Using optimal transport for trajectory inference

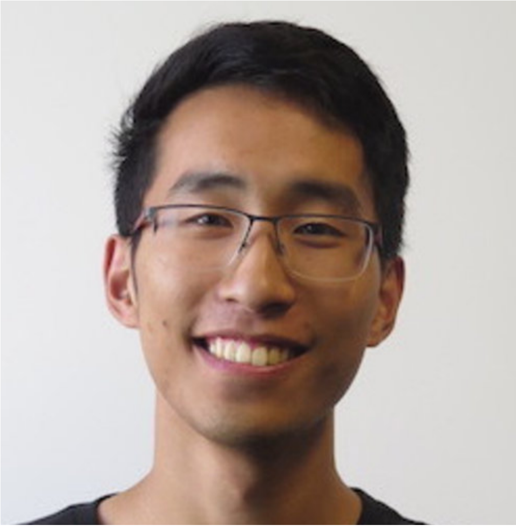
Hugo Lavenant

Bocconi University

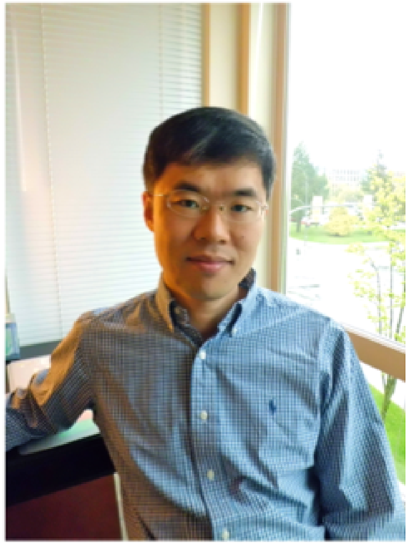
When AI meets Biology: a workshop, Lyon (online), October 1st, 2021

Lavenant*, Zhang*, Kim, Schiebinger (2021). Towards a mathematical theory of trajectory inference. Arxi 2102.09204

Joint work with:



Stephen Zhang



Young-Heon Kim

Geoff Schiebinger

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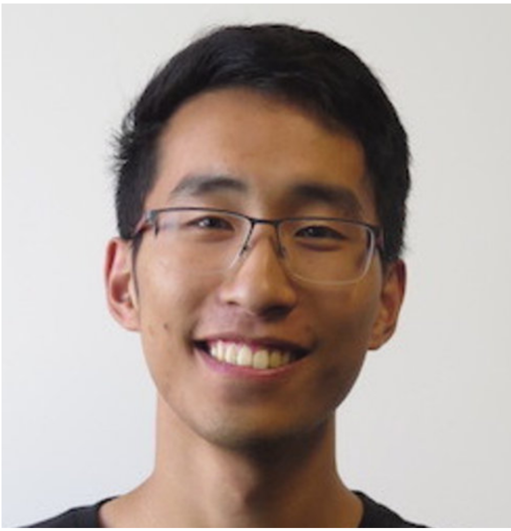

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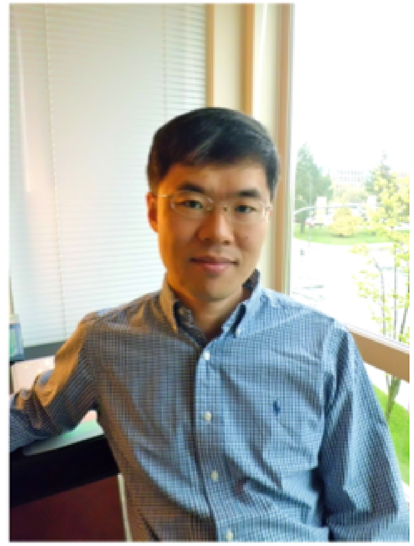


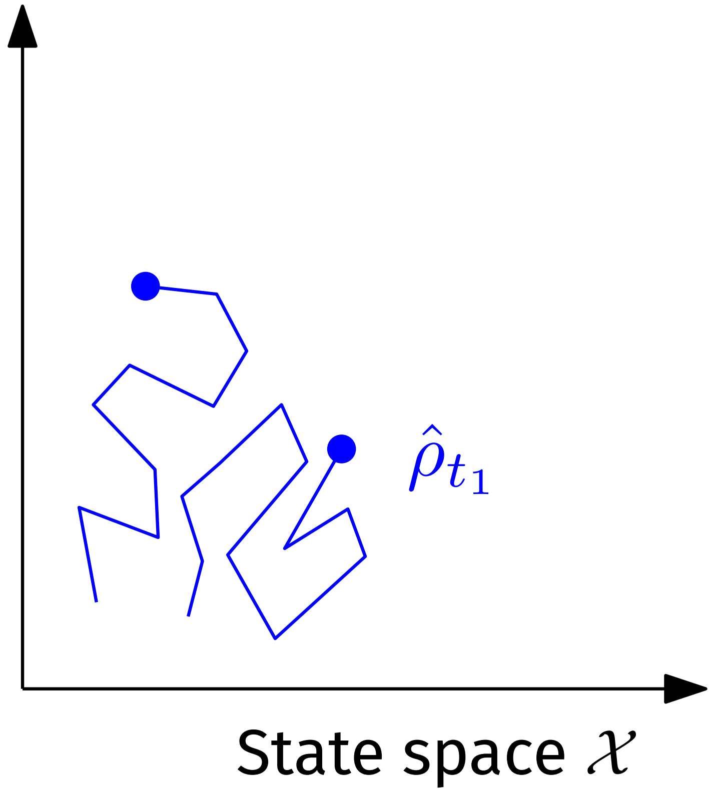
Young-Heon Kim

Geoff Schiebinger

Disclaimer

I am not a biologist, nor a statistican.
My background: convex analysis, PDE, Optimal Transport.

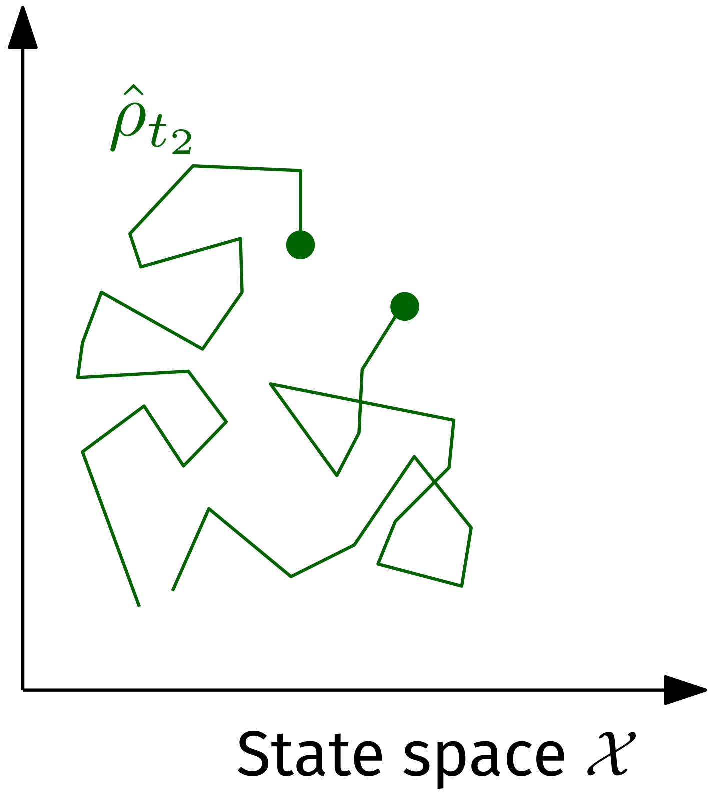
A preview of the mathematical problem



Stochastic process X_t

Samples from law of X_{t_1}

A preview of the mathematical problem

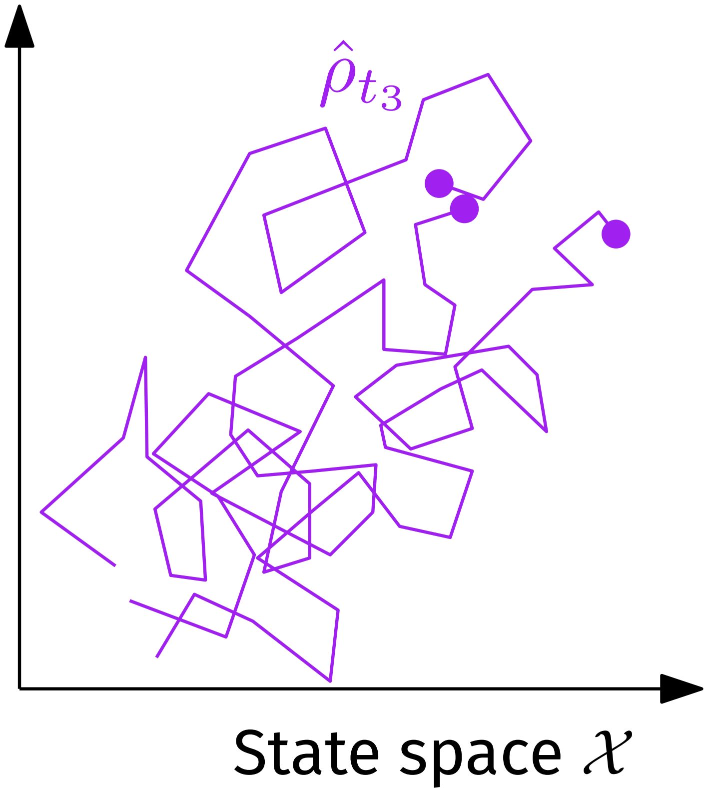


Stochastic process X_t

Samples from law of X_{t_2}

(independent from the previous samples)

A preview of the mathematical problem

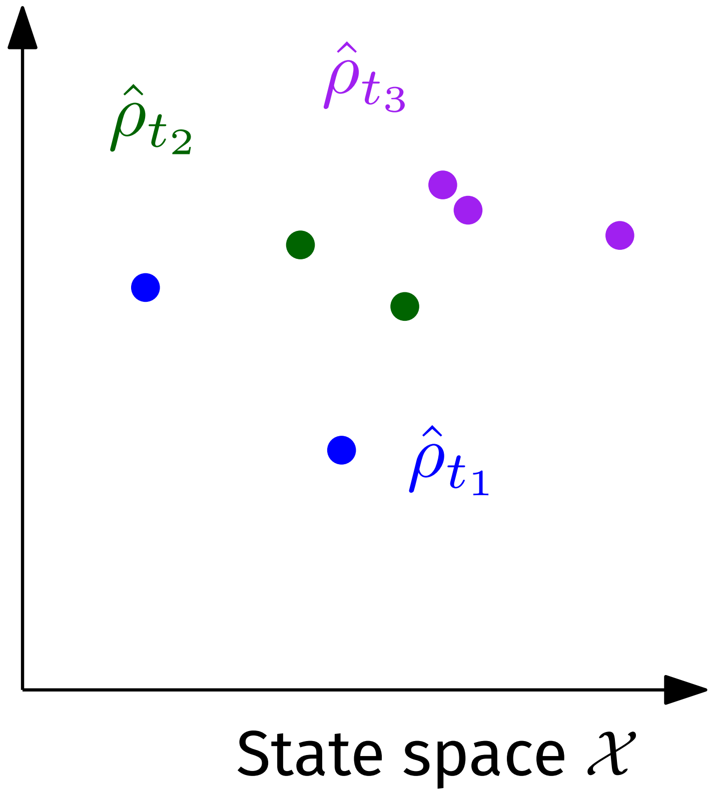


Stochastic process X_t

Samples from law of X_{t_3}

(independent from the previous samples)

A preview of the mathematical problem



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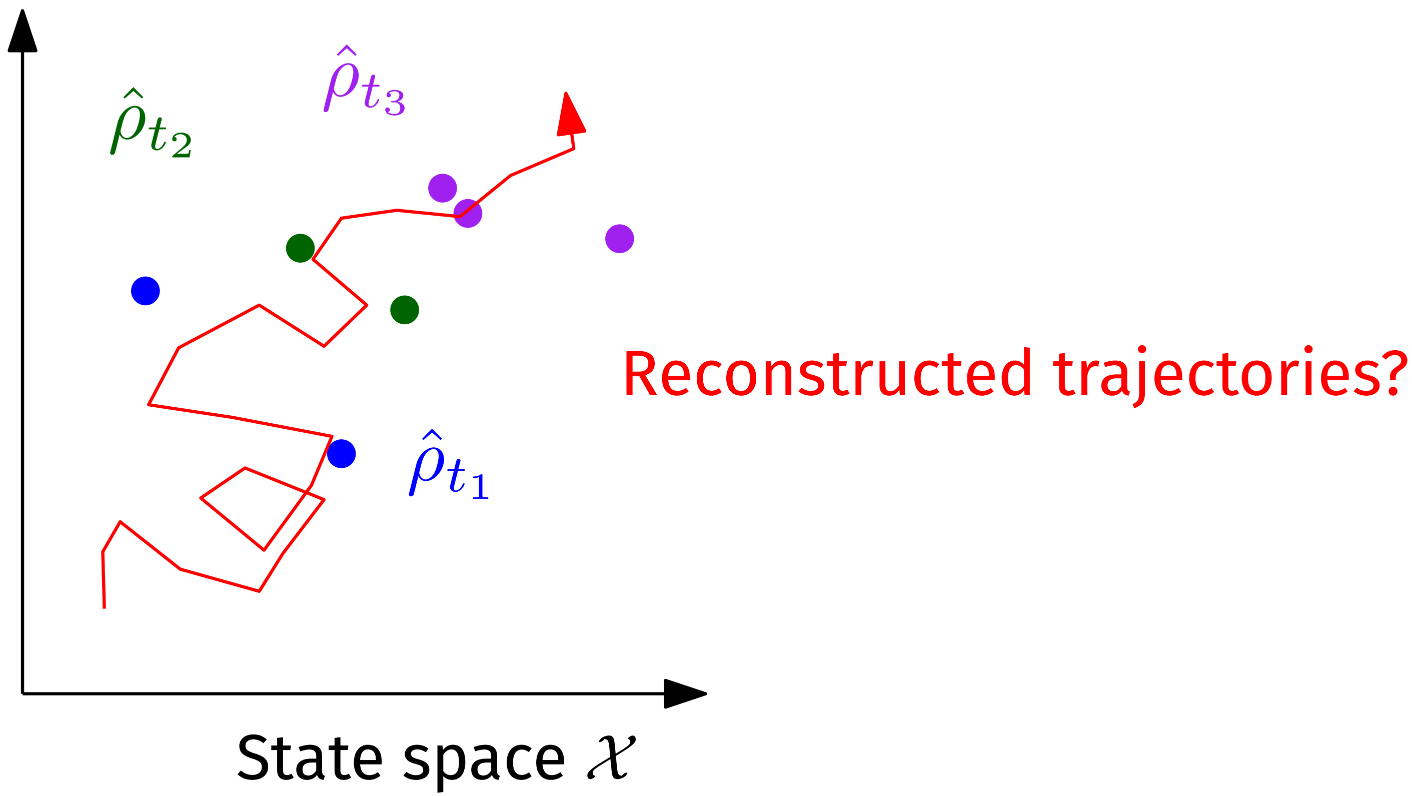
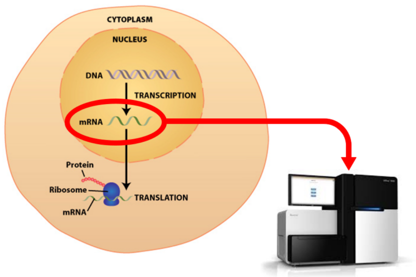
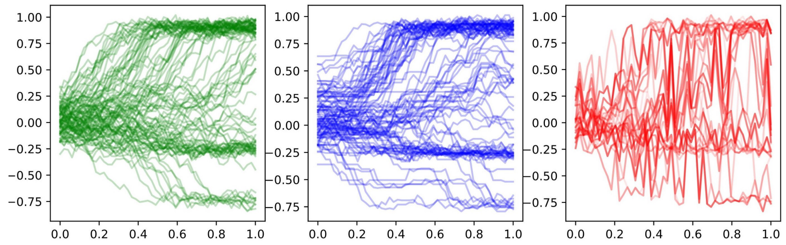


Goal: reconstruct the law of the trajectories X_t from samples of the temporal marginals.

