Medical Genomics Practical #2: Multi-omic analyses in R

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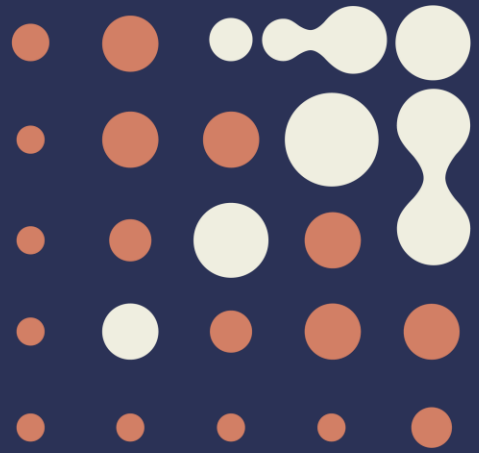
Rare Cancers Genomics Team

November 22th & 29th 2023



International Agency for Research on Cancer

World Health Organization

RARE CANCERS GENOMICS

Plan

Practical (3.5 hrs)

- **Concepts**: interfacing R and python, reminder of MOFA model, MOFA2 implementation
- **Practical**: unsupervised analyses of rare lung cancers

Projects (0.5 hrs)

- **Choice**
- **Quickstart**

Concepts | *Interfacing R and python*

Why choose between python and R?

R Vs Python: What's the Difference?

R and Python are both open-source programming languages with a large community. New libraries or tools are added continuously to their respective catalog. R is mainly used for statistical analysis while Python provides a more general approach to data science.

R and Python are state of the art in terms of programming language oriented towards data science. Learning both of them is, of course, the ideal solution. R and Python requires a time-investment, and such luxury is not available for everyone. Python is a general-purpose language with a readable syntax. R, however, is built by statisticians and encompasses their specific language.

In this tutorial, you will learn

- R
- Python
- Popularity index
- Job Opportunity
- Analysis done by R and Python
- Percentage of people switching
- Difference between R and Python
- R or Python Usage

Python vs R for Data Science: And the winner is..

Data-Driven Science Jan 31, 2018 · 8 min read

About: Data-Driven Science (DDS) provides training for people building a career in Artificial Intelligence (AI). Follow us on Twitter.

R vs Python for Data Analysis — An Objective Comparison

Concepts | *Interfacing R and python*

Why choose between python and R?

- The **core of the MOFA method is in python** (mofapy, mofapy2) and uses the powerful python machine learning packages (e.g., scikit-learn)
- The **downstream analyses** and **graphical functions are in R** and leverage the contributions of the enormous R community of computational biologists and statisticians

Issues

- Need to correctly **interface python and R**
- **Many dependencies** in both languages, making the code **difficult to set up and fragile**

Concepts | *Interfacing R and python*

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Solutions

1. (earlier MOFA and MOFA+ releases) **R package reticulate:** allows to specify a python install or conda env, run python functions, transfer R and Pandas data frames, or R matrices and NumPy arrays
2. (newer MOFA+ releases) **R bioconductor package basilisk**: allows R to directly create and handle conda environments with specific python dependencies, allowing smooth usage of incompatible python installs within a same R session

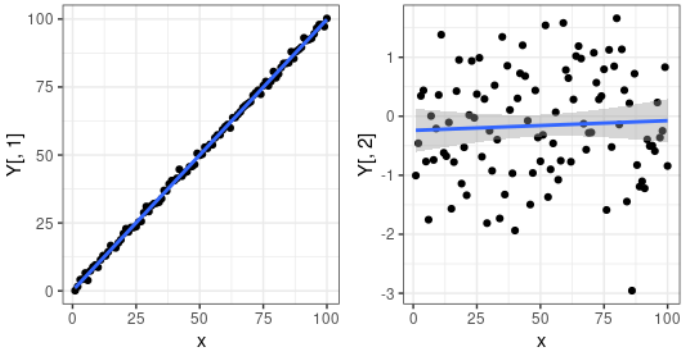
Concepts | *Multivariate regression reminder*

