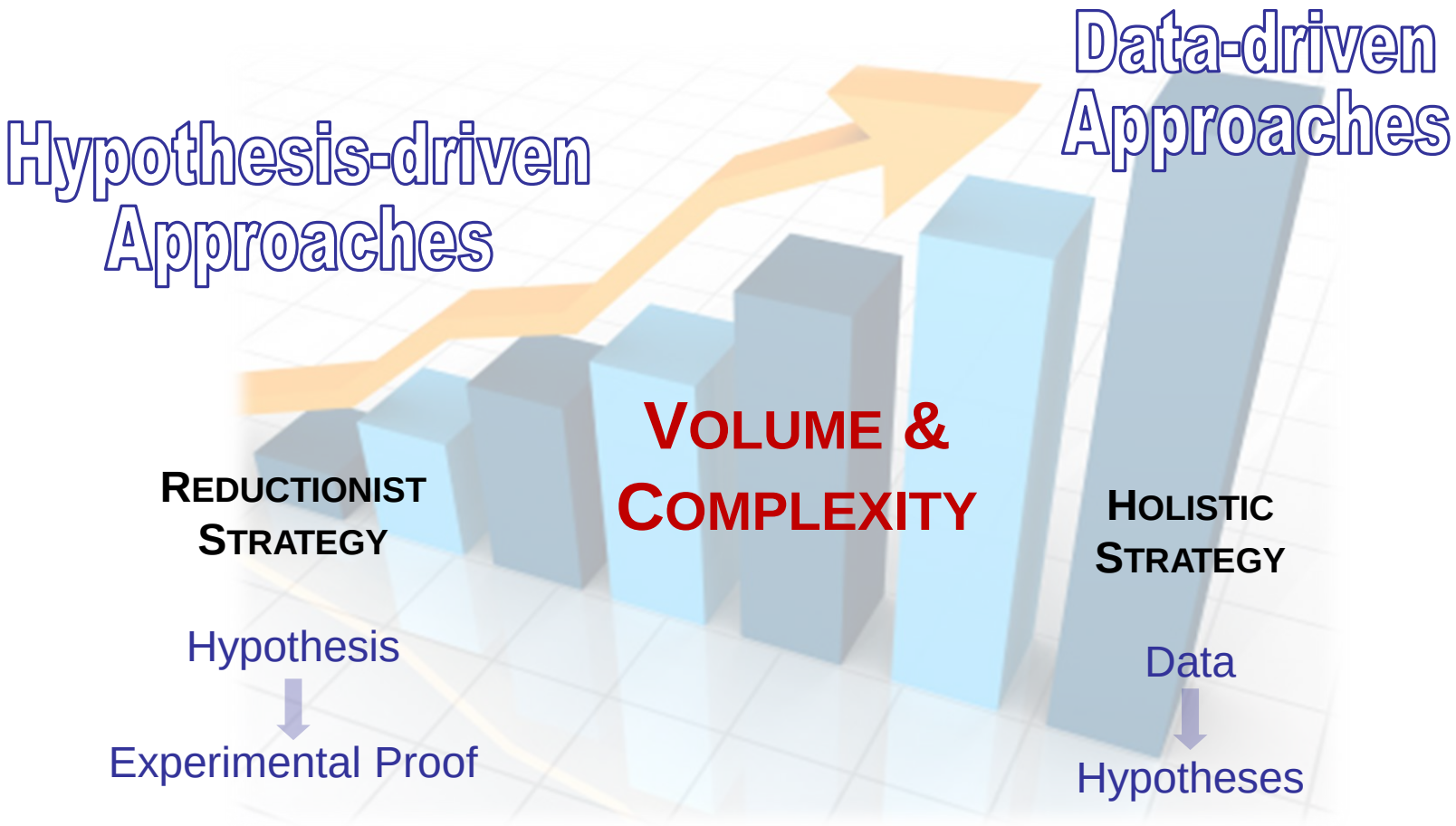
SIB
Swiss Institute of Bioinformatics

PART II

MULTIOMICS DATA INTEGRATION

The Omics Data Explosion

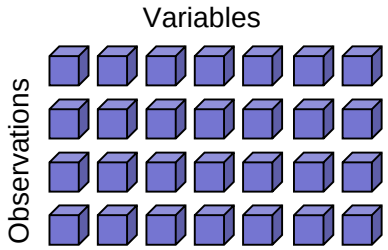
Modern scientific technologies are able to generate massive datasets to describe specific phenotypes illustrating a biological phenomenon

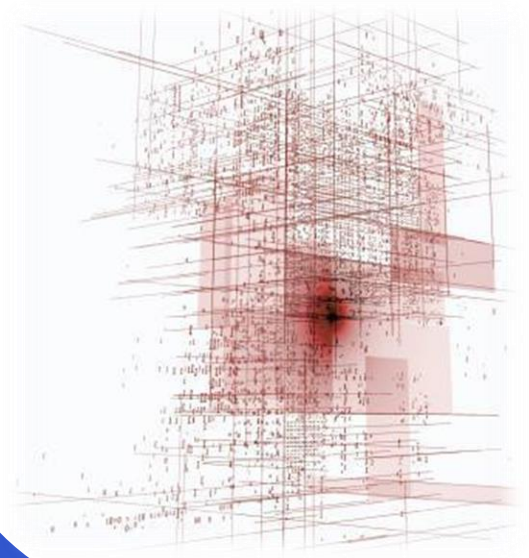


Data Structures

- One-way data is a vector, with a single data value for each element of the single dimension (n)

- Two-way data is a matrix, with a single data value for each element of two separate dimensions (n,p)





High dimensionality (n << p)
Multicollinearity between variables
Missing values
Biological/analytical variability

Adding extra dimensions leads to an exponential increase of the hypothesis space size
→ Relevant hypotheses become harder to find

!

Knowledge Discovery In Omics

Analytics

Data Production
- ✓ Sample preparation
- ✓ Data acquisition

Data Processing
- ✓ Signal extraction
- ✓ Filtering
- ✓ Normalisation
- ✓ Annotation

Signal

Data Mining

Knowledge

Information Content

Biological Interpretation
- ✓ Extract relevant information
- ✓ Link to existing knowledge
- ✓ Biological validation

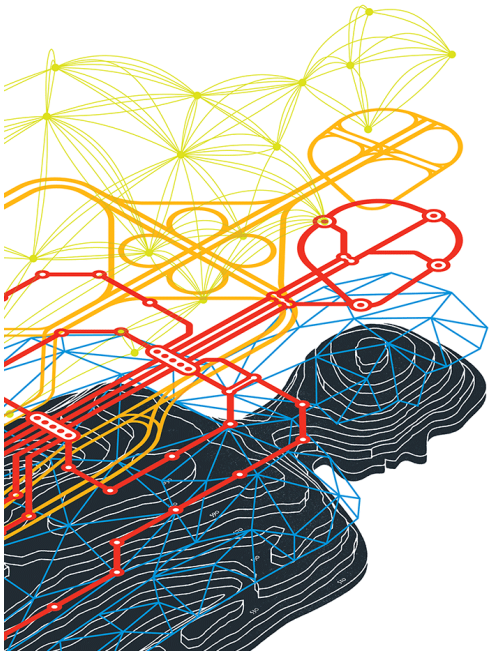
Chemometrics

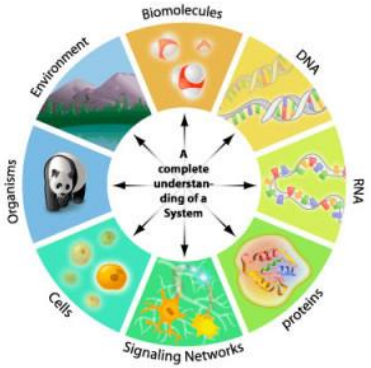
Multivariate Analysis
- ✓Exploration
- ✓ Classification
- ✓ Pattern Recognition
- ✓ Variables contribution

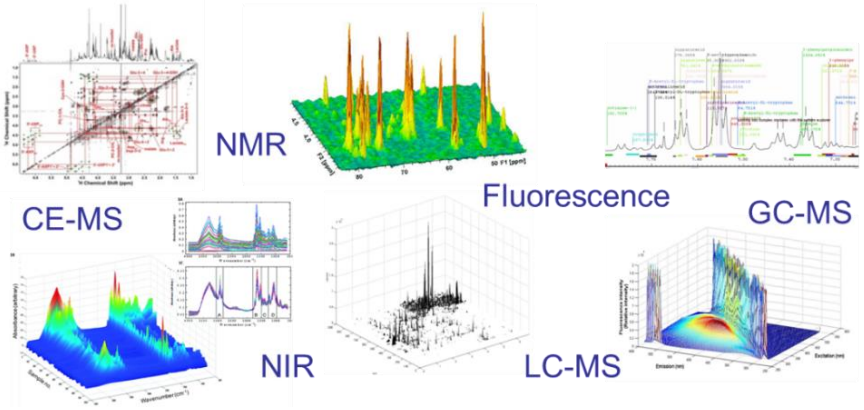
Bioinformatics

Multiple Data Sources Omics

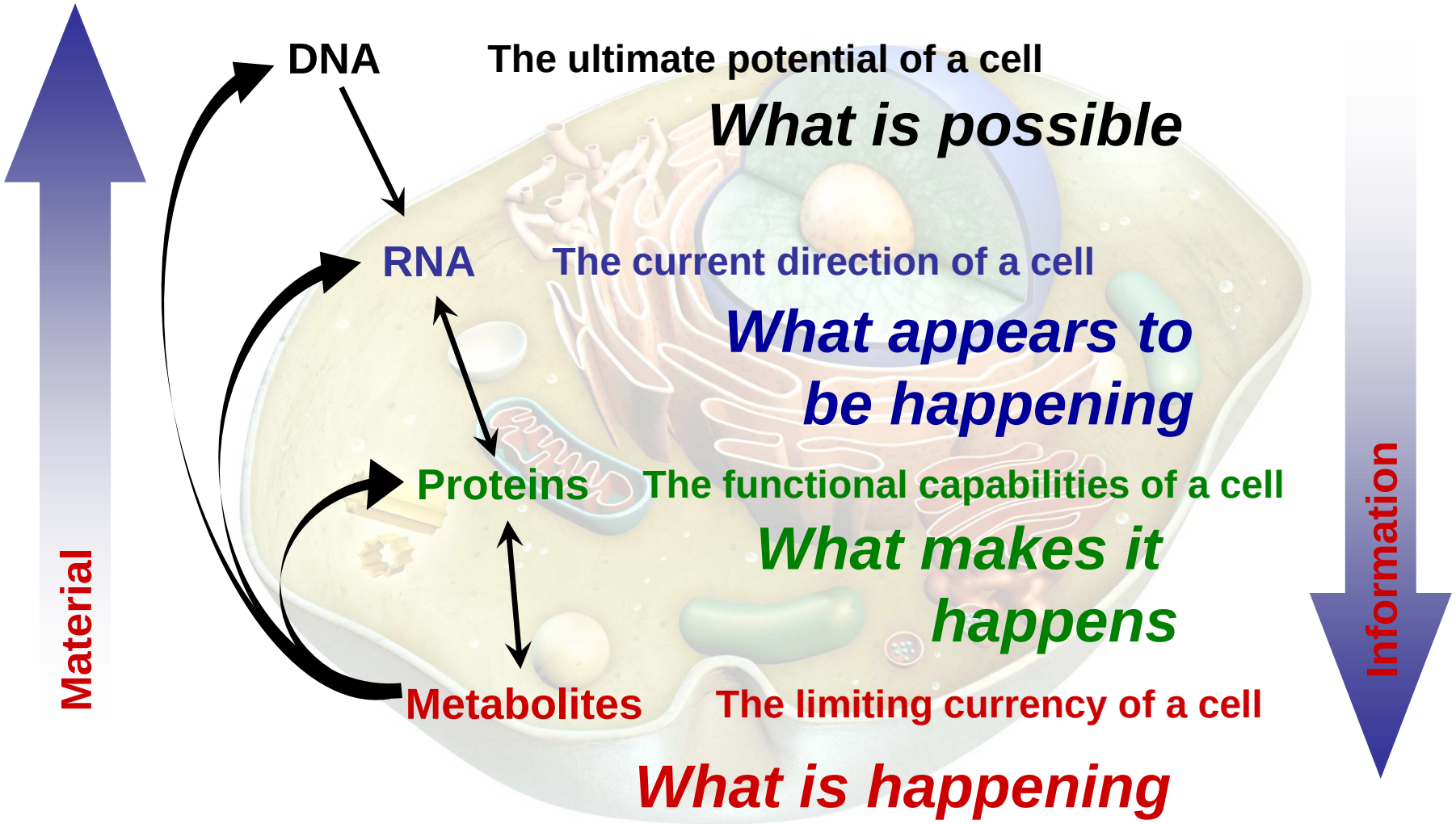
- ✓ Different biological scales
  - ✓ Cell/tissue/organism
  - ✓ Systems biology
- ✓ Different stages of a process
  - ✓ Dose
  - ✓ Toxicity
  - ✓ Disease progression
- ✓ Different analytical techniques
  - ✓ Heterogeneous data
  - ✓ Separation or spectral methods







MultiOmics & Systems Roles



Embracing Complexity

How does a complex system work?

Examine separately springs, gears, shafts, etc. how they fit together

or

Consider all the elements at once and how they fit and interact together

DATA INTEGRATION

MULTIGROUP ANALYSIS

MULTIVIEW ANALYSIS

DATA FUSION

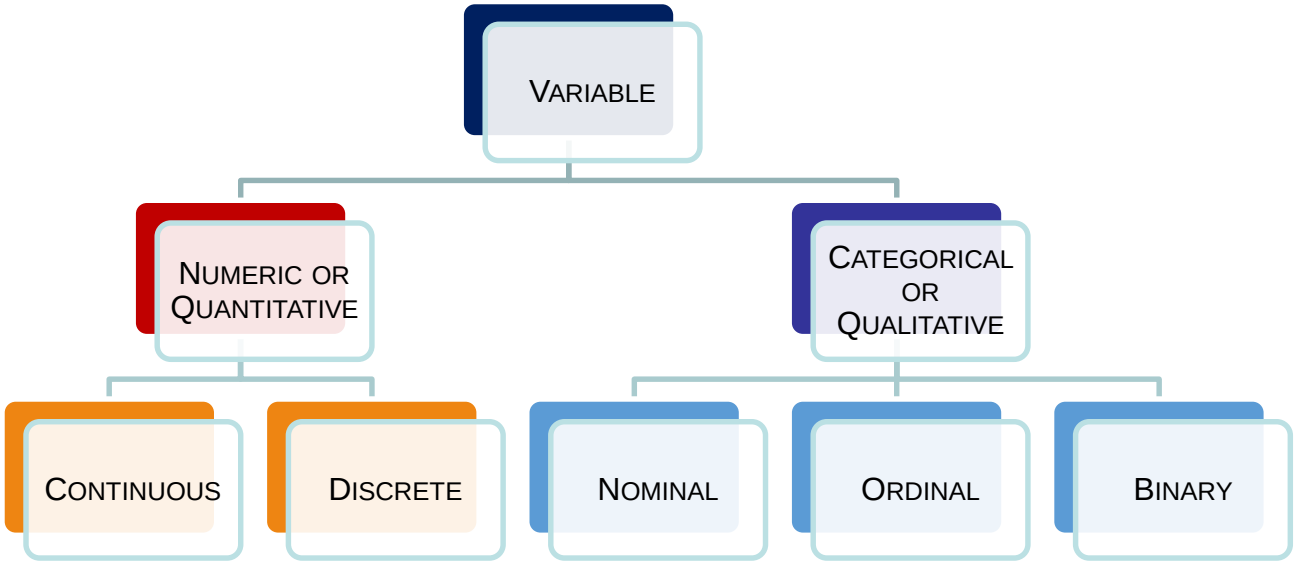
?

