Analysis and Implementation of Robust Numerical Methods to Solve Mathematical Models of HIV and Malaria Co-infection

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KEYWORDS

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Numerical Methods

ABSTRACT

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Mathematical modelling of malaria has flourished since the days of Ross at the beginning of the previous century whereas that of HIV infections has started around 1980s. The global epidemiology of HIV/AIDS and malaria overlap because a significant number of HIV-infected individuals live in regions with different levels of malaria transmission. There is a growing interest in the dynamics of the co-infection of these two diseases. In this thesis, firstly we focus on studying the effect of a distributed delay representing the incubation period for the malaria parasite in the mosquito vector to possibly reduce the initial transmission and prevalence of malaria. This model can be regarded as a generalization of SEI models (with a class for the latently infected mosquitoes) and SI models with a discrete delay for the incubation period in mosquitoes. We study the possibility of occurrence of backward bifurcation. We then extend these ideas to study a full model of HIV and malaria co-infection. To get further inside into the dynamics of the model, we use the geometric singular perturbation theory to couple the fast and slow models from the full model. Finally, since the governing models are very complex, they cannot be solved analytically and hence we develop and analyze a special class of numerical methods to solve them.

June 2011.

DECLARATION

I declare that *Analysis and Implementation of Robust Numerical Methods to Solve Mathematical Models of HIV and Malaria Co-infection* is my own work, that it has not been submitted before for any degree or examination at any other university, and that all sources I have used or quoted have been indicated and acknowledged by complete references.

Sara Mohamed Ahmed Suleiman Elsheikh June 2011

Signed .....

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DEDICATION

To the soul of my lovely brother Alrayah. May his soul rest in Peace.

Contents

List of Tables

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List of Publications

Part of this thesis has been submitted in the form of the research papers listed below. We also have some technical reports whose revised form is being submitted to prestigious international journals for publications.

1. S.M.A.S. Elsheikh, R. Ouifki and K.C. Patidar, Analysis of a Malaria model with a distributed delay, submitted for publication.

2. S.M.A.S. Elsheikh, R. Ouifki and K.C. Patidar, Mathematical analysis of HIV-Malaria co-infection model using singular perturbation techniques, submitted for publication.

3. S.M.A.S. Elsheikh, R. Ouifki and K.C. Patidar, A nonstandard finite difference method to solve a model of HIV-Malaria co-infection, submitted for publication.

4. S.M.A.S. Elsheikh, R. Ouifki and K.C. Patidar, Analysis of a HIV-Malaria co-infection model with a distributed delay, Report Nr. UWC-MRR 2011/24, University of the Western Cape, 2011.

5. S.M.A.S. Elsheikh, R. Ouifki and K.C. Patidar, Decoupling of fast and slow dynamics of HIV-Malaria co-infection, Report Nr. UWC-MRR 2011/25, University of the Western Cape, 2011.

6. K.C. Patidar and S.M.A. Suleiman, Numerical simulations of mathematical model on HIV and Malaria co-infection, Report Nr. UWC-MRR 2009/10, University of the Western Cape, 2009.

Chapter 1

General introduction

The global epidemiology of HIV/AIDS and malaria overlap because a significant number of HIV-infected individuals live in regions with different levels of malaria transmission. Although the consequences of co-infection with HIV and malaria parasites are not fully understood, available evidence suggests that the infections act synergistically and together result in worse outcomes. Both infections are of a great public-health importance in tropical countries, particularly in sub-Saharan Africa, that any potential interaction should make us worry. The studies showed that there is an estimated 5 % increase in malaria deaths due to HIV infection in Sub-Saharan Africa. Since the co-infections were recorded, malaria has seen a 28 % increase in its prevalence. Malaria associated death rates have nearly doubled for those with co-infections.

In this thesis, firstly we focus on studying the effect of a distributed delay representing the incubation period for the malaria parasite in the mosquito vector to possibly reduce the initial transmission and prevalence of malaria. The model can be regarded as a generalization of SEI models (with a class for the latently infected mosquitoes) and SI models with a discrete delay for the incubation period in mosquitoes. A possibility of occurrence of backward bifurcation is also studied. These ideas are then extended to study a full model of HIV and malaria co-infection. Due to the complexity of the model equations, we develop a special class of numerical methods to solve such models.

Since HIV and malaria infections occur in two different time scales, therefore make

use of the techniques of the singular perturbation theory to decouple the full model into a model with two time scales and separated into fast time-scale model for the dynamics of malaria and slow time-scale model for the dynamics of HIV. The dimensions of the subsystems are usually much lower. We therefore study the dynamical behavior of the simplified subsystems to understand the properties of the original system.

The mathematical models developed or considered in this thesis are described by autonomous systems of nonlinear ordinary differential equations. Very often, such systems are so complex that their exact solutions are difficult to obtain and hence the need for robust numerical methods arises. Therefore, we design numerical methods known as nonstandard finite difference methods (NSFDMs) to solve these systems. The methods preserve a number of essential properties.

A brief background for HIV and malaria co-infections is presented in the next section.

1.1 HIV-malaria co-infection

Malaria remains one of the most prevalent and lethal human infection worldwide. It is caused by the protozoan Plasmodium, transmitted to vertebrates by female genus Anopheles mosquitoes when they feed on blood. Four species of the parasite, namely: Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale and Plasmodium malariae infect humans. Of the four species, P. falciparum is the most virulent and potentially lethal to humans. It is responsible for the greatest number of deaths and clinical cases and is the most widespread in the tropics. Its infection can lead to serious complications affecting the brain, lungs, kidneys and other organs. Of the 300–600 million episodes of clinical malaria that occur in tropical and sub-tropical regions of the world each year, approximately 1–2 million result in death [57].

Malaria is the most lethal human parasitic infection. Although approximately 90% of malaria-associated deaths occur in Africa, almost half the global population lives in areas where malaria infection is a risk [57]. The individuals most at risk of significant

morbidity and mortality owing to malaria are children under the age of 5 years and pregnant women [7, 86]. However, as a result of varying transmission intensity, population flux and transmigration, adults lacking acquired immunity might also develop severe malaria.

An estimated 34–47 million people were infected with HIV/AIDS in 2006, with approximately 4.3 million of these being newly diagnosed infections [137]. Most new HIV infections occur in young adults aged 15–24 years of age, with children under the age of 15 years accounting for approximately 13% of all new HIV infections. In 2006, approximately 63% of all adults and children living with HIV lived in sub-Saharan Africa and approximately 72% of all deaths due to AIDS/HIV occurred in this region [137]. Most of these HIV/AIDS-infected people are women over 15 years of age (59%) [137].

The distribution of HIV and malaria overlaps in many regions of the world, particularly in sub-Saharan Africa, Southeast Asia, Latin America and the Caribbean. Approximately 25 million HIV-infected individuals live in sub-Saharan Africa [137]. Although there is a variation in the prevalence and geographic overlap (rural vs urban) of both HIV and malaria within each region, there is a significant risk of co-infection in many areas. In sub-Saharan Africa, the high burden of both malaria and HIV translates into high incidences of co-infection in many regions [145]. The most severely affected areas include Zambia, Zimbabwe, Mozambique, Malawi and the Central African Republic. In these countries, HIV prevalence is over 10% and 90% of the population is exposed to malaria.

Factors influencing the epidemiology of malaria and HIV co-infection are

- Poverty: HIV and malaria are common in the poorest populations.
- Immunity: Groups at risk include those living in areas with stable malaria and generalized HIV epidemics; however, the effect owing to co-infection might be more apparent in unstable malaria settings.
- Age and gender: Most malaria morbidity and mortality occurs in children under

the age of 5 years and pregnant women. HIV infection rates are higher in adults.

- Transmission dynamics: Changes in malaria-vector breeding (water sanitation and drainage etc.) and contact with human hosts; urban or peri-urban versus rural settings, altered HIV transmission owing to genital ulcer disease and lack of circumcision.

- High-risk groups: Blood-transfusion recipients, injecting drug users, temporary workers, commercial sex workers, refugees. These groups might facilitate HIV transmission and lead to co-infection in areas with malaria transmission.

Applications of mathematics to biology began in 1628. One of the aims of mathematical modelling in science is for it to no longer be distinguishable as a separate enterprise, but simply used as a language to discuss concepts integral to a discipline. Familiarity with models as everyday research tools demystifies the modelling process, and promotes realistic, tempered expectations. Ever since the pioneering work of Kermack and McKendrick in the 1930s [76, 77, 78], numerous compartmental mathematical models have been developed and used to help gain insights into the transmission and control mechanisms of diseases like HIV and their interactions with others. These models are often of the form of systems of non-linear differential equations, which are highly complex in nature and therefore their closed-form solutions are not easily obtainable.

1.2 Multiscale problems in biology

The use of mathematical modelling, increasingly influencing the theory, and practice of disease management and control. This is because they can help in figuring out decisions that are of significant importance on the outcomes and provide comprehensive examinations that enter into decisions in a way that human reasoning and debate cannot. The multi-scale modelling has a major role in this direction.

Systems in nature often evolve on time scales differing several orders of magnitude, or take place on various length scales. In this section, we list some of these models that

arise in biology and whenever available, we also indicate the techniques to solve them.

Modelling biological systems implies dealing with systems involving a large number of variables. These populations are divided into various sub-populations corresponding to ages, stages, individual states or activities, phenotypes, genotypes, spatial patches etc. There are a large number of components that are involved at different time scales and thus make these models very complicated. There is a very huge literature that can be accounted on the use of multiscale modelling. Examples where this modelling can be useful in biology includes but not limited to are the Heart, Cancer, Intestinal Edema, etc. Some of the works pertaining to the multiscale models in epidemiology are being reviewed in the next section.

1.3 Literature review

The literature on the mathematical models for communicable diseases is vast. Below we mention some selected works on HIV, malaria and their co-infection. However, to keep the presentations in the chapters self-contained, some of the literature is also reviewed in individual chapters.

Mathematical modelling of malaria has flourished since the days of Ross [120], who was the first to model the dynamics of malaria transmission and Macdonald [94, 95, 96] who expounded on work of Ross, introducing the theory of super infection. On the other hand, the mathematical models used to describe the dynamics of HIV spread tend to be quite complex. As a consequence, mathematical models involving complex HIV transmission mechanisms usually do not lend themselves to conventional mathematical control techniques such as dynamic programming and convex optimization. There is a growing interest in the dynamics of the co-infection of these two diseases. However there is a very little literature available on mathematical models for the synergy between HIV and malaria.

The model proposed by Abu-Raddad *et al.* [1] was probably the first compartmental model for the co-infection of HIV and malaria. It was an extension of conventional

systems in theoretical epidemiology [3]. It consists of twenty coupled non-linear ordinary differential equations, eighteen of which described the host population (humans), and two dedicated to the vector population (female Anopheles mosquitoes). By modeling only the sexually active population, they calculated the size of the epidemiological synergy between HIV-1 and malaria. Their calculations established a considerable population-level epidemiological synergy between HIV and malaria though the lack of precise assessment for the duration of heightened viral load and malaria-morbidity effect on sexual behavior, prevented them from precisely quantifying the magnitude of the synergy.

They divide the total population of human into two sexual risk populations, the general population (low risk) and the core group (high risk). They model the mosquitoes population through an SI model with a delay representing the incubation period in the mosquito, also they account for the seasonal variations in the mosquito population. Their model calculates the size of the epidemiologic synergy between HIV-1 and malaria. The synergy is defined as the net effect of the presence of heightened viral load, enhanced susceptibility to malaria in HIV patients, reduction in sexual activity during malaria episodes and enhanced malaria mortality in advanced HIV patients. Although these authors presented an elegant model, they did not gave the qualitative analysis of it.

After the model of Abu-Raddad *et al.* [1], the second popular model was given by Mukandavire *et al.* [106], who formulated and analyzed a realistic mathematical model for HIV-malaria co-infection. They carried out a detailed qualitative analysis of the resulting model; an activity not carried out in [1]. This make their study a first modelling work that provides an in-depth analysis of the qualitative dynamics of HIV-malaria co-infection. Additionally, there are some important differences between their model and the one given by Abu-Raddad [1]. For instance, while they used an exponential distribution waiting time to model the exposed class, a discrete time delay was used for the same purpose in [1]. Further, seasonality variations were used in [1] to model the birth rate of mosquitoes, whereas a constant birth rate was used in [106].

Mathematically speaking, while the model considered in [1] is non-autonomous, the one presented in [106] is autonomous. Furthermore, unlike in many other modelling studies of HIV transmission dynamics in a population, their study assumes that individuals in the AIDS stage of HIV infection do transmit the disease to susceptible individuals. This is owing to the fact that epidemiologic evidence supports the hypothesis that AIDS patients are capable of, and do engage in, risky sexual behavior defined in terms of inconsistent condom use or having multiple sex partners [106].

Their main theoretical results that they have are as follows:

(i) The HIV-only model has a globally-asymptotically stable disease-free equilibrium whenever a certain epidemiological threshold ($\mathcal{R}_H$) is less than unity; and unstable if this threshold exceeds unity.

(ii) The HIV-only model has a unique endemic equilibrium whenever the aforementioned threshold exceeds unity. For the case where no AIDS-related mortality is considered, this endemic equilibrium is globally-asymptotically stable whenever it exists.

(iii) Unlike the HIV-only model, the malaria-only model undergoes the phenomenon of backward bifurcation, where the associated stable disease-free equilibrium co-exists with a stable endemic equilibrium when the corresponding reproduction number ($\mathcal{R}_M$) is less than unity.

(iv) The full HIV-malaria model is shown to have a locally-asymptotically stable disease-free equilibrium when its reproductive threshold is less than unity, and unstable if the threshold exceeds unity. It also undergoes the phenomenon of backward bifurcation under certain conditions.

The numerical simulations of their full HIV-malaria model show the following:

(a) The two diseases co-exist whenever the reproduction number of each of the two diseases exceed unity (regardless of which number is larger).

(b) The number of new cases of malaria at steady state seems to always exceeds that of HIV.

(c) The assumed reduction in sexual activity of individuals with malaria symptoms results in decrease in the number of new cases of HIV and the mixed HIV-malaria infection, while increasing the number of new cases of malaria.

(d) The HIV-induced increase in susceptibility to malaria infection has marginal effect on the number of new cases of HIV, but significantly increases the number of new cases of the dual HIV-malaria infection.

In [148] Xiao and Bossert proposed a first mathematical model for the interaction of the immune system with HIV viruses and malaria parasites in an individual host. There model consists of a system of three coupled ordinary differential equations, which represents the rate of change in the concentration of malaria parasites, HIV viruses and immunity effector within a host, respectively. Their theoretical model gives insight into the biological balance between pathogen replication and the immune response to the pathogen: persistence versus elimination of the pathogen, which determines the outcome of infection. Through dynamical analysis they showed that the outcomes of the interactions between the immune system of the host with either malaria parasites or HIV viruses are dramatic such as malaria infection promoting proliferation of HIV virus, HIV infection increasing the risk from malaria and the immune system of the host failing to keep the diseases under control, etc. Their results provide a new perspective for understanding of the complexity mechanisms of the co-infection with malaria and HIV in a host. Their conclusions are that the effects of the co-infection may vary greatly among individuals, depending on many factors such as immunologic factor, pathogenic factor, amount of initial pathogens, strength of immunostimulation and the immunity thresholds in the host.

In [10], Bara and Lemos studied a non-linear control model of HIV-1 infection, having as state variables the number of healthy and infected $CD4^+$T-cells and the number of virion particles. Firstly they obtained a reduced model, using a simple

singular perturbation approximation, feedback linearization, and LQ regulation based on state feedback, and used them to design a control law. They shown that the controlled system remains stable in the presence of significant changes of the model parameter with respect to the nominal value.

By collecting data from a certain area, Chattopadhyay *et al.* [22] developed a linear regression model which describes the pattern of the malignant malaria curve under important environmental and social influences. Then, they estimated the Macdonald's stability index for the system under environmental fluctuation, with the help of the technique developed by Sarkar *et al.* [128].

To assess the potential impact of personal protection, treatment and possible vaccination strategies on the transmission dynamics of malaria, Chiyaka *et al.* [23] formulated a deterministic model with two latent periods in the non-constant host and vector populations. Through qualitative analysis they deduced that personal protection has a positive impact on disease control but to eradicate the disease in the absence of any other control measures the efficacy and compliance should be very high. Among the interesting dynamical behaviours of the model, their numerical simulations show a backward bifurcation which lead to a challenge to the designing of effective control measures.

According to the best of our knowledge, Chiyaka *et al.* [24] formulated a first model using delay differential equation to study the combined effect of vaccination with treatment and personal protection in malaria transmission dynamics. To determine criteria for control of a malaria epidemic, they analyzed the model qualitatively and computed the threshold vaccination and treatment rates necessary for control of malaria. They found that under certain conditions the model exhibits the phenomenon of backward bifurcation where a stable disease-free equilibrium coexists with a stable endemic equilibrium. They concluded that vaccination and personal protection can effectively slow down the development of malaria, whereas treatment may increase the development of the epidemic unless some conditions are met.

By modifying a model by Culshaw and Ruan [33], which is a simplification of a

model by Perelson *et al.* [118], Jiang *et al.* in [70] considered a system of delay differential equations that describes HIV infection of $CD4^+$T-cells. Their main purpose was to study the stability and Hopf bifurcation of the system. They derived formulas which determine the stability, the direction, and the periodic of bifurcating period solutions, by using the normal form theory and center manifold arguments.

Ishikawa *et al.* [65] developed a mathematical model for the transmission of Plasmodium vivax malaria quantitatively. They incorporated a phenomenon of renewed infections caused by a relapse into their model. By the simulations of their model, they aimed at understanding the dynamics of parasite rate, and evaluating the decline in prevalence caused by executing programs of selective mass drug administration (MDA) [29], and vector control such as the distribution of permethrin-treated bed nets.

Iwami *et al.* [68] considered a mathematical analysis of their two earlier models [66] and [67]. They studied the effect of viral diversity on the human immune system with the frequency dependent proliferation rate of cytotoxic T-lymphocytes (CTLs), and the elimination rate of infected cells by CTLs. Their model had very complex mathematical structures such as limit cycle, quasi-periodic attractors, and chaotic attractors. They concluded that increasing of the diversity leads to a loss of the recognition ability of the immune cells, and the efficiency between infections of the virus and eliminations of the immune cells is shifted in favor of the virus in the high viral diversity.

To investigate the optimal methodology for administering antiretroviral therapies to fight HIV infection, Karrakchou *et al.* [75] obtained and solved a non-linear optimal control system.

Kovacs [80] considered an HIV/AIDS autonomous model which describes the dynamics of sexual transmitted disease between the groups of susceptibles, educated, and the infected group. Because the class of infectives need a time, he incorporated a delay effect into the system, which was considered as a bifurcation parameter. Through the stability analysis he showed that existence of a critical value of the delay for which Hopf bifurcation takes place.

Mukandavire *et al.* [105] presented a mathematical model to study the effects of

public health educational campaigns as a single control strategy on sexual transmission of HIV/AIDS in the continuing absence of a preventative vaccine. Their discrete time delay differential equations system was an extension of the model [31]. They concluded that public health educational campaigns can slow down the epidemic and are more effective when given to both sexually immature (pre- and early adolescence) and sexually mature individuals (adults) concurrently.

Rowland-Jones and Lohman [124] reviewed the interactions between malaria and HIV infection. According to them, HIV-infected people are more likely to experience clinical malaria, and acute malaria can up-regulate HIV replication, leading to higher plasma viral loads. This is most serious in pregnant women, where HIV infection increases the risk of placental malaria, leading to increased infant morbidity and mortality. Through this work, they tried to answer the following questions: Does HIV infection have an impact on the clinical course of malaria? Does malaria affect the natural history of HIV infection? How does HIV infection affect malaria in pregnancy? Does HIV affect the efficacy of anti-malarial therapy, and do anti-malarial and antiretroviral drugs interact, etc.

Sani and Kroese [127] formulated some mathematical control problems for HIV spread in mobile heterosexual populations, and showed how optimal regional control strategies can be obtained that minimize the national spread of HIV. They applied the cross-entropy method to solve these highly multi-modal and non-linear optimization problems.

Skinner-Adams *et al.* [130] discussed recent findings on the impact of HIV/AIDS and malaria co-infection and the possible roles of chemotherapy in improving the treatment of these diseases.

In [129], Shiri *et al.* modified one of their earlier models (see, [49]). Their primary goal was to establish the effects of drugs on HIV RNA viral load and on T-lymphocyte ($CD4^+$T-cells and CTLs) count of treatment naive patients using a two strain viral immune dynamic model that assumes one viral strain is resistant to therapy. They used the fourth-order Runge-Kutta scheme to numerically simulate the effects of drugs and

they concluded that if the immune control and drugs are potent enough to maintain infected $CD4^+$T-cells at low levels, then there are clinical benefits, a dynamic equilibrium between viral load and CTL response, and drug resistance which is the major factor that makes complete disease eradication by therapy is impossible.

In [136], Tumwiine *et al.* modeled the dynamics of malaria in the human host and mosquito vector. Their model based on the susceptible-infective-immune SIRS in human population, assuming that all the new born are susceptible to the infection, and there is no vertical transmission. For the mosquito vector population they considered an SI model and analyzed it for the stability and equilibria.

The model in [147] by Wyse *et al.* consisted of a system of non-autonomous non-linear ordinary differential equations that models mathematically the dynamic of malaria transmission considering the different treatment levels accessible to the infected people and the seasonal factors which affect the vector evolution.

Uneke and Ogbonna [139] reviewed the impact of treatment using antimalarial and antiretroviral agents in pregnant women with malaria and HIV co-infection. They evaluated safety and operational feasibility of use of antimalarial and antiretroviral agents to treat co-infected pregnant women. Although use of these therapies was shown to improve the health of pregnant women with co-infection, low adherence, poor-quality drugs, resource scarcity, lack of infrastructure and inadequate treatment in sub-Saharan Africa continue to hamper treatment outcome. The absence of studies on interaction between antimalarials and antiretrovirals, as well as mounting evidence of treatment failure due to drug resistance and adverse drug reactions, in most parts of sub-Saharan Africa, make the establishment of new guidelines for the prevention of malaria and HIV infection during pregnancy imperative.

When studying multi-scale systems, simplifying assumptions may be of great help; if not to understand the full system, then at least to get a first insight in the system's behaviour [59].

The geometric singular perturbation theory was introduced around 1980. This is an approach used for the problems with a clear separation in time scales. It uses invariant

manifolds in phase space in order to understand the global structure of the phase space or to construct orbits with desired properties. The foundation of the slow-fast systems approach was given by Fenichel [46]. The general ideas are based on previous works by Fenichel [43, 44, 45] and by Hirsch *et al.* [61]. Since then, the methods have evolved and found their way towards applications, of which many have a biological background. Recent work on the Hodgkin-Huxley equations (Moehlis [102]; Rubin and Wechselberger [123]) again serves as examples [59].

Feng *et al.* [41, 42], developed a mathematical model that explicitly couples malaria transmission dynamics with changes in the frequency of the S-gene (sickle-cell gene), and use the model to examine the temporal scales over which human population genetics respond to malaria. They apply singular perturbation techniques to separate the dynamics of the model into two time-scales with a faster time-scale for the epidemics and a slower time-scale for the change in gene frequencies. They presented the analysis of the dynamics on the slow manifold, which provides insights into how malaria epidemics may have an impact on the maintenance of the S-gene in a population where malaria is prevalent.

As suggested by Levins [88], Lakin and van den Driessche in [85] considered a generalization of the logistic equation of population biology in which the species being modeled is linked to its larger ecosystem through introduction of a lower trophic level consisting of a renewable resource. The resource adjusts rapidly to demand compared to population growth making this dynamical process associated with time scales of different orders of magnitude. Using singular perturbation techniques, they exploited this fact. Their numerical result shows that even for moderate values of the parameter, the asymptotic results are highly accurate.

Auger and Poggiale [8] considered a model which includes many sub-populations and details taking into account the complexity of the initial model. They presented aggregation and emergence methods in large-scale dynamical systems with different timescales, a fast model describing migration on spatial patches is coupled to a slow growth model on each patch. The existence of different timescales makes it possible to

use perturbation methods to aggregate systems of ODE's which are composed of fast and slow parts. Perturbation methods allow them to aggregate large systems into a smaller system which is described by a few global variables. Aggregation corresponds to the reduction of the dimension of a dynamical system which is replaced by a smaller model for a small number of global variables at a slow timescale. Their aim was to show that different scenarios for the fast migration can lead to different growth models.

In [62], Hochman and Kim mentioned that HIV and malaria have similar global distributions. Annually, 500 million are infected and 1 million die because of malaria. 33 million have HIV and 2 million die from it each year. This has motivated them to study the impact of HIV and malaria co-infection. They found that minor effects of one infection on the disease course or outcome for the other would significantly impact public health because of the sheer number of people at risk for co-infection. They mentioned that more recent work suggests that those with HIV have more frequent episodes of symptomatic malaria and that malaria increases HIV plasma viral load and decreases $CD4^+T$ cells. They concluded that further investigation of the interactions between HIV and malaria is needed to better define effects of the co-infection.

Franke *et al.* [47] examined the cross-sectional relationships between malaria parasitemia and CD4 T-cell count and viral load among human immunodeficiency virus (HIV)-infected pregnant women. They found that although there is no strong evidence in support of an overall association between parasitemia and progression to HIV disease stage 3 or 4 or acquired immune deficiency syndrome (AIDS)-related death (ARD), the rate of ARD was elevated among two sub-groups: HIV-infected individuals with lower levels of immunosuppression and those with low parasitemia. The association between parasitemia and ARD in women with baseline CD4 T cell counts ≥ 500 cells/μL was statistically significant, whereas the relationship between low parasitemia, versus none, and ARD was of borderline statistical significance.

In [103], Muhangi *et al.* studied the associations between mild-to-moderate anaemia in pregnancy and helminth, malaria and HIV infection in Entebbe, Uganda. Their study suggested that among pregnant women, malaria and HIV are more important

infectious causes of anaemia than helminths. It is mentioned in this work that no association was observed between mild-to-moderate anaemia and any species of helminth, and a weak association between anaemia and increasing intensity of hookworm infection was reduced after adjusting for confounding factors.

Kublin *et al.* [82] did a prospective cohort study in Malawi to assess the effect of Plasmodium falciparum malaria on concentrations of HIV in blood. Their findings showed that the concentration of HIV-1-RNA in the blood increases significantly with malaria. The greatest increases in HIV-1-RNA occur with fever and parasite density of $2000/\mu L$ or greater, and when baseline CD4 counts are more than 300 cells per μL. Furthermore, they found that increases in HIV-1-RNA coincide with malaria even in the absence of other systemic febrile illnesses that could contribute to increases in viral load.

A study was conducted to determine the relationship between fever, malaria parasitaemia and human immunodeficiency virus (HIV) infection by Nwanyanwu *et al.* [111] in Malawi. They found that a significantly higher proportion of individuals with HIV infection reported fever than did HIV negative individuals and hence fever or a recent history of fever is not highly predictive of malaria. Indeed, fever was much more likely to be associated with HIV infection than with malaria parasitaemia.

Except some of the works mentioned above, we could hardly find mathematical models on HIV-malaria co-infections, but from biological perspectives, the reader may wish to look at the work on the dynamics of co-infection in [11, 12, 16, 51, 63, 74, 83, 99, 100, 112, 119, 143]. However the other works dealing with HIV only infections are [9, 15, 17, 18, 19, 30, 32, 34, 35, 53, 58, 68, 69, 79, 84, 87, 104, 131, 142, 149, 150], whereas those dealing with malaria only are [27, 28, 50, 52, 54, 89, 132, 133, 135].

The numerical method that we will exploring in detail is a special class of numerical methods, called the non-standard finite difference methods. These methods were used very successfully for singularly perturbed problems, see, e.g. [73, 90, 91, 92, 93, 107, 115, 116, 117]. An exhaustive account of work that use such methods is provided in the survey article by Patidar [114].

1.4 Some preliminary results useful for this thesis

In this section we summarize some mathematical results which will be used in the rest of the thesis.

Some theoretical results for ODEs

Definition 1.4.0.1. ([14])**(Lipschitz condition).** *A family of vector feilds $X(x,t)$ satisfies Lipschitz condition in a region $\mathfrak{R}$ of (x,t)-space if and only if, for some Lipschitz constant L,*

$$|X(x,t) - X(s,t)| \leq L|x-s| \quad if \quad (x,t) \in \mathfrak{R}, \quad (s,t) \in \mathfrak{R}. \tag{1.4.0.0.1}$$

Theorem 1.4.0.1. ([14])**(Comparison Theorem).** *Let f and g be solutions of the system*

$$\begin{aligned} y' &= F(x,y), \\ z' &= G(x,y), \end{aligned} \tag{1.4.0.0.2}$$

respectively, where $F(x,y) \leq G(x,y)$ in the strip $a \leq x \leq b$ and F or G satisfies a Lipschitz condition (1.4.0.0.1). Let also $f(a) = g(a)$. Then $f(x) \leq g(x)$ for all $x \in [a,b]$.

Definition 1.4.0.2. ([140]) **(Basic reproduction number).** *The basic reproduction number, denoted by $\mathcal{R}_0$, is the expected number of secondary cases produced in a completely susceptible population, by a typical infective individual. If $\mathcal{R}_0 < 1$, then on average an infected individual produces less than one new infected individual over the course of its infectious period, and the infection cannot grow. Conversely, if $\mathcal{R}_0 > 1$, then each infected individual produces, on average, more than one new infection, and the disease can invade the population.*

To determine the local stability of the disease free equilibrium of a system of ordi-

nary differential equations, the following theorem is normally used.

Theorem 1.4.0.2. ([140]) *Consider the disease transmission model given by (1.4.0.0.3) with $f(x)$ satisfying conditions (A1)-(A5) given below. 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 the basic reproduction number as defined in Definition (1.4.0.2).*

Define X_s to be the set of all disease free states. That is

$$X_s = \{x \geq 0 | x_i = 0, i = 1, \ldots, m\}.$$

Let $\mathcal{F}_i(x)$ be the rate of appearance of new infections in compartment i, $\mathcal{V}_i^+(x)$ be the i rate of transfer of individuals into compartment i by all other means, and $\mathcal{V}_i^-(x)$ be the i rate of transfer of individuals out of compartment i. It is assumed that each function is continuously differentiable at least twice in each variable. The disease transmission model consists of non-negative initial conditions together with the following system of equations:

$$\dot{x}_i = f_i(x) = \mathcal{F}_i(x) - \mathcal{V}_i(x), \quad i = 1, 2, \ldots, n, \tag{1.4.0.0.3}$$

where $\mathcal{V}_i(x) = \mathcal{V}_i^-(x) - \mathcal{V}_i^+(x)$ and the functions satisfy assumptions (A1)-(A5) described below. Since each function represents a directed transfer of individuals, they are all non-negative. Thus

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

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

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

(A4) If $x \in X_s$ 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, where $Df(x_0)$ is the Jacobian matrix of system (1.4.0.0.3) evaluated at x_0.

Theorem 1.4.0.3. ([20]) *For the system:*

$$\begin{aligned} \frac{dX}{dt} &= F(X,Y), \\ \frac{dY}{dt} &= G(X,Y),\ G(X,0)=0, \end{aligned} \tag{1.4.0.0.4}$$

where the components of the column-vector $X \in \mathbb{R}^m$ denotes the number of uninfected individuals and the components of vector $Y \in \mathbb{R}^n$ denotes the number of infected individuals including the latent and the infectious. The disease free equilibrium, $Q_0 = (X^*, 0)$, of system (1.4.0.0.4) is globally asymptotically stable for this system provided that $R_0 < 1$ (locally asymptotically stable) and the following two conditions satisfied:

(H_1) *For $\frac{dX}{dt} = F(X,0)$, X^* is globally asymptotically stable,*

(H_2) *$G(X,Y) = AY - \hat{G}(X,Y)$, $\hat{G}(X,Y) \geq 0$ for $(X,Y) \in \Omega_0$,*

where $A = D_Y G(X^*, 0)$ is an M-matrix with the off-diagonal elements are non-negative, and Ω_0 is the region where the model is well defined.

To determine the local stability of an endemic equilibrium, we will use the following theorem, which depends on the general center manifold theory.

Theorem 1.4.0.4. ([21]) *Consider a general system of ODEs with a parameter ϕ:*

$$\frac{dx}{dt} = f(x,\phi), \quad f : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R}^n \ \text{ and } \ f \in \mathbb{C}^2(\mathbb{R}^n \times \mathbb{R}). \tag{1.4.0.0.5}$$

Without loss of generality, it is assumed that 0 is an equilibrium for system (1.4.0.0.5) for all values of the parameter ϕ, i.e.,

$$f(0,\phi) \equiv 0 \text{ for all } \phi. \tag{1.4.0.0.6}$$

Now, assume

- $A = D_x f(0,0) = \left(\frac{\partial f_i}{\partial x_j}(0,0)\right)$ *is the linearization matrix of system (1.4.0.0.5) around the equilibrium* 0 *with* ϕ *evaluated at* 0*. Zero is a simple eigenvalue of* A *and all other eigenvalues of* A *have negative real parts;*

- *Matrix* A *has a nonnegative right eigenvector* w *and a left eigenvector* v *corresponding to the zero eigenvalue.*

Let f_k *be the* k*-th component of* f *and*

$$a = \sum_{k,i,j=1}^{n} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0), \tag{1.4.0.0.7}$$

$$b = \sum_{k,i=1}^{n} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0,0). \tag{1.4.0.0.8}$$

The local dynamics of (1.4.0.0.5) around 0 *are totally determined by* a *and* b*.*

Case I. $a > 0,\ b > 0$ *: When* $\phi < 0$ *with* $|\phi| \ll 1$, 0 *is locally asymptotically stable, and there exists a positive unstable equilibrium; when* $0 < \phi \ll 1$, 0 *is unstable and there exists a negative and locally asymptotically stable equilibrium;*

Case II. $a < 0, b < 0$ *: When* $\phi < 0$ *with* $|\phi| \ll 1$, 0 *is unstable; when* $0 < \phi \ll 1$, 0 *is locally asymptotically stable, and there exists a positive unstable equilibrium;*

Case III. $a > 0, b < 0$ *: When* $\phi < 0$ *with* $|\phi| \ll 1$, 0 *is unstable, and there exists a locally asymptotically stable negative equilibrium; when* $0 < \phi \ll 1$, 0 *is stable, and a positive unstable equilibrium appears;*

Case IV. $a < 0, b > 0$ *: When* ϕ *changes from negative to positive,* 0 *changes its stability from stable to unstable. Correspondingly a negative unstable equilibrium becomes positive and locally asymptotically stable.*

Theorem 1.4.0.5. ([2])**(Routh Hurwitz Criteria).** *Given the polynomial,*

$$P(\lambda) = \lambda^n + a_1\lambda^{n-1} + \cdots + a_{n-1}\lambda + a_n, \tag{1.4.0.0.9}$$

where the coefficients a_i are real constant, $i = 1, ...n$; define the n Hurwitz matrices using the coefficients a_i of the characteristic polynomial:

$$
\begin{aligned}
H_1 &= (a_1), \\
H_2 &= \begin{pmatrix} a_1 & 1 \\ a_3 & a_2 \end{pmatrix}, \\
H_3 &= \begin{pmatrix} a_1 & 1 & 0 \\ a_3 & a_2 & a_1 \\ a_5 & a_4 & a_3 \end{pmatrix}, \\
H_n &= \begin{pmatrix} a_1 & 1 & 0 & 0 & \cdots & 0 \\ a_3 & a_2 & a_2 & 1 & \cdots & 0 \\ a_5 & a_4 & a_3 & a_2 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \cdots & \vdots \\ 0 & 0 & 0 & 0 & \cdots & a_n \end{pmatrix},
\end{aligned}
$$

where $a_j = 0$ if $j > n$. All of the roots of the polynomial $P(\lambda)$ are negative or have negative real part iff the determinants of all Hurwitz matrices are positive:

$$\det H_j > 0, \quad j = 1, 2, ..., n.$$

For example, the Routh Hurwitz criteria for polynomials of degree $n = 2, 3$ are

$$
\begin{aligned}
n &= 2 : a_1 > 0 \ \ and \ \ a_2 > 0. \\
n &= 3 : a_1 > 0, \ \ a_3 > 0, \ \ and \ \ a_1 a_2 > a_3. \\
n &= 4 : a_1 > 0, \ \ a_3 > 0, \ \ a_4 > 0, and \ \ a_1 a_2 a_3 > a_3^2 + a_1^2 a_4.
\end{aligned}
$$

Some theoretical results for DDEs

Consider the following characteristic equation (which may arise from the linearization of the delay model around the equilibria)

$$D(\lambda,\tau)=\lambda^2+a(\tau)\lambda+b(\tau)\lambda e^{-\lambda\tau}+c(\tau)+d(\tau)e^{-\lambda\tau}=0, \tag{1.4.0.0.10}$$

or equivalently

$$D(\lambda,\tau)=P_n(\lambda,\tau)+Q_m(\lambda,\tau)e^{\lambda\tau}=0, \tag{1.4.0.0.11}$$

where

$$P_n(\lambda,\tau)=\lambda^2+a(\tau)\lambda+c(\tau),\quad Q_m(\lambda,\tau)=b(\tau)\lambda+d(\tau).$$

Here $\tau\in\mathbb{R}_{+0}$ and $a(\tau),b(\tau),c(\tau),d(\tau):\mathbb{R}_{+0}\to\mathbb{R}$ are differentiable functions of class $C^1(\mathbb{R}_{+0})$ such that $c(\tau)+d(\tau)\neq 0$ for all $\tau\in\mathbb{R}_{+0}$, and for any τ, $b(\tau),d(\tau)$ are not simultaneously zero.

Assume that $P_n(\lambda,\tau)$ and $Q_m(\lambda,\tau)$ cannot have common imaginary roots. That is, for any real number ω, $P_n(i\omega,\tau)+Q_m(i\omega,\tau)\neq 0$. We have

$$\begin{aligned} F(\omega,\tau) &= |P_n(i\omega,\tau)|^2-|Q_m(i\omega,\tau)|^2, \\ &= (c-\omega^2)^2+\omega^2a^2-(\omega^2b^2+d^2). \end{aligned} \tag{1.4.0.0.12}$$

Assume that $I\subseteq\mathbb{R}_{+0}$ is the set where $\omega(\tau)$ is a positive root of (1.4.0.0.12) and for $\tau\in I$, $\omega(\tau)$ is not definite. Then for all τ in I, $\omega(\tau)$ satisfies that $F(\omega,\tau)=0$ which implies

$$\omega^4-\omega^2(b^2+2c-a^2)+(c^2-d^2)=0, \tag{1.4.0.0.13}$$

and its roots are given by

$$\omega_+^2 = \frac{1}{2}\left\{(b^2 + 2c - a^2) + \Delta^{\frac{1}{2}}\right\} \tag{1.4.0.0.14}$$

and

$$\omega_-^2 = \frac{1}{2}\left\{(b^2 + 2c - a^2) - \Delta^{\frac{1}{2}}\right\}, \tag{1.4.0.0.15}$$

where

$$\Delta = (b^2 + 2c - a^2)^2 - 4(c^2 - d^2)^2. \tag{1.4.0.0.16}$$

Therefore, the following holds:

$$2\omega_\pm^2 - (b^2 + 2c - a^2) = \pm\Delta^{\frac{1}{2}}. \tag{1.4.0.0.17}$$

Furthermore, $P_R(i\omega, \tau) = c(\tau) - \omega^2(\tau)$, $P_I(i\omega, \tau) = \omega(\tau)a(\tau)$, $Q_R(i\omega, \tau) = d(\tau)$, $Q_I(i\omega, \tau) = \omega(\tau)b(\tau)$. Hence (2.16) becomes

$$sin\theta(\tau) = \frac{-(c - \omega^2)\omega b + \omega ad}{\omega^2 b^2 + d^2}, \tag{1.4.0.0.18}$$

and

$$cos\theta(\tau) = -\frac{(c - \omega^2)d + \omega^2 ab}{\omega^2 b^2 + d^2}, \tag{1.4.0.0.19}$$

which jointly with (1.4.0.0.13) defines the maps

$$S_n(\tau) := \tau - \tau_n(\tau), \quad \tau \in I, \quad n \in N_0. \tag{1.4.0.0.20}$$

Now, from (1.4.0.0.12) we have

$$\begin{aligned} F'_{\omega}(\omega,\tau) &= 2(c-\omega^2)(-2\omega)+2\omega a^2-2\omega b^2, \\ &= 2\omega[2\omega^2-(b^2+2c-a^2)], \\ &= 2\omega_{\pm}[\pm\Delta^{\frac{1}{2}}], \end{aligned} \tag{1.4.0.0.21}$$

where $\omega_{\pm}(\tau) > 0$.

Theorem 1.4.0.6. ([13]) *The characteristic equation (1.4.0.0.10) has a pair of simple and conjugate pure imaginary roots $\lambda = \pm i\omega(\tau^*)$, $\omega(\tau^*)$ real, at $\tau^* \in I$ if $S_n(\tau^*) = \tau^* - \tau_n(\tau^*) = 0$ for some $n \in \mathbb{N}_0$. If $\omega(\tau^*) = \omega_+(\tau^*)$, this pair of simple conjugate pure imaginary roots crosses the imaginary axis from left to right if $\delta_+(\tau^*) > 0$ and crosses the imaginary axis from right to left if $\delta_+(\tau^*) < 0$, where*

$$\delta_+(\tau^*) := sign\left\{\frac{d\Re\lambda}{d\tau}|_{\lambda=i\omega_+(\tau^*)}\right\} = sign\left\{\frac{dS_n(\tau)}{d\tau}|_{\tau=\tau^*}\right\}.$$

If $\omega(\tau^*) = \omega_-(\tau^*)$, this pair of simple conjugate pure imaginary roots crosses the imaginary axis from left to right if $\delta_-(\tau^*) > 0$ and crosses the imaginary axis from right to left if $\delta_-(\tau^*) < 0$, where

$$\delta_-(\tau^*) := sign\left\{\frac{d\Re\lambda}{d\tau}|_{\lambda=i\omega_-(\tau^*)}\right\} = -sign\left\{\frac{dS_n(\tau)}{d\tau}|_{\tau=\tau^*}\right\}.$$

Some theoretical results for discrete time systems

Theorem 1.4.0.7. ([2]) *Assume the functions $f(x,y)$ and $g(x,y)$ have continuous first-order partial derivatives in x and y on some open set in $\mathbb{R}^2$ that contains the point $(\bar{x},\bar{y})$. Then the equilibrium point $(\bar{x},\bar{y})$ of the nonlinear system*

$$x_{t+1} = f(x_t,y_t), \quad y_{t+1} = g(x_t,y_t),$$

is locally asymptotically stable if the eigenvalues of the Jacobian matrix J evaluated at

the equilibrium satisfy $|\lambda_i| < 1$ *which is possible iff*

$$|Tr(J)| < 1 + \det(J) < 2.$$

The equilibrium is unstable if some $|\lambda_i| > 1$*, i.e., if any of the following three inequalities is satisfied,*

$$Tr(J) > 1 + \det(J), \quad Tr(J) < -1 - \det(J), \ \textit{or} \ \det(J) > 1.$$

Some results from the singular perturbation theory

Consider the standard form of a singularly perturbed system

$$\begin{cases} \dot{u}_t = f(u, v, \epsilon), \\ \dot{v}_t = \epsilon g(u, v, \epsilon), \end{cases} \tag{1.4.0.0.22}$$

where $u \in \mathbb{R}^k$ and $v \in \mathbb{R}^l$ with $k, l \geq 1$ in general. The parameter ϵ is a small parameter $(0 < \epsilon \ll 1)$, which gives the system a singular character. The functions f and g are assumed to be sufficiently smooth.

With a change of time scale $\tau = \epsilon t$, system (1.4.0.0.22) can be reformulated as

$$\begin{cases} \epsilon \dot{u}_\tau = f(u, v, \epsilon), \\ \dot{v}_\tau = g(u, v, \epsilon). \end{cases} \tag{1.4.0.0.23}$$

The time scale given by t is said to be fast whereas that for τ is slow. Thus (1.4.0.0.22) is called the fast system and (1.4.0.0.23) the slow system. Both systems are equivalent as long as $\epsilon \neq 0$. Each of the scalings is naturally associated with a limit as $\epsilon \to 0$.

These limits are respectively given by

$$\begin{cases} \dot{u}_t = f(u, v, 0), \\ \dot{v}_t = 0, \end{cases} \tag{1.4.0.0.24}$$

and

$$\begin{cases} 0 = f(u, v, 0), \\ \dot{v}_\tau = g(u, v, 0). \end{cases} \tag{1.4.0.0.25}$$

The latter is called the reduced system [59]. The goal of geometric singular perturbation theory is now to analyze the dynamics of system (1.4.0.0.22) with ϵ nonzero but small by suitably combining the dynamics of these two limits. In general it is natural to expect that the set $f(u, v, 0) = 0$ of critical points of (1.4.0.0.24) is, at least locally, an l-dimensional manifold in $\mathbb{R}^{k+l}$, since it is obtained by solving k equations and f was assumed to be sufficiently smooth. If indeed M_0 is an l-dimensional manifold contained in $f(u, v, 0) = 0$, and M_0 is normally hyperbolic, then Fenichel's first theorem ([46]) stats that this manifold persists for small nonzero ϵ as a manifold M_ϵ with a slow flow on it. This results was stated in [59] as follows:

Theorem 1.4.0.8. *Suppose $M_0 \subset f(u, v, 0) = 0$ is compact, possibly with boundary, and normally hyperbolic, that is, all the eigenvalues λ of the Jacobian $\frac{\partial f(u,v,0)}{\partial u}|_{M_0}$ satisfy $\Re(\lambda) \neq 0$. Suppose f and g are smooth. Then for $\epsilon > 0$ and sufficiently small, there exists a manifold M_ϵ, $O(\epsilon)$ close and diffeomorphic to M_0, that is locally invariant under the flow of the full problem (1.4.0.0.22).*

A quick tour to Gamma distribution

The gamma distribution is a two-parameter family of continuous probability distributions. It has a scale parameter b and a shape parameter n. If n is an integer, then the distribution represents an Erlang distribution, which is the sum of n independent

exponentially distributed random variables, each of which has a mean b. The gamma distribution is frequently a probability model for waiting times.

The equation defining the probability density function of a gamma-distributed random variable x is

$$g(x; n, b) = \frac{x^{n-1}e^{-x/b}}{b^n\,(n-1)!} \text{ for } x \geq 0 \text{ and } n,\, b > 0. \tag{1.4.0.0.26}$$

The mean value is $\bar{x} = nb$, the variance is nb^2, and the peak is $(n-1)b$.

When $n = 1$, gamma distribution reduces to an exponential distribution and (1.4.0.0.26) becomes

$$g(x; 1, b) = \frac{e^{-x/b}}{b} \text{ for } x \geq 0 \text{ and } b > 0, \tag{1.4.0.0.27}$$

with mean value b and variance b^2.

Following theorem implies that if n is an integer and we sum n independent Gamma $(1, b)$ random variables, the resultant sum has is Gamma (n, b).

Theorem 1.4.0.9. ([98]) *If X_1, X_2 are independent Gamma (n_1, b) and Gamma (n_2, b) variates, then $Z = X_1/(X_1 + X_2)$ and $Y = X_1 + X_2$ are independent variates with the Beta (n_1, n_2) and the Gamma $(n_1 + n_2, b)$ distributions respectively. Conversely, if (Z, Y) are independent variates with the later pair of distributions, then $X_1 = YZ$, $X_2 = Y(1 - Z)$ have the indicated Gamma distributions.*

Theorem 1.4.0.10. ([121])**(Central Limit Theorem).** *Let X_1, X_2, ..., X_n be a sequence of independent and identically distributed random variables each having mean μ and variance σ^2. Then for n large, the distribution of $X_1 + \cdots + X_n$ is approximately normal with mean $n\mu$ and variance $n\sigma^2$.*

According to Theorem 1.4.0.10, when n is large, Gamma distribution can be approximated by the Normal distribution with mean $\mu = \bar{x}$ and variance $\sigma^2 = (\bar{x})^2/n$, i.e.,

$$g(x;\, n, b) \approx f(x;\, \mu, \sigma^2) = \frac{1}{\sqrt{2\pi\sigma^2}} e^{\frac{-(x-\mu)^2}{2\sigma^2}}.$$

When $n \to \infty$, $\sigma^2 = (\bar{x})^2/n \to 0$ and then the Normal distribution approaches to a delta function, i.e.,

$$f(x;\, \mu, \sigma^2) = f(x, \bar{x}, 0) = \delta(x - \bar{x}).$$

Note that the delta function has the properties:

$$\delta(x - \bar{x}) = \begin{cases} \infty & x = \bar{x} \\ 0 & x \neq \bar{x}. \end{cases}$$

and

$$\int_{-\infty}^{\infty} \delta(x - \bar{x})dx = 1 \text{ and } \int_{-\infty}^{\infty} y(x)\delta(x - \bar{x})dx = y(\bar{x}).$$

While some of results presented in this section are preliminary intended to keep the smooth reading of the thesis, the others will be used to prove some important assertions inside individual chapters.

1.5 Outline of the thesis

This thesis deals with the analysis and implementation of robust numerical methods to solve mathematical models of HIV and malaria co-infection. We first studied the sub-models and then the full model. More specific details are provided below.

In Chapter 2, we consider a vector-host model for the transmission dynamics of malaria with a gamma distributed delay representing the incubation period of the disease in the vector. The model can be regarded as a generalization of SEI models (with a class for the latently infected mosquitoes) and SI models with a discrete delay for the incubation period in mosquitoes.

Chapter 3 deals with the investigation of the effect of the distributed delay on the transmission dynamics of HIV-malaria co-infection. We first analyze the HIV only and Malaria only sub-models and then study the full model. The *basic reproduction number* $\mathcal{R}_M^{n,\bar{\tau}}$ for malaria only sub-model is calculated and shown to be decreasing with respect

to the mean delay and the shape parameter of the gamma distribution. Also, when the disease is established, increasing these parameters leads to an endemic steady state with more healthy and less infected humans and mosquitoes. The threshold value of $\mathcal{R}_M^{n,\bar{\tau}}$ below which the disease can be eradicated is expressed in terms of the mean delay and shape parameter. We found that when the mean delay is between the critical value of the incubation period of the SEI model and that of the SI model with a discrete delay, the shape parameter has an important effect on the disease eradication or establishment (the critical value is the one below which the disease will persist). In this case, we determine a critical value for the shape parameter above which the disease can be completely eradicated. This suggests that any intervention that is aimed at reducing the initial transmission, by delaying the incubation of the disease in the vector, should account for the shape of the delay's distribution as well.

We further investigate the eradication/persistence by exploring the existence of steady states and their stability. The local stability of the disease free equilibrium (DFE) is studied analytically while that of the endemic equilibria is investigated numerically only. We also determined explicit conditions under which the system exhibits either a transcritical or backward bifurcation.

We then perform a sensitivity analysis by calculating the sensitivity index to compare the relative impact of the mean delay $\bar{\tau}$ and the shape parameter n on both the initial transmission and on the disease prevalence at the (endemic) equilibria.

Chapter 4 is devoted for the construction and analysis of the non-standard finite difference method to solve the co-infection model.

We considered in Chapter 5 the full model presented in Chapter 3 for the special case when $n = 1$. We investigate in details the effect of malaria on HIV infection. Using singular perturbation techniques, we develop the two-time scales model and sperate it into fast time-scale for malaria dynamics and slow time-scale for the dynamics for the HIV infection. The analysis of the fast model showed that it has two normal hyperbolic equilibria. Singular perturbation theory allows us to study the perturbed system by studying the reduced slow systems associated with these two equilibria.

The reduced slow systems are derived and studied in Chapter 6. We first study the dynamics on the slow manifold associated with the disease free equilibrium of the fast model. The *basic reproduction number* for this model is calculated. The slow model has a global asymptotical DFE. We also show that under some conditions the endemic equilibrium is also global asymptotical stable. Furthermore, for the slow manifold associated with the endemic equilibrium of the fast model, a thorough mathematical analysis of a model that incorporates both malaria disease and HIV infection is conducted.

Finally several conclusions are drawn from this study. These are mentioned in Chapter 7 where we also indicate scope of some future research.

Chapter 2

Analysis of a malaria model with a distributed delay

In this chapter, we consider a vector-host model for the transmission dynamics of malaria with a gamma distributed delay representing the incubation period of the disease in the vector. We calculate the basic reproduction numbers and equilibria and study their stability for some special cases of the model with distributed delay. A bifurcation analysis is also carried out for these models.

2.1 Introduction

Mathematical modelling of malaria has flourished since the days of Ross [120], who was the first to model the dynamics of malaria transmission and MacDonald [94, 95, 96] who expounded on Ross' work, introducing the theory of superinfection. The classical Ross-MacDonald model is a simple SI model that assumes that infected mosquitoes and humans become infectious immediately after infection. In reality, malaria parasites must undergo some development within the host before this one becomes infectious. The time required for this development (incubation period) ranges from 10 to 21 days in mosquitoes, depending on the parasite species and the temperature.

