Applied Mathematics

Two Inference Problems in Dynamical Systems from Mathematical and Computational Biology

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PIMS Postdoc Seminar
03.26.2025

Two inference problems

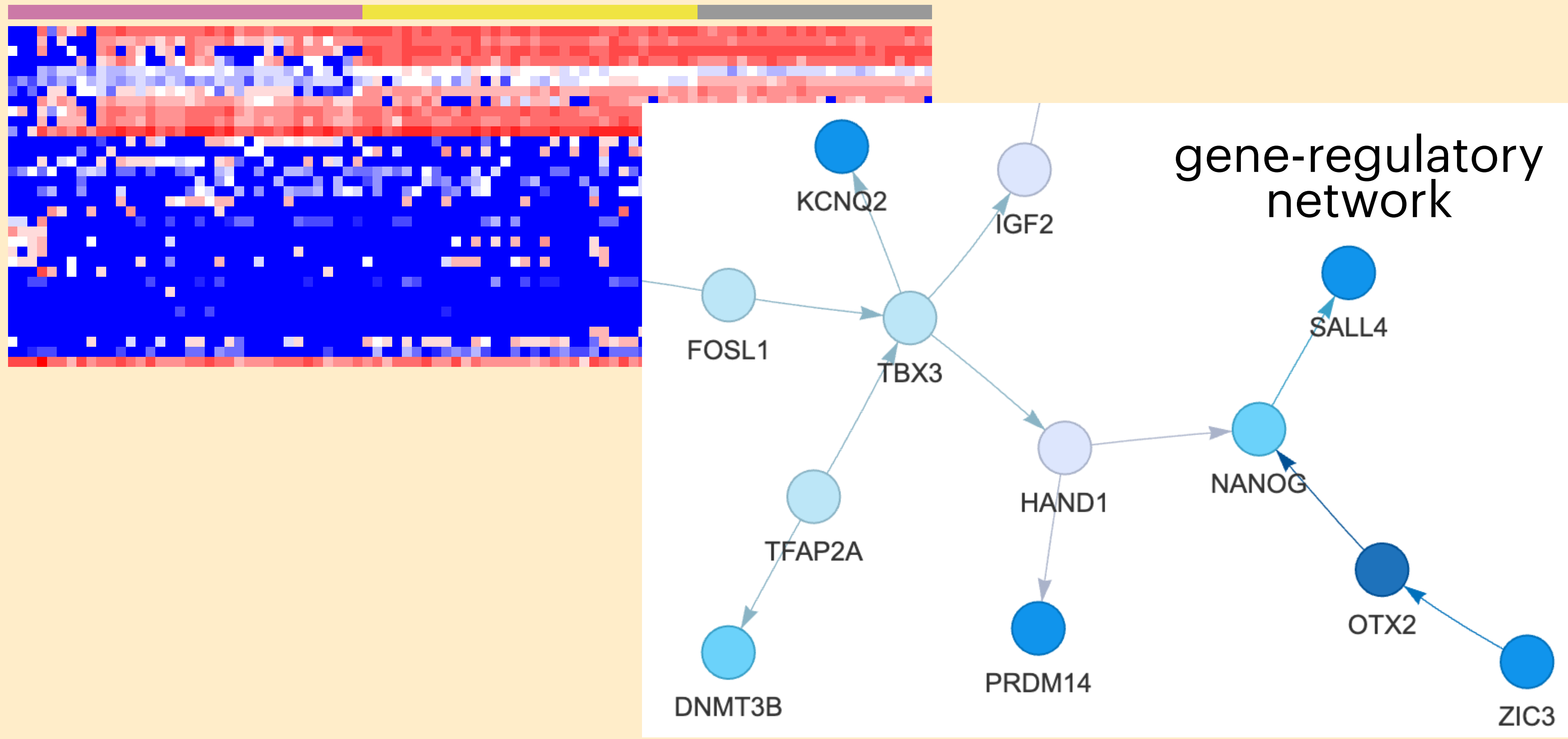
Inferring mechanisms from single-cell sequencing data

Joint work with

Bjorn Sandstede

Ritambhara Singh

Erica Larschan



Quantifying Turing patterns and their bifurcation

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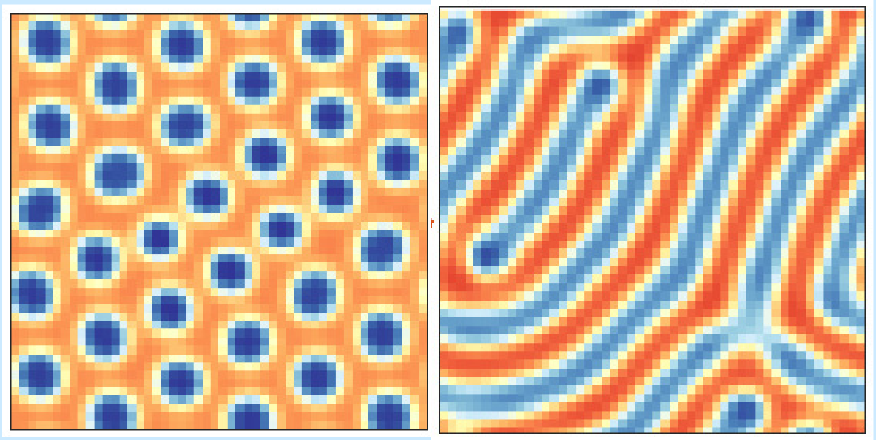
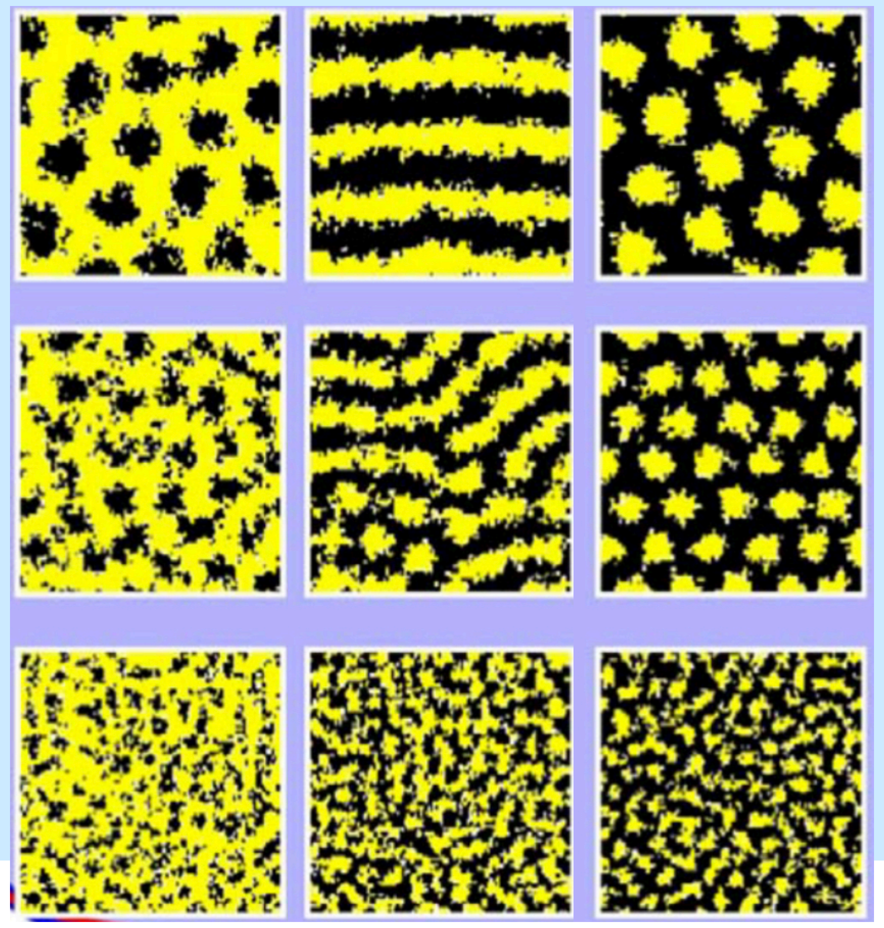
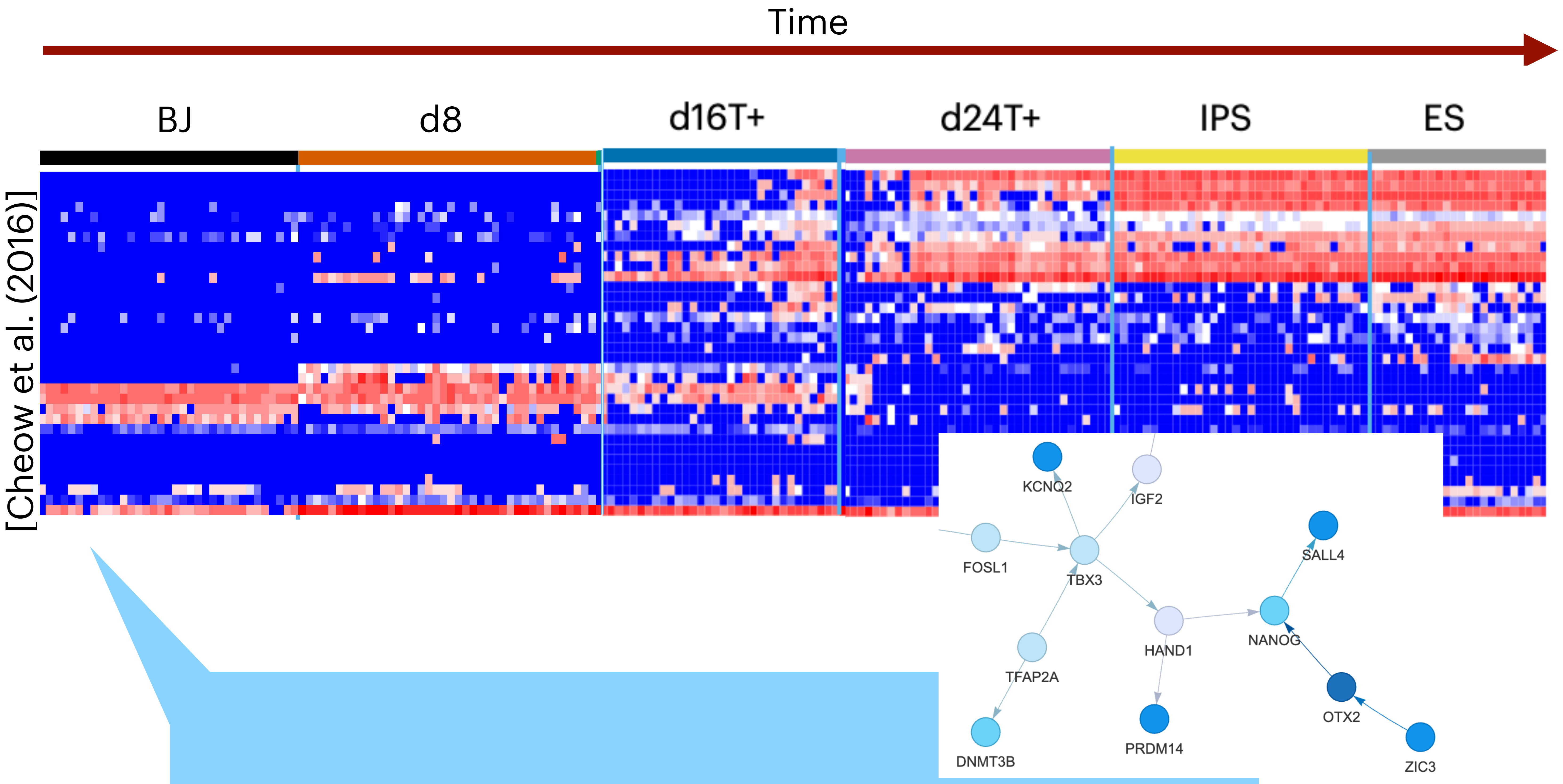


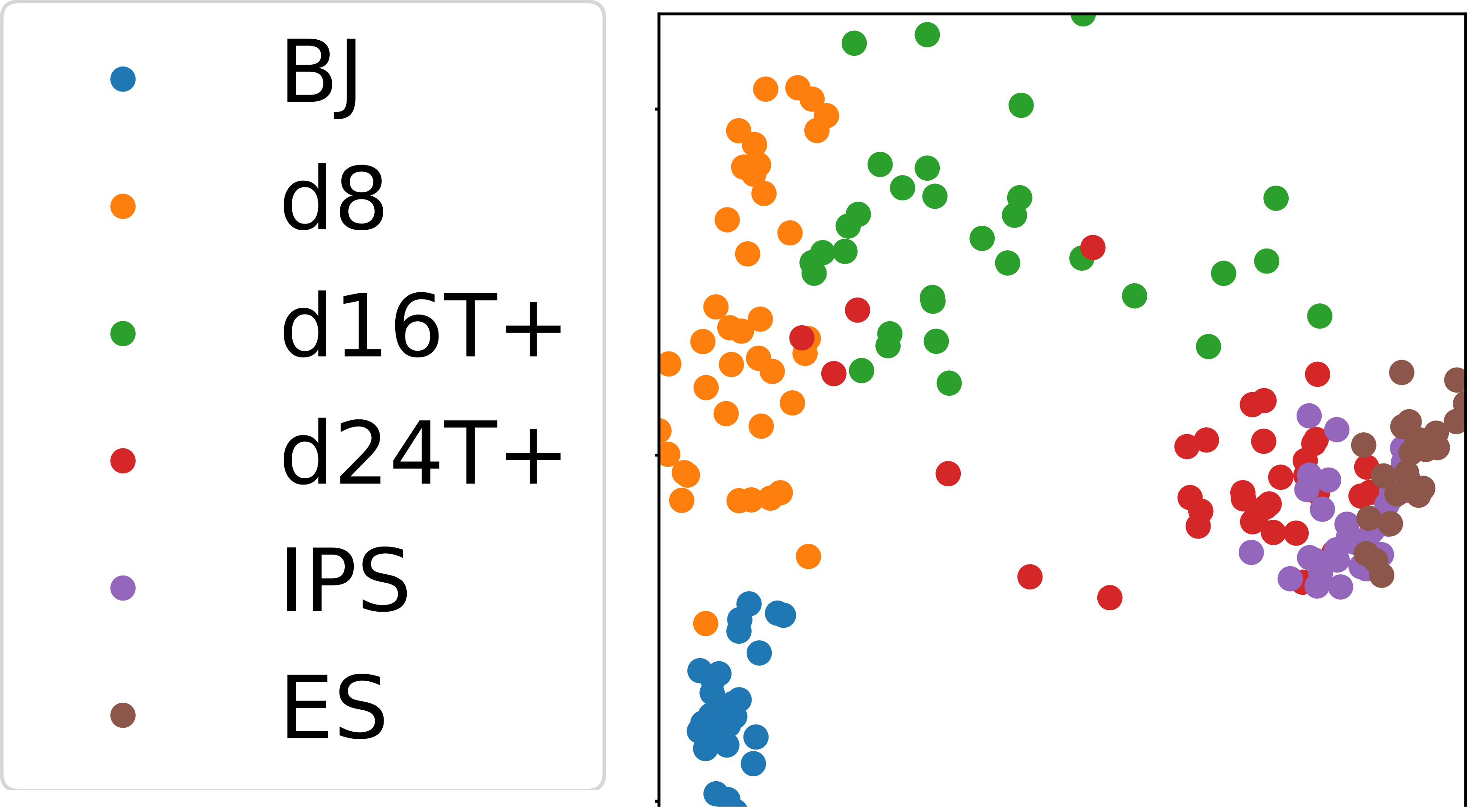


Problem statement



[Cheow et al. (2016)]

Which gene (row) activated/ inhibited which gene (row)?



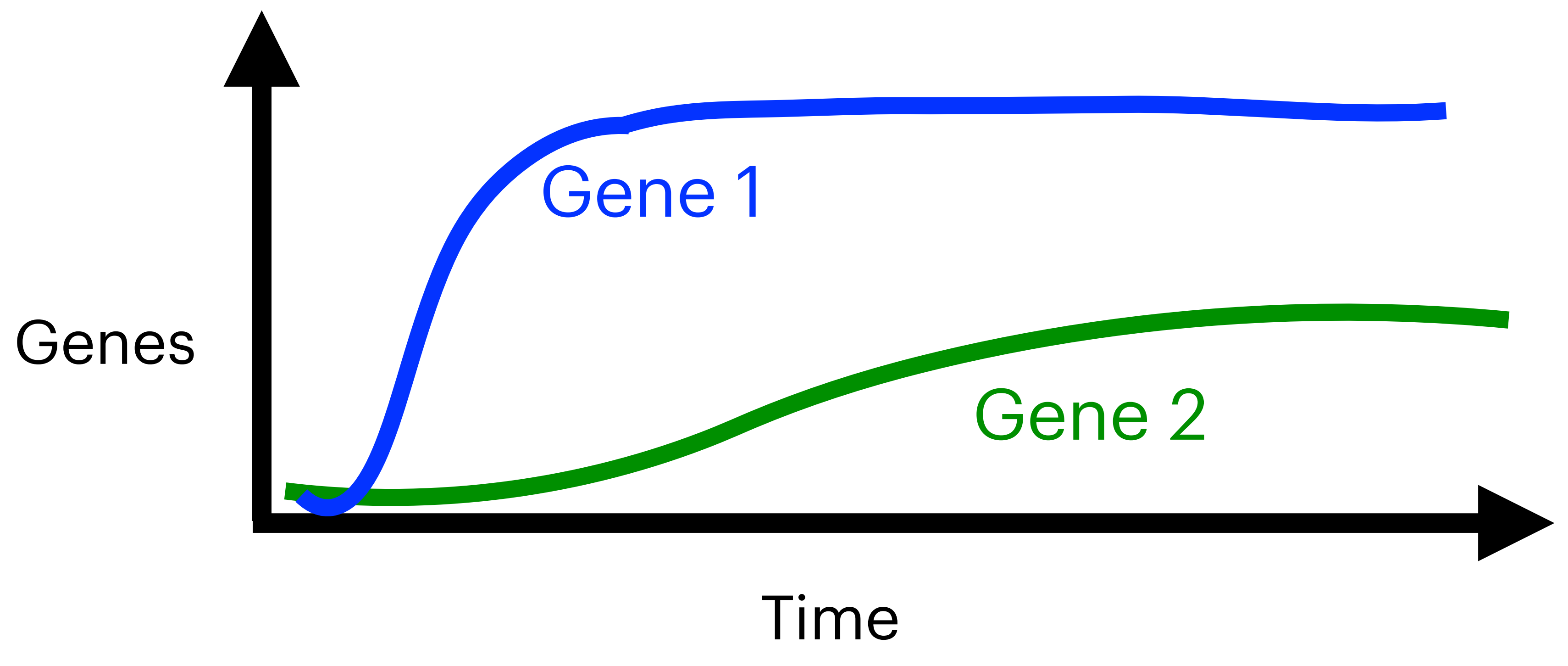
Cell types

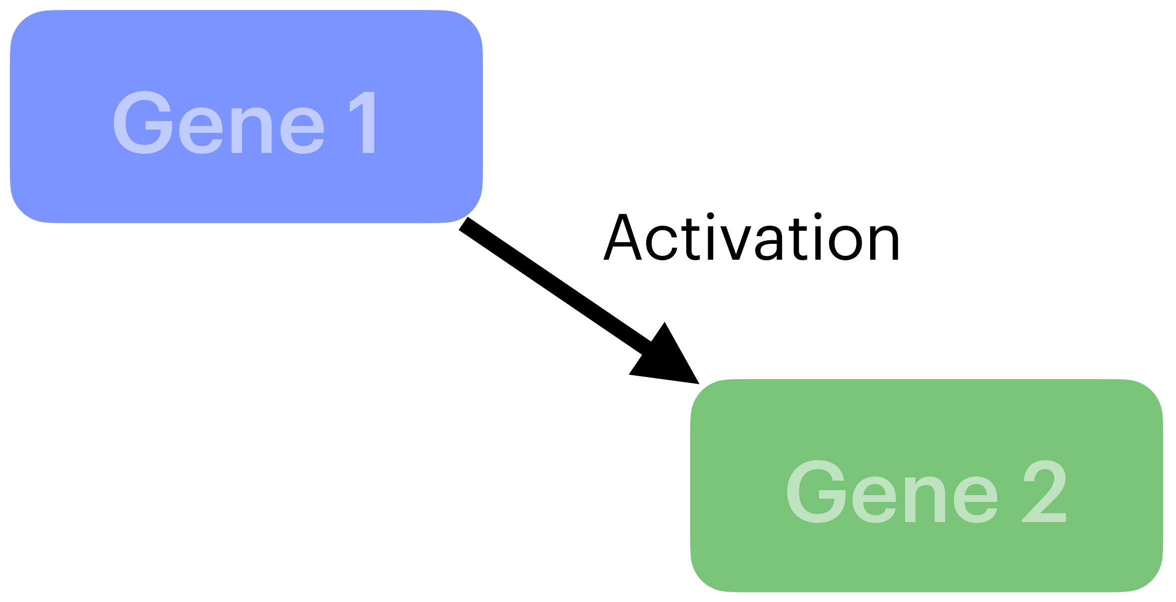
First 2 PCs

Causation between time series

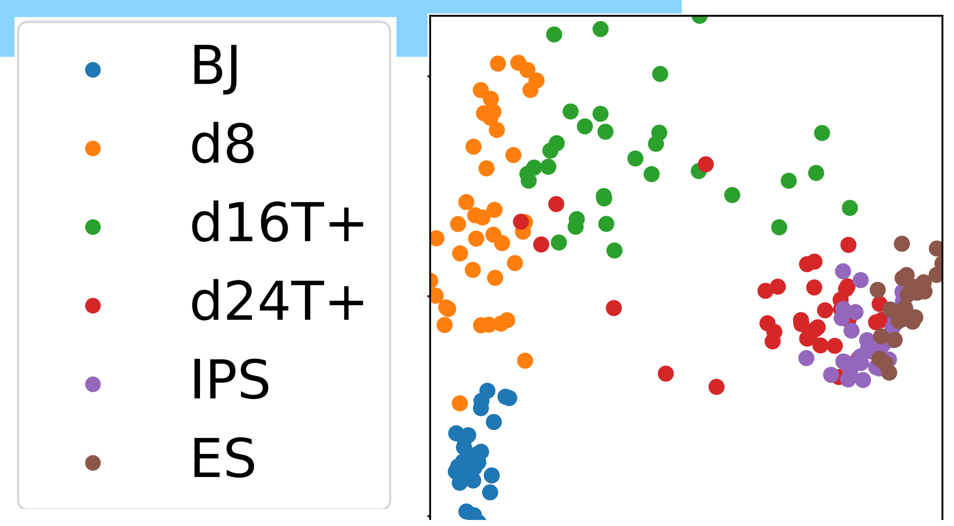
Granger causality:

