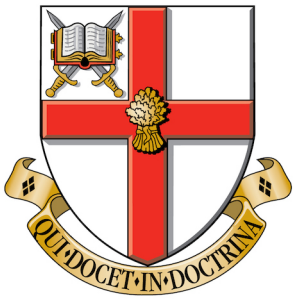


University of Chester

# Mathematical Analysis of Some Virus models

by

Paul Fatiye Useni

A Dissertation Submitted to the School of Computer Science and Mathematics, Faculty of Science and Engineering in partial fulfilment of the requirements for the degree of Master of Science in Mathematics

at the

UNIVERSITY OF CHESTER

September 2014

Certified by .....

Dr. Nikos Kavallaris
Senior Lecturer
Dissertation Supervisor

# Declaration of Authorship

I, Paul Fatiye Useni, declare that this thesis titled, 'Mathematical Analysis of Some Virus models' and the work presented in it are my own. I confirm that:

- this work was undertaken completely while in candidature for a Masters of Science degree at this University.
- Where I have consulted the published work of others, this is always clearly attributed.
- where I have quoted from the work of others, the source is always given.

Signed: 

Date: February 5, 2015

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## Abstract

The Mathematical Analysis of some virus models such as $SIR$ epidemic model, $HIV$ infection model and Ebola virus model are hereby presented. The stability of both the $SIR$ and $HIV$ infection models were investigated using linearization method. The $SIR$ model has an endemic infection when the equilibrium is unstable i.e $R_0 > 1$, and attain a disease-free equilibrium with regards to the existing population when the equilibrium is asymptotically stable i.e $R_0 = \frac{r}{a+\mu} < 1$. The analysis shows that the threshold behavior is directly related to the relative removal rate $\rho$ and that an epidemic will reach its maximum when $S = \rho$ with a condition that $I(t) = 0$. Also, there is an oscillatory behavior of susceptible and that of infective at the zero point and highest point respectively. Then the homosexual population and T-cell infection models consisting of supply rate solution and that of clonal production solution were discussed. In particular the stability of T-cell infection model was also investigated for $HIV$ virus and it was proven that the unique critical point is globally asymptotically stable.In the last chapter of this thesis, the formulation of EVD model and its numerical solution using Euler's method is also presented. Finally, the conclusion and future work suggestions are stated.

Dissertation Supervisor: Dr. Nikos Kavallaris
Title: Senior Lecturer in Mathematics

*This work is dedicated to my dear wife Patricia Nokdet Paul and my lovely children Precious, Praise and Patience with love.*

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# Contents

**List of Illustrations** **vii**
Figures . . . vii
Tables . . . vii

**1 Introduction** **1**
1.1 History of Epidemic Models. . . . 1
1.2 General Epidemic Models . . . 4

**2 The SIR Model** **8**
2.1 The SIR Epidemic Model . . . 8
2.2 The SIS and SEIR Models . . . 9
2.2.1 The SIS Model . . . 9
2.2.2 The SEIR Model . . . 9
2.3 Phase - plane Analysis of classic SIR epidemic model . . . 11
2.4 Stability of the SIR Model . . . 18
2.5 Demographic Effects on the SIR Model . . . 18
2.6 The Endemic Equilibrium . . . 21
2.7 The SIR Model for heterosexual spread of infection . . . 22
2.8 Discussion . . . 25

**3 The HIV INFECTION MODEL** **27**
3.1 AIDS Epidemic in Homosexual Population . . . 27
3.2 The T-cell Infection model . . . 30
3.3 Formulation of the T - Cell infection model . . . 34
3.4 The T-cell Model Agrees with Biological Constraints : . . . 35
3.5 Stability of the T-cell infection model . . . 36
3.6 An Alternative Approach . . . 39
3.7 Discussion . . . 42

**4 The EBOLA VIRUS MODEL** **44**
4.1 Background . . . . . 44
4.2 Assumptions of the model . . . . . 45
4.3 Formulation of the model . . . . . 46
4.4 Future work . . . . . 49

**Appendices** **52**

**Bibliography** **56**

# List of Illustrations

## Figures


2.1 SIR Model simulation . . . . . 14
2.2 Phase portraits. . . . . 15
2.3 Criss-cross of S I R . . . . . 22
2.4 Criss-cross of S I . . . . . 23

3.1 Time Versus Number of T-cells per cubic millimetre. . . . . 32
3.2 Time Versus Number of T-cells count with a reduced thymus function. . . . . 33

4.1 A numerical solution of the Ebola Model . . . . . 48


## Tables


3.1 Parameters for case I . . . . . 32
3.2 Parameters for case II . . . . . 33

# Chapter 1

# Introduction

## 1.1 History of Epidemic Models.

The study of epidemics with its long history has been characterized by an astonishing variety of models and explanations for the spread and causes of epidemic outbreak in our society which has become a major concern today.
Epidemics have been a great challenge for human kind and we are still moved by dramatic descriptions that arrive to us from the past, as in Lucretius's sixth book of "De RerumNatura" and also in other more recent descriptions that we find in the literature. The "Black Death", the plague that spread across Europe and from 1347 to 1352 and made 25 millions of victims, seems to be far from our lives, but more recent events remind us that epidemics remain a great problem facing our health institutions today [16].

At the beginning of the $1980s$, the syndrome of Acquired Immune Deficiency Syndrome (AIDS) was for the first time descovered in the United State. It was observed in a group of homosexual men in California and New York who had opportunistic infections and specific tumors [17].
A retrovirus, now termed Human Immunodeficiency Virus type 1 (HIV-1), was subsequently identified as the causative agent of what has since become one of the most devastating infectious diseases to have emerged in recent history (Barre-Sinoussi et al. 1983; Gallo et al. 1984; Popovic et al. 1984) [29], $HIV-1$ spreads by sexual, percutaneous, and perinatal routes, however, 80% of adults acquire HIV-1 following exposure at mucosal surfaces, and AIDS is thus primarily a sexually transmitted disease.
Mathematical modeling has proven to be valuable in understanding the dynam-

ics of HIV-1 infection. Since the discovery of the Human Immune Deficiency Virus type. (HIV-1) in the early 1980$s$, and which was first isolated in 1983, the disease has spread in successive waves to most regions around the globe. It is reported that HIV has infected more than 60 million people, and over one third of them subsequently died [7].

Over the last two decades, there has been a great effort in the mathematical modeling of HIV infection and treatment strategies. These models mainly investigated the dynamics of the target cells and infected cells, viral production and clearance and the efforts of antiviral drugs treatment [15],they also used a simple mathematical model to analyze a set of viral load data, collected from infected patients after the administration of a protease inhibitor, and the virus clearance rate, the rate of loss of productively cells, and the viral production rate were estimated. These estimates were minimal estimates since the effects of 100% effective and cells were assumed to produce new virus immediately after they were infected [7].

The Human Immunodeficiency Virus,**HIV**, leads to Acquired Immune Deficiency Syndrome,**AIDS.** HIV is a retrovirus and like most of the viruses in this family, the retrovirus only replicate in dividing cells [22]. Infection by the virus HIV-1, the most common variety has many highly complex characteristics, most of which are still not understood. The fact that the disease progression can last more than 10 years from the first day of infection is just one of them. Another problem is that while most viral infections can be eliminated by an immune response, HIV is only briefly controlled. HIV primarily infects a class of white blood cells or lymphocytes, called $CD4^+T$-cells, but also infects other cells such as dendrite cells [22].

Although, levels of $HIV$ in circulation remain low during the asymptomatic phase, a gradual but steady decline in the numbers of $CD4^+T$-cells continues. Once the $CD4^+T$-cells numbers reach below a threshold, the $HIV$ concentration in circulation begins to rise rapidly (reaching levels $> 10^6$ visions/ml blood) and the patient exhibits a precipitous loss of immunity to many other pathogens [10]. This last phase of $HIV$ disease is referred to as AIDS during which the patient invariably acquires life threatening opportunistic infections that might lead to death. Notable feature are persistence of high concentrations of $HIV$ in circulation with minimal $CD4^+T$-cells count.
The key to understanding the origin of $HIV$ was the discovery that closely

related viruses - Simian Immunodeficiency Virus (SIVs), were present in a wide variety of African Primates. Collectively, $HIV$ and $SIV$ comprise the Primate lent viruses, and $SIVs$ have been isolated in more than 20 African Primate Species. Importantly, in no case (other than laboratory - associated infections of Asian Macaque Monkeys) has it been shown that the $SIVs$ cause disease in their hosts, although only a few studies of their natural history in wild populations have been undertaken [27].

Ever since $HIV-1$ was reported, the reasons for its sudden emergence, epidemic spread, and unique pathogenic have been a subject of intense study. A first clue came in 1986 when a morphologically similar but antigenicity distinct virus was found to cause AIDS in patients in West African ( Clavel et al. 1986). Curiously, this new virus, termed Human Immunodeficiency Virus type 2 (HIV-2) was only distantly related to $HIV-1$, but was closely related to Simian Virus that caused Immunodeficiency in Captive Macaques (Chakrabarti et al. 1987; Guyoder et al. 1987). Soon thereafter, additional viruses, collectively termed $SIVs$ with a suffix to denote their species of origin were found in different primates from sub-Saharan African, including African green Monkeys, Sooty Manganese, mandrills, Chimpanzees and others.

Surprisingly, these viruses appeared to be largely nonpathogenic in their natural hosts, despite clustering together with the human and Simian AIDS viruses in a single phylogeny lineage within the radiation of lent-viruses [29]. Interestingly, close Simian relatives of $HIV-1$ and $HIV-2$ were found in Chimpanzees (Huet at al.1990) and sooty Manganese (Hirsch et al. 1989), respectively. These relationships provided the first evidence that AIDS had emerged in both humans and Macaques as a consequence of cross-species infections with lent-viruses from different primate species (Sharp et al. 1994).

Indeed, subsequent studies confirmed that Simian was not a natural pathogen of Macaques (which are Asian Primates) but had been generated inadvertently in US primate centers by inoculating various species of macaques with blood and / or tissues from naturally infected sooty manganese. (Apetrei et al. 2005, 2006). One aspect of AIDS (Acquired Immune Deficiency Syndrome) epidemic is the myth of denial, not uncommon phenomenon with certain diseases where, for example, there is a perceived social stigma or a strong economic elements; the brief highly pertinent article by Weiss (1996) discuses some recent examples of this regarding AIDS and suggests some of the modern reasons for it.

The major horror of the AIDS epidemic is in Africa where around 70% of the total AIDS deaths in the world have occurred and, as recently stated (July, 1999) by Dr. Peter Piot, Head of the United Nations AIDS (UNAIDS) programs, half of all new born babies in Africa are $HIV$ positive. Due to the regular early ludicrous demands in the $1980s$ of its existence by some African leaders. ('There is no AIDS in my Country") [22].

The most important aspect of defense against infectious diseases is unquestionable surveillance which characterizes the pattern of each disease. Although, there are social problems associated with gathering data on the number of people who have the $HIV$, it is unlikely that the epidemic will be contained, if this information is not made available [22].

The lack of knowledge about $HIV$ creates enormous difficulties in designing effective control programs, not to mention poor health care facilities. Education programs as to how it can spread are the minimum requirement. Those that have been pursued have had some success but even their continuing use and new ones have often been blocked by the religious establishments without the knowledge of the reservoir of the disease, it is extremely difficult to evaluate effective prevention and control strategies.

According to a depressing UNAIDS Report (Global HIV /AIDS Epidemic December 1997), there are an estimated $16,000$ new cases a day and that around 27 million people are $HIV$ positive but do not know it. AIDS is just one disease where surveillance has been disastrously inadequate and the misuse of antibiotics which is giving rise to resistant strains of bacteria.

## 1.2 General Epidemic Models

The cause of infection and progression to AIDS is highly variable. Immediately after infection there may be an acute illness with fever, diarrhea, and encephalopathy that has been likened to an infectious mononucleosis [17].

Acute encephalitis has also been described at this stage [17], this acute phase may correspond with rising amounts of free virus in the blood. There is then a

fall in free virus as antibodies appear. This appearance of antibodies has been reported to occur in $19 - 56$ days or longer [17].

According to [22], one epidemic which has exercised classical scholars for a very long time is the Plaque of Athens $(430 - 428BC)$. This was described in great detail by Thucydides to include the symptoms and disease progression. He gave some figures that 1050 of 4000 soldiers on an expedition died of the disease and even to the fact that dogs who ate the dead bodies also suffered, which has been source of numerous articles over some hundreds of years, with cases been made for an incredible rage of disease such as bubonic plaque, measles, Malta fever, small pox, scarlet fever, typhus, typhoid fever and many others.

In USA, the first major epidemic was the Yellow Fever epidemic Philadelphia in 1793 in which about 5000 people died out of a population of around $50,000$, although estimates suggest that about $20,000$ fled the City, see the interesting Scientific American article by Foster *et al.*(1998) [22] and the book by Powell(1993). A leading physician was the strongest advocate of bleeding as the appropriate treatment while others recommended cleanliness, rest, Peruvian bark and wine. This epidemic had a major impact on the subsequent life and politics of the country.

