Predicting Proximity to Pathology for Single-Cell Data in Alzheimer's Disease

1. Understanding Alzheimer's Disease:

- One of the *most impactful* neurodegenerative diseases
- Build up of harmful proteins in the brain (amyloid plaque)
- No cure yet → need more research on a cellular level

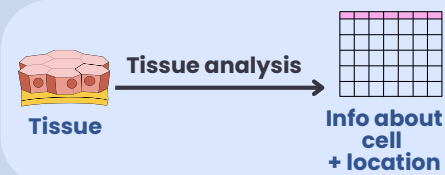## Methods for observing gene expressions

Single-cell RNA-seq (scRNA-seq):
- Provides detailed analysis of the gene expressions in a cell
- In the process, loses spatial context of the cell :(

Spatial Transcriptomics:
- Provides less details than scRNA-seq for single cells
- Preserves spatial location within tissue - can observe cell-cell interactions

Can we have the best of both worlds?

2. Research Question:

Can we predict a cell's distance to nearest plaque from single-cell RNA data?
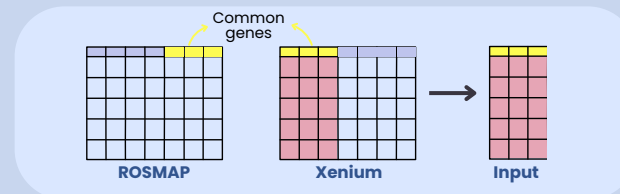
3. Data:

Focus on microglia - immune cells that cluster around plaque

- **ROSMAP Microglia** [1]- single-cell RNA dataset
- **Xenium** [2]- spatial transcriptomics dataset

4. Predicting distance to plaque from single-cell data

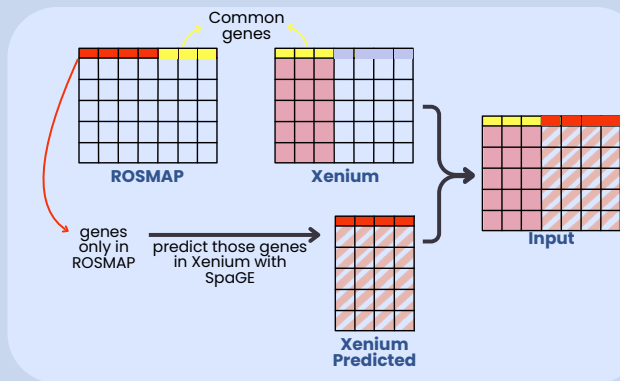### Model 1: Predict distance using shared genes across datasets

1. Align datasets by selecting common genes

2. Weighted k-Nearest Neighbor Regressor

Model 2: Predict distance using full gene set from scRNA-seq dataset

1. Predict missing genes in Xenium with integration algorithm SpaGE [3] and combine with shared genes

2. Weighted k-Nearest Neighbor Regressor

5. Predictions

- Measure of accuracy - Mean Absolute Error (**MAE**) in μm
- Error threshold: **200 μm** (max distance for cell-cell signals [4])

- $MAE_{Model\ 1} = 119μm$, $MAE_{Model\ 2} = 125μm$
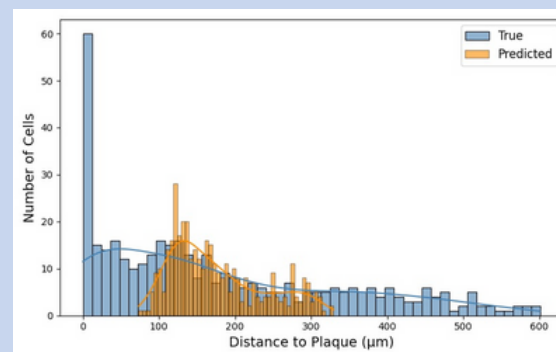- **Model 1** performs better with sufficiently low error

