Latent Trajectory Inference with Drift Prior

Anming Gu
Supervised by: Ed Chien, Kristjan Greenewald

May 3rd, 2024

Table of Contents

Motivation: computational biology applications

Goal: understand biological processes

Issue: we cannot observe full cell development process

Data consists of population snapshots at different time points

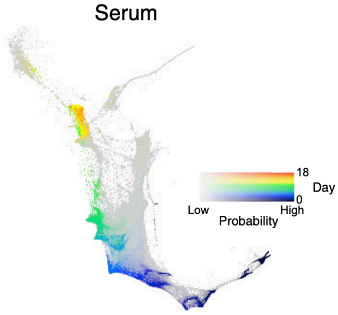


Figure from Schiebinger et al., 2019

What is trajectory inference?

Let $\mathcal{X}$ be the ambient space and $\Omega = C([0,1] : \mathcal{X})$ be the path space

Goal: estimate the ground truth stochastic process $\mathbf{P} \in \mathcal{P}(\Omega)$

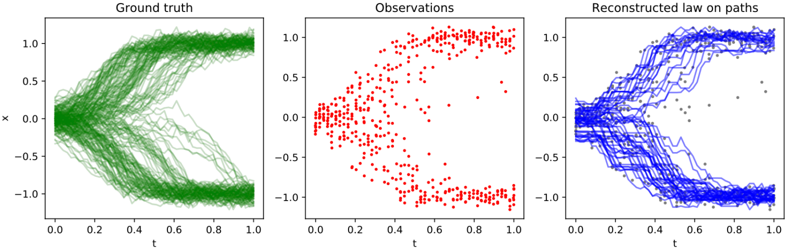


Figure from Lavenant et al., 2021

Mathematical model of trajectory inference

Let $X_t \in \mathcal{X}$ be an unobserved state vector evolving according to the following SDE for $t \in [0, 1]$:

$$dX_t = -\Xi(t, X_t)dt - \nabla\Psi(t, X_t)dt + \sqrt{\tau}dB_t \tag{1}$$

- initial condition $X_0 \sim \mu_0$
- divergence-free velocity prior $\Xi \in C([0, 1] \times \mathcal{X} : \mathcal{X})$ is *known*
- potential $\Psi \in C^2([0, 1] \times \mathcal{X})$ is *unknown*
- $\tau > 0$ is the variance, $\{B_t\}$ is a standard Brownian motion

This is our ground truth $\mathbf{P} \in \mathcal{P}(\Omega)$

Measurement Model

Smooth function $g : \mathcal{X} \to \mathcal{Y}$ transforming X_t into the observation space $\mathcal{Y}$:

$$Y_t = g(X_t)$$

T observation times with $0 \leq t_1^T < \cdots < t_T^T \leq 1$, and we observe N_i^T i.i.d. samples from the marginal distribution of Y_{t_i}:

$$\{Y_{i,j}^T\}_{j=1}^{N_i^T} \overset{\text{i.i.d.}}{\sim} g_\sharp \mathbf{P}_{t_i^T} := \mathbf{Q}_{t_i^T}.$$

Smooth empirical distribution by h-wide heat kernel Φ_h:

$$\hat{\rho}_i^T = \Phi_h \left(\frac{1}{N_i^T} \sum_{i=1}^{N_i^T} \delta_{Y_{i,j}^T} \right)$$

Goal: recover $\mathbf{P}$ from $(\hat{\rho}_1^T, \ldots, \hat{\rho}_T^T)$ and the known velocity field Ξ

Observability assumption

Ψ is unknown, but restricted to a class $\mathcal{C}_\Psi$.

$(g, \Xi, \mathcal{C}_\Psi)$ is $\mathcal{C}_\Psi$*-marginal-observable* if, given g, Ξ, σ, and all marginals $\mathbf{Q}_t = g_\sharp \mathbf{P}_t$ of Y_t for all $t \in [0,1]$, the marginals $\mathbf{P}_t$ of X_t are uniquely determined for all $t \in [0,1]$

With this assumption, we can infer the latent dynamics solely from the marginals $\mathbf{Q}_t$

Setting for synthetic experiments:

- Ξ is linear, time-invariant and Ψ is time-invariant
- g is of the form $(x_1, \ldots, x_n) \mapsto (x_1, \ldots, x_k)$ for some $k < n$
- "classical observability" holds
- Ψ only affects $(x_{k+1}, \ldots, x_k)$

Why is our setting important?

