



sxSNF: A Novel Single-Cell Multi-Modal Data Integration Method Combining Similarity Network Fusion and Deep Graph Learning

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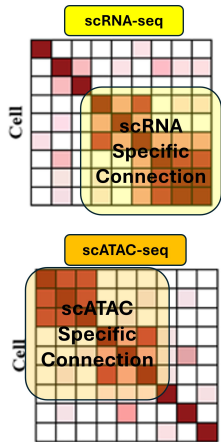
Single Cell Multi-Modal Integration

Challenges:

- **Cell Group Connection Variability:** Cell connections vary in dynamics, resulting in shifted group representation
- **Limited Complementary Leveraging:** Previous methods not leveraging modality complementary information
- **Batch Effects:** Modality specific distortions

Our Proposed Algorithm (sxSNF):

- **Similarity Network Fusion (SNF):** Initially in ref. [1], align complementary similarities through soft mutual diffusive process
- **Dual Graph Representation:** Preserve modality-specific structures during the diffusion
- **Network-based Representation Learning:** Not prone to batch effects





Methods of Fusion

- **Simple Concatenation**

$$X_{combined} = [X^{(1)}, X^{(2)}, \dots, X^{(M)}]$$

- Loses intrinsic structure of each modality; Suffers from scale differences; ...

- **Weighted Integration**

$$X_{fused} = \sum_{m=1}^M \alpha_m X^{(m)}, \quad \sum_{m=1}^M \alpha_m = 1$$

- Difficult to determine optimal weights; Static weighting ignores modal-specific structure; ...

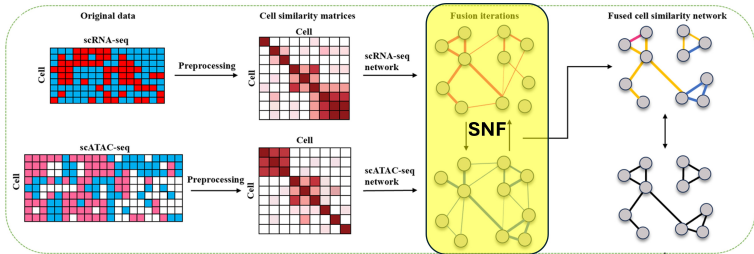
- **Our Idea: bring in SNF Fusion**

$$P^{(m)}(t+1) = S^{(m)} \frac{\sum_{k \neq m} P^{(k)}(t)}{M-1} (S^{(m)})^T$$

- $P^{(m)}$: cross-modal similarity matrix ; $S^{(m)}$: modality-specific similarity matrix; M total modalities.
- **Core Idea:** SNF enables information flow in fusion while retaining local structures



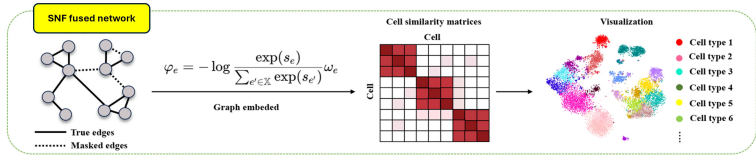
sxSNF: SNF-based Cross-modal Graph Fusion



- Preprocess modal specific similarity matrices (e.g. scRNA-seq / scATAC-seq)
- Build modality-specific cell connection graphs (KNN)
- Apply SNF to iteratively exchange neighborhood information between modals
- Output a modal fused cell similarity network



sxSNF: GNN Representation and Clustering



- Use each cell's adjacency vector from the SNF fused network as initial features
- Train GNN on the fused graph with masked-edge prediction
- Obtain low-dimensional embeddings of the fused cell characteristics
- Recompute similarity \rightarrow clustering \rightarrow UMAP visualization



sxSNF Algorithm (scRNA + scATAC)

