Mathematical modeling of population dynamics of HIV with antiretroviral treatment and herbal medicine

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Abstract

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Herbal medicines have been an important part of health and wellness for hundreds of years. Recently the World Health Organization estimated that 80% of people worldwide rely on herbal medicines. Herbs contain many substances that are good for protecting the body and are therefore used in the treatment of various illnesses. Along with traditional medicines, herbs are often used in the treatment of chronic diseases such as rheumatism, migraine, chronic fatigue, asthma, eczema, and irritable bowel syndrome, among others. Herbal medicines are also applied in certain traditional communities as treatment against infectious diseases such as flu, malaria, measles, and even human immunodeficiency virus HIV-infection. Approximately 34 million people are currently infected with the human immunodeficiency virus (HIV) and 2.5 million newly infected. Therefore, HIV has become one of the major public health problems worldwide. It is important to understand the impact of herbal medicines used on HIV/AIDS. Mathematical models enable us to make predictions about the qualitative behaviour of disease outbreaks and evaluation of the impact of prevention or intervention strategies.

In this dissertation we explore mathematical models for studying the effect of usage of herbal medicines on HIV. In particular we analyze a mathematical model for population dynamics of HIV/AIDS. The latter will include the impact of herbal medicines and traditional healing methods. The HIV model exhibits two steady states; a trivial steady state (HIV-infection free population) and a non-trivial steady state (persistence of HIV infection). We investigate the local asymptotic stability of the deterministic epidemic model and similar properties in terms of the basic reproduction number. Furthermore, we investigate for optimal control strategies. We study a stochastic version of the deterministic model by introducing white noise and show that this model has a unique global positive solution. We also study computationally the stochastic stability of the white noise perturbation model. Finally, qualitative results are illustrated by means of numerical simulations.

Some articles from the literature that feature prominently in this dissertation are
[14] of Cai et al, [10] of Bhunu et al., [86] of Van den Driessche and Watmough, [64] of Naresh et al.,

Through the study in this dissertation, we have prepared a research paper [1], jointly with the supervisors to be submitted for publication in an accredited journal.

The author of this dissertation also contributed to the research paper [2], which close to completion.

1. Abdulaziz Y.A. Mukhtar, Peter J. Witbooi and Gail D. Hughes. A mathematical model for population dynamics of HIV with ARV and herbal medicine.

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Key words

KEYWORDS

HIV/AIDS

Compartmental model

Epidemiology

Chemotherapy

Herbal medicines

Differential equations

Stochastic differential equations

Basic reproduction number

Stability

Optimal control

Numerical simulation.

Declaration

I declare that *Mathematical modeling of population dynamics of HIV with antiretroviral treatment and herbal medicine* is my own work, that it has not been submitted before for any degree or examination in any other university, and that all the sources I have used or quoted have been indicated and acknowledged by complete references.

Abdulaziz Mukhtar February 27, 2014

Signed: .....

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Chapter 1

General Introduction

1.1 HIV/AIDS epidemiology

The Human Immunodeficiency Virus (HIV) is the etiological agent of Acquired Immunodeficiency Syndrome (AIDS) and has become one of the major public health problems worldwide. This virus has been killing people for more than 3 decades and will continue doing so if no advances are made towards better condition. According to UNAIDS there are an estimated of 34 million people living with HIV in the world with 2.5 million newly infected and 1.7 million AIDS deaths occurring. Of these, 23.5 million live in Sub-Saharan Africa. In South Africa alone, about 5.6 million are living with HIV/AIDS, and an estimated of 1000 AIDS related deaths occur on a daily basis [85]. According to the statistics, Sub-Saharan Africa is more heavily affected by HIV and AIDS than any other region of the world. In 2011, around 1.2 million people died from AIDS in Sub-Saharan Africa, and 1.8 million people became infected with HIV [85]. Since the beginning of the epidemic, more than eleven million children have been orphaned by AIDS [30]. In the absence of massively expanded prevention, treatment and care efforts, it is expected that the AIDS death toll in Sub-Saharan Africa will continue to rise. This means that the impact of the AIDS epidemic on societies will be felt most strongly in the course of the next ten years and beyond. The AIDS epidemic in sub-Saharan Africa threatens to devastate whole

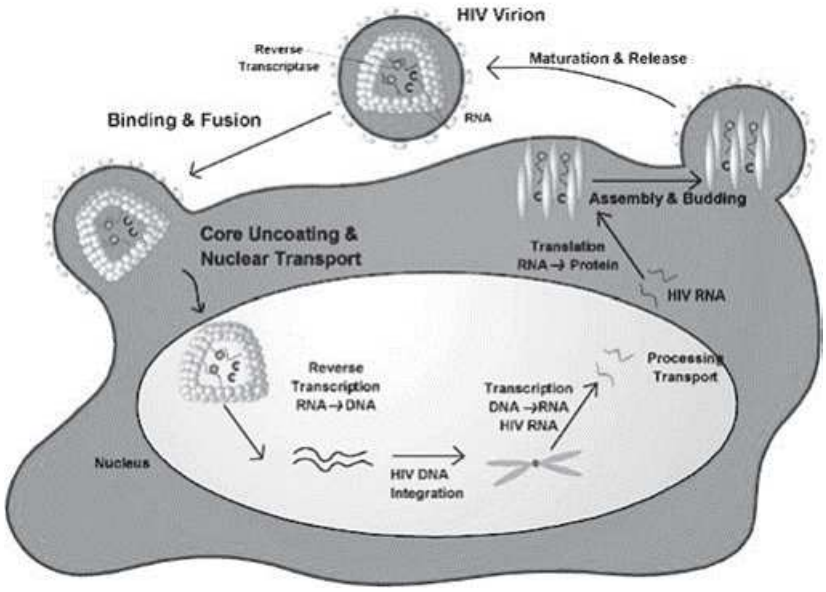


Figure 1.1: Source: [87], The life cycle of the HIV in the host CD4+.

communities, rolling back decades of development progress. Up to now, there is no cure, neither is there a vaccine to control this epidemic.

The HIV is mostly transmitted through: (1) sexual intercourse, (2) contaminated blood products or syringes, and (3) mother to child transmission during birth or through breast-feeding. An individual may advance through several infective stages before developing full blown AIDS [47]. The virus attacks certain white blood cells that are important to immune system function, known as helper T cells or more specifically, CD4+ T cells. The helper T cells are responsible for enhancing the production of antibodies by B cells. T cells and B cells are produced in the bone marrow, but T cells migrate to the thymus, where they mature [2]. On their surfaces, they possess proteins that can bind to foreign substances, such as HIV. At these connectors, the HIV is fused into the host CD4+ T cell. Since HIV is a retrovirus, the RNA of the virus is converted into DNA inside the CD4+ T cell. Thus, the DNA of the virus is duplicated and new virus particles bud from the CD4+ T cell [76]. This process proceed slowly and it gradually destroys the immune sys-

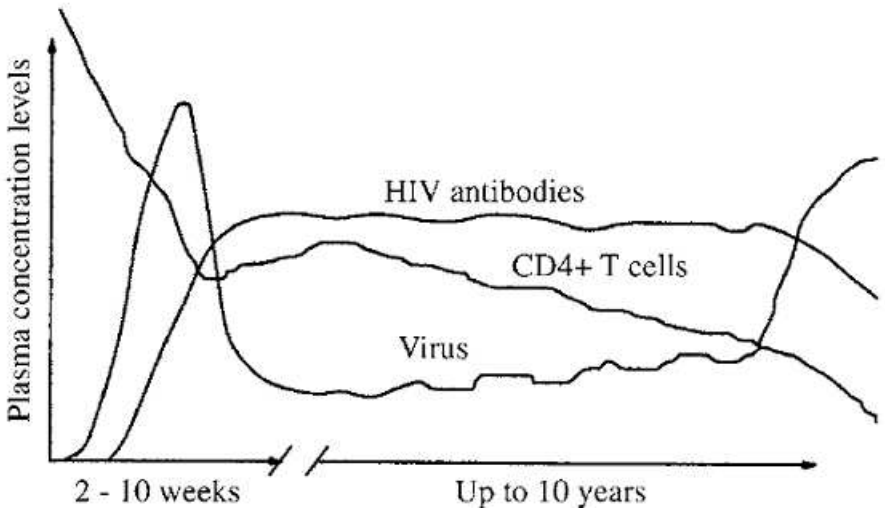


Figure 1.2: [61] Schematic time course of a typical HIV infection in an infected adult.

tem until it becomes unable to fight infections that would normally have been prevented. With the deterioration of the immune system, the body develops opportunistic infections that lead to Acquired Immunodeficiency Syndrome (AIDS). The figure 1.1 shows the life cycle and the relationship between the viral load and the CD4+ T cells counts.

The body produces on average of approximately one billion new virions daily, and the immune system destroys and removes not all but most of them, which are infectious [73]. An equal number of CD4+T cells are produced by the body and destroyed by virions, creating a balance of power between the virus and the CD4+T cells. This phenomenon continues up to three months on average. The number of CD4+ cells is small and the number of viruses is large. This leads to the slow depletion of CD4+ cells from about 2000 CD4+ cells per micro liter of blood in a healthy human. When the CD4+ count drops below 200 CD4+ cells per micro liter of blood, the immune system becomes compromised, leading to an increased susceptibility to infection [15, 61]. As a result, the number of CD4+ cells and viral load will remain lower for longer (about ten years) after the initial infection when the viral load starts increasing and the number of CD4+ cells decrease and the person is said to be in the final phase of HIV infection. The Figure 1.2 shows a typical course of HIV infection [61].

The progression of a typical HIV infection can take eight to ten years before the clinical syndrome (AIDS) occurs, and the progression goes through several distinct stages, marked by drastically different CD4+ T-cell counts and viral RNA levels. HIV-infected individuals are highly infectious in the first few weeks after infection, then remain in an asymptotic stage of low infectiousness for many years, and become gradually more infectious as their immune system becomes compromised, until they develop AIDS [30].

1.2 Herbal and traditional medicines

Herbal medicines have been an important part of health and wellness for hundreds years. Recently the World Health Organization estimated that 80% of people worldwide rely on herbal medicines. Herbs contain many substances that are good for protecting the body and therefore the use of herbal medicines are widespread in many chronic illnesses, and also on human immunodeficiency virus (HIV) infection, along with traditional medicines. Herbal medicines, are defined as products derived from plants or parts of plants for use in primary treatment in Africa [58]. The term traditional medicine (TM) has been conceptualized largely and it has been described with different terminologies by different authors [3]. According to the World Health Organization (WHO), it is a term used to describe Chinese medicine and various forms of indigenous medicine like the African traditional medicine. The therapies of TM may include among others the use of herbs, animal parts, minerals as well as non-medication therapies which includes the acupuncture, manual therapies and spiritual therapies which may involve incantations to appease the spirits as in the case of the African traditional medicine [3].

1.3 Motivation

Mathematical models based on the underlying transmission of HIV can help us to better understand how the disease spreads in the community, and can help investigate how

changes in the various assumptions and parameter values affect the epidemic. Various mathematical models have been proposed to describe the population dynamics of HIV/AIDS, see for example [92, 55, 56]. These models tended to focus on the theoretical study of the HIV/AIDS. Incorporation of interventions into these models has attracted significant attention in recent years [14, 35, 63]. The epidemiology of HIV/AIDS has moved beyond the virus and the risk factors associated with its transmission to a more detailed understanding of the mechanisms associated with the spread, distribution and impact of interventions on the population [50]. From the initial models of May and Anderson [5, 33] various refinements have been added into modeling frameworks, and specific issues have been addressed by researchers. In particular, Doyle et al. [22] developed a model for the spread of HIV in a heterosexual population by taking into account the group contact constraint conserves the number of new sexual partnerships and carried out equilibrium analysis. Greenhalgh et al. [29] studied the impact of condom use on sexual transmission of HIV and AIDS amongst a homogeneously mixing male population. A similar approach was considered earlier by Hyman et al. [35], with differential infectivity and staged progression models. Garira et al. [60] present a mathematical model to study the effects of public health educational campaigns as a single control strategy on HIV/AIDS in the continuing absence of a preventative vaccine or cure for HIV/AIDS. In this thesis we study the dynamics of HIV infection in patients receiving alternative treatment.

1.4 Aims and objectives

In view of the above, the idea is to harness mathematical models that represent the population as a system, that is changing over time. The behaviour of the system can be modified by controlling one or more variables that can be manipulated (e.g., treatment) to achieve a desired outcomes. Based on such a representation, decision rules may be determined using mathematical control principles. Population model of HIV with ARV treatment and with some individuals following traditional methods used to understand

the behaviour of modeling.

The main goal of this dissertation is to construct a mathematical model for the purpose of studying the extent and effect of the use of herbal traditional medicines on the transmission dynamics of HIV in the human population, and understanding the interplay between the variables and parameters that determine the course of infections. The model is obtained by sub-dividing the infected and uninfected populations into treated and untreated categories. The type of traditional treatment used is the administration of herbal medicines and chemotherapy to infectious persons (which acts to delay progression to disease). We present an optimal control problem in which the coefficient of the infection production term in the control results from chemotherapy. We seek to minimize the objective function. The optimal control is characterized using Pontryagin's Maximum Principle. We utilize the representation of the optimal control and solve numerically the optimality system. We also consider the corresponding stochastic model obtained from the deterministic model by introducing white noise. For this stochastic version, the global existence and positivity of the solution is showed. Comprehensive numerical simulations of the proposed model are carried out in order to understand the HIV dynamics.

1.5 Methodology

The epidemiology of HIV/AIDS has moved beyond the virus and the risk factors associated with its transmission to a more detailed understanding of the mechanisms associated with the spread, distribution and impact of interventions on the population. In most stages of HIV models infected individuals are assumed to have the same probabilities of disease transmission per contact in every class and the same rate of progression to the next class (compartment)[77]. In our work, we will take into account that infected individuals in one stage have different probability of infectiousness and rate of progression to AIDS depending on the type of the treatment that will be use.

In this dissertation, the following points have been our methodologies to attain our objectives:

- Present a basic model of an HIV/AIDS epidemic which refers to an SIR epidemic models by considering infected individuals to have the same effect for the dynamics of the disease throughout the course of the infection. This model gives a background of deterministic HIV/AIDS models.

- Formulate and analyse a staged progression HIV/AIDS model by regard the population to be of size $N(t)$ at time t, and divided into five compartments: S the susceptibles, I infected but not on any treatment, H infected and on alternative(non-ARV) treatment, J infected and on ARV-treatment, and finally, A denotes the class of individuals with full blown AIDS.

- Investigate the asymptotic behaviour of solutions and the stability analysis.

- Introduce a stochastic version for the HIV model by adding random fluctuations onto the deterministic model.

- investigate for optimal rollout of treatment strategies.

- Verify analytic solutions using numerical simulations.

1.6 Dissertation structure

Chapter 1 describes the biological background of HIV/AIDS. It discusses the role of mathematical models in epidemiology. The aims and objectives of the dissertation are laid out and the introductory chapter is concluded with a description of the structure of the dissertation.

Chapter 2 provides a literature review in mathematical modeling of HIV and of the use of herbs. The first part of the chapter is an overview of the mathematical models of the human immunodeficiency virus (HIV). The overview includes the assumptions and

results. The second part gives a review on herbal and traditional medicines.

Chapter 3 provides some mathematical tools that are used throughout the rest of this dissertation. We present some definitions and notation about dynamical systems and stability analysis, and theories that are required to analyze such systems. Theorems and lemmas from optimal control theory and stochastic differential equations used in epidemiology modeling are presented.

Chapter 4 provides an analysis of a basic model of an HIV/AIDS epidemic which refers to an SIR epidemic models. We also give examples on how to construct multipopulation models and the relationships between them. It is possible to develop analytical and numerical results of this model but mathematical analysis is kept to the minimum here.

Chapter 5 develops a mathematical model based on the underlying transmission of HIV, with part of the population using herbal medicine in an effort to curb or resist the virus. We calculate the basic reproduction number $\mathcal{R}_0$. We study two steady states of the system. These are the disease free equilibrium which biologically means the disease dies out and the endemic equilibrium. Further we carry out sensitivity analysis of $\mathcal{R}_0$ and the endemic equilibrium.

Chapter 6 incorporates quantitative and qualitative analysis into the model described in Chapter 5. Mathematical analysis of the HIV in terms of basic reproduction number $\mathcal{R}_0$ is showed. The numerical simulations are carried out to examine the qualitative behaviour of the model. The estimates of some of the parameter values used for the simulations are also presented.

Chapter 7 presents an optimal control problem relating to the model presented in Chapter 5, in which the level of ARV treatment is the control variable. We solve the control problem analytically and run some numerical simulation to illustrate the behaviour of the

solution.

Chapter 8 develops a stochastic version of the HIV model by adding random fluctuations onto the deterministic model. The positivity of the solutions is showed. Finally, qualitative results are illustrated by means of numerical simulations to verify stability.
We conclude and summarize the main results in Chapter 9.

Chapter 2

Literature review

2.1 Review around HIV epidemic

The fight against infectious diseases has had a long history, and great progress has been achieved, especially during the 20th century. While smallpox outbreaks have occurred from time to time for thousands of years, the disease has now been eradicated after a successful worldwide vaccination program. In 2006, less than 2000 cases were reported by the world health organization [53]. There are some other infectious diseases, such as diphtheria, measles, pertussis, and tetanus, that can be serious and fatal, but have been brought significantly under control in many countries. While the great achievements and progresses in the prevention and control of infectious diseases are promising and inspiring, there is a long way to go and it may be impossible to completely eradicate infectious diseases in the world.

To prevent and to control infectious diseases more effectively, it is important to fully understand the mechanisms of the spread and the transmission dynamics of the diseases. This will provide a useful basis for predictions so that better strategies can be established. The research on infectious diseases can be basically classified as descriptive, analytic, experimental and theoretic. The study of epidemic dynamics is an important theoretic

approach to investigate the transmission dynamics of infectious diseases. It formulates mathematical models to describe the mechanisms of disease transmission and dynamics of infectious agents. The mathematical models are based on population dynamics, behaviour of disease transmissions, features of the infectious agents, and the connections with other social and physiological factors. Through quantitative and qualitative analysis, sensitivity analysis, control theory and numeric simulations, mathematical models can give us a good understanding of how infectious diseases spread, the general principles governing the transmission dynamics of the diseases and sensitivity of parameters. This enable us to make reliable predictions and provide useful prevention and control strategies and guidance. We now present a brief survey of the numerous papers of mathematical models developed for HIV/AIDS transmission.

Del Valle et al., [21] present a novel model to incorporate genetic heterogeneity into HIV/AIDS epidemiology. In this study, they look at the impact of education, temporarily effective vaccines and therapies on the dynamics of HIV in homosexually active populations. In their model, they classify the homosexually active population into three classes of susceptible individuals: non-resistant (S_1), partially resistant (S_2) and fully resistant (S_3) to HIV infection. Infected individuals are classified as rapid (I_1), normal (I_2) and slow (I_3) progressors. In the model it is assumed that some individuals possess an allele that prevents the successful invasionor replication of HIV. The basic reproductive number for this model was derived and the relative contributions from different cases were discussed. Their results support the conclusions of Shu-Fang Hsu Schmitz [25], that some integrated intervention strategies (i.e., vaccination and treatment) are far superior to those based on a single approach.

Garira et al. [60] present a new mathematical model modified from [21] to study the effects of public health educational campaigns as a single control strategy on HIV/AIDS in the continuing absence of a preventative vaccine or cure for HIV/AIDS. They classify the sexually active population into four classes: susceptibles S, educated E, infected I,

and AIDS cases who are ill or showing AIDS symptoms A at time t. The threshold and equilibrium for the model are determined and stabilities are examined. Qualitative analysis of the model is also presented. They show that, the analysis of the model illustrates that public health education campaigns can reduce the basic reproductive number $\mathcal{R}_0$ to values below unity as intended for disease control. The obtained results show that effective control of the epidemic can easily be achieved when the effectiveness of education is high, and if $\mathcal{R}_0$ is not large.