Goal: recover $\mathbf{P}$ from $(\hat{\rho}_1^T, \ldots, \hat{\rho}_T^T)$ and the known velocity field Ξ

Our contributions:

- Trajectory inference without observing whole particles
- Entropy minimization using reference measure with drift

Applications:

- More robust optimization using drift prior
- Smoother trajectories and more accurate prediction of final particle positions
- Privacy: don't need to release full data
- May be useful for studying diffusion models
- Interpretability: biology datasets are very high dimensional

Outline of algorithm

Algorithm 1 Framework for latent trajectory inference

Require: Collection of observations $(\hat{\rho}_1, \ldots, \hat{\rho}_t)$, velocity prior Ξ, number of iterations for MFL dynamics N, number of particles m

Initialize m particles for each t: $(\hat{m}_1, \ldots, \hat{m}_t) \in \mathcal{X}^{m \times t}$

for N iterations **do**

  for $i \in [t-1]$ **do** $\triangleright$ $\Delta t_i := t_{i+1} - t_i$

    $\{C_{j,k}\}_{j,k=1}^{m} \leftarrow \frac{1}{2}\|\hat{m}_{i,j} - \frac{\Delta t_i}{2}\Xi(t_i, \hat{m}_{i,j}) - \hat{m}_{i,k} + \frac{\Delta t_i}{2}\Xi(t_{i+1}, \hat{m}_{i,k})\|^2$

    $T_t \leftarrow \mathrm{Sinkhorn}(\hat{m}_i, \hat{m}_{i+1}, C_i, \lambda \cdot \Delta t_i)$ $\triangleright$ $T_t \in \Pi(\hat{m}_i, \hat{m}_{i+1})$

  end for

  $\hat{\mathbf{m}} \leftarrow \mathrm{MFL}(\hat{\mathbf{m}}, \mathbf{T}, \hat{\boldsymbol{\rho}})$ $\triangleright$ $\mathbf{m} := (\hat{m}_1, \ldots, \hat{m}_t)$, etc.

end for

Output collection of particles $\hat{\mathbf{m}}$, trajectories $T_{t-1} \circ \cdots \circ T_1$

Table of Contents

Data-fitting term

Let $\Delta t_i := t^T_{i+1} - t^T_i$. Fit function: $\mathrm{Fit}^{\lambda,\sigma} : \mathcal{P}(\mathcal{Y})^T \to \mathbb{R}$:

$$\mathrm{Fit}^{\lambda,\sigma}(\mathbf{Q}_{t^T_1}, \ldots, \mathbf{Q}_{t^T_T}) := \frac{1}{\lambda} \sum_{i=1}^{T} \Delta t_i \mathrm{DF}^{\sigma}(g_\sharp \mathbf{R}_{t^T_i}, \hat{\rho}^{T,h}_i),$$

$$\begin{aligned}\mathrm{DF}^{\sigma}(g_\sharp \mathbf{R}_{t^T_i}, \hat{\rho}^{T,h}_i) &:= \int_{\mathcal{Y}} - \log \left[\int_{\mathcal{X}} \exp \left(-\frac{\|g(x) - y\|^2}{2\sigma^2} \right) d\mathbf{R}_{t^T_i}(x) \right] d\hat{\rho}^{T,h}_i(y) \\ &= H(\hat{\rho}^{T,h}_i | g_\sharp \mathbf{R}_{t^T_i} * \mathcal{N}_\sigma) + H(\hat{\rho}_{t^T_i}) + C,\end{aligned}$$

where $\mathcal{N}_\sigma$ is the Gaussian kernel with variance σ^2, $C > 0$ is a constant

- Negative log-likelihood under the noisy observation model $\hat{Y}^T_{i,j} = g(X^T_{i,j}) + \sigma Z_{i,j}$, where $\hat{Y}^T_{i,j}$ is the observation and $Z_{i,j} \overset{i.i.d.}{\sim} \mathcal{N}(0, I)$.
- DF^{σ} is jointly convex in $(\mathbf{R}_{t^T_i}, \hat{\rho}^{T,h}_i)$ and linear in $\hat{\rho}^{T,h}_i$.

