Modeling Neural Stem Cell Dynamics

Mathematical Description of Spatiotemporal Homeostasis maintaining in the Zebrafish Brain

HGS MathComp Membership Colloquium

Théo André (P.I.: Prof. Dr. Anna Marciniak-Czochra)

Heidelberg University

October 28th, 2024.

HGS MathComp

UNIVERSITÄT HEIDELBERG
ZUKUNFT SEIT 1386

ABOUT ME

Théo André

Ph.D. student

EDUCATION

2018 | 2019 | 2020 | 2021 | 2022 | 2023 | 2024 | …

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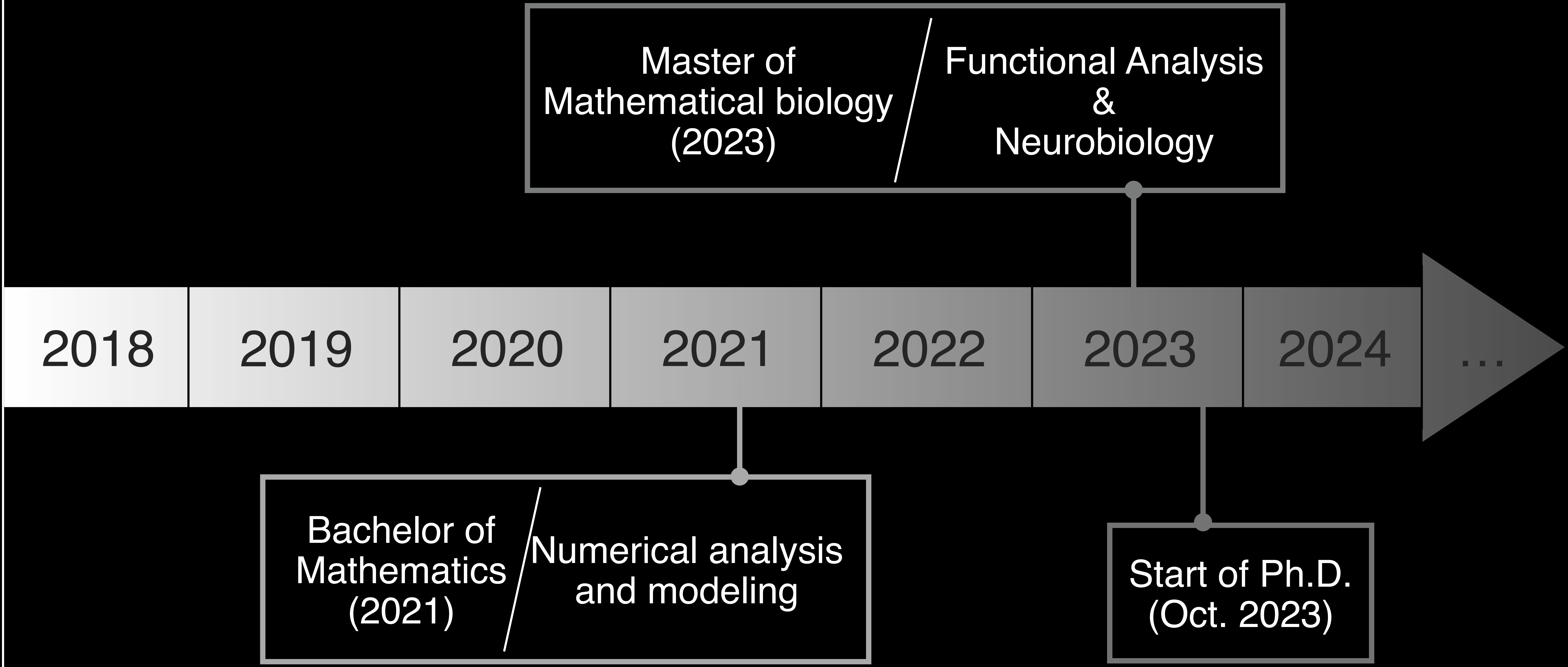

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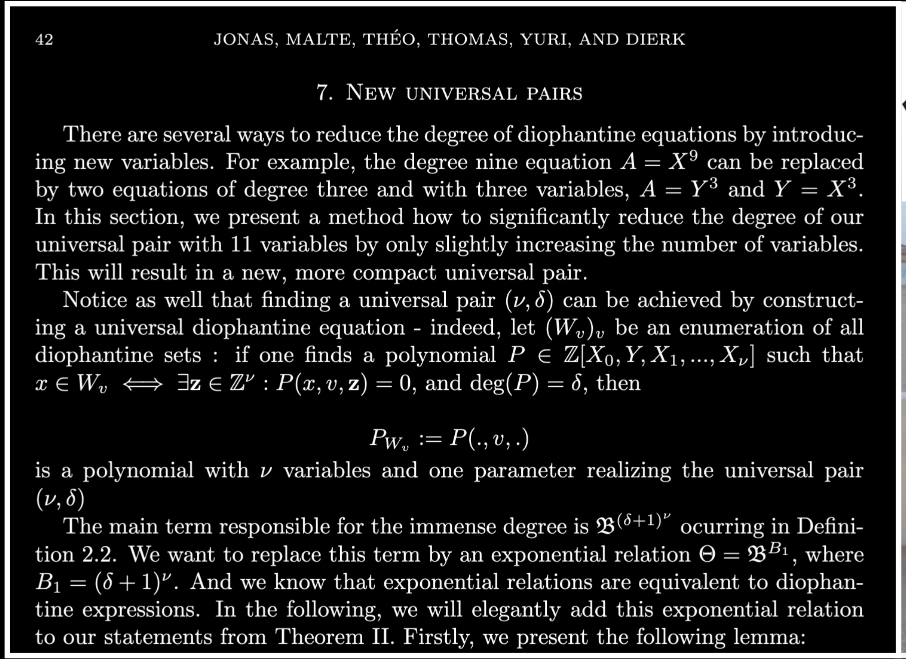

42 JONAS, MALTE, THÉO, THOMAS, YURI, AND DIERK

7. New universal pairs

There are several ways to reduce the degree of diophantine equations by introducing new variables. For example, the degree nine equation $A = X^9$ can be replaced by two equations of degree three and with three variables, $A = Y^3$ and $Y = X^3$. In this section, we present a method how to significantly reduce the degree of our universal pair with 11 variables by only slightly increasing the number of variables. This will result in a new, more compact universal pair.

Notice as well that finding a universal pair (ν, δ) can be achieved by constructing a universal diophantine equation - indeed, let $(W_v)_v$ be an enumeration of all diophantine sets : if one finds a polynomial $P \in \mathbb{Z}[X_0, Y, X_1, ..., X_\nu]$ such that $x \in W_v \iff \exists \mathbf{z} \in \mathbb{Z}^\nu : P(x, v, \mathbf{z}) = 0$, and $\deg(P) = \delta$, then

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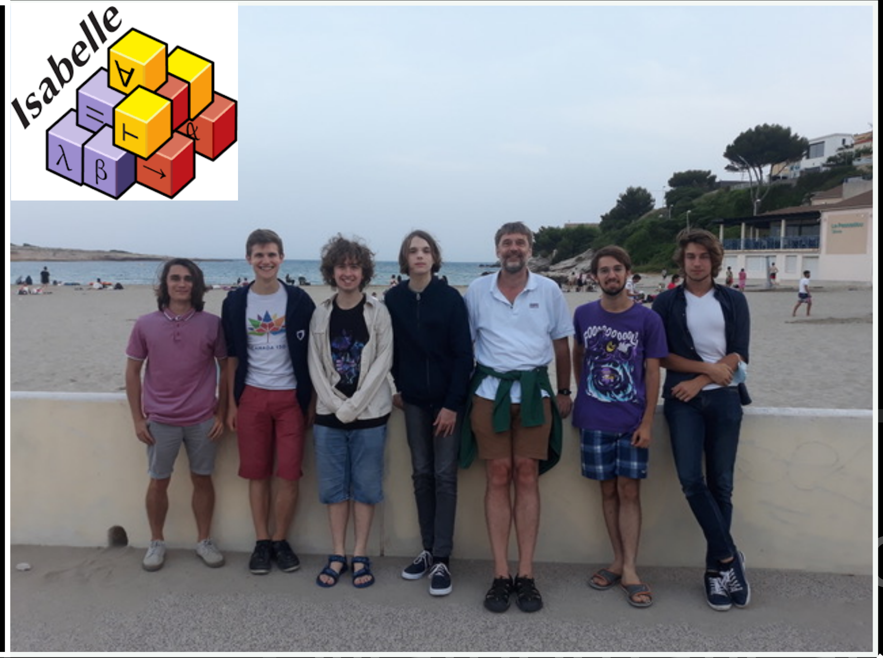

Bounds on Diophantine Equations and Formalization of Hilbert Xth Problem's proof in Isabelle
(D. Schleicher, Y. Matiyassevich)

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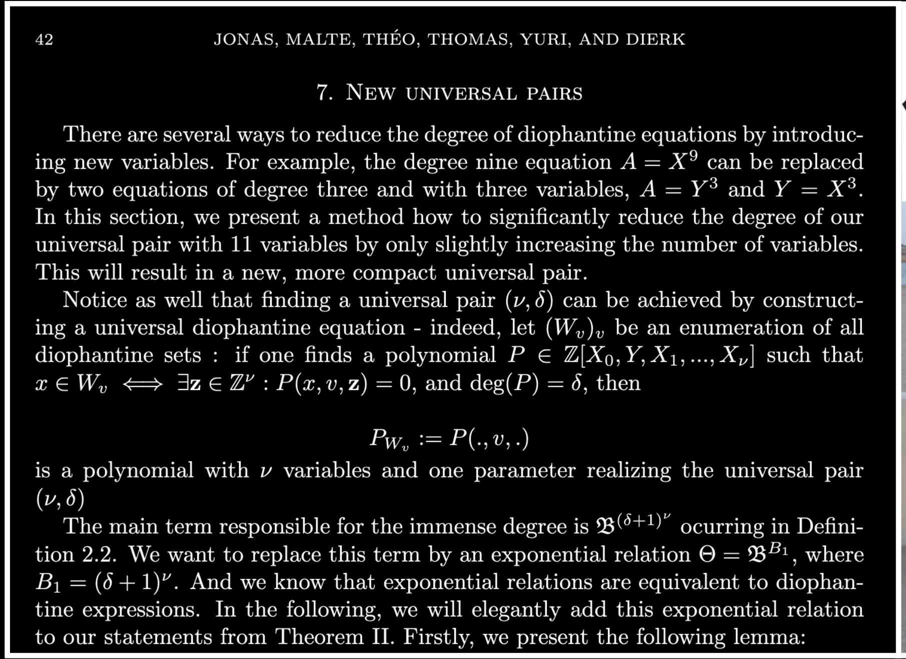

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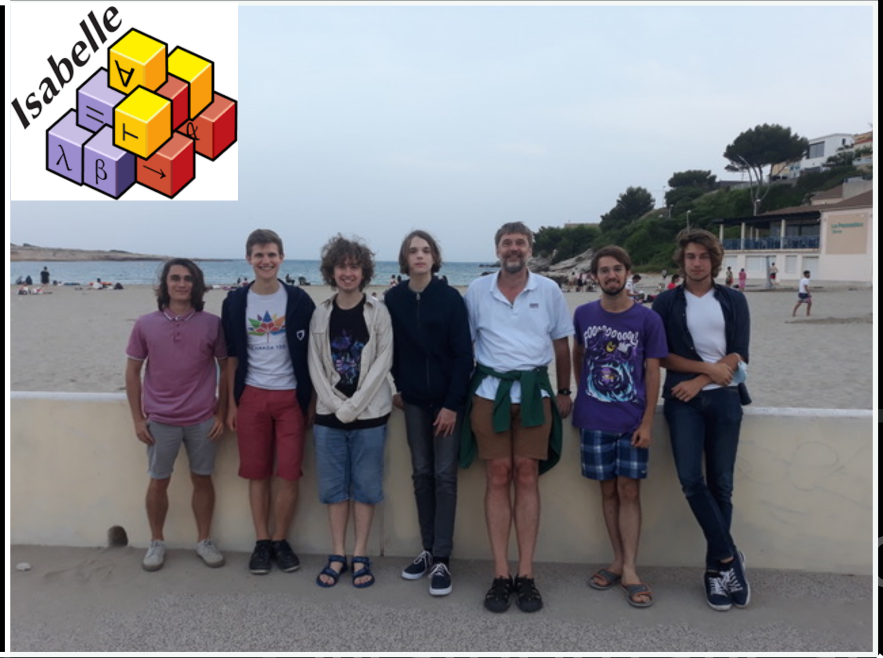

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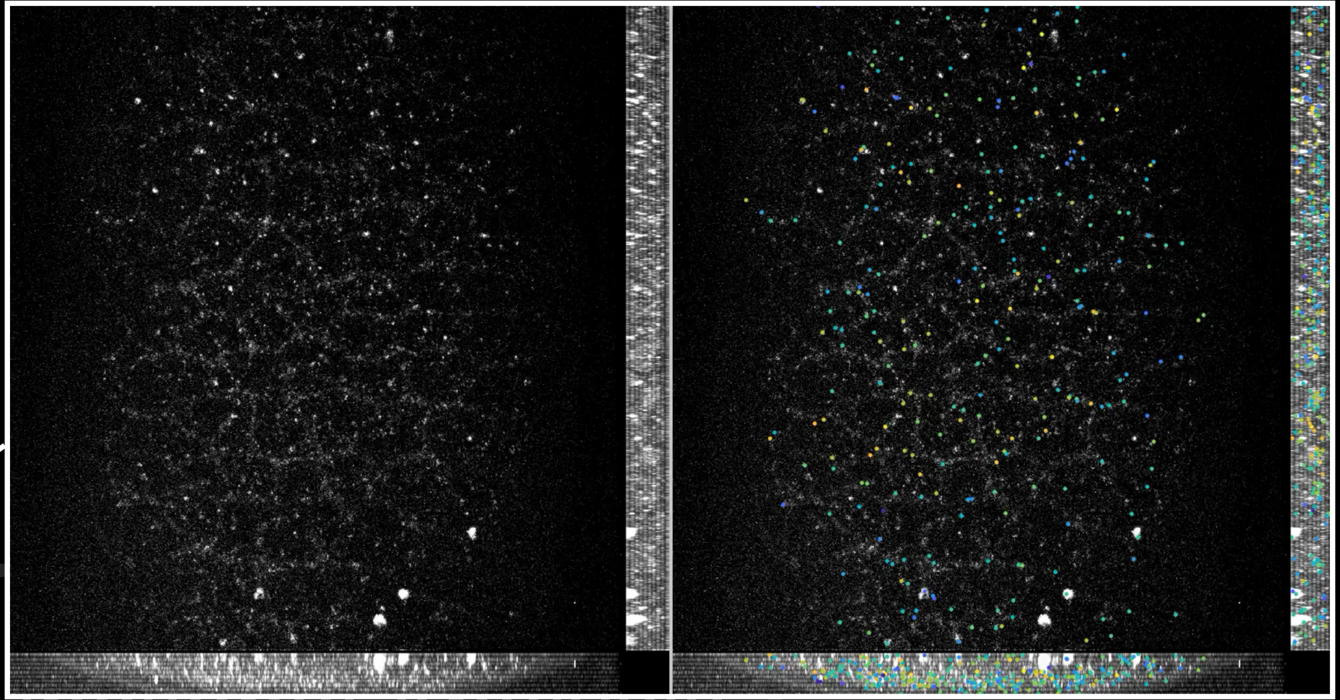