Mukandavire et al. [59] developed a sex-structured model for heterosexual transmission of HIV/AIDS with explicit incubation period for modelling male circumcision as a preventive strategy HIV/AIDS in a community. They extended the model to incorporate condom use based on efficacy and compliance. The model consists of eight compartments, three for female populations and five for male populations. The female and male populations were each partitioned into three sub-populations; susceptible, infective and AIDS. The male susceptible and infectives were further categorized into two groups representing the uncircumcised and circumcised populations. Males in the AIDS group were assumed to be sexually inactive and thus were taken to be in the same category of uncircumcised population. The model also catered for emigration except for the individuals in the AIDS class. The model's numerical simulations were done to assess the effects of male circumcision and condom use in the absence of HIV/AIDS treatment. The model suggested that male circumcision has a potential of reducing the transmission of HIV/AIDS. They concluded that more effective results can be obtained if male circumcision is combined with condom use.

Anderson et al. [33] formulate a simple mathematical model to describe the transmission dynamics of HIV infection in homosexual communities. In conjunction with a survey of the available epidemiological data on HIV infection and the incidence of AIDS, their models are used to assess how various processes influence the course of the initial epidemic following the introduction of the virus. They mentioned that the models of the early

stages of viral spread provide crude methods for estimating the basic reproductive rate of the virus, given a knowledge of the incubation period of the disease (AIDS) and the initial doubling time of the epidemic. They formulated more complex models in order to assess the influence of variation in the incubation period and heterogeneity in sexual activity.

Tripathi et al. [65] developed a nonlinear mathematical model to study the effect of contact tracing on reducing the spread of HIV/AIDS in a homogeneous population with constant immigration of susceptibles. The model monitors four populations; susceptibles or HIV negatives, HIV positives or infectives that do not know they are infected, HIV positives that know they are infected and that of AIDS patients. The aware of the HIV infected population comprises of individuals that have contracted the virus and are known to be infected after being detected by random screening and by contact tracing. Susceptibles are assumed to become infected via sexual contacts with (both types of) infectives and all infectives move with constant rates to develop AIDS. They analysis their model using stability theory of differential equations and numerical simulation. They show that the endemic equilibrium is locally asymptotically stable and it becomes globally asymptotically stable under certain conditions. It is also found that the disease becomes more endemic due to immigration and the endemicity of the disease decreases when the infectives become aware of their infection after screening and contact tracing and do not take part in sexual interaction whereas it increases in the absence of contact tracing.

Daabo, I.M. et al. [18] proposed a mathematical model to study the combined effect of irresponsible infectives and irresponsible susceptible immigrants on the spread of HIV/AIDS and policies such as control on the number of careless immigrants into the given population could help control the spread of the disease. They consider a population of size $N(t)$, which is subdivided into five classes: careful susceptibles, careless susceptibles, careless infectives, careful infectives, and full-blown AIDS patients $S_1(t)$, $S_2(t)$, $I_1(t)$, $I_2(t)$ and $A(t)$ respectively. They presented stability analysis of the model and performed numerical simulations of the model. It is shown that the basic reproductive number, corresponds

to a disease free equilibrium, indicating that the disease is under control. The disease however becomes endemic when and thus the disease remains in the population.

Nyabadza and Mukandavire [68] present deterministic HIV/AIDS model that incorporates condom use, screening through HIV counseling and testing (HCT), regular testing and treatment as control strategies. The model looks at the recently launched HCT campaign, to model its impact on the dynamics of the disease. They investigate the global stabilities of the equilibrium point under the conditions of basic reproduction number. Their model shows that HCT itself has very little impact in reducing the prevalence of HIV, unless the efficacy of the campaigns exceed an evaluated threshold in the absence of backward bifurcation. The model also embodies plausible assumptions regarding screening and treatment. They carry out numerical simulations and the model is fitted to data on HIV prevalence in South Africa.

Nicholas et al. [28] employed a novel deterministic model of HIV transmission that allows for heterogeneity in sexual and drug-injecting behaviour, different patterns of mixing among IDUs and the sexually active population, and the presence of a bacterial STI that can enhance HIV transmission. In addition, a fraction of the female IDU population may be involved in sex work, associated with higher rates of sexual partner change but also increased condom usage. The model is not age-stratified and does not allow for geographic dispersion and migration. However, the demographic parameters of the model are defined to reflect best estimates of the dynamics of populations of both IDUs and the adult population as a whole. Further, they do not include male to male transmission through sex between men due to a lack of behavioral data and estimates of the size of this risk group in the region. Behavioral data used to classify sexual activity into five levels, and drug injecting into six levels. Their model analyses also suggest the significant impact that improved diagnosis and treatment of other STIs can have on future HIV prevalence. Although more significant early in the epidemic, due to co-occurrence of HIV in the name individuals and recovery rates remain a strong determinant of HIV prevalence through-

out an epidemic, even after accounting for uncertainty in the degree of HIV transmission enhancement.

Raimundo et al. [74] presents a deterministic HIV-1 model to examine the mechanisms underlying the emergence of drug-resistance during therapy. Their model's assumption is that drug-resistance can evolve directly during the therapy for whatever reason. The above assumptions lead to the model being divided into five epidemiologic classes: susceptible individuals; treatment-naive patients with drug-sensitive HIV-1 infection; treatment-naive patients with drug-resistant HIV-1 infection; successfully treated patients with drug-sensitive HIV-1 infection; and HIV-1 infected individuals in therapeutic failure. They study to determine whether, and how fast, antiretroviral therapy may determine the emergence of drug resistance by calculating the basic reproductive numbers. However, they study local stability of equilibriums. By performing numerical simulations they show that Hopf bifurcation may occur. Note that the model does not consider a class of individuals with clinical AIDS, composed of patients who progress to full-blown AIDS. They assumed this because of their illness, these patients do not play a role in the transmission of the drug-resistant HIV-1 infection.

Okosun et al. [70] derived and analyzed a deterministic model for the transmission of the HIV/AIDS disease to examine the recruitment effect of susceptible and infected individuals in order to assess the productivity of an organizational labor force in the presence of HIV/AIDS with preventive and HAART treatment measures in enhancing labour productivity in the workforce. The model sub-divides the total human population at time t, denoted by $N(t)$, into the following sub-populations of susceptible productive workers $S_p(t)$, susceptible non-productive workers $S_n(t)$, infected non-productive workers $I_n(t)$, infected productive individuals on HAART treatment $I_p(t)$, and that of full-blown AIDS individuals $A(t)$. They carried out a stability analysis of the equilibrium and the model is found to exhibit backward and Hopf bifurcations, implying that for the disease to be eradicated. Furthermore, they also performed an optimal control analysis of the model.

Finally, numerical simulations are performed to illustrate the analytical results.

Zhang et al. [94] considered an epidemic model that discusses the spread of HIV/AIDS in Yunnan, China. The total population in their model is restricted within high risk population. By the epidemic characteristics of HIV/AIDS in Yunnan province, the model classifies the high risk population into two groups: injecting drug users (IDUs) and people engaged in commercial sex which include female sex workers and clients of female sex workers. The susceptibles are subclassified according to their behaviours. If a susceptible individual uses drugs with others by sharing injectors, then he/she belongs to the IDUs group $S1(t)$. The infectives and AIDS are defined by their transmission modes. The conditions and thresholds for the existence of four equilibria are established. They compute the reproduction number for each group independently, and show that when both the reproduction numbers are less than unity, the disease-free equilibrium is globally stable. The local stability for other equilibria including two boundary equilibria and one positive equilibrium are figured out. When they omit the infectivity of AIDS patients, global stability of these equilibria are obtained. For the simulation, they carried out the parameter estimation and projection of HIV in Yunnan and it shows that the HIV infection maintains a higher prevalence in IDUs.

Sani and Kroese [78] developed three different models to describe the spread of HIV infectives in multiple, sexually active populations, where individuals are allowed to migrate among populations. In the first two models they assume that the individuals do not make an actual move among patches but that there is a force of infection from infected patches to others. The mode of transmission is assumed to be via sexual contact only between partners of opposite sex. This assumption is mainly because heterosexual contact is still the primary mode of HIV infection worldwide. Individuals in each population are divided into four groups (compartments): female susceptibles, female infectives, male susceptibles, and male infectives and assume that males are fewer then females and males choose a female partner from the female subpopulation. They introduce a simple alternative

method by employing a cross-entropy (CE) technique to solve these highly multi-modal and non-linear optimization problems. The numerical experiments suggest that the controls for the different patches are highly synchronized. Moreover, they indicate that the optimal trajectories qualitatively have similar form.

2.2 Review on herbal and traditional medicines

No known herbal remedy has been shown to cure AIDS or even reduce chances of AIDS-related infections. Nevertheless some HIV-infected people use herbs for potential cure. For example, in China and South Africa herbs are used as primary treatments for HIV/AIDS and for HIV-related problems [58]. Some clinical studies have shown that herbal medicines might have the potential to alleviate symptoms, reduce viral load, and increase CD4+ cells for HIV-infected individuals and AIDS patients [49]. In Africa, herbal medicines are often used as primary treatment for HIV/AIDS and for HIV-related problems. A new scientific study has shown that there is little evidence to support claims that garlic, onions, olive oil and the African potato are effective in the fight against HIV/AIDS and warned that they may even be harmful [83]. Hypoxis hemerocallidea (African potato) and Bulbine natalensis (rooiwortel) are commonly and inappropriately used in South Africa for the alleviation of many immune related ailments, and for treatment of HIV/AIDS, due to the inaccessibility of antiretroviral drugs [24].

Herbs that have proven antiviral effect, by building the immune system to eliminate viruses, include Bay La Sun and Elderberry (Sambucus nigra). Elderberry is believed to be one of the strongest plants that have anti-virus agents. Some proteins in the the Bay La Sun contains an element called Onteveran (antivirin), which has been shown to disrupt the ability of influenza virus by preventing it from invading healthy cells [6]. Garlic is antiviral and antibacterial, and many sulfur compounds in garlic are effective against the flu virus. Fresh garlic have been proven to counteract viral infections such as measles, mumps, chicken pox, herpes simplex, zoster, viral hepatitis and scarlet fever.

Licorice, echinacea, aloe vera, St. Johnswort, and ginseng are just a few of the herbs used to treat HIV/AIDS. Taking immunity-boosting herbs (such as astragalus, echinacea, and ginkgo) may help revive an ailing immune system, and certain herbs may help battle bacteria and viruses. Licorice root is a powerful anti-virus, which contains many compounds including acid Algelesarhizak glycyrrhizic acid. This acid prevents the growth of several viruses in the laboratory, including the herpes virus, human immunodeficiency virus (HIV) and the SARS virus (SARS) [62]. Licorice also can work to soothe the mouth and throat ulcers that often accompany full-blown AIDS [6]. However even if these herbs have these powers, it is not yet understood just how they work in fighting AIDS or whether using them really makes a significant difference in the course of the disease [62].

A woody vine that grows in the rainforests of Peru was used for centuries by the Ashanica Indians for treating a wide range of illnesses. Today it helps relieve the suffering of AIDS and cancer patients. It effectively reduces the side effects of treatments such as AZT and radiation therapy. This miraculous herb has been used for centuries by the Ashanica Indians to stimulate the immune system and treat a wide variety of health problems [62]. Worldwide research on this powerful herb has led scientists to patent many of the single chemicals found in it for use in treating cancer, arthritis, AIDS and other diseases. However, still some herbs can be used safely and in consultation with a qualified practitioner who not only understands herbs but also has experience in treating AIDS and HIV infection. In addition, WHO intends to develop information sources and guidelines to enhance safety, quality, and efficacy of traditional medicines.

Acemannan is a complex sugar extracted from the aloe vera plant. It is approved for veterinary use in the United States, particularly for feline leukemia, which is caused by a retrovirus. Some people with HIV have tried using acemannan and other concentrated aloe products to manage HIV infection. However, when in the test tube it inhibits HIV and increases the function of some immune cells [51]. Listing all of the herb-drug interactions,

which potentially impact people living with HIV, is not possible. A few more of the popular herbals used by the general population in USA and also in India as herbal medicine are Ginseng, St. John's Wort, ma-hung, kava, ginkgo biloba, fever few, ginger, saw palmetto, comfrey, pokweed, hawthorne, dongquai, and cat's claw [72]. Despite all the attempts, there is as yet no cure for HIV and neither is there a vaccine.

Chapter 3

Mathematical preliminaries

3.1 Introduction

In this chapter we present some definitions and theorems required to analyze model systems in this dissertation. We present concepts such as existence and uniqueness of solutions, Lyapunov function theorem, Pontryagins Maximum Principle and the basic reproduction number $\mathcal{R}_0$, for a general compartmental disease transmission model based on a system of ordinary differential equations. The Hurwitz condition, and the M-matrix condition in unified and simplified forms are also discussed. Finally, we will discuss mathematical definitions and geometrical explanations of various stability and attraction concepts. Readers are refered to the indicated references for the proofs of the results.

3.2 Fundamental theorems of ordinary differential equations

Consider the first order ordinary differential equation initial value problem of the form,

$$\frac{dx}{dt} = F(x,t),\ x(0) = x_0 \tag{3.1}$$

where $F(x)$ is bounded in a neighborhood of the initial condition.

Definition 3.1 (See Birkhoff and Rota [12])(Lipschitz condition). A vector-valued function $X(x,t)$ satisfies the Lipschitz condition in a region $\mathbb{R}$ of $(x,t)-$space if and only if, for some constant L,

$$|X(x,t) - X(y,t)| \leq L|x-y| \text{ if } (x,t) \text{ and } (y,t) \in \mathbb{R} \tag{3.2}$$

Theorem 3.2 *Let E be an open subset of $\mathbb{R} \times F^n$ containing x_0 and assume that $F \subseteq C^1(E)$. Then there exists an $a > 0$ such that the initial value problem*

$$\dot{x} = f(x); \quad x(0) = x_0,$$

has a unique solution $x(t)$ on the interval $[-a, a]$.

Theorem 3.3 (See [12])(Comparison Theorem). *Let f and g be solutions of the the differential equations*

$$\dot{y} = F(x,y) \text{ and } \dot{x} = G(x,y)$$

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

3.3 Basic Reproduction Number $\mathcal{R}_0$

The basic reproduction number, denoted by $\mathcal{R}_0$, plays a vital role in the control and eradication of epidemics. It has been defined as the average number of secondary infections that occur when one infective is introduced into a completely susceptible host population [86], by a single infective. If $\mathcal{R}_0 < 1$, then on average, an infected individual produces less than one new infected individual and the epidemic dies out. On the other hand, if $\mathcal{R}_0 > 1$, then each infected individual produces, on average, more than one new infection and the epidemic invades the population. Thus the basic reproduction number $\mathcal{R}_0$ is often regarded as the threshold quantity that determines when an infection can invade and persist in a new host population [32]. For simple models, $\mathcal{R}_0$ is simply the product

of the infection rate and the mean duration of the infection [86].

For simple models, when there is only a single infected compartment, the value for $\mathcal{R}_0$ is simply the product of the infection rates and the duration of the infection. Watmough and van den Driessche's [86] have developed a method for computing $\mathcal{R}_0$, and this method has since been used very popularly. We explain the method. Now, we consider the following system of equations for the disease transmission model (epidemic model)

$$\dot{x}_i = f_i(x) = \mathcal{F}_i(x) - \mathcal{V}_i(x), i = 1, ..., n, \tag{3.3}$$

where

$$f(x) = \begin{pmatrix} f_1(x) \\ 0 \\ 0 \\ 0 \\ f_n(x) \end{pmatrix}, \text{ and } x = \begin{pmatrix} x_1 \\ 0 \\ 0 \\ 0 \\ x_n \end{pmatrix}. \tag{3.4}$$

Models the rate of change of x_i (where $x_i \geq 0$, is the number of individuals in the compartment i'th). We write

$$\mathcal{V}_i = \mathcal{V}_i^- - \mathcal{V}_i^+$$

with

- $\mathcal{V}_i(x)$ being the rate of appearance of new infections in compartment i,
- $\mathcal{V}_i^-(x)$ being the rate of transfer out of the i^{th} compartment,
- $\mathcal{V}_i^+(x)$ being the rate of transfer into the i^{th} compartment,

and these functions are assumed to be continuously differentiable at least twice. Also,

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

Here $\mathcal{X}_s$ represents the set of all disease-free states. We assume that these functions satisfy the assumptions $\mathcal{H}_1, \ldots, \mathcal{H}_5$ as described below:

$\mathcal{H}_1$: If $x_i \geq 0$, then $\mathcal{V}_i(x)$, $\mathcal{V}_i^-(x)$, $\mathcal{V}_i^+(x) \geq 0$ for $i = 1, ..., n$.

$\mathcal{H}_2$: If $x_i = 0$, then $\mathcal{V}_i^-(x) = 0$ and in particular, $\mathcal{V}_i^+(x) = 0$, if $X \in \mathcal{X}_s$ for $i = 1, ..., m$ this implies that there can be no transfer of individuals out of an empty compartment by any means. These two assumptions imply that if $x_i = 0$, then $f_i(x) \geq 0$. Therefore (3.3) is positively invariant [88]; that for each nonnegative initial condition there is a unique, nonnegative solution.

$\mathcal{H}_3$: $\mathcal{F}_i = 0$ if $i > m$ holding for the fact that the rate at which infection occurs (incidence of infection) in an uninfected compartment is zero.

$\mathcal{H}_4$: $\mathcal{F}_i = 0$ and $\mathcal{V}_i^+(x) = 0$ if $x \in \mathcal{X}_s$, $i = 1, ..., m$. This condition is to guard against the disease-free subspace being altered and this assumption ($\mathcal{H}_4$) implies that if a population is free of disease then it remains free with no room for immigration of infectives into the compartment.

$\mathcal{H}_5$: If $\mathcal{F}(x)$ is set to zero, then all eigenvalues of $Df(x_0)$ have negative real parts.

The following lemma assures that, under conditions $(\mathcal{H}_1), \cdots, (\mathcal{H}_5)$ the Jacobian, $Df(x_0)$ can be partitioned into a matrix of new infection and that of transfer of individuals in and out of a compartment.

Lemma 3.4 [86]. *If x_0 is a disease free equilibrium of system(3.3) and $\mathcal{F}_i(x)$ satisfies the assumptions ($\mathcal{H}_1$) through ($\mathcal{H}_5$), then the derivatives $DF(x_0)$ and $DV(x_0)$ are partitioned as*

$$D\mathcal{F}(x_0) = \begin{pmatrix} F & 0 \\ 0 & 0 \end{pmatrix}, \text{ and } D\mathcal{V}(x_0) = \begin{pmatrix} V & 0 \\ J_3 & J_4 \end{pmatrix},$$

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

$$F = [\ \tfrac{\partial \mathcal{F}_i}{\partial x_j}(x_0)\ ], \text{ and } V = [\ \tfrac{\partial \mathcal{V}_i}{\partial x_j}(x_0)\ ], \text{ where } 1 \leq i, j \leq m.$$

Further, F is non-negative, V is a non-singular M -matrix and all the eigenvalues of J_4 have positive real parts. Thus the matrix V^{-1} is non-negative, and so is FV^{-1}.

If an infected individual is introduced into a compartment k of a disease free population, then the (j,k) entry of V^{-1} can be interpreted as the average length of time this individual spends in compartment j during its lifetime. The (i,j) entry of F can be interpreted as the rate at which infected individuals in compartment j produce new infections in compartment i.