MULTISET ANALYSIS

MULTITABLE ANALYSIS

MULTIBLOCK ANALYSIS

Nature Of The Data



QUANTITATIVE

- Continuous: numeric variables that can take any value between a certain set of real numbers
- Discrete: numeric variables that only consist of integers

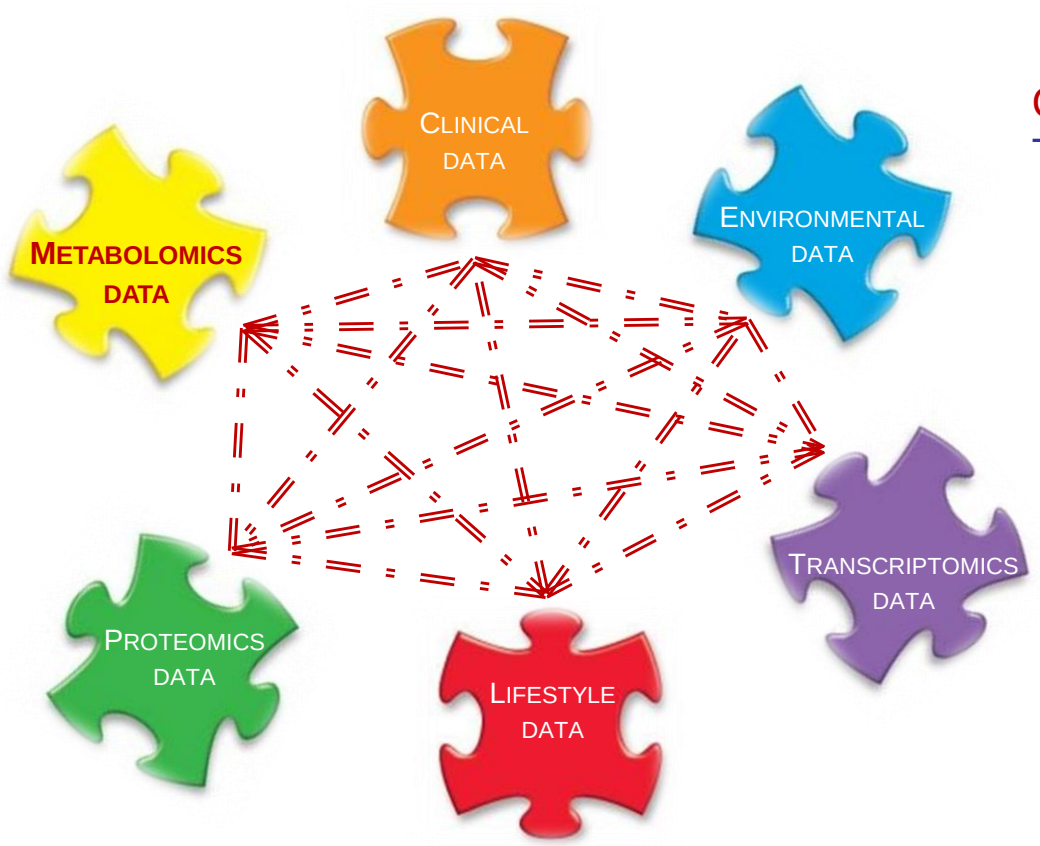
QUALITATIVE

- Nominal: categorical variable that cannot be ranked
- Ordinal: categorical variable that can be ranked
- Binary: categorical variable that is either true or false

Data Homo/Heterogeneity

Homogeneous data: data blocks all measured on the same scale
e.g. quantitative data

Heterogeneous data: data blocks measured on different scales
e.g. quantitative, ordinal, qualitative, binary



Continuous
Transcripts/Proteins/Metabolites

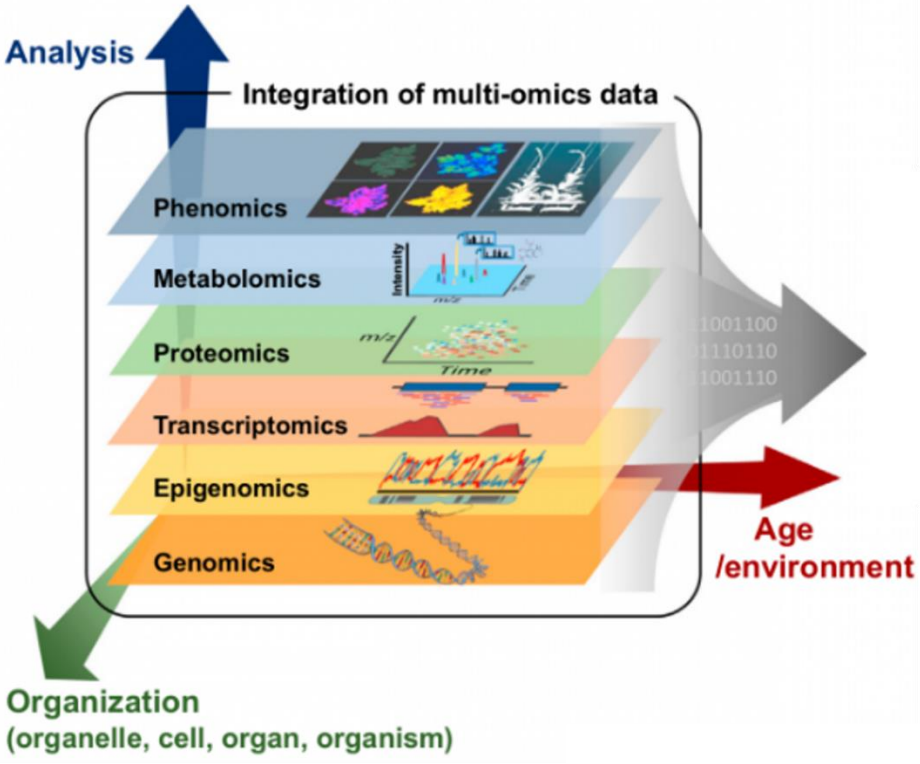
Discrete
Clinical scores

Ordinal
Lifestyle

Nominal
SNPs
Clinical data

Binary
Methylation
Clinical conditions

MultiOmics Data Integration

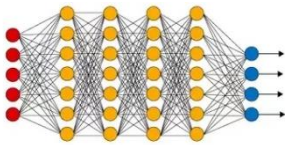


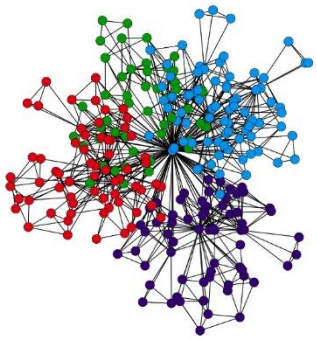
AIMS

- Molecular signatures
- Biological processes
- Mechanistic insights
- Interplay between layers
- Holistic view

METHODS

- Matrix Factorization
- Network-based approaches (multiplex, multilayer)
- Bayesian approaches
- Machine learning (embeddings)





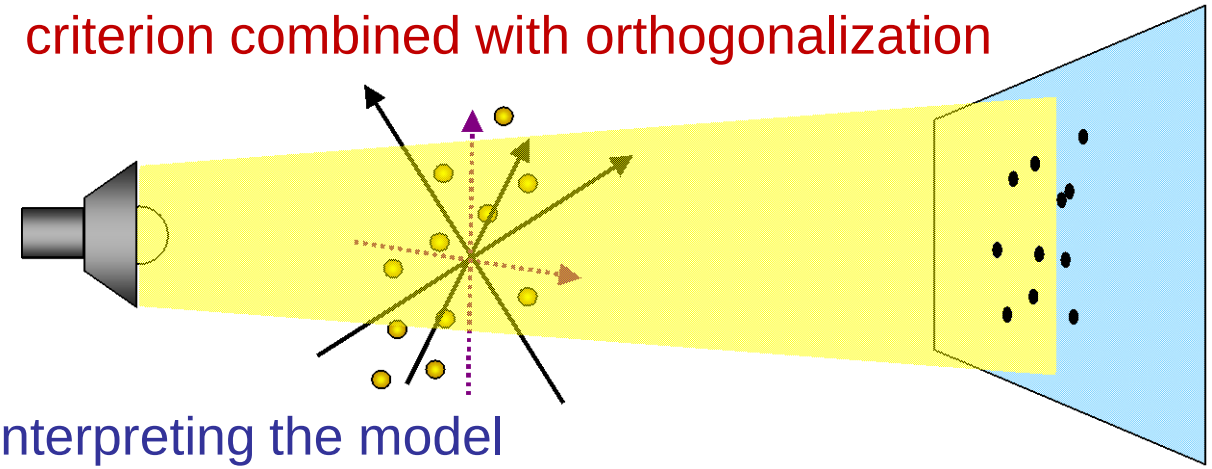
Methods Based On Components

Data High Dimensionality
Variables Correlations
Biological Variability
Experimental Noise

Projection methods

- ✓ analyze datasets of high dimensionality
- ✓ provide knowledge about systems
- ✓ find unsuspected relationships
- ✓ summarize the data with a small number of factors

Linear combination of the initial variables
→ maximization/minimization some criterion combined with orthogonalization



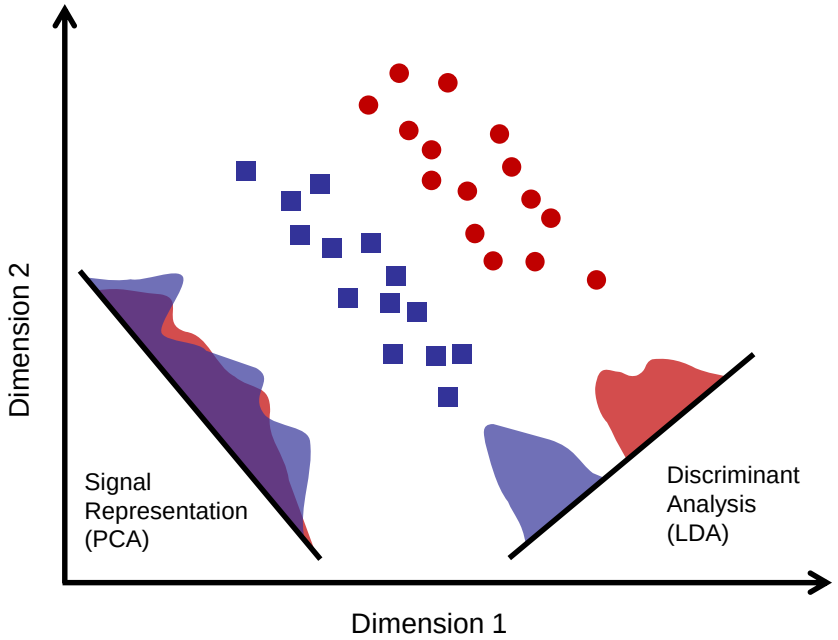
Interpreting the model

- Visualize the samples' distribution
- Visualize correlations between variables

Model Objectives

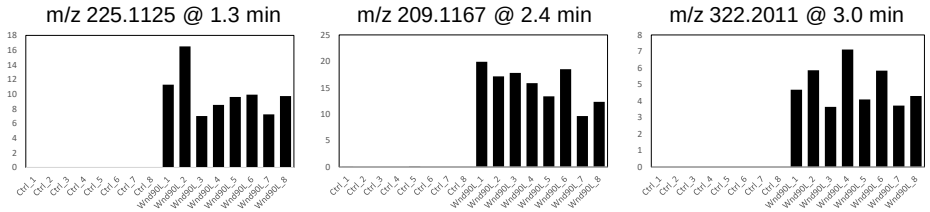
Search for a subspace providing an effective representation of the data
Build a multivariate model (PCA, PLS, OPLS)
Analyse the model

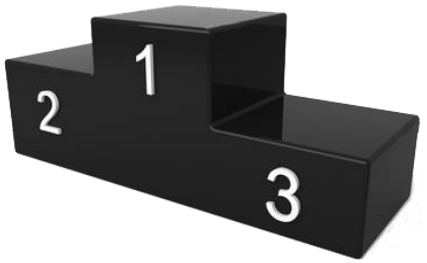
✓ Search for patterns/groupings
✓ Prediction performance



Evaluate the variables' contributions
Rank the variables

Find the most relevant biomarkers

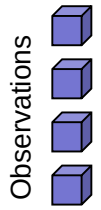




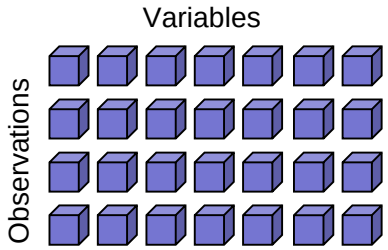
→ **MOLECULAR SIGNATURES**

Data Structures

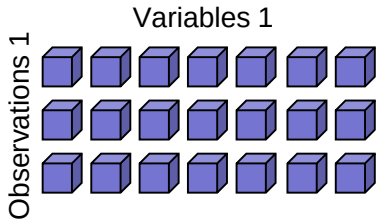
- One-way data is a vector, with a single data value for each element of the single dimension (n)

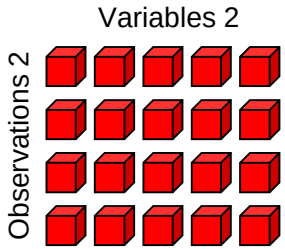


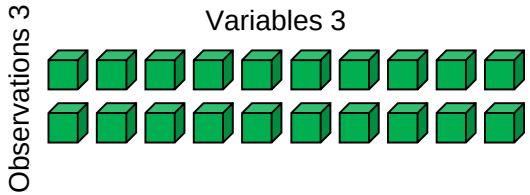
- Two-way data is a matrix, with a single data value for each element of two separate dimensions (n,p)



- Multiblock data can be seen as a collection of matrices

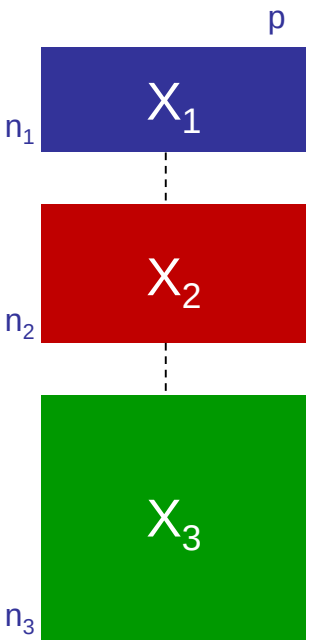




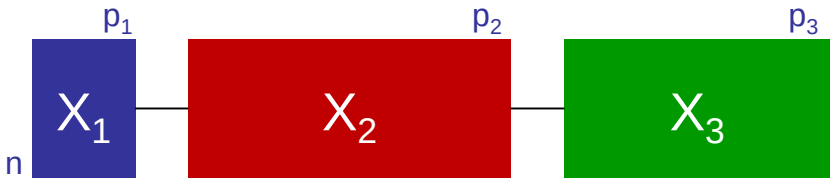


Multiblock Data Structure

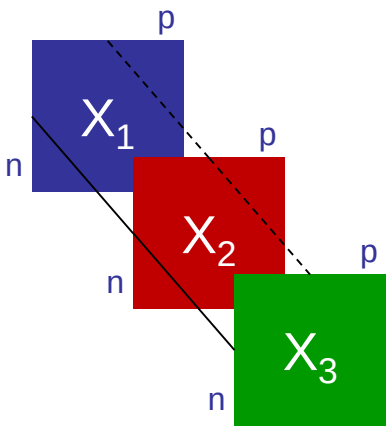
- Shared Observation mode ?
- Shared Variable mode ?
- Shared Observation or Variable mode ?
- Shared Observation and Variable mode ?



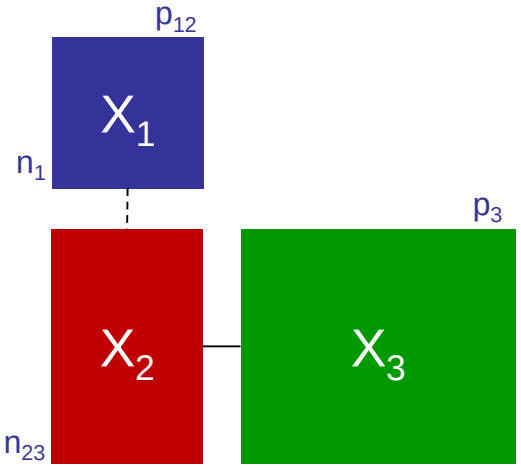
Vertical (multigroup)



Horizontal (multiview)



Tensorial (multiway)



L-shape

A Horizontal Multiblock Data Structure

The Observation mode (rows) is shared (n observations)
The Variables mode (columns) is specific (p_1, p_2, p_3 variables)
Many more variables than observations

Goals are the same as single-block data analysis

Find components (linear combinations of the initial variables) to
Describe – Discriminate – Classify – Predict

Objectives

✓ Specific applications: Collaboration or Competition

Combine data sources

→ Gain an extended understanding of complex systems

- coverage
- mechanisms

→ Improved prediction of new observations

- more sensitive
- more specific

Compare data sources

→ Rank data sources (*e.g.* analytical methods)

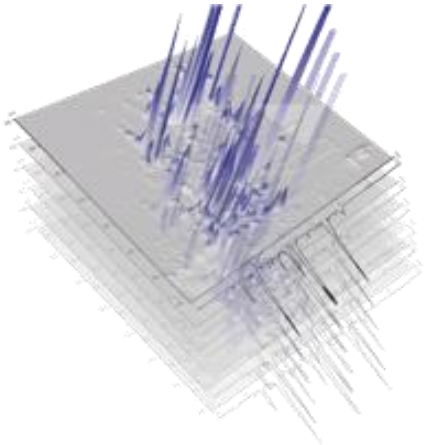
→ Block subsets selection

FAIRNESS BETWEEN BLOCKS ?

Data Complementarity

Relations between the input data sources:

- Complementary
  - → The information represents different parts of the system
  - → Obtain more complete or new information
  - (*e.g.* improved omics coverage or systems biology)



- Redundant
  - → Two or more sources provide the same information
  - → Increase the confidence
  - (*e.g.* multiple analytical platforms, biological layers)

COMMON AND/OR DISTINCT VARIATIONS ?

