On pattern formation modelling in a specialized SMJM model

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Abstract

This thesis builds upon previous work pioneered by Anna Marciniak-Czochra [10], in using coupled reaction-diffusion equations to ODE to model receptor dynamics in Hydra, a freshwater polyp known for its regenerative abilities. Previous studies have shown that such models can successfully capture the emergence of spatial patterns of gene expression during regeneration, and have identified key signaling molecules such as Wnt, β-catenin and Notch as playing a critical role in this process. In this work, we come back to the model presented in [10] that integrates a reaction-diffusion-ODE system (1 ODE + 2 PDE) and see how far we can go in reducing the amount of parameters and investigating the phenomenon of pattern formation after reduction.

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Contents

"In the 300 years since Newton, mankind has come to realize that the laws of physics are always expressed in the language of differential equations"

— *Steven Strogatz*

1 Biological motivation: Hydra Morphogenesis

1.1 Anatomy of a Hydra

Hydras (*diploblastic metazoan hydra* or *hydra vulgaris*) are fascinating creatures. Largely studied by Abraham Trembley in 1744 ([ref]), they are freshwater polyps about 5mm of length in average. Most of the scientific interest about hydras comes from the fact that they are capable of showing extraordinary regenerative properties that allow them to fully reconstruct their body out of a very small portion of tissue (1.1).

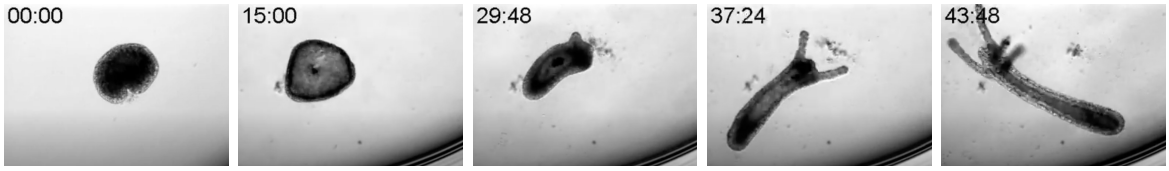

Figure 1: Hydra is capable of regenerating an entirely functional individual from a small piece of tissue ($\sim 100\mu$m) in the span of two to three days.

The body of Hydra is composed of essentially three regions (2): the head, body column and foot. Spatially speaking, the small cnidarian is symmetrically organized around an oral-aboral axis in a hollow, tubular shape. Taking a closer look on each part, one can notice that the head is composed of two sub-regions: one being a set of tentacles while the other one is called hypostome and acts as a mouth (it is also the only orifice in the whole organism). The foot, on the other hand is composed of a basal disc that allows hydras to stick to underwater leaves and rocks or other kind of surfaces. Lastly, the body column is a long hollow tube made of cells undergoing constant mitosis through the life of the polyp. This process ensures a constant cellular turnover of the derm and experimentation have shown that hydras replace the entirety of their cells within the span of 20 days.

Remark 1 (Hydra reproduction)**.** *The way hydras reproduce is very peculiar but is of great interest to the scientific community since they are able to give birth either sexually or through natural cloning, see figure 3 (the latter being the most common way of reproduction in labs). The main difference between these two methods is that asexual reproduction preserves the totality of information in one individual, letting one the ability to duplicate a specific hydra with nice genetic information if they wish. This considerably enhances the pace at which experiments occur while reducing the randomness factor due to genetics (therefore improving reproducibility of experiments).*

This is not [5]

Figure 2: Photomicrograph of hydra exposing their different body parts: the head (mouth surrounded by tentacles), the body axis up to the foot.

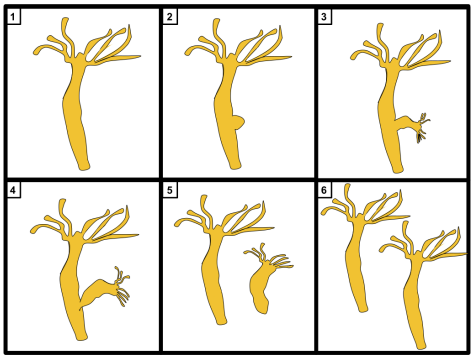

Figure 3: Illustrated process of asexual reproduction (natural cloning) in Hydra. A new head grows on the body column at the top of the peduncle (this small lump is familiarly call "the bud") and keeps growing until it detaches from the "adult"'s body. Once detached, the new individual sticks to nearby rocks or leaves and keeps growing until adult size is reached. (credit: picture from [8])

1.2 A few words about Wnt proteins

1.3 Position-based regrowth and grafting experiments

2 General Theory

This chapter is dedicated to the analytical study of general forms of RD-ODE systems. For that, we start by introducing the two definitions

Definition 1 (Sobolev spaces)**.** *Let $\Omega \subset \mathbb{R}^d$ be a bounded domain with $\partial\Omega \in \mathcal{C}^1$. We denote by $W^{k,p}(\Omega)$ the Sobolev space defined by*

$$W^{k,p}(\Omega) := \left\{ u \in L^p(\Omega) : \forall \alpha \in \mathbb{N}^d, \varphi \in \mathcal{C}^\infty(\Omega), \exists v \in L^p(\Omega) : \int_\Omega v\varphi = (-1)^{|\alpha|} \int_\Omega u \partial^\alpha \varphi \right\}$$

Definition 2 (Laplace operator)**.** *We define the **Laplace operator** Δ on a bounded domain $\Omega \subset \mathbb{R}^d$ endowed with Neumann boundary conditions ($\partial_\nu = 0$ on $\partial\Omega$) through the relation*

$$\Delta_\nu = \sum_{i=1}^{d} \frac{\partial^2}{\partial x_i^2}.$$

Furthermore, $-\Delta_\nu$ *has a discrete spectrum consisting of a sequence of non-decreasing, non-negative eigenvalues* $\{\mu_j\}_{j\geqslant 0}$ *with* $\mu_0 = 0$, $\mu_n \xrightarrow{n\to\infty} \infty$ *and has domain* $\mathrm{Dom}(-\Delta_\nu) = W^{2,p}_\nu(\Omega)$ *(the space of functions* $u \in W^{2,p}(\Omega)$ *such that* $\partial_\nu u_{|\partial\Omega} = 0$*).*

For the sake of notation, we also drop the ν symbol in the Laplace operator. i.e., we will write $\Delta_\nu = \Delta$.