A model for smallpox was formulated and solved by Daniel Bernouli (1760), involving a nonlinear ordinary differential equation in order to evaluate and also consider the effect of cowpox inoculation on the spread of smallpox virus [13]. It is probably the first time that a mathematical model was used to assess the practical advantages of vaccination.
Models can also be extremely useful in giving reasoned estimates for the level of vaccination for the control of directly transmitted infectious disease. A paper written by Schuette and Hethcote (1999) discusses vaccination protocols in connection with chickenpox and shingles and highlights certain dangers of extensive vaccination.
The classical theoretical papers on epidemic models by Kermack and McKendrick (1927, 1932, and 1933) have had a major influence in the development of mathematical models and are still relevant in a surprising number of epidemic situations.

The effectiveness of improved sanitation, antibodies, and vaccination programs

created a confidence in the $1960s$ that infectious would soon be eliminated. Consequently, chronic diseases such as cardiovascular disease and cancer received more attention in the United States and industrialized countries. But infection diseases have continued to be the major causes of suffering and mortality in developing countries. Moreover, infectious disease agents adapts an resolved that new infectious diseases have emerged and some existing diseases have re-emerged [20].

Newly identify diseases include Lyme disease (1975), Legionnaire's disease (1976), toxic-shock syndrome (1978), hepatitis C(1989), hepatitis E(1990) and antivirus (1993). The antibiotic -resistant strains of tuberculosis, pneumonia, and gonorrhea have evolved. Malaria, dengue, and yellow fever have reemerged and are spreading into new regions as climate changes occur. Diseases such as plague, cholera, and hemorrhagic fevers ( Bolivian, Ebola, Lassa, Marburg, etc.) continue to erupt occasionally. Surprisingly, new infectious agents called prions have recently joined the previously known agents: Viruses, bacteria, protozoa, and helming (worms).

Recent popular books have given us exciting accounts of the emergence and detection of new diseases [9, 26] . It is clear that human or animal invasions of new ecosystems, global warming, environmental degradation, increased international travel, and changes in economic patterns will continue to provide opportunities for new and existing infectious [21]. Mathematical models have become important tools in analyzing the spread and control of infectious diseases. The model formulation process clarifies assumptions, variables, and parameters, moreover, models provide conceptual results such as thresholds, basic reproduction numbers, contact numbers, and replacement numbers. Mathematical models are used in comparing, planning, implementing, evaluating, and optimizing various detection, prevention, therapy, and control programs. Epidemiology modeling can contribute to the design and analysis of epidemiological surveys, suggest crucial data that should be collected, identify trends, make general forecasts, and estimate the uncertainty in future [12, 14].

In the $20^{th}$ century, Hamer formulated and analyzed a discrete time model in his attempt to understand the recurrence of measles epidemics [11]. His model may have been the first to assume that the incidence (number of new cases per unit time) depends on the product of the densities of the susceptible and infective. Ross was interested in the incidence and control of malaria, so he

developed differential equation models for malaria as a host-vector disease in [28]. Mathematical epidemiology seems to have grown exponentially starting in the middle of the 20th century, (the first edition in 1957 of Bailey's book is an important landmark) [4], so that a tremendous variety of models have now been formulated, analyzed and applied to infectious diseases as will be seen in this work.

# Chapter 2

# The SIR Model

The problem of virus propagation has attracted huge interest. Here in this section, we shall focused on some of the related epidemic thresholds. Among the many proposed models for viral propagation, two have gained global acceptance. The first, called the $SIR$ model, being that once healed, an individual is considered removed ($R$) from the population and immune to further infection and the second is called $SIS$ model, which considers individuals as being either susceptible ($S$) or infective, then heal herself with some probability to become susceptible again.
The class of epidemiological models that are most widely used are the so-called homogeneous models in [3], because homogeneous models assumes that every individual has equal contact to others in the population and that the rate of infection is largely determined by the density of the infected population.

We shall think of it as a kind of mean field model with a well-mixed population. Most epidemic models are based on dividing the host population into a small number of compartments, each containing individuals that are identical in terms of their status with respect to the disease in question.

## 2.1 The SIR Epidemic Model

Underlying all dynamical systems, models of epidemiological processes is the S-I frame work of Kermack and Mckendrick [18], that was foreshadowed by the work of Enko [6]. We will use the terminology $SIR$ to describe a disease which confers immunity against re-infection, to indicate that the passage of individuals is from the susceptible class $S$ to the infective class $I$ to the re-

moved class $R$. The basic SIR models have the following assumptions:

**S** The Susceptible: who can catch the disease i.e. individuals who have no immunity to the infectious agent, so might become infected if exposed.

**I** the infectious: Individuals who are currently infected and can transmit the infection to susceptible individuals who they contact.

**R** the removed class, those who have either had the disease, or are removed, Immune or isolated until recovered.

It is traditional to denote the number of individuals in each of these compartments as S, I and R respectively. The total host population size is

$$N = S + I + R. \tag{2.1}$$

And such models are often called **SIR** models.

## 2.2 The SIS and SEIR Models

### 2.2.1 The SIS Model

We will use the terminology $SIS$ to describe a disease with no immunity against re-infection, to indicate that the passage of individuals is from the susceptible class to the infective class and then back to the susceptible class. Hence, there is no $R$ class and the population is composed from the susceptibles and the infectives only. The corresponding model is known as an $SIS$ model and this type of model only have **S**: Susceptible and **I**:Infected class.

$$S \to I \to S$$

### 2.2.2 The SEIR Model

This models have **S**: a Susceptible,**E**:a class in which the disease is latent, **I**:an Infectious class , and **R**: a Recovered or dead class.

$$S \to E \to I \to R$$

Note that the choice of which compartments to include in a model depends on the characteristics of the particular disease being modelled and the purpose of the model.

The following remarks can be made from the **SEIR model**:

i. This model solely depends on the host's ability to transmit the pathogen.

ii. The health status of the host is therefore irrelevant i.e it is not important whether the individual is showing symptoms, also an individual who feels perfectly healthy can be excreting large amounts of pathogens.

iii. Note that in reality, boundaries between exposed, infectious and recovered are fuzzy because the ability to transmit is not binary (on-off).

iv. Also, complications due to variability in response depends on individuals and the level of pathogens over the period of infectious.

We now focus on SIR model, having compartmentalized the host population, we now need a set of equations that specify how the sizes of the compartments change over time. The number of individuals in each compartment must be integers, of course, but if the host population size $N$ is sufficiently large we can treat S,I and R as continuous variables and express our model on how they change in terms of a system of differential equations.

The following assumptions can be made about the transmission of the infection and incubation period which are very important in any model. These are reflected in terms of the equations and the parameters, with $S(t)$, $I(t)$ and $R(t)$ as the number of individuals in each class, we then assume here that:

i. The number of infectious class increases at a rate proportional to both the number of infective and susceptible; i.e $rSI$, where $r > 0$ is a constant parameter. The number of susceptible decreases at the same rate, $r$ is called the infection rate

ii. The rate of removal of infective to the removed class is proportional to the number of infective, that is $aI$, where $a > 0$ is a constant, $\frac{1}{a}$ is a measure of the time spent in the infectious state.

iii. The incubation time is negligible, so that a susceptible that catches the disease becomes infectious immediately.

## 2.3 Phase - plane Analysis of classic SIR epidemic model

Here, we considered the rate of change, and some further assumption of a well-mixed population, where every pair of individuals has the same probability of getting into contact, we can write the following model, which is a kind of mean field model:

$$\frac{dS}{dt} = -rSI \tag{2.2}$$

$$\frac{dI}{dt} = rSI - aI \tag{2.3}$$

$$\frac{dR}{dt} = aI \tag{2.4}$$

Where $r > 0$ is the infectious rate and $a > 0$ the removal rate of infective.
Some other useful analytical results from this model can be derived.
The constant population size is built into the system of equations $(2.2) - (2.4)$ since on adding the three equations we obtain

$$\frac{dS}{dt} + \frac{dI}{dt} + \frac{dR}{dt} = 0 \implies S(t) + I(t) + R(t) = N. \tag{2.5}$$

Where $N$ is the total size of the population.
We can now complete the formulation when given appropriate initial conditions such as $S(0) = S_0 > 0$, $I(0) = I_0 > 0$, $R(0) = 0$ The conservation of $N = S + I + R$ is ensued by the equations $(2.2) - (2.4)$.

An important thing to note here is that given $r, a, S_0$ and $I_0$, whether the infectious will spread out or not and if it does, how will it develop in time and when will it start to decline?. From (2.3) we observed that $\frac{dS}{dt} < 0$ for all $''t''$, $\frac{dS}{dt} > 0$ if and only if $S_0 < \rho$ where $(\rho = \frac{a}{r})$.Thus (I) infection starts to increase so long as $S_0 > \rho$). but since $S$ decreases for all $''t''$, infection will ultimately decreases and tends towards zero. If $S_0 < \rho$, infection decreases to zero i.e there will be an epidemic but if $S_0 > \rho$, infection will first increases to a maximum (attained when $S = \rho$) and then later decreases to zero, implying that, in this case, there is an existence of epidemic.

The picture is that of a threshold phenomenon [22], and that $\rho$ is the relative removal rate while it's reciprocal is the contact rate $(\frac{r}{a})$.

If we let $R_0 = rS(0)/a$ be the basic reproduction number, if $R_0 < 1$, the infection dies out, but if $R_0 > 1$, there is epidemic. For more understanding, we shall consider an example to know the severity and duration of an epidemics as contain in [2] as follows:

Suppose, for a certain disease, one infective is introduced into a population of 500 susceptible individuals. Using the $SIR$ model, we shall assume that the time steps of 1 day is adequate for describing this disease. Suppose, additionally, that data indicate that the likelihood a healthy individual becomes infected from a contact with an infective is 0.1% and that, once taken ill, an infective is contagious for 10 days.
To justify that $r = 0.001$ and $a = 0.1\%$ in the $SIR$ model for this parameter values, we find $\rho = \frac{a}{r} = \frac{0.1}{0.001} = 100$. This means that we expect about $\frac{1}{\rho} = \frac{1}{100}$ of the susceptibles, or

$$R_0 = \frac{r}{a}S_0 = \frac{1}{\rho}S_0 = 0.01S_0 = (0.01)500 = 5$$

individuals to become infected with the illness as a result of contact with the original sick person. Moreover, because $R_0 = 5 > 1$. We expect an epidemic to occur. Infact, with such a large value of $R_0$, we might expect a rather devastating epidemic to occur. See figures 2.1 and 2.2, and section 2.4 for a more rigorous approach.

Next, there is no exact solution that exists, but we can obtain some important information about the behaviour of the solution of the model by considering the following relationship:

($a$) Considering the ratio (interaction) between the Infective and the Susceptible.

$$\frac{dI}{dS} = \frac{(rS - a)I}{-rSI} = -1 + \frac{a}{r}S = -1 + \frac{\rho}{S}, \text{ where } \rho = \frac{a}{r}(I \neq 0)$$

Integrating the above equation we obtain $(I, S)$ which is known as phase plane trajectories
if we let $(I(0), S(0)) = c \implies (I, S) = -S + \rho lnS + c$, $I_0 = -S_0 + \rho lnS_0 + c \implies c = I_0 + S_0 - \rho lnS_0$ which can be expressed as

$$I + S - \rho lnS = constant = I_0 + S_0 - \rho lnS_0 \tag{2.6}$$

Considering a population of size $k$, into which a small number of infective is introduced, so that $S(0) \approx k$, $I(0) \approx 0$ and $R_0 = \frac{rk}{a}$.
Also, we know that $\lim_{t\to\infty} I(t) = 0$, let $\lim_{t\to\infty} S(t) = S_\infty$. Then, the relation $I(0), S(0) = (0, S(0)$ gives

$$k - \rho log(S_0) = S_\infty - \rho log(S_\infty)$$
$$k - S_\infty = \rho log(S_0) - \rho log(S_\infty)$$
$$\rho = \frac{log(S_0)/S_\infty}{k - S_\infty} \tag{2.7}$$

and $R_0$ can be estimated from (2.7) ($0 < S_\infty < k$ so that part of the population escape infection).

An epidemic will exists and be at it's maximum when $S = \rho$ where $\frac{dI}{dt} = 0$, this maximum number of infectives is given by

$$I_{max} = \rho lnS - S + I_0 + S_0 - \rho lnS_0$$

$$I_{max} = I_0 + (S_0 - \rho) + \rho ln(\frac{\rho}{S_0})$$
$$I_{max} = N - \rho + \rho ln(\frac{\rho}{S_0}). \tag{2.8}$$

In this case the number of infected remains below $I_0$ and goes to zero as $t \to \infty$, and noting that this can only be possible when $S_0 > \rho$, and also when $I_{max} = I_0$ for $S_0 \leq \rho$.
In order to prevent the occurance of epidemic when infectives are introduced into a population, it is necessary to reduce the basic reproduction number $R_0$ below one. Here,

$$R_0 = \frac{rS_0}{a}$$

is the reproduction rate of the infection and $\frac{1}{a}$ is the average infectious period.

