



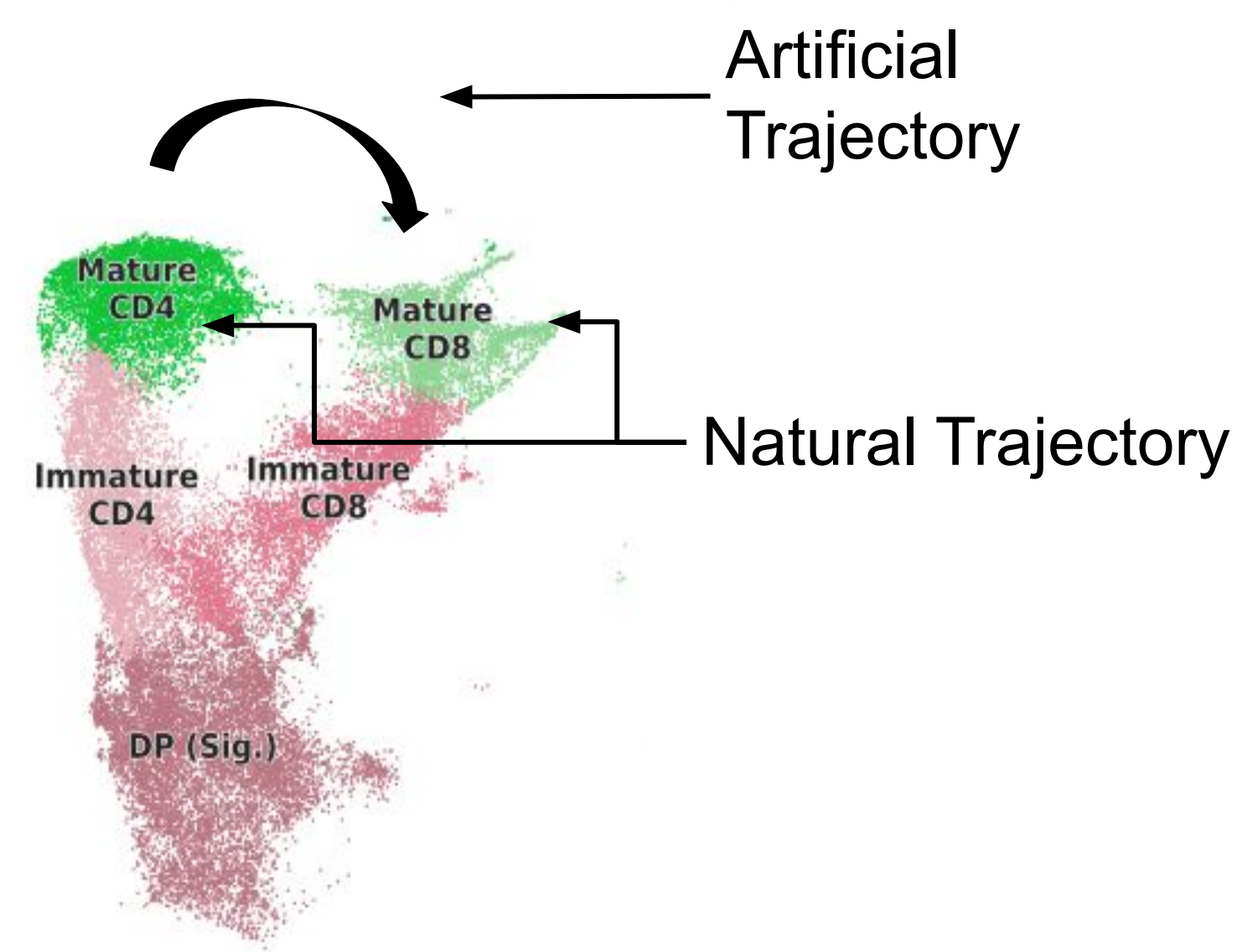
SYNTHETIC CELL TRAJECTORIES: COMPUTATIONAL MODELING OF PREDICTED CELL TRANSITIONS

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Introduction

- CD8 T cells (Killer/cytotoxic T cells) directly destroys virus-infected or cancerous cells. CD4 T cells (Helper T cells) coordinate immune responses by activating other immune cells.
- CD4 T cells and CD8 T cells has the same root (Double Positive), but during development, each cell must commit to one lineage [1].
- Normally, a CD4 cell will not later become a CD8 cell. This irreversibility is enforced by some regulatory genes.
- Given the strict separation of CD4+ and CD8+ lineages, **"Could a CD4+ T cell ever transform into a CD8+ T cell, and what changes would that involve?"** This is a "what-if" scenario – it does not occur naturally, but we can simulate it computationally.



