ANALYSIS OF DYNAMICS OF HTLV TYPE 1 INFECTION ON $CD4^+$ T-CELLS WITH CELL-TO- CELL AND MITOTIC TRANSMISSIONS USING FRACTIONAL ORDER MODEL

By

CHEPNG'ENO MARY

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DECLARATION

This research project is my original work and has not been presented for a degree in any other university or any award.

Mary Chepngeno

Signature……. Date……

Department of Mathematics and Actuarial Science.

I confirm that the work reported in this research project was carried out by the above candidate under my supervision.

Dr. Isaac Chepkwony

Signature……. Date……

Department of Mathematics

School of pure and applied sciences

Kenyatta University

DEDICATION

I dedicate this work to my late father and mother.

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First and foremost, i take pride in acknowledging God for providing me with the ability, understanding, skills, and chance to begin this investigational study and see it through. This accomplishment would not have been possible without his approval.

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TABLE OF CONTENT

LIST OF TABLES

LIST OF FIGURES

ACRONYMS AND ABBREVIATION

SYMBOLS	MEANING
ATL	Adult T-cell leukemia
FODE	Fractional order differential equation.
HAM/TSP	HTLV type 1 associated myelopathy/tropical spastic paraparesis
HTLV-1	Human T lymphotropic virus-1 infection
t	Time

ABSTRACT

Human T lymphotropic virus-1 which attacks $CD4^+$ T-cells is a serious epidemic throughout the world. Even though research has been done extensively on the virus, it is still a threat in various parts of the world. In this research project, we formulate a fractional order model of Human T lymphotropic virus type 1 infection on CD4 cells. The model is made up of three nonlinear differential equations with fractional derivatives defined using caputo. The main aim is to develop and to explore the dynamics of infection of CD4 cells by the virus using fractional order model. The uniqueness of solution was discussed and positivity of solution provided using generalized fractional mean value theorem. Making use of the next generation matrix mathematical method, the basic reproduction number, Ro, is calculated. Model eqilibria are determined. The Routh-Hurwitz stability requirement and the LaSalle's invariance principle are used to investigate the stability of model equilibria. The global stability of equilibria is determined using the Lyapunov functional method. From the investigation done on stability, both endemic equilibrium point and the equilibrium point free of disease were discovered to be globally and locally asymptotically stable whenever the number of reproductions is more than one and when it is less than one respectively. To acquire numerical results, we used a numerical methodology that involves writing the differential equations with fractional order as an infinite system of ordinary differential equations of the first order. Then by using relatively small number of terms, the solutions are obtained by use of Runge-Kutta method of fourth order applied with the help of python. Finally, we presented the results obtained for various values of alpha graphically. The findings point to the need to control mitotic transmission during therapeutic intervention as well as the benefits of employing fractional order to model viral infection on CD4 cells.

CHAPTER 1

INTRODUCTION

This chapter entails the following: background of the study, statement of the problem, objectives and justification of the study, significance of the study and definition of terms.

1.1 Background to the study

Type 1 human T-cell lymphotropic virus which attacks CD4cells,is currently a serious epidemic in intertropical Africa, Japan, South America and the Caribbean (Asquith and Bangham, 2007, Bangham, 2000,Bangham*et al*., 1999, Asquith and Bangham, 2008 and Utano, Yoshihisa & Steven, 2005). Between ten and twenty million people have the infection worldwide (Cook, Elemans, Rowan & Asquith; Proietti *et al*., 2005). Currently, no cure for the virus has been found nor a vaccine to prevent it and there is neither an adequate treatment for diseases caused by this virus(Charles, 2000 and Proietti, Carneiro-Proietti, Catalan-Soares; Murphy, 2005). There are two clinically independent disease caused by HTLV type i.e HAM/TSP which is a nervous system disease that progresses slowly. (Saito and Bangham, 2012) and ATL which is a fast growing Malignant T-cell tumor which usually causes death to an individual ailing from the disease within a period of twelve months (Satou and Matsuoka, 2012).

A high percentage of people infected with HTLV-1 present no symptoms throughout life, while a small percentage i.e less than 3% of people infected with HTLV type 1 develop HAM/TSP (Saito and Bangham, 2012). The transmission of the virus is via breast milk given to a child by a mother who is infected, sexual encounter with an individual who is infected and also viatrans fusion of blood (Utano *et al*., 2005). CD4cells carry approximately 92% of the proviral load in chronic HTLV-1 infection and CD8 cells carry approximately 8%(Koyanagi*et al*, 1993; Cho *et al*., 1995; Tattermusch and Bangham, 2012; Bangham,

2000). HTLV-1 transmission primarily happens through two routes. The first one is horizontal or infectious spread of the provirus to uninfected cells through infected cell– to – uninfected cell contact. An organized structure termed as viral synapse which is firmly attached to the host cell that is not infected is formed through rearrangement of the cytoskeleton of proviral cell, and therefore the HTLV-1 virions enveloped are transmitted through the viral synaptic space from infected to uninfected cells without exiting to outer parts. When HTLV-1 virions enter the cytoplasm, reverse transcriptase enzyme integrates viral DNA into DNA of uninfected host cell (Pique and Jones, 2012) and the other is "Clonal expansion, which encourages division of cells which are infected. This route is referred to as vertical or mitotic transmission"(Pique and Jones, 2012).

HTLV type 1 infection in an individual is assumed to occur in two stages; first the HTLV type 1 is believed to first spread from infected cells to uninfected cell, mainly CD4cells, and thereafter by mitotic transmission of cells that are infected and active (Tattermusch and Bangham, (2012).

The research that has been done on HTLV-1 has mostly been done using integer order models and very few on fractional order models. Real world phenomena are accurately modeled by making use of fractional order differential equations instead of integer order ones since systems having memory and which exist in many biological systems are naturally associated to FODE (Jumarie, 2006).This motivates us to modelHTLV-1 on CD4+ T cells by using fractional order.

1.2 Statement of the problem

HTLV-1 infection is a worldwide problem with HTLV-1 infection being reported from, South America, Caribbean, Japan and intertropical Africa. At the moment there is no vaccine to prevent the virus or a treatment for it. The spread of HTLV-1 infection can be minimized by

understanding its infection pattern. The research that has been done on the virus has mostly been done using integer order models and very few on fractional order models. Suggestion in the recently done research is that real world phenomena is accurately modeled by making use of fractional order differential equations instead of integer order ones. And due to its flexibility, it explains a dynamic system better. The goal of this study is to create a model of fractional order of HTLV-1 infection on CD4 cells that includes cell-to-cell infection and mitotic transmission. The model will then be examined to produce informative data revealing the virus' infection pattern on CD4 cells as well as determining the effect of mitotic transmission and the fractional derivative's order α, on the infection pattern to advise healthcare practitioners on how to limit HTLV-1 infection..

1.3 Objectives of the study

1.3.1 General Objectives

This study aims to develop and analyze fractional order model for the dynamics of HTLV-1 infection on $CD4^{+}T$ cells with both cell-to- cell and mitotic transmissions.

1.3.2 Specific Objectives

The following objectives will guide this research:

i. Develop a fractional order model for the dynamics of HTLV-1 infection on $CD4^{+}T$ cells.
ii. Perform stability analysis on the HTLV-1 free equilibrium and HTLV-1 persistence equilibrium.
iii. Determine the impact of mitotic transmission on HTLV-1 infection.
iv. Determine the effect of the fractional derivative's order.

1.4 Justification of the study

HTLV type 1 causes no problem at all in most of the people infected with it. But approximately 5% of people infected with the virus will develop one of two serious conditions i.e. ATL which is a form of cancer characterized by unusually rapid growth of white blood cells and HAM/TSP which is a chronic nerve system disorder that damages the spinal cord. It is from this statistics and effects that we observe that there is need to develop mathematical model to look at HTLV-1 infection.

1.5 Significance of the study

The purpose of this research is to formulate a fractional order model of HTLV-1 infection on $CD4^+$T cells. Through this research, an understanding of the dynamics of the virus infection will be highlighted. This will help health workers make more accurate projections on the spread of the virus among $CD4^+$T cells. The results obtained from this study will help to understand the infection pattern of HTLV-1 infection. The analysis of the simulations of the model would be used in the formulation of sound policies that will counter the spread of HTLV-1. Additionally, this research will assist medical professionals in comprehending that mitotic transmission is a significant factor in the spread of HTLV-1 infection of CD4+T cells, as well as the need to control it in therapeutic measures to minimize the spread. Also fractional derivative's order α has a role to play in HTLV-1 infection on CD4 cells and the need to be looked into.

1.6 Definition of Terms

Fractional order system-is a system that is dynamic and can be illustrated mathematically by making use of differential equation having orders which are fractional.

HTLV-1-It is also known as Human T-cell leukemia virus type 1/Human T lmphotropic virus type 1. It is a retrovirus causing T-cell leukemia (cancer of the white blood cell).

Retrovirus- It's an RNA-based virus rather than a DNA-based one. They have an enzyme called reverse transcriptase, which converts RNA to DNA once inside a cell.

R_0- It's a mathematical term that describes a disease's infectiousness. The reproduction number is another name for it. R_0 represents the number of infected cells on average caused by an infected cell.

Local and global stability of an equilibrium-A system is described as locally stable in case it returns to equilibrium after a sufficiently small perturbation (one that only changes virus density by a sufficiently small amount from its equilibrium values), whereas a system is described as globally stable in case it returns to equilibrium after any possible perturbation that does not actually eliminate a virus.

Lyapunov function - A scalar function defined on phase space is the Lyapunov function. It is an essential tool in analyzing stability systems which are dynamical. It is used both in theory and application.

Mitotic transmission-The division of a single actively infected cell into two new infected cells.

Infectious transmission – The process by which actively infected cell infected an healthy cell when they come in contact with each other.

Tax-Also known as HTLV-1 transactivator protein. It is a protein of significant interest in HTLV-1 pathogenesis as it is a potent activator of a variety of transcription pathways. If an infected cell expresses tax, then it means it is an actively infected cell. But if an infected cell expresses no tax, then it means it is an inactively infected cell.

Python- is a high-level programming language that is widely used in data analytics.

CHAPTER 2

LITERATURE REVIEW

The first retrovirus to be discovered in the world is HTLV-1. This virus causes an infection on CD4 cells (Bangham, 2000).Transmission through mitosis rather than through infected cell-to- uninfected cell contact is important (Pique and Jones, 2012 and Mortreux, Gabet, Wattel, 2003). (Asquith and Bangham, 2008) have proposed a model of HTLV-1 persistence by combining mathematical and experimental approaches. Replication of the virus mainly occurs through mitosis and HTLV type 1 proteins, especially Tax, needs to be expressed so that cells that are infected can replicate, though expression of viral protein Tax occur in minority of cells which are infected (Cook *et al*., 2013; Hollsberg, 1999; Mesnard and Devaux, 1999; Bex and Gaynor, 1998). Fast multiplication of infected cell showing Tax occurs than those infected but express no Tax (Asquith and Bangham, 2008).Infected T cell proliferation induced by the HTLV-1 Tax protein maintains the very high provirus load in HTLV type 1 infection (Wodarz and Bangham, 2000). In HAM/TSP patients, tax expression is notably greater than in asymptotic carriers at any given proviral load (Asquith *et al*., 2005). Therefore presence of tax is a strong predictor of HAM/TSP disease (Asquith and Bangham, 2008). A number of research studies on this virus have been done through formulation of models.

(Nowak & Bangham, 1996) investigated the evolution of long-lasting viral immunity in viruses such as HTLV and HIV. To determine the association between antiviral immunity responses, virus load and virus variety, a mathematical model was built and investigated. The findings revealed that the virus load has no link with immunity responses in HTLV and HIV infection, despite the fact that immunity responses are believed to contribute significantly in virus management.

(Gomez-Acevado & Li, 2005) in a mathematical model of CD4 cells infection with HTLV type 1, backward bifurcation was examined. Cells without infection and cells with infection were included in a mathematical model. Backward bifurcation could be a natural part of the infection cycle of HTLV-1, according to the model's study. Finally, they suggested greater study into the dynamics of HTLV-1 infection should be undertaken using more realistic mathematical models, with the results validated using clinical data.

(Asquith *et al*., 2005) studied how virus interacts in a host with human T lymphotropic virus type I. In the study they quantify the contribution of protein expression by the virus and cytotoxic T lymphocyte lysis of the cell that is infected to proviral load and found that a low proportion of lysis of T lymphocytes that are cytotoxic and a high level proportion of Tax expression have independent and significant association with a proviral load that is high. In conclusion they make a proposal that rather than a high proviral load, a high expression tax has association with the Pathogenesis of HAM/TSP.

(Li & Lim, 2011) studied the Tax expression's function in HTLV-1 persistence in Vivo. A Compartmental model with three dimensional was constructed. The model described the dynamic interactions among target cells which are infected but inactive, activation of target cells and responses of immunity to the virus.

(Li& Zhou, 2014) used an integer order model to study the dynamics of HTLV type 1 infection on$CD4^{+}$T lymphocyte infection from infected cell to uninfected cell infection and also through mitosis. A mathematical model was developed and tested. The model is divided into three sections: uninfected cells, inactive infected cells, and cells with active infection. The findings discovered that increasing the fraction of cells expressing tax resulted in a reduction of percentage of proviral cells at the point of equilibrium. In conclusion they

recommended that in the therapeutic intervention, tax expression should be controlled to be able to decrease the likelihood of the disease HAM/TSP.

The research that has been done on HTLV-1 has mostly been done using integer order models and very few on fractional order models. Real world phenomena are accurately modeled by making use of fractional order differential equations instead of integer order ones since systems having memory and which exist in many biological systems are naturally associated to FODE (Jumarie, 2006). This motivates us to model HTLV-1 on CD4+ T cells by using fractional order.

