Data Integration Using MOFA

EBI Course Systems Biology

10.07.2025

Omics Data is High-Dimensional

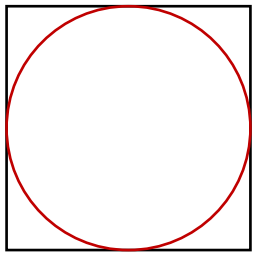
Modality	**Number of features / dimensions**
Proteome	e.g. 10 000 proteins
Transcriptome	e.g. 20 000 genes
Genome	e.g. 5 million SNPs
Epigenome	e.g. 20 million CpG sites

... often in just 100s to 1000s of cells / samples →

$$n_{dimensions} \gg n_{observations}$$

Curse of Dimensionality with Unit Spheres

”Put a unit sphere (radius = 1) in a box and compute the ratio of the volumes”

D = 1	D = 2	D = 3	D = ...
			
$\frac{1}{1} = 1$	$\frac{\pi \cdot 0.5^2}{1} \cong 0.78$	$\frac{\frac{4}{3}\pi \cdot 0.5^3}{1} \cong 0.52$	$\cong 0$

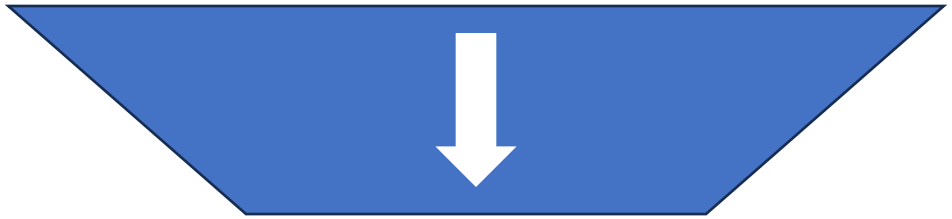
In very high dimensions...

- spheres around data points fill vanishingly small volumes
- it becomes difficult to establish relations between data points

→ High dimensions are typically not suitable for direct analysis

Dimensionality Reduction Methods

	Gene 1	Gene 2	Gene 3	...	Gene D
Cell 1	2	5	2	...	0
...	...	...	...	...	..
Cell N	2	1	0	...	0



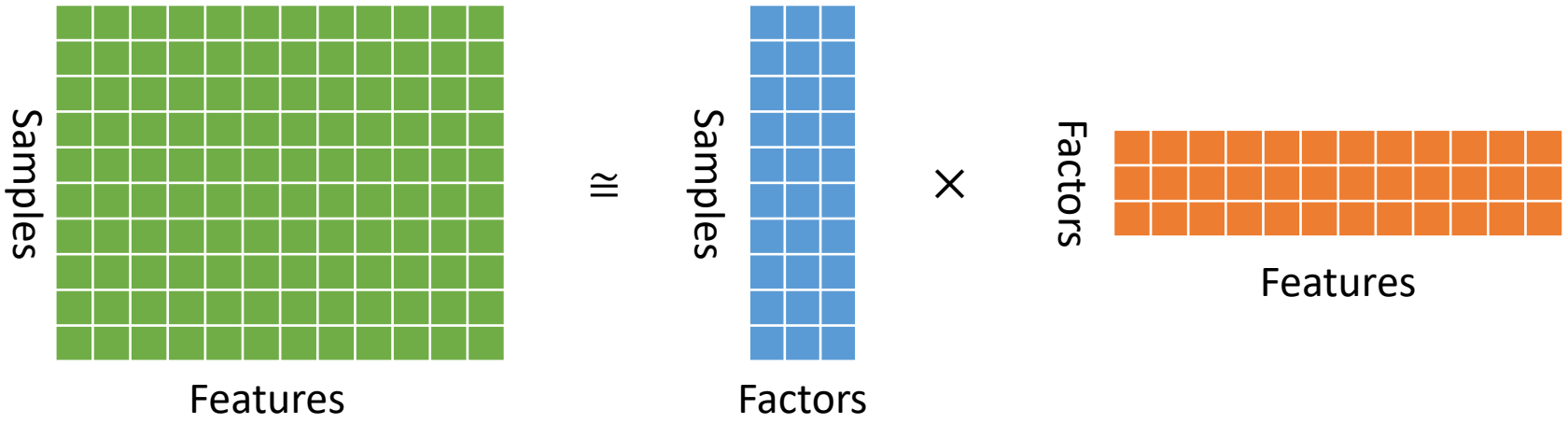
	Dim 1	Dim 2
Cell 1	0.4	-6.2
...	...	...
Cell N	0.0	9.1

Linear Methods
Principal Component Analysis (PCA)
Independent Component Analysis (ICA)
Latent Dirichlet Allocation (LDA)
Factor Analysis (FA)
Non-Negative Matrix Factorization (NMF)
...

