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Pattern formation in reaction-diffusion-ODE models with two diffusing components

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1. Introduction and biological motivations

The classical approach to pattern formation modelling, in particular the phenomena of the symmetry breaking and *de novo* pattern formation, is based on the search for system components whose interactions correspond to Turing-type models, *i.e.* they contain two diffusing components with sufficiently different diffusion coefficients and follow an appropriate scheme of interactions such as, *e.g.*, the activator, inhibitor interaction from the Gierer-Meinhardt model[1].

Often, the identification of such molecular substances does not succeed, as was the case in research on Hydra patterning, where for two decades an inhibitor for the Wnt signalling pathway fulfilling the assumptions of the Gierer-Meinhardt model has been sought to explain spontaneous symmetry breaking and pattern formation within this signalling pathway. This motivates research on an alternative mechanisms for pattern formation in Hydra, in parallel to mathematical modelling and analysis of the Wnt signalling pathway.

One mechanism that has been proposed is based on mechano-chemical interactions in the tissue, [14]. Another concept proposes to focus on taking into account the coupling of intercellular communication via diffusing substances coupled to non-linear interactions within or on the cell surface [ref]. The latter, leads to coupling of reaction-diffusion equations describing cell-to-cell communication with space-dependent ordinary equations describing cell-localised processes.

Such models may exhibit a range of unexpected phenomena such as emergence of patterns with jump discontinuity [ref] and DDI-induced finite- or inifinite-time mass concentration [ref]. So far reaction-diffusion-ODE systems and their ability for pattern formation have been systematically studied only in the case of coupling a scalar reaction-diffusion equation to a scalar or a system of ODEs. Comprehensive analytical results on the stablility of such systems can be found in [ref].

The aim of this project is to investigate the role of a second diffiusive component. To streamline the analysis, we focus on a system coupling a scalar ODE with two reaction-diffusion equations in the special case of the receptor-based model from [AnnaThesis].

2. Organization of thesis

In chapter one, we present the hydra organism together with some key experiments. We then introduce our receptor-based model with an approach similar to compartmental modelling. In a third section, we talk about the quasi steady-state approximation method, with a direct application on our model's equations. And finally, we proceed to rescale the model in order to reduce the amount of parameters.

Chapter two is dedicated to proving analytical properties of this model. We start by showing the existence of local, solutions using some classical results from the theory of semigroup of operators and the notion of mild-solutions. Once local-in-time existence of

[1] This model, introduced in 1972, is one of the first to describe the regulation of concentrations between a short-range autocatalytic substance and its long-range antagonist with partial differential equations (reaction-diffusion system). See `http://www.scholarpedia.org/article/Gierer-Meinhardt_model`

solutions is shown, we extend them into global solutions using the framework of invariant regions that provide L^∞ estimates for all times. A last, short, section is dedicated to a first analysis of steady-states of the system.

The fourth and final chapter addresses the notion of Turing Instability or diffusion-driven instability. We will start from the definition of the notion, investigate properties of the system's behavior around steady states, and confidently make our way to the main results of this thesis. We dedicate the last section of this chapter to a direct application of our results with simulations using MATLAB.

3. Acknowledgements

I would like to express my deepest gratitude to my supervisor, Anna Marciniak-Czochra. Her understanding, patience and help has enabled me to evolve in a free and happy atmosphere throughout this journey. Her exceptional background and dedication provided me the knowledge to complete this thesis from knowing almost nothing about the field of reaction-diffusion equations.

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Lastly, I would like to thank my parents and my sister for their love and unwavering support in every situation.

CHAPTER 1

Modelling pattern formation

We start by briefly presenting an example of a biological model of symmetry breaking and pattern formation that motivates the search for new pattern formation mechanisms and the study of toy models that allow us to understand the fundamental features of specific pattern formation mechanisms. One of the oldest basic experimental models of developmental pattern formation is Hydra.

1. An overview of 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 .

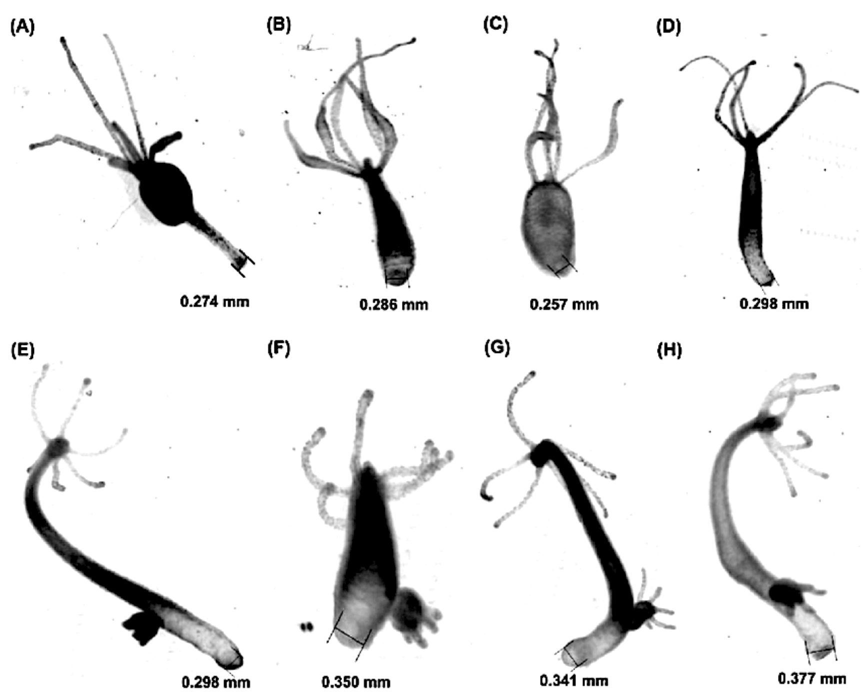


FIGURE 1. Zoo of hydras captured under a traditional microscope, all the credit for this figure goes to [9]

The body of hydras is composed of essentially three regions[1]: the head, the body-column and the foot. From a spatial point of view, the small cnidarian is symmetrically organized around an oral-aboral axis in a hollow, tubular shape.

1.1. Experimental evidence for pattern formation. Regeneration properties of hydra have been known since the work of Trembley. Cutting experiments at different position showed that cells of the animal are capable of reconstituting the missing structure according to their position. The regeneration process occurs by morphallaxis (reconstruction of the entire animal from a small fragment by reorganizing existing cells) and still occurs in the famous extreme case where the organism is cut in half. In that case, one part generates a new head, the other, a new foot, resulting in two functional organisms. (see figure [fig])

This shows the ability of the cells at the site of the cut, which were previously body column cells, to differentiate towards head cells but towards foot cells, depending on their relative position on the body axis. However, unlike the mythological hydra from which the polyp got its name, the existing head blocks the formation of an additional head, whose induction requires additional chemical stimulation.

The evidence of the organizer role of the hypostome was shown by Ethel Browne already in [Browne, 1909] through lateral grafting experiments. In other words, these experiments showed that the hypostome is a signalling center, well before the scientific community was aware of how such a center works.

Modern hydra research focuses on the study of molecular regulators of cellular function. In particular, it is known that the organizer centers associated with head formation are determined by the expression of the *Wnt* gene (*Wnt3*), and the position on the body axis can be linked to gradients in Wnt signaling pathway activity.

Another important experiment demonstrating the essence of pattern formation in Hydra is based on the phenomenon of symmetry breaking in cell aggregates obtained from dissociated cells from several organisms. Cells form spatially homogeneous spheroids, which then develop into new organisms, the formation of which begins with the formation of *Wnt* expression patterns.

1.2. Activator-inhibitor model. Both cutting and aggregates experiments suggest *de novo* pattern formation, which motivates the search for system components whose interactions and spatial communication would lead to the Turing pattern formation mechanism. Such an abstract model for Hydra was proposed by Gierer and Meinhardt in 1972 and is known as the activator-inhibitor model.

The model describes the relation of an activator molecule (a) produced with at a nonlinear rate a^2. Activator production is slowed down by its antagonist inhibitor (h), what is modelled by a Hill function $1/(h+1)$ (or just by $1/h$). Both molecules are subject to natural decay, scaled by parameters μ and ν, and the cell-to-cell transport of molecules

[1] We omit the budding area which is involved in the asexual reproduction process, see `https://www.youtube.com/watch?v=d5-hPkcQDrU`

(molecular diffusion) is modelled by the Laplace operator. The difference in diffusion rates of activators and inhibitors is represented by D_a, D_h. To avoid invasion of activators, inhibitors have to diffuse faster, which is achieved with the condition $D_a \ll D_h$. Put together, this yields the following system of equations:

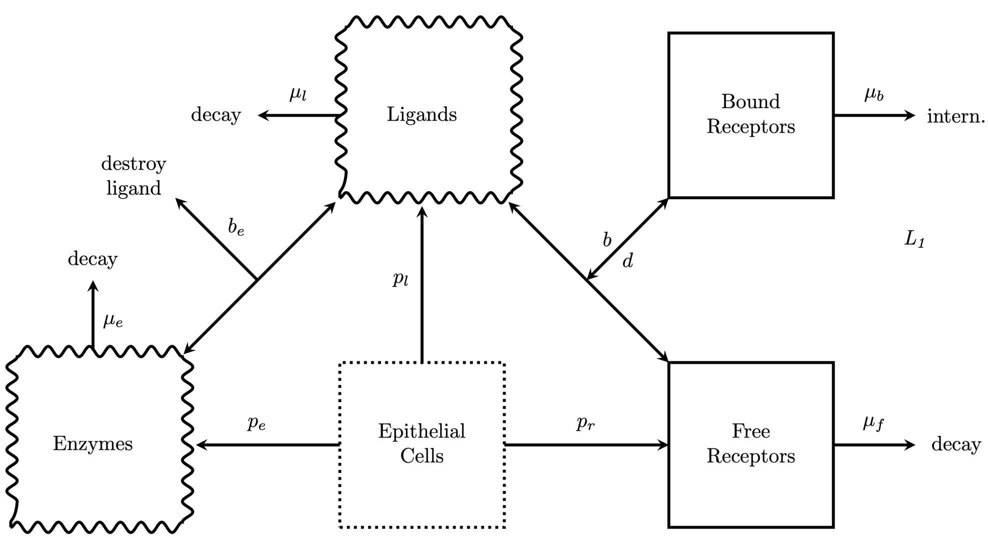
$$\text{(G-M)} \qquad \begin{cases} \partial_t a = D_a \Delta a + \varrho \left(\frac{a^2}{1+h} - \mu a \right) \\ \partial_t h = D_h \Delta h + \varrho \left(a^2 - \nu h \right) \end{cases}$$

This model is famous for the rich diversity of patterns it exhibits and its capacity to replicate real-life patterns such as the skin of the discus (small fish), the coat of a zebra, or even the mix of stripes and spots on a leopard's tail. For its wide range of applications, the Gierer-Meinhard model is considered a major turning point in the history of morphogenesis modelling.

