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MODELLING HUMAN IMMUNE RESPONSE TO VIRUS INFECTIOUS DISEASES

BY

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DECLARATION

I hereby declare that this submission is my own work towards the Master of Philosophy (MPhil) and that to the best of my knowledge, it contains no material previously published by another person nor material which has been accepted for the award of any other degree of the University, except where due acknowledgement has been made in the text.

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ABSTRACT

This study is aimed at modelling human immune response to virus infectious diseases. The issue of humans' defense against viral infections and the reaction of immune system to these infections are the main problems in practical immunology. In addition to antiviral defense, the human immune system plays a decisive role in compatibility reactions such as autoimmune diseases and other allergies.

Four systems of differential equations have been developed, analyzed and the numerical solutions found. These systems have been used to model different stages of the human immune response to viral infection. The first three differential equations describe the behaviour of lymphocytes in the absence of virus cells. The next two differential equations also describe the first line of defense in the innate immune response stage. The overlapping stage of innate and adaptive immune responses comprises a system of four differential equations. The last three equations describe the adaptive immune response which is the final stage of combating viral infection.

The steady states and their stability for these differential models are deduced. Each of the models permits the existence of two types of stationary states. There is the state of no infection, with no virus cells while the other is the state of coexistence where a virus cell persists against the background of immune response. The state of no infection is asymptotically stable and a state of infection is unstable. It was found from the study that the state of no infection represents the immune state.

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CHAPTER 1

INTRODUCTION

1.0 OVERVIEW

In this chapter, we present the background of the study, the statement of the problem, the objectives of the study, the methodology, the significance of the study, the scope of the study and finally present the organization of the study.

1.1 BACKGROUND OF THE STUDY

Infections of humans range from childhood diseases, such as measles, diphtheria and chickenpox, to faecal–oral infections, such as cholera and rotavirus, vector-borne diseases including malaria and even sexually transmitted gonorrhea (Hethcote &Yorke 1984). Despite the near ubiquity of this phenomenon, the causes and consequences of seasonal patterns of incidence are poorly understood. Infectious diseases account for more death and disability worldwide than either noninfectious disease or injury.

Wikipedia encyclopedia (2010), explains an infectious disease as a clinically evident illness resulting from the presence of pathogenic microbial agents, including pathogenic viruses, pathogenic bacteria, fungi, protozoa, multicellular parasites and aberrant proteins known as prions. These pathogens are able to cause disease in animals and or plants.

The most important infectious diseases throughout the world today include African trypanosomiasis, cholera, hepatitis A, B and C, HIV/AIDS, influenza, common cold, malaria, meningitis, onchocerciasis, tuberculosis and typhoid. Accurate caseload numbers are difficult to

determine especially because so many of these diseases are endemic in developing countries where many people do not have access to modern medical care.

The World Health Organization estimates that approximately half of all deaths caused by infectious disease each year can be attributed to just three diseases; tuberculosis, malaria and AIDS. Together, these diseases cause over three hundred million illness and more than five million deaths each year.

A fact of life is that at some point we all get sick. Catching a cold is as commonplace as morning coffee. In an effort to stay healthy, people take vitamin C supplements, get good exercise, and even consume herbal concoctions in an effort to keep their “resistance” up. However, do they know what their “resistance” entails? It is true that when an individual’s resistance is low, one can become sick. But, what is “resistance” and how does it work?

Resistance is better known as immunity. The immune system is the body’s defense mechanism against illness. The immune system includes the organs, tissues, cells and molecules responsible for immunity. The immune response is the collective and coordinated response to the introduction of foreign substances. The system enables the body to know the difference between self, and non-self. The body sees any illness or outside nuisance such as pollen, as a foreign substance. The body does not like foreign substances because they result in illness, pain, and other physically negative phenomena. That is why the body is set up to battle against what it perceives as an invader.

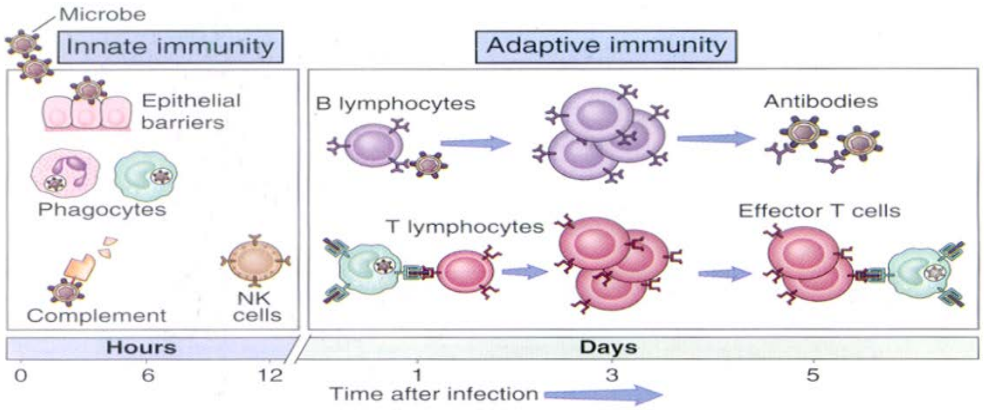
There are two types of immunity. The first is innate (natural or native or nonspecific) which refers to the basic resistance to disease that an individual is born with. The second one is the

specific or acquired or adaptive immunity which requires the activity of a functional immune system involving cells called lymphocytes and their products.

Innate defense mechanisms provide the first line of host defense against invading pathogens until an acquired immune response develops. They are present in all individuals and are effective at birth and function without requiring prior exposure to a microorganism or its antigens. Innate immunity, sometimes referred to as natural immunity, is present from birth, is nonspecific and includes numerous elements. These elements include body surfaces or barriers and internal components. Body surfaces, such as the skin, mucous membranes and the cough reflex, provide effective barriers to many microorganisms. Chemical influences, such as an acid pH and secretion of fatty acids and enzymes, also serve as barriers against invasion by foreign substances.

Acquired or adaptive or specific immunity reflects the presence of a functional immune system that is capable of specifically recognizing and selectively eliminating foreign microorganisms. It is not effective fully at birth and requires time to develop after exposure to the infecting agent or its antigens. Specific immunity may be acquired naturally by infection or artificially by immunization.

Figure 1.1 illustrates the various components of innate and acquired immunity.



Human immune system is a very complex and dynamic system that involves many different types of cells and immunological pathways. These cells are called lymphocytes which are T cells, B cells and natural killer cells. Natural killer (NK) cells are a part of innate immune system and play a major role in defending the host from both tumors and virally infected cells. NK cells distinguish infected cells and tumors from normal and uninfected cells by recognizing level changes of a surface molecule called MHC (major histocompatibility complex) class I. NK cells are activated in response to a family of cytokines called interferon. Activated NK cells release cytotoxic (cell-killing) granules which then destroy the altered cells.

T cells (Thymus cells) and B cells (bone cells) are the major cellular components of the adaptive immune response. T cells are involved in cell-mediated immunity whereas B cells are primarily responsible for humoral immunity (relating to antibodies). The function of T cells and B cells is to recognize specific “non-self” antigens, during a process known as antigen presentation. Once they have identified an invader, the cells generate specific responses that are tailored to maximally eliminate specific pathogens or pathogen infected cells. B cells respond to pathogens by producing large quantities of antibodies which then neutralize foreign objects like bacteria

and viruses. Following activation, B cells and T cells leave a lasting legacy of the antigens they have encountered, in the form of ***memory cells***. Throughout the lifetime of an animal these memory cells will "remember" each specific pathogen encountered, and are able to mount a strong response if the pathogen is detected again.

The immune response to infections also comes in different stages. Mathematical modeling using differential equations and dynamical systems has been used in the studies of immune response to various infections, most notably that of the HIV. The question now is how does the human body develop immunity or immune response to these infectious diseases such as viruses? The mathematical biologists (Anderson and May, 1992) proposed a theory and a mathematical model to explain this phenomenon.

A virus is a small infectious agent that can pass through filters that are designed to trap most bacteria. It is not a cell but simply a genetic informational molecule-DNA or RNA enclosed in a protein coat. Biologists do not consider a virus to be alive because it does not metabolize, respond to stimuli or even reproduce on its own. Some viruses' lack the enzymes required for nucleic acid replication and are dependent on the host cell for these functions also (Anderson and May, 1992). A virus requires a living host cell to manufacture more of it which is really all it can do. In the process, the virus usually damages or destroys the host cell, which is how disease begins. All kinds of organisms are therefore susceptible to viral infection.

A viral infection begins as a virus binds to a specific molecule on a cell surface and then injects its genetic material or is engulfed. Some viruses can integrate into the host's chromosome or remain as an extra piece of DNA within the cell and be perpetuated, sometimes for many years and even from generation to generation. The number of genes carried by different viruses may be

as few as 3 or as many as 250 but this is still much fewer than even the simplest bacterium. The illness produced by virus range from acute (death or recovery from infection), recurrent (repeated growth and decay in the virus population within an individual), unapparent (dormant infectious where the virus is not readily detectable), or subclinical (symptomless infection where the virus can be detected) (Anderson and May, 1992). Understanding of regularities in human immune response provides us with new powerful tool for stimulation of the immune system in order to increase its efficiency in the struggle against viral invasion. In view of this, the construction of models of human immune response to viral infection seems to be the only right tactics in the cognition of such regularities.

1.2 STATEMENT OF THE PROBLEM

At the dawn of the twenty first century humankind is faced with new, more resilient diseases including HIV/AIDS and hepatitis B that come along with a death toll from preventable infectious diseases that remain high due to poor sanitation and malnutrition among other conditions in many parts of the world. A good understanding of the dynamics of viral infections, modes in which diseases act is gained and an equally important understanding of how humans also respond to these diseases is gained will be helpful so that our natural countermeasures can be augmented with modern medicinal techniques.

1.3 OBJECTIVES OF THE STUDY.

The main objective of this study is to use an effective mathematical model to predict human immune systems' response to virus infectious diseases.

The specific objectives are as follows:

- To investigate the behaviour of lymphocytes in the human body in the absence of the virus.
- To investigate the behaviour of lymphocytes in the human body in the presence of the virus.
- To determine the stability of the systems of differential equations.

1.4 METHODOLOGY

Using the alarming rates of infectious diseases in developing countries over time, differential equations model is developed to predict human immune response to virus infectious diseases. Equilibrium points and their stability characteristics are analyzed for the set of systems of differential equations. Numerical methods through computer Matlab programs are used to determine solutions and investigate their behaviour.

1.5 SIGNIFICANCE OF THE STUDY

Ghana our beloved country is now caught in the tangle-web of both non-communicable and communicable diseases like malaria, hepatitis B, HIV/AIDS and tuberculosis and these pose a herculean health threat to the citizenries. Ghana Web (2004) reported that seven hundred and

twenty thousand people in Ghana were infected with the HIV/AIDS. The combination of non-communicable with the already gigantic load of communicable diseases in a third world country like Ghana is heavy enough to impact negatively on national efforts, peace, productivity and economic that are pertinent in its development.

All these facts support the need to research into infectious diseases. Even though, most researchers have done research in health related issues, they have not delved into the mechanisms undying how the human body develops immunity against such infections. It is my hope that the outcome of this study will help to reduce this alarming rate of infectious diseases. The outcomes of this study will help policy makers and stakeholders in the country to design programs for the control of virus infectious diseases. The results and recommendations are likely to create the much needed awareness and attention among citizens including health workers. The findings will also provide useful information to policy makers, stakeholders and especially educators who usually train greater percentage of the youth who are so vulnerable to such infectious diseases. This study can suggest new avenues for further research that will enhance techniques for effective control interventions.

Finally, it is an undisputable fact to say that the findings would add to the existing body of knowledge in the mechanisms undying human immunity and infectious diseases, their prevention and eradication.

1.6 THE SCOPE OF THE STUDY

The dynamics of viral infectious diseases and their immune response may be quite different. The mathematical biologists Anderson and May (1992) postulate that there are a large number (around 100 different types) of cold viruses and each of these requires its own immune response. This means that the results of this study should be interpreted with caution.

1.7 ORGANIZATION OF THE STUDY

The study is organized in five chapters as follows. Chapter one provides general background issues of the study. It also provides the statement of problem and it sets out the objectives of the study, provides the significance of the study as well as the scope of the study.

Chapter two reviews pertinent literature related to the study including some models of epidemiology. Chapter three describes systems of differential equations that are of the study. It also describes mathematical software (MATLAB) for solving the systems of these differential equations. Chapter three also considers the model, its development, the behaviour of lymphocytes. Chapter four discusses the methodological issues of the study and also discusses the empirical results and interprets the results. It also considers the analysis of equilibrium points of the model. The final chapter, which is chapter five, summarizes the main findings of the study and provides suggestions and recommendations.

CHAPTER 2

LITERATURE REVIEW

2.0 OVERVIEW.

The purpose of this chapter is to set the present study in the context of other studies of mathematical epidemiology. The mathematical theory of infectious diseases pioneered by Ross, MacDonald, Kermack, McKendrick, Anderson, May and others has played a major role in the study of the control and prevention of infectious diseases. In this section of the literature review, I will present the history of infectious diseases; in addition, I will discuss literature on compartmental models; the discussion will be based on compartments without births and deaths as well as compartments including births and deaths. I will also discuss mathematical methods that are required to analyze and solve the mathematical models. These methods include solution of ordinary differential equations and finally literature on human immune response to virus infectious diseases. These will be helpful for understanding the material presented in this thesis.

2.1 HISTORY OF VIRUS INFECTIOUS DISEASES.

According to topTnez.net (2008), of the top ten infectious diseases some of them have vaccinations, some have preventive measures while others are simply deadly with little chance of survival. To be included on this list, the virus has to be a major cause of death in history with ranking based on fatality rates and impact worldwide.

First on the list is human immunodeficiency virus (HIV) which leads to acquired immune deficiency syndrome (AIDS), which cripples a human's immune system. AIDS has been categorized as an epidemic by the CDC and the life expectancy has been extended despite the

lack of a vaccination or cure. While on its own, the Ebola virus is much more deadly in the short term, most AIDS victims eventually succumb to death from an AIDS related sickness. The first case of HIV/AIDS was reported in the year 1981 (Soar Media; 2010). It has killed about 25 million people worldwide.

Second on the list is the Ebola virus which was discovered in the last 30 years, this strain of viruses has a fatality rate between 50-89 percent. Known to be devastating to both humans and animals, Ebola will kill a person within a week to two weeks usually from multiple organ failure or hypodermic shock. A Canadian company recently reported that they have created a vaccine that is effective in 99 percent of the test cases of monkeys. Unfortunately, no vaccine or treatment has been approved for humans at this time.

The third on the list is Severe acute respiratory syndrome (SARS) has been only one major outbreak in Asia a few years ago. In most cases, the disease in its viral pneumonia form has a fatality rate of about 70 percent with the highest fatality rate among victims over the age of 65.

Influenza being the eighth on the list is perhaps the scariest virus on this list and is one that anyone anywhere can contract – influenza. Luckily, the flu is easily identified and in most countries easily combated. First cases were reported in 1918 -1920 worldwide killing an estimated number of 100 million people worldwide (Soar Media; 2010). However, young children and the elderly are particularly susceptible to flu. And the most famous strain was the Spanish Flu, which was estimated to have killed 2-5 percent of the human population in 1918-1919. Thankfully, that strain has never been seen again; however, the flu virus is famous for mutating from animals to humans.

The tenth on the list is Small pox. This variola virus had many forms and continues to be a required vaccination for many countries. Smallpox in its worse forms – hemorrhagic and flat – had the highest fatality rates with only a 10 percent or less chance of survival. Fortunately this disease has been the only one on this list to be completely eradicated from nature since it is only contagious through humans.

In 2002, American researchers reported the first polio-like paralysis stemming from West Nile virus. (www.cbc.ca/technology/story/2008/08/19) Poliomyelitis (from the Greek Polios (grey) and myelos (marrow); also known as infantile paralysis) was first recognized as a distinct human disease by Jacob Heine in 1840. A major causative agent of poliomyelitis is poliovirus. (www.nature.com/nrmicro/journal /vs./n12/box).

The West Nile virus was first isolated in the West District of Uganda in 1937. The West Nile virus (WNV) is currently distributed over a wide area encompassing Africa, Europe, the Middle East, Central Asia, West Asia and North America. (Burnet, 1944). It first appeared in the United States in 1999.

Hepatitis was first identified as being transmitted through blood in Germany in 1883 but it was not until 1947 that the term Hepatitis B is the leading cause of liver cancer in the world .(The Hepatitis Foundation of New Zealand,2007). Hepatitis B virus, the most serious type of viral hepatitis can cause infection chronic carrier status and chronic hepatitis (The World Health Organization, 2000). A researcher works on a vaccine for H1N1 flu virus at the infectious Disease Laboratory at the centers for Disease Control in Atlanta, Georgia-G ENEVA as stated by the head of the World Health Organization (2009).

Ross River virus is also an infectious disease characterized by fever, swollen painful joints and skin rashes. It first occurred in Australia in 1928. (www.cigna.com/healthinfo/novol 145.html).

In 2003, there were more than half a million deaths worldwide caused by measles. The majority of these deaths were children. (Mann, 2009).