- Why CD4 generation is important:
 - In diseases like cancer or viral infections, having more CD8+ T cells could be beneficial.
 - If we could safely reprogram CD4+ helper T cells into CD8+ T cells, it might boost immune responses.
 - Genes identified as drivers of the transition could be targets for drug discovery.

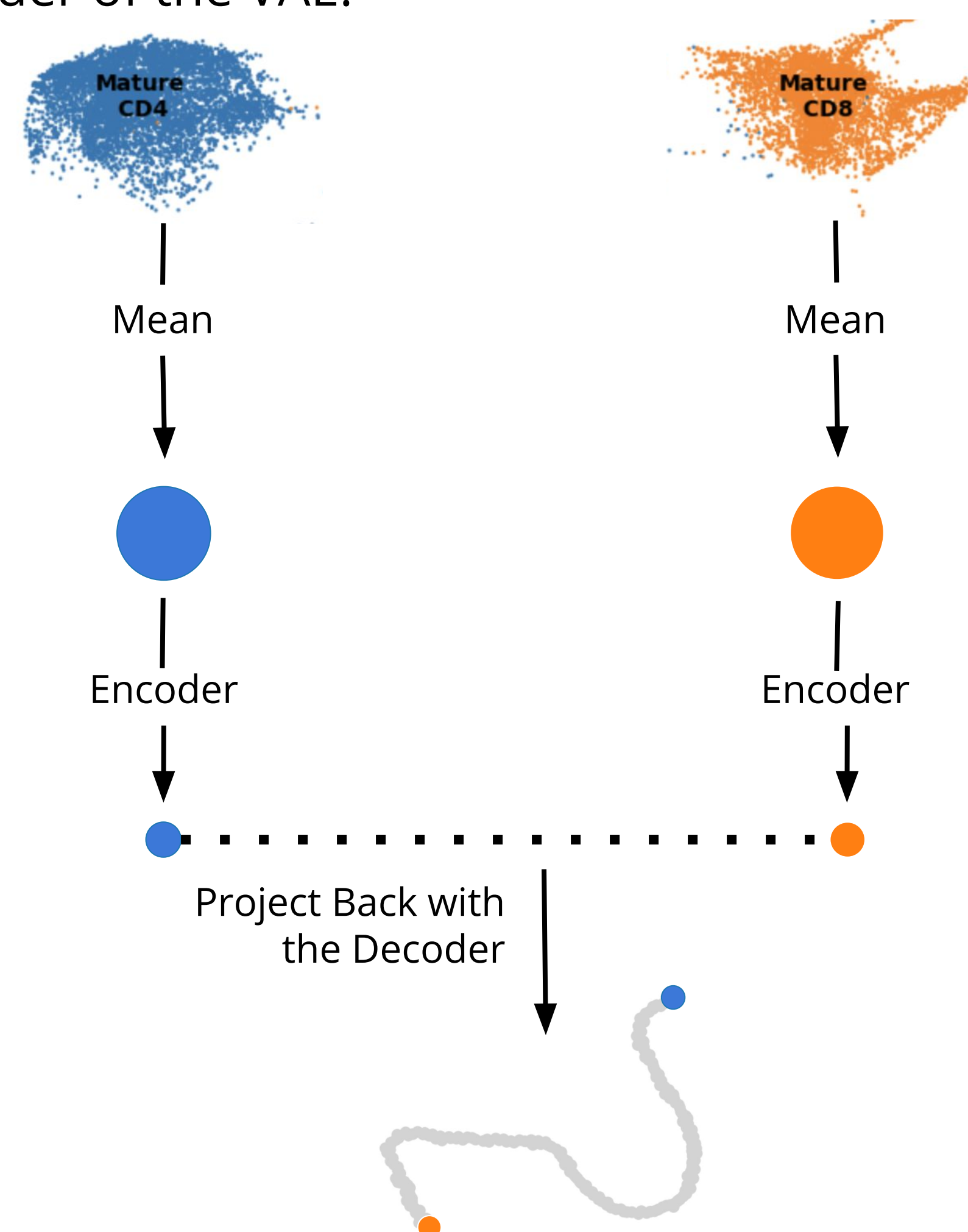
Goal and Approach

- **Simulate an Unnatural CD4+→CD8+ Transition:** We generate a synthetic trajectory, pinpoint potential key regulatory genes that drive the transition.
- **Validate on a Natural Trajectory:** By applying our computational model, we can see if we correctly recover known driver genes that biologists have discovered for CD4+ T cell development.