The FV^{-1} matrix is called the next generation matrix for the model [86]. The (i,k) entry of the next generation matrix is the expected number of new infections in compartment i produced by the infected individual originally placed into compartment k. The basic reproduction number $\mathcal{R}_0$, is obtained as

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

where $\rho(FV^{-1})$ denotes the spectral radius of the FV^{-1}.

Thus, from [86], and above analysis we state theorem below.

Theorem 3.5. *Consider the disease transmission model given by (3.3) with $f(x)$ satisfying conditions $(\mathcal{H}_1)$-$(\mathcal{H}_5)$. If x_0 is a disease free equilibrium of the model, then x_0 is locally asymptotically stable if $\mathcal{R}_0 < 1$, but unstable if $\mathcal{R}_0 > 1$, where $\mathcal{R}_0$ is defined by (3.5).*

3.4 Stability for ordinary differential equations

Consider the following n-dimensional initial value autonomous system:

$$\begin{aligned} \frac{dX}{dt} &= F(X), \\ x(0) &= x_0, \end{aligned} \tag{3.6}$$

where $x \in \mathbb{R}^n$ and $F : \mathbb{R}^n \to \mathbb{R}^n$; with all the properties needed.

Definition 3.6. An *equilibrium solution* (steady-state solution, fixed point, or critical point) of the differential system (3.1) is a constant solution x of the equation

$$F(x) = 0. \tag{3.7}$$

In order to derive sufficient conditions for the global stability and asymptotic stability of such a rest point we will apply the so called direct method of Lyapunov and the Routh-Hurwitz Criteria. The Routh-Hurwitz Criteria is an important set of necessary and sufficient conditions for all of the roots of the characteristic polynomial to lie in the left half of the complex plane. The Routh-Hurwitz Criteria are used in Chapter 5 to determine local stability of an equilibrium for a non-linear system of differential equations.

Theorem 3.7 (see Allen [2]) **Routh-Hurwitz Criteria**. *Given the polynomial*

$$P(\lambda) = \lambda^n + a_1\lambda^{n-1} + .. + a_{n-1}\lambda + a_n;$$

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

$$H_1 = (a_1),\ H = \begin{pmatrix} a_1 & 1 \\ a_3 & a_2 \end{pmatrix},\ H = \begin{pmatrix} a_1 & 1 & 0 \\ a_3 & a_2 & a_1 \\ a_5 & a_4 & a_3 \end{pmatrix},$$

and

$$H = \begin{pmatrix} a_1 & 1 & 0 & 0 & ... & 0 \\ a_3 & a_2 & a_1 & 1 & ... & 0 \\ a_5 & a_4 & a_3 & a_2 & ... & 0 \\ \vdots & \vdots & \vdots & \vdots & ... & \vdots \\ 0 & 0 & 0 & 0 & ... & a_n \end{pmatrix}$$

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

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

When $n = 2$ the Routh-Hurwitz Criteria simplify to $\det H_1 = a_1 > 0$ and

$$\det H_2 = \det \begin{pmatrix} a_1 & 1 \\ 0 & a_2 \end{pmatrix} = a_1 a_2 > 0.$$

or $a_1 > 0$ and $a_2 > 0$. For a polynomial of degree $n = 2, 3, 4$ and 5, the Routh-Hurwitz Criteria are summarized as follows:

Routh-Hurwitz Criteria for $n = 2, 3, 4,$ and 5

$n = 2 : a_1 > 0$ and $a_2 > 0$.

$n = 3 : a_1 > 0, a_3 > 0$ and $a_1 a_2 > a_3$.

$n = 4 : a_1 > 0$ and $a_2 > 0, a_4 > 0$ and $a_1 a_2 a_3 > a_3^2 + a_1^2 a_4$.

$n = 5 : a_i > 0$ $i = 1, 2, 3, 4, 5, a_1 a_2 a_3 > a_3^2 + a_1^2 a_4$ and

$(a_1 a_4 - a_5)(a_1 a_2 a_3 - a_3^2 - a_1^2 a_4) > a_5(a_1 a_2 - a_3)^2 + a_1 a_5^2$.

Definition 3.8 (see Allen [2]). Let U be an open subset of $\mathbf{R}^n$ containing the origin. A real-valued $C^1(U)$ function, $V : U \to \mathbf{R}$, $[(x, y) \in U, V(x, y) \in \mathbf{R}]$ is said to be positive definite on the set U if the following two conditions hold.

(i) $V(0, 0) = 0$

(ii) $V(x, y) > 0$ for all $(x, y) \in U$ with $(x, y) \neq 0$.

The function V is said to be negative definite if $-V$ is positive definite.

Definition 3.9 (see Jordan and Smith [40]). $V(x)$ is said to be *positive (negative) definite* in a neighborhood U of the origin if $V(x) > 0$ $(V(x) < 0)$ for all $x \neq 0$ in U, and $V(0) = 0$. $V(x)$ is positive (negative) semidefinite in a neighborhood U of the origin if $V(x) \geq 0$ $(V(x) \leq 0)$ for all $x \neq 0$ in U, and $V(0) = 0$.

Theorem 3.10 (see Jordan and Smith [40]). *Let $X^*(t) = 0$, $t \geq t_0$, be the zero solution of the regular system $\dot{X} = X(x)$, where $X(0) = 0$. Then $X(x(t))$ is uniformly stable for $t \geq t_0$ if there exists $V(x)$ with the following properties in some neighborhood of $X = 0$:*

(i) $V(x)$ and its partial derivatives are continuous;

(ii) $V(x)$ is positive definite;

(iii) $\dot{V}(x)$ is negative semidefinite.

Theorem 3.11. *Suppose that all the conditions of the Theorem (3.10) apply, except that condition (iii) is replaced by*

(iii)′ $\dot{V}$ *is negative definite.*

Then the zero solution is asymptotically stable (and such a function V *is called a strong Lyapunov function for the system).*

Theorem 3.12 (see Castillo-Chavez and Song [16]). *Consider the following general system of ordinary differential equations with a parameter* φ*:*

$$\frac{dx}{dt} = f(x, \varphi), \ f : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R}^n \text{ and } f \in C^2(\mathbb{R}^n \times \mathbb{R}). \tag{3.8}$$

where 0 *is an equilibrium for system (3.9) for all values of the parameter* φ *is that*

$$F(x, \varphi) \equiv 0 \text{ for all } \varphi.$$

Assume

- $A = D_x f(0,0) = (\frac{\partial x_i}{\partial x_j}(0,0))$ *is the linearization matrix of system (3.8) 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* v *and a left eigenvector* u *corresponding to the zero eigenvalue.*

Let f_k *be the* k^{th} *component of* f *and*

$$\begin{aligned} a &= \sum_{k,i,j=1}^{n} v_k u_i u_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0), \\ b &= \sum_{k,i,j=1}^{n} v_k u_i \frac{\partial^2 f_k}{\partial x_i \partial \varphi}(0,0). \end{aligned}$$

The local dynamics of (3.8) around 0 *are totally determined by* a *and* b*.*

1. $a > 0,\ b > 0$ *: When* $\varphi < 0$ *with* $|\varphi| \ll 1$*, the point* 0 *is locally asymptotically stable, and there exists a positive unstable equilibrium; when* $0 < \varphi \ll 1$*, the point* 0 *is unstable and there exists a negative and locally asymptotically stable equilibrium;*
2. $a < 0,\ b < 0$ *: When* $\varphi < 0$ *with* $|\varphi| \ll 1$*, the point* 0 *is unstable; when* $0 < \varphi \ll 1$*, the point* 0 *is locally asymptotically stable, and there exists a positive unstable equilibrium;*
3. $a > 0,\ b < 0$ *: When* $\varphi < 0$ *with* $|\varphi| \ll 1$*, the point* 0 *is unstable, and there exists a locally asymptotically stable negative equilibrium; when* $0 < \varphi \ll 1$*, is stable, and a positive unstable equilibrium appears;*
4. $a < 0,\ b > 0$ *: 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.*

Particularly, if $a > 0,\ b > 0$ *then a backward bifurcation occurs at* $\varphi = 0$.

3.5 The general optimal control problem

In an optimal control problem for ordinary differential equations, we use $u(t)$ for the control and $x(t)$ for the state variables. The state variable satisfies a differential equation which depends on the control variable:

$$\dot{x}(t) = g(t, x(t), u(t))$$

where $\dot{x}$ denote the derivative with respect to time t. Both $u(t)$ and $x(t)$ affect the goal, as the control function changes, the solution to the differential equation will also change. The basic optimal control problem consists of finding a piecewise continuous control $u(t)$ and the associated state variable $x(t)$ to maximize or minimize the given objective functional depending on the situation. Let us consider the former for this case, i.e.,

$$\text{Maximize } J(u) = \int_0^T f(t, x(t), u(t))dt$$

subject to

$$\dot{x(t)} = g(t, x(t), u(t)) \tag{3.9}$$

where

$$x(0) = x_0 \text{ and } x(T) \text{ is free.}$$

We assume that the controls are piecewise continuous functions with values in a set u. However, one can also use Lebesgue measurable functions. The optimal control, denoted by $u(t)$, achieves the maximum. One can substitute $u(t)$ into the state ODEs and obtain the corresponding optimal state $x(t)$. We say $u(t)$, $x(t)$ is an optimal pair. Presented next is a brief derivation of the necessary conditions. That is, if $u(t)$, $x(t)$ is an optimal pair, then these conditions will hold. These necessary conditions for optimal control theory for ODEs was developed by Pontryagin and his collaborators around 1950. They developed the key idea of introducing the adjoint function to attach the differential equation to the objective functional. This idea is similar to Lagrange multipliers that attach the constraints when finding the maximum of a function in multi-dimensional calculus subject to some equation constraints.

The principal technique for such an optimal control problem is to solve a set of necessary conditions that an optimal control and corresponding state must satisfy.

Define an objective functional in terms of the control as

$$J(u) = \int_0^T f(t, x(t), u(t))dt.$$

The following theorem (known as Pontryagins Maximum Principle), provide necessary conditions for the optimal control using the Hamiltonian [79].

Theorem 3.13 (Pontryagins Maximum Principle) *If u^* and x^* are optimal for equation (3.9), subject to the ODEs defining the given dynamical system, then there exists a piecewise differentiable adjoint variable $\lambda(t)$ such that*

$$H(t, x^*(t), u(t), \lambda(t)) \leq H(t, x^*(t), u^*(t), \lambda(t))$$

for each control u at each time t, where the Hamiltonian H is

$$H = f(t, x(t), u(t)) + \lambda g(t, x(t), u(t))$$

and

$$\lambda^{'}(t) = \frac{\partial H(t, x^*(t), u^*(t), \lambda(t))}{\partial x},$$
$$\lambda(T) = 0,$$

where f is the integrand of the objective functional and g, the right hand side of the given dynamical system. The optimal control u^* must maximize the Hamiltonian.

3.6 Stochastic Differential Equations

We now return to the possible solutions $X_t(\omega)$ of the stochastic differential equation

$$\frac{dX_t}{dt} = b(t, X_t) + \sigma(t, X_t)B_t, \quad b(t, x) \in \mathbb{R}, \ \sigma(t, X_t) \in \mathbb{R} \tag{3.10}$$

where B_t is 1-dimensional 'white noise'. Interpretation of (3.11) is that X_t satisfies the stochastic integral equation

$$X_t = X_0 + \int_0^t b(s, X_s)ds + \int_0^t \sigma(s, X_s)dB_s$$

or in differential form

$$dX_t = b(t, X_t)dt + \sigma(t, X_t)dB_t, \tag{3.11}$$

Therefore, to get from (3.10) to (3.11), we formally just replace the white noise B_t by $\frac{dB_t}{dt}$ in (3.10) and multiply by dt.

Consider the d-dimensional stochastic differential equation

$$dX(t) = f(x(t), t)dt + g(x(t), t)dB(t), \tag{3.12}$$

where $f : U \to \mathbb{R}^n$; $g : U \to \mathbb{R}^{n\times p}$; $U \subset \mathbb{R}^n$, ($\mathbb{R}^n$ is the set of real number) in a given range,

$X = (x_1, x_2, ..., x_n) \in U$;

$B = (B_1, B_2, ..., B_p)$ is the given d-dimensional Brownian motion.

On $t_0 \leq t \leq T$, with initial value $x(t_0) = x_0$. The first term represents f the continuous

deterministic component or drift coefficient and the second term represent g the continuous random component or diffusion coefficient [17]. We regard f as an m-vector-valued function, g is an $m \times d$ matrix-valued function.

Definitions 3.14 For any given initial value $x_0 \in U$, equation (3.12) has a unique global solution such that $X(t_0) = X_0$, and is denoted by $X(t; t_0, X_0)$. If $f(0,t) = 0$ and $g(0,t) = 0$ for all $t > t_0$, then equation (3.13) has the solution $X(t) = 0$ corresponding to the initial value X_0, the solution is called the trivial solution or equilibrium position.

Theorem 3.15 see [71] (Existence and uniqueness theorem for stochastic differential equations).
Let $T > 0$ and $b(\cdot,\cdot) : [0,T] \times \mathbf{R}^n \to \mathbf{R}^n$, $\sigma(\cdot,\cdot) : [0,T] \times \mathbf{R}^n \to \mathbf{R}^{n\times m}$ be measurable functions satisfying

$$|b(t,x)| + |\sigma(t,x)| \leq C(1 + |x|); \quad x \in \mathbf{R}^n, t \in [0,T] \tag{3.13}$$

for some constant C, (where $|\sigma|^2 = \sum |\sigma_i j|^2$) and such that

$$|b(t,x) - b(t,y)| + |\sigma(t,x) - \sigma(t,y)| \leq D\,|x - y|); \quad x, y \in \mathbf{R}^n, t \in [0,T] \tag{3.14}$$

for some constant D. Let Z be a random variable which is independent of the σ-algebra $\mathcal{F}_\infty^{(m)}$ generated by $B_s(\cdot)$, $s \geq 0$ and such that

$$E[|Z|^2] < \infty.$$

Then the stochastic differential equation

$$dX_t = b(t, X_t)dt + \sigma(t, X_t)dB_t, \quad 0 \leq t \leq T, \; X_0 = Z \tag{3.15}$$

has a unique t-continuous solution $X_t(\omega)$ with the property that $X_t(\omega)$ is adapted to the filtration $\mathcal{F}_t^Z$ generated by Z and $B_s(\cdot)$; $s \leq t$
and

$$E\left[\int_0^T |X_t|^2\, dt\right] < \infty. \tag{3.16}$$

Chapter 4

A basic model of an HIV/AIDS epidemic

Infectious diseases such as HIV, measles, etc are modeled by classifying individuals in the population according to their status with respect to the disease: healthy, infected, and immune, etc. An infection can be transmitted through contact between the infective and susceptible (horizontal transmission) and for some diseases, from an infective parent to an unborn or newly born offspring (vertical transmission). The disease states, S, I, and A are defined as susceptible, infected, and AIDS class respectively. A model with these three states are referred to as an SIA epidemic models. We now introduce three models that have a bearing to our work. Firstly, we consider a simple transmission model which consists of three ordinary differential equations that represent the epidemiology of human immunodeficiency virus (HIV) with discussion. The model we consider here is based on the compartment model studied by Zhien Ma and Jia Li [53]. The model divides the population into three groups based on their epidemiological status; Susceptible individuals (S), the HIV infectives (I) and the class of individuals with full blown AIDS (A). Secondly, we briefly introduce a multistage model and finally introduce a multipopulation model.

4.1 Model formulation

We consider an SIA model which describes the transmission of HIV in a population as a system of three ordinary differential equations. For the model we denote by (S) the susceptibles, (I) the HIV infectives and (A) the class of individuals with full blown AIDS , i.e., those individuals in the population that exhibit clear symptoms of the AIDS disease. The main feature of the model is that the force of infection is obtained by averaging the probability of exposure of a susceptible individual to an infectious equipment with respect to the group size. The number of susceptible individuals can increase due to newly recruited individuals, while the number can decrease due to new infection as a result of interaction with infected individuals in class $I(t)$ and also due to natural death. Infected individuals who joined the class $I(t)$ can progress into $A(t)$ or may die due to natural death. After progression to class $A(t)$, individuals are removed from this class due to natural or disease induced death. The total population size at time t is denoted by $N(t)$, with $N(t) = S(t) + I(t) + A(t)$.

Table 4.1: Definitions of Parameters

Parameters	Description
Λ	constant recruitment of population,
β	the probability that a susceptible will become infected by one infectious individual
c	per capita contact rate for HIV
μ	natural mortality rate
k	the transfer rate from I to A,
δ	the disease induced death rate for individuals

From the assumptions stated above and the model diagram figure 4.1 we have the following system of Ordinary Differential Equations:

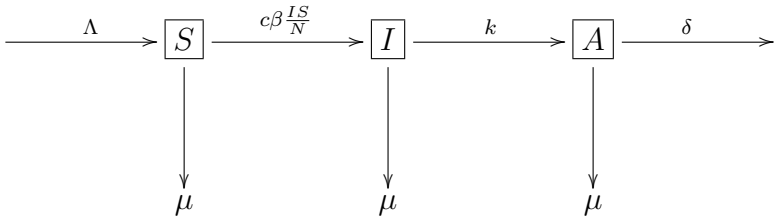


Figure 4.1: The flow diagram of the basic HIV/AIDS model

$$\begin{cases} \dot{S} &= \Lambda - \mu S - c\beta IS \\ \dot{I} &= c\beta IS - \mu I - kI \\ \dot{A} &= kI - \mu A - \delta A \end{cases} \tag{4.1}$$

with initial conditions, $S(0) = S_0 > 0$, $I(0) = I_0 > 0$, $A(0) = A_0 > 0$.

The first important assumption is that only individuals in the I class is considered to be active is spreading the disease to susceptible and the SI expression in the dynamical system is known as an interaction term. Interaction occurs when there is a contact between a susceptible and an infected individuals. This explain the product of S and I in system (4.2) below. For instance, sexual contact, between an HIV-negative person and an HIV-positive person. When this happens, the infected individuals increase their population by reducing the susceptible population.

Thus, we can ignore the equation in $\dot{A}(t)$ and obtain an equivalent reduced system of differential equations:

$$\left.\begin{aligned} \dot{S} &= \Lambda - c\beta IS - \mu S \\ \dot{I} &= c\beta IS - (\mu + k)I \end{aligned}\right\} \tag{4.2}$$

From system (4.2), we derive that the total active population $T(t)$ evolves according to

$$\frac{dT}{dt} = \Lambda - \mu T - kT,$$

independent of the force of infection $c\beta IS$. Therefore,

$$\Lambda - (\mu + k)T \leq \frac{dT}{dt} \leq \Lambda - \mu T.$$

Hence, the following inequalities hold
$T(t) - \frac{\Lambda}{\mu} \leq (T(0) - \frac{\Lambda}{\mu})e^{-\mu t}, \quad T(t) - \frac{\Lambda}{\mu+k} \geq (T(0) - \frac{\Lambda}{\mu+k})e^{-(\mu+k)t}.$

Proposition 4.1 [82] *For $\mu > 0$, if $T(0) \leq \frac{\Lambda}{\mu}$, then $T(t) \leq \frac{\Lambda}{\mu}$, for any $t \geq 0$. In particular the set*

$$\Phi = \left\{ (S, I) \in \mathbb{R}^2_+ \,\middle|\, \frac{\Lambda}{\mu + k} \leq S + I \leq \frac{\Lambda}{\mu} \right\}$$

is a compact, convex and invariant set for system (4.2).

