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CENTRE FOR ORGANISMAL STUDIES

VELTEN GROUP

HGS MathComp

Interdisciplinary Center for Scientific Computing

European Laboratory for Learning and Intelligent Systems

# MULTI-MODAL DATA ANALYSIS
## USING PROBABILISTIC FACTOR MODELS

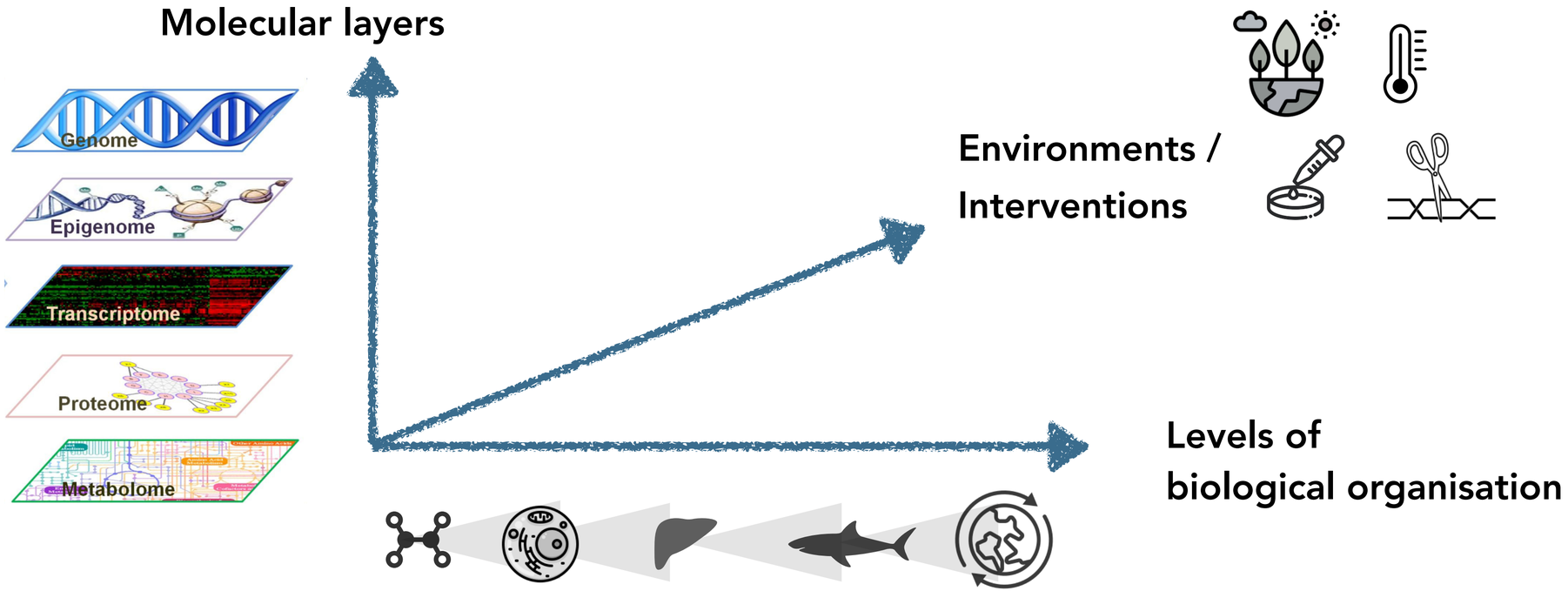
Francisca Gaspar Vieira

"Autumn School for Single Cell-ers"

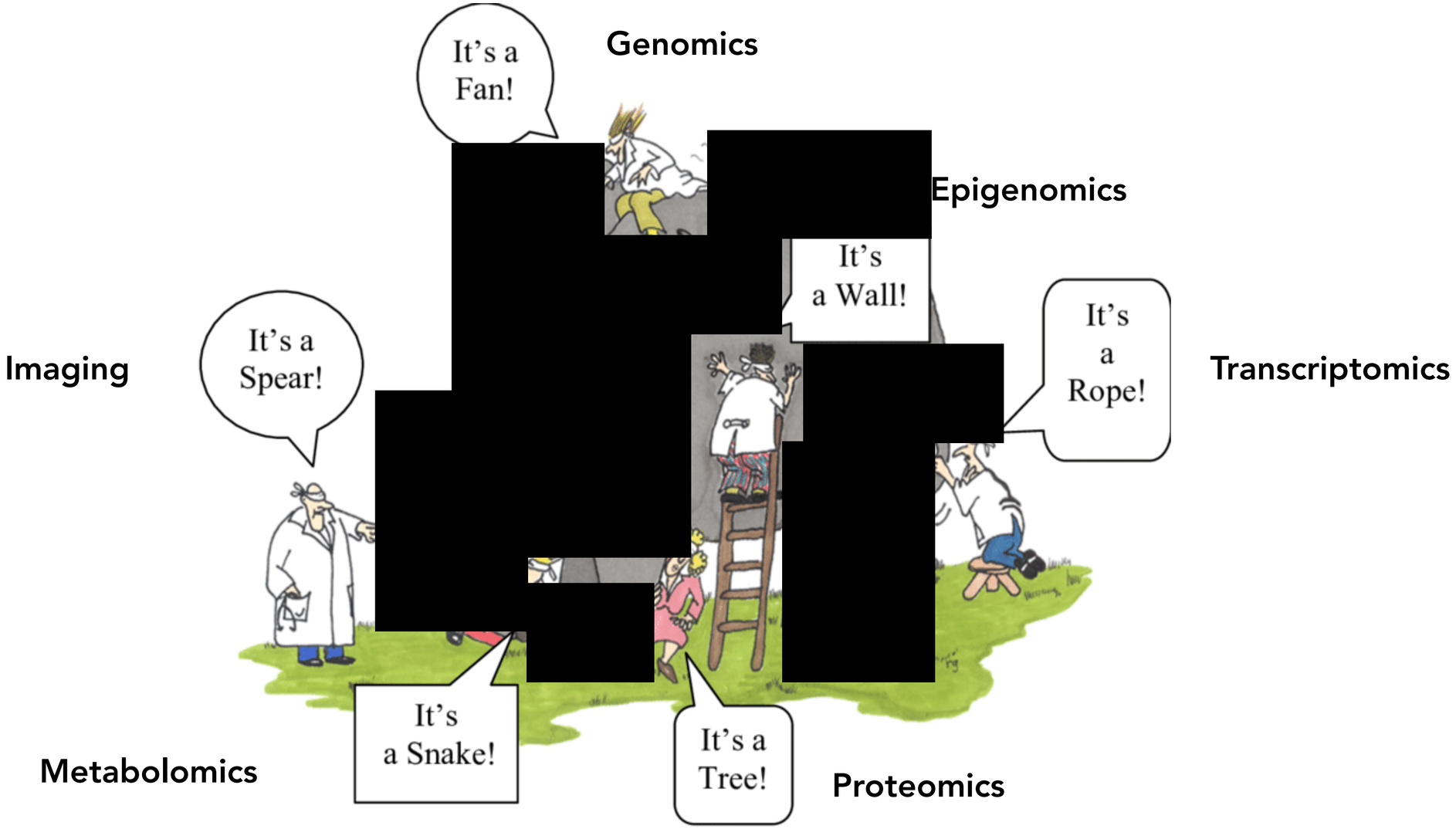
October 2025

1. Motivation
2. Intuition and core idea
3. The maths behind MOFA
4. Guide for factor interpretation
5. MEFISTO
6. Case studies

# A holistic understanding of biological processes requires multi-dimensional approaches

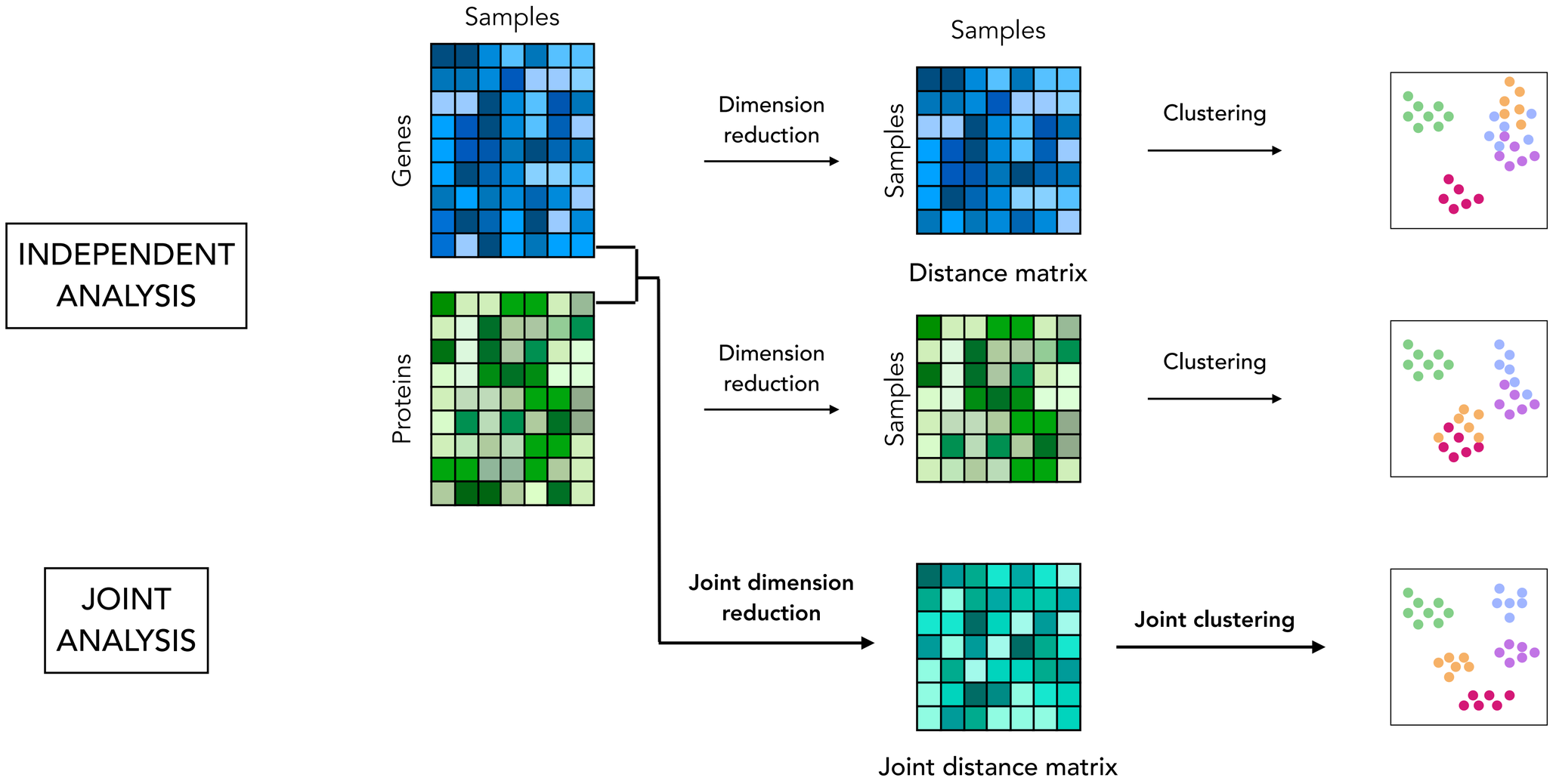


# Why do we (often) need to study different omic types together?




Adapted from Daigneault, Methodological Innovations Online 2013

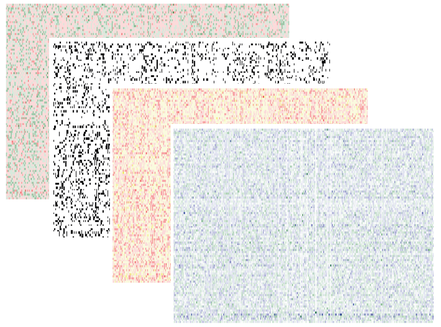
# Joint analysis can identify new sample subgroups and feature relationships



