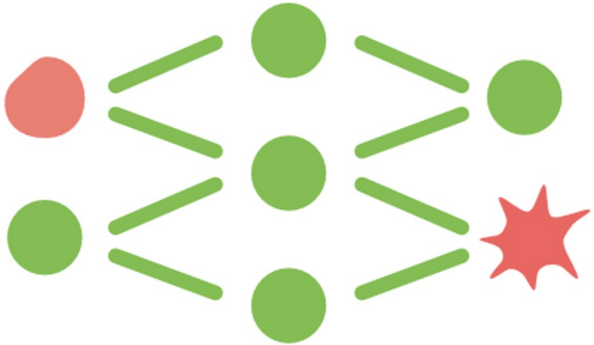
Deep Learning in Life Sciences



Models for multimodal data integration

Britta Velten
Heidelberg University
https://velten-group.org/

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SORBONNE UNIVERSITÉ
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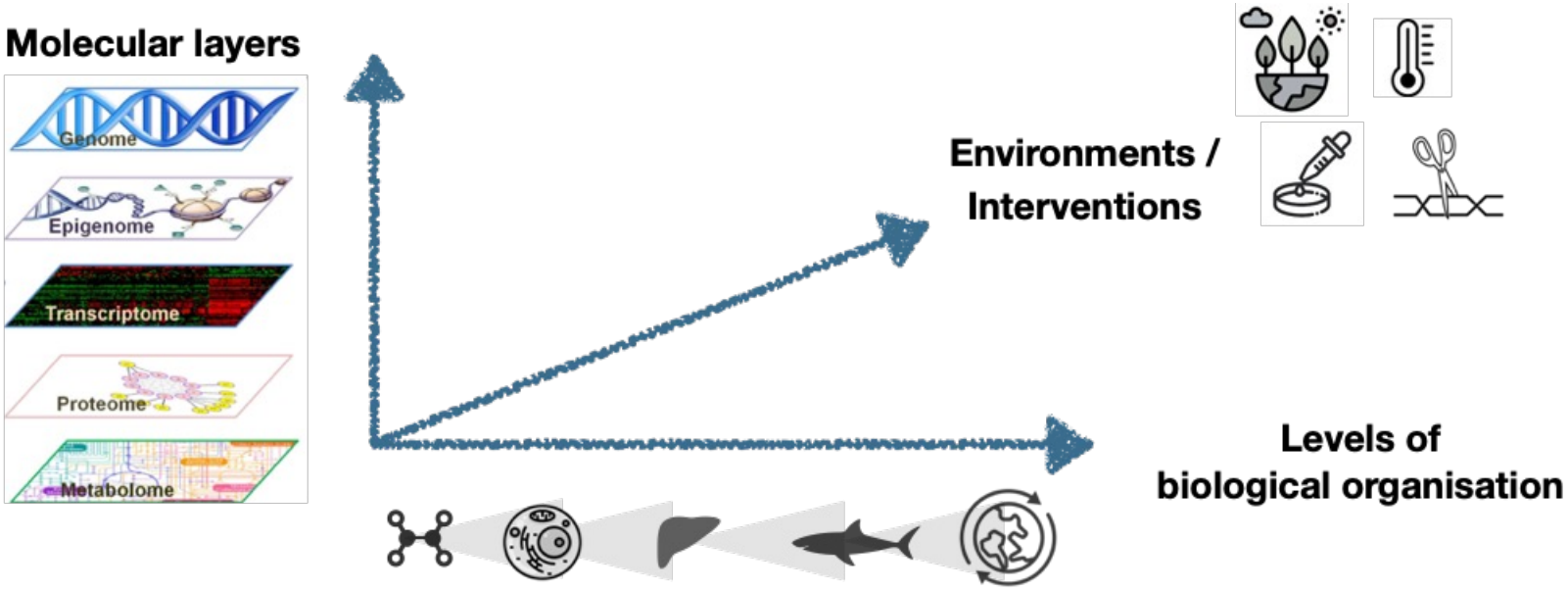
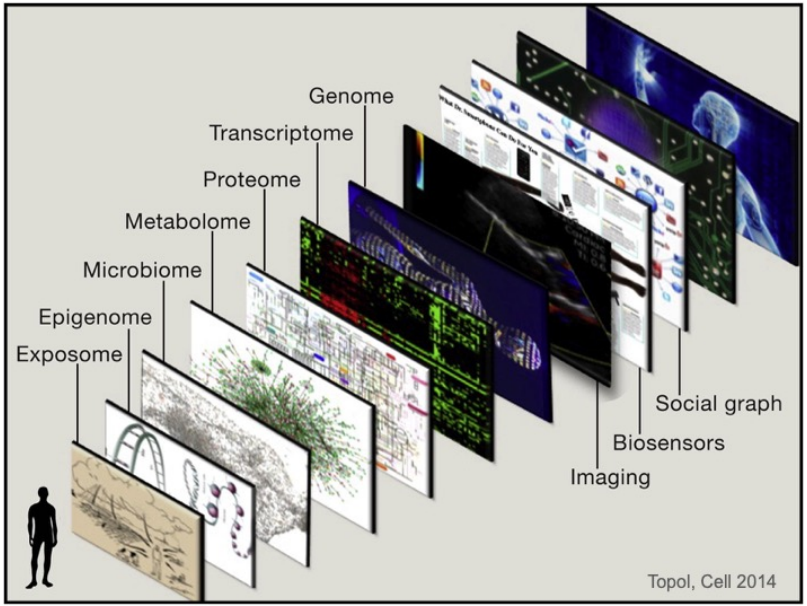
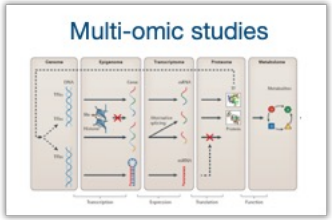
What are multi-modal data and why are they important?

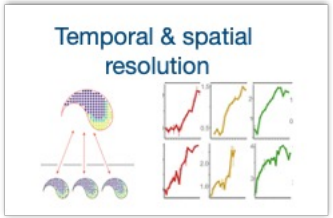
A holistic understanding of biological processes requires multi-dimensional approaches

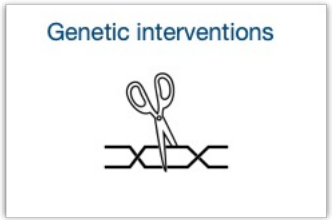


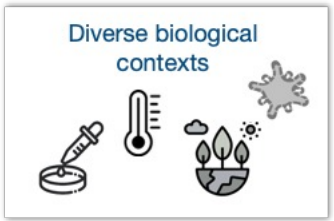
Technologies & data sources

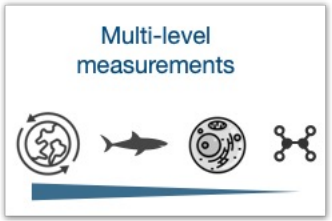






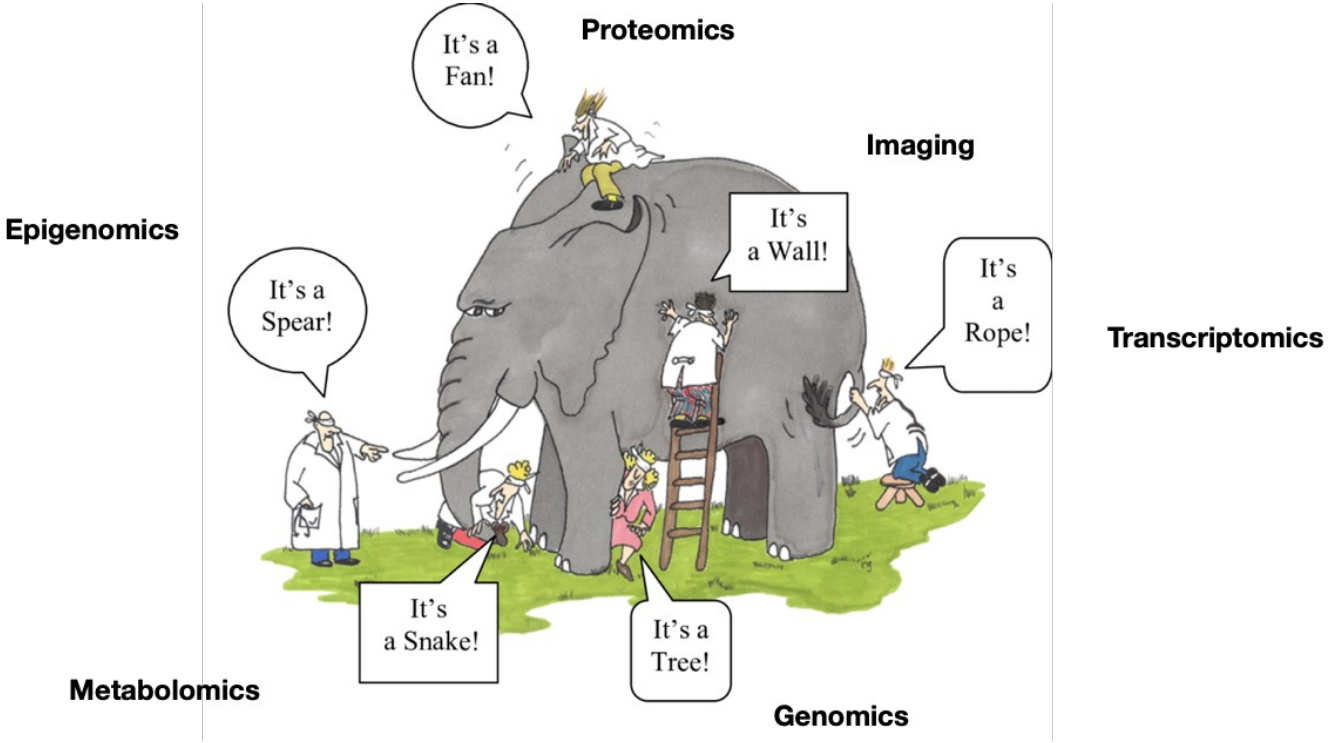






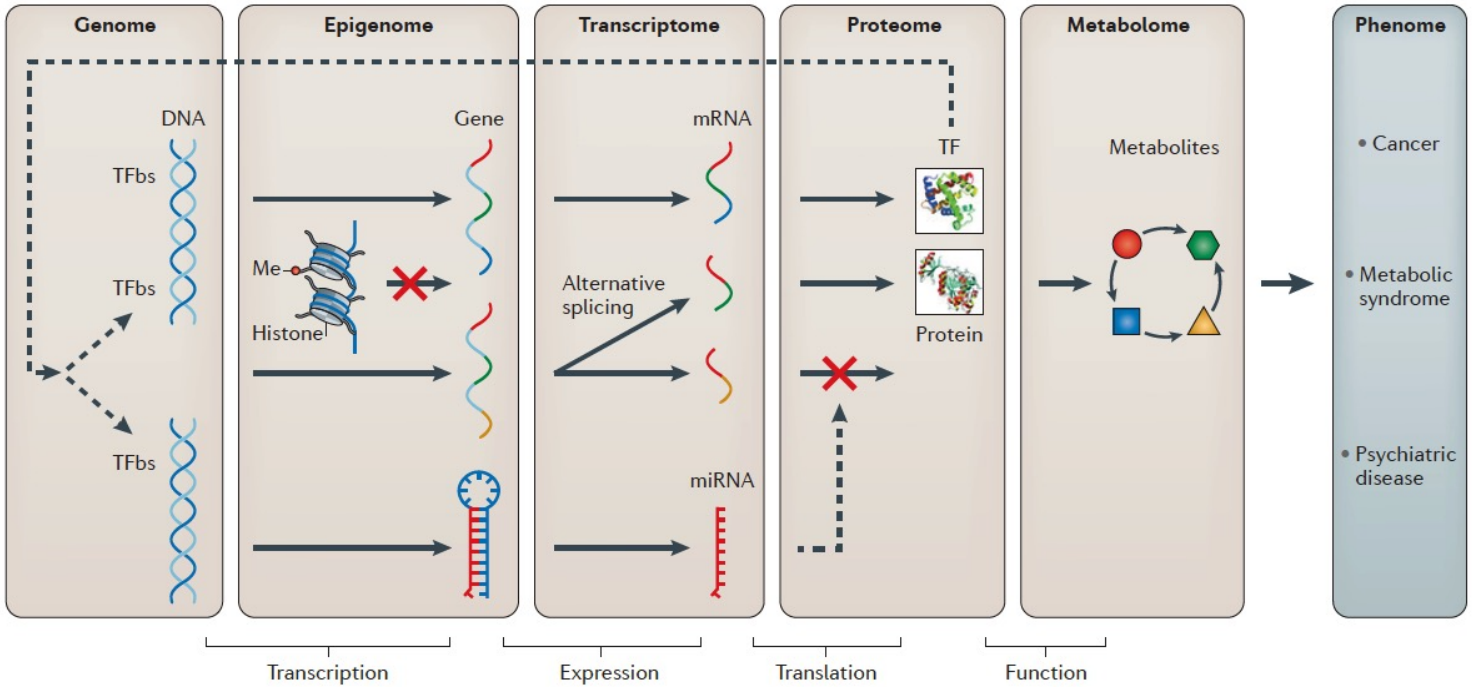
Challenge: *Interpretable data integration*

