Single-cell Deep Learning in Alzheimer's Disease

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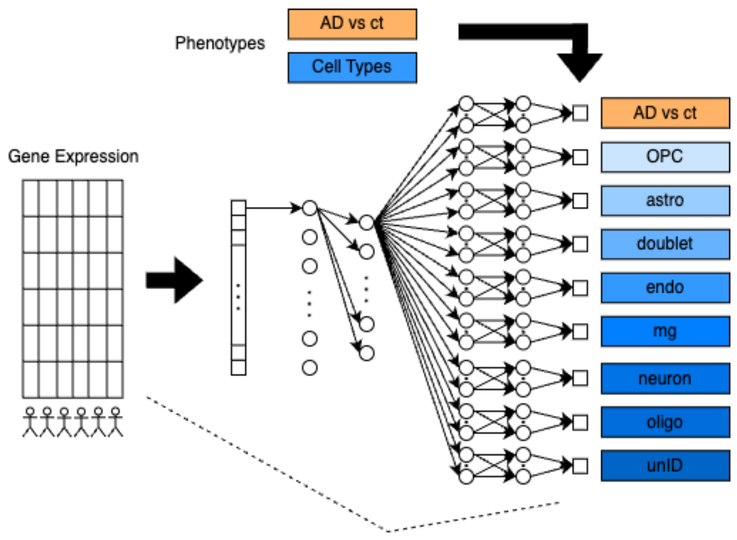
Introduction / Background

- **Alzheimer's Disease (AD)** is the most common form of dementia and the 7th leading cause of death in the United States. In the United States alone, approximately 6.9 million people currently live with AD, and this is projected to rise to nearly 14 million by 2060.
- Two major challenges to treating AD are **the significant heterogeneity** in clinical and biological presentation and a **limited understanding of its molecular mechanisms**
- Unlike traditional bulk RNA sequencing, **single-cell RNA sequencing (scRNA-seq)** enables the dissection of complex cellular environments, providing insights into the diversity of cell types, states, and their contributions to AD pathology.

Model: Single-cell MD-AD (scMD-AD)

- We applied deep neural networks to scRNA-seq measurements by adapting Beebe-Wang et al's MD-AD framework for **joint learning of AD classification and cell type classification** [1].
- The framework aims to address the challenge of linking molecular heterogeneity to clinical phenotypes, offering a scalable and effective solution for analyzing high-dimensional single-cell data in AD research and other neurodegenerative diseases.
- This version of scMD-AD was trained on scRNA-seq measurements taken from **entorhinal cortex samples** of control and AD individuals (n=6 per group) [2].
- A significant challenge in working with scRNA-seq measurements involves addressing overdispersion, dropouts, batch effects, filtering noise, and identifying relevant features. As a result, careful preprocessing of the data was required, all of which was done using Scanpy and AnnData.



Previous Work

- This project builds primarily upon the Multi-task Deep learning for Alzheimer's Disease neuropathology (**MD-AD**) proposed by Beebe-Wang et. al, which utilizes a unified framework to jointly learn neuropathological measures of AD from bulk RNA sequencing [1].
- Mathys et. al, used scRNA-seq to profile gene expression of AD, conducting differential expression and pathway analyses to investigate associated molecular mechanisms. Findings were validated using immunohistochemistry and fluorescence in situ hybridization [3].

Future Directions

- Train and evaluate scMD-AD on **larger, more complex datasets**, such as those from the ssREAD database or the SEA-AD dataset [4, 5]

Braak staging | Thal phasing | CERAD score | Dementia | Comorbidities

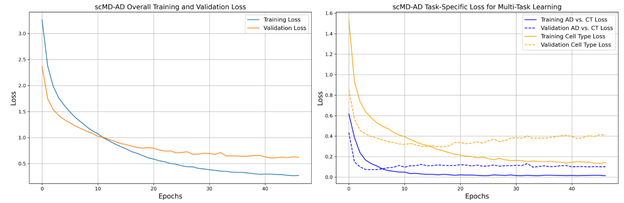
* Phenotypes of Interest from SEA-AD dataset

- Assess scMD-AD performance **across species** (e.g., mouse models of AD) and **across brain regions** (e.g., prefrontal cortex)
- Incorporating **explainable AI techniques**, such as the Integrated Gradients algorithm, to estimate the importance of input features on the model's predictions

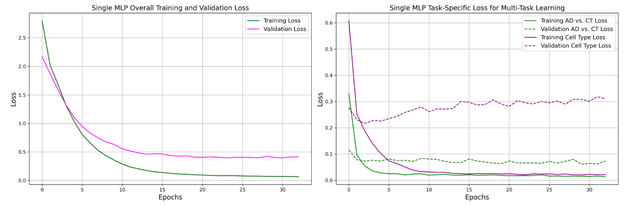
Results

- scMD-AD achieved a **validation loss of 0.6079** at epoch 42, with strong AD classification performance (0.1030) and effective cell type classification (0.3771).
- MLP converged faster and achieved lower cell type classification loss but likely will struggle with more complex datasets that require capturing nuanced relationships between tasks

scMD-AD Loss Plots



Single MLP Loss Plots



References

[1] Beebe-Wang, N., Celik, S., Weinberger, E. et al. Unified AI framework to uncover deep interrelationships between gene expression and Alzheimer's disease neuropathologies. Nat Commun 12, 5369 (2021).

[2] Grubman, A., Chew, G., Ouyang, J.F. et al. A single-cell atlas of entorhinal cortex from individuals with Alzheimer's disease reveals cell-type-specific gene expression regulation. Nat Neurosci 22, 2087–2097 (2019).

[3] Mathys, H., Davila-Velderrain, J., Peng, Z. et al. Single-cell transcriptomic analysis of Alzheimer's disease. Nature 570, 332–337 (2019).

[4] Wang, C., Acosta, D. & McNutt, M. et al. A single-cell and spatial RNA-seq database for Alzheimer's disease (ssREAD). Nat Commun 15, 4710 (2024).

[5] Gabitto, M.I., Travaglini, K.J., Rachleff, V.M. et al. Integrated multimodal cell atlas of Alzheimer's disease. Nat Neurosci (2024).