Joint Velocity-Growth Flow Matching for Single-Cell Dynamics Modeling

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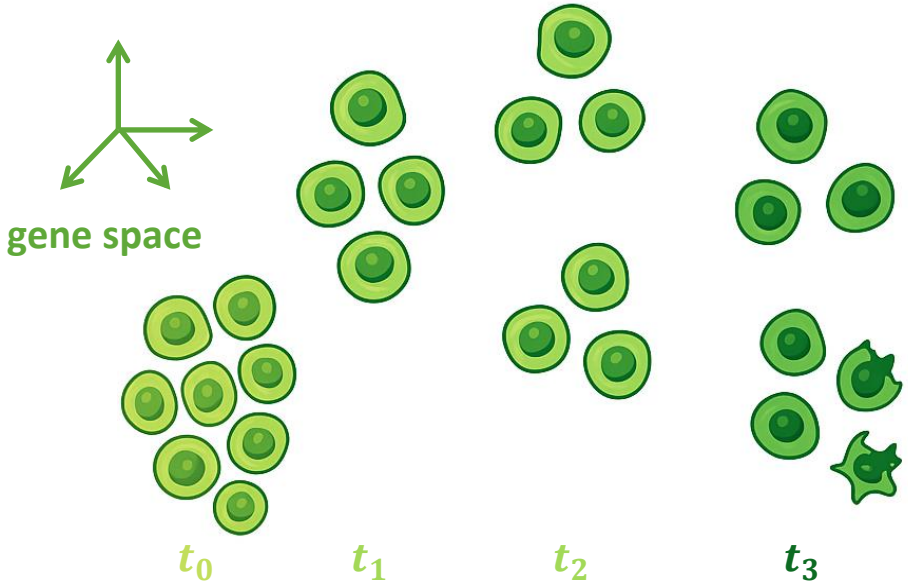
Code

Paper

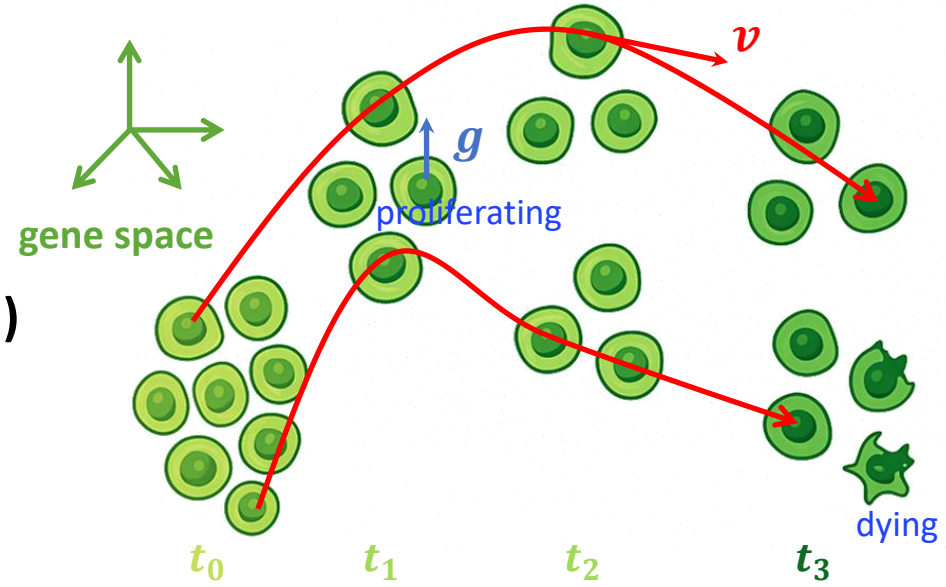
Introduction

- Single-cell RNA seq can measure the gene expressions of individual cells.
- …yet yields unpaired and unbalanced data.

destructive measurements | cell proliferation/death



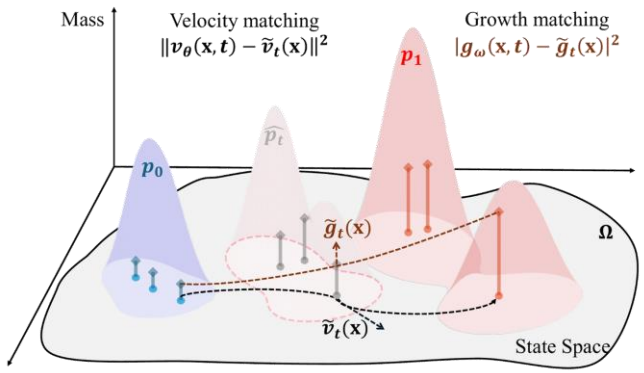
Task : reconstruct cellular dynamics (trajectories, growth…) given unpaired snapshots data



Motivation

- Simulation-based models (eg. TIGON[1], DeepRUOT[2])
  - Explicitly models velocity field and growth rate.
  - Require heavy numerical simulations and have difficulty scaling to high dimensions.
- Simulation-free models (eg. OT-CFM[3], SF2M[4])
  - Use flow matching to achieve better training efficiency and scalability.
  - Only models velocity field, ignore the unbalanced nature of single-cell data.