CHAPTER 3

RESEARCH METHODOLOGY

In this chapter an idea concerning fractional calculus is first given theoretically, and then we shall derive the model and analyze it.

3.1 FRACTIONAL CALCULUS

Extensive utilization of the concept of fractional calculus has been done in many fields (Ahmed & Elgazzar, 2007 and Matignon, 1996). Real processes have been modeled via the usage of fractional calculus by a lot of applied researchers and also mathematician. A model illustrating a human root dentin which is mathematical in nature and having fractional order was formulated by (Petrovic, Spasic, & Atanackovic, 2005). Biological organisms' cell membranes have been deduced to possess electrical conductance of fractional order by(Cole, 1993&Podlubny, 1999) consequently modeling them, requires non-integer order models. Important features of the way pattern formation in colonies of bacteria behave are embodied by fractional derivatives (El-sayed, Rida &Arafa, 2009). Again (Anastasio, 1994) has demonstrated the extra benefits of using equation with fractional derivatives to model the way brainstem vestibule-oculo motor behave rather than using classical integer-order models. Systems having memory and which exist in majority of systems in biology are naturally associated to FODE (Jumarie, 2006). There is a number of fractional (integrals) derivatives definitions e.g. Riemann Liouville and Caputo. We will make use of the definition of caputo that is a modified form of definition of Riemann-Liouville and deals appropriately with initial value problems.

3.1.1 Definition of fractional integral

(Podlubny, 1999) defined the fractional integral of Riemann-Liouville of order α greater than zero of a function $g : R^{+} \to R$ as;

$$I^{\alpha}g(x)=\frac{1}{\Gamma(\alpha)}\int_0^x(x-t)^{(\alpha-1)}g(t)dt, x>0$$

Where $\Gamma(.)$ is Euler's gamma function, which is given by;

$$\Gamma(n)=\int_0^{\infty}t^{n-1}e^{-t}dt$$

This function of Euler gamma is a form of factorial generalization stated below

$$\Gamma(n)=(n-1)!$$

3.1.2 Definition of fractional derivative

(Podlubny, 1999) gave a definition of fractional derivative of Caputo of order $\alpha>0, n-1<\alpha<n$ and $n\in N$ as;

$$D^{\alpha}g(t)=I^{n-\alpha}D^{n}g(t)=\frac{1}{\Gamma(n-\alpha)}\int_0^t\frac{g^{n}(s)}{(t-s)^{(\alpha+1-n)}}ds$$

Where

$$t>0, n-1<\alpha<n$$

Up to order $(n-1)$, the derivatives of the function $g(t)$ are continuous.

For $1<\alpha<n$, then

$$D^{\alpha}g(t)=\frac{1}{\Gamma(1-\alpha)}\int_0^t\frac{g^{1}(s)}{(t-s)^{\alpha}}ds,$$

3.2 Description and derivation of the model.

In this category, it is important to note that an integer order model of HTLV-1 infection of $CD4^+$T-cells has been formulated by (Li and Zhou, 2014). But for us, we construct a fractional order model of three compartments. These are: $X_1(t), X_2(t), X_3(t)$ which represent quantity of $CD4^+$T cells at time t which are not infected, infected but inactive and infected and active respectively. Bone marrow produced healthy $CD4^+$T cells at the rate λ. The healthy $CD4^+$T cells can become infected by coming in contact with infected $CD4^+$T cells. This infection is represented by $\beta X_1(t) X_3(t)$, where β is the infectious transmission rate among $CD4^+$T cells. The new cells infected experience attack by the immune system. A small fraction σ survive the attack and express no tax hence becoming infected but inactive cells i.e $\sigma\beta X_1(t) X_3(t)$. Daily a small fraction τ of infected but inactive cells express tax i.e $\tau X_2(t)$ hence becomes infected and active cells. Infected and active cells undergo mitotic transmission at the rate r generating new infected cells. A small fraction ε of these cells express no tax hence becoming infected but inactive cells i.e $\varepsilon r X_3(t)$, while the remaining fraction $(1-\varepsilon)$ express tax hence remaining in infected and active $CD4^+$T cells compartment i.e $(1-\varepsilon) r X_3(t)$. In the model the natural death rate of the number of $CD4^+$T cells which are healthy is μ_1, infected but inactive is μ_2 and infected and active is μ_3.

Table 3.1 and Table 3.2 below summarize the definitions of the symbols used to represent the variables and parameters in the suggested model.

Table 3.1 Symbols and descriptions of state variables considered in the proposed model

Variable	Description
$X_1(t)$	quantity of $CD4^+$T-cells that are healthy
$X_2(t)$	quantity of $CD4^+$T-cells infected but inactive
$X_3(t)$	quantity of $CD4^+$T-cells infected and active

Table 3.2 Symbols and definitions of parameters utilized in the proposed model.

Parameter	Description
λ	Rate of birth of healthy CD4 cells.
μ_1	Healthy CD4 cell population's natural mortality rate.
μ_2	Infected but inactive CD4 cell population's natural mortality rate.
μ_3	Infected and active CD4 cell population's natural mortality rate.
β	Infectious transmission coefficient.
σ	Fraction of cells which are newly infected via infectious transmission that withstand the immunological response and express no tax.
$(1-\sigma)$	Fraction of cells which are newly infected via infectious transmission that doesn't withstand the immunological response.
τ	Rate of spontaneous Tax expression.
r	Rate of mitotic transmission of actively infected cells.
ε	Fraction of cells which are newly infected via mitotic transmission that withstand the immunological response but don't express tax.
$(1-\varepsilon)$	Fraction of cells which are newly infected via mitotic transmission that withstand the immunological response and express Tax.
α	Order of the fractional derivative

The flow chart of HTLV-1 infection is described in below

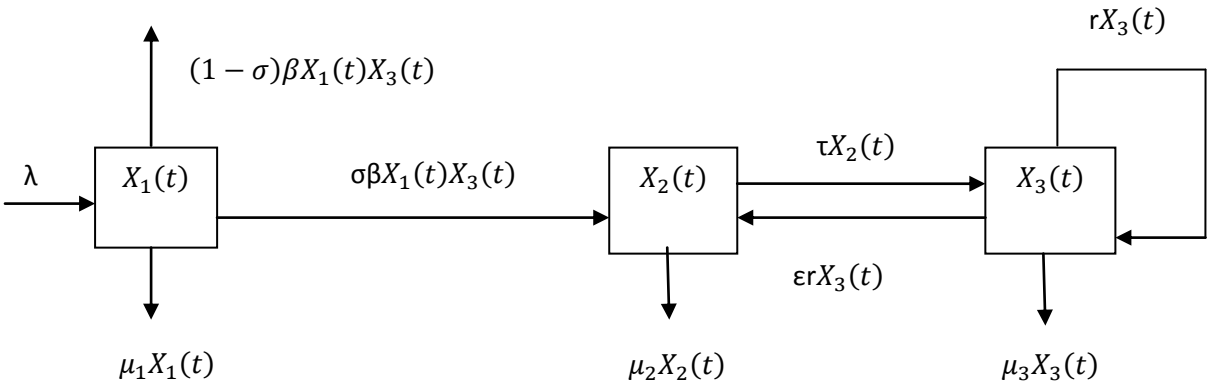

Figure 3.1: The model diagram

The model description and figure 3.1 result in the following system of nonlinear fractional order differential equations.

$$\left.\begin{aligned} D^{\alpha}X_1(t) &= \lambda-\beta X_1(t)X_3(t)-\mu_1 X_1(t)\\ D^{\alpha}X_2(t) &= \sigma\beta X_1(t)X_3(t)+\varepsilon r X_3(t)-\tau X_2(t)-\mu_2 X_2(t)\\ D^{\alpha}X_3(t) &= \tau X_2(t)+(1-\varepsilon)rX_3(t)-\mu_3 X_3(t)\end{aligned}\right\} \quad (3.1)$$

The motive of the use of differential equations with fractional order is because in nature, FODEs are associated to systems having memory. This is because fractional derivative definition entails an integration which is an operator that is non-local. Simply because definition of integration operator is on interval, therefore fractional derivative is an operator that is non-local. In other way, computing time-fractional derivative of let say a function $g(t)$ at time $t=t_2$ needs all the previous history that is all $g(t)$ from the time $t=0$ to the time $t=t_2$. In addition, FODEs have a close relationship with fractals which are many in systems of biology. The outcomes derived from the systems of fractional order are naturally more

broadly. But, when it comes to application, FODEs are extensively applied because their fundamental results have scaling properties which are useful. The results are affected by order of the fractional derivatives therefore not the same as those obtained from a system that is standard. Fractional order integration and derivation concept is traceable to the beginning calculus of order of integers.

3.3 Model analysis

Under this category, we'll analyze model(3.1) to show the positivity, existence and uniqueness of the solutions and this is supported by appropriate theorems and lemmas. The equilibrium points and reproduction number are clearly calculated and supported by appropriate theorems and lemmas. Finally we shall discuss both local and global asymptotic stability equilibrium points.

3.3.1 Positive solution's existence and uniqueness

Here we study uniqueness and positivity of solution of model by taking the initial conditions of system (3.1) to satisfy;

$$\left.\begin{aligned} X_1(0) &\geq 0 \\ X_2(0) &\geq 0 \\ X_3(0) &\geq 0 \end{aligned}\right\} \tag{3.2}$$

3.3.2 Uniqueness of solution

In order to find out uniqueness of solution, we take into consideration the system of fractional order given below;

$$D^{\alpha} X(t) = g\left(t, X(t)\right)$$

$$X(t_0) = X_0$$

And α is greater than zero but less or equals to one, $t_0 \in \mathbf{R}^+$ and $X_0 \in \mathbf{R}^3$

Then the following lemma is required.

Lemma 3.1

(Diethelm and Ford, 2002). Supposing function $g : \mathbf{R}^+ \times \mathbf{R}^3 \to \mathbf{R}^3$ in vector form conforms to the conditions (1) to (3) as stated below:

(1) On $\mathbf{R}^3, g\left(t, X(t)\right)$ and also $\dfrac{\partial\left(t, X(t)\right)}{\partial X}$ are continuous in relation to $X(t)$.

(2) $g\left(t, X(t)\right)$ is measurable with Lebesgue measure in relation to t on $\in \mathbf{R}^+$;

(3) $\left\|g(t, X) - g(t, Y)\right\| \le Z\left\|X - Y\right\|$, for any $t \in \mathbf{R}^+$ and $X, Y \in \mathbf{R}^3$.

If system (3.1) satisfies the above three conditions, then it has a unique solution

Now we provide the uniqueness of solution in form of theorem then prove it.

Theorem 3.2

For every set of initial values that satisfy condition, $X(t)$ is a solution of system (3.1)and is equals to $\left[X_1(t), X_2(t), X_3(t)\right]^T$ on $[0, +\infty]$ which is unique.

Proof

The vector function of system is

$$D^{\alpha} X(t) = B_1 X(t) + X_1 B_2 X(t) + B_3$$

$$X(0) = X_0$$

Where

$$B_1 = \begin{pmatrix} -\mu_1 & 0 & 0 \\ 0 & -(\tau + \mu_2) & 0 \\ 0 & \tau & -\mu_3 \end{pmatrix}$$

$$B_2 = \begin{pmatrix} 0 & 0 & -\beta \\ 0 & 0 & \sigma\beta \\ 0 & 0 & 0 \end{pmatrix}$$

$$B_1 = \begin{pmatrix} \lambda \\ 0 \\ 0 \end{pmatrix}$$

$$X(t) = \begin{pmatrix} X_1(t) \\ X_2(t) \\ X_3(t) \end{pmatrix}$$

- Proving the first condition by letting

$$g(t, X(t)) = B_1 X(t) + X_1 B_2 X(t) + B_3,$$

$$X(0) = X_0$$

$g(t, X(t))$ is continuous everywhere on $\mathbf{R}^3$

Then, with respect to $X(t)$, the partial derivative of $g(t, X(t))$ is given by

$$\frac{\partial(t, X(t))}{\partial X} = B_1 + X_1 B_2$$

Which is also continuous on the entire $\mathbf{R}^3$.Therefore condition $(1)$is satisfied

- Proving the second condition

$$g\left(t,X\left(t\right)\right)=B_1X\left(t\right)+X_1B_2X\left(t\right)+B_3$$

Since from condition (1) this function is continuous, then it is lebesgue measurable.Therefore condition (2) is satisfied

- Proving condition (3)

$$g\left(t,X\left(t\right)\right)=B_1X\left(t\right)+X_1B_2X\left(t\right)+B_3$$

Therefore

$$\left\|g\left(t,X\left(t\right)\right)-g\left(t,Y\left(t\right)\right)\right\|\leq\left\|B_1\left\{X\left(t\right)-Y\left(t\right)\right\}+X_1B_2X\left(t\right)-X_1B_2Y\left(t\right)+X_1B_2X\left(t\right)-Y_1B_2Y\left(t\right)\right\|$$

$$\leq\left\{\left\|B_1\right\|+\left\|X_1\right\|\left\|B_2\right\|+\left\|B_2\right\|\left\|Y\left(t\right)\right\|\right\}\left\|X\left(t\right)-Y\left(t\right)\right\|$$

$$\leq T\left\|X\left(t\right)-Y\left(t\right)\right\|$$

Whereby

$$\left\|X\left(t\right)\right\|=\sum_{i=1}^{3}\sup\left|X_i\left(t\right)\right|$$

$$Z=\left\|B_1\right\|+\left\|B_2\right\|\left\{\left\|X_1\right\|+\left\|Y\left(t\right)\right\|\right\}$$

Therefore condition (3)is satisfied

The vector function of the model(3.1) has satisfied all the three conditions of Lemma 3.1, therefore system has a unique solution.

