Data handling for multi-modal single cell data using muon

EMBO Practical Course
Integrative analysis of multi-omics data

EMBL
September 21, 2022


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Max Frank


Ilia Kats

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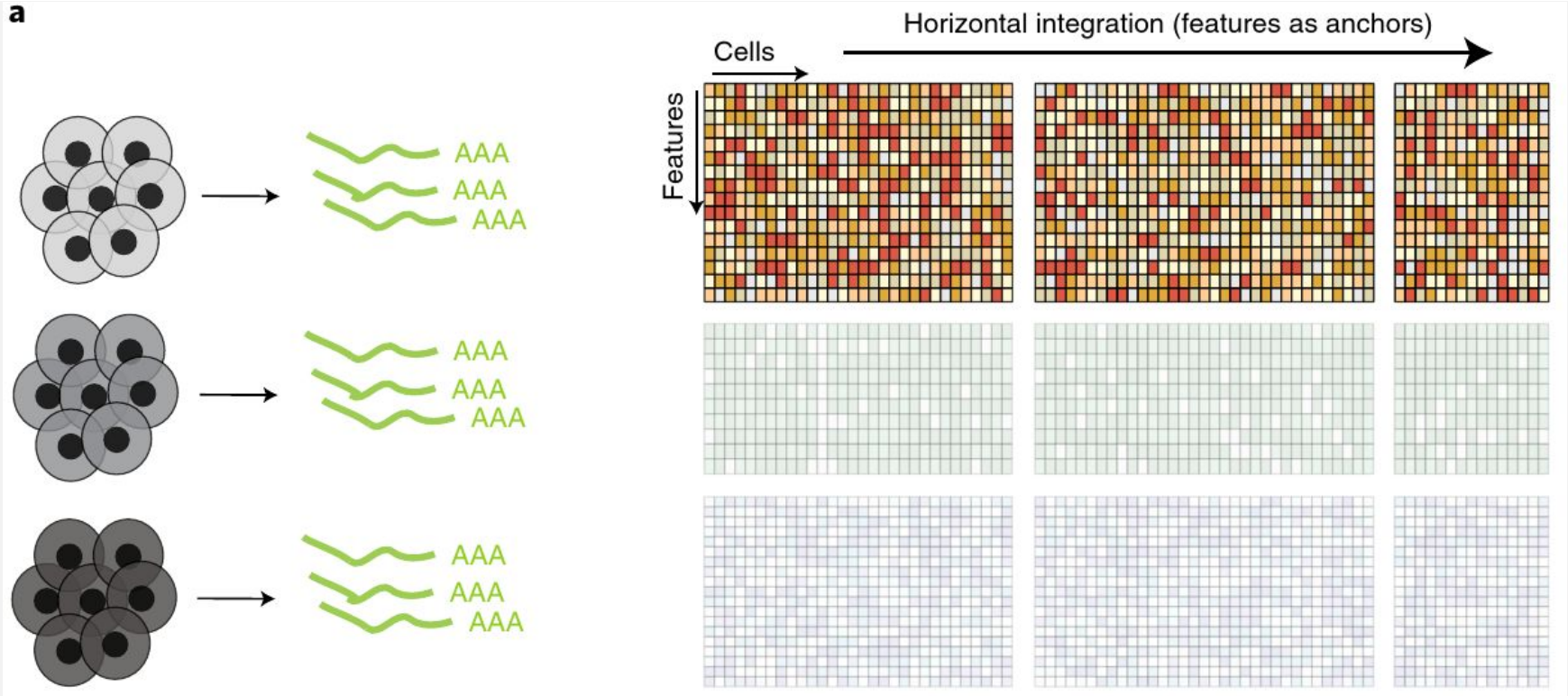
Outline

1. Types of multimodal data integration
2. Single-cell data
3. Intro to AnnData and MuData
    a. Generic solution, primary focus is single-cell data
4. MuData for scATAC (peaks, windows), CITE-seq (prot counts), scNMT-seq data
5. Cross-language functionality (R)

6. Notebook: AnnData / MuData. Example MuData CITE-seq dataset.

Three types of data integration



Argelaguet et al., 2021

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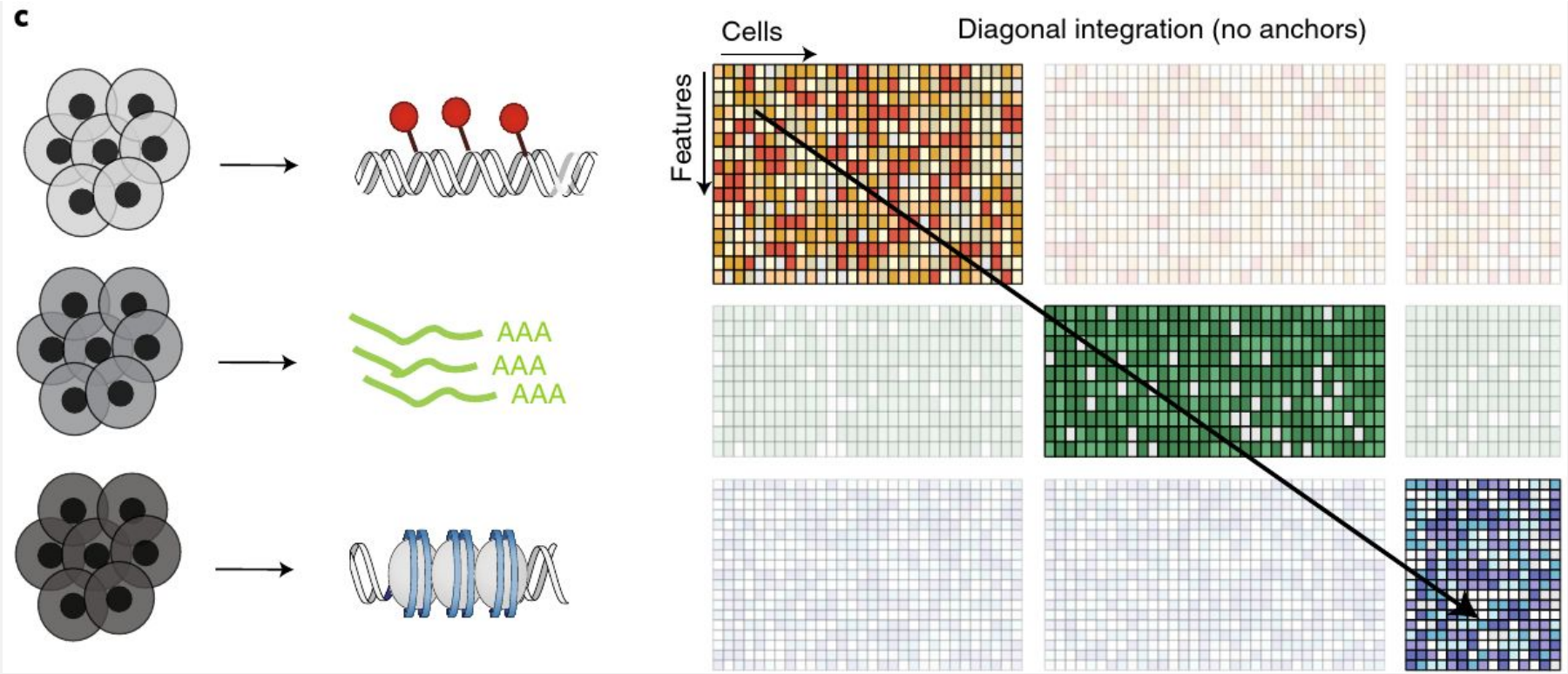
Three types of data integration



Argelaguet et al., 2021

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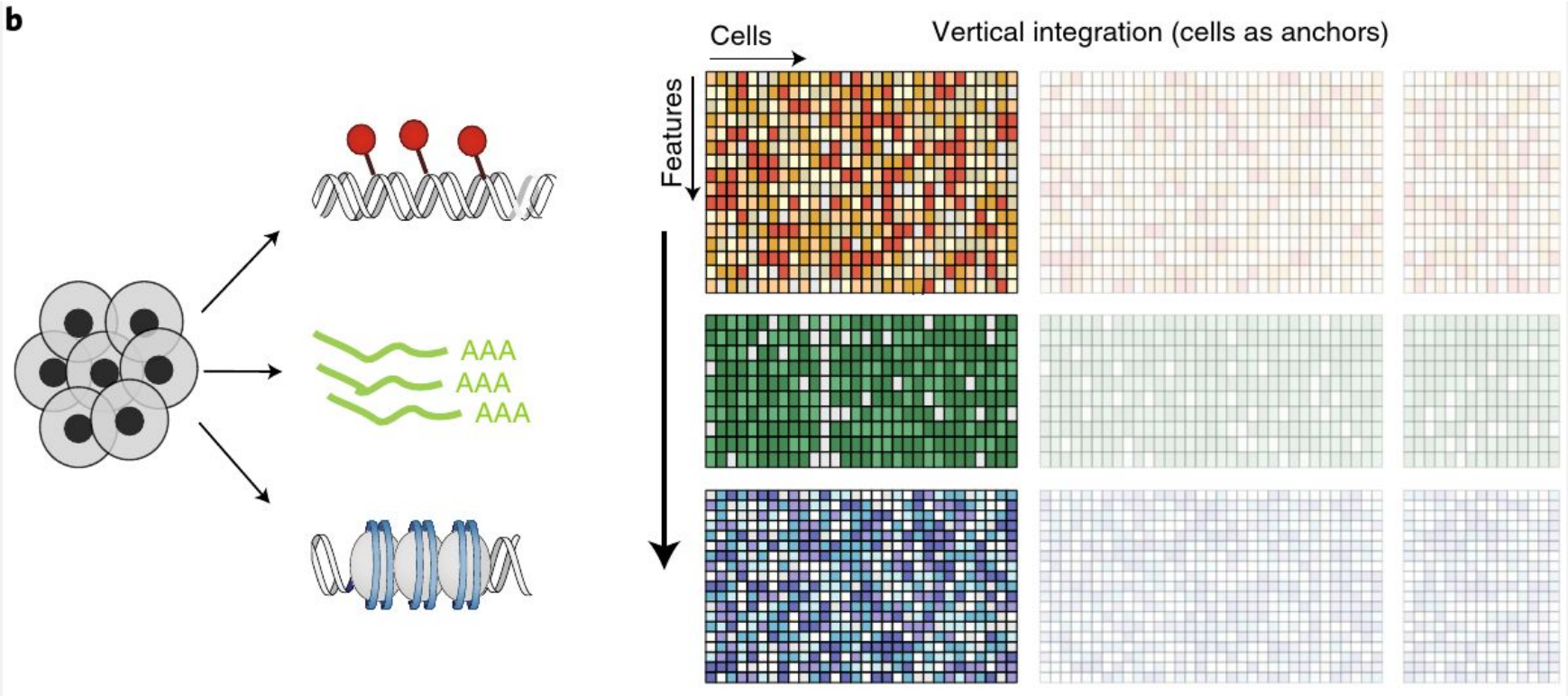
Three types of data integration



