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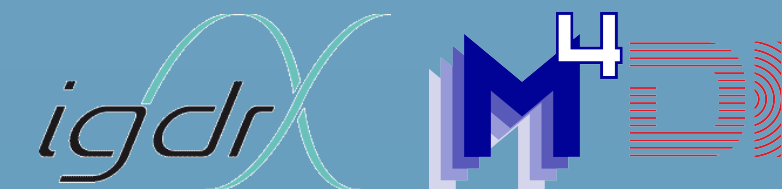
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# Simulation of data-driven multi-omic benchmark data for cellular deconvolution methods evaluation

Hugo Barbot<sup>1</sup>, David Causeur<sup>1</sup>, Yuna Blum<sup>2</sup>, Magali Richard<sup>3</sup>

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## Cell Deconvolution

Cellular heterogeneity in a bulk:

→ refers to the variety of cell types within the bulk,

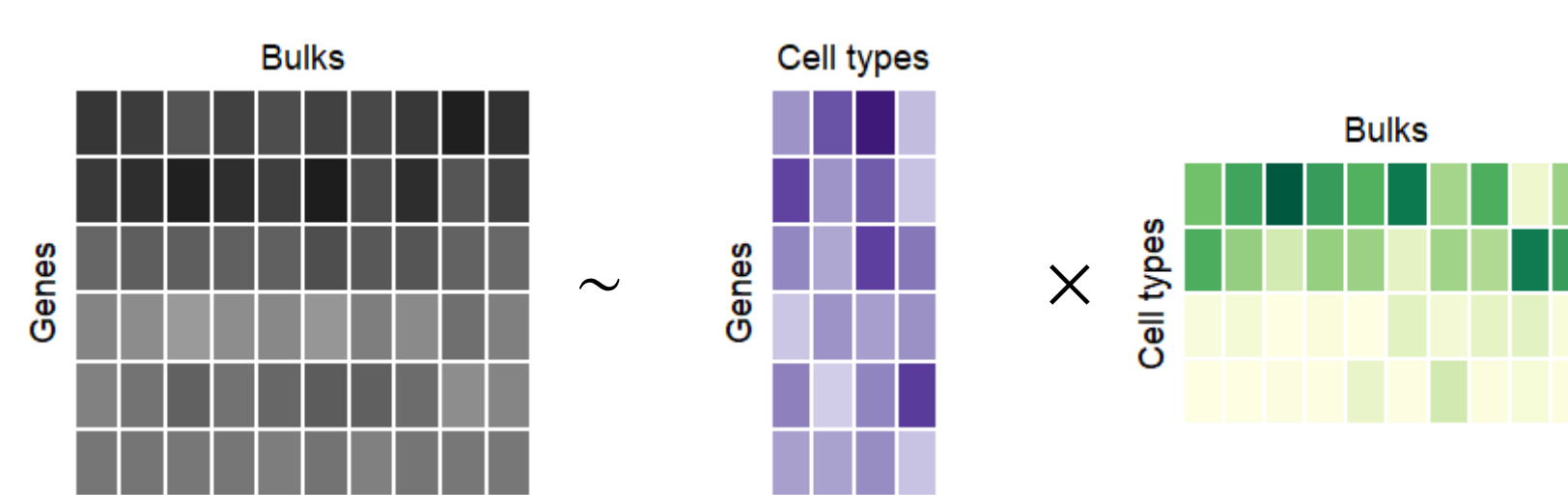
→ reflects progression of **disease state**,

→ is a **complex mixture** signal,

→ is **difficult to assess** from bulk molecular profiles.

⇒ Cell deconvolution **infers** relative abundance of cell types using **one or more -omic data** [1].