Chizat et al., 2022

Min-entropy estimator

Functional $\mathcal{F} : \mathcal{P}(\Omega) \to \mathbb{R}$

$$\mathcal{F}(\mathbf{R}) := \mathrm{Fit}^{\lambda,\sigma}(\mathbf{Q}_{t_1^T}, \ldots, \mathbf{Q}_{t_T^T}) + \tau H(\mathbf{R}|\mathbf{W}^{\Xi,\tau}), \quad \mathbf{R}^{T,\lambda,h} := \arg\min \mathcal{F}(\mathbf{R})$$

- $\mathbf{W}^{\Xi,\tau} \in \mathcal{P}(\Omega)$ is the law of the SDE $dZ_t = -\Xi(t, Z_t)\, dt + \sqrt{\tau}\, dB_t$
- $H(\mu|\nu) = \int \log(d\mu/d\nu)\, d\mu$ is relative entropy
- Fit term on previous slide

Theorem (Consistency, Lavenant et al., 2021, Thm. 2.3)

If $\{t_i^T\}_{i\in[T]}$ becomes dense in $[0,1]$ as $T \to \infty$,

$$\lim_{\lambda,h\to 0} \lim_{T\to\infty} \mathbf{R}^{T,\lambda,h} = \mathbf{P}$$

weakly, almost surely.

High level ideas for proof of consistency

Tools: stochastic calculus, Γ-convergence, analysis, heat flow on manifolds

1. Stochastic arguments
   - $\mathbf{P}$ follows the SDE $dX_t = -\Xi(t, X_t)dt - \nabla\Psi(t, X_t)dt + \sqrt{\tau}dB_t$ and $\mathbf{W}^{\Xi,\tau}$ follows the SDE $dZ_t = -\Xi(t, Z_t)dt + \sqrt{\tau}dB_t$
   - Drift term in Z_t cancels out drift term of X_t, e.g. check via Girsanov
2. Take $T \to \infty$
   - Show that sequence of minimizers (for discrete measurements) converges to minimizer for continuous curve
   - Contraction for minimization problem under heat flow (path-space counterpart for contraction of entropy under heat flow)
3. Take $\lambda, h \to 0$
   - Use same contraction results and Fatou's lemma

Table of Contents

Our entropic optimal transport problem

Goal: reduce the problem over the space $\mathcal{P}(\mathcal{X}^T)$ to use the mean-field Langevin (MFL) dynamics

Let $\tau_i := \Delta t_i \cdot \tau$ and consider the entropic OT problem:

$$\begin{aligned} T_{\tau_i,\Xi}(\mu,\nu) &:= \min_{\gamma\in\Pi(\mu,\nu)} \int c^{\Xi}_{\tau_i}(x,y)\, d\gamma(x,y) + \tau_i H(\gamma|\mu\otimes\nu) \\ &= \min_{\gamma\in\Pi(\mu,\nu)} \tau_i H(\gamma|p^{\Xi}_{\tau_i}\mu\otimes\nu) \end{aligned}$$

- set of transport plans $\Pi(\mu,\nu)$, e.g. probability measures in $\mathcal{P}(\mathcal{X}\times\mathcal{X})$ with marginals μ,ν
- cost function $c^{\Xi}_{\tau_i}(x,y) := -\Delta t_i \log(p^{\Xi}_{\tau_i}(x,y))$
- $p^{\Xi}_{\tau_i}$ transition probability density of $\mathbf{W}^{\Xi}$

Chizat et al., 2022

Representer theorem

Optimization over $\mathcal{P}(\Omega)$:

$$\mathcal{F}(\mathbf{R}) := \mathrm{Fit}^{\lambda,\sigma}(\mathbf{Q}_{t_1^T}, \ldots, \mathbf{Q}_{t_T^T}) + \tau H(\mathbf{R}|\mathbf{W}^{\Xi,\tau})$$

Reduced optimization over $\mathcal{P}(\mathcal{X})^T$:

$$F(\boldsymbol{\mu}) := \underbrace{\mathrm{Fit}^{\lambda,\sigma}(g_\sharp \boldsymbol{\mu}) + \sum_{i=1}^{T-1} \frac{1}{\Delta t_i} T_{\tau_i,\Xi}(\boldsymbol{\mu}^{(i)}, \boldsymbol{\mu}^{(i+1)})}_{G(\boldsymbol{\mu})} + \tau \underbrace{\sum_{i=1}^{T} H(\boldsymbol{\mu}^{(i)})}_{H(\boldsymbol{\mu})}.$$

Theorem (Chizat et al., 2022)

A minimizer for $\mathcal{F}$ can be built from a minimizer for F.