3.3.3 Positivity of solution

To find out existence of non-negative solution. We first denote

$$\mathbf{R}_{+}^{3}=\left\{X\left(t\right)\in\mathbf{R}^{3};X\left(t\right)\geq 0\right\}$$

And

$$X\left(t\right)=\left[X_{1}\left(t\right),X_{2}\left(t\right),X_{3}\left(t\right)\right]^{T}$$

Then in order to establish non negativity of solution, the following lemmas is required

Lemma 3.3

The Theorem of Generalized Mean Value by (Odibat and Shawagfeh, 2007).

Assuming $X\left(t\right)\in C\left[a,b\right]$ as well as $D^{\alpha}X\left(t\right)\in C\left[a,b\right]$ for $0<\alpha\leq 1$

Therefore,

$$X\left(t\right)=X\left(a\right)+\frac{1}{\Gamma\left(\alpha\right)}D^{\alpha}X\left(\xi\right)\left(t-a\right)^{\alpha}$$

With $a<\xi<t$, for all $t\in(a,b]$

Lemma 3.4

(Odibat and Shawagfeh, 2007)Assuming $X\left(t\right)\in C\left[a,b\right]$ as well as $D^{\alpha}X\left(t\right)\in C\left[a,b\right]$ for $0<\alpha\leq 1$ therefore;

- $X\left(t\right)$ is at all times not decreasing for every t belonging to $\left[a,b\right]$ in case $D^{\alpha}X\left(t\right)$ is greater or equal to zero, for all $t\in\left[a,b\right]$.
- $X\left(t\right)$ is at all times not increasing for every t belonging to $\left[a,b\right]$ in case $D^{\alpha}X\left(t\right)$ is less or equal to zero, for all $t\in\left[a,b\right]$.

Now we state the positivity of solution of system in form of theorem then prove it.

Theorem 3.5

System does have a solution $\left[X_1(t), X_2(t), X_3(t)\right]^T$ along any initial values satisfying condition for any $t \geq 0$.

From system we now get;

$$D^{\alpha} X_1(t)|_{X_1=0} = \lambda \geq 0$$

$$D^{\alpha} X_2(t)|_{X_2=0} = (\sigma\beta X_1 + \varepsilon r) X_3(t) \geq 0$$

$$D^{\alpha} X_3(t)|_{X_3=0} = \tau X_2 \geq 0$$

We conclude that the solution of system is positive using lemma 3.3 and lemma 3.4.

3.3.4 Calculation of equilibrium points

An equilibrium point is any point that makes all rates zero simultaneously.

The right side of model has to be equated to 0, to obtain equilibrium points.

$$\left.\begin{aligned} &\lambda - \beta X_1(t) X_3(t) - \mu_1 X_1(t) = 0 \\ &\sigma\beta X_1(t) X_3(t) + \varepsilon r X_3(t) - \tau X_2(t) - \mu_2 X_2(t) = 0 \\ &\tau X_2(t) + (1-\varepsilon) r X_3(t) - \mu_3 X_3(t) = 0 \end{aligned}\right\} \quad (3.3)$$

From the 1st equation of system (3.3)

$$\lambda - \beta X_1(t) X_3(t) - \mu_1 X_1(t) = 0$$

$$\lambda - (\beta X_3 + \mu_1) X_1 = 0$$

$$X_1 = \frac{\lambda}{\beta X_3 + \mu_1}$$

If $X_3 = 0$, then

$$X_1 = \frac{\lambda}{\mu_1}$$

From the above calculation, we get the point $\left(\frac{\lambda}{\mu_1}, 0, 0\right)$

In this point since the disease classes are zeros, we can call it disease free equilibrium point and we denote it $E_0 = (X_0, 0, 0)$

Where $X_0 = \frac{\lambda}{\mu_1}$

If $X_3 \neq 0$ and $X_1 = \frac{\lambda}{\beta X_3 + \mu_1}$

Making X_2 in the 3rd equation of system(3.3) we get

$$\tau X_2(t) + (1-\varepsilon) r X_3(t) - \mu_3 X_3(t) = 0$$

$$\tau X_2 - \left((1-\varepsilon) r + \mu_3\right) X_3 = 0$$

$$X_2 = \frac{\left[\mu_3 - (1-\varepsilon) r\right] X_3}{\tau}$$

Substituting

$X_1 = \frac{\lambda}{\beta X_3 + \mu_1}$ and $X_2 = \frac{\left[\mu_3 - (1-\varepsilon)r\right]X_3}{\tau}$ to the 2nd equation of system (3.3), we get X_3

$$X_3 = \frac{\mu_1}{\beta}(R_0 - 1)\frac{(\tau + \mu_2)\mu_3}{(\tau + \mu_2)\mu_3 - \tau r - \mu_2(1 - \varepsilon)r}$$

These give us a point where none of the state variable is 0, we call this point endemic equilibrium point and we denote it $E_1 = \left(X_1^*, X_2^*, X_3^*\right)$

Where

$$X_1^* = \frac{\lambda}{\beta X_3 + \mu_1}$$

$$X_2^* = \frac{\left[\mu_3 - (1-\varepsilon)r\right]X_3}{\tau}$$

$$x_3^* = \frac{\mu_1}{\beta}(R_0 - 1)\frac{(\tau + \mu_2)\mu_3}{(\tau + \mu_2)\mu_3 - \tau r - \mu_2(1 - \varepsilon)r}$$

As a result, there are two steady states in the proposed nonlinear fractional epidemic model, namely.

- Disease free steady state, $E_0 = \left(\frac{\lambda}{\mu_1}, 0, 0\right)$
- unique endemic steady state, $E_1 = \left(X_1^*, X_2^*, X_3^*\right)$

3.3.5 Calculation of basic reproductive number

Assuming the whole populations of cells are vulnerable to infection, the basic reproductive number of an infectious virus refers to the number of cells that acquire the virus from a cell that has been infected.

Using a mathematical approach based on the next generation matrix, we easily calculate the basic reproductive number R_0(Diekmann, Heesterbeek & Roberts, 2010 and Van den Driessche & Watmough, 2002).

The spectral radius of the product of F and V^{-1} is R_0.

From the system(3.1), the disease classes are;

$$D^{\alpha}X_2(t) = \sigma\beta X_1(t)X_3(t) + \varepsilon r X_3(t) - \tau X_2(t) - \mu_2 X_2(t)$$

$$D^{\alpha}X_3(t) = \tau X_2(t) + (1-\varepsilon) r X_3(t) - \mu_3 X_3(t)$$

Using the disease classes to find F and ν

Where F contains terms with infection rate and ν contains the other terms

$$\mathrm{F} = \begin{bmatrix} \sigma\beta X_1 X_3 \\ (1-\varepsilon) r X_3 \end{bmatrix}$$

$$\nu = \begin{bmatrix} -\tau X_2 - \mu_2 X_2 \\ \tau X_2 - \mu_3 X_3 \end{bmatrix}$$

We then obtain F, a matrix of partial derivatives of F with respect to original dependent variables and we perform similar derivation for V based on ν

$$F = \begin{bmatrix} \sigma\beta X_3 & \sigma\beta X_1 + \varepsilon r \\ 0 & (1-\varepsilon) r \end{bmatrix}$$

$$V = \begin{bmatrix} -(\tau + \mu_2) & 0 \\ \tau & -\mu_3 \end{bmatrix}$$

Calculating the inverse of V i.e. V^{-1}

We first need to get the determinant of V which is equals to $(\tau + \mu_2)\mu_3$. Therefore

$$V^{-1} = \frac{1}{(\tau + \mu_2)\mu_3} \begin{bmatrix} \mu_3 & 0 \\ \tau & -(\tau + \mu_2) \end{bmatrix}$$

Finding the product of F and inverse of V i.e. FV^{-1}

$$FV^{-1} = \begin{bmatrix} \dfrac{-\sigma\beta X_3\mu_3 - \sigma\beta\mu_3 X_1\tau - \varepsilon r\tau}{(\tau + \mu_2)\mu_3} & \dfrac{-(\tau + \mu_2)(\sigma\beta X_1 + \varepsilon r)}{(\tau + \mu_2)\mu_3} \\ \dfrac{-\tau(1-\varepsilon) r}{(\tau + \mu_2)\mu_3} & \dfrac{-(\tau + \mu_2)(1-\varepsilon) r}{(\tau + \mu_2)\mu_3} \end{bmatrix}$$

At disease free equilibrium E_0 where $X_1 = X_0, X_2 = 0, X_3 = 0$

$$FV^{-1} = \begin{bmatrix} \dfrac{-\sigma\beta X_0\tau - \varepsilon r\tau}{(\tau + \mu_2)\mu_3} & \dfrac{-(\tau + \mu_2)(\sigma\beta X_0 + \varepsilon r)}{(\tau + \mu_2)\mu_3} \\ \dfrac{-\tau(1-\varepsilon) r}{(\tau + \mu_2)\mu_3} & \dfrac{-(\tau + \mu_2)(1-\varepsilon) r}{(\tau + \mu_2)\mu_3} \end{bmatrix}$$

Lastly we find the eigenvalues of FV^{-1} and select the dominant one; which yields R_0

To get eigenvalue, we find $\left| FV^{-1} - \lambda i \right|$

$$\left|FV^{-1}-\lambda i\right|=\begin{bmatrix}\dfrac{-\sigma\beta X_0\tau-\varepsilon r\tau}{(\tau+\mu_2)\mu_3}-\lambda & \dfrac{-(\tau+\mu_2)(\sigma\beta X_0+\varepsilon r)}{(\tau+\mu_2)\mu_3}\\ \dfrac{-\tau(1-\varepsilon)r}{(\tau+\mu_2)\mu_3} & \dfrac{-(\tau+\mu_2)(1-\varepsilon)r}{(\tau+\mu_2)\mu_3}-\lambda\end{bmatrix}$$

$$\lambda_1=\frac{-\sigma\beta X_0\tau-\varepsilon r\tau}{(\tau+\mu_2)\mu_3},$$

$$\lambda_2=\frac{-(\tau+\mu_2)(1-\varepsilon)r}{(\tau+\mu_2)\mu_3}$$

Therefore,

$$|\lambda_1|=\frac{\sigma\beta X_0\tau}{(\tau+\mu_2)\mu_3}+\frac{\varepsilon r\tau}{(\tau+\mu_2)\mu_3},$$

$$|\lambda_2|=\frac{(1-\varepsilon)r}{\mu_3}$$

But $X_0=\dfrac{\lambda}{\mu_1}$

Therefore

$$\lambda_1=\frac{\sigma\beta\lambda\tau}{(\tau+\mu_2)\mu_3}+\frac{\varepsilon r\tau}{(\tau+\mu_2)\mu_3},\lambda_2=\frac{(1-\varepsilon)r}{\mu_3}$$

Since both the two eigenvalues are dominant, we add to get R_0

$$R_0=\lambda_1+\lambda_2$$

$$R_0=\frac{\sigma\beta\lambda\tau}{(\tau+\mu_2)\mu_3}+\frac{\varepsilon r\tau}{(\tau+\mu_2)\mu_3}+\frac{(1-\varepsilon)r}{\mu_3}$$

3.3.6 Local asymptotic stability of the equlibria

We propose the following lemma to establish the equilibrium points' local asymptotic stability**.**

Lemma 3.6

Routh Hurwitz stability requirements by (Matignon, 1996).

Let (x_*, y_*) be the point of equilibrium of the following system of fractional derivatives;

$$D^{\alpha} X(t) = g_1(x, y)$$

$$D^{\alpha} Y(t) = g_2(x, y)$$

$X(0) = X_0, Y(0) = Y_0$, with $0 < \alpha \leq 1$

And its jacobian matrix be: $$J = \begin{bmatrix} \frac{\partial g_1}{\partial x} & \frac{\partial g_1}{\partial y} \\ \frac{\partial g_2}{\partial x} & \frac{\partial g_2}{\partial y} \end{bmatrix}$$

Therefore (x_*, y_*) is locally asymptotically stable incase each and every eigenvalue of Jacobian matrix computed at the equilibrium points comply with the condition stated below:

$\left|\arg\left(eig(J)\right)\right|$ is greater than $\frac{\alpha\pi}{2}$

Therefore System jacobian's matrix is given by

$$J = \begin{bmatrix} -\beta X_3 - \mu_1 & 0 & -\beta X_1 \\ \sigma\beta X_3 & -(\tau + \mu_2) & \sigma\beta X_1 + \varepsilon r \\ 0 & \tau & (1-\varepsilon) r - \mu_3 \end{bmatrix} \tag{3.4}$$

Now we state in form of theorems local asymptotic results of the equilibria and prove them

Theorem 3.7

If R_0 is lower than one, the disease-free equilibrium E_0 of system (3.1) is locally asymptotically stable.

Proof

The jacobian matrix of system(3.1), which is matrix(3.4), evaluated at the equilibrium point free of disease, E_0 ,is stated as

$$J(E_0)=\begin{bmatrix} -\mu_1 & 0 & \frac{\lambda}{\mu_1}\beta \\ 0 & -(\tau+\mu_2) & \frac{\lambda}{\mu_1}\sigma\beta+\varepsilon r \\ 0 & \tau & (1-\varepsilon)r-\mu_3 \end{bmatrix}$$

The linearized system's characteristic equation is as follows:

$$(k+\mu_1)(k^2+b_0k+c_0)=0$$

Where

$$b_0=\mu_3\left(1-R_0+\frac{(\sigma\beta\tau X_0)+\tau\varepsilon r}{(\tau+\mu_2)\mu_3}\right)+\tau+\mu_2$$

$$c_0=(1-R_0)(\tau+\mu_2)\mu_3$$

$(k+\mu_1)=0$ which gives us one root $k_1=-\mu_1$

And $k^2+b_0k+c_0=0$ gives us two roots which are both negative when $R_0<1$

Therefore all the eigen values are negative if $R_0 < 1$ and according to lemma 3.6, if R_0 is less than one then E_0 is locally asymptotically stable.