4.2 Equilibria and Basic Reproduction Number

For the model (4.2), we denote the basic reproduction number by $\mathcal{R}_0$. If $\mathcal{R}_0 < 1$ the number of infected individuals will decrease from one generation to the next and the disease dies out asymptotically. However, if $\mathcal{R}_0 > 1$ the number of infected individuals will increase from one generation to the next with a ratio $\mathcal{R}_0 > 1$ and the disease will persist. The basic reproduction number $\mathcal{R}_0$ can be determined using the method of next-generation matrix.
Taking the infectious compartment to be I, from the system (4.2) we have,

$$\mathcal{F}(x) = \left[\; c\beta IS \; \right],$$

and

$$\mathcal{V}(x) = \left[\; (\mu + k)I \; \right],$$

where $\mathcal{F}$and $\mathcal{V}$ are transmission and transition matrices, respectively.
At the disease free equilibrium $E_0 = (\frac{\Lambda}{\mu}, 0)$ we have:

$$f = \left[\; \frac{c\beta\Lambda}{\mu} \; \right],$$

and

$$v = \left[\ (\mu + k) \ \right].$$

The next generation matrix is given by

$$K = fv^{-1},$$

then the basic reproduction number $\mathcal{R}_0$, is given by the spectral radius of the matrix K. That is,

$$\mathcal{R}_0 = \rho(K) = \frac{c\beta\Lambda}{\mu(\mu + k)}.$$

The expression of $\mathcal{R}_0$ is a product of probability of infecting per effective contact, rate of contact per unit of time t, and $\frac{1}{\mu+k}$ the life expectancy of infected individuals in $I(t)$ before leaving the class by natural death or progression to AIDS.

To determine the stability of this model we must first evaluate the equilibrium or steady state points of the reduced systems of the ODEs (4.2). The points to be found are disease-free (where $I = 0$), and endemic (where $I \neq 0$). We solve for the equilibrium values of S and I as

$$\Lambda - c\beta IS - \mu S = 0 \tag{4.3}$$

$$c\beta IS - \mu I - kI = 0 \tag{4.4}$$

From equation (4.4), we have $I\Big(c\beta S - (\mu + k)\Big) = 0$ which has solutions $I = 0$ or $c\beta S - (\mu + k) = 0$, $S = \frac{(\mu+k)T}{c\beta}$, but from the model $\mathcal{R}_0$ is defined as $\mathcal{R}_0 = \frac{c\beta\Lambda}{\mu(\mu+k)}$. Hence equation (4.4) has solutions; $I = 0$, $S = \frac{\Lambda}{\mu\mathcal{R}_0}$. We then substitute I and S into equation (4.3) to get the following equilibrium points:

- Disease free equilibrium $E_0 = (S_0, I_0) = (\frac{\Lambda}{\mu}, 0)$
- Endemic equilibrium $D = (S^*, I^*) = \left(\frac{\Lambda}{\mu\mathcal{R}_0}, \frac{\mu\mathcal{R}_0 - \mu}{c\beta}\right)$

4.3 Stability of the Disease Free Equilibrium

The Jacobian corresponding to 4.2 is given by

$$J = \begin{pmatrix} -c\beta I - \mu & -c\beta S \\ c\beta I & c\beta S - (\mu + k) \end{pmatrix}.$$

Therefore the Jacobian J_0 at the disease free equilibrium E_0 when $S = \frac{\Lambda}{\mu}$, and $i = 0$ evaluate as

$$J_0 = \begin{pmatrix} -\mu & \frac{-c\beta\Lambda}{\mu} \\ 0 & \frac{c\beta\Lambda}{\mu} - (\mu + k) \end{pmatrix}.$$

The characteristic equation corresponding to the above matrix is

$$(\lambda + \mu)(\lambda + \frac{c\beta\Lambda}{\mu} - (\mu + k)) = 0 \tag{4.5}$$

For E_0 to be asymptotically stable, both eigenvalues $\lambda_i < 0$, (i = 1, 2) of J_0 must be negative. From (4.5), it is clear that $\lambda_1 = -\mu$ is negative and therefore if $\lambda_2 = \frac{c\beta\Lambda}{\mu} - (\mu + k) < 0$, then both eigenvalues are negative. The condition $\lambda_2 < 0$ implies that $\frac{c\beta\Lambda}{\mu} < (\mu + k)$. Hence the disease-free equilibrium is locally asymptotically stable if the basic reproduction number, $\mathcal{R}_0 = \frac{c\beta\Lambda}{\mu(\mu+k)} < 1$.

Theorem 4.1 (see Van den Driessche and Watmough [86]). *The disease free equilibrium of system (4.2), E_0 , is locally asymptotically stable if $\mathcal{R}_0 < 1$*

4.4 Stability of the endemic equilibrium

Now let us assume that $\mathcal{R}_0 > 1$. The Jacobian J_e at $D = (S^*, I^*) = \left(\frac{\Lambda}{\mu\mathcal{R}_0}, \frac{\mu\mathcal{R}_0 - \mu}{c\beta}\right)$ is given by

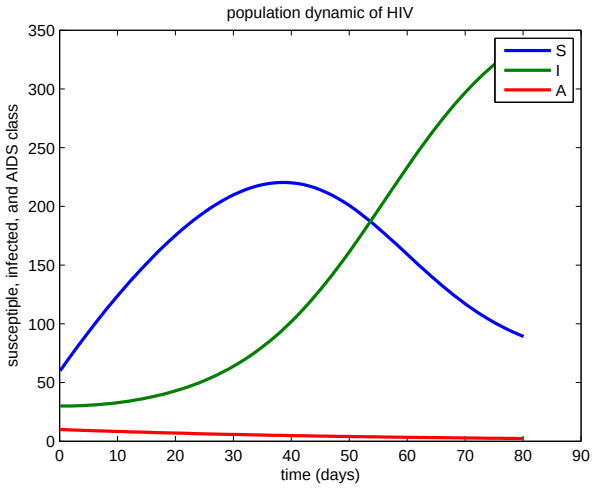


Figure 4.2: Showing graphical profile of each class of system (4.1) for: $\Lambda = 20$, $\mu = 0.02$, $\beta = 0.95$, $c = 0.08$ $k = 0.025$, $\delta = 0.05$.

$$J_e = \begin{pmatrix} -\mu\mathcal{R}_0 & \frac{-c\beta\Lambda}{\mu\mathcal{R}_0} \\ \mu\mathcal{R}_0 - \mu & \frac{c\beta\Lambda}{\mu\mathcal{R}_0} - (\mu + k) \end{pmatrix}.$$

The characteristic equation of J_e is given by.

$$\lambda^2 + (\mu\mathcal{R}_0 + \mu + k - \frac{c\beta\Lambda}{\mu\mathcal{R}_0})\lambda + ((\mu + k)\mu\mathcal{R}_0 - \frac{c\beta\mu}{\mathcal{R}_0}) = 0 \tag{4.6}$$

Since the trace of J_e is less than zero and its determinant, is positive, the endemic equilibrium is asymptotically stable. This conclusion is true since $\mathcal{R}_0 > 1$.

Theorem 4.2. *The endemic equilibrium D, of system (4.2) is locally asymptotically stable if $\mathcal{R}_0 > 1$ and unstable if $\mathcal{R}_0 < 1$.*

4.5 Multistage Model

The staged-progression of HIV disease is an important aspects of the disease, where HIV-infected individuals pass through sequential infection stages; being highly infectious during

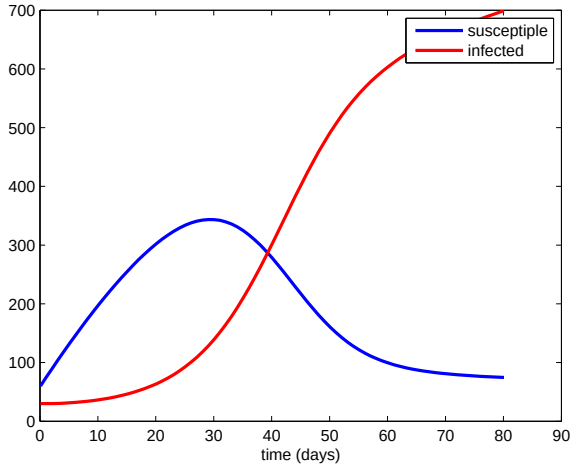


Figure 4.3: Showing graphical profile of each class of system (4.2) for: $\Lambda = 20$, $\mu = 0.02$, $\beta = 0.95$, $c = 0.08$ $k = 0.025$, $\delta = 0.05$.

primary infection (first few weeks of infection), having low infectivity in the asymptomatic phase (lasting many years) and becoming more infectious in the AIDS stage. According to Hollingsworth et al. [33], the primary infection stage is 26 times more infectious than at the asymptomatic stage and the symptomatic stage is 7 times more infectious as compared to the asymptomatic stage. Therefore, multistage models have been proposed in the literature to describe the transmission dynamics of infectious diseases in heterogeneous host populations, and much research has been done on various forms of multistage models; For instance, the models [36, 10, 37]. In addition to the assumptions and descriptions of the basic model of Section 1, we consider the model of Bhunu et al [10]. In this model the infected class is further divided into three classes according to the probability of infecting for susceptible individuals. They divided the entire population into: the susceptibles (S); the people who are HIV positive and do not know their status (I_1); the people who are HIV positive and know their status and reduce their risky sexual behaviour as a result of knowing their status (I_2); the people who are HIV positive and know their status and have increased their risky sexual behaviour as a result of knowing their status (I_3); HIV positive people who are sexually inactive (I_4); AIDS patients (A). In this case the dynamics of

the disease is given by the following system of non-linear differential equations

$$\begin{cases} \dot{S} &= \Lambda - (\lambda + \mu)S \\ \dot{I}_1 &= \lambda S - (\alpha + \mu + \delta)I_1 \\ \dot{I}_2 &= f\delta - (\theta + \mu + \sigma)I_2 \\ \dot{I}_3 &= (1-f)\delta - (\theta + \mu + \sigma)I_3 \\ \dot{I}_4 &= (I_2 + I_3)\theta - (\mu + \sigma)I_4 \\ \dot{A} &= (I_1 + I_2 + I_3)\sigma - (\mu + \nu)A \end{cases} \tag{4.7}$$

Here it is assumed that the rate of infection λ, depends on the transmission probability β; c is the effective contact rate; μ the natural death rate in all classes. A proportion f of HIV positive people knowing their status will move into the class I_2 and the complementary $(1-f)$ will move into the class I_3, respectively. Bhunu et al. [10] gives an analysis of this model including basic reproduction number and local stability. Modification of the above system is discussed in the research paper [2].

4.6 Multipopulation model

The model 4.8 can be extended to a multi-population. When one considers the spread of an infection, one should take into account not only the different means of infection, but also, not less important, possible structure within the active population. For example many of the social parameters included in the model may depend upon social, age, level of syringe-sharing and other heterogeneities. In particular, the probability α of infection might depend upon age, as the rate k of infectives who develop AIDS symptoms may depend on age and/or social factors. In order to take into account such kind of heterogeneities, the total population is divided into m subpopulations T_i, $i = 1, ..., m$. For each of them, S_i denote the number of susceptibles, I_i the number of infectives, A_i the number of individuals with AIDS and $T_i = S_i + I_i$ is the number of active individuals [82]. In such

a case, the force of infection acting on each susceptibles of the i^{th} group is given by

$$\lambda_i \alpha_i \beta_i (S, I),$$

where $S = (S_1, ..., S_m)^T$ and $I = (I_1, ..., I_m)^T$
Hence, model (4.1) can be extended to the multi-population case as follow:

$$\left.\begin{array}{ll} \frac{dS_i}{dt} & = \Lambda_i - \mu_i S_i - \lambda_i \alpha_i \beta_i (S, I) \\ \frac{dI_i}{dt} & = \lambda_i \alpha_i \beta_i (S, I) - \mu_i I_i - k_i I_i \\ \frac{dA_i}{dt} & = k_i I_i - \mu_i A_i - \delta_i A_i \end{array}\right\} \tag{4.8}$$

This is a general case whether model with m number of compartments introduced, and did not consider any specific disease. In such a model, in order to obtain an explicit expression for $\alpha_i \beta_i (S, I)$, it is necessary to specify the contact rates among individuals of different subpopulation.

Chapter 5

Model of HIV/AIDS with treatment

5.1 Brief introduction

In the classical paper [42] of Kermack and McKendrick the population dynamics of an infectious disease was studied as a system of ordinary differential equations. HIV being such a disease permits similar modeling. Various population models of HIV/AIDS have been studied over the past few decades. Examples of such papers are those of [14] Cai et al., [67] of Nyabadza et al., and [64] of Naresh et al. Specific models were designed to respond to specific problems. Our model is meant to capture the effect of an intervention of an informal type. A particular case in point is the case where a part of the population goes on to traditional treatment in an effort to curb or resist the virus. The main objective of modeling is to understand the time courses of the impact of the disease in the population, and to develop efficient regimes for treatments. Such interventions may include some highly efficient combination therapies. In this dissertation, we study the dynamics of the human immunodeficiency virus (HIV) in a given population with intervention. We modify the model in the paper [14] by Cai et al., by introducing a new class of infectious individuals, which accommodates the slow phase of virus growth. The paper [64] of Naresh et al., and [45] of Lasalle, are very important for qualitative analysis of a dynamical system. We include the effect of using herbal medicine, which we assume will counteract the growth

of the virus. There are safety concerns related to the use of two specific African herbals in HIV: African Potato and Sutherlandia, [81]. Traditional herbal medicine are most commonly used in areas where it is difficult to access Western medicine. For instance in South Africa, there is a large proportion of HIV positives using traditional health care, despite no published clinical evidence for efficacy and safety of traditional medicine in the treatment of HIV [9]. In fact, the reason behind alternative therapies is because antiretroviral therapies which work to reduce mortality resulting from HIV infection is expensive and generally unavailable in resource constrained areas. In general, traditional medicines are not well researched, and are poorly regulated. Therefore more research needs to be done in order to develop an understanding of whether and how we should engage with the traditional health sector, and identify better approaches for improving the biomedical/traditional health interface [54].

The process of HIV-1 pathogenesis can be slowed down or reversed to a certain extent by Highly Active Antiretroviral Treatment (HAART). Primarily HAART inhibits the process of virus particle formation. This keeps the viral load down and in turn increases the quantity of CD4 cells [95]. In this chapter the basic properties and behaviour of the system, such as positivity of solutions, existence of critical points and the basic reproduction number are discussed. A control problem is formulated and solved in Chapter 7.

5.2 The Model Description

The epidemiological model formulated here is for population dynamics of HIV with different treatment types. For the purpose of the modelling, we regard the population to be of size $N(t)$ at time t, as being divided into five compartments. These compartments are susceptibles S, I infected but not on any treatment, H infected and on alternative (non-ARV) treatment, J infected and on ARV-treatment, and finally, A denotes the class of individuals with full blown AIDS. Thus we have

$$N(t) = S(t) + I(t) + H(t) + J(t) + A(t).$$

The model we study is a deterministic model of population dynamics of the HIV epidemic including the effect of HAART and herbal medicine. A stochastic version of this model will be explored in Chapter 8

A flow diagram of the HIV epidemic model is sketched in Figure 5.1.

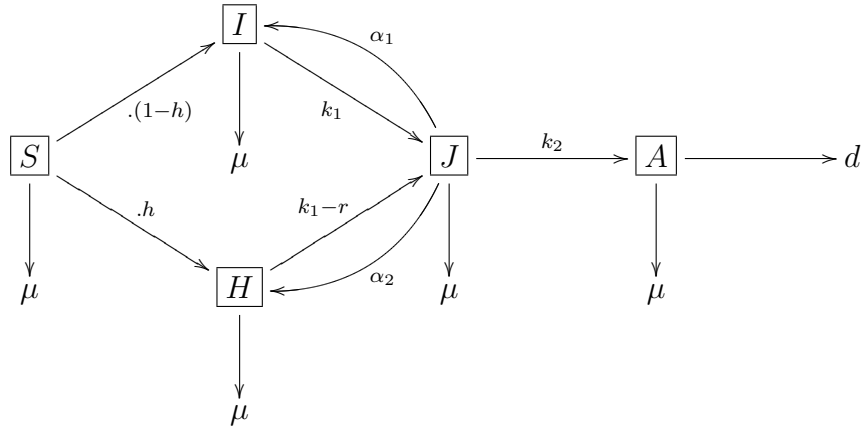


Figure 5.1: The flow diagram for the model

The following system of equations describe the population dynamics. In the special case with $h = h_1 = 0$, the model coincides with the model [14] Cai et al.

$$\left.\begin{aligned}
\tfrac{dS}{dt} &= \mu k - c\beta(I + H + bJ)S - \mu S \\
\tfrac{dI}{dt} &= (1-h)c\beta(I + H + bJ)S - (\mu + k_1)I + \alpha(1-h_1)J \\
\tfrac{dH}{dt} &= hc\beta(I + H + bJ)S - (\mu + k_1 - r)H + \alpha h_1 J \\
\tfrac{dJ}{dt} &= k_1 I + (k_1 - r)H - (\mu + k_2 + \alpha)J \\
\tfrac{dA}{dt} &= k_2 J - (\mu + d)A
\end{aligned}\right\} \tag{5.1}$$

We now explain the parameters that appear in the above equations:

- μ is the mortality rate,
- k is recruitment rate of the population,
- α is the antiretroviral therapy rate,
- c is the average numbers of contacts between individual per unit of time,
- β and $b\beta$ are the probabilities of disease transmission per contact by an infective in the asymptomatic compartment I and the symptomatic compartment J respectively,
- k_1 is the transfer rate from the asymptomatic stage to the symptomatic stage,
- r relate to the retardation effect of herbal treatment,
- k_2 is the transfer rate from the symptomatic stage to the AIDS compartment A,
- h is the fraction of new individuals infected and moved into the herbal compartment before ARV therapy,
- h_1 is the fraction of new individuals infected and moved into the herbal compartment after ARV therapy,
- d is the disease related mortality due to HIV/AIDS.

The variable A of system (5.1) does not appear in the first four equations. This is so because we assume that when an HIV-positive person reaches the late stage of the disease (full blown AIDS), the person becomes very weak or die and hence cannot infect others. In particular, we can suppress the 5th equation in the analysis that follow.

The S, I, H and J classes are considered to be the active classes. Thus, the term in the $\dot{S}$- expression of the dynamical system which carries all 4 of these variable S, I, H, J is known as an interaction term. This reflects the frequency of contact between a susceptible and an infected individual, for instance, sexual contact between an HIV-negative person and an HIV-positive person. When this happens, the infected individuals increase

their population by reducing the susceptible population. That is why there is a minus sign against the expression in the $\dot{S}$-rate equation and a positive sign in the $\dot{I}$, $\dot{H}$, $\dot{J}$-rate equations. In the subsequent analysis we only consider the subsystem:

$$\left.\begin{aligned} \dot{S} &= \mu k - c\beta(I + H + bJ)S - \mu S \\ \dot{I} &= (1-h)c\beta(I + H + bJ)S - (\mu + k_1)I + \alpha(1-h_1)J \\ \dot{H} &= hc\beta(I + H + bJ)S - (\mu + k_1 - r)H + \alpha h_1 J \\ \dot{J} &= k_1 I + (k_1 - r)H - (\mu + k_2 + \alpha)J \end{aligned}\right\} \tag{5.2}$$

5.3 Positivity of solutions

Since the model monitors changes in the human population, the variables and the parameters are assumed to be positive for all $t \geq 0$. System (5.1) will therefore be analyzed in a suitable feasible region Γ of biological interest [67].

$$\Gamma = \{(S, I, H, J) \in \mathbb{R}^4_+ : S + I + H + J \leq K\}.$$

We note that the model describes a population and therefore it is very important to prove that all the state variables (S, I, H, J and A) are *non-negative* for all time. More precisely if the system (5.1) has non-negative initial data, then the solution will remain inside Γ for all time $t > 0$, i.e., the set Γ is positively invariant. We thus state the following theorem.

