Patterns Analysis in Coupled Parabolic-ODE Systems

Théo ANDRÉ

Turing Center For Living Systems & Aix-Marseille Université

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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 [6] 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{ ...}`

Contents

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

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

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

this notation is the one from [2], maybe it is unnecessarly developped 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*

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

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

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

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 allows 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 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 ensures a constant cellular turnover of the derm (+ add why is it good).

Figure 1: Sequence of pictures taken under a traditional microscope. It shows how a Hydra is capable of regenerating its entire body from a small extracted sample of tissue coming from the body column (tissue diameter about 100 μm) of another Hydra. The timestamp on each picture is formatted as "hours:minutes", meaning the entire regeneration process takes place within the span of two days only.

2.2 Hydra reproduction and selection

The way Hydras reproduce is very beneficial to the scientific community since they are able to reproduce either sexually or asexually (with the second one being the most common way of reproduction). The main difference between these two methods is that asexual reproduction preserves the totality of information in one individual, letting one the ability to "keep" a specific Hydra with nice genetic information for further reproduction. It is possible to repeatedly multiply a specific organism through asexual reproduction yielding

2.3 The importance of Wnt signaling

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

$$\begin{aligned} \partial_t u &= d_1 \Delta u + f(u,v) && \text{on } \mathbb{R}^+ \times \Omega \\ \partial_t v &= d_2 \Delta v + g(u,v) && \text{on } \mathbb{R}^+ \times \Omega \qquad (3.1) \\ \partial_\nu u &= 0; \quad \partial_\nu v = 0 && \text{on } \partial\Omega \\ u(0,x) &= u_0(x); \quad v(0,x) = v_0(x) && u_0, v_0 \in X \qquad (3.2) \end{aligned}$$

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 $\boldsymbol{f} : \mathbb{R}^k \times \mathbb{R}^m \longrightarrow \mathbb{R}^{m+k}$ describe the reaction kinetics. We aim to investigate properties of the reaction-diffusion-ODE problem

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

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

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

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

.

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 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.

5.1 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, they 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 2. *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 $(d + \mu_b)\boldsymbol{r_b} = b\boldsymbol{uv}$, therefore

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

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

$$\frac{\partial}{\partial_t}\boldsymbol{u} = -\mu_f \boldsymbol{u} + m_1 \frac{\alpha \boldsymbol{u}\boldsymbol{v}}{1+\alpha \boldsymbol{u}\boldsymbol{v}} - b\boldsymbol{u}\boldsymbol{v} + d\alpha \boldsymbol{u}\boldsymbol{v}$$

$$\frac{\partial}{\partial_t}\boldsymbol{v} = \frac{1}{\gamma}\frac{\partial^2 \boldsymbol{v}}{\partial x^2} - \mu_l \boldsymbol{v} + m_2 \frac{\alpha \boldsymbol{u}\boldsymbol{v}}{1+\alpha \boldsymbol{u}\boldsymbol{v}} - b\boldsymbol{u}\boldsymbol{v} + d\alpha \boldsymbol{u}\boldsymbol{v} - b_e \boldsymbol{v}\boldsymbol{w} \tag{5.1}$$

$$\frac{\partial}{\partial_t}\boldsymbol{w} = \frac{d_2}{\gamma}\frac{\partial^2 \boldsymbol{w}}{\partial x^2} - \mu_e \boldsymbol{w} + m_3 \frac{\alpha \boldsymbol{u}\boldsymbol{v}}{1+\alpha \boldsymbol{u}\boldsymbol{v}}$$

5.2 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	$\tilde{\boldsymbol{u}}$	$\tilde{\boldsymbol{v}}$	$\tilde{\boldsymbol{w}}$	$\tilde{m}_1$	$\tilde{m}_2$	$\tilde{m}_3$	$\tilde{\mu_b}$
value	$\sqrt{\alpha}\boldsymbol{u}$	$\sqrt{\alpha}\boldsymbol{v}$	$b_e \boldsymbol{w}$	$\sqrt{\alpha} m_1$	$\sqrt{\alpha} m_2$	$\sqrt{\alpha} m_3$	$\sqrt{\alpha}\mu_b$

the new system is then simpliying down to

$$\frac{\partial}{\partial_t}\tilde{\boldsymbol{u}} = -\mu_f \tilde{\boldsymbol{u}} + \tilde{m}_1 \frac{\tilde{\boldsymbol{u}}\tilde{\boldsymbol{v}}}{1+\tilde{\boldsymbol{u}}\tilde{\boldsymbol{v}}} - \tilde{\mu_b}\tilde{\boldsymbol{u}}\tilde{\boldsymbol{v}}$$

$$\frac{\partial}{\partial_t}\tilde{\boldsymbol{v}} = \frac{1}{\gamma}\frac{\partial^2 \tilde{\boldsymbol{v}}}{\partial x^2} - \mu_l \tilde{\boldsymbol{v}} + \tilde{m}_2 \frac{\tilde{\boldsymbol{u}}\tilde{\boldsymbol{v}}}{1+\tilde{\boldsymbol{u}}\tilde{\boldsymbol{v}}} - \tilde{\mu_b}\tilde{\boldsymbol{u}}\tilde{\boldsymbol{v}} - \tilde{\boldsymbol{v}}\tilde{\boldsymbol{w}} \tag{5.2}$$

$$\frac{\partial}{\partial_t}\tilde{\boldsymbol{w}} = \frac{d_2}{\gamma}\frac{\partial^2 \tilde{\boldsymbol{w}}}{\partial x^2} - \mu_e \tilde{\boldsymbol{w}} + \tilde{m}_3 \frac{\tilde{\boldsymbol{u}}\tilde{\boldsymbol{v}}}{1+\tilde{\boldsymbol{u}}\tilde{\boldsymbol{v}}}$$

