

2023 ICML Workshop on Computational Biology (Contributed Talk)

# Single-cell RNA-seq data imputation using Feature Propagation

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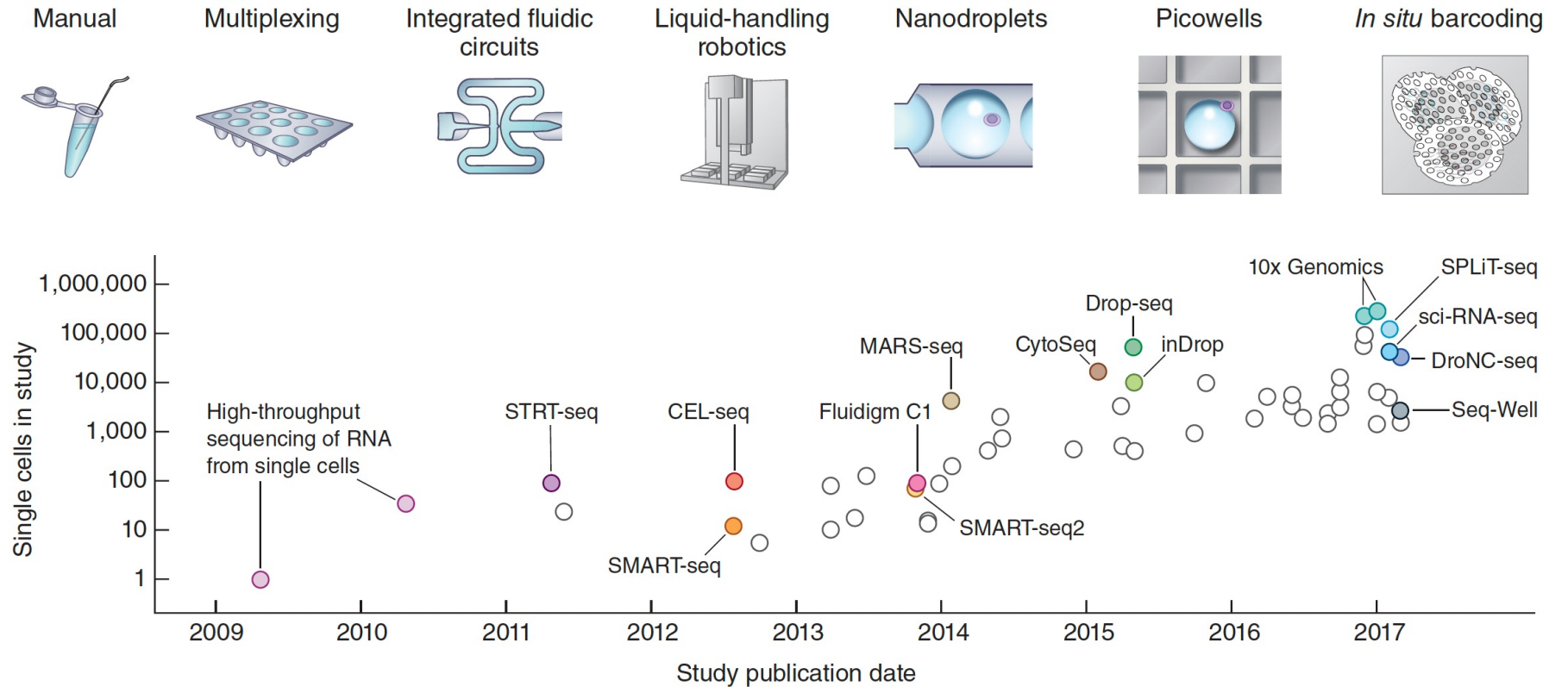
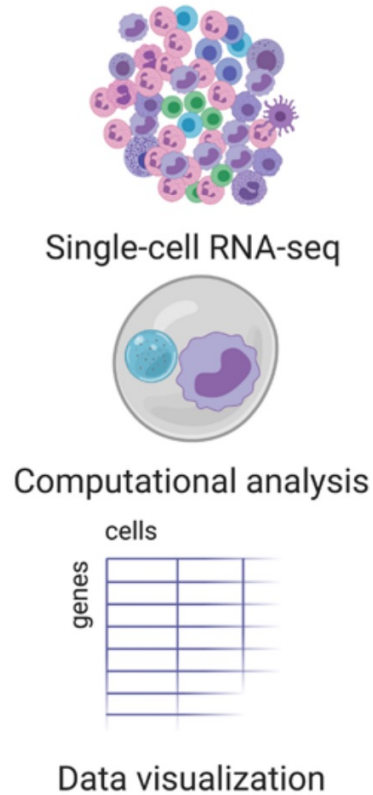
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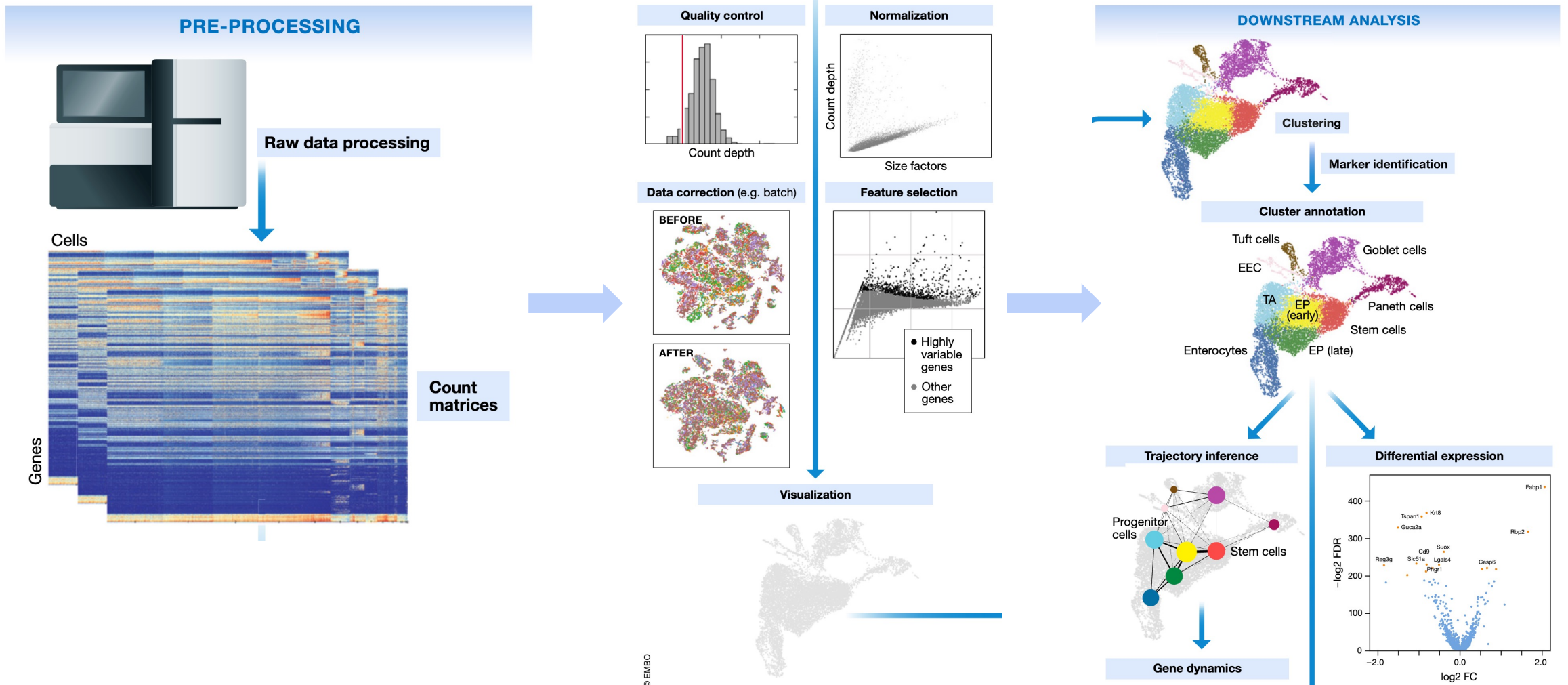
# BACKGROUND: SINGLE-CELL RNA-SEQ

## Advances in single-cell RNA-seq



# BACKGROUND: SINGLE-CELL RNA-SEQ

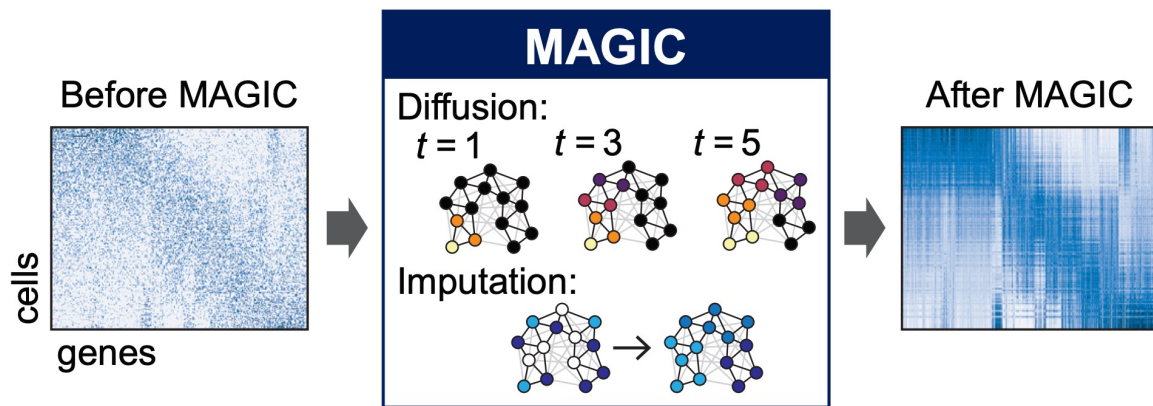
## Workflow of single-cell RNA-seq (scRNA-seq) analysis



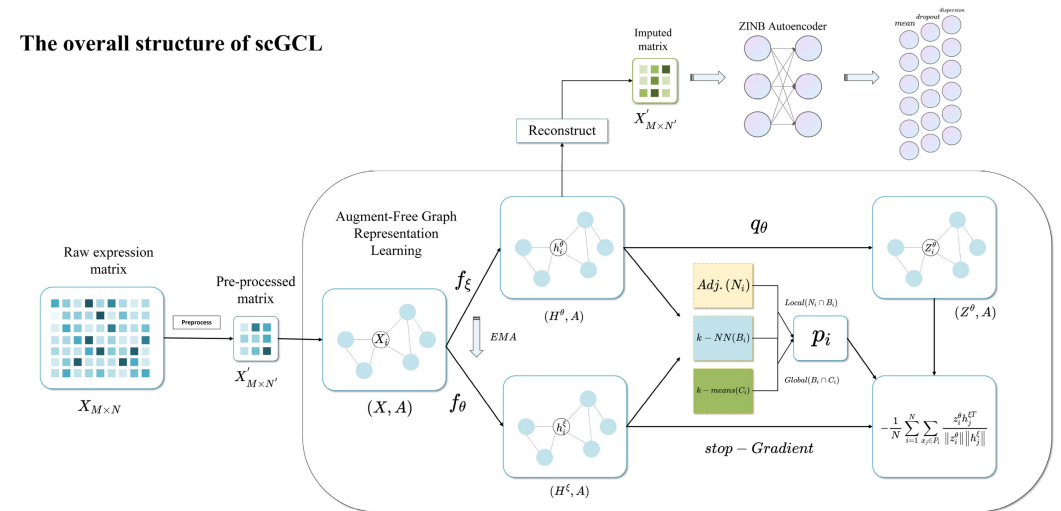
# BACKGROUND: AS A GRAPH

## Cell-Gene Matrix as a Graph Structure

- Graphs facilitate clustering algorithms such as the min-cut algorithm (spectral clustering)
- Graphs enable a better understanding of paths of progression or trajectories of differentiation
- Graphs capture relationships among cells and facilitate message-passing schemes for information propagation