2.1 Reaction-Diffusion-ODE problems

Reaction-diffusion-ODE systems are what one obtains when writing evolution equations for coupled diffusive and non-diffusive quantities. Mathematically, this rewrites under the formed of Until recently, the matrix D in (A.1) was mainly chosen as a diagonal matrix $D = diag(d_1, ..., d_d)$, with $d_i > 0$, $i = 1, ..., d$. Taking a coefficient $d_i = 0$ results in canceling the effect of the Laplace operator, thus transforming equation i into a classical ODE coupled to the PDE system. In this paragraph, we inspect the properties of such systems coupling $k > 0$ ODE to $m > 0$ reaction-diffusion equations. For that, let $n \in \mathbb{N}$ such that $m + k = n$ and a bounded domain $\Omega \subset \mathbb{R}^n$. Let us consider the $\mathcal{C}^2$-nonlinearities $\boldsymbol{f} : \mathbb{R}^k \times \mathbb{R}^m \longrightarrow \mathbb{R}^{m+k}$ describing the reaction kinetics between each components of the system. We aim to investigate properties of

$$\begin{aligned}
&\partial_t \boldsymbol{u} = \mathbf{D}\Delta \boldsymbol{u} + \boldsymbol{f}(\boldsymbol{u}) && \text{on } \Omega \times \mathbb{R}^+ \\
&\partial_\nu u_i = 0 && \text{on } \partial\Omega \times \mathbb{R}^+, \text{ for } i \in [\![m+1, k]\!] \\
&\boldsymbol{u}(\cdot, 0) = \boldsymbol{u}_0(\cdot) && \text{on } \Omega.
\end{aligned}$$

2.1.1 Existence of solutions

The goal of this section is to show that for an autonomous abstract Cauchy problem, if the operator A is the infinitesimal generator of an analytic C_0-semigroup of operators, then the problem admits a unique solution whose regularity depends on the regularity of the initial condition.

Definition 3 (Abstract Cauchy problem)**.** *La définition du problème de Cauchy abstrait nous vient de E. Hille*

$$\begin{aligned}
\partial_t u &= Au + f(u) \\
u(0) &= u_0
\end{aligned}$$

- Abstract Cauchy Problem
-

Theorem 1 (Spectral Mapping Theorem)**.** *Consider a locally compact space X. Let A be the generator of a positive, bounded, compact, strongly continuous group on $\mathcal{C}_0(X)$, denoted by $(L(t))_{t\in\mathbb{R}}$. Then*

$$\sigma(L(t)) = \overline{\exp(t\sigma(A))}$$

Proof. see Theorem 1.1. from [2] □

Proof. It is a straightforward computation. The result is obtained by expanding and refactoring the expression $\det(A - \lambda)$ □

- Linear / NonLinear decomposition
- Bound on the Nonlinear part $\mathcal{N}$
- Why is the spectrum so important here
- Define DDI
- Maybe include Finn's result on the d_1 d_2 ? (and add full acknowledgement to his work)
- linearization of a PDE system
- Solving for the eigenvalue problem

3 A receptor based model for hydra morphogenesis

3.1 Introduction of the model

3.1.1 Biological derivation and description of kinetics

We put ourselves in the following scenario: Epithelial cells continuously produce receptors, ligands and enzymes. At first, receptors are in an unbound state and are called *free receptors*. When a *ligand* reversibly binds to a free receptor, the pair is then called *bound receptor*. Similarly, an interaction between an *enzyme* and ligand results in the destruction of the ligand. We consider the space Ω to be a closed medium in which molecules can meet and interact (see 3.1.1 for a schematic representation of the situation). Additionally, we assume that both ligands and enzymes are subject to molecular diffusion while free (and bound) receptors are not. Let

$$r_f := \frac{\#\text{free receptors}}{|\Omega|}, \quad r_b := \frac{\#\text{bound receptors}}{|\Omega|}, \quad l := \frac{\#\text{ligands}}{|\Omega|}, \quad e := \frac{\#\text{enzymes}}{|\Omega|},$$

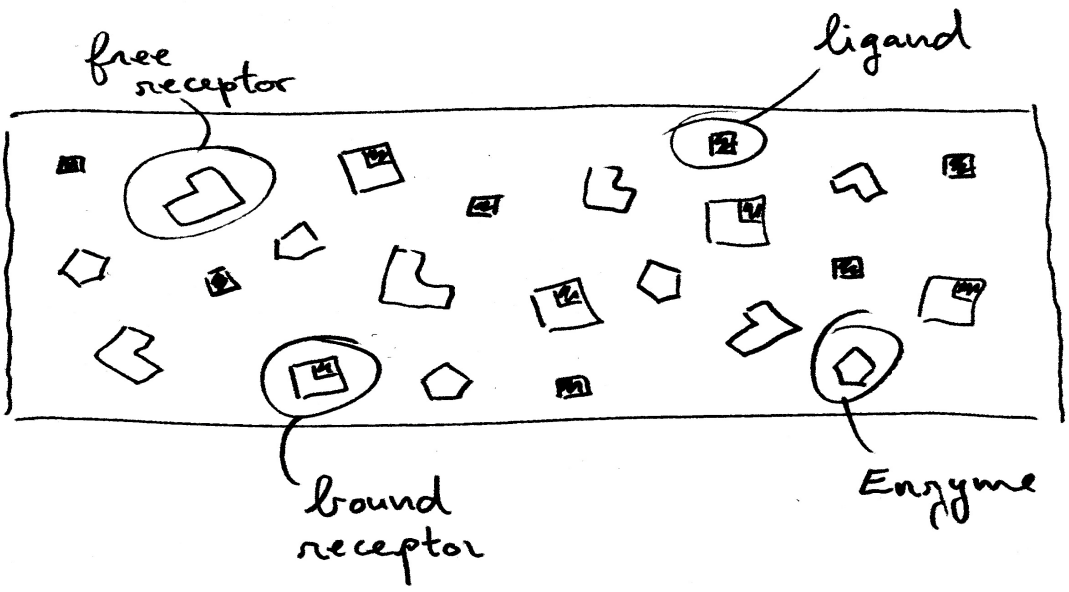

Figure 4: Maybe replace with a tikz figure to have things look cleaner

denote the concentration of each molecule. We use methods from chemical kinetics and statistical physics to infer equations describing the reaction.

All binding processes (receptors-ligands, ligands-enzymes) are assumed to be governed by the law of mass action kinetics. Free receptors, ligands and enzymes are produced by epithelial cells at rate p_r, p_l, p_b and degraded at rates μ_r, μ_l, μ_e. On the other hand bound ligands are internalized by the cell at rate μ_b. Binding and dissociation rates between ligands and receptors are denoted by letters b and d. Enzymes bind to ligands with rate b_e, leading to the destruction of said ligands. And finally, we let D^l and D^e denote the diffusion rates of ligands and enzymes respectively. Altogether, we end up with the following set of equations

$$\partial_t r_f = -\mu_f(r_f) + p_r(r_f, r_b) - b(r_f, l) + d(r_b) \tag{3.1}$$

$$\partial_t r_b = -\mu_b(r_b) + b(r_f, l) - d(r_b) \tag{3.2}$$

$$\partial_t l = \varepsilon d_1 \partial_x^2 l - \mu_l(l) - b(r_f, l) + p_l(r_f, r_b) + d(r_b) - b_e(l, e) \tag{3.3}$$

$$\partial_t e = \varepsilon d_2 \partial_x^2 e - \mu_e(e) + p_e(l, r_b) \tag{3.4}$$

Supplemented with homogeneous Nmann boundary conditions on $\Omega = (0, L)$ (which physically represents a one-dimension sheet of epithelial cells along the body column). Later, we will pick $\Omega = (0, 1)$ and focus

