Aix-Marseille Université
Faculté des Sciences

Master's degree in Computational And Mathematical Biology
Departement of Applied Mathematics

# Investigating Pattern Formation in a modified SMJM Model

Author

Théo André

Examining Board:

Prof. Laurence RODER .....
Prof. Florence HUBERT .....
Prof. Dr. Anna MARCINIAK-CZOCHRA .....

Candidate:

Théo ANDRÉ .....

Submitted on June 23 2023
Academic year 2022-2023

# Contents

## 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 $L^\infty$ 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, also called diffusion-driven instability or DDI for short. We will start from the definition of DDI and make our way to the main results of this thesis.

## 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.

These last two years of Master's degree were an extraordinary experience. I want to address a hearty thanks to Florence Hubert and Laurence Roder. They are excellent teachers and researchers who have always shown support and enabled me to meet a lot of fantastic people, from my classmates to the CENTURI team and CIRM researchers. I'm very honored to have them on the examining board.

Many friends supported me since the beginning of this thesis, and I am thankful to all of them. I'd particularly like to thank one of them who has always been there, through thick and thin: Thomas Serafini. He's a brilliant mathematician and the very definition of a true friend. He has proved that distance means nothing and pushes me to be a better person every day. I do not count the memories we share and cannot imagine the ones to come.

I would also like to thank my lab mates: Finn Münnich, Christian Düll, Denis Brazke, Filip Klaw, Diana-Patricia Danciu, Alexey Kazarnikov, Carolin Lindow and Joseph Holten. I have learned something from each one of them.

Lastly, I would like to thank my parents and my sister for their love and unconditional 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 .

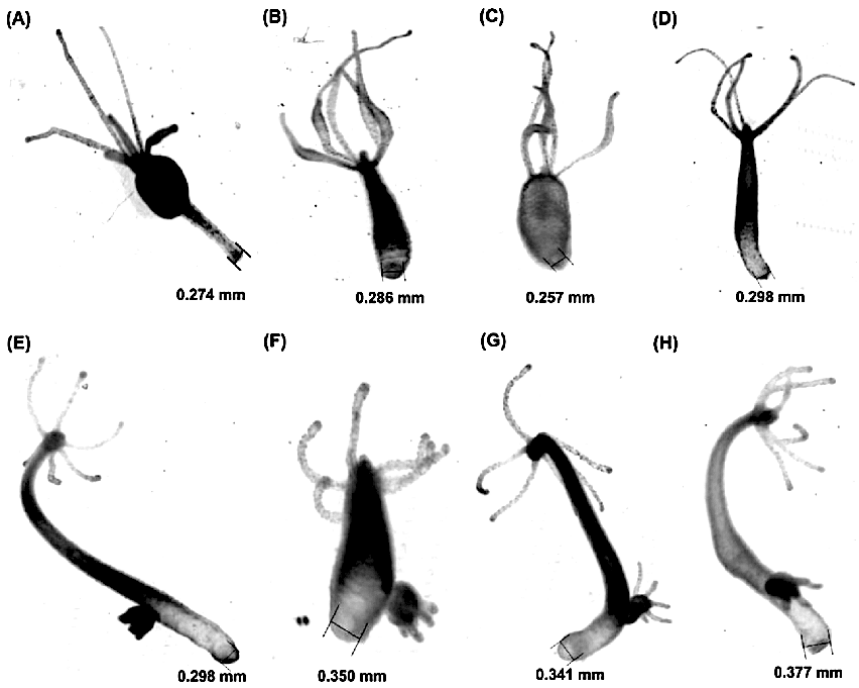



FIGURE 1. Zoo of hydras captured under a traditional microscope, all the credit for this figure goes to [9]

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. Cutting and grafting Experiments.** 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 gets its name, the existing head blocks the formation of no additional glow, 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 ($h$), by a factor $1/h$. Both molecules are subject to natural decay, scaled by parameters $\mu$ and $\nu$, and the brownian motion (molecular diffusion) is represented by the Laplace operator. The difference in diffusion rates of activators and inhibitors is represented by $D_a, D_h$. To avoid