While the activator-inhibitor model can explain a number of regenerative experiments, it does not explain observations at the molecular level, in particular within the *Wnt* signaling pathway. While *Wnt3* could be linked to an activator due to the self-enhancing function of the canonical *Wnt* signaling, a component of this signaling pathway that could explain the inhibitor's action in the activator-inhibitor model has not been identified so far. More precisely, no known *Wnt* inhibitor meets the assumptions of the model allowing to describe the pattern formation mechanism.

2. Receptor-based models for pattern formation

Receptor-based models is a class of models that are developped under the assumption that the positional value of a cell is determined by the density of cell-surface receptors, which regulate the expression of genes responsible for cell differentiation. Our journey begins with an example of such models and can be schematically represented by the following diagram:



We use the convention that each box drawn with a continuous stroke represents one of the quantities studied in model (free receptors r_f, bound receptors r_b, ligands ℓ, and enzymes e). Interactions between components are signaled by a directed arrow, and the nature of each interaction is described by the function or rate attached to associated arrow.

Each quantity of the system is subject to natural decay, which occurs at a rate depending on the quantity. Epithelial cells behave as a source, producing ligands and free receptors at a certain production rate but whose dynamic is outside the scope of our study (just like a battery, we know it generates power but do not care about how it is generated inside the battery). A box with squiggles indicates that the quantity is diffusive, while straight boxes are for non-diffusive components of the system. A further assumption is made, correlating the production rate of each component to the concentration of bound receptors.

Enzymes are assumed to be diffusive components interacting with ligands. Such an interaction occurs with some probability (rate) b_e that an enzyme binds to a ligand and results in the destruction of the latter while the enzyme persits. All-in-all, we get the following set of equations:

$$\begin{cases} \partial_t r_f &= -\mu_f r_f + p_r(r_b) - b r_f \ell + d r_b, \\ \partial_t r_b &= -\mu_b r_b + b r_f \ell - d r_b, \\ \partial_t \ell &= d_1 \Delta \ell - \mu_\ell \ell + p_\ell(r_b) - b r_f \ell + d r_b, \\ \partial_t e &= d_2 \Delta e - \mu_e e + m_3 p_e(r_b). \end{cases} \tag{1.1}$$

This model has been studied extensively in [AnnaThesis] and yields fruitful results concerning the modelling of symmetry breaking in hydra. write transition to next section

3. Quasi steady-state approximation (QSSA)

3.1. Generalities on the QSSA. The quasi steady-state approximation, or QSSA as we should call it from now on, is a technique inspired from the field of chemistry, more precisely, biochemistry. The purpose of such an approximation is to simplify the analysis of chemical systems kinetics (often described by systems of ODEs and PDEs) by assuming that some species are reaching their steady-state concentrations faster than others.

One of the first occurences of the method goes back to Bodenstein when he was trying to derive the rate equation for a reaction in chemical kinetics. From this point onwards, the theory behind QSSA has been thoroughly developped and is now carefully described thanks to the framework provided by singular perturbation theory. This approach truly shines for equations describing interactions between molecules and, by essence, fits perfectly in the case of the study of reaction-diffusion systems.

For the sake of illustration, let us picture an simple example. Take a system of two ODEs modelling the kinetics of two chemical substances U and V. For instance

$$\frac{d}{dt}U = f_1(U,V), \tag{1.2}$$

$$\frac{d}{dt}V = f_2(U,V), \tag{1.3}$$

where f_1, f_2 have all the properties one would want to have to carry out computations peacefully. Now, suppose V is transient $i.e.$, it comes back to its steady-state concentration faster than U. The QSSA method suggests that we choose $\varepsilon > 0$ and look at the slightly modified system

$$\frac{d}{dt}U_\varepsilon = f_1(U_\varepsilon, V_\varepsilon) \tag{1.4}$$

$$\varepsilon\frac{d}{dt}V_\varepsilon = f_2(U_\varepsilon, V_\varepsilon) \tag{1.5}$$

One sees that if $\varepsilon = 1$ yields the original system, and that for sufficiently small values of ε, (in practical, we take the limit as ε goes to 0) the approximation $f_2(U_\varepsilon, V_\varepsilon) = 0$ seems reasonable. Provided f_2 is "nice enough" that is, we can extract an expression of the type $V_\varepsilon = \mathcal{H}(U_\varepsilon)$ out of the relation $f_2(U,V) = 0$, we can simplify the previous system to

$$\frac{d}{dt}U_\varepsilon = f_1(U_\varepsilon, \mathcal{H}(U_\varepsilon)) \tag{1.6}$$

$$V_\varepsilon = \mathcal{H}(U_\varepsilon) \tag{1.7}$$

This eliminates one of the two differential equations. One can now solve the equation on U_ε and naturally deduce the solution $(U_\varepsilon, V_\varepsilon)$ from $\mathcal{H}$. This concludes the short example.

It is, however, good to keep in mind that QSSA can be proven to be physically irrelevant when applied to some systems. That is to say, QSSA will always provide a new system of equations, but the obtained system can model a completely different phenomenon. Moreover, the case of ODE systems is easier to deal with (theorem name) compared to systems of reaction-diffusions-ODE where more work is required.

Coming back to the example system we define, provided they exists, the two limits $u := \lim_{\varepsilon\to 0} U_\varepsilon$ and $v := \lim_{\varepsilon\to 0} V_\varepsilon$. A common technique to ensure the stability of the model by approximation is to prove that, as ε goes to 0, the solutions $U_\varepsilon, V_\varepsilon$ are close in L^1-norm to u, v (in L^1_{loc} precisely). In symbols, we ideally would like to have

$$\lim_{\varepsilon\to 0} |U_\varepsilon - u|_{L^1} \leqslant \varepsilon C_1, \qquad \lim_{\varepsilon\to 0} |V_\varepsilon - v|_{L^1} \leqslant \varepsilon C_2$$

For constants C_1, C_2.

3.2. Approximation of r_b. Following the steps taken in the previous simpler example, we perform a QSSA on system (1.1), wherein r_b is seen as the transient (fast) variable. It follows

$$\begin{cases} \partial_t r_f &= -\mu_f r_f + m_1 \dfrac{r_b}{1+r_b} - b r_f \ell + d r_b, \\ \varepsilon \partial_t r_b &= -\mu_b r_b + b r_f \ell - d r_b \\ \partial_t \ell &= d_1 \Delta \ell - \mu_l \ell + m_2 \dfrac{r_b}{1+r_b} - b r_f \ell + d r_b - b_e \ell e, \\ \partial_t e &= d_2 \Delta e - \mu_e e + m_3 \dfrac{r_b}{1+r_b}. \end{cases} \tag{1.8}$$

Then take the limit as ε goes to 0, in a way that $\varepsilon \partial_t r_b$ is so small that one can assume

$$-\mu_b r_b + b r_f \ell - d r_b = 0. \tag{1.9}$$

A brief algebraic manipulation, yields

$$r_b = \alpha r_f \ell, \qquad \left(\alpha := \frac{b}{d + \mu_b} \right).$$

One can now question the quality of the approximation. Is it rough? Does it make any sense? Well, the coefficient α still has a biological interpretation here, since it is the ratio of parameters in the model with "birth" terms on the numerator and "death" terms in the denominator. We allow ourself to make the parallel with population dynamics and virology where such a coefficient is traditionally refered to as the famous "reproduction rate" which we heard about quite a lot in the recent years.

Pushing the interpretation a little further, we read that the value of r_b will be aproximated by the total amount of possible encounters between ligands and free receptors[2], scaled by this reproduction rate factor. Everything is coherent thus far, so let us plug the newly found value of r_b to conclude this first simplification step.

$$\begin{cases} \partial_t r_f &= -\mu_f r_f + m_1 \dfrac{\alpha r_f \ell}{1+\alpha r_f \ell} - b r_f \ell + d \alpha r_f \ell, \\ \partial_t \ell &= d_1 \Delta \ell - \mu_l \ell + m_2 \dfrac{\alpha r_f \ell}{1+\alpha r_f \ell} - b r_f \ell + d \alpha r_f \ell - b_e \ell e, \\ \partial_t e &= d_2 \Delta e - \mu_e e + m_3 \dfrac{\alpha r_f \ell}{1+\alpha r_f \ell}. \end{cases} \tag{1.10}$$

Remark: It is absolutely crucial to understand that, during this manipulation, the right-hand side of equation (1.8) is the term being approximated by zero. Even though it is a technical detail, it would be fundamentally incorrect to assume $\partial_t r_b = 0$,.

Remark: By definition of α, we can have a slightly better expression for the reaction term in equations on r_f and ℓ by noticing that $-b r_f \ell + d \alpha r_f \ell = -\alpha \mu_b r_f \ell$, which we implicitely substitute for further computations.

[2]This deduction follows from the elementary "lemme des bergers", as it is called in French

4. Model rescaling through reparametrization

Having a too much parameters in a model can be obnoxious. While they allow more flexibiliy with respect to modelling relaity, we quickly face the infamous phenomenon of curse of dimensionality. Indeed, a large amount of parameter significantly complexifies the analysis of a model so there a tradeoff to find between realism and analysability of the model. As of now, the model contains a total of ten parameters:

$$\mu_f,\ \mu_b,\ \mu_\ell,\ \mu_e,\ m_1,\ m_2,\ m_3,\ b,\ d,\ b_e,$$

which is already too many. The simplest way to reduce this amount is yet to simply kick some parameters out of the model. This, however, is a little blunt and may lead the model to fail in identifying some key feature in the system it is attached to.