Theorem 5.1 *Given the system (5.1), suppose that* $S(0) \geq 0$, $I(0) \geq 0$, $H(0) \geq 0$, $J(0) \geq 0$, $A(0) \geq 0$ *for all* t. *Then,*
(a) the solution $(S(t), I(t), H(t), J(t), A(t))$ *of the model remain positive for all time* $t > 0$
(b)

$$\lim_{t \mapsto \infty} N(t) \leq K.$$

(c) if

$$N(0) \leq K \text{ then } N(t) \leq K.$$

In particular, the region Γ *is positively invariant.*

Proof. (a) We argue by contradiction. Let us assume that the set X below is bounded.

$$X = \{\tau \geq 0 : S(t) > 0, I(t) > 0, H(t) > 0, J(t) > 0 \ \forall \ 0 \leq t \leq \tau\}.$$

Then X has a supremum T. Since S, I, H, and J are continuous, we have $T > 0$. From the first equation of system (5.1) we have

$$\frac{dS}{dt} = \mu k - c\beta(I + H + bJ)S - \mu S.$$

Let $\lambda^0 = c\beta(I + H + bJ)$, let $B(t) = \exp\{\mu t + \int_0^t \lambda^0(s)ds\}$, and note that $B(0) = 1$. Then we have

$$\begin{aligned} \frac{d}{dt}S(t).B(t) &= \dot{S}(t).B(t) + S(t).\dot{B}(t) \\ &= \dot{S}(t).B(t) + S(t).B(t)(\mu + \lambda^0(t)) \\ &= B(t)[\dot{S}(t) + S(t).(\mu + \lambda^0(t))] \\ &= \mu k B(t). \end{aligned}$$

Hence

$$S(T).B(T) - S(0).B(0) = \int_0^T \mu k B(t)dt,$$

so that

$$S(T) = B(T)^{-1}[S(0) + \int_0^T \mu k B(t)dt].$$

Note that $B(t) > 0$ for all $t < T$, and so $S(0) \geq 0$. Therefore $S(T) > 0$.

A similar reasoning on the remaining equations shows that I, H and J are always positive for $t > 0$. This contradicts T being the supremum of X. Therefore, the statement (a) is true.

(b) By adding the equations of the system (5.1), since $N = S + I + H + J$, we have

$$\frac{dN}{dt} = \mu k - \mu N(t) - K_2 J(t).$$

Since $N(t) \geq J(t) > 0$, using a standard comparison, Theorem (3.3) in Chapter 3, we obtain

$$N(0)\exp -(\mu+k_2)t+\frac{\mu k}{\mu+k_2}(1-\exp -(\mu+k_2)t) \leq N(t) \leq N(0)\exp -\mu t+\frac{\mu k}{\mu}(1-\exp -\mu t). \tag{5.3}$$

Therefore,

$$\frac{\mu k}{\mu+k_2} \leq \lim_{t\mapsto\infty} \sup N(t) \leq K.$$

(c) Concerning the invariance properties, it is easy to obtain from (5.3) that if

$$N(0) \leq K \text{ then } N(t) \leq K.$$

This establishes the invariance of X as claimed. □

5.4 Existence of critical points(equilibria)

To determine the stability of this model we must first evaluate the equilibrium or critical points of the reduced systems of ODEs (5.2). The points to be found are the disease-free equilibrium and the endemic equilibrium. We set the right-hand side of the equations in system (5.2) to zero and then solve for the various values of S, I, H, and J as

$$\frac{dS}{dt} = \frac{dI}{dt} = \frac{dH}{dt} = \frac{dJ}{dt} = 0$$

This gives the system

$$\begin{cases} 0 &= \mu k - c\beta(I+H+bJ)S - \mu S \\ 0 &= (1-h)c\beta(I+H+bJ)S - (\mu+k_1)I + \alpha(1-h_1)J \\ 0 &= hc\beta(I+H+bJ)S - (\mu+k_1-r)H + \alpha h_1 J \\ 0 &= k_1 I + (k_1-r)H - (\mu+k_2+\alpha)J \end{cases}$$

which yields two critical points:

1. The trivial critical point E_0 with no infected individuals ($S_0 \neq 0, I_0 = 0, H_0 = 0, J_0 = 0$) is $(k, 0, 0, 0)$,

2. Nontrivial critical point $E_1(S_1, I_1, H_1, J_1)$ is given by

$$S_1 = \frac{(\mu + k_1)\lambda_1 - \mu\alpha(1 - h_1)r}{c\beta[\lambda_3 + hr(\mu + k_2 - b\mu) + \alpha h_1 r]} \tag{5.3}$$

$$I_1 = \frac{\mu k[(1 - h)\lambda_1 + (k_1 - r)\alpha(1 - h_1)]}{(\mu + k_1)\lambda_1 - \mu\alpha(1 - h_1)r} \tag{5.4}$$

$$H_1 = \frac{\mu k[h\lambda_2 + k_1\alpha h_1]}{(\mu + k_1)\lambda_1 - \mu\alpha(1 - h_1)r} \tag{5.5}$$

$$J_1 = \frac{\mu k[(\mu + k_1 - r)k_1 - h\mu r]}{(\mu + k_1)\lambda_1 - \mu\alpha(1 - h_1)r} \tag{5.6}$$

where

$\lambda_1 = (\mu + k_1 - r)(\mu + k_2 + \alpha) - \alpha(k_1 - r)$,

$\lambda_2 = (\mu + k_1)(\mu + k_2 + \alpha) - \alpha(k_1)$,

$\lambda_3 = (\mu + k_1 - r)(\mu + k_2 + \alpha + bk_1)$.

5.5 Basic Reproduction Number

For the purpose of our model, the basic reproduction number of the system (5.2) can be obtained by using the next generation matrix as presented in [86]. We use all equations of the system (5.2). But we further ignore the S compartment since we require only the infected compartments (I, H, and J). We now proceed as follows. Let $\mathcal{F}(x)$ be the rate of appearance of new infections in compartments I, H and J and, let $\mathcal{V}(x)$ be the rate at which the population in each compartment changes due to compartmental transfers as a

result of status changes caused by the disease dynamics. In Proposition 5.2 we compute the basic reproduction number for the system as follows.

Proposition 5.2. *The basic reproduction number of the system (5.2) is*

$$\mathcal{R}_0 = \frac{c\beta k[\lambda_3 + hr(\mu + k_2 - b\mu) + \alpha h_1 r]}{(\mu + k_1)\lambda_1 - \mu\alpha(1 - h_1)r}.$$

Proof. Set $x = (I, H, J, S)^{\text{tr}}$. Then System (5.2) can be written as $\dot{x} = \mathcal{F}(x) - \mathcal{V}(x)$, where

$$\mathcal{F}(x) = \begin{pmatrix} (1-h)c\beta(I + H + bJ)S \\ hc\beta(I + H + bJ)S \\ 0 \\ 0 \end{pmatrix},$$

$$\mathcal{V}(x) = \begin{pmatrix} (\mu + k_1)I - \alpha(1 - h_1)J \\ (\mu + k_1 - r)H - \alpha h_1 J \\ -k_1 I - (k_1 - r)H + (\mu + k_2 + \alpha)J \\ -\mu k + c\beta(I + H + bJ)S + \mu S \end{pmatrix}.$$

At the disease free equilibrium $E_0 = (k, 0, 0, 0)$ we have:

$$\frac{\partial \mathcal{F}}{\partial x}(E_0) = \begin{pmatrix} F_{3\times 3} & 0 \\ 0 & 0 \end{pmatrix}, \frac{\partial \mathcal{V}}{\partial x}(E_0) = \begin{pmatrix} V_{3\times 3} & \dots & 0 \\ c\beta k & c\beta k & cb\beta k \end{pmatrix}.$$

where

$$F = \begin{pmatrix} (1-h)c\beta k & (1-h)c\beta k & (1-h)cb\beta k \\ hc\beta k & hc\beta k & hcb\beta k \\ 0 & 0 & 0 \end{pmatrix},$$

and

$$V = \begin{pmatrix} \mu + k_1 & 0 & -\alpha(1-h_1) \\ 0 & \mu + k_1 - r & -\alpha h_1 \\ -k_1 & -(k_1 - r) & (\mu + k_2 + \alpha) \end{pmatrix}.$$

Then F is a nonnegative matrix of rank one and can be written as the product of the vectors, and V is a nonsingular M-matrix [7]. According to theory of [86, 49], the basic reproduction number $\mathcal{R}_0$ is the spectral radius of the matrix FV^{-1}. We recall that the spectral radius $\rho(A)$ of a matrix A is defined as maximum modulus of eigenvalues of A, and that a non-negative matrix has a real eigenvalue equal to its spectral radius [7]
To determine the spectral radius of FV^{-1}, we first represent the inverse of V by the following matrix:

$$V^{-1} = \frac{1}{(\mu+k_1)\lambda_1 - \mu r\alpha(1-h_1)} \begin{pmatrix} V_{11} & \alpha(1-h_1)(k_1-r) & \alpha(1-h_1)(\mu+k_1-r) \\ k_1\alpha h_1 & V_{22} & (\mu+k_1)\alpha h_1 \\ k_1(\mu+k_1-r) & (\mu+k_1)(k_1-r) & (\mu+k_1)(\mu+k_1-r) \end{pmatrix},$$

where

$V_{11} = (\mu + k_1 - r)(\mu + k_2 + \alpha) - (k_1 - r)\alpha h_1,$

$V_{22} = (\mu + k_1)(\mu + k_2 + \alpha) - k_1\alpha(1 - h_1).$

Since matrix F has rank 1, the spectral radius $\rho(FV^{-1})$ is equal to the trace of matrix FV^{-1}. Thus, the basic reproduction number for the system (2.2) is

$$\mathcal{R}_0 = \rho(FV^{-1}) = \frac{c\beta k[\lambda_3 + hr(\mu + k_2 - b\mu) + \alpha h_1 r]}{(\mu + k_1)\lambda_1 - \mu r\alpha(1 - h_1)}.$$

□

5.6 Sensitivity of $\mathcal{R}_0$ and the endemic equilibrium

In this section, It is important to understand how change in various parameters affects the stability of our system. The reproductive number is an essential tool for this analysis. We will study the rates of change of this threshold value with respect to the parameters necessary for our study described in Table (6.1), to determine the effect of varying or perturbing the parameters in the model that drive HIV infection progression. Then the

normalised forward index with respect to parameters are given by:

$$\begin{aligned}
\frac{\partial \mathcal{R}_0}{\partial c} \times \frac{c}{\mathcal{R}_0} &= 1 \\
\frac{\partial \mathcal{R}_0}{\partial h} \times \frac{h}{\mathcal{R}_0} &= 1 - \frac{\lambda_3 + \alpha h_1 r}{\lambda_3 + hr(\mu + k_2 - b\mu) + \alpha h_1 r} \\
\frac{\partial \mathcal{R}_0}{\partial h_1} \times \frac{h_1}{\mathcal{R}_0} &= \frac{\alpha h_1 r}{\lambda_3 + hr(\mu + k_2 - b\mu) + \alpha h_1 r} - \frac{h_1}{(1 - h_1)} \\
\frac{\partial \mathcal{R}_0}{\partial r} \times \frac{r}{\mathcal{R}_0} &= 1 + \frac{-r(\mu + k_2 + \alpha + bk_1) + hr(\mu + k_2 - b\mu) + \alpha h_1 r}{(\lambda_3 + hr(\mu + k_2 - b\mu) + \alpha h_1 r)} + \frac{(\mu + k_2)}{\lambda_1} \\
\frac{\partial \mathcal{R}_0}{\partial k_1} \times \frac{k_1}{\mathcal{R}_0} &= \frac{(\mu + k_2 + \alpha + \mu b - br) + 2bk_1}{\lambda_3} - \frac{2(\mu + k_1)(\mu + k_2 + \alpha) - 2\alpha k_1 + (r - \mu\alpha)}{(\mu + k_1)\lambda_1} \\
\frac{\partial \mathcal{R}_0}{\partial k_2} \times \frac{k_2}{\mathcal{R}_0} &= \frac{\lambda_1(\mu + k_1 - r + hr) - (\mu + k_1 - r)(\lambda_3 + hr(\mu + k_2 - b\mu) + \alpha h_1 r)}{\lambda_1(\lambda_3 + hr(\mu + k_2 - b\mu) + \alpha h_1 r)} \\
\frac{\partial \mathcal{R}_0}{\partial \alpha} \times \frac{\alpha}{\mathcal{R}_0} &= \frac{\alpha[(\mu + k_1 - r + h_1 r)\lambda_1 - (\mu + k_1 - r)(1 - k_1 + r)(\lambda_3 + hr(\mu + k_2 - b\mu) + \alpha h_1 r)]}{(\lambda_3 + hr(\mu + k_2 - b\mu) + \alpha h_1 r)\lambda_1}
\end{aligned}$$

Parameters	Parameter value	Sensitivity
k_1	0.01	+0.000254
α	0.01	+0.003764
k_2	0.02	+0.006127
c	3	+1
h	0.02	+0.0005267
h_1	0.007	-0.0070
r	0.001	-28.4457

We need to estimate parameters so that we can get a better understanding of the sensitivity of each parameter. Hence we evaluate the sensitivity indices at the baseline parameter values. The reproductive number $\mathcal{R}_0$ increases as the average numbers of contacts between individual per unit of time increases. An increase in the fraction of new individuals infected therefore increases recruitment rate of the population. We have some parameters such as α, r which are directly and inversely proportional to $\mathcal{R}_0$, that means increasing them would decrease the $\mathcal{R}_0$ even when their effects are not drastic. We carry out sensitivity analysis of the endemic equilibrium at some parameter described in Theorem 6.1.

Sensitivity of I_1 respect to the parameters h, h_1, α and r:

$$\begin{aligned}
\frac{\partial I_1}{\partial h} \times \frac{h}{I_1} &= \frac{-h\lambda_1}{(1-h)\lambda_1 + (k_1 - r)(1-h_1)\alpha} \\
\frac{\partial I_1}{\partial h_1} \times \frac{h_1}{I_1} &= \frac{-\alpha(k_1 - r)h_1}{(1-h)\lambda_1 + (k_1 - r)(1-h_1)\alpha} - \frac{h_1}{1-h_1} \\
\frac{\partial I_1}{\partial \alpha} \times \frac{\alpha}{I_1} &= 1 + \frac{\alpha(\lambda_1 - \mu\alpha)(k_1 - r)(1-h_1)\alpha}{\lambda_1((1-h)\lambda_1 + (k_1 - r)(1-h_1)\alpha)} \\
\frac{\partial I_1}{\partial r} \times \frac{r}{I_1} &= 1 + \frac{\alpha^2(1-h_1)(k_1 - r\lambda_1)}{\lambda_1((1-h)\lambda_1 + (k_1 - r)(1-h_1)\alpha)}
\end{aligned}$$

Sensitivity of H_1 respect to the parameters h, h_1, α and r:

$$\begin{aligned}
\frac{\partial H_1}{\partial h} \times \frac{h}{H_1} &= 1 - \frac{kh_1\alpha}{h\lambda_2 + k_{h1}\alpha} \\
\frac{\partial H_1}{\partial h_1} \times \frac{h_1}{H_1} &= 1 - \frac{h\lambda_2 + kh_1^2\alpha}{(1-h_1)(h\lambda_2 + k_{h1}\alpha)} \\
\frac{\partial H_1}{\partial \alpha} \times \frac{\alpha}{H_1} &= 1 + \frac{k_1 h_1(\lambda_2 - \mu\alpha}{\lambda_2(h\lambda_2 + k_{h1}\alpha)} \\
\frac{\partial H_1}{\partial r} \times \frac{r}{H_1} &= 1 + \frac{(\mu + k_2)r}{\lambda_2 - \mu\alpha(1-h_1)r}
\end{aligned}$$

Sensitivity of J_1 respect to the parameters h, h_1, α and r:

$$\begin{aligned}
\frac{\partial J_1}{\partial h} \times \frac{h}{J_1} &= \frac{-\mu hr}{(\mu + k_1 - r)k_1 - h\mu r} \\
\frac{\partial J_1}{\partial h_1} \times \frac{h_1}{J_1} &= \frac{-h_1}{(1-h_1)} \\
\frac{\partial J_1}{\partial \alpha} \times \frac{\alpha}{J_1} &= 1 - \frac{\mu\alpha}{(\lambda_1 - \mu\alpha(1-h_1)r)} \\
\frac{\partial J_1}{\partial r} \times \frac{r}{J_1} &= 1 + \frac{(\mu + k_2)((\mu + k_1 - r)k_1 - h\mu r) - \lambda_1(k_1 + h\mu)}{(\lambda_1((\mu + k_1 - r)k_1 - \mu hr)}
\end{aligned}$$

Chapter 6

Stability analysis of the critical points

6.1 Brief introduction

In this chapter, we study the stability properties of the two possible equilibrium points in order to understand the behaviour of the system as well as the conditions under which the disease may be eradicated or be endemic. An important invariant in this regard is the basic reproduction number. We calculate the basic reproduction number, which is defined as the expected number of secondary infections arising from a single individual during his or her entire infectious period, in a population of susceptibles. It immediately follows from Theorem 5.2 that the disease-free equilibrium is locally asymptotically stable when the *basic reproduction number* of the model is less than unity. Further, we demonstrate that the endemic equilibrium point is locally asymptotically stable under the simple condition that the *basic reproduction number* is greater than unity. We also resort to numerical simulations to obtain insights into the dynamics of the model.

The behaviour of the system (5.2) near the equilibrium points can be analysed by the nature of the real parts of the eigenvalues of its Jacobian matrix. The Jacobian matrix is

given by:

$$M(S,I,H,J) = \begin{bmatrix} \frac{\partial f_1}{\partial S} & \frac{\partial f_1}{\partial I} & \frac{\partial f_1}{\partial H} & \frac{\partial f_1}{\partial J} \\ \frac{\partial f_2}{\partial S} & \frac{\partial f_2}{\partial I} & \frac{\partial f_2}{\partial H} & \frac{\partial f_2}{\partial J} \\ \frac{\partial f_3}{\partial S} & \frac{\partial f_3}{\partial I} & \frac{\partial f_3}{\partial H} & \frac{\partial f_3}{\partial J} \\ \frac{\partial f_4}{\partial S} & \frac{\partial f_4}{\partial I} & \frac{\partial f_4}{\partial H} & \frac{\partial f_4}{\partial J} \end{bmatrix},$$

where

$$f_1(S,I,H,J) = \mu k - c\beta(I+H+bJ)S - \mu S$$

$$f_2(S,I,H,J) = (1-h)c\beta(I+H+bJ)S - (\mu+k_1)I + \alpha(1-h_1)J$$

$$f_3(S,I,H,J) = hc\beta(I+H+bJ)S - (\mu+k_1-r)H + \alpha h_1 J$$

$$f_4(S,I,H,J) = k_1 I + (k_1-r)H - (\mu+k_2+\alpha)J.$$

Therefore, M at (S,I,H,J) as follows. On order to have the matrix display more elegantly we write $h_2 = 1-h$, $h_3 = (1-h_1)\alpha$, $\mu_1 = \mu+k_1$, and $\mu_2 = \mu+k_2$. Then M becomes:

$$\begin{pmatrix} -c\beta(I+H+bJ)-\mu & -c\beta S & -c\beta S & -cb\beta S \\ h_2 c\beta(I+H+bJ) & h_2 c\beta S - \mu_1 & h_2 c\beta S & h_2 cb\beta S + h_3 \\ hc\beta(I+H+bJ) & hc\beta S & hc\beta S - (\mu_1 - r) & hcb\beta S + \alpha h_1 \\ 0 & k_1 & (k_1 - r) & -(\mu_2+\alpha) \end{pmatrix}.$$

If all the eigenvalues of the Jacobian matrix have negative real parts, then the equilibrium point is locally asymptotically stable, but unstable if at least one of the eigenvalues has a positive real part.