Can we develop a model which jointly learns the velocity field and growth rate of single-cell evolution by **flow matching?**



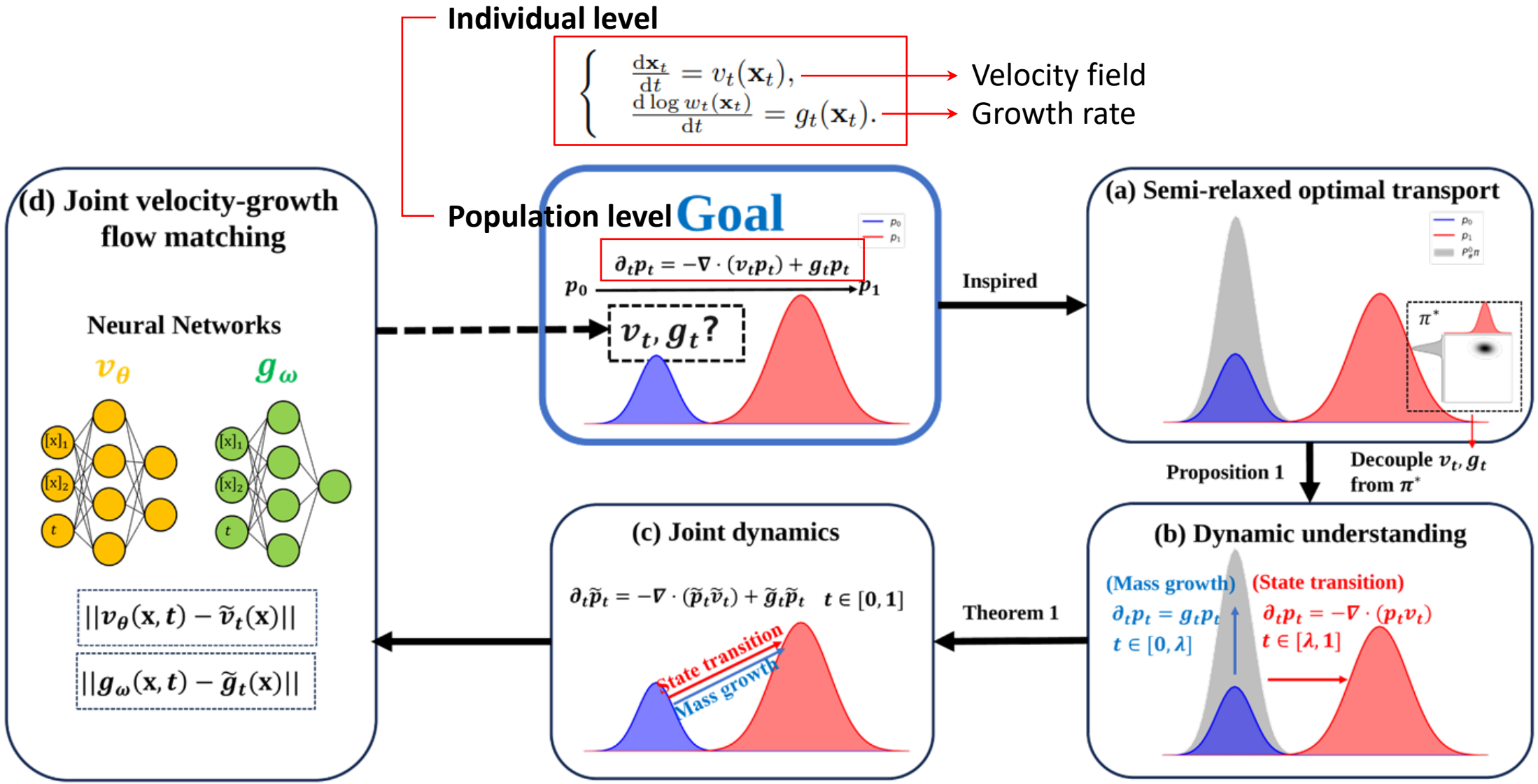
$$\begin{cases} \frac{\mathrm{d}\mathbf{x}_t}{\mathrm{d}t} = v_t(\mathbf{x}_t), \\ \frac{\mathrm{d}\log w_t(\mathbf{x}_t)}{\mathrm{d}t} = g_t(\mathbf{x}_t). \end{cases}$$

→ Velocity field

→ Growth rate

[1] Sha et al., Reconstructing growth and dynamic trajectories from single-cell transcriptomics data. Nature Machine Intelligence, 2024.
[2] Zhang et al., Learning stochastic dynamics from snapshots through regularized unbalanced optimal transport. ICLR, 2025.
[3] Tong et al., Improving and generalizing flow-based generative models with minibatch optimal transport. TMLR, 2024.
[4] Tong et al., Simulation-free Schrödinger bridges via score and flow matching. AISTATS, 2024.