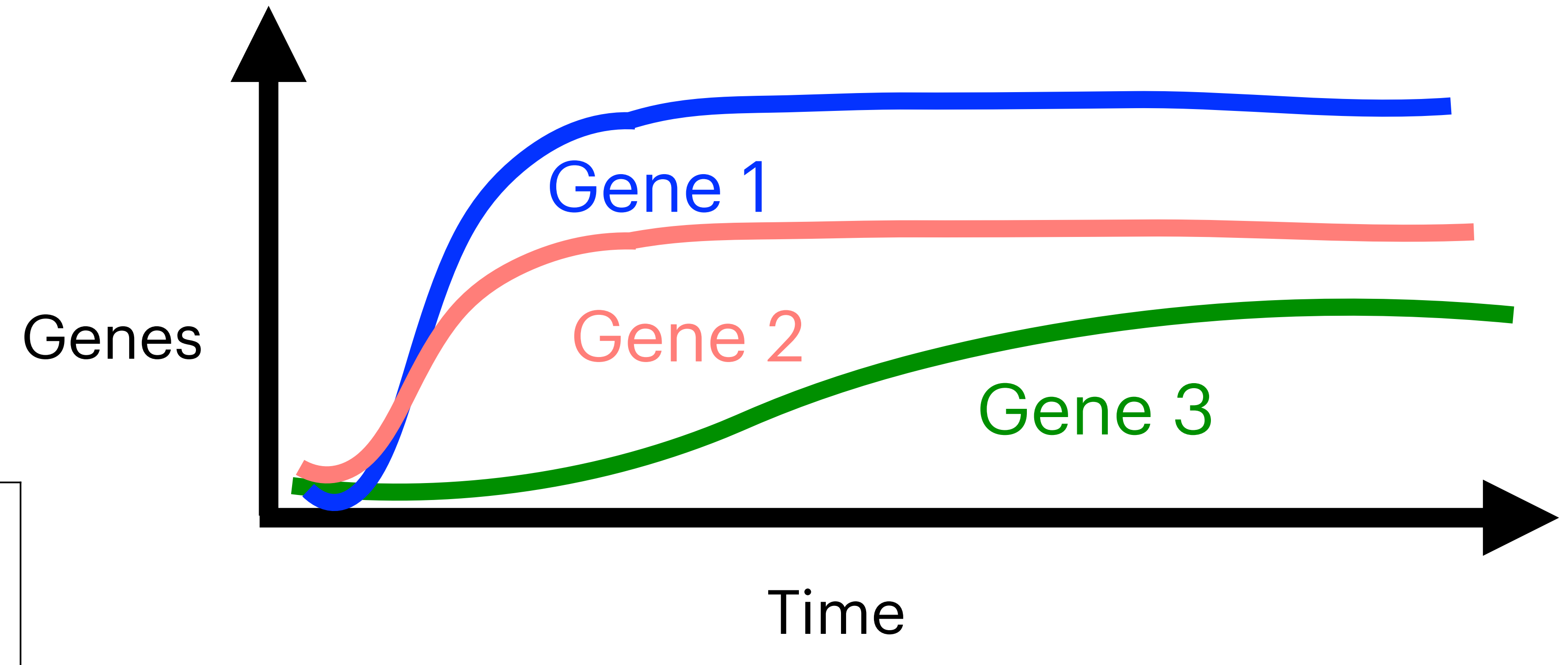
- (1) The cause happens prior to its effect
- (2) The cause has unique information about the future values of its effect

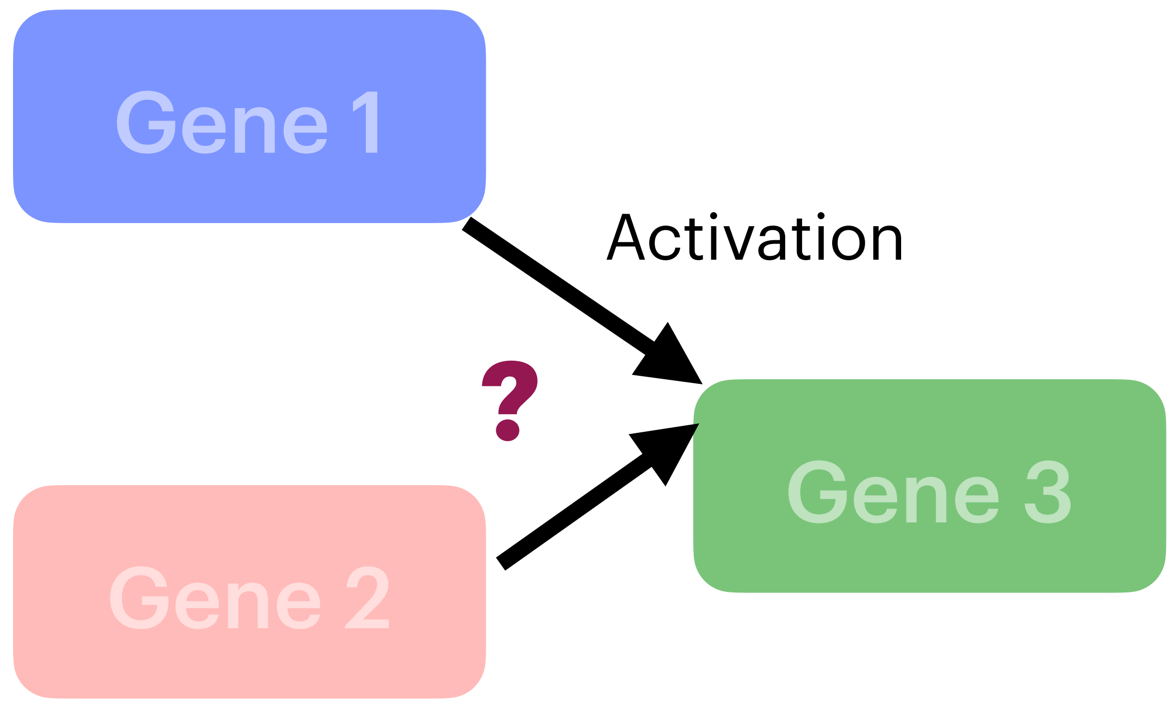




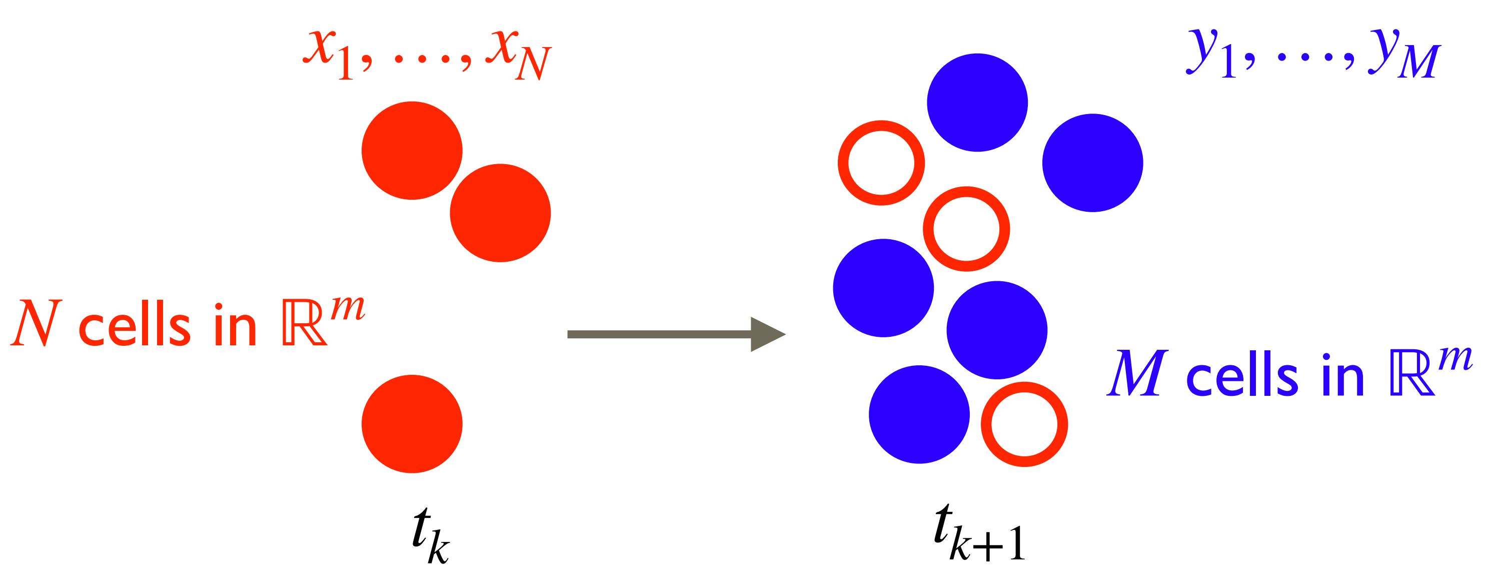
Problem:
No actual time series:
Cells are destroyed during measurement







Trajectory inference through optimal transport



Find joint probability distribution Γ

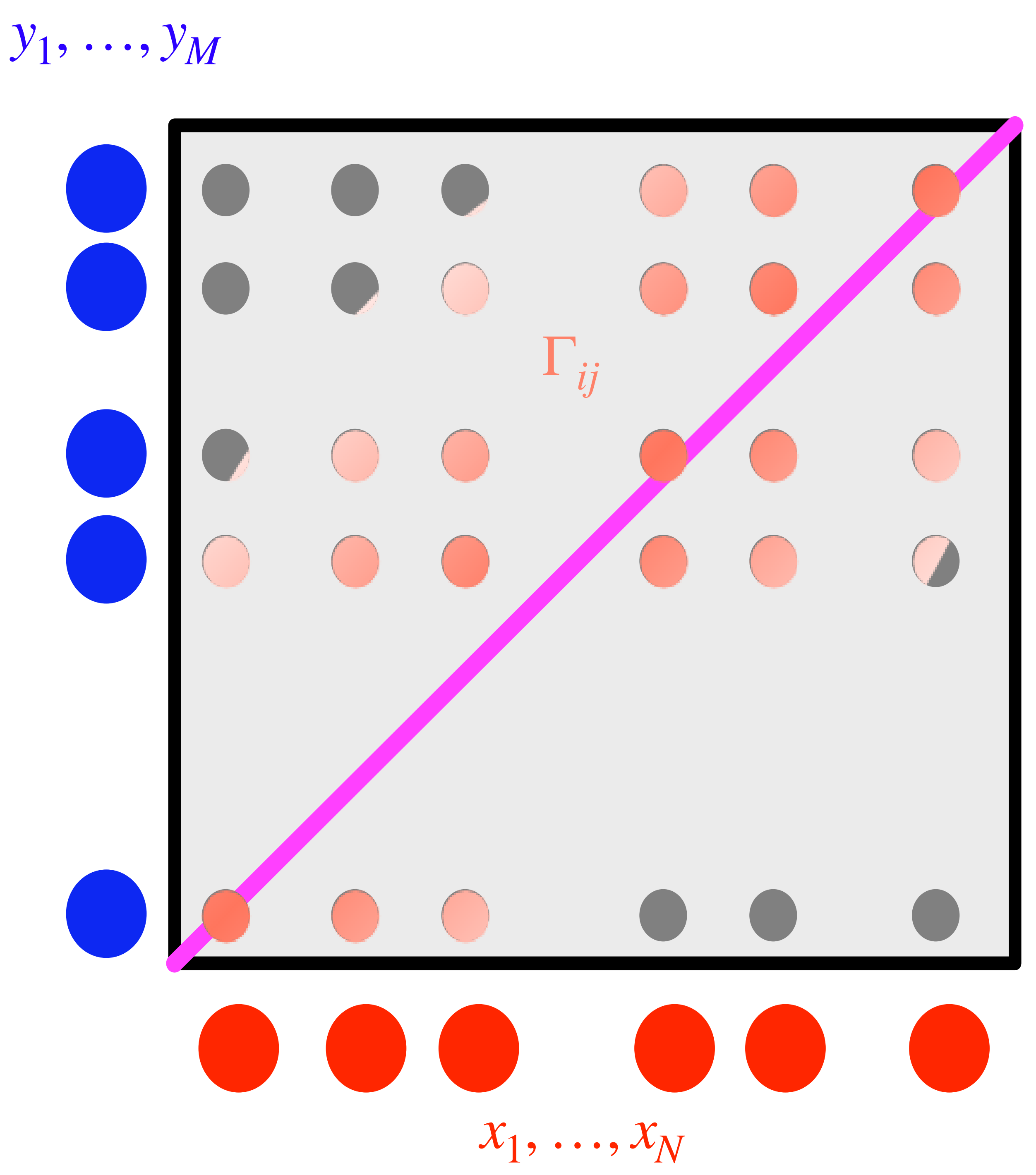
($\Gamma_{ij} \geq 0,\ \sum_{i=1}^{N} \Gamma_{ij} = \frac{1}{M},\ \sum_{j=1}^{M} \Gamma_{ij} = \frac{1}{N}$) as solution to

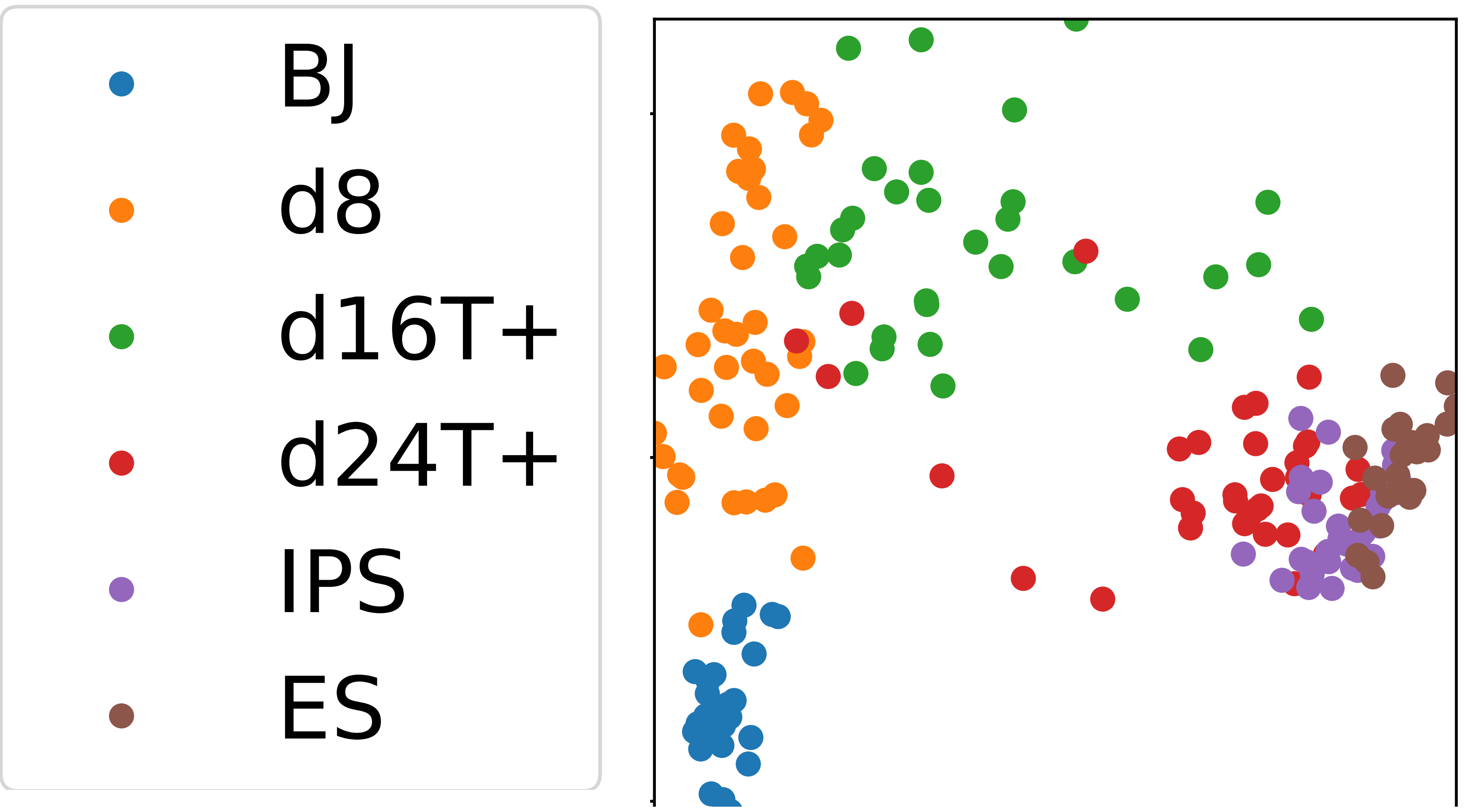
$$\Gamma = \arg\min_{\Gamma} \sum_{\substack{i=1,\ldots,N \\ j=1\ldots,M}} |x_i - y_j|^2_{\mathbb{R}^m}\, \Gamma_{ij}$$

We interpret Γ_{ij} as the probability that x_i is mapped to y_j

Barycentric projection:

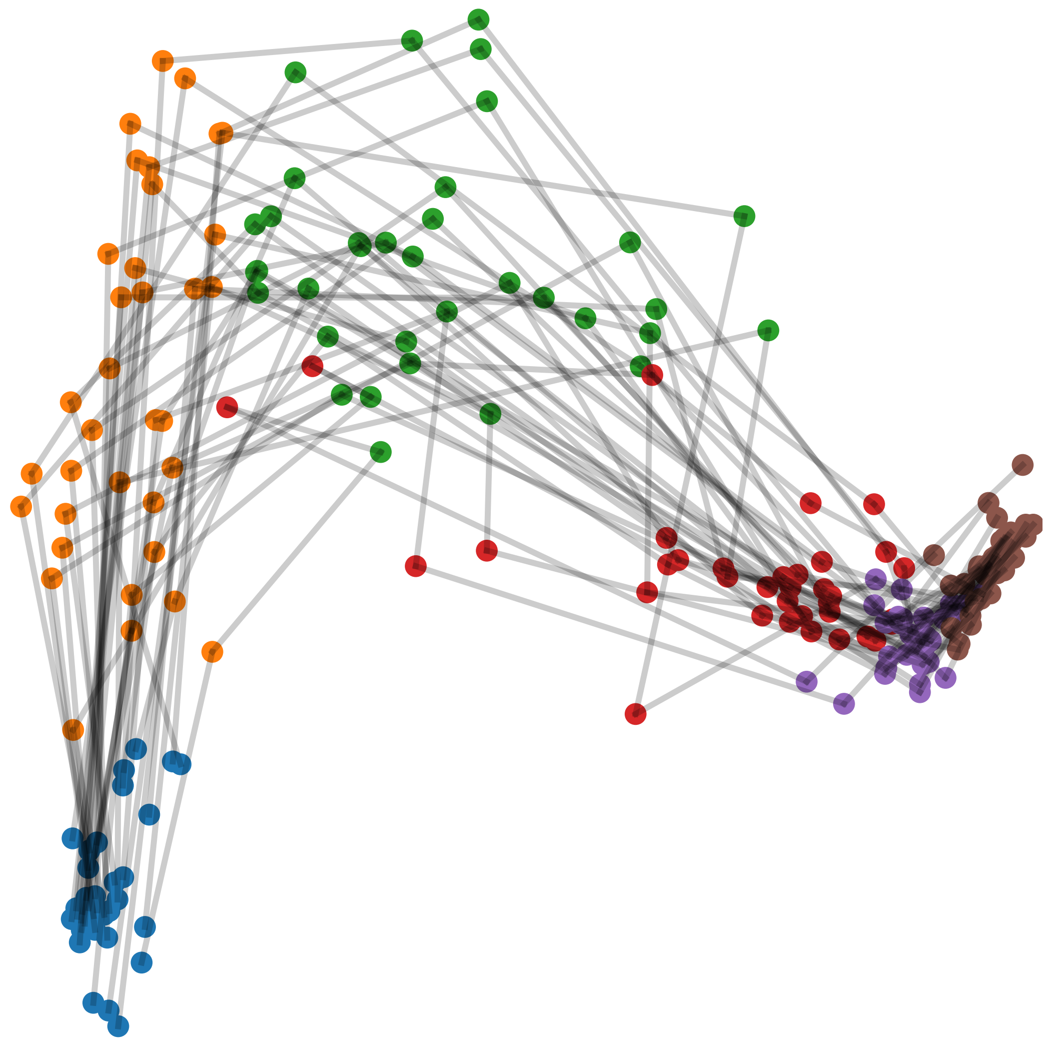
$$x_{i,t-1} \to \sum_j \frac{\Gamma_{i,j}}{\sum_k \Gamma_{i,k}} x_{j,t}$$