Methodology

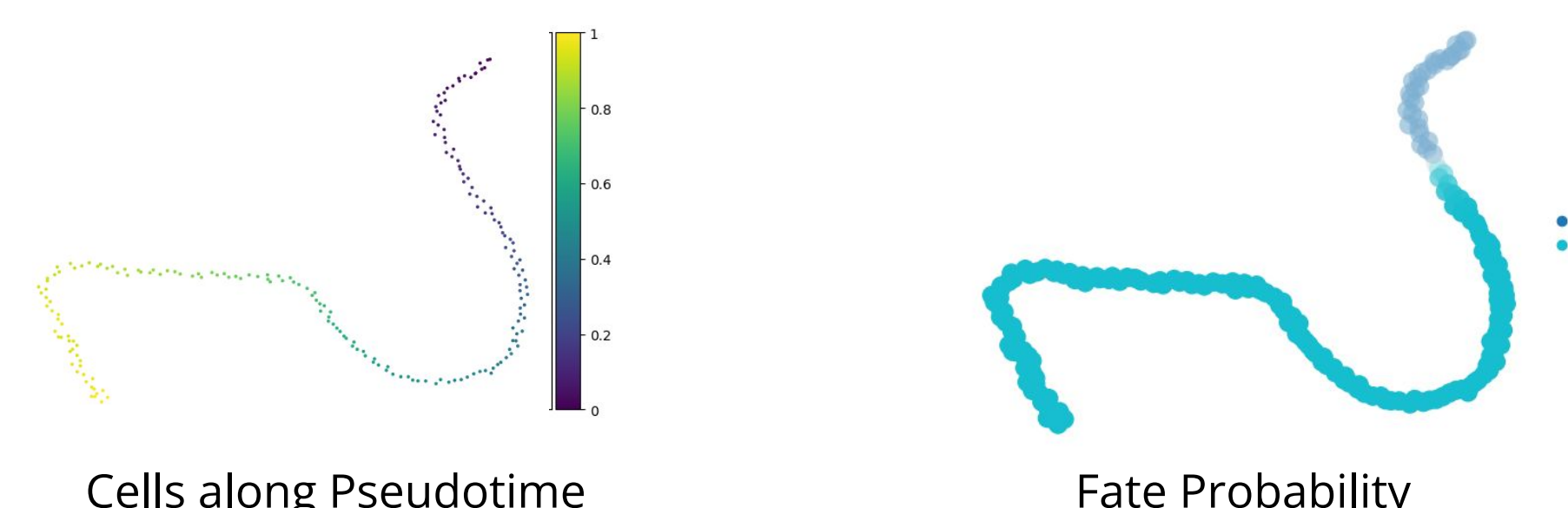
➤ Synthetic Cell Trajectory Generation:

At first, we trained a Variational Autoencoder (VAE) [2] to learn a map or distribution of cell states. We utilized the encoder of the VAE to get the latent (encoded) representation of the cells. Then we linearly interpolated two cells in latent space. We again projected the cells in latent space back to the original dimension using the decoder of the VAE.



➤ Analyzing the fake transition:

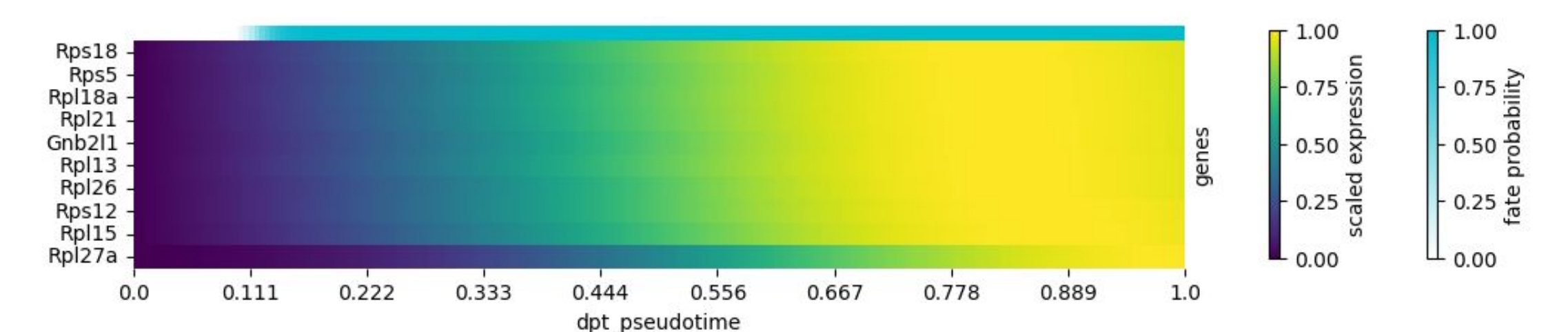
We then applied CellRank [3] to this sequence of synthetic cells. We at first sorted the cells along a pseudotime trajectory and treated the first point as "initial state" (CD4 T cell) and the last point as "terminal fate" (CD8 T cell). CellRank computed the "fate probability" of becoming the CD8 end state for each intermediate cell. We can see that it naturally goes from 0% at the pure CD4 start to 100% at the CD8 end. By correlating gene expression with this "CD8-fate probability," CellRank identified driver genes of the transition.



