2009-03-26

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## Recommended Citation

Coburn, Brian John, "Multi-Species Influenza Models with Recombination" (2009). *Open Access Dissertations*. 363.
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UNIVERSITY OF MIAMI

# MULTI-SPECIES INFLUENZA MODELS WITH RECOMBINATION

By

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A DISSERTATION

Submitted to the Faculty
of the University of Miami
in partial fulfillment of the requirements for
the degree of Doctor of Philosophy

Coral Gables, Florida

May 2009

UNIVERSITY OF MIAMI

A dissertation submitted in partial fulfillment of
the requirements for the degree of
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# MULTI-SPECIES INFLUENZA MODELS WITH RECOMBINATION

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COBURN, BRIAN (Ph.D., Mathematics)
Multi-Species Influenza (May 2009)
Models with Recombination

Abstract of a dissertation at the University of Miami.

Dissertation supervised by Professors Chris Cosner and Shigui Ruan.
No. of pages of text. (131)

Avian influenza strains have been proven to be highly virulent in human populations, killing approximately 70 percent of infected individuals. Although the virus is able to spread across species from birds-to-humans, some strains, such as H5N1, have not been observed to spread from human-to-human. Pigs are capable of infection by both avian and human strains and seem to be likely candidates as intermediate hosts for co-infection of the inter-species strains. A co-infected pig potentially acts as a "mixing vessel" and could produce a new strain as a result of a recombination process. Humans could be immunologically naive to these new strains, hence making them super-strains.

We propose an interacting host system (IHS) for such a process that considers three host species that interact by sharing strains; that is, a primary and secondary host species can both infect an intermediate host. When an intermediate host is co-infected with the strains from both the other hosts, co-infected individuals may become carriers of a super-strain back into the primary host population. The model is formulated as a classical susceptible-infectious-susceptible (SIS) model, where the primary and intermediate host species have a super-infection and co-infection with recombination structure, respectively. The intermediate host is coupled to the other host species at compartments of given infectious subclasses of the primary and secondary hosts.

We use the model to give a new perspective for the trade-off hypothesis for disease virulence, by analyzing the behavior of a highly virulent super-strain. We give permanence conditions for a number of the subsystems of the IHS in terms of basic reproductive numbers $\mathcal{R}_0$ of independent strains. We also simulate several relevant scenarios showing complicated dynamics and connections with epidemic forecasting.

# ACKNOWLEDGMENTS

I would like to express my deepest gratitude to my co-advisors Dr. Chris Cosner and Dr. Shigui Ruan for their constant help and support. I am deeply grateful for their constant encouragement, guidance, and patience. I would like to thank Dr. Robert Stephen Cantrell and Dr. Donald L. DeAngelis for their valuable comments and thorough revision of this work. I would also like to thank Dr. Herb Freedman, Dr. Simon A. Levin, and Dr. Robert Smith? for their input and support. Further, I would like to thank the faculty and staff of the Mathematics Department for all the knowledge and affection they shared with me. To my family and friends for their love, support and understanding during the long years of my education.

# Contents

# Chapter 1

# Introduction

Influenza, also know as “the flu”, is an RNA virus that is commonly found in birds and mammals. The virus typically is spread from infected mammals through the air by sneezing and coughing and from infected birds through their droppings. Seasonal influenza epidemics spread across the world annually and, in some cases, result in high mortality in humans. These seasonal epidemics are mainly attributed to the genetically unstable structure of the virus that allows strains to change from year-to-year. In rare cases, influenza strains have emerged for which most humans have little to no immunity, and the resulting outbreaks have been catastrophic.

The virus is classified into three main types: A, B, and C. Type A virus is the most common of the three types and is shared between a variety of host species. Types B and C are commonly found in humans, but their outbreaks are typically limited in size [5]. Earn *et al.* [14] describe type A influenza as “the most significant epidemiologically and the most interesting from an ecological and evolutionary standpoint, because it is found in a wide variety of bird and mammal species and can undergo major shifts in immunological structure.” Throughout this project, the term “influenza” will refer to influenza A. Influenza A viruses are classified further by antigenic characteristics of two surface proteins called hemagglutinin (HA) and neuraminidase (NA); see [5, 14]. Sixteen HA and nine NA subtypes have been isolated from birds, lower mammals, and humans [6], resulting in 144 possible combinations of subtypes. For example, the subtype H5N1, an avian influenza strain that can cause serious illness in a number of different species, is composed of the fifth type of HA and first type of NA. All the subtypes of HA and NA are found in aquatic birds, in particular migrating water fowl [47].

A pandemic is an epidemic that spans a vast geographic region. There have been several influenza pandemics over the past centuries. These outbreaks occurred when a new highly transmissible strain was introduced in the human population. Historical pandemics of the twentieth century include the *Spanish Flu* 1918-1919 (H1N1), *Asian Flu* 1957-1958 (H2N2), and *Hong Kong Flu* 1968 (H3N2) [10]. Of these outbreaks, the Spanish Flu was one of the most catastrophic events to the human population in the 20th century, killing between 20 to 40 million people throughout the world [35]. One theory suggests the deadly virus came from birds through swine and was then transmitted to humans.

More recently, highly virulent strains of avian influenza have emerged in Southeast Asia. These avian strains are not transmissible from human-to-human; however, they have proven to be a major threat to human populations, killing approximately 70 percent of infected individuals [48]. It is hypothesized that the interaction of avian and human strains might recombine to form a super-strain that is highly transmissible and highly virulent.

## 1.1 Background

Influenza is a zoonotic disease, meaning it is shared amongst a variety of different host species. Wild ducks and wading birds are considered a reservoir for influenza becasue they can carry all subtypes and the virus is avirulent to its avian hosts. In addition, the avian virus is found in other birds such as domestic ducks and poultry. Influenza viruses of avian origin have also been found in a variety of mammals, such as seals, whales, pigs, and humans; see [46]. Many of the different strains are specific to individual species; however, the strains shared across species seem to pose the greatest potential threat. That is, the newly infected host may be immunologically naive to the strain that evolved in another host species (e.g., the case of humans and swine during the 1918 epidemic [43]).

In more recent decades, the number of avian influenza cases transmitted to humans has significantly grown; see [10]. Although these strains cannot pass from human-to-human, their emergence has attracted global attention because the strains are highly virulent in the human population [42]. The virus, in some cases, is thought to be passed to humans due to interaction with an intermediate host species, such as domestic poultry and/or swine. When an intermediate species is co-infected with avian and human influenza strains, there is a possibility of genetic recombination in the pathogens that could lead to potential super-strains of avian flu that can spread from human-to-human.

### The Role of Virulence

From an ecological perspective, virulence is the host's loss in fitness from parasitic infection. In the context of this research, virulence is defined as the potential for a pathogen to produce morbidity or mortality in a host population. Virulence plays an important role in the evolution of a pathogen. A highly virulent strain can drastically decrease host populations, hence, depleting the numbers necessary for the strain's long-term survival. With a limited host population, the number of infected individuals would diminish and the strain could not sustain itself beyond an invasive transient period. Natural selection suggests that a less virulent strain is more likely to co-exist with the host population because mobile, living hosts will transmit the strains most effectively [33]. In other words, the less virulent strain does not diminish the host population, thus creating a habitat more suitable for the strain's survival.

A system of differential equations is a natural mathematical approach for epidemiology and allows disease virulence to be treated as a parameter in the equations. The resulting system can be analyzed by the behavior near steady states, which is characterized by threshold constants of the system's parameters. These constants typically determine when the long term dynamics of a pathogen will become endemic in or be eradicated from the host population. Virulence is a usual parameter in threshold constants that can contribute to pathogen evolution.

"Conventional wisdom" about pathogen virulence suggests that a fully evolved parasite would not damage its host. We propose a new perspective to the theory that suggests a highly virulence, with respect to mortality, would lower a strain's chances of long-term survival. In other words, we challenge the "conventional wisdom" that a highly virulent strain is not able to sustain an epidemic and, hence, is eradicated from the host population. This "conventional wisdom" refers to a single host population with no outside reservoirs, as in the case of birds with influenza; however, the virus may be able to maintain highly virulent strains in certain host species if birds remain as a reservoir.

One explanation for a pathogen to maintain high virulence is the trade-off hypothesis, which suggests that virulent strain presence in a population can reach an optimal level if there is a balance between transmission and virulence [33]. That is, a highly virulent pathogen would need to be proportionally highly transmissible in order to sustain reproduction over a long time period [15]. To illustrate this mathematically, we introduce the *basic reproductive number* $\mathcal{R}_0$ for an infectious disease. The basic reproductive number is the mean number of secondary cases from a typical infected individual. The value of $R_0$ determines the long-term dynamics of a disease; in other words, the disease will die out of the population for $\mathcal{R}_0 < 1$, and spread for $\mathcal{R}_0 > 1$. Mills *et al.* [35] calculated the basic reproductive number for influenza A to be approximately 2-3. We consider the following example from [30] to describe the trade-off hypothesis with a given $\mathcal{R}_0$. The basic reproductive number for a host-parasite model is given by

$$\mathcal{R}_0 = \frac{\beta N}{\alpha + b + v},$$

where $\beta$ is the rate of infection (or incidence), $\alpha$ is the rate of disease-induced mortality (or virulence), $b$ is the natural mortality rate (i.e., independent of the parasite), $v$ is the rate of recovery, and $N$ is the total population size. The $\mathcal{R}_0$ from [30] is in a typical form for an epidemic model, since the transmission parameter (or incidence rate) is in the numerator and the virulence (or disease-induced mortality rate) $v$ is in the denominator of the basic reproductive number. If the virulence constant is increased, then the value of $\mathcal{R}_0$ decreases; hence, for a sufficiently large $v$, $\mathcal{R}_0 < 1$ and the parasite would naturally be eradicated from the host population after a transient period. A disease's incidence rate $\beta$ needs to increase to offset erradication (or the survival of the pathogen), so a trade-off must occur. A further discussion and methods for the calculation of $\mathcal{R}_0$ are given in Section 3.1.

There are a number of perspectives on the "conventional wisdom" of the trade-off hypothesis in different studies. Many of the classical mathematical epidemic models have disease transmission and virulence as independent parameters and are consistent with the trade-off hypothesis. Lipsitch and Moxon [33] explain research that links transmissibility and virulence; however, Ebert and Bull [15] argue that many of these studies are "system-specific" and do not relate to the simple models. Nowak and May [38] found circumstances in which natural selection favors strains with higher levels of virulence; however, the model required a super-infection structure with multiple strains to obtain such dynamics. Hence, the modeling required a specific structure to counter the trade-off hypothesis.

In our modeling approach, we will consider species interaction and genetic recombination in a co-infected subclass. The strains that are endemic (i.e., less virulent, in host species populations, such as birds and humans) are unlikely to cross infect each other; however, they are both capable of simultaneously infecting an intermediate host, such as domestic pigs [42]. Once an intermediate host is co-infected, a recombination process at the molecular level between the co-cirulating strains can lead to super-strains (for our interest) in the human population [42, 46]. This modeling approach will allow us to explore the impact of highly virulent strains that emerge from a recombination process.

## Mathematical Models for Influenza

Since Kermack and McKendrick [29] proposed the first susceptible-infectious-recovered (SIR) model to study pathogen spread in a host population, mathematical models have found a natural place in epidemiology theory. This modeling approach divides a given population (or multiple populations) into subclasses, where individuals are classified by the capability of being infected, of infecting, or of being immune. Mathematical rules, typically in the form of dynamical systems, describe the transport of individuals from compartment-to-compartment. To model influenza, we will consider a susceptible-infectious-susceptible (SIS) model with multiple infectious classes to represent many strains of influenza. The SIS structure differs from the SIR because infected individuals return directly to the susceptible class without undergoing a recovered or immune state. A general description of our model is given later in this section, and a more detailed description is given in Chapter 2.

A wide variety of mathematical models have been used to study the spread of influenza. These models focus on a variety of approaches, which include features ranging from genetic aspects to seasonal changes. Pease [40] introduced a model for antigenic shift in a single strain by considering changes in amino acid substitutions. The Pease model was initially modified by Inaba [28] for stability analysis. Magal and Ruan [34] considered another variation and showed the mechanism could generate periodic solutions. Andreasen [1] proposed a model conceptually similar to Pease's, where discrete subclasses model annual influenza epidemics. Lin *et al.* [32] considered an influenza A drift model of three co-circulating strains, where individuals previously infected with certain strains develop partial cross-immunity against other strains; see also [2]. Lin *et al.* [31] modeled antigenic drift of influenza A in the population by considering the virus drift as a diffusion process along a one-dimensional axis to mimic changes along a phylogenetic tree. In Dushoff *et al.* [13], an oscillating effect was built into a simple SIR-type model to understand effects of seasonal changes on epidemics.

Holt and Pickering [25] considered a mathematical model in which two host species shared a single pathogen; see also [20]. The Holt-Pickering model was used to address conditions for coexistence and competition when a disease is shared between two hosts. It was further studied by Chen and Price [8] seeking persistent and periodic solutions. Similarly, Zhang *et al.* [50] considered a system of two hosts, where two strains are shared between the host populations with a potential of co-infection.

A rich body of previous work exists to address a number of fundamental questions regarding a pathogen's ability to adapt and sustain itself as an endemic strain in a host [3, 19]. Researchers have considered different approaches to understanding the evolution of virulence in a pathogen; see [38]. Some approaches consider genetic aspects [28, 31], while others consider inter-species dynamics [8, 50]; however, few models consider the interplay of both approaches.

We focus our efforts on influenza because it is a perfect candidate to capture these dynamics due to its many genetically unstable strains and ability to inhabit different host species. Our specific research hypothesis is that virulent strains, which would otherwise be eradicated from a given host species, can be sustained if there is a continued external input of highly virulent strains from a second host species where such strains arise from recombination.

We need to explore the role of inter-species dynamics while genetic changes occur to gain insight with respect to the disease dynamics and epidemic forecasting. The theoretical model helps advance the field of mathematical epidemiology, while giving insight to more practical approaches to disease prevention. Our main goal is to develop a theoretical model that gives a framework for understanding the role of inter-species dynamics and genetic recombination in influenza.

## An Inter-species Influenza Model with Recombination

In the following chapter, we introduce a model for influenza that considers both species interaction and recombination in certain strains. Each species has a set of susceptible-infectious-susceptible (SIS) type differential equations that govern the spread of certain strains in that population. The avian model consists of a susceptible and an infectious subclass; the human model consists of a susceptible subclass and two infectious subclasses, one of which is a super-infectious subclass that can infect both of the other subclasses; and the intermediate host model consists of a susceptible subclass, two infectious subclasses for avian and human strains, a co-infected subclass, and a subclass consisting of a super-strain due to recombination. Moreover, some host species can infect other species with specific strains, but this ability is generally not symmetric. For example, birds can infect pigs with an avian strain, but the pigs cannot pass the avian strain back into the avian population. More in-depth discussions of this are given in Chapters 2 and 4. The three host species are coupled as an interacting host system (IHS), where the couplings are external inputs of avian and human strains from the respective hosts to the intermediate host and a super-strain external input from the intermediate host to the humans. Similarly to the Holt-Pickering model, we will consider a model where a single strain is shared between two hosts; however, our interest is to understand co-infection and recombination in an intermediate host as a result of infectious strains from other host species.

We asked the following question – *Can virulent strains, too virulent to independently sustain themselves in a host population, continue to reemerge in a host population due to a recombination process in an intermediate host?* To address this question, we consider two open problems about uniform persistence theory in SIS type models:

1. *What are the conditions for permanence in certain subsystems for single and multiple host species?*
2. *Is it possible to find conditions under constraints for uniform persistence that would suggest otherwise if there were no interactions between host species?*

In Section 1.2, we will introduce certain definitions and notations that will be used in the following chapters. In Chapter 2, we develop the IHS in detail to model species interaction of influenza strains. In Chapter 3, we consider single host subsystems of the IHS, which include a basic model, a super-infection model, and a co-infection model. For each subsystem, we determine the basic reproductive numbers and permanence conditions. In Chapter 4, we consider subsystems with two host species, in which one host can infect the other but not visa versa. We approximate an initial model from Section 4.1 by a two dimensional SIS model in Section 4.2 with an external input. In Chapter 4.3, we calculate the basic reproductive number $\mathcal{R}_0$ for the IHS and simulate several relevant scenarios showing complicated dynamics and connections with epidemic forecasting. We present a summary of content and results from Chapters 2 through 4.3 along with a discussion of epidemiological ramifications in Chapter 6.

## 1.2 Definitions and Notation

In this section, we give some of the basic definitions and notations that we will use throughout the analysis. The majority of definitions and notation arise in dynamical systems and permanence/persistence theory. We use the definitions and notations from [4, 18, 22, 41, 27].

### Dynamical Systems Theory

Let $\mathcal{X}$ denote a metric space with metric $d$ and $\mathbb{R}$ denote the set of real numbers. Let $\mathbb{R}^+$ and $\mathbb{R}^-$ denote the sets of nonnegative and nonpositive real numbers, respectively. We denote the continuous flow $\Im = (X, \mathbb{R}, \pi)$ defined on $\mathcal{X}$, where $\pi : \mathcal{X} \times \mathbb{R} \to \mathcal{X}$ is a continous map with the properties:

i. $\pi(x, 0) = x$ for all $x \in \mathcal{X}$.

ii. $\pi(\pi(x, t), s) = \pi(x, t + s)$ for $x \in \mathcal{X}$ and $s, t \in \mathbb{R}$.

If $M \subset \mathcal{X}$ and $K \subset \mathbb{R}$, then $\pi(M, K)$ denotes the set

$$\{\pi(x, t) : x \in M,\ t \in K\}.$$

For a subset $M \subset \mathcal{X}$, we denote

$$\gamma(M) = \phi(M, \mathbb{R}), \quad \gamma^+(M) = \phi(M, \mathbb{R}^+), \quad \gamma^-(M) = \pi(M, \mathbb{R}^-)$$

Then for the singleton set $M = \{x\}$, these denote the sets $\gamma(x)$, $\gamma^+(x)$, and $\gamma^-(x)$. The *boundary* and *interior* of a set $M \subset \mathcal{X}$ are denoted by $\partial M$ and $\overset{\circ}{M}$, respectively.

For any $\epsilon > 0$ and $M \subset \mathcal{X}$, we define

$$S[M, \epsilon] = \{x \in \mathcal{X} : d(x, M) \leq \epsilon\}.$$

**Definition 1.1.** We call a subset $U$ of $\mathcal{X}$

(i) *forward invariant* if for all $u \in U$, $\gamma^+(u) \subseteq U$.

(ii) *invariant* if for all $u \in U$, $\gamma(u) \subseteq U$.

A continuous mapping $T$ on a complete metric space $\mathcal{X}$ is said to be *point dissipative* (*compact dissipative*) (*bounded dissipative*) on $\mathcal{X}$ if there is a bounded set $B$ in $\mathcal{X}$ such that $B$ attracts each point of $\mathcal{X}$ (each compact set of $\mathcal{X}$) (each bounded set of $\mathcal{X}$) under $T$; see [21]. If a system is either compact or bounded dissipative, it follows that the system is point dissipative. The systems in Chapters 3 through 4.3 are all bounded and compact dissipative; hence, when a system is *dissipative*, we mean it is bounded and compact dissipative. The arguments for dissipativity throughout this project involve solving a differential inequality to show that each population subclass of the system will be attracted to a bounded, compact set of the ambient space.

## Persistence/Permanence Theory

It is convenient to classify the long-term population densities of a species by using Permanence Theory. We address two forms of permanence: *abstract permanence* and *ecological permanence*. Ecological permanence is a property of a system (i.e., all species or compartments) that characterizes the long-term population densities. A system *exhibits permanence* or *is permanent* when each component of the population remains in a positive, bounded state for all time. Abstract permanence is a more mathematical concept that requires the model to be in the form of a dynamical or semi-dynamical system, and the conclusions are in terms of a metric on a given metric space. This general approach encompasses a much larger spectrum of models, which include discrete time models, ordinary differential equations, reaction-diffusion equations, and delay differential equations. Cantrell and Cosner [4] give a more detailed discussion of abstract and ecological permanence. Since the model is a system of ordinary differential equations, we will use abstract permanence methods, in most cases, to find ecological permanence conditions on our system. The system is defined on the nonnegative Euclidean space $\mathcal{X} = \mathbb{R}^n_+$ $(n \leq 10)$ with the Euclidean metric.

Consider the system of ordinary differential equations

$$\frac{du_i}{dt} = f_i(u) \quad (i = 1, \ldots, n). \tag{1.1}$$

Let $u(t) = (u_1(t), \ldots, u_n(t))^T$ be a solution of system (1.1).

**Definition 1.2.** System (1.1) is said to be

(i) *weakly persistent* if

$$\limsup_{t\to\infty} u_i(t) > 0$$

(ii) *persistent* if

$$\liminf_{t\to\infty} u_i(t) > 0$$

(iii) *weakly uniformly persistent* if there exists $\epsilon_0 > 0$ such that

$$\limsup_{t\to\infty} u_i(t) > \epsilon_0$$

(iv) *uniformly persistent* if there exists $\epsilon_0 > 0$ such that

$$\liminf_{t\to\infty} u_i(t) > \epsilon_0$$

for $i = 1, \ldots, n$.

We will use the same definitions for a given subclass that individually satisfies the above conditions; e.g., we say subclass $i$ is persistent if $\liminf_{t\to\infty} u_i(t) > 0$. A subclass can satisfy one of the persistence definitions regardless of the system's classification; however, if a system assumes a classification, then all its subclasses assume the label.

The system (1.1) is said to be *permanent* if there are numbers $m$ and $M$ with $0 < m < M < \infty$ such that given any $u_0 \in \text{int}(\mathbb{R}^n_+)$, there is a $T$ such that

$$m \leq u_i(t) \leq M \quad (t > T,\ i = 1, \ldots, n).$$

In other words, a system that is strongly uniformly persistent and bounded above is permanent. A dissipative system is bounded above; hence, the dissipativity and strong uniform persistence imply permanence.

# Chapter 2

# The Model

## 2.1 A Model with Two Strains Circulating and Three Host Species Interacting

The goal of this section is to construct a model in which strains of two species interact by means of an intermediate host. We consider two parasitic strains circulating in three species' populations - the species are labeled as the primary host, intermediate host, and secondary host populations. The primary and secondary hosts each have a single strain circulating within their respective population; however, neither species can directly share its strain with the other species. We label the respective strains as the primary and secondary strain. The intermediate host acts as a medium between the two other populations, in that it interacts by sharing respective strains with given host populations. The primary host's population is divided into subclasses which follow the dynamics of the SIR model with interaction from an infectious subclass of the intermediate host. We will assume the co-infected subclass of the intermediate host is not infectious to the primary host.

We begin by constructing the model for the primary and secondary host populations in the absence of interaction with the intermediate host. We will use the subscripts $i = 1$ and $i = 2$ for the primary and secondary hosts, respectively. Let $S_i(t)$ be the density of susceptible individuals at time $t$ and $I_i(t)$ be the density of individuals infected with strain at time $t$. We denote the total population at time $t$ by $N_i(t)$ so that $N_i(t) = S_i(t) + I_i(t)$. Recruitment is into the susceptible subclass, so the birth term is going to be logistic and based on the entire population. We label the intrinsic growth rate $r_i$ and carrying capacity $K_i$. 'The contact rates are denoted by $\beta_i$, the disease-induced death rates are denoted by $v_i$, and the recovery rates are denoted by $\alpha_i$. See **Figure 2.1**. The following system of differential equations describes

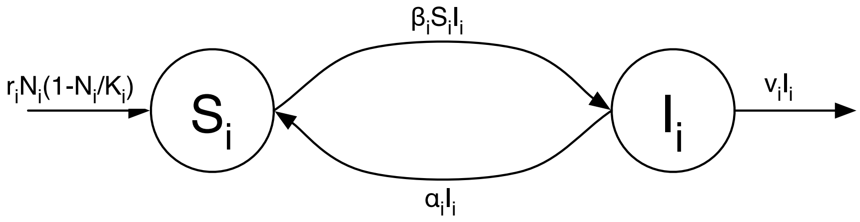

**Figure 2.1:** *Scheme diagram for the primary and secondary hosts without interaction for System (2.1).*

the dynamics of the primary and secondary host species

$$\begin{aligned} \frac{dS_i}{dt} &= r_i N_i \left(1 - \frac{N_i}{K_i}\right) - \beta_i S_i I_i + \alpha_i I_i \\ \frac{dI_i}{dt} &= \beta_i S_i I_i - (\alpha_i + v_i) I_i \end{aligned} \tag{2.1}$$

The description of parameters and variables is given in **Table 2.1**.

**Table 2.1:** *Description of Parameters and Variables in System (2.1)*

| Character | Description |
|---|---|
| $S_i$ | Susceptible subclass for species $i$ |
| $I_i$ | Infectious subclass for species $i$ |
| $N_i$ | Total population for species $i$ |
| $r_i$ | Intrinsic growth rate for species $i$ |
| $K_i$ | Carrying capacity for species $i$ |
| $\beta_i$ | Incidence rate for species $i$ |
| $\alpha_i$ | Immunity rate for species $i$ |
| $v_i$ | Disease-induced death rate for species $i$ |

We continue by constructing the model for the intermediate host population in the absence of interaction with the primary and secondary host. Let $X(t)$ be the density of susceptible or non-infected individuals at time $t$; $Y_1(t)$ and $Y_2(t)$ be the density of individuals infected with the primary and secondary strain at time $t$, respectively; and $Y_{12}(t)$ be the density of individuals co-infected with both strains. In this case, the term *non-infected* is more appropriate for the subclass $X$. That is, the subclasses $Y_1$ and $Y_2$ are infectious subclasses and are able to infect individuals from the susceptible subclass and the other infectious subclass. For example, individuals in $Y_1$ can infect individuals from $X$ and $Y_2$. A susceptible individual in $X$ infected with strain one would then join the subclass $Y_1$, while individuals in $Y_1$ infected from $Y_2$ would then join the co-infected subclass $Y_{12}$. We will also assume that individuals can only be infected by one strain at a time; that is, if a non-infected individual is infected by a co-infected individual, then the individual will be either infected by the primary strain or the secondary strain but not both. For simplicity, we will only allow the co-infected subclass to infect the non-infected subclass. It is already possible for individuals in the subclasses $Y_1$ and $Y_2$ to transfer into the co-infected subclass, so having a stronger transfer due to the co-infected subclass would only complicate the model. The total population at time $t$ is denoted by $N_X(t)$, then $N_X(t) = X(t) + Y_1(t) + Y_2(t) + Y_{12}(t)$. Recruitment is into the susceptible subclass, so the birth term is going to be logistic and based on the entire population. We label the intrinsic growth rate $r_X$ and carrying capacity $K_X$. The contact rates are denoted by $b_i$, the disease-induced death rates are denoted by $u_i$, and the recovery rates are denoted by $a_i$. The rate at which co-infected individuals infect susceptible individuals with strain $i$ is given by $b_i \cdot d_i$. See **Figure 2.2**.

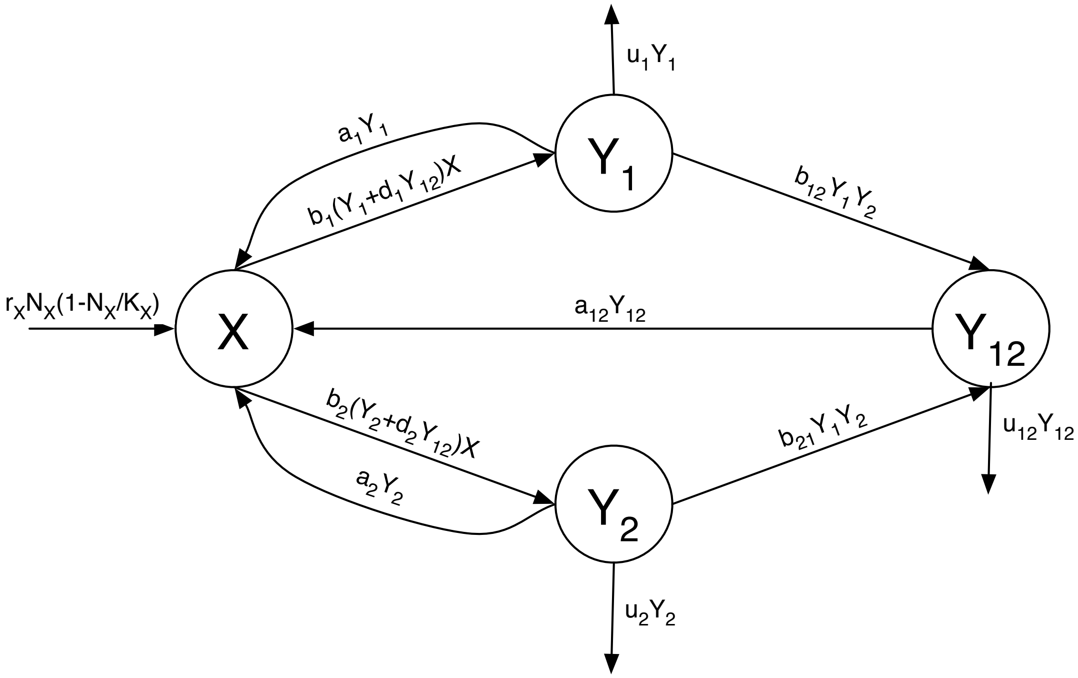

**Figure 2.2:** *Scheme diagram for the intermediate host without interaction.*

The dynamics are captured mathematically by

$$
\begin{aligned}
\frac{dX}{dt} &= r_X N_X \left(1 - \frac{N_X}{K_X}\right) - \sum_{i=1}^{2} b_i (Y_i + d_i Y_{12}) X + a_1 Y_1 + a_2 Y_2 + a_{12} Y_{12} \\
\frac{dY_1}{dt} &= b_1 (Y_1 + d_1 Y_{12}) X - b_{12} Y_1 Y_2 - (a_1 + u_1) Y_1 \\
\frac{dY_2}{dt} &= b_2 (Y_2 + d_2 Y_{12}) X - b_{21} Y_1 Y_2 - (a_2 + u_2) Y_2 \\
\frac{dY_{12}}{dt} &= (b_{12} + b_{21}) Y_1 Y_2 - (a_{12} + u_{12}) Y_{12}.
\end{aligned} \tag{2.2}
$$

**Table 2.2** gives a description of the parameters and variables in system (2.2). The

**Table 2.2:** *Description of Parameters and Variables in System (2.2)*

| Character | Description |
|---|---|
| $X$ | Susceptible subclass |
| $Y_i$ | $i$th infectious subclass |
| $N_X$ | Total population |
| $r_X$ | Intrinsic growth rate |
| $K_X$ | Carrying capacity |
| $b_i$ | Contact rate for the $i$th infectious subclass |
| $a_i$ | Immunity rate for the $i$th infected subclass |
| $u_i$ | Disease-induced death rate of the $i$th subclass |
| $b_i \cdot d_i$ | Co-infected individuals infect a susceptible individual with strain $i$ |

intermediate host infectious class $Y_i$ will infect individuals in $S_i$, sending them to the subclass $I_i$ at the rate $\gamma_i$. Hence, the interacting systems for the primary and secondary hosts are given by

$$\begin{aligned}\frac{dS_i}{dt} &= r_i N_i \left(1 - \frac{N_i}{K_i}\right) - \beta_i S_i I_i - \gamma_i S_i Y_i + \alpha_i I_i \\ \frac{dI_i}{dt} &= \beta_i S_i I_i + \gamma_i S_i Y_i - (\alpha_i + v_i) I_i.\end{aligned} \tag{2.3}$$

The interaction of the primary and secondary hosts with the intermediate host will both follow the assumption that infectious individuals will only infect individuals in the corresponding susceptible subclasses. The primary host infectious class $I_1$ will infect individuals in $X$, sending them to the subclass $Y_1$ at the rate $g_1$. The same assumption is made with respect to the secondary host interacting with the intermediate host at rate $g_2$. For simplicity, we will assume that the infectious members of the primary and secondary host populations will only infect individuals in the susceptible subclass of the intermediate host population; however, one could imagine the primary and secondary hosts could also infect members of the other infected subclass to produce more co-infected individuals. Summarizing, the dynamics in the intermediate host system (IHS) are given by

$$
\begin{aligned}
\frac{dX}{dt} &= r_X N_X \left(1 - \frac{N_X}{K_X}\right) - \sum_{i=1}^{2} b_i(Y_i + d_i Y_{12})X - \sum_{i=1}^{2} g_i X I_i + a_1 Y_1 + a_2 Y_2 + a_{12} Y_{12} \\
\frac{dY_1}{dt} &= b_1(Y_1 + d_1 Y_{12})X - b_{12} Y_1 Y_2 + g_1 X I_1 - (a_1 + u_1) Y_1 \\
\frac{dY_2}{dt} &= b_2(Y_2 + d_2 Y_{12})X - b_{21} Y_1 Y_2 + g_2 X I_2 - (a_2 + u_2) Y_2 \\
\frac{dY_{12}}{dt} &= (b_{12} + b_{21}) Y_1 Y_2 - (a_{12} + u_{12}) Y_{12}.
\end{aligned}
\tag{2.4}
$$

Notice now that the primary and secondary hosts share their respective strain with the intermediate host; however, respective strains are not shared between the primary and secondary host. Individuals in the co-infected subclass of the intermediate host are infected with strains from two different species.