Velocity-growth flow matching framework



Step 1: Two-period dynamic understanding of SOT

➢ Static formulation

$$\min_{\pi \geq 0} \mathcal{J}_{\text{sot}}(\pi) \triangleq \int_{\Omega^2} c(\mathbf{x}_0, \mathbf{x}_1)\, \mathrm{d}\pi(\mathbf{x}_0, \mathbf{x}_1) + \mathrm{KL}(\mathrm{P}^0_{\#}\pi \| p_0) \quad \text{s.t.} \quad \mathrm{P}^1_{\#}\pi = p_1$$

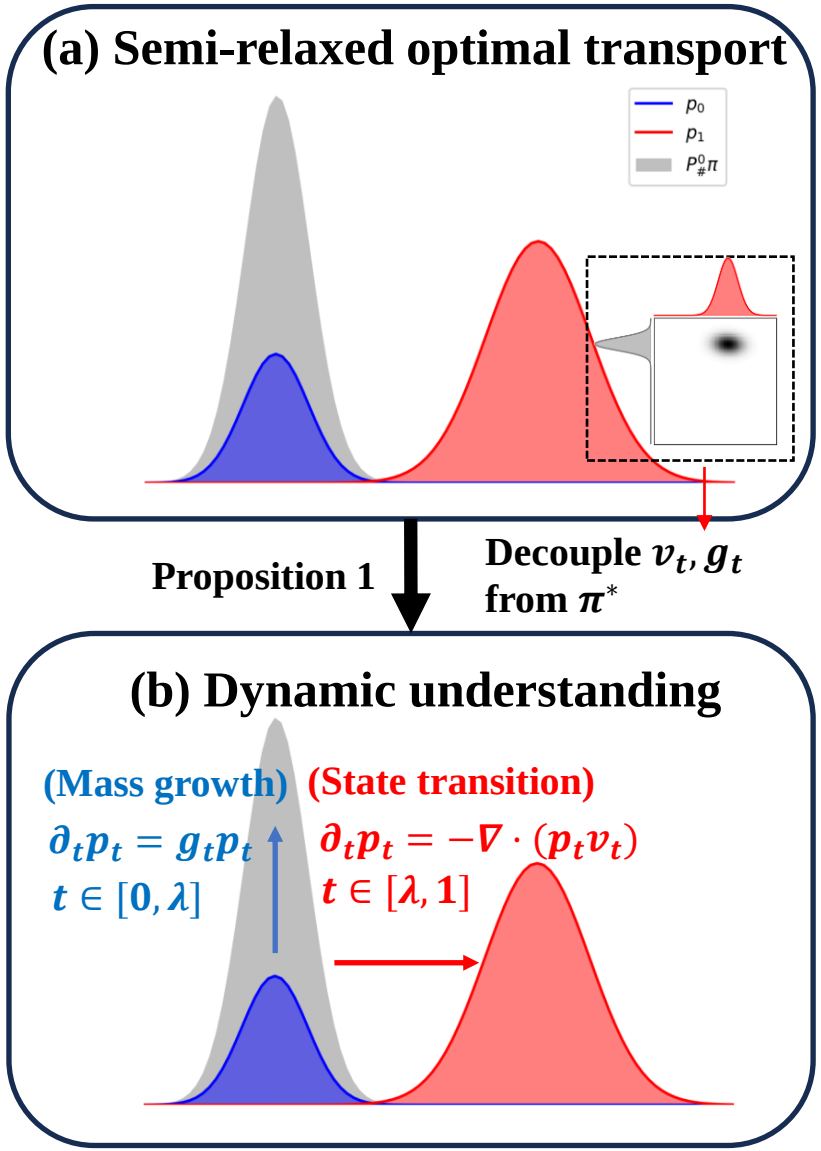
Proposition 1. *Assume* $c(\mathbf{x}_0, \mathbf{x}_1) = \|\mathbf{x}_0 - \mathbf{x}_1\|^2$ *and if we enforce* $\mathrm{P}^0_{\#}\pi$ *and* p_0 *to share the same support for admissible solution* π *to problem (4), then we have* $\min_\pi \mathcal{J}_{\text{sot}}(\pi) = \min_{v_t, g_t} \mathcal{J}^\lambda_{\text{tpt}}(v_t, g_t), \forall \lambda \in (0,1)$. *Moreover, for any* $\lambda \in (0,1)$, *given the optimal transport plan* π^* *to problem (4), let* $p^*_\lambda \triangleq \mathrm{P}^0_{\#}\pi^*$, *then* π^* *can be expressed as* $\pi^* = (\mathrm{Id}, T^*)_{\#} p^*_\lambda$ *where* T^* *is the Monge map between* p^*_λ *and* p_1. *Meanwhile, there exist a* g^*_t *such that* $p^*_\lambda = p_0(\mathbf{x}) e^{\int_0^\lambda g^*_t(\mathbf{x})\mathrm{d}t}$, *and a* v^*_t *given by* $v^*_t\left(\mathbf{x} + \frac{t-\lambda}{1-\lambda}(T^*(\mathbf{x}) - \mathbf{x})\right) = \frac{T^*(\mathbf{x}) - \mathbf{x}}{1-\lambda}$, *satisfying* $(v^*_t, g^*_t) \in \arg\min_{v_t, g_t} \mathcal{J}^\lambda_{\text{tpt}}(v_t, g_t)$.