The spread of infectious disease continue to attract attention despite the numerous researches conducted and control measures put in place. This is because data on infectious diseases and especially virus infectious diseases have for many years being with us and continue to be part of us. It should be noted that the spread of these infectious diseases in a population depends on many factors such as the behaviour of the disease and also the structure of the population.

It is an established fact that there are some individuals in a population who have many interactions with others which are sufficient to bring about infection while others have only a few interactions which are not sufficient to bring about infection. For instance, school children have many more opportunities to contract and spread diseases such as measles and chickenpox then most adults have. In other sense, people with more sexual partners are able to contract and spread diseases than their counterparts with fewer sexual partners. Realistic analysis of disease transmission in a heterogeneous population often requires the model to include subpopulations each of which is homogenous in the sense that individuals in it have similar contact rates with other subpopulations and have similar recovery rates. (Hethcote, 1985). This makes it so important to discuss compartmental model as a basis of the model to be developed to enhance understanding of the study.

2.2 COMPARTMENTAL MODEL.

In order to model the progress of an epidemic in a large population comprising many different individuals in various fields, such population diversity must be reduced to a few key characteristics which are relevant to the infection under consideration. For instance, for most common childhood diseases that confer long-lasting immunity it is important to divide the population into those who are susceptible to the disease, those who are infected and those who have recovered and are immune. These subdivisions of the population are called **compartments**. A model in which members of a host population are assigned to compartments on the basis of their infection status or other attribute, and the changes in the size of compartments are described as a dynamic system (Roberts and Heesterbeek 2003). Generally, diseases transmitted by viral agents, such as influenza, measles, rubella (German measles), and chicken pox, confer immunity against reinfection, while diseases transmitted by bacteria, such as tuberculosis, meningitis, and gonorrhea, confer no immunity against reinfection. Other diseases, such as malaria, are transmitted not directly from human to human but by vectors, which are agents (usually insects) who are infected by humans and who then transmit the disease to humans. I will be concerned with both epidemics which are sudden outbreaks of a disease, and endemic situations, in which a disease is always present.

2.2.1 THE KERMACK–MCKENDRICK MODEL.

This is a compartmental model with the population under study being divided into compartments and with assumptions about the nature and time rate of transfer from one compartment to another. Diseases that confer immunity have a different compartmental structure from diseases without immunity. They used the terminology **SIR** to describe diseases which confer immunity

against re-infection. This was used to indicate that the passage of individuals is from the susceptible class **S** to the infective class **I** to the removed **R** (either by immunity, death or isolated) class. On the other hand, the terminology **SIS** was used to describe a disease with no immunity against re-infection to indicate that the passage of individual is from the susceptible class to the infective class and then back to the susceptible class. Other possibilities include **SEIR** and **SIRS** models with exposed between being infected and becoming infective and **SIRS** models with temporary immunity on recovery from infection. The independent variable in their compartmental models is the time ***t*** and the rates of transfer between compartments are expressed mathematically as derivatives with respect to time of the sizes of the compartments, and as a result their models were formulated initially as ***differential equations***.

In order to model such an epidemic they divided the population being studied into three classes labeled ***S, I,*** and ***R***. They let ***S* (*t*)** denote the number of individuals who are susceptible to the disease, that is, who are not (yet) infected at time ***t.*** ***I* (*t*)** denoted the number of infected individuals, assumed infectious and able to spread the disease by contact with susceptible. *R* (*t*) denoted the number of individuals who have been infected and then removed from the possibility of being infected again or of spreading infection. Removal was carried out either through isolation from the rest of the population or through immunization against infection or through recovery from the disease with full immunity against re-infection or through death caused by the disease. These characterizations of removed members are different from an epidemiological perspective but are often equivalent from a modeling point of view which takes into account only the state of an individual with respect to the disease.

In formulating models in terms of the derivatives of the sizes of each compartment they assumed that the number of members in a compartment is a differentiable function of time. This may be a

reasonable approximation if there are many members in a compartment, but it is certainly suspect otherwise. In formulating models as differential equations, they assumed that the epidemic process is *deterministic*, that is, the behaviour of a population is determined completely by its history and by the rules which describe the model.

The special case of the model proposed by Kermack and McKendrick (1927), which is the starting point for the study of epidemic models, is

$$S' = -\beta SI \tag{2.01}$$

$$I' = BsI - \alpha I \tag{2.02}$$

$$R' = \alpha I \tag{2.03}$$

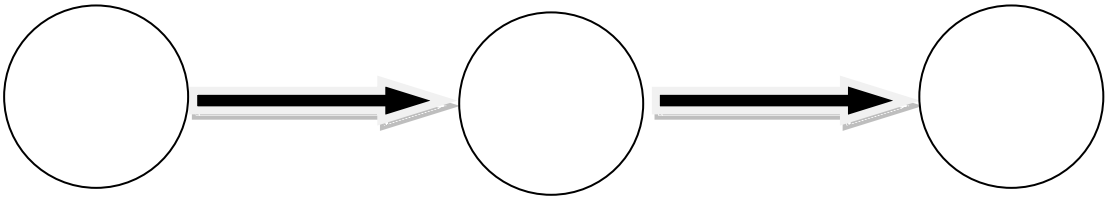


Figure 2.1: A flow chart of SIR model.

2.2.1.1 Assumptions of Kermack-Mckendrick Model

(1) An average member of the population makes contact sufficient to transmit infection with ***βN*** others per unit time, where **N** represents total population size (mass action incidence).

(2) Infective leave the infective class at rate ***αI*** per unit time.

(3) There is no entry into or departure from the population, except possibly through death from the disease. According to assumption 1, the probability that a random contact by an infective is with a susceptible, who can then transmit infection, is ***S/N,*** therefore the number of new infections in unit time per infective is ***(βN)(S/N),*** giving a rate of new infections ***(βN)(S/N)I =***

βSI. Alternately, we may argue that for a contact by a susceptible the probability that this contact is with an infective is ***I/N*** and thus the rate of new infections per susceptible is **(*βN*) (*I/N*),** giving a rate of new infections **(*βN*)(*I/N*)*S* = *βSI*.** It is important for us to note that both approaches give the same rate of new infections which means that there are situations which one may be more appropriate than the other. Algebraic expression for ***N*** was neglected since it cancels out of the final model, but it should be noted that for a disease that is fatal to all who are infected ***N* = *S*+*I*;** while, for a disease from which all infected members recover with immunity, ***N* = *S* +*I* +*R*.** The hypothesis (3) really says that the time scale of the disease is much faster than the time scale of births and deaths so that demographic effects (births and deaths) on the population may be ignored. An alternative view is that they were only interested in studying the dynamics of a single epidemic outbreak.

The assumption (2) requires a fuller mathematical explanation, since the assumption of a recovery rate proportional to the number of infective has no clear epidemiological meaning. They considered the "cohort" of members who were all infected at one time and let ***u*(*s*)** denoted the number of those who were still infective '***s***' time units after having been infected. If a fraction ***α*** of those who leave the infective class in unit time then

$u' = -\alpha u$, and the solution of this elementary differential equation is

$u(s) = u(0)\, e^{-\alpha s}$

Thus, the fraction of infective remaining infective '***s***' time units after having become infective is $e^{-\alpha s}$, so that the length of the infective period is distributed exponentially with mean

$\int_0^\infty e^{-\alpha s} ds = 1/\alpha$, and this is what (2) really assumes. The assumptions of a rate of contacts proportional to population size N with constant of proportionality β, and of an exponentially distributed recovery rate are unrealistically simple.

In their model R is determined since S and I are known, and they dropped the R equation from their model, leaving the system of two equations

$$S' = -\beta SI \qquad (2.04)$$

$$I' = (BsI - \alpha) I \qquad (2.05)$$

They were unable to solve this system analytically but they learnt a great deal about the behaviour of its solutions by the following qualitative approach. They made the assumption that the model makes sense when $S(t)$ and $I(t)$ remain non-negative. Thus if either $S(t)$ or $I(t)$ reaches zero they considered the system to have terminated. They observed that $S \leq 0$ for all t and $I \geq 0$ if and only if $S > \alpha/\beta$. Thus I increases so long as $S > \alpha/\beta$ but since S decreases for all t, I ultimately decreases and approaches zero. If $S(0) < \alpha/\beta$, I decreases to zero (no epidemic), while if $S(0) > \alpha/\beta$, I first increases to a maximum attained when $S = \alpha/\beta$ and then decreases to zero (epidemic). The quantity $\beta S(0)/\alpha$ is a threshold quantity, the ***basic reproduction number*** and denoted by R_0, which determines whether there is an epidemic or not. If $R_0 < 1$ the infection dies out, while if $R_0 > 1$ there is an epidemic. For their model the basic reproduction number was given by

$$R_0 = \frac{K\beta(K)}{\alpha}$$

because a single infective introduced into a wholly susceptible population makes $C(K) = K\beta(K)$ contacts in unit time, all of which are with susceptible and thus produce new infections, and the mean infective period is $1/\alpha$.

The Kermack-Mckendrick model in 1927 did not factor demographic effects (birth and death). This means that the model can only be applied to epidemic situations in which the disease outbreak is of a very short period. Anderson and May extended and explored in more detail this model by including demographic effect.

2.2.2. FRED BRAUER'S MODEL.

They described and analyzed compartmental models for disease transmission. They began with models for epidemics, showing how to calculate the basic reproduction number and the final size of the epidemic. They also studied models with multiple compartments, including treatment or isolation of infectives. They then considered models including births and deaths in which there may be an endemic equilibrium and studied the asymptotic stability of equilibria. They concluded by studying age of infection models which give a unifying framework for more complicated compartmental models.

They were concerned both with epidemics which are sudden outbreaks of a disease, and endemic situations, in which a disease is always present. Epidemics such as the 2002 outbreak of SARS, the Ebola virus and avian flu outbreaks are events of concern and interest to many people. The1918 Spanish flu epidemic caused millions of deaths, and a recurrence of a major influenza epidemic is a dangerous possibility. Their goal was to provide introduction to mathematical epidemiology, including the development of mathematical models for the spread of disease as well as tools for their analysis.

They began with an introduction to epidemic models and extended it to incorporate demographic effects into the models to explore endemic states and they finally described models with infectivity depending on the age of infection. The approach they used was a qualitative one. That is rather than attempting to find explicit solutions of the systems of differential equations which will form their models; they were concerned with the asymptotic behaviour, which is the behavior as $t \longrightarrow \infty$ of solutions.

2.2.3 MATHEMATICS OF EQUILIBRIUM POINT AND STABILITY OF DYNAMICAL SYSTEMS.

In this section we review the mathematical methods for analyzing equilibrium points and their stability for a system of first-order nonlinear differential equations. The definitions of equilibrium point and stability are as follows:

Definition: A point Xe is an *equilibrium point* (or stationary point or singular point or critical point or rest point) of the differential equation

$\frac{dX}{dt} f(t, X)$ if there exists a finite time t* such that $f(t,X) = 0$ for all $t \geq t^*$

Note: In the special case of an autonomous system in which **f** is a function of X only,

i.e., $f(t, X) = f(X)$, then if Xe is an equilibrium point of $\frac{dX}{dt} = f(X)$ at t*, then it is an equilibrium point for all $t \geq t^*$

Definition: An equilibrium point x^* of the scalar differential equation

$\frac{\mathbf{dx}}{\mathbf{dt}} = \mathbf{f(x)}$ is a point for which $f(x^*) = 0$.

Definition: An equilibrium point Xe of $\frac{dx}{dt} = f(x)$ is *stable* if for every $\delta > 0$ and any $t_0 \in R^+$ there is $\omega(\delta, t_0) > 0$ such that $|u(t, t0, \gamma) - Xe| < \delta$ for every $t \geq t_0$ whenever $\gamma - Xe < \omega(\delta, t_0)$ where $u(t, t_0, \gamma)$ is a solution of $\frac{dx}{dt} = f(x)$ with the initial condition $X(t_0) = \gamma$

Definition: The equilibrium point Xe of $\frac{dx}{dt} = f(x)$ is *asymptotically stable* if

1. it is stable and

2. for every $t_0 \geq 0$ there is an $\varepsilon(t_0) > 0$ such that

$$\lim_{t \to \infty} u(t, t_0,) = Xe$$

whenever $|\gamma - Xe| < \varepsilon(t_0)$

Definition The equilibrium point X=Xe of $\frac{dx}{dt} f(t, X)$ is unstable if it is not stable.

2.2.4 BASIC REPRODUCTION RATE.

The Basic Reproduction rate sometimes called number or ratio is one of the most useful threshold parameters which characterize mathematical problems concerning infectious diseases. The Basic Reproduction rate is widely used in mathematical epidemiology models. It is formally defined as follows:

Definition: The *basic reproduction rate* R_0 is the average number of secondary infections produced when one infected individual is introduced into a host virgin population.

Note that if R0 <1 then the number of secondary infections is less than the number of initial infections and the disease will die out. If R0 >1 then the number of secondary infections is greater than the number of initial infections and the number of people infected with the disease

will increase and an epidemic may occur. The basic reproduction rate also gives a measure of the stability of any disease-free equilibrium point of the mathematical model of the disease.

2.2.5 LINEARIZATION STABILITY ANALYSIS.

Although it is usually not easy to determine the stability of an equilibrium point of a system of differential equations, the determination of the asymptotic stability is usually quite easy. The method involves linearization of the equations about the equilibrium point and the determination of the stability of the linearized equations. Solving a differential equation can be done in three major ways: analytical, qualitative, and numerical. Some of these analytical techniques (for example: linear, separable, and Bernoulli equations) and Euler's Method illustrate the use of numerical techniques in solving differential equations. For the qualitative approach, drawing slope field of a differential equation can show how this can be helpful when other techniques fail. When the differential equation is autonomous, more can be said about the solutions using qualitative techniques. The numerical calculation of eigenvalues of matrices can now easily be carried out with many mathematical software packages (e.g., Matlab, Maple, Mathematica). The linearization method examines the behaviour of the system close to equilibrium point. The stability of the equilibrium point can be determined by finding the eigenvalues of the system. The linear system in $\frac{dx}{dt}$ f (t, X) has an equilibrium point at x*=0. In the theory of equilibrium points of linear systems of the form $\frac{dx}{dt}$ J(x*) x, it is known that x = 0 is an equilibrium point and that solutions have the time dependence $e^{\lambda t}$, where λ is an eigenvalue of J(x*).Therefore the equilibrium point 0 is asymptotically stable if the real parts of all eigenvalues of J(x*) are negative and not asymptotically stable if the real part of some eigenvalue is greater than zero. A

critical value for asymptotic stability is therefore that the real part of some eigenvalue is zero and the real parts of all eigenvalues are less than or equal to zero.

Using the linear results, the linearized test for the equilibrium point of a nonlinear system will be asymptotically stable if the real parts of all eigenvalues of the Jacobian are negative and not asymptotically stable if the real part of some eigenvalues is positive. The test fails if the real part of any eigenvalue is zero. The equilibrium point is a stable node if the eigenvalues are real and negative. It is an unstable node if the eigenvalues are both real and positive. The equilibrium point is unstable saddle point if the eigenvalues are real and opposite in sign. It is a stable focus if the eigenvalues are complex with negative real parts. The equilibrium point is unstable focus if the eigenvalues are complex with positive real parts. The equilibrium point is a center if its eigenvalues are complex with zero real parts.

2.2.6 THE ANDERSON AND MAY SIR MODEL.

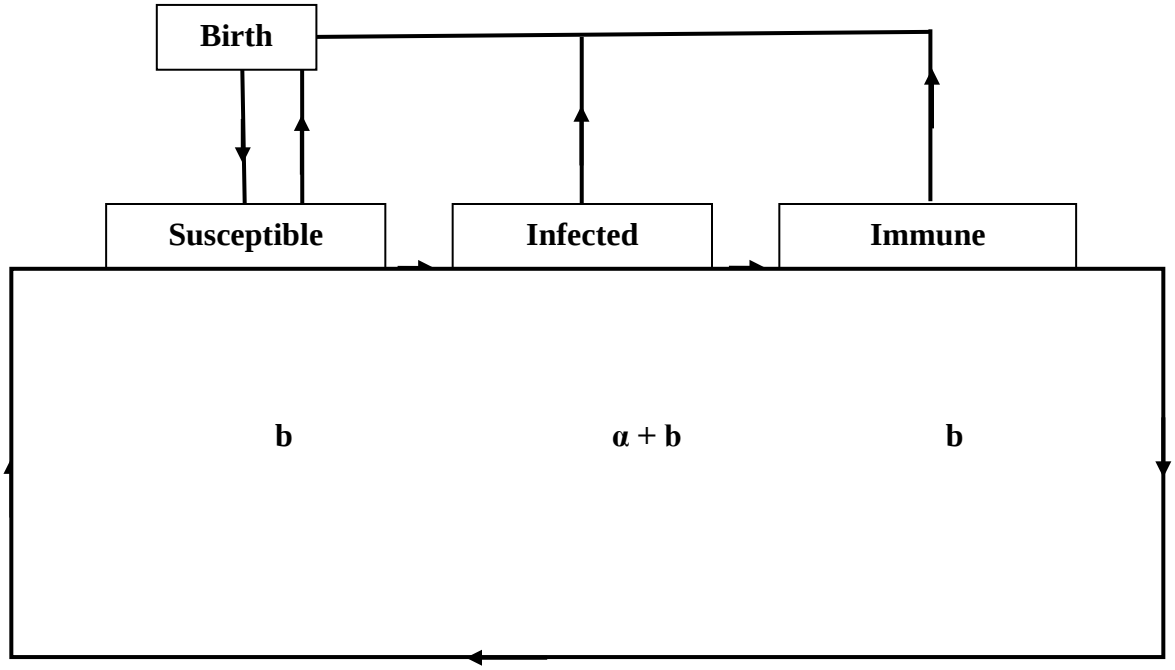


Figure 2.2

Schematic representation of the flow of hosts between susceptible **(X (t)),** infected **(Y (t))** and immune or recovered **(Z (t))** classes which records the dynamic interaction between a directly transmitted micro parasite and its host population. In this diagram, hosts reproduce at a per capita rate **'a'** and die at a per capita rate **'b'**. The infected hosts experience an additional death rate **'α'**, induced by micro parasitic infection. The average durations of stay in the infected and immune classes are denoted by $1/\nu$ and $1/\gamma$ respectively. The transmission coefficient which determines the rate at which new infections arise as a consequence of mixing between the susceptible and infected individuals is defined by **β.** They also showed the relationship between the incubation, latent and infections periods for a hypothetical micro parasitic infection.