## 2.2 Recombination in the Intermediate Host's Co-Infected Subclass

In the event an individual is co-infected, the parasites of each strain interact within the host. In some cases, the interaction leads to genetic recombination and an antigenic shift in one of the strains. Thus, the recombination produces a new strain. We will assume that recombination occurs in the co-infected class of the intermediate host. In the model, the recombination process is thought of as a birth process, producing a new subclass of infected individuals $Y_3$ of individuals infected/infectious with a new strain. For now, we assume the primary host is susceptible to the third strain in the intermediate host, but the secondary host is not. The third strain is infectious only to the subclasses $X$, $Y_1$, and $Y_2$ of the intermediate host; that is, $Y_3$ is not infectious to the subclass $Y_{12}$ that produces the third strain. This is plausible since members of $Y_{12}$ would have antibodies the from primary and secondary strains and $Y_3$ would be built from the subclasses $Y_1$ and $Y_2$. See **Figure 2.3**. The subclass $Y_3$ carries a super-strain that infects individuals in the primary host population. We denote the super-infectious subclass of the primary host by $J$.

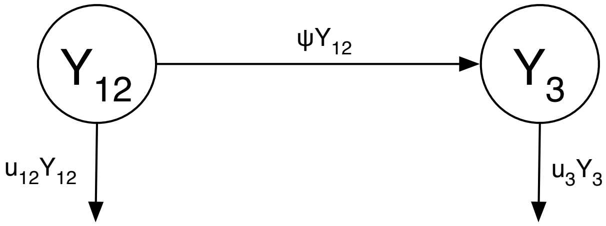

**Figure 2.3:** *Scheme diagram for the recombination in the intermediate host's subclass* $Y_{12}$*, producing the infected subclass* $Y_3$*.*

The primary host system then becomes

$$
\begin{aligned}
\frac{dS_1}{dt} &= r_1 N_1 \left(1 - \frac{N_1}{K_1}\right) - \beta_1 S_1 I_1 - \beta_3 S_1 J - \gamma_3 S_1 Y_3 + \alpha_1 I_1 + \alpha_3 J \\
\frac{dI_1}{dt} &= \beta_1 S_1 I_1 - \delta I_1 J - (\alpha_1 + v_1) I_1 \qquad (2.5) \\
\frac{dJ}{dt} &= \beta_3 S_1 J + \delta I_1 J + \gamma_3 S_1 Y_3 - (\alpha_3 + v_3) J.
\end{aligned}
$$

Here $J$ is the subclass of individuals infected with the super strain; the infectious class $I_1$ in system (2.1) is subscripted with one, $I_1$; and $\beta_3$ is the incidence rate in which individuals in the primary host population are infected by individuals in the intermediate host population with the super strain. Notice in this case, there is no co-infected subclass of individual - it is assumed the super strain is the overwhelming strain in the primary host. However, there is a super-infectious term, where individuals infected with the first strain are allowed to be infected with the third strain with incidence rate $\delta$. In other words, the susceptible and infectious subclass are both susceptible relative to the super strain. We will refer to $\delta$ as the super-incidence rate.

The system for the intermediate host is given by

$$\begin{aligned}
\frac{dX}{dt} &= r_X N_X \left(1 - \frac{N_X}{K_X}\right) - \sum_{i=1}^{2} b_i(Y_i + d_i Y_{12})X - b_3 X Y_3 - \sum_{i=1}^{2} g_i X I_i + \sum_{i=1}^{3} a_i Y_i + a_{12} Y_{12} \\
\frac{dY_1}{dt} &= b_1(Y_1 + d_1 Y_{12})X - b_{12} Y_1 Y_2 - b_{13} Y_1 Y_3 + g_1 X I_1 - (a_1 + u_1) Y_1 \\
\frac{dY_2}{dt} &= b_2(Y_2 + d_2 Y_{12})X - b_{21} Y_1 Y_2 - b_{23} Y_2 Y_3 + g_2 X I_2 - (a_2 + u_2) Y_2 \\
\frac{dY_{12}}{dt} &= (b_{12} + b_{21}) Y_1 Y_2 - (a_{12} + u_{12} + \psi) Y_{12} \\
\frac{dY_3}{dt} &= \psi Y_{12} + b_3 X Y_3 + b_{13} Y_1 Y_3 + b_{23} Y_2 Y_3 - (a_3 + u_3) Y_3.
\end{aligned} \tag{2.6}$$

In this case, we allow individuals in the subclass $Y_3$ to infect individuals of the subclass $Y_1$ and $Y_2$ but not the subclass $Y_{12}$. That is, the individuals of $Y_{12}$ already feed into subclass $Y_3$ due to recombination.

The complete model is then given by the primary host of system (2.5), the intermediate host in system (2.6), and the secondary host of system (2.3). We are now ready to analyze the subsystems of the complete model.

# Chapter 3

# Subsystems of a Single Host

## 3.1 The Basic SIS Model

We begin by considering a simple SIS model. The total population is divided into two subclasses of infectious and susceptible individuals. We denote the total population density at time $t$ by $N(t)$ and the population density of the subclasses of infectious and susceptible individuals at time $t$ by $I(t)$ and $S(t)$, respectively. We note that $N(t) = S(t) + I(t)$. Recruitment into the susceptible subclass so that the birth term is going to be logistic and based on the total population. We label the intrinsic growth rate $r$ and carrying capacity $K$.

$$\frac{dS}{dt} = rN\left(1 - \frac{N}{K}\right) - \beta SI + \alpha I$$

$$\frac{dI}{dt} = \beta SI - (\alpha + v)I \tag{3.1}$$

with $S(0) \geq 0,\ I(0) \geq 0$.

This system is the same as system (2.1) from section 2 of Chapter 2. System (3.1) is also the subsystem (2.3) for the secondary host with $\gamma_2 = 0$ (i.e., without interaction with the intermediate host). The subscripts for the variables and parameters have been omitted, since the results for system (3.1) will be used throughout the analysis for a number of different subsystems.

If we look at the sum of the two equations of system (3.1), then the differential equation for the total population is given by

$$\frac{dN}{dt} = rN\left(1 - \frac{N}{K}\right) - vI, \tag{3.2}$$

implying

$$\frac{dN}{dt} \leq rN\left(1 - \frac{N}{K}\right). \tag{3.3}$$

Solving the differential inequality, we get the carrying capacity bound on the total population as $t \to \infty$, that is,

$$\limsup_{t\to\infty} N(t) \leq K.$$

Setting $S = 0$ and $I = 0$, we can clearly see that the population growth rate is zero. If $S + I \leq K$, $I \geq 0$ and $S = 0$, then $dS/dt \geq 0$. Also, if $I = 0$ and $S \geq 0$, then $dI/dt = 0$. Hence, the space with $S \geq 0$ and $I \geq 0$ is invariant. Moreover, system (3.1) attracts to a compact set and is dissipative. We denote the space

$$\mathcal{X} = \{(S, I) \in \mathbb{R}^2 : 0 \leq S, I\},$$

and the attracting region

$$E = \{(S, I) \in \mathcal{X} : S + I \leq K\}.$$

We are now ready to solve for the equilibria. Clearly, system (3.1) has the disease free equilbria (DFE) at $(0, 0)$ and $(K, 0)$.

The basic reproductive number $\mathcal{R}_0$ is "The expected number of secondary cases produced by a typical infected individual during its entire period of infectiousness in a completely susceptible population" and "is mathematically defined as the dominant eigenvalue of a positive linear operator" [12]. In the case of system (3.1), the positive linear operator is the next generation matrix that is described below.

To calculate the basic reproductive number $\mathcal{R}_0$ for system (3.1), we use the framework given in [44]. We begin by denoting the population subclasses by $x_i$. Let $x = (x_1, \ldots, x_n)^t$ with each $x_i \geq 0$, be the density of individuals in each population subclass. The compartments are sorted so that the first $m$ compartments are the infectious individual subclasses. We denote the disease free states by

$$\mathcal{X}_s = \{x \geq 0 : x_i = 0,\ i = 1, \ldots, m\}.$$

Let $\mathcal{F}_i(x)$ be the rate of appearance of new infections in compartment $i$, $\mathcal{V}_i^+(x)$ be the transfer of individuals into compartment $i$, and $\mathcal{V}_i^-(x)$ be the rate of transfer of individuals out of compartment $i$. We will begin by rewriting system (3.1) in the form

$$\dot{x}_i = f_i(x) = \mathcal{F}_i(x) - \mathcal{V}_i(x), \quad i = 1, \ldots, n, \tag{3.4}$$

where $\mathcal{V}_i = \mathcal{V}_i^- - \mathcal{V}_i^+$. The functions $\mathcal{F}_i$, $\mathcal{V}_i$, $\mathcal{V}_i^-$, and $\mathcal{V}_i^+$ must satisfy the following assumptions:

(A1) if $x \geq 0$, then $\mathcal{F}_i$, $\mathcal{V}_i^-$, and $\mathcal{V}_i^+ \geq 0$ for $i = 1, \ldots, n$.

(A2) if $x_i = 0$ then $\mathcal{V}_i^- = 0$. In particular, if $x \in \mathcal{X}_s$ then $\mathcal{V}_i^- = 0$ for $i = 1, \ldots, m$.

(A3) $\mathcal{F}_i = 0$ if $i > m$.

(A4) if $x \in \mathcal{X}_s$ then $\mathcal{F}_i(x) = 0$ and $\mathcal{V}_i^+(x) = 0$ for $i = 1, \ldots, m$.

(A5) if $\mathcal{F}(x)$ is set to zero, then all eigenvalues of $Df(x_0)$ have negative real parts.

**Lemma 3.1** (van den Driessche and Watmough [44]). *If $x_0$ is a DFE of (3.4) and $f_i(x)$ satisfies (A1)-(A5), then the derivatives $D\mathcal{F}(x_0)$ and $D\mathcal{V}(x_0)$ are partitioned as*

$$D\mathcal{F}(x_0) = \begin{bmatrix} F & 0 \\ 0 & 0 \end{bmatrix}, \quad D\mathcal{V}(x_0) = \begin{bmatrix} V & 0 \\ J_3 & J_4 \end{bmatrix},$$

*where $F$ and $V$ are the $m \times m$ matrices defined by*

$$F = \left[ \frac{\partial \mathcal{F}_i}{\partial x_j}(x_0) \right] \quad \text{and} \quad V = \left[ \frac{\partial \mathcal{V}_i}{\partial x_j}(x_0) \right] \quad \text{with} \quad 1 \leq i,\ j \leq m.$$

*Furthermore, $F$ is non-negative, $V$ is a non-singular M-matrix and all eigenvalues of $J_4$ have positive real part.*

The matrix $FV^{-1}$ is then called the *next generation matrix* for the model and the basic reproductive number is defined as

$$\mathcal{R}_0 = \rho(FV^{-1}), \tag{3.5}$$

where $\rho(A)$ denotes the spectral radius of the matrix $A$. The following theorem classifies the stability of the DFE under the conditions of $\mathcal{R}_0$ as a threshold parameter.

**Theorem 3.2** (van den Driessche and Watmough [44])**.** *Consider the disease transmission model given by (3.4) with $f(x)$ satisfying conditions (A1)-(A5). If $x_0$ is a DFE of the model, then $x_0$ is locally asymptotically stable if $\mathcal{R}_0 < 1$, but unstable if $\mathcal{R}_0 > 1$, where $\mathcal{R}_0$ is defined by (3.5).*

**Proposition 3.3.** *$\mathcal{R}_0$ for system (3.1) is defined by*

$$\mathcal{R}_0 = \frac{\beta K}{\alpha + v}.$$

*For any positive parameter values, $(0,0)$ is a saddle. The following conditions characterize the stability of $(K,0)$:*

*i. If $\mathcal{R}_0 < 1$, then $(K,0)$ is locally asymptotically stable.*

*ii. If $\mathcal{R}_0 > 1$, then $(K,0)$ is unstable.*

*Proof.* We begin by letting $x_1 = I$, $x_2 = S$,and $\vec{x} = (x_1, x_2)$. Now we can write system (3.1) in the form

$$\dot{x}_i = \mathcal{F}_i(x) - \mathcal{V}_i(x),$$

where

$$\mathcal{F} = \begin{bmatrix} \beta SI \\ 0 \end{bmatrix} \quad \text{and} \quad \mathcal{V} = \begin{bmatrix} (\alpha + v)I \\ -rN\left(1 - \frac{N}{K}\right) + \beta SI - \alpha I \end{bmatrix}.$$

We then define

$$\mathcal{V}^+ = \begin{bmatrix} 0 \\ rN\left(1 - \frac{N}{K}\right) + \alpha I \end{bmatrix} \quad \text{and} \quad \mathcal{V}^- = \begin{bmatrix} (\alpha + v)I \\ \beta SI \end{bmatrix},$$

where $\mathcal{V}_i = \mathcal{V}_i^- - \mathcal{V}_i^+$. We now demonstrate the assumptions (A1)-(A5) in [44] are satisfied for $\mathcal{F}_i$, $\mathcal{V}_i^+$, and $\mathcal{V}_i^-$. We note $n = 2$ and $m = 1$ for system (3.1) and the set of all disease free states is given by

$$\mathcal{X}_s = \{(0,0),\ (K,0)\}.$$

We label the equilibria $x_0 = (0,0)$ and $x_K = (K,0)$ so that the labels $x_0$ and $x_K$ remain despite rearranging coordinate positions.

(A1) Given $S > 0$ and $I > 0$, then clearly $\beta SI > 0$ and $(\alpha + v)I > 0$ for $\alpha$, $\beta$, and $v > 0$. Hence, $\mathcal{F}_i \geq 0$ and $\mathcal{V}_i^- \geq 0$ for $i = 1,\ 2$. It is possible to have $\mathcal{V}_i^+ < 0$ so we impose the condition

$$N \leq \frac{K}{2}\left(1 + \sqrt{1 + \frac{4\alpha}{rK}I}\right)$$

for $\mathcal{V}_i^+ \geq 0$ for $i = 1,\ 2$. It is noted that the right hand side of the inequality is greater than the population carrying capacity $K$, which is the greater than the bound $S + I \leq K$ on the attracting region $E$.

(A2) Since $m = 1$, set $x_1 = 0$ (which is the same as $I = 0$). Then $\mathcal{V}_i^- = 0$ for $i = 1,\ 2$. Moverover, if $x \in \mathcal{X}_s$ then $\mathcal{V}_i^- = 0$ for $i = 1,\ 2$.

(A3) Clearly, $\mathcal{F}_2 = 0$. So $\mathcal{F}_i = 0$ for $i > m$.

(A4) Consider the disease free states $x_0$ and $x_K$. Then $\beta SI = 0$, implying $\mathcal{F}_i = 0$ for $i = 1,\ 2$. In either case $N = 0$ or $N = K$ along with $I = 0$, we have $rN(1 - N/K) + \alpha I = 0$, implying $\mathcal{V}_i^+ = 0$ for $i = 1,\ 2$.

(A5) To satisfy this assumption, we analyze the Jacobian of system (3.1) when $\mathcal{F}(x)$ is set to zero. That is, we consider the Jacobian of $-\mathcal{V}$ at the DFE $x_K$ given by

$$-D\mathcal{V}(x_K) = \begin{bmatrix} -(\alpha+v) & 0 \\ -r-\beta K+\alpha & -r \end{bmatrix}, \tag{3.6}$$

which has the negative eigenvalues $\lambda_1 = -(\alpha+v)$ and $\lambda_1 = -r$.

Assumptions (A1)-(A5) are now satisfied, so we can use Lemma 3.1. We then have

$$D\mathcal{F}(x_K) = \begin{bmatrix} F & 0 \\ 0 & 0 \end{bmatrix} \quad \text{and} \quad D\mathcal{V}(x_K) = \begin{bmatrix} V & 0 \\ J_3 & J_4 \end{bmatrix}, \tag{3.7}$$

where

$$F = \beta K, \quad V = \alpha + v, \quad J_3 = r + \beta K - \alpha, \quad \text{and} \quad J_4 = r.$$

Furthermore, we note $F$ is nonnegative, $V$ is nonsingular, and $J_4$ has positive real eigenvalues. Then we have

$$\rho(FV^{-1}) = \frac{\beta K}{\alpha + v}.$$

The basic reproductive number is given by $\mathcal{R}_0 = \rho(FV^{-1})$. The equilibrium point is stable for $\mathcal{R}_0 < 1$ and a saddle when $\mathcal{R}_0 > 1$ as a consequence of Theorem 3.2. Now that $\mathcal{R}_0$ for system (3.1) is established, we examine the stability at the origin. We can look at the original formulation. Evaluating the Jacobian at $x_0$, we get

$$J(x_0) = \begin{bmatrix} r & r+\alpha \\ 0 & -(\alpha+v) \end{bmatrix}, \tag{3.8}$$

which has the eigenvalues

$$\lambda_1 = r \quad \text{and} \quad \lambda_2 = -(\alpha + v).$$

The corresponding eigenvectors are given by

$$w_1 = \begin{bmatrix} 1 \\ 0 \end{bmatrix} \quad \text{and} \quad w_2 = \begin{bmatrix} -\frac{\alpha+r}{\alpha+r+v} \\ 1 \end{bmatrix},$$

respectively. **Figure 3.1** shows the stable and unstable manifolds about the origin. The S-coordinate of $w_2$ is always negative, so the stable manifold of $x_0$ is not in the region $\mathbb{R}^+ \times \mathbb{R}^+$. All trajectories in the positive quadrant that are local to $x_0$ will attract toward the S-axis. $\square$

Proposition 3.3 states that the origin is a saddle; however, since the stable manifold touches the space $\mathcal{X}$ only at the origin and the space $\mathcal{X}$ is invariant, then the origin is unstable relative to the space $\mathcal{X}$. See **Figure 3.1**. In other subsystems throughout this chapter, we observe the similar cases for instability about the origin due to the stable manifold being tangent to the positive space and the invariance in the positive space.

Solving the system of equations

$$\begin{aligned} rN\left(1 - \frac{N}{K}\right) - \beta SI + \alpha I = 0 \\ \beta S - (\alpha + v) = 0, \end{aligned} \tag{3.9}$$

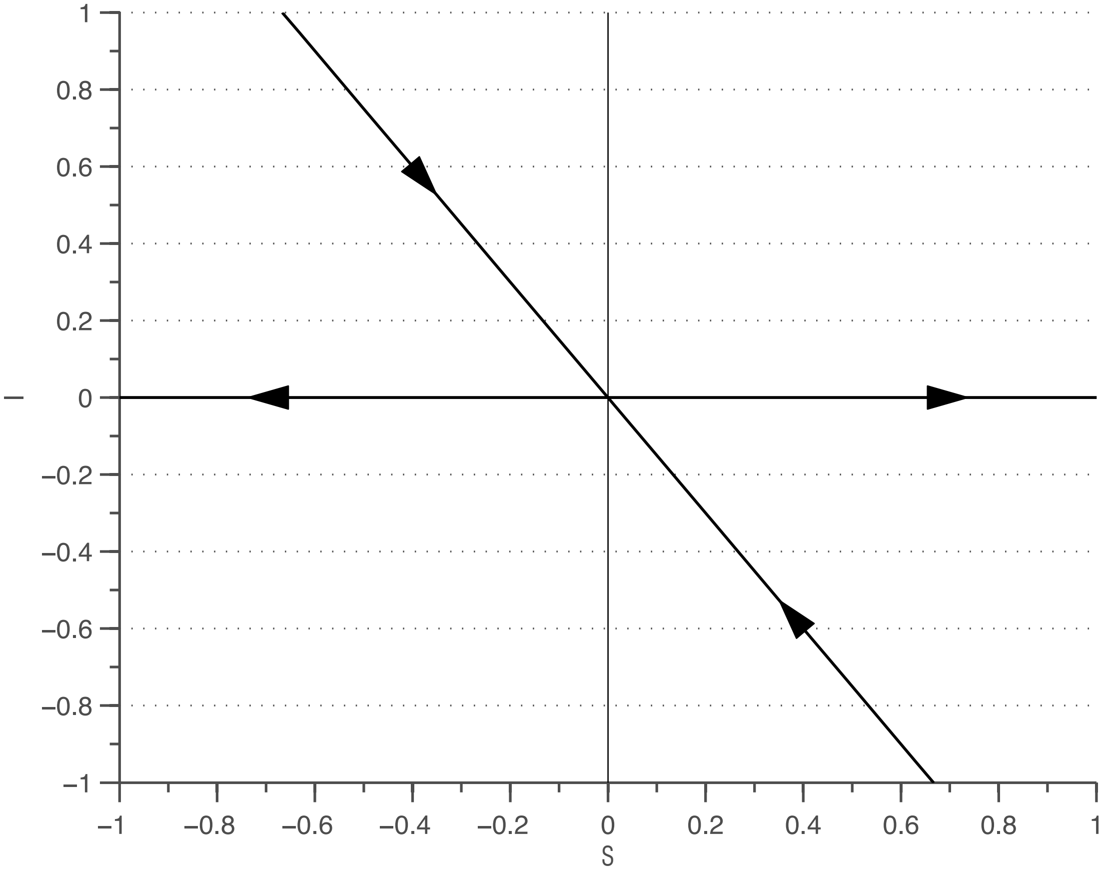

**Figure 3.1:** *The stable and unstable manifolds about the origin. The unstable and stable manifold corresponds to the eigenvector* $w_1$ *and* $w_2$*, respectively. Notice the stable manifold is tangent to the region* $\mathcal{X}$*, which implies the origin is unstable relative to the space* $\mathcal{X}$*.*

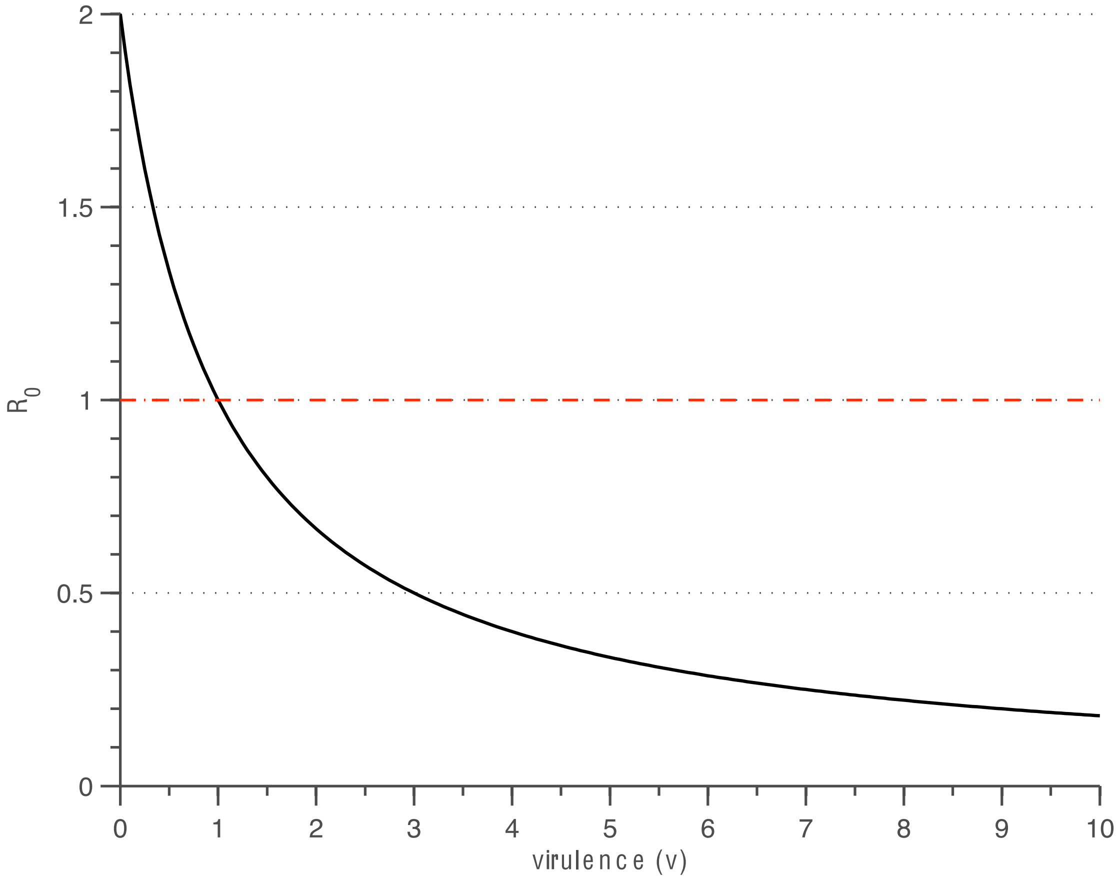

**Figure 3.2:** *Graph of* $R_0$ *versus virulence parameter for system (3.1). Parameter values are* $K = 1$, $\alpha = 0.2$, *and* $\beta = 0.5$.

we obtain a nontrivial equilibrium point $(\hat{S}, \hat{I})$ defined by

$$\left( \frac{\alpha + v}{\beta}, \frac{K}{2}\left(1 - \frac{v}{r}\right) - \hat{S} + \sqrt{\frac{K^2}{4}\left(1 - \frac{v}{r}\right)^2 + \frac{vK\hat{S}}{r}} \right).$$

**Proposition 3.4.** *The nontrivial equilibrium point $(\hat{S}, \hat{I})$ exists for system (3.1) if and only if $\mathcal{R}_0 > 1$. Suppose $(\hat{S}, \hat{I})$ exists, then it is locally asymptotically stable. Moreover, the condition $\mathcal{R}_0 > 1$ gives rise to a locally asymptotically stable, disease endemic equilibrium point.*

*Proof.* We begin the proof by first examining the existence of $(\hat{S}, \hat{I})$. Define $\hat{N}$ to be the sum $\hat{S} + \hat{I}$. $\hat{S}$ is clearly positive, so $\hat{I} > 0$ is a sufficient condition for existence. $\hat{I} > 0$ is equivalent to $\hat{S} < K$, which is then equivalent to $\mathcal{R}_0 > 1$. Therefore, $(\hat{S}, \hat{I})$ exists if and only if $\mathcal{R}_0 > 1$.

Now we examine local stability of $(\hat{S}, \hat{I})$. Evaluating the Jacobian at $(\hat{S}, \hat{I})$, we have

$$\hat{J} = \begin{bmatrix} r\left(1 - \frac{2\hat{N}}{K}\right) - \beta\hat{I} & r\left(1 - \frac{2\hat{N}}{K}\right) - v \\ \beta\hat{I} & 0 \end{bmatrix}, \tag{3.10}$$

which has the trace and determinant

$$tr(\hat{J}) = r\left(1 - \frac{2\hat{N}}{K}\right) - \beta\hat{I} \quad \text{and} \quad \det(\hat{J}) = -\beta\hat{I}\left(r\left(1 - \frac{2\hat{N}}{K}\right) - v\right).$$

Using the equations (3.9), we can rewrite the trace and determinant in the forms

$$tr(\hat{J}) = -\beta\frac{\hat{I}^2}{\hat{N}} - \alpha\frac{\hat{I}}{\hat{N}} - \frac{r\hat{N}}{K}$$

and

$$\det(\hat{J}) = \beta \frac{\hat{I}}{\hat{N}} \left( v\hat{S} + \frac{\hat{N}}{K} \right).$$

Clearly, $tr(\hat{J}) < 0$ and $\det(\hat{J}) > 0$, implying the equilibrium point $(\hat{S}, \hat{I})$ is locally stable. Therefore, $\mathcal{R}_0 > 1$ gives the existence of a stable disease endemic equilibrium point. $\square$

**Lemma 3.5.** *System (3.1) has no limit cycles on the region $E$.*

*Proof.* Clearly the region $E$ is simply connected in $\mathbb{R}^2$. Now define the Dulac function

$$B(S, I) = \frac{1}{SI}.$$

Then

$$\begin{aligned} \bigtriangledown \cdot (Bf) &= \frac{\partial}{\partial S} B \cdot S' + \frac{\partial}{\partial I} B \cdot I' \\ &= \frac{\partial}{\partial S} \left( r \left( \frac{1}{I} + \frac{1}{S} \right) \left( 1 - \frac{S+I}{K} \right) - \beta + \frac{\alpha}{S} \right) + \frac{\partial}{\partial I} \left( \beta - \frac{(\alpha + v)}{S} \right) \\ &= -\frac{r}{S^2} \left( 1 - \frac{S+I}{K} \right) - \frac{r}{K} \left( \frac{1}{S} + \frac{1}{I} \right) - \frac{\alpha}{S^2} \end{aligned}$$

On the region $E$, we have that $0 \leq S + I \leq K$, which in turn implies $\bigtriangledown \cdot (Bf) < 0$. In other words, $\bigtriangledown \cdot (Bf)$ is not identically zero and does not change sign in $E$. Hence, system (3.1) satisfies Dulac's Criteria. We are now able to conclude system (3.1) has no limit cycles on the region $E$. $\square$

We are now ready to make our claim about the global analysis of system (3.1).

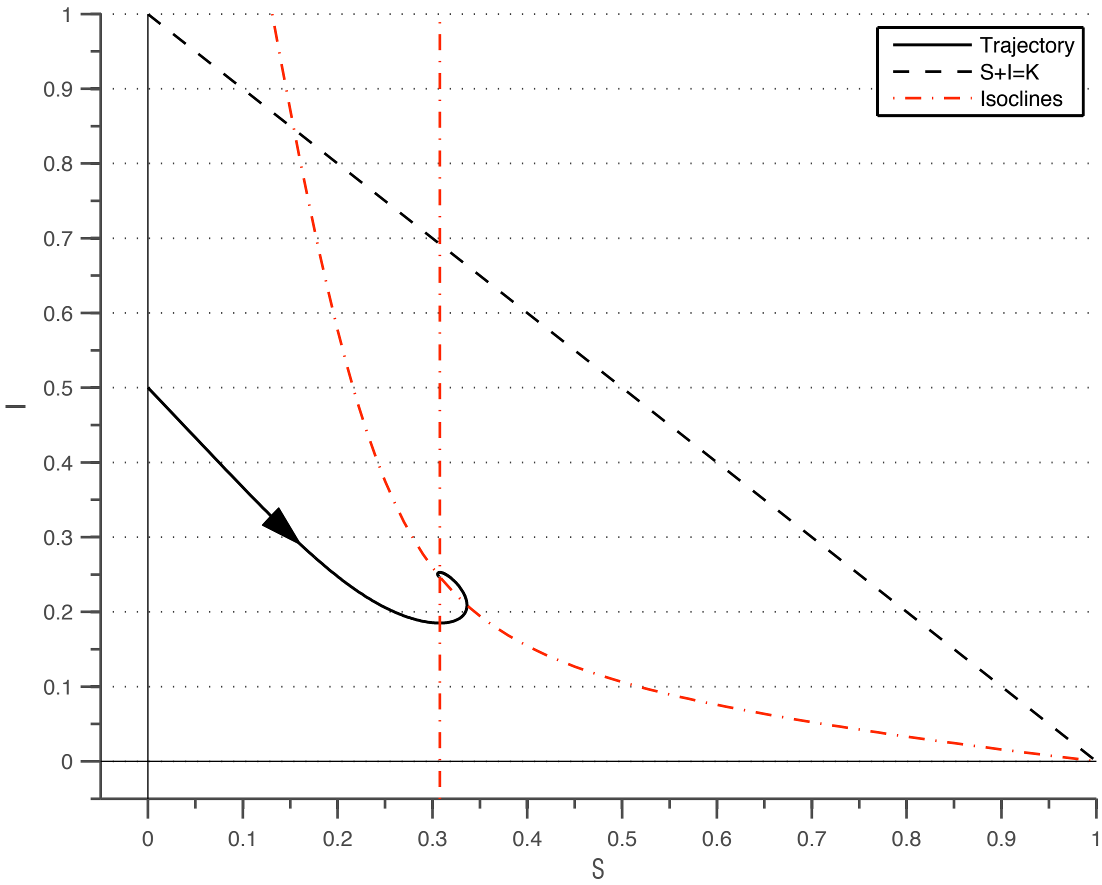

**Figure 3.3:** *Phase portrait for system (3.1). Parameter values are* $r = 0.2$, $K = 1$, $\alpha = 0.2$, $\beta = 1.3$, *and* $v = 0.2$. *Initial conditions are set to* $S(0) = 0$ *and* $I(0) = 0.5$.

