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Molecular Biology

scMultiNODE: Integrative and Scalable Framework for Multi-Modal Temporal Single-Cell Data

Jiaqi Zhang

Department of Computer Science

Brown University

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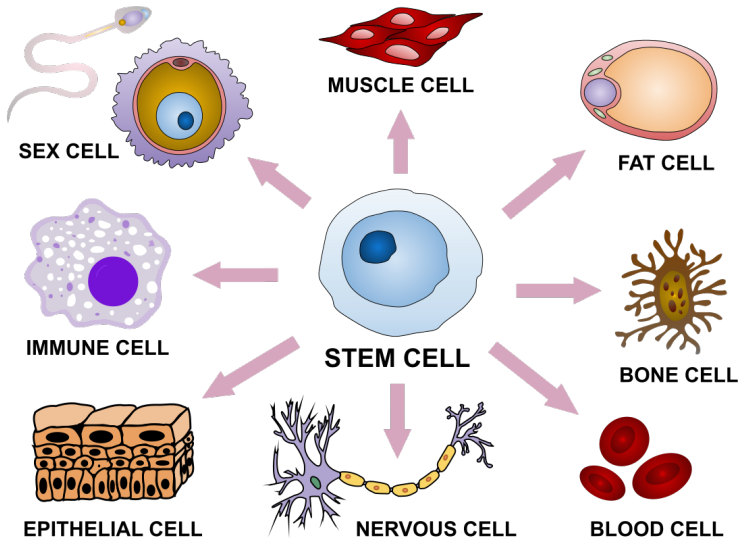
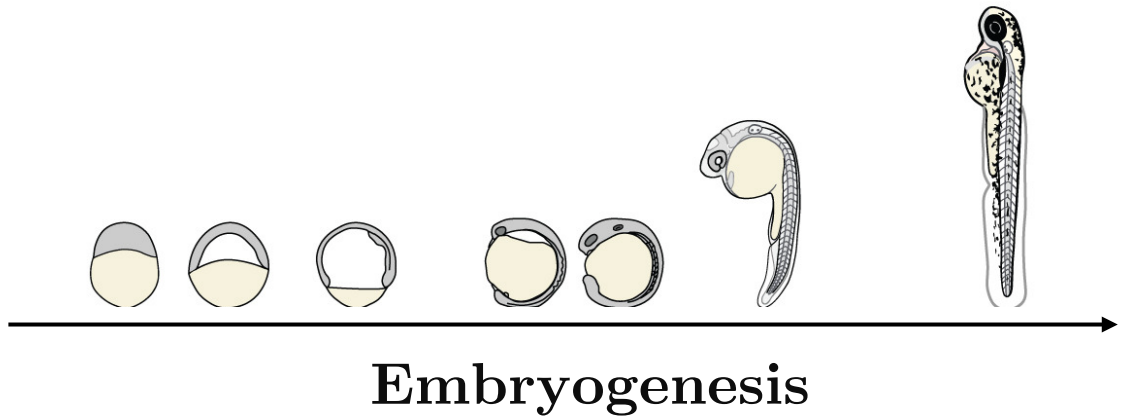
Dynamics, The "Hidden Law" of Biology



Cell Differentiation

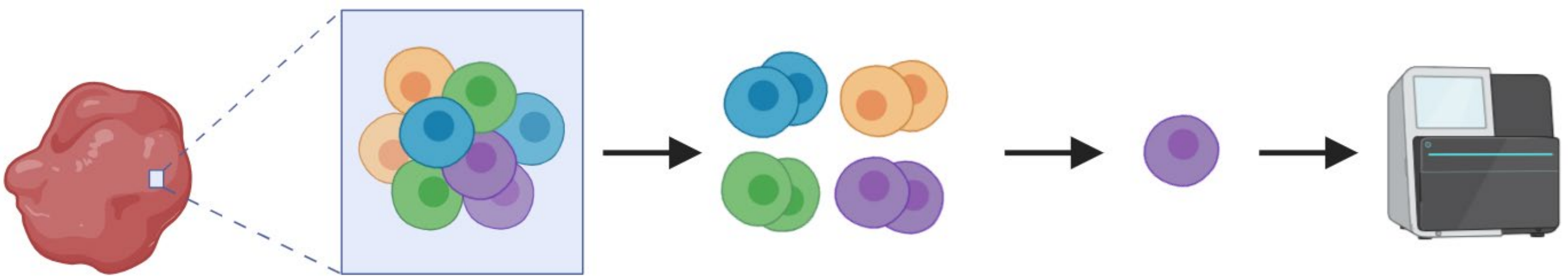


Embryogenesis

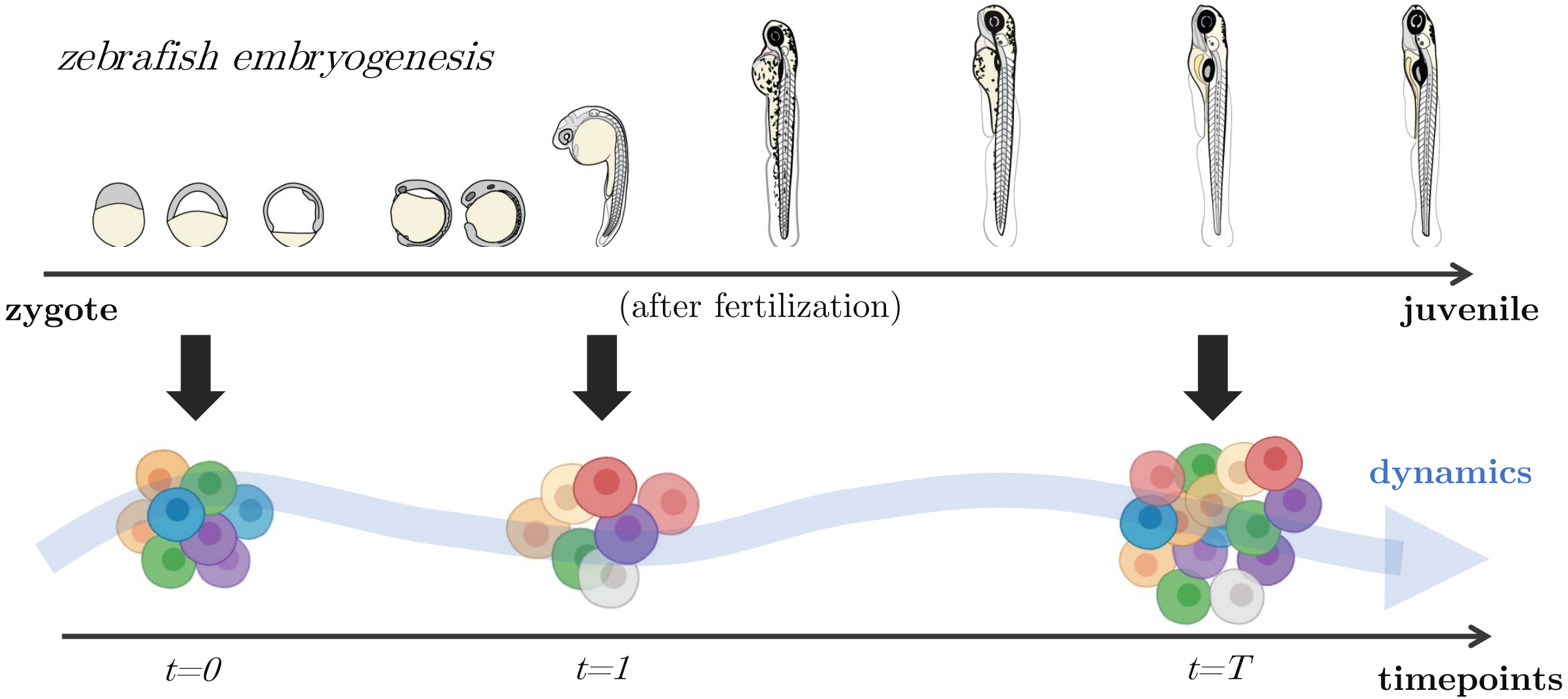
(figure adopted from [Haywood, *J Appl Neurosci*, 2024])

(figure adopted from *Wikipedia & Daniocell*)

Single-Cell Technology Offer High-Resolution Cell-Level Insights about Heterogeneous Biological Systems

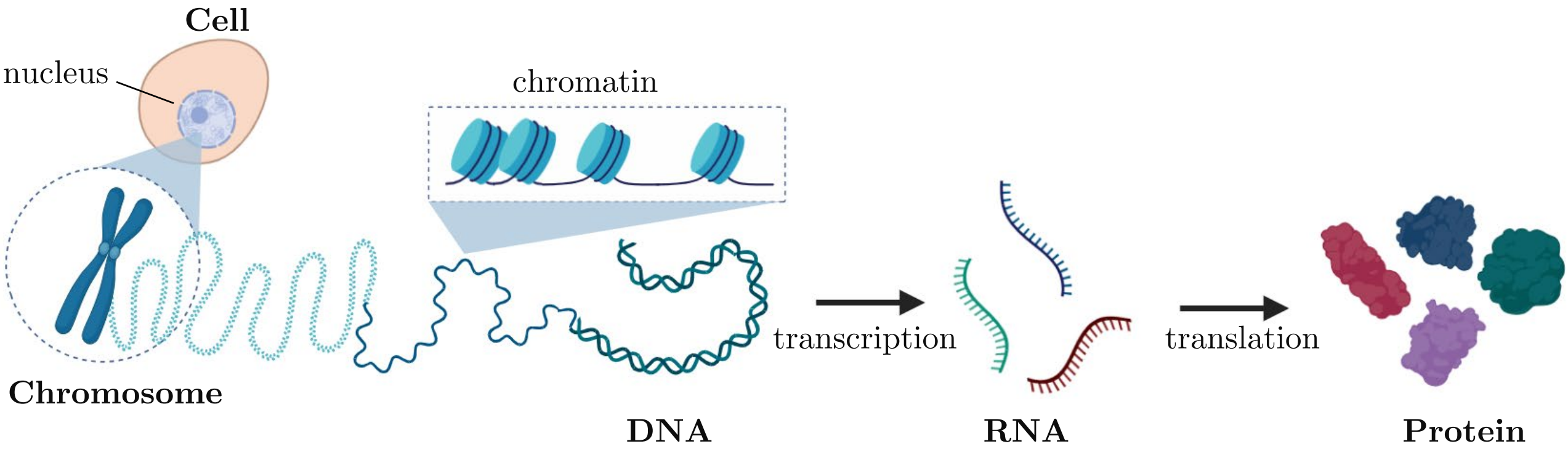


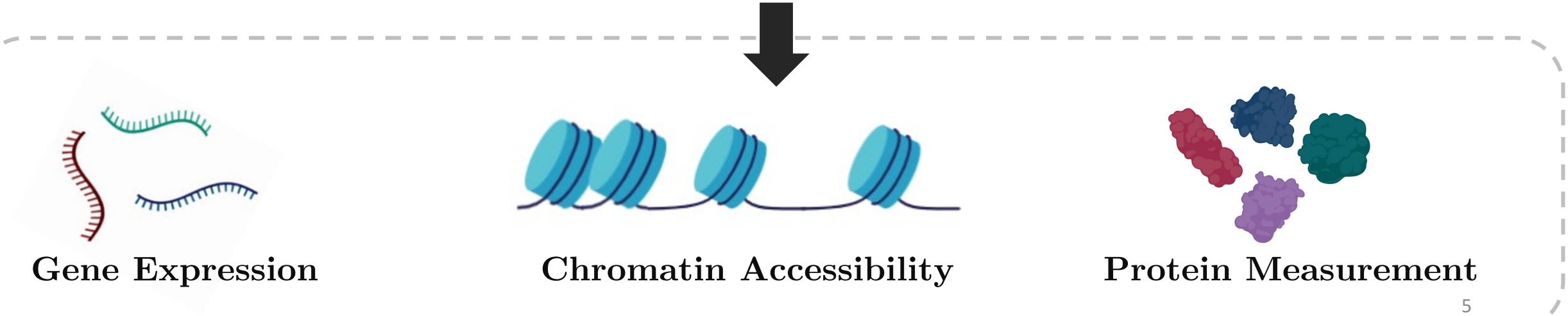
Temporally Resolved Single-Cell Data Offers Critical Dimension for Understanding Dynamics



[Sur, et.al., Dev. Cell, 2023]

Advances in Technology Enable Multi-Modal Views of Single Cells

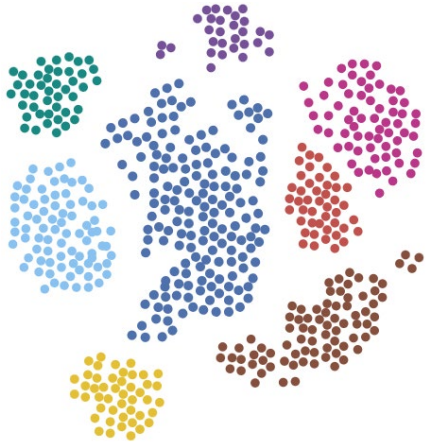




Each Modality Has Inherent Noises & Biases

Gene Expression

Chromatin Accessibility



joint analysis is important

+ diverse cell population

- sensitive to technical/biological biases
(e.g., mRNA degradation)

+ regulatory landscape

- less cell-type-specific
(e.g., robust to mRNA level)

[Lähnemann, et.al., Gen. Bio., 2020] [Chen, et.al., Gen. Bio., 2019]

Integrating Multiple Modalities Provides Comprehensive Cell Profile

- Integration between different single-cell modalities

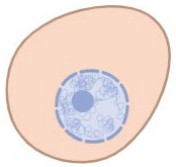
Image
(modality 1)

+

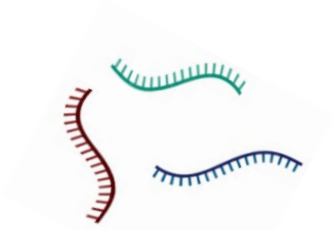
a dog running through the snow, with a frisbee

Text
(modality 2)

integration → comprehensive representation of object



Cell



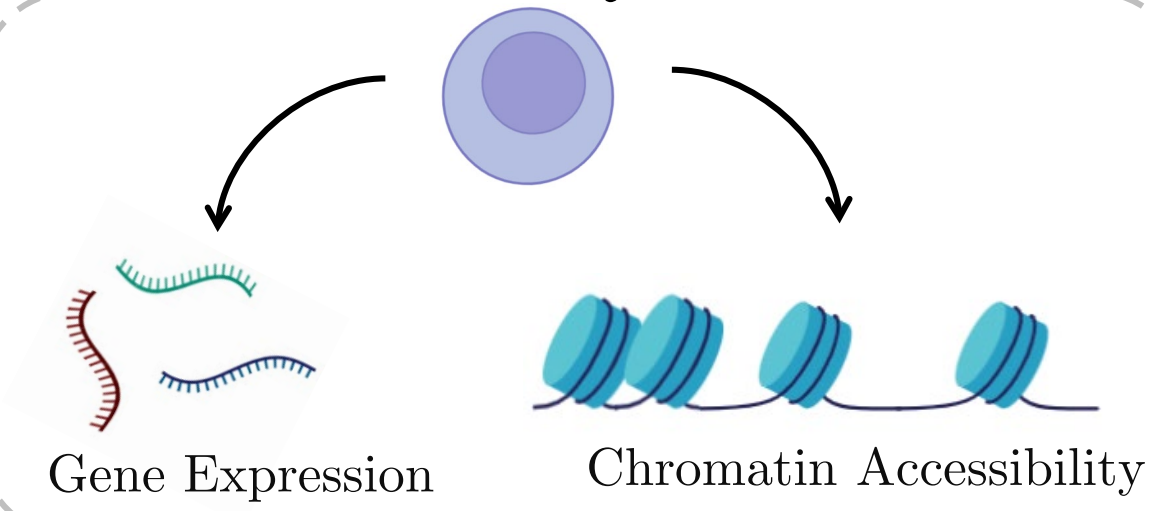
Gene Expression
(modality 1)

