



Single-Cell Environment and Proximal Trajectory Inference using Collaborative Agent Reinforcement

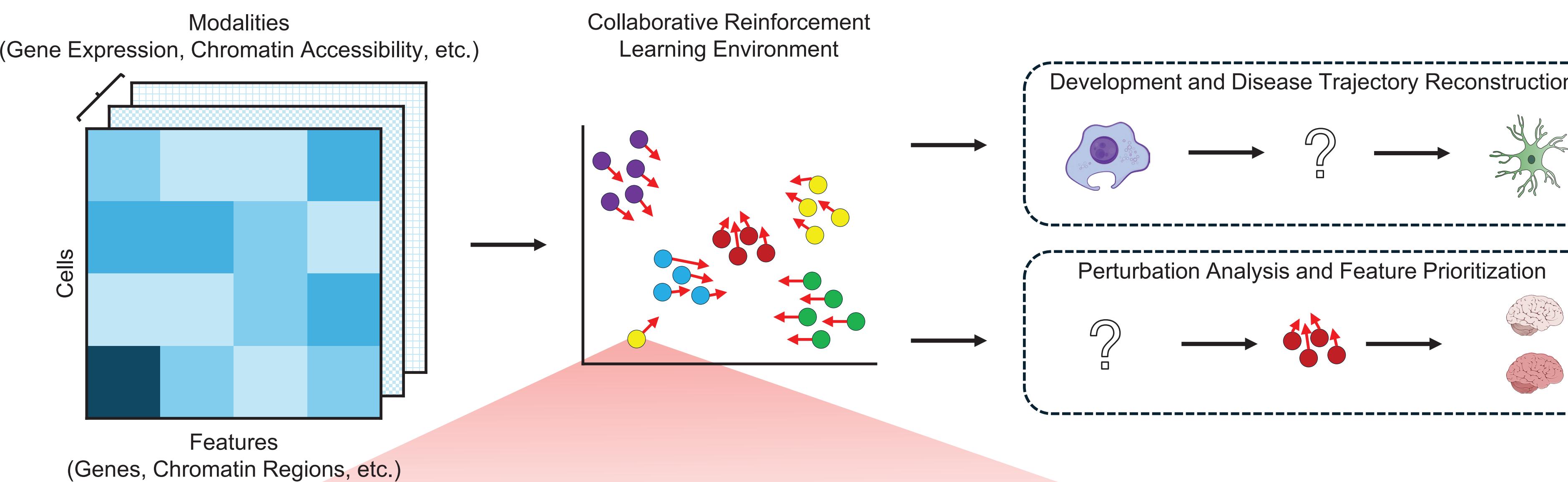
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Abstract

Recent techniques enable functional characterization of single-cells, which allows the study of cellular and molecular mechanisms in complex biological processes including cell development. Many methods have been developed to utilize these single-cell datasets to reveal cell developmental trajectories such as dimensionality reduction and pseudotime. However, these methods generally produce static snapshots of the data, challenging a deeper understanding of the mechanistic dynamics underlying cell development. To address this, we have developed scEPTIC-RL, a multi-agent reinforcement learning model to recapitulate the dynamic progression of cells during development. scEPTIC-RL takes single-cell data, either single or multimodality, and trains a collaborative reinforcement learning model that governs cell-cell dynamic interactions driving development. Particularly, it models single cells as individual agents which coordinate progression on a latent space through interacting with neighboring cells. The trained model can further prioritize cellular features and in-silico predict the dependencies of cell development from feature perturbations (e.g., gene knockout).

