

ICML 2025

Global Context-aware Representation Learning for Spatially Resolved Transcriptomics

Yunhak Oh*, Junseok Lee*, Yeongmin Kim, Sangwoo Seo, Namkyeong Lee, & Chanyoung Park†

*: Equal Contribution

†: Corresponding Author

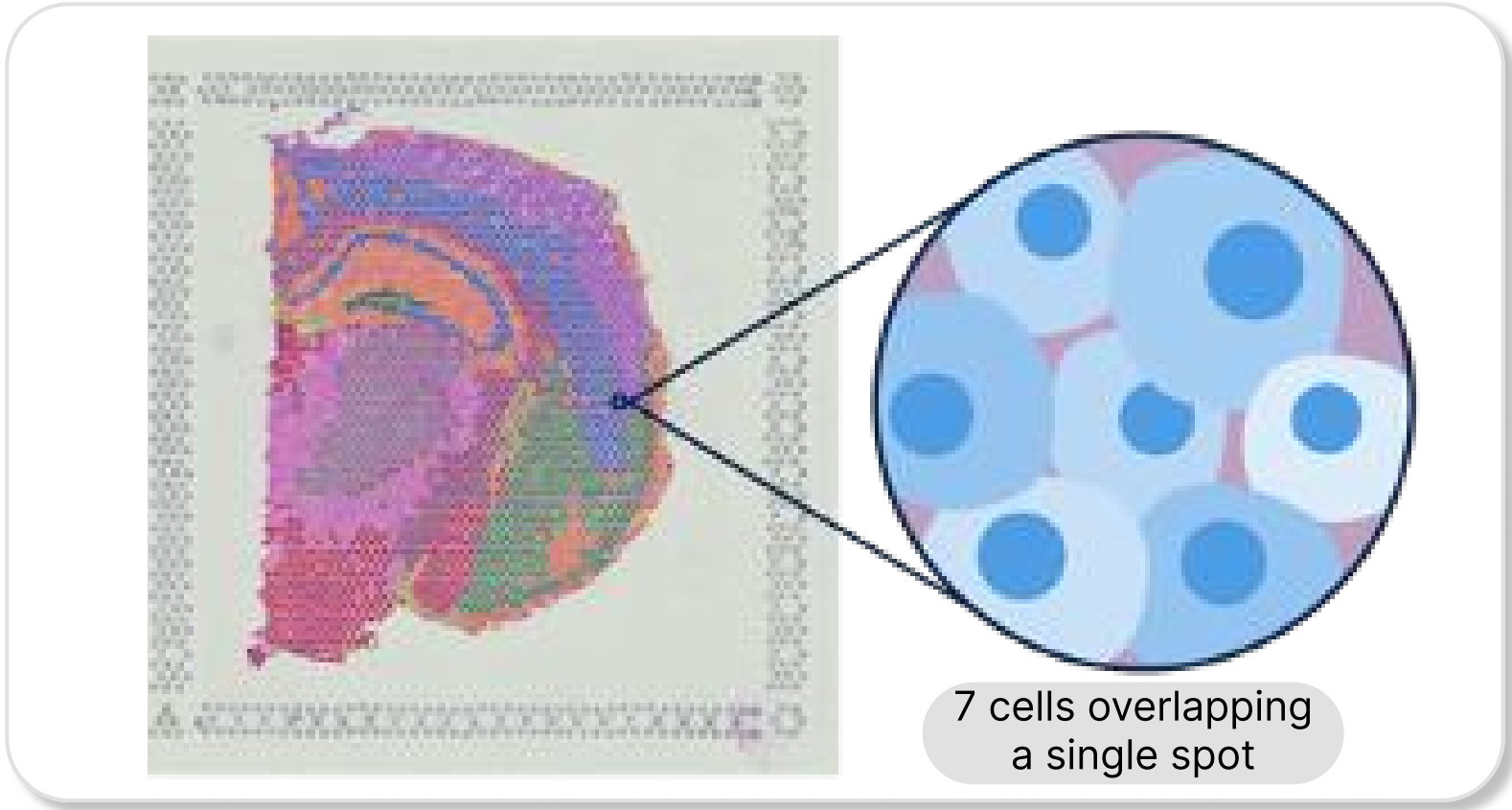


KAIST

DSAIL Data Science &
Artificial Intelligence



Spatially Resolved Transcriptomics (SRT) BACKGROUND

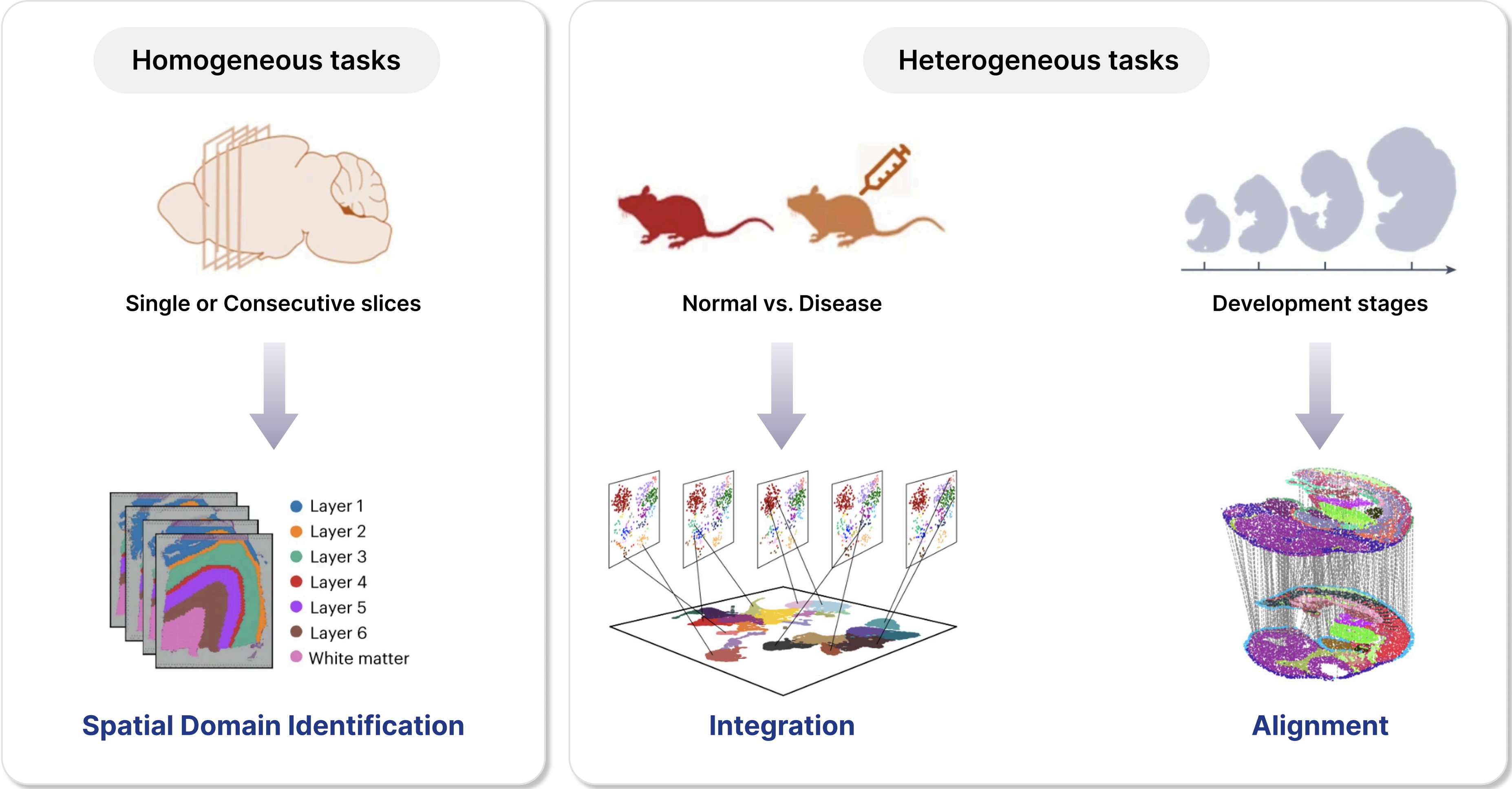


	Gene 1	Gene 2	Gene 3	Gene 4
Spot 1	18	1010	0	22
Spot 2	0	506	49	0
Spot 3	0	0	0	72

- SRT incorporate the **spatial context** and gene expression of cells
 - allowing for the identification of **where specific genes are expressed** within tissue
 - **enables the study of diseases**, such as cancer, by observing gene expression patterns in different tissue regions

Spatially Resolved Transcriptomics (SRT) BACKGROUND

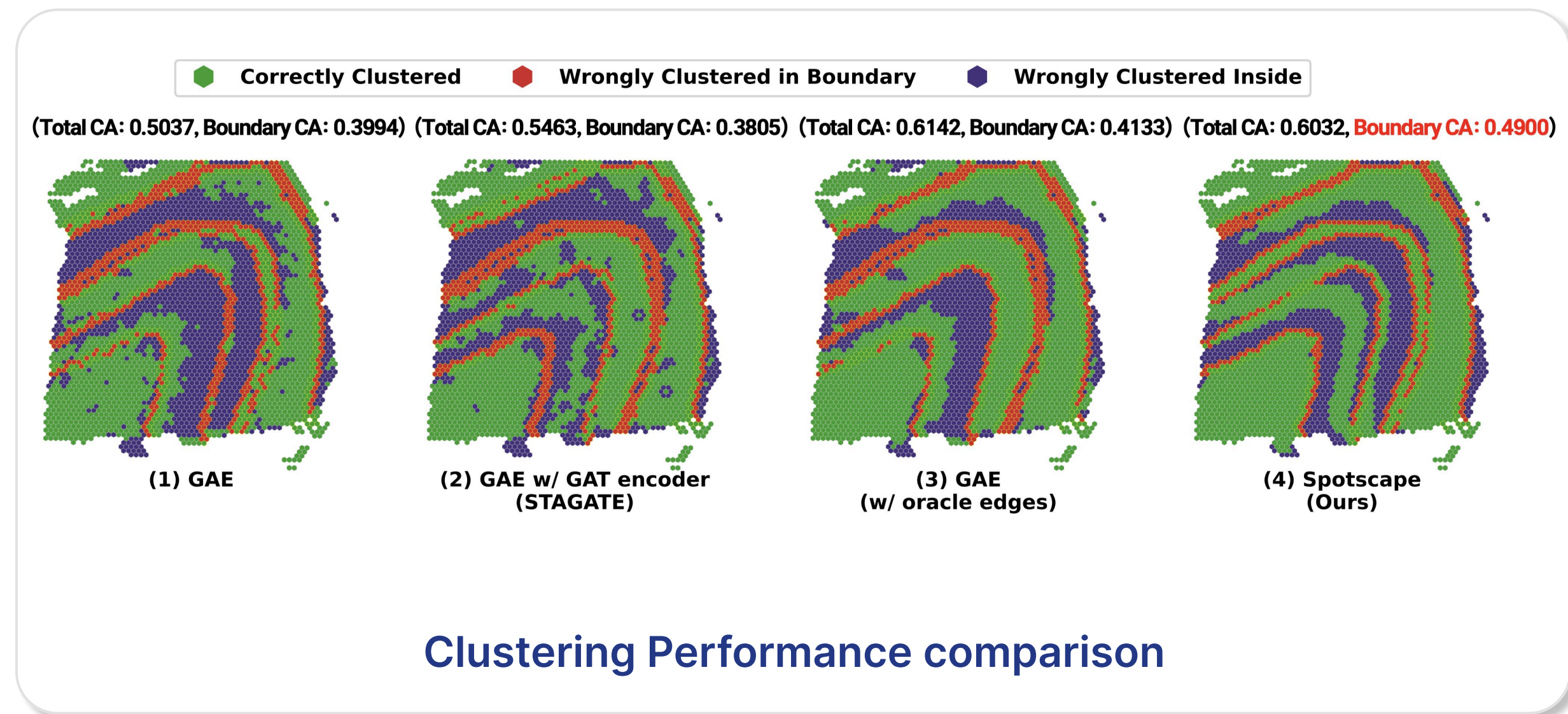
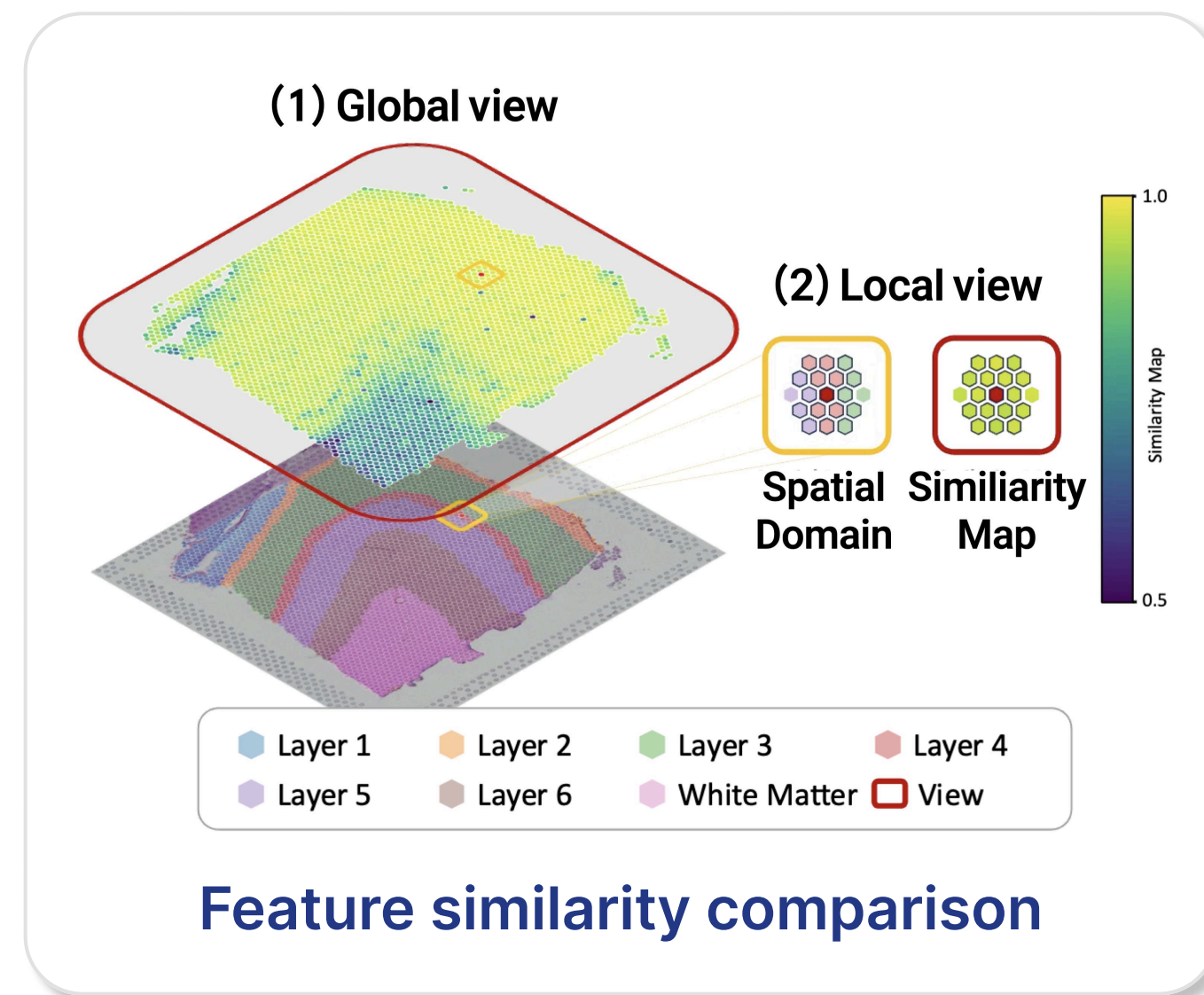
Representation Learning on SRT data for **various downstream tasks**



