Multi-omics data integration with mixOmics

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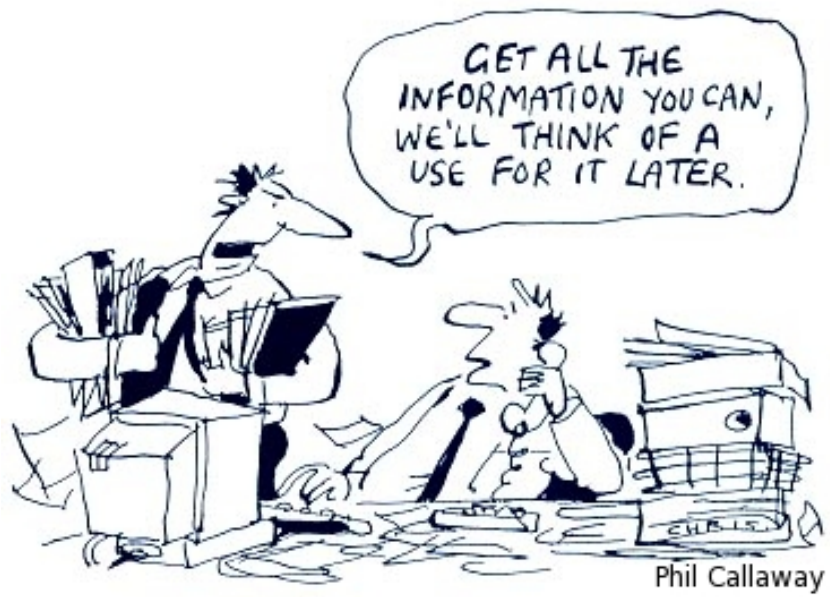
When biology and statistics meet

"Data don't make any sense,
we will have to resort to statistics."

When biology and statistics meet

A close interaction between statisticians, bioinformaticians and molecular biologists is essential to provide meaningful results



- Unlimited quantity of data from multiple and heterogeneous sources
- Computational issues to foresee
- Biological interpretation for validation
- Keep pace with new technologies

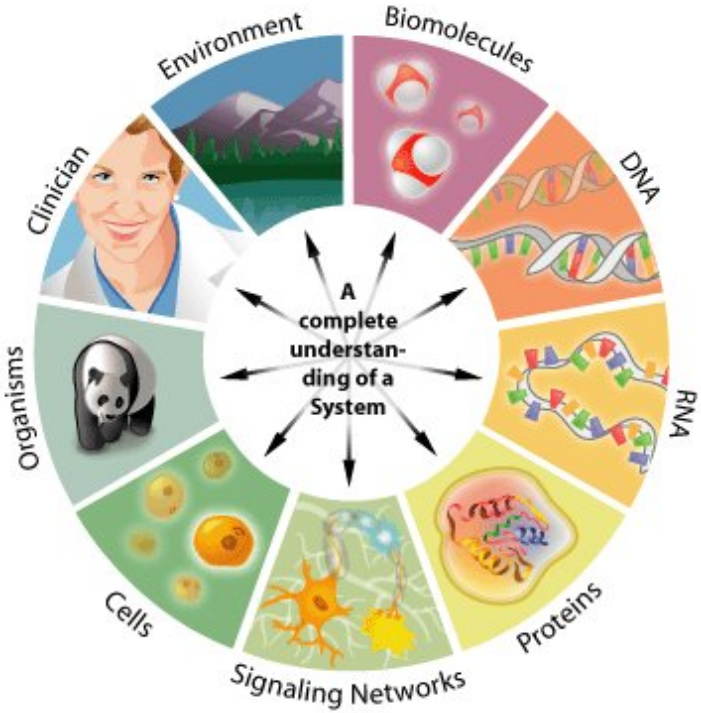
A holistic view of a biological system

From reductionism ...

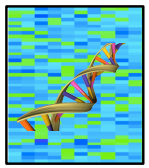
1 gene = 1 hypothesis = 1 statistical test

... to holism:

Thousands of molecules = ??

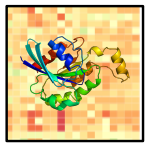


The 'omes and the biological dogma? not that straighforward



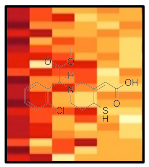
Transcriptomics
$\sim 100,000$ transcripts

↓

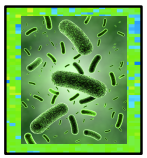


Proteomics
$\sim 1,000,000$ proteins

↓



Metabolomics
$\sim 2,500$ compounds

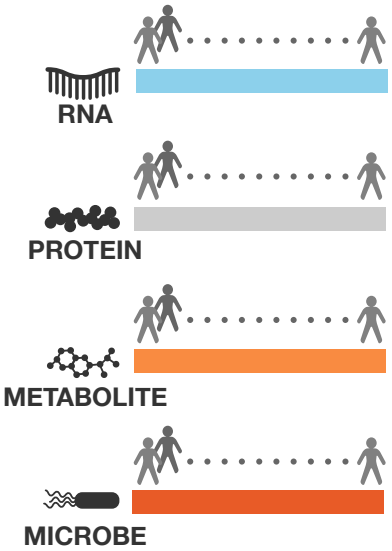


Microbiome
$\sim 1,500$ trillion microbes

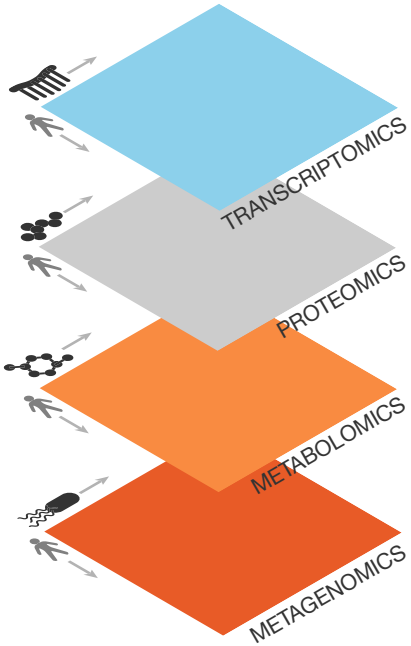
⋮

Clinical data
many

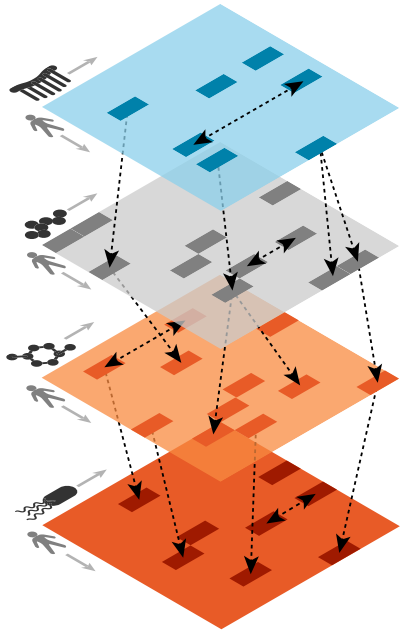
A new research field to establish



Conventional molecular biology
(Reductionist)