To account for the incubation period, many different models have been developed

to extend the Ross-MacDonald malaria models by including a class for latently infected humans/mosquitoes. For example, Ngwa and Shu [109] modeled the human and the mosquito populations by SEIRS and SEI patterns respectively. Later on this model is extended by Ngwa in [110] and Chitnis *et al.* in [25, 26]. Mukandavire *et al.* [106] modeled the human and mosquito populations as SEIS and SEI model respectively. In these models the time needed for an infected mosquito/human to become infectious follows a Poisson distribution with a mean value equal to the incubation period.

Another way of accounting for the incubation period is to use models with time delays. In [1], Abu-Raddad *et al.* proposed a compartmental model for the co-infection of HIV and malaria with a delay representing the incubation period in mosquitoes. Chiyaka *et al.* [23] formulated a transmission model of malaria in a partially immune population with three discrete delays representing the duration of partial immunity and the latent periods in the human and mosquito populations. Ruan *et al.* [122] modified the classical Ross-MacDonald model [94, 95, 96] to include time delays that describe the incubation periods of parasites within both the human and the mosquito. By modifying a standard model in Anderson and May [3], Saker [126] studied a malaria model with two latent periods; one for humans and the other for mosquito vectors. These models assume that infected mosquitoes become infectious after a period of time which is equal to the (discrete) delay in the model. This means that the incubation period follows a Dirac-delta distribution.

Both the Poisson and Dirac functions are particular cases of gamma distributions. In fact, Dirac (resp. Poisson) distributions are obtained by tending the shape parameter of gamma distributions to infinity (resp. to one).

In this chapter, we consider a vector-host model for the transmission dynamics of malaria with a gamma distributed delay representing the incubation period of the disease in the vector. We analyze the spacial cases of the model with a distributed delay. We find equilibria, discuss their stability analysis and present bifurcation analysis for these models.

The rest of this chapter is organized as follows. The model description is presented

in Section 2.2 and its analysis is carried out in Section 2.3. Section 2.4 is devoted to the discussion of the results.

2.2 Description of the model

The model that we consider here is a standard SI model for malaria transmission considered with a distributed delay representing the time needed for infected mosquitoes to become infectious. In this model, we divide the total population of humans (N_H) into two sub-populations, susceptible (S_H) and infectious (I_M). The total mosquito population (N_V) is divided into susceptible mosquitoes (S_V) and infectious mosquitoes (I_V).

It is assumed that susceptible humans are recruited into the population at a constant rate Λ_H. They either die from natural causes (at a rate μ_H) or acquire infection with malaria following effective contact with infected mosquitoes (at a rate λ_M) and move to the infectious class (I_M). Infected Individuals either recover with partial immunity and move into susceptible class (at a rate ν_1) or die from the disease (at a rate α_M) or from natural causes (at a rate μ_H). Susceptible mosquitoes are recruited into the population at a constant rate Λ_V. They either die (at a rate μ_V) or acquire malaria infection (following effective contacts with infected humans) (at a rate λ_V). Each infected mosquito becomes infectious and move to the infectious class (I_V) after a time delay τ with a gamma distribution:

$$\mathsf{g}_{n,\bar{\tau}}(\tau) = \frac{n^n \tau^{n-1}}{(n-1)!\bar{\tau}^n} e^{-n\tau/\bar{\tau}}, \tag{2.2.0.0.1}$$

where $\bar{\tau} > 0$ is the mean value and $n \geq 1$ is an integer-valued shape parameter (Erlang distribution).

With the above assumptions and notations, the model is written as follows

$$\begin{aligned}
\dot{S}_H(t) &= \Lambda_H + \nu_1 I_M(t) - \mu_H S_H(t) - \lambda_M(t) S_H(t), \\
\dot{I}_M(t) &= \lambda_M(t) S_H(t) - (\mu_H + \alpha_M + \nu_1) I_M(t), \\
\dot{S}_V(t) &= \Lambda_V - \mu_V S_V - \lambda_V(t) S_V(t), \\
\dot{I}_V(t) &= \int_0^\infty \mathrm{g}_{n,\bar{\tau}}(\tau) \lambda_V(t-\tau) S_V(t-\tau) e^{-\mu_V \tau} d\tau - \mu_V I_V(t),
\end{aligned} \tag{2.2.0.0.2}$$

where the malaria host-to-vector and vector-to-host forces of infections are given by

$$\lambda_M(t) = \frac{\beta_M \theta I_V(t)}{N_H(t)}, \quad \lambda_V(t) = \frac{\beta_V \theta I_M(t)}{N_H(t)}.$$

Here, θ is the per capita biting rate of mosquitos, β_M (resp. β_V) is the transmission probability per bite for human (resp. mosquito) infection. The use of this force of infection is due to the fact that female mosquitoes only take a fixed number of blood meals per unit of time, irrespective of the absolute numbers of mosquitoes and human [3].

We recall that Gamma distribution is a general distribution that generates a Poisson and Dirac-delta distribution. When $n = 1$ gamma distribution reduces to an exponential distribution and (2.2.0.0.2) reads

$$\begin{aligned}
\dot{S}_H(t) &= \Lambda_H + \nu_1 I_M(t) - \mu_H S_H(t) - \lambda_M(t) S_H(t), \\
\dot{I}_M(t) &= \lambda_M(t) S_H(t) - (\mu_H + \alpha_M + \nu_1) I_M(t), \\
\dot{S}_V(t) &= \Lambda_V - \mu_V S_V - \lambda_V(t) S_V(t), \\
\dot{I}_V(t) &= \frac{1}{\bar{\tau}} \int_0^\infty e^{-(1/\bar{\tau} + \mu_V)\tau} \lambda_V(t-\tau) S_V(t-\tau) d\tau - \mu_V I_V(t).
\end{aligned} \tag{2.2.0.0.3}$$

Let

$$E_V(t) = \int_0^\infty e^{-(1/\bar{\tau} + \mu_V)\tau} \lambda_V(t-\tau) S_V(t-\tau) d\tau,$$

then we have

$$\begin{aligned}
\dot{E}_V(t) &= \frac{d}{dt}\left(\int_0^\infty e^{-(1/\bar{\tau}+\mu_V)\tau}\lambda_V(t-\tau)S_V(t-\tau)d\tau\right), \\
&= -\int_0^\infty e^{-(1/\bar{\tau}+\mu_V)\tau}\frac{d(\lambda_V(t-\tau)S_V(t-\tau))}{d\tau}d\tau, \\
&= -\left[e^{-(1/\bar{\tau}+\mu_V)\tau}\lambda_V(t-\tau)S_V(t-\tau)\right]_{\tau=0}^{\tau=\infty} \\
&\quad -\left(\frac{1}{\bar{\tau}}+\mu_V\right)\int_0^\infty e^{-(1/\bar{\tau}+\mu_V)\tau}\lambda_V(t-\tau)S_V(t-\tau), \\
&= \lambda_V(t)S_V(t) - \left(\frac{1}{\bar{\tau}}+\mu_V\right)E_V(t).
\end{aligned}$$

Let $\gamma_V = 1/\bar{\tau}$, then system (2.2.0.0.3) becomes

$$\begin{aligned}
\dot{S}_H(t) &= \Lambda_H + \nu_1 I_M(t) - \mu_H S_H(t) - \lambda_M(t)S_H(t), \\
\dot{I}_M(t) &= \lambda_M(t)S_H(t) - (\mu_H + \alpha_M + \nu_1)I_M(t), \\
\dot{S}_V(t) &= \Lambda_V - \mu_V S_V - \lambda_V(t)S_V(t), \\
\dot{E}_V(t) &= \lambda_V(t)S_V(t) - (\gamma_V + \mu_V)E_V(t), \\
\dot{I}_V(t) &= \gamma_V E_V(t) - \mu_V I_V(t).
\end{aligned} \tag{2.2.0.0.4}$$

When the mean delay $\bar{\tau} = 0$, that is, the mean time that individuals spend in the exposed class (E_V) is zero, (i.e., $1/\gamma_V = 0$), then we receive an SI model

$$\begin{aligned}
\dot{S}_H(t) &= \Lambda_H + \nu_1 I_M(t) - \mu_H S_H(t) - \lambda_M(t)S_H(t), \\
\dot{I}_M(t) &= \lambda_M(t)S_H(t) - (\mu_H + \alpha_M + \nu_1)I_M(t), \\
\dot{S}_V(t) &= \Lambda_V - \mu_V S_V - \lambda_V(t)S_V(t), \\
\dot{I}_V(t) &= \lambda_V(t)S_V(t) - \mu_V I_V(t).
\end{aligned} \tag{2.2.0.0.5}$$

When $n \to \infty$, gamma distribution approaches a delta function $\delta(\tau - \bar{\tau})$, and

$$\int_0^\infty \delta(\tau-\bar{\tau})\lambda_V(t-\tau)S_V(t-\tau)e^{-\mu_V\tau}d\tau = \lambda_V(t-\bar{\tau})S_V(t-\bar{\tau})e^{-\mu_V\bar{\tau}},$$

therefore system (2.2.0.0.2) becomes

$$\begin{aligned}
\dot{S}_H(t) &= \Lambda_H + \nu_1 I_M(t) - \mu_H S_H(t) - \lambda_M(t) S_H(t), \\
\dot{I}_M(t) &= \lambda_M(t) S_H(t) - (\mu_H + \alpha_M + \nu_1) I_M(t), \\
\dot{S}_V(t) &= \Lambda_V - \mu_V S_V - \lambda_V(t) S_V(t), \\
\dot{I}_V(t) &= \lambda_V(t - \bar{\tau}) S_V(t - \bar{\tau}) e^{-\mu_V \bar{\tau}} - \mu_V I_V(t),
\end{aligned} \tag{2.2.0.0.6}$$

which is a model with a discrete delay.

2.3 Analysis of the models

In this section we analyze the model (2.2.0.0.2) from various perspectives. In particular, we study its well-posedness, discuss the feasibility region as well as stability and bifurcation.

2.3.1 Well-posedness and feasibility region

Existence conditions for equations with finite delays, are not obviously true in general for infinite delays. The main difficulty is that the interval $]-\infty, 0[$ is not compact, and the images of a solution map of closed and bounded sets in $C(]-\infty, 0], \mathbb{R}^n)$ with uniform norm may not be compact in the same space. Indeed, the Banach space BC of bounded and continuous functions from $]-\infty, 0]$ into $\mathbb{R}^n$ with uniform norm may cause problems for even the usual well-posedness questions related to delay differential equations of unbounded delay [81]. To overcome these difficulties, the author in [81] choose the following more friendly space, often referred to as fading memory space. Following this work, we consider, for each $\alpha > 0$, the Banach space of fading memory type

$$\begin{aligned}
UC_\alpha := \{\varphi \in C(]-\infty, 0], \mathbb{R}) : s \to \varphi(s) e^{\alpha s} \text{ is uniformly continuous on }]-\infty, 0] \\
\text{and } \sup_{s \leq 0} |\varphi(s)| \, e^{\alpha s} < \infty \big\},
\end{aligned}$$

endowed with the norm

$$\|\varphi\|_\alpha = \sup_{s\leq 0} |\varphi(s)|\, e^{\alpha s}.$$

According to [55], standard existence and uniqueness results hold for system (2.2.0.0.2) in UC_α.

We analyze (2.2.0.0.2) in a biologically-feasible region for both human and mosquito populations.

Letting

$$UC_\alpha^+ = \{\varphi \in UC_\alpha : \varphi(s) \geq 0 \text{ for each } s \in]-\infty, 0]\},$$

we have the following result:

Proposition 2.3.1. *If the initial condition is in UC_α^{+4} then the corresponding solution $(S_H(t), I_M(t), S_V(t), I_V(t))$ of the malaria model (2.2.0.0.2) is non-negative for all $t > 0$. Moreover,*

$$\lim_{t\to\infty} N_H(t) \leq \frac{\Lambda_H}{\mu_H}, \lim_{t\to\infty} S_V(t) \leq \frac{\Lambda_V}{\mu_V} \text{ and } \lim_{t\to\infty} I_V(t) \leq \frac{\theta\beta_V\Lambda_V}{\mu_V^2}. \qquad (2.3.1.0.7)$$

Furthermore, we have the following invariance properties:

i. If $N_H(0) \leq \frac{\Lambda_H}{\mu_H}$ then $N_H(t) \leq \frac{\Lambda_H}{\mu_H}$

ii. If $S_V(0) \leq \frac{\Lambda_V}{\mu_V}$ then $S_V(t) \leq \frac{\Lambda_V}{\mu_V}$ and if in addition $I_V(0) \leq \frac{\theta\beta_V\Lambda_V}{\mu_V^2}$ then $I_V(t) \leq \frac{\theta\beta_V\Lambda_V}{\mu_V^2}$.

In particular, the regions $\mathcal{D}_H \times UC_\alpha^{+2}$ and $UC_\alpha^{+2} \times \mathcal{D}_V$ with

$$\begin{aligned}
\mathcal{D}_H &= \left\{(\phi_H, \psi_H) \in UC_\alpha^{+2} : \phi_H(0) + \psi_H(0) \leq \frac{\Lambda_H}{\mu_H}\right\}, \\
\mathcal{D}_V &= \left\{(\phi_V, \psi_V) \in UC_\alpha^{+2} : \phi_V(0) \leq \frac{\Lambda_V}{\mu_V}, \psi_V(0) \leq \frac{\theta\beta_V\Lambda_V}{\mu_V^2}\right\},
\end{aligned}$$

are positively-invariant.

Proof. Denote by t_{max} the upper bound of the maximum interval of existence corresponding to $(S_H(t), I_M(t), S_V(t), I_V(t))$. To show that the solution is positive and bounded in $[0, +\infty[$, it is sufficient to show the positivity and boundedness results in $[0, t_{max}[$.

Let

$$t_1 = \sup\{0 \leq t < t_{max} : S_H, I_M, S_V \text{ and } I_V, \text{ are positive on } [0, t]\}.$$

Since $S_H(0)$, $I_M(0)$, $S_V(0)$ and $I_V(0)$ are non-negative we have $t_1 > 0$. If $t_1 < t_{max}$ then, by using the variation of constants formula ([56]) to the first equation of system (2.2.0.0.2), we have

$$S_H(t_1) = S_H(0)e^{-\mu_H t_1 - \int_0^{t_1} \lambda_M(v)dv} + \int_0^{t_1} e^{-\mu_H(t_1-u) - \int_u^{t_1} \lambda_M(v)dv}(\Lambda_H + \nu_1 I_M(u))du > 0.$$

It can be shown in the same manner that the other variables are also positive at t_1. This contradicts the fact that t_1 is the supremum because at least one of the variables should be equal to zero at t_1. Therefore $t_1 = t_{max}$ and the solution is positive on its maximal interval of existence $[0, t_{max}[$.

Next, we show that the solution is bounded on $[0, t_{max}[$. By using a standard comparison theorem ([14]) and by accounting for the positivity of the solution on $[0, t_{max}[$, we obtain from the first two equations of system (2.2.0.0.2)

$$e^{-(\mu_H+\alpha_M)t}N_H(0) + \frac{\Lambda_H}{\mu_H+\alpha_M}(1 - e^{-(\mu_H+\alpha_M)t}) \leq N_H(t) \leq e^{-\mu_H t}N_H(0) + \frac{\Lambda_H}{\mu_H}(1 - e^{-\mu_H t}). \tag{2.3.1.0.8}$$

Therefore $N_H(t)$ is bounded on $[0, t_{max}[$.

The positivity of the solution also implies that

$$\begin{aligned} \dot{S}_V(t) &\leq \Lambda_V - \mu_V S_V(t), \\ \dot{I}_V(t) &\leq \theta\beta_V \int_0^{\infty} \mathrm{g}_{n,\bar{\tau}}(\tau) S_V(t-\tau)e^{-\mu_V \tau}d\tau - \mu_V I_V(t). \end{aligned} \tag{2.3.1.0.9}$$

Now, from the first equation of (2.3.1.0.9) we obtain

$$0 \leq S_V(t) \leq S_V(0)e^{-\mu_V t} + \tfrac{\Lambda_V}{\mu_V}\left(1 - e^{-\mu_V t}\right). \tag{2.3.1.0.10}$$

Thus $S_V(t)$ is bounded on $[0, t_{max}[$. Furthermore from (2.3.1.0.9) and (2.3.1.0.10) we obtain

$$\dot{I}_V(t) \leq \theta\beta_V \left(S_V(0)e^{-\mu_V t} + \frac{\Lambda_V}{\mu_V}\left(1 - e^{-\mu_V t}\right)\right) - \mu_V I_V(t),$$

which implies that

$$0 \leq I_V(t) \leq e^{-\mu_V t}I_V(0) + \frac{\theta\beta_V\Lambda_V}{\mu_V^2}\left(1 - e^{-\mu_V t}\right) + \theta\beta_V\left(S_V(0) - \frac{\Lambda_V}{\mu_V}\right)te^{-\mu_V t}. \tag{2.3.1.0.11}$$

Thus $I_V(t)$ is also bounded on $[0, t_{max}[$. Hence $t_{max} = \infty$ which proves the global existence and positivity results.

Concerning the invariance properties, it is easy to obtain from (2.3.1.0.8) that if $N_H(0) \leq \Lambda_H/\mu_H$ then $N_H(t) \leq \Lambda_H/\mu_H$. Similarly, from (2.3.1.0.10) we obtain that if $S_V(0) \leq \Lambda_V/\mu_V$ then $S_V(t) \leq \Lambda_V/\mu_V$ and

$$0 \leq I_V(t) \leq I_V(0)e^{-\mu_V t} + \frac{\theta\beta_V\Lambda_V}{\mu_V^2}\left(1 - e^{-\mu_V t}\right).$$

If in addition $I_V(0) \leq \theta\beta_V\Lambda_V/\mu_V^2$ then $I_V(t) \leq \theta\beta_V\Lambda_V/\mu_V^2$. This establishes the invariance of the regions as required. The results (2.3.1.0.7) follow immediately from (2.3.1.0.8), (2.3.1.0.10) and (2.3.1.0.11). □

Before we analyze the malaria model with a distributed delay (2.2.0.0.2), we first analyze the special cases.

2.3.2 Analysis of an SI malaria model

In this section we present the stability and bifurcation analysis of the SI malaria model (2.2.0.0.5).

2.3.2.1 The basic reproduction number

The DFE of an SI model (2.2.0.0.5) is given by

$$\mathsf{E}^0 = (\tfrac{\Lambda_H}{\mu_H}, 0, \tfrac{\Lambda_V}{\mu_V}, 0).$$

The stability of the DFE be investigated using the next generation operator [140]. We verify that system (2.2.0.0.5) satisfy the conditions (A1)-(A5) in [140].

Firstly, we rewrite model (2.2.0.0.5) in the order that the first 2 compartments correspond to infected individuals

$$\begin{aligned}
\dot{I}_M(t) &= \frac{\beta_M \theta I_V(t)}{S_H(t) + I_M(t)} S_H(t) - (\mu_H + \alpha_M + \nu_1) I_M(t), \\
\dot{I}_V(t) &= \frac{\beta_V \theta I_M(t)}{S_H(t) + I_M(t)} S_V(t) - \mu_V I_V(t), \\
\dot{S}_H(t) &= \Lambda_H + \nu_1 I_M(t) - \mu_H S_H(t) - \frac{\beta_M \theta I_V(t)}{S_H(t) + I_M(t)} S_H(t), \\
\dot{S}_V(t) &= \Lambda_V - \mu_V S_V - \frac{\beta_V \theta I_M(t)}{S_H(t) + I_M(t)} S_V(t).
\end{aligned} \tag{2.3.2.1.1}$$

Let $x = (I_M, I_V, S_H, S_V)^t = (x_1, x_2, x_3, x_4)^t$, with each $x_i \geq 0$, be the number of individuals in each compartment. Define X_s to be the set of all disease free states, i.e.,

$$X_s = \{x \geq 0 \mid x_i = 0, i = 1, 2\} = \left\{ \left(0, 0, \frac{\Lambda_H}{\mu_H}, \frac{\Lambda_V}{\mu_V}\right)^t \right\}.$$

System (2.3.2.1.1) can be written in the form

$$\dot{x} = f(x) = \mathcal{F}(x) - \mathcal{V}(x), \tag{2.3.2.1.2}$$

where $\mathcal{V}(x) = \mathcal{V}^-(x) - \mathcal{V}^+(x)$. Since each function represents a directed transfer of individuals, they are all non-negative, and given by

$$\mathcal{F}(x) = \begin{pmatrix} \frac{\beta_M \theta x_2}{x_1 + x_3} x_3 \\ \\ \frac{\beta_V \theta x_1}{x_1 + x_3} x_4 \\ \\ 0 \\ \\ 0 \end{pmatrix}, \quad \mathcal{V}^+(x) = \begin{pmatrix} 0 \\ 0 \\ \Lambda_H + \nu_1 x_1 \\ \Lambda_V \end{pmatrix} \quad \text{and} \quad \mathcal{V}^-(x) = \begin{pmatrix} (\mu_H + \alpha_M + \nu_1) x_1 \\ \\ \mu_V x_2 \\ \\ \left(\mu_H + \frac{\beta_M \theta x_3}{x_1 + x_3}\right) x_3 \\ \\ \left(\mu_V + \frac{\beta_V \theta x_1}{x_1 + x_3}\right) x_4 \end{pmatrix}.$$

From the above functions we found:

(A1) if $x \geq 0$, then $\mathcal{F}_i(x), \mathcal{V}_i^+(x), \mathcal{V}_i^-(x) \geq 0$ for $i = 1, \ldots, 4$,

(A2) if $x_i = 0$, then $\mathcal{V}_i^-(x) = 0$. In particular, if $x \in X_s$ then $\mathcal{V}_i^-(x) = 0$ for $i = 1, 2$,

(A3) $\mathcal{F}_i = 0$ for $i > 2$,

(A4) if $x \in X_s$ then $\mathcal{F}_i(x) = 0$ and $\mathcal{V}_i^+(x) = 0$ for $i = 1, 2$,

(A5) if $\mathcal{F}(x) = 0$, then the Jacobian matrix of system (2.3.2.1.2) is given by

$$Df(x_0) = \begin{pmatrix} -(\mu_H + \alpha_M + \nu_1) & 0 & 0 & 0 \\ \\ 0 & -\mu_V & 0 & 0 \\ \\ \nu_1 & 0 & -\mu_H & 0 \\ \\ 0 & 0 & 0 & -\mu_V \end{pmatrix}. \qquad (2.3.2.1.3)$$

The eigenvalues of $Df(x_0)$ are

$$-\mu_H, \; -(\mu_H + \alpha_M + \nu_1) \text{ and } -\mu_V \text{ (of multiplicity two)}.$$

It follows that all eigenvalues of $Df(x_0)$ have negative real parts.

Then the matrices $\mathbf{F}$ and $\mathbf{V}$ denoting the new infection terms and the remaining transfer terms are, respectively, given by

$$\mathbf{F} = \begin{pmatrix} 0 & \beta_M\theta \\ \dfrac{\beta_V\theta\mu_H\Lambda_V}{\Lambda_H\mu_V} & 0 \end{pmatrix} \text{ and } \mathbf{V} = \begin{pmatrix} \mu_H+\alpha_M+\nu_1 & 0 \\ 0 & \mu_V \end{pmatrix}.$$

Note that the reproductive number, $\mathcal{R}_0$, is equal to the spectral radius of the *next generation operator* $\mathbf{FV}^{-1}$ [140]. The eigenvalues of $\mathbf{FV^{-1}}$ are

$$\pm\sqrt{\frac{\beta_M\beta_V\theta^2\mu_H\Lambda_V}{\Lambda_H\mu_V^2(\mu_H+\alpha_M+\nu_1)}}.$$

It follows therefore that

$$\rho(\mathbf{FV^{-1}}) = \sqrt{\frac{\beta_M\beta_V\theta^2\mu_H\Lambda_V}{\Lambda_H\mu_V^2(\mu_H+\alpha_M+\nu_1)}},$$

which gives us $\mathcal{R}_0$. However in this type of models (vector-host) the initial transmission of the disease (when we introduce one infective (human/mosquito) in a susceptible population) is given by $\mathcal{R}_0^2$, the square root in the expression for $\mathcal{R}_0$ arises from the two 'generations' required for an infected vector or host to 'reproduce' itself [140]. Therefore we consider $\mathcal{R}_0$ to be the squared value of $\rho(\mathbf{FV^{-1}})$ i.e.,

$$\mathcal{R}_0 = \frac{\beta_M\beta_V\theta^2\mu_H\Lambda_V}{\Lambda_H\mu_V^2(\mu_H+\alpha_M+\nu_1)}.$$

2.3.2.2 Stability of the disease-free equilibrium

Using Theorem 2 of [140], the following result is established.

Theorem 2.3.2.1. *The DFE of the SI model (2.2.0.0.5) is locally-asymptotically stable if $\mathcal{R}_0 < 1$, and unstable if $\mathcal{R}_0 > 1$.*

2.3.2.3 Existence of backward bifurcation

In this section, we discuss that the system (2.2.0.0.5) undergoes a backward bifurcation where a stable DFE co-exists with a stable endemic equilibrium for some values of $\mathcal{R}_0 < 1$. The possibility of backward phenomenon in the system (2.2.0.0.5) is investigated below.

To find conditions for the existence of an equilibrium denoted by $\mathsf{E}^* = (S_H^*, I_M^*, S_V^*, I_V^*)$, for which malaria is endemic in the population (i.e., at least one of I_M^* and I_V^* is non-zero), the equations in (2.2.0.0.5) are solved in terms of the force of infection at steady-state (λ_M^*), given by

$$\lambda_M^* = \frac{\beta_M \theta I_V^*}{S_H^* + I_M^*}. \tag{2.3.2.3.1}$$

Setting the right hand sides of the model to zero (and noting that $\lambda_M = \lambda_M^*$ at equilibrium) we obtain

$$\begin{aligned} S_H^* &= \frac{\Lambda_H(\mu_H + \alpha_M + \nu_1)}{\mu_H(\mu_H + \alpha_M + \nu_1) + \lambda_M^*(\mu_H + \alpha_M)}, \\ I_M^* &= \frac{\Lambda_H \lambda_M^*}{\mu_H(\mu_H + \alpha_M + \nu_1) + \lambda_M^*(\mu_H + \alpha_M)}, \\ S_V^* &= \frac{\Lambda_V}{\mu_V + \lambda_V^*}, \\ I_V^* &= \frac{\Lambda_V \lambda_V^*}{\mu_V(\mu_V + \lambda_V^*)}, \end{aligned} \tag{2.3.2.3.2}$$

where

$$\lambda_V^* = \frac{\beta_V \theta I_M^*}{S_H^* + I_M^*}. \tag{2.3.2.3.3}$$

Substituting (2.3.2.3.2) and (2.3.2.3.3) into (2.3.2.3.1) we see that the endemic equilibria of the malaria model (2.2.0.0.5) satisfy the following polynomial (in λ_M^*)

$$\lambda_M^*(A(\lambda_M^*)^2 + B\lambda_M^* + C) = 0, \tag{2.3.2.3.4}$$

where

$$\begin{aligned} A &= \Lambda_H \mu_V (\mu_V + \beta_V \theta), \\ B &= \frac{\Lambda_H \mu_V^2 (\mu_H + \alpha_M + \nu_1)(\mu_H + \alpha_M)}{\mu_H} (K - \mathcal{R}_0), \\ C &= \Lambda_H \mu_V^2 (\mu_H + \alpha_M + \nu_1)^2 (1 - \mathcal{R}_0), \end{aligned} \tag{2.3.2.3.5}$$

with

$$K = \frac{\mu_H (2\mu_V + \beta_V \theta)}{\mu_V (\mu_H + \alpha_M)}.$$

Clearly, $K > 1$ if and only if $\theta > \theta_0 := \mu_V(\alpha_M - \mu_H)/\beta_V \mu_H$.

The root $\lambda_M^* = 0$ of (2.3.2.3.4) corresponds to the DFE (E^0) and the roots of the quadratic

$$A(\lambda_M^*)^2 + B\lambda_M^* + C = 0, \tag{2.3.2.3.6}$$

correspond to the existence of multiple endemic equilibria. We examine the quadratic equation (2.3.2.3.6) for possibility of backward bifurcation. From the expressions above, it is clear that A is always positive. B is positive (negative) if $\mathcal{R}_0 < K$ ($\mathcal{R}_0 > K$), respectively, and C is positive (negative) if $\mathcal{R}_0 < 1$ ($\mathcal{R}_0 > 1$), respectively. We therefore established the following theorem.

Theorem 2.3.2.2. *1. If $\theta \geq \theta_0$, then system (2.2.0.0.5) exhibits transcritical bifurcation.*

2. If $\theta < \theta_0$, then system (2.2.0.0.5) exhibits backward bifurcation. That is there exists $\mathcal{R}_c$ in $(0, 1)$ such that

i. If $\mathcal{R}_0 \geq 1$, then (2.2.0.0.5) has one endemic equilibrium.

ii. If $\mathcal{R}_c < \mathcal{R}_0 < 1$, then (2.2.0.0.5) has two endemic equilibria.

iii. If $\mathcal{R}_0 = \mathcal{R}_c$, then (2.2.0.0.5) has one unique endemic equilibrium.

iv. If $\mathcal{R}_0 < \mathcal{R}_c$ (2.2.0.0.5) has no endemic equilibrium.

Proof. 1. If $\theta \geq \theta_0$, then $K \geq 1$. In this case,

i. If $\mathcal{R}_0 > 1$, then $C < 0$. Thus (2.3.2.3.6) has a unique positive solution.

ii. If $\mathcal{R}_0 \leq 1$, then $B > 0$ ($\mathcal{R}_0 \leq 1 \leq K$) and $C > 0$. This with $A > 0$ implies that (2.3.2.3.6) has no positive solution.

2. If $\theta < \theta_0$, then $K < 1$. In this case,

i. If $\mathcal{R}_0 \geq 1$, then $B \leq 0$ ($K < 1 \leq \mathcal{R}_0$) and $C \leq 0$. Thus (2.3.2.3.6) has a unique positive solution.

ii. If $\mathcal{R}_0 \leq K < 1$, then $B \geq 0$ and $C > 0$. Thus (2.3.2.3.6) has no positive solution.

iii. If $K < \mathcal{R}_0 \leq 1$, then $B < 0$ and $C \geq 0$. We consider the discriminant of (2.3.2.3.6), i.e., $\triangle(\mathcal{R}_0) := B^2 - 4AC$. One can see that $\triangle(K) := -4AC < 0$ and $\triangle(1) := B^2 > 0$. Therefore there exists $\mathcal{R}_c \in (K, 1)$ such that $\triangle(\mathcal{R}_c) = 0$ and $\triangle < 0$ for $\mathcal{R}_0 \in (K, \mathcal{R}_c)$ and $\triangle > 0$ for $\mathcal{R}_0 \in (\mathcal{R}_c, 1)$. Thus we have that

a. If $K < \mathcal{R}_0 < \mathcal{R}_c$, then (2.3.2.3.6) has no positive solution.

b. If $\mathcal{R}_0 = \mathcal{R}_c$. This implies that (2.3.2.3.6) has one positive solution.

c. If $\mathcal{R}_c < \mathcal{R}_0 < 1$, then (2.3.2.3.6) has two real solutions which are positive since $B < 0$ and $C > 0$. □

Theorem (2.3.2.2) establishes the existence of two endemic equilibria for $\mathcal{R}_0$ in $(\mathcal{R}_c, 1)$ which indicates the possibility of backward bifurcation in the model (2.2.0.0.5) when $\theta < \theta_0$.

The possibility of backward bifurcation is explored using the Center Manifold theory. Let $S_H = x_1$, $I_M = x_2$, $S_V = x_3$ and $I_V = x_4$. Using vector notation $x = (x_1, x_2, x_3, x_4)^T$, the malaria model (2.2.0.0.5) can be written in the form $dx/dt = F(x)$,

with $F = (f_1, f_2, f_3, f_4)^T$, as follows

$$\begin{aligned}
\frac{dx_1}{dt} &= f_1 = \Lambda_H + \nu_1 x_2 - \mu_H x_1 - \lambda_M x_1, \\
\frac{dx_2}{dt} &= f_2 = \lambda_M x_1 - (\mu_H + \alpha_M + \nu_1) x_2, \\
\frac{dx_3}{dt} &= f_3 = \Lambda_V - \lambda_V x_3 - \mu_V x_3, \\
\frac{dx_4}{dt} &= f_4 = \lambda_V x_4 - \mu_V x_4,
\end{aligned} \tag{2.3.2.3.7}$$

with

$$\lambda_M = \frac{\beta_M \theta x_4}{x_1 + x_2} \text{ and } \lambda_V = \frac{\beta_V \theta x_2}{x_1 + x_2}.$$

The Jacobian of system (2.2.0.0.5) at DFE is given by

$$J^0_{SI} = \begin{pmatrix} -\mu_H & \nu_1 & 0 & -\beta_M \theta \\ 0 & -(\mu_H + \alpha_M + \nu_1) & 0 & \beta_M \theta \\ 0 & -\dfrac{\beta_V \theta \mu_H \Lambda_V}{\Lambda_H \mu_V} & -\mu_V & 0 \\ 0 & \dfrac{\beta_V \theta \mu_H \Lambda_V}{\Lambda_H \mu_V} & 0 & -\mu_V \end{pmatrix}. \tag{2.3.2.3.8}$$

Suppose $\beta_M = \beta^*$ is chosen as a bifurcation parameter. Solving for $\mathcal{R}_0 = 1$, we obtain

$$\beta^* = \frac{\Lambda_H \mu_V^2 (\mu_H + \alpha_M + \nu_1)}{\beta_V \theta^2 \mu_H \Lambda_V}.$$

The Jacobian $J^0_{SI}\mid_{\beta_M=\beta^*}$ denoted by J_{β^*} is given by

$$J_{\beta^*}=\begin{pmatrix} -\mu_H & \nu_1 & 0 & -\frac{\Lambda_H\mu_V^2(\mu_H+\alpha_M+\nu_1)}{\beta_V\theta\mu_H\Lambda_V} \\ 0 & -(\mu_H+\alpha_M+\nu_1) & 0 & \frac{\Lambda_H\mu_V^2(\mu_H+\alpha_M+\nu_1)}{\beta_V\theta\mu_H\Lambda_V} \\ 0 & -\frac{\beta_V\theta\mu_H\Lambda_V}{\Lambda_H\mu_V} & -\mu_V & 0 \\ 0 & \frac{\beta_V\theta\mu_H\Lambda_V}{\Lambda_H\mu_V} & 0 & -\mu_V \end{pmatrix}.$$

The eigenvalues of J_{β^*} are

$$0, -\mu_H, -(\mu_H+\alpha_M+\nu_1) \text{ and } \mu_V.$$

That is J_{β^*} has a simple zero eigenvalue (with all other eigenvalues having negative real part). Also J_{β^*} has a right eigenvector w and a left eigenvector v corresponding to the zero eigenvalue.

Eigenvectors of J_{β^*}: The right eigenvector of J_{β^*} is given by $w=[w_1,w_2,w_3,w_4]^T$ can be found by solving the system $J_{\beta^*}w=0$ which gives

$$\begin{aligned} w_1 &= -\frac{(\mu_H+\alpha_M)\beta^*\theta w_4}{\mu_H(\mu_H+\alpha_M+\nu_1)}, \\ w_2 &= \frac{\beta^*\theta w_4}{\mu_H+\alpha_M+\nu_1}, \\ w_3 &= -w_4, \\ w_4 &= w_4. \end{aligned}$$

Further, the Jacobian J_{β^*} has a left eigenvector $v=[v_1,v_2,v_3,v_4]$ which can be found

by solving the system $vJ_{\beta^*} = 0$ which gives

$$\begin{aligned} v_1 &= 0, \\ v_2 &= v_2, \\ v_3 &= 0, \\ v_4 &= \frac{\beta^*\theta v_2}{\mu_V}. \end{aligned}$$

From the theorem by Castillo-Chavez and Song [21], the local dynamics of system (2.3.2.3.7) around 0 are totally determined by a and b, where

$$\begin{aligned} a &= \sum_{k,i,j=1}^{4} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0), \\ b &= \sum_{k,i=1}^{4} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0,0). \end{aligned}$$

Computations of a and b: For the system (2.3.2.3.7), the associated non-zero partial derivatives of F (at the DFE) are given by

$$\begin{aligned} \frac{\partial^2 f_1}{\partial x_2 \partial x_4} &= \frac{\partial^2 f_1}{\partial x_4 \partial x_2} = \frac{\beta_M \theta \mu_H}{\Lambda_H}, \\ \frac{\partial^2 f_2}{\partial x_2 \partial x_4} &= \frac{\partial^2 f_2}{\partial x_4 \partial x_2} = -\frac{\beta_M \theta \mu_H}{\Lambda_H}, \\ \frac{\partial^2 f_3}{\partial x_1 \partial x_2} &= \frac{\partial^2 f_3}{\partial x_2 \partial x_1} = \frac{\beta_V \theta \mu_H^2 \Lambda_V}{\Lambda_H^2 \mu_V}, \\ \frac{\partial^2 f_3}{\partial x_2^2} &= \frac{2\beta_V \theta \mu_H^2 \Lambda_V}{\Lambda_H^2 \mu_V}, \\ \frac{\partial^2 f_3}{\partial x_2 \partial x_3} &= \frac{\partial^2 f_3}{\partial x_3 \partial x_2} = -\frac{\beta_V \theta \mu_H}{\Lambda_H}, \\ \frac{\partial^2 f_4}{\partial x_1 \partial x_2} &= \frac{\partial^2 f_4}{\partial x_2 \partial x_1} = -\frac{\beta_V \theta \mu_H^2 \Lambda_V}{\Lambda_H^2 \mu_V}, \\ \frac{\partial^2 f_4}{\partial x_2^2} &= -\frac{2\beta_V \theta \mu_H^2 \Lambda_V}{\Lambda_H^2 \mu_V}, \\ \frac{\partial^2 f_4}{\partial x_2 \partial x_3} &= \frac{\partial^2 f_4}{\partial x_3 \partial x_2} = \frac{\beta_V \theta \mu_H}{\Lambda_H}. \end{aligned}$$

It follows from the above expressions that

$$\begin{aligned} a &= v_2 \sum_{i,j=1}^{4} w_i w_j \left(v_2 \frac{\partial^2 f_2}{\partial x_i \partial x_j} + v_4 \frac{\partial^2 f_4}{\partial x_i \partial x_j} \right), \\ &= 2v_2 w_2 w_4 \frac{\partial^2 f_2}{\partial x_2 \partial x_4} + v_4 \left(2w_1 w_2 \frac{\partial^2 f_4}{\partial x_1 \partial x_2} + w_2^2 \frac{\partial^2 f_4}{\partial x_2^2} + 2w_2 w_3 \frac{\partial^2 f_4}{\partial x_2 \partial x_3} \right), \\ &= \frac{-2v_4 w_2 w_3 \beta_V \theta \mu_H}{\Lambda_H} \left(\frac{v_2 w_4 \beta_M \Lambda_H \mu_V + v_4 (w_1 + w_2) \beta_V \mu_H \Lambda_V}{v_4 w_3 \beta_V \Lambda_H \mu_V} - 1 \right), \\ &= \frac{-2v_4 w_2 w_3 \beta_V \theta \mu_H (\Theta - 1)}{\Lambda_H}, \end{aligned}$$

where

$$\Theta = \frac{v_2 w_4 \beta_M \Lambda_H \mu_V + v_4 (w_1 + w_2) \beta_V \mu_H \Lambda_V}{v_4 w_3 \beta_V \Lambda_H \mu_V}.$$

Hence, $a > 0$ whenever $\Theta < 1$ or equivalently

$$\begin{aligned} \beta_M &< \frac{v_4 \beta_V (w_3 \Lambda_H \mu_V - (w_1 + w_2) \mu_H \Lambda_V)}{v_2 w_4 \Lambda_H \mu_V}, \\ &= \beta^* \left(-\frac{\beta_V \theta}{\mu_V} + \frac{\alpha_M}{\mu_H} \left(\frac{\beta^* \beta_V \theta^2 \mu_H \Lambda_V}{\Lambda_H \mu_V^2 (\mu_H + \alpha_M + \nu_1)} \right) \right), \\ &= \beta^* \left(-\frac{\beta_V \theta}{\mu_V} + \frac{\alpha_M}{\mu_H} \mathcal{R}_0^2 |_{\beta_M = \beta^*} \right), \\ &= \beta^* \left(-\frac{\beta_V \theta}{\mu_V} + \frac{\alpha_M}{\mu_H} \right), \\ &= \beta^* \left(\frac{-\mu_H \beta_V \theta + \alpha_M \mu_V}{\mu_H \mu_V} \right). \end{aligned} \tag{2.3.2.3.9}$$

At $\beta_M = \beta^*$, (2.3.2.3.9) becomes

$$\beta^* < \beta^* \left(\frac{-\mu_H \beta_V \theta + \alpha_M \mu_V}{\mu_H \mu_V} \right),$$

that is

$$1 < \frac{-\mu_H\beta_V\theta + \alpha_M\mu_V}{\mu_H\mu_V},$$

or $\mu_H\mu_V < -\mu_H\beta_V\theta + \alpha_M\mu_V$ which yields $\theta < \mu_V(\alpha_M - \mu_H)/\mu_H\beta_V = \theta_0$. Then it follows that at $\beta_M = \beta^*$ or equivalently at $\mathcal{R}_0 = 1$, $a > 0$ if and only if $\theta < \theta_0$.

For the sign of b, it can be shown that the associated non-vanishing partial derivative of F is

$$\begin{aligned}\frac{\partial^2 f_1}{\partial x_4 \partial\phi} &= -\theta,\\ \frac{\partial^2 f_2}{\partial x_4 \partial\phi} &= \theta.\end{aligned}$$

Therefore

$$\begin{aligned} b &= v_2 w_4 \frac{\partial^2 f_2}{\partial x_4 \partial\phi},\\ &= v_2 w_4\theta\\ &> 0.\end{aligned}$$

Thus, we have established the following result.

Theorem 2.3.2.3. *The SI malaria model (2.2.0.0.5) undergoes a backward bifurcation at $\mathcal{R}_0 = 1$ whenever $\theta < \theta_0$.*

2.3.3 Analysis of an SEI malaria model

In this section we present the stability and bifurcation analysis of the malaria model (2.2.0.0.4).

2.3.3.1 The basic reproduction number

The DFE of the SEI model (2.2.0.0.4) is given by,

$$\mathsf{E}^0_E = (\tfrac{\Lambda_H}{\mu_H}, 0, \tfrac{\Lambda_V}{\mu_V}, 0, 0).$$

The stability of the DFE be investigated using the next generation operator [140]. We verify that system (2.2.0.0.4) satisfy the conditions (A1)-(A5) in [140].

Firstly, we rewrite model (2.2.0.0.4) in the order that the first 3 compartments correspond to infected individuals

$$\begin{aligned}
\dot{I}_M(t) &= \frac{\beta_M \theta I_V(t)}{S_H(t)+I_M(t)} S_H(t) - (\mu_H + \alpha_M + \nu_1) I_M(t),\\
\dot{E}_V(t) &= \frac{\beta_V \theta I_M(t)}{S_H(t)+I_M(t)} S_V(t) - (\mu_V + \gamma_V) E_V(t),\\
\dot{I}_V(t) &= \gamma_V E_V(t) - \mu_V I_V(t),\\
\dot{S}_H(t) &= \Lambda_H + \nu_1 I_M(t) - \mu_H S_H(t) - \frac{\beta_M \theta I_V(t)}{S_H(t)+I_M(t)} S_H(t),\\
\dot{S}_V(t) &= \Lambda_V - \mu_V S_V - \frac{\beta_V \theta I_M(t)}{S_H(t)+I_M(t)} S_V(t).
\end{aligned} \tag{2.3.3.1.1}$$

Let $x = (I_M, E_V, I_V, S_H, S_V)^t = (x_1, x_2, x_3, x_4, x_5)^t$, with each $x_i \geq 0$, be the number of individuals in each compartment. Define X_s to be the set of all disease free states, i.e.,

$$X_s = \{x \geq 0 \mid x_i = 0, i = 1, 2, 3\} = \left\{ \left(0, 0, 0, \frac{\Lambda_H}{\mu_H}, \frac{\Lambda_V}{\mu_V}\right)^t \right\}.$$

System (2.3.3.1.1) can be written in the form

$$\dot{x} = f(x) = \mathcal{F}(x) - \mathcal{V}(x), \tag{2.3.3.1.2}$$

where $\mathcal{V}(x) = \mathcal{V}^-(x) - \mathcal{V}^+(x)$. Since each function represents a directed transfer of individuals, they are all non-negative, and given by

$$\mathcal{F}(x) = \begin{pmatrix} \frac{\beta_M \theta x_3}{x_1 + x_4} x_4 \\ \frac{\beta_V \theta x_1}{x_1 + x_4} x_5 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \quad \mathcal{V}^+(x) = \begin{pmatrix} 0 \\ 0 \\ \gamma_V x_2 \\ \Lambda_H + \nu_1 x_1 \\ \Lambda_V \end{pmatrix} \quad \text{and} \quad \mathcal{V}^-(x) = \begin{pmatrix} (\mu_H + \alpha_M + \nu_1) x_1 \\ (\mu_V + \gamma_V) x_2 \\ \mu_V x_3 \\ \left(\mu_H + \frac{\beta_M \theta x_3}{x_1 + x_4}\right) x_4 \\ \left(\mu_V + \frac{\beta_V \theta x_1}{x_1 + x_4}\right) x_5 \end{pmatrix}.$$

From the above functions we found that

(A1) if $x \geq 0$, then $\mathcal{F}_i(x), \mathcal{V}_i^+(x), \mathcal{V}_i^-(x) \geq 0$ for $i = 1, \ldots, 5$,

(A2) if $x_i = 0$, then $\mathcal{V}_i^-(x) = 0$. In particular, if $x \in X_s$ then $\mathcal{V}_i^-(x) = 0$ for $i = 1, 2, 3$,

(A3) $\mathcal{F}_i = 0$ for $i > 3$,

(A4) if $x \in X_s$ then $\mathcal{F}_i(x) = 0$ and $\mathcal{V}_i^+(x) = 0$ for $i = 1, 2, 3$,

(A5) if $\mathcal{F}(x) = 0$, then the Jacobian matrix of system (2.3.3.1.2) is given by

$$Df(x_0) = \begin{pmatrix} -(\mu_H + \alpha_M + \nu_1) & 0 & 0 & 0 & 0 \\ 0 & -(\mu_V + \gamma_V) & 0 & 0 & 0 \\ 0 & \gamma_V & -\mu_V & 0 & 0 \\ \nu_1 & 0 & 0 & -\mu_H & 0 \\ 0 & 0 & 0 & 0 & -\mu_V \end{pmatrix}. \quad (2.3.3.1.3)$$

The eigenvalues of $Df(x_0)$ are

$$-\mu_H,\ -(\mu_H+\alpha_M+\nu_1),\ -(\mu_V+\gamma_V) \text{ and } -\mu_V \text{ (of multiplicity two).}$$

It follows that all eigenvalues of $Df(x_0)$ have negative real parts.

The matrices $\mathbf{F_E}$ and $\mathbf{V_E}$ denoting the new infection terms and the remaining transfer terms are, respectively, given by

$$\mathbf{F_E}=\begin{pmatrix} 0 & 0 & \beta_M\theta \\ \dfrac{\beta_V\theta\mu_H\Lambda_V}{\Lambda_H\mu_V} & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix} \quad \text{and} \quad \mathbf{V_E}=\begin{pmatrix} \mu_H+\alpha_M+\nu_1 & 0 & 0 \\ 0 & (\mu_V+\gamma_V) & 0 \\ 0 & -\gamma_V & \mu_V \end{pmatrix}.$$

The eigenvalues of $\mathbf{F_E V_E^{-1}}$ are

$$\pm\sqrt{\frac{\beta_M\beta_V\theta^2\mu_H\Lambda_V\gamma_V}{\Lambda_H\mu_V^2(\mu_H+\alpha_M+\nu_1)(\mu_V+\gamma_V)}}.$$

As in 2.3.2.1, we consider the *basic reproduction number*, $\mathcal{R}_E$, to be the squared value of $\rho(\mathbf{F_E V_E^{-1}})$ i.e.,

$$\begin{aligned} \mathcal{R}_E &= \frac{\beta_M\beta_V\theta^2\mu_H\Lambda_V\gamma_V}{\Lambda_H\mu_V^2(\mu_H+\alpha_M+\nu_1)(\mu_V+\gamma_V)}, \\ &= \frac{\gamma_V}{(\mu_V+\gamma_V)}\mathcal{R}_0, \\ &= \frac{1}{(1+\mu_V\bar{\tau})}\mathcal{R}_0, \end{aligned}$$

where $\mathcal{R}_0$ is the *basic reproduction number* for the SI model (2.2.0.0.5) and $\bar{\tau}=1/\gamma_V$ is the mean time for the incubation period (Mosquito from the exposed class enter the infectious class at a rate that is the reciprocal of the duration of the incubation period).

Notice that, when $\bar{\tau}=0$, then $\mathcal{R}_E=\mathcal{R}_0$. If $\mathcal{R}_0<1$ then $\mathcal{R}_E<1$ for all $\bar{\tau}$. If $\mathcal{R}_0>1$, then $\mathcal{R}_E>1$ if and only if

$$\bar{\tau}<(\bar{\tau}_{crit})_E:=\frac{1}{\mu_V}(\mathcal{R}_0-1).$$

It follows that $\mathcal{R}_E > 1$ if and only if $\bar{\tau} < (\bar{\tau}_{crit})_E$. This means that for $\mathcal{R}_E$ to be less than unity, $\bar{\tau}$ must be greater than a critical value.

2.3.3.2 Stability of the disease-free equilibrium

Using Theorem 2 of [140], the following result is established.

Theorem 2.3.3.1. *The DFE of an SEI model (2.2.0.0.4) is locally-asymptotically stable if $\mathcal{R}_E < 1$, and unstable if $\mathcal{R}_E > 1$.*

2.3.3.3 Existence of backward bifurcation

System (2.2.0.0.4) undergoes a backward bifurcation. The possibility of backward phenomenon in the system (2.2.0.0.4) is investigated below.

To find conditions for the existence of $\mathsf{E}^*_E = (S^*_{HE}, I^*_{ME}, S^*_{VE}, E^*_{VE}, I^*_{VE})$ we equate the right hand side of system (2.2.0.0.4) to zero (and noting that $\lambda_M = \lambda^*_{ME} = \beta_M \theta I^*_{VE}/(S^*_{HE} + I^*_{ME})$ at equilibrium), we obtain

$$\begin{aligned}
S^*_{HE} &= \frac{\Lambda_H(\mu_H + \alpha_M + \nu_1)}{\mu_H(\mu_H + \alpha_M + \nu_1) + \lambda^*_{ME}(\mu_H + \alpha_M)},\\
I^*_{ME} &= \frac{\Lambda_H \lambda^*_{ME}}{\mu_H(\mu_H + \alpha_M + \nu_1) + \lambda^*_{ME}(\mu_H + \alpha_M)},\\
S^*_{VE} &= \frac{\Lambda_V}{\mu_V + \lambda^*_{VE}},\\
E^*_{VE} &= \frac{\Lambda_V \lambda^*_{VE}}{(\mu_V + \lambda^*_{VE})(\mu_V + \gamma_V)},\\
I^*_{VE} &= \frac{\Lambda_V \lambda^*_{VE} \gamma_V}{\mu_V(\mu_V + \lambda^*_{VE})(\mu_V + \gamma_V)},
\end{aligned} \tag{2.3.3.3.1}$$

where $\lambda^*_{VE} = \beta_V \theta I^*_{ME}/(S^*_{HE} + I^*_{ME})$. The endemic equilibria of the SEI malaria model (2.2.0.0.4) satisfy the same polynomial for the existance of the endemic equilibrium of the SI model (2.3.2.3.6), but in term of λ^*_{ME} instead of λ^*_M. Therefore we have the same analytical results as in an SI model (2.2.0.0.5) (Theorem (2.3.2.2) and Theorem (2.3.2.3)) with $\mathcal{R}_E$ instead of $\mathcal{R}_0$.

2.3.4 Analysis of an SI malaria model with a discrete delay

In this section we present the stability and bifurcation analysis of the malaria model (2.2.0.0.6).