6.2 Stability of the trivial critical point

The basic reproduction number, denoted by $\mathcal{R}_0$, plays a vital role in the propagation of the relevant epidemic. In general it happens that when $\mathcal{R}_0 < 1$, then the epidemic dies out eventually. Following Theorem 2 of [86], we have the following result on the local

stability of E_0.

Theorem 6.1. *If $\mathcal{R}_0 < 1$, disease-free equilibrium E_0 is locally asymptotically stable and unstable otherwise.*

6.3 Stability of the nontrivial critical point

An equilibrium means that the disease persists and is endemic in the system or given population. Its stability is established using the Jacobian matrix stated above. We rewrite E_1 in terms of $\mathcal{R}_0$.

Theorem 6.2.*The endemic equilibrium E_1 is stable if $\mathcal{R}_0 > 1$ and is unstable if and only if $\mathcal{R}_0 < 1$*

Proof. At the endemic equilibrium point the Jacobian matrix of this system, expressed in terms of $\mathcal{R}_0$, becomes

$$M(E_1) = \begin{pmatrix} -p & -m_2 & -m_2 & -bm_2 \\ h'm_1 & m_3 & m_4 & m_5 \\ hm_1 & hm_2 & m_6 & m_7 \\ 0 & k_1 & (k_1 - r) & -m_8 \end{pmatrix},$$

where

$p = \mu + m_1$ with $m_1 = \mu\mathcal{R}_0$, $m_2 = \frac{c\beta k}{\mathcal{R}_0}$, $m_3 = \mu - m_4$ with $m_4 = \frac{h'c\beta k}{\mathcal{R}_0}$,
$m_5 = m_4 + (1 - h_1)\alpha$, $m_6 = (\mu - r) - hm_2$,
$m_7 = hm_2 + h_1\alpha$ and $m_8 = (\mu + k_2 + \alpha)$.

The characteristic equation corresponding to $M(E_1)$ is given by

$$p(\lambda) = \lambda^4 + a_1\lambda^3 + a_2\lambda^2 + a_3\lambda + a_4 = 0, \tag{6.1}$$

where

$a_1 = p + m_8 - m_3 - m_6,$

$a_2 = m_1m_2 + m_3m_6 + pm_8 - pm_3 - hm_2m_4 - m_5k_1 - m_3m_8,$

$a_3 = m_1m_2m_8 + m_1m_2(h'(hm_3 - m_6) + h(m_4 - m_3) + b(h'k_1 + h(k_1 - r)))$

$+k_1(m_5m_6 - m_4m_7) + (k_1 - r)(m_3m_7 - hm_2m_5) + m_8(m_3m_6 - hm_2m_4)$

$+p(m_5k_1 + m_7(k_1 - r)) + pm_6(m_3 - m_8) - p(m_3m_8 + hm_2m_4),$

$a_4 = bm_1m_m2((hm_4k_1 - k_1 + r) + (h'hm_2(k_1 - r) - m_6k_1)) + m_1m_2m_7(hk_1 - h'(k_1 - r))$

$+pm_8(m_3m_6 - hm_2m_4) + p(k_1 - r)(m_3m_7 - m_2m_3) + pk_1(m_3m_6 - m_4m_7)$

$+h'm_1m_2m_8(h'(hm_2 - m_6) + hm_4 - hm_3) + m_1m_2m_5(h(k_1 - r) - hk_1).$

At this point we opt to use a numerical computation for investigating the non trivial equilibrium point E_1 of the model (5.2), with a given set of parameter values. We assign the following values which are similar to those used in [14].

$\alpha = 0.01$, $\beta = 0.00005$, $\mu = 0.02$, $b = 0.3$, $c = 3$, $k = 120$, $k_1 = 0.01$, $k_2 = 0.02$, together with the following:

$h = 0.02$, $h_1 = .03$, $r = 0.023$.

Note that this set of parameter values yield $\mathcal{R}_0 = 1.2 > 1$. We show that E_1 is locally asymptotically stable.

The characteristic equation corresponding to $M(E_1)$ is given by

$p(\lambda) = \lambda^4 + 0.1009\lambda^3 + 0.0020\lambda^2 + 4.7145 \times 10^{-05}\lambda + 2.0506 \times 10^{-06} = 0$

It can be seen that $a_i = 0.1009, 0.0020, 4.7145 \times 10^{-05}, 2.0506 \times 10^{-06} > 0$ $(i = 1, 2, 3, 4)$ and $a_1a_2 - a_3 > 0$. Also the condition $a_3(a_1a_2 - a_3) - a_1^2a_4 > 0$ is satisfied. From the

Routh Hurwitz criterion it follows that E_1 is locally asymptotically stable. □

6.4 Numerical Simulations

In this section we provide the numerical solution of the model system (5.2), and our first step in computing numerically is to declare parameters. Uncertainty analysis of these parameters was done by [14] Cai et al., and some of the parameters are estimated. Those which are not in [14] are r, related to the retardation effect of herbal treatment, h which is the fraction of new individuals infected into the herbal compartment before ARV therapy, and h_1 which is the fraction of new individuals infected into the herbal compartment after ARV therapy.

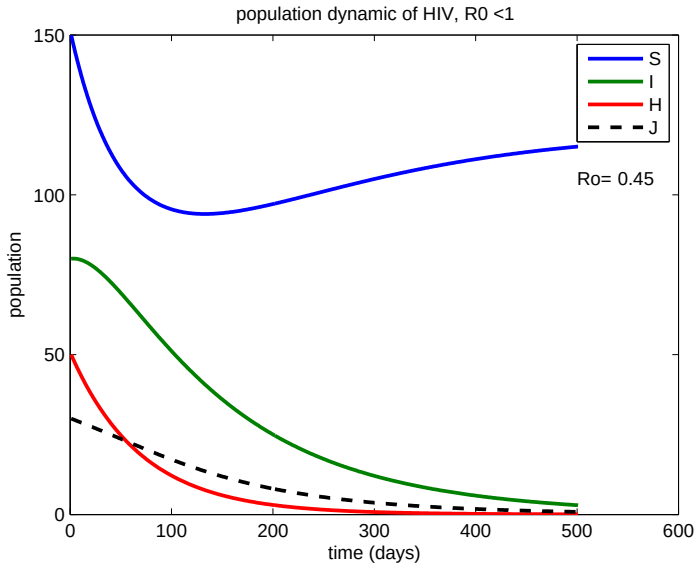


Figure 6.1: Diagram of Global Stability of E_0, for parameter values : $k = 120$, $\beta = 0.000035$, $b = 0.3$, $\mu = 0.02$, $c = 3$, $k_1 = 0.01$, $k_2 = 0.02$, $\alpha = 0.01$, $h = 0.01$, $r = 0.001$, $h_1 = 0.02$.

We obtain the following numerical plots with some brief descriptions given in each caption.

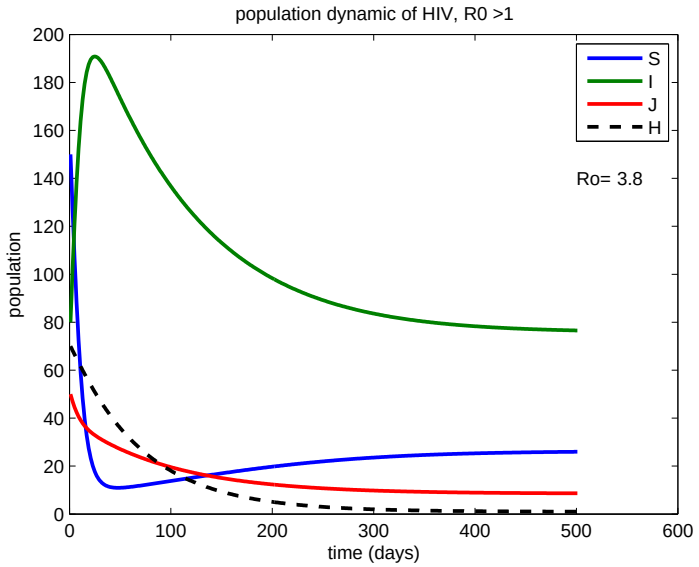


Figure 6.2: Diagram of Local Stability of E_1 for parameter values : $k = 120$, $\beta = 0.0005$, $b = 0.3$, $\mu = 0.02$, $c = 3$, $k_1 = 0.01$, $k_2 = 0.02$, $\alpha = 0.01$, $h = 0.01$, $r = 0.001$, $h_1 = 0.02$.

Figure 6.1, the dynamics of the disease for compartments with increasing time. It shows that HIV clears from the population whenever the reproduction number is less that unity. We observe that the class of susceptible individuals initially decreases as the number of infectives increase and then increases as the number of infected individuals decreases to zero. Thus, this justified the analytical results of disease free-equilibrium E_0. The population of infected without treatment I individuals, infected with ARV treatment J individuals and infected with alternative treatment H individuals decrease approached to zero with respect to time as shown in Figure 6.3.

In Figure 6.2, we observe that the population of susceptible individuals initially decreases then start to increase asymptotically to endemic equilibrium state as time increases, while the class of infected individuals without treatment I, infected individuals with ARV treatment J and infected individuals with alternative treatment H, eventually decrease to endemic equilibrium point with increasing time. This shows that the disease does not clear from the population when $\mathcal{R}_0 > 1$, i.e, the disease persists as shown in Figure 6.4.

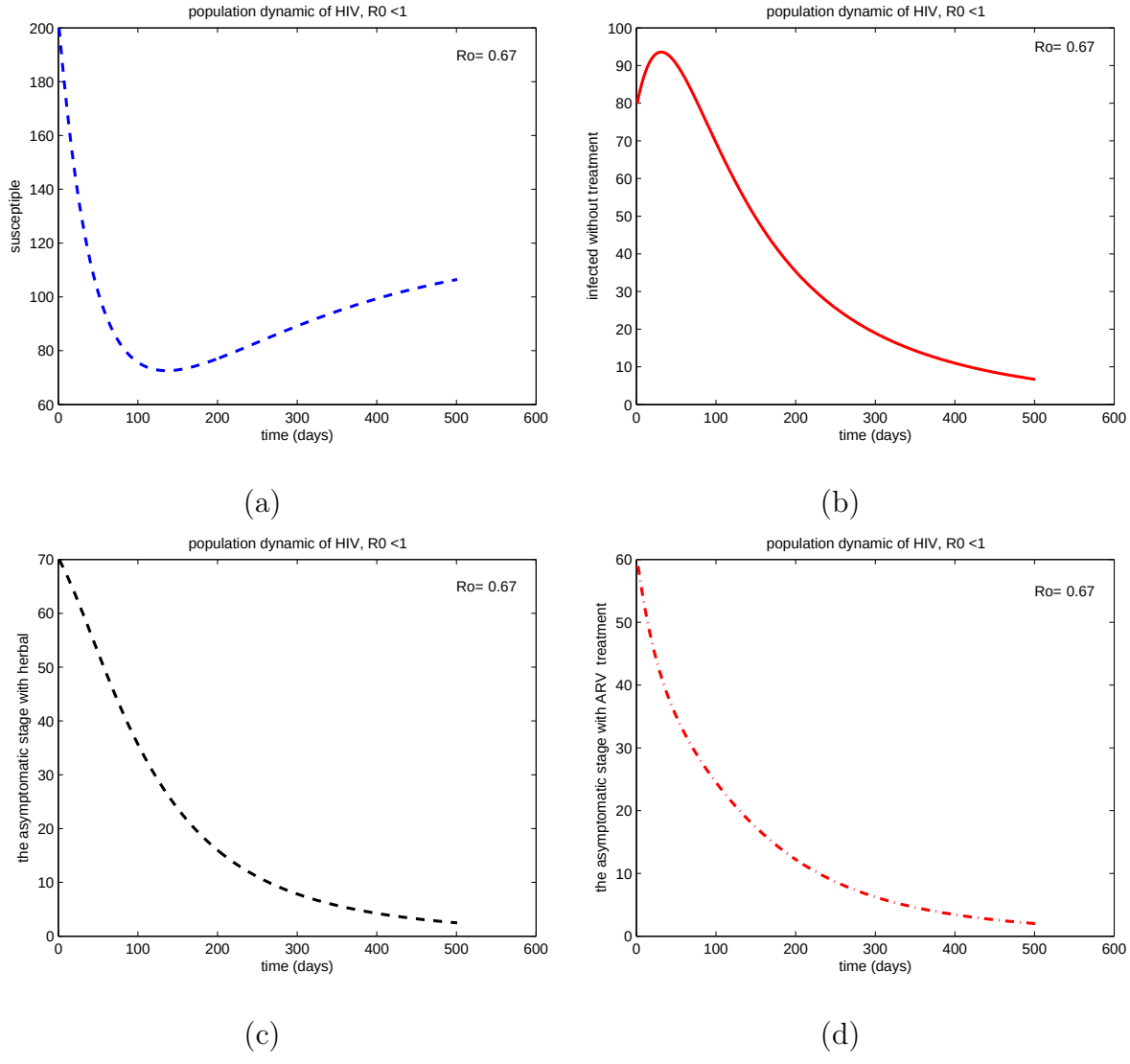


Figure 6.3: Shows the changes in the four classes for $\mathcal{R}_0 < 1$ with control. (a) susceptibles (S), (b) asymptomatic stage (I), (c) asymptomatic stage (H) with herbal treatment, and (d) symptomatic stage (J).

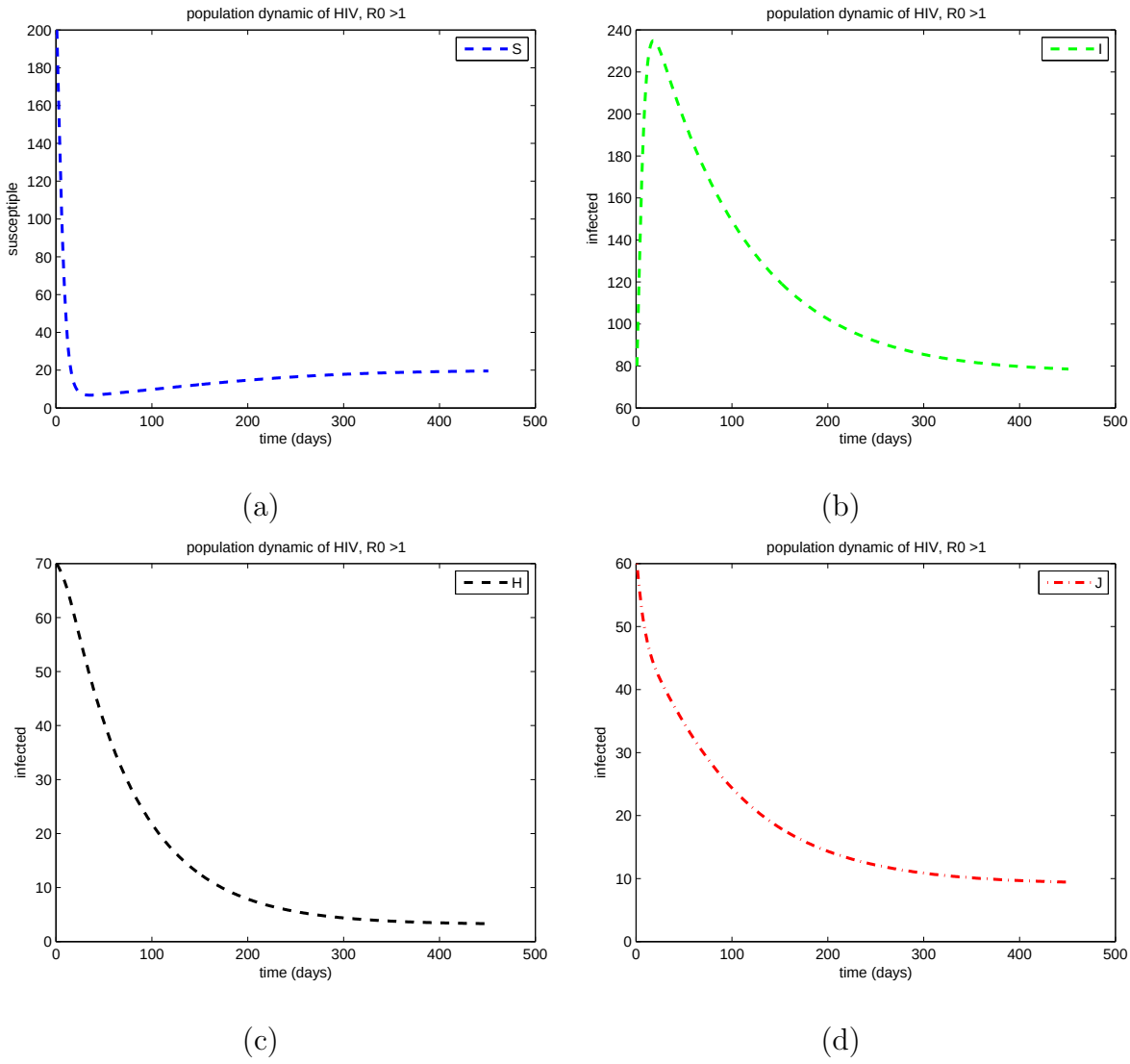


Figure 6.4: Shows the changes in the four classes for $\mathcal{R}_0 > 1$ (a) Variation of susceptible (S) population, (b) Variation of the asymptomatic stage (I), (c) Variation of the asymptomatic stage (H) with herbal treatment, and (d) Variation of the symptomatic stage (J) with control.

Chapter 7

Optimal control problem

7.1 Introduction

Optimal control theory has been a powerful mathematical technique and is useful in decision making regarding complex situations. The behaviour of a dynamical system is described by the state variable(s). The assumption is that there is a way to control the state variable(s) x by acting upon it with a suitable control. Thus the dynamics of the system depends on the control u. The ultimate goal is to adjust the control u to minimize or maximize a given objective functional, $J(u(t), x(t), t)$. Pontryagins Maximum Principle allows the calculation of the optimal control for an ordinary differential equations model system with given constraints. Optimal control techniques have been applied quite extensively in biomathematics.

7.2 Review on optimal control theory

In this section we highlight some previous work that has been done on optimal control theory. For example, what percentage of the population should be vaccinated as time evolves in a given epidemic model to minimize the number of the infected and the cost of implementing the vaccination strategy. The desired outcome, depends on the particular situations. The main purpose then is to identify the parameters that have the most

significant effect on reducing the number of (new) infectives. Many different models with different objective functions have been studied.

In 2008 A. Sani and D.P. Kroese [78] formulate various mathematical control models for HIV spread, which incorporate complex characteristics such as hetero-sexual transmission and migration among regions, and show how optimal regional control strategies can be obtained that minimize the national spread of HIV. The mode of transmission is assumed to be via sexual contact only between partners of the opposite sex. This assumption is mainly because heterosexual contact is still the primary mode of HIV infection worldwide. The model consists of four compartments: female susceptibles, female infectives, male susceptibles, and male infectives. The numerical experiments suggest that the controls for the different patches are highly synchronized. Moreover, they indicate that the optimal trajectories qualitatively have similar form. Considering other control parameters such as isolating infectives, HIV/AIDS campaign programming, contact tracing, etc., in a more complex model with an age structure, risk groups and levels of infectivity could also be a future study.

Kwon [43] presents a mathematical model which is in the form of a system of ordinary differential equations. These equations describe the dynamics of the immune system, human immunodeficiency virus (HIV), and drug-resistant mutants. They used techniques and ideas from control theory to design therapy protocols to combat the HIV infection. The mathematical model for HIV infection includes five compartments for target cells, wild-type virus-infected cells, mutant virus-infected cells, wild-type virus and mutant virus. This model regards the drug therapy (reverse transcriptase inhibitors) as a controller. They derive optimal treatment strategies by solving the corresponding optimality systems with a gradient method. In addition, suboptimal structured treatment interruptions (STI) are found by using ideas from Model Predictive Control. They demonstrate that an important advantage of the resulting suboptimal STI strategies is that the mutant virus load is controlled at very low levels. The pharmaceutical side effects are also reduced. Thus this approach suggests that dynamic optimal strategies, such as those described in this paper, could lead to control of viral systems that mutate in response to drug

administration.