$Y$  bulk matrix  $M \times N$      $X$  reference matrix  $M \times K$      $\beta$  proportion matrix  $K \times N$



More robust methods + testing limits

⇒ Simulations

recreating the complex variability

from many omics data types

## Dependance with high dimensionnality

For now, we want **control on 4 hypotheses** of our deconvolution model based on Ordinary Least Squares optimisation:

$$\begin{cases} \forall i \in \llbracket 1; N \rrbracket & Y_i = X\beta_i + \varepsilon_i, \\ \mathcal{L}(\varepsilon_i) = \mathcal{N}(0, \sigma^2 I_M). \end{cases} \quad \text{u.c. for each } \beta_i \begin{cases} \sum_{k=1}^K \beta_{ik} = 1, \\ 0 \leq \beta_{ik} \leq 1. \end{cases}$$

Normality    Independence    Homoscedasticity    Centrality

Leads to a variety of algorithmic solutions.

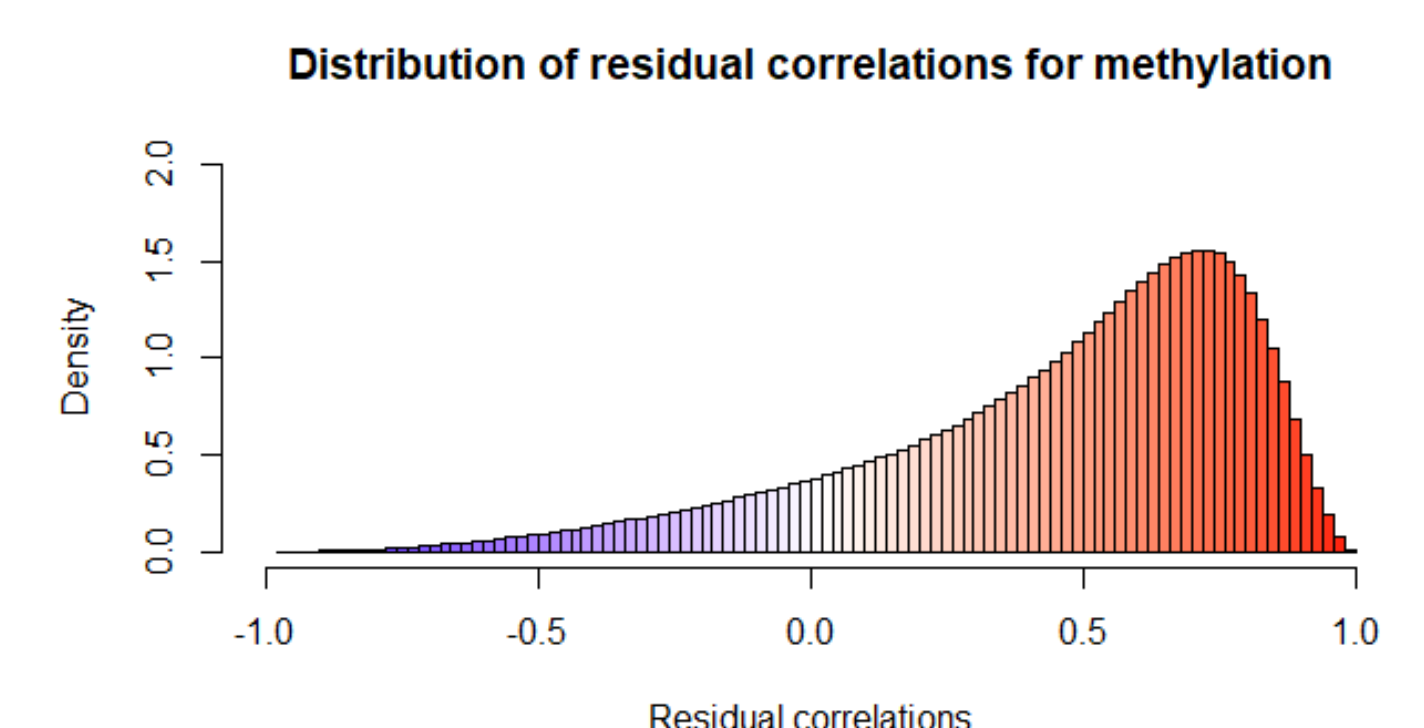
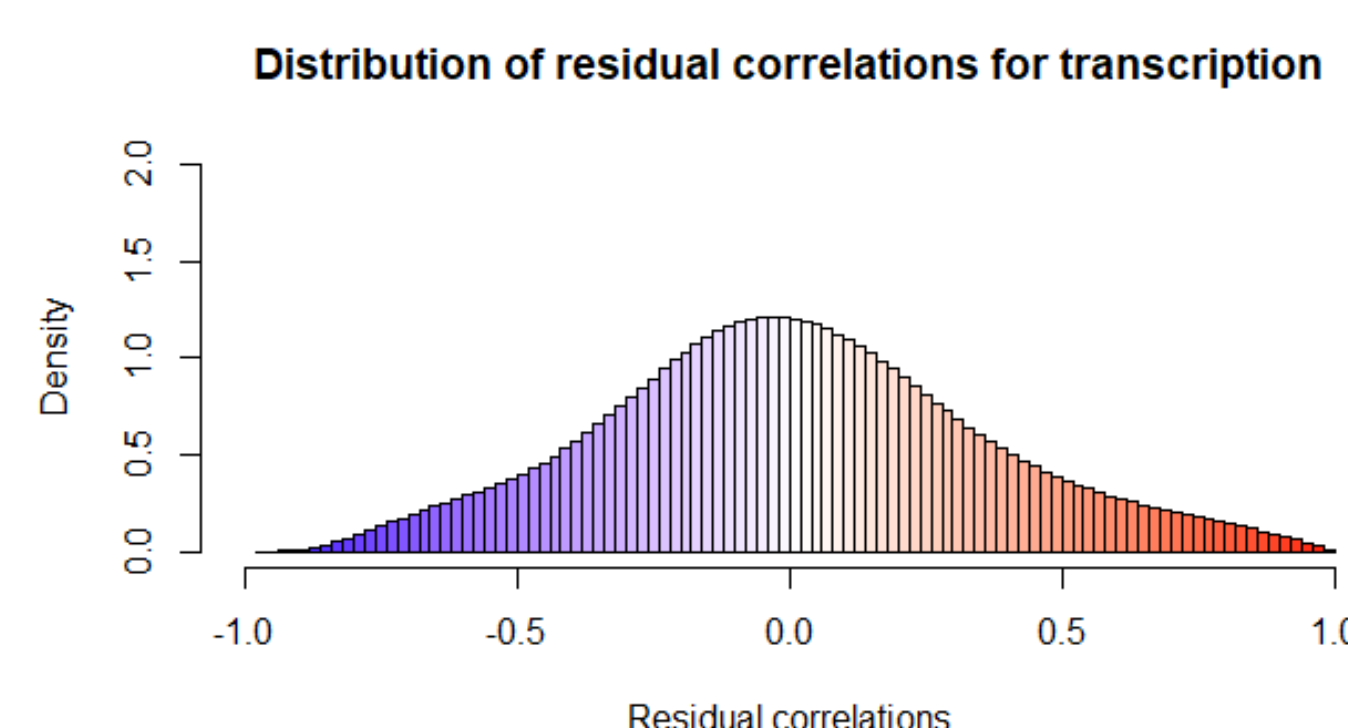
Natural way to deal with dependant data is by using a multivariate normal law. However, inferring a conditional correlation matrix with  $\sim 20000$  or  $\sim 800000$  features (gene/probe) is time consuming and quite inoperable for simulation with this approach.

## Benchmark dataset

A benchmark **dataset generated in vitro** is accessible (from COMETH project [2]) with:

- 21104 gene expressions,
- $\sim 800000$  CpG probes methylation,
- $N = 30$  **independent** bulk,
- $K = 9$  cell types commonly found in **PDAC**.

