

# Patterns Analysis in Coupled Parabolic-ODE Systems

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## Abstract

This thesis builds upon previous work pioneered by Anna Marciniak-Czochra in using coupled reaction-diffusion equations to ODE to model pattern formation 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 and Notch as playing a critical role in this process. However, these models have largely ignored the physical properties of the tissues in which regeneration occurs. In this thesis, we come back to the model presented in [7] that integrates coupled reaction-diffusion to ODE models and see if we can reduce the amount of parameters, exhibit hysteresis and investigate the phenomenon of Turing Patterns / Far-From-Equilibrium patterns. Ultimately, this thesis aims to provide classical results on the topic and use these notions to further extend the analysis of the model.

**Remark 1** (Color code for Editing). *Each color has a meaning:*

*Pink text:* A remark / Comment: `\com{ ... }`

*Green text:* Potential text to include but has the wrong formulation: `\incl{ ... }`

*Blue text:* A reference that is missing and has to be included in the bibliography : `\bref{ ... }`

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<https://www.youtube.com/watch?v=6rr5oLEjMmY> : How to collect polyps and medusae

[https://youtu.be/hmkeZ7\\_6owI](https://youtu.be/hmkeZ7_6owI) : Hydra morphogenesis symposium

“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 Notations and Definitions

In the entirety of the thesis, we use the following naming conventions

- $\Delta$ : The Neumann Laplace operator defined by  $\Delta f = \sum_{j=1}^n \frac{\partial^2 f}{\partial x_j^2}$  with domain

$$\mathcal{D}(\Delta) = \left\{ f \in \bigcap_{p \geq 1} W_{loc}^{2,p}(\Omega) : f, \Delta f \in \mathcal{C}(\Omega) \text{ and } \frac{\partial f}{\partial \nu} = 0 \text{ on } \partial\Omega \right\}$$

this notation is the one from [2], maybe it is unnecessarily developed for this thesis

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

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

**Definition 2** (spectral bound). *Let  $(L, \mathcal{D}(L))$  be a linear operator with spectrum  $\sigma(L)$ . We define the spectral bound  $s(L)$  by*

$$s(L) = \sup \{ \Re(\lambda) : \lambda \in \sigma(L) \}$$

**Definition 3** (Growth Exponent). *We call the growth exponent of an exponentially bounded  $\mathcal{C}^0$ -semigroup  $(T(t))_{t \geq 0}$  the real number  $w$  defined by*

$$w = \inf_{\mathbb{R}} \left\{ w : \exists M > 1, \forall t \geq 0, \|T(t)\| \leq M e^{wt} \right\}$$

## 2 Hydra Morphogenesis and regenerative properties

### 2.1 Anatomy of a Hydra

Hydras are fascinating organisms. Despite their rather small size (roughly 5mm of length in average), they are capable of extraordinary regenerative properties that allow them to fully reconstruct their body out of a very small portion of tissue (see figure 2.1).

Their body is composed of essentially three regions: the head, body column and foot. Spatially speaking, the small cnidarian is symmetrically organized around the oral-aboral axis giving it its hollow, tubular shape. Taking a step closer on each parts, one can notice that the head is composed of two sub-regions, one being a set of tentacles

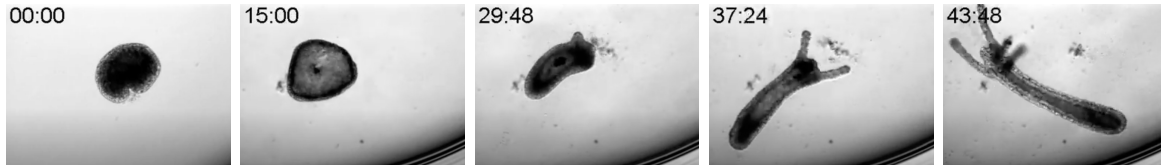


Figure 1: Sequence of pictures taken under a traditional microscope. It shows how hydras are capable of regenerating their entire body using small extracted samples of tissue coming from the body column of another hydra (tissue diameter is about  $100\ \mu\text{m}$ ). The timestamp on each picture is formatted as "hours:minutes", meaning the entire regeneration process takes less than two days to occur.

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 leaves and rocks - among others - underwater. 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.