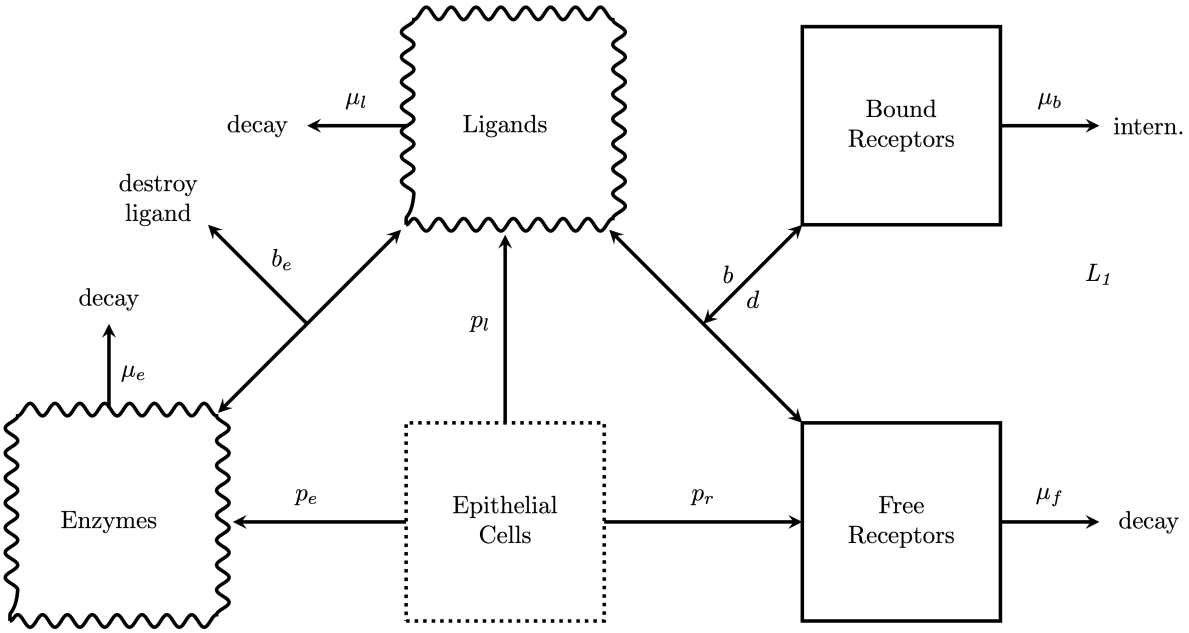

Figure 5: Diagram representation of the model

3.1.2 Choosing kinetic functions

Again in [10], two choices of kinetics are explored to study (3.1)-(3.4). Some results can be proved about the model in the general case with weak assumptions on each functions, but then we cannot make use of numerics to get a visual grasp of the situation. This is why we decide to define each function in the model using one of the choices in [10] (and keep the other one as an extension for further researches). In what follows, we define every rates $b, d, b_e, \mu_f, \mu_b, \mu_l, \mu_e$:

$$\begin{aligned}
b(r_f, l) &= b r_f l & b &\in \mathbb{R}_{>0} \\
b_e(l, e) &= b_e l e & b_e &\in \mathbb{R}_{>0} \\
d(r_b) &= d r_b & d &\in \mathbb{R}_{>0} \\
\mu_f(r_f) &= \mu_f r_f & \mu_f &\in \mathbb{R}_{>0} \\
\mu_b(r_b) &= \mu_b r_b & \mu_b &\in \mathbb{R}_{>0} \\
\mu_l(l) &= \mu_l l & \mu_l &\in \mathbb{R}_{>0} \\
\mu_e(e) &= \mu_e e & \mu_e &\in \mathbb{R}_{>0}
\end{aligned}$$

And the production rates are the same given by Michaelis-Mentel-like reaction terms

$$p_r(r_f, l) = m_1 \frac{r_b}{1 + r_b} \qquad m_1 \in \mathbb{R}_{>0}$$
$$p_l(l, e) = m_2 \frac{r_b}{1 + r_b} \qquad m_2 \in \mathbb{R}_{>0}$$
$$p_e(r_b) = m_3 \frac{r_b}{1 + r_b} \qquad m_3 \in \mathbb{R}_{>0}$$

3.2 Model reduction and properties

The system of PDE defined in (3.1)-(3.4) has been extensively studied in [10]. It has been shown that such a model can exhibit Turing patterns under some conditions on the Jacobian of the linearized system. In this thesis, we proceed in a similar fashion, but there is a twist. The next paragraphs are dedicated to reducing the model using quasi-steady-state approximation and re-parametrization.

3.2.1 Quasi-steady-state approximation

The Quasi-Steady-State Approximation (QSSA) is a technique inspired from the field of chemical kinetics or more generally biochemistry. When introduced, the purpose of such an approximation is to simplify the analysis by assuming that certain chemical species are reaching their steady-state concentrations quicker than other species in the system.

First used in an *ad hoc* fashion by biologists, they theory behind QSSA has been thoroughly explored and is now carefully described thanks to the framework provided by singular perturbation theory. This approach turns out to be particularly efficient for equations emerging from chemistry. When performing QSSA, the rate of change of concentrations of these slower species is assumed to be negligible compared to the rates of other reactions in the system. Therefore, the concentrations of these species can be approximated as constants during the time course of the reaction.

Remark 2. *Although the QSSA can be proven to be physically relevant when applied to some systems (e.g., it works in our case maybe prove it if time ?), the approximation may not always hold true under certain conditions.*

Coming back to our system, we perform a QSSA on the quantity r_b, *i.e.*, we assume $\partial_t r_b = 0$. and find $(d + \mu_b) r_b = buv$ from substituting the value of $\partial_t r_b$ by 0 in (3.2) and solving for r_b. Some rearranging yields

$$r_b = \frac{b}{d + \mu_b} uv.$$

From now on, we let $\alpha = b/(d + \mu_b)$ and replace the newly found value of r_b in (3.1)-(3.4):

$$\partial_t u = -\mu_f u + m_1 \frac{\alpha uv}{1 + \alpha uv} - buv + d\alpha uv, \tag{3.5}$$

$$\partial_t v = \varepsilon d_1 \partial_x^2 v - \mu_l v + m_2 \frac{\alpha uv}{1 + \alpha uv} - buv + d\alpha uv - b_e vw, \tag{3.6}$$

$$\partial_t w = \varepsilon d_2 \partial_x^2 w - \mu_e w + m_3 \frac{\alpha uv}{1 + \alpha uv}. \tag{3.7}$$

3.2.2 Change of variable

Now that we have reduced the amount of variables from four to three, let us also operate surgery on the system to get rid of some parameters. First, a quick computation shows that $d\alpha - b = -\mu_b \alpha$. Then, we introduce the set of new variables (and parameters)

$$\tilde{u} = \sqrt{\alpha} u, \qquad \tilde{v} = \sqrt{\alpha} v, \qquad \tilde{w} = b_e w, \qquad \tilde{\mu}_b = \sqrt{\alpha}\mu_b,$$

$$\tilde{m_1} = \sqrt{\alpha} m_1, \qquad \tilde{m_2} = \sqrt{\alpha} m_2, \qquad \tilde{m_3} = b_e m_3,$$

which, once substituted back in equations (3.5)-(3.7), yields the fully reduced system

$$\partial_t \tilde{u} = -\mu_f \tilde{u} + \tilde{m}_1 \frac{\tilde{u}\tilde{v}}{1 + \tilde{u}\tilde{v}} - \tilde{\mu}_b \tilde{u}\tilde{v}, \tag{3.8}$$

$$\partial_t \tilde{v} = \varepsilon d_1 \partial_x^2 \tilde{v} - \mu_l \tilde{v} + \tilde{m}_2 \frac{\tilde{u}\tilde{v}}{1 + \tilde{u}\tilde{v}} - \tilde{\mu}_b \tilde{u}\tilde{v} - \tilde{v}\tilde{w}, \tag{3.9}$$

$$\partial_t \tilde{w} = \varepsilon d_2 \partial_x^2 \tilde{w} - \mu_e \tilde{w} + \tilde{m}_3 \frac{\tilde{u}\tilde{v}}{1 + \tilde{u}\tilde{v}}. \tag{3.10}$$