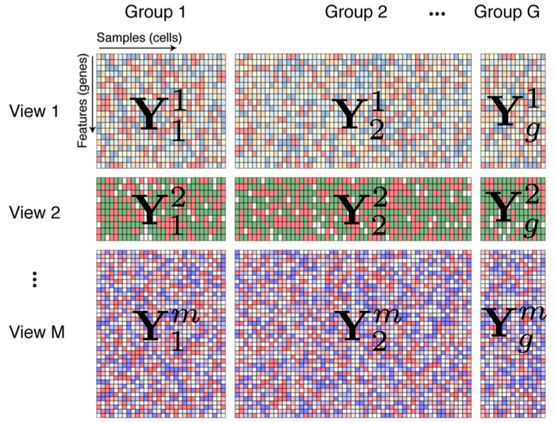

Adapted from Stuart & Satija, Nat Rev Gen 2019

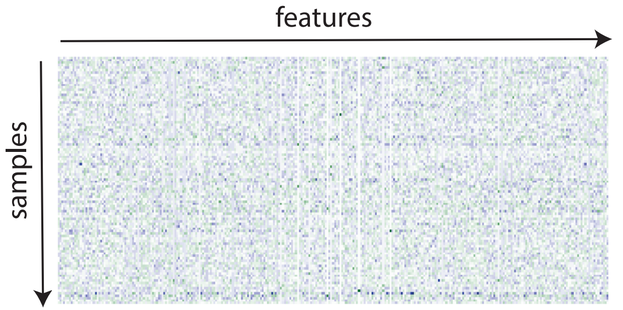
# Challenges in the integration of multi-modal data

- **Heterogeneous data** from different techniques come with distinct statistical properties and inherent structure
- Complex **correlation structures** and hidden confounders
- **High-dimensional** data requires appropriate **regularization** strategies
- Algorithms need to be **scalable** to large data sets
- Large amounts (and different patterns) of **missing values**



heterogeneous



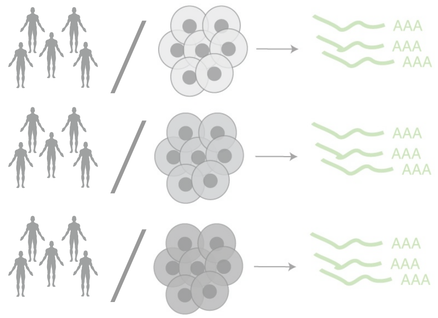



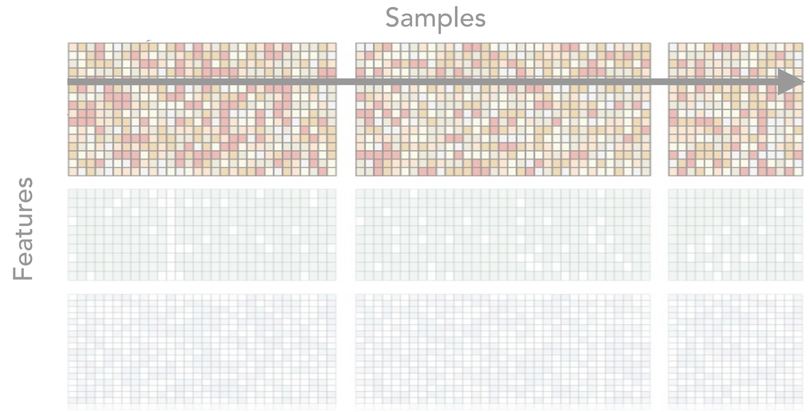

high-dimensional

Adapted from Stuart & Satija, Nat Rev Gen 2019

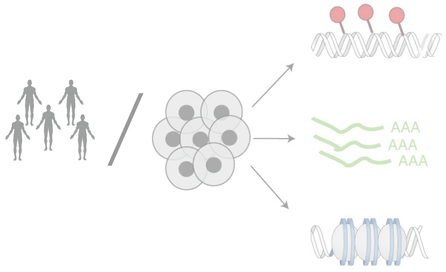
# How to integrate multi-modal data?

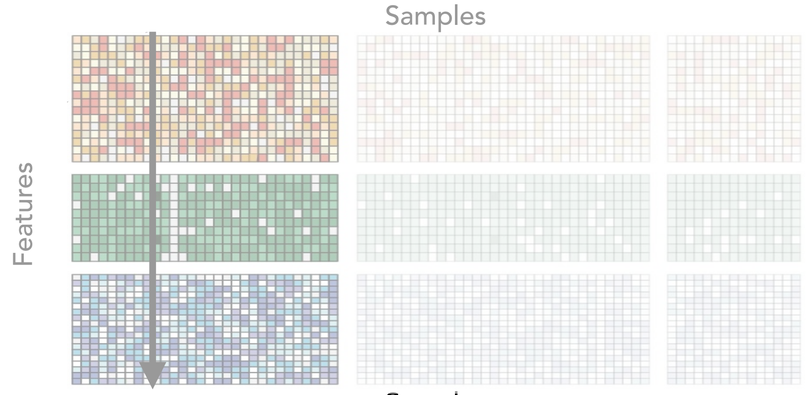
Horizontal integration
(features as anchors)



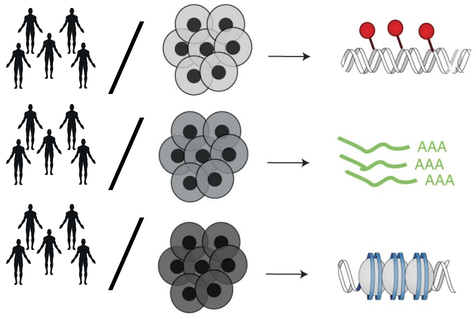



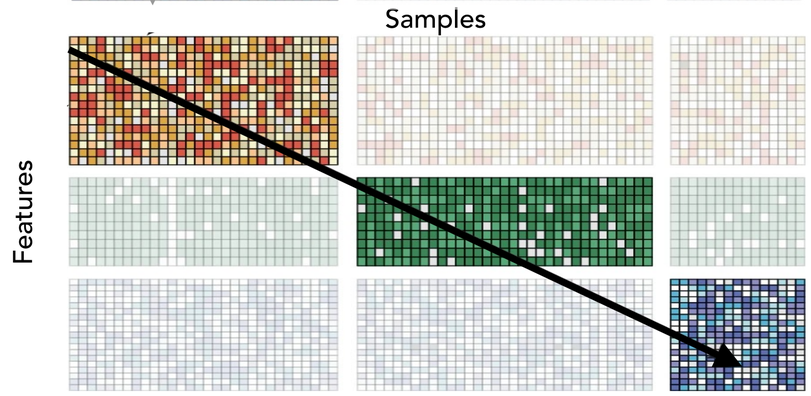

Vertical integration
(samples as anchors)




Diagonal integration
(no anchors)



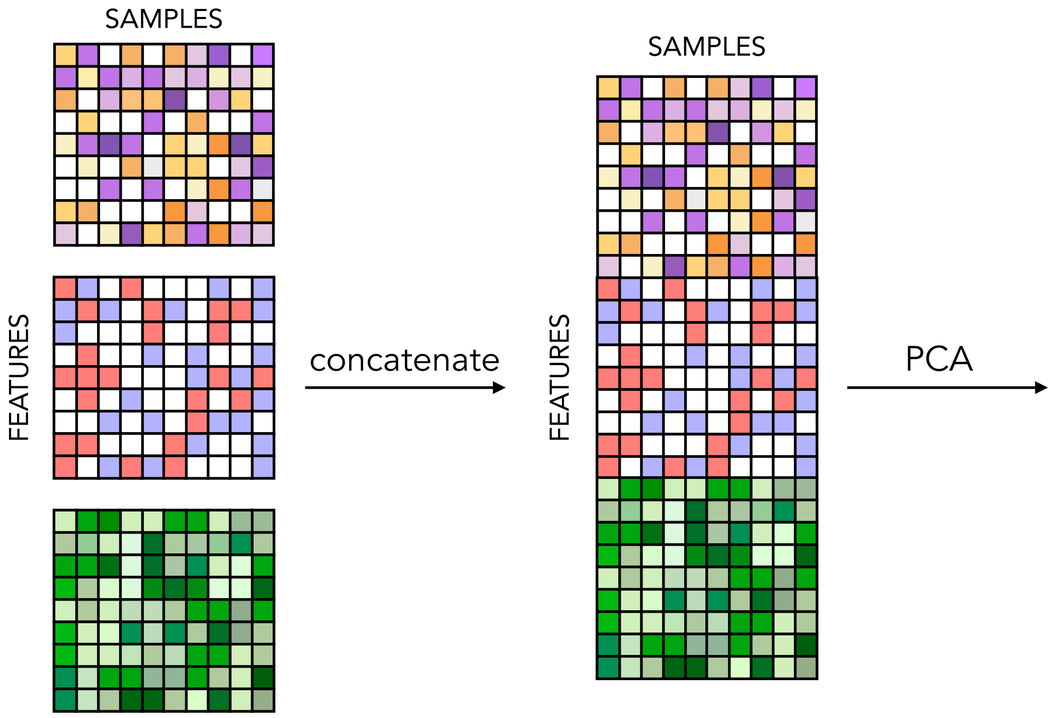



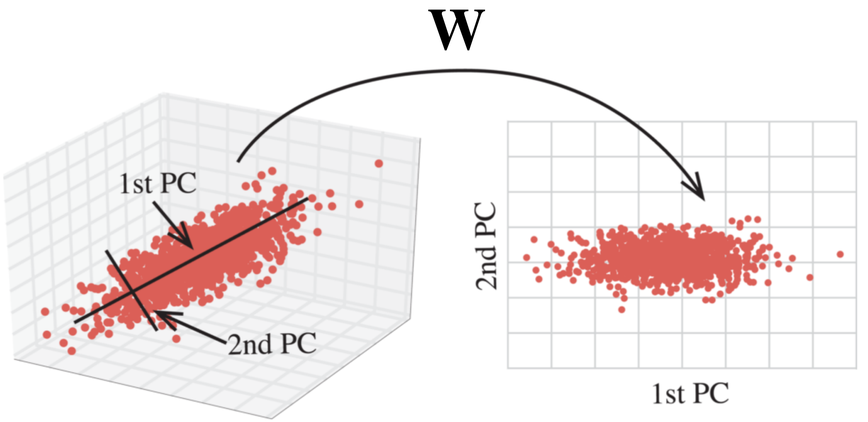

Adapted from Argelaguet*, Cuomo* et al. Nature Biotech 2021

# Latent variable models are a useful tool for global analysis and dimension reduction

PCA is widely used linear example that uses a linear mapping f that maps the observations $\mathbf{Y} \in \mathbb{R}^{N \times D}$ to latent representations $\mathbf{Z} \in \mathbb{R}^{N \times K}$ via an orthogonal weight matrix $\mathbf{W} \in \mathbb{R}^{D \times K}$.