**Remark 2** (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 not, see figure ?? (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 opens the door to further reproduction preserving genetics and repeated multiplication of specimens. This considerably enhances the pace at which experiments occur while reducing randomness factor linked to genetics (therefore improving reproducibility of experiments).*

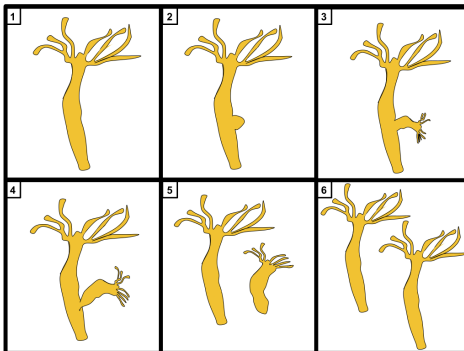


Figure 2: Illustrated process of asexual reproduction in Hydra. A new head grows on the body column at the top of the peduncle (this small lump is familiarly call "the bud") and keeps growing until it detaches from the "adult"'s body. Once detached, the new individual sticks to nearby rocks or leaves and keeps growing until adult size is reached. (credit: picture from [5])

## 2.2 The importance of Wnt signaling

What's up ? pal

## 3 Emergence of Patterns and Diffusion-Driven Instability

How do patterns form? Pattern formation is the result of the collaboration of a large amount of biological processes ranging from the nanoscopic up to the microscopic scale.

Together, they form motifs, which we define as the structural organization of cells in space and time, often leading to pretty shapes such as the fur coat in animals or that on the wings of a butterfly. In his pioneer paper published in 1952 [ref], Alan Turing proposes a chemical model for pattern formation involving two chemical species: one Activator ( $u$ ), one Inhibitor ( $v$ ) (Probably inspired from the Lotka-Volterra prey-predator model introduced in 1910 which was itself applied to mathematical biology for the first time in 1926). The concentration of each specie is described with 2-morphogens reaction-diffusion equations with appropriate boundary conditions, *i.e.* equations of the form

$$\begin{aligned}\partial_t u &= d_1 \Delta u + f(u, v) && \text{on } \mathbb{R}^+ \times \Omega \\ \partial_t v &= d_2 \Delta v + g(u, v) && \text{on } \mathbb{R}^+ \times \Omega\end{aligned}\tag{3.1}$$

$$\begin{aligned}\partial_\nu u &= 0; \quad \partial_\nu v = 0 && \text{on } \partial\Omega \\ u(0, x) &= u_0(x); \quad v(0, x) = v_0(x) && u_0, v_0 \in X\end{aligned}\tag{3.2}$$

for a specific choice of  $f$  and  $g$  describing the chemical kinetics of the reaction. This choice is usually what determines the model type. To cite a few, we enumerate the Gray-Scott Model, Gierer-Meinhardt, Fitzhugh-Nagumo, Bard-Lauder, Schnakenberg, Belousov-Zhabotinskii, the list goes on... [B. Perthame]

## 4 General Theory

Consider positive integers  $k, m, n \in \mathbb{N}$  such that  $m + k = n$  and a bounded domain  $\Omega \subset \mathbb{R}^n$ . Let the  $\mathcal{C}^2$ -function  $\mathbf{f} : \mathbb{R}^k \times \mathbb{R}^m \longrightarrow \mathbb{R}^{m+k}$  describe the reaction kinetics. We aim to investigate properties of the reaction-diffusion-ODE problem

$$\begin{aligned}\partial_t \mathbf{u} &= \mathbf{D} \Delta \mathbf{u} + \mathbf{f}(\mathbf{u}) && \text{on } \Omega \times \mathbb{R}^+ \\ \nabla u_i \cdot \nu &= 0 && \text{on } \partial\Omega \times \mathbb{R}^+, \text{ for } i \in \llbracket m+1, k \rrbracket \\ \mathbf{u}(\cdot, 0) &= \mathbf{u}_0(\cdot) && \text{on } \Omega,\end{aligned}\tag{4.1}$$

### 4.1 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 4** (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 [1] □

**Definition 5** (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  $1 \leq i, j \leq n$ , we introduce the notation  $A_{ij}$  to be the  $2 \times 2$ -matrix whose entries are formed by the entries of  $A$  on line and column  $i, j$ .*

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

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

*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

## 5 Introduction of the model

## 6 Reduction of the Model

In order to simplify the system, we use a two-step approach. First, by applying a quasi-steady-state approximation, and then by using a change of variable to further reduce the amount of parameters.