Data Pre-processing

- Centering
- Within-block scaling
  - usual scaling as performed for a single data block
    e.g. unit variance or Pareto scaling

- Between-block scaling
  - each block of data is simultaneously scaled
  - different block weights = special properties

High-dimensional blocks will have more influence
→ Scaling according to the number of variables (1/VarNb)

Block with large range will have more influence
→ Scaling according to block inertia/norm

NB: Some methods are invariant to certain types of scaling

Data Fusion Terminology

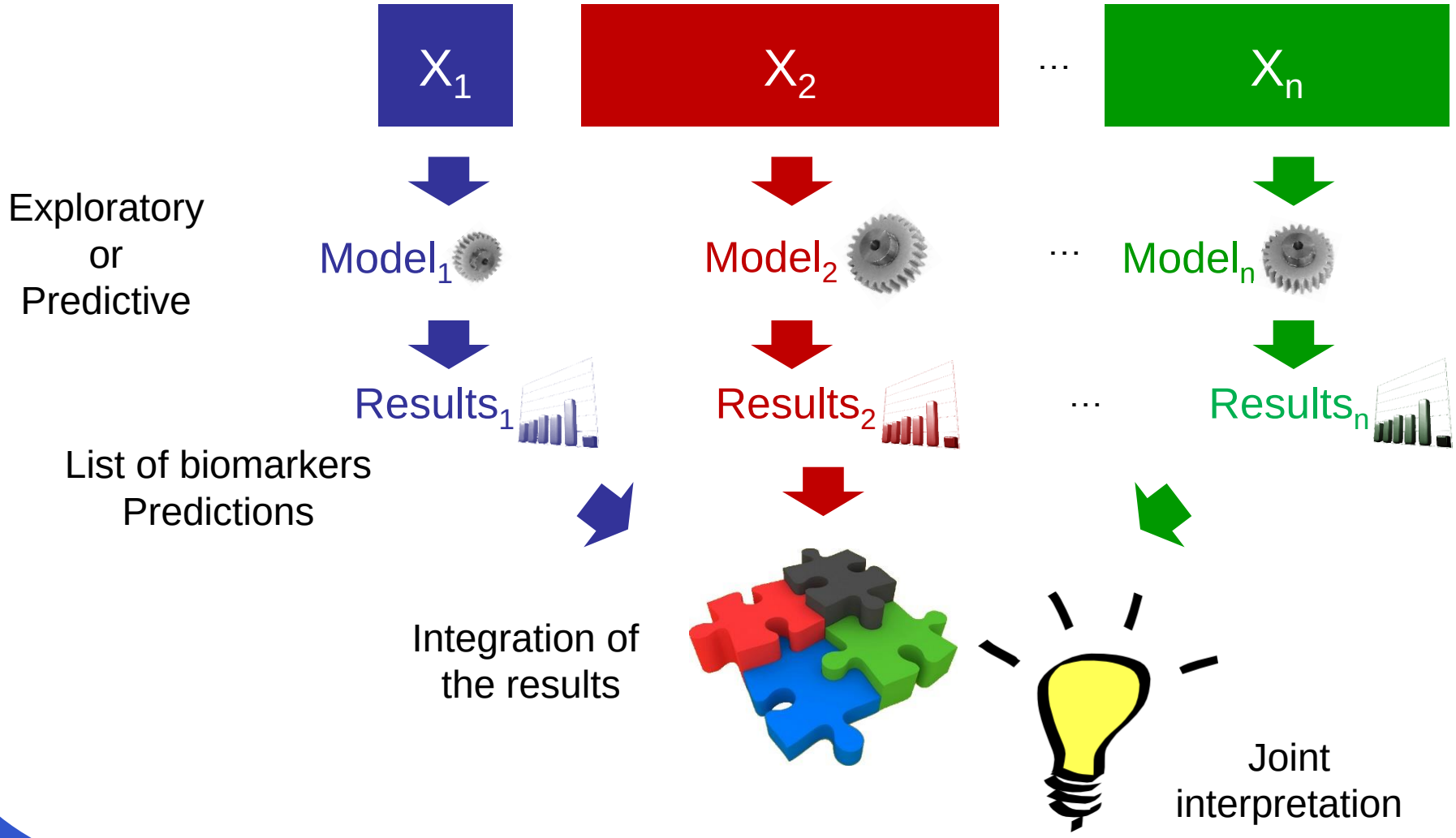
Strategies for data integration based on abstraction levels

- High-level (symbolic representations or decisions)
  → information/decision fusion
- Mid-level (patterns or subsets extracted from the sources)
  → characteristics employed for other tasks
- Low-level (signals)
  → data fusion/aggregation/association

The terminology depends on the application domain

High-level Data Fusion

Integration of results from single blocks models



High-level Data Fusion

Separate evaluation of each data sources

The samples can be different between blocks → more flexibility

Fusion of outputs (unsupervised)

→ Joint interpretation of biomarker patterns or scores

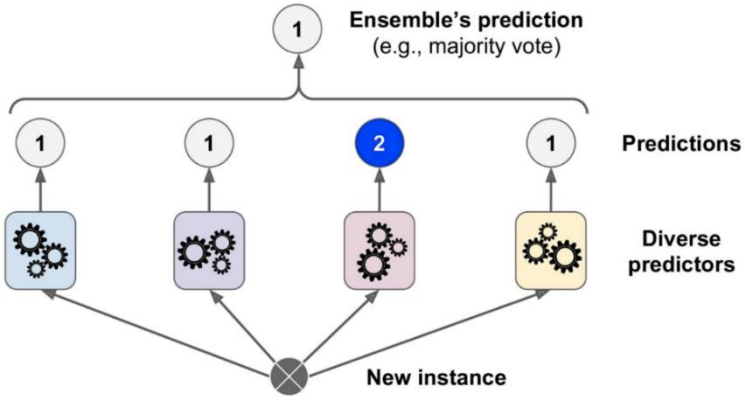
e.g. ontologies, over-representation analysis)

Decision fusion (supervised)

→ Joint prediction (ensemble learning)

Voting schemes

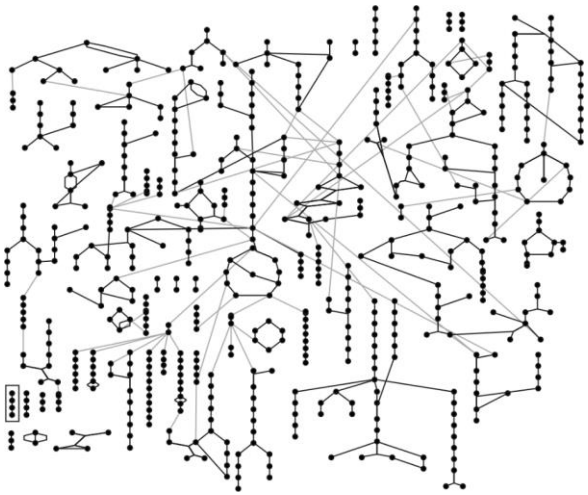
e.g. majority voting the class with the highest number of votes wins



→ Combining classification or prediction results for improved accuracy

Biological Networks

- Networks often represented as graphs
- Nodes represent metabolites, proteins or genes
- Edges represent the functional links between nodes (e.g. biochemical reaction, regulation or binding)
- Changes in topology can result in novel properties (comparisons of specific situations)



A metabolic network for Escherichia coli

✓ Visualization of the results

Contribute to mechanistic interpretation

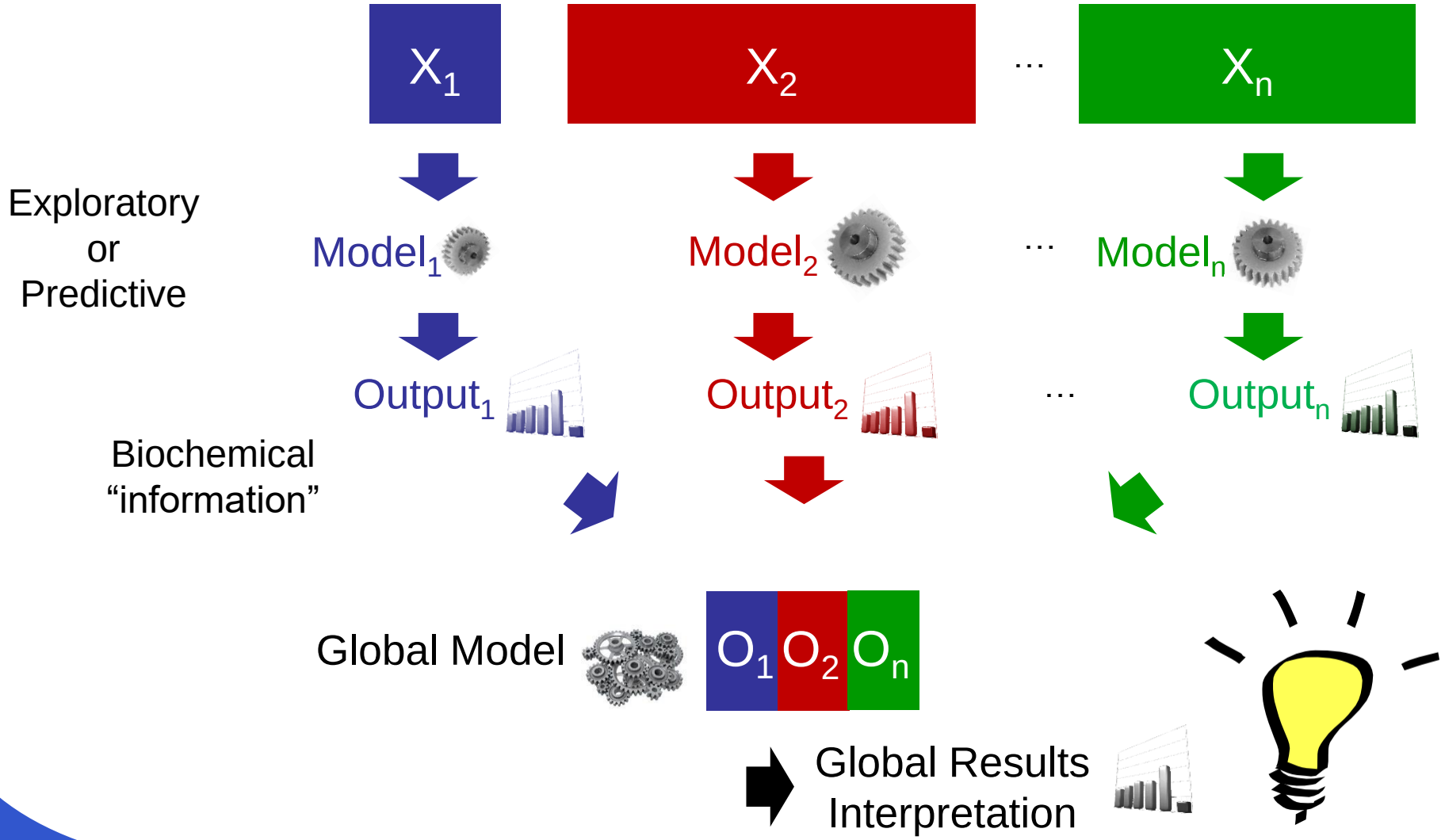
- most relevant biological processes
- regulatory relationships

Types of interactions:

- protein– metabolite (metabolic pathways)
- protein – protein (cell signaling, protein interactions)
- protein – gene (genetic networks)

Mid-level Data Fusion

Integration of results from single blocks models

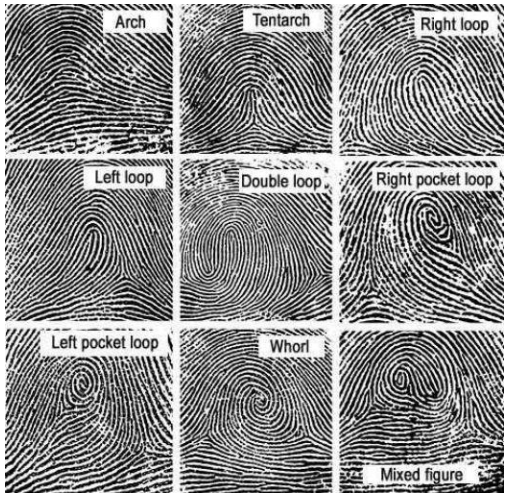


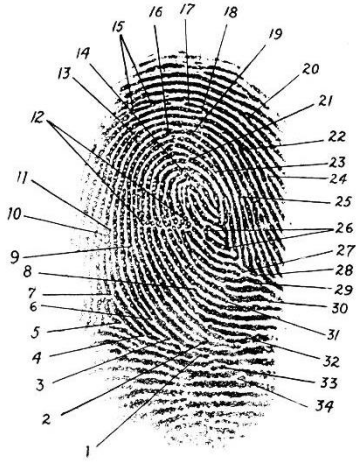
Feature Extraction vs. Selection

Several features can be combined together without loss or even with gain of information

→ Feature extraction

Combine the original variables into a smaller set of synthetic variables with Projection Methods





Some variables bear little or no useful information

→ Feature selection

Choose a subset of important features, ignoring the remaining unimportant variables with Subset Selection Algorithms

Mid-level Data Fusion

2-step procedure 

- Middle-Up
  i. Multivariate model (PCA, CA, PLS) → dimensionality reduction
  ii. Second analysis based on the concatenated scores (PCA, PLS, clustering)
  - ✓ Handle heterogeneous datasets
  - ? What about model interpretation?
  - ? How many components to keep?

- Middle-Down
  i. Model or test (PLS, Fold change) → local variable selection
  ii. Second analysis based on the concatenated variables subsets
  - ✓ Easy interpretation of the final model
  - ? How to handle heterogeneous datasets?
  - ? How many variables to keep?

Limitations of High/Mid-level Data Integration

No insight into the links between initial data blocks
Individual models may lead to a substantial loss of biological information

Results may be contradictory/heterogeneous

- Unsupervised: biological interpretation can be tedious
- Supervised: the result can be inconclusive in the case of ties

The combination of information may not be relevant

Different subsets of observations may lead to conflicting conclusions within multiple data sources

Interpretable patterns may be impaired by combining with other data sources

Low-level Multiblock Analysis

Consider the fact that the same observations are in the different blocks
→ assess the relationship between the variables and the data tables

Unsupervised analysis

→ explorative analysis looking for structures and patterns

- links between variables in a single data block
- links across data blocks

Supervised analysis

→ predictive data analysis, emphasis is on a response block of data Y

- connections to one or more blocks of data
- some blocks are dependent and others are independent

Multiblock Data Modeling

✓ Think global by building a compromise accounting for all data with adequate weights

✓ Act local by maximizing the link between data blocks under a specific criterion, *e.g.* canonical correlation, co-inertia, partial least squares

Find the relevant information

- ✓ Role/importance of each data table
- ✓ Common/specific trends
- ✓ Links between variables of different nature

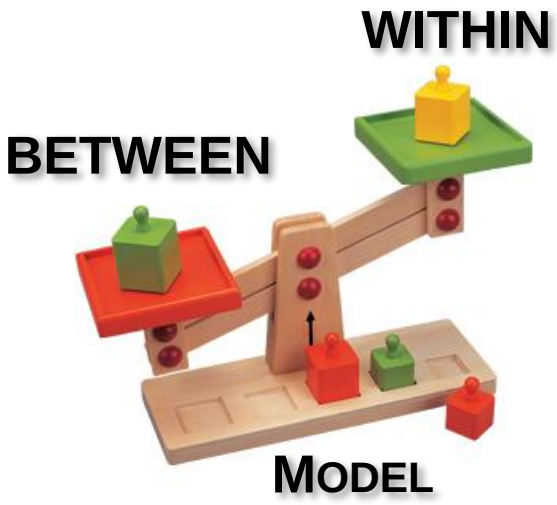
Low-level Data Fusion

Factor analysis can be applied to blocks instead of initial variables !

Each LV related to one block is connected to all the LVs related to the other blocks and/or to a global component

Block components should verify two properties simultaneously

- Block components explain well their own block
- Block components are as correlated as possible with related blocks



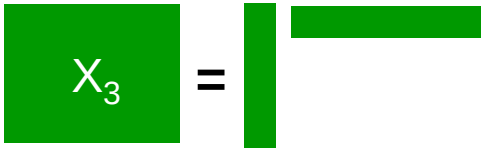
The multiblock model build components as a compromise for explaining between-block and within-block variation

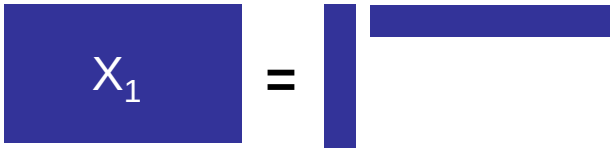
Different methods favor explaining more within- or between-block variation

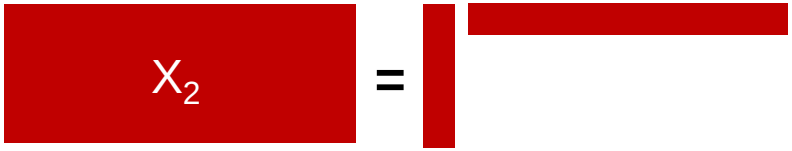
Matrix Factorization

$$F_3 = X_3^1 w_3^1 + X_3^2 w_3^2 + \cdots + X_3^{n3} w_3^{n3}$$

$$F_1 = X_1^1 w_1^1 + X_1^2 w_1^2 + \cdots + X_1^n w_1^n$$







$$F_2 = X_2^1 w_2^1 + X_2^2 w_2^2 + \cdots + X_2^{n2} w_2^{n2}$$

How To Build components
How To Link components

?

Co-variance criterion

!

$$max \sum_{j,k=1}^{n} cov \quad (X_j w_j, X_k w_k)$$

Correlation, Variance and Covariance

Correlation is widely used to describe the relationship between variables

- linear relation between two variables (Pearson)
- non-metric relation based on the ranks of the variables (Spearman)

$$corr(x,y) = \frac{cov(x,y)}{\sqrt{var(x)} + \sqrt{var(y)}}$$

It can be extended to describe the relationship between data blocks !