Naive approach: Concatenation



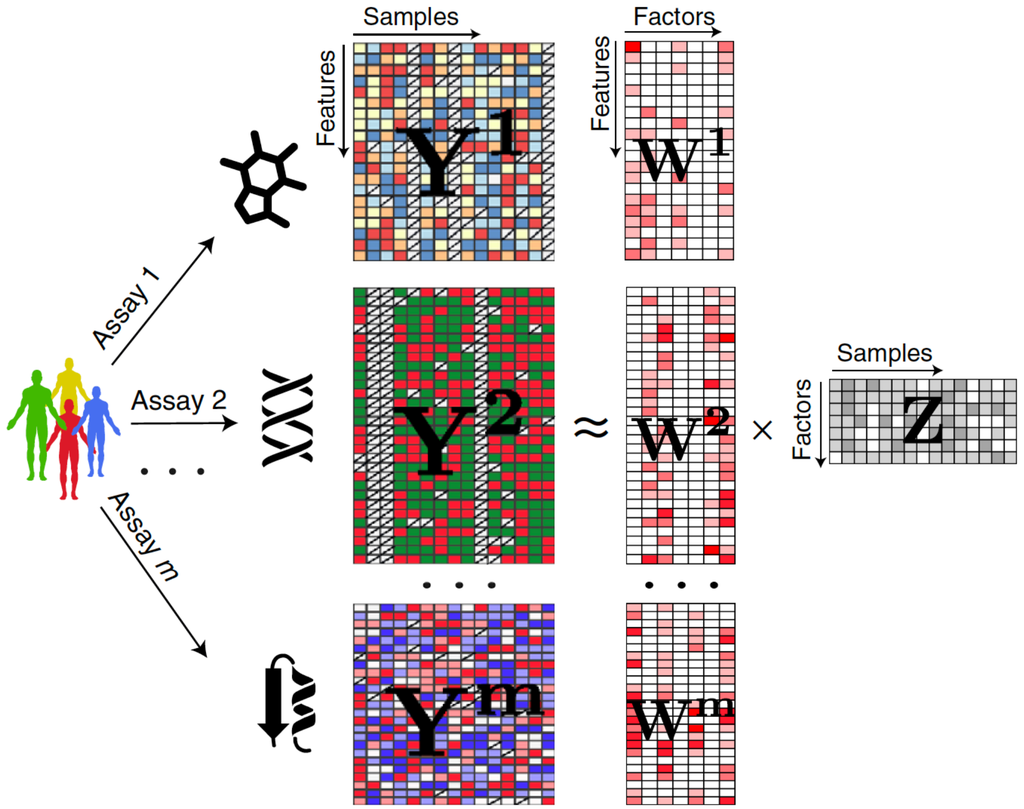




**Problems:**

- Does not respect heterogeneity of data modalities
- Cannot provide information on the relationships between data modalities (only between individual features)
- Data modalities with many features dominate the embedding

# MOFA extend PCA to multiple layers using *structured* matrix factorisation

**Bayesian factor model** to infer a joint low-dimensional representation of multi-modal data in terms of (hidden) factors representing the principal axes of variation




- Interpretable model using a **two-level sparsity priors**
  - *Which modalities are important for a factor?*
  - *Which features are important for a factor?*

- **Scalable inference** using (stochastic) variational Bayes

MOFA: Argelaguet* & Velten* et al *Mol Sys Bio*. 2018
MOFA+: Argelaguet*, Arnol*, Bredikhin* et al *Genome Biology*. 2020

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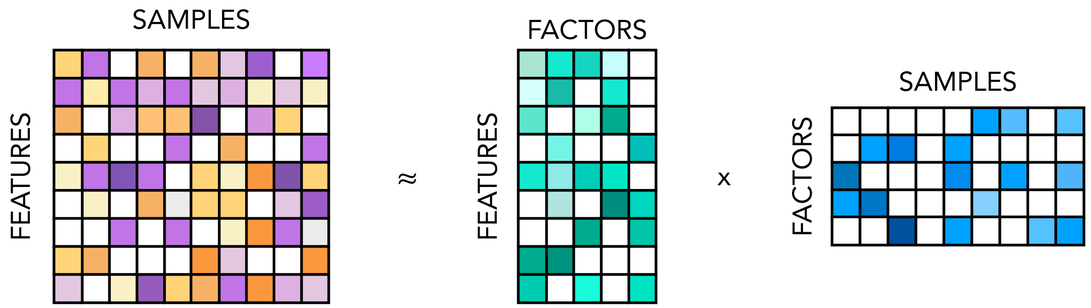
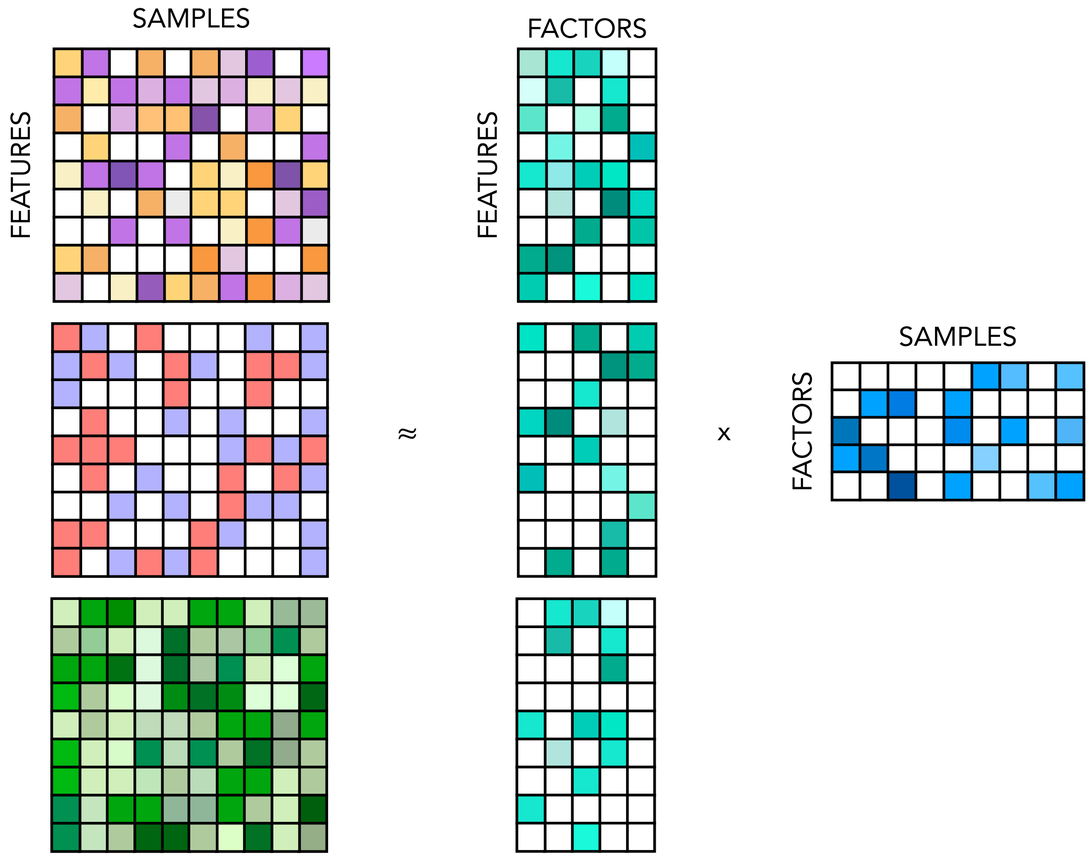
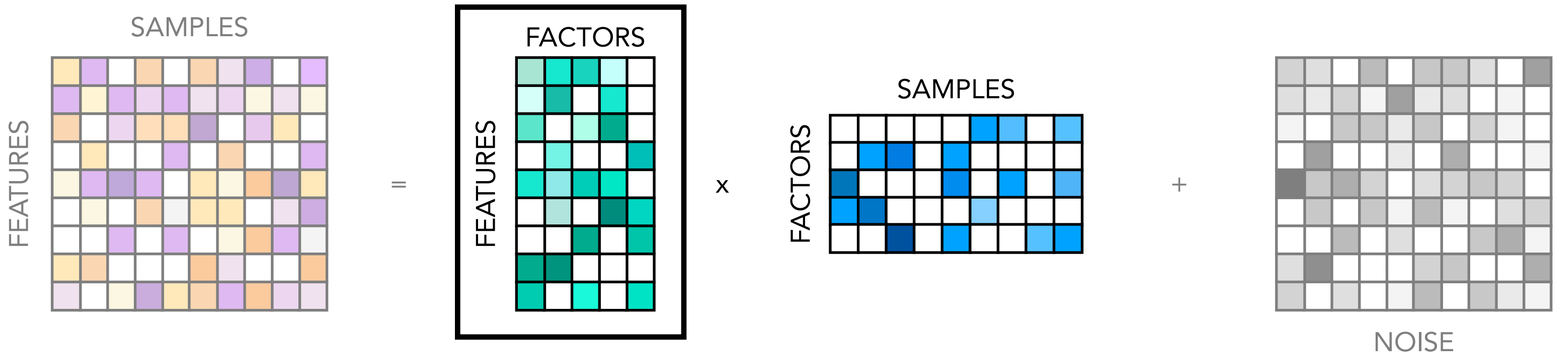
# MOFA is based on factor analysis