2.3.4.1 The basic reproduction number

The DFE of the discrete delay model (2.2.0.0.6) is given by

$$\mathsf{E}_D^0 = (S_{HD}^0, I_{MD}^0, S_{VD}^0, I_{VD}^0) = (\tfrac{\Lambda_H}{\mu_H}, 0, \tfrac{\Lambda_V}{\mu_V}, 0).$$

Rewriting system (2.2.0.0.6) by substituting the expression of $\lambda_M(t)$ and $\lambda_V(t)$ as

$$\begin{aligned}
\dot{S}_H(t) &= \Lambda_H + \nu_1 I_M(t) - \mu_H S_H(t) - \frac{\beta_M \theta I_V(t)}{S_H(t) + I_M(t)} S_H(t), \\
\dot{I}_M(t) &= \frac{\beta_M \theta I_V(t)}{S_H(t) + I_M(t)} S_H(t) - (\mu_H + \alpha_M + \nu_1) I_M(t), \\
\dot{S}_V(t) &= \Lambda_V - \mu_V S_V - \frac{\beta_V \theta I_M(t)}{S_H(t) + I_M(t)} S_V(t), \\
\dot{I}_V(t) &= \frac{\beta_V \theta I_M(t-\bar{\tau})}{S_H(t-\bar{\tau}) + I_M(t-\bar{\tau})} S_V(t-\bar{\tau}) e^{-\mu_V \bar{\tau}} - \mu_V I_V(t).
\end{aligned}$$

The disease basic reproduction number, $\mathcal{R}_D$, represents the number of new infections produced by a typical individual during the time it spends in the infectious class, then consider a single newly infectious mosquito entering the disease free population at equilibrium. This mosquito spends $1/\mu_V$ time in the infectious class [60, 140], infects humans at rate

$$\frac{\beta_M \theta}{S_H(t) + I_M(t)} S_H(t) \Big|_{DFE} = \beta_M \theta.$$

Hence the total number of humans who become infectious due to this mosquito during its entire infectious period is approximately

$$\frac{\beta_M \theta}{\mu_V} = \mathcal{R}_D^{V \to H}.$$

Consider again a single infectious human entering the disease free population at equilibrium. This human, spends $1/(\mu_H + \alpha_M + \nu_1)$ time in the infectious class, infects

mosquitoes at a rate

$$\frac{\beta_V \theta}{S_H + I_M} S_V \Big|_{DFE} = \frac{\beta_V \theta \Lambda_V \mu_H}{\mu_V \Lambda_H},$$

which become infectious at some time $t \geq \bar{\tau}$ with a probability $e^{-\mu_V \bar{\tau}}$. Therefore the total number of mosquitoes which become infectious because of this human is approximately

$$\frac{\beta_V \theta \mu_H \Lambda_V}{\Lambda_H \mu_V (\mu_H + \alpha_M + \nu_1)} e^{-\mu_V \bar{\tau}} = \mathcal{R}_D^{H \to V}.$$

In the above, $\mathcal{R}_D^{V \to H}$ and $\mathcal{R}_D^{H \to V}$ are the disease reproductive numbers from mosquitoes to humans and from humans to mosquitoes. The product $\mathcal{R}_D^{V \to H} \mathcal{R}_D^{H \to V} = \mathcal{R}_D$ gives the disease reproductive number. Therefore, the basic reproduction number of malarial infection is

$$\mathcal{R}_D = \frac{\beta_M \beta_V \theta^2 \mu_H \Lambda_V e^{-\mu_V \bar{\tau}}}{\Lambda_H \mu_V^2 (\mu_H + \alpha_M + \nu_1)} = \mathcal{R}_0 e^{-\mu_V \bar{\tau}},$$

where $\mathcal{R}_0$ is the basic reproduction number for the SI model (2.2.0.0.5).
Notice that when $\bar{\tau} = 0$, then $\mathcal{R}_D = \mathcal{R}_0$.

If $\mathcal{R}_0 < 1$ then $\mathcal{R}_D < 1$ for all $\bar{\tau}$. If $\mathcal{R}_0 > 1$, then $\mathcal{R}_D > 1$ if and only if

$$\bar{\tau} < (\bar{\tau}_{crit})_D := \frac{1}{\mu_V} \ln(\mathcal{R}_0).$$

It follows that $\mathcal{R}_D > 1$ if and only if $\bar{\tau} < (\bar{\tau}_{crit})_D$. This means that for $\mathcal{R}_D$ to be less than unity, $\bar{\tau}$ must be greater than a critical value.

2.3.4.2 Stability of the disease-free equilibrium

The stability of the DFE can be obtained from studying the eigenvalues of the Jacobian matrix evaluated at the equilibrium point. If all the eigenvalues have negative real parts, then the equilibrium point is stable. We now linearize the system at $\mathsf{E}_D^0 = (S_{HD}^0, I_{MD}^0, S_{VD}^0, I_{VD}^0)$. Define

$$x_D(t) = S_H(t) - S_{HD}^0,\ y_D(t) = I_M(t) - I_{MD}^0,$$

$$z_D(t) = S_V(t) - S^0_{VD} \text{ and } w_D(t) = I_V(t) - I^0_{VD}.$$

Then the associated linearized system is

$$\begin{aligned}
\dot{x}_D(t) &= -\mu_H x_D(t) + \nu_1 y_D(t) - \beta_M \theta w_D(t), \\
\dot{y}_D(t) &= -(\mu_H + \alpha_M + \nu_1) y_D(t) + \beta_M \theta w_D(t), \\
\dot{z}_D(t) &= -\frac{\beta_V \theta \mu_H \Lambda_V}{\Lambda_H \mu_V} y_D(t) - \mu_V z_D(t), \\
\dot{w}_D(t) &= \frac{\beta_V \theta \mu_H \Lambda_V e^{-\mu_V \bar{\tau}}}{\Lambda_H \mu_V} y_D(t - \bar{\tau}) - \mu_V w_D(t). \qquad (2.3.4.2.1)
\end{aligned}$$

Suppose that the above system also has exponential solutions, i.e., we can write

$$(x_D(t), y_D(t), z_D(t), w_D(t)) = (a_1 e^{\lambda t}, a_2 e^{\lambda t}, a_3 e^{\lambda t}, a_4 e^{\lambda t}).$$

Substituting this into system (2.3.4.2.1), we get

$$\begin{aligned}
\lambda a_1 e^{\lambda t} &= -\mu_H a_1 e^{\lambda t} + \nu_1 a_2 e^{\lambda t} - \beta_M \theta a_4 e^{\lambda t}, \\
\lambda a_2 e^{\lambda t} &= -(\mu_H + \alpha_M + \nu_1) a_2 e^{\lambda t} + \beta_M \theta a_4 e^{\lambda t}, \\
\lambda a_3 e^{\lambda t} &= -\frac{\beta_V \theta \mu_H \Lambda_V e^{\lambda t}}{\Lambda_H \mu_V} a_2 - \mu_V a_3 e^{\lambda t}, \\
\lambda a_4 e^{\lambda t} &= \frac{\beta_V \theta \mu_H \Lambda_V e^{-\mu_V \bar{\tau}} e^{\lambda (t - \bar{\tau})}}{\Lambda_H \mu_V} a_2 - \mu_V a_4 e^{\lambda t}.
\end{aligned}$$

Discarding $e^{\lambda t}$ from both sides and rearranging the terms, we get

$$\begin{aligned}
(\lambda + \mu_H) a_1 - \nu_1 b + \beta_M \theta a_4 &= 0, \\
(\lambda + (\mu_H + \alpha_M + \nu_1)) a_2 - \beta_M \theta a_4 &= 0, \\
\frac{\beta_V \theta \mu_H \Lambda_V}{\Lambda_H \mu_V} a_2 + (\lambda + \mu_V) a_3 &= 0, \\
-\frac{\beta_V \theta \mu_H \Lambda_V e^{-(\lambda + \mu_V)\bar{\tau}}}{\Lambda_H \mu_V} a_2 + (\lambda + \mu_V) a_4 &= 0.
\end{aligned}$$

The characteristic matrix is given by

$$\triangle_D(\lambda) = \begin{pmatrix} \mu_H + \lambda & -\nu_1 & 0 & \beta_M\theta \\ 0 & \lambda + (\mu_H + \alpha_M + \nu_1) & 0 & -\beta_M\theta \\ 0 & \frac{\beta_V\theta\mu_H\Lambda_V}{\Lambda_H\mu_V} & \lambda + \mu_V & 0 \\ 0 & -\frac{\beta_V\theta\mu_H\Lambda_V e^{-(\lambda+\mu_V)\bar{\tau}}}{\Lambda_H\mu_V} & 0 & \lambda + \mu_V \end{pmatrix}.$$

The determinant of this matrix is given by

$$\det \triangle_D(\lambda) = (\lambda + \mu_H)(\lambda + \mu_V)\Phi_D(\lambda),$$

where

$$\Phi_D(\lambda) = \lambda^2 + (\varrho + \mu_V)\lambda + \mu_V\varrho - \frac{\beta_M\beta_V\theta^2\mu_H\Lambda_V e^{-(\lambda+\mu_V)\bar{\tau}}}{\Lambda_H\mu_V}.$$

with

$$\varrho = \mu_H + \alpha_M + \nu_1$$

Since $\mathcal{R}_D = (\beta_M\beta_V\theta^2\mu_H\Lambda_V e^{-\mu_V\bar{\tau}})/(\Lambda_H\mu_V^2\varrho)$, we have $(\beta_M\beta_V\theta^2\mu_H\Lambda_V e^{-\mu_V\bar{\tau}})/(\Lambda_H\mu_V) = \mu_V\varrho\mathcal{R}_D$. Hence

$$\Phi_D(\lambda) \;=\; \lambda^2 + (\mu_H + \varrho)\lambda + \mu_V\varrho(1 - e^{-\lambda\bar{\tau}}\mathcal{R}_D). \qquad (2.3.4.2.2)$$

Now, the stability of the DFE can be obtained from studying the roots of the quasi-polynomial

$$\det \triangle_D(\lambda) = 0.$$

If any of the roots of this quasi-polynomial have positive real parts, then the DFE is unstable. If they all have negative real parts, then the DFE is stable.
The roots of $\det \triangle_D(\lambda)$ are $-\mu_H$, $-\mu_V$ and those of $\Phi_D(\lambda)$ in (2.3.4.2.2). Since the first two roots are negative, it follows that the stability of the DFE is determined by the roots of (2.3.4.2.2).
Now, suppose $\lambda = x + iy$ is a root of $\Phi_D(\lambda)$ in (2.3.4.2.2) then

$$\begin{aligned}
\Phi_D(x+iy) &= (x+iy)^2 + (\mu_V+\varrho)(x+iy) + \mu_V\varrho - \mu_V(\varrho)\mathcal{R}_D e^{-(x+iy)\bar{\tau}}, \\
&= x^2 + i2xy - y^2 + (\mu_V+\varrho)x + i(\mu_V+\varrho)y \\
&\quad +\mu_V\varrho - \mu_V\varrho\mathcal{R}_D e^{-x\bar{\tau}}(\cos(y\bar{\tau}) - \sin(y\bar{\tau})), \\
&= x^2 - y^2 + (\mu_V+\varrho)x + \mu_V\varrho - \mu_V\varrho\mathcal{R}_D e^{-x\bar{\tau}}\cos(y\bar{\tau}) \\
&\quad +i(2xy + (\mu_V+\varrho)y + \mu_V\varrho\mathcal{R}_D e^{-x\bar{\tau}}\sin(y\bar{\tau})) = 0.
\end{aligned}$$

Separating the real and imaginary part we obtain

$$x^2 - y^2 + (\mu_V+\varrho)x + \mu_V\varrho = \mu_V\varrho\mathcal{R}_D e^{-x\bar{\tau}}\cos(y\bar{\tau}),$$

and

$$2xy + (\mu_V+\varrho)y = -\mu_V\varrho\mathcal{R}_D e^{-x\bar{\tau}}\sin(y\bar{\tau}).$$

Taking the squares on both sides of above two equations and adding together gives the following equation

$$(x^2 - y^2 + (\mu_V+\varrho)x + \mu_V\varrho)^2 + (2xy + (\mu_V+\varrho)y)^2 = (\mu_V\varrho\mathcal{R}_D e^{-x\bar{\tau}})^2. \quad (2.3.4.2.3)$$

Let $\bar{\tau} > (\bar{\tau}_{crit})_D$ that is $\mathcal{R}_D < 1$. If $x \geq 0$, then $(\mu_V \varrho \mathcal{R}_D e^{-x\bar{\tau}})^2 < (\mu_V \varrho)^2$. This with (3.3.3.2.3) lead to

$$(x^2 - y^2 + (\mu_V + \varrho)x)^2 + 2\mu_V \varrho(x^2 + (\mu_V + \varrho)x) + 4(xy)^2 + 4(\mu_V + \varrho)xy^2 + (\mu_V^2 + \varrho^2)y^2 < 0,$$

which is impossible. Hence, for $\mathcal{R}_D < 1$ all the roots of (2.3.4.2.2) have non-positive real parts and the DFE of model (2.2.0.0.6) is asymptotically stable.

Let $\bar{\tau} < (\bar{\tau}_{crit})_D$ that is $\mathcal{R}_D > 1$. By substituting the expression for $\mathcal{R}_D$, (2.3.4.2.2) reads as

$$\lambda^2 + (\mu_V + \varrho)\lambda + \mu_V \varrho(1 - \mathcal{R}_0 e^{-\mu_V \bar{\tau}} e^{-\lambda \bar{\tau}}) = 0. \tag{2.3.4.2.4}$$

Equation (2.3.4.2.4) has a delay dependent parameter ($e^{-\mu_V \bar{\tau}}$), we examine the distribution of its roots following [13] and [113].
Substituting $\bar{\tau} = 0$, we obtain from (2.3.4.2.4)

$$\lambda^2 + (\mu_V + \varrho)\lambda + \mu_V \varrho(1 - \mathcal{R}_0) = 0.$$

Since $\mathcal{R}_D > 1$ we have $\mathcal{R}_0 e^{-\mu_V \bar{\tau}} > 1 \Rightarrow \mathcal{R}_0 > e^{\mu_V \bar{\tau}} > 1$. Then by the Routh-Hurwitz criterion (2.3.4.2.4) has at least one root with positive real part.

As $\bar{\tau}$ increases, the number of roots of (2.3.4.2.4) with positive real parts may change only if one or many roots cross the imaginary axis. Since $\mathcal{R}_0 > 1$, it follows that 0 is not a solution of (2.3.4.2.4), this implies that the crossing of the imaginary axis may occur only at pure imaginary roots. Without loss of generality, we can consider the possibility that $\lambda = i\omega$, $\omega > 0$, is a solution of (2.3.4.2.4), that is,

$$(-\omega^2 + \mu_V \varrho - \mu_V \varrho \mathcal{R}_0 e^{-\mu_V \bar{\tau}} \cos(\omega \bar{\tau})) + i((\mu_V + \varrho)\omega + \mu_V \varrho \mathcal{R}_0 e^{-\mu_V \bar{\tau}} \sin(\omega \bar{\tau})) = 0.$$

Separating the real and imaginary part, we obtain

$$\begin{aligned}\cos(\omega\bar{\tau}) &= \frac{(-\omega^2+\mu_V\varrho)e^{\mu_V\bar{\tau}}}{\mu_V\varrho\mathcal{R}_0},\\ \sin(\omega\bar{\tau}) &= \frac{-(\mu_V+\varrho)\omega e^{\mu_V\bar{\tau}}}{\mu_V\varrho\mathcal{R}_0}.\end{aligned} \tag{2.3.4.2.5}$$

This leads to the following equation

$$F(\omega,\bar{\tau}) = \omega^4 + (\mu_V^2+\varrho^2)\omega^2 + \mu_V^2\varrho^2(1-\mathcal{R}_0^2e^{-2\mu_V\bar{\tau}}) = 0, \tag{2.3.4.2.6}$$

which has exactly one positive root given by

$$\omega(\bar{\tau}) = \sqrt{\frac{1}{2}\left(-(\mu_V^2+\varrho^2)+\sqrt{(\varrho^2-\mu_V^2)^2+4\mu_V^2\varrho^2\mathcal{R}_0^2e^{-2\mu_V\bar{\tau}}}\right)}, \tag{2.3.4.2.7}$$

In order for $\lambda = i\omega(\bar{\tau})$ to be a root of (2.3.4.2.4), $\omega(\bar{\tau})$ must satisfy (2.3.4.2.5). Since $\sin(\omega\bar{\tau})$ is always negative we obtain

$$\omega(\bar{\tau})\bar{\tau} = 2\pi - \arccos\left(\frac{(-\omega^2+\mu_V\varrho)e^{\mu_V\bar{\tau}}}{\mu_V\varrho\mathcal{R}_0}\right) + 2k\pi, \quad k\in\mathbb{N}.$$

That is $\bar{\tau} = \bar{\tau}_k(\bar{\tau})$ where $\bar{\tau}_k(\bar{\tau})$ is a function defined on $I = [0, (\bar{\tau}_{crit})_D[$ by

$$\begin{aligned}\bar{\tau}_k(\bar{\tau}) &= \frac{1}{\omega(\bar{\tau})}\left[2(k+1)\pi - \arccos\left(\frac{(-\omega^2+\mu_V\varrho)e^{\mu_V\bar{\tau}}}{\mu_V\varrho\mathcal{R}_0}\right)\right], \quad k\in\mathbb{N},\\ &= \frac{2k\pi}{\omega(\bar{\tau})} + \bar{\tau}_0(\bar{\tau}), \quad k\in\mathbb{N}.\end{aligned}$$

Let us introduce the functions $S_k : I \to \mathbb{R}$,

$$\begin{aligned}S_k(\bar{\tau}) &= \bar{\tau} - \bar{\tau}_k(\bar{\tau})\\ &= S_0(\bar{\tau}) - \frac{2k\pi}{\omega(\bar{\tau})}, \quad k\in\mathbb{N}.\end{aligned}$$

According to Theorem 2.2 in [13], the zeros of $S_k(\bar{\tau})$ determine the values of the delays at which the stability may switch. More precisely, the stability of the steady state may change at some positive value $\bar{\tau}$ say, $\bar{\tau}^*$ if $S_k(\bar{\tau}^*) = 0$ for some $k \in \mathbb{N}$ and the transversality condition $F'_\omega(\omega(\tilde{\tau}), \tilde{\tau})S'_k(\tilde{\tau}) \neq 0$.

Since (2.3.4.2.4) has only one feasible root ω, stability switches occur only at the roots of $S_0(\bar{\tau})$ ([13]), or equivalently of

$$Z_0(\bar{\tau}) = \omega(\bar{\tau})S_0(\bar{\tau}) = \omega(\bar{\tau})\bar{\tau} + \arccos\left(\frac{(-\omega^2 + \mu_V\varrho)e^{\mu_V\bar{\tau}}}{\mu_V\varrho\mathcal{R}_0}\right) - 2\pi.$$

Since (2.3.4.2.6) has only one root $\omega > 0$, $S_0(\bar{\tau})$ and $Z_0(\bar{\tau})$ have the same zeros [13]. Furthermore

$$\begin{aligned} Z'_0(\bar{\tau}^*) &= \omega(\bar{\tau}^*)S'_0(\bar{\tau}^*) + \omega'(\bar{\tau}^*)S_0(\bar{\tau}^*) \\ &= \omega(\bar{\tau}^*)S'_0(\bar{\tau}^*) \quad (\text{Since } S_0(\bar{\tau}^*) = 0). \end{aligned}$$

Since $\omega > 0$, $sign\{S'_0(\bar{\tau})\} = sign\{Z'_0(\bar{\tau})\}$ at the same zero as $S_0(\bar{\tau})$ and $Z_0(\bar{\tau})$.

The direction of the crossing is determined by

$$\delta(\tilde{\tau}) = \text{sign}\, F'_\omega(\omega(\tilde{\tau}), \tilde{\tau})\, \text{sign}\, S'_0(\tilde{\tau}) = \text{sign}\, F'_\omega(\omega(\tilde{\tau}), \tilde{\tau})\, \text{sign}\, Z'_0(\tilde{\tau}).$$

At $\tilde{\tau}$, the imaginary roots of (2.3.4.2.4) cross the imaginary axis from left to right if $\delta(\tilde{\tau}) > 0$ and cross the imaginary axis from right to left if $\delta(\tilde{\tau}) < 0$, see [13].

Since $F'_\omega(\omega(\bar{\tau}), \bar{\tau}) := 4\omega^3(\bar{\tau}) + 2(\mu_V^2 + \varrho^2)\omega(\bar{\tau}) > 0$, for every $\bar{\tau} > 0$, it follows that $\delta(\tilde{\tau}) = \text{sign}\, Z'_0(\tilde{\tau})$.

When $\bar{\tau} = 0$ the DFE is unstable which implies that the stability may switch only if $Z'(\tilde{\tau}) < 0$. From Lemma 2.3.4.1, below and Figure 2.3.4.2.1 we deduce that $Z_0(\bar{\tau})$ has exactly two roots $\tilde{\tau}^0$ and $\tilde{\tau}^1$ in $]0, (\bar{\tau}_{crit})_D[$, $\tilde{\tau}^0 < \tilde{\tau}^1$, $Z'_0(\tilde{\tau}^0) > 0$ and $Z'_0(\tilde{\tau}^1) < 0$. In this case, as $\bar{\tau}$ is increased, the number of roots of (2.3.4.2.2) with positive real part is increased by two when $\bar{\tau}$ passes through $\tilde{\tau}^0$ which implies that the DFE remains unstable. When $\bar{\tau}$ passes through $\tilde{\tau}^1$ the number of roots with positive real part is

decreased by two and becomes the same as for $\bar{\tau} < \tilde{\tau}^0$ meaning that the DFE remains unstable in this case as well.

Hence the DFE is locally-asymptotically stable if $\bar{\tau} > (\bar{\tau}_{crit})_D$, and unstable if $\bar{\tau} < (\bar{\tau}_{crit})_D$. These results are summarized in the following theorem.

Theorem 2.3.4.1. *The DFE of the discrete delay model (2.2.0.0.6) is locally asymptotically stable when $\bar{\tau} > (\bar{\tau}_{crit})_D$ and unstable when $\bar{\tau} < (\bar{\tau}_{crit})_D$.*

Lemma 2.3.4.1. *For*

$$Z_0(\bar{\tau}) = \omega(\bar{\tau})\bar{\tau} + \arccos\left(\frac{(-\omega^2(\bar{\tau}) + \mu_V\varrho)e^{\mu_V\bar{\tau}}}{\mu_V\varrho\mathcal{R}_0}\right) - 2\pi,$$

in the interval $]0, (\bar{\tau}_{crit})_D[$, only one of the following assertions holds

1. *Z_0 has no root in $]0, (\bar{\tau}_{crit})_D[$.*
2. *Z_0 has exactly two roots $\bar{\tau}^0$ and $\bar{\tau}^1$ in $]0, (\bar{\tau}_{crit})_D[$, $\bar{\tau}^0 < \bar{\tau}^1$, $Z_0'(\bar{\tau}^0) > 0$ and $Z_0'(\bar{\tau}^1) < 0$.*

Proof. We have

$$Z_0'(\bar{\tau}) = \omega + \omega'\bar{\tau} + \frac{2\omega\omega' + \mu_V\omega^2 - \mu_V^2\varrho}{\sqrt{\mu_V^2\varrho^2\mathcal{R}_0^2e^{-2\mu_V\bar{\tau}} - (-\omega^2 + \mu_V\varrho)^2}}.$$

Since, $\omega^4 + (\varrho^2 + \mu_V^2)\omega^2 + \mu_V^2\varrho^2(1 - \mathcal{R}_0^2e^{-2\mu_V\bar{\tau}}) = 0$. Then

$$\begin{aligned} Z_0'(\bar{\tau}) &= \omega + \omega'\bar{\tau} + \frac{2\omega\omega' + \mu_V\omega^2 - \mu_V^2\varrho}{(\mu_V + \varrho)\omega}, \\ &= \frac{((\mu_V + \varrho)\bar{\tau} + 2)\omega\omega' + (2\mu_V + \varrho)\omega^2 - \mu_V^2\varrho}{(\mu_V + \varrho)\omega}. \end{aligned}$$

From the expression of ω, we obtain: $\omega\omega' = \frac{-\mu_V^3\varrho^2\mathcal{R}_0^2e^{-2\mu_V\bar{\tau}}}{2\omega^2+\varrho^2+\mu_V^2}$, and then

$$Z_0'(\bar{\tau}) = \frac{\chi(\bar{\tau})}{(\mu_V + \varrho)\omega(2\omega^2 + \varrho^2 + \mu_V^2)},$$

where

$$\begin{aligned}\chi(\bar{\tau}) &= (\mu_V+\varrho)[(-\mu_V\bar{\tau}+2)\mu_V^2\varrho^2\mathcal{R}_0^2e^{-2\mu_V\bar{\tau}}-(\varrho^2+\mu_V\varrho+2\mu_V^2)\omega^2-3\mu_V^2(\mu+\nu_1)^2\\ &\quad -\mu_V^3(\mu+\nu_1)].\end{aligned}$$

If $\bar{\tau} > (2/\mu_V) = \bar{\tau}^*$, then $\chi(\bar{\tau}) < 0$. Since $\bar{\tau}^* < (\bar{\tau}_{crit})_D$ then $\chi(\bar{\tau}) < 0$ for any $\bar{\tau} \in]\bar{\tau}^*, (\bar{\tau}_{crit})_D[$. Therefore $Z_0(\bar{\tau})$ is monotonic decreasing and then it changes its sign at most once. Since $Z_0((\bar{\tau}_{crit})_D) < 0$, then according to the sign of $Z_0(\bar{\tau}^*)$, we have either (i) $Z_0(\bar{\tau}) < 0$ for any $\bar{\tau} \in]\bar{\tau}^*, (\bar{\tau}_{crit})_D[$ or (ii) there exists $\breve{\tau}_1$ in $]\bar{\tau}^*, (\bar{\tau}_{crit})_D[$ such that $Z_0(\bar{\tau}) > 0$ for any $\bar{\tau} \in]\bar{\tau}^*, \breve{\tau}_1[$ and $Z_0(\bar{\tau}) < 0$ for any $\bar{\tau} \in]\breve{\tau}_1, (\bar{\tau}_{crit})_D[$.
Now, suppose $\bar{\tau} < \bar{\tau}^*$ then

$$\chi'(\bar{\tau}) = \frac{(\mu_V+\varrho)\mu_V^3\varrho^2\mathcal{R}_0^2e^{-2\mu_V\bar{\tau}}}{2\omega^2+\varrho^2+\mu_V^2}\chi_1(\bar{\tau}),$$

where

$$\chi_1(\bar{\tau}) = (2(\mu_V\bar{\tau}-2)-1)(2\omega^2+\varrho^2+\mu_V^2)+2(\varrho^2+\mu_V\varrho+2\mu_V^2),$$

with,

$$\chi_1'(\bar{\tau}) = \mu_V(2\omega^2+\varrho^2+\mu_V^2)+4(2(2-\mu_V\bar{\tau})+1)\frac{\mu_V^3\varrho^2\mathcal{R}_0^2e^{-2\mu_V\bar{\tau}}}{2\omega^2+\varrho^2+\mu_V^2}.$$

If $\bar{\tau} < \bar{\tau}^*$ then $\chi_1'(\bar{\tau}) > 0$ for any $\bar{\tau} \in]0, \bar{\tau}^*[$ therefore $\chi_1(\bar{\tau})$ is monotonic increasing. Since $\chi_1(0) < 0$, then according to the sign of $\chi_1(\bar{\tau}^*)$, we have either: (1) $\chi(\bar{\tau})$ is monotonic decreasing for any $\bar{\tau} \in]0, \bar{\tau}^*[$ or (2) there exists $\breve{\tau}_2$ in $]0, \bar{\tau}^*[$ such that $\chi(\bar{\tau})$ is monotonic decreasing for any $\bar{\tau} \in]0, \breve{\tau}_2[$ and monotonic increasing for any $\bar{\tau} \in]\breve{\tau}_2, \bar{\tau}^*[$. Since $\text{sign}(Z_0'(\bar{\tau})) = \text{sign}(\chi(\bar{\tau}))$, then either (i) or (ii) with (1) or (2) is valid for $Z_0'(\bar{\tau})$. If (i) holds, since $Z_0(0) < 0$, then we have either assertion (1) or (2) of Lemma 2.3.4.1. The assertion (ii) implies that assertion (2) holds. This concludes the proof of the lemma. □

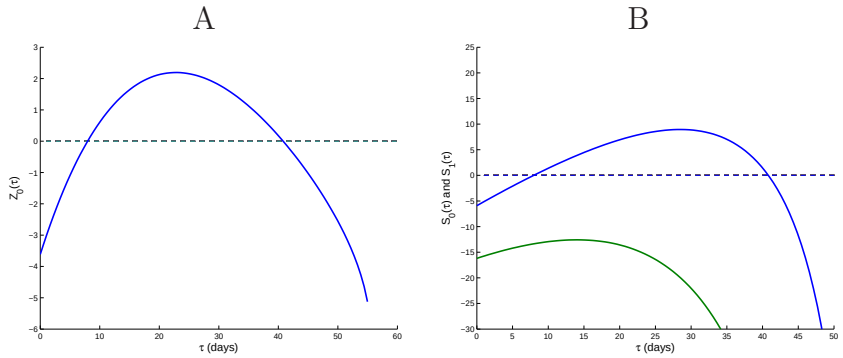

Figure 2.3.4.2.1: Profile of (A) $Z_0(\bar{\tau})$, (B) $S_0(\bar{\tau})$ (top curve) and $S_1(\bar{\tau})$ (bottom curve). Parameter values are taken from Table 3.5.0.3.7 with $\alpha_M = 0.2$, $\mu_H = 0.02$, $\mu_V = 0.06$.

2.3.4.3 Existence of backward bifurcation

Like the SI and SEI models, system (2.2.0.0.6) also undergoes a backward bifurcation where a stable DFE co-exists with a stable endemic equilibrium for some values of $\mathcal{R}_D < 1$.

To find conditions for the existence of an equilibrium denoted by $\mathsf{E}^*_D = (S^*_{HD}, I^*_{HD}, S^*_{VD}, I^*_{VD})$, the equations in (2.2.0.0.6) are solved in terms of the force of infection at steady-state (λ^*_{MD}) given by

$$\lambda^*_{MD} = \frac{\beta_M \theta I^*_{VD}}{S^*_{HD} + I^*_{MD}}. \tag{2.3.4.3.1}$$

Setting the right hand sides of (2.2.0.0.6) to zero gives

$$\begin{aligned} S^*_{HD} &= \frac{\Lambda_H(\varrho)}{\mu_H(\mu_H + \alpha_M + \nu_1) + \lambda^*_{MD}(\mu_H + \alpha_M)}, \\ I^*_{MD} &= \frac{\Lambda_H \lambda^*_{MD}}{\mu_H(\mu_H + \alpha_M + \nu_1) + \lambda^*_{MD}(\mu_H + \alpha_M)}, \\ S^*_{VD} &= \frac{\Lambda_V}{\mu_V + \lambda^*_{VD}}, \\ I^*_{VD} &= \frac{\Lambda_V \lambda^*_{VD} e^{-\mu_V \bar{\tau}}}{\mu_V(\mu_V + \lambda^*_{VD})}, \end{aligned} \tag{2.3.4.3.2}$$

where

$$\lambda^*_{VD} = \frac{\beta_V \theta I^*_{MD}}{S^*_{HD} + I^*_{MD}}. \quad (2.3.4.3.3)$$

Substituting (2.3.4.3.2) and (2.3.4.3.3) into (2.3.4.3.1) we obtain the similar form to the characteristic equation (2.3.2.3.6) for the SI model (2.2.0.0.5), but in term of λ^*_{MD} instead of λ^*_M. Therefore we have the same result as in the SI model (2.2.0.0.5) (Theorem (2.3.2.2)) with $\mathcal{R}_D$ instead of $\mathcal{R}_0$.

2.4 Summary and discussion

In this chapter we analyzed a basic malaria transmission model with a gamma distributed delay representing the incubation period of the disease in the vector. The model can be regarded as a generalization of SEI models (with a class for the latently infected mosquitoes) and SI models with a discrete delay for the incubation period in mosquitoes. It is a basic model in the sense that it does not account for many aspects of the disease transmission such as incubation period in humans, spontaneous recovery etc. The idea behind choosing such a simple model is to investigate the effect of the distributed delay only on the transmission dynamics of malaria.

We analyze the SI, SEI and SI model with a discrete delay. For each model we calculate the basic reproduction number and study the stability of the equilibria.

The basic reproduction numbers for the SEI ($\mathcal{R}_E$) and SI model with a discrete delay ($\mathcal{R}_D$) are shown to be decreasing with respect to the mean delay. The threshold values of $\mathcal{R}_E$ and $\mathcal{R}_D$ below which the disease can be eradicated is expressed in terms of the mean delay.

The eradication/persistence is further investigated by exploring the existence of steady states and their stability. The local stability of the DFE is studied analytically while that of the endemic equilibria is investigated numerically. Furthermore, we determined explicit conditions under which the system exhibits either a transcritical or

backward bifurcation.

In next chapter we present the analysis of the model with a gamma distributed delay for general n and study the effect of the distributed delay on the co-infection dynamics of HIV and malaria.

Chapter 3

Analysis of an HIV-malaria co-infection model with a distributed delay

In this chapter, we consider a model for the co-infection of HIV and malaria. The model accounts for the incubation period of the malaria parasite in the mosquitoes vector. A gamma distributed delay representing this incubation period is considered. We analyze the HIV-only sub-model, malaria-only sub-model and the full model of HIV and malaria. For the malaria-only model, we analyze the impact of the delay on the steady states and their stability, and determine a threshold value for the mean delay at which the system undergoes either a transcritical or backward bifurcation. We show that, the critical value depends on the shape parameter of the gamma distribution implying that the eradication or establishment of malaria does not depend only on the mean value of the delay but also depend on the shape parameter. Then we perform a sensitivity analysis by calculating the sensitivity index of the basic reproduction number and the endemic steady states in order to compare the effect of the mean delay and shape parameter on the initial disease transmission as well as on the disease prevalence at the equilibrium. Numerical simulations are carried out to confirm the theoretical

findings to investigate the impact of the delay on the prevalence of the disease

3.1 Introduction

An estimated 34–47 million people were infected with HIV/AIDS in 2006, with approximately 4.3 million of these being newly diagnosed infections [137]. Most new HIV infections occur in young adults aged 15–24 years of age, with children under the age of 15 years accounting for approximately 13% of all new HIV infections. In 2006, approximately 63% of all adults and children living with HIV lived in sub-Saharan Africa and approximately 72% of all deaths due to AIDS/HIV occurred in this region [137]. Most HIV/AIDS-infected people are women over 15 years of age (59%) [137].

The distribution of HIV and malaria overlaps in many regions of the world, particularly in sub-Saharan Africa, Southeast Asia, Latin America and the Caribbean. Approximately 25 million HIV-infected individuals live in sub-Saharan Africa [137]. Interactions between the two diseases pose major public health problems. Together they accounted for over 3 million deaths in 2007 [138, 146].

Many different models have been developed to account for the incubation period. For example, Mukandavire *et al.* [106] modeled the human and mosquito populations as SEIS and SEI model respectively, whereas in [1], Abu-Raddad *et al.* proposed a compartmental model for the co-infection of HIV and malaria with a delay representing the incubation period in mosquitoes.

In this chapter, we consider a model for HIV-malaria co-infection with a gamma distributed delay representing the incubation period of the malaria parasite in the vector. The human and vector populations are modeled by SIS and SI patterns respectively. We investigate the effect of the shape parameter and the mean value of the delay on the dynamics of HIV, malaria and co-infection with HIV and malaria.

We first calculate the basic reproduction number for the HIV-only model and analyze the stability of the equilibria. Then we calculate the basic reproduction number for the malaria-only model and analyze the local stability of the disease-free equilib-

rium. We determine a trade-off between the mean value of the delay and the shape parameter for the system to exhibit either a transcritical or a backward bifurcation. We then analyze the full model followed by a sensitivity analysis on the basic reproduction number for the malaria-only model to determine the relative importance of model parameters to disease transmission. Numerical simulations are carried out to confirm the mathematical findings.

The rest of this chapter is organized as follows. The model is described in Section 3.2 whereas its analysis is carried out in Section 3.3. Section 3.4 deals with sensitivity analysis. Numerical simulations are presented in Section 3.5. Section 3.6 is devoted to the summary and discussion on the results.

3.2 Description of the model

In this model, we divide the total population of humans (N_H) into four sub-populations, susceptible (S_H), malaria only infectious (I_M), HIV only infectious (I_H) and dually-infectious with HIV and malaria (I_{HM}). The total mosquito population (N_V) is divided into susceptible mosquitoes (S_V) and infectious mosquitoes (I_V).

It is assumed that susceptible humans are recruited into the population at a constant rate Λ_H. They either acquire infection with malaria following effective contact with infected mosquitoes (at a rate λ_M) and move to the malaria infectious class (I_M) or acquire infection with HIV following effective contact with infected humans (at a rate λ_H) and move to the HIV infectious class (I_H). Infected individuals with malaria only either recover with partial immunity and move into susceptible class (at a rate ν_1) or acquire infection with HIV following effective contact with infected humans (at a rate $\sigma\lambda_H$, where the parameter $0 < \sigma \leq 1$ models the expected decrease in sexual activity (contact) by individuals with malaria infection (because of ill health) [106]) and move to the HIV malaria dually-infectious class (I_{HM}). They die from the disease (at a rate α_M). Infected individuals with HIV only either acquire infection with malaria following effective contact with infected mosquitoes (at a rate $\vartheta\lambda_M$, where $\vartheta > 1$ accounts for

the assumed increase in susceptibility to malaria infection as a result of HIV infection [106]) and move to the HIV malaria dually-infectious class (I_{HM}) or die from HIV (at rate α_H). Dually-infected individuals either recover with partial immunity and move into HIV only infectious class (at a rate ν_2) or die from the malaria (at a rate $\kappa\alpha_M$, where $\kappa \geq 1$ accounts for the increased mortality of the I_{HM} individuals in comparison to individuals with malaria infection but not infected with HIV [106]) or from HIV (at a rate $d\alpha_H$, where $d \geq 1$ accounts for the increased mortality of the I_{HM} individuals in comparison to individuals with HIV infection but not infected with malaria [106]). The death due to natural causes occurs in all human classes at rate (μ_H). Susceptible mosquitoes are recruited into the population at a constant rate Λ_V. They either die (at a rate μ_V) or acquire malaria infection (following effective contacts with infected humans) (at a rate λ_V). Each infected mosquito becomes infectious and move to the infectious class (I_V) after a time delay τ with a gamma distribution;

$$\mathrm{g}_{n,\bar{\tau}}(\tau) = \frac{n^n \tau^{n-1}}{(n-1)!\bar{\tau}^n} e^{-n\tau/\bar{\tau}}, \tag{3.2.0.3.1}$$

where $\bar{\tau} > 0$ is the mean value and $n \geq 1$ is an integer-valued shape parameter (Erlang distribution).

With the above assumptions and notations, the model is written as follows

$$\begin{aligned}
\dot{S}_H &= \Lambda_H + \nu_1 I_M - \lambda_M S_H - \lambda_H S_H - \mu_H S_H, \\
\dot{I}_M &= \lambda_M S_H - \sigma\lambda_H I_M - (\mu_H + \alpha_M + \nu_1) I_M, \\
\dot{I}_H &= \lambda_H S_H + \nu_2 I_{HM} - \vartheta\lambda_M I_H - (\mu_H + \alpha_H) I_H, \\
\dot{I}_{HM} &= \sigma\lambda_H I_M + \vartheta\lambda_M I_H - (\mu_H + \kappa\alpha_M + d\alpha_H + \nu_2) I_{HM}, \\
\dot{S}_V &= \Lambda_V - \mu_V S_V - \lambda_V S_V \\
\dot{I}_V &= \int_0^\infty \mathrm{g}_{n,\bar{\tau}}(\tau)\lambda_V(t-\tau) S_V(t-\tau) e^{-\mu_V \tau} d\tau - \mu_V I_V,
\end{aligned} \tag{3.2.0.3.2}$$

where the HIV, malaria host-to-vector and vector-to-host forces of infection are given

by

$$\begin{aligned}\lambda_H &= \frac{\beta_H(I_H + \eta_{HM} I_{HM})}{N_H},\\ \lambda_M &= \frac{\beta_M \theta I_V}{N_H},\\ \lambda_V &= \frac{\beta_V \theta(I_M + \eta_V I_{HM})}{N_H}.\end{aligned}$$

Here β_H is the effective contact rate for HIV infection, the modification parameter $\eta_{HM} \geq 1$ accounts for the relative infectiousness of individuals dually-infected with HIV and malaria (I_{HM}) in comparison to those with HIV only infection (I_H) [106]. For malaria, θ is the per capita biting rate of mosquitoes, β_M (resp. β_V) is the transmission probability per bite for human (resp. mosquito) infection. $\eta_V \geq 1$ is a modification parameter accounting for the increased likelihood of infection of vectors from humans with dual HIV-malaria infection in relation to acquiring infection from humans with malaria only [106]. The use of this force of infection is due to the fact that female mosquitoes only take a fixed number of blood meals per unit of time, irrespective of the absolute numbers of mosquitoes and human [3].

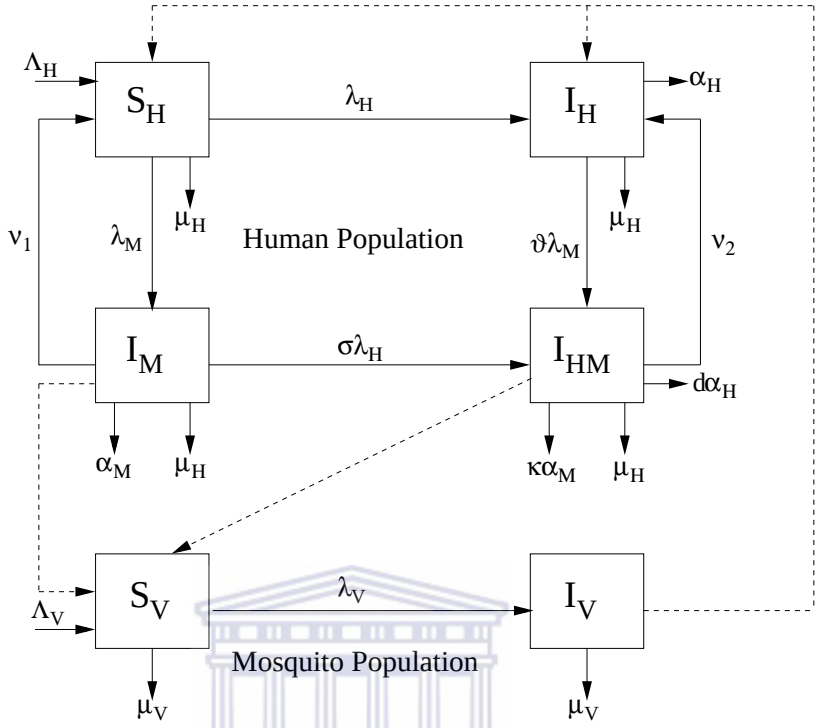

Figure 3.2.0.3.1: Flow diagram of the HIV-malaria co-infection model.

3.3 Analysis of the model

In this section we analyze the model (3.2.0.3.2) from various perspectives. In particular, we study its well-posedness, discuss the feasibility region as well as stability and bifurcation.

3.3.1 Well-posedness and feasibility

As in Chapter 2, we consider, for each $\alpha > 0$, the Banach space of fading memory type

$$UC_\alpha := \{\varphi \in C(]-\infty, 0], \mathbb{R}) : s \to \varphi(s)e^{\alpha s} \text{ is uniformly continuous on }]-\infty, 0] \text{ and } \sup_{s\leq 0} |\varphi(s)|\, e^{\alpha s} < \infty\}$$

endowed with the norm

$$\|\varphi\|_\alpha = \sup_{s\leq 0} |\varphi(s)|\, e^{\alpha s}.$$

According to [55], standard existence and uniqueness results hold for system (3.2.0.3.2) in UC_α. We analyze (3.2.0.3.2) in a biologically-feasible region for both human and mosquito populations.

letting $UC_\alpha^+ = \{\varphi \in UC_\alpha : \varphi(s) \geq 0 \text{ for each } s \in]-\infty, 0]\}$, we have the following result:

Proposition 3.3.1. *If the initial condition is in UC_α^{+6} then the corresponding solution $(S_H(t), I_M(t), I_H(t), I_{HM}(t), S_V(t), I_V(t))$ of the malaria model (3.2.0.3.2) is non-negative for all $t > 0$.*

Moreover,

$$\lim_{t\to\infty} N_H(t) \leq \frac{\Lambda_H}{\mu_H},\ \lim_{t\to\infty} S_V(t) \leq \frac{\Lambda_V}{\mu_V} \text{ and } \lim_{t\to\infty} I_V(t) \leq \frac{\theta\beta_V\Lambda_V}{\mu_V^2}.$$

Furthermore, we have the following invariance properties:

i. if $N_H(0) \leq \frac{\Lambda_H}{\mu_H}$ then $N_H(t) \leq \frac{\Lambda_H}{\mu_H}$

ii. if $S_V(0) \leq \frac{\Lambda_V}{\mu_V}$ then $S_V(t) \leq \frac{\Lambda_V}{\mu_V}$ and if in addition $I_V(0) \leq \frac{\theta\beta_V\Lambda_V}{\mu_V^2}$ then $I_V(t) \leq \frac{\theta\beta_V\Lambda_V}{\mu_V^2}$.

In particular, the regions $\mathcal{D}_H \times UC_\alpha^{+4}$ and $UC_\alpha^{+2} \times \mathcal{D}_V$ with

$$\mathcal{D}_H = \{(\phi_H, \psi_M, \psi_H, \psi_{HM}) \in UC_\alpha^{+4} : \phi_H(0) + \psi_H(0) + \psi_M(0) + \psi_H(0) + \psi_{HM}(0) \leq \frac{\Lambda_H}{\mu_H}\Big\},$$

$$\mathcal{D}_V = \Big\{(\phi_V, \psi_V) \in UC_\alpha^{+2} : \phi_V(0) \leq \frac{\Lambda_V}{\mu_V}, \psi_V(0) \leq \frac{\theta\beta_V\Lambda_V}{\mu_V^2}\Big\},$$

are positively-invariant.

The proof of the above proposition is similar to that of Proposition 2.3.1 in Chapter 2.

We first start by re-scaling system (3.2.0.3.2) to ensure that the same set of equilibria is maintained when the delay is set to zero. The re-scaled system is given by

$$\begin{aligned}
\dot{S}_H &= \Lambda_H + \nu_1 I_M - \lambda_M S_H - \lambda_H S_H - \mu_H S_H,\\
\dot{I}_M &= \lambda_M S_H - \sigma\lambda_H I_M - (\mu_H + \alpha_M + \nu_1) I_M,\\
\dot{I}_H &= \lambda_H S_H + \nu_2 I_{HM} - \vartheta\lambda_M I_H - (\mu_H + \alpha_H) I_H,\\
\dot{I}_{HM} &= \sigma\lambda_H I_M + \vartheta\lambda_M I_H - (\mu_H + \kappa\alpha_M + d\alpha_H + \nu_2) I_{HM},\\
\dot{S}_V &= \Lambda_V - \mu_V S_V - \lambda_V S_V,\\
\dot{I}_V &= \xi^{n,\bar{\tau}} \int_0^\infty \mathsf{g}_{n,\bar{\tau}'}(\tau)\lambda_V(t-\tau) S_V(t-\tau) d\tau - \mu_V I_V,
\end{aligned} \tag{3.3.1.0.3}$$

where $\bar{\tau}' = \bar{\tau}/(1 + \mu_V \frac{\bar{\tau}}{n})$ and $\xi^{n,\bar{\tau}} = 1/(1 + \mu_V \frac{\bar{\tau}}{n})^n$.

Before analyzing the dynamics of the full model (3.3.1.0.3), it is instructive to analyze the sub-models (HIV-only and Malaria-only) first of all. This is done below.

3.3.2 Analysis of HIV-only sub-model

The HIV-only model is obtained by setting $I_M = I_{HM} = S_V = I_V = 0$ in (3.3.1.0.3) given by

$$\begin{aligned}
\dot{S}_H(t) &= \Lambda_H - \lambda_H(t) S_H(t) - \mu_H S_H(t),\\
\dot{I}_H(t) &= \lambda_H(t) S_H(t) - (\mu_H + \alpha_H) I_H(t),
\end{aligned} \tag{3.3.2.0.4}$$

where the HIV force of infection is given by

$$\lambda_H(t) = \frac{\beta_H I_H(t)}{N_H(t)},$$

where β_H is the effective contact rate for HIV infection and $N_H(t) = S_H(t) + I_H(t)$.

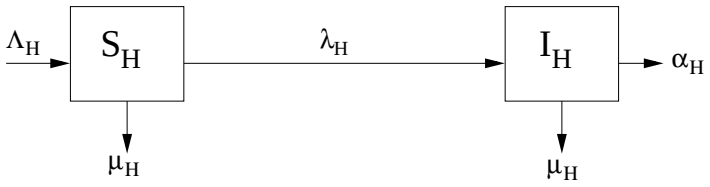

Figure 3.3.2.0.2: Flow diagram of the HIV-only sub-model.

3.3.2.1 Positivity of the solution

Proposition 3.3.2. *If the initial condition is non-negative then the corresponding solution $(S_H(t), I_H(t))$ of the HIV model (3.3.2.0.4) is non-negative for all $t > 0$. Moreover,*

$$\lim_{t\to\infty} N_H(t) \leq \frac{\Lambda_H}{\mu_H}.$$

Furthermore, we have the following invariance property:

$$\text{if } N_H(0) \leq \tfrac{\Lambda_H}{\mu_H} \text{ then } N_H(t) \leq \tfrac{\Lambda_H}{\mu_H}$$

In particular, the region

$$\Omega_H = \left\{(S_H, I_H) \in \mathbb{R}^2_+ : S_H + I_H \leq \frac{\Lambda_H}{\mu_H}\right\},$$

is positively-invariant for the model (3.3.2.0.4) with non-negative initial conditions in $\mathbb{R}^2_+$.

The proof of the above proposition is similar to that one of Proposition 2.3.1 in Chapter 2. In the view of Proposition 3.3.2 above, the dynamics of the HIV-only model (3.3.2.0.4) will be considered in Ω_H.

3.3.2.2 The basic reproduction number

The DFE of the HIV-only model (3.3.2.0.4) is given by

$$\mathsf{E}^0 = (S_H^0, I_H^0) = (\tfrac{\Lambda_H}{\mu_H}, 0).$$

Using the next generation matrix [140] we calculated $\mathcal{F}$ and $\mathcal{V}$ as

$$\mathcal{F} = \begin{pmatrix} 0 \\ \\ \lambda_H(t)S_H(t) \end{pmatrix} \quad \text{and} \quad \mathcal{V} = \begin{pmatrix} -\Lambda_H + \lambda_H(t)S_H(t) + \mu_H S_H(t) \\ \\ (\mu_H + \alpha_H)I_H(t) \end{pmatrix}.$$

Now differentiating $\mathcal{F}$ and $\mathcal{V}$ with respect to the infected compartment evaluated at the DFE we get the matrices $\mathbf{F}$ and $\mathbf{V}$, for the new infection terms and the remaining transfer terms are, respectively, given by

$$\mathbf{F} = \begin{pmatrix} \beta_H \end{pmatrix} \text{ and } \mathbf{V} = \begin{pmatrix} \mu_H + \alpha_H \end{pmatrix}.$$

The reproductive number, $\mathcal{R}_H$, is equal to the spectral radius of the *next generation operator* $\mathbf{FV}^{-1}$ [140]. It follows that the *basic reproduction number*, $\mathcal{R}_H$, is given by

$$\mathcal{R}_H = \rho(\mathbf{FV^{-1}}) = \frac{\beta_H}{\mu_H + \alpha_H}.$$

3.3.2.3 Stability of the disease-free equilibrium

Lemma 3.3.2.1. *The DFE of model (3.3.2.0.4) is locally-asymptotically stable if* $\mathcal{R}_H < 1$*, and unstable if* $\mathcal{R}_H > 1$.

Proof. Linearizing system (3.3.2.0.4) around E^0, we have the following Jacobian matrix

$$J(\mathsf{E}^0) = \begin{pmatrix} -\mu_H & -\beta_H \\ \\ 0 & \beta_H - (\mu_H + \alpha_H) \end{pmatrix}. \tag{3.3.2.3.1}$$

Being a triangular matrix, its eigenvalues are the entries along the main diagonal, i.e., the eigenvalues of J are $\lambda_1 = -\mu_V$ and $\lambda_2 = \beta_H - (\mu_H + \alpha_H)$. $\lambda_1 < 0$ and $\lambda_2 < 0$ if and only if $\mathcal{R}_H < 1$. Hence, we deduce that the DFE of model (3.3.2.0.4) is locally-asymptotically stable if $\mathcal{R}_H < 1$, and unstable if $\mathcal{R}_H > 1$. □

Theorem 3.3.2.1. *The DFE of the HIV-only model (3.3.2.0.4), given by* E^0*, is globally-asymptotically stable whenever* $\mathcal{R}_H \leq 1$.