Limitations of single omics



Adapted from Daigneault, Methodological Innovations Online 2013

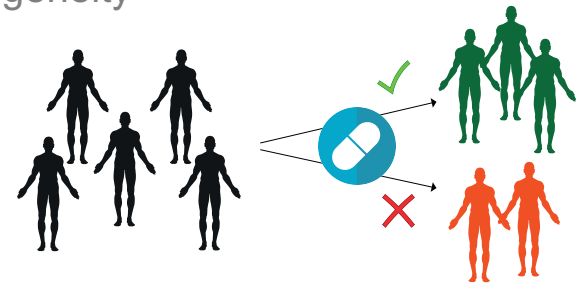
Interactions between molecular layers



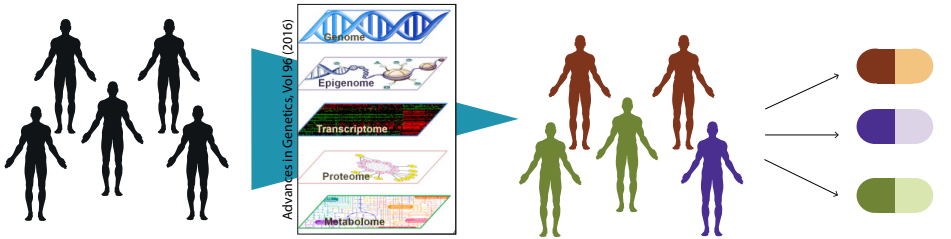
Ritchie et al, *Nat Rev Genet* 2015

Example 1: Precision Medicine

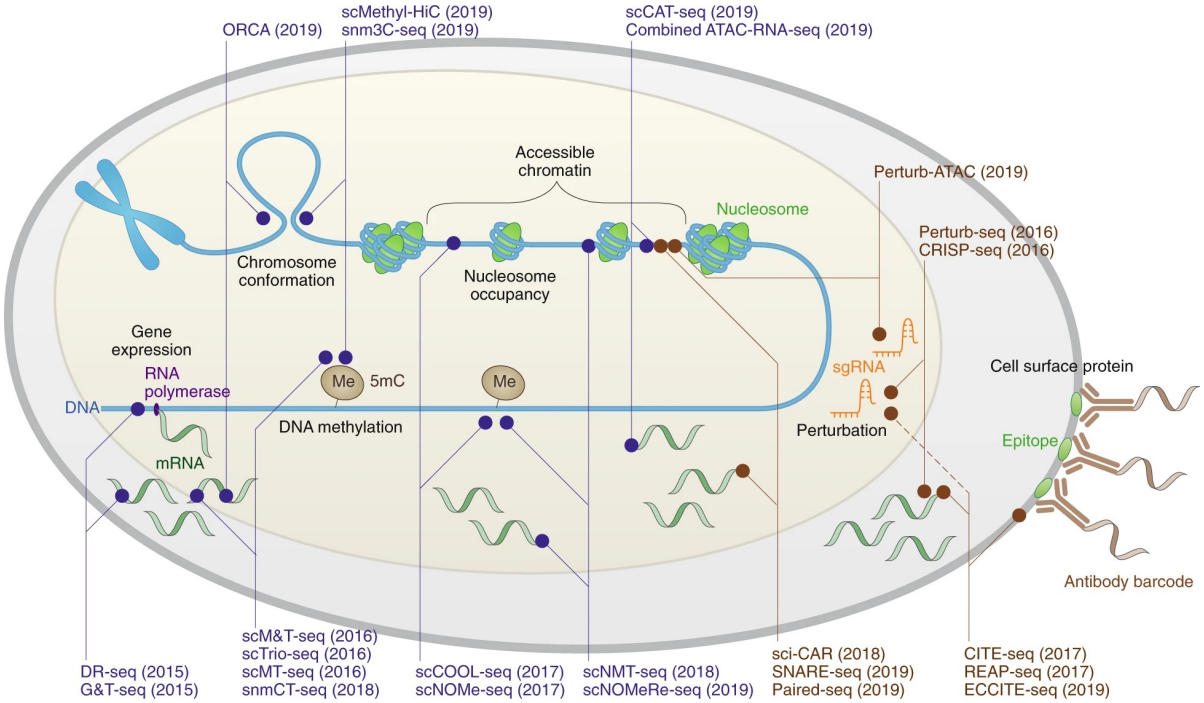
Challenge: Patient heterogeneity



Potential solution: Stratification based on multi-omics profiles

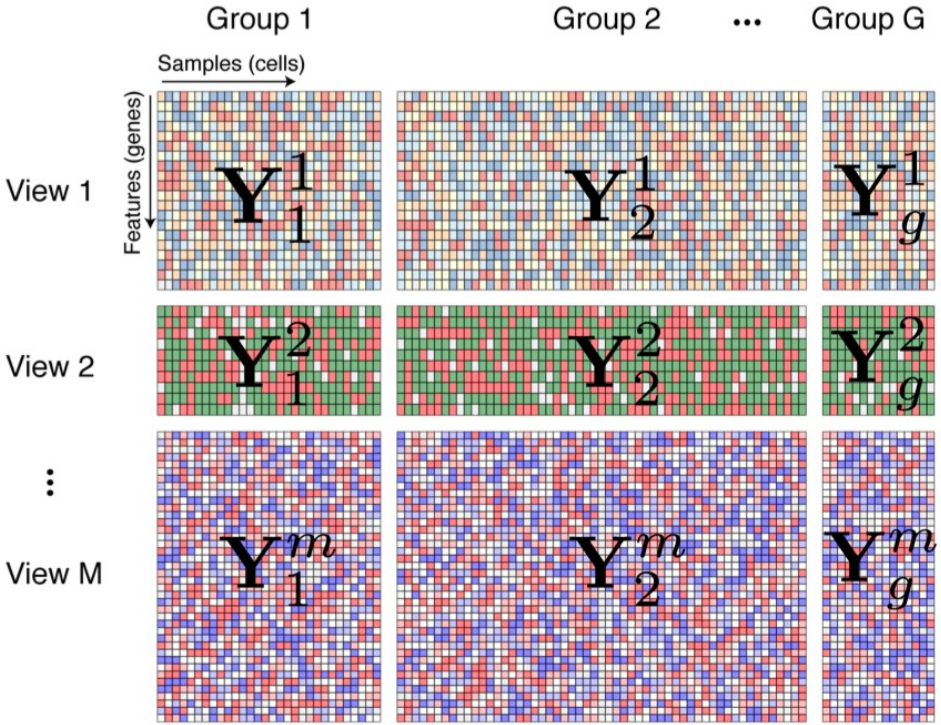


Example 2: Single cell biology



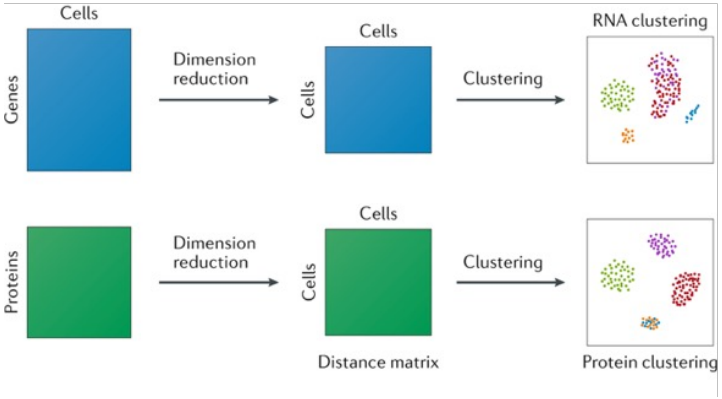
Zhu et al, Nat Meth 2020

Multi-modal data

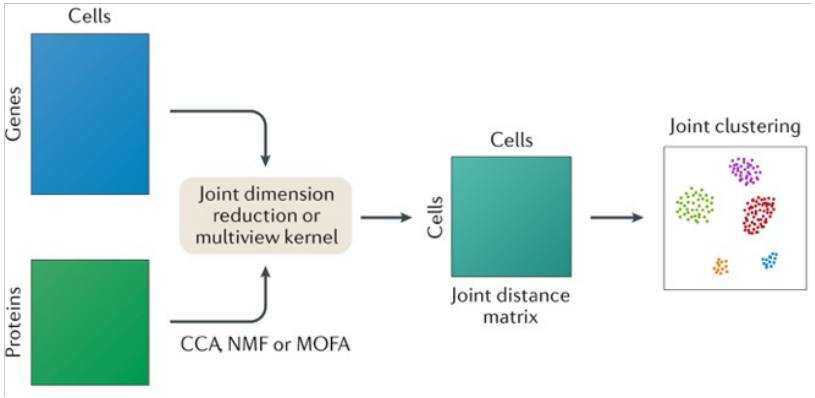


Why a joint analysis?

Separate analysis



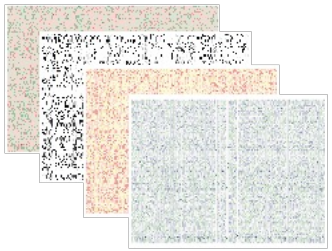
Joint analysis



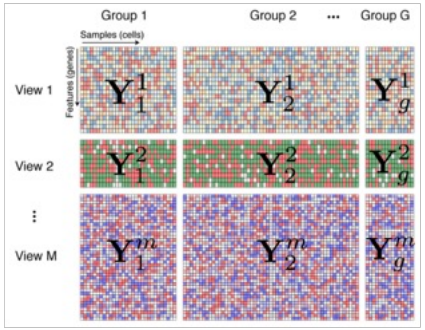
Adapted from Stuart & Satija, Nat Rev Gen 2019

Challenges

- **Heterogeneous data:** 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

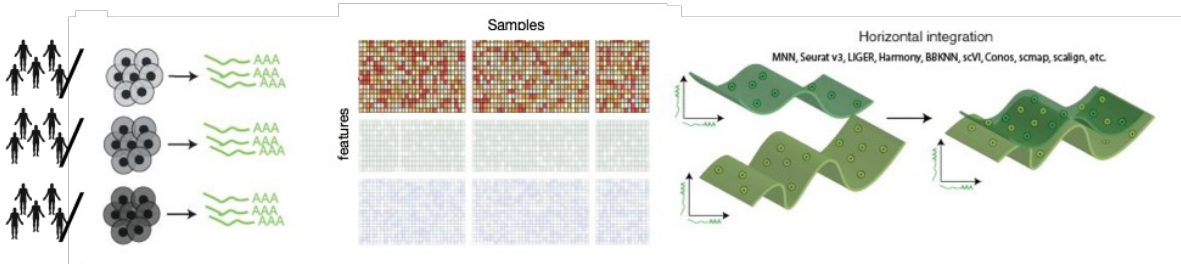


high-dimensional

How to integrate multi-modal data?

Step 1: Choose an anchor for integration

Horizontal integration
(features as anchors)

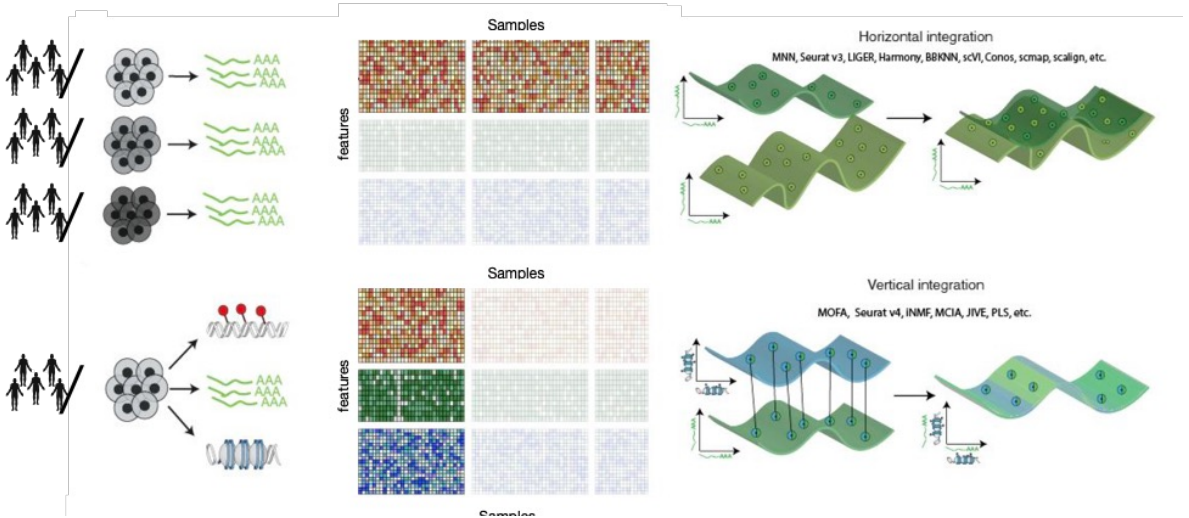


Adapted from Argelaguet*, Cuomo* et al. Nature Biotech 2021

Step 1: Choose an anchor for integration

Horizontal integration
(features as anchors)

Vertical integration
(samples as anchors)



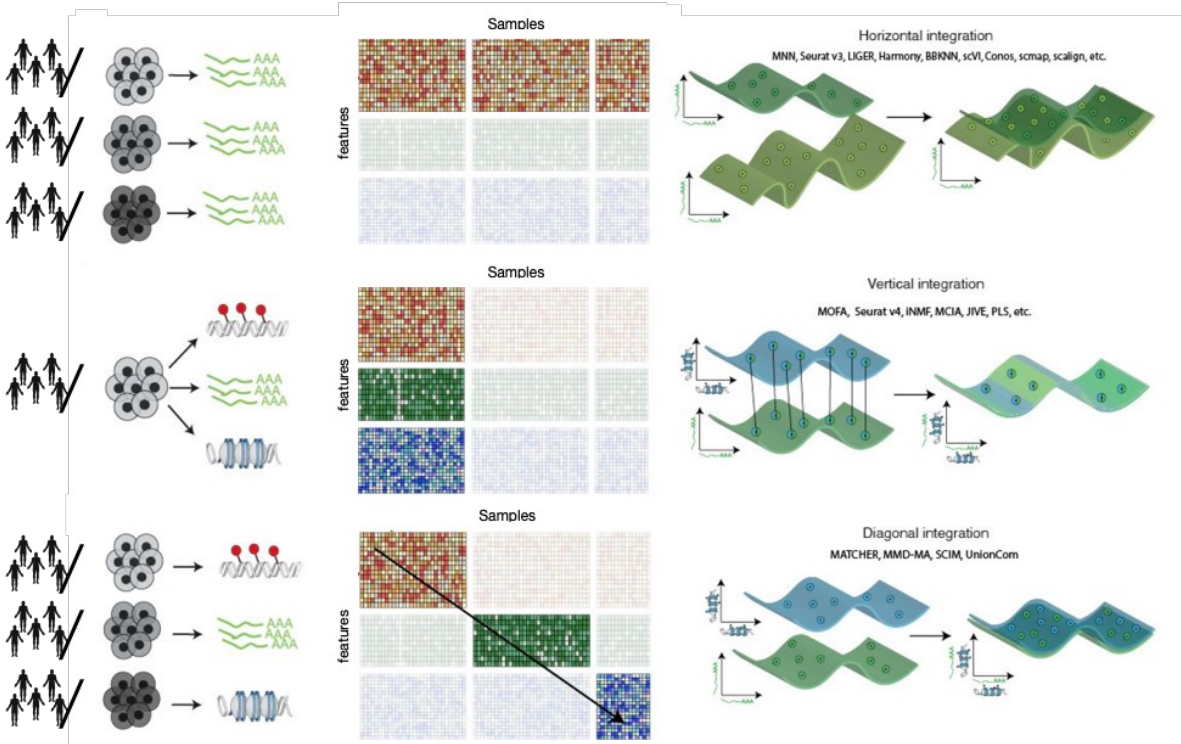
Adapted from Argelaguet*, Cuomo* et al. Nature Biotech 2021

Step 1: Choose an anchor for integration

Horizontal integration
(features as anchors)

Vertical integration
(samples as anchors)

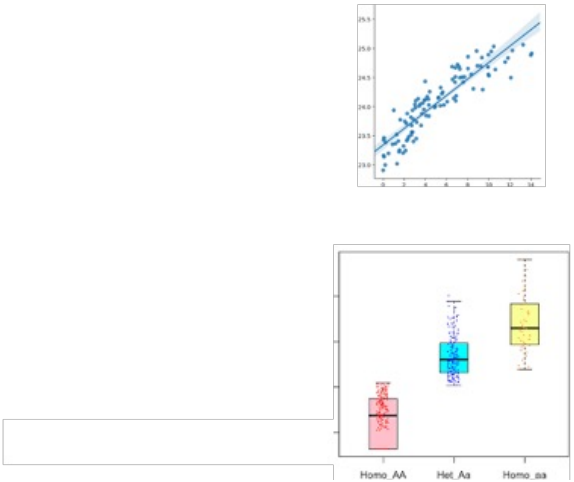
Diagonal integration
(no anchors)



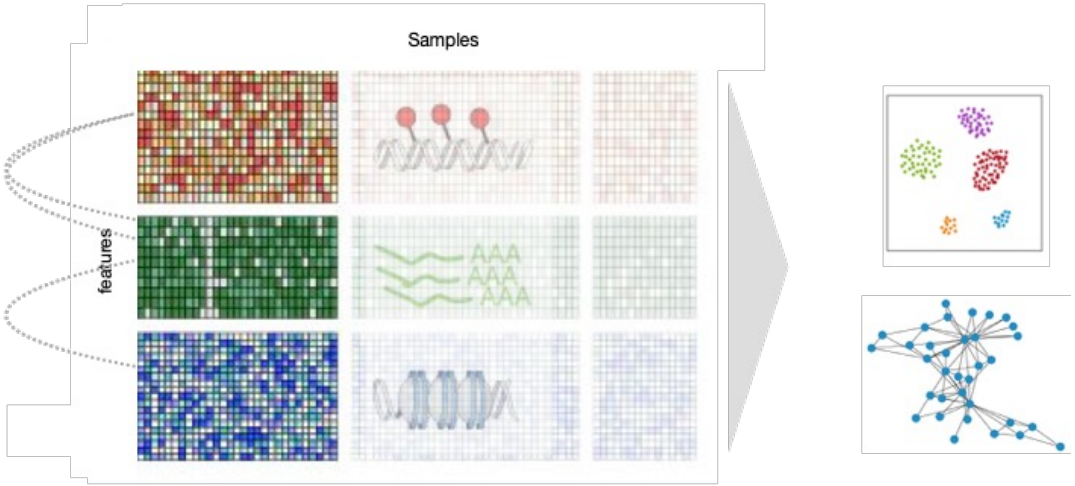
Adapted from Argelaguet*, Cuomo* et al. Nature Biotech 2021

Step 2: What type of associations?

Local analysis



Global analysis



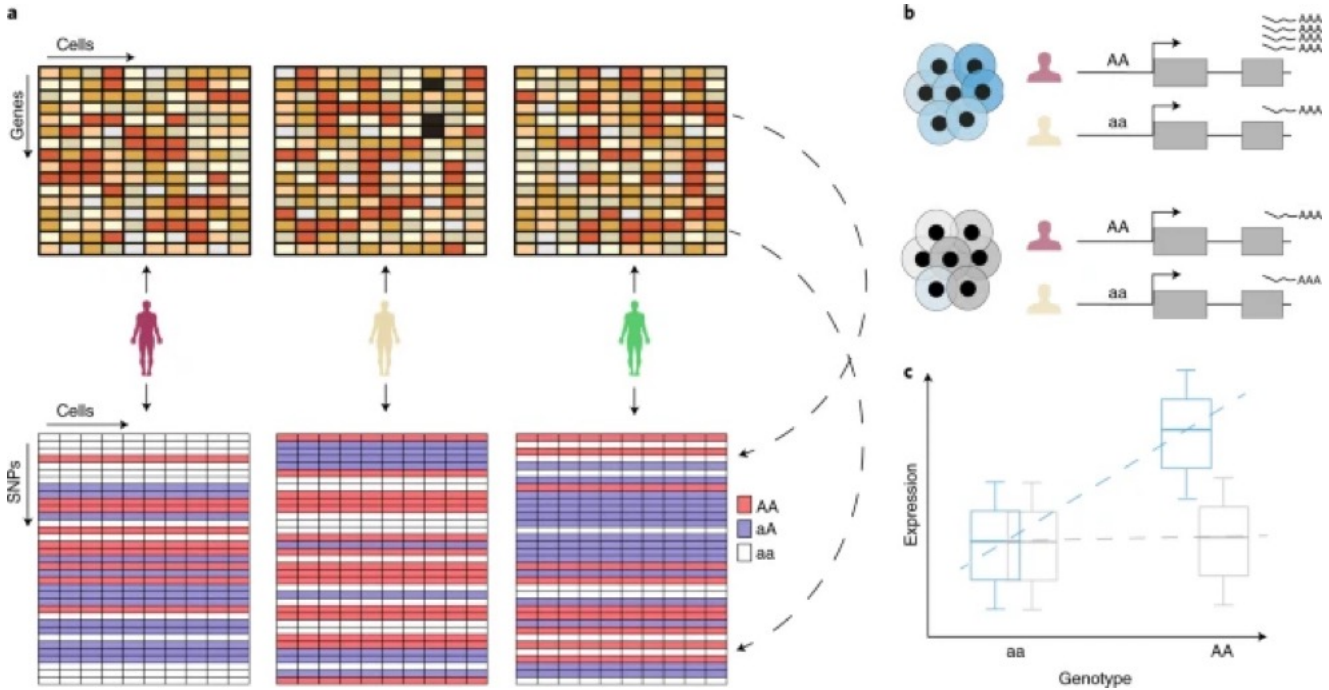
Local analysis

- **Aim**: Find associations between individual features across molecular layers
  - **eQTL studies**: SNP S changes the expression of gene A
  - **Pharmacogenomics**: drug response depends on expression of genes A, B and C

- **Methods**: supervised models, e.g.
  - regression or classification models
  - association tests

$$\mathbf{Y} = \mathbf{X}\boldsymbol{\alpha} + \boldsymbol{\varepsilon}$$

Example: single cell eQTL analysis



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

Considerations for local analysis

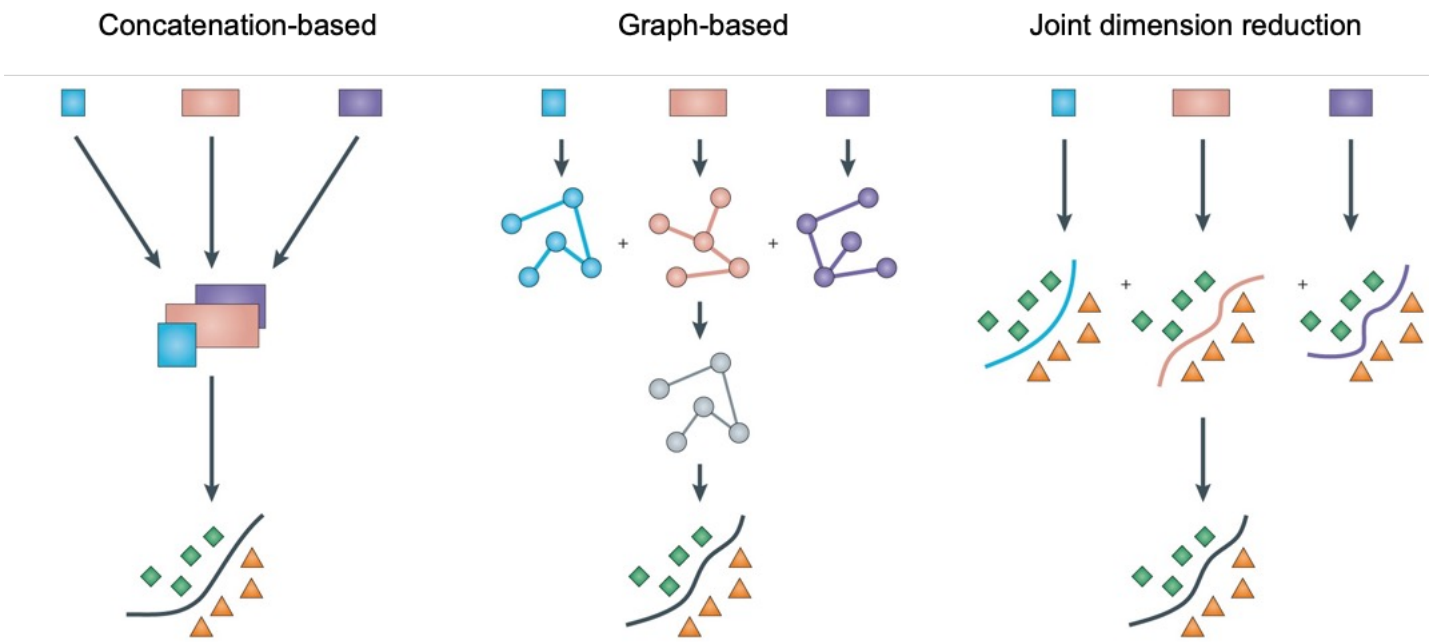
- Linear or non-linear relationship Y = f(X)
- Univariate or multivariate X, need for regularisation?
- Noise model?
- Confounding factors, error covariance?