Bayesian Filtering and Multiscale Tracking of Endocytosis across biological scales
(T.Lecuit, P. Roudot, C. Collinet)

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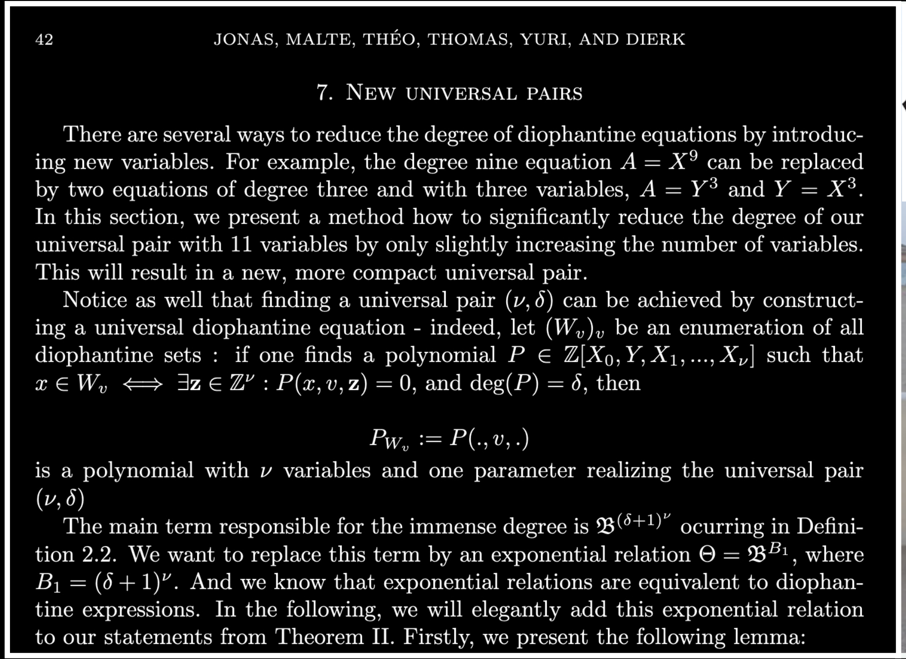

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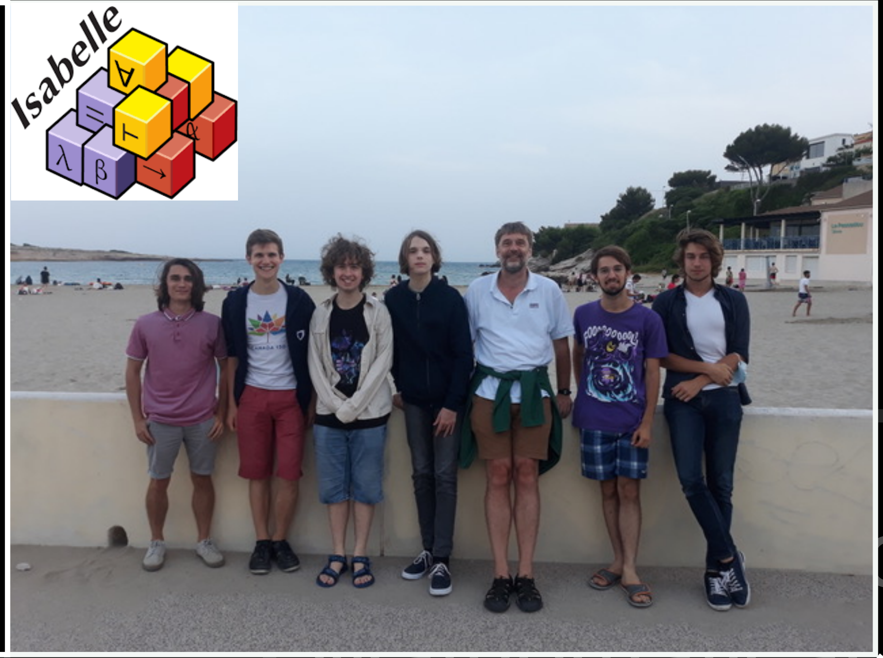

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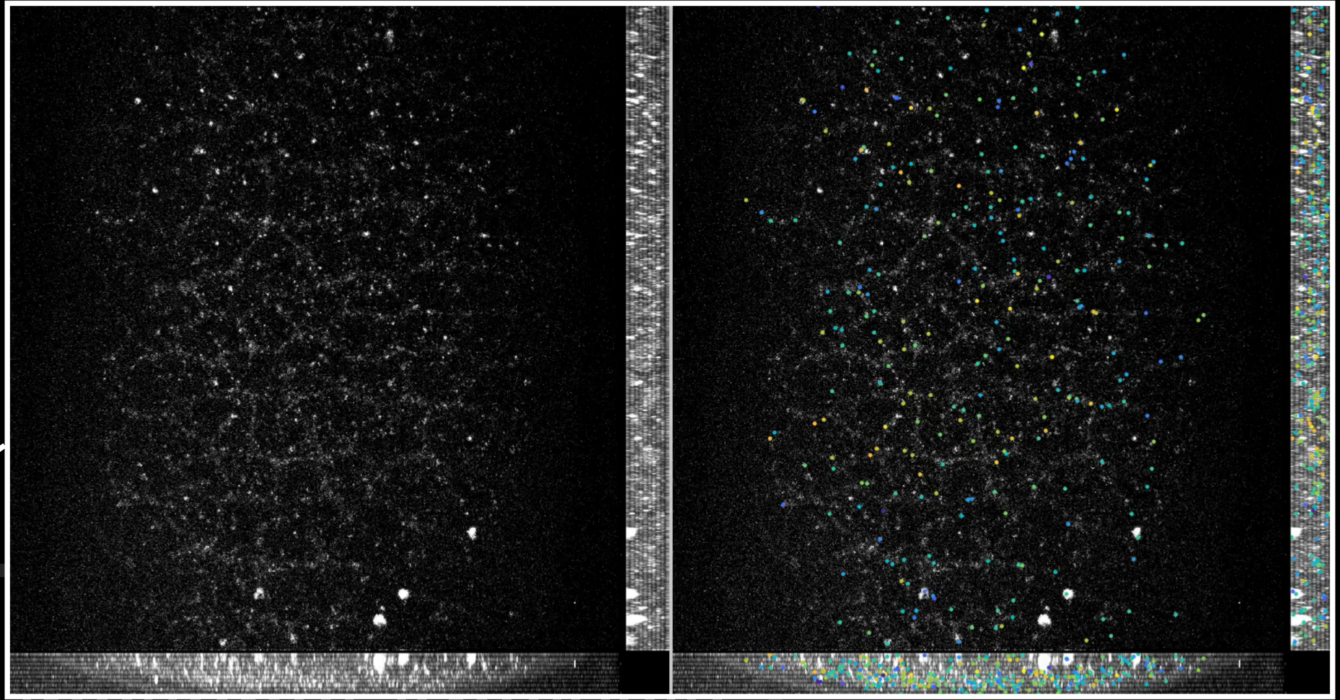

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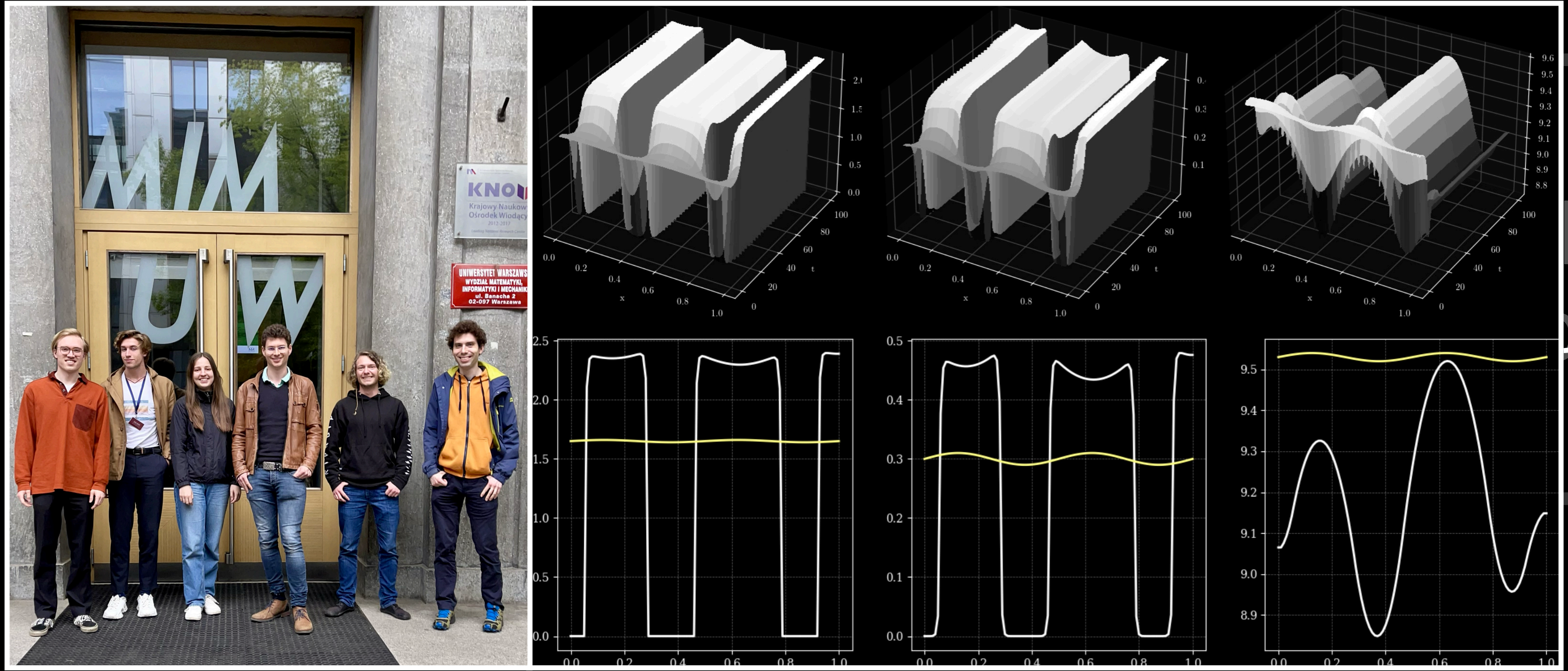

... l analysis ... odeling

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Diffusion-Driven Instability and Pattern formation in Reaction-Diffusion Equations with two diffusive components
(A. Marciniak-Czochra)

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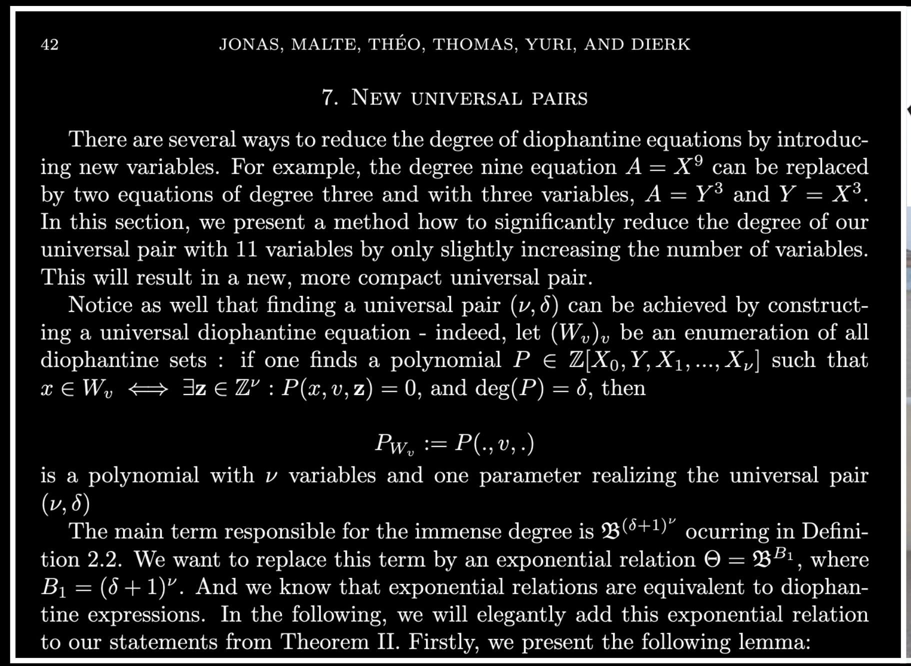

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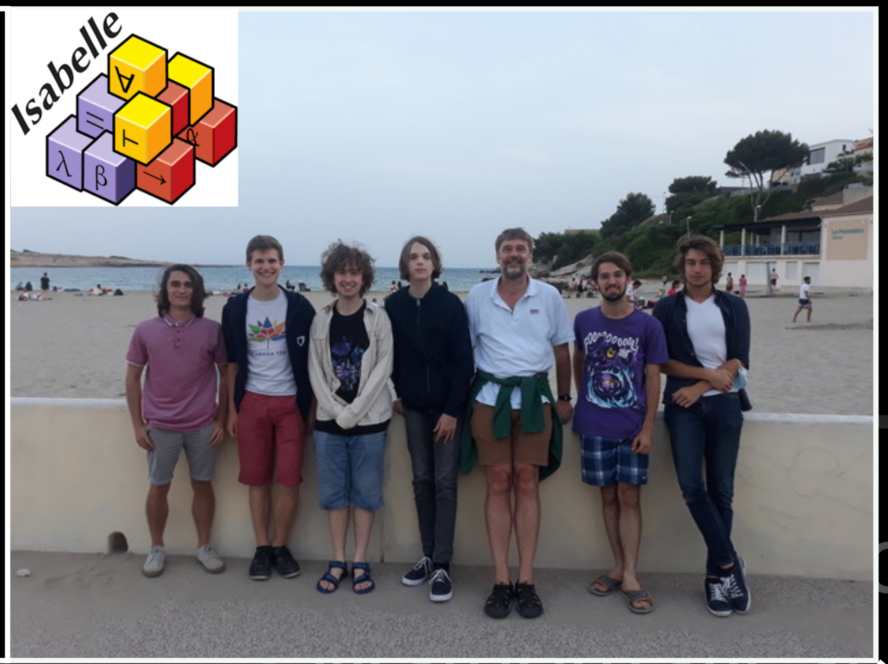