Composition of optimal transport plans:

$$\mathbf{R}_{t_i,\ldots,t_T}(dx_1, \ldots, dx_T) = \gamma_{1,2}(dx_1, dx_2)\gamma_{2,3}(dx_3|x_2)\cdots\gamma_{T-1,T}(dx_T|x_{T-1})$$

Approximation of the entropic OT problem

We still cannot solve F! Why?

$p^{\Xi}_{\tau_i}$ is generally not well-defined

Idea: approximate $T_{\tau_i,\Xi}(\mu,\nu)$ using an Euler-Maruyama discretization

Consider two time points $t_1 \leq t_2$. Define

$$\Xi^{\Delta t}_{\sharp}\mu_{t_1} := \mu_{t_1} - \Xi(t_1, \mu_{t_1}) \cdot \Delta t$$

Consider $T_{\tau_i}(\Xi^{\Delta t}_{\sharp}\mu_{t_1}, \mu_{t_2})$ instead of $T_{\tau_i,\Xi}(\mu_{t_1}, \mu_{t_2})$, where

$$T_{\tau_i}(\mu,\nu) := \min_{\gamma \in \Pi(\mu,\nu)} \tau_i H(\gamma | p_{\tau_i}\mu \otimes \nu)$$

is the entropic OT cost corresponding to the transition probability density of the Brownian motion $p_t(x, y)$

Approximation of the entropic OT problem (cont.)

Theoretical justification:

Proposition

Assume $\mathcal{X}$ is a bounded domain, e.g. $\operatorname{diam}\mathcal{X} < +\infty$. *Let* $\Delta t := t_2 - t_1$ *and* $\tau_i := \tau\Delta t$. *Define* $\xi^{\Delta t}(x) := x - \Xi(t_1, x) \cdot \Delta t$. *We have*

$$\lim_{\Delta t \to 0} \int_{\mathcal{X}\times\mathcal{X}} \left| \log(p^{\Xi}_{\tau_i}(x,y)) - \log(p_{\tau_i}(\xi^{\Delta t}(x), y)) \right| dx\, dy = 0.$$

Proof idea: use triangle inequality, Taylor approximation, dominated convergence, and fact that transition kernel is Dirac delta in the limit.

No rate of convergence

Discussion of approximation

- Computationally, consider: $T_{\tau_i}(\Xi_\sharp^{\Delta t/2}\mu_{t_1}, \Xi_\sharp^{-\Delta t/2}\mu_{t_2})$.
- Varadhan's approximation:

$$\tilde{c}^{\Xi}_{\tau_i}(x,y) \approx \frac{1}{2}\left\| y + \frac{\Delta t}{2}\Xi(t_2, y) - x + \frac{\Delta t}{2}\Xi(t_1, x) \right\|^2,$$

  which holds for τ_i small
- Consistency result: justifies using Ξ in entropic OT problem
- Intuition for robustness: $\mathbb{E}[|\Xi_\sharp^{\Delta t/2}\mu_{t_1} - \Xi_\sharp^{-\Delta t/2}\mu_{t_2})|] \approx 0$ even if the particles move a large distance

Table of Contents

Mean-field Langevin dynamics

For convex $G : \mathcal{P}(\mathcal{X}) \to \mathbb{R}_{\geq 0}$, MFL dynamics solves the following optimization problem:

$$\min_{\mu \in \mathcal{P}_2(\mathcal{X})} F_\tau(\mu) := G(\mu) + H(\mu)$$

Let $V[\mu] := \frac{\delta G}{\delta \mu}(\mu) \in C^1(\mathcal{X})$ be the *first variation* of G:

$$\lim_{\epsilon \to 0^+} \frac{1}{\epsilon}[G((1-\epsilon)\mu + \epsilon)) - G(\mu)] = \int_{\mathcal{X}} V[\mu](x)\, d(\nu - \mu)(x)$$

for all μ, ν.