Non-Linear Methods
(Variational) Autoencoder (VAE)
Deep Matrix Factorization
t-SNE
UMAP
Spectral Embedding
scDoRI ☺
...

What is a Factor Model Intuitively?

- **Factors** can be seen as **meta-features** that summarise the behaviour of groups of features
- The reduced **data** is represented as **factor scores** (a matrix of dimensions $n_{samples} \times n_{factors}$
- Factors are linked to all the original features via **factor loadings** (a matrix of dimensions $n_{factors} \times n_{features}$)

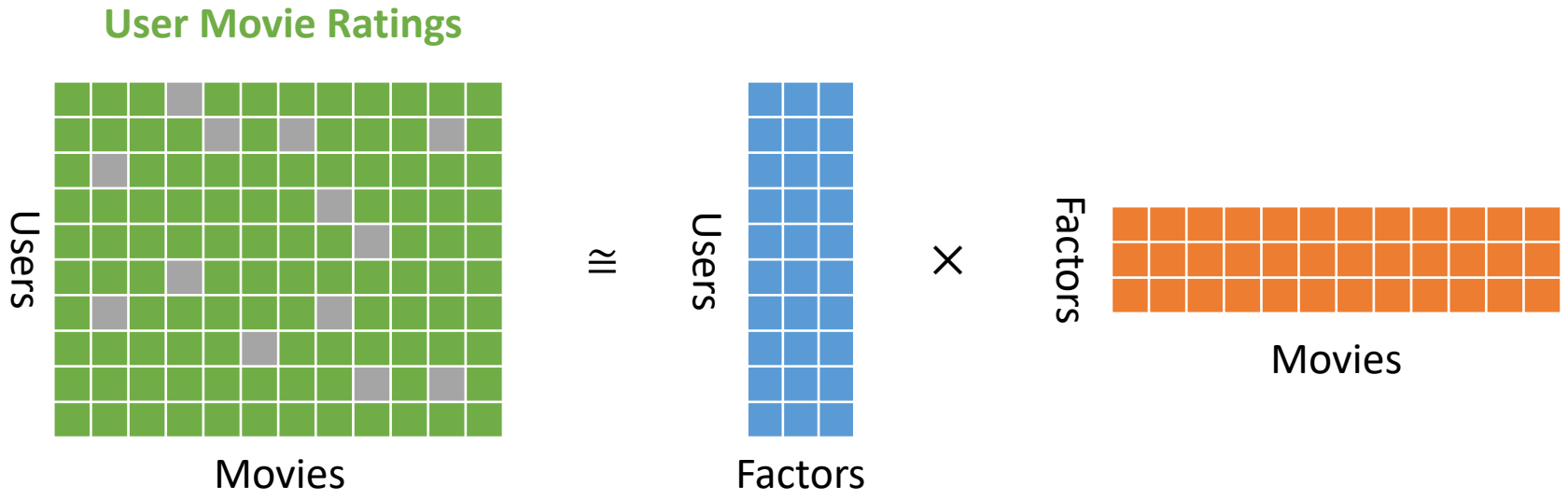


An Example: Movie Recommendations

- A streaming service has access to the **star ratings** its users have given for different **movies**.
- The service wants to know **how much a user would like another movie** to provide better recommendations
- What could the factors represent in this situation? Do they always represent something “real”?
- What about positive and negative factor scores and loadings?
- How could movie ratings be predicted?

Samples = Observations
Features = Variables

Scores = Factors
Loadings = Weights



What is a Factor Model Mathematically?

- Factor scores and loadings are called **latent variables**
- Given the **observed data**, the goal is to **infer** the latent variables

Matrix Factorisation

$$y_{nd} \cong \sum_{k=1}^{K} z_{nk} w_{kd}$$

$Y \in \mathbb{R}^{NxD}$ Observed data
$Z \in \mathbb{R}^{NxK}$ Factor scores
$W \in \mathbb{R}^{KxD}$ Factor loadings