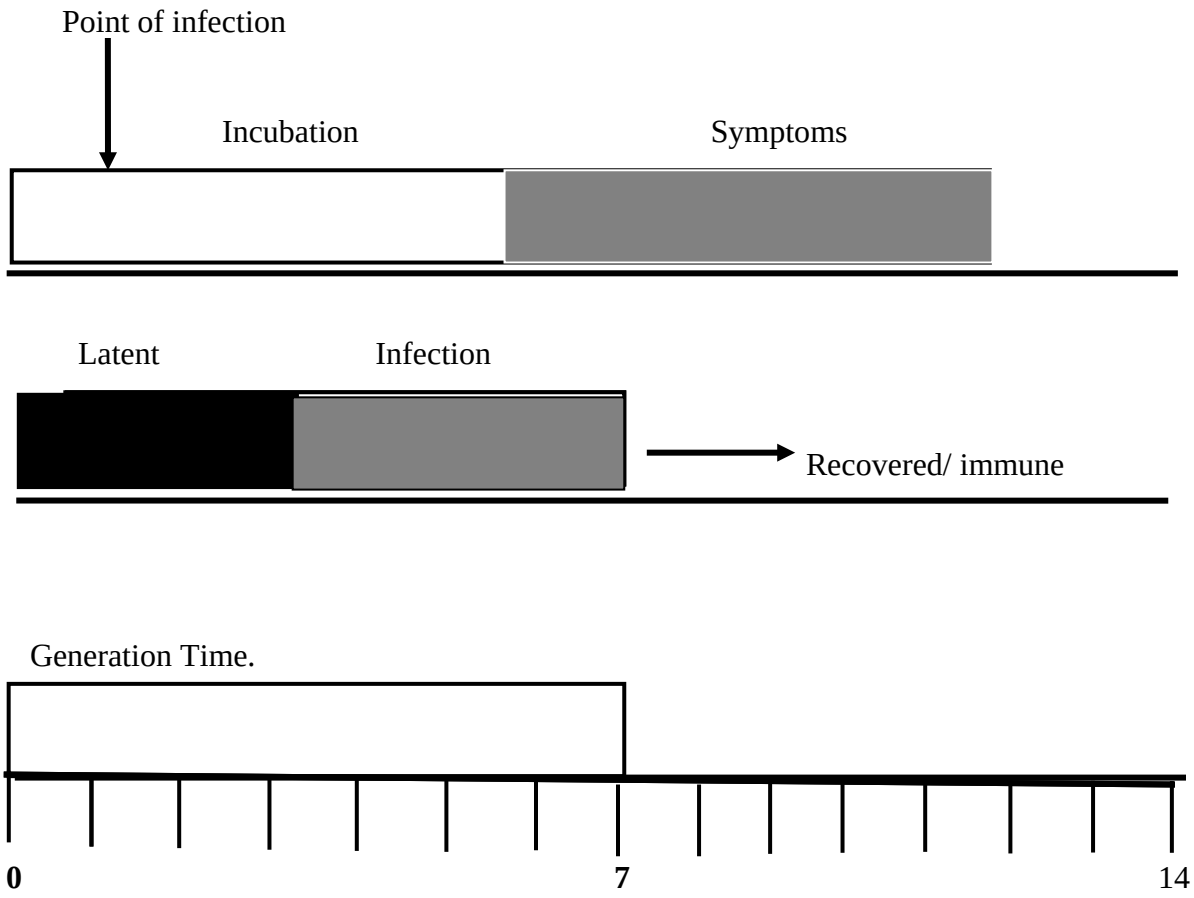


Figure 2.3: Diagrammatic illustration of the relationship between the incubation, latent and infectious periods for a hypothetical micro parasitic infection. They questioned us to note that the infectious period and the duration of symptoms of disease are not necessarily simultaneous.

2.2.7 ANDERSON AND MAY MODEL ON HUMAN IMMUNE RESPONSE TO VIRUS INFECTIOUS DISEASES.

According to Anderson and May (1992), viruses must enter a host cell to proliferate since they lack the necessary machinery to manufacture proteins and metabolize sugars. Some viruses also lack the enzymes required for nucleic acid replication and are dependent on the host cell for these functions also. The number of genes carried by different viruses may be as few as 3 or as

many as 250, but this is still much fewer than even the simplest bacteria. They continued to say that a typical virus infection starts with local invasion of an epithelial surface and then after one or more phases of replication and population growth (viraemic phases) results in infection of the target organ such as the skin, lungs and the nervous system.

They also said that the relevance of any particular immunological defense mechanism (that antibody or cell mediated immunity) depends on the way the viral antigens (largely proteins or glycoprotein) and viron (a single infective virus unit) are uncounted by the hosts defense system (Roitt et al, 1985). They explained that a viral antigen binds to the small number of cells that initially recognize it and induces them to proliferate so that they now constitute sufficient cells to mount (via antibody production by the B cells) an effective immune response. That is an antigen selects the specific clones of antigen – bonding cells and causes their proliferation. This process occurs both for the B-lymphocytes which proliferate and mature into antibody cells and for the T lymphocytes which are involved in the recognition and destruction of virally infected cells.

They continued to explain that following the infection of the host at time t = 0, viral abundance grows exponentially until the effectors cell population (stimulated to proliferate by the presence of the virus) is of sufficient size to cause a decline in the size of the virus population.

They said that once an immune response is initiated by viral infection, the components of the response such as B and T cells are capable of immense replication. Experiments involving the transfer of stimulated lymphocytes into irradiated recipient hosts (that is the immunological system of the recipient is effectively inactivated) demonstrate that if given the opportunity a clone of B cells will continue to expand indefinitely (Bach et al.1979). It is thus evident that some form of feedback mechanism must act to regulate the immune system. An alternative

hypothesis advanced by Jerne (1974), is that regulation is achieved even in the absence of foreign antigens by interactions between cell and antibody types within the host. In its simplest form such regulation is envisaged as a symmetric network in which cell type 1 acts as antigen to cell type 2 and vice versa. Thus 1 mounts an immune response to 2 and suppresses its abundance and 2 mount an immune response to 1 which concomitantly limits 1's abundance. A useful conceptual analogy is to envisage 1 and 2 operating in a two-way predator-prey interaction in which 1 is both predator and prey to 2 and vice-versa. In its original form, Jerne's so-called network regulation theory was symmetrical in form such that cell type 1 acted as antigen to 2, 2 acted as antigen to 3, 3 acted as antigen to 4 and so on (Jerne, 1974).

They defined two types of effectors cells (lymphocytes) whose abundances are denoted by E_1 (t) and E_2 (t) at time t. Their study was in two parts. The first part consisted of the behaviour of lymphocytes in the absence of the virus while the second part consisted of the behaviour of lymphocytes in the presence of the virus.

2.2.7.1. BEHAVIOUR OF LYMPHOCYTES IN THE ABSENCE OF THE VIRUS.

Anderson and May posit the existence of two lymphocyte populations (effectors cells) whose abundances are denoted by E_1 (t) and E_2 (t) at time t. In the absence of the virus, the populations of the lymphocytes are regulated by interactions between them. They came out with assumptions based on the key properties of the lymphocytes.

2.2.7.1.1 The Assumptions of the Model.

- New cells of type I are recruited from the bone marrow at constant rates A_1 and A_2
- Cells of type I die at a per capita rate $\boldsymbol{\mu_1}$and $\boldsymbol{\mu_2}$.

- Cells of type 1 are triggered to proliferate by contact with cell type 2 and vice versa.
- The respective proliferation responses saturate to a maximum net rate which is dependent on the product of their respective densities.

They explained that these assumptions in the absence of foreign antigens lead to the following pair of predator-prey –like interaction equations.

$$\frac{dE_1}{dt} = A_1 - \mu_1 E_1 + \frac{a_1 E_1 E_2}{1 + b_1 E_1 E_2} \tag{2.06}$$

$$\frac{dE_2}{dt} = A_2 - \mu_2 E_2 + \frac{a_2 E_1 E_2}{1 + b_2 E_1 E_2} \tag{2.07}$$

The terms a_i and b_i are arbitrary constants that determine the degrees of proliferation arising from cell-cell interaction and the levels at which the net rates of proliferation saturate. The first two terms on the right of each equation correspond to the first two properties or assumptions. The complicated term that follows models the interaction between the two types of lymphocytes. They made us aware that for small values of the product E_1E_2, this term accounts for a rate of increase that is roughly proportional to the product. It should also be noted that as the product increases, the rate of increase goes no higher than $\frac{a_i}{b_i}$.

It is seen that the general form of both equations (2.1) and (2.2) are in the form as presented below;

$$E'_i = A_i - \mu_i E_i + \frac{a_i E_i E_i}{1 + b_i E_1 E_2} \tag{2.08}$$

They explained that the growth of the lymphocytes population is determined by three factors; the constant rate A_i at which lymphocytes are being produced by bone marrow, the self-decay of the lymphocytes at the rate $\boldsymbol{\mu_i}$ and the interaction between the two populations of lymphocytes which saturates, that is approaches $\frac{\mathbf{a_i}}{\mathbf{b_i}}$ as $\mathbf{E_1E_2} \longrightarrow \infty$. The systems of equations were extremely difficult to solve explicitly. Therefore, the approach used was to gain a general understanding of how solutions to the system behave without finding the solutions outright.To begin with, they assigned the constants the following values:

$A = A_1 = A_2 = 1$, $\mu = \mu_1 = \mu_2 = 1.25$, $a = a_1 = a_2 = 0.252$ and $b = b_1 = b_2 = 0.008$

Since the system display a high degree of symmetry, they proceeded by finding the equilibrium points, that is, the points at which $\mathbf{E'_1 = E'_2 = 0}$. Setting the equations equal,

$$A_1 - \boldsymbol{\mu}_1 E_1 + \frac{\mathbf{a_1 E_1 E_2}}{\mathbf{1 + b_1 E_1 E_2}} = A_2 - \boldsymbol{\mu}_2 E_2 + \frac{\mathbf{a_2 E_1 E_2}}{\mathbf{1 + b_2 E_1 E_2}} \quad (2.09)$$

$$0 = A - \boldsymbol{\mu} E + \frac{\mathbf{a E^2}}{\mathbf{1 + b E^2}} \quad (2.10)$$

$$0 = \boldsymbol{\mu} b E^3 + (a + Ab)\,\mathbf{E^2} - \boldsymbol{\mu E} + A \quad (2.11)$$

The solution was found explicitly using Cardano's Formula.

The equilibrium points were found in the positive quadrant.The three equilibrium points were found to $\binom{\mathbf{E_1}}{\mathbf{E_2}} = \binom{\mathbf{1}}{\mathbf{1}}, \binom{\mathbf{5}}{\mathbf{5}}$ **and** $\binom{\mathbf{20}}{\mathbf{20}}$

The system was linearnized by calculating a two by two matrix of the partial derivatives,called the Jacobian (J) and is given by;

$$J(E_1,E_2) = \begin{bmatrix} \frac{\partial E'_1}{\partial E_1} & \frac{\partial E'_1}{\partial E_2} \\ \frac{\partial E'_2}{\partial E_1} & \frac{\partial E'_2}{\partial E_2} \end{bmatrix} \quad (2.12)$$

$$J(E_1, E2) = \begin{bmatrix} -\mu_1 + \frac{a_1 E_2}{(1+b_1 E_1 E_2)^2} & \frac{a_1 E_1}{(1+b_1 E_1 E_2)^2} \\ \frac{a_1 E_1}{(1+b_1 E_1 E_2)^2} & -\mu_2 + \frac{a_1 E_2}{(1+b_1 E_1 E_2)^2} \end{bmatrix} \quad (2.13)$$

The system was analyzed by calculating the Jacobian at each equilibrium point and the corresponding eigenvalues were found.

TABLE 2.1: CLASSIFICATION OF THE EQUILIBRIUM POINTS.

EQUILIBRIUM POINT	EIGENVALUES	CLASSIFICATION
(1, 1)	λ_1= - 1.25, λ_2= -0.75	Nodal Sink
(5, 5)	λ_1= -1.25, λ_2= 0.50	Saddle Point
(20, 20)	λ_1= -1.25, λ_2= - 0.68	Nodal Sink

The classification of the equilibrium points allowed them to qualitatively describe the behavior of the system for all initial values. The two nodal sinks will attract solution curves that begin near them and that between these two is a saddle point that will 'bend' solution curves near it. They based on this to predict that there will be two basins of attraction, one for each nodal sink that are bounded by an unstable solution curve that passes through the saddle point

2.2.7.2 BEHAVIOUR OF THE LYMPHOCYTES IN THE PRESENCE OF THE VIRUS.

According to them, when the body is invaded by the virus, the interaction between the lymphocytes and the virus has the following properties:

(1) The virus cells have an intrinsic growth rate r.

(2) Lymphocytes of type 1 kill virus cells in proportion to the numbers of contacts between them and they proliferate because of these contacts.

(3) Lymphocytes of type 2 do not directly interact with virus but they continue to regulate the growth of cells of type 1 as before. They let V (t) denote the number of virus cells in the body. As a result of these interactions, they came out with these systems of differential equations;

$$\mathbf{E'}_1 = A_1 - \boldsymbol{\mu_1} E_1 + \frac{\mathbf{a_1 E_1 E_2}}{\mathbf{1 + b_1 E_1 E_2}} + KVE_1 \qquad (2.14)$$

$$\mathbf{E'}_2 = A_2 - \boldsymbol{\mu_2} E_2 + \frac{\mathbf{a_2 E_2 E_2}}{\mathbf{1 + b_2 E_1 E_2}} \qquad (2.15)$$

$$\mathbf{V'} = rV - kVE_1 \qquad (2.16)$$

The term $\boldsymbol{rV}$ represents the intrinsic growth rate of the virus and $\boldsymbol{kVE_1}$ represents the rate at which virus cells are destroyed by type 1 lymphocytes. The term $\boldsymbol{KVE_1}$ represents the rate of growth of type 1 lymphocytes due to interactions with the virus.The equations show that only one population of lymphocytes actively attacks virus cells while the other merely regulates both lymphocytes populations.

To analyze the system, they again found the equilibrium points. According to them if

V = 0, $\mathbf{V}' = 0$ and the term in equation (2.9) that interacts with (3.0) is also eliminated. Therefore, the equilibrium points are similar to those already found $\begin{pmatrix} \mathbf{E_1} \\ \mathbf{E_2} \\ \mathbf{E_3} \end{pmatrix} = \begin{pmatrix} \mathbf{1} \\ \mathbf{1} \\ \mathbf{1} \end{pmatrix}, \begin{pmatrix} \mathbf{5} \\ \mathbf{5} \\ \mathbf{5} \end{pmatrix}$ and $\begin{pmatrix} \mathbf{20} \\ \mathbf{20} \\ \mathbf{20} \end{pmatrix}$.

The eigenvalues determined from the characteristic polynomial of the Jacobians and the stability of each equilibrium point is given in table 2.2.

TABLE 2.2 CLASSIFICATIONS OF THE EQUILIBRIUM POINTS.

EQUILIBRUIM POINT	EIGENVALUES	CLASSIFICATION
(1, 1, 0)	λ_1= - 1.25, λ_2= -0.75397, λ_3= 0.09	Unstable
(5, 5, 0)	λ_1= -1.25, λ_2= 0.5, λ_3= 0.05	Unstable
(20, 20, 0)	λ_1= -1.25, λ_2= - 0.67857, λ_3= -0.1	Asymptotically table

It is now clear that the only stable equilibrium point in the presence of a virus is at (20, 20, 0), they therefore predicted that all solution curves approach $E_1 = E_2 = 20$ and V= 0 as t $\longrightarrow$0.