Global analysis

- **Aim**: Find major sources of variation and identify sample structures based on multiple molecular layers, e.g.
  - Single cell clustering
  - Patient stratification

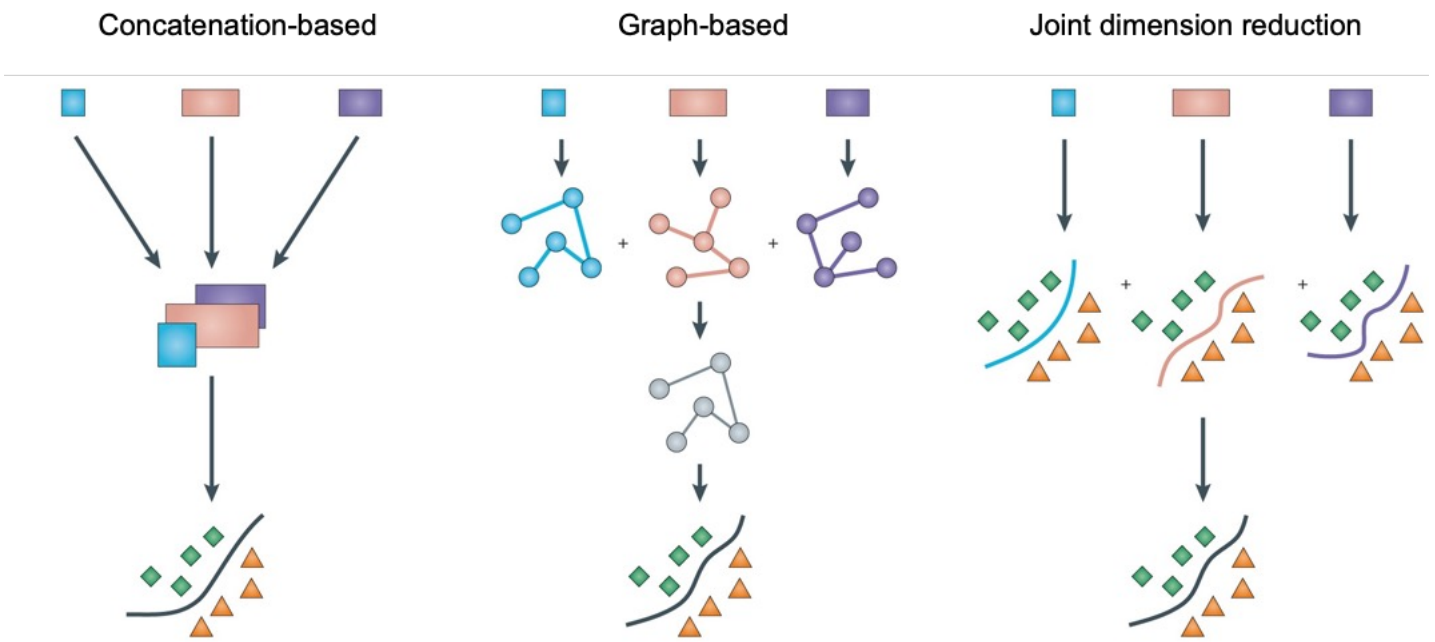
- **Methods**: Mostly unsupervised models, e.g.
  - joint dimension reduction or clustering
  - analysis of covariance structures among features
  - graph-based models

Global analysis



Adapted from Ritchie et al, Nat Rev Gen 2015

Global analysis



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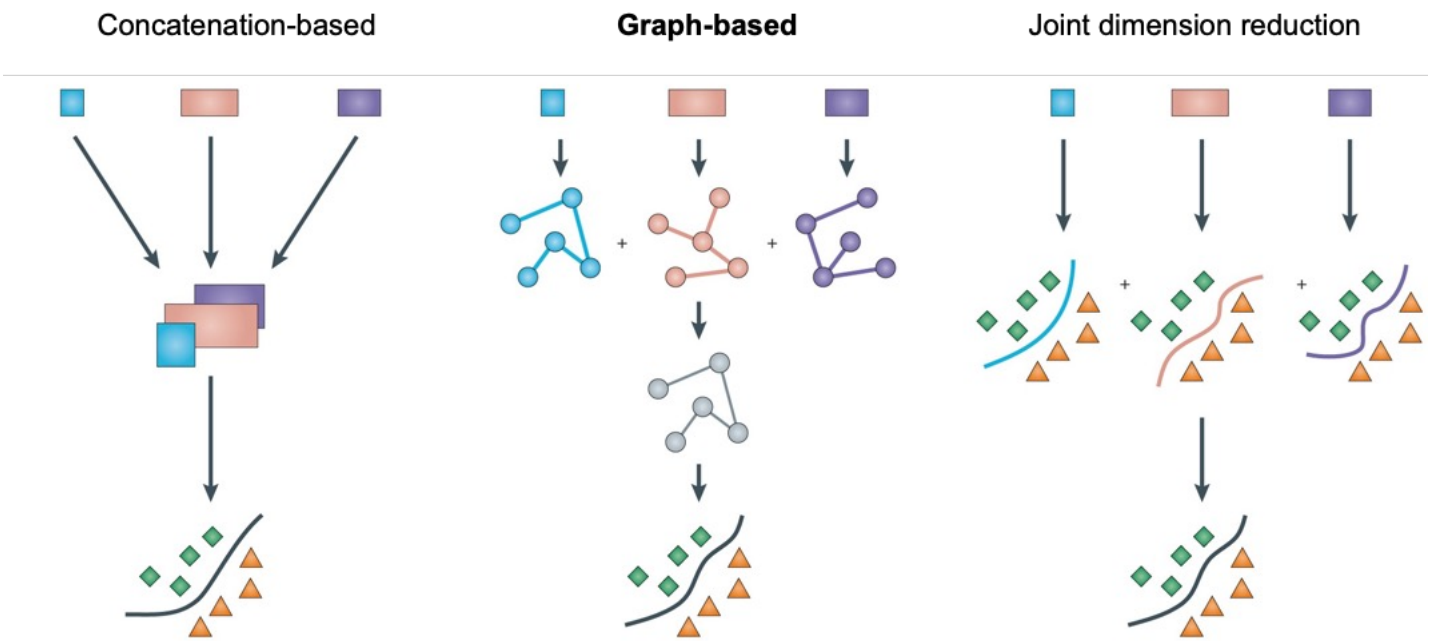
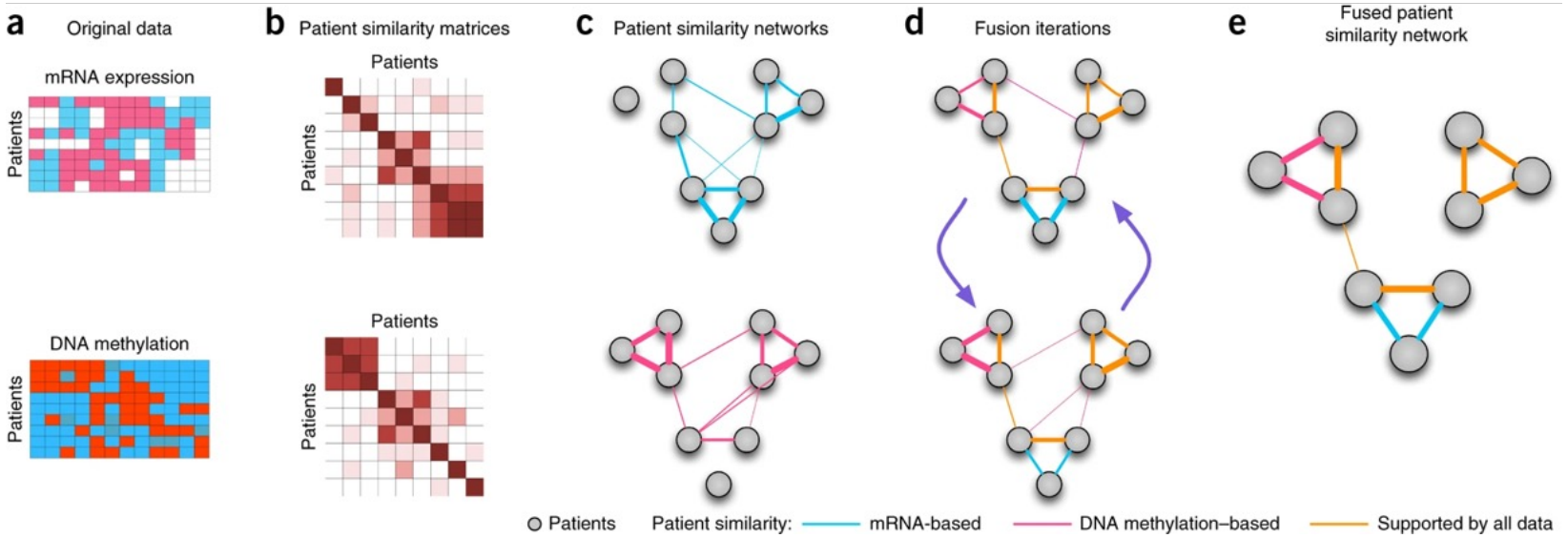
Global analysis



Adapted from Ritchie et al, Nat Rev Gen 2015

Examples for graph based-methods

Similarity network fusion (SNF)

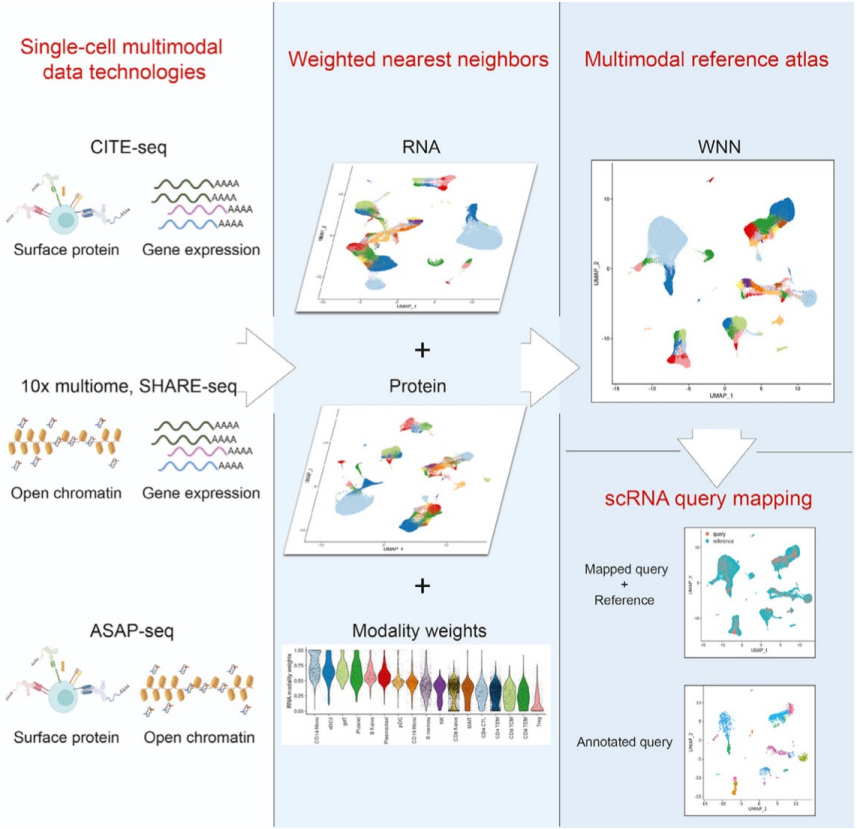


Wang et al 2014

Examples for graph based-methods

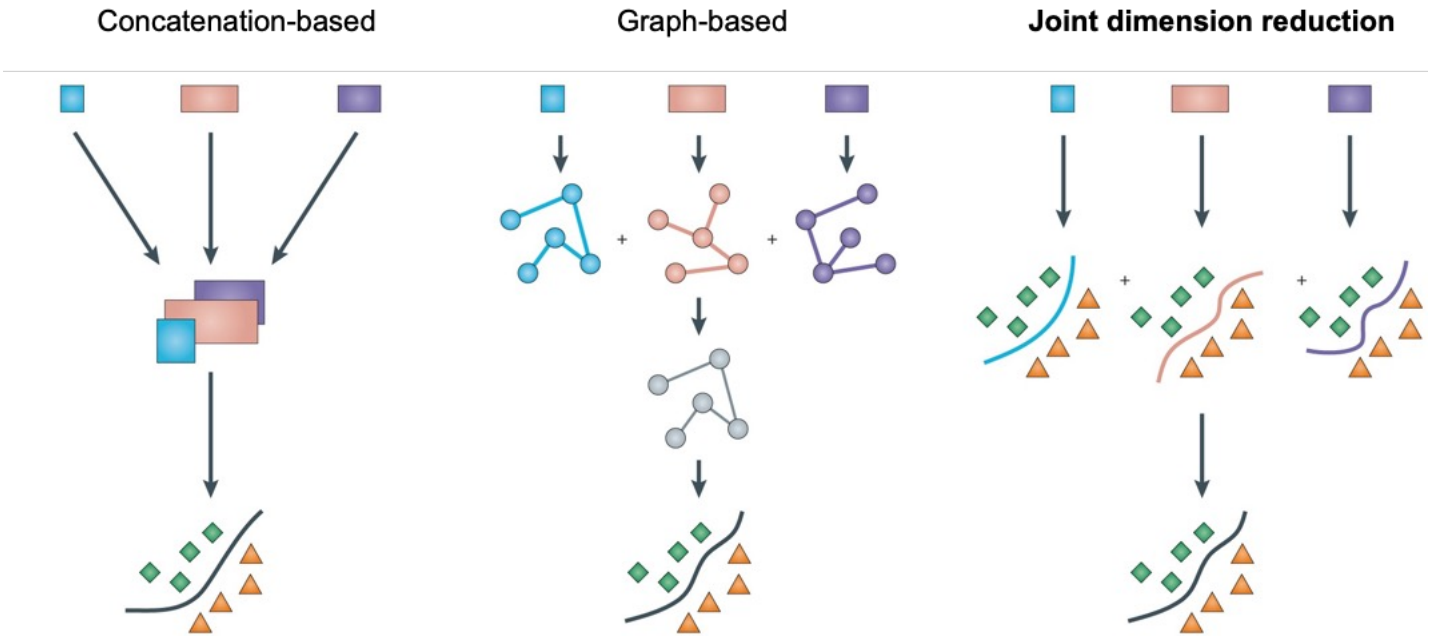
Weighted Nearest Neighbors

- Compare prediction performace in one modality using nearest neighbors from another modality
- Similarity graph based on resulting sample-wise weights

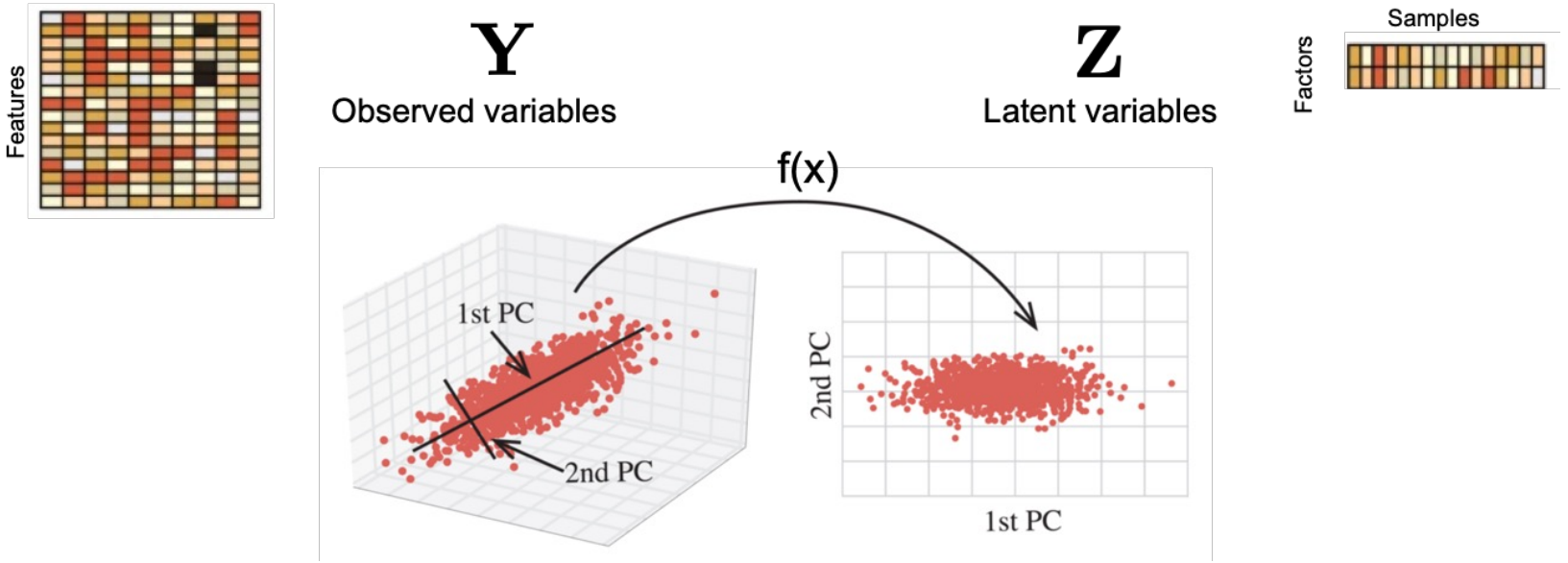


Hao, Hao et al, Cell 2021

Global analysis



Recap: Latent variable models



Examples: AEs, VAEs, PCA, factor analysis, Gaussian-process LVMs, principal curves….