Chizat et al., 2022

Noisy particle gradient descent

Optimization by running noisy particle gradient descent on $G_m : (\mathcal{X}^m)^T \to \mathbb{R}$ defined as $G_m(\hat{X}) := G(\hat{\boldsymbol{\mu}}_{\hat{X}})$, where

$$\hat{\boldsymbol{\mu}}^{(i)}_{\hat{X}} = \frac{1}{m} \sum_{j=1}^{m} \delta_{\hat{X}^{(i)}_j}.$$

Optimization procedure is:

$$\begin{cases} \hat{X}^{(i)}_j[k+1] = \hat{X}^{(i)}_j[k] - \eta \nabla V^{(i)}[\hat{\boldsymbol{\mu}}[k]](\hat{X}^{(i)}_j[k]) + \sqrt{2\eta(\tau+\epsilon)} Z^{(i)}_{j,k}, \\ \hat{\boldsymbol{\mu}}^{(i)}[k] = \frac{1}{m} \sum_{j=1}^{m} \delta_{\hat{X}^{(i)}_j[k]} \quad i \in [T], \end{cases}$$

- $\hat{X}^{(i)}_j[0] \overset{i.i.d.}{\sim} \boldsymbol{\mu}^{(i)}_0$
- $\eta > 0$ is a step-size
- $Z^{(i)}_{j,k}$ are i.i.d. standard Gaussian variables

Chizat et al., 2022

Exponential convergence

Theorem (Chizat, 2022)

Let $\boldsymbol{\mu}_0 \in \mathcal{P}(\mathcal{X})^T$ be such that $F(\boldsymbol{\mu}_0) < \infty$. Then for $\epsilon \geq 0$, there exists a unique solution $(\boldsymbol{\mu}_s)_{s \geq 0}$ to the MFL dynamics. For $\epsilon > 0$, $\mathcal{X}$ the d-torus, and moreover assuming that $\boldsymbol{\mu}_0$ has a bounded absolute log-density, it holds

$$F_\epsilon(\boldsymbol{\mu}_s) - \min F_\epsilon \leq e^{-Cs}(F_\epsilon(\boldsymbol{\mu}_0) - \min F_\epsilon),$$

where $C = \beta e^{-\alpha/\epsilon}$ for some $\alpha, \beta > 0$ independently of $\boldsymbol{\mu}$ and ϵ.

Taking ϵ_s decaying slowly enough, $\boldsymbol{\mu}_s$ converges weakly to the minimizer $\boldsymbol{\mu}^*$.

Chizat et al., 2022; Chizat, 2022

Sketch of proof of exponential convergence

Chizat, 2022 is workhorse: 3 assumptions to check

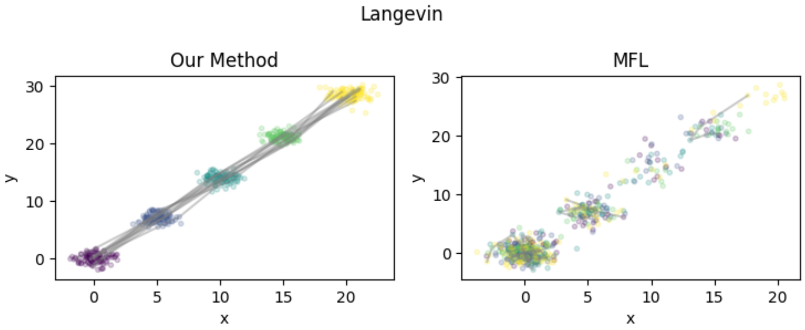
- Smoothness of G: first-variation V is Lipschitz continuous
- Convexity of F_0 and existence of minimizer for F_ϵ
- uniform log-Sobolev inequality: $\exists \rho_\tau > 0$ s.t. $\forall \mu \in \mathcal{P}_2(\mathbb{R}^d)$, we have $\nu \propto e^{-V[\mu]/\tau} \in L^1(\mathbb{R}^d)$ s.t.