Proof. Consider the following Layapunov function:

$$\mathcal{F} = (\mu_H + \alpha_H) I_H,$$

with Lyapunov derivative (with respect to t),

$$\begin{aligned}
\dot{\mathcal{F}} &= (\mu_H + \alpha_H)\dot{I}_H, \\
&= (\mu_H + \alpha_H)(\lambda_H S_H - (\mu_H + \alpha_H) I_H), \\
&= (\mu_H + \alpha_H)\lambda_H S_H - (\mu_H + \alpha_H)^2 I_H, \\
&= (\mu_H + \alpha_H)\lambda_H S_H - \frac{(\mu_H + \alpha_H)^2 \lambda_H N_H}{\beta_H}, \\
&= \frac{(\mu_H + \alpha_H)^2 \lambda_H N_H}{\beta_H} \left(\frac{\beta_H S_H}{(\mu_H + \alpha_H) N_H} - 1 \right), \\
&\leq \frac{(\mu_H + \alpha_H)^2 \lambda_H N_H}{\beta_H} \left(\frac{\beta_H}{(\mu_H + \alpha_H)} - 1 \right), (\text{since } S_H \leq N_H) \\
&= \frac{(\mu_H + \alpha_H)^2 \lambda_H N_H}{\beta_H} (\mathcal{R}_H - 1) \leq 0 \ for \ \mathcal{R}_H \leq 1.
\end{aligned}$$

Since all the model parameters are nonnegative, it follows that $\dot{\mathcal{F}} \leq 0$ for $\mathcal{R}_H \leq 1$ with $\dot{\mathcal{F}} = 0$ if and only if $I_H = 0$. Hence, $\mathcal{F}$ is a Lyapunov function on Ω_H. By the Lyapunov-LaSalle invariance principle ([144]) the largest compact invariant set in $\{(S_H, I_H) \in \Omega_H : \dot{\mathcal{F}} = 0\}$ is the set where $I_H = 0$. In this set $\dot{S}_H(t) = \Lambda_H - \mu_H S_H(t) \to (\Lambda_H/\mu_H)$ as $t \to \infty$. Therefore, every solution to the equations of the model (3.3.2.0.4), with initial conditions in, Ω_H, approaches E^0 as $t \to \infty$, whenever $\mathcal{R}_H \leq 1$. □

3.3.2.4 Existence and stability of the endemic equilibrium

To find conditions for the existence of an endemic equilibrium for HIV-only model, denoted by $\mathsf{E}^* = (S_H^*, I_H^*)$, the equations in (3.3.2.0.4) are solved in terms of the force of infection at steady-state λ_H^*, given by

$$\lambda_H^* = \frac{\beta_H I_H^*}{S_H^* + I_H^*}. \tag{3.3.2.4.1}$$

Setting the right hand sides of the model to zero, gives

$$S_H^* = \frac{\Lambda_H}{\mu_H + \lambda_H^*},$$
$$I_H^* = \frac{\Lambda_H \lambda_H^*}{(\mu_H + \lambda_H^*)(\mu_H + \alpha_H)}. \tag{3.3.2.4.2}$$

Using (3.3.2.4.2) in the expression for λ_H^* in (3.3.2.4.1) shows that the endemic equilibria of the model satisfy

$$\lambda_H^*(\lambda_H^* + B) = 0, \tag{3.3.2.4.3}$$

where

$$B = (\mu_H + \alpha_H)(1 - \mathcal{R}_H).$$

It is clear that $B > 0$ (< 0) for $\mathcal{R}_H < 1$ (> 1). Thus, the linear system (3.3.2.4.3) has a unique positive solution, given by $\lambda_H^* = -B$, whenever $\mathcal{R}_H > 1$. Noting that $\mathcal{R}_H < 1$ implies that $B < 0$. Thus, for $\mathcal{R}_H < 1$, the force of infection at steady-state (λ_H^*) is negative (which is biologically meaningless). Hence, the model has no positive equilibria in this case. These results are summarized below.

Lemma 3.3.2.2. *The HIV-only model (3.3.2.0.4) has a unique endemic equilibrium if and only if* $\mathcal{R}_H > 1$.

After substitute the value of B, λ_H^* is given by

$$\lambda_H^* = -B = (\mu_H + \alpha_H)(\mathcal{R}_H - 1).$$

Then the endemic equilibrium (3.3.2.4.2) is given by

$$\begin{aligned} S_H^* &= \frac{\Lambda_H}{\mu_H \mathcal{R}_H + \alpha_H(\mathcal{R}_H - 1)}, \\ I_H^* &= \frac{\Lambda_H(\mathcal{R}_H - 1)}{\mu_H \mathcal{R}_H + \alpha_H(\mathcal{R}_H - 1)}. \end{aligned} \tag{3.3.2.4.4}$$

Lemma 3.3.2.3. *The endemic equilibrium (3.3.2.4.4) of model (3.3.2.0.4) is locally-asymptotically stable if* $\mathcal{R}_H > 1$.

Proof. Linearizing system (3.3.2.0.4) around E^*, we have the following Jacobian matrix

$$J(\mathsf{E}^*) = \begin{pmatrix} -\mu_H - \dfrac{\lambda_H^* I_H^*}{S_H^* + I_H^*} & \dfrac{S_H^*(\lambda_H^* - \beta_H)}{S_H^* + I_H^*} \\ \dfrac{\lambda_H^* I_H^*}{S_H^* + I_H^*} & -\dfrac{S_H^*(\lambda_H^* - \beta_H)}{S_H^* + I_H^*} - (\mu_H + \alpha_H) \end{pmatrix} \tag{3.3.2.4.5}$$

with determinant:

$$\lambda^2 + A_1\lambda + A_2,$$

where

$$\begin{aligned} A_1 &= \mu_H + (\mu_H + \alpha_H)(\mathcal{R}_H - 1), \\ A_2 &= (\mu_H + \alpha_H)(\mathcal{R}_H - 1)\left(\mu_H + \frac{\alpha_H(\mathcal{R}_H - 1)}{\mathcal{R}_H}\right). \end{aligned}$$

Since $A_1 > 0$ and $A_2 > 0$ for $R_H > 1$. Using Routh-Hurwitz Criterion, E^* is stable if and only if $R_H > 1$. □

The proof of the following lemma can be found in [106].

Lemma 3.3.2.4. *The endemic equilibrium (3.3.2.4.4) of model (3.3.2.0.4) with* $\alpha_H = 0$ *is globally stable in* $\Omega_H \backslash \Omega_{H0} = \{(S_H, I_H) \in \Omega_H | I_H = 0\}$ *if* $\mathcal{R}_{Hc} = \mathcal{R}_H|_{\alpha_H=0} > 1$.

Proof. See [106]. □

3.3.3 Analysis of malaria-only sub-model

The malaria-only model is obtained by setting $I_H = I_{HM} = 0$ in (3.3.1.0.3) given by

$$\begin{aligned}
\dot{S}_H &= \Lambda_H + \nu_1 I_M - \lambda_M S_H - \mu_H S_H, \\
\dot{I}_M &= \lambda_M S_H - (\mu_H + \alpha_M + \nu_1) I_M, \\
\dot{S}_V &= \Lambda_V - \mu_V S_V - \lambda_V S_V, \\
\dot{I}_V &= \xi^{n,\bar{\tau}} \int_0^\infty \mathrm{g}_{n,\bar{\tau}'}(\tau) \lambda_V (t-\tau) S_V (t-\tau) d\tau - \mu_V I_V,
\end{aligned} \tag{3.3.3.0.6}$$

where malaria host-to-vector and vector-to-host forces of infection are given by

$$\begin{aligned}
\lambda_M &= \frac{\beta_M \theta I_V}{N_H}, \\
\lambda_V &= \frac{\beta_V \theta I_M}{N_H},
\end{aligned}$$

with $N_H = S_H + I_M$.

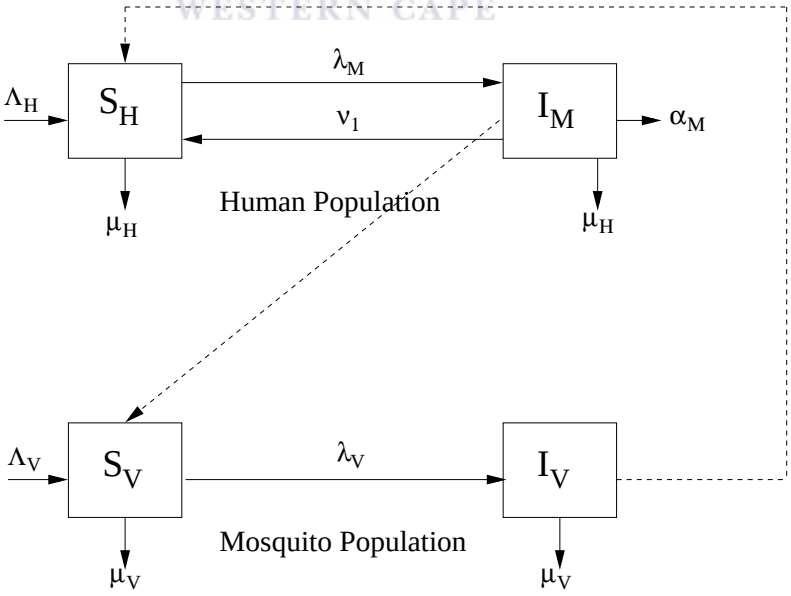

Figure 3.3.3.0.1: Flow diagram of the malaria-only sub-model.

3.3.3.1 Basic reproduction number

The disease free equilibria (DFE) of system (3.3.3.0.6) is given by $\mathsf{E}_n^0 = \left(\frac{\Lambda_H}{\mu_H}, 0, \frac{\Lambda_V}{\mu_V}, 0\right)$. The *basic reproduction number* for system (3.3.3.0.6) is given by

$$\mathcal{R}_M^{n,\bar{\tau}} = \mathcal{R}_0 \xi^{n,\bar{\tau}},$$

where $\mathcal{R}_0$ is a *basic reproduction number* for system (3.3.3.0.6) when there is no delay. Notice that when $\bar{\tau} = 0$, the basic reproduction number $\mathcal{R}_M^{n,\bar{\tau}}$ reduces to that of the model without delay, $\mathcal{R}_0$. When $n = 1$, $\mathcal{R}_M^{n,\bar{\tau}}$ reduces to that of an SEI model, $\mathcal{R}_E$. Also, when n tends to ∞, $\mathcal{R}_M^{n,\bar{\tau}}$ tends to the basic reproduction number of the discrete delay model (2.2.0.0.6); $\mathcal{R}_M^{n,\bar{\tau}} = \mathcal{R}_0 e^{-\mu_V \bar{\tau}} = \mathcal{R}_D$.

If $\mathcal{R}_0 < 1$ then $\mathcal{R}_M^{n,\bar{\tau}} < 1$ for all n and $\bar{\tau}$. If $\mathcal{R}_0 > 1$, then $\mathcal{R}_M^{n,\bar{\tau}} > 1$ if and only if

$$\bar{\tau} < \bar{\tau}_{crit}(n) := \frac{1}{\mu_V} n(\mathcal{R}_0^{\frac{1}{n}} - 1).$$

Note that $\bar{\tau}_{crit}(1) = (\bar{\tau}_{crit})_E$ and $\bar{\tau}_{crit}(\infty) = (\bar{\tau}_{crit})_D$.

In the following lemma we show how the critical value of the mean delay $\bar{\tau}_{crit}(n)$ depends on the shape parameter n.

Lemma 3.3.3.1. *$\mathcal{R}_M^{n,\bar{\tau}}$ is decreasing with respect to $\bar{\tau}$ and n. Moreover, the critical value $\bar{\tau}_{crit}(n)$ is also decreasing with respect to n.*

Proof. The monotonicity with respect to $\bar{\tau}$ follows from the fact that $\partial \mathcal{R}_M^{n,\bar{\tau}} / \partial \bar{\tau} = -\mu_V \mathcal{R}_M^{n,\bar{\tau}} / (1 + \mu_V \bar{\tau}/n) < 0$. The monotonicity with respect to n is a consequence of the fact that the sensitivity index is negative (see Proposition 3.4.1 and its proof). A straightforward calculation shows that $\bar{\tau}'_{crit}(n) = (\Pi(n) - 1)/\mu_V$, where $\Pi(n) = \mathcal{R}_0^{\frac{1}{n}}(1 - (\ln(\mathcal{R}_0)/n))$. Moreover, $\Pi'(n) = ((\ln(\mathcal{R}_0))^2/n^3)\mathcal{R}_0^{\frac{1}{n}} > 0$ and $\lim_{n\to\infty} \Pi(n) = 1$, then $\Pi(n) < 1$ for all $n \geq 1$. Hence $\bar{\tau}'_{crit}(n) < 0$ for all $n \geq 1$. □

The previous lemma shows that $\mathcal{R}_M^{n,\bar{\tau}}$ decreases if either the mean delay or the shape parameter increases. In the following proposition we determine the regions in the $(\bar{\tau}, n)$

space where $\mathcal{R}_M^{n,\bar{\tau}}$ becomes less (or greater) than one.

Proposition 3.3.3. *1. If $\bar{\tau} > \frac{1}{\mu_V}(\mathcal{R}_0 - 1)$, then $\mathcal{R}_M^{n,\bar{\tau}} < 1$ for all n.*

2. If $\bar{\tau} \leq \frac{1}{\mu_V}\ln(\mathcal{R}_0)$, then $\mathcal{R}_M^{n,\bar{\tau}} > 1$ for all n.

3. If $\frac{1}{\mu_V}\ln(\mathcal{R}_0) < \bar{\tau} \leq \frac{1}{\mu_V}(\mathcal{R}_0 - 1)$, then there exists $n_{crit}(\bar{\tau}) > 1$ such that $\mathcal{R}_M^{n,\bar{\tau}} = 1$ for $n = n_{crit}(\bar{\tau})$, $\mathcal{R}_M^{n,\bar{\tau}} > 1$ for $n < n_{crit}(\bar{\tau})$ and $\mathcal{R}_M^{n,\bar{\tau}} < 1$ for $n > n_{crit}(\bar{\tau})$.

Proof. The proof is a direct consequence of the previous lemma, $\bar{\tau}_{crit}(1) = (\mathcal{R}_0 - 1)/\mu_V$ and $\lim_{n\to\infty} \bar{\tau}_{crit}(n) = \ln(\mathcal{R}_0)/\mu_V$. □

Note that $\ln(\mathcal{R}_0)/\mu_V$ is the critical value for the mean delay of the discrete delay model and $(\mathcal{R}_0 - 1)/\mu_V$ is the one for the SEI model.

Proposition 3.3.3 shows that the eradication or establishment of malaria does not depend only on the mean value of the delay but on the shape parameter as well. In fact when $\ln(\mathcal{R}_0)/\mu_V < \bar{\tau} \leq (\mathcal{R}_0 - 1)/\mu_V$ eradication is possible if the value of the shape parameter is high enough, otherwise the disease will persist. However, when the mean delay is small (or high) enough the shape parameter has no effect on the eradication or presence of the disease. These conditions can be expressed in terms of $\rho := \bar{\tau}\mu_V$ which is the ratio between the mean delay and the average life span of infected mosquitoes who are infected but not yet infective; $\rho = \bar{\tau}/(1/\mu_V)$.

3.3.3.2 Stability of the disease-free equilibrium

The characteristic equation of the DFE is given by

$$(\lambda + \mu_H)(\lambda + \mu_V)\left[\lambda^2 + (\mu_V + \varrho)\lambda + \mu_V\varrho(1 - \mathcal{R}_M^{n,\bar{\tau}}F(\lambda, \bar{\tau}'))\right] = 0, \quad (3.3.3.2.1)$$

where $\varrho = \mu_H + \alpha_M + \nu_1$ and $F(\lambda, \bar{\tau}')$ is the Laplace transform of $\mathsf{g}_{n,b'}(\tau)$, i.e., $F(\lambda, \bar{\tau}') = \left(1 + \lambda\frac{\bar{\tau}'}{n}\right)^{-n}$.

The roots of (3.3.3.2.1) are $-\mu_H$, $-\mu_V$ and those of

$$\Phi_n(\lambda, \bar{\tau}) := \lambda^2 + (\mu_V + \varrho)\lambda + \mu_V\varrho(1 - \mathcal{R}_M^{n,\bar{\tau}}F(\lambda, \bar{\tau}')) = 0. \quad (3.3.3.2.2)$$

We investigate how the stability of (3.3.3.2.2) varies with $\bar{\tau}$ and n.

Suppose $\lambda = x + iy$ is a root of $\Phi_n(\lambda, \bar{\tau})$ in (3.3.3.2.2) then

$$\begin{aligned}\Phi_n(x+iy,\bar{\tau}) &= x^2 - y^2 + (\mu_V + \varrho)x + \mu_V\varrho + i(2xy + (\mu_V+\varrho)y) \\ &\quad -\mu_V\varrho\mathcal{R}_M^{n,\bar{\tau}}F(x+iy,\bar{\tau}') = 0.\end{aligned}$$

This implies that

$$x^2 - y^2 + (\mu_V + \varrho)x + \mu_V\varrho + i(2xy + (\mu_V+\varrho)y) = \mu_V\varrho\mathcal{R}_M^{n,\bar{\tau}}F(x+iy,\bar{\tau}').$$

Taking the squares of the modulus of both sides gives the following equation

$$(x^2 - y^2 + (\mu_V + \varrho)x + \mu_V\varrho)^2 + (2xy + (\mu_V+\varrho)y)^2 = (\mu_V\varrho\mathcal{R}_M^{n,\bar{\tau}}|F(x+iy,\bar{\tau}'|)^2, \quad (3.3.3.2.3)$$

where

$$|F(x+iy,\bar{\tau}')| \leq \int_0^\infty \mathrm{g}_{n,\bar{\tau}'}(\tau)e^{-x\tau}d\tau.$$

Let $\bar{\tau} > \bar{\tau}_{crit}(n)$ that is $\mathcal{R}_M^{n,\bar{\tau}} < 1$. If $x \geq 0$, then $|F(x+iy,\bar{\tau}')| \leq 1$, which along with (3.3.3.2.3) leads to

$$(x^2 - y^2 + (\mu_V + \varrho)x)^2 + 2\mu_V\varrho(x^2 + (\mu_V+\varrho)x) + 4(xy)^2 + 4(\mu_V+\varrho)xy^2 + (\mu_V^2 + \varrho^2)y^2 < 0,$$

which is impossible. Hence, for $\bar{\tau} > \bar{\tau}_{crit}(n)$ all the roots of (3.3.3.2.2) have non-positive real parts and hence the DFE is asymptotically stable.

Let $\bar{\tau} < \bar{\tau}_{crit}(n)$, that is, $\mathcal{R}_M^{n,\bar{\tau}} > 1$. By substituting the expression for $\mathcal{R}_M^{n,\bar{\tau}}$, we get from (3.3.3.2.2)

$$\lambda^2 + (\mu_V + \varrho)\lambda + \mu_V\varrho(1 - \mathcal{R}_0\xi^{n,\bar{\tau}}F(\lambda,\bar{\tau}')) = 0. \quad (3.3.3.2.4)$$

From MacDonald [97], the conditions for stability for any n are the same as for the

case $n \to \infty$. From Theorem (2.3.4.1), we have that the DFE is locally-asymptotically stable if $\bar{\tau} > \bar{\tau}_{crit}(\infty)$, and unstable if $\bar{\tau} < \bar{\tau}_{crit}(\infty)$. From MacDonald [97], we conclude that this is the case for all $n \geq 1$. These results are summarized in the following theorem.

Theorem 3.3.3.1. *The DFE of (3.3.3.0.6) is locally asymptotically stable when $\bar{\tau} > \bar{\tau}_{crit}(n)$ and unstable when $\bar{\tau} < \bar{\tau}_{crit}(n)$.*

3.3.3.3 Existence of backward bifurcation

Backward bifurcation occurs when a stable DFE co-exists with a stable endemic equilibrium for some values of $\mathcal{R}_M^{n,\bar{\tau}} < 1$. Epidemiologically, this implies that for the disease to be eradicated $\mathcal{R}_M^{n,\bar{\tau}}$ must be below a critical value less than one.
The steady states of (3.3.3.0.6) are determined by solving

$$\begin{aligned} S_{Hn}^* &= \frac{\Lambda_H(\mu_H + \alpha_M + \nu_1)}{\mu_H(\mu_H + \alpha_M + \nu_1) + \lambda_{Mn}^*(\mu_H + \alpha_M)}, \\ I_{Mn}^* &= \frac{\Lambda_H \lambda_{Mn}^*}{\mu_H(\mu_H + \alpha_M + \nu_1) + \lambda_{Mn}^*(\mu_H + \alpha_M)}, \\ S_{Vn}^* &= \frac{\Lambda_V}{\mu_V + \lambda_{Vn}^*}, \\ I_{Vn}^* &= \frac{\Lambda_V \lambda_{Vn}^* \xi^{n,\bar{\tau}}}{\mu_V(\mu_V + \lambda_{Vn}^*)}, \end{aligned} \tag{3.3.3.3.1}$$

where $\lambda_{Vn}^* = \frac{\beta_V \theta I_M^*}{S_H^* + I_M^*}$ and $\lambda_{Mn}^* = \frac{\beta_M \theta I_V^*}{S_H^* + I_M^*}$.
Thus the endemic equilibria of system (3.3.3.0.6) also satisfy the same polynomial (2.3.2.3.6) for the existance of the endemic equilibrium of the SI model (2.2.0.0.5), but in term of λ_{Mn}^* instead of λ_M^*, that is,

$$A(\lambda_M^*)^2 + B\lambda_M^* + C = 0, \tag{3.3.3.3.2}$$

where A, B and C are given in (2.3.2.3.5) with $\mathcal{R}_M^{n,\bar{\tau}}$ instead of $\mathcal{R}_0$.

Therefore we have the same result as in an SI model (2.2.0.0.5) (Theorem (2.3.2.2)) with $\mathcal{R}_M^{n,\bar{\tau}}$ instead of $\mathcal{R}_0$.

Backward bifurcation occurs when K is reduced below one, this can be achieved by decreasing $\mu_H, \theta, \beta_V, \mu_V$ or by increasing α_M.

Due to the complexity of the expressions of the endemic equilibria, the analytical study of their stability is difficult and will be investigated numerically only. For this, we vary the mean value of the incubation period for mosquito, $\bar{\tau}$, fix the other parameter and calculate the numerical values of the endemic equilibria for each $\bar{\tau}$. The numerical investigation follows the same steps as the analytical ones for the DFE. We investigate the existence of imaginary roots of the characteristic polynomial associated with the linearized system of (3.3.3.0.6) at the endemic equilibria and check the transversality condition. The results are shown in the bifurcation diagram in Figure 3.3.3.3.1. In Figure 3.3.3.3.1(A) the values of the fixed parameters are taken from Table 3.5.0.3.7, we observe a transcritical bifurcation indicating an exchange of stability between the disease free and endemic equilibria. In Figure 3.3.3.3.1(B) the values of the fixed parameters are taken from [25], the graph shows a backward bifurcation implying that the classical epidemiological requirement for the eradication of the disease $\mathcal{R}_M^{n,\bar{\tau}} < 1$ is no longer sufficient, though necessary.

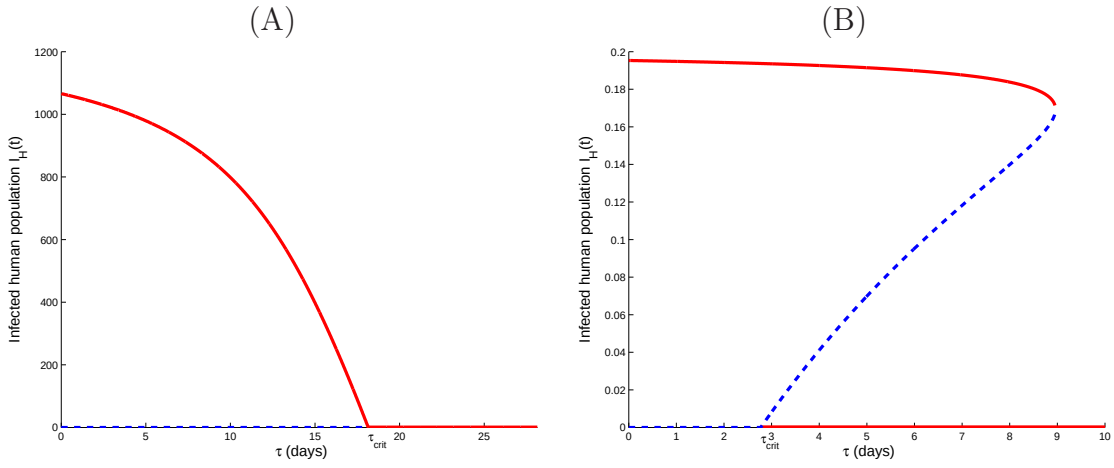

Figure 3.3.3.3.1: Bifurcation diagram of malaria model (3.3.3.0.6). Using various values of $\bar{\tau}$ with: (A) Parameter values are taken from Table 3.5.0.3.7 with $\alpha_M = 0.00041$, $\mu_H = 0.000039$, $\mu_V = 0.035$, $n = 100$. (The threshold $K = 1.3045$) and (B) $\Lambda_H = 0.00007666$, $\theta = 0.58$, $\beta_M = 0.02$, $\nu_1 = 0.003704$, $\alpha_M = 0.0003454$, $\mu_H = 0.00004212$, $\Lambda_V = 0.4$, $\beta_V = 0.08333$, $\mu_V = 0.1429$, $n = 10$. (The threshold $K = 0.2713$).

From (3.3.3.3.2) the expressions of the force of infection at the endemic equilibria when they exist are given by $\lambda_M^{*\pm} = (-B \pm \sqrt{B^2 - 4AC})/(2A)$.

Based on our numerical results, the endemic equilibrium point λ_M^{*+} is stable, and we refer to it as the stable endemic equilibrium point while the one corresponding to λ_M^{*-} is unstable, we call it the unstable endemic equilibrium point.

The following proposition describes the way the stable and unstable equilibria depend on the mean delay $\bar{\tau}$ and the shape parameter n.

Proposition 3.3.4. *In both human and mosquito populations, the number of susceptibles, at the stable (resp. unstable) endemic equilibrium point, increases (resp. decreases) with both $\bar{\tau}$ and n, while the number of infectives decreases (resp. increases).*

Proof. We prove the result for $\bar{\tau}$ only as the one for n can be done in a similar way. Differentiating (3.3.3.3.2) with respect to $\bar{\tau}$ we obtain

$$\frac{\partial \lambda_M^*}{\partial \bar{\tau}} = \frac{C_1 + B_1 \lambda_M^*}{2A\lambda_M^* + B} \frac{\partial \mathcal{R}_M^{n,\bar{\tau}}}{\partial \bar{\tau}},$$

where $B_1 = \Lambda_H \mu_V^2 (\mu_H + \alpha_M + \nu_1)(\mu_H + \alpha_M)/\mu_H > 0$ and $C_1 = \Lambda_H \mu_V^2 (\mu_H + \alpha_M + \nu_1)^2 > 0$. Since $\partial \mathcal{R}_M^{n,\bar{\tau}}/\partial \bar{\tau} < 0$ (Lemma 3.3.3.1) then $\partial \lambda_M^*/\partial \bar{\tau}$ has the opposite sign of $2A\lambda_M^* + B$. Since $2A\lambda_M^{*\pm} + B = \pm\sqrt{B^2 - 4AC}$ then $\frac{d\lambda_M^{*+}}{d\bar{\tau}} < 0$ and $\frac{d\lambda_M^{*-}}{d\bar{\tau}} > 0$. The rest of the proof follows immediately from the differentiation of the left hand side of (3.3.3.3.1) with respect to λ_M^*. □

The interpretations of the results in Proposition 3.3.4 are the following: In addition to the effects that the mean delay and shape parameter have on the initial transmission of the disease ($\mathcal{R}_M^{n,\bar{\tau}}$) they have an important impact on the disease when it is established. In the case where no backward bifurcation occurs, only the stable endemic steady state exists. Any intervention that increases the incubation period (increasing $\bar{\tau}$ and/or n) would result in a reduction in the number of infectives and an increase in the number of susceptibles. The other interpretation is that when the system exhibits backward bifurcation, $\bar{\tau}$ and n have a negative impact on the unstable steady state.

The reality is that this negative impact results in an increase in the region of attractiveness of the disease free steady state by pushing the dashed curve in Fig. 3.3.3.3.1(B) up allowing for the disease to be eradicated even for larger initial infections.

3.3.4 Analysis of the HIV-malaria full model

3.3.4.1 Basic reproduction number

The disease free equilibria (DFE) of system (3.3.1.0.3) is given by

$$\mathsf{E}_n^0 = (S_H^0, I_M^0, I_H^0, I_{HM}^0, S_V^0, I_V^0) = \left(\frac{\Lambda_H}{\mu_H}, 0, 0, 0, \frac{\Lambda_V}{\mu_V}, 0\right).$$

Rewrite system (3.3.1.0.3) by substitute the expression of λ_M, λ_H and λ_V as

$$\begin{aligned}
\dot{S}_H &= \Lambda_H + \nu_1 I_M - \frac{\beta_M \theta I_V}{N_H} S_H - \frac{\beta_H (I_H + \eta_{HM} I_{HM})}{N_H} S_H - \mu_H S_H, \\
\dot{I}_M &= \frac{\beta_M \theta I_V}{N_H} S_H - \sigma \frac{\beta_H (I_H + \eta_{HM} I_{HM})}{N_H} I_M - (\mu_H + \alpha_M + \nu_1) I_M, \\
\dot{I}_H &= \frac{\beta_H (I_H + \eta_{HM} I_{HM})}{N_H} S_H + \nu_2 I_{HM} - \vartheta \frac{\beta_M \theta I_V}{N_H} I_H - (\mu_H + \alpha_H) I_H, \\
\dot{I}_{HM} &= \sigma \frac{\beta_H (I_H + \eta_{HM} I_{HM})}{N_H} I_M + \vartheta \frac{\beta_M \theta I_V}{N_H} I_H - (\mu_H + \kappa \alpha_M + d\alpha_H + \nu_2) I_{HM}, \\
\dot{S}_V &= \Lambda_V - \mu_V S_V - \frac{\beta_V \theta (I_M + \eta_V I_{HM})}{N_H} S_V, \\
\dot{I}_V &= \xi^{n,\bar{\tau}} \int_0^\infty \mathsf{g}_{n,\bar{\tau}'}(\tau) \frac{\beta_V \theta (I_M(t-\tau) + \eta_V I_{HM}(t-\tau))}{N_H(t-\tau)} S_V(t-\tau) d\tau - \mu_V I_V.
\end{aligned} \tag{3.3.4.1.1}$$

The basic reproduction number for malaria, $\mathcal{R}_M^{n,\bar{\tau}}$, represents the number of new infections of malaria produced by a typical individual during the time it spends in the infectious class, then consider a single newly infectious mosquito entering the disease free population at equilibrium. This mosquito spends $1/\mu_V$ time in the infectious class [140, 60], infects humans at rate

$$\left.\frac{\beta_M \theta}{N_H} S_H\right|_{DFE} = \beta_M \theta.$$

Hence the total number of humans who become infectious due to this mosquito during its entire infectious period is approximately

$$\frac{\beta_M \theta}{\mu_V} = \mathcal{R}_M^{n,\bar{\tau}^{V\to H}}.$$

Consider again a single infectious human entering the disease free population at equilibrium. This human, spends $1/(\mu_H + \alpha_M + \nu)$ time in the infectious class, infects mosquitoes at a rate

$$\frac{\beta_V \theta}{N_H} S_V \Big|_{DFE} = \frac{\beta_V \theta \Lambda_V \mu_H}{\mu_V \Lambda_H},$$

which become infectious at some time $t \geq \bar{\tau}$ with a probability $\xi^{n,\bar{\tau}}$, Therefore the total number of mosquitoes which become infectious because of this human is approximately

$$\frac{\beta_V \theta \mu_H \Lambda_V}{\Lambda_H \mu_V (\mu_H + \alpha_M + \nu)} \xi^{n,\bar{\tau}} = \mathcal{R}_M^{n,\bar{\tau}^{H\to V}}.$$

Therefore $\mathcal{R}_M^{n,\bar{\tau}^{V\to H}}$ and $\mathcal{R}_M^{n,\bar{\tau}^{H\to V}}$ are the disease reproductive numbers from mosquitoes to humans and from humans to mosquitoes. The product

$$\mathcal{R}_M^{n,\bar{\tau}^{V\to H}} \mathcal{R}_M^{n,\bar{\tau}^{H\to V}} = \mathcal{R}_M^{n,\bar{\tau}},$$

gives the disease reproductive number. Therefore, the basic reproduction number of malarial infection is

$$\mathcal{R}_M^{n,\bar{\tau}} = \frac{\beta_M \beta_V \theta^2 \mu_H \Lambda_V \xi^{n,\bar{\tau}}}{\Lambda_H \mu_V^2 (\mu_H + \alpha_M + \nu)} = \mathcal{R}_0 \xi^{n,\bar{\tau}},$$

where $\mathcal{R}_0$ is the basic reproduction number for the SI model (2.2.0.0.5) i.e., when there is no delay.

Since $\mathcal{R}_H$ represents the number of new infections of HIV produced by a typical individual during the time it spends in the infectious class, then consider a single newly infectious human entering the disease free population at equilibrium. This human,

spends $1/(\mu_H + \alpha_H)$ time in the infectious class, infects human at a rate

$$\frac{\beta_H}{N_H} S_H \Big|_{DFE} = \beta_H.$$

Therefore the total number of humans which become infectious because of this human is approximately

$$\frac{\beta_H}{(\mu_H + \alpha_H)} = \mathcal{R}_H,$$

and then

$$\mathcal{R}_{HM} = \max\{\mathcal{R}_H, \mathcal{R}_M^{n,\bar{\tau}}\}.$$

3.3.4.2 Stability of the disease-free equilibrium

The stability of the DFE can be obtained from studying the eigenvalues of the Jacobian matrix evaluated at the equilibrium point. If all the eigenvalues have negative real parts, then the equilibrium point is stable. We linearize system (3.3.4.1.1) at $\mathsf{E}^0 = (S_H^0, I_M^0, I_H^0, I_{HM}^0, S_V^0, I_V^0)$. Define

$$x_1(t) = S_H(t) - S_H^0,\ x_2(t) = I_M(t) - I_M^0,\ x_3(t) = I_H(t) - I_H^0,$$
$$x_4(t) = I_{HM}(t) - I_{HM}^0,\ y_1(t) = S_V(t) - S_V^0 \text{ and } y_2(t) = I_V(t) - I_V^0.$$

Then, the associated linearized system is

$$\begin{aligned}
\dot{x}_1 &= -\mu_H x_1 + \nu_1 x_2 - \beta_H(x_3 + \eta_{HM} x_4) - \beta_M \theta y_2,\\
\dot{x}_2 &= -(\mu_H + \alpha_M + \nu_1)x_2 + \beta_M \theta y_2,\\
\dot{x}_3 &= (\beta_H - (\mu_H + \alpha_H))x_3 + (\beta_H \eta_{HM} + \nu_2)x_4,\\
\dot{x}_4 &= -(\mu_H + \kappa\alpha_M + \nu_2 + d\alpha_H)x_4,\\
\dot{y}_1 &= -\frac{\beta_V \theta \mu_H \Lambda_V}{\Lambda_H \mu_V}(x_2 + \eta_V x_4) - \mu_V y_1,\\
\dot{y}_2 &= \xi^{n,\bar{\tau}} \left(\frac{\beta_V \theta \mu_H \Lambda_V}{\Lambda_H \mu_V}\right) \int_0^\infty \mathsf{g}_{n,\bar{\tau}'}(\tau)(x_2(t-\tau) + \eta_V x_4(t-\tau))d\tau - \mu_V y_2.
\end{aligned} \tag{3.3.4.2.1}$$

Suppose that the linear system (3.3.4.2.1) also has exponential solutions, i.e., we can write

$$(x_1, x_2, x_3, x_4, y_1, y_2) = (a_1e^{\lambda t}, a_2e^{\lambda t}, a_3e^{\lambda t}, a_4e^{\lambda t}, b_1e^{\lambda t}, b_2e^{\lambda t}).$$

Substituting this into system (3.3.4.2.1), we get

$$\begin{aligned}
\lambda a_1e^{\lambda t} &= -\mu_H a_1e^{\lambda t} + \nu_1 a_2e^{\lambda t} - \beta_H(a_3 + \eta_{HM}a_4)e^{\lambda t} - \beta_M\theta b_2e^{\lambda t},\\
\lambda a_2e^{\lambda t} &= -(\mu_H + \alpha_M + \nu_1)a_2e^{\lambda t} + \beta_M\theta b_2e^{\lambda t},\\
\lambda a_3e^{\lambda t} &= (\beta_H - (\mu_H + \alpha_H))a_3e^{\lambda t} + (\beta_H\eta_{HM} + \nu_2)a_4e^{\lambda t},\\
\lambda a_4e^{\lambda t} &= -(\mu_H + \kappa\alpha_M + \nu_2 + d\alpha_H)a_4e^{\lambda t},\\
\lambda b_1e^{\lambda t} &= -\frac{\beta_V\theta\mu_H\Lambda_V e^{\lambda t}}{\Lambda_H\mu_V}(a_2 + \eta_V a_4) - \mu_V b_1e^{\lambda t},\\
\lambda b_2e^{\lambda t} &= \xi^{n,\bar{\tau}}\left(\frac{\beta_V\theta\mu_H\Lambda_V}{\Lambda_H\mu_V}(a_2 + \eta_V a_4)\right)F(\lambda, \bar{\tau}')e^{\lambda t} - \mu_V b_2e^{\lambda t},
\end{aligned}$$

Discarding $e^{\lambda t}$ from both sides and rearranging, we get

$$\begin{aligned}
(\lambda + \mu_H)a_1 - \nu_1 a_2 + \beta_H(a_3 + \eta_{HM}a_4) + \beta_M\theta b_2 &= 0,\\
(\lambda + (\mu_H + \alpha_M + \nu_1))a_2 - \beta_M\theta b_2 &= 0,\\
(\lambda - \beta_H + (\mu_H + \alpha_H))a_3 - (\beta_H\eta_{HM} + \nu_2)a_4 &= 0,\\
(\lambda + (\mu_H + \kappa\alpha_M + \nu_2 + d\alpha_H)a_4 &= 0,\\
\frac{\beta_V\theta\mu_H\Lambda_V}{\Lambda_H\mu_V}(a_2 + \eta_V a_4) + (\lambda + \mu_V)b_1 &= 0,\\
-\xi^{n,\bar{\tau}}\left(\frac{\beta_V\theta\mu_H\Lambda_V}{\Lambda_H\mu_V}(a_2 + \eta_V a_4)\right)F(\lambda, \bar{\tau}') + (\lambda + \mu_V)b_2 &= 0.
\end{aligned}$$

The characteristic matrix is given by

$$\triangle(\lambda) = \begin{pmatrix} J_1 & -\nu_1 & \beta_H & \beta_H\eta_{HM} & 0 & \beta_M\theta \\ 0 & J_2 & 0 & 0 & 0 & -\beta_M\theta \\ 0 & 0 & J_3 & -(\beta_H\eta_{HM}+\nu_2) & 0 & 0 \\ 0 & 0 & 0 & J_4 & 0 & 0 \\ 0 & \frac{\beta_V\theta\mu_H\Lambda_V}{\Lambda_H\mu_V} & 0 & \frac{\beta_V\theta\mu_H\Lambda_V\eta_V}{\Lambda_H\mu_V} & \lambda+\mu_V & 0 \\ 0 & -\frac{\xi^{n,\bar\tau}\beta_V\theta\mu_H\Lambda_V}{\Lambda_H\mu_V}F(\lambda,\bar\tau') & 0 & -\frac{\xi^{n,\bar\tau}\beta_V\theta\mu_H\Lambda_V\eta_V}{\Lambda_H\mu_V}F(\lambda,\bar\tau') & 0 & \lambda+\mu_V \end{pmatrix},$$

where

$$\begin{aligned} J_1 &= \lambda+\mu_H, \\ J_2 &= \lambda+(\mu_H+\alpha_M+\nu_1), \\ J_3 &= \lambda+(\mu_H+\alpha_H-\beta_H), \\ J_4 &= \lambda+(\mu_H+\kappa\alpha_M+\nu_2+d\alpha_H). \end{aligned}$$

The characteristic equation of the DFE, is given by the determinant of $\triangle(\lambda)$

$$(\lambda+\mu_H)(\lambda+\mu_V)(\lambda+(\mu_H+\nu_2+\kappa\alpha_M+d\alpha_H))Eq_HEq_M = 0, \qquad (3.3.4.2.2)$$

where

$$\begin{aligned} Eq_H &= \lambda+(\mu_H+\alpha_H)(1-\mathcal{R}_H), \\ Eq_M &= \lambda^2+(\mu_H+\alpha_M+\nu_1+\mu_V)\lambda+\mu_V(\mu_H+\alpha_M+\nu_1)(1-\mathcal{R}_M^{n,\bar\tau}F(\lambda,\bar\tau')). \end{aligned}$$

Note that Eq_M is the characteristic equations of the DFE of malaria-only sub model.

The roots of (3.3.4.2.2) are $-\mu_H$, $-\mu_V$, $-(\mu_H+\nu_2+\kappa\alpha_M+d\alpha_H)$ and those of Eq_H and Eq_M. Eq_H has one root given by $-(\mu_H+\alpha_H)(1-\mathcal{R}_H)$, which is negative if $\mathcal{R}_H<1$ and positive if $\mathcal{R}_H>1$. From the analysis of malaria-only sub model we found that the roots of Eq_M has negative real parts if $\mathcal{R}_M^{n,\bar{\tau}}<1$ and at least one of these roots have positive real part if $\mathcal{R}_M^{n,\bar{\tau}}>1$. Thus all roots of Eq (3.3.4.2.2) have negative real parts if $\max\{\mathcal{R}_H,\mathcal{R}_M^{n,\bar{\tau}}\}<1$ and at least one of these roots have positive real part if $\max\{\mathcal{R}_H,\mathcal{R}_M^{n,\bar{\tau}}\}>1$. These results are summarized in the following theorem.

Theorem 3.3.4.1. *The DFE of (3.3.1.0.3) is locally asymptotically stable when* $\mathcal{R}_{HM}<1$ *and unstable when* $\mathcal{R}_{HM}>1$.

3.3.4.3 Existence of the endemic equilibria

To find conditions for the existence of endemic equilibria, denoted by $\mathsf{E}^*=(S_H^*,I_M^*,I_H^*,I_{HM}^*,I_V^*,S_V^*)$, the equations in (3.3.1.0.3) are solved in terms of the forces of infections at a steady-state (λ_H^* and λ_M^*)

$$\lambda_H^* = \frac{\beta_H(I_H^*+\eta_{HM}I_{HM}^*)}{S_H^*+I_M^*+I_H^*+I_{HM}^*}, \tag{3.3.4.3.1}$$

$$\lambda_M^* = \frac{\beta_M\theta I_V^*}{S_H^*+I_M^*+I_H^*+I_{HM}^*}, \tag{3.3.4.3.2}$$

to obtain the following implicit expressions for the equilibria of system (3.3.1.0.3)

$$S_H^* = \frac{\Lambda_H(\sigma\lambda_H^* + \mu_H + \alpha_M + \nu_1)}{(\lambda_H^* + \mu_H)(\sigma\lambda_H^* + \mu_H + \alpha_M + \nu_1) + \lambda_M^*(\sigma\lambda_H^* + \mu_H + \alpha_M)},$$

$$I_M^* = \frac{\Lambda_H\lambda_M^*}{(\lambda_H^* + \mu_H)(\sigma\lambda_H^* + \mu_H + \alpha_M + \nu_1) + \lambda_M^*(\sigma\lambda_H^* + \mu_H + \alpha_M)},$$

$$I_H^* = \frac{\Lambda_H\lambda_H^*((\mu_H + \kappa\alpha_M + \nu_2 + d\alpha_H)(\sigma\lambda_H^* + \mu_H + \alpha_M + \nu_1) + \nu_2\sigma\lambda_M^*)}{((\sigma\lambda_H^* + \mu_H + \alpha_M)(\lambda_H^* + \lambda_M^* + \mu_H) + \nu_1(\lambda_H^* + \mu_H))D_1}, \tag{3.3.4.3.3}$$

$$I_{HM}^* = \frac{\Lambda_H\lambda_H^*\lambda_M^*(\sigma(\vartheta\lambda_H^* + \mu_H + \alpha_H) + \vartheta(\sigma\lambda_M^* + \mu_H + \alpha_M + \nu_1))}{((\sigma\lambda_H^* + \mu_H + \alpha_M)(\lambda_H^* + \lambda_M^* + \mu_H) + \nu_1(\lambda_H^* + \mu_H))D_1},$$

$$S_V^* = \frac{\Lambda_V}{\mu_V + \lambda_V^*},$$

$$I_V^* = \frac{\xi^{n,\bar{\tau}}\Lambda_V\lambda_V^*}{\mu_V(\mu_V + \lambda_V^*)},$$

where $D_1 = ((\vartheta\lambda_M^* + \mu_H + \alpha_H)(\kappa\alpha_M + d\alpha_H + \mu_H) + \nu_2(\mu_H + \alpha_H))$ and
$\lambda_V^* = \beta_V\theta(I_M^* + \eta_V I_{HM}^*)/(S_H^* + I_M^* + I_H^* + I_{HM}^*)$.
By substituting (3.3.4.3.3) in (3.3.4.3.1) and (3.3.4.3.2), we obtain the following characteristic equations

$$\begin{aligned} F(\lambda_H^*, \lambda_M^*) &= \lambda_H^*[f_1(\lambda_M^*)(\lambda_H^*)^2 + f_2(\lambda_M^*)\lambda_H^* + f_3(\lambda_M^*)], \\ G(\lambda_H^*, \lambda_M^*) &= \lambda_M^*[g_1(\lambda_H^*)(\lambda_M^*)^4 + g_2(\lambda_H^*)(\lambda_M^*)^3 + g_3(\lambda_H^*)(\lambda_M^*)^2 + g_4(\lambda_H^*)\lambda_M^* + g_5(\lambda_H^*)], \end{aligned} \tag{3.3.4.3.4}$$

where each of f_1, f_2 and f_3 are polynomials of order two in λ_M^*, and g_i, $i = 1 \ldots 5$, are polynomials of order four in λ_H^*. From the nature of these equations, one can see that the system is difficult to solve analytically. We therefore solve it numerically and the results are presented in the tables below. Parameters values are taken from Table

3.5.0.3.8.

When both reproduction numbers less than unity and the only visible equilibria is the DFE.

In Table 3.3.4.3.1, the malaria reproduction number, $\mathcal{R}_M^{n,\bar{\tau}}$, is less than unity, while the HIV one, $\mathcal{R}_H$, is greater than unity. We found that system (3.3.1.0.3) has a HIV equilibrium.

Whereas, in Table 3.3.4.3.2, the malaria reproduction number, $\mathcal{R}_M^{n,\bar{\tau}}$, is greater than unity, while the HIV one, $\mathcal{R}_H$, is less than unity. We found that system (3.3.1.0.3) has a malaria equilibrium.

In Table 3.3.4.3.3, both reproduction numbers greater than unity and system (3.3.1.0.3) has a co-infection equilibrium.

Table 3.3.4.3.1: Existence of the endemic equilibria for the HIV-malaria co-infection model ($\mathcal{R}_M^{n,\bar{\tau}} < 1, \mathcal{R}_H > 1$).

$\bar{\tau}$	λ_H^*	λ_M^*	S_H^*	I_M^*	I_H^*	I_{HM}^*	S_V^*	I_V^*
9	0.001048	0	45.998160	0	50.636630	0	41.987404	0
10	0.001048	0	45.998160	0	50.636630	0	41.987404	0
11	0.001048	0	45.998160	0	50.636630	0	41.987404	0
12	0.001048	0	45.998160	0	50.636630	0	41.987404	0
13	0.001048	0	45.998160	0	50.636630	0	41.987404	0
14	0.001048	0	45.998160	0	50.636630	0	41.987404	0
15	0.001048	0	45.998160	0	50.636630	0	41.987404	0
16	0.001048	0	45.998160	0	50.636630	0	41.987404	0
17	0.001048	0	45.998160	0	50.636630	0	41.987404	0
18	0.001048	0	45.998160	0	50.636630	0	41.987404	0
19	0.001048	0	45.998160	0	50.636630	0	41.987404	0
20	0.001048	0	45.998160	0	50.636630	0	41.987404	0
21	0.001048	0	45.998160	0	50.636630	0	41.987404	0

Table 3.3.4.3.2: Existence of the endemic equilibria for the HIV-malaria co-infection model ($\mathcal{R}_M^{n,\bar{\tau}} > 1, \mathcal{R}_H < 1$)

$\bar{\tau}$	λ_H^*	λ_M^*	S_H^*	I_M^*	I_H^*	I_{HM}^*	S_V^*	I_V^*
9	0	0.063057	12.145928	128.840554	0	0	6.215263	10.668564
10	0	0.054869	13.938629	128.658672	0	0	6.283205	9.3893810
11	0	0.047733	15.996427	128.449894	0	0	6.361112	8.2741596
12	0	0.041503	18.363383	128.209750	0	0	6.450616	7.3001096
13	0	0.036054	21.092981	127.932814	0	0	6.553690	6.4478079
14	0	0.031281	24.250850	127.612427	0	0	6.672745	5.7006636
15	0	0.027092	27.918515	127.240317	0	0	6.810764	5.0444704
16	0	0.023410	32.198649	126.806068	0	0	6.971484	4.4670317
17	0	0.020169	37.222623	126.296352	0	0	7.159660	3.9578437
18	0	0.017311	43.161589	125.693803	0	0	7.381449	3.5078259
19	0	0.014786	50.243282	124.975317	0	0	7.644984	3.1090886
20	0	0.012551	58.778351	124.109376	0	0	7.961269	2.7547260
21	0	0.010570	69.203364	123.051688	0	0	8.345625	2.4386236

Table 3.3.4.3.3: Existence of the endemic equilibria for the HIV-malaria co-infection model ($\mathcal{R}_M^{n,\bar{\tau}} > 1, \mathcal{R}_H > 1$)

$\bar{\tau}$	λ_H^*	λ_M^*	S_H^*	I_M^*	I_H^*	I_{HM}^*	S_V^*	I_V^*
9	0.001698	0.165720	1.066112	23.116666	0.385946	31.321830	4.718080	11.115080
10	0.001697	0.145876	1.205544	23.013160	0.439534	31.309006	4.731177	9.7975285
11	0.001696	0.128583	1.360625	22.898249	0.499997	31.294049	4.745867	8.6492983
12	0.001695	0.113488	1.532754	22.770972	0.568173	31.276589	4.762323	7.6469257
13	0.001693	0.100290	1.723399	22.630329	0.644999	31.256189	4.780737	6.7704289
14	0.001691	0.088732	1.934099	22.475295	0.731527	31.232338	4.801323	6.0027576
15	0.001689	0.078594	2.166450	22.304824	0.828934	31.204433	4.824313	5.3293354
16	0.001687	0.069689	2.422105	22.117861	0.938537	31.171773	4.849967	4.7376767
17	0.001685	0.061855	2.702756	21.913356	1.061807	31.133540	4.878568	4.2170682
18	0.001682	0.054954	3.010125	21.690279	1.200386	31.088784	4.910431	3.7583001
19	0.001679	0.048865	3.345943	21.447635	1.356105	31.036406	4.945902	3.3534419
20	0.001675	0.043487	3.711941	21.184490	1.530994	30.975143	4.985364	2.9956526
21	0.001672	0.038730	4.109821	20.899986	1.727307	30.903547	5.029241	2.6790215

From Table 3.3.4.3.3, we observe that, there would always be more cases of malaria at steady-state than cases of HIV infection in the community. It is the same as been observed in [106].

We observe that, like malaria only-model the full model undergoes a backward bifurcation for some values for the *basic reproduction number* associated with malaria,

$\mathcal{R}_M^{n,\bar{\tau}}$, less than unity. The result is shown in Tables 3.3.4.3.4 and 3.3.4.3.5 and Figure 3.5.0.3.2. Parameter values are taken from [106]. The graph shows a backward bifurcation implying that the classical epidemiological requirement for the eradication of the disease $\mathcal{R}_{HM} < 1$ is no longer sufficient, though necessary.