scEPTIC-RL Model Usage and Architecture



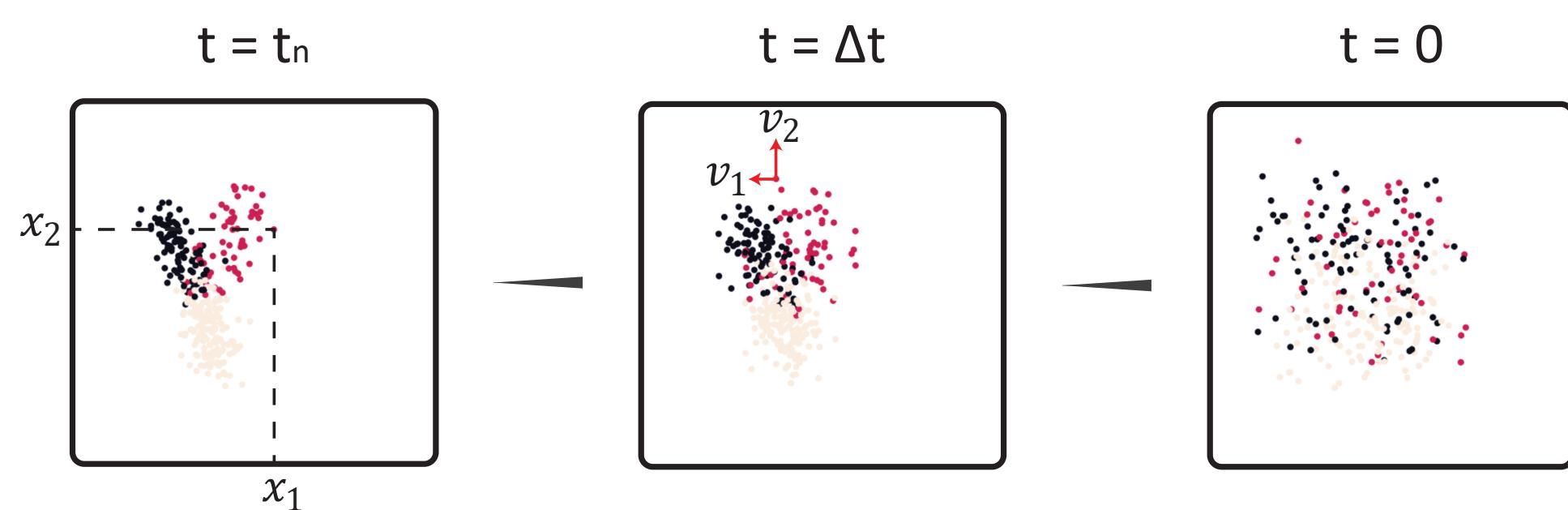
Algorithm

$$L_{\text{CLIP}}(\theta) = \min \left(\frac{\pi_\theta(a_t|s_t)}{\pi_{\theta_{\text{old}}}(a_t|s_t)} \hat{A}_t, \text{CLIP} \left(\frac{\pi_\theta(a_t|s_t)}{\pi_{\theta_{\text{old}}}(a_t|s_t)}, 1 - \epsilon, 1 + \epsilon \right) \hat{A}_t \right)$$