Probabilistic Formulation

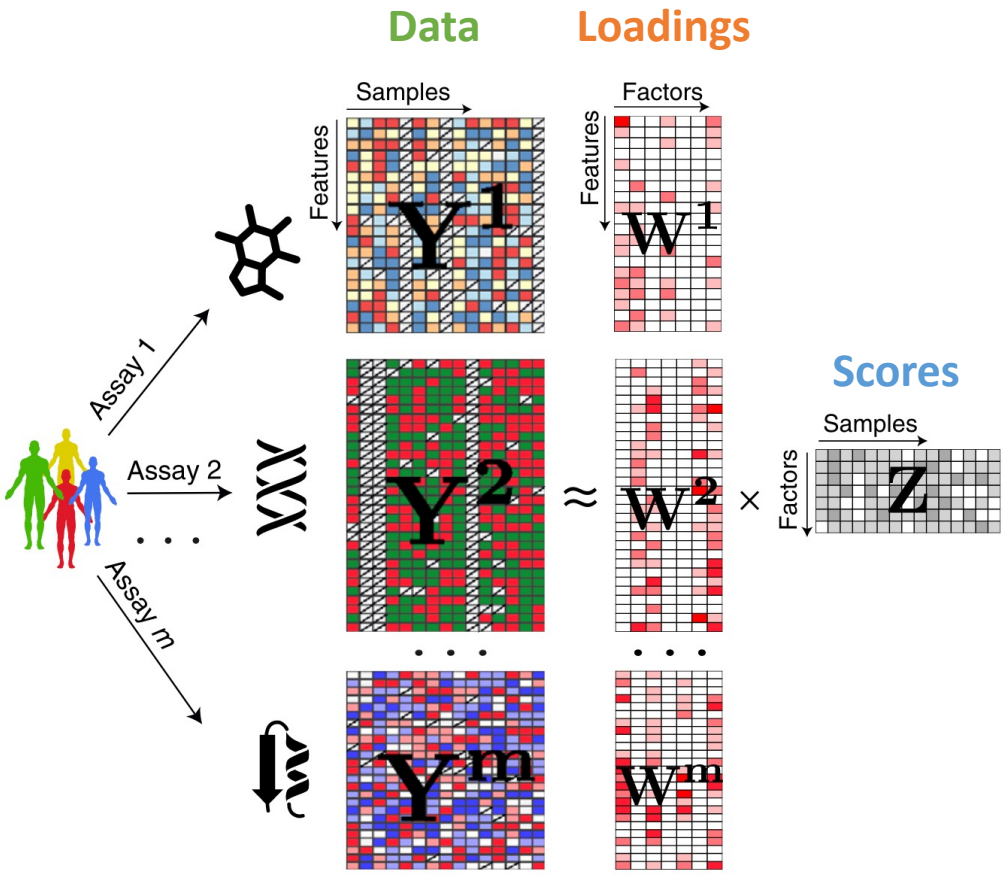
$$y_{nd} \sim \mathcal{N}(\mu_{nd}, \sigma_d^2)$$

$$\mu_{nd} = \sum_{k=1}^{K} z_{nk} w_{kd}$$

$$z_{nk} \sim p(z_{nk})$$

$$w_{kd} \sim p(w_{kd})$$

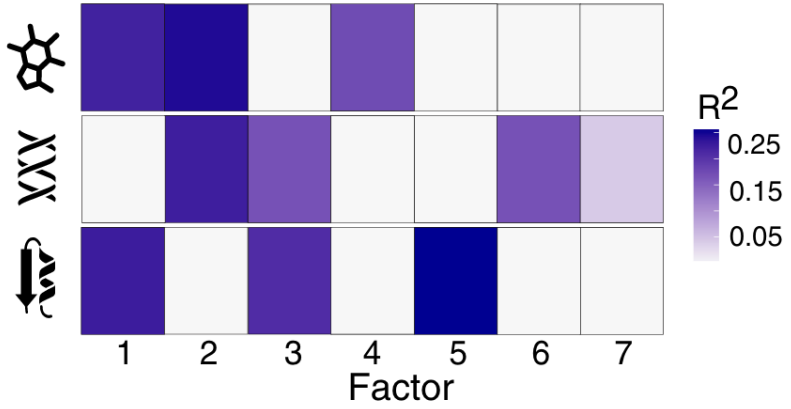
Multi-Omics Factor Analysis (MOFA)



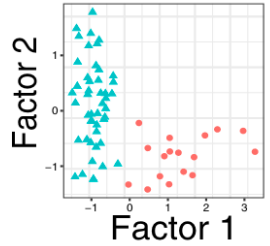
Argelaguet, Ricard, et al. "Multi-Omics Factor Analysis—a framework for unsupervised integration of multi-omics data sets." *Molecular systems biology* 14.6 (2018): e8124.