Theorem 3.8

E_1 is an endemic equilibrium that is locally asymptotically stable, whenever R_0 is greater than one.

Proof

The Jacobian matrix of system(3.1), which is equation (3.4) evaluated at endemic equilibrium $E_1 = \left(X_1^*, X_2^*, X_3^*\right)$ is given as

$$J\left(E_1\right) = \begin{bmatrix} -\beta X_3^* - \mu_1 & 0 & -\beta X_1^* \\ \sigma\beta X_3^* & -\left(\tau + \mu_2\right) & \sigma\beta X_1^* + \varepsilon r \\ 0 & \tau & \left(1-\varepsilon\right)r + \mu_3 \end{bmatrix}$$

The characteristic equation of the linearized system is as follows:

$$p\left(k\right) = k^3 + c_1 k^2 + c_2 k + c_3 = 0$$

Where

$$c_1 = \mu_3 + \left(1-\varepsilon\right)r + \tau + \mu_2 + \beta X_3^* + \mu_1$$

$$c_2 = \left(\tau + \mu_2\right)\left[\mu_3\left(1-\varepsilon\right)r\right] + \left(\beta X_3^* + \mu_1\right)\left[\mu_1\left(1-\varepsilon\right)r\right] + \left(\beta X_3^* + \mu_1\right)\left[\tau + \mu_2\right] - \left(\sigma\beta\tau X_1^* + \tau\varepsilon r\right)$$

$$C_3 = \mu_1\mu_3(\tau + \mu_2)(R_0 - 1)$$

Having the polynomial $p\left(k\right)$ and letting $D\left(p\right)$ to serve as its discriminant, then;

$$D\left(p\right) = 18c_1c_2c_3 + \left(c_1c_2\right)^2 - 4c_1^3c_3 - 4c_2^3 - 27c_3^2 \qquad (3.5)$$

To find out if the endemic equilibrium point is locally asymptotically stable, we require the following results obtained by (Ahmed, El-sayed & El-saka, 2006 and Ahmed, El-sayed & El-saka, 2007) following Routh-Hurwitz conditions:

Corollary 3.9

E_1 is locally asymptotically stable endemic equilibrium point of the system (3.1)f or R_0 greater than one, if the polynomial $p(k)$ and coefficients c_1, c_2, and c_3 meet at least one of the following requirements

(i)In case $D(p)$ is greater than zero and $c_1 > 0, c_3 > 0, c_1 c_2 > c_3$, then E_1 is said to be locally asymptotically stable.

(ii)In case $D(p)$ is less than zero and $c_1 \geq 0, c_2 \geq 0, c_3 \geq 0, \alpha < \frac{2}{3}$, therefore E_1 is locally asymptotically stable.

(iii)In case $D(p)$ is less than zero and $c_1 < 0, c_2 < 0, \alpha > \frac{2}{3}$, therefore E_1 is unstable.

(iv)In case $D(p)$ is less than zero and $c_1 > 0, c_2 > 0, c_1 c_2 = c_3, \alpha \in (0,1]$, therefore E_1 is said to be locally asymptotically stable.

We can see from the characteristic equation that $c_1 > 0$, $c_2 > 0$, and $c_3 > 0$ if $R_0 > 1$. Therefore all roots of equation (3.5)satisfy the Routh Hurwitz conditions. Further, we have $c_1 c_2 > c_3$ and hence$D(p) > 0$. Therefore requirement (i) in corollary 3.9 is satisfied and hence E_1 is locally asymptotically stable if $R_0 > 1$.

3.3.7 The equilibria's global asymptotic stability

In order to establish global stability of equilibria, we first consider the autonomous system

$$D^{\alpha}X(t)=g(x) \tag{3.6}$$

Let $\Omega\in\mathbf{R}^{n}$ and $V\in C^{1}\left(\Omega,\mathbf{R}^{n}\right)$

Thus the derivative of V alongside the solution of equation (3.6)is

$$D^{\alpha}V|_{(3.6)}=I^{1-\alpha}DV|_{(3.6)}=I^{1-\alpha}\left(\frac{dV}{dx}\quad\frac{dx}{dt}\right)$$

Where $0<\alpha\leq 1$

Then we put forward the following lemmas

Lemma3.10:

Here we have generalized integer Lasalle invariance principle (LaSalle, 1976) into fractional Lasalle invariance principle. Suppose that D is a positively invariant, closed and bounded set in relation to $D^{\alpha}X(t)=g(x)$. This means every solution of $D^{\alpha}X(t)=g(x)$ that starts inside the set will always stay inside the set.

Assume V is a function that can be differentiated continuously and that maps to R from D in such a way that $D^{\alpha}V|_{(3.6)}\leq 0$.

Where $D^{\alpha}V|_{(3.6)}\leq 0$, consider E to represent a collection of all points in D

In E, consider M to be the invariant set with the largest size. Then as $t\to\infty$ every solution beginning in Dapproaches M.

Lemma 3.11

(Vargas-De-León, 2015).For any given instant in time, $t \geq t_0$, consider a derivable and continuous function $X(t) \in \mathbf{R}^+$.

$$D_t^{\alpha}\left(X(t) - X^* - X^* \ln \frac{X(t)}{X^*} \right) \leq \left(1 - \frac{X^*}{X(t)} \right) D_t^{\alpha} X(t) \tag{3.7}$$

Where $\alpha \in (0,1)$

By making use of lyapunov theorems, we present the global asymptotic stability results of the equilibria as theorems then prove them.

Theorem 3.12

If R_0 is less than one, E_0 which is equals to $\left(\frac{\lambda}{\mu_1}, 0, 0 \right)$ of model proposed(3.1) is globally asymptotically stable.

Proof

Defining the function of lyapunov $V_1(t)$ in the way below

$$V_1(t) = X_1(t) - X_0 - X_0 \ln \frac{X_1(t)}{X_0} + \frac{\tau}{\tau + \mu_2} X_2(t) + X_3(t)$$

The derivative of $V_1(t)$ is computed alongside the solutions of Eqs (3.1), and the results in (Vargas-De-León, 2015) are then used, we get

$$D^{\alpha} V_1(t) \leq \left(1 - \frac{X_0}{X_1(t)} \right) \left[X_0 - \mu_1 X_1(t) - \beta X_1(t) X_1(t) \right] + \frac{\tau}{\tau + \mu_2} \left[\sigma\beta X_1 X_3 + \varepsilon r X_3 - \tau X_2 - \mu_2 X_2 \right] + \left[\tau X_2 + (1 - \varepsilon) r X_3 - \mu_3 X_3 \right]$$

$$=\frac{\left[-\mu_1 X_1^2(t)+2\mu_1 X_0 X_1(t)-\mu_1 X_0^2\right]}{X_1(t)}+X_3(t)\left[\frac{\sigma\beta\tau X_1(t)}{(\tau+\mu_2)}+\frac{\tau\varepsilon r}{(\tau+\mu_2)}+[1-\varepsilon]r-\mu_3\right]$$

$$=-\mu_1\frac{\left[X_1^2(t)-2X_0X_1(t)+X_0^2\right]}{X_1(t)}+X_3(t)\left[\frac{\sigma\beta\tau\frac{\lambda}{\mu_1}}{(\tau+\mu_2)}+\frac{\tau\varepsilon r}{(\tau+\mu_2)}+[1-\varepsilon]r-\mu_3\right]$$

$$=-\mu_1\frac{\left[X_1^2(t)-2X_0X_1(t)+X_0^2\right]}{X_1(t)}+\mu_3X_3(t)\left[\frac{\sigma\beta\tau\lambda}{(\tau+\mu_2)\mu_1\mu_3}+\frac{\tau\varepsilon r}{(\tau+\mu_2)\mu_3}+\frac{[1-\varepsilon]r}{\mu_3}-1\right]$$

Substituting R_0 gives

$$D^{\alpha}V_1(t)=-\mu_1\frac{\left(X_1(t)-X_0\right)^2}{X_1(t)}+\mu_3X_3(t)(R_0-1)$$

Therefore if $R_0<1$ then

$$D^{\alpha}V_1(t)\le 0$$

To add, notice that $D^{\alpha}V_1(t)=0$ as long as $X_1(t)$ is equal to X_0 and $X_3(t)$ is equal to zero. If $X_3(t)$ is equal to zero and is substituted in the 2nd equation of model (3.1)it gives $X_2(t)$ equals to zero. Hence the invariant set which is largest for $\left[(X_1,X_2,X_3)\in D:D^{\alpha}V_1(t)=0\right]$ is therefore the singleton set $[E_0]$. We understand that all of the solution in D approaches E_0, in accordance to (Lasalle, 1976) invariance principle, and hence the disease free equilibrium point of model (3.1) is globally asymptotically stable as long as R_0 is higher than one.

Theorem 3.13

The endemic infection equilibrium $E_1 = \left(X_1^*, X_2^*, X_3^* \right)$ of proposed model (3.1) is globally asymptotically stable when R_0 is greater than one.

Proof

Defining the function of lyapunov $V_2(t)$ in the way below

$$V_2(t) = \frac{1}{\mu_1}\left(X_1(t) - X_1^* - X_1^* \ln \frac{X_1(t)}{X_1^*} \right) + \frac{R_0 - 1}{\tau + \mu_2}\left(X_2(t) - X_2^* - X_2^* \ln \frac{X_2(t)}{X_2^*} \right) + \frac{1}{\mu_3}\left(X_3(t) - X_3^* - X_3^* \ln \frac{X_3(t)}{X_3^*} \right)$$

The derivative of $V_2(t)$ computed alongside solutions of system (3.1), and the results in (Vargas-De-León, 2015) are then used, we get

$$D^\alpha V_2(t) \le D^\alpha \left\{ \frac{1}{\mu_1}\left(X_1(t) - X_1^* - X_1^* \ln \frac{X_1(t)}{X_1^*} \right) + \frac{R_0 - 1}{\tau + \mu_2}\left(X_2(t) - X_2^* - X_2^* \ln \frac{X_2(t)}{X_2^*} \right) + \frac{1}{\mu_3}\left(X_3(t) - X_3^* - X_3^* \ln \frac{X_3(t)}{X_3^*} \right) \right\}$$

$$\le \frac{1}{\mu_1}\left(X_1(t) - \frac{X_1^*}{X_1(t)} \right) D^\alpha X_1(t) + \frac{R_0 - 1}{\tau + \mu_2}\left(X_2(t) - \frac{X_2^*}{X_2(t)} \right) D^\alpha X_2(t) + \frac{1}{\mu_3}\left(X_3(t) - \frac{X_3^*}{X_3(t)} \right) D^\alpha X_3(t)$$

$$\le \frac{1}{\mu_1}\left(X_1(t) - \frac{X_1^*}{X_1(t)} \right)\left[\lambda - \beta X_1(t) X_3(t) - \mu_1 X_1(t) \right] + \frac{R_0 - 1}{\tau + \mu_2}\left(X_2(t) - \frac{X_2^*}{X_2(t)} \right)\left[\sigma\beta X_1(t) X_3(t) + \varepsilon r X_3(t) - \tau X_2(t) - \mu_2 X_2(t) \right]$$
$$+ \frac{1}{\mu_3}\left(X_3(t) - \frac{X_3^*}{X_3(t)} \right)\left[\tau X_2(t) + (1 - \varepsilon) r X_3(t) - \mu_3 X_3(t) \right]$$

Substituting endemic conditions stated below

$$\lambda - \beta X_1^* X_3^* - \mu_1 X_1^*$$

$$\sigma\beta X_1^* X_3^* + \varepsilon r X_3^* - \tau X_2^* - \mu_1 X_2^*$$

$$\tau X_2^* + (1-\varepsilon) r X_3^* - \mu_3 X_3^*$$

We get

$$\leq \frac{1}{\mu_1}\left(X_1(t) - \frac{X_1^*}{X_1(t)}\right)\left[\lambda - \beta X_1^* X_3^* - \mu_1 X_1^*\right] + \frac{R_0 - 1}{\tau + \mu_2}\left(X_2(t) - \frac{X_2^*}{X_2(t)}\right)\left[\sigma\beta X_1^* X_3^* + \varepsilon r X_3^* - \tau X_2^* - \mu_1 X_2^*\right]$$
$$+ \frac{1}{\mu_3}\left(X_3(t) - \frac{X_3^*}{X_3(t)}\right)\left[\tau X_2^* + (1-\varepsilon) r X_3^* - \mu_3 X_3^*\right]$$

$$\leq \frac{\left(X_1(t) - X_1^*\right)^2}{X_1(t)} - \frac{\left(X_2(t) - X_2^*\right)^2}{X_2(t)}(R_0 - 1) - \frac{\left(X_3(t) - X_3^*\right)^2}{X_3(t)}$$

Hence if $R_0 > 1$ then

$$D^{\alpha} V_2(t) \leq 0$$

To add, notice that $D^{\alpha} V_2(t) = 0$ as long as $X_1(t)$ is equivalent to X_1^*, $X_2(t)$ is equivalent to X_2^* and also $X_3(t)$ is equivalent to X_3^* Hence the invariant set which is largest for $\left[(X_1, X_2, X_3) \in D : D^{\alpha} V_2(t) = 0\right]$ is therefore the singleton set $[E_1]$. We understand that all of the solution in D approaches E_1, in accordance to (Lasalle, 1976) invariance principle, and hence the endemic equilibrium point of model (3.1) is globally asymptotically stable as long as R_0 is higher than one.

3.4 Numerical techniques

Numerical techniques we have developed in our study are presented in this category.