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

5.3 Invariant Region

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

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

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

is f-invariant, i.e. the vector field ϕ_f generated by f never points outwards of Σ

Proof. 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

$$\Sigma = \Sigma_0 \cap \Sigma_A =: \bigcap_i \Big(\{G_i \leqslant 0\} \cap \{H_i \leqslant 0\} \Big), \qquad i \in \{u, v, w\}$$

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

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

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

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

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

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

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

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

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

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

This proves that Σ_0 is invariant by f. Let us proceed in similar fashion to prove that Σ_A is also f-invariant. First, we notice that

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

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

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

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 $(\nabla H_u \cdot \phi_f)(X)|_{u=A_u} = f^1(A_u, v, w) \leqslant 0$. The same logic applies to show

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

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

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

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

This powerful theorem enables us to guarantee the existence of solutions to 5.2 coupled with homogeneous Neumann boundary conditions under biologically relevant initial conditions.

6 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 5.2. 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 exists.

7 Behavior of the system

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

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

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

$$f^1(u, v, w) = 0 \qquad f^2(u, v, w) = 0 \qquad f^3(u, v, w) = 0 \tag{7.1}$$

7.1 In a neighborhood of the origin

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

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

which, by positivity of μ_f, μ_b, μ_e is unconditionally stable. Take a moment to convince yourself that in this case, there is no hope for DDI (to see why, notice that $\operatorname{tr}(A - \boldsymbol{\mu} D) < 0$ 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 2).

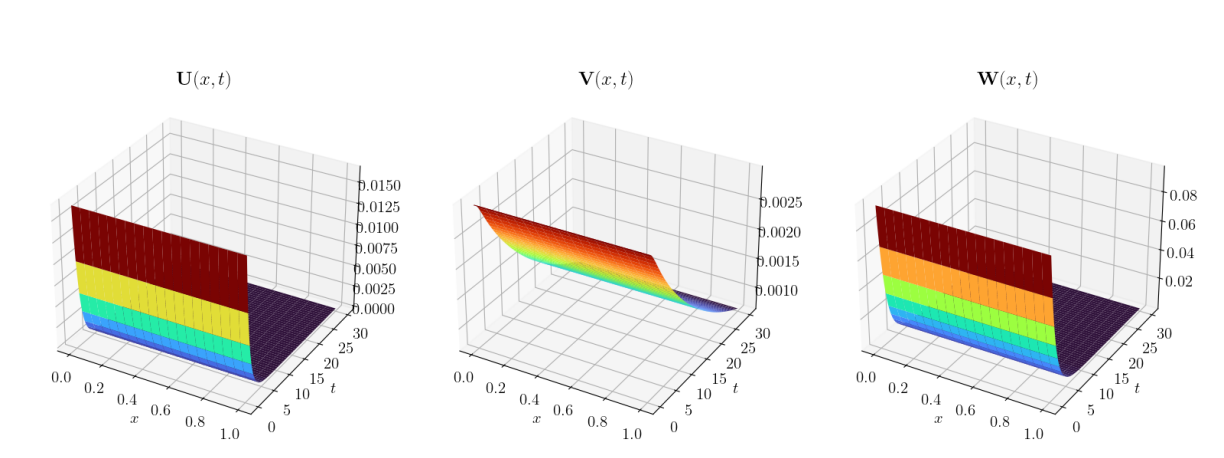

Figure 2: space-time plot of numerical solutions u, v, w to 5.2 with constant initial condition $\boldsymbol{X}_0 = (\boldsymbol{u}_0, \boldsymbol{v}_0, \boldsymbol{w}_0)$ close to the origin. One clearly sees how each quantity converges towards 0

7.2 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 7.1 to derive

$$m_1 \frac{\boldsymbol{v}}{1+\boldsymbol{uv}} = \mu_f + \mu_b \boldsymbol{v} \qquad m_2 \frac{\boldsymbol{u}}{1+\boldsymbol{uv}} = \mu_l + \mu_b \boldsymbol{u} + \boldsymbol{w} \qquad m_3 \frac{\boldsymbol{uv}}{1+\boldsymbol{uv}} = \mu_e \boldsymbol{w} \tag{7.2}$$

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

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

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

$$a_{11} = -\mu_f - \mu_b \boldsymbol{v} + m_1 \frac{\boldsymbol{v}}{1+\boldsymbol{uv}} - m_1 \frac{\boldsymbol{uv}^2}{(1+\boldsymbol{uv})^2} \overset{7.2}{=\!=} -m_1 \frac{\boldsymbol{uv}^2}{(1+\boldsymbol{uv})^2}$$

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

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

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

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

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

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 3 (Minimum). *The function $\mu \longmapsto |A - \mu D|$ 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*

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

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

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