MOFA Downstream Analysis

Variance decomposition by factor

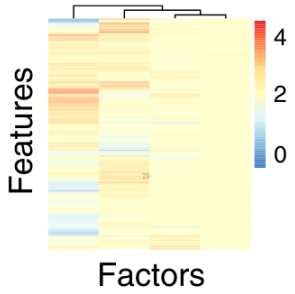


Inspection of factors

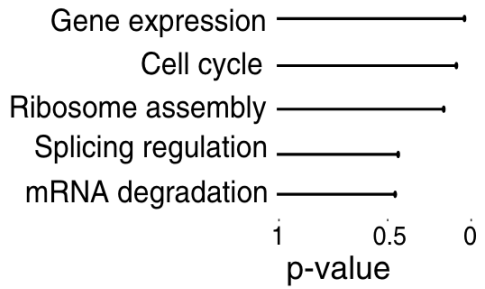


Annotation of factors

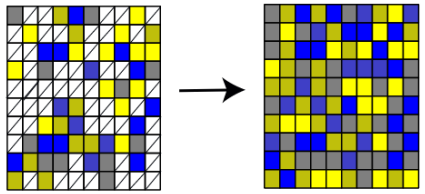
Inspection of loadings



Feature set enrichment analysis



Imputation of missing values



Argelaguet, Ricard, et al. "Multi-Omics Factor Analysis—a framework for unsupervised integration of multi-omics data sets." *Molecular systems biology* 14.6 (2018): e8124.

Gene Set Enrichment Analysis (GSEA)

Loadings

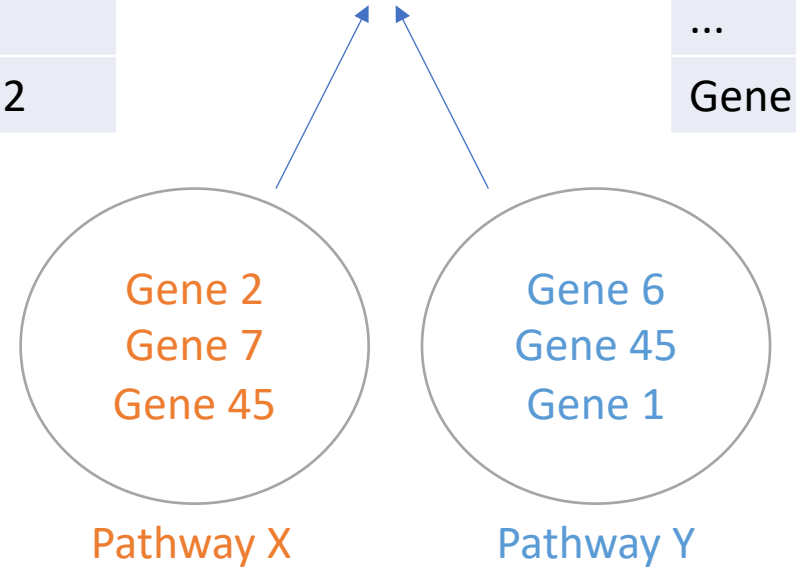
Gene 1	0.2
Gene 2	-5.1
Gene 3	1.1
…	…
Gene D	4.0

Sorting

Gene 2	-5.1
Gene 7	-4.9
Gene 45	-4.5
…	…
Gene 9	5.2

GSEA

Gene 2	-5.1
Gene 7	-4.9
Gene 45	-4.5
…	…
Gene 9	5.2



Bayesian Latent Variable Models

Generative Model
("Telling a story of the data")

Data → $y_{nd} \sim \mathcal{N}(\mu_{nd}, \sigma_d^2)$ ← Data Likelihood

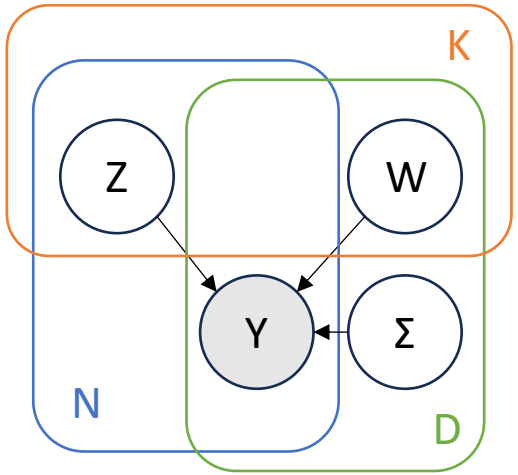
$$\mu_{nd} = \sum_{k=1}^{K} z_{nk} w_{dk}$$

$$w_{dk} \sim p(w_{dk})$$
$$z_{nk} \sim p(z_{nk})$$
$$\sigma_d \sim p(\sigma_d)$$