➢ Dynamic formulation

$$\min_{(v_t, g_t) \in \mathcal{C}_\lambda(p_0, p_1)} \mathcal{J}^\lambda_{\text{tpt}}(v_t, g_t) \triangleq (1-\lambda) \int_\Omega \int_\lambda^1 p_t(\mathbf{x}) \|v_t(\mathbf{x})\|^2 \mathrm{d}t\mathrm{d}\mathbf{x} + \mathcal{H}(g_t, p_t)$$

$$\mathcal{H}(g_t, p_t) = \int_\Omega p_0(\mathrm{x})(e^{\int_0^\lambda g_t(\mathrm{x})\mathrm{d}t}(\int_0^\lambda g_t(\mathrm{x})\mathrm{d}t - 1) + 1)\mathrm{d}x$$

$$\mathcal{C}_\lambda(p_0, p_1) = \{(v_t, g_t) : \partial_t p_t = g_t p_t, t \in [0, \lambda]; \partial_t p_t = -\nabla \cdot (p_t v_t), t \in (\lambda, 1]\}$$



Step 2: Building joint unbalanced dynamics

The two-period evolution does not align with the behavior observed in biological systems. We want transport and growth occur simultaneously.

Theorem 1. *Given the initial distribution p_0, denote the ending distribution of the two-period dynamics*

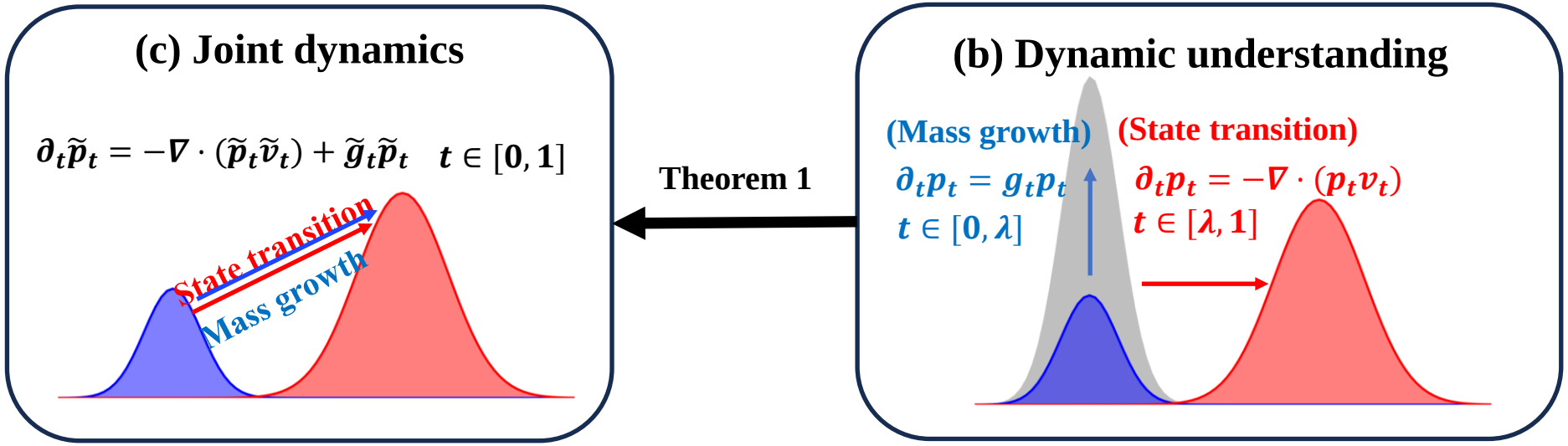
$$\partial_t p_t = g_t p_t, t \in [0, \lambda]; \quad \partial_t p_t = -\nabla \cdot (p_t v_t), t \in (\lambda, 1], \tag{7}$$