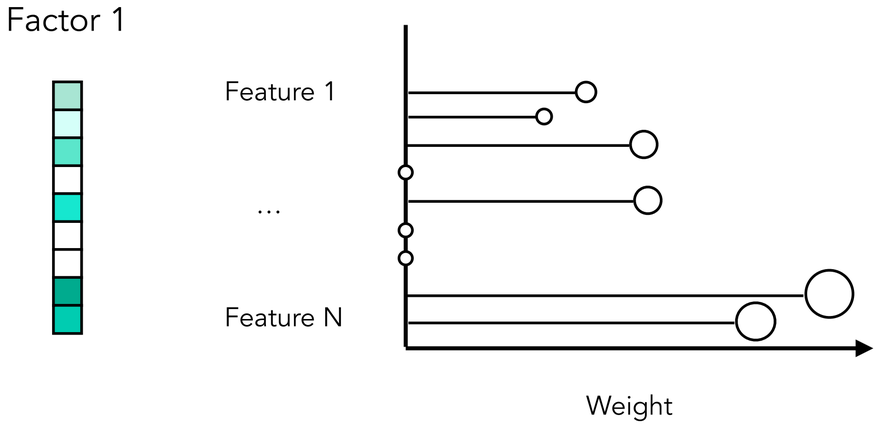


# Factor analysis can be extended to multi-view factor analysis



# What information can we get from the matrices?



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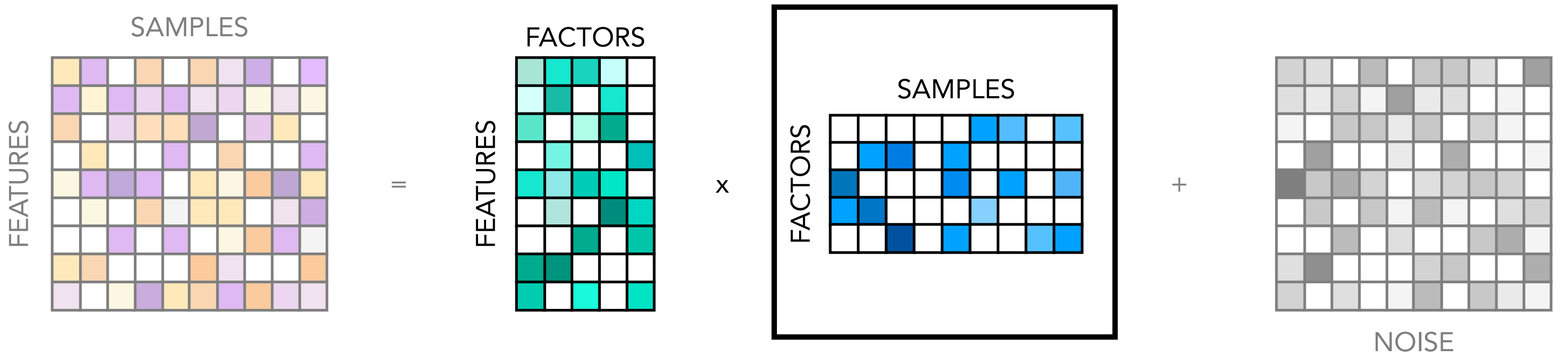
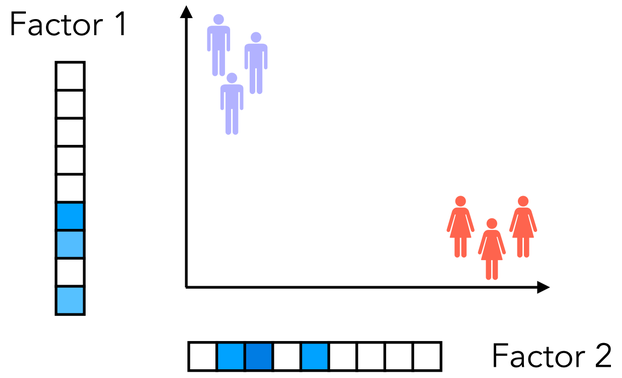
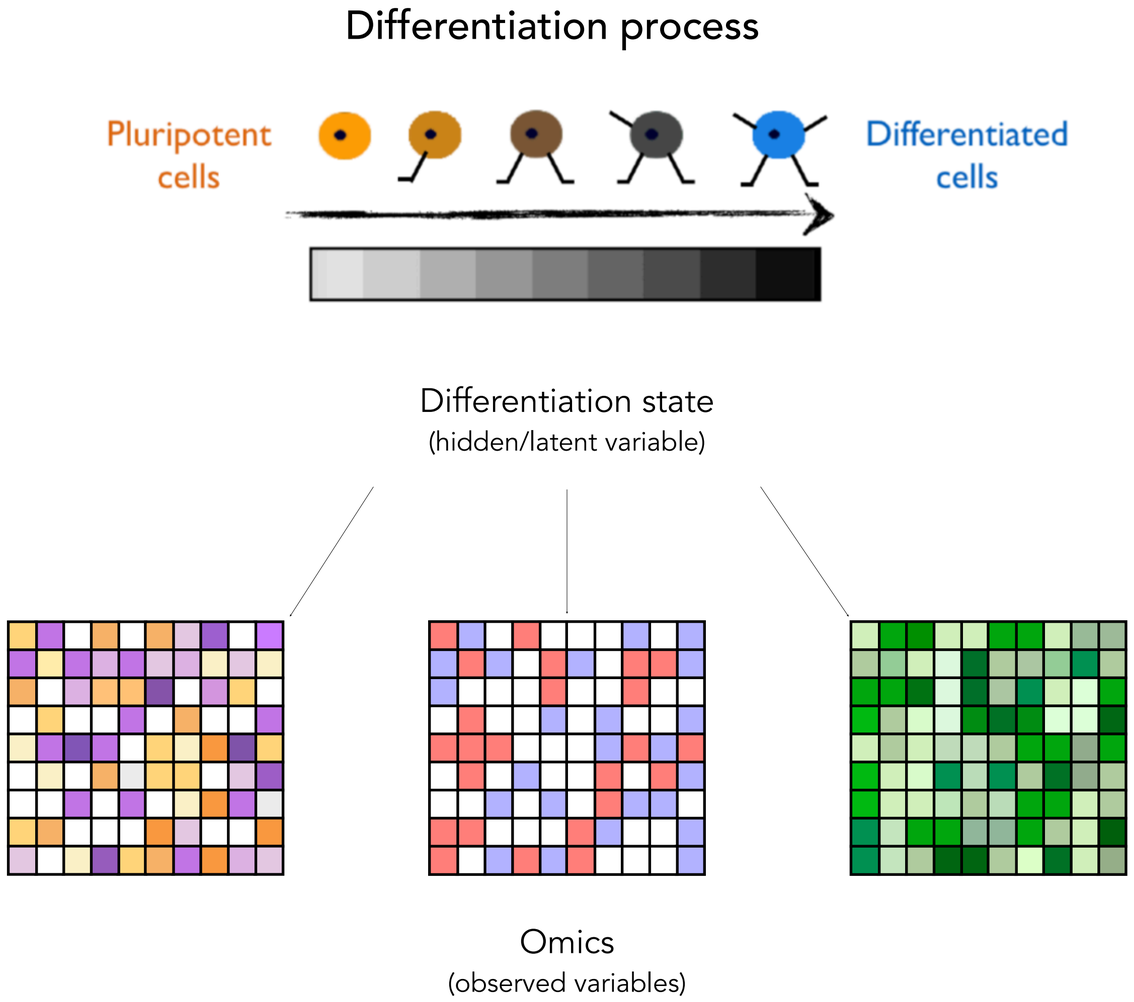
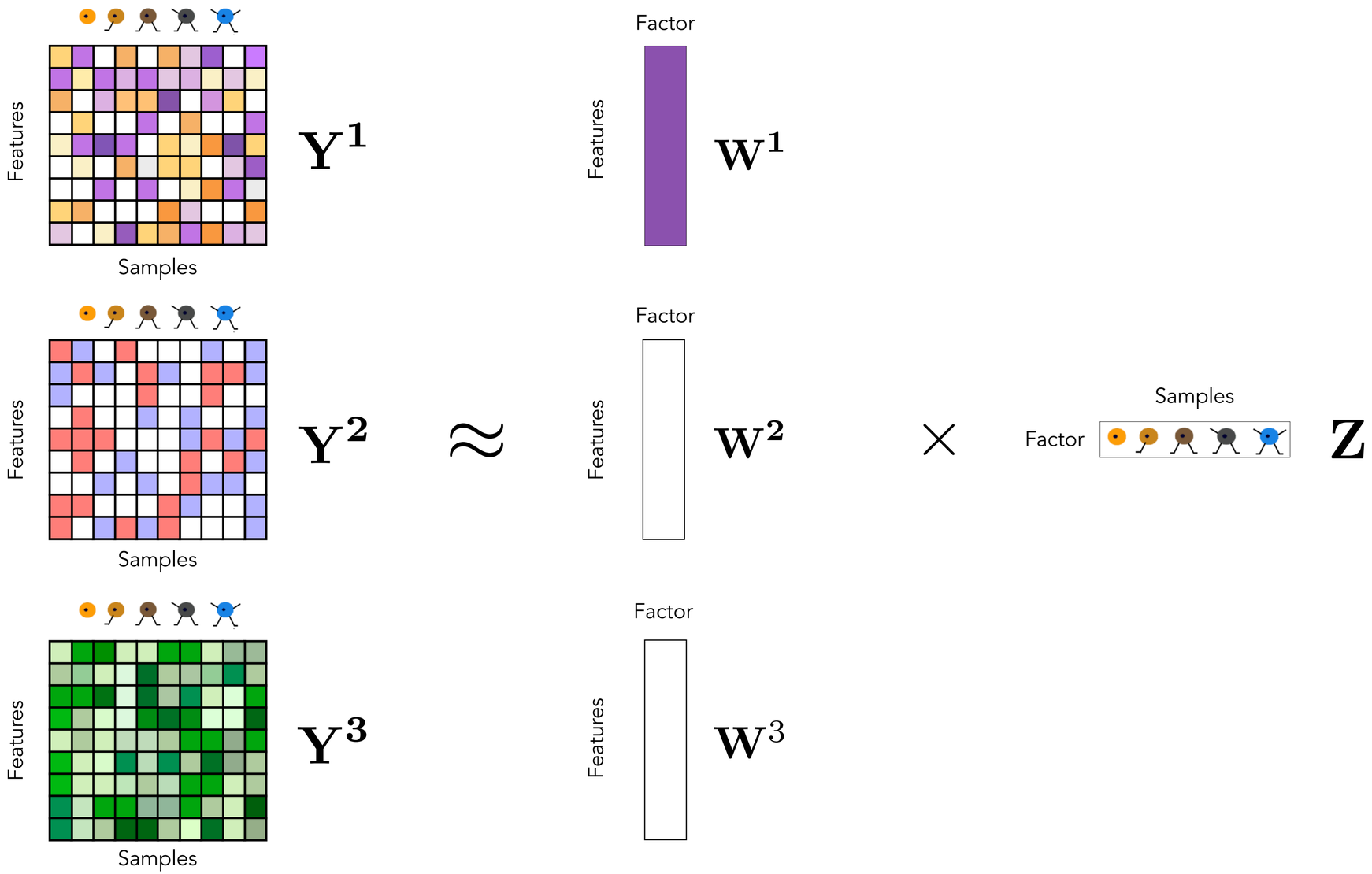