A slightly more sophisticated, but still simple, way to reduce the amount of parameters without altering the model too much is to find a conventient change of variable. Let us illustrate this statement by directly finding a nice change of variable for our system.

$$u = \sqrt{\alpha} r_f, \quad v = \sqrt{\alpha}\ell, \quad w = b_e e, \quad \tilde{\mu}_b = \sqrt{\alpha}\mu_b,$$

$$\tilde{m}_1 = \sqrt{\alpha} m_1, \quad \tilde{m}_2 = \sqrt{\alpha} m_2, \quad \tilde{m}_3 = b_e m_3.$$

Once injected back into (1.10), we obtain

$$\begin{cases} \partial_t u &= -\mu_f u + \tilde{m}_1 \dfrac{uv}{1+uv} - \tilde{\mu}_b uv, \\ \partial_t v &= d_1 \Delta v - \mu_l v + \tilde{m}_2 \dfrac{uv}{1+uv} - \tilde{\mu}_b uv - vw, \\ \partial_t w &= d_1 \Delta w - \mu_e w + \tilde{m}_3 \dfrac{uv}{1+uv}. \end{cases} \tag{1.11}$$

This set of equation is the one which is at the heart of this thesis. For convenience, we drop the tilde ($\sim$) notation throughout.

Write transition to chapter 2

CHAPTER 2

Analytical properties of the model

Here, we show that there exists local solutions using classical results from the theory of semigroups of operators and spectral analysis. We then bridge from local to global solutions with invariant rectangles to prove that these solutions, provided we use biologically relevant initial data (all nonnegative quantities), will stay nonnegative and bounded over time. Lastly, being unable to find spatially nonhomogeneous steady-states, we show that the origin is always an equilibrium of (M) and derive a set of conditions to obtain the existence of another nonnegative constant steady-states under a biologically meaningful assumption on the parameters.

We first recall the definition of the model:

$$\text{(M)} \qquad \begin{cases} \partial_t u &= -\mu_f u + m_1 \dfrac{uv}{1+uv} - \mu_b uv, \\ \partial_t v &= d_1 \Delta v - \mu_l v + m_2 \dfrac{uv}{1+uv} - \mu_b uv - vw, \\ \partial_t w &= d_2 \Delta w - \mu_e w + m_3 \dfrac{uv}{1+uv}. \end{cases} \qquad (x,t) \in \Omega \times \mathbb{R}_{\geqslant 0}$$

where

$$u : \Omega \times \mathbb{R}_{>0} \to \mathbb{R}_{>0},$$
$$v : \Omega \times \mathbb{R}_{>0} \to \mathbb{R}_{>0},$$
$$w : \Omega \times \mathbb{R}_{>0} \to \mathbb{R}_{>0}.$$

Solutions are sought on a bounded domain $\Omega = (0, L) \subset \mathbb{R}$, (we choose $L = 1$ for now), supplemented with Neumann boundary conditions $\partial_\nu v = 0$ and $\partial_\nu w = 0$ on $\partial\Omega$ with initial data $u_0, v_0, w_0 \in L^\infty(\Omega, \mathbb{R})$. The operator $\Delta = \Delta_\nu^\Omega$ is the Laplacian on Ω with Neumann boundary condition, the quantities $\mu_f, \mu_b, \mu_l, \mu_e, m_1, m_2, m_3$ are parameters of the model. For convenience, we also introduce the notation

$$f(u,v,w) = -\mu_f u + m_1 \frac{uv}{1+uv} - \mu_b uv, \tag{2.1}$$

$$g(u,v,w) = -\mu_l v + m_2 \frac{uv}{1+uv} - \mu_b uv - vw, \tag{2.2}$$

$$h(u,v,w) = -\mu_e w + m_3 \frac{uv}{1+uv}. \tag{2.3}$$

For abbreviation, we let $\boldsymbol{f} := (f, g, h)$ denote the vector field generated by the reaction term in (M). Our goal for this chapter is to investigate on the properties of this model.

1. Existence of local solutions

To show the existence of a local-in-time solution, we introduce a few notions from operator semigroup theory. The aim of this section is not to provide a robust, rigorous introduction to the theory but rather sketch the key ideas on how to prove the existence of such solutions. We start by considering system (M) in the form

$$\text{(AC)} \qquad \begin{cases} \partial_t \boldsymbol{u} = \mathcal{A}[\boldsymbol{u}] + \boldsymbol{f}(\boldsymbol{u}), \\ \boldsymbol{u}(0) = \boldsymbol{u}_0, \end{cases}$$

where the operator $\mathcal{A} := D\Delta$ is defined for $D := \mathrm{diag}(0, d_1, d_2)$, with real diffusion coefficients $d_1, d_2 > 0$. The problem is now an *abstract Cauchy problem.* The operator $\mathcal{A}$ is defined on the domain

$$\mathcal{D}(\mathcal{A}) := \{(u, v, w) \in L^\infty(\Omega) \times (H^2(\Omega))^2 : \partial_\nu v = 0, \partial_\nu w = 0 \text{ on } \partial\Omega\}.$$

This way of writing is more tailored to the presentation of the following results. Before we state the main theorem, we need a few definitions, starting with the definition of a semigroup of operators.

Definition 1. *Let X be a Banach space. A one parameter family $T(t)$, $0 \leqslant t < \infty$, of bounded linear operators from X into X is a semigroup of bounded linear operators on X if*
- (i) $T(0) = I$,
- (ii) $T(t+s) = T(t)T(s)$ *for every* $t, s \geqslant 0$ *(semigroup property)*

We can ask $T(t)$ to have slightly more structure by adding the constraint

$$\lim_{t \downarrow 0} T(t)x = x, \quad \forall\, x \in X.$$

When this relation holds, then $T(t)$ is called *C_0 − semigroup* (read strongly continuous semigroup). An example of such family is the shift operator:

$$S(t) : L^2(\mathbb{R}) \to L^2(\mathbb{R}), \quad S(t)[f] = f(\cdot + t),$$

for functions $f : L^2(\mathbb{R}) \to L^2(\mathbb{R})$. It is clear that $S(0)[f] = f(\cdot + 0) = f$, and that for any $s, t \geqslant 0$, we have

$$S(t+s)[f] = f((\cdot + s) + t) = S(t)[f(\cdot + s)] = S(t)S(s)[f].$$

So the semigroup property is satisfied.

Remark: The domain of the operator is essential for the properties of an operator. On $L^2, S(t)$ is a C_0-semigroup, but on L^∞ it is not. To see why, take the function $f(x) = \mathbb{1}_{[0,1]}(x)$ and see that $\|S(t)f - f\|_\infty = 1$ for all $t \neq 0$.

For a semigroup of operators $(T(t))_{t \geqslant 0}$, one can define the operator $(A, \mathcal{D}(A))$ as

$$\mathcal{D}(A) = \left\{ x \in X : \lim_{t \downarrow 0} \frac{T(t)x - x}{t} \text{ exists} \right\}, \quad Ax = \lim_{t \downarrow 0} \frac{T(t)x - x}{t}, \quad \text{for } x \in \mathcal{D}(A).$$

This operator is called *infinitesimal generator* of the semigroup $T(t)$ with domain $\mathcal{D}(A)$ and we say that A generates $T(t)$. A is nothing but the right derivative of T at the origin. Coming back to the example of the shift operator, one has that for a differentiable $f \in L^2(\mathbb{R})$

$$A = \lim_{t\downarrow 0} \frac{S(t)[f](x) - f(x)}{t} = \lim_{t\downarrow 0} \frac{f(x+t) - f(x)}{t} = f'(x),$$

is exactly the right derivative of the function itself. We omit the derivation of the domain $\mathcal{D}(A)$ since these computations are technical and involve some results that require more detail than we want to give in this section.

The way we presented things is by first introducing a semigroup $(T(t))_{t\geqslant 0}$ and then its infinitesimal generator A. In a general setting, knowledge on the family $T(t)$ is helpful to deduce properties on A, but one could also look at it the other way and deduce properties on $T(t)$ based on properties of A. To this end, we introduce the notion of sectoriality.

DEFINITION 2. *We call a linear operator A in a Banach space X a sectorial operator if it is a closed, densely defined operator such that, for some ϕ in $(0, \pi/2)$ and some $M \geqslant 1$ and real a, the sector*

$$S_{a,\phi} := \{\lambda : \phi \leqslant |\arg(\lambda - a)| \leqslant \pi,\ \lambda \neq a\},$$

is contained in the resolvent set of A and that $\|(\lambda - A)^{-1}\| \leqslant M|\lambda - a|^{-1}$ for all $\lambda \in S_{a,\phi}$.

Knowing that an operator is sectorial gives crucial cues on the behavior of its spectrum and is used (among others) to prove the asymptotic stability of steady states of the linearized problem[1]under relatively weak assumptions. In our case, we also have

LEMMA 1. *Any sectorial operator generates a C_0-semigroup.*

This is a technical lemma whose proof can be found in [K.J. Engel, result], and it is of prime importance to the next theorem from [AnnaThesis]

THEOREM 1. *For each $x \in X$, there exists a unique weak solution $\boldsymbol{u}$ of (AC) on $[0, T]$ satisfying $\boldsymbol{u}(0) = \boldsymbol{u}_0$ if and only if A is the infinitesimal generator of a C_0-semigroup $T(t)$ of bounded linear operators on X. In this case, $\boldsymbol{u}$ is given by*

$$\boldsymbol{u}(\cdot, t) = T(t)\boldsymbol{u}_0 + \int_0^t T(t-s)[\boldsymbol{f}\big(\boldsymbol{u}(\cdot, s)\big)]ds.$$

Remark: By weak solution we mean that, if $A^\star$ is the dual operator of A, for every $\boldsymbol{v}^\star \in \mathcal{D}(A^\star)$, the duality bracket $\langle \boldsymbol{u}, \boldsymbol{v}^\star \rangle$ is absolutely continuous on $[0, T]$ and

$$\partial_t \langle \boldsymbol{u}, \boldsymbol{v}^\star \rangle = \langle \boldsymbol{u}, \boldsymbol{A}^\star \boldsymbol{v}^\star \rangle + \langle \boldsymbol{f}(\boldsymbol{u}), \boldsymbol{v}^\star \rangle, \quad a.e. \text{ on } [0, T].$$

Remark: The integral in the theorem is defined for Banach-valued functions, so we have to use the definition in the sense of Bochner.