Joshi [39] derived an optimal control of an HIV immunology model by using a system of ordinary differential equation model taken from Kischner and Webb (1998). This system of ODES described the interaction of HIV and T-cells in the immune system. The boundedness of solution for finite time interval to prove the existence of an optimal control of pair. Thus the optimal control pair obtained gives an optimal treatment strategy for the HIV infected patient under two types of drug treatment, namely treatment aimed at reducing viral population and treatment aimed at improving immune response. Joshi solved the optimality system by using an iterative method with a Runge-Kutta fourth order scheme.

Karrakchou et al. [41] developed a model describing the interaction of the HIV virus and the immune system of the human body, and utilize it to determine the optimal methodology for administering anti-viral medication therapies to fight HIV infection. More exactly, they seek to a maximize the count of healthy cells with a minimum dose of the administered drugs. In this work also they investigate the fundamental role of chemotherapy treatment in controlling the virus reproduction. To introduce a control to the above mentioned model, they analyze the interactions of healthy CD4+T cells, infected CD4+T cells and free virus: two major categories of anti-retroviral drugs to combat HIV are reverse transcriptase inhibitors (RTIs) and protease inhibitors (PIs). RTIs prevent new HIV infection by disrupting the conversion of viral RNA into DNA inside of T cells. PIs reduce the number of viruses particles produced by an actively-infected T cells. Finally by numerical experiments, they compare the disease progression before and after the treatment chemotherapy.

Okosun et al. [69] present optimal control analysis for HIV/AIDS model. They showed the impact screening of unaware infectives on the transmission dynamics of the disease in a homogeneous population with constant immigration of susceptibles incorporating use of condom, screening of unaware infectives and treatment of the infected. They consider the model by sub-divides the total human population at time t, denoted by N, into the following sub-populations of susceptible individuals S, infective individuals who do

not know that they are infected I_1, HIV positive individuals that know that they are infected I_2 and that of the AIDS population A. They calculated the basic reproduction number and investigate the existence and stability of equilibria. The model is found to exhibit transcritical bifurcation. They further investigate the impact of combinations of the strategies in the control of HIV/AIDS.

Ramirez et al. [75] used the stochastic optimal control theory to develop protocols for the treatment of human diseases. They model time dependent uncertainties as Itô processes. That results in an optimal control problem where the constraints are stochastic differential equations and the objective function is an integral equation. The optimality conditions of the problem are obtained through the stochastic maximum principle, which results in a boundary value problem. The boundary value problem is solved iteratively by using a combination of the gradient method and a stochastic version of the Runge-Kutta method derived in this work. As an illustration of the proposed approach, they solve a mathematical model to determine the evolution of a generic disease and obtain regimens for applying therapeutic agents in a manner that maximizes efficacy while minimizing side effects. They show that stochastic optimal control theory can indeed help develop clinical insight in treating illness under uncertainty in model parameters.

7.3 Optimal control of treatment in the presence of herbal use

In Chapter 6, with the stability analysis, we showed the effect of treatment in our model. Here we consider optimal control methods to derive optimal ARV treatments as functions of time. We present necessary conditions for optimality (see, e.g., [46, 1] for details on these procedures). We attempt to control HIV propagation in finite time intervals using a control function $\alpha(t)$ which represents the proportion of individuals on ARV satisfying $0 \leq a \leq \alpha(t) \leq b < 1$, and then solve the problem numerically using an interactive method with a Runge Kutta fourth order scheme.

As the objective functional we choose, for some time horizon $[0, T]$ and some constants C, and τ the following:

$$V(\alpha(t)) = \int_0^T [C\alpha^2(t) - \tau S]dt, \tag{7.1}$$

Our quest is now to minimize V with respect to $\alpha(t)$, subject to the equations of motion. In this functional, the first term under the integral is related to the cost of treatment C, and α is taken squared in order to make the Hamiltonian to be quadratic in α, and hence concave. We shall put only initial conditions on the state variables, leaving the time $t = T$ values to be free and $\alpha(t)$ is assumed to be bounded, $a \leq \alpha(t) \leq b$.
Let us present the problem formally.

Problem 7.1. *Minimize $V(\alpha(t))$ with respect to α, and subject to the constraint equations (5.1)*

In order to derive necessary conditions for the optimal control, we use Pontryagin's maximum principle.
The Hamiltonian associated with Problem 4.1 is as follows:

$$\begin{aligned} H &= C\alpha^2 J - \tau S + \lambda_s[\mu k - c\beta(I + L + bJ)S - \mu S] \\ &\quad + \lambda_I[(1-h)c\beta(I + L + bJ)S - (\mu + k_1)I + \alpha(t)(1 - h_1)J] \\ &\quad + \lambda_L[hc\beta(I + L + bJ)S - (\mu + k_1 - r)L + \alpha(t)h_1 J] \\ &\quad + \lambda_J[k_1 I + (k_1 - r)L - (\mu + k_2 + \alpha(t))J] \\ &\quad + \lambda_A[k_2 J - (\mu + d)A] \end{aligned}$$

We now proceed towards solving problem 7.1.

Theorem 7.2 *Given optimal control α^* and solution $S^*,\ I^*,\ L^*,\ J^*,\ A^*$ of problem 7.1, then the adjoint variables $\lambda_S,\ \lambda_I,\ \lambda_L,\ \lambda_J,\ \lambda_A$ satisfies the following ODEs:*

$$\lambda_A = 0,$$

$$\begin{aligned}
\dot{\lambda_S} &= \tau + \lambda_s[c\beta(I+L+bJ)+\mu] - \lambda_I c\beta(1-h)(I+L+bJ) - \lambda_L hc\beta(I+L+bJ),\\
\dot{\lambda_I} &= \lambda_s c\beta S - \lambda_I[(1-h)c\beta S - (\mu+k_1)] + \lambda_L hc\beta S - \lambda_J k_1,\\
\dot{\lambda_L} &= \lambda_s c\beta S - \lambda_I(1-h)c\beta S - \lambda_L[hc\beta S - (\mu+k_1-r)] - \lambda_J(k_1-r),\\
\dot{\lambda_J} &= \lambda_s c\beta bS - \lambda_I[(1-h)c\beta bS + \alpha(t)(1-h_1)] - \lambda_L[hc\beta bS + \alpha(t)h_1]\\
&\quad + \lambda_J(\mu+k_2+\alpha(t)),
\end{aligned}$$

where $\lambda_S(T) = \lambda_I(T) = \lambda_L(T) = \lambda_J(T) = \lambda_A(T) = 0$, *are the transversality condition. Furthermore the following characterization holds*

$$\alpha^*(t) = \min\Big(\max(a, \frac{\lambda_J - (1-h_1)\lambda_I - h_1\lambda_L}{2C}), b\Big). \tag{7.2}$$

Proof. We differentiate the Hamiltonian with respect to states variables, S, I, L, J, and A respectively, and then the adjoint system can be written as:

$$\dot{\lambda_X} = -\frac{\partial H}{\partial X}, \text{ for } X \in \{S, I, L, J, A\}.$$

In particular we note that

$$\begin{aligned}
\dot{\lambda_A} &= -\frac{\partial H}{\partial A} = (\mu+d)A,\\
\Longrightarrow \lambda_A(t) &= B\exp(\mu+d)t
\end{aligned}$$

for some constant B. But, the transversality conditions state that
$\lambda_A(1) = 0$. This implies that $B\exp(\mu+d)(1) = 0$, then $B = 0$.
Thus, $\lambda_A \equiv 0$, so that λ_A is identically zero.
The other $\dot{\lambda}$-equations follow from the adjoint equations and transversality conditions are standard results from Pontryagin's Maximum Principle. The first order conditions require us to minimize H with respect to α. We proceed as follows.

$$0 = \frac{\partial H}{\partial \alpha}|_{\alpha^*} = 2C\alpha J + (1-h_1)\lambda_I J + h_1\lambda_L(J) + \lambda_J(-J)$$

So we get, while $J(t) \neq 0$, that

$$\alpha^*(t) = \frac{\lambda_J - (1-h_1)\lambda_I - h_1\lambda_L}{2C}. \tag{7.3}$$

Taking the bounds on $\alpha(t)$ into account, we obtain the characterization of α^* in (7.2). □

7.4 Numerical simulation

We investigate numerically the effect of optimal control strategies on the spread of HIV in the population, by using treatment control $\alpha(t)$, to optimize the objective function which shows a significant difference in the infected with control compared to the situation where there is no control. We solve the optimal control problem 7.1 by using an iterative method with Runge-Kutta fourth order scheme. Starting with a guess for the adjoint variables, the state equations are solved forward in time. Then those preliminary solution are used to solve the adjoint equations backward in time. The iterations continue until convergence is obtained. For background on such iterative algorithms see [46].

Implementation of Runge-Kutta Fourth Order Method For Numerical Solution

We give a brief description of the Runge-Kutta method of order four (RK4) for the system of equations 5.2. We first develop *slopes* for all variables at the initial value. These slopes (a set of $k's$) are then used to make predictions of the dependent variable at the midpoint of the interval. These are then employed to make predictions at the end of the interval that are used to develop slopes at the end of the interval (the $k'_{4j}s$). Finally, the $k's$ are combined into a set of increment functions as in Eq(1.1-1.4) and brought back to the beginning to make the final prediction. The following illustrates the approach.
We start with initial conditions

$$t = 0, \quad S(t_0) = S_0, \quad I(t_0) = I_0, \quad H(t_0) = H_0, \quad J(t_0) = J_0,$$

we assume that the values S_i, I_i, H_i and J_i has been computed, where $i = 0(1)n$.
Now we calculate $S_{i+1}, I_{i+1}, H_{i+1}$ and J_{i+1} by Runge Kutta forth order method as,

$$S_{i+1} = S_i + \frac{1}{6}\left[k_{11} + 2(k_{21} + k_{31}) + k_{41}\right] \tag{7.3}$$

$$I_{i+1} = I_i + \frac{1}{6}\left[k_{12} + 2(k_{22} + k_{32}) + k_{42}\right] \tag{7.4}$$

$$H_{i+1} = H_i + \frac{1}{6}\left[k_{13} + 2(k_{23} + k_{33}) + k_{43}\right] \tag{7.5}$$

$$J_{i+1} = J_i + \frac{1}{6}\left[k_{14} + 2(k_{24} + k_{34}) + k_{44}\right] \tag{7.6}$$

with

$$k_{1j} = hf_j\left(t_0, S_i, I_i, H_i, J_i\right),$$
$$k_{2j} = hf_j\left(t_0 + \frac{h}{2}, S_i + \frac{k_{11}}{2}, I_i + \frac{k_{12}}{2}, H_i + \frac{k_{13}}{2}, J_i + \frac{k_{14}}{2}\right),$$
$$k_{3j} = hf_j\left(t_0 + \frac{h}{2}, S_i + \frac{k_{21}}{2}, I_i + \frac{k_{22}}{2}, H_i + \frac{k_{23}}{2}, J_i + \frac{k_{24}}{2}\right),$$
$$k_{4j} = hf_j\left(t_0 + h, S_i + k_{31}, I_i + k_{32}, H_i + k_{33}, J_i + k_{34}\right),$$

where $j = 1(1)4$ and $f_1 = S, f_2 = I, f_3 = H, f_4 = J$.

This gives us the next approximate values of S, I, H and J. Then t is set to $t_0 + h$ and the values of S, I, H and J are iterated with the above formula.

Some of the numerical parameter values used here are similar as in the paper [14] of Cai et al.

$k = 120$; $\beta = 0.0005$; $b = 0.3$; $\mu = 0.02$; $c = 3$; $k_1 = 0.01$; $k_2 = 0.02$; $h1 = .0001$; $\tau = 50$; $r = 0.0045$; $h = 0.08$; $C = 50$.

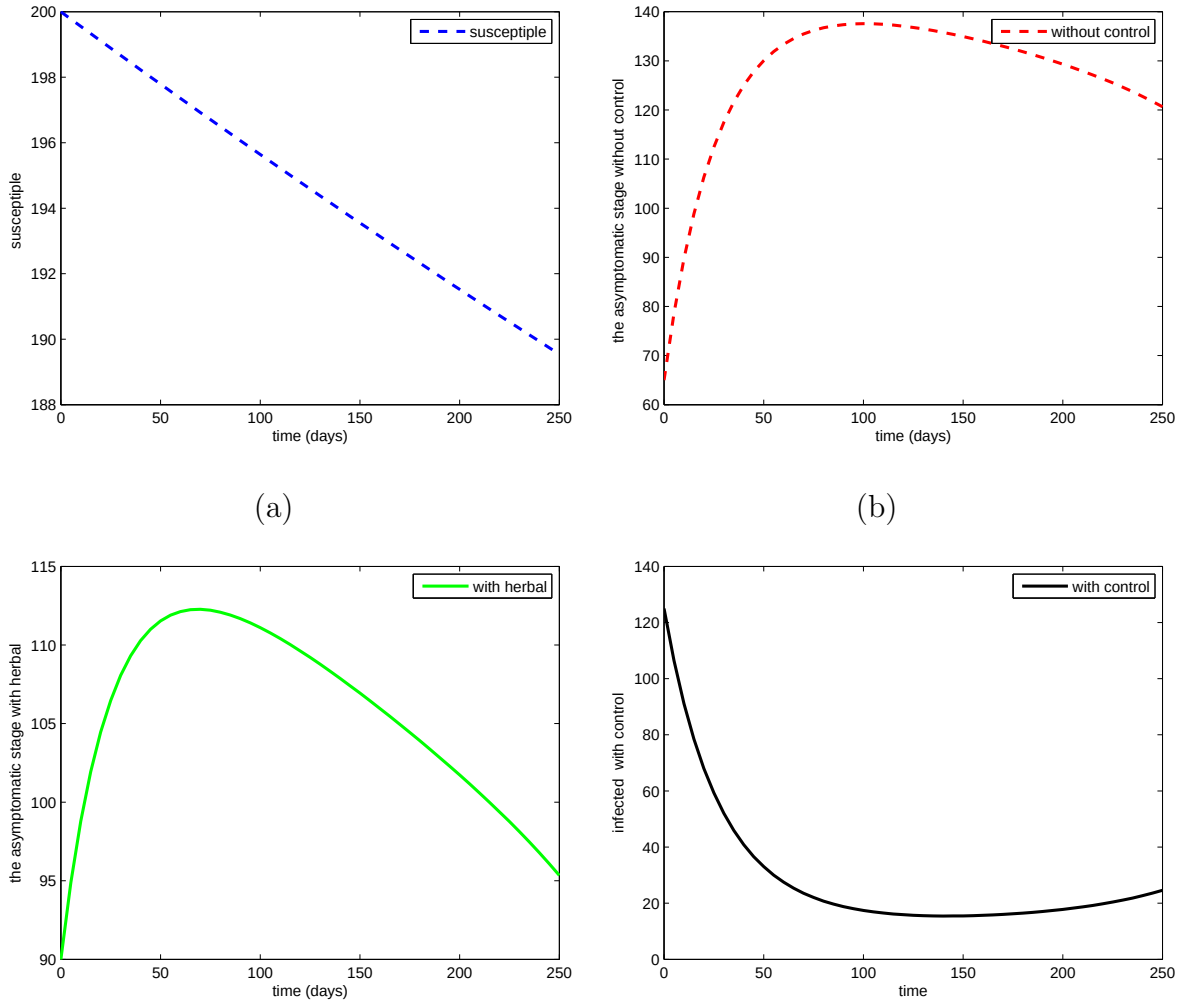
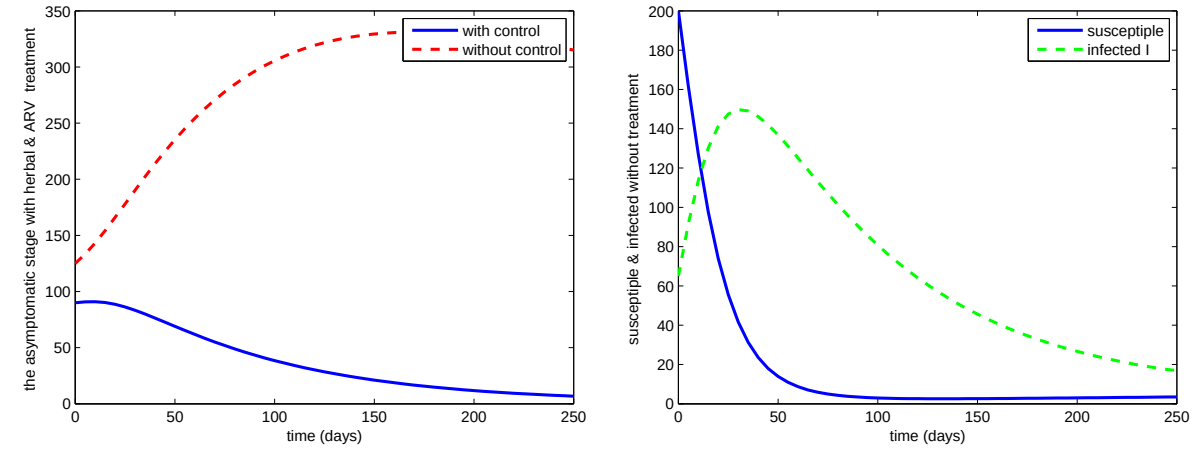
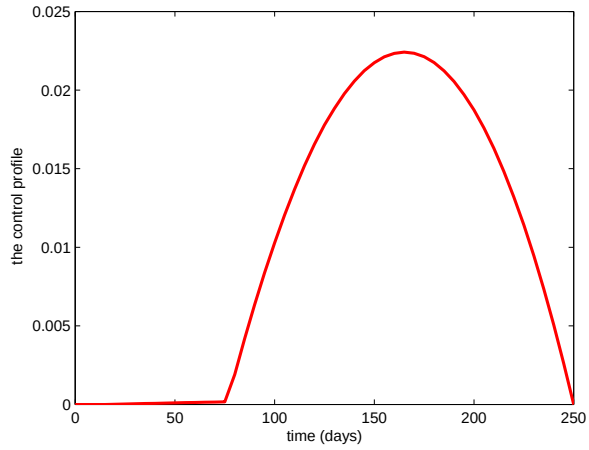


Figure 7.1: Simulations of the model individual showing effect of optimal strategy on the spread of HIV.