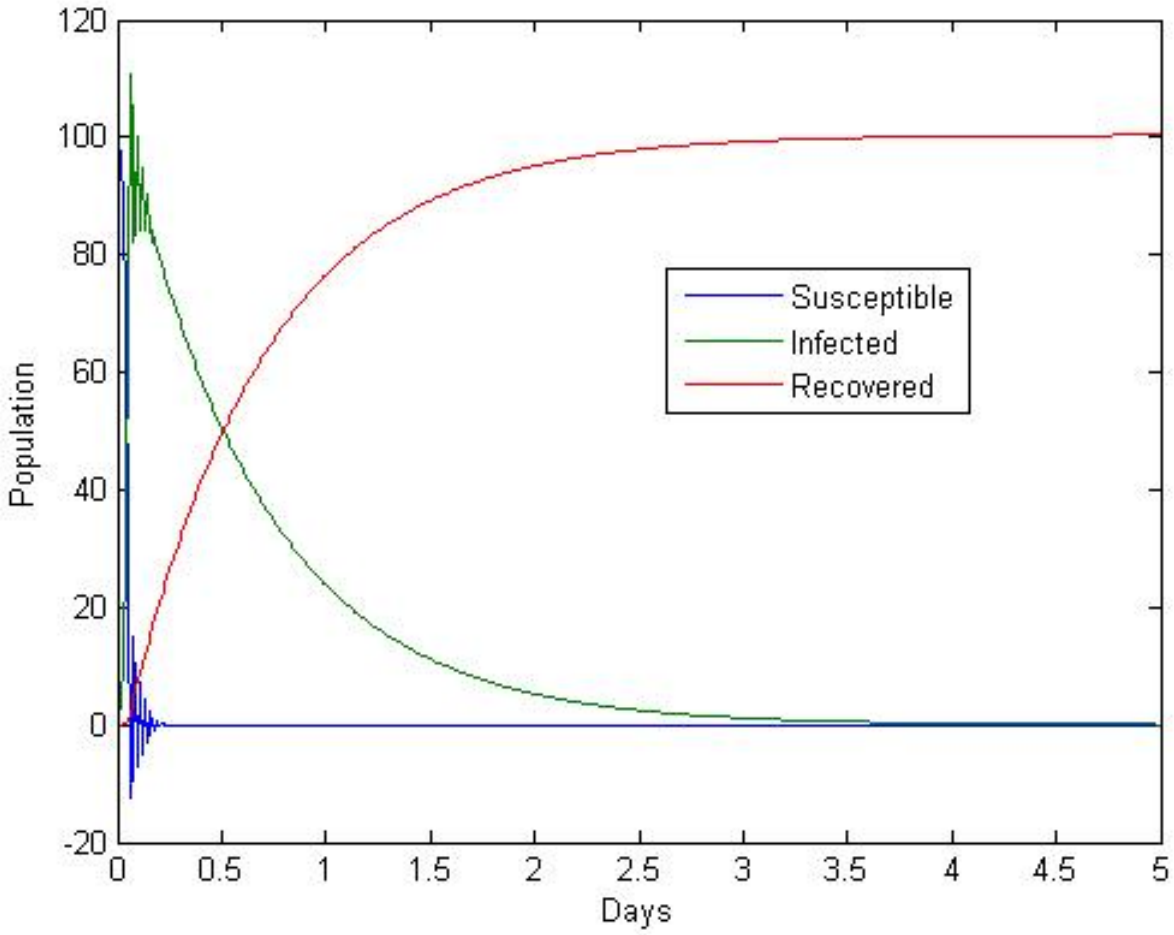


Figure 2.1: SIR Model simulation

(*b*) Considering the relationship between the Susceptible and Recovered.

$$\frac{dS}{dR} = -\frac{S}{\rho}$$

Integrating the above, we have

$$S = S_0 e^{-R/\rho} \geq S_0 e^{-N/\rho} > 0 \tag{2.9}$$

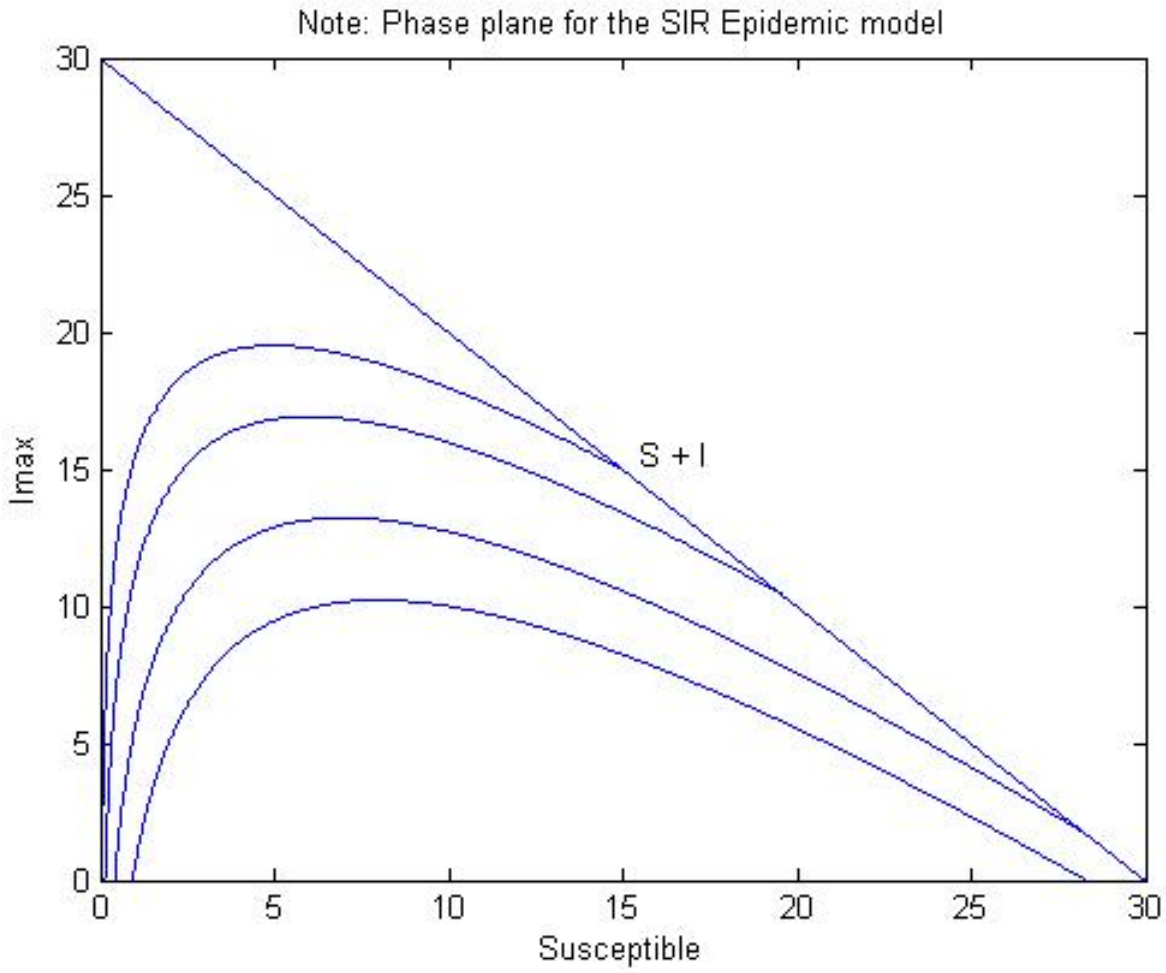


Figure 2.2: Phase portraits.
The phase portrait above is the numerical solution of the $SIR$ epidemic model of equation $(2.2) - (2.4)$, where the curve lines indicate the phase plane trajectories and the straight line $S + I = S_0 + I_0$.

Implying that

$$0 < S_\infty \leq N.$$

It was observed that $0 < S(\infty) < \rho$
And since $I(\infty)$ we have that $R_\infty = N - S_\infty$. So from equation (2.9)

$S_\infty = S_0 e^{R_\infty/\rho} = S_0 e^{\frac{N-R_\infty}{\rho}}$ and so $S_\infty$ is positive and not $0 < z < \rho$ of the transcendental equation.

$$S_0 e^{(N-z)/\rho)} = z. \tag{2.10}$$

We then get the total number of Susceptibles who catch the disease in the cause of the epidemic to be given by

$$I_{total} = I_0 + S_0 - S_\infty. \tag{2.11}$$

Where $S_\infty < S_0$ is the positive solution $z$ of (2.10).

An important consequence of this analysis, is that when $I(t) \to 0$ then, $S(t) \to S_\infty > 0$, means that the disease dies out due to lack of infective, and not because it lacks Susceptible. The epidemic does not grow unlimited to infect the whole population. There will always be some Susceptible that did not get the disease.
Another general remark is that the threshold behaviour is directly related to the relative removal rate $\rho$. For a given disease, the relative removal rate varies with the area, and it determines why an epidemic of a certain disease can occur in a certain area and not in another. For instance, if the density of Susceptible is high ($S_0$ is large) and the removal rate **a** is small (either for ignorance, lack of adequate medical care, etc), then an epidemic is likely to occur, other things equal, **a** can be high if the disease is very serious and kills the infected fast [1].

In real life where there is epidemics, it is difficult to know how many new infective are there for each day. Only those that are removed can be known. To apply the model to real situations, we need to know the number of removal per unit time.

(*c*) Considering (2.4) and (2.9), we get an equation for $R$ alone. i.e

$$\frac{dR}{dt} = aI = a(N - R - S) = a\left[N - R - S_0 e^{(-R/\rho)}\right]. \tag{2.12}$$

Knowing the parameters. It is easy to compute the solution numerically. Unfortunately, the parameters are rarely known, and a fitting has to be

made, assuming that the epidemic is well described by the model. In practice, if the epidemic is not large $\frac{R}{\rho}$ we can expand the exponent in (2.12) to find

$$\frac{dR}{dt} = a\left[N - S_0 + (\frac{S_0}{\rho} - 1)R - \frac{S_0 R^2}{2\rho^2}\right]. \tag{2.13}$$

This approximate equation can be integrated to obtain:

$$R(t) = \frac{\rho^2}{S_0}\left[(\frac{S_0}{\rho} - 1) + \alpha \tanh(\frac{\alpha a t}{2} - \phi)\right]. \tag{2.14}$$

Where

$$\alpha = \left[(\frac{S_0}{\rho} - 1)^2 + \frac{2S_0(N - S_0)}{\rho^2}\right]^{1/2}. \tag{2.15}$$

And

$$\phi = \frac{tanh^{-1}(\frac{S_0}{\rho} - 1)}{\alpha}. \tag{2.16}$$

From the above equations, the removal rate is found to be

$$\frac{dR}{dt} = \frac{a\alpha^2\rho^2}{2S_0} sech^2(\frac{\alpha a t}{2} - \phi). \tag{2.17}$$

With only three parameters, $a\alpha^2\rho^2/2S_0$, $a\alpha$ and $\phi$.

# Remarks

From figure 2.1, the graph shows that, the number of infectives rises to 100 and immediately drop and intercept the recovery at the population approximately 45 for about half a day ($12hrs$) and decline to zero to coincide with susceptible. Though, there is a bit oscillatory behavior of the susceptibles at the zero ponit and that of infectives at the highest point as shown on the graph. Mathematically, an information about the spread of epidemics can be determine by noting that the maximum number of infectives occur exactly when $I(t)$ changes from positive to negative.

## 2.4 Stability of the SIR Model

Considering equations $(2.2)-(2.4)$ and applying linearization method it gives:

$$J(S,I,R) = \begin{pmatrix} \frac{\partial f_1}{\partial S} & \frac{\partial f_1}{\partial I} & \frac{\partial f_1}{\partial R} \\ \frac{\partial f_2}{\partial S} & \frac{\partial f_2}{\partial I} & \frac{\partial f_2}{\partial R} \\ \frac{\partial f_3}{\partial S} & \frac{\partial f_3}{\partial I} & \frac{\partial f_3}{\partial R} \end{pmatrix} = \begin{pmatrix} -rI & -rS & 0 \\ rI & rS-a & 0 \\ 0 & a & 0 \end{pmatrix}$$

Finding the equilibrium points of equations $(2.2)-(2.4)$ we have $(0,0,0)$, $(\frac{a}{r},0,0)$.
Linearization of system $(2.2)-(2.4)$ at $(0,0,0)$, gives the Jacobian matrix

$$\begin{pmatrix} -rI & -rS & 0 \\ rI & rS-a & 0 \\ 0 & a & 0 \end{pmatrix} = \begin{pmatrix} 0 & 0 & 0 \\ 0 & -a & 0 \\ 0 & a & 0 \end{pmatrix}$$

With determinant of $det(J(0,0,0)-\lambda) = \begin{vmatrix} -\lambda & 0 & 0 \\ 0 & -a-\lambda & 0 \\ 0 & a & -\lambda \end{vmatrix} = 0$
and this gives the corresponding eigenvalues of $\lambda_1 = \lambda_2 = 0$ (0 has multiplicity as an eigenvalue) and $\lambda_3 = -a$. Applying the theorem in [32, 23], since each eigenvalue is negative, we derive that $(0,0,0)$ is **asymptotically stable** [24].
Now at the equilibrium point of $(\frac{a}{r},0,0)$ , we have the Jacobian matrix
$J(\frac{a}{r},0,0) = \begin{pmatrix} 0 & -a & 0 \\ 0 & a & 0 \\ 0 & a & 0 \end{pmatrix}$ and determinant of $det(J(\frac{a}{r},0,0)-\lambda) = \begin{vmatrix} -\lambda & -a & 0 \\ 0 & a-\lambda & 0 \\ 0 & a & -\lambda \end{vmatrix} =$
0,
and this gives the corresponding eigenvalues of $\lambda_1 = \lambda_2 = 0$ and $\lambda_3 = a$.
Applying the same theorem in [32, 23], we have that at $(\frac{a}{r},0,0)$, the equilibrium point is **unstable**. Therefore, the threshold for this model is the basic reproduction number $R_0 < 1$, which actually verifies the picture described in figure 1.1. The latter implies that the infection will eventually dies out.