To conclude this section, we use the fact that the operator $\mathcal{A} := D\Delta$ in (AC) is sectorial (proof in [AnnaThesis]), and therefore there exists a unique weak solution of the problem. This unique weak solution can then be extended into a classical solution using a theorem from [Rothe].

[1]the problem $\partial_t \boldsymbol{u} = \mathcal{A}[\boldsymbol{u}] + \mathbf{Jac}_{\boldsymbol{f}}(x)\boldsymbol{u}$

2. Existence of global solutions

Now is the time for us to build global solutions to system (M) by building upon local solutions. For that, we introduce elements of the theory of invariant regions established by Smoller in the 70's, (and thoroughly developped in [21]) in the context of general semilinear parabolic equations of the type

$$\begin{cases} \partial_t \boldsymbol{v} = \varepsilon D(\boldsymbol{v}, x)\Delta \boldsymbol{v} + \sum_{j=1}^n M^j(\boldsymbol{v}, x)\partial_j \boldsymbol{v} + \boldsymbol{\phi}(\boldsymbol{v}, t), & (x \in \Omega,\ t \geqslant 0) \\ \boldsymbol{v}(x, 0) = v_0(x). \end{cases} \tag{2.4}$$

We first introduce the formal definition of invariant regions together with the notion of invariant rectangles for such equations.

Definition 3. *A closed subset $\Sigma \subset \mathbb{R}^n$ is called a (positively) invariant region for the local solution of (2.4) 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 $t \geqslant 0$.*

It is a good sanity-check to verify that our system indeed fits this category of problems. To see that, we take the domain-rescaling parameter $\varepsilon = 1$, the matrix of diffusion terms $D = \mathrm{diag}(0, d_1, d_2)$ with constant, positive entries d_1, d_2, set all matrices M^j equal to zero and, finally, $\boldsymbol{\phi}(\cdot, t) = \boldsymbol{f}(\cdot)$ to land back on our system.

In the general case, most invariant regions, Σ, are defined by an intersection of $(n-1)$-dimensional hypersurfaces (half spaces) which are sets of points satisfying some constraints $G_i \leqslant 0$, $i = 1, ..., m$. In other words, regions of the form

$$\Sigma = \bigcap_{i=1}^{m} \{G_i \leqslant 0\}, \tag{2.5}$$

where every $G_i = G_i(u, v, w)$ are smooth, real-valued functions defined on a domain $\mathrm{Dom}(G_i) \supset \mathrm{im}(\boldsymbol{u})$ such that ∇G_i never vanishes. In the special case where Σ is invariant and generated by linear constraints ($G_i(\boldsymbol{v}) = \boldsymbol{v} - \alpha$, for some $\alpha \in \mathbb{R}$), Σ is referred to as an invariant rectangle. Additionally, in the special case where D, M^j are diagonal matrices, as in our case, it is shown under weak assumptions that any invariant region must be a rectangular region. [ref].

The case of rectangular regions is particularly easy to deal with since it is only needed to show that the gradient of the active constraint G_i points inwards Σ. More precisely, if $v \in \partial\Sigma$ denotes a point on the boundary of Σ *i.e.*, there is an index i for which $G_i(v) = 0$, then

$$\nabla G_i(v) \cdot \boldsymbol{f} \leqslant 0.$$

To ensure the proper introduction of this new notion, we propose the following geometric interpretation of invariant regions. Visually speaking, if Σ is an invariant region and $\boldsymbol{u}$ a solution of (2.4), then we can show that if $\boldsymbol{u}$ touches the edge of Σ, the solution immediately bounces back inside the region, trapping the solution inside the rectangle, see figure 2.

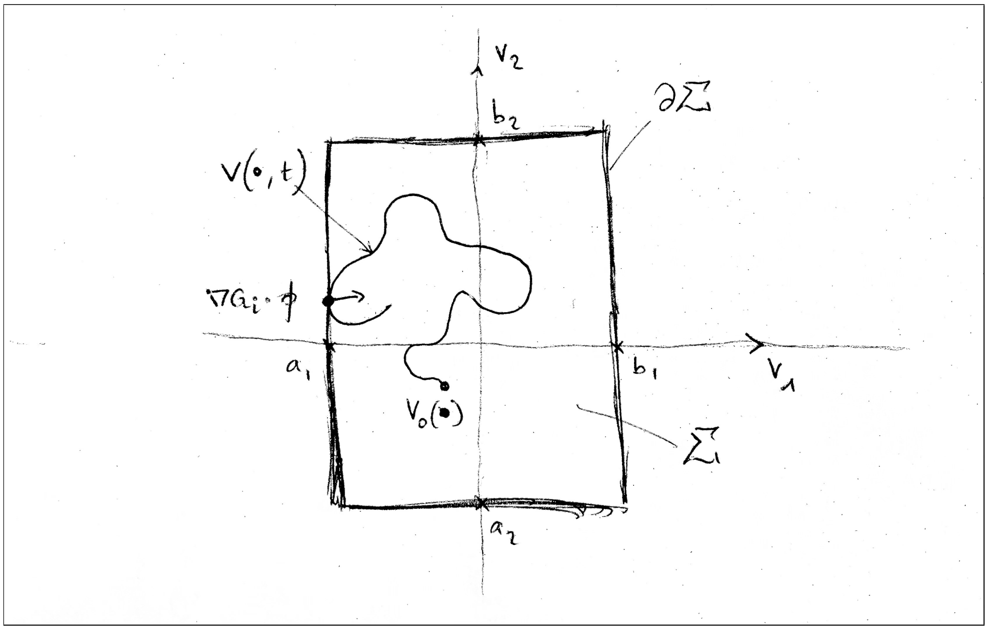


FIGURE 2. Schematic representation of an invariant rectangle Σ in the two-dimensional case. At initial time, the solution sits at the point $v_0(\cdot)$ and starts travelling as t grows. For some time $t > 0$, the solution represented by the point $v(\cdot, t)$ eventually touches the border of Σ and bounces back to the interior of the region.

THEOREM 2 (Existence of an invariant rectangle). *There exists three positive reals A_u, A_v, A_w, large enough, such that the region*

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

is an invariant rectangle of (M)

PROOF. In order to define the rectangular region, we introduce the following smooth functions

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

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

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

together with the sets

$$\Sigma_0 := \bigcap_{\kappa=u,v,w} \{G_\kappa \leqslant 0\}, \qquad \Sigma_A := \bigcap_{\kappa=u,v,w} \{H_\kappa \leqslant 0\}.$$

Now let $\Sigma := \Sigma_0 \cap \Sigma_A$ so that

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

is the boundary of Σ. To show the gradient always points inside Σ, we consider a point $(u, v, w) \in \partial\Sigma$ and proceed case-by-case. Let $\boldsymbol{u}$ denote such a point. If $u = 0$, then

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

The case $v = 0$ is similar as

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

Finally, since $\boldsymbol{u} \in \partial\Sigma_0$, it holds that $u, v \geqslant 0$, so that $w = 0$ implies

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

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 $\boldsymbol{u} \in \Sigma$, 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 $(\nabla H_u \cdot \boldsymbol{f})(\boldsymbol{u})|_{u=A_u} = f(A_u, v, w) \leqslant 0$. 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 $(\nabla H_v \cdot \boldsymbol{f})(\boldsymbol{u})|_{v=A_v} \leqslant 0$. 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 $(\nabla H_w \cdot \boldsymbol{f})(\boldsymbol{u})|_{w=A_w} \leqslant 0$, concluding the proof. □

We have thus showed the existence of an invariant rectangle. This provides an upper bound for each solution, and we finally use theorem 14.9, [21] to deduce the existence of the solution to (M) for all times $t > 0$ provided we take the initial data $\boldsymbol{u}_0$ continuous, bounded with values $\boldsymbol{u}_0(x) \in \Sigma$, $x \in \Omega$. In particular, we can guarantee the existence of a global solution under reasonable assumptions on our model.

Remark: We actually used two assumptions under the hood for this result (that are verified in our case but worth mentioning nonetheless). The first one is that the system we work with is $\boldsymbol{f}-$*stable*, in the sense of [Smoller1994], which allows the proof to be valid even though the gradient vanishes on $\partial\Sigma$ as soon as one quantity is zero. The second one is that the Banach space in which our solutions u, v, w live in is *admissible*, say a few words about admissible Banach Spaces still in the sense of [Smoller1994], which allows us to use the theorem in the first place.

3. Finding steady states of the model

Finding steady states of the model was, by far, the most exploratory part of this work. unfortunately formulating satisfying results regarding steady states of the system for arbitrary choices of parameters was out of reach.