as p_1, and denote the ending distribution of the joint dynamics starting from p_0

$$\partial_t \tilde{p}_t = -\nabla \cdot (\tilde{p}_t \tilde{v}_t) + \tilde{g}_t \tilde{p}_t, \quad t \in [0, 1], \quad \tilde{p}_0 = p_0, \tag{8}$$

as $\tilde{p}_1$, then it holds that $\tilde{p}_1 = p_1$.

$$\tilde{v}_t(\mathbf{x}) = (1-\lambda) \cdot v_{(1-\lambda)t+\lambda}(\mathbf{x}),$$
$$\tilde{g}_t(\mathbf{x}) = \lambda \cdot g_{\lambda t}\left(\psi^{-1}_{\tilde{v},t}(\mathbf{x})\right),$$



Step 3: Regress velocity and growth by flow matching

By proposition 1 and theorem 1, we have

$$\tilde{v}_t(\psi_{\tilde{v},t}(\mathbf{x}_0)) = T^*(\mathbf{x}_0) - \mathbf{x}_0, \quad \tilde{g}_t(\psi_{\tilde{v},t}(\mathbf{x}_0)) = \log \mathrm{P}^0_{\#}\pi^*(\mathbf{x}_0) - \log p_0(\mathbf{x}_0), \text{ where } \mathbf{x}_0 \sim p_0.$$

$$\min_{\theta,\omega} \mathbb{E}_{\mathbf{x}_0}\mathbb{E}_t \left[\|v_\theta(\psi_{\tilde{v},t}(\mathbf{x}_0), t) - \tilde{v}_t(\psi_{\tilde{v},t}(\mathbf{x}_0))\|^2 + |g_\omega(\psi_{\tilde{v},t}(\mathbf{x}_0), t) - \tilde{g}_t(\psi_{\tilde{v},t}(\mathbf{x}_0))|^2 \right]$$

In practice, we only have limited samples.

approximate the optimal transport plan by solving the entropy-regularized semi-relaxed transport problem using Sinkhorn-based algorithm

$$\pi^{0\to1} = \arg\min_{\pi\geq 0} \sum_{i,j} c_{ij}\pi_{ij} + \epsilon H(\pi) + \tau \mathrm{KL}(\pi \mathbf{1}_m || \mathbf{1}_n), \quad \text{subject to} \quad \pi^\top \mathbf{1}_n = \mathbf{1}_m$$

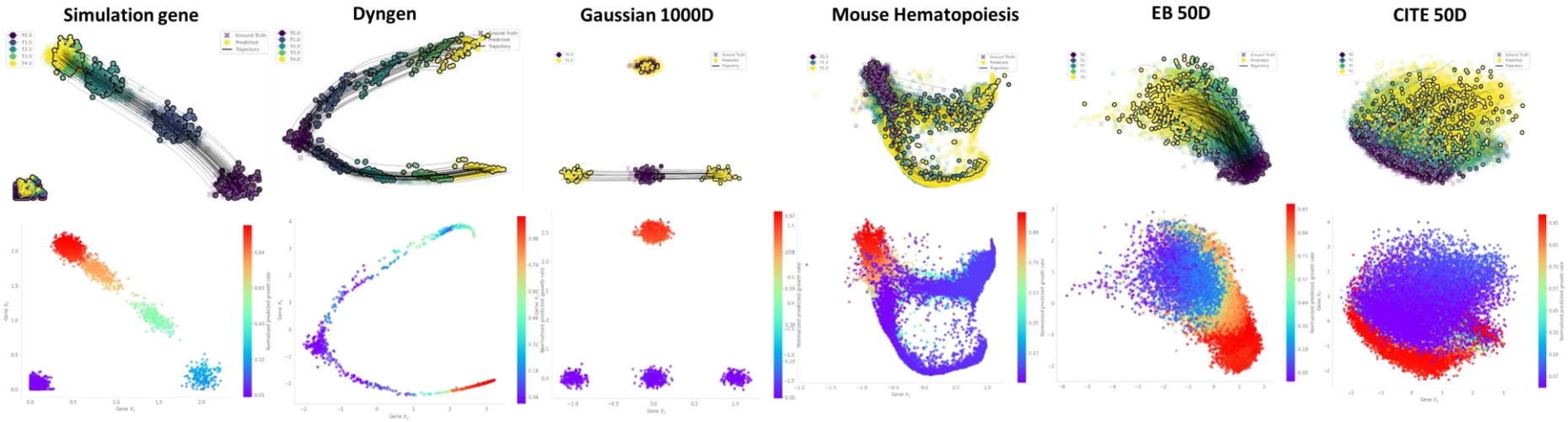
$$\mathcal{L}_{\mathrm{VGFM}}(\theta,\omega) = \sum_{i=1}^{n}\sum_{j=1}^{m} \pi_{ij}^{0\to1} \mathbb{E}_t \left[\left\| v_\theta(\mathbf{x}_t, t) - (\mathbf{x}_1^j - \mathbf{x}_0^i) \right\|^2 + \left| g_\omega(\mathbf{x}_t, t) - \log([\pi^{0\to1}\mathbf{1}_m]_i) \right|^2 \right]$$