Continuous Nature CHALLENGE 1

Continuous nature of biological systems (SRT data)

→ Gene expression values vary smoothly along spatial coordinates



Observations

- Local (spatially close) spots have high similarity, regardless of the spatial domain
 - Results in a negative effect on GNNs by acquiring information from **heterophilic nodes**
 - Difficult to learn the appropriate attention scores** that gives high scores to homophilic nodes due to their low feature difference
 - Even if it can learn appropriate edges (attentions), **local view has insufficient information**

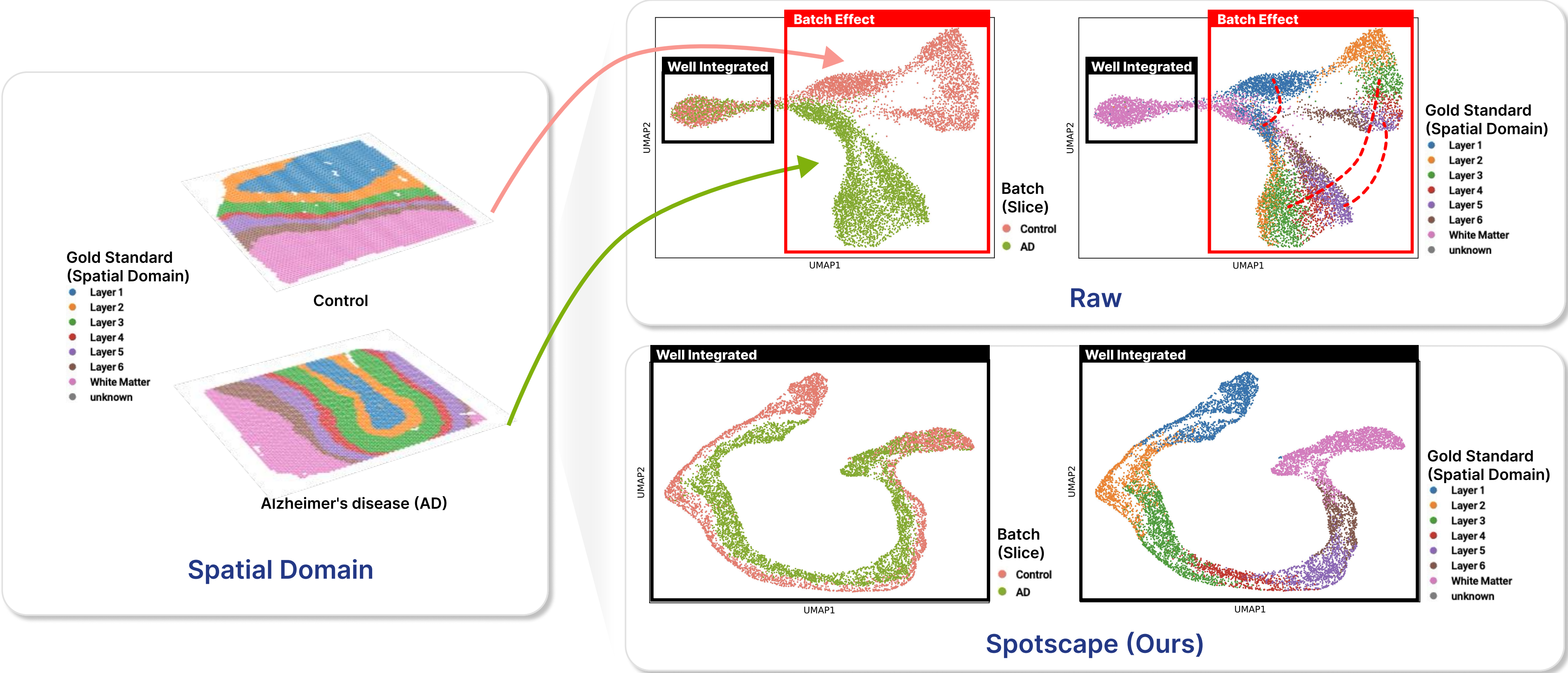
Should capture the **relationships** between spots in **global context**

Batch Effects

CHALLENGE 2

Batch effects in SRT data

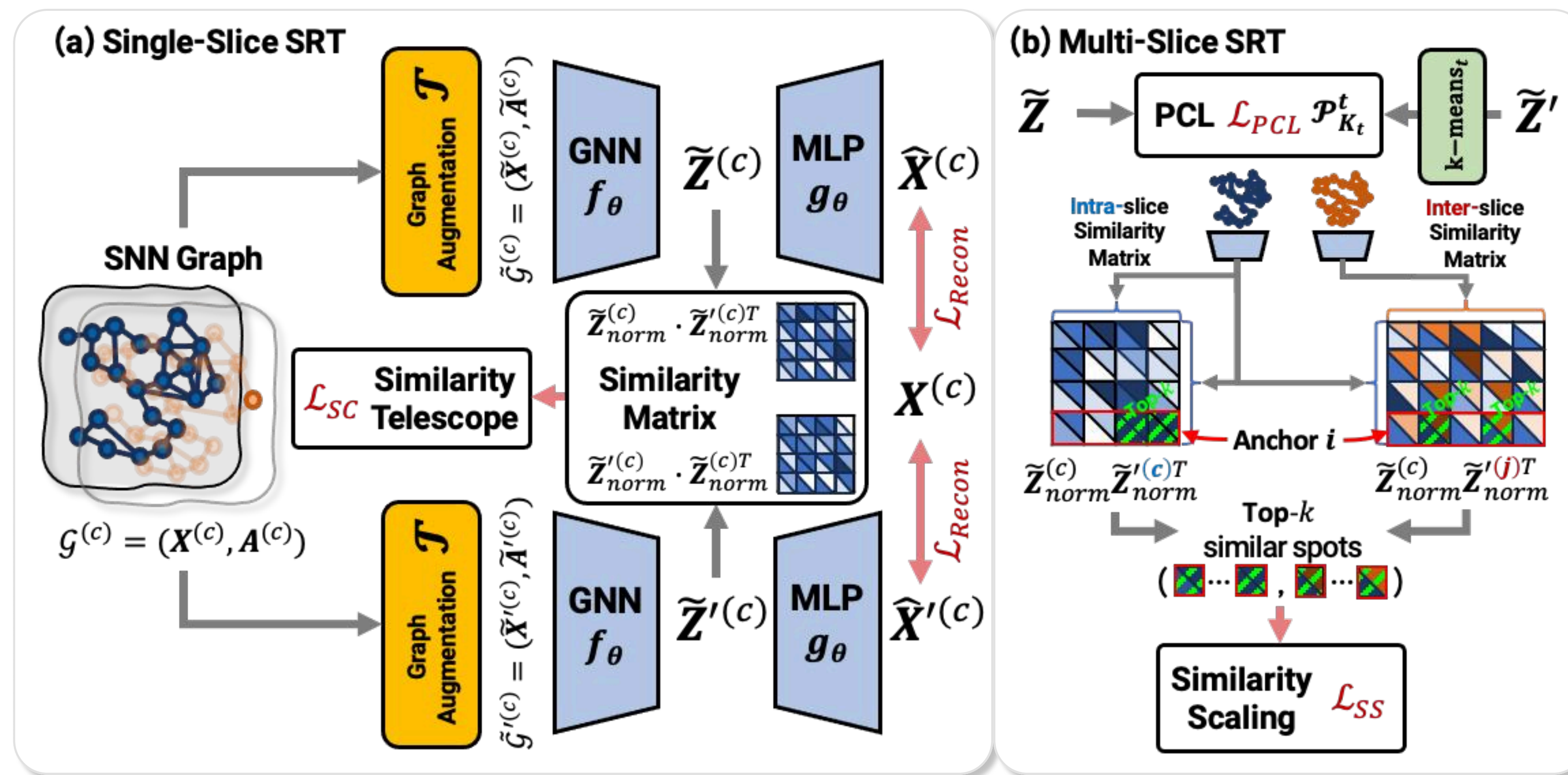
→ Gene expression profiles from the same slice cluster together unexpectedly, regardless of their biological relevance



Should alleviate batch effects to extend multi-slices tasks

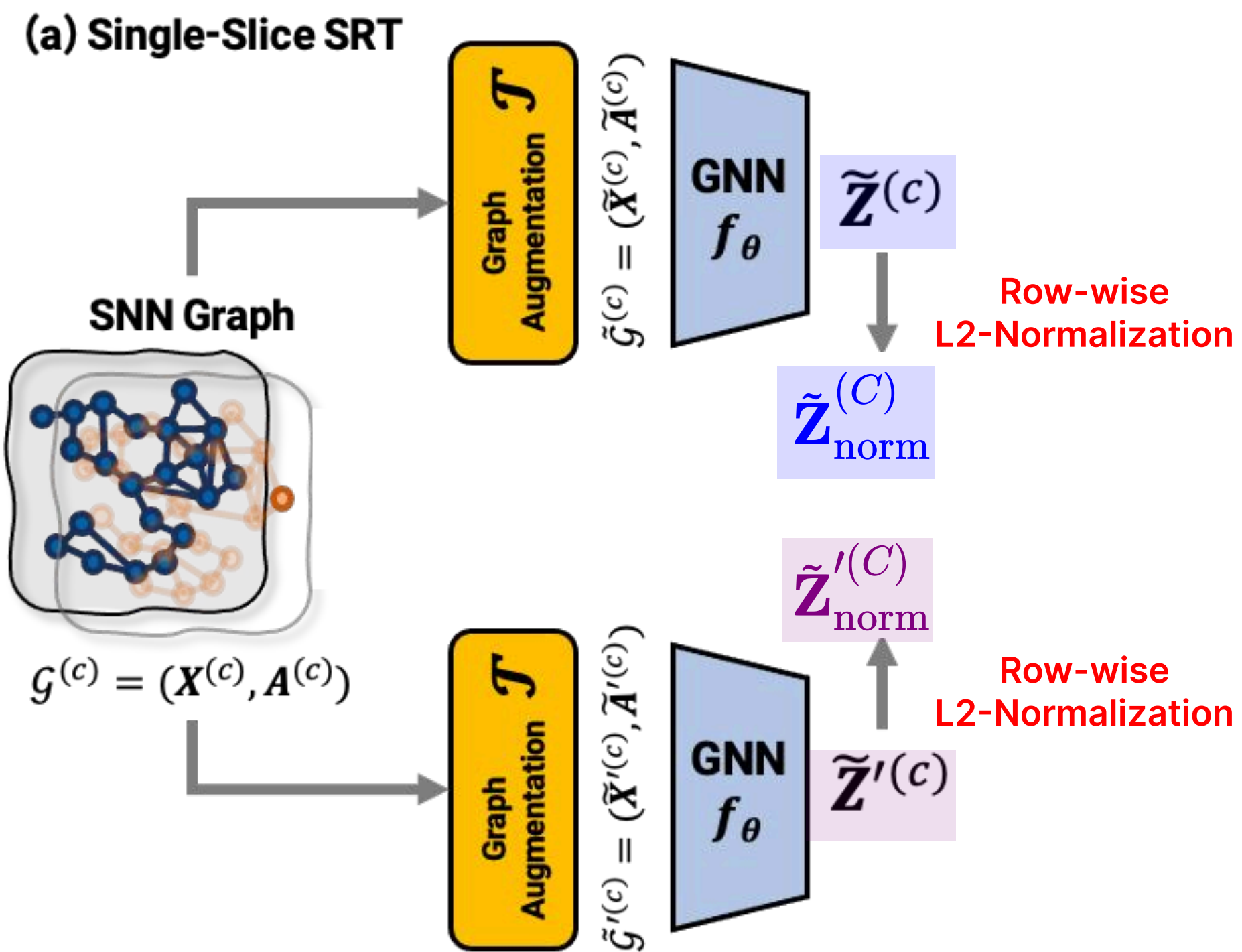
Key Ideas of Spotscape

- Capturing **global relationships** between cells by learning **robust similarities** with respect to different augmentations
- Explicitly **balances the similarity scales of inter- and intra-relationships** to mitigate batch effects
- **Grouping spots from the same spatial domain** while **distancing others** in latent space using PCL scheme to mitigate batch effects