That being said, we were able to obtain some estimates and analytical formulas for the location of steady-states. We recall that steady states of (M) are the points (functions) $\bar{\boldsymbol{u}} := (\bar{u}, \bar{v}, \bar{w})$ such that $\partial_t \bar{\boldsymbol{u}} = 0$. Using equations of (M), we find that such points must obey the relation

$$-\mu_f \bar{u} + m_1 \frac{\bar{u}\bar{v}}{1 + \bar{u}\bar{v}} - \mu_b \bar{u}\bar{v} = 0, \tag{2.6}$$

$$d_1 \Delta \bar{v} - \mu_l \bar{v} + m_2 \frac{\bar{u}\bar{v}}{1 + \bar{u}\bar{v}} - \mu_b \bar{u}\bar{v} - \bar{v}\bar{w} = 0, \tag{2.7}$$

$$d_2 \Delta \bar{w} - \mu_e \bar{w} + m_3 \frac{\bar{u}\bar{v}}{1 + \bar{u}\bar{v}} = 0. \tag{2.8}$$

From this expression, it immediately foolows that the trivial solution $\bar{\boldsymbol{u}} = (0, 0, 0)$ will always be a steady state of (M). Let us look for more interesting ones by assuming $\bar{\boldsymbol{u}}$ has only nonzero coordinates, which allows us to divide by $\bar{u}$ in (2.6). After some algebraic manipulations, we find

$$\bar{u} = \underbrace{\frac{m_1}{\mu_f + \mu_b \bar{v}} - \frac{1}{\bar{v}}}_{=:\mathcal{R}(\bar{v})},$$

and

$$d_1 \Delta \bar{v} = -m_2 \frac{\mathcal{R}(\bar{v})\bar{v}}{1 + \mathcal{R}(\bar{v})\bar{v}} + \mu_l \bar{v} + \mu_b \mathcal{R}(v)\bar{v} - \bar{v}\bar{w}, \tag{2.9}$$

$$d_2 \Delta \bar{w} = -m_3 \frac{\mathcal{R}(\bar{v})\bar{v}}{1 + \mathcal{R}(\bar{v})\bar{v}} + \mu_e \bar{w}, \tag{2.10}$$

which we rewrite as

$$d_1 \Delta \bar{v} = -m_2 \left(1 - \frac{\mu_f + \mu_b \bar{v}}{m_1 \bar{v}}\right) + \mu_l \bar{v} + \mu_b \left(\frac{m_1 \bar{v}}{\mu_f + \mu_b \bar{v}} - 1\right) - \bar{v}\bar{w}, \tag{2.11}$$

$$d_2 \Delta \bar{w} = -m_3 \left(1 - \frac{\mu_f + \mu_b \bar{v}}{m_1 \bar{v}}\right) + \mu_e \bar{w}. \tag{2.12}$$

So finding steady states of (M) boils down to finding the solution of a system of elliptic partial differential equations with highly nonlinear terms. Put differently, we need to find another angle of attack... A possible solution is to look for constant (spatially homogeneous) steady states instead. Not only are they ones we are interested in when dealing with Turing instabiliy (more on that in the next chapter), they are also slightly easier to find than their nonconstant (spatially nonhomogeneous) counterparts.

Limiting our scope to spatially homogeneous steady states only, the Laplace operator vanishes (constant functions are harmonic), so that the previous system reduces to

$$m_2\left(1 - \frac{\mu_f + \mu_b\bar{v}}{m_1\bar{v}}\right) = \mu_l\bar{v} + \mu_b\left(\frac{m_1\bar{v}}{\mu_f + \mu_b\bar{v}} - 1\right) - \bar{v}\bar{w}, \tag{2.13}$$

$$m_3\left(1 - \frac{\mu_f + \mu_b\bar{v}}{m_1\bar{v}}\right) = \mu_e\bar{w}, \tag{2.14}$$

Dividing by μ_e in (2.14) allows to express $\bar{w}$ as a function of $\bar{v}$. This allows us to formulate the following result.

LEMMA 2. *Let $\mathcal{P} : x \longmapsto Ax^3 + Bx^2 + Cx + D$ be the third order polynomial with coefficients given by*

$$\begin{aligned}
A &= -\mu_l\mu_b - \frac{m_3\mu_b}{\mu_e} + \frac{m_3\mu_b^2}{m_1\mu_e},\\
B &= -\mu_l\mu_f + m_2\mu_b - \frac{m_2\mu_b^2}{m_1} + \mu_b^2 - m_1\mu_b - \frac{m_3\mu_f}{\mu_e} + \frac{2\mu_f\mu_b m_3}{\mu_e m_1},\\
C &= m_2\mu_f - \frac{2\mu_f\mu_b m_2}{m_1} + \mu_f\mu_b + \frac{m_3\mu_f^2}{\mu_e m_1},\\
D &= -\frac{m_2\mu_f^2}{m_1}.
\end{aligned}$$

Then, the following statements are equivalent

(i) *V is a real root of $\mathcal{P}$.*

(ii) *The point $\left(\frac{m_1}{\mu_f+\mu_b V} - \frac{1}{V},\ V,\ \frac{m_3}{\mu_e} - \frac{m_3(\mu_f+\mu_b V)}{\mu_e m_1 V}\right)$ is a constant steady state of (M).*

Remark: Although $\mathcal{P}$ may have several real roots, we only care about those yielding positive values of $(\bar{u}, \bar{v}, \bar{w})$, because not only we have proved global existence for nonnegative initial data, but we also showed that solutions with positive initial conditions will stay positive for all times. Due to biological reasons, negative solutions are not of interest for us. Since they represent concentrations of molecules, having negative values would go against every known physical laws.

From the expression of steady state, one can derive a lower bound on $\bar{v}$ to guarantee the positivity of the steady states, that is

PROPOSITION 1. *Assume that the choice of parameters is such that $\mu_b < m_1$. Let $S_{\mathcal{P}}$ denote the set of real roots of $\mathcal{P}$ from lemma 2. If*

$$\sup_{V \in S_{\mathcal{P}}} V < \frac{\mu_f}{m_1 - \mu_b},$$

then the origin is the only steady state in the positive quadrant.

Remark: The assumption $\mu_b < m_1$ is biologically relevant when looking at the nature of both parameters. μ_b being seen as a rate, we expect its value to be between 0 and 1 while m_1 is a mass that we expect to be above 1.

PROOF. The proof is a direct computation. Take any root $V \in S_{\mathcal{P}}$. By definition V is real and nonzero, then the condition that the steady state has only nonnegative coordinates is (using (ii) in lemma 2):

$$\frac{m_1}{\mu_f + \mu_b V} - \frac{1}{V} \geqslant 0,$$
$$V \geqslant 0,$$
$$\frac{m_3}{\mu_e}\left(1 - \frac{\mu_f + \mu_b V}{m_1 V}\right) \geqslant 0.$$

The first and third equations are redundant and provide the same estimate, *i.e.*, the steady state has only nonnegative entries if and only iff

$$V \geqslant 0 \quad \text{and} \quad V \geqslant \frac{\mu_f}{m_1 - \mu_b}.$$

The condition $V \geqslant 0$ becomes redundant as well, and we deduce by contraposition that $V < \mu_f(m_1 - \mu_b)^{-1}$ implies that at least one coordinate is negative. We conclude by taking the supremum on both sides. □

Another way to see those constant steady states is to think of each equation $f = 0, g = 0, h = 0$ as the algebraic equation of a hypersurface. This way, steady states become the intersection points between those three manifolds, which enables some visual intuition about the location of these equilibria, see figure (3).

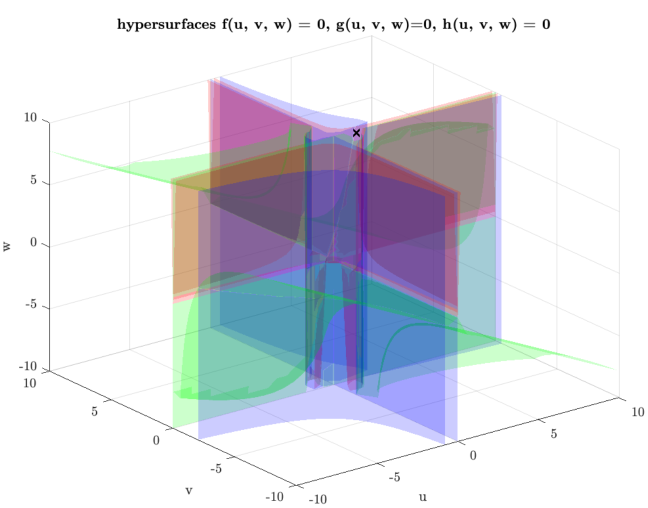


FIGURE 3. Three-dimensional plot of algebraic hypersurfaces associated to the equations $f \equiv 0$ (blue), $g \equiv 0$ (green) and $h \equiv 0$ (red). Parameters values are fixed and each curve is plotted on $[-10, 10]$. The black cross highlight the only steady state with only (strictly) positive coordinates, *i.e.*, the intersections of these hypersurfaces in the positive quadrant.

CHAPTER 3

Diffusion-Driven Instability and Turing-like patterns

The Laplace operator is well-known for its smoothing properties and intuition begs to reckon that adding diffusion in a system will make it more stable. That was until the middle of the last century, when Turing showed [Turing52] that, for a choice of appropriate diffusion coefficients, the Laplace operator could turn a stable steady-state into an unstable one. In this chapter, we proceed to characterize the circumstances under which the so-called phenomenon of difusion-driven-instability can occur for a constant, positive, steady-state of (M), which constitutes the main result of this thesis.

1. Diffusion-Driven Instability (DDI) in our model

1.1. Definitions and elements of theory. Diffusion-driven instability is the phenomenon that occurs when a steady state is stable with respect to spatially homogeneous perturbation, but unstable to spatially inhomogeneous perturbations. For convenience, we introduce the associated ODE system (M') to our model (M)

$$\begin{cases} \partial_t u &= f(u,v,w), \\ \partial_t v &= g(u,v,w), \\ \partial_t w &= h(u,v,w), \end{cases} \tag{M'}$$

with initial data $u_0, v_0, w_0 \in \mathbb{R}_{\geqslant 0}$. By essence, any constant steady state $\bar{\boldsymbol{U}}$ of (M') is also a steady state of (M), this motivates the following alternative definition for DDI:

Definition 4. *We say that the (constant) steady state $\bar{\boldsymbol{U}}$ of system (M) is exhibiting diffusion-driven instability (DDI) whenever*

(i) *$\bar{\boldsymbol{U}}$ is an asymptotically stable steady state of (M').*

(ii) *$\bar{\boldsymbol{U}}$ is linearly unstable with respect to spatially heterogeneous perturbations for the full system (M).*

From now on, we assume the vector field $\boldsymbol{f}$ to have a nontrivial positive equilibrium, that is, a point $\bar{\boldsymbol{U}} := (\bar{u}, \bar{v}, \bar{w})$, $\bar{u}, \bar{v}, \bar{w} > 0$ satisfying $\boldsymbol{f}(\bar{\boldsymbol{U}}) = 0$. It is crucial to understand that having $\bar{\boldsymbol{U}}$ to exhibit DDI is a necessary condition for us to observe patterns. Otherwise, the steady state is simply stable under all circumstances and will attract solutions when perturbated. We thus instagate the inspection of each condition in definition 4.