For the sake of readability, we drop the $\sim$ notation in the future and let $\boldsymbol{f} = (f, g, h)$ denote the kinetic part of system (3.8)-(3.10), i.e.:

$$f(u, v, w) = -\mu_f u + m_1 \frac{uv}{1 + uv} - \mu_b uv, \tag{3.11}$$

$$g(u, v, w) = -\mu_l v + m_2 \frac{uv}{1 + uv} - \mu_b uv - vw, \tag{3.12}$$

$$h(u, v, w) = -\mu_e w + m_3 \frac{uv}{1 + uv}. \tag{3.13}$$

This is the model we seek to investigate in this thesis. In coming sections, we prove that there exists solutions to the system for an arbitrary time $t > 0$. A soon as existence

of solutions is past us, we focus on the steady-states of the system based on the choice of parameters and perform a bifuraction analysis with respect to μ_b. Finally, we focus on the linear stability using tools developed in section (**??**) and move on to simulations.

3.3 Existence of solutions

In this section, we prove the global existence of solutions to system (3.8)-(3.10) using the theory established by Smoller in [15]. In this direction, we introduce the notion of invariant regions, invariant rectangles and $\boldsymbol{\phi}$-stability together with a few theorems that we use to reach our result. We already know from (theorem 14.4, [15]) that there exists local solutions to system (3.8)-(3.10) defined on a short interval $[0, \delta)$. Therefore, let us extend these local solutions to global solutions of the reaction-diffusion problem. First, we need

Definition 4 (Invariant region, [15])**.** *A closed subset $\Sigma \subset \mathbb{R}^n$ is called a (positively) invariant region for the local solution defined by*

$$\partial_t \boldsymbol{v} = \varepsilon D \partial_x^2 \boldsymbol{v} + M \partial_x v + \boldsymbol{\phi}(v, t), \tag{3.14}$$

$$\boldsymbol{v}(x, 0) = v_0(x) \quad x \in \Omega,$$

if any solution $\boldsymbol{v}(x, t)$ having all of its boundary and initial values in Σ, satisfies $\boldsymbol{v}(x, t) \in \Sigma$ for all $x \in \Omega$ and for all $t \in [0, \delta)$.

Notice that this results works for a more general class of equations than ours. Indeed, here, $\varepsilon = 1$, D is a diagonal matrix with constant positive entries, $M = 0$ and $\boldsymbol{\phi}$ is independent of time (system is autonomous). As far as we are concerned, all regions of interest can be described by the intersection of $(n-1)$-dimensional hypersurfaces

$$\Sigma = \bigcap_{i \in \mathcal{I}} \{G_i \leqslant 0\}, \tag{3.15}$$

where $G_i = G_i(u, v, w)$ are smooth, real-valued function defined on $\mathrm{Dom}(G_i) \supset \mathrm{im}(\boldsymbol{u})$ such that ∇G_i never vanishes for all $i \in \mathcal{I}$. In the special case where Σ is invariant and generated by affine constraints ($G_i(\boldsymbol{v}) = \boldsymbol{v} - \alpha$, for some $\alpha \in \mathbb{R}$), Σ is referred to as invariant rectangle. We also introduce

Definition 5 ($\boldsymbol{\phi}-$stability [15])**.** *A system of the form*

$$\partial_t \boldsymbol{v} = D \partial_x^2 \boldsymbol{v} + \boldsymbol{\phi}(v), \tag{3.16}$$

is said to be $\boldsymbol{\phi}-$stable if, whenever $\boldsymbol{\phi}$ is the limit of functions $\boldsymbol{\phi}_n$ in the $\mathcal{C}^1-$topology on compacta, for all $t > 0$ then any solution of 3.16 supplemented with initial condition is the limit in the compact-open topology, of solutions of 3.16, where $\boldsymbol{\phi}$ is replaced by $\boldsymbol{\phi}_n$

Once again, taking into account the fact that our nonlinearities $\boldsymbol{f}$ are smooth, this general "regularity" statement allows us to use a stronger theorem with less points to verify in order to get global existence. The theorem is the following

Theorem 2 (Conditions for invariance, [15])**.** *Let Σ be defined as in (3.15), and consider the system 3.14 with $M = 0$, D positive definite and $\boldsymbol{\phi} = \boldsymbol{\phi}(\boldsymbol{v}, t)$. Suppose that this system is $\boldsymbol{\phi}$-stable. Then Σ is a positively invariant region for 3.14) for fixed $\varepsilon > 0$ if and only if the following hold at each boundary point $\boldsymbol{v}_0$ of Σ (so $G_i(\boldsymbol{v}_0) = 0$):*

a) *∇G_i is a left eigenvector of D*

b) *G_i is quasi-convex at $\boldsymbol{v}_0$*

c) *$\nabla G_i(\boldsymbol{\phi}) \leqslant 0$*

Proof. See theorem 14.3 from [15]. □

Next, we will show that system (3.8)-(3.10) has an invariant rectangle Σ. One shows that it is$\boldsymbol{f}$-stable and our choice of constraints will always satisfy property **a)** from theorem 2. The reason why is because we choose G_i such that ∇G_i is constant and has only one non-zero component. Therefore ∇G_i will be a left eigenvector of D with eigenvalue d_j where d_j is the j-th diagonal entry of D and j is the index where ∇G_i is non-zero (notice that 0 can be an eigenvalue in our case). Since each G_i is an affine constraint, it is naturally quasi-convex and it is therefore only left to verify **c)** to obtain the wanted result.

Proposition 1 (Existence of an invariant rectangle)**.** *There exists three positive reals A_u, A_v, A_w such that the region*

$$\Sigma = \big\{(u, v, w) : 0 \leqslant u \leqslant A_u, \quad 0 \leqslant v \leqslant A_v, \quad 0 \leqslant w \leqslant A_w, \big\},$$

is an invariant rectangle of system (3.8)-(3.10)

Proof. We start by writing

$$\Sigma = \Sigma_0 \cap \Sigma_A =: \bigcap_i \Bigg(\underbrace{\{G_\kappa \leqslant 0\}}_{\Sigma_0} \cap \underbrace{\{H_\kappa \leqslant 0\}}_{\Sigma_A} \Bigg), \qquad \kappa = u, v, w.$$