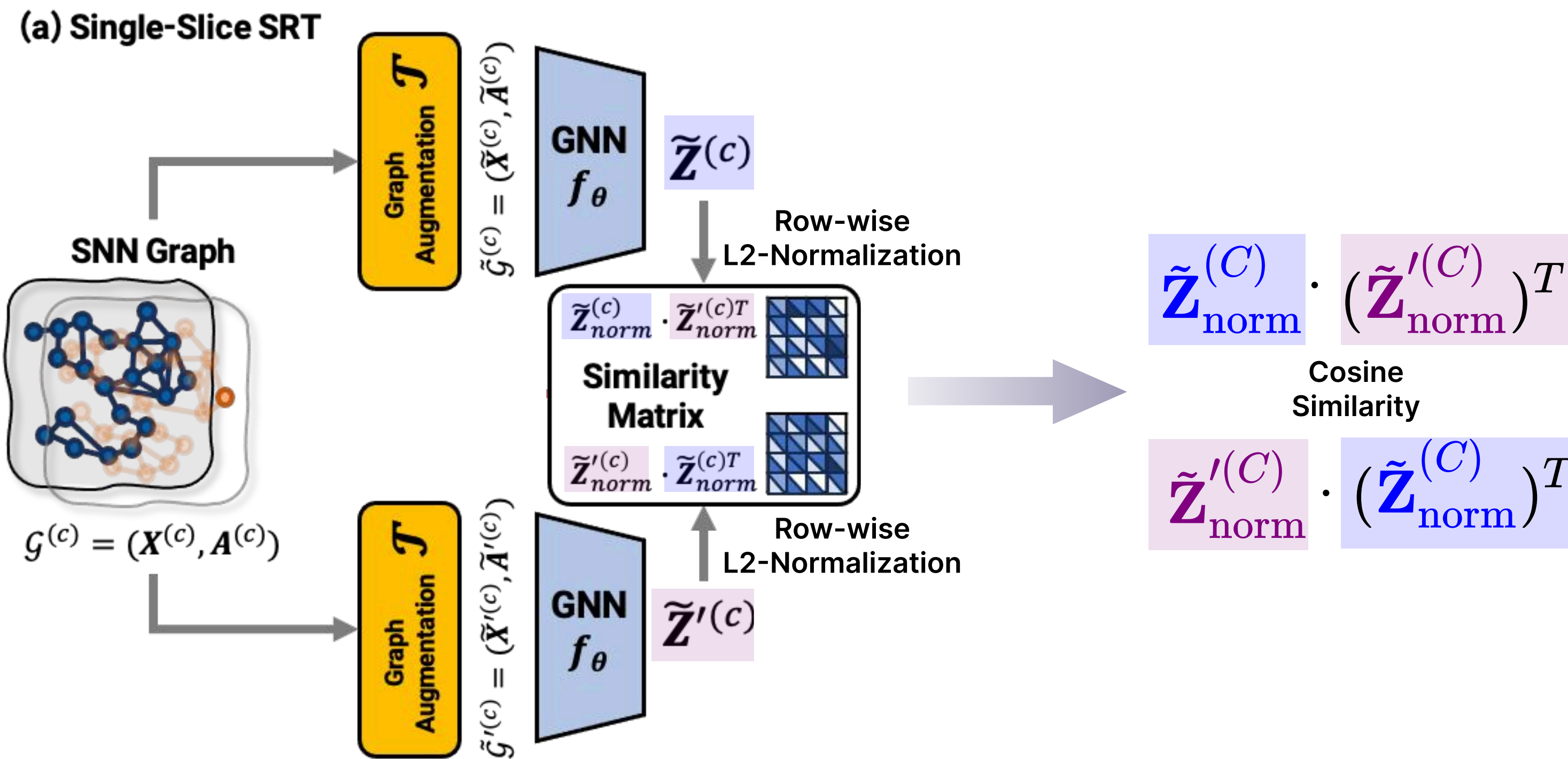
Key Ideas of Spotscape

- Capturing **global relationships** between cells by learning **robust similarities** with respect to different augmentations
- Explicitly balances the similarity scales of inter- and intra-relationships to mitigate batch effects
- Grouping spots from the same spatial domain while distancing others in latent space using PCL scheme to mitigate batch effects



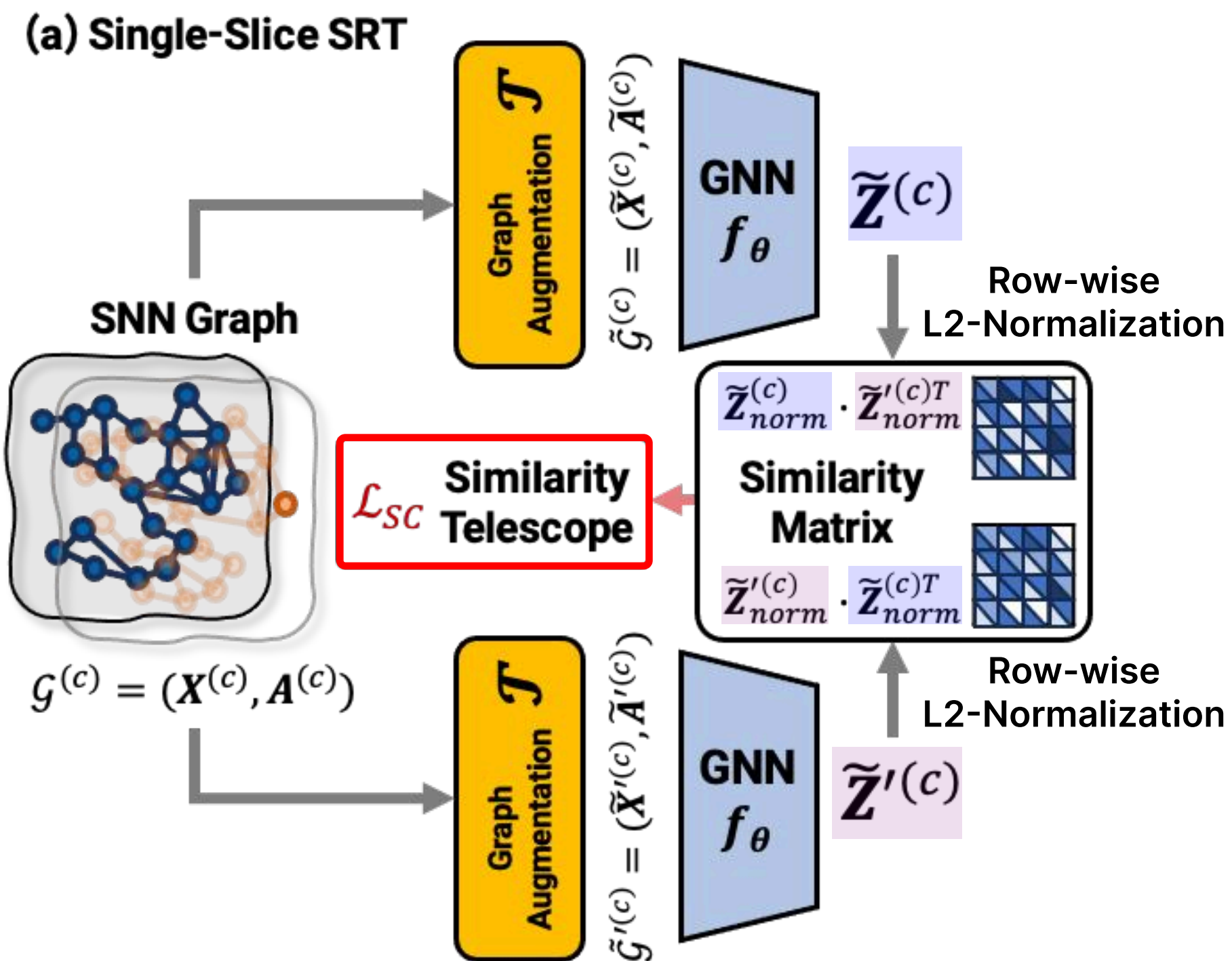
Key Ideas of Spotscape

- Capturing **global relationships** between cells by learning **robust similarities** with respect to different augmentations
- Explicitly balances the similarity scales of inter- and intra-relationships to mitigate batch effects
- Grouping spots from the same spatial domain while distancing others in latent space using PCL scheme to mitigate batch effects



Key Ideas of Spotscape

- Capturing **global relationships** between cells by learning **robust similarities** with respect to different augmentations
- Explicitly balances the similarity scales of inter- and intra-relationships to mitigate batch effects
- Grouping spots from the same spatial domain while distancing others in latent space using PCL scheme to mitigate batch effects

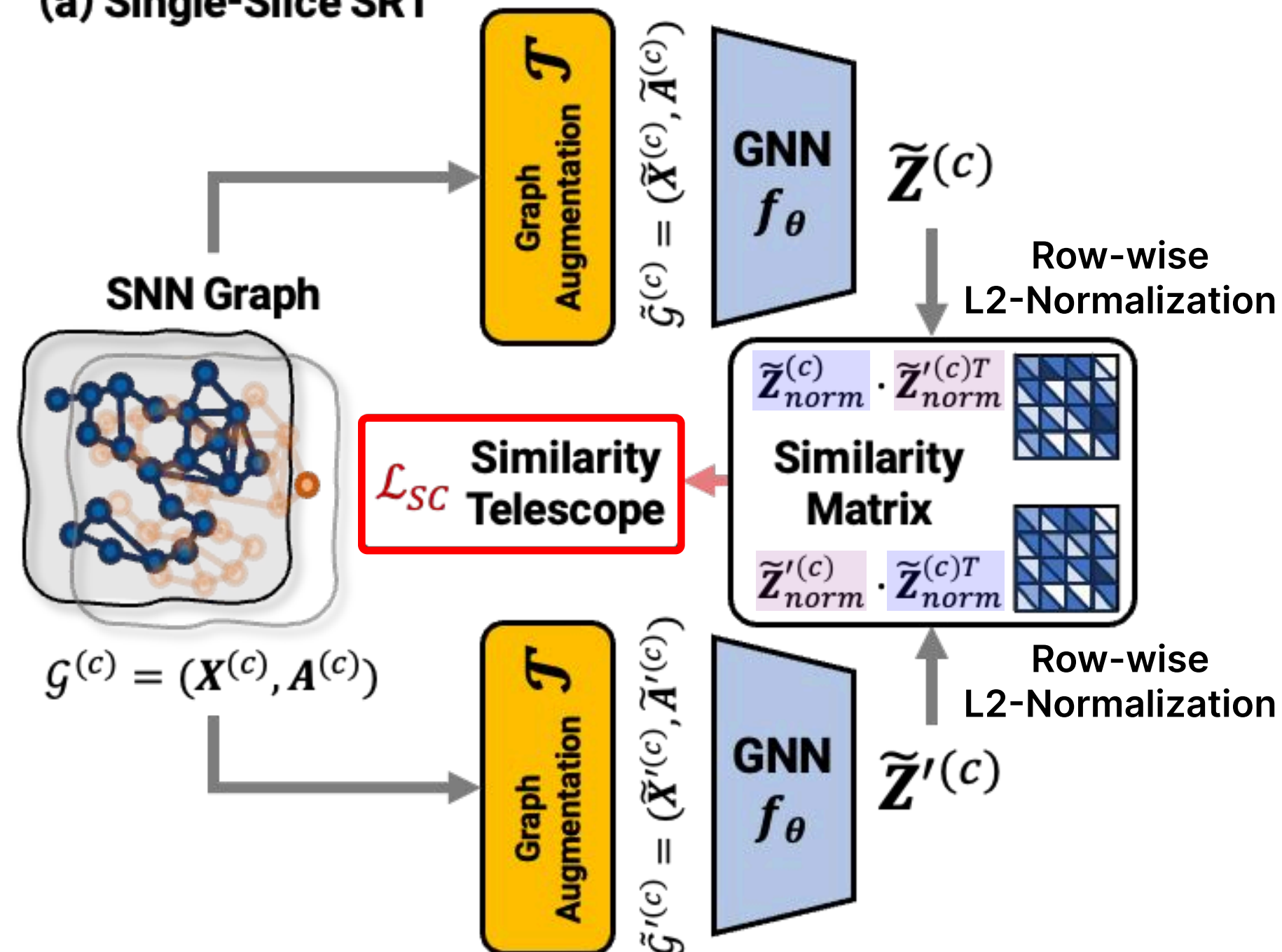


$$\mathcal{L}_{sc}(\tilde{\mathbf{Z}}^{(c)}, \tilde{\mathbf{Z}}'^{(c)}) = \text{MSE}(\tilde{\mathbf{Z}}_{\text{norm}}^{(c)} (\tilde{\mathbf{Z}}'_{\text{norm}}{}^{(c)})^T, \tilde{\mathbf{Z}}'_{\text{norm}}{}^{(c)} (\tilde{\mathbf{Z}}_{\text{norm}}^{(c)})^T)$$

