



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

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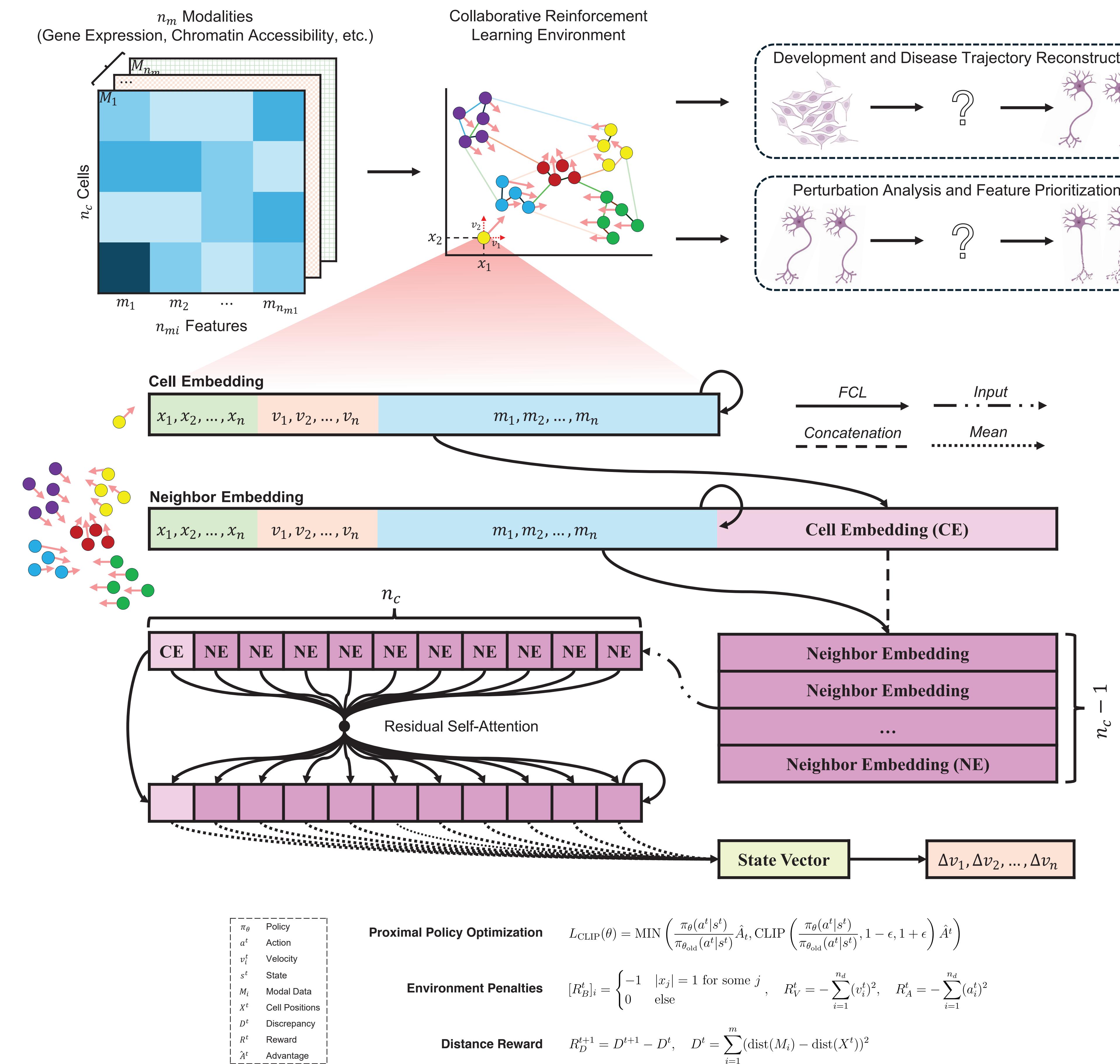
Abstract

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 (single-cell Environment and Proximal Trajectory Inference using Collaborative Reinforcement Learning), 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). We apply scEPTIC-RL to both simulation and real-word single-cell multimomics datasets including brain development and cancers, revealing potential novel mechanistic insights on gene expression and regulation in those complex developmental processes.