Multivariate linear models

- model **Y = AX + ε**,
- where **Y** is the matrix of observations for *M* features (rows) and *N* sample (columns)
- **X** is the known covariable matrix (*K* by *N*)
- **A** is the unknown weights matrix (*M* by *K*)
- **ε** is the residual noise (*M* by *N*)

Example: effect of smoking on gene expression in 100 patients

- Y: 2 genes x 100 patients
- X: smoking in pack-years for 100 patients
- A=[1,0]^t



Example MLM. The expression of the first gene (Y[1,]) is associated with smoking (x). The expression of the second gene (Y[2,]) is independent of (x)

Concepts | *Multivariate regression reminder*

Principal Component Analysis/Factor Analysis

- model **Y = WZ + ε**,
- where **Y** is the matrix of observations for *M* features (rows) and *N* samples (columns)
- **Z** is the unknown latent variable matrix (*K* by *N*)
- **W** is the unknown weights matrix (*M* by *K*)
- **ε** is the residual noise (*M* by *N*)

=> similar to regression but we do not have access to the "true covariable" explaining the variation in Y, we try to guess

Concepts | *Multivariate regression reminder*

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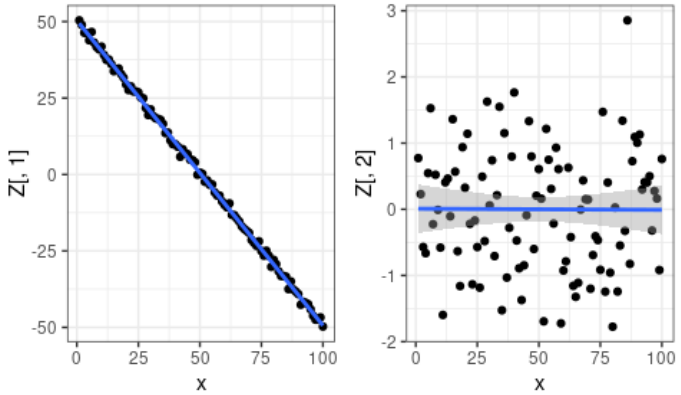
Example: unknown effect of smoking on gene expression in 100 patients

- Y: 2 genes x 100 patients
- X: smoking in pack-years for 100 patients is unknown
- Z: 2 latent variables x 100 patients, obtained by the PCA
- W=[-1,0]^t, direction is not important

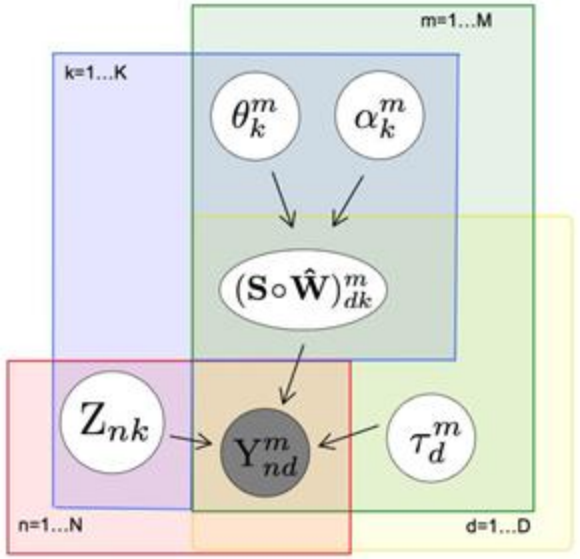


Example PCA. The first latent variable (Z[,1]) recapitulates smoking (x) although the model was blind to x, because the first gene (Y[,1]) is highly variable and strongly correlated with x **=> the PCA "found" the hidden covariable x**

Concepts | *MOFA reminder*

Multi-Omics Factor Analysis (MOFA)