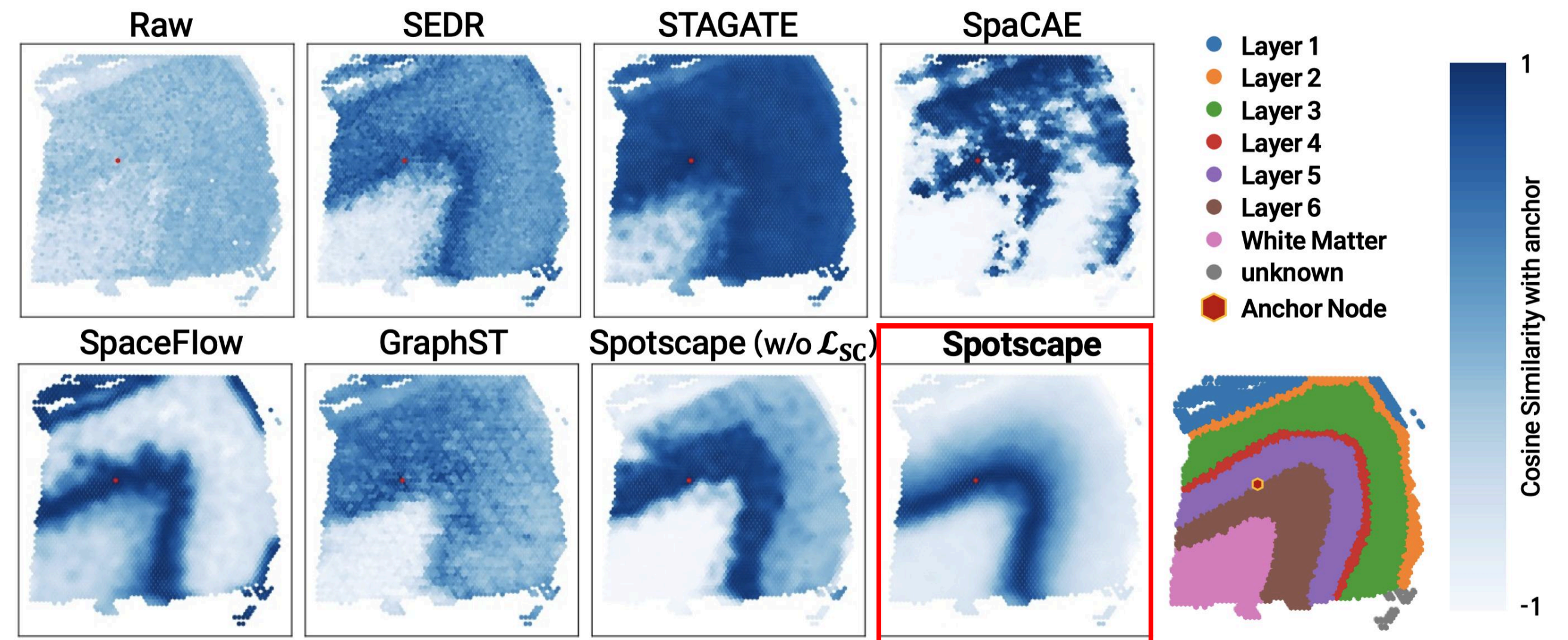
Key Ideas of Spotscape

- Capturing **global relationships** between cells by learning **robust similarities** with respect to different augmentations
- Explicitly balances the similarity scales of inter- and intra-relationships to mitigate batch effects
- Grouping spots from the same spatial domain while distancing others in latent space using PCL scheme to mitigate batch effects

(a) Single-Slice SRT



Similarity Consistency Loss

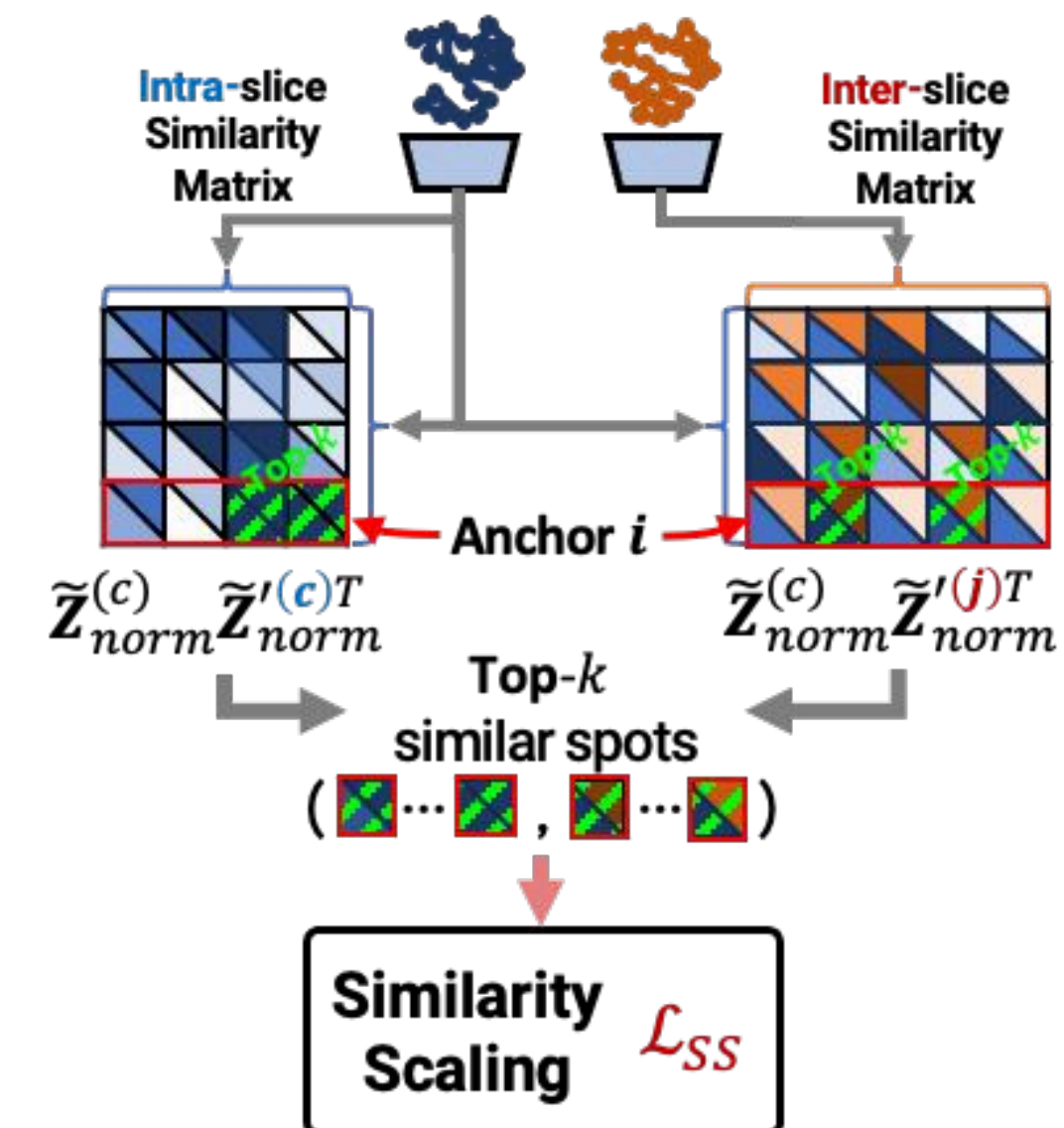


- Spotscape **captures relative similarities between spots**, aligning with the spatial dynamics of SRT data, unlike other baselines
- Spotscape exhibits varying similarity levels based on the true spatial domains, accurately reflecting spatial distance relationships

Key Ideas of Spotscape

- Capturing global relationships between cells by learning robust similarities with respect to different augmentations
- Explicitly balances the similarity scales of inter- and intra-relationships to mitigate batch effects
- Grouping spots from the same spatial domain while distancing others in latent space using PCL scheme to mitigate batch effects

(b) Multi-Slice SRT

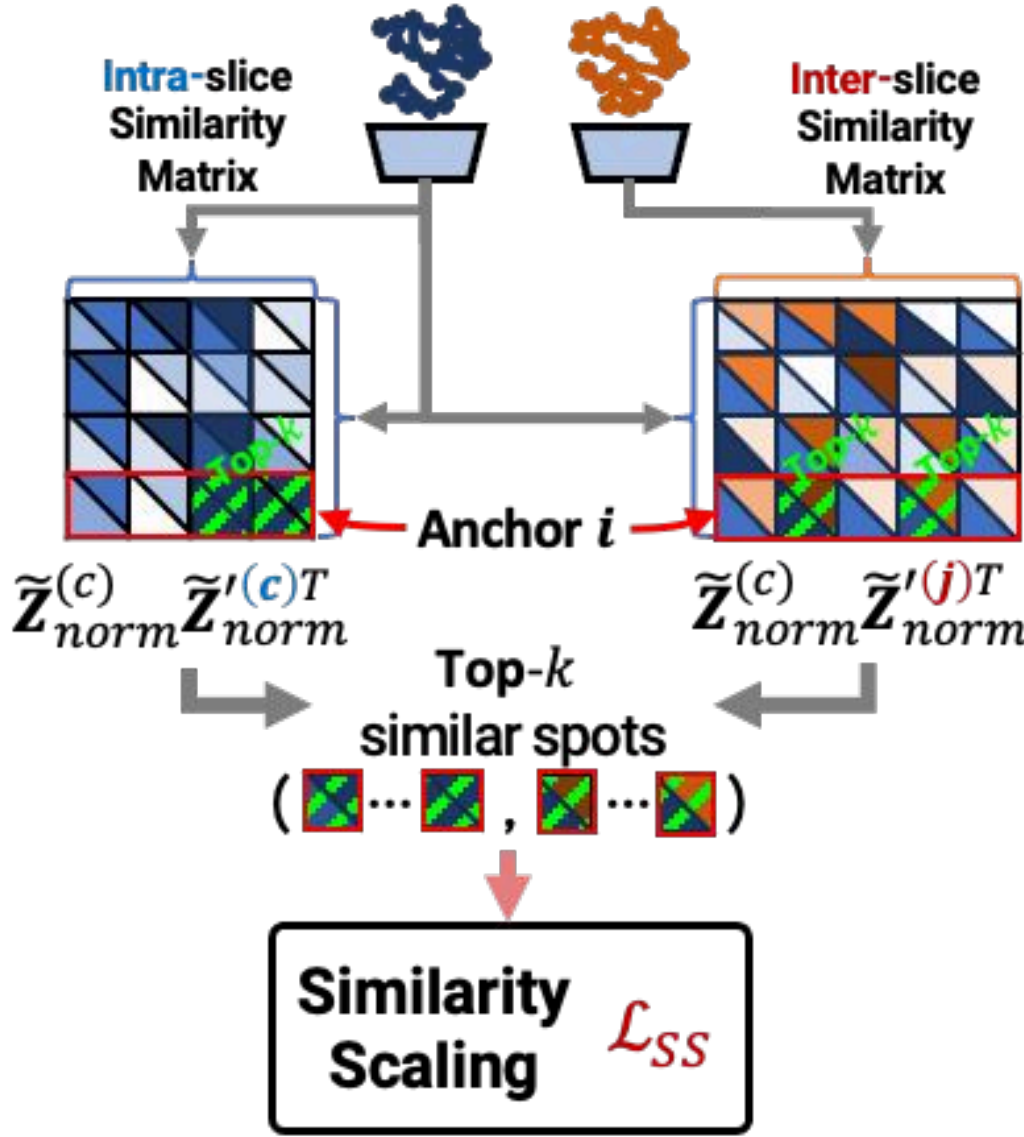
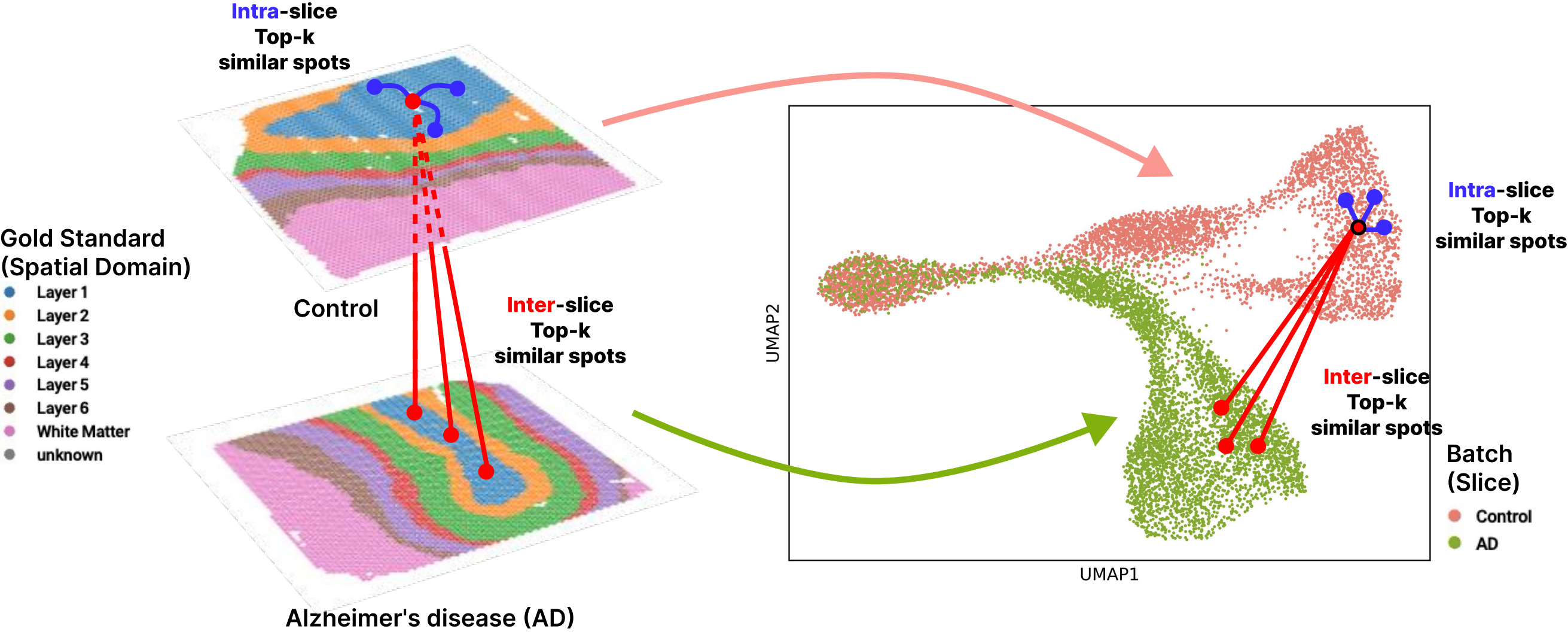


