Inferring Single-Cell Spatial Transcriptomics from H&E Histology via Graph Deep Learning Approaches

Ashank Shah
Sunset High School

Dartmouth Health

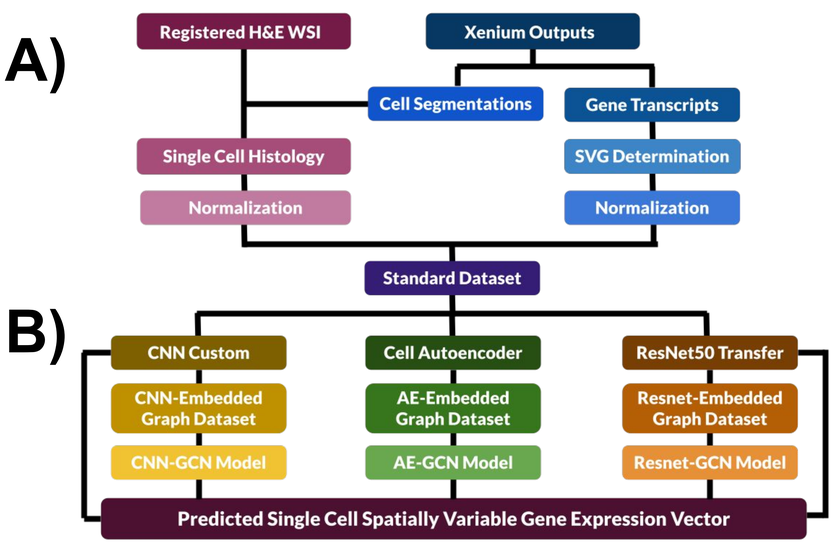
ABSTRACT

- Single cell **spatial transcriptomics (ST)**, **facilitates enhanced clinical and research outcomes,** but access is limited and costly
- **H&E histology** is an **accessible data** format that clearly delineates morphological features in tissue
- We explore machine-learning based methods with standard and graph networks to **infer single cell gene expression from H&E histology**
- We find that graph approaches that encapsulate spatially contextual information enhance ST inference
- Urge **further research scaling the developed approaches to more diverse and larger datasets** for more robust results

INTRODUCTION

- **H&E staining** is an extremely **common** tissue staining practice that clearly **distinguishes nucleic and cytoplasmic boundaries** in the tissue which is often sufficient for unimodal diagnoses
- However, for complex tasks including biomarker identification, tumor microenvironment studies, and complex diagnoses/prognoses, spatially localized gene expression data, or **spatial transcriptomics data, is an informative alternative**
  - **ST data** remains **inaccessible** due to **costs** ($3600 per slide) and often required **specialized expertise** in operation
- Prior literature has demonstrated **utility of deep-learning approaches** in untraditional derivation of gene expression data from histology **on spot level granularity** (e.g. Visium prediction)
  - Single-cell granularity spatial transcriptomics, such as Xenium generation, remains largely unexplored
- **Graph neural networks** are a modeling approach that leverage message passing layers to incorporate contextual information to make more informed predictions
  - Have demonstrated utility in cell graphs for more informed diagnoses and potential in gene expression inference
- We propose a **computational pipeline** for single cell Xenium gene expression vector prediction (specifically prediction of spatially-variable genes) that experiments with both localized and relatively global-based prediction approaches

Figure 1. Methodology Workflow for Gene Expression Prediction: **A)** dataset preprocessing and construction; **B)** modeling approaches



METHODOLOGY

- **Dataset Preprocessing & Construction**
  - **Histology:** Extract single cell H&E histology bounding boxes using registered segmentation masks from Xenium output
  - **Gene Expression:** Patch-level vector aggregation for spatially variable gene (SVG) determination. Vector normalization and log transformation
- **Feature Extraction & Base Modeling Approaches**
  - **Convolutional Neural Network:** 4 layer convolutional neural network approach, followed by 2 dense fully-connected layers. Intermediate dense layer size 128 as latent representation for future graph representations
  - **Fine-Tuned ResNet50:** Transfer learning from pre-trained ResNet50 on ImageNet fine-tuned to cell dataset and task. Additionally experiment with resizing input to 224x224. Modified model head to predict 10 length vector with intermediate dense layer size 128 for latent representation
  - **Autoencoder:** Specialized model for latent representation extraction with key morphological features to reconstruct cell histology
- **Graph Modeling Approaches**
  - **Graph Dataset:** Construct patch-level geometric objects with latent representation embeddings from CNN, ResNet50, and AE, targets as SVGs, and edges constructed via k-nearest neighbors algorithm (k=10)
  - **Graph Convolutional Models:** Employ message passing layers to train three graph convolutional network architectures aware of spatial context using distinct graph datasets with various embedding methods
- **Evaluation**
  - **Quantitative:** Calculate Spearman Correlation Coefficient for all model architectures
  - **Qualitative:** Observe relationship between predicted and truth gene activity