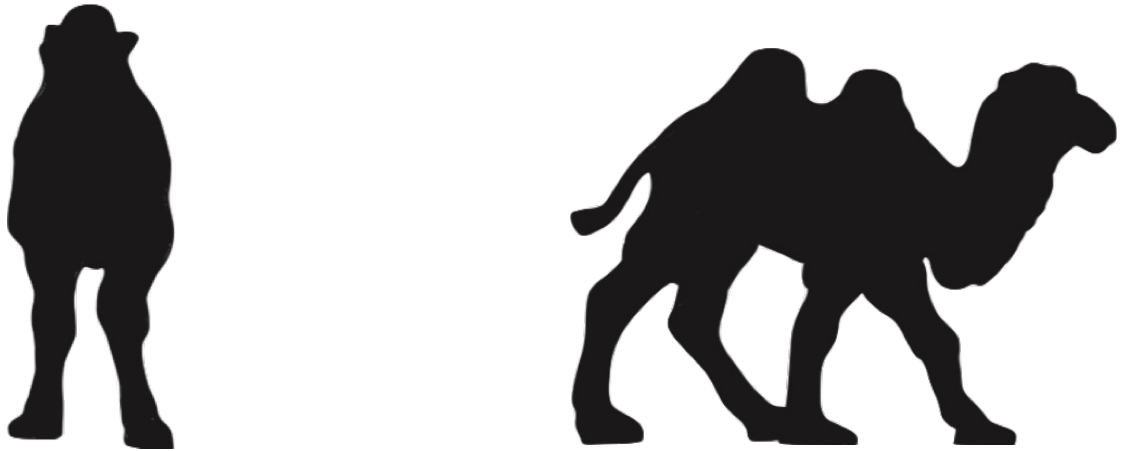
Common Aim

Maximize variance / minimize recontruction error in the low-dimensional space

Adapted from Homes & Huber, Modern Statistics for Moden Biology (MSMB)

Common Aim

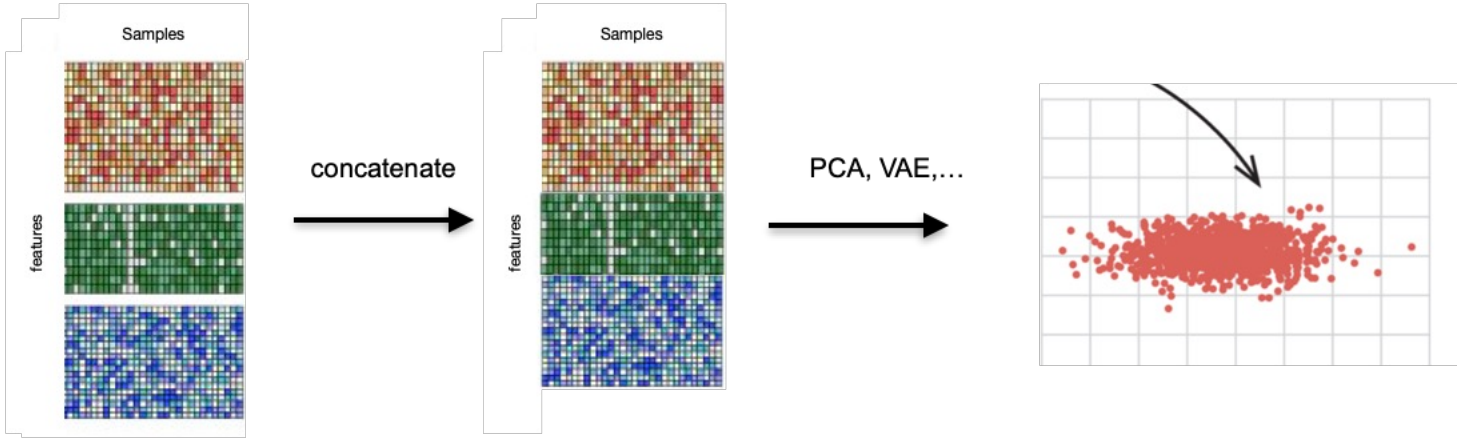
Maximize variance / minimize recontruction error in the low-dimensional space



Adapted from Homes & Huber, Modern Statistics for Moden Biology (MSMB)

How to find joint embeddings from multiple data modalities?

Naïve approach: Concatenation



Problems:

- does not respect heterogeneity of data modalities (e.g. noise model, quality,…)
- No information on relationships between modalities (only between individual features)
- Data modalities with many features dominate the embedding

Tailored approaches (Examples)

Canonical correlation analysis (CCA)

Co-inertia analysis (CoIA)

Integrative NMF

Bayesian group factor analysis & MOFA

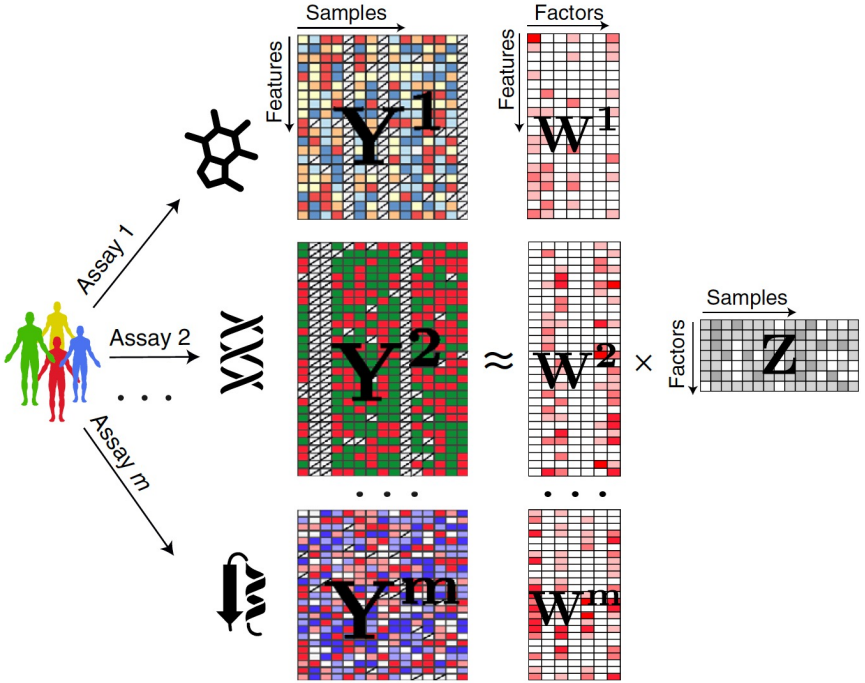
Consensus PCA

Partial least squares (PLS)

Multi-view variational auto-encoders

MOFA: Probabilistic factor model for multi-modal data

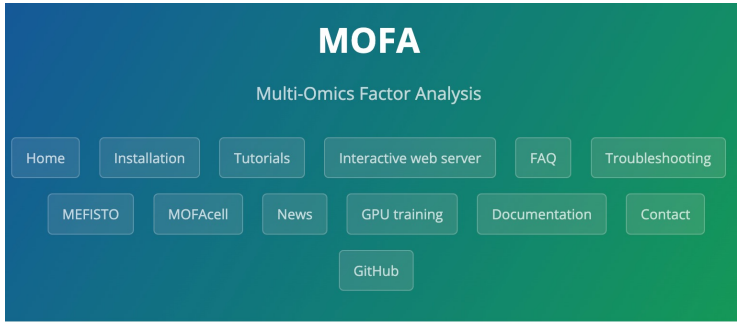
- joint **low-dimensional representation** in terms of (hidden) factors representing the principal axes of variation
- Interpretable model using a **two-level sparsity priors**
  - *Which modalities are important for a factor?*
  - *Which features are important for a factor?*
- **Scalable inference** using (stochastic) variational Bayes



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

MOFA - Software

https://biofam.github.io/MOFA2/index.html

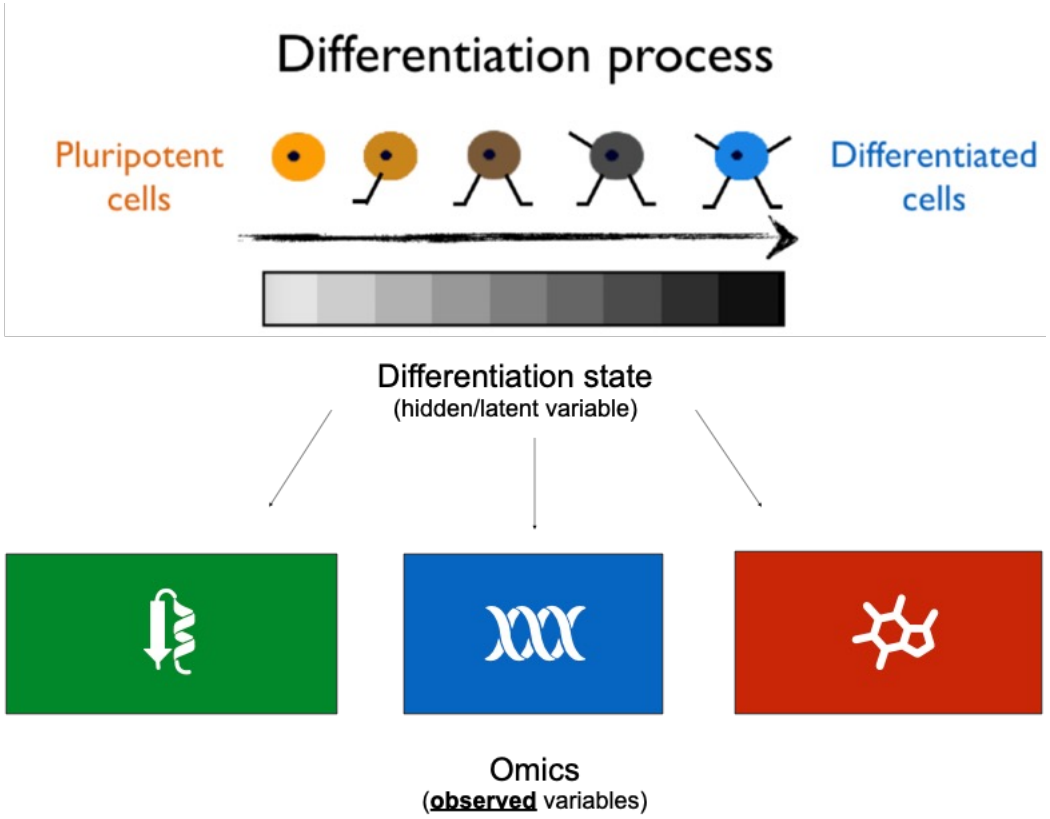


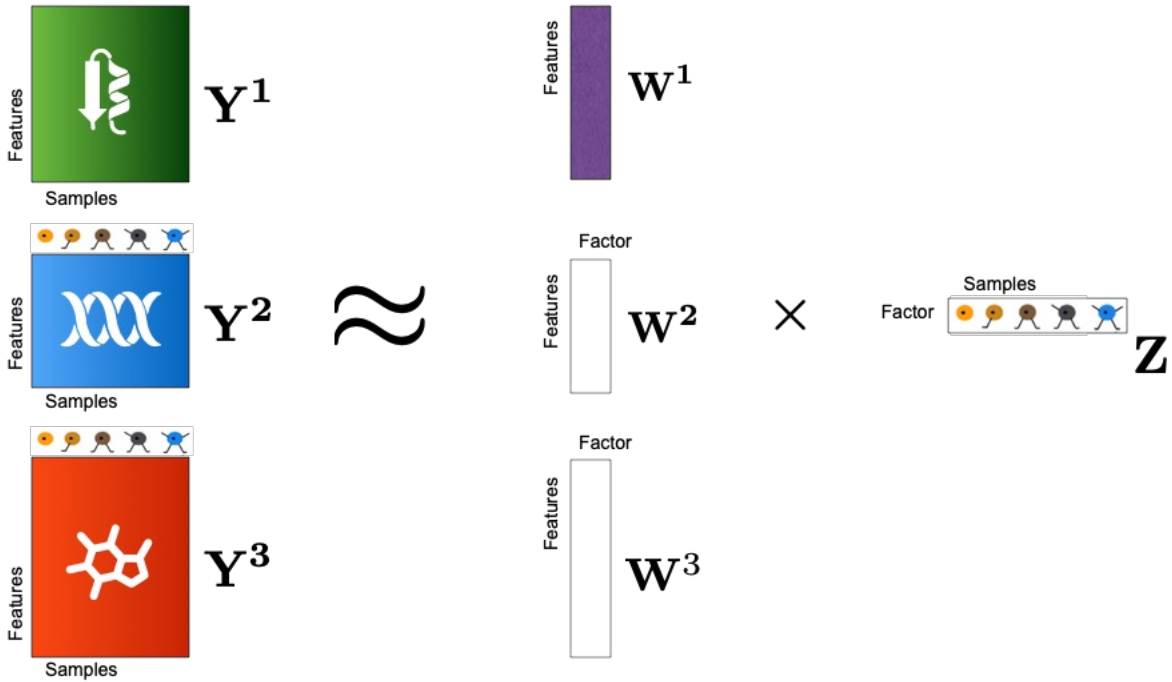
Overview

MOFA is a factor analysis model that provides a **general framework for the integration of multi-omic data sets** in an unsupervised fashion. Intuitively, MOFA can be viewed as a versatile and statistically rigorous generalization of principal component analysis to multi-omics data. Given several data matrices with measurements of multiple -omics data types on the same or on

Python: mofapy2, muon
R: MOFA2

What is the intuition behind MOFA?


Differentiation process
Pluripotent cells
Differentiated cells
Differentiation state
(hidden/latent variable)
Omics
(observed variables)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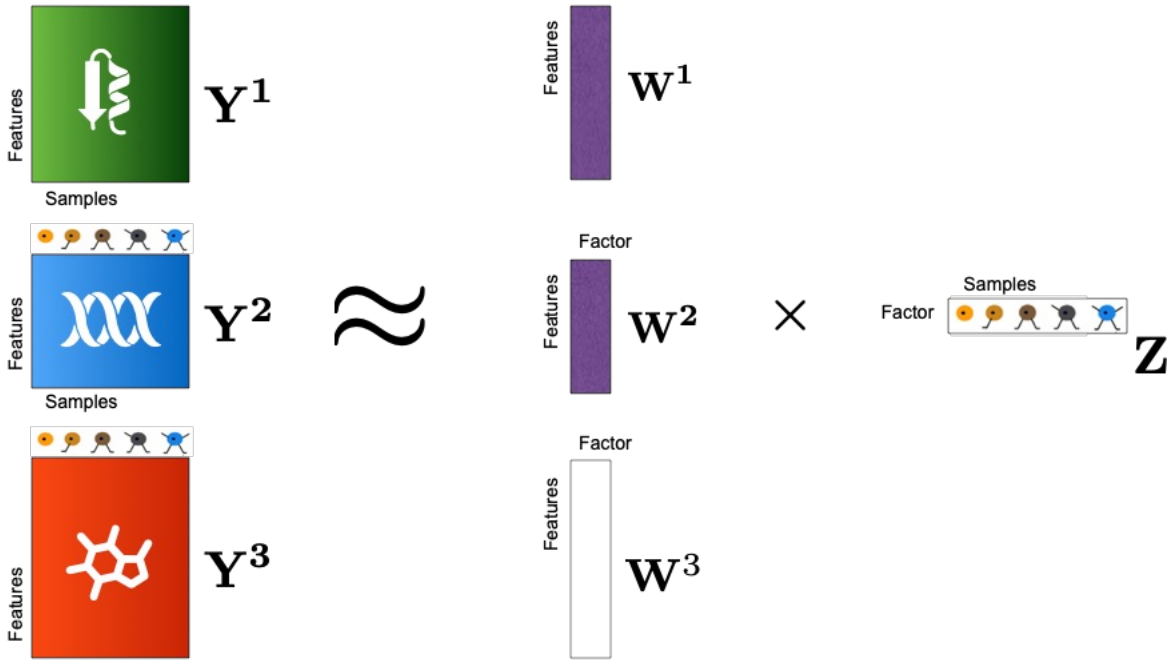
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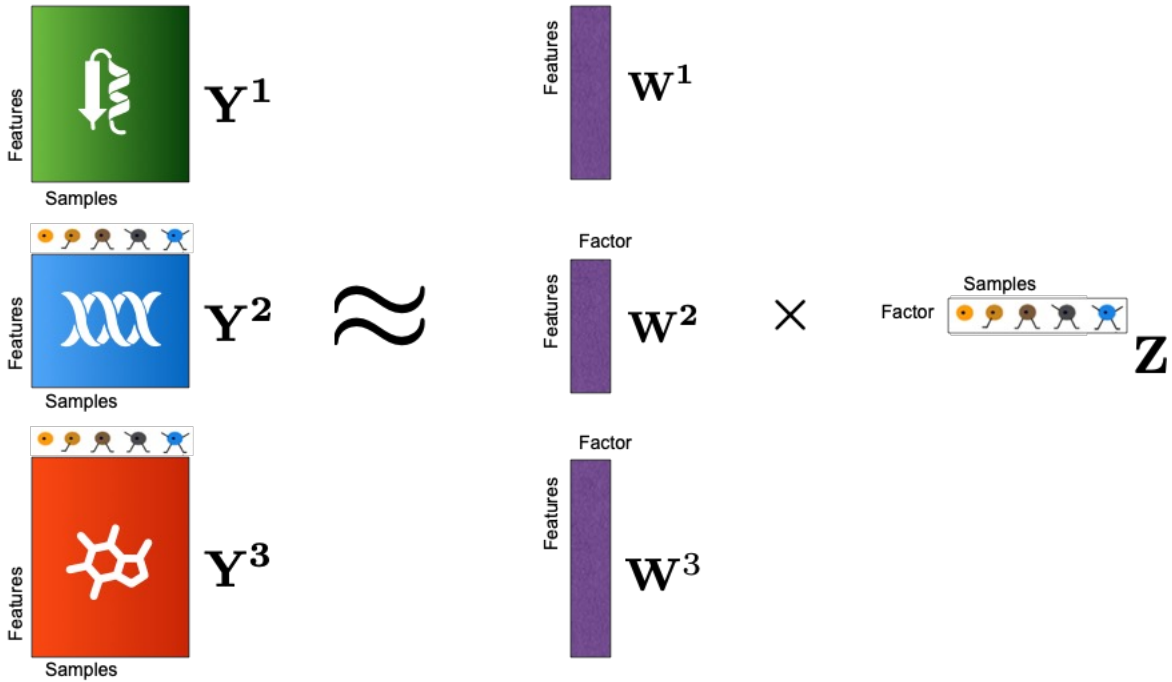
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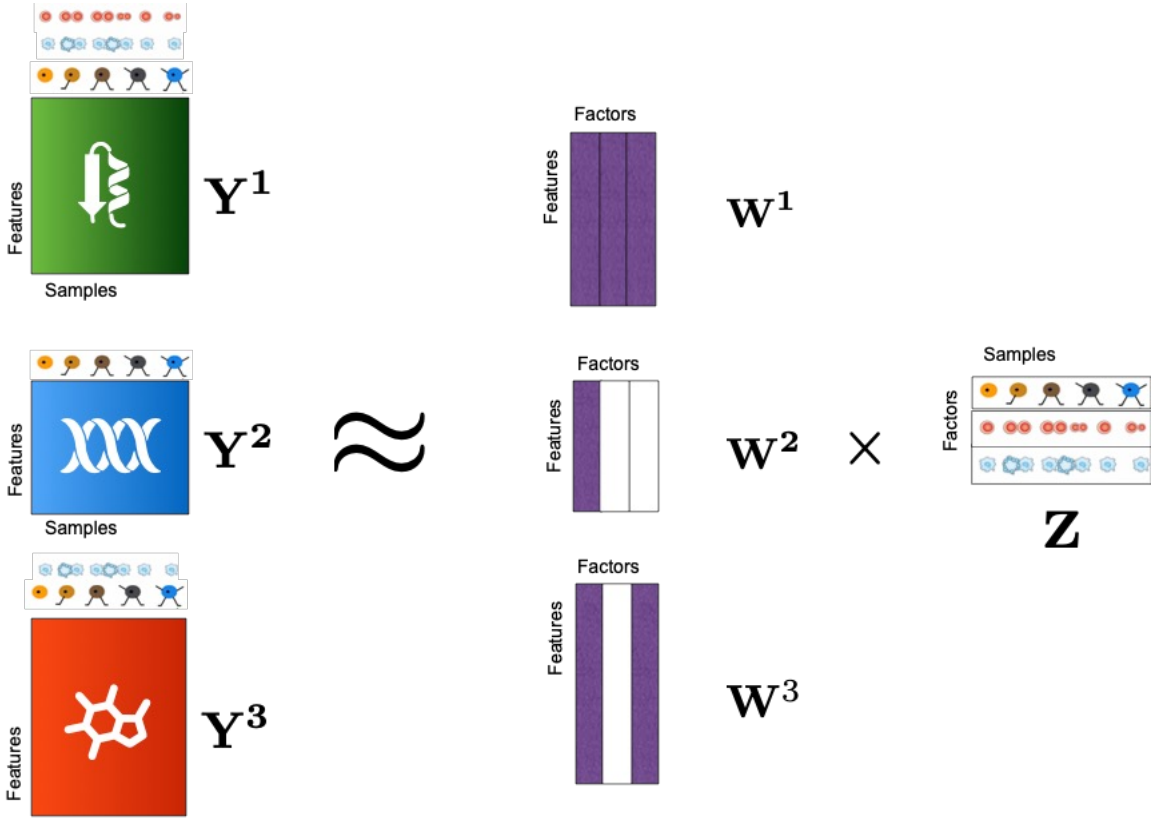
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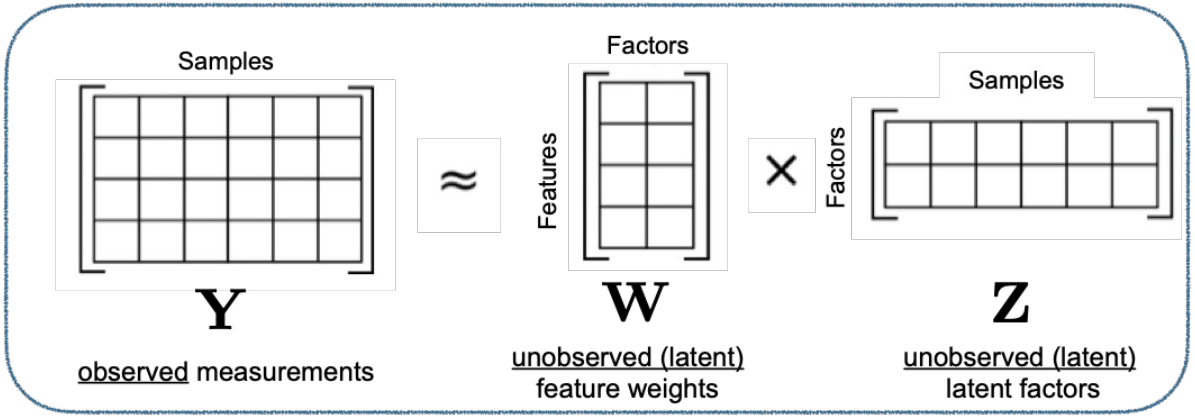
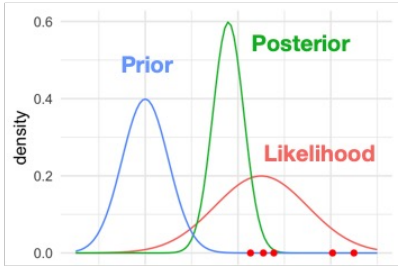
What is the mathematical model behind MOFA?