Cell types

First 2 PCs



Recovered cell trajectories

OT velocity

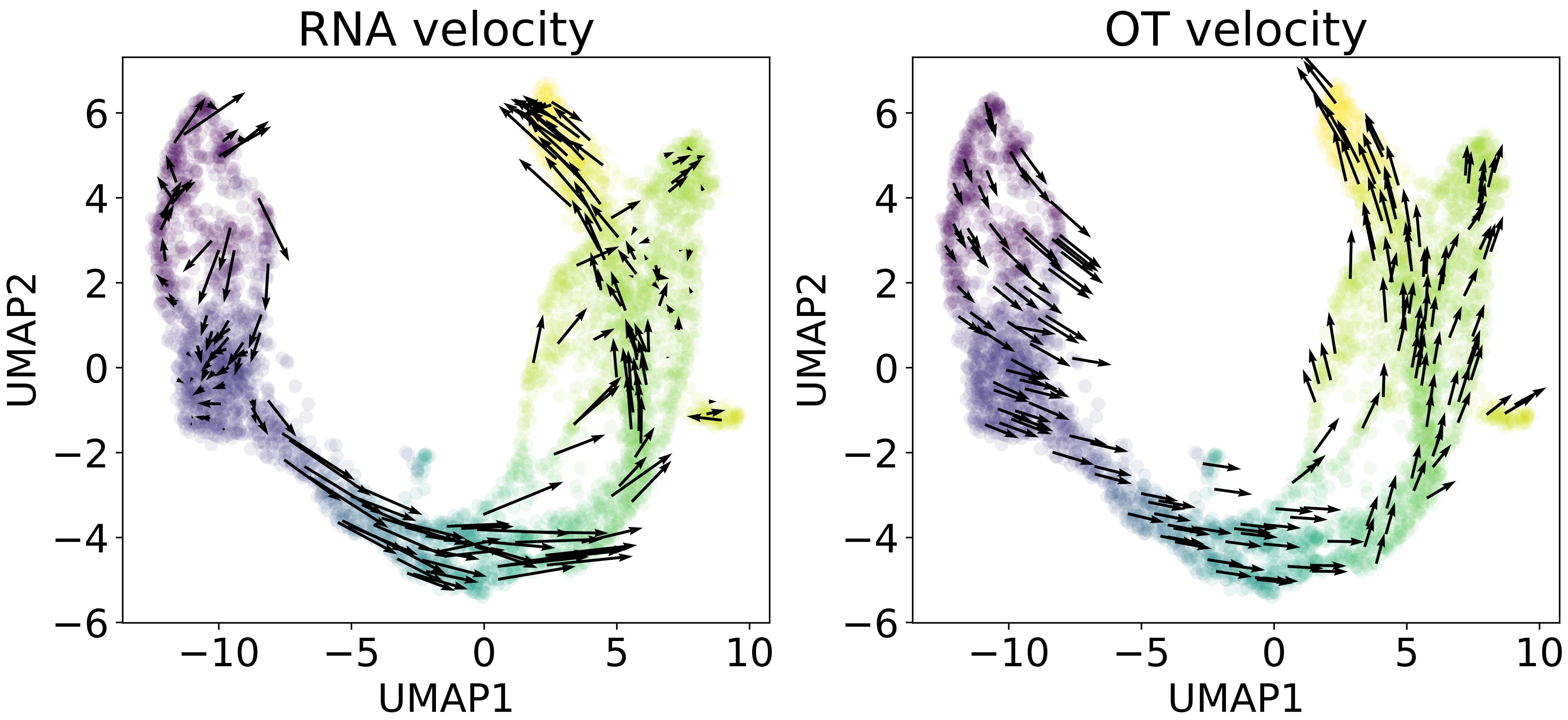
- Solve the trajectory problem via OT as mentioned

For cell $x_{i,t} \in \mathbb{R}^m$, infer its past $\hat{x}_{i,t-1}$ and future $\hat{x}_{i,t+1}$ via barycentric projection

- Estimate the ‘OT velocity’ for each cell via finite difference

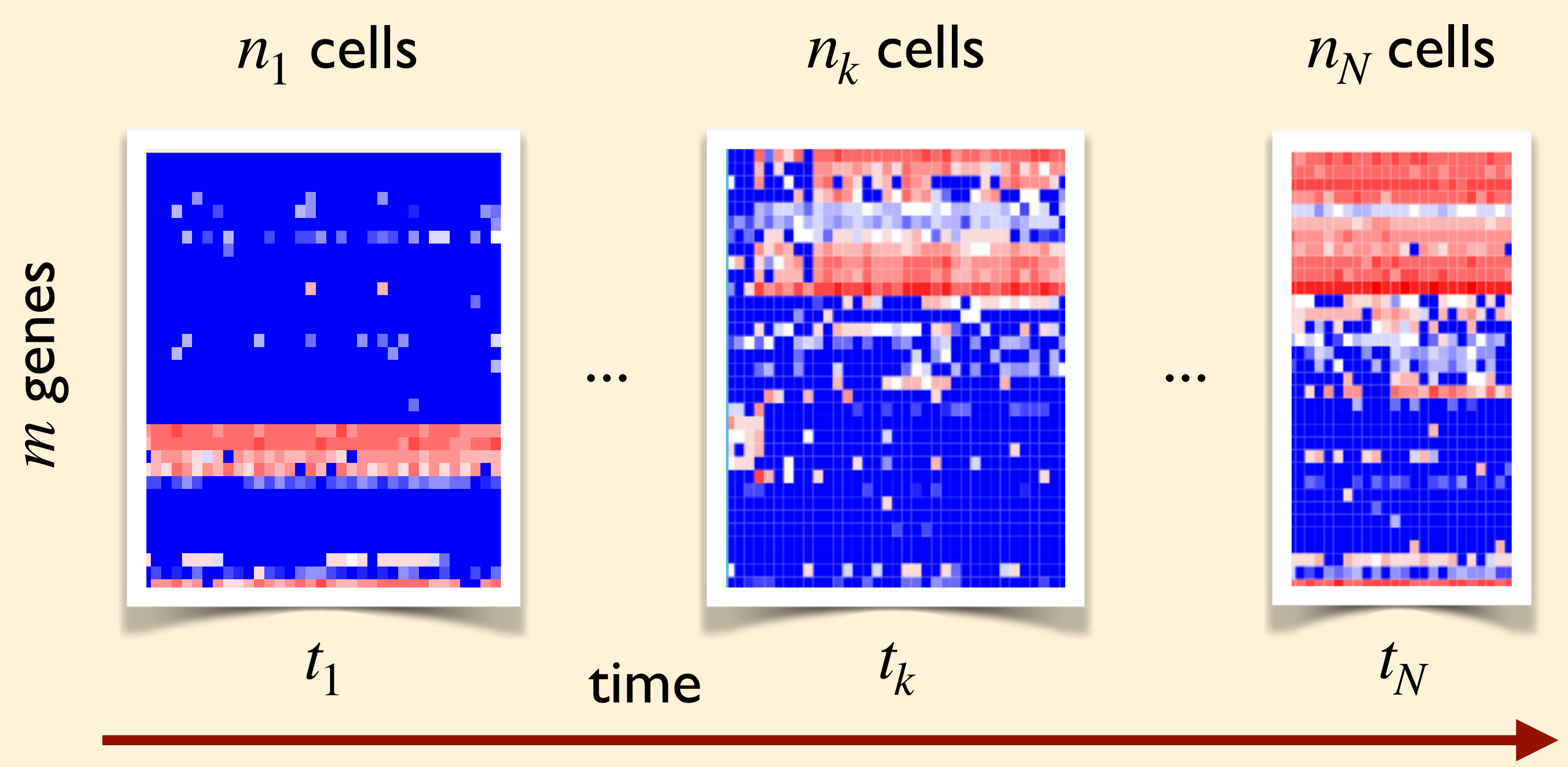
Velocity for gene g in each cell: $v_{i,t}^{g} = \dfrac{dx_{i,t}^{g}}{dt} \approx \dfrac{\hat{x}_{i,t+1}^{g} - \hat{x}_{i,t-1}^{g}}{2}$

Validation:
(1) OT velocity is similar to RNA velocity (a method using reaction model for unspliced/spliced RNA counts);
(2) RNA velocity is only available in deeply sequenced datasets.

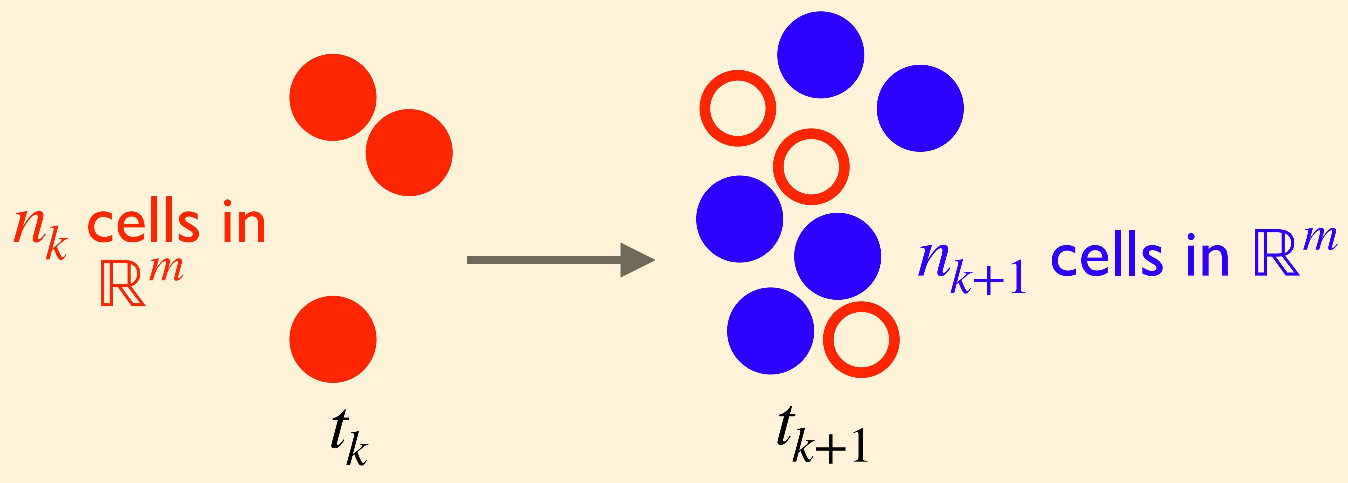


Pipeline...

Time-stamped single-cell RNA data

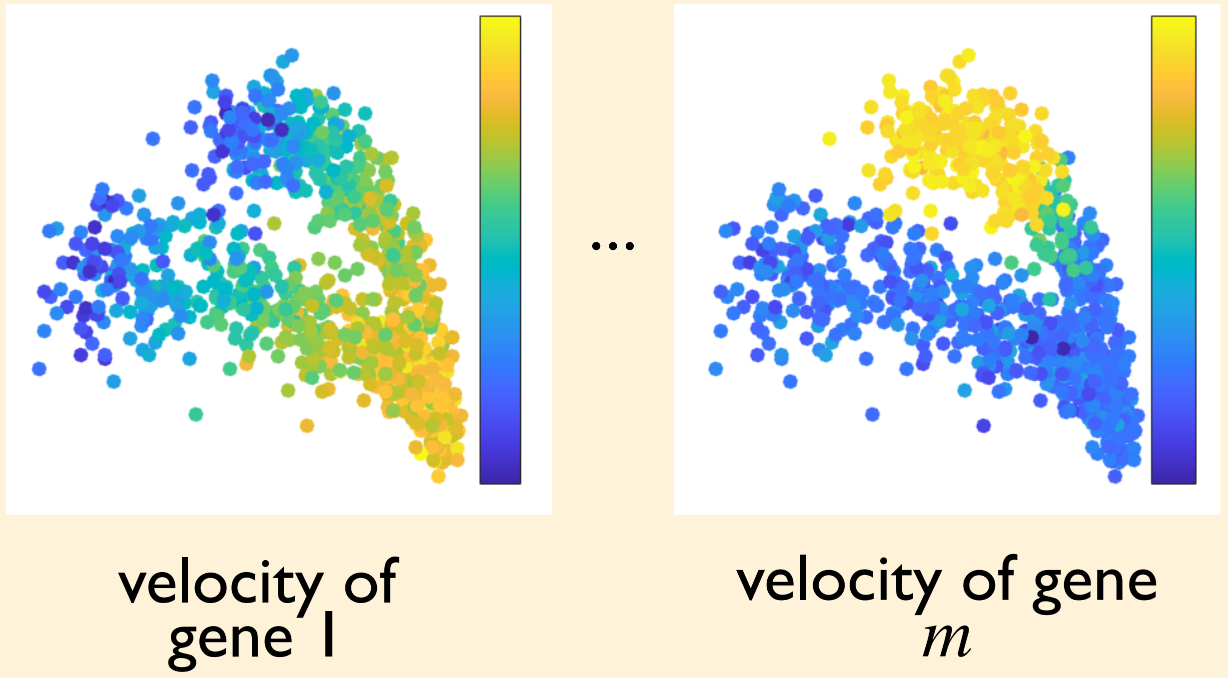


Optimal transport



predict cell trajectories

Finite differences on cell trajectories



infer OT velocity $v(x,t) \in \mathbb{R}^m$

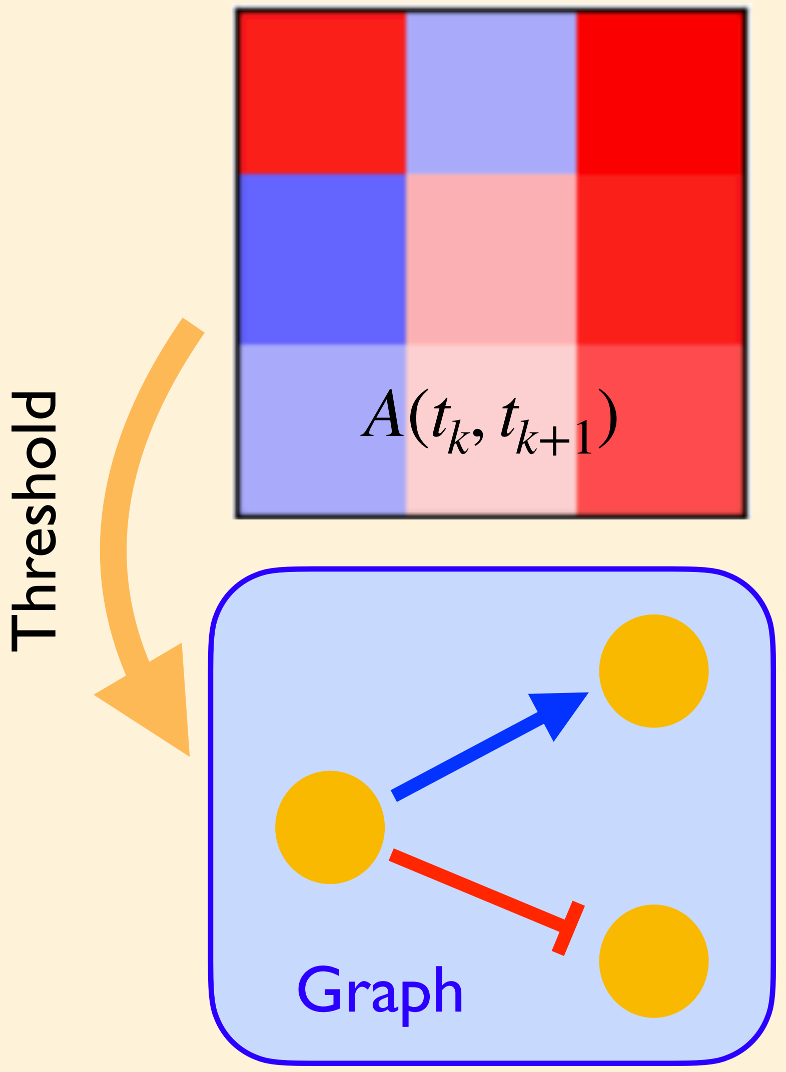
Granger causality with linear reduction

$$v(x,t_{k+1}) = A(t_k,t_{k+1})v(x,t_k)$$

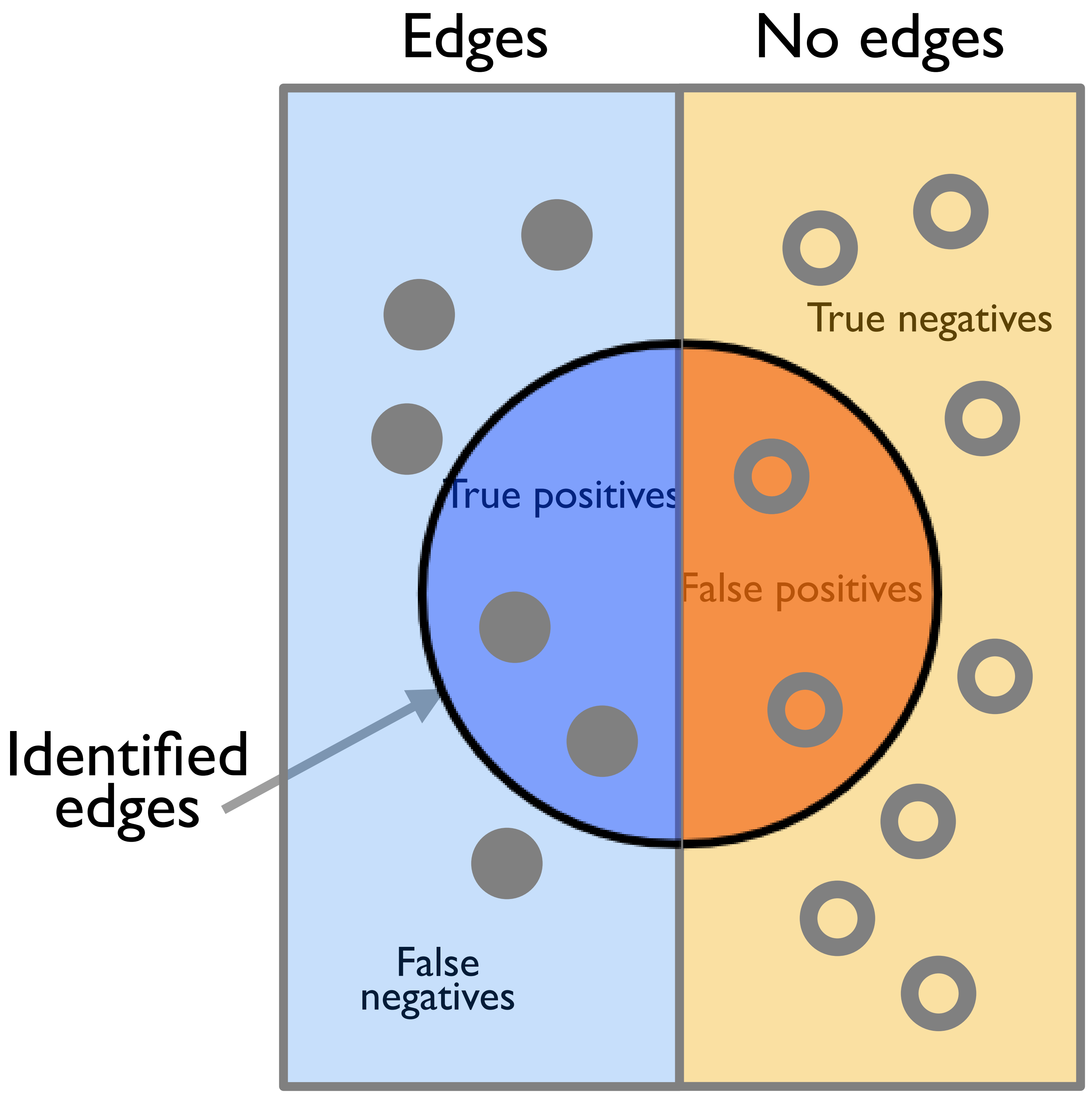
$$A(t_k,t_{k+1}) \in \mathbb{R}^{m \times m}$$

