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Contraction Analysis of Functional Competitive Lotka-Volterra Systems: Understanding Competition Between Modified Bacteria and Plasmodium within Mosquitoes.

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Graduate Program in Applied Mathematics
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Abstract

We propose and analyze an extension to the classic Competitive Lotka-Volterra (CLV) model. The goal is to model competition between species, with a response from the environment. This response is a function of the population of all species and can represent numerous physical phenomena including resource limitation and immune response of a host due to infection. We name this new system a Functional Competitive Lotka Volterra (FCLV) model. We mainly use the construction of contraction metrics, to determine global properties of the model. We use this result to analyze the competition between *Plasmodium* sp. and genetically engineered bacteria within the midgut of a mosquito. We find that the effect of the immune response of the mosquito on invaders has a significant effect on whether *Plasmodium* or the genetically engineered bacteria dominates, but that under certain conditions the bacterium can eliminate the *Plasmodium* from the mosquito.

Lay Abstract

The burden of malaria on the human race, especially in developing countries demands the development of novel approaches to fight the spread of *Plasmodium* sp. parasites which cause malaria, and are transmitted by mosquitoes. One of the most promising is paratransgensis, a technique for eliminating a parasite from a disease vector populations (in this case mosquitoes) through the genetic engineering of a common colonizer of the host. We propose a simple model that can describe many different different examples of paratransgenesis, which we term a Functional Competitive Lotka Volterra (FCLV) system. Our main focus is analyzing FCLV systems with contraction analysis, which we believe has been underused, but has great promise in the area of model analysis. We show that using contraction theory the analysis of an FCLV model can be reduced to a system of two dimensions less. This allows us to reach the conclusion that given a sufficiently strong genetically modified bacteria, once introduced into a mosquito it will always eliminate *Plasmodium* sp. within a mosquito.

Keywords: Dynamical Systems, Competitive Lotka Volterra System, Microbiota Modelling, Contraction Analysis, Within Host Dynamics

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Chapter 1

Introduction

The burden of malaria on the human race, especially in developing countries demands the development of novel approaches to fight the spread of *Plasmodium* parasites which cause malaria. One strategy that has been developed is to engineer symbiotic bacteria to render the mosquito resistant to the parasite. We present here a brief summary of the use of engineered bacteria in mosquitoes to combat the spread of malaria and an ordinary differential equation (ODE) model, which models the competition between *Plasmodium* and engineered bacteria within the midgut of the mosquito.

Of all known vector born diseases, mosquito borne infectious diseases (MBID) have the greatest disease burden [33]. In particular malaria contributes the most to this burden, with it disproportionally affecting developing countries. In the future, if current climate change trends continue, there will be a large increase in global malaria rates. The worse case prediction being that a billion people will be exposed within the next century [32]. Given the human costs associated with MBIDs better methods are needed to control the spread of malaria. Comparing the relative effectiveness of mosquito control is outside the scope of this thesis, see the following reviews for more information on different strategies [5, 27]. We limit the discussion to modelling a specific strategy, paratransgensis.

Paratransgensis is a technique for eliminating a pathogen from a host vector by transmitting a symbiont to kill/out-compete the undesired pathogen. The goal is not to kill the mosquitoes, but rather convert them to ineffective diease vectors. There are examples of successful paratransgensis with both non-mosquitoes and mosquito hosts, though the real world success of these trials is limited due to numerous factors[1] [11, 40]. The ultimate factors that limit the success of paratransgensis are the following [11, 40]:

1. The symbiont fails to colonize the host.
2. The initial colonisation is successful, but the long term population of the symbiont is unstable within the host and the population collapses.
3. The symbiont fails to be transmitted to other members of the host population.

---

[1] The closest widely applied strategy with real world success is infecting mosquitoes with genetically modified *Wolbachia* bacteria. Male mosquitoes infected with *Wolbachia* are infertile. There are long term concerns on over the effectiveness of the treatment mainly accidental gene transfer and low fitness of genetically modified *Wolbachia* compared to Wild *Wolbachia* [29].

4. There are unintended side effects of paratransgensis (e.g. unintentional gene transfer, unintended damage on the host microbiome, reduced host fitness).

5. The symbiont fails to be transmitted between life stages of the same host (this is known as transstadial transmission).

We will focus the rest of discussion on factors 1, 2, and 5, as 3 has been modelled extensively for similar strategies including *Wolbachia*[2] [29] and 4 is dependent on specific ecological interactions. We create a simple model to better understand factors 1 and 2 within a specific example. We then generalize the model into what we term the Functional Competitive Lotka Volterra model ($FCLV(n)$). We then develop tools to better understand the global properties of the $FCLV(n)$ and similar models. The specific example of paratransgensis was chosen because it is an example of paratransgensis designed to eliminate malaria within a mosquito host which has evidence that it can be transmitted multiple ways between members of the host population (See Figure 1.1).

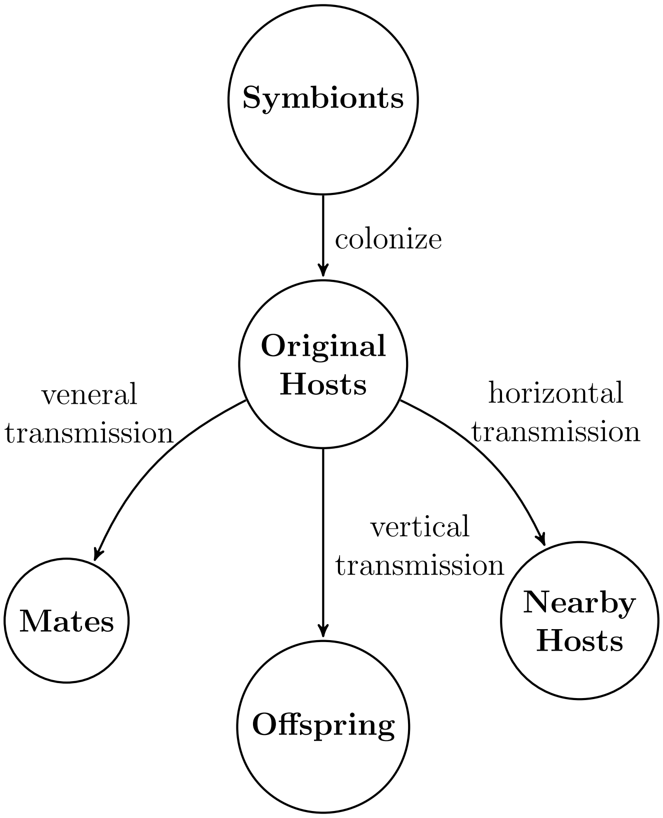

Figure 1.1: Transmission pathways for symbionts between hosts in a paratransgensis strategy. There is evidence that the genetically modified bacteria AS1 can be transmitted by all of these pathways [38]. Note that for horizontal transmission of AS1 is by water. In other species horizontal transfer occurs through behaviours such as biting and scratching.

---

[2] Note there is still the potential for future complex models which focus on the unique modelling challenges of paratransgensis strategies.

1.1 AS1 Bacteria and Mosquito Biology

In the paper by Wang et al. [38], a new strain of *Serratia* bacteria named AS1 was isolated from *Anopheles stephensi* ovaries and genetically engineered to secrete anti-*Plasmodium*[3] effector proteins[4]. The main benefit of this new strain compared to previous recombinant bacteria is the limited effect on mosquito fitness, its ability to readily colonize the mosquito midgut that is already populated, the ability to spread via blood meals, water, transmission via ovaries to offspring, and venereally from male to female mosquitoes. When fed to male mosquitoes AS1 bacteria colonized their accessory glands. In the laboratory a 5 percent infection rate is enough to infect the rest of the population and their progeny. This implies the infection is spread vertically, horizontally and transstadially through the mosquito population and life cycle. This success can be attributed to the fact a close relative of AS1, *Serratia marcescens*, is the most populous species in the microbiome of many different mosquito species [4, 6–8, 13, 21, 24]. Previous attempts for a promising symbiont used easily modified laboratory species such as *E. coli*, which are not native to the mosquito midgut.

To understand why AS1 is an ideal candidate for paratransgensis and for modelling the paratransgensis in mosquitoes, we need to discuss *Plasmodium* biology within mosquitoes. To hinder the development of *Plasmodium* within a mosquito it is best to focus on an appropriate life stage to target. The most obvious target is the life stages within the mosquito midgut [10]. Once the oocyst life stage travels past the midgut epithelium into the hemolymph (the blood of the insects), *Plasmodium* will eventually reach the mosquito salivary glands where *Plasmodium* can be transferred to another organism see Figure 1.2 [37]. As the lumen and epithelium of the midgut are the major physical barriers that prevent *Plasmodium* from reaching the salivary glands and the most vulnerable life stages of *Plasmodium* are in the midgut, it is important that AS1 can colonize the midgut.

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[3] The *Plasmodium* genus is the parasite genus the causes malaria in humans. The five most common species that infect humans are *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale*, and *P. knowlsei.*

[4] Unless otherwise noted whenever we refer to AS1, we are referring to genetically modified AS1.

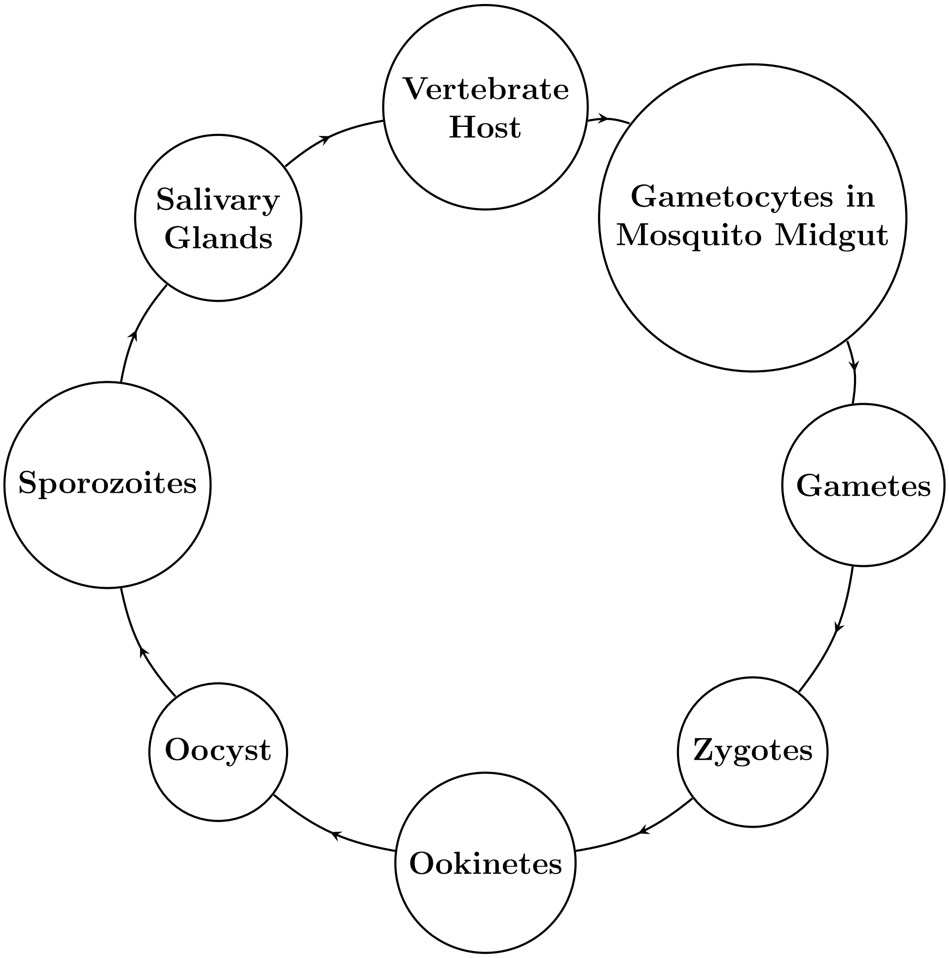

Figure 1.2: Life stages and migration of *Plasmodium* in a mosquito host. After ingesting a blood meal from a malaria infected vertebrate host, ingested gametocytes produce male and female gametes in the midgut. Fertilisation produces zygotes, which develop into mobile ookinetes. This life stage will transverse the midgut epithelium. The mosquito immune system kills the majority of *Plasmodium* during this life cycle. Once *Plasmodium* has matured into oocysts on the other side of the midgut epithelium, several thousand sporozoites will emerge travelling through the mosquito hemolymph eventually reaching the salivary glands of the mosquito. Once *Plasmodium* has reached the salivary ducts they can be ejected into a new vertebrate host. For more details on the life stages of see [37].

Colonizing the mosquito midgut is a challenge. The mosquito midgut itself is host to a large complex microbiome within the midgut, with the main food source being the mosquito's blood meal [9]. As mentioned, previous attempts to create engineered bacteria to colonize the midgut failed, as the engineered bacteria in the midgut were outcompeted. But another challenge is transstadial transmission from pre-molting to post-molting mosquito life stages. Although larva gut microbiota are eliminated during mosquito metamorphosis, AS1 continues to proliferate in the midguts of the adult mosquito [24, 38]. In order to be able to recolonize the midgut, the bacteria must be in a reservoir outside of the midgut where AS1 can reside during the transition (currently unknown but likely to be the hemolymph, or an organ in direct contact with hemolymph). This and the observation that AS1 colonizes the ovaries of mosquitoes given only a blood meal means that at some point AS1 must cross the midgut epithelium.

The third main participant in this interaction is mosquito's immune system. Mosquitoes, unlike most of their vertebrate hosts, do not posses an adaptive immune response [10]. Without AS1 present the mosquito's immune system initiates the innate response which consists of two responses, cellular and humoral. The cellular response consists of hemocytes (insect blood cells in the hemolymph) engulfing or surrounding (known as phagocytosis and encapsulation) *Plasmodium.* The humoral response to pathogens involve melanization and antimicrobial effector molecules. Melanization kills microbes by generating melanin and free radicals. Likewise the production of antimicrobial effector molecules are regulated by intracellular immune signalling pathways that are activated by pattern recognition receptors (PRRs) upon interaction with pathogen associated molecular patterns (PAMPs). This is important to consider as there is evidence that bacteria within the mosquito midgut plays an important role in reducing *Plasmodium* in mosquitoes by stimulating the immune response [10]. The non-specificity of the immune response means that an increase in either AS1 or *Plasmodium* will increase the activation of the innate mosquito immune response, with an increased immune response there should be a decrease in both populations.

With the mosquito's biology considered we can develop a simplistic mechanistic model, in the next section.

1.2 A simple model of paratransgensis

Our goal is to establish a model to understand the dynamics of AS1 paratransgensis, and outline tools for the analysis of the model. Ideally we want a model whose analysis can be expanded to other biological systems. We can think of paratransgensis within a single host to be modelled by two feedback loops:

- Inter- and intraspecific competition of colonizing species within the host act as a negative feedback mechanism, preventing one or more species from growing without bound. An example of this type of feedback is the classic Competitive Lotka Volterra (CLV) model [42].

- Between the immune system and the microbiota community there is an feedback response. For a host with only the innate immune response, higher populations

> of microbes will increase its immune response. Once activated the innate immune response lowers the populations of foreign organisms. However once immune response decreases the microbiota will increase if not eliminated. This feedback is highly dependent on the host organism's immune system. If the immune system is adaptive, the relationship becomes more complicated, with the primary factor being that when the foreign organism is present within the host, either the host acquires resistance to the foreign invader, the invader is commensalistic with the host, or invader organism overcomes the adaptive immune response (e.g. retroviruses).

For the purposes of modelling we can summarize the complex interactions in the following simple heuristic model demonstrated in Figure 1.3. Here the mosquito is simplified into two compartments: the "midgut" and all other parts within the mosquito which are considered to be part of the "hemolymph". The main assumptions behind this heuristic model are the following:

- The main physical barrier that prevents *Plasmodium* from colonizing the salivary glands is the midgut lumen/epithelium.
- The main factors that limit the growth of *Plasmodium* within the mosquito is AS1 and mosquito immune system.
- AS1 and *Plasmodium* have a reduced carrying capacity outside of the mosquito midgut (based on the assumption that organisms in the midgut has access to the mosquito's blood meals supporting larger populations).
- AS1 can reach the hemolymph.
- AS1 can re-enter the midgut from the hemolymph.
- We only consider one life stage for both *Plasmodium* and AS1.
- AS1 releases only one anti-*Plasmodium* molecule or combinations of multiple anti-*Plasmodium* molecules are not synergistic [5].

---

[5] We say two or more anti-*Plasmodium* molecules have synergy when they have a greater anti-*Plasmodium* effect than when expressed individually. Because potential synergy is not our focus, we assume that synergy can be modelled as a single strong anti-*Plasmodium* molecule.

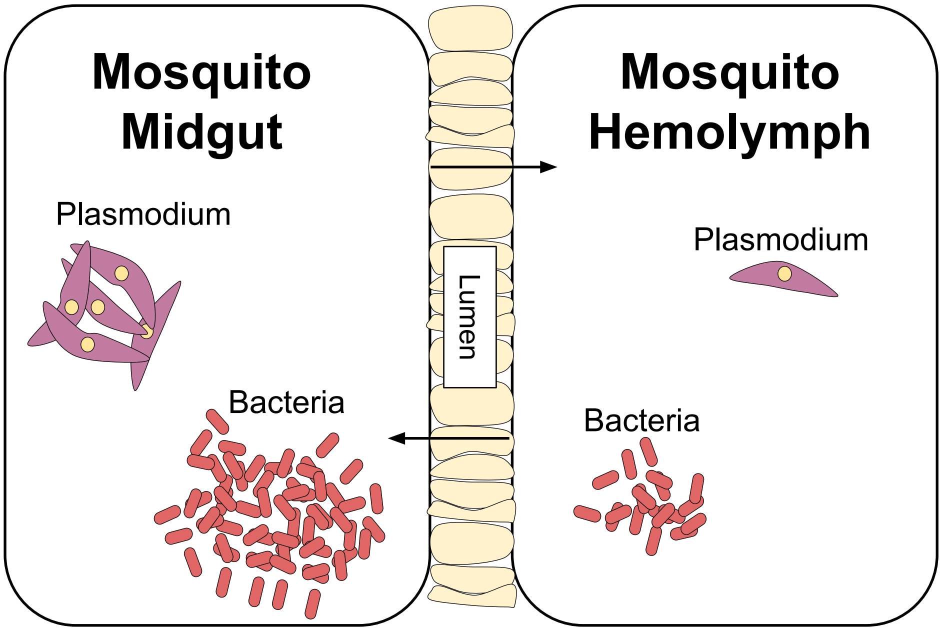

Figure 1.3: A simple heuristic model of *Serratia* bacteria (AS1) and *Plasmodium* parasites in a mosquito. The model only considers the interactions between AS1, *Plasmodium* and the mosquitoe's immune system. Within a mosquito, two simplified compartments are considered: midgut and hemolymph.

We can express this heuristic model as the following system of ordinary differential equations (ODE).

$$I'(t) = f(P,B) - \mu I, \tag{1.1a}$$

$$P_1'(t) = r_1 P_1 (1 - \frac{\alpha B_1 + P_1}{K_1}) - d_1 I P_1 - m P_1, \tag{1.1b}$$

$$P_2'(t) = r_2 P_2 (1 - \frac{\alpha B_2 + P_2}{K_2}) - d_2 I P_2 + m P_1, \tag{1.1c}$$

$$B_1'(t) = \overline{r_1} B_1 (1 - \frac{B_1}{\overline{K_1}}) - \bar{d}_1 I B_1 - \bar{m}(B_1 - B_2), \tag{1.1d}$$

$$B_2'(t) = \overline{r_2} B_2 (1 - \frac{B_2}{\overline{K_2}}) - \bar{d}_2 I B_2 - \bar{m}(B_2 - B_1). \tag{1.1e}$$

Here parameters with the subscript 1 refers to parameters for the midgut, and the subscript 2 refers to parameters in the mosquito's hemolymph. Bar parameters refers to parameters effecting bacteria, parameters without bars refer to parameters effecting *Plasmodium*. Detailed explanations of model parameters are in Table 1.1. All model parameters are positive and non-zero.

Within the mosquito midgut there are three primary interactions that will determine the growth rate of *Plasmodium*: intraspecific competition, AS1 killing *Plasmodium* and deaths caused by the immune system of the mosquito. In contrast to *Plasmodium*, the growth of AS1 bacteria is not limited by *Plasmodium*. The immune system also reduces the growth of *Plasmodium* and AS1. Different constants are choosen for each of these factors to reflect the fact that AS1 and Plasmodium have different growth rates, and interact with the mosquito immune system differently. In addition there is movement between the midgut and the hemolymph. Based on the information available for AS1 and *Plasmodium* in the literature we should expect *Plasmodium* to migrate from the midgut to the hemolymph and AS1 to have the ability to move both to and from the midgut (if this is not true than it is difficult to explain why AS1 can persist in mosquito midgut after the moulting stage).

$f(P, B)$ is a general function that represents the activation of the immune response by the population of *Plasmodium* and AS1. As the mosquito immune system consists of only an innate response and not an adaptive response we assume that the immune response depends only on the populations of microbiota within the mosquito and is an autonomous function that does not depend directly on time. While the exact form of $f(P, B)$ (which we shall call the immune response function) is not specified, we assume that it has the properties discussed in Section 2.1. Possible candidates to model the immune response function include, but are not limited to:

$$f(P, B) = \sigma P + \bar{\sigma} B, \tag{1.2}$$

$$f(P, B) = \sigma \frac{P}{1+P} + \bar{\sigma} \frac{B}{1+B}, \tag{1.3}$$

$$f(P, B) = \frac{P^n}{\sigma + P^n} + \frac{B^n}{\bar{\sigma} + B^n}, \quad n \geq 1. \tag{1.4}$$

We include a decay term in the differential equation for I, so the immune response decays in the absence of *Plasmodium* and bacteria.

Table 1.1: State functions and model parameters.

Symbol	Description
$I(t)$	strength of immune response at time t
$P(t)$	total population of *Plasmodium* at time t
$P_1(t)$	population of *Plasmodium* at time t, within the midgut of the mosquito
$P_2(t)$	population of *Plasmodium* at time t, within the hemolymph of the mosquito
$B(t)$	total population of bacteria at time t
$B_1(t)$	population of bacteria at time t, within the midgut of the mosquito
$B_2(t)$	population of bacteria at time t, within the hemolymph of the mosquito
σ,$\bar{\sigma}$	controls the growth of the immune response rate of the mosquito in response to *Plasmodium*, or bacteria, see equation (1.2)
μ	decay rate of the immune response
r_1,r_2,$\overline{r_1}$,$\overline{r_2}$	growth rates of *Plasmodium* (in the midgut and hemolymph) and bacteria (in the midgut and hemolymph)

Table 1.1: State functions and model parameters.

Symbol	Description
α	competitive effect of bacteria on *Plasmodium*
K_1,K_2,$\overline{K_1}$,$\overline{K_2}$	carrying capacity of *Plasmodium* (in the midgut and hemolymph) and bacteria (in the midgut and hemolymph)
d_1,d_2,$\overline{d_1}$,$\overline{d_2}$	death rates of *Plasmodium* (in the midgut and hemolymph) and bacteria (in the midgut and hemolymph) due to the immune response of the mosquito
m,$\overline{m}$	permeability of the midgut epithelium to *Plasmodium* or bacteria

In (1.1), we have implicitly assumed that the amount of anti-*Plasmodium* proteins that an individual AS1 bacteria produces does not depend on the population of *Plasmodium.* In addition, we do not assume that the transport of AS1 depends on whether the midgut or the hemolymph has a higher population of *Plasmodium.* This is because genetically modified AS1 does not have the ability to sense the population of *Plasmodium* or control the production of anti-*Plasmodium* proteins as a function of *Plasmodium* (that is it lacks the ability to sense *Plasmodium*).

When neglecting the permeability of the midgut epithelium (i.e. letting $m = 0 = \overline{m}$), we end up with a one compartment system of the form:

$$I'(t) = f(P, B) - \mu I, \tag{1.5a}$$

$$P'(t) = rP(1 - \frac{\alpha B + P}{K}) - dIP, \tag{1.5b}$$

$$B'(t) = \bar{r}B(1 - \frac{B}{\overline{K}}) - \bar{d}IB. \tag{1.5c}$$

This form is useful if we are interested only in the dynamics within the midgut or hemolymph.

We can generalize (1.1) and (1.5) into what we term as the Functional Competitive Lotka Volterra system[6]. We denote the Functional Competitive Lotka Volterra systems ($FCLV(n)$) as[7]:

$$\begin{aligned}
\frac{dx_0}{dt} &= F_0(x) = f(x_1, ..., x_n) - x_0 \\
\frac{dx_i}{dt} &= F_i(x) = x_i(1 - \sum_{j=0}^{n} a_{ij}x_j) \quad a_{ij} > 0, i = 1, ..., n,\ j = 0, ..., n.
\end{aligned} \tag{1.6}$$

---

[6] The name was chosen because there is a "Functional" response from the environment combined with a traditional Competitive Lotka Volterra system ($CLV(n)$) [42].

[7] Note that (1.1) and (1.5) have more parameters that $FCLV(n)$. We reduce the number of parameters through nondimensionalization.

where a_{ij} are positive non-zero constants (the matrix $a_{ij} \in A$ is called the community matrix), and $f(x_1, ..., x_n) \in C^1$, which we term the functional response[8]. Note n in $FCLV(n)$, refers to the number of species to make it more comparable to Competitive Lotka Volterra models with the same number of species. If we are considering movement between two compartments we can adapt (2.1) into:

$$\begin{aligned}
\frac{dx_0}{dt} &= F_0(x) = f(x_1, ..., x_n, x_{n+1}, ..., x_{n+n}) - x_0, \\
\frac{dx_i}{dt} &= F_i(x) = x_i(1 - \sum_{j=0}^{n} a^1_{ij} x_j) - m_i(x_i - x_{n+i}), \\
\frac{dx_{n+i}}{dt} &= F_{n+i}(x) = x_{n+i}(1 - \sum_{j=0}^{n} a^2_{ij} x_{n+j}) - m_i(x_{n+i} - x_i), \\
a^1_{ij} &> 0, a^2_{ij} > 0, i = 1, ..., n.
\end{aligned} \tag{1.7}$$

Note that a^1_{ij}, a^2_{ij} refers to constants (the notation is chosen such the community matrices $a^1_{ij} \in A^1, a^2_{ij} \in A^2$ have the same dimensions as the community matrix associated with (2.1)). The focus of the rest of the paper is to develop a general theory that covers $FCLV(n)$ systems. Before the main result is proven we need to introduce the appropriate mathematical background which we cover in sections 1.3 and 3.