## 2.5 Demographic Effects on the SIR Model

Here, we shall briefly consider our assumption of a constant population. In most societies, individuals enter and leave the population either through immigration or by birth and death. We have not included any of these ideas in

our model so far.
Considering a more complex but also a more realistic model, we incorporate into our equations the term $\mu k$, representing immigrants or births per unit time and a natural mortality rate $\mu$ (per capita) as it affects the SIR model, then our systems becomes:

$$\frac{dS}{dt} = \mu k - rSI - \mu S \tag{2.18}$$
$$\frac{dI}{dt} = rSI - aI - \mu I \tag{2.19}$$
$$\frac{dR}{dt} = aI - \mu R \tag{2.20}$$

The equilibrium points of systems $(2.18) - (2.20)$ are $(1, \frac{\mu(k-1)}{r}, 0)$, $(1, 0, 0)$ and $(0, 1, \frac{a}{\mu})$.

$$J(S, I, R) = \begin{pmatrix} \frac{\partial f_1}{\partial S} & \frac{\partial f_1}{\partial I} & \frac{\partial f_1}{\partial R} \\ \frac{\partial f_2}{\partial S} & \frac{\partial f_2}{\partial I} & \frac{\partial f_2}{\partial R} \\ \frac{\partial f_3}{\partial S} & \frac{\partial f_3}{\partial I} & \frac{\partial f_3}{\partial R} \end{pmatrix} = \begin{pmatrix} -rI - \mu & -rS & 0 \\ rI & rS - a - \mu & 0 \\ 0 & a & -\mu \end{pmatrix}$$

Linearization of the system $(2.18) - (2.20)$ at $(1, \frac{\mu(k-1)}{r}, 0)$ gives the Jacobian matrix

$$\begin{pmatrix} -\mu k & -r & 0 \\ \mu k - \mu & r - a - \mu & 0 \\ 0 & a & -\mu \end{pmatrix}$$

With determinant $detJ\left(1, \frac{\mu(k-1)}{r}, 0) - \lambda\right) = \begin{vmatrix} -\mu k - \lambda & -r & 0 \\ \mu k - \mu & r - a - \mu - \lambda & 0 \\ 0 & a & -\mu - \lambda \end{vmatrix} =$
0
and the corresponding eigenvalues of $\lambda_1 = -\mu k < 0$, $\lambda_2 = (r - a - \mu) < 0$ and $\lambda_3 = -\mu) < 0$. Also, at $(1, 0, 0)$ gives the Jacobian matrix

$$\begin{pmatrix} -\mu & -r & 0 \\ 0 & r - a - \mu & 0 \\ 0 & a & -\mu \end{pmatrix}$$

With the determinant

$$detJ\,(1,0,0)-\lambda) = \begin{vmatrix} -\mu-\lambda & -r & 0 \\ 0 & r-a-\mu-\lambda & 0 \\ 0 & a & -\mu-\lambda \end{vmatrix} = 0$$

And the corresponding eigenvalues of $\lambda_1 = \lambda_2 = -\mu < 0$ and $\lambda_3 = (r-a-\mu) < 0$ .

Now at the equilibrium point $(0, 1, \frac{a}{\mu})$ , we have the Jacobian matrix

$$J(0,1,\frac{a}{\mu}) = \begin{pmatrix} -r-\mu & 0 & 0 \\ r & -a-\mu & 0 \\ 0 & a & -\mu \end{pmatrix}$$

With the determinant $detJ\left(0,1,\frac{a}{\mu})-\lambda\right) = \begin{vmatrix} -r-\mu-\lambda & 0 & 0 \\ 0 & -a-\mu-\lambda & 0 \\ 0 & a & -\mu-\lambda \end{vmatrix} = 0.$

And the corresponding eigenvalues of $\lambda_1 = -(r+\mu) < 0$, $\lambda_2 = -(a+\mu) < 0$ and $\lambda_3 = (-\mu) < 0$.

Summarizing, we have that the equilibrium points $(1, \frac{\mu(k-1)}{r}, 0), (1, 0, 0)$ and $(0, 1, \frac{a}{\mu})$ are asymptotically stable under the condition $R_0 = \frac{r}{a+\mu} < 1$. Thus, the model has a reproduction rate ($R_0 = \frac{r}{a+\mu} < 1$) indicating that there is a disease elimination and hence, attained a disease- free equilibrium at that point. Therefore, the equilibrium is asymptotically stable [24], by implication, this implies that when a small population of infective is introduced into the system, it would not cause a persistent infection. In other words, if a small number of infective were added to the population, it would return to the disease - free State after some time.

Furthermore, if

$$R_0 = \frac{r}{a+\mu} = r\beta$$

where

$$\beta = \frac{1}{a+\mu}$$

We shall note here that $\beta$ is the mean duration of infection because of the term $-(a+\mu)$ which can be seen as the probability that a person is removed from $I$ either by natural causes (the $\mu$ term) or progression to $R$ (the $a$ term).

Similarly, if we consider the case where $R_0 = \frac{r}{a+\mu} > 1$ i.e $R_0 > 1$ so that the system has an endemic infection, then the equilibrium is unstable, which means that an introduction of infective will result in a persistent infection. Furthermore, $R_0$ can also be thought as , if the system is near the disease -free equilibrium and one infective person is added to the population, then $R_0$ is the number of newly infective person. Also if the added infective produces more than one new infective, then, the infection will definitely persist, but if the added infective produces less than one new infective, the infection will die out.

## 2.6 The Endemic Equilibrium

To find the endemic equilibrium, set RHS of (2.18) − (2.20) to zero and also assume that $R = 0$, this reduces the system to

$$\mu k - rSI - \mu S = 0 \tag{2.21}$$

$$rSI - aI - \mu I = 0$$

it follows that

$$rS = \frac{\mu(K - S)}{I} \tag{2.22}$$

$$rS = a + \mu$$

so then

$$S = K - \frac{(a+\mu)I}{\mu} \tag{2.23}$$

Also from equation (2.22)

$$rS = a + \mu$$

$$\frac{r}{a+\mu}S = 1$$

Since $R_0 = \frac{r}{a+\mu}$, we have

$$S^* = \frac{1}{R_0} \tag{2.24}$$

Finally, substituting (2.24) into (2.23) and solving for $I$, i.e

$$S = K - \frac{(a+\mu)I}{\mu}$$

$$\frac{1}{R_0} = K - \frac{(a+\mu)I}{\mu}$$

$$I^* = \frac{\mu(K - \frac{1}{R_0})}{a + \mu} \tag{2.25}$$

Hence, the endemic equilibrium points are

$$E_e = (S^*, I^*) = \left( \frac{1}{R_0}, \frac{\mu(K - \frac{1}{R_0})}{a + \mu} \right)$$

Pathogen has suffered extinction and everyone in the population is Susceptible. From equation (2.19), consider $\frac{dI}{dt} = 0 \implies rSI-(a+\mu)I = 0$. After factoring for $I$, $I(rS-(a+\mu)) = 0$ above is satisfied when $I^* = 0$, or $S^* = \frac{a+\mu}{r}$ for $I^* = 0$ is a disease-free equilibrium and $S^* = \frac{a+\mu}{r} = \frac{1}{R_0}$. Hence, endemic equilibrium which means that the disease is always present without any re-introduction. This is characterized by the fraction of Susceptible in the population being the inverse of $R_0$ . Since, $S^* = \frac{1}{R_0}$, this shows that the endemic equilibrium is unstable if $R_0 > 1$ .

## 2.7 The SIR Model for heterosexual spread of infection

In this section, we present a simple classical epidemic model which incorporates some of the basic elements in the heterosexual spread of infection (disease).For this model, we assume there is uniformly promiscuous behaviour in the population we are considering. The population consists of two interacting classes, males and females, and infection is passed from a member of one class to the other and vice versa. It is regarded as a criss-cross type of disease in which each class is the disease host for the other [22].

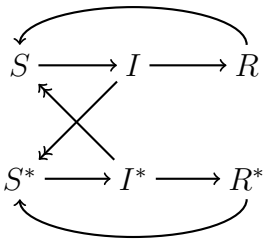


Figure 2.3: Criss-cross of S I R

Since the incubation period for some diseases is usually quite short, we divide the promiscuous male population into susceptible S, infective I and a removed class R. The similar female groups are denoted by $S^*$, $I^*$ and $R^*$. If the Susceptible group do not include any transition from the removed class, the infection dynamics is schematically given as:

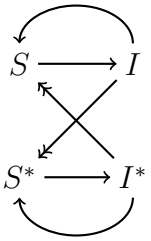


Figure 2.4: Criss-cross of S I

Here $I^*$ infects $S$ and I infects $S^*$. As we noted above, the contraction of disease does not confer Immunity and so an individual removed for treatment becomes Susceptible again after recovery, but here we shall only consider a simpler version involving Susceptible and infective class, where we shall take the total number of males and females to be constant and equal to $N$ and $N^*$ respectively. Then

$$S(t) + I(t) = N, S^*(t) + I^*(t) = N^* \tag{2.26}$$

We take the rate of decrease of male Susceptible to be proportional to the male susceptible times the infectious female population with a similar form for the female rate. We also need to know that once infective have recovered they rejoin the susceptible class.

$$\frac{dS}{dt} = -rSI^* + aI, \frac{dS^*}{dt} = -r^*S^*I + a^*I^* \tag{2.27}$$

$$\frac{dI}{dt} = rSI^* - aI, \frac{dI^*}{dt} = r^*S^*I - a^*I^*$$

Where $r, a, r^*$ and $a^*$ are positive parameters. We are interested in the progress or growth of the disease when given initial conditions.

$$S(0) = S_0, I(0) = I_0, S^*(0) = S_0^*, I^*(0) = I_0^* \tag{2.28}$$

From equation (2.28) $S = N - I$ and $S^* = N^* - I^*$. Therefore, equation (2.29) reduces to two equations, either $S$ and $S^*$ or $I$ and $I^*$ as follows:

$$\frac{dI}{dt} = rI^*(N - I) - aI, \frac{dI^*}{dt} = r^*I(N^* - I^*) - a^*I^*. \tag{2.29}$$

The equilibrium points of (2.31) are $I = 0 = I^*$, and

$$I_s = \frac{NN^* - \rho\rho^*}{\rho + N^*}, I_s^* = \frac{NN^* - \rho\rho^*}{\rho + N} \tag{2.30}$$

where $\rho = \frac{a}{r}$, $\rho^* = \frac{a^*}{r^*}$ Hence, we have that, the non-zero positive steady state levels of the infective populations exist only if $NN^*/\rho\rho^* > 1$, which represent the threshold condition. If the positive steady state exists then the zero steady state is unstable. In particular, the eigenvalues $\lambda$ for the linearization of equation (2.31) about $I = 0 = I^*$ are given by:

$$\begin{vmatrix} -a - \lambda & rN \\ r^*N^* & -a^* - \lambda \end{vmatrix} = 0$$

Using quadratic formula

$$2\lambda = -(a + a^*) \pm \left[(a + a^*)^2 + 4aa^*(\frac{NN^*}{\rho\rho^*} - 1)\right]^{1/2}$$

so if the threshold condition $\frac{NN^*}{\rho\rho^*} > 1$ holds, then $\lambda_1 < 0 < \lambda_2$ and the origin is a saddle point in the $(I, I^*)$ phase plane.
On the other hand, if the threshold condition is not satisfied, that is $\frac{NN^*}{\rho\rho^*} < 1$, then the origin is stable since both the eigenvalues are negative i.e. $\lambda < 0$. And this implies that $I_s$ and $I_s^*$ are negative which practically means that such an equilibrium does not exist.
Hence, the threshold condition for a non-zero steady state infected population is given by

$$\frac{NN^*}{\rho\rho^*} = (rN/a)(r^*N^*/a^*) > 1,$$

which can then be interpreted as follows:
If every male is susceptible then $rN/a$ is the average number of males contacted

by a female infective during her infections period, and a reciprocal interpretation holds for $r^*N^*/a^*$. i.e. If every female is susceptible then $r^*N^*/a^*$ is the average number of females contacted by a male infective during his infections period. Where the quantities $rN/a$ and $r^*N^*/a^*$ are the maximal male and female contact rates respectively.