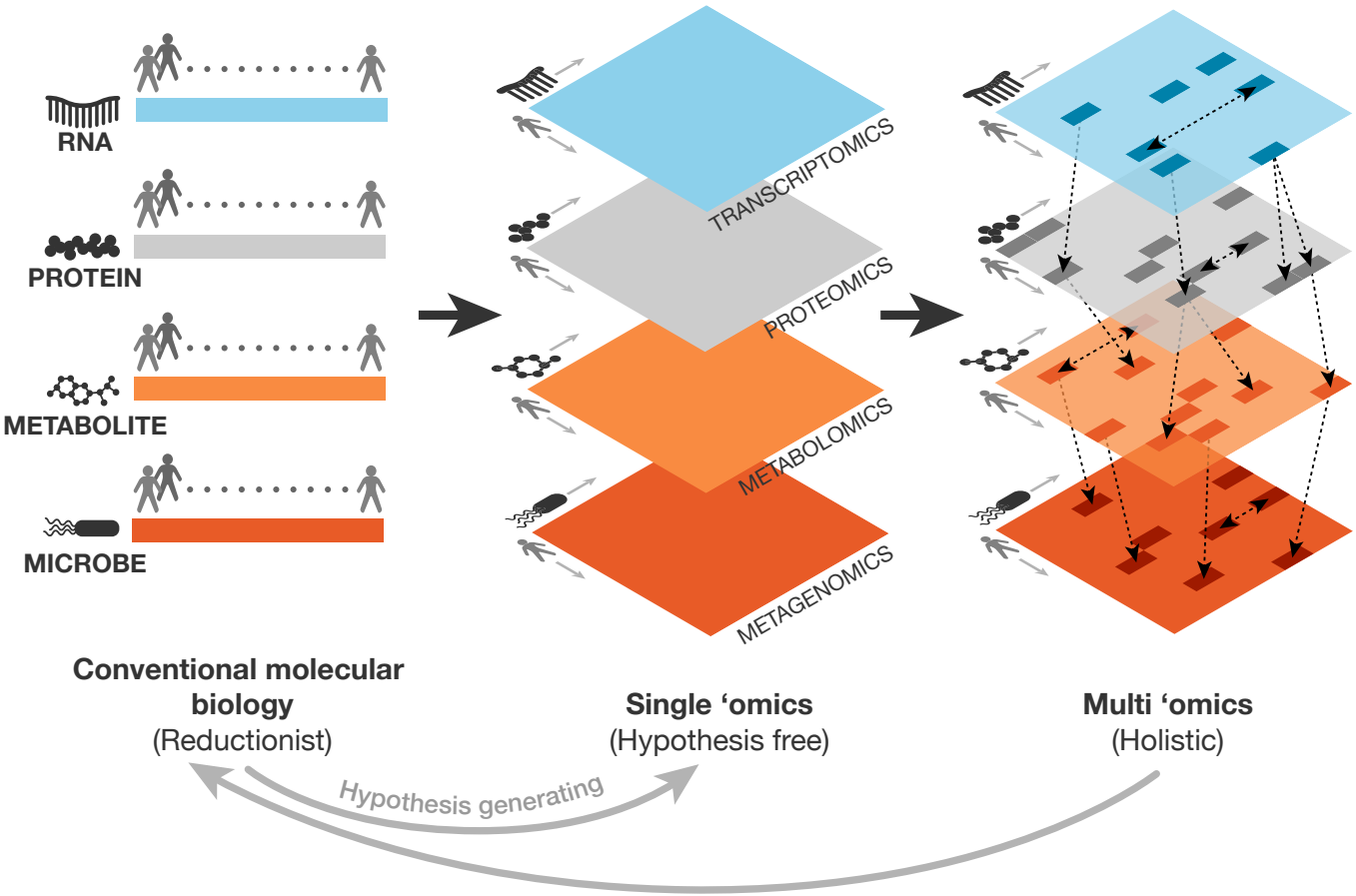


Single 'omics
(Hypothesis free)