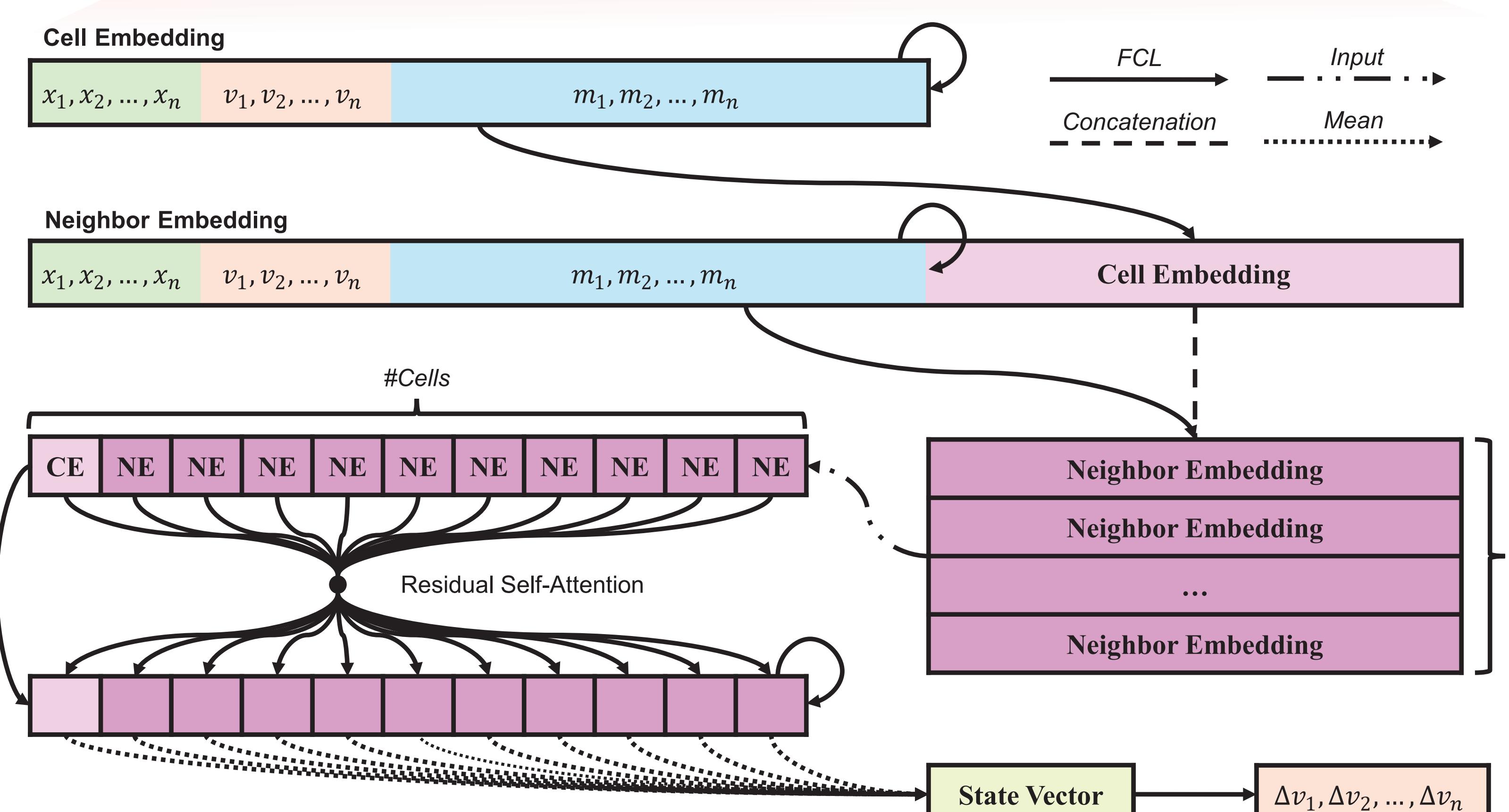
$$R_D^{t+1} = D^{t+1} - D^t, \quad D^t = \sum_{i=1}^m (\text{dist}(M_i) - \text{dist}(X^t))^2$$

$$[R_B^t]_i = \begin{cases} -1 & |x_j| = 1 \text{ for some } j \\ 0 & \text{else} \end{cases}, \quad R_V^t = -\sum_{i=1}^{n_d} (v_i^t)^2, \quad R_A^t = -\sum_{i=1}^{n_d} (a_i^t)^2$$