3.4.1 Numerical approach derived by (Atanackovic and Stankovic, 2004, 2008)

In this section, we present a numerical technique that was derived by (Atanackovic and Stankovic, 2004, 2008) that we have adopted for obtaining solution of system of fractional differential equations numerically. The strategy of this technique involves writing the

differential equations with fractional order as an infinite system of ordinary differential equations of the first order. Then by using relatively small number of terms, the solutions are obtained. This numerical approach has been examined on a number of examples and the findings were consistent with those obtained through other methodologies. In (Atanackovic and Stankovic, 2004, 2008) it was demonstrated $D^{\alpha}g(t)$ which satisfy $0<\alpha<1$ can be written as;

$$D^{\alpha}g(t)=\frac{1}{\Gamma(2-\alpha)}\left\{\frac{g^{(1)}(t)}{t^{\alpha-1}}\left[1+\sum_{k=1}^{\infty}\frac{\Gamma(k-1+\alpha)}{\Gamma(\alpha-1)k!}\right]-\left[\frac{\alpha-1}{t^{\alpha}}g(t)+\sum_{k=2}^{\infty}\frac{\Gamma(k-1+\alpha)}{\Gamma(\alpha-1)(k-1)!}\left(\frac{g(t)}{t^{\alpha}}+\frac{B_k(g)(t)}{t^{k-1+\alpha}}\right)\right]\right\} \quad (3.8)$$

Where,

$$B_k(g)(t)=-(k-1)\int_0^t \tau^{k-2}g(\tau)(d\tau), k=2,3,4.... \quad (3.9)$$

And having the properties as follows

$$\frac{d}{dt}B_k(g)=-(k-1)t^{k-2}g(t), k=2,3,4.... \quad (3.10)$$

By using M terms in Equation (3.8)we have

$$\left.\begin{aligned} D^{\alpha}g(t)=\frac{1}{\Gamma(2-\alpha)}\{&\frac{g^{(1)}(t)}{t^{\alpha-1}}[1+\sum_{k=1}^{M}\frac{\Gamma(k-1+\alpha)}{\Gamma(\alpha-1)k!}]-[\frac{\alpha-1}{t^{\alpha}}g(t)\\ &+\sum_{k=2}^{M}\frac{\Gamma(k-1+\alpha)}{\Gamma(\alpha-1)(k-1)!}(\frac{g(t)}{t^{\alpha}}+\frac{B_k(g)(t)}{t^{k-1+\alpha}})]\} \end{aligned}\right\} \quad (3.11)$$

Simplifying equation (3.11)gives:

$$D^{\alpha}g(t)\square Q(\alpha,t,M)g^{(1)}(t)+Y(\alpha,t,M)g(t)+\sum_{k=2}^{M}A(\alpha,t,k)\frac{B_k(g)(t)}{t^{k-1+\alpha}} \quad (3.12)$$

Where,

$$Q(\alpha,t,M)=\frac{1+\sum_{k=1}^{M}\frac{\Gamma(k-1+\alpha)}{\Gamma(\alpha-1)k!}}{\Gamma(2-\alpha)t^{\alpha-1}}$$

$$R(\alpha,t)=\frac{1-\alpha}{t^{\alpha}\Gamma(2-\alpha)}$$

$$A(\alpha,t,k)=-\frac{\Gamma(k-1+\alpha)}{\Gamma(2-\alpha)(\alpha-1)(k-1)!}$$

$$Y(\alpha,t,M)=R(\alpha,t)+\sum_{k=2}^{M}\frac{A(\alpha,t,k)}{t^{\alpha}}$$

3.4.2 Application of Numerical approach derived by (Atanackovic and Stankovic, 2004, 2008) to the proposed model.

Under this category, the numerical technique described above is applied to system (3.1). First setting;

$H_1(t)$ equivalent to $X_1(t)$,

$H_{M+1}(t)$ equivalent to $X_2(t)$,

$H_{2M+1}(t)$ equivalent to $X_3(t)$,

$H_k(t)$ equivalent to $B_k\left(X_1(t)\right)$,

$H_{M+k}(t)$ equivalent to $B_k\left(X_2(t)\right)$,

$H_{2M+k}(t)$ equivalent to $B_k\left(X_3(t)\right)$, k equivalent to $2,3,4...$

And applying equation(3.12) to model (3.1)gives;

$$\left.\begin{aligned}
&Q(\alpha,t,M)H_1'(t)+Y(\alpha,t,M)H_1(t)+\sum_{k=2}^{M}A(\alpha,t,k)\frac{H_k(t)}{t^{k-1+\alpha}}\\
&=\lambda-\beta H_1(t)H_{2M+1}(t)-\mu_1 H_1(t)\\
&Q(\alpha,t,M)H_{M+1}'+Y(\alpha,t,M)H_{M+1}(t)+\sum_{k=2}^{M}A(\alpha,t,k)\frac{H_{M+k}(t)}{t^{k-1+\alpha}}\\
&=\sigma\beta H_1(t)H_{2M+1}(t)+\varepsilon r H_{2M+1}(t)-\tau H_{M+1}(t)-\mu_2 H_{M+1}(t)\\
&Q(\alpha,t,M)H_{2M+1}'+Y(\alpha,t,M)H_{2M+1}(t)+\sum_{k=2}^{M}A(\alpha,t,k)\frac{H_{2M+k}(t)}{t^{k-1+\alpha}}\\
&=\tau H_{M+1}(t)-(1-\varepsilon)rH_{2M+1}(t)-\mu_3 H_{2M+1}(t)
\end{aligned}\right\} \quad (3.13)$$

Where,

$$\left.\begin{aligned}
&H_k(t)=-(k-1)\int_0^t \tau^{k-2}H_1(\tau)d\tau,\\
&H_{M+k}(t)=-(k-1)\int_0^t \tau^{k-2}H_{M+1}(\tau)d\tau,\\
&H_{2M+k}(t)=-(k-1)\int_0^t \tau^{k-2}H_{2M+1}(\tau)d\tau, k=2,3,4...
\end{aligned}\right\} \quad (3.14)$$

Making $H_1'(t)$, and $H_{M+1}'(t)$ and $H_{2M+1}'(t)$ the subject of the equations in Equations(3.13) and finding the derivative of the functions in equation (3.14) we get;

$$
\begin{aligned}
&H_1^{'}(t)=\frac{1}{Q(\alpha,t,M)}[\lambda-\beta H_1(t)H_{2M+1}(t)-\mu_1 H_1(t)\\
&-Y(\alpha,t,M)H_1(t)-\sum_{k=2}^{M}A(\alpha,t,k)\frac{H_k(t)}{t^{k-1+\alpha}}]\\
&H_k^{'}(t)=-(k-1)t^{k-2}H_1(t),k=2,3,4...M\\
&H_{M+1}^{'}(t)=\frac{1}{Q(\alpha,t,M)}[\sigma\beta H_1(t)H_{2M+1}(t)+\varepsilon r H_{2M+1}(t)-\tau H_{M+1}(t)-\mu_2 H_{M+1}(t)\\
&-Y(\alpha,t,M)H_{M+1}(t)-\sum_{k=2}^{M}A(\alpha,t,k)\frac{H_{M+k}(t)}{t^{k-1+\alpha}}]\\
&H_{M+k}^{'}(t)=-(k-1)t^{k-2}H_{M+1}(t),k=2,3,4...M\\
&H_{2M+1}^{'}(t)=\frac{1}{Q(\alpha,t,M)}[\tau H_{M+1}(t)+(1-\varepsilon)r H_{2M+1}(t)-\mu_3 H_{2M+1}(t)\\
&-Y(\alpha,t,M)H_{2M+1}(t)-\sum_{k=2}^{M}A(\alpha,t,k)\frac{H_{2M+k}(t)}{t^{k-1+\alpha}}]\\
&H_{2M+k}^{'}(t)=-(k-1)t^{k-2}H_{2M+1}(t),k=2,3,4...M
\end{aligned}
\qquad (3.15)
$$

Having initial conditions as follows:

$$
\begin{aligned}
&H_1(\psi) = X_1(0),\\
&H_k(\psi) = -\frac{(k-1)}{2}\Delta t^{k-1} X_1(0)\\
&H_{M+1}(\psi) = X_2(0),\\
&H_{M+k}(\psi) = -\frac{(k-1)}{2}\Delta t^{k-1} X_2(0)\\
&H_{2M+1}(\psi) = X_3(0),\\
&H_{2M+k}(\psi) = -\frac{(k-1)}{2}\Delta t^{k-1} X_3(0), k = 2,3,4...M
\end{aligned}
\qquad (3.16)
$$

3.4.3 Runge –Kutta fourth order method

(Tan et al., 2012) illustrated Runge-Kutta fourth order. For numerical solution of ordinary differential equation of first order, we develop this technique.

Consider a differential equation of the design

$$\frac{dy}{dx} = g(x, y),$$

With initial condition

$$g(x_0) = y_0$$

The normal 4^{th} order formula established by Runge-Kutta is defined below.

Initial point (x_0, y_0) is the beginning point and then sequence of approximation are then developed using the equation below

$$y_{i+1} = y_i + \frac{1}{6}(b_1 + 2b_2 + 2b_3 + b_4)$$

Where

$$b_1 = \eta g(x_i, y_i)$$

$$b_2 = \eta g\left(x_i + \frac{\eta}{2}, y_i + \frac{b_1}{2}\right)$$

$$b_3 = \eta g\left(x_i + \frac{\eta}{2}, y_i + \frac{b_2}{2}\right)$$

$$b_4 = \eta g(x_i + \eta, y_i + b_3)$$

Where $i = 0,1,2,3$

And η is the step size

In chapter four, we numerically solve a system of ordinary differential equation (3.15)having initial conditions (3.16)by using Runge-Kutta method of fourth order with the help of python.

CHAPTER 4

NUMERICAL RESULTS AND DISCUSSION

We will present the outcomes numerically and discuss them in this portion of the study.

4.1 Numerical results

We will solve system (3.15) having initial conditions (3.16) using Runge-Kutta fourth order method with the help of python. We use Parameter values in Table 4.1which are nonnegative and per day.

Table 4.1 Parameter values that are biologically relevant

Parameter	Range (per day)	Point-value	Source
λ	20	20	Kirschner and webb (1996)
β	0.0005-0.003	0.001	Perelson (1989)
r	0.04-0.4	0.05	Kirschner and Webb (1996)
σ	0-1	0.1	Assumed
ε	0-1	0.8	Assumed
τ	0.0003 to 0.03	0.03	Asquith et al. (2007)
μ_1	0.01 to 0.05	$1/30$	(Kirschner and Webb 1996; Nelson et al. 2000)
μ_2	0.01 to 0.05	0.02	(Kirschner and Webb 1996; Nelson et al. 2000)
μ_3	0.01 to 0.05	0.09	(Kirschner and Webb 1996; Nelson et al. 2000)

Figure 4.1, Figure 4.2 and Figure 4.3 below represent geometric trajectories of system(3.15) with initial condition(3.16). The parameter values for these figures are obtained from Table 4.1 in the column of point-value i.e $\lambda = 20,\ \beta = 0.001,\ \sigma = 0.1,\ \varepsilon = 0.8,\ r = 0.05,\ \tau = 0.03,\ \mu_1 = \frac{1}{30},\ \mu_2 = 0.02,\ \mu_3 = 0.09.$

And taking $\alpha = 0.65, 0.75, 0.85, 0.95,\ M = 10$ and $X_1(0) = 10,\ X_2(0) = 2.5,\ X_3(0) = 1.5$

Approximation of the results were done at $\psi = \Delta t = 0.01$.

Substituting the above parameter values to reproduction number R_0 and to disease free equilibrium $E_0 = \left(\frac{\lambda}{\mu_1}, 0, 0\right)$ gives;

$$R_0 = \frac{\sigma\beta\lambda\tau}{(\tau+\mu_2)\mu_1\mu_3} + \frac{\tau\varepsilon r}{(\tau+\mu_2)\mu_3} + \frac{(1-\varepsilon)r}{\mu_3}$$

$$\frac{(0.1)(0.001)(20)(0.03)}{(0.03+0.02)\left(\frac{1}{30}\right)(0.09)} + \frac{(0.03)(0.8)(0.05)}{(0.03+0.02)(0.09)} + \frac{(1-0.8)(0.05)}{(0.09)}$$

Therefore $R_0 = 0.7778$

$E_0 = \left(\frac{\lambda}{\mu_1}, 0, 0\right)$, but $\frac{\lambda}{\mu_1} = \frac{20}{1/30}$

Therefore $E_0 = (600, 0, 0)$

From the above computation $R_0 = 0.7778$ and is less than one, therefore the equilibrium point free of disease, $E_0 = (600, 0, 0)$ is globally asymptotically stable.