**Theorem 3.6.** *Assume $R_0 > 1$. For any initial conditions $S(0) \geq 0$ and $I(0) > 0$, the disease endemic equilibrium point $(\hat{S}, \hat{I})$ is globally attractive. In the case $S(0) > 0$ and $I(0) = 0$, the disease free equilibrium point $(K, 0)$ is globally attractive.*

*Proof.* The $\omega$-limit set for system (3.1) is contained in the attracting region $E$. Lemma 3.5 rules out the possibility of limit cycles in the region $E$. Ruling out limit cycles in a two-dimensional space, the Generalized Poincaré–Bendixson Theorem implies that the $\omega$-limit set consists of a finite number of critical points. See [22] and [41] for statements of theorems. Moreover, the equilibria in the region $E$ are $(0, 0)$, $(K, 0)$, and $(\hat{S}, \hat{I})$, whose asymptotic behavior is classified by Propositions 3.3 and 3.4. Hence, given the condition $\mathcal{R}_0 > 1$, we can conclude the global stability of the equilibrium point corresponding to the given initial conditions. □

## 3.2 The Super-Infection Subsystem

In this section, we consider a super-infection subsystem of the primary host. We take the primary host system of section 2 and remove the interaction with the intermediate host (i.e., $\gamma_1 = \gamma_3 = 0$). The resulting system assumes the third or super strain is already present in the primary host given $J > 0$. That is, one may assume that the resulting system is the primary host scenario after a super strain has emerged and infected the primary host. The resulting super-infection subsystem is given by

$$\begin{aligned}
\frac{dS_1}{dt} &= r_1 N_1 \left(1 - \frac{N_1}{K_1}\right) - \beta_1 S_1 I_1 - \beta_3 S_1 J + \alpha_1 I_1 + \alpha_3 J \\
\frac{dI_1}{dt} &= \beta_1 S_1 I_1 - \delta I_1 J - (\alpha_1 + v_1) I_1 \\
\frac{dJ}{dt} &= \beta_3 S_1 J + \delta I_1 J - (\alpha_3 + v_3) J
\end{aligned} \tag{3.11}$$

with $S_1(0) \geq 0,\ I_1(0) \geq 0,\ J(0) \geq 0.$

Notice, if we set $J = 0$, then the resulting system is the same in form as system (3.1). Super-infection models were considered in [36, 38].

If we look at the sum of the equations of system (3.11), then the differential equation for the total population is given by

$$\frac{dN_1}{dt} = r_1 N_1 \left(1 - \frac{N_1}{K_1}\right) - v_1 I_1 - v_3 J. \tag{3.12}$$

Then comparing to the right-hand side of the inequality (3.3), we get the dissipativity of system (3.11); that is, we have

$$0 \leq \limsup_{t \to \infty} N_1(t) \leq K_1.$$

We denote the space

$$\mathcal{X} = \{(S_1, I_1, J) \in \mathbb{R}^3 : 0 \leq S_1, I_1, J\},$$

and the compact attracting region

$$E = \{(S_1, I_1, J) \in \mathcal{X} : S_1 + I_1 + J \leq K_1\}.$$

### 3.2.1 Qualitative Analysis

Clearly, system (3.11) has the disease free equilbria at $(0, 0, 0)$ and $(K_1, 0, 0)$. We are now ready to calculate the basic reproductive number $\mathcal{R}_0$ for system (3.11). In the case of system (3.11), the $\mathcal{R}_0$ calculated following the framework of [44] is a threshold value that determines when both strains are eradicated when the value is less than one or the existence of an infectious individuals of an unspecified strain type when greater than one. We will denote this threshold parameter by $\mathcal{R}_0^{\max}$. This parameter is somewhat limited for our interest, since it does not determine the existence of both equilibria that are disease free of only one strain; that is, it does not determine the existence of the nontrivial boundary equilibria. To resolve this issue, we will later define the parameter $\mathcal{R}_0^{\min}$ that determines the existence of these boundary equilibria. We define the independent strains' basic reproductive numbers

$$\mathcal{R}_{0,i} = \frac{\beta_i K_1}{\alpha_i + v_i} \quad \text{for } i = 1, 3.$$

**Proposition 3.7.** $\mathcal{R}_0^{\max}$ *for system (3.11) is defined by*

$$\mathcal{R}_0^{\max} = \max_{i=1,3} \{\mathcal{R}_{0,i}\}.$$

*For any positive parameter values,* $(0, 0, 0)$ *is a saddle. The following conditions characterize the stability of* $(K_1, 0, 0)$*:*

*i. If* $\mathcal{R}_0^{\max} < 1$*, then* $(K_1, 0, 0)$ *is locally asymptotically stable.*

*ii. If* $\mathcal{R}_0^{\max} > 1$*, then* $(K_1, 0, 0)$ *is unstable.*

*Proof.* We label the equilibria $x_0 = (0,0,0)$ and $x_K = (K_1, 0, 0)$ so that the labels $x_0$ and $x_K$ remain despite rearranging coordinate positions. We now let $x_1 = I_1$, $x_2 = J$ and $x_3 = S_1$, and $\vec{x} = (x_1, x_2, x_3)$. Now we can write system (3.11) in the form

$$\dot{x}_i = \mathcal{F}_i(\vec{x}) - \mathcal{V}_i(\vec{x}),$$

where

$$\mathcal{F} = \begin{bmatrix} \beta_1 S_1 I_1 \\ \beta_3 S_1 J + \delta I_1 J \\ 0 \end{bmatrix} \quad \text{and} \quad \mathcal{V} = \begin{bmatrix} \delta I_1 J + (\alpha_1 + v_1) I_1 \\ (\alpha_3 + v_3) J \\ -r_1 N_1 \left(1 - \frac{N_1}{K_1}\right) + \beta_1 S_1 I_1 + \beta_3 S_1 J - \alpha_1 I_1 - \alpha_3 J \end{bmatrix}.$$

We then define

$$\mathcal{V}^+ = \begin{bmatrix} 0 \\ 0 \\ r_1 N_1 \left(1 - \frac{N_1}{K_1}\right) + \alpha_1 I_1 + \alpha_3 J \end{bmatrix} \quad \text{and} \quad \mathcal{V}^- = \begin{bmatrix} \delta I_1 J + (\alpha_1 + v_1) I_1 \\ (\alpha_3 + v_3) J \\ \beta_1 S_1 I_1 + \beta_3 S_1 J \end{bmatrix},$$

where $\mathcal{V}_i = \mathcal{V}_i^- - \mathcal{V}_i^+$. It is not difficult to demonstrate conditions (A1)-(A4) in [44] are satisfied, so we draw our attention to condition (A5).

(A5) To satisfy this assumption, we analyze the Jacobian of system (3.11) when $\mathcal{F}(x)$

is set to zero. That is, we consider the Jacobian of $-\mathcal{V}$ at the DFE $x_K$ given by

$$-D\mathcal{V}(x_K) = \begin{bmatrix} -(\alpha_1 + v_1) & 0 & 0 \\ 0 & -(\alpha_3 + v_3) & 0 \\ -r_1 - \beta_1 K_1 + \alpha_1 & -r_1 - \beta_3 K_1 + \alpha_3 & -r_1 \end{bmatrix}, \tag{3.13}$$

which has the negative eigenvalues $\lambda_1 = -(\alpha_1 + v_1)$, $\lambda_2 = -(\alpha_3 + v_3)$, and $\lambda_3 = -r_1$.

Conditions (A1)-(A5) are now satisfied, so we can use Lemma 1 in [44]. We now have

$$D\mathcal{F}(x_K) = \begin{bmatrix} F & 0 \\ 0 & 0 \end{bmatrix} \quad \text{and} \quad D\mathcal{V}(x_K) = \begin{bmatrix} V & 0 \\ J_3 & J_4 \end{bmatrix}, \tag{3.14}$$

where

$$F = \begin{bmatrix} \beta_1 K_1 & 0 \\ 0 & \beta_3 K_1 \end{bmatrix}, \quad V = \begin{bmatrix} \alpha_1 + v_1 & 0 \\ 0 & \alpha_3 + v_3 \end{bmatrix},$$

$$J_3 = \begin{bmatrix} r_1 + \beta_1 K_1 - \alpha_1 & r_1 + \beta_3 K_1 - \alpha_3 \end{bmatrix}, \quad \text{and} \quad J_4 = r_1.$$

Furthermore, we note $F$ is nonnegative, $V$ is nonsingular, and $J_4$ is positive. Then we have the next generation matrix

$$FV^{-1} = \begin{bmatrix} \dfrac{\beta_1 K_1}{\alpha_1 + v_1} & 0 \\ 0 & \dfrac{\beta_3 K_1}{\alpha_3 + v_3} \end{bmatrix},$$

which gives the spectral radius

$$\rho(FV^{-1}) = \max_{i=1,3}\left\{\frac{\beta_i K_1}{\alpha_i + v_i}\right\}.$$

The basic reproductive number is given by $\mathcal{R}_0^{\max} = \rho(FV^{-1})$. The equilibrium point is stable for $\mathcal{R}_0^{\max} < 1$ and unstable when $\mathcal{R}_0^{\max} > 1$.

Now that $\mathcal{R}_0$ for system (3.11) is established, we examine the stability at the origin. Evaluating $J$ at $x_0$, we get

$$J(x_0) = \begin{bmatrix} r_1 & r_1 + \alpha_1 & r_1 + \alpha_3 \\ 0 & -(\alpha_1 + v_1) & 0 \\ 0 & 0 & -(\alpha_3 + v_3) \end{bmatrix}, \tag{3.15}$$

which has the eigenvalues

$$\lambda_1 = r_1, \quad \lambda_2 = -(\alpha_1 + v_1), \quad \text{and} \quad \lambda_3 = -(\alpha_3 + v_3).$$

The corresponding eigenvectors are given by

$$w_1 = \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix}, \quad w_2 = \begin{bmatrix} -\frac{\alpha_1 + r_1}{\alpha_1 + v_1 + r_1} \\ 1 \\ 0 \end{bmatrix} \quad \text{and} \quad w_3 = \begin{bmatrix} -\frac{\alpha_3 + r_1}{\alpha_3 + v_3 + r_1} \\ 0 \\ 1 \end{bmatrix},$$

respectively. The stable manifold of $x_0$ is tangent to the region $E$. All trajectories in the positive quadrant that are local to $x_0$ will attract toward the S-axis. □

We now examine the boundary of $\mathcal{X}$. Define the index set $\Lambda = \{0,1,2\}$. We denote the hyperplanes

$$\begin{aligned} H_0 &= \{(S_1, I_1, J) \in \mathcal{X} : S_1 = 0\}, \\ H_1 &= \{(S_1, I_1, J) \in \mathcal{X} : I_1 = 0\}, \\ H_2 &= \{(S_1, I_1, J) \in \mathcal{X} : J = 0\}. \end{aligned}$$

The boundary of $\mathcal{X}$ is then given by

$$\partial\mathcal{X} = \bigcup_{\sigma\in\Lambda} H_\sigma.$$

Considering the restriction to $H_0$, the trajectories with at least one nonzero component (i.e., we rule out the possibility that all components are zero) of system (3.11) will flow off of $\partial\mathcal{X}$ into the interior of $\mathcal{X}$. Turning to the hyperplanes $H_1$ and $H_2$, system (3.11) is then reduced to system (3.1) on each hyperplane respectively. For example on $H_1$, all terms with $I_1$ in system (3.11) are zeroed out, and the time derivative of $I_1$ is set to zero; hence, the system becomes system (3.11) with subscripts of 2 on the respective parameters. This allows us to apply the results from section (3.1) on $H_1$ and $H_2$. It is then noted that $H_1$ and $H_2$ are the only invariant subspaces of the boundary.

Each of the invariant boundary subspaces has an equilibrium point that is disease free of one strain and disease endemic in the other strain. The nontrivial boundary equilibrium points are denoted by $(\hat{S}_1, \hat{I}_1, 0) \in H_2$ and $(\check{S}_1, 0, \check{J}) \in H_1$. Define the threshold parameter

$$\mathcal{R}_0^{\min} = \min_{i=1,3} \{\mathcal{R}_{0,i}\}.$$

Then condition that $\mathcal{R}_0^{\min} > 1$ is sufficient for each point to exist and to be globally asymptotically stable when the flow is restricted to the relative invariant subspace. We now develop stability conditions for each equilibrium point relative to the whole space $\mathcal{X}$. We continue with the following proposition:

**Proposition 3.8.** *Consider system (3.11) on the space $\mathcal{X}$, and suppose the condition*

$$\mathcal{R}_{0,1} > 1 \tag{3.16}$$

*holds. Define*

$$\mathcal{R}_1 = \frac{\beta_3 \hat{S}_1 + \delta \hat{I}_1}{\alpha_3 + v_3}$$

*Then the following conditions classify the stability of $(\hat{S}_1, \hat{I}_1, 0)$*

*i. If $\mathcal{R}_1 < 1$, then $(\hat{S}_1, \hat{I}_1, 0)$ is locally asymptotically stable.*

*ii. If $\mathcal{R}_1 > 1$, then $(\hat{S}_1, \hat{I}_1, 0)$ is unstable.*

*Proof.* We evaluate the Jacobian of system (3.11) at $(\hat{S}_1, \hat{I}_1, 0)$ to get

$$J(\hat{S}_1, \hat{I}_1, 0) = \begin{bmatrix} r_1\left(1 - \frac{2\hat{N}_1}{K_1}\right) - (\alpha_1 + v_1) & r\left(1 - \frac{2\hat{N}_1}{K_1}\right) - v_1 & r_1\left(1 - \frac{2\hat{N}_1}{K_1}\right) - \beta_3 \hat{S}_1 + \alpha_3 \\ \beta_1 \hat{I}_1 & 0 & -\delta \hat{I}_1 \\ 0 & 0 & \beta_3 \hat{S}_1 + \delta \hat{I}_1 - (\alpha_3 + v_3) \end{bmatrix},$$

where $\hat{N}_1 = \hat{S}_1 + \hat{I}_1$. The upper left $2 \times 2$ matrix of $J(\hat{S}_1, \hat{I}_1, 0)$ is the matrix (3.10) subscripted with index 1, so the condition (3.16) is sufficient to show the two corresponding eigenvalues have negative real part. The third eigenvalue is then given by the lower right entry

$$\lambda = \beta_3 \hat{S}_1 + \delta \hat{I}_1 - (\alpha_3 + v_3).$$

This eigenvalue is real-valued, and whether it is positive or negative is equivalent to $\mathcal{R}_1$ being greater than or less than one, respectively. $\square$

**Proposition 3.9.** *Consider system (3.11) on the space $\mathcal{X}$, and suppose the condition*

$$\mathcal{R}_{0,3} > 1 \tag{3.17}$$

*holds. Define*

$$\mathcal{R}_3 = \frac{\beta_1 \check{S}_1}{\delta \check{J} + \alpha_1 + v_1}$$

*Then the following conditions classify the stability of $(\check{S}_1, 0, \check{J})$*

*i. If $\mathcal{R}_3 < 1$, then $(\check{S}_1, 0, \check{J})$ is locally asymptotically stable.*

*ii. If $\mathcal{R}_3 > 1$, then $(\check{S}_1, 0, \check{J})$ is unstable.*

*Proof.* We evaluate the Jacobian of system (3.11) at $(\check{S}_1, 0, \check{J})$ to get

$$J(\check{S}_1, 0, \check{J}) = \begin{bmatrix} r_1\left(1 - \frac{2\check{N}_1}{K_1}\right) - (\alpha_3 + v_3) & r\left(1 - \frac{2\check{N}_1}{K_1}\right) - \beta_1 \check{S}_1 + \alpha_1 & r_1\left(1 - \frac{2\check{N}_1}{K_1}\right) - v_3 \\ 0 & \beta_1 \check{S}_1 - \delta \check{J} - (\alpha_1 + v_1) & 0 \\ \beta_3 \check{J} & \delta \check{J} & 0 \end{bmatrix}.$$

where $\check{N} = \check{S}_1 + \check{J}$. The eigenvalues of $J(\check{S}_1, 0, \check{J})$ are the same as the Jacobian (3.10) given the corresponding subscripts and

$$\lambda = \beta_1 \check{S}_1 - \delta \check{J} - (\alpha_1 + v_1).$$

This eigenvalue is real-valued, and it is positive or negative is equivalent to $\mathcal{R}_3$ greater than or less than one, respectively. $\square$

To prove permanence in system (3.11), we follow arguments proposed in [18]. We look at the flow $\Im$ on the boundary of $\mathcal{X}$. We denote the restriction of $\Im$ to $\partial\mathcal{X}$ by $\partial\Im$ on $\partial\mathcal{X}$. Let $\mathcal{N}$ be the maximal invariant set of $\partial\Im$ on $\partial\mathcal{X}$. We then find a cover $\{\mathcal{N}_\sigma\}_{\sigma\in\Lambda}$, where $\Lambda$ is an index set. $\mathcal{N}_\sigma \subset \partial\mathcal{X}$, $\mathcal{N} \subset \cup_{\sigma\in\Lambda}\mathcal{N}_\sigma$, and $\mathcal{N}_\sigma$ $(\sigma \in \Lambda)$ are pairwise disjoint closed invariant sets. The sets must also satisfy the following hypothesis:

**(H)** (a) All $\mathcal{N}_\sigma$ are isolated invariant sets of the flow $\Im$.

(b) $\{\mathcal{N}_\sigma\}_{\sigma\in\Lambda}$ is acyclic, that is, any finite subset of $\{\mathcal{N}_\sigma\}_{\sigma\in\Lambda}$ does not form a cycle.

(c) Any compact subset of $\partial E$ contains, at most, finitely many sets of $\{\mathcal{N}_\sigma\}_{\sigma\in\Lambda}$.

Once the invariant sets $\mathcal{N}_\sigma$ satisfy the three conditions of hypothesis **(H)** for all $\sigma \in \Lambda$, the following theorem is applied to establish uniform persistence.

**Theorem 3.10** (Freedman, Ruan, Tang [18])**.** *Let $Y$ be a closed positively invariant subset of $\mathcal{X}$ on which a continuous flow $\Im$ is defined. Suppose there is a constant $\alpha > 0$ such that $\Im$ is point dissipative on $S[\partial Y, \alpha] \cap \mathring{Y}$ and the assumption* **(H)** *holds. Then the flow $\Im$ is uniformly persistent if and only if*

$$W^+(\mathcal{N}_\sigma) \cap S[\partial Y, \alpha] \cap \mathring{Y} = \emptyset$$

*for any $\sigma \in \Lambda$, where $W^+(\mathcal{N}_\sigma) = \{y \in \mathcal{X} : \gamma^+(y) \subset \mathcal{N}_\sigma\}$.*

A dissipative system is bounded, so it follows that it is also point dissipative. That is, system (3.11) is dissipative on the $\mathring{\mathcal{X}}$, so clearly it is point dissipative for any $\alpha > 0$ on $S[\partial\mathcal{X}, \alpha] \cap \mathring{\mathcal{X}}$. Therefore, the conditions that assumption **(H)** holds and $W^+(\mathcal{N}_\sigma) \cap \mathring{\mathcal{X}} = \emptyset$ are sufficient to satisfy the premises of Theorem 3.10.

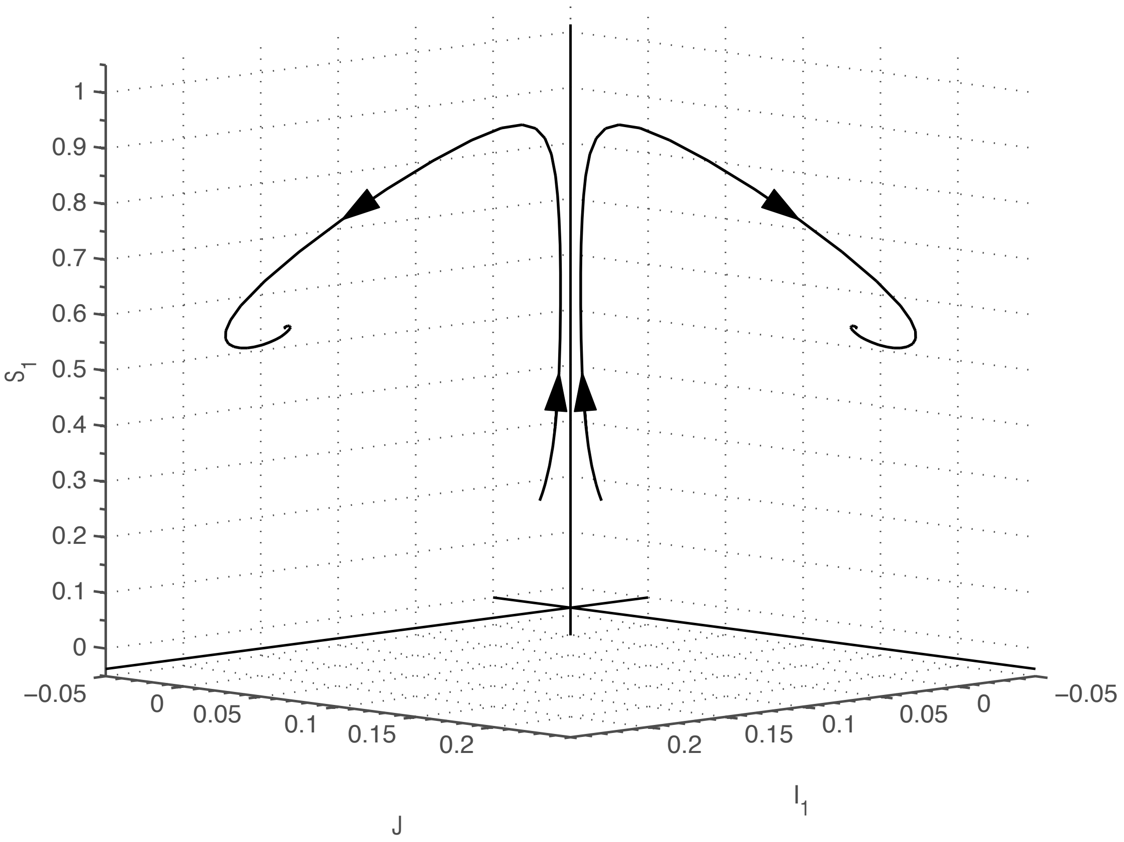

**Figure 3.4:** *The trajectories on the boundary of $E$ for subsystem (3.11). Given the condition $\mathcal{R}_0^{\min} > 1$, there exist an interior equilibrium point on each of the invariant sets $\mathcal{N}_1$ and $\mathcal{N}_2$. These equilibria are both globally stable relative to the respective invariant set; hence, $\{\mathcal{N}_\sigma\}_{\sigma\in\Lambda}$ is acyclic, and condition (b) of hypothesis* **(H)** *is satisfied.*

We are now ready to prove conditions for permanence in system (3.11). $\Lambda = \{0, 1, 2\}$ is the nonempty index set. The maximal invariant set $\mathcal{N}$ of $\partial\Im$ is $\mathcal{N} = H_1 \cup H_2$. We note $\mathcal{N}$ is a closed invariant set and define the cover $\{\mathcal{N}_\sigma\}_{\sigma\in\Lambda}$ of $\mathcal{N}$ by

$$\begin{aligned}
\mathcal{N}_0 &= \{(S_1, I_1, J) \in \mathcal{X} : I_1 = J = 0\}, \\
\mathcal{N}_1 &= \{(S_1, I_1, J) \in \mathcal{X} : I_1 > 0, J = 0\}, \\
\mathcal{N}_2 &= \{(S_1, I_1, J) \in \mathcal{X} : I_1 = 0, J > 0\},
\end{aligned}$$

and we note

$$\mathcal{N} = \bigcup_{\sigma\in\Lambda} \mathcal{N}_\sigma$$

and $\mathcal{N}_\sigma \subset \partial\mathcal{X}$. We also note that $\mathcal{N}_\sigma$ $(\sigma \in \Lambda)$ are pairwise disjoint closed invariant sets.

**Lemma 3.11.** *Suppose $\mathcal{R}_0^{\min} > 1$. The pairwise disjoint closed invariant sets given by $\mathcal{N}_\sigma$ $(\sigma \in \Lambda)$ satisfy hypothesis* **(H)**.

*Proof.* Assumption (a). First, we consider the flow $\Im$ restricted to $\mathcal{N}_0$. $I_1$ and $J$ are equal to zero and hence their respective differential equations of system (3.11) are set to zero. Moreover, system (3.11) is reduced to the logistic growth differential equation with respect to the susceptive subclass. Hence, $\mathcal{N}_0$ is an isolated invariant set of the flow $\Im$. Next, we consider the flow $\Im$ restricted to $\mathcal{N}_1$. In this case, $J = 0$ and $S_1 \geq 0$, $I_1 > 0$, and system (3.11) is reduced to system (3.1) on $\mathcal{N}_1$. That is, given $\mathcal{R}_0^{\min} > 1$, any initial conditions on $\mathcal{N}_1$ globally attract to the equilibrium point $(\hat{S}_1, \hat{I}_1, 0)$ (see Theorem 3.6). Hence, $\mathcal{N}_1$ is an isolated invariant set of the flow $\Im$. Finally, the case of $\mathcal{N}_2$ is analogous to the case of $\mathcal{N}_1$ with trajectories globally attracting toward $(\check{S}_1, 0, \check{J})$ on $\mathcal{N}_2$ for $\mathcal{R}_0^{\min} > 1$. Therefore, assumption (a) is satisfied.

Assumption (b). Given $\mathcal{R}_0^{\min} > 1$, $(K_1, 0, 0)$ is globally attractive on $\mathcal{N}_0$ with the exception of the origin. $(\hat{S}_1, \hat{I}_1, 0)$ is globally attractive on $\mathcal{N}_1$ as a consequence of Theorem 3.6. $(\check{S}_1, 0, \check{J})$ is globally attractive on $\mathcal{N}_2$. Hence, given $\mathcal{R}_0^{\min} > 1$, no trajectories can form a cycle for any finite collection of $\{\mathcal{N}_\sigma\}_{\sigma\in\Lambda}$. **Figure 3.4** shows the acyclic behavior on the boundary of $E$. Therefore, $\{\mathcal{N}_\sigma\}_{\sigma\in\Lambda}$ is acyclic, and assumption (b) is satisfied.

Assumption (c). There are a finite number of sets of $\{\mathcal{N}_\sigma\}_{\sigma\in\Lambda}$ , so clearly any compact set of the boundary will contain only a finitely many sets of $\{\mathcal{N}_\sigma\}_{\sigma\in\Lambda}$. Hence, assumption (c) is satisfied. □

**Theorem 3.12.** *Suppose* $\mathcal{R}_0^{\min} > 1$ *and* $\mathcal{R}_i > 1$ *for* $i = 1, 3$. *For any initial conditions not contained in the maximal invariant set* $\mathcal{N}$, *system (3.11) exhibits permanence. Moreover, there exists an equilibrium point with all components positive.*

*Proof.* First, we note that for $\mathcal{R}_0^{\min} > 1$, $\mathcal{R}_1 > 1$, and $\mathcal{R}_3 > 1$, $W^+(\mathcal{N}_i) = \mathcal{N}_i$ for $i = 0,\ 1,\ 2$, respectively. Hence, $W^+(\mathcal{N}_\sigma) \cap \mathring{\mathcal{X}} = \emptyset$ for all $\sigma \in \Lambda$. This result together with Lemma 3.11, we are now able to apply Theorem 3.10. Hence, the flow of system (3.11) is uniformly persistent. The upper-bound from the dissipativity of system (3.11) implies uniformly persistent is equivalent to permanence. □

To establish the existence of equilibria on $\mathring{\mathcal{X}}$, we use the following three theorems from [27]. The first two theorems are accredited to Schauder and Horn, respectively.

**Theorem 3.13** (Schauder [49])**.** *Let* $U$ *be a nonempty bounded open convex subset of the Banach space* $E$, *and suppose that* $A : E \to E$ *is completely continuous. Assume that for some fixed prime* $p \geq 2$, $A^k\bar{U} \subset U$ *for* $k = p,\ p + 1$. *Then* $A$ *has a fixed point.*

**Theorem 3.14** (Horn [26]). *Let* $U_0 \subset U_1 \subset U_2$ *be convex subsets of the Banach space* $E$ *with* $U_0$ *and* $U_2$ *compact and* $U_1$ *open in* $U_2$*. Let* $A : U_2 \to E$ *be continuous and assume that* $A^j U_1 \subset U_2$ $(j \in \mathbb{Z}^+)$*. Suppose also that there exists an integer* $m > 0$ *such that* $A^j U_1 \subset U_0$ *for* $j \geq m$*. Then* $A$ *has a fixed point in* $U_0$*.*

**Theorem 3.15** (Hutson, Schmitt [27]). *Suppose that permanence holds for the set of differential equations (3.11). Then there exists an equilibrium point in* $\overset{\circ}{\mathcal{X}}$*.*

To calculate the equilibria in $\overset{\circ}{\mathcal{X}}$, we first note the equilibria will satisfy the system of equations

$$\begin{aligned} r_1 N_1 \left(1 - \frac{N_1}{K_1}\right) - v_1 I_1 - v_3 J &= 0 \\ \beta_1 S - \delta J - (\alpha_1 + v_1) &= 0 \\ \beta_3 S + \delta I - (\alpha_3 + v_3) &= 0. \end{aligned}$$

Using the second and third equations, we can write the variables $N_1$, $I_1$, and $J$ as linear equations of $S_1$, as follows

$$J = \frac{\beta_1}{\delta} S - \frac{v_1 + \alpha_1}{\delta}, \quad I_1 = -\frac{\beta_3}{\delta} S + \frac{v_3 + \alpha_3}{\delta},$$

$$\text{and} \quad N_1 = \left(1 + \frac{\beta_1 - \beta_3}{\delta}\right) S + \frac{1}{\delta}\left((v_3 + \alpha_3) - (v_1 + \alpha_1)\right).$$

Then the $S_1$-coordinates of the equilibria are a solution to the quadratic equation

$$c_2 S_1^2 + c_1 S_1 + c_0 = 0,$$

where

$$\begin{aligned}
c_2 &= \left(1+\frac{\beta_1-\beta_3}{\delta}\right)^2\\
c_1 &= \left[2\left(\frac{\alpha_3+v_3}{\delta}-\frac{\alpha_1+v_1}{\delta}\right)-K_1\right]\left(1+\frac{\beta_1-\beta_3}{\delta}\right)+\frac{K_1}{r_1\delta}(v_3\beta_1-v_1\beta_3)\\
c_0 &= \left(\frac{\alpha_3+v_3}{\delta}-\frac{\alpha_1+v_1}{\delta}\right)\left(\frac{\alpha_3+v_3}{\delta}-\frac{\alpha_1+v_1}{\delta}-K_1\right)+\frac{K_1}{r_1\delta}\left(v_1\alpha_3-v_3\alpha_1\right).
\end{aligned} \tag{3.18}$$

Hence, the $S_1$-coordinates of the equilibria satisfy the quadratic formula

$$S* = \frac{-c_1 \pm \sqrt{c_1^2-4c_0c_2}}{2c_2},$$

and the equilibria in $\overset{\circ}{\mathcal{X}}$ have the form

$$\left(S*,\ -\frac{\beta_3}{\delta}S*+\frac{v_3+\alpha_3}{\delta},\ \frac{\beta_1}{\delta}S*-\frac{v_1+\alpha_1}{\delta}\right).$$

We now consider other possibilities for permanence in system (3.11). That is, we give conditions for permanence when $\mathcal{R}_0^{\max} > 1$ and $\mathcal{R}_0^{\min} < 1$. We state the following proposition:

**Proposition 3.16.** *Suppose* $\mathcal{R}_0^{\max} > 1$ *and* $\mathcal{R}_0^{\min} < 1$.

*i. Let* $\mathcal{R}_{0,1} > 1$ *and* $\mathcal{R}_{0,3} < 1$. *If* $\mathcal{R}_1 > 1$, *then system (3.11) exhibits permanence.*

*ii. If* $\mathcal{R}_{0,1} < 1$ *and* $\mathcal{R}_{0,3} > 1$, *then system (3.11) does not exhibit permanence.*

*Proof.* In the first case, since $\mathcal{R}_{0,1} > 1$ and $\mathcal{R}_{0,3} < 1$, the only nontrivial boundary equilibrium point is at $(\hat{S}_1, \hat{I}_1, 0)$. $(\hat{S}_1, \hat{I}_1, 0)$ is unstable when $\mathcal{R}_1 > 1$. We use a similar argument to Theorem 3.12. Therefore, system (3.11) exhibits permanence when $\mathcal{R}_1 > 1$. In the latter case, if $\mathcal{R}_{0,1} < 1$ then $\mathcal{R}_3 < 1$, and all interior trajectories converge to $(\check{S}_1, 0, \check{J})$; hence there is no permanence. $\square$

Proposition 3.16 suggests system (3.11) exhibits permanence despite $\mathcal{R}_{0,3} < 1$; that is, the super-strain can persist with its independent basic reproductive number less than one. The conditions $\mathcal{R}_{0,1} > 1$, $\mathcal{R}_{0,3} < 1$, and $\mathcal{R}_1 > 1$ is another sufficient parameter spaces for the system to exhibit permanence; however, to satisfy such a condition, a necessary but not sufficient requirement is $\delta > \beta_3$.

### 3.2.2 Quantitative Analysis and Simulations

To simulate an example of seasonal and avian influenza strains in a population, we use data from Thailand. Thailand is a likely locale here, due to the surveillance of influenza strains throughout the country and the prevalence of the avian strain H5N1.