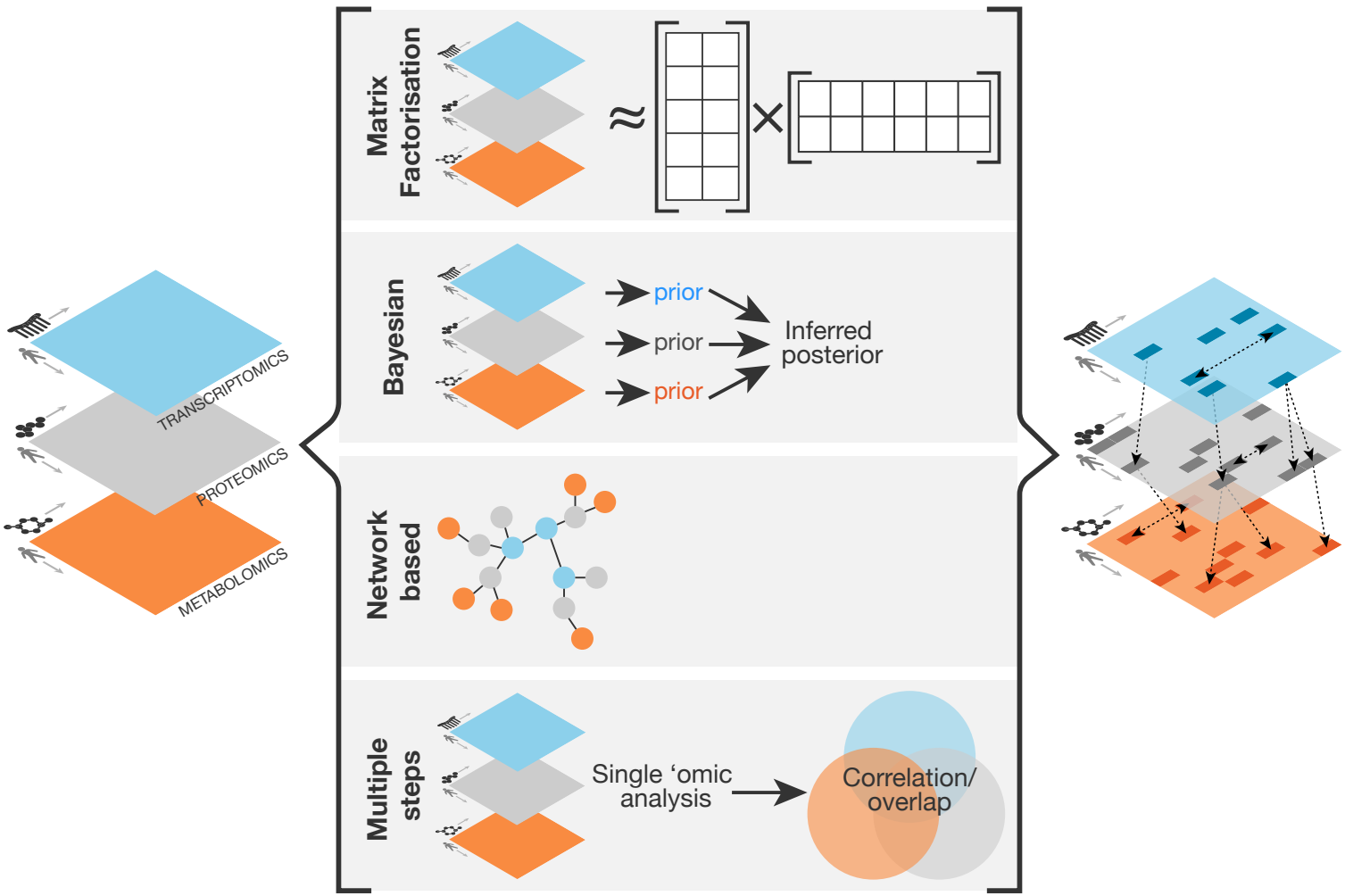
Multi 'omics
(Holistic)

A new research field to establish



Start with a holistic view, rather than a traditional, reductionist, hypothesis-driven view, then generate new hypotheses.

Data integration from an analytical point of view



Aims

Molecular entities act together to trigger cells' responses. We need to shift the 'one-gene hypothesis' paradigm to obtain deeper insight into biological systems.

Multivariate analysis:

- Identify a combination rather than univariate biomarkers
- Reduce the dimension of the data for a better understanding of complex biological systems
- Integrate multiple sources of biological data

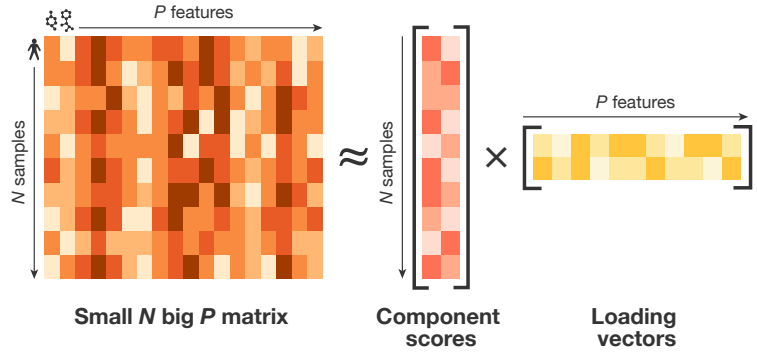
Expectations from 'omics data integration

- ☐ An overview of the role of each 'omics in a biological system
- ☐ A better understanding of the relationship between 'omics types
- ☐ A molecular signature with insights into molecular mechanisms
- ☐ A predictive analytical model
- ☐ All of the above!

Matrix factorisation methods

Build components that aggregate observable *variables* (e.g. genes, transcripts, proteins) to summarise sources of variation in the data

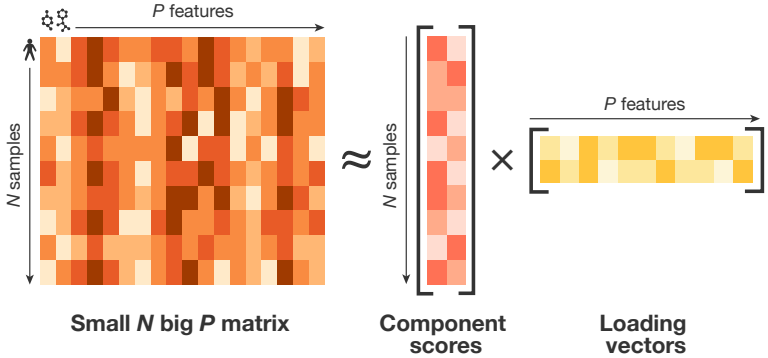
- Reduce data dimension
- Handle data characteristics (difficult otherwise with conventional statistical methods)
- Capture and explain variation (information) in the data



Example of multivariate methods: Principal Component Analysis (PCA), Projection to Latent Structures (PLS) models for data integration