Moreover, both omics have significant conditional two by two correlations between features:



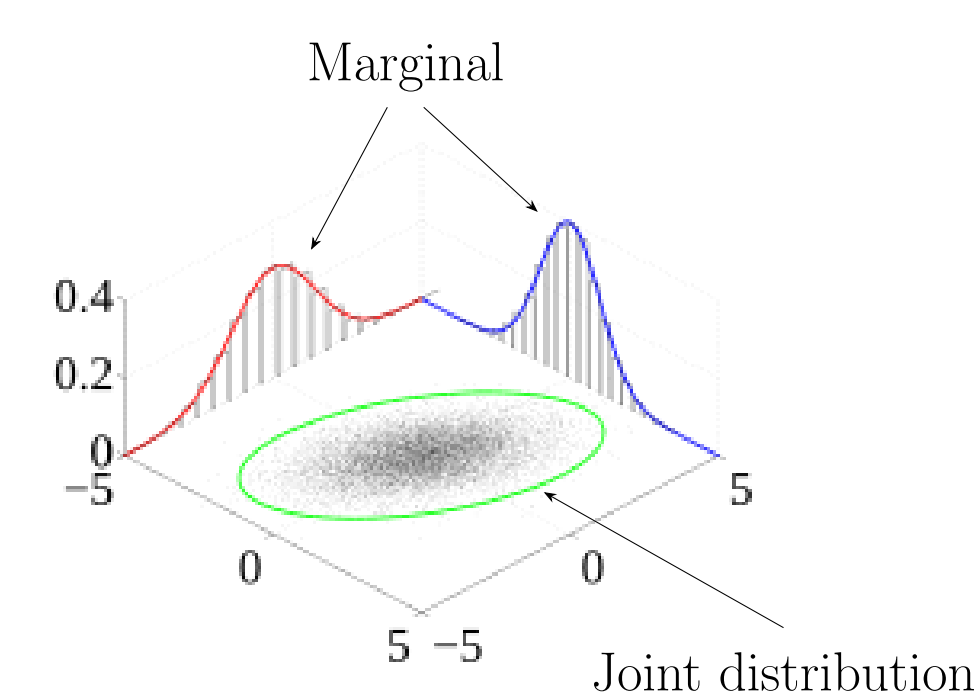
The true proportions of each cell type in each bulk are controlled and therefore can be assumed to be known.

We propose **two different simulation methodologies** for dependent data following specific marginals distribution functions:

## Copulas

Thanks to Sklar theorem [3], Copulas:

- **defines how the joint behavior** of multiple random variables is **structured**, regardless of their individual distributions,
- allow us to **characterise various complex forms of dependence**, such as non-linear or tail dependence between multiple variables.