Argelaguet et al., 2021

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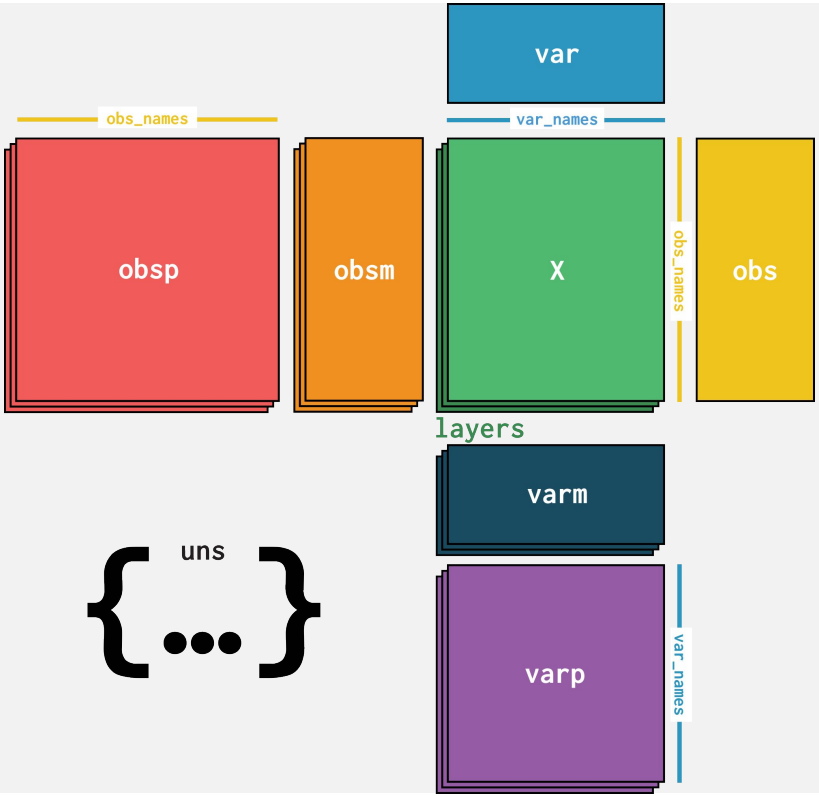
Single-cell vs bulk

Compared to bulk (classical) sequencing data, single-cell data is

- Much sparser: many features are not detected in many cells (drop-outs)
- Noisier: Coefficient of variation for Poisson sequencing noise decreases with sequencing depth
- Contains more technical artifacts: doublets, ambient RNA

Data structures for single-cell data: AnnData



Count matrix with metadata

- `X`: count matrix
- `var`: DataFrame with gene metadata
- `var_names`: index of `var` with gene names
- `obs`: DataFrame with observation (cell) metadata
- `obs_names`: index of obs with (usually) cell barcodes
- `varm`, `obsm`: dictionaries of arrays or DataFrames, aligned to `var` and `obs`
- `varp`, `obsp`: dictionaries of arrays with pairwise annotation, e.g. pairwise distances
- `uns`: dictionary with arbitrary data

https://anndata.readthedocs.io

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Data structures for single-cell data: AnnData

```
Python 3.10.6 (main, Aug  3 2022, 17:39:45) [GCC 12.1.1 20220730]
Type 'copyright', 'credits' or 'license' for more information
IPython 8.5.0 -- An enhanced Interactive Python. Type '?' for help.

In [1]: import anndata
   ...: import numpy as np
   ...: from scipy.sparse import csr_matrix
   ...: counts = csr_matrix(np.random.poisson(1, size=(100, 2000)))
   ...: adata = anndata.AnnData(counts, dtype=np.float32)
   ...: adata
   ...:
Out[1]: AnnData object with n_obs × n_vars = 100 × 2000
```

```
In [6]: adata
Out[6]:
AnnData object with n_obs × n_vars = 100 × 2000
    obs: 'cell_type'
```

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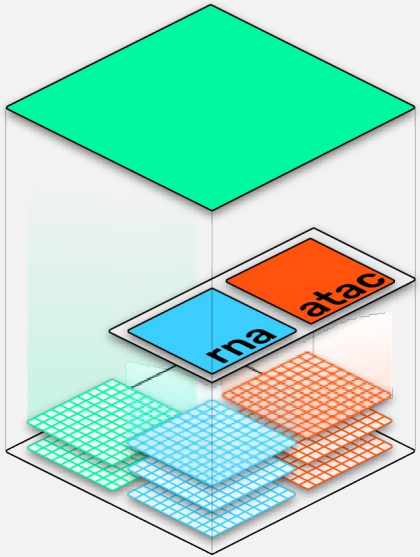
Data structures for single-cell multimodal data: MuData



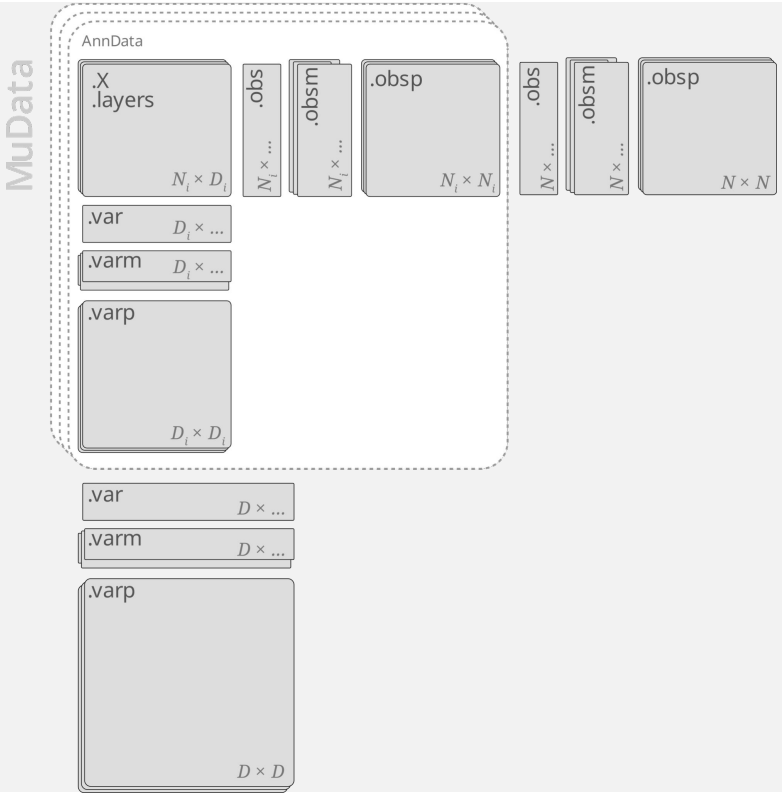
MuData –
a multimodal
data container

Individual
modalities

Count matrices
Metadata
Derived data

Dictionary of AnnData objects

Data structures for single-cell multimodal data: MuData



- AnnData objects are aligned to observations
- Assumption: each AnnData has different variables, but observations can overlap
- Joint subsetting of AnnData objects
- Additional metadata on the global level
- Easy access to individual modalities

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Data structures for single-cell multimodal data: MuData

```
In [20]: import mudata as md

In [21]: bdata.var_names = [f"Protein_{i}" for i in range(bdata.n_vars)]

In [22]: mudata = md.MuData({"rna": adata, "prot": bdata})

In [23]: mudata
Out[23]:
MuData object with n_obs × n_vars = 100 × 4000
  2 modalities
    rna:        100 x 2000
      obs:      'cell_type'
      layers:   'log_transformed'
    prot:       35 x 2000
      obs:      'cell_type'
      layers:   'log_transformed'
```

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1. Gene expression
2. ...
3. ...
4. ...
5. ...
6. ...

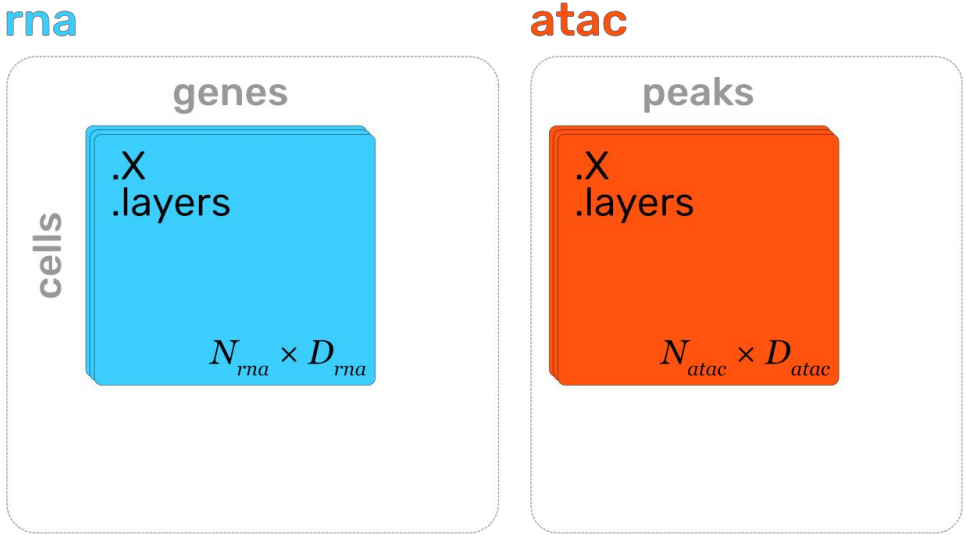
Multimodal single-cell datasets

1. Gene expression
2. Chromatin accessibility
3. DNA methylation
4. Histone modifications
5. Chromatin conformation
6. Protein abundance (intranuclear, surface)

Multimodal single-cell datasets

MuData for ...