The special case of the model proposed by Anderson and May (1992) had been the starting point of my study. Even though much credit is given to these scholars, they remained silent on the activities of natural killer cells which provide the first line of defense as the B and T lymphocytes get recruited when the body is invaded with the virus. This study therefore takes into consideration the activities of these natural killer cells in addition to the B and T lymphocytes. The behaviour of lymphocytes in the absence of the virus will be considered but instead of considering two lymphocytes population, three lymphocytes populations will be considered. Again, the behaviour of lymphocytes in the presence of the virus will also be

considered. Under this, the behaviour of these lymphocytes in the innate immune response stage of the viral infection, the behaviour of the lymphocytes in the adaptive immune response stage of viral infection and finally consider the combined effects of both innate and adaptive immune responses stage. This is the stage where the adaptive immune response had just begun and the innate is just about to end. Instead of using Cardano's formula in evaluating the roots of the characteristics equation which Anderson and May (1992), MATLAB will be used to solve the differential equations as well as drawing the solution curves and the phase planes of the systems of differential equations.

CHAPTER 3

METHODOLOGY

3.0 OVERVIEW

In this chapter, we present the model that will be used to study the human immune response to virus infectious diseases. The model is an extension of the two systems of differential equations model for virus infectious diseases as discussed by Anderson and May (1992). The equilibrium points and their stability for the systems of the extended differential equations will be analyzed. The methods for numerical solution of these equations using Matlab will then be discussed.

3.1 DEVELOPMENT OF THE MODEL

The model has been considered in two phases. The first phase describes the behaviour of lymphocytes in the absence of the virus. The second phase describes the behaviour of the lymphocytes in the presence of the virus. This second phase model describes three main stages. The first is the innate immune response stage of viral infection; the second is the overlap of innate and adaptive immune responses stage of viral infection and lastly the adaptive immune response stage. The first model involves three types of lymphocyte populations denoted by T(t), B(t) and N(t). The innate immune response stage of viral infection model involves one type of lymphocyte population denoted by N(t) and the virus population denoted by V(t) . The overlap of innate and the adaptive immune responses stage of viral infection model also involves three types of lymphocyte populations denoted by T(t), B(t) and N(t) and also the virus population denoted by V(t).

3.1.1 BEHAVIOUR OF LYMPHOCYTES IN THE ABSENCE OF THE VIRUS

There exist three lymphocyte populations T(t), B(t) and N(t). In the absence of the virus, there is a limited number of each of these population types and these populations are regulated by the interactions between them. The following assumptions have been made based on the key properties of these three population types;

- new lymphocytes of type i are produced by the bone marrow at a constant rates $A_{1,}$ A_2 and A_3 respectively.
- lymphocytes of type i die at a per capita rate of $\boldsymbol{\mu}$.
- lymphocytes of the three types proliferate due to contact with one another at a rate that saturates for large values of T, B and N.

The assumptions lead to this system of differential equations;

$$T' = A_1 - \mu_1 T + \frac{a_1 TBN}{(1+b_1 TBN)} \quad (3.01)$$

$$B' = A_2 - \mu_2 B + \frac{a_2 TBN}{(1+b_2 TBN)} \quad (3.02)$$

$$N' = A_3 - \mu_3 N + \frac{a_3 TBN}{(1+b_3 TBN)} \quad (3.03)$$

3.1.2 BEHAVIOUR OF LYMPHOCYTES IN THE PRESENCE OF THE VIRUS

When the body is invaded by the virus, the natural killer cells denoted by N(t) provide a first line of defense as the T and B lymphocytes get recruited to fight these invaders. The interaction between the lymphocytes and the virus cells are in two phases which have been presented below.

3.1.2.1 INNATE IMMUNE RESPONSE (1^{ST} - 7^{TH} DAY)

The interaction between the virus cells and the natural killer cells occurs at the first day of the viral infection as they try to provide a first line of defense when the human body is infected with virus. The interaction between these two cells has the following key properties;

- new lymphocytes of type 3 are produced by the bone marrow at a constant rate A_3.
- lymphocytes of type 3 die at a per capita rate of $\boldsymbol{\mu}$.
- lymphocytes of type 3 kill virus cells in proportion to the number of contacts between them.
- the virus cells have an intrinsic growth rate when they enter a living being.

These assumptions lead to this system of differential equations;

$$N' = A_3 - \mu_3 N + \gamma NV \tag{3.04}$$

$$V' = rV - kVN \tag{3.05}$$

The term A_3 corresponds to new lymphocytes of type 3 produced. $\mu_3 N$ corresponds to the rate at which lymphocytes of type 3 die. γNV corresponds to the rate of growth of lymphocytes of type 3 due to interactions with the virus cells. The term rV represents the intrinsic growth of the virus cells while kVN corresponds to the rate at which the virus cells die due to the interactions with lymphocytes of type 3.

3.1.2.2: OVERLAP OF INNATE AND ADAPTIVE IMMUNE RESPONSES

This stage is where the T and B cells have just taken charge to fight the virus cells. In this case, all the three lymphocytes population types will still be in the human body. The interaction with the virus cells have the following key properties;

- new lymphocytes of type 3 are produced by the bone marrow at a constant rate A_3.
- lymphocytes of type 3 die at a per capita rate of $\boldsymbol{\mu}$.

- ❖ lymphocytes of type 3 kill virus cells in proportion to the number of contacts between them.
- ❖ the virus cells have an intrinsic growth rate as they are in a living being.
- ❖ lymphocytes of type 1 kill virus cells in proportion to the number of contacts between wthem and they proliferate because of these contacts.
- ❖ lymphocytes of type 2 (T cells) do not directly interact with the virus, but they continue ato regulate the growth of cells of type 1(B cells).

These key properties lead to this system of differential equations;

$$\frac{dN}{dt} = A_3 - \mu_3 N + \gamma NV \quad (3.06)$$

$$\frac{dB}{dt} = A_1 - \mu_1 B + \frac{a_1 TB}{(1+b_1 TB)} + KVB \quad (3.07)$$

$$\frac{dT}{dt} = A_2 - \mu_2 T + \frac{a_2 TB}{(1+b_2 TB)} \quad (3.08)$$

$$\frac{dV}{dt} = rV - KVB - kVN \quad (3.09)$$

3.1.2.3. ADAPTIVE IMMUNE RESPONSE (7TH DAY ONWARDS)

Lymphocytes of type 1 and type 2 (B and T) have been recruited to take charge on the 7th day of viral infection. This is because lymphocytes of type 3 (Natural killer cells) are overwhelmed by the virus cells. Here, T cells activate B cells to produce antibodies to fight the virus. The interaction between the lymphocytes and the virus has the following properties;

- ❖ the virus cells have an intrinsic growth rate as they are in a living being.

- ❖ lymphocytes of type 1 kill virus cells in proportion to the number of contacts between them and they proliferate because of these contacts.
- ❖ lymphocytes of type 2 (T cells) do not directly interact with the virus, but they continue to regulate the growth of cells of type 1(B cells) .

The interaction of these cells results in the following system of differential equations;

$$T' = A_1 - \mu_1 T + \frac{a1TB}{(1+b1TB)} \tag{3.10}$$

$$B' = A_2 - \mu_2 B + \frac{a2TB}{(1+b2TB)} + KVB \tag{3.11}$$

$$V' = rV - KVB \tag{3.12}$$

The term rV represents the intrinsic growth rate of the virus cells and kVB represents the rate at which virus cells are destroyed by B lymphocytes. The term KVB in equation (3.11) represents the rate of growth of B lymphocytes due to interactions with the virus.

3.2 MODEL ANALYSIS

We present how to obtain the steady states for the various stages of immune response. We also present the Jacobian matrices of all the models.

3.2.1 EXISTENCE OF STEADY STATES IN THE ABSENCE OF VIRUSES.

The approach used was to gain a general understanding of how solutions to the systems behave without finding the solution outright. Steady states are obtained by solving the equations for all time derivatives equal to zero. By system of equations (3.01) – (3.03), we obtain steady states by putting derivatives to zero.

$$A_1 - \mu_1 T + \frac{a_1 TBN}{(1+b_1 TBN)} = 0 \tag{3.13}$$

$$A_2 - \mu_2 B + \frac{a_2 TBN}{(1+b_2 TBN)} = 0 \quad (3.14)$$

$$A_3 - \mu_3 N + \frac{a_3 TBN}{(1+b_3 TBN)} = 0 \quad (3.15)$$

We obtain (T*, B*, N*) = (0, 0, 0) as a trivial steady state of the system. We obtain the characteristics equation of the system (3.12) - (3.13).

$$A_1 - \boldsymbol{\mu}_1 T + \frac{\mathbf{a_1 TBN}}{(\mathbf{1+b_1 TBN})} = A_2 - \boldsymbol{\mu}_2 B + \frac{\mathbf{a_2 TBN}}{(\mathbf{1+b_2 TBN})}$$

$$= A_3 - \boldsymbol{\mu}_3 N + \frac{\mathbf{a_3 TBN}}{(\mathbf{1+b_3 TBN})} = 0 \quad (3.16)$$

$$A - \boldsymbol{\mu} T + \frac{\mathbf{a T^3}}{(\mathbf{1+b T^3})} = 0 \quad (3.17)$$

$$A\,(1+b\mathbf{T^3}) - \boldsymbol{\mu} T\,(1+b\mathbf{T^3}) + a\mathbf{T^3} = 0 \quad (3.18)$$

$$A + Ab\mathbf{T^3} - \boldsymbol{\mu} T - b\boldsymbol{\mu}\mathbf{T^4} + a\mathbf{T^3} = 0 \quad (3.19)$$

$$b\boldsymbol{\mu}\mathbf{T^4} - (Ab + a)\mathbf{T^3} + \boldsymbol{\mu} T - A = 0 \quad (3.20)$$

We linearized the system by finding the Jacobian matrix of first partial derivatives.

$$T' = A_1 - \mu_1 T + \frac{a_1 TBN}{(1+b_1 TBN)} = f_1 \quad (3.21)$$

$$B' = A_2 - \mu_2 B + \frac{a_2 TBN}{(1+b_2 TBN)} = f_2 \quad (3.22)$$

$$N' = A_3 - \mu_3 N + \frac{a_3 TBN}{(1+b_3 TBN)} = f_3 \quad (3.23)$$

$$J(f_1, f2, f3) = \begin{bmatrix} \frac{\partial f_1}{\partial T} & \frac{\partial f_1}{\partial B} & \frac{\partial f_1}{\partial N} \\ \frac{\partial f_2}{\partial T} & \frac{\partial f_2}{\partial B} & \frac{\partial f_2}{\partial N} \\ \frac{\partial f_3}{\partial T} & \frac{\partial f_3}{\partial B} & \frac{\partial f_3}{\partial N} \end{bmatrix} \quad (3.24)$$

Subtituting into (3.23), we have

$$J(T,B,N)=\begin{pmatrix} -\boldsymbol{\mu_1} + \frac{\mathbf{a_1 BN}}{(\mathbf{1+b_1 TBN})^2} & \frac{\mathbf{a_1 TN}}{(\mathbf{1+b_1 TBN})^2} & \frac{\mathbf{a_1 T}}{(\mathbf{1+b_1 TBN})^2} \\ \frac{\mathbf{a_2 BN}}{(\mathbf{1+b_2 TBN})^2} & -\boldsymbol{\mu_2} + \frac{\mathbf{a_2 TN}}{(\mathbf{1+b_2 TBN})^2} & \frac{\mathbf{a_2 TB}}{(\mathbf{1+b_2 TBN})^2} \\ \frac{\mathbf{a_3 BN}}{(\mathbf{1+b_3 TBN})^2} & \frac{\mathbf{a_3 TN}}{(\mathbf{1+b_3 TBN})^2} & -\boldsymbol{\mu_3} + \frac{\mathbf{a_3 TB}}{(\mathbf{1+b_3 TBN})^2} \end{pmatrix} \quad (3.25)$$

3.2.2 EXISTENCE OF STEADY STATES IN THE PRESENCE OF VIRUSES.

In the presence of virus cells in the human body, we consider three main stages. These are the innate immune response stage, the overlap of innate and adaptive immune responses stage and finally the adaptive immune response stage.

3.2.2.1 INNATE IMMUNE RESPONSE

By system of equations (3.04) – (3.05), we obtain steady states by putting derivatives to zero.

$$A_3 - \mu_3 N + \gamma NV = 0 \quad (3.26)$$

$$rV - kVN = 0 \quad (3.27)$$

Similarly, we obtain (N*,V*) = (0,0) as a trivial steady state solution. We obtain Jacobian matrix of system (3.4)-(3.5) as

$$N' = A_3 - \mu_3 N + \gamma NV = f_1 \quad (3.28)$$

$$V' = rV - kVN = f_2 \quad (3.29)$$

$$J(f_1,f_2) = \begin{bmatrix} \frac{\partial f_1}{\partial N} & \frac{\partial f_1}{\partial V} \\ \frac{\partial f_2}{\partial N} & \frac{\partial f_2}{\partial V} \end{bmatrix} \quad (3.30)$$

By substituting into (3.25), we obtain,

$$J(N,V) = \begin{bmatrix} -\mu 3 + \gamma V & \gamma N \\ -kV & \gamma - KN \end{bmatrix} \quad (3.31)$$

3.2.2.2 OVERLAP OF INNATE AND ADAPTIVE IMMUNE RESPONSES.

By system of equations (3.6) – (3.9), we obtain steady states by putting derivatives to zero.

$$A_3 - \mu_3 N + \gamma NV = 0 \quad (3.32)$$

$$A_1 - \mu_1 B + \frac{a_1 TB}{(1+b_1 TB)} + KVB = 0 \quad (3.33)$$

$$A_2 - \mu_2 T + \frac{a_2 TB}{(1+b_2 TB)} = 0 \quad (3.34)$$

$$rV - KVB - kVN = 0 \quad (3.35)$$

We obtain (N*,B*,T*,V*) = (0,0,0,0) as a trivial steady state solution. Similarly, we obtain the Jacobian matrix as

$$A_3 - \mu_3 N + \gamma NV = f_1 \quad (3.36)$$

$$A_1 - \mu_1 B + \frac{a_1 TB}{(1+b_1 TB)} + KVB = f_2 \quad (3.37)$$

$$A_2 - \mu_2 T + \frac{a_2 TB}{(1+b_2 TB)} = f_3 \quad (3.38)$$

$$rV - KVB - kVN = f_4 \quad (3.39)$$

$$J(f_1,f_2,f_3,f_4) = \begin{bmatrix} \frac{\partial f_1}{\partial N} & \frac{\partial f_1}{\partial B} & \frac{\partial f_1}{\partial T} & \frac{\partial f_1}{\partial V} \\ \frac{\partial f_2}{\partial N} & \frac{\partial f_2}{\partial B} & \frac{\partial f_2}{\partial T} & \frac{\partial f_2}{\partial V} \\ \frac{\partial f_3}{\partial N} & \frac{\partial f_3}{\partial B} & \frac{\partial f_3}{\partial T} & \frac{\partial f_3}{\partial V} \\ \frac{\partial f_4}{\partial N} & \frac{\partial f_4}{\partial B} & \frac{\partial f_4}{\partial T} & \frac{\partial f_4}{\partial V} \end{bmatrix} \quad (3.40)$$

Subtituting into (3.38), we obtain,

$$J(N,B,T,V) = \begin{bmatrix} -\mu_3 + \gamma V & 0 & 0 & \gamma N \\ 0 & -\mu_1 + \frac{a_1 T}{(1+b_1 TB)^2} + KV & \frac{a_1 B}{(1+b_2 TB)^2} & KB \\ 0 & \frac{a_2 T}{(1+b_2 TB)^2} & -\mu_2 + \frac{a_2 B}{(1+b_2 TB)^2} & 0 \\ -kV & -KV & 0 & r - KB - kN \end{bmatrix} \quad (3.41)$$

3.2.2.3 ADAPTIVE IMMUNE RESPONSE

By system of equations (3.10) – (3.12), we obtain steady states by putting derivatives to zero.

$$A_1 - \mu_1 T + \frac{a_1 TBN}{(1+b_1 TBN)} = 0 \quad (3.42)$$

$$A_2 - \mu_2 B + \frac{a_2 TBN}{(1+b_2 TBN)} + KVB = 0 \quad (3.43)$$

$$rV - KVB = 0 \quad (3.44)$$

We obtain the Jacobian matrix as;

$$A_1 - \mu_1 T + \frac{a_1 TBN}{(1+b_1 TBN)} = f_1 \quad (3.45)$$

$$A_2 - \mu_2 B + \frac{a_2 TBN}{(1+b_2 TBN)} + KVB = f_2 \quad (3.46)$$

$$rV - KVB = f_3 \quad (3.47)$$

$$J(f1,f2,f3) = \begin{bmatrix} \frac{\partial f_1}{\partial T} & \frac{\partial f_1}{\partial B} & \frac{\partial f_1}{\partial V} \\ \frac{\partial f_2}{\partial T} & \frac{\partial f_2}{\partial B} & \frac{\partial f_2}{\partial V} \\ \frac{\partial f_3}{\partial T} & \frac{\partial f_3}{\partial B} & \frac{\partial f_3}{\partial V} \end{bmatrix} \quad (3.48)$$

$$J(B,T,V) = \begin{bmatrix} \mu_1 + \frac{a_1 T}{(1+b_1 TB)^2} + KV & \frac{a_1 B}{(1+b_1 TB)^2} & KB \\ \frac{a_2 T}{(1+b_2 TB)^2} & \mu_2 + \frac{a_2 B}{(1+b_2 TB)^2} & 0 \\ -kV & 0 & r - kB \end{bmatrix} \quad (3.49)$$

Solving system (3.10)-(3.12) at equilibrium gives

$$A_1 = \boldsymbol{\mu}_1 T + \frac{\mathbf{a_1 TB}}{(\mathbf{1}+\mathbf{b_1 TB})} = A_2 = \boldsymbol{\mu}_2 T + \frac{\mathbf{a_2 TB}}{(\mathbf{1}+\mathbf{b_2 TB})} = 0 \quad (3.50)$$

CHAPTER 4

RESULTS, ANALYSIS AND DISCUSSION

4.0 OVERVIEW

In this chapter, we present the result of the study and use numerical methods to study the mathematical model for virus infectious diseases developed in Chapter 3. Numerical solutions of the equations for a range of initial values that appear reasonable for the study will be used. We present the phase portraits of these systems of differential equations and analyze the systems qualitatively. Matlab ordinary differential equation solver **'ode45'** is used to compute the numerical solution of the systems of differential equations.