Probabilistic factor model

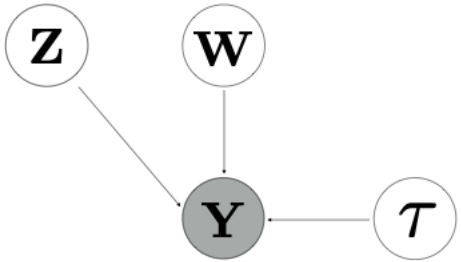


Probabilistic (Bayesian) models combine
- a *likelihood function* (statistical model for the observed data)
- a *prior* (distribution of unobserved components)

This can provide **regularisation** & incorporation of **prior information** (prior) and an explicit model of **uncertainties**



Likelihood model



Observed variable

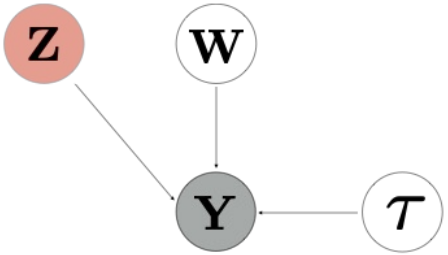
Unobserved variable

$$\mathbf{Y} = \mathbf{Z}\mathbf{W}^T + \mathcal{N}(\mathbf{0}, \tau^{-1})$$

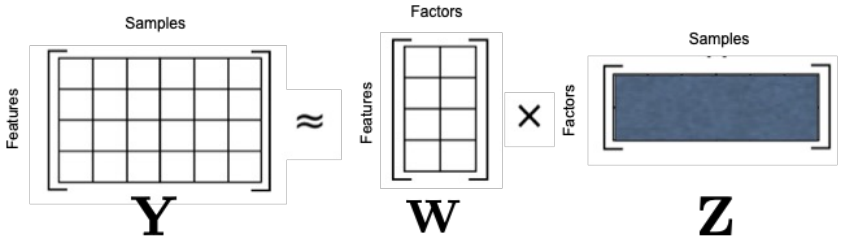
		Dimensions
$\mathbf{Y}$	Observation matrix	(N,D)
$\mathbf{Z}$	Latent variable matrix	(N,K)
$\mathbf{W}$	Weight matrix	(D,K)
τ	Noise vector	(D,)

N is the number of samples
D is the number of features
K is the number of factors

Prior for factors

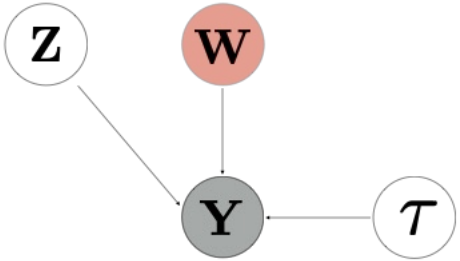


$$p(\mathbf{Z}) = \prod_{n=1}^{N} \prod_{k=1}^{K} \mathcal{N}(0,1)$$



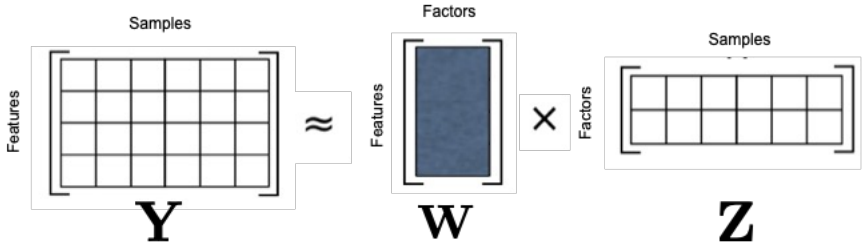
N is the number of samples
D is the number of features
K is the number of factors

Prior for weights



Automatic Relevance Determination (ARD)

$$p(\mathbf{W}|\alpha) = \prod_{k=1}^{K} \mathcal{N}(\mathbf{w}_{:,\mathbf{k}}|0, \alpha_k^{-1}\mathbf{I})$$



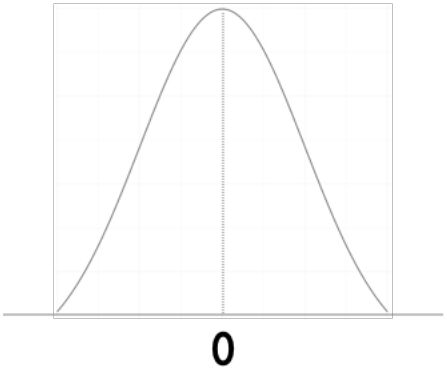
N is the number of samples
D is the number of features
K is the number of factors

Automatic relevance determination prior

$$p(w|\alpha) = \mathcal{N}(w|0, \frac{1}{\alpha})$$

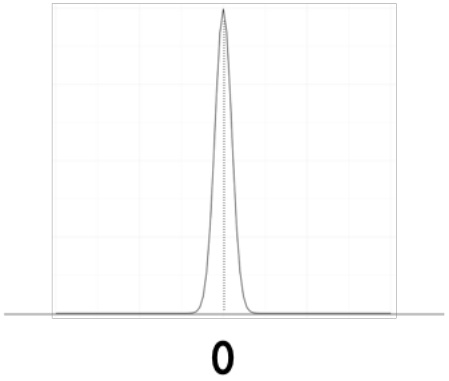
If precision α is small:

Broad distribution

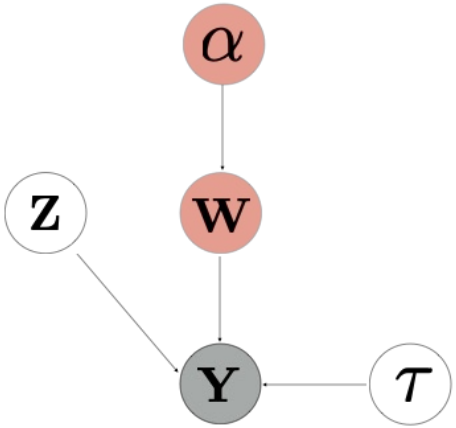


If precision α is large:

Distribution peaked at 0



Automatic relevance determination prior

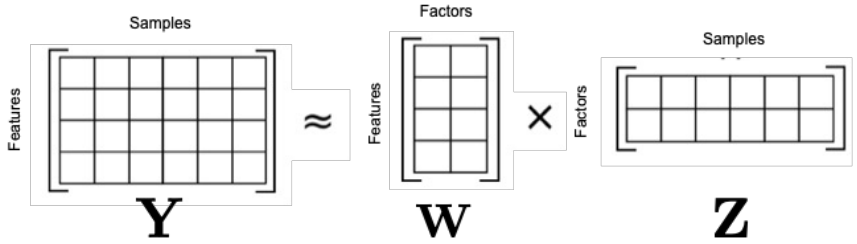


$$p(\mathbf{W}|\alpha) = \prod_{k=1}^{K} \mathcal{N}(\mathbf{w}_{:,\mathbf{k}}|0, \alpha_k^{-1}\mathbf{I})$$

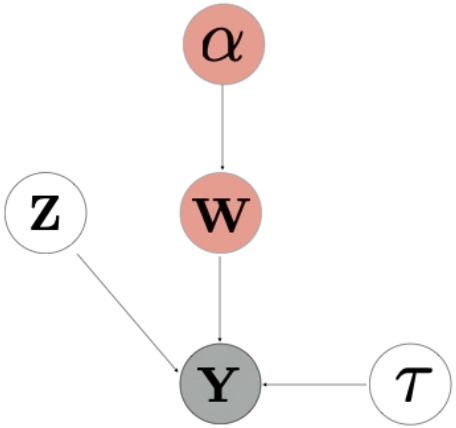
$$p(\alpha_k) = \mathcal{G}(a_0^{\alpha}, b_0^{\alpha})$$

Uninformative gamma prior

N is the number of samples
D is the number of features
K is the number of factors



Automatic relevance determination prior



$$p(\mathbf{W}|\alpha) = \prod_{k=1}^{K} \mathcal{N}(\mathbf{w}_{:,\mathbf{k}}|0, \alpha_k^{-1}\mathbf{I})$$

$$p(\alpha_k) = \mathcal{G}(a_0^{\alpha}, b_0^{\alpha})$$

Uninformative gamma prior

N is the number of samples
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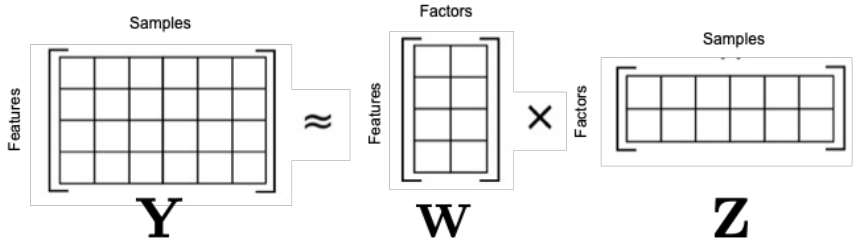
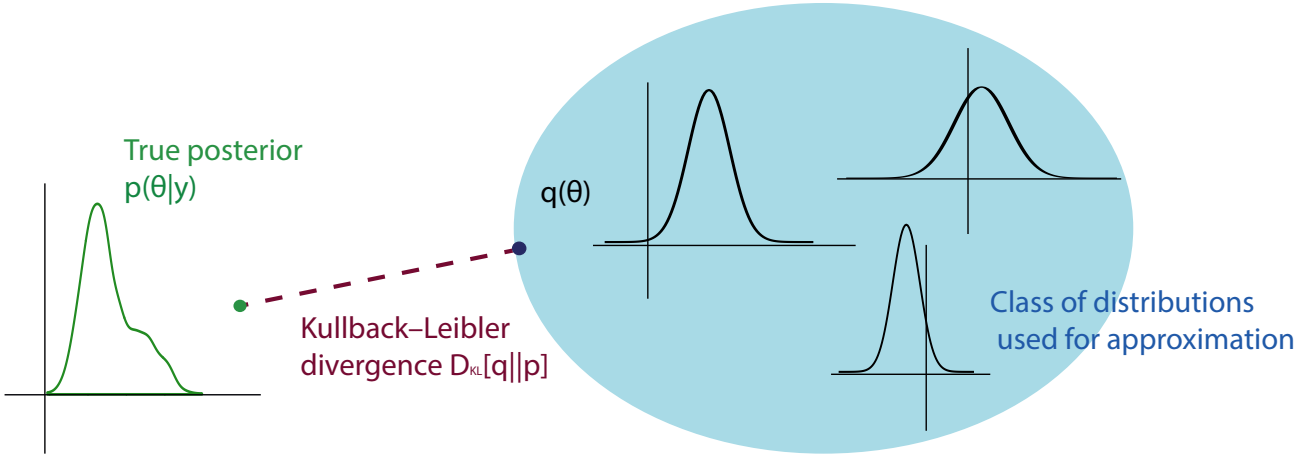
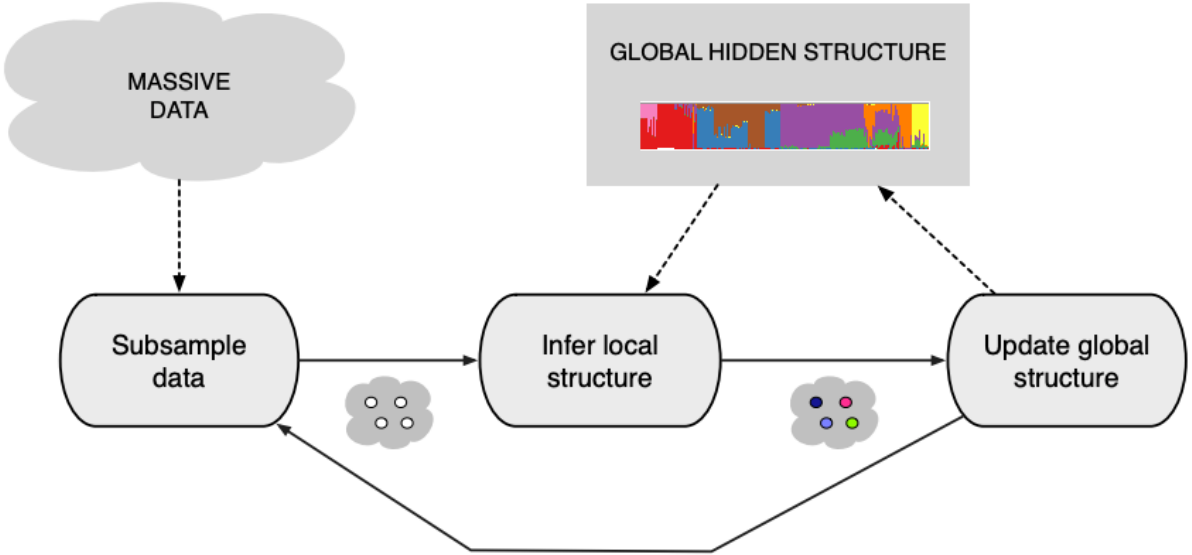


Finding the posterior $p(Z, W, \alpha|Y)$



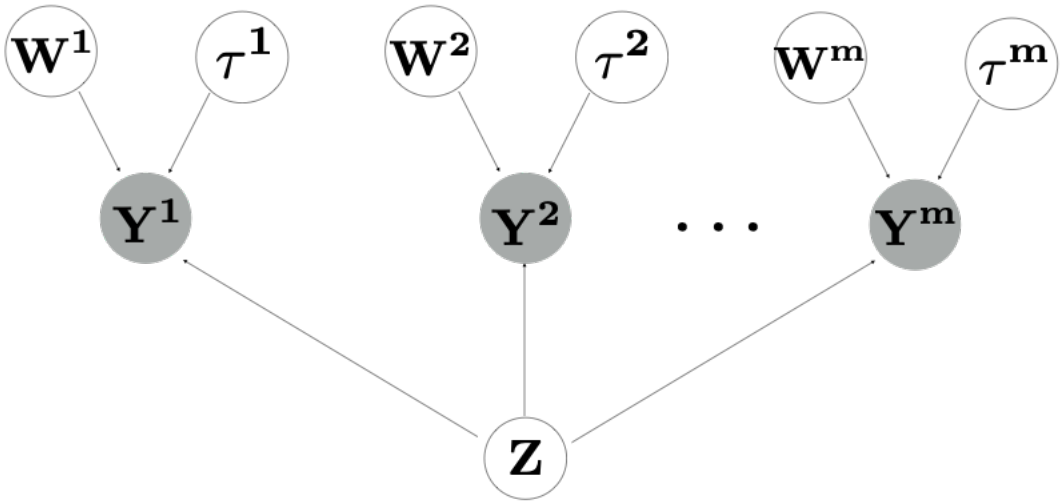
Variational inference provides an approximation of the posterior from a restricted class of distributions.