1 - Biological Context





2 - Algorithms and results

3 - Theoretical analysis

$$\boxed{\mathrm{d}X_t = \mathbf{v}(t, X_t)\mathrm{d}t + \sigma \mathrm{d}B_t}$$

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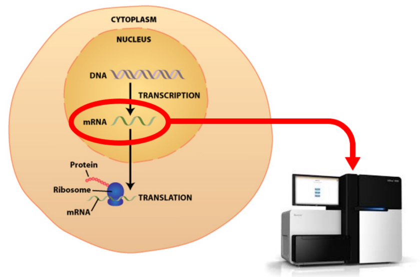

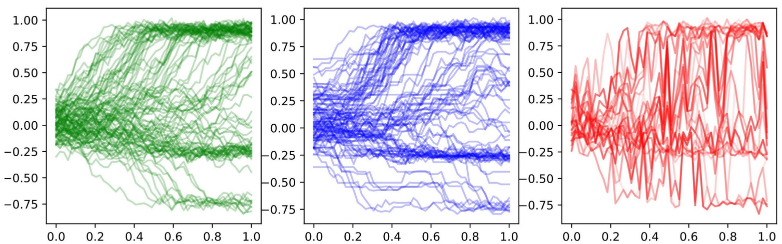

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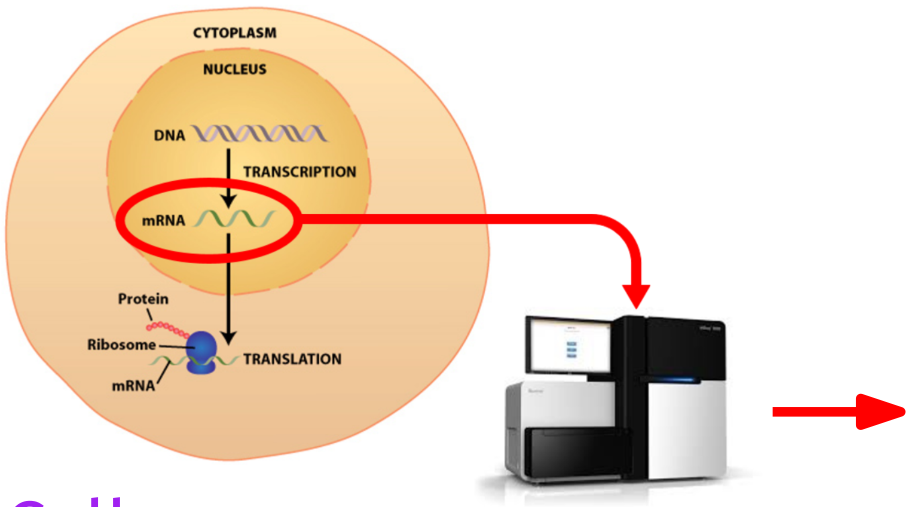
Single-cell RNA sequencing



Cell

Gene expression profile

$$\begin{pmatrix} \text{Number RNA gene 1} \\ \text{Number RNA gene 2} \\ \vdots \\ \text{Number RNA gene N} \end{pmatrix}$$

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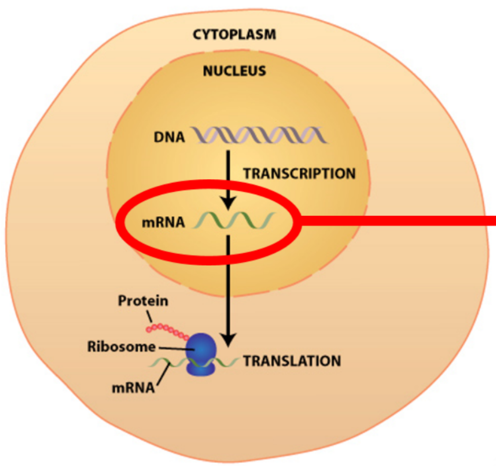

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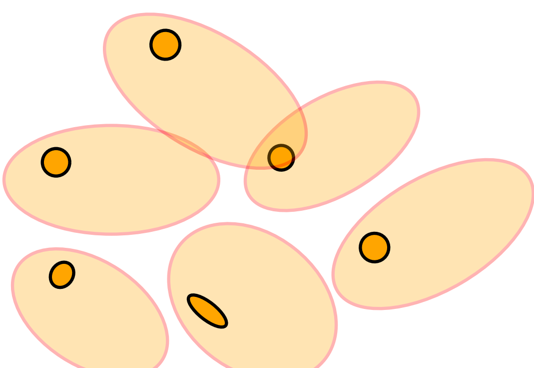
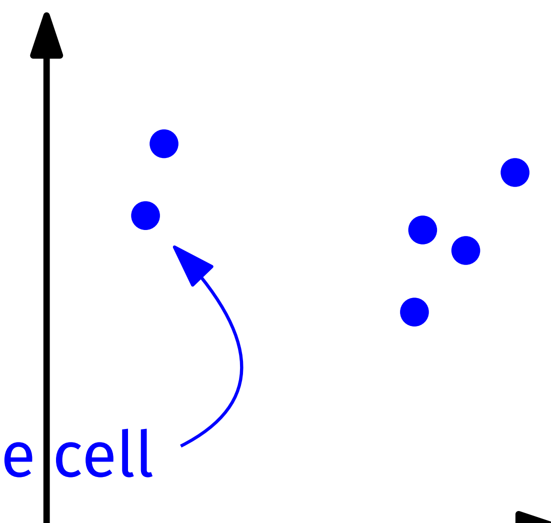


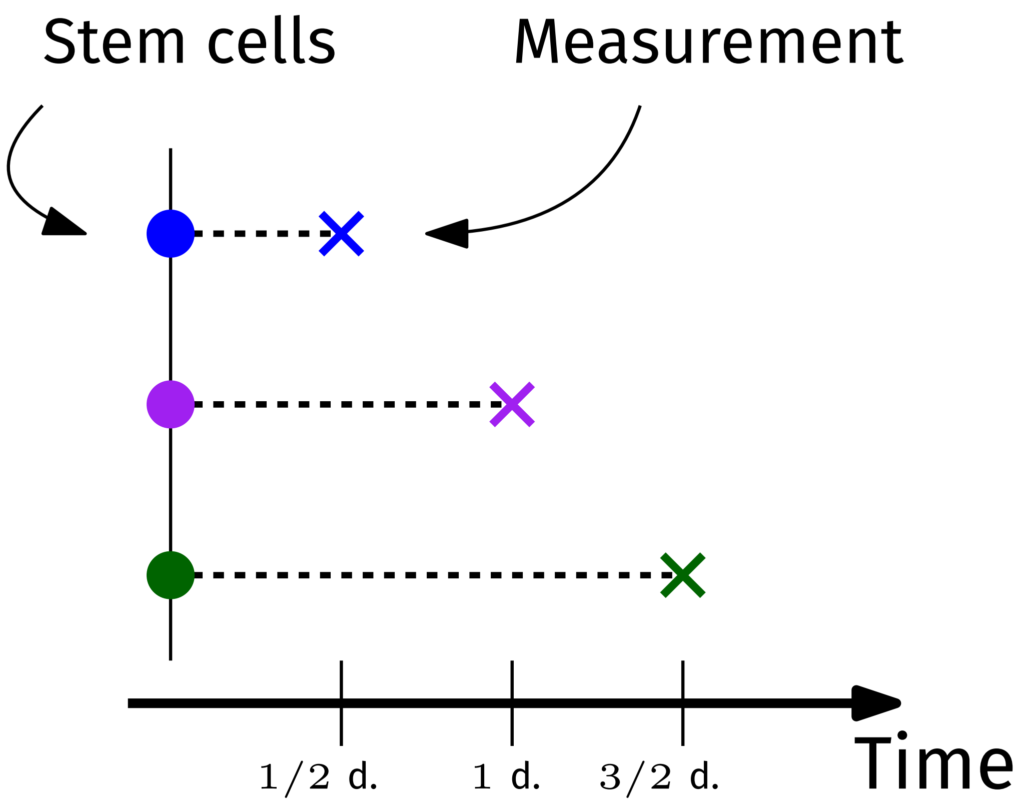
Population of cells



State of one cell

Gene expression space $\mathcal{X}$

Investing cell differentiation



Schiebinger et al. (2019). Reconstruction of developmental landscapes by optimal-transport analysis of single-cell gene expression sheds light on cellular reprogramming.

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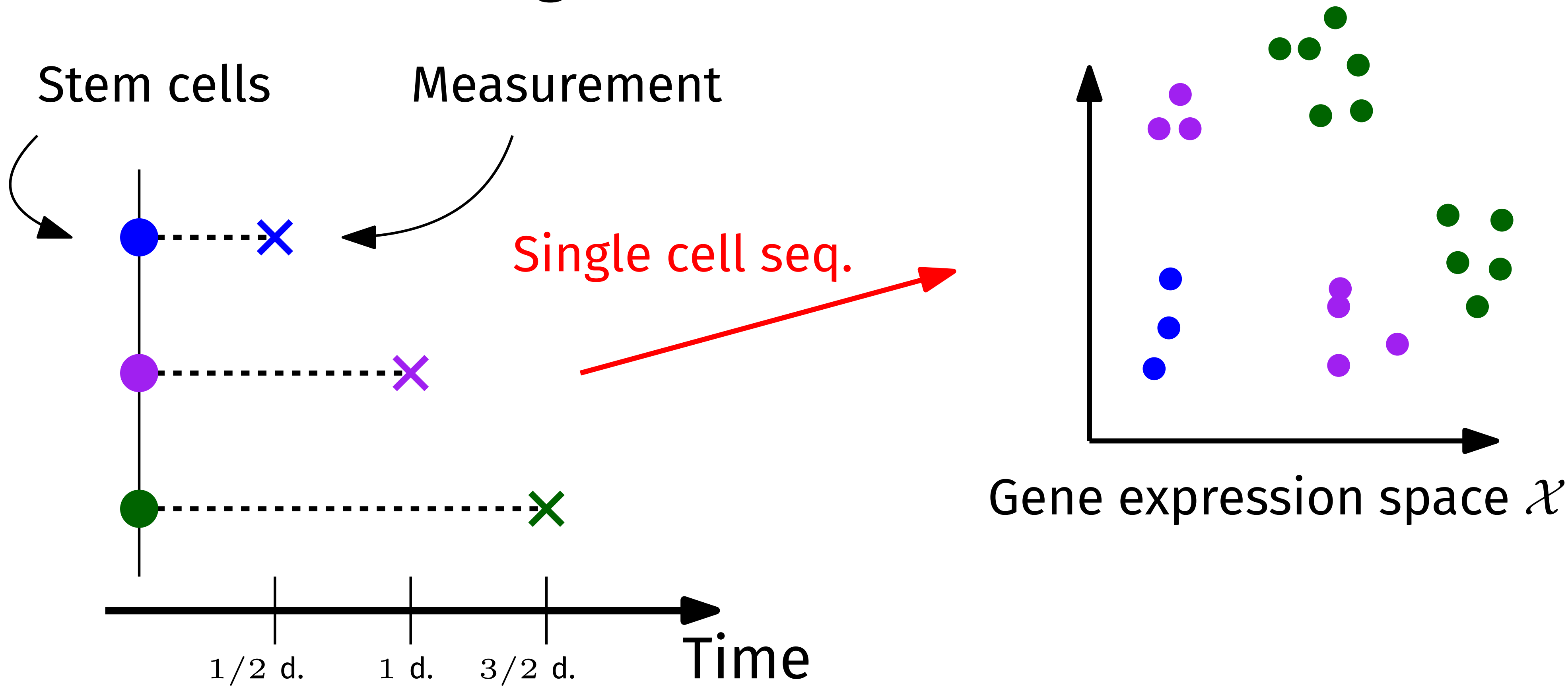

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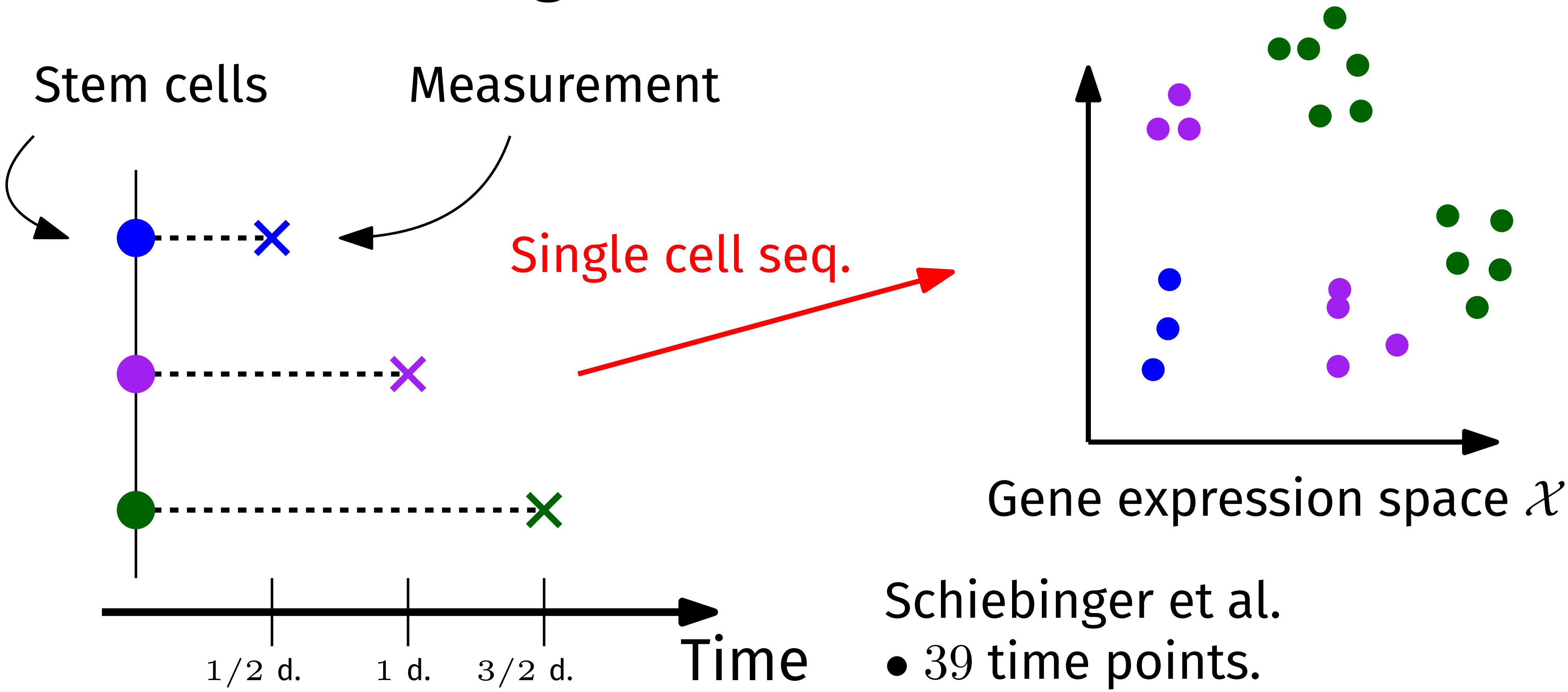