Chromatin Accessibility
(modality 2)

integration → comprehensive map of cell

Unaligned Datasets Pose Extra Challenges

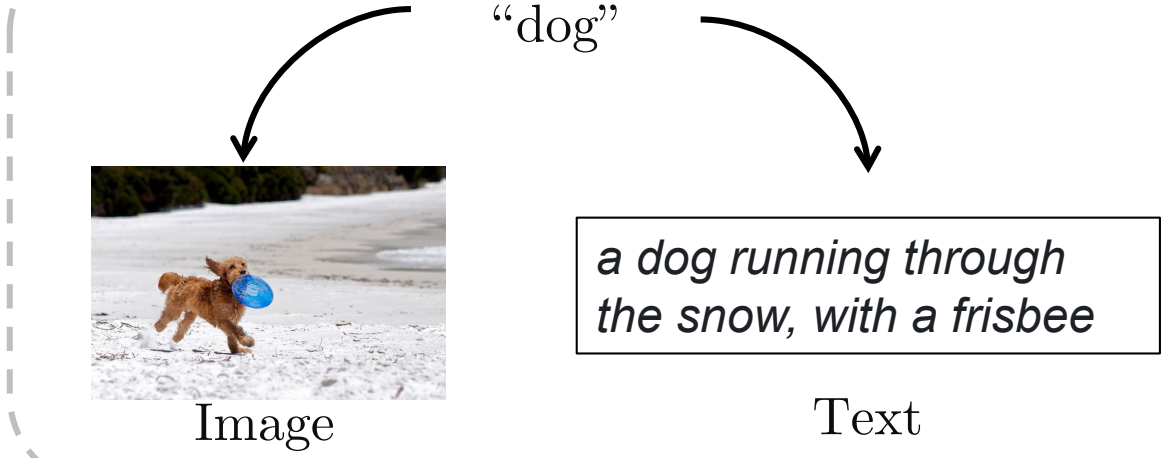
Co-Assay Data



Gene Expression

Chromatin Accessibility

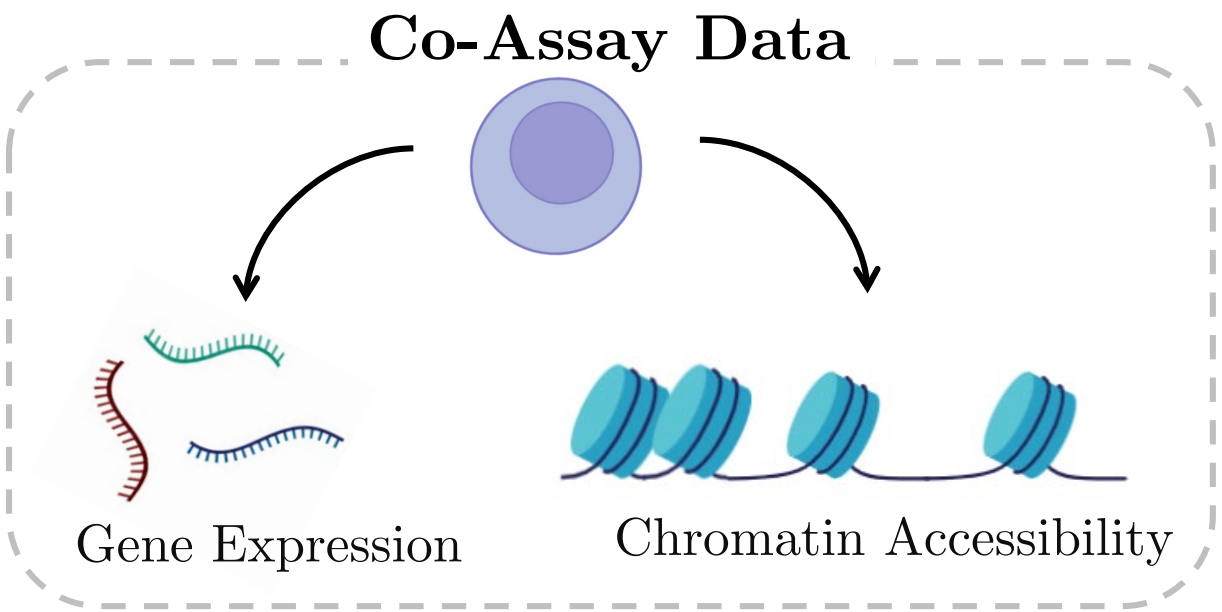
Image-Text Pair

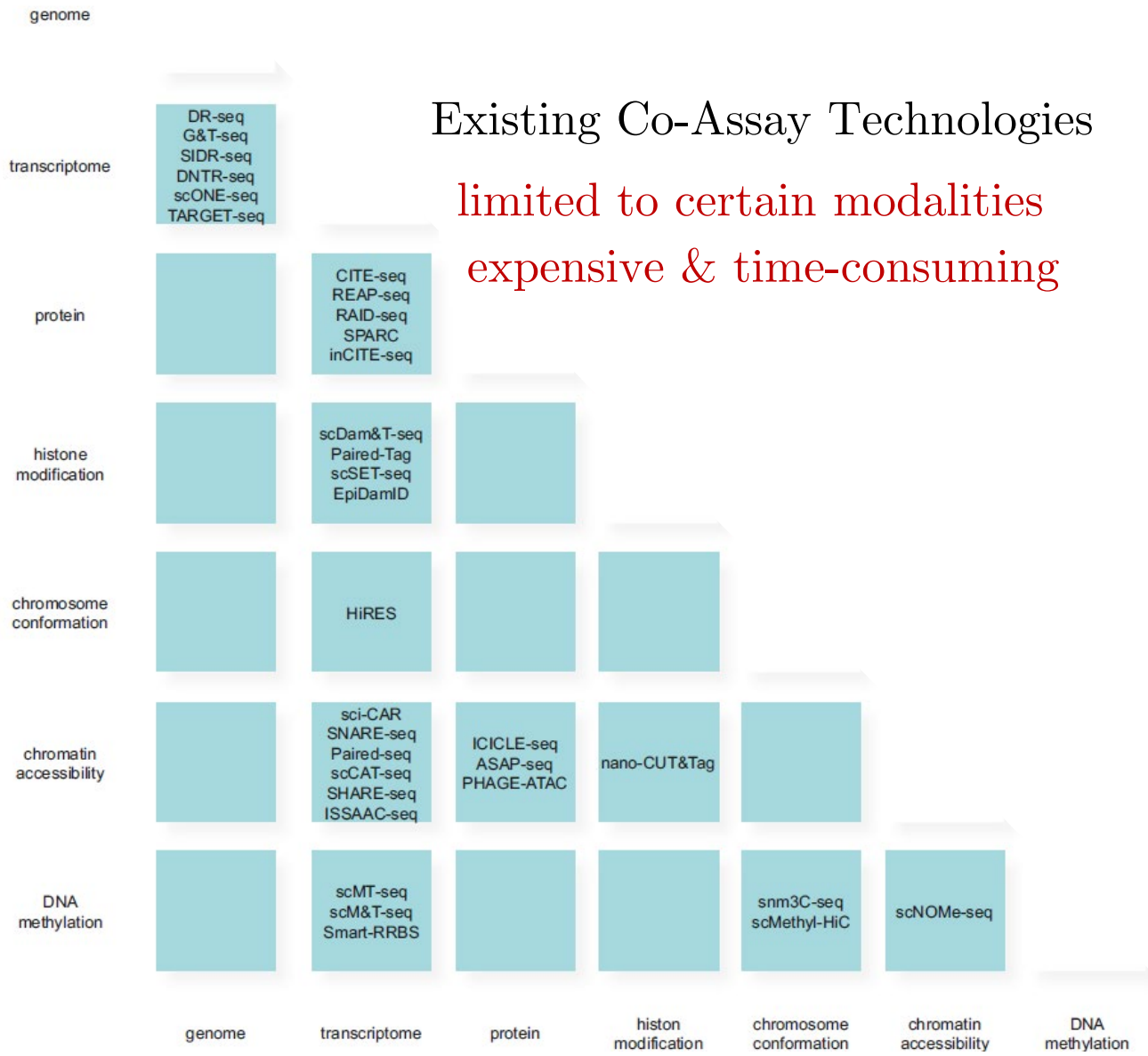


Image

Text

Unaligned Datasets Pose Extra Challenges (cont.)





Existing Co-Assay Technologies

limited to certain modalities

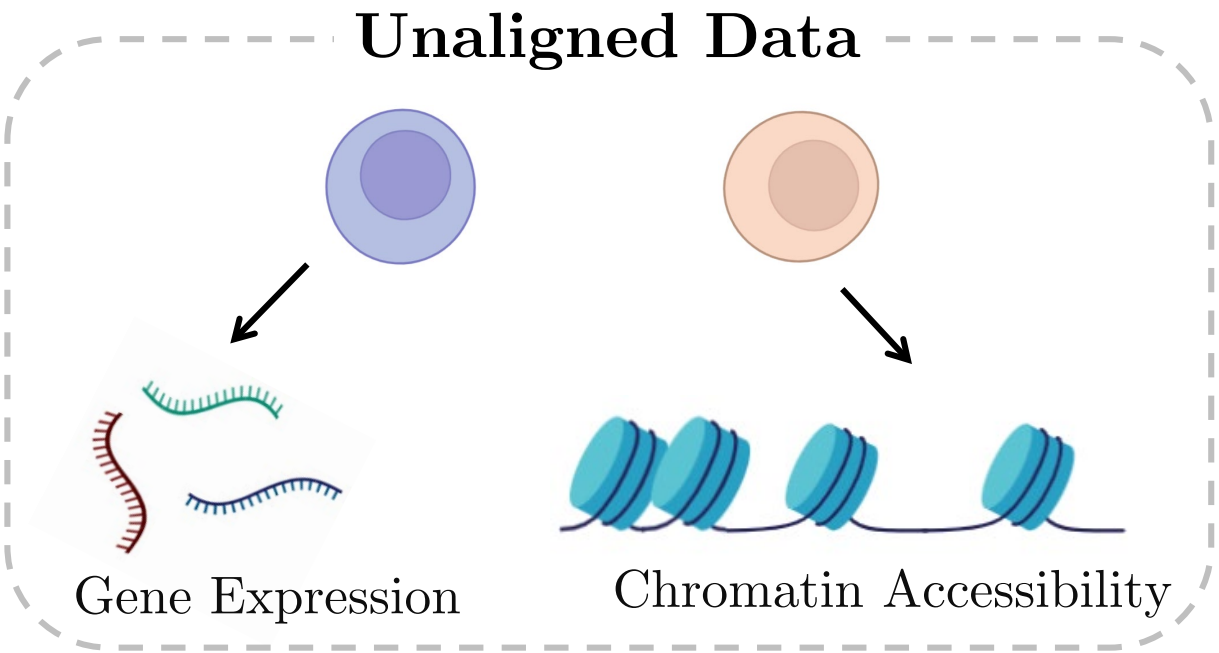
expensive & time-consuming

- Limits co-assay scalability across development stages and complex tissues

[Lim et. al., EMM, 2024]

Unaligned Datasets Pose Extra Challenges (cont.)

- Majority of temporal multi-modal datasets remain unaligned across modalities



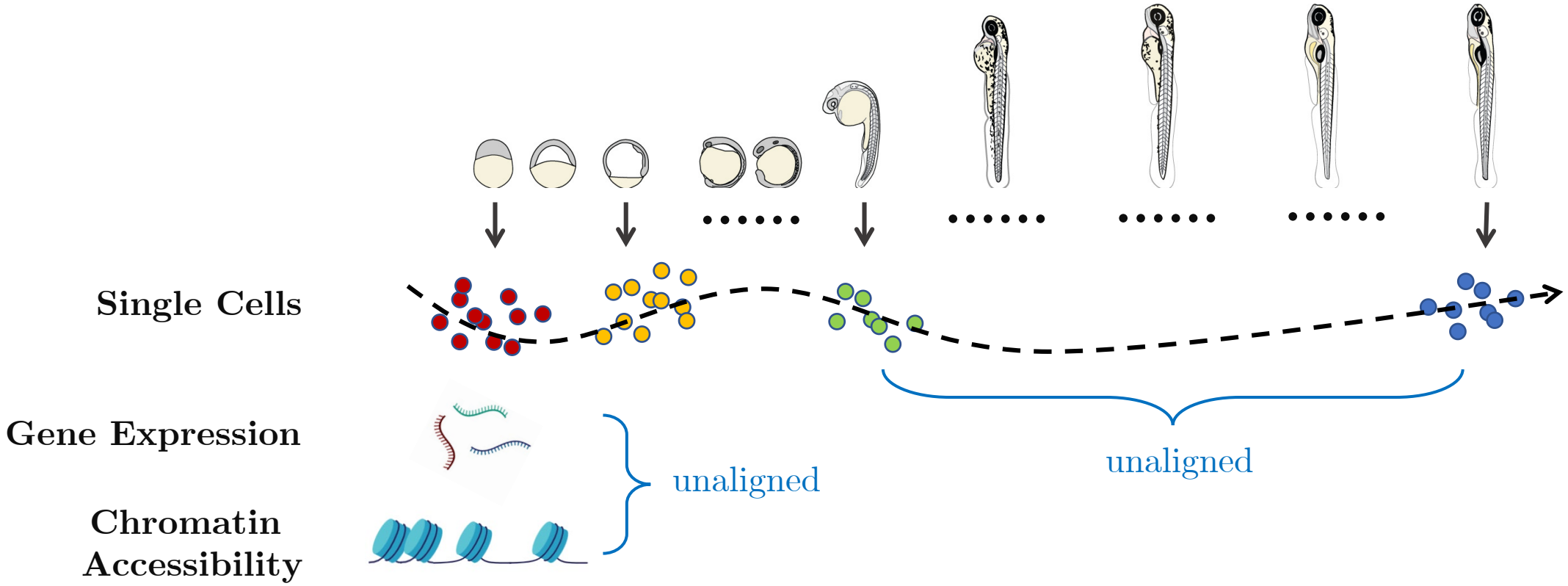
- Each modality is profiled on different sets of cells

Unaligned Datasets Pose Extra Challenges (cont.)

- Different set of cells are measured at each timepoint (destruction of single-cell tech.)

Unaligned Datasets Pose Extra Challenges (cont.)

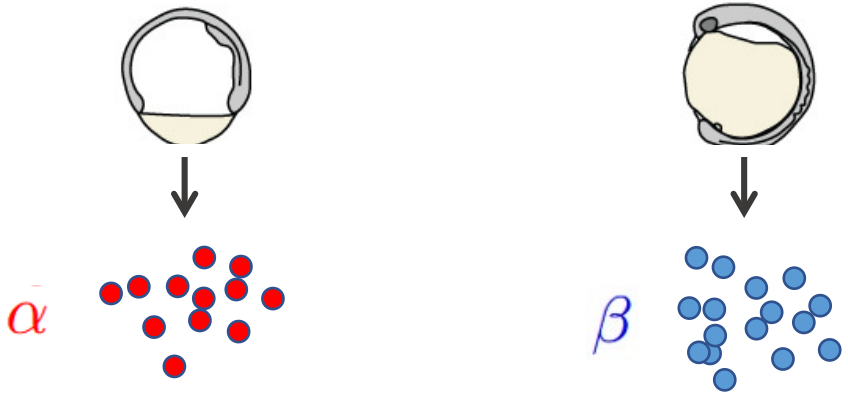
- Different set of cells are measured at each timepoint (destruction of single-cell tech.)



Problem I: unsupervised cell correspondence across modalities & timepoints

Unsupervised Cell Alignment Through Optimal Transport

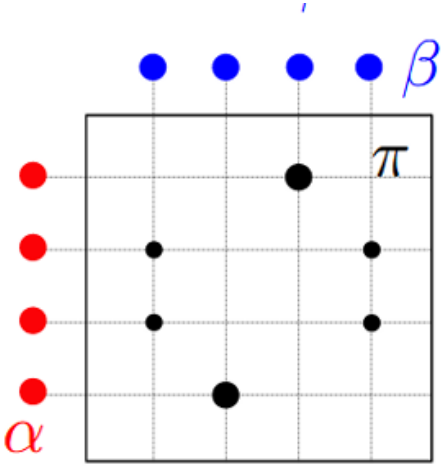
- **Problem I**: unsupervised cell correspondence across modalities & **timepoints**
- **Solution: cell alignment with optimal transport**



Transport cost $\mathbf{D}$

Pair-wise distance between masses of two distributions

$$\mathbf{D}_{ij} = \| i - j \|_2 \quad \text{with } i \in \alpha \text{ and } j \in \beta$$



Transport plan π

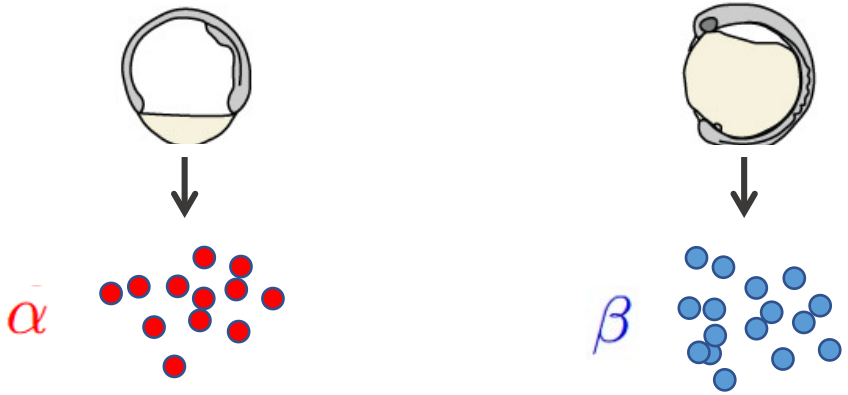
Mapping masses of two distributions

- Optimal transport find the best cell correspondence between two set of cells

(https://www.wias-berlin.de/people/dvureche/) [Schiebinger, et.al., Cell, 2019] [Forrow and Schiebinger, Nat. Commun., 2021]

Unsupervised Cell Alignment Through Optimal Transport

- **Problem I**: unsupervised cell correspondence across **modalities** & timepoints
- **Solution: cell alignment with optimal transport**

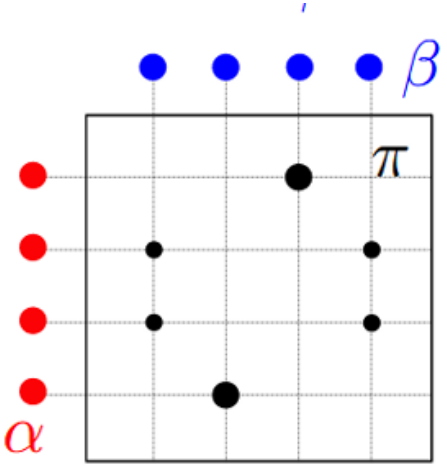


Transport cost $\mathbf{D}$

Pair-wise distance between masses of two distributions

$\mathbf{D}_{ij} = \| i - j \|_2$ with $i \in \alpha$ and $j \in \beta$

different modality has different feature space
distance computation is inapplicable



Transport plan π

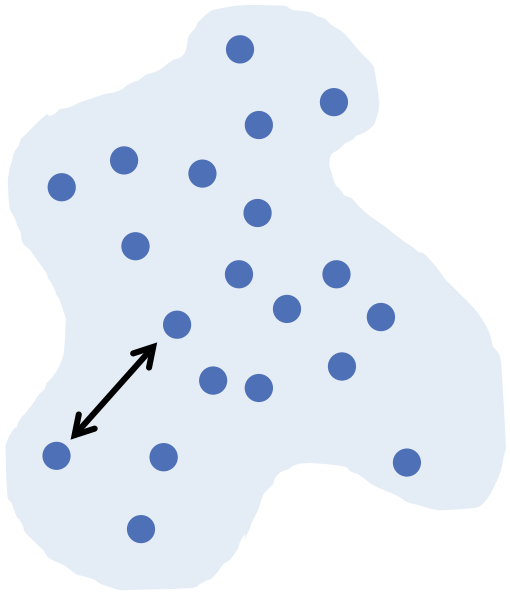
Mapping masses of two distributions

(https://www.wias-berlin.de/people/dvureche/) [Schiebinger, et.al., Cell, 2019] [Forrow and Schiebinger, Nat. Commun., 2021]

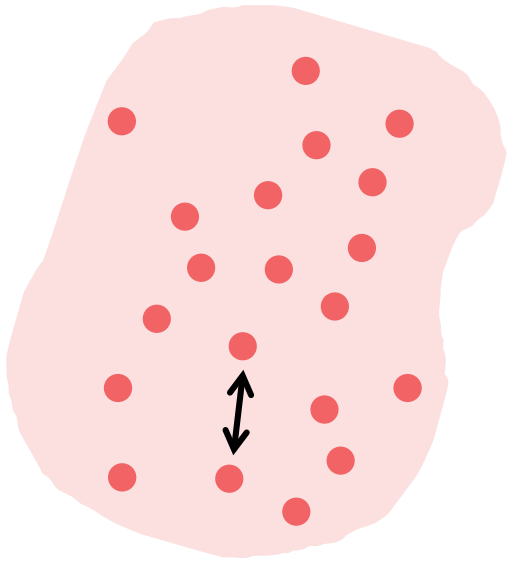
Unsupervised Cell Alignment Through Optimal Transport (cont.)