1. scRNA+scATAC-seq
   a. SNARE-seq
   b. SHARE-seq
   c. 10x Multiome
2. CITE-seq
3. scNMT-seq



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MuData for ...

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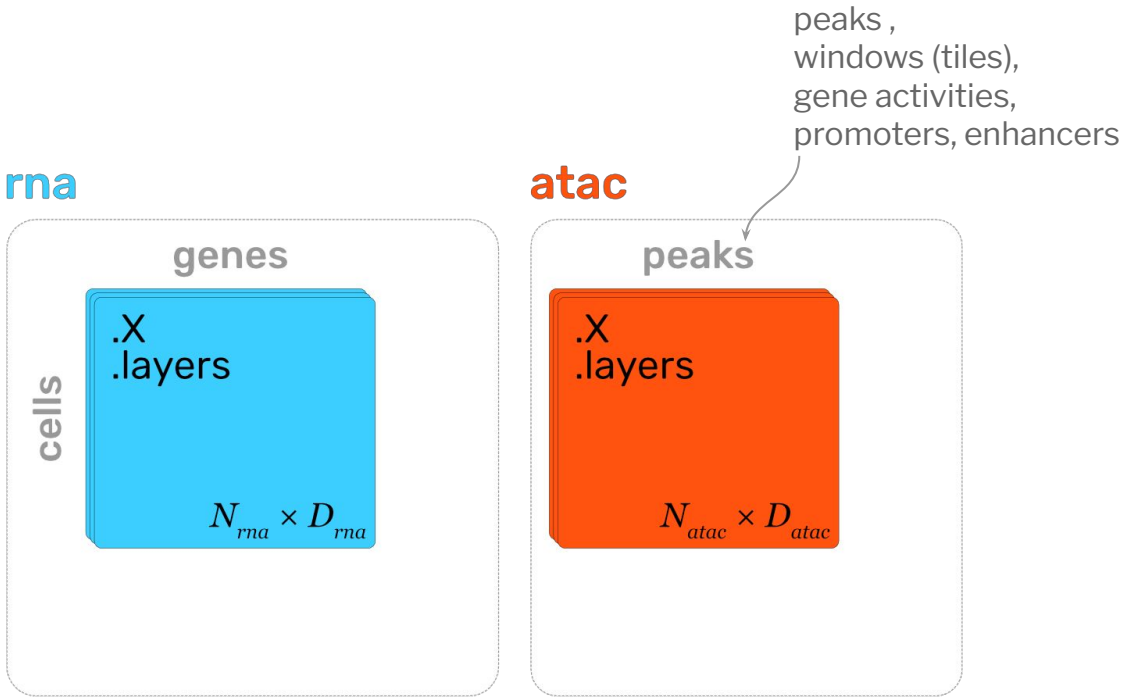

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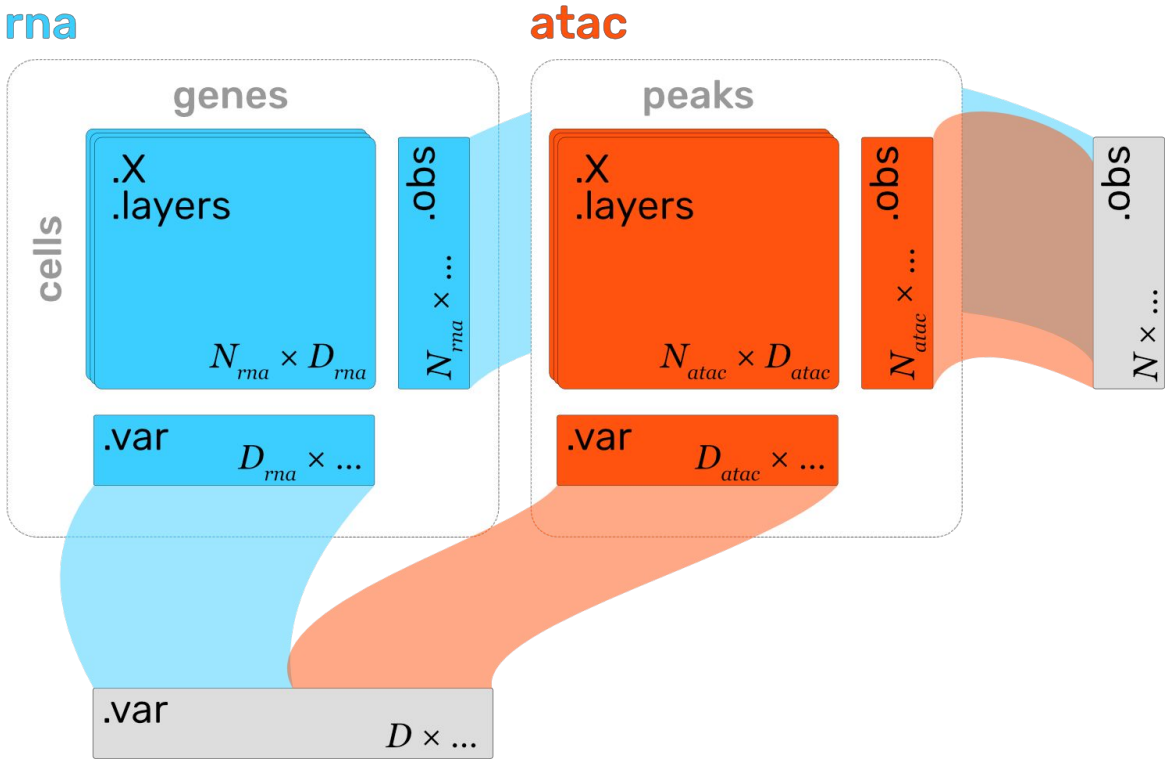

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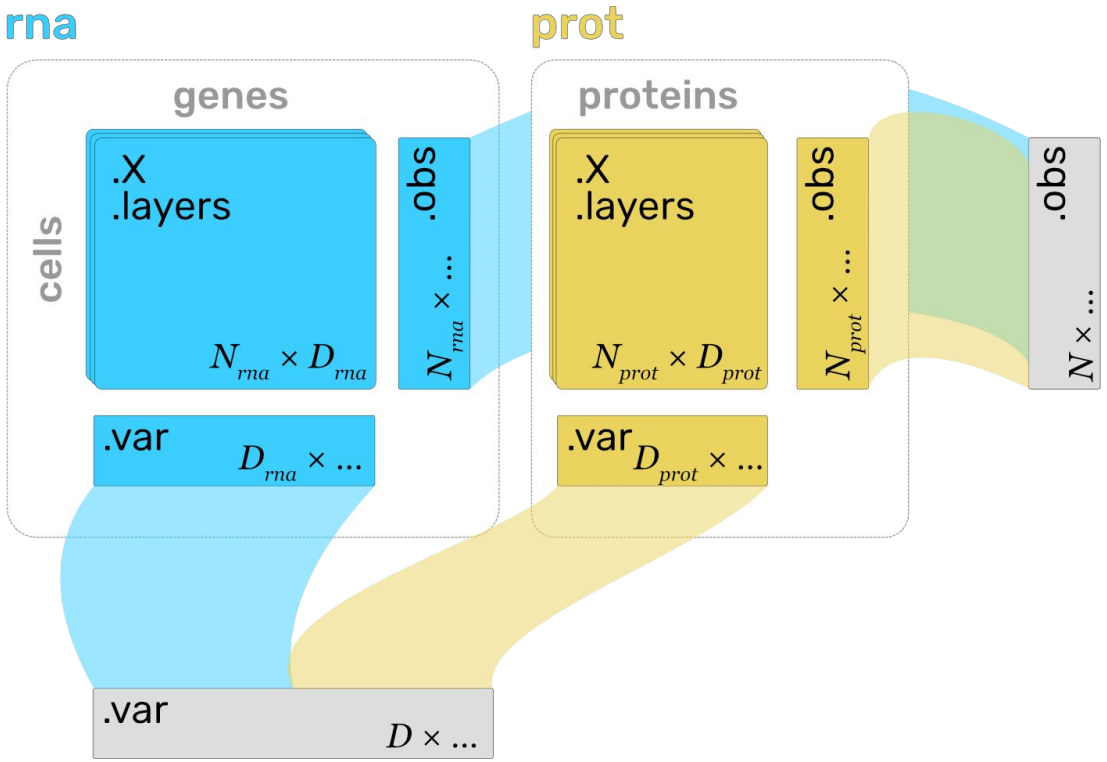

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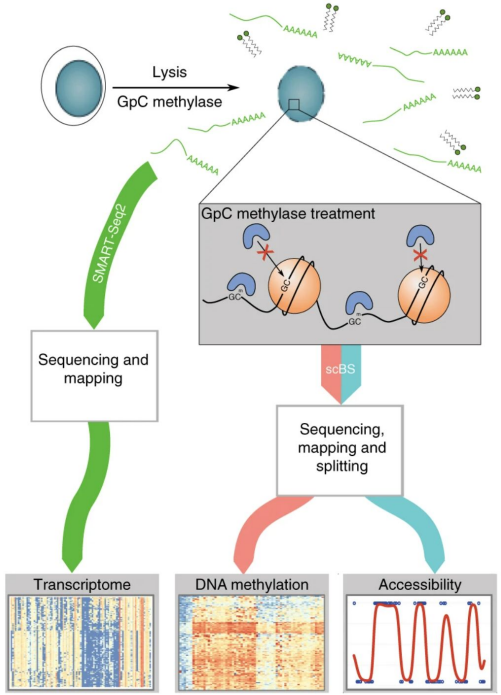
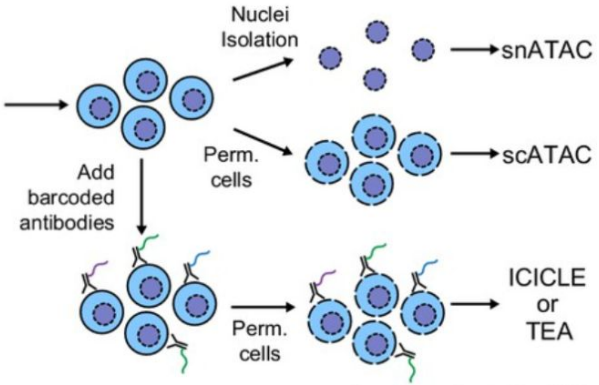
MuData for ...