Stochastic variational inference



Adapted from David Blei, NIPS tutorial 2016

Multi-view probabilistic factor analysis



$$\mathbf{Y}^m = \mathbf{Z}\mathbf{W}^m + \mathcal{N}(0, \tau_m)$$

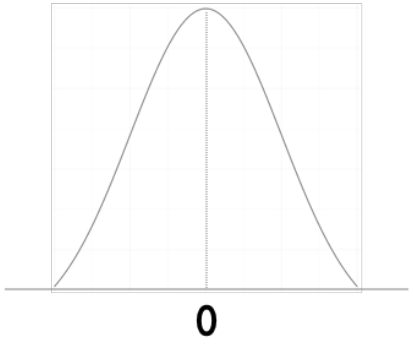
M is the number of “views” (omics)

Determining activity of factors per view

$$p(w_k^{(m)} \mid \alpha_k^{(m)}) = N\left(w_k^{(m)} \mid 0, \frac{1}{\alpha_k^{(m)}}\right)$$

If precision $\alpha_k^{(m)}$ is small:

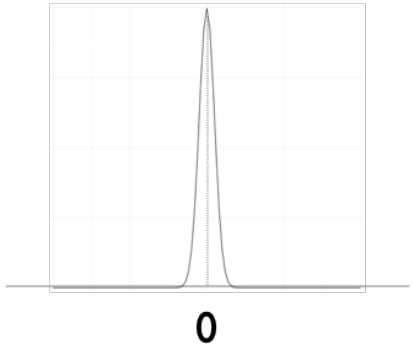
Broad distribution



Factor k is active in view m

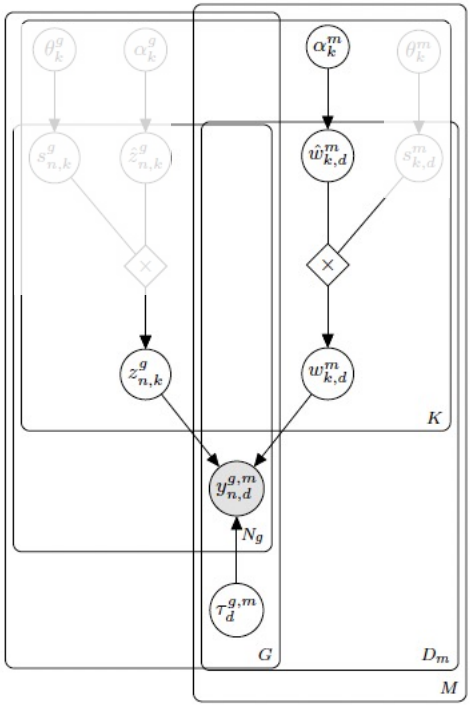
If precision $\alpha_k^{(m)}$ is large:

Distribution peaked at 0



Factor k is not active in view m

Plate notation of graphical model

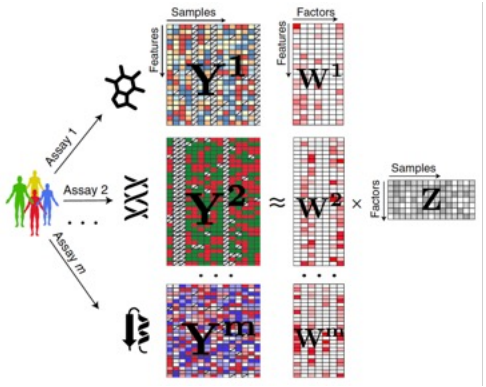


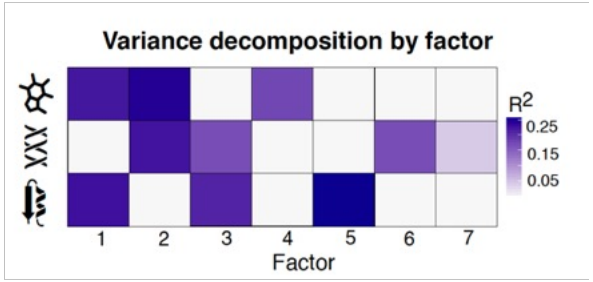
pyro


```python
from pyro.nn import PyroSample


class BayesianRegression(PyroModule):
    def __init__(self, in_features, out_features):
        super().__init__()
        self.linear = PyroModule[nn.Linear](in_features, out_features)
        self.linear.weight = PyroSample(dist.Normal(0., 1.).expand([out_features, in_featu
        self.linear.bias = PyroSample(dist.Normal(0., 10.).expand([out_features]).to_event

    def forward(self, x, y=None):
        sigma = pyro.sample("sigma", dist.Uniform(0., 10.))
        mean = self.linear(x).squeeze(-1)
        with pyro.plate("data", x.shape[0]):
            obs = pyro.sample("obs", dist.Normal(mean, sigma), obs=y)
        return mean
```

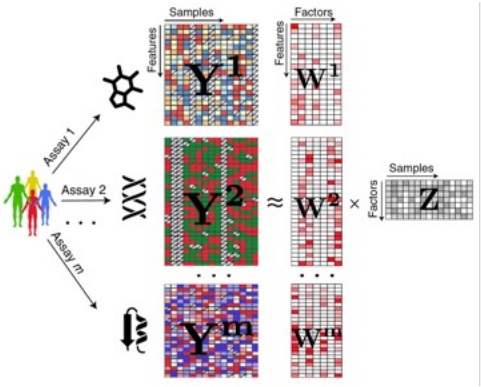
What can be done with such models?

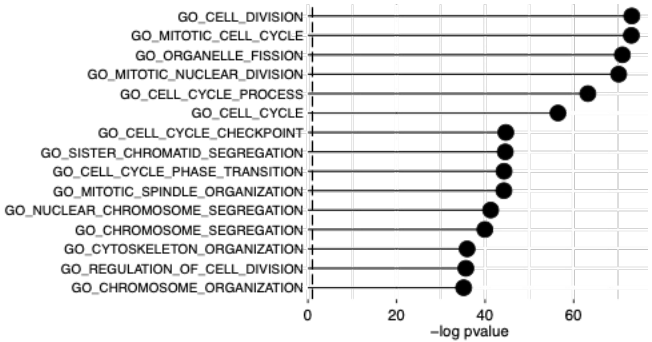
Variance decomposition



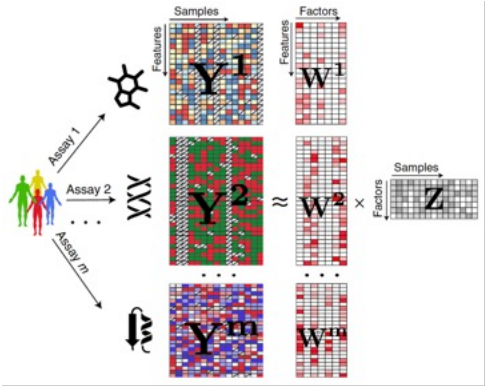


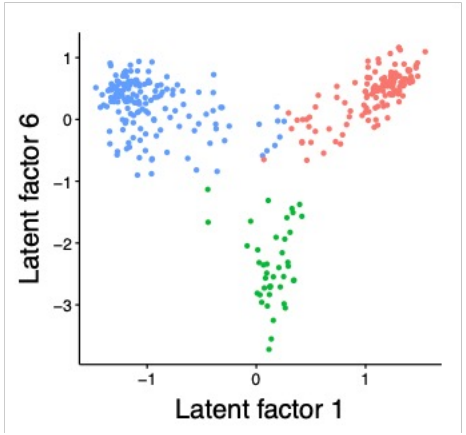
Inspection of weights



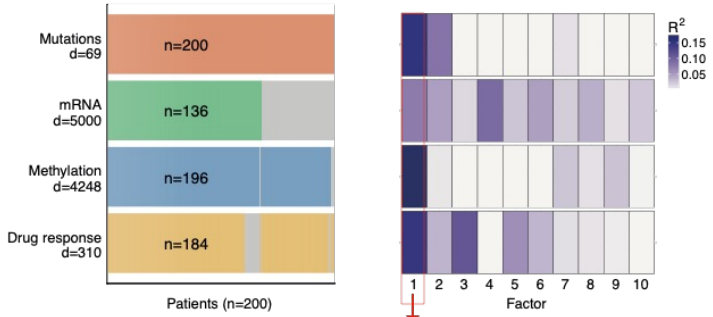


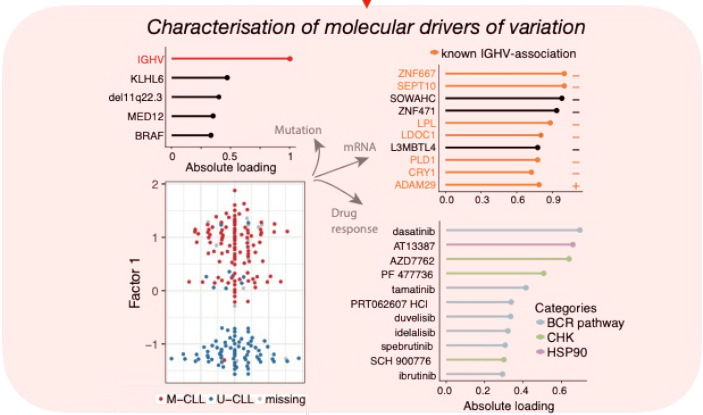
Visualisation of samples





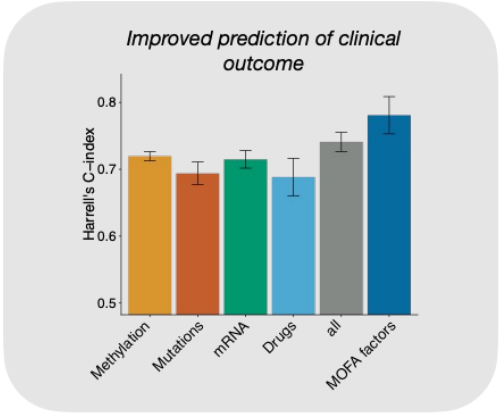
Example I: Precision medicine





200 chronic lymphocytic leukaemia samples (incompletely) characterised by

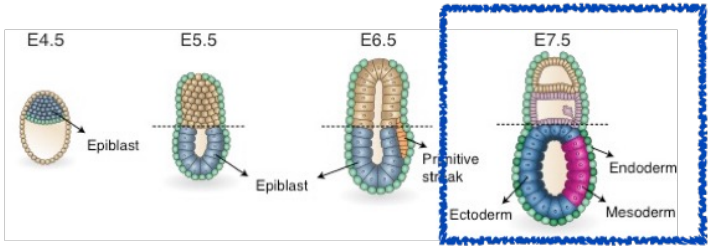
- genomic sequencing
- RNA-seq
- methylation arrays
- ex-vivo drug response assays



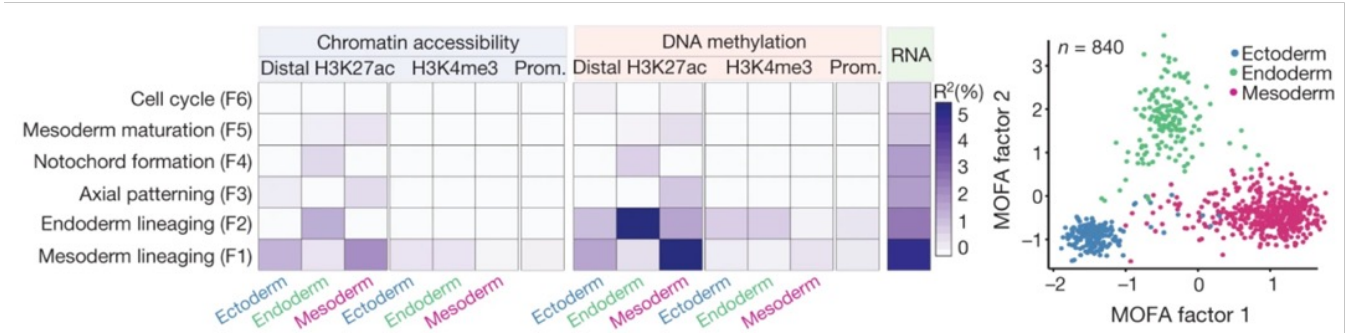
Argelaguet* & Velten* et al Mol Sys Bio. 2018

Example II: Single cell studies of development

scNMT-seq on cells from day E7.5 of mouse development provides information on DNA methylation, chromatin accessibility and transcription for each cell.



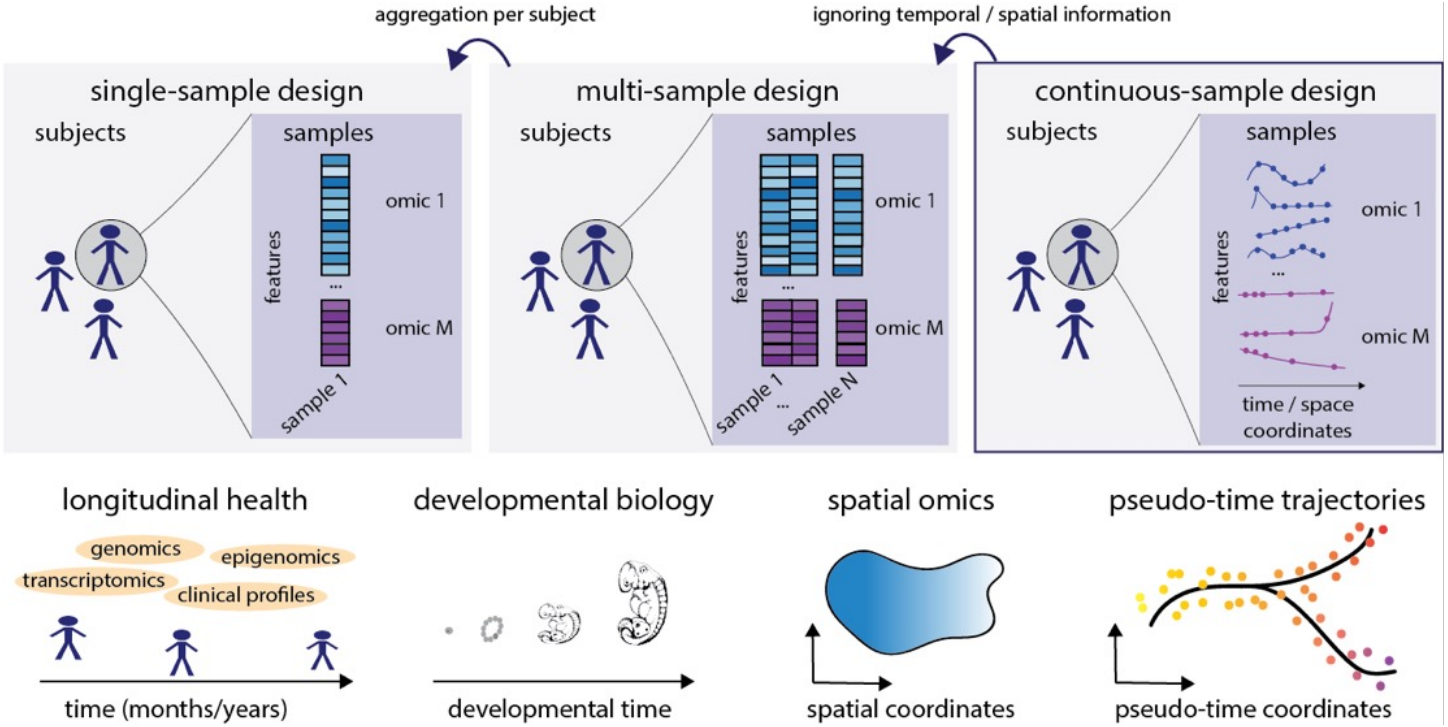
MOFA factors 1 and 2 capture the emerge of different germ layers and reveal coordinated transcriptional and epigenetic variation (latter mostly present at enhancers sites).



Argelaguet, Mohammed, Clark et al. Nature 2019

Multi-modal data with time and space resolution

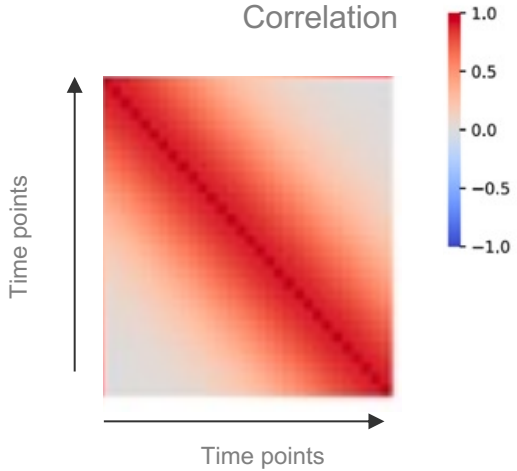
Temporal or spatial resolution

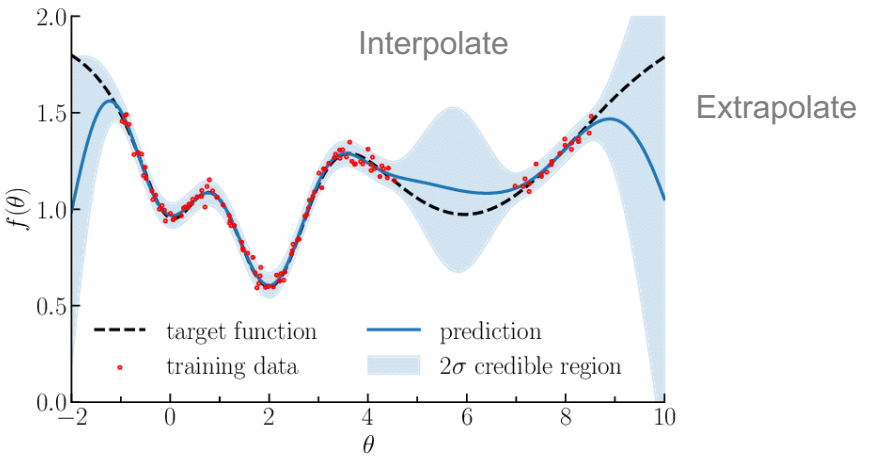


Velten & Stegle, Nath Methods 2023

What changes?