- **Generalization of Principal Component Analysis to multiple modalities** *M*
- model $\mathbf{Y}^m = \mathbf{W}^m\mathbf{Z} + \boldsymbol{\varepsilon}^m$,
- where $\mathbf{Y}^m$ is the matrix of observations for each feature *d* (rows) and each sample *n* (columns) for modality *m* (e.g., genomic alterations, expression)
- **Z** is the latent factors matrix (*K* by *N*) shared by all modalities *m*
- $\mathbf{W}^m$ is the weights (loadings) matrix (M by *K*) of *m*
- $\boldsymbol{\varepsilon}^m$ is the residual noise (*M* by *N*)



MOFA directed acyclic graph. *Source: Argelaguet et al. Mol Syst Biol 2018.*

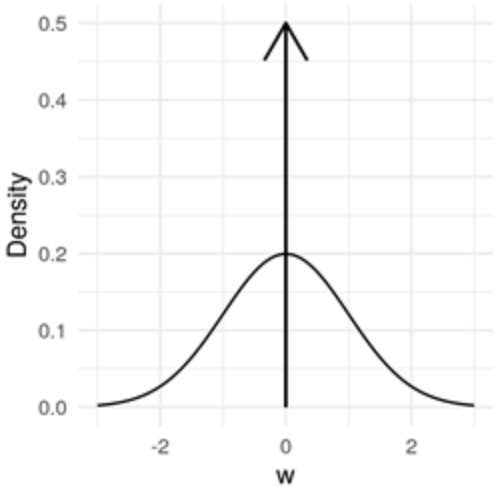
Concepts | *MOFA implementation*

Multi-Omics Factor Analysis (MOFA)

- Model $\mathbf{Y}^m = \mathbf{W}^m\mathbf{Z} + \boldsymbol{\varepsilon}^m$

Bayesian inference of elements of $\mathbf{Z}$ and $\mathbf{W}^m$

- *Sparse* (Automatic Relevance Determination X "spike-and-slab") priors on weights $w^m_{d,k} = s^m_{d,k}\hat{w}^m_{d,k}$, with priors $s^m_{d,k} \sim$ Bernoulli(Θ^m_k) and $\hat{w}^m_{d,k} \sim$ Normal(0,1/α^m_k), **so in modality *m*, if Θ^m_k is close to 0, factor *k* is sparse (most features have 0 weights), and if α^m_k is large factor k is not active (e.g., the factor does not explain any variation)**



Spike and slab prior. The arrow represents a Dirac point mass at 0.

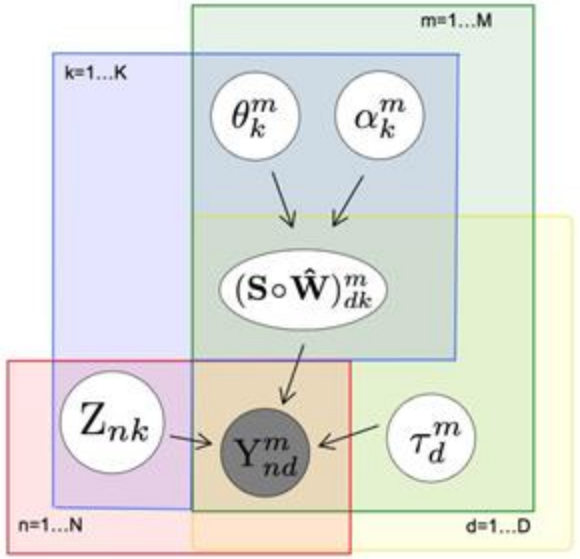
Concepts | *MOFA implementation*

Multi-Omics Factor Analysis (MOFA)

- Model $\mathbf{Y}^m = \mathbf{W}^m\mathbf{Z} + \boldsymbol{\varepsilon}^m$

Bayesian inference of elements of **Z** and $\mathbf{W}^m$

- *Gaussian* (for continuous data, e.g. normalized expression data and methylation *M* values), *Bernoulli* (for binary data, e.g. genomic alterations), or *Poisson* (for count data, e.g. as expression in read counts) **prior distributions on noise** $\varepsilon^m{}_n$