Incorporate few-steps distribution fitting loss (Wasserstein distance) to improve performance:

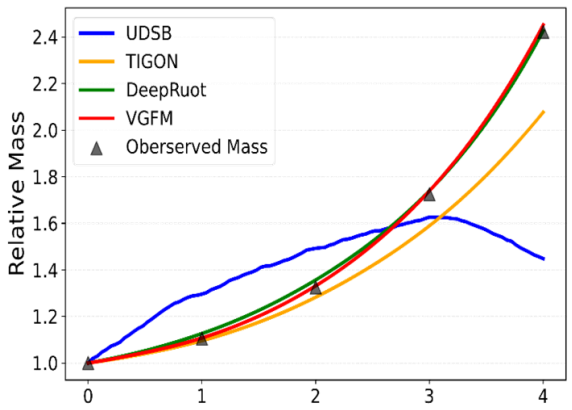
$$\mathcal{L}(\theta,\omega) = \mathcal{L}_{\mathrm{VGFM}}(\theta,\omega) + \mathcal{L}_{\mathrm{OT}}(\theta,\omega)$$

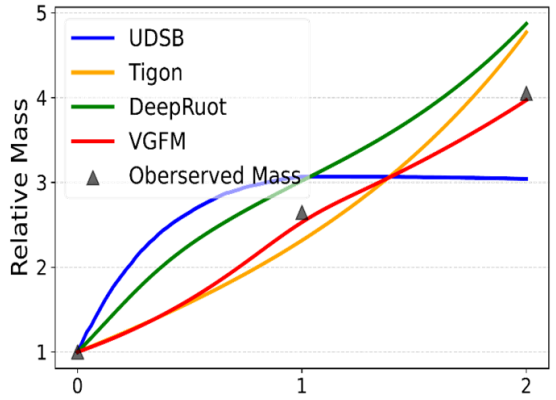
Experiment

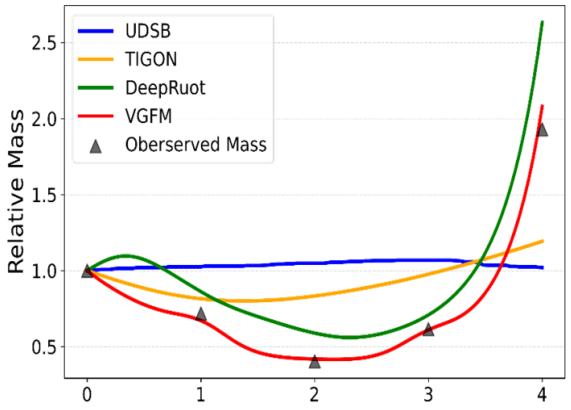
➢ Trajectory and growth reconstruction

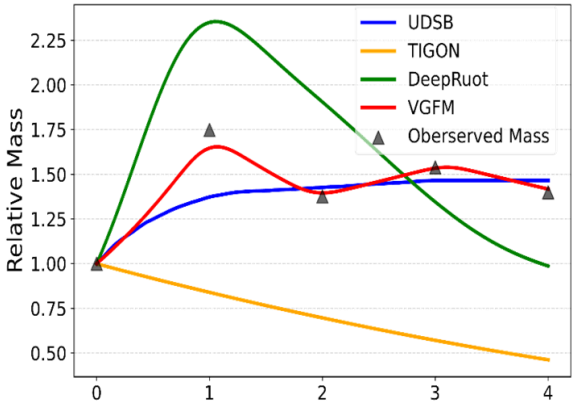


➢ Mass consistency









Experiment

➢ Numerical results

Table 1: Mean $\mathcal{W}_1$ and RME over all time on synthetic datasets. *OT-CFM and OT-MFM do not model the growth function, thus, RME is not computed. "N/C" means "not converge".