1. scRNA+scATAC-seq
   a. SNARE-seq
   b. SHARE-seq
   c. 10x Multiome
2. CITE-seq
3. scNMT-seq, TEA-seq, ...





Clark, Argelaguet et al., 2018; Swanson et al., 2021

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Language-agnostic data serialisation

1. **.h5ad/.h5mu**
2. **MuData(MAE)**
3. MuDataSeurat
4. Muon.jl

```
> library(MuData)
> (mdata ← readH5MU("pbmc5k_citeseq.h5mu", backed = TRUE))
# A MultiAssayExperiment object of 2 listed
#  experiments with user-defined names and respective classes.
#  Containing an ExperimentList class object of length 2:
#  [1] prot: SingleCellExperiment with 32 rows and 3891 columns
#  [2] rna: SingleCellExperiment with 17806 rows and 3891 columns
> class(assays(mdata[["prot"]])[['counts']])
# [1] "DelayedMatrix"
# attr(,"package")
# [1] "DelayedArray"
```

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Language-agnostic data serialisation

1. **.h5ad/.h5mu**
2. MuData(MAE)
3. **MuDataSeurat**
4. Muon.jl

```
library(MuDataSeurat)
(mdata <- ReadH5MU("pbmc5k_citeseq.h5mu"))
# An object of class Seurat
# 17838 features across 3891 samples within 2 assays
# Active assay: prot (32 features, 32 variable features)
#  1 other assay present: rna
#  6 dimensional reductions calculated: MOFA, UMAP, protPCA, #
protUMAP, rnaPCA, rnaUMAP
```

Language-agnostic data serialisation

1. **.h5ad/.h5mu**
2. MuData(MAE)
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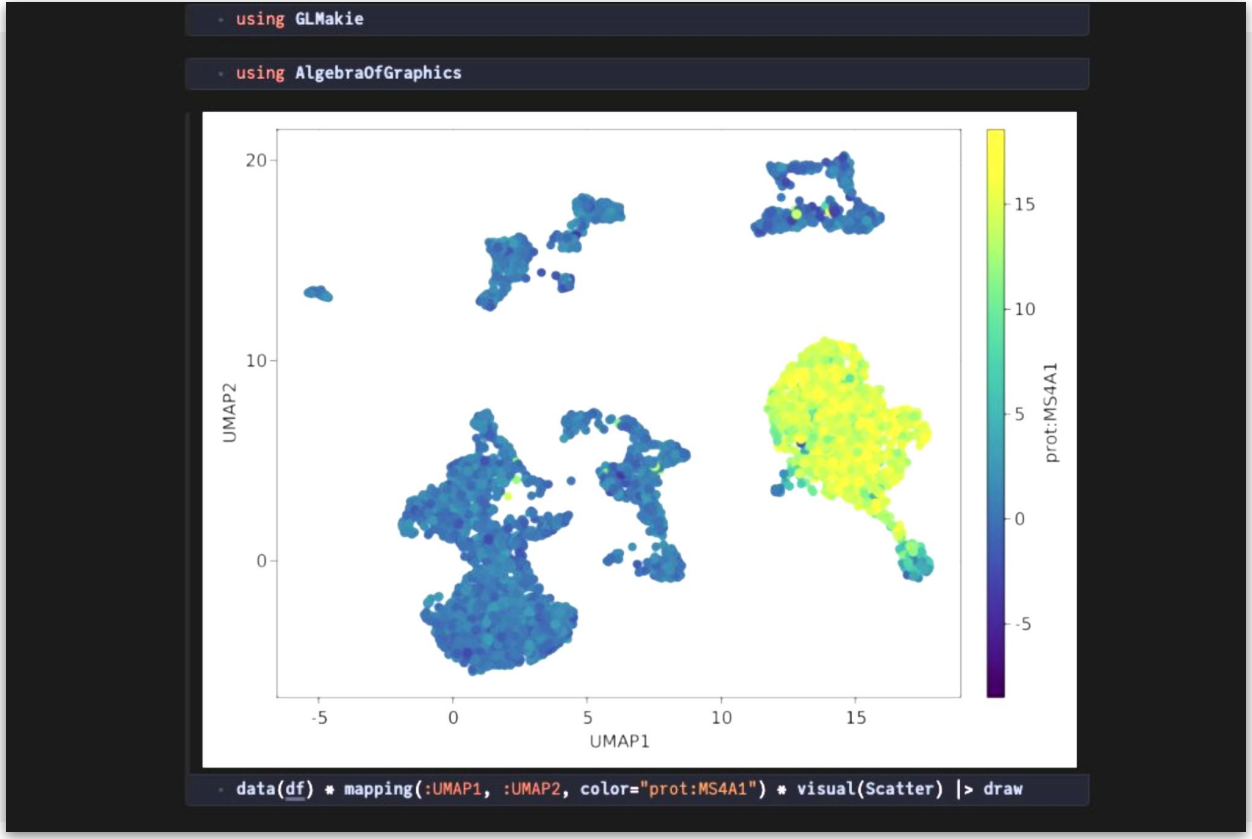

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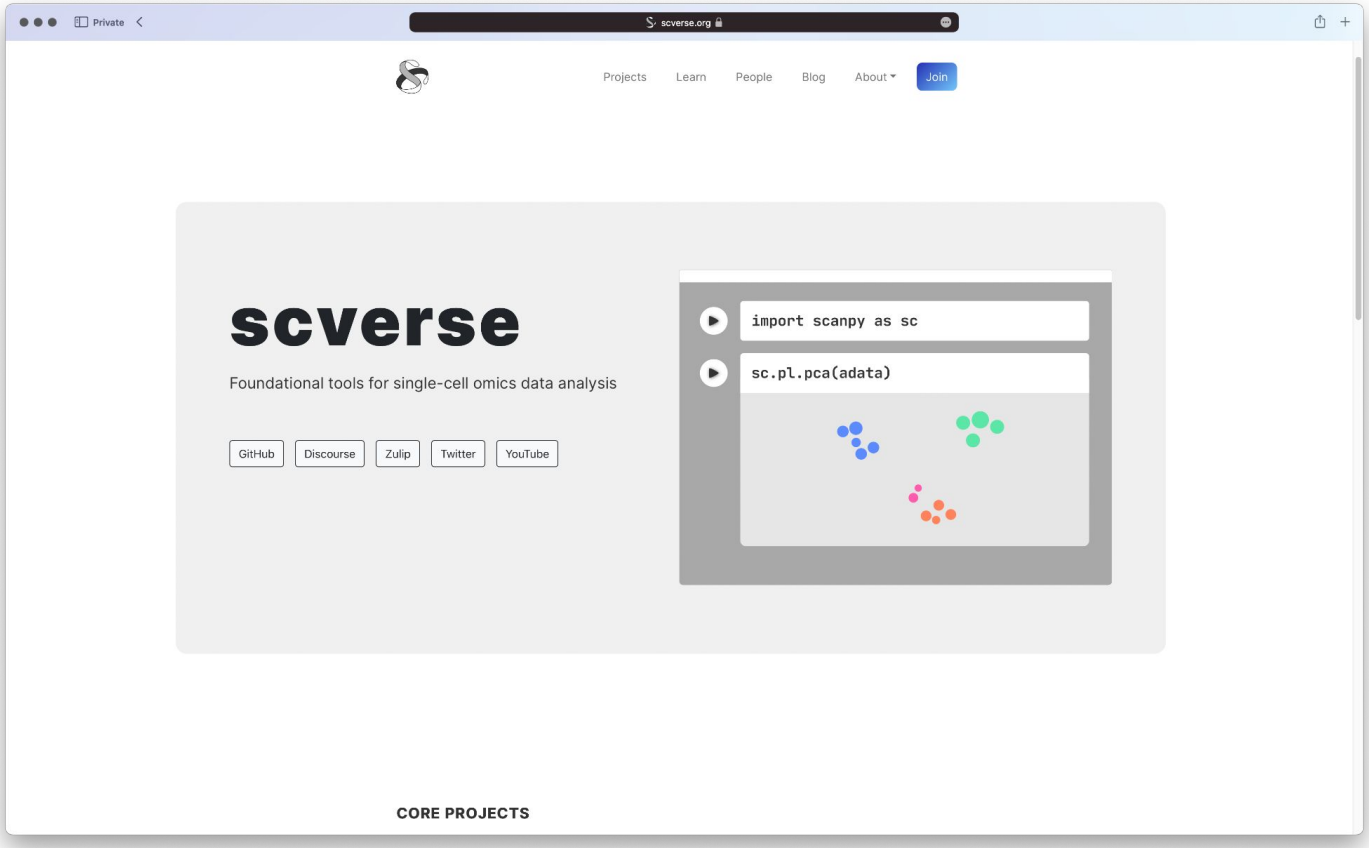
scverse