MOFA directed acyclic graph. *Source: Argelaguet et al. Mol Syst Biol 2018.*

Concepts | *MOFA implementation*

Multi-Omics Factor Analysis (MOFA)

Variational Bayes (or VI) implementation:

- *Rationale*: when fitting complex Bayesian models, the posterior distribution of the parameters is often intractable; we **need an approximation**
- *Method (VI)*: a **lower bound on the model likelihood (the Evidence Lower Bound--ELBO) is optimized** (E-M algorithm), using a simpler factorized form for the posterior
- *Note*: less computer-intensive alternative to the popular Monte Carlo Markov Chains (MCMC)

Practical 2

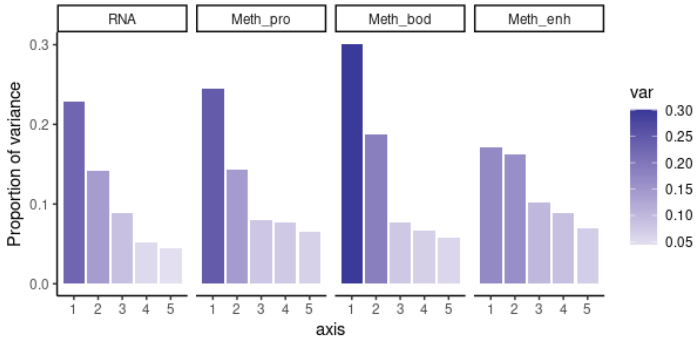
Using MOFA to build a molecular map of expression and methylation of the rare lung neuroendocrine neoplasms
https://github.com/IARCbioinfo/medical_genomics_course/wiki/Practical-2

- **preprocessing** with RNA-seq pipeline from Practical 1 and the DNA methylation array processing script at https://github.com/IARCbioinfo/Methylation_analysis_scripts
- **normalize expression data** with the VST function
- **convert methylation into M-values** (<0 for unmethylation, >0 for methylated)
- **split methylation data** into 3 datasets according to location (sites within gene promoter regions, within gene bodies, and within enhancers)
- **select the 5000 most variable features** for each of the 4 datasets

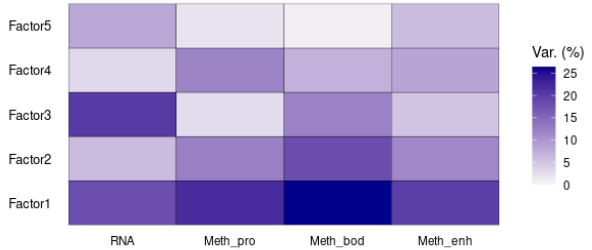
Understanding MOFA | *Link with PCA*

MOFA factors explain variance across the input matrices

- *Independent factorization with PCAs on each 'omic layer (input matrix):*
  - *Variance decreases monotonously with PC #*
  - *PCs do not necessarily match across PCAs*



- *Joint factorization with MOFA*
  - *Sum of variance decreases monotonously but not necessarily the variance of each 'omic layer*
  - *Factors are shared across 'omic layers*