Table 4.1: Parameters Values Supplied by Anderson and May (1992).

Lymphocytes	Initial Production	Rate of increase	Rate of increase	Death rate
T	$A_1 = 1$	$a_1 = 0.252$	$b_1 = 0.008$	$\mu_1 = 1.25$

B	$A_2 = 1$	$a_2 = 0.252$	$b_2 = 0.008$	$\boldsymbol{\mu}_2 = 1.25$
N	$A_3 = 1$	$a_3 = 0.252$	$b_3 = 0.008$	$\boldsymbol{\mu}_3 = 1.25$

4.1 BEHAVIOUR OF STEADY STATES IN THE ABSENCE OF VIRUSES.

We substitute parameter values into (3.19) which yields;

$$\mathbf{T^4} - 26\mathbf{T^3} + 125\mathrm{T} - 100 = 0 \qquad (4.01)$$

The roots of this quartic equation were found using Matlab and the roots are;

(25.8183, -2.4193, 1.6010, 1.0000.)

It has already been shown that T = B = N, it then shows that there exits four equilibrium points at $\begin{pmatrix} \boldsymbol{T}* \\ \boldsymbol{B}* \\ \boldsymbol{N}* \end{pmatrix} = \begin{pmatrix} \mathbf{25.82} \\ \mathbf{25.82} \\ \mathbf{25.8} \end{pmatrix}, \begin{pmatrix} \mathbf{-2.4} \\ \mathbf{-2.4} \\ \mathbf{-2.4} \end{pmatrix}, \begin{pmatrix} \mathbf{1.6} \\ \mathbf{1.6} \\ \mathbf{1.6} \end{pmatrix}$ and $\begin{pmatrix} \mathbf{1} \\ \mathbf{1} \\ \mathbf{1} \end{pmatrix}$.

Substituting the parameters in Table 4.1, (3.22) becomes;

$$\mathrm{J(T,B,N)} = \begin{pmatrix} -\mathbf{1.25} + \frac{\mathbf{0.252BN}}{(\mathbf{1+0.008TBN})^2} & \frac{\mathbf{0.252TN}}{(\mathbf{1+0.008TBN})^2} & \frac{\mathbf{0.252T}}{(\mathbf{1+0.008TBN})^2} \\ \frac{\mathbf{0.252BN}}{(\mathbf{1+0.008TBN})^2} & -\mathbf{1.25} + \frac{\mathbf{0.252TN}}{(\mathbf{1+0.008TBN})^2} & \frac{\mathbf{0.252TB}}{(\mathbf{1+0.008TBN})^2} \\ \frac{\mathbf{0.252BN}}{(\mathbf{1+0.008TBN})^2} & \frac{\mathbf{0.252TN}}{(\mathbf{1+0.008TBN})^2} & -\mathbf{1.25} + \frac{\mathbf{0.252TB}}{(\mathbf{1+TB0.008N})^2} \end{pmatrix} \qquad (4.02)$$

At (T*,B*,N*) = (1,1,1), we obtain;

$$J(1,1,1)=\begin{pmatrix} -1.25+\frac{0.252BN}{(1+0.008TBN)^2} & \frac{0.252TN}{(1+0.008TBN)^2} & \frac{0.252TB}{(1+0.008TBN)^2} \\ \frac{0.252BN}{(1+0.008TBN)^2} & -1.25+\frac{0.252TN}{(1+0.008TBN)^2} & \frac{0.252TB}{(1+0.008TBN)^2} \\ \frac{0.252BN}{(1+0.008TBN)^2} & \frac{0.252TN}{(1+0.008TBN)^2} & -1.25+\frac{0.252TB}{(1+TB0.008N)^2} \end{pmatrix} \quad (4.03)$$

$$J(1,1,1)=\begin{bmatrix} -1.00198 & 0.248017 & 0.248017 \\ 0.248017 & -1.00198 & 0.248017 \\ 0.248017 & 0.248017 & -1.00198 \end{bmatrix} \quad (4.04)$$

The eigenvalues were obtained to be λ_1= -1.2500, λ_2= -1.2500 and λ_3= -0.5059

At (T*,B*,N*) = (1.6,1.6,1.6), we obtain;

$$J(1.6,1.6,1.6)=\begin{bmatrix} -0.645168 & 0.604832 & 0.604832 \\ 0.604832 & -0.645168 & 0.604832 \\ 0.604832 & 0.604832 & -0.645168 \end{bmatrix} \quad (4.05)$$

The eigenvalues were found to be; λ_1= -1.2500, λ_2= -1.2500 and λ_3= 0.5645.

At (T*,B*,N*) = (-2.4,-2.4,-2.4), we obtain;

$$J(-2.4,-2.4,-2.4)=\begin{bmatrix} 0.584935 & 1.83494 & 1.83494 \\ 1.83494 & 0.584935 & 1.83494 \\ 1.83494 & 1.83494 & 0.584935 \end{bmatrix} \quad (4.06)$$

The eigenvalues were found to be; λ_1= -1.2500, λ_2= -1.2500 and λ_3= 4.2548.

At (T*,B*,N*) = (25.8,25.8,25.8), we obtain;

$$J(25.8, 25.8, 25.8) = \begin{bmatrix} \mathbf{112.9214} & \mathbf{114.1714} & \mathbf{114.1714} \\ \mathbf{114.1714} & \mathbf{112.9214} & \mathbf{114.1714} \\ \mathbf{114.1714} & \mathbf{114.1714} & \mathbf{112.9214} \end{bmatrix} \quad (4.07)$$

The eigenvalues were found to be; $\boldsymbol{\lambda}_1$=-1.2500, $\boldsymbol{\lambda}_2$= -1.2500 and $\boldsymbol{\lambda}_3$= 431.2642.

TABLE 4.2: CLASSIFICATION OF THE EQUILIBRIUM POINTS

EQUILIBRIUM POINT	EIGENVALUES	CLASSIFICATION
(1, 1, 1)	λ_1= - 1.25, λ_2= -1.25, λ_3= -1.25	Asymptotically stable
(1.6, 1.6, 1.6)	λ_1= -1.25, λ_2= 0.50, λ_3= 4.25	Unstable Point
(25.8, 25.8, 25.8)	λ_1= -1.25, λ_2= - 1.25, λ_3= 4312642.00	Unstable Point
(-2.4,-2.4,-2.4)	λ_1= -1.25, λ_2= - 1.25, λ_3= 4.25	Unstable Point

Table 4.3: Parameters Values In the Model

Parameter	Description	Value
r	Growth Rate of Virus Cells	0.10
$\boldsymbol{\gamma}$	Growth Rate of NK Cells	0.05
$\boldsymbol{\mu_3}$	Death Rate of NK ells	1.25
K	Death Rate of Virus Cells	1.25

4.2 BEHAVIOUR OF STEADY STATES IN THE PRESENCE OF VIRUSES.

We obtain the equilibrium points for all the models by considering the innate immune response stage, the overlap of innate and adaptive immune responses stage and finally the adaptive immune response stage.

4.2.1 INNATE IMMUNE RESPONSE

We obtain the equilibrium points of systems (3.24) and (3.25) by substituting the parameter values of table 4.3.

$$1\text{-}1.25N+0.05NV = 0 \tag{4.08}$$

$$0.1V\text{-}1.25VN = 0 \tag{4.09}$$

The equilibrium points were determined by Universal Mathematics Equation Solver. There exists two equilibrium points and these are; $\begin{pmatrix} N^* \\ V^* \end{pmatrix} = \begin{pmatrix} 0.8 \\ 0 \end{pmatrix}$ and $\begin{pmatrix} 0.08 \\ -225 \end{pmatrix}$.

Substituting the values of the parameters of table 4.3 into (3.29), we have;

$$J(N, V) = \begin{bmatrix} -1.25 + 0.05V & 0.05N \\ -1.25V & 0.1 - 1.25N \end{bmatrix} \tag{4.10}$$

At (N*,V*) = (0.8,0), we obtain

$$J(0.8, 0) = \begin{bmatrix} -1.25 & 0.04 \\ 0 & -0.9 \end{bmatrix} \tag{4.11}$$

The corresponding eigenvalues were found to be; $\lambda_1 = -1.2500$ and $\lambda_2 = -0.9000$

At (N*,V*) = (10,-255), we obtain

$$J(10, -225) = \begin{bmatrix} \mathbf{-12.5} & \mathbf{0.004} \\ \mathbf{281.25} & \mathbf{0} \end{bmatrix} \quad (4.12)$$

The corresponding eigenvalues are; $\boldsymbol{\lambda}_1 = -12.5894$ and $\boldsymbol{\lambda}_2 = 0.0894$

TABLE 4.4: CLASSIFICATION OF THE EQUILIBRIUM POINTS

EQUILIBRIUM POINT	EIGENVALUES	CLASSIFICATION
(0.8, 0)	$\lambda_1 = -1.2500$, $\lambda_2 = -0.9000$	Asymptotically Stable
(0.08,-225)	$\lambda_1 = -12.5894$, $\lambda_2 = 0.0894$	Saddle Point

4.2.2: OVERLAP OF INNATE AND ADAPTIVE IMMUNE RESPONSES

We obtain the equilibrium points of systems (3.34) and (3.37) by substituting the parameter values of Table 4.2.

$$\frac{dN}{dt} = 1 - 1.25N + 0.05NV \quad (4.13)$$

$$\frac{dB}{dt} = 1 - 1.25B + \frac{0.252TB}{(1+0.008TB)} + 0.05VB \quad (4.14)$$

$$\frac{dT}{dt} = 1 - 1.25T + \frac{0.252TB}{(1+0.008TB)} \quad (4.15)$$

$$\mathbf{\frac{dV}{dt}} = 0.1V - 0.05VB - 1.25VN \quad (4.16)$$

We assume that T, B and N are distinct. Matlab was then used to find the equilibrium points as;

$$\begin{pmatrix} N* \\ B* \\ T* \\ V* \end{pmatrix} = \begin{pmatrix} 1 \\ 0.8 \\ 1 \\ 0 \end{pmatrix}, \begin{pmatrix} 5 \\ 0.8 \\ 5 \\ 0 \end{pmatrix}, \begin{pmatrix} 20 \\ 0.8 \\ 20 \\ 0 \end{pmatrix}, \begin{pmatrix} 50.0781 \\ 0.07686 \\ 0.8128 \\ -235.1599 \end{pmatrix} \text{ and } \begin{pmatrix} 1.9392 \pm 1.3439i \\ 0.00243 \pm 0.0538i \\ -18.6564 \pm 29.7030i \\ 8.2050 \pm 371.287i \end{pmatrix}$$

We realized that two of these equilibrium points involve complex numbers and therefore are neglected. By substituting parameter values into (3.39), we obtain, J(N,B,T,V) =

$$\begin{bmatrix} -1.25 + 0.05V & 0 & 0 & 0.05N \\ 0 & -1.25 + \frac{0.252T}{(1+0.008TB)^2} + 0.05V & \frac{0.252B}{(1+0.008TB)^2} & 0.05B \\ 0 & \frac{0.05T}{(1+0.008TB)^2} & -1.25 + \frac{0.252B}{(1+0.008TB)^2} & 0 \\ -1.25V & -0.05V & 0 & 0.1 - 0.05B - 1.25N \end{bmatrix} \quad (4.17)$$

At (N*, B*, T*, V*) = (1, 0.8, 1, 0), we obtain,

$$J(1,0.8,1,0) = \begin{bmatrix} -1.25 & 0 & 0 & 0.05 \\ 0 & -1.0012 & 0.1990 & 0.04 \\ 0 & 0.2480 & -1.0516 & 0 \\ 0 & 0 & 0 & -1.1900 \end{bmatrix} \quad (4.18)$$

The corresponding eigenvalues were found to be; λ_1= -1.2500, λ_2= -0.8028, λ_3= - 1.2500 and λ_4= -1.2500

At (N*, B*, T*, V*) = (5, 0.8,51, 0), we obtain,

$$J(5,0.8,5,0) = \begin{bmatrix} -1.25 & 0 & 0 & 0.25 \\ 0 & -0.0669 & 0.1893 & 0.04 \\ 0 & 1.1831 & -1.0671 & 0 \\ 0 & 0 & 0 & -6.1900 \end{bmatrix} \quad (4.19)$$

The corresponding eigenvalues were found to be; λ_1= -1.2555, λ_2= 0.1215, λ_3= - 1.2500 and λ_4= -6.1900.

At (N*, B*, T*, V*) = (20,0.8,20,0), we obtain,

$$J(20,0.8,20,0) = \begin{bmatrix} \mathbf{-1.25} & \mathbf{0} & \mathbf{0} & \mathbf{0.05} \\ \mathbf{0} & \mathbf{2.7110} & \mathbf{0.1584} & \mathbf{0.04} \\ \mathbf{0} & \mathbf{3.9611} & \mathbf{-1.0916} & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \mathbf{0} & \mathbf{-24.94} \end{bmatrix}$$

(4.20)

The corresponding eigenvalues were found to be; λ_1= -1.2427, λ_2= 3.0621, λ_3= - 1.2500 and

λ_4= -24.9400.

At (N*, B*, T*, V*) = (0.0781, 0.07686, 0.8126,-235.1599), we obtain,

$$J(0.0781,0.07686,0.8126,-235.1599)=\begin{bmatrix} \mathbf{-13.008} & \mathbf{0} & \mathbf{0} & \mathbf{0.0039} \\ \mathbf{0} & \mathbf{-12.8034} & \mathbf{0.01935} & \mathbf{0.0038} \\ \mathbf{0} & \mathbf{0.2046} & \mathbf{-1.2307} & \mathbf{0} \\ \mathbf{293.950} & \mathbf{11.758} & \mathbf{0} & \mathbf{-0.0015} \end{bmatrix}$$

(4.21)

The corresponding eigenvalues were found to be; λ_1= 0.0628, λ_2= -13.0697, λ_3= - 12.8064 and

λ_4= -1.2304

TABLE 4.5: CLASSIFICATION OF THE EQUILIBRIUM POINTS

EQUILIBRIUM POINT	EIGENVALUES	CLASSIFICATION
(1, 0.8, 1, 0)	λ_1= -1.250, λ_2= -0.803, λ_3= - 1.250 and λ_4= -1.1900	Asymptotically Stable
(5, 0.8,5, 0)	λ_1= -1.255, λ_2= 0.1215, λ_3= - 1.2500 and λ_4= -6.1900	Saddle Point
(20, 0.8, 20, 0)	λ_1= -1.2427, λ_2= 3.0621, λ_3= - 1.2500 and $\lambda_{4=-}$24.94	Saddle Point

(0.078, 0.0769, 0.813, -235.16)	λ_1= 0.06, λ_2= -13.07 and λ_3= - 12.806 and λ_4= -1.230,	Saddle Point

4.2.3: ADAPTIVE IMMUNE RESPONSE

We obtain the equilibrium points of (3.48) by substituting the parameter values of table 4.2.

$$\mathbf{T^3} - 26\mathbf{T^2} + 125T - 100 = 0 \tag{4.22}$$

The roots of this polynomial were found using Universal Mathematics Solver and these roots are;

$$\begin{pmatrix} \boldsymbol{B}* \\ \boldsymbol{T}* \\ \boldsymbol{V}* \end{pmatrix} = \begin{pmatrix} \mathbf{1} \\ \mathbf{1} \\ \mathbf{0} \end{pmatrix}, \quad \begin{pmatrix} \mathbf{5} \\ \mathbf{5} \\ \mathbf{0} \end{pmatrix} \boldsymbol{and} \quad \begin{pmatrix} \mathbf{20} \\ \mathbf{20} \\ \mathbf{0} \end{pmatrix} \tag{4.23}$$

We evaluate the equilibrium points by first substituting the parameter values of table 4.3.

$$J(B,T,V) = \begin{bmatrix} -1.25 + \frac{0.252T}{(1+0.008TB)^2} + 0.05V & \frac{0.252B}{(1+0.008TB)^2} & 0.05B \\ \frac{0.252T}{(1+b_2TB)^2} & -1.25 + \frac{0.252B}{(1+0.008TB)^2} & 0 \\ -0.01V & 0 & 0.1 - 0.01B \end{bmatrix} \tag{4.24}$$

At (B*,T*,V*)=(1,1,0), we obtain,

$$J(1,1,0) = \begin{bmatrix} \mathbf{-1.002} & \mathbf{0.248} & \mathbf{0.05} \\ \mathbf{0.248} & \mathbf{-1.002} & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \mathbf{0.09} \end{bmatrix} \tag{4.25}$$

The corresponding eigenvalues were found as; λ_1= -0.754, λ_2= -1.25 and λ_3= 0.09

At (B*,T*,V*)=(5,5,0), we obtain,

$$J(5,5,0) = \begin{bmatrix} \mathbf{-0.375} & \mathbf{0.875} & \mathbf{0.25} \\ \mathbf{0.875} & \mathbf{-0.375} & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \mathbf{0.05} \end{bmatrix} \quad (4.26)$$

The eigenvalues were found as; λ_1= 0.500, λ_2= -1.25 and λ_3= 0.050

At (B*,T*,V*)=(20,20,0), we obtain,

$$J(20,20,0) = \begin{bmatrix} \mathbf{-0.9643} & \mathbf{0.2857} & \mathbf{1} \\ \mathbf{0.2857} & \mathbf{-0.9643} & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \mathbf{-0.1} \end{bmatrix} \quad (4.27)$$

The corresponding eigenvalues were found as; λ_1=- 6786, λ_2= -1.25 and λ_3= - 0.100

TABLE 4.6: CLASSIFICATION OF THE EQUILIBRIUM POINTS

EQUILIBRIUM POINT	EIGENVALUES	CLASSIFICATION
(1, 1, 0)	λ_1= - 0.7540, λ_2= -1.2500, λ_3= 0.0900	Unstable Point
(5, 5, 0)	λ_1= 0.5000, λ_2= -1.2500, λ_3= 0.0500	Unstable Point
(20, 20, 0)	λ_1= -0.6786, λ_2= -1.2500, λ_3= -0.1000	Asymptotically Stable

Table 4.6 displays the classification of equilibrium points of the adaptive immune response. Out of the three equilibrium points found on this table only (20, 20, 0) is asymptotically stable.