## 6.1 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.

Previously used in an *ad hoc* fashion by biologists, the theory behind QSSA has been thoroughly explored and is now carefully described thanks to the framework provided by singular perturbation theory. In particular 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 3.** *Although the QSSA can be proven to be physically relevant when applied to some systems (Reaction-Diffusion equations are a good example), 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  $\frac{\partial r_b}{\partial t} \equiv 0$ . and find that  $(d + \mu_b)r_b = buv$ , therefore

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

For what follows, we define  $\alpha = b/(d + \mu_b)$  and replace the newly found value of  $r_b$  in the system.

$$\begin{aligned} \frac{\partial}{\partial t} \mathbf{u} &= -\mu_f \mathbf{u} + m_1 \frac{\alpha uv}{1 + \alpha uv} - buv + d\alpha uv \\ \frac{\partial}{\partial t} \mathbf{v} &= \frac{1}{\gamma} \frac{\partial^2 \mathbf{v}}{\partial x^2} - \mu_l \mathbf{v} + m_2 \frac{\alpha uv}{1 + \alpha uv} - buv + d\alpha uv - b_e v \mathbf{w} \\ \frac{\partial}{\partial t} \mathbf{w} &= \frac{d_2}{\gamma} \frac{\partial^2 \mathbf{w}}{\partial x^2} - \mu_e \mathbf{w} + m_3 \frac{\alpha uv}{1 + \alpha uv} \end{aligned} \quad (6.1)$$

## 6.2 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 notice that  $d\alpha - b = -\mu_b\alpha$ , and then proceed to the change of variable

new variable / parameter	$\tilde{\mathbf{u}}$	$\tilde{\mathbf{v}}$	$\tilde{\mathbf{w}}$	$\tilde{m}_1$	$\tilde{m}_2$	$\tilde{m}_3$	$\tilde{\mu}_b$
value	$\sqrt{\alpha} \mathbf{u}$	$\sqrt{\alpha} \mathbf{v}$	$b_e \mathbf{w}$	$\sqrt{\alpha} m_1$	$\sqrt{\alpha} m_2$	$\sqrt{\alpha} m_3$	$\sqrt{\alpha} \mu_b$

the new system is then simplifying down to

$$\begin{aligned}
\frac{\partial}{\partial t} \tilde{\mathbf{u}} &= -\mu_f \tilde{\mathbf{u}} + \tilde{m}_1 \frac{\tilde{\mathbf{u}} \tilde{\mathbf{v}}}{1 + \tilde{\mathbf{u}} \tilde{\mathbf{v}}} - \tilde{\mu}_b \tilde{\mathbf{u}} \tilde{\mathbf{v}} \\
\frac{\partial}{\partial t} \tilde{\mathbf{v}} &= \frac{1}{\gamma} \frac{\partial^2 \tilde{\mathbf{v}}}{\partial x^2} - \mu_l \tilde{\mathbf{v}} + \tilde{m}_2 \frac{\tilde{\mathbf{u}} \tilde{\mathbf{v}}}{1 + \tilde{\mathbf{u}} \tilde{\mathbf{v}}} - \tilde{\mu}_b \tilde{\mathbf{u}} \tilde{\mathbf{v}} - \tilde{\mathbf{v}} \tilde{\mathbf{w}} \\
\frac{\partial}{\partial t} \tilde{\mathbf{w}} &= \frac{d_2}{\gamma} \frac{\partial^2 \tilde{\mathbf{w}}}{\partial x^2} - \mu_e \tilde{\mathbf{w}} + \tilde{m}_3 \frac{\tilde{\mathbf{u}} \tilde{\mathbf{v}}}{1 + \tilde{\mathbf{u}} \tilde{\mathbf{v}}}
\end{aligned} \tag{6.2}$$

For the sake of readability, we drop the  $\sim$  notation in the future.