Step 1: Modality-specific Preprocessing

scRNA-seq preprocessing:

$$X_{i,j}^{RNA} = \log \left(1 + \frac{X_{i,j}^{RNA} \times 10^4}{\sum_{g,j} X_{g,j}^{RNA}} \right)$$

scATAC-seq preprocessing:

$$X_{i,j}^{ATAC} = \text{TF-IDF}(X_{peaks}^{ATAC}) = \log \left(1 + \frac{tX_{i,j}^{ATAC} \times \log(\frac{N}{dX_j^{ATAC}})}{\|tX_i^{ATAC}\|_2} \right)$$

Step 2: Similarity Network Construction

For each modality m , construct cell similarity network:

$$S_{ij}^{(m)} = P_{ij}^{(m)}(0) = \text{KNN}_k \left(\exp \left(-\frac{d_{\cos}^2(x_i^{(m)}, x_j^{(m)})}{\tau^2} \right) \right)$$

where $d_{\cos}(\cdot)$ is cosine distance, τ controls neighborhood size, k is number of nearest neighbours.



sxSNF Algorithm (cont'd)

Step 3: SNF Cross-modal Diffusion Process

Two-modal diffusion:

$$P^{(m)}(t+1) = S^{(m)} \times P^{(k)}(t) \times (S^{(m)})^T$$

Convergence: Iterate until $\|P^{(m)}(t+1) - P^{(m)}(t)\|_F < \epsilon$

Step 4: Train GNN (self-supervised with masked edge prediction):

$$\mathbf{h}_i^{(l+1)} = \sigma \left(\sum_{j \in \mathcal{N}(i)} \alpha_{ij} \mathbf{W}^{(l)} \mathbf{h}_j^{(l)} \right)$$

with objective:

$$\mathcal{L}_i = - \sum_{j \in \mathcal{N}(i)} \log \frac{\exp(\mathbf{h}_i^\top \mathbf{h}_j)}{\sum_{j'} \exp(\mathbf{h}_i^\top \mathbf{h}_{j'})}$$

Symbol definitions:

- \mathbf{x}_i : input feature of cell i ; \mathbf{h}_i : hidden representation; α_{ij} : edge weight; $\mathbf{W}^{(l)}$: weight matrix; $\mathcal{N}(i)$: neighbor set; E, \mathcal{V} : edge/node sets



Datasets and Evaluation

Benchmark Datasets:

Dataset	Platform	Cells	Modalities	Cell Types
PBMC-10x	10X Genomics	11,909	scRNA+scATAC	19 immune
SHARE-seq	SHARE-seq	34,774	scRNA+scATAC	20 skin
SNARE-seq	SNARE-seq	15,390	scRNA+scATAC	13 brain

Evaluation Methods:

- **Clustering Quality:** ARI, NMI, AMI
- **Biological Validation:** Marker gene enrichment analysis
- **Model Interpretability:** Low-dimension visualization by TSNE and UMAP



Benchmark Results (PBMC-10x)

Methods	sxSNF	SIMBA	scMIC	SNF+scMIC	Guanlab	DCCA
ARI	0.5584	0.4854	0.1142	0.3523	0.2683	0.3375
NMI	0.7274	0.6839	0.2841	0.5732	0.5164	0.5798
AMI	0.7260	0.6822	0.2802	0.5710	0.5140	0.5777

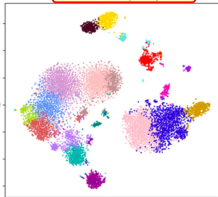
Method Descriptions:

- **SIMBA** [2]: Contrastive learning for multimodal integration (Chen et al., Nature Methods, 2024)
- **scMIC** [3]: Mutual information maximization approach (Zhan et al., IEEE JBHI, 2023)
- **SNF+scMIC**: Hybrid of SNF and scMIC strategies (An extension of the model scMIC by SNF)
- **Guanlab-dengkw** [4]: Sparse regularization and graph learning (Hu et al., Nature Methods, 2024)
- **DCCA** [5]: Deep canonical correlation analysis (Zuo et al., Bioinformatics, 2021)