4.3 RESULTS OF THE STUDY

This study is an extension of Anderson and May (1992) model on human immune response to virus infectious diseases and it has yielded results that are in consistent with these workers. We realized that there is stability in the human body when the virus cells have not entered the body.

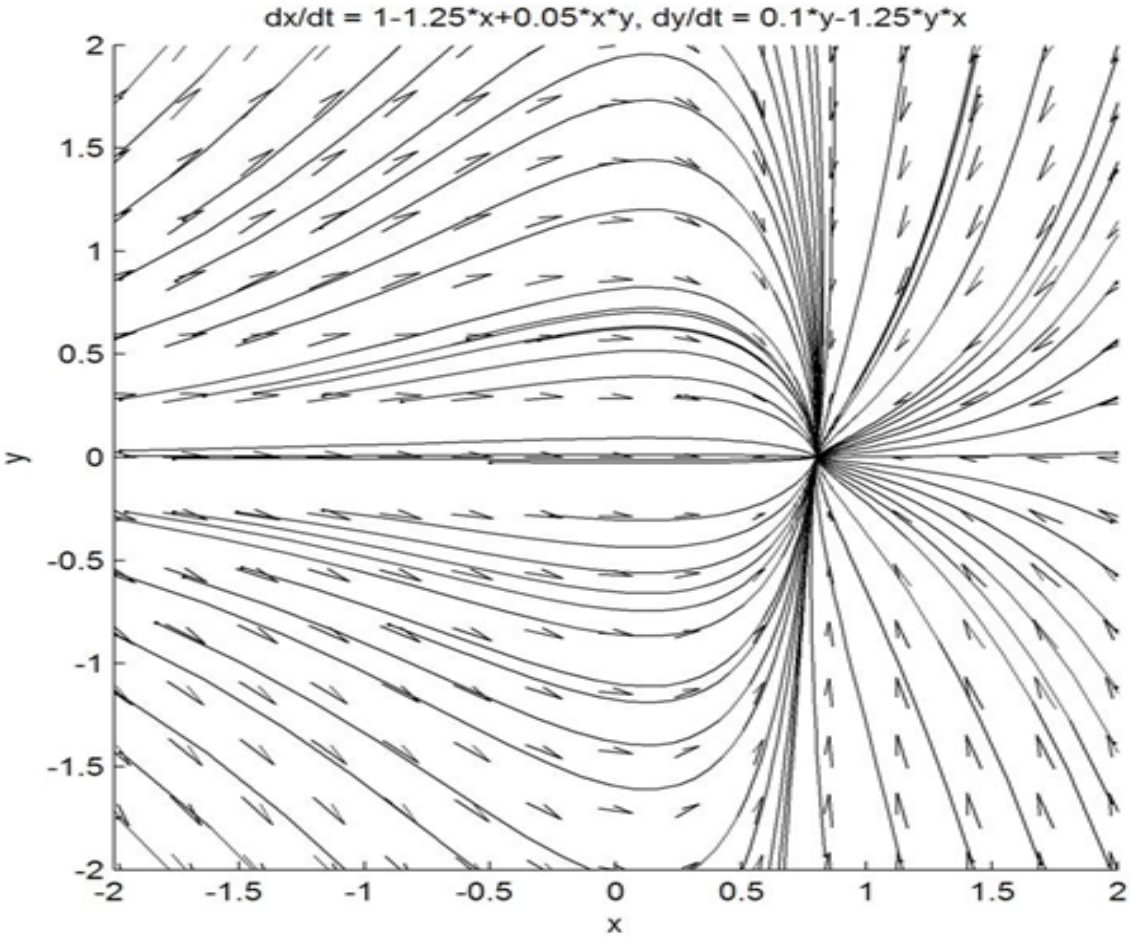


Figure 4.1 represents the interaction between the natural killer cells and the virus cells. The y-axis represents the NK cells whiles the x-axis represents the Virus cells. We observe that all the arrows converge to a particular point (0.8,0). This confirms that there is stability when the virus cells enter the the human body for the first week. The natural killer cells are able to suppress viral abundance to a very low level in the host within this first week.

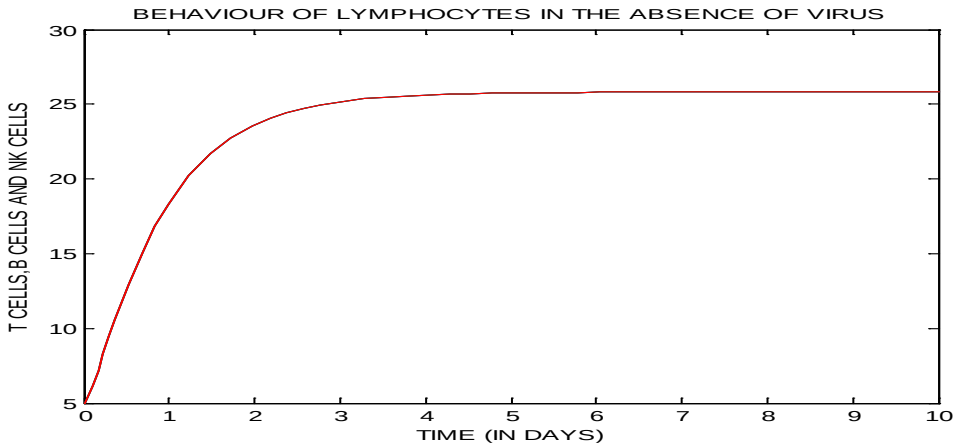


Figure 4.2: Illustrates the behaviour of lymphocytes in the absence of the virus cells. The curve shows that all the lymphocyte population types increases with time when viruses have not invaded the human body. We observe that the cells (T, B and NK) grow exponentially and reach a constant endemic value of 25 which represent the carrying capacity. This confirms the logistic growth nature of the lymphocytes population.

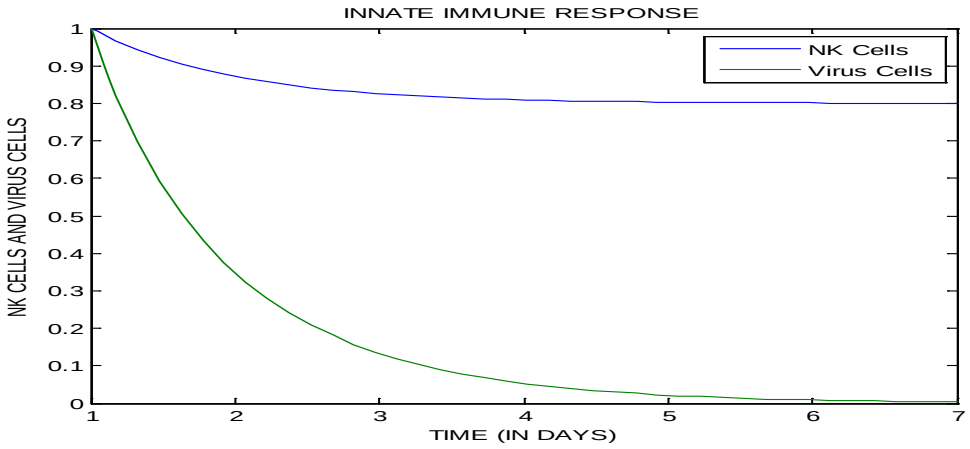


Figure 4.3: Illustrates the interaction between the NK cells and the virus cells in the innate immune response stage. In this figure, we plot NK cells and Virus cells against time. The curve shows both cells decreases with time but the rate of decrease of the virus cells is greater than the rate of decrease of the NK cells. The virus cells decrease drastically with time. We observe that the virus cells die faster than the Natural Killer cells as time increases. As a result of the

interaction of the two cells, both cells decrease asymptotically as time increases. Besides, the virus cells approach a constant endemic value of about 0.001 whereas the NK cells approach a fixed value of 0.8.

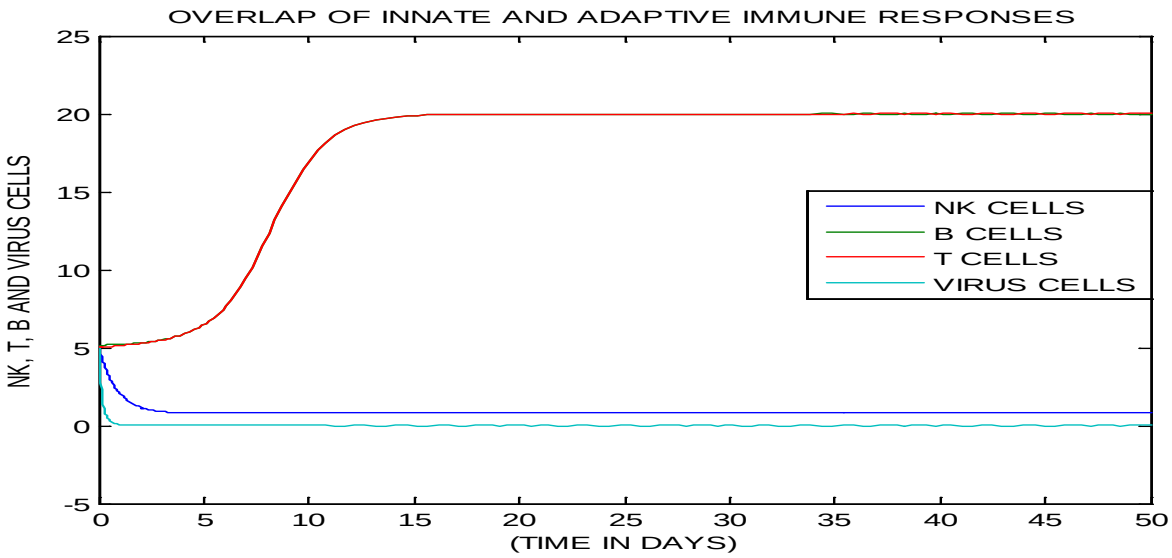


Figure 4.4: Illustrates the overlap of innate and adaptive immune response. In this figure, we plot NK cells, T cells, B cells and Virus cells against time. We observe that the B and T cells increase to a certain peak value of 20 and approach this constant endemic value as time increases. However, the NK killer cells and the Virus cells decrease to certain constants values of about 0.8 and 0.0001 respectively. This confirms the fact that the NK cells get overwhelmed and become inactive after the 7^{th} day of viral infection.

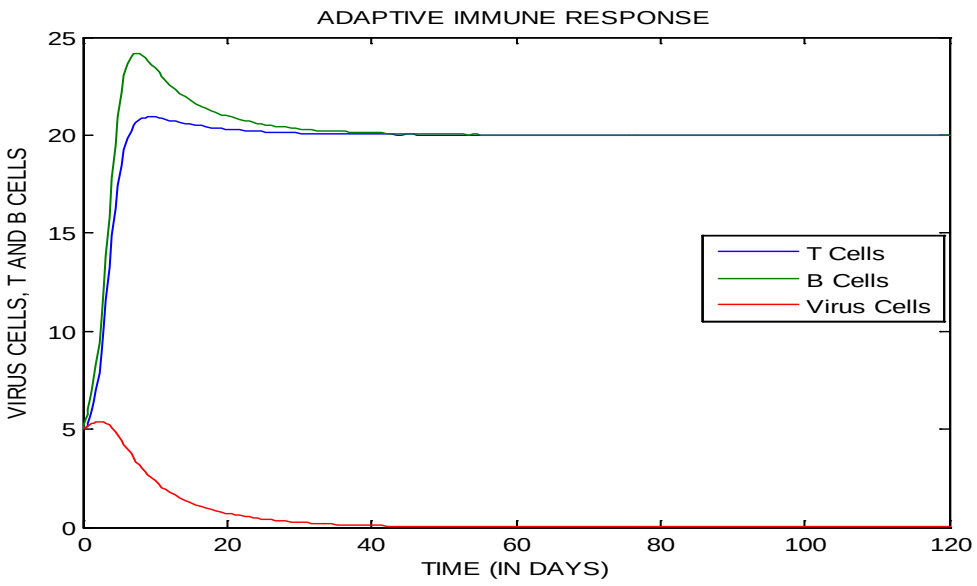


Figure 4.5: Illustrates the adaptive immune response which involves the interaction between the T cells, the B cells and the Virus cells. In this figure, we plot T cells, B cells and Virus cells against time. We observe that T cells and B cells rise to peak values of 21.2 and 24.0 respectively. B cells decrease slightly sharper than T cells and both reach and endemic constant value of 20.0 as time increases. On the other hand, virus cells decreases drastically towards zero. The actual figures for these curves have been displayed in appendix c.

4.4: DISCUSSION

This results is in consistent with the results of Anderson and May (1992) even though their model was on two lymphocyte population types and this study also considered three lymphocyte types. We observed that as time increases, an infected person shows no signs of infection. Asymptotical decreasing of virus cells to zero implies that an infected person shows no signs of infection as time increases eventhough such an individual may have a minimal number of virus cells in such an individual's system.This happens when the individual's immune system works very well.

We realized from the study that when the human body is invaded with virus cells, the first line of defence is provided by lymphocytes of type 3 (Natural killer cells) for 7 days as lymphocytes of types 1 and 2 (B cells and T cells) undergo cloning and multiply to take over. The Natural Killer cells (NK) are not able to concer these virus cells but are able to suppress its abundance. During this period, the human body is able to attain stability to bring about immune state to this infection There was the period of overlapping when the T cells and B cells get into the system after the Natural Killer cells get overhelmed. This period was after the 7^{th} day of the infection. This signifies that the effector cells (lymphocytes) even at high abundance are unable to completely eliminate the virus from the human body within the very short time.

There is also the period when the T cells and B cells have taken full control to fight these virus cells. This phase has two possibilities. These possibilities are:

- the few active Natural Killer cells are also intereacting with some of the virus cells as T and B cells are also fighting the virus cells.
- T cells and B cells alone fight the virus cells.

With the first possibility, the human body attains stability and hence immune state.We can say that following the suppression of viral population abundance to a very low level by the NK cells, it becomes very easy for the T and B cells to achieve stability and attain immunity to this viral infection.The second possibility is when T and B cells are the only lymphocytes fighting the virus cells. This is the possibility which was considered by Anderson and May (1992). The body achieves stability and corresponding immunity.

In the last phase of immune response, we observed that the body is able to fight against virus infection as time increases.

CHAPTER 5

CONCLUSION AND RECOMMENDATIONS

5.0 OVERVIEW

In this chapter, we present the conclusion of the study. We also present some recommendations based on the work done for further research.

5.1 CONCLUSION

By numerical simulation analysis, the cells (T, B and NK) grow exponentially and reach a carrying capacity as time‘t’ increases. It is observed that when viruses enter the human body, these lymphocytes increase in number to reduce the abundance of the virus cells. In the last phase of immune response, we observed that the body is able to fight against virus infection if these lymphocytes types fight against the virus cells. These findings are in consistent with the qualitative method used by Anderson and May (1992). Each of the models permits the existence of two types of stationary states. There is the state of no infection, with no virus cells while the other is the state of coexistence where a virus cell persists against the background of immune response. It was found from the study that the state of no infection is asymptotically stable and a state of infection is unstable. This state of no infection represents the immune state.