### 6.3 Invariant Region

In this section, we prove the existence of a region  $\Sigma$  such that, whenever the initial condition lies in  $\Sigma$ , we have existence of solutions for all  $t > 0$ . For that we consider the function  $f = (f^1, f^2, f^3)$  such that  $\partial_t(u, v, w) = f(u, v, w)$  and introduce the definition

**Definition 6** ( $f$ -stability (from [12])). *A system of the form*

$$\partial_t u = D \partial_{xx}^2 u + f(u), \tag{6.3}$$

*is said to be  $f$ -stable if, whenever  $f$  is the limit of functions  $f_n$  in the  $\mathcal{C}^1$ -topology on compacta, for all  $t > 0$  then any solution of 6.3 supplemented with initial condition is the limit in the compact-open topology, of solutions of solutions of 6.3, where  $f$  is replaced by  $f_n$*

**Lemma 1** (boundedness of solutions). *There exists three positive reals  $A_u, A_v, A_w$  such that the region*

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

*is  $f$ -invariant, i.e. the vector field  $\phi_f$  generated by  $f$  never points outwards of  $\Sigma$*

*Proof.* Assuming 6.2 is  $f$ -stable, we proceed in two steps. First we show that solutions with a non-negative initial condition will always stay non-negative for all  $t > 0$ , which is significant from a biological modeling point of view. Then we prove that there exists an upper bound for each quantity (no explosion in finite time). Let us start by rewriting

$$\Sigma = \Sigma_0 \cap \Sigma_A =: \bigcap_i \left( \{G_i \leq 0\} \cap \{H_i \leq 0\} \right), \quad i \in \{u, v, w\}$$

The rectangular region (which is clearly convex) where each  $G_i$  and  $H_i$  are smooth functions prescribing the constraints on  $\Sigma$ . They are defined as follows

$$\begin{aligned}
G_u(u, v, w) &= -u & H_u(u, v, w) &= u - A_u \\
G_v(u, v, w) &= -v & H_v(u, v, w) &= v - A_v \\
G_w(u, v, w) &= -w & H_w(u, v, w) &= w - A_w
\end{aligned}$$



Then, we define  $\partial\Sigma := \{X \in \Sigma : \exists i, G_i(X) = 0 \vee H_i(X) = 0\} = \partial\Sigma_0 \cap \partial\Sigma_A$ . Let us take  $X \in \partial\Sigma_0$ . If  $u = 0$ , then

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

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

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

Finally, since  $X \in \partial\Sigma_0$ , it holds that  $u, v \geq 0$ , which means that if  $w = 0$ , then

$$(\nabla G_w \cdot \phi_f)(X)|_{w=0} = -m_3 \frac{uv}{1+uv} < 0$$

This proves that  $\Sigma_0$  is invariant by  $f$ . Let us proceed in similar fashion to prove that  $\Sigma_A$  is also  $f$ -invariant. First, we notice that

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

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

$$f^1(u, v, w) \leq m_1 - \min(\mu_f, \mu_b)u.$$

In other words, we can find a real  $A_u \in \mathbb{R}_{>0}$  such that  $A_u > m_1/\min(\mu_f, \mu_b)$ . This implies  $(\nabla H_u \cdot \phi_f)(X)|_{u=A_u} = f^1(A_u, v, w) \leq 0$ . The same logic applies to show

$$f^2(u, v, w) \leq m_2 - \min(\mu_f, \mu_b, 1)v.$$

Thus, by picking  $A_v \geq m_2/\min(\mu_f, \mu_b, 1)$ , we get  $(\nabla H_v \cdot \phi_f)(X)|_{v=A_v} \leq 0$ . To conclude this proof, we show that

$$f^3(u, v, w) \leq m_3 - \mu_e w,$$

and take  $A_w \geq m_3/\mu_e$  to obtain  $(\nabla H_w \cdot \phi_f)(X)|_{w=A_w} \leq 0$ . Theorem (3.16) from [AMC] strikes the final blow.  $\square$

This powerful theorem enables us to guarantee the existence of solutions to 6.2 coupled with homogeneous Neumann boundary conditions under biologically relevant initial conditions.

## 7 Finding equilibria and bounds on parameters

Depending on the choice of parameters, there is either one (stable), two (stable-unstable) or three (stable-unstable-stable) equilibria to 6.2. In each scenario, the origin  $(0, 0, 0)$  is a steady state and will always be stable. For a specific range of parameters, another stable, positive equilibrium arises whose value turns out to be rather cumbersome due to the "Michaelis-Menten" term in the kinetics equations. However, having in mind that the choice of parameters directly impacts the value of  $\bar{X}$ , one can derive a set of conditions  $\bar{X}$  must satisfy in order for this positive steady-state to exist.