Datasets

Dataset Citation	Cells	RNA-seq	Features	ATAC-seq	Methylation
Liu et al. [1]	300		Simulation Data (1,000 + 2,000)		
Argelaguet et al. [2]	1,940	5,000		2,500	2,500
Trevino et al. [3]	8,981	34,104		19,836	
Cao and Gao [4]	9,190	28,930		241,757	

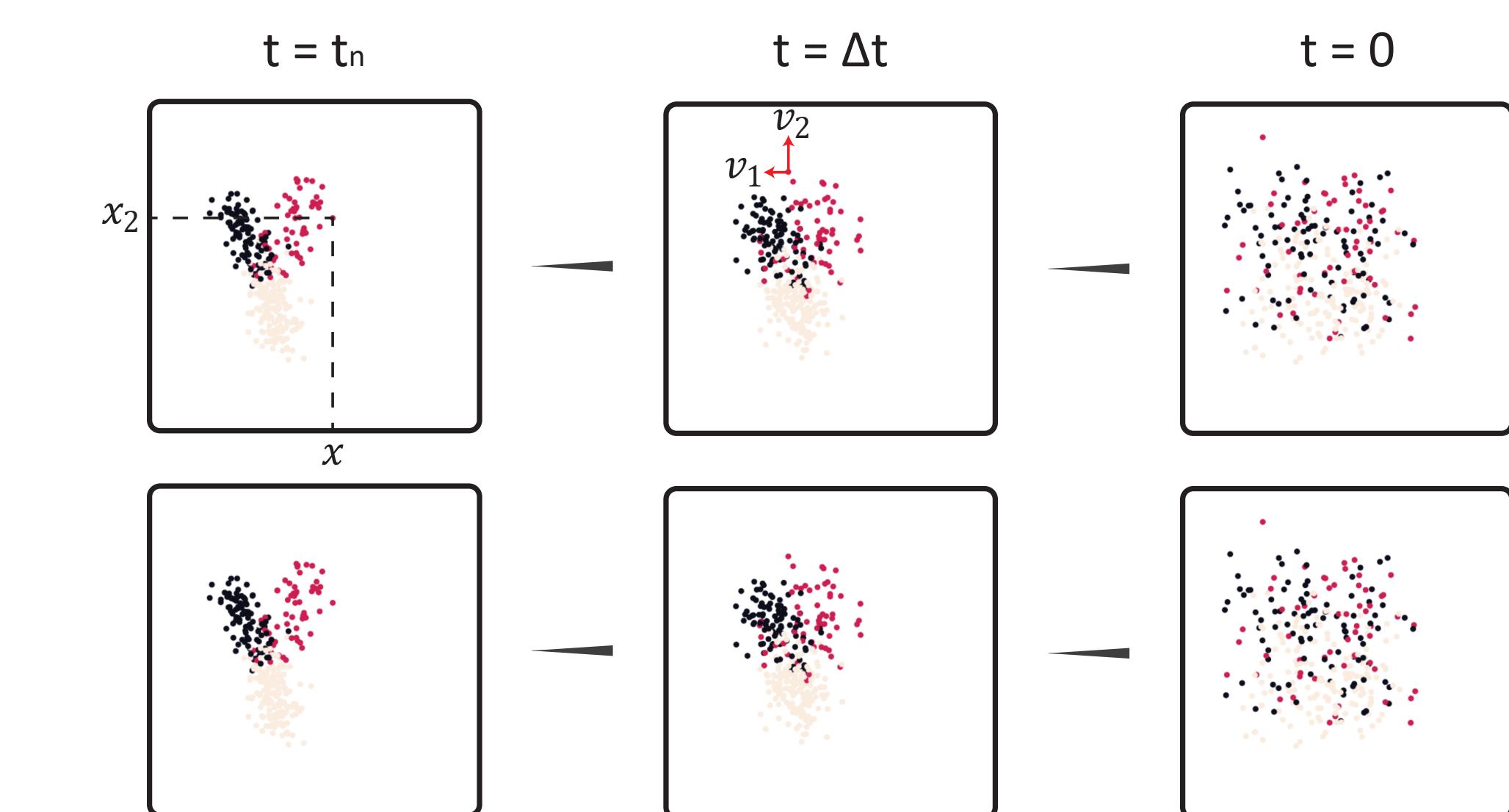
scEPTIC-RL Model Usage and Architecture



Algorithm

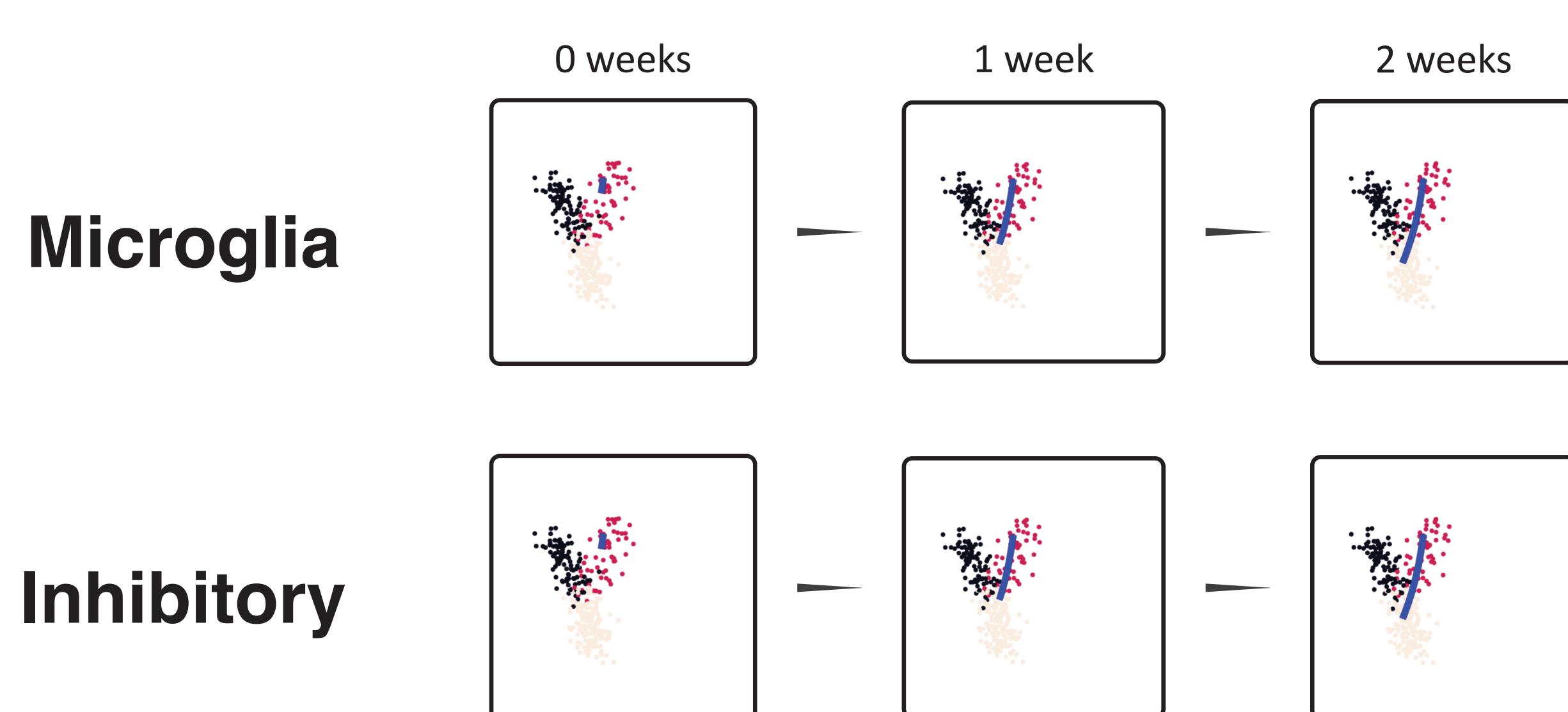
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Algorithm 1 scEPTIC-RL
Input:  $M_1, M_2, \dots, M_n$ 
Parameters: #max.timesteps, #update.timesteps, #epochs,  $\gamma$ 
Output:  $\pi_\theta$ 
1: Randomly initialize environment  $e$  and model  $\pi_\theta$ 
2:  $t \leftarrow 1$ 