Key Ideas of Spotscape

- Capturing global relationships between cells by learning robust similarities with respect to different augmentations
- Explicitly balances the similarity scales of inter- and intra-relationships to mitigate batch effects
- Grouping spots from the same spatial domain while distancing others in latent space using PCL scheme to mitigate batch effects

Batch Effects: Experimental condition or noise >> Biological relevance

(b) Multi-Slice SRT

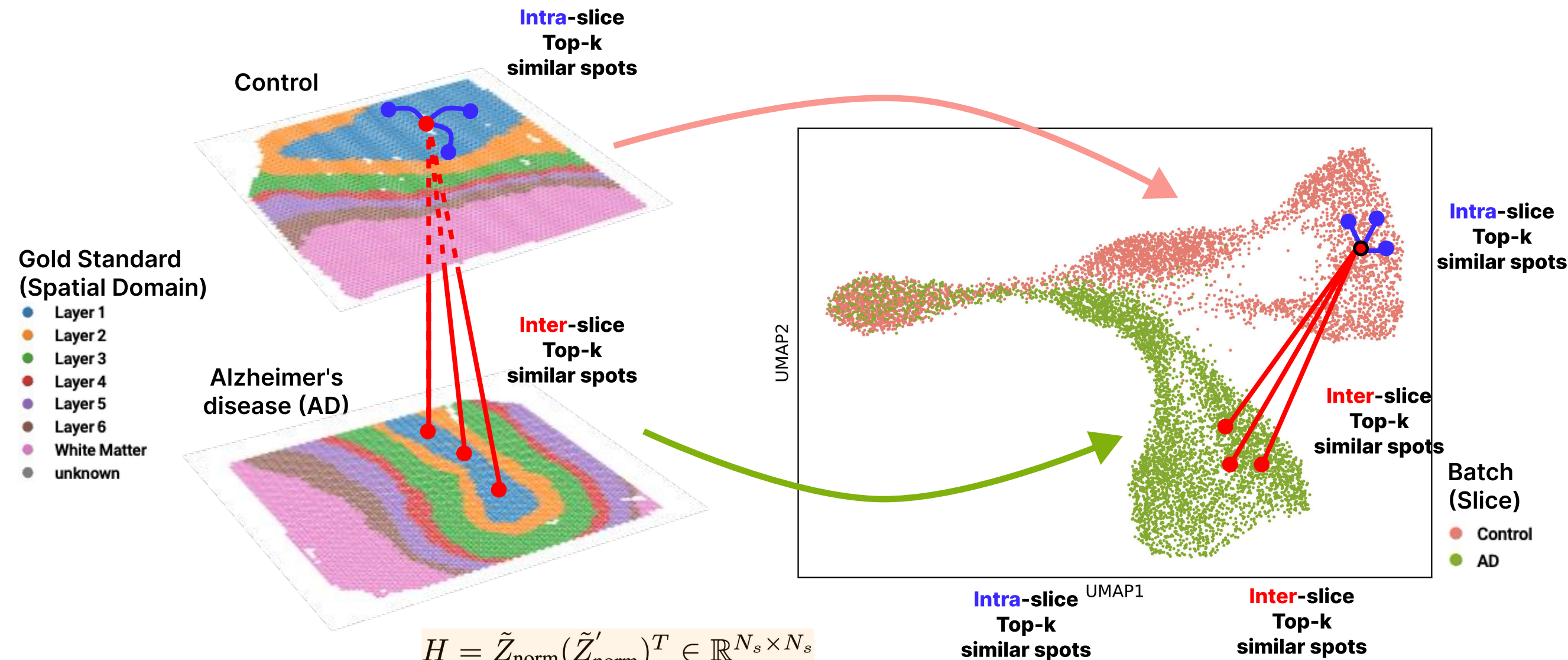


Key Ideas of Spotscape

- Capturing global relationships between cells by learning robust similarities with respect to different augmentations
- Explicitly **balances the similarity scales of inter- and intra-relationships** to mitigate batch effects
- Grouping spots from the same spatial domain while distancing others in latent space using PCL scheme to mitigate batch effects

Batch Effects: Experimental condition or noise $\gg$ Biological relevance

(b) Multi-Slice SRT

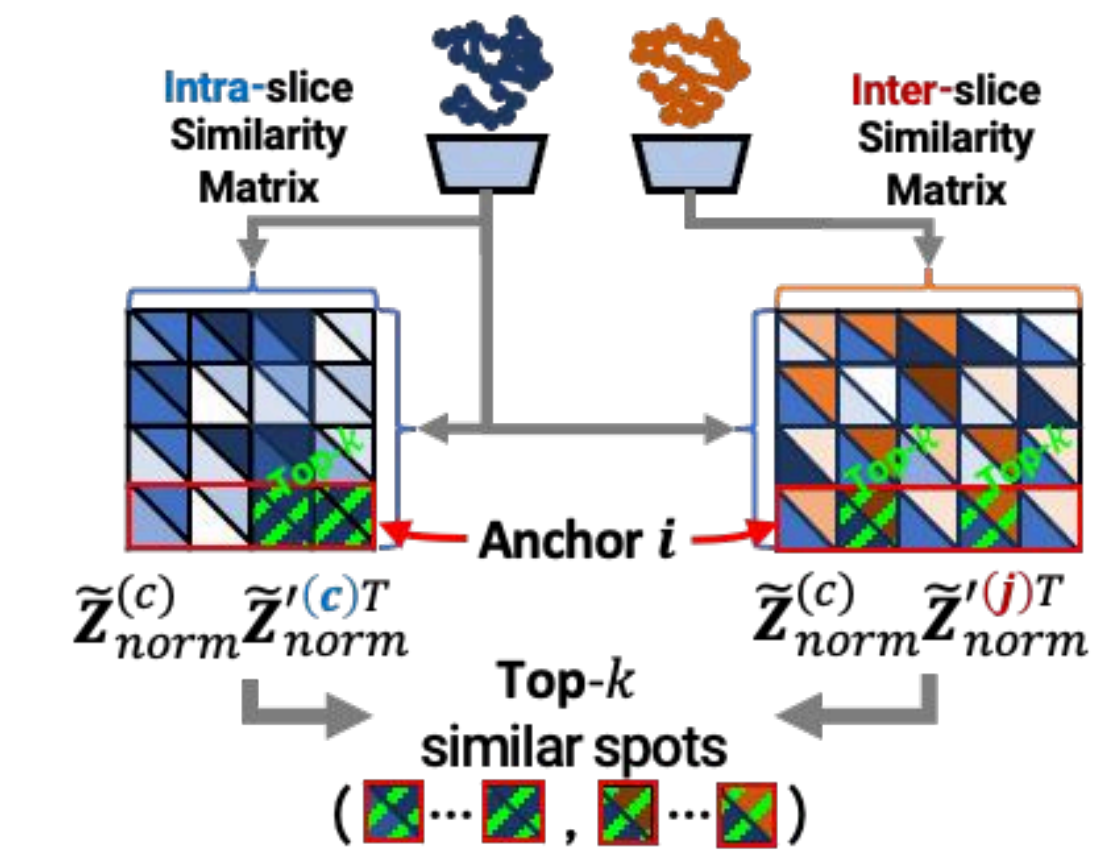


$$H = \tilde{Z}_{\text{norm}} (\tilde{Z}'_{\text{norm}})^T \in \mathbb{R}^{N_s \times N_s}$$

$$l_{\text{ss}}(H_i, \mathcal{G}^{(j)}) = (\text{Mean}(S_{\text{top}}^{(c)}) - \text{Mean}(S_{\text{top}}^{(j)}))^2, \text{ for } i \in \mathcal{G}^{(c)}$$

$$\text{where } S_{\text{top}}^{(c)} = \text{Top-}k_{l \in \mathcal{G}^{(c)}}(H_i[l]) = (a_1, a_2, \dots, a_k),$$

$$S_{\text{top}}^{(j)} = \text{Top-}k_{l \in \mathcal{G}^{(j)}}(H_i[l]) = (b_1, b_2, \dots, b_k)$$

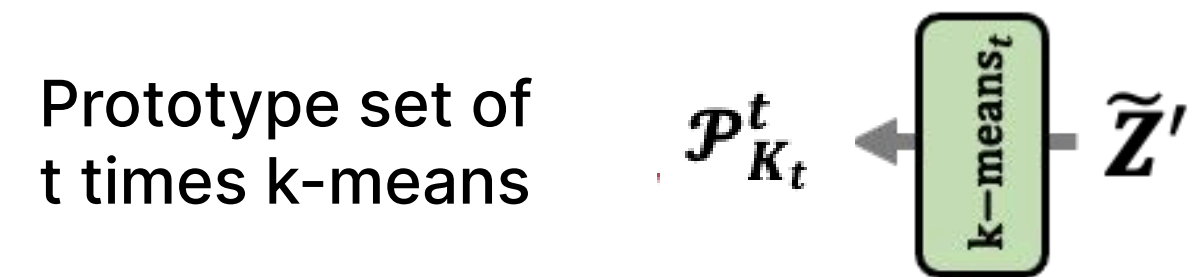


Similarity Scaling $\mathcal{L}_{\text{ss}}$

$$\mathcal{L}_{\text{ss}} = \frac{1}{N_s(N_d - 1)} \sum_{i=1}^{N_s} \sum_{j=1}^{N_d} \mathbb{1}(i \notin \mathcal{G}^{(j)}) \cdot l_{\text{ss}}(H_i, \mathcal{G}^{(j)})$$

Key Ideas of Spotscape

- Capturing global relationships between cells by learning robust similarities with respect to different augmentations
- Explicitly balances the similarity scales of inter- and intra-relationships to mitigate batch effects
- **Grouping spots from the same spatial domain** while **distancing others** in latent space using PCL scheme to mitigate batch effects

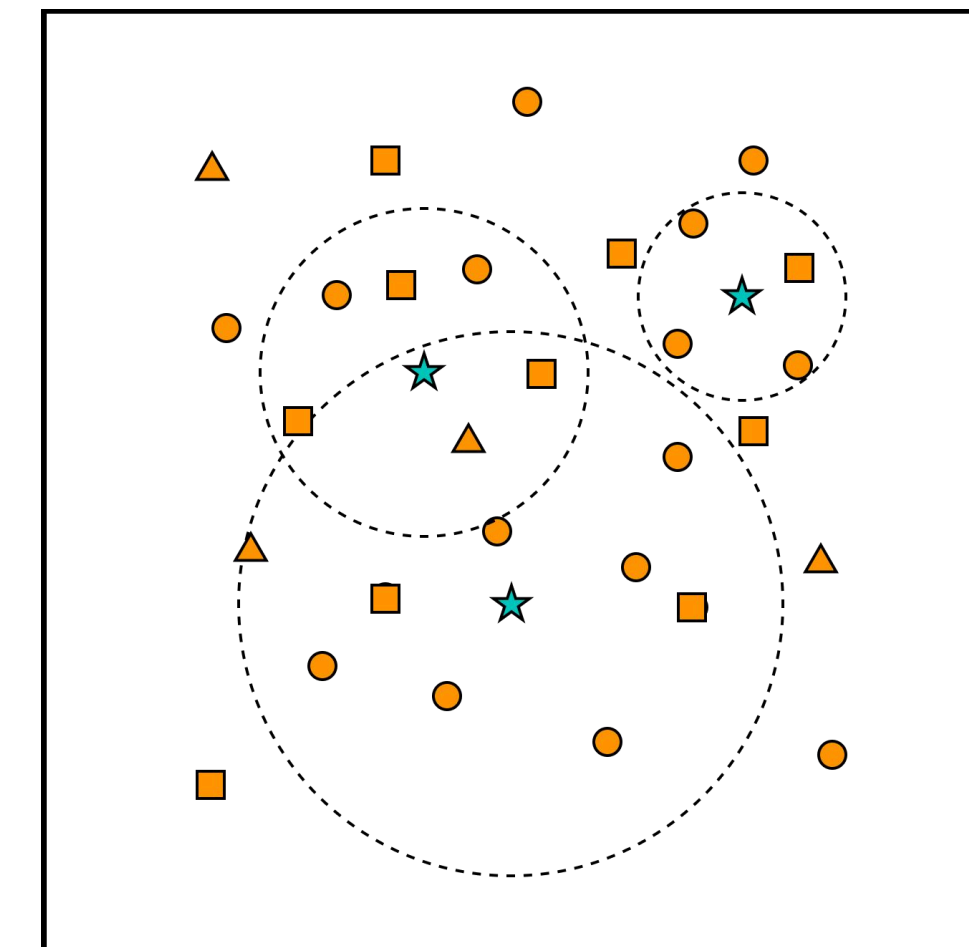
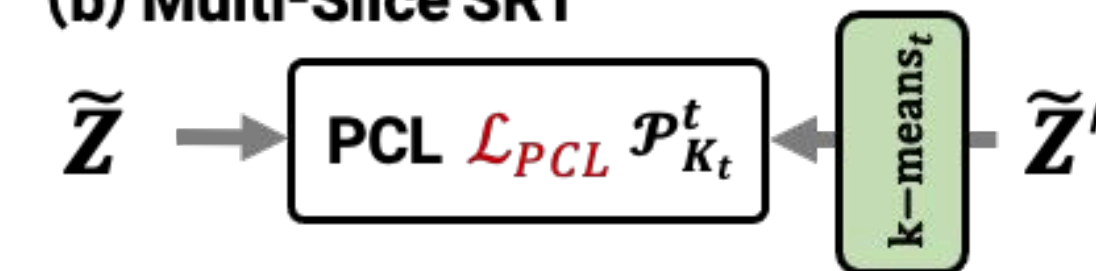


$$l_{\text{PCL}}(\tilde{Z}_i, P_{\text{set}}) = \frac{1}{T} \sum_{t=1}^T \log \frac{e^{(\text{sim}(\tilde{Z}_i, p_{\text{map}_t(i)}^t)/\tau)}}{\sum_{j=1}^{K_t} e^{(\text{sim}(\tilde{Z}_i, p_j^t)/\tau)}},$$

$$\mathcal{L}_{\text{PCL}} = -\frac{1}{N_s} \sum_{i=1}^{N_s} l_{\text{PCL}}(\tilde{Z}_i, P_{\text{set}}).$$