Correlation
Average

Variance
Single block PCA

Covariance
Compromise

Extracting Structures From Data

Similar relations can be estimated between matrices and components

MATRICES

Similarity can be defined in very many different ways

The RV coefficient compares the configurations of the samples

- blocks with different numbers of variables
- modified version for high-dimensional data

COMPONENTS

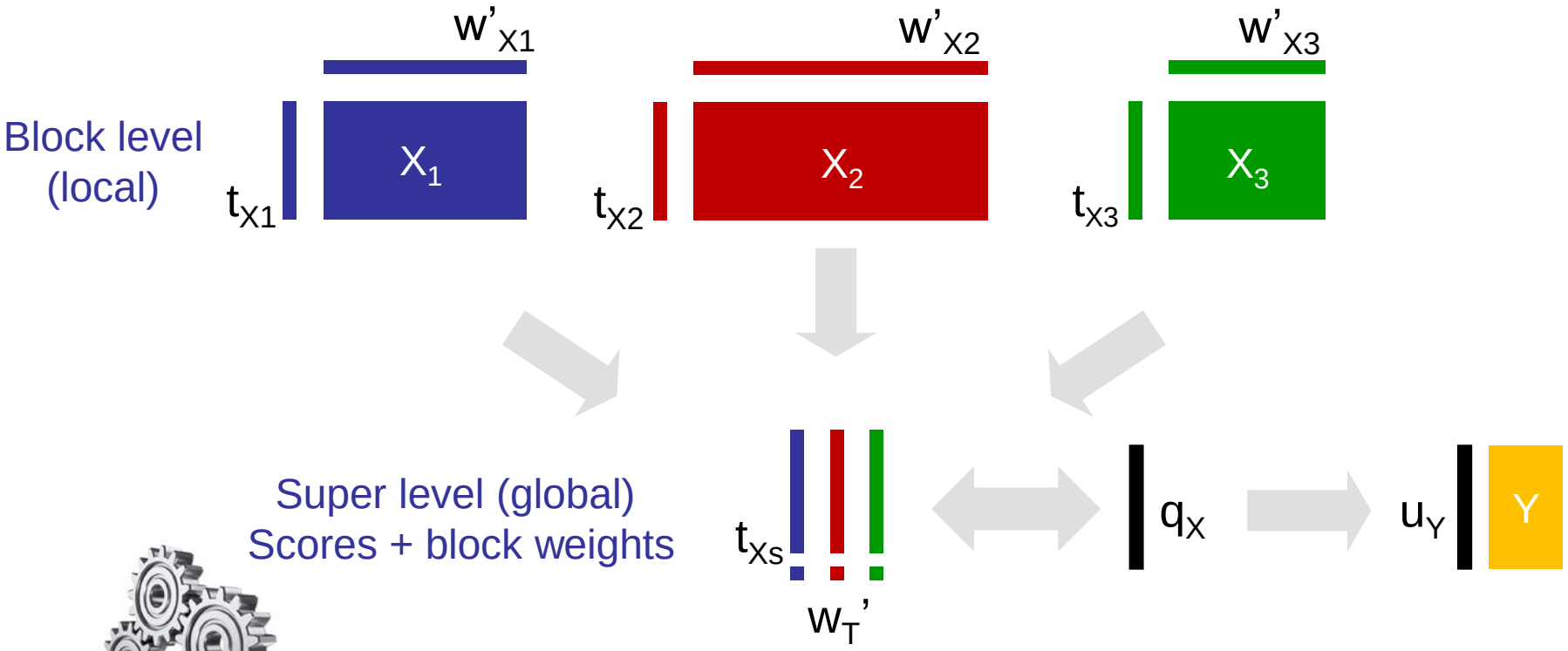
Components are linear combinations of the initial variables $\boldsymbol{X}_j\boldsymbol{w}_j$

Links between components extracted from two blocks:

$$cov^2\left(\boldsymbol{X}_j\boldsymbol{w}_j, \boldsymbol{X}_k\boldsymbol{w}_k\right) = var(\boldsymbol{X}_j\boldsymbol{w}_j)cor^2\left(\boldsymbol{X}_j\boldsymbol{w}_j, \boldsymbol{X}_k\boldsymbol{w}_k\right)var(\boldsymbol{X}_k\boldsymbol{w}_k)$$

Low-level Horizontal Multiblock Analysis

A collection of data blocks with shared observations

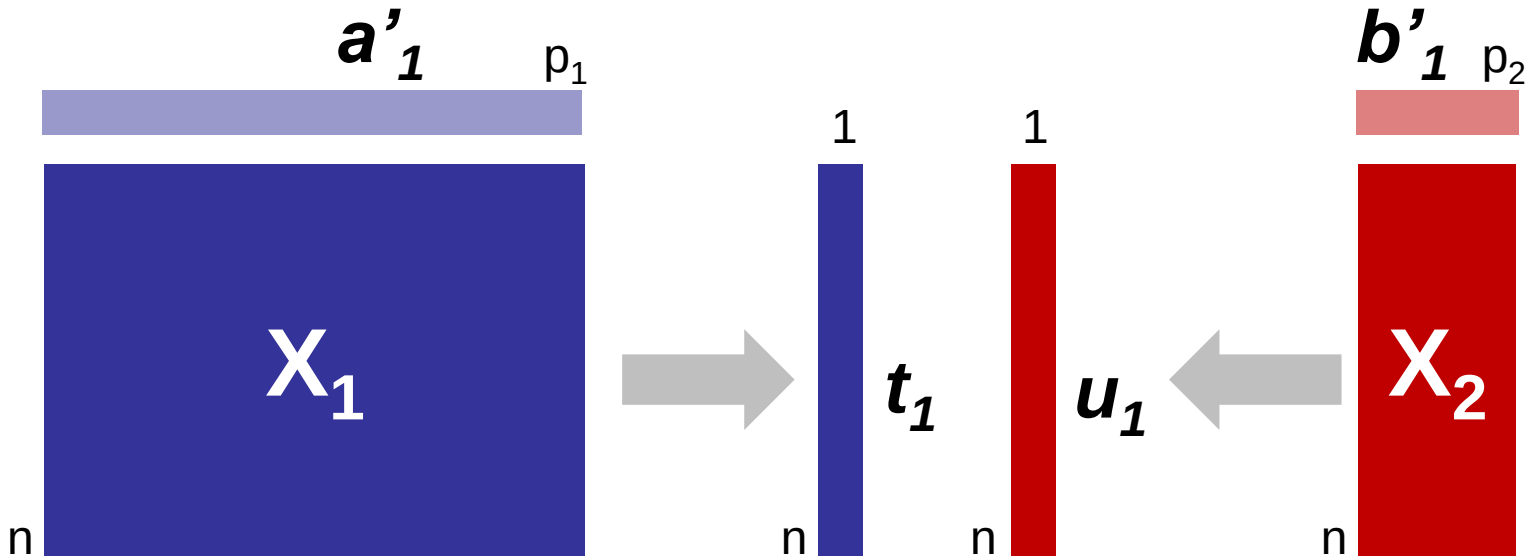


? How to build the super level

It depends on the model !

Relating Two Data Blocks – Multiblock

Linking function between latent variables
e.g. identity link, flexible link, partial identity link



$\mathbf{t_1 = Xa_1}$ and $\mathbf{u_1 = Yb_1}$
maximising the link between t_1 and u_1

→ Find common trends in data blocks

Methods and Criteria To Be Optimized

Many multiblock methods make implicitly or explicitly a choice on which type of variation is modelled

Covariance represents the amount of variation between the blocks but also describes to some extent the variation within the blocks

Method	Criterion	PLS path model	Mode	Scheme
(1) SUMCOR (Horst 1961)	$Max \sum_{j,k} Cor(F_j, F_k)$ or $Max \sum_j Cor\left(F_j, \sum_k F_k\right)$	Hierarchical	B	Centroid
(2) MAXVAR (Horst 1961) or GCCA (Carroll 1968)	$Max \{\lambda_{first}[Cor(F_j, F_k)]\}$ **(a)** or $Max \sum_j Cor^2(F_j, F_{j+1})$	Hierarchical	B	Factorial
(3) SsqCor (Kettenring 1971)	$Max \sum_{j,k} Cor^2(F_j, F_k)$	Confirmatory	B	Factorial
(4) GenVar (Kettenring 1971)	$Min \{\det[Cor(F_j, F_k)]\}$			
(5) MINVAR (Kettenring 1971)	$Min \{\lambda_{last}[Cor(F_j, F_k)]\}$ **(b)**			
(6) Lafosse (1989)	$Max \sum_j Cor^2\left(F_j, \sum_k F_k\right)$			
(7) Mathes (1993) or Hanafi (2005)	$Max \sum_{j,k} \lvert Cor(F_j, F_k)\rvert$	Confirmatory	B	Centroid
(8) MAXDIFF (Van de Geer, 1984 & Ten Berge, 1988)	$Max_{all \lVert w_j\rVert=1} \sum_{j \neq k} Cov(X_j w_j, X_k w_k)$			
(9) MAXBET (Van de Geer, 1984 & Ten Berge, 1988)	$Max_{all \lVert w_j\rVert=1} \sum_{j,k} Cov(X_j w_j, X_k w_k)$			
(10) MAXDIFF B (Hanafi and Kiers 2006)	$Max_{all \lVert w_j\rVert=1} \sum_{j \neq k} Cov^2(X_j w_j, X_k w_k)$			
(11) (Hanafi and Kiers 2006)	$Max_{all \lVert w_j\rVert=1} \sum_{j \neq k} \lvert Cov(X_j w_j, X_k w_k)\rvert$			
(12) ACOM (Chessel and Hanafi 1996) or Split PCA (Lohmöller 1989)	$Max_{all \lVert w_j\rVert=1} \sum_j Cov^2(X_j w_j, X_{j+1} w_{j+1})$ or $Min_{F, P_j} \sum_j \left\lVert X_j - F p_j^T \right\rVert^2$	Hierarchical	A	Path-weighting
(13) CCSWA (Hanafi et al., 2006) or HPCA (Wold et al., 1996)	$Max_{all \lVert w_j\rVert=1, Var(F)=1} \sum_j Cov^4(X_j w_j, F)$ or $Min_{\lVert F\rVert=1} \sum_j \left\lVert X_j X_j^T - \lambda_j F F^T \right\rVert^2$			
(14) Generalized PCA (Casin 2001)	$Max \sum_j R^2(F, X_j) \sum_h Cor^2\left(x_{jh}, \hat{F}_j\right)$ **(c)**			
(15) MFA (Escofier and Pagès 1994)	$Min_{F, P_j} \sum_j \left\lVert \frac{1}{\sqrt{\lambda_{first}\left[Cor(x_{jh}, x_{jl})\right]}} X_j - F p_j^T \right\rVert^2$	Hierarchical (applied to the reduced X_j) **(d)**	A	Path-weighting
(16) Oblique maximum variance method (Horst 1965)	$Min_{F, P_j} \sum_j \left\lVert X_j \left(\frac{1}{n} X_j^T X_j\right)^{-1/2} - F p_j^T \right\rVert^2$	Hierarchical (applied to the transformed X_j) **(e)**	A	Path-weighting

M. Tenenhaus et al., Handbook of Partial Least Squares (2010) 99-124.

Different Weighting Strategy

How to balance the influence of the different blocks in a global analysis?

The block combination is based on specific weighting schemes:

- Data concatenation

→ each block as a weight of one (SUM-PCA, MBPCA)

- Unsupervised methods

→ weights depend on block dispersion or agreement with a compromise (Multiple Factor Analysis, STATIS, CCSWA)

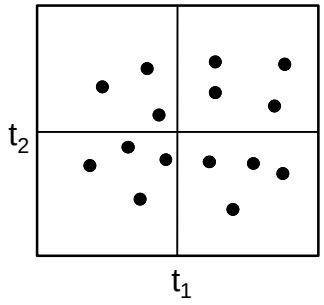
- Supervised methods

→ block weights are driven by the Y response (MBPLS, block-PLS, consensus OPLS)

Multiblock Model Outputs

New common subspace

Common/distinct component(s)



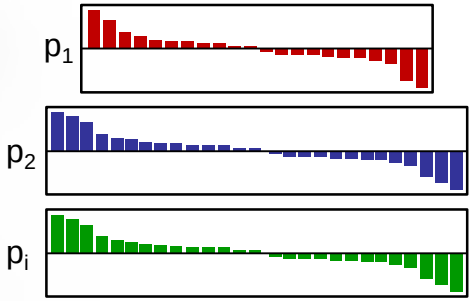
Global/Local scores

Global/local observations scores

→ Pattern recognition

Blocks weights (contributions)

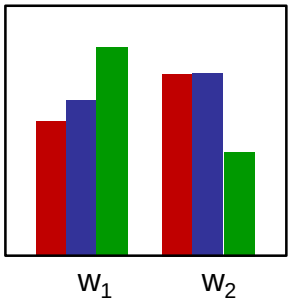
Loadings of the initial variables



Variables loadings

Common/specific variation(s)

→ Balance between block weights



Blocks weights

More complete interpretation:

- Links between variables
- Links between blocks

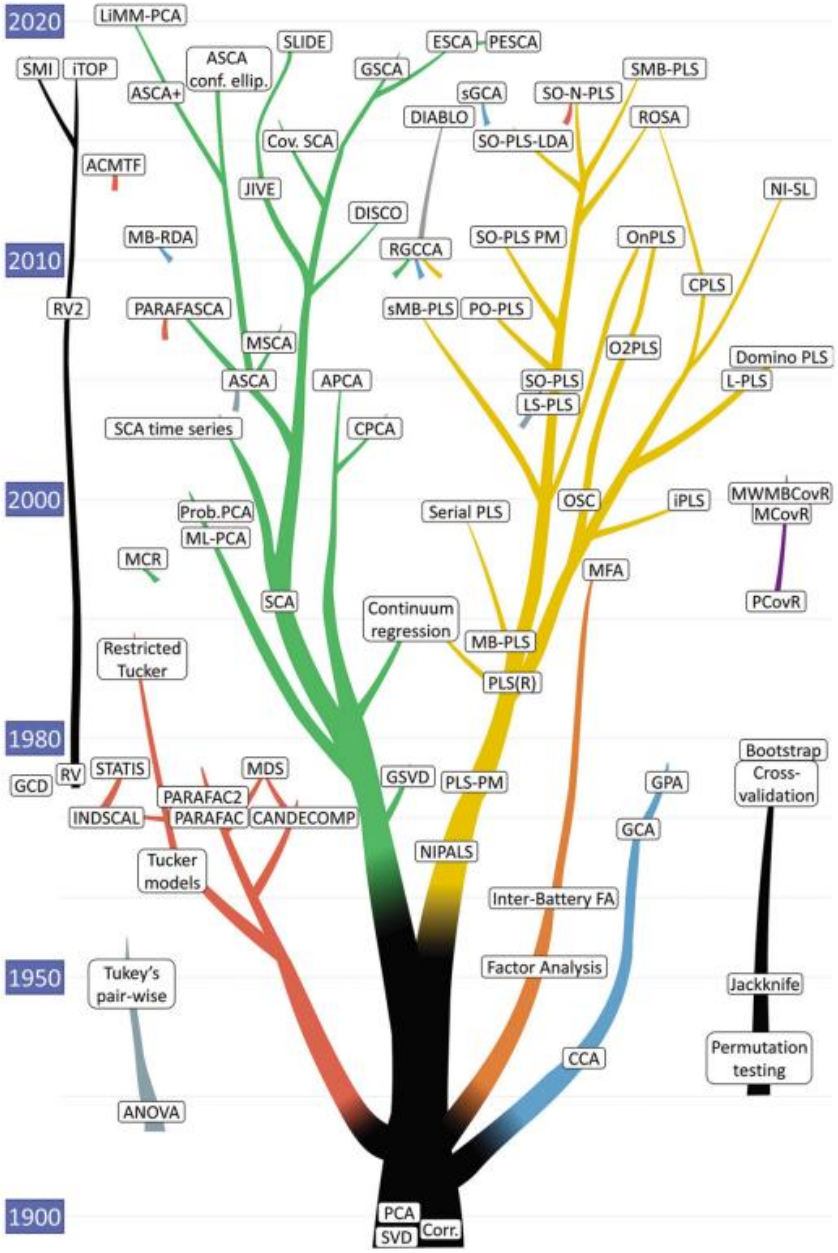
Joint Matrix Factorization

Phylogeny of some multiblock methods and relations to basic data analysis methods

Green branch: Unsupervised multiblock
Yellow branch: Supervised multiblock

Red branch: Multiway
Blue branch: Correlation
Orange branch: Factor analysis

Black branch: Model validation

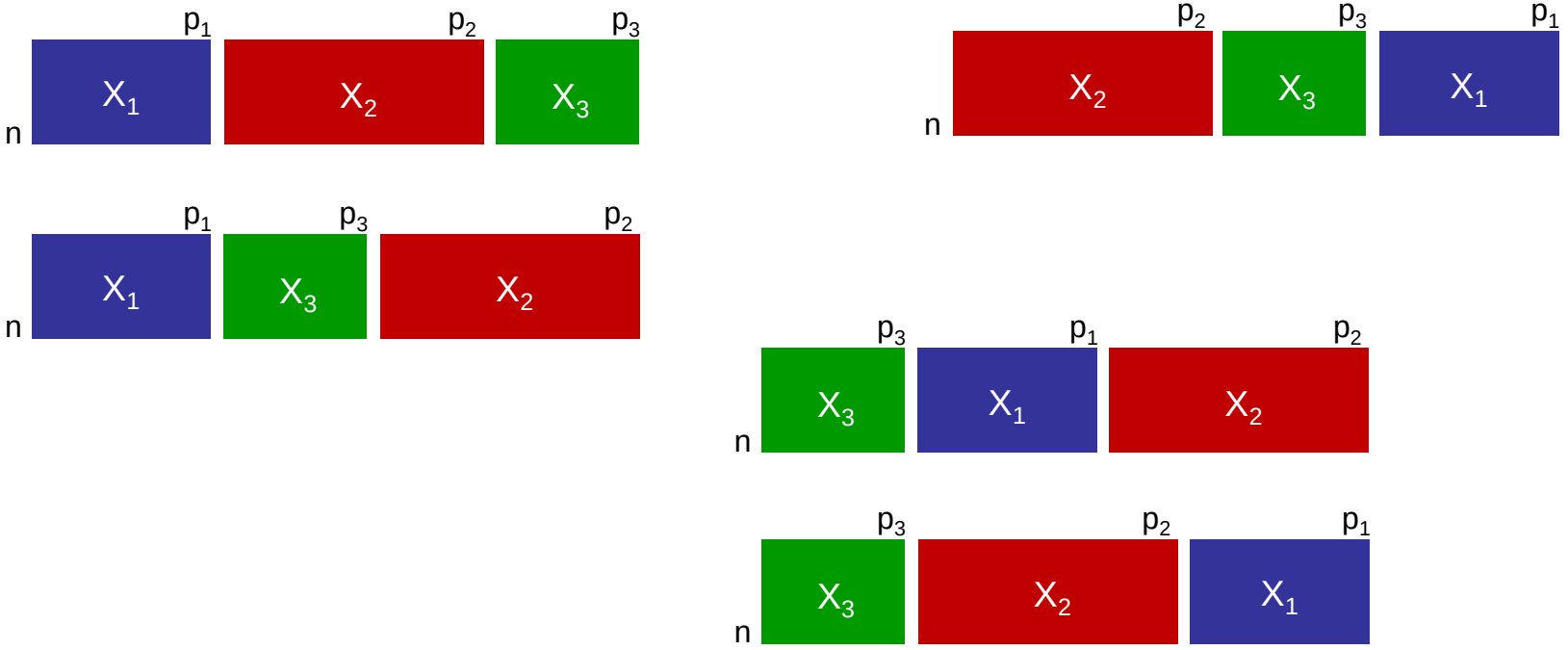


Multiblock Data Fusion in Statistics and Machine Learning: Applications in the Natural and Life Sciences
Wiley 2022

Age K. Smilde, Tormod Næs, Kristian Hovde Liland

Unsupervised Multiblock Analysis

Generate hypotheses from the data blocks
Undirected links
All blocks are treated in the same way
→ the blocks are exchangeable
→ no block sequence



Data Concatenation

First simple idea (*e.g.* SUM-PCA) :

1) Block concatenation
2) Standard multivariate method

Block Concatenation

Super matrix

Focus on common variation only
Do not explain explicitly the relationship between the tables

Block weight is a function of the number of variables and variance
→ Some blocks may play a more important role due to their size/scale

Limitations of Data Concatenation

FAIRNESS BETWEEN BLOCKS

Weight of each block depends on its size/range

? Do all blocks contribute equally to the model?
Should all blocks play a role in each component?
Would it be useful to give more weight to informative blocks?