Matrix decomposition & dimension reduction

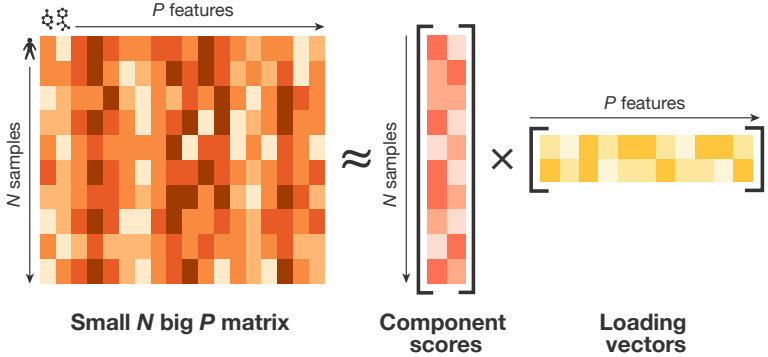
PCA: Data exploration



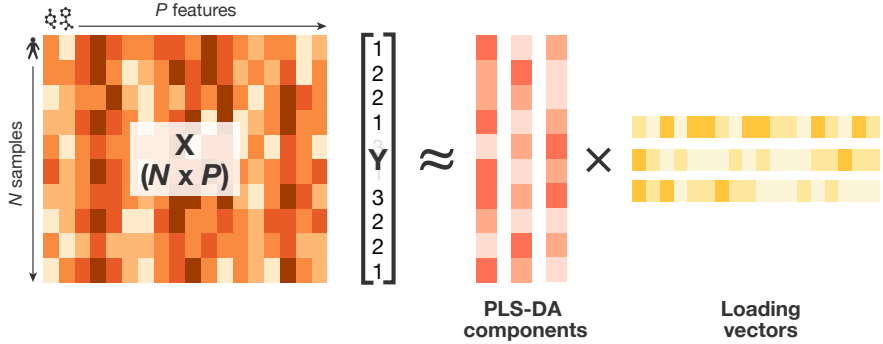
- Component scores are linear combination of features ($\ll P$)
- Loading weights indicate the importance of each feature in the linear combination
- Feature selection: weights shrunk to zero using Lasso penalisation

Matrix decomposition & dimension reduction

PCA: Data exploration



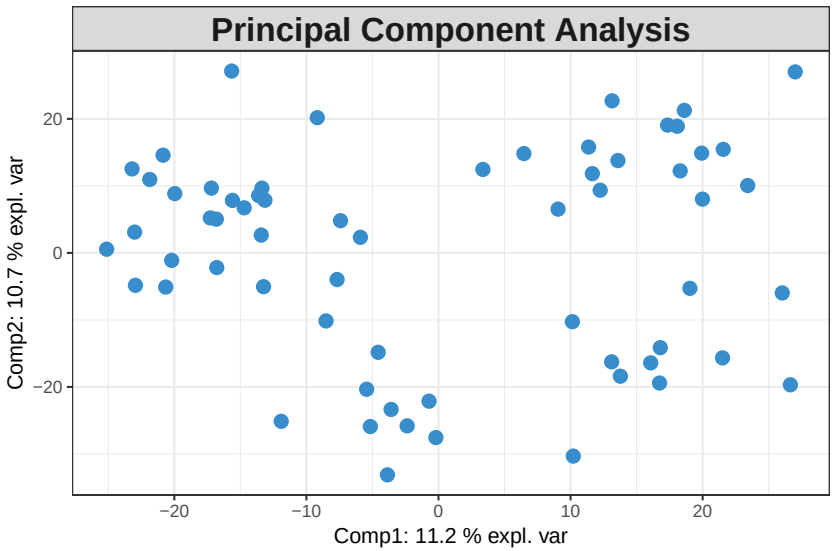
PLS - Discriminant Analysis

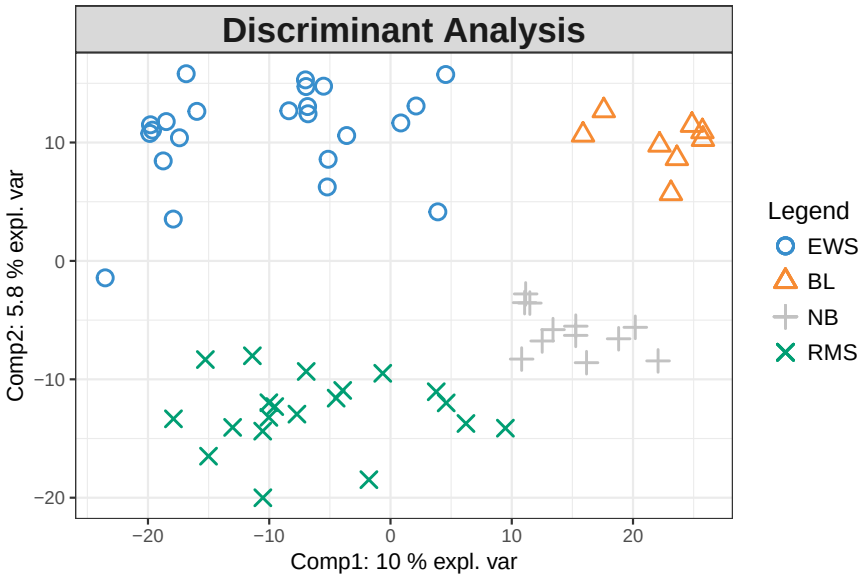


- Component scores are linear combination of features ($\ll P$) that discriminate the sample groups
- Loading weights indicate the importance of each feature in the discriminative linear combination
- Feature selection: weights shrunk to zero using Lasso penalisation

Sample visualisation in a reduced space

Example: SRBCT data with 63 samples and 3,116 genes

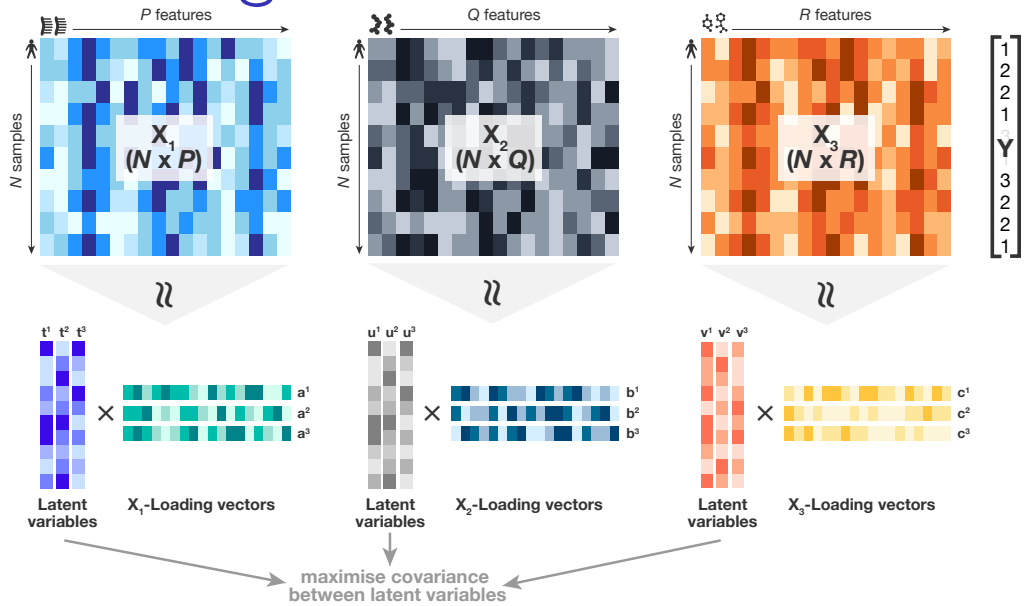




- Unsupervised exploratory analysis: 'similar' samples cluster but no information about sample groups is included in the analysis