## 8 Behavior of the system

Looking at the kinetics system, the Jacobian matrix  $A$  is given by  $A(\mathbf{u}, \mathbf{v}, \mathbf{w}) = (a_{ij})_{1 \leq i, j \leq n}$ , with

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

The jacobian can actually be represented in a nicer form. Since we are only interested of value of the jacobian taken at steady states, we can make use of the following identities

$$f^1(u, v, w) = 0 \quad f^2(u, v, w) = 0 \quad f^3(u, v, w) = 0 \quad (8.1)$$

### 8.1 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  $\mu_f, \mu_b, \mu_e$  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 3).

### 8.2 Around the other steady state

Let us move our interest to the other stable steady state (provided the choice of parameters allows it to exist). Using the fact that each term  $u, v, w$  is positive, we can operate some surgery on identities 8.1 to derive

$$m_1 \frac{\mathbf{v}}{1 + \mathbf{u}\mathbf{v}} = \mu_f + \mu_b \mathbf{v} \quad m_2 \frac{\mathbf{u}}{1 + \mathbf{u}\mathbf{v}} = \mu_l + \mu_b \mathbf{u} + \mathbf{w} \quad m_3 \frac{\mathbf{u}\mathbf{v}}{1 + \mathbf{u}\mathbf{v}} = \mu_e \mathbf{w} \quad (8.2)$$

Now notice that by virtually adding '0', we get

$$m_1 \frac{\mathbf{v}}{(1 + \mathbf{u}\mathbf{v})^2} = m_1 \frac{\mathbf{v} + \mathbf{u}\mathbf{v}^2 - \mathbf{u}\mathbf{v}^2}{(1 + \mathbf{u}\mathbf{v})^2} = m_1 \left( \frac{\mathbf{v}}{1 + \mathbf{u}\mathbf{v}} - \frac{\mathbf{u}\mathbf{v}^2}{(1 + \mathbf{u}\mathbf{v})^2} \right)$$

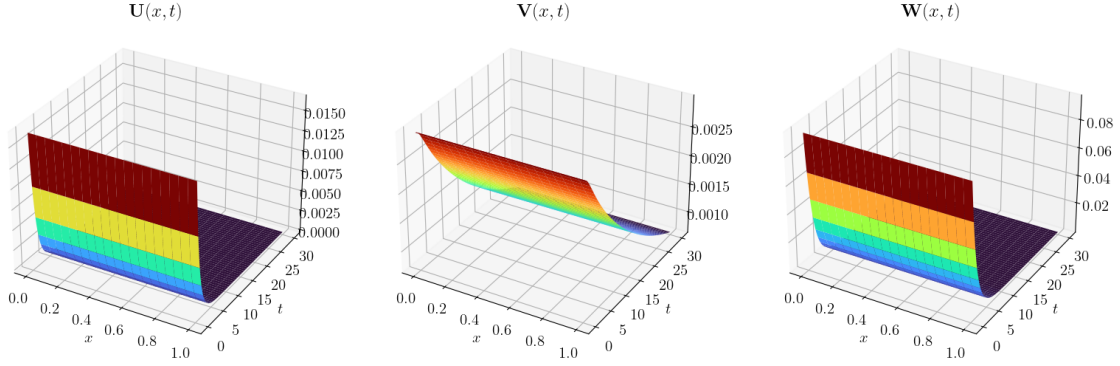


Figure 3: space-time plot of numerical solutions  $u, v, w$  to 6.2 with constant initial condition  $\mathbf{X}_0 = (\mathbf{u}_0, \mathbf{v}_0, \mathbf{w}_0)$  close to the origin. One clearly sees how each quantity converges towards 0

Hence, the coefficient  $a_{11}$  of the Jacobian becomes

$$a_{11} = -\mu_f - \mu_b \mathbf{v} + m_1 \frac{\mathbf{v}}{1 + \mathbf{uv}} - m_1 \frac{\mathbf{uv}^2}{(1 + \mathbf{uv})^2} \stackrel{8.2}{=} -m_1 \frac{\mathbf{uv}^2}{(1 + \mathbf{uv})^2}$$

**Theorem 2** (Routh-Hurwitz criterion of order 3). *Take a matrix  $M \in \mathcal{M}_3(\mathbb{R})$ . Then all the roots of  $\chi_M$  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*

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

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

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

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  $a_2a_1 > a_0$ .

**Lemma 2** (Necessary condition for DDI). *Let  $B := A - \lambda D$  denote the matrix of the linearized system. We claim that we obtain DDI if and only if  $\det(B_{12}) < 0$  and*

**Remark 4** (Minimum). *The function  $\mu \mapsto |A - \mu D|$  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

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

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

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