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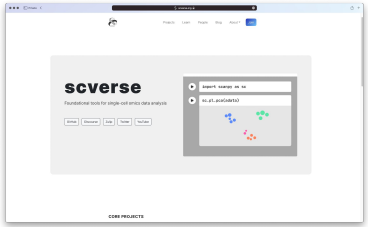
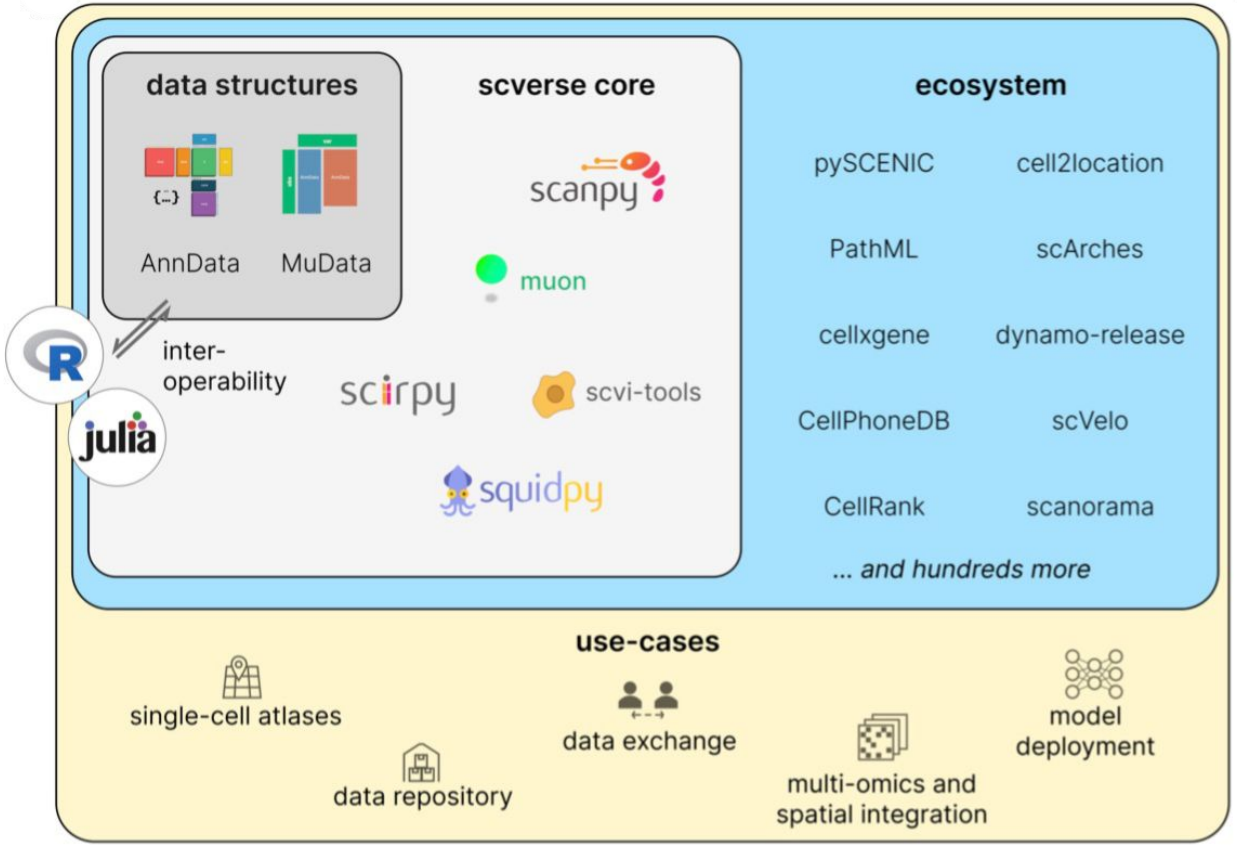
scverse





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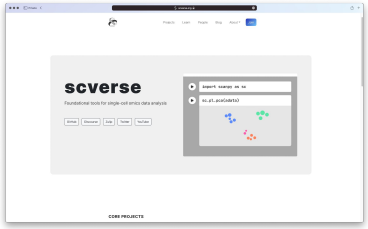
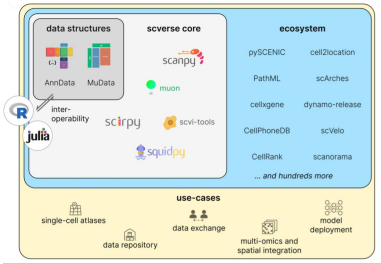
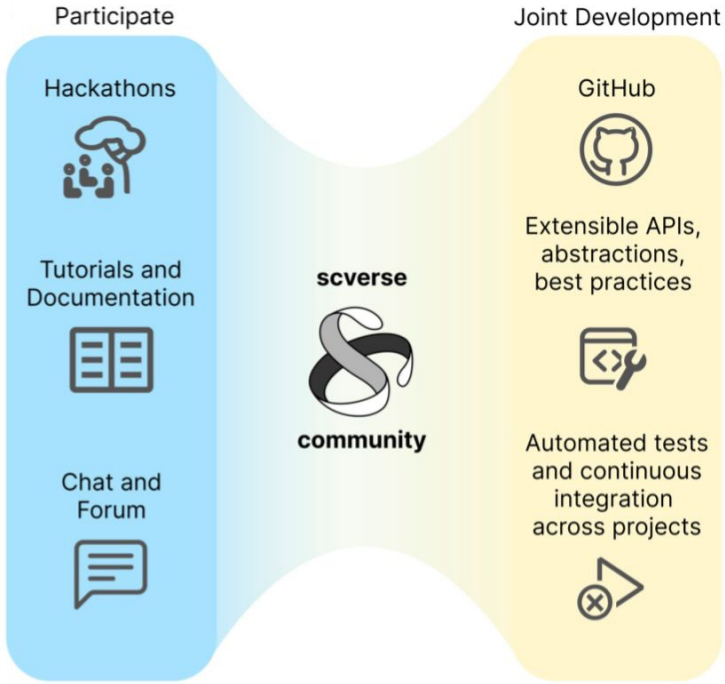
scverse

scverse.org github.com/scverse scverse.zulipchat.com
twitter.com/scverse_team discourse.scverse.org/







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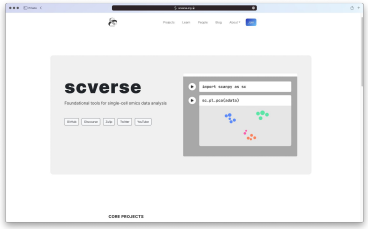
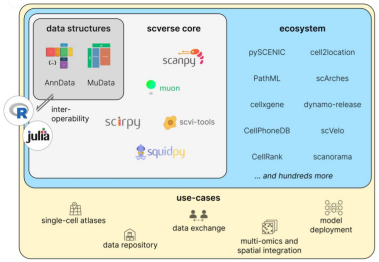
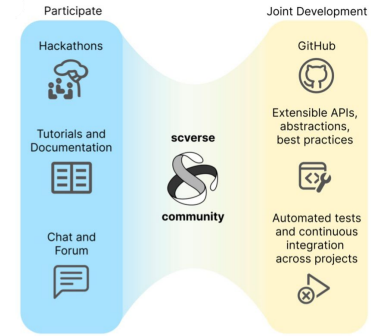
scverse







Core people...

Danila Bredikhin | Adam Gayoso | Lukas Heumos | Ilia Kats | Giovanni Palla | Gregor Sturm | Isaac Virshup

Francesca Finotello | Oliver Stegle | Fabian Theis | Alex Wolf | Nir Yosef

Bonnie Berger | Dana Pe'er | Aviv Regev | Sarah Teichmann

... and hundreds contributors!

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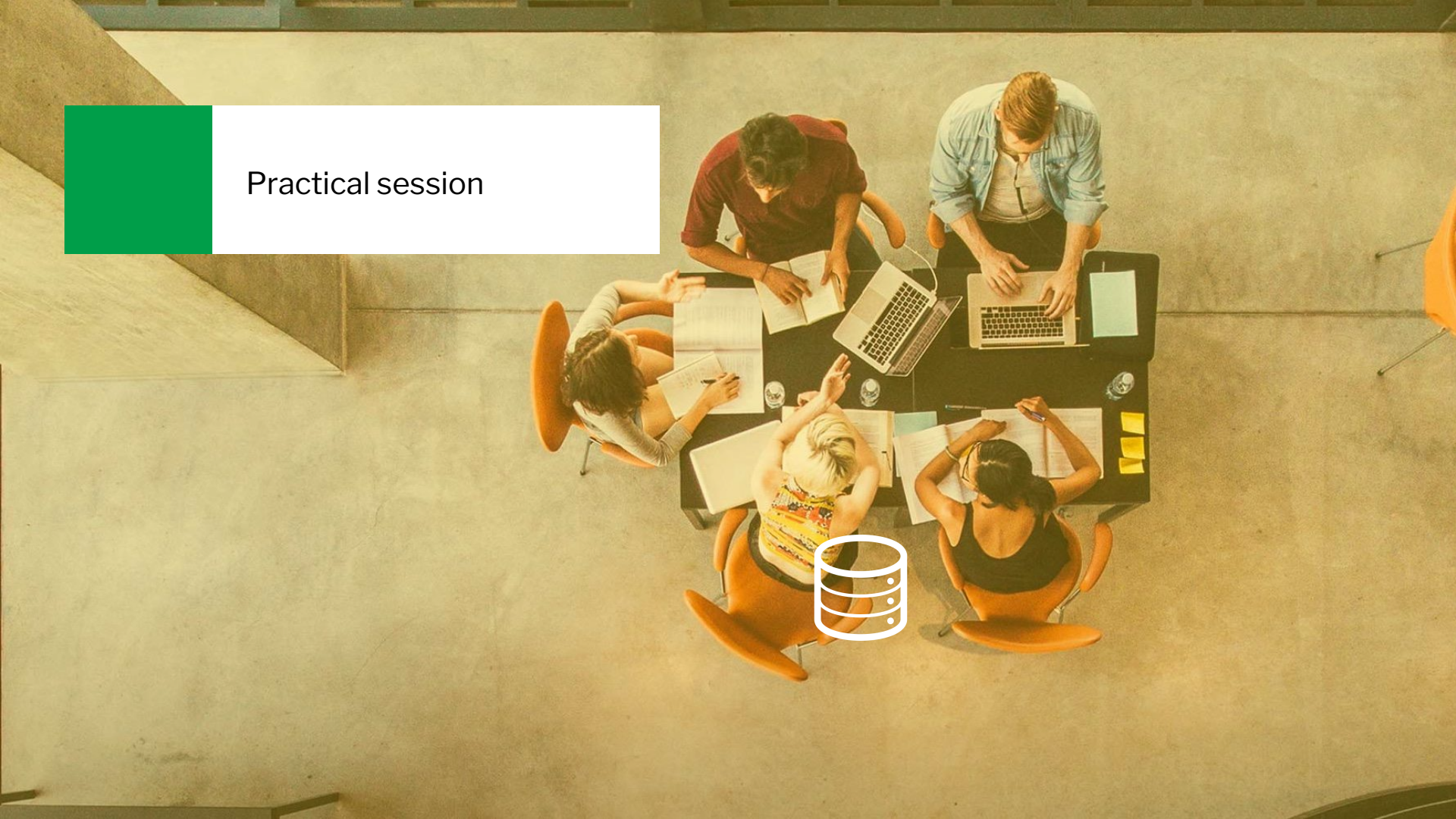
Practical session