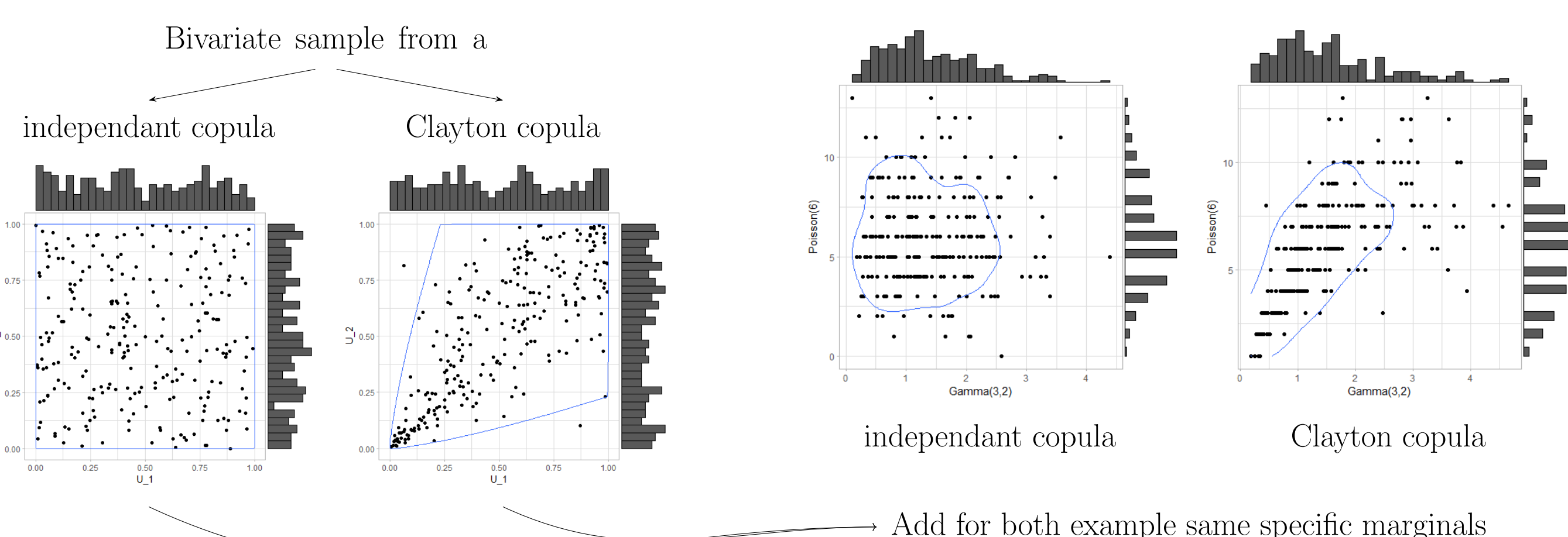
### Generation procedure

→ Copulas generate dependant **uniform** random vectors  $(U_1, \dots, U_M)$

This allows us to see those uniform values as **quantile**. Then we only have to **define or infer the marginal law of each feature to simulate any data types**, thanks to the inversion of the Cumulative Distribution Function:

$$(X_1, \dots, X_M) = (F_1^{-1}(U_1), \dots, F_M^{-1}(U_M)),$$

where here  $X_j$  represents values for the **specific** feature  $j$  (gene/probe) and  $F_j$  is the marginal distribution function defined or inferred for the **specific** feature  $j$  (gene/probe) with its **specific** parameter which can change for each feature.



## Factor model

Based on a **low-rank factor approximation** [4] of  $R$  the square conditional correlation matrix between features:

$$R = \Psi + \underbrace{BB'}_{\text{Shared variance}}$$

- $\Psi \in \mathcal{M}_{M,M}(\mathbb{R})$  diagonal,
- $B \in \mathcal{M}_{M,q}(\mathbb{R})$ ,

where  $1 \leq q < N$  is the number of factors chosen. Matrix  $B$  can be seen as a matrix of loadings for each feature on each factor.

### Generation procedure

$$\varepsilon_{generated} = \mathcal{N}(0, \Psi) + B \times \mathcal{N}(0, I_q), \quad \varepsilon_{generated} \in \mathcal{M}_{M,N}(\mathbb{R}).$$

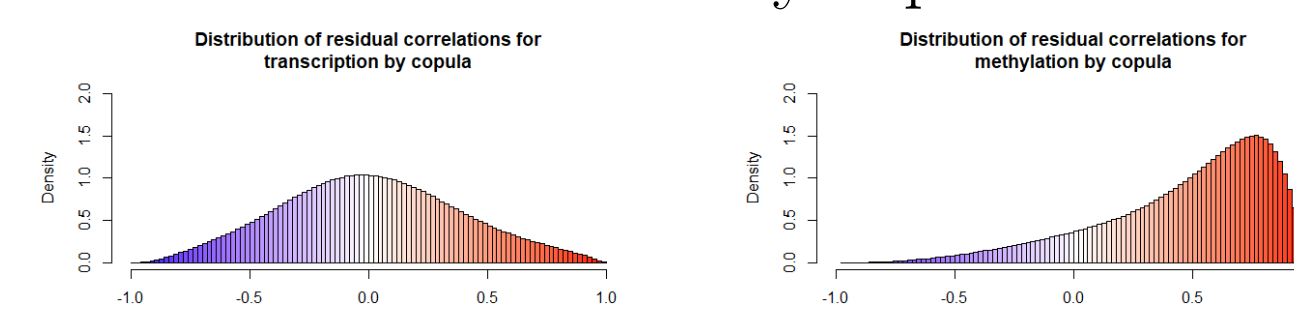
Since  $\Psi$  and  $B$  result from a decomposition of a correlation matrix, each line of  $\varepsilon_{generated}$  is centered and scaled residuals.