By Hartman-Grobman, condition (i) holds whenever the Jacobian $A := \mathbf{Jac}_{\boldsymbol{f}}(\bar{\boldsymbol{U}})$ has all its eigenvalues with real part in the negative plane. If $\sigma(A)$ denotes the spectrum of A, this is equivalent to saying

$$s(A) := \sup_{\lambda \in \sigma(A)} \mathbf{Re}\{\lambda\} < 0.$$

Remark: The quantity $s(A)$ is called *spectral bound* of the matrix A and is a notion generally introduced in a broader context for operators.

Prove that DDI can occur if and only if A_{12} has negative determinant (otherwise every subsystem is stable, result from [AnmaSakamoto]).

To verify condition (ii), we look at the linearized system around the steady state $\bar{\boldsymbol{U}}$. If $\xi \in \mathbb{R}^3$ is a small perturbation in space, we write $\boldsymbol{U} = \bar{\boldsymbol{U}} + \xi$ and use a Taylor formula to get the linearized system (written in vector form)

$$\partial_t \xi = D\Delta\xi + A\xi \; . \tag{3.1}$$

For $\mathcal{L} := D\Delta + A$ denoting this linear differential operator, we recall the following result from [FinnChrisAnna]

$$\sigma(\mathcal{L}) = \{\partial_u \boldsymbol{f}(\bar{\boldsymbol{U}})\} \cup \left(\bigcup_{k \geqslant 0} \sigma\big(A - \mu_k^2 D\big) \right).$$

Therefore, (3.1) is unstable if there exists an integer k (called wavenumber) for which $s(A - \mu_k^2 D) > 0$, where μ_k denotes the k-th eigenvalue of Δ_ν^Ω (*i.e.*, $\mu_k^2 = k^2\pi^2/L^2$ since Ω is one-dimensional). For $\mu \geqslant 0 \in \mathbb{R}$, $\tilde{A}(\mu) := A - \mu D$ is a 3×3 matrix, hence qualitative information about the localisation of its roots in the complex plane can be extracted using the *Routh-Hurwitz* (RH) criterion for polynomials of degree three (this follows from the fact that the $\tilde{A}(\mu)$ has itself a characteristic polynomial of degree three). More precisely, we know that all the roots of any 3×3 matrix M lie in the left part of the complex plane if the set of inequalities holds

$$\Delta_1 := -\mathrm{tr}(M) > 0, \tag{3.2}$$

$$\Delta_2 := -|M| > 0, \tag{3.3}$$

$$\Delta_3 := -\mathrm{tr}(M) \sum_{i<j} |M_{ij}| + |M| > 0, \tag{3.4}$$

Remark: For a 3×3 matrix $M := (m_{ij})_{1 \leqslant i,j \leqslant 3}$, we use the convention $M_i = m_{ii}$ (diagonal coefficients), and let M_{ij} denote the submatrix whose entries are the intersection of rows and columns i and j in M. Since this is an important notation, we propose to list all submatrices M_{ij} as an example:

$$M_{12} = \begin{bmatrix} m_{11} & m_{12} \\ m_{21} & m_{22} \end{bmatrix}, \quad M_{13} = \begin{bmatrix} m_{11} & m_{13} \\ m_{31} & m_{33} \end{bmatrix}, \quad M_{23} = \begin{bmatrix} m_{22} & m_{23} \\ m_{32} & m_{33} \end{bmatrix}, \tag{3.5}$$

Coming back to our system, we introduce for short quantities

$$p_1 := -\mathrm{tr}(A) \qquad p_2 := \textstyle\sum_{i<j} |A_{ij}| \qquad p_3 := -|A|,$$

$$p_1(\mu) := -\mathrm{tr}(\tilde{A}(\mu)) \qquad p_2(\mu) := \textstyle\sum_{i<j} |\tilde{A}_{ij}(\mu)| \qquad p_3(\mu) := -|\tilde{A}(\mu)|.$$

Recall that we want the stability of A ($s(A) < 0$) and that there exists a real μ such that $s(\tilde{A}(\mu)) > 0$. This condition can be written by using the Routh-Hurwitz criterion on A and its contraposition on $\tilde{A}(\mu)$ for a fixed $\mu \in \mathbb{R}_{\geqslant 0}$:

$$\text{(RH1)} \qquad \big(p_1 > 0\big) \quad \wedge \quad \big(p_3 > 0\big) \quad \wedge \quad \big(p_1 p_2 - p_3 > 0\big),$$

$$\text{(RH2)} \qquad \big(p_1(\mu) < 0\big) \quad \vee \quad \big(p_3(\mu) < 0\big) \quad \vee \quad \big(p_1(\mu)p_2(\mu) - p_3(\mu) < 0\big).$$

Remarking that only (RH2) depends on μ, we can ensure the possibility of DDI by defining the parameter set

$$\boldsymbol{\Theta} := \left\{ \boldsymbol{\Pi} := (\mu_f, \mu_b, \mu_l, \mu_e, m_1, m_2, m_3) \in \mathbb{R}^7 \;\middle|\; \bar{\boldsymbol{U}} \text{ exists} \;\wedge\; |A_{12}| < 0 \;\wedge\; s(A) < 0 \right\},$$

which is nonempty since at least the point (0.87, 0.68, 0.05, 0.6, 5.36, 9.68, 17.27) belongs to $\boldsymbol{\Theta}$ (found heuristically). This allows us to focus only on condition (RH2). In our quest for Turing patterns, we choose our parameters $\boldsymbol{\Pi} \in \boldsymbol{\Theta}$ and use d_1, d_2 as bifurcation parameters for DDI.

Remark: It is possible that the set $S := \{\mu \in \mathbb{R}_{>0} \mid \text{(RH2) holds}\}$ is nonempty but $\mu_k^2 \notin S$ for all $k \in \mathbb{N}$ (see figure). In such case, DDI does not occur. However, an appropriate rescaling of the domain $\Omega \longmapsto L\Omega$, $L > 0$, fixes the issue for L large enough

Overall, for DDI to be able to occur at $\bar{U}$, we require a specific choice of parameters yielding the existence of a positive steady state of (M), stability of the jacobian A, existence of at least one unstable subsystem of A. We now explore all possible scenarios that would make (RH2) true.

1.2. Identifying sources of DDI. We will show that the only possible way for (RH2) to hold, is to have $p_3(\mu) < 0$ by proving that $p_1(\mu), p_2(\mu) > 0$ for all $\mu \geqslant 0$.

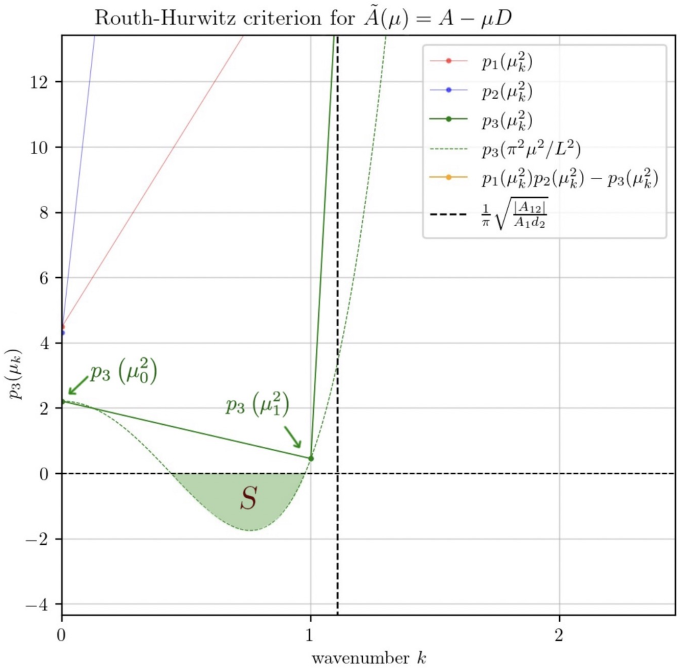
Case 1: Investigating $\boldsymbol{p_1(\mu)}$: Is it possible for $p_1(\mu)$ to turn negative for some value of μ? It turns out the answer to this question is no. This is an easy statement to show:

PROOF. Since $d_1, d_2, \mu > 0$ and, by hypothesis $p_1 > 0$, it follows

$$p_1(\mu) = -\mathrm{tr}(A - \mu D) = -\mathrm{tr}(A) + \mu\mathrm{tr}(D) = p_1 + \mu(d_1 + d_2) > 0.$$

□

Therefore, whatever the value of $\mu > 0$, $p_1(\mu)$ cannot become negative. Hence, if DDI occurs at $\bar{\boldsymbol{U}}$, it is not because $p_1(\mu)$ breaks in the Routh-Hurwitz criterion.



Case 2: Investigating $p_1(\mu)p_2(\mu) - p_3(\mu)$: In a likely manner, we prove that $p_1(\mu)p_2(\mu) - p_3(\mu) < 0$ cannot occur for $\mu \geqslant 0$. To see why, we expand the expression $\Delta_3(\mu) = p_1(\mu)p_2(\mu) - p_3(\mu)$ so that we obtain a third-order polynomial with respect to the variable μ

$$\Delta_3(\mu) = p_1(0)p_2(0) - p_3(0) \tag{3.6}$$

$$+ \left[\Big(|A_{12}| + |A_{23}| + (\mathrm{tr}A)(\mathrm{tr}A_{13})\Big)d_1 + \Big(|A_{23}| + |A_{13}| + (\mathrm{tr}A)(\mathrm{tr}A_{12})\Big)d_2\right]\mu \tag{3.7}$$

$$+ \left[(-\mathrm{tr}A_{13})d_1^2 + (-\mathrm{tr}A_{12})d_2^2 + 2(-\mathrm{tr}A)d_1 d_2\right]\mu^2 \tag{3.8}$$

$$+ \left[d_1^2 d_2 + d_2^2 d_1\right]\mu^3. \tag{3.9}$$

Let J, K, L, M temporarily describe the coefficients of $\Delta_3(\mu)$ in a way that

$$\Delta_3(\mu) = J\mu^3 + K\mu^2 + L\mu + M$$

By definition, J, K and M are all positive. Consequently, if we were to show that L is always positive, we would have $J, K, L, M > 0$ and therefore $\Delta_3(\mu) > 0$ for every $\mu \geqslant 0$.

