PACE: Geometry-Aware Bridge Transport for Single-Cell Trajectory Inference

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01 Problem & motivation



Destructive snapshots are ill-posed

No cell identities, cross-time correspondences or intermediate paths. **Many couplings fit the same marginals.**

We observe single-cell point clouds at anchor times. Our goal is to **infer trajectories and a velocity field** that transports adjacent distributions and generates a continuous time course.



Euclidean proximity can misalign cells

Nearby cells may occupy **different pseudotime stages**, **fate branches**, stalled states or refractory populations.

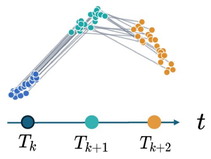
PACE intuition

Favor **local tangent motion** and **penalize normal motion** to select plausible dynamics. Individual histories remain **unidentifiable**.

02 Geometry-aware bridge transport

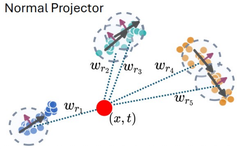
Time: T_k T_{k+1} T_{k+2} | Tangent: Normal:

Unpaired snapshots



Local anisotropic metric

Local PCA Induced Normal Projector



Metric at (x,t)

$$G(x,t) = I + \alpha \sum_r \omega_r(x,t) P_N^{(r)}$$

Tangent direction (low cost)

Normal direction (high cost)

Geometry-aware action

Objective

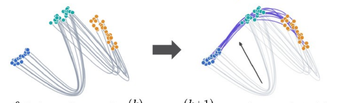
$$\min_{\pi_k \in \Pi(\rho_k, \rho_{k+1}),\, \theta} \sum_{i,j} \pi_{ij}^{(k)} c_{ij}^{\text{path}}(\theta)$$

Path Cost

$$c_{ij}^{\text{path}}(\theta) = \int_0^1 u_{\theta,ij}(\tau)^\top G_k(\gamma_{\theta,ij}(\tau), t_{k,\tau}) u_{\theta,ij}(\tau)\, d\tau$$

1 Bridge update

Poor Initial Paths → Geometry-aligned Paths



$$\gamma_{ij}^\theta(\tau) = (1-\tau)x_i^{(k)} + \tau x_j^{(k+1)} + \tau(1-\tau)\psi_\theta(\cdot)$$

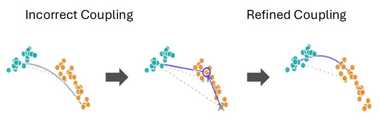
$$u_{ij}^\theta(\tau) = \partial_\tau \gamma_{ij}^\theta(\tau).$$

Update rule

$$\theta^{r+1} = \arg\min_\theta \sum_{i,j} \pi_{ij}^r c_{ij}^{\text{path}}(\theta)$$

2 Coupling refinement

Incorrect Coupling → Refined Coupling

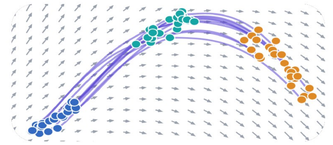


Update rule

$$\pi^{r+1} = \arg\min_{\pi \in \Pi(\rho_k, \rho_{k+1})} \sum_{i,j} \pi_{ij} c_{ij}^{\text{path}}(\theta^r)$$

Iterative bridge / coupling update

3 Velocity distillation

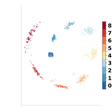


Velocity distillation

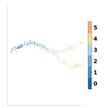
$$\min_\phi \mathbb{E}_{k,(i,j)\sim\pi_k,\tau\sim U(0,1)} \left[\left\| v_\phi(\gamma_{\theta,ij}(\tau), t_{k,\tau}) - \frac{1}{\Delta t_k} u_{\theta,ij}(\tau) \right\|^2 \right]$$

03 Datasets

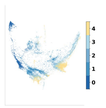
7 datasets cover controlled dynamics, EB differentiation, mouse and human reprogramming, and multimodal single-cell time courses.



