A deep generative model for capturing cell to phenotype relationships

Ethan Weinberger*, Patrick Yu*, Su-In Lee

1. Motivation

- Single-cell cohorts now commonly collected at the **patient level** [1] to uncover **molecular bases** of patient **phenotypes**

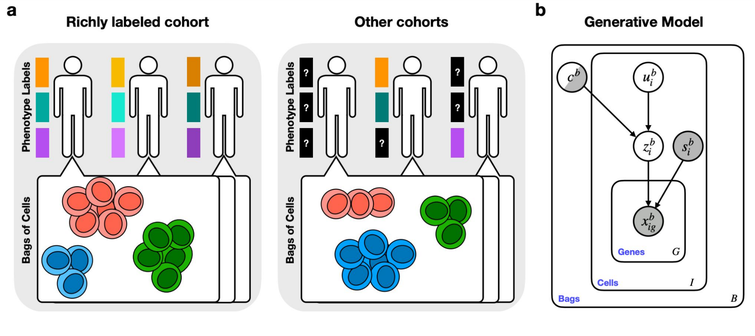
- Challenges:
  1) Phenotypes may be **missing** for some patients,
  2) Some cells (e.g. distinct cell types) may be more **important** than other cells for phenotype prediction

2. milVI

- milVI **infers** patient phenotypes from single-cell profiles

- milVI learns embeddings for each cell in a patient, aggregated via **attention-based multiple instance learning (ABMIL)** [2] to form a single, unified patient embedding for phenotype prediction tasks

- Attention weights in the ABMIL module provide **cell-level interpretability** by quantifying the importance of a given patient cell towards predicting a phenotype of interest



3. Evaluation

- milVI was compared against alternative approaches for patient phenotype prediction:
  1) **LR (Cell-level)**: Train logistic regression classifier to predict phenotypes for individual cells, then average phenotype predictions across cells in a patient
  2) **LR (Pseudobulk):** Train/test logistic regression classifier to predict phenotypes from patient psuedobulk data *(pseudobulk = average gene expression for all cells in a patient)*

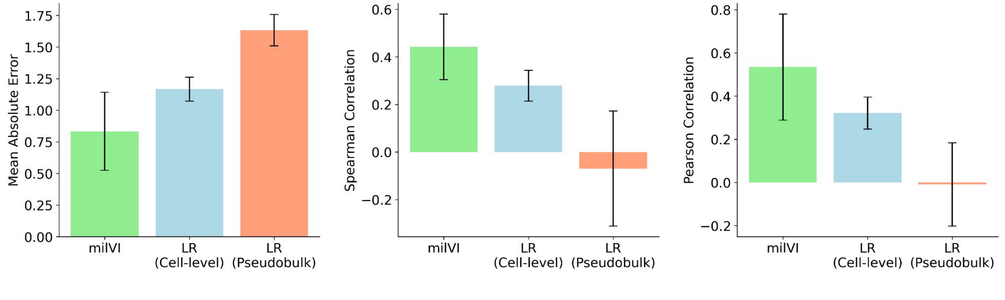
- Evaluated milVI & baselines on predicting **Braak staging** [3] in held-out Alzheimer's disease patients from [1] via 3 evaluation metrics: Mean Absolute Error (MAE), Spearman correlation, and Pearson correlation

4. Results

- Through all three evaluation metrics, milVI outperforms baseline approaches in predicting patients' Braak staging

- However, all methods exhibited high variances in performance, possibly due to overfitting on the small (48) number of patients

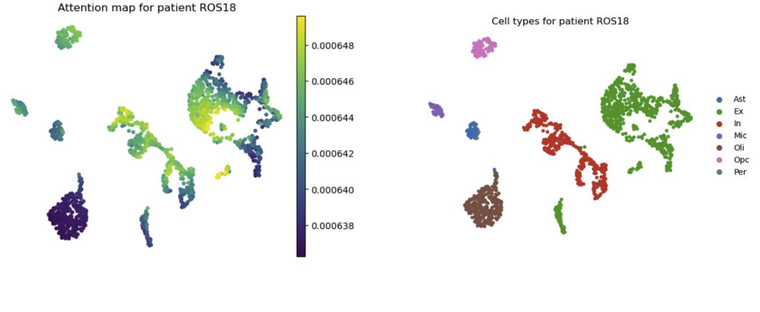
- milVI's attention scores highlight important cell subtypes towards phenotype prediction, which can help in facilitating future biological analysis/interpretation



5. Analysis and Future Work

- milVI provides an effective framework for inferring patient phenotypes from patient-level single-cell profiles

- Future work includes testing milVI's generalization capabilities on larger patient cohorts, as well as analyzing and interpreting the important cell subtypes detected by milVI (via attention scores)



References

[1] Hansruedi Mathys, Jose Davila-Velderrain, Zhuyu Peng, Fan Gao, Shahin Mohammadi, Jennie Z Young, Madhvi Menon, Liang He, Fatema Abdurrob, Xueqiao Jiang, et al. Single-cell transcriptomic analysis of Alzheimer's disease. *Nature*, 570(7761):332–337, 2019.

[2] Maximilian Ilse, Jakub Tomczak, and Max Welling. Attention-based Deep Multiple Instance Learning. In *International Conference on Machine Learning,* pages 2127–2136. PMLR, 2018.

[3] Heiko Braak, Irina Alafuzoff, Thomas Arzberger, Hans Kretzschmar, and Kelly Del Tredici. Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. *Acta Neuropathologica* 112, 389–404 (2006).