Pattern formation modelling in dynamical biological systems

(Through reaction-diffusion-ODE systems)

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The *hydra* organism

&

Pattern formation modelling

Neha Khetan, Shagun Maheshwari, and Chaitanya A. Athale. Quantitative Detachment Mechanics of Hydra from Substrates. Proc. Indian Natl. Sci. Acad., 99(1), October 2018

Friendly reminder on Differential Equations (1)

Differential equation (DE): An equation whose solution is a function.

example:

(cell division)

$$\begin{cases} f'(t) = f(t) & t \in \mathbb{R} \\ f(0) = f_0 & cst. \end{cases}$$

solution:

$$f(t) = f_0 \exp(t)$$

Exercise: Check that I am not lying to you!

$$' = \frac{\mathrm{d}}{\mathrm{d}t}$$

Friendly reminder on Differential Equations (2)

More generally we look at <u>evolution equations</u> *i.e.,* equations of the form

$$\begin{cases} \dfrac{\partial \boldsymbol{F}}{\partial t}(t,\boldsymbol{x}) = \mathcal{A}[\boldsymbol{F}](t,\boldsymbol{x}) \quad (t,\boldsymbol{x}) \in [0,\infty) \times \Omega_{\boldsymbol{x}} \\ \text{I.C. + B.C.} \end{cases}$$

With $\boldsymbol{F}(t,x) \in \mathbb{R}^d$, $\Omega_x \subseteq \mathbb{R}^d$ and a given differential operator $\mathcal{A}[.]$

<u>side note</u>: For biological relevance, we chose homogeneous Neuman boundary conditions (B.C.) $\nabla \boldsymbol{F} \cdot \nu_{\Omega_{\boldsymbol{x}}} = 0$ for all points $x \in \partial \Omega_{\boldsymbol{x}}$

<u>side note 2</u>: Technically, we have $\mathcal{A}[\boldsymbol{F}] := \tilde{\mathcal{A}}[\boldsymbol{F}] + \boldsymbol{f}(\boldsymbol{F})$.

Brief history of pattern formation modelling

Turing-type models:

$$\begin{cases} \dfrac{\partial A}{\partial t}(t,\boldsymbol{x}) = d_1 \Delta A(t,\boldsymbol{x}) + f(A,H) \\ \dfrac{\partial H}{\partial t}(t,\boldsymbol{x}) = d_2 \Delta H(t,\boldsymbol{x}) + g(A,H) \end{cases}$$

(I.C. + B.C.)

Remark: such equations are called “reaction-diffusion equations”

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Molecular / Chemical diffusion

Jittery motion
(~noise) of chemicals

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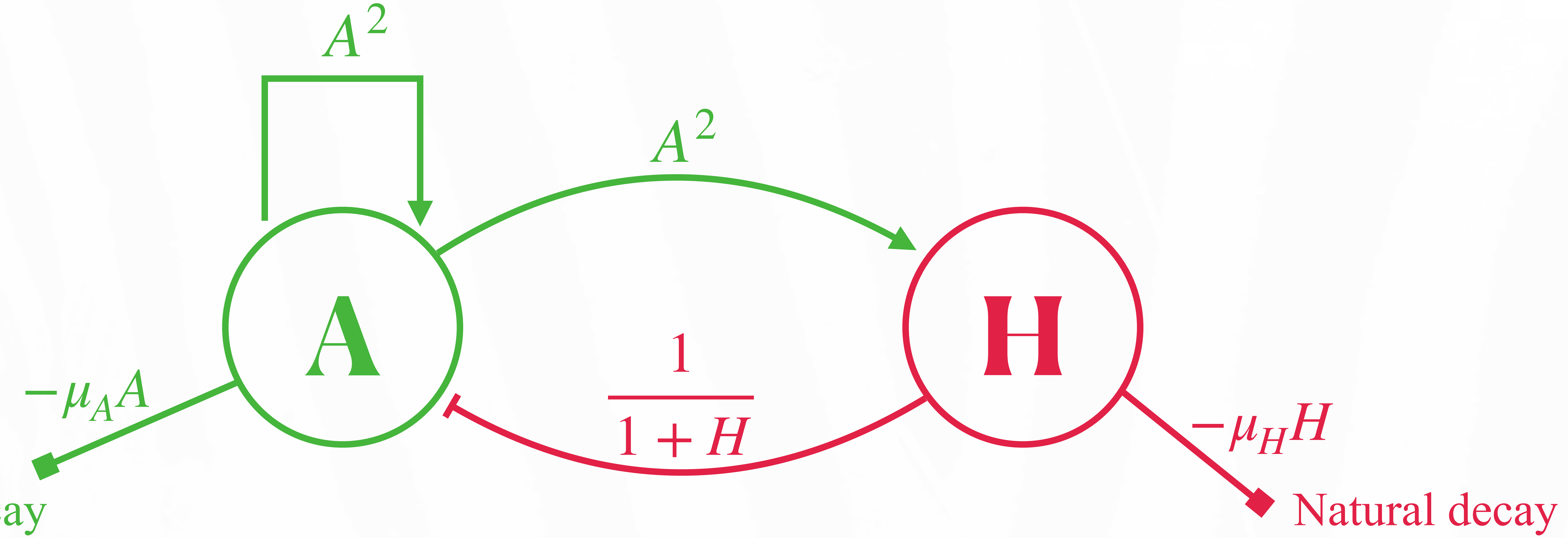
Interaction scheme

Usually what defines the name of the model

Brief history of pattern formation modelling

Gierer-Meinhardt

$$\begin{cases} \dfrac{\partial A}{\partial t}(t,\boldsymbol{x}) = d_1 \Delta A(t,\boldsymbol{x}) + \varrho\left(\dfrac{A^2(t,\boldsymbol{x})}{1+H(t,\boldsymbol{x})} - \mu_A A(t,\boldsymbol{x})\right) \\ \dfrac{\partial H}{\partial t}(t,\boldsymbol{x}) = d_2 \Delta H(t,\boldsymbol{x}) + \varrho\left(A^2(t,\boldsymbol{x}) - \mu_H H(t,\boldsymbol{x})\right) \end{cases} \quad (\text{I.C.} + \text{B.C.})$$