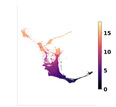
Ocean



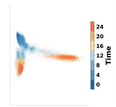
Two-Branch



EB (PHATE)



Schiebinger2019

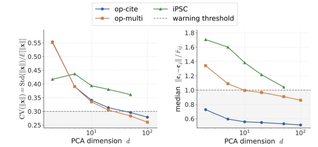


iPSC-Liu

OP-Cite
OP-Multi

100D multimodal single-cell data

High-dimensional diagnostics



Global distance contrast **weakens with dimension**. Euclidean probability mass and pairwise costs become concentrated.

04 Held-out distributions

Time-averaged low-dimensional results. Lower is better.

Method	EB PHATE			iPSC-Liu			Schiebinger2019		
	MMD ↓	W_1 ↓	W_2 ↓	MMD ↓	W_1 ↓	W_2 ↓	MMD ↓	W_1 ↓	W_2 ↓
Action Matching	0.2436	0.4553	0.5273	0.5230	0.8005	0.9730	0.4057	0.4161	0.4754
Aligned CFM	0.1056	0.2657	0.3243	0.5428	0.6594	0.8320	0.3239	0.3175	0.3931
CURLY	0.1384	0.3223	0.4422	0.5613	0.7186	0.9216	0.7687	1.3684	1.4660
DMSB	0.1325	0.3053	0.4341	0.6456	1.0244	1.1023	0.3030	0.2774	0.3662
MFM	0.1518	0.3704	0.4451	0.5533	0.6657	0.8838	0.6990	1.5897	1.7942
OT-CFM	0.1069	0.2784	0.3622	0.5228	0.7166	0.9261	0.8072	1.9095	2.0235
PACE (ours)	**0.0674**	**0.2087**	**0.2803**	**0.4385**	**0.4853**	**0.6238**	**0.2084**	**0.2067**	**0.2840**

PACE wins all reported EB / iPSC-Liu low-D metrics and 7 of 9 Schiebinger metric-time entries.

EB trajectory rollouts

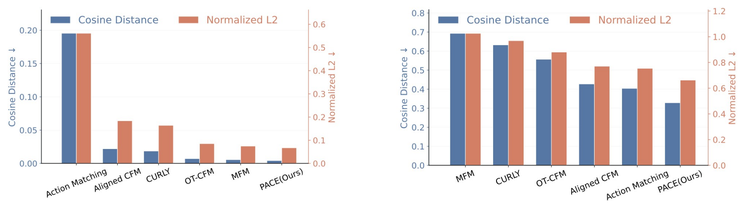


EB PHATE, Stage 2
Held-out time: t = 3

Crosses: held-out cells
Red circles: predictions

05 Velocity alignment

PACE best aligns with velocity references.



(a) Ocean (b) EB PHATE

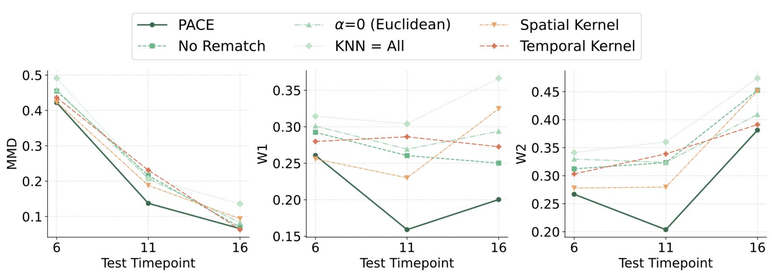
Ocean trajectory comparison



Simulator / RNA velocities are **withheld from training** and used **only for evaluation**. No pairing, lineage or velocity supervision is required.

06 Ablation

Removing any key component hurts performance.



Rematching, anisotropic geometry, local neighborhoods, and spatial / temporal kernels **each contribute to the result**.

PACE is best on all 10D and 50D averaged metrics.

Key Takeaways

- **Matching snapshots leaves dynamics underdetermined**. The key modeling choice is the prior on motion between observations.
- Local tangent geometry provides a **weak developmental prior**: PACE gains **23.7% on average** and improves **RNA-velocity alignment by 15.4%**.
- Training needs **no lineage or velocity labels**. The next step is to **propagate uncertainty in local geometry** into inferred trajectories.

Code

Paper

[1] Moon et al., Nature Biotechnology (2019). [2] Schiebinger et al., Cell (2019). [3] Liu et al., Nature (2020).