**MAGIC** (van Dijk et al., 2018)

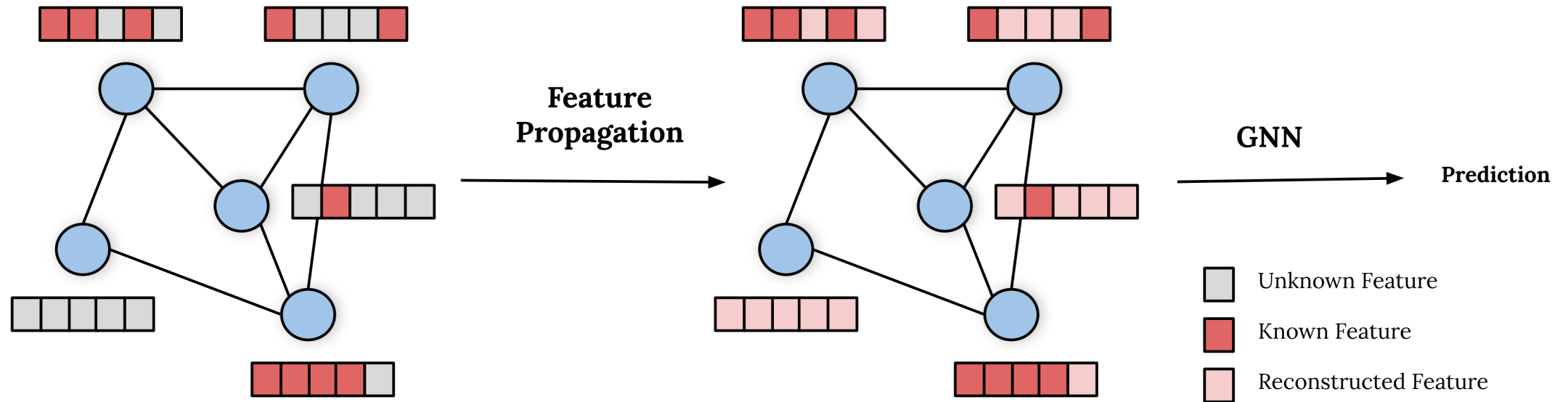


**scGCL** (Xiong et al., 2023)

# BACKGROUND: AS A GRAPH

## ▪ Feature Propagation (Rossi et al., 2022)

- **Motivation:** In many real-world applications, features are partially available
- **Idea:** General approach for handling missing features in graph machine learning based on minimizing Dirichlet energy



# BACKGROUND: AS A GRAPH

## ▪ Feature Propagation (Rossi et al., 2022)

- **Motivation:** In many real-world applications, features are partially available
- **Idea:** General approach for handling missing features in graph machine learning based on minimizing Dirichlet energy

### Analytic Approach

#### *Dirichlet Energy*

$$\ell(\mathbf{x}, G) = \frac{1}{2} \mathbf{x}^\top \Delta \mathbf{x} = \frac{1}{2} \sum_{ij} \tilde{a}_{ij} (x_i - x_j)^2$$

#### *Gradient flow*

$$\dot{\mathbf{x}}(t) = -\nabla \ell(\mathbf{x}(t)) = -\Delta \mathbf{x}(t)$$

#### *Heat Diffusion Equation*

$$\dot{\mathbf{x}}(t) = -\Delta \mathbf{x}(t) \quad (\text{IC}) \quad \mathbf{x}(0) = \begin{bmatrix} \mathbf{x}_k \\ \mathbf{x}_u(0) \end{bmatrix} \quad (\text{BC}) \quad \mathbf{x}_k(t) = \mathbf{x}_k$$

$$\begin{bmatrix} \dot{\mathbf{x}}_k(t) \\ \dot{\mathbf{x}}_u(t) \end{bmatrix} = - \begin{bmatrix} \mathbf{0} & \mathbf{0} \\ \Delta_{uk} & \Delta_{uu} \end{bmatrix} \begin{bmatrix} \mathbf{x}_k \\ \mathbf{x}_u(t) \end{bmatrix} = - \begin{bmatrix} \mathbf{0} \\ \Delta_{uk} \mathbf{x}_k + \Delta_{uu} \mathbf{x}_u(t) \end{bmatrix}$$

$$\nabla_{\mathbf{x}_u} \ell = \mathbf{0} \longrightarrow \boxed{\mathbf{x}_u = -\Delta_{uu}^{-1} \Delta_{ku}^\top \mathbf{x}_k} \quad \mathcal{O}(|\mathcal{V}_u|^3)$$

# BACKGROUND: AS A GRAPH

## ▪ Feature Propagation (Rossi et al., 2022)

- **Motivation:** In many real-world applications, features are partially available
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### Analytic Approach

Dirichlet Energy

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Gradient flow

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Heat Diffusion Equation

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$$\nabla_{\mathbf{x}_u} \ell = \mathbf{0} \longrightarrow \mathbf{x}_u = -\Delta_{uu}^{-1} \Delta_{ku}^\top \mathbf{x}_k$$

### Iterative Approach

Euler Scheme

$$\begin{aligned} \mathbf{x}^{(k+1)} &= \mathbf{x}^{(k)} - h \begin{bmatrix} \mathbf{0} & \mathbf{0} \\ \Delta_{uk} & \Delta_{uu} \end{bmatrix} \mathbf{x}^{(k)} \\ &= \left( \mathbf{I} - \begin{bmatrix} \mathbf{0} & \mathbf{0} \\ h\Delta_{uk} & h\Delta_{uu} \end{bmatrix} \right) \mathbf{x}^{(k)} = \begin{bmatrix} \mathbf{I} & \mathbf{0} \\ -h\Delta_{uk} & \mathbf{I} - h\Delta_{uu} \end{bmatrix} \mathbf{x}^{(k)} \end{aligned}$$

when  $h = 1$ ,

$$\tilde{\mathbf{A}} = \mathbf{I} - \Delta = \begin{bmatrix} \mathbf{I} & \mathbf{0} \\ \mathbf{0} & \mathbf{I} \end{bmatrix} - \begin{bmatrix} \Delta_{kk} & \Delta_{ku} \\ \Delta_{uk} & \Delta_{uu} \end{bmatrix} = \begin{bmatrix} \mathbf{I} - \Delta_{kk} & -\Delta_{ku} \\ -\Delta_{uk} & \mathbf{I} - \Delta_{uu} \end{bmatrix}$$

$$\mathbf{x}^{(k+1)} = \begin{bmatrix} \mathbf{I} & \mathbf{0} \\ \tilde{\mathbf{A}}_{uk} & \tilde{\mathbf{A}}_{uu} \end{bmatrix} \mathbf{x}^{(k)}$$

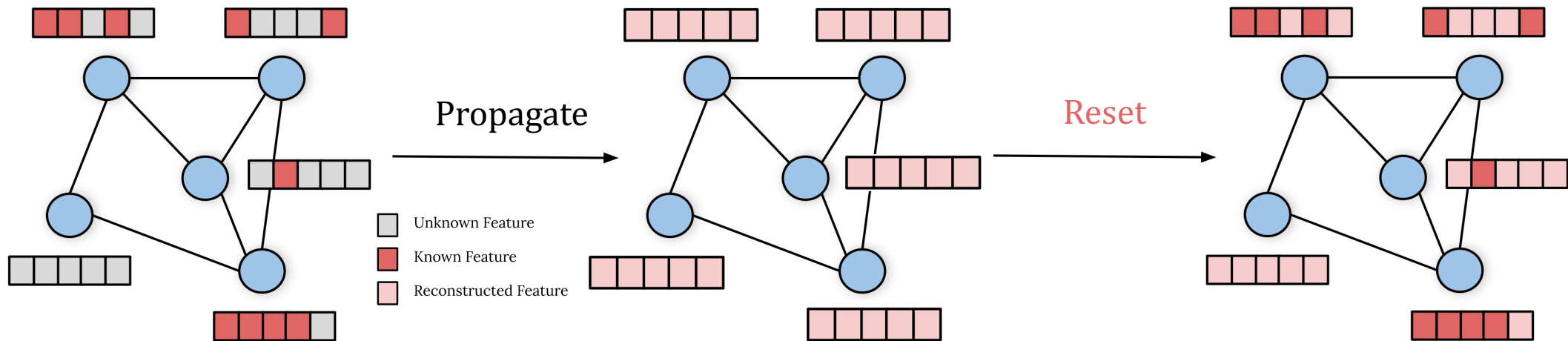


# BACKGROUND: AS A GRAPH

## Feature Propagation (Rossi et al., 2022)

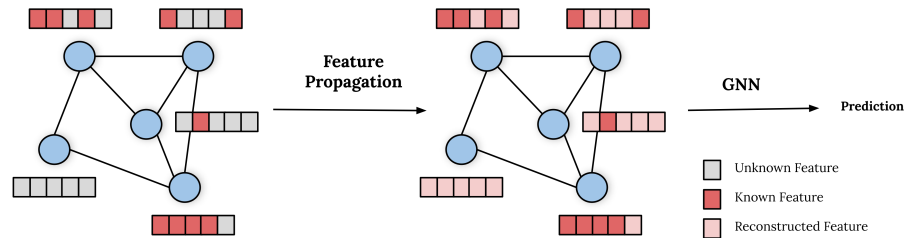
- **Motivation:** In many real-world applications, features are partially available
- **Idea:** General approach for handling missing features in graph machine learning based on minimizing Dirichlet energy

$$\mathbf{x}^{(k+1)} = \begin{bmatrix} \mathbf{I} & \mathbf{0} \\ \tilde{\mathbf{A}}_{uk} & \tilde{\mathbf{A}}_{uu} \end{bmatrix} \mathbf{x}^{(k)} \quad \left| \quad \begin{array}{l} 1) \text{ Propagate: } \mathbf{x}^{(k+1)} = \tilde{\mathbf{A}}\mathbf{x}^{(k)} = \begin{bmatrix} \tilde{\mathbf{A}}_{kk} & \tilde{\mathbf{A}}_{ku} \\ \tilde{\mathbf{A}}_{uk} & \tilde{\mathbf{A}}_{uu} \end{bmatrix} \cdot \begin{bmatrix} \mathbf{x}_k^{(k)} \\ \mathbf{x}_u^{(k)} \end{bmatrix} = \begin{bmatrix} \tilde{\mathbf{A}}_{kk}\mathbf{x}_k^{(k)} + \tilde{\mathbf{A}}_{ku}\mathbf{x}_u^{(k)} \\ \tilde{\mathbf{A}}_{uk}\mathbf{x}_k^{(k)} + \tilde{\mathbf{A}}_{uu}\mathbf{x}_u^{(k)} \end{bmatrix} \\ 2) \text{ Reset: } \mathbf{x}_k^{(k+1)} = \mathbf{x}_k^{(0)} \rightarrow \mathbf{x}^{(k+1)} = \begin{bmatrix} \mathbf{x}_k^{(0)} \\ \tilde{\mathbf{A}}_{uk}\mathbf{x}_k^{(k)} + \tilde{\mathbf{A}}_{uu}\mathbf{x}_u^{(k)} \end{bmatrix} \end{array}$$