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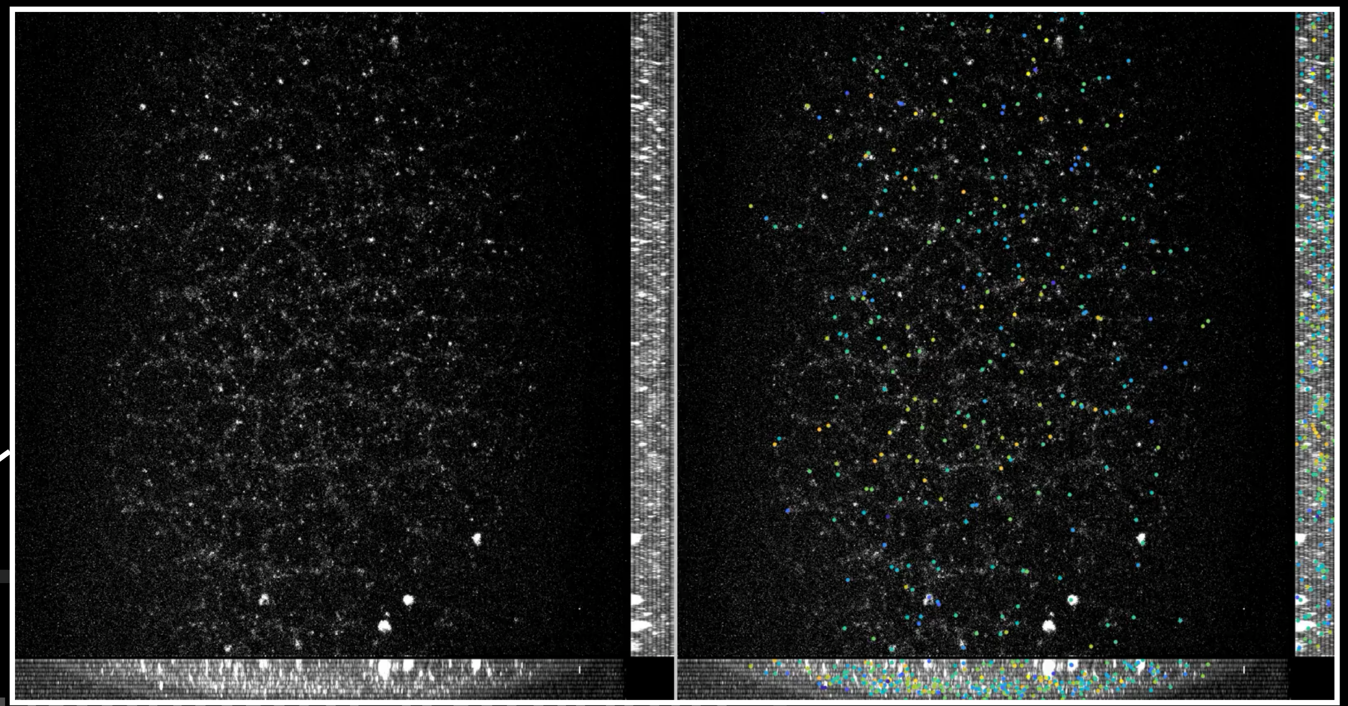

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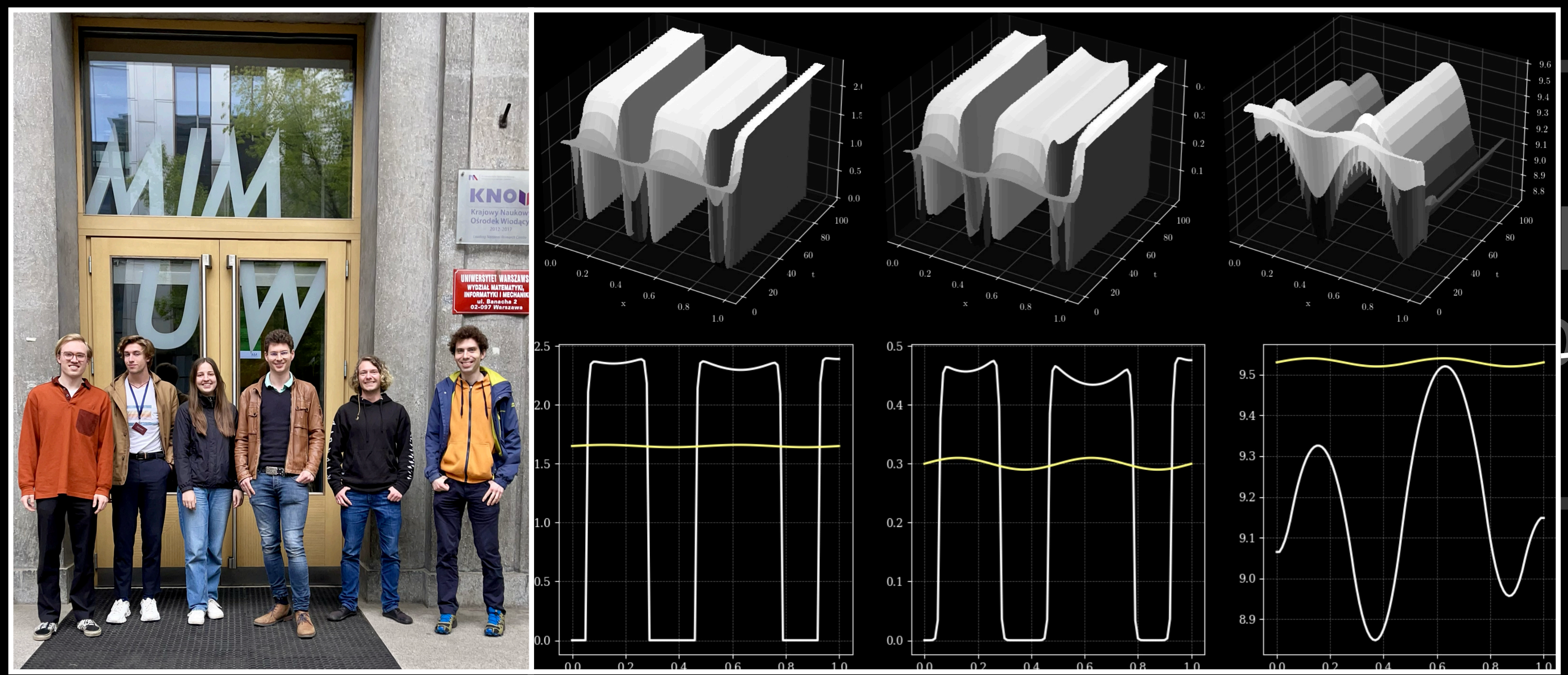

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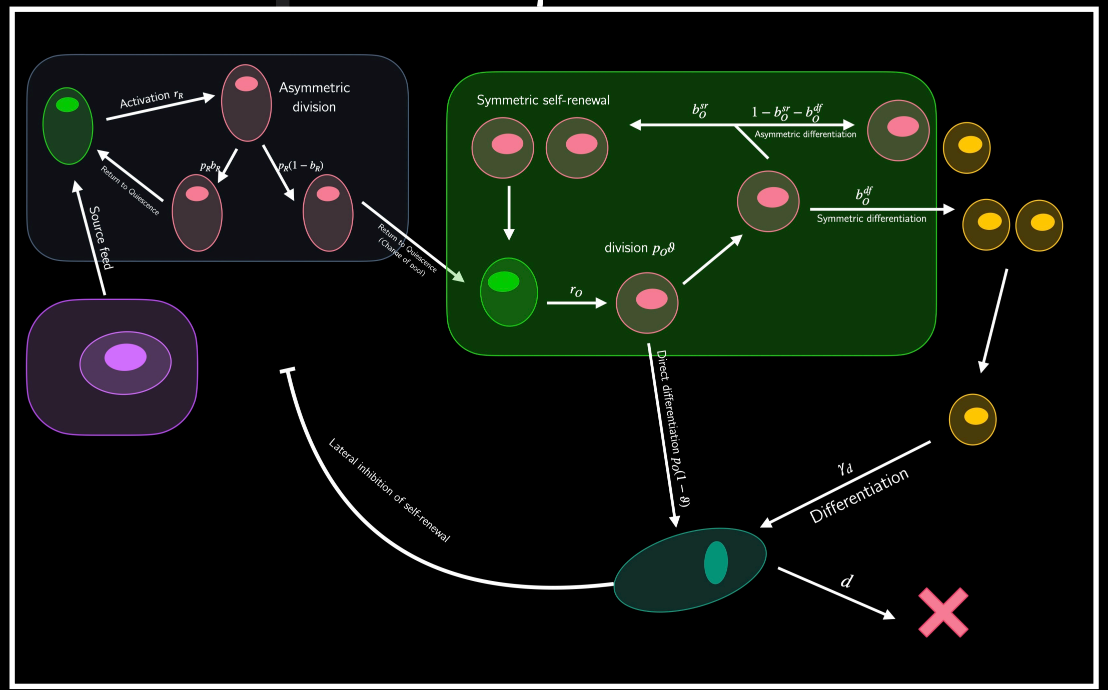

Spatiotemporal modeling of Neurogenesis and maintaining of homeostasis in adult *Danio Rerio*
(A. Marciniak-Czochra) (Ongoing…)

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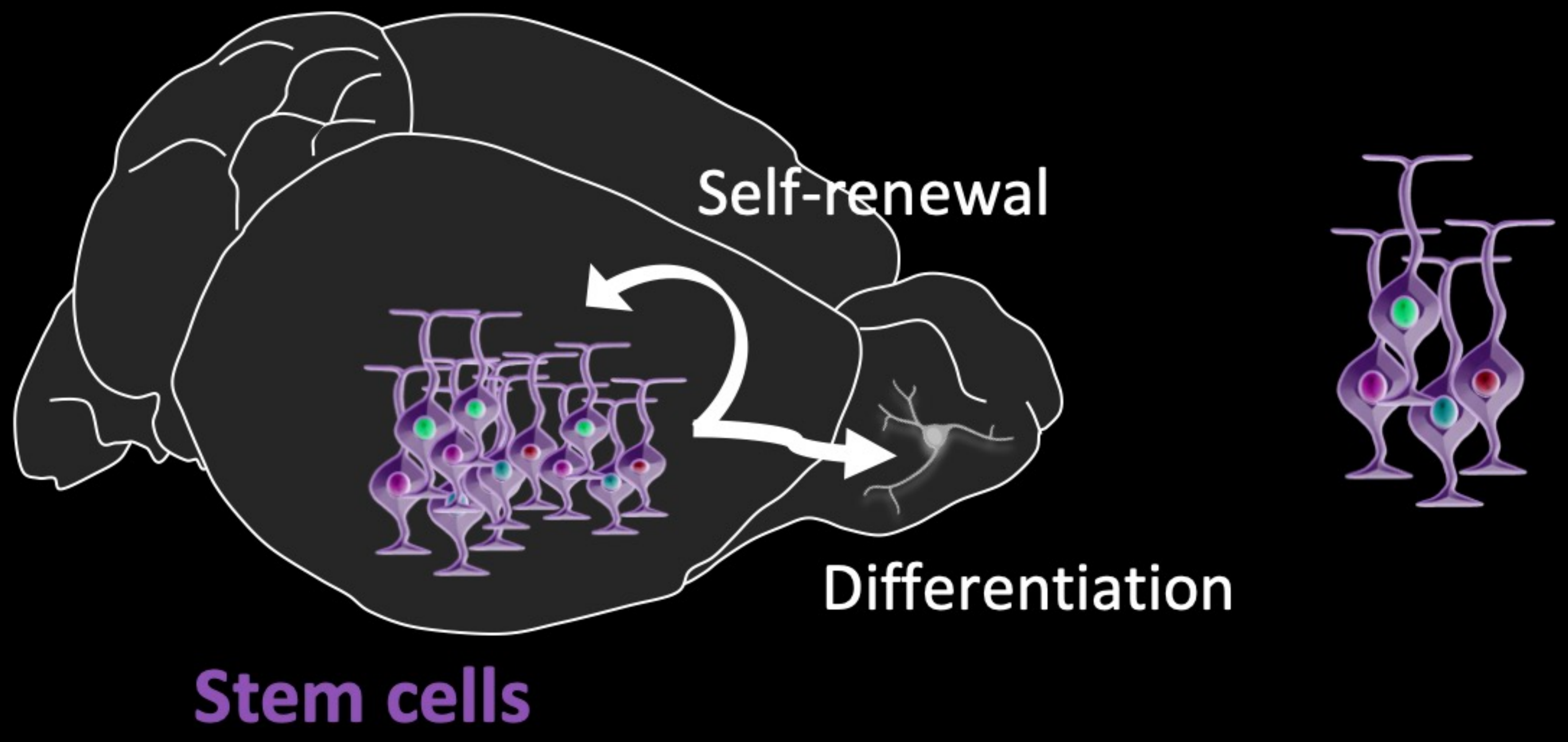
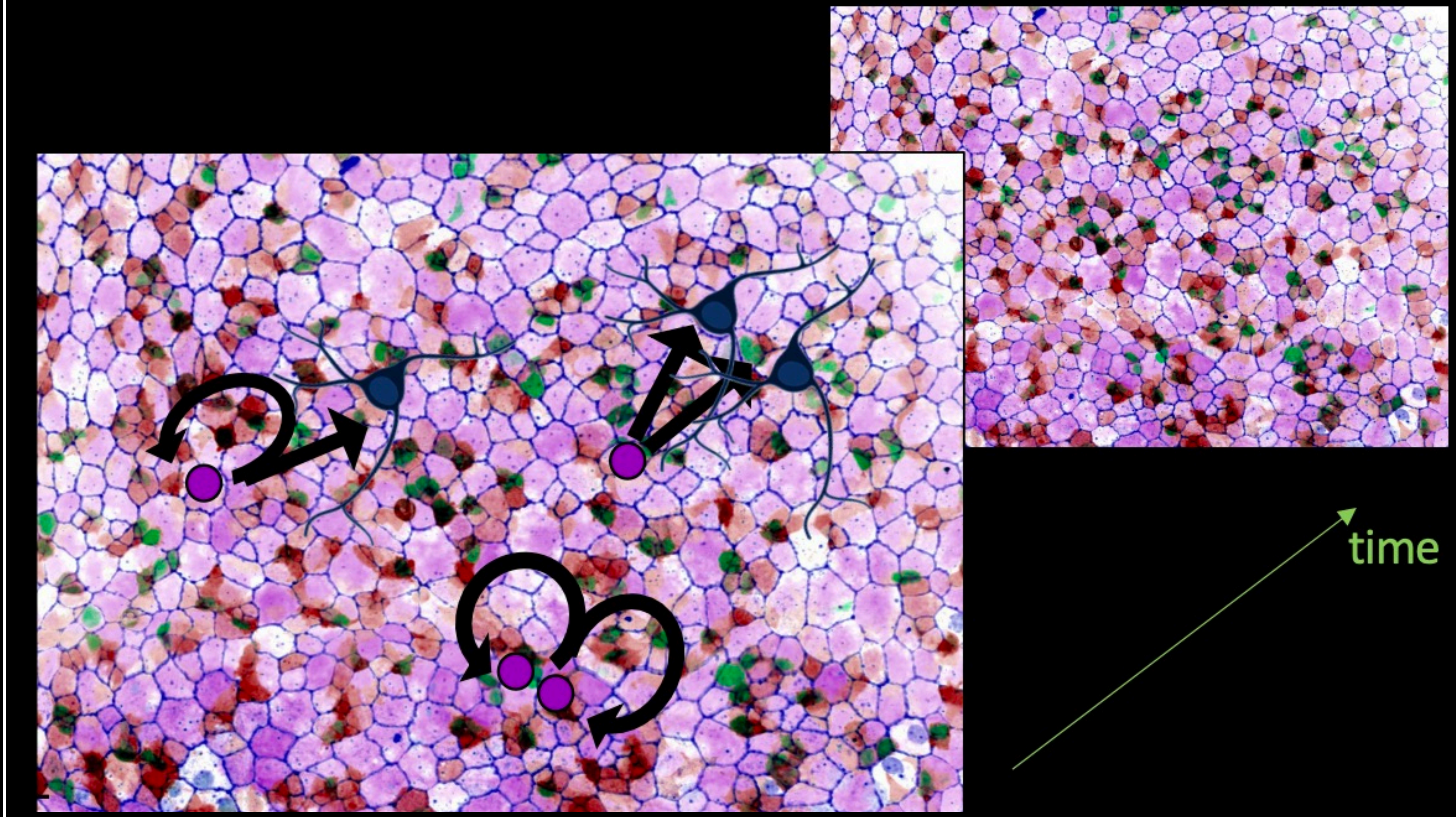
GOAL: Develop mathematical methodology for modelling and analysis of spatially-distributed stem cell (SC) systems.