estimate gene-interaction matrix

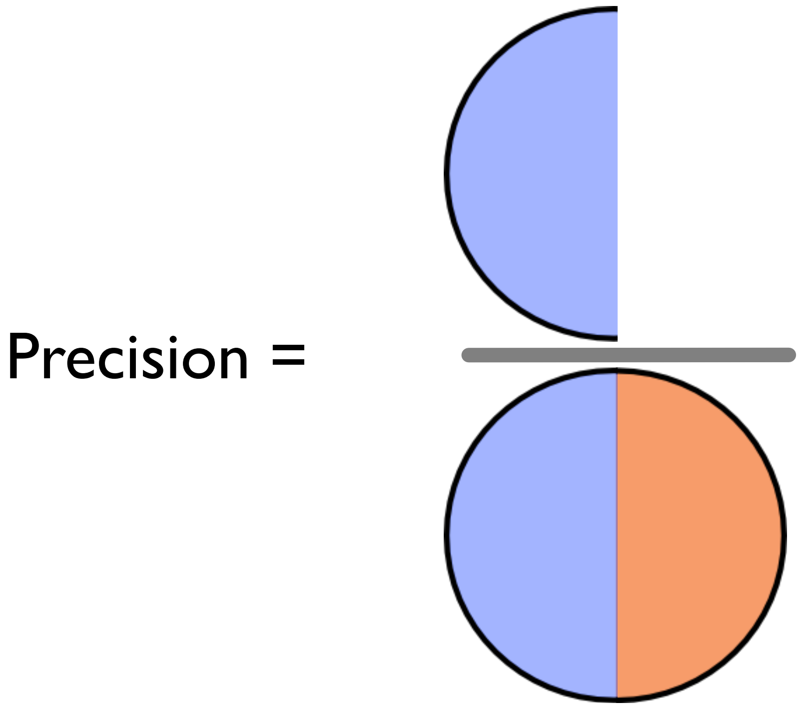
Gene regulatory network



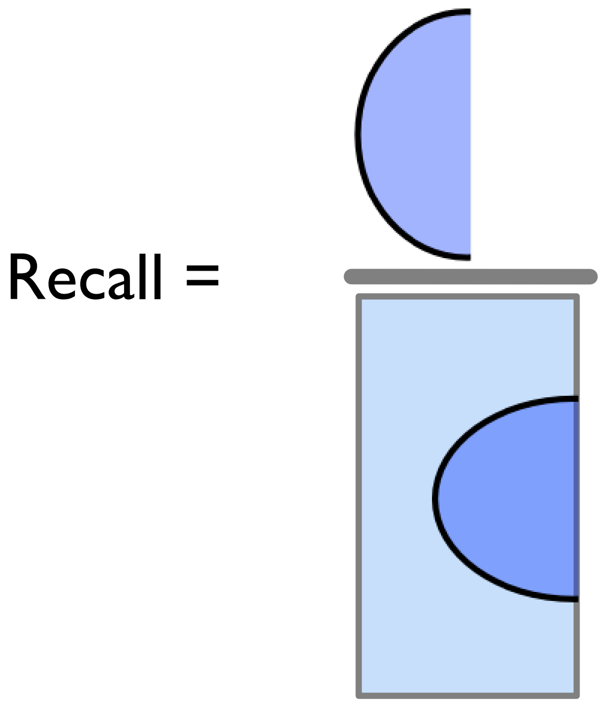
Performance quantification

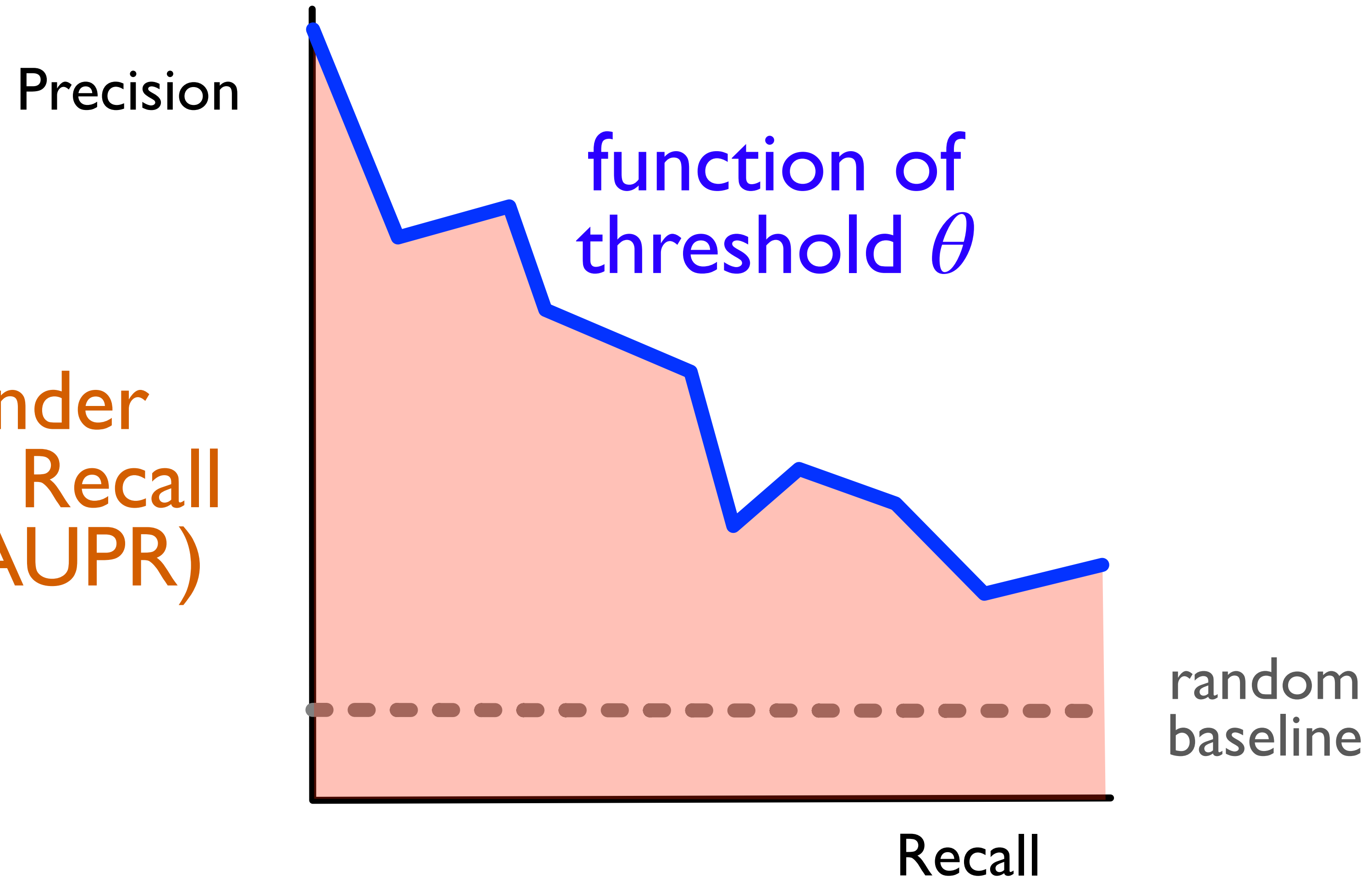


How many identified edges are ground-truth edges?



How many ground-truth edges are identified?





Area under Precision Recall Curve (AUPR)

Features for AUPR:

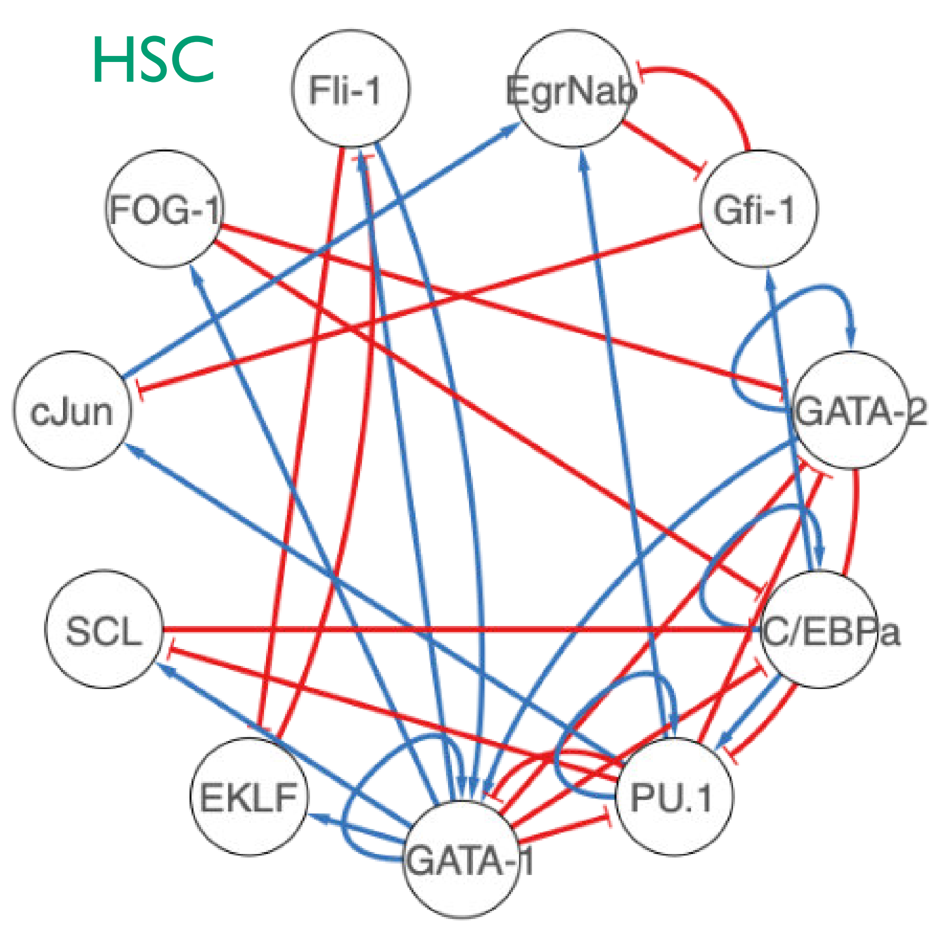
(1) Requires ground truth;
(2) Bounded between 0 and 1;
(3) Higher is better;
(4) Random baseline = density of truth.

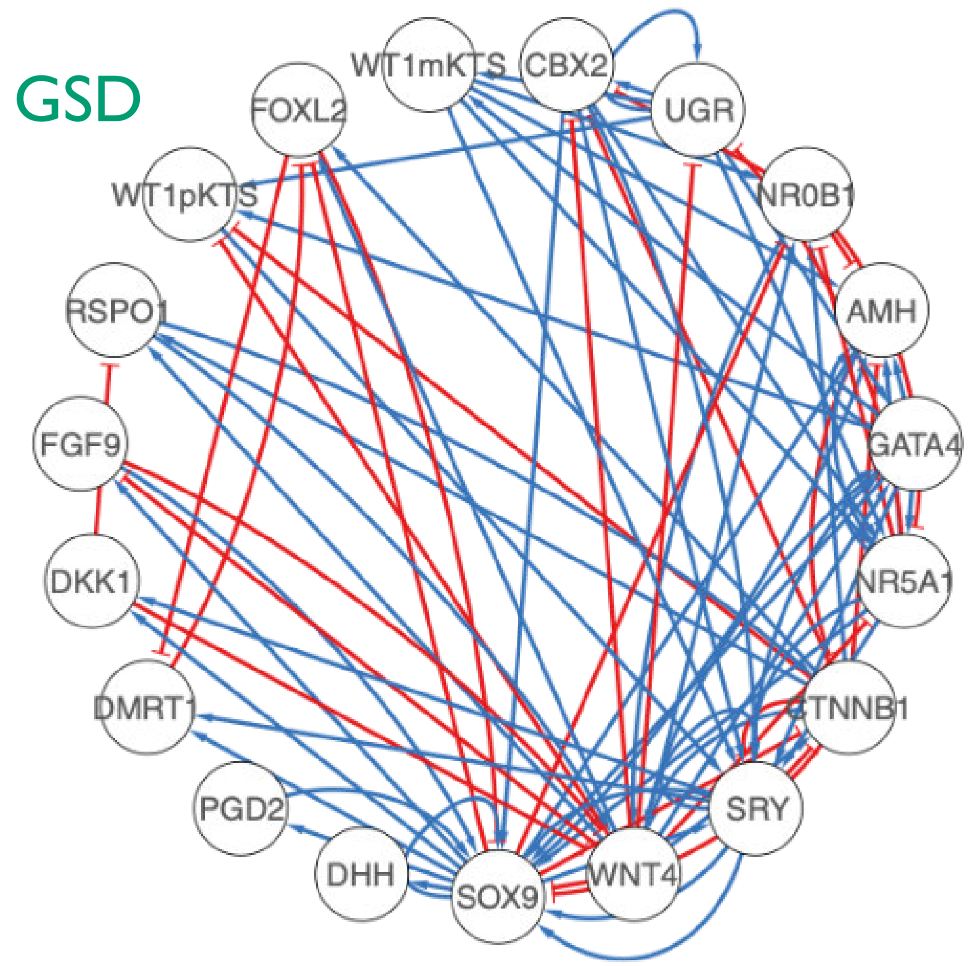
Result on simulated data

Beeline datasets

Real networks: (1) Hematopoietic Stem Cell Differentiation (HSC) (2) Gonadal Sex Determination (GSD)

Count matrices simulated from SDEs



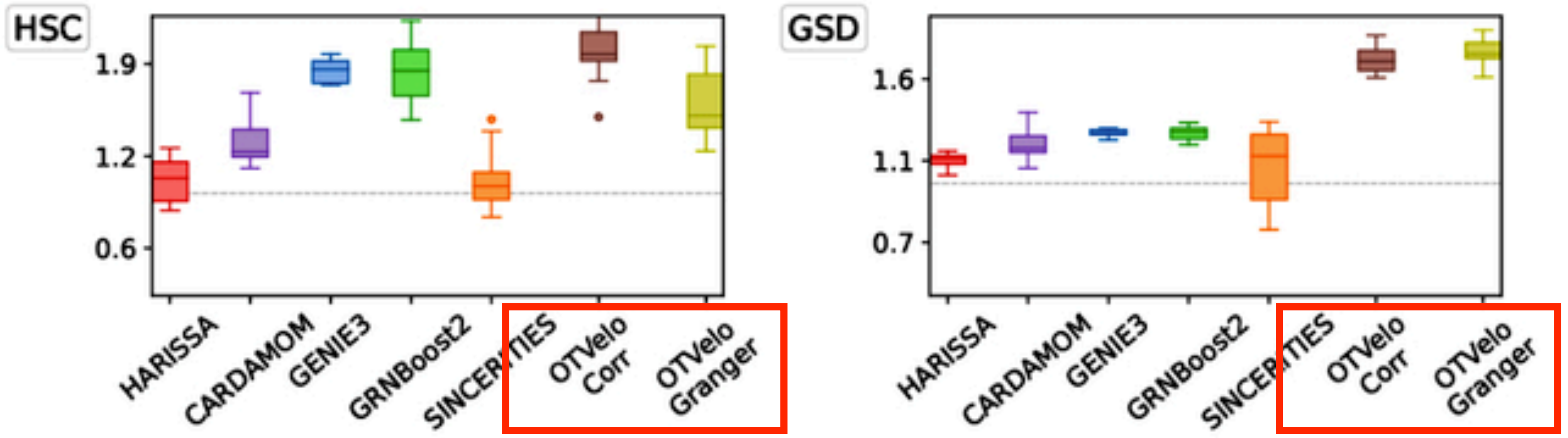


Metrics:

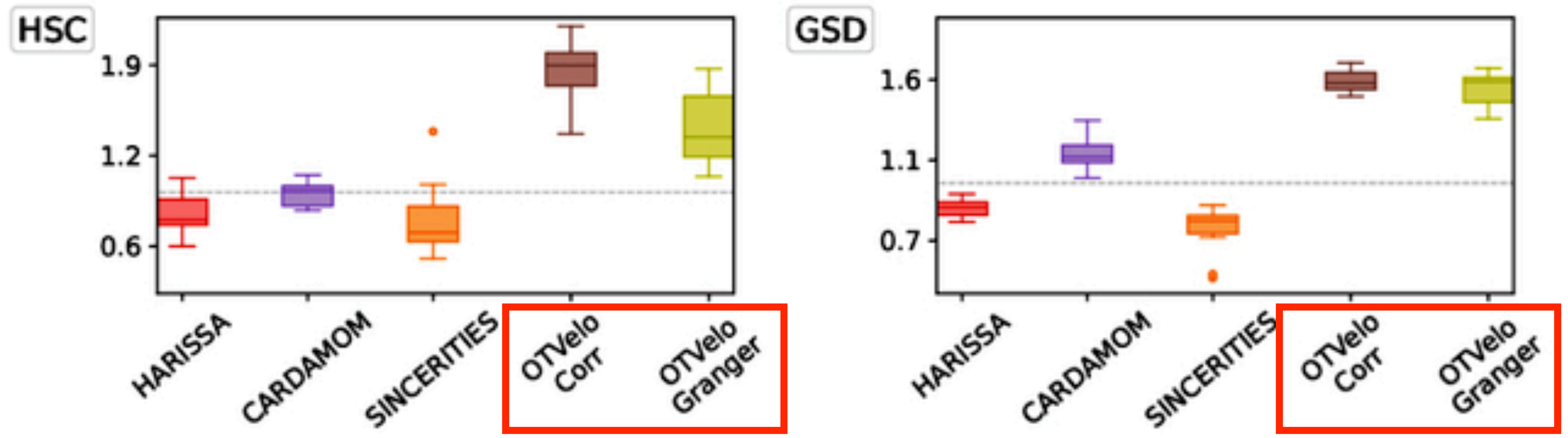
(1) AUPR ratio = AUPR over random baseline;

(2) For signed prediction, 'true positive' requires correct sign. Some algorithms don't have signed prediction.