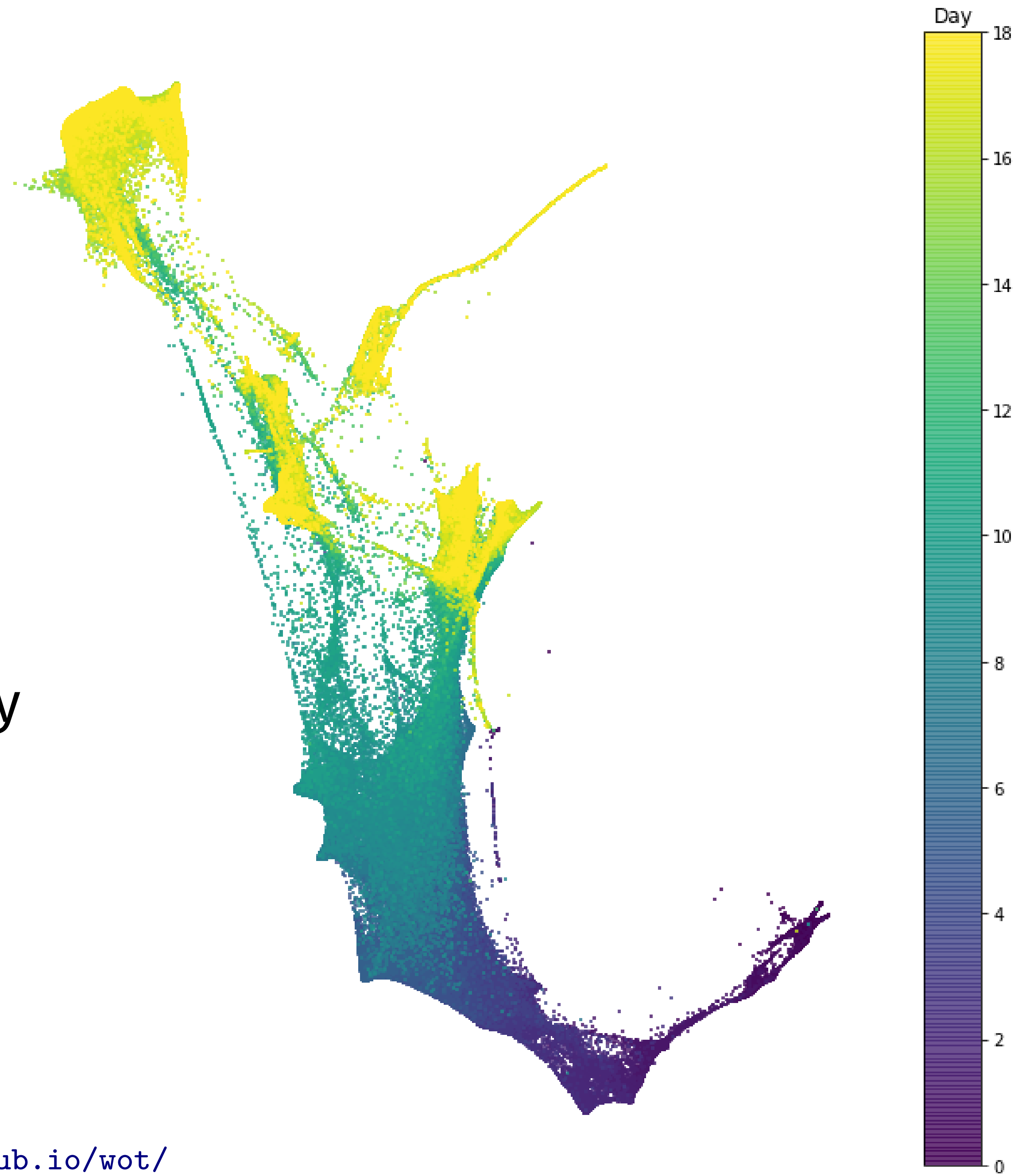
Schiebinger et al.

- 39 time points.
- Total $250,000$ cells measured.

(Biological) goal: reconstruct fate of cells, unravel the regulatory network.

Schiebinger et al. (2019). Reconstruction of developmental landscapes by optimal-transport analysis of single-cell gene expression sheds light on cellular reprogramming.

Dataset

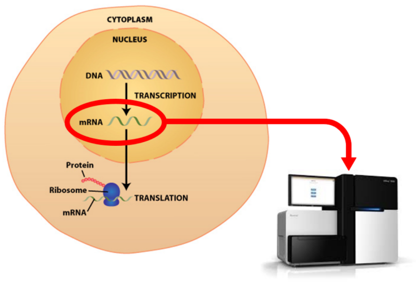


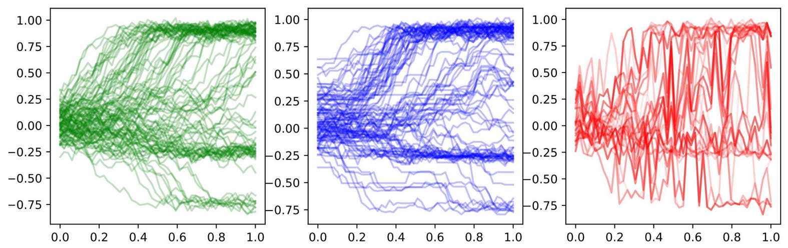
Displayed with **Force Layout Embedding** (FLE), a dimensionality reduction technique

https://broadinstitute.github.io/wot/

Disclaimer: for the moment, we ignore branching.

1 - Biological Context





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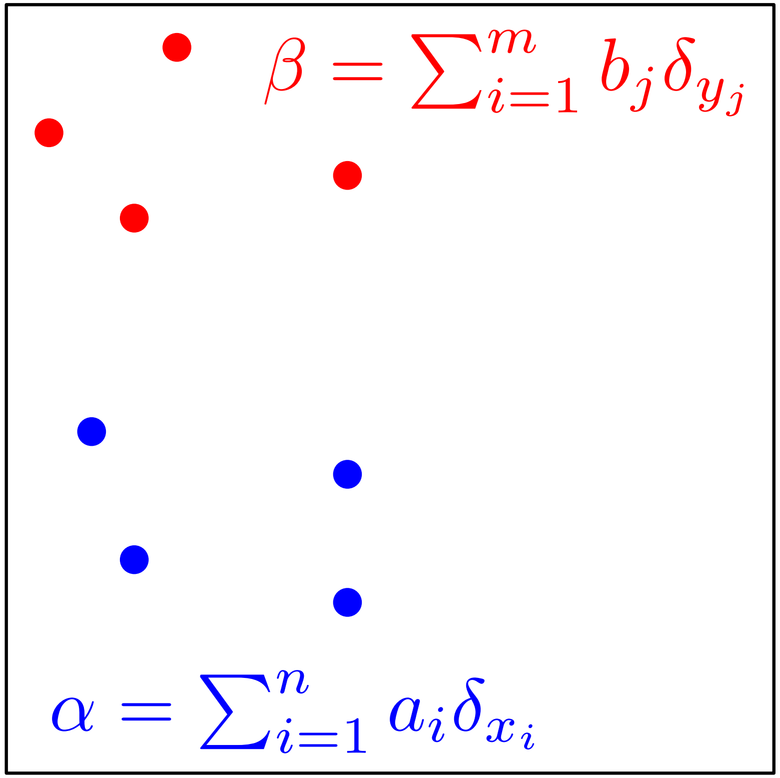
(Entropic) optimal transport

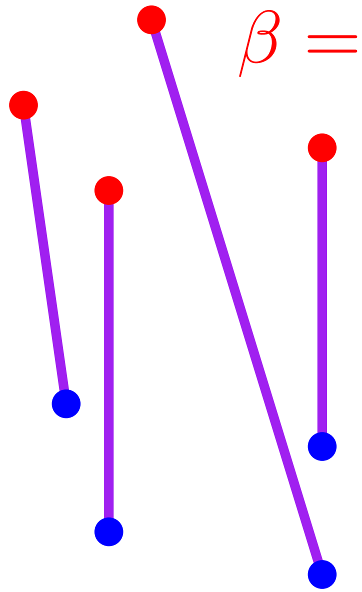


Probability distributions:

$$\sum_i a_i = \sum_j b_j = 1$$

(Entropic) optimal transport

$\beta = \sum_{i=1}^{m} b_j \delta_{y_j}$



$\alpha = \sum_{i=1}^{n} a_i \delta_{x_i}$

Probability distributions:

$\sum_i a_i = \sum_j b_j = 1$

Find $\pi \geq 0$ such that

$$\begin{cases} \sum_j \pi_{ij} = a_i \\ \sum_i \pi_{ij} = b_j \end{cases}$$

and which minimizes

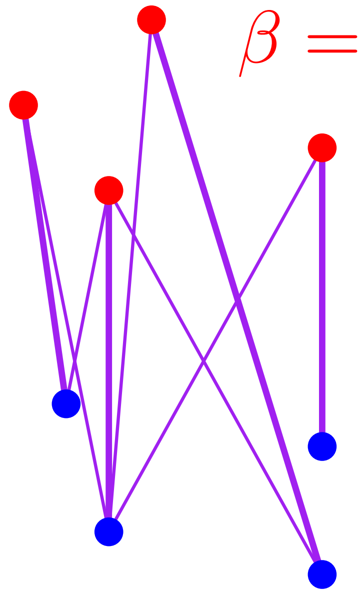
$$\sum_{ij} \pi_{ij} |x_i - y_j|^2$$

π law of (X, Y) with $X \sim \alpha$ and $Y \sim \beta$:

$$\mathbb{P}(X = x_i, Y = y_j) = \pi_{ij}$$

Peyré and Cuturi. (2019). Computational Optimal Transport.

(Entropic) optimal transport



$\beta = \sum_{i=1}^{m} b_j \delta_{y_j}$

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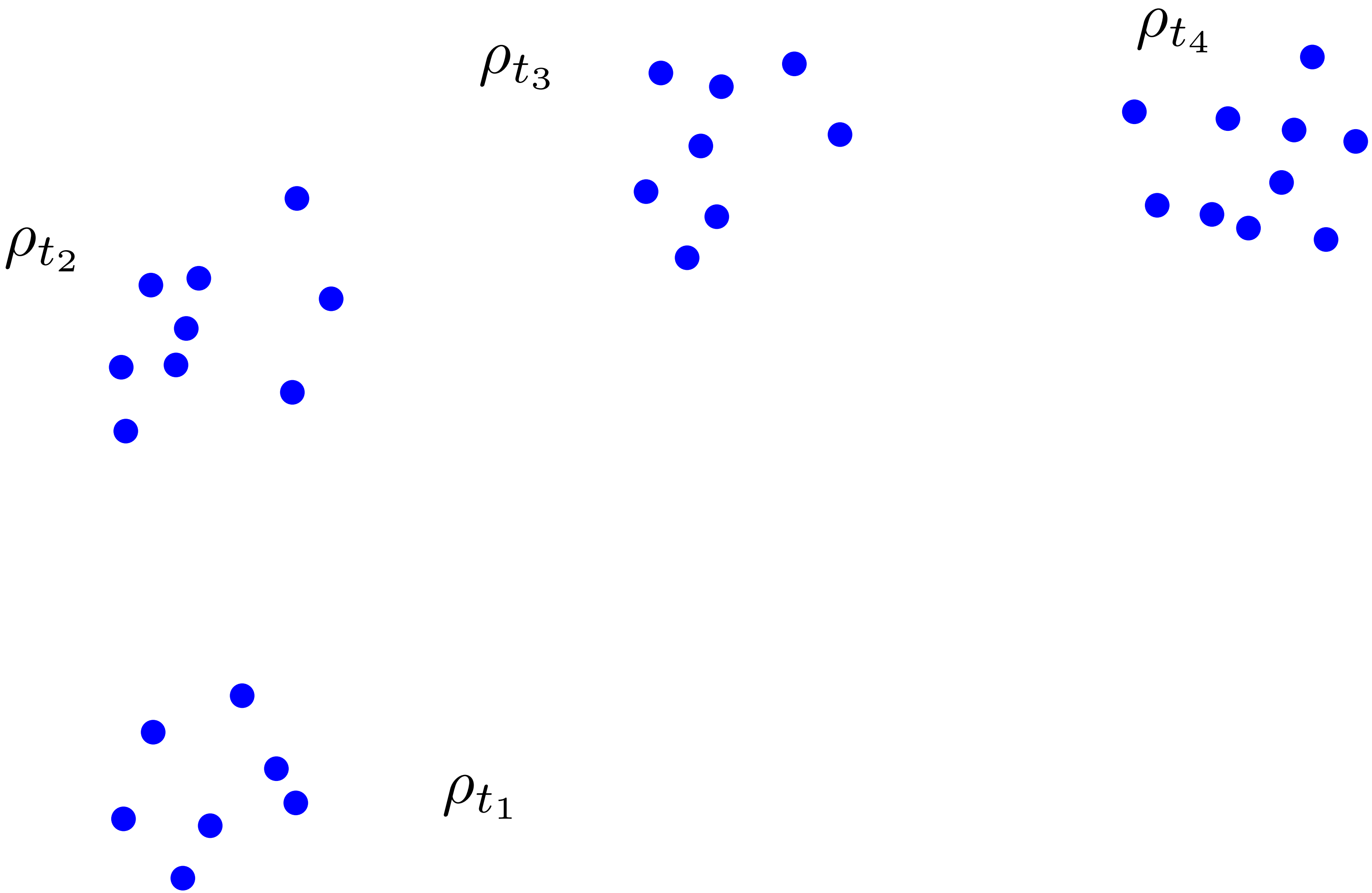
A description of (a simplified) Waddington OT

Input: $\rho_{t_1}, \rho_{t_2}, \ldots \rho_{t_T}$ probability measures
Ouptut: R law of reconstructed trajectories.



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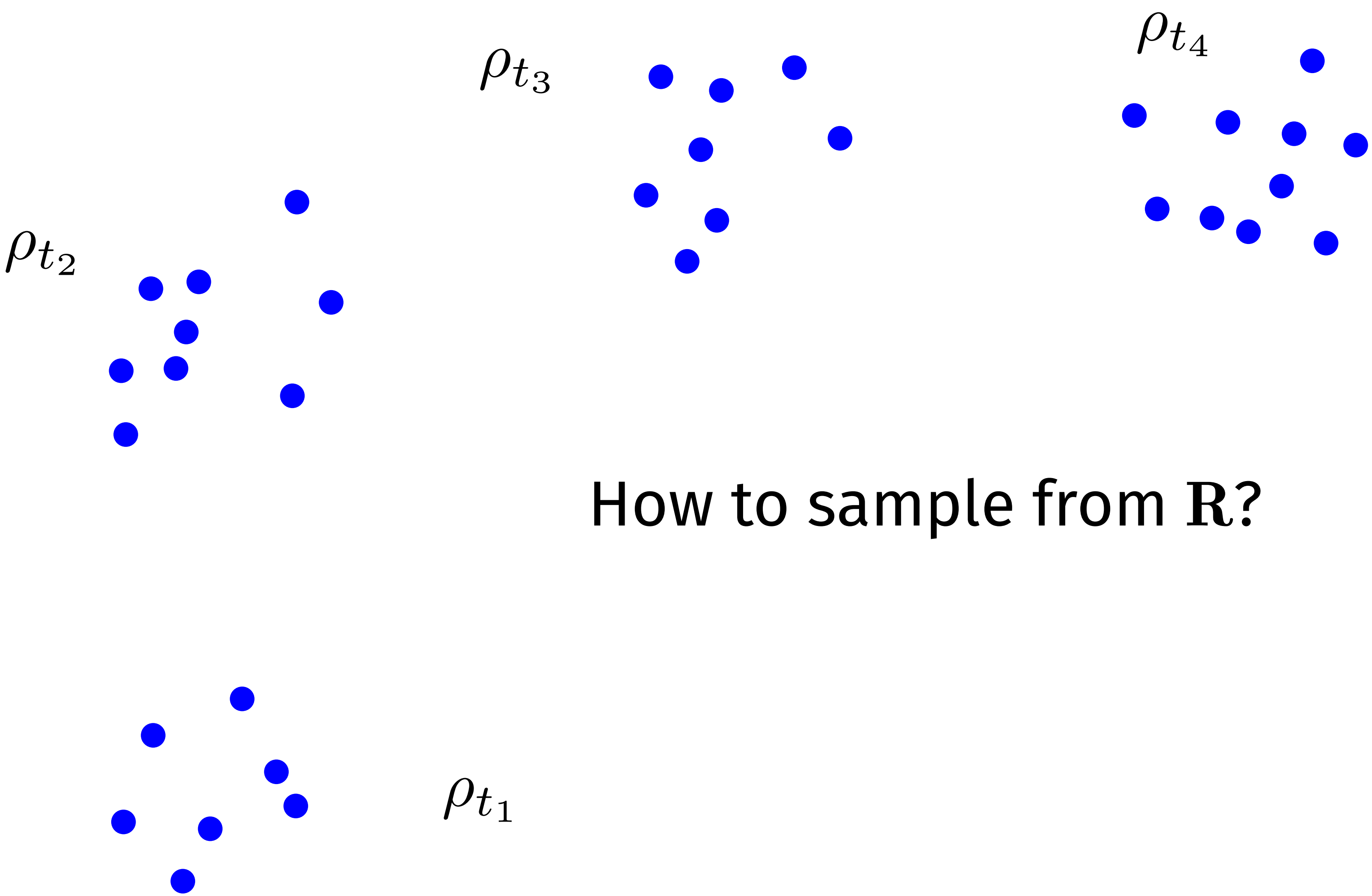

How to sample from $\mathbf{R}$?