- We adopt Gromov-Wasserstein (GW) optimal transport to align cells across modalities

$\mathbf{X}$
(modality 1)



$\mathbf{Y}$
(modality 2)



$\mathbf{D}$

$$\mathbf{D}_{ij} = \| \mathbf{X}_i - \mathbf{X}_j \|_2$$

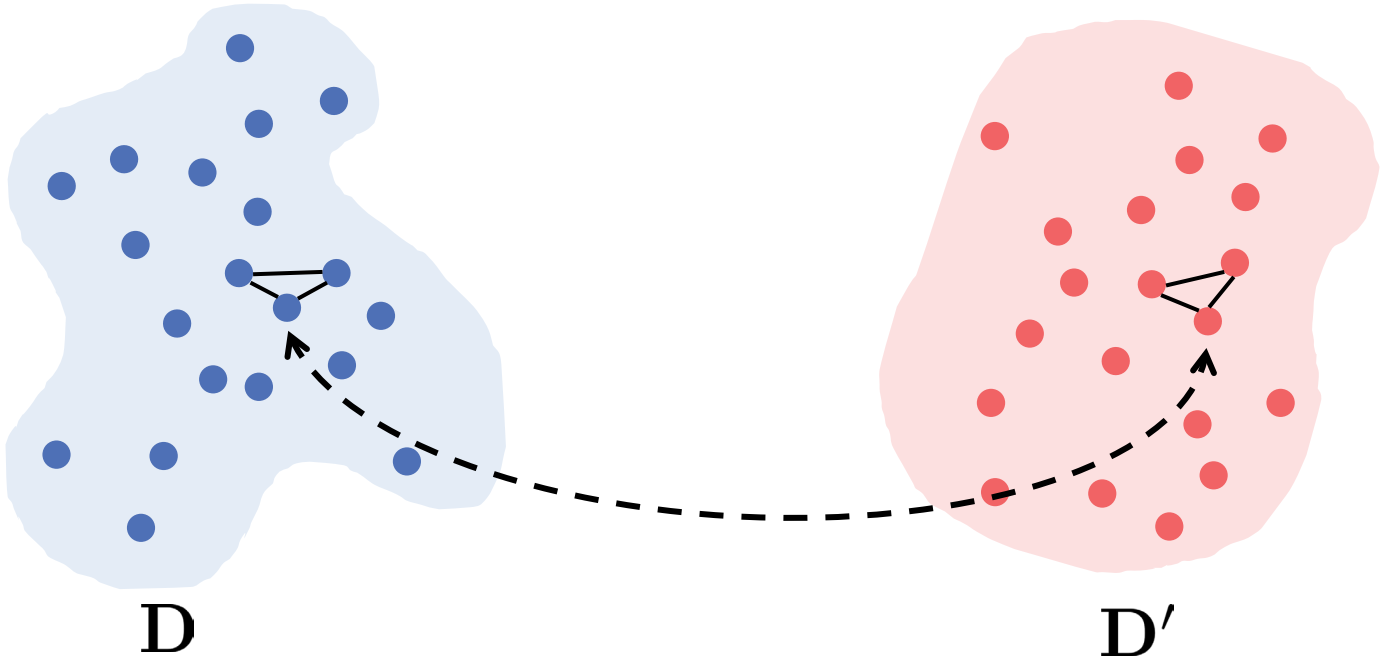
$\mathbf{D}'$

$$\mathbf{D}'_{ij} = \| \mathbf{Y}_i - \mathbf{Y}_j \|_2$$

- Step 1: compute pair-wise distance within each modality

Unsupervised Cell Alignment Through Optimal Transport (cont.)

- We adopt Gromov-Wasserstein (GW) optimal transport

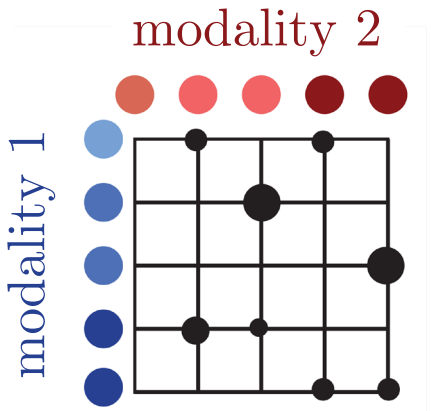


$$\min \sum_{i,i',j,j'} \| \mathbf{D}_{ii'} - \mathbf{D}'_{jj'} \|^2 \pi_{ij} \pi_{i'j'}$$

local structure of modality 1

local structure of modality 2

- Step 1: compute pair-wise distance within each modality
- Step 2: align two cells if they have similar local structures



Transport plan π

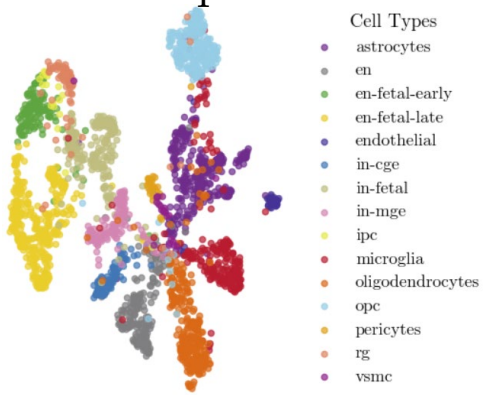
Mapping cells of two modalities while keeping local geometry

Existing Aligning Methods Overlook Underlying Cellular Dynamics

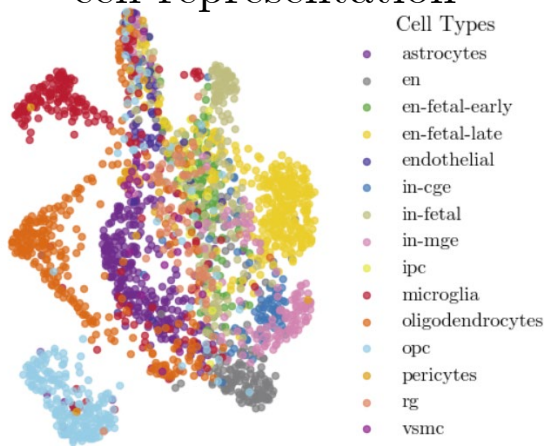
- Previous integration methods focus on separating different cell types and ignore the cell transition dynamics

cell type separations + cell developmental trajectories ?

Gene expression (mod. 1) cell representation



Chromatin accessibility (mod. 2) cell representation



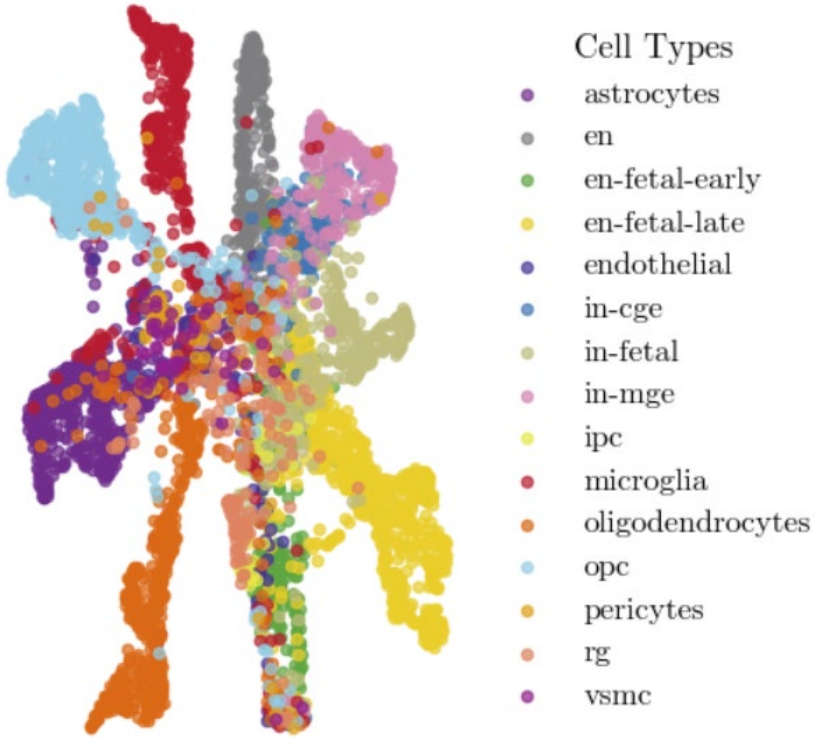
local cell cluster ✓

global cell dynamic ✗

Problem II: cellular dynamics are ignored during integration

Integration of a SCOTv2

[Demetci,, et. al., *J. Comput. Biol.*, 2022]

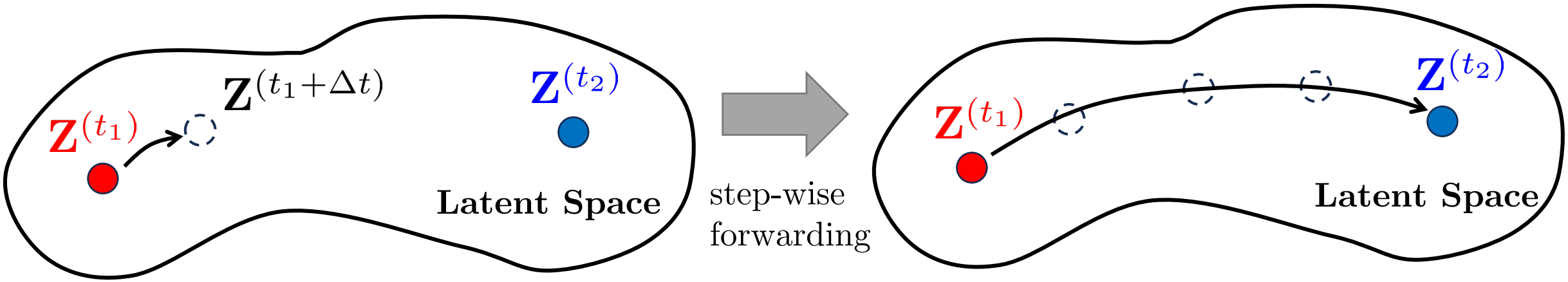


Existing Aligning Methods Overlook Underlying Cellular Dynamics (cont.)

(unsolved in previous works)

- **Problem II**: cellular dynamics are ignored during integration
- **Solution**: incorporate dynamics with differential equations

- Adopt differential equation in latent space to capture cell dynamics



$$\mathbf{Z}^{(t_1+\Delta t)} = \mathbf{Z}^{(t_1)} + f\left(\mathbf{Z}^{(t_1)}\right)\Delta t$$

- Adjust the latent space with cellular dynamics captured in modelling

Limitations of Existing Works

- **Problem I**: unsupervised cell correspondence across modalities & timepoints

  Solution: cell alignment with Gromov-Wasserstein Optimal Transport

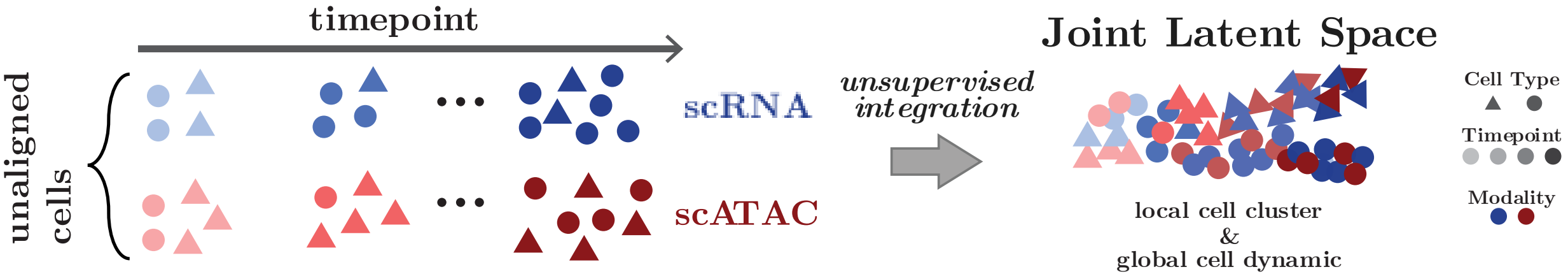
- **Problem II:** cellular dynamics are ignored during integration

  Unsolved in previous works

  Solution in our work: adjust the latent space with cellular dynamics

Limitations of Existing Works (cont.)

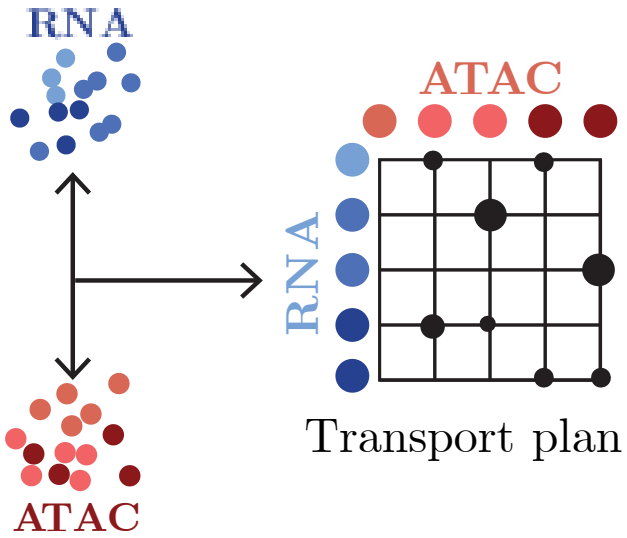
- **Goal:** during multi-modal single-cell integration, preserve both
  - local cell relationships (e.g., cell type distinctions)
  - global cellular dynamics (e.g., complex developmental trajectories)

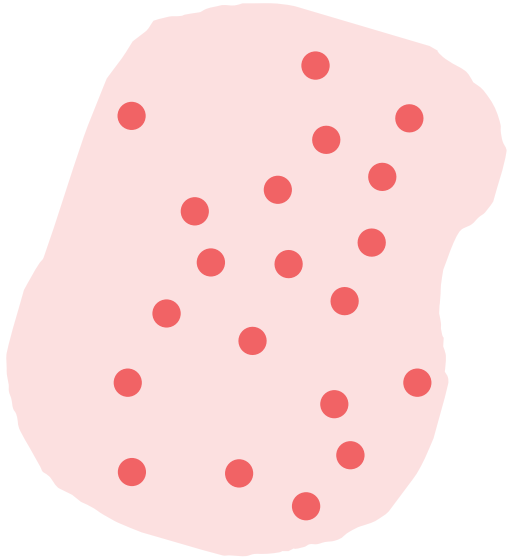


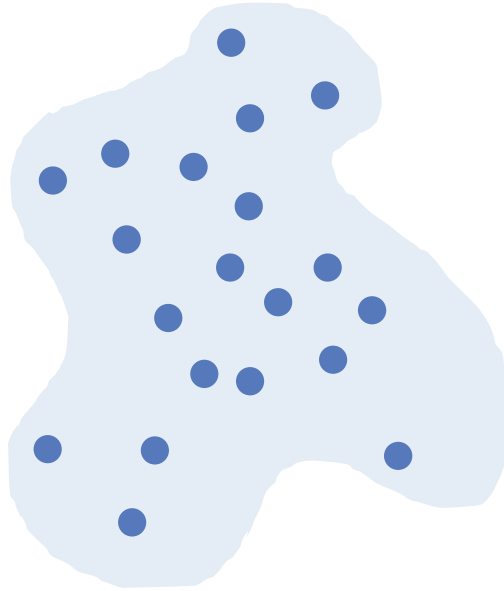
(scRNA-seq: gene expression; scATAC-seq: chromatin accessibility)

Our Method: single-cell Multi-Modal Neural Ordinary Differential Equation (scMultiNODE)