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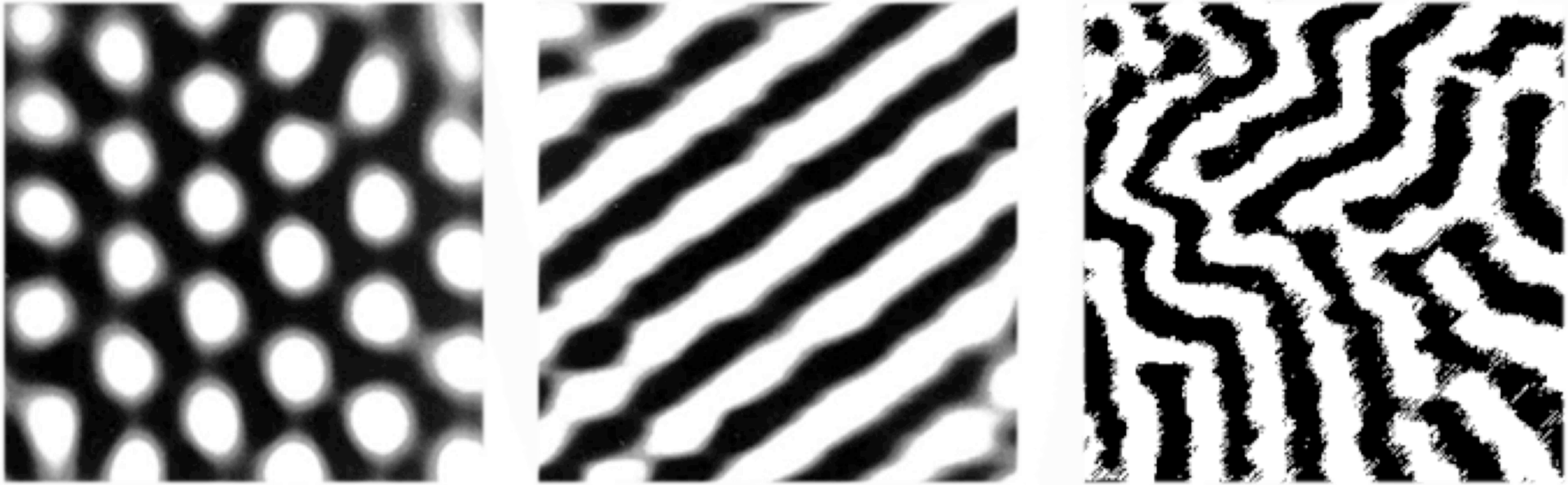

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