1.3 Mathematical Introduction

We cover here notations used and review the relevant parts of the theory of monotone dynamical systems. Those who are familiar with the content of Hal Smith's book [34] on monotone dynamical systems can skip this section. There is a separate section (Section 3) devoted to contraction theory, which we expect most readers to not be familiar with, so we do not include it here in the introduction.

1.3.1 Notations Used Throughout

Table 1.2 gives a list of common abbreviations and symbols used. We clarify some notation choices that may confuse some readers. Superscripts on vectors or scalars are used repeatedly to enumerate vectors and scalars, while subscripts are used to denote components of vectors. Next it is common in the literature to denote the carrying simplex with Σ (the carrying simplex is explained in Section 1.3.2), sums will always come with an index to distinguish them from carrying simplexes and avoid confusion. Finally for each non-empty set $\Omega \subset \mathbb{R}^n$ and each $x \in \mathbb{R}^n$, we denote the distance of x to Ω by

$$|x|_\Omega := \inf_{y \in \Omega} ||x - y||. \tag{1.8}$$

For example $|x|_{\{0\}}$ is equivalent is the Euclidean norm.

---

[8] We use f, $f(x)$, and $f(x_1, ..., x_n)$ interchangeably to refer to the functional response depending on context.

Table 1.2: List of abbreviations and symbols

x^1, x^2	Two scalars/vectors x^1, x^2
x_1, x_2	First and second component of the vector x
$\|\|x\|\|$	Euclidean norm of the vector x
$\|x\|_\Omega$	The point to set distance of x to the set Ω
Ω	Some subset of $\mathbb{R}^n$
K	Any positive cone
K_+	The standard positive cone
K^*	The dual of a positive cone
$x \leq_K y$	$x - y \in K$ and $\leq_K$ is the partial order generated by the positive cone K
C	The cone defined by the Cartesian product $C = K \times (-K)$
Σ_{CLV}	The carrying simplex of competitive Lotka Volterra system
$J(f(x))$	Jacobian of the vector field $f(x)$
$\mathcal{X}(\mathbb{R}^n)$	The space of continuously differentiable vector fields on $\mathbb{R}^n$

Comparison functions are also used throughout. We define the most used comparison function $\mathcal{KL}$ below:

Definition 1.3.1. (Kappa-Ell Class of Comparison Functions) A continuous function $\beta : [0, a) \times [0, \infty) \to [0, \infty)$ belongs to the $\mathcal{KL}$ (Kappa-Ell) class if:

- For fixed x, the function $\beta(x, t)$ is strictly increasing in t and $\beta(0, t) = 0$.
- For fixed t, the function $\beta(x, t)$ is strictly decreasing in x and $\beta(x, t)$ goes to zero as $t \to \infty$.

For a summary of the properties of comparison functions see [20].

1.3.2 Monotone Systems Review

Monotone dynamical systems are defined on subsets of ordered Banach spaces. We are mainly concerned with the standard positive cone $K = R^n_+$ which induces the partial order $\geq_K$ on $\mathbb{R}^n$. We say two vectors x^1, x^2 are ordered with respect to the partial order $x^1 \geq_K x^2$ if and only if $x^1 - x^2 \in K$. Note that any property we discuss here applies to any other positive but if K is the standard positive cone then $x^1 \geq_K x^2$ also means that each coordinate of x^1 is greater or equal to x^2. Strict ordering is denoted by $x^1 >_K x^2$

meaning that $x^1 \geq_K x^2$ and $x^1 \neq x^2$. With a partial order established, we can say a non-linear system,

$$\frac{dx}{dt} = f(x), \tag{1.9}$$

is monotone, if $x^1(t) \geq_K x^2(t)$, whenever $x^1(t^0) \geq_K x^2(t^0) \quad \forall t \geq t^0$. An important sufficient condition used to determine if a system is monotone is the Kamke condition. System (1.9) satisfies the Kamke condition in Ω if for each i, $f_i(a) \geq_K f_i(b)$ for any two points $a, b \in \Omega$ satisfying $a \geq_K b$ and $a_i = b_i$.

A important subset of monotone systems is cooperative and competitive systems. We say that system (1.9) is called cooperative on a convex set $\Omega \subseteq \mathbb{R}^n$ if

$$\frac{\partial f_i(x)}{\partial x_j} \geq 0 \quad i \neq j \; \forall x \in \Omega. \tag{1.10}$$

Likewise a system is term competitive on Ω if

$$\frac{\partial f_i(x)}{\partial x_j} \leq 0 \quad i \neq j \; \forall x \in \Omega. \tag{1.11}$$

There are several important properties for cooperative and competitive systems, with one of the most being the following theorem.

Theorem 1 (Theorem 3.4 in [34]). *The flow on a compact limit set of a competitive or cooperative system in $\mathbb{R}^n$ is topologically equivalent to a flow on a compact invariant set of Lipschitz system of differential equations $\mathbb{R}^{n-1}$*

The most interesting case of the invariant set in $\mathbb{R}^{n-1}$ is the carrying simplex which is exactly $n-1$ dimensional called the carrying simplex (Theorem 1 does not guarantee that the invariant set is not a single point or that the set is connected). A unique carrying simplex is a set $\Sigma \subset \mathbb{R}^n_+ \setminus \{0\}$ which has the following properties [15]:

- Σ is compact and invariant.
- For every $x^1 \in \mathbb{R}^n_+ \setminus \{0\}$, the trajectory of x^1 is asymptotic with some $x^2 \in \Sigma$.
- Σ is unordered with respect to the partial order. That is if $x^1, x^2 \in \Sigma$ and $x^1 \geq_k x^2$ then $x^1 = x^2$.

From the above it follows that Σ is $n-1$ dimensional (see [15]). It can be difficult to determine if a dynamical system admits a single unique carrying simplex, though Hirsch [15] has provided some conditions which a dynamical system much have if it has a unique carrying simplex. The simplest (non-trivial) example of a system with a unique carrying simplex are Competitive Lotka Volterra (CLV) systems. We denote the space of n-dimensional CLV systems ($CLV(n)$) by

$$\frac{dx_i}{dt} = x_i(1 - \sum_{j=1}^{n} a_{ij}x_j), a_{ij} > 0, i = 1, ..., n, j = 1, ..., n, \tag{1.12}$$

where a_{ij} are positive non-zero constants. $CLV(n)$ systems are well studied though there are still some open questions (mainly the qualitative behaviour of $CLV(n)$ for $n \geq 3$, on the carrying simplex Σ_{CLV}). We will mention the properties of $CLV(n)$ systems when we use them for proofs. For those interested in the general properties of $CLV(n)$ we recommend [42] which explains the general patterns of Σ_{CLV}. For more specific results see the following [17, 18, 35, 41].

The Competitive Lotka Volterra (CLV) model is a very well understood, and describes the competition between multiple species. It is well understood in part because it is a monotone system of differential equations, as the partial order relation between the initial conditions is preserved by the dynamics of the system with respect to the positive cone $\mathbb{R}^n_+$. CLV models are competitive as the off diagonal elements of the Jacobian matrix at every point in $\mathbb{R}^n_+$ are non-positive. If the entries are non-negative the system is instead referred to as a cooperative system. By Theorem 1, a limit set of the system can be no more complicated than those of a general dynamical system of $n-1$ dimension.

The Competitive Lotka Volterra model has been used numerous times to model many problems from ecology, epidemiology, and chemistry. There are also several examples in the literature of models which have extended the CLV model to include features such as movement between compartments[9], delays and stochasticity. The analysis behind the papers on each of these extensions relies on the CLV models being monotone (specifically being competitive). In contrast to these methods the extension we propose here, adding a functional response from the environment that creates a strong negative feedback loop, renders the system nonmonotone. We use here a combination of techniques to show the existence of a topological conjugacy between this extended Competitive Lotka Volterra model which we term as Functional Competitive Lotka Volterra (FCLV) system[10] and a traditional CLV model.

If system (1.9) consists of cooperative and competitive parts it becomes difficult to determine the global properties of such systems, as often these systems are no longer monotone with respect to K_+. We focus here on systems (1.9) that can be thought of two non-linear connected systems. That is, systems (1.9) that can be written as

$$\frac{dy}{dt} = g(y,z) \tag{1.13}$$

$$\frac{dz}{dt} = h(y,z) \tag{1.14}$$

where $x = (y,z), f(x) = (g(y,z), h(y,z))$. Using mainly contraction theory and the theory of monotone systems we will derive a general scheme for understanding such systems if $\frac{dy}{dt} = g(y,z)$ is monotone for constant z and $\frac{dz}{dt} = h(y,z)$ is monotone for constant y. Using this framework we can obtain global results for the functional competitive Lotka-Volterra system (FCLV). We then apply the results to a specific biological system which was introduced in Section 1.

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[9] or depending on context the term habitat or environment is used.

[10] Another appropriate name would be Feedback Competitive Lotka Volterra (FCLV)

1.4 Statement of Results

The rest of the thesis is organized as follows. In Section 3 we introduce the basics of contraction theory and provide the necessary background for later proofs. One important idea that appears in contraction theory is the difference between incremental stability (i.e. trajectories coming closer to each other) and convergent stability (i.e. trajectories moving closer to a point), using [30] we can formally define these two notions of stability in Section 3.3. We then discuss when these notions are different and when they are equivalent. We then prove the main result in Section 4 which is a theorem that combines monotone systems theory and contraction theory giving necessary and sufficient conditions for convergence to a subset. We then apply this theorem to $FCLV(n)$ systems and derive global results in 4. We finish by a discussion concerning the interpretation of the main result in regards to biological models in general.

Chapter 2

The Functional Competitive Lotka Volterra Model

Having covered the background to the Functional Competitive Lotka Volterra (FCLV) model in the previous chapter, we now focus solely on the analysis of the FCLV model. This section focuses on the basic analysis of the FCLV model using common tools of dynamical systems. We establish here properties such as boundness of solutions, number of fixed points and so on. We will go further into properties of $FCLV(n)$ systems in Section 4 using the theory reviewed in Section 3 to determine the global dynamics of $FCLV(n)$ systems. Section 5 looks at specific examples of the FCLV model including competition between the Immune system of a mosquito, bacteria and parasites within the mosquito midgut. We include a more general discussion on what biological systems are appropriate to model as $FCLV(n)$ systems.

2.1 Definition of $FCLV(n)$

We denote the Functional Competitive Lotka Volterra systems as:

$$FCLV(n) : \begin{cases} \dfrac{dx_0}{dt} = F_0(x) = f(x_1, ..., x_n) - x_0, \\ \dfrac{dx_i}{dt} = F_i(x) = x_i(1 - \displaystyle\sum_{j=0}^{n} a_{ij}x_j) \quad a_{ij} > 0, i = 1, ..., n, \end{cases} \tag{2.1}$$

where a_{ij} are positive non-zero constants (the matrix $a_{ij} \in A$ is called the coefficient matrix), and $f(x_1, ..., x_n) \in C^1$ which we term the functional response. The name Functional Competitive Lotka Volterra comes from the resemblance of the vector field $(F_1, ..., F_n)$ to a $CLV(n)$ system and the component F_0 including the functional response f. We specifically use the notation $FCLV(n)$ rather than $FCLV(n+1)$ to refer to $n+1$ dimensional systems to emphasize this connection between $CLV(n)$ systems and $FCLV(n)$ systems. As a $CLV(n)$ model describes the behaviour of n competing species, we say $FCLV(n)$ models the behaviour of n competing species with a functional response f.

We only consider a subset of the $FCLV(n)$ family where the matrix of coefficients $A = (a_{ij})$ $i = 1, ..., n,$ $j = 0, 1, ..., n$, has rank equal to n. If $rank(A) \neq n$, this means that one or more of the nullclines

$$N_i(x) = 1 - \sum_{j=0}^{n} a_{ij}x_j \ i = 1, ..., n, \tag{2.2}$$

overlap. For $CLV(n)$, the matrix A is known as the community matrix and $CLV(n)$ systems which do not have community matrix with full rank are known as degenerate Competitive Lotka Volterra systems [42]. Degenerate $CLV(n)$ systems are not the focus of study in the literature, as their analysis reduces to a system of dimension rank(A). If rank(A) = 1 the $\omega-$limit set is a line of fixed points. We thus focus only on non-degenerate $FCLV(n)$ systems.

2.1.1 Functional Response f

Important to understanding the dynamics of $FCLV(n)$ are the two feedback loops present. $CLV(n)$ systems also have a feedback mechanism, in that the higher population of any species leads to lower growth of all species, conversely, a lower population of any species leads to a higher growth rate in all species[1]. The functional response f in F_0 creates a different feedback loop. If $f(x) \neq x_0$, then x_0 either decreases or increases appropriately. So the $FCLV(n)$ model has two negative feedbacks loops which feed into each other. We refer to the first type of negative feedback loop present in a Functional Competitive Lotka-Volterra model as the *competitive feedback loop* and the second type of feedback loop as the *functional feedback loop.* To focus the analysis of $FCLV(n)$ models and to ensure biological realism we assume the functional response f has the following properties:

(H.1) $f(x) : \mathbb{R}^n_+ \to \mathbb{R}_+$ and $f \in C^1$.

(H.2) $f(x)$ is bounded by a constant for $(x_1, ..., x_n) \in \{x \in \mathbb{R}^n_+ : 0 \leq x_i \leq \frac{1}{a_{ii}}, 1 \leq i \leq n\}$.

(H.3) For $x \neq 0$, $f(x)$ is positive[2]; if $x = 0$ then $f(0) = 0$.

(H.4) $f(x)$ is a monotone with respect to each x_i for each $i \in \{1, ..., n\}$.

Examples of f satisfying the above conditions include f:(σ_i and α_i are constants):

- Linear functions: e.g. $f(x_1, ..., x_n) = \sigma_1 x_1 + ... + \sigma_n x_n$.
- Saturating functions, that is functions that approach a constant as $(x_1, ..., x_n)$ approaches infinity: e.g. $f(x_1, ..., x_n) = \dfrac{\sigma_1 x_1}{\alpha_1 + x_1} + ... + \dfrac{\sigma_n x_n}{\alpha_n + x_n}$.

In addition, the coefficients a_{i0} can be chosen to help tune the effect of f, so that the effect on each species is different.

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[1] This comes with the caveat that if the population of any individual species is zero, it remains zero for all time.

[2] We use 0 to denote the zero vector $(0, ..., 0)$ in addition to the scalar zero.

2.2 Basic Properties of $FCLV(n)$

In this section we prove basic properties of $FCLV(n)$ that are easily obtained through basic dynamical systems theory.

Lemma 2. *Assume $f(x)$ satisfies conditions (H.1)-(H.4). Then $FCLV(n)$ is positively invariant in $\mathbb{R}_+^{n+1}$. In addition, for any initial value in $\mathbb{R}_+^{n+1}$, the corresponding solution* (2.1) *is bounded.*

Proof. The positive invariance of $\mathbb{R}_+^{n+1}$ is trivial, as trajectories cannot cross the boundary of $\mathbb{R}_+^{n+1}$ given the restriction on the functional response [34]. We sketch here a boundedness argument for large t via a comparison to a bounded system of differential equations. For each $i = 1, ..., n$

$$\frac{dx_i}{dt} = x_i(1 - \sum_{j=0}^{n} a_{ij}x_j) \leq x_i(1 - a_{ii}x_i), \tag{2.3}$$

so

$$\lim_{t\to\infty} \sup x_i(t) \leq \frac{1}{a_{ii}}. \tag{2.4}$$

Because of condition (H.2) we have the following

$$\frac{dx_0}{dt} = f(x_1, ..., x_n) - x_0 \leq f_{max} - x_0, \tag{2.5}$$

$$\lim_{t\to\infty} \sup x_0(t) \leq f_{max}, \tag{2.6}$$

where f_{max} is the maximum value on $(x_1, ..., x_n) \in \Omega = \{x \in \mathbb{R}_+^n : 0 \leq x_i \leq \frac{1}{a_{ii}}, 1 \leq i \leq n\}$. Let

$$m = \max\left\{\frac{1}{a_{11}}, ..., \frac{1}{a_{nn}}, f_{max}\right\}. \tag{2.7}$$

The above analysis shows that the bounded set $\{x \in \mathbb{R}_+^{n+1} : 0 \leq x_i \leq m, 0 \leq i \leq n\}$ attracts all initial conditions in $\mathbb{R}_+^{n+1}$. Hence for any initial value in $\mathbb{R}_+^{n+1}$, the corresponding solution remains bounded. $\square$

Lemma 3. *The trivial equilibrium point of* (2.1), *$x = 0$, is a saddle point having a one dimensional stable manifold and n dimensional unstable manifold.*

Proof. By the stable manifold theorem [26], if the Jacobian of a dynamical system at a fixed point has k eigenvalues with negative real part and $n + 1 - k$ eigenvalues with positive real part, then W^s, the stable manifold, is k dimensional and W^u, the unstable manifold, is $n + 1 - k$ dimensional. The Jacobian of $FCLV(n)$ is

$$J(x) \tag{2.8}$$

$$= \begin{pmatrix} -1 & \frac{\partial f(x_1,...,x_n)}{\partial x_1} & \frac{\partial f(x_1,...,x_n)}{\partial x_2} & \cdots & \frac{\partial f(x_1,...,x_n)}{\partial x_n} \\ -a_{10}x_1 & 1 - a_{11}x_1 - \sum_{j=0}^n a_{1j}x_j & -a_{12}x_1 & \cdots & -a_{1n}x_1 \\ -a_{20}x_2 & -a_{21}x_2 & 1 - a_{22}x_2 - \sum_{j=0}^n a_{2j}x_j & \cdots & -a_{2n}x_2 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ -a_{n0}x_n & -a_{n1}x_n & -a_{n2}x_n & \cdots & 1 - a_{nn}x_n - \sum_{j=0}^n a_{nj}x_j \end{pmatrix}.$$

At the trivial fixed point, $x = 0$, it becomes

$$J(0) = \begin{pmatrix} -1 & \dfrac{\partial f(0)}{\partial x_1} & \dots & \dots & \dots & \dfrac{\partial f(0)}{\partial x_n} \\ 0 & 1 & 0 & 0 & \dots & 0 \\ \vdots & 0 & 1 & 0 & \dots & 0 \\ \vdots & 0 & 0 & 1 & \dots & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & 0 & \dots & 1 \end{pmatrix}, \tag{2.9}$$

which has the characteristic equation $-(\lambda+1)(\lambda-1)^n = 0$. So there are n positive eigenvalues and one negative eigenvalue. By the stable and unstable manifolds theorems, this means that there is a one dimensional stable manifold and a n dimensional unstable manifold. □

With respect to Lemma 3, note that the unstable manifold is tangential to the $(x_1, ..., x_n)$ hyperplane and the stable manifold is tangential to the x_0-axis. This is important as it tells how all solutions approach the trivial equilibrium. The lowest possible point on the x_0-axis which does not repel local trajectories, is

$$x_0 = \min_{i \in [1,n]} \left\{ \frac{1}{a_{i0}} \right\}. \tag{2.10}$$

At this value of x_0 the i-th derivative is negative definite as

$$1 - \sum_{j=0}^{n} a_{ij} x_j = 0 < 0, \tag{2.11}$$

so this point attracts local trajectories on the x_0, x_i plane. Consequently if the x_0 component of the solution $x(t)$ is sufficiently large for some t, mainly

$$x_0 \geq \max_{i \in [1,n]} \frac{1}{a_{i0}}, \tag{2.12}$$

then solutions converge to the point on the x_0-axis (2.10). This is a significant difference between $FCLV(n)$ and $CLV(n)$ systems. No trajectories in $CLV(n)$ models are attracted to the trivial equilibrium point as the carrying simplex acts as a global attractor. Despite this difference the $FCLV(n)$ and $CLV(n)$ models share an important property, the number and type of fixed points are the same between the two.

Lemma 4. *If the functional response f satisfies (H.4), system* (2.1) *has at most* 2^n *fixed points. Each of the fixed points of $FCLV(n)$ can be classified as trivial, axial, planar, and interior fixed points.*

Proof. First note that the fixed points of any $CLV(n)$ model can can be classified into four distinct groups based on how many nullclines of the form

$$N_i(x) = 1 - \sum_{j=1}^{n} a_{ij} x_j = 0 \tag{2.13}$$

for $i = 1, ..., n$, intersect each other in $\mathbb{R}^n_+$ [42]. The four groups are:

- The trivial fixed point at the origin 0.
- Axial fixed points, located where the $N_i(x)$ nullcline meets the x_i-axis.
- planar fixed points, located where k number of N_j nullclines meet on the coordinate plane $x_i = 0$, where $k = n - 1$ and $j = 1, .., n$ such that $i \neq j$. For example, if $n = 3$, then $k = 2$ and $j = 1, 2, 3$, so their are there are three possible planar fixed points: 1) N_2, N_3 intersect on the $x_1 = 0$ plane, 2) N_1, N_3 intersect on the $x_2 = 0$ plane, 3) N_1, N_2 intersect on the $x_3 = 0$ plane.
- The interior fixed point, which is located at the intersection of all the nullclines N_i, $i = 1, ..., n$ in $\text{int}(\mathbb{R}^n_+)$.

Counting up all of the equilibrium points, the maximum number of equilibrium points for any given $CLV(n)$ model is 2^n. With $2^n - 1$ equilibrium points located on either the boundary or interior of the carrying simplex[3]. We now determine the maximum number of fixed points of $FCLV(n)$ by determining the number of axial, planar, and interior equilibrium points of $FCLV(n)$. The nullclines N_i have their analogues in $FCLV(n)$ as the following nucllines[4]

$$N_i^f(x) = 1 - \sum_{j=0}^{n} a_{ij} x_j = 0, \tag{2.14}$$

for $i = 1, ..., n$. As $f(0) = 0$ and f is monotone the total number of times the hyper surface $0 = f(x_1, ..., x_n) - x_0$ can cross the cross the nullclines N_i^f is once. This means that if a combination of the nullclines N_i^f intersect in $\mathbb{R}^{n+1}_+$, they can only intersect the hyper surface $0 = f(x_1, ..., x_n) - x_0$ once (that is the conditions on f means $0 = f(x_1, ..., x_n) - x_0$ cannot be parallel to any of the nullclines N_i^f). We can write formulas/conditions for each type of fixed point for $FCLV(n)$:

- The trivial fixed point at the origin 0.
- An axial fixed point occurs at each solution of,

  $$0 = f(x_1, ..., x_n) - x_0, \tag{2.15}$$
  $$0 = N_i^f(x), \tag{2.16}$$
  $$0 = x_i, \tag{2.17}$$

  for each i.
- A planar fixed point exists if k number of N_j nullclines meet at the intersection of $0 = f(x_1, ..., x_n) - x_0$ and the coordinate plane $x_i = 0$, where $k = n - 1$ and $j = 1, .., n$ such that $i \neq j$.

---

[3] This pattern comes from the carrying simplex being homeomorphic to a carrying simplex of dimension n. $2^n - 1$ is the total number of vertices, edges and faces of a $n-$dimensional simplex.

[4] Despite the notation the nullclines N_i^f have no dependence on f.

- The interior fixed point, exists if the following system.

$$0 = f(x_1, .., x_n) - x_0 \tag{2.18}$$

$$0 = N_i^f(x) \quad \forall i = 1, ..., n \tag{2.19}$$

has a solution in $\text{int}(\mathbb{R}_+^{n+1})$.

□

If we break the assumption in Lemma 4 that the functional response f is non-monotone, a $FCLV(n)$ model has at most $m(2^n) - 1$ fixed points. Where m is the number of regions where the partial derivatives of f change sign.

2.3 Defining Γ_f and Γ_{CLV}

As it is very useful for discussing the properties of $FCLV(n)$ systems we will define two sets Γ_f and Γ_{CLV}. The importance of these sets will become evident within the following sections. Heuristically we say that Γ_f is a subset of the state space where all solutions of $FCLV(n)$ tend to in the absence of the competitive feedback loop, while Γ_{CLV} is a subset of the state space where all solutions of $FCLV(n)$ tend to in the absence of the functional feedback loop.

We define Γ_f as the following set,

$$\Gamma_f = \{x \in \mathbb{R}_+^{n+1} | f(x_1, \ldots, x_n) = x_0\}. \tag{2.20}$$

The definition of Γ_{CLV} is more complex. For convenience we define the following system,

$$FCLV_c(n) : \begin{cases} \dfrac{dx_0}{dt} = F_0(x) = 0, \\ \dfrac{dx_i}{dt} = F_i(x) = x_i(1 - \displaystyle\sum_{j=0}^{n} a_{ij}x_j) \quad a_{ij} > 0, i = 1, ..., n, \end{cases} . \tag{2.21}$$

where (2.21) differs from (2.1) only in that x_0 remains constant and does not change from the initial condition. We define Γ_{CLV} as

$$\Gamma_{CLV} = \left\{ \bigcup_{x^0 \in \mathbb{R}_+^{n+1}} \omega(x^0) | \; \omega(x^0) \text{is the } \omega\text{-limit set of } FCLV_c(n) \right\}, \tag{2.22}$$

where x^0 is an initial condition. Unlike Γ_f, it is not possible to explicitly define a set of equations that defines Γ_{CLV}, as each x_0^0 gives rise to a $CLV(n)$ system, which has its own carrying simplex. Finding equations to define Γ_{CLV} would be equivalent to finding explicit equations for the carrying simplex of $CLV(n)$ (which remains a very difficult problem). However we do know Γ_{CLV} is continous [2]. Next, the ω-limit set of $FCLV_c(n)$ is monotone in the following sense; for $x_0^1 \geq x_0^2$ then $\omega(x^1) \geq \omega(x^2)$. The continuity property is guaranteed to hold true for monotone systems [2], while the ordering property comes from increasing x_0, effectively reducing the carrying capacity of the $CLV(n)$ part of the $FCLV_c(n)$ system. For a sketch of Γ_f and Γ_{CLV} see Fig. 2.1.