The rectangular region where each G_i and H_i are prescribing the constraints on Σ defined as follows

$$G_u(u,v,w) = -u \qquad H_u(u,v,w) = u - A_u$$

$$G_v(u,v,w) = -v \qquad H_v(u,v,w) = v - A_v$$

$$G_w(u,v,w) = -w \qquad H_w(u,v,w) = w - A_w$$

Each G_i and H_i is obviously smooth. Now let

$$\partial\Sigma := \left\{(u,v,w) \in \Sigma : \exists i, \quad G_i(u,v,w) = 0 \quad \text{or} \quad H_i(u,v,w) = 0\right\},$$

be the boundary of Σ, we consider a point $(u,v,w) \in \partial\Sigma$ and proceed case-by-base. Let X denote such a point and $\phi_{\boldsymbol{f}}$, the vector field generated by $\boldsymbol{f}$. If $u = 0$, then

$$(\nabla G_u \cdot \phi_{\boldsymbol{f}})(X)\big|_{u=0} = u\left(\mu_f + \mu_b v - m_1 \frac{v}{1+uv}\right)\Bigg|_{u=0} = 0.$$

The case $v = 0$ is similar in a way that

$$(\nabla G_v \cdot \phi_{\boldsymbol{f}})(X)\big|_{v=0} = v\left(\mu_l + \mu_b u + w - m_2 \frac{u}{1+uv}\right)\Bigg|_{v=0} = 0.$$

Finally, since $X \in \partial\Sigma_0$, it holds that $u, v \geqslant 0$, meaning that if $w = 0$, then

$$(\nabla G_w \cdot \phi_{\boldsymbol{f}})(X)\big|_{w=0} = -m_3 \frac{uv}{1+uv} < 0.$$

We proceed in similar fashion to take care of $\partial\Sigma_A$. First, we notice that

$$\begin{aligned} f(u,v,w) &= -\mu_f u + m_1 \frac{uv}{1+uv} - \mu_b uv \\ &\leqslant m_1 - \min(\mu_f, \mu_b) u(1+v). \end{aligned}$$

Using the fact that $X \in \Sigma$, we deduce $1 + v \geqslant 1$ and therefore we get rid of it in the product, leaving us with

$$f(u,v,w) \leqslant m_1 - \min(\mu_f, \mu_b) u.$$

In other words, we can find $A_u \in \mathbb{R}_{>0}$ satisfying $A_u > m_1/\min(\mu_f, \mu_b)$. This implies $(\nabla H_u \cdot \phi_{\boldsymbol{f}})(X)|_{u=A_u} = f(A_u, v, w) \leqslant 0$. The same logic applies to show

$$g(u,v,w) \leqslant m_2 - \min(\mu_f, \mu_b, 1) v.$$

Thus, by picking $A_v \geqslant m_2/\min(\mu_f, \mu_b, 1)$, we get $(\nabla H_v \cdot \phi_{\boldsymbol{f}})(X)|_{v=A_v} \leqslant 0$. Finally, we show that

$$h(u, v, w) \leqslant m_3 - \mu_e w,$$

and take $A_w \geqslant m_3/\mu_e$ to obtain $(\nabla H_w \cdot \phi_{\boldsymbol{f}})(X)|_{w=A_w} \leqslant 0$. This concludes the proof. □

-

We have thus proved the existence of an invariant rectangle. We finally use theorem 14.9, [15] to deduce the existence of the solution to (3.8)-(3.10) for all $t > 0$ provided we take initial data u_0 continuous, bounded with values $u_0(x) \in \Sigma$ for $x \in \Omega$. This results can be extended to bounded initial conditions $u_0 \in L^\infty(\Omega)$, but these proofs and tools are out of the scope of this thesis. Knowing we are now capable of guarantying the existence of a global solution under reasonable assumptions on our model, we can move to the analysis of steady-states.

3.4 Finding equilibria and bounds on parameters

We recall that a *steady state* of the system is a solution to the PDE, satisfying boundary conditions that does not depend on time, resulting in a vanishing time-derivative in equations. E.g., calling $\boldsymbol{\psi}$ a steady state of (3.8)-(3.10), it holds

$$0 = \partial_x^2 \boldsymbol{\psi} + \boldsymbol{f}(\boldsymbol{\psi}), \qquad \partial_x \boldsymbol{\psi}(0) = \partial_x \boldsymbol{\psi}(1) = 0.$$

By the look of things, an analytical derivation of all steady-states of this system seems a little bit too optimistic. That being said, one can look at *constant steady-states* $\bar{\boldsymbol{u}} = (\bar{u}, \bar{v}, \bar{w})$ with $\bar{u}, \bar{v}, \bar{w} \in \mathbb{R}$. Proceeding as such leads to the term $\partial_x^2 \bar{\boldsymbol{u}}$ vanishing, the problem reformulates into a less daunting one: finding a triplet of reals $\bar{\boldsymbol{u}}$ such that

$$\boldsymbol{f}(\bar{\boldsymbol{u}}) = 0.$$

Since we proved in the last section that solutions with positive initial values will stay positive for all time $t > 0$, we are only interested in *positive* equlibria of the system. Depending on the choice of parameters, one shows that there is either one (stable), two (stable-unstable) or three (stable-unstable-stable) such steady-states. In each scenario, the origin $(0, 0, 0)$ is a stable equilibrium point . For a specific range of parameters, another stable, positive equilibrium arises whose value turns out to be one of the roots of some third-order polynomial. To build geometrical intuition, the reader can see constant steady states as the intersection points of 3 hypersurfaces (see 3.4) algebraically described by the reaction term, i.e.,

$$\text{Steady states} = \left\{ \boldsymbol{x} \in \mathbb{R}^3 : \bigcap_{\kappa=f,g,h} \{\kappa(\boldsymbol{x}) = 0\} \right\}.$$

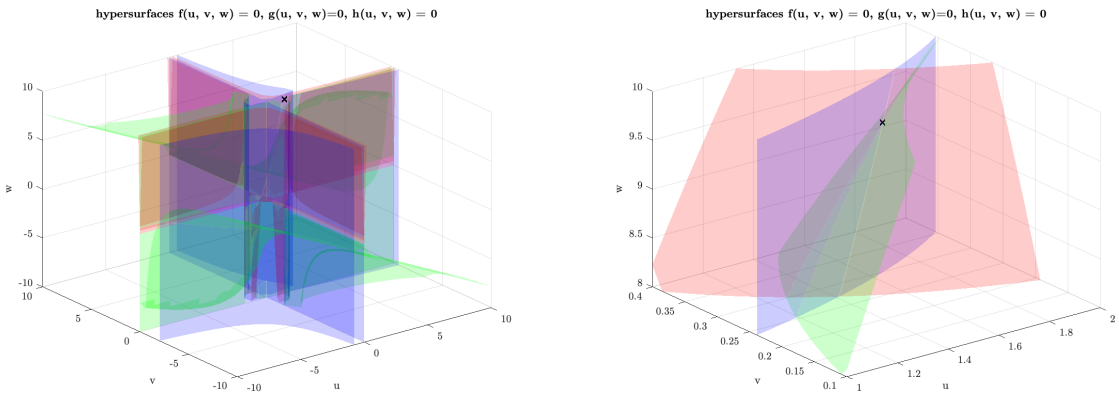

Figure 6: Three-dimensional plot of the algebraic hypersurfaces associated to equations $f \equiv 0$ (blue), $g \equiv 0$ (green) and $h \equiv 0$ (red). The choice of parameters $\mu_f = 0.87, \mu_b = 0.68, \mu_l = 0.05, \mu_e = 0.60, m_1 = 5.36, m2 = 9.68, m3 = 17.27$ is made so that three steady-states exist. The figure on the left-hand panel is plotted over the domain $[-10, 10]^3$ while the right-hand panel plotted in a neighborhood of the non-zero stable steady-state.