- **Step I:** uses Quantized Gromov-Wasserstein (QGW) to learn cross-modal cell alignment







$$\min \sum_{i,i',j,j'} \| \mathbf{D}_{ii'} - \mathbf{D}'_{jj'} \|^2 \pi_{ij} \pi_{i'j'}$$

local structure of RNA cells

local structure of ATAC cells

exact GW is NP-hard

expensive for large-scale single-cell data

Our Method: single-cell Multi-Modal Neural Ordinary Differential Equation (scMultiNODE)

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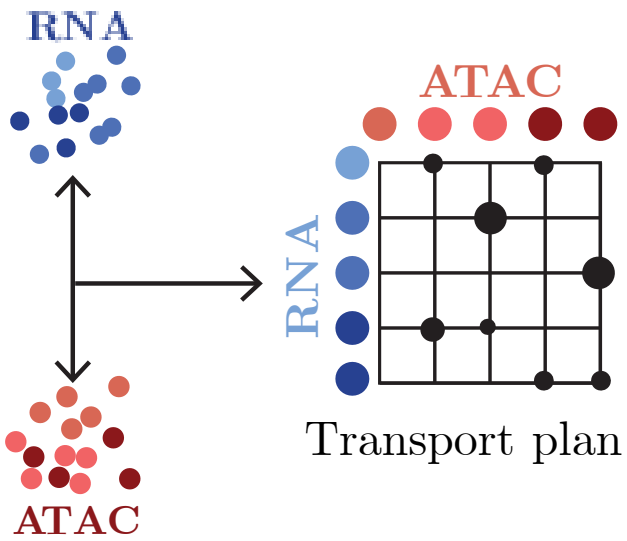

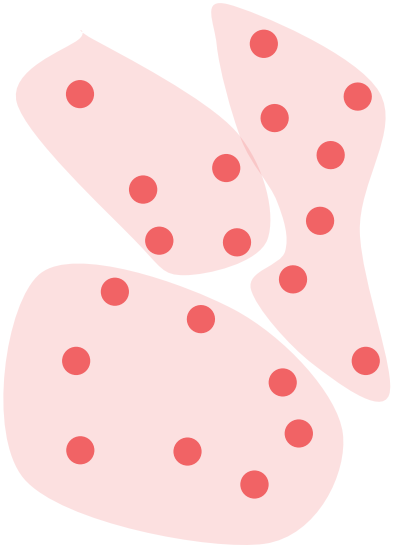

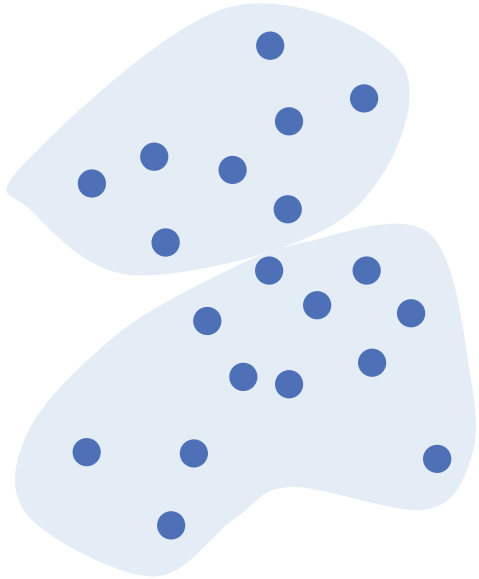

divide-and-conquer strategy

$$\min \sum_{i,i',j,j'} \| \mathbf{D}_{ii'} - \mathbf{D}'_{jj'} \|^2 \pi_{ij} \pi_{i'j'}$$

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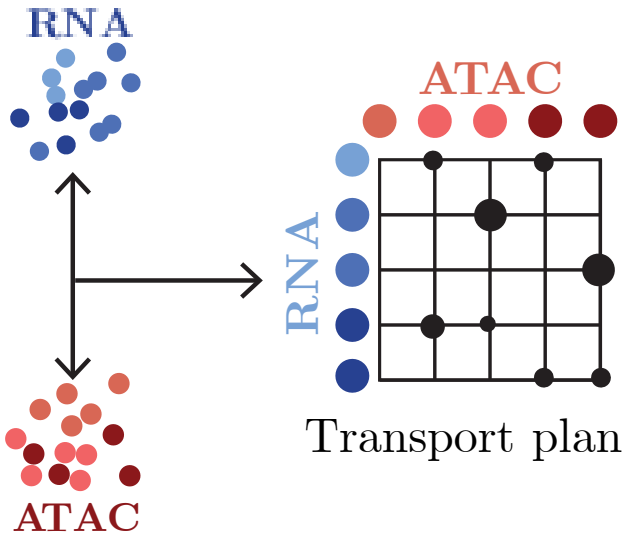

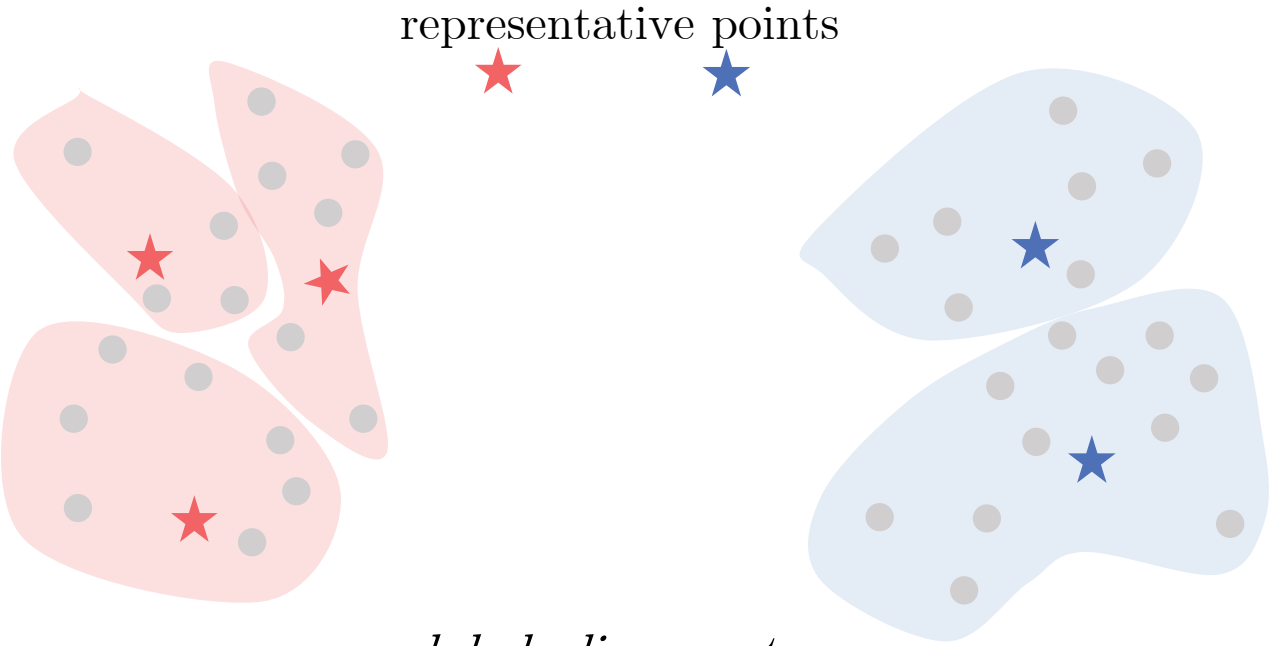

global alignment
π_{global}

$$\min \sum_{i,i',j,j'} \| \mathbf{D}_{ii'} - \mathbf{D}'_{jj'} \|^2 \pi_{ij} \pi_{i'j'}$$

distance of representative points

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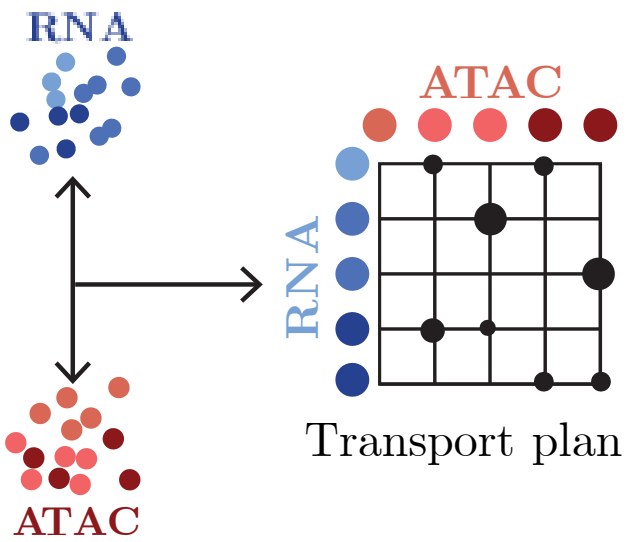

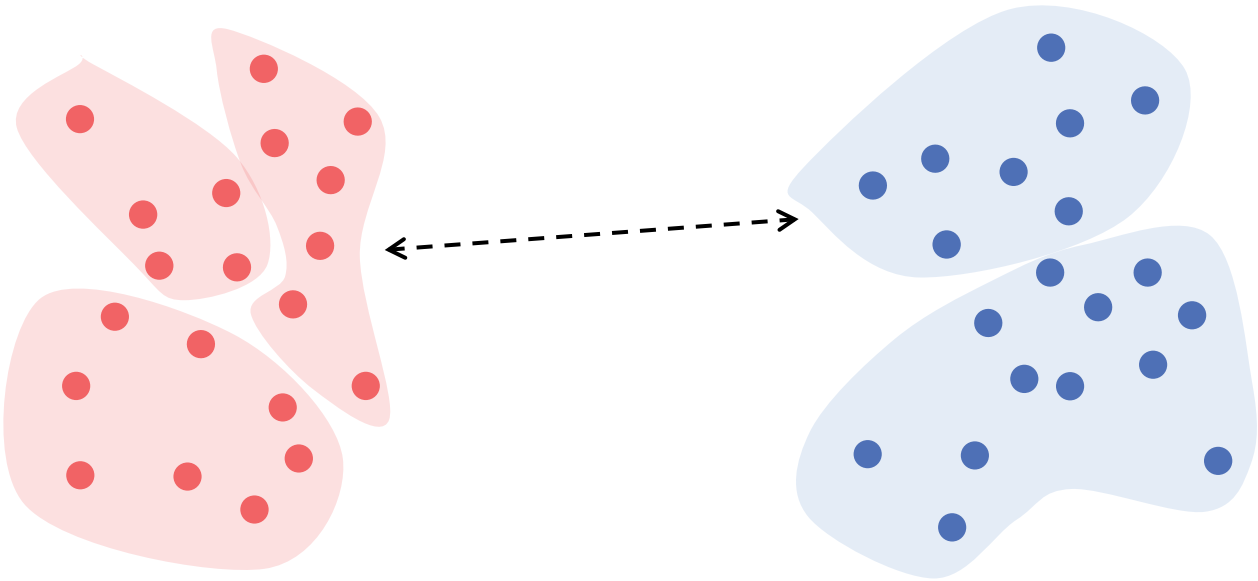

$$\min \sum_{i,i',j,j'} \| \mathbf{D}_{ii'} - \mathbf{D}'_{jj'} \|^2 \pi_{ij} \pi_{i'j'}$$

local alignment
π_{local}

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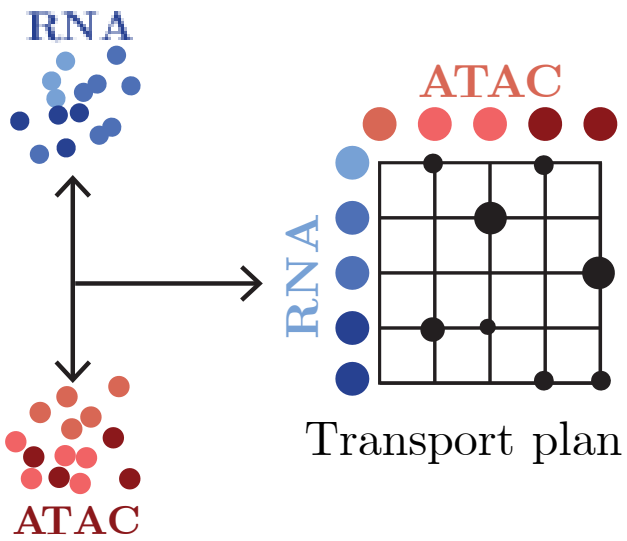
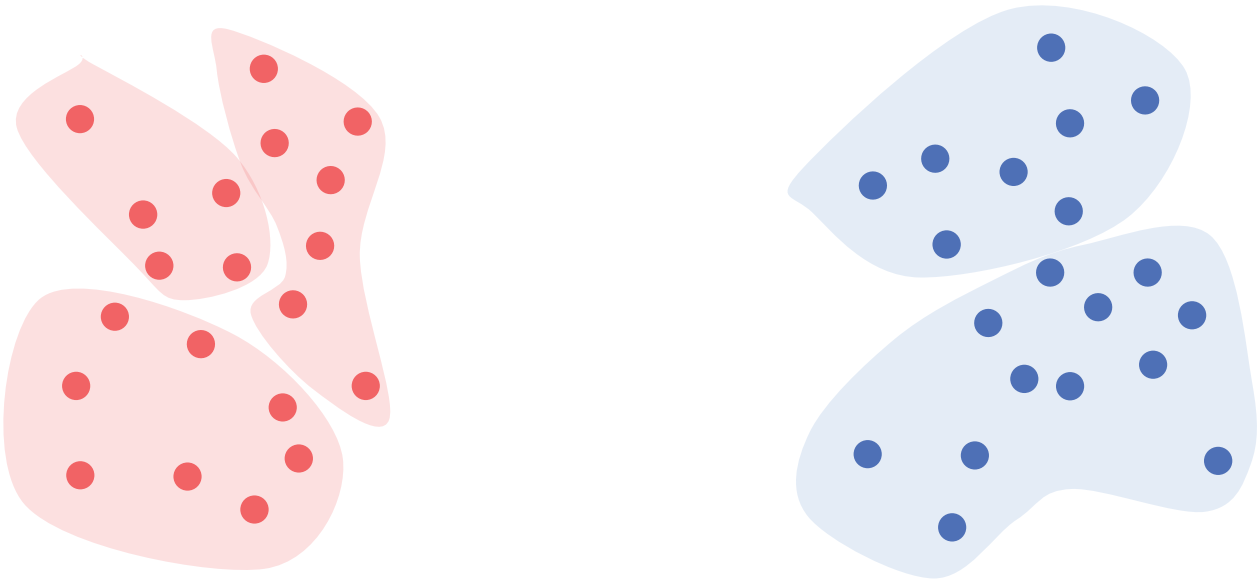


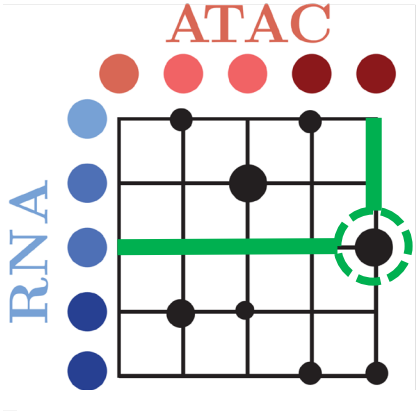


$$\textit{overall alignment} = \pi_{\text{global}} \times \pi_{\text{local}}$$

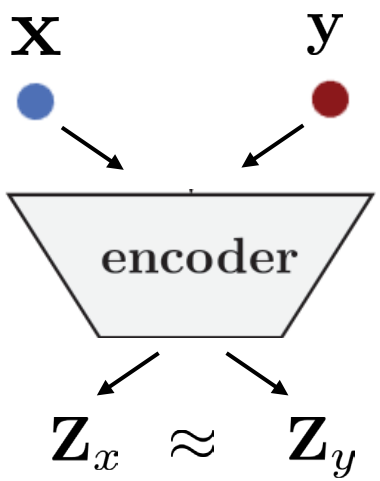
significantly reduce time costs

Our Method: single-cell Multi-Modal Neural Ordinary Differential Equation (scMultiNODE)

- **Step II:** mapping multi-modal cell profile to the joint latent space

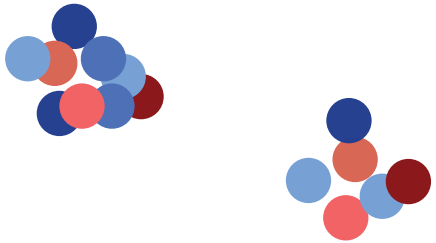


Assumption: **biologically similar cells**, despite being measured in different modalities, should **stay close**



$$\min \| \mathbf{Z}_x - \mathbf{Z}_y \| \text{ if } x \text{ and } y \text{ are aligned}$$

Joint Latent Space

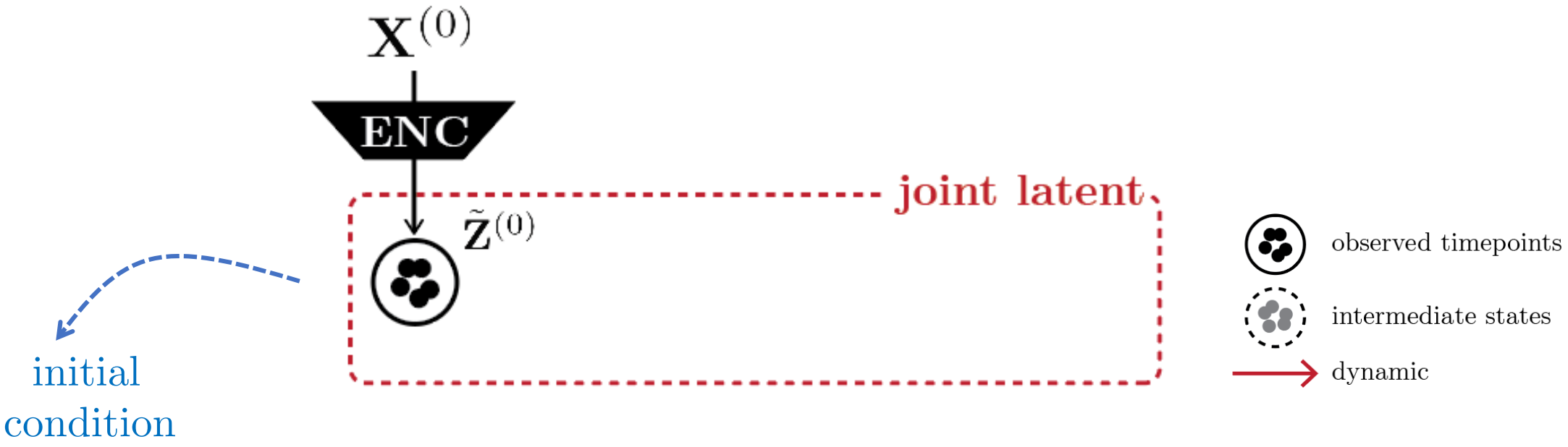


local cell cluster ✓

global cell dynamic ✗

Our Method: single-cell Multi-Modal Neural Ordinary Differential Equation (scMultiNODE)