Simulation Data

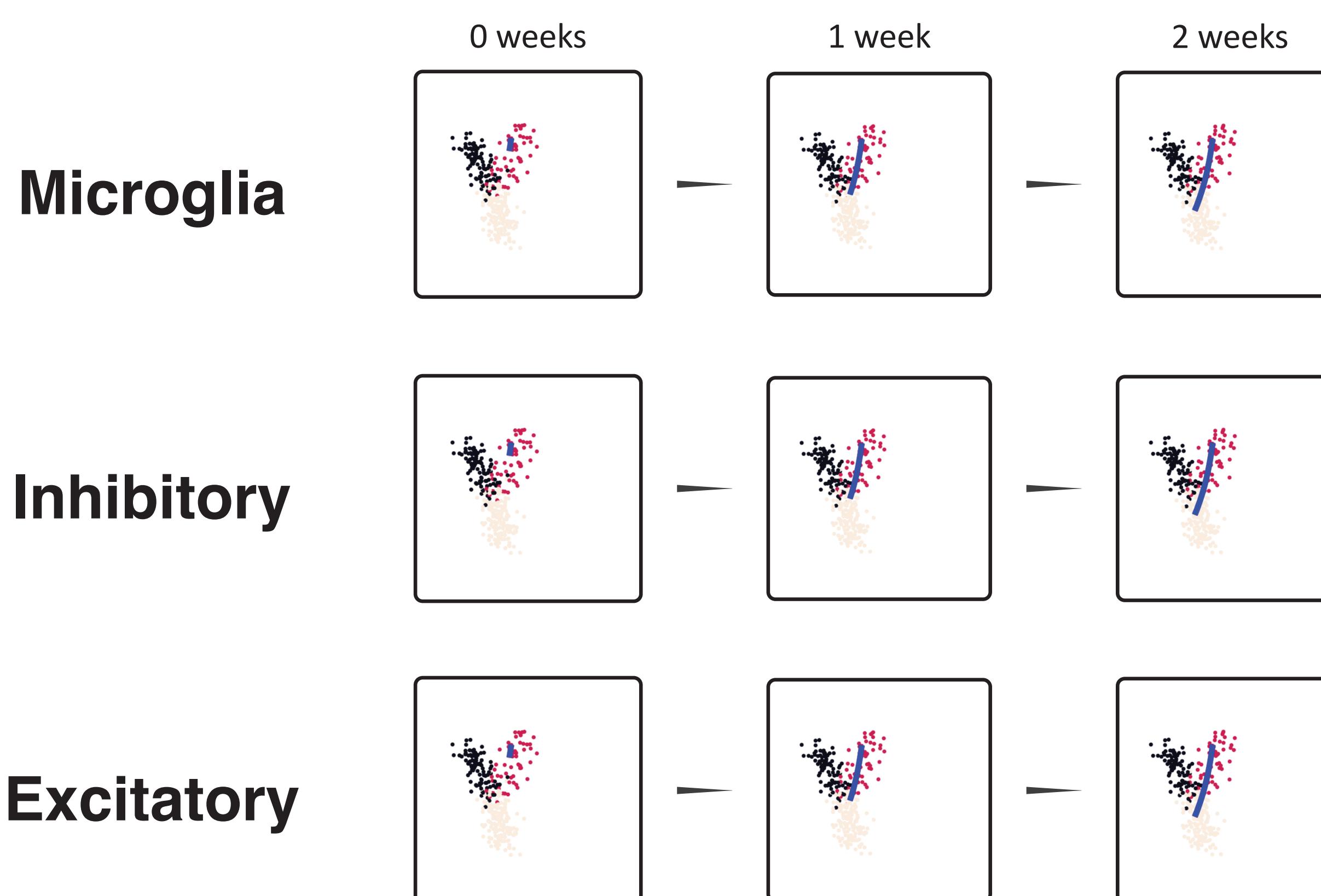


scEPTIC-RL is able to effectively generalize from a 50 cell training set to 300 cells and reconstruct a cell type-separated latent space with no annotation data provided.