TYPE OF VARIATION EXPLAINED

Average trends of variations between observations

✗ May not be relevant to explain block patterns

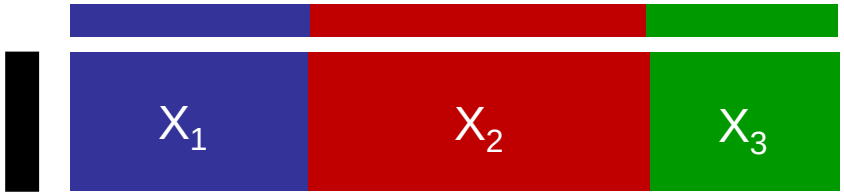
? Do we only want to explain common variation between blocks or also within blocks?

Multiple Factor Analysis

Data concatenation with block weighting based on the first latent variable

Balance between groups of variables:
Maximum axial inertia of a group is equal to one

Super level weighted blocks



B. Escofier et al., *Computational Statistics and data analysis* 18, 121-140, 1994

Multiple Factor Analysis

Focus on common variation only

Balancing maximum axial inertia rather than the total inertia
(= the number of variables in PCA with UV scaling)

→ Maximum axial inertia of each group equals one

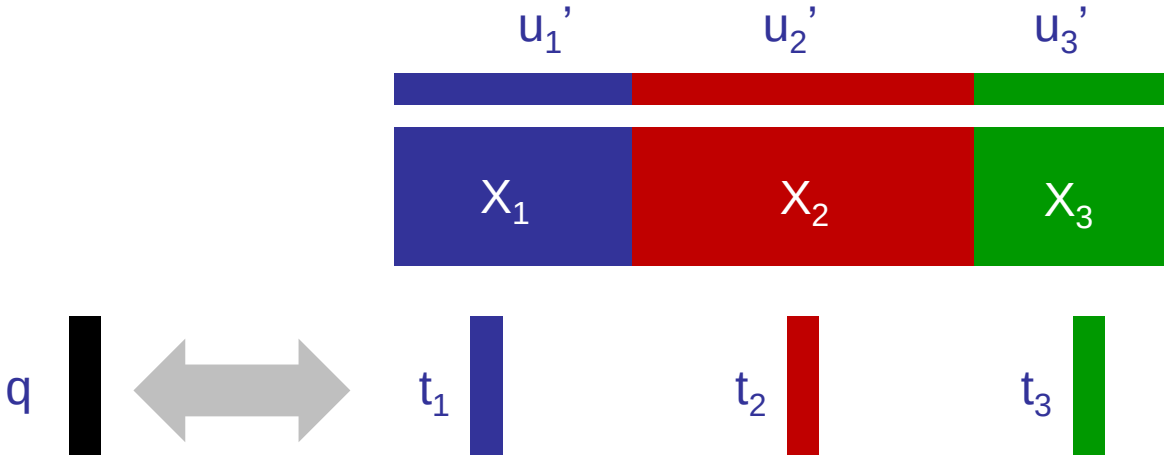
MFA assigns to each variable of group a weight equal to the inverse of the first eigenvalue of the individual analysis

MFA weighting scheme takes into account that a multidimensional group influences naturally more axes than a one-dimensional group

MFA is based on weighted concatenated PCA

Multiple Co-inertia Analysis

Maximization of the link between the canonical variables



q: first standardised principal component of the merged data matrix

$$max \sum_{k=1}^{n} cov^2(X_k w_k, q)$$ to maximize with $$\begin{cases} \text{q : super level} \\ t_k = X_k w_k \end{cases}$$

→ Emphasis is put on common information and structural similarities

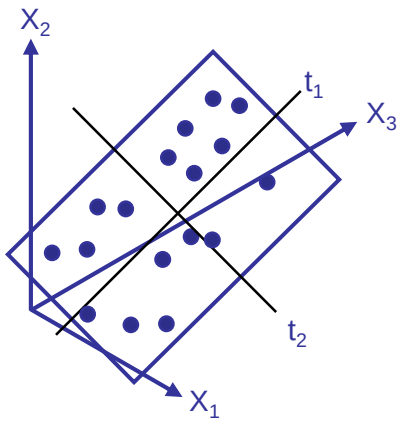
Chessel et al., *Revue Statistique Appliquée (1996) 44(2) 35-60*.

Multiple Co-inertia Analysis Model

Multiple Co-inertia Analysis (MCoA) components are extracted according to their explained variance
→ Similar to PCA

MCoA leads to components
- well explaining their own block
- as positively correlated as possible to the first principal component of the concatenated data table

Each block is deflated with respect to its associated vectors of loadings

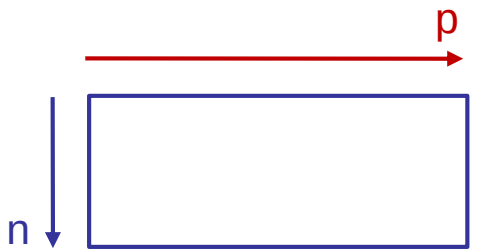


→ the vectors of loadings within each block are constrained to be orthogonal
→ global vectors of scores are also orthogonal

Different Types of Data Matrix

- **The data matrix**
  p variables for each of *n* samples
  presented in a rectangular matrix
  n rows and p columns

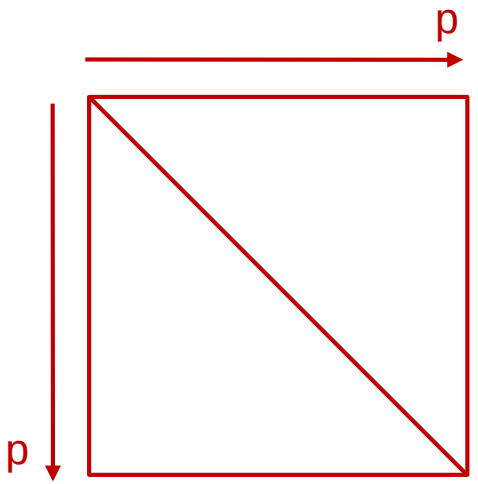
X



How to extract the
new axes of the subspace ?

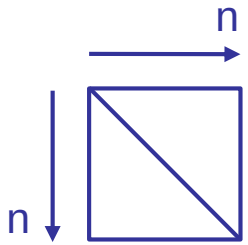
- **The covariance/correlation matrix**
  Similarity between every pair of
  ✓ variables

X'X



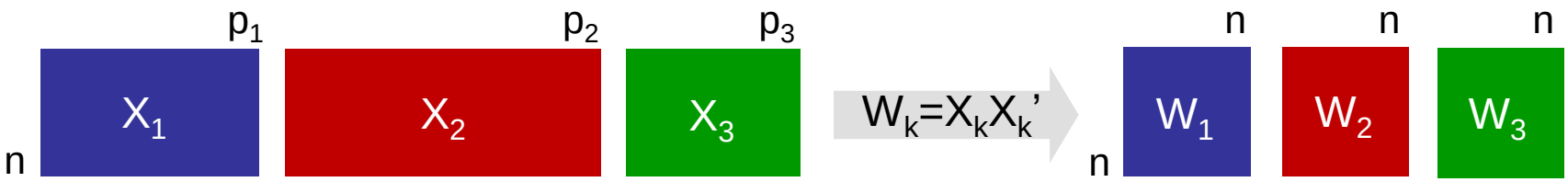
- **The association matrix**
  Similarity between every pair of
  ✓ samples

XX'



STATIS Method

The scalar product defines an association matrix for each data block
→ Similarity between observations within a block (covariances)



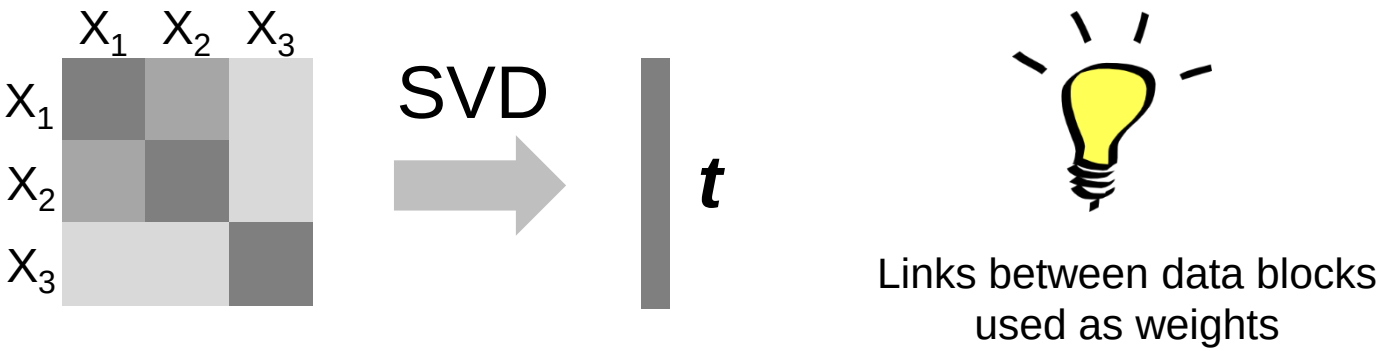
The weighting scheme is based on the RV coefficient between W_i
Cosine based on the Frobenius norm

$$R_V = \frac{\text{trace}\left\{\mathbf{X}\mathbf{X}^\top\mathbf{Y}\mathbf{Y}^\top\right\}}{\sqrt{\left(\text{trace}\left\{\mathbf{X}\mathbf{X}^\top\mathbf{X}\mathbf{X}^\top\right\}\right)\times\left(\text{trace}\left\{\mathbf{Y}\mathbf{Y}^\top\mathbf{Y}\mathbf{Y}^\top\right\}\right)}}$$

Decomposition of the matrix of similarities between all W_i
→ Identity link between data blocks

Escoufier et al., *Biométrie et temps* (1980), 18, 59-76.

STATIS Method



STATIS is based on weighted concatenated PCA

Variables are weighted similarly whether they contribute to the links between blocks and the compromise or not

The strength of the link between data blocks is evaluated without accounting for their dimension

→ Emphasis is put on global similarity (*i.e.* inter-structure analysis)

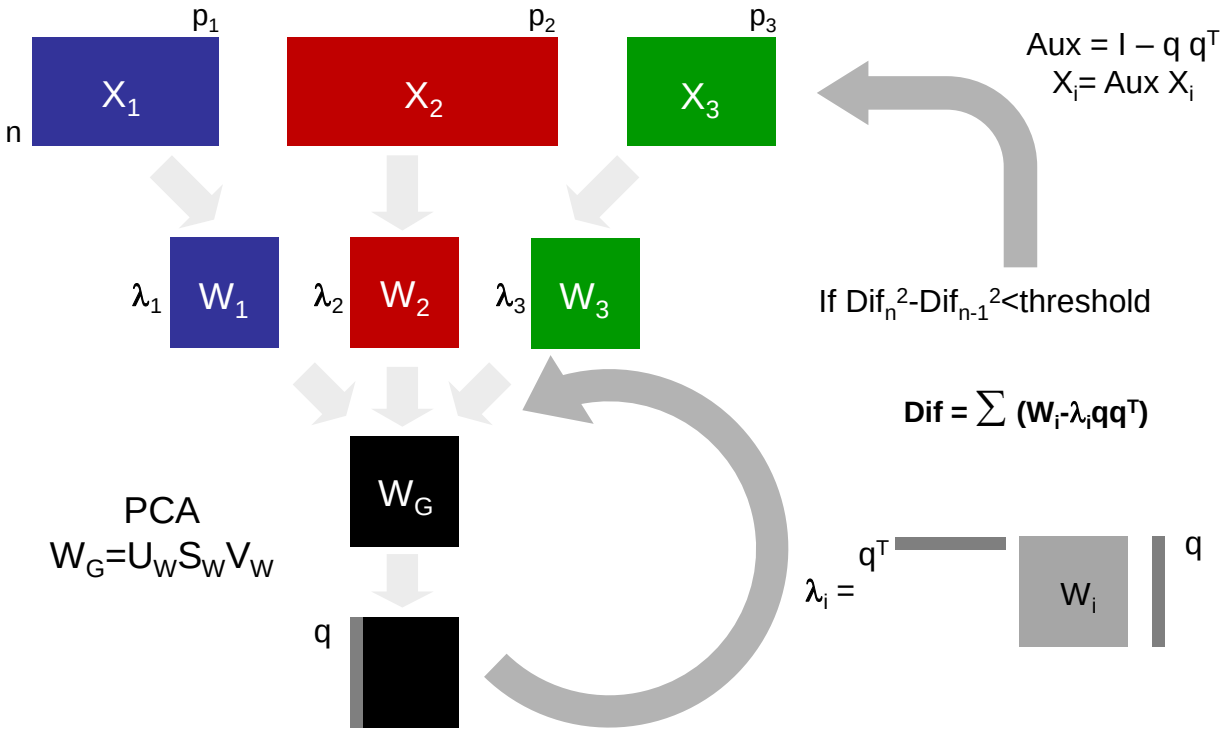
As a second step, the intra-structure can be investigated

→ Assess similarities/differences between individuals/variables

ComDim Method

Common Dimensions
Common Components and Specific Weights Analysis (CCSWA)

Scalar product + iterative block weighting
→ Block weighting is different from a component to another



Link between blocks: covariance[4]

$$max \sum_{k=1}^{n} cov^4(X_k w_k, q)$$

Qannari et al.,, *Food Quality Preference* 11, 151-154, 2000.

CCSWA Model

CCSWA components are extracted according to their explained variance
→ Similar to PCA

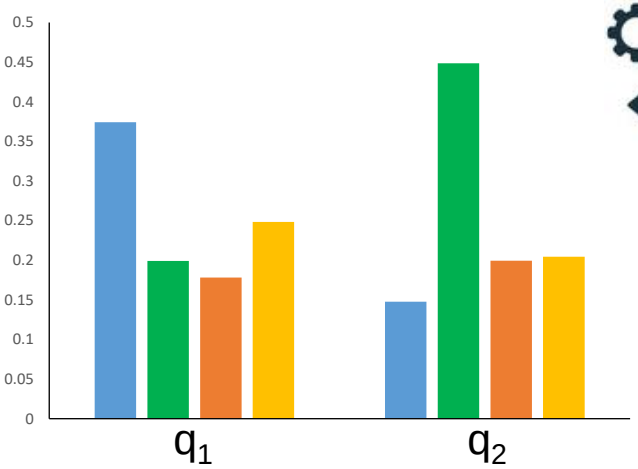
But more flexibility is included !