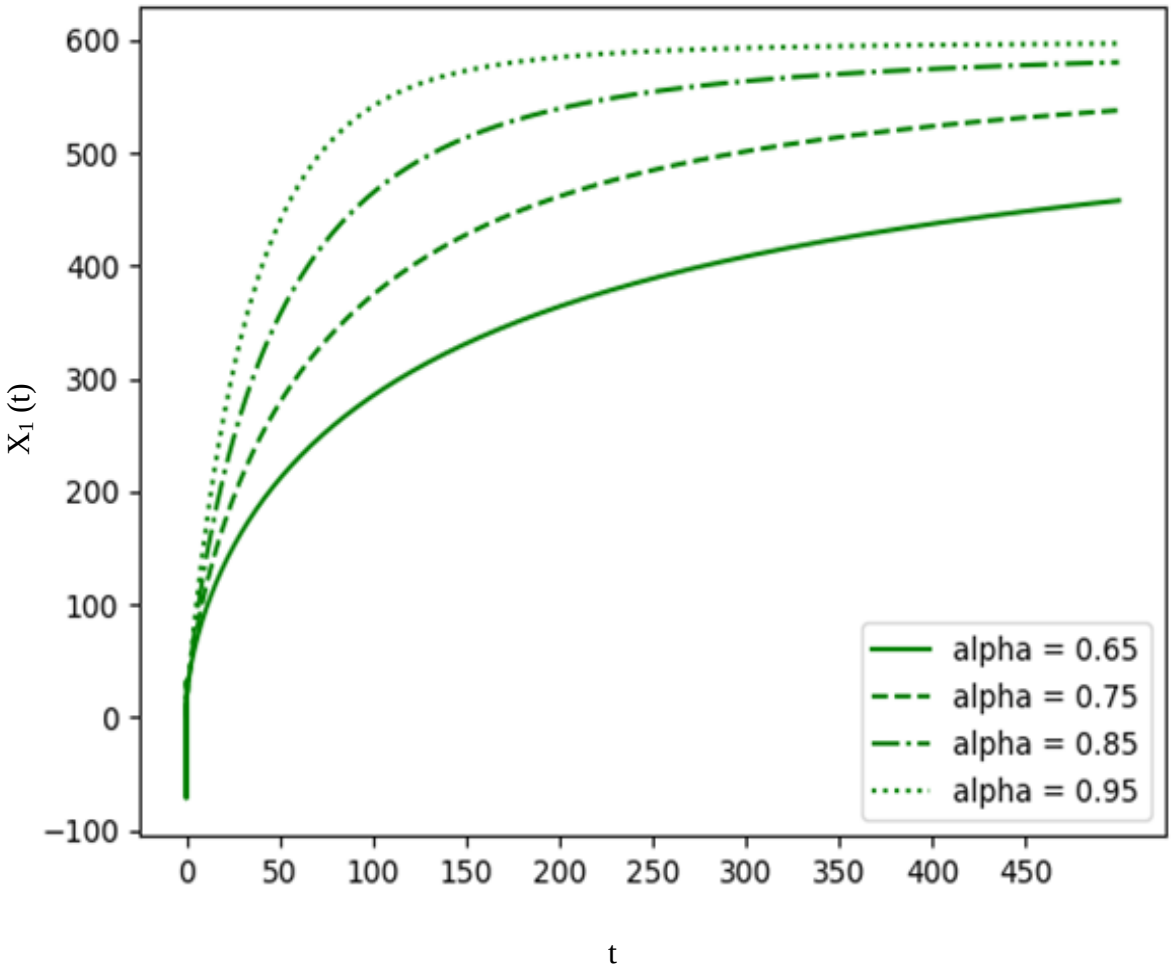

Figure 4.1 CD4^{+}T cell concentration in a healthy state, where r = 0.05, α = 0.65, 0.75, 0.85, 0.95 and $R_0 < 1$.

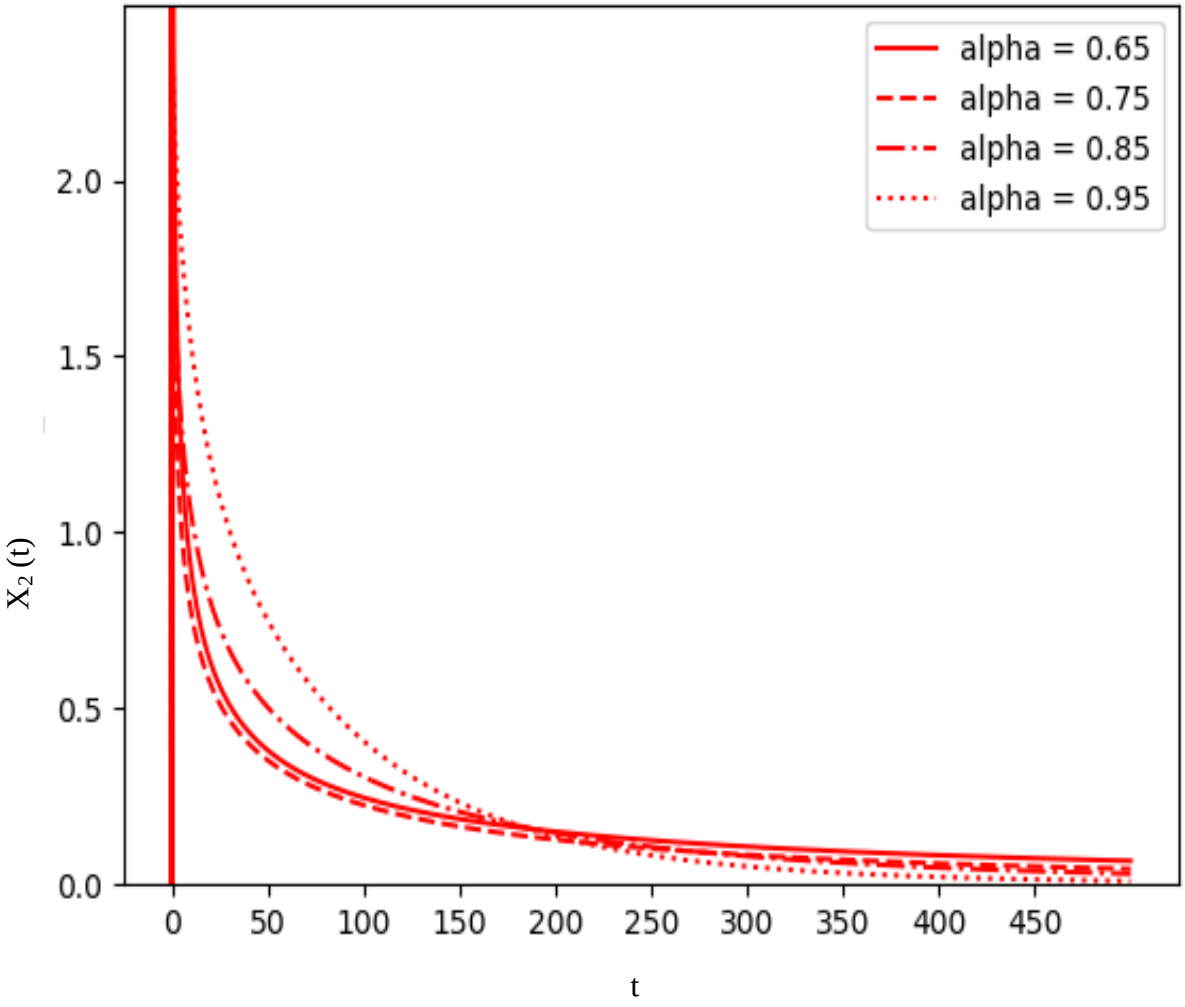

Figure 4.2 Infected and inactive CD4$^+$T cell concentration, where r = 0.05 , α = 0.65, 0.75, 0.85, 0.95 and $R_0 < 1$

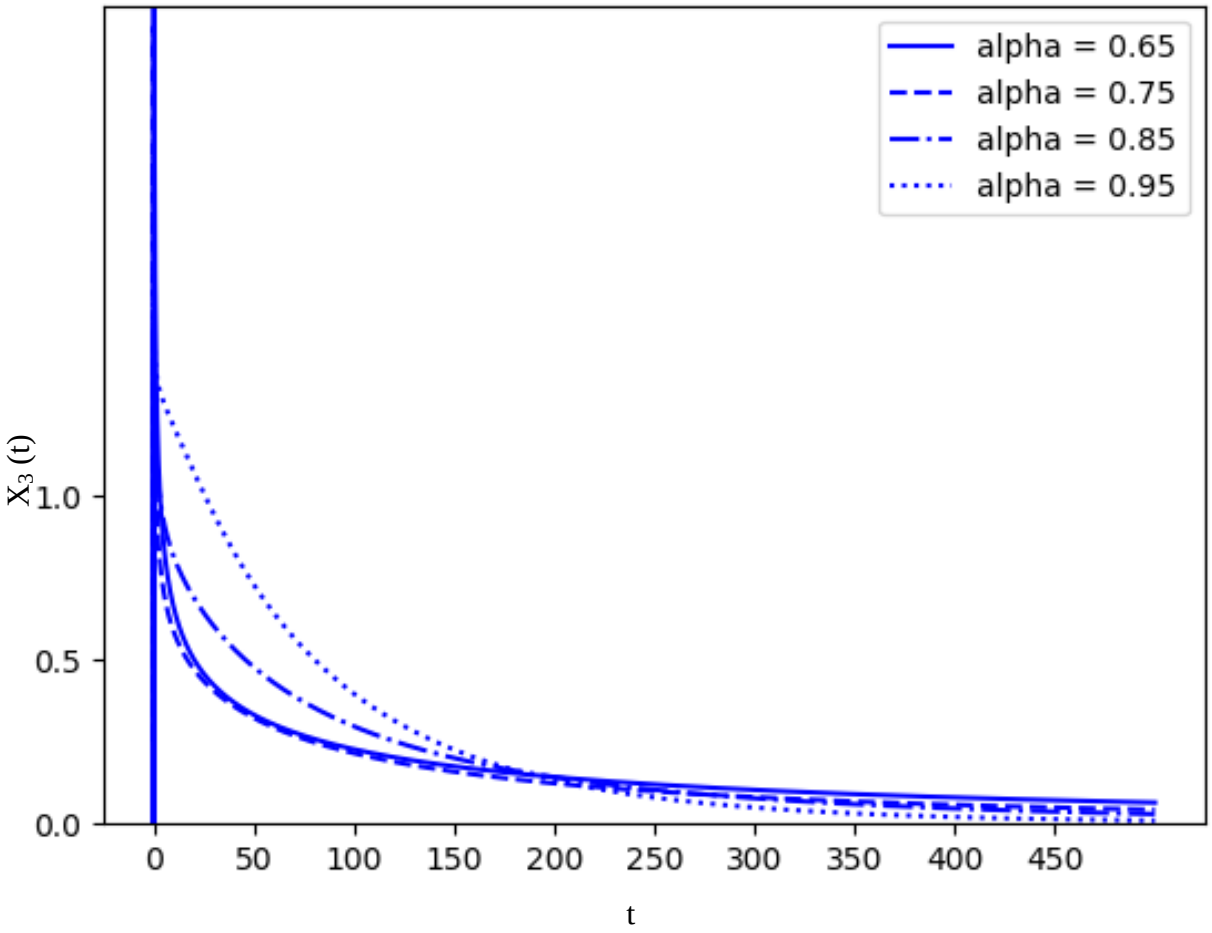

Figure 4.3 Infected and active CD4$^+$T cell concentration, where r = 0.05, α = 0.65, 0.75, 0.85, 0.95 and $R_0 < 1$

Figure 4.4, Figure 4.5 and Figure 4.6 below represents geometric trajectories of system with initial conditions (3.16). The parameter values for these figures are obtained from Table 4.1 in the column of point-value i.e $\lambda = 20,\ \beta = 0.001,\ \sigma = 0.1, \varepsilon = 0.8,\ \tau = 0.03,\ \mu_1 = \frac{1}{30},\ \mu_2 = 0.02,\ \mu_3 = 0.09$but taking $r = 0.1$

And taking$\alpha = 0.65, 0.75, 0.85, 0.95,\ M = 10$ and $X_1(0) = 10,\ X_2(0) = 250,\ X_3(0) = 150$

Approximation of the results were done at ψ = Δt = 0.01.

Substituting the above parameter values to reproduction number R_0 and to endemic equilibrium $E_1 = \left(X_1^*, X_2^*, X_3^*\right)$gives;

$$R_0 = \frac{\sigma\beta\lambda\tau}{\left(\tau+\mu_2\right)\mu_1\mu_3} + \frac{\tau\varepsilon r}{\left(\tau+\mu_2\right)\mu_3} + \frac{\left(1-\varepsilon\right)r}{\mu_3}$$

$$\frac{(0.1)(0.001)(20)(0.03)}{(0.03+0.02)\left(\frac{1}{30}\right)(0.09)} + \frac{(0.03)(0.8)(0.1)}{(0.03+0.02)(0.09)} + \frac{(1-0.8)(0.1)}{(0.09)}$$

Therefore $R_0 = 1.1556$

$$E_1 = \left(X_1^*, X_2^*, X_3^*\right)$$

$$X_1^* = \frac{\lambda}{\beta X_3^* + \mu_1}$$

$$= \frac{20}{(0.001)(21.2182)+\left(\frac{1}{30}\right)}$$

$$X_1^* = 366.6258$$

$$X_2^* = \frac{\left[\mu_3 - (1-\varepsilon)r\right]X_3^*}{\tau}$$

$$= \frac{[0.09-(1-0.8)0.1]21.2182}{0.03}$$

$$X_2^* = 49.5091$$

$$\mathrm{x}_3^* = \frac{\mu_1}{\beta}(R_0 - 1)\frac{(\tau+\mu_2)\mu_3}{(\tau+\mu_2)\mu_3 - \tau r - \mu_2(1-\varepsilon)r}$$

$$= \frac{1/30}{0.001}(1.1556 - 1)\frac{(0.03+0.02)(0.09)}{(0.03+0.02)0.09 - (0.03)(0.1) - (0.02)(1-0.8)(0.1)}$$

$$\mathrm{x}_{3=}^* 21.2182$$

Therefore$\mathrm{E}_1 = (366.6258, 49.5091, 21.2182)$

From the above computation, $R_0 = 1.1556 > 1$, therefore endemic equilibrium $\mathrm{E}_1 = (366.6258, 49.5091, 21.2182)$ is globally asymptotically stable.