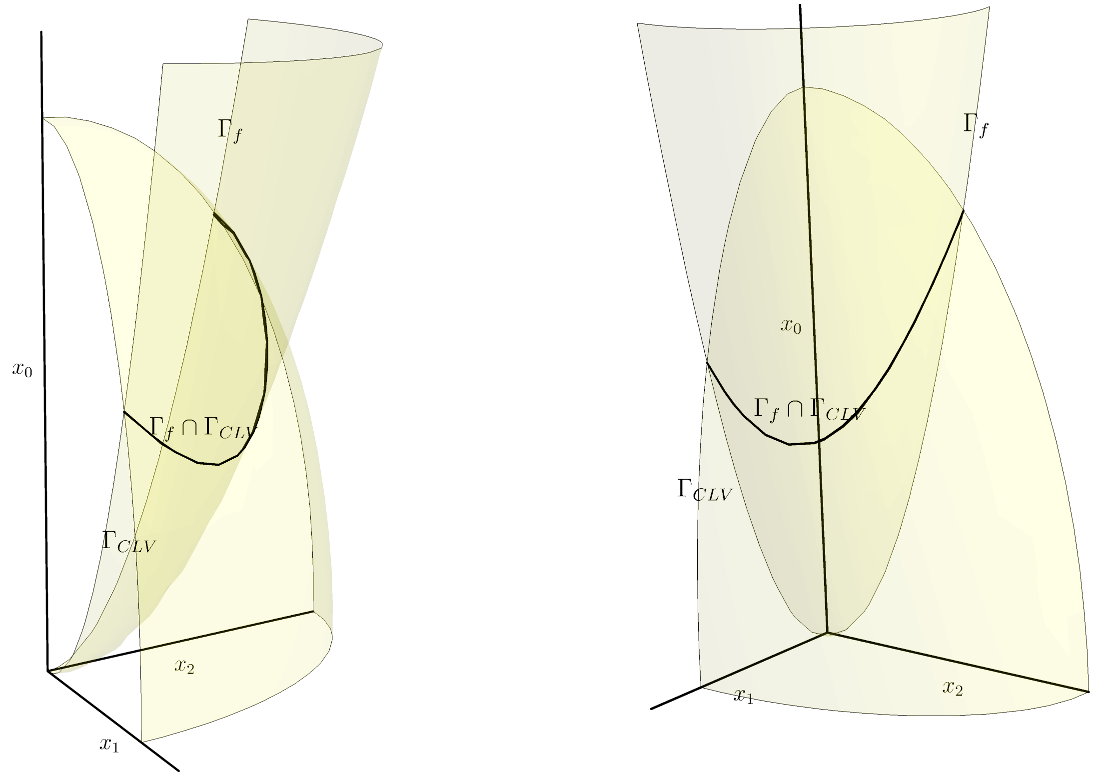

Figure 2.1: Sketch of Γ_f and Γ_{CLV} for a $FCLV(2)$ system. The different views are for visual clarity. The sketch is to help visualize the shape of Γ_{CLV}, and the order relation $x_0^1 \geq x_0^2$ implies $\omega(x^1) \geq \omega(x^2)$. Note that the concavity of Γ_{CLV} does need to stay the same for increasing x_0. The Immune response function used for this sketch is $f(x_1, x_2) = x_1^2 + x_2^2$.

In accordance with the definitions of Γ_f and Γ_{CLV} the fixed points of $FCLV(n)$ lie in the intersection of $\Gamma_f \cap \Gamma_{CLV}$ (other than the origin which is located only on Γ_f) as, Γ_f is the x_0-nucline and the intersections of the $x_1, ..., x_n$ nuclines are in Γ_{CLV}. In follows that the stability properties of $FCLV(n)$ can be phrased in terms of questions related to Γ_f and Γ_{CLV}. e.g. Do solutions converge to $\Gamma_f \cap \Gamma_{CLV}$ or do some solutions diverge away from $\Gamma_f \cap \Gamma_{CLV}$? Contraction analysis (specifically the results in Section 4.3) provides a definite answer to most of these related questions.

Chapter 3

Contraction Analysis

This section is meant to serve as a review of contraction analysis using contraction metrics and is necessary background for the theorems in the section. Those who are familiar with contraction analysis can skip this section, for a introductory review see [19].

Consider a non-linear system[1]

$$\frac{dx}{dt} = f(x), \tag{3.1}$$

where $x \in \mathbb{R}^n$ and $f : \mathbb{R}^n \to \mathbb{R}^n$. Assuming $f \in C^1$, there exists the exact differential relation

$$\delta\dot{x} = J(f(x))\delta x, \tag{3.2}$$

where $J(f(x))$ is the Jacobian of f evaluated at x, and δx formally defines a linear tangent differential form[2]. Note that differential forms are well defined mathematical objects that appear in a wide variety of fields including differential geometry and calculus of variations [28]. If we now consider two neighbouring trajectories governed by equation (3.1) and the infinitesimal displacement δx between them, the squared distance between the two trajectories is given by $\delta x^T \delta x$. If f is continuously differentiable, the rate of change between trajectories at a point is given by

$$\frac{d}{dt}(\delta x^T \delta x) = 2\delta x^T \delta\dot{x} = 2\delta x^T J(f(x))\delta x \leq 2\lambda_{max}\delta x^T \delta x, \tag{3.3}$$

where λ_{max} is the largest eigenvalue of the symmetric part of the Jacobian $J(f(x))$, which we denote as $J_s(f(x)) = \frac{1}{2}(J(f(x)) + J^T(f(x)))$. Hence

$$||\delta x|| \leq ||\delta x_0|| e^{\int_{t_0}^{t} \lambda_{max}(x,t)dt}, \tag{3.4}$$

---

[1] Note that the background covered here applies to non-autonomous systems as well, but we exclude these as our focus is on autonomous systems. Those who are interested in non-autonomous systems should read the related references given in the text.

[2] Note δx can be thought of an infinitesimal displacement for fixed time and that $\delta\dot{x} = \frac{d\delta x}{dt}$ is the rate of change of the differential.

and so, if λ_{max} is uniformly strictly negative, any infinitesimal length $||\delta x||$ converges exponentially to zero.

Now, consider a differential coordinate transformation

$$\delta z = \Theta \delta x, \tag{3.5}$$

where $\Theta(x) \in \mathbb{R}^{n \times n}$ is a uniformly invertible square matrix. Then, the rate of change of $\delta z^T \delta z$ is given by

$$\frac{d}{dt}(\delta z^T \delta z) = 2\delta z^T \delta \dot{z} = 2\delta z^T (\dot{\Theta} + \Theta J(f(x)))\Theta^{-1} \delta z. \tag{3.6}$$

Note that $\dot{\Theta}_{ij}(x) = \nabla \Theta_{ij}(x) \cdot f(x)$, and $J_g(f(x)) = (\dot{\Theta} + \Theta J(f(x)))\Theta^{-1}$ is called the generalized Jacobian[3]. So the exponential convergence of $||\delta z||$ to zero is guaranteed if the symmetric part of the generalized Jacobian,

$$J_{gs}(f(x)) = \frac{1}{2}(J_g(f(x)) + J_g^T(f(x)), \tag{3.7}$$

is uniformly negative definite. With this we can definite two central concepts of contraction analysis; contraction metrics and contracting systems.

Definition 3.0.1. (Contraction metric) For any Θ defining the transformation (3.5) the matrix $M(x) \in \mathbb{R}^{n \times n}$ defined by

$$M(x) = \Theta^T \Theta. \tag{3.8}$$

is called a contraction metric for system (3.1), if it is positive definite (which is guaranteed for uniformly invertible square matrix, Θ) and the associated J_{gs} is negative definite.

This definition comes from the generalization of squared length as $\delta z^T \delta z = \delta x^T \Theta^T \Theta \delta x = \delta x^T M \delta x$. $M(x)$ is a symmetric and continuously differentiable metric. A contraction metric, $M(x)$ exists if and only if there is a neighbourhood around x where nearby trajectories are moving closer to each other at an exponential rate. See [22] for a proof.

Definition 3.0.2. (Contracting System) A dynamical system is contracting on some set if there exists a positive definite contraction metric $M(x)$ on that set.

Note that equation (3.6) can be written in terms of $M(x)$ and δx

$$\frac{d}{dt}(\delta z^T \delta z) = \frac{d}{dt}(\delta x^T M(x) \delta x) = \delta x^T (J^T(f(x))M + \dot{M} + MJ(f(x)))\delta x. \tag{3.9}$$

We also define here, the related term "partial contraction" [22, 39].

---

[3] It is called the generalized Jacobian, because it is the Jacobian expressed in any coordinate change defined by $\Theta(x)$

Definition 3.0.3. (Partially Contracting) Consider a nonlinear system of the form

$$\frac{dx}{dt} = f(x, x), \tag{3.10}$$

and assume the the auxiliary system[4]

$$\frac{dy}{dt} = f(y, x), \tag{3.11}$$

is contracting with respect to y, that is there exists a contraction metric $M(y)$ for any x. Then the original system is said to be partially contracting.

If a particular solution of the auxiliary system verifies a smooth specific property[5], then all trajectories of the original system verify this property exponentially. This is because the auxiliary system has two particular solutions, namely $y(t) = x(t)$ for all $t \geq t_0$ and the solution with a specific property (i.e. the solution where $y(t) \neq x(t)$ for all $t \geq t_0$). As all trajectories of the auxiliary system converge to a single trajectory, it implies that $x(t)$ converges to $y(t)$ exponentially.

Initially the relationship between contraction and partial contraction is not obvious. The connection is that partial contractions are the generalizations of contractions (based on the definitions presented here). If a system is globally contracting then all solutions converge to a single trajectory, that is, initial conditions are "quickly forgotten". In contrast, the long term behaviour of partially contracting systems (in general) depends on initial conditions. The theory of partially contracting systems only guarantees that the $y(t)$ solution converges to the $x(t)$ solution. Despite being more general, in many cases it is much simpler to find partial contractions, see [39].

The following Lemma (which is Example 2.1 in [39]) is the basis for many results in contraction analysis. We present it here as it is very useful for most applications of partial contraction analysis as many systems can be written into convenient forms similar to (3.13).

Lemma 5 (Example 2.1 in [39])**.** *Consider a system of the form*

$$\frac{dx}{dt} = c(x) + d(x), \tag{3.12}$$

where $x \in \mathbb{R}^n_+$, $c, d \in C^1$. *If the auxiliary system*

$$\frac{dy}{dt} = c(y) + d(x), \tag{3.13}$$

is contracting for any x, *then any smooth property that* (3.13) *satisfies system* (3.12) *exponentially*

Proof. System (3.12) is partially contracting. □

---

[4] Note that y is the same dimension as x.

[5] e.g. convergence to a equilibrium point, satisfying a Lyapunov function, periodicity

In addition we note that partial contraction should not be confused with semi-contraction.

Definition 3.0.4. (Semi-Contracting) If a contraction metric $M(x) \in \mathbb{R}^{n \times n}$ is only positive semi-definite and $J_{gs}(f(x))$ is uniform negative semi-definite then system (3.1) is semi-contracting.

If system (3.1) is semi-contracting, then there are some principal directions p_i corresponding to uniformly positive definite eigenvalues of $M(x)$. As $J_{gs}(f(x))$ is uniformly negative definite, then this implies exponential convergence to zero of the components of $||\delta x||$ on the linear subspace spanned by p_i. An example of a system that is semi-contracting (this example comes from the Appendix of [39]) is the following Van der Pol oscillator

$$\frac{dx}{dt} = \omega y - \frac{\alpha}{3}x^3 - \beta x, \tag{3.14}$$

$$\frac{dy}{dt} = -\omega x. \tag{3.15}$$

Note that ω, β, α are positive constants. The Van der Pol oscillator, has the following Jacobian

$$J = \begin{bmatrix} -\beta - \alpha x^2 & \omega \\ -\omega & 0 \end{bmatrix}, \tag{3.16}$$

which is negative semi-definite. Further analysis shows that $\delta z^T \delta z$ (where $\delta z = [\delta x, \delta y]^T$) tends to a lower limit, which implies that δx tends to 0. Because the Van der Pol oscillator is two dimensional this implies that all solutions converge to a single trajectory, independent of initial conditions. If system was three dimensional the system would not converge to a single trajectory.

3.1 Convergence in a Sphere

Having covered the background for contraction metrics, we focus on the most basic and important results from contraction analysis as it is the basis of properties of contraction metrics (Note the following lemma is adapted from Theorem 2 in [22]).

Lemma 6. *Assume system* (3.1) *is a contracting system. Any trajectory of* (3.1) *which starts in a ball of constant radius with respect to a contraction metric* $M(x)$ *centred at a given trajectory (which we will call the reference trajectory) and contained at all times in a contraction region with contraction metric* $M(x)$*, remains in that ball and converges exponentially to this trajectory.*

Proof. We provide an abbreviated proof here see [22] for more details. Consider a ball of constant radius, such that a given trajectory remains in the ball and within a contraction region for all $t \geq t_0$. Once this reference trajectory has been established, as it is in a contraction region any distance between trajectories within the ball decreases exponentially. In addition, any trajectory starting within the ball remains in the ball (since the center of the ball is at a particular system trajectory) and converges exponentially to the reference trajectory. See Figure 3.1 for a sketch of this proof. □

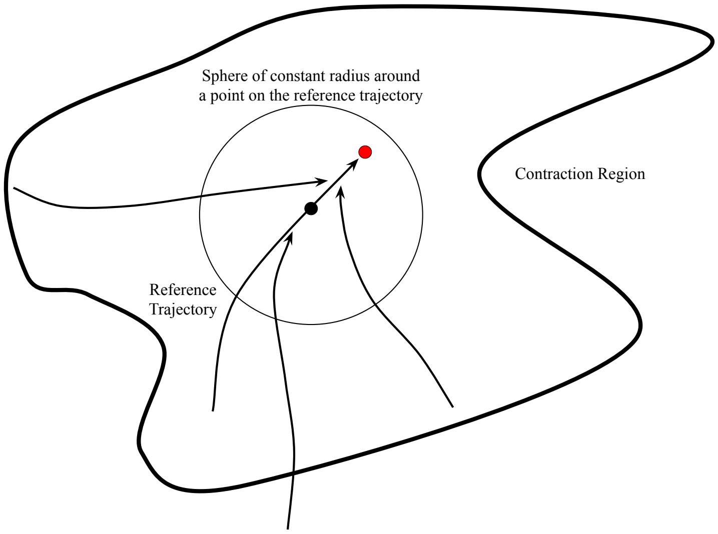

Figure 3.1: Convergence of trajectories within in a contraction region. Black dot is the point which the sphere is centred at. The red dot is a fixed point where the reference trajectory ends at. All neighbouring trajectories within the contraction region converge to the reference trajectory.

3.2 Properties of Contraction Metrics

We summarize here many of the properties of the contraction metrics not covered in Sections 3 and 3.1. While many of these properties are not used, they are necessary to understand the applications of contraction metrics. Unless otherwise cited, the properties of contraction metrics come from [22, 39].

- The following statements are equivalent for equation (3.1) on some $\Omega \subseteq \mathbb{R}^n$.
  - $(J^T M + \dot{M} + MJ) \leq -\beta M$ where β is a positive constant and $M(x)$ is uniformly positive definite.
  - $J_{gs}(f(x))$ is uniformly negative definite and $M(x)$ is uniformly positive definite.
  - equation (3.1) is contracting on Ω.
- The results in all of Section 3 can be extended to other vector norms and their induced matrix norms, see [1].

- A convex contraction region contains at most one equilibrium point, since any length between two trajectories shrinks exponentially in that region. If a contracting system is autonomous, the system converges exponentially to a fixed point.
- If system (3.1) is contracting, then the function $V(x) = f^T(x)M(x)f(x)$ is a Lyapunov function for (3.1). Indeed, taking the derivative of $V(x)$ yields

  $$\frac{dV(x)}{dt} = f^T(x)(J^T(f(x))M + \dot{M} + MJ(f(x)))f(x) \leq -\beta V. \tag{3.17}$$

  This shows that V satisfies the requirement of a Lypunov function as the equilibrium point contained in the contraction region is exponentially stable.
- The types of contraction metrics that we discussed thus far are not suitable for determining the stability of periodic trajectories. What is needed is a contraction metric that can be used to determine whether nearby trajectories contract in a direction transverse to the periodic trajectory (this is in contrast to definition 3.0.1 which is for contraction in every direction, not just the transverse direction). Recently a linear first order matrix valued PDE was found whose solution is a contraction metric that determines if the system is contracting in the transverse direction [12, 23].
- Similar to Lyapunov functions, there is no known general method to find $M(x)$ analytically.
- There are methods to find $M(x)$ numerically for any given system [3]. If a contraction region can be found around a fixed point it proves exponential stability in the region that the contraction metric exists.
- Contraction analysis as presented here, is a generalized version of Krasovskii's Theorem [14]. The difference being the constant matrix is replaced with the contraction metric $M(x)$. Note that if the system is linear, $M(x)$ is constant.
- $M(x)$ is not unique for a given system.
- Contraction theory can be used to show the opposite of convergence, exponential divergence of neighbouring trajectories; if the minimal eigenvalue λ_{min} of J_{gs} is strictly positive, then $||\delta x^T \delta x||$ is exponentially increasing, implying that nearby trajectories exponentially diverge away from each other.

3.3 Relation between Incremental and Convergent Stability

We highlight in this section the difference between two notations of incremental stability and convergent stability and when they are equivalent. The definitions are important as they establish and important connection between monotone systems and contraction. The existence of carrying simplex implies that $CLV(n)$ systems are contracting outside of Σ_{CLV}. This is important to $FCLV(n)$ systems because it establishes that the Jacobian of the $CLV(n)$ part is negative definite. We note that the definitions and theorems in Section 3.3.1 are the same as in [30].

3.3.1 Definitions related to Incremental and Convergent Stability

Consider a system

$$\frac{dx(t)}{dt} = f(x,t), \tag{3.18}$$

with $f : \mathbb{R}^{n+1} \to \mathbb{R}^n$ being locally Lipschitz in $x \in \mathbb{R}^n$ and measurable in t. These assumptions are to guarantee local existence and uniqueness of solutions.

Definition 3.3.1. (Uniform Convergence) Definition 1 in [30] System (3.18) is uniformly convergent in a positively invariant set $\Omega \subset \mathbb{R}^n$ if:

- All solutions $x(t)$ exist for all $t \geq t_0$ for all initial conditions in Ω.
- There exists a unique solution $\bar{x}(t)$ in Ω defined and bounded for all t
- The solution $\bar{x}(t)$ is uniformly asymptotically stable in Ω, that is, there exists a function $\beta \in \mathcal{KL}$ such that for all $(x_0, t_0) \in \Omega \times \mathbb{R}$ and $t \geq t_0$,

$$||x(t, x_0, t_0) - \bar{x}(t)|| \leq \beta(||x_0 - \bar{x}(t_0)||, t - t_0). \tag{3.19}$$

If the above holds for $\mathbb{R}^n$, the system (3.18) is globally uniformly convergent.

Note that this definition of stability is the standard notion of stability used in most of dynamical systems and Lyapunov stability theory.

Definition 3.3.2. (Incrementally Stability) Definition 2 in [30] System (3.18) is incrementally asymptotically stable in a positively invariant set $\Omega \subset \mathbb{R}^n$ if there exists a function $\beta \in \mathcal{KL}$ such that for all $\xi_1, \xi_2 \in \Omega$ and $t \geq t_0$,

$$||x(t, \xi_1, t_0) - x(t, \xi_2, t_0)|| \leq \beta(||\xi_1 - \xi_2||, t - t_0). \tag{3.20}$$

If the above holds for $\mathbb{R}^n$, the system (3.18) is globally incrementally stable[6].

In general these two notions of stability are equivalent under appropriate conditions.

Theorem 7 (Theorems 8 and 11 in [30]). *System* (3.18) *is uniformly convergent on a compact set* Ω*, if and only if, it is also incrementally stable on that set.*

---

[6] Note that a system is contracting if and only if exponentially, incrementally stable $||x(t, \xi_1, t_0) - x(t, \xi_2, t_0)|| \leq ||\xi_1 - \xi_2|| e^{t^0 - t}$ [19].

Theorem 7 is necessary as there systems that are either uniform convergent or incrementally stable but not both. We provide two examples that demonstrate these different between the notions of stability. Consider the following system

$$\frac{dx}{dt} = -x + t, \tag{3.21}$$

which has the solution

$$x(t) = x^0 e^{t^0 - t} - (t^0 - 1)e^{t^0 - t} + (t - 1). \tag{3.22}$$

With the initial condition (x^0, t^0) the solution $x(t)$ is unbounded. Hence the system (3.21) cannot be globally convergent as the definition of uniform convergence (Definition 3.3.1) requires $x(t)$ to be bounded, so any system with an unbound attracting solution cannot be globally convergent. If we take $\xi^1, \xi^2 \in \mathbb{R}$ then

$$\frac{d}{dt}\left(x(t, t^0, \xi^1) - x(t, t^0, \xi^2)\right) = -(x(t, t^0, \xi^1) - x(t, t^0, \xi^2)), \tag{3.23}$$

this implies

$$||x(t, t^0, \xi^1) - x(t, t^0, \xi^2)|| \leq ||\xi^1 - \xi^2|| e^{t^0 - t}. \tag{3.24}$$

Inequality (3.24) provides a $\mathcal{KL}$ bound on the difference between any two solutions, so the system (3.21) is globally incrementally stable.

Now for our second example we consider the following system (which is example 3 in [30]) in polar coordinates

$$\frac{dr}{dt} = -r, \tag{3.25a}$$
$$\frac{d\phi}{dt} = r^2, \tag{3.25b}$$

where r is the radius and ϕ is the angle in the counter clockwise direction. From inspection it is obvious system (3.25) converges to the origin for all initial values and so is globally uniformly convergent. We now determine whether the system is globally incrementally stable. System (3.25) has the following solution

$$r(t) = r^0 e^{-t}, \tag{3.26}$$
$$\phi(t) = \phi^0 + (1 - e^{-2t})\frac{(r^0)^2}{2}, \tag{3.27}$$

then let $z(t) = (r(t), \phi(t))$ and $\bar{z}(t) = (\cos(t), \sin(t))$. Let us consider a region such that $r = R > 1$ be large enough such that the two solutions $z^1(t), z^2(t)$ starting at the initial conditions $(r^1, phi^1, t^0) = (\sqrt{R + M} + 1, 0, 0)$ and $(r^2, phi^2, t^0) = (\sqrt{R} + 1, 0, 0)$ (with $M = \frac{2\pi e}{e-1}$) satisfies

$$||z^i(t) - \bar{z}(t)|| > 1, \ i = 1, 2 \quad \forall t \in \left[0, \frac{1}{2}\right]. \tag{3.28}$$

We note that

$$||(r^1, phi^1, t^0) - (r^2, phi^2, t^0)|| = \sqrt{M + \sqrt{R}(2\sqrt{R} - 2\sqrt{R+M})} \leq \sqrt{M}. \tag{3.29}$$

With these two initial conditions at time $t = \frac{1}{2}$ the distance between the two solutions is

$$||z^1(1/2) - z^2(1/2)|| = \frac{\sqrt{R+M} + \sqrt{R}}{\sqrt{e}}. \tag{3.30}$$

As the two solutions move further apart after the initial time, there cannot be a $\mathcal{KL}$ bound such that the definition of globally incrementally stable is satisfied, hence system (3.25) is not globally incrementally stable.

While we use Theorem 7 for other proofs, for the sake of completeness we mention theorems for the requirements for globally uniform convergence and global incremental stability.

Theorem 8 (Theorems 7 and 10 in [30]). *Assume that system* (3.18) *is globally uniformly convergent, and that it is continuous in* t *and* C^1 *in* x. *Also assume, that* $f(x,t)$ *Jacobian* $J(f(x))$ *with respect to* x *is bounded, uniformly in* t. *In addition, assume there is a positive definite matrix* $P \in \mathbb{R}^{n\times n}$, *a continuous positive definite function* $\alpha : \mathbb{R}_+ \to \mathbb{R}_+$, *and a positive constant* $C > 0$ *such that for all times* $t \in \mathbb{R}$ *and all* $x^1, x^2 \in \mathbb{R}^n$

$$(x^1 - x^2)^T P(f(x^1,t) - f(x^2,t)) \leq \begin{cases} -\alpha(||x^1 - x^2||) & \textit{if } max\{||x^1||, ||x^2||\} \geq C, \\ 0 & \textit{otherwise.} \end{cases} \tag{3.31}$$

Then the system (3.18) *is globally incrementally stable.*

Note there is a known class of systems which satisfy Theorem 8, called quadratically convergent systems [25].

Theorem 9 (Theorems 12 in [30]). *Suppose that the system* (3.18) *is globally incrementally stable. Then, the following statements hold:*

- *There exists a sufficiently small* $c \geq 0$ *such that if* $c \geq ||f(0,t)||$ *for all* t, *then system* (3.18) *is globally uniformly convergent.*
- *If there exists a compact* $\Omega \subset \mathbb{R}^n$ *that is positively invariant, then system* (3.18) *is globally uniformly convergent.*

3.3.2 Minor Lemmas

The lemmas define a form of contraction that is slower than described in Section 3. This is needed as the contraction is very restrictive and limits direct application to some systems which converge slowly.

Lemma 10. *Uniform asymptotic convergence does not imply asymptotic incremental stability.*

Proof. We do a proof by contradiction. Assume that uniform asymptotic convergence does imply asymptotic incremental stability. Consider the following simple example[7]

$$\frac{dx}{dt} = -x^3, \tag{3.32}$$

which has the following solution for the initial conditions (x^0, t^0)

$$x(t) = \frac{\pm 1}{\sqrt{2(t-t_0) + \frac{1}{(x^0)^2}}}. \tag{3.33}$$

The equation (3.32) converges asymptotically to zero by Definition 3.3.1 as

$$\left\| \frac{1}{\sqrt{2(t-t_0) + \frac{1}{(x^0)^2}}} - 0 \right\| \leq \beta(||x(t) - 0||, t - t_0), \tag{3.34}$$

as the left hand side is a $\mathcal{KL}$ function, so (3.32) is asymptotically stable. It is not exponentially stable as $x(t)$ converges at a rate proportional to $\frac{1}{\sqrt{2t}}$ which is slower than exponential convergence.