## 2.8 Discussion

The history of epidemic and $HIV$ models is given in Chapter one which gives the genesis of epidemics and $HIV$ infections. It is then followed with the history of some general epidemic models which gives some briefs on how diseases are spread and $HIV$ could be transmitted.
The mathematical analysis of $SIR$ and some $HIV$ models are presented. The choice of which compartments to be included in a model depends on the characteristics of the particular disease or infection been modelled and the purpose of the model.

A set of ordinary differential equation (ODE) is used in this work to analyse the models by ensuring that the number of individuals in each compartment is an integer and that the host population size $N$ must be sufficiently large, so that, we can treat $S$, $I$ and $R$ as continuous variables by expressing our models in terms of system of differential equations.

In the phase plane analysis of section 2.3, it shows that an epidemic will occur when the basic reproduction rate $R_0 > 1$ and the infection dies out when $R_0 < 1$ as illustrated in figure 2.2. The consequences of this analysis is that when $I(t) \to 0$ then, $S(t) \to S_\infty > 0$ meaning that the disease dies out due to lack of infective and not because it lacks Susceptible. Also the threshold behaviour is directly related to the relative removal rate $\rho$. Which indicated that an epidemic will exists and be at it maximum when $S = \rho$ whenever $\frac{dI}{dt} = 0$, see equation (2.8), meaning that if $S_0 > \rho$ then $I(t)$ starts to increase implying that there is an epidemic.

The stability of $SIR$ model was also determined by using the linearization method [32]. In section 2.4, when equilibrium points are $(0, 0, 0)$ and $(\frac{a}{r}, 0, 0)$, the points are **unstable** and **asymptotically stable** respectively [23]. Also in section 2.5, we observed that the equilibrium points $(1, \mu\frac{k-1}{r}, 0)$, $(1, 0, 0)$

and $(0, 1, \frac{a}{\mu})$ are asymptotically stable under the condition that $R_0 = \frac{r}{a+\mu} < 1$, indicating that there is a disease elimination and hence, attained a disease - free equilibrium at that point.

However, in real life situation this means that a small population of infective when introduced into the system would not cause a persistent infection where as in section 2.6, when $R_0 = \frac{r}{a+\mu} > 1$, i.e $R_0 > 1$ shows that the equilibrium is unstable and the system has an endemic infection implying that an introduction of infective will result in a persistent infection.

In section 2.7, we see how an individual removal for treatment can become susceptible again after recovery as shown in figures 2.2 and 2.3 . Here, the non - zero positive steady state of the infective populations exist only if $\frac{NN^*}{\rho\rho^*} > 1$ which is the threshold condition and this makes the zero steady state to be unstable but if the threshold condition is not stable, then it practically means that an equilibrium does not exist hence, the threshold condition is then given by

$$\frac{NN^*}{\rho\rho^*} = (\frac{rN}{a})(\frac{r^*N^*}{a^*}) > 1,$$

which simply means that if every male is susceptible then $\frac{rN}{a}$ is the average number of males contacted by female infective during her infection period.

# Chapter 3

# The HIV INFECTION MODEL

## 3.1 AIDS Epidemic in Homosexual Population

In this chapter, we are interested in the development of an AIDS epidemic model in a homosexual population. We shall assume that the immigration rate Q of Susceptible males is constant into a population of size $N(t)$. Let $X(t), Y(t), A(t)$ and $Z(t)$ denote respectively the number of Susceptibles, infectious males, AIDS patients and the number of HIV- positive or seropositive men who are non-infectious.
We also assume that Susceptibles die naturally at a rate $\mu$, if there was no AIDS. The steady state population is then given by $N^* = a/\mu$. We assume that AIDS patients die at rate $d$; $1/d$ is of the order of months to years. Considering a uniform mixing, a reasonable model describing the above is given below:

$$\frac{dX}{dt} = Q - \mu X - \lambda cX, \quad \lambda = \frac{\beta Y}{N}, \tag{3.1}$$

$$\frac{dY}{dt} = \lambda cX - (v + \mu)Y \tag{3.2}$$

$$\frac{dA}{dt} = pvY - (d + \mu)A \tag{3.3}$$

$$\frac{dZ}{dt} = (1 - p)vY - \mu Z \tag{3.4}$$

$$N(t) = X(t) + Y(t) + Z(t) + A(t). \tag{3.5}$$

Where $Q$ is the recruitment rate of Susceptible, $\mu$ is the natural (non-AIDS-related) death rate, $\lambda$ is the probability of acquire infection from a randomly

chosen partner equal to $\beta Y/N$ where $\beta$ is the transmission probability. Besides, $c$ is the number of sexual partners, $d$ is the AIDS-related death rate, $p$ is the proportion of HIV- positive who are infections and $v$ is the rate of conversion from infection to AIDS in this model, which is taken to be constant. Furthermore $1/v$ equals to $D$, which is the average incubation time of the disease. We can also say that $\lambda$ is actually approximated by $\beta Y/(X+Y+Z)$ when $A$ is considered quite small compared with $N$.

We must note here that, in this model, the total population $N(t)$ is not constant as it was in chapter 2. Adding equations $(3.1)-(3.4)$ above, we obtain

$$\frac{dN}{dt} = Q - dA - \mu(X+Y+A+Z).$$

Simplifying further by substituting $N$ for $X+Y+A+Z$ , we get

$$\frac{dN}{dt} = Q - \mu N - dA. \tag{3.6}$$

Set

$$B = \begin{pmatrix} -(\mu+\lambda c) & 0 & 0 & 0 \\ \lambda c & -(v+\mu) & 0 & 0 \\ 0 & pv & -(d+\mu) & 0 \\ 0 & (1-p)v & 0 & -\mu \end{pmatrix}. \tag{3.7}$$

Thus, from equation (3.5) if we let $t=0$, an infected individual is introduced into an otherwise infection-free population of Susceptible, we have initially $X \approx N$, and so near $t=0$ due to the continuity of $X(t)$.
From equation (3.2), we have

$$\frac{dY}{dt} \approx (\beta c - v - \mu)Y \approx v(R_0 - 1)Y \tag{3.8}$$

under the assumption that the average incubation time $(1/v)$ is much bigger than the average life expectancy $(1/\mu)$, of Susceptible population. Therefore, equation (3.8) gives a condition for an epidemic to start with

$$R_0 \approx \frac{\beta c}{v} > 1. \tag{3.9}$$

Note that, the basic reproductive rate $R_0$ is given in terms of the sexual partners $c$, the transmission probability $\beta$ and the average incubation time of the

disease $1/v$, through when an epidemic began, the system $(3.1) - (3.4)$ evolves to a steady state given by

$$X^* = \frac{(v+\mu)N^*}{c\beta}, \tag{3.10}$$

$$Y^* = \frac{(d+\mu)(Q-\mu N^*)}{pvd} \tag{3.11}$$

$$Z^* = \frac{(1-p)(d+\mu)(Q-\mu N^*)}{pv\mu} \tag{3.12}$$

$$A^* = \frac{(Q-\mu N^*)}{d} \tag{3.13}$$

$$N^* = \frac{Q\beta\left[\mu(v+d+\mu)+vd(1-p)\right]}{(v+\mu)(b(d+\mu)-pv)}. \tag{3.14}$$

Now, we can get some interesting information from an analysis of the system during the early stages of an epidemic. As earlier, we assumed that the population consists of almost all Susceptible and so $X \approx N$ and the equation for the growth of the infectious, i.e HIV- positive, Y-class is approximated by equation (3.8), the solution of which is

$$Y(t) = Y(0)e^{v(R_0-1)t} = Y(0)e^{rt}. \tag{3.15}$$

Where $R_0$ is the basic reproductive rate, $1/v$ is the average infectious period and $Y(0)$ is the initial number of infectious people introduced into the Susceptible population. The intrinsic growth rate, $r = v(R_0 - 1)$ is positive only if an epidemic exists i.e $(R_0 > 1)$, and from equation (3.15) we can then obtain the doubling time for the epidemic $t_d$ when $Y(t_d) = 2Y(0)$ given as

$$t_d = r^{-1}ln2 = \frac{ln2}{v(R_0-1)}. \tag{3.16}$$

Which has clearly shown that the larger the basic reproductive rate $R_0$ the shorter the doubling time.
Now, if we substitute equation (3.15) into equation (3.3) for the AIDS patients, we obtain,

$$\frac{dA}{dt} = pvY(0)e^{rt} - (d+\mu)A.$$

If $A(0) = 0$, it implies that in the epidemic, there are no AIDS patients and so the solution is given by

$$A(t) = pvY(0)\frac{e^{rt} - e^{-(d+\mu)t}}{r+d+\mu}.$$

## 3.2 The T-cell Infection model

In this section, we present an epidemic model for T-cell infection by HIV. This model consists of four components, equations for three types of T-cells whereas the virus itself requires a fourth equation system for its description. Here we shall first present a simplified equation for T-cells in the absence of infection [30].
In forming a mathematical model of T-cell population, we must make the following assumptions:

a. Some Immune competent T-cells are produced by the lymphatic system over a short period of time with their production rate been constant and independent of the number of T-cells present. Also for a larger period of time, their production rate adjusts to help in maintaining a constant T-cell concentration in adulthood. The supply rate is denoted by $s$.

b. The T-cells are only produced through clonal selection if an appropriate antigen is present and the total number of T-cells does not increase unboundedly. This can be modelled using a logistic term of the form, $rT(1 - T/T_{max})$ with per capita growth rate $r$.

c. The T-cells have a finite natural life time after which they are removed from circulation. This can be modelled using a death rate term, $\mu T$, with a fixed per capita death rate $\mu$. The differential equation model is given by

$$\frac{dT}{dt} = s + rT\left(1 - \frac{T}{T_{max}}\right) - \mu T. \tag{3.17}$$

Where T is the T-cell population in cells per cubic millimetre. We must ensure that, the model should have the property that solutions, $T(t)$, that start in the interval $[0, T_{max}]$ stay there. Using equation (3.17), this can only happen, if the derivative $\frac{dT}{dt}$ is positive when $T = 0$, i.e $\frac{dT}{dt}|_{T=0} = s$ which shows that $s$ is positive and negative when

$$T = T_{max}. \tag{3.18}$$

Provided

$$\mu T_{max > S}.$$

The biological implication of this statement is that when the number of T-cells has reached the maximum value $T_{max}$, then there are more cells dying than being produced by the lymphatic system.
The steady state of equation (3.17) can be found by solving the equation

$$s + rT(1 - T/T_{max}) - \mu T = 0,$$

or equivalently

$$-\frac{r}{T_{max}}T^2 + (r - \mu)T + s = 0.$$

The roots of this quadratic equation are

$$T = \frac{T_{max}}{2r}\left((r - \mu) \pm \sqrt{(r - \mu)^2 + 4s\frac{r}{T_{max}}}\right). \tag{3.19}$$

Note that since the product $\frac{4sr}{T_{max}}$ is positive, the square root term exceeds $|r - \mu|$ ,i.e

$$\sqrt{(r - \mu)^2 + 4s\frac{r}{T_{max}}} > |r - \mu|.$$

And therefore, one of the roots of the quadratic equation is positive, while the other is negative. But in this model, only the positive root is biologically important, and shall be denoted by $T_0$, as the "**zero virus**" which is the stationary point.
We now show that $T_0$ must lie between $[0, T_{max}]$. As seen from equation (3.17) where the right hand side (RHS) is positive in the interval when $T = 0$ and negative when $T = T_{max}$. Therefore, it must have a root between 0 and $T = T_{max}$, and this is our positive root $T_0$.
Then $T_0$ is calculated from equation (3.19) by choosing the positive sign. We shall refer to the difference $p = r - \mu$ as the T-cell proliferation rate, in terms of it.
In the absence of virus, the T-cells population has a steady state value given by

$$T_0 = \frac{T_{max}}{2r}\left(p + \sqrt{p^2 + 4s\frac{r}{T_{max}}}\right). \tag{3.20}$$

And this root $T_0$ is the only (biologically consistent) stationary point of (3.17). We shall then consider the two biological cases:

Case I. Supply Rate Solution

In the absence of an infection, or at least an environmental antigen, the clonal production rate $r$ can be smaller than the natural death rate $\mu$, which will result in a negative proliferation rate $p$. In this case, the supply rate $s$ must be high in order to maintain a fixed T-cell concentration of about 1000 per cubic millimetre see [30] , with the given data, the stationary value of $T_0$ can be calculated using (3.19) and the trajectories for case I is presented in figure 3.1 using the given parameters in table 3.1

Table 3.1: Parameters for case I

| Parameters | Descriptiion | Value |
|---|---|---|
| s | T-cell from precursor supply rate | $10/mm^3/day$ |
| r | normal T-cell growth rate | $0.03/day$ |
| $Tmax$ | maximum T-cell population | $1500/mm^3$ |
| $\mu$ | T-cell death rate | $0.02/day$ |

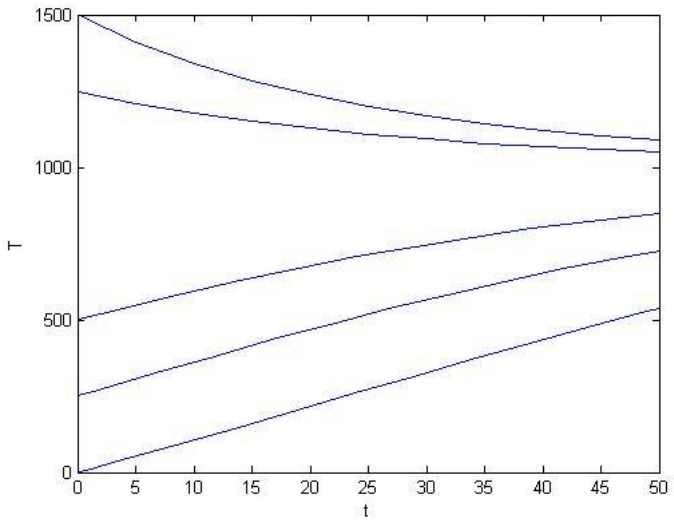


Figure 3.1: Time Versus Number of T-cells per cubic millimetre.