To determine the carrying capacity, initial susceptible population size, and population growth rate, we consider data on the total population of Thailand [37]. **Table 3.1** shows the data from the National Statistics Office of Thailand. The current Thai population of 65,493,298 [7] was also included in the data. We then best-fit the data to the to the solution of the logistic equation given by

$$p(t) = \frac{KP_0e^{rt}}{K + P_0(e^{rt} - 1)},$$

using the method of least squares. The parameters were determined using iterative methods: $K = 87.3291,\ S_0 = 3.983,\ r = 0.038$. **Figure 3.5** is the graph of the data with the best-fit logistic solution. In a study by the National Institute of Health in Thailand [45], case specimens of influenza were taken from patients in 2004 and 2005.

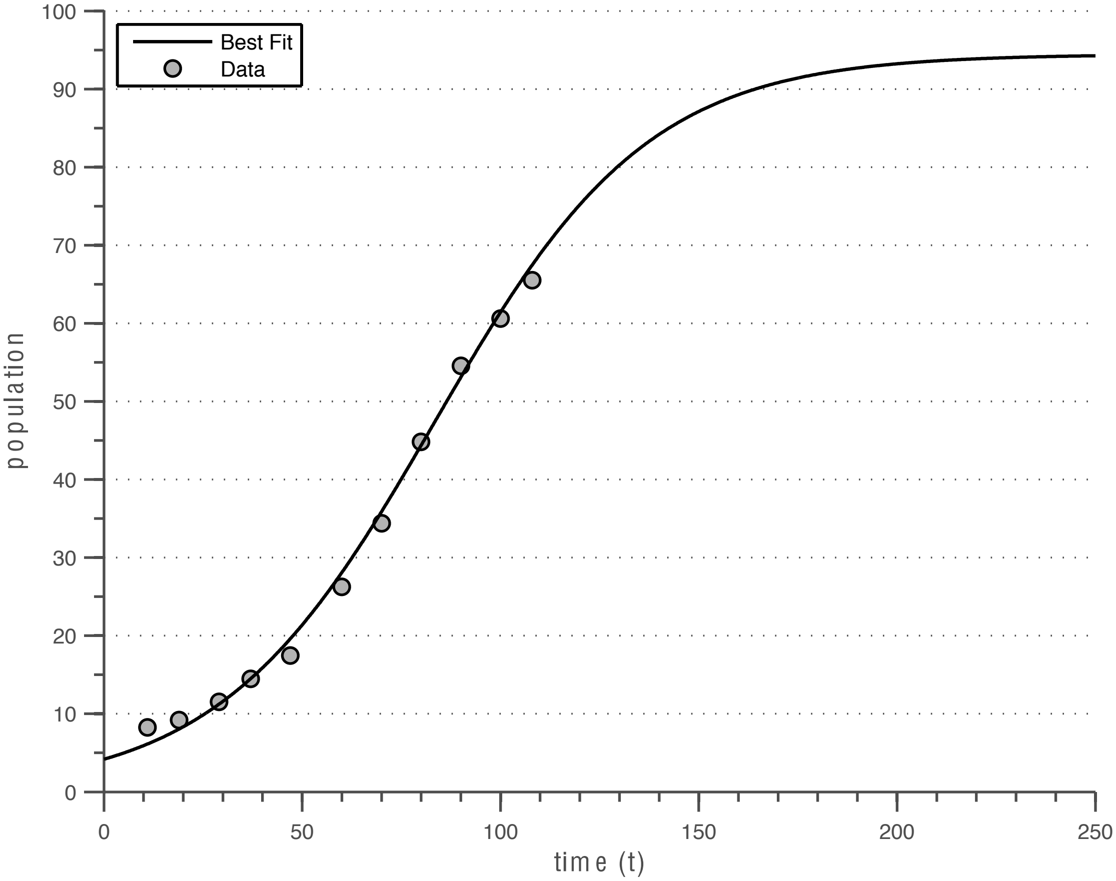

**Figure 3.5:** *Graph of the data from the National Statistics Thailand [37] and the best-fit solution of the logistic solution. Parameter values are* $K = 87.33,\ S_0 = 3.98,\ \textit{and}\, r = 0.038.$ $R^2 = 1 - (\textit{Residual sum of squares})/(\textit{Corrected sum of squares}) = 0.977.$

**Table 3.1:** *Population of Thailand from 1911 to 2000. Information provided by the National Statistics Office Thailand [37].*

| Year | Population |
|---|---|
| 1911 | 8,266,408 |
| 1919 | 9,207,355 |
| 1929 | 11,506,207 |
| 1937 | 14,464,105 |
| 1947 | 17,442,689 |
| 1960 | 26,257,916 |
| 1970 | 34,397,374 |
| 1980 | 44,824,540 |
| 1990 | 54,548,530 |
| 2000 | 60,606,947 |

It was determined that the number of cases of influenza-like illness (ILI) for 2004 and 2005 were 21,176 and 21,351 cases per 100,000 population. The study reported influenza positive specimens. For 2004, it was determined that 12.0% of the specimens were determined to have influenza A, and of those positive for Influenza A, 3.3% were determined to have H5N1 while 96.7% did not. **Table 3.2** shows the data of the different influenza types and subtypes from the study. This information is applied to the reports that the total number of clinical cases of ILI in 2004 was 21,176 cases per 100,000 population. From these data, we chose the seasonal incidence of influenza to

**Table 3.2:** *Table 1 of [45]. This table gives a breakdown of the influenza types and subtypes from the case specimens in 2004-2005.*

| Year | No. of specimens | No. of positives | Type | | Subtype of A | |
|---|---|---|---|---|---|---|
| | | | Influenza A | Influneza B | H1N1 | H3N2 |
| 2004 | 3,854 | 539 | 461 | 78 | 249 | 197 |
| 2005 | 3,834 | 748 | 492 | 256 | 55 | 437 |

$\beta_1 = 0.0245$ and the avian strain to be $\beta_3 = 0.00084$. A summary report on influenza in Asian countries [23] from 1999 cites the annual mortality due to pneumonia was 176 per 100,000 population, so we let $v_1 = 0.00176$ and $\alpha_1 = 1 - v_1 = 0.99824$. The World Health Organization report on June 19, 2008 [48] recorded the number of confirmed 25 cases and 17 deaths due to H5N1 in Thailand, so we let $v_3 = 0.68$ and $\alpha_3 = 1 - v_3 = 0.32$. The incidence rate $\delta$ is left undefined as a bifurcation parameter.

Calculating the basic reproductive values, we get $\mathcal{R}_0^{\min} = 0.079$ and $\mathcal{R}_0^{\max} = 2.313$. This result implies that the only nontrivial boundary equilibrium is at $(\hat{S}, \hat{I}_1, 0) = (40.8, 51.1, 0)$. Hence, the condition for permanence is $\mathcal{R}_1 > 1$. The calculated value of $\mathcal{R}_1$ in terms of $\delta$ is given by $\mathcal{R}_1 = 0.0343 + 51.1\delta$. Then the condition that $\delta > 0.0189$ is equivalent to $\mathcal{R}_1 > 1$. Therefore, it is noted that subclass $J$ infected by the super-strain eradicates for $\delta < 0.0189$.

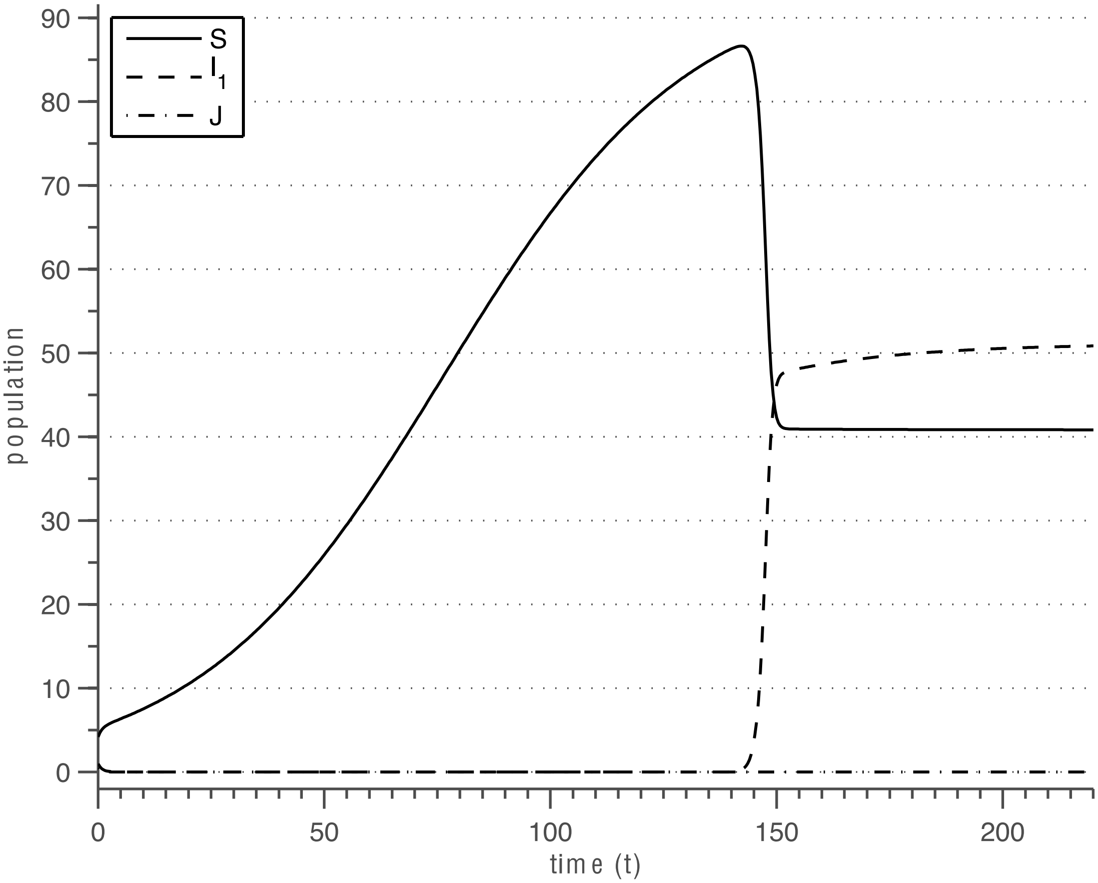

**Figure 3.6:** *Population densities of the subclasses of system (3.11) versus time. Parameter values are* $r_1 = 0.037$*,* $K_1 = 94.455$*,* $\beta_1 = 0.0245$*,* $\beta_3 = 0.00084$*,* $\alpha_1 = 0.99824$*,* $\alpha_3 = 0.32$*,* $v_1 = 0.00176$*,* $v_3 = 0.68$*, and* $\delta = 0.00084$*. Initial conditions are set to* $S(0) = 4.181$*,* $I_1(0) = 1.0$*, and* $J(0) = 0.483$*. The trajectories attract to the super-strain free equilibrium point* $(40.8, 51.1, 0.0)$.

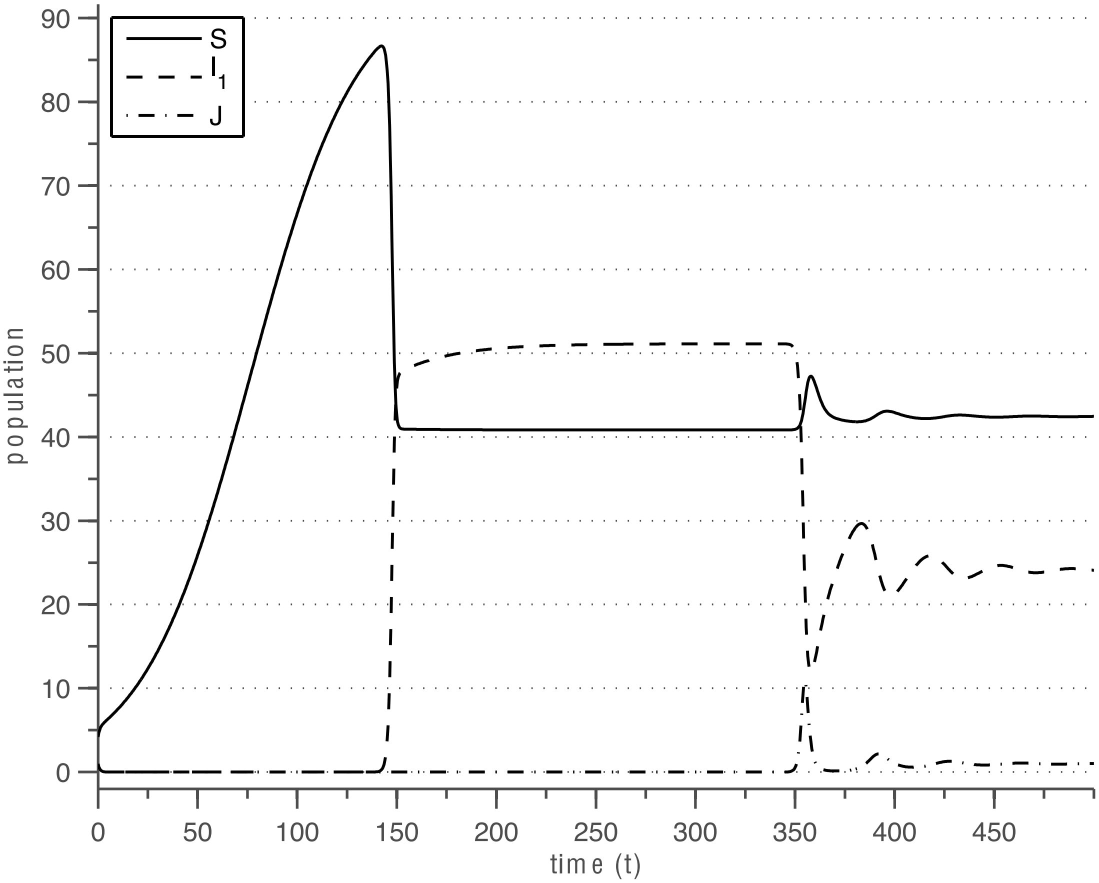

**Figure 3.7:** *Population densities of the subclasses of system (3.11) versus time. Parameter values are* $r_1 = 0.037$, $K_1 = 94.455$, $\beta_1 = 0.0245$, $\beta_3 = 0.00084$, $\alpha_1 = 0.99824$, $\alpha_3 = 0.32$, $v_1 = 0.00176$, $v_3 = 0.68$, *and* $\delta = 0.04$. *Initial conditions are set to* $S(0) = 4.181$, $I_1(0) = 1.0$, *and* $J(0) = 0.483$. *The trajectories attract to the endemic equilibrium point* $(42.4, 24.1, 1.0)$.

## 3.3 The Co-Infection Subsystem

In this section, we consider a co-infection subsystem of the intermediate host. We take the intermediate host system of Section 2 and remove the interaction with the primary and secondary host (i.e., $g_1 = g_2 = 0$). The resulting system assumes two strains are already present in the intermediate host system. In this scenario, there is no possibility of genetic recombination in the co-infected subclass. The resulting co-infection subsystem is given by

$$\begin{aligned}
\frac{dX}{dt} &= r_X N_X \left(1 - \frac{N_X}{K_X}\right) - \sum_{i=1}^{2} b_i (Y_i + d_i Y_{12}) X + a_1 Y_1 + a_2 Y_2 + a_{12} Y_{12} \\
\frac{dY_1}{dt} &= b_1 (Y_1 + d_1 Y_{12}) X - b_{12} Y_1 Y_2 - (a_1 + u_1) Y_1 \\
\frac{dY_2}{dt} &= b_2 (Y_2 + d_2 Y_{12}) X - b_{21} Y_1 Y_2 - (a_2 + u_2) Y_2 \\
\frac{dY_{12}}{dt} &= (b_{12} + b_{21}) Y_1 Y_2 - (a_{12} + u_{12}) Y_{12}
\end{aligned} \tag{3.19}$$

with $X(0) \geq 0,\ Y_1(0) \geq 0,\ Y_2(0) \geq 0,\ Y_{12}(0) \geq 0.$

If we look at the sum of the equations of system (3.19), then the differential equation for total population is given by

$$\frac{dN_X}{dt} = r_X N_X \left(1 - \frac{N_X}{K_X}\right) - u_1 Y_1 - u_2 Y_2 - u_{12} Y_{12}. \tag{3.20}$$

Again, comparing to the right-hand side of the inequality (3.3), we get the dissipativity of system (3.19); that is, we have

$$0 \leq \limsup_{t\to\infty} N_X(t) \leq K_X.$$

We denote the space

$$\mathcal{X} = \{(X, Y_1, Y_2, Y_{12}) \in \mathbb{R}^4 : 0 \leq X, Y_1, Y_2, Y_{12}\},$$

and the attracting region

$$E = \{(X, Y_1, Y_2, Y_{12}) \in \mathcal{X} : X + Y_1 + Y_2 + Y_{12} \leq K_X\}.$$

### 3.3.1 Qualitative Analysis

Clearly, system (3.19) has the disease free equilbria $(0, 0, 0, 0)$ and $(K_X, 0, 0, 0)$. We are now ready to calculate the basic reproductive number $\mathcal{R}_0$ for system (3.19). As in the case of the super-infection system (3.11), there lies the issue of two strains circulating in the population, so we denote the threshold parameter by $\mathcal{R}_0^{\max}$. Again, $\mathcal{R}_0^{\max}$ is calculated using the methods from [44].

**Proposition 3.17.** $\mathcal{R}_0^{\max}$ *for system (3.19) is defined by*

$$\mathcal{R}_0^{\max} = \max_{i=1,2}\left\{\frac{b_i K_X}{a_i + u_i}\right\}.$$

*For any positive parameter values,* $(0, 0, 0, 0)$ *is a saddle. The following conditions characterize the stability of* $(K_X, 0, 0, 0)$*:*

*i. If* $\mathcal{R}_0^{\max} < 1$*, then* $(K_X, 0, 0, 0)$ *is locally asymptotically stable.*

*ii. If* $\mathcal{R}_0^{\max} > 1$*, then* $(K_X, 0, 0, 0)$ *is unstable.*

*Proof.* We label the equilibria $x_0 = (0, 0, 0, 0)$ and $x_K = (K_X, 0, 0, 0)$ so that the labels $x_0$ and $x_K$ remain despite rearranging coordinate positions. We now let $x_1 = Y_1$, $x_2 = Y_2$, $x_3 = Y_{12}$ and $x_4 = X$, and $\vec{x} = (x_1, x_2, x_3, x_4)$. Now we can write system (3.19) in the form

$$\dot{x}_i = \mathcal{F}_i(\vec{x}) - \mathcal{V}_i(\vec{x}),$$

where

$$\mathcal{F} = \begin{bmatrix} b_1(Y_1 + d_1 Y_{12})X \\ b_2(Y_2 + d_2 Y_{12})X \\ (b_{12} + b_{21})Y_1 Y_2 \\ 0 \end{bmatrix}$$

and

$$\mathcal{V} = \begin{bmatrix} b_{12} Y_1 Y_2 + (a_1 + u_1) Y_1 \\ b_{21} Y_1 Y_2 + (a_2 + u_2) Y_2 \\ (a_{12} + u_{12}) Y_{12} \\ -r_X N_X \left(1 - \frac{N_X}{K_X}\right) + \sum_{i=1}^{2} b_i (Y_i + d_i Y_{12}) X - a_1 Y_1 - a_2 Y_2 - a_{12} Y_{12} \end{bmatrix}.$$

We then define

$$\mathcal{V}^+ = \begin{bmatrix} 0 \\ 0 \\ 0 \\ r_X N_X \left(1 - \frac{N_X}{K_X}\right) + a_1 Y_1 + a_2 Y_2 + a_{12} Y_{12} \end{bmatrix} \quad \text{and} \quad \mathcal{V}^- = \begin{bmatrix} b_{12} Y_1 Y_2 + (a_1 + u_1) Y_1 \\ b_{21} Y_1 Y_2 + (a_2 + u_2) Y_2 \\ (a_{12} + u_{12}) Y_{12} \\ \sum_{i=1}^{2} b_i (Y_i + d_i Y_{12}) X \end{bmatrix},$$

where $\mathcal{V}_i = \mathcal{V}_i^- - \mathcal{V}_i^+$. It is not difficult to demonstrate conditions (A1)-(A4) in [44] are satisfied, so we draw our attention to condition (A5).

(A5) To satisfy this assumption, we analyze the Jacobian of system (3.11) when $\mathcal{F}(x)$ is set to zero. That is, we consider the Jacobian of $-\mathcal{V}$ at the DFE $x_K$ given by

$$-D\mathcal{V}(x_K) = \begin{bmatrix} -(a_1+u_1) & 0 & 0 & 0 \\ 0 & -(a_2+u_2) & 0 & 0 \\ 0 & 0 & -(a_{12}+u_{12}) & 0 \\ -r_X - b_1K_X + a_1 & -r_X - b_2K + a_2 & -r_X - (b_1d_1+b_2d_2)K_X + a_{12} & -r_X \end{bmatrix}, \tag{3.21}$$

which has the negative eigenvalues $\lambda_1 = -(a_1+u_1)$, $\lambda_2 = -(a_2+u_2)$, $\lambda_3 = -(a_{12}+u_{12})$, and $\lambda_4 = -r_X$.

Conditions (A1)-(A5) are satisfied, so we can use Lemma 1 in [44]. We now have

$$D\mathcal{F}(x_K) = \begin{bmatrix} F & 0 \\ 0 & 0 \end{bmatrix} \quad \text{and} \quad D\mathcal{V}(x_K) = \begin{bmatrix} V & 0 \\ J_3 & J_4 \end{bmatrix}, \tag{3.22}$$

where

$$F = \begin{bmatrix} b_1K_X & 0 & b_1d_1K_X \\ 0 & b_2K_X & b_2d_2K_X \\ 0 & 0 & 0 \end{bmatrix}, \quad V = \begin{bmatrix} a_1+u_1 & 0 & 0 \\ 0 & a_2+u_2 & 0 \\ 0 & 0 & a_{12}+u_{12} \end{bmatrix},$$

$$J_3 = \begin{bmatrix} r_X + b_1K_X - a_1 & r_X + b_2K_X - a_2 & r_X + (b_1d_1+b_2d_2)K_X - a_{12} \end{bmatrix}, \text{ and } J_4 = r_X.$$

Furthermore, we note $F$ is nonnegative, $V$ is nonsingular, and $J_4$ is positive. Then we have

$$FV^{-1} = \begin{bmatrix} \dfrac{b_1 K_X}{a_1 + u_1} & 0 & \dfrac{b_1 d_1 K_X}{a_{12} + u_{12}} \\ 0 & \dfrac{b_2 K_X}{a_2 + u_2} & \dfrac{b_2 d_2 K_X}{a_{12} + u_{12}} \\ 0 & 0 & 0 \end{bmatrix},$$

which gives the spectral radius

$$\rho(FV^{-1}) = \max_{i=1,2} \left\{ \frac{b_i K_X}{a_i + u_i} \right\}.$$

The basic reproductive number is given by $\mathcal{R}_0^{\max} = \rho(FV^{-1})$. The equilibrium point is stable for $\mathcal{R}_0^{\max} < 1$ and unstable when $\mathcal{R}_0^{\max} > 1$.

Now that $\mathcal{R}_0$ for system (3.19) is established, we examine the stability at the origin. Evaluating $J$ at $x_0$, we get

$$J(x_0) = \begin{bmatrix} r_X & r_X + a_1 & r_X + a_2 & r_X + a_{12} \\ 0 & -(a_1 + u_1) & 0 & 0 \\ 0 & 0 & -(a_2 + u_2) & 0 \\ 0 & 0 & 0 & -(a_{12} + u_{12}) \end{bmatrix}. \tag{3.23}$$

which has the eigenvalues

$$\lambda_1 = r_X, \quad \lambda_2 = -(a_1 + u_1), \quad \lambda_3 = -(a_2 + u_2), \quad \text{and} \quad \lambda_4 = -(a_{12} + u_{12}).$$

The corresponding eigenvectors are given by

$$e_1 = \begin{bmatrix} 1 \\ 0 \\ 0 \\ 0 \end{bmatrix}, \quad e_2 = \begin{bmatrix} -\frac{a_1+r_X}{a_1+u_1+r_X} \\ 1 \\ 0 \\ 0 \end{bmatrix}, \quad e_3 = \begin{bmatrix} -\frac{a_2+r_X}{a_2+u_2+r_X} \\ 0 \\ 1 \\ 0 \end{bmatrix}, \quad \text{and} \quad e_4 = \begin{bmatrix} -\frac{a_{12}+r_X}{a_{12}+u_{12}+r_X} \\ 0 \\ 0 \\ 1 \end{bmatrix},$$

respectively. The stable manifold of $x_0$ touches the region $E$ at the origin. All trajectories in the positive quadrant that are local to $(0, 0, 0, 0)$ will attract toward the S-axis. □

We now examine the boundary of X. We denote the hyperplanes

$$\begin{aligned} H_0 &= \{(X, Y_1, Y_2, Y_{12}) \in \mathcal{X} : X = 0\}, \\ H_1 &= \{(X, Y_1, Y_2, Y_{12}) \in \mathcal{X} : Y_1 = 0\}, \\ H_2 &= \{(X, Y_1, Y_2, Y_{12}) \in \mathcal{X} : Y_2 = 0\}, \\ H_{12} &= \{(X, Y_1, Y_2, Y_{12}) \in \mathcal{X} : Y_{12} = 0\}. \end{aligned}$$

The boundary of $\mathcal{X}$ is then given by

$$\partial\mathcal{X} = \bigcup_{i=0,1,2,12} H_i.$$

Considering the restriction to $H_0$, the trajectories with at least one nonzero component (i.e., we rule out the posiblity that all components are zero) of system (3.19) will flow off of $\partial\mathcal{X}$. On the hyperplane $H_{12}$, the flow also lifts off of the plane onto the interior. On hyperplanes $H_1$ and $H_2$, the flow lifts off the boundary unless $Y_{12} = 0$ and $Y_i = 0$ on the respective hyperplace. That is, since there is a co-infection variable

$Y_{12}$ in the differential equations for $Y_1$ and $Y_2$ for the system (3.19), infected individuals for the corresponding infectious subclass will continue to reproduce in the case $Y_1 = 0$ or $Y_2 = 0$ given $Y_{12} > 0$. The closed invariant subspaces of the boundary are on the sets $H_1 \cap H_{12}$ and $H_2 \cap H_{12}$. The equilibria on $\partial X$ are then given by $(0, 0, 0, 0)$, $(K_X, 0, 0, 0)$, $(\hat{X}, \hat{Y}_1, 0, 0)$, and $(\check{X}, 0, \check{Y}_2, 0)$, where the values are the same as $(\hat{S}, \hat{I})$ for system (3.1) with the corresponding change in variables and proper subscripts. For example, $(\check{X}, 0, \check{Y}_2, 0)$ is given by

$$\left( \frac{a_2 + u_2}{b_2},\ 0,\ \frac{K_X}{2}\left(1 - \frac{u_2}{r_X}\right) - \check{X} + \sqrt{\frac{K_X^2}{4}\left(1 - \frac{u_2}{r_X}\right)^2 + \frac{u_2 K_X \check{X}}{r_X}},\ 0 \right).$$

Notice all equilibria lie on the boundary of $H_{12}$, that is, if the equilibria is disease free of either strain, then the density of the co-infected subclass is also zero. Take for example the interior of the hyperplane $H_1$. The differential equation for the $Y_1$ subclass is then given by

$$\frac{dY_1}{dt} = b_1 d_1 Y_{12} X$$

on $H_1$ (setting $Y_1 = 0$), which implies for any $y \in \mathring{H}_1$, $\gamma^+(y) \notin H_1$. Hence, the only closed invariant subspaces on the boundary are on $H_1 \cap H_{12}$ and $H_2 \cap H_{12}$, that is, the system (3.19) behaves like the system (3.1) on the subspaces $H_1 \cap H_{12}$ and $H_2 \cap H_{12}$. Define the threshold parameter

$$\mathcal{R}_0^{\min} = \min_{i=1,2} \left\{ \frac{b_i K_X}{a_i + u_i} \right\}.$$

The condition that $\mathcal{R}_0^{\min} > 1$ is sufficient for each point to exist and to be globally asymptotically stable on the relative invariant subspace. We now develop stability conditions for each equilibrium point relative to the whole space $\mathcal{X}$. We continue with the following proposition:

**Proposition 3.18.** *Consider system (3.19) on the space* $\mathcal{X}$*, and suppose the condition*

$$\frac{b_1 K}{a_1 + u_1} > 1 \tag{3.24}$$

*holds. Define the constants*

$$\mathcal{R}_1 = \frac{b_2 \hat{X}}{b_{21}\hat{Y}_1 + a_2 + u_2 + a_{12} + u_{12}}$$

*and*

$$\mathcal{R}_{12} = \frac{(a_{12} + u_{12})(b_{21}\hat{Y}_1 + a_2 + u_2)}{b_2 \hat{X}(a_{12} + u_{12} + d_2(b_{12} + b_{21})\hat{Y}_1)}$$

*Then the following conditions classify the stability of* $(\hat{X}, \hat{Y}_1, 0, 0)$

*i.* $(\hat{X}, \hat{Y}_1, 0, 0)$ *is locally asymptotically stable for* $\mathcal{R}_1 < 1$ *and* $\mathcal{R}_{12} > 1$.

*ii.* $(\hat{X}, \hat{Y}_1, 0, 0)$ *is unstable for either: (1a)* $\mathcal{R}_1 < 1$ *and* $\mathcal{R}_{12} < 1$*, or (1b)* $\mathcal{R}_1 > 1$ *and* $\mathcal{R}_{12} < 1$.

*Proof.* We begin by evaluating the Jacobian of system (3.19) at $(\hat{X}, \hat{Y}_1, 0, 0)$. The result has the form

$$J(\hat{X}, \hat{Y}_1, 0, 0) = \begin{bmatrix} A & B \\ 0 & C \end{bmatrix}, \tag{3.25}$$

where

$$A = \begin{bmatrix} r_X\left(1 - \frac{2\hat{N}_X}{K_X}\right) - b_1\hat{Y}_1 & r_X\left(1 - \frac{2\hat{N}_X}{K_X}\right) - u_1 \\ b_1\hat{Y}_1 & 0 \end{bmatrix}$$

and

$$C = \begin{bmatrix} b_2\hat{X} - b_{21}\hat{Y_1} - (a_2 + u_2) & b_2 d_2 \hat{X} \\ (b_{12} + b_{21})\hat{Y_1} & -(a_{12} + u_{12}) \end{bmatrix},$$

noting $\hat{N_X} = \hat{X} + \hat{Y_1}$. Matrices $A$, $B$, and $C$ are all $2 \times 2$, and the upper triangular block form of $J(\hat{X}, \hat{Y_1}, 0, 0)$ implies the eigenvalues of matrices $A$ and $C$ are the eigenvalues of $J(\hat{X}, \hat{Y_1}, 0, 0)$. The matrix $A$ has the form of the matrix (3.10), so it has eigenvalues have negative real part. Since the off-diagonal entries of the matrix $C$ are positive, the eigenvalues of $C$ are real. We are now ready to develop conditions to characterize the local stability for $(\hat{X}, \hat{Y_1}, 0, 0)$.