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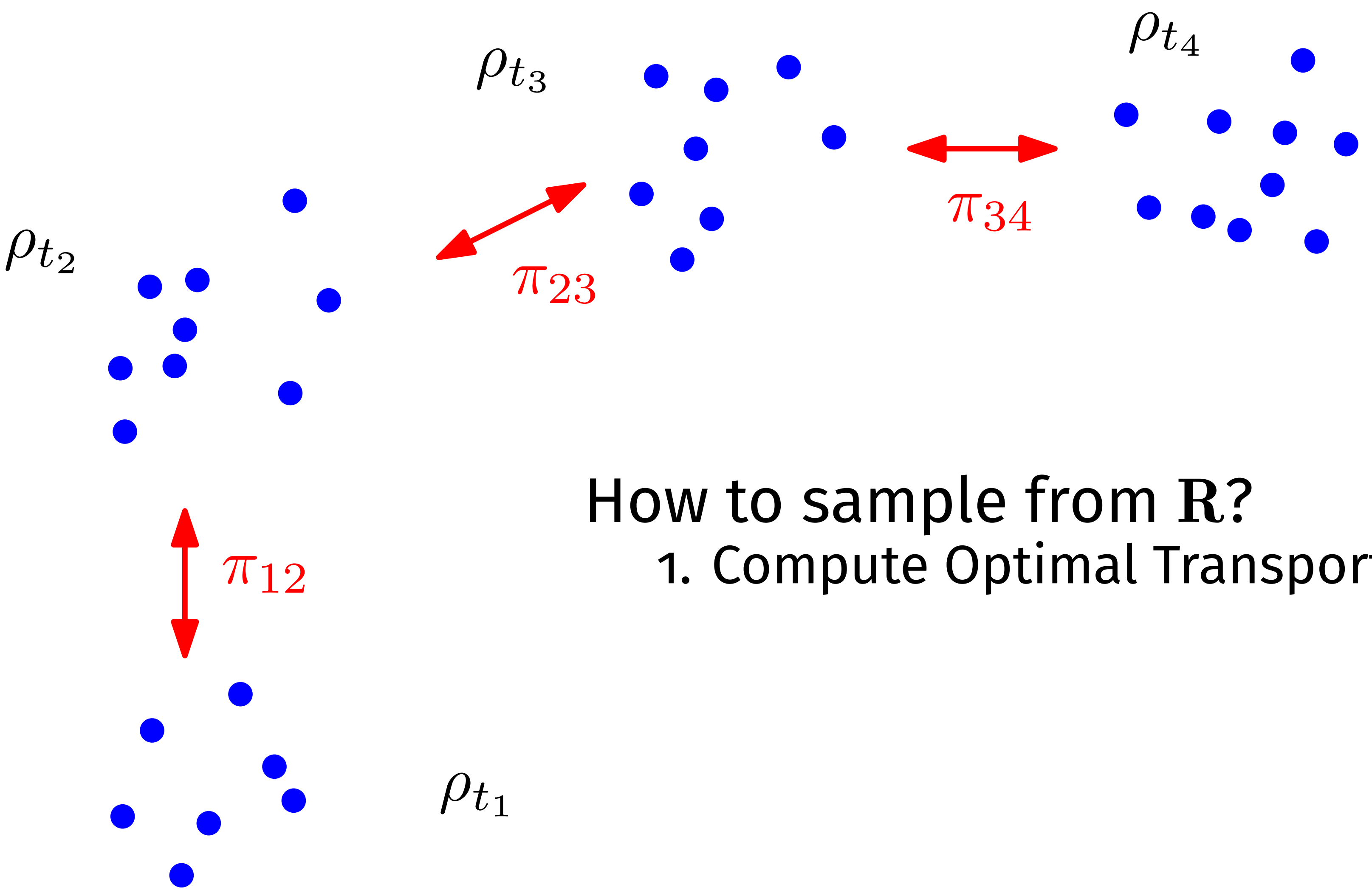

How to sample from $\mathbf{R}$?

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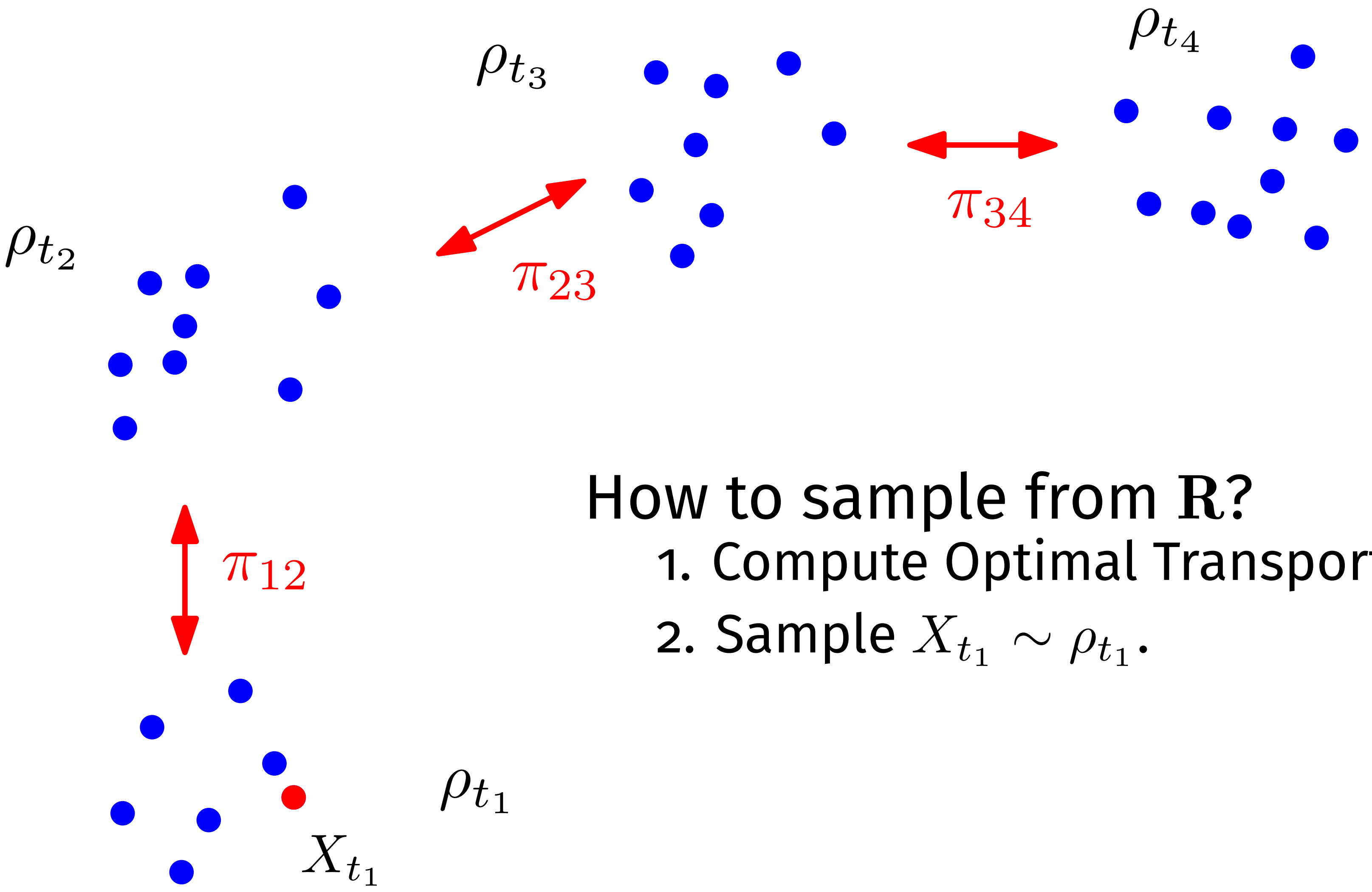

How to sample from $\mathbf{R}$?

1. Compute Optimal Transport couplings.
2. Sample $X_{t_1} \sim \rho_{t_1}$.

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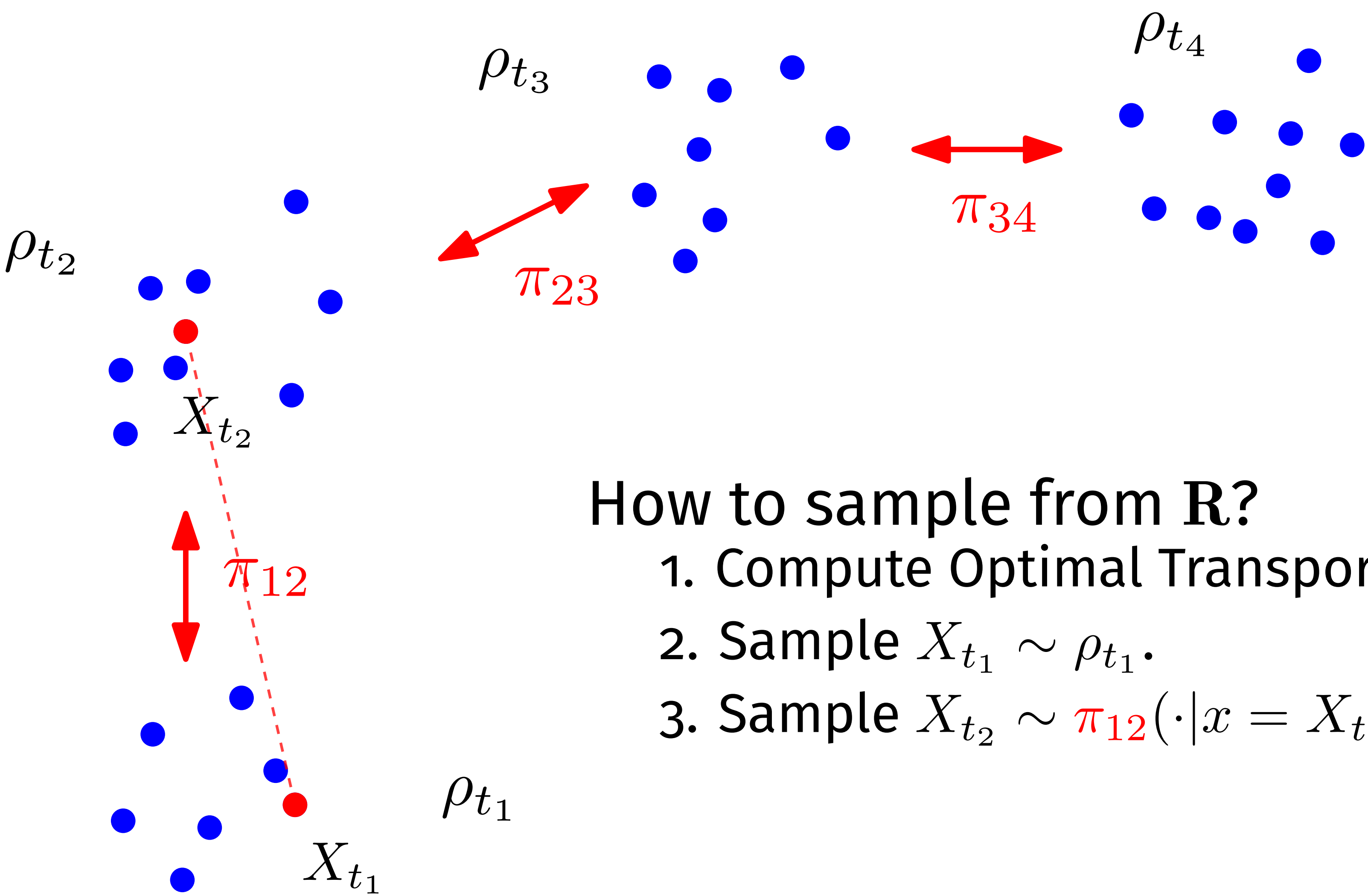

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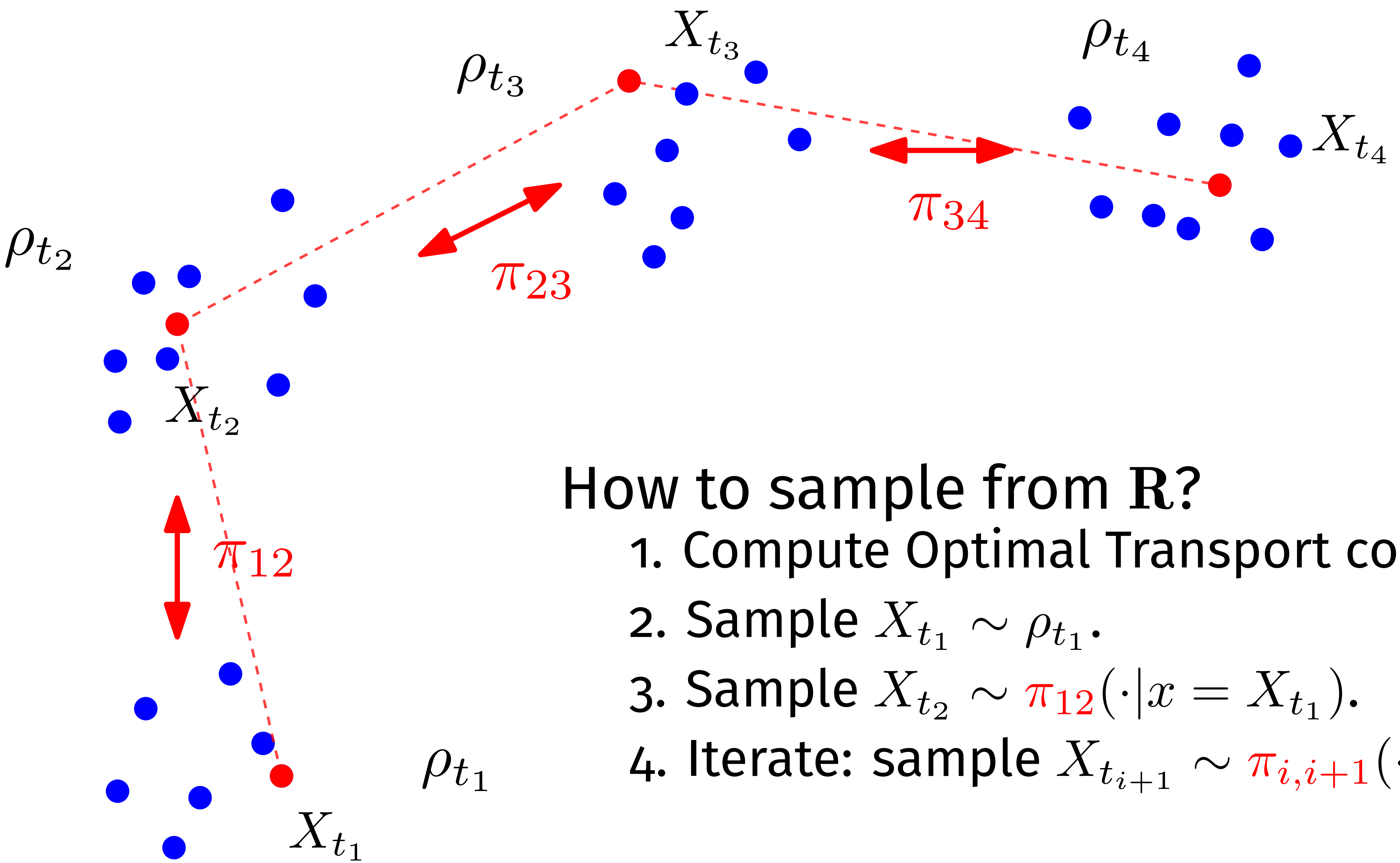

How to sample from $\mathbf{R}$?