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

invasion of activators, inhibitors have to diffuse faster, which is achieved with the condition $D_a \ll D_h$. In order to guarantee pattern formation, we artificially add small production rates independent on population size $\sigma_a, \sigma_h$ to ensure the patterning process. Put together, this yields the following system of equations:

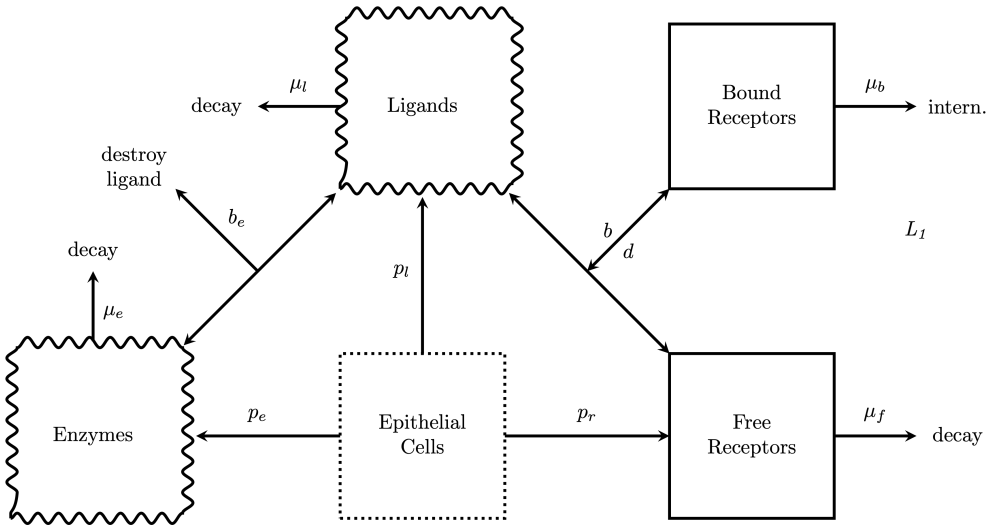
$$\begin{cases} \partial_t a = D_a \Delta a + \varrho \left( \frac{a^2}{h} - \mu a \right) + \sigma_a \\ \partial_t h = D_h \Delta h + \varrho \left( a^2 - \nu h \right) + \sigma_b \end{cases}$$

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 Wnt 3 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 $\ell$, 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:

$$\partial_t r_f = -\mu_f r_f + p_r(r_b) - b r_f \ell + d r_b, \tag{1.1}$$

$$\partial_t r_b = -\mu_b r_b + b r_f \ell - d r_b, \tag{1.2}$$

$$\partial_t \ell = d_1 \Delta \ell - \mu_\ell \ell + p_\ell(r_b) - b r_f \ell + d r_b, \tag{1.3}$$

$$\partial_t e = d_2 \Delta e - \mu_e e + m_3 p_e(r_b). \tag{1.4}$$

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

## 3. Quasi steady-state approximation (QSSA)

**3.1. A few words about 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

$$\frac{d}{dt}U = f_1(U,V), \tag{1.5}$$

$$\frac{d}{dt}V = f_2(U,V), \tag{1.6}$$

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

$$\frac{d}{dt}U_\varepsilon = f_1(U_\varepsilon, V_\varepsilon) \tag{1.7}$$

$$\varepsilon\frac{d}{dt}V_\varepsilon = f_2(U_\varepsilon, V_\varepsilon) \tag{1.8}$$

One sees that if $\varepsilon = 1$ yields the original system, and that for sufficiently small values of $\varepsilon$, (in practical, we take the limit as $\varepsilon$ 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 $f_2(U,V) = 0$. This enables one to simplify the previous system to

$$\frac{d}{dt}U_\varepsilon = f_1(U_\varepsilon, \mathcal{H}(U_\varepsilon)) \tag{1.9}$$

$$V_\varepsilon = \mathcal{H}(U_\varepsilon) \tag{1.10}$$

This eliminates one of the two differential equations. One can now solve the equation on $U_\varepsilon$ 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.