Homeostasis? Repair? Growth?

GOAL: Develop mathematical methodology for modelling and analysis of spatially-distributed stem cell (SC) systems.

MOTIVATION: SC systems are complex. Description of their spatio-temporal dynamics NEEDS a robust mathematical framework.



Connecting disconnected observations?

Stemness maintenance?

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WHY? Applications to biology, e.g., *post*-injury regeneration and, sometimes, cancers dynamics.

Journal of Mathematical Biology (2019) 79:1587–1621
https://doi.org/10.1007/s00285-019-01404-w

Mathematical Biology

Check for updates

A structured population model of clonal selection in acute leukemias with multiple maturation stages

Tommaso Lorenzi[1] · Anna Marciniak-Czochra[2] · Thomas Stiehl[3]

Received: 27 September 2018 / Revised: 5 July 2019 / Published online: 26 July 2019

Abstract
Recent progress in genetic techniques has shed light on the complex co-evolution of malignant cell clones in leukemias. However, several aspects of clonal selection still remain unclear. In this paper, we present a multi-compartmental continuously structured population model of selection dynamics in acute leukemias, which consists of a system of coupled integro-differential equations. Our model can be analysed in a more efficient way than classical models formulated in terms of ordinary differential equations. Exploiting the analytical tractability of this model, we investigate how clonal selection is shaped by the self-renewal fraction and the proliferation rate of leukemic cells at different maturation stages. We integrate analytical results with numerical solutions of a calibrated version of the model based on real patient data. In summary, our

Applications to biology: Focus on Neural Stem Cell (NSC) systems.

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MOUSE

Well-established collaboration with **Ana Martin Villalba**'s group (Heidelberg)

ZEBRAFISH

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Observation: Decay / Exhaustion of NSC pool over time

Diana-Patricia Danciu

+

Joaa Hooli

+

Ana Martin Villalba's group

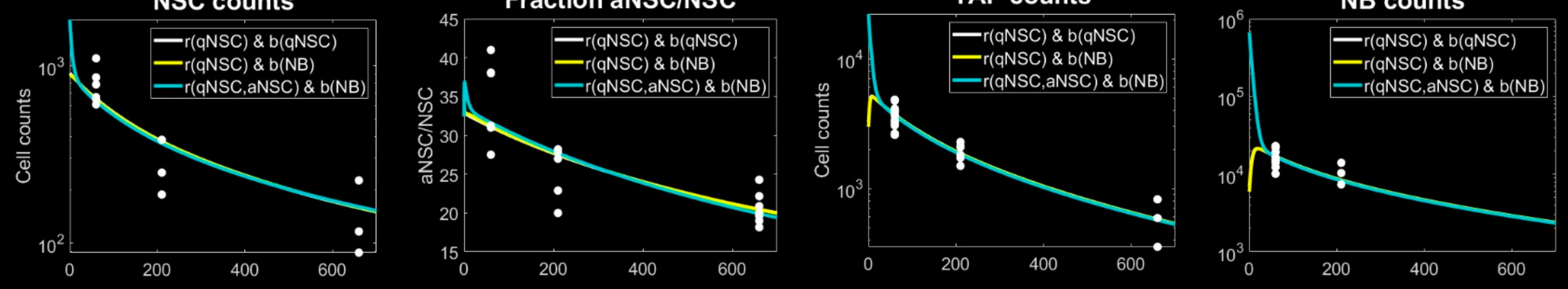
$$r = r_{max} \cdot S_1$$

$$\frac{dS_1}{dt} = \underbrace{cells(t)}_{\text{Production by lineage cells}} - \underbrace{K_r S_1(t)}_{\text{Degradation}} - \underbrace{cells(t) S_1(t)}_{\text{Consumption by lineage cells}}$$

$$b = b_{max} \cdot S_2$$

The picture can't be displayed.

$$\frac{dS_2}{dt} = \underbrace{\quad}_{\text{Production by niche (non-lineage cells)}} - \underbrace{S_2(t)}_{\text{Degr.}} - \underbrace{\beta_b \cdot cells(t) S_2(t)}_{\text{Consumption by lineage cells}}$$



All the credit goes to Diana-Patricia Danciu for the pictures

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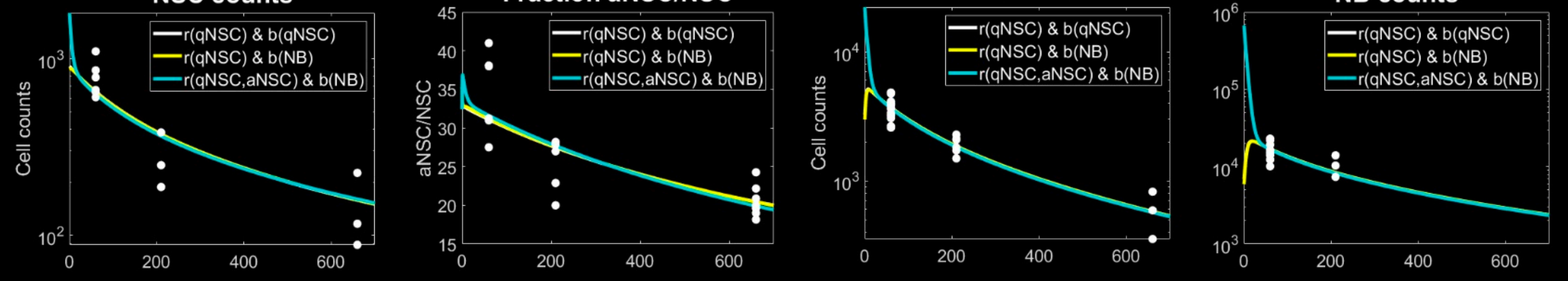

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Observation: dynamical *homeostasis* of NSC pool over time

T. A.

+

Laure Bally-Cuif's group

+

More?

Dense biological literature!

Neural stem cell pools in the vertebrate adult brain: Homeostasis from cell-autonomous decisions or community rules?

Nicolas Dray[1] | Emmanuel Than-Trong[1,2] | Laure Bally-Cuif[1]

STEM CELLS

Apical size and *deltaA* expression predict adult neural stem cell decisions along lineage progression

Laure Mancini[1,2†], Boris Guirao[3], Sara Ortica[1], Miriam Labusch[1,2], Felix Cheysson[4‡], Valentin Bonnet[5,6], Minh Son Phan[7], Sébastien Herbert[7§], Pierre Mahou[8], Emilie Menant, Sébastien Bedu[1], Jean-Yves Tinevez[7], Charles Baroud[5,6], Emmanuel Beaurepaire[8], Yohanns Bellaiche[3], Laure Bally-Cuif[1*], Nicolas Dray[1*]

Lineage hierarchies and stochasticity ensure the long-term maintenance of adult neural stem cells

Emmanuel Than-Trong[1,2], Bahareh Kiani[3], Nicolas Dray[1], Sara Ortica[1], Benjamin Simons[4,5,6], Steffen Rulands[3,7], Alessandro Alunni[1*†], Laure Bally-Cuif[1*†]

Cell Stem Cell

Dynamic spatiotemporal coordination of neural stem cell fate decisions occurs through local feedback in the adult vertebrate brain

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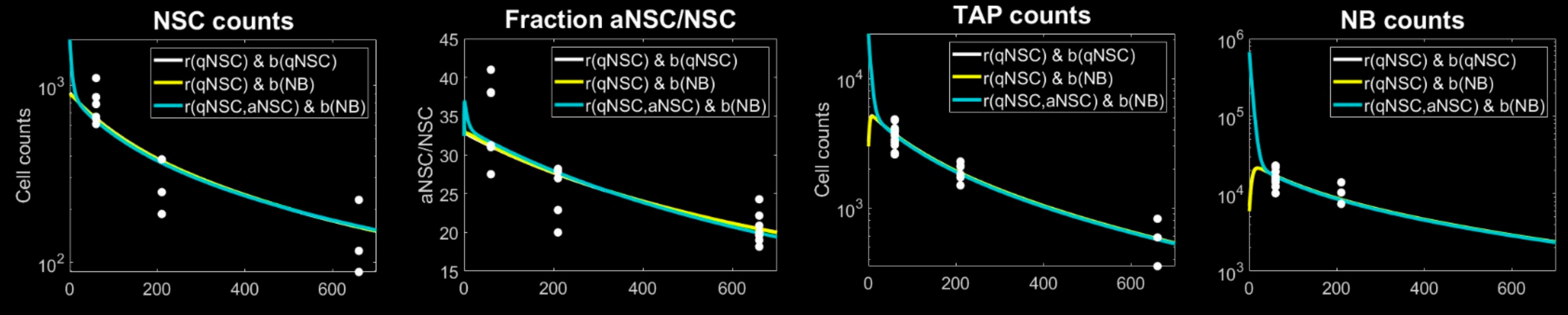

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WHAT ARE THE MECHANISMS MAINTAINING HOMEOSTASIS IN THE ZEBRAFISH BRAIN?

Current State of NSC Modeling:

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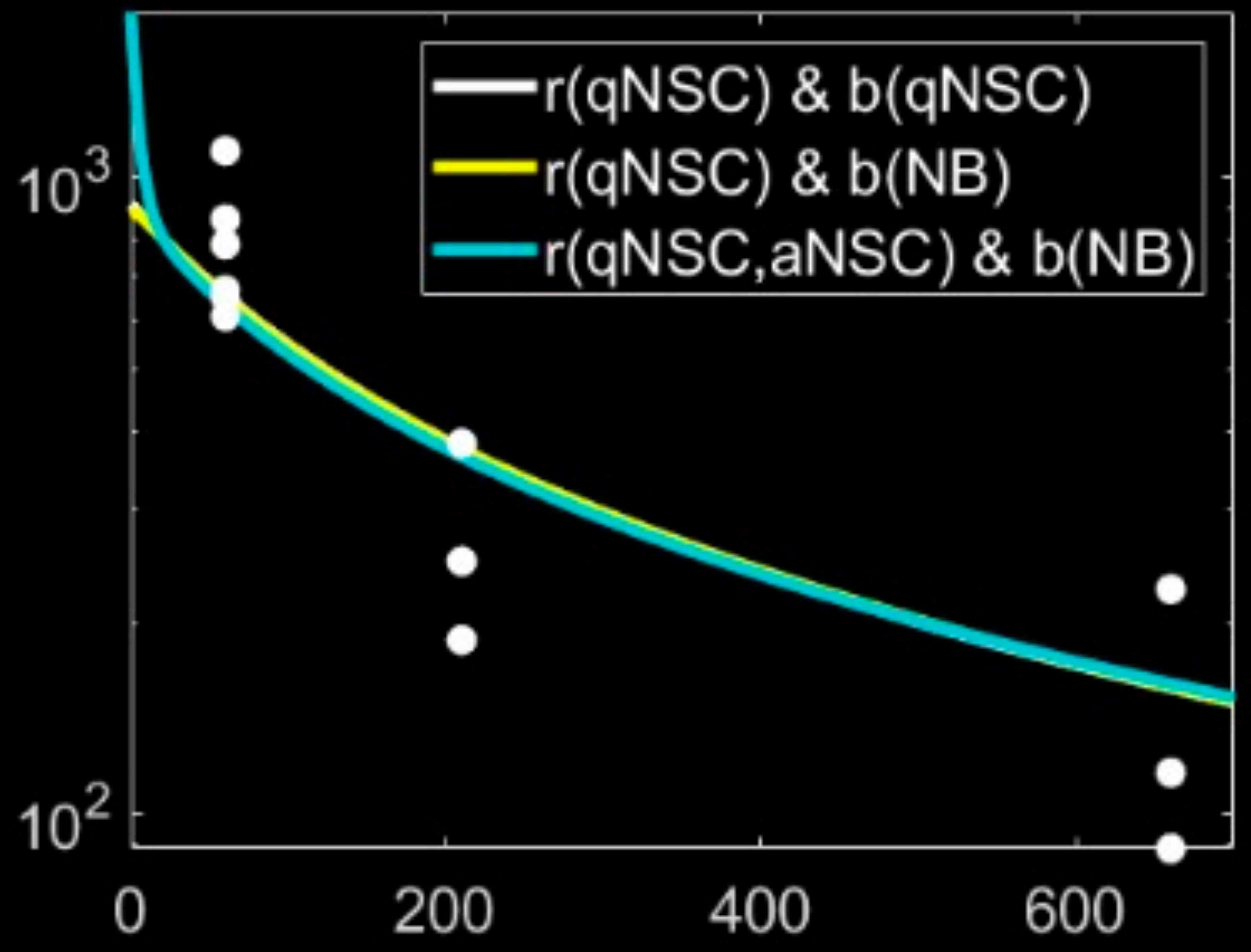
Ordinary Differential Equations
Population scale but no space