It can be concluded that an infected person attains immunity if the virus cells are reduced to a very minimal number or are completely destroyed in the human body.

5.2 RECOMMENDATIONS FOR FURTHER STUDY

In this thesis we have not attempted to model a particular virus disease. The use of parameter values of New York could be replaced by estimated parameter values in Ghana or elsewhere. Further research can also be done with variations in the parameter values (Bifurcation). It is also recommended that stakeholders use this study to educate people on the need to take precautionary measures on how to keep these lymphocytes strong always to keep their immune system. For instance, good nutrition will help to enhance strong immune system.

REFERENCES

1. Anderson, R.M, and May, R.M. Infectious Diseases of Humans:Dynamics and Control. Oxford University Press, 1992, pages 528-530.

2. Abedon, S. T. Basic Principles for Specific Immunity and Immunology (1999). The Ohio State University. Pages 509-542.

3. Blanchard,P. and Devaney, R.L. Differential Equations, 1998,Gary W. Ostedt, USA, Pages 1- 132.

4. Bailey N.T.J. The mathematical theory of infectious diseases and its applications, (1975) Griffin; London, UK. Pages. 105–107.

5. DiPrima, R.E. and Boyce, W.E. Elementary Differential Equations and Boundary Value Problems, 1992, John Wiley and Sons, New York, pages 89-100.

6. Gerster and Kristler, Spiking Neuron Models .Cambridge University Press, 2002, pages 5-20.

7. Grassly, N.C. and Fraser, C. Seasonal Infectious Disease Epidemiology. Biological Sciences. 2006 doi: 10.1098/rspb.2006.3604.

8. Hethcote, H.W. The Mathematical of Infectious Diseases. SIAM publications, 2000, Pages 1-20.

9. Howard, P. Solving ODE in MATLAB, (2007), New York, USA. Pages 1-22.

10. Hethcote H.W, Yorke J.A. Lecture notes in biomathematics. (1984) vol. 56. Springer; Berlin, Germany: Gonorrhea transmission dynamics and control. Page 105.

11. Luenberger, D.G., Introduction to Dynamical Systems: Theory, Models and Applications, John Wiley and Sons, New York, 1979. Pages 1-23.

12. Molenaar, J. and Mattheij,R.M. Ordinary Differential Equations in Theory and Practice. United States of America, 2002, pages 1-23.

13. Murray, J.D. Mathematical Biology II: Spatial Models and Biomedical Applications, Springer, New York, pages 4-30.

14. Strogatz, S.H. Nonlinear Dynamics and Chaos with Applications to Physics, Biology, Chemistry and Engineering, (1999), Perseus books Ltd, Massuchusetts. Pages 145-150.

15. Sakdanupaph,W. (2007). A delay differential Equation Model for Dengue Fever Transmission in Selected Countries of South-East Asia. A thesis submitted to the Department of Mathematics King Mongkurt's University of Technology North Bangkok.

16. Shonkwiler, R.W. and Herod, J. Mathematical Biology, Springer Street, New York, 2000, pages 5-10.

17. "Clinical Infectious Diseases Dissertation."Available from: http://www.phd-dissertations.com.

18. Fraser, C. and Grassly, N.C. Seasonal Infectious Disease Epidemiology. An article published Biological Sciences. (2006), The Royal Society also available from: dio 10.1089/rspb.2006.3604.

19. "International Journal of Epidemiology" Available from: http://ije.oupjournals.org.

20. "Numerical Methods for Chemical Engineering". Available from: http://www.amazon.com/Numerical.

APPENDIX A

MATLAB PROGRAMMING FOR FINDING THE ROOTS AND EIGENVALUES

M-File to Find the Roots and Eigenvalues

```
##### SOURCE BEGIN #####
eqs1='1-1.25*x+0.05*x*y, 0.1*y-1.25*x*y';
[X, y]=solve (eqs1)
eqs2='1-1.25*n+0.05*n*v,1-
1.25*b+(0.252*t*b)/(1+0.008*t*b)+0.05*v*b,1-
1.25*t+0.252*t*b/(1+0.008*t*b),0.1*v-0.05*v*b-1.25*v*n';
[n,b,t,v]=solve (eqs2)
p= [1,-26, 125,-100];
r=roots (p)
p= [1,-26, 125,-100];
r=roots (p)
A=[-1.25,0.05,0,0,0;0,-0.08,0,0,0;0,0,-1.0505,0.1996,0.04;0,0,0.1996,-
1.0505,0;0,0,0,0,-0.9];
Lambda=eig (A)
B=[-1.21,0.05,0,0,0;-0.008,-1.24,0,0,0;0,0,-1.25,0,0.04;0,0,0,-
1.25,0;0,0,0,0,0.99];
Lambda=eig (B)
C=[-1.21,0.05,0,0,0;-0.008,-6.25,0,0,0;0,0,-1.25,0,0.25;0,0,0,-
1.25,0;0,0,0,0,0.05];
Lambda=eig(C)
D=[-1.21,1,0,0,0;-0.008,-24.99,0,0,0;0,0,-1.25,0,1;0,0,0,-1.25,0;0,0,0,0,-
0.1];
Lambda=eig (D)
E=[-1.246,0.004,0,0,0;-0.0008,-0.09166,0,0,0;0,0,-12.5,0,0.0407;0,0,0,-
1.25,0;0,0,2.25,0,0.0919];
Lambda=eig (E) A=[-1.25,0,0,0.05;0,-1.0012,0.1990,0.04;0,0.2480,-
1.0516,0;0,0,0,-1.1900];
lambda=eig(A)
H=[-1.25,0,0,0.2500;0,-0.0669,0.1893,0.04;0,1.1831,-1.0671,0;0,0,0,-6.1900];
lambda=eig(H)
G=[-1.25,0,0,1;0,2.9110,0.1584,0.04;0,3.9611,-1.0916,0;0,0,0,-24.94];
lambda=eig(G)
Y=[-13.008,0,0,0.0039;0,-12.8034,0.01935,0.0038;0,0.2046,-
1.2307,0;203.9499,11.758,0,-0.0015];
lambda=eig(Y)

##### SOURCE END #####
```

APPENDIX B

NUMERICAL SOLUTION

M-File to Find the Numerical Solutions of the Models

```
function yprft =yprft(t,y)
yprft(1) =1-1.25*y(1)+0.252*y(1)*y(2)*y(3)/(1+0.008*y(1)*y(2)*y(3));
yprft(2) =1-1.25*y(2)+0.252*y(1)*y(2)*y(3)/(1+0.008*y(1)*y(2)*y(3));
yprft(3) =1-1.25*y(3)+0.252*y(1)*y(2)*y(3)/(1+0.008*y(1)*y(2)*y(3));
yprft = [yprft(1) yprft(2) yprft(3)]';

function ydm=ydm(t,y)
ydm=[1-1.25*y(1)+0.05*y(1)*y(2);0.1*y(2)-1.25*y(1)*y(2)];

function overlap =overlap(t,y)
overlap(1)=1-1.25*y(1)+0.05*y(1)*y(4);
overlap(2)=1-1.25*y(2)+0.252*y(3)*y(2)/(1+0.008*y(3)*y(2))+0.05*y(4)*y(2);
overlap(3) =1-1.25*y(3)+0.252*y(2)*y(3)/(1+0.008*y(2)*y(3));
overlap(4) =0.1*y(4)-0.05*y(4)*y(2)-1.25*y(4)*y(1);

overlap = [overlap(1) overlap(2) overlap(3) overlap(4)]';

function ypmf =ypmf (t,y)
ypmf (1)=1-1.25*y(1)+0.05*y(1)*y(2);
ypmf (2)=0.1*y(2)-1.25*y(1)*y(2);
ypmf (3) =1-1.25*y(4)+0.252*y(4)*y(3)/(1+0.008*y(4)*y(3));
ypmf(4) =1-1.25*y(3)+0.252*y(3)*y(4)/(1+0.008*y(4)*y(3))+0.05*y(2)*y(3);

ypmf = [ypmf(1) ypmf(2) ypmf(3) ypmf(4)]';

function yftf =yftf (t,y)

yftf(1)=0.1*y(3)-0.01*y(2)*y(3);
yftf(2) =1-1.25*y(2)+0.252*y()*y(3)/(1+0.008*y(3)*y(3));
yftf(3) =1-1.25*y(2)+0.252*y(2)*y(1)/(1+0.008*y(1)*y(2))+0.05*y(2)*y(3);
yftf = [yftf(1) yftf(2) yftf(3)]';
```

APPENDIX C

ACTUAL FIGURES OF NUMERICAL SOLUTION

```
   t0=0;
>> tf=10;
>> y0=[5,5,5];
[t,y]=ode45('yftg',[t0,tf],y0)
t =
   0
   0.2010
   0.4019
   0.6029
   0.8038
   1.0538
   1.3038
   1.5538
   1.8038
   2.0538
   2.3038
   2.5538
   2.8038
   3.0538
   3.3038
   3.5538
   3.8038
   4.0538
   4.3038
   4.5538
   4.8038
   5.0538
   5.3038
   5.5538
   5.8038
   6.0538
   6.3038
   6.5538
   6.8038
   7.0538
   7.3038
   7.5538
   7.8038
   8.0538
   8.3038
   8.5538
   8.8038
   9.0538
   9.3038
   9.5538
   9.8038
   9.8529
   9.9019
   9.9510
  10.0000

y =
   5.0000   5.0000   5.0000
   5.0212   5.2507   5.0492
   5.0832   5.5047   5.0964
   5.1848   5.7690   5.1412
   5.3257   6.0511   5.1837
   5.5577   6.4386   5.2326
   5.8595   6.8804   5.2766
   6.2401   7.3928   5.3146
   6.7095   7.9932   5.3454
   7.2787   8.6985   5.3677
   7.9581   9.5233   5.3798
```

8.7504	10.4739	5.3799	20.3483	24.0552	3.6513
9.6483	11.5454	5.3665	20.4958	24.1353	3.5249
10.6342	12.7207	5.3381	20.6132	24.1733	3.4023
11.6763	13.9658	5.2937	20.7054	24.1768	3.2838
12.7384	15.2403	5.2331	20.7765	24.1524	3.1695
13.7837	16.5011	5.1568	20.8302	24.1061	3.0595
14.7785	17.7066	5.0660	20.8693	24.0423	2.9537
15.6996	18.8263	4.9622	20.8964	23.9650	2.8521
16.5321	19.8392	4.8477	20.9136	23.8777	2.7545
17.2698	20.7331	4.7245	20.9228	23.7833	2.6609
17.9136	21.5042	4.5949	20.9253	23.6840	2.5711
18.4678	22.1560	4.4609	20.9225	23.5814	2.4850
18.9387	22.6950	4.3243	20.9153	23.4772	2.4023
19.3350	23.1304	4.1869	20.9135	23.4567	2.3865
19.6664	23.4730	4.0499	20.9116	23.4362	2.3708
19.9407	23.7342	3.9144	20.9095	23.4156	2.3553
20.1655	23.9248	3.7813	20.9073	23.3951	2.3398

```
>> tspan=[1,7];
y0=[1,1];
[t,y]=ode45('ydm',tspan,y0)
t =
   1.0000
   1.0437
   1.0874
   1.1311
   1.1747
   1.3247
   1.4747
   1.6247
   1.7747
   1.9247
   2.0747
   2.2247
   2.3747
   2.5247
   2.6747
   2.8247
   2.9747
```

3.1247	4.6247	6.1247
3.2747	4.7747	6.2747
3.4247	4.9247	6.4247
3.5747	5.0747	6.5747
3.7247	5.2247	6.6811
3.8747	5.3747	6.7874
4.0247	5.5247	6.8937
4.1747	5.6747	7.0000
4.3247	5.8247	
4.4747	5.9747	

y =					
1.0000	1.0000	0.8356	0.1813	0.8036	0.0230
0.9914	0.9512	0.8305	0.1575	0.8031	0.0201
0.9832	0.9052	0.8261	0.1369	0.8027	0.0176
0.9753	0.8619	0.8223	0.1190	0.8023	0.0153
0.9677	0.8209	0.8191	0.1036	0.8020	0.0134
0.9440	0.6965	0.8164	0.0902	0.8017	0.0117
0.9235	0.5935	0.8141	0.0786	0.8015	0.0102
0.9058	0.5077	0.8121	0.0685	0.8013	0.0089
0.8906	0.4355	0.8104	0.0597	0.8011	0.0078
0.8775	0.3746	0.8089	0.0521	0.8010	0.0068
0.8663	0.3229	0.8076	0.0455	0.8008	0.0059
0.8568	0.2789	0.8066	0.0397	0.8007	0.0052
0.8486	0.2413	0.8057	0.0346	0.8007	0.0047
0.8416	0.2091	0.8049	0.0302	0.8006	0.0043
		0.8042	0.0264	0.8005	0.0039

```
>> t0=0;
>> tf=50;
>> y0=[5;5;5;5];
>>
[t,y]=ode45('overlap',[t0,tf],y
0)

t =

         0
    0.0078
    0.0157
    0.0235
    0.0314
    0.0640
    0.0966
    0.1291
    0.1617
    0.1951
    0.2284
    0.2617
    0.2950
    0.3323
    0.3695
    0.4067
    0.4440
    0.4861
    0.5281
    0.5702
    0.6123
    0.6605
    0.7087
    0.7569
    0.8051
    0.8610
    0.9170
    0.9729
    1.0288
    1.0942
    1.1596
    1.2250
    1.2904
    1.3674
    1.4443
    1.5212
    1.5982
    1.6885
    1.7788
    1.8691
    1.9594
    2.0644
    2.1694
    2.2744
    2.3793
    2.4993
    2.6192
    2.7392
    2.8591
    2.9931
    3.1270
    3.2610
    3.3950
    3.5406
    3.6863
    3.8319
    3.9776
    4.1314
    4.2851
    4.4389
    4.5927
    4.7667
    4.9408
    5.1149
```

5.2890	13.1616	24.2600
5.4906	13.6574	24.7741
5.6923	14.1532	25.2882
5.8940	14.6490	25.7544
6.0956	15.1481	26.2206
6.3278	15.6472	26.6868
6.5600	16.1463	27.1530
6.7922	16.6454	27.5383
7.0244	17.0707	27.9235
7.2919	17.4959	28.3088
7.5595	17.9212	28.6941
7.8271	18.3464	29.0593
8.0947	18.7155	29.4246
8.4049	19.0847	29.7898
8.7151	19.4538	30.1550
9.0252	19.8229	30.5791
9.3354	20.2112	31.0031
9.7063	20.5994	31.4271
10.0771	20.9877	31.8511
10.4480	21.3760	32.3549
10.8188	21.8400	32.8587
11.2806	22.3039	33.3626
11.7423	22.7678	33.8664
12.2041	23.2317	34.3705
12.6658	23.7458	34.8746

35.3788	40.5485	46.7626
35.8829	41.0185	47.1408
36.3027	41.4886	47.5189
36.7226	41.9587	47.8971
37.1424	42.4288	48.2567
37.5623	42.9517	48.6164
37.9231	43.4746	48.9761
38.2839	43.9975	49.3358
38.6447	44.5204	49.5018
39.0055	44.9864	49.6679
39.3912	45.4524	49.8339
39.7770	45.9185	50.0000
40.1627	46.3845	

y =

5.0000	5.0000	5.0000	5.0000
4.9685	5.0096	5.0000	4.7557
4.9368	5.0187	5.0001	4.5248
4.9048	5.0273	5.0003	4.3064
4.8728	5.0355	5.0005	4.0998
4.7388	5.0655	5.0019	3.3536
4.6043	5.0898	5.0041	2.7582
4.4706	5.1096	5.0069	2.2816
4.3387	5.1257	5.0102	1.8976
4.2065	5.1392	5.0139	1.5798
4.0773	5.1503	5.0179	1.3224
3.9515	5.1593	5.0221	1.1131
3.8295	5.1668	5.0266	0.9418
3.6976	5.1737	5.0317	0.7857
3.5705	5.1793	5.0370	0.6594
3.4484	5.1838	5.0423	0.5568
3.3311	5.1877	5.0478	0.4728
3.2043	5.1913	5.0539	0.3954
3.0835	5.1943	5.0601	0.3329
2.9684	5.1969	5.0663	0.2821