← Prior distributions

Latent variables

Graphical Model



Bayes' Theorem

Thomas Bayes
1701 – 1761
Statistician and Presbyterian minister

Posterior **Likelihood** **Prior**

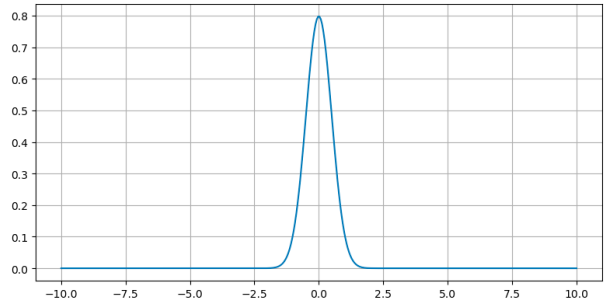
$$p(A \mid B) = \frac{p(B \mid A)p(A)}{p(B)}$$

Marginal likelihood

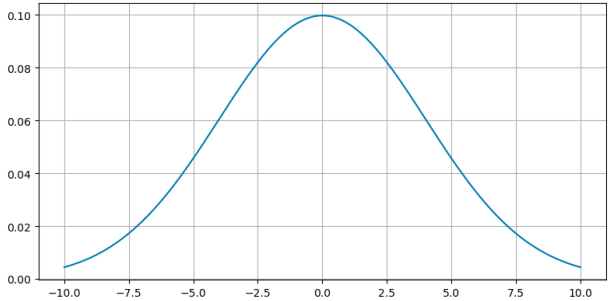
The Power of Prior Distributions

$$p(w_{dk}) = ?$$
$$p(z_{nk}) = ?$$
$$p(\sigma_d) = ?$$

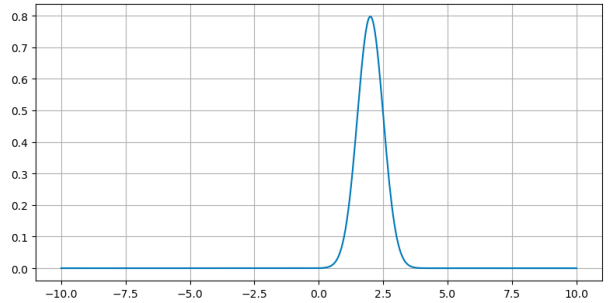
Prior distributions encode **a-priori assumptions about the variables** before seeing any data



”Values should be close to 0”