- Supervised analysis: Samples cluster according to their respective group

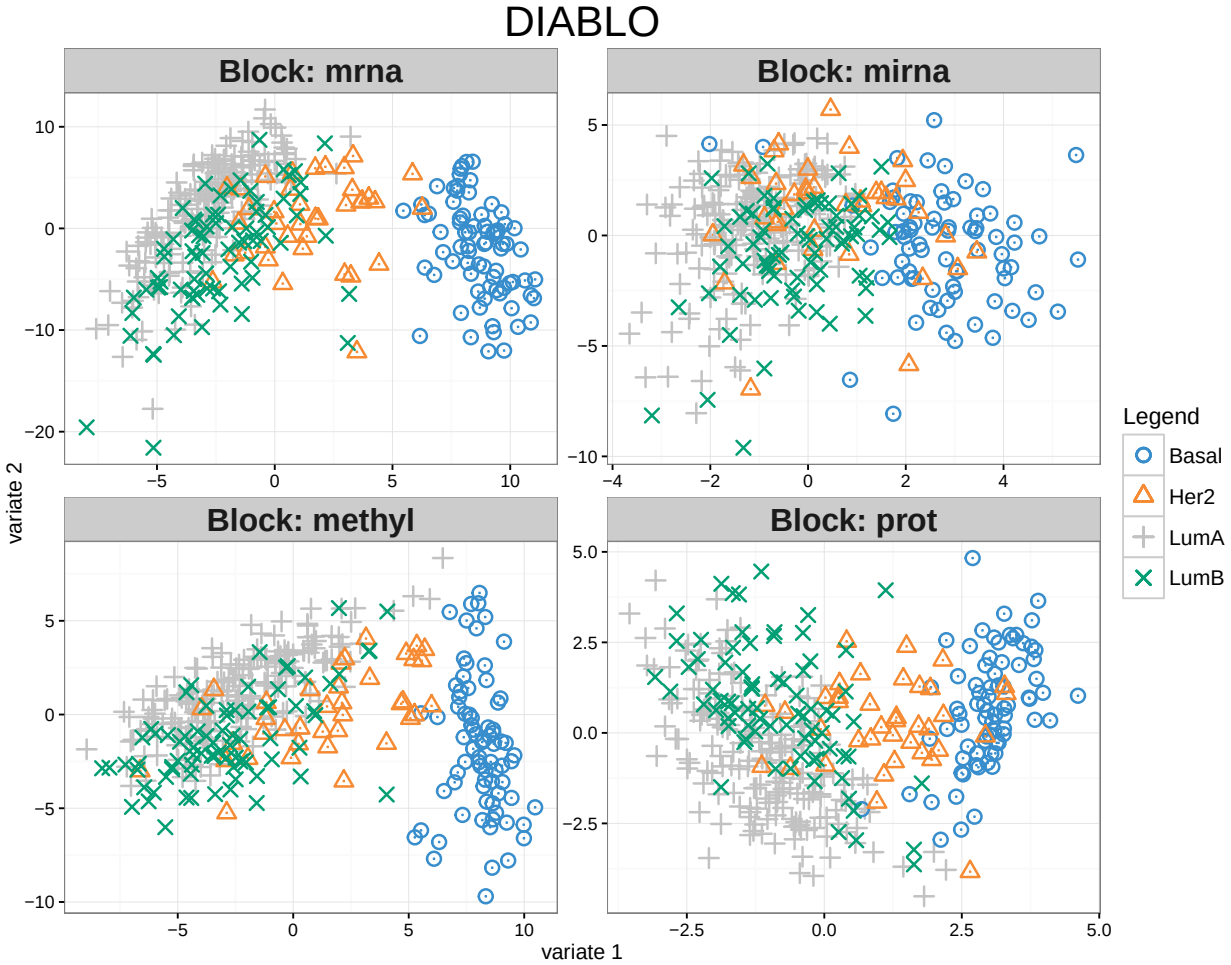
Multi-omics data integration with DIABLO



- Component scores are linear combination of a subset of selected features that are highly correlated across omics
- Loading weights indicate the importance of each selected feature in the linear combination

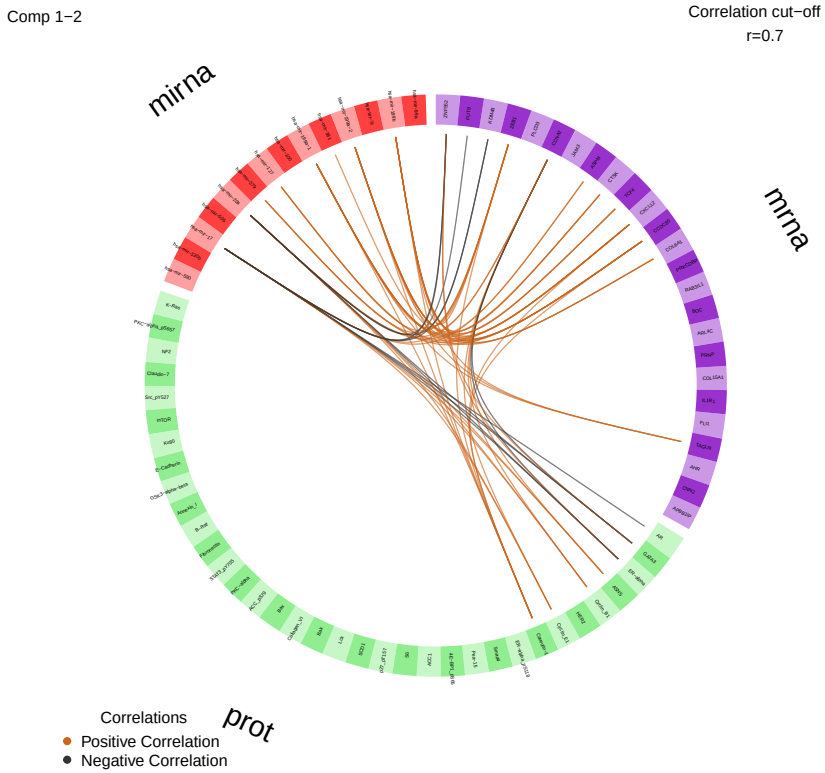
Singh A, Gautier B, Shannon C, Vacher M, Rohart F, Tebbutt S, Lê Cao K-A (2019). DIABLO: identifying key molecular drivers from multi-omic assays, an integrative approach. *Bioinformatics* 35 (17).