# MOTIVATION: scRNA-SEQ DATA IMPUTATION USING FEATURE PROPAGATION

- Research Direction: **Feature Propagation on scRNA-seq data**



*Euler Scheme*

$$\begin{aligned} \mathbf{x}^{(k+1)} &= \mathbf{x}^{(k)} - h \begin{bmatrix} \mathbf{0} & \mathbf{0} \\ \Delta_{uk} & \Delta_{uu} \end{bmatrix} \mathbf{x}^{(k)} \\ &= \left( \mathbf{I} - \begin{bmatrix} \mathbf{0} & \mathbf{0} \\ h\Delta_{uk} & h\Delta_{uu} \end{bmatrix} \right) \mathbf{x}^{(k)} = \begin{bmatrix} \mathbf{I} & \mathbf{0} \\ -h\Delta_{uk} & \mathbf{I} - h\Delta_{uu} \end{bmatrix} \mathbf{x}^{(k)} \end{aligned}$$

when  $h = 1$ ,

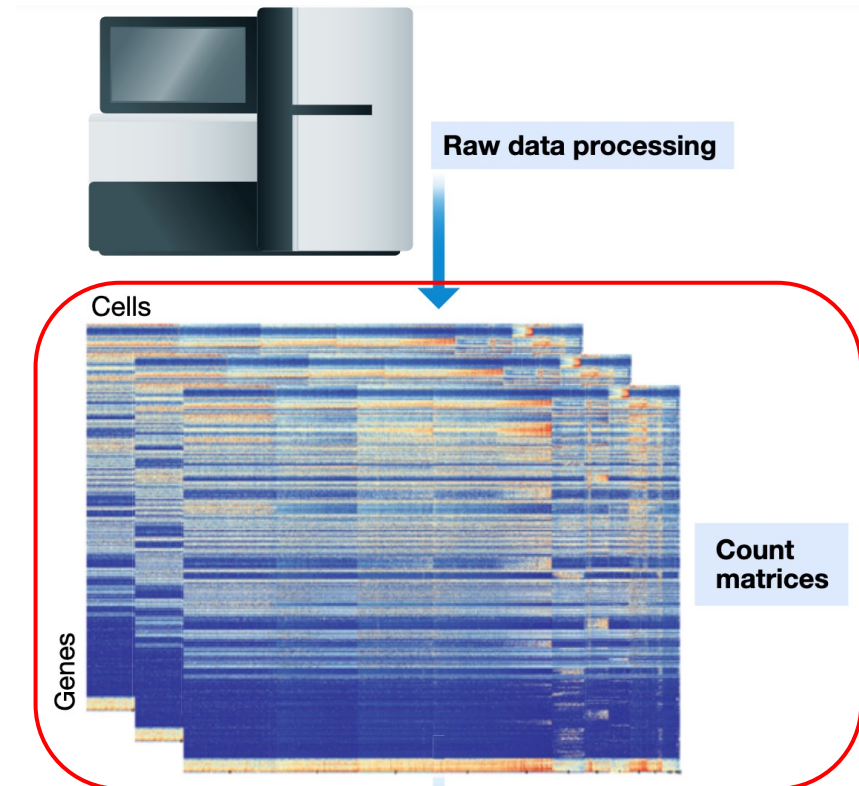
$$\tilde{\mathbf{A}} = \mathbf{I} - \Delta = \begin{bmatrix} \mathbf{I} & \mathbf{0} \\ \mathbf{0} & \mathbf{I} \end{bmatrix} - \begin{bmatrix} \Delta_{kk} & \Delta_{ku} \\ \Delta_{uk} & \Delta_{uu} \end{bmatrix} = \begin{bmatrix} \mathbf{I} - \Delta_{kk} & -\Delta_{ku} \\ -\Delta_{uk} & \mathbf{I} - \Delta_{uu} \end{bmatrix}$$

$$\mathbf{x}^{(k+1)} = \begin{bmatrix} \mathbf{I} & \mathbf{0} \\ \tilde{\mathbf{A}}_{uk} & \tilde{\mathbf{A}}_{uu} \end{bmatrix} \mathbf{x}^{(k)}$$

**Iterative Approach**

## \* Challenges

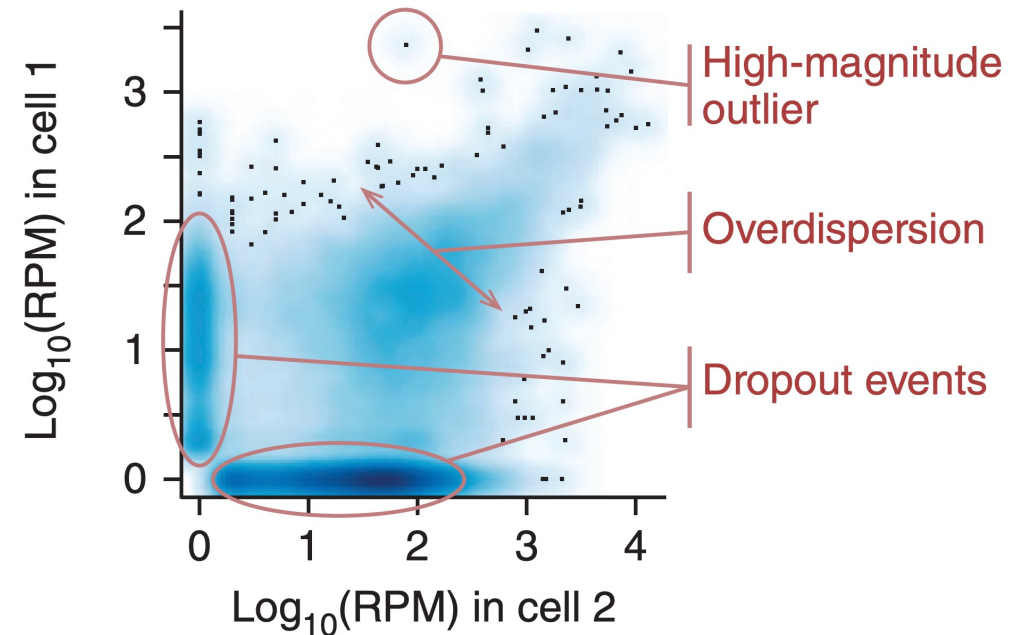
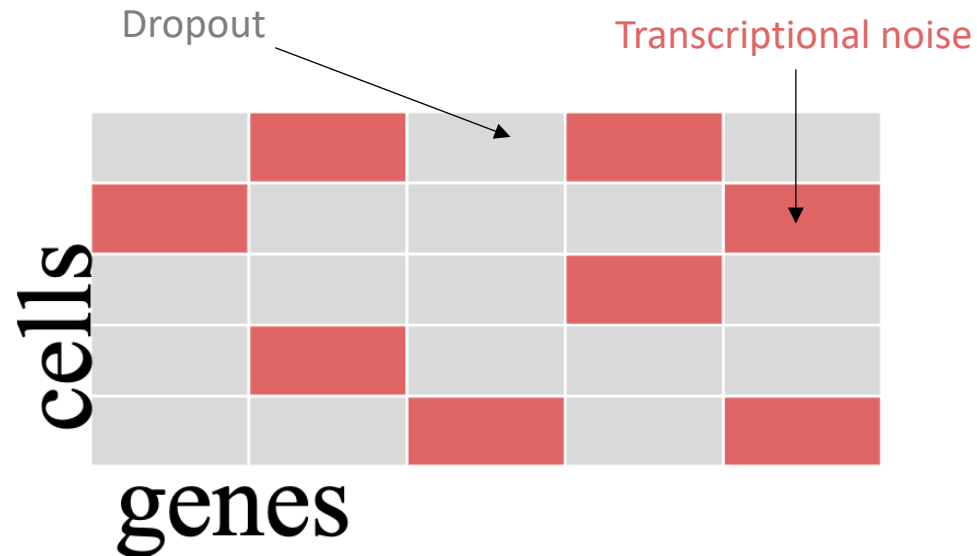
1. The information regarding which features are missing or noisy is not provided
2. Biologically relevant graph structure is not provided



# MOTIVATION: scRNA-SEQ DATA IMPUTATION USING FEATURE PROPAGATION

## ▪ Challenge 1) Missing and noise in cell-gene matrix

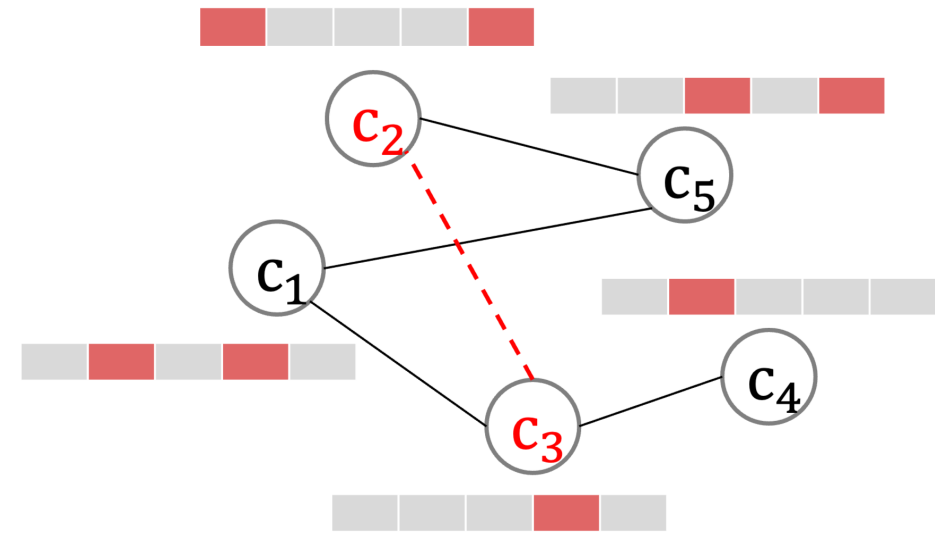
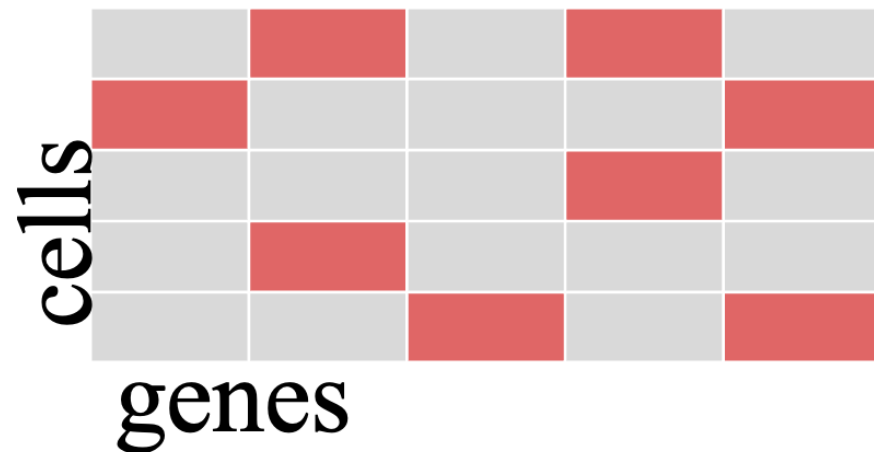
- Zero-values (Missing): Often regarded as a dropout (e.g., false-zeros)
- Non-zero values (Noise): Might capture biologically irrelevant signals (e.g., batch effects, transcriptional noise)