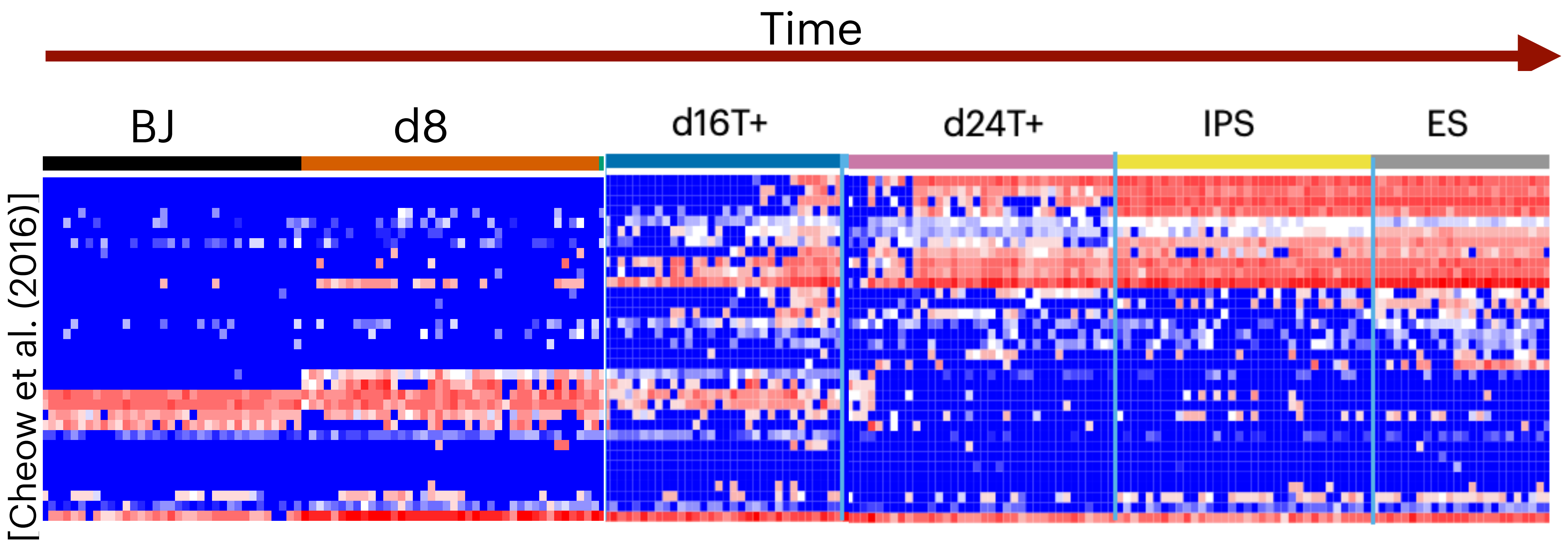
AUPR ratio (unsigned)



AUPR ratio (signed)



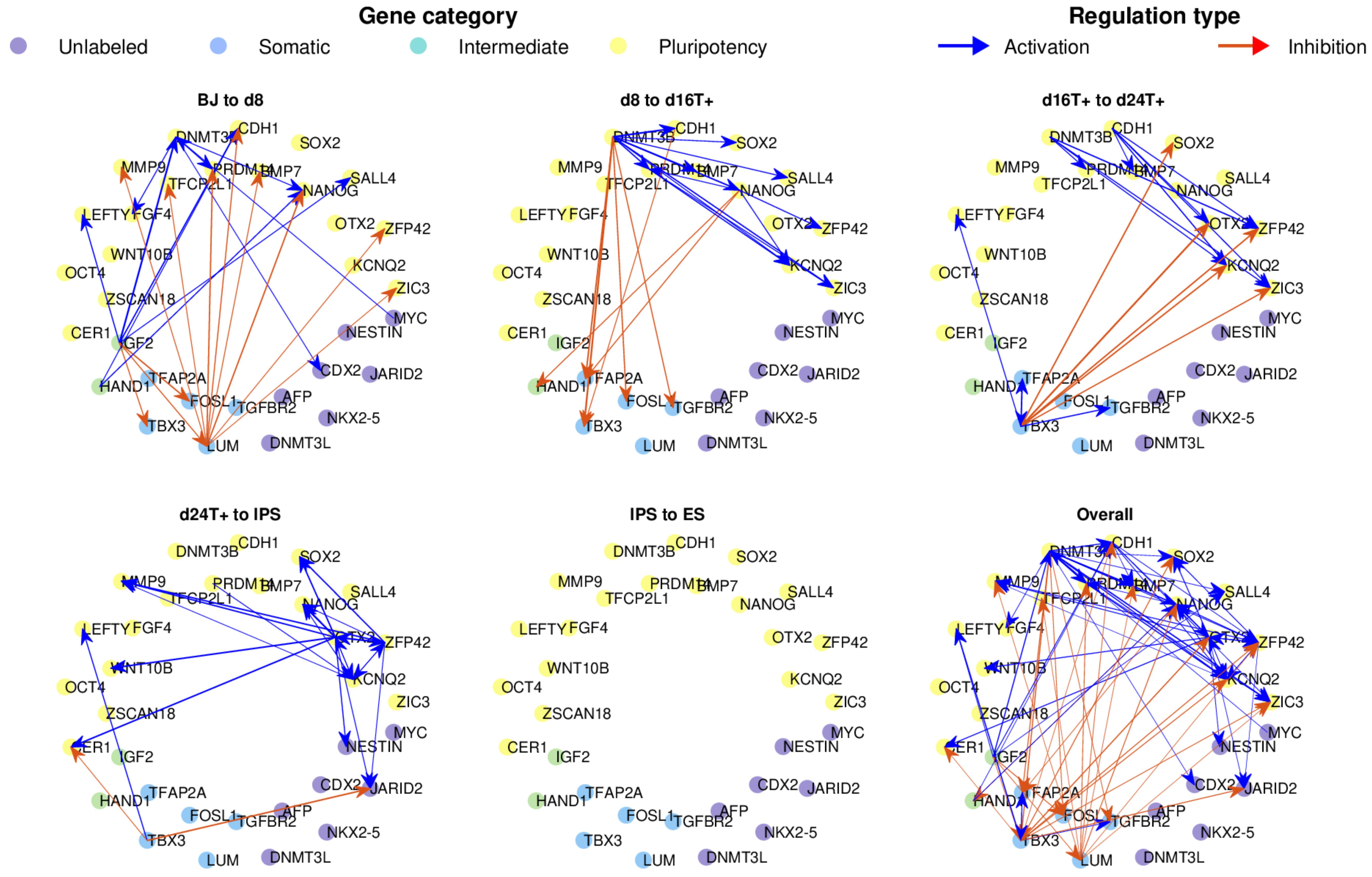
Result on real data



[Cheow et al. (2016)]

	experimental network	
	AUPRC	AUROC
GENIE3	0.027	0.592
GRNBoost2	**0.033**	0.616
SINCERITIES	0.018	0.474
HARISSA	0.028	0.586
CARDAMOM	0.024	0.566
OTVelo-Corr	0.031	**0.667**
OTVelo-Granger	0.020	0.480

Table: AUC values across different methods compared against experimental network
Random baselines: 0.02 and 0.5



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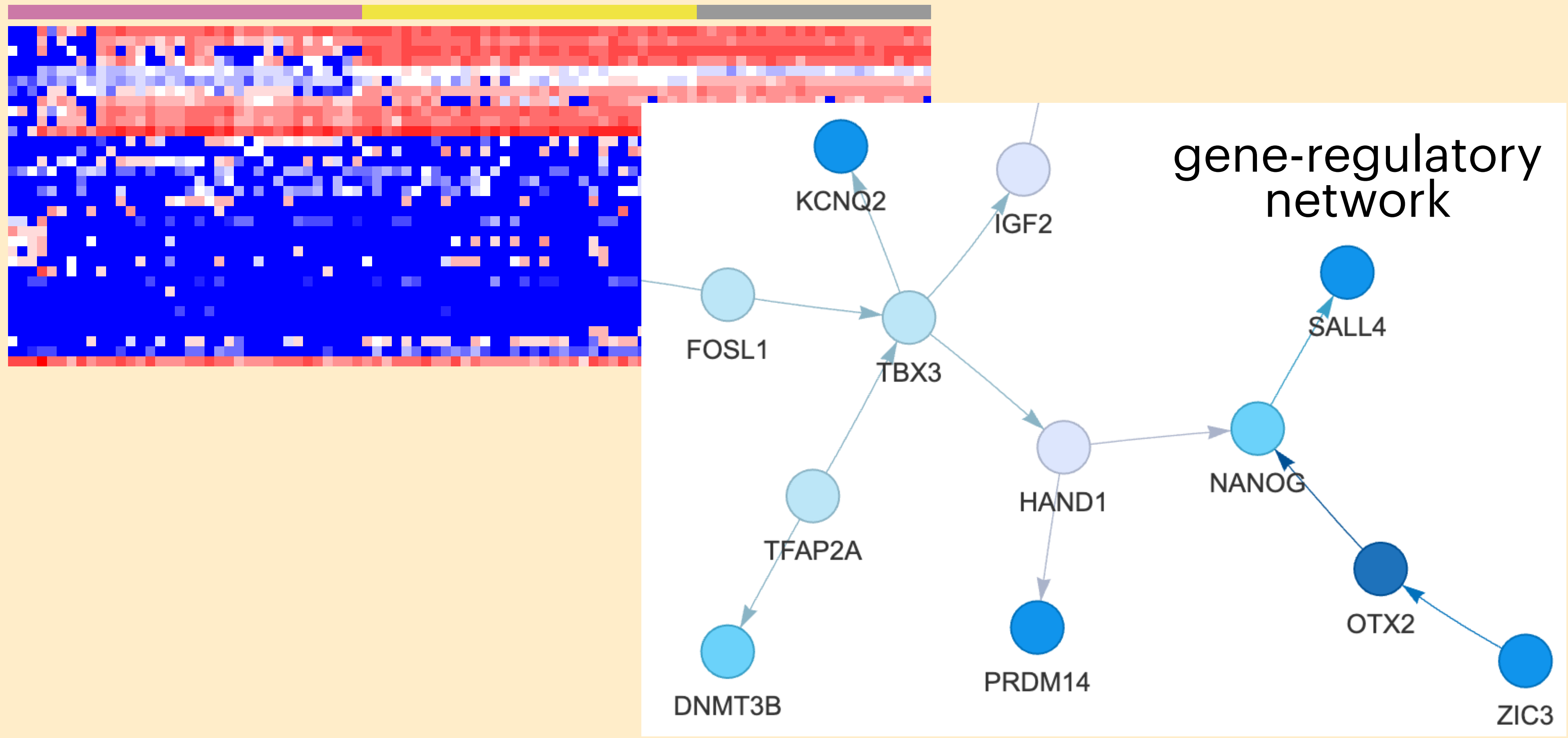

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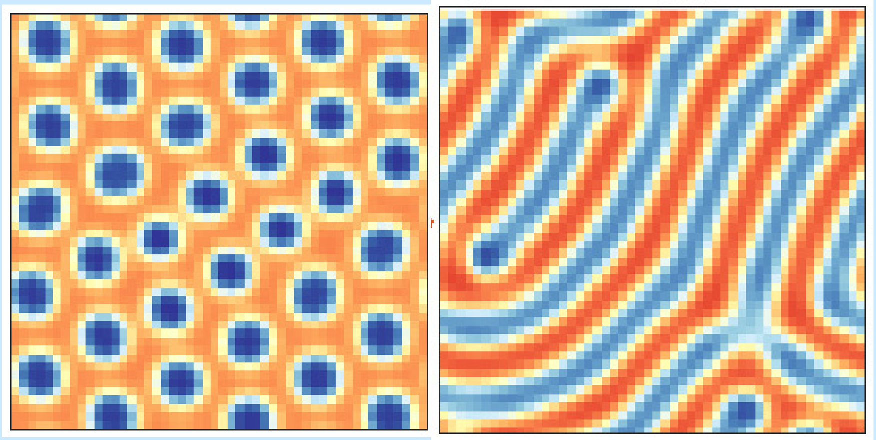
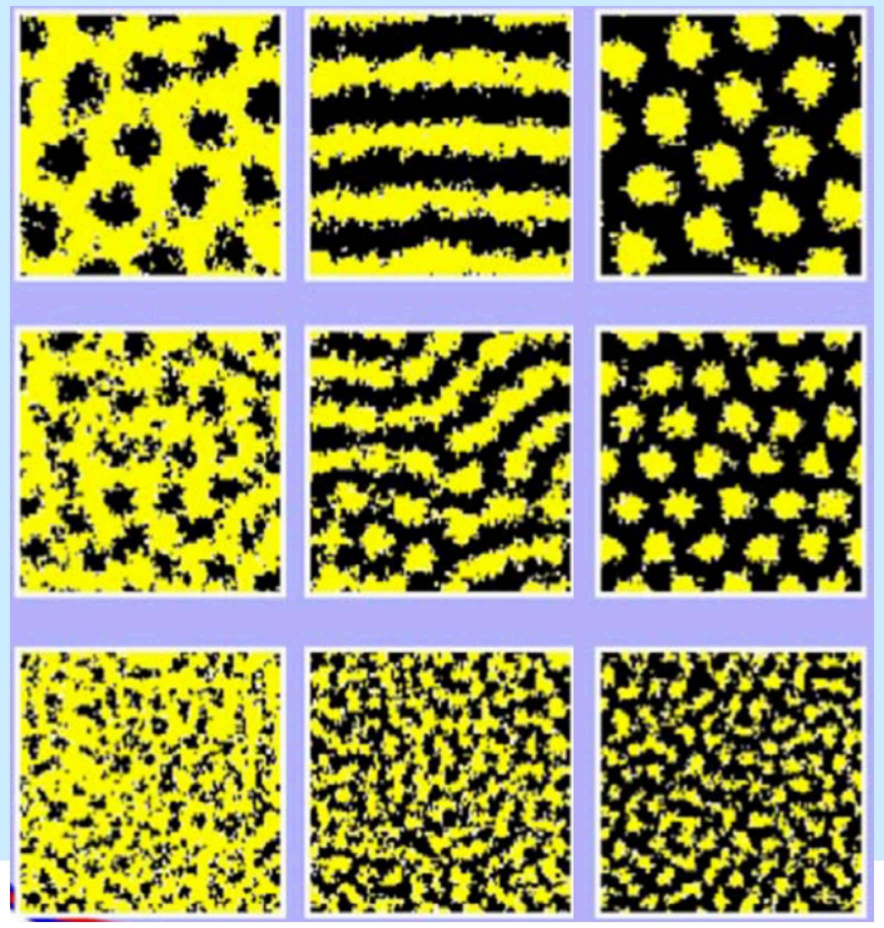
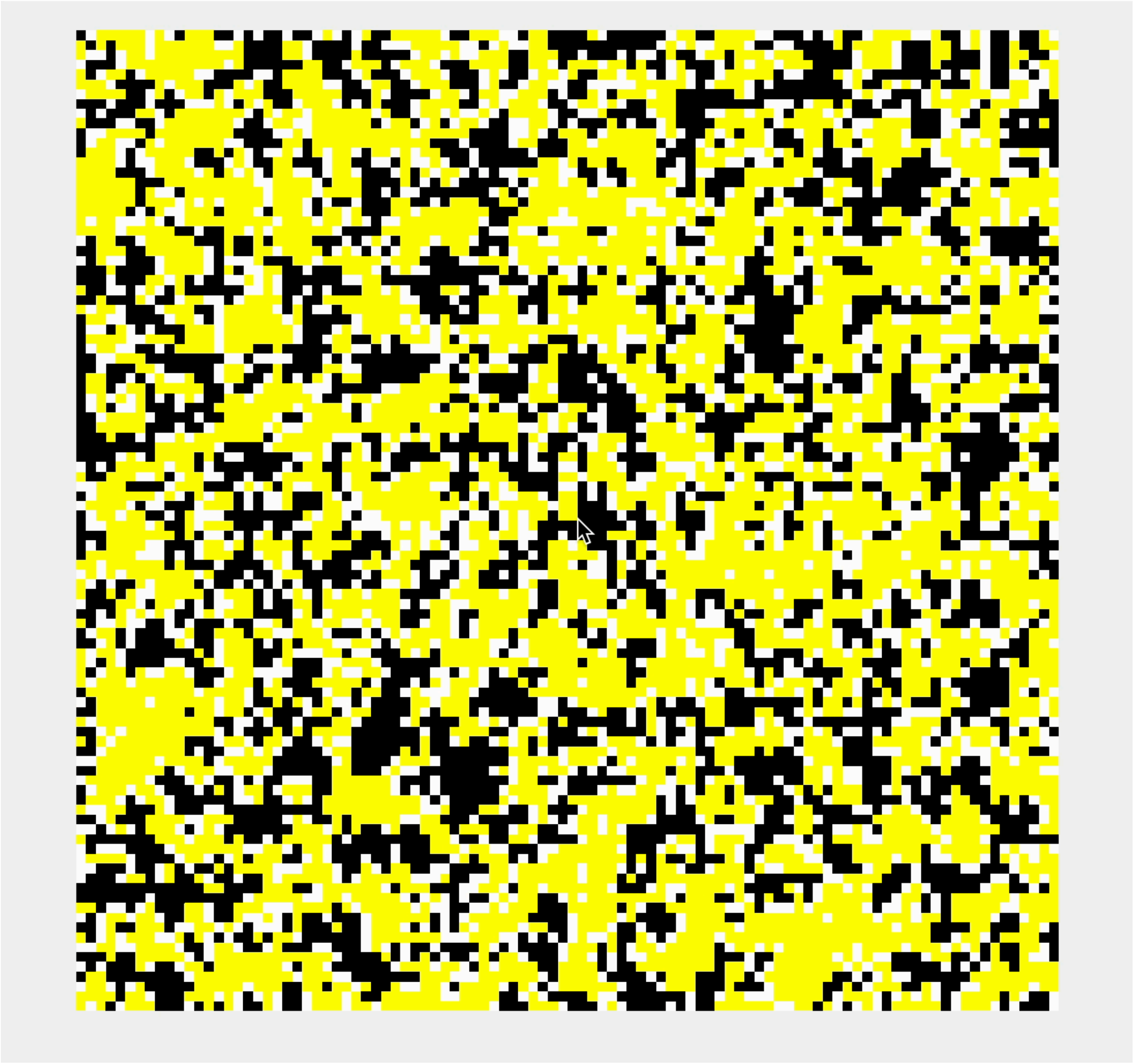


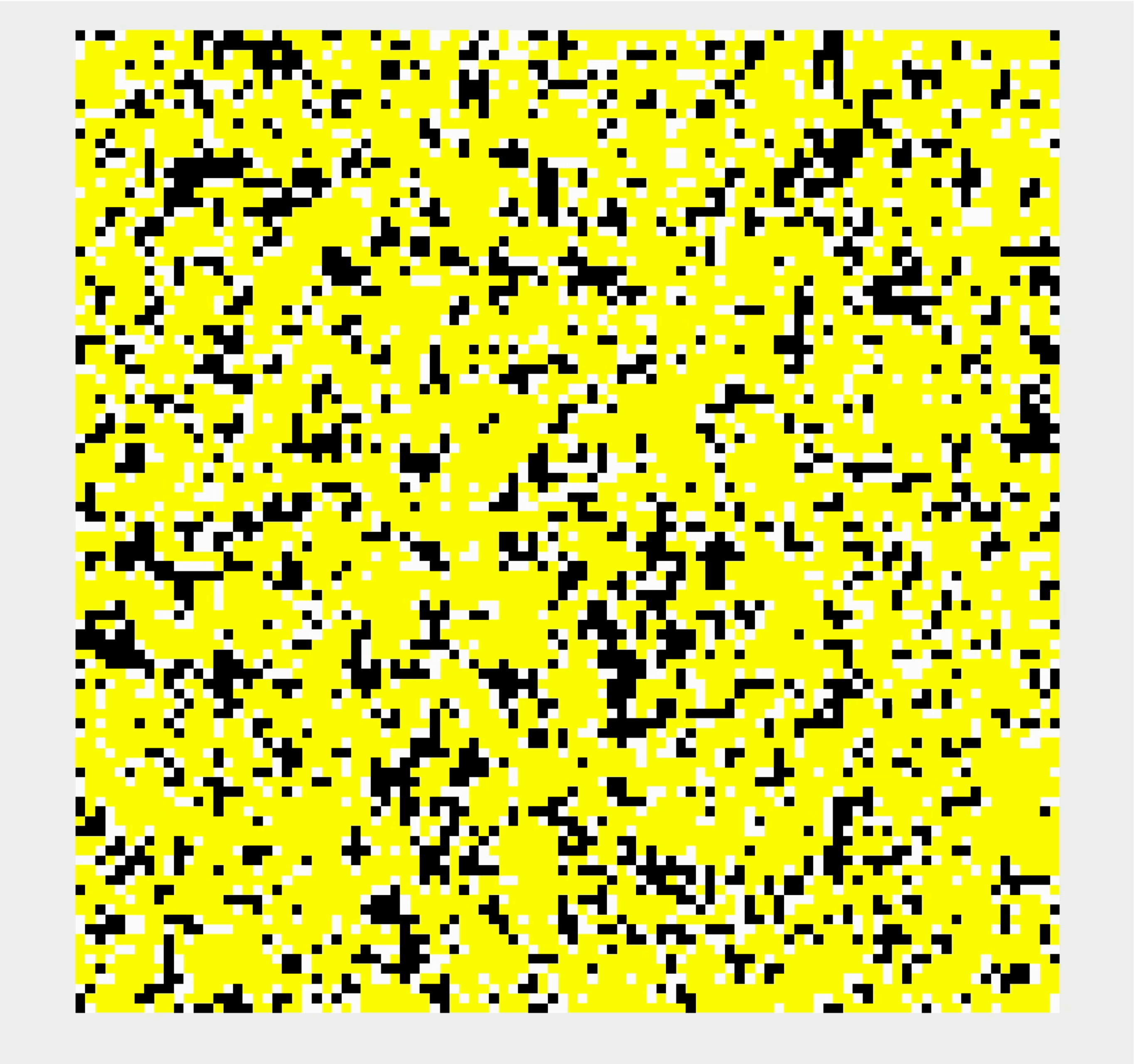


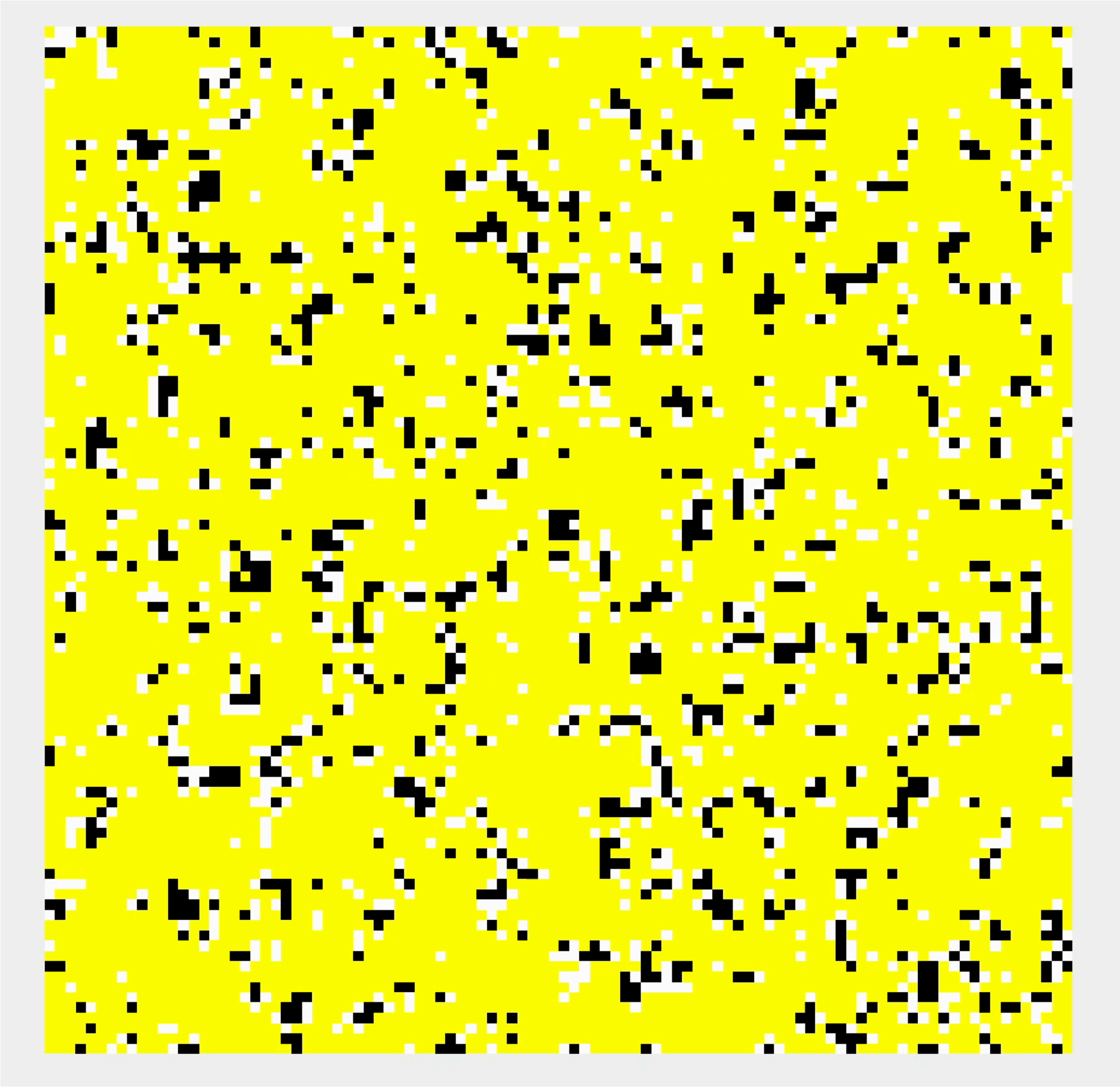
How to distinguish different patterns?