Data blocks can contribute or not to a component

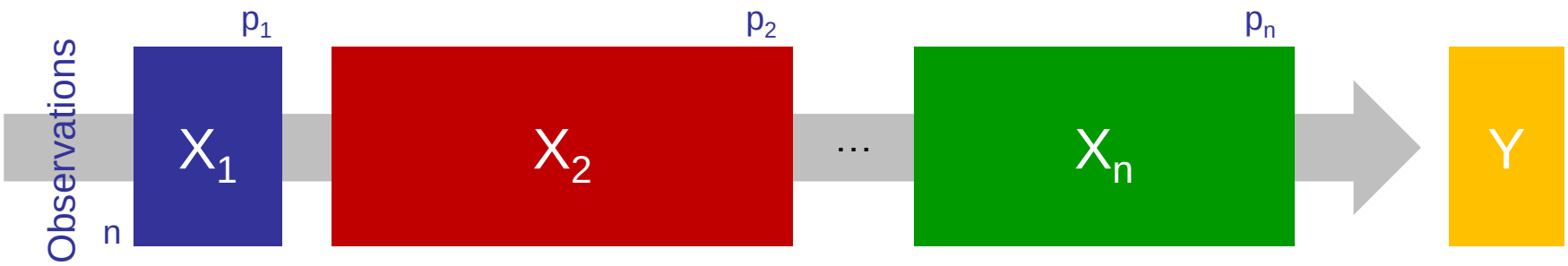
- First components will tend to aggregate several data blocks
  → large variance

- Higher components may grasp more specific trends
  → lower variance

Block saliences



Multiblock Supervised Analysis



Add an another block, but with a different role in the system
→ the blocks are no longer exchangeable

Predictive relationship
→ regression approach (usually PLS-type)

BOTH PREDICTION ABILITY AND INTERPRETATION ARE IMPORTANT !

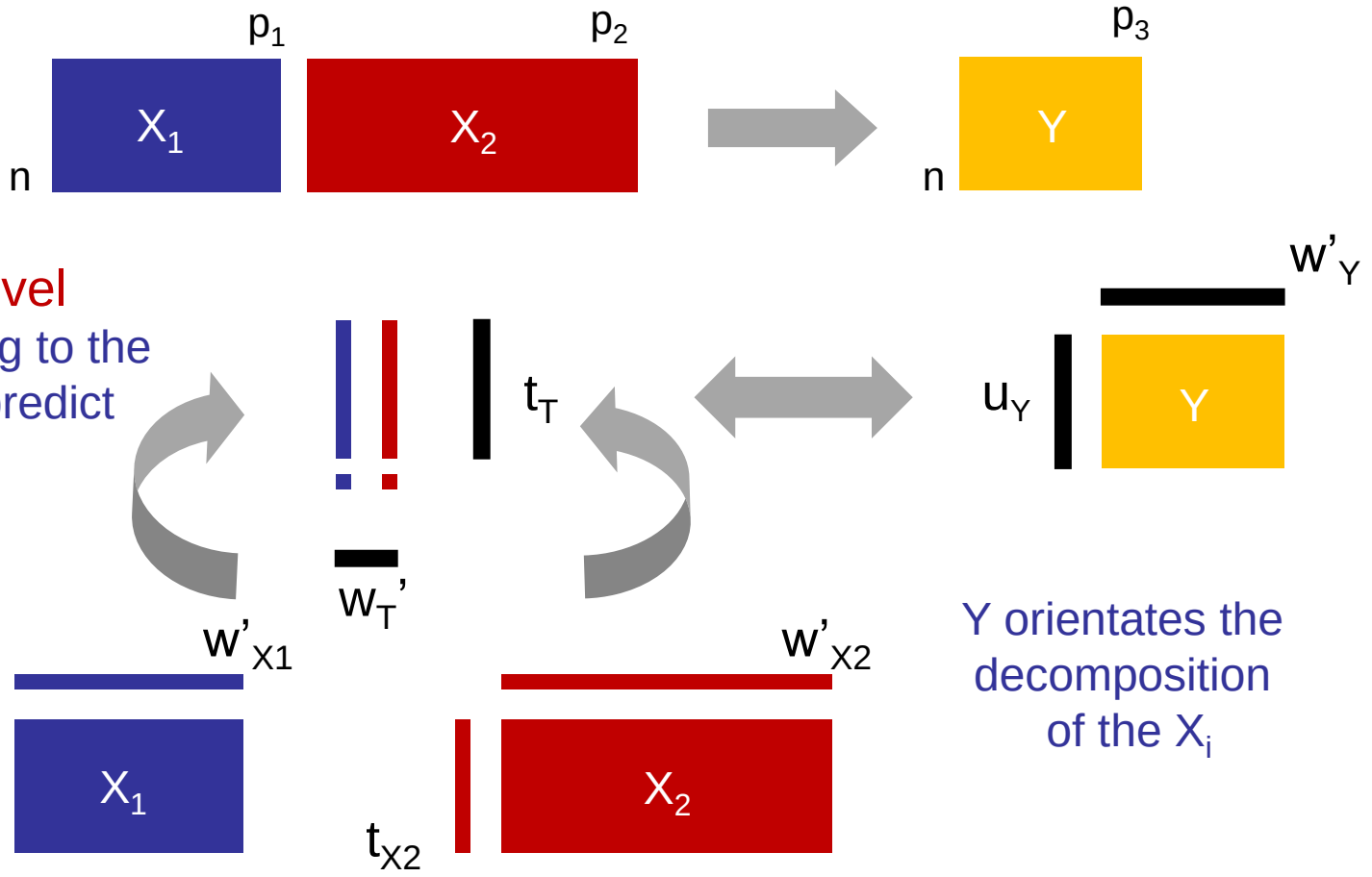
Some methods account for the sequence of blocks (hierarchy)
Choosing the linking structure is an a priori decision (domain-specific)

Multiblock Prediction Using PLS

A collection of X_i blocks and one Y response block

→ Multiblock PLS (MBPLS)

→ Scaling with the square root of the number of variables for each block



Westerhuis et al., *Journal of Chemometrics*, 15, 485-493, 2001

Deflation In Multiblock PLS

Several multiblock PLS algorithms have been presented in the literature

→ the deflation strategy is different

Deflation of X

- using block scores leads to inferior prediction of Y
- using super scores gives the same predictions as concatenated PLS

BUT

the information of the blocks gets mixed up

If Y is deflated using the super score, these problems disappear

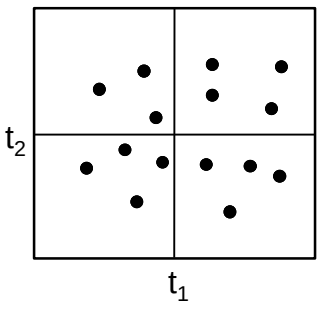
Conclusion (somewhat disappointing) :

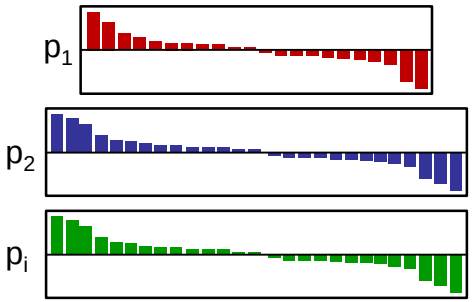
1) calculate a PLS model using concatenated data
2) estimate the multiblock parameters from this model

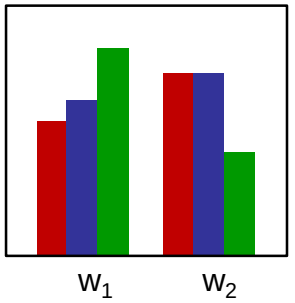
Westerhuis et al., *Journal of Chemometrics*, 15, 485-493, 2001

Multiblock PLS

Interpretation is typically based on score and loading plots





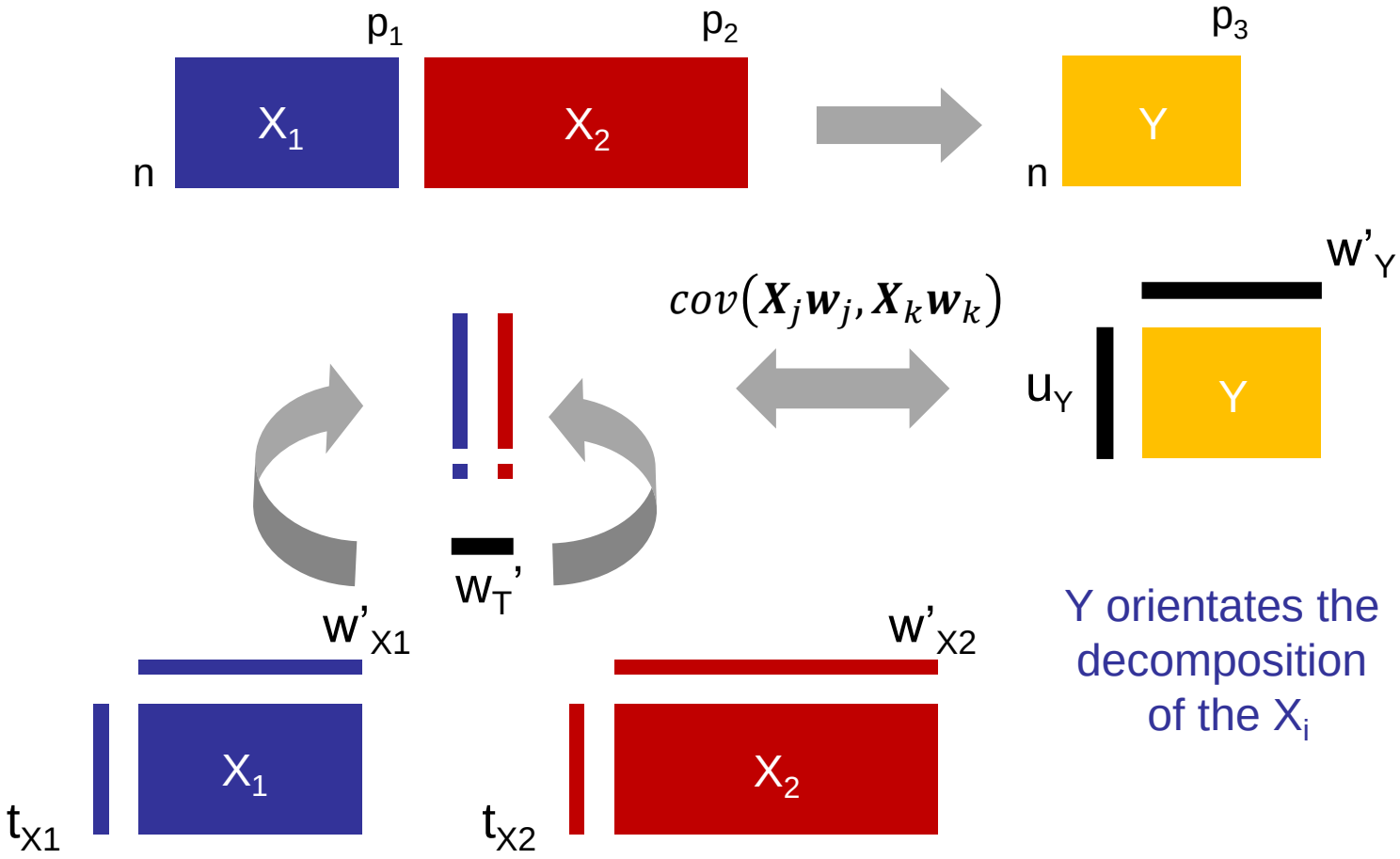


The same number of components is extracted for all blocks
→ This may complicate interpretation in cases with very different underlying dimensionality

Prediction ability (Q^2Y) is usually measured by cross-validation and/or test set prediction

Block-PLS

The covariance between pairs of components is maximized
→ special case of Generalized Canonical Correlation Analysis



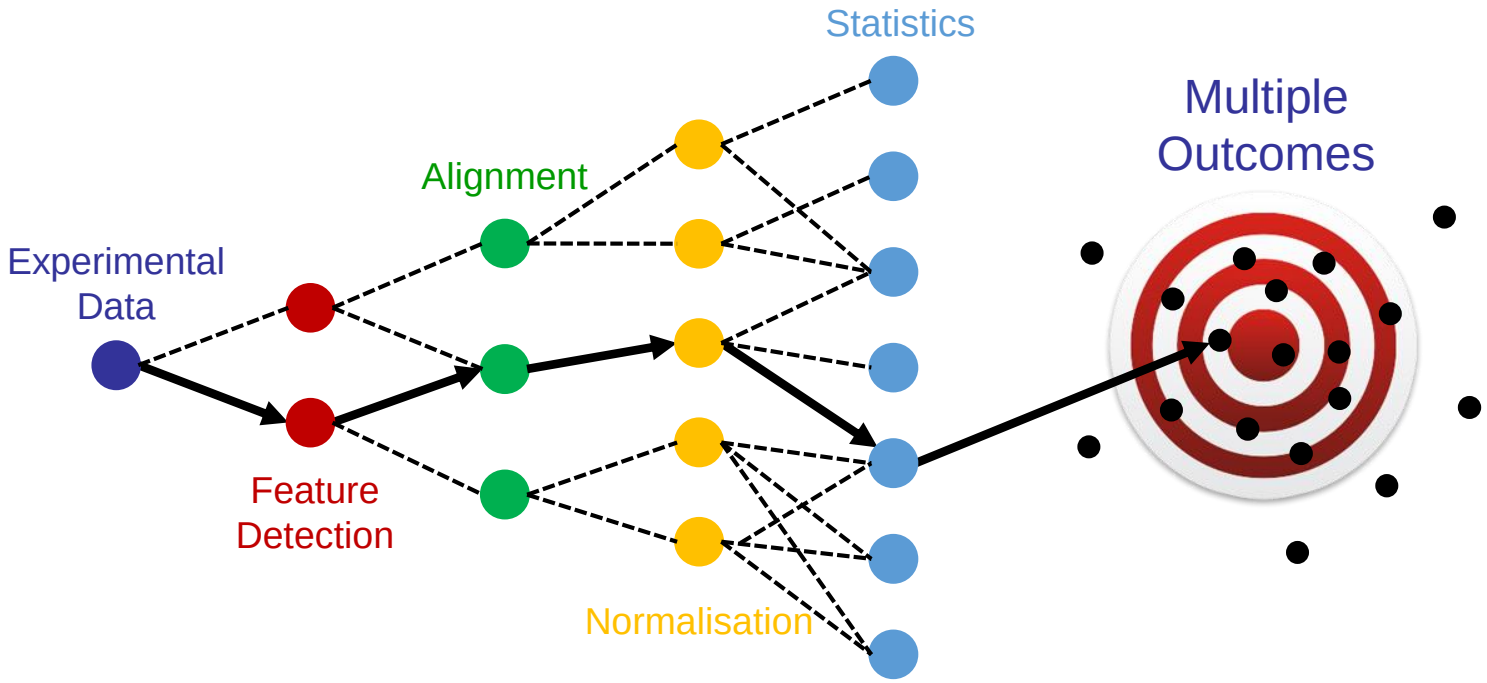
Y orientates the decomposition of the X_i

Data Processing Parameter Space

Data can lead to different results depending on processing parameters
→ The parameter space in data processing is huge

Each model obtained is just one of many representations of the actual data

Evaluation of the sensitivity of crucial parameter to find proper values
→ better understand the underlying data structure



Model Validation

Validation needs to be done at different levels!

- Theoretical appropriateness:
  Does the model used fit the goal and the data structure?
- Computational correctness
  Is the solution a local or a global optimum?
- Statistical reliability
  Are the assumptions appropriate?
  Are the solutions stable under resampling?
- Explanatory validity
  Can new knowledge be gained from the model?

Statistical Model Evaluation

How well does the model describe the data?

- too little structure (underfitting): poor prediction/description
- too much noise (overfitting): poor generalization ability

The ideal model captures

- ✓ all of the replicable structure in the data
- ✓ none of the noise

CRITERIA TO INVESTIGATE

Unsupervised

- stability of found patterns

Supervised

- predictive model performance (generalization ability)
- significance of contributions to a model (factors, blocks or variables)

Model Evaluation

Indexes of model quality:
R^2X : how well the model describes the X blocks
R^2Y : how accurate are the model predictions

BUT with a limited number of observations:
✘ not sufficiently informative
✘ completely optimistic

How to evaluate the generalization ability of a model?