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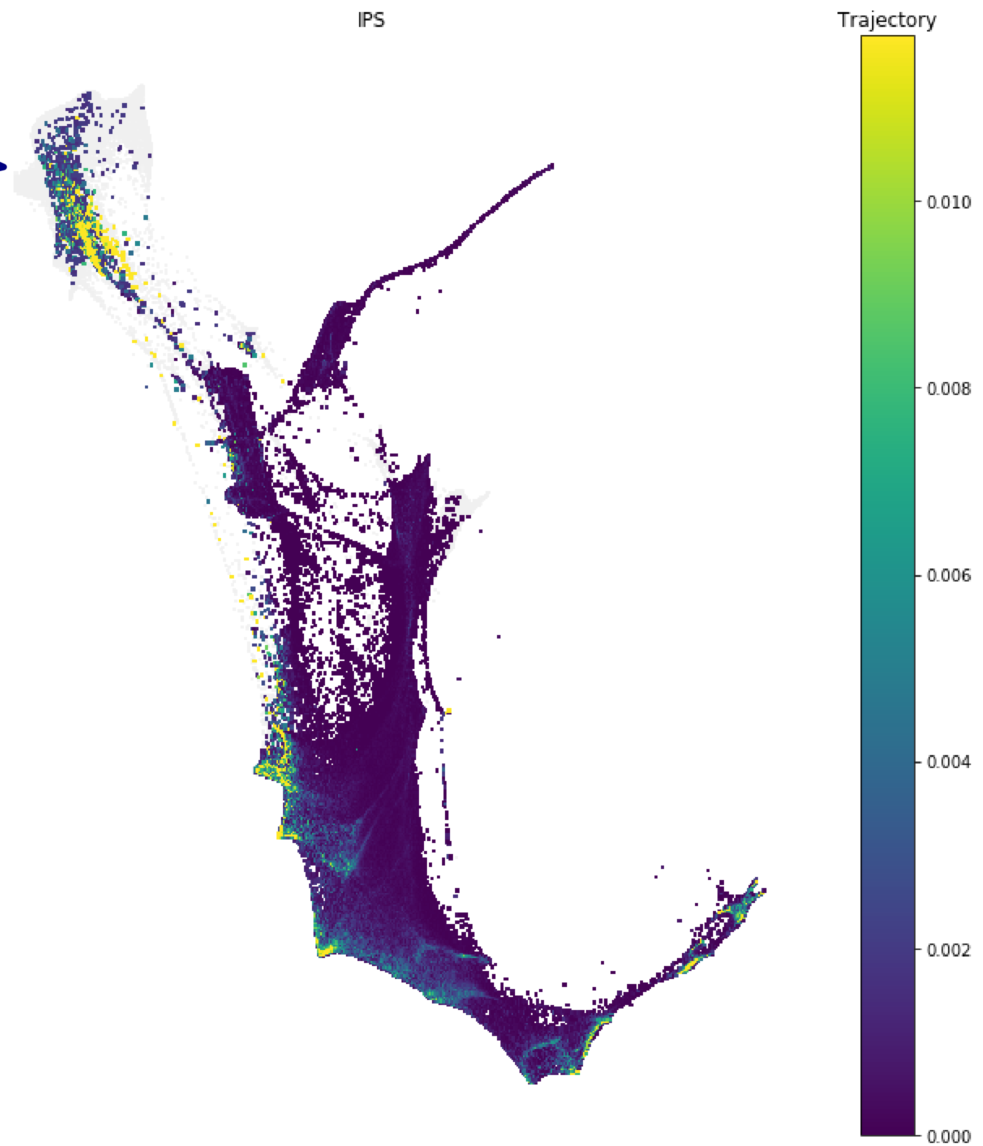
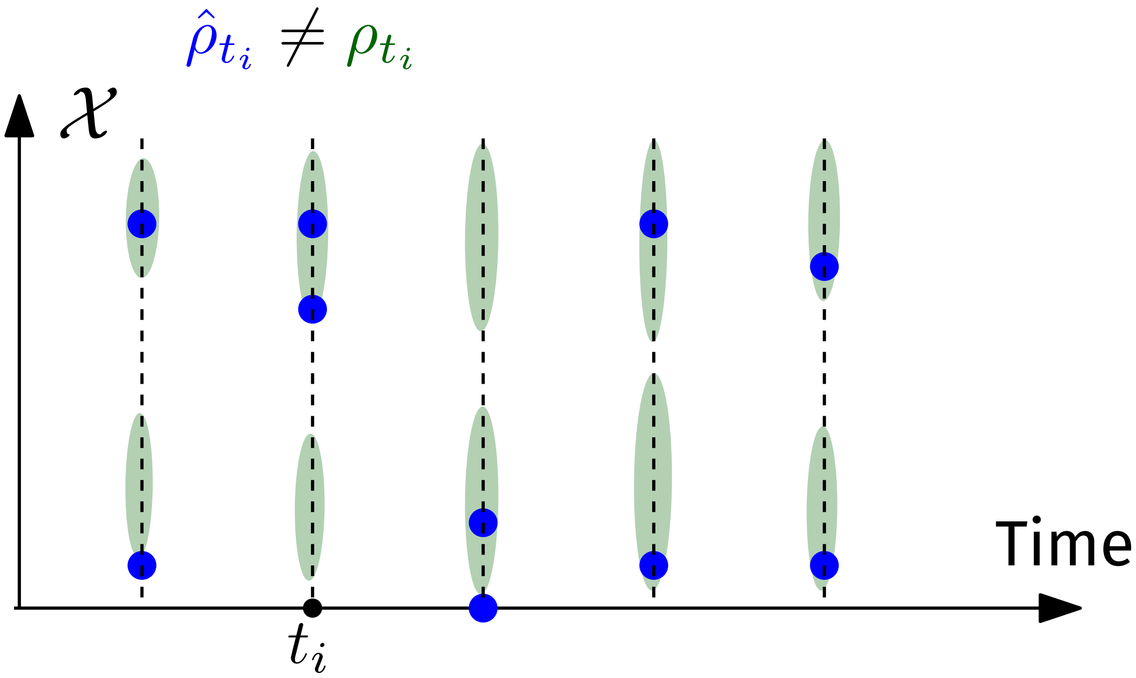
2. Sample $X_{t_1} \sim \rho_{t_1}$.
3. Sample $X_{t_2} \sim \pi_{12}(\cdot|x = X_{t_1})$.
4. Iterate: sample $X_{t_{i+1}} \sim \pi_{i,i+1}(\cdot|x = X_{t_i})$.

Example on the dataset of Schiebinger et al.

Looking at the ancestors
of a particular set of cells



"Sparse data" framework



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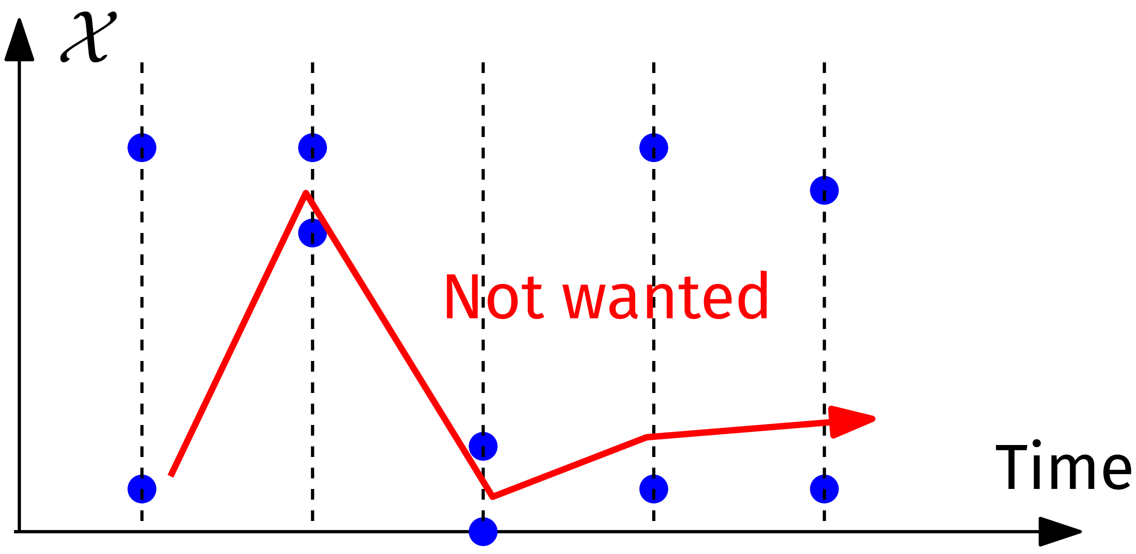

Few samples per time point, need to share information across time points.

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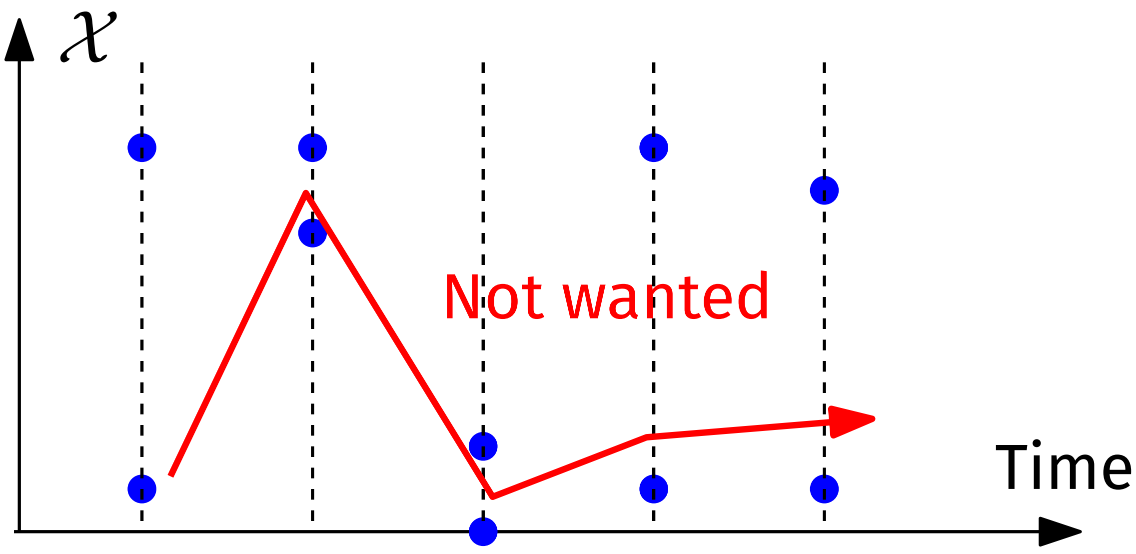


Few samples per time point, need to share information across time points.

Idea: **data fitting + regularization**

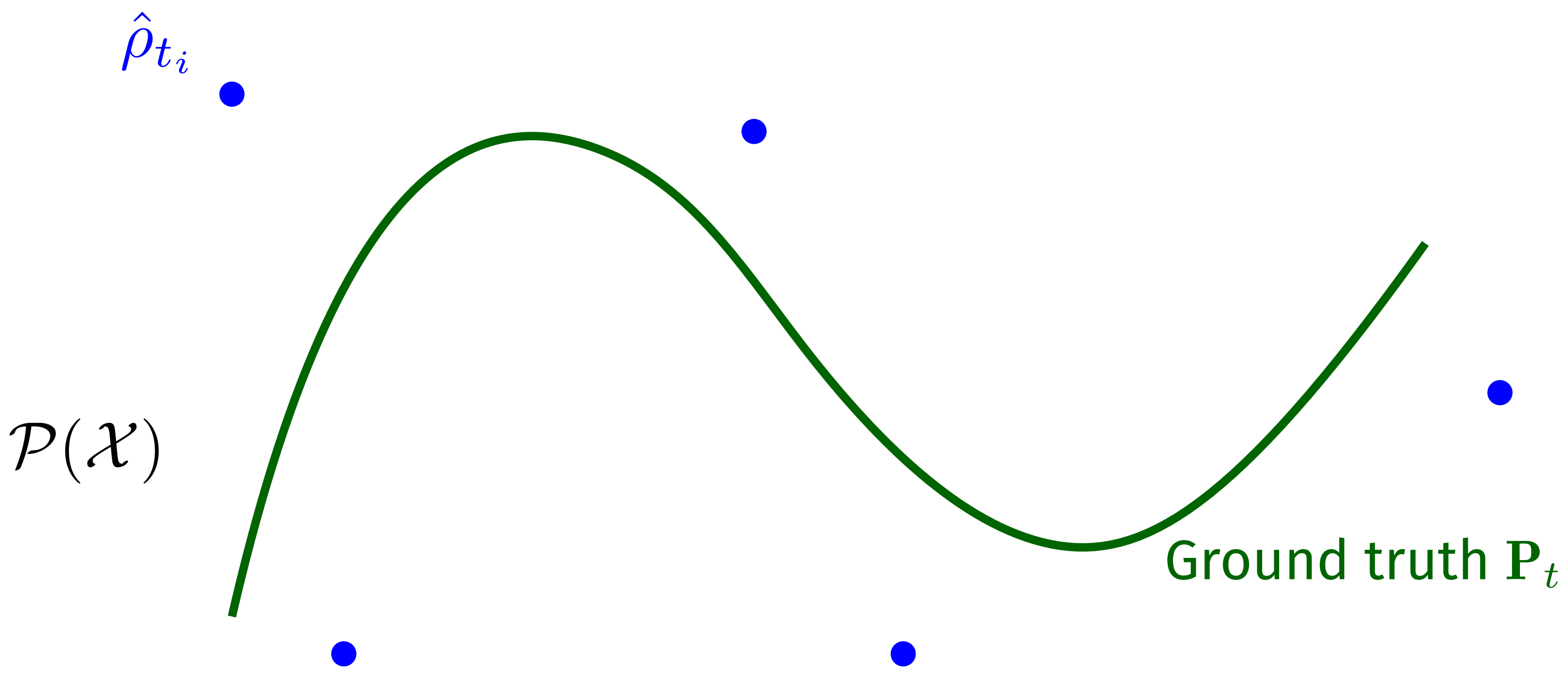
Cross entropy $H(\hat{\rho}_{t_i}|\mathbf{R}_{t_i})$ between data $\hat{\rho}_{t_i}$ and reconstructed marginal $\mathbf{R}_{t_i}$