Captures general behavior s

(But not space…)

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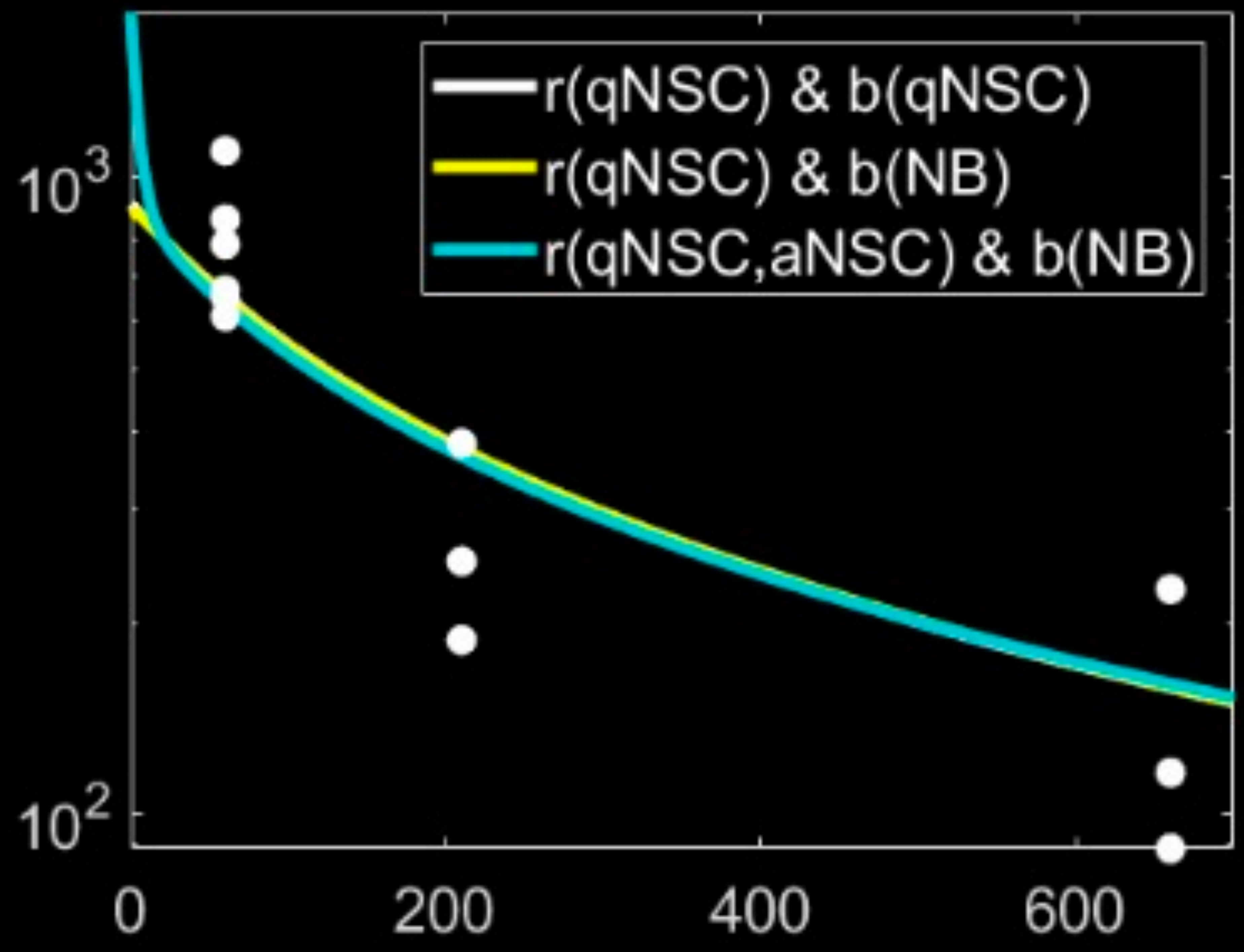

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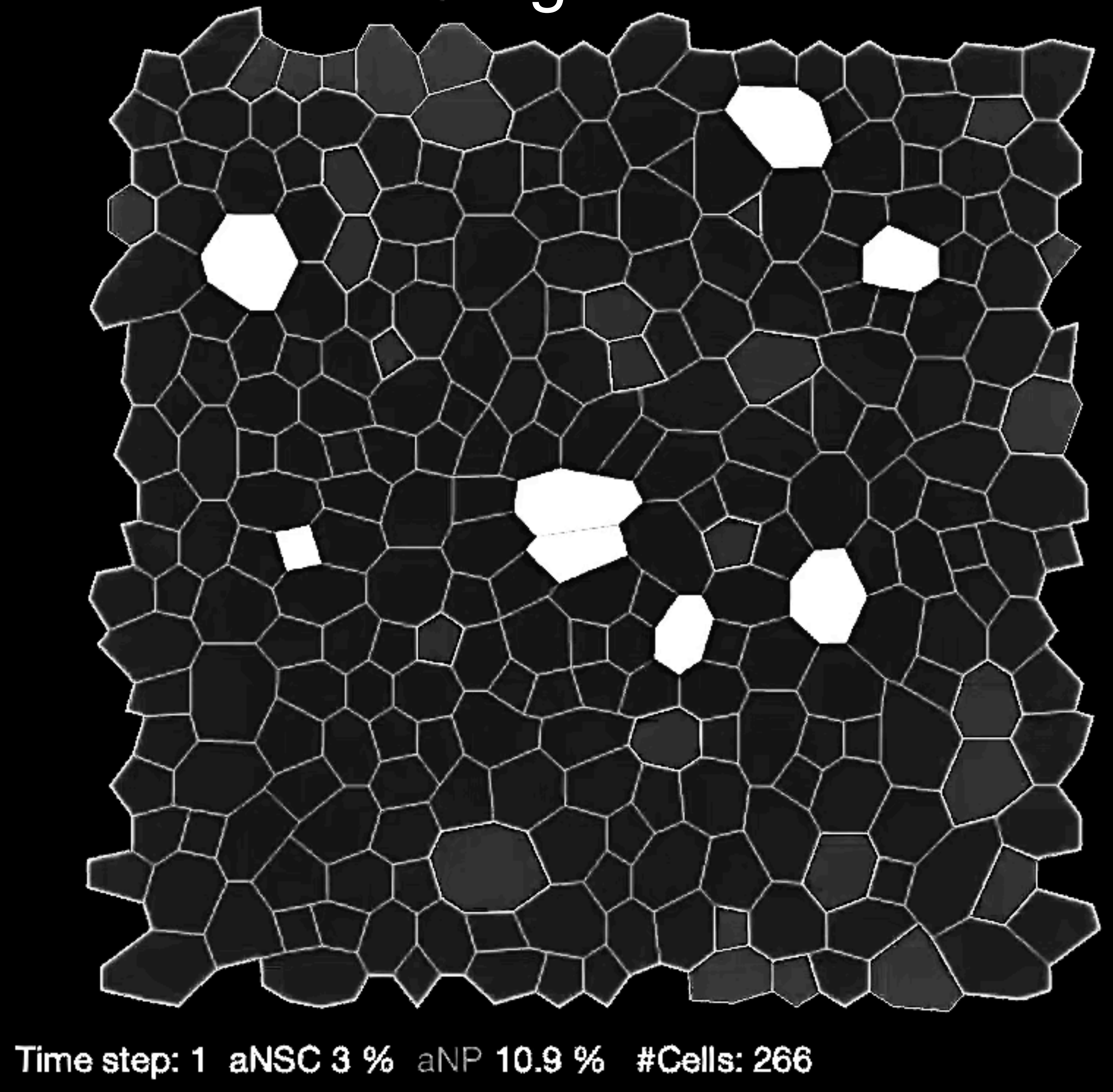
Individual-Based Models
Single-cell scale and space integration



Captures (some) geometry, and spatial and individual details

(But no tools for param. estimation or analysis)

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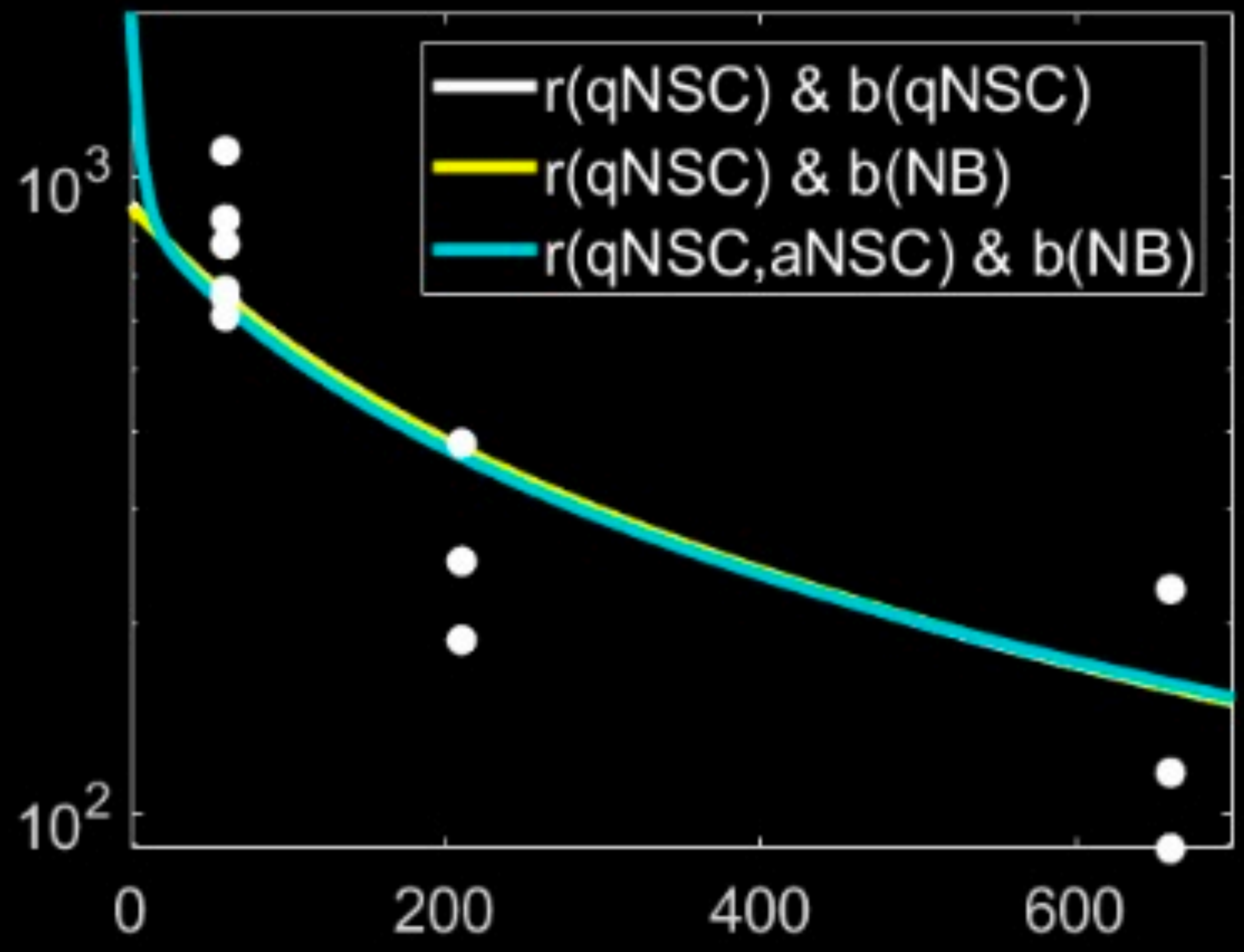

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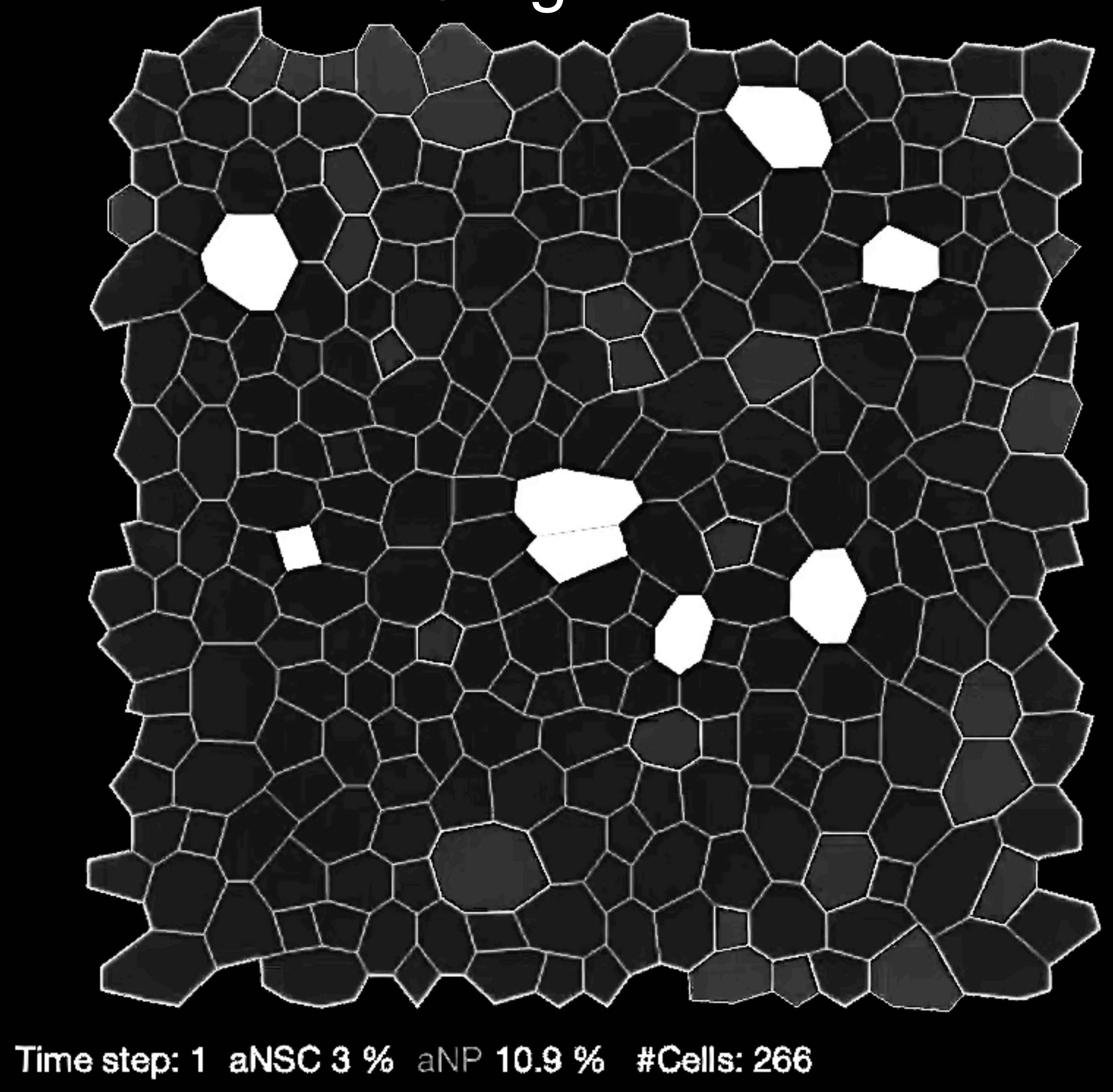

CAN WE GET BOTH?