$$\varepsilon_{generated} \leftarrow (\varepsilon_{generated} \times \hat{\sigma}_{feature}) + \hat{\mu}_{feature}$$

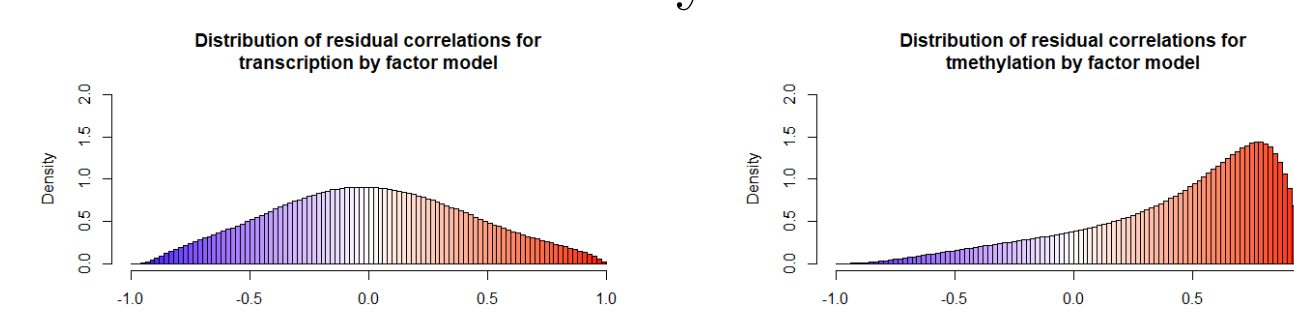
The procedure mimics the behaviour of the data provided.

## Results

Distributions of simulated conditionnal correlations by copula:



Distributions of simulated conditionnal correlations by factor model:



Score of NNLS, a basic deconvolution algorithm with late omics integration, on:

| Benchmark dataset              | rmse      | mae       |
|--------------------------------|-----------|-----------|
| nnismultimodal                 | 0.0856219 | 0.0544927 |
| No dependant simulated dataset | rmse      | mae       |
| nnismultimodal                 | 0.0209714 | 0.0148217 |
| Copula simulated dataset       | rmse      | mae       |
| nnismultimodal                 | 0.0796089 | 0.0509681 |
| Factor model simulated dataset | rmse      | mae       |
| nnismultimodal                 | 0.0801569 | 0.0519525 |

## Perspectives

Both methodologies:

→ are computationally **fast**,

→ **reproduce** and make explicit hypothesis on **different levels of complexity** (dependencies, intrinsic nature of data, ...),

→ need at least one *in vivo* or *in vitro* dataset with **known and controlled ground truth**, however more datasets are needed to avoid overfitted simulation procedure.

Ongoing works:

Here, Copulas and factor model methodology capture dependance structure empirically. We focus now on defining controlled parameters for each approach to simulate different scenarios.

[1] Clémentine Decamps, Alexis Arnaud, Florent Petitprez, et al. DECONbench: a benchmarking platform dedicated to deconvolution methods for tumor heterogeneity quantification. *BMC Bioinformatics*, 22(1):473, October 2021.

[3] M Sklar. Fonctions de répartition à n dimensions et leurs marges. *Annales de l'ISUP*, 8(3):229-231, 1959.

[2] Yuna Blum, Jérôme Cros, Sergio Escalera et al. COMETH - COmputational METHods in Health.

[4] Chloé Friguet, Maëla Kloareg, and David Causeur. A factor model approach to multiple testing under dependence. *Journal of the American Statistical Association*, 104(488):1406-1415, 2009.