Lemma 3. *We claim that the quantity*

$$L := \Big(\underbrace{|A_{12}| + |A_{23}| + (\mathrm{tr}A)(\mathrm{tr}A_{13})}_{=:L_1}\Big)d_1 + \Big(\underbrace{|A_{23}| + |A_{13}| + (\mathrm{tr}A)(\mathrm{tr}A_{12})}_{=:L_2}\Big)d_2$$

is always positive.

PROOF. First, notice that $L_2 d_2 > 0$ follows from the stability of A, properties of $\boldsymbol{f}$, and the positivity of d_2. Next, we move our focus to the first parenthesis. By assumption $p_2 > 0$, therefore

$$|A_{12}| + |A_{23}| > -|A_{13}| \quad \Longleftrightarrow \quad L_1 = |A_{12} + |A_{23}| + (\mathrm{tr}A)(\mathrm{tr}A_{13}) > -|A_{13}| + (\mathrm{tr}A)(\mathrm{tr}A_{13}).$$

Expanding this last expression yields

$$L_1 > a_{11}^2 + a_{33}^2 + a_{11}a_{33} + a_{22}a_{11} + a_{22}a_{33} > 0.$$

The quantity $a_{13}a_{31}$ disappeared since $a_{13} = 0$. This shows $L = L_1 d_1 + L_2 d_2$ is positive. $\square$

Therefore, $\Delta_3(\mu)$ is a degree three polynomial with positive coefficients. We arrive at the conclusion that $\Delta_3(\mu) > 0$ for $\mu \geqslant 0$. It follows that DDI occuring at $\bar{\boldsymbol{U}}$ is not a byproduct of $\Delta_3(\mu) < 0$. All in all, there is only one option left to explore.

Case 3: Investigating $\boldsymbol{p_3(\mu)}$: This case is by far the most interesting one: We show that we can extract conditions on d_1, d_2 under which DDI occurs at $\bar{\boldsymbol{U}}$. Let us compute $p_3(\mu)$:

$$p_3(\mu) = -|A| + \Big[|A_{13}|d_1 + |A_{12}|d_2\Big]\mu + \Big[-A_1 d_1 d_2\Big]\mu^2. \tag{3.10}$$

This is a polynomial of degree two, with expression $a\mu^2 + b\mu + c$ with $a > 0$. Its minimum is reached at the point $\mu_{\min} := -b/2a$ and is equal to $p_3(\mu_{\min}) = -b^2/4a + c$. In other words, the condition $p_3(\mu) < 0$ is equivalent to

$$-\frac{\big(|A_{13}|d_1 + |A_{12}|d_2\big)^2}{4(-A_1)d_1 d_2} - |A| < 0.$$

Moving terms, multiplying by $4(-A_1) > 0$, and putting d_1, d_2 inside the square results in the condition

$$\left(\sqrt{\frac{d_1}{d_2}}|A_{13}| + \sqrt{\frac{d_2}{d_1}}|A_{12}|\right)^2 > 4A_1|A|.$$

This is a mapping of the form $\sqrt{\Lambda} \longmapsto (\alpha\sqrt{\Lambda} + \beta/\sqrt{\Lambda})^2 > \gamma$ with $\Lambda = d_1/d_2$. Solving for the equality case boils down to finding the roots of $\alpha^2\Lambda^2 + (2\alpha\beta - \gamma)\Lambda - \gamma$, which occurs at

$$\Lambda_\pm = \frac{\gamma - 2\alpha\beta \pm \sqrt{\gamma(\gamma - 4\alpha\beta)}}{2\alpha^2}.$$

Plugging the correct values for α, β, γ yields an interval $\boldsymbol{M} := \big(0, \Lambda_-\big) \;\cup\; \big(\Lambda_+, \infty\big)$ with two roots being given by the relation

$$\Lambda_- = 2\frac{A_1|A|}{|A_{13}|^2} - \frac{|A_{12}|}{|A_{13}|} - 2\frac{\sqrt{A_1|A|(A_1|A| - |A_{12}||A_{13}|)}}{|A_{13}|^2} := P + Q - \sqrt{S}, \tag{3.11}$$

$$\Lambda_+ = 2\frac{A_1|A|}{|A_{13}|^2} - \frac{|A_{12}|}{|A_{13}|} + 2\frac{\sqrt{A_1|A|(A_1|A| - |A_{12}||A_{13}|)}}{|A_{13}|^2} := P + Q + \sqrt{S}. \tag{3.12}$$

LEMMA 4. *If the ratio of diffusion coefficients d_1/d_2 belongs to the interval (Λ_+, ∞), then DDI cannot occur.*

PROOF. The proof is based on Routh-Hurwitz criterion applied to degree-two polynomials. It states that the polynomial $P(s) = s^2 + a_1 s + a_0$ has both roots in the complex plane with negative real part if both $a_0 > 0$ and $a_1 > 0$. We thus homogenize $p_3(\mu)$ with a division by its leading coefficient

$$p_3(\mu) = \Big[-A_1 d_1 d_2\Big]\Big[\mu^2 + \frac{|A_{13}|d_1 + |A_{12}|d_2}{(-A_1)d_1 d_2}\mu + \frac{|A|}{A_1 d_1 d_2}\Big],$$

and hereafter identify both coefficients

$$a_0 := \frac{|A|}{A_1 d_1 d_2} \quad \text{and} \quad a_1 := \frac{|A_{13}|d_1 + |A_{12}|d_2}{(-A_1)d_1 d_2}.$$

By assumption, $|A|, A_1 < 0$ and thus $a_0 > 0$ unconditionally. The quantity a_1, however, depends on the choice of d_1 and d_2. Using $A_1 < 0$ and $|A_{13}| > 0$, a short reformulation shows $a_1 > 0$ if and only if

$$\frac{d_1}{d_2} > -\frac{|A_{12}|}{|A_{13}|} = Q.$$

From this we learn that for $d_1/d_2 > \Lambda_+ \geqslant Q$, we have $p_3(\mu_{\min}) < 0$, but both real roots are negative. Hence, $p_3(\mu) > 0$ for every $\mu \geqslant 0$ making $\bar{\boldsymbol{U}}$ linearly stable as steady state of (M), *i.e.*, this proves this lemma and no DDI occurs. □

Combining the result of our investigation, we are finally in good position to present

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

PROOF. We take $\Lambda = \Lambda_-$ from **case study 3** and show that $d_1/d_2 \in (0, \Lambda)$ is a necessary and sufficient condition for DDI.

(Necessary) Suppose $\lambda := d_1/d_2$ does not belong to the interval $(0, \Lambda)$. We split $\mathbb{R}_{>0}\backslash(0, \Lambda)$ in two parts:

$$\mathbb{R}_{>0}\backslash(0, \Lambda) = [\Lambda_-, \Lambda_+) \cup [\Lambda_+, \infty) = J_1 \cup J_2.$$

We already proved that $\lambda \in J_2$ forces both roots $\mu_\pm$ of $p_3(\mu)$ to have negative real part in the proof of lemma 4. The polynomial $p_3(\mu)$ being an upwards-oriented parabola, it is clear that for a nonnegative μ, one finds $p_3(\mu) > 0$, which means $\bar{\boldsymbol{U}}$ exhibits no DDI in this case. Now take $\lambda \in J_1$. Then, it is true that

$$p_3(\mu_{\min}) = -\frac{1}{4(-A_1)}\left(\sqrt{\frac{d_1}{d_2}}|A_{13}| + \sqrt{\frac{d_2}{d_1}}|A_{12}|\right)^2 - |A| \geqslant 0,$$

Hence, no DDI in that case either. This ends the "necessary" part of the proof.

(Sufficient) We show that $\lambda \in (0, \Lambda)$ yields the existence of a positive μ such that $p_3(\mu) < 0$. By definition of Λ, it holds that $\lambda \in (0, \Lambda)$ implies directly

$$p_3(\mu_{\min}) = -\frac{1}{4(-A_1)}\left(\sqrt{\frac{d_1}{d_2}}|A_{13}| - \sqrt{\frac{d_2}{d_1}}|A_{12}|\right)^2 + |A| < 0.$$

Thus, $p_3(\mu)$ has two real roots μ_- and μ_+. Next, we prove that $\mu_{\min} > 0$. Indeed, the condition is met whenever $d_1/d_2 < Q$. So we only need to show that $\Lambda < Q$, where.

$$\Lambda = Q + \frac{2}{|A_{13}|^2}\left(A_1|A| - \sqrt{A_1|A|\big(A_1|A| - |A_{12}||A_{13}|\big)}\right).$$

Let $Y := A_1|A| > 0$ and $q := -|A_{12}||A_{13}| > 0$. Because the mapping $x \longmapsto \sqrt{x}$ is monotone increasing and that $qY > 0$, it follows $Y - \sqrt{Y^2 + qY} < 0$ and

$$\Lambda = Q + \frac{2}{|A_{13}|^2}\left(Y - \sqrt{Y^2 + qY}\right) < Q.$$

Therefore, $\lambda < \Lambda$ implies $\mu_{\min} > 0$ as well as $p_3(\mu_{\min}) < 0$. This proves that we can choose L such that $s(A - \mu_k^2 D) > 0$ for some $\mu_k^2 := k^2\pi^2/L^2$, i.e, $\bar{\boldsymbol{U}}$ exhibits DDI (up to transferring the problem on the new domain $(0, L)$). $\square$

2. Selecting unstable eigenmodes

Here, we prove that within the already established possible range for d_1, d_2 yielding diffusion, there exists a choice of d_2 such that we have DDI at $\bar{\boldsymbol{U}}$ without requiring domain rescaling. For that, we show that below some critical threshold, all eigenmodes μ_k^2 with k below that threshold can become negative for a choice of d_2 large enough. We start with a short proposition

Proposition 2. *The function $p_3(\mu_k^2)$ has an affine dependence on the parameter d_2.*

Proof. For a fixed μ_k^2, a short reordering of each term shows

$$p_3(\mu_k^2) = \underbrace{\left(|A_{12}|\mu_k^2 - A_1 d_1 \mu_k^4\right)}_{\alpha} d_2 + \underbrace{\left(|A_{13}|d_1\mu_k^2 - |A|\right)}_{\beta}.$$

□

Using assumptions on A, it is clear that $\beta > 0$ for any choice of d_1, $k \geqslant 0$ while the sign of α can change. Before proving the main result of this section, we formulate the following lemma to restrict the size of d_1's playfield.