Careful handling of both zero-values and non-zero values is crucial

# MOTIVATION: scRNA-SEQ DATA IMPUTATION USING FEATURE PROPAGATION

- Challenge 2) **Biologically relevant graph structure is not provided**
  - *k*NN Graph based on initial sparse matrix may not be optimal

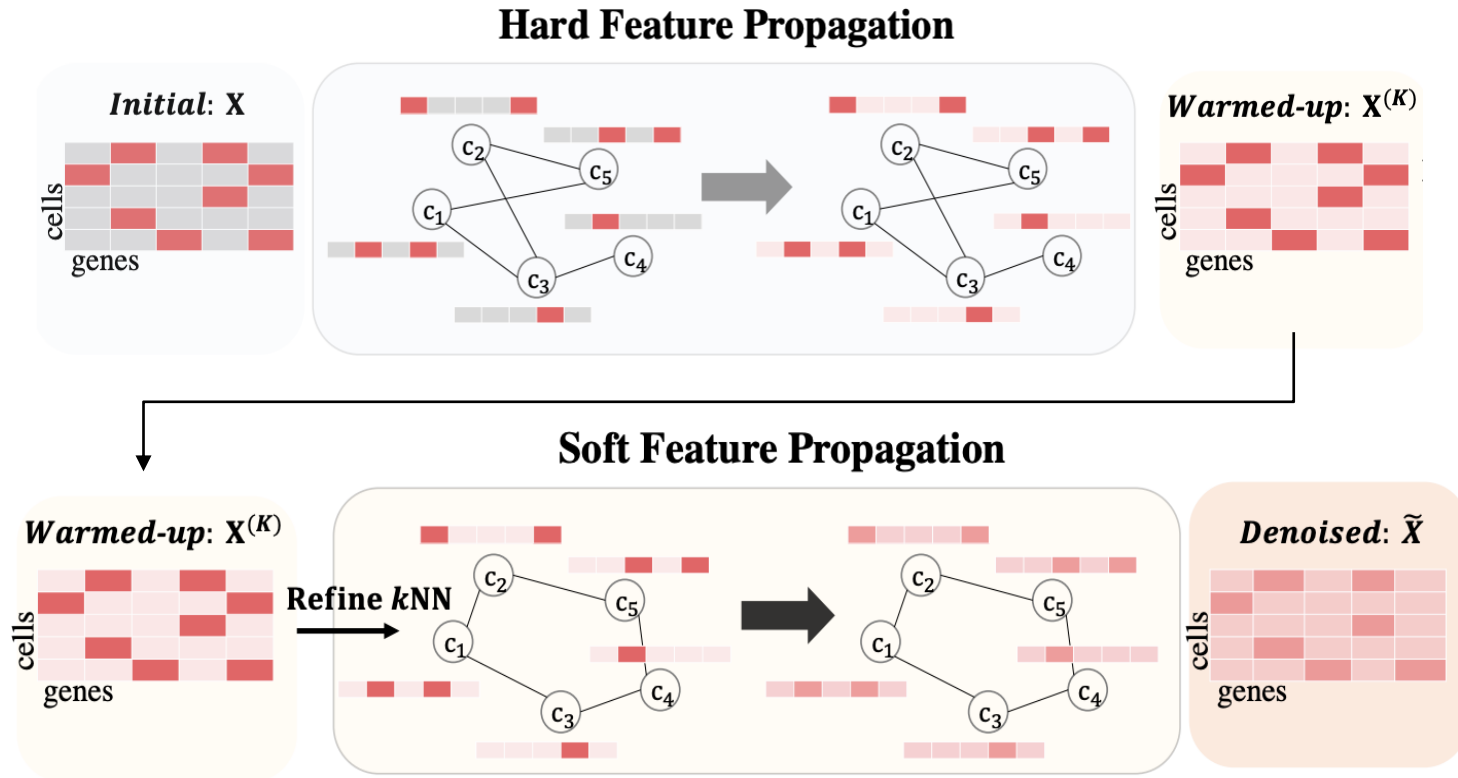


< *k*NN Graph on sparse cell-gene matrix >

When generating a graph, it is essential to carefully consider the biologically relevant relationships among cells

# scFP: single-cell FEATURE PROPAGATION

## Overall Framework of scFP



1) Hard Feature Propagation

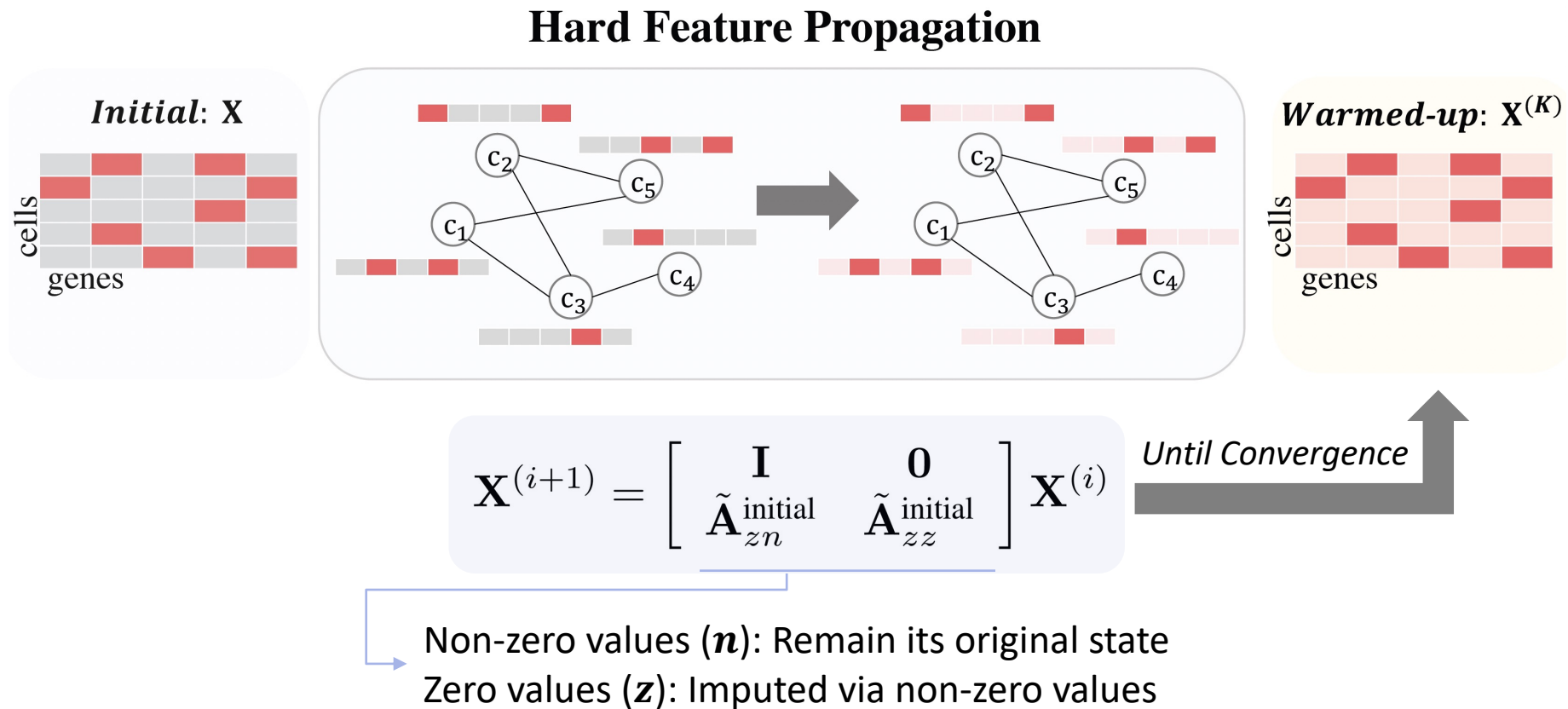
2) Refine  $k$ NN Graph

3) Soft Feature Propagation

# scFP: single-cell FEATURE PROPAGATION

## 1) Hard Feature Propagation

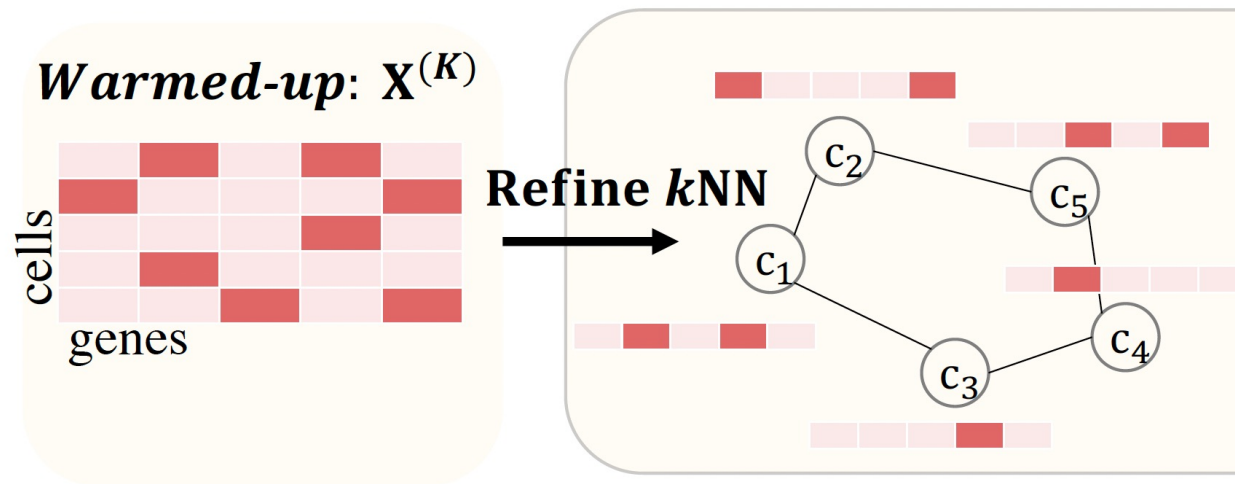
- Impute zero values (dropout) via observed gene expression and obtain warmed-up cell-gene matrix
- *Assumption: Imputing zeros (dropout) is more significant than denoising non-zeros at the initial stage*