Method	Simulation Gene (2D)		Dyngen (5D)		Gaussian (1000D)	
	$\mathcal{W}_1$	RME	$\mathcal{W}_1$	RME	$\mathcal{W}_1$	RME
OT-CFM* [22]	0.302	—	3.926	—	10.126	—
OT-MFM* [38]	0.311	—	3.976	—	11.008	—
UDSB [57]	0.665	0.192	1.914	0.658	N/C	N/C
TIGON [23]	0.099	0.065	1.029	0.542	N/C	N/C
DeepRUOT [26]	0.068	0.016	0.474	0.199	N/C	N/C
VGFM	**0.046**	**0.006**	**0.420**	**0.053**	**3.010**	**0.037**

Table A-9: $\mathcal{W}_1$ and RME over all time on mouse hematopoiesis data. Part of the results were adopted from [26].

Models	t_1		t_2	
	$\mathcal{W}_1$	RME	$\mathcal{W}_1$	RME
SF^{2}M [41]	0.167	—	0.190	—
uAM[44]	0.745	—	0.777	—
UDSB [57]	0.388	0.159	0.128	0.249
TIGON [23]	0.314	0.124	0.342	0.177
DeepRUOT [26]	0.145	0.140	0.132	0.202
VGFM	**0.115**	**0.043**	**0.094**	**0.019**

Table 3: Ablation study on EB (50D) dataset. For comparison, we also report the results of the SOTA approach DeepRUOT [26] in this table.

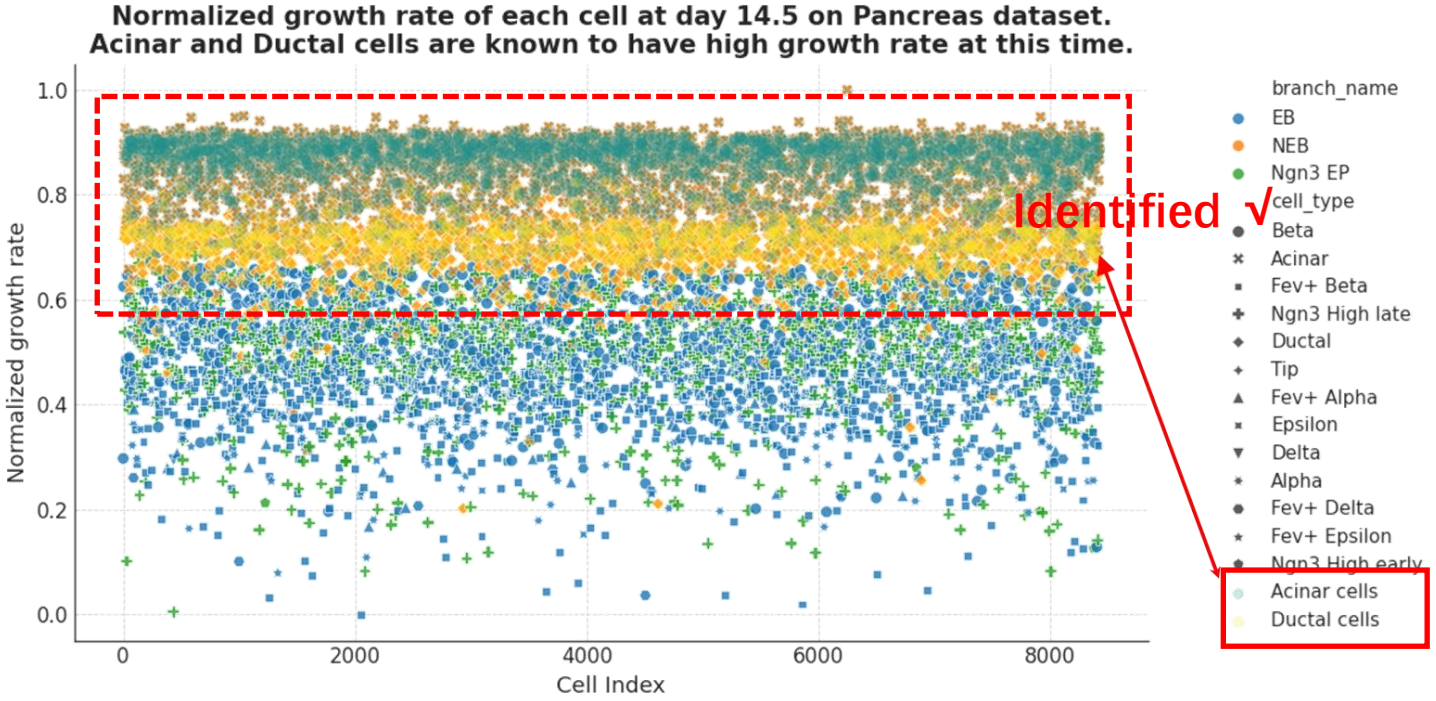
Method	t_1		t_2		t_3		t_4		Training time
	$\mathcal{W}_1$	RME	$\mathcal{W}_1$	RME	$\mathcal{W}_1$	RME	$\mathcal{W}_1$	RME	
DeepRUOT [26]	8.169	0.416	9.041	0.415	9.348	0.119	9.808	0.296	90 (mins)
VGFM (w/o $\mathcal{L}_{\text{OT}}$)	8.915	0.020	10.590	0.098	10.915	0.067	11.635	0.088	6 (mins)
VGFM (w/o $\mathcal{L}_{\text{VGFM}}$)	8.644	0.650	10.167	0.710	11.052	0.823	11.530	0.862	62 (mins)
VGFM	7.951	0.089	**8.747**	0.042	9.244	**0.019**	9.620	**0.044**	13 (mins)
VGFM (*)	**7.902**	**0.018**	8.767	**0.013**	**9.063**	0.083	**9.507**	0.096	9 (mins)