Sum of optimal transport distances

Global Waddington OT

Unknowns: marginals $\mathbf{R}_{t_i}$,

$$\mathrm{Reg}((\mathbf{R}_{t_i})_i) \sim \sum_{i=1}^{T-1} \mathrm{OT}_\varepsilon(\mathbf{R}_{t_i}, \mathbf{R}_{t_{i+1}})$$



Global Waddington OT

Optimal transport cost

Unknowns: marginals $\mathbf{R}_{t_i}$,

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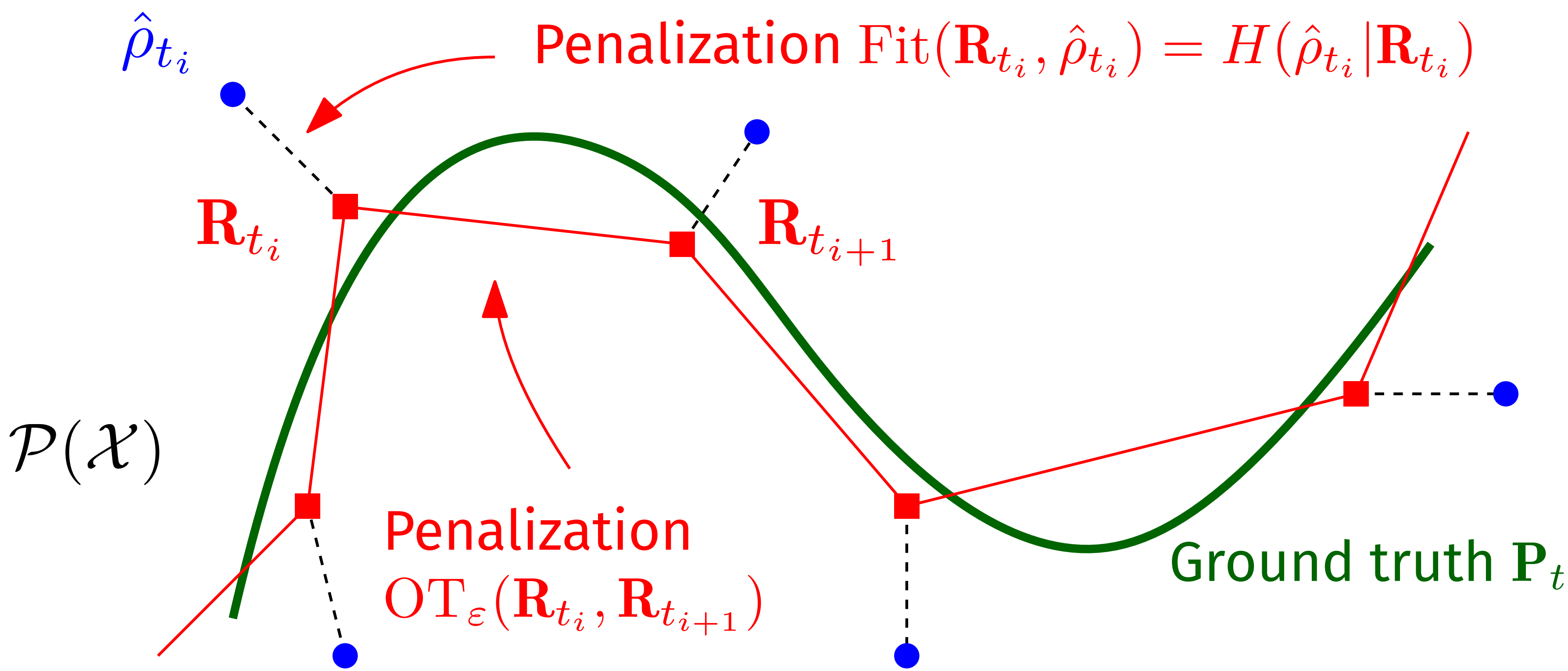
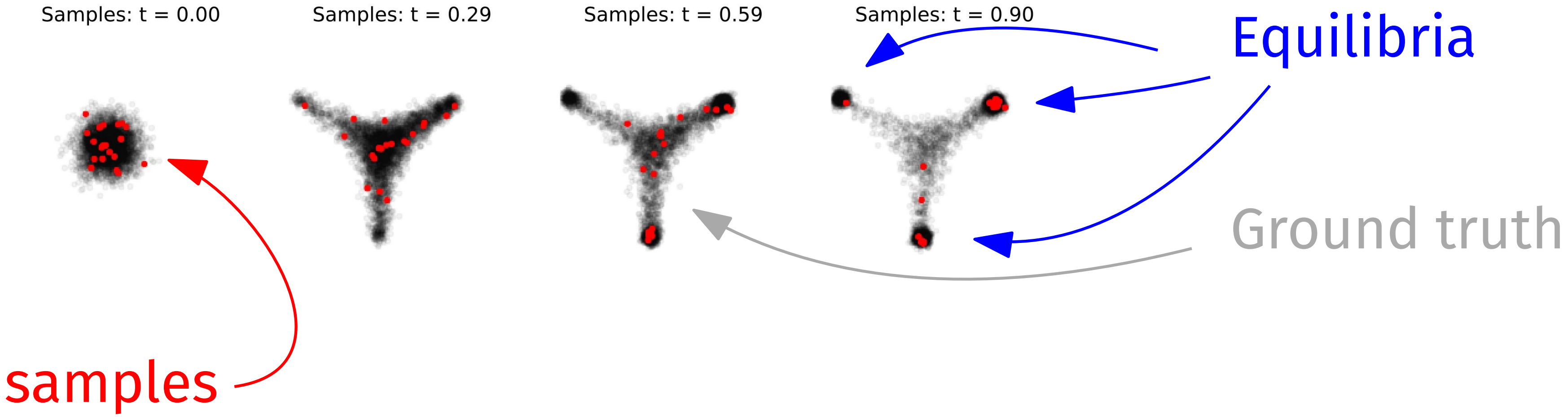


Numerical results (synthetic)



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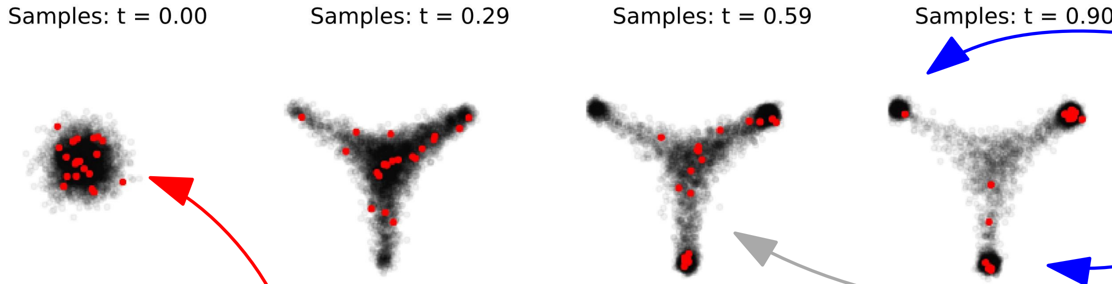
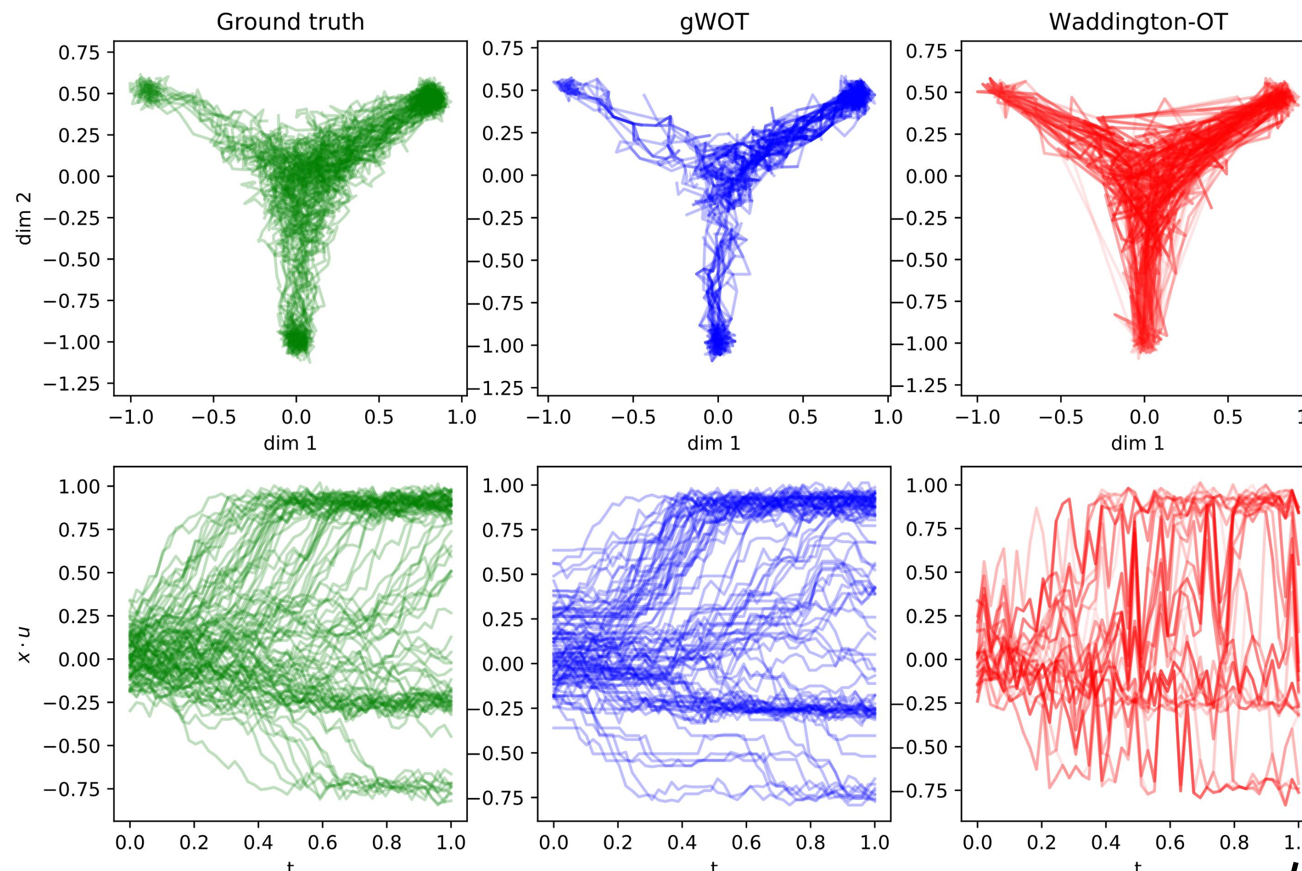


Equilibria

Ground truth

samples

Solving the inference problem



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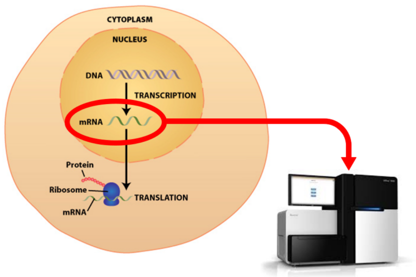

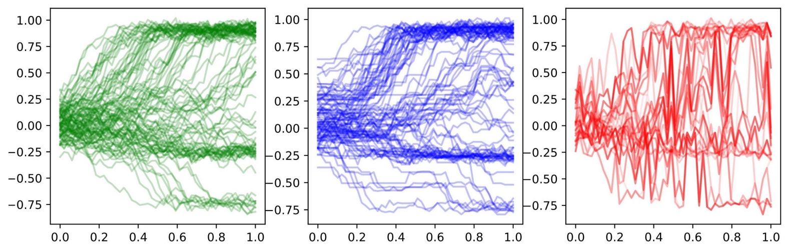

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Questions about (global) Waddington OT

In short: temporal couplings are given by optimal transport.

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In short: temporal couplings are given by optimal transport.

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3. Does it converge with more and more marginals?

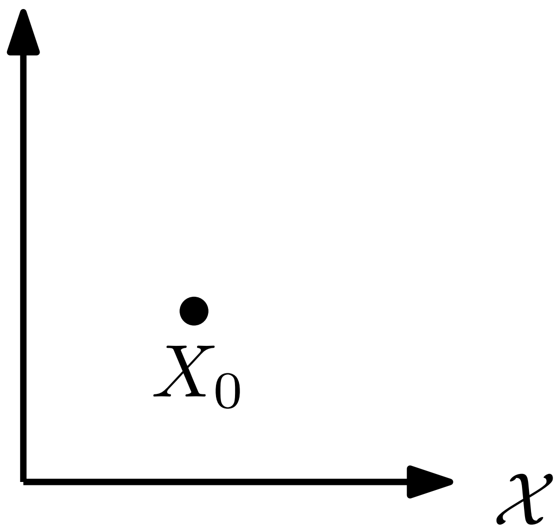
Short answer:

- Works if data is generated by a **potential** Stochastic Differential Equation.
- Choose $\varepsilon = \sigma^2 \Delta t$ with σ noise level in the SDE.

Generative model

The position of each cell X_t follows a **Stochastic Differential Equation** (SDE):

$$\boxed{\mathrm{d}X_t = \mathbf{v}(t, X_t)\mathrm{d}t + \sigma \mathrm{d}B_t.}$$



Le Gall (2016). Brownian motion, martingales, and stochastic calculus.

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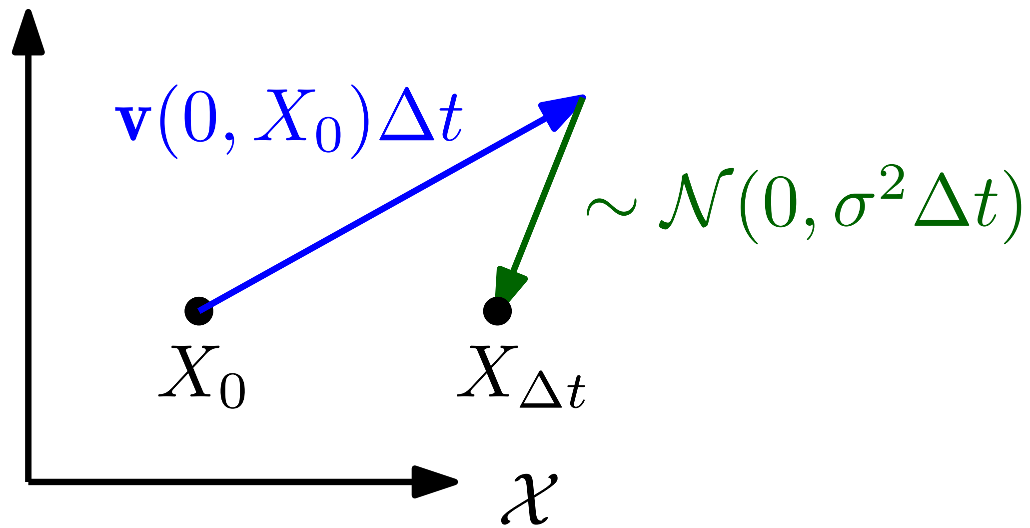