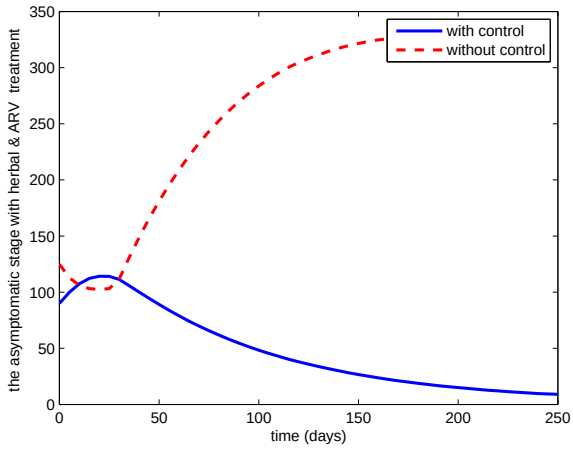


(a)

(b)

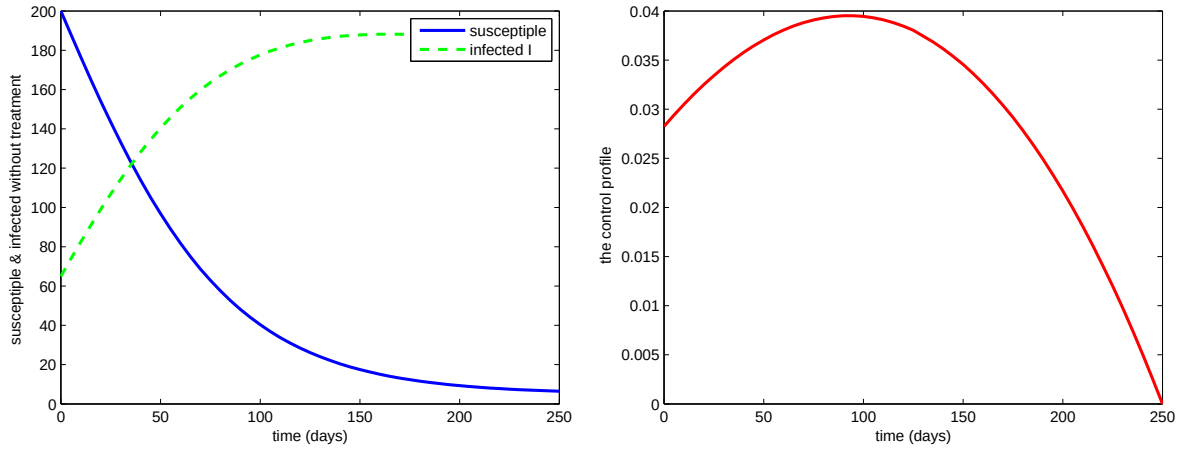


(c)



(d)

Figure 7.2: Graph of the solution of the optimality system with different values of the shape parameter for (a-b)$\beta = 0.000005$, $h = 0.22$ and (c-d) $\beta = 0.004$, $h = 0.08$.



(a) (b)

Figure 7.3: represent the control variable for $\beta = 0.00005$

Chapter 8

HIV model with stochastic perturbation

8.1 Introduction

Stochastic differential equation (SDE) models play an important role in a range of application areas including biology, epidemiology and population dynamics, mostly because they can provide an additional degree of realism as compared to their deterministic counterparts [71]. Considering that real life is full of randomness and stochasticity, a stochastic model can accommodate a distribution of the predicted outcomes. Therefore it is essential to understand and investigate the influence of noise on the dynamics. In many cases the noise simply blurs the underlying dynamics without qualitatively affecting it, as is the case with measurement noise or in many linear systems. In general, stochastic effects influence the dynamics, and may enhance, diminish or even completely change the dynamic behavior of the system. In this chapter, we briefly introduce an overview on stochastic modelling in epidemiology and eventually see its impact in some known results. We also consider the stochastic model corresponding to the deterministic model (5.1) by introducing a random perturbation. In Section 8.4, the positivity of the solution is showed and proved under some suitable conditions. We obtained numerically the conditions for

stochastic stability of the disease-free equilibrium.

8.2 Review on stochastic stability

There are different possible approaches for including random perturbations in the models, which result in different effects on the population. In [52], it is observed that the noise does not only have a destabilizing effect but can also have a stabilizing effect in an sde system. Even a relatively small noise can suppress explosions in population dynamics. Lahrouz et al. [44] present an $SIRS$ epidemic model with saturated incidence rate and disease-inflicted mortality. They proved that the deterministic model has a unique endemic equilibrium E_1 which is globally asymptotically stable if the reproduction number is greater than one. Concerning the stochastic model, they obtained sufficient conditions for stochastic stability of the disease-free equilibrium P_0 in pth moment and the almost sure exponential stability by using a suitable Lyapunov function and other techniques of stochastic analysis. The investigation of this stochastic model revealed that the stochastic stability of P_0 depends on the magnitude of the intensity of noise as well as the parameters involved within the model system. Yu et al. [38] proved that the endemic equilibrium of a certain two-group SIR model with random perturbation is stochastically asymptotically stable.

Dalal et al. [20] considered stochasticity in an HIV model with condom use, and they study the so-called parameter perturbation. They augmented the parameter (the per capita rate at which infected individuals develop AIDS) by a white noise term. The positivity of the solutions were proved in the paper. Furthermore, they arrive at the conclusion that the noise term tended to stabilize the system for almost sure exponential stability and stability in probability. In another paper, Dalal et al. [19] consider a stochastic model representing HIV internal virus dynamics. The stochasticity in the model is again introduced by way of parameter perturbation. They show that the model established in their paper possesses non-negative solutions as this is essential in any population dynamics model. They approximate one of the variables by a mean reverting process and

determine the mean and variance of this process. Tornatore et al. [84] considered the case that the disease transmission coefficient was subject to stochastic perturbations in SIR models with or without distributed time delay. They demonstrated numerically that the introduction of stochastic perturbations modified the stability threshold of the system for an epidemic to occur. In addition, under the same conditions the disease free equilibrium was globally asymptotically stable in the stochastic SIR model without time delay, and it was stable in probability in the stochastic SIR model with time delay. These results reveal the significant effect of the environmental noise on some epidemic models, because the stochastic models can provide some additional degree of realism compared to their deterministic counterparts.

8.3 White noise stochastic perturbations on the model parameters

The dynamics of a population can be considered as having both deterministic (predictable) and stochastic (unpredictable) components that operate simultaneously. We introduce white noise stochastic perturbations on each of the state variables of our basic model (5.1), and we formulate the necessary assumptions hitherto. Let us assume $(\Omega, \mathcal{F}, \{\mathcal{F}_t\}_{t\geq t_0}, P)$ to be a complete probability space which is right continuous with a filtration $\{\mathcal{F}_t\}_{t\geq t_0}$. Let $B_0(t)$, $B_1(t)$, $B_2(t)$, $B_3(t)$ be mutually independent Wiener process defined on this probability space. We propose the following system of stochastic differential equations to be the stochastic version of our model (5.1):

$$\left.\begin{aligned} dS &= [\mu k - c\beta(I+H+bJ)S - \mu S]dt + \sigma_0 S dB_0 \\ dI &= [(1-h)c\beta(I+H+bJ)S - (\mu+k_1)I + \alpha(1-h_1)J]dt + \sigma_1 I dB_1 \\ dH &= [hc\beta(I+H+bJ)S - (\mu+k_1-r)H + \alpha h_1 J]dt + \sigma_2 H dB_2 \\ dJ &= [k_1 I + (k_1-r)H - (\mu+k_2+\alpha)J]dt + \sigma_3 J dB_3 \end{aligned}\right\} \tag{8.1}$$

$$dA = [k_2 J - (\mu + d)A]dt \Big\} \tag{8.2}$$

with suitable initial conditions.

Here σ_0 and $\sigma_i > 0,\ i = 1, .., 3$, represent the intensities associated with B_0 and $B_i(t),\ i = 1, .., 3$, respectively.

8.4 Non-negative solutions

It is important to prove that the variables of system (8.1) are nonnegative for all time $t > 0$, when dealing with a model of population dynamics is concerned. Hence for this reason we prove the positivity of the solutions, Theorem 8.2 below.

Now we can observe that the coefficients of the system (8.1) are locally Lipschitz continuous functions of the variables S, I, H and J. Thus, for any given value (S_0, I_0, H_0, J_0) there is a unique local solution $X(t) = (S(t), I(t), H(t), J(t))$.

Let us define subsets Δ of $\mathbb{R}^4$ as follows

$$\Delta = \{x \in \mathbb{R}^4 |\ x_1 > 0, x_2 > 0, x_3 > 0, x_4 > 0\}.$$

Then a feasible region for solutions $X(t) = (S(t), I(t), H(t), J(t))$ of system is the set Δ.

Remark 8.1. Let us consider a real-valued function $f = f(S(t), I(t), J(t), A(t))$ of the variables in the model. In particular we note that $\frac{\partial f}{\partial t} = 0$. For convenience we write down the formula for the differential of f. We apply the multi-dimensional Itô formula, and we note in particular that $dSdI = dSdH = dSdJ = dIdH = dIdJ = dHdJ = 0$. Thus we obtain:

$$df = \frac{\partial f}{\partial S}dS + \frac{\partial f}{\partial I}dI + \frac{\partial f}{\partial H}dH + \frac{\partial f}{\partial J}dJ$$

$$+\frac{1}{2}\left[\frac{\partial^2 f}{\partial S^2}dSdS+\frac{\partial^2 f}{\partial I^2}dIdI+\frac{\partial^2 f}{\partial H^2}dHdH+\frac{\partial^2 f}{\partial I^2}dJdJ\right]$$

Theorem 8.2. *Let $(S_0, I_0, H_0, J_0) \in \Delta$. Then the system (8.1) admits a unique solution $(S(t), I(t), H(t), J(t))$ on $t \geq 0$, and this solution remains in Δ with probability 1.*

Proof. Since the coefficients of the system (8.1) are locally Lipschitz continuous, for any given initial value $(S_0, I_0, H_0, J_0) \in \mathbb{R}^4_+$. Thus there exists a unique local solution $(S(t), I(t), H(t), J(t))$ on $t \in [0, \tau_e)$ where τ_e is the explosion time [44]. Assume $m_0 \geq 0$ be sufficiently large so that $S_0, I_0, H_0, J_0 \in (1/m_0, m_0)$; for $m \geq m_0$, consider the stopping times

$$\begin{aligned}\tau_m &= \inf\{t \in [0,\tau_e) : \min\{S(t), I(t), H(t), J(t)\} \leq 1/m_0 \\ &\qquad \text{or } \max\{S(t), I(t), H(t), J(t)\} \geq m_0\}.\end{aligned}$$

To complete the proof all we need to show is that $\tau_\infty = \infty$ a.s. If this statement is false, then there is a pair of constants $T > 0$ and $\epsilon \in (0, 1)$ such that

$$P\{\tau_\infty \leq T\} > \epsilon.$$

Since $\tau_\infty = \lim_{m\to\infty} t_m$, there exists an integer $m_1 \geq m_0$, such that

$$P\{\tau_m \leq T\} > \epsilon \text{ for all } m \geq m_1. \tag{8.1}$$

Consider the function V defined for $X(S, I, H, J) \in \mathbb{R}^4_+$ by

$$V(x) = S - \ln S + I - \ln I + H - \ln H + J - \ln J$$

Applying the Itô formula, we obtain

$$\begin{aligned}dV(x) &= (1-\frac{1}{S})dS + (1-\frac{1}{I})dI + (1-\frac{1}{H})dH + (1-\frac{1}{J})dJ \\ &\quad + \frac{1}{2}\left[\frac{1}{S^2}dSdS + \frac{1}{I^2}dIdI + \frac{1}{H^2}dHdH + \frac{1}{J^2}dJdJ\right] \\ &= (1-\frac{1}{S})\left([\mu k - c\beta(I + H + bJ)S - \mu S]dt + \sigma_0 S dB_0\right)\end{aligned}$$

$$
\begin{aligned}
&+ (1-\frac{1}{I})\left([(1-h)c\beta(I+H+bJ)S-(\mu+k_1)I+\alpha(1-h_1)J]dt+\sigma_1 I dB_1\right)\\
&+ (1-\frac{1}{H})\left([hc\beta(I+H+bJ)S-(\mu+k_1-r)H+\alpha h_1 J]dt+\sigma_2 H dB_2\right)\\
&+ (1-\frac{1}{J})\left([k_1 I+(k_1-r)H-(\mu+k_2+\alpha)J]dt+\sigma_3 J dB_3\right)\\
&+ \frac{1}{2}(\sigma_0^2+\sigma_1^2+\sigma_2^2+\sigma_3^2)dt\\
\leq\ & LVdt+\sigma_0(S-1)dB_0+\sum_{i=1}^{3}\sigma_i(I_i-1)dB_i,
\end{aligned}
$$

where

$$
\begin{aligned}
LV &= \mu K-(S+I+H+J)\mu-k_2 J-\frac{\mu K}{S}+c\beta(I+H+bJ)+\mu\\
&\quad -(1-h)c\beta(I+H+bJ)\frac{S}{I}+(\mu+k_1)-\alpha(1-h_1)\frac{J}{I}\\
&\quad -hc\beta(I+H+bJ)\frac{S}{H}+(\mu+k_1-r)-\alpha h_1\frac{J}{H}\\
&\quad -k_1\frac{I}{J}-(k_1-r)\frac{H}{J}+(\mu+k_2+\alpha)\\
&\quad +\frac{1}{2}(\sigma_0^2+\sigma_1^2+\sigma_2^2+\sigma_3^2)\\
&= \mu K+4\mu+2k_1+k_2+\alpha+c\beta(I+H+bJ)+\frac{1}{2}(\sigma_0^2+\sigma_1^2+\sigma_2^2+\sigma_3^2),
\end{aligned}
$$

and $I_i,\ i=1,..,3$, represent I, H, J, respectively.

$$I<K,\ H<K, \text{and } J<K.$$

Then

$$LV\leq \mu K+4\mu+2k_1+k_2+\alpha+c\beta K(2+b)+\frac{1}{2}(\sigma_0^2+\sigma_1^2+\sigma_2^2+\sigma_3^2)=:\Lambda$$

Therefore, by integration we obtain

$$\int_0^{\tau_m\wedge T} dV(X)\leq \int_0^{\tau_m\wedge T}\Lambda\ dt+\int_0^{\tau_m\wedge T}\sigma_0(S-1)\ dB_0+\sum_{i=1}^{3}\sigma_i(I_i-1)\ dB_i,$$

Taking expectation, yields

$$E[V(X(\tau_m\wedge T))]\leq V(S(0),\ I(0),\ H(0),\ J(0))+\Lambda\ T. \tag{8.2}$$

By (8.1) let $\Phi_m = \{\tau_m \leq T\}$ for $m \geq m_1$, then $P(\Phi_m) \geq \epsilon$. Note that for every $\upsilon \in \Phi_m$ there is some component of $X(\tau_m, \upsilon)$ which takes the value equals either m or $1/m$. Consequently,

$$E[V(X(\tau_m \wedge T))] \geq [m - \ln m] \wedge [\frac{1}{m} - \ln \frac{1}{m}].$$

Then it follow from (8.1) and (8.2) that

$$\begin{aligned} V(S(0),\ I(0),\ H(0),\ J(0)) + A\ T &\geq E[V(X(\tau_m \wedge T))] \\ &\geq [m - \ln m] \wedge [\frac{1}{m} - \ln \frac{1}{m}]. \end{aligned}$$

Letting $m \to \infty$ leads to the contradiction $V(S(0),\ I(0),\ H(0),\ J(0)) + \Lambda\ T = \infty$. Therefore we must have $\tau_\infty = \infty$ a.s. □

8.5 Simulations

The SDE model was numerically solved using the Euler-Maruyama method. Figs 1 to 4 show the stochastic trajectories of $S(t)$; $I(t)$; $H(t)$ and $J(t)$ over time, with the following parameter values:

$k = 120$, $\beta = 0.0005$, $b = 0.01$, $\mu = 0.02$, $c = 0.06$, $k_1 = 0.025$, $k_2 = 0.09$, $\alpha = 0.005$, $h = 0.001$, $r = 0.001$, $h_1 = 0.02$.

The initial values are $S(0) = 65,\ I(0) = 35,\ H(0) = 20,\ J(0) = 10$,

with different intensities of white noise. We note that the model (8.1) has a disease free equilibrium E_0 as in the deterministic case only if $\sigma_0 = 0$.

In Fig.1 we choose $\sigma_0 = 0$, $\sigma_1 = 0.08$, $\sigma_2 = 0.06$, $\sigma_3 = 0.05$, with parameter values stated above, except c and β. It clearly shows $I(t)$, $H(t)$, and $J(t)$ converging to zero in the stochastic model. Hence, we observe that disease-free equilibrium E_0 is stochastically stable. In Fig 8.2 (b) and Fig 8.3 (b) one can see the stochastic effects very clearly in comparison to Fig. 8.2 (a) and Fig. 8.3 (a) respectively where $\sigma_0 = \sigma_1 = \sigma_2 = \sigma_3 = 0$. Therefore, in this case it does not guarantee almost sure exponential stability.Whatever

the intensity is so large, the endemic equilibrium becomes unstable and the solution of the system (8.1) converges to E_0, as showed in Fig 8.4.

Figure 8.1: Stochastic trajectories of the system (8.1) when $\mathcal{R}_0 < 1$: left column when $\beta = 0.003$, $c = 0.12$ (first row), $c = 0.15$ (second row) and right column when $\beta = 0.005$, $c = 0.075$ (first row), $c = 0.076$ (second row).

(a) (b)

Figure 8.2: This figure shows that simulations for both the deterministic and stochastic cases when $c = 0.09$: (a) $\sigma_0 = \sigma_1 = \sigma_2 = \sigma_3 = 0$. (b) when $\sigma_0 = 0.01$, $\sigma_1 = 0.08$, $\sigma_2 = 0.06$, $\sigma_3 = 0.05$.

(a) (b)

Figure 8.3: This figure shows that simulations for both the deterministic and stochastic cases when $c = 0.01$: (a) $\sigma_0 = \sigma_1 = \sigma_2 = \sigma_3 = 0$. (b) $\sigma_0 = 0.01$, $\sigma_1 = 0.08$, $\sigma_2 = 0.06$, $\sigma_3 = 0.05$.

(a) (b)

Figure 8.4: This figure shows that the susceptible, infected without treatment I, infected with ARV treatment J and infected with alternative treatment H with parametric values as stated in the text with different noise intensity $\sigma_0 = 0.03$ in (a), $\sigma_0 = 0.005$ in (b)

Chapter 9

Conclusions

Presently, the world is concerned about the rising prevalence of HIV which causes a lot of deaths in different communities while there is no cure, neither a vaccine to control this epidemic. The propagation of HIV and other infectious diseases in the last decade has been attributed to environmental and social influences. However, almost all developing countries have increasingly recognised the need to find effective prevention and control strategies for the diseases. This research work informs how the use of herbal medicine in conjunction with ARV treatment can control and possibly eradicate HIV/AIDS in this our generation so that our children may see an HIV free generation. We have addressed three aspects on our population modeling of HIV:

- Model with herbal and ARV treatment,
- Model with optimal control,
- Model with stochastic perturbation.

The conclusions from the model presented in Chapter 5, discussed a number of important issues related to the investigation of HIV infection together with the effect of the use of herbal traditional medicines. The model is shown to have locally asymptotically stable endemic equilibrium when the reproduction number is greater than unity. The stability properties of the disease free equilibrium is important because the stability nature of

solutions will determine the extent to which the disease will disappear from the population. Numerical simulations of the model are carried out in order to insights into the HIV/AIDS dynamics in usage of ARV and herbal medicine.

Chapter 7 concentrated on the analysis of optimal strategies for control of the intensity of the treatment effort over time. This enables health authorities to roll out resources in the most effective manner. It promotes the chances of success in the combat of the disease with effective treatment regime and control of the proportion of individuals on treatment. The graphs show the extent to which herbal medicine can help suppress the spread of HIV. It is observed that there is a significant difference in the infected with control compared to the situation where there is no control. This study, alongside other sociological and behavioural interventions is important in areas which lack the necessary resources.

In Chapter 8 of this dissertation, the model takes into account the effect of stochastic perturbation of the model. Such stochasticity is actually very much prevalent in reality. Moreover, in the paper [52], for instance, it is shown how stochastic perturbation can improve the stability of the disease free equilibrium. As a follow-up on this work, one can more thoroughly study the effect of stochastic perturbation on this system.

The model was developed in accordance with previous models in the literature, especially [14]. It will be helpful to obtain good estimates for the newly introduced parameters, used most especially, the reactivation rate of individuals infected. Our work may require additional information to improve on the findings for future research studies, extensions, modifications and analysis of the models. Thus, as a future prospect, it would be important also to understand more clearly, the impact of herbal medicine on the prevalence and incidence of HIV/AIDS.

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