Data-driven methods based on resampling
→ No underlying distribution assumptions
(i) Cross-validation (Leave-One-Out, K-fold)
(ii) Permutation testing
(iii) Bootstrap

Cross-Validation

Cross-validation is a statistical method for validating a predictive model

Main idea: predictive virtues can only be assessed for unseen data

a) Divide the data into a training set and a validation set
b) Fit a model to the training set
c) Predict the validation set with the model
d) Repeat the procedure with other training and test sets

Average the quality of the predictions across the validation sets

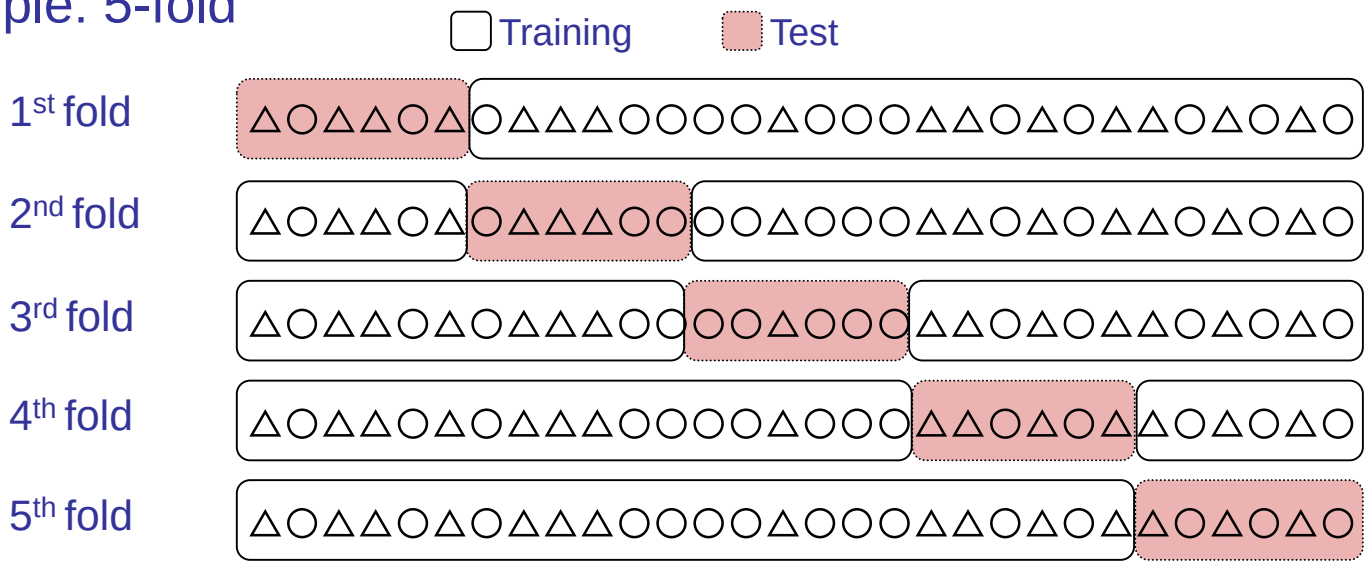
→ overall measure of the prediction accuracy

→ quality index: goodness of prediction Q^2Y

K-fold Cross-Validation

- ✓ The dataset is randomly partitioned into K subsets
- ✓ A single subset is retained as the validation data for testing the model
- ✓ The remaining K−1 subsets are used as training data
- ✓ The cross-validation process is then repeated K times (the folds)
- ✓ Each of the K subsets is used exactly once as the validation data
- ✓ The K results from the folds are then combined

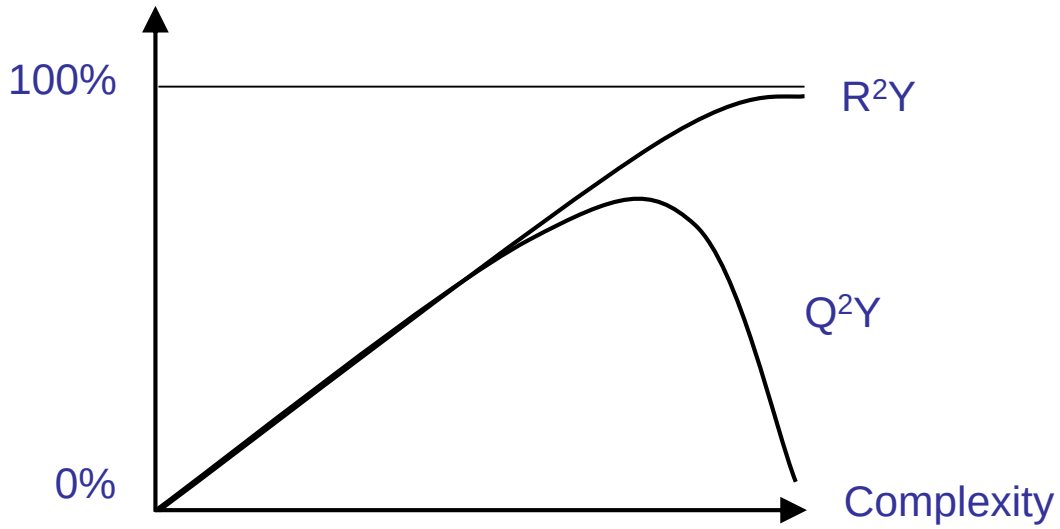
Example: 5-fold



R^2Y vs. Q^2Y

R^2Y: goodness of fit (the portion of data fitted by the model)
→ converge to 100% when adding successive parameters (increasing the complexity of the model)

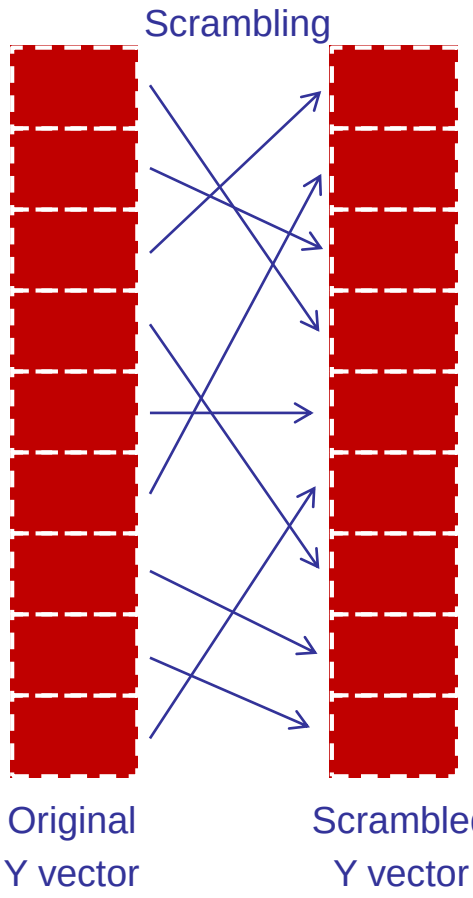
Q^2Y: cross-validated goodness of prediction
✓ increase if valuable predictors are added
✗ decrease if worthless predictors are added

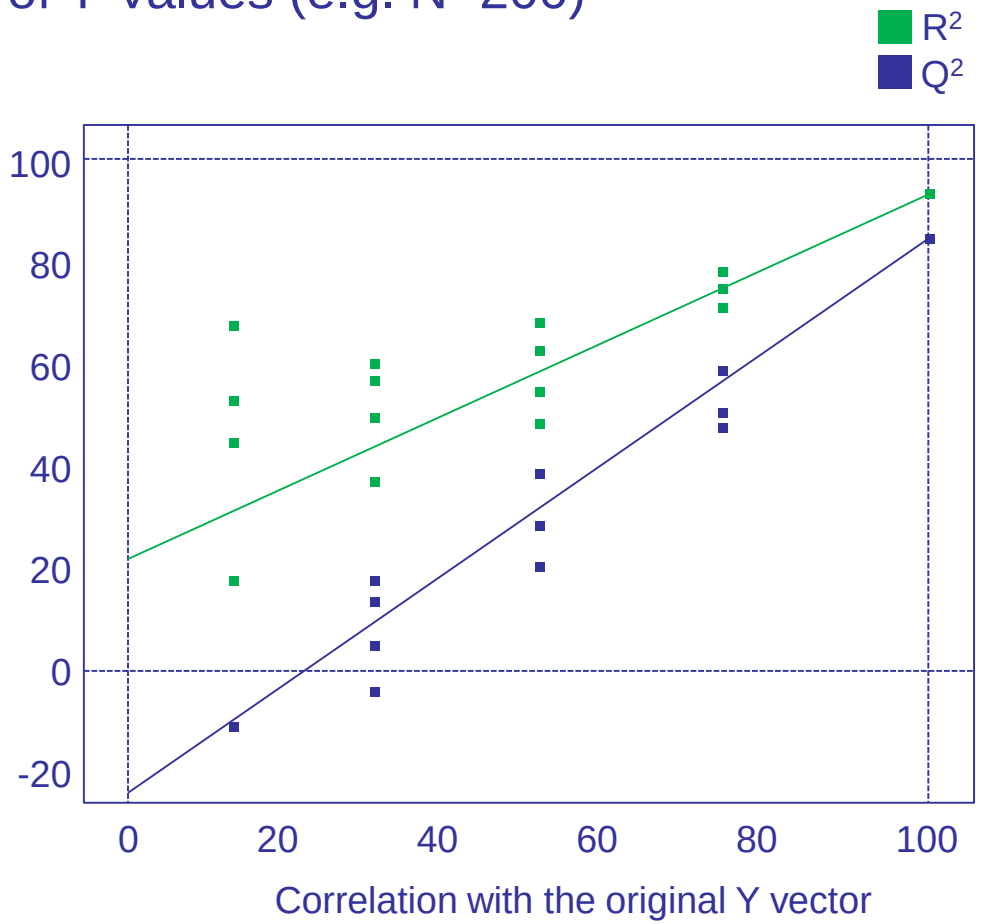


Permutation Tests

Y-scrambling or Y-shuffling

→ Random Permutations of Y Values (e.g. N=200)



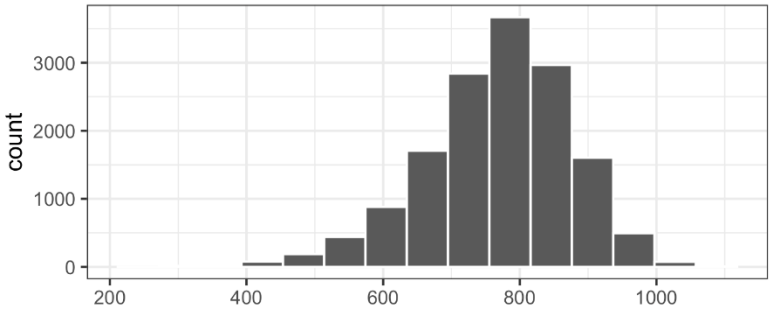


→ Diagnostic by examining the intercepts

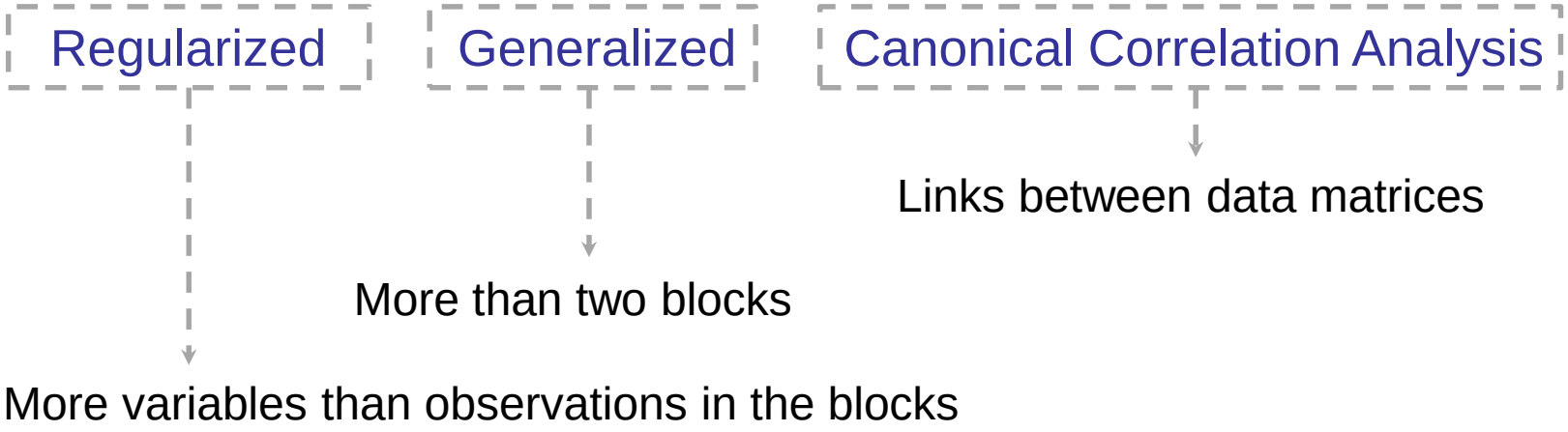
Bootstrap

- The bootstrap is a flexible and powerful statistical tool to quantify uncertainty associated with model parameters
- The basic idea is to randomly draw datasets with replacement from the training data (same size as the original training set)
- This is done *n* times, producing *n* bootstrap datasets and *n* corresponding sets of model parameters
- The distribution of the model parameters can then be estimated from the bootstrap sampling (*e.g.* variance)

Simulation-based distribution



RGCCA



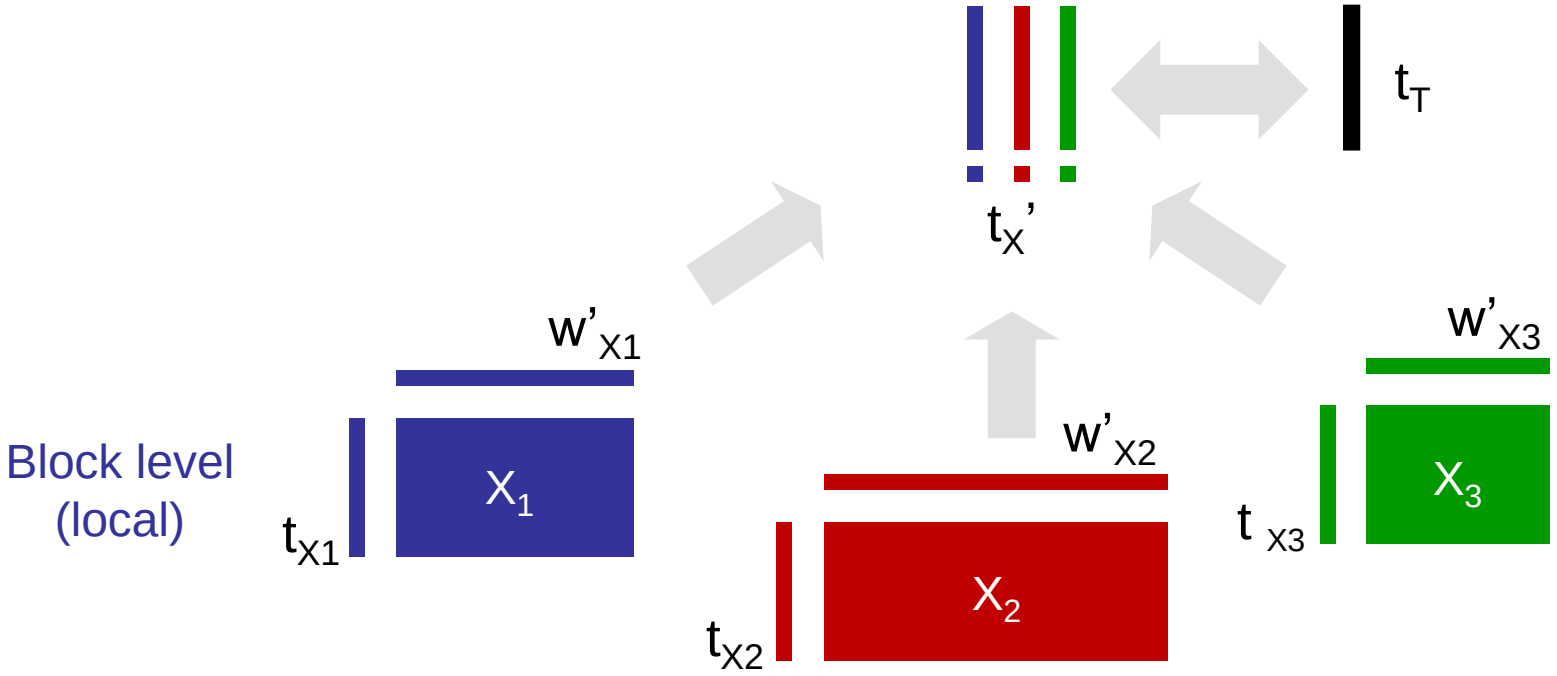
RGCA is a very versatile method
It covers many multiblock data methods as special cases
→ Unifying framework for sequential multiblock methods

Fairness between blocks is related to the dispersion of the correlations
Small variance indicates fairness
Large variance indicates a block selection behavior

Tenenhaus et al., *Psychometrika,* 82(3), 737-777, 2017

RGCCA

Maximize the sum of covariances between linear combinations of the blocks under specific constraints (shrinkage)



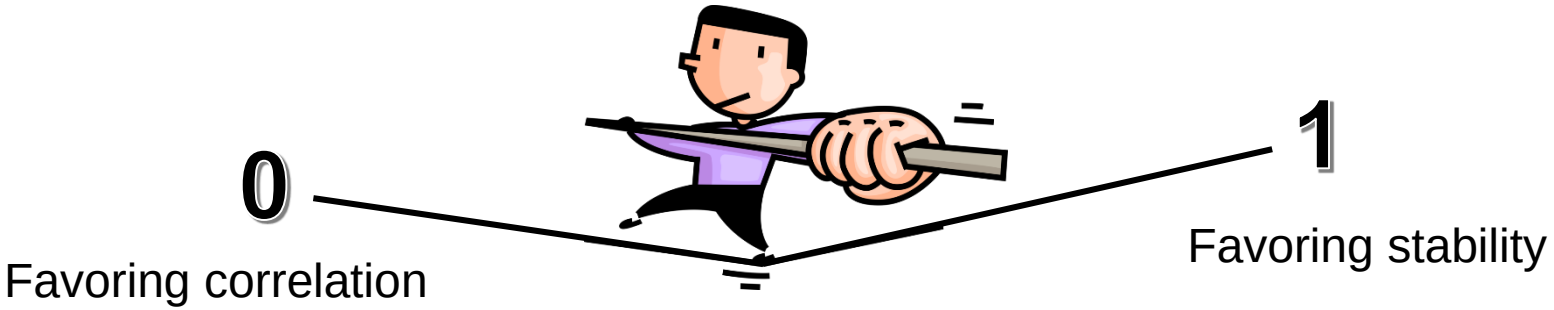
$$max \sum_{j,k=1}^{J} c_{jk} g\left(cov\left(\left(\boldsymbol{X}_j \boldsymbol{w}_j, \boldsymbol{X}_k \boldsymbol{w}_k\right)\right)\right) \; s.t.\; \boldsymbol{w}_j^t \boldsymbol{M}_j \boldsymbol{w}_j = 1, \forall j$$

$$\boldsymbol{M}_j = \tau_j \boldsymbol{I} + (1-\tau_j)(1/\mathrm{n}) \boldsymbol{X}_j^t \boldsymbol{X}_j$$