# scFP: single-cell FEATURE PROPAGATION

## ▪ 2) Refine $k$ NN Graph

- Build  $k$ NN Graph via warmed-up cell-gene matrix
- Compared to initial  $k$ NN Graph, it would potentially reveal hidden or implicit graph structures



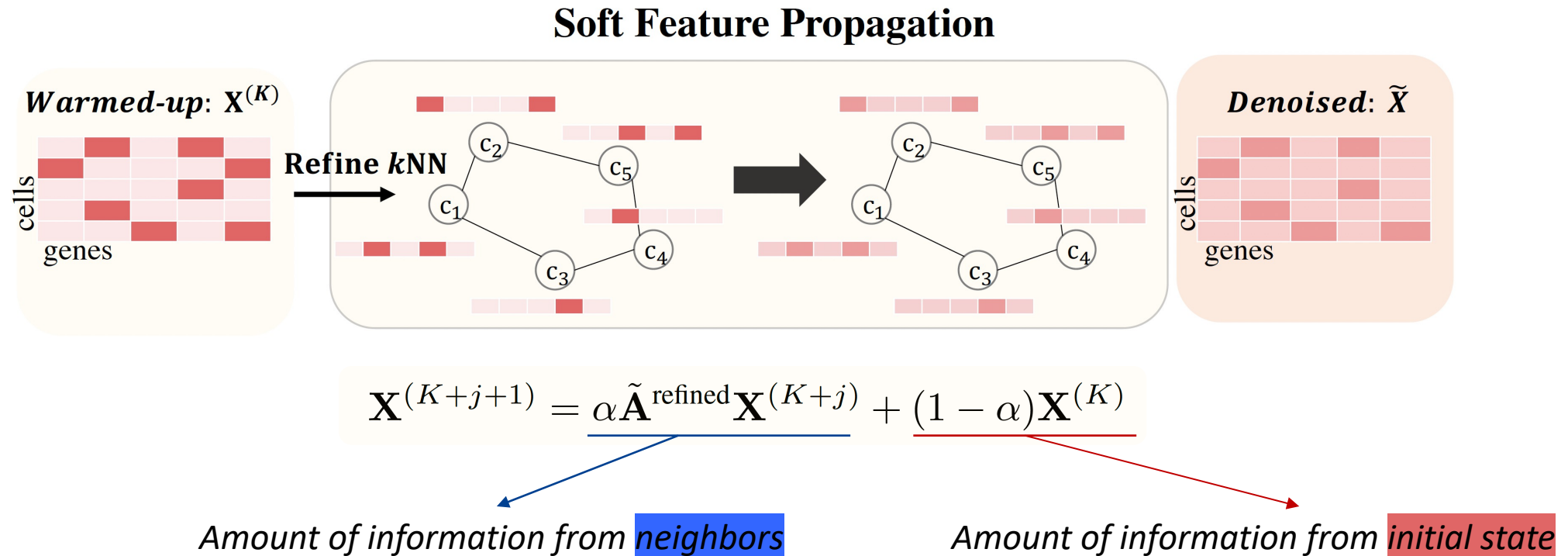
$$\tilde{\mathbf{A}}^{\text{refined}} = k\text{NN}(\mathbf{X}^{(K)})$$

Warmed-up matrix obtained from Hard FP

# scFP: single-cell FEATURE PROPAGATION

## ▪ 3) Soft Feature Propagation

- Denoise observed gene expression (irrelevant signals)
  - Focus on updating non-zero values → used constant  $\alpha$  as 0.99 during experiments

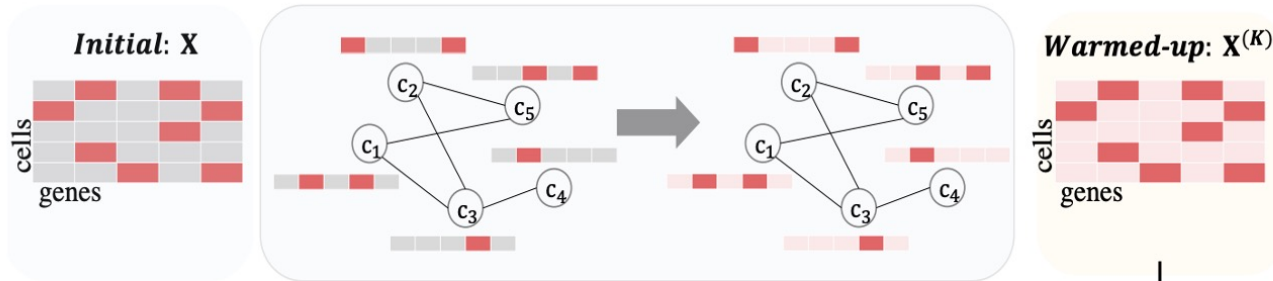




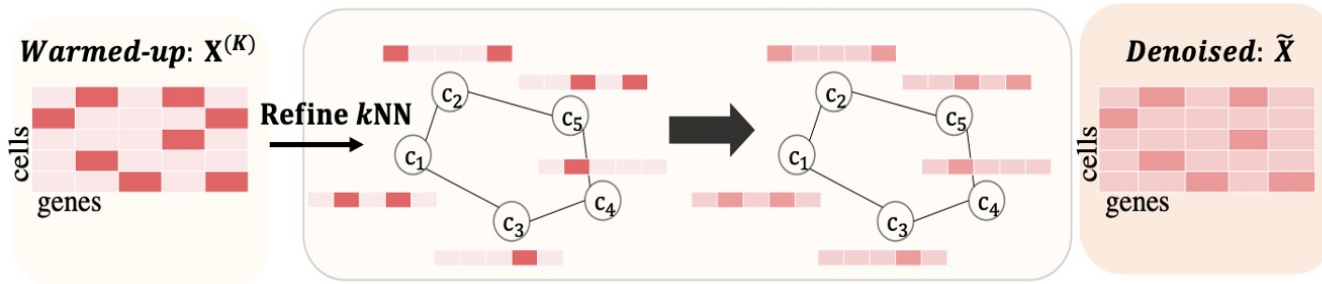
# scFP: single-cell FEATURE PROPAGATION

- In a nutshell,

## Hard Feature Propagation



## Soft Feature Propagation



## Algorithm 1 single-cell Feature Propagation (scFP)

**Input:** Cell-Gene Matrix  $\mathbf{X}$ , Initial  $k$ NN  $\tilde{\mathbf{A}}^{\text{initial}}$

**Output:** Denoised Cell-Gene Matrix  $\tilde{\mathbf{X}}$

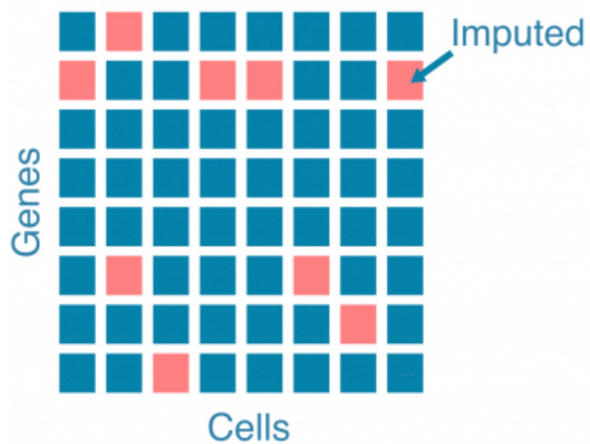
- 1:  $\mathbf{Y} \leftarrow \mathbf{X}$
- 2: **while**  $\mathbf{X}$  has not converged **do**
- 3:      $\mathbf{X} \leftarrow \tilde{\mathbf{A}}^{\text{initial}} \mathbf{X}$
- 4:      $\mathbf{X}_{k,d} \leftarrow \mathbf{Y}_{k,d} \forall k \in \mathcal{V}_{k,d}, \forall d \leq M$      **Hard Clamping**
- 5: **end while**
- 6:  $\tilde{\mathbf{A}}^{\text{refined}} = k\text{NN}(\mathbf{X}^{(K)})$      **Refine  $k$ NN**
- 7: **while**  $\mathbf{X}^{(K)}$  has not converged **do**
- 8:      $\mathbf{X}^{(K)} \leftarrow \alpha \tilde{\mathbf{A}}^{\text{refined}} \mathbf{X}^{(K)} + (1 - \alpha) \mathbf{X}^{(K)}$      **Soft Clamping**
- 9: **end while**

Impute zeros (Dropouts)  $\rightarrow$  Refine  $k$ NN Graph  $\rightarrow$  Denoise non-zeros (Irrelevant signals)

# EXPERIMENTS

## ▪ Data Statistics & Evaluation Metrics

Data	# of Cells	# of Genes	# of Subgroups
Baron Mouse	1,886	14,861	13
Mouse ES cells	2,717	24,047	4
Mouse bladder cells	2,746	19,771	16
Zeisel	3,005	19,972	7
Baron Human	8,569	20,125	14
Shekhar mouse retina cells	27,499	13,166	19



Imputation



Cell Clustering

### 1) Imputation Task

- **Root Mean Square Error (RMSE)**

$$RMSE = \sqrt{\frac{\sum_{i=1}^N \frac{y_i - \hat{y}_i}{N}}{N}}$$

$N$ : # of cells  
 $y_i$ : ground-truth gene expression  $i$ -th cell  
 $\hat{y}_i$ : predicted gene expression  $i$ -th cell

### 2) Cell Clustering Task

- **Adjusted Rand Index (ARI)**

$$ARI = \frac{RI - E[RI]}{\max(RI) - E[RI]} \quad RI = \frac{a + b}{NC_2}$$

$a$ : # of pairs successfully belong to the same cluster  
 $b$ : # of pairs correctly labeled as different cluster

- **Normalized Mutual Information (NMI)**

$$NMI = \frac{2 \times I(S; C)}{[H(S) + H(C)]}$$

$S$ : ground-truth cell type  
 $C$ : cluster assignment by model  
 $I(\cdot, \cdot)$ : mutual information  
 $H(\cdot)$ : entropy

- **Clustering Accuracy (CA)**

$$CA = \max_m \frac{\sum_{i=1}^N \mathbb{1}[s_i = m(c_i)]}{N}$$

$N$ : # of cells  
 $m(\cdot)$ : matching function  
 $s_i$ : ground-truth cell type of  $i$ -th cell  
 $c_i$ : cluster assignment of  $i$ -th cell