However, the derivative of the right hand side of (3.32) is strictly negative definite (except at zero) and so there exists a contraction metric for equation (3.32) and it must be exponentially incrementally stable. This directly contradicts the statement that uniform asymptotic convergence implies asymptotic incremental stability, so th onlye statement is false. □

The above lemma is important as it shows that the speed of uniform convergence and the speed of incremental stability of a system are not necessarily linked.

Lemma 11. *If system*[8] (3.1) *or* (3.18) *is incrementally stable by Definition 3.3.1, on a compact set it is contracting.*

Proof. In [19, 22] if a system is incrementally stable either the general Jacobian is uniformly negative definite or the maximum eigenvalue of the Jacobian satisfies the following

$$\int_t^{t+T} \lambda_{max}(x,t)\, d\tau < 0, \tag{3.35}$$

for some $T > 0$. In the first case the system is exponentially contracting, while in the second case it is contracting but at an asymptotic rate. □

The above lemma implies that for any $CLV(n)$ system outside of Σ_{CLV} there exists a contraction metric.

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[7] Global uniqueness of the solutions of (3.32) is not important for the analysis.

[8] Note a system which is C^1 is also locally Lipschitz.

Chapter 4

Application of Contraction Theory to $FCLV(n)$ Systems

Having covered the necessary background on contraction theory we now focus on applications to $FCLV(n)$. We organize our thoughts and results as follows. In Section 4.1 we explain in detail why in general the combination of two contracting systems does not imply that the combination is contracting. This is important because the functional part and the $CLV(n)$ part are both contracting for constant $x_1, \dots x_n$ and x_0 respectively. Once this argument is presented it is clear that unless an explicit contraction metric for any $CLV(n)$ is found (which is equivalent in difficulty to finding a Lyapunov function for any $CLV(n)$ system, an open problem that has not been solved despite the wide interest in $CLV(n)$ systems) it is necessary to use estimates to determine stability of $FCLV(n)$. We cover estimates/sufficient conditions for stability in Section 4.2 derived using contraction theory. Finally in Section 4.3 we provide a simple proof that shows that any initial condition all solutions of $FCLV(n)$ converges to Γ_f if the immune response function is strictly monotone increasing. The information from these sections is used in the examples in Section 5.

Note that most of these sections focus on contraction metrics in the interior of $\mathbb{R}^n_+$ as a well known property of $CLV(n)$ systems is that in any facet on the boundary of $\mathbb{R}^n_+$, $CLV(n)$ behaves as a lower dimensional $CLV(n)$ system (e.g. For $CLV(3)$ the $x_3 = 0$ plane is equivalent to a $CLV(2)$ system). $FCLV(n)$ has this same property (expect that the $x_0 = 0$ plane resembles a $CLV(n)$ system and is not invariant), hence our focus on the interior of $\mathbb{R}^n_+$.

4.1 On connections between subsystems

As discussed in Section 3, the functional part and the $CLV(n)$ part of $FCLV(n)$ are contracting when not connected. This brings up the natural question, what conditions ensure that two contracting dynamical systems when connected in a non-linear way is still contracting? We explore the answer to this question in this section.

A well known property of contracting systems [39] is given a nonlinear system with generalized virtual nonlinear displacements δz_i,

$$\begin{bmatrix} \delta \dot{z}_1 \\ \delta \dot{z}_2 \end{bmatrix} = J_{gs}(f(x)) \begin{bmatrix} z_1 \\ z_2 \end{bmatrix}, \tag{4.1}$$

where $J_{gs}(f(x))$ is the generalized Jacobian and has the form,

$$J_{gs}(f(x)) = \begin{bmatrix} J_{1gs} & G \\ G^T & J_{2gs} \end{bmatrix}, \tag{4.2}$$

if J_{1gs} and J_{2gs} are uniformly negative definite in the same metric by assumption (they can be thought of as the dynamics of $f_1(x)$ and $f_2(x)$ independent of each other), the overall system is contracting ($J_{gs}(f(x))$ is negative definite) if and only if the following matrix inequality holds

$$J_{2gs} < G^T J_{2gs}^{-1} G. \tag{4.3}$$

Note the reason this inequality is necessary is that it is the sufficient and necessary condition for a block matrix to be negative definite [16].

However this statement by itself is not very useful (e.g. How can we verify that J_{1gs} and J_{2gs} are contracting in the same metric? What metric is G contracting in?). We do the following calculations to provide more context. We start with the following non-linear system

$$\frac{dx}{dt} = g(x), \tag{4.4}$$

and assume it can be written as

$$\frac{dx_1}{dt} = g_1(x_1, x_2), \tag{4.5a}$$
$$\frac{dx_2}{dt} = g_2(x_1, x_2), \tag{4.5b}$$

with $dim(x_1) + dim(x_2) = dim(x)$. The virtual dynamics of the system are then given by

$$\delta \dot{x}_1 = J_{1,1} \delta x_1 + J_{1,2} \delta x_2, \tag{4.6}$$
$$\delta \dot{x}_2 = J_{2,1} \delta x_1 + J_{2,2} \delta x_2, \tag{4.7}$$

where $J_{i,j} = \frac{\partial g_i(x)}{\partial x_j}$. For reasons that will be obvious shortly it is much more convenient to express the above as the matrix equation

$$\begin{bmatrix} \delta \dot{x}_1 \\ \delta \dot{x}_2 \end{bmatrix} = \begin{bmatrix} J_{1,1} & J_{1,2} \\ J_{2,1} & J_{2,2} \end{bmatrix} \begin{bmatrix} \delta x_1 \\ \delta x_2 \end{bmatrix}. \tag{4.8}$$

We assume that the coordinate transformation $\delta z = \Theta \delta x$ can be written as four submatrices

$$\begin{bmatrix}\delta z_1\\ \delta z_2\end{bmatrix} = \begin{bmatrix}\Theta_{1,1} & \Theta_{1,2}\\ \Theta_{2,1} & \Theta_{2,2}\end{bmatrix}\begin{bmatrix}\delta x_1\\ \delta x_2\end{bmatrix}. \tag{4.9}$$

Using the property with these base assumptions we can now calculate $\delta \dot{z}$ in terms of δz.

$$\begin{bmatrix}\delta \dot{z}_1\\ \delta \dot{z}_2\end{bmatrix} = \begin{bmatrix}\dot{\Theta}_{1,1} & \dot{\Theta}_{1,2}\\ \dot{\Theta}_{2,1} & \dot{\Theta}_{2,2}\end{bmatrix}\begin{bmatrix}\delta x_1\\ \delta x_2\end{bmatrix} + \begin{bmatrix}\Theta_{1,1} & \Theta_{1,2}\\ \Theta_{2,1} & \Theta_{2,2}\end{bmatrix}\begin{bmatrix}\delta \dot{x}_1\\ \delta \dot{x}_2\end{bmatrix}, \tag{4.10}$$

$$= \begin{bmatrix}\dot{\Theta}_{1,1} & \dot{\Theta}_{1,2}\\ \dot{\Theta}_{2,1} & \dot{\Theta}_{2,2}\end{bmatrix}\begin{bmatrix}\Theta_{1,1} & \Theta_{1,2}\\ \Theta_{2,1} & \Theta_{2,2}\end{bmatrix}^{-1}\begin{bmatrix}\delta z_1\\ \delta z_2\end{bmatrix} \tag{4.11}$$

$$+ \begin{bmatrix}\Theta_{1,1} & \Theta_{1,2}\\ \Theta_{2,1} & \Theta_{2,2}\end{bmatrix}\begin{bmatrix}J_{1,1} & J_{1,2}\\ J_{2,1} & J_{2,2}\end{bmatrix}\begin{bmatrix}\Theta_{1,1} & \Theta_{1,2}\\ \Theta_{2,1} & \Theta_{2,2}\end{bmatrix}^{-1}\begin{bmatrix}\delta z_1\\ \delta z_2\end{bmatrix}, \tag{4.12}$$

$$= \left(\begin{bmatrix}\dot{\Theta}_{1,1} & \dot{\Theta}_{1,2}\\ \dot{\Theta}_{2,1} & \dot{\Theta}_{2,2}\end{bmatrix} + \begin{bmatrix}\Theta_{1,1} & \Theta_{1,2}\\ \Theta_{2,1} & \Theta_{2,2}\end{bmatrix}\begin{bmatrix}J_{1,1} & J_{1,2}\\ J_{2,1} & J_{2,2}\end{bmatrix}\right)\begin{bmatrix}\Theta_{1,1} & \Theta_{1,2}\\ \Theta_{2,1} & \Theta_{2,2}\end{bmatrix}^{-1}\begin{bmatrix}\delta z_1\\ \delta z_2\end{bmatrix}. \tag{4.13}$$

Note that matrix on the right of (4.13) is the generalized Jacobian of $g(x)$. Further caclulation is very tedious if we don't make additional assumptions. For the purposes of our argument, the most reasonable assumption is that $\Theta_{1,2} = \Theta_{2,1} = 0$ then

$$\begin{bmatrix}\delta \dot{z}_1\\ \delta \dot{z}_2\end{bmatrix} = \left(\begin{bmatrix}\dot{\Theta}_{1,1} & 0\\ 0 & \dot{\Theta}_{2,2}\end{bmatrix} + \begin{bmatrix}\Theta_{1,1} & 0\\ 0 & \Theta_{2,2}\end{bmatrix}\begin{bmatrix}J_{1,1} & J_{1,2}\\ J_{2,1} & J_{2,2}\end{bmatrix}\right)\begin{bmatrix}\Theta_{1,1}^{-1} & 0\\ 0 & \Theta_{2,2}^{-1}\end{bmatrix}\begin{bmatrix}\delta z_1\\ \delta z_2\end{bmatrix}, \tag{4.14}$$

$$= \begin{bmatrix}\left(\dot{\Theta}_{1,1} + \Theta_{1,1}J_{1,1}\right)\Theta_{1,1}^{-1} & \Theta_{1,1}J_{1,2}\Theta_{2,2}^{-1}\\ \Theta_{2,2}J_{2,1}\Theta_{1,1}^{-1} & \left(\dot{\Theta}_{2,2} + \Theta_{2,2}J_{2,2}\right)\Theta_{2,2}^{-1}\end{bmatrix}\begin{bmatrix}\delta z_1\\ \delta z_2\end{bmatrix}. \tag{4.15}$$

Then if the systemic part of $J_{1g} = \left(\dot{\Theta}_{1,1} + \Theta_{1,1}J_{1,1}\right)\Theta_{1,1}^{-1}$ and $J_{2g} = \left(\dot{\Theta}_{2,2} + \Theta_{2,2}J_{2,2}\right)\Theta_{2,2}^{-1}$ are negative definite the independent systems:

$$\frac{dx_1}{dt} = g_1(x_1, x_2) \quad x_2 \text{ held constant}, \tag{4.16}$$

$$\frac{dx_2}{dt} = g_2(x_1, x_2) \quad x_1 \text{ held constant}, \tag{4.17}$$

are contracting with two different contraction metrics $M_1 = \Theta_1^T\Theta_1$ and $M_2 = \Theta_2^T\Theta_2$. As mentioned before this is a necessary condition to ensure that system (4.5) is contracting, but by itself does not ensure that the symmetric part of (4.15) is negative definite. This is true only if the following matrix inequality holds

$$J_{2gs} < G^T J_{1gs} G, \tag{4.18}$$

$$\begin{aligned} J_{2gs} < \frac{1}{4}&\left((\Theta_{2,2}J_{2,1}\Theta_{1,1}^{-1})^T + \Theta_{1,1}J_{1,2}\Theta_{2,2}^{-1}\right)^T \\ &J_{1gs}\left((\Theta_{2,2}J_{2,1}\Theta_{1,1}^{-1})^T + \Theta_{1,1}J_{1,2}\Theta_{2,2}^{-1}\right). \end{aligned} \tag{4.19}$$

Note that a sufficient condition for the above inequality to hold is [39],

$$\lambda_{max}(J_{2gs}) < \lambda_{min}(J_{1gs}^{-1})\sigma^2(G), \tag{4.20}$$

where $\lambda_{max}(J_{2gs})$ is the largest eigenvalue of J_{2gs}, $\lambda_{min}(J_{1gs})$ is the smallest eigenvalue of J_{1gs} and $\sigma^2(G)$is the largest singular value of G.

To apply this in the $FCLV(n)$ system we replace g_1 with F_0 and g_2 with $F_1, ..., F_n$. It is obvious from the calculations above that M_1 can be any positive scalar to ensure that J_{1gs} is negative definite. M_2 would then be a contraction metric to ensure that J_{2gs} is negative definite. Explicitly finding a contraction metric for any $FCLV(n)$ for $n \geq 3$ is a significant challenge as this would be equivalent to finding a Lyapunov function for $CLV(n)$ systems, an open problem despite significant interest. Thus verifying whether inequality (4.19) does or does not hold is exceedingly difficult if M_2 is the contraction metric that makes J_{2gs} negative definite. We cover two ways to surpass to limitations, obtaining estimates for regions of contraction in Section 4.2 derived using contraction theory. Another approach is presented in Section 4.3 is based instead on finding a contraction metric such that $\Theta_{1,1}J_{1,2}\Theta_{2,2}^{-1} + \Theta_{2,2}J_{2,1}\Theta_{1,1}^{-1} = 0$, then the symmetric part of equation (4.15) becomes

$$\begin{bmatrix} \delta\dot{z}_1 \\ \delta\dot{z}_2 \end{bmatrix} = \begin{bmatrix} J_{1gs} & 0 \\ 0 & J_{2gs} \end{bmatrix} \begin{bmatrix} \delta z_1 \\ \delta z_2 \end{bmatrix}. \tag{4.21}$$

Such a matrix represents a hierarchical or cascading system [22], that is the first and second equations do not depend on each other. So the convergence of δz_1 to zero only depends on the negative definiteness of J_{1gs} and likewise the convergence of δz_2 to zero only depends on the negative definiteness of J_{2gs}. Details of this process and the implications are covered in Section 4.3.

4.1.1 A Note on the $\dot{\Theta}$ in combination with other systems.

We have ignored a small issue when looking at combinations of contracting systems, which we will now address. The is problem is we have assumed that a change of coordinates matrix $\Theta(x)$ will be suitable when we consider two systems that are connected and contracting. To express this problem more concretely consider the following nonlinear system,

$$\frac{dx_1}{dt} = g_1(x_1, x_2) \quad \text{with } x_2 \text{ held constant}, \tag{4.22}$$

and the nonlinear system (4.5). With systems (4.22) and (4.5) in mind the following question occurs, under what conditions does the negative definiteness of generalized Jacobian $(\dot{\Theta} + \Theta\frac{\partial f(x_1,x_2))}{\partial x_1})\Theta^{-1}$ for system (4.22) imply that the same submatrix in the generalised Jacobian of (4.5) is negative definite.

Lemma 12. *If the generalised Jacobian* (4.22) *is negative definite the principle submatrix of the generalized Jacobian system* (4.5) *is also negative definite if one of the following sufficient conditions is met*

1. *Θ is a constant matrix.*
2. *Θ is a function of only x_1 but not x_2.*
3. *The matrix $\frac{\partial}{\partial x_2}\big(\Theta(x)\big)\Theta^{-1}$ is negative definite.*

Proof. The difference between $(\dot{\Theta} + \Theta\frac{\partial f(x_1,x_2))}{\partial x_1})\Theta^{-1}$ in (4.22) and (4.5) is that $\dot{\Theta}$ has a different value for system (4.5). From the background on contracting systems the ij-th entry of $\dot{\Theta}$ is

$$\dot{\Theta}_{i,j} = \nabla\Theta_{i,j} \cdot \frac{dx}{dt}. \tag{4.23}$$

Since x_2 is constant for system (4.22) and non-constant in (4.5) it is obvious why sufficient conditions 1 and 2 are true. For sufficient condition 3,

$$\left(\dot{\Theta} + \Theta\frac{\partial f(x_1,x_2))}{\partial x_1}\right)\Theta^{-1} \tag{4.24}$$

$$= \left(\frac{\partial}{\partial x_1}\big(\Theta(x)\big) + \frac{\partial}{\partial x_2}\big(\Theta(x)\big) + \Theta\frac{\partial f(x_1,x_2))}{\partial x_1}\right)\Theta^{-1}, \tag{4.25}$$

$$= \left(\frac{\partial}{\partial x_1}\big(\Theta(x)\big) + \Theta\frac{\partial f(x_1,x_2))}{\partial x_1}\right)\Theta^{-1} + \frac{\partial}{\partial x_2}\big(\Theta(x)\big)\Theta^{-1}. \tag{4.26}$$

By the assumptions of the theorem $\left(\frac{\partial}{\partial x_1}\big(\Theta(x)\big) + \Theta\frac{\partial f(x_1,x_2))}{\partial x_1}\right)\Theta^{-1}$ is negative definite, if $\frac{\partial}{\partial x_2}\big(\Theta(x)\big)\Theta^{-1}$ is negative definite there sum is negative definite. Note that by negative definite we mean that the symmetric part of $\left(\frac{\partial}{\partial x_1}\big(\Theta(x)\big) + \Theta\frac{\partial f(x_1,x_2))}{\partial x_1}\right)\Theta^{-1}$ and $\frac{\partial}{\partial x_2}\big(\Theta(x)\big)\Theta^{-1}$ is negative definite. □

4.2 Estimating Regions of Contraction

As explained in Section 4.1 unless a nonlinear dynamical system has a special form it is usually not possible analytically to construct a contraction metric from combining metrics from two independently contracting systems. Without contrary evidence, in general we should not expect two contracting systems when combined together in a non-linear fashion to be contracting. However while the analytical construction of contraction methods is limited, conditions for contraction can be used to estimate regions of contraction (this should not be confused with the numerical construction of contraction metrics, which is similar to searching for Lyapunov functions of a specific function, see [3]). In this section we examine a few simple estimates for $FCLV(n)$ systems. Note that it is not possible to find a contraction region that covers all of $\mathbb{R}^n_+$ for $FCLV(n)$ and $CLV(n)$ systems as explained in the following minor lemma.

Lemma 13. *There is no contraction metric that defines a contraction region for all of $\mathbb{R}^n_+$ for $FCLV(n)$ and $CLV(n)$ systems.*

Proof. There are two reasons why there cannot be a single contraction region that covers all of $\mathbb{R}^n_+$. First there is a region around the origin that is repelling. As covered in the background on contraction theory it is not possible for a contraction metric to exist at an repelling fixed point. Next there are always n-axial fixed points for $CLV(n)$ and $FCLV(n)$ systems. A single contraction region which covers all of $\mathbb{R}^n_+$ would contain all of these points. The existence of such a contraction region would be a contradiction as the existence of a contraction metric implies the convergence of all trajectories to a single point and no other fixed points in that region (as solutions which start fixed points do not converge to each other). To resolve the contradiction, there must be subsets within $\mathbb{R}^n_+$ where either no contraction metric exists or two subsets have two different contraction metrics. $\square$

With Lemma 13 in mind, if we have a condition that implies contraction, we should expect that condition to not hold at the boundary between basins of attraction. For example consider a bistable $CLV(2)$ system (there are two one species population that are stable) versus a $CLV(2)$ system in which only one species has a stable population. In the interior of $\mathbb{R}^n_+$ there must be at least two subsets where any condition required for the existence of a contraction metric does not hold. Likewise for the system with one stable population there must be at least one subset where any condition required for the existence of a contraction metric does not hold (near the origin). So if we know if a system does not have periodic orbits we can estimate regions of contraction by whether the conditions for contraction hold or not.

4.2.1 Contraction with respect to the Identity Metric

When looking for stability properties with contraction metrics, it is best to test what is possible to discern from the using the simplest contraction metric $M(x) = I$ (i.e. there is no change of coordinates from the original system). We obtain sufficient conditions for stability based on contraction theory for $FCLV(n)$ systems.

We first explain solutions near the origin, because the analysis is simple. From the basic properties of $FCLV(n)$ systems section (see Section 2.2) we know that the origin 0 is locally repelling in all directions except the x_0-axis. That is the stable manifold is the x_0-axis and the $x_0 = 0$ plane is the unstable manifold. Independent of the stable/unstable manifold theorems, contraction theory implies that the local neighbourhood around 0 is a region of expansion except if we are restricted to the x_0-axis. Along the x_0-axis all solutions move to the origin. So $FCLV(n)$ is contracting along the x_0-axis. If we move from the origin along the x_0-axis we find the point on the x_0-axis that that attracts solutions outside x_0-axis. The Jacobian along the x_0-axis is

$$\begin{pmatrix} -1 & \dfrac{\partial f(0,\dots,0)}{\partial x_1} & \dots & \dots & \dots & \dfrac{\partial f(0,\dots,0)}{\partial x_n} \\ 0 & 1-a_{10}x_0 & 0 & 0 & \dots & 0 \\ \vdots & 0 & 1-a_{20}x_0 & 0 & \dots & 0 \\ \vdots & 0 & 0 & 1-a_{30}x_0 & \dots & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & 0 & \dots & 1-a_{n0}x_0 \end{pmatrix}. \tag{4.27}$$

As the Jacobian is upper triangular the eigenvalues are the diagonal entries of this matrix. Therefore the lowest point on the x_0-axis, which does not have n-positive eigenvalues is

$$x_0 = \min_{i\in[1,n]} \left\{ \frac{1}{a_{i0}} \right\}. \tag{4.28}$$

If we move further up x_0-axis until we reach the point where

$$x_0 = \max_{i\in[1,n]} \left\{ \frac{1}{a_{i0}} \right\}. \tag{4.29}$$

At that point $FCLV(n)$ is fully contracting, and there is a neighbourhood that is contractive around that point. So the basin of attraction for origin extends from this neighbourhood. Similarly if x_0 is large enough (anywhere not just x_0-axis) then the Jacobian of $FCLV(n)$ is negative definite, because the Jacobian is either row or column diagonally dominant and the Gershgorin disc theorem guarantees that such matrices have all negative eigenvalues [16]. Thus for large enough x_0 there should be a sequence of points that form solutions that will converge to the x_0-axis and therefore the origin. We can determine the basin of attraction of x_0 by the following process. For each point $(x_1,\dots,x_n)$ determine the smallest x_0 such that $J(FCLV(n))$ is not longer diagonally dominant at $(x_0,x_1,\dots,x_n)$. That point is part of the edge of the basin of attraction for the origin.