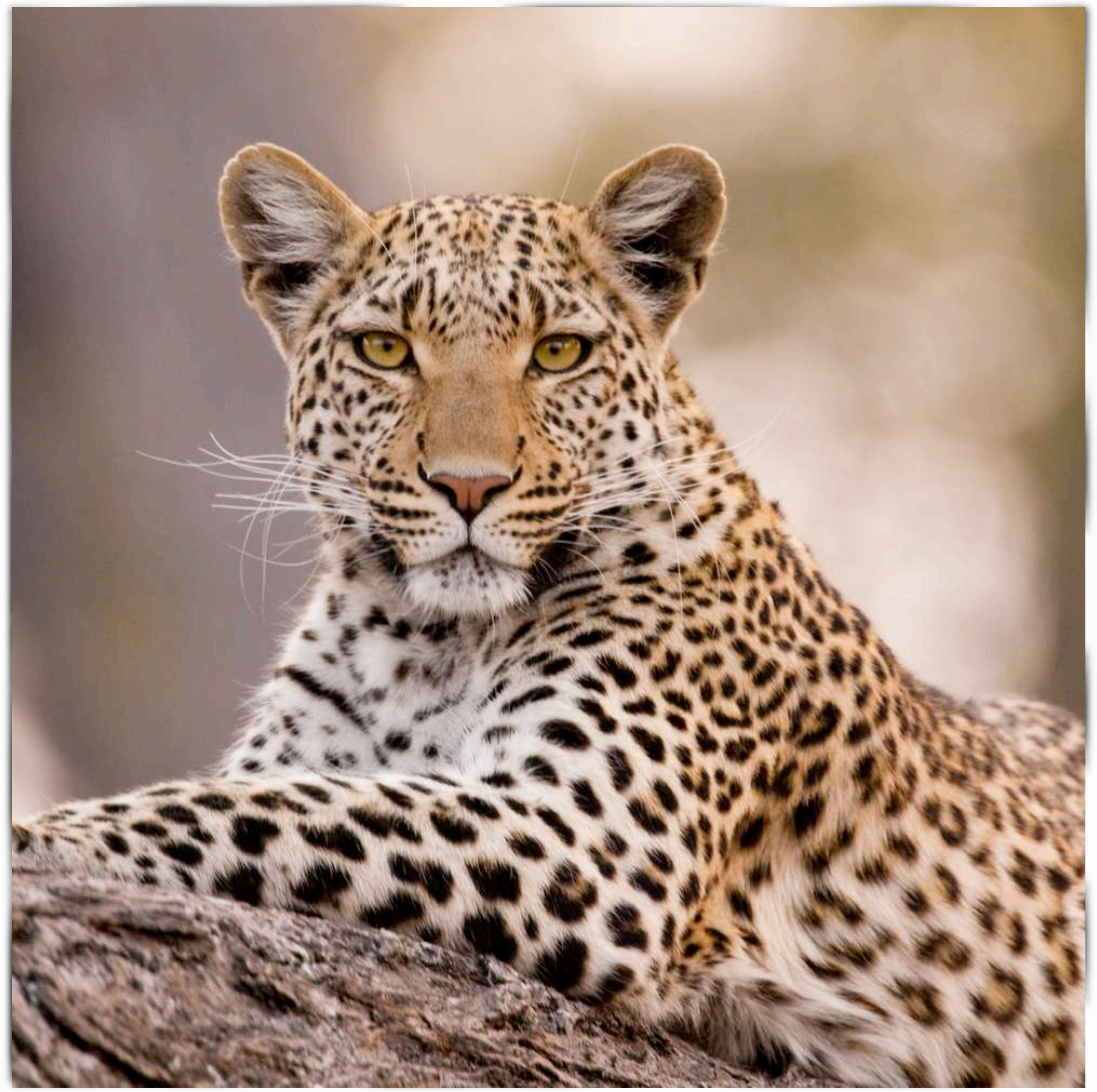
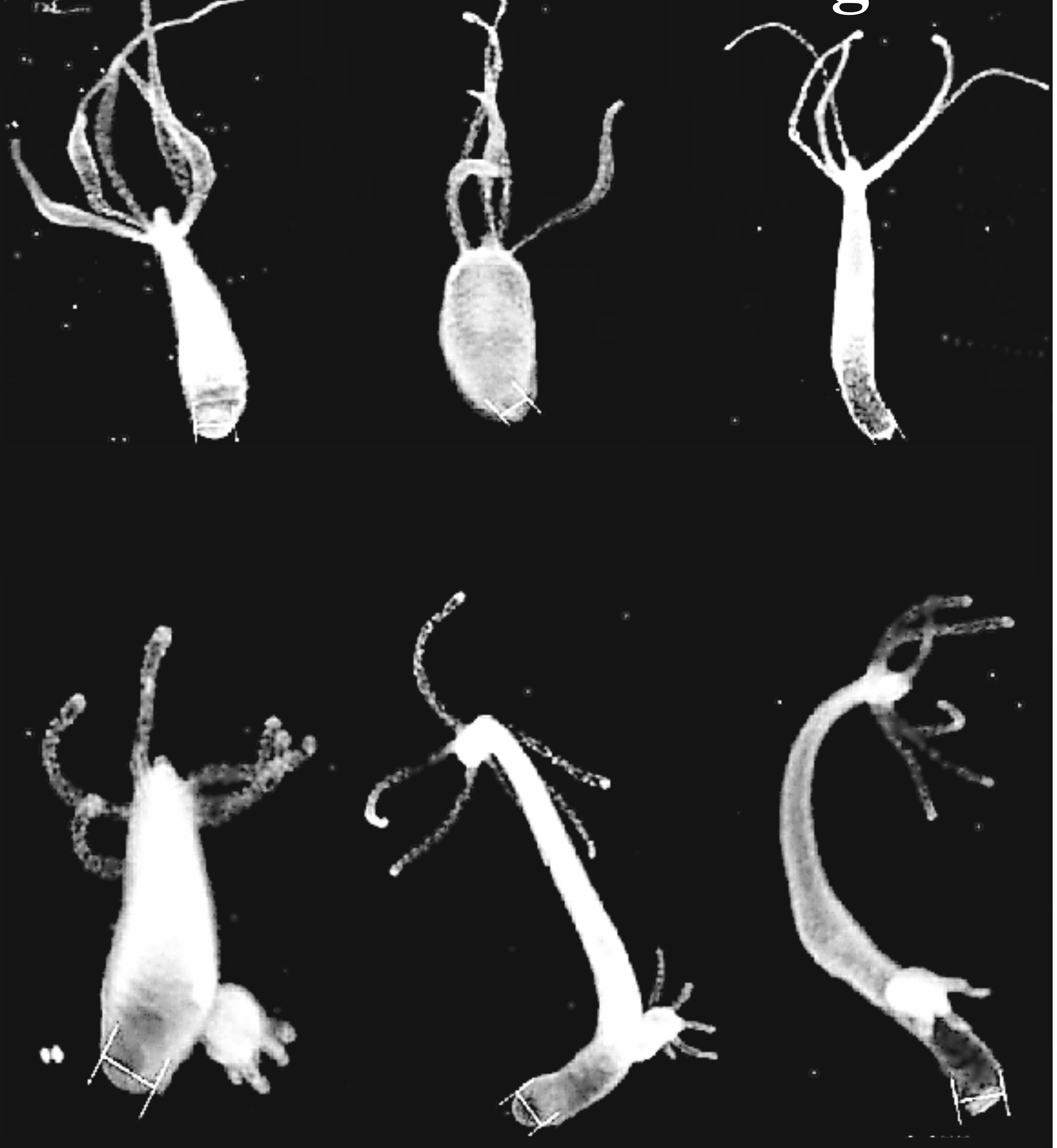
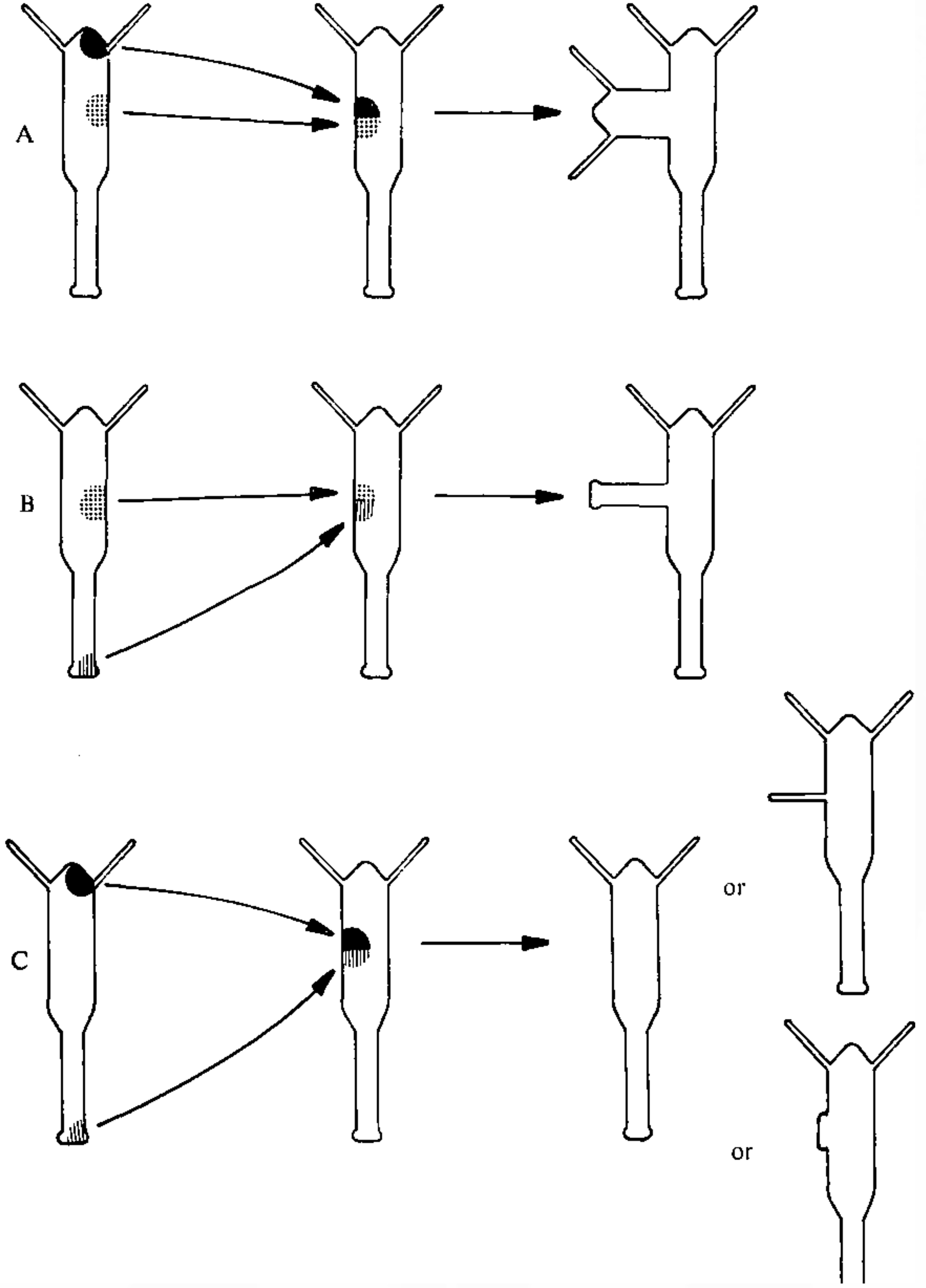