DIABLO: sample visualisation

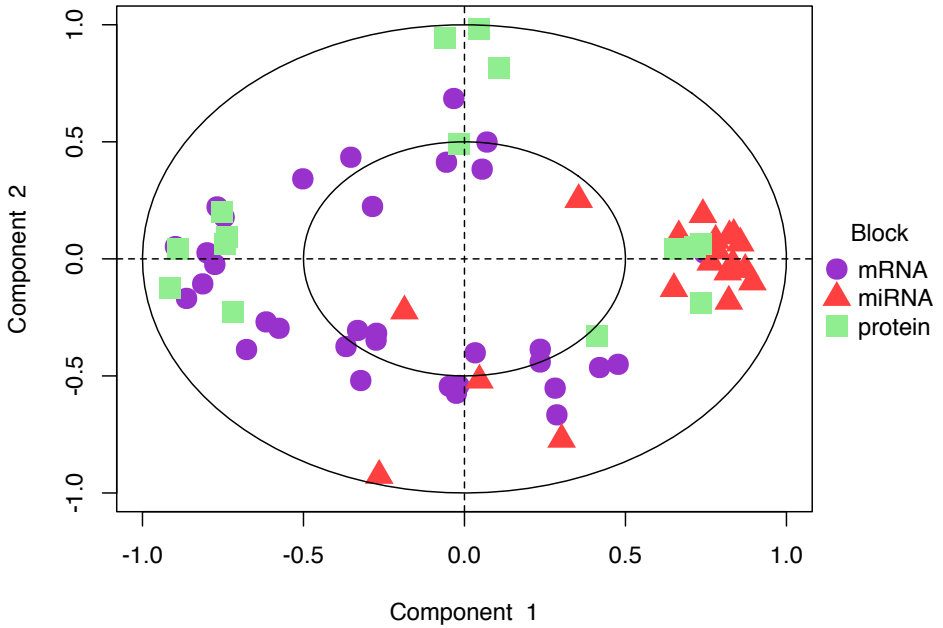


Consensus plot also possible

DIABLO: multi-omics signatures

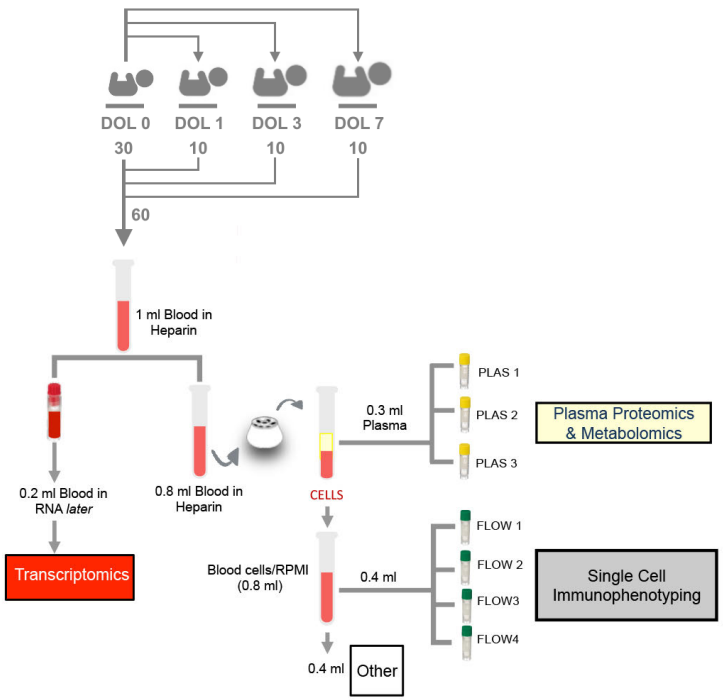


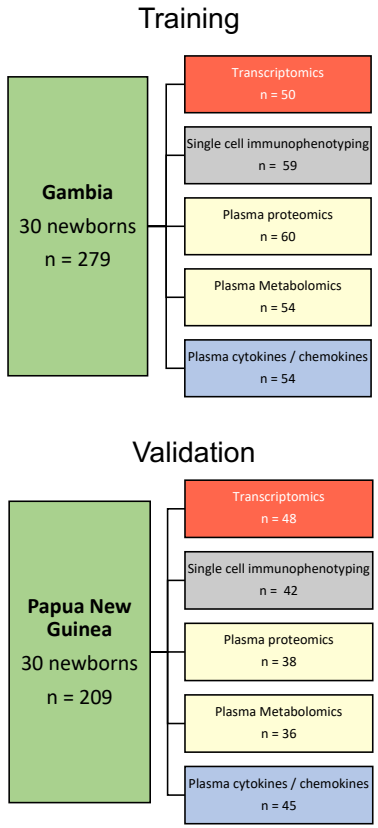
Circos plot



Correlation circle plot

#smallbig study: the first week of human life

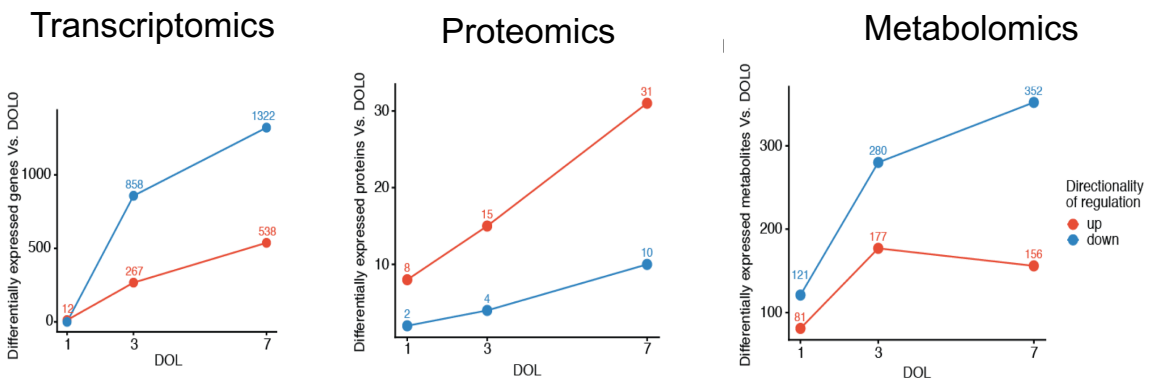


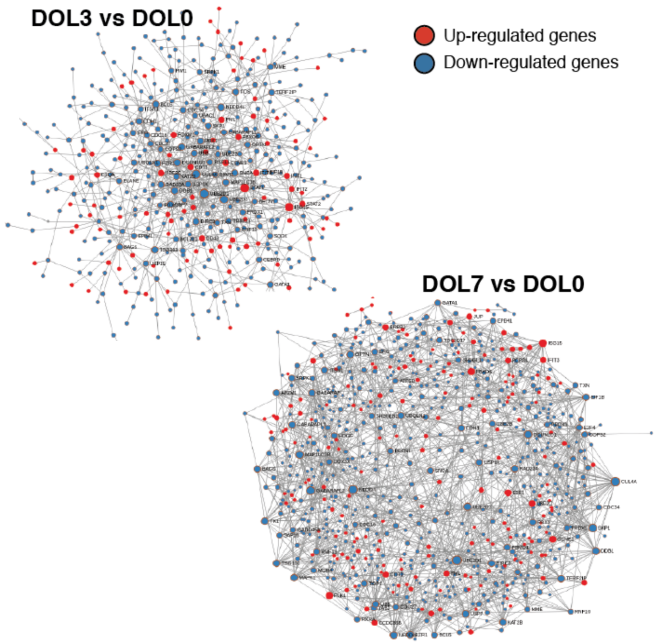


Small biosample amount: < 1ml of blood from newborns, five data types