$$H(\mu|\nu) \leq \frac{1}{2\rho} I(\mu|\nu)$$

In our setting: still true

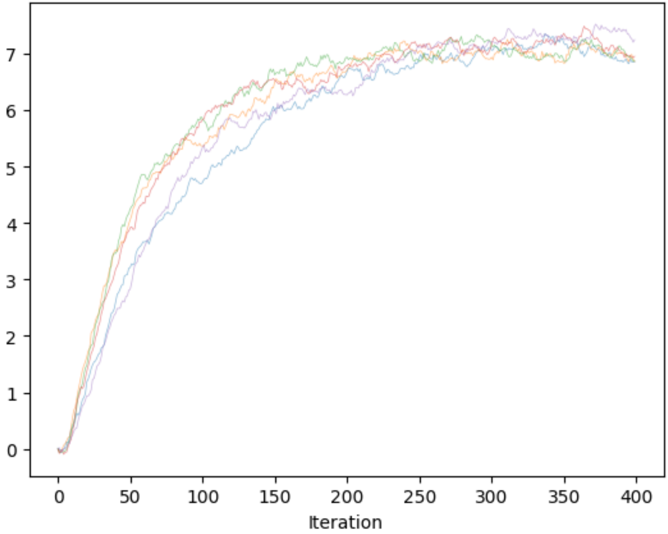
Table of Contents

Velocity model: robustness

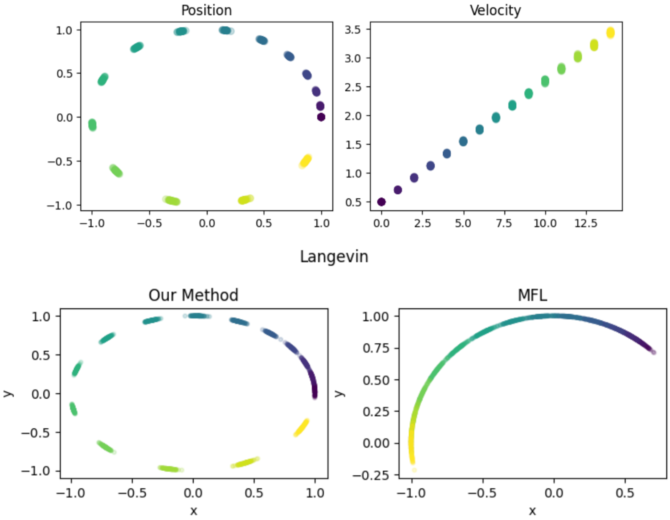


- Initial condition is at the origin
- x velocity: 5, y velocity: 7
- MFL fails to converge

Velocity model: exponential convergence



Circular motion model: recovered position



Circular motion model: recovered velocity

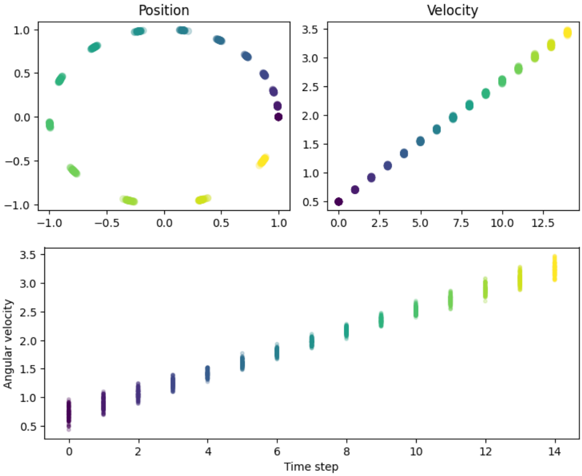


Table of Contents

Future work

Conjecture

For every $t_1 < t_2$, with $\Delta t := t_2 - t_1$ sufficiently small, we have

$$|T_{\tau_i,\Xi}(\mu_{t_1}, \mu_{t_2}) - T_{\tau_i}(\Xi_\sharp^{\Delta t}\mu_{t_1}, \mu_{t_2})| = O(\Delta t)$$

and

$$|H(\gamma_\Xi|\mathbf{W}_{t_1,t_2}^{\Xi,\tau}) - H(\gamma|\mathbf{W}_{t_1,t_2}^{\tau})| = O(\Delta t),$$

where γ_Ξ and γ are the corresponding optimal transport plan to $T_{\tau_i,\Xi}(\mu_{t_1}, \mu_{t_2})$ and $T_{\tau_i}(\Xi_\sharp^{\Delta t}\mu_{t_1}, \mu_{t_2})$, respectively.

- Statistical properties of the estimator
- Relaxed assumptions on g, Ξ
- Empirical validation of predicting outcomes of individuals

Conclusion

- Trajectory inference without observing whole particles
- Entropy minimization using reference measure with drift
- Approximation to obtain well-posed entropic OT problem
- Experimental validation

Questions?

References

- Schiebinger, Shu, Tabaka, Cleary, et al. Optimal-transport analysis of single-cell gene expression identifies developmental trajectories in reprogramming, 2019.
- Lavenant, Zhang, Kim, Schiebinger, 2021. Towards a mathematical theory of trajectory inference.
- Chizat, Zhang, Heitz, Schiebinger, 2022. Trajectory inference vi mean-field Langevin in path space.
- Chizat, 2022. Mean Field Langevin Dynamics: Exponential convergence and annealing