Case II. Clonal Production Solution

An alternative scenario is that adult thyme atrophy has occurred or a thyme tony has been performed. One could assume as a hypothetical and limiting situation that $s = 0$ and see how $r$ must change to maintain a comparable $T_0$ using the parameters in table 3.2, which gives the trajectories for case II as presented in figure 3.2.

Table 3.2: Parameters for case II

| Parameters | Descriptiion | Value |
|---|---|---|
| s | T-cell from precursor supply rate | $0/mm^3/day$ |
| r | normal T-cell growth rate | $0.06/day$ |
| $Tmax$ | maximum T-cell population | $1500/mm^3$ |
| $\mu$ | T-cell death rate | $0.02/day$ |

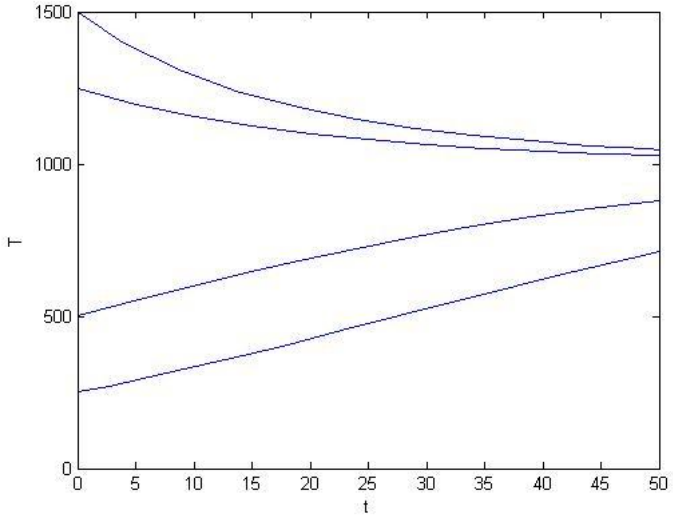


Figure 3.2: Time Versus Number of T-cells count with a reduced thymus function.

Note that in all cases $T_0$ is 1000 T-cells per cubic millimetre.

## Remarks

The above analysis shows that upon adult thyme atrophy or thyme tony, the response of T-cell population is much slower which implies that one would find differences in the dynamics of T-cell depletion due to an HIV infection in people of different ages. Obviously, there is a need for $r$, the T-cell growth rate to be large in compensation, when the supply rate $s$, is small.

## 3.3 Formulation of the T - Cell infection model

Next, in formulation of T-cell infection model, we incorporate an HIV infection into the above model following the approach taken by Perelson, Krischner, and DeBoer [34], where the three kinds of T-cells are denoted by $T$ as before. There are T-cells infected with provirus but not producing free Virus. The number of these latently infected T-cells is denoted by $T_L$. Also, in addition, there are T-cells that are infected with Virus and are actively producing new Virus, the number of these is denoted by $T_A$.

The interaction between Virus is denoted by $V$, and T-cells is reminiscent of a predator-prey relationship. However, it is only the active type T-cells produce Virus, while only the normal T-cells can be infected, a mass action term is used to qualify the interaction. Hence, we therefore, consider the following models:

$$\frac{dT}{dt} = s + rT(1 - \frac{T + T_L + T_A}{T_{max}}) - \mu T - K_1 VT, \tag{3.21}$$

$$\frac{dT_L}{dt} = K_1 VT - \mu T_L - K_2 T_L \tag{3.22}$$

$$\frac{dT_A}{dt} = K_2 T_L - \beta T_A \tag{3.23}$$

$$\frac{dV}{dt} = N\beta T_A - K_1 VT - \alpha V. \tag{3.24}$$

i. Equation (3.21) is the modification of (3.17) with the addition of an infection term having mass action parameter $K_1$. When the normal T-cells get infected, they immediately get reclassified as the latent type. In addition, note that the sum of all three types of T-cells counts towards the

T-cell limit, $T_{max.}$

ii. The first term in (3.22) corresponds to the reclassification of newly infected normal T-cells. These cells disappear from (3.21) but then reappear in (3.22) . Also, in addition, (3.22) includes a per capita death rate term and a term to account for the transition of these latent - type cells to activate type with rate parameter $K_2$.

iii. The first term of (3.23) balances the disappearance of latent T-cells upon becoming active, with their appearance as active-type T-cells. It also includes a per capita death rate term with parameter $\beta$ which correspond to the breaking down of these cells after releasing vast numbers of replicated virus. It is obvious that T-cells active in this sense die or (perish) much faster than the normal T-cells, resulting to a situation where $\beta$ is much larger than $\mu$, i.e.

$$\beta \gg \mu. \tag{3.25}$$

iv. Finally, equation (3.24) accounts for the population dynamics of the Virus. The first term - $N\beta T_A$, comes from the manufacture of virus by the "active" - type T-cells, but the number produced will be $N$ is a large value which can be adjusted. The second term - $K_1VT$ reflects the fact that as a virus invades or infects a T-cell, it drops out of the pool of free virus particles, and the last term - $\alpha V$, with per capita rate parameter $\alpha$ which corresponds to loss of virus through the body's defence mechanisms.

Here, we should note that, in the absence of virus, i.e $V = 0$, then both $T_L$ and $T_A$ are 0 as well as setting these values into system (3.20), we observed that this new model agrees with (3.17).

## 3.4 The T-cell Model Agrees with Biological Constraints :

Here, we ensure that the model is well constructed which means that no population becomes negative and unbounded. To achieve this, we first establish that the derivatives $\frac{dT}{dt}$, $\frac{dT_L}{dt}$, $\frac{dT_A}{dt}$, and $\frac{dV}{dt}$, are all positive whenever $T, T_L, T_A$

or $V = 0$, respectively. This means that each population will increase, at low population sizes.
From equation (3.21), if $T = 0$, we then have $\frac{dT}{dt} = s > 0$ and if $T_L = 0$, then equation (3.22) gives $\frac{dT_L}{dt} = K_1 VT > 0$. Similarly, if $T_A = 0$, equation (3.23) becomes $\frac{dT_A}{dt} = K_2 T_L > 0$. Also, equation (3.24) becomes $\frac{dV}{dt} = N\beta T_A > 0$ when $V = 0$.
The above analysis shows that all the quantities are positive and so the corresponding derivatives are all positive as well. Following [34], we prove that the total T-cell population as described by the model remains bounded and defined to be $T_\epsilon = T + T_L + T_A$, and it actually satisfies the differential equation obtained by summing the RHS of equations $(3.21) - (3.23)$, i.e.

$$\frac{dT_\epsilon}{dt} = s + rT\left(1 - \frac{T_\epsilon}{T_{max}}\right) - \mu T - \mu T_L - \beta T_A. \tag{3.26}$$

Now, if we suppose $T_\epsilon = T_{max}$,then equation (3.26) becomes

$$\frac{dT_\epsilon}{dt} = s - \mu T - \mu T_L - \beta T_A + \mu T_A - \mu T_A. \tag{3.27}$$

And substituting the sum of the second, third and last term in (3.27) as $-\mu T_{max}$ then we deduce

$$\frac{dT_\epsilon}{dt} = s - \mu T_{max} - (\beta - \mu)T_A < s - \mu T_{max}.$$

Where also (3.25) has been used to obtain the inequality. Using now (3.18), we then find that

$$\frac{dT_\epsilon}{dt} < 0,$$

if $T_\epsilon = T_{max}$ proving that $T_\epsilon$ cannot increase beyond $T_{max}$.
In summary, system $(3.21) - (3.24)$ has been proved to be consistent with the biological constraints that solutions remain positive and bounded.

## 3.5 Stability of the T-cell infection model

We need to find the stationary points of the T-cell HIV model system given by $(3.21) - (3.24)$. If we set $T_\epsilon = T_{max}$ and $S = 0$ then automatically the RHS of (3.21) becomes zero, [34].
From equation (3.23)

$$\frac{dT_A}{dt} = 0 \implies K_2 T_L - \beta T_A = 0,$$

or

$$T_A = \frac{K_2 T_L}{\beta}. \tag{3.28}$$

Substitute $T_A$ into equation (3.24) we have

$$N\beta T_A - K_1 VT - \alpha V = 0,$$

and

$$NK_2 T_L - K_1 VT - \alpha V = 0. \tag{3.29}$$

By equation (3.22) we have that

$$\frac{dT_L}{dt} = 0 \implies K_1 VT - \mu T_L - K_2 T_L = 0,$$

or

$$T_L = \frac{K_1 VT}{K_2 + \mu}. \tag{3.30}$$

Substituting $T_L$ back into equation (3.29) and simplifying all through gives

$$NK_2 K_1 T - K_1 TK_2 + \mu K_1 T - \alpha K_2 - \alpha\mu = 0,$$

or equivalently

$$N = \frac{(\alpha + K_1 T_0)(K_2 + \mu)}{K_2 K_1 T_0}.$$

Now if

$$N < \frac{(\alpha + K_1 T_0)(K_2 + \mu)}{K_2 K_1 T_0} = N_c, \tag{3.31}$$

and using reasonable initial conditions for infection by free Virus only, we consider $T(0) = T_0, T_L(0) = 0, T_A(0) = 0, V(0) = V_0$. System (3.21) – (3.24) has two steady states: the uninfected steady state $E_0 = (T_0, 0, 0, 0)$ and the (positive) infected steady state $\bar{E} = \left(\bar{T}, \bar{T_L}, \bar{T_A}, \bar{V}\right)$, where

$$\bar{T} = \frac{\alpha K_1 (K_2 + \mu)}{K_1 N\beta - K_1 (K_2 + \mu)}, \tag{3.32}$$

$$\bar{T_L} = \frac{K_1 \bar{V}\bar{T}}{(K_2 + \mu)}, \tag{3.33}$$

$$\bar{T_A} = \frac{K_2 K_1 \bar{V}\bar{T}}{(K_2 + \mu)}, \tag{3.34}$$

$$\bar{V} = \frac{(K_2+\mu)\left[(s+(r-\mu T)\bar{T})T_{max} - r\bar{T}^2\right]}{\bar{T}\left[K_1 r\bar{T} + K_1(\mu+K_2)T_{max}\right]}. \tag{3.35}$$

Following the analysis in [25],we can see that $N_c$ is a bifurcation parameter. Indeed if

$$N < \frac{(\alpha + K_1T_0)(K_2+\mu)}{K_2K_1T_0} = N_c.$$

Then, the uninfected steady state $E_0$ is stable and the infected steady state $\bar{E}$ does not exist **(unphysical)**. When $N > N_c$, $E_0$ becomes unstable and $\bar{E}$ exists.
To discuss the local stability of the positive infected steady states $\bar{E}$, for $N > N_c$, we consider the linearized system of $(3.21) - (3.24)$ at $\bar{E}$. The Jacobian matrix at $\bar{E}$ is given by (3.36).

$$J(\bar{T},\bar{T_L},\bar{T_A},\bar{V}) = \begin{pmatrix} -\left(\mu T + \frac{r(2\bar{T}+T_L\bar{T_A})}{T_{max}} + K_1\bar{V} - r\right) & -\frac{r\bar{T}}{T_{max}} & \frac{r\bar{T}}{T_{max}} & -K_1\bar{T} \\ K_1\bar{V} & -(K_2+\mu) & 0 & 0 \\ 0 & K_2 & -\beta & 0 \\ -K_1\bar{V} & 0 & N\beta & -(K_1\bar{T}+\alpha) \end{pmatrix}. \tag{3.36}$$

We denote $G = \mu T + \frac{r(2\bar{T}+T_L\bar{T_A})}{T_{max}} + K_1\bar{V} - r$ for convenience, then after some algebraic calculations and simplification, the characteristic equation of the linearized system is given by

$$\lambda^4 + \lambda^3 a_1 + \lambda^2 a_2 + \lambda a_3 + a_4 = 0. \tag{3.37}$$

Here

$$\begin{aligned}
a_1 =& K_1\bar{T} + \alpha + \beta + K_2 + \mu + G, \\
a_2 =& K_1^2\bar{V}\bar{T} + \frac{rK_1\bar{V}\bar{T}}{T_{max}} + K_1K_2\bar{T} + K_1\bar{T}\mu + K_2\alpha + \alpha\mu \\
&+ K_2\beta + \beta\mu + G(K_2+\mu) + G\beta + GK_1\bar{T} + \alpha G + K_1\bar{T}\beta + \beta\alpha \\
a_3 =& K_1\bar{T}K_2\beta + K_1\bar{T}\beta\mu + \beta\alpha K_2 + G\beta K_1\bar{T} + G\beta\alpha \\
&+ G(K_1\bar{T}K_2 + K_1\bar{T}\mu + \alpha\mu) + G\beta K_2 + G\beta\mu \\
&+ \frac{rK_1\bar{V}\bar{T}\beta}{T_{max}} + \frac{K_1^2\bar{V}\bar{T}^2}{T_{max}} + \frac{rK_1\bar{V}\bar{T}\alpha}{T_{max}} + \frac{rK_1\bar{V}\bar{T}K_2}{T_{max}}
\end{aligned}$$

$$\begin{aligned}
a_4 =& -\frac{rK_1^2K_2\bar{V}\bar{T}^2}{T_{max}} + \frac{rK_1\bar{V}\bar{T}\alpha K_2}{T_{max}} + \frac{rK_1^2\bar{V}\bar{T}^2\beta}{T_{max}} + \frac{rK_1\bar{V}\bar{T}\alpha\beta}{T_{max}} \\
&+ G\beta K_2K_1\bar{T} + G\beta\mu\alpha.
\end{aligned}$$

Therefore, it follows by the Routh-Hurwitz criterion in [31], that all the eigenvalues of the matrix (3.36) have negative real parts if and only if

$$a_1 > 0, a_3 > 0, a_4 > 0$$

and

$$a_1 a_2 a_3 > a_3^2 + a_1^2 a_4.$$

This implies that the infected steady state $\bar{E}$ is asymptotically stable.