Lee, Shannon, ..., Lê Cao, ... & Kollman (2019) Dynamic molecular changes during the first week of human life follow a robust developmental trajectory. *Nat Comm* 10:1092.

Single omics

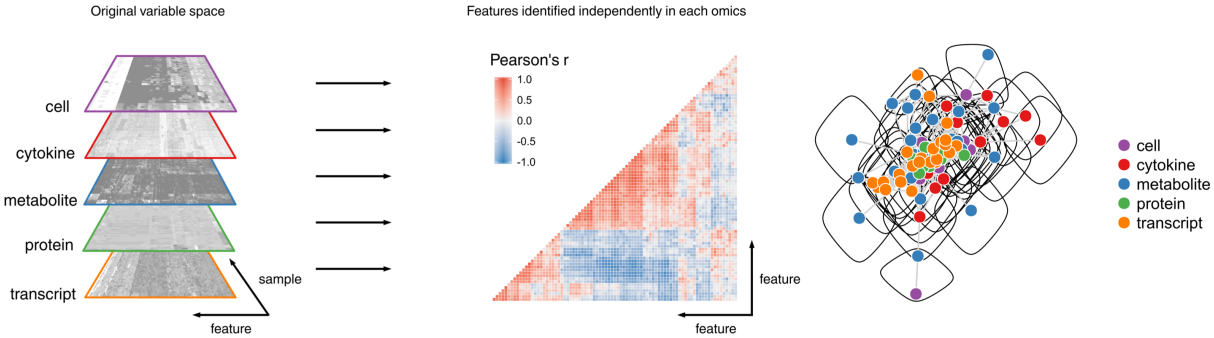




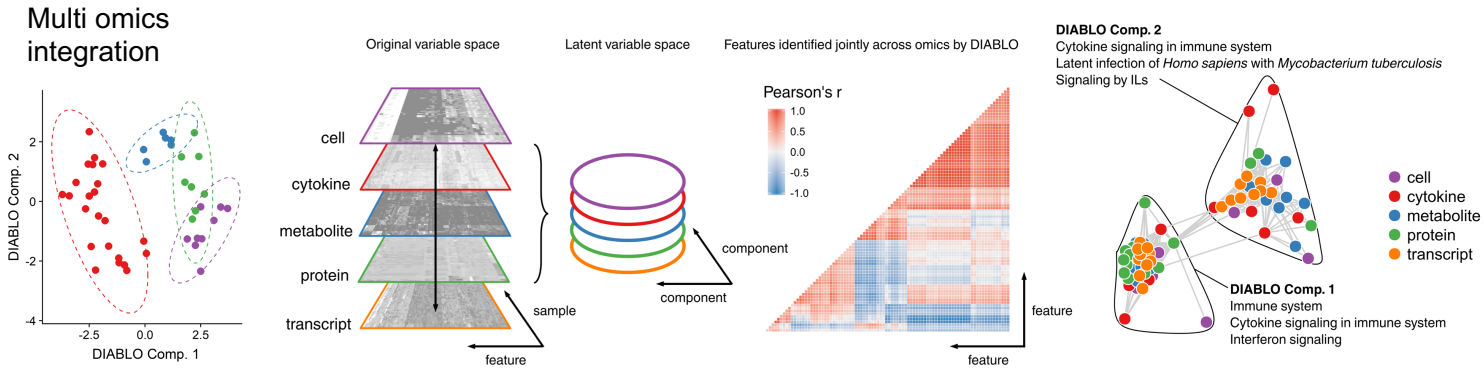
Dramatic developmental changes emerge when comparing later days of life to D0 but the correlation structure is a hairball mess!