- **Step III:** incorporate cell dynamics with neural Ordinary Differential Equation (ODE)



Our Method: single-cell Multi-Modal Neural Ordinary Differential Equation (scMultiNODE)

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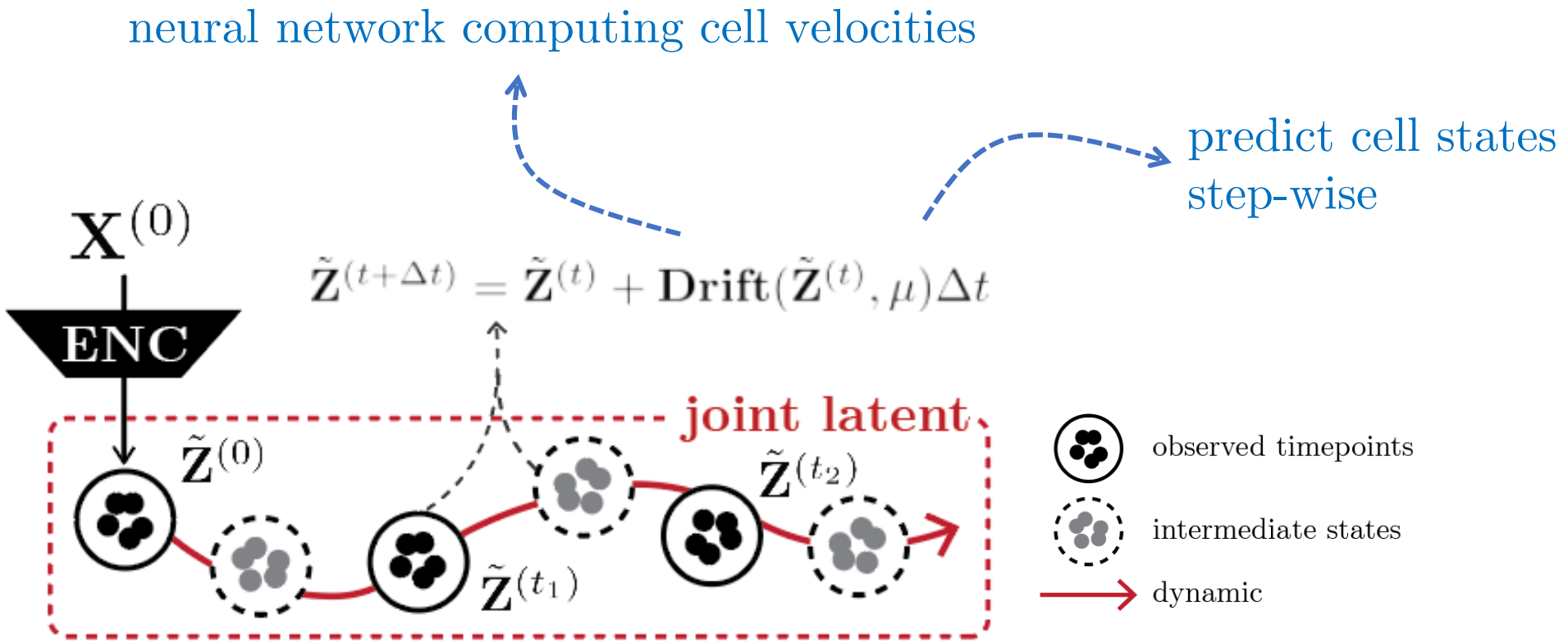
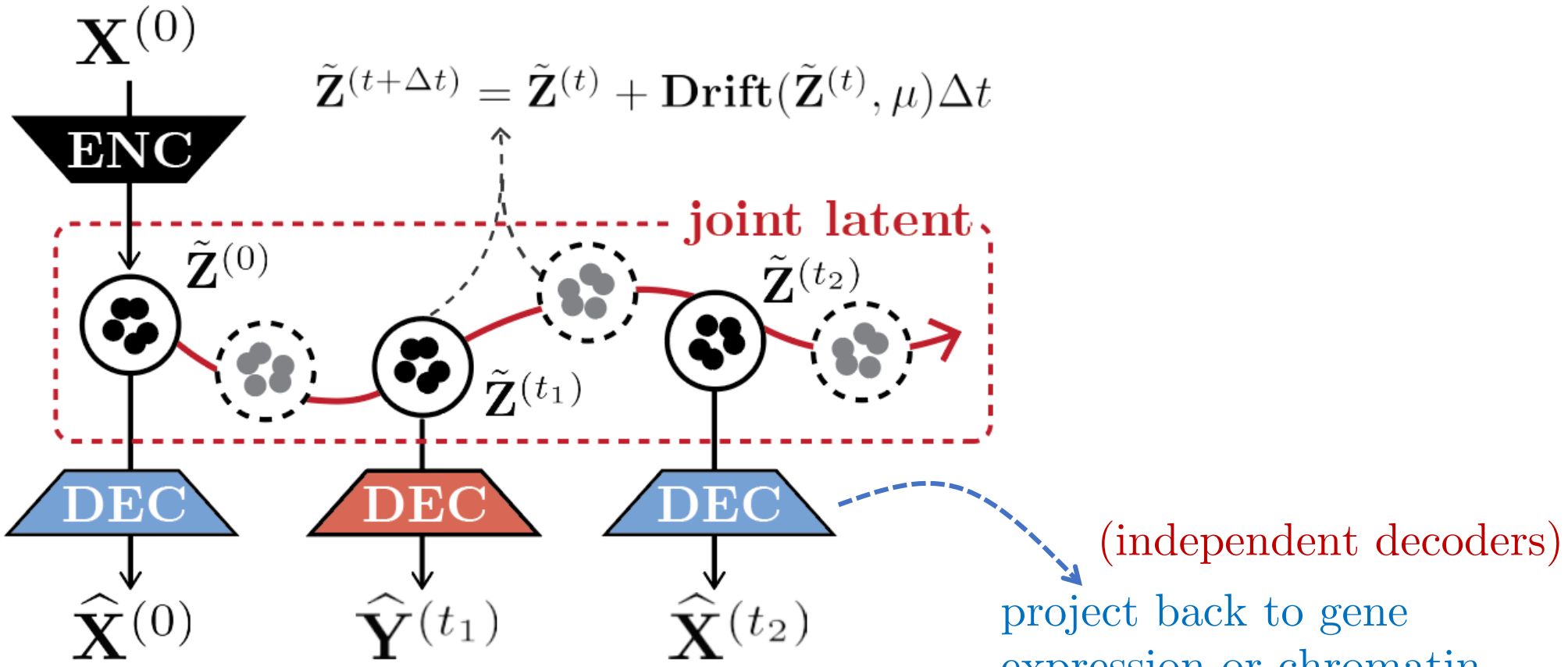


Our Method: single-cell Multi-Modal Neural Ordinary Differential Equation (scMultiNODE)

- **Step III:** incorporate cell dynamics with neural Ordinary Differential Equation (ODE)

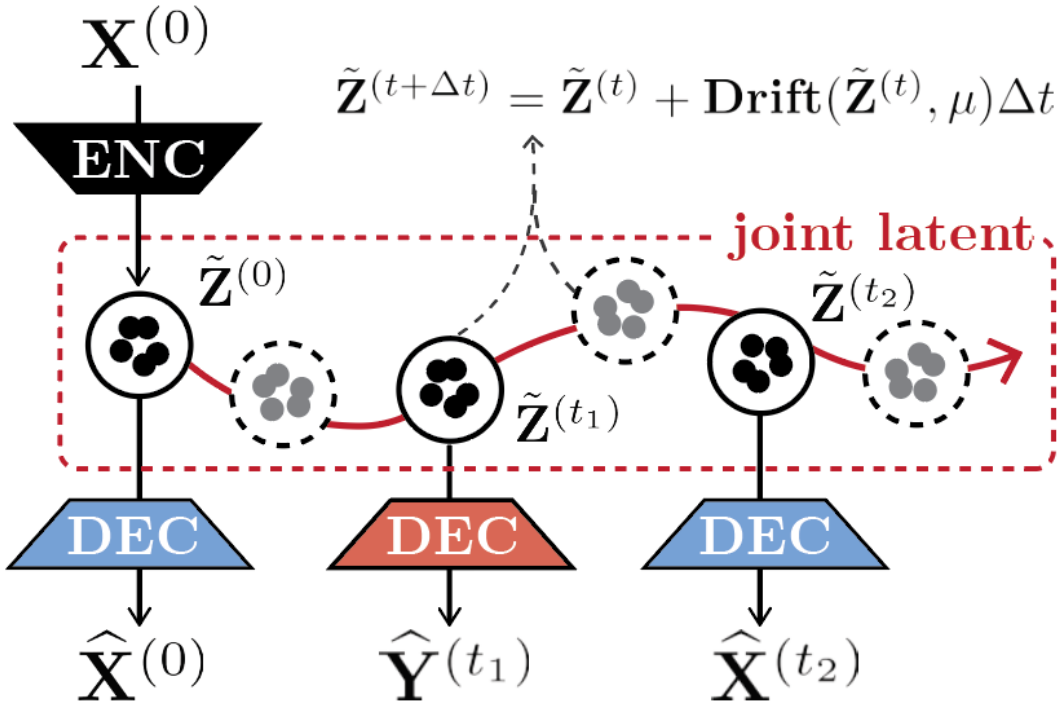


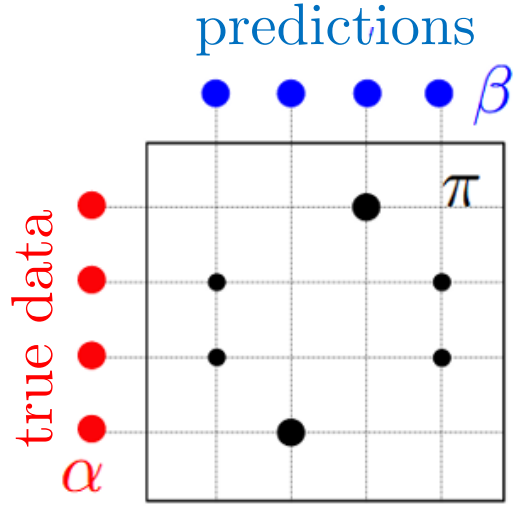
Our Method: single-cell Multi-Modal Neural Ordinary Differential Equation (scMultiNODE)

- **Loss function:** reconstruction loss + dynamic regularization
- Reconstruction loss:
  - Use optimal transport distance as reconstruction loss
  - Wasserstein distance between ground truth & predictions

for RNA
$$\sum_{t\in\mathcal{T}} \text{Wasserstein}(X^{(t)}, \widehat{X}^{(t)})$$

for ATAC
$$\sum_{t\in\mathcal{T}} \text{Wasserstein}(Y^{(t)}, \widehat{Y}^{(t)})$$



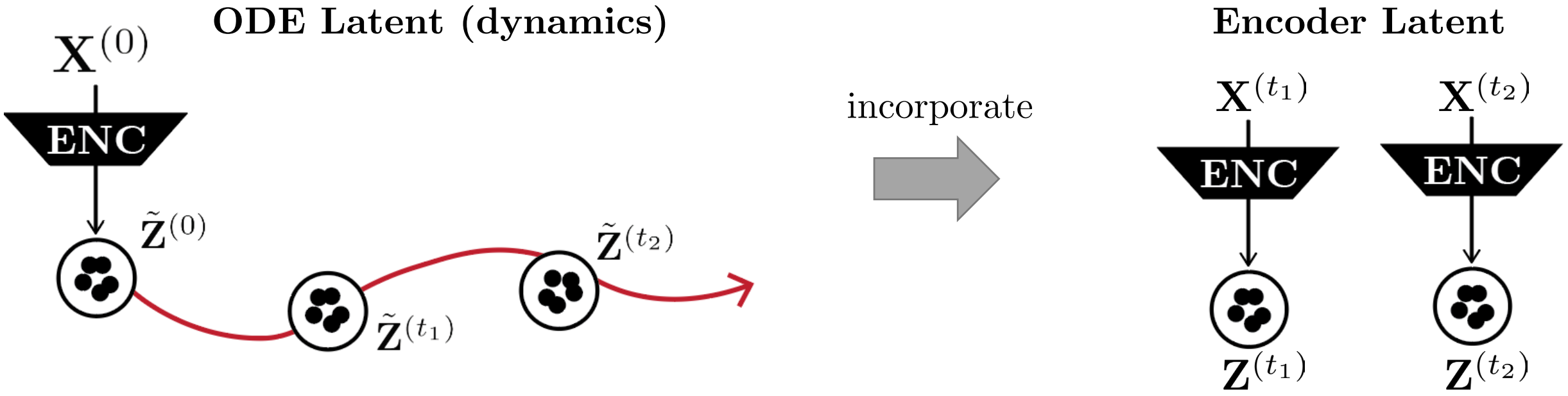


$$\text{Wass}(\alpha, \beta) = \left(\min_{\pi} \sum_{i,j} D_{ij}^2 \pi_{ij} \right)^{1/2}$$

Our Method: single-cell Multi-Modal Neural Ordinary Differential Equation (scMultiNODE)

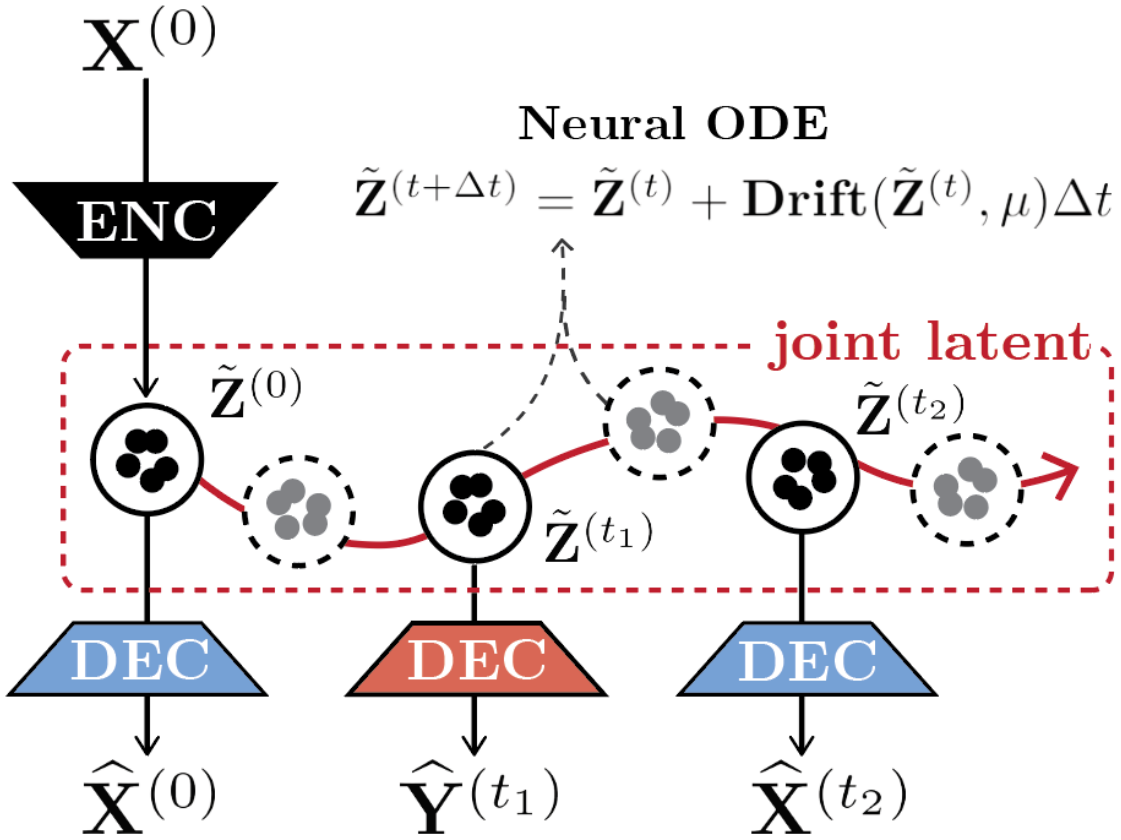
- **Loss function:** reconstruction loss + dynamic regularization
- Dynamic regularization:
  - Enforces latent space to incorporate dynamics learned by neural ODE

$$\text{Wasserstein(Encoder latent, ODE latent)} \rightarrow \text{Wasserstein}(\tilde{\mathbf{Z}}^{(t)}, \mathbf{Z}^{(t)})$$



Our Method: single-cell Multi-Modal Neural Ordinary Differential Equation (scMultiNODE)

- **Step III:** incorporate cell dynamics with neural Ordinary Differential Equation (ODE)