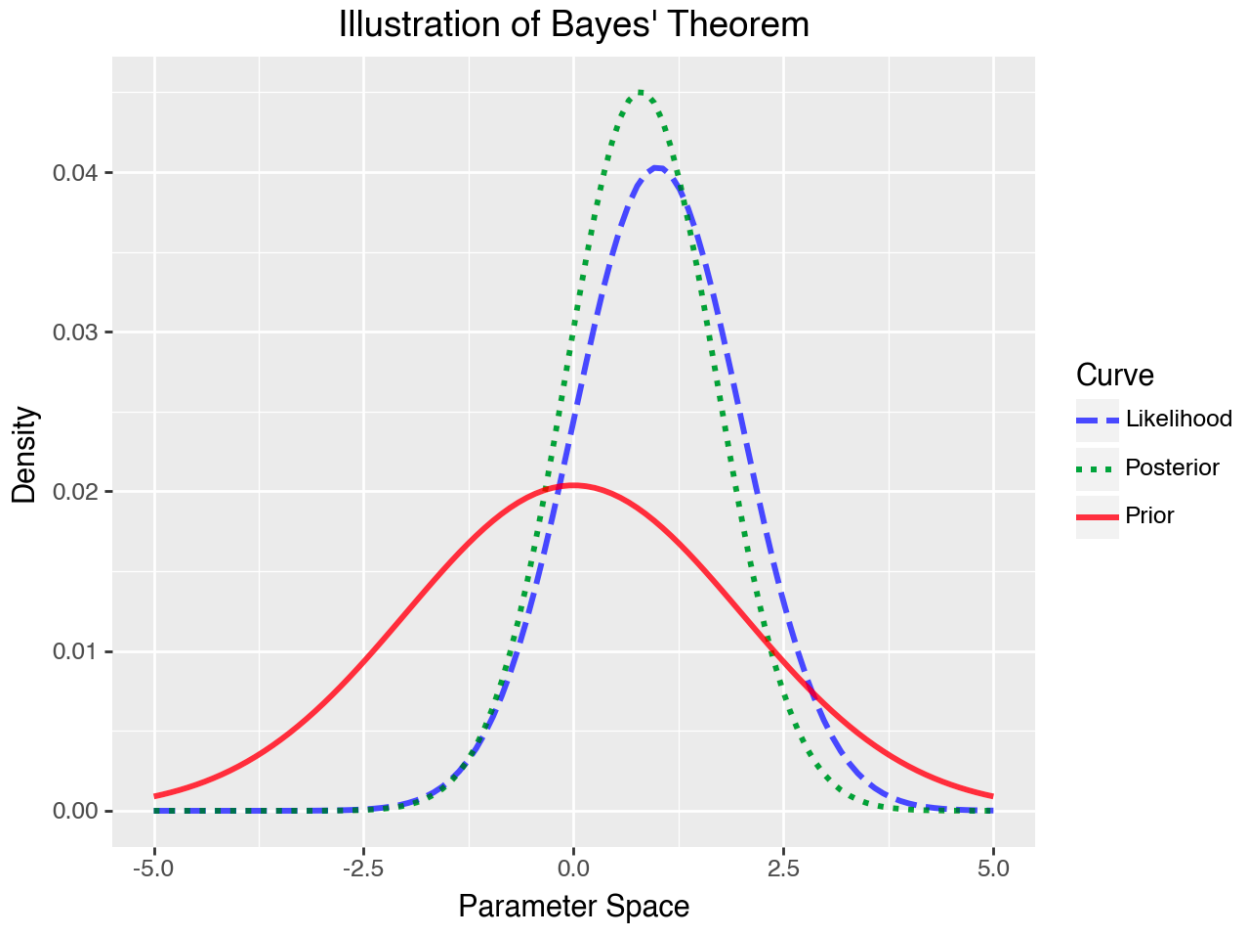


”Values could also be quite large”



”Values should (for whatever reason) be close to 2”

The Posterior Distribution – A Tradeoff Between Data Fit and Prior Distribution



Bayesian Inference

Given the prior distribution and data likelihood, the posterior should be easy to compute...