3.4.1 Analytical expression of constant steady-states

The strategy here is to first find, if any, functions $\mathcal{H}$ and $\mathcal{G}$ such that $\bar{u} = \mathcal{H}(\bar{v})$ and $\bar{w} = \mathcal{G}(\bar{v})$ and then derive a condition on $\bar{v}$ to conclude. We formulate

Proposition 2 (Constant stationary solutions)**.** *Let $\bar{\boldsymbol{u}} = (\bar{u}, \bar{v}, \bar{w})$ be a constant steady-state of (3.8)-(3.10). Then, either $(\bar{u}, \bar{v}, \bar{w}) = (0, 0, 0)$ or $\bar{u} = \mathcal{H}(\bar{v}), \bar{w} = \mathcal{G}(\bar{v})$ and all possible values of $\bar{v}$ are given by the roots of $\mathcal{P}$ where*

$$\mathcal{H}(x) = \frac{m_1}{\mu_f + \mu_b x} - \frac{1}{x}, \qquad \mathcal{G}(x) = \frac{m_3}{\mu_e}\left(1 - \frac{\mu_f + \mu_b}{m_1 x}\right)$$

and $\mathcal{P}$ is given by

$$\begin{aligned}\mathcal{P}(x) = &\left(-\mu_l\mu_b - \frac{m_3\mu_b}{\mu_e} + \frac{m_3\mu_b^2}{m_1\mu_e}\right)x^3 \\ &+ \left(-\mu_l\mu_f + m_2\mu_b - \frac{m_2\mu_b^2}{m_1} + \mu_b^2 - m_1\mu_b - \frac{m_3\mu_f}{\mu_e} + \frac{2\mu_f\mu_b m_3}{\mu_e m_1}\right)x^2 \\ &+ \left(m_2\mu_f - \frac{2\mu_f\mu_b m_2}{m_1} + \mu_f\mu_b + \frac{m_3\mu_f^2}{\mu_e m_1}\right)x - \frac{m_2\mu_f^2}{m_1}. \quad (3.17)\end{aligned}$$

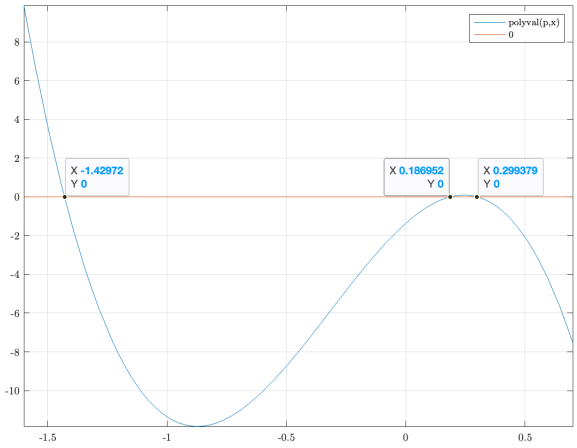

Figure 7: Roots of $\mathcal{P}$ for $\mu_f = 0.87$, $\mu_b = 0.68$, $\mu_l = 0.05$, $\mu_e = 0.60$, $m_1 = 5.36$, $m2 = 9.68$, $m3 = 17.27$ (same parameters as in figure (3.4))

Proof. The proof consists of straightforward computations that are carried out in details in appendix [NOM APPENDIX]. □

While this is quite a ludicrous task to achieve, one could derive the exact analytical expression for spatially homogeneous stationary solutions of (3.8)-(3.10) using the cubic formula and by differentiating cases with positive (negative) discriminant to toss away imaginary roots. An important thing to notice is that some choices of parameters will lead $\mathcal{P}$ to have roots v such that one coordinate of $\bar{\boldsymbol{u}}$ is negative, or complex-valued. Since we always choose an initial condition $\boldsymbol{u}_0 > 0$, this is contradictory with the results proven in the last section. When this happens, it is an indicator that the system will converge towards the origin instead of another steady-state. maybe try to find parameters such that only one root is positive and two are complex-conjugate, e.g. $(r_1, r_2, r_3) = (3, 1+i, 1-i)$ such that $\mathcal{H}(r_1), \mathcal{G}(r_1) > 0$ to see if it is possible to get another steady state that is not the origin.

Example 1 (Numerical computations of the roots)**.** *In MATLAB, we implement the polynomial $\mathcal{P}$ as well as $\mathcal{G}$ and $\mathcal{H}$. We then use the function* `roots` *to find all eventual steady states (see figure (1)). Using the exact values returned by the machine, we find four steady-states*

$$\bar{\boldsymbol{u}}_3 = (0,0,0), \quad \bar{\boldsymbol{u}}_2 = (-51.6587, -1.4300, 28.3989)$$

$$\bar{\boldsymbol{u}}_3 = (1.6527, 0.2994, 9.5284), \quad \bar{\boldsymbol{u}}_4 = (0.0138, 0.1864, 0.0739)$$

As previously mentioned, we can rule out $\bar{\boldsymbol{u}}_2$ because it has at least one negative coordinate. From there, using the Jacobian (computed in the next section) we can deduce the nature of $\bar{\boldsymbol{u}}_1, \bar{\boldsymbol{u}}_3, \bar{\boldsymbol{u}}_4$ and it reveals that the origin and $\bar{\boldsymbol{u}}_3$ are stable while $\bar{\boldsymbol{u}}_4$ is unstable.

3.4.2 Snack break: finding bounds on asymptotically stable spatially homogeneous stationary solutions

Assuming we know the values of the non-zero steady-state $\bar{u}, \bar{v}, \bar{w}$, one can use $f(\bar{\boldsymbol{u}}) = g(\bar{\boldsymbol{u}}) = h(\bar{\boldsymbol{u}})$ to derive a lower bound for each quantity.

Proposition 3 (Lower bounds on $\boldsymbol{u}$.)**.** *Assume the parameters $m_1, m_2 > \mu_b$ and that $\bar{u}, \bar{v}, \bar{w} > 0$. Then*

$$\bar{u} > \frac{\mu_f}{m_1 - \mu_b}, \qquad \bar{v} > \frac{\mu_l}{m_2 - \mu_b}, \qquad w > \frac{m_3}{\mu_e}$$

Proof. We drop the $\bar{\cdot}$ (bar) notation for simplicity and start with $f(\boldsymbol{u}) = 0$. Substituting f by its value from the system leads to

$$0 = -\mu_f u + m_1 \frac{uv}{1+uv} - \mu_b uv = u\left(-\mu_f + m_1 \frac{v}{1+uv} - \mu_b v\right).$$

We now use $\bar{u} \neq 0$ and rearrange the left-and-right-hand side.

$$m_1 v = (\mu_f + \mu_b v) \underbrace{(1+uv)}_{>1} > \mu_f + \mu_b v \quad \iff \quad v > \frac{\mu_f}{m_1 - \mu_b}$$