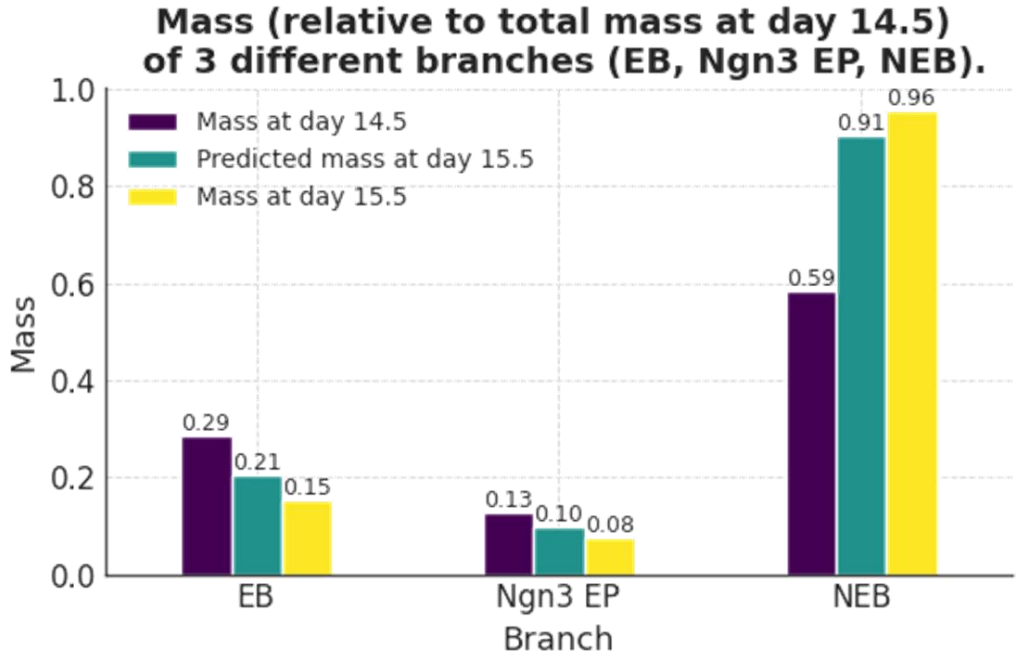
Table 2: Mean hold-one-out results on EB and CITE datasets over hold-out times.

Method	EB	CITE	
	5D	5D	50D
OT-CFM [22]	0.790	0.882	38.756
SF^{2}M [41]	0.793	0.920	38.524
UDSB [57]	1.206	2.023	44.168
OT-MFM [38]	0.713	**0.724**	**36.394**
DeepRUOT [26]	0.774	0.845	38.681
VGFM	**0.676**	0.745	37.386

Experiment

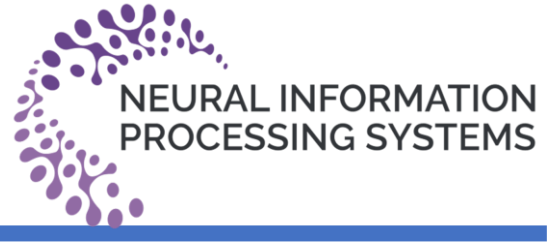
➢ Interpretation of $g_\omega(x,t)$: Pancreas dataset (2000-dimensions)





VGFM Successfully reconstructed cell type-wise growth rate without being given any prior knowledge of the cell types.





Thanks for your attention!

https://github.com/DongyiWang-66/VGFM

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Code

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