Define the threshold constants

$$\mathcal{R}_1 = \frac{b_2\hat{X}}{b_{21}\hat{Y_1} + a_2 + u_2 + a_{12} + u_{12}},$$

and

$$\mathcal{R}_{12} = \frac{(a_{12} + u_{12})(b_{21}\hat{Y_1} + a_2 + u_2)}{b_2\hat{X}(a_{12} + u_{12} + d_2\hat{Y_1}(b_{12} + b_{21}))}$$

Then the condition $\mathcal{R}_1 < 1$ implies $tr(C) < 0$, and $\mathcal{R}_1 > 1$ implies $tr(C) > 0$. Similarly, the condition $\mathcal{R}_{12} < 1$ implies $\det(C) < 0$, and $\mathcal{R}_{12} > 1$ implies $\det(C) > 0$. In the case when $\mathcal{R}_1 < 1$, we clearly have at least one negative eigenvalue, so $\mathcal{R}_{12} < 1$ (or $\mathcal{R}_{12} > 1$) implies the other eigenvalue is positive (or negative). On the other hand, given $\mathcal{R}_1 > 1$ at least one eigenvalue is positive, so the condition

$\mathcal{R}_{12} < 1$ implies the other eigenvalue is negative. We note that when $\mathcal{R}_1 > 1$, then $b_2\hat{X} > b_{12}\hat{Y}_1 + a_2 + u_2 + a_{12} + u_{12}$. We then have

$$\begin{aligned} \frac{1}{\mathcal{R}_{12}} &> \frac{b_{12}\hat{Y}_1 + a_2 + u_2 + a_{12} + u_{12}}{b_{12}\hat{Y}_1 + a_2 + u_2} \cdot \frac{d_2(b_{12} + b_{21})\hat{Y}_1 + a_{12} + u_{12}}{a_{12} + u_{12}} && (3.26) \\ &> \left(1 + \frac{a_{12} + u_{12}}{b_{12}\hat{Y}_1 + a_2 + u_2}\right) \cdot \left(1 + \frac{d_2(b_{12} + b_{21})\hat{Y}_1}{a_{12} + u_{12}}\right) > 1, && (3.27) \end{aligned}$$

which implies $\mathcal{R}_{12} < 1$. Hence, the equilibrium point $(\hat{X}, \hat{Y}_1, 0, 0)$ is locally asymptotically stable when $\mathcal{R}_1 < 1$ and $\mathcal{R}_{12} > 1$. $(\hat{X}, \hat{Y}_1, 0, 0)$ is unstable when either: (1a) $\mathcal{R}_1 < 1$ and $\mathcal{R}_{12} < 1$, or (1b) $\mathcal{R}_1 > 1$ and $\mathcal{R}_{12} < 1$. □

The symmetry of system (3.19) with respect to the $Y_1$ and $Y_2$ variables and respective parameters give a similar result to proposition (3.18) for the equilibrium point $(\check{X}, 0, \check{Y}_2, 0)$. That is, we can define a threshold constant

$$\mathcal{R}_2 = \frac{b_1\check{X}}{b_{12}\check{Y}_2 + a_1 + u_1 + a_{12} + u_{12}},$$

and

$$\mathcal{R}_{21} = \frac{(a_{12} + u_{12})(b_{12}\check{Y}_2 + a_1 + v_1)}{b_1\check{X}(a_{12} + u_{12} + d_1\check{Y}_2(b_{12} + b_{21}))}$$

that characterizes the local stability. $\mathcal{R}_2 < 1$ and $\mathcal{R}_{21} > 1$ implies $(\check{X}, 0, \check{Y}_2, 0)$ is local asymptotically stable. $(\check{X}, 0, \check{Y}_2, 0)$ is unstable for either (2a) $\mathcal{R}_{21} < 1$ and $\mathcal{R}_{21} < 1$, or (2b) $\mathcal{R}_2 > 1$ and $\mathcal{R}_{21} < 1$. We are now ready to define conditions for permanence.

We are now ready to prove conditions for permanence in system (3.11). Define the nonempty index set $\Lambda = \{0, 1, 2\}$, and let $\partial\Im$ denote the restriction of the flow to $\partial\mathcal{X}$. Let $\mathcal{N}$ be the maximal invariant set of $\partial\Im$, which in this case

$\mathcal{N} = (H_1 \cap H_{12}) \cup (H_2 \cap H_{12})$. We note $\mathcal{N}$ is a closed invariant set and define the cover $\{\mathcal{N}_\sigma\}_{\sigma\in\Lambda}$ of $\mathcal{N}$ by

$$\begin{aligned}
\mathcal{N}_0 &= \{(X, Y_1, Y_2, Y_{12}) \in \mathcal{X} : Y_1 = Y_2 = Y_{12} = 0\},\\
\mathcal{N}_1 &= \{(X, Y_1, Y_2, Y_{12}) \in \mathcal{X} : Y_1 > 0, Y_2 = Y_{12} = 0\},\\
\mathcal{N}_2 &= \{(X, Y_1, Y_2, Y_{12}) \in \mathcal{X} : Y_2 > 0, Y_1 = Y_{12} = 0\},
\end{aligned}$$

and we note

$$\mathcal{N} = \bigcup_{\sigma\in\Lambda} \mathcal{N}_\sigma$$

and $\mathcal{N}_\sigma \subset \partial\mathcal{X}$. We also note that $\mathcal{N}_\sigma$ $(\sigma \in \Lambda)$ are pairwise disjoint closed invariant sets. The following lemma show the closed invariant sets of the cover $\{\mathcal{N}_\sigma\}_{\sigma\in\Lambda}$ satisfy hypothesis **(H)** of [18].

**Lemma 3.19.** *Suppose* $\mathcal{R}_0^{\min} > 1$ *for system (3.19). The pairwise disjoint closed invariant sets given by* $\mathcal{N}_\sigma$ *(*$\sigma \in \Lambda$*) satisfy hypothesis* **(H)**.

*Proof.* Assumption (a). We first note that $(0, 0, 0, 0)$ is invariant in $\mathcal{N}_0$. Otherwise, the flow $\Im$ on $\mathcal{N}_0$, $\mathcal{N}_1$, and $\mathcal{N}_2$ globally attract to the equilibria $(K_X, 0, 0, 0)$, $(\hat{X}, \hat{Y}_1, 0, 0)$, and $(\check{X}, 0, \check{Y}_2, 0)$, respectively (see the proof of assumption (a) in Lemma 3.11). Hence, all $\mathcal{N}_\sigma$ are isolated sets of the flow $\Im$.

The proof of assumptions (b) and (c) are completely analogous to the proofs of the same assumptions in Lemma 3.11. □

As in the case of system (3.11), system (3.19) is dissipative and hence point dissipative. We can then note hypothesis **(H)** and $W^+(\mathcal{N}_\sigma) \cap \mathring{\mathcal{X}} = \emptyset$ are sufficient to satisfy the premise of Theorem 3.10.

We define the conditions:

(1) Condition (1a) or (1b) is satisfied for $(\hat{X}, \hat{Y_1}, 0, 0)$.

(2) Condition (2a) or (2b) is satisfied for $(\hat{X}, 0, \hat{Y_2}, 0)$.

We are now ready to state the theorem that establishes permanence in system (3.19).

**Theorem 3.20.** *Suppose* $\mathcal{R}_0^{\min} > 1$ *and that conditions (1) and (2) are satisfied. Then for any initial conditions not in the maximal invariant set* $\mathcal{N}$*, system (3.19) exihibits permanence. Moreover, there exists a positive equilibrium point.*

*Proof.* $\mathcal{R}_0^{\min} > 1$ implies $W^+(\mathcal{N}_0) = \mathcal{N}_0$. If condition (1) is satisfied, then Proposition 3.18 implies $W^+(\mathcal{N}_1) = \mathcal{N}_1$. Similarly, we get $W^+(\mathcal{N}_2) = \mathcal{N}_2$ when condition (2) is satisfied. Hence, $W^+(\mathcal{N}_\sigma) \cap \mathring{\mathcal{X}} = \emptyset$ for all $\sigma \in \Lambda$. This result together with Lemma 3.19, we are now able to apply Theorem 3.10. Hence, the flow of system (3.19) is uniformly persistent. The upper-bound from the dissipativity of system (3.19) implies uniformly persistent is equivalent to permanence. $\square$

Consider the case with $\mathcal{R}_0^{\min} > 1$ with conditions $\mathcal{R}_1 > 1$ and $\mathcal{R}_2 > 1$. Then for any initial condition off of the closed invariant subspaces $H_1 \cap H_{12}$ and $H_2 \cap H_{12}$, the system (3.19) will persist. Notice this implies that both strains need to be present for the system to exhibit permanence; however, this requires the density in both the subclasses $Y_1$ and $Y_2$ must be positive or in the co-infected subclass and either of the other infectious subclasses.

### 3.3.2 Quantitative Analysis and Simulations

The co-infection subsystem (3.19) represents an intermediate host that acts as a "mixing vessel" of two parasitic strains. That is, a single host has the potential of being infected by two different strains at a given moment. For our interest in influenza, pigs serve as ideal candidates in that they can become infected with both avian and human strains of the virus; see [9, 42].

To simulate a system consistent with the simulations for the super-infection model of Section 3.2, we consider data from the Food and Agriculture Organization of the United Nations (FAO) on pig populations in Thailand. **Table 3.3** shows the data from [16, 17]. The population growth rate and capacity were calculated to be $r_X = 0.093$ and $K_X = 9.16$, using numerical methods of nonlinear regression with the solution to the logistic equation. Due to the inconsistency with the data for the years 1995 and 1996, these years were omitted from the regression calculation. There is a steady growth trend of the data for the swine population values prior to 1995, and the trend continues from 1999 on. We omit the data from the years 1995 and 1996, since they deviate from the increasing trend of the other statistics; see **Table 3.3**. Due to the limited data on swine influenza virus transmissibility, the remaining parameters

**Table 3.3:** *Pig populations of Thailand reported by the Food and Agriculture Organization of the United Nations (FAO) on [16, 17].*

| Year | Population (millions) |
|---|---|
| 1991 | 4.9 |
| 1992 | 4.7 |
| 1993 | 5.0 |
| 1994 | 5.3 |
| 1995 | 4.5 |
| 1996 | 4.0 |
| 1999 | 6.4 |
| 2000 | 6.6 |
| 2001 | 6.7 |
| 2002 | 6.7 |

are chosen as reasonable values that set conditions to exhibit permanence. For the incidence rates, let $b_1 = 0.23$, $b_2 = 0.13$, $b_{12} = 0.2$, and $b_{21} = 0.0013$ with $d_1 = 1$ and $d_2 = 1$. The corresponding recovery and disease induced mortality rates are $a_1 = 0.9$, $u_1 = 0.07$, $a_2 = 0.0125$, $u_2 = 0.08$, $a_{12} = 0.025$, and $u_{12} = 0.03$.

Calculating the basic reproductive values, we get $\mathcal{R}_0^{\min} = 2.172$ and $\mathcal{R}_0^{\max} = 12.87$. Since both values are greater than one, this implies the existence of both nontrivial boundary equilibria at $(\hat{X}, \hat{Y}_1, 0, 0) = (4.2, 2.4, 0, 0)$ and $(\check{X}, 0, \check{Y}_2, 0) = (0.7, 0.5.7, 0)$. The remaining constants are $\mathcal{R}_1 = 3.64$, $\mathcal{R}_{12} = 0.11$, $\mathcal{R}_2 = 0.08$, and $\mathcal{R}_{21} = 0.27$. Since $\mathcal{R}_1 > 1$, we have the $(\hat{X}, \hat{Y}_1, 0, 0)$ is a saddle as a consequence of proposition 3.18. Since $\mathcal{R}_2 < 1$ and $\mathcal{R}_{21} < 1$, we have $(\check{X}, 0, \check{Y}_2, 0)$ is also a saddle. Hence, there exists an equilibrium point in $\mathring{\mathcal{X}}$. Simulations with the initial conditions $X(0) = 0.002$, $Y_1(0) = 0.001$, $Y_2(0) = 0.001$, and $Y_{12}(0) = 0.001$ attract to the interior equilibrium point $(0.66, 0.02, 2.33, 0.20)$. **Figure 3.8** shows the population versus time for the given values.

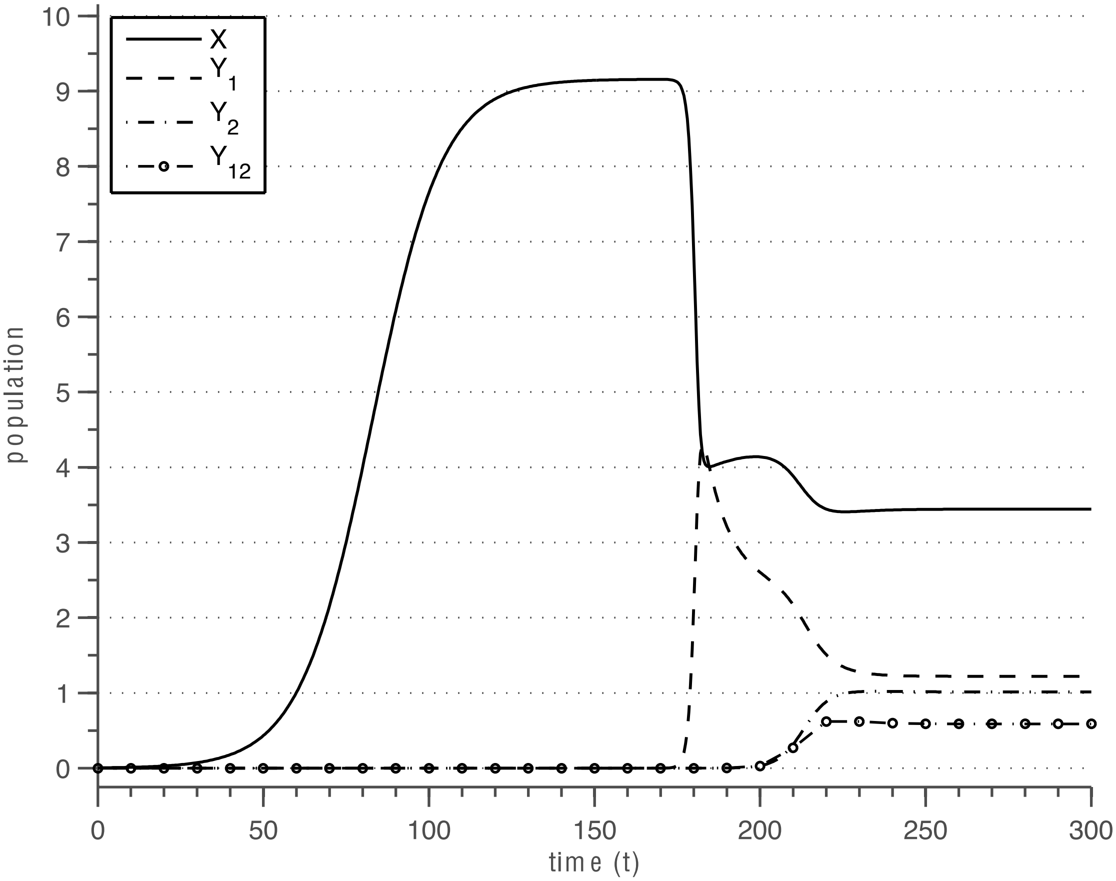

**Figure 3.8:** *Population densities of the subclasses of system (3.19) versus time. Parameter values are* $r_X = 0.093$, $K_X = 9.16$, $b_1 = 0.23$, $b_2 = 0.2$, $b_{12} = 0.2$, *and* $b_{21} = 0.17$ *with* $d_1 = 1$, $d_2 = 1$, $a_1 = 0.9$, $u_1 = 0.07$, $a_2 = 0.8$, $u_2 = 0.08$, $a_{12} = 0.75$, *and* $u_{12} = 0.03$. *Initial conditions are set to* $X(0) = 0.002$, $Y_1(0) = 0.001$, $Y_2(0) = 0.001$, *and* $Y_{12}(0) = 0.001$. *The trajectories attract to the endemic equilibrium point* $(3.44, 1.22, 1.01, 0.59)$.

# Chapter 4

# Subsystems with Multiple Hosts

## 4.1 An SIS Model of Two Interacting Hosts

We begin by considering an SIS model with two host species, a primary host and a secondary host, each with a strain circulating in the respective populations. Each host has the total population divided into two subclasses of infectious and susceptible individuals. We denote the total population density for each species together at time $t$ by $N(t)$. For the primary host, we consider the system (2.1). For the intermediate host, we let $X$ denote the susceptible subclass and $Y_1$ denote the infectious subclass. The total population density of primary and intermediate host species at time $t$ are $N_1(t)$ and $N_X(t)$, respectively. That is, $N_1(t) = S_1(t) + I_1(t)$ and $N_X(t) = X(t) + Y_1(t)$. Susceptible individuals of the intermediate host population are infected by infectious individuals of the primary host by the mass action term $gXI_1$. In other words, infectious individuals of the primary host population are capable of infecting susceptible individuals of the intermediate host population through species interaction.

$$\begin{aligned}
\frac{dS_1}{dt} &= r_1 N_1 \left(1 - \frac{N_1}{K_1}\right) - \beta_1 S_1 I_1 + a_1 I_1 \\
\frac{dX}{dt} &= r_X N_X \left(1 - \frac{N_X}{K_X}\right) - b_1 X Y_1 - g X I_1 + a_1 Y_1 \\
\frac{dI_1}{dt} &= \beta_1 S_1 I_1 - (\alpha_1 + v_1) I_1 \qquad (4.1) \\
\frac{dY_1}{dt} &= b_1 X Y_1 + g X I_1 - (a_1 + u_1) Y_1
\end{aligned}$$

with $S_1(0) \geq 0,\ X(0) \geq 0,\ I_1(0) \geq 0,\ Y_1(0) \geq 0.$

If we look at the sum the two equations of each species for system (4.1), then the differential equations for total population of each species is given by

$$\frac{dN_1}{dt} = r_1 N_1 \left(1 - \frac{N_1}{K_1}\right) - v_1 I_1 \tag{4.2}$$

and

$$\frac{dN_X}{dt} = r_X N_X \left(1 - \frac{N_X}{K_X}\right) - u_1 Y_1, \tag{4.3}$$

implying

$$\frac{dN_1}{dt} \leq r_1 N_1 \left(1 - \frac{N_1}{K_1}\right) \quad \text{and} \quad \frac{dN_X}{dt} \leq r_X N_X \left(1 - \frac{N_X}{K_X}\right), \tag{4.4}$$

respectively. Solving the differential inequality, we get the carrying capacity bound on the total population as $t \to \infty$, that is,

$$\limsup_{t\to\infty} N_1(t) \leq K_1 \quad \text{and} \quad \limsup_{t\to\infty} N_X(t) \leq K_X.$$

Setting $S_1 = 0$, $X = 0$, $I_1 = 0$ and $Y_1 = 0$, we can clearly see that the population growth rate is zero; moreover, the density of each species of system (4.1) is attracted to the compact set $[0, K_i]$ $(i = 1, X)$ and the system is dissipative. For the total population (including the population densities of both populations), we have

$$0 \leq \limsup_{t\to\infty} N(t) \leq K,$$

where $K = K_1 + K_X$. We denote the space

$$\mathcal{X} = \{(S_1, X, I_1, Y_1) \in \mathbb{R}^4 : 0 \leq S_1, X, I_1, Y_1\},$$

and the attracting region

$$E = \{(S_1, X, I_1, Y_1) \in \mathcal{X} : S_1 + I_1 \leq K_1, X + Y_1 \leq K_X\}.$$

We are now ready to solve for the equilibria. The subspaces

$$Z_1 = \{(S_1, X, I_1, Y_1) \in \mathcal{X} : X = Y_1 = 0\}$$

and

$$Z_2 = \{(S_1, X, I_1, Y_1) \in \mathcal{X} : S_1 = I_1 = 0\}.$$

are the invariant subspaces that consist only of the subclasses of primary and intermediate host individuals, respectively. System (4.1) has the disease free equilbria $(0,0,0,0)$, $(K_1,0,0,0)$, $(0,K_X,0,0)$ and $(K_1,K_X,0,0)$. We are now ready to calculate the basic reproductive number $\mathcal{R}_0$ for system (4.1) following the framework given in [44].

**Proposition 4.1.** $\mathcal{R}_0^{\max}$ *for system (4.1) is defined by*

$$\mathcal{R}_0^{\max} = \max\left\{\frac{\beta_1 K_1}{\alpha_1+v_1}, \frac{b_1 K_X}{a_1+u_1}\right\}.$$

*For any positive parameter values,* $(0,0,0,0)$ *is a saddle. The following conditions characterize the stability of* $(K_1,K_X,0,0)$*:*

- *i. If* $\mathcal{R}_0^{\max} < 1$*, then* $(K_1,K_X,0,0)$ *is locally asymptotically stable.*
- *ii. If* $\mathcal{R}_0^{\max} > 1$*, then* $(K_1,K_X,0,0)$ *is unstable.*

*Proof.* We label the equilibria $x_0 = (0,0,0,0)$ and $x_K = (K_1,K_X,0,0)$ so that the labels $x_0$ and $x_K$ remain despite rearranging coordinate positions. We let $x_1 = I_1$, $x_2 = Y_1$, $x_3 = S_1$ and $x_4 = X$, and $\vec{x} = (x_1,x_2,x_3,x_4)$. Now we can write system (4.1) in the form

$$\dot{x}_i = \mathcal{F}_i(x) - \mathcal{V}_i(x),$$

where

$$\mathcal{F} = \begin{bmatrix} \beta_1 S_1 I_1 \\ b_1 X Y_1 + g X I_1 \\ 0 \\ 0 \end{bmatrix} \quad \text{and} \quad \mathcal{V} = \begin{bmatrix} (\alpha_1+v_1)I_1 \\ (a_1+u_1)Y_1 \\ -r_1 N_1\left(1-\frac{N_1}{K_1}\right) + \beta_1 S_1 I_1 - \alpha_1 I_1 \\ -r_X N_X\left(1-\frac{N_X}{K_X}\right) + b_1 X Y_1 + g X I_1 - a_1 Y_1 \end{bmatrix}.$$

We then define

$$\mathcal{V}^+ = \begin{bmatrix} 0 \\ 0 \\ r_1 N_1 \left(1 - \frac{N_1}{K_1}\right) + \alpha_1 I_1 \\ r_X N_X \left(1 - \frac{N_X}{K_X}\right) + a1Y_1 \end{bmatrix} \quad \text{and} \quad \mathcal{V}^- = \begin{bmatrix} (\alpha_1 + v_1)I \\ (a_1 + u_1)I \\ \beta_1 S_1 I_1 \\ b_1 X Y_1 + g X I_1 \end{bmatrix},$$

where $\mathcal{V}_i = \mathcal{V}_i^- - \mathcal{V}_i^+$. It is not difficult to demonstrate conditions (A1)-(A4) in [44] are satisfied, so we draw our attention to condition (A5).

(A5) We now consider the Jacobian of system (4.1) when $\mathcal{F}(x)$ is set to zero. That is, we consider the Jacobian of $-\mathcal{V}$ at the DFE $x_K = (K_1, K_X, 0, 0)$ given by

$$-D\mathcal{V}(x_K) = \begin{bmatrix} -(\alpha_1 + v_1) & 0 & 0 & 0 \\ 0 & -(a_1 + u_1) & 0 & 0 \\ -r_1 - \beta_1 K_1 + \alpha_1 & 0 & -r_1 & 0 \\ gK_X & -r_X - b_1 K_X + a_1 & 0 & -r_X \end{bmatrix}, \qquad (4.5)$$

which has the eigenvalues

$$\lambda_1 = -r_1, \quad \lambda_2 = -r_X, \quad \lambda_3 = -(\alpha_1 + v_1) \quad \text{and} \quad \lambda_4 = -(a_1 + u_1).$$

Clearly, all the eigenvalues have negative real parts.

Conditions (A1)-(A5) are now satisfied, so we can use Lemma 1 in [44]. We now have

$$D\mathcal{F}(x_K) = \begin{bmatrix} F & 0 \\ 0 & 0 \end{bmatrix} \quad \text{and} \quad D\mathcal{V}(x_K) = \begin{bmatrix} V & 0 \\ J_3 & J_4 \end{bmatrix}, \qquad (4.6)$$

where

$$F = \begin{bmatrix} \beta_1 K_1 & 0 \\ g K_X & b_1 K_X \end{bmatrix}, \quad V = \begin{bmatrix} \alpha_1 + v_1 & 0 \\ 0 & a_1 + u_1 \end{bmatrix},$$

$$J_3 = \begin{bmatrix} r_1 + \beta_1 K_1 - \alpha_1 & 0 \\ g K_X & r_X + b_1 K_X - a_1 \end{bmatrix}, \quad \text{and} \quad J_4 = \begin{bmatrix} r_1 & 0 \\ 0 & r_X \end{bmatrix}.$$

Furthermore, we note $F$ is nonnegative, $V$ is nonsingular, and $J_4$ is positive. Then we have

$$FV^{-1} = \begin{bmatrix} \dfrac{\beta_1 K_1}{\alpha_1 + v_1} & 0 \\ \\ \dfrac{g K_X}{\alpha_1 + v_1} & \dfrac{b_1 K_X}{a_1 + v_1} \end{bmatrix},$$

which gives the spectral radius

$$\rho(FV^{-1}) = \max\left\{ \frac{\beta_1 K_1}{\alpha_1 + v_1}, \frac{b_1 K_X}{a_1 + u_1} \right\}.$$

The basic reproductive number is given by $\mathcal{R}_0^{\max} = \rho(FV^{-1})$. The equilibrium point is stable for $\mathcal{R}_0^{\max} < 1$ and unstable when $\mathcal{R}_0^{\max} > 1$. Now that $\mathcal{R}_0$ for system (4.1) is established, we examine the stability at the origin. Evaluating $J$ at $x_0$, we get

$$J(x_0) = \begin{bmatrix} r_1 & 0 & r_1 + \alpha_1 & 0 \\ 0 & r_X & 0 & r_X + a_1 \\ 0 & 0 & -(\alpha_1 + v_1) & 0 \\ 0 & 0 & 0 & -(a_1 + u_1) \end{bmatrix}, \qquad (4.7)$$

which has the eigenvalues

$$\lambda_1 = r_1, \quad \lambda_2 = r_X, \quad \lambda_3 = -(\alpha_1 + v_1), \quad \text{and} \quad \lambda_4 = -(a_1 + u_1).$$

The corresponding eigenvectors are given by

$$v_1 = \begin{bmatrix} 1 \\ 0 \\ 0 \\ 0 \end{bmatrix}, \quad v_2 = \begin{bmatrix} 0 \\ 1 \\ 0 \\ 0 \end{bmatrix} \quad \text{and} \quad v_3 = \begin{bmatrix} -\frac{\alpha_1 + r_1}{\alpha_1 + v_1 + r_1} \\ 0 \\ 1 \\ 0 \end{bmatrix}, \quad v_4 = \begin{bmatrix} 0 \\ 0 \\ -\frac{a_1 + r_X}{a_1 + u_1 + r_X} \\ 1 \end{bmatrix},$$

respectively. The stable manifold about the origin is tangent to the region $\mathcal{X}$, and the unstable manifold is simply the $S_1X$-plane. We can conclude that the origin is classified as a saddle. □

The following proposition characterizes the stability of $(K_1, 0, 0, 0)$ and $(0, K_X, 0, 0)$ in the space $\mathcal{X}$, and the species specific subspaces $Z_1$ and $Z_2$.

**Proposition 4.2.** *Consider the equilibria* $(K_1, 0, 0, 0)$ *and* $(0, K_X, 0, 0)$. *The given equilibria are both saddles relative to the space* $\mathcal{X}$. *For considering* $(K_1, 0, 0, 0)$ *and* $(0, K_X, 0, 0)$ *on the species hyperplanes* $H_1$ *and* $H_2$, *we denote*

$$\mathcal{R}_{0,1} = \frac{\beta_1 K_1}{\alpha_1 + v_1} \quad \textit{for} \quad \mathcal{R}_{0,X} = \frac{b_1 K_X}{a_1 + u_1}.$$

*The condition* $\mathcal{R}_{0,1} > 1 (< 1)$ *implies* $(K_1, 0, 0, 0)$ *is a saddle (asymptotically stable) on* $Z_1$. *Similarly,* $\mathcal{R}_{0,K} > 1 (< 1)$ *implies* $(0, K_X, 0, 0)$ *is a saddle (asymptotically stable) on* $Z_2$.

*Proof.* Evaluating the Jacobian of system (4.1) at $(K_1, 0, 0, 0)$, we have

$$J(K_1,0,0,0) = \begin{bmatrix} -r_1 & 0 & -r_1 - \beta_1 K_1 + \alpha_1 & 0 \\ 0 & r_X & 0 & r_X + a_1 \\ 0 & 0 & \beta_1 K_1 - (\alpha_1 + v_1) & 0 \\ 0 & 0 & 0 & -(a_1 + u_1) \end{bmatrix},$$

which has the eigenvalues

$$\lambda_1 = -r_1, \quad \lambda_2 = r_X, \quad \lambda_3 = \beta_1 K_1 - (\alpha_1 + v_1), \quad \text{and} \quad \lambda_4 = -(a_1 + u_1).$$

Hence, the positive eigenvalues $\lambda_2$ implies the equilibrium point $(K_1, 0, 0, 0)$ is a saddle with respect to the space $\mathcal{X}$. The condition that $\lambda_3 < 0 (> 0)$ is equivalent to the condition $\mathcal{R}_{0,1} < 1 (> 1)$.

Similarly, evaluating the Jacobian of system (4.1) at $(0, K_X, 0, 0)$, we have

$$J(0,K_X,0,0) = \begin{bmatrix} r_1 & 0 & r_1 + \alpha_1 & 0 \\ 0 & -r_X & -gK_X & -r_X - b_1 K_X + a_1 \\ 0 & 0 & -(\alpha_1 + v_1) & 0 \\ 0 & 0 & gK_X & b_1 K_X - (a_1 + u_1) \end{bmatrix},$$

which yields the eigenvalues

$$\lambda_1 = r_1, \quad \lambda_2 = -r_X, \quad \lambda_3 = -(\alpha_1 + v_1), \quad \text{and} \quad \lambda_4 = b_1 K_X - (a_1 + u_1).$$

The desired result follows from similar methods as applied in the case of the equilibrium point $(K_1, 0, 0, 0)$. □

Notice that in absence of one of the species populations (e.g., $S_1 = 0$ and $I_1 = 0$ for the primary host), system (4.1) is reduced to system (3.1) in terms of one of the species. Using the result of system (3.1) in Section 3.1 of Chapter 3, we can determine the existence of a equilibrium point that is persistent relative to the given species. For example, suppose $X = Y_1 = 0$ and $\mathcal{R}_{0,1} > 1$, then there exists the equilibrium point $(\hat{S}_1, 0, \hat{I}_1, 0)$ that is globally asymptotically stable for initial conditions satisfying $S_1(0) \geq 0$ and $I_1(0) > 0$ on the subspace $Z_1$. In this case, system (4.1) exhibits persistence relative to the primary host species. Moreover, $Z_1$ is a closed invariant subspace of $\mathcal{X}$. An analogous result holds for intermediate host species. We denote the equilibrium point by $(0, \hat{X}, 0, \hat{Y}_1)$ and the corresponding closed invariant subspace by $Z_2$. We are now ready to examine the stability criterion for $(\hat{S}_1, 0, \hat{I}_1, 0)$ and $(0, \hat{X}, 0, \hat{Y}_1)$ relative to the entire space $\mathcal{X}$.

**Proposition 4.3.** *Suppose* $\mathcal{R}_0^{\min} > 1$*. Then there exist the equilibria* $(\hat{S}_1, 0, \hat{I}_1, 0)$ *and* $(0, \hat{X}, 0, \hat{Y}_1)$ *for system (4.1). Define the parameter constants*

$$\mathcal{R}_{11} = \frac{r_X}{g\hat{I}_1 + a_1 + u_1}, \quad \textit{and} \quad \mathcal{R}_{12} = \frac{g u_1 \hat{I}_1}{r_X(g\hat{I}_1 + a_1 + u_1)}.$$

*For any positive parameter values,* $(0, \hat{X}, 0, \hat{Y}_1)$ *is unstable. The following conditions characterize the stability of* $(\hat{S}_1, 0, \hat{I}_1, 0)$*:*

*i.* $(\hat{S}_1, 0, \hat{I}_1, 0)$ *is asymptotically stable for* $\mathcal{R}_{11} < 1$ *and* $\mathcal{R}_{12} > 1$*.*

*ii.* $(\hat{S}_1, 0, \hat{I}_1, 0)$ *is unstable for either: (1)* $\mathcal{R}_{11} > 1$ *and* $\mathcal{R}_{12} < 1$*, or (2)* $\mathcal{R}_{11} < 1$ *and* $\mathcal{R}_{12} < 1$*.*

*Proof.* $\mathcal{R}_0^{\min} > 1$ implies the existences of both $(\hat{S}_1, 0, \hat{I}_1, 0)$ and $(0, \hat{X}, 0, \hat{Y}_1)$ on $Z_1$ and $Z_2$, respectively. The Jacobian of system (4.1) evaluated at $(\hat{S}_1, 0, \hat{I}_1, 0)$ is

$$J(\hat{S}_1, 0, \hat{I}_1, 0) = \begin{bmatrix} r_1\left(1 - \frac{2\hat{N}_1}{K_1}\right) - \beta_1\hat{I}_1 & 0 & r_1\left(1 - \frac{2\hat{N}_1}{K_1}\right) - v_1 & 0 \\ 0 & r_X - g\hat{I}_1 & 0 & r_X + a_1 \\ \beta_1\hat{I}_1 & 0 & 0 & 0 \\ 0 & g\hat{I}_1 & 0 & -(a_1 + u_1) \end{bmatrix}, \tag{4.8}$$

By applying matrix column and row operations, the matrices given by

$$A = \begin{bmatrix} r_1\left(1 - \frac{2\hat{N}_1}{K_1}\right) - \beta_1\hat{I}_1 & r_1\left(1 - \frac{2\hat{N}_1}{K_1}\right) - v_1 \\ \beta_1\hat{I}_1 & 0 \end{bmatrix}$$

and

$$B = \begin{bmatrix} r_X - g\hat{I}_1 & r_X + a_1 \\ g\hat{I}_1 & -(a_1 + u_1) \end{bmatrix}.$$

have the same eigenvalues as matrix $J(\hat{S}_1, 0, \hat{I}_1, 0)$. The matrix $A$ has the form of the Jacobian (3.10). Hence, as a consequence of Proposition (3.4), the eigenvalues of the matrix $A$ have negative real parts. Define the threshold constants

$$\mathcal{R}_{11} = \frac{r_X}{g\hat{I}_1 + a_1 + u_1},$$

and

$$\mathcal{R}_{12} = \frac{g u_1 \hat{I}_1}{r_X(g\hat{I}_1 + a_1 + u_1)}.$$

The condition that $\mathcal{R}_{11} > 1$ $(< 1)$ is equivalent to $tr(B) > 0 (< 0)$, and $\mathcal{R}_{12} > 1$ $(< 1)$ is equivalent to $\det(B) > 0 (< 0)$. Therefore, we can classify the stability criterion for $(\hat{S}_1, 0, \hat{I}_1, 0)$ by if $\mathcal{R}_{11} < 1$ and $\mathcal{R}_{12} > 1$ then the equilibrium is asymptotically stable. If $\mathcal{R}_{11} > 1$, then $\mathcal{R}_{12} < 1$. $(\hat{S}_1, 0, \hat{I}_1, 0)$ is unstable for either: (1) $\mathcal{R}_{11} < 1$ and $\mathcal{R}_{12} < 1$, or (2) $\mathcal{R}_{11} > 1$ and $\mathcal{R}_{12} < 1$.