- To avoid the risk of obtaining inaccurate prototypes, the PCL loss gets involved to the training procedure after a **warm-up period**

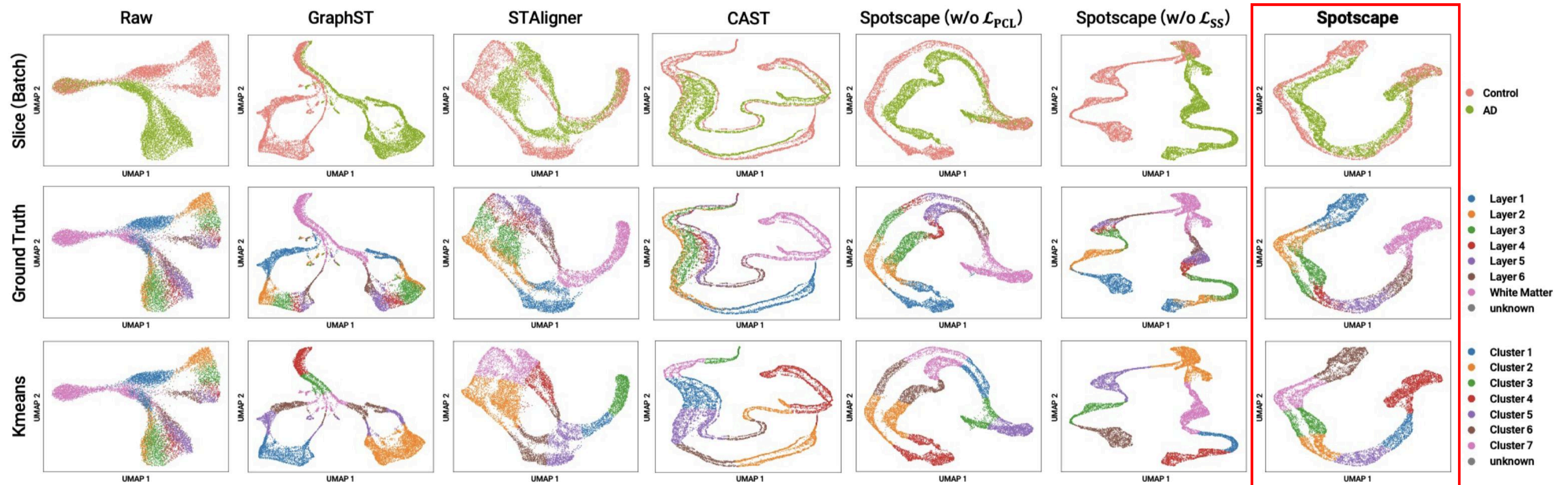
(b) Multi-Slice SRT



- □ △ : Representation of spots from difference slices
- ★ : Integrated prototypes

Key Ideas of Spotscape

- Capturing global relationships between cells by learning robust similarities with respect to different augmentations
- Explicitly balances the similarity scales of inter- and intra-relationships to mitigate batch effects
- Grouping spots from the same spatial domain while distancing others in latent space using PCL scheme to mitigate batch effects



- Spotscape effectively integrates spot representations across slices while preserving biological meaning

Various Downstream Tasks EXPERIMENTS

- Extensive experiments on both single- and multi-slice tasks

Single-Slice Tasks

- Spatial Domain Identification
- Trajectory Inference
- Denoising & Imputation

Multi-Slice Tasks

- Integration
- Alignment
- Differentially expressed gene (DEG) analysis

Various Downstream Tasks

EXPERIMENTS

Spatial Domain Identification

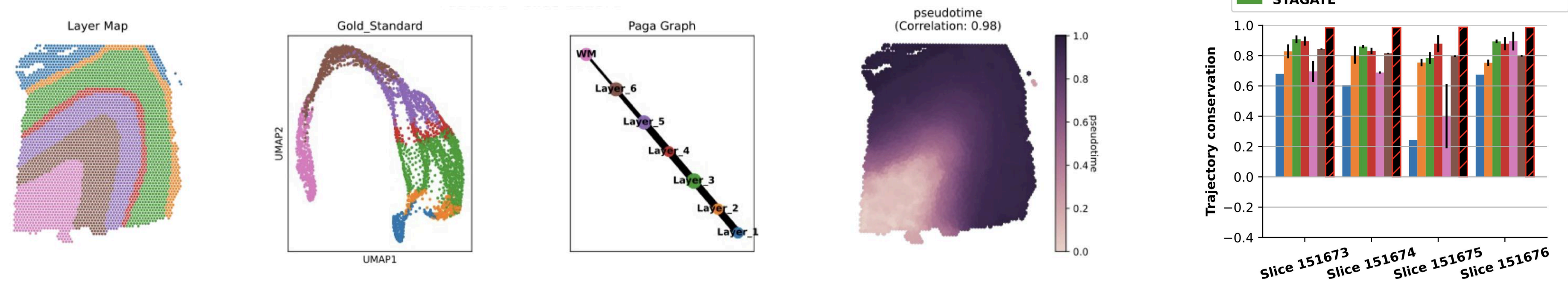
	(a) DLPFC (Patient 1)												
	Slice 151673			Slice 151674			Slice 151675			Slice 151676			
	ARI	NMI	CA	ARI	NMI	CA	ARI	NMI	CA	ARI	NMI	CA	
SEDR	0.36 (0.08)	0.49 (0.08)	0.55 (0.06)	0.37 (0.08)	0.48 (0.07)	0.51 (0.07)	0.33 (0.06)	0.45 (0.05)	0.51 (0.03)	0.29 (0.03)	0.41 (0.04)	0.47 (0.02)	
STAGATE	0.37 (0.04)	0.55 (0.03)	0.52 (0.04)	0.34 (0.03)	0.50 (0.02)	0.51 (0.03)	0.33 (0.03)	0.50 (0.03)	0.48 (0.03)	0.33 (0.00)	0.47 (0.01)	0.52 (0.01)	
SpaCAE	0.21 (0.01)	0.37 (0.01)	0.43 (0.01)	0.25 (0.03)	0.38 (0.01)	0.44 (0.03)	0.23 (0.03)	0.41 (0.03)	0.42 (0.04)	0.23 (0.02)	0.34 (0.02)	0.43 (0.03)	
SpaceFlow	0.42 (0.06)	0.57 (0.05)	0.57 (0.03)	0.37 (0.04)	0.51 (0.03)	0.53 (0.03)	0.38 (0.07)	0.55 (0.06)	0.53 (0.05)	0.38 (0.05)	0.51 (0.05)	0.53 (0.04)	
GraphST	0.20 (0.02)	0.34 (0.03)	0.41 (0.02)	0.27 (0.02)	0.41 (0.01)	0.46 (0.01)	0.22 (0.02)	0.34 (0.01)	0.40 (0.02)	0.26 (0.05)	0.40 (0.05)	0.45 (0.04)	
Spotscape	0.48** (0.02)	0.64** (0.01)	0.61** (0.02)	0.47** (0.04)	0.60** (0.02)	0.60** (0.03)	0.45** (0.02)	0.60* (0.01)	0.59** (0.02)	0.42* (0.05)	0.58** (0.04)	0.57* (0.03)	
	(a) DLPFC (Patient 2)												
	Slice 151507			Slice 151508			Slice 151509			Slice 151510			
	ARI	NMI	CA	ARI	NMI	CA	ARI	NMI	CA	ARI	NMI	CA	
SEDR	0.29 (0.06)	0.39 (0.07)	0.45 (0.06)	0.21 (0.02)	0.31 (0.02)	0.39 (0.02)	0.37 (0.04)	0.47 (0.04)	0.51 (0.05)	0.31 (0.05)	0.44 (0.04)	0.47 (0.04)	
STAGATE	0.41 (0.01)	0.53 (0.01)	0.59 (0.00)	0.32 (0.01)	0.49 (0.00)	0.54 (0.01)	0.41 (0.02)	0.57 (0.02)	0.61 (0.04)	0.32 (0.03)	0.50 (0.02)	0.50 (0.02)	
SpaCAE	0.28 (0.06)	0.41 (0.06)	0.46 (0.06)	0.20 (0.04)	0.31 (0.05)	0.40 (0.04)	0.31 (0.01)	0.44 (0.02)	0.50 (0.04)	0.27 (0.02)	0.42 (0.03)	0.45 (0.02)	
SpaceFlow	0.55 (0.03)	0.68 (0.02)	0.71 (0.05)	0.44 (0.04)	0.57 (0.03)	0.58 (0.04)	0.53 (0.05)	0.66 (0.02)	0.65 (0.04)	0.50 (0.03)	0.64 (0.01)	0.61 (0.02)	
GraphST	0.31 (0.01)	0.45 (0.01)	0.50 (0.01)	0.34 (0.01)	0.45 (0.02)	0.53 (0.02)	0.35 (0.01)	0.51 (0.01)	0.55 (0.02)	0.30 (0.02)	0.47 (0.01)	0.49 (0.03)	
Spotscape	0.60** (0.03)	0.72** (0.01)	0.76** (0.03)	0.48* (0.05)	0.64** (0.03)	0.63** (0.02)	0.59** (0.01)	0.71** (0.01)	0.70** (0.02)	0.53* (0.04)	0.67** (0.02)	0.64 (0.04)	
	(a) DLPFC (Patient 3)												
	Slice 151669			Slice 151670			Slice 151671			Slice 151672			
	ARI	NMI	CA	ARI	NMI	CA	ARI	NMI	CA	ARI	NMI	CA	
SEDR	0.24 (0.07)	0.40 (0.07)	0.48 (0.06)	0.24 (0.06)	0.39 (0.05)	0.48 (0.05)	0.37 (0.10)	0.50 (0.09)	0.59 (0.07)	0.49 (0.09)	0.58 (0.06)	0.66 (0.07)	
STAGATE	0.29 (0.05)	0.45 (0.07)	0.52 (0.04)	0.20 (0.01)	0.38 (0.01)	0.44 (0.01)	0.40 (0.07)	0.49 (0.03)	0.63 (0.06)	0.38 (0.02)	0.51 (0.04)	0.54 (0.01)	
SpaCAE	0.21 (0.02)	0.28 (0.03)	0.43 (0.02)	0.21 (0.03)	0.28 (0.02)	0.43 (0.04)	0.38 (0.16)	0.29 (0.01)	0.49 (0.05)	0.25 (0.04)	0.35 (0.05)	0.50 (0.01)	
SpaceFlow	0.30 (0.07)	0.48 (0.03)	0.51 (0.05)	0.34 (0.05)	0.50 (0.03)	0.56 (0.05)	0.54 (0.04)	0.67 (0.02)	0.67 (0.04)	0.60 (0.06)	0.70 (0.02)	0.73 (0.06)	
GraphST	0.17 (0.04)	0.26 (0.04)	0.43 (0.02)	0.14 (0.01)	0.23 (0.00)	0.37 (0.01)	0.30 (0.05)	0.38 (0.03)	0.54 (0.03)	0.23 (0.01)	0.32 (0.02)	0.49 (0.01)	
Spotscape	0.46** (0.02)	0.58** (0.01)	0.65** (0.02)	0.45** (0.04)	0.56** (0.03)	0.66** (0.03)	0.68** (0.10)	0.74** (0.04)	0.79** (0.08)	0.75** (0.04)	0.74** (0.02)	0.84** (0.05)	
	(b) MTG - Control Group			(b) MTG - AD Group			(c) Mouse Embryo			(d) NSCLC			
	ARI	NMI	CA	ARI	NMI	CA	ARI	NMI	CA	ARI	NMI	CA	
SEDR	0.41 (0.02)	0.59 (0.02)	0.52 (0.02)	0.43 (0.08)	0.59 (0.07)	0.57 (0.07)	SEDR	0.32 (0.02)	0.56 (0.01)	0.42 (0.02)	SEDR	0.44 (0.08)	0.46 (0.06)
STAGATE	0.54 (0.00)	0.65 (0.00)	0.59 (0.00)	0.51 (0.01)	0.61 (0.01)	0.59 (0.01)	STAGATE	0.36 (0.01)	0.60 (0.01)	0.47 (0.01)	STAGATE	0.35 (0.05)	0.41 (0.04)
SpaCAE	0.37 (0.03)	0.52 (0.00)	0.44 (0.03)	0.22 (0.01)	0.40 (0.01)	0.40 (0.01)	SpaCAE	0.34 (0.01)	0.60 (0.01)	0.48 (0.02)	SpaCAE	0.32 (0.05)	0.38 (0.03)
SpaceFlow	0.66 (0.03)	0.74 (0.01)	0.70 (0.03)	0.54 (0.01)	0.71 (0.00)	0.65 (0.01)	SpaceFlow	0.42 (0.03)	0.60 (0.02)	0.49 (0.03)	SpaceFlow	0.53 (0.03)	0.52 (0.02)
GraphST	0.38 (0.00)	0.51 (0.00)	0.48 (0.00)	0.43 (0.06)	0.55 (0.05)	0.55 (0.04)	GraphST	0.34 (0.01)	0.59 (0.02)	0.45 (0.01)	GraphST	0.30 (0.00)	0.38 (0.00)
Spotscape	0.73** (0.02)	0.78** (0.01)	0.75** (0.03)	0.68** (0.02)	0.75** (0.01)	0.77** (0.03)	Spotscape	0.44 (0.01)	0.63** (0.01)	0.54** (0.01)	Spotscape	0.57** (0.02)	0.57** (0.01)
												0.74 (0.01)	

All experiments are repeated over 10 runs with different random seeds, and we report the mean and standard deviation of the results. For all experimental results, **Bold** indicates the best performance, underlining denotes the second-best, and an asterisk (*) marks statistically significant improvements of Spotscape over the top-performing baseline based on a paired *t*-test (**: *p* < 0.01, *: *p* < 0.05), with the numbers in parentheses representing the standard deviation.