Choice of the shrinkage constant τ_j

$$\boldsymbol{M}_j = \tau_j \boldsymbol{I} + (1 - \tau_j)(1/\mathrm{n})\boldsymbol{X}_j^t \boldsymbol{X}_j$$

τ_j is a tunable parameter (shrinkage constant)



Optimal shrinkage constant values can be found automatically
e.g. using Schäfer & Strimmer formula

$$\tau_j^* = \underset{\tau_j}{argmin}\,\mathbb{E}\left[\left\|\widehat{\Sigma}_j(\tau_j) - \Sigma_j\right\|_F^2\right]$$

MOFA & DIABLO

Models based on factor analysis with penalties

Experience is required for selecting adequate parameters

- Multi-omics factor analysis (MOFA)

→ Model parameters estimated within a Bayesian approach with priors

→ Different penalties can be imposed on the weights

→ Probabilistic estimation (different distributions can be used for heterogeneous data)

→ Properties of the estimated scores and loadings are not always clear

- Data Integration Analysis for Biomarker discovery using a Latent component method for Omics studies (DIABLO)

→ Sparse implementation of RGCCA

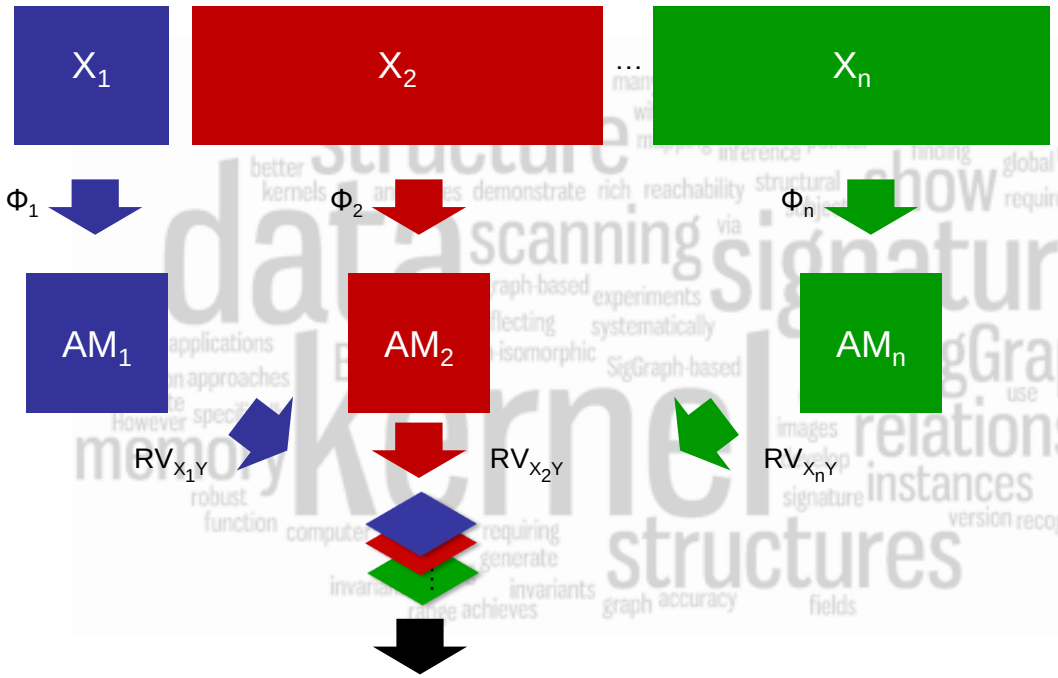
→ Lasso-type penalties on the weights

Kernel-based Data Integration

Data matrices

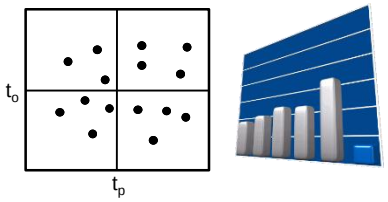
Kernel function
(n x n)

Consensus matrix



Consensus model

Analysis of global results
& joint interpretation
of data blocks

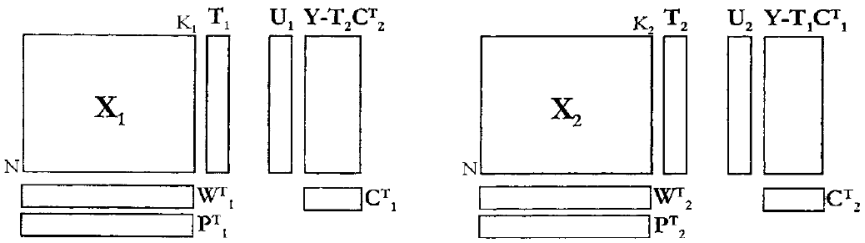


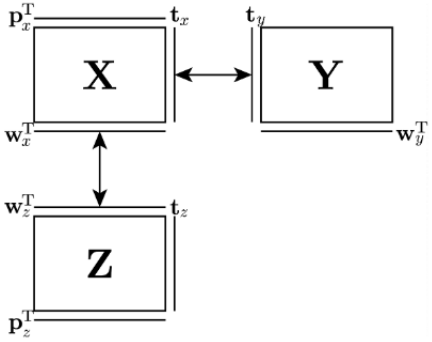
WHAT ABOUT INTERPRETATION ?

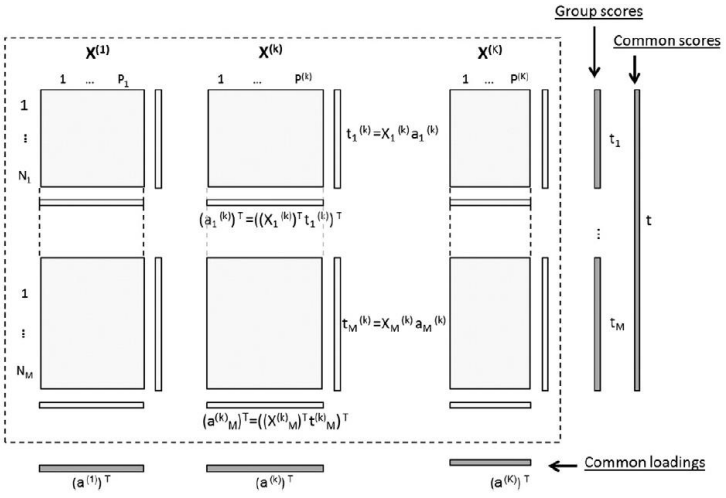
Other Multiblock Methods

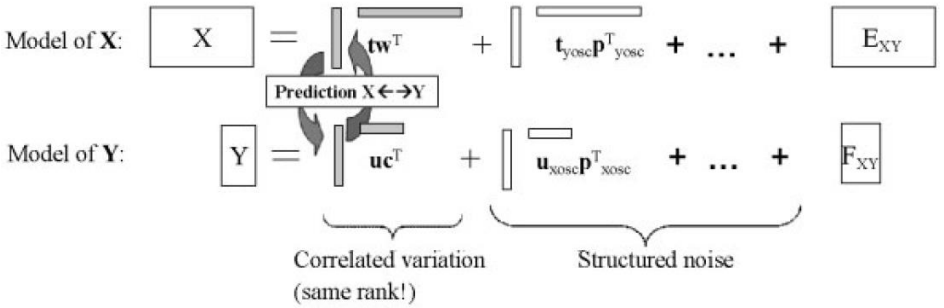
- Serial PLS
- L-PLS
- GOMCIA
- PLS-Path Modelling
- OnPLS
- DISCO
- JIVE
- NetPCA
- Sparse methods

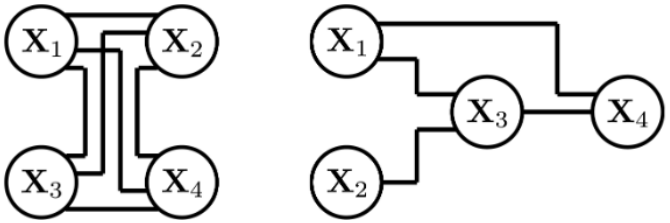
and more…











Data Storytelling

Probably the most important question is
which method to use in what situation?

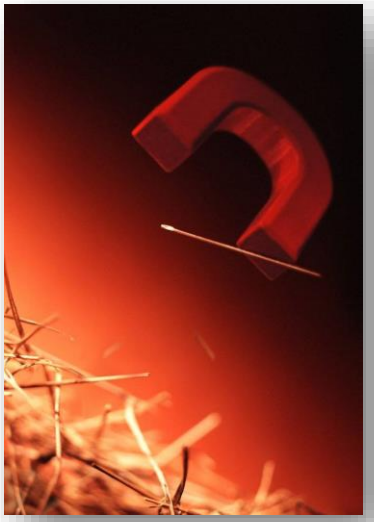
This depends on the goal of the analysis, on the knowledge domain and on the properties of the methods and the data

- Data can have very different nature/structure
- There is no ready made recipe
- Each dataset has its own specificities

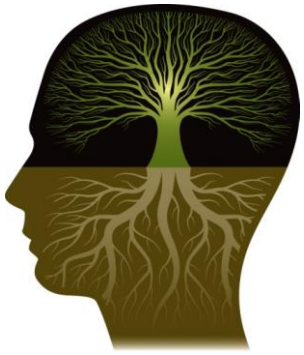
- Explore different approaches
- Be creative

Some Take Home Messages

- Different data sources can be combined for a more complete description of complex data using two-level of interpretation (global and local)
- Dedicated chemometric methods allow common and/or specific directions of variations to be extracted from the data blocks
- Unsupervised multiblock analysis takes the relationship between X_i blocks into account
- Supervised multiblock analysis takes the relationship with the Y response(s) into account



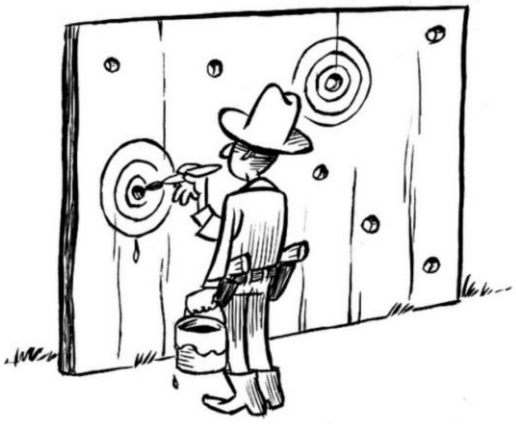
Toward Biological Insights



Understand links between multiblock data sets
Combine different biological layers
Compare data sources
Choose between analytical methods (or combinations)

Often makes interpretation easier
Relate data sources to common or specific patterns
Understand mechanisms leading to phenotypes
Highlight subsets of variables in different blocks

BUT
First define the question(s) to be answered !



Texas-sharpshooter fallacy

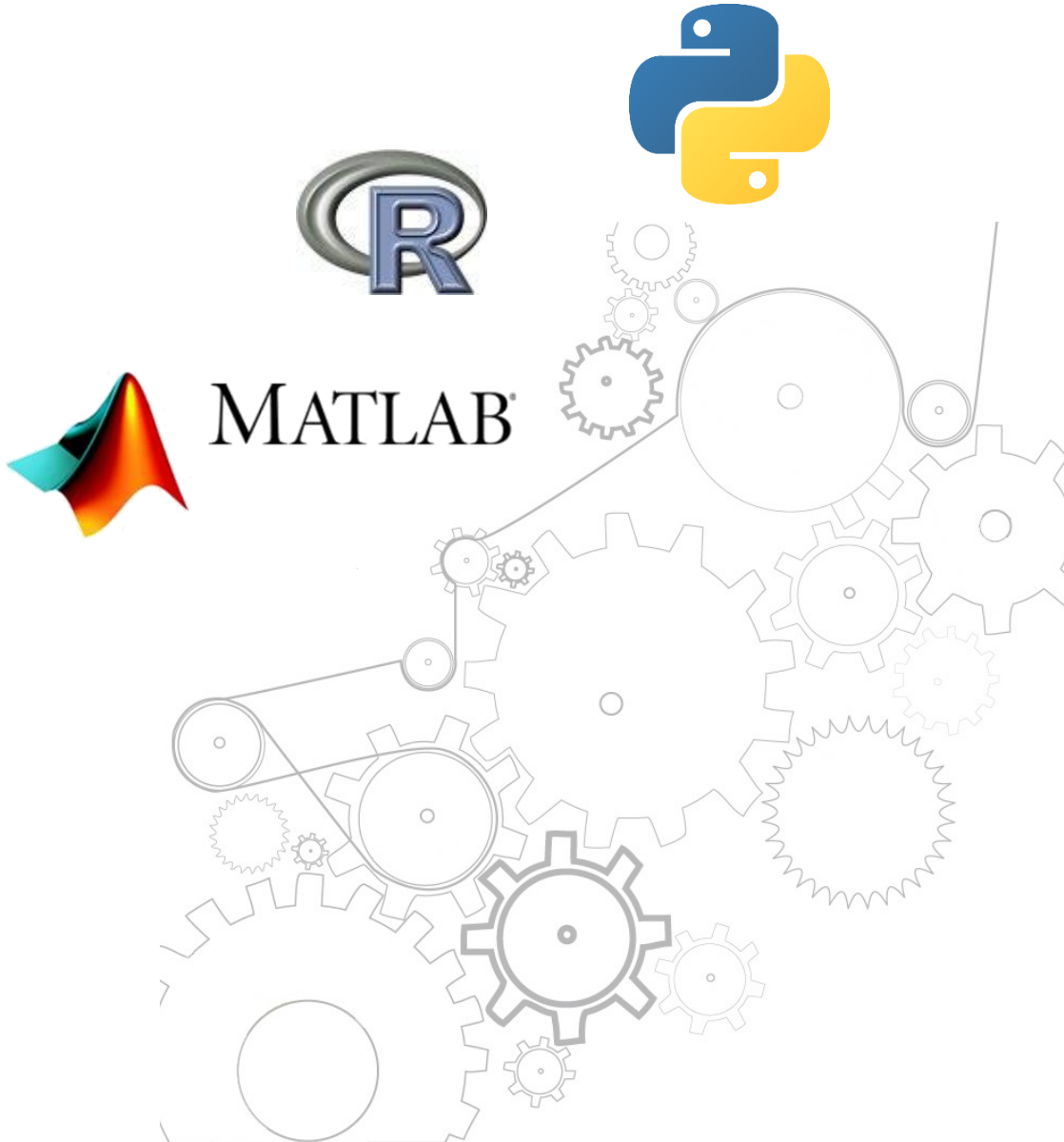
Toolboxes

Packages:

- MBAnalysis
- CCA
- mixOMics
- ade4
- omicade4
- multiblock

- SAISIR
- MBToolbox

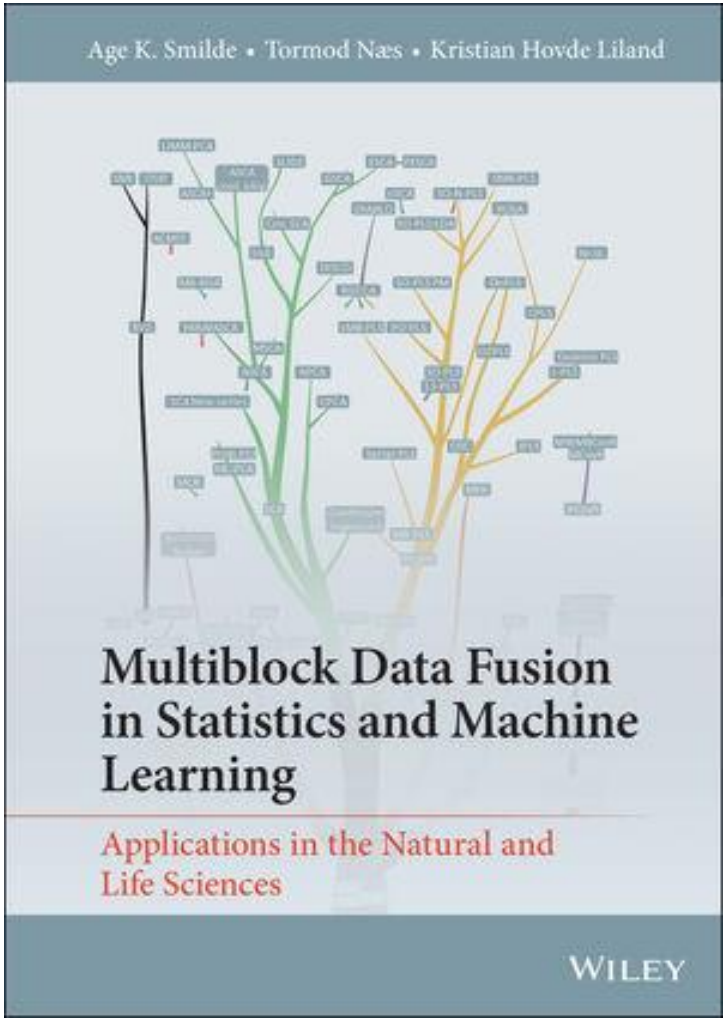
…many others



An Excellent Book For Further Reading

Multiblock Data Fusion in Statistics and Machine Learning: Applications in the Natural and Life Sciences
Wiley 2022
ISBN: 978-1-119-60097-8

Age K. Smilde
Tormod Næs
Kristian Hovde Liland



I. Concepts & Theory
II. Unsupervised/supervised methods
III. Complex structures
IV. Alternative methods
V. Software (multiblock R package)