Pattern formation modelling with Hydra





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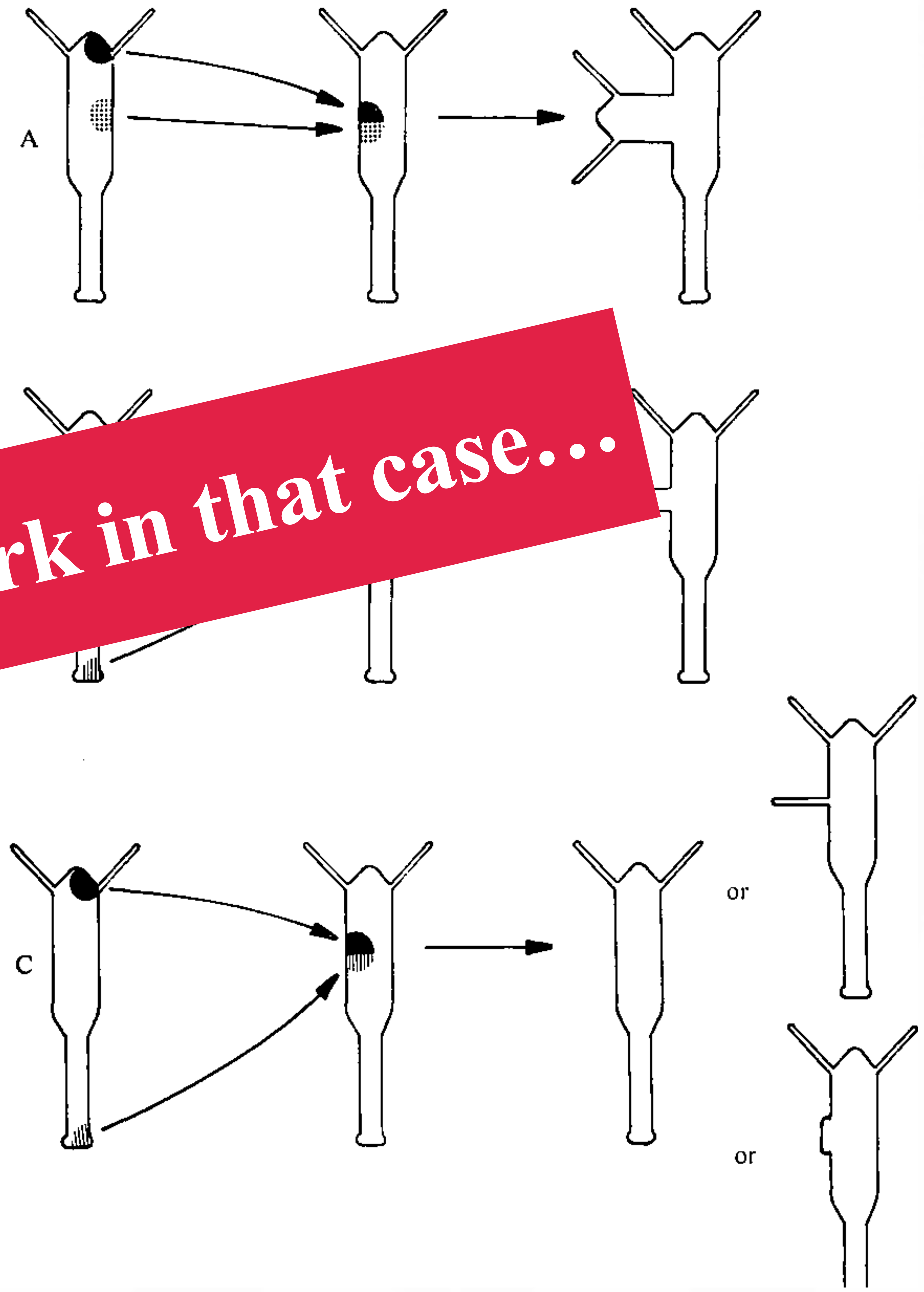

Turing-type models do not work in that case…

Pattern formation modelling with Hydra

Reaction-Diffusion-ODE models for pattern formation

Reaction-diffusion-ODE systems look like this:

$$\frac{\partial \boldsymbol{F}}{\partial t}(t,\boldsymbol{x}) = \mathbf{D}\Delta[\boldsymbol{F}](t,\boldsymbol{x}) + \boldsymbol{\phi}(\boldsymbol{F}(t,\boldsymbol{x}))$$

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But there is a twist…

$$\mathbf{D} = \begin{bmatrix} 0 & & & & & \\ & \ddots & & & & \\ & & 0 & & & \\ & & & d_1 & & \\ & & & & \ddots & \\ & & & & & d_n \end{bmatrix}$$

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- Lots of results when $n = 1$ (i.e., only one RD equation)
- Very few is known for two RD equations (or more…)

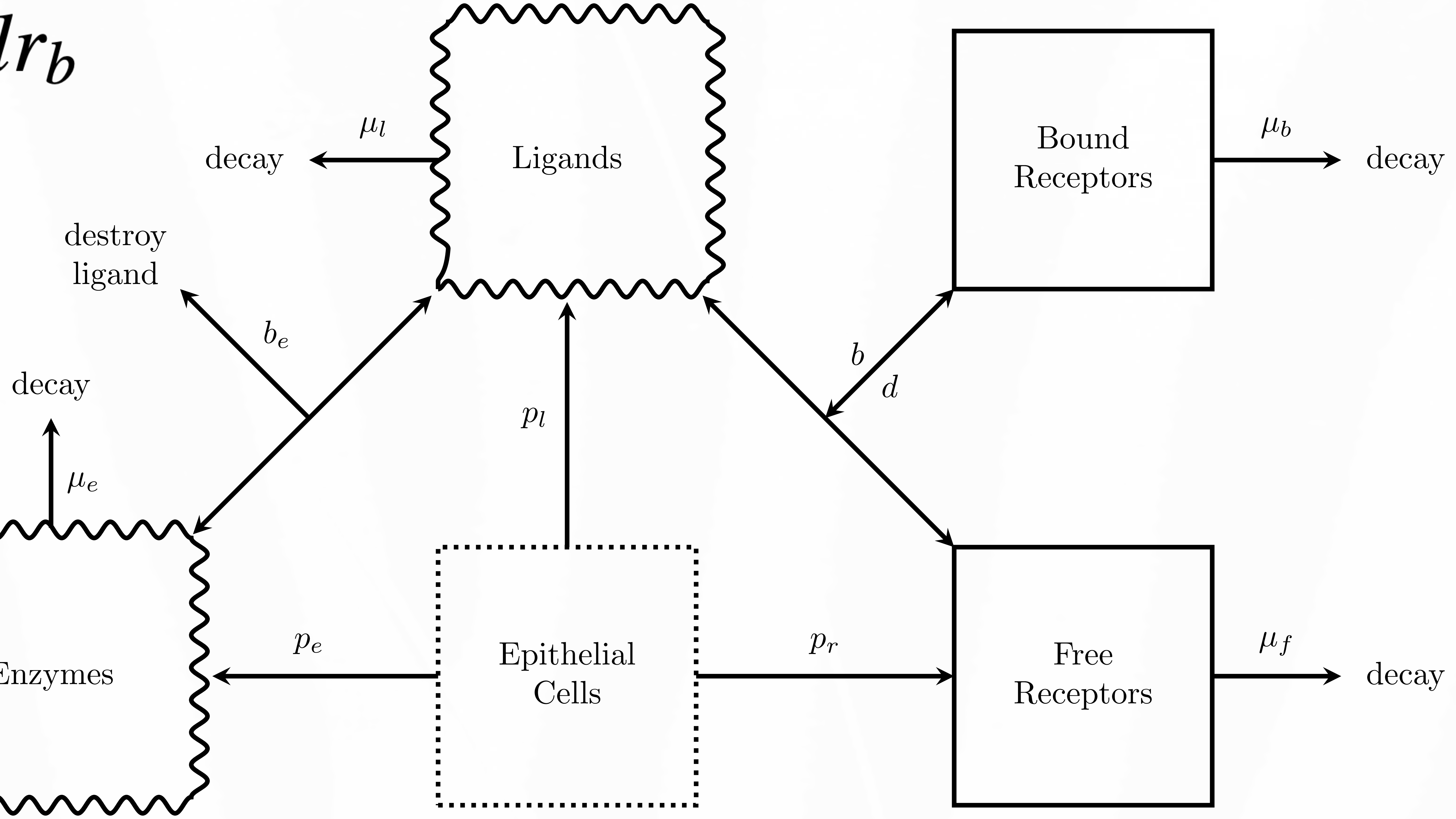
Reaction-Diffusion-ODE models for pattern formation

$$\begin{cases} \dfrac{\partial r_f}{\partial t} = -\mu_f r_f + p_r(r_b) - b r_f \ell + d r_b \\ \dfrac{\partial r_b}{\partial t} = -\mu_b r_b + b r_f \ell - d r_b \\ \dfrac{\partial \ell}{\partial t} = d_1 \Delta \ell - \mu_l \ell + p_\ell(r_b) - b r_f \ell + d r_b \\ \dfrac{\partial e}{\partial t} = d_2 \Delta e - \mu_e e + p_e(r_b) \end{cases}$$

(I.C. + B.C.)