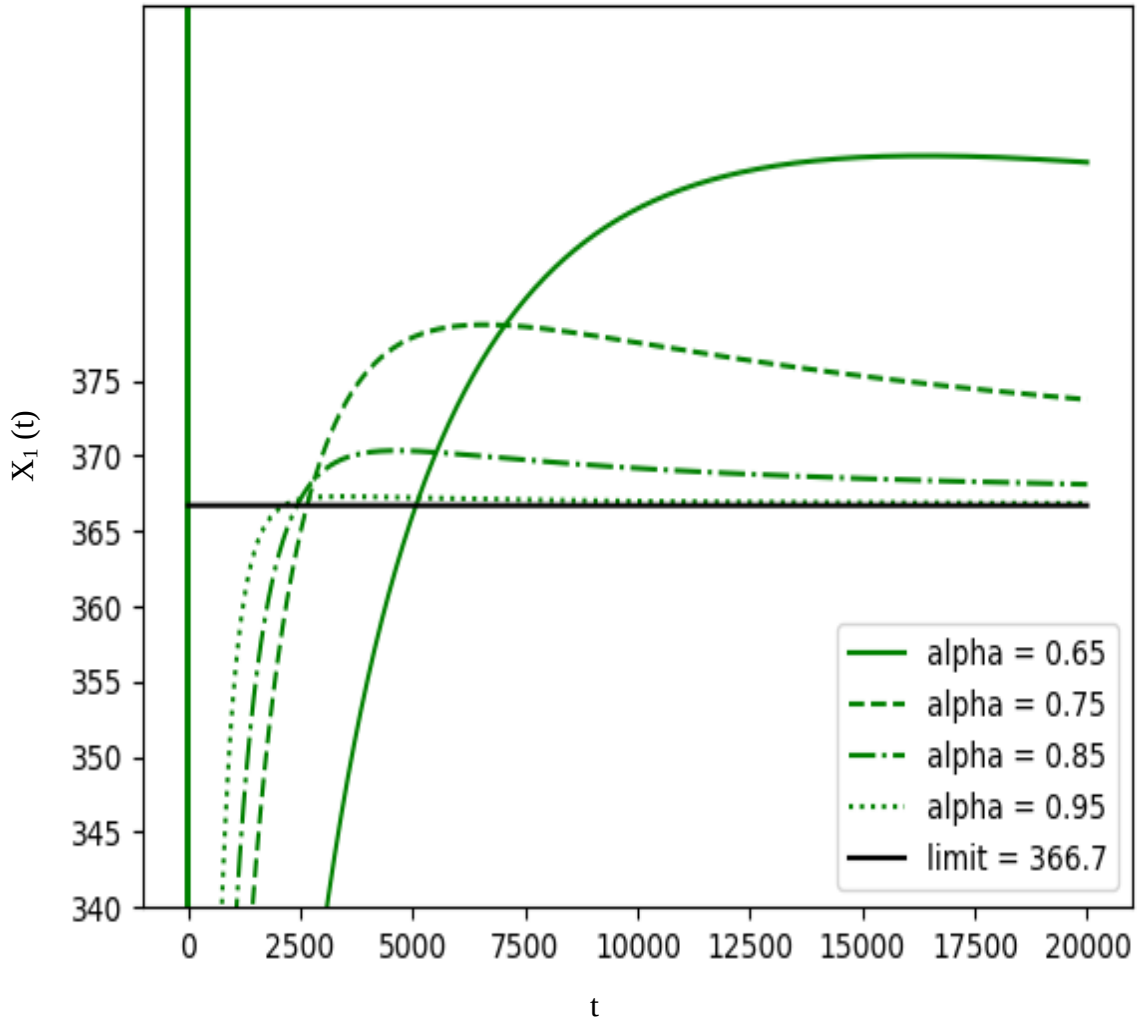

Figure 4.4 $CD4^+$T cell concentration in a healthy state, where r = 0.1, α = 0.65, 0.75, 0.85, 0.95 and $R_0 > 1$.

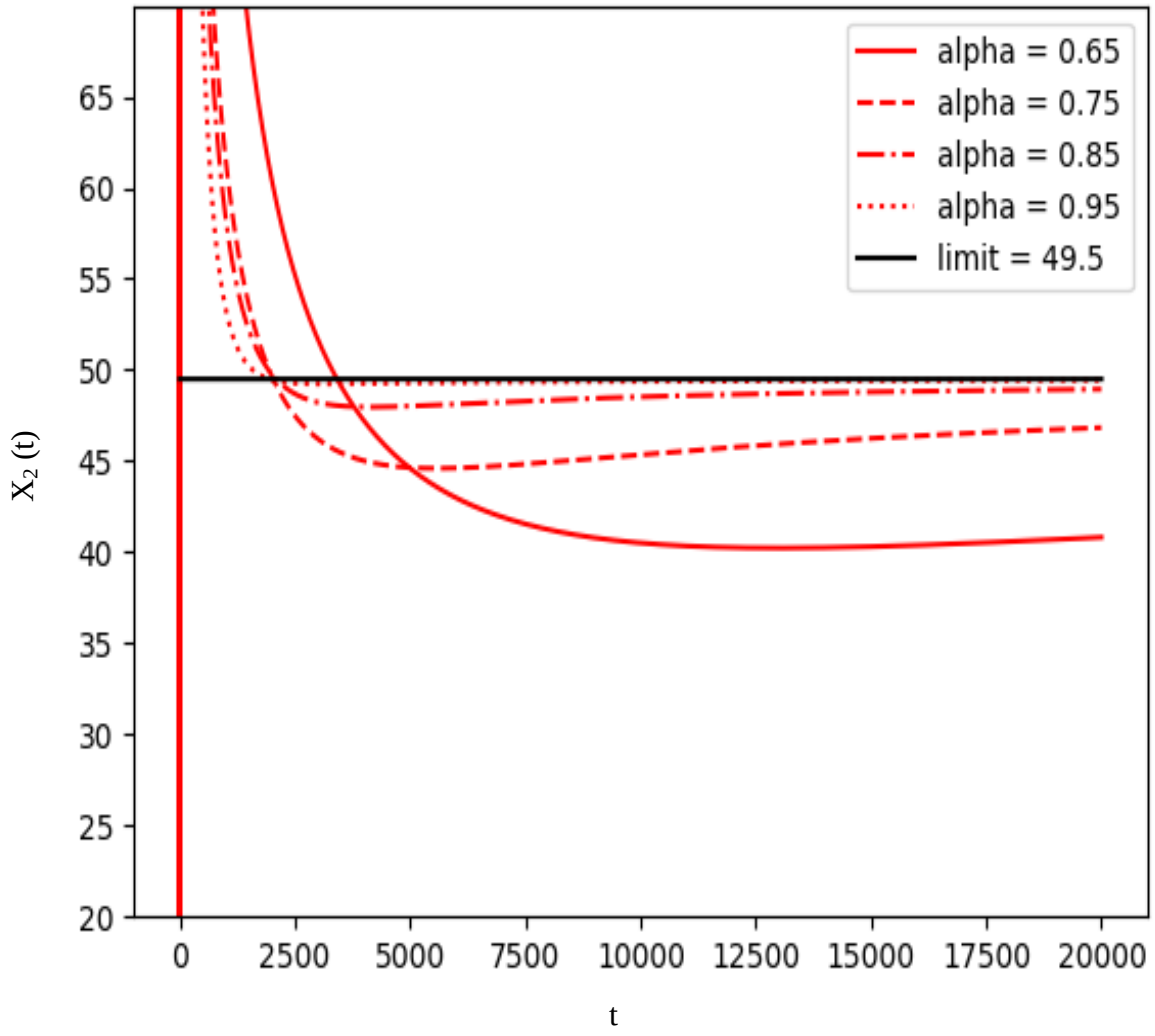

Figure 4.5 Infected and inactive CD4$^+$T cell concentration, where r = 0.1, α = 0.65, 0.75, 0.85, 0.95. and $R_0 > 1$.

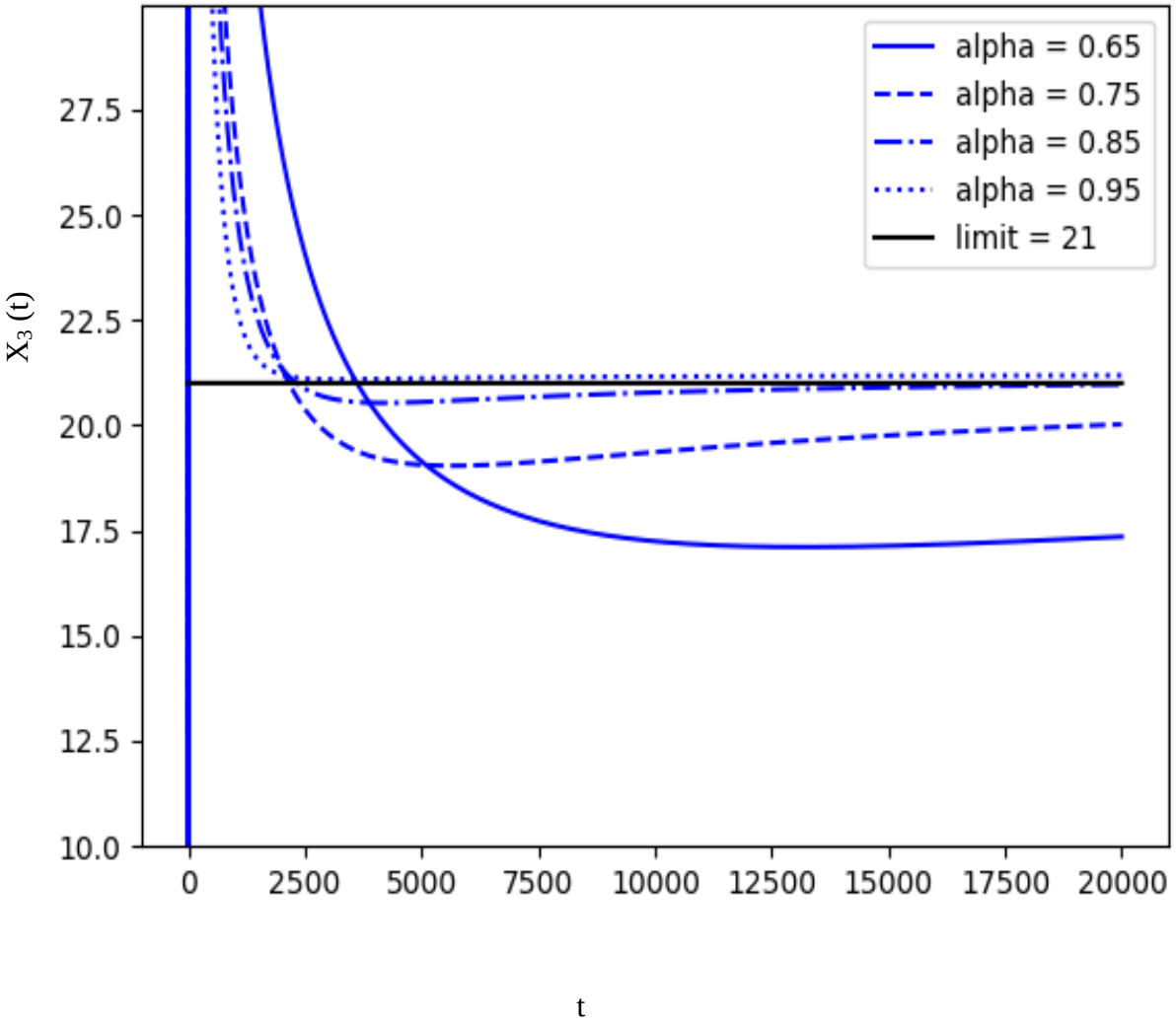

Figure 4.6 Infected and active CD4$^+$T cell concentration, where r = 0.1, α = 0.65, 0.75, 0.85, 0.95 and $R_0 > 1$.

4.2 Discussion

Figure 4.1, Figure 4.2 and Figure 4.3 present solutions of system(3.15) with initial conditions (3.16), where $r = 0.05$ and $R_0 = 0.7778$.The obtained numerical results based on these figures demonstrate that lowering the parametric value of r causes the quantity of healthy $CD4^+$T cells increase exponentially as shown in figure 4.1, while the numbers of infected cells both inactive and active decrease significantly as shown in figure 4.2 and 4.3 respectively. Again from these figures we see that the trajectories approach the disease free equilibrium point, $E_0 = (600, 0, 0)$ as t progresses towards infinity, which illustrates the theoretical results in theorem 3.12. We have in Figure 4.1 healthy CD4 cells increasing as α increases and in Figure 4.2 and Figure 4.3 where $t = 200$ and beyond we have inactive and active infected CD4 cells respectively decreasing as α increases. In these figures we associate increasing value of α with an immune system of an HTLV-1 infected individual that is becoming stronger day by day. A strong immune system takes control over the infection hence the virus die, causing healthy cells to rise and infected cells whether inactive or active to reduce. These numerical results imply that as t progresses towards infinity the virus gets cleared.

Figure 4.4, Figure 4.5 and Figure 4.6 present solutions of system(3.15) with initial conditions(3.16), where $r = 0.1$ and $R_0 = 1.1556$. The word limit used in the figures above represents equilibrium point. The obtained numerical results based on these figures demonstrate that raising the parametric value of r makes the quantity of healthy $CD4^+$T cells to decrease beyond $t = 5000$ as shown in figure 4.4 while the numbers of infected cells, both inactive and active to increase beyond $t = 5000$ as shown in figure 4.5 and 4.6 respectively. Again from these figures we see that the trajectories approach the endemic equilibrium point$E_1 = (366.6258, 49.5091, 21.2182)$ as t progresses towards infinity,

which illustrates the theoretical results in theorem 3.13. We have in Figure 4.4, healthy CD4 cells decreasing as α increases and in Figure 4.5 and Figure 4.6 where $t = 5000$ and beyond, we haveinactive and active infected CD4 cells respectively increasing as α increases. In these figures we associate increasing value of α with an immune system of an HTLV-1 infected individual that is becoming weaker day by day. A weak immune system is unable to actively deal with virus hence the virus persist. These numerical results imply that the virus persist as t progresses towards infinity.