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 $\varepsilon$ goes to 0, the solutions $U_\varepsilon, V_\varepsilon$ are close in $L^1$-norm to $u, v$ (in $L^1_{\text{loc}}$ 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 (.)-(.), wherein $r_b$ is seen as the transient (fast) variable. It follows

$$\partial_t r_f = -\mu_f r_f + m_1 \frac{r_b}{1+r_b} - b r_f \ell + d r_b, \tag{1.11}$$

$$\varepsilon \partial_t r_b = -\mu_b r_b + b r_f \ell - d r_b \tag{1.12}$$

$$\partial_t \ell = d_1 \Delta \ell - \mu_l \ell + m_2 \frac{r_b}{1+r_b} - b r_f \ell + d r_b - b_e \ell e, \tag{1.13}$$

$$\partial_t e = d_2 \Delta e - \mu_e e + m_3 \frac{r_b}{1+r_b}. \tag{1.14}$$

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

$$-\mu_b r_b + b r_f \ell - d r_b = 0. \tag{1.15}$$

Which, after algebraic manipulations, 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 $\alpha$ 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.

$$\partial_t r_f = -\mu_f r_f + m_1 \frac{\alpha r_f \ell}{1+\alpha r_f \ell} - b r_f \ell + d \alpha r_f \ell, \tag{1.16}$$

$$\partial_t \ell = d_1 \Delta \ell - \mu_l \ell + m_2 \frac{\alpha r_f \ell}{1+\alpha r_f \ell} - b r_f \ell + d \alpha r_f \ell - b_e \ell e, \tag{1.17}$$

$$\partial_t e = d_2 \Delta e - \mu_e e + m_3 \frac{\alpha r_f \ell}{1+\alpha r_f \ell}. \tag{1.18}$$

**Remark:** It is absolutely crucial to understand that, during this manipulation, the right-hand side of equation (1.12) 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 $\alpha$, we can have a slightly better expression for the reaction term in equations on $r_f$ and $\ell$ 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. A game of parentheses allows us to write

$$\partial_t r_f = -\mu_f r_f + m_1 \frac{(\sqrt{\alpha} r_f)(\sqrt{\alpha}\ell)}{1 + (\sqrt{\alpha} r_f)(\sqrt{\alpha}\ell)} - \mu_b (\sqrt{\alpha} r_f)(\sqrt{\alpha}\ell), \tag{1.19}$$

$$\partial_t \ell = d_1 \Delta \ell - \mu_l \ell + m_2 \frac{(\sqrt{\alpha} r_f)(\sqrt{\alpha}\ell)}{1 + (\sqrt{\alpha} r_f)(\sqrt{\alpha}\ell)} - \mu_b (\sqrt{\alpha} r_f)(\sqrt{\alpha}\ell) - \ell(b_e e), \tag{1.20}$$

$$\partial_t e = d_2 \Delta e - \mu_e e + m_3 \frac{(\sqrt{\alpha} r_f)(\sqrt{\alpha}\ell)}{1 + (\sqrt{\alpha} r_f)(\sqrt{\alpha}\ell)}. \tag{1.21}$$

This new writing strongly motivates the change of variable

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

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

which, once injected back into (.)-(.), results in

$$\partial_t u = -\mu_f u + \tilde{m}_1 \frac{uv}{1 + uv} - \tilde{\mu}_b uv, \tag{1.22}$$

$$\partial_t v = d_1 \Delta v - \mu_l v + \tilde{m}_2 \frac{uv}{1 + uv} - \tilde{\mu}_b uv - vw, \tag{1.23}$$

$$\partial_t w = d_1 \Delta w - \mu_e w + \tilde{m}_3 \frac{uv}{1 + uv}. \tag{1.24}$$

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 3