Single-cell multi omics integration

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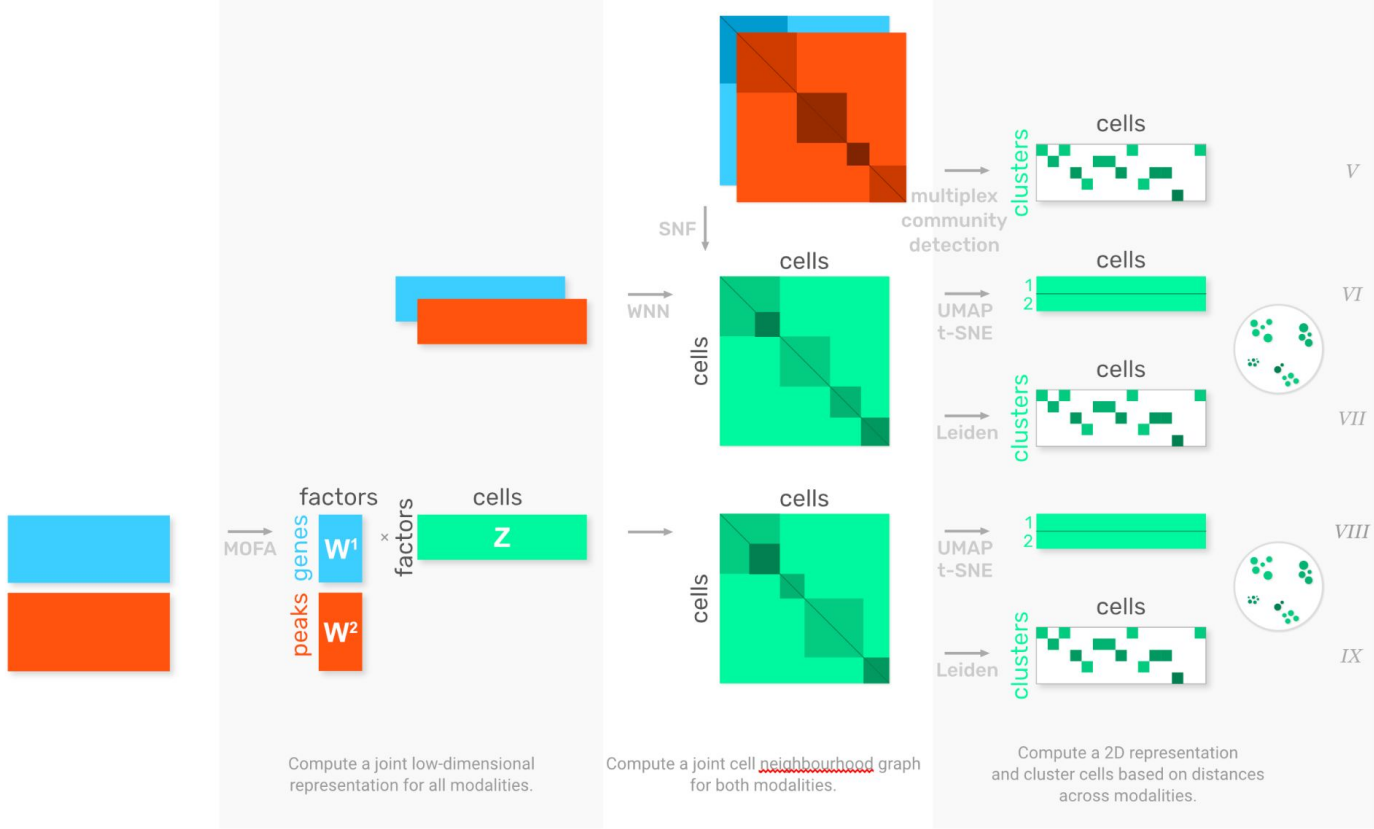
Outline

1. Integration strategies (MOFA, WNN, DL)
2. Integration examples
    a. scRNA + scATAC integration
    b. CITE-seq integration
    c. TEA-seq

3. Notebook: CITE-seq data integration with MOFA

Different integration strategies with a uniform API



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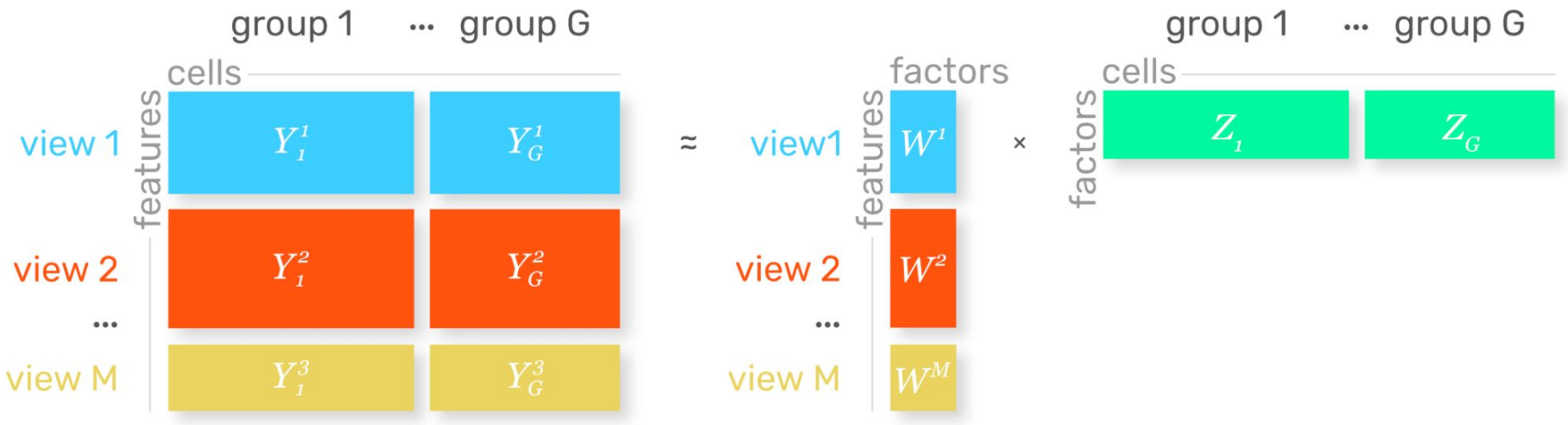
Multi-omics factor analysis (v2)



Argelaguet, Arnol, Bredikhin et al., 2020

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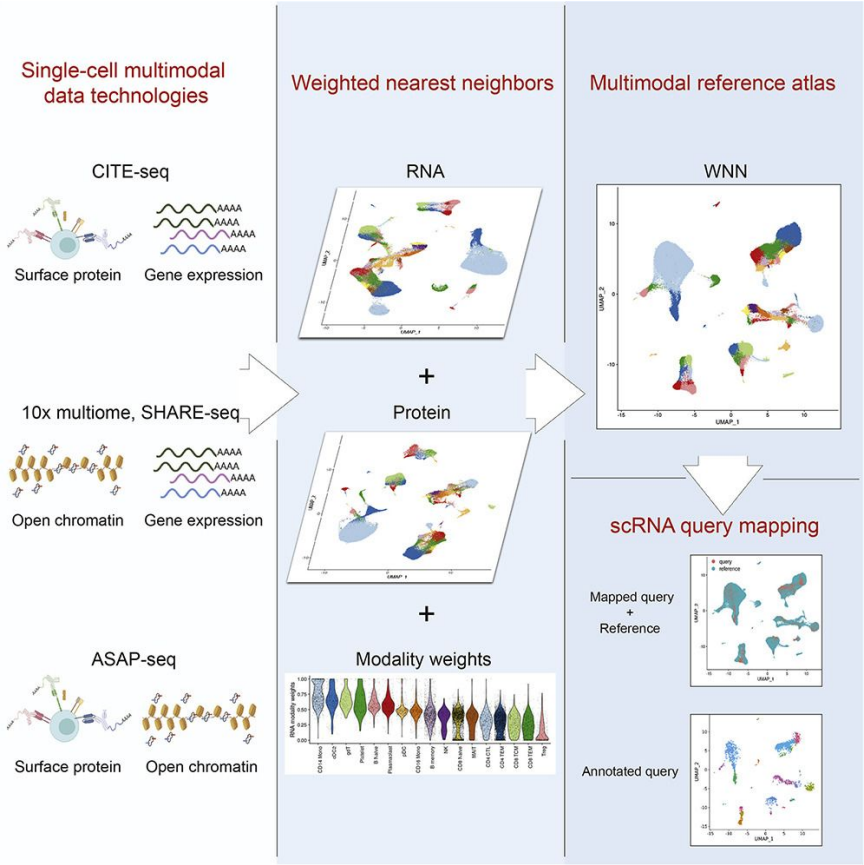
Weighted nearest neighbours (2 modalities)



Hao, Hao et al., 2021

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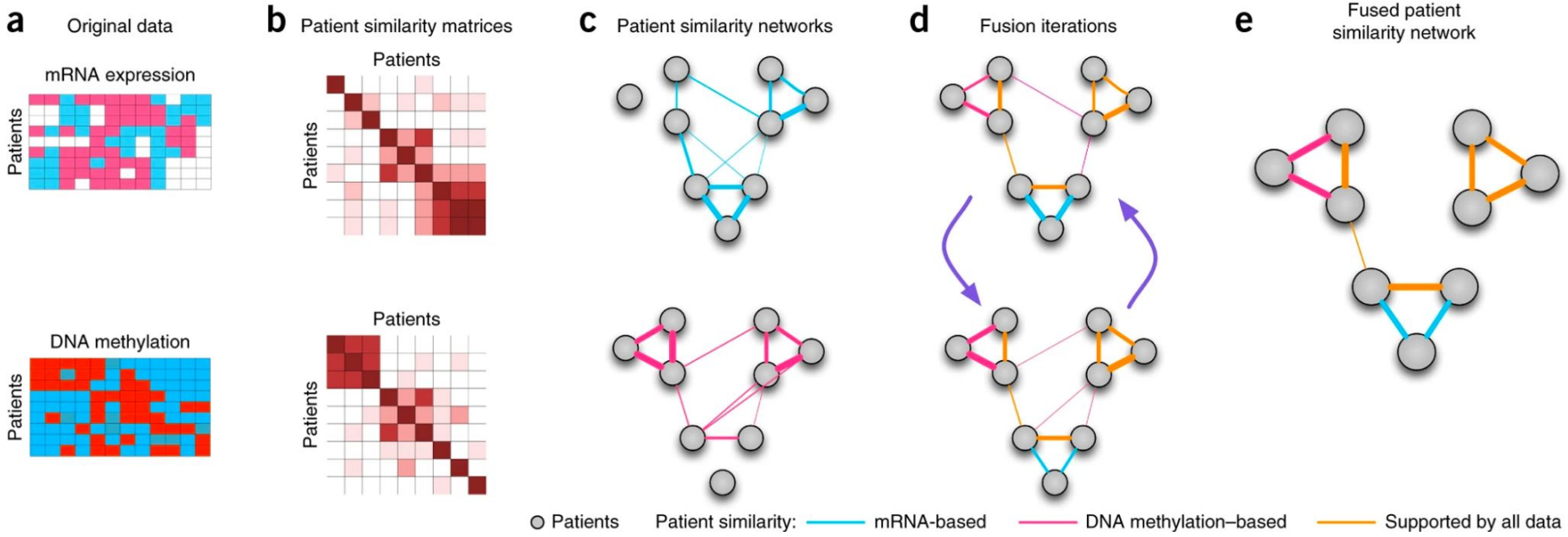
Similarity network fusion