2.8588	5.1992	5.0726	0.2404
2.7398	5.2016	5.0797	0.2015
2.6275	5.2038	5.0867	0.1701
2.5216	5.2059	5.0938	0.1446
2.4217	5.2079	5.1008	0.1236
2.3129	5.2104	5.1089	0.1038
2.2114	5.2129	5.1169	0.0878
2.1166	5.2156	5.1249	0.0749
2.0281	5.2184	5.1329	0.0642
1.9321	5.2220	5.1422	0.0540
1.8435	5.2259	5.1516	0.0458
1.7618	5.2301	5.1609	0.0391
1.6865	5.2346	5.1703	0.0336
1.6054	5.2404	5.1813	0.0283
1.5317	5.2467	5.1925	0.0241
1.4647	5.2534	5.2038	0.0206
1.4039	5.2607	5.2153	0.0177
1.3395	5.2700	5.2290	0.0150
1.2820	5.2800	5.2431	0.0127
1.2306	5.2907	5.2575	0.0109
1.1847	5.3022	5.2723	0.0093
1.1374	5.3166	5.2902	0.0079
1.0960	5.3321	5.3087	0.0067
1.0596	5.3487	5.3280	0.0057
1.0277	5.3665	5.3482	0.0049
0.9960	5.3883	5.3725	0.0041
0.9687	5.4119	5.3981	0.0035
0.9453	5.4372	5.4252	0.0030
0.9251	5.4643	5.4540	0.0025
0.9058	5.4970	5.4882	0.0021
0.8895	5.5324	5.5248	0.0018
0.8757	5.5705	5.5641	0.0015
0.8640	5.6118	5.6063	0.0013
0.8534	5.6603	5.6557	0.0011
0.8445	5.7131	5.7092	0.0009
0.8371	5.7704	5.7671	0.0007
0.8309	5.8327	5.8300	0.0006
0.8255	5.9044	5.9021	0.0005
0.8211	5.9827	5.9807	0.0004
0.8174	6.0682	6.0666	0.0003
0.8144	6.1617	6.1603	0.0003
0.8115	6.2780	6.2769	0.0002
0.8093	6.4068	6.4059	0.0002
0.8075	6.5492	6.5485	0.0002
0.8060	6.7068	6.7062	0.0001
0.8047	6.9103	6.9098	0.0001
0.8036	7.1388	7.1384	0.0001
0.8028	7.3949	7.3946	0.0001
0.8022	7.6812	7.6810	0.0000
0.8016	8.0515	8.0513	0.0000

0.8012	8.4682	8.4681	0.0000
0.8009	8.9333	8.9332	0.0000
0.8007	9.4466	9.4466	0.0000
0.8005	10.0951	10.0951	0.0000
0.8004	10.7962	10.7962	0.0000
0.8003	11.5371	11.5370	0.0000
0.8002	12.3010	12.3010	0.0000
0.8001	13.1901	13.1901	0.0000
0.8001	14.0552	14.0552	0.0000
0.8001	14.8723	14.8723	0.0000
0.8000	15.6237	15.6237	0.0000
0.8000	16.4212	16.4212	0.0000
0.8000	17.1049	17.1049	0.0000
0.8000	17.6777	17.6777	0.0000
0.8000	18.1492	18.1492	0.0000
0.8000	18.6175	18.6175	-0.0000
0.8000	18.9746	18.9746	-0.0000
0.8000	19.2407	19.2407	0.0000
0.8000	19.4384	19.4384	0.0000
0.8000	19.5977	19.5977	-0.0000
0.8000	19.7128	19.7128	-0.0000
0.8000	19.7931	19.7931	0.0000
0.8000	19.8503	19.8503	0.0000
0.8000	19.8937	19.8937	-0.0000
0.8000	19.9246	19.9246	-0.0000
0.8000	19.9458	19.9458	0.0000
0.8000	19.9608	19.9608	0.0000
0.8000	19.9707	19.9707	-0.0000
0.8000	19.9781	19.9781	-0.0000
0.8000	19.9835	19.9835	0.0000
0.8000	19.9876	19.9876	0.0000
0.8000	19.9903	19.9903	0.0000
0.8000	19.9925	19.9925	-0.0000
0.8000	19.9941	19.9941	0.0000
0.8000	19.9954	19.9954	0.0000
0.8000	19.9965	19.9965	0.0000
0.8000	19.9973	19.9973	-0.0000
0.8000	19.9979	19.9979	0.0000
0.8000	19.9984	19.9984	0.0000
0.8000	19.9988	19.9988	-0.0000
0.8000	19.9992	19.9992	-0.0000
0.8000	19.9994	19.9994	0.0000
0.8000	19.9995	19.9995	0.0000
0.8000	19.9997	19.9997	-0.0000
0.8000	19.9998	19.9998	-0.0000
0.8000	19.9998	19.9998	0.0000
0.8000	19.9999	19.9999	0.0000
0.8000	19.9999	19.9999	-0.0000
0.8000	19.9999	19.9999	-0.0000
0.8000	20.0000	20.0000	0.0000

0.8000	20.0000	20.0000	0.0000
0.8000	20.0000	20.0000	0.0000
0.8000	20.0000	20.0000	-0.0000
0.8000	20.0000	20.0000	0.0000
0.8000	20.0000	20.0000	0.0000
0.8000	20.0000	20.0000	0.0000
0.8000	20.0000	20.0000	-0.0000
0.8000	20.0000	20.0000	0.0000
0.8000	20.0000	20.0000	0.0000
0.8000	20.0000	20.0000	-0.0000
0.8000	20.0000	20.0000	-0.0000
0.8000	20.0000	20.0000	0.0000
0.8000	20.0000	20.0000	0.0000
0.8000	20.0000	20.0000	-0.0000
0.8000	20.0000	20.0000	-0.0000
0.8000	20.0000	20.0000	0.0000
0.8000	20.0000	20.0000	0.0000
0.8000	20.0000	20.0000	-0.0000
0.8000	20.0000	20.0000	-0.0000
0.8000	20.0000	20.0000	0.0000
0.8000	20.0000	20.0000	0.0000
0.8000	20.0000	20.0000	-0.0000
0.8000	20.0000	20.0000	-0.0000
0.8000	20.0000	20.0000	0.0000
0.8000	20.0000	20.0000	0.0000

0.8000	20.0000	20.0000	0.0000
0.8000	20.0000	20.0000	-0.0000
0.8000	20.0000	20.0000	0.0000
0.8000	20.0000	20.0000	0.0000
0.8000	20.0000	20.0000	0.0000
0.8000	20.0000	20.0000	-0.0000
0.8000	20.0000	20.0000	0.0000
0.8000	20.0000	20.0000	0.0000
0.8000	20.0000	20.0000	-0.0000
0.8000	20.0000	20.0000	-0.0000
0.8000	20.0000	20.0000	0.0000
0.8000	20.0000	20.0000	0.0000
0.8000	20.0000	20.0000	-0.0000
0.8000	20.0000	20.0000	-0.0000
0.8000	20.0000	20.0000	0.0000
0.8000	20.0000	20.0000	0.0000
0.8000	20.0000	20.0000	-0.0000
0.8000	20.0000	20.0000	-0.0000
0.8000	20.0000	20.0000	0.0000
0.8000	20.0000	20.0000	0.0000
0.8000	20.0000	20.0000	0.0000
0.8000	20.0000	20.0000	-0.0000
0.8000	20.0000	20.0000	0.0000
0.8000	20.0000	20.0000	0.0000
0.8000	20.0000	20.0000	0.0000

```
   0.8000   20.0000   20.0000   -0.0000
   0.8000   20.0000   20.0000    0.0000
   0.8000   20.0000   20.0000    0.0000
   0.8000   20.0000   20.0000    0.0000
   0.8000   20.0000   20.0000    0.0000
   0.8000   20.0000   20.0000    0.0000
   0.8000   20.0000   20.0000    0.0000
>> t0=0;
>> tf=50;
>> y0=[5;5;5;5];
>> [t,y]=ode45('overlap',[t0,tf],y0)

t =
```

	0	
	0.0078	
	0.0157	
	0.0235	
	0.0314	
	0.0640	
	0.0966	
	0.1291	
	0.1617	
	0.1951	
	0.2284	
	0.2617	
	0.6605	1.3674
	0.7087	1.4443
	0.7569	1.5212
0.2950	0.8051	1.5982
0.3323	0.8610	1.6885
0.3695	0.9170	1.7788
0.4067	0.9729	1.8691
0.4440	1.0288	1.9594
0.4861	1.0942	2.0644
0.5281	1.1596	2.1694
0.5702	1.2250	2.2744
0.6123	1.2904	2.3793

2.4993	6.5600	16.1463
2.6192	6.7922	16.6454
2.7392	7.0244	17.0707
2.8591	7.2919	17.4959
2.9931	7.5595	17.9212
3.1270	7.8271	18.3464
3.2610	8.0947	18.7155
3.3950	8.4049	19.0847
3.5406	8.7151	19.4538
3.6863	9.0252	19.8229
3.8319	9.3354	20.2112
3.9776	9.7063	20.5994
4.1314	10.0771	20.9877
4.2851	10.4480	21.3760
4.4389	10.8188	21.8400
4.5927	11.2806	22.3039
4.7667	11.7423	22.7678
4.9408	12.2041	23.2317
5.1149	12.6658	23.7458
5.2890	13.1616	24.2600
5.4906	13.6574	24.7741
5.6923	14.1532	25.2882
5.8940	14.6490	25.7544
6.0956	15.1481	26.2206
6.3278	15.6472	26.6868

27.1530	37.9231	48.6164
27.5383	38.2839	48.9761
27.9235	38.6447	49.3358
28.3088	39.0055	49.5018
28.6941	39.3912	49.6679
29.0593	39.7770	49.8339
29.4246	40.1627	50.0000
29.7898	40.5485	
30.1550	41.0185	
30.5791	41.4886	
31.0031	41.9587	
31.4271	42.4288	
31.8511	42.9517	
32.3549	43.4746	
32.8587	43.9975	
33.3626	44.5204	
33.8664	44.9864	
34.3705	45.4524	
34.8746	45.9185	
35.3788	46.3845	
35.8829	46.7626	
36.3027	47.1408	
36.7226	47.5189	
37.1424	47.8971	
37.5623	48.2567	

y =

5.0000	5.0000	5.0000	5.0000
4.9685	5.0096	5.0000	4.7557
4.9368	5.0187	5.0001	4.5248
4.9048	5.0273	5.0003	4.3064
4.8728	5.0355	5.0005	4.0998
4.7388	5.0655	5.0019	3.3536
4.6043	5.0898	5.0041	2.7582
4.4706	5.1096	5.0069	2.2816
4.3387	5.1257	5.0102	1.8976
4.2065	5.1392	5.0139	1.5798
4.0773	5.1503	5.0179	1.3224
3.9515	5.1593	5.0221	1.1131
3.8295	5.1668	5.0266	0.9418
3.6976	5.1737	5.0317	0.7857
3.5705	5.1793	5.0370	0.6594
3.4484	5.1838	5.0423	0.5568
3.3311	5.1877	5.0478	0.4728
3.2043	5.1913	5.0539	0.3954
3.0835	5.1943	5.0601	0.3329
2.9684	5.1969	5.0663	0.2821
2.8588	5.1992	5.0726	0.2404

2.7398	5.2016	5.0797	0.2015
2.6275	5.2038	5.0867	0.1701
2.5216	5.2059	5.0938	0.1446
2.4217	5.2079	5.1008	0.1236
2.3129	5.2104	5.1089	0.1038
2.2114	5.2129	5.1169	0.0878
2.1166	5.2156	5.1249	0.0749
2.0281	5.2184	5.1329	0.0642
1.9321	5.2220	5.1422	0.0540
1.8435	5.2259	5.1516	0.0458
1.7618	5.2301	5.1609	0.0391
1.6865	5.2346	5.1703	0.0336
1.6054	5.2404	5.1813	0.0283
1.5317	5.2467	5.1925	0.0241
1.4647	5.2534	5.2038	0.0206
1.4039	5.2607	5.2153	0.0177
1.3395	5.2700	5.2290	0.0150
1.2820	5.2800	5.2431	0.0127
1.2306	5.2907	5.2575	0.0109
1.1847	5.3022	5.2723	0.0093
1.1374	5.3166	5.2902	0.0079
1.0960	5.3321	5.3087	0.0067
1.0596	5.3487	5.3280	0.0057
1.0277	5.3665	5.3482	0.0049
0.9960	5.3883	5.3725	0.0041

0.9687	5.4119	5.3981	0.0035
0.9453	5.4372	5.4252	0.0030
0.9251	5.4643	5.4540	0.0025
0.9058	5.4970	5.4882	0.0021
0.8895	5.5324	5.5248	0.0018
0.8757	5.5705	5.5641	0.0015
0.8640	5.6118	5.6063	0.0013
0.8534	5.6603	5.6557	0.0011
0.8445	5.7131	5.7092	0.0009
0.8371	5.7704	5.7671	0.0007
0.8309	5.8327	5.8300	0.0006
0.8255	5.9044	5.9021	0.0005
0.8211	5.9827	5.9807	0.0004
0.8174	6.0682	6.0666	0.0003
0.8144	6.1617	6.1603	0.0003
0.8115	6.2780	6.2769	0.0002
0.8093	6.4068	6.4059	0.0002
0.8075	6.5492	6.5485	0.0002
0.8060	6.7068	6.7062	0.0001
0.8047	6.9103	6.9098	0.0001
0.8036	7.1388	7.1384	0.0001
0.8028	7.3949	7.3946	0.0001
0.8022	7.6812	7.6810	0.0000
0.8016	8.0515	8.0513	0.0000
0.8012	8.4682	8.4681	0.0000

0.8009	8.9333	8.9332	0.0000
0.8007	9.4466	9.4466	0.0000
0.8005	10.0951	10.0951	0.0000
0.8004	10.7962	10.7962	0.0000
0.8003	11.5371	11.5370	0.0000
0.8002	12.3010	12.3010	0.0000
0.8001	13.1901	13.1901	0.0000
0.8001	14.0552	14.0552	0.0000
0.8001	14.8723	14.8723	0.0000
0.8000	15.6237	15.6237	0.0000
0.8000	16.4212	16.4212	0.0000
0.8000	17.1049	17.1049	0.0000
0.8000	17.6777	17.6777	0.0000
0.8000	18.1492	18.1492	0.0000
0.8000	18.6175	18.6175	-0.0000
0.8000	18.9746	18.9746	-0.0000
0.8000	19.2407	19.2407	0.0000
0.8000	19.4384	19.4384	0.0000
0.8000	19.5977	19.5977	-0.0000
0.8000	19.7128	19.7128	-0.0000
0.8000	19.7931	19.7931	0.0000
0.8000	19.8503	19.8503	0.0000
0.8000	19.8937	19.8937	-0.0000
0.8000	19.9246	19.9246	-0.0000
0.8000	19.9458	19.9458	0.0000

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    0.8000   19.9608   19.9608    0.0000
    0.8000   19.9707   19.9707   -0.0000
    0.8000   19.9781   19.9781   -0.0000
    0.8000   19.9835   19.9835    0.0000
    0.8000   19.9876   19.9876    0.0000
    0.8000   19.9903   19.9903    0.0000
    0.8000   19.9925   19.9925   -0.0000
    0.8000   19.9941   19.9941    0.0000
    0.8000   19.9954   19.9954    0.0000
    0.8000   19.9965   19.9965    0.0000
    0.8000   19.9973   19.9973   -0.0000
    0.8000   19.9979   19.9979    0.0000
    0.8000   19.9984   19.9984    0.0000
    0.8000   19.9988   19.9988   -0.0000
t0=0;
tf=20;
y0=[5;5;5];
[t,y]=ode45('yprft',[t0,tf],y0)


t =


         0
    0.0239
    0.0478
    0.0718
```

0.0957

0.1647

0.2336

0.3026

0.3715

0.5251

0.6786

0.8321

0.9856

1.2323

1.4789

1.7256

1.9722

2.1741

2.3759

2.5778

2.7796

3.0367

3.2938

3.5509

3.8080

4.1156

4.4231

4.7307

5.0383

5.4271

5.8158

6.2046

6.5933

7.0933

7.5933

8.0933

8.5933

9.0933

9.5933

10.0933

10.5933

11.0933

11.5933

12.0933

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13.0933

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14.0933

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15.0933

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16.0933

16.5933

17.0933

17.5933

18.0933

18.5933

18.9450

19.2967

19.6483

20.0000

y =

5.0000	5.0000	5.0000
5.2617	5.2617	5.2617
5.5442	5.5442	5.5442
5.8471	5.8471	5.8471
6.1692	6.1692	6.1692
7.1895	7.1895	7.1895
8.2990	8.2990	8.2990
9.4435	9.4435	9.4435
10.5805	10.5805	10.5805
12.9533	12.9533	12.9533
15.0427	15.0427	15.0427
16.8279	16.8279	16.8279
18.3289	18.3289	18.3289
20.2629	20.2629	20.2629

21.7069	21.7069	21.7069
22.7632	22.7632	22.7632
23.5442	23.5442	23.5442
24.0418	24.0418	24.0418
24.4307	24.4307	24.4307
24.7327	24.7327	24.7327
24.9686	24.9686	24.9686
25.1999	25.1999	25.1999
25.3684	25.3684	25.3684
25.4881	25.4881	25.4881
25.5751	25.5751	25.5751
25.6531	25.6531	25.6531
25.7063	25.7063	25.7063
25.7400	25.7400	25.7400
25.7628	25.7628	25.7628
25.7854	25.7854	25.7854
25.7991	25.7991	25.7991
25.8052	25.8052	25.8052
25.8085	25.8085	25.8085
25.8142	25.8142	25.8142
25.8171	25.8171	25.8171
25.8167	25.8167	25.8167
25.8161	25.8161	25.8161
25.8174	25.8174	25.8174
25.8180	25.8180	25.8180

25.8179 25.8179 25.8179

25.8178 25.8178 25.8178

25.8181 25.8181 25.8181

25.8182 25.8182 25.8182

25.8182 25.8182 25.8182

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