For all the other fixed points, which are located in $\Gamma_f \cap \Gamma_{CLV}$, we can consider the Jacobian of $FCLV(n)$ as the following block matrix

$$J(FCLV(n)) = \begin{pmatrix} -1 & \nabla f(x_1,\dots,x_n) \\ (-a_{i0}x_i)_{i\in[1,n]} & J(CLV(n,x_0)) \end{pmatrix}, \tag{4.30}$$

where $J(CLV(n,x_0))$ is used to denote the dependence on x_0. We note that

$$\begin{aligned} J(CLV(n,x_0)) &= \mathrm{Diag}(1-A_{1,n}x_{1,n}) - \mathrm{Diag}(x_{1,n})A_{1,n} - \mathrm{Diag}((a_{i0}x_0)_{i\in[1,n]})), && (4.31)\\ &= J(CLV(n)) - \mathrm{Diag}((a_{i0}x_0)_{i\in[1,n]}), && (4.32) \end{aligned}$$

where $J(CLV(n))$ denotes the Jacobian of an $CLV(n)$ system, $A_{1,n}$ denotes the elements of the community matrix of $FCLV(n)$ without a_{i0} elements, $x_{1,n}$ denotes the vector $(x_1,...,x_n)$, and $\mathrm{Diag}(\cdot)$ denotes a diagonal matrix whose entries come from the argument vector. An important observation is that if $J(CLV(n))$ is negative definite than $J(CLV(n, x_0))$ is negative definite. If we assume $J(CLV(n))$ is negative definite (that is the competitive Lotka-Volterra part of the $FCLV(n)$ is contracting) then in order for $J(FCLV(n))$ to be negative definite we need the symmetric Jacobian $J_s(FCLV(n))$ to be negative definite. For $J_s(FCLV(n))$ is negative definite if and only if the following matrix inequality holds (see as well Section 4.1),

$$\begin{aligned} J_s(CLV(n, x_0)) &< G^T(-1)^{-1}G, && (4.33) \\ &< -G^TG, && (4.34) \end{aligned}$$

where $G = \frac{1}{2}\left(\frac{\partial f(x)}{\partial x_1} - a_{10}x_1, \ldots, \frac{\partial f(x)}{\partial x_n} - a_{n0}x_n\right)$. For $FCLV(2)$ we can write the matrix G^TG as

$$\frac{1}{4}\begin{bmatrix} f_{x_1}^2 + a_{10}^2(x_1)^2 - 2f_{x_1}a_{10}x_1 & f_{x_1}f_{x_2} - a_{10}x_1f_{x_2} - a_{20}x_2f_{x_1} + a_{10}a_{20}x_1x_2 \\ f_{x_1}f_{x_2} - a_{10}x_1f_{x_2} - a_{20}x_2f_{x_1} + a_{10}a_{20}x_1x_2 & f_{x_2}^2 + a_{20}^2(x_2)^2 - 2f_{x_2}a_{20}x_2 \end{bmatrix},$$

which has eigenvalues

$$\begin{aligned} \lambda_1 &= \frac{1}{4}\left(\frac{\partial f(x)}{\partial x_1} - a_{10}x_1\right)^2 + \frac{1}{4}\left(\frac{\partial f(x)}{\partial x_2} - a_{20}x_2\right)^2, && (4.35) \\ \lambda_2 &= 0. && (4.36) \end{aligned}$$

The pattern continues for $FCLV(n)$ with G^TG having $n-1$ eigenvalues

$$\begin{aligned} \lambda_1 &= \frac{1}{4}\left(\frac{\partial f(x)}{\partial x_1} - a_{10}x_1\right)^2 + \ldots + \frac{1}{4}\left(\frac{\partial f(x)}{\partial x_n} - a_{n0}x_n\right)^2, && (4.37) \\ \lambda_2 &= 0, && (4.38) \\ &\vdots \\ \lambda_{n-1} &= 0. && (4.39) \end{aligned}$$

From [39] a sufficient condition for the inequality (4.33) to hold is

$$\begin{aligned} \lambda_{max}(J_s(CLV(n, x_0))) &< (-1)\sigma_{max}^2(G), && (4.40) \\ &< -\lambda_{max}(G^TG), && (4.41) \\ &< -\frac{1}{4}\left(\frac{\partial f(x)}{\partial x_1} - a_{10}x_1\right)^2 + \ldots + \frac{1}{4}\left(\frac{\partial f(x)}{\partial x_n} - a_{n0}x_n\right)^2, && (4.42) \end{aligned}$$

where $\sigma_{max}^2(G)$ is the largest singular value of G. Note that $\sigma_{max}^2(G) = \lambda_{max}(G^TG)$. We can see that $\lambda_{max}(G^TG)$ can be thought as a destabilizing influence (the larger $\lambda_{max}(G^TG)$ the less likely $FCLV(n)$ is to be contracting). We can be a bit more specific as (note we use $\lambda_{max,s}(A)$ to denote the largest eigenvalue of the symmetric part of A)

$$\begin{aligned} &\lambda_{max}(J_s(CLV(n, x_0))) = && (4.43) \\ &\lambda_{max}\left(\mathrm{Diag}(1 - A_{1,n}x_{1,n}) - \mathrm{Diag}(x_{1,n})A_{1,n} - \mathrm{Diag}((a_{i0}x_0)_{i\in[1,n]})\right), && (4.44) \\ &\leq \lambda_{max}\left(\mathrm{Diag}(1 - A_{1,n}x_{1,n}) - \mathrm{Diag}((a_{i0}x_0)_{i\in[1,n]})\right) - \lambda_{max,s}(\mathrm{Diag}(x_{1,n})A_{1,n}), && (4.45) \end{aligned}$$

as for the sum of symmetric matrices this property holds. With the note that

$$\max_{i\in[1,n]}\left\{1-\sum_{j=0}^{n}a_{ij}x_j\right\}=\lambda_{max}\left(\mathrm{Diag}(1-A_{1,n}x_{1,n})-\mathrm{Diag}((a_{i0}x_0)_{i\in[1,n]})\right). \tag{4.46}$$

So we have the inequality

$$\begin{aligned}&\lambda_{max,s}(\mathrm{Diag}(x_{1,n})A_{1,n})>\\&\frac{1}{4}\left(\frac{\partial f(x)}{\partial x_1}-a_{10}x_1\right)^2+\ldots+\frac{1}{4}\left(\frac{\partial f(x)}{\partial x_n}-a_{n0}x_n\right)^2+\max_{i\in[1,n]}\left\{1-\sum_{j=0}^{n}a_{ij}x_j\right\}.\end{aligned} \tag{4.47}$$

At a fixed point x^* (other than the origin) of $FCLV(n)$ this inequality becomes

$$\lambda_{max,s}(\mathrm{Diag}(x^*_{1,n})A_{1,n})>\frac{1}{4}\left(\frac{\partial f(x^*)}{\partial x_1}-a_{10}x^*_1\right)^2+\ldots+\frac{1}{4}\left(\frac{\partial f(x^*)}{\partial x_n}-a_{n0}x^*_n\right)^2. \tag{4.48}$$

4.2.2 Contraction with Respect to Other Metrics

We have some far focused on contraction with respect to the euclidean norm $|\cdot|$ and its induced matrix norm $||\cdot||$. If we consider contraction with respect to other norms we can obtain other conditions for contraction other than determining the positive definiteness of a matrix. To do so we need to introduce the matrix measure. Given a norm $|\cdot|$ and it's induced matrix norm $||\cdot||$, the associated matrix measure is [1]:

$$\mu(A)=\lim_{h\to 0^+}\frac{1}{h}(||I+hA||-1). \tag{4.49}$$

A nonlinear system is contracting if there exists a uniformly invertible matrix $\Theta(x)$ such that

$$\exists c>0,\quad \mu(J_g(f(x)))\leq -c,\quad \forall x\in\mathbb{R}^n, \tag{4.50}$$

where $J_g(f(x))$ is the generalized Jacobian of the nonlinear system [1]. The most common matrix measures used for contraction analysis are induced by the p-norms $1, 2$ and ∞. The induced matrix measures given a square matrix A with entries a_{ij} are respectively

$$\mu_1(A)=\max_j\left(a_{jj}+\sum_{i\neq j}|a_{ij}|\right), \tag{4.51}$$

$$\mu_2(A)=\text{Largest eigenvalue of }\frac{A+A^T}{2}, \tag{4.52}$$

$$\mu_\infty(A)=\max_i\left(a_{ii}+\sum_{i\neq j}|a_{ij}|\right). \tag{4.53}$$

As expected $\mu_2(J_g(f(x))) \leq -c$ is the same as requiring the symmetric part of $J_g(f(x))$ to be negative definite. Now again after a change of coordinates $\delta z = \Theta(x)\delta x$, the virtual dynamics of a nonlinear system is

$$\delta\dot{z} = J_g(f(x,t))\delta z. \tag{4.54}$$

Which can be bounded by the Coppel inequality ([36]; which is just a generalized version of the same inequality (3.4) in the Section 3)

$$\begin{aligned} |\delta z|_i \leq& |\delta z^0|_i e^{\int_0^t \mu_i(J_g(f(x(\tau),\tau)))d\tau}, && (4.55)\\ |\delta z|_i \leq& |\delta z^0|_i e^{c_i t}, && (4.56)\end{aligned}$$

where $c_i = \max\{\mu_i(J_g(f(x,t)))\}$ and is the rate at which the system contracts. It is clear the contraction rate is highly dependent on the particular norm being used. However there is a clear relationship between the contraction rates associated with different norms. For finite dimensional systems all vector norms are equivalent [16], that is

$$|x|_\infty \leq |x|_2 \leq |x|_1 \leq \sqrt{n}|x|_2 \leq n|x|_\infty. \tag{4.57}$$

where n is the dimension[1] of x. Thus convergence with respect to one norm also implies convergence to the Euclidean norm with some rescaling factor (and visa versa). Suppose that contraction has been established for the 1-norm, with rate c_1 with dimension n. We then have

$$|\delta z|_2 \leq \sqrt{n}|\delta z^0|_2 e^{c_1 t}, \tag{4.58}$$

or equivalently

$$|\delta z|_2 \leq |\delta z^0|_2 e^{c_1(t - \frac{\ln n}{2c_1})}. \tag{4.59}$$

So changing types of norms means a rescaling or time shifting the bound. See [1,31] for more details. Note that contraction with respect to the $1, \infty$-norms is strongly connected to Gershgorin disk Theorem [16] as $\mu_1(J_g(f(x))), \mu_\infty(J_g(f(x))) \leq -c$ is equivalent to the requirement that all of the Gershgorin disks of $J_g(f(x))$ are on left side of complex plane.

Applying this to $FCLV(n)$ systems we have the following statement: *A sufficient condition for a $FCLV(n)$ system to be contracting is for $J(FCLV(n))$ or $J_g(FCLV(n))$ to be row or column diagonally dominant.* The simplest useful contraction metric, other that the identity matrix, for this statement is a constant diagonal matrix

$$\Theta = \begin{pmatrix} q_0 & \dots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \dots & q_n \end{pmatrix}. \tag{4.60}$$

---

[1] The scaling factors needed for inequality to hold depend on the dimension of the dynamical system being analysed.

Note $q_0, q_1, \ldots, q_n$ do not have to positive, but do have to be non-zero. Any $FCLV(n)$ system with this metric can be written as

$$J_g(FCLV(n)) = \begin{pmatrix} -1 & \frac{q_0}{q_1} f_{x_1} & \cdots & \frac{q_0}{q_n} f_{x_n} \\ -a_{10}\frac{q_1}{q_0} x_1 & 1 - a_{11}x_1 - \sum_{j=0}^{n} a_{1j}x_j & \cdots & -a_{1n}\frac{q_1}{q_n} x_1 \\ \vdots & \vdots & \ddots & \vdots \\ -a_{n0}\frac{q_n}{q_0} x_n & -a_{n1}\frac{q_n}{q_1} x_n & \cdots & 1 - a_{nn}x_n - \sum_{j=0}^{n} a_{nj}x_j \end{pmatrix}. \tag{4.61}$$

We can choose q_0 to be small small enough such that

$$1 > \left| \frac{q_0}{q_1} f_{x_1} \right| + \ldots + \left| \frac{q_0}{q_n} f_{x_n} \right| \tag{4.62}$$

and if remaining rows can be made diagonally dominant by choosing appropriate $q_1, \ldots, q_n$ then the system is contracting. Note that we can do the same for column diagonal dominance. We suggest another appropriate contraction metric for this analysis in Section 4.3.

4.3 Semi Contraction of $FCLV(n)$

So far we have used contraction theory to provide the estimates for regions of stability $FCLV(n)$. The usefulness of contraction theory, like monotone theory, is that it can greatly simplify the analysis of nonlinear systems given the appropriate conditions are satisfied. We layout here a theorem, which is simple to prove with the necessary background, that describes very well the general behaviour of any $FCLV(n)$ based on the concept of semi contraction.

Theorem 14. *For $FCLV(n)$ if the immune response function is monotone and increasing all solutions converges to Γ_f and $\delta x_0^T \delta x_0$ decreasing to zero.*

Proof. We focus on $FCLV(2)$ systems, first as there is a simple pattern that can be expanded to general $FCLV(n)$ systems. The conclusion of the theorem comes from searching for a contraction metric that simplifies any $FCLV(n)$ system to a n-dimensional system. Specifically we look for a metric $M(x)$ such that

$$M_{dot} = \dot{M} + MJ(FCLV(n)) + J^T(FCLV(n))M < 0 \tag{4.63}$$

and the first row and columns of M_{dot} are as simple as possible for further analysis. After trial and error searching through the space of diagonal contraction metrics[2]. Our choice

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[2] It is significantly easier to search through just the space of diagonal matrices to find a suitable contraction metric rather than any general matrix both to ensure $M(x)$ is positive definite and M_{dot} is negative definite

of contraction metric is

$$M(x) = \begin{pmatrix} 1 & 0 & 0 \\ 0 & \frac{f_{x_1}}{a_{10}x_1} & 0 \\ 0 & 0 & \frac{f_{x_2}}{a_{20}x_2} \end{pmatrix} \tag{4.64}$$

where we denote partial derivatives as $f_{x_i} = \frac{\partial f(x_1, x_2)}{\partial x_i}$ for convenience. Note that because $M(x)$ is a diagonal matrix and we are only considering a monotone immune response function $M(x)$ is a positive definite matrix. Calculating M_{dot} we have

$$\begin{aligned} &M_{dot} \\ &= \dot{M} + MJ(FCLV(n)) + J^T(FCLV(n))M, \end{aligned} \tag{4.65}$$

$$\begin{aligned} &= \begin{pmatrix} 0 & 0 & 0 \\ 0 & \frac{-\dot{x}_1 f_{x_1}}{a_{10}x_1^2} + \frac{\dot{x}_2 f_{x_1x_2} + \dot{x}_1 f_{x_1x_1}}{a_{10}x_1} & \\ 0 & 0 & \frac{-\dot{x}_2 f_{x_2}}{a_{20}x_2^2} + \frac{\dot{x}_1 f_{x_1x_2} + \dot{x}_2 f_{x_2x_2}}{a_{20}x_2} \end{pmatrix} \\ &+ \begin{pmatrix} -1 & f_{x_1} & f_{x_2} \\ -f_{x_1} & \frac{(1 - a_{10}x_0 - 2a_{11}x_1 - a_{12}x_2) f_{x_1}}{a_{10}x_1} & -\frac{a_{12} f_{x_1}}{a_{10}} \\ -f_{x_2} & -\frac{a_{21} f_{x_2}}{a_{20}} & \frac{(1 - a_{20}x_0 - a_{21}x_1 - 2a_{22}x_2) f_{x_2}}{a_{20}x_2} \end{pmatrix} \\ &+ \begin{pmatrix} -1 & f_{x_1} & f_{x_2} \\ -f_{x_1} & \frac{(1 - a_{10}x_0 - 2a_{11}x_1 - a_{12}x_2) f_{x_1}}{a_{10}x_1} & -\frac{a_{12} f_{x_1}}{a_{10}} \\ -f_{x_2} & -\frac{a_{21} f_{x_2}}{a_{20}} & \frac{(1 - a_{20}x_0 - a_{21}x_1 - 2a_{22}x_2) f_{x_2}}{a_{20}x_2} \end{pmatrix}^T, \end{aligned} \tag{4.66}$$

$$= \begin{pmatrix} -2 & 0 & 0 \\ 0 & \frac{-2a_{11}x_1^2 f_{x_1} + \dot{x}_1 f_{x_1} - x_1(\dot{x}_2 f_{x_1x_2} + \dot{x}_1 f_{x_1x_1})}{a_{10}x_1^2} & -\frac{a_{12} f_{x_1}}{a_{10}} - \frac{a_{21} f_{x_2}}{a_{20}} \\ 0 & -\frac{a_{12} f_{x_1}}{a_{10}} - \frac{a_{21} f_{x_2}}{a_{20}} & \frac{-2a_{22}x_2^2 f_{x_2} + \dot{x}_2 f_{x_2} - x_2(\dot{x}_1 f_{x_1x_2} + \dot{x}_2 f_{x_2x_2})}{a_{20}x_2^2} \end{pmatrix}. \tag{4.67}$$

We can extended the pattern of matrix (4.67) to $FCLV(n)$ systems, with

$$M(x) = \begin{pmatrix} 1 & 0 & \dots & 0 \\ 0 & \frac{f_{x_1}}{a_{10}x_1} & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \dots & \frac{f_{x_n}}{a_{n0}x_n} \end{pmatrix}. \tag{4.68}$$

The resulting lower block matrix M_{dot} for $FCLV(n)$ systems, has off-diagonal entries $-\frac{a_{ij} f_{x_j}}{a_i} - \frac{a_{ji} f_{x_i}}{a_j}$ and diagonal entries[3] $\frac{-2a_{ii}x_i^2 + \dot{x}_i f_{x_i} - x_i(f_{x_i t})}{a_{i0}x_i^2}$ for all $i, j \in [1, \dots, n]$.

Now from definition in the background section on contraction (Section 3)

$$\frac{d}{dt}(\delta x^T M(x) \delta x) = \delta x^T M_{dot}(x) \delta x. \tag{4.69}$$

---

[3] Note that $f_{x_i t} = \frac{\partial^2 f(x_1, \dots, x_n)}{\partial x \partial t}$

For any δx

$$\frac{d}{dt}(\delta x^T M(x)\delta x) = -2(\delta x_0)^2 + \mathcal{O}(\delta x_1\delta x_2, \dots, \delta x_{n-1}\delta x_n) + \mathcal{O}((\delta x_1)^2, ..., (\delta x_n)^2) \quad (4.70)$$

where $\mathcal{O}((\delta x_1)^2, ..., (\delta x_n)^2)$ is all δx_i terms of order 2 and $\mathcal{O}(\delta x_1\delta x_2, \dots, \delta x_{n-1}\delta x_n)$ is all terms of order 2 that are combinations of $\delta x_i, \delta x_j$ terms. This is the sufficient and necessary condition to ensure that $FCLV(n)$ is always semi-contracting[4] which respect to x_0. That is, no matter the initial condition, the solutions of a $FCLV(n)$ system with a monotone immune response will always converge to constant x_0 that is, $\delta x_0^T\ \delta x_0 \to 0$ as $t \to 0$. This implies that all solutions of $FCLV(n)$ converge to Γ_f given sufficient time. Note however this does not imply (by itself) convergence to fix points. Solutions converge to the interior fixed point of $FCLV(n)$ if and only if the lower block matrix of M_{dot} is negative definite. □

Theorem 14 can also be used to show that all solutions of $FCLV(n)$ converge to a $n-1$ dimensional subset of $\mathbb{R}^+_{n+1}$ (see Theorem 18).

4.3.1 Notes on Theorem 14 and Related Lemmas

There are a few important notes for Theorem 14:

- Without further analysis Theorem 14 does not tell which level set of Γ_f solutions of $FCLV(n)$ converge to.

- The contraction metric for Theorem 14 is only for the interior of $\mathbb{R}^+_{n+1}$. If we are restricted to the boundary of $\mathbb{R}^+_{n+1}$ we can adjust $M(x)$. For example if we are considering only $\mathbb{R}^+_{n+1}$ with $x_1 = 0$ then we can choose the following contraction metric:

$$M(x) = \begin{pmatrix} \frac{1}{f_{x_1}} & 0 & \dots & 0 \\ 0 & 1 & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \dots & \frac{f_{x_n}}{a_{n0}x_n f_{x_1}} \end{pmatrix} \quad (4.71)$$

.

- Similarly if we are interested in a region where the immune response function is monotone decreasing we can use the following contraction metric:

$$M(x) = \begin{pmatrix} 1 & 0 & \dots & 0 \\ 0 & -\frac{f_{x_1}}{a_{10}x_1} & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \dots & -\frac{f_{x_n}}{a_{n0}x_n} \end{pmatrix} \quad (4.72)$$

.

---

[4] Not to be confused with partial contraction.

- If the immune response function is constant we can use the identity matrix as the contraction metric to obtain similar conclusions as Theorem 14.

- From the conclusions of Theorem 14, M_{dot} eventually represents the dynamics of $FCLV(n)$ constrained to a level set of Γ_f. As any level set of Γ_f is a $CLV(n)$ system which depends on x_0, whether $FCLV(n)$ has periodic orbits thus depends on n. It is well known that for $n \leq 2$ it is not possible for a $CLV(n)$ system to have a periodic trajectory as the dimension of the carrying simplex is less than 2.

- In addition it is not possible for a $FCLV(n)$ system to have a periodic orbit outside of $\Gamma_f \cap \Gamma_{CLV}$. Suppose that such a periodic orbit exists. Assume that there exists a periodic trajectory that oscillates in and out of any $x_0 = \epsilon$, where ϵ is a positive non-zero constant. It is impossible for all points along such a trajectory to have $\delta x_0^T \delta x_0 = 0$ which is a contradiction to Theorem 14. Now instead assume that a periodic trajectory is instead contained within $x_0 = \epsilon$. Such a level set of $FCLV(n)$ is equivalent to a $CLV(n)$ system which depends on x_0 (which is constant). Unless the periodic orbit is contained entirely instead the carrying simplex (Γ_{CLV}) then monotone theory guarantees that such a periodic trajectory cannot exist. Any other periodic orbit is a combination of these two cases so any periodic trajectory is not possible unless it is contained within $\Gamma_f \cap \Gamma_{CLV}$

- Note that semi contraction for δx_0 does not imply that x_0 monotonically approaches Γ_f, only that it approaches Γ_f asymptotically. It fact even for the simplest strictly increasing monotone immune response function (linear) x_0 oscillates around $\Gamma_f \cap \Gamma_{CLV}$.

In addition we can apply the estimates from Section 4.2 to the lower block matrix of M_{dot} in Theorem 14 to determine if this matrix is negative definite or not (and so ensure $FCLV(n)$ is contracting). For convenience we use $M_{dot,L}$ to denote this lower matrix. The entries of the contraction metric chosen in Theorem 14 (other than $M_{0,0}(x) = 1$) can be thought of as the ratio between the rate of change of the immune response function, over the rate of change of a species in response to the change in the immune response. The following is lemma is an sufficient condition in terms of these ratios to ensure the stability of $FCLV(n)$ in the interior of $\mathbb{R}^n_+$.

Lemma 15. *$FCLV(n)$ (with a strictly increasing monotone immune response function) is contracting in the interior of $\mathbb{R}^n_+$ if either $\mu_1(M_{dot,L})$ or $\mu_\infty(M_{dot,L})$ is negative definite (given by equations* (4.76) *and* (4.77) *respectively).*

Proof. We focus on $FCLV(2)$ first then generalize for $n \geq 3$. We denote the diagonal entries of $M(x)$ as $M_{i,i}$ with $i \in [0, n]$ with $M_{0,0}$ being the first entry (to keep the notation consistent to the $FCLV(n)$ system). $M_{dot,L}$ for $FCLV(2)$ in terms of $M_{i,i}(x)$ is as follows.

$$M_{dot,L} = \begin{pmatrix} 2M_{1,1}(1 - a_{10}x_0 - 2a_{11}x_1 - a_{12}x_2) + \frac{dM_{1,1}}{dt} & -a_{12}M_{1,1}x_1 - a_{21}M_{2,2}x_2 \\ -a_{12}M_{1,1}x_1 - a_{21}M_{2,2}x_2 & 2M_{2,2}(1 - a_{20}x_0 - a_{21}x_1 - 2a_{22}x_2) + \frac{dM_{2,2}}{dt} \end{pmatrix}. \tag{4.73}$$

Note that a necessary condition for negative definiteness of a matrix (for matrix measures μ_1, μ_2, μ_∞) is that the trace of a matrix is negative definite. Using this and the fact that $M_{dot,L}$ is symmetric we have the following inequality:

$$\begin{aligned}\lambda_{max}(M_{dot,L}) \leq &\max\{2M_{1,1}(1 - a_{10}x_0 - 2a_{11}x_1 - a_{12}x_2) + \frac{dM_{1,1}}{dt} \\ &+ 2M_{2,2}(1 - a_{20}x_0 - a_{21}x_1 - 2a_{22}x_2) + \frac{dM_{2,2}}{dt}\} \\ &+ a_{12}M_{1,1}x_1 + a_{21}M_{2,2}x_2.\end{aligned} \tag{4.74}$$

Note that the largest eigenvalue of the matrix,

$$\begin{pmatrix} 0 & -a_{12}M_{1,1}x_1 - a_{21}M_{2,2}x_2 \\ -a_{12}M_{1,1}x_1 - a_{21}M_{2,2}x_2 & 0 \end{pmatrix}, \tag{4.75}$$

is $a_{12}M_{1,1}x_1 + a_{21}M_{2,2}x_2$. To extend this result to $M_{dot,L}$ for $FCLV(n)$ we use the condition that contraction with respect to μ_1, μ_∞ requires a negative definite diagonal entries and diagonal dominance. We have the following (note i subscript denotes rows and j subscript denotes columns):

$$\mu_1(M_{dot,L}) = \max_{j\in[1,n]}\left\{2M_{i,i}(1 - a_{ii}x_i - \sum_{j=0}^{n} a_{ij}x_j) + \frac{dM_{i,i}}{dt} + \sum_{i\neq j}\left(a_{ij}M_{i,i}x_i + a_{ji}M_{j,j}x_j\right)\right\}, \tag{4.76}$$

$$\mu_\infty(M_{dot,L}) = \max_{i\in[1,n]}\left\{2M_{i,i}(1 - a_{ii}x_i - \sum_{j=0}^{n} a_{ij}x_j) + \frac{dM_{i,i}}{dt} + \sum_{i\neq j}\left(a_{ij}M_{i,i}x_i + a_{ji}M_{j,j}x_j\right)\right\}, \tag{4.77}$$

$$\lambda_{max}(M_{dot,L}) \leq \min\{\mu_1(M_{dot,L}), \mu_\infty(M_{dot,L})\}. \tag{4.78}$$

Thus if $\mu_1(M_{dot,L})$ or $\mu_\infty(M_{dot,L})$ is negative definite all the eigenvalues are of M_{dot} are negative definite and thus $FCLV(n)$ is contracting in the interior of $\mathbb{R}^n_+$. □

Finally using Theorem 14 we can note a connection between $FCLV(n)$ systems and $CLV(n)$ systems.

Lemma 16. *Consider a $FCLV(n)$ system and $CLV(n,b)$ system (a $CLV(n)$ with dependence on vector b) with the following community matrix $A = \left(\frac{a_{ij}}{a_{i0}}\right)_{ij}, i,j \in [1,n]$ and the components of b are $b_i = \frac{1}{a_{i0}} - f(x^*)$. By construction if $FCLV(n)$ has a interior fixed point, then both systems have an interior fixed point and same $x_1^*, \ldots, x_n^*$ components.*

The interior fixed point of a $FCLV(n)$ system with $\frac{\partial f}{\partial x_i} = x_i \ \forall i \in [1,n]$ is locally stable if and only if the interior fixed point of $CLV(n,b)$ is locally stable.