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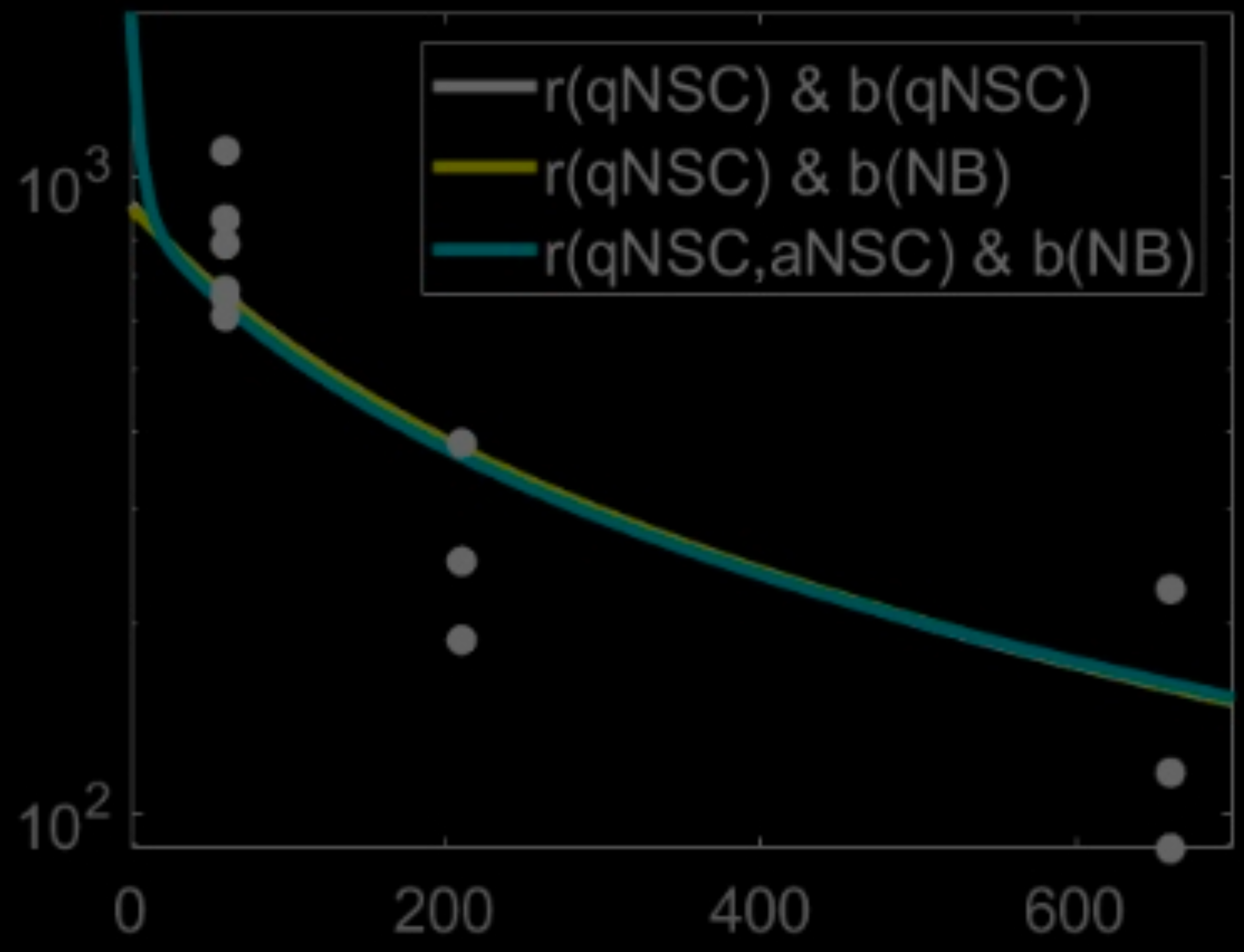

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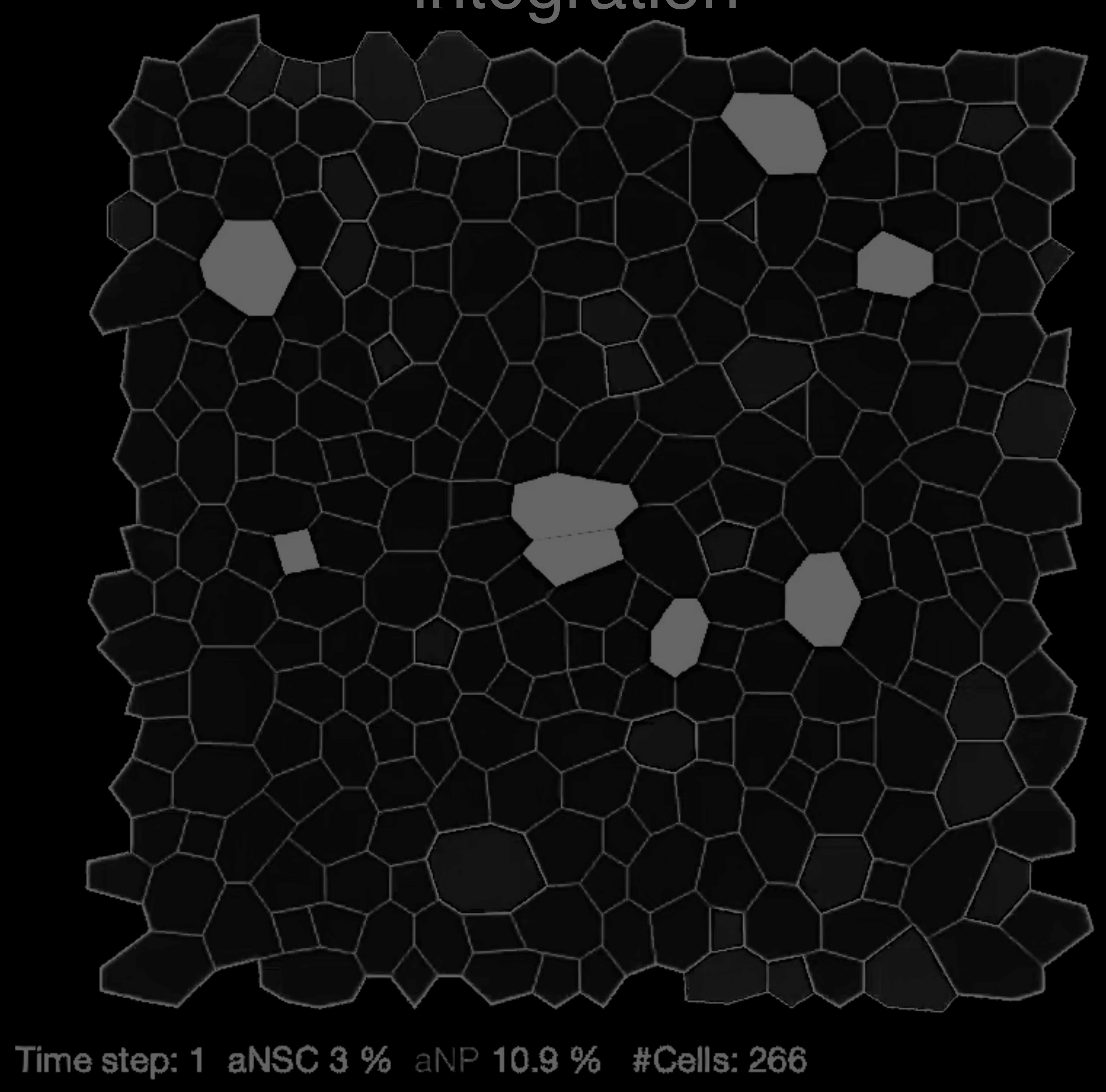

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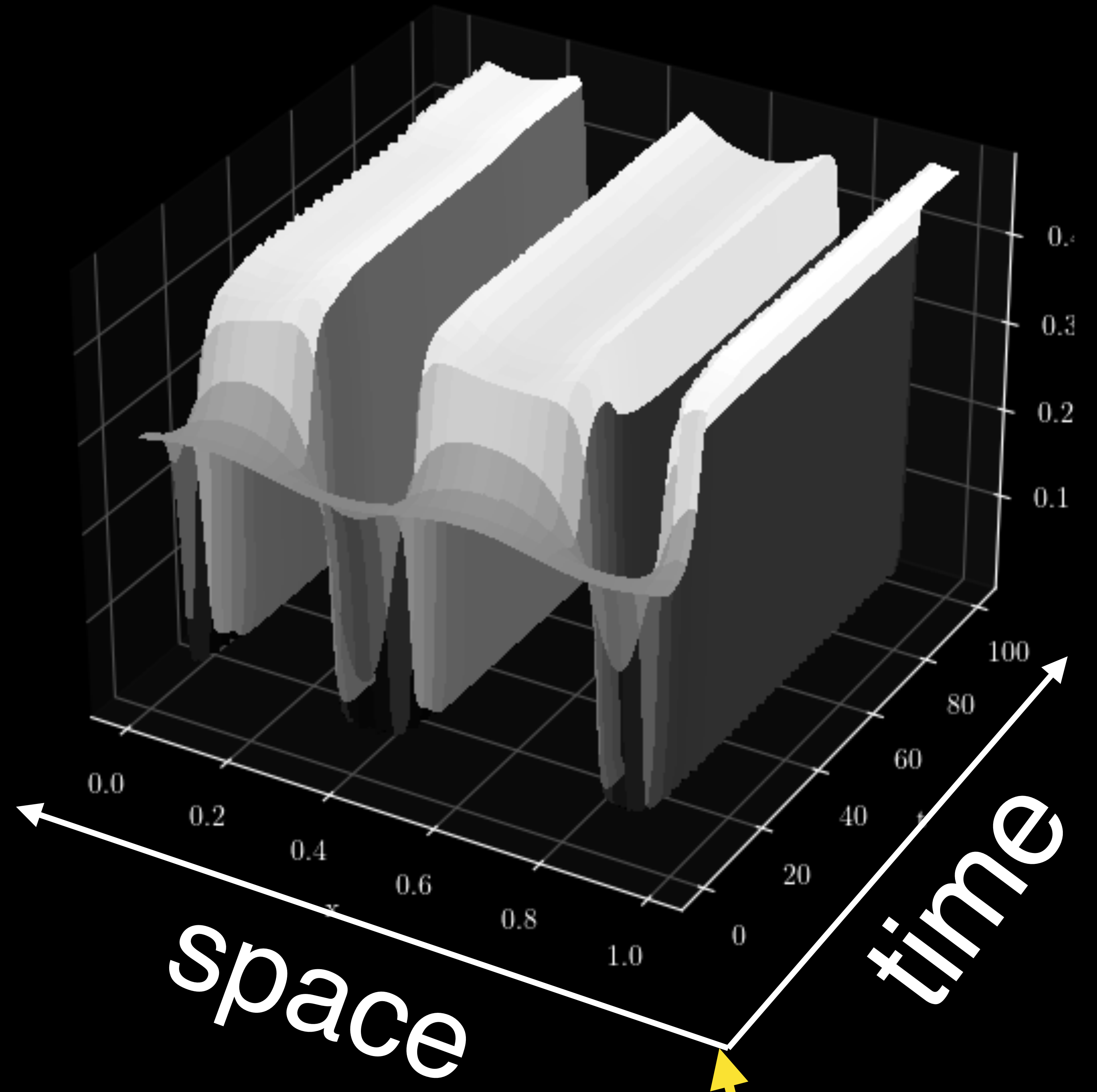
Partial Differential Equations
Population scale <u>AND</u> space



Integrates the geometry and captures general behaviors!

Many phenomena to take into account:

- Cellular motion/migration,
- Stochasticity,
- Local cell-cell interactions,
- Long-range feedback signaling,
- Nonlinear interactions
- ...

