SpatialTransformerGNN: A Transformer-Augmented Bilevel Graph Neural Network for Spatially Informed Cell Type Classification

1. Introduction and Motivation

Single-cell RNA sequencing (scRNA-seq) and spatial transcriptomics (ST) are critical tools for studying cellular heterogeneity and tissue organization. While scRNA-seq provides high-resolution transcriptomic profiles, it lacks spatial context. Conversely, spatial transcriptomics preserves spatial organization but often suffers from lower gene coverage and resolution. Integrating these modalities is essential for a comprehensive understanding of cellular function in tissues.

Graph neural networks (GNNs) have been widely used for modeling cell-cell interactions, but their effectiveness is often constrained by limited spatial awareness. Meanwhile, transformer-based models have demonstrated success in genomics and natural language processing by capturing long-range dependencies. However, their application to spatially informed single-cell analysis remains largely unexplored. This proposal seeks to develop SpatialTransformerGNN, a hybrid transformer-augmented bilevel GNN designed to enhance spatially aware cell-type classification by integrating both local (GNN-based) and global (transformer-based) information from scRNA-seq and spatial transcriptomics data.

2. Related Work

Several recent studies have attempted to address challenges in spatially aware single-cell analysis:
- scBiGNN (Zhou et al., 2023) introduced bilevel GNNs for cell-type classification but lacked spatial context.
- SpaGCN (Hu et al., 2021) leveraged graph convolutional networks (GCNs) for spatial transcriptomics but failed to capture long-range dependencies.
- STAGATE (Chen et al., 2022) utilized self-supervised learning on spatial transcriptomics but did not integrate scRNA-seq data.
- Transformer-based Models (Ji et al., 2021) have been applied in genomics but not for spatially informed cell-type annotation.

Existing models either fail to incorporate both transcriptomic and spatial information effectively or lack a framework that models both local and long-range spatial dependencies. SpatialTransformerGNN aims to bridge this gap by combining GNNs for local neighborhood modeling with transformers for global spatial pattern recognition.

3. Research Objectives

This project aims to develop a novel transformer-augmented bilevel graph neural network (SpatialTransformerGNN) for integrating scRNA-seq and spatial transcriptomics data, enhancing the accuracy of spatially informed cell-type classification.

Specific objectives include:

1. Constructing a bilevel graph framework that models both gene-gene and cell-cell interactions.

2. Enhancing spatial representation learning through transformer-based attention mechanisms.

3. Developing a cross-modal fusion mechanism to align and integrate scRNA-seq and spatial transcriptomics embeddings.

4. Benchmarking against existing models using publicly available datasets and evaluating classification performance.

4. Methodology

4.1. Graph Construction

- Gene-Gene Interaction Graph: Constructed using expression correlation networks from scRNA-seq data.

- Cell-Cell Spatial Graph: Built from spatial transcriptomics spot locations to model physical proximity.

4.2. Transformer-Augmented Representation Learning

- Local Feature Learning (GNNs): Captures fine-grained cell-cell and gene-gene relationships.

- Global Feature Learning (Transformers): Captures long-range spatial dependencies within tissue microenvironments.

- Cross-Modal Attention: Aligns scRNA-seq and spatial transcriptomics embeddings to enhance integration.

4.3. Model Training and Evaluation

- Datasets: Publicly available multi-omics datasets such as STOmicsDB, CROST, and the Human Cell Atlas.

- Evaluation Metrics: Accuracy, F1-score, neighborhood preservation, and spatial coherence.

5. Expected Challenges and Mitigation Strategies

Challenge	Mitigation Strategy
High computational cost of Transformer models	Utilize cloud GPUs (I have GPU Resources at home) and model pruning techniques
Alignment issues between scRNA-seq and spatial transcriptomics	Implement cross-modal contrastive learning for better feature alignment
Data sparsity in ST datasets	Apply graph-based imputation methods to infer missing gene expression values

6. Project Timeline

Week	Task
Week 1 (March 1-7, 2025)	Conduct literature review, finalize dataset selection
Week 2 (March 8-14, 2025)	Preprocess scRNA-seq and spatial transcriptomics data
Week 3 (March 15-21, 2025)	Implement bilevel graph construction (gene-gene, cell-cell graphs)
Week 4 (March 22-28, 2025)	Develop transformer-enhanced spatial embedding layer
Week 5 (April 1-7, 2025)	Train baseline GNN model and evaluate performance
Week 6 (April 8-14, 2025)	Fine-tune transformer-GNN architecture, optimize hyperparameters
Week 7 (April 15-21, 2025)	Perform model validation on external datasets, write initial report
Week 8 (April 22-30, 2025)	Finalize report and prepare presentation

Final Presentation: April 30, 2025

Final Report Submission: April 30, 2025

7. Conclusion

This research proposes SpatialTransformerGNN, a transformer-augmented bilevel graph neural network that integrates scRNA-seq and spatial transcriptomics data for cell-type classification. By addressing the limitations of existing GNNs and transformer-based models, this approach aims to provide a more accurate and biologically meaningful representation of tissue architecture at the single-cell level. The proposed model has potential applications in computational bioinformatics, precision medicine, and spatially resolved single-cell analysis.

8. References

Chen, W. et al. (2022). STAGATE: Self-supervised learning for spatial transcriptomics. Bioinformatics, 38(4), 1063–1071.

Hu, J. et al. (2021). SpaGCN: Integrating gene expression with spatial information using graph neural networks. Nature Communications, 12(1), 5249.

Ji, Y. et al. (2021). DNABERT: Pre-trained transformers for DNA sequence classification. Bioinformatics, 37(15), 2112–2118.

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