$\Omega = (0, L) \subset \mathbb{R}$

$t \in [0, \infty)$



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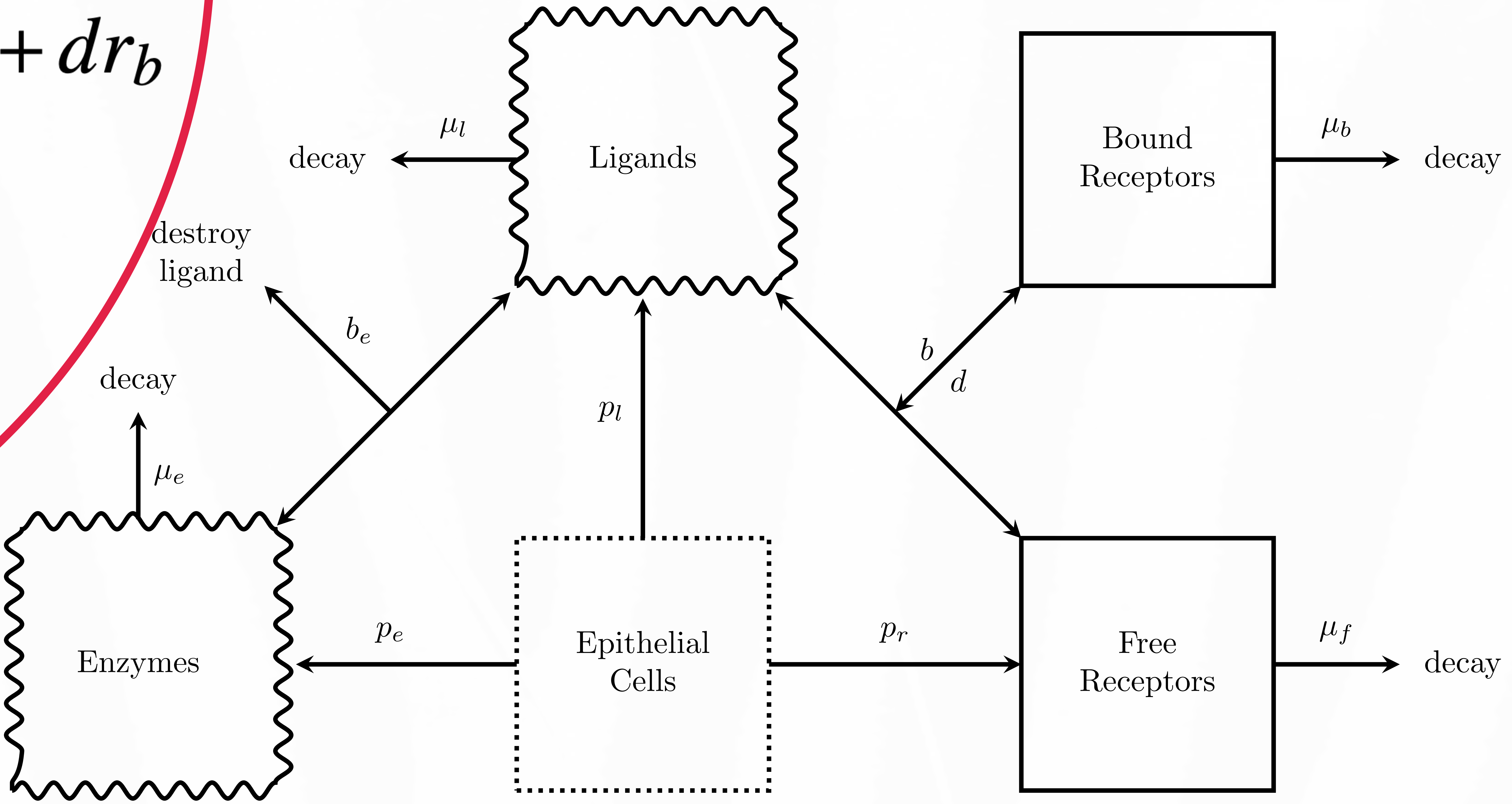
Use quasi-static approximation and parameter rescaling to simplify the model



Reaction-Diffusion-ODE models for pattern formation

$$\begin{cases} \dfrac{\partial u}{\partial t} = -\mu_f u + m_1 \dfrac{uv}{1+uv} - \mu_b uv \\ \dfrac{\partial v}{\partial t} = d_1 \Delta v - \mu_l v + m_2 \dfrac{uv}{1+uv} - \mu_b uv + vw \\ \dfrac{\partial w}{\partial t} = d_2 \Delta w - \mu_e w + m_3 \dfrac{uv}{1+uv} \end{cases}$$

(I.C. + B.C.)

$\Omega = (0, L) \subset \mathbb{R}$

$t \in [0, \infty)$

THEOREM 1. *Assume* $\boldsymbol{f}$ *is locally bounded, Lipschitz continuous, i.e., for every bound* $\subseteq \mathbb{R}^3$, *there exists* $L(B) > 0$ *such that*

$$\|\boldsymbol{f}(x)\| \leqslant L(B), \quad \text{and} \quad \|\boldsymbol{f}(x) - \boldsymbol{f}(y)\| \leqslant L(B)\|x - y\|, \quad \forall\, x, y, \in B$$

over, assume $\boldsymbol{u}_0 \in L^\infty(\Omega)^3$. *Then the following properties hold*

(i) *There exists* $T_{\max} \in (0, \infty) \cup \{\infty\}$ *such that (AC) has a unique mild solution* $\boldsymbol{u}$ *on the half-open interval* $[0, T)$, *with* $\boldsymbol{u} \in \mathcal{C}([0, T]; L^2(\Omega)^3)$ *for all* $T < T_{\max}$.

(ii) *The existence time* $T_{\max} \in (0, \infty) \cup \{\infty\}$ *can be chosen maximal. If* $T_{\max} < \infty$, *then* $\lim_{t \to T_{\max}} \|\boldsymbol{u}(\cdot, t)\|_\infty = \infty$

(iii) *If we consider regular initial data* $\boldsymbol{u}_0 \in \mathcal{C}^{0,\alpha}(\bar{\Omega}) \times \mathcal{C}^{2,\alpha}(\bar{\Omega})^2$, *then* $\boldsymbol{u}$ *is smooth* [4] *and is also a classical solution.*

LEMMA 5 (DDI threshold on d_1). *Fix parameters* $\boldsymbol{\Pi} \in \boldsymbol{\Theta}$ *and t Then, for any choice of diffusion coefficients*