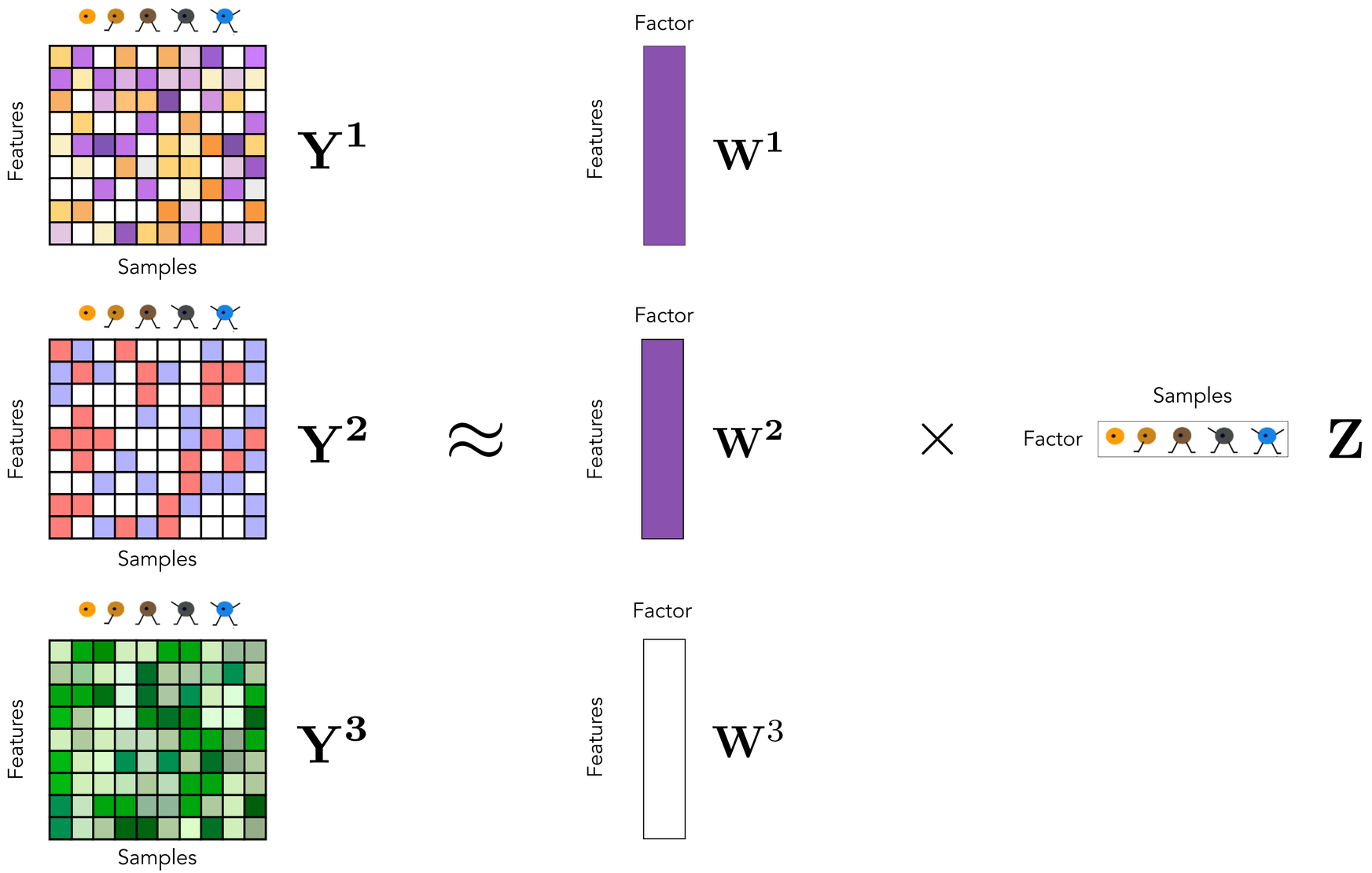
# Intuition behind MOFA



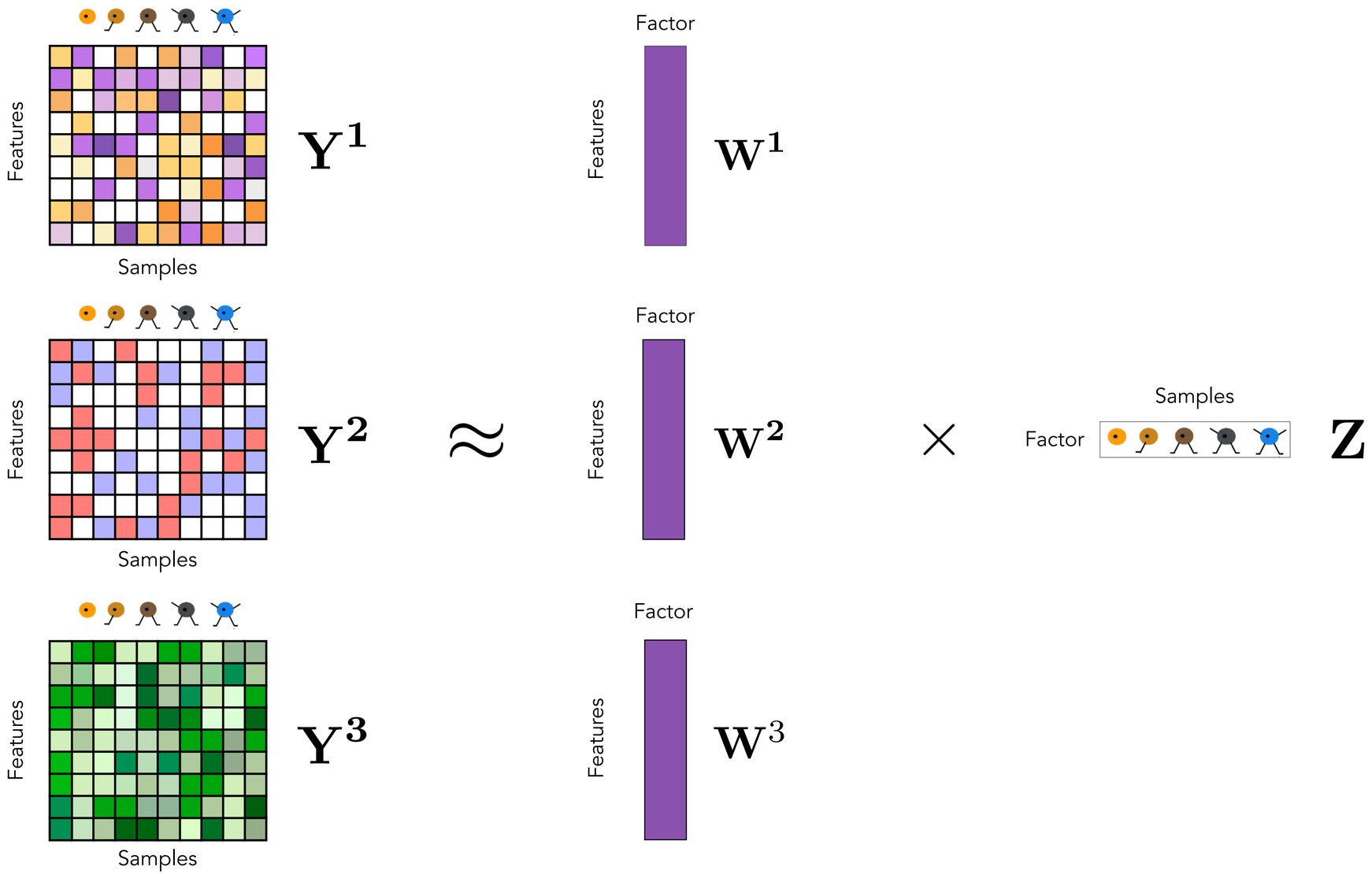
# The differentiation state is a driver of variation in transcriptomics only



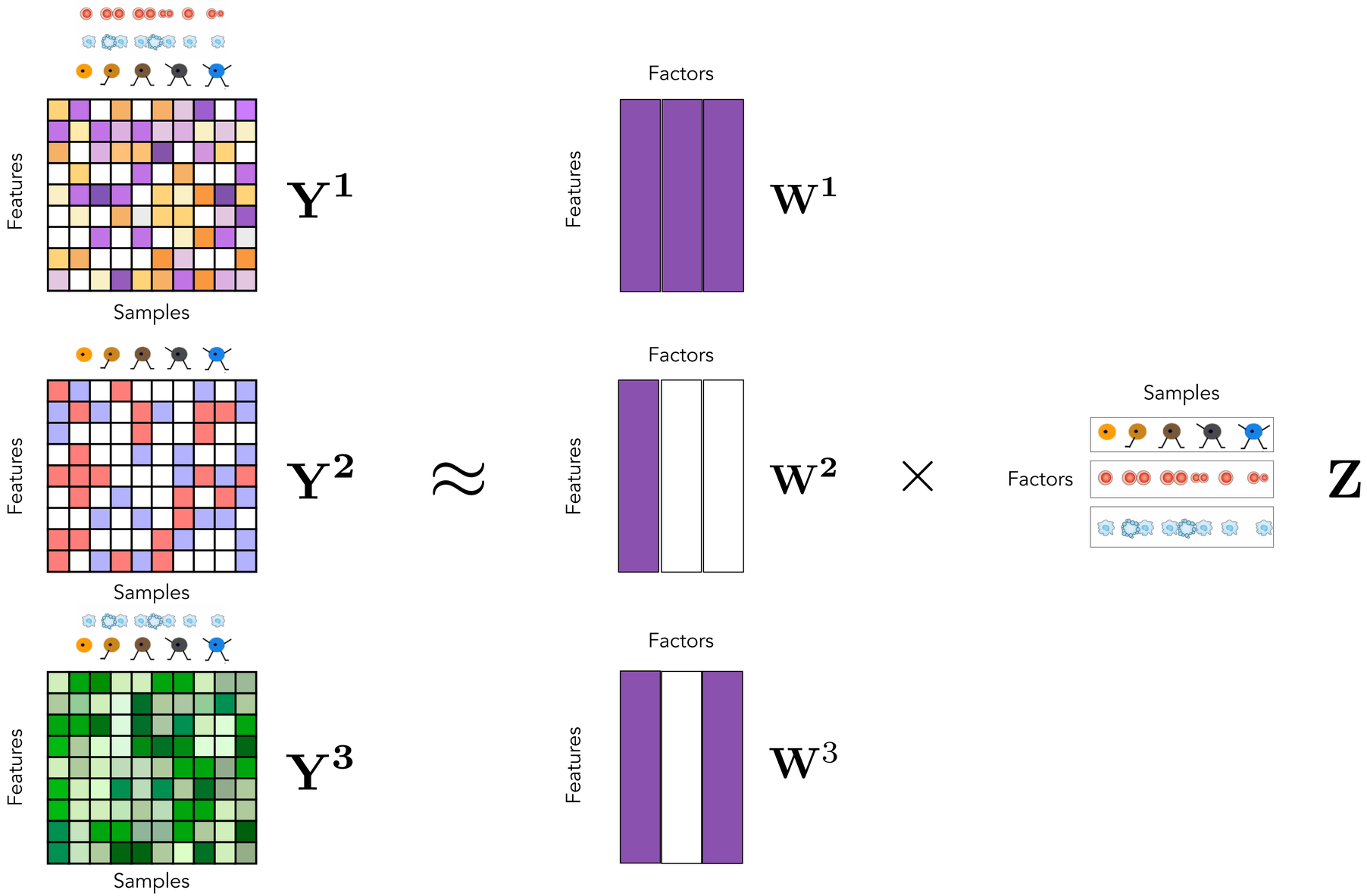
# The differentiation state is a driver of variation in transcriptomics and genomics