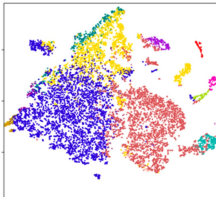


T-SNE Visualization (SNARE-seq)

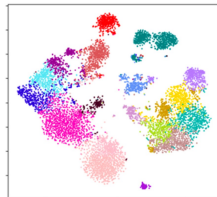
sxSNF (Our)



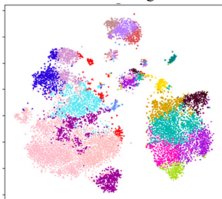
scMIC



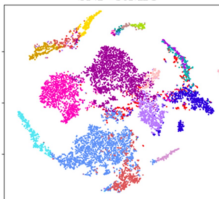
SIMBA



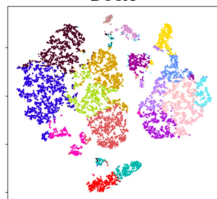
Guanlab-dengkw



SNF+scMIC

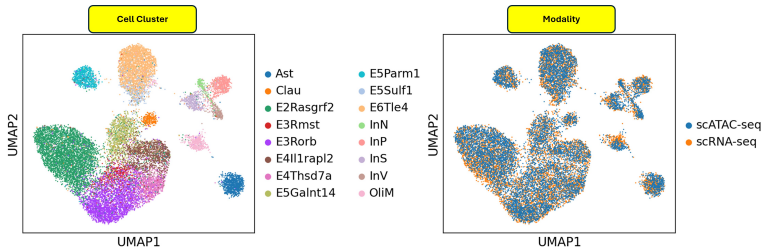


DCCA





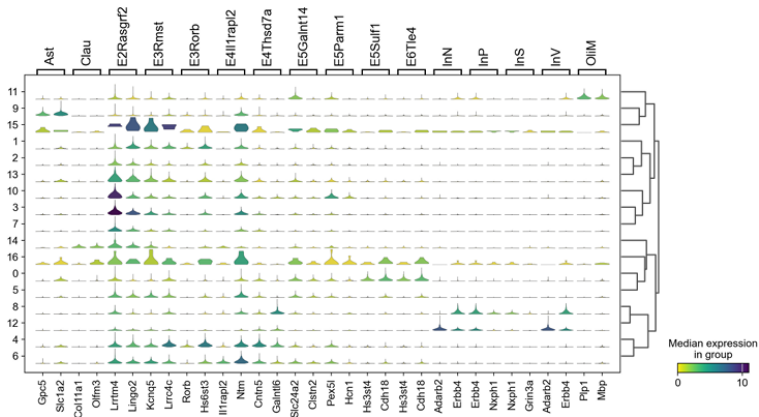
UMAP Visualization (SHARE-seq)



- **Clear separation of cell types (left panel)**
 - Joint embedding yields well-defined clusters with sharp boundaries
- **Effective cross-modal alignment (right panel)**
 - scRNA-seq (orange) and scATAC-seq (blue) cells are well mixed within clusters
 - Indicates successful integration of complementary modalities



Marker Gene Expression (SNARE-seq)



- Distinct marker gene expression patterns validate the identified cell clusters
- Hierarchical clustering reveals lineage relationships among cell types



Summary

- We developed **sxSNF** - a **novel** tool combines Similarity Network Fusion (SNF) with Graph Neural Networks for single-cell multi-modal data integration
- It **preserves modality-specific structures** while enabling **cross-modal information flow** through iterative neighborhood exchange
- Its **self-supervised GNN learning** with masked edge prediction captures and embeds both modal-specific and cross-modal relationships
- It **achieves superior performance** across benchmark datasets (PBMC-10x, SHARE-seq, SNARE-seq) over current SOTA methods and demonstrates clear cell-type separation
- **sxSNF** is available for public use at <https://github.com/labxscut/sxSNF>



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