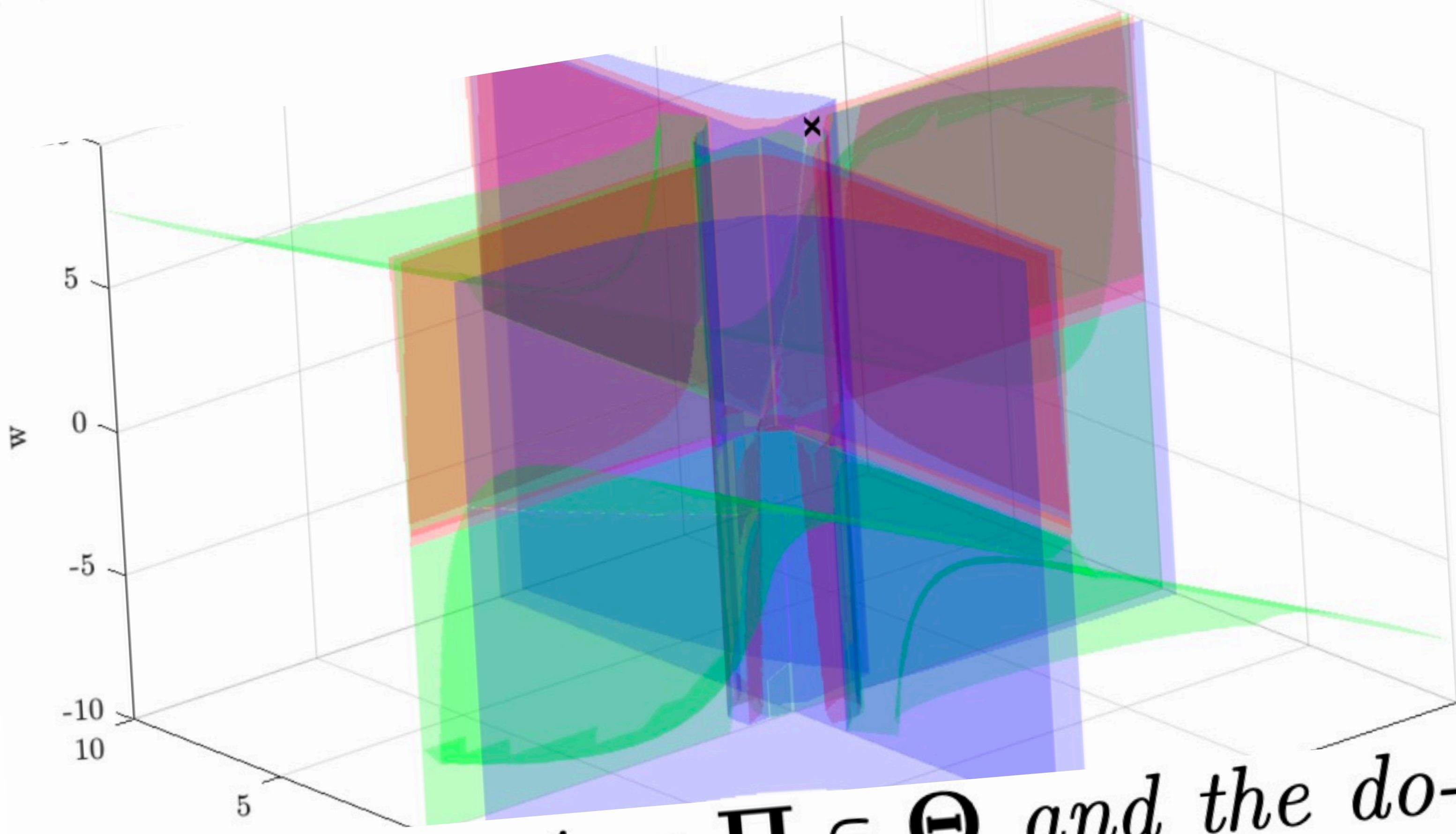
$$d_2 > 0, \quad \text{and} \quad d_1 \geqslant \frac{1}{\mu_1^2} \frac{|A_{12}|}{A_1} =: d_1^{(c)}, \tag{3.18}$$

DDI cannot occur.

THEOREM 2. *There exists three positive reals* A_u, A_v, A_w, *large enough, such that the region*

$$\Sigma = \{(u, v, w) \in \mathbb{R}^3 \mid 0 \leqslant u \leqslant A_u, \quad 0 \leqslant v \leqslant A_v, \quad 0 \leqslant w \leqslant A_w, \},$$

is an invariant rectangle of (M).



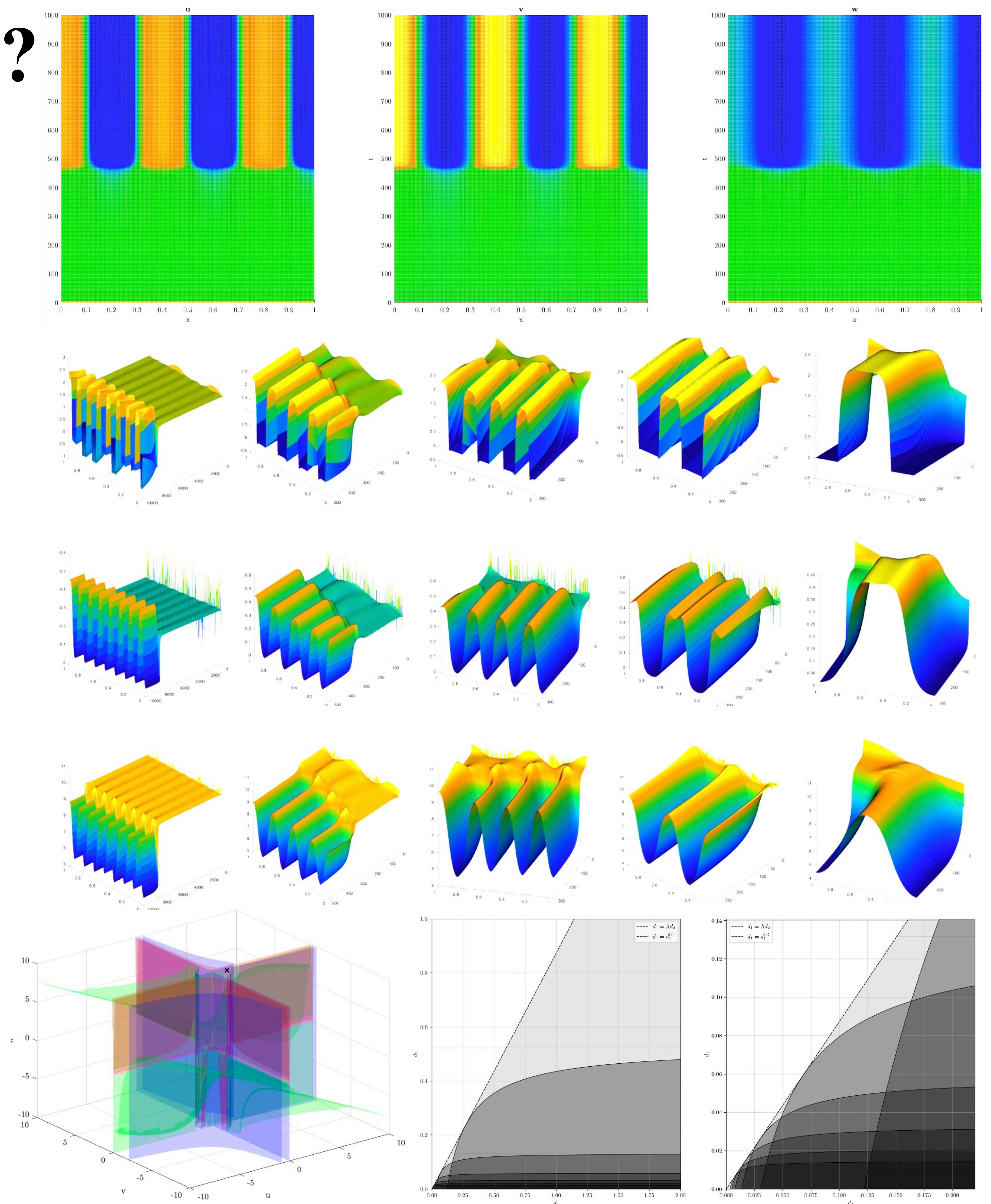
THEOREM 3 (Sufficient and Necessary condition for DDI). *Consider system (M), with ssociated reaction kinetics having a nontrivial, positive steady-state* $\bar{\boldsymbol{U}}$. *Let* $A = \mathbf{Jac}_{\boldsymbol{f}}(\bar{\boldsymbol{U}})$ *nd assume the choice of parameters* $\boldsymbol{\Pi} \in \boldsymbol{\Theta}$. *Then there exists a real* $\Lambda := P + Q - \sqrt{S} > 0$ *uch that* $\bar{\boldsymbol{U}}$ *exhibits DDI if and only if* $d_1/d_2 \in (0, \Lambda)$.