Example 1: fish skin model

- How does fish skin form their patterns?
- Example [Bullara & Decker] on-lattice model
- Stripe/Spots/Nothing?
- Depends on spatial extent and strength of interaction between cells







How to distinguish different patterns?

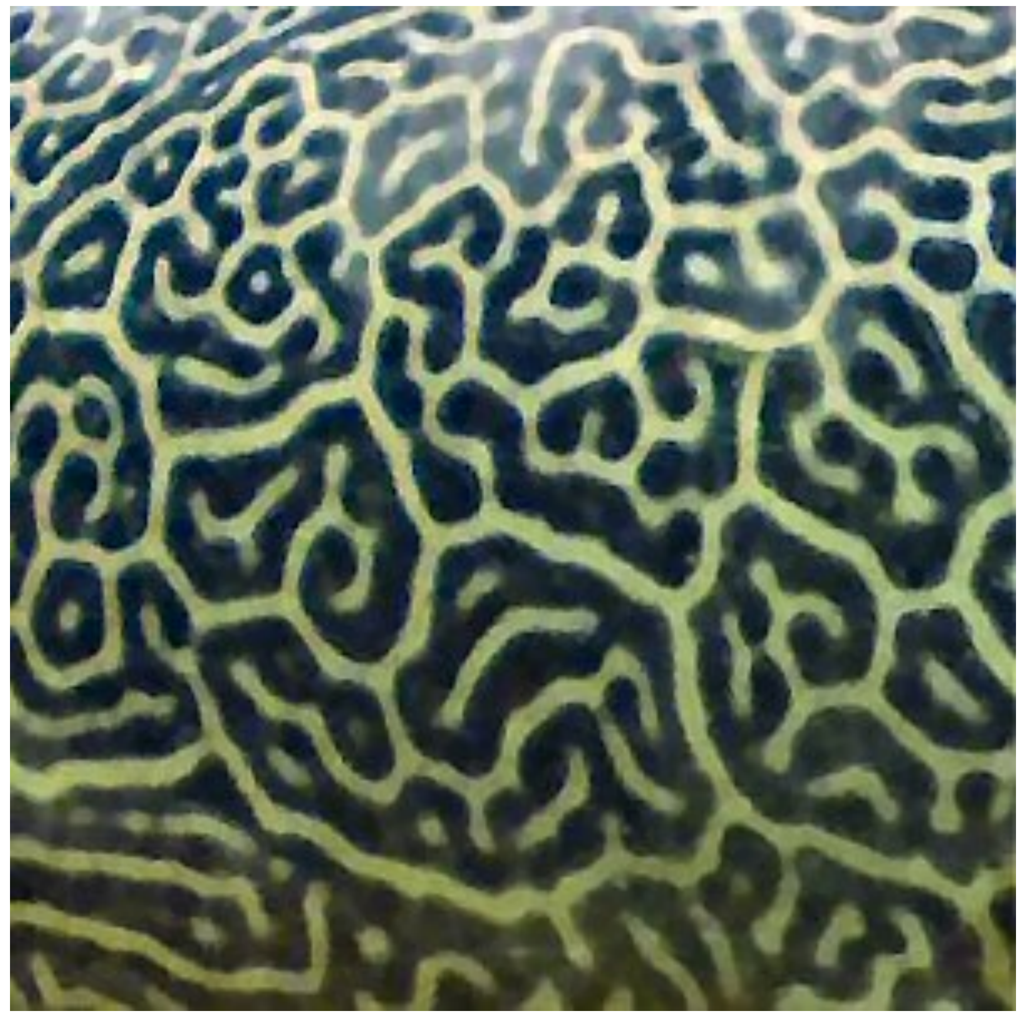
Example 2: reaction-diffusion equation

- Turing patterns: introduced by Alan Turing in 1952 to describe patterns in nature;
- Spatially extended reaction-diffusion systems are known to generate such patterns, such as Brusselator (we focus on the case with $x = (x_1, x_2) \in \mathbb{R}^2$):

$$\begin{aligned} \partial_t u &= \boxed{D_0 \nabla^2 u} + \boxed{a - (1+b)u + vu^2} \\ \partial_t v &= \boxed{D_1 \nabla^2 v} + \boxed{bu - vu^2} \end{aligned}$$

Diffusion

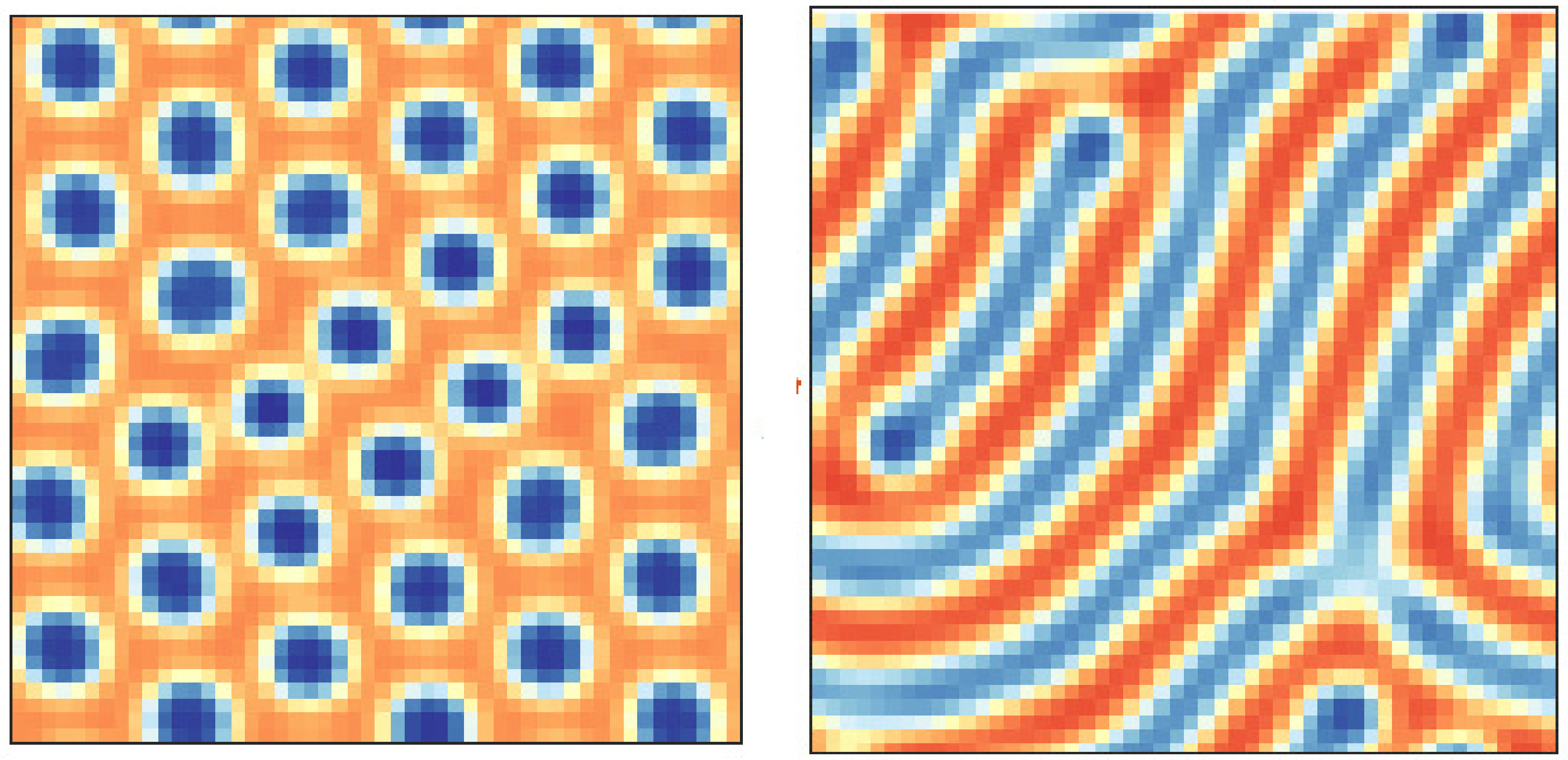
Reaction



Wikipedia (Pufferfish skin)

Wikipedia (Patterned vegetation)

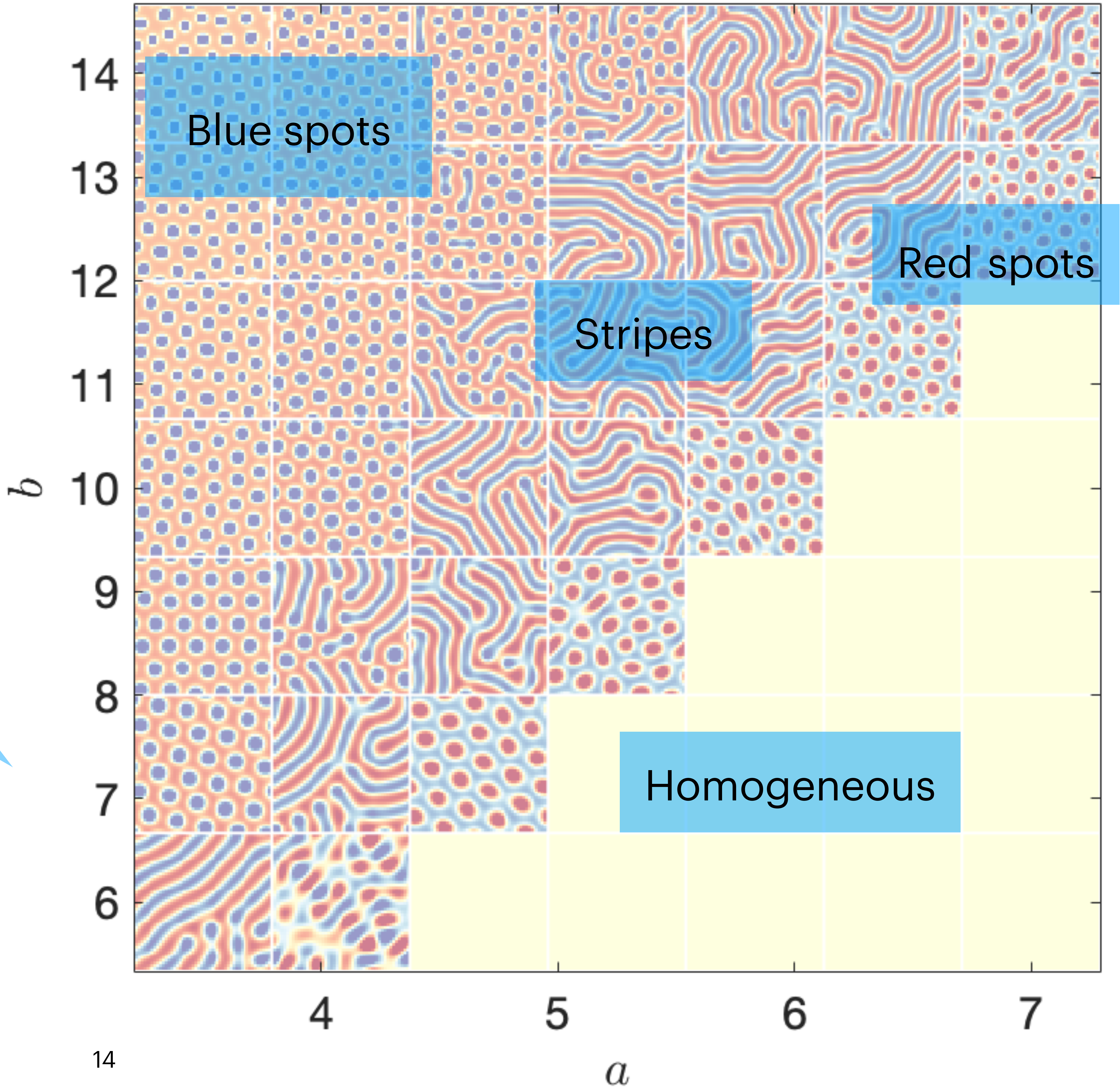
$u(x_1, x_2, T)$ for $T \gg 1$



Bifurca

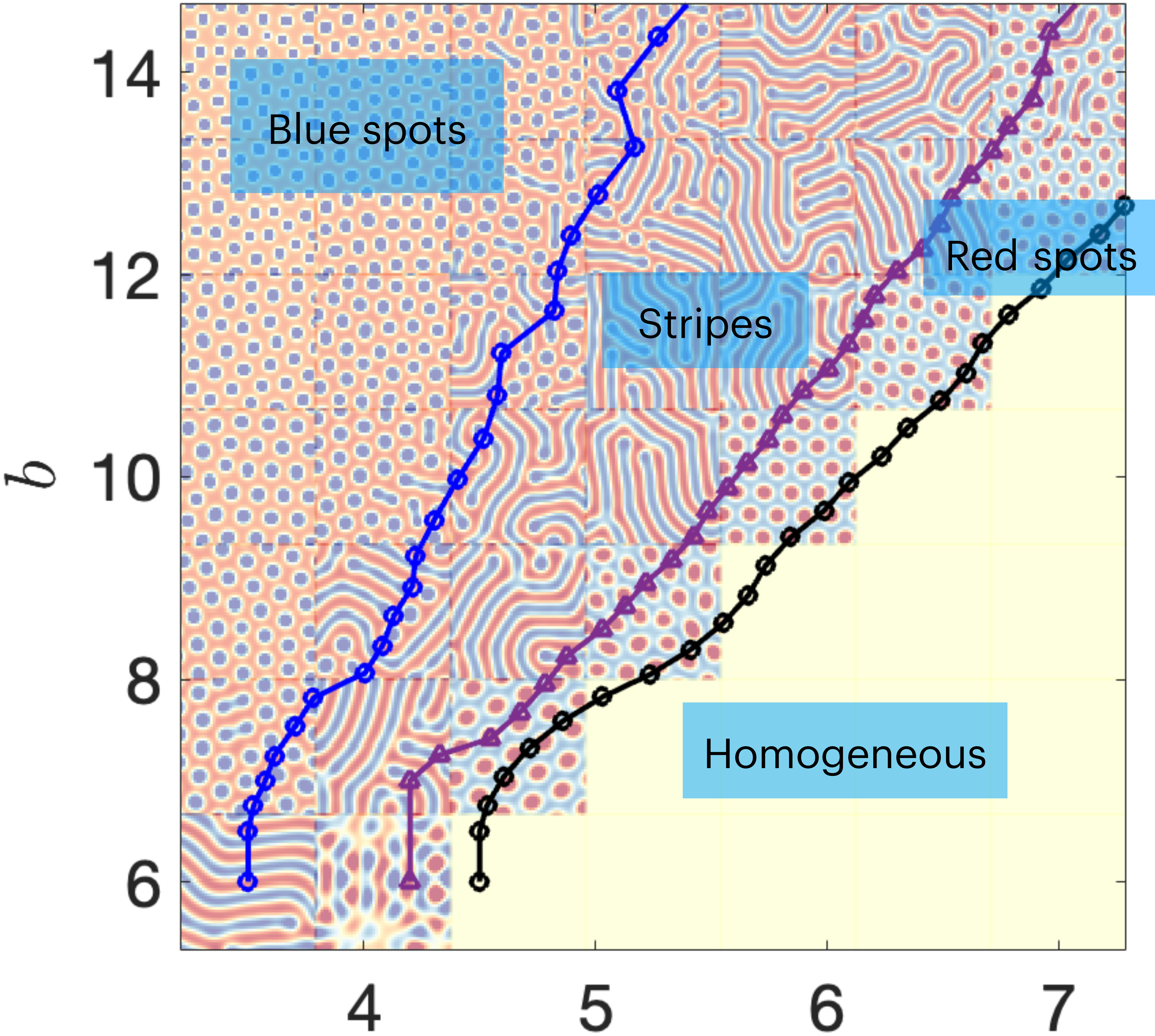
$$\partial_t u = D_0 \nabla^2 u + a - (1 + b) u +$$
$$\partial_t v = D_1 \nabla^2 v + bu - vu^2$$

Where does the pattern transition happen in the parameter space?



Spoiler (what we found)

Where does the pattern transition happen in the parameter space?



Challenges

Traditional approaches:

- Visual inspection for direct simulation: **cheap, but** **less accurate**
- Existing software (continuation): given initial value problems, compute each pattern and their stability and find their interfaces between different patterns.

  accurate, but **expensive and specialized** (wave number selection? bistability?)

  They don’t work for agent-based models like the fish skin!

Solve a classification problem via neural network?

- Requires a training set with pre-labeled solutions — lots of human effort…
- Interpretability?
- Active learning (collect data strategically, only near bifurcation curve)?

Data-driven algorithm via cheap, direct simulation?

Sure, but how should we *quantify the patterns*?

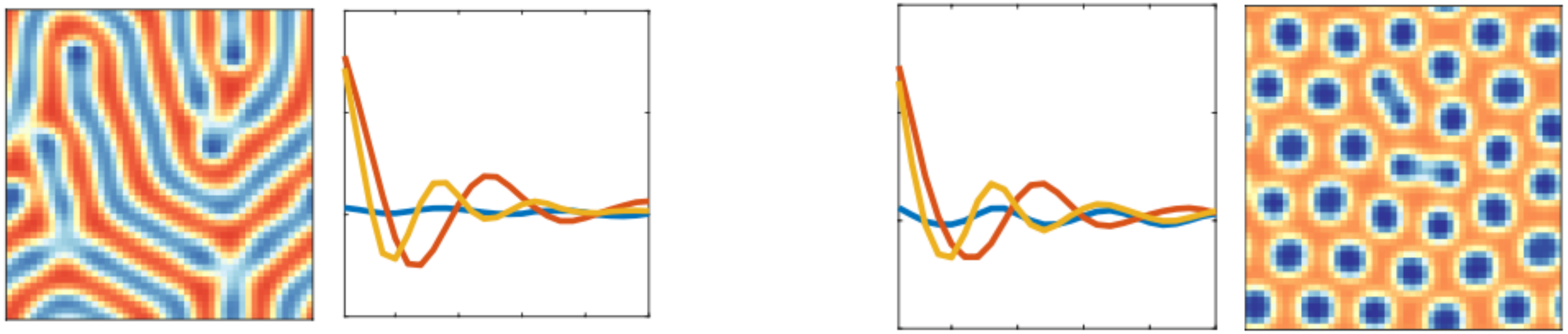
Furthermore, how do we *compare the patterns*?

Some options for pattern quantification

- Option 1: 2D Fourier coefficients
- Option 2: pattern correlation function [Gavagnin et al 2018]:

$$f(m) = \frac{c(m)}{\mathbb{E}[c(m)]}, \quad c(m) = \left|\{(x, y) \in \text{sublevel set} \mid \|x - y\| = m\}\right|$$

- They are not good enough at distinguishing spots/stripes with random orientations!