The Jacobian of system (4.1) evaluated at $(0, \hat{X}, 0, \hat{Y}_2)$ is

$$J(0, \hat{X}, 0, \hat{Y}_2) = \begin{bmatrix} r_1 & 0 & r_1 + \alpha_1 & 0 \\ 0 & r_X\left(1 - \frac{2\hat{N}_X}{K_X}\right) - b_1\hat{Y}_1 & -g\hat{X} & r_X\left(1 - \frac{2\hat{N}_X}{K_X}\right) - u_1 \\ 0 & 0 & -(\alpha_1 + v_1) & 0 \\ 0 & b_1\hat{Y}_1 & g\hat{X} & 0 \end{bmatrix}, \tag{4.9}$$

By applying matrix column and row operations, the matrices given by

$$C = \begin{bmatrix} r_1 & r_1 + \alpha_1 \\ 0 & -(\alpha_1 + v_1) \end{bmatrix}$$

and

$$D = \begin{bmatrix} r_X\left(1 - \frac{2\hat{N}_X}{K_X}\right) - b_1\hat{Y}_1 & r_X\left(1 - \frac{2\hat{N}_X}{K_X}\right) - u_1 \\ b_1\hat{Y}_1 & 0 \end{bmatrix}$$

have the same eigenvalues as $J(0, \hat{X}, 0, \hat{Y}_2)$. The eigenvalues of $C$ are $\lambda_1 = r_1$ and $\lambda_2 = -(\alpha_1 + v_1)$. The matrix $D$ has the same form as the Jacobian matrix (3.10) in Section 3.1; hence, the two eigenvalues of $D$ have negative real parts. We then have the that eigenvalues of $J(0, \hat{S}_2, 0, \hat{I}_2)$ consist of a positive real eigenvalue and three eigenvalues with negative real parts. Therefore, the equilibrium point $(0, \hat{S}_2, 0, \hat{I}_2)$ is unstable. $\square$

We now have stability criteria for all the boundary equilibria and are ready to prove permanence for system (4.1). The closed invariant subspaces of the boundary of $\mathcal{X}$ are $Z_1$ and $Z_2$. The maximal invariant set $\mathcal{N}$ of $\partial\Im$ is $\mathcal{N} = Z_1 \bigcup Z_2$. We note $\mathcal{N}$ is a closed and invariant and define the cover $\{\mathcal{N}_\sigma\}_{\sigma\in\Lambda}$ of $\mathcal{N}$ by

$$\begin{aligned}
\mathcal{N}_0 &= \{(S_1, X, I_1, Y_1) \in \mathcal{X} : I_1 = Y_1 = 0\}, \\
\mathcal{N}_1 &= \{(S_1, X, I_1, Y_1) \in \mathcal{X} : X = Y_1 = 0, I_1 > 0\}, \\
\mathcal{N}_2 &= \{(S_1, X, I_1, Y_1) \in \mathcal{X} : S_1 = I_1 = 0, Y_1 > 0\}.
\end{aligned}$$

Then

$$\mathcal{N} = \bigcup_{\sigma\in\Lambda} \mathcal{N}_\sigma$$

and $\mathcal{N}_\sigma \subset \partial\mathcal{X}$. We also note that $\mathcal{N}_\sigma$ $(\sigma \in \Lambda)$ are pairwise disjoint closed invariant sets. The equilibria $(\hat{S}_1, 0, \hat{I}_1, 0)$ and $(0, \hat{X}, 0, \hat{Y}_1)$ are asymptotically stable when restricted to the invariant spaces $\mathcal{N}_1$ and $\mathcal{N}_2$, respectively. Proposition 4.3 suggests that the equilibria are both unstable, under certain conditions, when considered on the entire space $\mathcal{X}$. Therefore, $\{\mathcal{N}_\sigma\}_{\sigma\in\Lambda}$ is acyclic, and condition (b) of hypothesis **(H)** is satisfied.

**Theorem 4.4.** *Suppose $\mathcal{R}_0^{\min} > 1$ and either: (1) $\mathcal{R}_{11} < 1$ and $\mathcal{R}_{12} < 1$, or (2) $\mathcal{R}_{11} > 1$ and $\mathcal{R}_{12} < 1$. Then system (4.1) exhibits permanence.*

*Proof.* As $\mathcal{R}_0^{\min} > 1$, we have the boundary equilibria: $(0,0,0,0)$, $(K_1,0,0,0)$, $(0,K_X,0,0)$, $(K_1,K_X,0,0)$, $(\hat{S}_1, 0, \hat{I}_1, 0)$, and $(0, \hat{X}, 0, \hat{Y}_1)$. $(\hat{S}_1, 0, \hat{I}_1, 0)$ is the only boundary equilibrium point that is not immediately classified as unstable. Since either (1) $\mathcal{R}_{11} < 1$ and $\mathcal{R}_{12} < 1$, or (2) $\mathcal{R}_{11} > 1$ and $\mathcal{R}_{12} < 1$, it follows from Proposition 4.3 that $(\hat{S}_1, 0, \hat{I}_1, 0)$ is unstable.

The classification of the boundary equilibria as unstable implies $W^+(\mathcal{N}_i) = \mathcal{N}_i$. It then follows that $\mathcal{N}_i \bigcap \mathring{\mathcal{X}} = \emptyset$. Now, Theorem 3.10 applies so that the system is uniformly persistent, which then implies the system exhibits permanence due to the dissipativity. □

## 4.2 SIS Model with an External Input

Since we have shown conditions for persistence in system (4.1), we can assume these conditions will hold for primary host species and analyze the dynamics under these conditions for intermediate host species. More specifically, if system (4.1) is persistent with respect to the primary host's infectious subclass (i.e., for some time $t_0 > 0$, $I_1(t) \geq I_1(0) > 0$ for $t > t_0$), then we can consider the intermediate host system with a feed from the primary host. That is, we assume that $I_1(t) > 0$ for $t$ large enough via sufficient conditions for permanence.

Since the existence of an interior equilibrium point does not determine the asymptotic behavior of that point, we define the constant external input parameter $\phi$ in a couple of scenarios. Suppose $I_1(t)$ converges to a real number $I*$ as $t \to \infty$, then we define the constant external input parameter by

$$\phi = g \cdot I * .$$

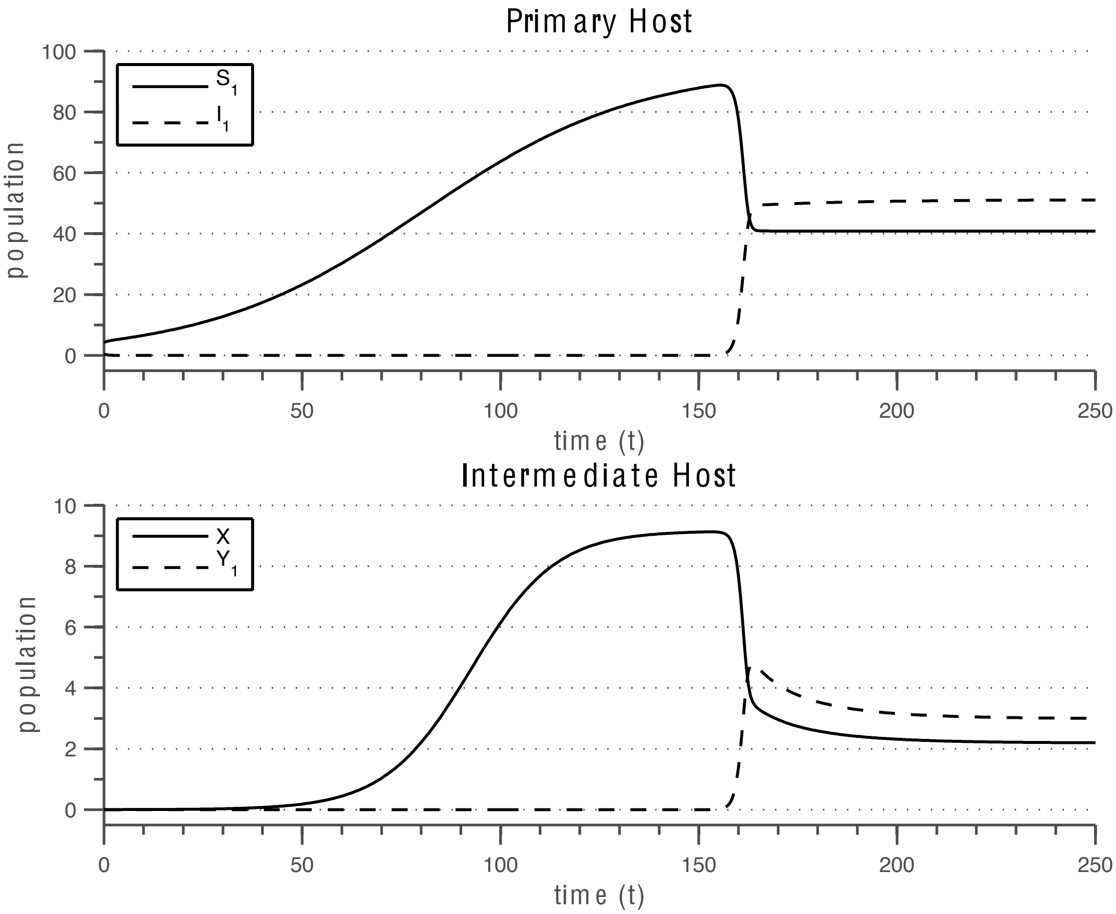

**Figure 4.1:** *Population densities of the subclasses of system (4.1) versus time. Note the two graphs represent the densities for the interacting species. The upper graph represents the primary host, and the lower graph represents the intermediate host. Parameter values for the primary host are* $r_1 = 0.037$, $K_1 = 94.455$, $b_1 = 0.2449$, $a_1 = 0.998$, *and* $v_1 = 0.0018$. *Parameter values for the intermediate host are* $r_X = 0.093$, $K_X = 9.16$, $a_1 = 0.9$, *and* $u_1 = 0.07$ *and* $g = 0.02445$. *Initial conditions are set to* $S(0) = 4.181$, $X(0) = 0.001$, $I_1(0) = 0.483$, *and* $Y_1(0) = 0$. *The trajectories attract to the endemic equilibrium point* $(40.82, 2.19, 51.14, 2.99)$.

If $I_1(t)$ converges to a limit cycle with period $T$, we can define the parameter by

$$\phi = g \cdot \frac{\int_{t_0}^{t_0+T} I(t)dt}{T}.$$

Another possibility could be to simply take the $\min I_1(t)$ for $t > t_0$, then define the parameter by

$$\phi = g \cdot \min I_1(t).$$

In any case, mentioned or not, we have a constant feed parameter $\phi$ that is introduced to the system. In other words, the constant feed parameter $\phi$ is a mechanism that infects individuals in the susceptible population subclass from an outside force. In the case of the interacting species model, the constant infection parameter suggests the primary host population will constantly infect individuals of the intermediate host population with the first strain. Since the primary infectious subclass of system (4.1) approaches a positive equilibrium value (say $I*$), it is reasonable to assume the constant feed parameter $\phi$ is equal to $g \cdot I*$. We can then introduce the subsystem of system (4.1) of one host

$$\begin{aligned} \frac{dX}{dt} &= r_X N_X \left(1 - \frac{N_X}{K_X}\right) - \phi X - b_1 X Y_1 + a_1 Y_1 \\ \frac{dY_1}{dt} &= b_1 X Y_1 + \phi X - (a_1 + u_1) Y_1 \end{aligned} \tag{4.10}$$

with $X(0) \geq 0,\ Y_1(0) \geq 0,$

noting that $\phi X$ is the rate at which species two infects members of the species one's susceptible class. Summing the equations and solving the differential inequality, we get the dissipative condition

$$0 \leq \limsup_{t \to \infty} N_X(t) \leq K_X.$$

We denote the space

$$\mathcal{X} = \{(X, Y_1) \in \mathbb{R}^2 : 0 \leq X, Y_1\},$$

and the attracting region

$$E = \{(X, Y_1) \in \mathcal{X} : X + Y_1 \leq K_X\}.$$

We are now ready to solve for the equilibria.

Clearly, system (4.10) has the disease free equilibrium point $(0,0)$. However, $(K_X, 0)$ is not an equilibrium point for $\phi > 0$. We are now ready to establish the stability criterion for $(0,0)$.

**Proposition 4.5.** *Define the parameter constants*

$$\mathcal{R}_1 = \frac{r_X}{a_1 + u_1 + \phi} \quad \text{and} \quad \mathcal{R}_2 = \frac{\phi u_1}{r_X(a_1 + u_1 + \phi)}. \tag{4.11}$$

*The disease free equilibrium point* $(0,0)$ *for the system (4.10) is locally asymptotically stable when* $\mathcal{R}_1 < 1$ *and* $\mathcal{R}_2 > 1$. $(0,0)$ *is unstable for either: (1)* $\mathcal{R}_1 < 1$ *and* $\mathcal{R}_2 < 1$, *or (2)* $\mathcal{R}_1 > 1$ *and* $\mathcal{R}_2 < 1$.

*Proof.* The Jacobian of system (4.10) is

$$J(X, Y_1) = \begin{bmatrix} r_X\left(1 - \frac{2N_X}{K_X}\right) - b_1 Y_1 - \phi & r_X\left(1 - \frac{2N_X}{K_X}\right) - b_1 X + a_1 \\ b_1 Y_1 + \phi & b_1 X - (a_1 + u_1) \end{bmatrix}, \tag{4.12}$$

and evaluating at $(0,0)$, we get

$$J(0,0) = \begin{bmatrix} r_X - \phi & r_X + a_1 \\ \phi & -(a_1 + u_1) \end{bmatrix}, \tag{4.13}$$

which has the eigenvalues

$$\lambda_{\pm} = \frac{r_X - (a_1 + u_1 + \phi)}{2} \pm \frac{\sqrt{(r_X - (a_1 + u_1 + \phi))^2 - 4\phi u_1}}{2}.$$

We define the constants

$$\mathcal{R}_1 = \frac{r_X}{a_1 + u_1 + \phi} \quad \text{and} \quad \mathcal{R}_2 = \frac{\phi u_1}{r_X(a_1 + u_1 + \phi)}.$$

If $\mathcal{R}_1 > 1$, then $\mathcal{R}_2 < 1$, so we eliminate the case $\mathcal{R}_1 > 1$ and $\mathcal{R}_2 > 1$. $(0,0)$ is stable when $\mathcal{R}_1 < 1$ or $\mathcal{R}_2 > 1$, and $(0,0)$ is unstable for either: (1) $\mathcal{R}_1 < 1$ and $\mathcal{R}_2 < 1$ or (2) $\mathcal{R}_1 > 1$ and $\mathcal{R}_2 < 1$. □

The only invariant set on $\partial\mathcal{X}$ is at the origin, hence, system (4.10) exhibits permanence when either: (1) $\mathcal{R}_1 < 1$ and $\mathcal{R}_2 < 1$ or (2) $\mathcal{R}_1 > 1$ and $\mathcal{R}_2 < 1$. We will now examine the asymptotic behavior of system (4.10) on the interior of $\mathcal{X}$.

Assume either: (1) $\mathcal{R}_1 < 1$ and $\mathcal{R}_2 < 1$ or (2) $\mathcal{R}_1 > 1$ and $\mathcal{R}_2 < 1$, then there exists an interior equilibrium point, denoted by $(\hat{X}, \hat{Y}_1)$. There may exist more than one equilibrium point. However, our interest is focused on the existence of such a point. $(\hat{X}, \hat{Y}_1)$ satisfies the equations

$$\begin{aligned} r_X N_X \left(1 - \frac{N_X}{K_X}\right) - b_1 X Y_1 - \phi X + a_1 Y_1 = 0, \\ b_1 X Y_1 + \phi X - (a_1 + u_1) Y_1 = 0. \end{aligned} \tag{4.14}$$

Then the solution of equations (4.14) is equivalent to the solution of the equation

$$\begin{aligned} Y_1 &= \frac{r_X}{u_1 K_X} \cdot N_X \left(K_X - N_X\right), \\ N_X &= Y_1 + \frac{a_1 + u_1}{b_1} - \frac{\phi(a_1 + u_1)}{b_1} \frac{1}{b_1 Y_1 + \phi}. \end{aligned}$$

**Lemma 4.6.** *Suppose either $\mathcal{R}_1 > 1$ or $\mathcal{R}_2 < 1$. Consider the functions*

$$\begin{aligned} f(x) &= x + \frac{a_1 + u_1}{b_1} - \frac{\phi(a_1 + u_1)}{b_1} \frac{1}{b_1 x + \phi} \\ g_{\pm}(x) &= \frac{K_X}{2} \left(1 \pm \sqrt{1 - 4 \frac{u_1}{r_X K_X} x}\right), \end{aligned}$$

*where all parameters are positive. Then the graphs of $f$ and $g_-$ intersect at the origin and $g_+$ or $g_-$ at a unique point in the positive quadrant.*

*Proof.* We begin by noting that the domain of $g_+$ and $g_-$ is $[0, r_X K_X / 4u_1]$. We have two possibilities:

$$\frac{r_X}{a_1 + u_1 + \phi} > 1 \quad \text{or} \quad \frac{\phi u_1}{r_X (a_1 + u_1 + \phi)} < 1.$$

Suppose the first inequality holds, then

$$\frac{a_1 + u_1 + \phi}{r_X} < 1$$

and $u_1/r_X < 1$ or $r_X/u_1 > 1$. Clearly, $f(0) = 0$ and $g_-(0) = 0$. Now the derivatives of $f$ and $g_-$ with respect to $x$ are given by

$$\begin{aligned} f'(x) &= 1 + \frac{\phi(a_1 + u_1)}{(b_1 x + \phi)^2} \\ g'_-(x) &= \frac{u_1}{r_X} \frac{1}{\sqrt{1 - 4\frac{u_1}{r_X K_X} x}}. \end{aligned}$$

Then we have

$$\begin{aligned} f'(0) &= 1 + \frac{a_1 + u_1}{\phi} \\ g'_-(0) &= \frac{u_1}{r_X}, \end{aligned}$$

implying $f'(0) > g'_-(0)$ (using $u_1/r_X < 1$). That is, f(x) is monotonically increasing and is inside the parabola formed by the functions $g_+$ and $g_-$ for values of $x$ close to zero. $f(x) \to \infty$ as $x \to \infty$; therefore, $f$ intersects the parabola at exactly one point.

Now suppose the second inequality holds, then

$$\frac{u_1}{r_X} < \frac{a_1 + u_1 + \phi}{\phi} = \frac{a_1 + u_1}{\phi} + 1.$$

Again, it is easy to see $f'(0) > g'_-(0)$, so there is exactly one intersection point with $f$ and the parabola formed by the functions $g_+$ and $g_-$. □

Since $f$ and $g_-$ are continuous functions on $[0, r_X K_X/4u_1]$, we can set $h(x) = g_-(x) - f(x)$. We note $h(0) = 0$ and

$$h(x) = \frac{u_1}{r_x} \frac{1}{\sqrt{1 - (4u_1/r_X K_X)}} - 1 + \frac{\phi(a_1 + u_1)}{b_1 x + \phi)^2}.$$

Suppose $u_1/r_X > 1$. If $x \in [0, r_X K_X/4u_1]$, then $h'(x) > 0$ ($g'_-(x) > f(x)$). Moreover, the only intersections of the graphs $f$ and $g_-$ is at the origin. In this case, the only equilibrium point is $(0,0)$, which is stable Lemma 4.6 shows the existence of an intersection point of the equations (4.14); that is, there exists a unique endemic equilibrium point of system (4.10). The endemic equilibrium point is denoted by $(\hat{X}, \hat{Y}_1)$. We are now ready to classify the stability criterion for $(\hat{X}, \hat{Y}_1)$.

**Proposition 4.7.** *Suppose either: (1) $\mathcal{R}_1 < 1$ and $\mathcal{R}_2 < 1$ or (2) $\mathcal{R}_1 > 1$ and $\mathcal{R}_2 < 1$. Then there exists an nontrivial equilibrium point $(\hat{X}, \hat{Y}_1)$ that is locally asymptotically stable.*

*Proof.* Evaluating the Jacobian of system (4.10) at $(\hat{X}, \hat{Y}_1)$, we get

$$tr(\hat{J}) = r_X \left(1 - \frac{2\hat{N}_X}{K_X}\right) - b_1\hat{Y}_1 - \phi + b_1\hat{X} - (a_1 + u_1)$$

and

$$\begin{aligned} \det(\hat{J}) \;\; = \;\; & \left(r_X \left(1 - \tfrac{2\hat{N}_X}{K_X}\right) - b_1\hat{Y}_1 - \phi\right)\left(b_1\hat{X} - (a_1 + u_1)\right) \\ & -(b_1\hat{Y}_1 + \phi)\left(r_X \left(1 - \tfrac{2\hat{N}_X}{K_X}\right) - b_1\hat{X} + a_1\right), \end{aligned}$$

where $\hat{J} = J(\hat{X}, \hat{Y}_1)$. Using the equations (4.14), we can rewrite the trace and determinant in the forms

$$tr(\hat{J}) = -b_1\frac{\hat{Y}_1^{\,2}}{\hat{N}_X} - (a_1 + \phi)\frac{\hat{Y}_1}{\hat{N}_X} - \frac{r_X\hat{N}_X}{K_X} - \frac{\phi\hat{X}}{\hat{Y}_1}$$

and

$$
\begin{aligned}
\det(\hat{J}) &= \frac{\phi\hat{X}}{\hat{Y_1}} \cdot \left( \frac{b_1\hat{Y_1}^2}{\hat{N_X}} + (a_1+\phi)\frac{\hat{I}}{\hat{N_X}} + \frac{r_X\hat{N_X}}{K_X} \right) \\
&\quad -(a_1+u_1)\frac{\hat{Y_1}}{\hat{X}} \left( -\frac{b_1\hat{X}^2}{\hat{N_X}} + (\phi+a_1)\frac{\hat{X}}{\hat{N_X}} - \frac{r_X\hat{N_X}}{K_X} \right) \\
&= (a_1+u_1+\phi)\frac{b_1\hat{X}\hat{Y_1}}{\hat{N_X}} + \phi(a_1+\phi)\frac{\hat{X}}{\hat{N_X}} \\
&\quad -(a_1+u_1)(a_1+\phi)\frac{\hat{Y_1}}{\hat{N_X}} + \left( \phi\frac{\hat{X}}{\hat{Y_1}} + (a_1+u_1)\frac{\hat{Y_1}}{\hat{X}} \right) \frac{r_X\hat{N_X}}{K_X} \\
&> (a_1+\phi)\frac{\beta\hat{X}\hat{Y_1}}{\hat{N_X}} + \phi(a_1+\phi)\frac{\hat{X}}{\hat{N_X}} - (a_1+u_1)(a_1+\phi)\frac{\hat{Y_1}}{\hat{N_X}} \\
&= (a_1+\phi)\left( \frac{\beta\hat{S}\hat{I}}{\hat{N}} + \phi\frac{\hat{S}}{\hat{N}} - (a_1+u_1)\frac{\hat{I}}{\hat{N}} \right) \\
&= (a_1+\phi)\left( (a_1+u_1)\frac{\hat{Y_1}}{\hat{N_X}} - \phi\frac{\hat{X}}{\hat{N_X}} + \phi\frac{\hat{X}}{\hat{N_X}} - (a_1+u_1)\frac{\hat{Y_1}}{\hat{N_X}} \right) = 0.
\end{aligned}
$$

Clearly, $tr(\hat{J}) < 0$ and $\det(\hat{J}) > 0$, implying the equilibrium point $(\hat{X}, \hat{Y})$ is locally stable. □

**Lemma 4.8.** *System (4.10) has no limit cycles on the region $E$.*

*Proof.* Clearly the region $E$ is simply connected in $\mathbb{R}^2$. Now define the Dulac function

$$B(X, Y_1) = \frac{1}{XY_1}.$$

Then

$$\begin{aligned}
\bigtriangledown\cdot(Bf) &= \frac{\partial}{\partial X}B\cdot X' + \frac{\partial}{\partial Y_1}B\cdot Y_1' \\
&= \frac{\partial}{\partial X}\left(r_X\left(\frac{1}{X}+\frac{1}{Y_1}\right)\left(1-\frac{X+Y_1}{K_X}\right)-b_1-\frac{\phi}{Y_1}+\frac{a_1}{X}\right) \\
&\quad +\frac{\partial}{\partial Y_1}\left(b_1+\frac{\phi}{Y_1}-\frac{(a_1+u_1)}{X}\right) \\
&= -\frac{r_X}{X^2}\left(1-\frac{X+Y_1}{K_X}\right)-\frac{r_X}{K_X}\left(\frac{1}{X}+\frac{1}{Y_1}\right)-\frac{a_1}{X^2}-\frac{\phi}{Y_1^2}
\end{aligned}$$

On the region $E$, we have that $0 \leq X+Y_1 \leq K_X$, which in turn implies $\bigtriangledown\cdot(Bf) < 0$. In other words, $\bigtriangledown\cdot(Bf)$ is not identically zero and does not change sign in $E$. Hence, system (4.10) satisfies Dulac's Criteria. We are now able to conclude system (4.10) has no limit cycles on the region $E$. □

We are now ready to make our claim about the global analysis of system (4.10).

**Theorem 4.9.** *Suppose* $\mathcal{R}_1 < 1$ *and* $\mathcal{R}_2 > 1$. *Then for any initial conditions* $X(0) \geq 0$ *and* $Y_1(0) \geq 0$, *the trajectories globally attract to the disease free equilibrium point* $(0,0)$. *Suppose either: (1)* $\mathcal{R}_1 < 1$ *and* $\mathcal{R}_2 < 1$ *or (2)* $\mathcal{R}_1 > 1$ *and* $\mathcal{R}_2 < 1$, *then the trajectories globally attract to the unique disease endemic equilibrium point* $(\hat{X},\hat{Y_1})$ *for any initial conditions* $X(0) \geq 0$ *and* $Y_1(0) \geq 0$ *(with the exception of* $X(0) = Y_1(0) = 0$*).*

*Proof.* The proof follows from Proposition 4.5, Lemma 4.6, Proposition 4.7, and Lemma 4.8. □

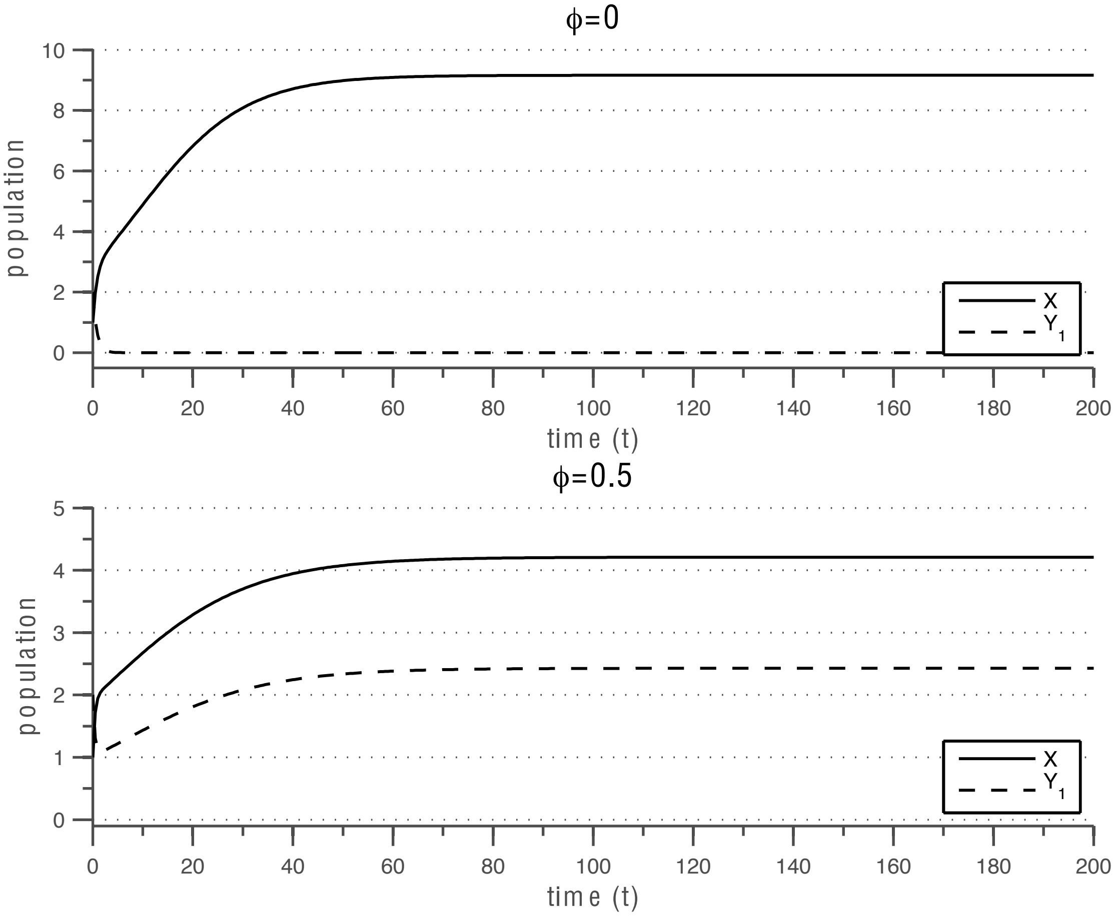

**Figure 4.2:** *Population densities of the subclasses of system (4.10) versus time. Note the two graphs are the represents the densities for intermediate species when* $\phi = 0$ *and* $\phi = 0.5$. *The other parameter values are* $r_X = 0.093$, $K = 9.16$, $b_1 = 0.2449$, $a_1 = 0.9$, *and* $u_1 = 0.07$ *and* $g = 0.02445$. *Initial conditions are set to* $X(0) = 0.02$ *and* $Y_1(0) = 2$. *The trajectories attract to the endemic equilibrium points* $(9.16, 0)$ *and* $(2.59, 2.92)$ *in the respective cases.* $\mathcal{R}_0 = 0.23$, *so notice the infectious feed parameter,* $\phi$, *forces the strain to become endemic in the host population.*

## 4.3 Other Models with an External Input

In this section, we use the idea of an external input of infection, as in section (4.2), with a super- and co- infection model, similar to that of sections 3.11 and 3.19.

First, we consider the case with a co-infection model with an inter-species feed. That is, we consider the super-infection system (3.11) from section 3.2, resulting in the system of differential equations

$$\begin{aligned}
\frac{dS_1}{dt} &= r_1 N_1 \left(1 - \frac{N_1}{K_1}\right) - \beta_1 S_1 I_1 - \beta_3 S_1 J - \gamma S_1 + \alpha_1 I_1 + a_3 J \\
\frac{dI_1}{dt} &= \beta_1 S_1 I_1 - \delta I_1 J - (\alpha_1 + v_1) I_1 \\
\frac{dJ}{dt} &= \beta_3 S_1 J + \delta I_1 J + \gamma S_1 - (\alpha_3 + v_3) I_2 \\
&\text{with } S_1(0) \geq 0,\ I_1(0) \geq 0,\ J(0) \geq 0.
\end{aligned} \tag{4.15}$$

Using an argument similar to that of section (3.2), we get system (4.3) is dissipative. Denote the set

$$\mathcal{X} = \{(S, I_1, J) \in \mathbb{R}^3 : 0 \leq S, I_1, J\}$$

and the compact attractor

$$E = \{(S, I_1, J) \in \mathcal{X} : S + I_1 + J \leq K_1\}.$$

The only boundary equilibria of system (4.3) are at the origin and the point $(\hat{S}_1, 0, \hat{J})$. That is, the equilibrium point $(\hat{S}, 0, \hat{J})$ corresponds to the equilibrium point $(\hat{S}, \hat{I})$ of section 3.1. Moreover, the only invariant spaces of the boundary are the spaces $\mathcal{N}_0$ and $\mathcal{N}_1$ as described in Section 3.2. That is, the feed will force any trajectory to flow off of the space $\mathcal{N}_2$. Therefore, the system cannot form a cycle on the boundary, and $\{\mathcal{N}_\sigma\}_{\sigma\in\Lambda}$ is acyclic. Hence, condition (b) of hypothesis **(H)** is satisfied. A condition similar to conditions on $\mathcal{R}_1$ and $\mathcal{R}_3$ is sufficient to have stability with respect to the hyperplane of $\mathcal{X}$ where $I_1 = 0$. In all other cases of in which the analogous condition strictly fails, system (4.3) would exhibit persistence with respect to the super-infectious strain $J$.