# The differentiation state is a driver of variation in all omics



# In addition, there can be other sources of variation



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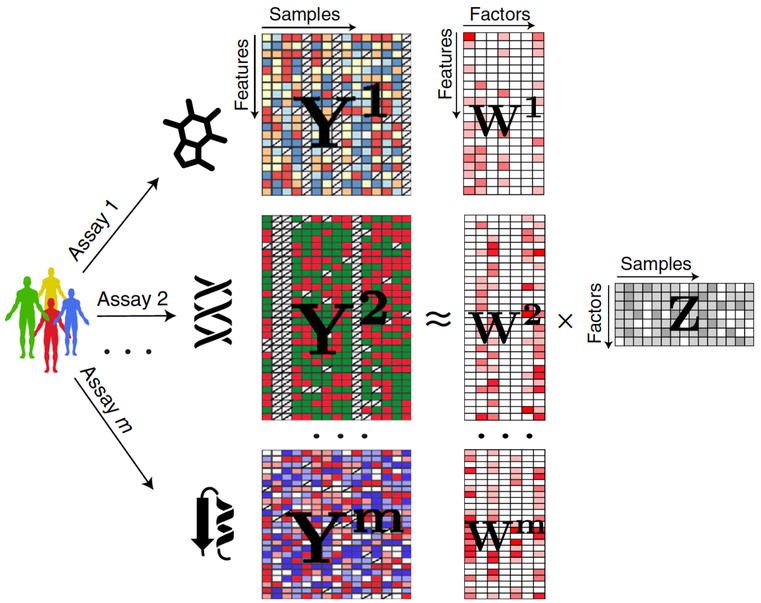
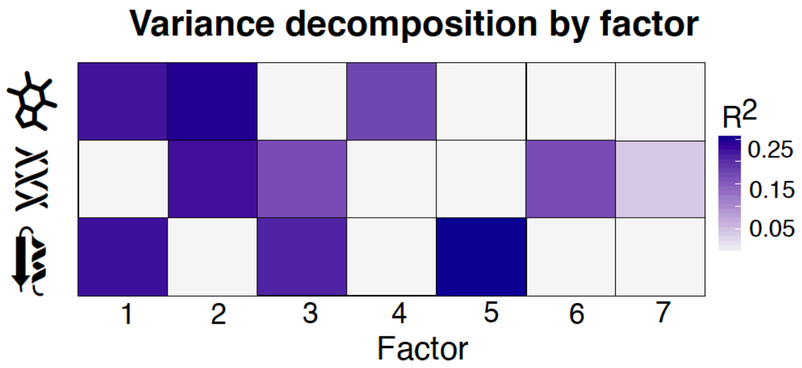
# Downstream analysis: Variance decomposition

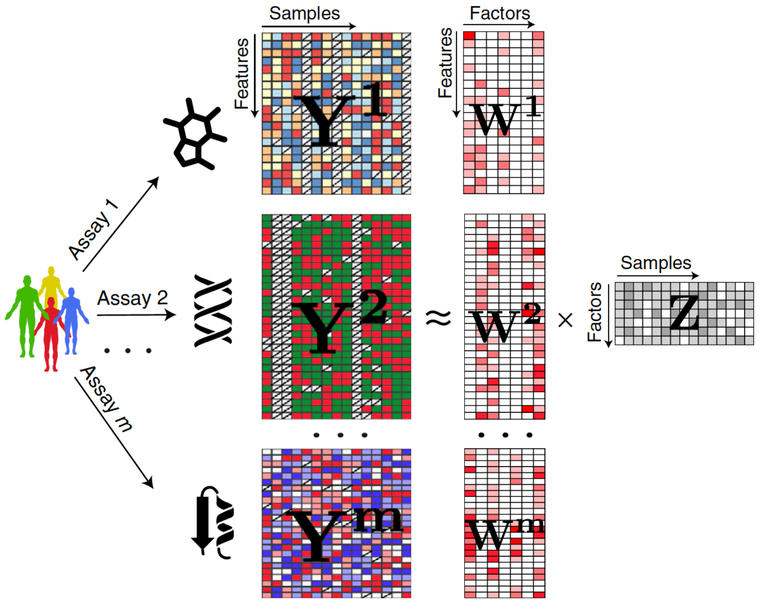
MOFA quantifies how much variance each factor explains in each view

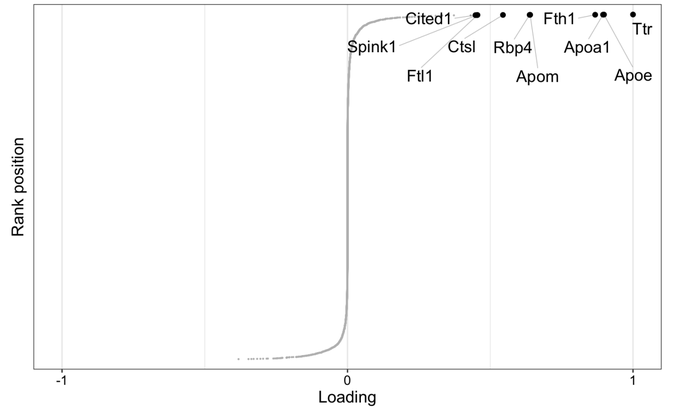


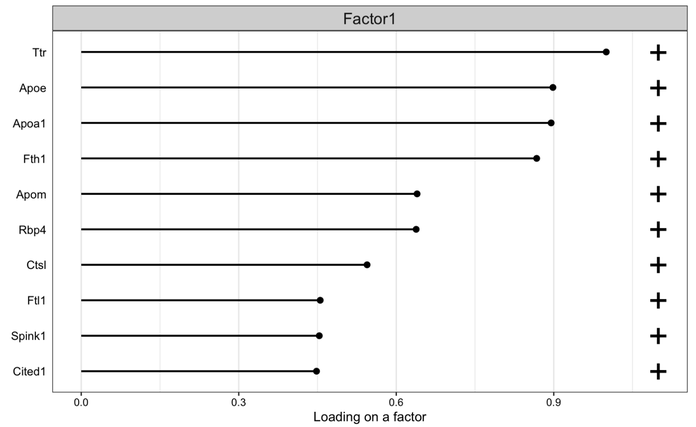



# Downstream analysis: Inspection of weights

Weights of a factor in each view can give insight into its molecular signature

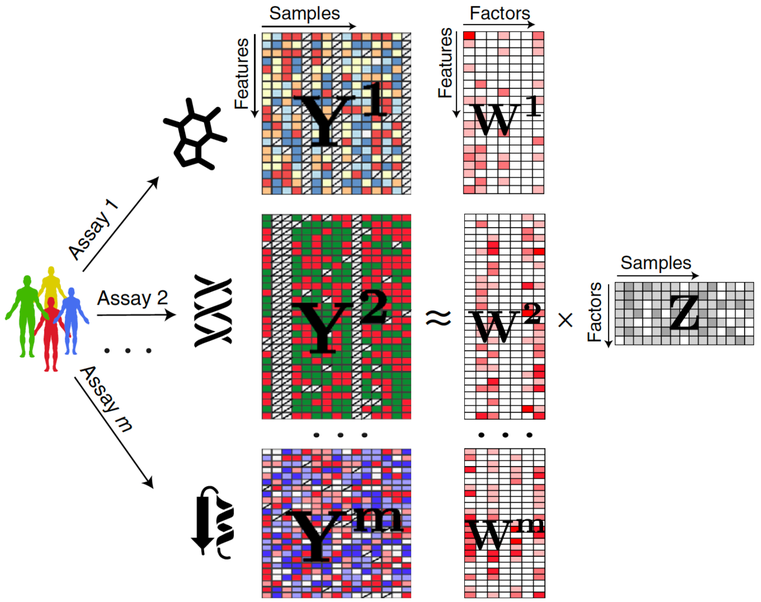


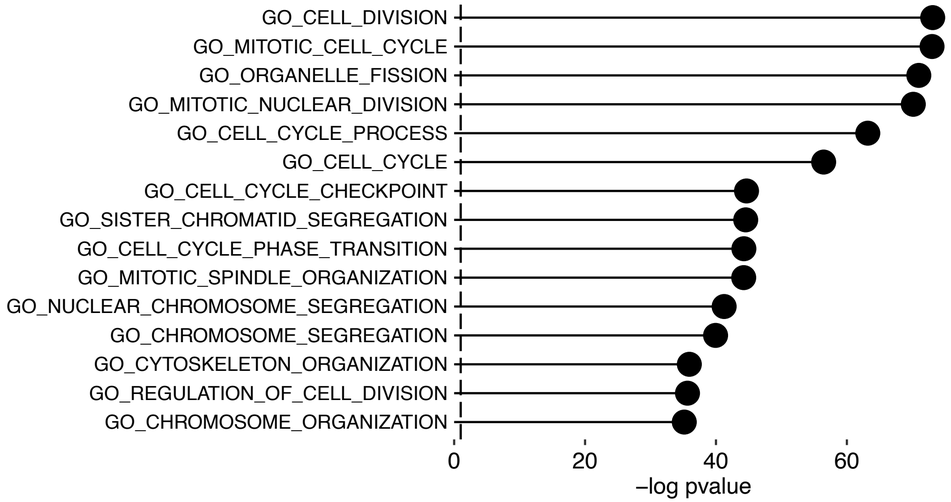



# Downstream analysis: Gene set enrichment analysis

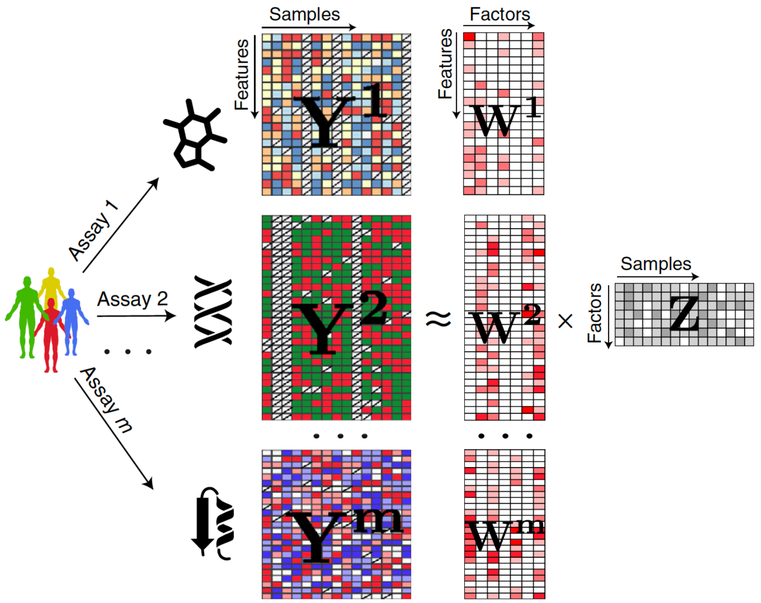
Enrichment analysis of the weights can be used to test for gene sets linked to a factor.

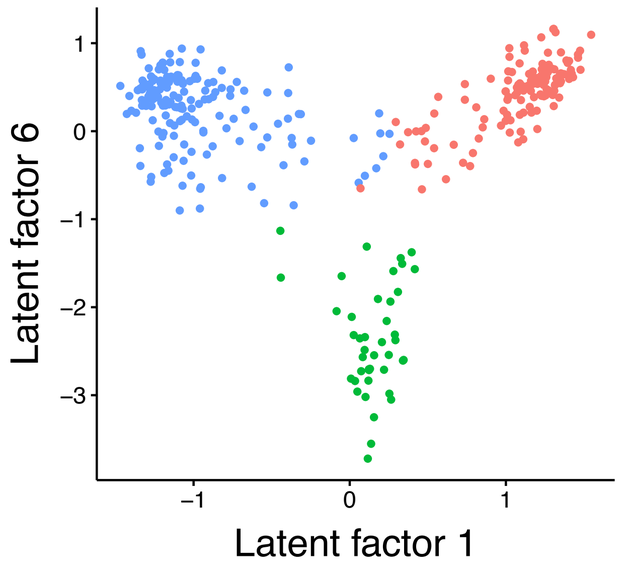


# Downstream analysis: Visualisation of samples in factor space

The factor space can be used to visualise or cluster samples or used as input for predictive models.