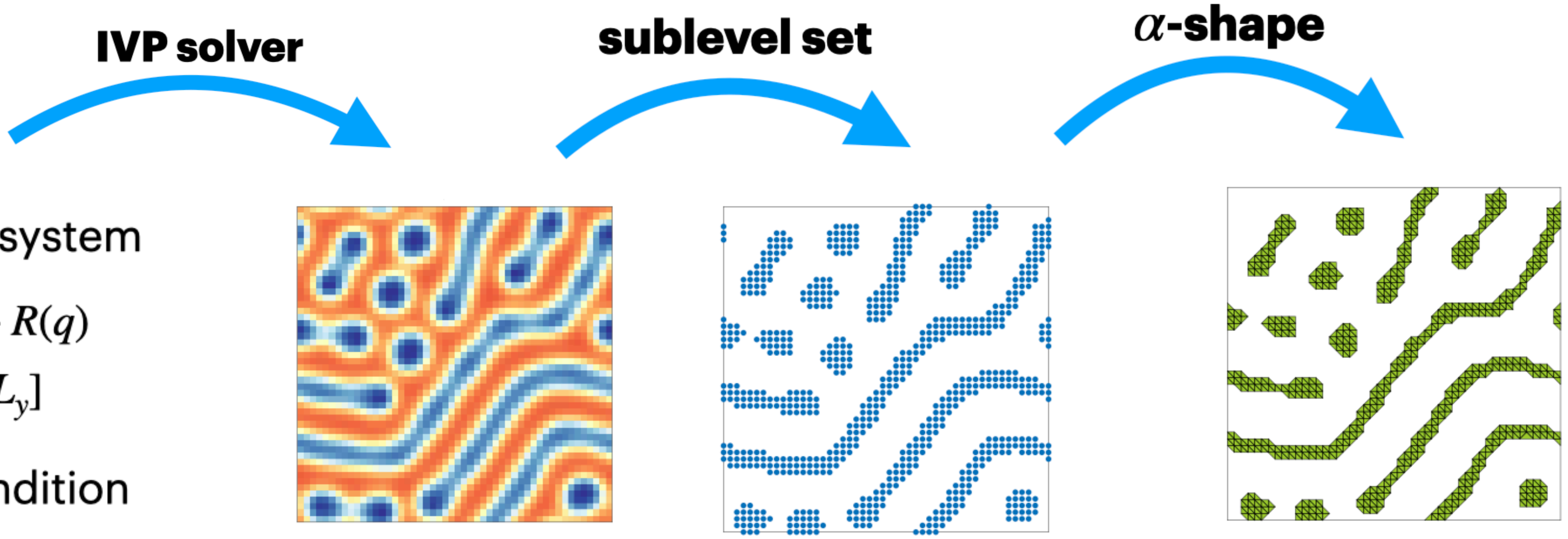
Our approach: from PDE solution to patterns

Reaction-diffusion system

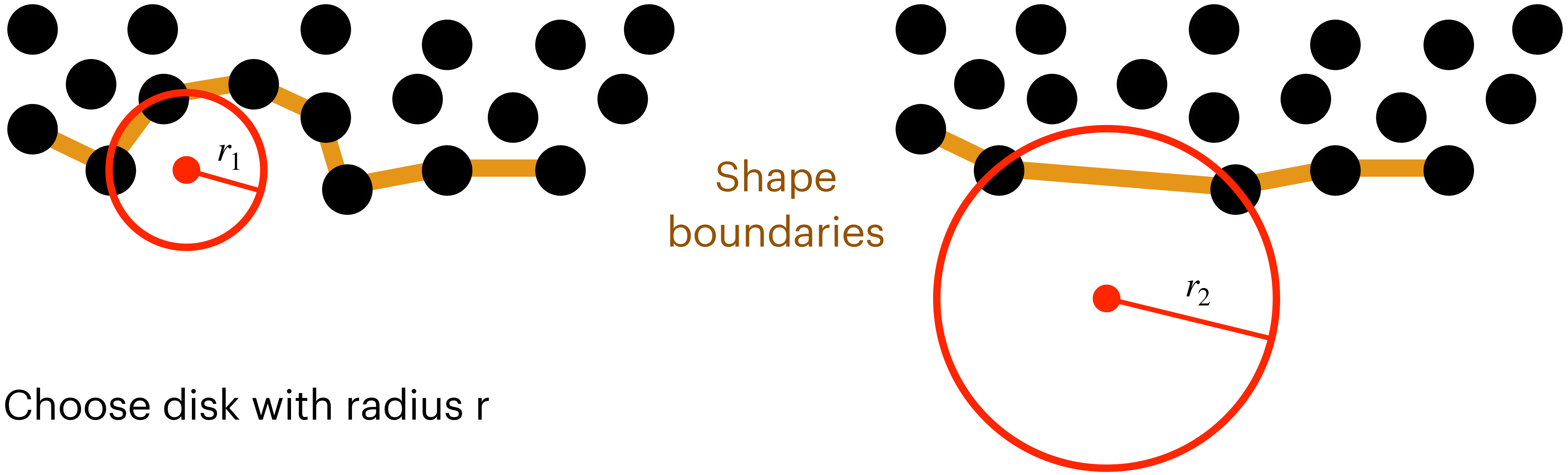
$$\partial_t q(x,t) = D\nabla^2 q + R(q)$$

$$x \in [0,L_x] \times [0,L_y]$$

Random initial condition



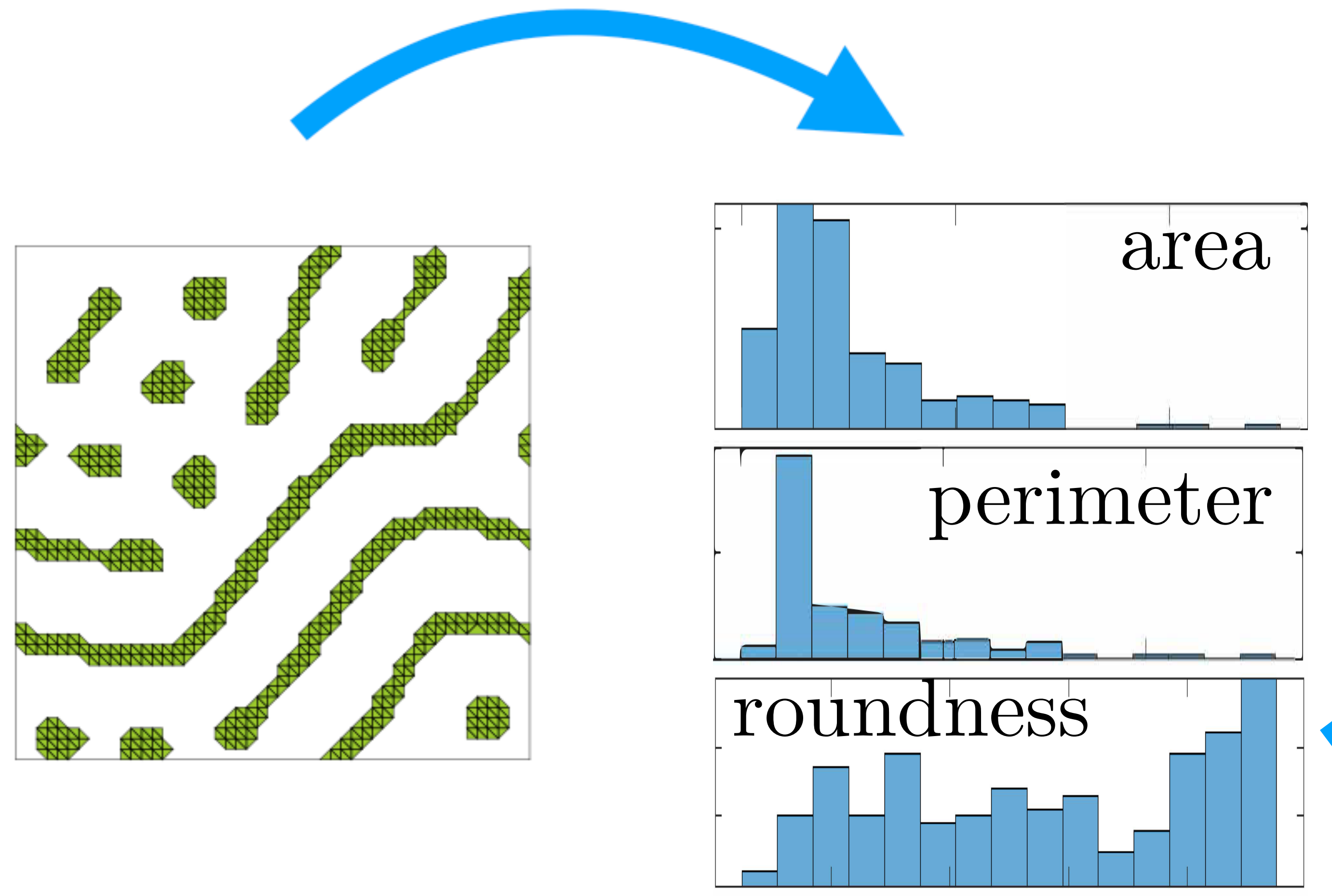
α-shapes



- Choose disk with radius r
- Connect two data points precisely when we can position the disk so that it contains only these two data points

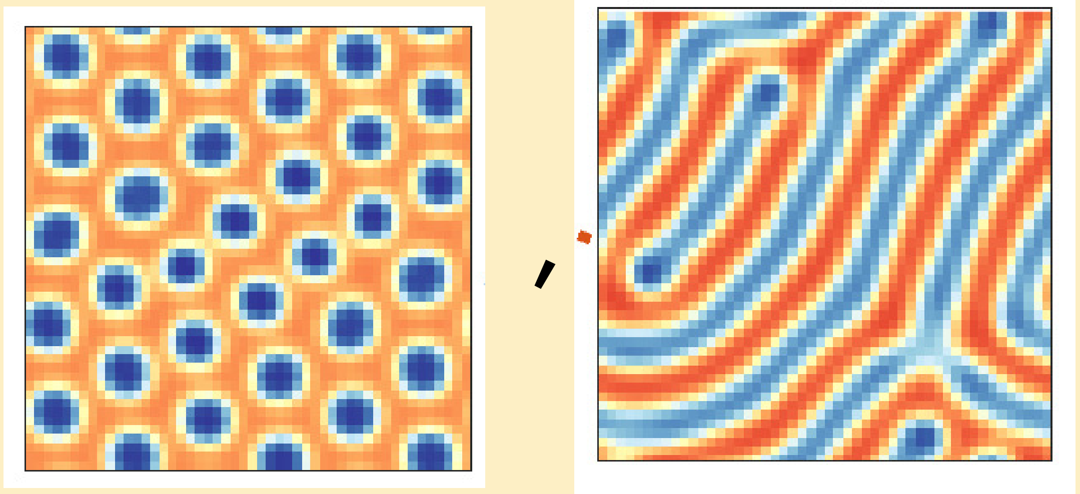
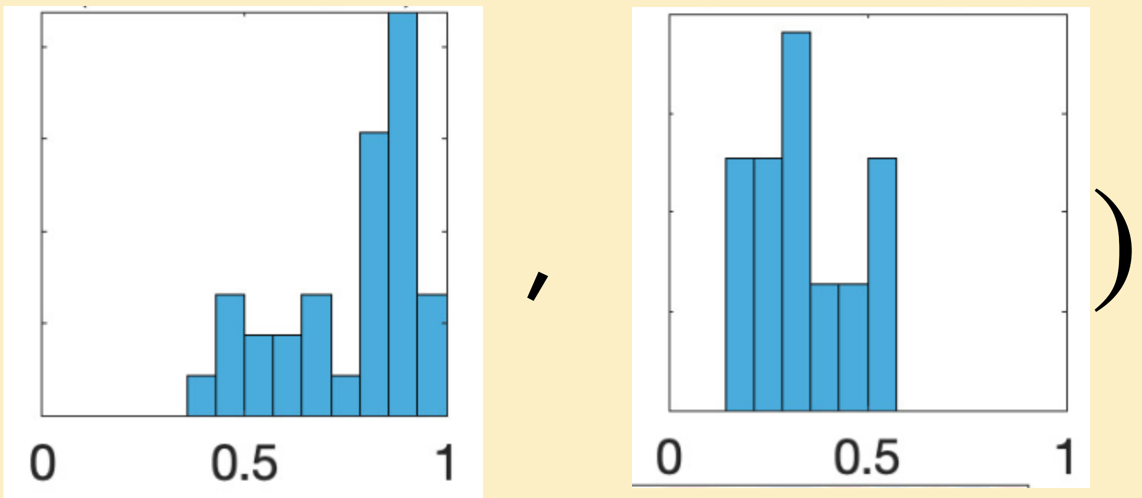
Our approach: from patterns to metric

cluster-wise features



$roundness = \frac{4\pi \times area}{perimeter^2}$, bounded between 0 (stripes) and 1 (spots)

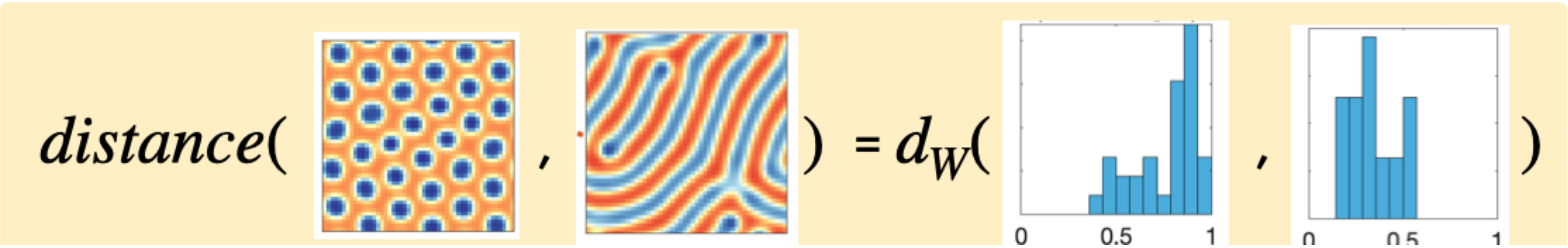
2-Wasserstein distance

$distance($  $) = d_W($  $)$

Theorem (under some assumptions): The pattern statistics $\mu_f : \mathbb{R}^2 \longrightarrow \mathrm{Prob}(\mathcal{Z}),\ p \longmapsto \mu_f(p)$

is continuous in the Wasserstein metric on $\mathrm{Prob}(\mathcal{Z})$

Empirical evaluation of Wasserstein distance in feature space

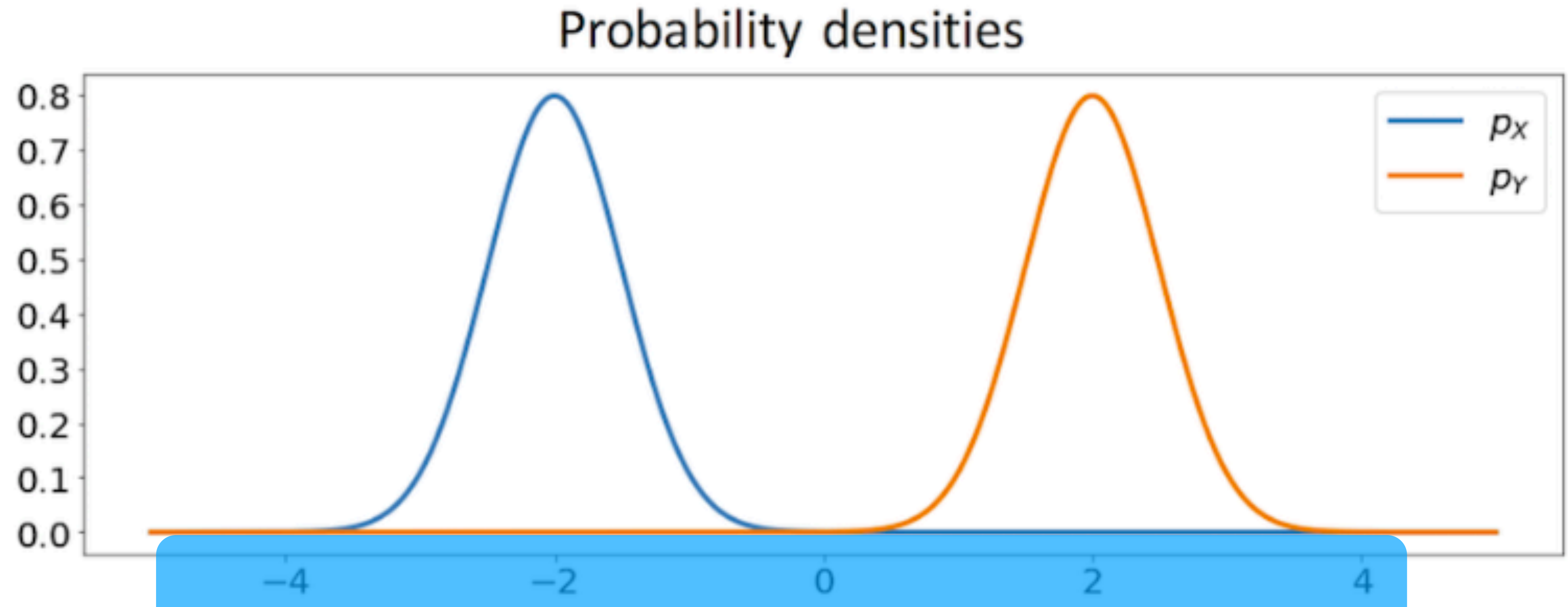


- For 1D histograms (our case!), with Euclidean cost, it reduces to:

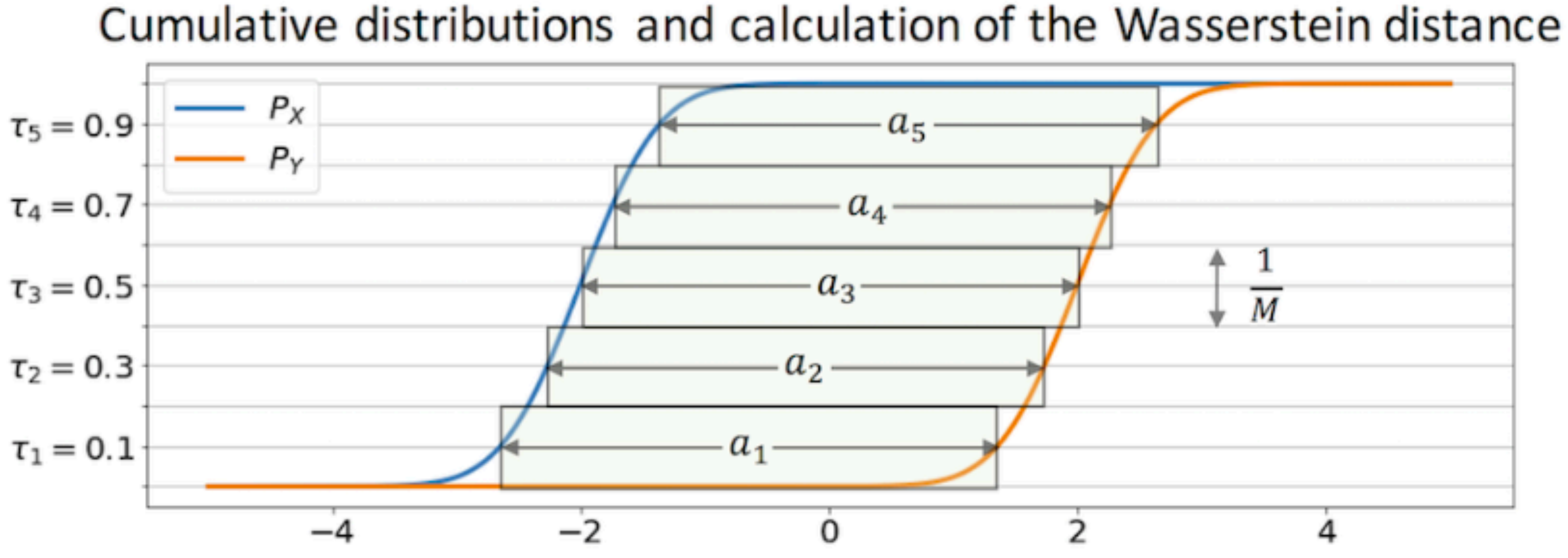
$$d_W^2(\rho,\mu) = \int_0^1 (F_\rho^{-1}(p) - F_\mu^{-1}(p))^2 \, dp,$$ [Kolouri and Martin 2018]

where $F_\rho^{-1}(p)$ is the inverse cumulative density function of ρ.