Proof. We consider a $CLV(n,b)$ system with the community matrix described in the conditions of the lemma. The Jacobian for any $CLV(n,b)$ system can be written as

$$J(CLV(n,b)) = \mathrm{Diag}(b - Ax) - \mathrm{Diag}(x)A. \tag{4.79}$$

Note that at the interior fixed point x^* of $CLV(n,b)$

$$J(CLV(n,b)) = -\text{Diag}(x^*)A. \tag{4.80}$$

The symmetric part of $J(CLV(n,b))$ at x^* is

$$J_s(CLV(n,b)) = \begin{pmatrix} -\frac{a_{11}}{a_{10}}x_1^* & \frac{1}{2}(-\frac{a_{12}}{a_{10}}x_1^* - \frac{a_{21}}{a_{20}}x_2^*) & \dots & \frac{1}{2}(-\frac{a_{1n}}{a_{10}}x_1^* - \frac{a_{n1}}{a_{n0}}x_n^*) \\ \frac{1}{2}(-\frac{a_{12}}{a_{10}}x_1^* - \frac{a_{21}}{a_{20}}x_2^*) & -\frac{a_{22}}{a_{20}}x_2^* & \dots & \frac{1}{2}(-\frac{a_{2n}}{a_{20}}x_2^* - \frac{a_{n2}}{a_{n0}}x_n^*) \\ \vdots & \vdots & \ddots & \vdots \\ \frac{1}{2}(-\frac{a_{1n}}{a_{10}}x_1^* - \frac{a_{n1}}{a_{n0}}x_n^*) & \frac{1}{2}(-\frac{a_{2n}}{a_{20}}x_2^* - \frac{a_{n2}}{a_{n0}}x_n^*) & \dots & -\frac{a_{nn}}{a_{n0}}x_n^* \end{pmatrix}. \tag{4.81}$$

From Theorem 14 at the interior fixed point x^* of $FCLV(n)$ the matrix $M_{dot,L}$ is

$$M_{dot,L}(x^*) = \begin{pmatrix} -2\frac{a_{11}}{a_{10}}f_{x_1}(x^*) & -\frac{a_{12}}{a_{10}}f_{x_1}(x^*) - \frac{a_{21}}{a_{20}}f_{x_2}(x^*) & \dots & -\frac{a_{1n}}{a_{10}}f_{x_1}(x^*) - \frac{a_{n1}}{a_{n0}}f_{x_n}(x^*) \\ -\frac{a_{12}}{a_{10}}f_{x_1}(x^*) - \frac{a_{21}}{a_{20}}f_{x_2}(x^*) & -\frac{a_{22}}{a_{20}}f_{x_2}(x^*) & \dots & -\frac{a_{2n}}{a_{20}}f_{x_2}(x^*) - \frac{a_{n2}}{a_{n0}}f_{x_n}(x^*) \\ \vdots & \vdots & \ddots & \vdots \\ -\frac{a_{1n}}{a_{10}}f_{x_1}(x^*) - \frac{a_{n1}}{a_{n0}}f_{x_n}(x^*) & -\frac{a_{2n}}{a_{20}}f_{x_2}(x^*) - \frac{a_{n2}}{a_{n0}}f_{x_n}(x^*) & \dots & -\frac{a_{nn}}{a_{n0}}f_{x_n}(x^*) \end{pmatrix}. \tag{4.82}$$

It is clear to see that $M_{dot,L} = 2J_s(CLV(n,b))$ if $\frac{\partial f}{\partial x_i} = x_i \ \forall i \in [1,n]$ and that if either is negative definite both systems are contracting at x^* (which is equivalent to x^* being locally stable). □

The above lemma suggests shows that there is a link between the stability of $FCLV(n)$ systems and $CLV(n)$ systems with a carrying capacity b. Lemma 16 is for the case where the stability for both types of systems is *exactly* the same near the interior equilibrium. For more complex immune response functions the connection becomes more tenuous.

4.3.2 Discussion on Semi Contraction

Theorem 14 is similar to the behaviour of cascading systems in that the contraction behaviour of one or more components is independent the rest of the system. We can think of the choice of contraction metric in Theorem 14 as the one which transforms $FCLV(n)$ into system which has cascading behaviour. However use of this contraction metric comes with its own catch, the $CLV(n)$ part of the $FCLV(n)$ becomes $M_{dot,L}$ which is much more difficult to analyse in general. Nevertheless the use of metric is useful as it qualitative conclusions to be proved easily. Admittedly the biggest restriction of Theorem 14 is that it has been limited to apply to immune response functions whose partial derivatives do not change sign. Observant readers who have read the notes for Theorem 14 may say why not combine the proposed contraction metrics into a single piecewise continuous contraction metric. To the authors best knowledge there has been no significant research into the area of partially continuous contraction metrics. There are obvious problems with piecewise continuous contraction metrics, for example, while the existence of a contraction metric implies convergence to a single fixed point in the region in which it is defined, a piecewise continuous metric constructed by combining continuous metrics would not have this property.

4.4 Convergence Rates to Γ_f

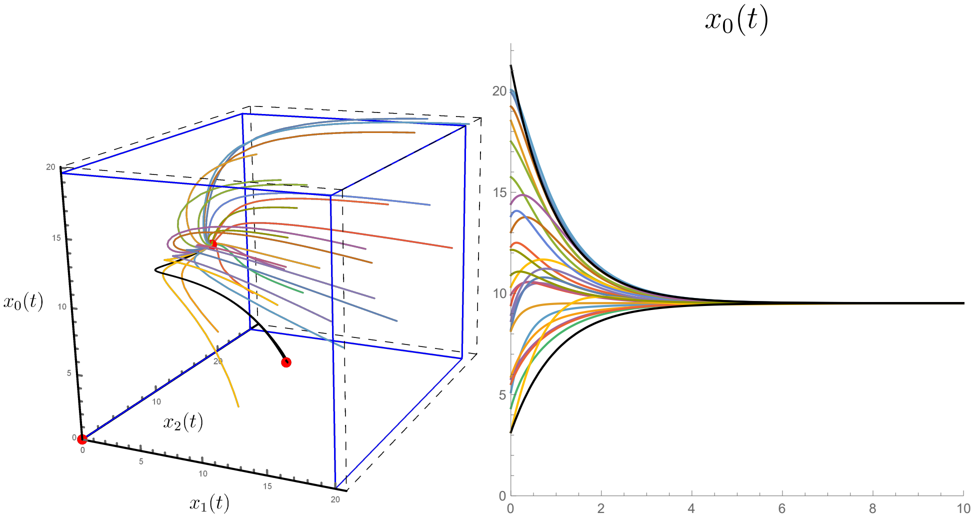
We expand on Section 4.3 by showing the rate at which the solutions of $FCLV(n)$ converge to Γ_f. Using the contraction metric given by Theorem 14 we have the following for the x_0-component

$$\frac{d}{dt}(\delta x_0 M \delta x_0) \leq -\beta(\delta x_0)^2. \tag{4.83}$$

The rate at which $FCLV(n)$ semi-contracts, β, in this case is equal to 2. So for any initial conditions x^1, x^2 if $f(P, B)$ is strictly increasing then

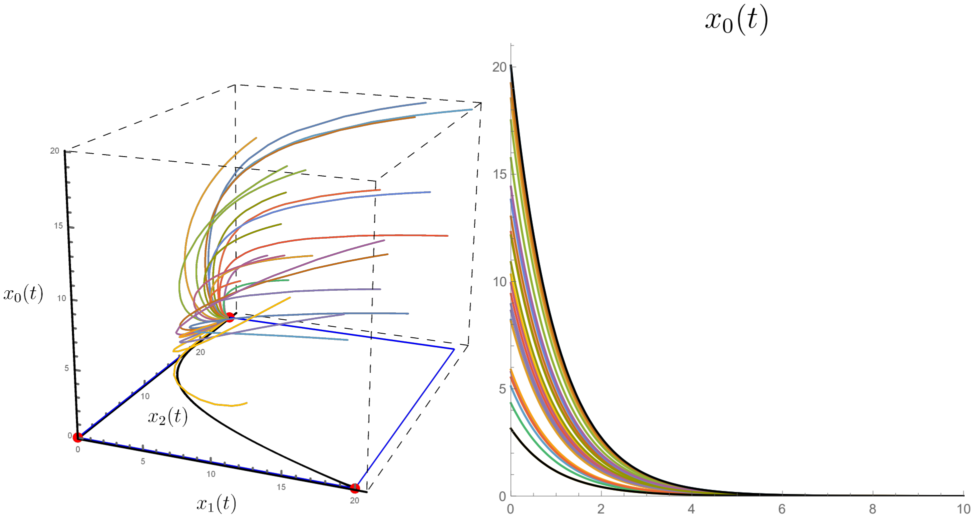
$$||x_0(x_0^1, t) - x_0(x_0^2, t)|| \leq k||x_0^1 - x_0^2||e^{-\beta t}, \tag{4.84}$$
$$||x_0(x_0^1, t) - x_0(x_0^2, t)|| \leq ||x_0^1 - x_0^2||e^{-2t}. \tag{4.85}$$

Note that for the value of k is given by Lemma 1 in [19] and that the bound (4.85) is a local result (if $FCLV(n)$ only had one attracting fixed point it would be global). It does not hold if x^1 and x^2 are within two different basins of attraction. Fig. 4.1 shows an example $FCLV(2)$ system and a plot of the competent of the x_0 trajectories bounded by (4.85). Notice that some of the trajectories over shoot Γ_f, that is they move Γ_f then bend back towards Γ_f. We know which trajectories have a local maxima or minima in Fig. 4.1b. This overshooting causes some of the trajectories to oscillate around $\Gamma_f \cap \Gamma_{CLV}$. If we increase the partial derivatives of f the magnitude of oscillations become move extreme. Conversely if $f(x) = 0$ there are no oscillations and all x_0 components decrease monotonically (see Fig. 4.2).



(a) Phase plot (b) x_0 components

Figure 4.1: A example $FCLV(2)$ system with $f(P,B) = \frac{P}{2} + 10\frac{B}{1+B}$ and community matrix (5.52). Fig. 4.1a is the phase plot of the system, where the black line is $\Gamma_f \cap \Gamma_{CLV}$. Fig. 4.1b is the x_0-component versus time graph the black lines indicate the upper and lower bounds given by inequality (4.85), given the random initial starting trajectories. Because there is one stable fixed point on $\Gamma_f \cap \Gamma_{CLV}$ with $x_0 \approx 9.5$ all trajectories x_0-component converges to this value. Note that some trajectories oscillate around $\Gamma_f \cap \Gamma_{CLV}$.



(a) Phase plot (b) x_0 components

Figure 4.2: The same system as in Fig. 4.1 (including same initial conditions) except $f(P,B) = 0$. The black lines indicate the bounds given by $x_0 = x_0^0 e^{-t}$, where x_0^0 is the initial value of the x_0 component. In comparison to Fig. 4.1b, Fig. 4.2b shows that the system components converge in a monotone manner.

While convergence to Γ_f is guaranteed the invariance of Γ_f is not from semi-contraction alone. We lay out here two different arguments one that is conditional on the speed at which $x_1, ...x_n$ contract based on perturbation theory, the other is much stronger and guarantees the eventually monotonicity and convergence of solutions of $FCLV(n)$ to a $n-1$ invariant subspace.

Lemma 17. *If we assume that the x_0 contracts faster than $x_1, ..., x_n$ then $FCLV(n)$ systems are eventually monotone.*

Proof. Because x_0 is always semi-contracting while the $x_1, ..., x_n$ are not guaranteed to be semi-contracting in general it is safe to assume that x_0' will vanish faster than $x_1', ..., x_n'$. In that case we can write a $FCLV(n)$ system as the following singular perturbation problem with $0 < \epsilon << 1$,

$$\begin{aligned} \epsilon \frac{dx_0}{dt} &= f(x_1, ..., x_n) - x_0, \\ \frac{dx_i}{dt} &= x_i(1 - \sum_{j=0}^{n} a_{ij} x_j) \quad a_{ij} > 0, i = 1, ..., n. \end{aligned} \tag{4.86}$$

As $\epsilon \to 0$ then $x_0 \to f(x_1, ..., x_n)$, the resulting system

$$\frac{dx_i}{dt} = x_i(1 - a_{10} f(x_1, ..., x_n) - \sum_{j=1}^{n} a_{ij} x_j) \quad a_{ij} > 0, i = 1, ..., n, \tag{4.87}$$

has a Jacobian

$$\begin{pmatrix} 1 - \sum_{j=1}^{n} a_{1j} x_j - a_{10} f(x) - x_1(a_{11} + a_{10} \frac{\partial f}{\partial x_1}) & \dots & (-a_{1n} - a_{10} \frac{\partial f}{\partial x_1}) x_1 \\ \vdots & \ddots & \vdots \\ (-a_{n1} - a_{n0} \frac{\partial f}{\partial x_1}) x_n & \dots & 1 - \sum_{j=1}^{n} a_{nj} x_j - a_{n0} f(x) - x_n(a_{nn} + a_{n0} \frac{\partial f}{\partial x_n}) \end{pmatrix}. \tag{4.88}$$

with negative off diagonal entries meaning the system is competitive. So as long as the assumption holds $FCLV(n)$ systems will be eventually monotone. □

Theorem 18. *Because $FCLV(n)$ systems are monotone on Γ_f, $FCLV(n)$ systems are eventually monotone and will reach an invariant subset within Γ_f.*

Proof. To prove the statement of the theorem we need to note that any periodic orbit needs to either be contained in within Γ_f or pass through Γ_f twice. If there was a periodic orbit that did not satisfy this requirement it would contradict the x_0 component of the vector field. On Γ_f (the local vector field is monotone (see system (4.87) and it's associated Jacobian (4.88)). The monotone nature of the system on Γ_f means that each time a solution passes through Γ_f it moves closer towards Γ_{CLV} (the ω-limit set of a $FCLV(n)$ if x_0 is held constant). For a solution that keeps entering and exiting Γ_f the radius of the periodic trajectory must decrease moving towards $\Gamma_f \cap \Gamma_{CLV}$ upon each time it enters Γ_f. Therefore there cannot be a periodic or recurrent trajectory outside of $\Gamma_f \cap \Gamma_{CLV}$. The curve $\Gamma_f \cap \Gamma_{CLV}$ is invariant as the $x_0, x_1, ..., x_n$ components of the vector field point inwards. Therefore once solutions reach $\Gamma_f \cap \Gamma_{CLV}$ solutions will be monotone and so $FCLV(n)$ will be eventually monotone.

If $FCLV(n)$ was not monotone convergence to Γ_f does occur but there could be periodic trajectories or recurrent behaviour outside of $\Gamma_f \cap \Gamma_{CLV}$ and thus the system would not be eventually monotone. □

Now that we have fully covered how to apply contraction theory to a general $FCLV(n)$ system. In the next section we specially focus on $FCLV(2)$ systems focusing on examples and additional theorems specific to the $n = 2$ case.

Chapter 5

Characterization of $FCLV(2)$ Systems With Focus on Competition Between ***Plasmodium*** and AS1

Having established the semi-contraction of $FCLV(n)$ systems in Section 4.3, in the x_0 direction it is relatively simple to determine the remaining properties of $FCLV(2)$ systems because the possibility of periodic orbits and chaotic behaviour has been eliminated. We now focus on our original motivation analysing the competition between *Plasmodium* and AS1. We demonstrate the simple model of one compartment competition between *Plasmodium* and AS1 can be nondimensionalized to have the same number of parameters as a $FCLV(2)$. Next using methods traditional dynamical systems methods to analyse the stability of fixed points. We finish by providing so examples of $FCLV(2)$ systems where we should how contraction region gives rough estimates for basins of attraction.

5.1 Notes on Figures

To avoid excessive repetition in the explanation of figures we explain elements common to most figures in Section 5. First to reduce clutter, instead of listing the a_{ij} parameters of each example $FCLV(n)$ and $CLV(n)$ system in the main text, the values are organized into A matrices which can all be found in Section 5.5, and we will refer to the section as needed. Next, most figures use random initial conditions, with each trajectory starting from an different initial condition being coloured differently. These initial conditions are within what we call the bounding box (which is included in some figures as a blue box). We define the bounding box as

$$\text{Bounding Box} = \{x \in \mathbb{R}^{n+1} : l_0 \leq x_0 \leq k_0 \wedge \ldots \wedge l_n \leq x_n \leq k_n\} \tag{5.1}$$

$$p_{min} = \{l_0, l_1, \ldots, 1_n\} = \{0, \ldots, 0\} \quad \text{Lower corner of the box} \tag{5.2}$$

$$p_{max} = \{k_0, k_1, \ldots, k_n\} = \{f_{max}, \frac{1}{a_{11}}, \ldots, \frac{1}{a_{nn}}\} \quad \text{Upper corner of the box} \tag{5.3}$$

where f_{max} is the maximum value of f on $\Omega = \{x \in \mathbb{R}^n_+ : 0 \leq x_i \leq \frac{1}{a_{ii}}, 1 \leq i \leq n\}$ and $\wedge$ denotes the wedge product. We called this box the bounding box because all solutions of $FCLV(n)$ (or $CLV(n)$ systems if we remove the x_0 coordinate) converge to some region within the bounding box (see Section 2.2). If we choose initial conditions too far away from the bounding box, some initial conditions maybe in the basin of attraction of the origin (we will take about this case more in Section 5.4.1). As we are mostly interested in the behaviour of $FCLV(n)$ systems not in the basin of attraction of the origin or the boundary of $\mathbb{R}^n_+$, we choose random initial conditions near the bounding box that are in the interior of $\mathbb{R}^n_+$ (as initial conditions on the boundary of $\mathbb{R}^n_+$ are invariant). Finally, fixed points are always denoted with a red sphere and on some figures we include either the carrying simplex (for $CLV(n)$ systems) or $\Gamma_f \cap \Gamma_{CLV}$ (for $FCLV(n)$ systems) as a black line or black outline. These are generated by perturbing initial conditions around unstable fixed points and then following solutions[1].

For figures which show contraction regions we use colouring and shading, to show regions where one or more eigenvalues (of the symmetric part of the Jacobian) are negative definite. The meaning of the colouring and shading for each region is defined within figure captions. For regions where only one eigenvalues is negative definite, solutions will converge to one dimensional subspace and solutions will escape such regions, unless the solution converges to a chaotic trajectory, periodic trajectory, or fixed point contained entirely within the region.

Finally we drop the x_0, x_1, x_2 notation used throughout the previous sections for $FCLV(n)$ and $CLV(n)$ for I, P, B respectively (though we change the order to P, B, I) to emphasize the connection to modelling competition between the bacterium AS1 and *Plasmodium*.

5.2 Notes on $FCLV(2)$ for Modelling Competition in the Mosquito Midgut

We now expand a bit more on the one compartment model for AS1 and *Plasmodium* competition seen originally seen in Section 1.2, which we restate below,

$$I'(t) = f(P, B) - \mu I, \tag{5.4a}$$

$$P'(t) = rP\left(1 - \frac{\alpha B + P}{K}\right) - dIP, \tag{5.4b}$$

$$B'(t) = \bar{r}B\left(1 - \frac{B}{\bar{K}}\right) - \bar{d}IB. \tag{5.4c}$$

Instead of stating the results in terms of the original model parameters in System 5.4 we use nondimensionalization to reduce the number of parameters in equations and rewrite (5.4a),(5.4b), and (5.4c) into a form which is equivalent to a $FCLV(n)$ system. We assume the following scaling:

$$I = \widetilde{I}\widehat{I}, \quad P = \widetilde{P}\widehat{P}, \quad B = \widetilde{B}\widehat{B}, \quad t = \tilde{t}\hat{t},$$

---

[1] As far as the authour is aware this is the simplest method for visualizing $\Gamma_f \cap \Gamma_{CLV}$.

where $\widetilde{I}, \widetilde{P}, \widetilde{B}, \tilde{t}$ are dimension-carrying scales to be chosen, and $\widehat{I}, \widehat{P}, \widehat{B}, \hat{t}$ are the dimensionless variables. Subbing these into our ODEs leads to

$$\frac{d(\widetilde{I}\widehat{I})}{d(\tilde{t}\hat{t})} = f(\widetilde{P}\widehat{P}, \widetilde{B}\widehat{B}) - \mu\widetilde{I}\widehat{I}, \tag{5.5}$$

$$\frac{d(\widetilde{P}\widehat{P})}{d(\tilde{t}\hat{t})} = \widetilde{P}\widehat{P}(r - r\frac{\alpha\widetilde{B}\widehat{B} + \widetilde{P}\widehat{P}}{K} - d\widetilde{I}\widehat{I}), \tag{5.6}$$

$$\frac{d(\widetilde{B}\widehat{B})}{d(\tilde{t}\hat{t})} = \widetilde{B}\widehat{B}(\overline{r} - \overline{r}\frac{\widetilde{B}\widehat{B}}{\overline{K}} - \overline{d}\widetilde{I}\widehat{I}). \tag{5.7}$$

For f we let the nondimensionalization function $\hat{f}$ be defined as

$$\hat{f}(\widehat{P}, \widehat{B}) \equiv \frac{1}{\mu} f(\widetilde{P}\widehat{P}, \widetilde{B}\widehat{B}). \tag{5.8}$$

Dividing both sides by the dimension-carrying scales we obtain,

$$\frac{d\widehat{I}}{d\hat{t}} = \left[\frac{\tilde{t}\mu}{\widetilde{I}}\right] \hat{f}(\widehat{P}, \widehat{B}) - [\mu\tilde{t}]\,\widehat{I}, \tag{5.9}$$

$$\frac{d\widehat{P}}{d\hat{t}} = \widehat{P}(\left[r\tilde{t}\right] - \left[\frac{r\tilde{t}\alpha\widetilde{B}}{K}\right]\widehat{B} - \left[\frac{r\tilde{t}\widetilde{P}}{K}\right]\widehat{P} - \left[d\tilde{t}\widetilde{I}\right]\widehat{I}), \tag{5.10}$$

$$\frac{d\widehat{B}}{d\hat{t}} = \widehat{B}(\left[\overline{r}\tilde{t}\right] - \left[\frac{\overline{r}\tilde{t}\widetilde{B}}{\overline{K}}\right]\widehat{B} - \left[\overline{d}\tilde{t}\widetilde{I}\right]\widehat{I}), \tag{5.11}$$

which can be rewritten as,

$$\frac{d\widehat{I}}{d\hat{t}} = \left[\frac{\tilde{t}\mu}{\widetilde{I}}\right] \hat{f}(\widehat{P}, \widehat{B}) - [\mu\tilde{t}]\,\widehat{I}, \tag{5.12}$$

$$\frac{d\widehat{P}}{d\hat{t}} = \widehat{P}(1 - \left[\frac{\alpha\widetilde{B}}{K}\right]\widehat{B} - \left[\frac{\widetilde{P}}{K}\right]\widehat{P} - \left[\frac{d\widetilde{I}}{r}\right]\widehat{I}), \tag{5.13}$$

$$\frac{d\widehat{B}}{d\hat{t}} = \widehat{B}(1 - \left[\frac{\widetilde{B}}{\overline{K}}\right]\widehat{B} - \left[\frac{\overline{d}\widetilde{I}}{\overline{r}}\right]\widehat{I}), \tag{5.14}$$

where the square brackets indicate the number of independent choices for the dimension-carrying scales $\widetilde{I}, \widetilde{P}, \widetilde{B}, \tilde{t}$. Out of the possible choices we set

$$\left[\frac{\tilde{t}\mu}{\widetilde{I}}\right] = 1, \quad [\mu\tilde{t}] = 1,$$

so that the ODE system matches a $FCLV(n)$ system. This implies that

$$\tilde{t} = \frac{1}{\mu}, \quad \widetilde{I} = 1.$$

We can now rewrite (5.4a),(5.4b), and (5.4c) as

$$\begin{aligned} I'(t) &= f(P,B) - I, \\ P'(t) &= P(1 - a_{11}P - a_{12}B - a_{10}I), \\ B'(t) &= B(1 - a_{22}B - a_{20}I). \end{aligned} \tag{5.15}$$

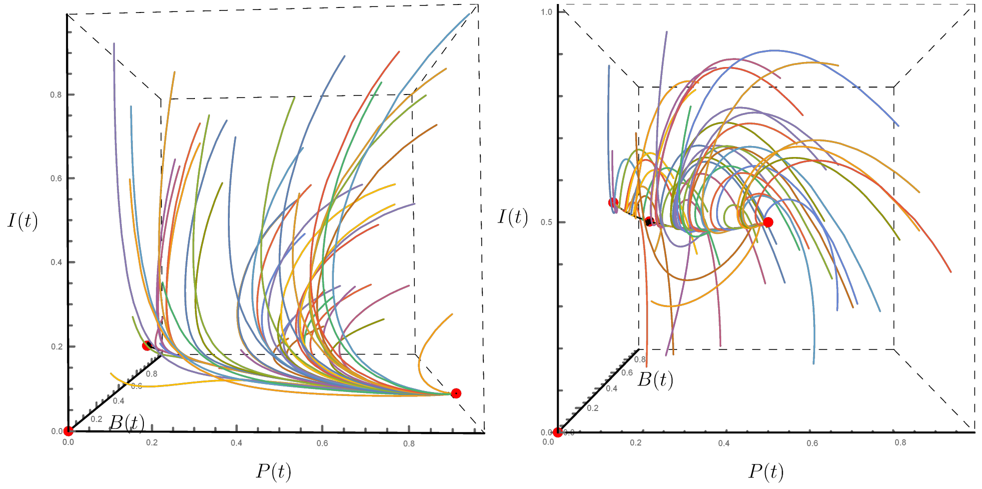
Where the constants are given by entries in the following community matrix

$$A = \begin{pmatrix} a_{11} & a_{12} & a_{10} \\ a_{21} & a_{22} & a_{20} \end{pmatrix} = \begin{pmatrix} \dfrac{\widetilde{P}}{K} & \dfrac{\alpha\widetilde{B}}{K} & \dfrac{d}{r} \\ 0 & \dfrac{\widetilde{B}}{\bar{K}} & \dfrac{\bar{d}}{\bar{r}} \end{pmatrix}, \tag{5.16}$$

and the accents have been dropped for simplicity. From herein refer to the nondimensionalized system (5.15) rather than the original (5.4) unless otherwise noted. Fortunately the nondimensionalized parameters have clear and distinct biological interpretation. a_{i0} is proportional to the death rate of the species from the immune response of the mosquito over the growth rate of the species, a_{ii} is inversely proportional to the carrying capacity of *Plasmodium* and the AS1 bacteria in the midgut, and a_{12} is proportional to the competitive effect of bacteria on *Plasmodium*, α. While the model for competition between bacteria and *Plasmodium* in the mosquito model can be reduced to a $FCLV(2)$ type model there is an important distinction that we have so far ignored. In the analysis of $FCLV(n)$ models we only did analysis for models with non zero $a_{i,j}$ constants. With $a_{21} = 0$, the analysis becomes very simple and we are able to obtain some of our strongest results. We focus now on the stability of the fixed points (for completeness we find the stability of general $FCLV(2)$ systems first then for system (5.15)), the dimension of the stable/unstable manifolds, and then basins of attractions. This combined with the previous theorems on contraction provide a complete view on the role of the immune response function in the competition between *Plasmodium* and AS1.

5.2.1 On the Existence of the Interior Fixed Point for $FCLV(2)$ Systems

Before continuing we want to make a comment on the immune response function and the existence of the interior equilibrium point. Consider the $FCLV(2)$ systems depicted in Fig. 5.1a and Fig. 5.1b. The both have the same coefficient matrices (5.55), but the stability of each fixed point has changed (even the basin of attraction of P-axial fixed point has changed).