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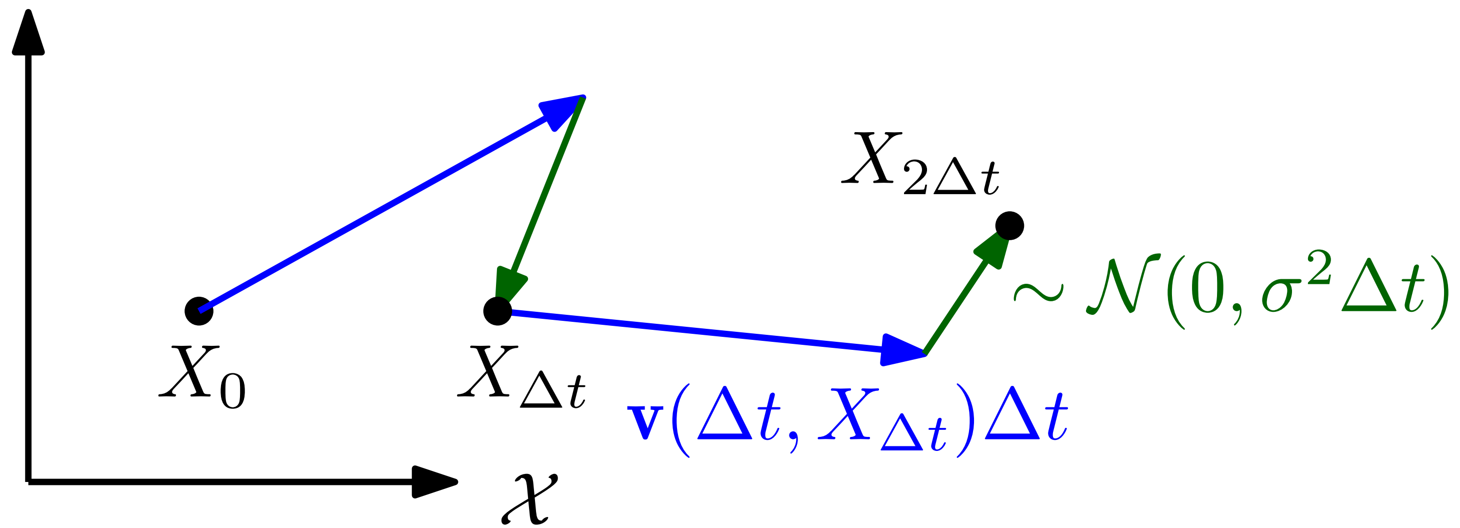

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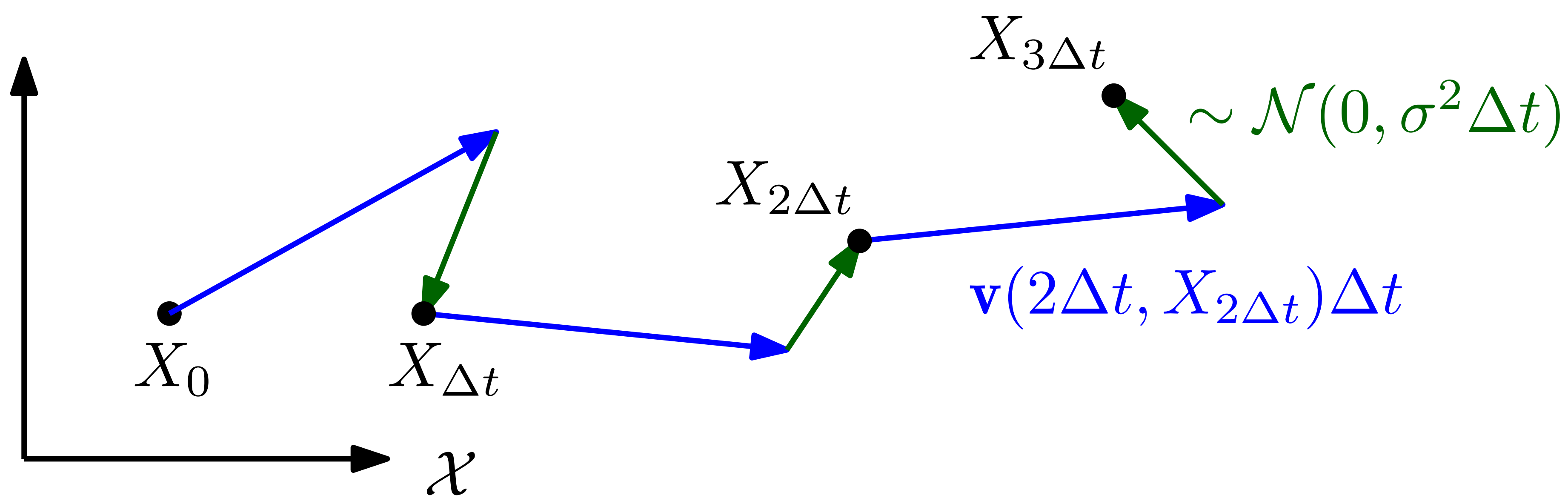

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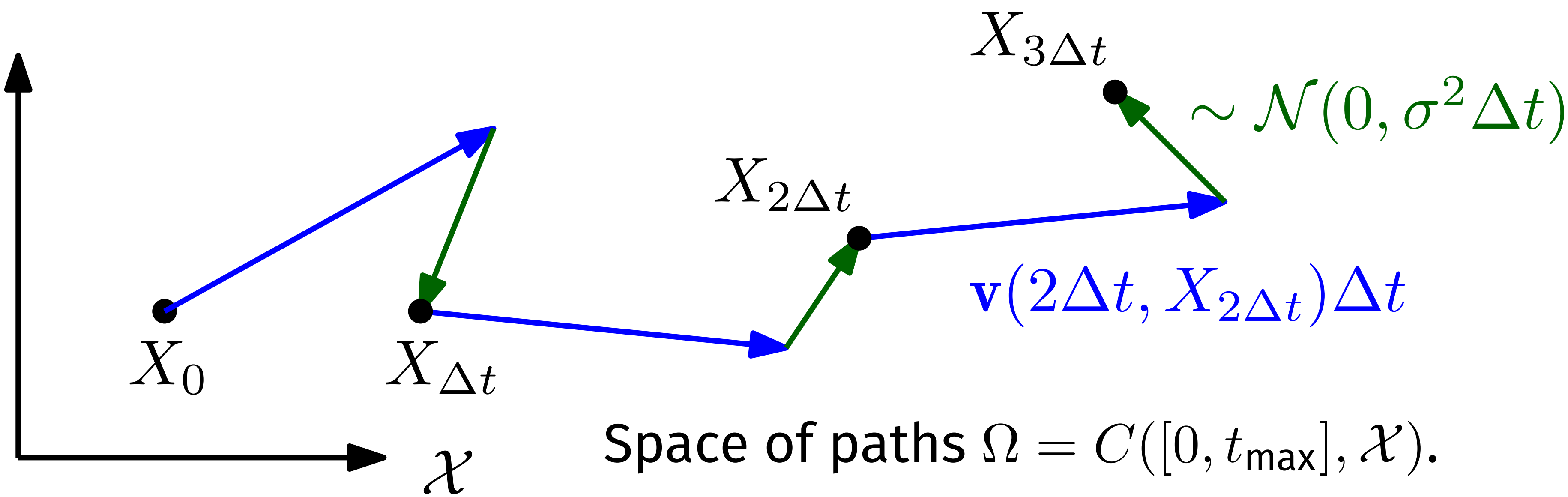


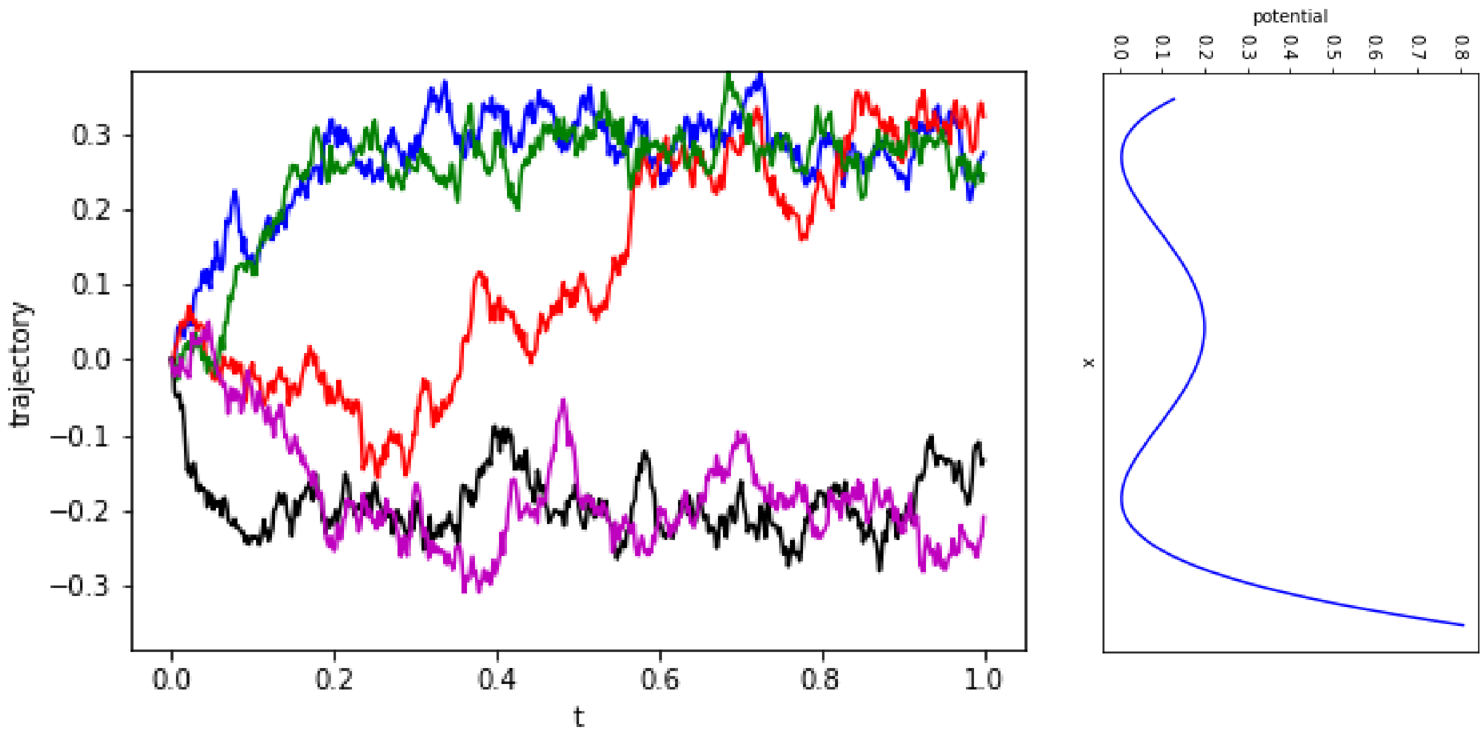
Space of paths $\Omega = C([0, t_{\mathsf{max}}], \mathcal{X})$.

A SDE is entirely characterized by $(\mathbf{v}, \sigma)$, or by $\mathbf{P} \in \mathcal{P}(\Omega)$ the probability distribution it induces on Ω.

Le Gall (2016). Brownian motion, martingales, and stochastic calculus.

Potential SDEs

Potential $\Psi = \Psi(t,x)$ such that $\mathbf{v}(t,x) = -\nabla\Psi(t,x)$



Informal result: SDE and optimal transport

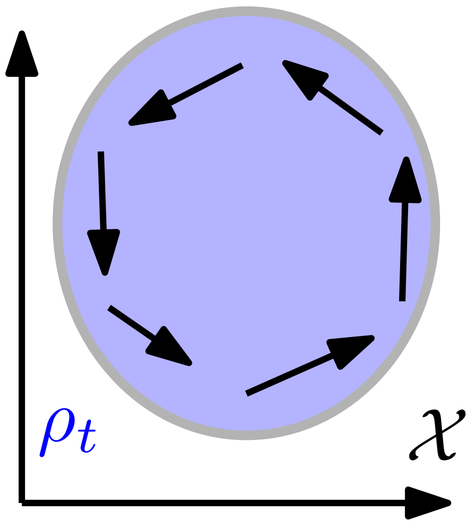
Take the potential SDE

$$\mathrm{d}X_t = -\nabla\Psi(t, X_t)\mathrm{d}t + \sigma \mathrm{d}B_t.$$

If Δt small enough, the law of $(X_t, X_{t+\Delta t})$ is well approximate by the solution of

$$\mathrm{OT}_{\sigma^2\Delta t}(\mathrm{Law}(X_t), \mathrm{Law}(X_{t+\Delta t}))$$

Intuitive explanation: removing identifiability issue



Impossible to distinguish periodic motion from cells at rest.

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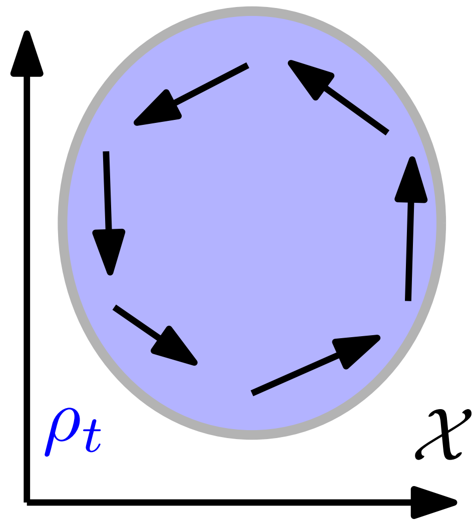

Impossible to distinguish periodic motion from cells at rest.

Assuming

$$\boxed{\mathbf{v}(t,x) = -\nabla\Psi(t,x)}$$

prevents the velocity field to create periodic motion

Weinreb et al. (2018). Fundamental limits on dynamic inference from single-cell snapshots.

Rigorous result: a variational characterization

$\Omega = C([0, t_{\mathsf{max}}])$, unknown $\mathbf{R} \in \mathcal{P}(\Omega)$.

$$\mathrm{Reg}((\mathbf{R}_{t_i})_i) \sim \sum_{i=1}^{T-1} \mathrm{OT}_{\sigma^2 \Delta t}(\mathbf{R}_{t_i}, \mathbf{R}_{t_{i+1}}) \sim H(\mathbf{R}|\mathbf{W}^{\sigma})$$

where $\mathbf{W}^{\sigma}$ law of Brownian motion with diffusivity σ.

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Take $\mathbf{P} \in \mathcal{P}(\Omega)$ law of the SDE

$$\mathrm{d}X_t = -\nabla\Psi(t, X_t)\mathrm{d}t + \sigma \mathrm{d}B_t.$$

For any $\mathbf{R} \in \mathcal{P}(\Omega)$ such that
$\forall t \in [0, t_{\mathsf{max}}]$, $\mathrm{Law}_{\mathbf{P}}(X_t) = \mathrm{Law}_{\mathbf{R}}(X_t)$, then

$$H(\mathbf{P}|\mathbf{W}^\sigma) \leq H(\mathbf{R}|\mathbf{W}^\sigma).$$

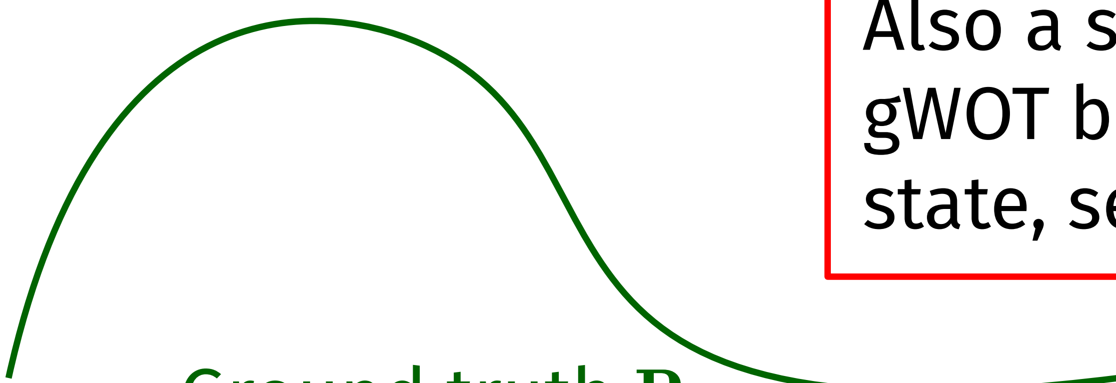
Conclusion: a rigorous result

Take $\mathbf{P} \in \mathcal{P}(\Omega)$ (and $\rho_t = \mathrm{Law}_{\mathbf{P}}(X_t)$) the law of the SDE

$$\mathrm{d}X_t = -\nabla\Psi(t, X_t)\mathrm{d}t + \sigma \mathrm{d}B_t.$$

For $0 \leqslant t_1 \leqslant t_2 \ldots \leqslant t_T \leqslant 1$, run WOT with $\varepsilon_i = \sigma^2(t_{i+1} - t_i)$ and call $\mathbf{R}^T$ the output.