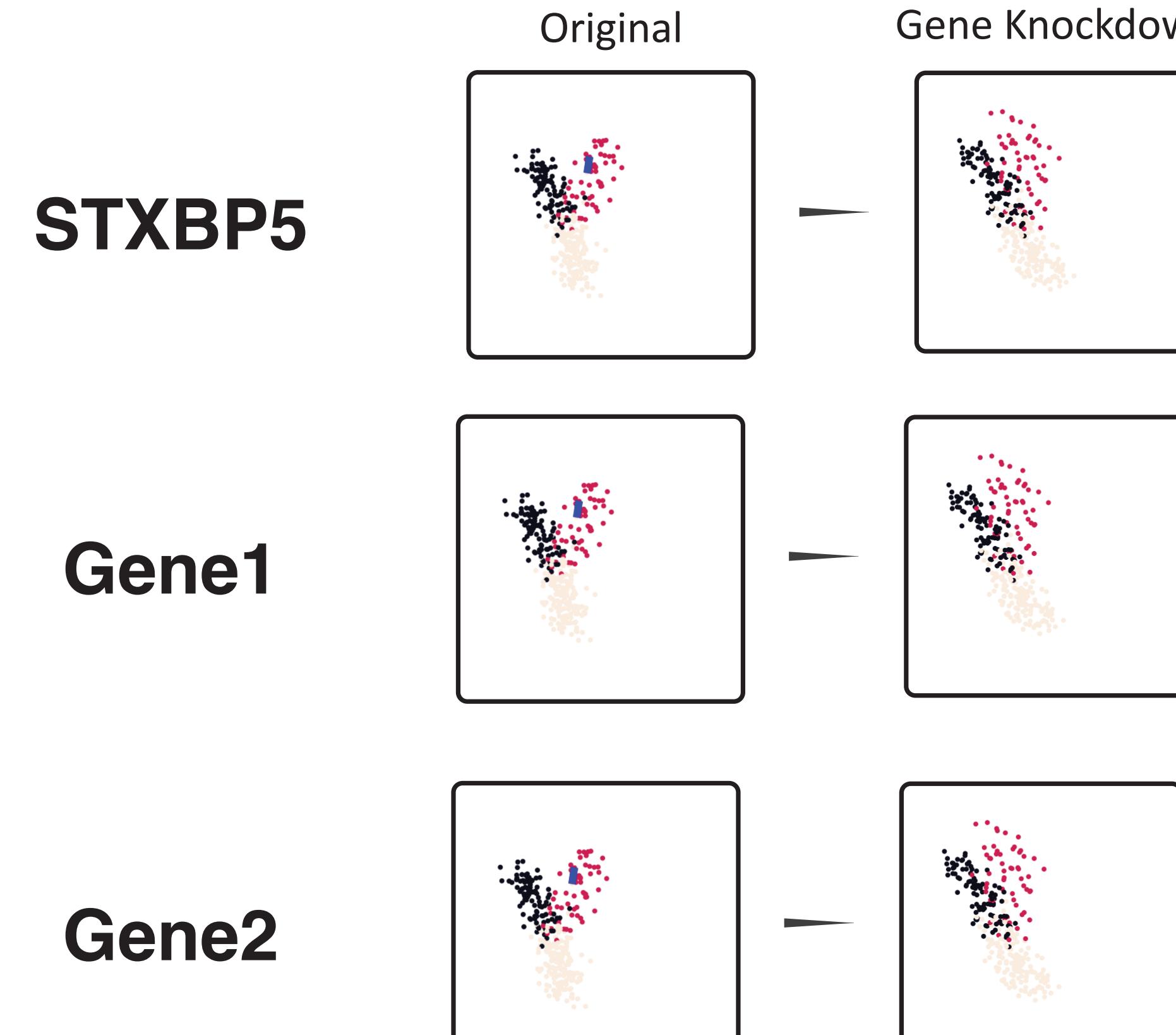


Datasets

Recovery of Disease Progression Trajectories



Feature Perturbation Analysis



Conclusions

- ★ scEPTIC-RL is able to effectively separate cells by phenotype, such as cell type
- ★ scEPTIC-RL reliably reconstructs cell developmental and disease progression trajectories
- ★ scEPTIC-RL consistently prioritizes genes and cell features important to development and phenotype

Overall, scEPTIC-RL provides reliable trajectory reconstructions for cell progression and disease development in an easily distributable and highly generalizable manner. Future applications include extension to further applications in disease development and imputation.

[1] Jie Liu, Yuanhao Huang, Ritambhara Singh, Jean-Philippe Vert, and William Stafford Noble. "Jointly Embedding Multiple Single-Cell Omics Measurements". en. In: Algorithms Bioinform 143 Sept. 2019.

[2] Alejandro E. Trevino, Fabian M'uller, Jimena Andersen, Lakshman Sundaram, Arwa Kathiria, Anna Shcherbina, Kyle Farh, Howard Y. Chang, Anca M. Pas, ca, Anshul Kundaje, Sergiu P. Pas, ca, and William J. Greenleaf. "Chromatin and gene-regulatory dynamics of the developing human cerebral cortex at single-cell resolution". In: Cell 184.19 (Sept. 2021), 50535069.e23, issn: 0092-8674, doi: 10.1016/j.cell.2021.07.039, url: <https://doi.org/10.1016/j.cell.2021.07.039>.

[3] Zhi-Jie Cao and Ge Gao. "Multi-omics single-cell data integration and regulatory inference with graph-linked embedding". In: Nature Biotechnology 40.10 (Oct. 2022), pp. 1454-1466, issn: 1546-1696, doi: 10.1038/s41587-022-01284-4, url: <https://doi.org/10.1038/s41587-022-01284-4>.