Zebrafish brain developing — EMBL (Youtube)

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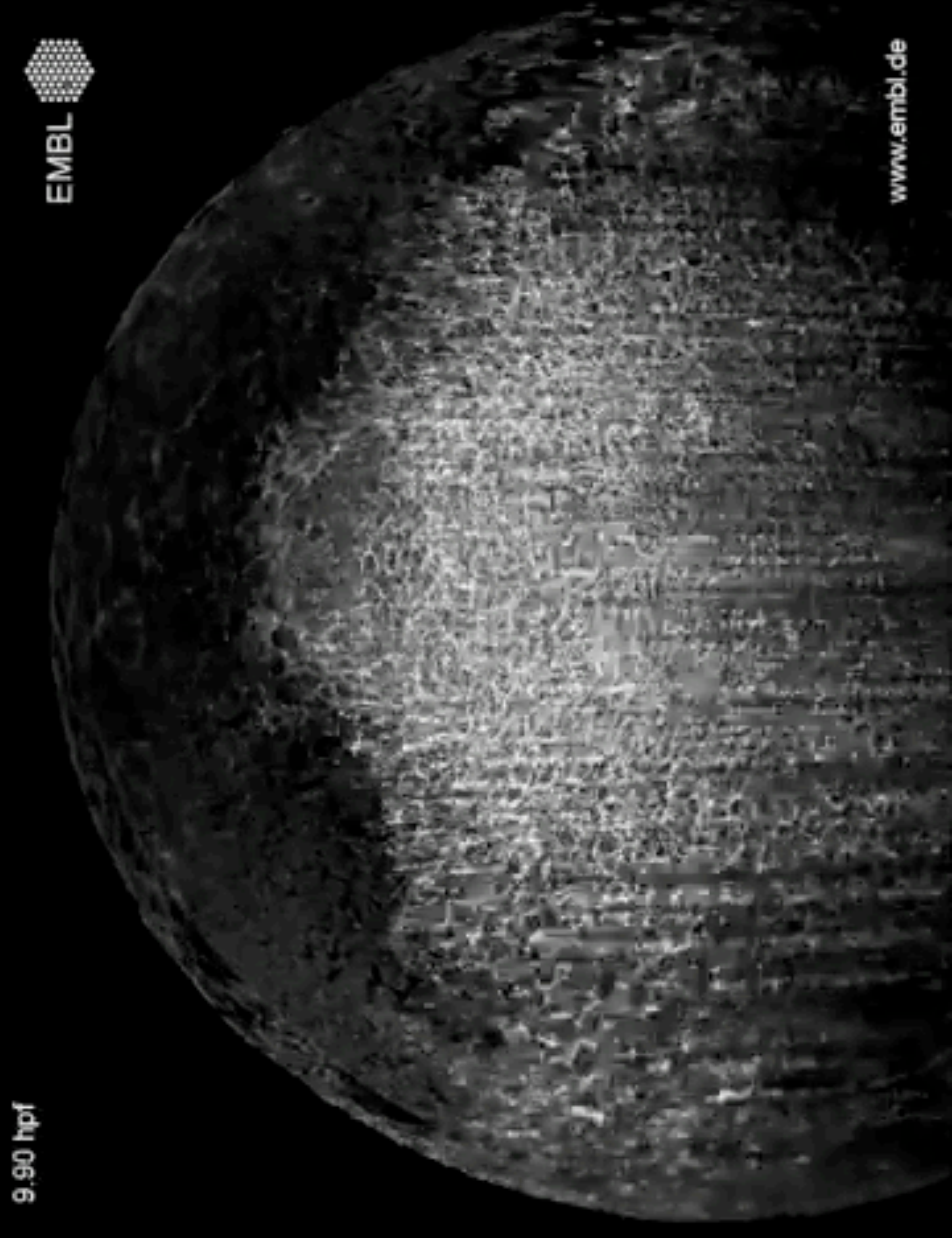
Coupling between local and global dynamics

- Systems of PDEs coupled to multiple infinite families of ODEs,
- Sparse literature and few results,
- Mechanism of pattern formation is poorly understood…



Zebrafish brain developing — EMBL (Youtube)

Preliminary project:

(inspired by) AMC. Developmental models with cell surface receptor densities defining morphological position. [2004]

Free Receptors

Ligands

Enzymes

Boundary Conditions

Initial Conditions

$$
\begin{cases}
\dfrac{\partial u}{\partial t} = -\mu_f u + m_1 \dfrac{uv}{1+uv} - \mu_b uv & \text{for } x \in \Omega, t > 0 \\
\dfrac{\partial v}{\partial t} = d_1 \Delta v - \mu_l v + m_2 \dfrac{uv}{1+uv} - \mu_b uv - vw & \text{for } x \in \Omega, t > 0 \\
\dfrac{\partial w}{\partial t} = d_2 \Delta w - \mu_e w + m_3 \dfrac{uv}{1+uv} & \text{for } x \in \Omega, t > 0 \\
\dfrac{\partial v}{\partial \nu} = 0, \quad \dfrac{\partial w}{\partial \nu}(t,x) = 0 & \text{for } x \in \partial\Omega, t \geq 0 \\
u(0,x) = u_0, \quad v(0,x) = v_0, \quad w(0,x) = w_0 & \text{for } x \in \Omega
\end{cases}
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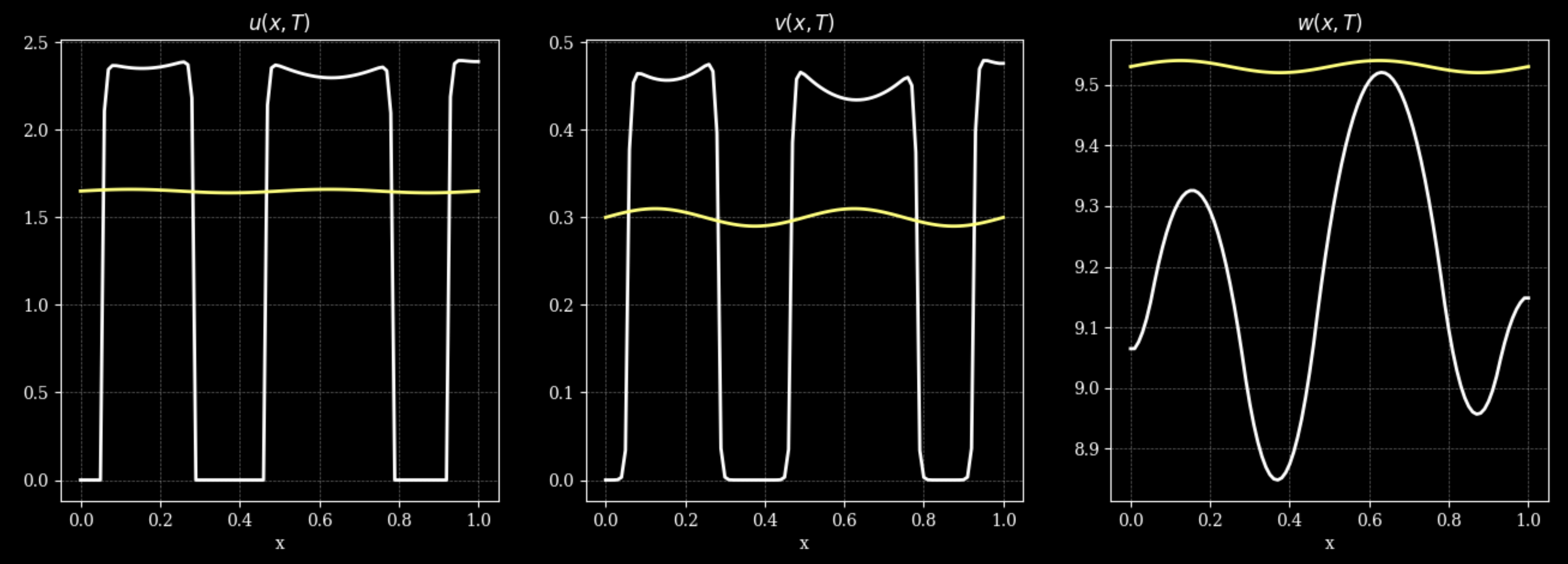
Can we obtain Turing-like patterns?



Results: Methodology for obtaining (jump-) patterns in models featuring 1ODE and 2PDEs

1. Bistability and hysteresis:

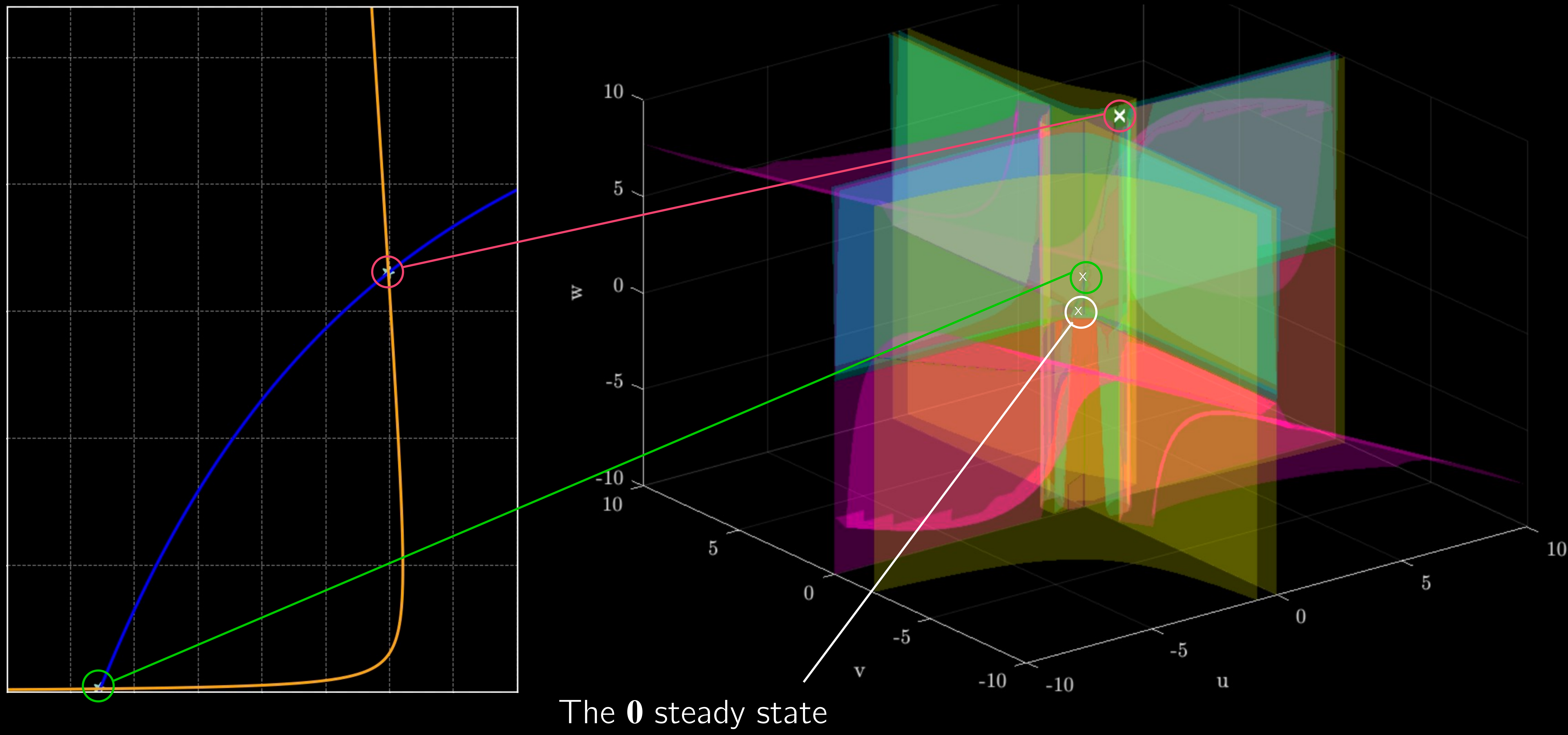
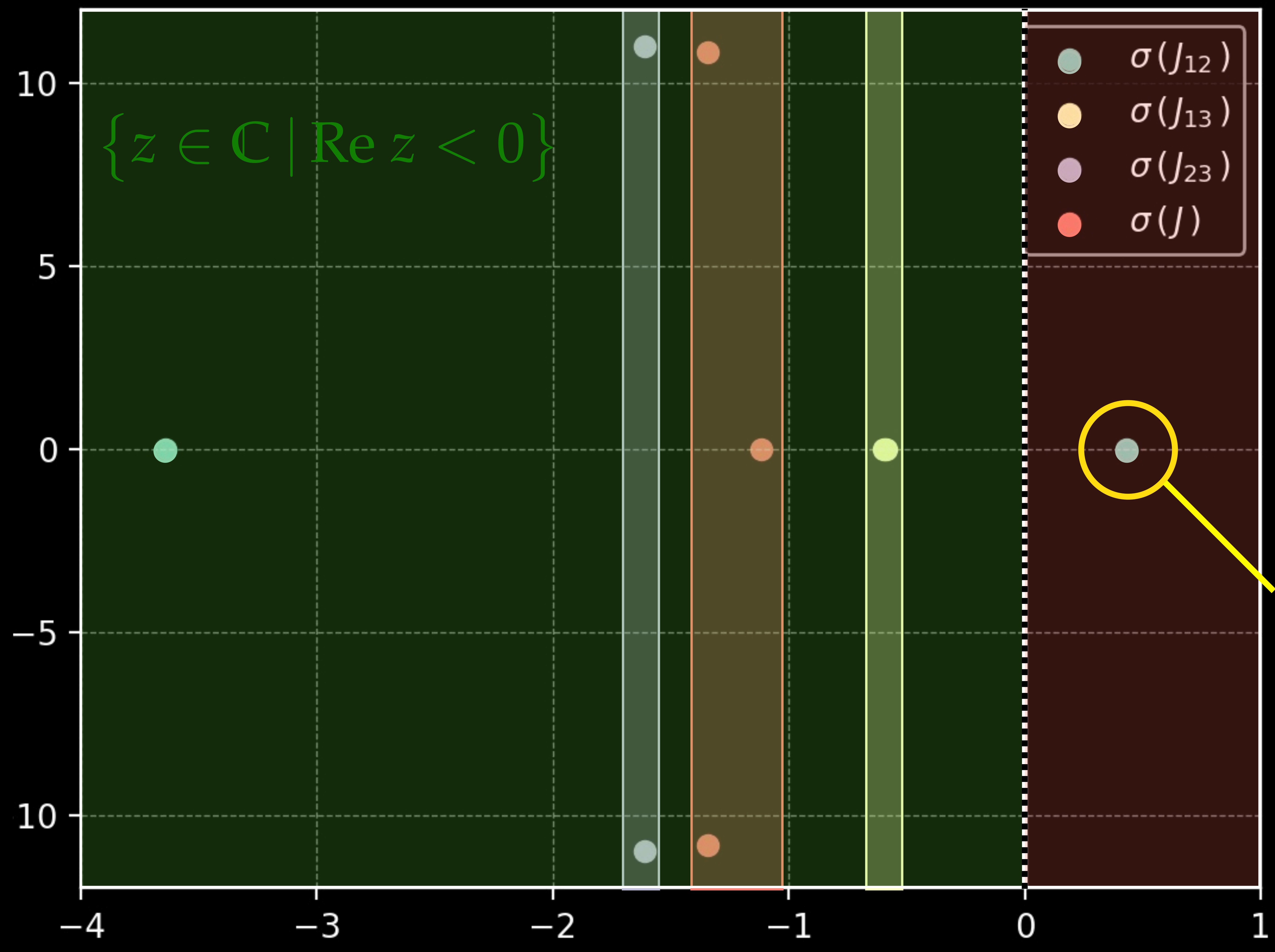


Figure: Existence of three positive steady states. The origin, 0, and two additional $\bar{\mathbf{X}}_{2,3}$, given by the intersection of nullclines (left). The right plot represents the manifold $\mathscr{M} = \{(u,v,w) \,|\, f(u,v) = g(u,v,w) = h(u,v,w) = 0\}$

Results: Methodology for obtaining (jump-) patterns in models featuring 1ODE and 2PDEs

1. Bistability and hysteresis:

2. Turing Instability:



Eigenvalue with positive real part in the spectrum of J_{12}...