Multi-omics integration

Single omics

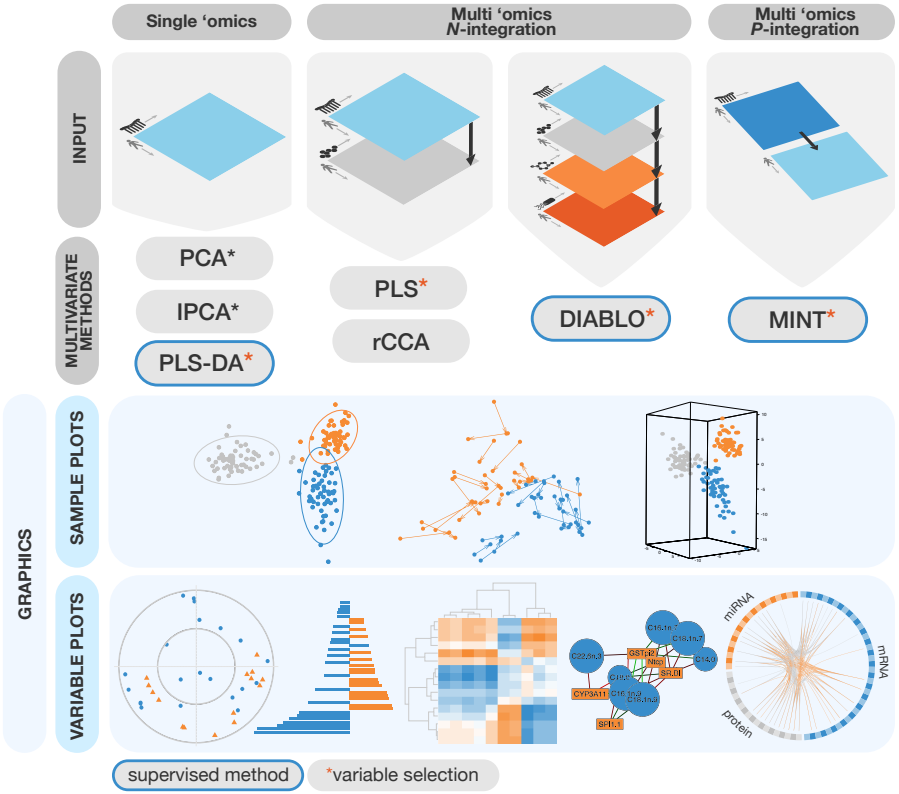


Multi omics integration



New biological insights not revealed by single omics analysis (e.g. prostaglandin-endoperoxide synthase 2) and pathways common to all data types (interferon, neutrophil degranulation pathways, complement cascade).

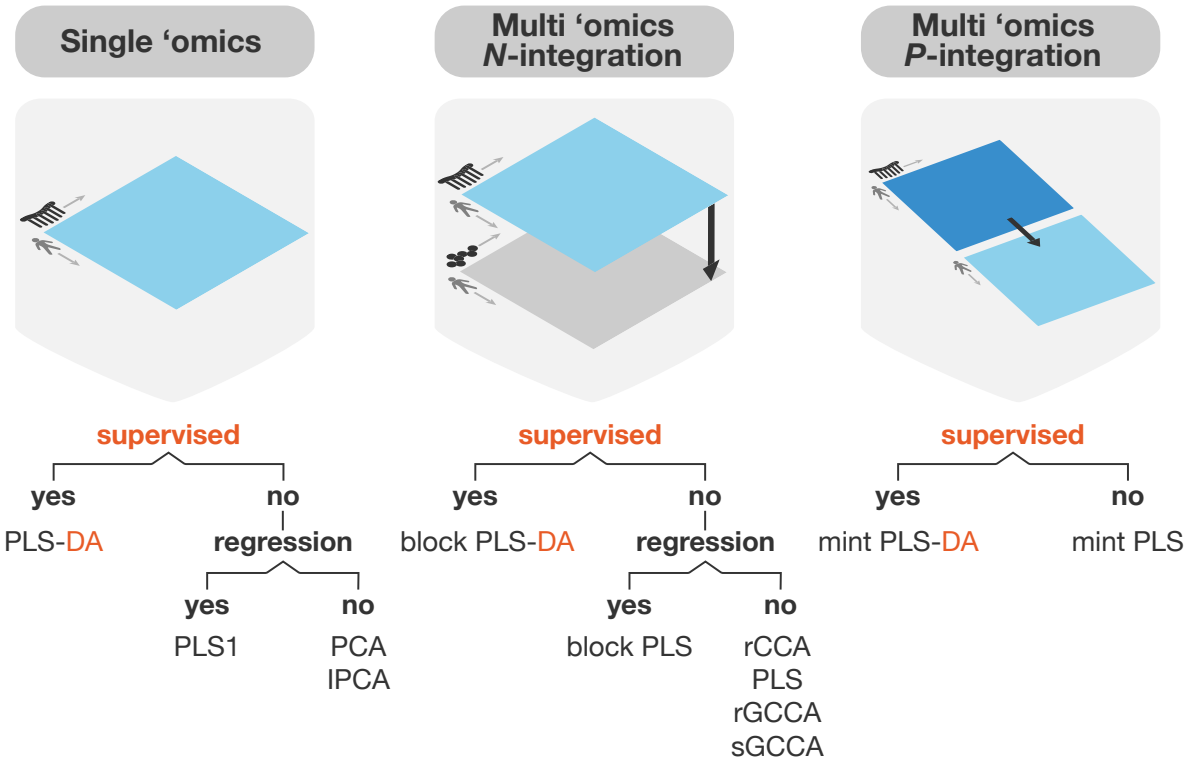
An R toolkit for multivariate data analysis and statistical integration of biological 'omics data



Rohart F, Gautier B, Singh, M, Lê Cao K-A. mixOmics: an R package for 'omics feature selection and multiple data integration. *PLoS Comp Biol* 13(11).

Nineteen multivariate methods (13 novel)

Each method can answer a specific biological question



↪ watch this space on www.mixOmics.org for a handbook and online courses.

Want to go further? Here are our latest extensions

- Integration of microbiome and omics
  T1D TrialNet prevention study: proteomics, 16S and metaproteomics (Gavin et al. 2018 *Diabetes Care*)
- Integration of time course omics data to identify coordinated profiles
  Method paper + application (Bodein et al. 2019 *Frontiers in Genetics*)
- Inclusion of pathway information for a hybrid data & knowledge-driven integration
  Method + application (Singh et al. 2019 DIABLO *Bioinformatics*)
- Removal of batch effects (esp. microbiome)
  Manuscript (Wang et al. *bioRxiv* 2020 358283)

Take-home messages

- We are entering a new era that first requires data-driven approaches to make sense of big biological data
- From a holistic to a hypothesis-generating approach
- Does not exclude *a priori* biological knowledge (e.g. pathway analysis) in computational methods
- New field emerges that blends computationally savvy biological scientists and vice-versa
- Development of computational tools is important to advance knowledge

Acknowledgements

mixOmics team

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Lê Cao lab alumni and members

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Ankylosing Spondylitis: Matt Brown (KCL)
Microbial bioprocesses: Olivier Chapleur (INRAE)
Stem cells: Christine Wells (UoM)
single cell multi-omics: Matt Ritchie, Luyi Tian (WEHI), Heather Lee (UoN)
timeOmics: Antoine Bodein, Arnaud Droit (ULaval)

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STEMCELLS AUSTRALIA

We are open to new collaborations and scientific exchanges!

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