(a) $f(P, B) = (P + B)/10$ (b) $f(P, B) = P + B$

Figure 5.1: A $FCLV(2)$ system with the same coefficient matrix (5.55) but two different immune response functions. In Fig. 5.1a the system has one stable fixed point (where P dominates) and one unstable fixed point. In Fig. 5.1b the coexisting fixed point repels and both of the single population points are stable.

So why is there a difference between the systems depicted in Fig. 5.1a and Fig. 5.1b? The difference is that the immune response function in Fig. 5.1a does intersect the crossing of the nullclines

$$0 = 1 - a_{11}P - a_{12}B - a_{10}I, \tag{5.17}$$
$$0 = 1 - a_{21}P - a_{22}B - a_{20}I, \tag{5.18}$$

while it does in Fig. 5.1b. In general the requirement for the immune response function to intersect the crossing of the nullclinlines is that $f(P, B)$ needs to cross the line (the equation below is written in vector form)

$$(P, B, I) = \frac{(a_{22} - a_{12}, a_{11} - a_{21}, 0)}{a_{11}a_{22} - a_{12}a_{21}} + \left(\frac{a_{12}a_{20} - a_{10}a_{22}}{a_{11}a_{22} - a_{12}a_{21}}, \frac{a_{10}a_{21} - a_{11}a_{20}}{a_{11}a_{22} - a_{12}a_{21}}, 1 \right) I. \tag{5.19}$$

We can see in Fig. 5.2 that the intersection of the nullclines does not occour for all values of $I \in [0, \min_{i\in[1,2]}\{\frac{1}{a_{i0}}\}]$ (that is the are values of I such that the line (5.19) is not in the positive quadrant), and so there as some immune response functions which do not cross the line (5.19). We emphasise this feature of $FCLV(2)$ systems as uncertainty in the immune response function has a serious effect on determining stability. That is, for certain values of a_{ij}, such that the line (5.19) is not present in the positive quadrant for $I \in [0, \min_{i\in[1,2]}\{\frac{1}{a_{i0}}\}]$ changes in the immune response function can dramatically change system dynamics. We will later discuss a special example in Lemma 26 were changing the immune response function does not change the dynamics of an $FCLV(2)$ system.

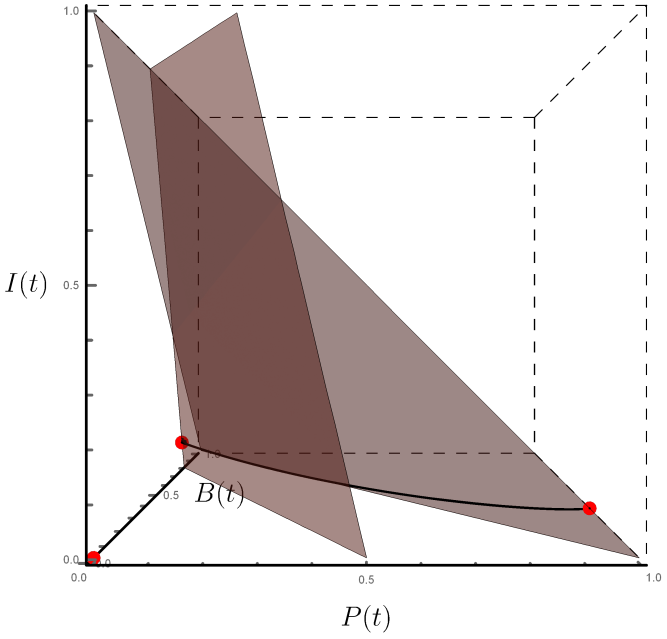


Figure 5.2: The P, B nullclines of the $FCLV(2)$ system pictured in Fig. 5.1a with $\Gamma_f \cap \Gamma_{CLV}$ being labelled as black.

5.2.2 Stability of Fixed Points

We cover here a collection of small lemmas that help determine the stability of fixed points for $FCLV(2)$ systems. We start by examining the fixed points where the only the *Plasmodium* population is non-zero and bacteria population is non-zero. We refer to those points as the P-axial and B-axial fixed points respectively (See Lemma 4 for more details).

Lemma 19. *The axial fixed points $(P^*, 0, I^*)$ and $(0, B^*, I^*)$ of a $FCLV(2)$ system are stable if and only if the inequalities hold respectively*

$$1 - a_{21}P^* - a_{20}I^* < 0, \tag{5.20}$$

$$1 - a_{12}B^* - a_{10}I^* < 0. \tag{5.21}$$

In addition both of these fixed points have a stable manifold of at least two dimensions.

Proof. We first prove the lemma for the fixed point $(P^*, 0, I^*)$. The Jacobian of a $FCLV(2)$ system at the fixed point $(P^*, 0, I^*)$ is (note $f_P = \frac{\partial f(P,B)}{\partial P}$ and $f_B = \frac{\partial f(P,B)}{\partial B}$)

$$J((P^*, 0, I^*)) = \begin{pmatrix} -1 & f_P & f_B \\ -a_{10}P^* & -a_{11}P^* & -a_{12}P^* \\ 0 & 0 & 1 - a_{21}P^* - a_{20}I^* \end{pmatrix}. \tag{5.22}$$

The characteristic polynomial of the Jacobian can be factored as

$$p(\lambda) = (\lambda - 1 + a_{21}P^* + a_{20}I^*)\left(\lambda^2 + (1 + a_{11}P^*)\lambda + a_{10}P^* f_P + a_{11}P^*\right). \tag{5.23}$$

As all the coefficients of the polynomial $\left(\lambda^2 + (1 + a_{11}P^*)\lambda + a_{10}P^* f_P + a_{11}P^*\right)$ are positive the Routh–Hurwitz stability criterion guarantees that the remaining eigenvalues are negative and there exists a stable manifold of at least two dimensions.

The same procedure as above can be used to show that the Jacobian of the fixed point $(0, B^*, I^*)$ has an eigenvalue of $1 - a_{12}B^* - a_{10}I^*$ and the rest of the eigenvalues are guaranteed to be negative. ☐

We can be more specific for system 5.15 thanks to our knowledge of the nullclines of $FCLV(2)$.

Lemma 20. *For system 5.15, the P-axial fixed point is always unstable, so long as the immune response function is monotone increasing and $f(0,0) = 0$.*

Proof. From Lemma 19 the stability of the P-axial fixed point is stable if and only if

$$1 - a_{20}I^* < 0, \tag{5.24}$$

$$I^* > \frac{1}{a_{20}}, \tag{5.25}$$

and at the I-axial fixed point,

$$f(P^*, 0) > \frac{1}{a_{20}}. \tag{5.26}$$

However $f(P^*, 0) < \frac{1}{a_{20}}$, because f is monotone, increasing and $f(0,0) = 0$, so Γ_f must cross the nucllines

$$0 = 1 - a_{11}P - a_{12}B - a_{10}I, \tag{5.27}$$

$$0 = 1 - a_{22}B - a_{20}I, \tag{5.28}$$

at points where the I-component is less than $\min\{\frac{1}{a_{10}}, \frac{1}{a_{20}}\}$. Therefore the P-axial point is always unstable. ☐

For the stability of the interior fixed point (also known as the coexistence fixed point as both *Plasmodium* and AS1 at this fixed point) we have the following Lemma.

Lemma 21. *If $a_{11}a_{22} - a_{12}a_{21} + (a_{10}a_{22} - a_{12}a_{20})\frac{\partial f(P,B)}{\partial P} + (a_{11}a_{20} - a_{10}a_{21})\frac{\partial f(P,B)}{\partial B}$ and $a_{11}a_{22} - a_{12}a_{21}$ are both positive definite then the interior fixed point of a $FCLV(2)$ system (if it exists) is stable.*

Proof. The Jacobian of $FCLV(n)$ at an interior equilibrium point is (note $f_P = \frac{\partial f(P,B)}{\partial P}$ and $f_B = \frac{\partial f(P,B)}{\partial B}$)

$$J((P^*, B^*, I^*)) = \begin{pmatrix} -1 & f_P & f_B \\ -a_{10}P^* & -a_{11}P^* & -a_{12}P^* \\ -a_{20}B^* & -a_{21}B^* & -a_{22}B^* \end{pmatrix}. \tag{5.29}$$

The characteristic polynomial of the Jacobian is

$$\begin{aligned} P(\lambda) &= \lambda^3 + q_2\lambda^2 + q_1\lambda + q_0, && (5.30)\\ q_2 &= 1 + a_{11}P^* + a_{22}B^*, \\ q_1 &= (a_{11}a_{22} - a_{12}a_{21})P^*B^* + (a_{11} + a_{10})P^*f_P + (a_{22} + a_{20})B^*f_B, && (5.31)\\ q_0 &= \big(a_{11}a_{22} - a_{12}a_{21} + (a_{10}a_{22} - a_{12}a_{20})f_P + (a_{11}a_{20} - a_{10}a_{21})f_B\big)\, P^*B^*. \end{aligned}$$

We can use Routh–Hurwitz stability criterion on the characteristic polynomial (5.30) to determine conditions under which all eigenvalues have negative real parts. The first condition in required by the Routh–Hurwitz stability criterion is that all coefficients are positive. This holds if $a_{11}a_{22} - a_{12}a_{21} > 0$ and $a_{11}a_{22} - a_{12}a_{21} + (a_{10}a_{22} - a_{12}a_{20})f_P + (a_{11}a_{20} - a_{10}a_{21})f_B > 0$. The second condition that needs to be satisfied is

$$\begin{aligned} &(1 + a_{11}P^* + a_{22}B^*)\big((a_{11}a_{22} - a_{12}a_{21})P^*B^* + (a_{11} + a_{10})P^*f_P + (a_{22} + a_{20})B^*f_B\big) \\ &> \big(a_{11}a_{22} - a_{12}a_{21} + (a_{10}a_{22} - a_{12}a_{20})f_P + (a_{11}a_{20} - a_{10}a_{21})f_B\big)\, P^*B^*. \qquad (5.32) \end{aligned}$$

Rearranging and simplifying we have

$$\begin{aligned} &(a_{11}P^* + a_{22}B^*)\big(1 + a_{11}P^* + a_{22}B^* + (a_{11}a_{22} - a_{12}a_{21})P^*B^*\big) \\ &+ (a_{10} + a_{10}a_{11}P^* + a_{12}a_{20}B^*)P^*f_P + (a_{20} + a_{20}a_{22}P^* + a_{21}a_{20}B^*)B^*f_B > 0 \end{aligned} \qquad (5.33)$$

which holds because we have already assumed that $a_{11}a_{22} - a_{12}a_{21} > 0$. We emphasize again that $a_{11}a_{22} - a_{12}a_{21} > 0$ and $a_{11}a_{22} - a_{12}a_{21} + (a_{10}a_{22} - a_{12}a_{20})f_P + (a_{11}a_{20} - a_{10}a_{21})f_B > 0$ are sufficient, easy to verify conditions, and are not the necessary conditions. The full necessary and sufficient conditions are given by the conditions of the Routh-Huritz stability criterion, that is the coefficients (5.31) satisfy $q_1 > 0, q_0 > 0, q_1q_2 - q_0 > 0$. □

We can delve a bit further than Lemma 21 by examining the Routh array from the Routh-Hurwitz conditions are derived from.

Lemma 22. *The interior fixed point of $FCLV(2)$ has a stable manifold of at least one dimension.*

Proof. The Routh array of the characteristic polynomial (5.30) is

$$\begin{pmatrix} 1 & q_1 \\ q_2 & q_0 \\ \frac{q_1q_2 - q_0}{q_2} & 0 \\ q_0 & 0 \end{pmatrix}, \qquad (5.34)$$

where q_2, q_1, q_0 are coefficients given in (5.31). The number of sign changes in the first column of (5.34) is the number of eigenvalues with positive real parts. As $q_2 > 0$ there can be at most two sign changes, that is $q_1q_2 - q_0 < 0, q_0 > 0$ so there are two eigenvalues with positive real parts. So the interior fixed point must have at least one negative eigenvalue, which from the stable manifold theorem, there is at least a one dimensional stable manifold. □

The Routh array in Lemma 22 also gives the necessary and sufficient conditions for one and two dimensional unstable manifolds. If the coefficients (5.31), satisfy $q_2 > 0, q_1q_2 - q_0 < 0, q_0 > 0$ there are two sign changes in the Routh array, so there is a two dimensional unstable manifold. If $q_1q_2 - q_0 < 0, q_0 < 0$ or $q_1q_2 - q_0 > 0, q_0 < 0$ there is one sign change in the Routh array, so there is a one dimensional unstable manifold. The existence of the one dimensional stable manifold is important because it divides the phase space into three basins of attraction (one for each fixed point). We have one final Lemma which clarifies this relationship further.

Lemma 23. *For system* (5.15) *if* $a_{10}a_{22} - a_{12}a_{20} > 0$ *or* $q_0 > 0$ *the interior fixed point is attracting. Otherwise if* $q_0 < 0$ *there is one dimensional unstable manifold which is composed of two heteroclinic orbits.*

Proof. The statement is obtained from Lemmas 21 and 22 if $a_{21} = 0$. If $a_{21} = 0$ then $q_1q_2 - q_0$ is always positive. Examining the Routh array (5.34) only q_0 can be negative thus if $q_0 > 0$ at the interior fixed point it is attracting and has a three dimensional stable manifold. Conversely if $q_0 < 0$ then the system has a one dimensional unstable manifold (as shown later with examples this agrees with contraction theory). To prove that the one dimensional unstable manifold is composed of two heteroclinic orbits we use two previous results. First the B and P axial points always exist, second the system is eventually monotone converging to a one dimensional space due to Theorem 18. Suppose that the one dimensional unstable manifold does not connect to the stable manifolds of the P-axial and B-axial fixed points on each side. Then we have a contradiction with Theorem 18 as the carrying simplex is not unique. This would cause a contradiction as the monotone system which a $FCLV(n)$ system converges to in Theorem 18, has a single carrying simplex. Therefore from an unstable interior fixed point there must be two heteroclinic orbits which connect to the axial fixed points. □

We mention but do not prove (the proof is similar to Lemma 23 and we provide examples that shows it is true) that if the fixed point is attracting there are still two heteroclinic orbits but the direction is from the axial fixed points to interior fixed point.

Now that the important theorems related to fixed points have been covered, we change our focus to the other benefit[2] of contraction theory, estimating basin of attractions.

5.3 Basins of Attraction for FCLV(2) Systems

Basins of attraction are important for understanding the behaviour of systems with multiple attractors. While it is necessary for a fixed point to have a contraction region around it, with a system with multiple fixed points or attractors contraction regions will under or overestimate basins of attraction for the following reasons:

- A basin of attraction includes regions which are not contracting. For example consider the region near the trivial fixed point of a $CLV(n)$ system whose ω-limit set consists of fixed points. The region repels all solutions, so it is cannot be a

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[2] The first main benefit the semi-contraction of I, which causes the system to be eventually monotone.

contracting region. Nevertheless all solutions which start in this region are in the basin of attraction for a fixed point. So any contraction region is an underestimate for the basins of attraction.

- Convergence to a fixed point is guaranteed only if the contraction region is spherical. If the region is not spherical it is possible for solutions to escape (if the region is convex rather than spherical the radial distance between trajectories decrease, but the tangential velocities do not vanish so trajectories can escape).As our examples will show, most contraction regions will not be spherical and so will overestimate basins of attraction. However if we just restrict ourselves to contraction regions within a closed ball centred at a fixed point we are underestimating the basin of attraction.

So at best contraction regions are estimates for basins of attraction. There are techniques which refine estimates for basins of attraction. In addition from the requirement that contraction regions need to be spherical to guarantee convergence, we come to the following small lemma.

Lemma 24. *If a $FCLV(2)$ has an interior fixed point then the largest possible region of contraction that guarantees convergence for an axial fixed points is*

$$\{(P,B,I)\in\mathbb{R}^n_+|d((P,B,I),(P^*_A,B^*_A,I^*_A))<r \text{ and } P,B,I\geq 0\} \tag{5.35}$$

where $r = d\big((P^*_A,B^*_A,I^*_A),(P^*_{int},B^*_{int},I^*_{int})\big)$, (P^*_A,B^*_A,I^*_A) *is the axial fixed point, and* $(P^*_{int},B^*_{int},I^*_{int})$ *is the interior fixed point.*

Proof. Again if the contraction region is not spherical then solutions can escape from it, so the region in the statement of the lemma must be spherical. Now that we have a specific shape (a ball) suppose that the contraction region is larger than the ball 5.35 centred at an axial fixed point. We would have a contradiction as the ball will contain two fixed points and be a region of contraction which is not possible, therefore the region needs to be smaller. An open ball (which does not include the interior fixed point) will be the largest region of contraction such that contracting solutions do not escape the region and contain only one fixed point. Note that the actual contracting region may be much smaller than the region suggested in this lemma. □

Before applying contraction metrics to $FCLV(2)$ systems to use as indicators of basin of attractions we lay out a few simple rules that are useful for determining basins of attractions.

5.3.1 Simple Rules for Contraction Metrics

We layout here simple rules for finding contraction metrics. These rules consist of suggestions and checks, designed to make it simple to find valid contraction metrics. In contrast to the literature who's focus is often on metrics found using computational methods[3],

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[3] If there isn't a focus on computational methods, the focus is on metrics which can cover the whole system, because the system has one fixed point.

the focus here is to get qualitative information quickly for systems with multiple fixed points. We believe these rules can and should be used for other systems to obtain a quick understanding of system behaviour[4].

- Contraction metrics should be as simple as possible with the least dependence on parameters as possible.
- If possible contraction metrics should be restricted to diagonal matrices. Choosing to find metrics in the space of non-diagonal matrices makes both the numerical and analytical search for good metrics significantly more complicated. At the time of writing it is not clear that the trade off in terms of complexity for examining non-diagonal contraction metrics is worth the insight into the dynamics.
- In most cases it is easier to find a Θ that is non singular and then calculate M, rather than finding a positive definite M and then finding Θ.
- Only eigenvalues at fixed points are coordinate invariant, but differ in the rest of the state space. That is for any fixed point x^*, $J(f(x^*))$ and $J_g(f(x^*))$ have the same eigenvalues for any Θ as

  $$J_g(f(x^*)) = J(f(x^*)), \tag{5.36}$$

  $$= \Theta J(f(x^*))\Theta^{-1}. \tag{5.37}$$

  So $J(f(x^*))$ and $J_g(f(x^*))$ are similar matrices and so have the same eigenvalues. But if $x \neq x^*$ then

  $$J_g(f(x^*)) = (\dot{\Theta} + \Theta J(f(x^*)))\Theta^{-1} \neq \Theta J(f(x^*)))\Theta^{-1}. \tag{5.38}$$

  However, in general, the eigenvalues of the symmetric part of the Jacobian are not coordinate invariant as

  $$J_{gs}(f(x^*)) = \frac{\Theta J_s(f(x^*))\Theta^{-1} + \Theta^{-T} J_s(f(x^*))\Theta^T}{2}. \tag{5.39}$$

  So $J(f(x^*))$ and $J_g(f(x^*))$ are similar matrices.
- If the contraction region is **not convex** it is possible for two fixed points to be present in the same region.
- As discussed in previous sections for systems with multiple equilibrium points it will not be possible to find a single contraction metric/change of coordinates such that the entire state space is contracting. When comparing multiple contraction metrics to study the same region, the condition for any point to be in a contraction region is for the largest eigenvalue of *any* generalized Jacobian at that point to be negative. Likewise for any point to be expanding (the opposite of contracting) the smallest eigenvalue of *every* generalized Jacobian at that point needs to be positive. It follows that it is much simpler to prove a point is in a contraction region rather than an expanding region.

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[4] As far as the authour is aware a collection of such rules has not been proposed in the literature.

- From the above it follows the ideally one should choose Θ that is non singular over the largest possible state space (and that it should be easy to verify that Θ is non-singular).

The main point which we emphasize here is that even non-optimal metrics can provide useful information.

5.3.2 Examples of Contracting Systems

We first consider a bistable $CLV(2)$ system depicted in Fig. 5.3. We can overlay information on the phase plot, starting with the eigenvalues associated with the identity metric in Fig. 5.4. We can see the $CLV(2)$ system is divided into four regions:

- Expanding region. All solutions are repelled from this region, which contains the origin.
- Semi-contracting region (non-dominant eigenvalue is negative).
- Semi-contracting region (dominant eigenvalue is negative).
- Fully contracting region. Solutions are fully contracting within the region, and because the system is bistable the ends of the carrying simplex are within this region, causing convergence to the P and B axial fixed points.

A visual interpretation of choosing different contraction metrics (or different methods to verify the eigenvalues) is that *size and total proportion* of each region changes. Fig. 5.5 shows the contraction regions with the change of the coordinates

$$\Theta(P, B) = \begin{pmatrix} (P+B)^n + n & 0 \\ 0 & (P+B)^n + n \end{pmatrix} \tag{5.40}$$

where $n = 2$ and the contraction metric is $M(P, B) = \Theta^T \Theta$ (changing n changes the size of the contraction regions). We see that using this metric refines what we previously knew from using just the identity metric, expanding the region which is contracting. Instead of using a different contraction metric we could look at contraction with respect to μ_1 or μ_∞ metrics, as contraction under either is sufficient to guarantee contraction (see Section 4.2.2 for details). Fig. 5.6 shows this for our example $CLV(n)$ system. If we want to know the largest contracting region we, can combine the fully contracting region in Figures 5.4,5.5,5.6 to obtain a more accurate picture of contraction.

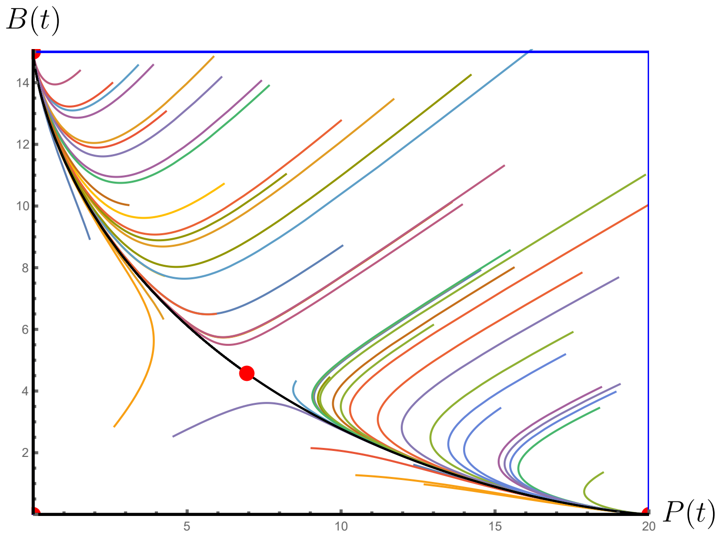

Figure 5.3: A bistable $CLV(2)$ system with community matrix (5.53). The black line is the carrying simplex.

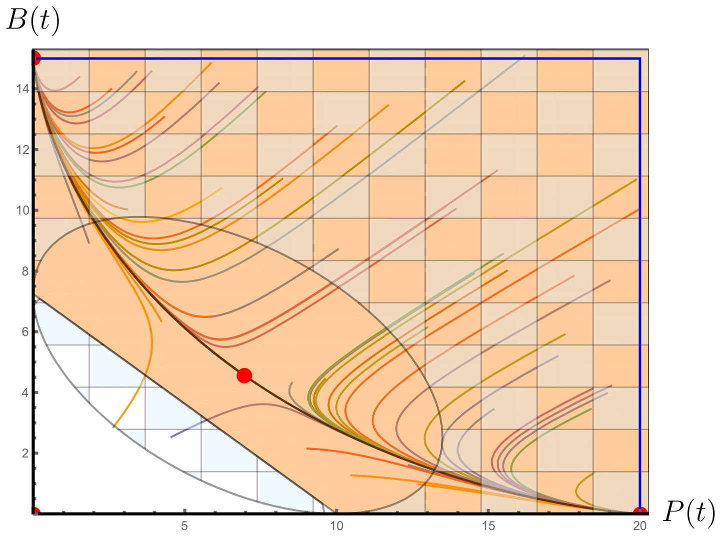

Figure 5.4: Same system as in Fig. 5.3 but with information about the eigenvalues of the symmetric part of the Jacobian overlayed on the phase plot. Regions where both eigenvalues of the Jacobian are negative are blue and orange chequered. If only one eigenvalue is negative the region is either solid orange or blue chequered. In the orange region (either solid or chequered) the largest eigenvalue by magnitude is negative, while in blue chequered region the smaller eigenvalue by magnitude is negative. Regions that are white have two positive eigenvalues.

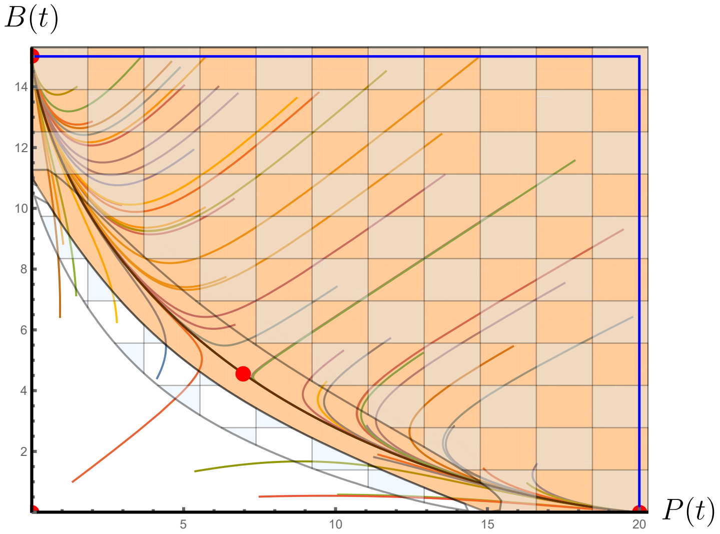

Figure 5.5: Same system as Fig. 5.3 but with information about the eigenvalues of the symmetric part of the generalized Jacobian (with change of coordinates matrix (5.40)) overlayed on the phase plot. Colouring of regions is the same as Fig. 5.4.