...but J is still stable!

Figure: Spectra of J and its principal minors. One sees J_{12} has a positive eigenvalue while $s(J) < 0$

Results: Methodology for obtaining (jump-) patterns in models featuring 1ODE and 2PDEs

1. Bistability and hysteresis:

2. Turing Instability:

3. The right diffusion regime:

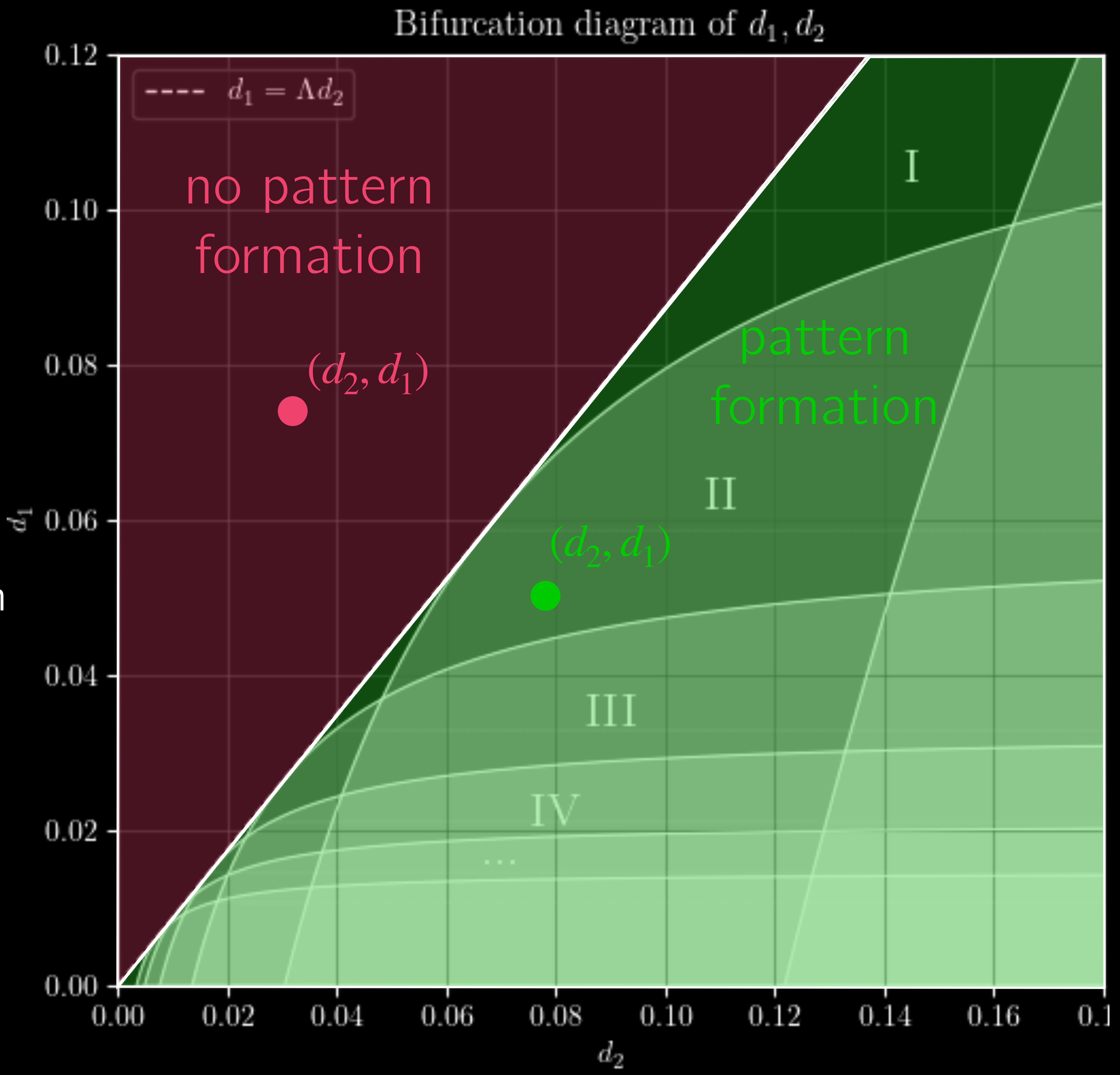
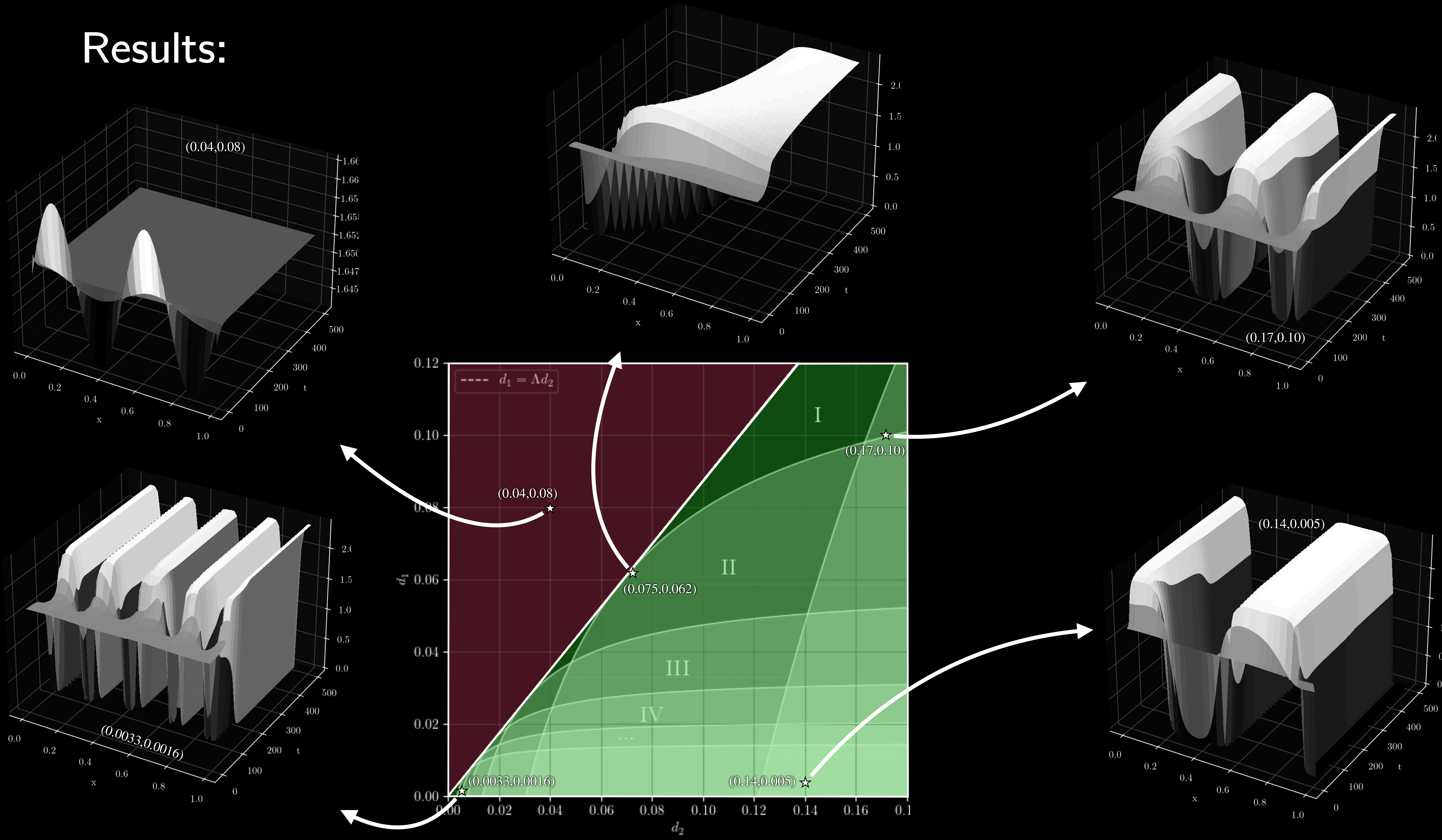


Figure: Bifurcation diagram for diffusion coefficients d_1, d_2. Subdivisions inside the green area classifies more precisely how many eigenvalues are unstable.

More unstable eigenvalues => More complex patterns

Results:



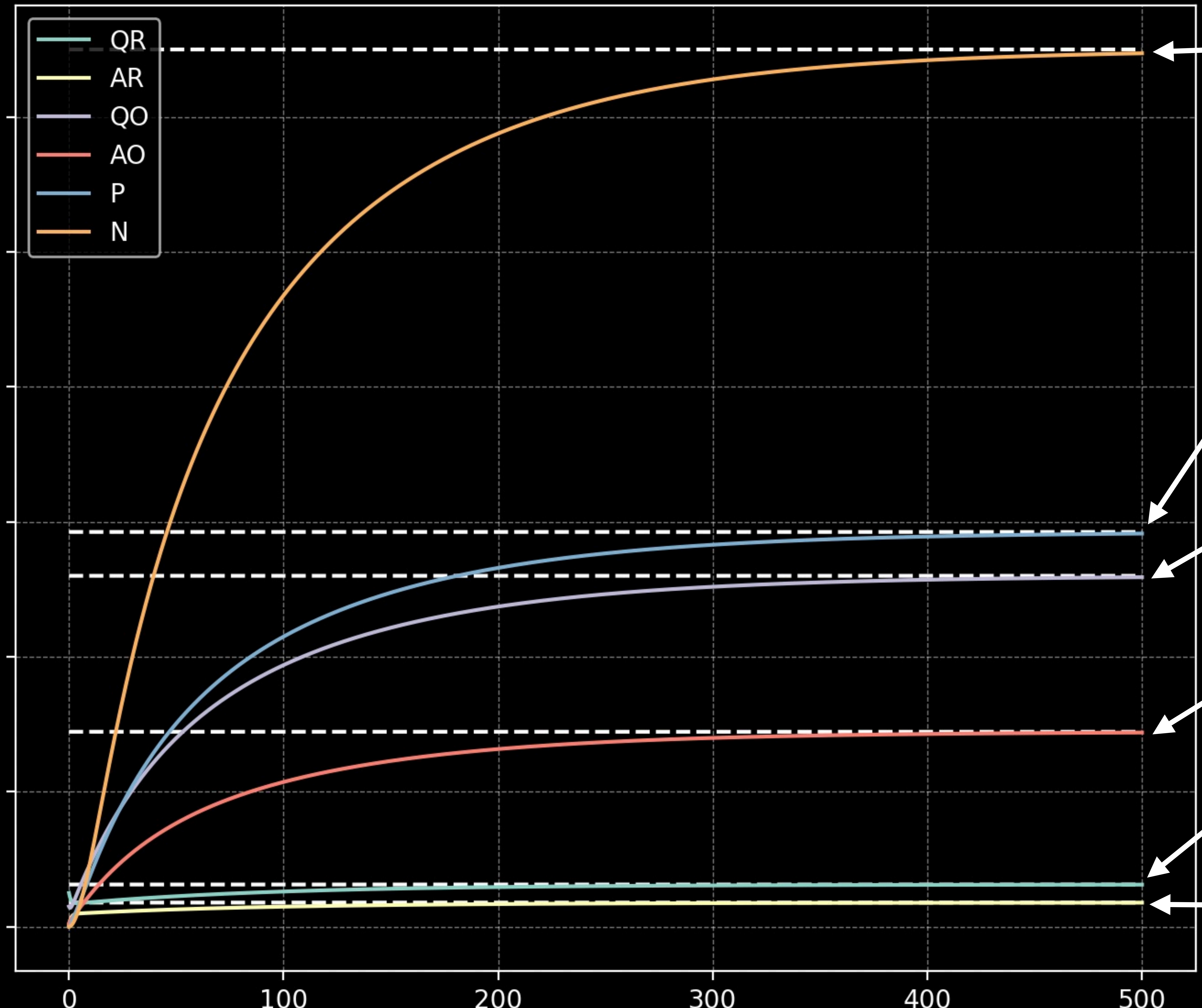
(0.04,0.08)
(0.17,0.10)
(0.14,0.005)
(0.0033,0.0016)
(0.075,0.062)
$d_1 = \Lambda d_2$
I
II
III
IV
d_1
d_2
x
t

Dray, Than-Trong, Bally-Cuif [2020] & Annual review: Foley, Thetio, Bally-Cuif [2024]

Full system:

$$\begin{cases} \dfrac{\partial Q_R}{\partial t} = -r_R Q_R + 2b_R p_R A_R + S \\ \dfrac{\partial A_R}{\partial t} = \quad r_R Q_R - p_R A_R \\ \dfrac{\partial Q_O}{\partial t} = -r_O Q_O + (1 + b_O^{sr} - b_O^{df})\vartheta p_O A_O + 2(1 - b_R) p_R A_R \\ \dfrac{\partial A_O}{\partial t} = \quad r_O Q_O - p_O A_O \\ \dfrac{\partial P}{\partial t} = -\gamma_d P + (1 - b_O^{sr} + b_O^{df})\vartheta p_O A_O \\ \dfrac{\partial N}{\partial t} = -dN + (1 - \vartheta) p_O A_O + \gamma_d P \end{cases}$$

Steady states:



$$\bar{N} = \frac{1}{d}\frac{2(1-b_R)(1-\vartheta(b_O^{sr}-b_O^{df}))S}{(1-2b_R)\left[1-(1+b_O^{sr}-b_O^{df})\vartheta\right]}$$

$$\bar{Q}_O = \frac{2(1-b_R)S}{(1-2b_R)\left[1-(1+b_O^{sr}-b_O^{df})\vartheta\right]r_O}$$

$$\bar{P} = \frac{1}{\gamma_d}\frac{2(1-b_R)(1-b_O^{sr}+b_O^{df})\vartheta S}{(1-2b_R)\left[1-(1+b_O^{sr}-b_O^{df})\vartheta\right]}$$

$$\bar{A}_0 = \frac{2(1-b_R)S}{(1-2b_R)\left[1-(1+b_O^{sr}-b_O^{df})\vartheta\right]p_O}$$

$$\bar{Q}_R = \frac{S}{(1-2b_R)r_R}$$

$$\bar{A}_R = \frac{S}{(1-2b_R)p_R}$$

Thank you for your attention!

questions?