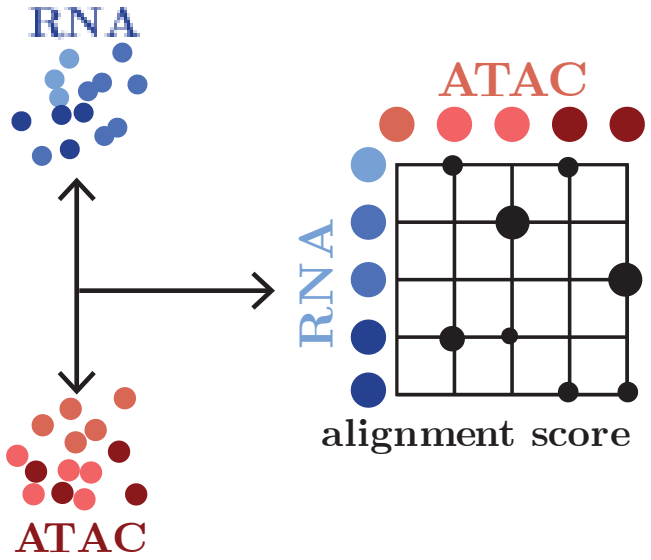
Joint Latent Space
(w/ dynamics)

local cell cluster ✓
global cell dynamic ✓

(Loss function: reconstruction loss + dynamic regularization)

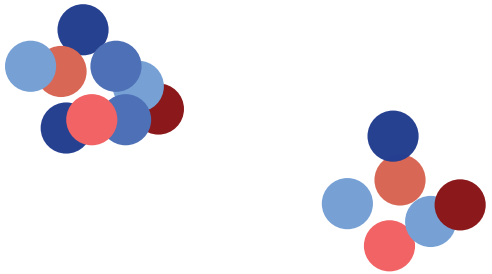
Our Method: single-cell Multi-Modal Neural Ordinary Differential Equation (scMultiNODE)

(Step I)
QGW optimal transport
unsupervised alignment



(Step II)
minimize distance
between aligned cells

Joint Latent Space



local cell cluster ✓
global cell dynamic ✗

(Step III)
incorporating cell dynamics
with neural ODE

Joint Latent Space
(w/ dynamics)

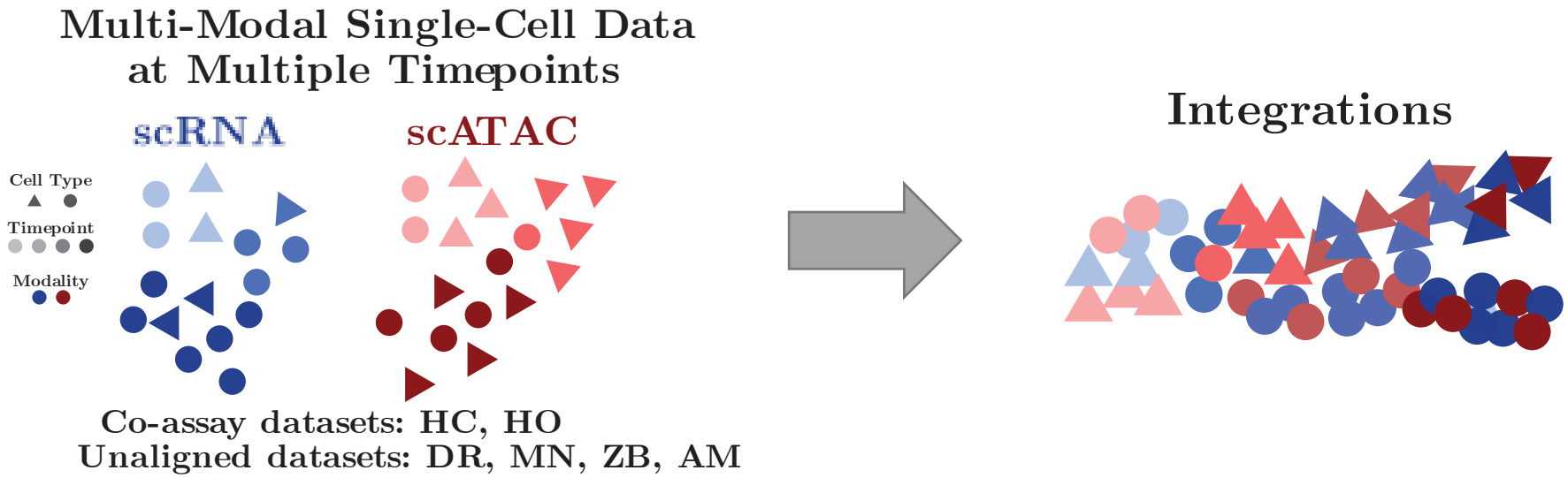
local cell cluster ✓
global cell dynamic ✓

Experiment Setup

- **Dataset**: six multi-modal single-cell datasets

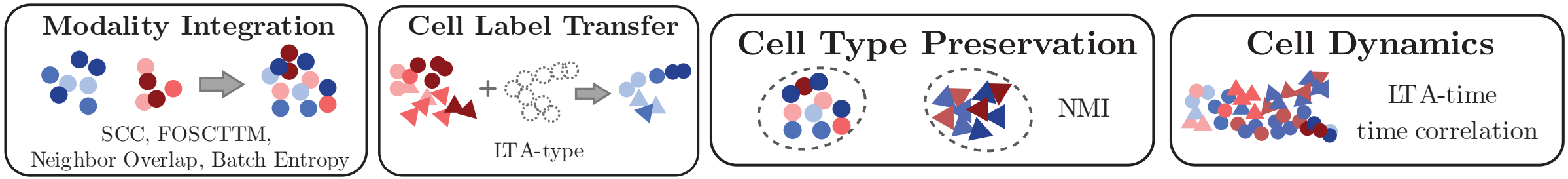
ID	Dataset	Species	# cells (RNA/ATAC)	# timepoints (RNA/ATAC)	Coassay	Source
HC	human cortex	*Homo sapiens*	2277/2277	10/10	Yes	[6]
HO	human organoid	*Homo sapiens*	10000/10000	11/11	Yes	[2]
DR	drosophila embryogenesis	*Drosophila melanogaster*	2738/4246	11/11	No	[1]
MN	mouse neocortex	*Mus musculus*	6098/1914	3/3	No	[5]
ZB	Zebrahub	*Danio rerio*	3692/9456	6/6	No	[3]
AM	amphioxus development	*Branchiostoma lanceolatum*	9630/3538	6/6	No	[4]

- **Setup**: temporally resolved multi-modal single-cell data integration



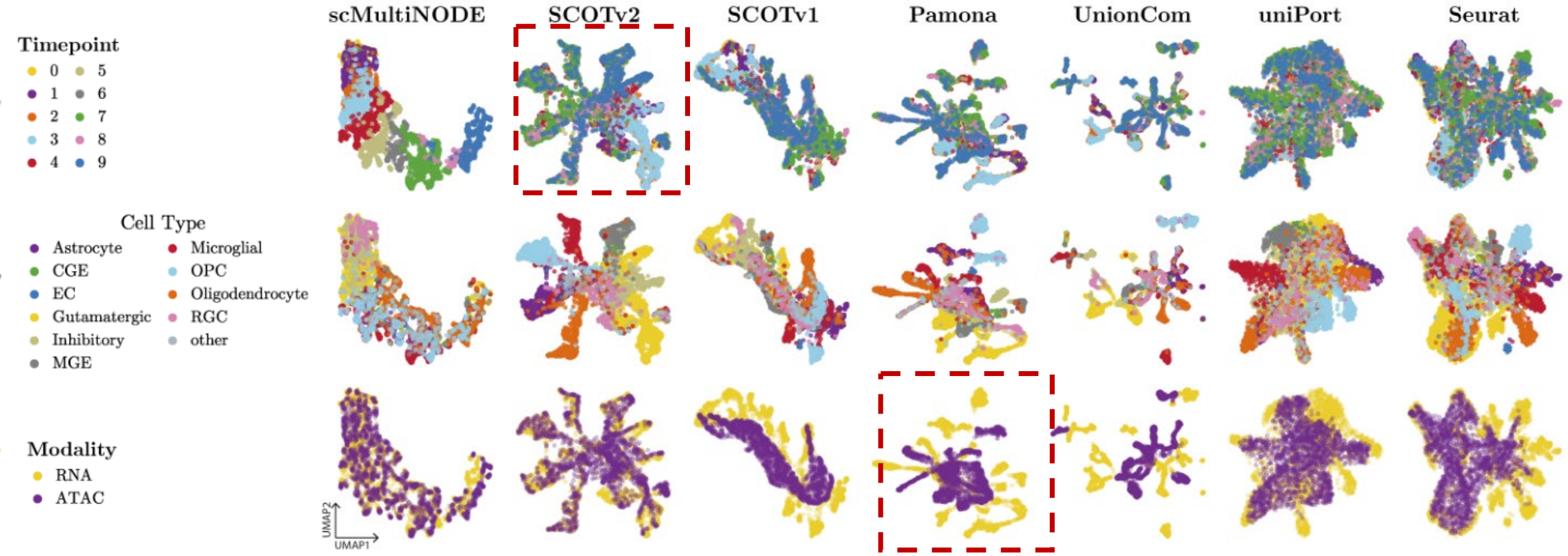
Experiment Setup

- **Evaluation:**



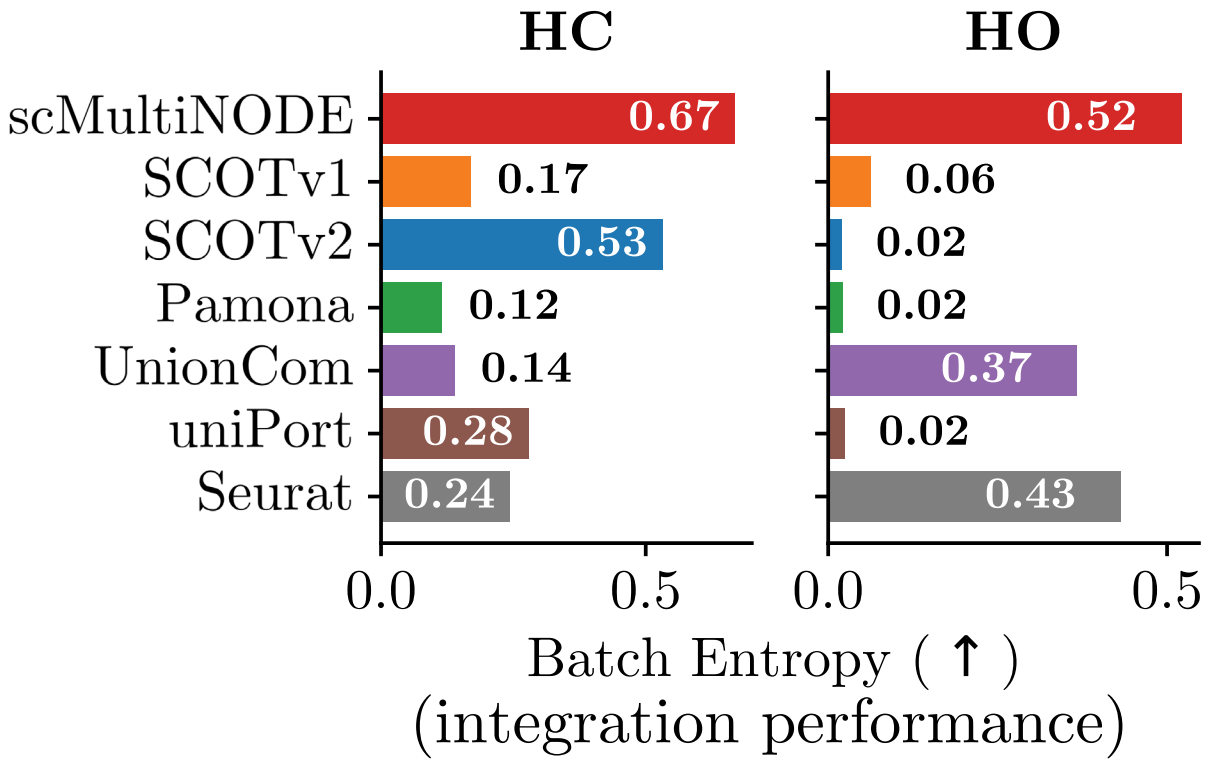
- **Baselines:** six state-of-the-art methods
  - SCOTv1 [Demetci,, et. al., *J. Comput. Biol.*, 2022]
  - SCOTv2 [Demetci,, et. al., *J. Comput. Biol.*, 2022]
  - Pamona [Cao, et. al., *Bioinformatics*, 2022]
  - UnionCom [Cao, et. al., *Bioinformatics*, 2020]
  - uniport [Cao, et. al., *Nat. Comm.*, 2022]
  - Seurat [Hao, et. al., *Nat. Biotech.*, 2024]

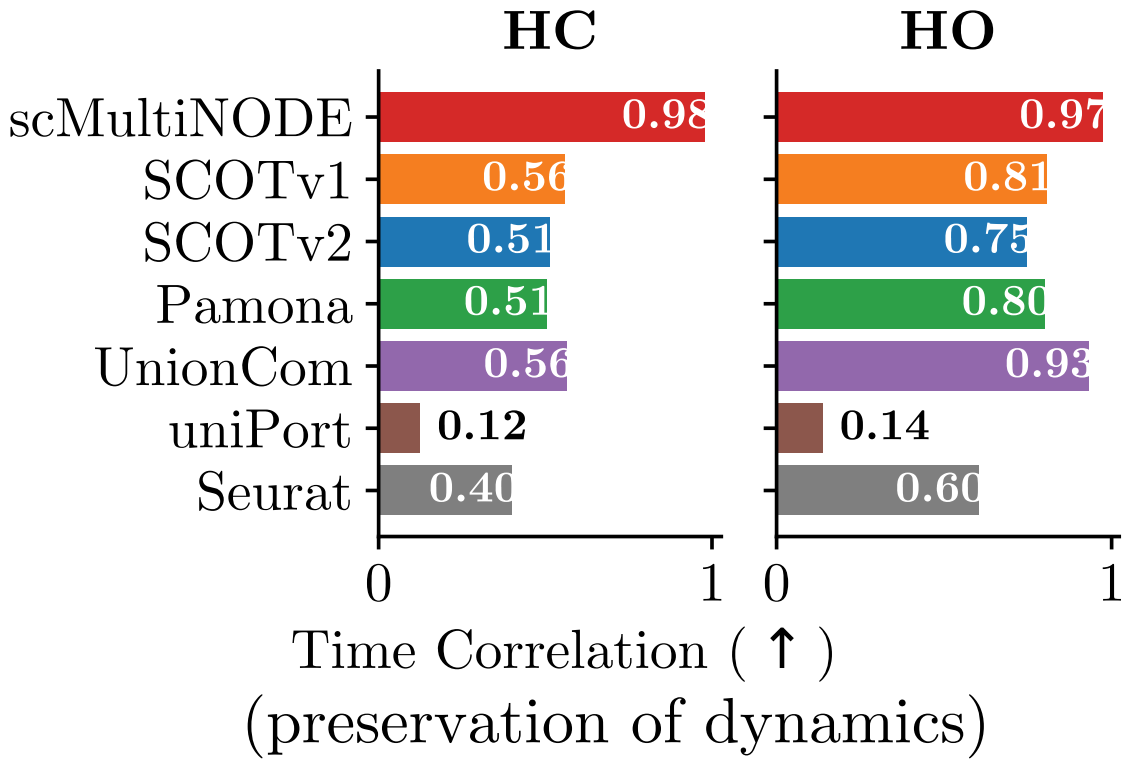
Experiment I: scMultiNODE captures cellular developmental dynamics during multi-modal integration



Experiment I: scMultiNODE captures cellular developmental dynamics during multi-modal integration (cont.)

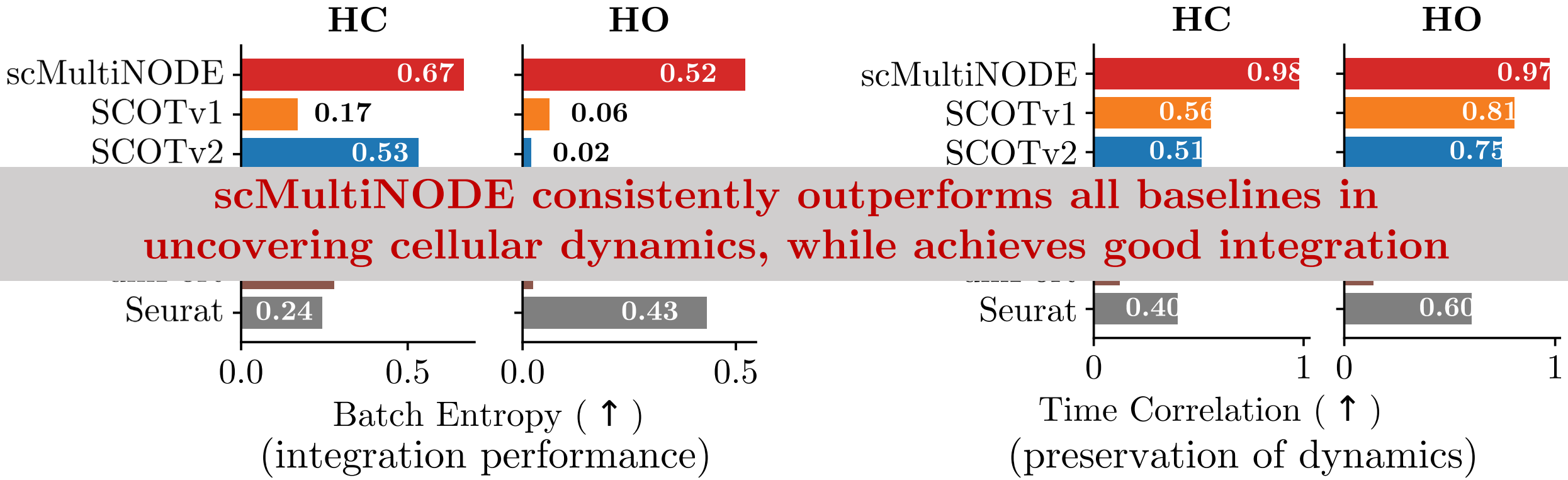
- *Human Cortex* (HC) and *Human Organoid* (HO) as examples





Experiment I: scMultiNODE captures cellular developmental dynamics during multi-modal integration (cont.)