- **Spotscape consistently outperforms all baselines across 4 datasets and 16 slices**
- **Moves beyond the limited insights** of local neighbor analysis by **capturing global contextual information**

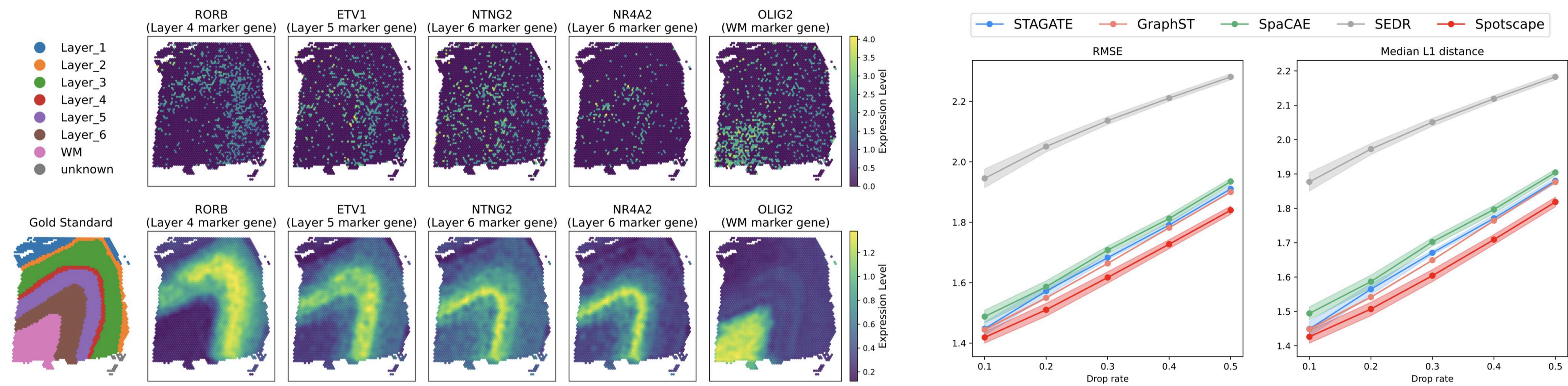
Various Downstream Tasks EXPERIMENTS

Trajectory Inference



- **Spotscape** accurately captured the known developmental sequence, demonstrating its ability to **model biologically meaningful patterns**

Denoising & Imputation



- **Spotscape** clarifies **marker gene expression** for easier identification in noisy raw data in **denoising task**
- **Spotscape** achieves **best performance in imputation**, leading baselines on RMSE and L1-distance metrics

Various Downstream Tasks EXPERIMENTS

Integration

Table 2. Homogeneous integration performance on DLPFC data.

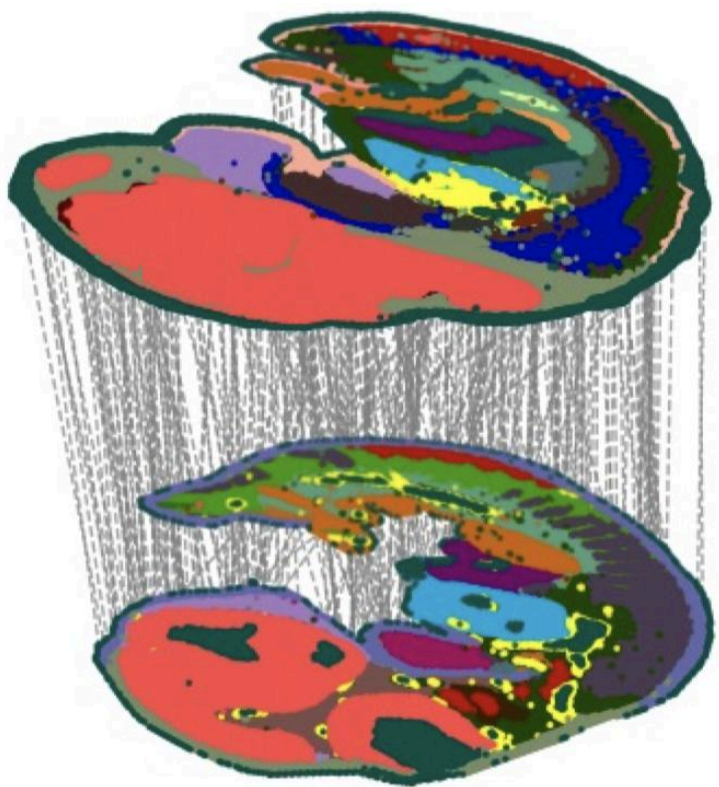
	Patient 1			Patient 2			Patient 3		
	ARI	NMI	CA	ARI	NMI	CA	ARI	NMI	CA
SEDR	0.38 (0.06)	0.49 (0.06)	0.56 (0.06)	0.32 (0.05)	0.44 (0.07)	0.48 (0.07)	0.43 (0.02)	0.51 (0.01)	0.56 (0.03)
STAGATE	0.31 (0.03)	0.46 (0.03)	0.49 (0.03)	0.30 (0.02)	0.46 (0.01)	0.48 (0.02)	0.31 (0.09)	0.43 (0.06)	0.54 (0.08)
SpaCAE	0.21 (0.03)	0.36 (0.02)	0.40 (0.02)	0.12 (0.06)	0.19 (0.07)	0.32 (0.05)	0.13 (0.05)	0.14 (0.05)	0.43 (0.06)
SpaceFlow	0.48 (0.03)	0.60 (0.02)	0.60 (0.02)	0.44 (0.05)	0.59 (0.02)	0.58 (0.04)	0.51 (0.02)	0.60 (0.01)	0.69 (0.05)
GraphST	0.18 (0.01)	0.32 (0.01)	0.38 (0.02)	0.25 (0.01)	0.39 (0.01)	0.42 (0.02)	0.25 (0.04)	0.30 (0.04)	0.50 (0.01)
PASTE	0.34 (0.00)	0.45 (0.00)	0.54 (0.00)	0.17 (0.00)	0.28 (0.00)	0.40 (0.00)	0.29 (0.00)	0.43 (0.00)	0.54 (0.00)
STAligner	0.38 (0.04)	0.52 (0.04)	0.55 (0.04)	0.29 (0.02)	0.45 (0.02)	0.48 (0.03)	0.37 (0.06)	0.47 (0.05)	0.59 (0.06)
CAST	0.26 (0.02)	0.37 (0.03)	0.42 (0.03)	0.30 (0.04)	0.43 (0.05)	0.47 (0.03)	0.38 (0.06)	0.40 (0.04)	0.56 (0.05)
Spotscape	0.57** (0.03)	0.70** (0.02)	0.67** (0.03)	0.53** (0.02)	0.67** (0.01)	0.63** (0.02)	0.63** (0.09)	0.68** (0.03)	0.75** (0.09)

Table 3. Heterogeneous integration performance on MTG data.

	Clustering Metric			Batch Effect Correction Metric			
	ARI	NMI	CA	Silhouette batch	kBET	Graph connectivity	PCR comparison
GraphST	0.23 (0.02)	0.42 (0.00)	0.39 (0.01)	0.56 (0.00)	0.02 (0.01)	0.65 (0.02)	0.00 (0.00)
STAligner	0.38 (0.03)	0.54 (0.03)	0.49 (0.02)	0.62 (0.04)	0.11 (0.08)	0.85 (0.04)	0.18 (0.10)
CAST	0.48 (0.07)	0.52 (0.06)	0.59 (0.06)	0.45 (0.02)	0.11 (0.02)	0.81 (0.06)	0.97 (0.03)
Spotscape (w/o $\mathcal{L}_{PCL}$)	0.61 (0.03)	0.71 (0.01)	0.70 (0.02)	0.67 (0.01)	0.03 (0.00)	0.79 (0.03)	0.50 (0.04)
Spotscape (w/o $\mathcal{L}_{SS}$)	0.47 (0.09)	0.60 (0.04)	0.59 (0.06)	0.24 (0.01)	0.00 (0.00)	0.63 (0.00)	0.00 (0.00)
Spotscape	0.72** (0.04)	0.76** (0.01)	0.81** (0.05)	0.69** (0.01)	0.08 (0.02)	0.86 (0.03)	0.60 (0.08)

All experiments are repeated over 10 runs with different random seeds, and we report the mean and standard deviation of the results. For all experimental results, **Bold** indicates the best performance, underlining denotes the second-best, and an asterisk (*) marks statistically significant improvements of Spotscape over the top-performing baseline based on a paired t -test (**: $p < 0.01$, *: $p < 0.05$), with the numbers in parentheses representing the standard deviation.

Alignment



	LTARI
PASTE2	0.21 (0.02)
CAST	0.10 (0.00)
STAligner	0.46 (0.01)
SLAT	0.41 (0.11)
Spotscape	0.51** (0.01)

- **Homogeneous Integration:** Consistently outperforms all baseline methods when integrating multiple tissue slices from the same patient sample
- **Heterogeneous Integration:** Integrates diverse samples (e.g., Control vs. AD) by correcting batch effects, significantly outperforming competitors
- **Multi-slice Alignment:** Outperforms even specialized tools, successfully aligning slices across different developmental stages and technologies

Various Downstream Tasks EXPERIMENTS

DEG Analysis

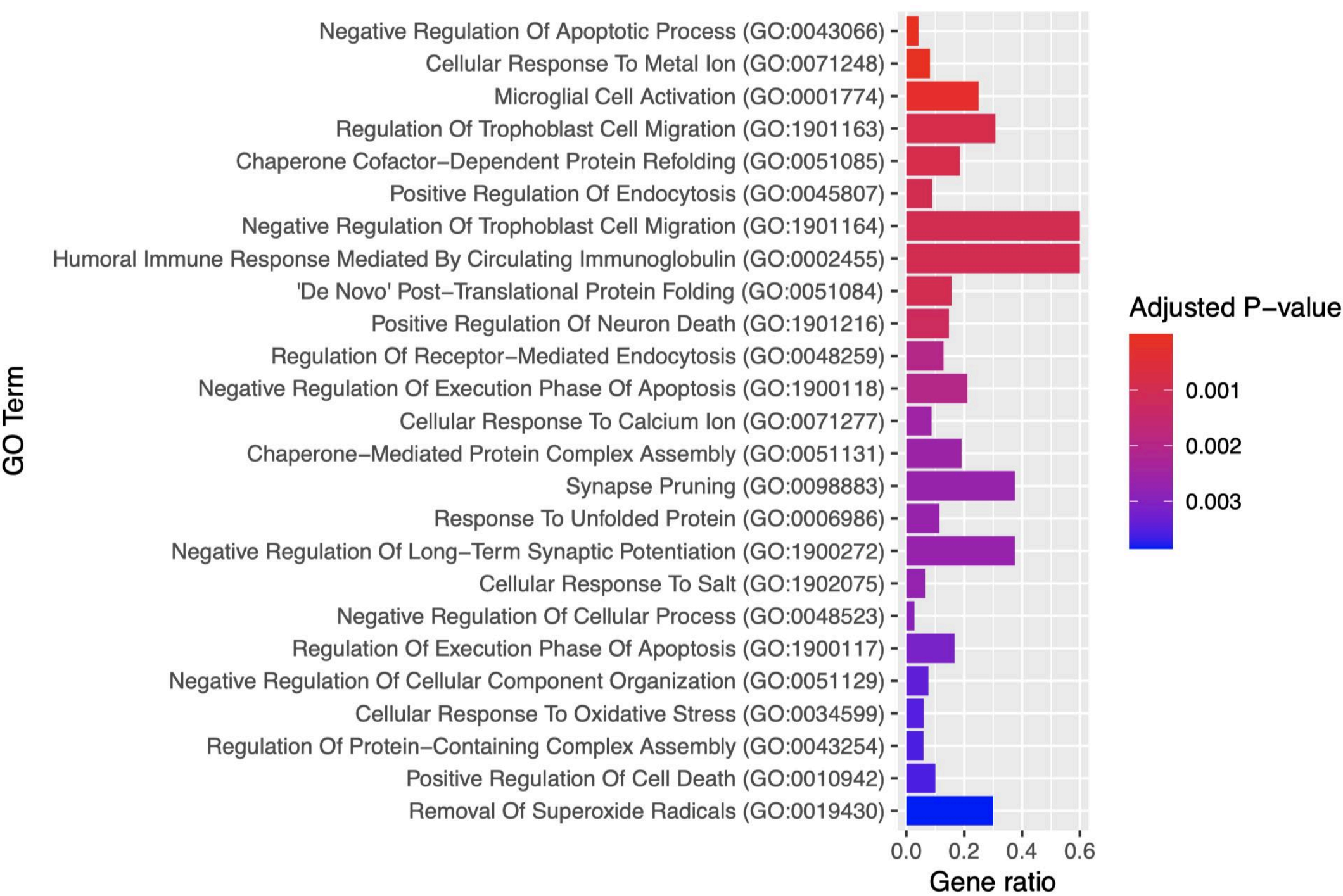


Figure 29. Top 25 biological process that DEGs between AD and Control enriched in a cluster assigned to layer 2.