Table 3.3.4.3.4: Existence of the endemic equilibria for the HIV-malaria co-infection model ($\mathcal{R}_M^{n,\bar{\tau}} < 1, \mathcal{R}_H < 1$): a case of backward bifurcation

$\bar{\tau}$	λ_H^*	λ_M^*	S_H^*	I_M^*	I_H^*	I_{HM}^*	S_V^*	I_V^*
9	0	2.764032	368.923818	9949.297294	0	0	6887.822502	3906.834978
10	0	2.739811	372.184639	9949.281349	0	0	6888.649854	3873.817665
11	0	2.715987	375.448831	9949.265389	0	0	6889.477741	3841.340643
12	0	2.692549	378.716398	9949.249410	0	0	6890.306165	3809.390745
13	0	2.669488	381.987347	9949.233415	0	0	6891.135121	3777.955229
14	0	2.646796	385.261685	9949.217406	0	0	6891.964613	3747.021758
15	0	2.624463	388.539418	9949.201376	0	0	6892.794638	3716.578389
16	0	2.602482	391.820553	9949.185333	0	0	6893.625204	3686.613552
17	0	2.580843	395.105097	9949.169272	0	0	6894.456309	3657.116048
18	0	2.559539	398.393056	9949.153196	0	0	6895.287951	3628.075011
19	0	2.538562	401.684436	9949.137101	0	0	6896.120132	3599.479914
20	0	2.517905	404.979245	9949.120989	0	0	6896.952851	3571.320558
21	0	2.497560	408.277488	9949.104860	0	0	6897.786119	3543.587044

Table 3.3.4.3.5: Existence of the endemic equilibria for the HIV-malaria co-infection model ($\mathcal{R}_M^{n,\bar{\tau}} < 1, \mathcal{R}_H > 1$): a case of backward bifurcation

$\bar{\tau}$	λ_H^*	λ_M^*	S_H^*	I_M^*	I_H^*	I_{HM}^*	S_V^*	I_V^*
9	0.001659	0.028610	5.326199 366	20.040545	2.368120	30.651830	15.101586	8.018337
10	0.001652	0.024893	5.977351 765	19.587027	2.736776	30.496377	15.270912	7.025821
11	0.001644	0.021657	6.690941 310	19.095408	3.161648	30.309139	15.462655	6.160338
12	0.001635	0.018836	7.470514 342	18.564896	3.651035	30.084164	15.679780	5.404218
13	0.001625	0.016372	8.319538 550	17.995069	4.214290	29.814622	15.925685	4.742403
14	0.001613	0.014218	9.241400 695	17.385909	4.861877	29.492751	16.204269	4.162039
15	0.001600	0.012333	10.23942 376	16.737820	5.605410	29.109823	16.520029	3.652123
16	0.001585	0.010680	11.31690 930	16.051624	6.457655	28.656147	16.878152	3.203224
17	0.001569	0.009230	12.47714 515	15.328543	7.432489	28.121095	17.284646	2.807235
18	0.001550	0.007957	13.72353 099	14.570145	8.544797	27.493196	17.746478	2.457177
19	0.001530	0.006838	15.05966 282	13.778279	9.810307	26.760277	18.271742	2.147027
20	0.001507	0.005854	16.48937 311	12.954979	11.24532	25.909680	18.869848	1.871577
21	0.001482	0.004989	18.01685 102	12.102361	12.86633	24.928563	19.551742	1.626315

3.4 Sensitivity analysis of $\mathcal{R}_M^{n,\bar{\tau}}$

To determine the relative importance of model parameters to the initial transmission of the disease and its prevalence, we perform a sensitivity analysis of the basic reproduction number and the endemic steady states with respect to the model's parameters. A special focus is given to the impact of the mean delay and shape parameters.

Definition 3.4.0.1. *The sensitivity index of a variable x with respect to a parameter p is given by*

$$\zeta_P^x = \frac{\partial x}{\partial p} \times \frac{p}{x}.$$

Using parameter values from Table 3.5.0.3.7, we calculate the sensitivity indices of $\mathcal{R}_M^{n,\bar{\tau}}$ with respect to θ, β_M, Λ_V, β_V, μ_H, ν_1, α_M and Λ_H. These values are given in Table 3.4.0.3.6 below.

Table 3.4.0.3.6: Sensitivity indices of the *basic reproduction number*, $\mathcal{R}_M^{n,\bar{\tau}}$, of the malaria model with distributed delay.

Parameter	Parameter description	Sensitivity index
θ	Biting rate of female mosquito	$+2$
β_M	Parasite transmission probability from mosquito to human	$+1$
Λ_V	Mosquito birth rate	$+1$
β_V	Parasite transmission probability from human to mosquito	$+1$
Λ_H	Human birth rate	-1
μ_H	Human death rate	$+0.9981$
ν_1	Rate of human recovery into the susceptible class from being infectious	-0.9780
α_M	Malaria-induced death rate	-0.0200

For the other parameters (μ_V, $\bar{\tau}$, n) we obtain

$$\begin{aligned}
\zeta_{\mu_V}^{\mathcal{R}_M^{n,\bar{\tau}}} &= -\left(2 + \frac{\mu_V \bar{\tau}}{1 + \mu_V \frac{\bar{\tau}}{n}}\right), \\
\zeta_{\bar{\tau}}^{\mathcal{R}_M^{n,\bar{\tau}}} &= -\frac{\mu_V \bar{\tau}}{1 + \mu_V \frac{\bar{\tau}}{n}}, \\
\zeta_{n}^{\mathcal{R}_M^{n,\bar{\tau}}} &= \frac{\mu_V \bar{\tau}}{1 + \mu_V \frac{\bar{\tau}}{n}} - n \ln\left(1 + \mu_V \frac{\bar{\tau}}{n}\right).
\end{aligned}$$

Proposition 3.4.1. *The sensitivity indices of $\mathcal{R}_M^{n,\bar{\tau}}$ with respect to μ_V and $\bar{\tau}$ are decreasing with respect to $\bar{\tau}$ and n, whereas the one with respect to n, $\zeta_n^{\mathcal{R}_M^{n,\bar{\tau}}}$, is decreasing with respect to $\bar{\tau}$. Moreover,*

1. *If $\bar{\tau} \leq \frac{2.1626}{\mu_V}$ then $\zeta_n^{\mathcal{R}_M^{n,\bar{\tau}}}$ is increasing with respect to n.*
2. *If $\bar{\tau} > \frac{2.1626}{\mu_V}$ then there exists $n_0 \approx \frac{\mu_V \bar{\tau}}{2.1626}$ such that*
   (a) *$\zeta_n^{\mathcal{R}_M^{n,\bar{\tau}}}$ is decreasing for all $n < n_0$,*
   (b) *$\zeta_n^{\mathcal{R}_M^{n,\bar{\tau}}}$ is increasing for all $n > n_0$.*

Furthermore, $\zeta_{\mu_V}^{\mathcal{R}_M^{n,\bar{\tau}}} = -2 + \zeta_{\bar{\tau}}^{\mathcal{R}_M^{n,\bar{\tau}}}$ and $\frac{\zeta_n^{\mathcal{R}_M^{n,\bar{\tau}}}}{\zeta_{\bar{\tau}}^{\mathcal{R}_M^{n,\bar{\tau}}}} < \mu_V \bar{\tau}$.

Proof. The last inequality of the proposition and the monotony of $\zeta_{\mu_V}^{\mathcal{R}_M^{n,\bar{\tau}}}$ and $\zeta_{\bar{\tau}}^{\mathcal{R}_M^{n,\bar{\tau}}}$ are obvious. For the monotony of $\zeta_n^{\mathcal{R}_M^{n,\bar{\tau}}}$, we define

$$Q(n) = \frac{\mu_V \bar{\tau}}{1 + \frac{\mu_V \bar{\tau}}{n}} - n \ln\Big(1 + \frac{\mu_V \bar{\tau}}{n}\Big).$$

A straightforward calculation shows that

$$Q'(n) = \frac{\frac{\mu_V \bar{\tau}}{n}\left(2\frac{\mu_V \bar{\tau}}{n} + 1\right)}{\left(1 + \frac{\mu_V \bar{\tau}}{n}\right)^2} - \ln\Big(1 + \frac{\mu_V \bar{\tau}}{n}\Big),$$

and

$$Q''(n) = \frac{\left(\frac{\mu_V \bar{\tau}}{n}\right)^2}{n\left(1 + \frac{\mu_V \bar{\tau}}{n}\right)^3}\left(\frac{\mu_V \bar{\tau}}{n} - 1\right).$$

If $n < \mu_V \bar{\tau}$, then $Q''(n) > 0$, which implies that $Q'(n)$ is increasing. If $n > \mu_V \bar{\tau}$, then $Q''(n) < 0$, it follows that $Q'(n)$ is decreasing. Since $\lim_{n\to 0} Q'(n) = -\infty$, $Q'(\mu_V \bar{\tau}) = \frac{3}{4} - \ln(2) > 0$ and $\lim_{n\to\infty} Q'(n) = 0$, then there is $n_0 \in (0, \mu_V \bar{\tau})$ such that $Q'(n_0) = 0$ ($n_0 \approx \frac{\mu_V \bar{\tau}}{2.1626}$). We have

1. If $\bar{\tau} \leq (2.1626/\mu_V)$ then $n_0 \leq 1$ and $Q'(1) > 0$ which implies $Q'(n) > 0$. Then it follows that $Q(n)$ is increasing with respect to n. Hence $Q(1) < Q(n) < Q(\infty) = 0$ implies $Q(n) < 0$ for all n.

2. If $\bar{\tau} > (2.1626/\mu_V)$ then $n_0 > 1$ and $Q'(1) < 0$ then $Q'(n) < 0$ for all $n < n_0$ and $Q'(n) > 0$ for all $n > n_0$. Then it follows that $Q(n)$ is decreasing for all $n < n_0$ $(Q(n_0) < Q(n) < \lim_{n\to 0} Q(n) = 0)$ and increasing for all $n > n_0$ $(Q(n_0) < Q(n) < Q(\infty) = 0)$.

In both cases above $Q(n) < 0$. Since $Q(n) = (\partial \mathcal{R}_M^{n,\bar{\tau}}/\partial n)(n/\mathcal{R}_M^{n,\bar{\tau}}) < 0$, it follows that $\mathcal{R}_M^{n,\bar{\tau}}$ is decreasing with respect to n. This conclude the proof of the Proposition. □

Proposition 3.4.1 indicates that the variation of the sensitivity index $\zeta_n^{\mathcal{R}_M^{n,\bar{\tau}}}$ depends on $\rho = \bar{\tau}\mu_V$. If $\rho \leq 2.1626$ then the larger the shape parameter is the higher its relative impact will be on $\mathcal{R}_M^{n,\bar{\tau}}$. In the case where $\rho > 2.1626$, as n increases, its impact on $\mathcal{R}_M^{n,\bar{\tau}}$ decreases before it (the impact) starts increasing at $n \approx (\mu_V\bar{\tau}/2.1626)$. However in reality, ρ is always less than 2.1626 which means that the relative impact of n on $\mathcal{R}_M^{n,\bar{\tau}}$ increases with increasing values of n.
Proposition 3.4.1 also indicates that the highest (in absolute values) sensitivity index of $\mathcal{R}_M^{n,\bar{\tau}}$ is with respect to μ_V. Moreover, since $\rho < 2.1626$ then $\zeta_n^{\mathcal{R}_M^{n,\bar{\tau}}} > 2.1626\zeta_{\bar{\tau}}^{\mathcal{R}_M^{n,\bar{\tau}}}$. This implies that $\mathcal{R}_M^{n,\bar{\tau}}$ is at least twice as sensitive to changes in n than in $\bar{\tau}$.

The sensitivity indices with respect to μ_V, $\bar{\tau}$ and n are given in Figure 3.4.0.3.1 below.

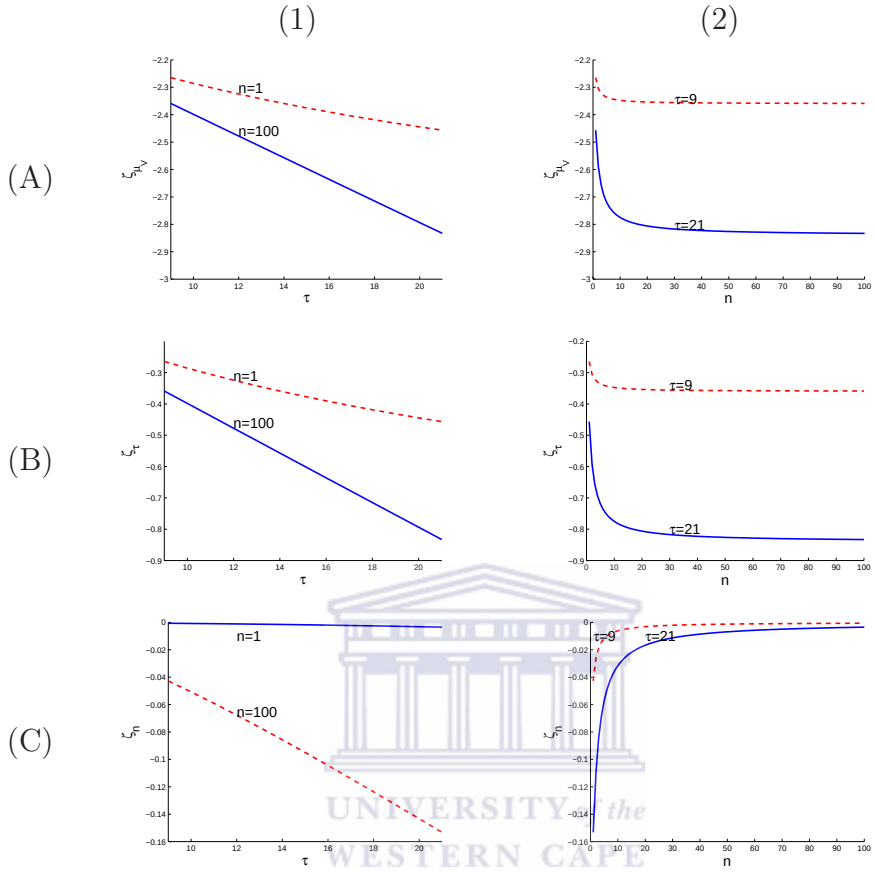

Figure 3.4.0.3.1: Sensitivity index of the *basic reproduction number* of system (3.3.3.0.6) with respect to (A) μ_V, (B) $\bar{\tau}$ and (C) n; using $\mu_V = 0.04$: (1) $n = 1, 100$ and (2) $\bar{\tau} = 9, 21$ (days).

From Figure 3.4.0.3.1, we see that as n varies from 1-100 and $\bar{\tau}$ varies from 9-21 days, we have $-2.8330 \leq \zeta_{\mu_V}^{\mathcal{R}_M^{n,\bar{\tau}}} \leq -2.2647$, $-0.8330 \leq \zeta_{\bar{\tau}}^{\mathcal{R}_M^{n,\bar{\tau}}} \leq -0.2647$ and $-0.1532 \leq \zeta_{n}^{\mathcal{R}_M^{n,\bar{\tau}}} \leq -0.0006$.

To investigate the impact on the disease prevalence of the mean delay and shape parameter, we compute the sensitivity index of I_M^* and I_V^* with respect to $\bar{\tau}$ and n.

Using the same notation as in Definition 3.4.0.1, we obtain

$$\begin{aligned}
\zeta_{\bar{\tau}}^{I_M^*} &= \Upsilon_H \zeta_{\bar{\tau}}^{\mathcal{R}_M^{n,\bar{\tau}}}, \\
\zeta_{n}^{I_M^*} &= \Upsilon_H \zeta_{n}^{\mathcal{R}_M^{n,\bar{\tau}}}, \\
\zeta_{\bar{\tau}}^{I_V^*} &= (\Upsilon_V + 1)\zeta_{\bar{\tau}}^{\mathcal{R}_M^{n,\bar{\tau}}}, \\
\zeta_{n}^{I_V^*} &= (\Upsilon_V + 1)\zeta_{n}^{\mathcal{R}_M^{n,\bar{\tau}}},
\end{aligned}$$

where

$$\Upsilon_H = \frac{\mu_H(\mu_H + \alpha_M + \nu_1)\mathcal{R}_M^{n,\bar{\tau}}}{\lambda_H^{*+}[\mu_H(\mu_H + \alpha_M + \nu_1) + \lambda_H^{*+}(\mu_H + \alpha_M)]} \times \left(\frac{C_1 + B_1\lambda_H^{*+}}{2A\lambda_H^{*+} + B}\right),$$

$$\Upsilon_V = \frac{\mu_V(\mu_H + \alpha_M + \nu_1)\mathcal{R}_M^{n,\bar{\tau}}}{\lambda_H^{*+}(\mu_V + \lambda_V^{*+})(\lambda_H^{*+} + \mu_H + \alpha_M + \nu_1)} \times \left(\frac{C_1 + B_1\lambda_H^{*+}}{2A\lambda_H^{*+} + B}\right),$$

with λ_V^{*+} is the force of infection of the vector population at the (stable) endemic equilibrium point.

We notice that the ratio of the sensitivity index with respect to $\bar{\tau}$ of the (stable) endemic equilibrium point to that with respect to n is the same as the ratio between the sensitivity indices of $\mathcal{R}_M^{n,\bar{\tau}}$ with respect to $\bar{\tau}$ and n. Therefore, the same conclusion can be drawn regarding the relative impact of $\bar{\tau}$ and n on the endemic equilibrium point.

3.5 Numerical simulations

To monitor the impact of the delay on the prevalence of malaria in a community, we make use of Matlab solver ode15s to integrate the equations of system (3.3.1.0.3). Because of the nature of the delay considered in this model, we extend the Matlab solver *ode15s* (which is designed to solve stiff problems) in the following manner: For each t generated through the t-vector in the *ode15s*, we calculate the infinite integral using a Matlab quadrature routine **quadgk** which supports infinite intervals. This

routine transforms an infinite interval into a finite one and generates discrete values for τ (τ-vector). Before substituting these values in the integrand function, we compare each value of τ in the τ-vector with t. If $t \leq \tau$ then the state variables at $(t-\tau)$ take the values from the history otherwise we can use the solutions that are generated by the *ode15s* solver (until this stage) to interpolate the values of the state variables at $(t-\tau)$.

Another remarkable point is the use of the solver *ode15s* as compared to *ode45*. We have experimented and observed that both can produce similar results with only exception that the latter is far slower than the former.

The parameter values used in the simulations are presented in tables 3.5.0.3.7 and 3.5.0.3.8 which are taken from [106].

Table 3.5.0.3.7: Parameter values for the malaria model with a distributed delay.

Description	Parameter	Value	Source
Recruitment rate of humans	Λ_H	0.55	[23]
Recruitment rate of mosquitoes	Λ_V	3.2	[23]
Natural death rate of humans	μ_H	0.000001-0.02	[23, 26]
Natural death rate of mosquitoes	μ_V	0.0010-0.10	[26]
Malaria-induced death rate	α_M	0.00041-0.2	[23, 26]
Transmission probability for malaria in humans	β_M	0.8	[23]
Transmission probability for malaria in vectors	β_V	0.8	[23]
Biting rate of mosquitoes	θ	0.57	[24]
Rate at which vectors exposed to malaria develop symptoms	γ_V	0.1	[106]
Recovery rate of humans from malaria	ν_1	0.02	[1]

Table 3.5.0.3.8: Parameter values for HIV-malaria co-infection.

Description	Parameter	Value
Recruitment rate of humans	Λ_H	$5 \times 10^{-2}\ day^{-1}$
Recruitment rate of mosquitoes	Λ_V	$6\ day^{-1}$
Natural death rate of humans	μ_H	$3.9 \times 10^{-5}\ day^{-1}$
Natural death rate of mosquitoes	μ_V	$0.1429\ day^{-1}$
HIV-induced death rate	α_H	$9.13 \times 10^{-4}\ day^{-1}$
Malaria-induced death rate	α_M	$3.454 \times 10^{-4}\ day^{-1}$
Effective contact rate for HIV infection	β_H	Variable
Transmission probability for malaria in humans	β_M	$0.8333\ day^{-1}$
Transmission probability for malaria in vectors	β_V	(0,1)
Biting rate of mosquitoes	θ	$(0.25,1)\ day^{-1}$
Rate at which vectors exposed to malaria develop symptoms	γ_V	$0.1\ day^{-1}$
Recovery rate of humans from malaria	ν_1, ν_2	0.00556, 0.002
Modification parameters	ϑ,d	1.002, 1.002
Modification parameters	σ, κ	1.00, 1.001
Modification parameters	η_{HM}, η_V	1.5030,1.5

Number of female mosquitoes per human host $m = 2$ ([122])

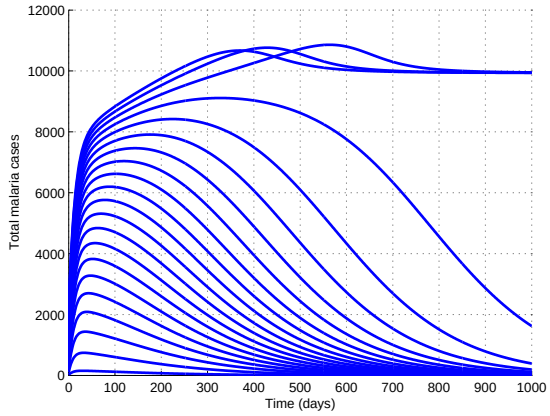

Figure 3.5.0.3.2: Simulation for model (3.3.1.0.3), showing the backward bifurcation phenomena; using $\Lambda_H = 1000$, $\Lambda_V = 100$, $\beta_H = 0.0015$, $\beta_M = 3.3$, $\beta_V = 0.005723$, $\theta = 0.58$, $\mu_H = 0.00049139$, $\alpha_H = 0.1$, $\alpha_M = 0.1$, $\eta_H M = 1$, $\eta_V = 1$, $\nu_1 = 0.002$, $\nu_2 = 0.004$, $\sigma = 1$, $\vartheta = 1.002$, $\kappa = 1.001$, $d = 1.002$, $\bar{\tau} = 14$ and $n = 5$

Figure 3.5.0.3.3 below shows a decrease in malaria prevalence when we increase the value of the mean delay of the incubation period and the shape parameter of gamma distribution.

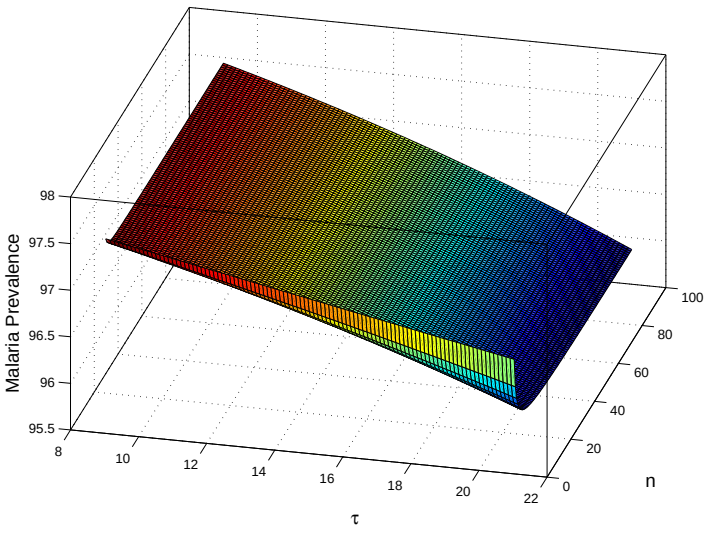

Figure 3.5.0.3.3: The relationship between malaria prevalence according to model (3.3.3.0.6) as a function of the shape parameter, n, and the mean value of the incubation period, $\bar{\tau}$. Parameter values are taken from Table 3.5.0.3.7 with $\alpha_M = 0.2$, $\mu_H = 0.02$, $\mu_V = 0.04$.

In Figure 3.5.0.3.4, we shows that the malaria prevalence for the model without delay. The graph shows a high increase in the prevalence when $\mathcal{R}_0 > 1$. When $\mathcal{R}_0 < 1$ the prevalence is slowly decreasing.

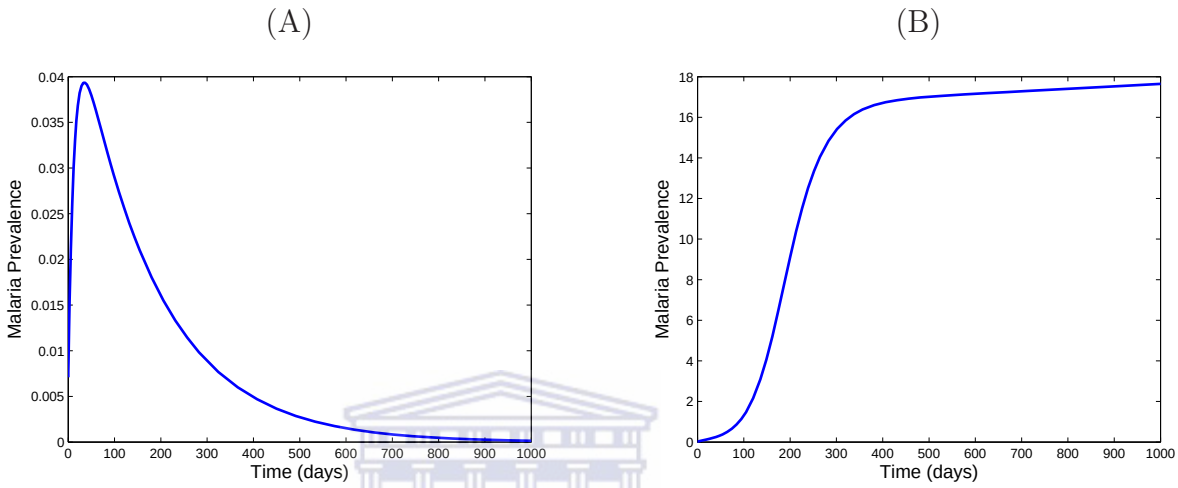

Figure 3.5.0.3.4: Malaria prevalence according to model (3.3.3.0.6). Parameter values are taken from Table 3.5.0.3.7 with $\alpha_M = 0.00041$, $\mu_H = 0.000039$, $\bar{\tau} = 0$ (A) $\mu_V = 0.06$ ($\mathcal{R}_0 = 0.6409$) (B) $\mu_V = 0.02$ ($\mathcal{R}_0 = 5.7683$).

The simulation for the behavior of the malaria prevalence for different values of n and $\bar{\tau}$ are given in Figure 3.5.0.3.5. The graphs show how $\mathcal{R}_M^{n,\bar{\tau}}$ varies with various values for $\bar{\tau}$ and n. When $\bar{\tau} > \ln(\mathcal{R}_0)/\mu_V$, $\mathcal{R}_M^{n,\bar{\tau}} < 1$ for all values of n. When $\bar{\tau} < (\mathcal{R}_0 - 1)/\mu_V$, $\mathcal{R}_M^{n,\bar{\tau}} > 1$ for all values of n. Whereas Figure 3.5.0.3.6 shows when $\ln(\mathcal{R}_0)/\mu_V < \bar{\tau} < (\mathcal{R}_0 - 1)/\mu_V$, $\mathcal{R}_M^{n,\bar{\tau}} > 1$ for all values of $n \leq n_{crit}$ and $\mathcal{R}_M^{n,\bar{\tau}} < 1$ for all values of $n > n_{crit}$.

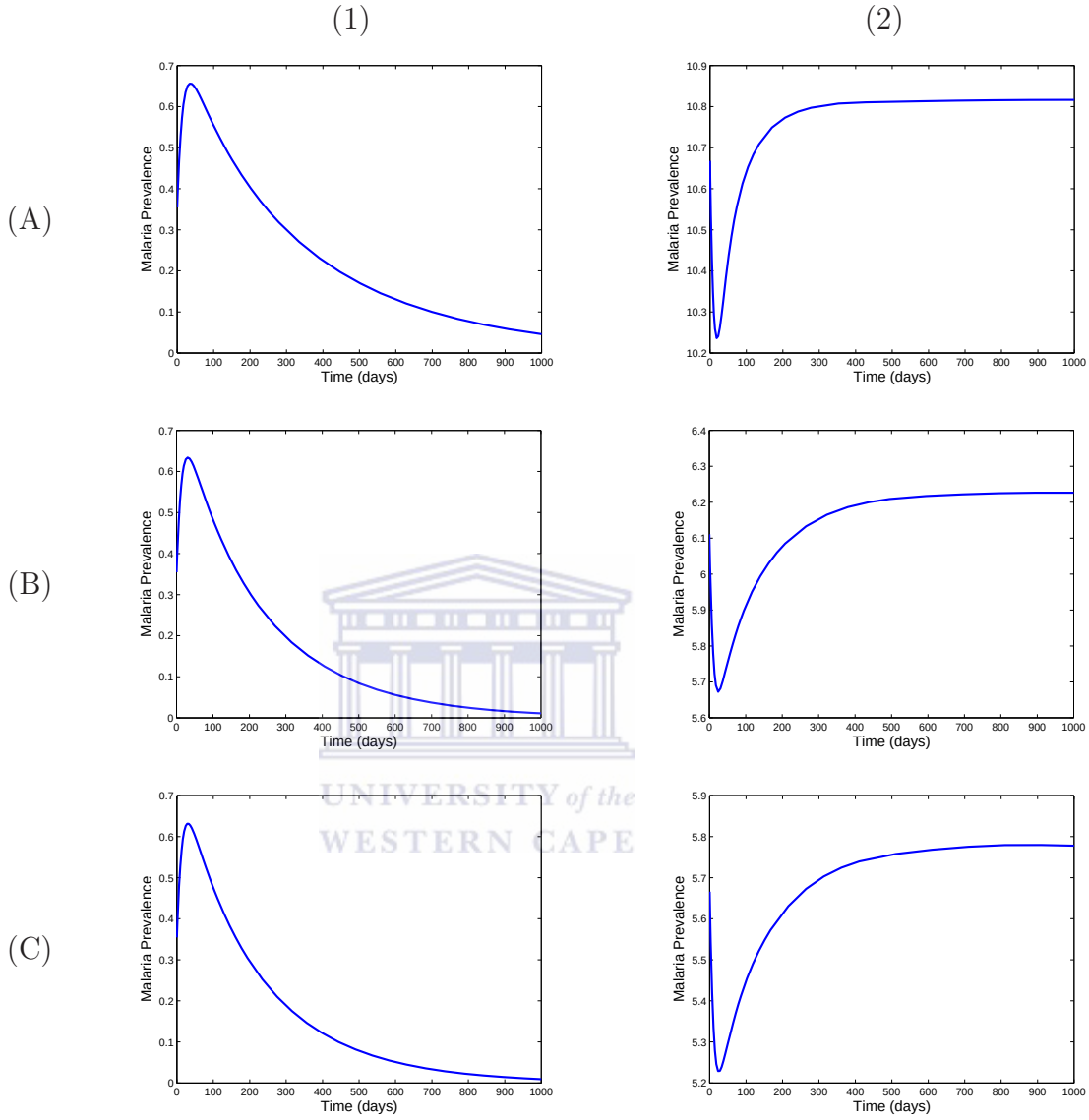

Figure 3.5.0.3.5: Malaria prevalence according to model (3.3.3.0.6). Parameter values are taken from Table 3.5.0.3.7 with $\alpha_M = 0.00041, \mu_H = 0.000039$, and various values for n: (A) $n = 1$ (B) $n = 10$, and (C) $n = 40$; with (1) $\mu_V = 0.04$, $\mathcal{R}_0 = 1.4421$, $\frac{1}{\mu_V}\ln(\mathcal{R}_0) = 9.1522$, $\frac{1}{\mu_V}(\mathcal{R}_0 - 1) = 11.0520$, $\bar{\tau} = 20$ ($\mathcal{R}_0^{1,20} = 0.8012$, $\mathcal{R}_0^{10,20} = 0.6680$, $\mathcal{R}_0^{40,20} = 0.6531$) and (2) $\mu_V = 0.035$, $\mathcal{R}_0 = 1.8835$, $\frac{1}{\mu_V}\ln(\mathcal{R}_0) = 18.09$, $\frac{1}{\mu_V}(\mathcal{R}_0 - 1) = 25.2438$, $\bar{\tau} = 14$ ($\mathcal{R}_0^{1,16} = 1.2641$, $\mathcal{R}_0^{10,16} = 1.1674$, $\mathcal{R}_0^{40,16} = 1.1573$).

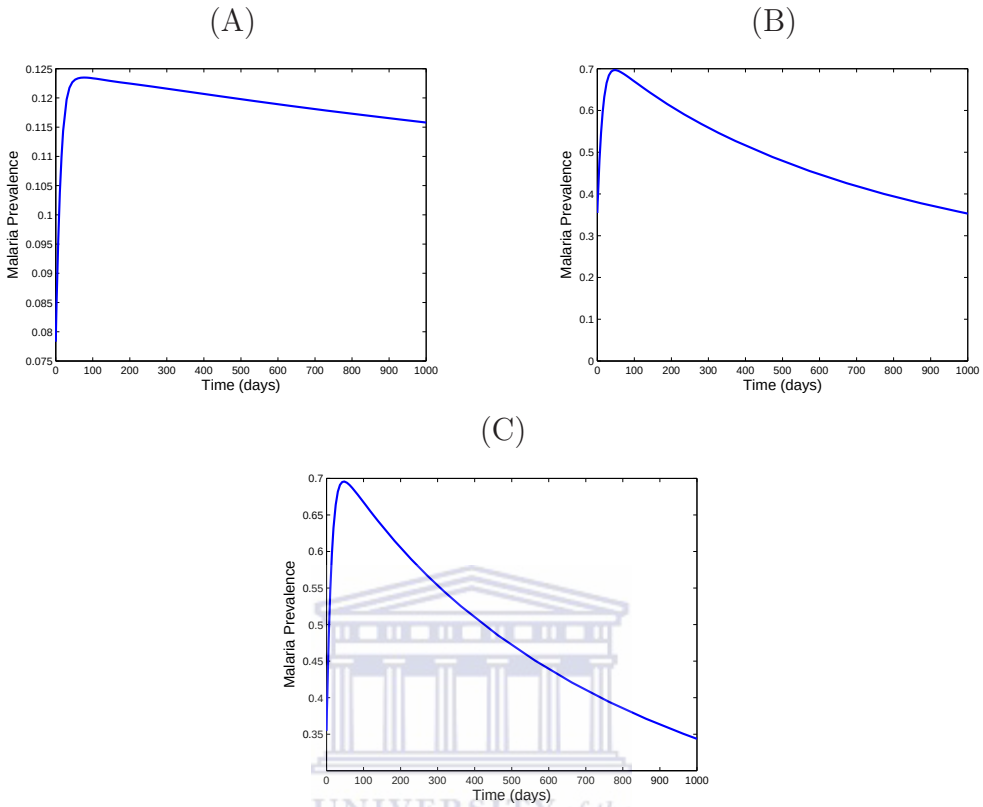

Figure 3.5.0.3.6: Malaria prevalence according to model (3.3.3.0.6). Parameter values are taken from Table 3.5.0.3.7 with $\alpha_M = 0.00041, \mu_H = 0.000039, \mu_V = 0.035$, and various values for n: (A) $n = 6$ (B) $n = 7$ and (C) $n = 8$; with $\mathcal{R}_0 = 1.8835$, $\frac{1}{\mu_V}\ln(\mathcal{R}_0) = 18.09$, $\frac{1}{\mu_V}(\mathcal{R}_0 - 1) = 25.2438$, $\bar{\tau} = 19$ ($\mathcal{R}_0^{6,19} = 1.0025$, $\mathcal{R}_0^{7,19} = 0.9979$, $\mathcal{R}_0^{8,19} = 0.9944$) ($n_{crit} = 7$).

In Figure 3.5.0.3.7, we plot the *basic reproduction number*, $\mathcal{R}_{HM}$, versus (A) the mean delay $\bar{\tau}$ and (B) the shape parameter n of the gamma distribution and it seems is a decreasing function with both of $\bar{\tau}$ and n. ($\mathcal{R}_H > 1$).

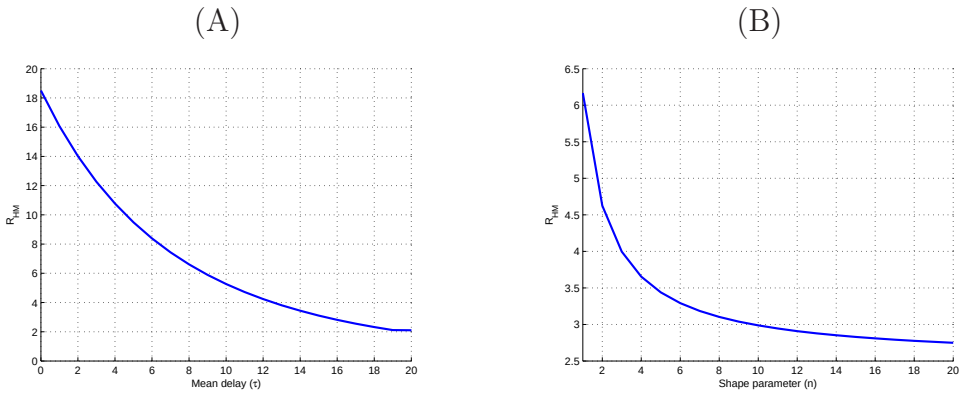

Figure 3.5.0.3.7: Profile of $\mathcal{R}_{HM}$ as a function of (A) the incubation period, (B) The shape parameter. Parameter values are taken from Table 3.5.0.3.8 with $\beta_H = 0.002$, $\beta_V = 0.9$, $\theta = 0.8$, (A) $n = 5$ and various values of $\bar{\tau}$, (B) $\bar{\tau} = 14$ and for various values of n.

Figures 3.5.0.3.8 and 3.5.0.3.9 show the effect of the mean delay $\bar{\tau}$ and the shape parameter n on the solution of system (3.3.1.0.3). The infectious I_M, I_{HM} and I_V are decreasing with the increasing values of $\bar{\tau}$ and n. Whereas I_H and the susceptibles S_H and S_V are shown increasing with the increasing values of $\bar{\tau}$ and n.

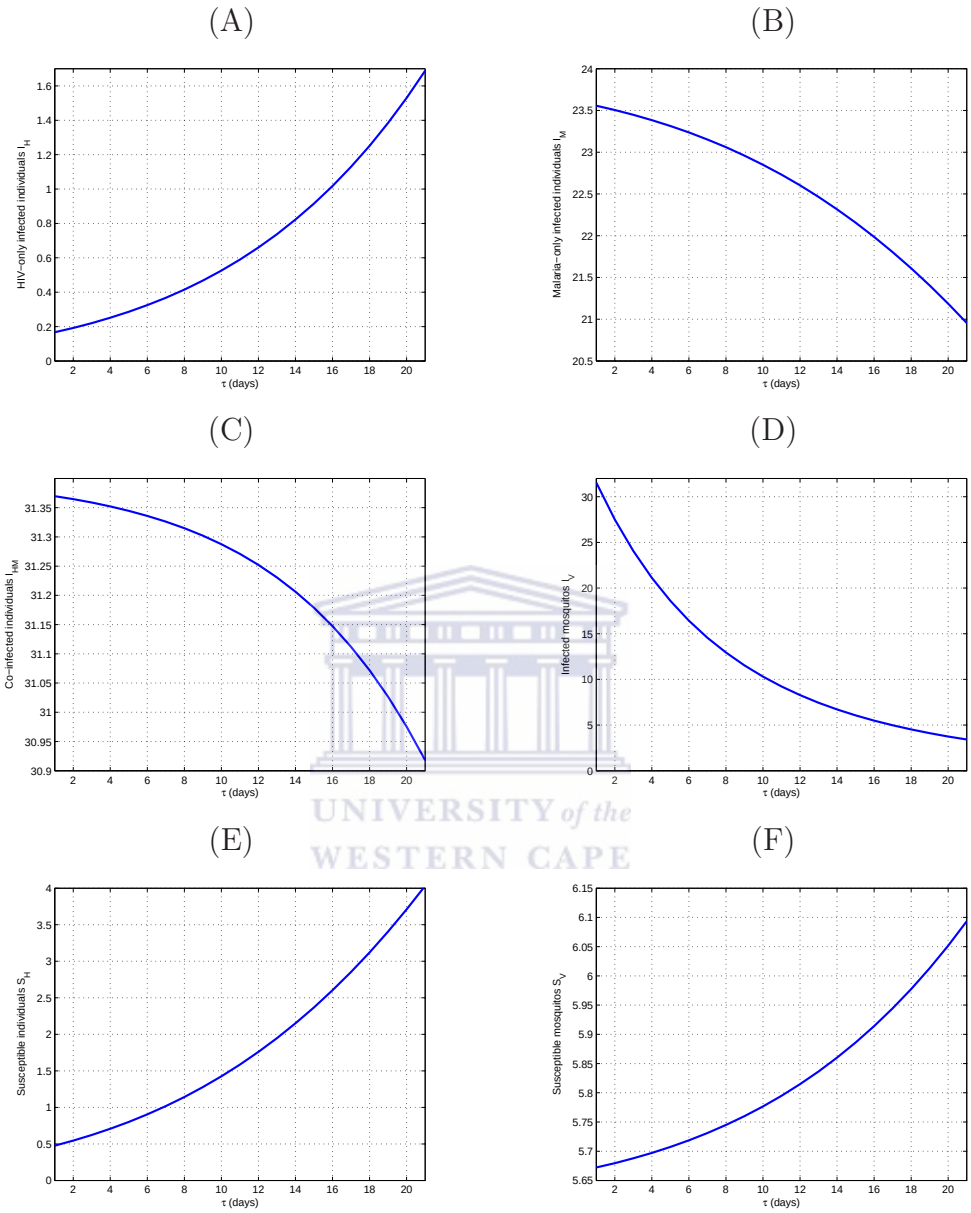

Figure 3.5.0.3.8: The effect of the incubation period on the dynamics of model (3.3.1.0.3). Parameter values are taken from Table 3.5.0.3.8 with $\beta_H = 0.002$, $\beta_V = 0.9$, $\theta = 0.8$, $n = 5$ and for various values of $\bar{\tau}$.

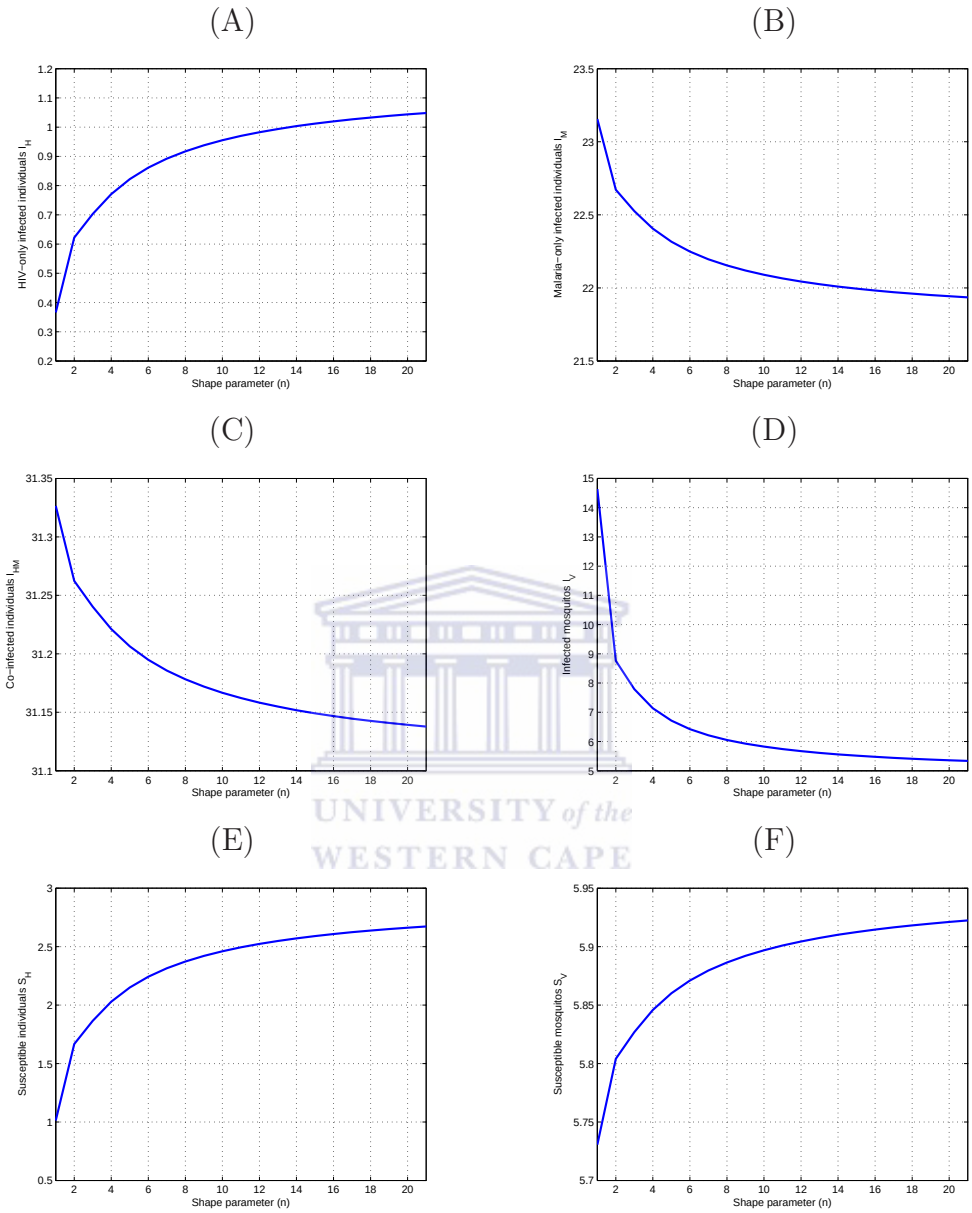

Figure 3.5.0.3.9: The effect of the shape parameter on the dynamics of model (3.3.1.0.3). Parameter values are taken from Table 3.5.0.3.8 with $\beta_H = 0.002$, $\beta_V = 0.9$, $\theta = 0.8$ $\bar{\tau} = 14$ and for various values of n.

3.6 Summary and discussion

In this chapter we analyzed an HIV-malaria co-infection model with a gamma distributed delay representing the incubation period of the disease in the vector. The

idea behind choosing this model is to investigate the effect of the distributed delay only on the transmission dynamics of HIV, malaria and HIV-malaria co-infection. The HIV-only and malaria-only models were qualitatively examined.

The HIV-only sub-model has a globally stable DFE and under certain condition it has a globally stable unique endemic equilibrium.

For the malaria-only sub-model, the basic reproduction number $\mathcal{R}_M^{n,\bar{\tau}}$ is calculated and shown to be decreasing with respect to the mean delay and the shape parameter of the gamma distribution. Also, when the disease is established, increasing these parameters leads to an endemic steady state with more healthy and less infected humans and mosquitoes. The threshold value of $\mathcal{R}_M^{n,\bar{\tau}}$ below which the disease can be eradicated is expressed in terms of the mean delay and shape parameter. We found that when the mean delay is between the critical value of the incubation period of the SEI model and that of the SI model with a discrete delay, the shape parameter has an important effect on the disease eradication or establishment (the critical value is the one bellow which the disease will persist). In this case, we determine a critical value for the shape parameter above which the disease can be completely eradicated.

The eradication/persistence is further investigated by exploring the existence of steady states and their stability. The local stability of the DFE is studied analytically while that of the endemic equilibria is investigated numerically. Furthermore, we determined explicit conditions under which the system exhibits either a transcritical or backward bifurcation.

We also performed a sensitivity analysis by calculating the sensitivity index to compare the relative impact of these two parameters on both the initial transmission and on the disease prevalence at the (endemic) equilibria. The results show that the sensitivity index of $\mathcal{R}_M^{n,\bar{\tau}}$ (and the endemic equilibrium point) is, as at least, twice as high in n than in $\bar{\tau}$.

For the co-infection model, the basic reproduction number $\mathcal{R}_{HM}$ is calculated and shown to be decreasing with respect to the mean delay and the shape parameter of the gamma distribution. Also, when the disease is established, increasing these parame-

ters leads to an endemic steady state with more healthy and less infected humans and mosquitoes. But it is shown that both the mean delay and the shape parameter of gamma distribution have no effect on the HIV-only individuals. It should further be noted that like the malaria-only model, the co-infection model also undergoes transcritical and backward bifurcations.

The above study suggests that any intervention that is aimed at reducing the initial transmission, by delaying the incubation of the disease in the vector, should account for the shape of the delay's distribution as well.

As one can see from (Table 3.3.4.3.3), that is for the set of parameters we use, there would always be more cases of malaria at steady state than the cases of HIV in a community. This because each of malaria and HIV infection occurs in two different time-scales. This motivates us to simplify our model by applying singular perturbation techniques to separate components into fast and slow parts, and analyze each separately. We will attend to this issue in Chapter 5.

It is worthy of mentioning here that the Matlab solvers are too slow in producing the numerical results for the full model and indeed give unreliable results. To this end, in the next chapter, we construct and analyzed an efficient numerical method to solve the model presented in this chapter. This method is in fact much faster than the in-built Matlab solvers that researchers normally use to solve systems of ODEs.

Chapter 4

Construction and analysis of a non-standard finite difference method for an HIV-malaria co-infection model with a distributed delay

In this chapter, we design and analyze a nonstandard finite difference numerical scheme for the numerical solution of the HIV-malaria co-infection model with a distributed delay presented in Chapter 3. To come up with the efficient numerical method for the full co-infection model, we study a number of qualitative properties of sub-models and then use the information while designing the numerical methods for these sub-models. One of the salient features of these methods is that they preserve positivity of the solution which is very essential while studying epidemiological models. We also present numerical simulations to confirm the theoretical findings.

4.1 Introduction

Nonstandard finite difference methods (NSFDMs) have been successfully applied in the past to solve a variety of problems arising in Sciences and Engineering. The inherent beauty of these methods is that they are very often dynamically consistent, a feature that one would always expect for biological models. Below we mention a few of these works.

A nonstandard numerical scheme for a SIRS seasonal epidemiological model for Respiratory Syncytial Virus (RSV) is developed by Arenas *et al.* in [6]. They compared their method with some well-known explicit methods and carried out some simulations with data from Gambia and Finland. They showed that the forward Euler and fourth order Runge-Kutta schemes do not converge unless the step-size used in the numerical simulations for these two methods is less than a critical step-size $h_c = 0.1$.

In [53], Gumel *et al.* investigated a class of NSFDMs for solving systems of differential equations arising in mathematical biology. They showed that their methods can often give numerical results that are asymptotically consistent with those of the corresponding continuous model by using a number of case studies in human epidemiology and ecology.

Jódar *et al.* [71] constructed two competitive implicit finite difference schemes for a deterministic mathematical model associated with the evolution of influenza in human population. They obtained numerical simulations with different sets of initial conditions, parameters values, time step-sizes.

Villanueva *et al.* [141] developed nonstandard finite difference schemes to solve the numerical solution of a mathematical model of infant obesity with constant population size. Their model consists of a system of coupled nonlinear ordinary differential equations. The numerical results showed that their methods have better convergence properties as compared to the classical Euler or the fourth-order Runge-Kutta methods and the Matlab routines in the sense that these routines give negative values for some of the state variables.

More details about this class of methods can be found in [5, 37, 38, 39, 64] whereas a thorough review on the other applications of these NSFDMs can be seen in [114].

The rest of this chapter is organized as follows. The construction of the NSFDM is presented in Section 4.2 and its analysis is carried out in Section 4.3. Numerical simulations are presented in Section 4.4. Section 4.5 is devoted to the discussion of the results.

4.2 Construction of the NSFDM

Let N_t be a positive integers that denote the number of subintervals in the t direction, and let $\ell(=\Delta t)=\frac{T}{N_t}$) be the step-size in that direction. The time interval $[0,T]$ is partitioned as

$$t_0=0<t_1<\cdots<t_{N_t-1}<t_{N_t}=T \quad \text{with } t_{k+1}=t_k+\ell,\ k=0(1)N_t-1.$$

As one can see from Figure 4.2.0.3.1, after a certain value of τ, we called it τ_{max}, the area under the curves looks insignificant, allow us to approximate the infinite integral with a finite one. i.e.,

$$\int_0^{\infty} \mathrm{g}_{n,\bar{\tau}'}(\tau)\lambda_V(t-\tau)S_V(t-\tau)d\tau \approx \int_0^{\tau_{max}} \mathrm{g}_{n,\bar{\tau}'}(\tau)\lambda_V(t-\tau)S_V(t-\tau)d\tau.$$

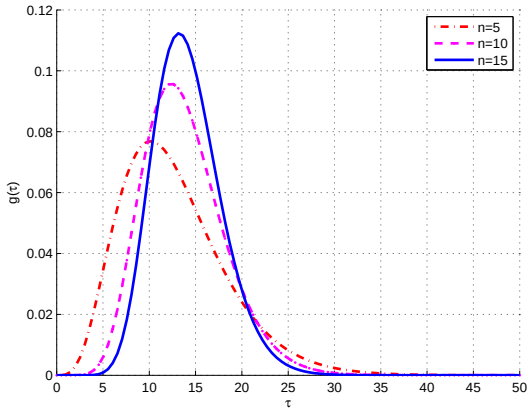

Figure 4.2.0.3.1: Profile of $\mathrm{g}_{n,\bar{\tau}'}(\tau)$. Parameter values used are $\mu_V = 0.06$, $\bar{\tau} = 20$ and for various values of τ.