Now, we consider the co-infection model with an external input of infection. That is, we consider the co-infection system (3.19) from Section (3.3), resulting in the differential equations

$$\begin{aligned}
\frac{dX}{dt} &= r_X N_X\left(1-\frac{N_X}{K_X}\right) - \sum_{i=1}^{2} b_i(Y_i + d_iY_{12} + g_i)X + \alpha_1 Y_1 + a_1 Y_2 + a_{12}Y_{12}\\
\frac{dY_1}{dt} &= b_1(Y_1 + d_1Y_{12} + g_1)X - b_{12}Y_1Y_2 - (a_1+u_1)Y_1\\
\frac{dY_2}{dt} &= b_2(Y_2 + d_2Y_{12} + g_2)X - b_{21}Y_1Y_2 - (a_1+u_2)Y_2\\
\frac{dY_{12}}{dt} &= (b_{12}+b_{21})Y_1Y_2 - (a_{12}+u_{12})Y_{12}\\
&\text{with } X(0)\ge 0,\ Y_1(0)\ge 0,\ Y_2(0)\ge 0,\ Y_{12}(0)\ge 0.
\end{aligned} \tag{4.16}$$

In this case, the rate in which susceptible individuals feed into the infectious subclass

$Y_i$ is $b_i g_i$. System (4.16) is dissipative by an argument similar to the dissipativity of system (3.19) of section (3.3).

The Jacobian of system (4.16) evaluated at the origin is given by

$$J(0,0,0,0) = \begin{bmatrix} r_X - b_1 g_1 - b_2 g_2 & r_X + a_1 & r_X + a_2 & r_X + a_{12} \\ b_1 g_1 & -(a_1 + u_1) & 0 & 0 \\ b_2 g_2 & 0 & -(a_2 + u_2) & 0 \\ 0 & 0 & 0 & -(a_{12} + u_{12}) \end{bmatrix}. \quad (4.17)$$

The characteristic polynomial of $J(0,0,0,0)$ is given by

$$p(\lambda) = (\lambda + a_{12} + u_{12})(\lambda^3 + c_1 \lambda^2 + c_2 \lambda + c_3),$$

where the coefficients are given by

$$\begin{aligned} c_1 &= a_1 + u_1 + a_2 + u_2 + b_1 g_1 + b_2 g_2 - r_X \\ c_2 &= (a_1 + u_1)(a_2 + u_2) - (a_1 + u_1 + a_2 + u_2)(r_X - b_1 g_1 - b_2 g_2) \\ &\quad -(b_1 g_1 (r_X + a_1) + b_2 g_2 (r_X + a_2)) \\ c_3 &= (b_1 g_1 + b_2 g_2 - r_X)(a_1 + u_1)(a_2 + u_2) - (b_1 g_1 (a_2 + u_2) + b_2 g_2 (a_1 + u_1)). \end{aligned}$$

We are now ready to establish the Routh-Hurwitz conditions for stability; that is, $c_1 > 0$, $c_3 > 0$, and $c_1 c_2 - c_3 > 0$. Hence, when conditions are satisfied, the origin is locally asymptotically stable. If any of the three conditions are not satisfied, the system exhibits permanence modulo the neutral stability cases.

# Chapter 5

# The System with Interacting Hosts and Recombination

In Chapter 2, a deterministic model for influenza A is introduced. The model features three interacting host species, in which an intermediate host acts as a “mixing vessel” for strains passed from the other host species. A co-infected individual in the intermediate host population can act to potentially produce super-strains that are highly virulent in the primary host population. In Chapters 3 and 4, a number of the subsystems of the model of Chapter 2 are analyzed and simulated. In this chapter, we will consider the entire model from Chapter 2.

## 5.1 The Interacting Host Model

The entire model proposed for influenza in Chapter 2 is given by the primary host of system (2.5), the intermediate host in system (2.6), and the secondary host of system (2.3). This model will be referred to as the interacting host system (IHS).

We begin by defining the total population for the primary, secondary, and intermediate host species by $N_1 = S_1 + I_1 + J$, $N_2 = S_2 + I_2$, and $N_X = X + Y_1 + Y_2 + Y_{12} + Y_3$, respectively. We determine that

$$0 \leq \limsup_{t \to \infty} N_i(t) \leq K_i$$

for $i = 1, 2, X$, by using the same methodology for the subsystems in Chapter 3. Hence, the system is dissipative. We let $y = (S_2, I_2, X, Y_1, Y_2, Y_{12}, Y_3, S_1, I_1, J)$, and the $i$-th component is denoted by $y_i$. The space is denoted by

$$\mathcal{X} = \{y \in \mathbb{R}^{10} : 0 \leq y_i\},$$

and the attracting region

$$E = \{y \in \mathcal{X} : \sum_{i=1}^{10} y_i \leq K\},$$

where $K = K_1 + K_2 + K_X$. The following proposition defines the basic reproductive number for the IHS, following the methods from [44].

**Proposition 5.1.** $\mathcal{R}_0^{\max}$ *for the IHS is defined by*

$$\mathcal{R}_0^{\max} = \max\left\{\frac{\beta_2 K_2}{\alpha_2 + v_2}, \frac{b_1 K_X}{a_1 + u_1}, \frac{b_2 K_X}{a_2 + u_2}, \frac{b_3 K_X}{a_3 + u_3}, \frac{\beta_1 K_1}{\alpha_1 + v_1}, \frac{\beta_3 K_1}{\alpha_3 + v_3}\right\}.$$

*For any positive parameter values,* $x_0 = (0, 0, 0, 0, 0, 0, 0, 0, 0, 0)$ *is a saddle. The following conditions characterize the stability of* $x_K = (K_2, 0, K_X, 0, 0, 0, 0, K_1, 0, 0)$*:*

*i. If* $\mathcal{R}_0^{\max} < 1$*, then* $x_K$ *is locally asymptotically stable.*

*ii. If* $\mathcal{R}_0^{\max} > 1$*, then* $x_K$ *is unstable.*

*Proof.* We begin by letting $x_1 = I_2$, $x_2 = Y_1$, $x_3 = Y_2$, $x_4 = Y_{12}$, $x_5 = Y_3$, $x_6 = I_1$, $x_7 = J$, $x_8 = S_2$, $x_9 = X$, and $x_{10} = S_1$, and $\vec{x} = (x_1, \dots, x_{10})$. Now we can write the IHS in the form

$$\dot{x}_i = \mathcal{F}_i(\vec{x}) - \mathcal{V}_i(\vec{x}),$$

where

$$\mathcal{F} = \begin{bmatrix} \beta_2 S_2 I_2 \\ b_1(Y_1 + d_1 Y_{12})X + g_1 X I_1 \\ b_2(Y_2 + d_1 Y_{12})X + g_2 X I_2 \\ (b_{12} + b_{21}) Y_1 Y_2 \\ \psi Y_{12} + b_3 X Y_3 + b_{13} Y_1 Y_3 + b_{23} Y_2 Y_3 \\ \beta_1 S_1 \\ \beta_3 S_1 J + \delta I_1 J + \gamma_3 S_1 Y_3 \\ 0 \\ 0 \\ 0 \end{bmatrix}$$

and

$$\mathcal{V} = \begin{bmatrix} (\alpha_2 + v_2) I_2 \\ b_{12} Y_1 Y_2 + b_{13} Y_1 Y_3 + (a_1 + u_1) Y_1 \\ b_{21} Y_1 Y_2 + b_{23} Y_2 Y_3 + (a_2 + U_2) Y_2 \\ (a_{12} + u_{12} + \psi) Y_{12} \\ (a_3 + u_3) Y_3 \\ \delta I_1 J + (\alpha_1 + v_1) I_1 \\ (\alpha_3 + v_3) J \\ -r_2 N_2 \left(1 - \frac{N_2}{K_2}\right) + \beta_2 S_2 I_2 - \alpha_2 I_2 \\ -r_X N_X \left(1 - \frac{N_X}{K_X}\right) + \sum_{i=1}^{2} b_i (Y_i + d_i Y_{12}) X + b_3 X Y_3 + \sum g_i X I_i - \sum_{i=1}^{3} a_i Y_i - a_{12} Y_{12} \\ -r_1 N_1 \left(1 - \frac{N_1}{K_1}\right) + \beta_1 S_1 I_1 + \beta_3 S_1 J - \alpha_1 I_1 - \alpha_3 J \end{bmatrix}.$$

We then define

$$\mathcal{V}^{+} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ r_2N_2\left(1 - \frac{N_2}{K_2}\right) + \alpha_2 I_2 \\ r_X N_X\left(1 - \frac{N_X}{K_X}\right) + \sum_{i=1}^{3} a_i Y_i + a_{12}Y_{12} \\ r_1N_1\left(1 - \frac{N_1}{K_1}\right) + \alpha_1 I_1 + \alpha_3 J \end{bmatrix}.$$

and

$$\mathcal{V}^{-} = \begin{bmatrix} (\alpha_2 + v_2)I_2 \\ b_{12}Y_1Y_2 + b_{13}Y_1Y_3 + (a_1 + u_1)Y_1 \\ b_{21}Y_1Y_2 + b_{23}Y_2Y_3 + (a_2 + U_2)Y_2 \\ (a_{12} + u_{12} + \psi)Y_{12} \\ (a_3 + u_3)Y_3 \\ \delta I_1 J + (\alpha_1 + v_1)I_1 \\ (\alpha_3 + v_3)J \\ \beta_2 S_2 I_2 \\ \sum_{i=1}^{2} b_i(Y_i + d_iY_{12})X + b_3XY_3 + \sum g_i X I_i \\ \beta_1 S_1 I_1 + \beta_3 S_1 J \end{bmatrix}.$$

where $\mathcal{V}_i = \mathcal{V}_i^- - \mathcal{V}_i^+$. It is not difficult to demonstrate conditions (A1)-(A4) in [44] are satisfied, so we draw our attention to condition (A5).

(A5) The eigenvalues for the matrix $-D\mathcal{V}(x_K)$ are $\lambda_1 = -(\alpha_2 + v_2)$, $\lambda_2 = -(a_1 + u_1)$, $\lambda_3 = -(a_2 + u_2)$, $\lambda_4 = -(a_{12} + u_{12})$, $\lambda_5 = -(a_3 + u_3)$, $\lambda_6 = -(\alpha_1 + v_1)$, $\lambda_7 = -(\alpha_3 + v_3)$, $\lambda_8 = -r_2$, $\lambda_9 = -r_x$, and $\lambda_{10} = -r_1$, which are all negative for positive parameter values. Therefore, the condition (A5) is satisfied.

The product of the matrices $F$ and $V^{-1}$ is

$$FV^{-1} = \begin{bmatrix} \frac{\beta_2 K_2}{\alpha_2+v_2} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \frac{b_1 K_X}{a_1+u_1} & 0 & \frac{b_1 d_1 K_X}{a_{12}+u_{12}+\psi} & 0 & \frac{g_1 K_X}{\alpha_1+v_1} & 0 \\ \frac{g_2 K_X}{a_2+u_2} & 0 & \frac{b_2 K_X}{a_2+u_2} & \frac{b_2 d_2 K_X}{a_{12}+u_{12}+\psi} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{\psi}{a_{12}+u_{12}+\psi} & \frac{b_3 K_X}{a_3+u_3} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \frac{\beta_1 K_1}{\alpha_1+v_1} & 0 \\ 0 & 0 & 0 & 0 & \frac{\gamma_1 K_1}{a_1+u_1} & 0 & \frac{\beta_3 K_1}{\alpha_1+v_1} \end{bmatrix},$$

which has the spectral radius

$$\rho(FV^{-1}) = \max\left\{\frac{\beta_2 K_2}{\alpha_2 + v_2}, \frac{b_1 K_X}{a_1 + u_1}, \frac{b_2 K_X}{a_2 + u_2}, \frac{b_3 K_X}{a_3 + u_3}, \frac{\beta_1 K_1}{\alpha_1 + v_1}, \frac{\beta_3 K_1}{\alpha_3 + v_3}\right\}.$$

Hence, the basic reproductive number is given by $\mathcal{R}_0^{\max} = \rho(FV^{-1})$.

Now that we have calculated the basic reproductive number, we consider the stability criterion at the equilibrium point $x_0$. Evaluating the Jacobian at $x_0$, we have

$$J(x_0) = \begin{bmatrix} A & 0 & 0 \\ 0 & B & 0 \\ 0 & 0 & C \end{bmatrix},$$

where the matrices are given by

$$A = \begin{bmatrix} r_2 & r_2 + \alpha_2 \\ 0 & -(\alpha_2 + v_2) \end{bmatrix},$$

$$B = \begin{bmatrix} r_X & r_x + a_1 & r_x + a_2 & r_x + a_{12} & r_x + a_3 \\ 0 & -(a_1 + u_1) & 0 & 0 & 0 \\ 0 & 0 & -(a_2 + u_2) & 0 & 0 \\ 0 & 0 & 0 & -(a_{12} + u_{12} - \psi) & 0 \\ 0 & 0 & 0 & \psi & -(a_3 + u_3) \end{bmatrix},$$

and

$$C = \begin{bmatrix} r_1 & r_1 + \alpha_1 & r_1 + \alpha_3 \\ 0 & -(\alpha_1 + v_1) & 0 \\ 0 & 0 & -(\alpha_3 + v_3) \end{bmatrix}.$$

The eigenvalues of $A$, $B$ and $C$ are the same as for $J(x_0)$, which are given by $\lambda_1 = r_2$, $\lambda_2 = -(\alpha_2 + v_2)$, $\lambda_3 = r_X$, $\lambda_4 = -(a_1 + u_1)$, $\lambda_5 = -(a_2 + u_2)$, $\lambda_6 = -(a_{12} + u_{12} + \psi)$, $\lambda_7 = -(a_3 + u_3)$, $\lambda_8 = r_1$, $\lambda_9 = -(\alpha_1 + v_1)$, and $\lambda_{10} = -(\alpha_3 + v_3)$. These eigenvalues are all real-valued and consist of positive and negative values. Hence, the equilibrium point $x_0$ is a saddle. $\square$

The values for computing $\mathcal{R}_0^{\max}$ are denoted by

$$\vec{\mathcal{R}_0} = \left[\frac{\beta_2 K_2}{\alpha_2 + v_2}, \frac{b_1 K_X}{a_1 + u_1}, \frac{b_2 K_X}{a_2 + u_2}, \frac{b_3 K_X}{a_3 + u_3}, \frac{\beta_1 K_1}{\alpha_1 + v_1}, \frac{\beta_3 K_1}{\alpha_3 + v_3}\right].$$

We now consider the remaining disease free equilibria:

$$\begin{aligned} e_2 &= (K_2, 0, 0, 0, 0, 0, 0, 0, 0, 0) \\ e_X &= (0, 0, K_X, 0, 0, 0, 0, 0, 0, 0) \\ e_1 &= (0, 0, 0, 0, 0, 0, 0, K_1, 0, 0) \\ e_{2X} &= (K_2, 0, K_X, 0, 0, 0, 0, 0, 0, 0) \\ e_{21} &= (K_2, 0, 0, 0, 0, 0, 0, K_1, 0, 0) \\ e_{X1} &= (0, 0, K_X, 0, 0, 0, 0, K_1, 0, 0). \end{aligned}$$

Denote the index set $\mathcal{A} = \{2, X, 1, 2X, 21, X1\}$. Then the Jacobian for $e_i$ for any $i \in \mathcal{A}$ has the form

$$J(e_i) = \begin{bmatrix} A_i & * & * \\ 0 & B_i & * \\ 0 & 0 & C_i \end{bmatrix}.$$

Then there are two choices for each of the matrices $A_i$, $B_i$, and $C_i$. The results for the equilibria $e_i$ ($i \in \mathcal{A}$) are similar to that of $\vec{0}$ and $x_0$. For example, when the corresponding species has zero components (e.g. matrices $e_X$, $e_1$, and $e_{X1}$ have zero components for the secondary host species), the result is the same eigenvalue computation is the same as for the equilibrium point $\vec{0}$ for the corresponding species.

Due to the large number of equations in the IHS, the computation of nontrivial equilibria is omitted. In the next section, we simulate several scenarios to gain insight to the dynamics for the IHS.

## 5.2 Simulations

Due to the number of equations of the IHS, it is difficult to analyze the IHS as in the cases of the subsystems. We will chose parameter values that will describe a number of different scenarios, and simulate the IHS using numerical methods. In these simulations, we will fix the secondary host's parameters to the values used in section 3.2 for the simulations of system (3.11) for the susceptible and infectious subclasses ($S_1$ and $I_1$ but not $J$). The purpose of the secondary host is to act as an agent that feeds infection individuals from the intermediate host's susceptible subclass into the infectious subclass $Y_2$. Although it is reasonable to convert this process into a feed parameter, say $\phi = g_2 \cdot I_2*$ with equilibrium value $I_2*$ for the secondary host's infectious subclass, we consider the dynamics of the secondary host to explore its dynamics as they impact the rest of the IHS. **Figure 5.1** shows the dynamics for the secondary host used throughout the simulations.

In the first scenario, we consider a situation in which there is no initial presence of a super-strain in the primary host population; however, through recombination in the intermediate host's co-infected subclass, the super-strain can emerge through species interaction. The parameter values are set similar to the simulations of the super-infection and co-infection subsystems described in sections 3.2 and 3.3 of chapter 3; however, the super-strain's incidence rates are significantly greater. For the intermediate host, the parameter values are set as follows: $r_X = 0.093$, $K_X = 9.16$, $b_1 = 0.23$, $b_2 = 0.2$, $b_{12} = 0.2$, and $b_{21} = 0.17$ with $d_1 = 1$, $d_2 = 1$, $a_1 = 0.9$, $u_1 = 0.07$, $a_2 = 0.8$, $u_2 = 0.08$, $a_{12} = 0.75$, and $u_{12} = 0.03$. The intermediate host's initial conditions are set to $X(0) = 0.002$, $Y_1(0) = 0.001$, $Y_2(0) = 0.001$, and $Y_{12}(0) = 0.001$. For the primary host, the parameter values are set as follows:

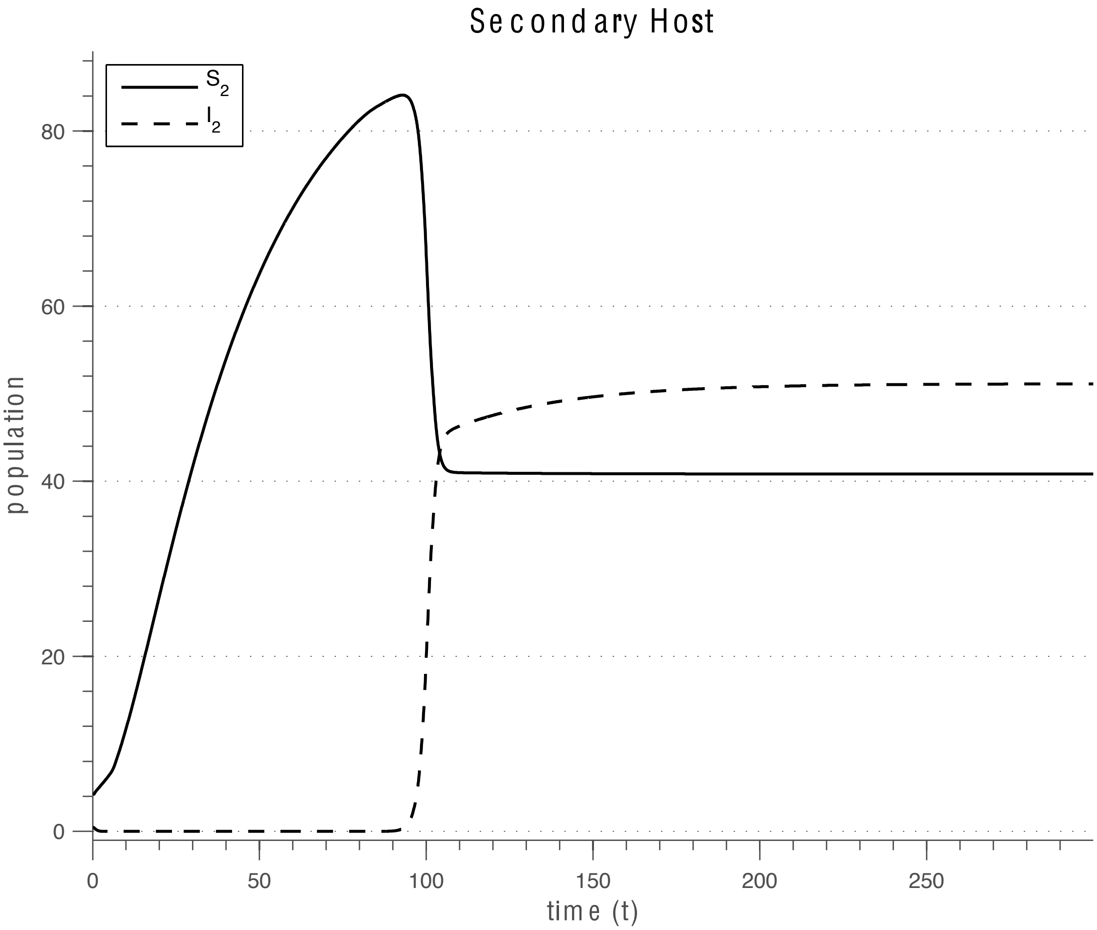

**Figure 5.1:** *Graph of the secondary host's population densities versus time. Parameter values are* $r_2 = 0.037$*,* $K_2 = 94.455$*,* $\beta_2 = 0.0245$*,* $\alpha_2 = 0.99824$*, and* $v_2 = 0.00176$*. Initial conditions are set to* $S_2(0) = 4.181$ *and* $I_2(0) = 1.0$*. The trajectories attract to the endemic equilibrium point* $(40.8, 51.1)$*.*

$r_1 = 0.037$, $K_1 = 94.455$, $\beta_1 = 0.0245$, $\beta_3 = 0.084$, $\alpha_1 = 0.99824$, $\alpha_3 = 0.32$, $v_1 = 0.00176$, $v_3 = 0.68$, and $\delta = 0.084$. The primary host's initial conditions are set to $S_1(0) = 4.181$, $I_1(0) = 1.483$, and $J(0) = 0$. Notice in this case, the infectious rates $\beta_3$ and $\delta$ for the super-strain, corresponding to the primary host subclass $J$, are set to 0.084 to demonstrate a highly transmissible strain, and the super-strain initial condition $J(0)$ is set to zero so that the strain is not initially present in the primary host population.

The interaction parameters are initially set so that the primary and secondary hosts are allowed to pass the primary and secondary strains to the intermediate host; however, the intermediate host is not allowed to pass the super-strain into the primary host population. That is, we set the interaction parameters as follows: $g_1 = 0.1$, $g_2 = 0.1$, and $\psi = 0$. The simulation show all three species exhibit uniform persistence with the exception of the primary host's super-strain subclass $J$. **Figures 5.2** and **5.3** display the resulting dynamics for intermediate and primary hosts, respectively.

We then increase the interaction parameters so that the primary and secondary hosts are allowed to pass the primary and secondary strains to the intermediate host; however, now the intermediate host is allowed to pass the super-strain into the primary host population. That is, we set the interaction parameters as follows: $g_1 = 0.1$, $g_2 = 0.1$, and $\psi = 0.05$. The resulting dynamics show that the super-strain becomes the dominating factor and disrupts the persistence of all the related primary strain subclasses. In other words, the super-strain invades the primary host population; the super-strain naturally eradicates the primary strain population; the eradication of the primary strain in the primary host population causes the strain

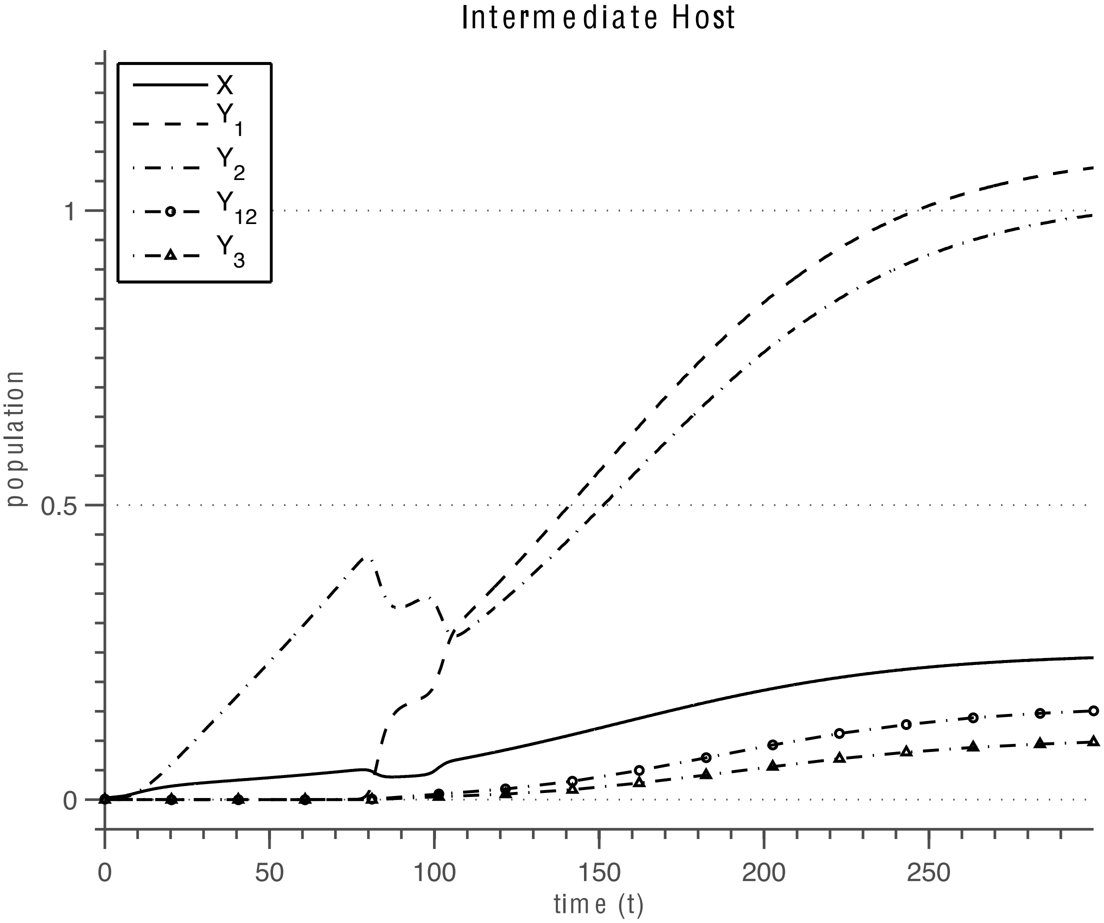

**Figure 5.2:** *Intermediate host population densities versus time for the IHS. This figure corresponds to the scenario in which the intermediate host is infected by the primary and secondary strains, but not the super-strain; that is,* $g_1 = 0.1$*,* $g_2 = 0.1$*, and* $\psi = 0$*.* **Figure 5.1** *and* **Figure 5.3** *are the corresponding simulations to this scenario. Parameter values are* $r_X = 0.093$*,* $K_X = 9.16$*,* $b_1 = 0.23$*,* $b_2 = 0.2$*,* $b_{12} = 0.2$*, and* $b_{21} = 0.17$ *with* $d_1 = 1$*,* $d_2 = 1$*,* $a_1 = 0.9$*,* $u_1 = 0.07$*,* $a_2 = 0.8$*,* $u_2 = 0.08$*,* $a_{12} = 0.75$*, and* $u_{12} = 0.03$*. Initial conditions are set to* $X(0) = 0.002$*,* $Y_1(0) = 0.001$*,* $Y_2(0) = 0.001$*,* $Y_{12}(0) = 0.001$*, and* $Y_3(0) = 0$*.*

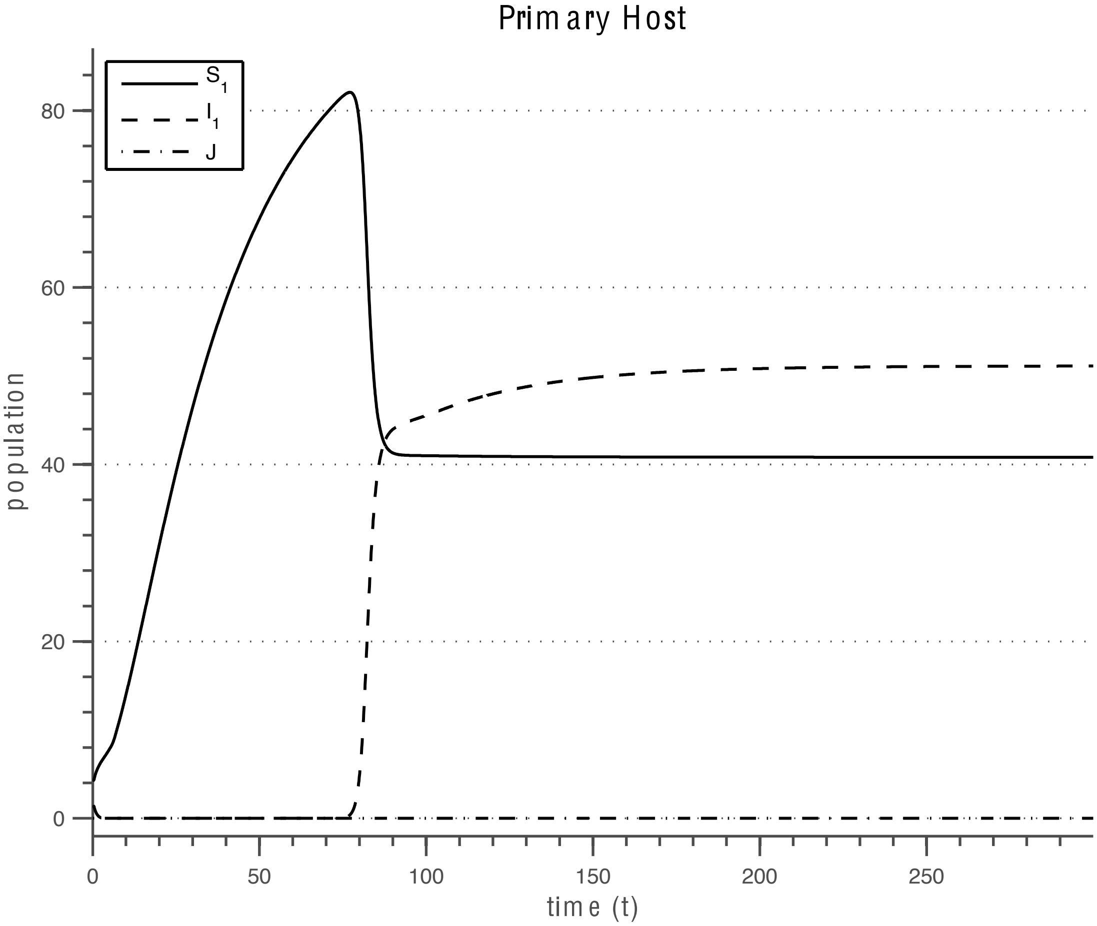

**Figure 5.3:** *Primary host population densities versus time for the IHS. This figure corresponds to the scenario in which the intermediate host is infected by the primary and secondary strains, but not the super-strain; that is,* $g_1 = 0.1$, $g_2 = 0.1$, *and* $\psi = 0$. **Figure 5.1** *and* **Figure 5.2** *are the corresponding simulations to this scenario. Parameter values are* $r_1 = 0.037$, $K_1 = 94.455$, $\beta_1 = 0.0245$, $\beta_3 = 0.084$, $\alpha_1 = 0.99824$, $\alpha_3 = 0.32$, $v_1 = 0.00176$, $v_3 = 0.68$, *and* $\delta = 0.084$. *Initial conditions are set to* $S_1(0) = 4.181$, *and* $I_1(0) = 1.483$ *and* $J(0) = 0$.

to be eradicated from the intermediate host population. Hence, the intermediate host exhibits persistence in the susceptible and secondary strain infectious subclasses ($X$ and $Y_2$), and the primary host exhibits persistence in the susceptible and super-strain infectious subclasses ($S_1$ and $J$). Moreover, the resulting intermediate host scenario reflects the situation of swine infected with avian influenza described in [11]. **Figures 5.4** and **5.5** display the resulting dynamics for intermediate and primary hosts, respectively.

The oscillating dynamics of the super-strain in the primary host population shows dampening epidemic spikes. The numerical data for the super-strain simulation was used to determine the peaks of the spikes. The mean time was determined to be approximately 36.3. In other words, the numerical analysis of these spikes suggests the model predicts an epidemic every 36.3 years. We apply the same analysis to the major influenza pandemics since the late nineteenth century; see **Table 5.1**. The initial year for each pandemic was taken, and the mean differences between each case was determined to be approximates 26.3 years.