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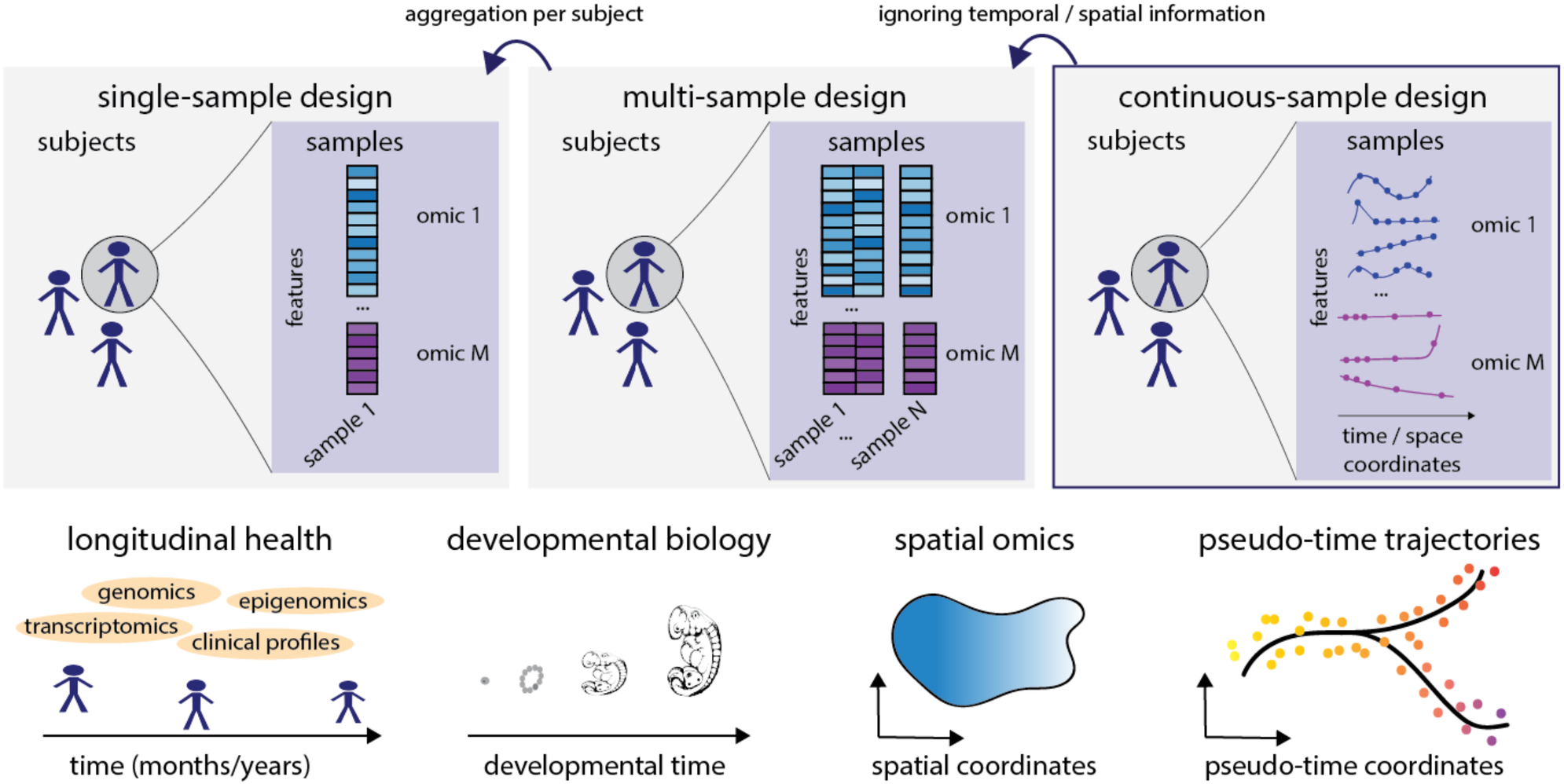
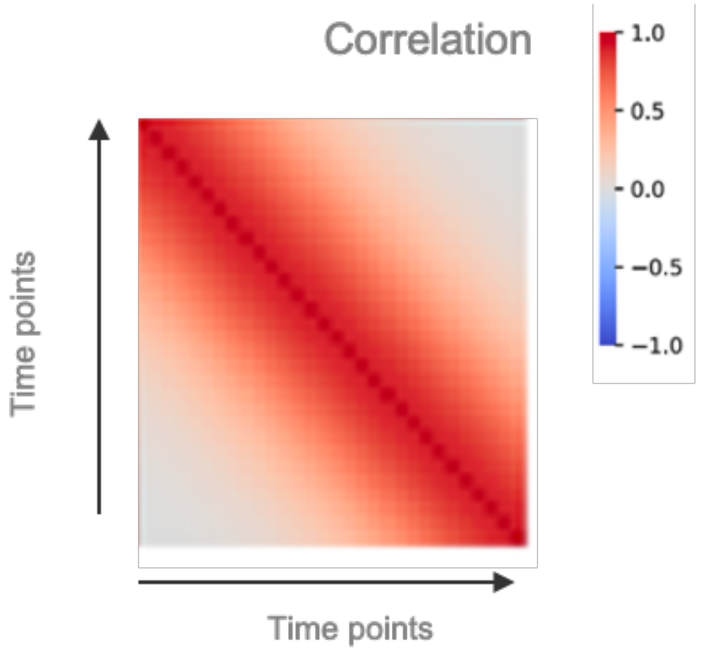
# Temporal and spatial resolution can give new insights into molecular dynamics and structures underlying biological processes

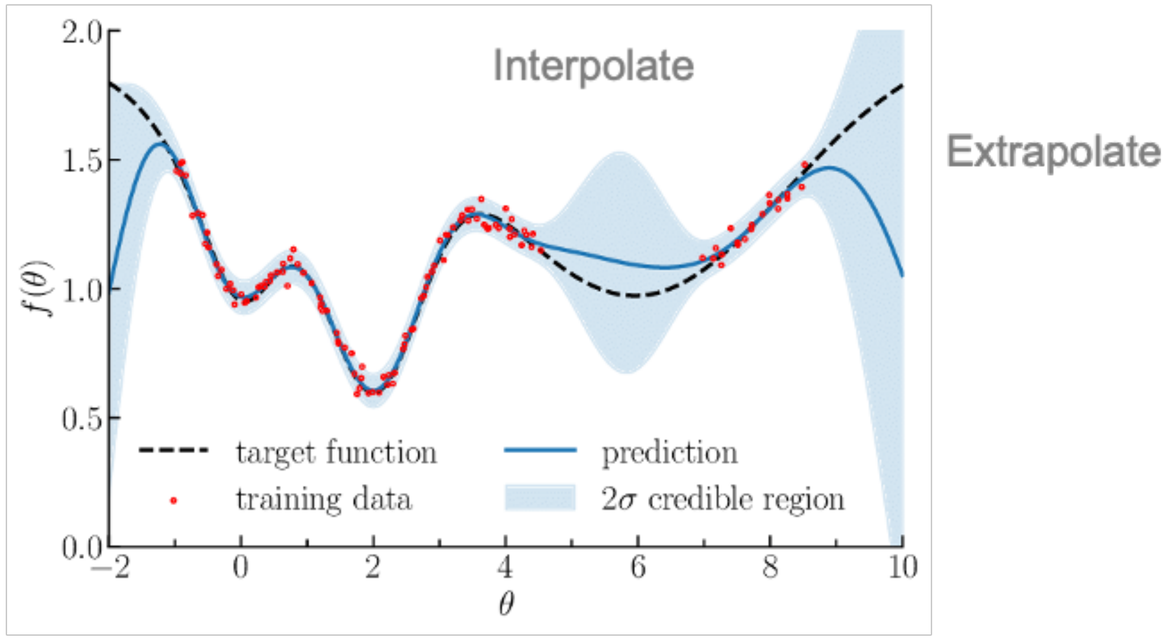



Velten & Stegle, Nath Methods 2023

# What is different in temporal and spatial data?

- Samples are **non-i.i.d**: Correlation across time points or spatial positions
- Assumptions of **smoothness** along time or space can help to
  - mitigate noise
  - interpolate or extrapolate to unmeasured time points or positions
- Need for **alignment** of temporal or spatial positions




Florent Leclercq, 2018

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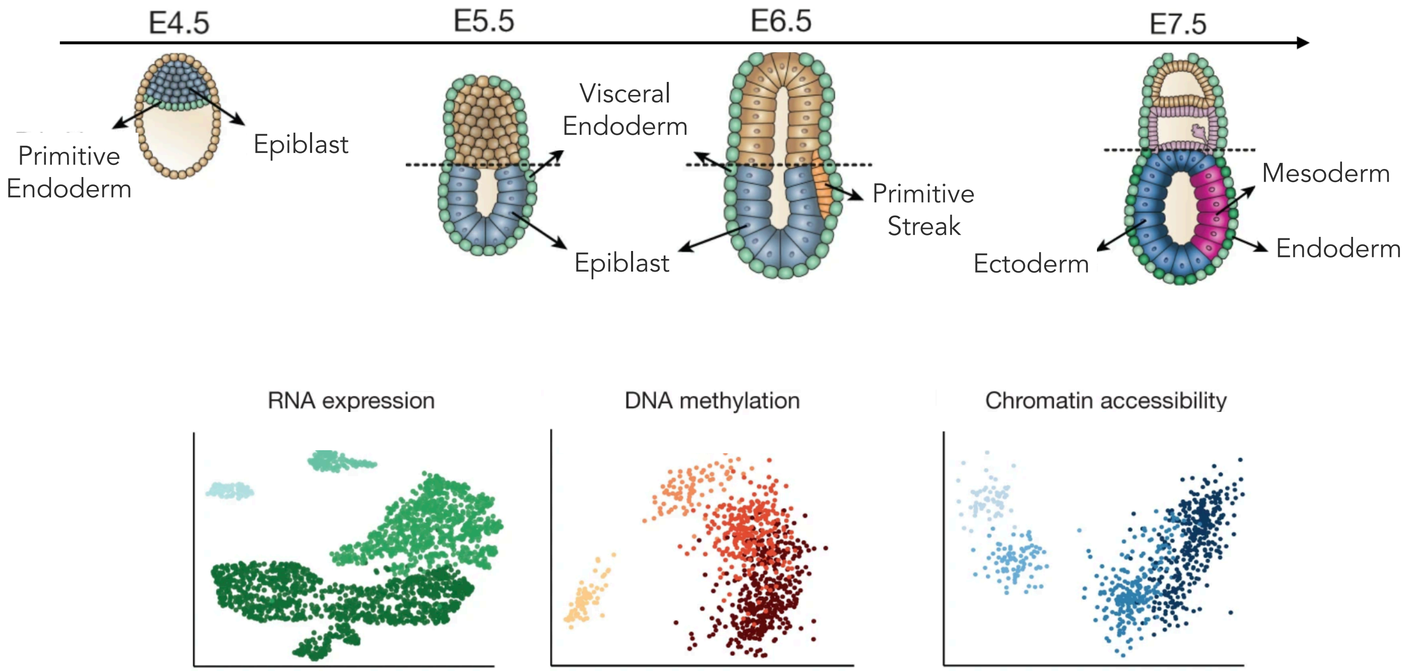
Article | Published: 11 December 2019

# Multi-omics profiling of mouse gastrulation at single-cell resolution

Ricard Argelaguet, Stephen J. Clark ✉, Hisham Mohammed, L. Carine Stapel, Christel Krueger, Chantriolnt-Andreas Kapourani, Ivan Imaz-Rosshandler, Tim Lohoff, Yunlong Xiang, Courtney W. Hanna, Sebastien Smallwood, Ximena Ibarra-Soria, Florian Buettner, Guido Sanguinetti, Wei Xie, Felix Krueger, Berthold Göttgens, Peter J. Rugg-Gunn, Gavin Kelsey, Wendy Dean, Jennifer Nichols, Oliver Stegle ✉, John C. Marioni ✉ & Wolf Reik ✉