Hence system (3.3.1.0.3) reads as

$$\begin{aligned}
\dot{S}_H &= \Lambda_H + \nu_1 I_M - \lambda_M S_H + \lambda_H S_H - \mu_H S_H,\\
\dot{I}_M &= \lambda_M S_H - \sigma\lambda_H I_M - (\mu_H + \alpha_M + \nu_1) I_M,\\
\dot{I}_H &= \lambda_H S_H + \nu_2 I_{HM} - \vartheta\lambda_M I_H - (\mu_H + \alpha_H) I_H,\\
\dot{I}_{HM} &= \sigma\lambda_H I_M + \vartheta\lambda_M I_H - (\mu_H + \kappa\alpha_M + d\alpha_H + \nu_2) I_{HM},\\
\dot{S}_V &= \Lambda_V - \mu_V S_V - \lambda_V S_V,\\
\dot{I}_V &= \xi^{n,\bar{\tau}} \int_0^{\tau_{max}} \mathrm{g}_{n,\bar{\tau}'}(\tau)\lambda_V(t-\tau)S_V(t-\tau)d\tau - \mu_V I_V,
\end{aligned} \tag{4.2.0.3.1}$$

and we assume for simplicity that $\int_0^{\tau_{max}} \mathrm{g}_{n,\bar{\tau}'}(\tau)d\tau = 1$.

Now, let N_τ be a positive integers that denote the number of subintervals of τ interval $[0, \tau_{max}]$, and let $\ell_\tau (= \Delta\tau) = \frac{\tau_{max}}{N_\tau}$ be the step-size. The τ interval $[0, \tau_{max}]$ is partitioned as

$$\tau_0 = 0 < \tau_1 < \cdots < \tau_{N_\tau - 1} < \tau_{N_\tau} = \tau_{max} \quad \text{with} \quad \tau_{r+1} = \tau_r + \ell,\ r = 0(1)N_\tau - 1.$$

The selection of N_t and N_τ should be done in such a way that the condition $\tau = r\ell$ is satisfied, where r is a positive integer.

At the grid point (t_k), we denote the approximations to $S_H(t_k)$, $I_M(t_k)$, $I_H(t_k)$, $I_{HM}(t_k)$, $S_V(t_k)$ and $I_V(t_k)$ by S_H^k, I_M^k, I_H^k, I_{HM}^k, S_V^k and I_V^k.

To construct the NSFDM, we discretized the system (4.2.0.3.1) based on the approximation of the temporal derivatives by a generalized first order method. For example, the discrete derivative for $S_H(t)$ is defined by

$$\frac{dS_H}{dt} = \frac{S_H^{k+1} - S_H^k}{\zeta(\ell)} + \mathcal{O}(\zeta(\ell)), \text{ as } \ell \to 0, \tag{4.2.0.3.2}$$

where ζ is a denominator function ([101]) which is a real-valued function and satisfies

$$\zeta(\ell) = \ell + \mathcal{O}(\ell^2), \text{ for all } \ell > 0.$$

The non-derivative terms are approximated locally, i.e., at the base time level. Besides these, the integral term is approximated by the Riemann sum, i.e.,

$$\int_0^{\tau_{max}} \mathrm{g}_{n,\bar{\tau}'}(\tau)\lambda_V(t-\tau)S_V(t-\tau)d\tau \approx \sum_{r=0}^{N_\tau - 1} \tau_r g(\tau_r)\lambda_V^{k-r} S_V^{k-r}.$$

Using the above notations and terminology, we propose the following nonstandard finite

difference method to discretize the system (4.2.0.3.1):

$$\begin{aligned}
\frac{S_H^{k+1}-S_H^k}{\zeta_1(\ell)} &= \Lambda_H + \nu_1 I_M^k - \lambda_H^k S_H^{k+1} - \lambda_M^k S_H^{k+1} - \mu_H S_H^{k+1},\\
\frac{I_M^{k+1}-I_M^k}{\zeta_2(\ell)} &= \lambda_M^k S_H^{k+1} - \sigma\lambda_H^k I_M^{k+1} - (\mu_H+\alpha_M+\nu_1) I_M^{k+1},\\
\frac{I_H^{k+1}-I_H^k}{\zeta_3(\ell)} &= \lambda_H^k S_H^{k+1} + \nu_2 I_{HM}^k - \vartheta\lambda_M^k I_H^{k+1} - (\mu_H+\alpha_H) I_H^{k+1},\\
\frac{I_{HM}^{k+1}-I_{HM}^k}{\zeta_4(\ell)} &= \sigma\lambda_H^k I_M^{k+1} + \vartheta\lambda_M^k I_H^{k+1} - (\mu_H+\kappa\alpha_M+d\alpha_H+\nu_2) I_{HM}^{k+1},\\
\frac{S_V^{k+1}-S_V^k}{\zeta_V(\ell)} &= \Lambda_V - \lambda_V^k S_V^{k+1} - \mu_V S_V^{k+1},\\
\frac{I_V^{k+1}-I_V^k}{\zeta_V(\ell)} &= \xi^{n,\bar{\tau}} \sum_{r=0}^{N_\tau-1} \tau_r g(\tau_r) \lambda_V^{k-r} S_V^{k-r} - \mu_V I_V^{k+1},
\end{aligned} \tag{4.2.0.3.3}$$

where r is the time needed by mosquitoes to become infectious (incubation period of the disease in the vector). The forces of infections λ_H^k, λ_M^k and λ_V^k are the approximation of the forces of infections at the grid point t_k which given by

$$\begin{aligned}
\lambda_H^k &= \frac{\beta_H(I_H^k + \eta_{HM} I_{HM}^k)}{N_H^k},\\
\lambda_M^k &= \frac{\beta_H \theta I_V^k}{N_H^k},\\
\lambda_V^k &= \frac{\beta_V \theta(I_M^k + \eta_V I_{HM}^k)}{N_H^k},
\end{aligned}$$

with $N_H^k = S_H^k + I_M^k + I_H^k + I_{HM}^k$.

With the initial condition

$$\begin{aligned} S_H^k &= S_H(t_k) = \phi_H(t_k) \geq 0, \\ I_M^k &= I_M(t_k) = \psi_M(t_k) \geq 0, \\ I_H^k &= I_H(t_k) = \psi_H(t_k) \geq 0, \\ I_{HM}^k &= I_{HM}(t_k) = \psi_{HM}(t_k) \geq 0, \\ S_V^k &= S_V(t_k) = \phi_V(t_k) \geq 0, \\ I_V^k &= I_V(t_k) = \psi_V(t_k) \geq 0, \quad t_k \in [-\tau, 0]. \end{aligned}$$

For simplicity we assume $\sum_{r=0}^{N_\tau - 1} \tau_r g(\tau_r) = 1$.

Remark 4.2.0.1. It is to be noted that besides the use of a non-classical denominator function, we have also used some non-local discretizations. As is mentioned in the literature (see, e.g., [101, 114]) a finite difference method is termed as a nonstandard finite difference method if either we use a denominator function or a non-local approximation. In this work, these denominator functions are considered as

$$\begin{aligned} \zeta_1(\ell) &= \frac{e^{\mu_H \ell} - 1}{\mu_H}, \\ \zeta_2(\ell) &= \frac{e^{(\mu_H + \alpha_M + \nu_1)\ell} - 1}{\mu_H + \alpha_H + \nu}, \\ \zeta_3(\ell) &= \frac{e^{(\mu_H + \alpha_H)\ell} - 1}{\mu_H + \alpha_H + \nu}, \\ \zeta_4(\ell) &= \frac{e^{(\mu_H + \kappa\alpha_M + d\alpha_H + \nu_2)\ell} - 1}{\mu_H + \alpha_H + \nu}, \\ \zeta_V(\ell) &= \frac{e^{\mu_V \ell} - 1}{\mu_V}. \end{aligned}$$

After some simplifications, system (4.2.0.3.3) reads as

$$
\begin{aligned}
S_H^{k+1} &= \frac{S_H^k + \zeta_1(\ell)(\Lambda_H + \nu_1 I_M^k)}{1 + \zeta_1(\ell)(\lambda_H^k + \lambda_M^k + \mu_H)}, \\
I_M^{k+1} &= \frac{I_M^k + \zeta_2(\ell)\lambda_M^k S_H^{k+1}}{1 + \zeta_2(\ell)(\sigma\lambda_H^k + \mu_H + \alpha_M + \nu_1)}, \\
I_H^{k+1} &= \frac{I_H^k + \zeta_3(\ell)(\lambda_H^k S_H^{k+1} + \nu_2 I_{HM}^k)}{1 + \zeta_3(\ell)(\vartheta\lambda_M^k + \mu_H + \alpha_H)}, \\
I_{HM}^{k+1} &= \frac{I_{HM}^k + \zeta_4(\ell)(\sigma\lambda_H^k I_M^{k+1} + \vartheta\lambda_M^k I_H^{k+1})}{1 + \zeta_4(\ell)(\mu_H + \kappa\alpha_M + d\alpha_H + \nu_2)}, \\
S_V^{k+1} &= \frac{S_V^k + \zeta_V(\ell)\Lambda_V}{1 + \zeta_V(\ell)(\lambda_V^k + \mu_V)}, \\
I_V^{k+1} &= \frac{I_V^k + \zeta_V(\ell)\xi^{n,\bar{\tau}} \sum_{r=0}^{N_\tau - 1} \tau_r g(\tau_r) \lambda_V^{k-r} S_V^{k-r}}{1 + \zeta_V(\ell)\mu_V}.
\end{aligned}
\tag{4.2.0.3.4}
$$

The positivity of the solution reflects from the above method (4.2.0.3.4), because if the initial data ϕ_H, ψ_M, ψ_H, ψ_{HM}, ϕ_V and ψ_V are non-negative, then the right hand side of (4.2.0.3.4) admits no negative terms for any of $k = 0, 1, 2, 3, ...$

4.3 Analysis of the NSFDM

As in the case of the continuous model (3.3.1.0.3), before analyzing the dynamics of the full model (4.2.0.3.3), it is instructive to analyze the sub-models (HIV-only and Malaria-only). This is done below.

4.3.1 Analysis of HIV-only sub-model

The HIV-only discrete model is obtained by setting $I_M^k = I_{HM}^k = S_V^k = I_V^k = 0$ in (4.2.0.3.3), given by

$$\begin{aligned} \frac{S_H^{k+1} - S_H^k}{\zeta_1(\ell)} &= \Lambda_H - \lambda_H^k S_H^{k+1} - \mu_H S_H^{k+1}, \\ \frac{I_H^{k+1} - I_H^k}{\zeta_3(\ell)} &= \lambda_H^k S_H^{k+1} - (\mu_H + \alpha_H) I_H^{k+1}. \end{aligned} \tag{4.3.1.0.5}$$

Then after arrangement we have

$$\begin{aligned} S_H^{k+1} &= \frac{S_H^k + \zeta_1(\ell)\Lambda_H}{1 + \zeta_1(\ell)(\lambda_H^k + \mu_H)}, \\ I_H^{k+1} &= \frac{I_H^k + \zeta_3(\ell)\lambda_H^k S_H^{k+1}}{1 + \zeta_3(\ell)(\mu_H + \alpha_H)}, \end{aligned} \tag{4.3.1.0.6}$$

where $\lambda_H^k = \frac{\beta_H I_H^k}{N_H^k}$, with $N_H^k = S_H^k + I_H^k$.

The positivity of the solution reflects from the above method (4.3.1.0.6), because if the initial values $S(0)$ and $I(0)$ are non-negative, then the right hand side of (4.3.1.0.6) admits no negative terms for any of $k = 0, 1, 2, 3, ...$

In the following section we determine the stability properties of system (4.3.1.0.5), and we verify that

(i) the continuous and the discrete models have the same equilibria, and

(ii) both models possess similar qualitative features near these equilibria.

4.3.1.1 Fixed points and stability analysis

We study in this section the stability and convergence properties of the fixed points of the proposed NSFDM numerical method (4.3.1.0.5).

We begin by noting that the fixed points $(\hat{S}_H, \hat{I}_H)$ of system (4.2.0.3.3) can be found

by solving

$$\begin{aligned} F_H(\hat{S}_H, \hat{I}_H) &= \hat{S}_H, \\ G_H(\hat{S}_H, \hat{I}_H) &= \hat{I}_H, \end{aligned} \tag{4.3.1.1.1}$$

where F_H and G_H can be obtained by considering the right hand sides in (4.3.1.0.6), i.e.,

$$\begin{aligned} F_H(\hat{S}_H, \hat{I}_H) &= \frac{\hat{S}_H + \zeta_1(\ell)\Lambda_H}{1 + \zeta_1(\ell)(\hat{\lambda}_H + \mu_H)}, \\ G_H(\hat{S}_H, \hat{I}_H) &= \frac{\hat{I}_H + \zeta_3(\ell)\hat{\lambda}_H \hat{S}_H}{1 + \zeta_3(\ell)(\mu_H + \alpha_H)}, \end{aligned} \tag{4.3.1.1.2}$$

where $\hat{\lambda}_H = \frac{\beta_H \hat{I}_H}{\hat{S}_H + \hat{I}_H}$.

Solving (4.3.1.1.1), we obtain the following equation for $\hat{\lambda}_H$

$$\hat{\lambda}_H(\hat{\lambda}_H - (\mu_H + \alpha_H)(\mathcal{R}_H - 1)) = 0. \tag{4.3.1.1.3}$$

In the above equation, $\hat{\lambda}_H = 0$ corresponds to the disease free equilibrium

$$\hat{E}_0 = \left(\frac{\Lambda_H}{\mu_H}, 0\right), \tag{4.3.1.1.4}$$

whereas any endemic equilibrium is given by

$$\hat{E} = \left(\frac{\Lambda_H}{\mu_H \mathcal{R}_H + \alpha_H(\mathcal{R}_H - 1)}, \frac{\Lambda_H(\mathcal{R}_H - 1)}{\mu_H \mathcal{R}_H + \alpha_H(\mathcal{R}_H - 1)}\right). \tag{4.3.1.1.5}$$

Form the above expressions we deduce that both systems (3.3.2.0.4) and (4.3.1.0.5) have the same characteristic equation and expressions of equilibria. Hence, we have the following result.

Remark 4.3.1.1. The continuous system (3.3.2.0.4) and the discrete system (4.3.1.0.5)

have the same equilibria.

The next theorems give us the stability properties for the discrete system (4.3.1.0.5). Moreover, we will show that both systems (the discrete as well as the continuous) behave similarly near their equilibria.

Theorem 4.3.1.1. *Let $\psi_1(\ell)$ and $\psi_3(\ell)$ be a real-valued functions such that $\psi_1(\ell) = \ell + O(\ell^2)$ and $\psi_3(\ell) = \ell + O(\ell^2)$. If $\mathcal{R}_H < 1$, then system (4.3.1.0.5) is unconditionally (i.e., regardless of the step-size ℓ) locally asymptotically stable at the disease free equilibrium, $\hat{E}_0 = \left(\frac{\Lambda_H}{\mu_H}, 0\right)$, and unstable otherwise.*

Proof. The Jacobian matrix of the system (4.3.1.0.5) evaluated at the disease free equilibrium, $\hat{E}_0$, is

$$J(\hat{E}_0) = \begin{pmatrix} \frac{1}{1+\zeta_1(\ell)\mu_H} & -\frac{\zeta_1(\ell)\beta_H}{1+\zeta_1(\ell)\mu_H} \\ 0 & \frac{1+\zeta_3(\ell)\beta_H}{1+\zeta_3(\ell)(\mu_H+\alpha_H)} \end{pmatrix}.$$

Being a triangular matrix, its eigenvalues are the entries along the main diagonal, i.e.,

$$\lambda_1 = \frac{1}{1+\zeta_1(\ell)\mu_H},$$

$$\lambda_2 = \frac{1+\zeta_3(\ell)\beta_H}{1+\zeta_3(\ell)(\mu_H+\alpha_H)}.$$

It should be noted that the inequality $|\lambda_1| < 1$ always holds. However, $|\lambda_2| < 1$ if $\beta_H < (\mu_H + \alpha_H)$, i.e., if $(\mu_H + \alpha_H)(\mathcal{R}_H - 1) < 0$, which is always true since $\mathcal{R}_H < 1$ for the disease free equilibrium. Hence, the spectral radius is strictly less than unity in magnitude if $\mathcal{R}_H < 1$ for all ℓ, and then using Theorem 2.10 in [2], the required result is obtained. □

Theorem 4.3.1.2. *The endemic equilibrium of system (4.3.1.0.5), $\hat{E}$, is unconditionally locally asymptotically stable if $\mathcal{R}_H > 1$.*

Proof. The Jacobian matrix of the system (4.3.1.0.5) evaluated at the endemic equilibrium

$$\hat{E} = \left(\frac{\Lambda_H}{\mu_H \mathcal{R}_H + \alpha_H(\mathcal{R}_H - 1)}, \frac{\Lambda_H(\mathcal{R}_H - 1)}{\mu_H \mathcal{R}_H + \alpha_H(\mathcal{R}_H - 1)} \right),$$

is

$$J(\hat{E}) = \begin{pmatrix} J_1 & -J_2 \\ J_3 & J_4 \end{pmatrix},$$

where

$$\begin{aligned} J_1 &= \frac{\mathcal{R}_H + \zeta_1(\ell)(\mu_H + \alpha_H)(\mathcal{R}_H - 1)}{\mathcal{R}_H(1 + \zeta_1(\ell)\mu_H + \zeta_1(\ell)(\mu_H + \alpha_H)(\mathcal{R}_H - 1))}, \\ J_2 &= \frac{\zeta_1(\ell)(\mu_H + \alpha_H)}{\mathcal{R}_H(1 + \zeta_1(\ell)\mu_H + \zeta_1(\ell)(\mu_H + \alpha_H)(\mathcal{R}_H - 1))}, \\ J_3 &= \frac{\zeta_3(\ell)(\mu_H + \alpha_H)(\mathcal{R}_H - 1)^2}{\mathcal{R}_H \tilde{B}}, \\ J_4 &= \frac{\mathcal{R}_H + \zeta_3(\ell)(\mu_H + \alpha_H)}{\mathcal{R}_H \tilde{B}}. \end{aligned}$$

with $\tilde{B} = 1 + \zeta_3(\ell)(\mu_H + \alpha_H)$. Since we have $\mathcal{R}_H > 1$, it should be noted that $J_1, J_2, J_3, J_4 > 0$ with $J_1, J_4 < 1$.

From Theorem 2.10 in [2], the endemic equilibrium $\hat{E}$ of system (4.3.1.0.5) is locally asymptotically stable if the eigenvalues of the Jacobian matrix $J(\hat{E})$ satisfy $|\lambda_i| < 1$ which can happen iff

$$|Tr(J(\hat{E}))| < 1 + \det(J(\hat{E})) < 2, \tag{4.3.1.1.6}$$

where $Tr(J(\hat{E})) = J_1 + J_4 > 0$ and $\det(J(\hat{E})) = J_1 J_4 + J_2 J_3 > 0$. To verify this inequality, we must show that

(i) $Tr(J(\hat{E})) < 1 + \det(J(\hat{E}))$ or equivalently $1 - Tr(J(\hat{E})) + \det(J(\hat{E})) > 0$,

(ii) $-Tr(J(\hat{E})) < 1 + \det(J(\hat{E}))$ or equivalently $1 + Tr(J(\hat{E})) + \det(J(\hat{E})) > 0$,

(iii) $1 + \det(J(\hat{E})) < 2$ or equivalently $\det(J(\hat{E})) < 1$.

We have

$$\begin{aligned} 1 - Tr(J(\hat{E})) + \det(J(\hat{E})) &= 1 - (J_1 + J_4) + J_1J_4 + J_2J_3, \\ &= (1 - J_1)(1 - J_4) + J_2J_3, \\ &> 0, \end{aligned} \tag{4.3.1.1.7}$$

as both J_1 and J_4 less than unity. Also

$$1 + Tr(J(\hat{E})) + \det(J(\hat{E})) > 0, \tag{4.3.1.1.8}$$

since both $Tr(J(\hat{E}))$ and $\det(J(\hat{E}))$ are greater than zero. Moreover, we have

$$\begin{aligned} \det(J(\hat{E})) &= J_1J_4 + J_2J_3, \\ &= \frac{\mathcal{R}_H + \zeta_3(\ell)(\mu_H + \alpha_H) + \zeta_1(\ell)(\mu_H + \alpha_H)(\mathcal{R}_H - 1)\tilde{B}}{\mathcal{R}_H(1 + \zeta_1(\ell)\mu_H + \zeta_1(\ell)(\mu_H + \alpha_H)(\mathcal{R}_H - 1))\tilde{B}}, \\ &< \frac{\mathcal{R}_H(1 + \zeta_3(\ell)(\mu_H + \alpha_H) + \zeta_1(\ell)(\mu_H + \alpha_H)(\mathcal{R}_H - 1)\tilde{B})}{\mathcal{R}_H(1 + \zeta_1(\ell)\mu_H + \zeta_1(\ell)(\mu_H + \alpha_H)(\mathcal{R}_H - 1))\tilde{B}}, \\ &= \frac{(1 + \zeta_1(\ell)(\mu_H + \alpha_H)(\mathcal{R}_H - 1))\tilde{B}}{(1 + \zeta_1(\ell)\mu_H + \zeta_1(\ell)(\mu_H + \alpha_H)(\mathcal{R}_H - 1))\tilde{B}}, \\ &< 1, \end{aligned} \tag{4.3.1.1.9}$$

since we have $\mathcal{R}_H > 1$.

From (4.3.1.1.7), (4.3.1.1.8) and (4.3.1.1.9), the inequality (4.3.1.1.6) hold. Therefore, the eigenvalues of the associated Jacobian matrix in this case are strictly less than unity in modulus when $\mathcal{R}_H > 1$ for all step-sizes ℓ. Hence, the numerical method (4.3.1.0.5)

is unconditionally stable at its endemic equilibrium $\hat{E}$. □

Remark 4.3.1.2. From the results in this section, we can conclude that both models (the continuous system (3.3.2.0.4) as well as the discrete one (4.3.1.0.5)) have the same equilibria, and they behave qualitatively similar near these equilibria. Therefore, the nonstandard finite difference method (4.3.1.0.5) is elementary stable.

4.3.2 Analysis of malaria-only sub-model

The malaria-only discrete model is obtained by setting $I_H^k = I_{HM}^k = 0$ in (4.2.0.3.3), given by

$$\begin{aligned}
\frac{S_H^{k+1} - S_H^k}{\zeta_1(\ell)} &= \Lambda_H + \nu I_M^k - \lambda_M^k S_H^{k+1} - \mu_H S_H^{k+1}, \\
\frac{I_M^{k+1} - I_M^k}{\zeta_2(\ell)} &= \lambda_M^k S_H^{k+1} - (\mu_H + \alpha_H + \nu) I_M^{k+1}, \\
\frac{S_V^{k+1} - S_V^k}{\zeta_V(\ell)} &= \Lambda_V - \lambda_V^k S_V^{k+1} - \mu_V S_V^{k+1}, \\
\frac{I_V^{k+1} - I_V^k}{\zeta_V(\ell)} &= \xi^{n,\bar{\tau}} \sum_{r=0}^{N_\tau - 1} \tau_r g(\tau_r) \lambda_V^{k-r} S_V^{k-r} - \mu_V I_V^{k+1},
\end{aligned} \tag{4.3.2.0.10}$$

where r is the time needed by mosquitoes to become infectious (incubation period of the disease in the vector). The forces of infection λ_M^k and λ_V^k are the approximation of the forces of infection at the grid point t_k and are given by

$$\begin{aligned}
\lambda_M^k &= \frac{\beta_H \theta I_V^k}{S_H^k + I_M^k}, \\
\lambda_V^k &= \frac{\beta_V \theta I_M^k}{S_H^k + I_M^k},
\end{aligned}$$

with the initial condition

$$\begin{aligned} S_H^k &= S_H(t_k) = \phi_H(t_k) \geq 0, \\ I_M^k &= I_M(t_k) = \psi_M(t_k) \geq 0, \\ S_V^k &= S_V(t_k) = \phi_V(t_k) \geq 0, \\ I_V^k &= I_V(t_k) = \psi_V(t_k) \geq 0, \quad t_k \in [-\tau, 0]. \end{aligned}$$

After some simplifications, system (4.3.2.0.10) reads as

$$\begin{aligned} S_H^{k+1} &= \frac{S_H^k + \zeta_1(\ell)(\Lambda_H + \nu I_M^k)}{1 + \zeta_1(\ell)(\lambda_M^k + \mu_H)}, \\ I_M^{k+1} &= \frac{I_M^k + \zeta_2(\ell)\lambda_M^k S_H^{k+1}}{1 + \zeta_2(\ell)(\mu_H + \alpha_H + \nu)}, \\ S_V^{k+1} &= \frac{S_V^k + \zeta_V(\ell)\Lambda_V}{1 + \zeta_V(\ell)(\lambda_V^k + \mu_V)}, \\ I_V^{k+1} &= \frac{I_V^k + \zeta_V(\ell)\xi^{n,\bar{\tau}} \sum_{r=0}^{N_\tau - 1} \tau_r g(\tau_r) \lambda_V^{k-r} S_V^{k-r}}{1 + \zeta_V(\ell)\mu_V}. \end{aligned} \tag{4.3.2.0.11}$$

The positivity of the solution reflects from the above method (4.3.2.0.11), because if the initial data ϕ_H, ψ_M, ϕ_V and ψ_V are non-negative, then the right hand side of (4.3.2.0.11) admits no negative terms for any of $k = 0, 1, 2, 3, ...$

In the following section we determine the stability properties of system (4.3.2.0.10), and we verify that the continuous and the discrete models have the same equilibria.

4.3.2.1 Fixed points and stability analysis

In this section we present the stability and convergence properties of the fixed points of the proposed NSFDM (4.3.2.0.10).

We begin by noting that the fixed points $(\hat{S}_H, \hat{I}_M, \hat{S}_V, \hat{I}_V)$ of system (4.3.2.0.10) can

be found by solving

$$\begin{aligned} F_H(\hat{S}_H, \hat{I}_M, \hat{S}_V, \hat{I}_V) &= \hat{S}_H, \\ G_M(\hat{S}_H, \hat{I}_M, \hat{S}_V, \hat{I}_V) &= \hat{I}_M, \\ F_V(\hat{S}_H, \hat{I}_M, \hat{S}_V, \hat{I}_V) &= \hat{S}_V, \\ G_V(\hat{S}_H, \hat{I}_M, \hat{S}_V, \hat{I}_V) &= \hat{I}_V, \end{aligned} \tag{4.3.2.1.1}$$

where F_H, G_M, F_V and G_V can be obtained by considering the right hand sides in (4.3.2.0.11), i.e.,

$$\begin{aligned} F_H(\hat{S}_H, \hat{I}_M, \hat{S}_V, \hat{I}_V) &= \frac{\hat{S}_H + \zeta_1(\ell)(\Lambda_H + \nu \hat{I}_M)}{1 + \zeta_1(\ell)(\hat{\lambda}_M + \mu_H)}, \\ G_M(\hat{S}_H, \hat{I}_M, \hat{S}_V, \hat{I}_V) &= \frac{\hat{I}_M + \zeta_2(\ell)\hat{\lambda}_M \hat{S}_H}{1 + \zeta_2(\ell)(\mu_H + \alpha_H + \nu)}, \\ F_V(\hat{S}_H, \hat{I}_M, \hat{S}_V, \hat{I}_V) &= \frac{\hat{S}_V + \zeta_V(\ell)\hat{\Lambda}_V}{1 + \zeta_V(\ell)(\hat{\lambda}_V + \mu_V)}, \\ G_V(\hat{S}_H, \hat{I}_M, \hat{S}_V, \hat{I}_V) &= \frac{\hat{I}_V + \zeta_V(\ell)\xi^{n,\bar{\tau}}\hat{\lambda}_V \hat{S}_V}{1 + \zeta_V(\ell)\mu_V}, \end{aligned} \tag{4.3.2.1.2}$$

where

$$\begin{aligned} \hat{\lambda}_M &= \frac{\beta_H \theta \hat{I}_V}{\hat{S}_H + \hat{I}_M}, \\ \hat{\lambda}_V &= \frac{\beta_V \theta \hat{I}_M}{\hat{S}_H + \hat{I}_M}. \end{aligned}$$

Solving (4.3.2.1.2), we obtain the following equation for $\hat{\lambda}_M$

$$\hat{\lambda}_M(A(\hat{\lambda}_M)^2 + B\hat{\lambda}_M + \hat{C}) = 0, \tag{4.3.2.1.3}$$

where

$$\hat{A} = \Lambda_H \mu_V(\mu_V + \beta_V\theta),$$

$$\hat{B} = \frac{\Lambda_H \mu_V^2(\mu_H + \alpha_H + \nu)(\mu_H + \alpha_H)}{\mu_H}\left(\hat{K} - \mathcal{R}_0^{n,\bar{\tau}}\right), \tag{4.3.2.1.4}$$

$$\hat{C} = \Lambda_H \mu_V^2(\mu_H + \alpha_H + \nu)^2(1 - \mathcal{R}_0^{n,\bar{\tau}}),$$

with

$$\hat{K} = \frac{\mu_H(2\mu_V + \beta_V\theta)}{\mu_V(\mu_H + \alpha_H)}.$$

In the above equation, $\hat{\lambda}_M = 0$ corresponds to the disease free equilibrium

$$\hat{E}_0 = \left(\frac{\Lambda_H}{\mu_H}, 0, \frac{\Lambda_V}{\mu_V}, 0\right), \tag{4.3.2.1.5}$$

whereas any endemic equilibrium satisfy

$$\hat{A}(\hat{\lambda}_M)^2 + \hat{B}\hat{\lambda}_M + \hat{C} = 0. \tag{4.3.2.1.6}$$

We examine the quadratic (4.3.2.1.6) for possibility of multiple equilibria. From the expressions above, it is clear that $\hat{A}$ is always positive and $\hat{B}$ (resp. $\hat{C}$) is positive if and only if $\mathcal{R}_M < K$ (resp. < 1).

The form of the above equation is similar to the characteristic equation (4.3.2.1.6) for the continuous systems (3.3.3.0.6). Therefore, both systems (3.3.3.0.6) and (4.3.2.0.10) have the same characteristic equation and expressions of equilibria.

4.3.3 Analysis of the HIV-malaria full model

4.3.3.1 Fixed points and stability analysis

In this section we present the stability and convergence properties of the fixed points of the proposed NSFDM numerical method (4.2.0.3.3).

We begin by noting that the fixed points $(\hat{S}_H, \hat{I}_M, \hat{I}_H, \hat{I}_{HM}, \hat{S}_V, \hat{I}_V)$ of system (4.2.0.3.3) can be found by solving

$$\begin{aligned}
F_H(\hat{S}_H, \hat{I}_M, \hat{I}_H, \hat{I}_{HM}, \hat{S}_V, \hat{I}_V) &= \hat{S}_H, \\
G_M(\hat{S}_H, \hat{I}_M, \hat{I}_H, \hat{I}_{HM}, \hat{S}_V, \hat{I}_V) &= \hat{I}_M, \\
G_H(\hat{S}_H, \hat{I}_M, \hat{I}_H, \hat{I}_{HM}, \hat{S}_V, \hat{I}_V) &= \hat{I}_H, \\
G_{HM}(\hat{S}_H, \hat{I}_M, \hat{I}_H, \hat{I}_{HM}, \hat{S}_V, \hat{I}_V) &= \hat{I}_{HM}, \\
F_V(\hat{S}_H, \hat{I}_M, \hat{I}_H, \hat{I}_{HM}, \hat{S}_V, \hat{I}_V) &= \hat{S}_V, \\
G_V(\hat{S}_H, \hat{I}_M, \hat{I}_H, \hat{I}_{HM}, \hat{S}_V, \hat{I}_V) &= \hat{I}_V,
\end{aligned} \tag{4.3.3.1.1}$$

where F_H, G_M, G_H, G_{HM}, F_V and G_V can be obtained by considering the right hand

sides in (4.2.0.3.4), i.e.,

$$
\begin{aligned}
F_H &= \frac{\hat{S}_H + \zeta_1(\ell)(\Lambda_H + \nu_1 \hat{I}_M)}{1 + \zeta_1(\ell)(\hat{\lambda}_H + \hat{\lambda}_M + \mu_H)}, \\
G_M &= \frac{\hat{I}_M + \zeta_2(\ell)\hat{\lambda}_M \hat{S}_H}{1 + \zeta_2(\ell)(\sigma\hat{\lambda}_H + \mu_H + \alpha_M + \nu_1)}, \\
G_H &= \frac{\hat{I}_H + \zeta_3(\ell)(\hat{\lambda}_H \hat{S}_H + \nu_2 \hat{I}_{HM})}{1 + \zeta_3(\ell)(\vartheta\hat{\lambda}_M + \mu_H + \alpha_H)}, \\
G_{HM} &= \frac{\hat{I}_{HM} + \zeta_4(\ell)(\sigma\hat{\lambda}_H \hat{I}_M + \vartheta\hat{\lambda}_M \hat{I}_H)}{1 + \zeta_4(\ell)(\mu_H + \kappa\alpha_M + d\alpha_H + \nu_2)}, \\
F_V &= \frac{\hat{S}_V + \zeta_V(\ell)\Lambda_V}{1 + \zeta_V(\ell)(\hat{\lambda}_V + \mu_V)}, \\
G_V &= \frac{\hat{I}_V + \zeta_V(\ell)\xi^{n,\bar{\tau}} \sum_{r=0}^{N_\tau - 1} \tau_r g(\tau_r)\hat{\lambda}_V \hat{S}_V}{1 + \zeta_V(\ell)\mu_V},
\end{aligned}
\tag{4.3.3.1.2}
$$

with

$$
\begin{aligned}
\hat{\lambda}_H &= \frac{\beta_H(\hat{I}_H + \eta_{HM}\hat{I}_{HM})}{\hat{N}_H}, \\
\hat{\lambda}_M &= \frac{\beta_H \theta \hat{I}_V}{\hat{N}_H}, \\
\hat{\lambda}_V &= \frac{\beta_V \theta(\hat{I}_M + \eta_V \hat{I}_{HM})}{\hat{N}_H},
\end{aligned}
$$

or

$$\hat{S}_H = \frac{\Lambda_H(\sigma\hat{\lambda}_H + \mu_H + \alpha_M + \nu_1)}{(\hat{\lambda}_H + \mu_H)(\sigma\hat{\lambda}_H + \mu_H + \alpha_M + \nu_1) + \hat{\lambda}_M(\sigma\hat{\lambda}_H + \mu_H + \alpha_M)},$$

$$\hat{I}_M = \frac{\Lambda_H\hat{\lambda}_M}{(\hat{\lambda}_H + \mu_H)(\sigma\hat{\lambda}_H + \mu_H + \alpha_M + \nu_1) + \hat{\lambda}_M(\sigma\hat{\lambda}_H + \mu_H + \alpha_M)},$$

$$\hat{I}_H = \frac{\Lambda_H\hat{\lambda}_H((\mu_H + \kappa\alpha_M + \nu_2 + d\alpha_H)(\sigma\hat{\lambda}_H + \mu_H + \alpha_M + \nu_1) + \nu_2\sigma\hat{\lambda}_M)}{((\sigma\hat{\lambda}_H + \mu_H + \alpha_M)(\hat{\lambda}_H + \hat{\lambda}_M + \mu_H) + \nu_1(\hat{\lambda}_H + \mu_H))\hat{D}_1},$$

$$\hat{I}_{HM} = \frac{\Lambda_H\hat{\lambda}_H\hat{\lambda}_M(\sigma(\vartheta\hat{\lambda}_H + \mu_H + \alpha_H) + \vartheta(\sigma\hat{\lambda}_M + \mu_H + \alpha_M + \nu_1))}{((\sigma\hat{\lambda}_H + \mu_H + \alpha_M)(\hat{\lambda}_H + \hat{\lambda}_M + \mu_H) + \nu_1(\hat{\lambda}_H + \mu_H))\hat{D}_1}, \tag{4.3.3.1.3}$$

$$\hat{S}_V = \frac{\Lambda_V}{\mu_V + \hat{\lambda}_V},$$

$$\hat{I}_V = \frac{\xi^{n,\bar{\tau}}\Lambda_V\hat{\lambda}_V}{\mu_V(\mu_V + \hat{\lambda}_V)},$$

where

$$\hat{D}_1 = ((\vartheta\hat{\lambda}_M + \mu_H + \alpha_H)(\kappa\alpha_M + d\alpha_H + \mu_H) + \nu_2(\mu_H + \alpha_H))$$

and

$$\hat{\lambda}_V = \beta_V\theta(\hat{I}_M + \eta_V\hat{I}_{HM})/(\hat{S}_H + \hat{I}_M + \hat{I}_H + \hat{I}_{HM}).$$

Solving (4.3.3.1.1), we obtain the following equations for $\hat{\lambda}_H$ and $\hat{\lambda}_M$

$$\begin{aligned}\hat{F}(\hat{\lambda}_H, \hat{\lambda}_M) &= \hat{\lambda}_H[f_1(\hat{\lambda}_M)(\hat{\lambda}_H)^2 + f_2(\hat{\lambda}_M)\hat{\lambda}_H + f_3(\hat{\lambda}_M)],\\ G(\hat{\lambda}_H, \hat{\lambda}_M) &= \hat{\lambda}_M[g_1(\hat{\lambda}_H)(\hat{\lambda}_M)^4 + g_2(\hat{\lambda}_H)(\hat{\lambda}_M)^3 + g_3(\hat{\lambda}_H)(\hat{\lambda}_M)^2 + g_4(\hat{\lambda}_H)\hat{\lambda}_M + g_5(\hat{\lambda}_H)],\end{aligned} \tag{4.3.3.1.4}$$

where each of $\hat{f}_1$, $\hat{f}_2$ and $\hat{f}_3$ are polynomials of order two in $\hat{\lambda}_M$, and $\hat{g}_i$, $i = 1 \ldots 5$, are

polynomials of order four in $\hat{\lambda}_H$. Solutions of system (4.3.3.1.4) in closed form are not obtainable due to the high nonlinear terms involved.

In the above equations, $\hat{\lambda}_H = \hat{\lambda}_M = 0$ corresponds to the disease free equilibrium

$$\hat{E}_0 = \left(\frac{\Lambda_H}{\mu_H}, 0, 0, 0, \frac{\Lambda_V}{\mu_V}, 0\right). \tag{4.3.3.1.5}$$

The form of the equations (4.3.3.1.4) is similar to the characteristic equations (4.3.3.1.4) for the continuous systems (3.3.1.0.3). Therefore, both systems (3.3.1.0.3) and (4.2.0.3.3) have the same characteristic equation and expressions of equilibria.

4.4 Numerical simulations

The parameter values used in these simulations are taken from [106] and presented in Table 3.5.0.3.8.

The maximum errors (E_ℓ) at all grid points are evaluated using the formula

$$E_\ell = \max |x^k(\ell) - x^{2k}(\ell/2)|, \quad k = 0(1)N_t - 1, \tag{4.4.0.1.6}$$

where $x^k(\ell)$ is approximation to $x(t_k)$ with step size ℓ.

These errors are presented in Table 4.4.0.1.1. It should be noted that the integral term is solved using techniques based on FFT.

Table 4.4.0.1.1: Maximum errors obtained by NSFDM for the co-infection model

x	$\ell = 3.2$	$\ell = 1.6$	$\ell = 0.8$	$\ell = 0.4$	$\ell = 0.2$	$\ell = 0.1$
S_H	$2.754e-01$	$1.451e-01$	$7.440e-02$	$3.770e-02$	$1.900e-02$	$9.500e-03$
I_M	$1.648e-01$	$8.900e-02$	$4.620e-02$	$2.360e-02$	$1.200e-02$	$6.000e-03$
I_H	$2.313e-01$	$1.245e-01$	$6.430e-02$	$3.280e-02$	$1.650e-02$	$8.300e-03$
I_{HM}	$1.222e-01$	$6.790e-02$	$3.580e-02$	$1.850e-02$	$9.400e-03$	$4.700e-03$
S_V	$3.020e-01$	$2.660e-01$	$1.692e-01$	$1.000e-01$	$5.470e-02$	$2.870e-02$
I_V	$3.490e-01$	$1.736e-01$	$8.620e-02$	$4.300e-02$	$2.150e-02$	$1.070e-02$

4.5 Summary and discussion

In this chapter, we designed and analyzed a non-standard finite difference method to solve the co-infection model. We found that this method is unconditionally stable for the HIV-only sub-model. We note that in these two cases, the malaria-only sub-model and the full model, the methods have the same set of equilibria as the corresponding continuous models have. These non-standard finite difference methods posses a number of biologically significant properties.

In next chapter, we consider a special case of system (3.2.0.3.2) when $n = 1$ and study the model using the techniques from the singular perturbation theory.

Chapter 5

An HIV-malaria co-infection model and its reduction to a two-scale model using singular perturbation techniques

In this chapter, we consider a special case of system (3.2.0.3.2) when $n = 1$ and develop a two time-scale model. Then using the geometric singular perturbation techniques, we decouple it into fast (for malaria) and slow (for HIV) parts, which are analyzed separately (fast model in this chapter and slow model in next chapter). For the fast sub-model, we calculate the basic reproduction number and the equilibria. We find that the disease free equilibrium is normally hyperbolic when the basic reproduction number is less than unity and there exists a normal hyperbolic stable endemic equilibrium when the basic reproduction number is greater than unity. By using the geometric singular perturbation theory, we deduce the presence of the two slow manifolds each one of which is associated with the equilibria of the fast model.

5.1 Introduction

Geometric singular perturbation theory is a very effective reduction method based. This method eliminates the fast and stable dynamics and gives the equations describing the slow ones [40]. The complex structure of most of the mathematical models, like the HIV-malaria co-infection model that we are considering in this chapter can be grouped into a class of two time scales problems.

Using this geometric singular perturbation techniques, the associated model is approximated by two simple subsystems whose dimensions are much low. These are the fast (malaria) and the slow (HIV) models. We analyze each of them separately. For the fast sub-model, we calculate the basic reproduction number and the equilibria. We find that the disease free equilibrium is normally hyperbolic when the basic reproduction number is less than unity and there exists a normal hyperbolic stable endemic equilibrium when the basic reproduction number is greater than unity. This helps us in understanding the properties of the original system through the study behaviors of those two simplified subsystems.

The rest of the chapter is organized as follows. The model description is mentioned in Section 5.2. The two-time scales model is devolop in Section 5.3. The fast model is presented and analyze in Section 5.4. Section 5.5 is devoted for the summary of this chapter.

5.2 Description of the model

As special case of model (3.2.0.3.2), we consider $n = 1$ to obtain the following system

$$\begin{aligned}
\dot{S}_H &= \Lambda_H + \nu_1 I_M - \lambda_M S_H - \lambda_H S_H - \mu_H S_H, \\
\dot{I}_M &= \lambda_M S_H - \sigma\lambda_H I_M - (\mu_H + \alpha_M + \nu_1) I_M, \\
\dot{I}_H &= \lambda_H S_H + \nu_2 I_{HM} - \vartheta\lambda_M I_H - (\mu_H + \alpha_H) I_H, \\
\dot{I}_{HM} &= \sigma\lambda_H I_M + \vartheta\lambda_M I_H - (\mu_H + \kappa\alpha_M + d\alpha_H + \nu_2) I_{HM}, \\
\dot{S}_V &= \Lambda_V - \lambda_V S_V - \mu_V S_V, \\
\dot{E}_V &= \lambda_V S_V - (\gamma_V + \mu_V) E_V, \\
\dot{I}_V &= \gamma_V E_V - \mu_V I_V,
\end{aligned} \tag{5.2.0.1.1}$$

where the HIV, malaria host-to-vector and vector-to-host forces of infection are given by

$$\begin{aligned}
\lambda_H &= \frac{\beta_H (I_H + \eta_{HM} I_{HM})}{N_H}, \\
\lambda_M &= \frac{\beta_M \theta I_V}{N_H}, \\
\lambda_V &= \frac{\beta_V \theta (I_M + \eta_V I_{HM})}{N_H}.
\end{aligned}$$

The total population sizes N_H and N_V can be determined from the differential equations

$$\begin{aligned}
\dot{N}_H &= \Lambda_H - \mu_H N_H - \alpha_M I_M - \alpha_H I_H - (\kappa\alpha_M + d\alpha_H) I_{HM}, \\
\dot{N}_V &= \Lambda_V - \mu_V N_V.
\end{aligned}$$

To simplify the analysis, we scale the population sizes in each class by the total population sizes. Let

$$s_H = \tfrac{S_H}{N_H},\ i_M = \tfrac{I_M}{N_H},\ i_H = \tfrac{I_H}{N_H},\ i_{HM} = \tfrac{I_{HM}}{N_H},\ s_V = \tfrac{S_V}{N_V},\ e_V = \tfrac{E_V}{N_V}, \text{ and } i_V = \tfrac{I_V}{N_V}.$$

Then $s_H + i_M + i_H + i_{HM} = 1$ and $s_V + e_V + i_V = 1$. Let n_1 denotes the individuals who infected with HIV, that is $n_1 = i_H + i_{HM}$. Then $i_H = n_1 - i_{HM}$, $s_H = 1 - (i_M + n_1)$ and $s_V = 1 - (e_V + i_V)$. Knowing that the number of mosquitoes per human is almost constant [3], we consider $m = N_V/N_H$ and therefore the forces of infection becomes

$$\begin{aligned} \lambda_H &= \beta_H(n_1 + (\eta_{HM} - 1)i_{HM}), \\ \lambda_M &= \beta_M \theta\, m\, i_V, \\ \lambda_V &= \beta_V \theta(i_M + \eta_V i_{HM}). \end{aligned}$$

Differentiating with respect to time t and simplifying we obtain the following reduced system of differential equations

$$\begin{aligned} \frac{di_M}{dt} &= \lambda_M(1 - (n_1 + i_M)) \\ &\quad - \left[\sigma\lambda_H + \alpha_M + \nu_1 + \frac{\Lambda_H}{N_H} - \alpha_M i_M - (\kappa\alpha_M + (d-1)\alpha_H)i_{HM} - \alpha_H n_1\right] i_M, \\ \frac{di_{HM}}{dt} &= \sigma\lambda_H i_M + \vartheta\lambda_M(n_1 - i_{HM}) \\ &\quad - \left[\kappa\alpha_M + d\alpha_H + \nu_2 + \frac{\Lambda_H}{N_H} - \alpha_M i_M - (\kappa\alpha_M + (d-1)\alpha_H)i_{HM} - \alpha_H n_1\right] i_{HM}, \\ \frac{dn_1}{dt} &= \lambda_H(1 - (n_1 + i_M)) + \sigma\lambda_H i_M - (\kappa\alpha_M + (d-1)\alpha_H)i_{HM} \\ &\quad - \left[\alpha_H + \frac{\Lambda_H}{N_H} - \alpha_M i_M - (\kappa\alpha_M + (d-1)\alpha_H)i_{HM} - \alpha_H n_1\right] n_1, \\ \frac{dN_H}{dt} &= \Lambda_H - \alpha_M i_M N_H - (\kappa\alpha_M + (d-1)\alpha_H)i_{HM}N_H - \alpha_H n_1 N_H - \mu_H N_H, \\ \frac{de_V}{dt} &= \lambda_V(1 - (e_V + i_V)) - \left[\gamma_V + \frac{\Lambda_V}{N_V}\right] e_V, \\ \frac{di_V}{dt} &= \gamma_V e_V - \frac{\Lambda_V}{N_V} i_V, \\ \frac{dN_V}{dt} &= \Lambda_V - \mu_V N_V. \end{aligned} \tag{5.2.0.1.2}$$

We have the following feasible regions $\Gamma = \Gamma_H \times \Gamma_V$, where the model makes biological sense

$$\Gamma_H = \{(i_M, i_{HM}, n_1, N_H) \in \mathbb{R}^{+4} : i_M \geq 0, i_{HM} \geq 0, i_M + i_{HM} \leq 1, i_{HM} \leq n_1 \leq 1, N_H \leq \tfrac{\Lambda_H}{\mu_H}\Big\},$$

$$\Gamma_V = \Big\{(e_V, i_V, N_V) \in \mathbb{R}^{+3} : e_V \geq 0, i_V \geq 0, e_V + i_V \leq 1, N_V \leq \tfrac{\Lambda_V}{\mu_V}\Big\}.$$

The mosquito population is on a fast time scale relative to the dynamics of the human population. In next section, we use this difference in time scales to simplify our model by applying singular perturbation techniques to separate components into fast and slow parts, and analyze each of them separately.

5.3 A model with two-time scales

The HIV infection parameters (β_H, α_H), malaria-induced death rate (α_M) and demographic parameters (Λ_H, μ_H) are on the order of $years^{-1}$, and the parameters involved in the malaria model, i.e., β_M, β_V, θ, ν_1, ν_2, Λ_V,γ_V, μ_V are on the order of $days^{-1}$. So the following two time scales can be defined

- a fast time scale associated with the malaria infection, and represented by the fast time variable t (the original time).
- a slow time scale associated with the HIV infection and demographic actions, and represented by the slow time variable t_{HIV}.

We then define the ratio between these two time scales as

$$\epsilon = \frac{t_{HIV}}{t}.$$

If malaria epidemic in a community is much faster than the HIV epidemic, then the ratio ϵ becomes a small parameter ($0 < \epsilon \ll 1$).

Since the time scale of malaria disease is much faster than that of demographic actions and HIV infection, we can use these two different time scales to simplify the HIV-malaria co-infection model (5.2.0.1.2). We can scale time either by slow or fast dynamics.

The HIV-malaria co-infection (5.2.0.1.2) can be decomposed into two subsystems, i.e., a slow one consisting of the dynamics of an HIV infection, and a fast one describing malaria transmission. To achieve such a decomposition, we mainly follow the approach given in [41].

Let $\beta_H = \epsilon\tilde{\beta}_H$, $\alpha_H = \epsilon\tilde{\alpha}_H$, $\alpha_M = \epsilon\tilde{\alpha}_M$, $\Lambda_H = \epsilon\tilde{\Lambda}_H$ and $\mu_H = \epsilon\tilde{\mu}_H$, hence the force of infection associated with HIV infection becomes $\lambda_H = \epsilon\tilde{\lambda}_H$ where

$$\tilde{\lambda}_H = \tilde{\beta}_H(n_1 + (\eta_{HM} - 1)i_{HM}).$$

Then system (5.2.0.1.2) can be written in the form

$$\begin{aligned} \frac{dU_f}{dt} &= \Phi(U_f, U_s, \epsilon) = \Phi^0(U_f, U_s) + \epsilon\Phi^1(U_f, U_s), \\ \frac{dU_s}{dt} &= \Psi(U_f, U_s, \epsilon) = \Psi^0(U_f, U_s) + \epsilon\Psi^1(U_f, U_s), \end{aligned} \tag{5.3.0.1.3}$$

where

$$U_f = \begin{pmatrix} i_M \\ i_{HM} \\ e_V \\ i_V \\ N_V \end{pmatrix}, \quad U_s = \begin{pmatrix} n_1 \\ N_H \end{pmatrix},$$

$$\Phi^0(U_f, U_s) = \begin{pmatrix} \lambda_M(1 - (n_1 + i_M)) - \nu_1 i_M \\ \vartheta\lambda_M(n_1 - i_{HM}) - \nu_2 i_{HM} \\ \lambda_V(1 - (e_V + i_V)) - \left[\gamma_V + \frac{\Lambda_V}{N_V}\right] e_V \\ \gamma_V e_V - \frac{\Lambda_V}{N_V} i_V \\ \Lambda_V - \mu_V N_V \end{pmatrix},$$

$$\Phi^1(U_f, U_s) = \begin{pmatrix} -(\sigma\tilde{\lambda}_H + \tilde{\alpha}_M + \tilde{\Pi})i_M \\ \sigma\tilde{\lambda}_H i_M - (\kappa\tilde{\alpha}_M + d\tilde{\alpha}_H + \tilde{\Pi})i_{HM} \\ 0 \\ 0 \\ 0 \end{pmatrix}$$

and

$$\Psi^0(U_f, U_s) = \begin{pmatrix} 0 \\ 0 \end{pmatrix}, \quad \Psi^1(U_f, U_s) = \begin{pmatrix} \tilde{f}(U_f, U_s) - (\tilde{\alpha}_H + \tilde{\Pi})n_1 \\ (\tilde{\Pi} - \tilde{\mu}_H)N_H \end{pmatrix},$$

with

$$\begin{aligned} \tilde{\Pi} &= \frac{\tilde{\Lambda}_H}{N_H} - \tilde{\alpha}_M i_M - (\kappa\tilde{\alpha}_M + (d-1)\tilde{\alpha}_H)i_{HM} - \tilde{\alpha}_H n_1, \\ \tilde{f}(U_f, U_s) &= \tilde{\lambda}_H(1 - (n_1 + i_M)) + \sigma\tilde{\lambda}_H i_M - (\kappa\tilde{\alpha}_M + (d-1)\tilde{\alpha}_H)i_{HM}. \end{aligned}$$

In (5.3.0.1.3), the components of U_f (i_M ,i_{HM}, e_V, i_V and N_V) are fast variables and the components of U_s (n_1 and N_H) are slow variables, when ϵ is assumed to be sufficiently small.