# EXPERIMENTS

## ▪ Performance on imputation and cell clustering task

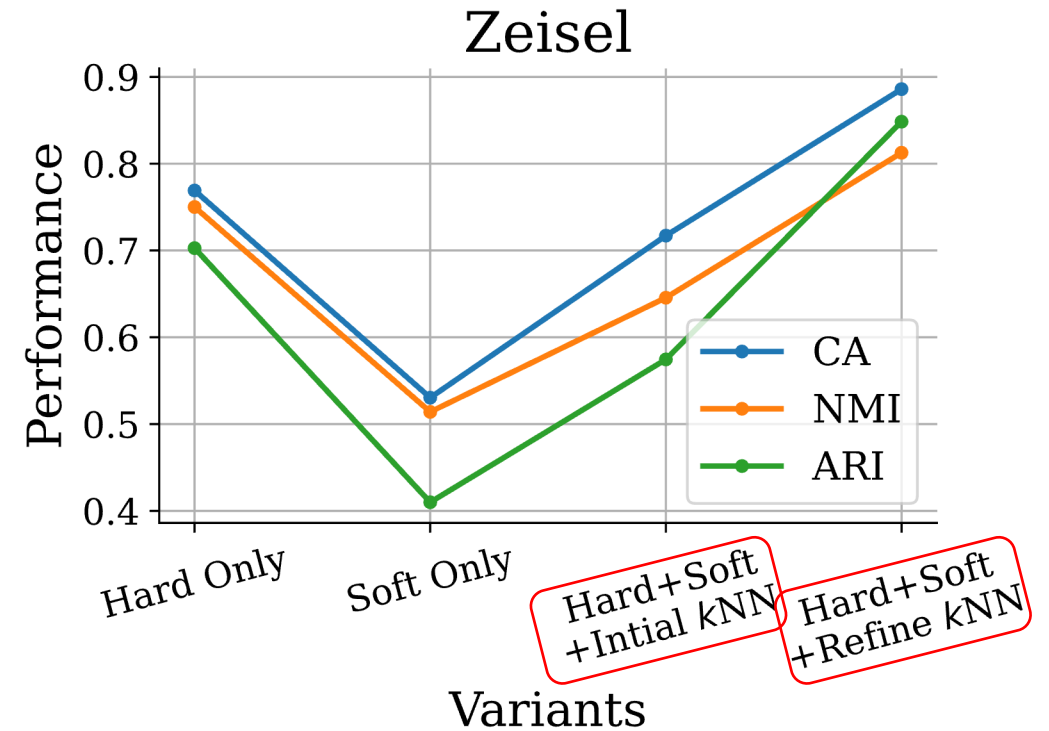
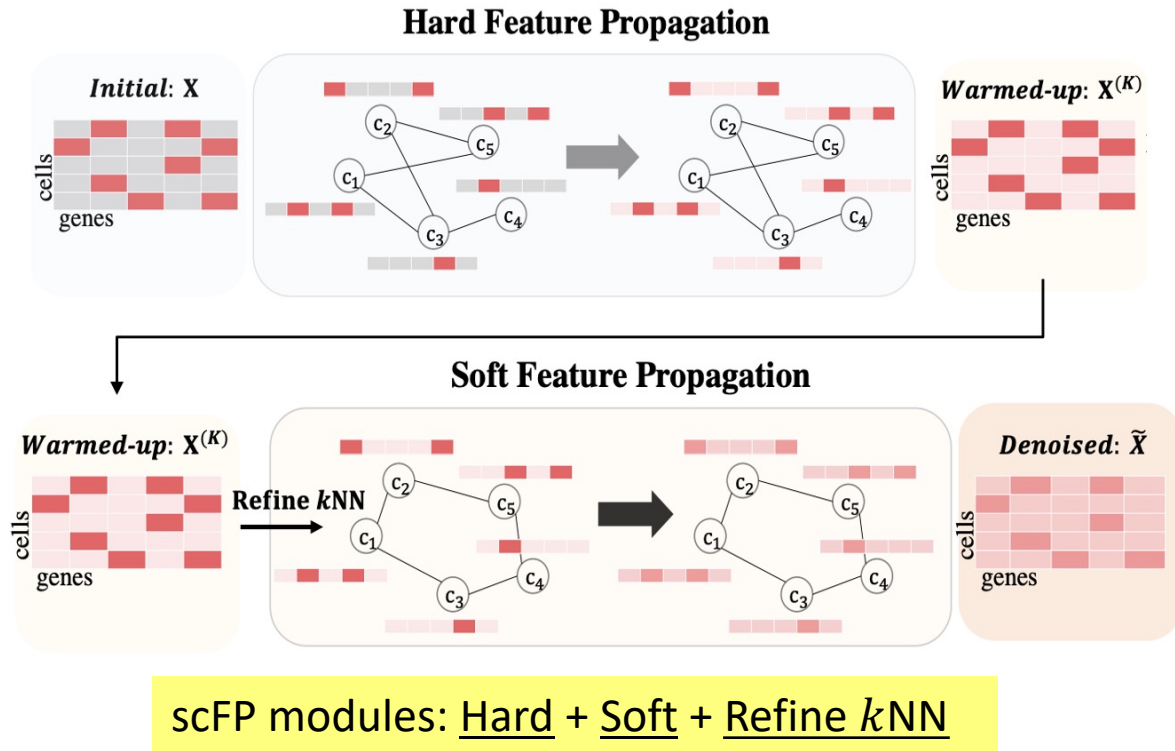
<i>Imputation</i>	Baron Mouse			Mouse ES			Mouse Bladder			Zeisel			Baron Human		
	Dropout Rates			Dropout Rates			Dropout Rates			Dropout Rates			Dropout Rates		
	20%	40%	80%	20%	40%	80%	20%	40%	80%	20%	40%	80%	20%	40%	80%
MAGIC	0.61	0.73	0.99	0.53	0.73	1.21	0.50	0.60	0.82	0.60	0.82	1.31	0.58	0.74	1.06
DCA	0.42	0.43	0.49	0.35	0.35	0.36	0.37	0.38	0.41	0.39	0.42	0.44	0.41	0.43	0.47
AutoClass	0.63	0.76	0.98	0.53	0.75	1.23	0.52	0.64	0.82	0.60	0.84	1.32	0.59	0.76	1.08
scGCL	0.64	0.74	0.97	0.59	0.75	1.16	0.51	0.62	0.81	0.66	0.82	1.29	0.63	0.77	1.08
scFP (Ours)	<b>0.36</b>	<b>0.37</b>	<b>0.43</b>	<b>0.32</b>	<b>0.32</b>	<b>0.36</b>	<b>0.26</b>	<b>0.26</b>	<b>0.31</b>	<b>0.39</b>	<b>0.40</b>	<b>0.44</b>	<b>0.33</b>	<b>0.34</b>	<b>0.39</b>

<i>Cell Clustering</i>	Baron Mouse			Mouse ES			Mouse Bladder			Zeisel			Baron Human		
	ARI	NMI	CA	ARI	NMI	CA	ARI	NMI	CA	ARI	NMI	CA	ARI	NMI	CA
Raw	0.44	0.71	0.56	0.74	0.75	0.79	0.59	0.75	0.68	0.70	0.75	0.77	0.44	0.71	0.56
MAGIC	0.42	0.72	0.57	0.80	<b>0.85</b>	0.83	0.55	0.75	0.64	0.70	0.75	0.76	0.56	0.78	0.59
DCA	0.46	0.69	0.59	0.76	0.78	0.81	0.39	0.59	0.54	0.67	0.72	0.75	0.53	0.74	0.55
AutoClass	0.44	0.71	0.52	0.74	0.75	0.81	0.51	0.75	0.64	0.71	0.75	0.77	0.44	0.71	0.52
scGCL	0.43	0.72	0.54	0.73	0.75	0.79	0.53	0.75	0.64	0.65	0.70	0.73	0.50	0.78	0.62
kNN-smoothing	0.43	0.72	0.55	0.72	0.74	0.79	0.59	0.76	0.68	0.68	0.73	0.76	0.56	0.78	0.56
scFP (Ours)	<b>0.61</b>	<b>0.82</b>	<b>0.76</b>	<b>0.82</b>	0.83	<b>0.85</b>	<b>0.65</b>	<b>0.77</b>	<b>0.73</b>	<b>0.85</b>	<b>0.81</b>	<b>0.89</b>	<b>0.68</b>	<b>0.83</b>	<b>0.73</b>

The denoised matrix obtained via scFP shows promising results in both imputation and the cell clustering task

# EXPERIMENTS

## ▪ Ablation on each module in scFP

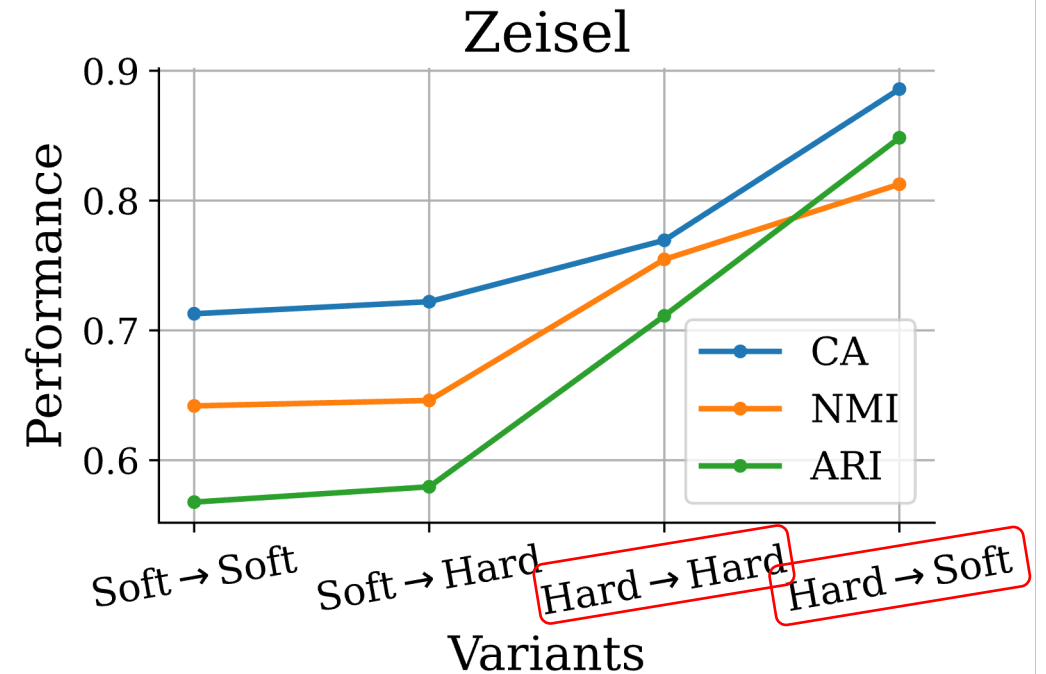
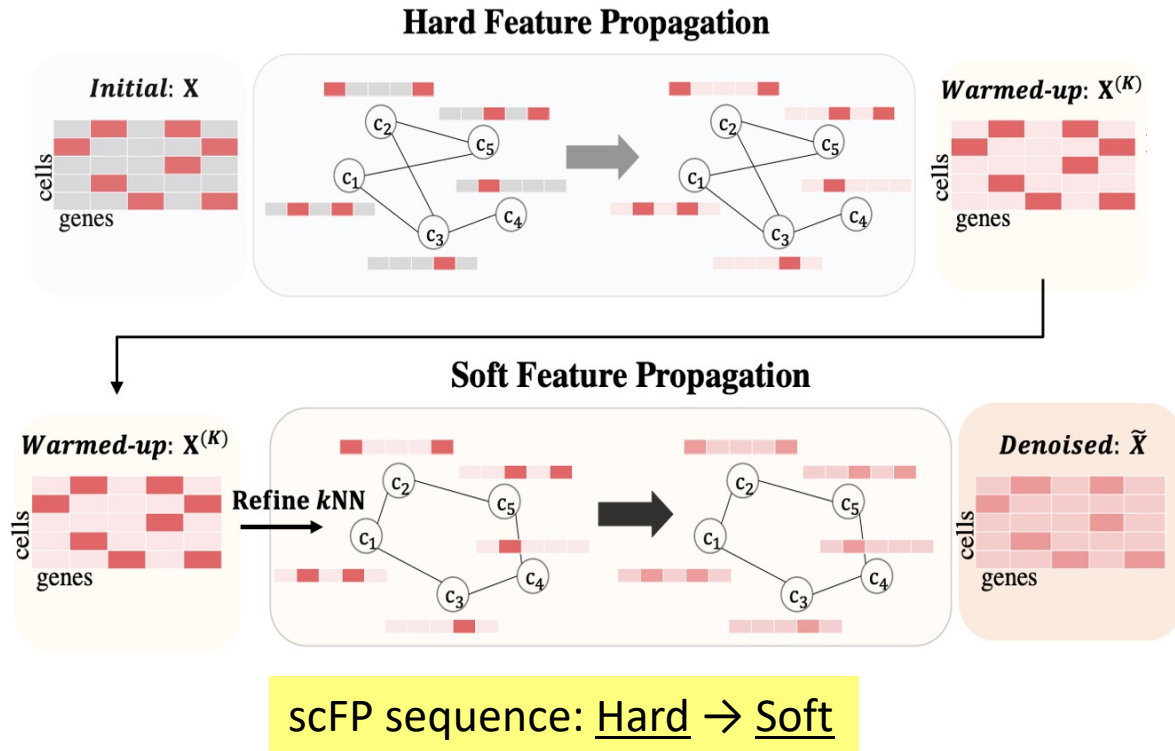