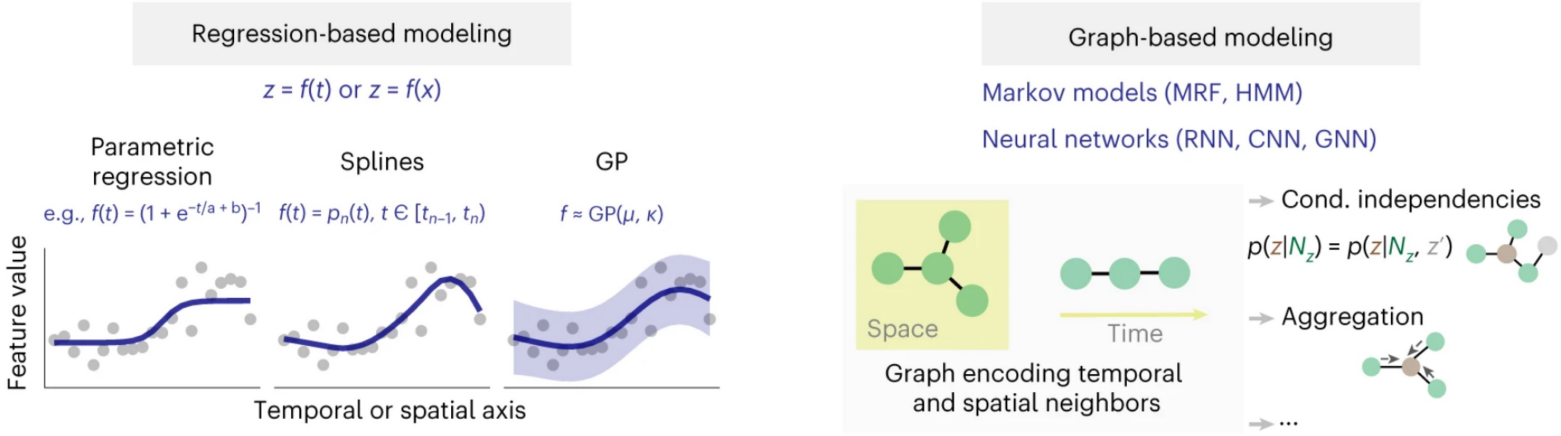
- Samples are non-i.i.d: nearby time points or spatial positions can be correlated
- Assumptions of smoothness along time or space can help to
  - mitigate noise
  - interpolate or extrapolate to unmeasured time points or positions





Florent Leclercq, 2018

Avenues for accounting for time & space



Velten & Stegle, Nath Methods 2023

Gaussian processes

Definition

A Gaussian process is a statistical distribution f_t, $t \in T$, for which any finite linear combination of samples has a joint Gaussian distribution.
A Gaussian process with mean function μ and covariance function k is denoted by

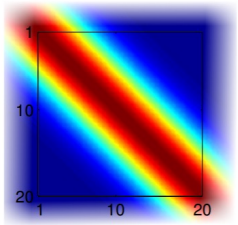
$$f \sim GP(\mu, k)$$

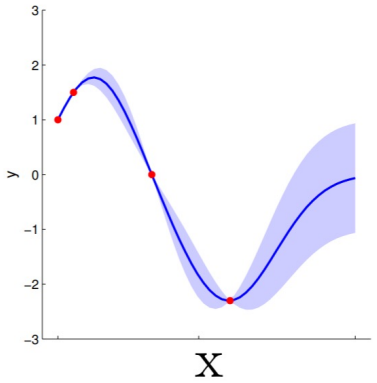
→ Probabilistic non-parametric method for learning functiona l relationships

$$\Sigma(x_1, x_2) = K(x_1, x_2) + I\sigma_y^2$$

$$K(x_1, x_2) = \sigma^2 e^{-\frac{1}{2l^2}(x_1 - x_2)^2}$$

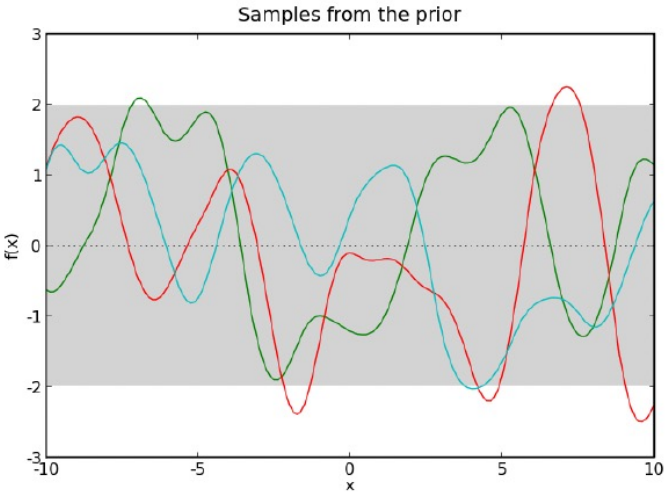
$\Sigma =$



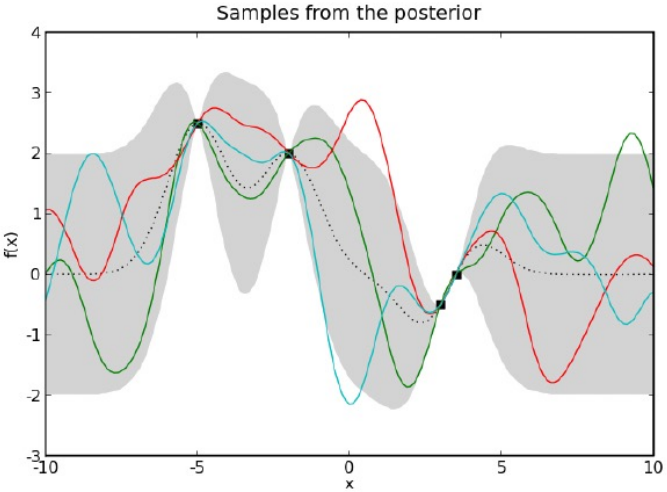


Gaussian processes

Before observing any data:

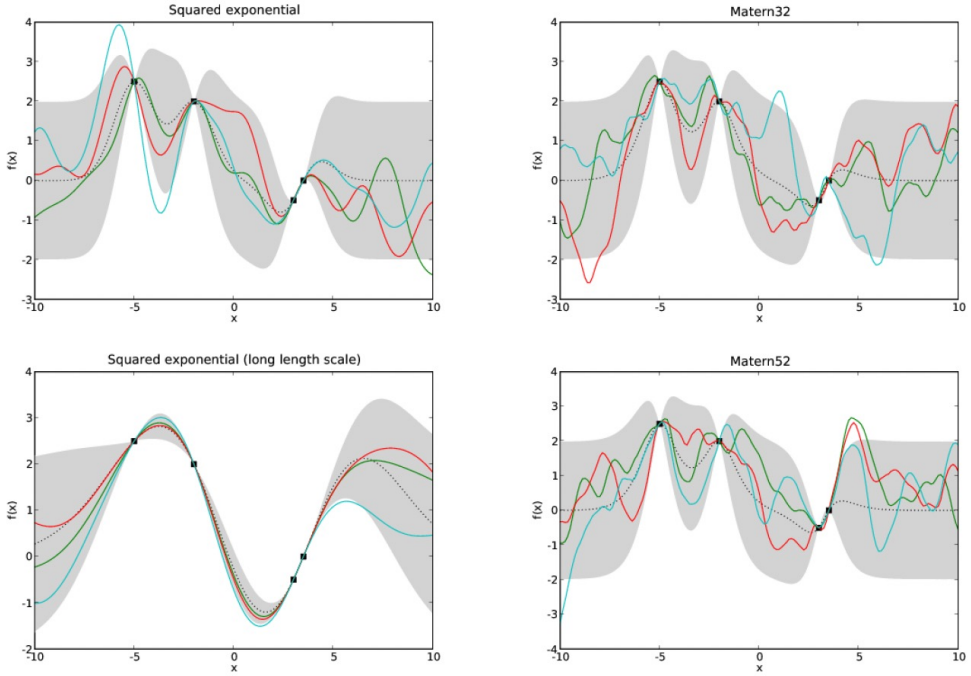


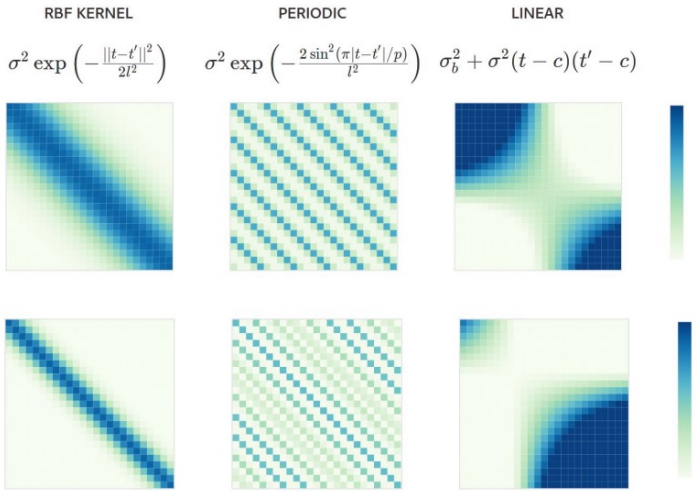
After measurements:



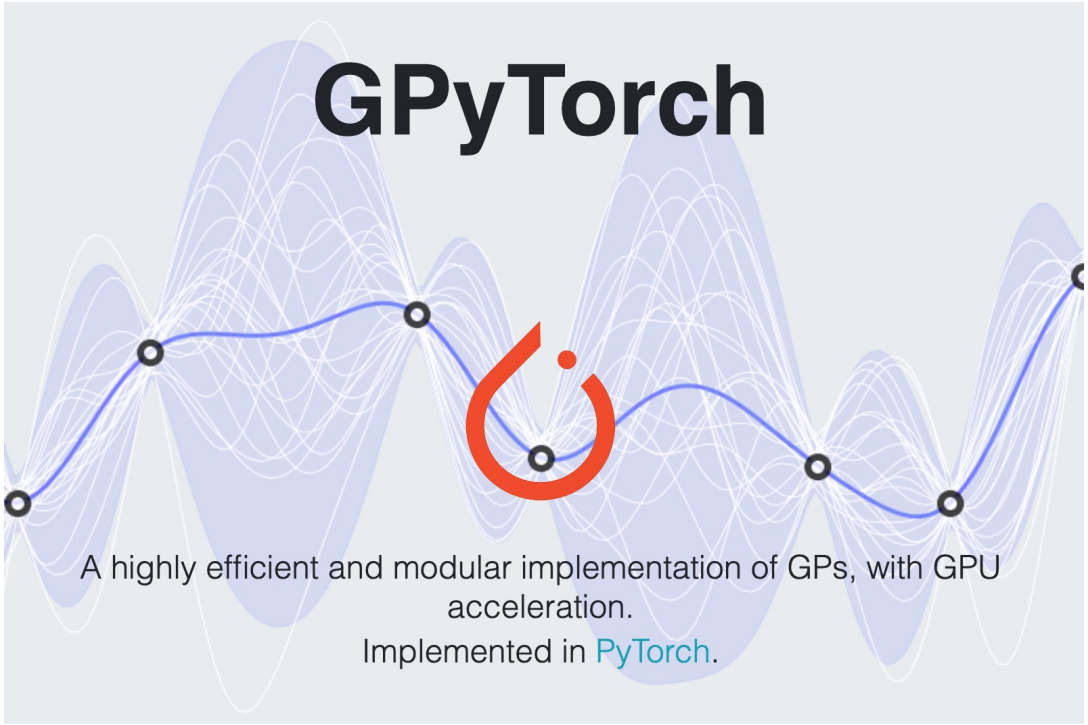
Gaussian processes

Choice of kernel / covariance function determines smoothness

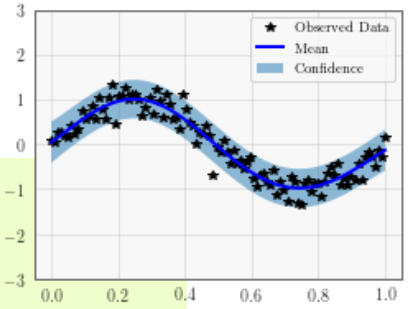




gpytorch


GPyTorch
A highly efficient and modular implementation of GPs, with GPU acceleration.
Implemented in PyTorch.

Example: Regression in gpytorch



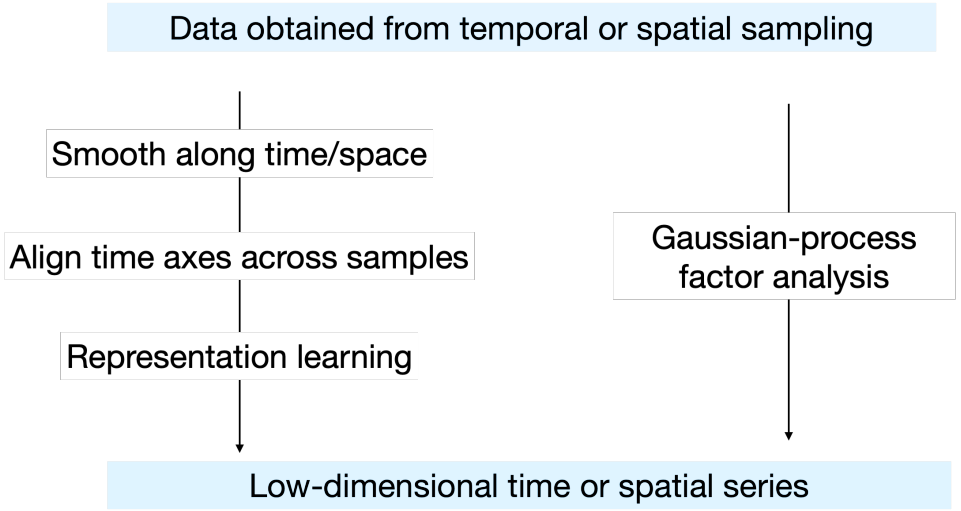

```python
class ExactGPModel(gpytorch.models.ExactGP):
    def __init__(self, train_x, train_y, likelihood):
        super(ExactGPModel, self).__init__(train_x, train_y, likelihood)
        self.mean_module = gpytorch.means.ConstantMean()
        self.covar_module = gpytorch.kernels.ScaleKernel(gpytorch.kernels.RBFKernel())

    def forward(self, x):
        mean_x = self.mean_module(x)
        covar_x = self.covar_module(x)
        return gpytorch.distributions.MultivariateNormal(mean_x, covar_x)

# initialize likelihood and model
likelihood = gpytorch.likelihoods.GaussianLikelihood()
model = ExactGPModel(train_x, train_y, likelihood)
```

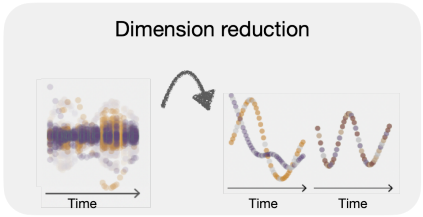
→ pytorch training loop

How to use Gaussian processes for dimenstion reduction and data integration?

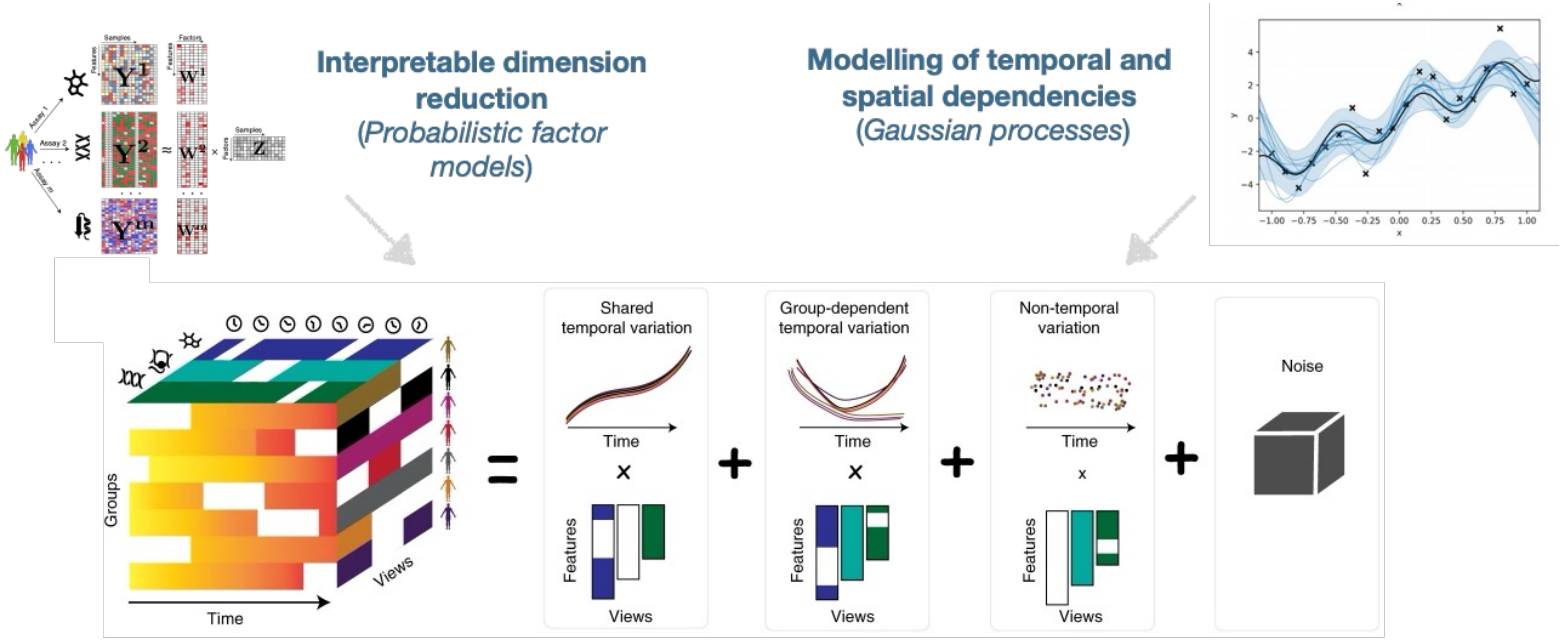
Gaussian process factor models (GPFA)

- Gaussian process priors in the latent space (factors)
- Joint dimension reduction and smoothing



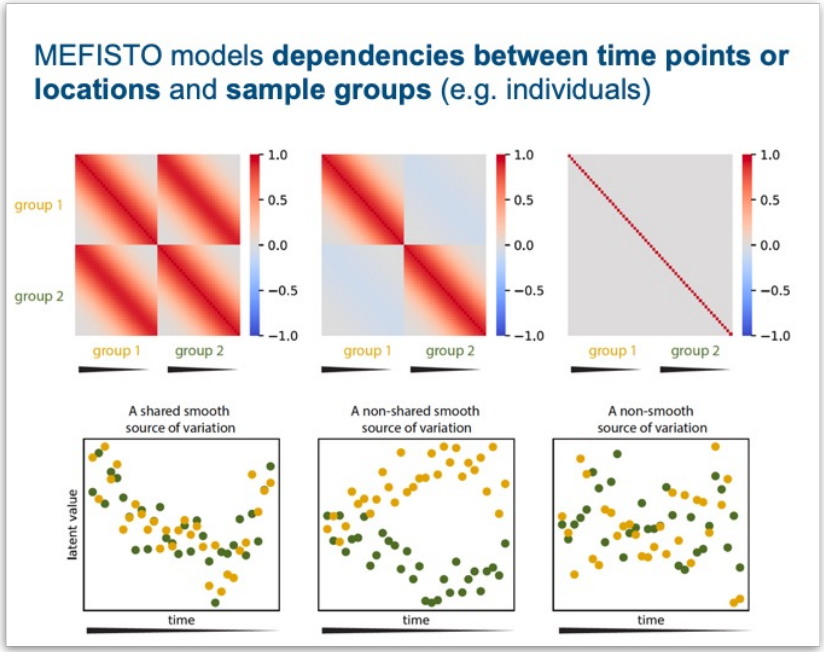


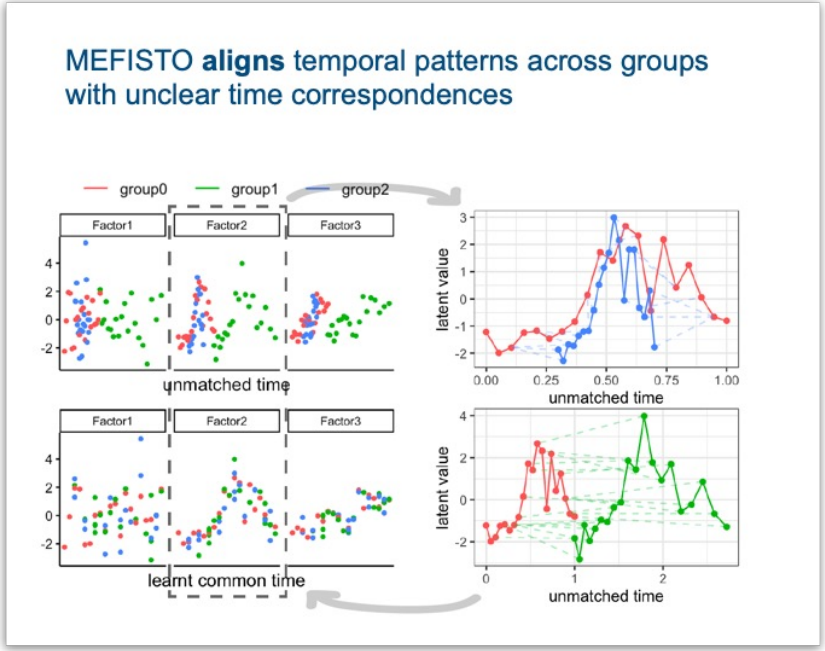
GPFA for multi-modal data: MEFISTO



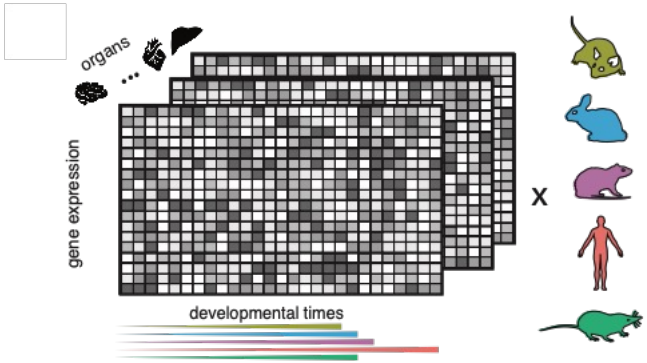
Integrated alignment of time points across individuals enables a meaningful comparisons of temporal patterns.