## 3.6 An Alternative Approach

A future work on this analysis could be carried out using an alternative method, which is called the direct Lyapunov method to determine the global stability of both $SIR$ and $HIV$ infection models. Linearization method works only for almost linear systems (nonlinear systems that can more or less become linear in a region of a critical point), whereas the direct Lyapunov method is a more general method and can be applied even to nonlinear systems that are not almost linear.

The direct Lyapunov method provides insight into other properties of the system, for example, it allows us to find and compare the rates of convergence towards an equilibrium state for different models and under different conditions. However, this could be employed in future work to determine the global stability and the convergence to the steady-states for the $SIR$ and $HIV$ infection models.
Below presented an illustration on how the Lyapunov method could be used to determine global stability of a $SIR$ model and follow the same steps as in [19].

Let the average life expectancy, average infective period, and an average period of immunity be denoted by $\frac{1}{\sigma}$, $\frac{1}{\delta}$ and $\frac{1}{\alpha}$, respectively, then the differential equations are

$$\dot{S} = (\gamma + \alpha)N - \beta\frac{SI}{N} - (\alpha + p\gamma)I - (\alpha + \sigma)S, \tag{3.38}$$

$$\dot{I} = \beta\frac{SI}{N} - (\delta + \sigma - p\gamma)I.$$

If immunity is permanent, then the average period of immunity $\frac{1}{\alpha}$ is infinite and $\alpha = 0$, so that the $SIRS$ model reduces to the $SIR$ model. We do not need an equation for the removed class $R$, since $N = S + I + R$ =constant. System (3.38) has two equilibria: an infection-free equilibrium $E_0 = (S_0, I_0)$, with

$$S_0 = \left(\frac{\alpha+\gamma}{\alpha+\sigma}\right) N, I_0 = 0,$$

and an endemic equilibrium $E_0 = (S^*, I^*)$, where

$$S^* = \left(\frac{\alpha+\gamma}{\alpha+\sigma}\right) \frac{N}{R_0},$$

$$I^* = \frac{\alpha+\gamma}{\alpha+\delta+\sigma}\left(1 - \frac{1}{R_0}\right) N.$$

The parameter

$$R_0 = \frac{\beta(\alpha+\gamma)}{(\alpha+\sigma)(\delta+\sigma-p\gamma)}$$

is often called the basic reproduction number.We assume here that the condition $R_0 > 1$ holds to ensures the existence of the positive endemic equilibrium state $E^*$.
By substituting $(S, I) \to (P, I)$ where $P = S + ((\alpha + p\gamma)/\beta)N$, then with respect to the new variables, we have

$$\dot{P} = \hat{\gamma}N - \beta\frac{PI}{N} - \hat{\sigma}P, \tag{3.39}$$

$$\dot{I} = \beta\frac{PI}{N} - \hat{\delta}I,$$

where $\hat{\gamma} = \gamma + \alpha + (\alpha+\sigma)(\alpha+p\gamma)/\beta$, $\hat{\delta} = \alpha + \delta + \sigma$, and $\hat{\sigma} = \alpha + \sigma$. From the above, the endemic equilibrium state $E^*$ has coordinates

$$P^* = \frac{\hat{\gamma}}{\hat{\delta}}\frac{N}{R_0},$$

$$I^* = \frac{\hat{\gamma}}{\hat{\delta}}\left(1 - \frac{1}{R_0}\right) N,$$

and $R_0 = \frac{\beta\hat{\gamma}}{\hat{\sigma}\hat{\delta}}$. it follows from (3.39) that

$$\beta\frac{P^*I^*}{N} = \hat{\gamma}N - \hat{\sigma}P^* = \hat{\delta}I^*. \tag{3.40}$$

Hence, the global properties of systems (3.38) and (3.39) are given by the following theorem.

## Theorem 3.1 (Stability of $E^*$)

The endemic equilibrium state $E^*$ of system (3.39) ( and hence, that of system (3.38)) is globally asymptotically stable.
**Proof**: A Lyapunov function of the form

$$V(P,I) = P^*\left(\frac{P}{P^*} - ln\frac{P}{P^*}\right) + I^*\left(\frac{I}{I^*} - ln\frac{I}{I^*}\right). \tag{3.41}$$

is defined and is continuous for all $P, I > 0$. Moreover the following relations are satisfied

$$\frac{\partial V}{\partial P} = 1 - \frac{P^*}{P},$$

and

$$\frac{\partial V}{\partial I} = 1 - \frac{I^*}{I}.$$

It is easy to see that the endemic equilibrium state $E^* = (P^*, I^*)$ is the only extremum and the global minimum of the function $V(P,I)$ in $\Re^2_+$, because for $\alpha, P \neq 0$, the positive quadrant $\Re^2_+$ of the $SI$ plane is not invariant set of system (3.38) i.e any solution with infected individuals at some time will not be free of infection for all time.
In the case of system (3.39), using (3.40), the function $V(P,I)$ satisfies

$$\dot{V}(P,I) = \hat{\gamma}N - \beta\frac{PI}{N} - \hat{\sigma}P - \hat{\gamma}N\frac{P^*}{P} + \beta\frac{P^*}{N}I + \hat{\sigma}P^* + \beta\frac{PI}{N} - \hat{\delta}I - \beta\frac{PI^*}{N} + \hat{\delta}I^*$$

$$= \hat{\gamma}N\left(1 - \frac{P^*}{P} - \frac{P}{P^*} + 1\right) + \frac{\hat{\sigma}\hat{\delta}}{\beta}N\left(-\frac{P}{P^*} + 1 + \frac{P}{P^*} - 1\right)$$

$$= -\hat{\gamma}N\frac{P^*}{P}\left(1 - \frac{P}{P^*}\right)^2 \leq 0,$$

for all $P, I \geq 0$.

Note that, the equality $\dot{V}(P,I) = 0$ holds only when $P = P^*$. Since the endemic equilibrium state $E^*$ is the only invariant set of system (3.39) when $P = P^*$, by the asymptotic stability theorem in [5], the equilibrium $E^*$ is globally asymptotically stable, hence the theorem is proven. ■

## 3.7 Discussion

In section 3.1, an AIDS epidemic model in a homosexual population was developed and this gives a lower triangular matrix with a positive product of its corresponding eigenvalues and this means that the number of secondary infections which arise from infection is greater than 1. Therefore, equation (3.8) gives a condition for an epidemic to start with an intrinsic growth rate $r = v(R_0 - 1)$ which is positive, if an epidemic exists ($R_0 > 1$) and also a doubling time for the epidemic - $t_d$ can also be determined using equation (3.16). These clearly show that the larger the basic reproduction rate $R_0$ the shorter the doubling time.

Furthermore, in section 3.2, the epidemic model for T-cell infection of $HIV$ is formulated consisting of three types of T-cells and a virus. These have been modelled using the logistic and death rate terms with a property that the supply rate $s$ will be both positive and negative, when $T = T_{max}$. This means that when the number of T-cells has reached the maximum value -$T_{max}$, there are more cells dying than being produced by the lymphatic system. Here in this model, only the positive root of the supply rate is biologically useful and denoted by $T_0$ which is refers here to be "zero virus" ( i.e. the equilibrium point), and that $T_0$ must lie between $0, T_{max}$ as proved in section 3.2.

However, in figures 3.1 and 3.2, we observed that upon adult thyme atrophy or thyme tony, the response of T-cell population is much slower implying that one would find differences in the T-cell depletion due to an $HIV$ infection in people with different ages. Hence, there is a need for T-cell growth rate $r$ to be large in compensation whenever the supply rate $s$ is small.

Also, section 3.3 gives us the interaction between the virus $v$ and T-cells which is regarded as a predator having a prey-relationship type. However, only the active type T-cells produce virus while the normal T-cells can be infected and the mass action term is used to quantify their interaction.
But when the normal T-cells get infected, they are reclassified as the latent - type see (3.22). The normal T-cells term disappear from (3.21) but then it reappears in (3.22) and this (3.22) includes a per capita death rate term $\mu$ and a term to account for the transition of these latent - type cells to activate type with rate parameter $K_2$.

The first term in (3.23) balances the disappearance of latent T-cells upon becoming active, with their appearance as active - type T-cells, which also includes a per capita death rate term with parameter $\beta$, corresponding to the survival of these cells after releasing vast number of replicated virus. It is noted here that the active T-cells die much faster than the normal T-cells resulting to a situation where $\beta$ is much larger than $\mu$ i.e $\beta \gg \mu$.

Similarly, in (3.24), this gives accounts for the population of the virus having $N\beta T_A$ term as the manufactured virus by the active - type T-cells, with the number produced $N$ which can be adjusted, $K_1VT$ term reflects the fact that as a virus infect a T-cell, it drops out of the pool of free virus particles. The per capita rate parameter-$\lambda$ representing the loss of virus through the body's defence mechanism.

The stability of the T-cell infection was determined in section 3.5 and shows that the system has two steady states, the uninfected steady state $E_0$ which has unstable stability and the infected steady state $\bar{E}$ which only exist when $N > N_c$ and $E_0$ then by using linearization method. Thus, it follows by the Routh - Hurwitz criterion [31] that the infected steady state $\bar{E}$ is asymptotically stable.

# Chapter 4

# The EBOLA VIRUS MODEL

## 4.1 Background

The origin of the Ebola virus is somewhat obscure. The Ebola virus was first recognized in 1976 in West Africa Countries. Since then, various strains of the virus have emerged and outbreaks have occurred. A fact that is interesting with the Ebola virus is that, it is a unique member of the ribonucleic acid virus family that has no exact origin, locations and natural habitat, known as the "natural reservoir", which remains unknown. However, based on the nature of similar viruses, reseachers believe that the virus is zoonotic. This means the virus is animal-borne i.e. a disease that can be tranmitted from animals to people or more specifically, a disease that normally exists in animals but that can infect humans, so it is likely believed that an animal host native to Africa where the virus naturally lives. It is un-probable that the virus is native to no where but Africa [33].
The Ebola-Reston strain was discovered in United States but the Monkeys were brought from Africa. What prevent humans and Primates from being the natural host is that, it destroys those infected with the virus so quickly [33].

The genetic analysis of the virus indicates that, it is closely related ( 97% identical) to variants of Ebola virus (species Zaire ebolavirus) identified earlier in the Democratic Republic of the Congo and Gabon [8].
Recently, the 2014 Ebola outbreak is one of the largest Ebola outbreaks in history and the first in West Africa. It is affecting four countries in West Africa: Guinea, Liberia, Nigeria and Sierra Leone, but does not pose a significant risk

to the U.S. public [8].
Ebola Virus Disease (EVD) can only be spread to others after symptoms begin. The incubation period of Ebola is $2-21$ days after exposure to ebolavirus, although the infections period is most commonly $4-10$ days. The onset of Ebola is characterized by fever, severe headaches, bloody diarrhea, vomiting, stomach pain, muscle pain, unexplained bleeding or bruising, weakness and lack of appetite [8].

Diagnosis of Ebola can be difficult, because Ebola is frequently misdiagnosed as typhoid and malaria; currently there is no treatment of Ebola [8].
. Ebola is transmitted through primary contact with health workers who are in direct contact with body fluids from the infected. It can also be transmitted through secondary contact by family members caring for the infected and also where infection control mechanisms are not in practice such as wearing gloves, or washing of hands etc.