With a change of time scale, $t_{HIV} = \epsilon\, t$ that is $\frac{d}{dt} \equiv \epsilon\frac{d}{dt_{HIV}}$, system (5.3.0.1.3) can be reformulated as:

$$\begin{aligned} \epsilon\frac{dU_f}{dt_{HIV}} &= \Phi(U_f, U_s, \epsilon) = \Phi^0(U_f, U_s) + \epsilon\Phi^1(U_f, U_s), \\ \frac{dU_s}{dt_{HIV}} &= \Psi(U_f, U_s, \epsilon) = \Psi^1(U_f, U_s). \end{aligned} \tag{5.3.0.1.4}$$

Thus (5.3.0.1.3) is called the fast system and (5.3.0.1.4) is called the slow system. Both systems are equivalent as long as $\epsilon \neq 0$ ([59]). Each of the scalings is naturally associated with a limit as $\epsilon \to 0$. These limits are respectively given by

$$\begin{aligned} \frac{dU_f}{dt} &= \Phi(U_f, U_s, 0) = \Phi^0(U_f, U_s), \\ \frac{dU_s}{dt} &= \Psi(U_f, U_s, 0) = \Psi^0(U_f, U_s) = 0, \end{aligned} \tag{5.3.0.1.5}$$

which is called the fast sub-system, and

$$\begin{aligned} 0 &= \Phi(U_f, U_s, 0) = \Phi^0(U_f, U_s), \\ \frac{dU_s}{dt_{HIV}} &= \Psi(U_f, U_s, 0) = \Psi^1(U_f, U_s). \end{aligned} \tag{5.3.0.1.6}$$

The latter is called the reduced system (see, e.g.,[59]). It is a differential algebraic system, that describes the evolution of the slow variable constrained to the set $\Phi(U_f, U_s, 0) = \Phi^0(U_f, U_s) = 0$. That set is exactly the set of critical points for (5.3.0.1.5).

Notice that under (5.3.0.1.5) the flow is defined in $\mathbb{R}^7$, but is in fact a two-parameter family of five-dimensional systems. Moreover, the flow under (5.3.0.1.5) on the two-dimensional set $\Phi(U_f, U_s, 0) = 0$ is trivial. On the other hand, (5.3.0.1.6) does prescribe a nontrivial flow on $\Phi(U_f, U_s, 0) = 0$, but at the same time its validity is limited to only this set ([59]). The essential idea behind the use of the Geometric singular perturbation is to deduce the behavior of the solution of the singular perturbation system (5.3.0.1.3) or (5.3.0.1.4) by combining the dynamics of the fast sub-system (5.3.0.1.5) and slow sub-system (5.3.0.1.6).

Suppose we are given an two-dimensional manifold M_0, which is contained in the set $\Phi(U_f, U_s, 0) = 0$. Suppose it is compact and normally hyperbolic, that is, the eigenvalues λ of the Jacobian $\frac{\partial \Phi(U_f, U_s, 0)}{\partial U_f}|_{M_0}$ are uniformly bounded away from the imaginary axis. Then this so-called critical manifold persists as a locally invariant slow manifold M_ϵ of the full problem (5.3.0.1.3) that is $O(\epsilon)$ close to M_0 [72]. The restriction of the flow (5.3.0.1.3) to M_ϵ is a small perturbation of the flow of the limiting problem (5.3.0.1.6). If

$$M_0 = \{(U_f, U_s) \in \mathbb{R}^7 | U_f = p_0(U_s)\},$$

then the perturbed manifold M_ϵ is described by a perturbation $p_\epsilon(U_s)$ of $p_0(U_s)$ as

$$M_\epsilon = \{(U_f, U_s) \in \mathbb{R}^7 | U_f = p_\epsilon(U_s)\}.$$

Substituting this into the slow model (5.3.0.1.4), one can see that the flow on M_ϵ is given by

$$\frac{dU_s}{dt_{HIV}} = \Psi(p_\epsilon(U_s), U_s, \epsilon). \tag{5.3.0.1.7}$$

Now, first we study the dynamics of the fast-sub system (5.3.0.1.5) and calculate that critical manifold M_0. Depending on the structure of M_0 we use the geometric singular perturbation theory to ensure the persistence of the slow manifold M_ϵ and describe the dynamics on M_ϵ. In next section we will give a full analysis of the fast sub-system.

5.4 Fast dynamics of malaria

The fast dynamics at the disease scale are given by (5.3.0.1.3) when taking $\epsilon = 0$, which describes the fast dynamics of malaria, that is

$$\frac{dU_f}{dt} = \Phi^0(U_f, U_s), \tag{5.4.0.1.8}$$

with $U_s \geq 0$ is a constant vector. System (5.4.0.1.8) is equivalent to the following system

$$\begin{aligned}
\frac{di_M}{dt} &= \lambda_M(1 - (n_1 + i_M) - \nu_1 i_M, \\
\frac{di_{HM}}{dt} &= \vartheta\lambda_M(n_1 - i_{HM}) - \nu_2 i_{HM}, \\
\frac{de_V}{dt} &= \lambda_V(1 - (e_V + i_V)) - \left[\gamma_V + \frac{\Lambda_V}{N_V}\right] e_V, \\
\frac{di_V}{dt} &= \gamma_V e_V - \frac{\Lambda_V}{N_V} i_V, \\
\frac{dN_V}{dt} &= \Lambda_V - \mu_V N_V,
\end{aligned} \tag{5.4.0.1.9}$$

where

$$\begin{aligned}\lambda_M &= \beta_M \theta\, m\, i_V,\\ \lambda_V &= \beta_V \theta (i_M + \eta_V i_{HM}),\end{aligned}$$

In the above n_1 is considered as a fixed parameter, satisfying $i_{HM} \leq n_1 \leq 1$.

5.4.1 Analysis of the fast dynamics of malaria

In this section we study the well-posedness, feasibility, stability and bifurcation of the malaria model (5.4.0.1.9).

Proposition 5.4.1. *If the initial condition is non-negative then the corresponding solution $(i_M(t), i_{HM}(t), e_V(t), i_V(t), N_V(t))$ of model (5.4.0.1.9) is non-negative for all $t > 0$.*
Moreover,

$$\begin{aligned}&\lim_{t\to\infty} i_{HM}(t) \leq n_1, \quad \lim_{t\to\infty} (i_M(t) + i_{HM}(t)) \leq 1,\\ &\lim_{t\to\infty} (e_V(t) + i_V(t)) \leq 1 \text{ and } \lim_{t\to\infty} N_V(t) = \frac{\Lambda_V}{\mu_V}.\end{aligned} \tag{5.4.1.0.10}$$

Furthermore, we have the following invariance properties:

i. *If $i_{HM}(0) \leq n_1$ then $i_{HM}(t) \leq n_1$.*

ii. *If $(i_M(0) + i_{HM}(0)) \leq 1$ then $(i_M(t) + i_{HM}(t)) \leq 1$.*

iii. *If $(e_V(0) + i_V(0)) \leq 1$ then $(e_V(t) + i_V(t)) \leq 1$.*

iv. *If $N_V(0) \leq \frac{\Lambda_V}{\mu_V}$ then $N_V(t) \leq \frac{\Lambda_V}{\mu_V}$.*

In particular, the regions $\mathfrak{D} = \mathfrak{D}_H \times \mathfrak{D}_V$ *with*

$$\begin{aligned}\mathfrak{D}_H &= \left\{(i_M, i_{HM}) \in \mathbb{R}^{+2} : i_M \geq 0, 0 \leq i_{HM} \leq n_1, i_M + i_{HM} \leq 1\right\},\\ \mathfrak{D}_V &= \left\{(e_V, i_V, N_V) \in \mathbb{R}^{+3} : e_V \geq 0, i_V \geq 0, e_V + i_V \leq 1, N_V \leq \frac{\Lambda_V}{\mu_V}\right\},\end{aligned}$$

is positively-invariant.

Proof. Denote by t_{max} the upper bound of the maximum interval of existence corresponding to $(i_M(t), i_{HM}(t), e_V(t), i_V(t), N_V(t))$. To show that the solution is positive and bounded in $[0, +\infty[$, it is sufficient to show the positivity and boundedness results in $[0, t_{max}[$.

Let

$$t_1 = \sup\{0 \leq t < t_{max} : i_M, i_{HM}, e_V, i_V \text{ and } N_V, \text{ are positive on } [0, t]\}.$$

Since $i_M(0)$, $i_{HM}(0)$, $e_V(0)$, $i_V(0)$ and $N_V(0)$ are non-negative then $t_1 > 0$. If $t_1 < t_{max}$ then, by using the variation of constants formula to the first equation of system (5.4.0.1.9), we have

$$i_M(t_1) = i_M(0)e^{-\nu_1 t_1 - \int_0^{t_1} \lambda_M(v)dv} + \int_0^{t_1} e^{-\nu_1(t_1-u) - \int_u^{t_1} \lambda_M(v)dv}(\lambda_M(u)(1-n_1))du > 0.$$

It can be shown in the same manner that the other variables are also positive at t_1. This contradicts the fact that t_1 is the supremum because at least one of the variables should be equal to zero at t_1. Therefore $t_1 = t_{max}$ and the solution is positive on its maximal interval of existence $[0, t_{max}[$.

Next, we show that the solution is bounded on $[0, t_{max}[$. From the last equation of (5.4.0.1.9) we obtain

$$0 < N_V(t) = N_V(0)e^{-\mu_V t} + \tfrac{\Lambda_V}{\mu_V}\left(1 - e^{-\mu_V t}\right). \qquad (5.4.1.0.11)$$

Therefore $N_V(t)$ is bounded on $[0, t_{max}[$.

The positivity of the solution also implies that

$$\begin{aligned}
\frac{di_M}{dt} &\leq \lambda_M(1-(n_1+i_M) \leq \vartheta\lambda_M(1-(n_1+i_M),\\
\frac{di_{HM}}{dt} &\leq \vartheta\lambda_M(n_1-i_{HM}),\\
\frac{de_V}{dt} &\leq \lambda_V(1-(e_V+i_V))-\gamma_V e_V,\\
\frac{di_V}{dt} &\leq \gamma_V e_V.
\end{aligned} \tag{5.4.1.0.12}$$

By adding the first two equations of (5.4.1.0.12) together and also adding the last two equation of (5.4.1.0.12) together, we have

$$\begin{aligned}
\frac{di_M}{dt}+\frac{di_{HM}}{dt} &\leq \vartheta\lambda_M(1-(i_M+i_{HM})),\\
\frac{de_V}{dt}+\frac{di_V}{dt} &\leq \lambda_V(1-(e_V+i_V)).
\end{aligned} \tag{5.4.1.0.13}$$

By using a standard comparison theorem [14], the second equation of (5.4.1.0.12) gives

$$\begin{aligned}
0 \leq i_{HM}(t) &\leq n_1 e^{-\int_0^t \vartheta\lambda_M(v)dv}\int_0^t e^{\int_0^u \vartheta\lambda_M(v)dv}\vartheta\lambda_M(u)du + Ce^{-\int_0^t \vartheta\lambda_M(v)dv},\ C \text{ const}\\
&= n_1 e^{-\int_0^t \vartheta\lambda_M(v)dv}e^{\int_0^t \vartheta\lambda_M(v)dv} + Ce^{-\int_0^t \vartheta\lambda_M(v)dv},\\
&= n_1 + Ce^{-\int_0^t \vartheta\lambda_M(v)dv},\\
&= i_{HM}(0)e^{-\int_0^t \vartheta\lambda_M(v)dv} + n_1 - n_1 e^{-\int_0^t \vartheta\lambda_M(v)dv}.
\end{aligned} \tag{5.4.1.0.14}$$

Similarly from the first equation of (5.4.1.0.13), we obtain

$$0 \leq (i_M(t) + i_{HM}(t)) \leq (i_M(0) + i_{HM}(0))e^{-\int_0^t \vartheta\lambda_M(v)dv} + 1 - e^{-\int_0^t \vartheta\lambda_M(v)dv}. \tag{5.4.1.0.15}$$

Thus $(i_M(t) + i_{HM}(t))$ is also bounded $[0, t_{max}[$. Moreover from the last equation of (5.4.1.0.13) we obtain

$$0 \leq (e_V(t) + i_V(t)) \leq (e_V(0) + i_V(0))e^{-\int_0^t \lambda_V(v)dv} + 1 - e^{-\int_0^t \lambda_V(v)dv}. \tag{5.4.1.0.16}$$

Therefore $(i_V(t) + i_V(t))$ is also bounded $[0, t_{max}[$. Hence $t_{max} = \infty$ which proves the global existence and the positivity results.

Concerning the invariance properties, it is easy to obtain from (5.4.1.0.11) that if $N_V(0) \leq \Lambda_V/\mu_V$ then $0 \leq N_V(t) \leq \Lambda_V/\mu_V$. Also, if $i_{HM}(0) \leq n_1$ then from (5.4.1.0.14) we obtain $i_{HM}(t) \leq n_1$. Similarly, from (5.4.1.0.15) and (5.4.1.0.16) we obtain that if $(i_M(0) + i_{HM}(0)) \leq 1$ and $(e_V(0) + i_V(0)) \leq 1$ then $(i_M(t) + i_{HM}(t)) \leq 1$ and $0 \leq (e_V(t) + i_V(t)) \leq 1$, respectively. This establishes the invariance of the regions as required. The results (5.4.1.0.10) follow immediately from (5.4.1.0.11), (5.4.1.0.14) (5.4.1.0.15) and (5.4.1.0.16). □

In the view of Proposition 5.4.1 above, we conclude that system (5.4.0.1.9) is epidemiologically feasible and mathematically well-posed in $\mathfrak{D}$.

5.4.1.1 Basic reproduction number

The disease free equilibria (DFE) of system (5.4.0.1.9) is given by

$$\mathsf{E}^0 = \Big(0, 0, 0, 0, \tfrac{\Lambda_V}{\mu_V}\Big).$$

The stability of the DFE be investigated using the next generation operator [140]. We verify that system (5.4.0.1.9) satisfy the conditions (A1)-(A5) in [140].

Firstly, we note that system (5.4.0.1.9) is in the order that the first 4 compartments correspond to infected individuals. Let $x = (i_M, i_{HM}, e_V, i_V, N_V)^t = (x_1, x_2, x_3, x_4, x_5)^t$,

with each $x_i \geq 0$, be the number of individuals in each compartment. Then model (5.4.0.1.9) can be written as

$$\begin{aligned}
\frac{dx_1}{dt} &= \beta_M \theta m x_4(1-(n_1+x_1)) - \nu_1 x_1, \\
\frac{dx_2}{dt} &= \vartheta \beta_M \theta m x_4(n_1 - x_2) - \nu_2 x_2, \\
\frac{dx_3}{dt} &= \beta_V \theta(x_1 + \eta_V x_2)(1-(x_3+x_4)) - \gamma_V x_3 - \frac{\Lambda_V}{x_5} x_3, \\
\frac{dx_4}{dt} &= \gamma_V x_3 - \frac{\Lambda_V}{x_5} x_4, \\
\frac{dx_5}{dt} &= \Lambda_V - \mu_V x_5.
\end{aligned} \tag{5.4.1.1.1}$$

Define X_s to be the set of all disease free states. That is

$$X_s = \{x \geq 0 \mid x_i = 0, i = 1, \ldots, 4\} = \left\{ \left(0, 0, 0, 0, \frac{\Lambda_V}{\mu_V}\right)^t \right\}.$$

Also system (5.4.1.1.1) can be written in the form

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

where $\mathcal{F}(x)$ and $\mathcal{V}(x) = \mathcal{V}^-(x) - \mathcal{V}^+(x)$ are all non-negative, (since each function represents a directed transfer of individuals), and given by

$$\mathcal{F}(x) = \begin{pmatrix} \beta_M \theta m x_4(1-(n_1+x_1)) \\ \vartheta \beta_M \theta m x_4(n_1 - x_2) \\ \beta_V \theta(x_1 + \eta_V x_2)(1-(x_3+x_4)) \\ 0 \\ 0 \end{pmatrix},$$

$$\mathcal{V}^+(x) = \begin{pmatrix} 0 \\ 0 \\ 0 \\ \gamma_V x_3 \\ \Lambda_V \end{pmatrix} \quad \text{and} \quad \mathcal{V}^-(x) = \begin{pmatrix} \nu_1 x_1 \\ \nu_2 x_2 \\ \gamma_V x_3 + \frac{\Lambda_V}{x_5} x_3 \\ \frac{\Lambda_V}{x_5} x_4 \\ \mu_V x_5 \end{pmatrix}.$$

From the above functions we found that:

(A1) if $x \geq 0$ (provided that $x_i \leq 1$, $i = 1, \ldots, 5$, $x_2 \leq n_1$ and $x_5 > 0$), then $\mathcal{F}_i(x), \mathcal{V}_i^+(x), \mathcal{V}_i^-(x) \geq 0$ for $i = 1, \ldots, 5$,

(A2) if $x_i = 0$, then $\mathcal{V}_i^-(x) = 0$. In particular, if $x \in X_s$ then $\mathcal{V}_i^-(x) = 0$ for $i = 1, \ldots, 4$,

(A3) $\mathcal{F}_i(x) = 0$ for $i > 4$,

(A4) if $x \in X_s$ then $\mathcal{F}_i(x) = 0$ and $\mathcal{V}_i^+(x) = 0$ for $i = 1, \ldots, 4$,

(A5) if $\mathcal{F}(x) = 0$, then the Jacobian matrix of system (5.4.1.1.1) is given by

$$Df(x_0) = \begin{pmatrix} -\nu_1 & 0 & 0 & 0 & 0 \\ 0 & -\nu_2 & 0 & 0 & 0 \\ 0 & 0 & -(\mu_V + \gamma_V) & 0 & 0 \\ 0 & 0 & \gamma_V & -\mu_V & 0 \\ 0 & 0 & 0 & 0 & -\mu_V \end{pmatrix}. \tag{5.4.1.1.2}$$

The eigenvalues of $Df(x_0)$ are

$$-\nu_1, -\nu_2, -(\mu_V + \gamma_V) \text{ and } -\mu_V \text{ (of multiplicity two)}.$$

Hence all eigenvalues of $Df(x_0)$ have negative real parts.

The matrices $\mathbf{F}$ and $\mathbf{V}$, for the new infection terms and the remaining transfer terms are, respectively, given by

$$\mathbf{F} = \begin{pmatrix} 0 & 0 & 0 & \beta_M \theta\, m\,(1-n_1) \\ 0 & 0 & 0 & \vartheta \beta_M \theta\, m\, n_1 \\ \beta_V \theta & \eta_V \beta_V \theta & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

and

$$\mathbf{V} = \begin{pmatrix} \nu_1 & 0 & 0 & 0 \\ 0 & \nu_2 & 0 & 0 \\ 0 & 0 & \mu_V + \gamma_V & 0 \\ 0 & 0 & -\gamma_V & \mu_V \end{pmatrix}.$$

$\mathbf{F}$ is a nonnegative matrix ($\mathbf{F} \geq 0$ entrywise) and $\mathbf{V}$ is a nonsingular M-matrix ($\mathbf{V}$ has the Z sign pattern ($\mathbf{V}_{ij} \leq 0$ for all $i \neq j$) and $s(\mathbf{V}) > 0$ (s($\mathbf{V}$) is the maximum real part of the eigenvalues of $\mathbf{V}$ (the spectral abscissa)), (The eigenvalues of $\mathbf{V}$ are μ_V, $(\mu_V + \gamma_V)$, ν_1 and ν_2) [140]. Hence the reproductive number, $\mathcal{R}_M$, is equal to the spectral radius of the *next generation operator* $\mathbf{FV}^{-1}$ [140]. The eigenvalues of $\mathbf{FV^{-1}}$ are

$$0 \text{ (of multiplicity two) and } \pm\sqrt{\mathcal{R}_M^0(1-n_1) + \mathcal{R}_M^1 n_1},$$

where

$$\mathcal{R}_M^0 = \frac{\beta_M \beta_V \theta^2 m \gamma_V}{\mu_V(\gamma_V + \mu_V)\nu_1},$$

$$\mathcal{R}_M^1 = \frac{\beta_M \beta_V \theta^2 m \gamma_V \vartheta \eta_V}{\mu_V(\gamma_V + \mu_V)\nu_2}.$$

The spectral radius of FV^{-1} is given by

$$\rho(\mathbf{FV^{-1}}) = \sqrt{\mathcal{R}_M^0(1-n_1) + \mathcal{R}_M^1 n_1}.$$

As in Chapter 2, we consider $\mathcal{R}_M$ to be the squared value of $\rho(\mathbf{FV^{-1}})$, i.e.,

$$\mathcal{R}_M = \mathcal{R}_M^0(1-n_1) + \mathcal{R}_M^1 n_1 \ .$$

Note that The basic reproduction number is the expected number of secondary cases produced, in a completely susceptible population, by a typical infective individual [36]. So, $\mathcal{R}_M^0(1-n_1)$, is the expected number of secondary infections that one infectious individual with malaria-only would create over the duration of the infectious period provided that all other members of both populations are susceptible. While $\mathcal{R}_M^1 n_1$, is the expected number of secondary infections that one infectious individual with dual infection with HIV and malaria would create over the duration of the infectious period provided that all other members of both populations are susceptible.

Since $\vartheta\nu_1\eta_V > \nu_2$, we have $\mathcal{R}_M^0 < \mathcal{R}_M^1$, hence $\mathcal{R}_M$ is increasing with respect to n_1 (see figure 5.4.1.1.1 below). Therefore $\mathcal{R}_M^0 < \mathcal{R}_M < \mathcal{R}_M^1$.

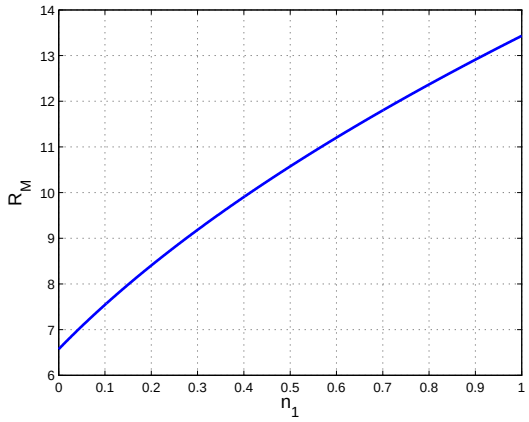

Figure 5.4.1.1.1: Profile of $\mathcal{R}_M$ as a function of n_1. Parameter values are taken from Table 3.5.0.3.8 with $\beta_V = 0.2$, $\beta_M = 0.8333$, $\theta = 0.5$, $\mu_V = 0.1429$ and for various values of n_1.

5.4.1.2 Stability of the disease-free equilibrium

Using Theorem 2 in [140], the following results are established.

Theorem 5.4.1.1. *The DFE of model (5.4.0.1.9) is locally-asymptotically stable if* $\mathcal{R}_M < 1$, *and unstable if* $\mathcal{R}_M > 1$.

Theorem 5.4.1.2. *The DFE of model (5.4.0.1.9) is globally-asymptotically stable if* $\mathcal{R}_M < 1$.

Proof. We verify that the conditions (H1) and (H2) as in [20] are satisfied:

First, we can rewrite our system (5.4.0.1.9) using the notation in [20] as

$$\begin{aligned} \frac{dX}{dt} &= F(X, Z), \\ \frac{dZ}{dt} &= G(X, Z), \quad G(X, 0) = 0, \end{aligned}$$

where

$$\begin{aligned} X &= (N_V), \\ Z &= (i_M, i_{HM}, e_V, i_V). \end{aligned}$$

The conditions (H1) and (H2) below must be met to guarantee local asymptotic stability.

(H1) For $\frac{dX}{dt} = F(X,0)$, X^* is globally asymptotically stable,

(H2) $G(X,Z) = AZ - \hat{G}(X,Z)$, $\hat{G}(X,Z) \geq 0$ for $(X,Z) \in \Omega$.

where $A = D_Z G(X^*, 0)$ is an M-matrix (the off diagonal elements of A are nonnegative) and Ω is the region where the model makes biological sense.
$F(X,0) = (\Lambda_V - \mu_V N_V)^T$,

$$A = \begin{pmatrix} -\nu_1 & 0 & 0 & \beta_M \theta\, m\,(1-n_1) \\ 0 & -\nu_2 & 0 & \vartheta \beta_M \theta\, m\, n_1 \\ \beta_V \theta & \eta_V \beta_V \theta & -(\mu_V + \gamma_V) & 0 \\ 0 & 0 & \gamma_V & -\mu_V \end{pmatrix}$$

and

$$\hat{G}(X,Z) = \begin{pmatrix} \beta_M \theta\, m\, i_V i_M \\ \vartheta \beta_M \theta\, m\, i_V i_{HM} \\ \beta_V \theta (i_M + \eta_V i_{HM})(e_V + i_V) + \frac{\mu_V e_V}{N_V}\left(\frac{\Lambda_V}{\mu_V} - N_V\right) \\ \frac{\mu_V i_V}{N_V}\left(\frac{\Lambda_V}{\mu_V} - N_V\right) \end{pmatrix}.$$

Notice that $\hat{G}(X,Z) \geq 0$ in $\mathfrak{D}$.

Then, from Theorem 1.4.0.3, we deduce that the DFE of model (5.4.0.1.9) is globally-asymptotically stable if $\mathcal{R}_M < 1$. □

Remark 5.4.1.1. The DFE of system (5.4.0.1.9) is normally hyperbolic for $\mathcal{R}_M < 1$.

The Jacobian matrix of the linearized system of (5.4.0.1.9) around E^0 is given by

$$J = \begin{pmatrix} -\nu_1 & 0 & 0 & \beta_M \theta\, m\,(1-n_1) & 0 \\ 0 & -\nu_2 & 0 & \vartheta \beta_M \theta\, m\, n_1 & 0 \\ \beta_V \theta & \eta_V \beta_V \theta & -(\mu_V + \gamma_V) & 0 & 0 \\ 0 & 0 & \gamma_V & -\mu_V & 0 \\ 0 & 0 & 0 & 0 & -\mu_V \end{pmatrix}. \tag{5.4.1.2.1}$$

The eigenvalues of J are $-\mu_V$ and the roots of

$$\lambda^4 + H_1\lambda^3 + H_2\lambda^2 + H_3\lambda + H_4 = 0, \tag{5.4.1.2.2}$$

where

$$\begin{aligned} H_1 &= 2\mu_V + \gamma_V + \nu_1 + \nu_2, \\ H_2 &= (2\mu_V + \gamma_V)(\nu_1 + \nu_2) + \mu_V(\mu_V + \gamma_V) + \nu_1\nu_2, \\ H_3 &= \nu_1\nu_2(2\mu_V + \gamma_V) + \mu_V(\mu_V + \gamma_V)(\nu_1(1 - \mathcal{R}_M^0(1-n_1)) + \nu_2(1 - \mathcal{R}_M^1 n_1)), \\ H_4 &= \nu_1\nu_2\mu_V(\mu_V + \gamma_V)(1 - \mathcal{R}_M). \end{aligned}$$

It is clear that $\lambda = 0$ is not a root of (5.4.1.2.2) when $\mathcal{R}_M \neq 0$, that is the linearized system of (5.4.0.1.9) around the DFE will behave in a similar way to the non-linear system (5.4.0.1.9) near the DFE. Thus we conclude that the DFE is normally hyperbolic.

5.4.1.3 Existence and stability of the endemic equilibrium

The steady states of (5.4.0.1.9) are determined by solving

$$\begin{aligned} i_M^* &= \frac{\lambda_M^*}{\nu_1 + \lambda_M^*}(1 - n_1), \\ i_{HM}^* &= \frac{\vartheta \lambda_M^*}{\nu_2 + \vartheta \lambda_M^*} n_1, \\ e_V^* &= \frac{\mu_V \lambda_V^*}{(\mu_V + \gamma_V)(\mu_V + \lambda_V^*)}, \\ i_V^* &= \frac{\gamma_V \lambda_V^*}{(\mu_V + \gamma_V)(\mu_V + \lambda_V^*)}, \\ N_V^* &= \frac{\Lambda_V}{\mu_V}, \end{aligned} \tag{5.4.1.3.1}$$

where $\lambda_V^* = \beta_V \theta (i_M^* + \eta_V i_{HM}^*)$ and $\lambda_M^* = \beta_M \theta \, m \, i_V^*$.

Thus

$$\lambda_M^* (A(\lambda_M^*)^2 + B\lambda_M^* + C) = 0, \tag{5.4.1.3.2}$$

where

$$\begin{aligned} A &= \vartheta(\mu_V + \beta_V \theta((1 - n_1) + \eta_V n_1)), \\ B &= \beta_V \theta(\nu_2(1 - n_1) + \vartheta \nu_1 \eta_V n_1) + \vartheta \mu_V \nu_1 (1 - \mathcal{R}_M^0 (1 - n_1)) \\ &\quad + \mu_V \nu_2 (1 - \mathcal{R}_M^1 n_1), \\ C &= \mu_V \nu_1 \nu_2 (1 - \mathcal{R}_M). \end{aligned} \tag{5.4.1.3.3}$$

The root $\lambda_H^* = 0$ of (5.4.1.3.2) corresponds to the DFE (E^0) and the positive roots of the quadratic equation

$$A(\lambda_M^*)^2 + B\lambda_M^* + C = 0. \tag{5.4.1.3.4}$$

We examine the quadratic (5.4.1.3.4) for possibility of existence of positive endemic equilibria. From the expressions above, it is clear that A is always positive and C is

positive if and only if $\mathcal{R}_M < 1$. Note that also $B > 0$ for $\mathcal{R}_M < 1$ which implies that Eq. (5.4.1.3.4) has no positive solution when $\mathcal{R}_M < 1$. When $\mathcal{R}_M > 1$, $C < 0$ which implies that Eq. (5.4.1.3.4) has one positive solution. We therefore established the following result.

Lemma 5.4.1.1. *When $\mathcal{R}_M > 1$, the malaria model (5.4.0.1.9) has precisely one positive endemic equilibrium $\mathsf{E}^* = (i_M^*, i_{HM}^*, e_V^*, i_V^*, N_V^*)$, where i_M^*, i_{HM}^*, e_V^*, i_V^* and N_V^* are given by (5.4.1.3.1), with $\lambda_V^* = \beta_V\theta(i_M^* + \eta_V i_{HM}^*)$ and λ_M^* is the positive solution of Eq. (5.4.1.3.4).*

To study the stability of the endemic equilibrium of system (5.4.0.1.9), let $n_{VI} = e_V + i_V$ then $e_V = n_{VI} - i_V$ and system (5.4.0.1.9) becomes

$$\frac{di_M}{dt} = \lambda_M(1 - (n_1 + i_M) - \nu_1 i_M,$$

$$\frac{di_{HM}}{dt} = \vartheta\lambda_M(n_1 - i_{HM}) - \nu_2 i_{HM},$$

$$\frac{dn_{VI}}{dt} = \lambda_V(1 - n_{VI}) - \frac{\Lambda_V}{N_V}n_{VI}, \tag{5.4.1.3.5}$$

$$\frac{di_V}{dt} = \gamma_V(n_{VI} - i_V) - \frac{\Lambda_V}{N_V}i_V,$$

$$\frac{dN_V}{dt} = \Lambda_V - \mu_V N_V.$$

It should be noted that, if $(i_M^*, i_{HM}^*, n_{VI}^*, i_V^*, N_V^*)$ is an equilibrium for system (5.4.1.3.5) then $(i_M^*, i_{HM}^*, n_{VI}^* - i_V^*, i_V^*, N_V^*)$ is an equilibrium of system (5.4.0.1.9). Since the two systems (5.4.1.3.5) and (5.4.0.1.9) have the same characteristic equation then they have the same set of the eigenvalues. It suffices to study the stability of (5.4.1.3.5).

The Jacobian matrix of the Linearized system of (5.4.1.3.5) around the endemic

equilibrium $(i_M^*, i_{HM}^*, n_{VI}^*, i_V^*, N_V^*)$ is given by:

$$J^* = \begin{pmatrix} -(\lambda_V + \nu_1) & 0 & 0 & \beta_M \theta\, m\,(1 - n_1 - i_M^*) & 0 \\ 0 & -(\vartheta\lambda_V + \nu_2) & 0 & \vartheta\beta_M \theta\, m\,(n_1 - i_{HM}^*) & 0 \\ \beta_V\theta(1 - n_{VI}^*) & \beta_V\theta\eta_V(1 - n_{VI}^*) & -(\lambda_V^* + \mu_V) & 0 & \frac{\mu_V^2 n_{VI}^*}{\Lambda_V} \\ 0 & 0 & 0 & -(\mu_V + \gamma_V) & \frac{\mu_V^2 i_V^*}{\Lambda_V} \\ 0 & 0 & 0 & 0 & -\mu_V \end{pmatrix}.$$

This Jacobian matrix can be written in the form $J^* = M - D$ where $M \geq 0$ (all elements of M are non-negative) and D is a diagonal matrix with positive diagonal elements. M and D given by

$$M = \begin{pmatrix} 0 & 0 & 0 & \beta_M \theta\, m\,(1 - n_1 - i_M^*) & 0 \\ 0 & 0 & 0 & \vartheta\beta_M \theta\, m\,(n_1 - i_{HM}^*) & 0 \\ \beta_V\theta(1 - n_{VI}^*) & \beta_V\theta\eta_V(1 - n_{VI}^*) & 0 & 0 & \frac{\mu_V^2 n_{VI}^*}{\Lambda_V} \\ 0 & 0 & 0 & 0 & \frac{\mu_V^2 i_V^*}{\Lambda_V} \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

and

$$D = \begin{pmatrix} (\lambda_V + \nu_1) & 0 & 0 & 0 & 0 \\ 0 & (\vartheta\lambda_V + \nu_2) & 0 & 0 & 0 \\ 0 & 0 & (\lambda_V^* + \mu_V) & 0 & 0 \\ 0 & 0 & 0 & (\mu_V + \gamma_V) & 0 \\ 0 & 0 & 0 & 0 & \mu_V \end{pmatrix}.$$

All eigenvalues of J^* have negative real parts if and only if the dominant eigenvalue of the matrix MD^{-1} is less than one [36, 41]. The eigenvalues of MD^{-1} are 0, $\sqrt[3]{\lambda}$, $\sqrt[3]{\lambda}\left(\frac{-1+\sqrt{3}i}{2}\right)$ and $\sqrt[3]{\lambda}\left(\frac{-1-\sqrt{3}i}{2}\right)$, where

$$\lambda = \frac{\beta_M\beta_V\theta^2\gamma_V\, m\,(1-n_1-i_M^*)(1-n_{VI}^*)}{(\lambda_M^*+\nu_1)(\lambda_V^*+\mu_V)(\mu_V+\gamma_V)} + \frac{\beta_M\beta_V\theta^2\gamma_V\, m\,\vartheta\eta_V(n_1-i_{HM}^*)(1-n_{VI}^*)}{(\vartheta\lambda_M^*+\nu_2)(\lambda_V^*+\mu_V)(\mu_V+\gamma_V)}.$$

Clearly $0 < 1$ to see that the other eigenvalues less than unity, it suffices to show that $\lambda < 1$. From the system (5.4.1.3.5), we have (at the endemic steady state)

$$\begin{aligned} \lambda_M^*(1-n_1-i_M^*) &= \nu_1 i_M^*, \\ \vartheta\lambda_M^*(n_1-i_{HM}^*) &= \nu_2 i_{HM}^*, \end{aligned}$$

and we recall that $\lambda_M^* = \beta_M\theta\, m\, i_V^*$ and $i_V^* = \frac{\gamma_V\lambda_V^*}{(\gamma_V+\mu_V)(\lambda_V^*+\mu_V)}$. Also notice that at the

endemic steady state $(\lambda_M^* + \nu_1) > \nu_1$ and $(\vartheta\lambda_M^* + \nu_2) > \nu_2$, then

$$\begin{aligned}
\lambda &= \frac{\beta_V\theta\gamma_V\lambda_M^*(1-n_1-i_M^*)(1-n_{VI}^*)}{(\lambda_M^*+\nu_1)(\lambda_V^*+\mu_V)(\mu_V+\gamma_V)i_V^*} + \frac{\beta_V\theta\gamma_V\lambda_M^*\vartheta\eta_V(n_1-i_{HM}^*)(1-n_{VI}^*)}{(\vartheta\lambda_M^*+\nu_2)(\lambda_V^*+\mu_V)(\mu_V+\gamma_V)i_V^*},\\
&= \frac{\beta_V\theta\nu_1 i_M^*(1-n_{VI}^*)}{(\lambda_M^*+\nu_1)\lambda_V^*} + \frac{\beta_V\theta\eta_V\nu_2 i_{HM}^*(1-n_{VI}^*)}{(\vartheta\lambda_M^*+\nu_2)\lambda_V^*},\\
&< \frac{\beta_V\theta i_M^*(1-n_{VI}^*)}{\lambda_V^*} + \frac{\beta_V\theta\eta_V i_{HM}^*(1-n_{VI}^*)}{\lambda_V^*},\\
&= \frac{\beta_V\theta(i_M^*+\eta_V i_{HM}^*)(1-n_{VI}^*)}{\lambda_V^*},\\
&= (1-n_{VI}^*),\\
&< 1.
\end{aligned}$$

It follows that $\lambda < 1$ and that the endemic steady state is locally asymptotically stable. Therefore we establish the following result.

Theorem 5.4.1.3. *The endemic equilibrium of the fast model (5.4.0.1.9) equilibrium is hyperbolically asymptotically stable whenever* $\mathcal{R}_M > 1$.

5.4.2 Sensitivity analysis of $\mathcal{R}_M$

To determine the relative importance of model parameters to the initial transmission of the disease, we perform a sensitivity analysis of the basic reproductive number with respect to the parameters of the model.

The sensitivity indices of $\mathcal{R}_M$ with respect to $\mathcal{R}_M^0$ and $\mathcal{R}_M^1$ are given by

$$\zeta_{\mathcal{R}_M^0}^{\mathcal{R}_M} = \frac{\mathcal{R}_M^0(1-n_1)}{\mathcal{R}_M},$$

$$\zeta_{\mathcal{R}_M^1}^{\mathcal{R}_M} = \frac{\mathcal{R}_M^1 n_1}{\mathcal{R}_M},$$

that is $\zeta_{\mathcal{R}_M^0}^{\mathcal{R}_M} + \zeta_{\mathcal{R}_M^1}^{\mathcal{R}_M} = 1$. We can write $\mathcal{R}_M^0 = \mathcal{R}_0/\nu_1$ and $\mathcal{R}_M^1 = \mathcal{R}_0\vartheta\eta_V/\nu_2$, where $\mathcal{R}_0 = \beta_M\beta_V\theta^2 m\gamma_V/\mu_V(\gamma_V+\mu_V)$.

The sensitivity indices of $\mathcal{R}_M^0$ and $\mathcal{R}_M^1$ with respect to any parameter p in the expression of $\mathcal{R}_0$ is given by

$$\zeta_p^{\mathcal{R}_M^0} = \frac{\partial \mathcal{R}_M^0}{\partial p} \times \frac{p}{\mathcal{R}_M^0},$$

$$= \frac{\partial \mathcal{R}_M^0}{\partial \mathcal{R}_0} \times \frac{\partial \mathcal{R}_0}{\partial p} \times \frac{\nu_1 p}{\mathcal{R}_0},$$

$$= \frac{\partial \mathcal{R}_0}{\partial p} \times \frac{p}{\mathcal{R}_0} = \zeta_p^{\mathcal{R}_0},$$

$$\zeta_p^{\mathcal{R}_M^1} = \zeta_p^{\mathcal{R}_0}.$$

Therefore, the sensitivity indices of $\mathcal{R}_M$ with respect to any parameter p in the expression of $\mathcal{R}_0$ is given by

$$\zeta_p^{\mathcal{R}_M} = \frac{\partial \mathcal{R}_M}{\partial p} \times \frac{p}{\mathcal{R}_M},$$

$$= \left[\frac{\partial \mathcal{R}_M}{\partial \mathcal{R}_M^0} \times \frac{\partial \mathcal{R}_M^0}{\partial p} + \frac{\partial \mathcal{R}_M}{\partial \mathcal{R}_M^1} \times \frac{\partial \mathcal{R}_M^1}{\partial p}\right] \frac{p}{\mathcal{R}_M},$$

$$= \zeta_p^{\mathcal{R}_0}.$$

Using parameter values from Table 3.5.0.3.8, we calculate the sensitivity indices of $\mathcal{R}_0$ with respect to θ, μ_V, β_M, β_V, m and γ_V. These values are given in Table 5.4.2.0.1 below.

Table 5.4.2.0.1: Sensitivity indices of $\mathcal{R}_0$.

Parameter	Parameter description	Sensitivity index
θ	Biting rate of female mosquito	$+2$
μ_V	Natural death rate of mosquitoes	-1.5883
β_M	Parasite transmission probability from mosquito to human	$+1$
β_V	Parasite transmission probability from human to mosquito	$+1$
m	Number of female mosquitoes per human host	$+1$
γ_V	Rate at which vectors exposed to malaria develop symptoms	$+0.5883$

For the other parameters (ν_1, ν_2, ϑ, η_V and n_1) we obtain

$$\zeta_{\nu_1}^{\mathcal{R}_M} = -\frac{\mathcal{R}_M^0(1-n_1)}{\mathcal{R}_M} = -\zeta_{\mathcal{R}_M^0}^{\mathcal{R}_M},$$

$$\zeta_{\nu_2}^{\mathcal{R}_M} = -\frac{\mathcal{R}_M^1 n_1}{\mathcal{R}_M} = -\zeta_{\mathcal{R}_M^1}^{\mathcal{R}_M},$$

$$\zeta_{\vartheta}^{\mathcal{R}_M} = \frac{\mathcal{R}_M^1 n_1}{\mathcal{R}_M} = \zeta_{\mathcal{R}_M^1}^{\mathcal{R}_M},$$

$$\zeta_{\eta_V}^{\mathcal{R}_M} = \frac{\mathcal{R}_M^1 n_1}{\mathcal{R}_M} = \zeta_{\mathcal{R}_M^1}^{\mathcal{R}_M},$$

$$\zeta_{n_1}^{\mathcal{R}_M} = \frac{(\mathcal{R}_M^1 - \mathcal{R}_M^0) n_1}{\mathcal{R}_M} = 1 - \frac{\mathcal{R}_M^0}{\mathcal{R}_M}.$$

5.5 Summary and discussion on the analysis of the fast sub-model

In this chapter, we develop a two time-scale model and then used the geometric singular perturbation techniques to decouple it into fast (for malaria) and slow (for HIV) parts.

We presented the analysis for the fast model in this chapter. For this model, we calculate the basic reproduction number and the equilibria. We find that the disease free equilibrium is normally hyperbolic when the basic reproduction number is less than unity and there exists a normal hyperbolic stable endemic equilibrium when the basic reproduction number is greater than unity. We further deduce the presence of the two slow manifolds each one of which is associated with the equilibria of the fast model.

We conclude that in the limiting case when $\epsilon = 0$, the set

$$\{(i_M, i_{HM}, e_V, i_V, N_V, n_1, N_H) | \Phi(i_M, i_{HM}, e_V, i_V, N_V, n_1, N_H, 0) = 0, n_1 \geq 0, N_H \geq 0\},$$

of system (5.3.0.1.3) consists of the parts

$$M_0^0 = \{(0, 0, 0, 0, \frac{\Lambda_V}{\mu_V}, n_1, N_H) | n_1 \geq 0, N_H \geq 0\}, \tag{5.5.0.0.6}$$

which is associated with the DFE and

$$M_0^* = \{(i_M^*, i_{HM}^*, e_V^*, i_V^*, N_V^*, n_1, N_H) | n_1 \geq 0, N_H \geq 0\}, \tag{5.5.0.0.7}$$

which is associated with the endemic equilibrium.

Since both of the DFE $E_0 = (0, 0, 0, 0, \frac{\Lambda_V}{\mu_V})$ and the endemic equilibrium $\mathsf{E}^* = (i_M^*, i_{HM}^*, e_V^*, i_V^*, N_V^*)$ are normally hyperbolic, we conclude that for system (5.3.0.1.3) with $\epsilon = 0$, the manifolds M_0^0 and M_0^* given by (5.5.0.0.6) and (5.5.0.0.7), respectively, are the set of equilibria which are all hyperbolically asymptotically stable. In terms of system (5.3.0.1.4), M_0^0 and M_0^* are the two-dimensional slow manifolds which are also normally hyperbolic [42]. By Fenichel's first theorem [46] we conclude that these manifolds persist for small nonzero ϵ as manifolds M_ϵ^0 and M_ϵ^* with a slow flow on them, i.e., for $0 < \epsilon \ll 1$ there are locally invariant slow manifolds M_ϵ^0 and M_ϵ^* that are $O(\epsilon)$ close and diffeomorphic to M_0^0 and M_0^*, respectively.

In the next chapter we analyze the system describing the slow dynamics.

Chapter 6

The slow dynamics of HIV model and its analysis

In the fast model (5.4.0.1.9) in Chapter 5 both the DFE and the endemic equilibrium are normally hyperbolic equilibria, that is there can be two models with the slow dynamics, one is associated with the DFE and the other is associated with the endemic equilibrium. In this chapter, we continue the analysis of that two-time scales model proposed in Chapter 5 by conducting the analysis for these two slow models, which provides insights into how malaria epidemics may have an impact on the HIV infection in a population where malaria is endemic.

6.1 Introduction

We recall that the essential idea behind the use of geometric singular perturbation theory is to deduce the behavior of the solution of the singularly perturbed system (5.3.0.1.3) or (5.3.0.1.4) (proposed in Chapter 5) by combining the dynamics of the fast sub-system (5.3.0.1.5) and slow sub-system (5.3.0.1.6).

Since the fast model (5.4.0.1.9) has two normally hyperbolic equilibria, singular perturbation theory allows us to study the system (5.3.0.1.4) by studying the reduced slow systems associated with these two equilibria. In this chapter we drive these two

reduced slow systems and study the dynamics of the slow manifolds on it. We calculate the basic reproduction number of the co-infection. A sensitivity analysis is performed by calculating the sensitivity index of the basic reproductive number to compare the effect of the epidemiological and demographic parameters on the initial transmission of HIV-malaria co-infection.

The rest of this chapter is organized as follows. The reduced model associated with the DFE of the fast model is derived and analyzed in Section 6.2. In Section 6.3, we derive and analyze the reduced model associated with the endemic equilibrium of the fast model. Sensitivity analysis is performed in Section 6.4. Numerical simulations are presented in Section 6.5. Section 6.6 is devoted to the discussion of the results.

6.2 Reduced model associated with the DFE of the fast model

As we mentioned in the previous chapter, the perturbed manifold M_ϵ^0 can be described as a graph $\{(U_f, U_s)|U_f = p_\epsilon^0(U_s), U_f \geq 0, U_s \geq 0\}$. Let

$$p_\epsilon^0(U_s) = p_0(U_s) + \epsilon p_1(U_s) + O(\epsilon^2),$$

where $p_0(U_s) = p_0^0(U_s) =$ DFE. The manifold M_ϵ^0 is invariant under the flow of (5.3.0.1.3) described in Chapter 5, if

$$\begin{aligned} &\frac{\partial p_\epsilon^0}{\partial U_s}(\Psi^0(p_\epsilon^0(U_s), U_s, \epsilon) + \epsilon\Psi^1(p_\epsilon^0(U_s), U_s, \epsilon)) \\ &\qquad = \Phi^0(p_\epsilon^0(U_s), U_s, \epsilon) + \epsilon\Phi^1(p_\epsilon^0(U_s), U_s, \epsilon). \end{aligned} \tag{6.2.0.0.1}$$

Expanding (6.2.0.0.1) around $p_0(U_s)$ and gathering terms of various orders of ϵ we obtain

$$\begin{aligned} O(1) &: 0 = \Phi^0(p_0(U_s)), \\ O(2) &: 0 = \Phi^{0\prime}(p_0(U_s))p_1, \\ &\vdots \\ &\text{etc}, \end{aligned}$$

since $\Phi^{0\prime}(p_0(U_s)) \neq 0$ it follows that $p_1 = 0$. This yields the approximation

$$p_\epsilon^0(U_s) = p_0(U_s). \tag{6.2.0.0.2}$$

For $\epsilon = 0$ the limit (5.3.0.1.6) prescribes the slow flow on M_0^0. For sufficiently small nonzero ϵ, the flow on M_ϵ^0 is a perturbation of this flow, that can be approximated by inserting $U_f = p_\epsilon^0(U_s)$ with $p_\epsilon^0(U_s)$ given by (6.2.0.0.2) into the equation for U_s that is

$$\frac{dU_s}{dt_{HIV}} = \Psi(\mathsf{E}^0, U_s, 0) = \Psi^1(\mathsf{E}^0, U_s). \tag{6.2.0.0.3}$$

Equation (6.2.0.0.3) describes the slow dynamics of HIV and is equivalent to the system

$$\begin{aligned} \frac{dn_1}{dt_{HIV}} &= n_1 \left[\tilde{\beta}_H(1-n_1) - \tilde{\alpha}_H(1-n_1) - \frac{\tilde{\Lambda}_H}{N_H} \right], \\ \frac{dN_H}{dt_{HIV}} &= \tilde{\Lambda}_H - (\tilde{\mu}_H + \tilde{\alpha}_H n_1)N_H. \end{aligned} \tag{6.2.0.0.4}$$

System (6.2.0.0.4) describes the community in the absence of malaria disease. Which is equivalent to the HIV-only model.

6.2.1 Dynamics on the slow manifold associated with the DFE of the fast model

In this section we analyze the model (6.2.0.0.4) from various perspectives. In particular, we study its well-posedness, discuss the feasibility region as well as stability and bifurcation.

Proposition 6.2.1. *If the initial condition is non-negative then the corresponding solution* $(n_1(t_{HIV}), N_H(t_{HIV}))$ *of model (6.2.0.0.4) is non-negative for all* $t_{HIV} > 0$. *Moreover,*

$$\lim_{t_{HIV}\to\infty} n_1(t_{HIV}) \leq 1 \text{ and } \lim_{t_{HIV}\to\infty} N_H(t_{HIV}) = \frac{\tilde{\Lambda}_H}{\tilde{\mu}_H}.$$

Furthermore, we have the following invariance properties:

i. If $n_1(0) \leq 1$ *then* $n_1(t_{HIV}) \leq 1$,

ii. If $N_H(0) \leq \frac{\tilde{\Lambda}_H}{\tilde{\mu}_H}$ *then* $N_H(t_{HIV}) \leq \frac{\tilde{\Lambda}_H}{\tilde{\mu}_H}$.

In particular, the region

$$\Omega_H = \left\{ (n_1, N_H) \in \mathbb{R}^{+2} : n_1 \geq 0, N_H \geq 0, n_1 \leq 1, N_H \leq \frac{\tilde{\Lambda}_H}{\tilde{\mu}_H} \right\},$$

is positively-invariant.

The proof of the above proposition is similar to that of Proposition 5.4.1 in Chapter 5.

6.2.1.1 Basic reproduction number

The DFE of the HIV-only model (6.2.0.0.4) is given by

$$\mathsf{E}^0_{dfe} = (n_1^{00}, N_H^{00}) = (0, \tfrac{\tilde{\Lambda}_H}{\tilde{\mu}_H}).$$

Linearizing system (6.2.0.0.4) around E^0_{dfe}, we have the following Jacobian matrix

$$J_0 = \begin{pmatrix} \tilde{\beta}_H - (\tilde{\alpha}_H + \tilde{\mu}_H) & 0 \\ -\frac{\tilde{\Lambda}_H \tilde{\alpha}_H}{\tilde{\mu}_H} & -\tilde{\mu}_H \end{pmatrix}. \tag{6.2.1.1.1}$$

The matrices F_0 and V_0, for the new infection terms and the remaining transfer terms are, respectively, given by

$$F_0 = \left(\tilde{\beta}_H\right) \text{ and } V_0 = \left(\tilde{\alpha}_H + \tilde{\mu}_H\right).$$

Then

$$\rho(F_0 V_0^{-1}) = \frac{\tilde{\beta}_H}{(\tilde{\alpha}_H + \tilde{\mu}_H)}.$$

It follows that the *basic reproduction number*, $\mathcal{R}_H$, is given by

$$\mathcal{R}_H = \frac{\tilde{\beta}_H}{(\tilde{\alpha}_H + \tilde{\mu}_H)}.$$

6.2.1.2 Stability of the DFE

Theorem 6.2.1.1. *The DFE of model (6.2.0.0.4) is locally-asymptotically stable if* $\mathcal{R}_H < 1$, *and unstable if* $\mathcal{R}_H > 1$.