THEOREM 4 (Threshold for eigenmode stability). *Fix parameters* $\boldsymbol{\Pi} \in \boldsymbol{\Theta}$ *and the domain* $\Omega = (0, L)$ *and* $d_1 < d_1^{(c)}$. *For any positive integer* k *satisfying*

$$k \leqslant \left\lfloor \frac{L}{\pi} \sqrt{\frac{1}{d_1} \frac{|A_{12}|}{A_1}} \right\rfloor,$$

Source: my thesis

What remains when the dust settles?



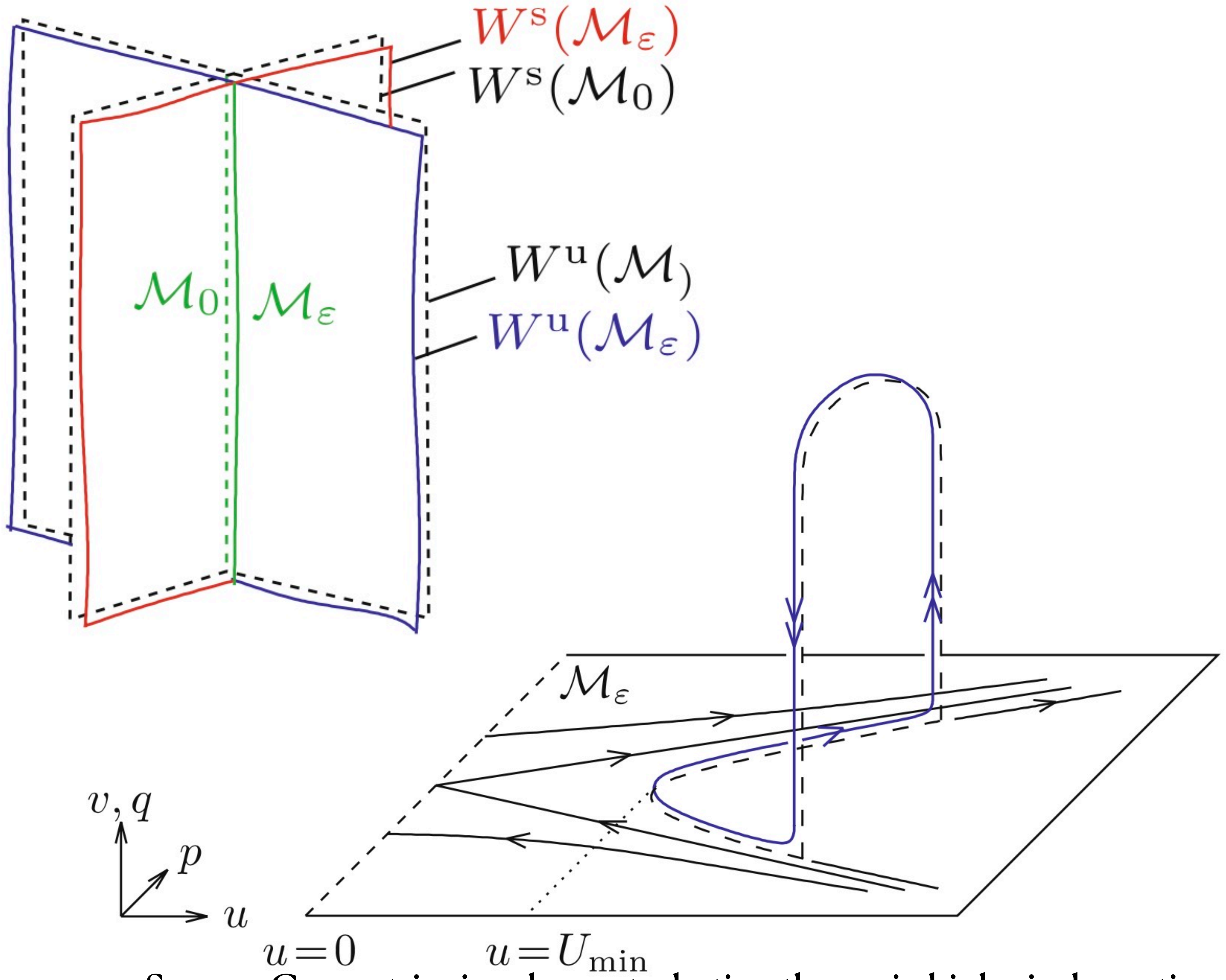
What we proved:

- The model has a unique global solution under relatively weak - and biologically relevant - assumptions
- Yes, we can observe patterns in this model. There is a whole familly of them
- We constructed a step-by-step method to find these patterns (if they exist)
- The quasi-static approximation is rigorous and properties of the smaller model can be extended to the larger one (under weak assumptions)

New giants arising…

<u>New natural questions</u> :

- Can we use GSPT theory to obtain better insight about patterns we get?
- Are there other types of patterns?
- How to solve the stationnary problem? (2 highly non-linear parabolic equations)
- What about 'unstable patterns'?
- …