RESULTS

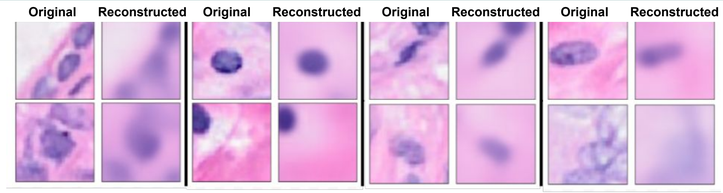


Figure 2. Original v.s. Reconstructed Cells via Autoencoder

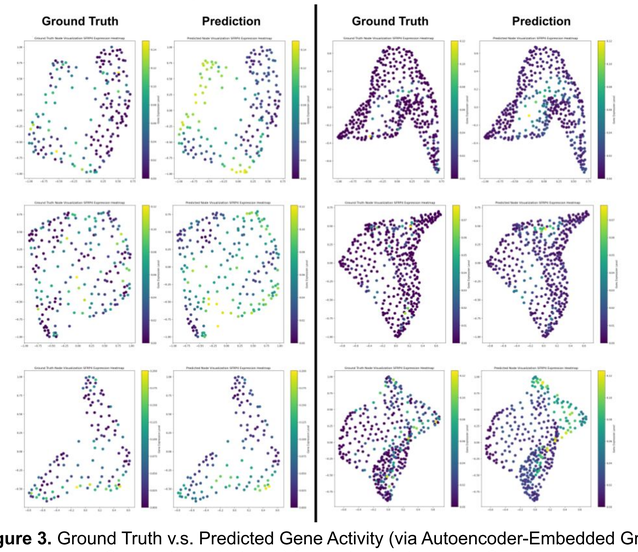
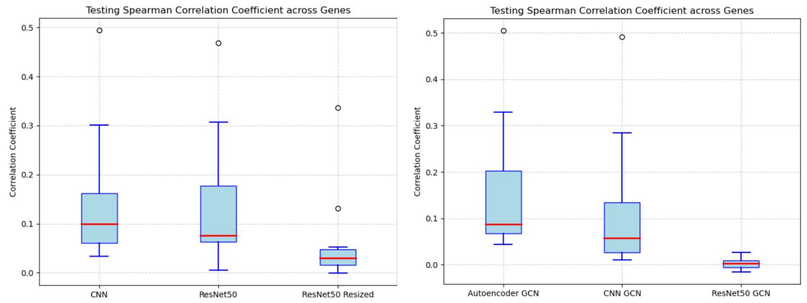


Figure 3. Ground Truth v.s. Predicted Gene Activity (via Autoencoder-Embedded Graph Convolutional Network) for best predicted gene: SFRP4

RESULTS



Model Architecture	Mean Testing Spearman Correlation Coefficient
Standard Convolutional Neural Network	**0.151**
Fine-Tuned ResNet50	**0.144**
Fine-Tuned ResNet50 with Resizing	**0.066**
Autoencoder-Embedded GCN	**0.163**
CNN-Embedded GCN	**0.124**
ResNet50-Embedded GCN	**0.002**

CONCLUSION

- **Key Findings & Impact**
  - Despite the limited dataset leveraged in this study, deep learning demonstrates promise in single-cell gene expression inference
  - The superior performance of the autoencoder-embedded GNN model, with a Spearman Correlation Coefficient of approximately 0.163, in comparison to a standard Convolutional Neural Network limited to localized cellular information, suggests that meaningful insights can be derived by incorporating relatively global structural information
  - We anticipate that scaling the developed solution will provide more robust genomics predictions and work towards more accessible, enhanced clinical and research outcomes.
- **Limitations**
  - Registered data only available for one patient, lack of training diversity and scale; lack of external assessment cohort
  - Potential semi-dependency between training, validation, and testing sets deriving from same patient
- **Future Directions**
  - Scaling current model architectures to larger and more diverse datasets for most robust predictions and attempting to predict larger portion of gene profile
  - Refining modeling approaches: experimenting with different latent sizes, multi-scale node embedding approaches, cross modal contrastive autoencoder-based encoding methods
  - Developing YOLO model to complete pipeline from H&E WSI to Xenium ST
- **Data and Code Availability**
  - Data openly sourced from 10x Genomics platform
  - Code privately at: https://github.com/ashankshah/xenium_inference
- **Acknowledgements:** Zarif Azher, Gokul Srinivasan, Dr. Joshua Levy, Emerging Diagnostics and Investigative Technologies Lab
- **References:** https://tinyurl.com/ashankxeniumreferences

edit.