Proof. The Jacobian matrix of the linearized system of (6.2.0.0.4) around the DFE is given by J_0 in (6.2.1.1.1). The eigenvalues of J_0 are $\lambda_1 = -\tilde{\mu}_H$ and $\lambda_2 = \tilde{\beta_H} - (\tilde{\mu}_H + \tilde{\alpha}_H)$. $\lambda_1 < 0$ and $\lambda_2 < 0$ if and only if $\mathcal{R}_H < 1$. Hence, we deduce that the DFE of model (6.2.0.0.4) is locally-asymptotically stable if $\mathcal{R}_H < 1$, and unstable if $\mathcal{R}_H > 1$. □

Theorem 6.2.1.2. *The DFE of the HIV-only model (6.2.0.0.4), given by* E^0_{dfe}, *is globally-asymptotically stable whenever* $\mathcal{R}_H \leq 1$.

Proof. Consider the following Layapunov function:

$$\mathcal{F} = n_1,$$

with Lyapunov derivative (with respect to t_{HIV}),

$$\begin{aligned}
\frac{d\mathcal{F}}{dt_{HIV}} &= \frac{dn_1}{dt_{HIV}} \\
&= \tilde{\beta}_H n_1(1-n_1) - \tilde{\alpha}_H n_1(1-n_1) - \frac{\tilde{\Lambda}_H}{N_H} n_1, \\
&= (\tilde{\beta}_H - (\tilde{\alpha}_H + \tilde{\mu}_H)) n_1(1-n_1) + \tilde{\mu}_H n_1(1-n_1) - \frac{\tilde{\Lambda}_H}{N_H} n_1, \\
&= -(\tilde{\alpha}_H + \tilde{\mu}_H)\left(1 - \frac{\tilde{\beta}_H}{(\tilde{\alpha}_H + \tilde{\mu}_H)}\right) n_1(1-n_1) - \tilde{\mu}_H n_1^2 + \tilde{\mu}_H n_1 - \frac{\tilde{\Lambda}_H}{N_H} n_1, \\
&= -(\tilde{\alpha}_H + \tilde{\mu}_H)(1-\mathcal{R}_H) n_1(1-n_1) - \tilde{\mu}_H n_1^2 - \frac{\tilde{\mu}_H}{N_H}\left(\frac{\tilde{\Lambda}_H}{\mu_H} - N_H\right) n_1, \\
&\leq 0
\end{aligned}$$

Since all the model parameters are nonnegative and $0 \leq n_1 \leq 1$ and $0 \leq N_H \leq \tilde{\Lambda}_H/\mu_H$ in Ω_H, it follows that $\dot{\mathcal{F}} \leq 0$ for $\mathcal{R}_H \leq 1$ with $\dot{\mathcal{F}} = 0$ if and only if $n_1 = 0$. Hence, $\mathcal{F}$ is a Lyapunov function on Ω_H. By the Lyapunov-LaSalle invariance principle ([144]) the largest compact inveriant set in $\{(n_1, N_H) \in \Omega_H : \dot{\mathcal{F}} = 0\}$ is the set where $n_1 = 0$. In this set $\frac{N_H}{dt_{HIV}} = \tilde{\Lambda}_H - \tilde{\mu}_H N_H$, shows that $N_H \to \tilde{\Lambda}_H/\tilde{\mu}_H$ as $t_{HIV} \to \infty$. Therefore, every solution to the equations of the model (6.2.0.0.4), with initial conditions in, Ω_H, approaches E^0_{dfe} as $t_{HIV} \to \infty$, whenever $\mathcal{R}_H \leq 1$. □

6.2.1.3 Existence and stability of the endemic equilibrium

To find conditions for the existence of an endemic equilibrium for HIV-only model, denoted by $\mathsf{E}^*_{dfe} = (n_1^{0*}, N_H^{0*})$, the equations in (6.2.0.0.4) are solved in terms of n_1^{0*}. Setting the right hand side of the second equation of the model to zero, gives $N_H^{0*} = \tilde{\Lambda}_H/(\tilde{\alpha}_H n_1^{0*} + \tilde{\mu}_H)$ substituting the expression for N_H^{0*} in the equation for n_1 shows that the endemic equilibria of the model satisfy

$$n_1^{0*}(\tilde{\beta}_H n_1^{0*} + B_0) = 0, \tag{6.2.1.3.1}$$

where

$$B_0 = (\tilde{\mu}_H + \tilde{\alpha}_H)(1 - \mathcal{R}_H).$$

It is clear that $B_0 > 0$ (< 0) for $\mathcal{R}_H < 1$ (> 1). Thus, the linear system (6.2.1.3.1) has a unique positive solution, given by $n_1^{0*} = -B_0/\tilde{\beta}_H$, whenever $\mathcal{R}_H > 1$. Noting that $\mathcal{R}_H < 1$ implies that $B_0 < 0$. Thus, for $\mathcal{R}_H < 1$, the infected steady-state (n_1^{0*}) is negative (which is biologically meaningless). Hence, the model has no positive equilibria in this case. These results are summarized below.

Lemma 6.2.1.1. *The HIV-only model (6.2.0.0.4) has a unique endemic equilibrium if and only if* $\mathcal{R}_H > 1$.

After substitute the value of B_0, n_1^{0*} is given by

$$n_1^{0*} = -\frac{B_0}{\tilde{\beta}_H} = \frac{(\tilde{\mu}_H + \tilde{\alpha}_H)(\mathcal{R}_H - 1)}{\tilde{\beta}_H} = \frac{(\mathcal{R}_H - 1)}{\mathcal{R}_H}.$$

Then N_H^{0*} is given by

$$N_H^{0*} = \frac{\tilde{\Lambda}_H \mathcal{R}_H}{\tilde{\alpha}_H(\mathcal{R}_H - 1) + \tilde{\mu}_H \mathcal{R}_H}.$$

Theorem 6.2.1.3. *The endemic equilibrium* E^*_{dfe} *of model (6.2.0.0.4) is locally asymptotically stable if* $\mathcal{R}_H > 1$.

Proof. Linearizing system (6.2.0.0.4) around E^*_{dfe}, we have the following Jacobian matrix

$$J^*_{dfe} = \begin{pmatrix} -\frac{(\tilde{\beta}_H - (\tilde{\alpha}_H + \tilde{\mu}_H))(\tilde{\beta}_H - \tilde{\alpha}_H)}{\tilde{\beta}_H} & \frac{(\tilde{\beta}_H - (\tilde{\alpha}_H + \tilde{\mu}_H)(\tilde{\beta}_H - \tilde{\alpha}_H)^2(\tilde{\alpha}_H + \tilde{\mu}_H)^2}{\tilde{\beta}_H^3 \tilde{\Lambda}_H} \\ -\frac{\tilde{\beta}_H \tilde{\alpha}_H \tilde{\Lambda}_H}{(\tilde{\beta}_H - \tilde{\alpha}_H)(\tilde{\alpha}_H + \tilde{\mu}_H)} & -\frac{(\tilde{\beta}_H - \tilde{\alpha}_H)(\tilde{\alpha}_H + \tilde{\mu}_H)}{\tilde{\beta}_H} \end{pmatrix}. \quad (6.2.1.3.2)$$

The eigenvalues of J^*_{dfe} are the roots of

$$\lambda^2 + A_1\lambda + A_2 = 0,$$

where

$$\begin{aligned} A_1 &= \tilde{\mu}_H + (\tilde{\mu}_H + \tilde{\alpha}_H)(\mathcal{R}_H - 1), \\ A_2 &= (\tilde{\mu_H} + \tilde{\alpha_H})(\mathcal{R}_H - 1)\left(\tilde{\mu_H} + \frac{\tilde{\alpha}_H(\mathcal{R}_H - 1)}{\mathcal{R}_H}\right). \end{aligned}$$

Since $A_1 > 0$ and $A_2 > 0$ for $R_H > 1$. Using Routh-Hurwitz criterion, E^*_{dfe} is stable if and only if $R_H > 1$. □

Global stability for the endemic equilibrium for special case when $\tilde{\alpha}_H = 0$. The global asymptotic stability property of the endemic equilibrium of the model (6.2.0.0.4) is given for the special case when the HIV-induced mortality is negligible ($\tilde{\alpha}_H = 0$) (see [106] and [125]). The model (6.2.0.0.4), with $\tilde{\alpha}_H = 0$, then reduces to

$$\begin{aligned} \frac{dn_1}{dt_{HIV}} &= n_1\left(\tilde{\beta}_H(1 - n_1) - \frac{\tilde{\Lambda}_H}{N_H}\right), \\ \frac{dN_H}{dt_{HIV}} &= \tilde{\Lambda}_H - \tilde{\mu}_H N_H. \end{aligned} \tag{6.2.1.3.3}$$

Now, $dN_H/dt_{HIV} = \tilde{\Lambda}_H - \tilde{\mu}_H N_H$, so that $N_H \to \tilde{\Lambda}_H/\tilde{\mu}_H$ and we can use $N_H = \tilde{\Lambda}_H/\tilde{\mu}_H$ in the equation for n_1 in (6.2.1.3.3).

The DFE equilibrium of the reduced model (6.2.1.3.3) is given by $(0, \frac{\tilde{\Lambda}_H}{\tilde{\mu}_H})$. The associated reproduction number of the reduced model (6.2.1.3.3) is given by

$$\mathcal{R}_{Hc} = \frac{\tilde{\beta}_H}{\tilde{\mu}_H}\ .$$

The reduced model (6.2.1.3.3) has a unique endemic equilibrium, given by $\mathsf{E}^{*0}_{dfe} = (\frac{\mathcal{R}_{Hc}-1}{\mathcal{R}_{Hc}}, \frac{\tilde{\Lambda}_H}{\tilde{\mu}_H})$ which is exists whenever $\mathcal{R}_{Hc} > 1$. Notice that $\mathcal{R}_{Hc} = \mathcal{R}_H|_{\tilde{\alpha}_H=0}$ and $\mathsf{E}^{*0}_{dfe} = \mathsf{E}^*_{dfe}|_{\tilde{\alpha}_H=0}$. Letting

$$\Omega_{H0} = \{(n_1, N_H) \in \Omega_H : n_1 = 0\},$$

we have the following result

Theorem 6.2.1.4. *The endemic equilibrium E^*_{dfe} of model (6.2.0.0.4) with $\tilde{\alpha}_H = 0$ is globally-asymptotically stable in $\Omega_H \backslash \Omega_{H0}$ if $\mathcal{R}_{Hc} > 1$.*

Proof. Consider the reduced model (6.2.1.3.3) and the following Layapunov function

$$\mathcal{L} = F(n_1, n_1^{0*}),$$

where

$$F(u, u^{0*}) = u - u^{0*} \ln u - u^{0*} + u^{0*} \ln u^{0*}.$$

Clearly $F(u, u^{0*})$ is an increasing function for $u \geq u^{0*}$, then it follows that $F(u, u^{0*}) \geq F(u^{0*}, u^{0*}) = 0$. By Proposition 6.2.1, all solutions are positive and bounded. Thus $\mathcal{L}$ is well defined and $\mathcal{L} \geq 0$, in which the equality holds if and only if $n_1 = n_1^{0*}$.
Differentiating $\mathcal{L}$ (with respect to t_{HIV}), and using the fact that at the equilibrium $\mu_H = \tilde{\beta}_H(1 - n_1^{0*})$, we obtain

$$\begin{aligned}
\dot{\mathcal{L}} &= \left(\frac{n_1 - n_1^{0*}}{n_1}\right) \frac{dn_1}{dt_{HIV}}, \\
&= (n_1 - n_1^{0*})(\tilde{\beta}_H(1 - n_1) - \tilde{\mu}_H), \\
&= -\tilde{\beta}_H (n_1 - n_1^{0*})^2, \\
&< 0.
\end{aligned}$$

That is $\dot{\mathcal{L}} \leq 0$ and $\dot{\mathcal{L}} = 0$ if and only if $n_1 = n_1^{0*}$. Hence, $\mathcal{L}$ is a Lyapunov function on $\Omega_H \backslash \Omega_{H0}$. By the Lyapunov-LaSalle invariance principle [144] the largest compact inveriant set in $\{(n_1, N_H) \in \Omega_H \backslash \Omega_{H0} : \dot{\mathcal{L}} = 0\}$ is the set where $n_1 = \mathcal{R}_{Hc} - 1/\mathcal{R}_{Hc}$ and $N_H = \tilde{\Lambda}_H / \tilde{\mu}_H$. Therefore, every solution of model (6.2.0.0.4), with initial conditions in, $\Omega_H \backslash \Omega_{H0}$, approaches E^{*0}_{dfe} as $t_{HIV} \to \infty$, whenever $\mathcal{R}_{Hc} > 1$. □

6.3 Reduced model associated with the endemic equilibrium of the fast model

To drive the slow model associated with the endemic equilibrium, we follow the approach in [4]. We note that system (5.3.0.1.3) can be written in the form

$$\frac{dU}{dt} = F^0(U) + \epsilon F^1(U), \tag{6.3.0.3.4}$$

where

$$U = \begin{pmatrix} U_f \\ U_s \end{pmatrix},$$

$$F^0(U) = \begin{pmatrix} \Phi^0(U_f, U_s) \\ \Psi^0(U_f, U_s) \end{pmatrix}$$

and

$$F^1(U) = \begin{pmatrix} \Phi^1(U_f, U_s) \\ \Psi^1(U_f, U_s) \end{pmatrix}.$$

The equation $F^0(U) = 0$ has two solutions each one has a two-parameter family of solutions $U_0^0 = M_0^0$ and $U_0^* = M_0^*$ given by (5.5.0.0.6) and (5.5.0.0.7), respectively, and these two solutions are stable for $\epsilon = 0$. The solution $U_0^0 = M_0^0$ has been discussed in the previous sub-section. For $U_0^* = M_0^*$, the Jacobian matrix of $F^0(U)$ at U_0^* $(DF^0(U_0^*))$ has 5 eigenvalues with negative real parts and two zero eigenvalues.

For $\epsilon \neq 0$ we search for solutions for system (6.3.0.3.4) close to the manifold M_0^*. These solutions will have the form

$$U(t) = U_0^*(U_s) + \epsilon U_1(t, \epsilon)$$

substitute this solution into system (6.3.0.3.4) yields

$$\begin{aligned}\frac{dU}{dt} &= U_0^{*\prime}(U_s)\frac{dU_s}{dt} + \epsilon\frac{\partial U_1}{\partial t} \\ &= F^0(U_0^*(U_s) + \epsilon U_1(t,\epsilon)) + \epsilon F^1(U_0^*(U_s) + \epsilon U_1(t,\epsilon)),\end{aligned}$$

where

$$U_0^{*\prime}(U_s) = \begin{pmatrix} \frac{di_M^*}{dn_1} & \frac{di_M^*}{dN_H} \\ \frac{di_{HM}^*}{dn_1} & \frac{di_{HM}^*}{dN_H} \\ \frac{de_V^*}{dn_1} & \frac{de_V^*}{dN_H} \\ \frac{di_V^*}{dn_1} & \frac{di_V^*}{dN_H} \\ \frac{dN_V^*}{dn_1} & \frac{dN_V^*}{dN_H} \\ \frac{dn_1}{dn_1} & \frac{dn_1}{dN_H} \\ \frac{dN_H}{dn_1} & \frac{dN_H}{dN_H} \end{pmatrix} = \begin{pmatrix} \frac{di_M^*}{dn_1} & 0 \\ \frac{di_{HM}^*}{dn_1} & 0 \\ \frac{de_V^*}{dn_1} & 0 \\ \frac{di_V^*}{dn_1} & 0 \\ \frac{dN_V^*}{dn_1} & 0 \\ 1 & 0 \\ 0 & 1 \end{pmatrix}.$$

Expanding $F^0(U_0^*(U_s) + \epsilon U_1(t,\epsilon))$ and $F^1(U_0^*(U_s) + \epsilon U_1(t,\epsilon))$ with Taylor expansions around U_0^* yields

$$U_0^{*\prime}(U_s)\frac{dU_s}{dt} + \epsilon\frac{\partial U_1}{\partial t} = F^0(U_0^*) + \epsilon DF^0(U_0^*)U_1 + \epsilon F^1(U_0^*) + O(\epsilon^2).$$

Notice that $F^0(U_0^*) = 0$ and $DF^0(U_0^*)$ has 5 eigenvalues with negative real parts and two zero eigenvalues.

Let

$$V = \begin{pmatrix} V_1 \\ V_2, \end{pmatrix} = \begin{pmatrix} 0_{2\times 5} & I_2 \end{pmatrix},$$

where $V_1 = (0,0,0,0,0,1,0)$ and $V_2 = (0,0,0,0,0,0,1)$ are the two left eigenvectors of $DF^0(U_0^*(U_s))$ corresponding to the two zero eigenvalues (The left eigenvector of $DF^0(U_0(U_s))$, w, is found by solving the system $wDF^0(U_0(U_s)) = 0$). Using the similar approaches in [4] we can separate the dynamics of U_s and U_0^*.

$$VU_0^{*\prime}(U_s)\frac{dU_s}{dt} + \epsilon V\frac{\partial U_1}{\partial t} = \epsilon VDF^0(U_0^*)U_1 + \epsilon VF^1(U_0^*) + O(\epsilon^2), \qquad (6.3.0.3.5)$$

the variable U_1 can be choosen such that $V\frac{\partial U_1}{\partial t} = 0$ ([4]). The product

$$VU_0^{*\prime}(U_s) = \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix} = I_2.$$

Hence, when neglecting higher order terms in ϵ, system(6.3.0.3.5) yields

$$\frac{dU_s}{dt} = \epsilon V F^1(U_0^*) = \epsilon \Psi^1(U_0^*), \tag{6.3.0.3.6}$$

with a change of time scale, $t_{HIV} = \epsilon\, t$ that is $\frac{d}{dt} \equiv \epsilon \frac{d}{dt_{HIV}}$, system (6.3.0.3.6) can be reformulated as

$$\frac{dU_s}{dt_{HIV}} = \Psi^1(U_0^*). \tag{6.3.0.3.7}$$

System (6.3.0.3.7) describes the community in which the malaria disease is endemic. In the next section we study the qualitative analysis of this model.

6.3.1 Dynamics on the slow manifold associated with the endemic equilibrium

In this section we study the well-posedness, feasibility and stability of the model (6.3.0.3.7).

The reduced model associated with the endemic equilibrium is given by (6.3.0.3.7) or equivalently by

$$\begin{aligned} \frac{dn_1}{dt_{HIV}} &= \tilde{\lambda}_H^*(1-(n_1+i_M^*)) + \sigma\tilde{\lambda}_H^* i_M^* - (\kappa\tilde{\alpha}_M + (d-1)\tilde{\alpha}_H) i_{HM}^* - \left(\tilde{\alpha}_H + \frac{\tilde{\Lambda}_H}{N_H}\right) n_1 \\ &\quad + (\tilde{\alpha}_M i_M^* + (\kappa\tilde{\alpha}_M + (d-1)\tilde{\alpha}_H) i_{HM}^* + \tilde{\alpha}_H n_1) n_1, \\ \frac{dN_H}{dt_{HIV}} &= \tilde{\Lambda}_H - (\tilde{\alpha}_M i_M^* + (\kappa\tilde{\alpha}_M + (d-1)\tilde{\alpha}_H) i_{HM}^* + \tilde{\alpha}_H n_1 + \tilde{\mu}_H)) N_H, \end{aligned} \tag{6.3.1.0.8}$$

where

$$\tilde{\lambda}_H^* = \tilde{\beta}_H(n_1 + (\eta_{HM} - 1)i_{HM}^*),$$

and

$$\begin{aligned} i_M^* &= \frac{\lambda_M^*}{\nu_1 + \lambda_M^*}(1 - n_1) \\ &= \left(1 - \frac{\nu_1}{\nu_1 + \lambda_M^*}\right)(1 - n_1), \end{aligned}$$

$$\begin{aligned} i_{HM}^* &= \frac{\vartheta\lambda_M^*}{\nu_2 + \vartheta\lambda_M^*} n_1 \\ &= \left(1 - \frac{\nu_2/\vartheta}{(\nu_2/\vartheta) + \lambda_M^*}\right) n_1, \end{aligned}$$

with $\lambda_M^* = \lambda_M^*(n_1)$ is the positive solution of (5.4.1.3.4), i.e.,

$$\lambda_M^*(n_1) = \frac{-B + \sqrt{\Delta}}{2A}, \tag{6.3.1.0.9}$$

where $\Delta = B^2 - 4AC$ and A, B and C are given by (5.4.1.3.3).

We can write

$$\Delta = \Delta_0 n_1^2 + 2\Delta_1 n_1 + \Delta_2,$$

where

$$\begin{aligned} \Delta_0 &= (\vartheta\nu_1(\mu_V\mathcal{R}_M^0 + \beta_V\theta\eta_V) - \nu_2(\mu_V\mathcal{R}_M^1 + \beta_V\theta))^2 \\ &\quad -4\vartheta\nu_1\nu_2\mu_V\beta_V\theta(\eta_V - 1)(\mathcal{R}_M^0 - \mathcal{R}_M^1), \\ \Delta_1 &= (\nu_2(\beta_V\theta + \mu_V) - \vartheta\nu_1\mu_V(\mathcal{R}_M^0 - 1))(\vartheta\nu_1(\mu_V\mathcal{R}_M^0 + \beta_V\theta\eta_V) \\ &\quad -\nu_2(\mu_V\mathcal{R}_M^1 + \beta_V\theta)) + 2\nu_1\nu_2\mu_V\vartheta((\mathcal{R}_M^1 - \mathcal{R}_M^0)(\beta_V\theta + \mu_V) \\ &\quad +\beta_V\theta(\eta_V - 1)(\mathcal{R}_M^0 - 1)), \\ \Delta_2 &= (\nu_2(\beta_V\theta + \mu_V) + \vartheta\nu_1\mu_V(\mathcal{R}_M^0 - 1))^2. \end{aligned}$$

Therefore we can write i_M^* and i_{HM}^* as

$$\begin{aligned} i_M^* &= (1 - Q_1(n_1))(1 - n_1), \\ i_{HM}^* &= (1 - Q_2(n_1))n_1, \end{aligned}$$

where

$$\begin{aligned} Q_1(n_1) &= \frac{\nu_1}{(\nu_1 + \lambda_M^*)}, \\ &= \frac{2\nu_1 A}{(-(B - 2\nu_1 A) + \sqrt{\Delta})}, \\ &= \frac{(B - 2\nu_1 A) + \sqrt{\Delta}}{2(\nu_2 - \vartheta\nu_1)(\mu_V \mathcal{R}_M^0 + \beta_V \theta)(1 - n_1)}, \\ &= \frac{W_1}{(1 - n_1)} \left(G_{10} + G_{11} n_1 + \sqrt{\Delta} \right), \end{aligned}$$

with

$$\begin{aligned} W_1 &= \frac{1}{2(\nu_2 - \vartheta\nu_1)(\mu_V \mathcal{R}_M^0 + \beta_V \theta)}, \\ G_{10} &= (\nu_2 - \vartheta\nu_1)(\mu_V + \beta_V \theta) - \vartheta\nu_1(\mu_V \mathcal{R}_M^0 + \beta_V \theta), \\ G_{11} &= \vartheta\nu_1(\mu_V \mathcal{R}_M^0 + \beta_V \theta) - (\beta_V \theta \nu_1 \eta_V \vartheta + \mu_V \nu_2 \mathcal{R}_M^1) - \beta_V \theta(\nu_2 - \vartheta\nu_1), \end{aligned}$$

and

$$\begin{aligned} Q_2(n_1) &= \frac{(\nu_2/\vartheta)}{((\nu_2/\vartheta)+\lambda_M^*)}, \\ &= \frac{2(\nu_2/\vartheta)A}{(-(B-2(\nu_2/\vartheta)A)+\sqrt{\Delta})}, \\ &= \frac{-(B-2(\nu_2/\vartheta)A)-\sqrt{\Delta}}{2(\nu_2-\vartheta\nu_1)(\mu_V\mathcal{R}_M^1+\eta_V\theta\beta_V)n_1}, \\ &= \frac{W_2}{n_1}\left(G_{20}+G_{21}n_1-\sqrt{\Delta}\right), \end{aligned}$$

with

$$\begin{aligned} W_2 &= \frac{1}{2(\nu_2-\vartheta\nu_1)(\mu_V\mathcal{R}_M^1+\eta_V\theta\beta_V)}, \\ G_{20} &= \nu_2(\beta_V\theta+\mu_V)+\vartheta\nu_1\mu_V(\mathcal{R}_M^0-1), \\ G_{21} &= \eta_V\beta_V\theta(\nu_2-\vartheta\nu_1)+\nu_2(\mu_V\mathcal{R}_M^1+\eta_V\beta_V\theta)-(\beta_V\theta\nu_2+\vartheta\nu_1\mu_V\mathcal{R}_M^0). \end{aligned}$$

Remark 6.3.1.1. Notice that $0 < Q_1(n_1) < 1$ and $0 < Q_2(n_1) < 1$. Moreover $n_1 = 1$ is a removable discontinuity of $G_{10}+G_{11}n_1+\sqrt{\Delta}$ and $n = 0$ is a removable discontinuity of $G_{20}+G_{21}n_1-\sqrt{\Delta}$, therefore $Q_1(n_1)$ and $Q_2(n_1)$ is well defined in $[0,1]$.

After substitute of $\tilde{\lambda}_H^*$, i_M^* and i_{HM}^* in (6.3.1.0.8) and arrangement

$$\begin{aligned} \frac{dn_1}{dt_{HIV}} &= n_1\left[\tilde{\beta}_H Y_1(n_1)+Y_2(n_1)-\frac{\tilde{\Lambda}_H}{N_H}-(\kappa\tilde{\alpha}_M+d\tilde{\alpha}_H)\right], \\ \frac{dN_H}{dt_{HIV}} &= \tilde{\Lambda}_H-(\tilde{\mu}_H+Y_3(n_1))N_H, \end{aligned} \tag{6.3.1.0.10}$$

where

$$Y_1(n_1) = (1-n_1)(1+(\eta_{HM}-1)(1-Q_2(n_1)))(Q_1(n_1)+\sigma(1-Q_1(n_1))),$$

$$\begin{aligned} Y_2(n_1) = (1-n_1)[\tilde{\alpha}_M(1-Q_1(n_1)) + ((\kappa\tilde{\alpha}_M + (d-1)\tilde{\alpha}_H)Q_2(n_1)] \\ + ((\kappa\tilde{\alpha}_M + d\tilde{\alpha}_H))n_1, \end{aligned} \tag{6.3.1.0.11}$$

$$Y_3(n_1) = \tilde{\alpha}_M(1-Q_1(n_1))(1-n_1) + ((\kappa\tilde{\alpha}_M + (d-1)\tilde{\alpha}_H)(1-Q_2(n_1)) + \tilde{\alpha}_H)n_1.$$

Note that we can, also, write $Y_2(n_1) = Y_3(n_1) + (\kappa\tilde{\alpha}_M + (d-1)\tilde{\alpha}_H)Q_2(n_1)$.

Proposition 6.3.1. *For system (6.3.1.0.10), the region Ω_H defined in Proposition 6.2.1 is positively-invariant.*

6.3.1.1 Basic reproduction number

The DFE ($\mathsf{E}^0_{ee} = (n_1^{*0}, N_H^{*0})$) (here the DFE is in the sense that the equilibrium when there is malaria but no HIV) of system (6.3.1.0.10) are given by

$$\begin{aligned} n_1^{*0} &= 0, \\ N_H^{*0} &= \frac{\tilde{\Lambda}_H}{\tilde{\mu}_H + Y_3(0)}, \\ &= \frac{\tilde{\Lambda}_H(\mu_V\mathcal{R}_M^0 + \beta_V\theta)}{\mu_V\tilde{\alpha}_M(\mathcal{R}_M^0 - 1) + \tilde{\mu}_H(\mu_V\mathcal{R}_M^0 + \beta_V\theta)}. \end{aligned} \tag{6.3.1.1.1}$$

The *basic reproduction number* of system (6.3.1.0.10) is calculated using next generation matrix. The matrices $\mathcal{F}$ and $\mathcal{V}$ are given by

$$\mathcal{F} = \begin{pmatrix} \tilde{\beta}_H Y_1(n_1)n_1 \\ \\ 0 \end{pmatrix} \quad \text{and} \quad \mathcal{V} = \begin{pmatrix} n_1[-Y_2(n_1) + \frac{\tilde{\Lambda}_H}{N_H} + (\kappa\tilde{\alpha}_M + d\tilde{\alpha}_H)] \\ \\ -\tilde{\Lambda}_H + (\tilde{\mu}_H + Y_3(n_1))N_H \end{pmatrix}.$$

Now differentiating $\mathcal{F}$ and $\mathcal{V}$ with respect to the infected compartments evaluated at the DFE we get the matrices $\mathbf{F}$ and $\mathbf{V}$, for the new infection terms and the remaining transfer terms are, respectively, given by

$$\hat{F} = \begin{pmatrix} J_1 \end{pmatrix} \text{ and } \hat{V} = \begin{pmatrix} J_2 \end{pmatrix},$$

where

$$J_1 = \frac{\tilde{\beta}_H(\sigma\mu_V(\mathcal{R}_M^0 - 1) + \mu_V + \beta_V\theta)(\eta_{HM}\vartheta\mu_V\nu_1(\mathcal{R}_M^0 - 1) + \nu_2(\mu_V + \beta_V\theta))}{(\vartheta\mu_V\nu_1(\mathcal{R}_M^0 - 1) + \nu_2(\mu_V + \beta_V\theta))(\mu_V\mathcal{R}_M^0 + \beta_V\theta)},$$

$$J_2 = \frac{\vartheta\mu_V\nu_1(\mathcal{R}_M^0 - 1)(\kappa\tilde{\alpha}_M + d\tilde{\alpha}_H + \tilde{\mu}_H) + \nu_2(\tilde{\alpha}_H + \tilde{\mu}_H)(\mu_V + \beta_V\theta)}{(\vartheta\mu_V\nu_1(\mathcal{R}_M^0 - 1) + \nu_2(\mu_V + \beta_V\theta))}.$$

The reproductive number, $\mathcal{R}_{HM}$, is equal to the spectral radius of the next generation operator $\hat{F}\hat{V}^{-1}$ [140]. It follows that the *basic reproduction number* of system (6.3.1.0.10), $\mathcal{R}_{HM}$, is given by

$$\mathcal{R}_{HM} = \frac{\tilde{\beta}_H(\sigma\mu_V(\mathcal{R}_M^0 - 1) + \mu_V + \beta_V\theta)(\eta_{HM}\vartheta\mu_V\nu_1(\mathcal{R}_M^0 - 1) + \nu_2(\mu_V + \beta_V\theta))}{(\mu_V\mathcal{R}_M^0 + \beta_V\theta)(\vartheta\mu_V\nu_1(\mathcal{R}_M^0 - 1)(\kappa\tilde{\alpha}_M + d\tilde{\alpha}_H + \tilde{\mu}_H) + \nu_2(\tilde{\alpha}_H + \tilde{\mu}_H)(\mu_V + \beta_V\theta))}.$$

The *basic reproduction number*, $\mathcal{R}_{HM}$, is the expected number of secondary cases produced, in a completely susceptible population (susceptible to HIV but malaria is epidemics), by a typical dually-infective individual with HIV and malaria.

6.3.1.2 Stability of the DFE

Theorem 6.3.1.1. *The DFE of system (6.3.1.0.10) is locally asymptotically stable if* $\mathcal{R}_{HM} < 1$ *and unstable if* $\mathcal{R}_{HM} > 1$.

Proof. Linearizing system (6.3.1.0.10) around E_{ee}^0, we have the following Jacobian matrix

$$J_{ee}^0 = \begin{pmatrix} J_1 - J_2 & 0 \\ \\ -J_3 & -J_4 \end{pmatrix}, \tag{6.3.1.2.1}$$

where

$$J_3 = \frac{\tilde{\Lambda}_H \tilde{J}}{(\mu_V \tilde{\alpha}_M(\mathcal{R}_M^0 - 1) + \tilde{\mu}_H(\mu_V \mathcal{R}_M^0 + \beta_V \theta))(\mu_V \nu_1 \vartheta(\mathcal{R}_M^0 - 1) + \nu_2(\mu_V + \beta_V \theta))},$$

$$J_4 = \frac{\mu_V \tilde{\alpha}_M(\mathcal{R}_M^0 - 1) + \tilde{\mu}_H(\mu_V \mathcal{R}_M^0 + \beta_V \theta)}{(\mu_V \mathcal{R}_M^0 + \beta_V \theta)},$$

with

$$\begin{aligned}\tilde{J} = {} & [\mu_V \nu_1 \vartheta((\kappa - 1)\tilde{\alpha}_M + d\alpha_H)(\mathcal{R}_M^0 - 1) + \nu_2 \tilde{\alpha}_H(\mu_V + \beta_V \theta)](\mu_V \mathcal{R}_M^0 + \beta_V \theta) \\ & + \mu_V \nu_2 \tilde{\alpha}_M(\mu_V + \beta_V \theta)(\mathcal{R}_M^1 - \mathcal{R}_M^0) - \mu_V \nu_1 \vartheta \tilde{\alpha}_M \beta_V \theta(\eta_V - 1)(\mathcal{R}_M^0 - 1).\end{aligned}$$

Being a triangular matrix, its eigenvalues are the entries along the main diagonal, i.e., the eigenvalues of J_{ee}^0 are $\lambda_1 = -J_4$ and $\lambda_2 = J_1 - J_2$. $\lambda_1 < 0$ and $\lambda_2 < 0$ if and only if $\mathcal{R}_{HM} < 1$. Hence, we deduce that the DFE of model (6.3.1.0.10) is locally-asymptotically stable if $\mathcal{R}_{HM} < 1$, and unstable if $\mathcal{R}_{HM} > 1$. □

It should be noted that the global stability of the DFE of system (6.3.1.0.10) can be proved following the standard tools.

6.3.1.3 Existence and stability of the endemic equilibrium

To find the endemic equilibria of system (6.3.1.0.10), ($\mathsf{E}_{ee}^* = (n_1^{**}, N_H^{**})$), we equate the right hand side of system (6.3.1.0.10) to zero and solve the system in term of $Q_1(n_1^{**})$ and $Q_2(n_1^{**})$, to obtain

$$N_H^{**} = \frac{\tilde{\Lambda}_H}{\tilde{\mu}_H + Y_3(n_1^{**})}.$$

then E_{ee}^* satisfy

$$\begin{aligned}&\tilde{\beta}_H Y_1(n_1^{**}) + Y_2(n_1^{**}) - Y_3(n_1^{**}) - (\kappa \tilde{\alpha}_M + d\tilde{\alpha}_H + \tilde{\mu}_H) = 0, \\ &\text{or} \\ &\tilde{\beta}_H Y_1(n_1^{**}) + (\kappa \tilde{\alpha}_M + (d-1)\tilde{\alpha}_H) Q_2(n_1^{**}) - (\kappa \tilde{\alpha}_M + d\tilde{\alpha}_H + \tilde{\mu}_H) = 0.\end{aligned} \tag{6.3.1.3.1}$$

Due to the complexity of the expressions of the system (6.3.1.0.10) and (6.3.1.3.1), the analytical study of the endemic equilibria and their stability are difficult and will be investigated numerically only. For this, we vary the value of the contact rate for HIV infection, β_H, fix the other parameters and calculate the numerical values of the endemic equilibria for each β_H. The results are shown in the bifurcation diagram Figure 6.3.1.3.1.

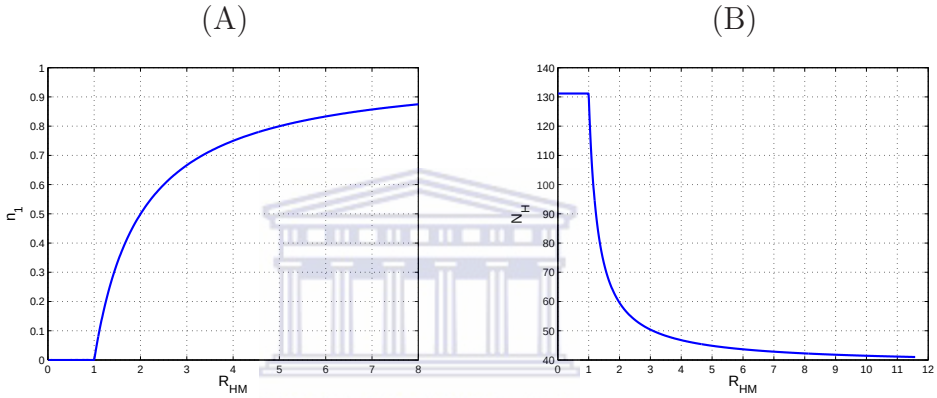

Figure 6.3.1.3.1: Bifurcation diagram of the slow model (6.3.1.0.10). Parameter values used are as in Table 3.5.0.3.8 with $\epsilon = 10^{-4}$ and various values of β_H.

This bifurcation diagram shows that when $\mathcal{R}_{HM} < 1$, there is a stable disease-free equilibrium. If any endemic equilibrium exists, it is unstable, and therefore cannot be shown numerically. When $\mathcal{R}_{HM} > 1$, there exists a stable endemic equilibrium. The other endemic equilibrium that exists is unstable since it could not be obtained by numerical methods used. Therefore we observe a transcritical bifurcation indicating an exchange of stability between the disease free and endemic equilibria. If $\mathcal{R}_{HM} < 1$, the disease free state is always stable. The disease establishes itself in a community at endemic levels when $\mathcal{R}_{HM} > 1$.

In the same manner as we did for system (6.2.0.0.4), we can prove the following result.

Theorem 6.3.1.2. *The endemic equilibrium of system (6.3.1.0.10) with ($\tilde{\alpha}_H = \tilde{\alpha}_M = 0$) is globally stable in $\Omega_H \backslash \Omega_{H0}$ whenever $\mathcal{R}_{HMc} = \mathcal{R}_{HM}|_{\tilde{\alpha}_H = \tilde{\alpha}_M = 0} > 1$.*

6.4 Sensitivity analysis of $\mathcal{R}_{HM}$

To determine the relative importance of the epidemiological and demographic parameters for the transmission of dual infection with HIV and malaria, we perform a sensitivity analysis of the *basic reproductive number* $\mathcal{R}_{HM}$ with respect to the model's parameters.

Using parameter values from Table 3.5.0.3.8, we calculate the sensitivity indices of $\mathcal{R}_{HM}$ with respect to the model's parameters. These values are given in Table 6.4.0.3.1 below. The sensitivity indices of $\mathcal{R}_{HM}$ with respect to $\mathcal{R}_M^0$ is also calculated and has the value +0.0002.

Table 6.4.0.3.1: Sensitivity indices of the *basic reproduction number*, $\mathcal{R}_{HM}$, of the reduced model associated with the endemic equilibrium of the fast model.

P	Parameter description	S.I
β_H	Scaled-effective contact rate for HIV infection	+1
η_{HM}	Relative infectiousness of HIV in individuals dually-infected with HIV and malaria	+0.9978
σ	Reduction in sexual activity by individuals with malaria infection	+0.9907
$\tilde{\alpha}_H$	Scaled-HIV-induced death rate	−0.7046
d	Increase in HIV mortality in individuals dually-infected with HIV and malaria	−0.7022
$\tilde{\alpha}_M$	Scaled-malaria-induced death rate	−0.2654
κ	Increase in malaria mortality in individuals dually-infected with HIV and malaria	−0.2654
ν_2	Recovery rate of humans from malaria	−0.1129
$\tilde{\mu}_H$	Scaled-natural death rate of humans	−0.0300
θ	Biting rate of mosquitoes	+0.0003
ϑ	Increase in susceptibility to malaria infection in individuals with HIV infection	+0.0002
β_M	Transmission probability for malaria in humans	+0.0002
m	Number of female mosquitoes per human host	+0.0002
μ_V	Natural death rate of mosquitoes	−0.0002
γ_V	Rate at which vectors exposed to malaria develop symptoms	+0.0001
β_V	Transmission probability for malaria in vectors	≈ 0
ν_1	Recovery rate of humans from malaria	≈ 0

From Table 6.4.0.3.1, we see that $\mathcal{R}_{HM}$ is more sensitive to the contact rate β_H, relative infectiousness of HIV in individuals dually-infected with HIV and malaria η_{HM} and reduction in sexual activity by individuals with malaria infection σ. For example decreasing (or increasing) σ by 10% decreases (or increases) $\mathcal{R}_{HM}$ by 9.9%. And decreasing (or increasing) d by 10% increases (or decreases) $\mathcal{R}_{HM}$ by 7%.

6.5 Numerical simulations

Using the geometric singular perturbation theory, we see that the case when $\epsilon \neq 0$, we can construct the dynamical behavior of the original system (5.3.0.1.4) through studying the reduced systems (5.4.0.1.9), (6.2.0.0.4) and (6.3.1.0.10).

We make use of Matlab solver ode15s to integrate the equations of systems (5.3.0.1.4), (5.4.0.1.9), (6.2.0.0.4) and (6.3.1.0.10). The parameter values used in these simulations are given in Table 3.5.0.3.8. Some of these parameters are varied to test the analytical results.

It should be noted that we have develop NSFDM for the original model (5.3.0.1.4) in Chapter 5, only. The reduced model (6.3.1.0.10) is solved numerically by Matlab solvers. The mere reason behind not using NSFDMs is that the reduced model is highly implicit. The numerical results show that when the basic reproduction number, $\mathcal{R}_M$, of the fast model (5.4.0.1.9) less than unity the behavior of the original HIV-malaria co-infection model (5.3.0.1.4) is determined by the reduced model associated with the DFE of the fast model(5.4.0.1.9) (system (6.2.0.0.4)). When $\mathcal{R}_M > 1$ then the dynamics of the original model (5.3.0.1.4) is approximated by the slow model associated with the endemic equilibrium of the fast model (5.4.0.1.9) (system (6.3.1.0.10)).

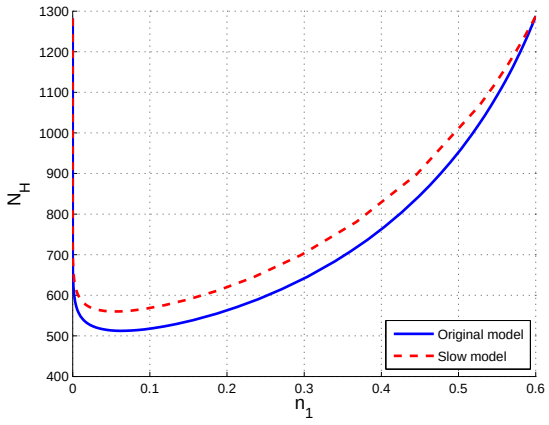

Figure 6.5.0.3.2: Phase portraits for model (6.2.0.0.4). Parameter values are taken from Table 3.5.0.3.8 with $\beta_V = 0.2$, $\theta = 0.2$, $\mu_V = 0.5$, $\beta_H = 0.0002$ and $\epsilon = 10^{-4}$ ($\mathcal{R}_H = 0.2101$).

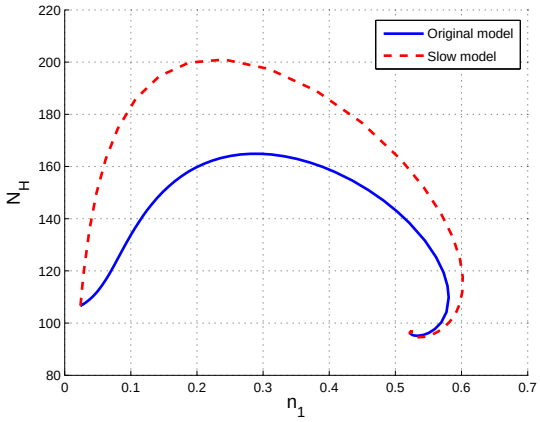

Figure 6.5.0.3.3: Phase portraits for model (6.2.0.0.4). Parameter values are taken from Table 3.5.0.3.8 with $\beta_V = 0.2$, $\beta_M = 0.5$, $\theta = 0.2$, $\mu_V = 0.5$, $\beta_H = 0.002$ and $\epsilon = 10^{-4}$ ($\mathcal{R}_H = 2.1008$).

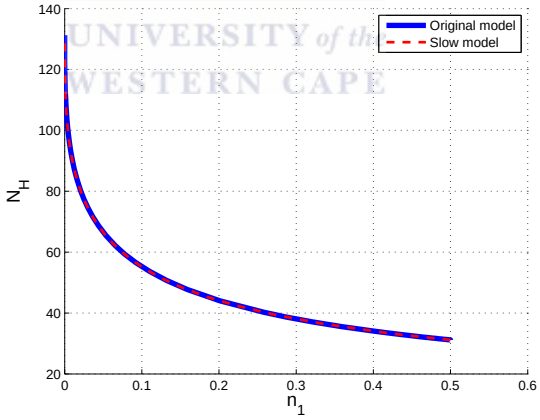

Figure 6.5.0.3.4: Phase portraits for model (6.3.1.0.10). Parameter values are taken from Table 3.5.0.3.8 with $\beta_V = 0.9$, $\beta_M = 0.8333$, $\theta = 1$, $\mu_V = 0.1429$, $\beta_H = 0.0002$ and $\epsilon = 10^{-4}$ ($\mathcal{R}_{HM} = 0.2316$).

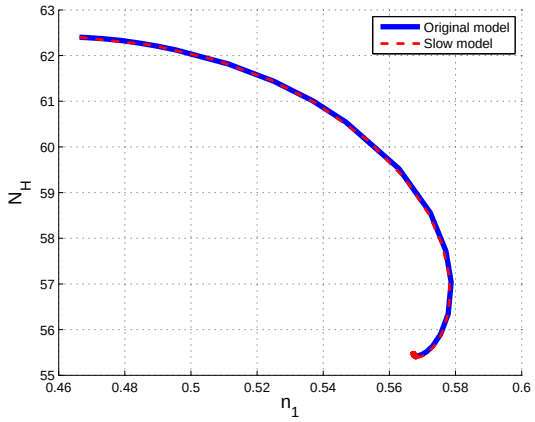

Figure 6.5.0.3.5: Phase portraits for model (6.3.1.0.10). Parameter values are taken from Table 3.5.0.3.8 with $\beta_V = 0.9$, $\beta_M = 0.8333$, $\theta = 1$, $\mu_V = 0.1429$, $\beta_H = 0.002$ and $\epsilon = 10^{-4}$ ($\mathcal{R}_{HM} = 2.3158$).

6.6 Summary and discussion

In this chapter, we have conducted a thorough mathematical analysis for a model that incorporates both malaria disease and HIV infection. The coupling of the processes of malaria epidemics and an HIV infection makes the analysis very challenging. The majority of existing mathematical models deal with the two diseases separately, i.e., the models consider either the epidemiology of malaria only (without HIV) or the HIV only (without the malaria disease dynamics). However, our results in this chapter show that the coupled model is capable of producing thresholds and dynamics that cannot be obtained from those simpler models.

For the the slow manifold associated with the endemic equilibrium of the fast model, a detailed mathematical analysis of a model that incorporates both malaria disease and HIV infection was conducted. The *basic reproduction number* of the co-infection was calculated, and was found more sensitive to the HIV contact rate, relative infectiousness of HIV in individuals co-infected with HIV and malaria and reduction in sexual activity by individuals with malaria infection. The slow model has a global asymp-

totical DFE. For some conditions we have shown that the endemic equilibrium is also global asymptotical stable. We also generated a bifurcation diagram for the slow dynamics which provides thresholds for coexistence of the individuals who are co-infected with HIV and malaria.

The threshold conditions derived in this chapter $\mathcal{R}_{HM}$ will allow us to address how the epidemiological and demographic parameters affect the dual infection with HIV and malaria.

Chapter 7

Concluding remarks and scope for future research

This thesis deals with the analysis and implementation of robust numerical methods to solve mathematical models of HIV and malaria co-infection. Below we give a very brief summary of what we have done in individual chapters.

In Chapter 2, we considered a vector-host model for the transmission dynamics of malaria with a gamma distributed delay representing the incubation period of the disease in the vector. The model can be regarded as a generalization of SEI models (with a class for the latently infected mosquitoes) and SI models with a discrete delay for the incubation period in mosquitoes.

Chapter 3 dealt with the investigation of the effect of the distributed delay on the transmission dynamics of HIV-malaria co-infection. We first analyze the HIV only and Malaria only sub-models and then study the full model. The *basic reproduction number* $\mathcal{R}_M^{n,\bar{\tau}}$ for malaria only sub-model is calculated and shown to be decreasing with respect to the mean delay and the shape parameter of the gamma distribution. Also, when the disease is established, increasing these parameters leads to an endemic steady state with more healthy and less infected humans and mosquitoes. The threshold value of $\mathcal{R}_M^{n,\bar{\tau}}$ below which the disease can be eradicated is expressed in terms of the mean delay

and shape parameter. We found that when the mean delay is between the critical value of the incubation period of the SEI model and that of the SI model with a discrete delay, the shape parameter has an important effect on the disease eradication or establishment (the critical value is the one below which the disease will persist). In this case, we determine a critical value for the shape parameter above which the disease can be completely eradicated. This suggests that any intervention that is aimed at reducing the initial transmission, by delaying the incubation of the disease in the vector, should account for the shape of the delay's distribution as well. We further investigated the eradication/persistence by exploring the existence of steady states and their stability. The local stability of the disease free equilibrium (DFE) is studied analytically while that of the endemic equilibria is investigated numerically only. We also determined explicit conditions under which the system exhibits either a transcritical or backward bifurcation. We then performed a sensitivity analysis by calculating the sensitivity index to compare the relative impact of the mean delay $\bar{\tau}$ and the shape parameter n on both the initial transmission and on the disease prevalence at the (endemic) equilibria. our results showed that the sensitivity index of $\mathcal{R}_M^{n,\bar{\tau}}$ (and the endemic equilibrium point) is, as at least, twice as high in n than in $\bar{\tau}$.

In Chapter 4, we designed and analyzed a non-standard finite difference method to solve the co-infection model. We found that this method is unconditionally stable for the HIV-only sub-model. In the other two cases, the method can be analyzed if the summation term is handled appropriately. However, one may note that in these two cases, the malaria-only sub-model and the full model, the methods have the same set of equilibria as their continuous counterparts. To come up with the efficient numerical method for the full co-infection model, we have studied a number of qualitative properties of sub-models and then kept them in mind while designing the numerical methods for these sub-models. These methods, terms as non-standard finite difference methods posses a number of biologically significant properties. One of the salient features of these methods is that they preserve positivity of the solution which is very essential while studying epidemiological models. It is to be noted that a number of works can be

found in the literature where the standard finite difference methods have completely failed in giving reliable numerical results for such biological models.

We considered in Chapter 5 the full model presented in Chapter 3 for the special case when $n = 1$. We investigate in details the effect of malaria on HIV infection. Using singular perturbation techniques, we develop the two-time scales model and sperate it into fast time-scale for malaria dynamics and slow time-scale for the dynamics for the HIV infection. The analysis of the fast model showed that it has two normal hyperbolic equilibria. Singular perturbation theory allows us to study the perturbed system by studying the reduced slow systems associated with these two equilibria.

The reduced slow systems are derived and studied in Chapter 6. We first study the dynamics on the slow manifold associated with the disease free equilibrium of the fast model. The *basic reproduction number* for this model is calculated. The slow model has a global asymptotical DFE. We also show that under some conditions the endemic equilibrium is also global asymptotical stable. Furthermore, for the slow manifold associated with the endemic equilibrium of the fast model, a thorough mathematical analysis of a model that incorporates both malaria disease and HIV infection is conducted. The *basic reproduction number* of the co-infection is calculated, and is found more sensitive to the HIV contact rate, relative infectiousness of HIV in individuals co-infected with HIV and malaria and reduction in sexual activity by individuals with malaria infection. For some conditions we have shown that the endemic equilibrium is also global asymptotical stable.

As far as the scope of our future research is concerned, we list down the following:

- Currently we are developing a number of techniques that can be applied to the model of HIV and malaria co-infection.

- We are also developing and analyzing numerical methods to solve the reduced model associated with the endemic equilibrium of the fast model.

- We may also extend our numerical methods to solve some systems that arise from the optimal control formulation of the extended models that involve the control

parameters catering for optimal amount of medications for the patients suffering from co-infection of HIV and malaria.

- It should be noted that the numerical methods developed in this thesis are mostly first order accurate and developed only for biological systems described by ordinary differential equations. The fact that despite of being low order accurate, they are very competitive as compared to other conventional higher order methods, e.g., RK-4. We are currently busy investigating as how to improve the order of convergence of these NSFDMs.

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