Eang et al., 2014

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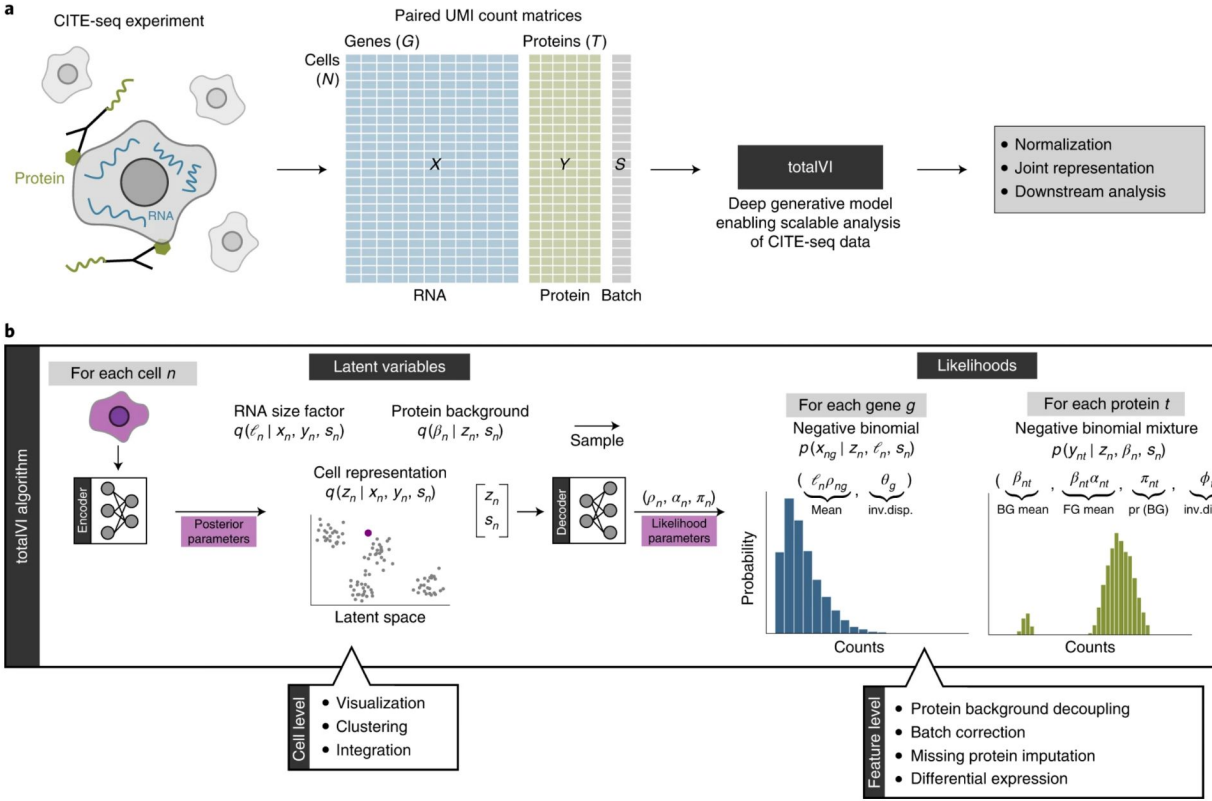
Deep learning-based (example: TotalVI)



Gayoso et al., 2021

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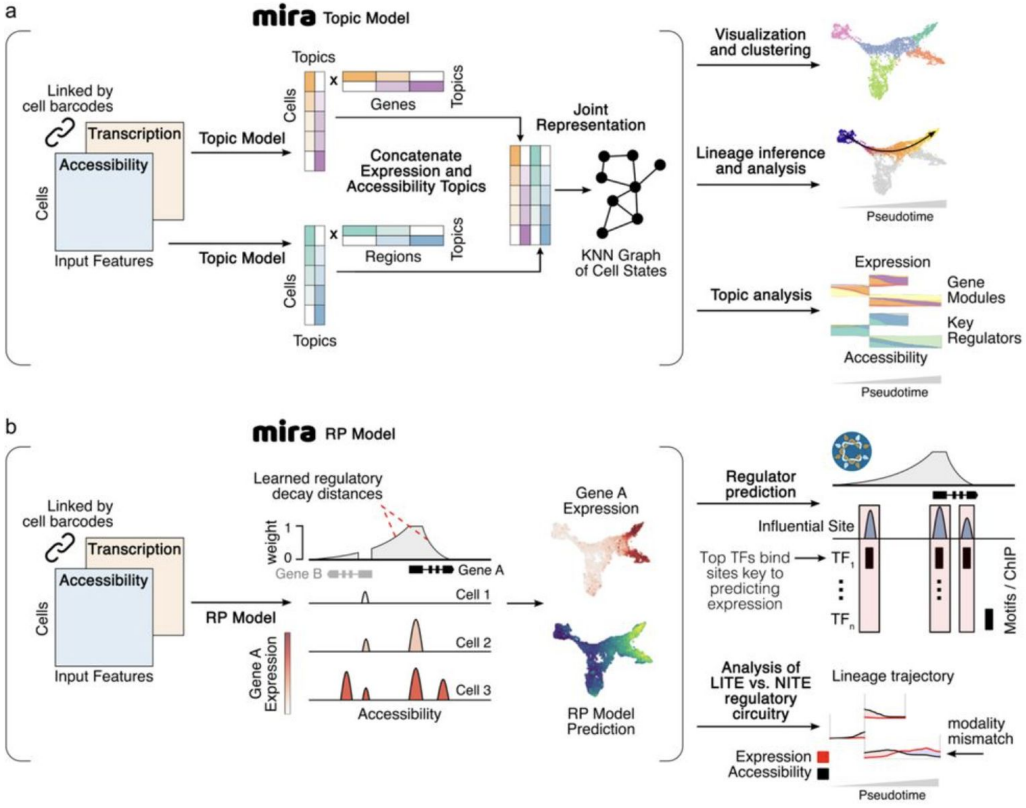
Deep learning-based (example: mira)



Lynch et al., 2022

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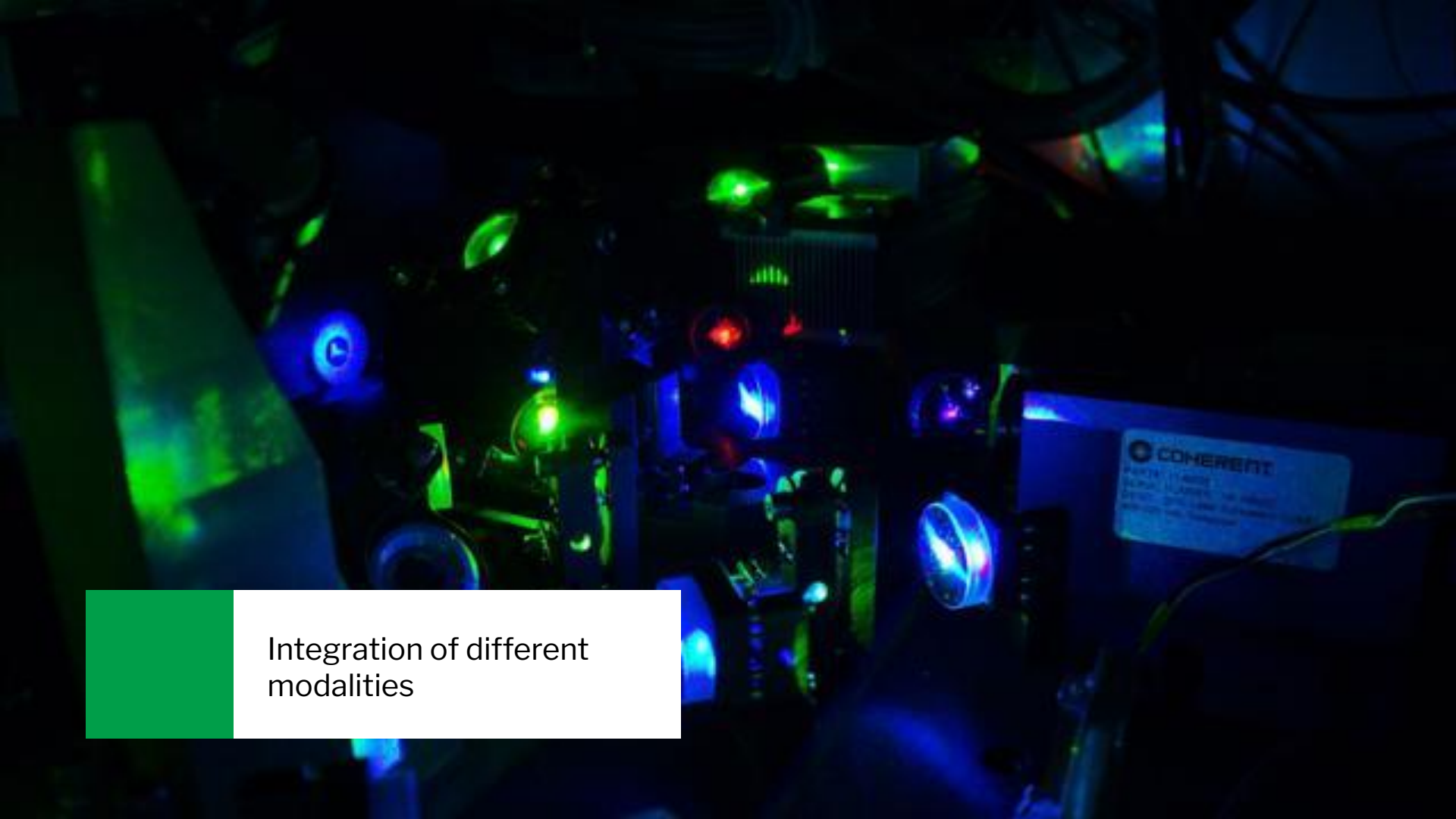
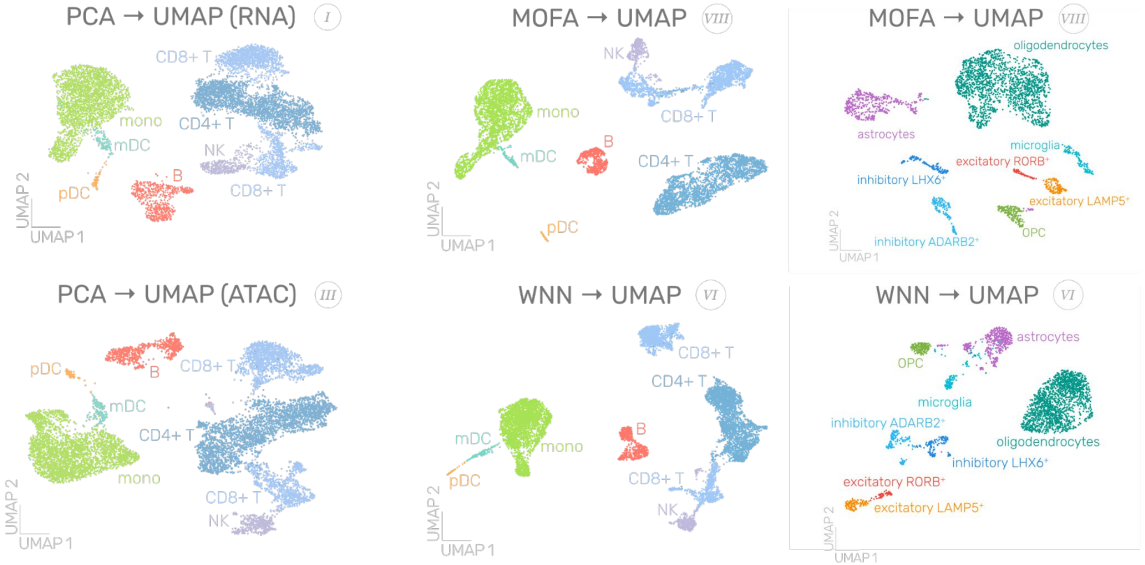
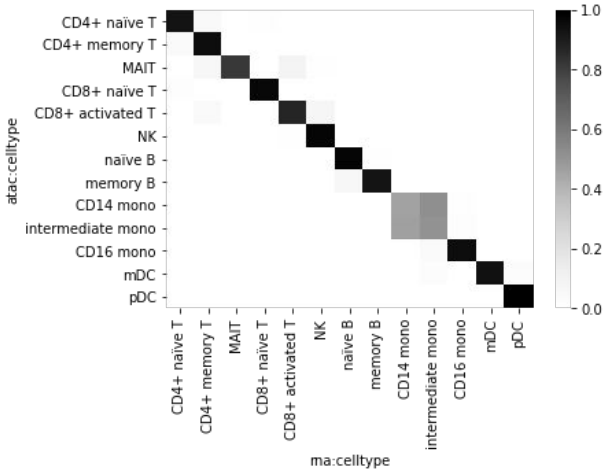