□

3.5 Linear dynamics and local behavior of the system

In order to meet the required conditions for DDI, we first have to make sure system (3.8)-(3.10) is stable in absence of diffusion when computed at a spatially homogeneous steady-state. This translates into saying that the Jacobian matrix $J = J_{\boldsymbol{f}}(u, v, w)$ of $\boldsymbol{f}$ at a steady-state satisfies $s(J) < 0$. A rapid computation shows

$$J = \begin{pmatrix} -\mu_f + \dfrac{m_1 v}{(1+uv)^2} - \mu_b v & \dfrac{m_1 u}{(1+uv)^2} - \mu_b u & 0 \\ \dfrac{m_2 v}{(1+uv)^2} - \mu_b v & -\mu_l + \dfrac{m_2 u}{(1+uv)^2} - \mu_b u - w & -v \\ \dfrac{m_3 v}{(1+uv)^2} & \dfrac{m_3 v}{(1+uv)^2} & -\mu_e \end{pmatrix}.$$

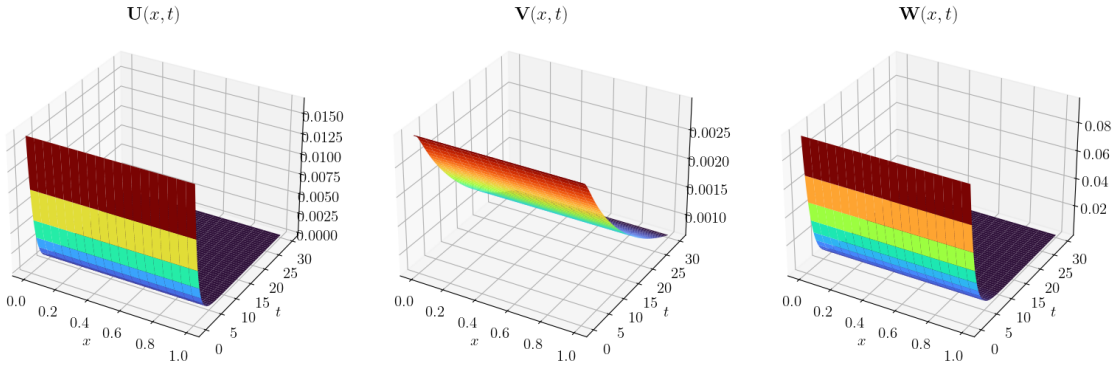

Figure 8: space-time plot of numerical solutions u, v, w to (3.8)-(3.10) with constant initial condition $\boldsymbol{X}_0 = (\boldsymbol{u}_0, \boldsymbol{v}_0, \boldsymbol{w}_0)$ close to the origin. One clearly sees how each quantity converges towards 0

When working around the origin, it is perfectly fine to work with J as it is. However, this form turns out to be rather impractical to work with when carrying out later computations around the other non-zero steady state. As a parry, we will later derive a set of useful equalities that will help us simplify the expression of J.

3.5.1 In a neighborhood of the origin

When taking $(u, v, w) = (0, 0, 0)$, almost all terms in the Jacobian disappear, leaving us with

$$A(0,0,0) = \begin{pmatrix} -\mu_f & 0 & 0 \\ 0 & -\mu_l & 0 \\ 0 & 0 & -\mu_e \end{pmatrix}$$

which, by positivity of μ_f, μ_b, μ_e is unconditionally stable. Take a moment to convince yourself that in this case, there is no hope for DDI (to see why, notice that $\text{tr}(A - \boldsymbol{\mu}D) < 0$ and $\det(A - \boldsymbol{\mu}D) = -\mu_f(\mu_l + \boldsymbol{\mu}/\gamma)(\mu_e + \boldsymbol{\mu}d_2/\gamma) < 0$ for all non-negative choices of $\boldsymbol{\mu}$). This tells us the system will always be stable, a statement that is corroborated by running a few simulations (see figure 8).

3.5.2 Around the other steady state

For the entirety of this part, we assume the steady state to be non-trivial (which, otherwise, would compromise most computations we carry on). Let us move our interest to the other stable steady state provided the choice of parameters allows it. Using the fact that each term u, v, w is positive, we can derive the following equalities from $f(u,v,w) = g(u,v,w) = h(u,v,w) = 0$

$$m_1 \frac{v}{1+uv} = \mu_f + \mu_b v \qquad m_2 \frac{u}{1+uv} = \mu_l + \mu_b u + w \qquad m_3 \frac{uv}{1+uv} = \mu_e w \tag{3.18}$$

Theorem 3 (Routh-Hurwitz criterion of order 3)**.** *Take a matrix $M \in \mathcal{M}_3(\mathbb{R})$. Then all the roots of χ_M lie in the negative half-plane (i.e. $\sigma(M) \subset \mathbb{R}_{<0}$) if and only if $\Delta_i(M) > 0$ for $i = 1, 2, 3$ holds, where we define*

$$\Delta_1(M) = -\mathrm{tr}(M)$$

$$\Delta_2(M) = -\mathrm{tr}(M) \sum_{i<j} \det(M_{ij}) + \det(M)$$

$$\Delta_3(M) = -\det(M)\Delta_2(M),$$

Alternatively, let $\tilde{\chi}_M(\lambda) = a_0 + a_1\lambda + a_2\lambda^2 + \lambda^3$ be the normalized characteristic polynomial of M. Then all roots of $\tilde{\chi}_M$ lie in the negative half-plane if and only if all coefficients are positive and $a_2 a_1 > a_0$.

Definition 6 (Submatrices defined by a pair of indices)**.** *Consider a matrix $A \in \mathcal{M}_n(\mathbb{R})$, for any couple of distinct indices (i,j) with $1 \leqslant i, j \leqslant n$, we introduce the notation A_{ij} to be the 2×2-matrix whose entries are formed by the entries of A on line and column i, j.*

Proposition 4 (Characteristic polynomial of a 3×3 matrix)**.** *Consider a matrix $A \in \mathcal{M}_3(\mathbb{R})$ whose entries are the a_{ij} for $1 \leqslant i, j \leqslant 3$. Then*

$$\chi_A(\lambda) = -\lambda^3 + \mathrm{tr}(A)\lambda^2 - \left(\sum_{i<j} \det(A_{ij})\right)\lambda + \det(A)$$

.