1) ( $H+S+Refine\ kNN$  outperforms  $H, S$  only): Using both Hard and Soft FP is beneficial

2) ( $H+S+Refine\ kNN$  outperforms  $H+S+Initial\ kNN$ ): Utilization of a refined  $kNN$  graph prior to applying Soft FP is essential

# EXPERIMENTS

## ▪ Ablation on sequence of scFP



- 1) ( $H \rightarrow \bullet$  outperforms  $S \rightarrow \bullet$ ): Initially, importance of imputing zeros surpasses the significance of denoising non-zeros
- 2) ( $H \rightarrow S$  outperforms  $H \rightarrow H$ ): Inclusion of Soft FP after Hard FP further enhances obtaining a denoised matrix

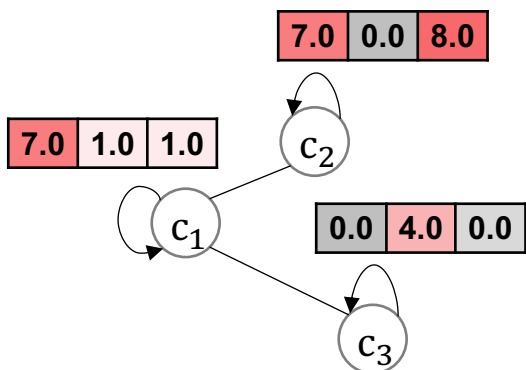
# EXPERIMENTS

- Simulation Study: Risk of diffusion of false-zeros (MAGIC vs scFP) – Low dropout rates

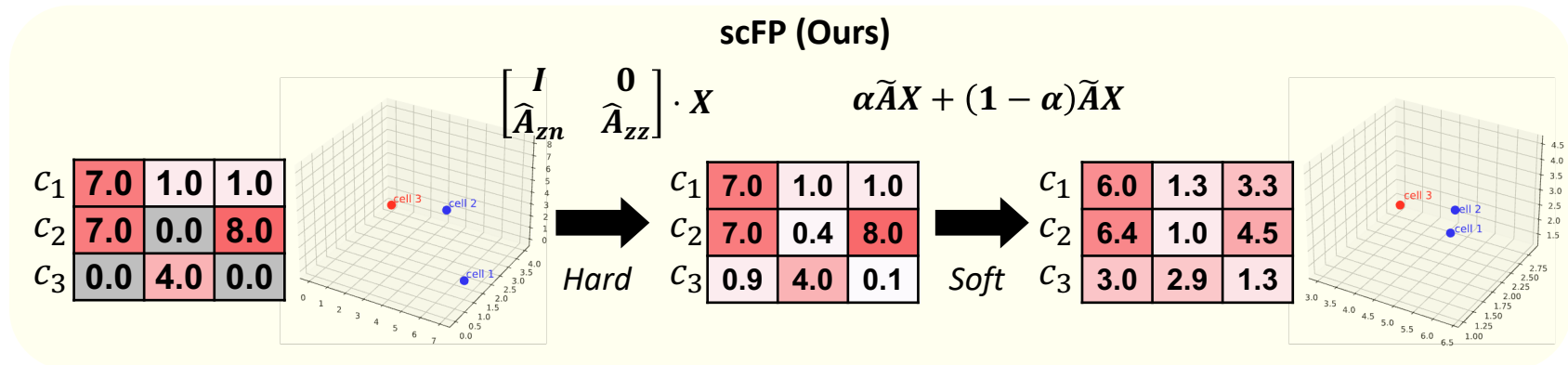
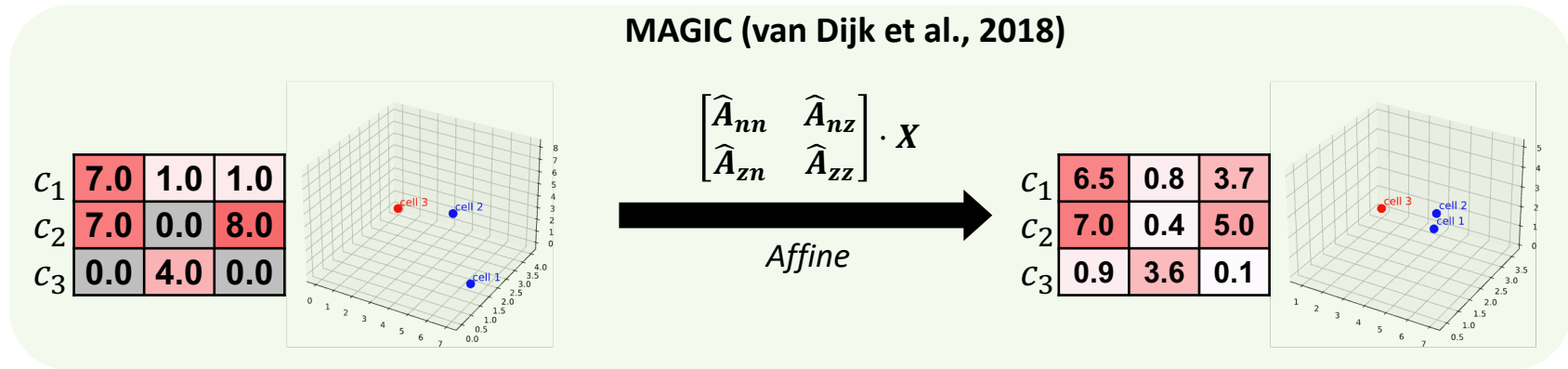
cells	7.0	1.0	1.0	} Same cell type!
	7.0	0.0	8.0	
	0.0	4.0	0.0	
genes				

< Cell-Gene Count Matrix (Dropout: 33%) >

$$X = \begin{bmatrix} 7 & 1 & 1 \\ 7 & 0 & 8 \\ 0 & 4 & 0 \end{bmatrix} \quad \hat{A} = D^{-1}A = \begin{bmatrix} 0.5 & 0.4 & 0.1 \\ 0.4 & 0.6 & 0 \\ 0.1 & 0 & 0.9 \end{bmatrix}$$



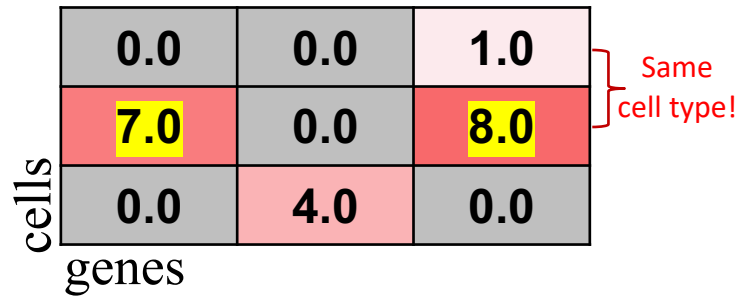
< Cell-Cell Graph ( $X, \hat{A}$ ) >



At low dropout rates, both MAGIC and scFP perform well on cell type clustering

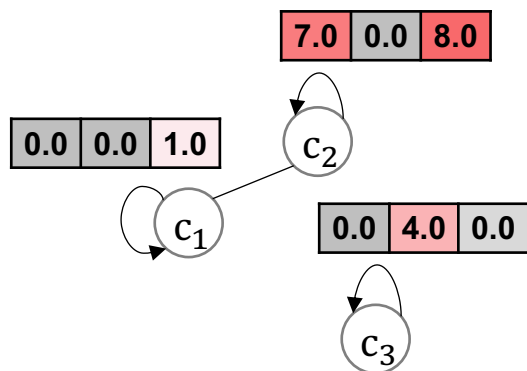
# EXPERIMENTS

- Simulation Study: Risk of diffusion of false-zeros (MAGIC vs scFP) – **High** dropout rates



< Cell-Gene Count Matrix (Dropout: 55%) >

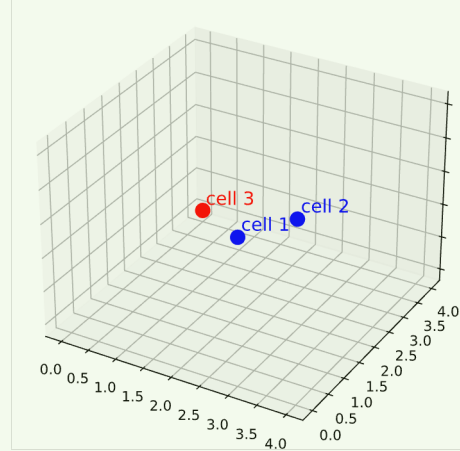
$$X = \begin{bmatrix} 0 & 0 & 1 \\ 7 & 0 & 8 \\ 0 & 4 & 0 \end{bmatrix} \quad \hat{A} = D^{-1}A = \begin{bmatrix} 0.6 & 0.4 & 0 \\ 0.4 & 0.6 & 0 \\ 0 & 0 & 1.0 \end{bmatrix}$$