- Its sample-based approximation can be computed efficiently via a sorting algorithm. Existing implementation: *https://github.com/nklb/wasserstein-distance*

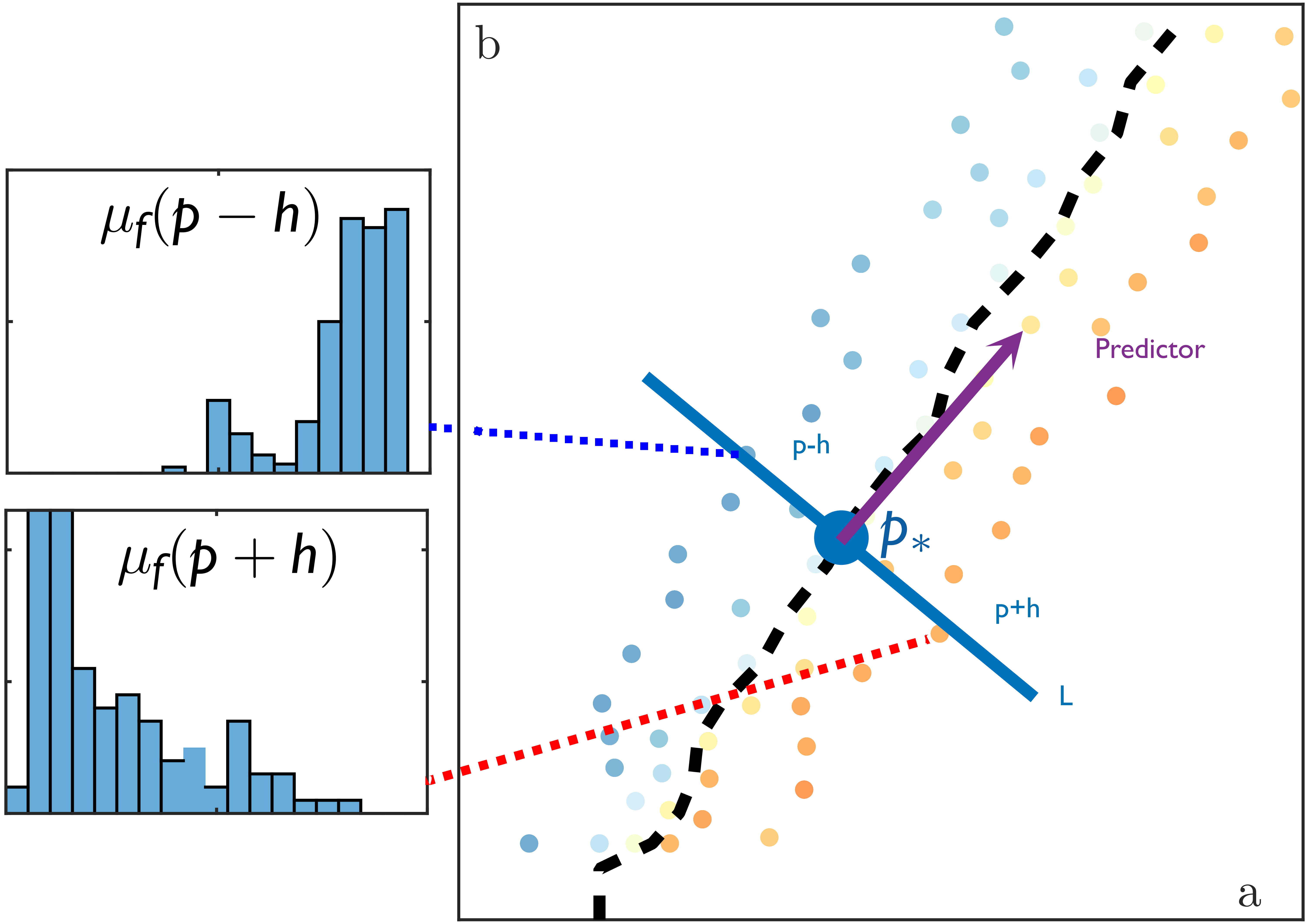


Intuitively, the metric measures the gap between all quantiles



Figures reproduced from [Kolouri and Martin 2018]

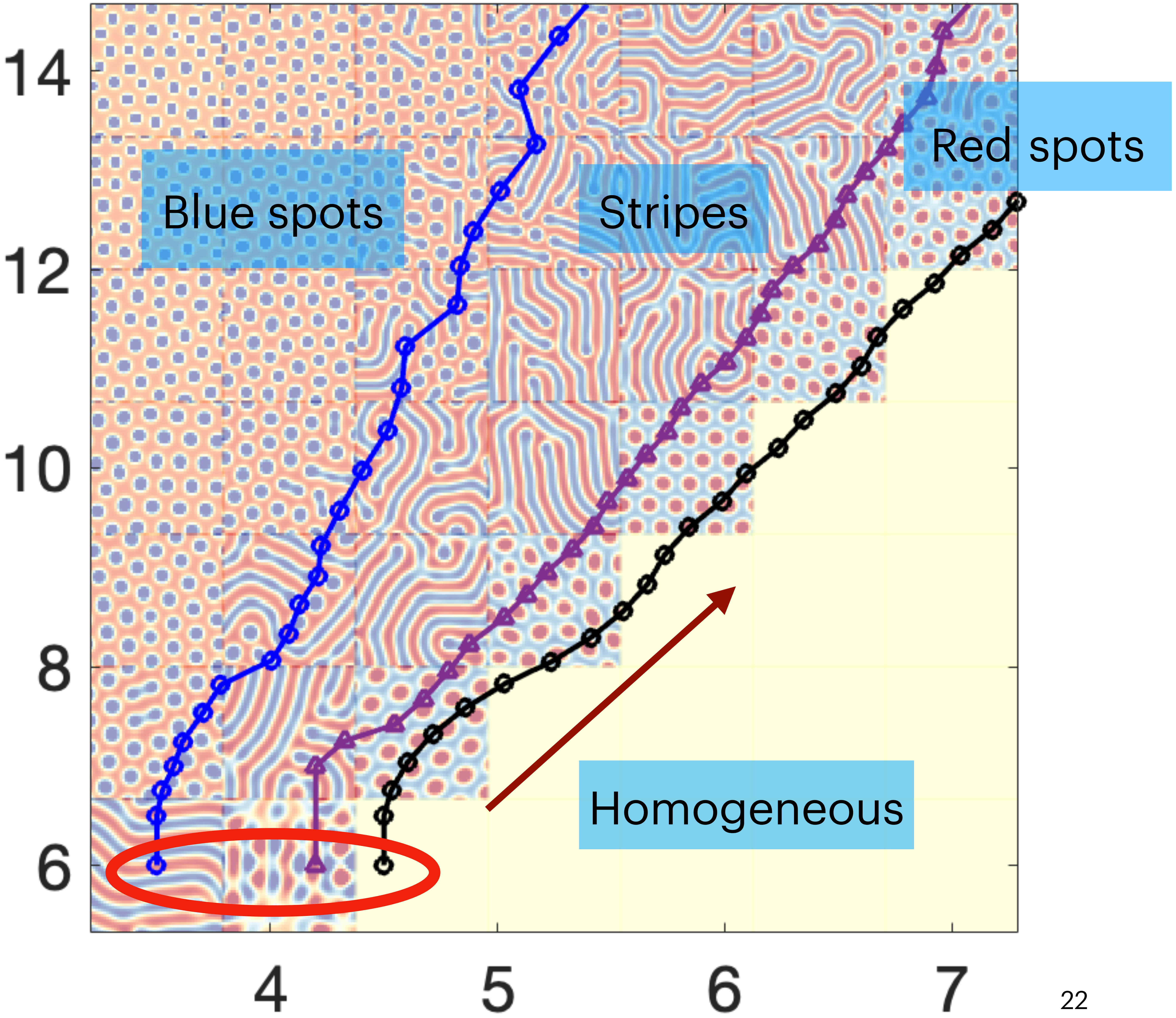
Numerical: continuation framework



Bifurcation curves are determined by maximizing Wasserstein distance of pattern statistics across curve

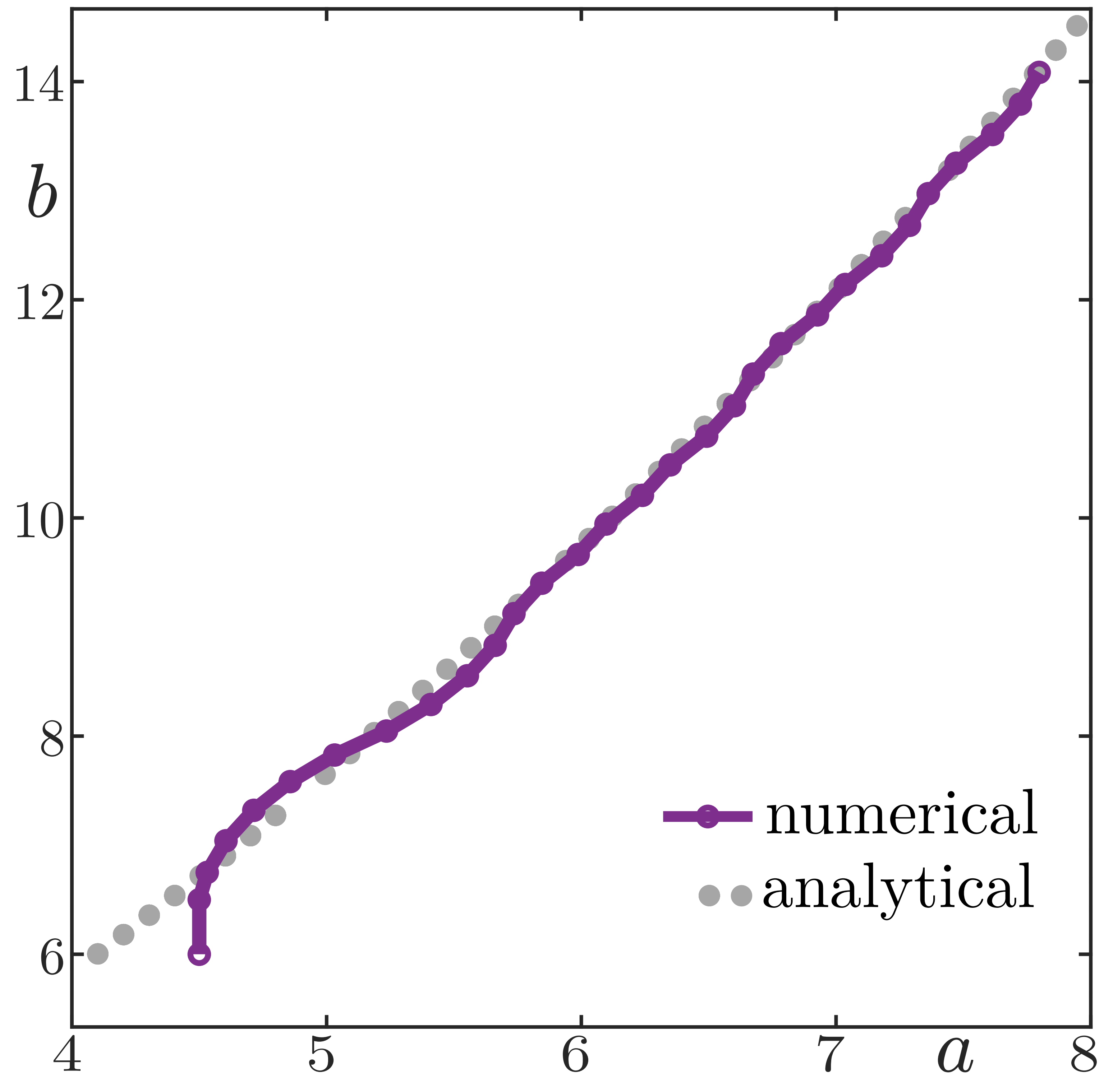
$$p_* := \arg\max_{p\in L} d_W(\mu_f(p-h), \mu_f(p+h))$$

Application: Brusselator model



Validation:

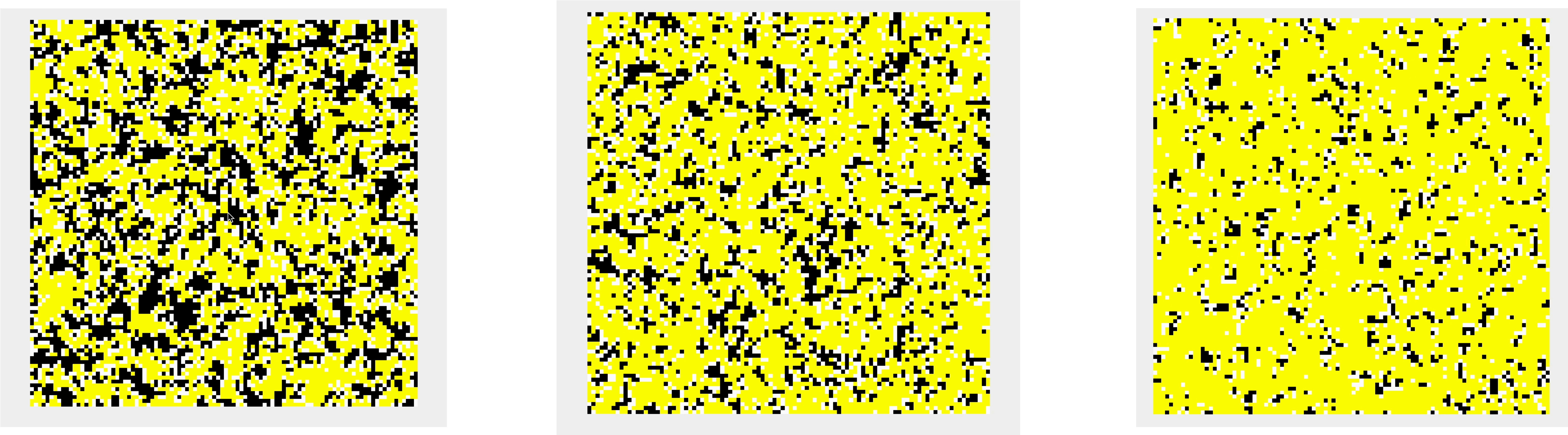
- Stripes/Spots: visual inspection…
- Homogeneous state: analytical solution



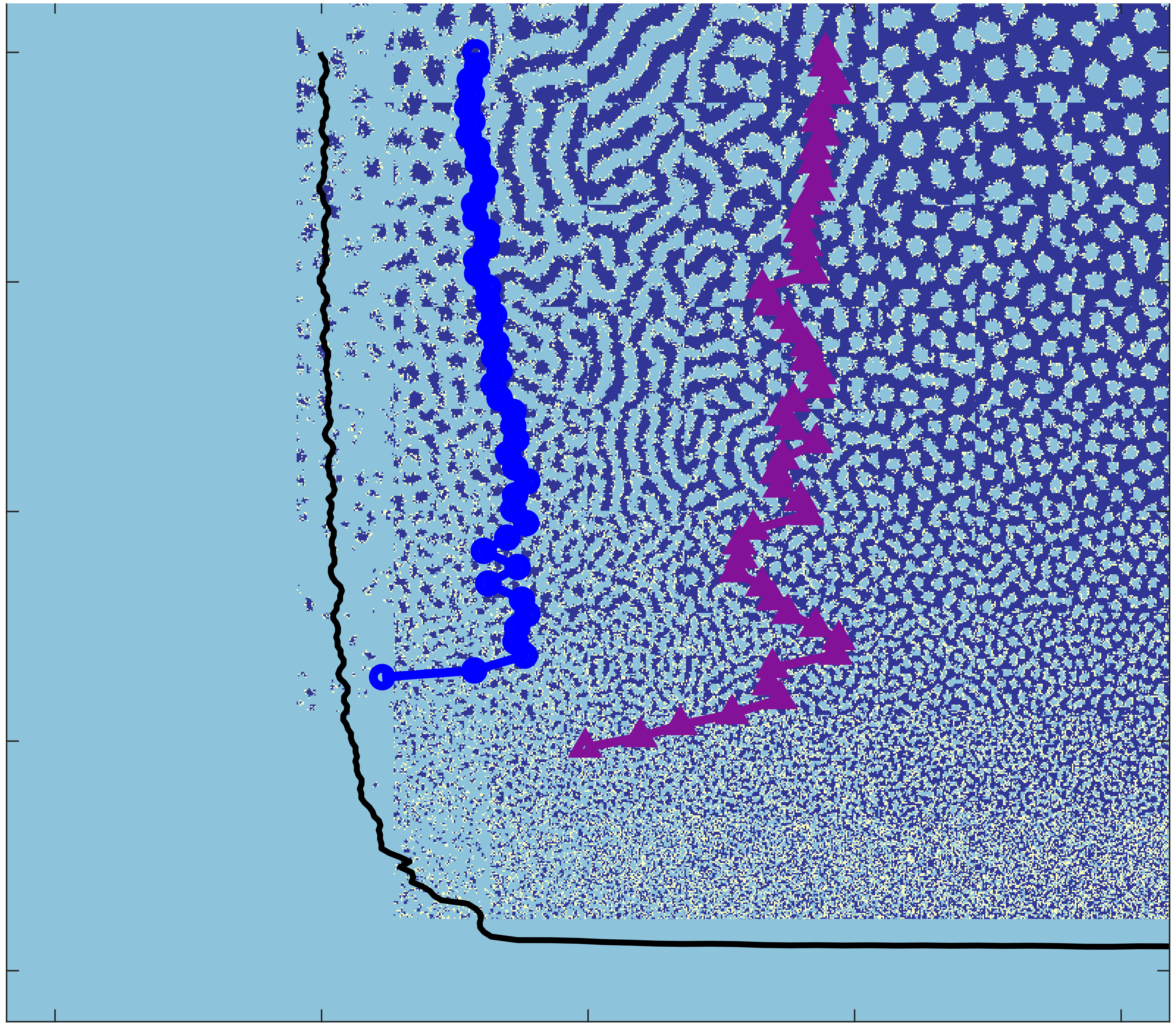
Moving back to the original motivation...

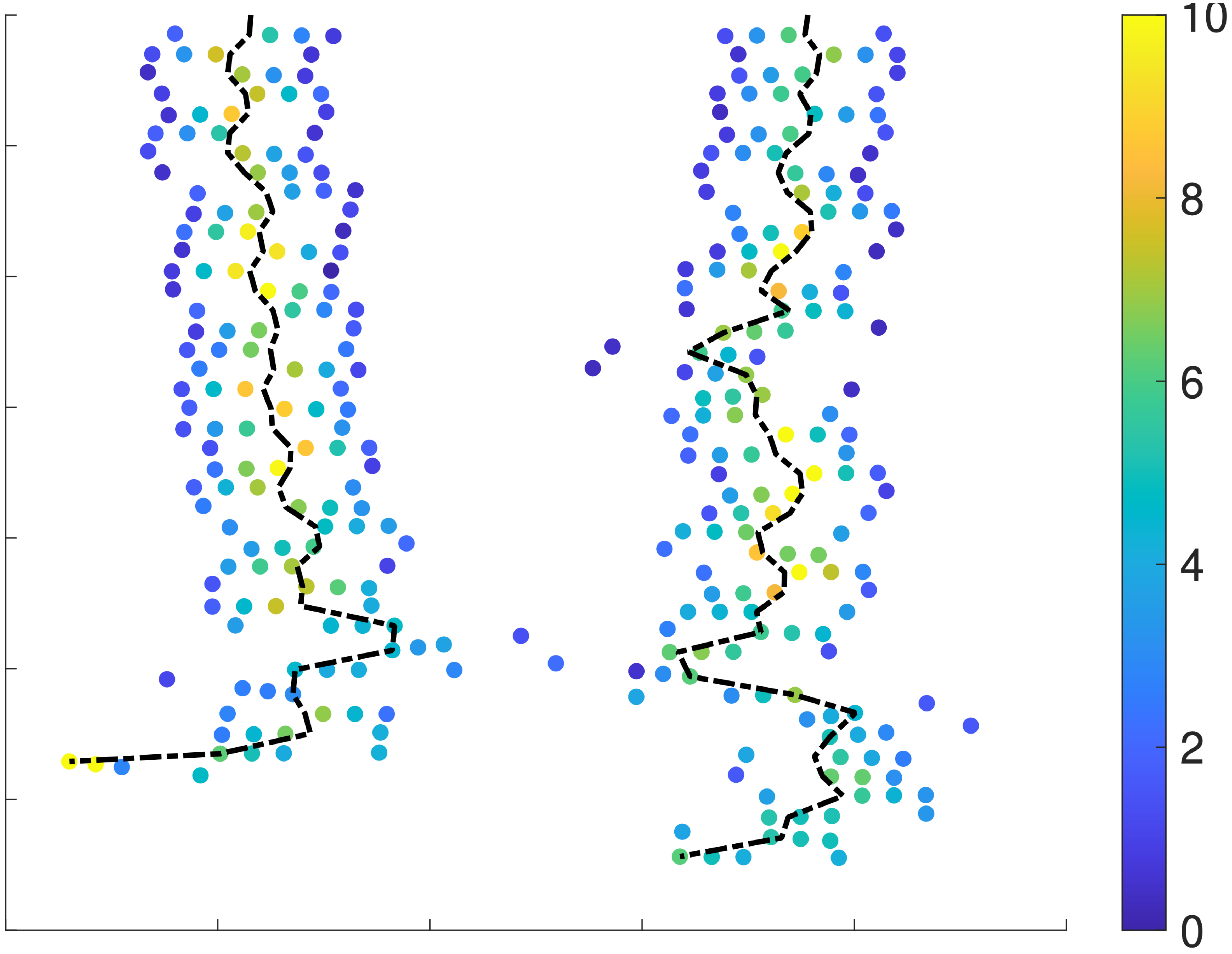
Example 1: fish skin model

- How does fish skin form their patterns?
- Example [Bullara & Decker] on-lattice model
- Stripe/Spots/Nothing?
- Depends on spatial extent and strength of interaction between cells



Fish skin model?





Horizontal: strength of interaction

Vertical: spatial extent of interaction

Wasserstein distance decreases when patterns are destroyed

Thanks! Questions?