3: for  $\# \text{max.timesteps}$  do
4:    $s^t \leftarrow e$ 's state
5:    $a^t \sim \pi_\theta(s^t)$ 
6:    $R^t, \text{terminal} \leftarrow$  perform actions  $a^t$  on environment  $e$ 
7:   Record  $(s^t, a^t, R^t)$ 
8:   if  $t = \# \text{update.timesteps}$  then
9:     Backpropagate rewards per episode using  $\gamma$  decay
10:    for  $\# \text{epochs}$  do
11:      Compute  $L_{CLIP}(\theta)$  from 2
12:      Backpropagate on  $\pi_\theta$ 
13:    end for
14:  end if
15:  if  $\text{terminal}$  then
16:    Reset environment
17:  end if
18:   $t \leftarrow t + 1$ 
19: end for
```

Simulation Data

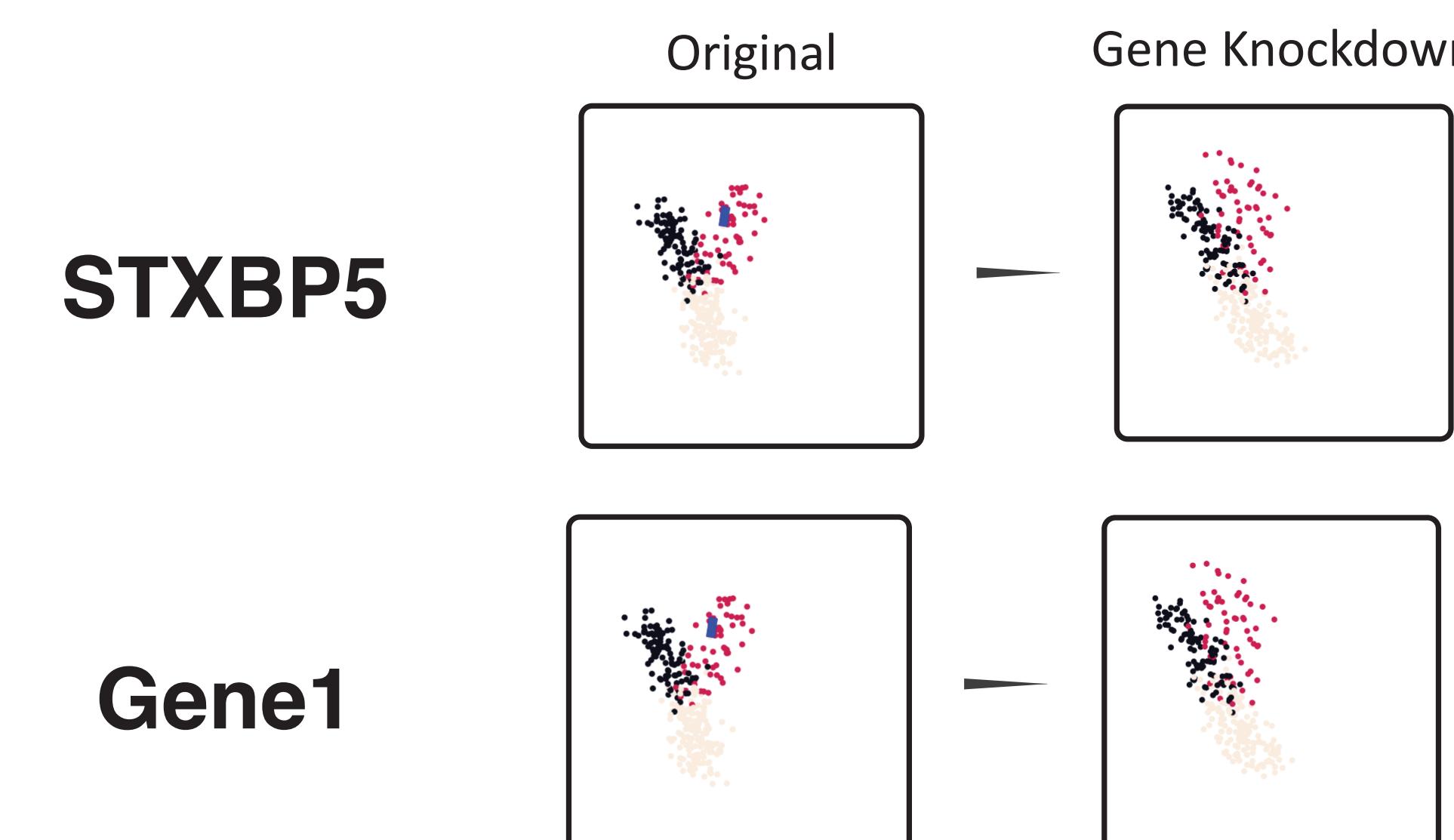


scEPTIC-RL is able to effectively generalize from a 50 cell training set to 300 cells and reconstruct a cell type-separated latent space with no annotation data provided.

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. Bioinformatics 143 (Sept. 2019).

[2] Alejandro E. Trevino, Fabian M'uller, Jimena Andersen, Lakshman Sundaram, Arwa Kathiria, Anna Shcherbinina, 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), 5053–5069.e23. issn: 0092-8674. doi: 10.1016/j.cell.2021.07.039. 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. 1458–1466. issn: 1546-1696. doi: 10.1038/s41587-022-01284-4. url: <https://doi.org/10.1038/s41587-022-01284-4>.