Understanding MOFA | *Link with PCA*

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- *Joint factorization with MOFA*
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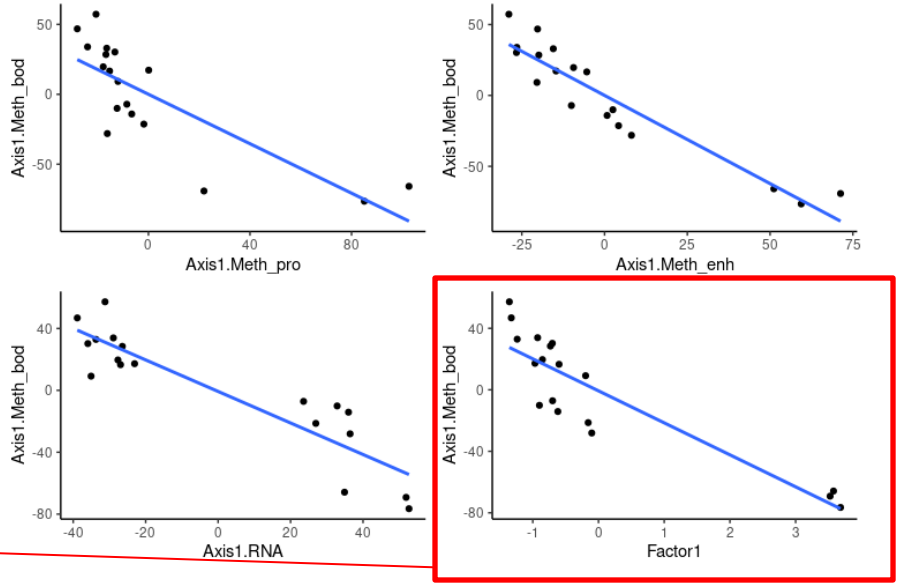
  - *Factors are shared across 'omic layers and correspond to a compromise between PCs*



MOFA

Understanding MOFA | *Link with PCA*

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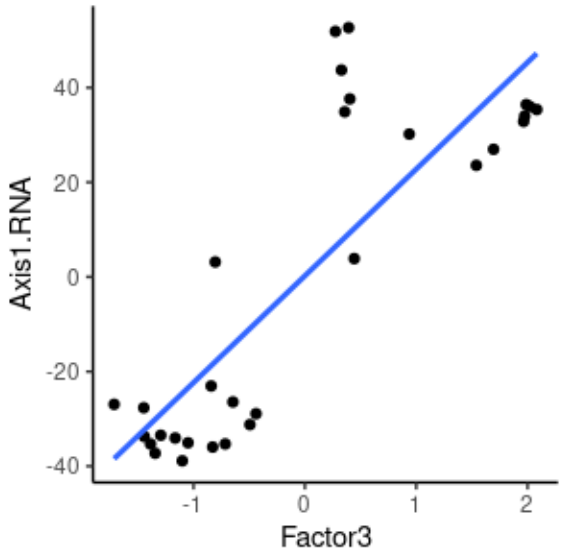

- *Joint factorization with MOFA*
  - *Sum of variance decreases monotonously but not necessarily the variance of each 'omic layer*
  - *Factors are shared across 'omic layers and correspond to a compromise between PCs, not necessarily in the same order*

Projects

Different flavors of computational biology for medical genomics

- I have heard of new analyses techniques that I want to try on my data => **Projects 1 and 2** (R scripting)
- I have new data that I want to explore and compare with previous data => **Project 3** (R scripting)
- I have scripts for a software that I want to implement in a reproducible workflow => **Project 4** (nextflow coding)
- I have data from new types/technologies and I want to explore their possibilities => **Project 5** (R scripting)

Projects

Schedule

- Projects start **today.** I will add you to team channels dedicated to each project where you can interact with the supervisor
- **Between now and next week: read the subject, download the data (or ask supervisor if data is protected), install the packages/software**
- **During next week's 4hr slot: expected to come with a list of questions** to ask to the supervisor about the subject (~30min / 1hr), divide tasks and start the analyses
- Between next week and the week after: work a bit on the analyses
- Last 4hr session: ask final questions with supervisor, start working on presentation
- Between last session and presentations: do the presentation, maybe doing some specific plots

Projects

Evaluation

General philosophy: you will receive your diploma soon and start working. Medical genomics is a team-oriented career, where team dynamics, integrating different skillsets and personalities is key.

- **Grade 1**: **team work**. Given by supervisor based on interactions during and between the project sessions (preparation between sessions count). Did the student divide tasks adequately and work together to solve problems? Did they make regular progress? Bonus if students were creative in the way they approach the problem.

- Grade 2: 10 min presentation and 5 min questions. Average of panel of supervisors' grades. Was the subject well understood (data, biological question, methods, results interpretation)? Can the students communicate their results in a simple but accurate way? Do they have constructive criticism about the methods and ideas of future steps?