*Nature* **576**, 487–491 (2019) | Cite this article



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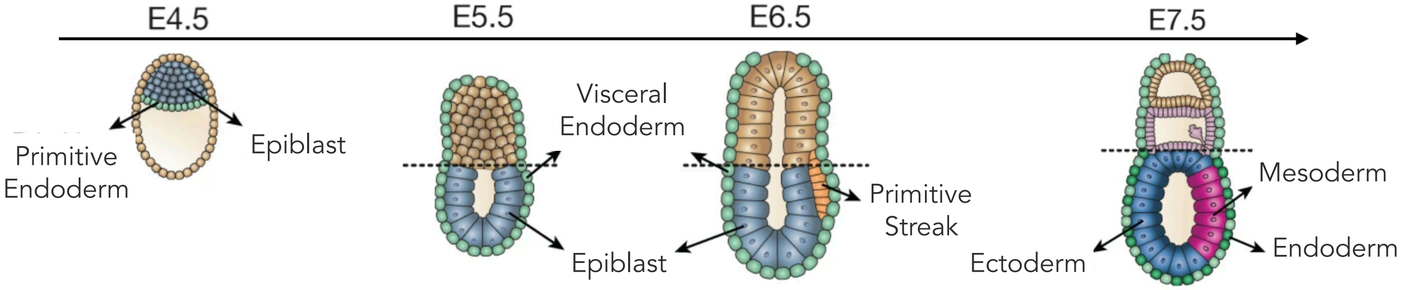
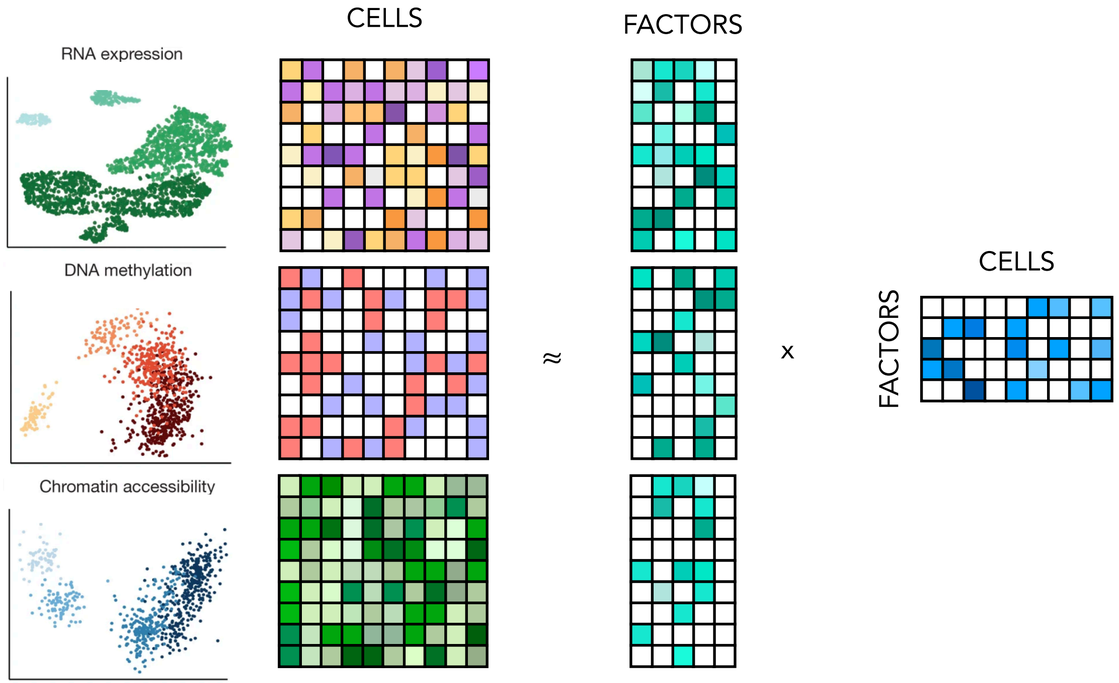



## 1. Multi-omics integration

**Goal**: uncover molecular coordination across omics and lineages




- Are certain factors shared across omics or specific to one modality?
- Which transcriptional programs are coordinated with epigenetic changes?
- Which cells are similar or distinct in their multi-omic profiles?

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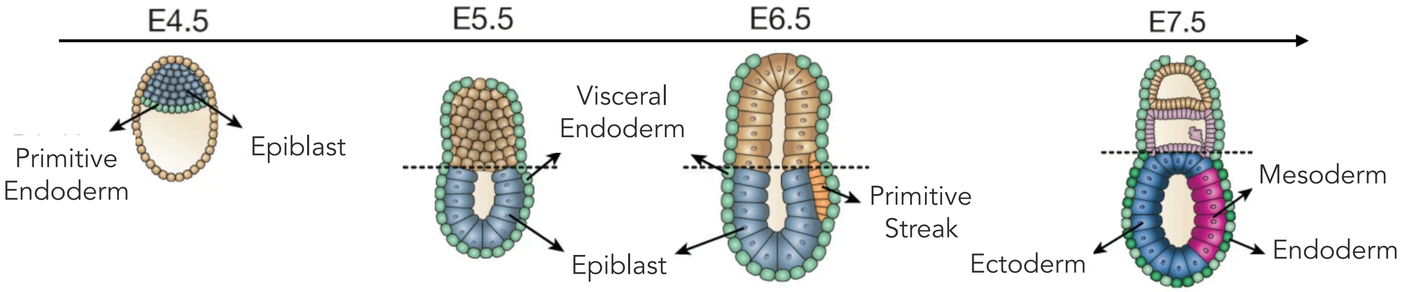
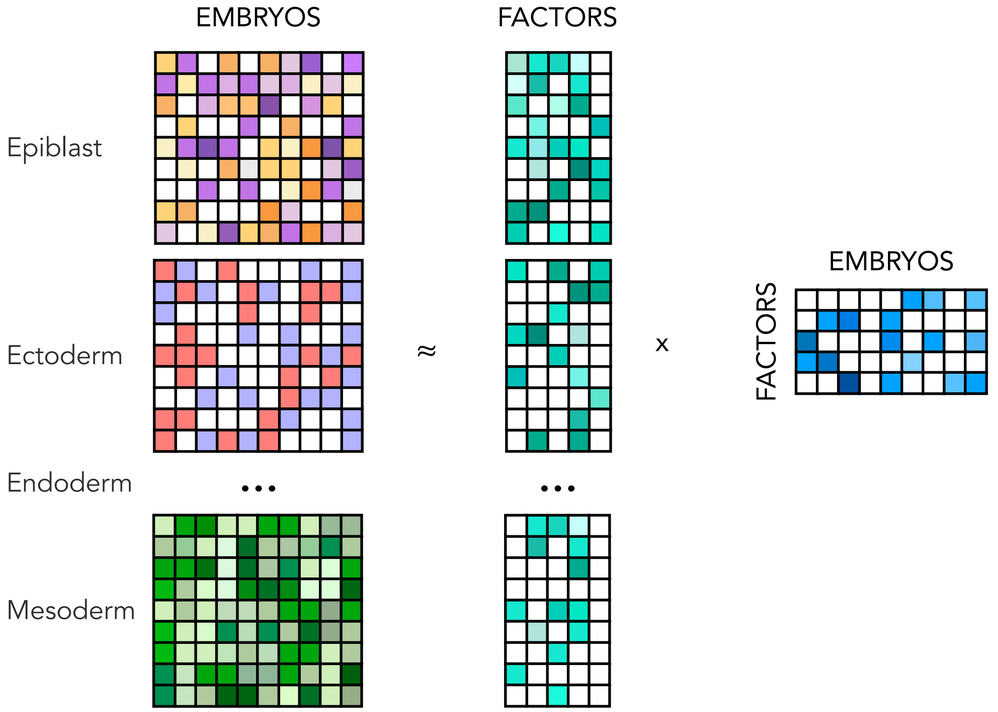



## 2. Cell lineage integration

**Goal**: uncover embryo-level programs across lineages: cross-lineage coordination




- Which embryo-level transcriptional programs are shared across multiple lineages?
- Which programs are lineage-specific, indicating unique differentiation pathways in particular lineages?
- How do these programs vary from embryo to embryo, and can we detect embryonic outliers or abnormal lineage patterns?

Article | Published: 11 December 2019

# Multi-omics profiling of mouse gastrulation at single-cell resolution

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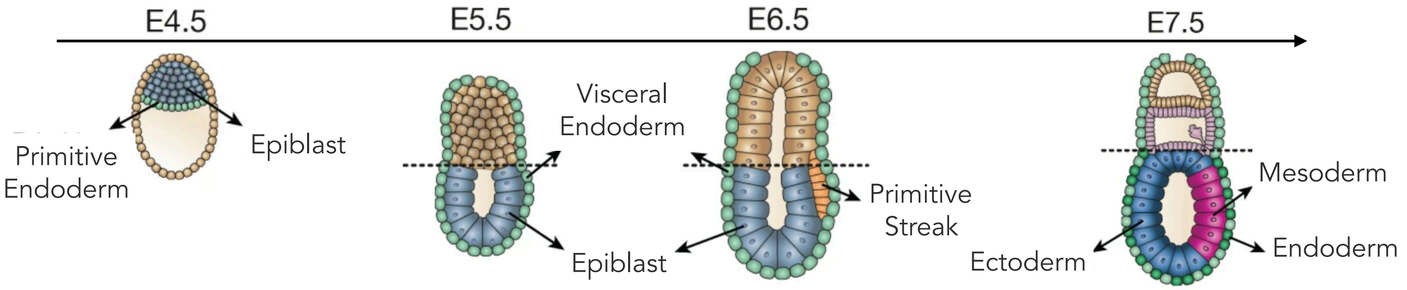
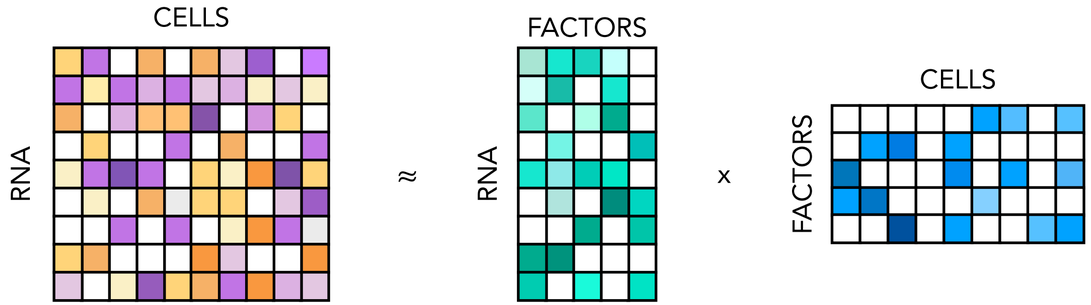



## 3. Stage modeling with MEFISTO

**Goal**: uncover smooth developmental programs across stages




- Which transcriptional programs evolve smoothly over development?
- Which genes drive each latent trajectory?