Lemma 5 (DDI threshold on d_1). *Fix the Jacobian A of the system with parameters $\boldsymbol{\Pi} \in \boldsymbol{\Theta}$. If L is fixed and*

$$d_1 \geqslant \frac{1}{\mu_1^2}\frac{|A_{12}|}{A_1} =: d_1^{(c)},$$

then DDI cannot occur.

Things are getting a little abstract. The schematic following plot enables us to get at least one foot on land and provides visual insights on the situation:

Proof. We know that $p_3 = p_3(\mu_0^2) > 0$ by assumption (Routh-Hurwitz for the ODE system). Our goal is then to prove that $p_3(\mu_1^2) > 0$ too. Let us take any $d_1 > d_1^{(c)}$, it follows

$$p_3(\mu_1^2) = \underbrace{\left(|A_{13}|d_1\mu_1^2 - |A|\right)}_{\text{positive}} + \left(|A_{12}|\mu_1^2 - A_1 d_1 \mu_1^4\right) d_2, \tag{3.13}$$

$$> \left(|A_{12}|\mu_1^2 - A_1 d_1 \mu_1^4\right) d_2, \tag{3.14}$$

$$> \left(|A_{12}|\mu_1^2 - A_1 \frac{1}{\mu_1^2}\frac{|A_{12}|}{A_1} \mu_1^4\right) d_2, \tag{3.15}$$

$$> \left(|A_{12}| - |A_{12}|\right)\mu_1^2 d_2 = 0. \tag{3.16}$$

Now that we have $p_3(\mu_1^2) > 0$, we show that $p_3(\mu_k^2) > p_3(\mu_1^2)$ for every $k > 1$. Introduce both quantities $\delta_{k^2} := \mu_k^2 - \mu_1^2$ and $\delta_{k^4} := \mu_k^4 - \mu_1^4$, it holds

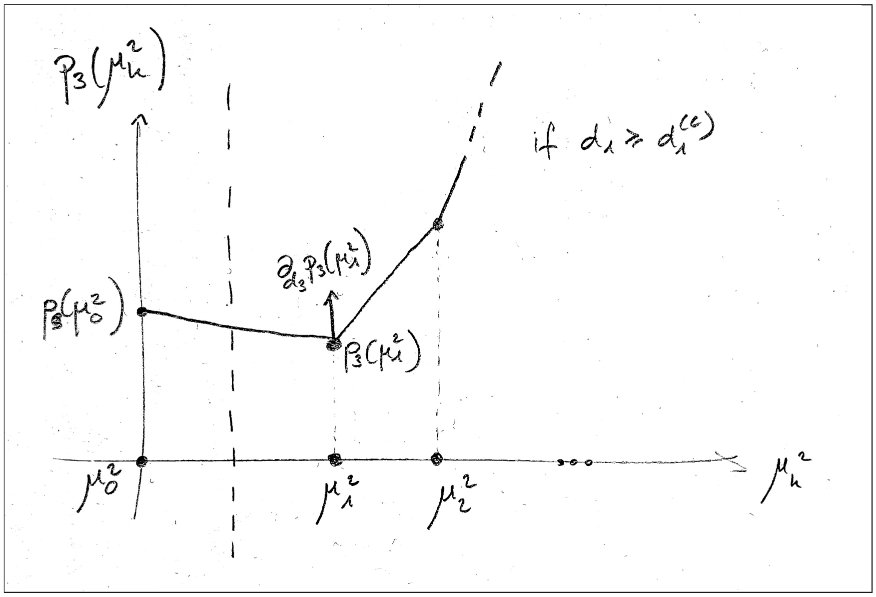


FIGURE 4. Discrete plot of $p_3(\mu_k^2)$ for several values of $k \geqslant 0$. show that if $d_1 \geqslant d_1^{(c)}$, then $p_3(\mu_1^2)$ is positive as well. The vertical dashed line is a threshold determined by the value of d_1, such that if k is bigger than the treshold, then $\partial_{d_3} p_3(\mu_k^2) > 0$. This property will be useful later in the nextx proof.

$$p_3(\mu_k^2) - p_3(\mu_1^2) = |A_{13}| d_1 \delta_{k^2} + \Bigg(|A_{12}| \delta_{k^2} - A_1 d_1 \delta_{k^4} \Bigg) d_2.$$

Since $|A_{13}| d_1 \delta_{k^2} > 0$ and $d_2 > 0$, we only need to investigate quantity between parentheses. It turns out

$$|A_{12}| \delta_{k^2} - A_1 d_1 \delta_{k^4} > |A_{12}| \left(\delta_{k^2} - \frac{\delta_{k^4}}{\mu_1^2} \right).$$

Where the estimate comes from $d_1 > d_1^{(c)}$. Now, from the definition of δ_{k^2} and δ_{k^4}, it is true that

$$p_3(\mu_k^2) - p_3(\mu_1^2) > |A_{12}| \left(\delta_{k^2} - \frac{\delta_{k^4}}{\mu_1^2} \right) > |A_{12}| \mu_k^2 \left(1 - k^2\right).$$

Since $k > 1, |A_{12}| < 0$, it follows that this last product is positive and therefore $p_3(\mu_k^2) > p_3(\mu_1^2) > 0$ for every k, i.e, no DDI occurs. □

Now that this is out of the way, we reach our second result, which is the following:

THEOREM 4 (Threshold for eigenmode stability). *Fix the Jacobian A of the system with parameters $\mathbf{\Pi} \in \mathbf{\Theta}$ and $d_1 < d_1^{(c)}$. For any positive integer k, if*

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

then there exists $d_2 = d_2(k) > 0$, large enough such that $p_3(\mu_k^2) < 0$ and therefore the steady state $\bar{\boldsymbol{U}}$ exhibits DDI.

PROOF. By proposition 2, $p_3(\mu_k^2) = \alpha d_2 + \beta$, where $\beta > 0$, and the sign of α is dependent on μ_k^2. The only way to get a negative $p_3(\mu_k^2)$ by adjusting d_2, is if there exists a μ_k^2 such that $\alpha < 0$and d_2 is large enough $(d_2 > -\alpha/\beta)$. Now, it we have

$$\alpha < 0 \quad \iff \quad \left(|A_{12}| - A_1 d_1 \mu_k^2\right)\mu_k^2 < 0 \quad \iff \quad \mu_k^2 < \frac{1}{d_1}\frac{|A_{12}|}{A_1},$$

It is only left to expand the definition of $\mu_k^2 := k^2\pi^2/L^2$ to find the condition

$$k^2 < \frac{L^2}{\pi^2}\frac{|A_{12}|}{d_1 A_1}.$$

The final estimate is obtained by taking the square root (since everything is positive) and then applying the floor function on both side of the inequality. This results in

$$\alpha < 0 \quad \iff \quad k \leqslant \left\lfloor \frac{L}{\pi}\sqrt{\frac{1}{d_1}\frac{A_{12}}{A_1}} \right\rfloor.$$

A choice of d_1 small enough clearly makes the right term large enough to get at least one integer $k \geqslant 1$ satisfying the inequality and therefore $p_3(\mu_k^2)$ gets negative for a large value of $d_2 > -\beta/\alpha$. $\square$

3. Numerical simulations and pattern formation

APPENDIX A

Jacobian of the system and properties

will be removed in the final version

We dedicate this appendix to presenting short results and properties that can be deduced from the Jacobian $A(u, v, w)$ and its coefficients at a glance. We start by computing the raw expression of the Jacobian

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

Working around the positive, nontrivial steady-states guarantees $\bar{u}, \bar{v}, \bar{w} > 0$. As such we can use the fact that $\bar{\boldsymbol{U}}$ is a steady state to work out equalities from $\boldsymbol{f}(\bar{\boldsymbol{U}}) = 0$. More precisely, one shows

$$m_1 \frac{\bar{v}}{1+\bar{u}\bar{v}} = \mu_f + \mu_b \bar{v}, \qquad m_2 \frac{\bar{u}}{1+\bar{u}\bar{v}} = \mu_l + \mu_b \bar{u} + \bar{w}.$$

This results in $A = A(\bar{\boldsymbol{U}})$ with the expression

$$A = \begin{bmatrix} -m_1 \dfrac{\bar{u}\bar{v}^2}{(1+\bar{u}\bar{v})^2} & \bar{u}\left(\dfrac{m_1}{(1+\bar{u}\bar{v})^2} - \mu_b\right) & 0 \\ \bar{v}\left(\dfrac{m_2}{(1+\bar{u}\bar{v})^2} - \mu_b\right) & -m_2 \dfrac{\bar{u}^2\bar{v}}{(1+\bar{u}\bar{v})^2} & -\bar{v} \\ m_3 \dfrac{\bar{v}}{(1+\bar{u}\bar{v})^2} & m_3 \dfrac{\bar{u}}{(1+\bar{u}\bar{v})^2} & -\mu_e \end{bmatrix}.$$

From there, one deduces the following properties for any choice of $\boldsymbol{\Pi}$ (as long as the positive steady state $\bar{\boldsymbol{U}}$ exists)

(A.1)	$A_1 := a_{11} < 0$	$\mathrm{tr} A_{13} < 0,$
(A.2)	$A_2 := a_{22} < 0$	$\lvert A_{13}\rvert > 0,$
(A.3)	$A_3 := a_{33} < 0$	$\mathrm{tr} A_{23} < 0,$
(A.4)	$a_{13} = 0$	$\lvert A_{23}\rvert > 0,$
(A.5)		$\mathrm{tr} A_{12} < 0.$

These properties by themselves prove that subsystems $A_1, A_2, A_3, A_{13}, A_{23}$ are always stable. However, if $\bar{\boldsymbol{U}}$ is stable as steady state of the (associated ODE) system without diffusion, then we need instability of at least one submatrix of the Jacobian A in order to destabilize $\bar{\boldsymbol{U}}$ by introducing diffusion. Thus, we have to choose $\mathbf{\Pi}$ in a way such that $|A_{12}| < 0$ (see, [Sakamoto])

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