Figure 1: Distribution of actual vs. predicted distances to plaque. The range of predictions is smaller and mainly captures mid-distance values.
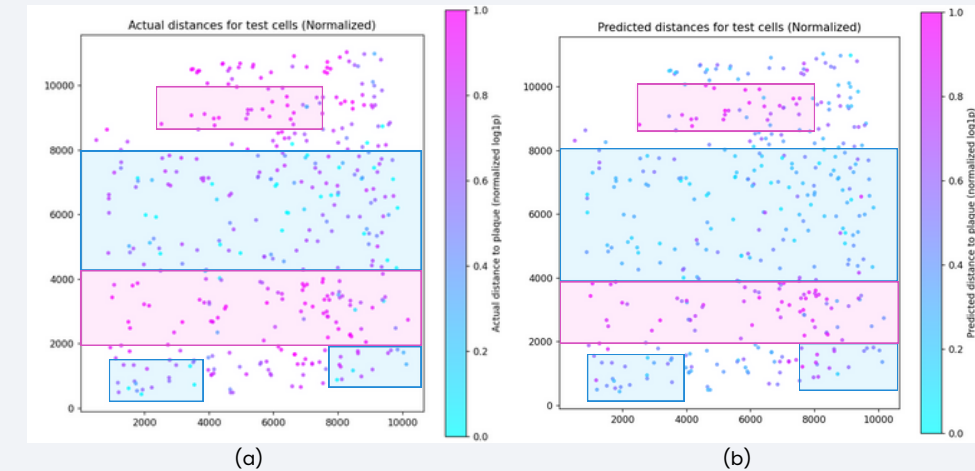

Figure 2: Spatial distribution in original coordinate space, colored by (a) actual and (b) predicted normalized distances to the nearest plaque. Colored rectangles highlight regions dominated by cells at similar distances - blue for cells close to plaque, pink for far. The correspondence in spatial gradients illustrates that the model preserves spatial patterns of relevant proximity.

6. Main Genes

- *APOE* - cholesterol transportation within bloodstream; recognized as a major genetic risk factor for Alzheimer's Disease [5].
- *LYVE1* - responsible for lymphatic drainage, has no direct link to AD; Spearman correlation between *LYVE1* expression and predicted distance is -0.38 → low *LYVE1* expression means closer to plaque.
- *SLC17A7* - neurotransmission in the brain; Spearman correlation between *SLC17A7* expression and predicted distance is -0.24 → low SLC17A7 expression means closer to plaque.

7.Conclusion & Future Work:

- Model that predicts distance to nearest plaque for single-cell data based on shared genes
- Identified *APOE, LYVE1, SLC17A7* as potentially associated with Alzheimer's Disease and microglial clustering around plaque.
- To further investigate:
  - Improve algorithm performance for close-range predictions - a classifier that accurately predicts a cell's overlap with plaque region
  - Use more data from different patients to analyze other pattern

References:
[1] AD Knowledge Portal, ROSMAP Study - AD Knowledge Portal, 2024. [Online]. Available: https://adknowledgeportal.org. [Accessed: May 12, 2025].
[2] Provided by Gonçalves Lab, "Gonçalves Lab at TU Delft." [Online]. Available: https://goncalveslab.tudelft.nl.
[3] Tamim Abdelaal, Soufiane Mourragui, Ahmed Mahfouz, and Marcel J T Reinders. SpaGE: Spatial Gene Enhancement using scRNA-seq. *Nucleic Acids Research*, 48(18):e107, October 2020.
[4] Sarah K. Longo, Ming G. Guo, Anna L. Ji, and Paul A. Khavari. Integrating single-cell and spatial transcriptomics to elucidate intercellular tissue dynamics. *Nature Reviews Genetics*, 22(10):627–644, 2021.
[5] Yun Chen, M. Seda Durakoglugil, Xue Xian, and Joachim Herz. Apolipoprotein e: Structural insights and links to alzheimer disease pathogenesis. *Neuron*, 109(2):205–221, 2021.

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