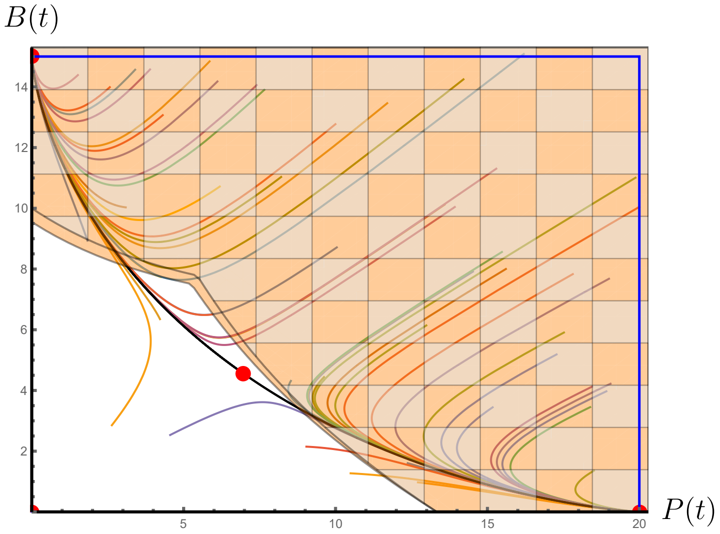

Figure 5.6: Same as system as Fig. 5.3 but overlayed is information on the position of the Gershgorin disks of the Jacobian (this is equivalent to contraction under the μ_1 or μ_∞ metrics). Orange regions have the Gershgorin disk associated with a_{11} entirely located in the left hand side of the complex plane. Blue chequered regions have the Greshgorin disk associated with a_{22} located in the left hand side of the complex plane. The blue and orange chequered region has all Greshgorin discs located in the left hand side of the complex plane.

We can now display regions of contraction for $FCLV(2)$ systems in two different ways. In Fig. 5.8 we show contraction regions on the surface Γ_f using the eigenvalues of $M_{dot,L}$ and can display that surface in the full three dimensional phase plot (See Fig. 5.9). The second method is to display contraction regions as a solid volume as seen in Fig. 5.10. Each figure uses the contraction metric in Theorem 14.

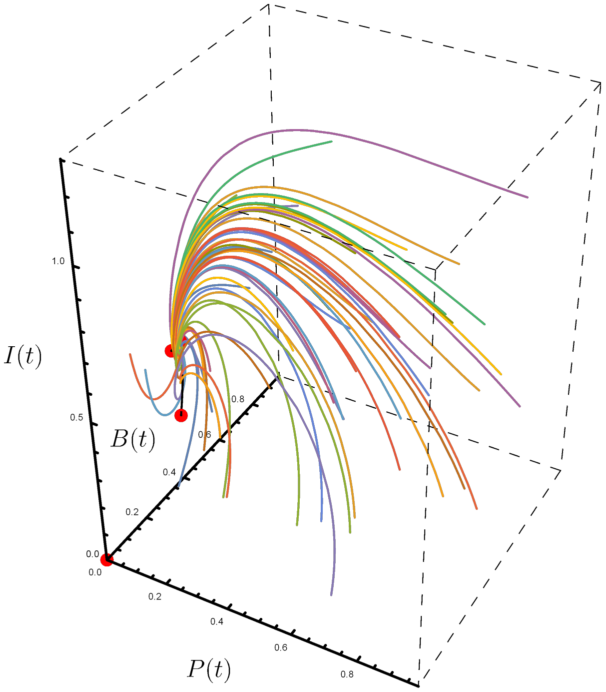

Figure 5.7: The phase plot of a $FCLV(2)$ system with a stable coexistence fixed point system with community matrix (5.56) and $f(P,B) = \frac{5P}{2+P} + \frac{3B}{2+B}$.

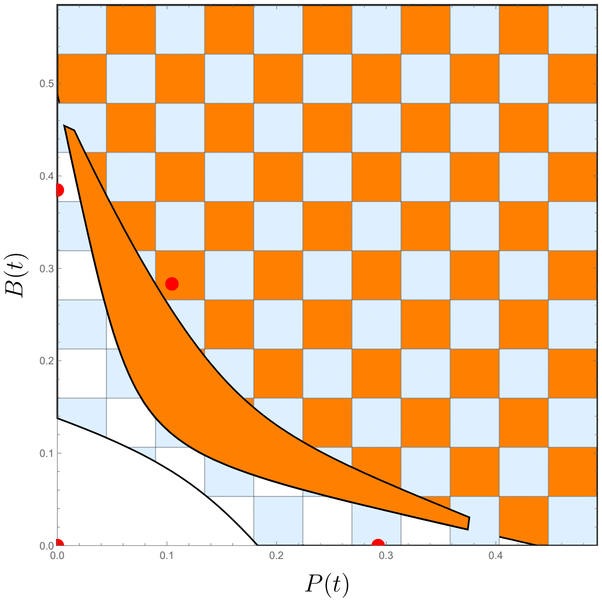

Figure 5.8: A stable $FCLV(2)$ coexistence interior fixed point system with community matrix (5.56) and $f(P,B) = \frac{5P}{2+P} + \frac{3B}{2+B}$. The regions shown are regions of contraction on Γ_f. Regions where both eigenvalues of $M_{dot,L}$ are negative are blue and orange chequered. If only one eigenvalue is negative the region is either solid orange or blue chequered. In the orange region the largest eigenvalue by magnitude is negative, while in blue chequered region the smaller eigenvalue by magnitude is negative. Regions that are white have two positive eigenvalues.

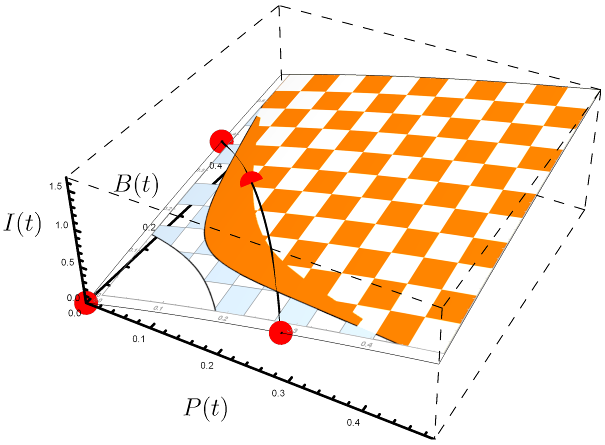

Figure 5.9: A stable $FCLV(2)$ coexistence interior fixed point system with community matrix (5.56) and $f(P,B) = \frac{5P}{2+P} + \frac{3B}{2+B}$. The regions shown are regions of contraction on Γ_f here shown in three dimensional space with $\Gamma_f \cap \Gamma_{CLV}$ added. Colouring of the regions are the same as Fig. 5.8.

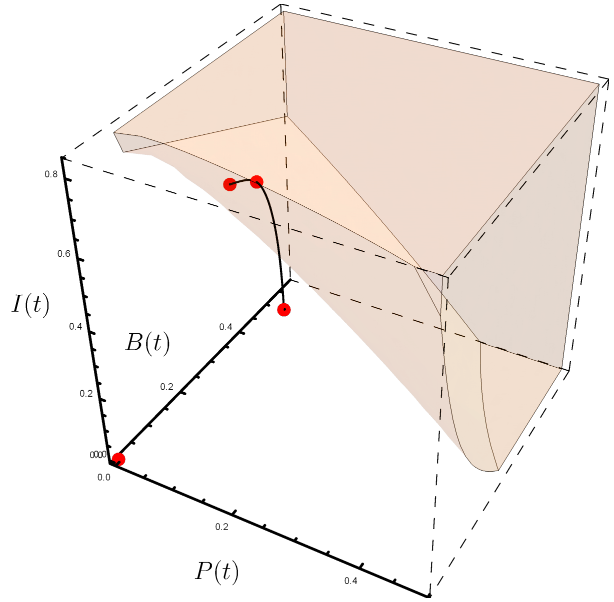

Figure 5.10: A stable $FCLV(2)$ coexistence interior fixed point system with community matrix (5.56) and $f(P,B) = \frac{5P}{2+P} + \frac{3B}{2+B}$. Here we show the fully contracting region of system where both eigenvalues of $M_{dot,L}$ are negative. As M_{dot} always has one negative eigenvalue we only need to track if the values of $M_{dot,L}$ are negative.

5.4 Important Questions in the Competition *Plasmodium* and AS1

We finish our investigate of system (5.15) by answering three important questions with regards to the competition between *Plasmodium* and AS1. The focus of these questions is what type of intervention specifically: Is adding more initial AS1 bacteria effective? Can the immune system of the mosquito change the competition outcome between *Plasmodium* and AS1? And most importantly how strong does AS1 need to be to eliminate Plasmodium?

5.4.1 The Effect of Introducing AS1 to a Mosquito Already Colonized by *Plasmodium*

One of the central questions that we want to answer is what are the necessary conditions to ensure that *Plasmodium* is eliminated from the mosquito midgut or reduce the population of *Plasmodium* in the long term. In the context of $FCLV(n)$ models this translates to if the fixed point $(I^*, P^*, 0)$ of the $FCLV(2)$ system (5.15) is stable under the introduction of non-zero population of AS1[5]. To solidify our ideas we use the

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[5] We do not say perturbation as it is not a realistic assumption that the introduced population of AS1 is small.

following notation

$$I_{new} = I^*_{old} \quad P_{new} = P^*_{old} \quad B_{new} = \Delta B \tag{5.41}$$

where $(I_{new}, P_{new}, B_{new})$ is the initial condition of system (5.15) after adding some sudden ΔB and I^*_{old}, P^*_{old} are the values of I^* and P^* at the P-axis fixed point (important note is that we do not assume that $0 = f(P_{new}, \Delta B) - I_{new}$ at least initially). The intervention of adding ΔB should be considered successful if the population of *Plasmodium* collapses (e.g. either both populations collapse or only the population of AS1 remains). We consider the intervention is semi-successful if the total population of *Plasmodium* is reduced but not eliminated (since periodic trajectories are not allowed) this means the long term behaviour is towards the coexistence fixed point which will always have a lower population of *Plasmodium* than the *Plasmodium* axial fixed point. The intervention will be considered unsuccessful if the *Plasmodium* population is not reduced (that is the solution converges to the *Plasmodium* axial fixed point). The population collapse case is interesting because it is not possible in a $CLV(n)$ system and depends highly on the immune response function chosen. Lemma 25 is a useful rule for detecting whether it is possible for a population to collapse.

Lemma 25. *A necessary condition for a particular solution of system* (5.15) *to reach the origin* $(0, 0, 0)$ *if the* I *component of the initial condition is* $I^0 < \min_{i\in 1,2} \frac{1}{a_{i0}}$ *is that* $\max\{f(B, P)\} > \min_{i\in 1,2} \frac{1}{a_{i0}}$.

Proof. As mentioned earlier in Section 2.2 there is a point on the I-axis, $(\min_{i\in 1,2} \frac{1}{a_{i0}}, 0, 0)$, which all points must travel to reach $(0, 0, 0)$. Except for the initial condition and the time it takes for the system to first cross $f(P, B) - I = 0$ the maximum value at which I can obtain is $\max\{f(P, B)\}$. So an initial condition $I^0 < \min_{i\in 1,2} \frac{1}{a_{i0}}$ will never reach $(\min_{i\in 1,2} \frac{1}{a_{i0}}, 0, 0)$ if $\max\{f(P, B)\} < \min_{i\in 1,2} \frac{1}{a_{i0}}$. However $\max\{f(P, B)\} > \min_{i\in 1,2} \frac{1}{a_{i0}}$ is not sufficient to guarantee that a solution will that initial condition to reach $(\min_{i\in 1,2} \frac{1}{a_{i0}}, 0, 0)$. The sufficient requirement is that $\max\{f(P, B)\}$ is sufficiently large such that when a solution crosses $f(P, B) - I = 0$ it reaches the I-axis before $I(t) < \min_{i\in 1,2} \frac{1}{a_{i0}}$. □

Lemma 25 is important as, for example, a system with $a_{10} = \frac{1}{4}, a_{20} = \frac{1}{5}$ and a saturating immune response function $f(P, B) = \frac{P}{1+P} + \frac{3B}{2+B}$ cannot have a population collapse given a initial condition $(I_{new}, P_{new}, \Delta B)$ as $\max\{f(P, B)\} = 2.5 < \min_{i\in 1,2} \frac{1}{a_{i0}} = 4$ and $I^* < \min_{i\in 1,2} \frac{1}{a_{i0}}$. This system has the immune response function that must cross the other nullclines at a point lower then which the P and B nullclines cross the I-axis. This shows that there are certain cases where no matter how large ΔB, *Plasmodium* will not eliminated. Likewise if there is no coexistence fixed point and the *Plasmodium* axial fixed point is unstable than any intervention will be successful. Likewise if the *Plasmodium* axial fixed point is stable any ΔB is not sufficiently large to cause a population collapse. We summarize the effect of interventions on systems within Tables 5.1 and 5.2.

	Successful	Semi-Successful	Unsuccessful
$1 \gg \Delta B > 0$	• Coexistence fp does not exist. • At P-axial fp $1 - a_{20}I^* > 0$ • At B-axial fp $1 - a_{12}B^* - a_{10}I^* < 0$	• Interior fp exists • $q_0 > 0$ at interior fp	• At P-axial fp $1 - a_{20}I^* < 0$
$\frac{1}{a_{22}} \geq \Delta B \gg 0$	• At B-axial fp $1 - a_{12}B^* - a_{10}I^* < 0$ • Solution in the basin of B-axial fp	• Interior fp exists • $q_0 > 0$ at interior fp exists	• At P-axial fp $1 - a_{20}I^* < 0$ • Solution in the basin of P-axial fp

Table 5.1: A summary of the possible results of adding a population of AS1, ΔB, as an intervention to eliminate *Plasmodium*. To keep the table compact we used the abbreviations fp for fixed point, and basin for basin of attraction. For larger interventions of ΔB, see Table 5.2.

	Both Populations Collapse	At Least One Species Remains
$\Delta B > \frac{1}{a_{22}}$	• Lemma 25 is satisfied. • Solution is within the basin of attraction of $(\min_{i \in 1,2}\{\frac{1}{a_{i0}}\}, 0, 0)$	See Row 2 of Table 5.1

Table 5.2: A summary of the possible results of adding a population of AS1, ΔB, as an intervention to eliminate *Plasmodium* for large ΔB. See Table 5.1 for the results of smaller interventions.

5.4.2 Can the Immune System Change the Outcome of *Plasmodium* and AS1 Competition?

An important question about system (5.15) is whether the immune system can change the outcome of competition of between *Plasmodium* and AS1. To clarify when we mean both the immune response function (which controls how much the immune system is activated in response to *Plasmodium* and AS1) and the a_{10}, a_{20} coefficients (which controls how much the growth rate of *Plasmodium* and AS1 are decreased when the immune response increases). If we refer to just changes in the immune response function, we will assume that the a_{10}, a_{20} do not change.

If we remove the immune system ($I(t)$ and a_{10}, a_{20} are removed) from system (5.15) we have a $CLV(2)$ system whose community matrix is

$$\begin{pmatrix} a_{11} & a_{12} \\ 0 & a_{22} \end{pmatrix}. \tag{5.42}$$

As the determinant, $a_{11}a_{22}$, is always positive the interior fixed point [6] if it exists is always stable, so given the constraints of $CLV(2)$ systems the B and P axial fixed points are unstable. Likewise if the fixed point does exist then the P-axial fixed point is unstable and the B axial point is stable[7]. From the lemmas in Section 5.2.2 it is apparent that the appropriate $f(P, B), a_{10}, a_{20}$ will reverse the effects competition (that is *Plasmodium* cannot be eliminated and/or the the interior fixed point if it exists is unstable).

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[6] The interior fixed point is $(P, B) = (\frac{a_{22} - a_{12}}{a_{11}a_{22}}, \frac{1}{a_{22}})$, so the interior fixed point exists if $a_{22} > a_{12}$.

[7] The P-axial fixed point always has an eigenvalue of 1. The B-axial fixed point has eigenvalues $1 - \frac{a_{12}}{a_{22}}, -1$. If $1 - \frac{a_{12}}{a_{22}} < 0$ the B axial fixed point is stable and the interior fixed point does not exist.

5.4.3 How strong does AS1 need to be to eliminate *Plasmodium*?

Out of all parameters in system (5.15) which experimenters have the most control over is a_{12} which controls the rate at which $AS1$ kills *Plasmodium.* The manner in which this can be altered is by changing the anti-*Plasmodium* effector molecule. The strength of AS1 (the magnitude of the a_{12} parameter) should be proportional to the effectiveness of the anti-*Plasmodium* effector molecule and the amount of the effector molecule that is produced per bacterium (we assumed earlier that AS1 cannot sense the population of *Plasmodium* present, so the amount of effector molecule is proportional to $a_{12}B$). The other a_{ij} parameters and the immune response function are in comparison immutable as they depend of the biology of wild type mosquitoes and *Plasmodium.*

So what changes in dynamic behaviour can we expect as a_{12} increases while other parameters are fixed? It is obvious for sufficiently large a_{12} the B^*-axial fixed point is stable ($a_{12} > \frac{1-a_{10}I^*}{B^*}$ where I^* and B^* are the values at the B^* fixed point). We can be more specific by using equation for the intersection of the nullclines (5.19) with $a_{21} = 0$,

$$(P, B, I) = \left(\frac{a_{22} - a_{12}}{a_{11}a_{22}}, \frac{1}{a_{22}}, 0\right) + (\frac{a_{12}a_{20} - a_{10}a_{22}}{a_{11}a_{22}}, -\frac{a_{20}}{a_{22}}, 1)I. \tag{5.43}$$

The following inequality guarantee the existence of the interior fixed point (in terms of $f(P, B)$ where P and B are on the line (5.43))

$$f(P, B) < \frac{1}{a_{20}} \text{ and } a_{10} < \frac{a_{22} + a_{12}(a_{11}a_{20}a_{22}f(P, B) - 1)}{a_{11}a_{22}^2 f(P, B)}. \tag{5.44}$$

Using this information we can write a lemma for how strong a_{12} needs to be to ensure that *Plasmodium* successfully eliminated regardless of the immune function response function.

Lemma 26. *If $a_{12}a_{20} - a_{10}a_{22} \leq 0$, then the fixed point if it exists is stable. However, if in addition $a_{12} \geq a_{22}$ then there can be no interior fixed point, and the B-axial fixed point is stable. As long as the initial condition is not on the P-axis, the immune response function is monotone increasing, and $f(0, 0) = 0$ then Plasmodium is eliminated.*

Proof. If $a_{12} > a_{22}$ then equation (5.43) shows, that the line on which the interior fixed points are found on begins outside of the positive quadrant (if $a_{12} = a_{22}$ the B-axial fixed point and the interior fixed point overlap). If $a_{12}a_{20} - a_{10}a_{22} > 0$ than for some $I > 0$ the line on which the interior fixed points occur on will cross into the positive quadrant. So if $\frac{a_{10}}{a_{20}} \geq \frac{a_{12}}{a_{22}} \geq 1$ the P coordinate of this line will never cross the B-axis. If (5.43) never reaches the interior of the positive quadrant than there cannot be an interior fixed point. If the line (5.43) crosses part of the interior of $\mathbb{R}^2_+$ it is still possible that there will be no interior fixed point (that is Γ_f does not cross the line (5.43)).

Now we need to verify whether $\frac{a_{10}}{a_{20}} \geq \frac{a_{12}}{a_{22}} \geq 1$ guarantees the stability of the B-axial fixed point. From Lemma 19 the condition needed for stability of the fixed point is

$$a_{12} > \frac{1 - a_{10}I^*}{B^*}. \tag{5.45}$$

Subbing in the values of I^* and B^* at the B-axial fixed point we have

$$a_{12} > \frac{1 - a_{10}f(0,B^*)}{\frac{1-a_{20}f(0,B^*)}{a_{22}}}, \tag{5.46}$$

$$\frac{a_{12}}{a_{22}} > \frac{1 - a_{10}f(0,B^*)}{1 - a_{20}f(0,B^*)}. \tag{5.47}$$

Now in order for both inequalities

$$\frac{a_{10}}{a_{20}} \geq \frac{a_{12}}{a_{22}} \geq 1 \quad \text{and} \quad \frac{a_{12}}{a_{22}} > \frac{1 - a_{10}f(0,B^*)}{1 - a_{20}f(0,B^*)}, \tag{5.48}$$

to hold we need

$$0 < f(0,B^*) < \frac{1}{a_{20}}. \tag{5.49}$$

Inequality (5.49) holds true because f is monotonically increasing and $f(0,0) = 0$, so Γ_f must cross the nucllines

$$0 = 1 - a_{11}P - a_{12}B - a_{10}I, \tag{5.50}$$

$$0 = 1 - a_{22}B - a_{20}I, \tag{5.51}$$

at points where the I-component is less than $\min\{\frac{1}{a_{10}}, \frac{1}{a_{20}}\}$. Thus inequality (5.49) holds.

Note that Lemma 20 shows that the P-axial fixed point is always unstable. Combining this with the semi-contraction of x_0 and any $FCLV(2)$ system being eventually monotone means that there can be only two possible points were all solutions of system (5.15) not on the P-axis (which is invariant) converge to either the B-axial fixed point or the origin. In either case System (5.15) satisfies the conditions in Lemma 26. *Plasmodium* is eliminated. □

5.5 Coefficient Matrices Used in Examples

There is a list of different community matrices used in Section 5. They have all been listed in this section to reduce clutter. The community matrices for $FCLV(n)$ systems are $A = (a_{ij}) \in \mathbb{R}^{n \times n+1}$ and $i \in [1,n], j \in [0,n]$ (the first column contains the coefficients a_{i0}). The community matrices for $CLV(n)$ systems are $A = (a_{ij}) \in \mathbb{R}^{n \times n}$ and $i, j \in [1,n]$.

$$A = \begin{pmatrix} \frac{1}{50} & \frac{1}{4} & \frac{1}{20} \\ \frac{1}{40} & 0 & \frac{1}{26} \end{pmatrix} \tag{5.52}$$

$$A = \begin{pmatrix} \frac{1}{20} & \frac{1}{7} \\ \frac{1}{10} & \frac{1}{15} \end{pmatrix} \tag{5.53}$$

$$A = \begin{pmatrix} \frac{1}{50} & \frac{1}{20} & \frac{1}{7} \\ \frac{1}{40} & \frac{1}{10} & \frac{1}{15} \end{pmatrix} \tag{5.54}$$

$$A = \begin{pmatrix} 1 & 1 & 1 \\ 0.475 & 1.31 & 2 \end{pmatrix} \tag{5.55}$$

$$A = \begin{pmatrix} 1.2 & 0.8 & 0.6 \\ 0.475 & 1.31 & 2 \end{pmatrix} \tag{5.56}$$

Chapter 6

Conclusion

Our simple model of the competition between AS1 and *Plasmodium* has lead to an investigation into contraction analysis. Contraction analysis while a powerful technique that generalizes different common notions in dynamical systems[1], has limitations. For complex non-linear systems use of contraction analysis over large regions is often analytically intractable. This becomes even more complex if there are multiple equilibrium points or periodic orbits in the phase space of the dynamical system because there cannot be one single contraction region that covers the entire phase space. This limits the conclusions that can be reached by using contraction theory alone. There have been three major ways to overcome this limitation in the literature; one: choose a system that has special properties that makes the Jacobian simple, two: choose a system that is partially contracting, three: show that a system contracts to smaller invariant region.

As far as the author is aware there is no dynamical system in the literature which has been analysed by contraction analysis, where convergence to a region that is *not invariant* was guaranteed and important to the analysis of the system. Although semi-contraction has been used since the original paper on which contraction analysis was originally purposed it has been underused. The main reason for the under use is that there is a trade off. The subset which the systems contracts to can be very complex and is usually non-invariant. Why semi-contraction is useful here is that the subset which the system converges to is monotone. The monotone nature prevents the trajectories that enter Γ_f from becoming periodic. A strong avenue for future research would be finding connections between semi-contraction and monotonicity. A natural question is what implies semi-contraction and monotonicity? Systems that semi-contract maintain monotonicity until they reach the region that they contract towards. We conjecture that there is a deeper connection between semi-contraction and monotonicity, but the scope of this connection is outside the scope of this work.

Successfully applying semi-contraction to $FCLV(n)$ systems leads to the conclusion

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[1] While contraction analysis generalizes can generalize many different concepts, a common comparison is between the eigenvalues of the symmetric part of the Jacobian and Lyapunov exponents [22]. That is the eigenvalues of the symmetric part of the Jacobian can be thought of as instantaneous Lyapunov exponent (Lyapunov exponents are not defined at a point; a finite time Lyapunov exponent is the instantaneous Lyapunov exponent to which we are referring.) and a Lyapunov exponent can be thought of as the average of the symmetric eigenvalue over time.

that all solutions converge to Γ_f (the surface $f(x_1, ..., x_n) - x_0 = 0$). Though Γ_f is not-invariant all solutions tend to Γ_f and when solutions pass through Γ_f their behaviour is determined by a $CLV(n)$-like system. This interaction causes $FCLV(n)$ systems to be eventually monotone on Γ_f. Thus the semi-contraction of $FCLV(n)$ in the x_0 direction reduces the possible ω-limit set by one dimension, once the system is monotone the ω-limit set is reduced further by one dimension. For $FCLV(2)$ systems this means that the ω-limit sets consists of a set of fixed points.

The simple model of AS1 and *Plasmodium* competition system (5.15), can be categorized as a $FCLV(2)$ model with one of the a_{ij} parameters is equal to zero ($a_{21} = 0$). Because semi-contraction shows that the system is eventually monotone all solutions eventually converge to one of the fixed points. Further analysis has shown two important results:

- The fixed point were the AS1 population is eliminated and *Plasmodium* is present is always unstable.

- To ensure that *Plasmodium* is eliminated regardless of the immune response it is necessary that the model parameters satisfy $\frac{a_{10}}{a_{20}} \geq \frac{a_{12}}{a_{22}} \geq 1$.

We hope that these results and the use of simple contraction metrics to determine qualitative behaviour can be used on other systems to obtain deeper insight. We believe our model demonstrates that given a symbiont has a high enough competitive effect *Plasmodium* can be eliminated from the mosquito midgut.

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