Integration of different modalities

scATAC-seq + scRNA-seq integration example





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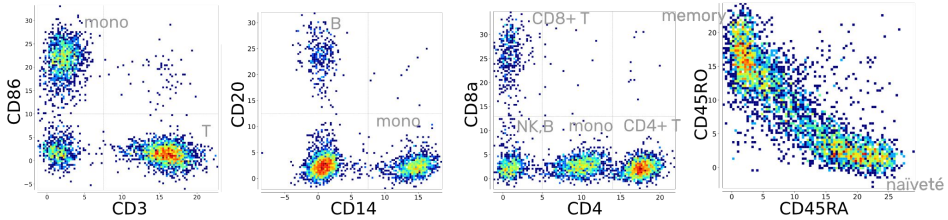
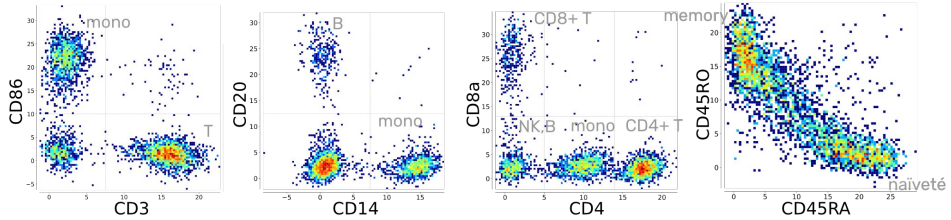
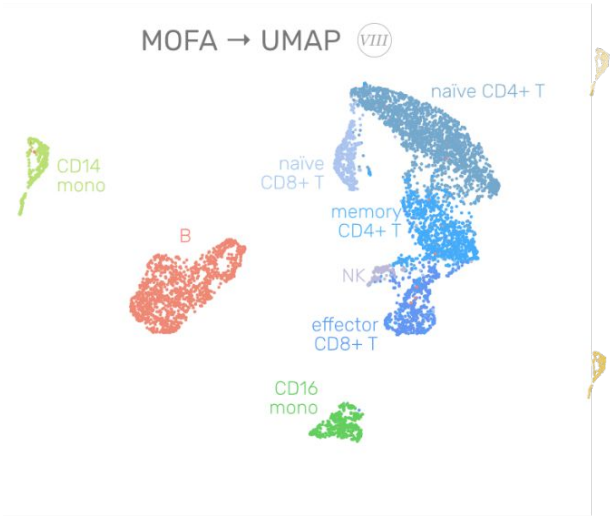
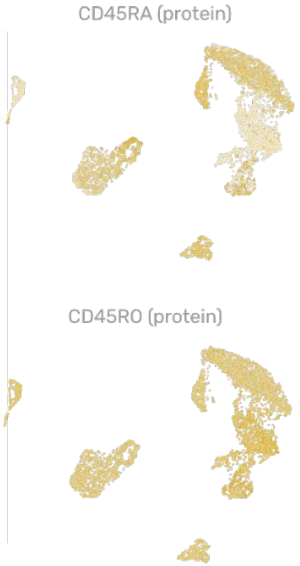
CITE-seq integration example

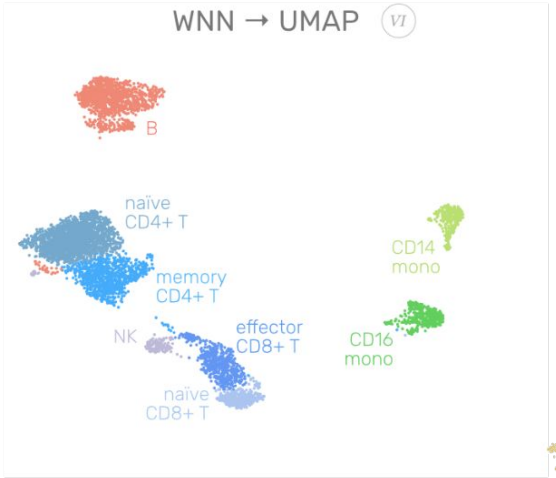


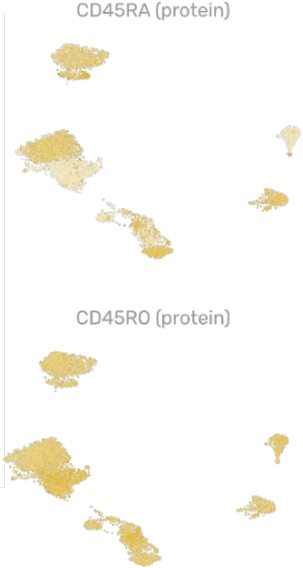
CITE-seq integration example











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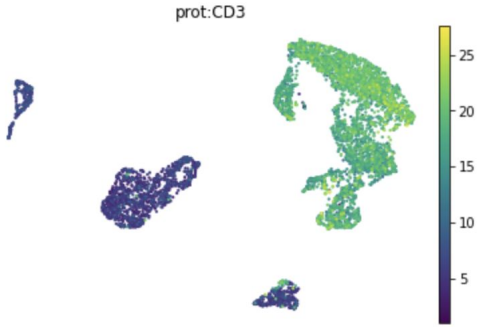
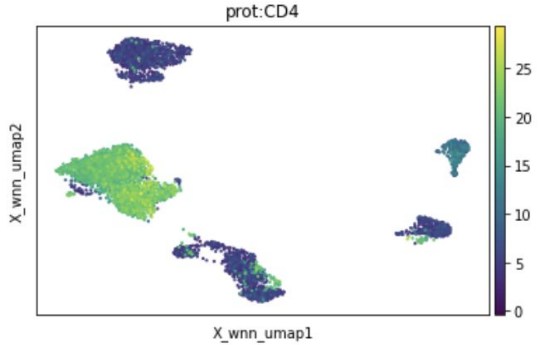
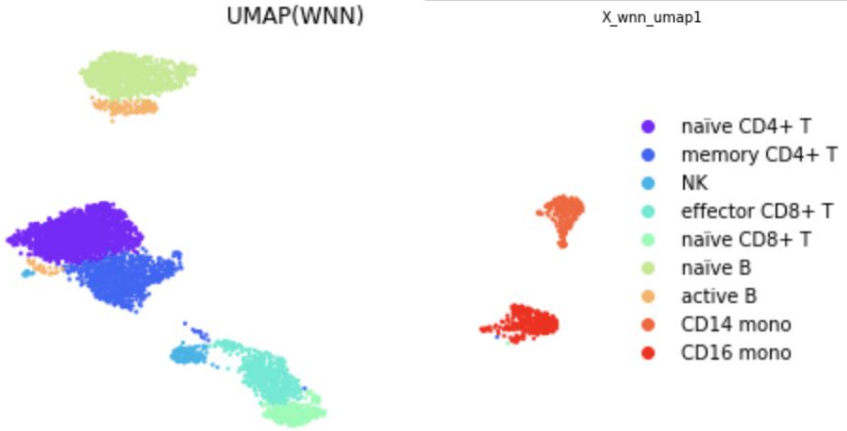
TEA-seq integration example (three modalities)

MOFA → UMAP



WNN → UMAP





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Practical session