GPFA for multi-modal data: MEFISTO





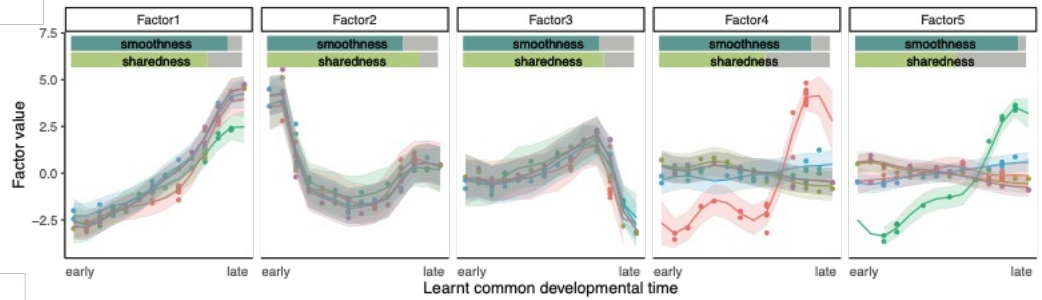
Example: Evo-devo data



Gene expression data for
- 5 species
- 5 organs
- 14-23 time points with unclear correspondences

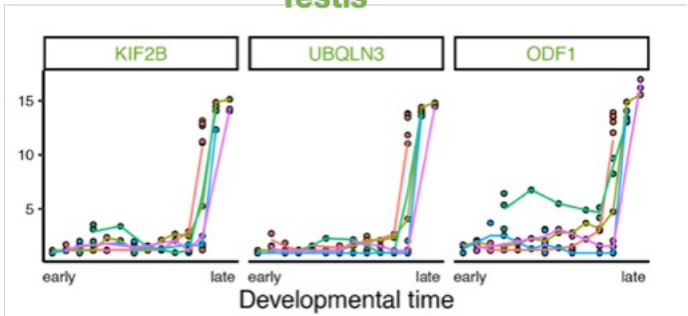
MEFISTO

Analysis of top weights in MEFISTO



Conserved developmental programs

Non-conserved developmental programs



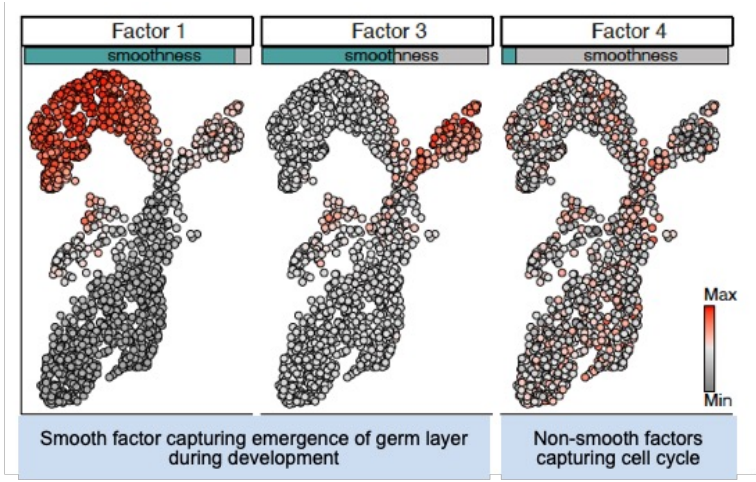
Velten et al, Nat Methods 2022

Example: Single cell data

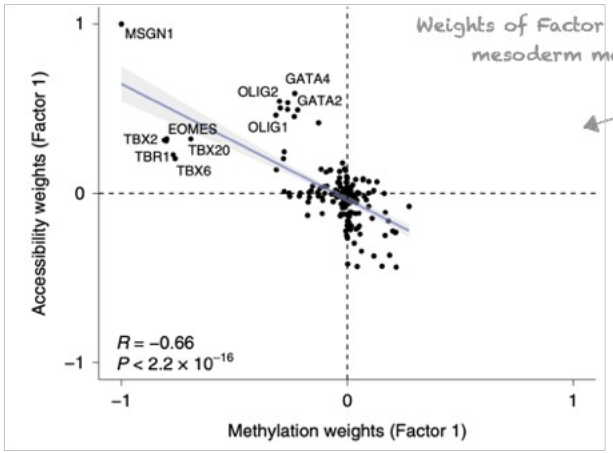
Data

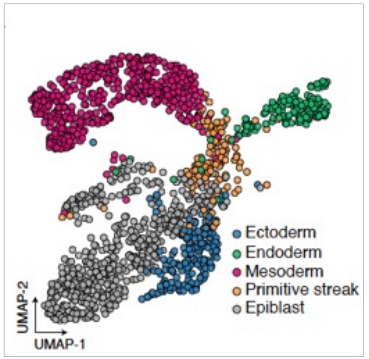
- 1,518 cells from multiple stages of early mouse development
- 3 omic layers (nucleosome, methylation, transcriptome)
- ~66 % of the cells only had transcriptome data

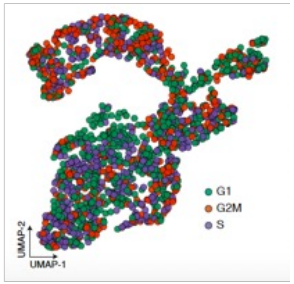
MEFISTO



Weights of Factor 1 pinpoint mesoderm makers

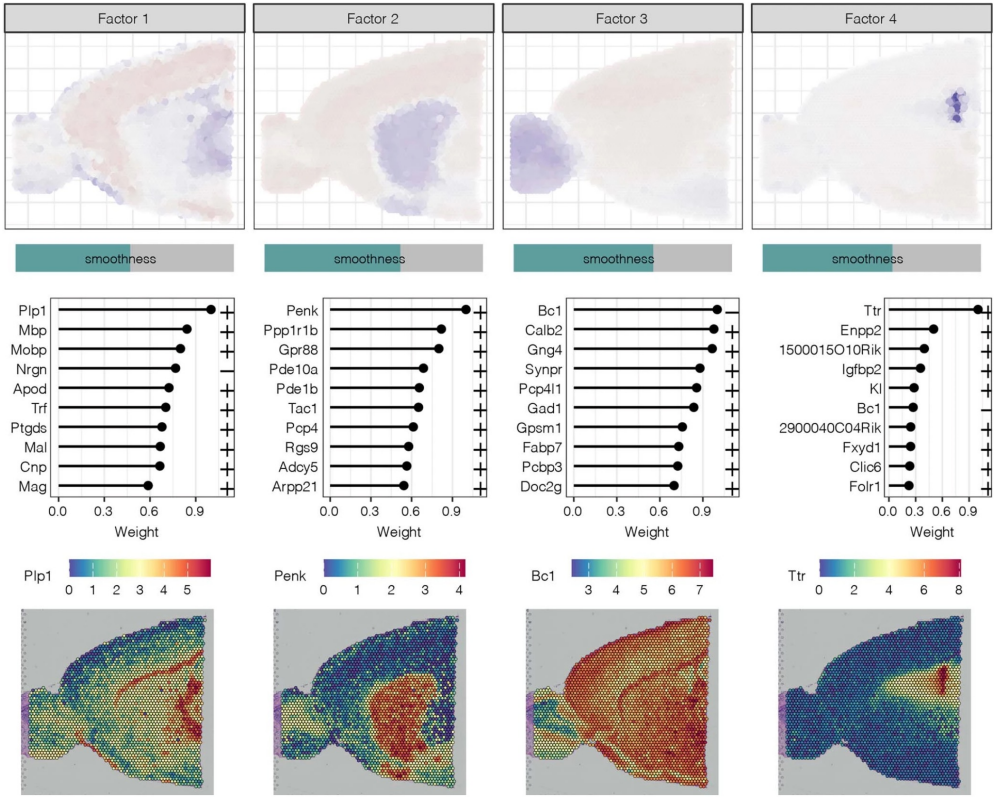






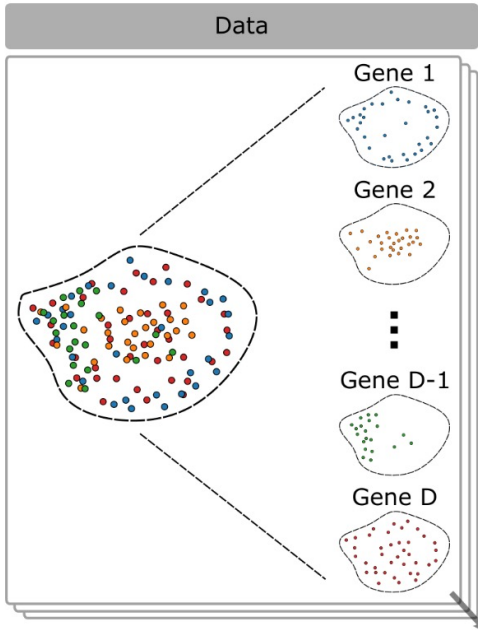
Velten et al, Nat Methods 2022

Example: Spatial data



Velten et al, Nat Methods 2022

Different likelihood models

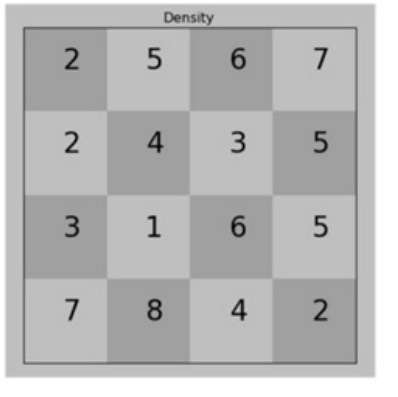


Cell with RNA molecule coordinates

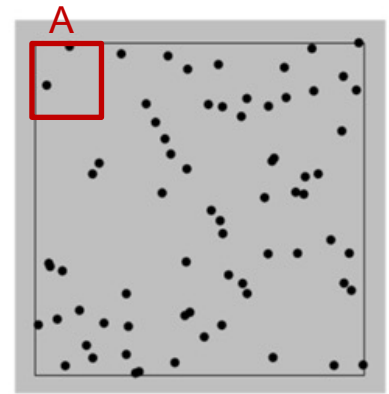
Walter et al, Bioinformatics 2023

Poisson point processes

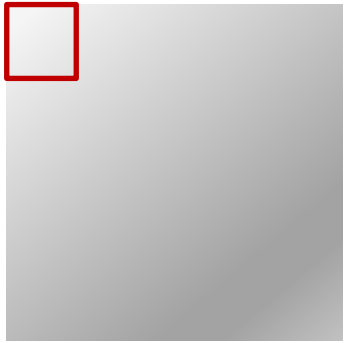
Spatial binning & Poisson likelihood



Poisson point process



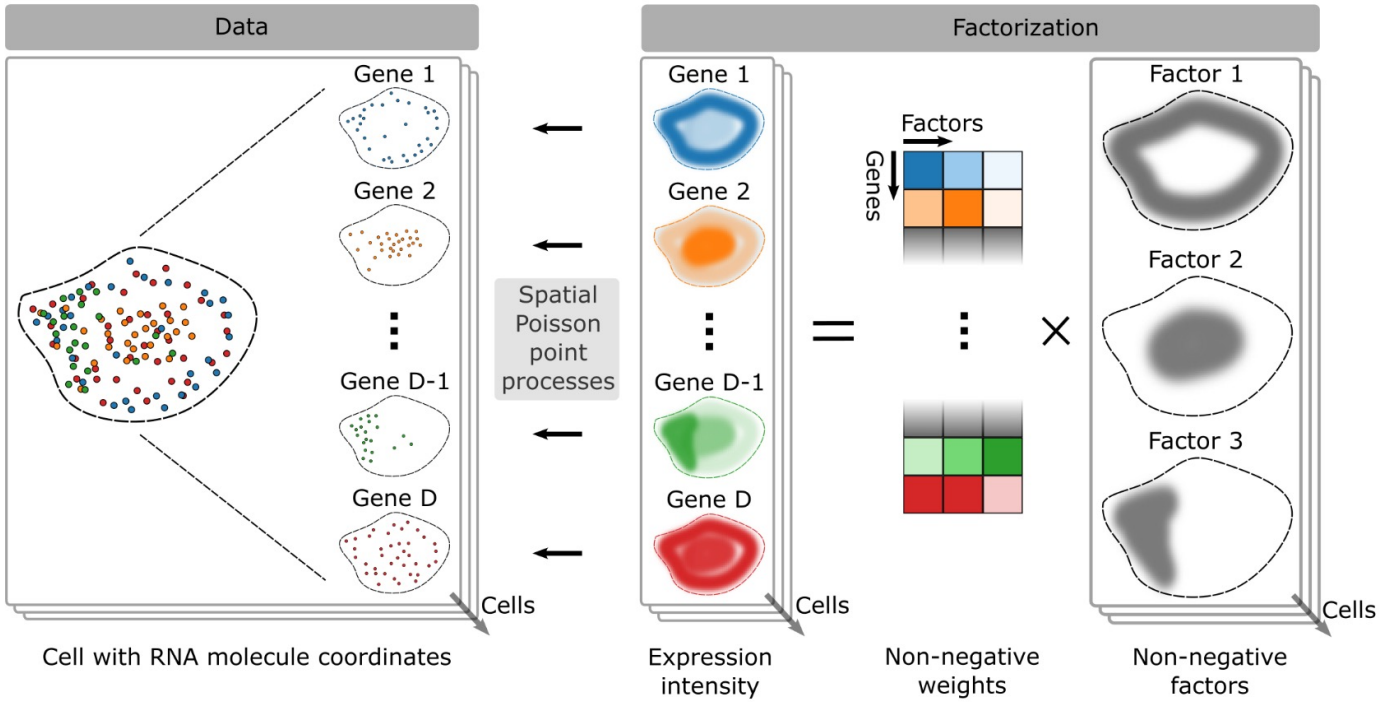
Intensity function λ



$$P\{N(A) = n\} = \frac{\lambda(|A|)^n}{n!} e^{-\lambda|A|}$$

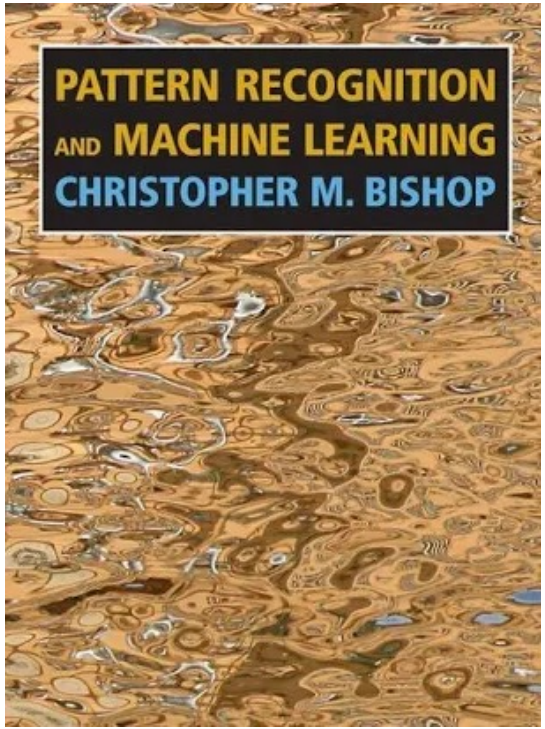
Adapted from here

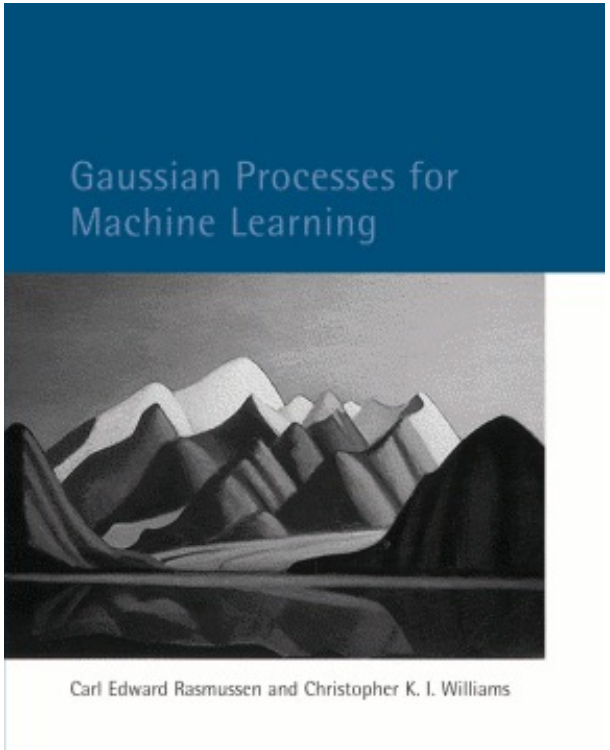
PP-GPFA for FISH data: FISHFactor



Walter et al, Bioinformatics 2023

Further reading





Questions?