$$p(A \mid B) = \frac{p(B \mid A)p(A)}{\cancel{p(B)}}$$

Computationally not tractable 😭

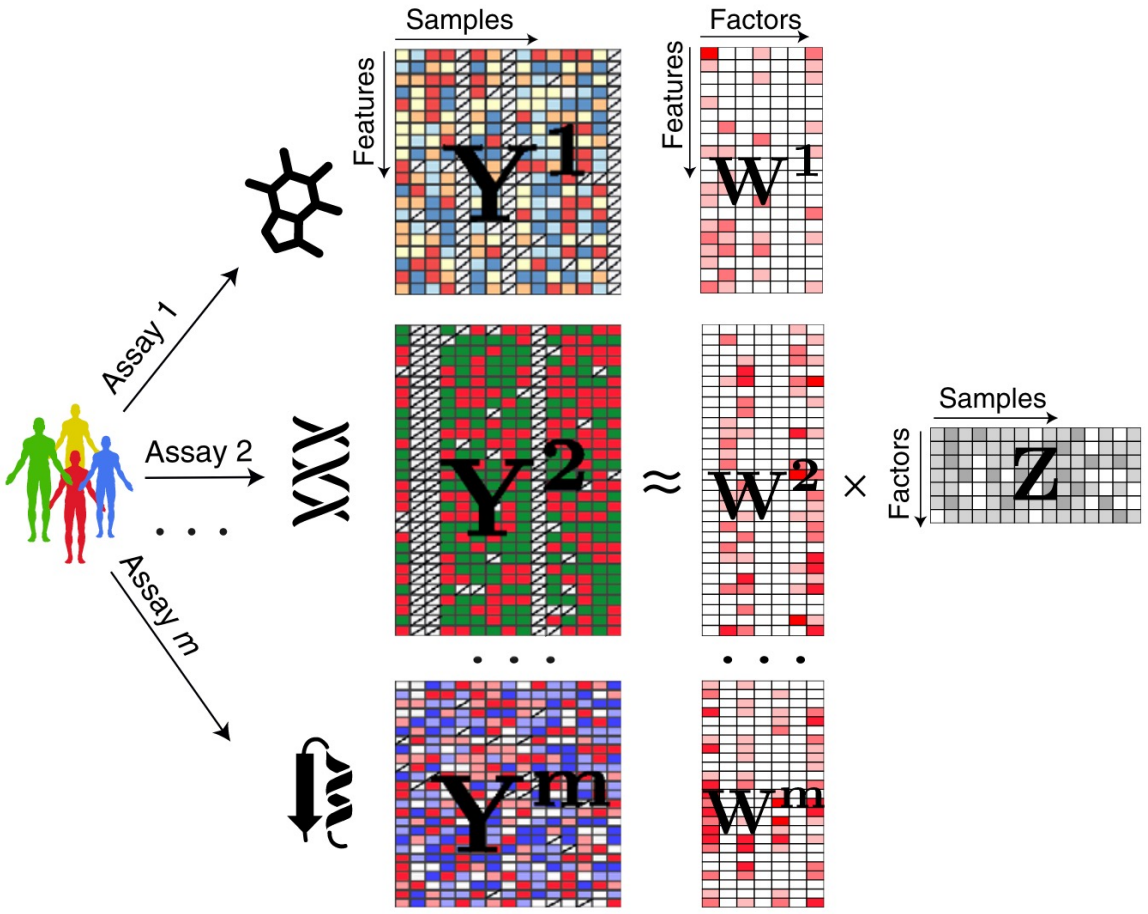
Solution: **Approximate inference**

$$q(A) \approx p(A \mid B)$$

$$\text{ELBO} = \ln(p(B)) - \text{D}_{KL}(q(A) \,||\, p(A \mid B))$$

Blei, David M., Alp Kucukelbir, and Jon D. McAuliffe. "Variational inference: A review for statisticians." *Journal of the American statistical Association* 112.518 (2017): 859-877.

Prior Distributions in MOFA



$$p(w_{dk}) = ?$$
$$p(z_{nk}) = ?$$

Matrix factorization is unidentifiable (= many solutions), but it gets better with **sparse loadings** (= many zeros).

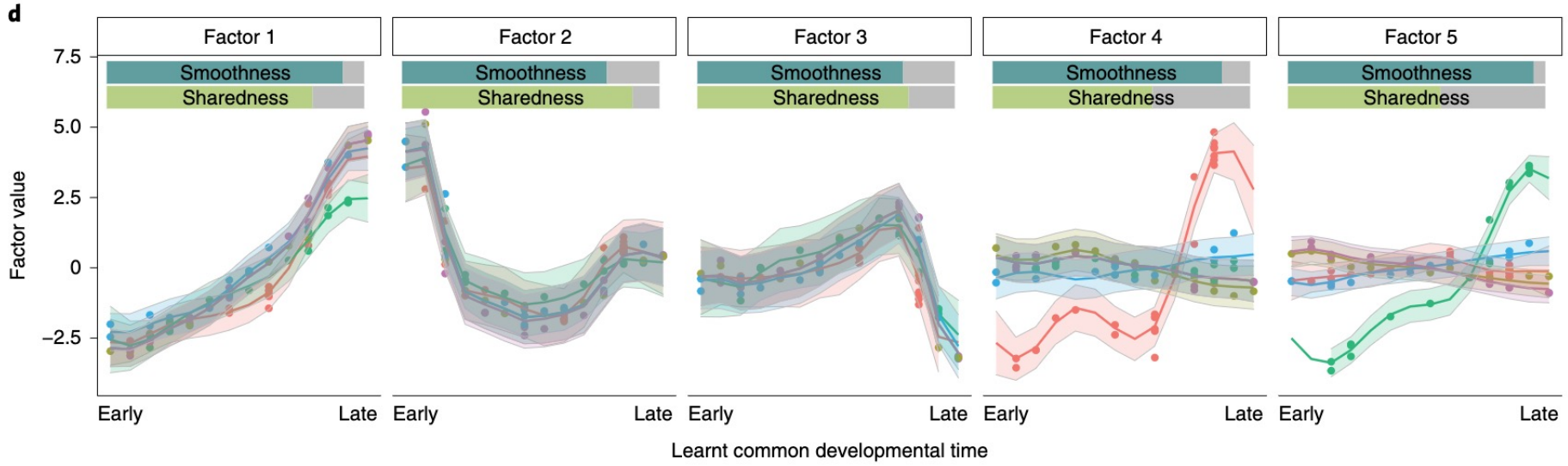
Sparsity on the level of:
- individual features
- whole factors in views

→ ARD prior, Horseshoe prior

Argelaguet, Ricard, et al. "Multi-Omics Factor Analysis—a framework for unsupervised integration of multi-omics data sets." *Molecular systems biology* 14.6 (2018): e8124.