It's clear from all the figures above that differential equations of fractional order are more informative than integer-order and biological systems are better described by their models. What we have observed is that the solutions of the model, with a range of values of alpha rely always on the fractional derivative's order α, but approaches faster to their equilibrium points as alpha tends to 0.95.The derivative order α can play the role of strength of the immune system in an HTLV-1 infected individual.

CHAPTER 5

CONCLUSION AND RECOMMENDATION

In this chapter we shall conclude our research study and give out recommendation

5.1 Conclusion

In this research project, a fractional order model of $CD4^+$T-cell infection with HTLV-1 taking into account transmission from cell to cell and mitotic has been developed. The solution to the proposed model is shown to be unique. Utilizing the generalized fractional mean value theorem, positivity of solution for the model system is presented. Using the next the generation matrix, the basic reproduction number, R_0 was obtained. Model equilibria are determined. The stability of the equilibrium points have been analyzed using Routh-Hurwitz stability requirements and Lasalle's invariance principle. The system's stability has been investigated in terms of R_0 values. If R_0 is a number less than one, the equilibrium point free of disease is asymptotically stable whether globally or locally, while the endemic equilibrium is asymptotically stable whether globally or locally if R_0 is a number higher than one. A numerical technique for writing differential equations of fractional order as a first-order system of ordinary differential equations was employed. The obtained differential equations are then solved using Runge-Kutta fourth order method with the help of python for different values of alpha. Lastly the obtained results were presented graphically.

The results obtained show that lowering the parametric value r makes the number of healthy $CD4^+$T cells increase substantially, while the numbers of inactive and active infected cells decrease dramatically. This means that mitotic transmission should be controlled in therapeutic intervention. The results also show that the derivative order α can play the role of strength of the immune system in an HTLV-1 infected individual. This indicates that

during a therapy session, an individual's immunity should be strengthened. In addition, the results show that differential equations of fractional order are more informative.

5.2 Recommendation

The results obtained from this study enabled us to give the following recommendations:

a) Policy makers should concentrate on controlling mitotic transmission of actively infected cell and strengthening immunity of infected individual to be able to reduce the risk of HTLV type 1 infection on CD4cells.

b) Again we recommend these results obtained from fractional order model for CD4cells infection by HTLV-1 as it is more informative.

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CHAPTER 6

APPENDICES

6.1 Appendix I: Python codes for simulations

```
importos
importnumpy as np
importmatplotlib.pyplot as plt
from math import gamma

M=10
alphatab=[0.65,0.75,0.85,0.95]

#The following values correspond to Figure 4.1, 4.2, 4.3 in the Word file
beta=0.001
lambd=20
sigma=0.1
epsilon=0.8
r=0.05
tau=0.03
mu1=1.0/30
mu2=0.02
mu3=0.09
maxt=450
dt=0.01
ski=dt
x=np.array([10,2.5,1.5])
H= np.zeros(3*M)
def A(alpha, t, k):
        if(k<=170):
```

```
            return -gamma(k-1+alpha)/(gamma(2-alpha)*gamma(alpha-
1)*gamma(k))
        else:
            return -(k**(alpha-1))/(gamma(2-alpha)*gamma(alpha-1))  #for big
integers (gamma approximation), this is if needed...


def Q(alpha, t, M):
        numerator=1
        for j in range(1,M+1):
            if(j<=169):
                numerator+= gamma(j-1+alpha)/(gamma(alpha-1)*gamma(j+1))
            else:
                numerator+= ((j+1)**(alpha-2))/gamma(alpha-1)


        return numerator/(gamma(2-alpha)*(t**(alpha-1)))


def R(alpha, t):
        return (1-alpha)/((t**alpha)*gamma(2-alpha))


def Y(alpha, t, M):
        summ= R(alpha,t)
        for j in range(2, M+1):
            summ+= A(alpha, t, j)/(t**alpha)


        returnsumm


def Hprim1Fun(H, t):
        sumpart=0
        for k in range(2,M+1):
            sumpart+= A(alpha,t,k)*H[k-1]/(t**(k-1+alpha))
```

```
            return (lambd-beta*H[0]*H[2*M]-mu1*H[0]-Y(alpha,t,M)*H[0]-
sumpart)/Q(alpha,t,M)


defHprimKFun(H, t, k):
        return -(k-1)*(t**(k-2))*H[0]


def HprimM1Fun(H, t):
        sumpart=0
        for k in range(2,M+1):
                sumpart+= A(alpha,t,k)*H[M+k-1]/(t**(k-1+alpha))


        return (sigma*beta*H[0]*H[2*M]+epsilon*r*H[2*M]-tau*H[M]-mu2*H[M]-
Y(alpha,t,M)*H[M]-sumpart)/Q(alpha,t,M)


defHprimMkFun(H, t, k):
        return -(k-1)*(t**(k-2))*H[M]


def Hprim2M1Fun(H, t):
        sumpart=0
        for k in range(2,M+1):
                sumpart+= A(alpha,t,k)*H[2*M+k-1]/(t**(k-1+alpha))


        return (tau*H[M]+(1-epsilon)*r*H[2*M]-mu3*H[2*M]-Y(alpha,t,M)*H[2*M]-
sumpart)/Q(alpha,t,M)


def Hprim2MkFun(H, t, k):
        return -(k-1)*(t**(k-2))*H[2*M]


def fun(H, t):
        Hprim= np.zeros(3*M)
```

```
    Hprim[0]= Hprim1Fun(H, t)

    for k in range(1, M):
        Hprim[k]=HprimKFun(H, t, k+1)

    Hprim[M]= HprimM1Fun(H, t)

    for k in range(1, M):
        Hprim[M+k]= HprimMkFun(H, t, k+1)

    Hprim[2*M]= Hprim2M1Fun(H, t)

    for k in range(1, M):
        Hprim[2*M+k]= Hprim2MkFun(H, t, k+1)

    returnHprim

def RK4(fcn, I, t, Nt):
    """ Classical Runge-Kutta method of 4th order """
    u = np.zeros((Nt,3*M))
    dt = t[1]-t[0]

    u[0] = I
    for n in range(Nt-1):
        k1 = dt * fcn(u[n], t[n])
        k2 = dt * fcn(u[n]+0.5*k1, t[n] + 0.5*dt)
        k3 = dt * fcn(u[n]+0.5*k2, t[n] + 0.5*dt)
        k4 = dt * fcn(u[n]+ k3, t[n+1])
        u[n+1] = u[n] + (k1 + 2.0*(k2 + k3) + k4)/6.0
```

```
        return u, t


#Initialisations
H[0]=x[0]
for k in range(1,M):
        H[k]=-k*(dt**k)*x[0]/2.0
H[M]=x[1]
for k in range(1,M):
        H[M+k]=-k*(dt**k)*x[1]/2.0
H[2*M]=x[2]
for k in range(1,M):
        H[2*M+k]=-k*(dt**k)*x[2]/2.0


#Application of the Runge-Kutta method
t=np.arange(dt,maxt,dt)
Nt=len(t)
Hsol=np.zeros((4,Nt,3*M))
for i in range(4):
        alpha=alphatab[i]
        Hsol[i], time = RK4(fun, H, t, Nt)


#Ploting
colors=["green","red","blue"]
for i in range(3):
        plt.figure("Figure of x_%d against t" %(i+1))
        plt.plot(time,Hsol[0,:,i*M],label="alpha = %f"
%(alphatab[0]),color=colors[i],linestyle="-")
        plt.plot(time,Hsol[1,:,i*M],label="alpha = %f"
%(alphatab[1]),color=colors[i],linestyle="--")
        plt.plot(time,Hsol[2,:,i*M],label="alpha = %f"
%(alphatab[2]),color=colors[i],linestyle="-.")
```

```
        plt.plot(time,Hsol[3,:,i*M],label="alpha = %f"
%(alphatab[3]),color=colors[i],linestyle=":")
        plt.legend()
        plt.xlabel("x=t")
        plt.ylabel("y=x_%d" %(i+1))
        plt.ion()
plt.show()


os.system("pause")


importos
importnumpy as np
importmatplotlib.pyplot as plt
from math import gamma


M=10
alphatab=[0.65,0.75,0.85,0.95]


#The following values correspond to Figure 4.4, 4.5, 4.6 in the Word file
beta=0.001
lambd=20
sigma=0.1
epsilon=0.8
r=0.1
tau=0.03
mu1=1.0/30
mu2=0.02
mu3=0.09
maxt=20000
dt=0.01
```

```
ski=dt

x=np.array([10,250,150])

H= np.zeros(3*M)


def A(alpha, t, k):

    if(k<=170):

        return -gamma(k-1+alpha)/(gamma(2-alpha)*gamma(alpha-
1)*gamma(k))

    else:

        return -(k**(alpha-1))/(gamma(2-alpha)*gamma(alpha-1))  #for big
integers (gamma approximation), this is if needed...


def Q(alpha, t, M):

    numerator=1

    for j in range(1,M+1):

        if(j<=169):

            numerator+= gamma(j-1+alpha)/(gamma(alpha-1)*gamma(j+1))

        else:

            numerator+= ((j+1)**(alpha-2))/gamma(alpha-1)


    return numerator/(gamma(2-alpha)*(t**(alpha-1)))


def R(alpha, t):

    return (1-alpha)/((t**alpha)*gamma(2-alpha))


def Y(alpha, t, M):

    summ= R(alpha,t)

    for j in range(2, M+1):

        summ+= A(alpha, t, j)/(t**alpha)
```

```
        returnsumm


def Hprim1Fun(H, t):
        sumpart=0
        for k in range(2,M+1):
                sumpart+= A(alpha,t,k)*H[k-1]/(t**(k-1+alpha))


        return (lambd-beta*H[0]*H[2*M]-mu1*H[0]-Y(alpha,t,M)*H[0]-
sumpart)/Q(alpha,t,M)


defHprimKFun(H, t, k):
        return -(k-1)*(t**(k-2))*H[0]


def HprimM1Fun(H, t):
        sumpart=0
        for k in range(2,M+1):
                sumpart+= A(alpha,t,k)*H[M+k-1]/(t**(k-1+alpha))


        return (sigma*beta*H[0]*H[2*M]+epsilon*r*H[2*M]-tau*H[M]-mu2*H[M]-
Y(alpha,t,M)*H[M]-sumpart)/Q(alpha,t,M)


defHprimMkFun(H, t, k):
        return -(k-1)*(t**(k-2))*H[M]
def Hprim2M1Fun(H, t):
        sumpart=0
        for k in range(2,M+1):
                sumpart+= A(alpha,t,k)*H[2*M+k-1]/(t**(k-1+alpha))


        return (tau*H[M]+(1-epsilon)*r*H[2*M]-mu3*H[2*M]-Y(alpha,t,M)*H[2*M]-
sumpart)/Q(alpha,t,M)
```

```
def Hprim2MkFun(H, t, k):
    return -(k-1)*(t**(k-2))*H[2*M]

def fun(H, t):
    Hprim= np.zeros(3*M)

    Hprim[0]= Hprim1Fun(H, t)

    for k in range(1, M):
        Hprim[k]=HprimKFun(H, t, k+1)

    Hprim[M]= HprimM1Fun(H, t)

    for k in range(1, M):
        Hprim[M+k]= HprimMkFun(H, t, k+1)

    Hprim[2*M]= Hprim2M1Fun(H, t)

    for k in range(1, M):
        Hprim[2*M+k]= Hprim2MkFun(H, t, k+1)

    returnHprim
def RK4(fcn, I, t, Nt):
    """ Classical Runge-Kutta method of 4th order """
    u = np.zeros((Nt,3*M))
    dt = t[1]-t[0]

    u[0] = I
    for n in range(Nt-1):
```

```
            k1 = dt * fcn(u[n], t[n])
            k2 = dt * fcn(u[n]+0.5*k1, t[n] + 0.5*dt)
            k3 = dt * fcn(u[n]+0.5*k2, t[n] + 0.5*dt)
            k4 = dt * fcn(u[n]+ k3, t[n+1])
            u[n+1] = u[n] + (k1 + 2.0*(k2 + k3) + k4)/6.0
    return u, t

#Initialisations
H[0]=x[0]
for k in range(1,M):
    H[k]=-k*(dt**k)*x[0]/2.0
H[M]=x[1]
for k in range(1,M):
    H[M+k]=-k*(dt**k)*x[1]/2.0
H[2*M]=x[2]
for k in range(1,M):
    H[2*M+k]=-k*(dt**k)*x[2]/2.0

#Application of the Runge-Kutta method
t=np.arange(dt,maxt,dt)
Nt=len(t)
Hsol=np.zeros((4,Nt,3*M))
for i in range(4):
    alpha=alphatab[i]
    Hsol[i], time = RK4(fun, H, t, Nt)

#Ploting
colors=["green","red","blue"]
for i in range(3):
    plt.figure("Figure of x_%d against t" %(i+1))
```

```
        plt.plot(time,Hsol[0,:,i*M],label="alpha = %f"
%(alphatab[0]),color=colors[i],linestyle="-")

        plt.plot(time,Hsol[1,:,i*M],label="alpha = %f"
%(alphatab[1]),color=colors[i],linestyle="--")

        plt.plot(time,Hsol[2,:,i*M],label="alpha = %f"
%(alphatab[2]),color=colors[i],linestyle="-.")

        plt.plot(time,Hsol[3,:,i*M],label="alpha = %f"
%(alphatab[3]),color=colors[i],linestyle=":")

        plt.legend()

        plt.xlabel("x=t")

        plt.ylabel("y=x_%d" %(i+1))

        plt.ion()

plt.show()


os.system("pause")
```

6.2 Appendix II: Certificate of a published Research Project