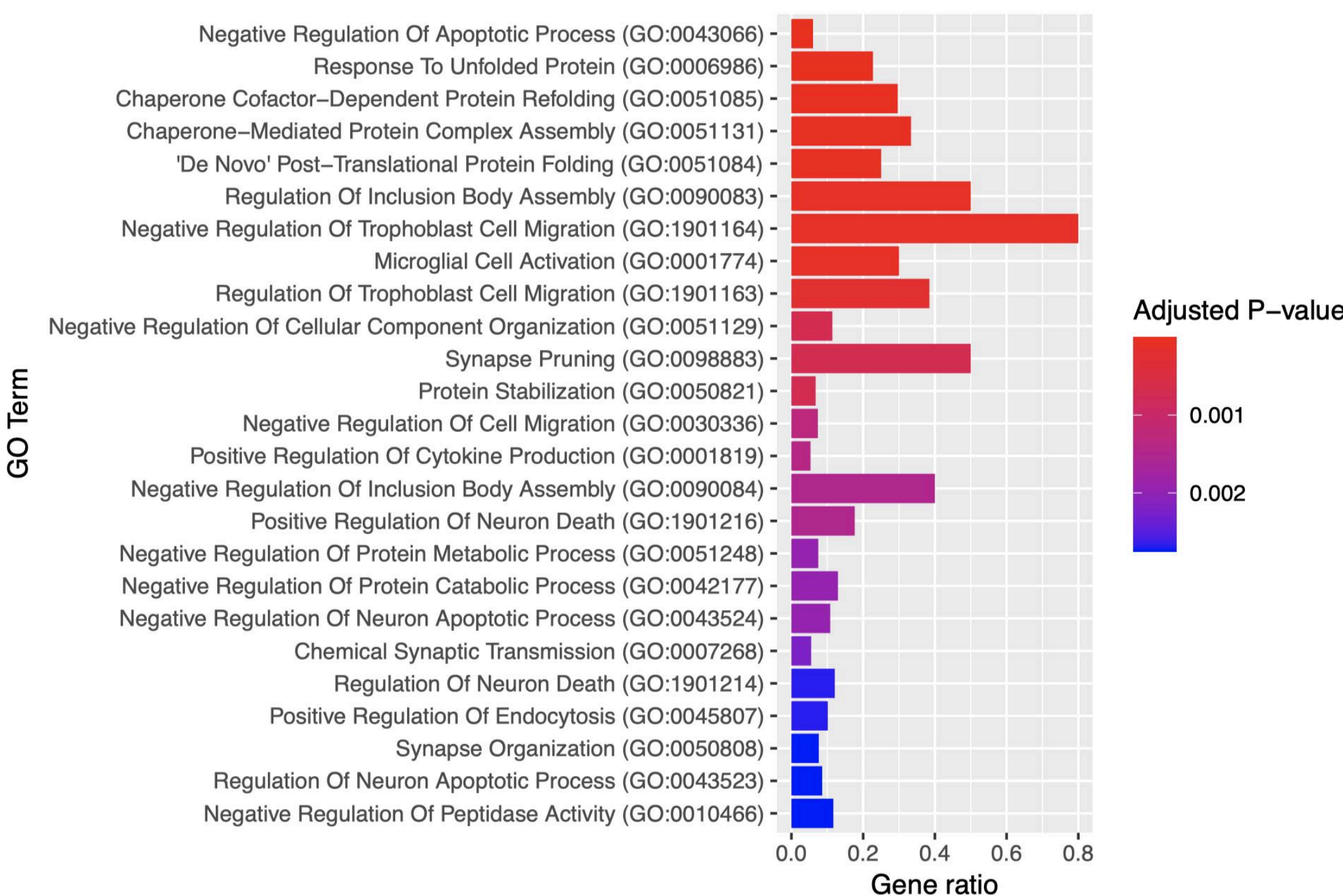
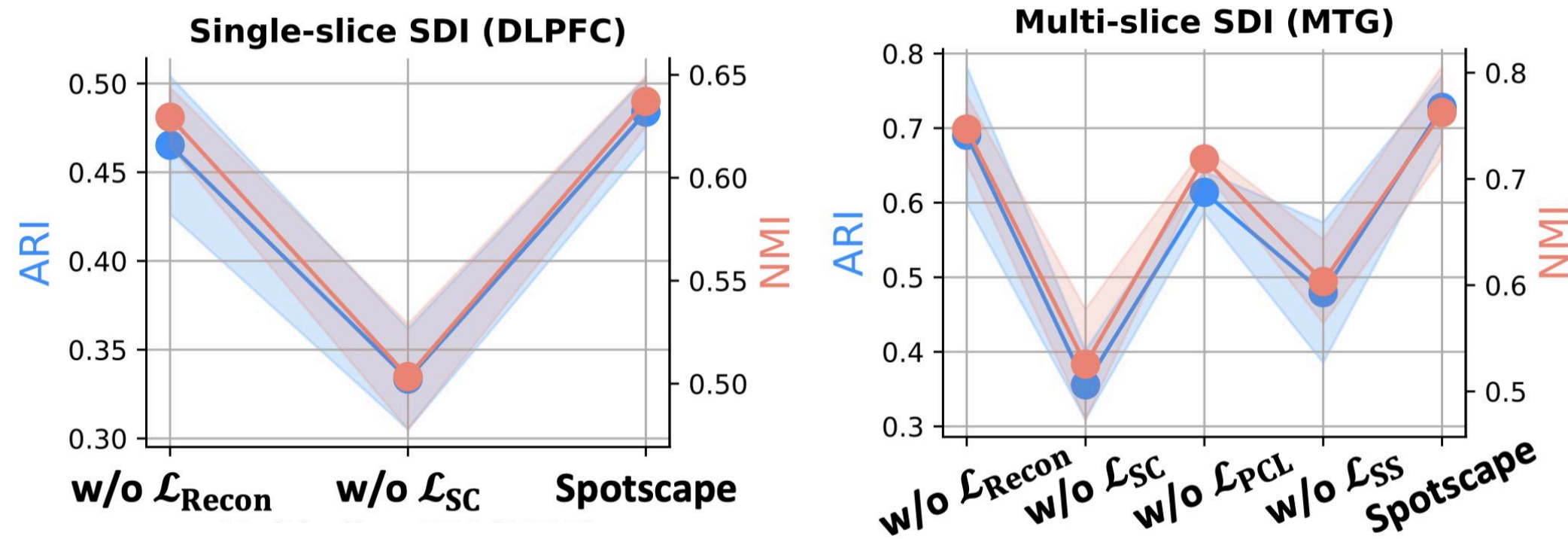


Figure 30. Top 25 biological process that DEGs between AD and Control enriched in a cluster assigned to layer 5.

- **Biological Validation:** Gene analysis of Control vs. Alzheimer's samples validates **Spotscape's** findings, as it correctly identified distinct early-stage (Layer 2) and late-stage (Layer 5) disease pathologies that align with known AD progression

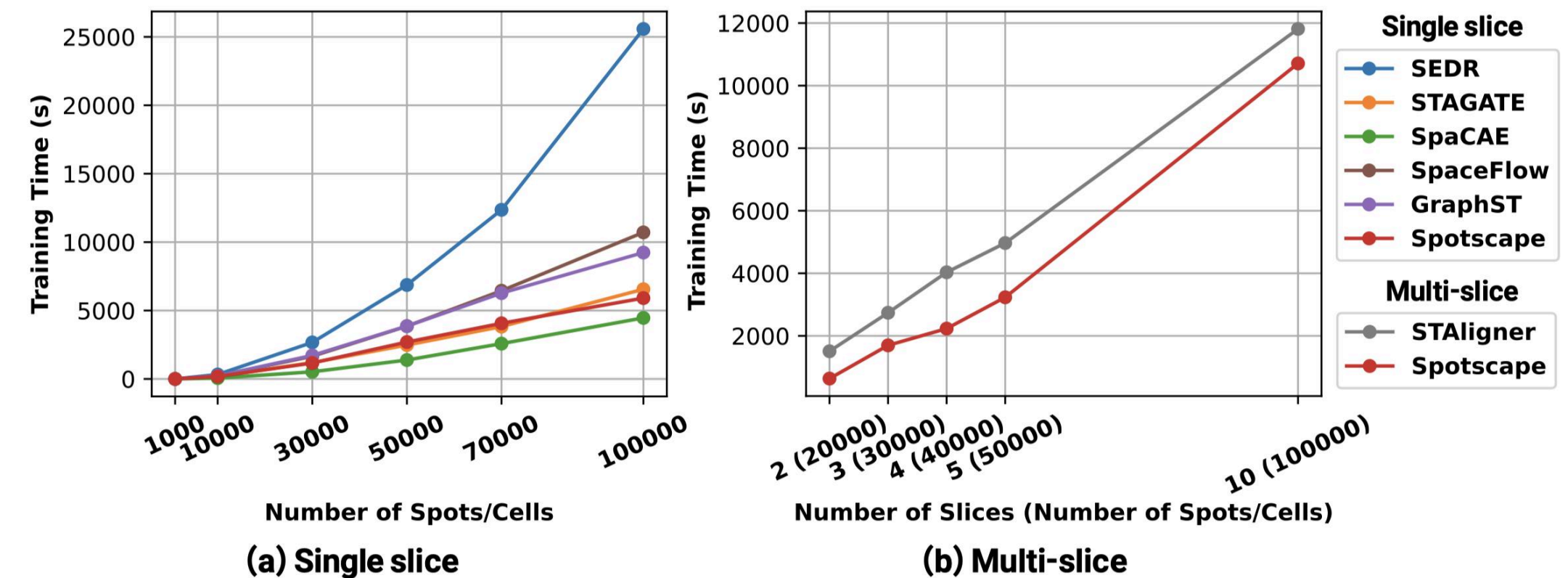
Various Downstream Tasks EXPERIMENTS

Ablation study



- **Ablation Study:** Removing key modules confirms their necessity; the Similarity Telescope (global context) , Prototypical Contrastive Learning (grouping) , and Similarity Scaling (batch effect) are all critical for performance, while reconstruction loss primarily prevents degenerate solutions
- **Scalability:** Spotscape is fast and practical for high-throughput analysis , showing efficient training times on datasets up to 100,000 spots

Running-time analysis



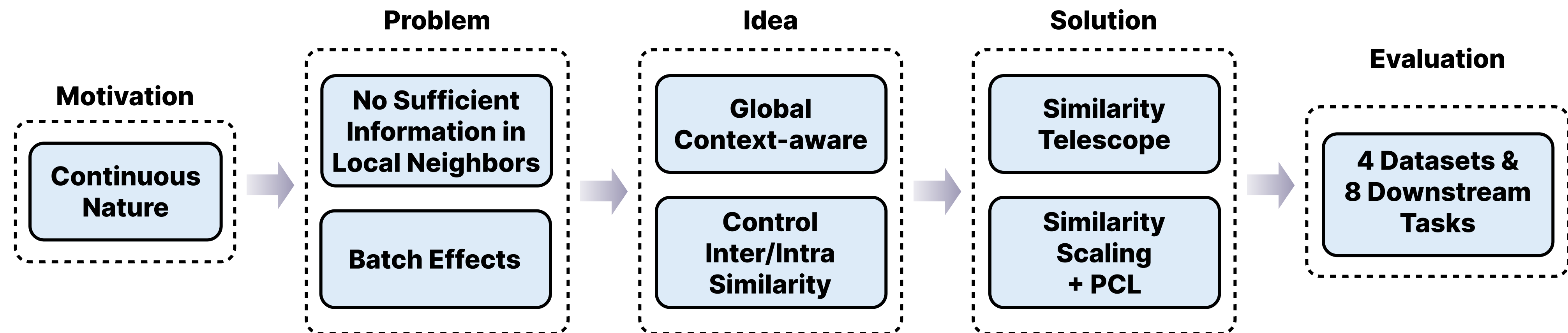
Conclusion

Limitations of previous works

- Harnessing relationships between only spatially close (local) points provides insufficient information to learn accurate representation
- Focusing on either spatial domain identification for a single slice or integration across multiple slices

Contributions of Spotscape

- Reflecting global relationship information by learning robust similarities w.r.t. augmentations
- Alleviate batch effects by explicitly balancing the intra- and inter- similarity



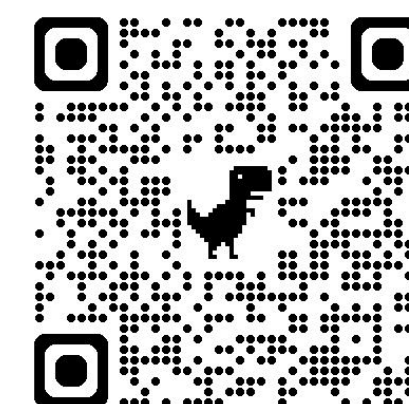
Global Context-aware Representation Learning for Spatially Resolved Transcriptomics

Paper: <https://arxiv.org/abs/2506.15698>

Code: <https://github.com/yunhak0/Spotscape>

Email: yunhak.oh@kaist.ac.kr

Paper



Code