**Table 5.1:** *Major influenza pandemics from the late nineteenth century. Pandemic, year, and subtype extracted from [24], and deaths taken from [39]*

| Pandemics | Years | Deaths | Subtype Involved |
|---|---|---|---|
| Asiatic (Russian) Flu | 1889-90 | 1 million | H2N2 proposed |
| Spanish Flu | 1918-19 | up to 50 million | H1N1 |
| Asian Flu | 1957-58 | 1 to 2 million | H2N2 |
| Hong Kong Flu | 1968-69 | 700,000 | H3N2 |

In the next scenario, we consider a situation in which a super strain can invade a population, despite the relative basic reproduction number suggesting otherwise. We fix all parameters for the three species in a manner similar to the first scenario,

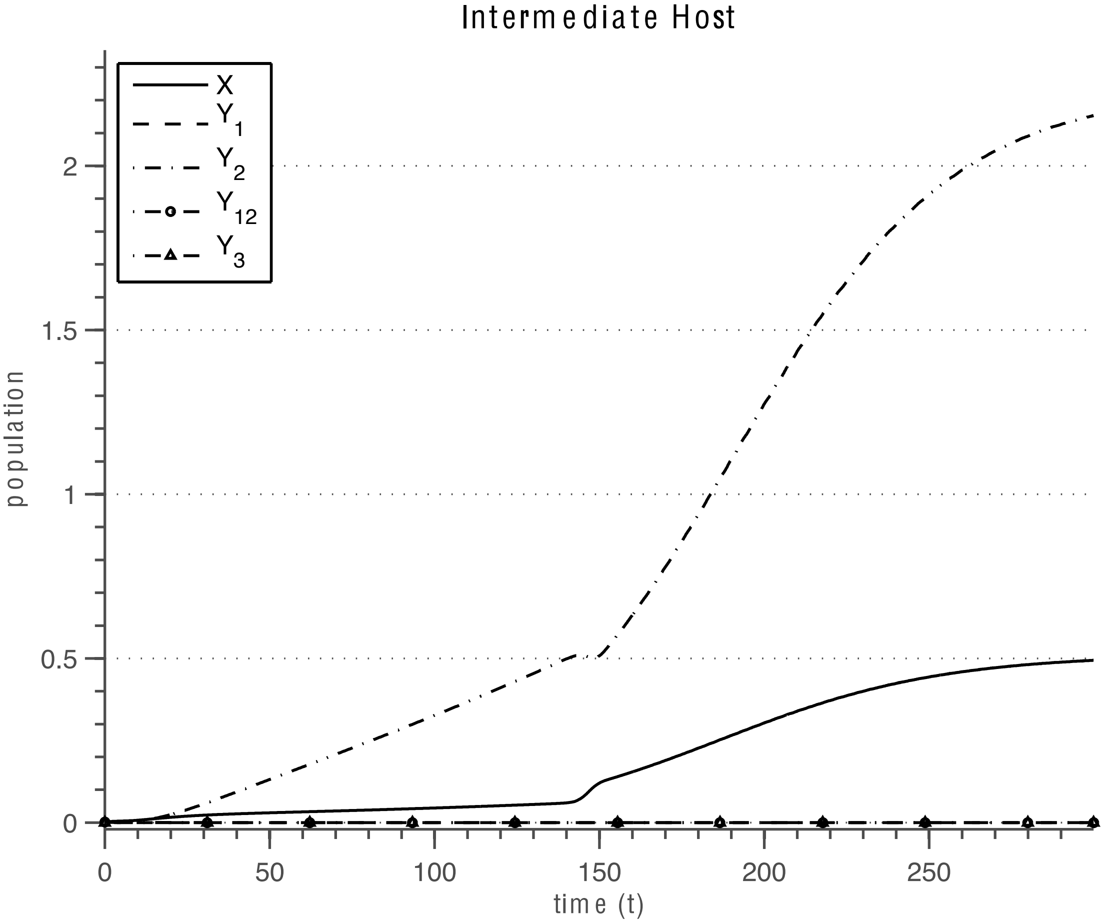

**Figure 5.4:** *Intermediate host population densities versus time for the IHS. This figure corresponds to the scenario in which the intermediate host is infected by the primary and secondary strains, but not the super-strain; that is,* $g_1 = 0.1$, $g_2 = 0.1$, *and* $\psi = 0.05$. **Figure 5.1** *and* **Figure 5.5** *are the corresponding simulations to this scenario. Parameter values are* $r_X = 0.093$, $K_X = 9.16$, $b_1 = 0.23$, $b_2 = 0.2$, $b_{12} = 0.2$, $b_{21} = 0.17$, $d_1 = 1$, $d_2 = 1$, $a_1 = 0.9$, $u_1 = 0.07$, $a_2 = 0.8$, $u_2 = 0.08$, $a_{12} = 0.75$, *and* $u_{12} = 0.03$. *Initial conditions are set to* $X(0) = 0.002$, $Y_1(0) = 0.001$, $Y_2(0) = 0.001$, $Y_{12}(0) = 0.001$, *and* $Y_3(0) = 0$.

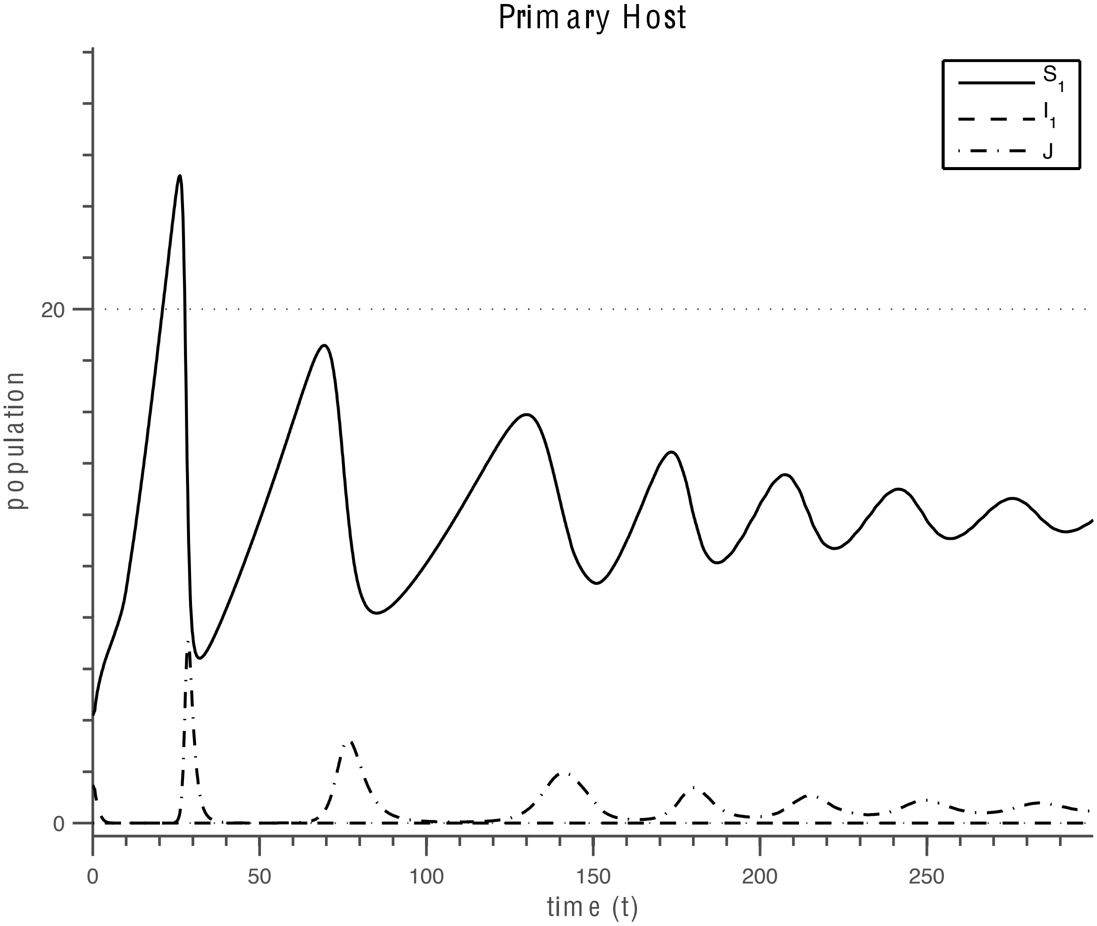

**Figure 5.5:** *Primary host population densities versus time for the IHS. This figure corresponds to the scenario in which the intermediate host is infected by the primary and secondary strains. In this case, the intermediate host infects the primary host with the super-strain; that is,* $\gamma_1 = 0.1$. **Figure 5.1** *and* **Figure 5.4** *are the corresponding simulations to this scenario. Parameter values are* $r_1 = 0.037$, $K_1 = 94.455$, $\beta_1 = 0.0245$, $\beta_3 = 0.084$, $\alpha_1 = 0.99824$, $\alpha_3 = 0.32$, $v_1 = 0.00176$, $v_3 = 0.68$, *and* $\delta = 0.084$. *Initial conditions are* $S_1(0) = 4.181$, $I_1(0) = 1.483$, *and* $J(0) = 0$.

with the exception of the parameters $\beta_3 = 0.0084$ and $\delta = 0.0084$. These super-strain parameters imply the strain's basic reproductive number is $\mathcal{R}_{0,3} = 0.793$, which traditionally implies the super-strain subclass population density would converge to zero (i.e., naturally eradicate). However, due to the species interaction, the intermediate host is able to feed the super-strain into the primary host population. The basic reproductive numbers are given by

$$\vec{\mathcal{R}_0} = [2.31, 2.11, 1.56, 1.83, 2.31, 0.79],$$

which implies $\mathcal{R}_0^{\max} = 2.31$. **Figure 5.6** shows the phase portrait for the primary host. Initially, the trajectory approaches the $S$-axis, suggesting the super-strain is naturally dying out. The primary host population is nearly free of all strain, and its susceptible subclass's population begins to grow. Once the susceptible subclass's density is large enough, the primary strain begins to spread in the population. During this time, the primary strain is feeding into the intermediate host population, which is (with the secondary strain) producing the super-strain out of the intermediate host's co-infected subclass. The super-strain then begins to invade the primary host population, and the trajectory converges to the asymptotically stable equilibrium point $(41.2, 12.9, 1.2)$. Hence, the system exhibits permanence in the primary host population contrary to the individual host species' threshold constants.

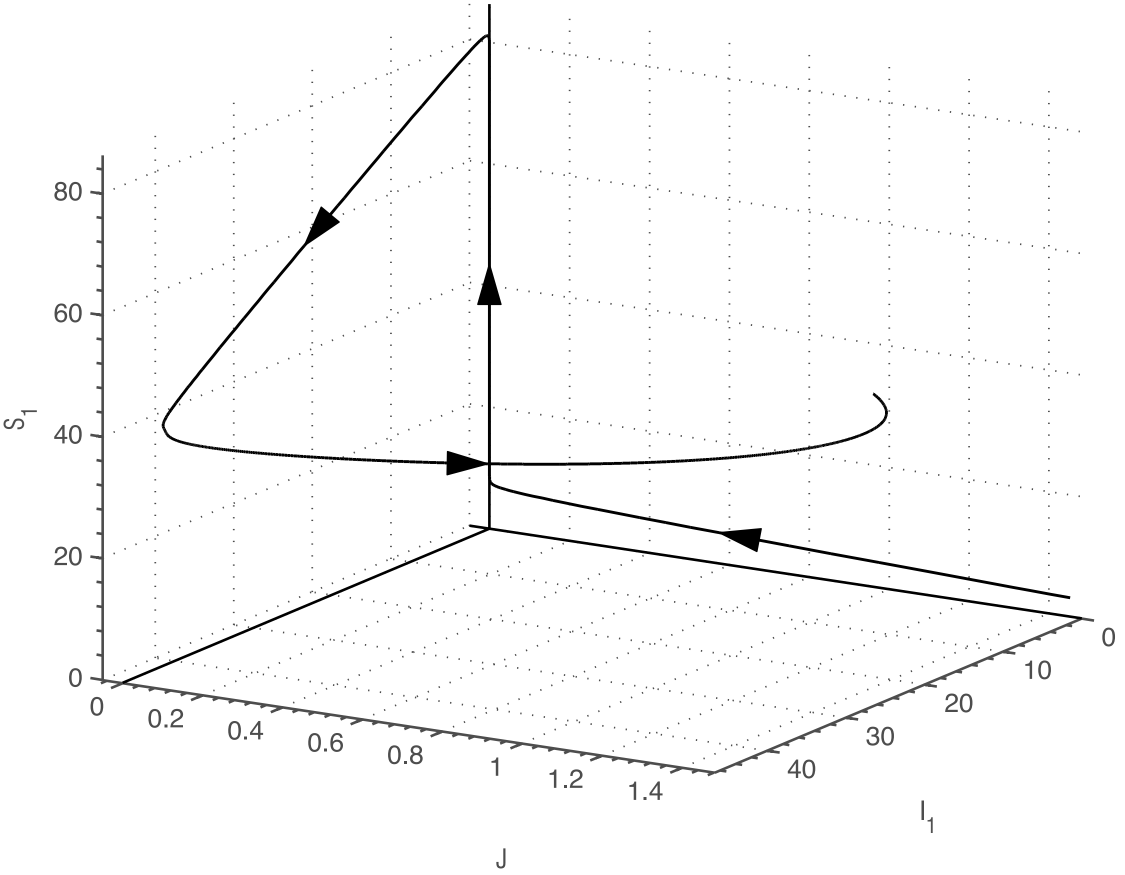

**Figure 5.6:** *Phase portrait for the primary host in the second scenario. Parameters values are* $r_1 = 0.037$*,* $K_1 = 94.455$*,* $\beta_1 = 0.0245$*,* $\beta_3 = 0.0084$*,* $\delta = 0.0084$*,* $v_1 = 0.00176$*,* $v_3 = 0.68$*,* $\alpha_1 = 0.99824$*,* $\alpha_3 = 0.32$*, and* $\gamma = 0.1$*. The initial conditions are* $S_1(0) = 4.181$*,* $I_1(0) = 1.483$*, and* $J(0) = 1.483$*. The trajectory converges to the equilibrium point* $(41.2, 12.9, 1.2)$*.*

# Chapter 6

# Results and Discussion

In Chapter 2, we introduced a mechanistic model for influenza, consisting of three interacting hosts with a recombination process. In Chapters 3 and 4, we proved permanence results on a number of the subsystems and simulated situations from collected data. In Chapter 4.3, we considered the complete model proposed in Chapter 2 and simulated a number of theoretical scenarios. In this chapter, we will summarize and discuss the results from Chapters 2 through 4.3.

## 6.1 Results

In this section, we will retrace the mathematical results from Chapters 2 though 4.3. Since there are a number of threshold constants with the same labels, we will identify these constants with the number of the corresponding system. For example, the constant $\mathcal{R}_0(3.1)$ is the parameter $\mathcal{R}_0$ for system (3.1). Generally, the following symbols with subscripts are defined as follows: $\beta$ and $b$ are incidence rates, $K$ is a carrying capacity, $\alpha$ and $a$ are immunity rates, and $v$ and $u$ are disease-induced mortality rate

In Chapter 2, we introduced the interacting host system (IHS) for influenza, featuring inter-species dynamics and genetic recombination. The model had three hosts: a primary, intermediate, and secondary host, and three strains: a primary, secondary and super-strain. The primary and secondary strains were shared between their intermediate and respective hosts. If a member of the intermediate host population was co-infected with the primary and secondary strains, then the individual was capable of producing a super-strain. The super-strain was shared with the primary and intermediate host and was able to infect individuals in the primary host's population in both the infectious (with respect to the primary strain) and susceptible subclasses. The complete model is then given by the primary host of system (2.5), the intermediate host of system (2.6), and the secondary host of system (2.3).

## Basic Model

In Chapter 3, we considered three individual host subsystems of the IHS: the basic two compartmental, super-infection, and co-infection subsystem. In Section 3.1, the basic subsystem was given by the system (3.1). The basic reproductive number was determined to be

$$\mathcal{R}_0(3.1) = \frac{\beta K}{\alpha + v}.$$

Theorem 3.6 summarizes the global behavior on the ambient space $\mathcal{X}$ when $\mathcal{R}_0(3.1) > 1$, showing that $(\hat{S}, \hat{I})$ is a global attractor for all initial conditions away from the origin.

## Super-Infection Model

In Section 3.2, the super-infection subsystem was given by (3.11). The basic reproductive number was given by

$$\mathcal{R}_0^{\max}(3.11) = \max_{i=1,3}\left\{\mathcal{R}_{0,i}(3.11)\right\},$$

where

$$\mathcal{R}_{0,i}(3.11) = \frac{\beta_i K_1}{\alpha_i + v_i},$$

for $i = 1,\ 3$. The threshold constant

$$\mathcal{R}_0^{\min}(3.11) = \min_{i=1,3}\left\{\mathcal{R}_{0,i}(3.11)\right\}$$

gives the existence of nontrivial, boundary equilibria at $(\hat{S}_1, \hat{I}_1, 0)$ and $(\check{S}_1, 0, \check{J})$ when $\mathcal{R}_0^{\min}(3.11) > 1$. Theorem 3.12 states $\mathcal{R}_0^{\min}(3.11) > 1$, $\mathcal{R}_1(3.11) > 1$, and $\mathcal{R}_3(3.11) > 1$ are sufficient conditions for permanence and the existence of an interior equilibrium point in $\mathcal{X}$. We also found permanence conditions when $\mathcal{R}_0^{\max} > 1$ and $\mathcal{R}_0^{\min} < 1$; see Proposition 3.16. To simulate system (3.11), data was taken from several sources [7, 37, 45] for the initial and parameter values. **Figures 3.6** and **3.7** show the simulations for different values of the super-incidence rate for the $\delta = 0.00084$ and $\delta = 0.04$, respectively. The simulation showed the trajectory converged to the equilibrium point $(40.8, 51.1, 0.0)$ when $\delta = 0.00084$ and $(42.4, 24.1, 1.0)$ when $\delta = 0.04$.

## Co-Infection Model

In Section 3.3, the co-infection subsystem was given by (3.19). The basic reproductive number was given by

$$\mathcal{R}_0^{\max}(3.19) = \max_{i=1,2} \{\mathcal{R}_{0,i}(3.19)\},$$

where

$$\mathcal{R}_{0,i}(3.19) = \frac{b_i K_X}{a_i + u_i},$$

for $i = 1,\ 3$. The threshold constant

$$\mathcal{R}_0^{\min}(3.11) = \min_{i=1,3} \{\mathcal{R}_{0,i}(3.11)\}$$

gives the existence of nontrivial, boundary equilibria at $(\hat{X}, \hat{Y}_1, 0, 0)$ and $(\check{X}, 0, \check{Y}_2, 0)$ when $\mathcal{R}_0^{\min}(3.19) > 1$. We define the threshold constants for $(\hat{X}, \hat{Y}_1, 0, 0)$

$$\mathcal{R}_1(3.19) = \frac{b_2 \hat{X}}{b_{21}\hat{Y}_1 + a_2 + u_2 + a_{12} + u_{12}}$$

and

$$\mathcal{R}_{12}(3.19) = \frac{(a_{12} + u_{12})(b_{21}\hat{Y}_1 + a_2 + u_2)}{b_2\hat{X}(a_{12} + u_{12} + d_2(b_{12} + b_{21})\hat{Y}_1)}.$$

The asymptotic behavior for $(\hat{X}, \hat{Y}_1, 0, 0)$ is: (i) asymptotically stable if $\mathcal{R}_1(3.19) < 1$ and $\mathcal{R}_{12}(3.19) > 1$, and (ii) unstable if either: (1a) $\mathcal{R}_1(3.19) > 1$ and $\mathcal{R}_{12}(3.19) < 1$, or (1b) $\mathcal{R}_1(3.19) < 1$ and $\mathcal{R}_{12}(3.19) < 1$. The symmetry of system (3.19) allowed an analogous result for the $(\check{X}, 0, \check{Y}_2, 0)$ with the threshold constants

$$\mathcal{R}_2(3.19) = \frac{b_1 \check{X}}{b_{12}\check{Y}_2 + a_1 + u_1 + a_{12} + u_{12}}$$

and

$$\mathcal{R}_{21}(3.19) = \frac{(a_{12}+u_{12})(b_{12}\check{Y}_2 + a_1 + v_1)}{b_1\check{X}(a_{12}+u_{12}+d_1\check{Y}_2(b_{12}+b_{21}))}.$$

Condition (1) is defined as the case when (1a) or (1b) is satisfied, and condition (2) is when either: (2a) $\mathcal{R}_2(3.19) > 1$ and $\mathcal{R}_{21}(3.19) < 1$, or (2b) $\mathcal{R}_2(3.19) < 1$ and $\mathcal{R}_{21}(3.19) < 1$. Theorem 3.20 states system (3.19) exhibits permanence when $\mathcal{R}_0^{\min}(3.19) > 1$ and conditions (1) and (2) are satisfied. To simulate system (3.19), data was taken from several sources on swine data in Thailand [16, 17]. **Figure 3.8** shows the simulation for system (3.19). The simulation showed the trajectory converged to the equilibrium point $(3.44, 1.22, 1.01, 0.59)$, hence exhibiting permanence.

## Two Interacting Hosts Model

In Chapter 4, we considered subsystems of the IHS with multiple host species. In Section 4.1, we considered the subsystem of the IHS with two host species with a single circulating strain given by system (4.1). The basic reproductive number was given by

$$\mathcal{R}_0^{\max}(4.1) = \max_{i=1,X}\left\{\mathcal{R}_{0,i}(4.1)\right\}.$$

where

$$\mathcal{R}_{0,1}(4.1) = \frac{\beta_1 K_1}{\alpha_1 + v_1} \quad \text{for} \quad \mathcal{R}_{0,X}(4.1) = \frac{b_1 K_X}{a_1 + u_1}.$$

The threshold constant

$$\mathcal{R}_0^{\min}(4.1) = \min_{i=1,X}\left\{\mathcal{R}_{0,i}(4.1)\right\}$$

gives the existence of nontrivial boundary equilibria at $(0, \hat{X}, 0, \hat{Y}_1)$ and $(\hat{S}_1, 0, \hat{I}_1, 0)$ when $\mathcal{R}_0^{\min}(4.1) > 1$. The nontrivial boundary equilibrium point $(0, \hat{X}, 0, \hat{Y}_1)$ is unstable and $(\hat{S}_1, 0, \hat{I}_1, 0)$ is classified by the threshold constants

$$\mathcal{R}_{11}(4.1) = \frac{r_X}{g\hat{I}_1 + a_1 + u_1}, \quad \text{and} \quad \mathcal{R}_{12}(4.1) = \frac{gu_1\hat{I}_1}{r_X(g\hat{I}_1 + a_1 + u_1)}.$$

as: (i) asymptotically stable if $\mathcal{R}_{11}(4.1) < 1$ and $\mathcal{R}_{12}(4.1) > 1$, and (ii) unstable if either: (1) $\mathcal{R}_{11}(4.1) > 1$ and $\mathcal{R}_{12}(4.1) < 1$, or (2) $\mathcal{R}_{11}(4.1) > 1$ and $\mathcal{R}_{12}(4.1) < 1$ . Theorem 4.4 states system (4.1) exhibits permanence when $\mathcal{R}_0^{\min}(4.1) > 1$ and either of the conditions $\mathcal{R}_{11}(4.1) < 1$ and $\mathcal{R}_{12}(4.1) > 1$ are not satisfied in the strict sense. **Figure 4.1** shows the simulation for system (4.1).

## External Input Models

In Section 4.2, we considered the system (4.10) that has an external input of infections. This system is an approximation of system (4.1) that assumes the primary host exhibits permanence. In this case, if $\mathcal{R}_{0,1}(4.1) > 1$ with $I_1(0) > 0$, then the susceptible and infectious subclasses of the primary host converge to positive steady states. The primary host's interaction term $g \cdot I_1$ in the intermediate host is replaced by the constant $\phi$. $(0, 0)$ is the only boundary equilibrium point for system (4.10) and is classified by the threshold constants

$$\mathcal{R}_1(4.10) = \frac{r_X}{a_1 + u_1 + \phi} \quad \text{and} \quad \mathcal{R}_2(4.10) = \frac{\phi u_1}{r_X(a_1 + u_1 + \phi)}.$$

as: (i) stable under the conditions $\mathcal{R}_1(4.10) < 1$ and $\mathcal{R}_2(4.10) > 1$, (ii) unstable if either: (1) $\mathcal{R}_1(4.10) < 1$ and $\mathcal{R}_2(4.10) < 1$, or (2) $\mathcal{R}_1(4.10) > 1$ and $\mathcal{R}_2(4.10) < 1$. These results are summarized in Theorem 4.9.

In Section 4.3, we introduced two more models with an external input: a super- and co- infection model. The super-infection model has an external input of infection for the super-strain, and the co-infection model has an external input for both the primary and secondary strains. In both cases, we noted the external inputs allow weaker conditions for permanence than the results from Sections 3.2 and 3.3. **Figure 4.2** shows the simulations for system (4.10) when $\phi = 0$ and $\phi = 0.5$.

## Interacting Host System (IHS)

In Chapter 4.3, we considered the interacting host system (IHS) originally proposed in Chapter 2. The basic reproductive number was given by

$$\mathcal{R}_0^{\max}(IHS) = \max\left\{\frac{\beta_2 K_2}{\alpha_2 + v_2}, \frac{b_1 K_X}{a_1 + u_1}, \frac{b_2 K_X}{a_2 + u_2}, \frac{b_3 K_X}{a_3 + u_3}, \frac{\beta_1 K_1}{\alpha_1 + v_1}, \frac{\beta_3 K_1}{\alpha_3 + v_3}\right\}.$$

We simulated two scenarios for the IHS. In the first scenario, we considered a situation where there was interaction with the intermediate host and the primary and secondary hosts with respect to the primary and secondary strains. The initial conditions were positive for all the subclasses for each species, with the exception of the super-strain subclasses for the primary and intermediate hosts; that is, $J(0) = 0$ and $Y_3(0) = 0$. Initially, we set the external input parameter $\psi$ equal to zero so that there is no interaction between the intermediate and primary hosts. We observed permanence in the intermediate and secondary host, while the primary host was persistent with respect to the susceptible and primary strain infectious subclasses. We then simulated the same scenario with $\psi = 0.05$. We observed dampening oscillations for the primary host's super-strain subclass $J$. The primary strain was eradicated from the primary and intermediate host populations. This removed the possibility of co-infected and super-infected subclasses in the intermediate host population. The predicted distance between the super-strain epidemics was determined to be approximately 36.3 years.

In the next scenario, we considered a situation where the super-strain could not persist in the primary host independent of the other host. That is, we chose parameter values so that $\mathcal{R}_{0,3}(3.11) < 1$. With interaction, the simulation showed that the IHS exhibits permanence with respect to the primary host. Moreover, the super-strain was able to persist in the primary host, despite the high level of virulence.

## 6.2 Discussion

Throughout this project, we addressed the specific hypothesis that virulent strains, which would otherwise be eradicated from a given host species, can be sustained if there is a continued external input of highly virulent strains via a recombination process in co-infected intermediate host species. We used certain aspects of influenza to construct the IHS as an SIS model with species interaction and recombination in an intermediate host species. We proved a number of results on the IHS and subsystems of the IHS; in particular, we found the basic reproductive numbers and gave conditions for permanence for each system. Given such a model, we were then able to address three questions pertinent to the permanence of highly virulent pathogens. We now return to these questions from Section 1.1.

*What are the conditions for permanence in certain subsystems for single and multiple host species?* In single host species, the conditions for permanence were given in the form of a region of parameter space that can be written in the form of basic reproductive numbers of independent strains. For example, the super-infection subsystem of Section 3.2 exhibits permanence given the conditions $\mathcal{R}_0^{\min}(3.11) > 1$, $\mathcal{R}_1(3.11) > 1$, and $\mathcal{R}_3(3.11) > 1$. In the case of multiple host species, we were able to find similar results with respect to the parameter space for permanence; however, we found that when an infecting host introduces a persistent strain into another host's population, the multi-host model can be approximated by a single host model with external input. In this case, permanence is equivalent to instability at the origin. If the host population is not dying out, then the system is permanent.

*Is it possible to find permanence conditions under constraints that would suggest otherwise if there were no interactions between host species?* In Chapter 3, we found permanence conditions for three single host subsystems of the IHS: a basic model, a super-infection model, and a co-infection model. Typically, the models required the basic reproductive number for each independent strain to be greater than one to exhibit permanence; however, the super-infection model was the exception. In this case, the system was able to exhibit permanence when the independent basic reproductive number of the super-strain $\mathcal{R}_{0,3}(3.11) < 1$ if $\mathcal{R}_0^{\max}(3.11) > 1$ and $\mathcal{R}_1(3.11) > 1$. However, the super-strain incidence rate $\delta$ for the primary infectious subclass $I_1$ must be significantly larger than the incidence rate $\beta_3$ of the susceptible subclass $S_1$ for such a situation to occur; that is, members of the super-infectious subclass $J$ must infect members of the primary infectious subclass $I_1$ at a rate significantly larger than the infecting rate of the susceptible subclass $S_1$. It is not empirically clear whether or not such a condition on parameters is reasonable to assume in reference to influenza. In all other situations, we found that the conditions for permanence in the single host system were based on basic reproductive numbers of independent strains; that is, these reproductive numbers had to be greater than one. If a strain's basic reproductive number was less than one, then it could not persist in the host population. Hence, species interaction is a reasonable mechanism to induce permanence in epidemic models. Moreover, for persistence in an intermediate host (i.e., co-infection system), basic reproductive numbers of individual strains must attain a sufficient level or have influence from an outside factor such as an external input via species interactions.

*Can virulent strains, too virulent to independently sustain themselves in a host population, continue to reemerge in a host population due to a recombination process in an intermediate host?* In the IHS, the super-infectious subclass $J$ of the primary host exhibited persistence despite the constrains that its independent basic reproductive number $\mathcal{R}_3(3.11)$ was below one and with $\mathcal{R}_1(3.11) < 1$. For this result to happen, the super-strain needed to act as a continuous external input into the primary host system from the intermediate host. The super-strain subclass of the intermediate host was persistent when the primary and secondary strains were persistent.

The conclusions about the three questions suggest that species interactions, under such circumstances, are a reasonable mechanism to sustain higher levels of virulence in certain strains of influenza. That is, as long as intermediate host species, such as pigs, can maintain significant levels of avian and human strains, new strains of influenza remain a threat to human populations. Moreover, we claim that not only are intermediate hosts a suitable candidate to facilitate recombination of strains [42], but may also be suitable for maintaining new or super- strains if avian and human strains are able to persist in intermediate host populations regardless of virulence. The conditions for permanence on the single co-infection model suggest that the two strains must have an independent basic reproductive number above one for the system to exhibit permanence. However, when an external input, such as from a primary (humans) or secondary (birds) host, influences infection, the co-infection model is able to exhibit permanence, contrary to the basic reproductive numbers of the two strains. Recombination between strains is more likely with a persistent subclass of co-infected hosts, which implies a higher probability of super-strains.

Several of the simulations of the IHS showed dynamics that reflected those of influenza. One example is the dynamics displayed in **Figure 5.5**. These showed reoccurring epidemic spikes of a super-pathogen, where each spike dampened a bit more than the previous, the first having the highest number of infected individuals. This simulation appeared similar to the major influenza pandemics of the 20th century (see **Table 5.1**) in that the largest epidemic was the first, the 1918 *Spanish Flu*, and successive outbreaks had less infected individuals than the previous pandemic. Another example is the situation described by Cyranoski [11], which states avian influenza may be infecting up to half of Java's pigs. This implies that a pig infected with a human strain has almost a 50 percent chance of acting as a "mixing vessel". The simulation of the intermediate host displayed in **Figure 5.4** reflects a similar situation to that of Java's pigs. The simulation showed once the super-strain invaded and eradicated the other strain in the primary host, the intermediate host population was left with a large number (much greater than 50 percent) of individuals infected by the secondary strain. Although the percentages of infected pigs as intermediate hosts differ, we note there is a consistency of high avian prevalence in both the simulation and in Java's pigs. More accurate statistics may give a better understanding of where the data fits into the parameter space of the model.

It is not clear whether the IHS captures influenza's dynamics enough to address more specific questions about influenza. The model was clearly able to address questions from a theoretical perspective and to display dynamics that reflect those of influenza, but may need further development to address more specific questions about influenza. A comparison of the simulations of the IHS and an analysis of empirical data is a natural approach to address such issues. Many of the statistics we used in the simulations of the IHS had a number of limitations. Most of the data was taken from studies in Southeast Asia [6, 7, 16, 17, 23, 45, 48]; however, these data sets vary by such factors as date, region, and strain-type. More accurate data could give insight on how to improve the model. Despite the issues with the data, the model was chosen in the given format to have interaction between three hosts with a simple recombination mechanism in the intermediate host. A model that considers factors such as multiple strains in certain hosts and a more complicated recombination scheme might be more adequate to address further questions that are pertinent to public health.

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