< Cell-Cell Graph ( $X, \hat{A}$ ) >

MAGIC (van Dijk et al., 2018)

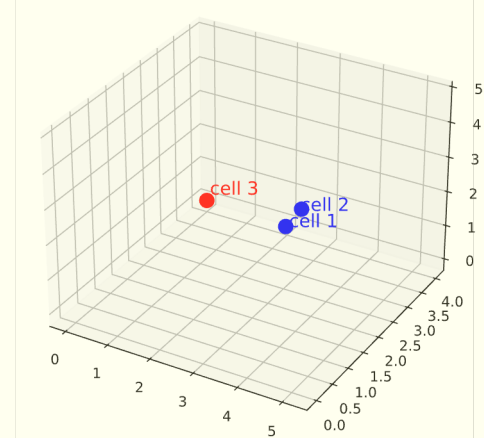
$C_1$	3.0	0.0	4.0
$C_2$	4.0	0.0	5.0
$C_3$	0.0	4.0	0.0



Affine

scFP (Ours)

$C_1$	4.8	0.0	4.2
$C_2$	5.2	0.0	4.8
$C_3$	0.0	4.0	0.0



Hard → Soft

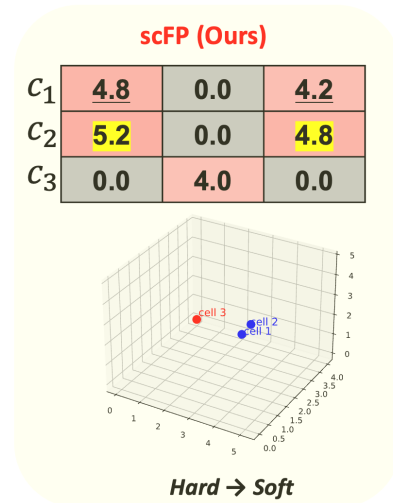
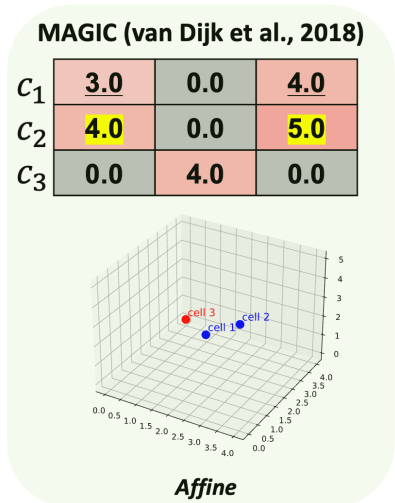
At **high** dropout rates, scFP better perseveres the scale of original non-zero values thanks to **Hard Feature Propagation**, while MAGIC is more vulnerable to false-zeros

# EXPERIMENTS

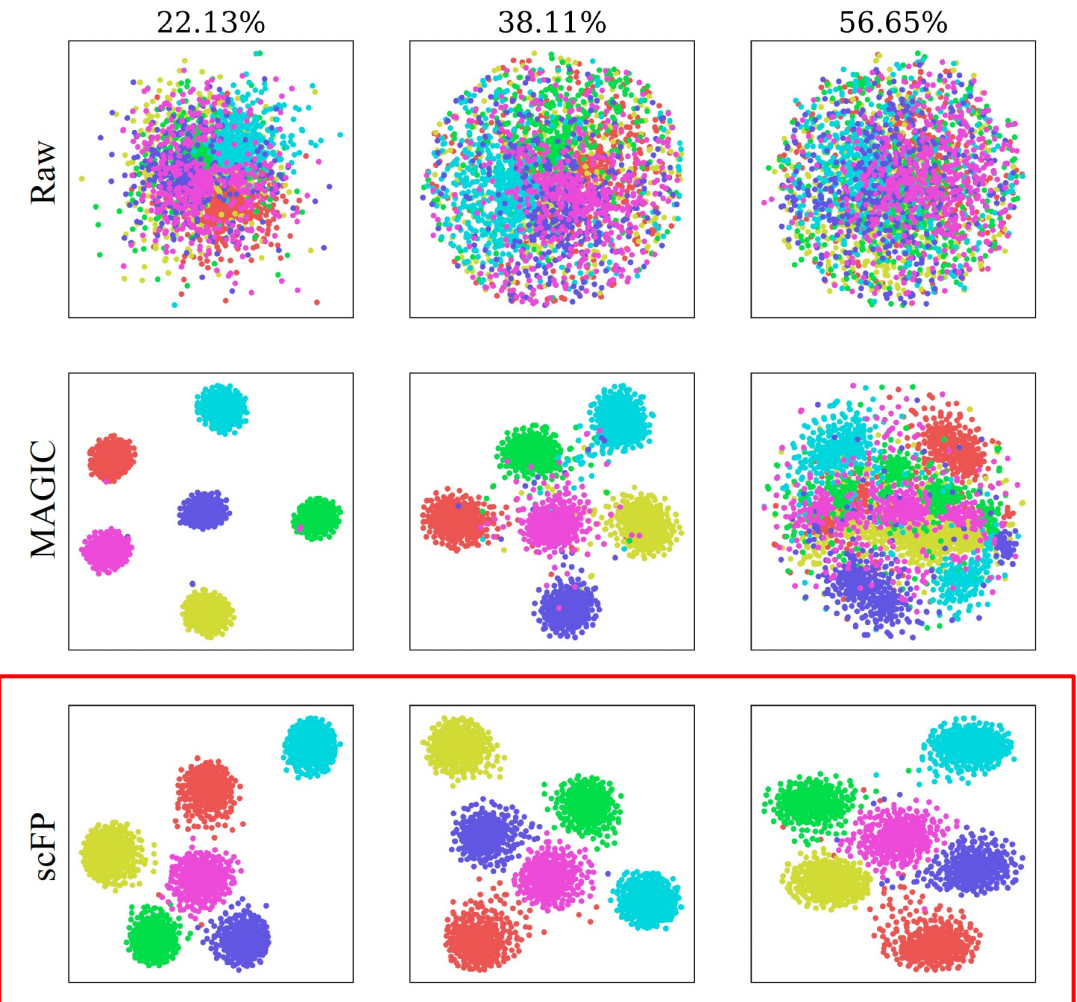
## Simulation Study: Risk of diffusion of false-zeros in simulation dataset

Simulation dataset from Splatter<sup>1</sup>

- # of Cells: 3918
- # of Genes: 11786
- # of subgroups: 6
- Dropout Rate: 22.13%, 38.11%, 56.65%



At **high** dropout rates, scFP better perseveres the scale of original non-zero values thanks to *Hard Feature Propagation*, while MAGIC is more vulnerable to false-zeros



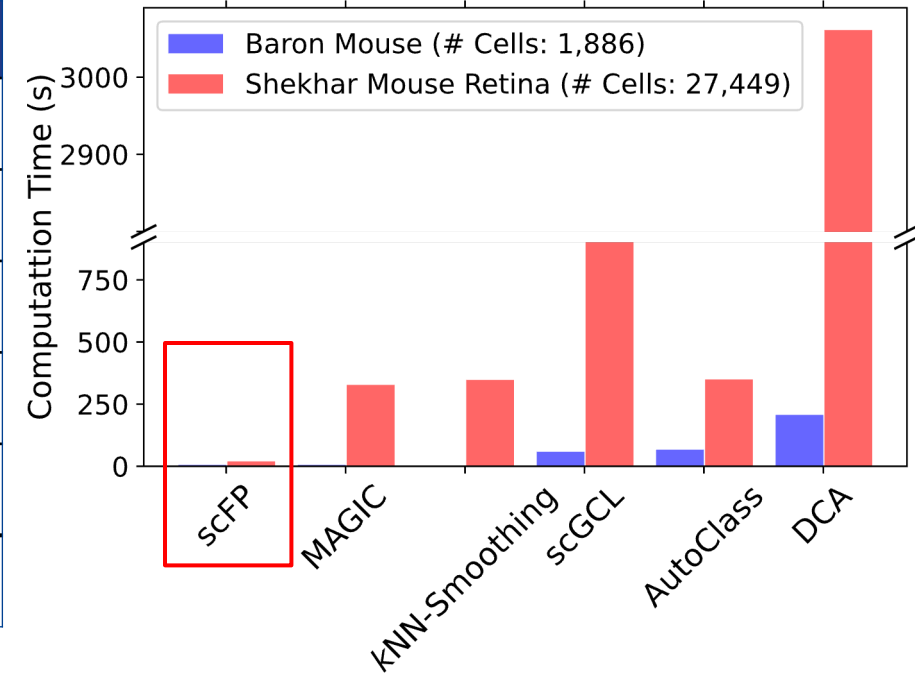
1) Zappia, L., Phipson, B. & Oshlack, A. Splatter: simulation of single-cell RNA sequencing data. *Genome Biol* **18**, 174 (2017). <https://doi.org/10.1186/s13059-017-1305-0>



# EXPERIMENTS

## Memory & Time Complexity

Model	Matrices & Parameters in GPU	Big-O
DCA (Eraslan et al., 2019)	$X, f_{enc}, f_{dec}, W_{\pi}, W_{\mu}, W_{\theta}$	$\mathcal{O}(NM) + \mathcal{O}(model)$
AutoClass (Li et al., 2022)	$X, f_{enc}, f_{dec}, f_{cls}$	$\mathcal{O}(NM) + \mathcal{O}(model)$
scGCL (Xiong et al., 2023)	$X, A, f_{o\_enc}, f_{t\_enc}, f_{dec}, W_{\pi}, W_{\mu}, W_{\theta}, q_{\theta}$	$\mathcal{O}(NM) + \mathcal{O}(N^2) + \mathcal{O}(model)$
kNN-Smoothing (Wagner et al., 2018)	$X, A$	$\mathcal{O}(NM) + \mathcal{O}(N^2)$
MAGIC (van Dijk et al., 2018)	$X, A$	$\mathcal{O}(NM) + \mathcal{O}(N^2)$
scFP (Ours)	$X, A$	$\mathcal{O}(NM) + \mathcal{O}(N^2)$



< Memory Complexity ( $N$ : # of Cells,  $M$ : # of Genes) >

< Time Complexity >

Proposed scFP shows notably lower computational cost compared to other graph-based baselines thanks to the absence of PCA computation and the use of sparse matrix multiplication

# CONCLUSION

- Nut: **scRNA-seq meets Feature Propagation!**
- Challenges lie in the presence of missing and noise in the cell-gene matrix and the lack of a biologically relevant graph
- To this end, we introduce scFP, a method that effectively denoises both zero values and non-zero values
- Experimental results on real-world datasets show the promising performance of scFP in imputation and cell clustering
- **Keywords for scFP**
  - **Hard Feature Propagation**
  - **Refine kNN**
  - **Soft Feature Propagation**