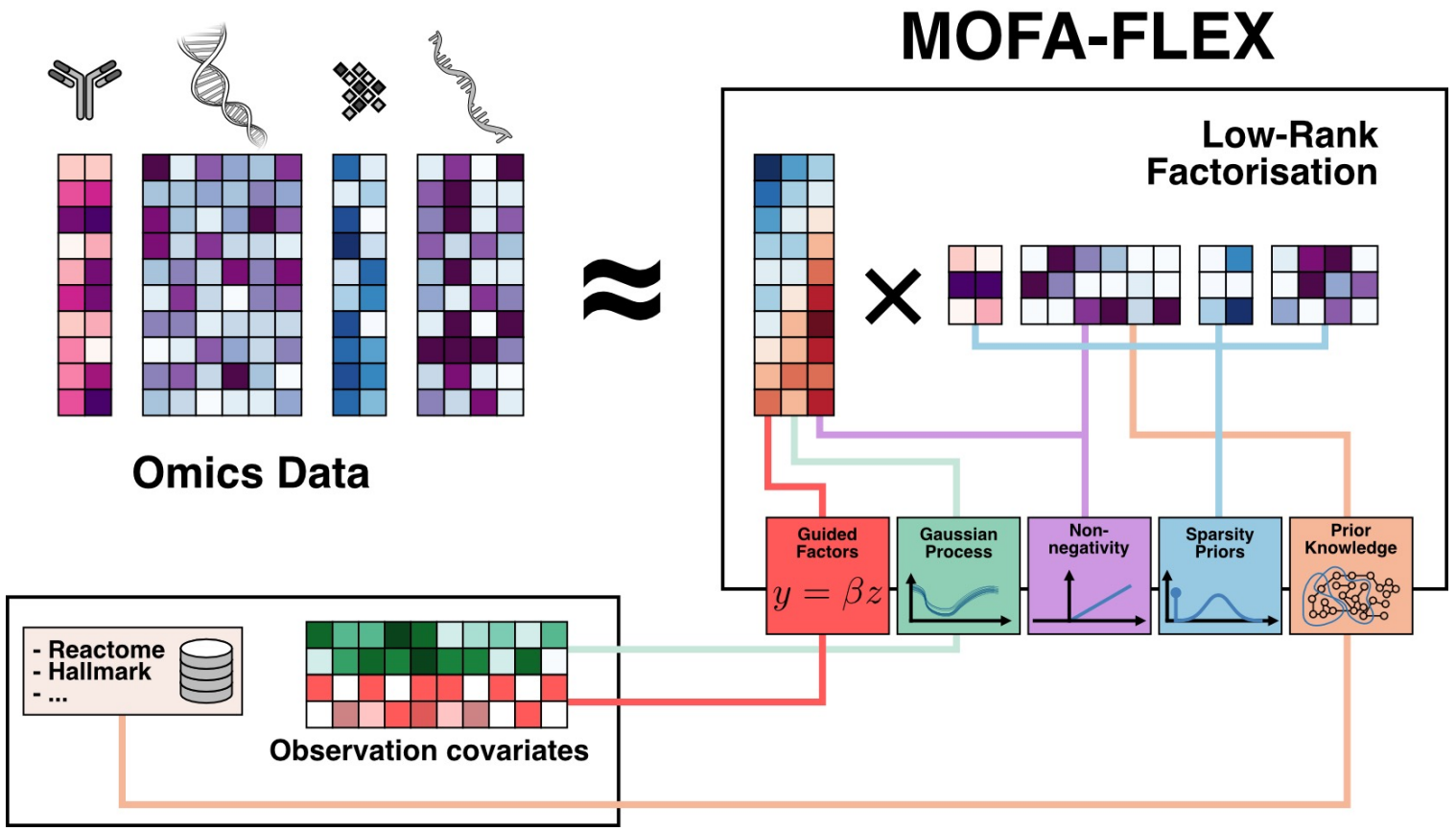
MEFISTO

- Observations in temporal / spatial data are not statistically independent
- MEFISTO is an extension of MOFA that includes temporal / spatial covariates and infers smooth factor score



Velten, Britta, et al. "Identifying temporal and spatial patterns of variation from multimodal data using MEFISTO." *Nature methods* 19.2 (2022): 179-186.

MOFA-FLEX



https://mofaflex.readthedocs.io/

Practical: Application to a chronic lymphocytic leukemia (CLL) data set

Somatic mutations	200 patients	69 mutation loci
Transcriptome	136 patients	5000 transcripts
DNA methylation	200 patients	200 methylation sites
Ex vivo drug response	200 patients	62 drugs (5 concentrations)

Patient metadata:

- Gender
- Age
- IC50 before treatment
- Treated after data collection
- Survival

```
git clone https://github.com/florinwalter/ebi_course_sysbio_25.git/
```