The World Health Organization (WHO), in partnership with the Ministries of Health in Guinea, Sierra Leone, Liberia, and Nigeria reported 2615 suspected and confirmed cases of $EVD$, including 1528 laboratory-confirmed cases, and 1427 deaths with the following breakdown. In Guinea, 607 cases of EVD, including 443 laboratory-confirmed cases, and 406 deaths; Liberia, 1082 clinical cases of EVD, including 269 laboratory-confirmed cases, and 624 deaths;Nigeria, 16 suspected cases of EVD, including 12 laboratory-confirmed cases, and 5 deaths; and Sierra Leone 910 suspect and confirmed cases of EVD, including 804 laboratory-confirmed cases, and 392 deaths. Currently, the Centers for Disease Control and prevention (CDC) is working with other U.S government agencies, the WHO, and other domestic and international partners in an international response to the current Ebola outbreak in West Africa [8].

## 4.2 Assumptions of the model

i. The total population of people used in this model is randomly distributed over an area of choice, allowing for a constant to be defined for the contact made between the susceptible and the infected.

ii. The virus will always kill a certain percent of infected people, but the

survivors will become the recovered group.

iii. Individuals that recovered are given no immunity i.e they have no resistance against the disease.

iv. The population involved remain constant i.e. no births or unrelated deaths.

v. The people should not get scared and they should not treat the infected with quarantine procedures, in essence, the susceptible and the infected should go about their normal duties.

## 4.3 Formulation of the model

The population is divided into four classes: The susceptible are described by $S(t)$, the infected by $I(t)$, the recovered by $R(t)$, and people that are killed by the Ebola virus disease are described by $D(t)$.
To formulate a model that describes the population of the susceptible group with respect to time, we start with the fact that the susceptible become infected at rate $\gamma$, this means that the change in population of the susceptible group is equal to the negative product of $\gamma S(t)$ and $I(t)$. this can be written as

$$\frac{dS(t)}{dt} = -\gamma S(t)I(t),$$

individuals from the recovery group become susceptible again at a certain rate $\mu$, this can be multiplied by $R(t)$ and added to the previous equation and written as

$$\frac{dS(t)}{dt} = -\gamma S(t)I(t) + \mu R(t).$$

This is the complete equation that describes the change in population of the susceptible group over time. The model that describes the population of the infected group will be obtained by adding up what was removed from the susceptible population i.e. $\gamma S(t)I(t)$, and can now be expressed as

$$\frac{dI(t)}{dt} = \gamma S(t)I(t).$$

The population of the infected group is reduced into two categories, people who can either recover or die by the $EVD$. Both options remove people from

the infected group, but when the infected recover, they join the recovery group at rate $\beta$, and when infected die they join the deceased group at rate $\alpha$, and this is given by

$$\frac{dI(t)}{dt} = \gamma S(t)I(t) - (\beta + \alpha)\, I(t).$$

The above system describes the change in population of the infected group over time. However, the recovery population is increased by those that recover from Ebola virus disease. Similarly, let the people who recovered from the EVD be denoted as rate $\beta$, this means that the population of the recovery is increased by $\beta$ multiplied by $I(t)$, this gives

$$\frac{dR(t)}{dt} = \beta I(t),$$

the recovery population is then reduced by the number of people that join the susceptible group. The recovered join the susceptible group at the rate $\mu$, subtracting $\mu R(t)$ from the immediate equation above, gives

$$\frac{dR(t)}{dt} = \beta I(t) - \mu R(t),$$

which describes the change in population of the infected group over time.

Next, the population of the deceased group is defined by the number of people that are killed by $EVD$ within the infected group. People who died at rate $\alpha$, are given by

$$\frac{dD(t)}{dt} = \alpha I(t).$$

Therefore, the sum of

$$S(t) + I(t) + R(t) + D(t) = constant.$$

Here, the inclusion of deceased into this model make a distinction between the people who die of the Ebola disease and the people who recover with immunity against reinfection, because, in the outbreak of EVD, there is high tendency of those infected with the EVD to die fast since the incubation period only last between $2 - 21$ days after exposure to Ebola virus and the recover group will not remain immune to the infection but will join the Susceptible at a certain rate, while that of $SIR$ model, the recovery group obtains immunity from the disease after they become infected .

Hence, the four-equations proposed model for the approximation of the outbreak of Ebola virus disease is

$$\frac{dS(t)}{dt} = -\gamma S(t)I(t) + \mu R(t), \tag{4.1}$$

$$\frac{dI(t)}{dt} = \gamma S(t)I(t) - (\beta + \alpha)\, I(t) \tag{4.2}$$

$$\frac{dR(t)}{dt} = \beta I(t) - \mu R(t) \tag{4.3}$$

$$\frac{dD(t)}{dt} = \alpha I(t). \tag{4.4}$$

where $\gamma$, $\beta$, $\mu$ and $\alpha$ are the rates of infection, recovery, susceptibility and death respectively.

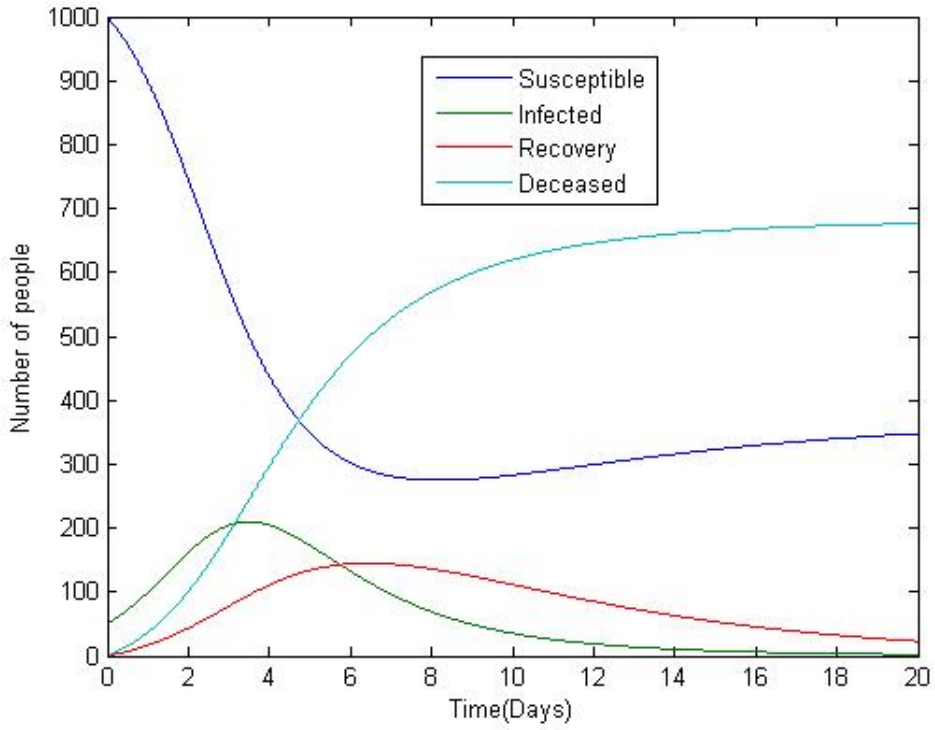


Figure 4.1: A numerical solution of the Ebola Model

Figure 4.1 is a plot of a numerical solution of the system (4.1) -(4.4) as obtained

by using Euler's method. Figure 4.1 shows a sharp decrease in the Susceptible group from 1000 to approximately 250 within five days, thereafter, it maintains a steady state as time increases.The figure also depicts a gradual increase in the number of infected individuals to a maximum of 200 people and further remains stable for a certain period of time before it finally converges to zero as the number of days increases.
Similarly, in the recovery group, there is also a steady increase in the number of people who recovered from the infection over a short period of time to a point of 100, it then maintains a steady state and later declines as time increases. In the deceased component, there is a rapid increase in the number of people who are killed by the EVD to the level of 600 infected people within 10 days. This may likely be as a result of the absence of any control measures.

## 4.4 Future work

This model does not have any vital dynamics, therefore, in my future work, I intend to include the vital dynamics such as birth and death rates since the EVD is likely to be endemic. Furthemore, I intend to incorporate control measures such as vaccination and quarantine of Susceptible group, treatment and isolation of infected group into the model. The model will be analysed for stability using the direct Lyapunov method. I will work in this direction with my future collaborators to develope more robust models.

# Conclusion

The Mathematical models of $SIR$ and $HIV$ have become important tools to health sector in analyzing the spread of virus infectious diseases and transmission of $HIV$. In this analysis, the models provided conceptual results such as thresholds, basic reproduction rate, contact numbers and the stability of the T-cell infection. The Ebola virus might likely spread over the period of time if there are no control measures put in place because the virus is extremely contagious. These models are very important because they can put an upper bound on the number of deaths that occur due to an outbreak of a disease. These can also be used by epidemiological experts to determine when a disease reached an endemic equilibrium point, i.e the system has an endemic infection when the equilibrium is unstable and will attain disease-free equilibrium with regards to the existing population when the equilibrium is asymtotically stable. This will also guide in the process of preventing the spread of diseases, planning, implementing and optimizing various detection for control programs. Furthermore, this can contribute to the designing and analyzing of epidemiological surveys and suggest the type of data that should be collected to estimate the uncertanty in future.

# Appendices

# Matlab code for figure 2.1

```
h=0.01;
tmax=5;
S=zeros(1,tmax/h+1);
I=zeros(1,tmax/h+1);
R=zeros(1,tmax/h+1);
D=zeros(1,tmax/h+1);
S(1)=100
I(1)=0.43
r=2;
a=1.5;
for n=1:(tmax/h)
    S(n+1)=S(n)+h*(-r*S(n)*I(n));
    I(n+1)=I(n)+h*(r*S(n)*I(n)-a*I(n));
    R(n+1)=R(n)+h*(a*I(n));
    end
t=0:h:tmax;
plot(t,S,t,I,t,R);
```

# Matlab code for figure 2.2

```
clear
I_0 =10;
S_0 =10;
rho =8;
N =30;
C = I_0+S_0-rho*log(S_0);
S =[0.01:0.01:N];
plot(S,rho*log(S)-S+C)
ylim([0,N])
hold on
I_0 =12;
S_0 =12;
rho =7;
C = I_0+S_0-rho*log(S_0);
Sbar=exp((N-C)/rho);
S =[0.01:0.01:Sbar];
```

```
plot(S,rho*log(S)-S+C)
ylim([0,N])
hold on
I_0 =14;
S_0 =14;
rho =6;
C = I_0+S_0-rho*log(S_0);
Sbar=exp((N-C)/rho);
S =[0.01:0.01:Sbar];
plot(S,rho*log(S)-S+C)
ylim([0,N])
hold on
I_0 =15;
S_0 =15;
rho =5;
C = I_0+S_0-rho*log(S_0);
Sbar=exp((N-C)/rho);
S =[0.01:0.01:Sbar];
plot(S,rho*log(S)-S+C)
ylim([0,N])
hold on
plot(0:0.01:N, N-[0:0.01:N])
xlabel('Susceptible')
ylabel('Imax')
title('Note: Phase plane for the SIR Epidemic model')
labelstr=sprintf('S + I',15.5,15.5);
text(15.5,15.5,labelstr);
```

# Matlab code for figure 3.1

```
clear
s=10;
r=0.03;
mu=0.02;
Tmaxi=1500;
p=[-r/Tmaxi (r-mu) s];
T0=max(roots(p));
```

```
%%%%%%%%%%%%%%%%%%%%%%%%

[t,T]=ode23('hiv1',[0,50],0);
plot(t,T); hold on
[t,T]=ode23('hiv1',[0,50],T0/4);plot(t,T);
[t,T]=ode23('hiv1',[0,50],T0/2);plot(t,T);
[t,T]=ode23('hiv1',[0,50],(T0+Tmaxi)/2);plot(t,T);
[t,T]=ode23('hiv1',[0,50],Tmaxi);plot(t,T);
xlabel('t')
ylabel('T')
```

# Matlab code for figure 3.2

```
clear
s=0;
r=0.06;
mu=0.02;
Tmaxi=1500;
p=[-r/Tmaxi (r-mu) s];
T0=max(roots(p));

%%%%%%%%%%%%%%%%%%%%%%%%

[t,T]=ode23('hiv2',[0,50],0);
plot(t,T); hold on
[t,T]=ode23('hiv2',[0,50],T0/4);plot(t,T);
[t,T]=ode23('hiv2',[0,50],T0/2);plot(t,T);
[t,T]=ode23('hiv2',[0,50],(T0+Tmaxi)/2);plot(t,T);
[t,T]=ode23('hiv2',[0,50],Tmaxi);plot(t,T);
xlabel('t')
ylabel('T')
```

# Matlab code for figure 4.1

```
h=0.01;
tmax=20;
S=zeros(1,tmax/h+1);
I=zeros(1,tmax/h+1);
R=zeros(1,tmax/h+1);
D=zeros(1,tmax/h+1);
S(1)=1000
I(1)=50
R(1)=0
D(1)=0
gamma=0.0015;
beta=0.25;
mu=0.2;
alpha=0.5;
for n=1:(tmax/h)
    S(n+1)=S(n)+h*(-gamma*S(n)*I(n)+mu*R(n));
    I(n+1)=I(n)+h*(gamma*S(n)*I(n)-beta*I(n)-alpha*I(n));
    R(n+1)=R(n)+h*(beta*I(n)-mu*R(n));
    D(n+1)=D(n)+h*(alpha*I(n))
end
t=0:h:tmax;
plot(t,S,t,I,t,R,t,D);
```

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