Results

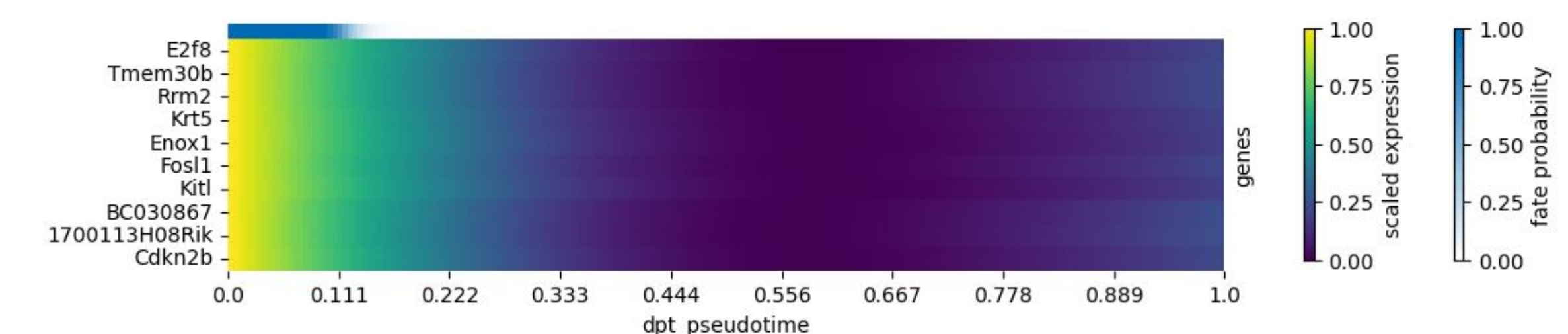
➤ Top 10 Upregulated Genes:

- All are either ribosomal proteins or associated with translation machinery
- Fits biological expectations: CD8 T cells need high protein synthesis activity



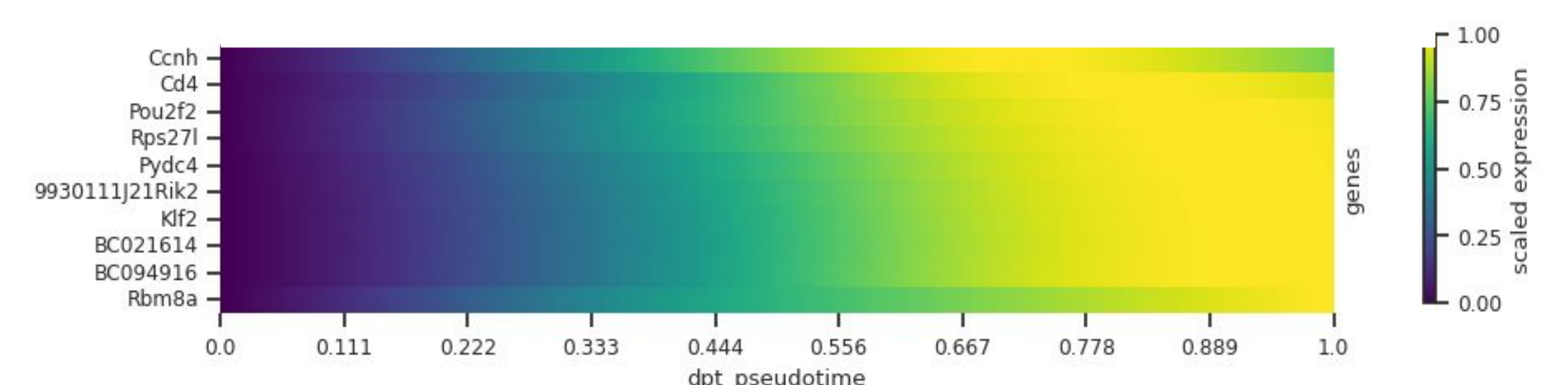
➤ Top 10 Downregulated Genes:

- We can see a reduction in proliferation and early developmental regulatory genes



Validation

- For validation, we generated the trajectory from immature CD4+ to mature CD4+ cells, which is possible naturally.
- Known markers of CD4 T cells increased.



Takeaway:

A Synthetic Trajectory from helper to killer T cells reveals the genetic switches that could power future immune cell reprogramming.

References

1. Steier, Zoë, et al. "Single-cell multiomic analysis of thymocyte development reveals drivers of CD4+ T cell and CD8+ T cell lineage commitment." Nature immunology 24.9 (2023): 1579-1590.
2. Kingma, Diederik P., and Max Welling. "Auto-encoding variational bayes." 20 Dec. 2013,
3. Lange, Marius, et al. "CellRank for directed single-cell fate mapping." Nature methods 19.2 (2022): 159-170.