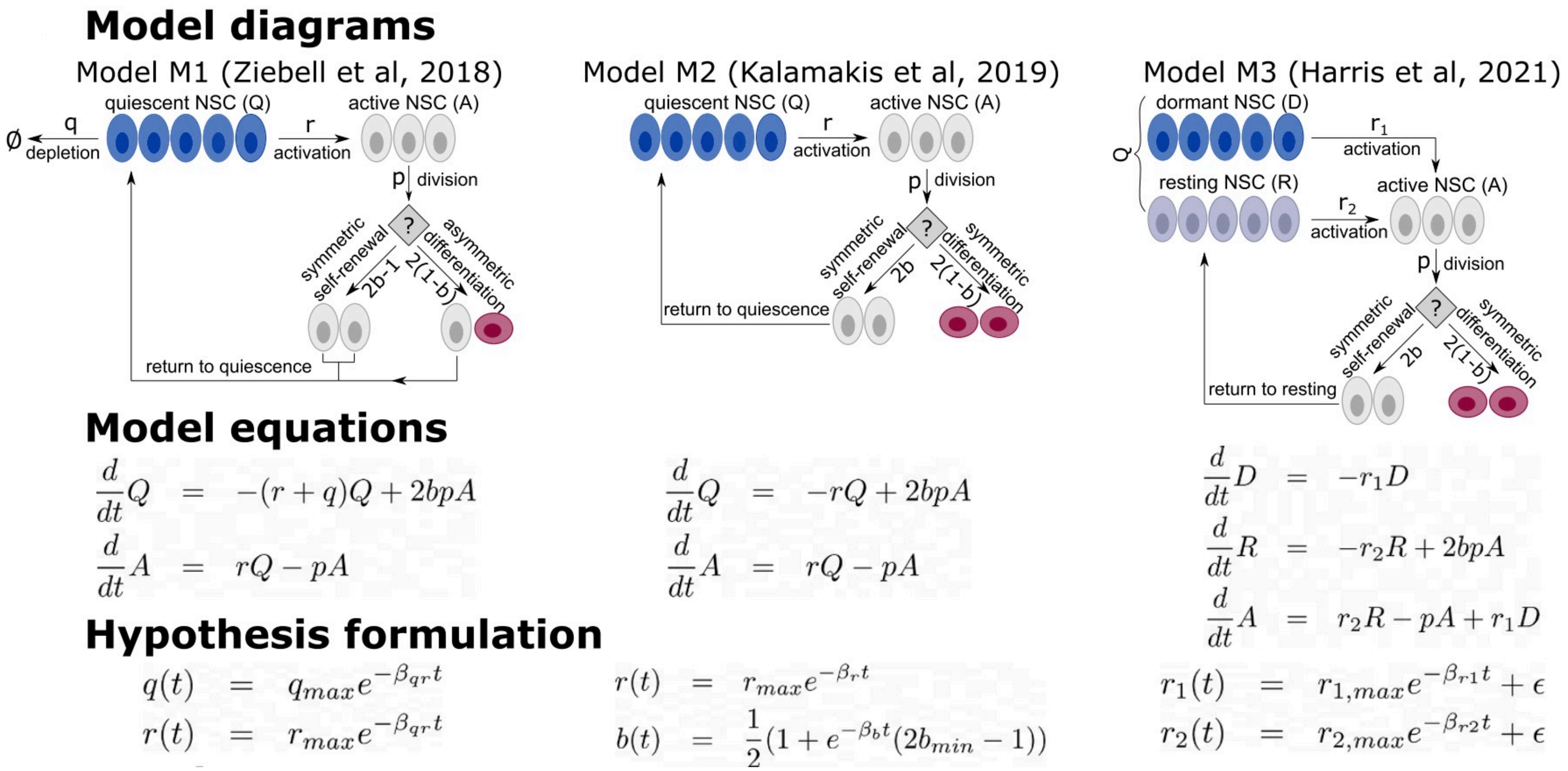
Source: Geometric singular perturbation theory in biological practice

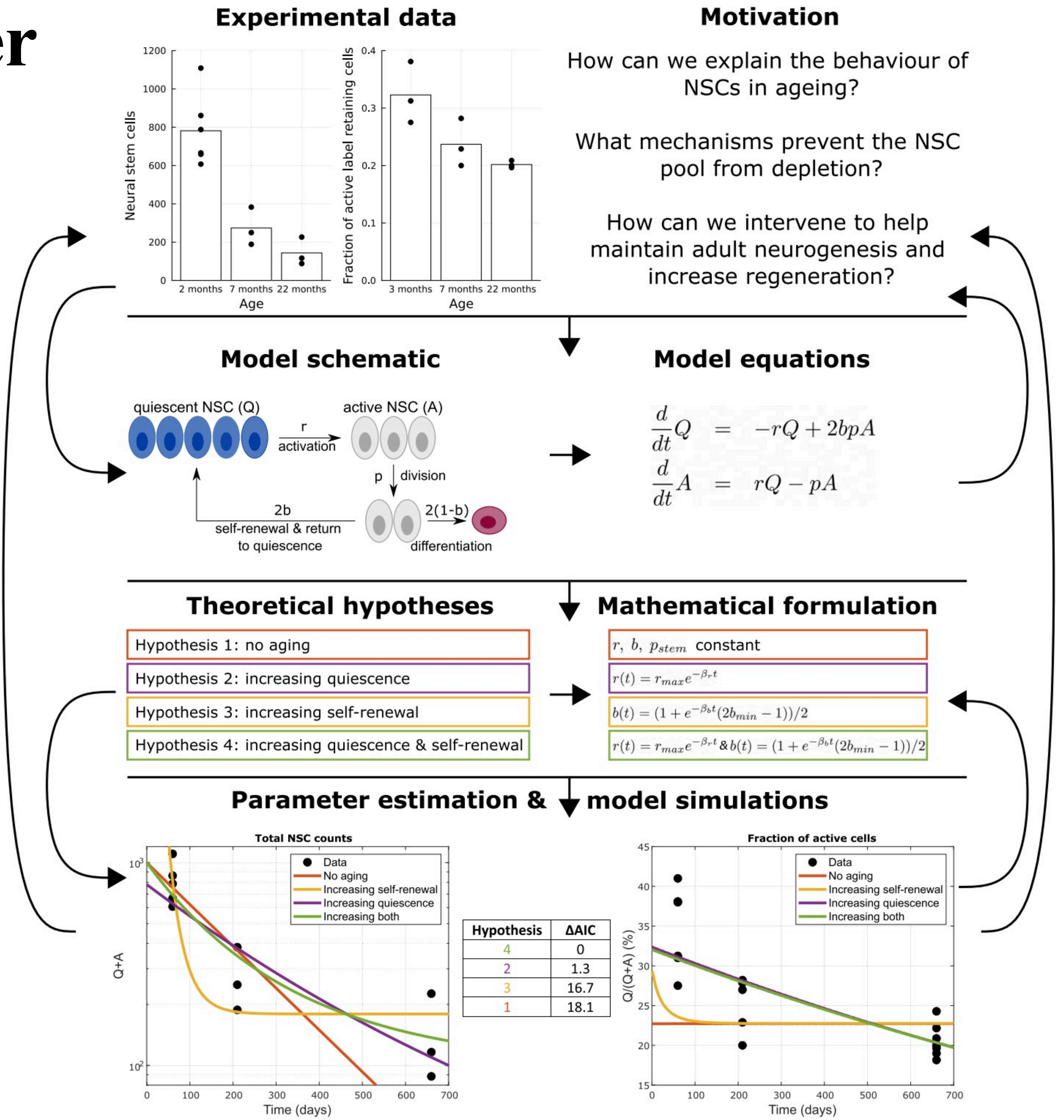
$$\begin{cases} d_1\Delta\bar{v} &= -m_2\left(1-\dfrac{\mu_f+\mu_b\bar{v}}{m_1\bar{v}}\right)+\mu_\ell\bar{v}+\mu_b\left(\dfrac{m_1\bar{v}}{\mu_f+\mu_b\bar{v}}-1\right)+\bar{v}\bar{w}, \\ d_2\Delta\bar{w} &= -m_3\left(1-\dfrac{\mu_f+\mu_b\bar{v}}{m_1\bar{v}}\right)+\mu_e\bar{w}. \end{cases}$$

Transferring knowledge to other models

Ideas for the future:

- Implement the notion of space in a recent model for neural stem cell differentiation
- Investigate the phenomenon of pattern formation with such nonlinearities
- Make sense of pattern formation in this model





Source: Mathematics of neural stem cells: Linking data and processes

Nice references to look at:

- Moritz Mercker, Dirk Hartmann, and Anna Marciniak-Czochra. A Mechanochemical Model for Embryonic Pattern Formation: Coupling Tissue Mechanics and Morphogen Expression. *PLoS One*, 8(12):e82617, December 2013.
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THANK YOU FOR YOUR ATTENTION!