Also a statement for gWOT but tedious to state, see article.



$\mathcal{P}(\mathcal{X})$

Ground truth $\mathbf{P}_t$

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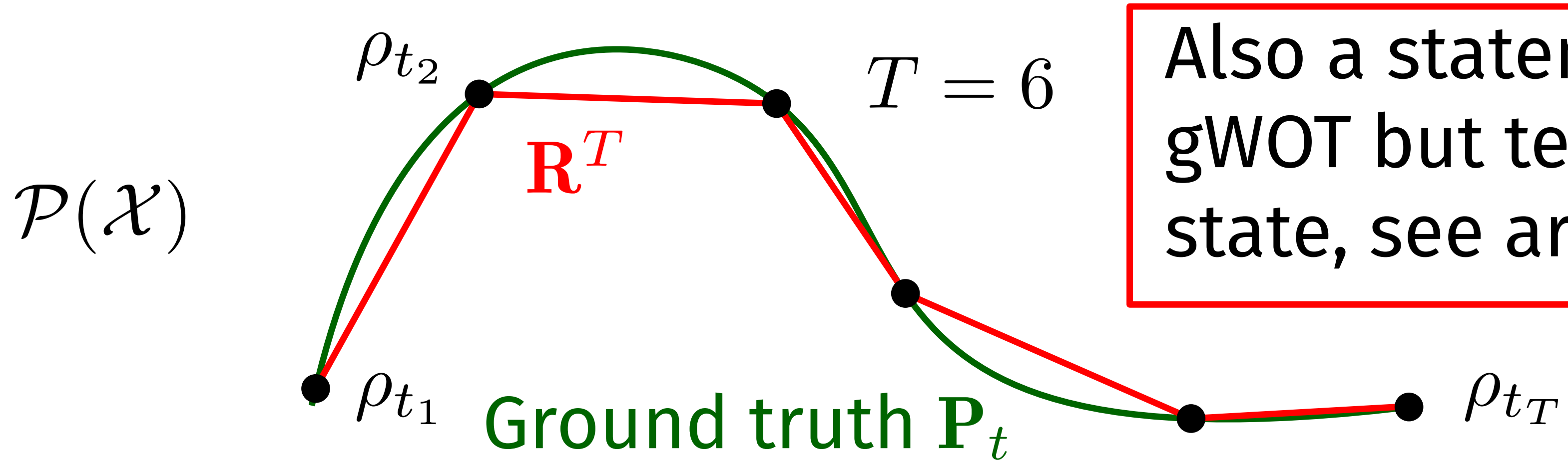

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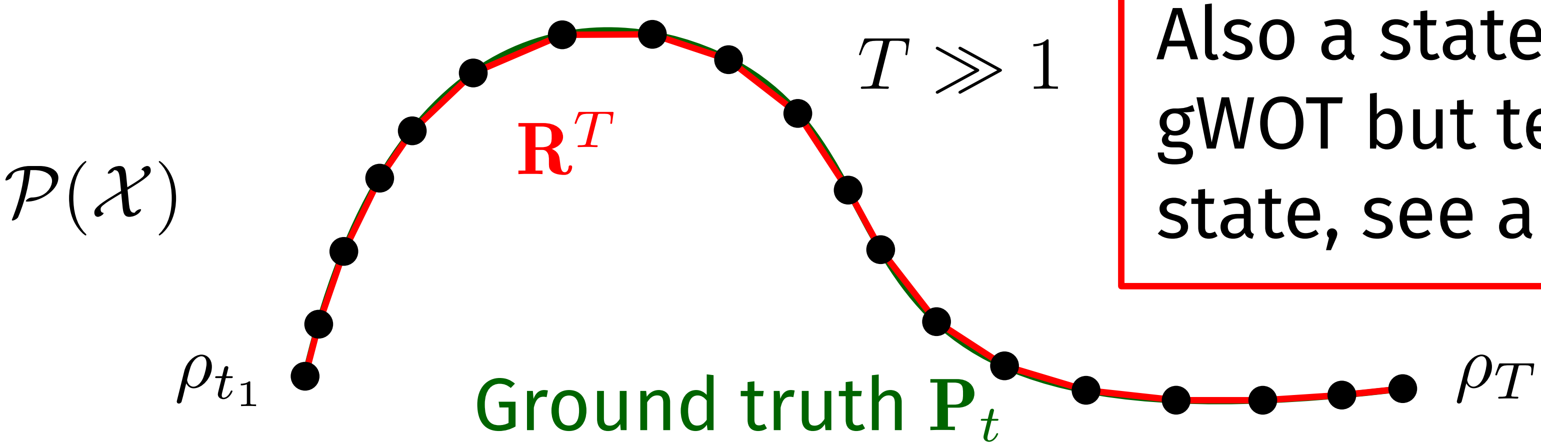

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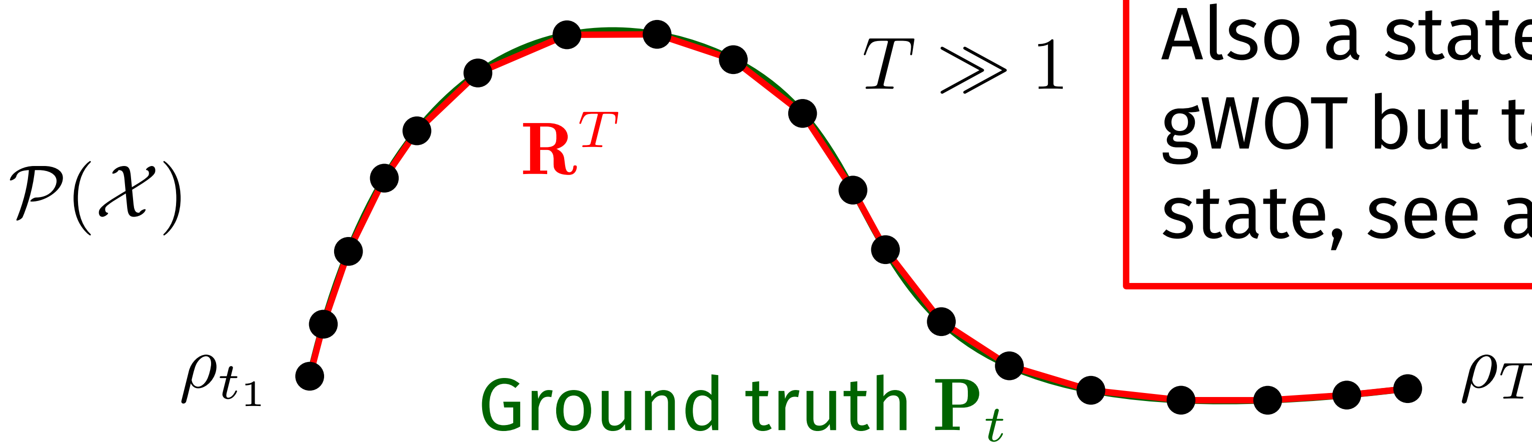
For $0 \leqslant t_1 \leqslant t_2 \ldots \leqslant t_T \leqslant 1$, run WOT with $\varepsilon_i = \sigma^2(t_{i+1} - t_i)$ and call $\mathbf{R}^T$ the output.

In the limit $T \to +\infty$ (**infinite sampling frequency**), the probability distribution $\mathbf{R}^T$ converges narrowly in $\mathcal{P}(\Omega)$ to the "ground truth" $\mathbf{P}$.



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Conclusion

- Mathematical framework for trajectory inference.
- Guarantees of reconstruction.
- Convex method, but with parameters tuning.

What I have not described

- How we handle branching.
- Extensive numerical experiments.

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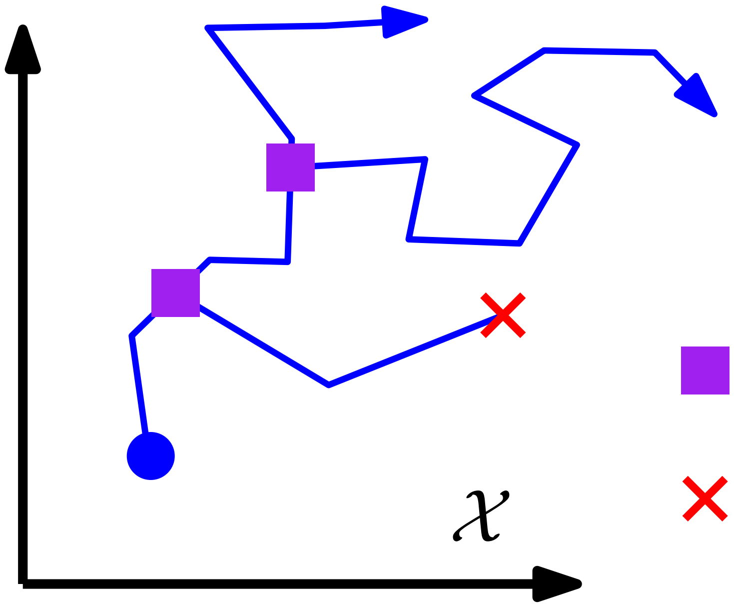
Thank you for your attention

What about branching?



In reality cells divide and die.

Branching

Death

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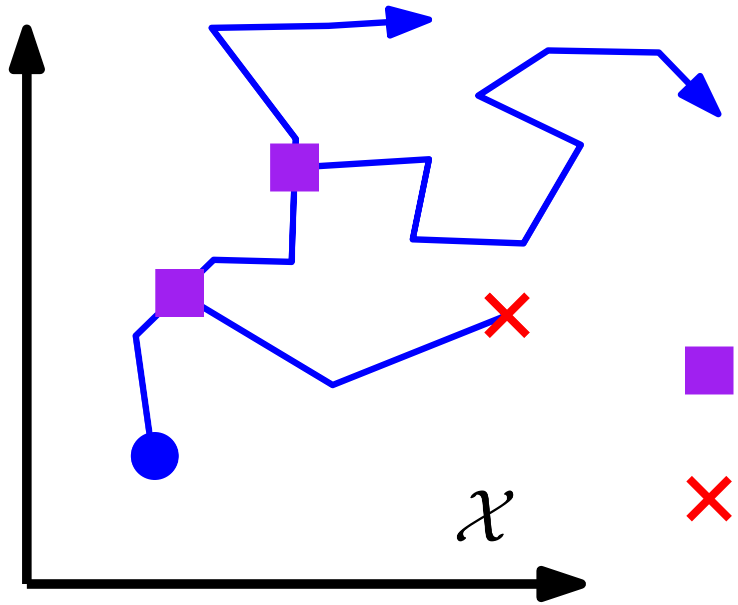

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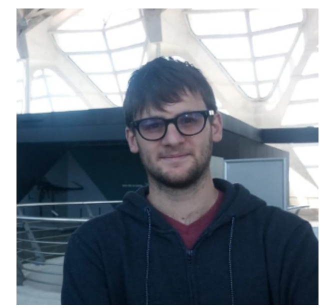

Lyon 1

In progress (with Aymeric Baradat): studying entropy minimization with respect to the law of the **Branching Brownian Motion**.

Baradat and L. (in progress). Regularized optimal transport is entropy minimization with respect to branching Brownian motion.

Handling growth in our paper: splitting

Unknowns: marginals $\mathbf{R}_{t_i}$,

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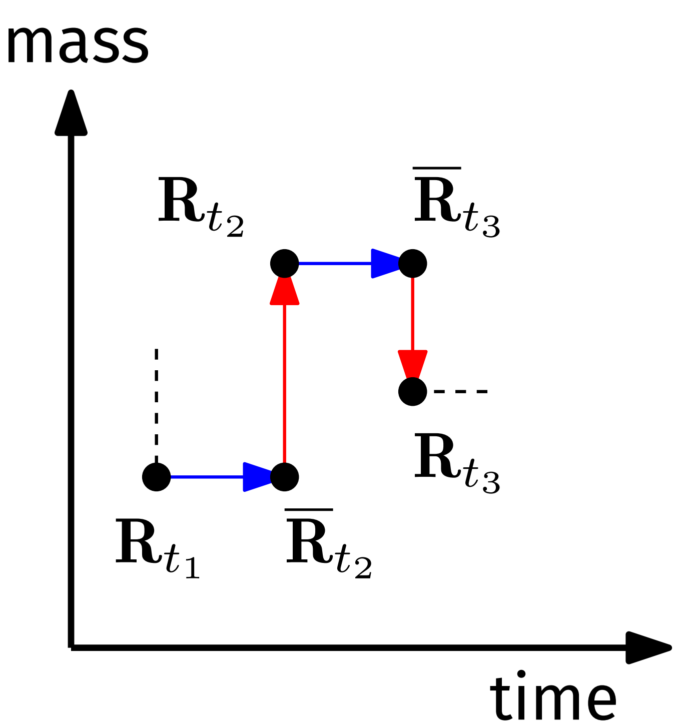
To handle **branching**: alternance of transport and growth phases.



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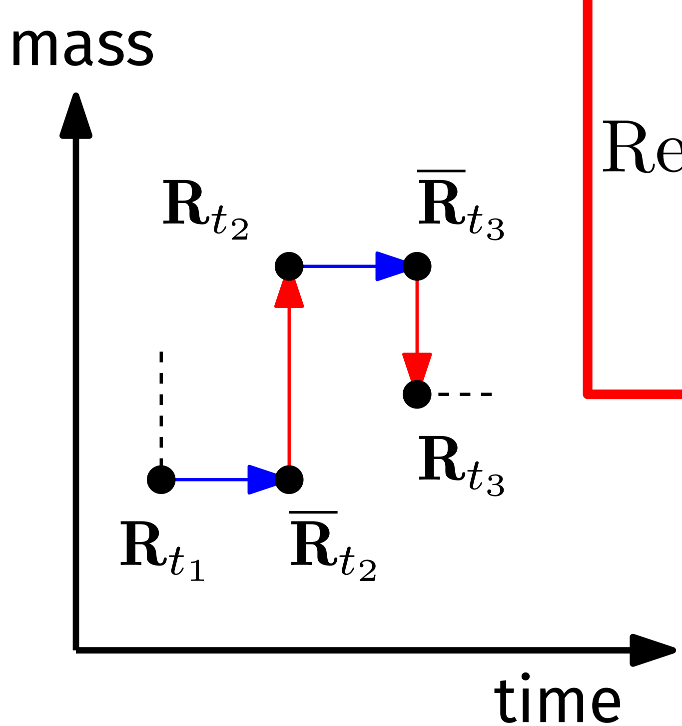

$$\boxed{\mathrm{Reg}((\mathbf{R}_{t_i})_i, (\overline{\mathbf{R}}_{t_i})_i) = \sum_i \mathrm{OT}_{\sigma^2 \Delta t}(\mathbf{R}_{t_i}, \overline{\mathbf{R}}_{t_{i+1}}) + G(\overline{\mathbf{R}}_{t_i}, \mathbf{R}_{t_i})}$$

$G(\overline{\mathbf{R}}_{t_i}, \mathbf{R}_{t_i})$ measures discrepancy (e.g. KL) between $\overline{\mathbf{R}}_{t_i}(x)\exp(\Delta t\, g(x))$ and $\mathbf{R}_{t_i}(x)$ with $g : \mathcal{X} \to \mathbb{R}$ a priori growth rate.