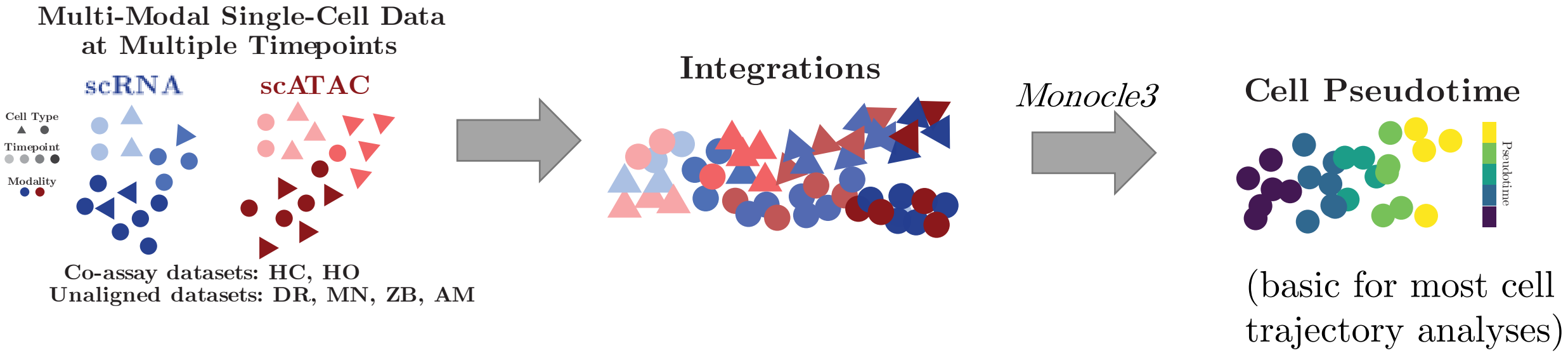
- *Human Cortex* (HC) and *Human Organoid* (HO) as examples



scMultiNODE consistently outperforms all baselines in uncovering cellular dynamics, while achieves good integration

Experiment II: scMultiNODE's latent space preserves multifurcating cell development trajectories

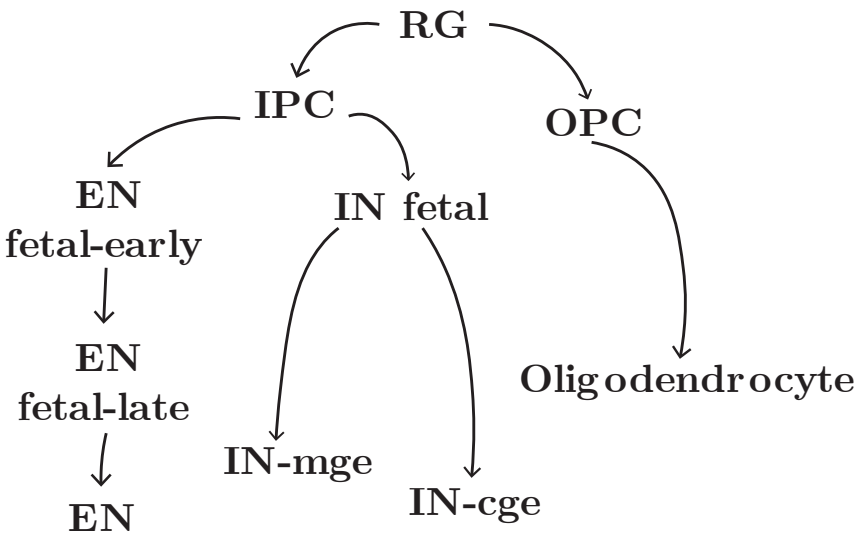
- **Setup**: predict cell pseudotime in the joint latent space



(basic for most cell trajectory analyses)

Experiment II: scMultiNODE's latent space preserves multifurcating cell development trajectories (cont.)

- Test on *human brain cortex* data



Reference Cell Lineage

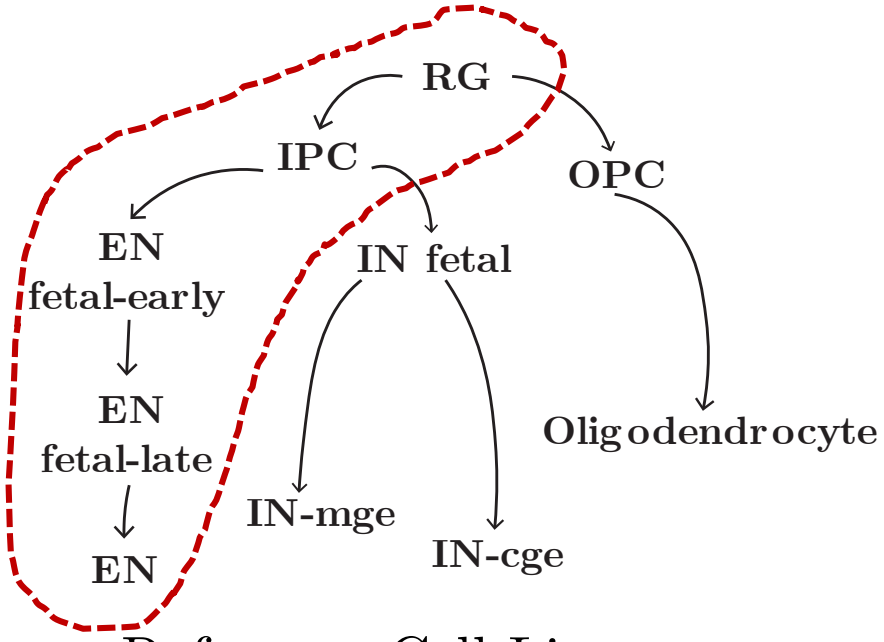
Spearman Correlation

evaluate consistency

Cell Pseudotime

Experiment II: scMultiNODE's latent space preserves multifurcating cell development trajectories (cont.)

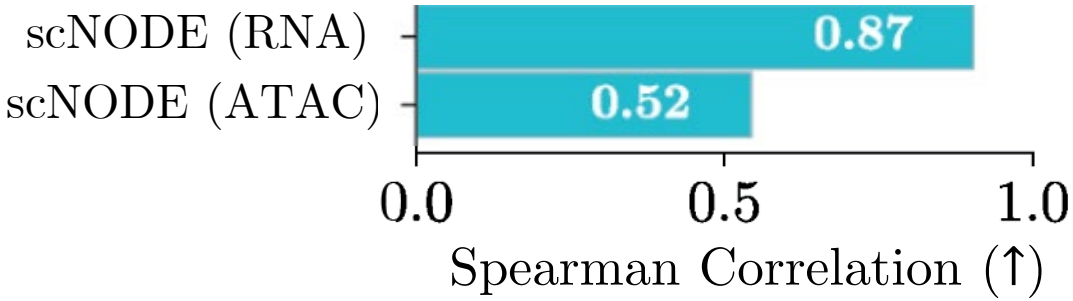
- Test on human brain cortex data



Reference Cell Lineage

(**scNODE**: single-modal dynamic modelling)
[Zhang,, et. al., *Bioinformatics.*, 2024]

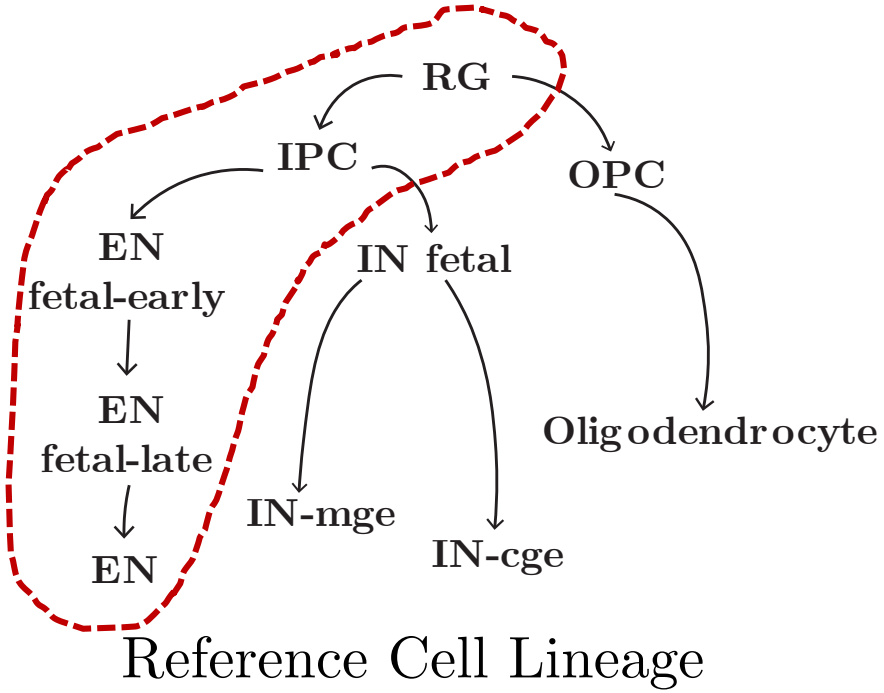
Single-modal trajectory



ATAC diminishes cell trajectories

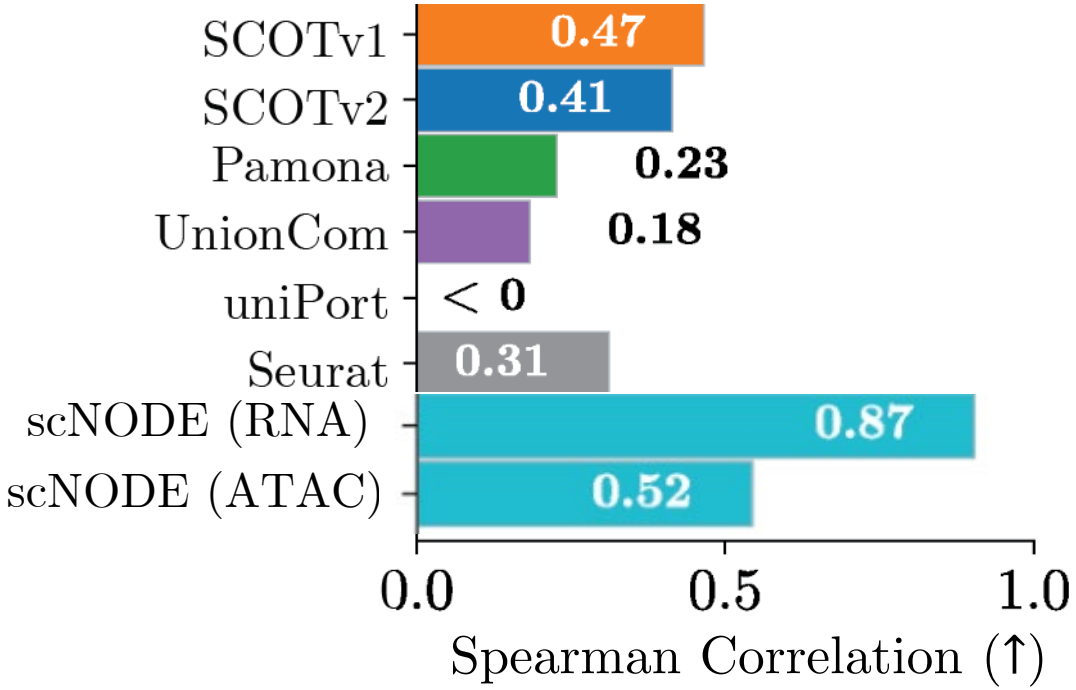
Experiment II: scMultiNODE's latent space preserves multifurcating cell development trajectories (cont.)

- Test on human brain cortex data



Reference Cell Lineage

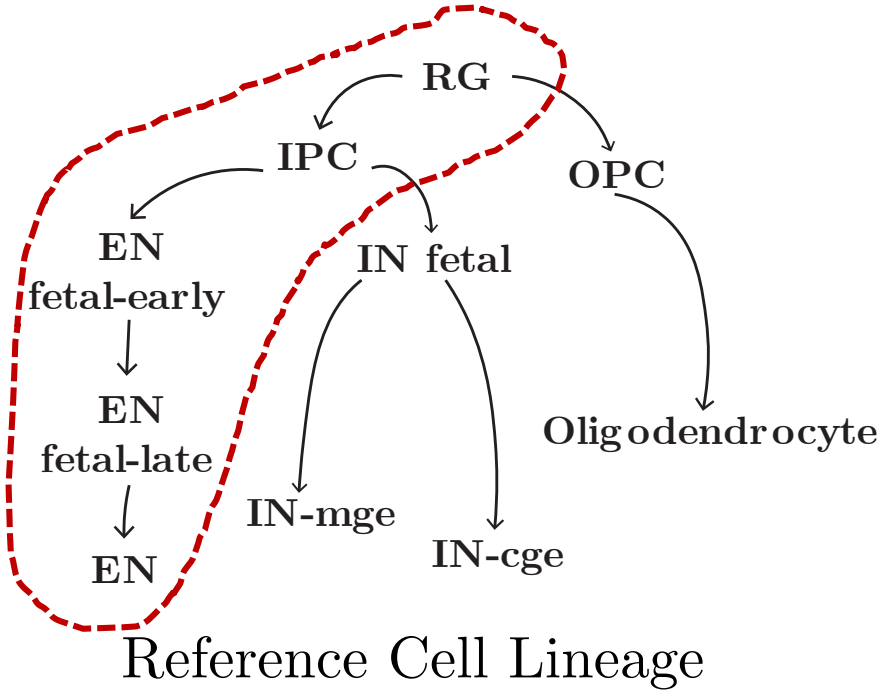
Integration vs. Single-modal trajectory



previous integration methods lose cell trajectories

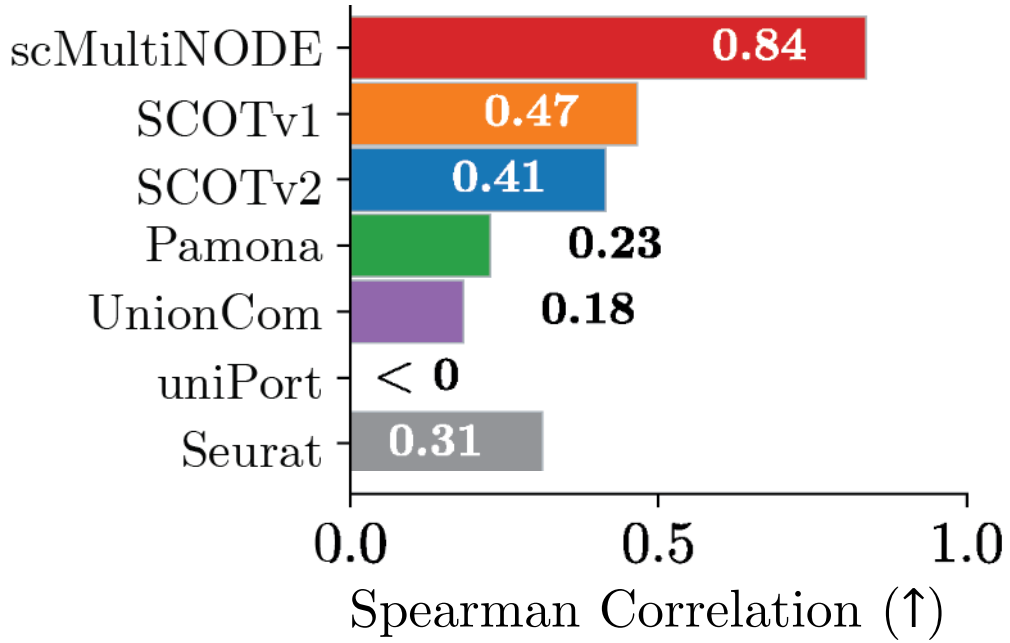
Experiment II: scMultiNODE's latent space preserves multifurcating cell development trajectories (cont.)