Lemma 1 (Necessary condition for DDI)**.** *Let $B := A - \lambda D$ denote the matrix of the linearized system. We claim that we can obtain DDI if and only if $\det(B_{12}) < 0$ and*

Remark 3 (Minimum)**.** *The function* $\mu \longmapsto |J-\mu D|$ *reaches its minimum at the point:*

$$\mu_{\min} = \frac{\gamma}{2}\left(\frac{1}{(1+uv)^2}\left(m_2 u - \frac{m_1 m_2 uv + \mu_b^2 uv(1+uv)^4 - \mu_b(m_1+m_2)uv(1+uv)^2}{m_1 v - \mu_f(1+uv)^2 - \mu_b v(1+uv)^2}\right) - \frac{\mu_e}{d_2} - \mu_l - \mu_b u - w\right)$$

Please do not make me compute $\det(A-\mu_{min}D)$ *;-;. Also*

$$\mu_{\min} > 0 \quad \Longleftrightarrow \quad \mu_f\left(m_2 - \mu_b u(1+uv)^2\right) > \left(\frac{\mu_e}{d_2} + \mu_l + w\right)\left(m_1 v - \mu_f(1+uv)^2 - \mu_b v(1+uv)^2\right)$$

$$\frac{|A_{12}| + |A_{13}|d_2}{2a_{11}d_2}$$

$$\bar{u}\bar{v} > \frac{\mu_l \mu_f}{(m_1-\mu_b)(m_2-\mu_b)} > 1(1)$$

$$|J_{12}| = A - (1-u^2v^2)B > 0 \quad \text{if}(1)$$

A Mathematical material

A.1 Deriving reaction-diffusion equations

In this section we seek to derive reaction-diffusion equations from scratch based on famous physical principles. We assume to have enough regularity for each quantity in order to carry out the computations. This derivation has for purpose to give the reader a physical intuition behind such equations. To this end, we first introduce the following divergence theorem

Theorem 4 (Gauss-Green theorem)**.** *Consider a bounded domain $\Omega \subset \mathbb{R}^d$, enclosed by the surface $\Gamma := \partial\Omega \subset \mathbb{R}^{d-1}$. Let $\boldsymbol{F}$ be an arbitrary smooth vector field and an application ν such that for all $\xi \in S$, $\nu(\xi)$ is the outward-pointing unit vector of S at ξ. Finally, if dA denotes the measure $dx_1...dx_d$ and ds is the surface measure on Γ, then the following equality holds*

$$\int_\Gamma (\boldsymbol{F} \cdot \nu)\, ds = \int_\Omega \nabla \cdot (\boldsymbol{F})\, dA.$$

Proof. Various well-known proofs exist in the literature (see [6] for the original derivation by G. Green) □

We are all set, let us proceed. General laws of conservation tell us that if u denotes a physical quantity (heat, amount of cells, gene expression, ...), then

$$\underbrace{\frac{\partial}{\partial t}\int_\Omega u d\Omega}_{\text{amount of material in } \Omega} = \underbrace{D\int_\Gamma (\nabla u \cdot \nu)\, d\Gamma}_{\text{flux of material crossing } \Gamma} + \underbrace{\int_\Omega f(u) d\Omega}_{\text{material created inside}\Omega} .$$

Where we obtained the diffusive flux of material crossing Γ using Fick's law. Now using the divergence theorem on the second integral yields

$$\int_\Omega \frac{\partial u}{\partial t} d\Omega = \int_\Omega D\nabla \cdot (\nabla u)\, d\Omega + \int_\Omega f(u) d\Omega.$$

After reordering the terms, we put everyone under the same integral and find

$$\int_\Omega \left(\frac{\partial u}{\partial t}(x,t) - D\Delta u(x,t) - f(u(x,t)) \right) d\Omega = 0.$$

Each term being integrated on an arbitrary Ω with size $\mu(\Omega) > 0$, we deduce that what is under the integral must vanish. i.e.,

$$\frac{\partial u}{\partial t}(x,t) = D\Delta u(x,t) + f(x,t) \tag{A.1}$$

Appropriate boundary conditions are to be chosen accordingly to the nature of the studied problem. As far as we are concerned, homogeneous Neumann (or *zero-flux*) boundary conditions will be considered

A.2 Rigorous convergence of the quasi-static approximation

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References

[1] Atsushi Anma, Kunimochi Sakamoto, and Tohru Yoneda. "Unstable subsystems cause Turing instability". In: *Kodai Mathematical Journal* 35.2 (June 2012). DOI: 10.2996/kmj/1341401049. URL: https://doi.org/10.2996/kmj/1341401049.

[2] Wolfgang Arendt and Günther Greiner. "The spectral mapping theorem for one-parameter groups of positive operators on Co(X)". In: *Semigroup Forum* 30.1 (Dec. 1984), pp. 297–330. DOI: 10.1007/bf02573461. URL: https://doi.org/10.1007/bf02573461.

[3] Szymon Cygan et al. "Instability of all regular stationary solutions to reaction-diffusion-ODE systems". In: *Journal of Differential Equations* 337 (Nov. 2022), pp. 460–482. DOI: 10.1016/j.jde.2022.08.007. URL: https://doi.org/10.1016/j.jde.2022.08.007.

[4] Klaus-Jochen Engel and Rainer Nagel. *One-parameter semigroups for linear evolution equations*. en. 2000th ed. Graduate Texts in Mathematics. New York, NY: Springer, Dec. 2000.

[5] Surendra Ghaskadbi. "Hydra: A Powerful Biological Model". In: *Resonance* 25.9 (Sept. 2020), pp. 1197–1213. DOI: 10.1007/s12045-020-1039-2. URL: https://doi.org/10.1007/s12045-020-1039-2.

[6] George Green. *An Essay on the Application of mathematical Analysis to the theories of Electricity and Magnetism*. 2008. DOI: 10.48550/ARXIV.0807.0088. URL: https://arxiv.org/abs/0807.0088.

[7] Chris Kowall, Anna Marciniak-Czochra, and Finn Münnich. *Stability Results for Bounded Stationary Solutions of Reaction-Diffusion-ODE Systems*. 2022. DOI: 10.48550/ARXIV.2201.12748. URL: https://arxiv.org/abs/2201.12748.

[8] Sagar Aryal Laxmi Neupane. *Hydra- Reproduction (Budding and Sexual), Regeneration, Immortality*. https://thebiologynotes.com/hydra-reproduction-regeneration/. [Online; accessed 15-April 2023]. 2022.

[9] A. Lepschy, G.A. Mian, and U. Viaro. "A Geometrical Interpretation of the Routh Test". In: *Journal of the Franklin Institute* 325.6 (Jan. 1988), pp. 695–703. DOI: 10.1016/0016-0032(88)90003-8. URL: https://doi.org/10.1016/0016-0032(88)90003-8.

[10] Anna Marciniak-Czochra. "Developmental models with cell surface receptor densities defining morphological position". In: (2004). DOI: 10.11588/HEIDOK.00004549. URL: http://archiv.ub.uni-heidelberg.de/volltextserver/id/eprint/4549.

[11] James D Murray. *Mathematical biology*. en. 1st ed. Biomathematics. Berlin, Germany: Springer, Nov. 1990.

[12] Amnon Pazy. *Semigroups of linear operators and applications to partial differential equations*. en. 1983rd ed. Applied mathematical sciences. New York, NY: Springer, Dec. 2012.

[13] Benoit Perthame. *Parabolic Equations in Biology*. Springer International Publishing, 2015. DOI: 10.1007/978-3-319-19500-1. URL: https://doi.org/10.1007/978-3-319-19500-1.

[14] Peter Philip. *Ordinary differential equations - LMU*. Sept. 2022. URL: https://www.mathematik.uni-muenchen.de/~philip/publications/lectureNotes/philipPeter_ODE.pdf.

[15] Joel Smoller. *Shock Waves and Reaction—Diffusion Equations*. Springer New York, 1994. DOI: 10.1007/978-1-4612-0873-0. URL: https://doi.org/10.1007/978-1-4612-0873-0.

[16] "The chemical basis of morphogenesis". In: *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences* 237.641 (Aug. 1952), pp. 37–72. DOI: 10.1098/rstb.1952.0012. URL: https://doi.org/10.1098/rstb.1952.0012.