- Test on human brain cortex data



Reference Cell Lineage

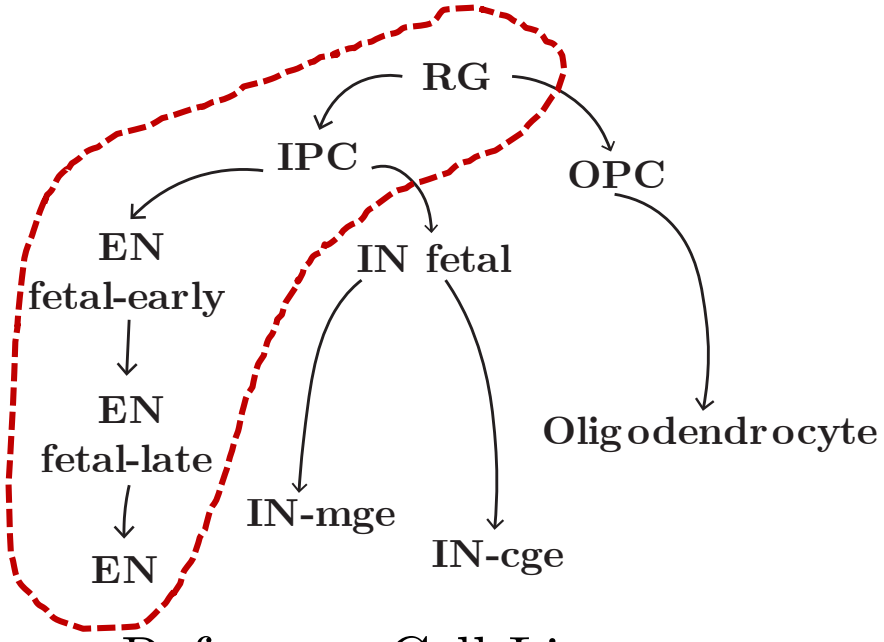
Our vs. other integrations



outperforms other multi-integration methods
on capturing complex cell trajectories

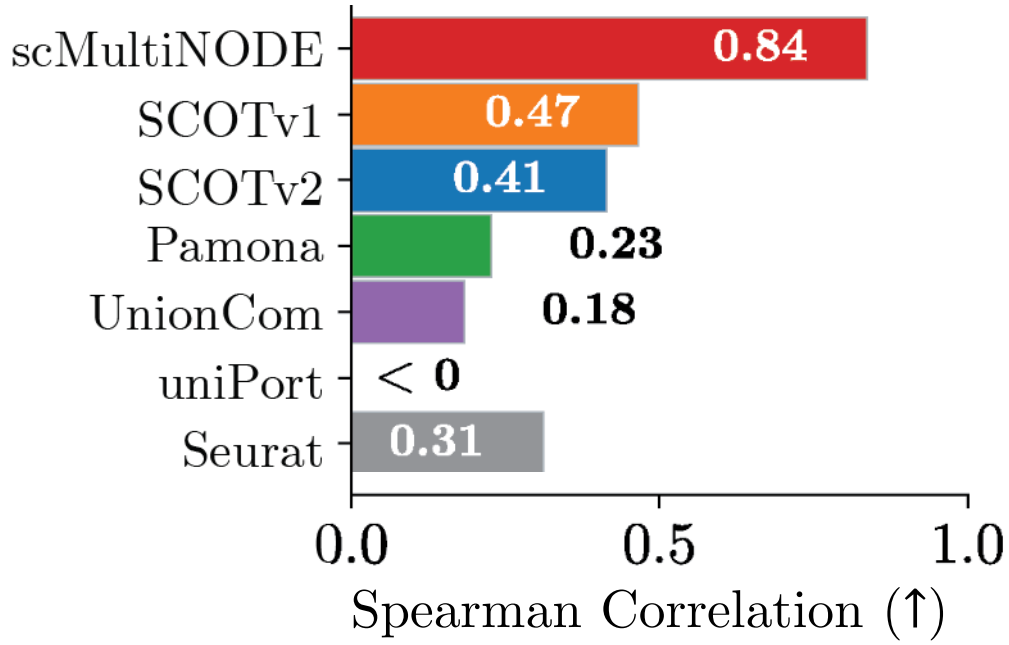
Experiment II: scMultiNODE's latent space preserves multifurcating cell development trajectories (cont.)

- Test on human brain cortex data

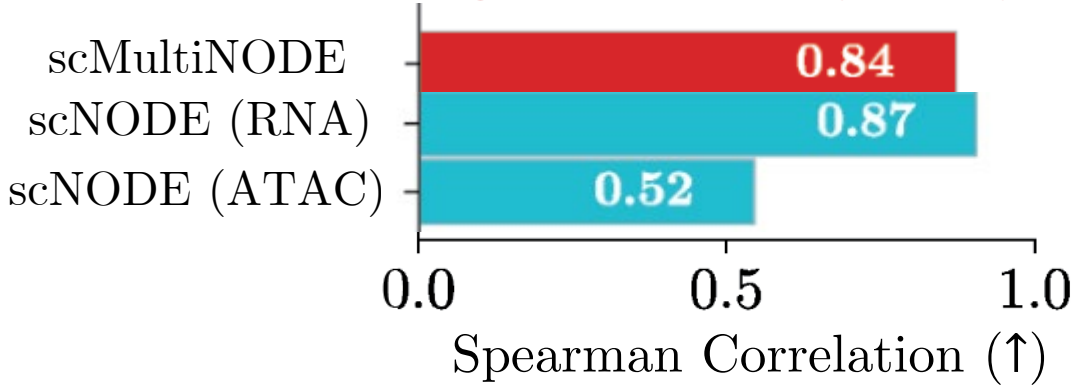


Reference Cell Lineage

Our vs. other integrations

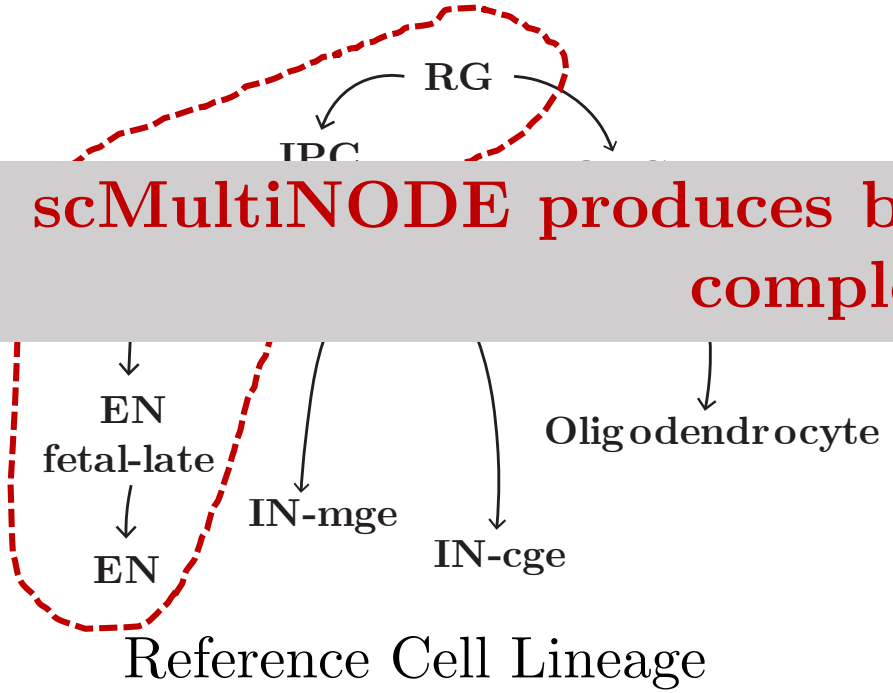


Our vs. single-modal trajectory



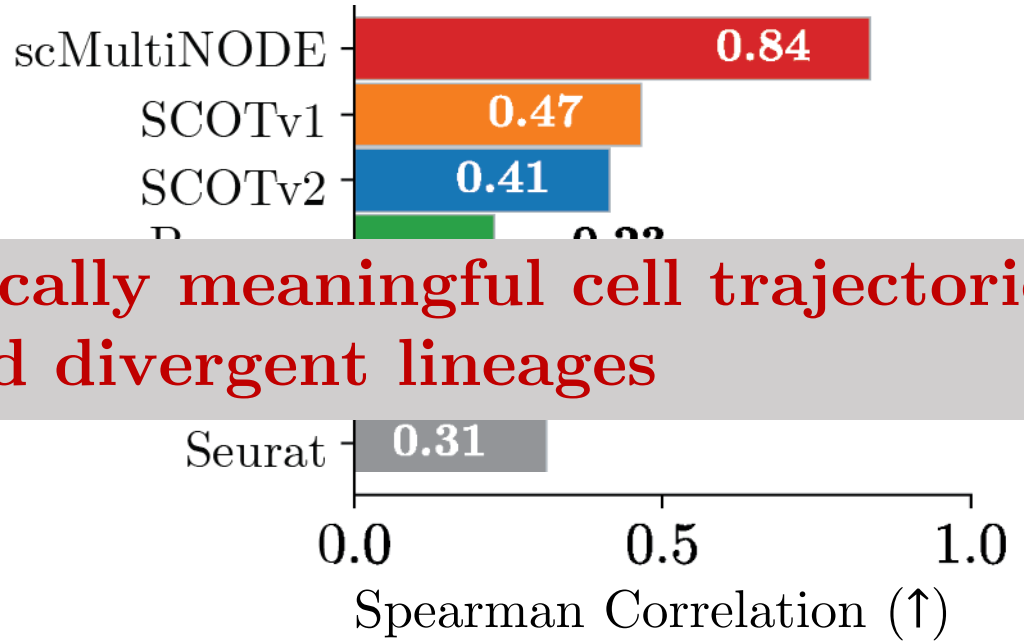
Experiment II: scMultiNODE's latent space preserves multifurcating cell development trajectories (cont.)

- Test on human brain cortex data



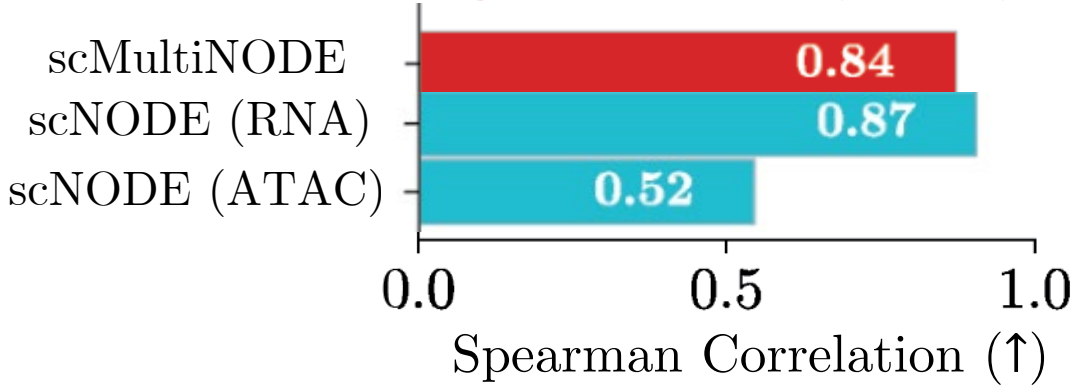
Reference Cell Lineage

Our vs. other integrations



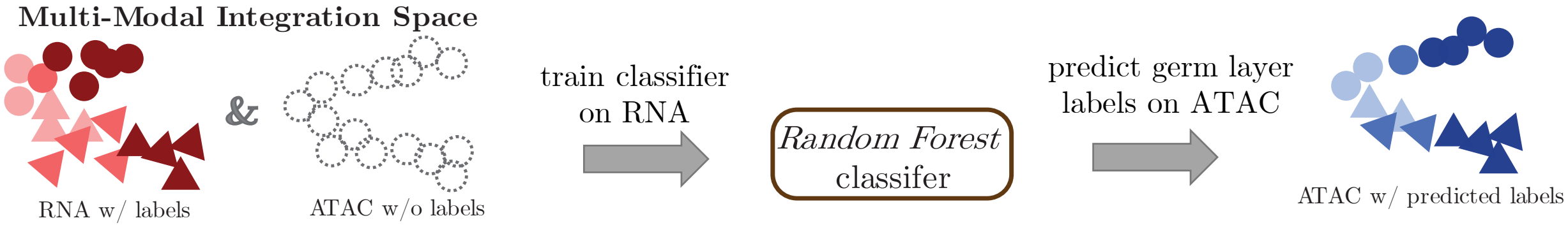
scMultiNODE produces biologically meaningful cell trajectories across complex and divergent lineages

Our vs. single-modal trajectory

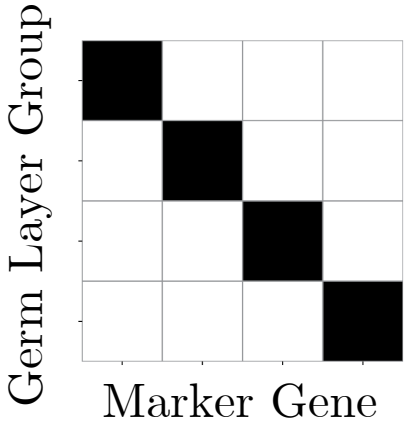


Experiment III: scMultiNODE enables germ layer label transfer across modalities

- **Setup**: germ layer label transfer across modalities



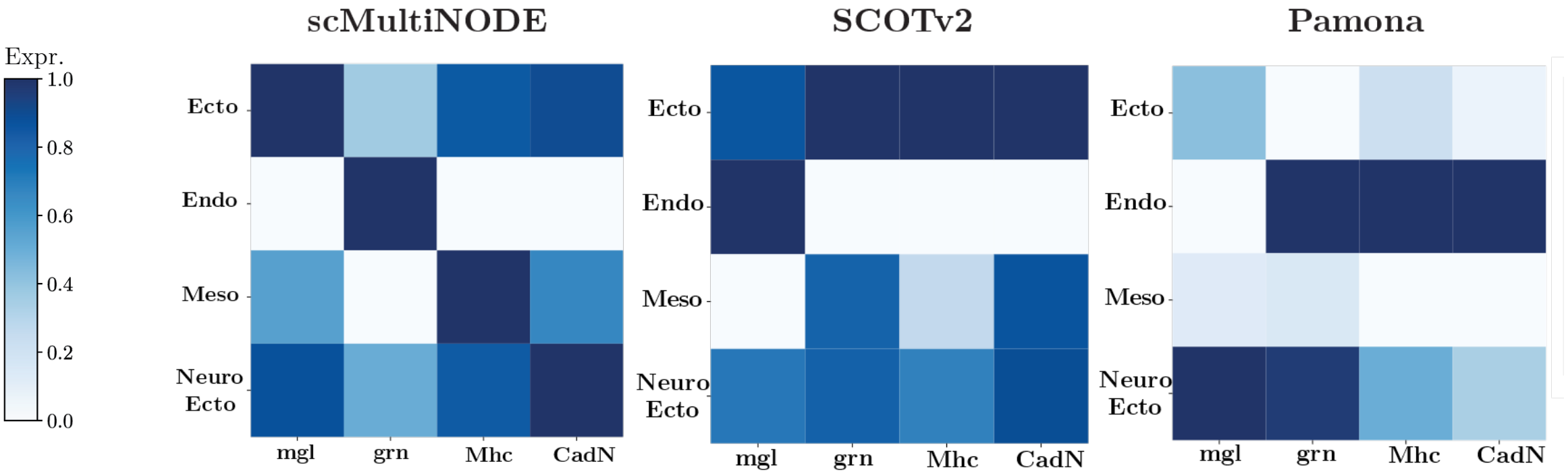
- **Evaluation**: marker gene expression across predicted germ layer groups
  - find marker genes of each germ layer group from RNA modality
  - check marker gene expression in ATAC modality with predicted labels



Expectation: marker genre only expressed in the corresponding group

Experiment III: scMultiNODE enables germ layer label transfer across modalities

- Result on the *Drosophila embryogenesis* data



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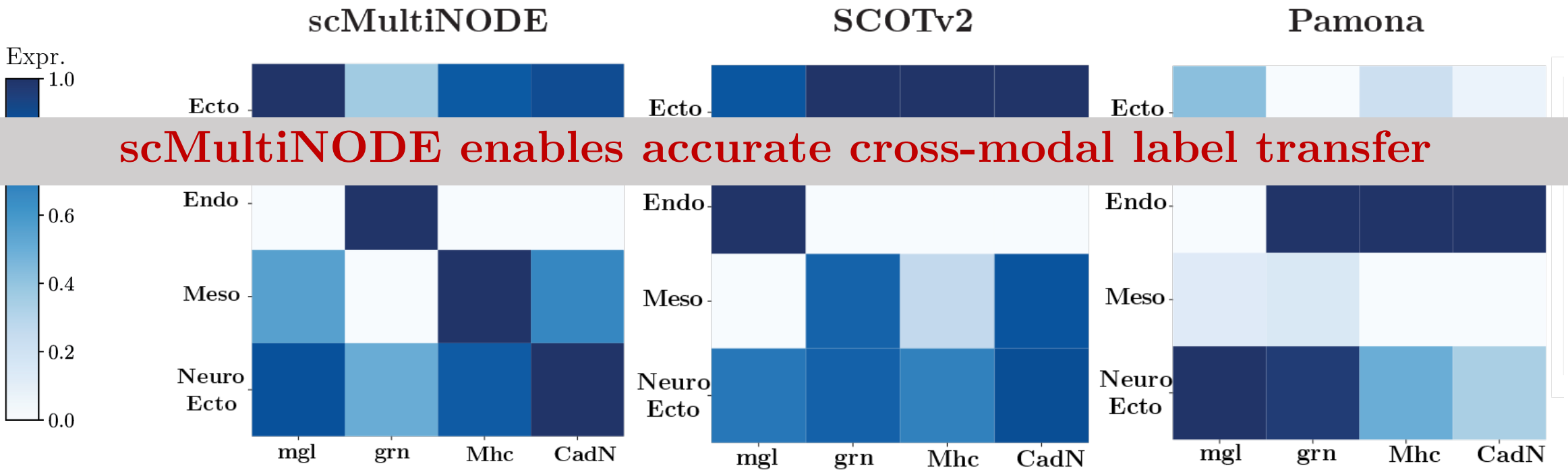
- Result on the *Drosophila embryogenesis* data



scMultiNODE enables accurate cross-modal label transfer

Takeaways

- scMultiNODE captures cellular dynamic while achieving good multi-modal integration
- scMultiNODE assists downstream analysis, including trajectory analysis and cross-modal label transfer

Jiaqi Zhang, Manav Chakravarthy, Ritambhara Singh,

"scMultiNODE: Integrative Model for Multi-Modal Temporal Single-Cell Data",

bioRxiv

Code availability: github.com/rsinghlab/scMultiNODE

Paper & Codes

Acknowledgement

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Ritambhara Singh

Manav Chakravarthy

Ghulam Murtaza

BROWN

CENTER FOR Computational Molecular Biology

NIH National Institutes of Health